Rhodium(II)-catalysed C–H insertion/ olefination strategy towards α-methylene-γ-butyrolactones: applications in natural product synthesis

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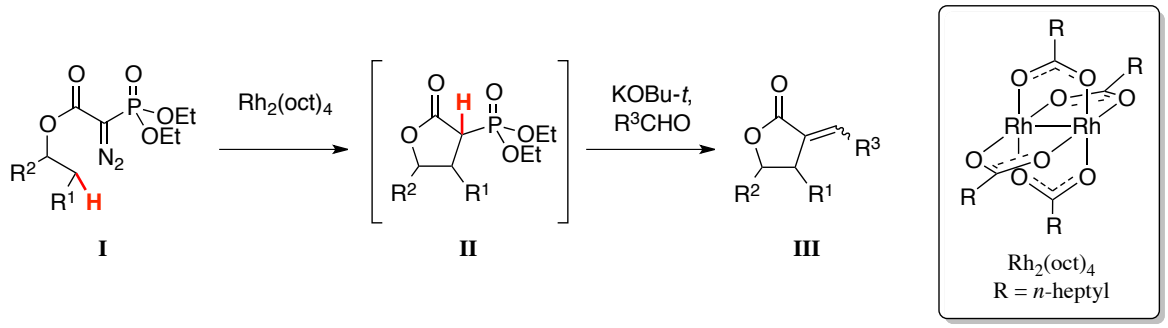
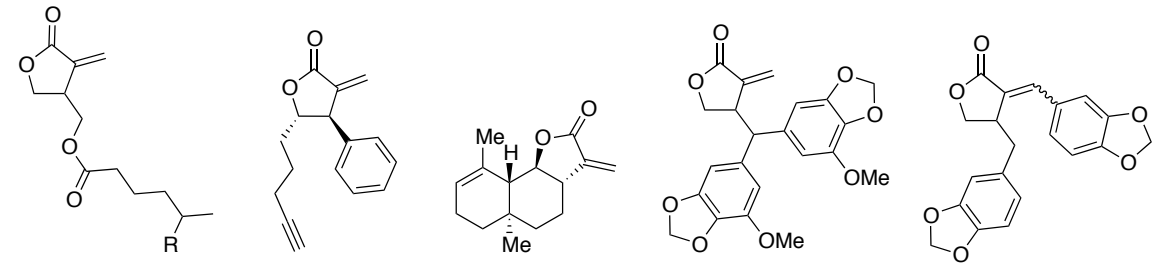
Abstract

This Thesis describes the development of telescoped rhodium(II)-catalysed transformations of α-diazo(diethoxyphosphoryl)acetates for the formation of α-methylene-γ-butyrolactones. An overview of synthetic approaches to α-methylene-γ-butyrolactones is given in Chapter 1, in addition to a discussion of published Rh(II)-catalysed C–H insertion reactions.

Previous efforts in the Taylor group have established effective methods for the synthesis of α-methylene-γ-butyrolactones, although these require relatively complex functionality in the precursors. The research in this Thesis focuses on the development of a one-pot Rh(II)-catalysed C–H insertion/olefination sequence for the synthesis of α-methylene-γ-butyrolactones **III** from α-diazo(diethoxyphosphoryl)acetates **I**, which are readily accessible from simple alcohols. The key C–H insertion step enables the formation of a new C–C bond in α-phosphonolactone **II**, *via* reaction of the rhodium carbenoid with a C–H bond typically considered completely unreactive.



The scope of the reaction is explored in detail, concluding with the synthesis of two natural products, cedarmycins A and B (**IV** and **V**) and a *Staphylococcus aureus* inhibitor **VI** (Chapter 2). The scope of the reaction was extended to the use of conformationally restricted substrates, facilitating the synthesis of α-methylene-γ-butyrolactones with complete diastereoselectivity, demonstrated through the synthesis of the natural product α-cyclocostunolide **VII** (Chapter 3). Finally, the development of a related procedure is described (Chapter 4). The rhodium(II)-catalysed cyclopropanation of allylic α-diazo(diethoxyphosphoryl)acetates is discussed as an alternative approach to the α-methylene-γ-butyrolactone framework. This work has been applied to the first total synthesis of peperomin E **VIII** as well as savinin **IX** and gadain **X** (Chapter 4).



cedarmycin A, R = Me, **IV**
cedarmycin B, R = H, **V**

S. aureus inhibitor, **VI**

α-cyclocostunolide **VII**

peperomin E **VIII**

savinin, *E*, **IX**
gadain, *Z*, **X**

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Author's Declaration

The work presented in this thesis is my own and was carried out at the University of York between October 2012 and March 2016. The work is, to the best of my knowledge, original except where due reference has been made to other workers and has not been submitted as part of any other award at this or any other institution.

Parts of this work have been reproduced in published papers, copies of which can be found in Appendices III, IV and V:

Lloyd, M. G.; Taylor, R. J. K.; Unsworth, W. P.; A One-Pot C–H Insertion/Olefination Sequence for the Formation of α-Alkylidene-γ-butyrolactones, *Org. Lett.* **2014**, *16*, 2772–2775.

Lloyd, M. G.; D'Acunto, M.; Taylor, R. J. K.; Unsworth, W. P.; α-Alkylidene-γ-butyrolactone synthesis via one-pot C–H insertion/olefination: substrate scope and the total synthesis of (±)-cedarmycins A and B, *Tetrahedron* **2015**, *71*, 7107–7123.

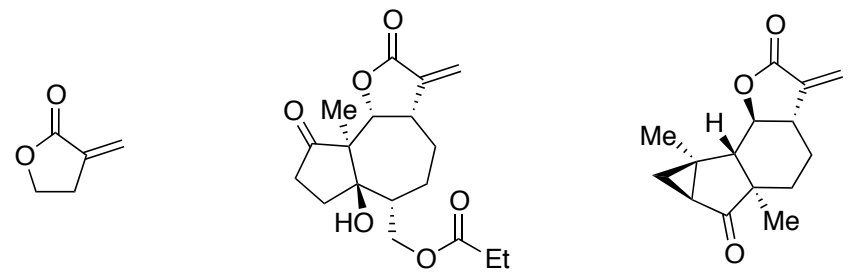
Lloyd, M. G.; D'Acunto, M.; Taylor, R. J. K.; Unsworth, W. P.; A selective C–H insertion/olefination protocol for the synthesis of α-methylene-γ-butyrolactone natural products, *Org. Biomol. Chem.* **2016**, *14*, 1641–1645.

Chapter 1 – Introduction

1.1 α-Methylene-γ-butyrolactones

1.1.1. Prevalence in Nature

The α-methylene-γ-butyrolactone functionality is prevalent in Nature, comprising approximately 3% of all known natural products.[1] This naturally occurring motif imparts a wide variety of biological effects including antibacterial, antifungal and anticancer activities. The simplest possible α-methylene-γ-butyrolactone is itself a natural product known as tulipalin A **1**, possessing anti-tumour properties and isolated from the common tulip *Tulipa gesneriana*.[2] Many of these natural products are also isolated from flowering plants; for example, hispitolide A **2** is isolated from *Parthenium hispitum*,[3] commonly known as feverfew, and ratibinolide **3** from *Ratibida latipalearis*, a genus of the daisy family (Figure 1).[4]



tulipalin A, **1** hispitolide A, **2** ratibinolide, **3**

Figure 1: Examples of α-methylene-γ-butyrolactone containing natural products.

The majority of α-methylene-γ-butyrolactone natural products are sesquiterpenes, derived from 3 isoprene units and containing 15 carbons. They can be further classified based on their structural frameworks (Figure 2). Many of these examples contain fused bicyclic rings, giving rise to both *cis*- and *trans*-skeletons (cf. hispitolide A and ratibinolide, Figure 1). In addition, there are many examples of diterpene α-methylene-γ-butyrolactones, containing 20 carbons, as well as non-terpenoid examples.[5]

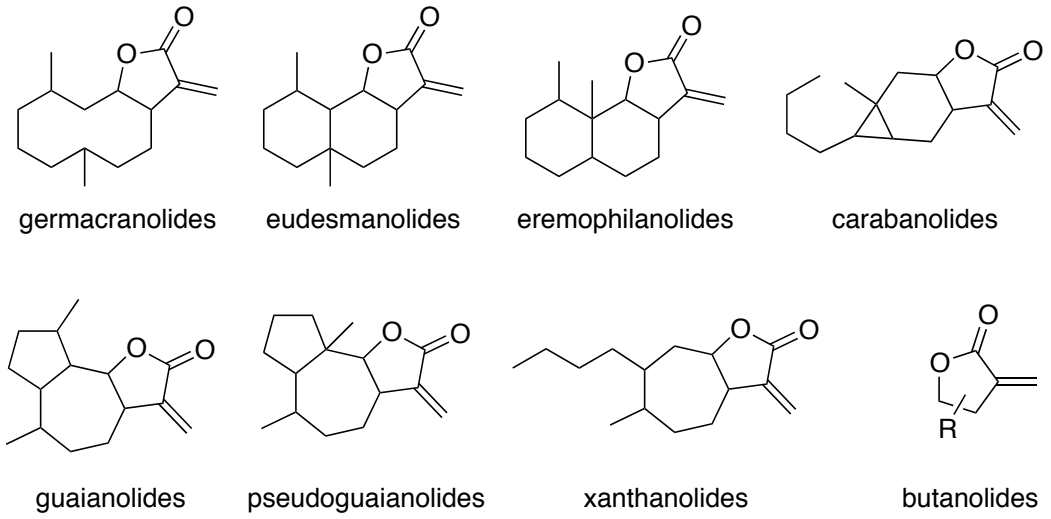
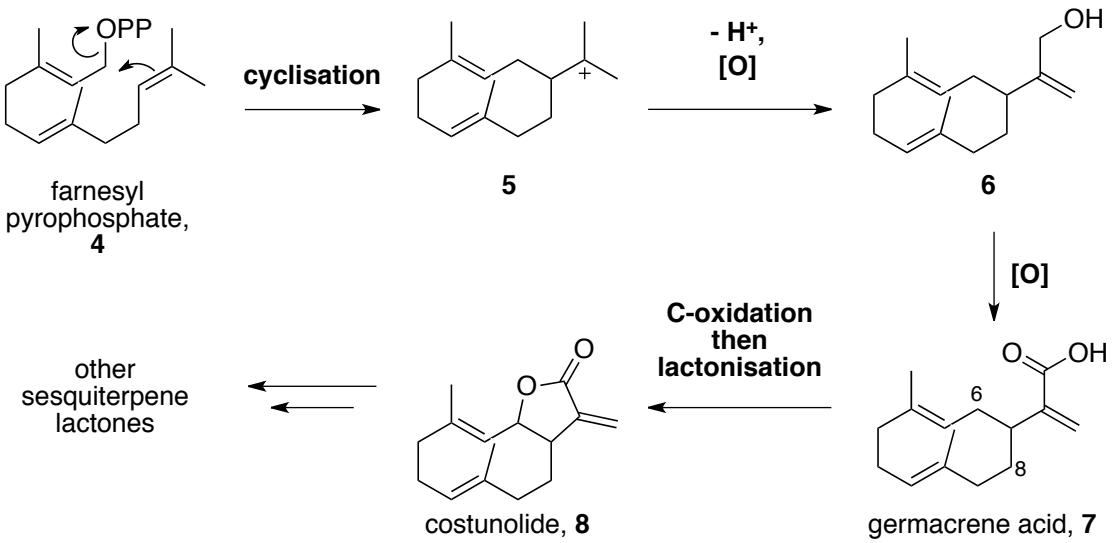


Figure 2: Commonly found sesquiterpene α-methylene-γ-butyrolactone frameworks and non-terpenoid butanolides.

Sesquiterpene lactones can also be found in food sources, with lettuce and chicory representing the most common method of consumption for humans. They also convey benefits for plants, acting as defence mechanism against fungi, bacteria and insects.[6] In addition to their medicinal applications, sesquiterpene lactones can also have negative effects, most commonly allergic reactions; for example, the pollen from plants that produce sesquiterpene α-methylene-γ-butyrolactones can cause allergic contact dermatitis, leading to sensitisation of the skin.[7]

The biological activity of sesquiterpene lactones stems from the electrophilic nature of the α,β-unsaturated ester, making these compounds susceptible to 1,4-addition reactions. *In vivo*, L-cysteine residues or thiol-containing enzymes react *via* conjugate addition to form adducts that reduce the growth of cells or aid drug-induced cell death.[5] Whilst the α-methylene-γ-butyrolactone functionality provides the main mode of reactivity leading to a range of effects it is other functional groups that enhance activity through chemical or steric influences.[6]

Studies have shown that the biosynthesis of α-methylene-γ-butyrolactones proceeds *via* the synthesis of a common precursor which then undergoes late-stage chemical transformations to form the array of natural product frameworks shown in Figure 2.[7] The pathway that produces terpene based α-methylene-γ-butyrolactones begins with an intramolecular cyclisation of farnesyl pyrophosphate **4** (Scheme 1). A series of oxidations affords germacrene acid **7** and costunolide **8**, further elaboration of which gives rise to the many different terpenoid frameworks.



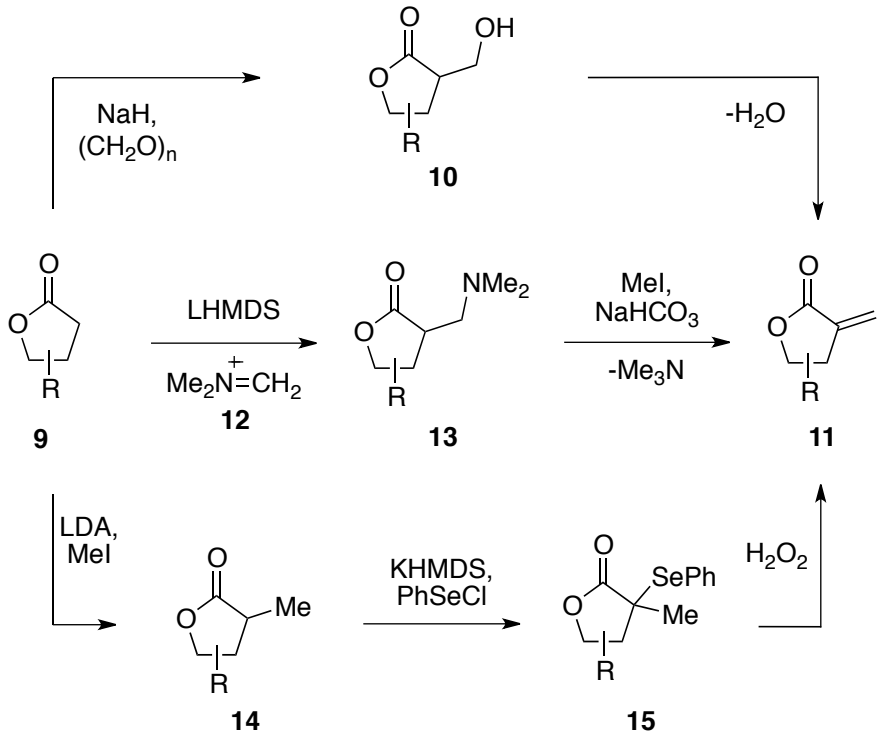
Scheme 1: Biosynthetic pathway towards terpenoid α-methylene-γ-butyrolactones.

The biological activity of α-methylene-γ-butyrolactones is both wide-ranging and significant for the purpose of both medicinal treatments, for example as antivirals,[8] and in agriculture as insect antifeedants,[1,6] thus the development of new efficient methods for their synthesis is of much interest.

1.1.2. Existing routes

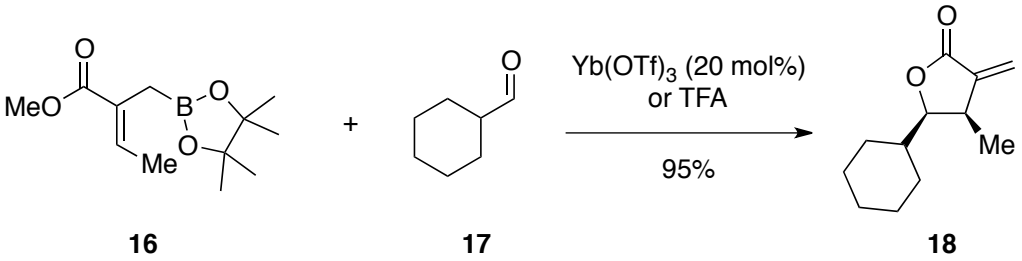
There are many existing synthetic routes to make α-methylene-γ-butyrolactones, many of which have been thoroughly reviewed before,[7] most recently in 2009.[1] A short summary is given herein along with some more recent examples.

The methylenation of lactones is one of the most common routes towards α-methylene-γ-butyrolactones. For example, the dehydration of α-hydroxy-γ-lactones **10**, either with or without prior derivatisation of the alcohol, generates α-methylene-γ-butyrolactone **11**. Eschenmoser's iminium salt **12**, can be used as an alternative reagent to formaldehyde, forming aminomethyl lactone **13**, which on alkylation in the presence of base generates the α-methylene-γ-butyrolactone **11** *via* a Hofmann elimination.[1,9] Another commonly used method to introduce the *exo*-methylene unit is by selenoxide elimination. Firstly, methylation of γ-butyrolactone **9** generates α-methyl-γ-butyrolactone **14**, which on treatment with phenylselenylchloride under basic conditions affords selenide **15**. Subsequent oxidation and selenoxide elimination in the presence of hydrogen peroxide furnishes α-methylene-γ-butyrolactone **11** (Scheme 2).[1]



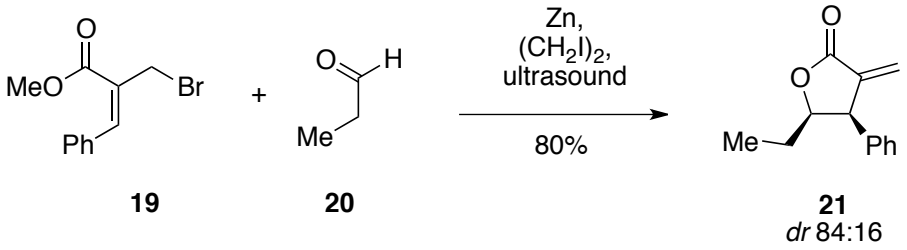
Scheme 2: Elimination-based methylenation approaches to α-methylene-γ-butyrolactones.

The formation of α-methylene-γ-butyrolactones by lactonisation is another commonly employed technique. The simplest approach of this type is the cyclisation of a γ-alcohol and carbonyl such as an ester, acid or acid chloride, yet many of these approaches involve an initial reaction to install the γ-alkoxy/alkoxide ester, which then undergoes a lactonisation reaction to form the desired α-methylene-γ-butyrolactone. For example, the treatment of crotylboronate **16** and aldehyde **17** with Lewis or Brønsted acid forms the γ-alkoxide ester, which subsequently undergoes *in situ* lactonisation delivering α-methylene-γ-butyrolactone **18** (Scheme 3).[10]



Scheme 3: Crotylboronate derived route to α-methylene-γ-butyrolactones.

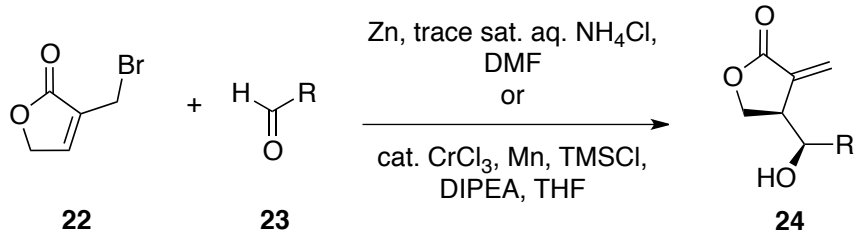
A similar approach, an example of which is shown in Scheme 4, utilises a 2-bromomethylacrylic ester **19** and aldehyde **20** and is known as the Dreiding–Schmidt procedure.[11] In this case, addition of zinc generates the organometallic reagent, which adds diastereostereoselectively into the aldehyde, before spontaneously cyclising to form the lactone **21**.



19 **20** **21**
dr 84:16

Scheme 4: Dreiding–Schmidt procedure for synthesis of α-methylene-γ-butyrolactones.

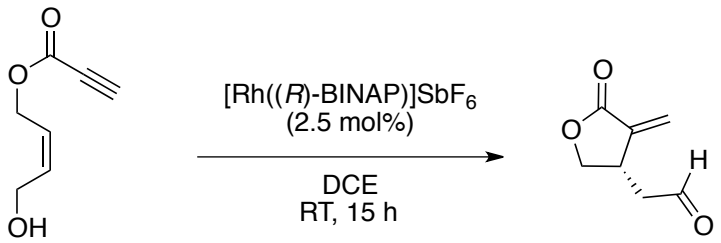
In 2011 Hodgson *et al*. reported a Barbier-type coupling,[12] similar to that of the Dreiding–Schmidt procedure, that produced β-hydroxymethyl-α-methylene-γ-butyrolactones **24** *via* coupling of bromolactone **22** with aldehydes **23** as shown in Scheme 5. They found that both metallic zinc or Cr(II) salts could successfully be employed to efficiently convert the aromatic and aliphatic aldehydes, respectively in good yield, regio- and stereocontrol.



22 **23** **24**
15 examples
55–94%
up to 99:1 dr

Scheme 5: Hodgson's Barbier-type allylation approach to α-methylene-γ-butyrolactones.

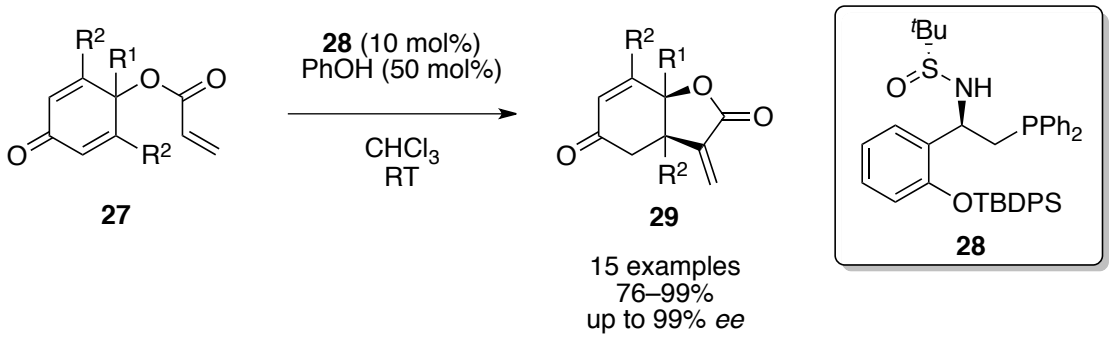
Hodgson also developed a Rh(I)-catalysed asymmetric enyne rearrangement of alkynyl allyl ester **25** to give α-methylene-γ-butyrolactone **26** (Scheme 6).[13] The novel reaction was employed in the first reported total synthesis of (+)-anthecotulide, a butanolide type sesquiterpene lactone.



25 **26**, 73%

Scheme 6: Hodgson's enyne rearrangement approach to α-methylene-γ-butyrolactone **26**.

A recent example of a lactone-forming approach is the Rauhut–Currier reaction (also known as a vinylogous Morita–Baylis–Hillman reaction) developed by Zhang and co-workers.[14] They utilised a novel chiral sulfonamide phosphine **27** to catalyse the intramolecular Rauhut–Currier reaction, affording α-methylene-γ-butyrolactones **29** in excellent *ee* and high yield (Scheme 7).



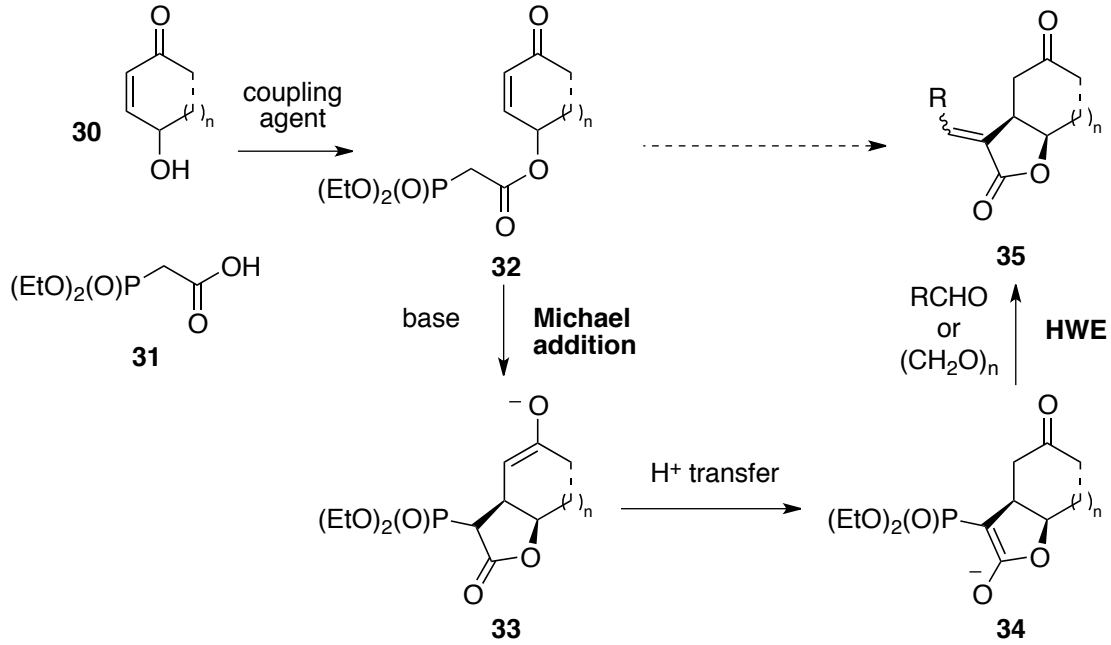
Scheme 7: Asymmetric Rauhut–Currier reaction affording α-methylene-γ-butyrolactones.

Many natural products possess an α-alkylidene-γ-butyrolactone core. In many cases the additional substitution at the exocyclic alkene can be built into the alkylidenation or lactonisation reaction. However, alternative transformations of α-methylene-γ-butyrolactones are also commonplace; for example by olefin cross-metathesis[15] and Heck cross-couplings.[16]

1.1.3. Taylor group methodologies

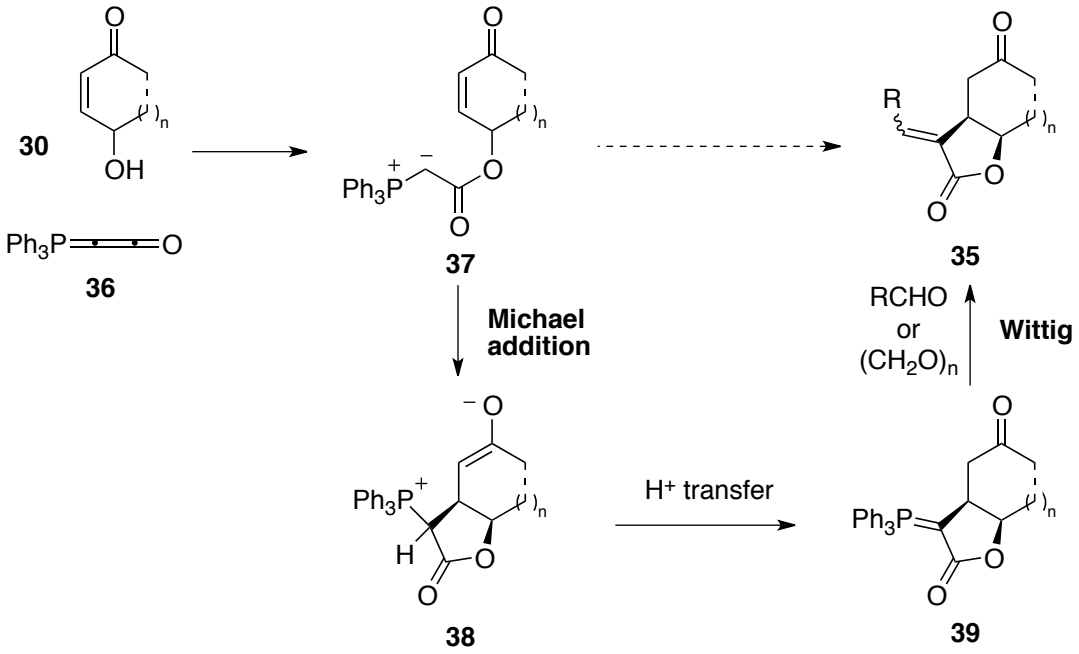
The synthesis of α-methylene-γ-butyrolactones has been the subject of much focus in the Taylor group in the past decade. Each of the routes developed comprises a lactonisation (*via* C–C bond formation) preceding a methylenation, with an emphasis towards developing one-pot tandem processes.[17, 18]

The first reported approach was the telescoped intramolecular Michael/olefination (TIMO) sequence (Scheme 8).[17] It was found that performing the two steps together was more efficient than sequentially with isolation of the intermediates. α-(Diethoxyphosphoryl)acetates **32** — readily prepared from alcohols **30** and diethoxyphosphonoacetic acid (DEPAA) **31** — are treated with base and, in the presence of the Michael acceptor, an intramolecular 1,4-addition occurs to afford bicyclic enolates **33** in a *syn*-selective fashion. Proton transfer and the addition of an aldehyde initiates a Horner–Wadsworth–Emmons (HWE) olefination reaction with paraformaldehyde to afford α-methylene-γ-butyrolactones **35** in an efficient, one-pot process. α-Arylidene-γ-butyrolactones were also synthesised with the use of substituted aldehydes.



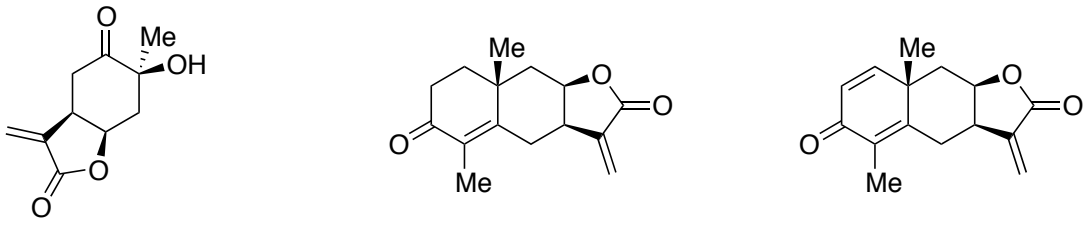
Scheme 8: Taylor's telescoped intramolecular Michael/olefination (TIMO) sequence.

A related approach to TIMO, also a one-pot process, uses acylated phosphoranes **37** that can be readily synthesised from alcohols **30** and Bestmann's ylide **36**.[18a] The advantages of this route over TIMO are that it is one-pot from the alcohol **30** and is base-free although, as expected, the Wittig reaction was found to be slower than the analogous HWE olefination (Scheme 9).



Scheme 9: Taylor's base-free Bestmann's ylide approach to α-methylene-γ-butyrolactones.

The TIMO methodology was successfully applied to the synthesis of three natural products, (+)-paeonilactone B[17a] **40** and (±)-3-oxodiplophyllin **41** (synthesised using both the TIMO and Bestmann's ylide approach), which was then converted into (±)-yomogin **42** (Figure 3).[18b]



(+)-paeonilactone B, **40** (±)-3-oxodiplophyllin, **41** (±)-yomogin, **42**

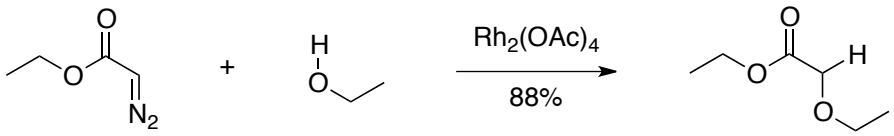
Figure 3: Natural products (+)-paeonilactone B, (±)-3-oxodiplophyllin and (±)-yomogin, successfully synthesised *via* TIMO methodology.

1.2 Rhodium(II)-catalysed C–H insertions

The functionalisation of unactivated sp^3 C–H bonds, normally considered inert, is an ambition for many within the synthetic community. With the development of a variety of achiral and chiral catalysts, the field of rhodium(II)-stabilised carbenoids derived from diazo compounds has blossomed.[19] The ability to perform chemo-, regio- and stereoselective C–H insertions is now possible, representing the backbone of many target-based syntheses.

Early studies within the area of diazo decomposition used copper to perform C–H insertion reactions.[20] However, since the first example of a rhodium(II) catalyst being used for C–H insertions, the use of copper has become less common. Recently there has been a revival in the area of copper catalysed C–H insertions but there are only limited reports with yields or *ee* comparable to those achievable using Rh(II) catalysis.[21] One reason for the relative lack of interest in copper is the high electrophilicity of the copper-carbenoids that tends to reduce chemo- and regioselectivity.[22]

The field of rhodium(II)-catalysed diazo decomposition commenced in the 1970's. Whilst working with $Rh_2(OAc)_4$, Teyssié reported the homogeneous rhodium(II)-catalysed insertion of ethyl diazoacetate **43** into the O–H bond of alcohols and other weak hydroxylic acids (Scheme 10).[23]



43 **44** **45**

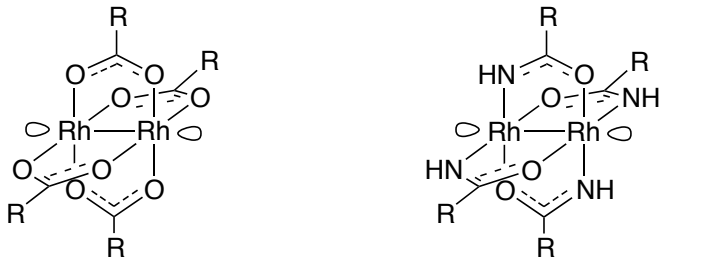
Scheme 10: Teyssié's original O–H insertion using $Rh_2(OAc)_4$.

This initial discovery concerned an O–H insertion, but there has since been a great variety of applications including cyclopropanations, cyclopropenations, aromatic cycloadditions, ylide formations, N–H, and C–H insertions.[24] It is the latter that is the focus of this overview.

1.2.1. Structure of Rh(II) catalysts

$Rh_2(OAc)_4$ along with other rhodium(II) carboxylates and carboxamidates possesses a binuclear core structure with two bridging rhodium atoms that have a formal Rh–Rh single bond between them.[25] The oxidation state of the dirhodium core is +4, giving each rhodium atom a formal +2 oxidation state (d^7 centre). The four acetate ligands in rhodium(II) acetate each bridge the rhodium atoms forming a cage-like structure, often referred to as a paddlewheel or lantern.[25c,26] Rhodium(II)

carboxylates **46** possess four oxygen atoms on each rhodium atom occupying the equatorial sites, giving overall D_{4h} symmetry (Figure 4).[24] In contrast, rhodium(II) carboxamidates **47** typically favour the binding of two nitrogen and two oxygen atoms to each rhodium atom, with the *cis* arrangement (*cis*-[2,2]) dominant, as displayed in Figure 4.[27]



$Rh_2(OC(O)R)_4$, **46** *cis*-[2,2]-$Rh_2(OC(N)R)_4$, **47**

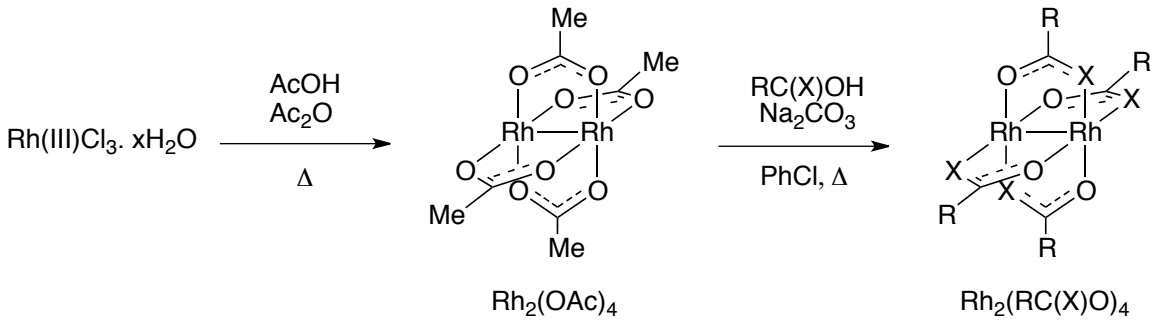
Figure 4: Rhodium(II) carboxylate and *cis*-[2,2]-carboxamidate catalysts, with lobes representing vacant axial sites.

With the adjacent rhodium atom occupying one axial site the other is free for coordination, giving a total of two free coordination sites. These sites may be occupied by weakly-bound donor ligands or solvents, e.g. nitriles, amines, phosphines or sulfoxides.[24,25c] Typically C–H insertion reactions are performed in a non-coordinating aprotic solvent such as DCM, DCE or toluene. Solvents such as THF or pyridine coordinate to, and hence deactivate,[28] the catalyst changing the electronic structure, which is usually discerned by a colour change. For example the characteristic green colour of rhodium(II) carboxylates can change to blue/green and red with oxygen and nitrogen donors, respectively.[29] Sulfur and phosphorus containing ligands can also coordinate, again changing the colour of the catalyst. Doyle's rhodium(II) carboxamidate catalysts typically appear red in the solid-state when coordinated by solvent molecules but blue under vacuum or in poorly coordinating solvents.[27]

The scarcity of rhodium means that it is expensive, with $Rh_2(OAc)_4$ costing approximately £250/g.[30] However, this cost is somewhat compensated for by its high activity with respect to diazo decomposition, considerably more so than copper(I).[31] A variety of chiral and achiral rhodium(II) catalysts are also commercially available. There are many methods currently being used in an effort to make rhodium(II) catalysis cheaper, for example, by immobilisation of the catalyst on solid supports.[32]

1.2.1.1. Preparation of Rh(II) catalysts

$Rh_2(OAc)_4$ is prepared by refluxing $RhCl_3$ in the presence of acetic anhydride in acetic acid. Rhodium(II) carboxylates, carboxamidates and other ligand families are typically prepared by ligand substitution from $Rh_2(OAc)_4$. A Soxhlet extractor is used, with an excess of the corresponding carboxylic acid or amide, refluxing in chlorobenzene, in the presence of base to trap the liberated acetic acid (Scheme 11).[27,33]

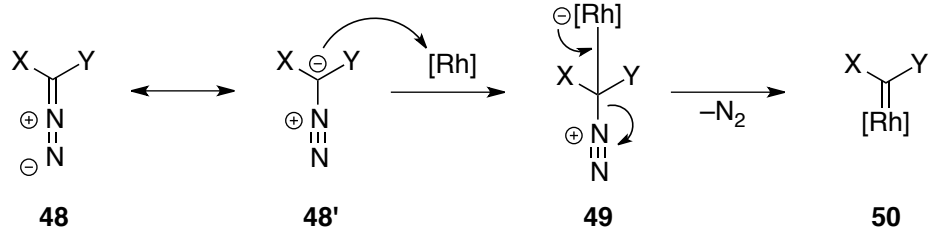


Scheme 11: Synthesis of dirhodium(II) complexes from rhodium(III) chloride.

Rhodium(II) carboxylates are stable to air and thermal degradation, whereas the carboxamidates, which are more readily oxidised, often require axially coordinated nitrile ligands in order to prolong their shelf-life.[24]

1.2.2. Mechanism of C–H insertion

For many years the exact mechanism of the C–H insertion has been the subject of much debate and will form the structure of the following discussion. The first step of the process is widely accepted to be the nucleophilic attack of the diazo compound **48** to the electrophilic rhodium catalyst *via* one of the vacant axial sites, generating ylide **49**.[34] This is then followed by the rate-determining step,[35] the extrusion of nitrogen gas, in which the reactive rhodium-stabilised carbenoid **50** is formed, as shown in Scheme 12.



Scheme 12: Diazo decomposition initiated by coordination to rhodium(II) species, [Rh] = Rh_2L_4.

It is believed that back-donation from the rhodium aids extrusion of the nitrogen gas. A simplified model of the orbital bonding interactions is shown in Figure 5. The rhodium carbenoid is singlet in nature with two paired electrons from the carbene sp^2 orbital contributing to the Rh–C σ-bond. The empty p-orbital on the carbenoid carbon is able to accept electrons *via* back-bonding from the occupied Rh_2 π* orbital.[36]

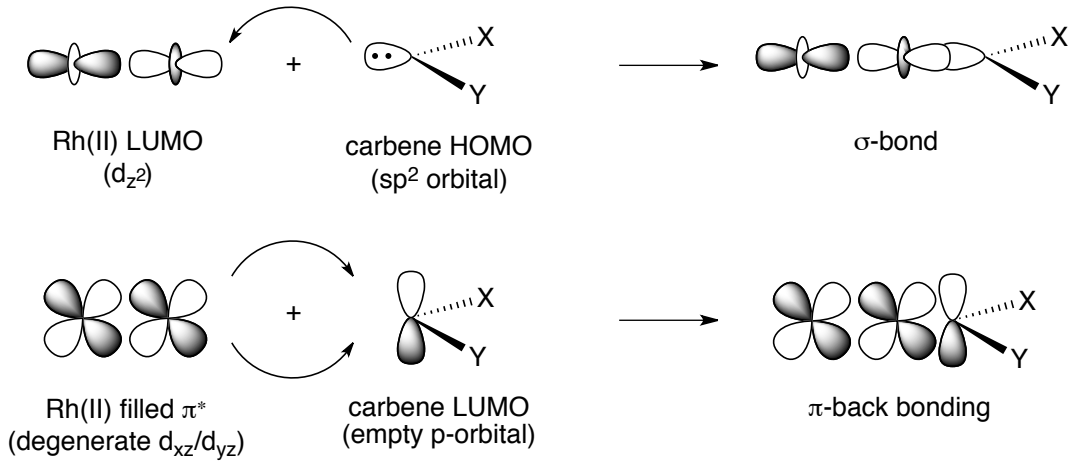
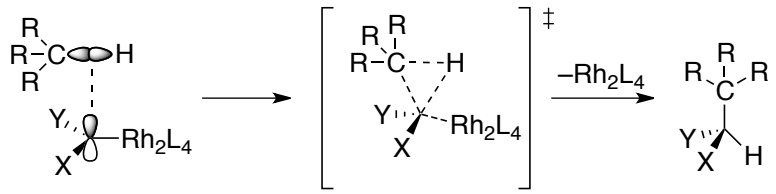


Figure 5: Orbital interactions responsible for bonding in Rh(II) carbenoid.

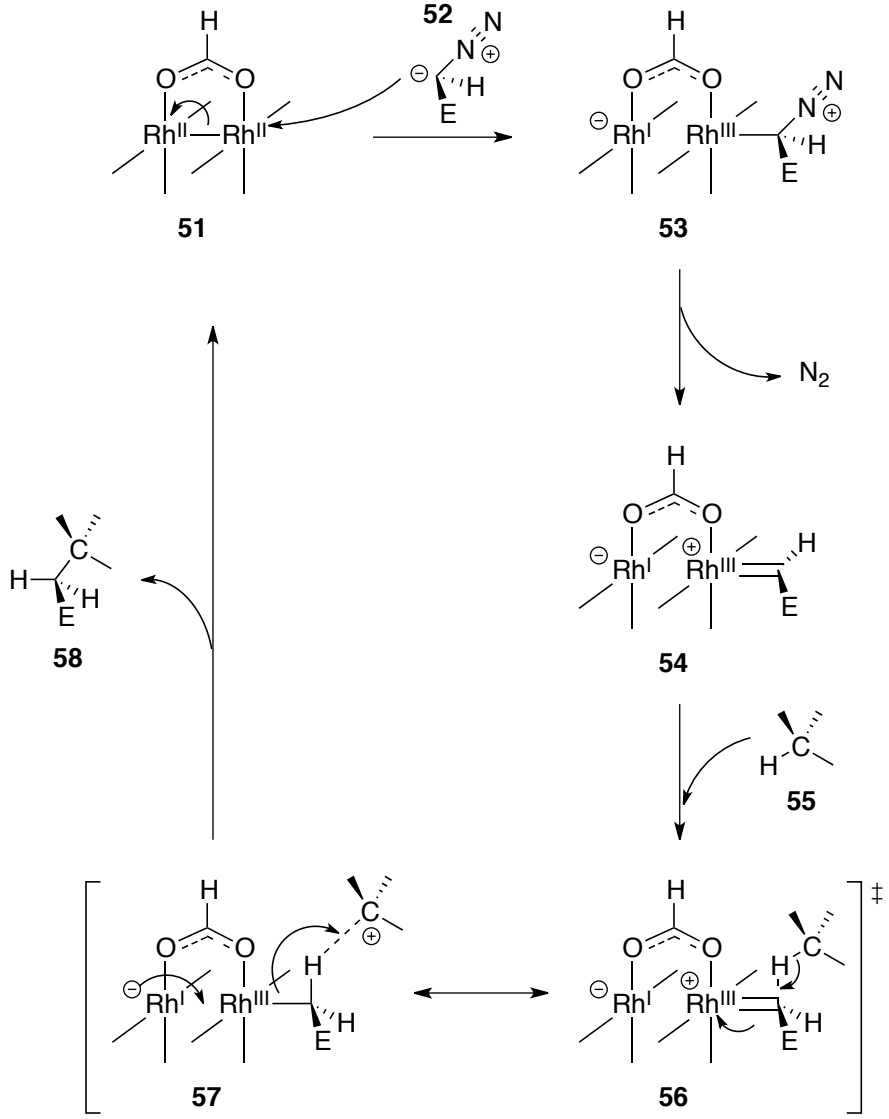
Following the diazo decomposition and formation of the carbenoid the C–H insertion step takes place. Doyle proposed one of the first transition state models for the C–H activation process. He suggested that the vacant p-orbital of the electrophilic carbene carbon atom overlaps with the σ-bond of the reacting C–H bond. This proceeds with simultaneous dissociation of the carbene bound rhodium catalyst in a three-centred concerted transition state, as shown in Scheme 13.[37] It should be noted that Taber *et al*. also suggested an alternative four-centred transition state, not shown.[38]



Scheme 13: Doyle's concerted three-centred transition state for C–H insertion.

It is Doyle's mechanism that is now widely accepted,[39] however, the exact nature of the order of the events leading to product formation have since been investigated in more detail by Nakamura *et al*. with the aid of computational modelling based on the reaction of methyl diazoacetate with alkanes, catalysed by a rhodium(II) carboxylate;[40] the proposed catalytic cycle is shown in Scheme 14.

Firstly, diazo **52** undergoes nucleophilic addition to rhodium(II) carboxylate **51**. This is followed by extrusion of nitrogen gas, aided by back-bonding from rhodium, forming carbenoid **54**. The first event in the C–H insertion (transition state **56**) is the hydride transfer from substrate **55**, which is followed by reformation of the Rh–Rh bond and concomitant C–C bond formation (transition state **57**), delivering product **58** and reforming catalyst **51**.



Scheme 14: Nakamura's model for the C–H insertion based on computational modelling.

Nakamura's findings are summarised below:

- Just one rhodium atom (Rh^1) takes part in the carbene binding process at any one time; the second rhodium atom (Rh^2) acts as a bifunctional electron pool. Firstly, acting as a mobile ligand with cleavage of the Rh^1–Rh^2 bond during the carbene formation process, enhancing the electrophilicity of the carbene and secondly, facilitating cleavage of the Rh^1–C bond during catalyst regeneration.

- During nitrogen extrusion, electron density is moved from the ligands but not Rh^2. Thus, highly electrophilic ligands enhance diazo coordination but decelerate the nitrogen extrusion step. The ligands also act as a tether for Rh^2.
- Overall the C–H insertion is described as a concerted but non-synchronous three-centred transition state with hydride transfer from the substrate preceding C–C bond formation and catalyst regeneration.
- The rhodium atoms do not directly interact with the C–H bond.

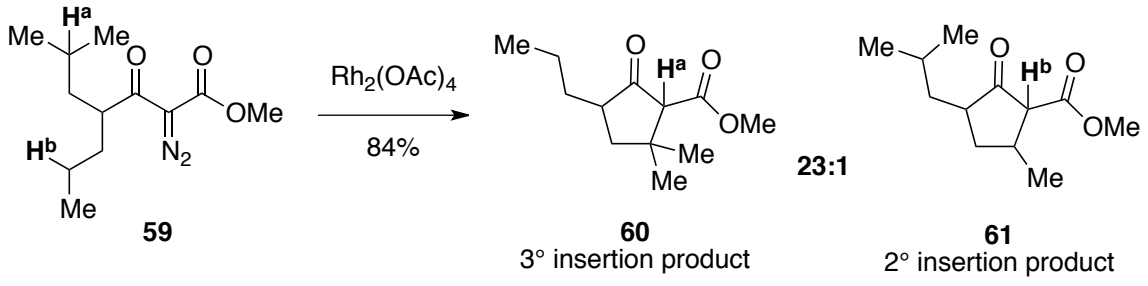
In 2015, a report by Fürstner *et al*. documented the first crystal structure of a reactive dirhodium complex, an important milestone for future mechanistic investigations.[41]

1.2.3. General reactivity trends

There are various factors that contribute towards the outcome of rhodium(II)-catalysed C–H insertion reactions of diazo compounds. The rhodium(II)-stabilised carbene is electrophilic, and through careful choice of the ligands around the dirhodium core as well as the groups adjacent to the carbene centre, this electrophilicity can be modulated. The nature of the substrate also influences the reaction outcome; based on electronic, steric and conformational effects.[22]

1.2.3.1. Stereoelectronic effects

Taber *et al*. conducted early studies into the electronic and steric effects of substrates.[42] By studying a series of β-keto esters it quickly became apparent there was a preference for which C–H bond is inserted into. In the case of substrate **59**, tertiary C–H insertion, forming product **60** predominated over that of the secondary C–H insertion product **61** (Scheme 15).[43]



Scheme 15: Electronic effects of substrate.

From Taber's studies two important general observations were made:

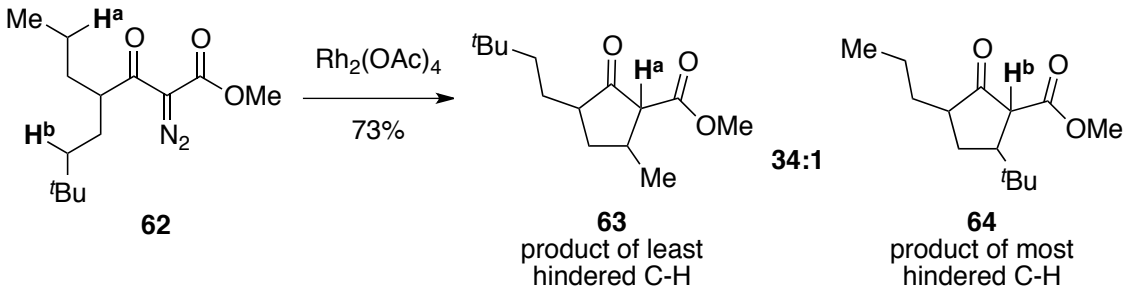
1) An order of reactivity exists for C–H bonds: 3°>2°>1°. This is due to inductive effects, which stabilise the build up of positive charge at the reacting centre.

2) The formation of 5-membered rings is favoured over that of 4- or 6-membered rings, an observation that has been key to the development of this field ever since.

More recently there have been examples in which 4- or 6-membered rings are favoured over 5-membered rings, however the general rule is still widely applicable.[44,45] The formation of 4-membered rings often occurs when there is activation by a donor group such as oxygen or nitrogen which directs the C–H insertion. Conversely, electron-withdrawing groups such as esters and acetyl groups are strongly deactivating.[22] The power of neighbouring group activation has even been demonstrated by the formation of 3-membered rings.[46] Lack of conformational flexibility, or indeed varying bond lengths can lead to 6-membered rings being formed.[47]

It was noted by Adams and Spero in 1991,[48] and later confirmed by Davies,[49] that sites capable of stabilising positive charge, such as allylic, benzylic and α-heteroatom positions (e.g. ethers), are more susceptible to C–H insertions by rhodium carbenoids.

Taber also investigated the steric effects of substrates on reaction outcome.[42b] Using substrate **62** that contains two similar methylene C–H insertion sites, one with a methyl substituent (H^a) and the other with *t*-butyl (H^b), it was found that the insertion occurred almost entirely into the least hindered C–H site (H^a) forming product **63** predominantly over product **64** (Scheme 16).



Scheme 16: Steric effects of substrate in rhodium(II)-catalysed C–H insertions.

1.2.3.2. Catalyst control

The ligands surrounding the dirhodium core also have a significant effect on the reactivity of the catalyst towards diazo decomposition. The more electron-deficient the rhodium catalyst, the more reactive it will be towards the diazo compound.[31]

The use of $Rh_2(OAc)_4$ for diazo decomposition was first observed by Teyssié and was found to be highly active for O–H bond insertions. Since then various studies by Doyle and Padwa have enabled reactivity trends to be established by variation of the bridging dirhodium ligands.[25c,37,50] By careful selection of the catalyst the regio- and stereoselectivity of reactions can be tuned. The general trend of reactivity for ligands is shown in Figure 6.[31]

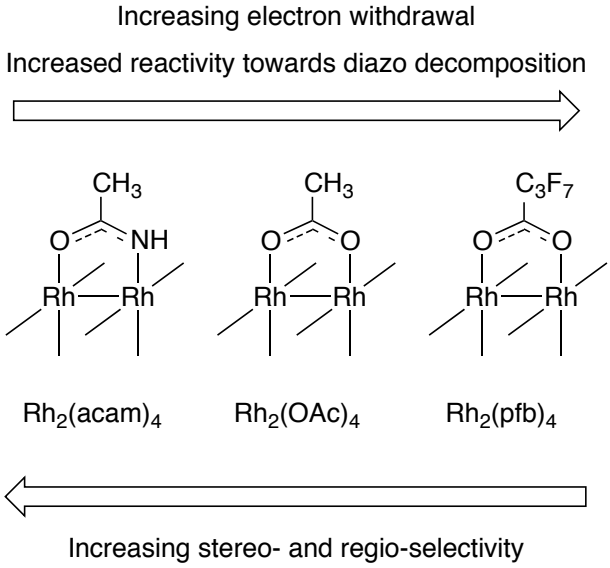
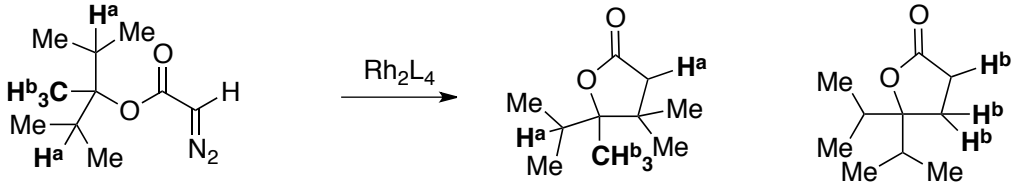


Figure 6: Reactivity profile for rhodium(II) catalysts by variation of bridging ligands.

The more electron-withdrawing perfluorobutyrate ligand (pfb) makes the rhodium catalyst more electrophilic thus more reactive towards diazo decomposition. However, this was also found to confer reduced regio- and stereoselectivity, as demonstrated by Doyle in 1989 (Table 1).[51] Based on the observations by Taber, insertion into a primary C–H site over a tertiary was not expected. Yet, both $Rh_2(pfb)_4$ and $Rh_2(OAc)_4$ led to indiscriminate reaction with both sites of diazo compound **65**, whereas the less reactive rhodium(II) acetamidate ($Rh_2(acam)_4$) was almost completely selective for the tertiary site. The more reactive catalysts led to reduced isolated yields of **66** and **67**, with carbenoid dimerisation the major competing pathway.

Table 1: Rhodium(II) catalyst ligand effects on chemoselectivity.

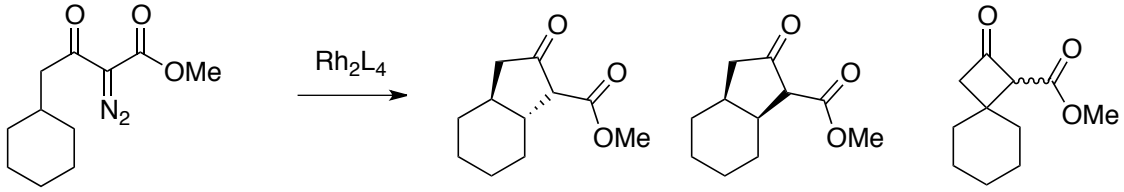


65 | **66** 3° insertion product | **67** 1° insertion product

Rh_2L_4	Isolated Yield, %	Relative ratio (66:67)
$Rh_2(pfb)_4$	56	32:68
$Rh_2(OAc)_4$	81	53:47
$Rh_2(acam)_4$	96	>99:<1

Ikegami *et al*. were able to demonstrate the importance of the ligand's steric bulk. They showed that by using a more sterically hindered catalyst, namely rhodium(II) triphenylacetate ($Rh_2(tpa)_4$), the ratio of products could be dramatically improved compared to that of $Rh_2(OAc)_4$. The exceptional levels of diastereocontrol were best achieved in tethered cyclic systems in which bicyclic products are formed. For example, the C–H insertion of diazo compound **68** generated *trans*-bicyclic lactone **69** with excellent diastereoselectivity using $Rh_2(tpa)_4$, whereas with $Rh_2(OAc)_4$ a mixture of products was observed (Table 2).[52]

Table 2: Exceptional diastereocontrol using a bulky rhodium catalyst, $Rh_2(tpa)_4$.



68 | **69** | **70** | **71**

Rh_2L_4	Relative ratio (69:70:71)
$Rh_2(OAc)_4$	50:19:31
$Rh_2(tpa)_4$	94:1:5

1.2.4. α-Diazocarbonyl compounds

One of the key controlling factors in C–H insertion reactions are the groups adjacent to the carbene centre. Variation of these groups impacts the electrophilicity and hence the reactivity, chemo-, regio- and stereoselectivity of the insertion reactions. Diazo compounds and their corresponding rhodium carbenoids can be classified into three major groups; donor/acceptor, acceptor and acceptor/acceptor.[22]

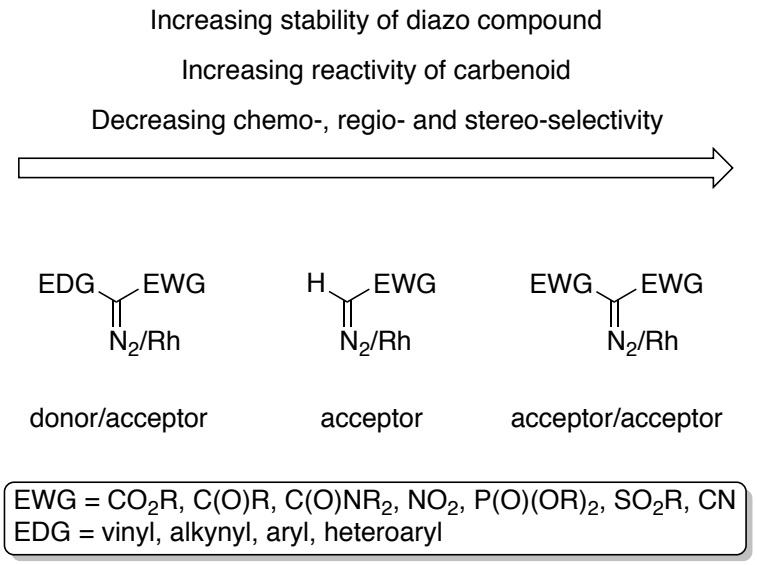


Figure 7: Classes of diazo compound/rhodium(II) carbenoid.

Acceptor groups are those that withdraw electron density through resonance making the diazo compound less nucleophilic, hence less reactive towards diazo decomposition. Conversely, once the carbenoid is formed the acceptor groups increase the reactivity, as electron density is withdrawn from the already electrophilic centre. Donor groups, in contrast increase the reactivity towards diazo decomposition and decrease carbenoid reactivity. Hence, the presence of a donor group attenuates the reactivity of the acceptor group,[49] leading to enhanced chemo-, regio- and stereoselectivity. The use of chiral rhodium(II) catalysts for enantioselective C–H insertions has been reviewed previously,[22,31,45,49,53] and a short insight is provided below with a particular focus towards the intramolecular reactions of acceptor/acceptor carbenoids.

1.2.4.1. Donor/Acceptor Carbenoids

Donor/acceptor-substituted carbenoids have received by far the most attention in recent years due to their unique reactivity.[49] The opposing electronic characteristics allow the reactivity to be modulated, i.e. the donor group reduces the extreme reactivity given by the acceptor group. As such, chemo-, regio- and stereoselectivity can be carefully controlled and has led to the development of a variety of chiral rhodium(II) catalysts for asymmetric C–H insertions, many of which are derived from amino acids (Figure 8).

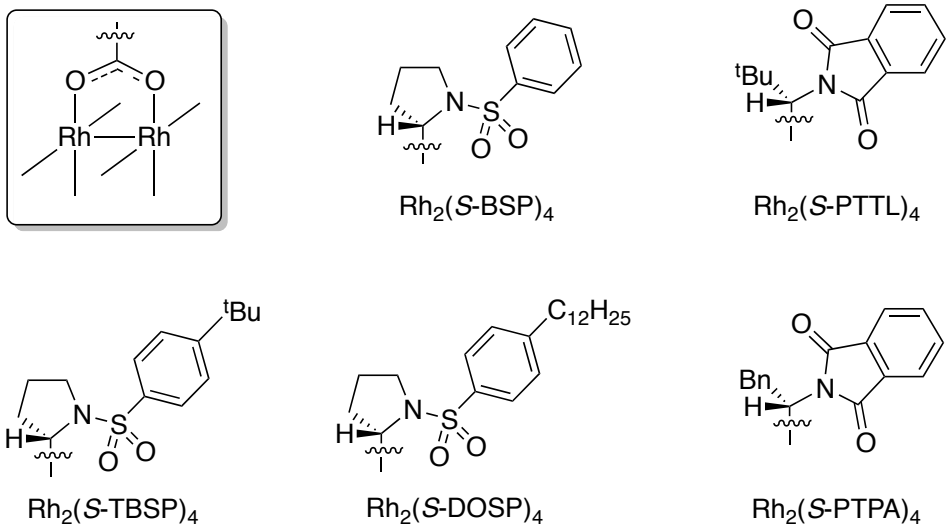
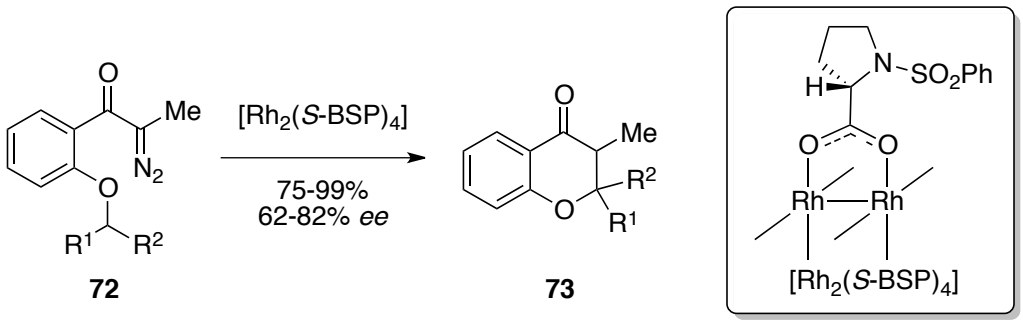


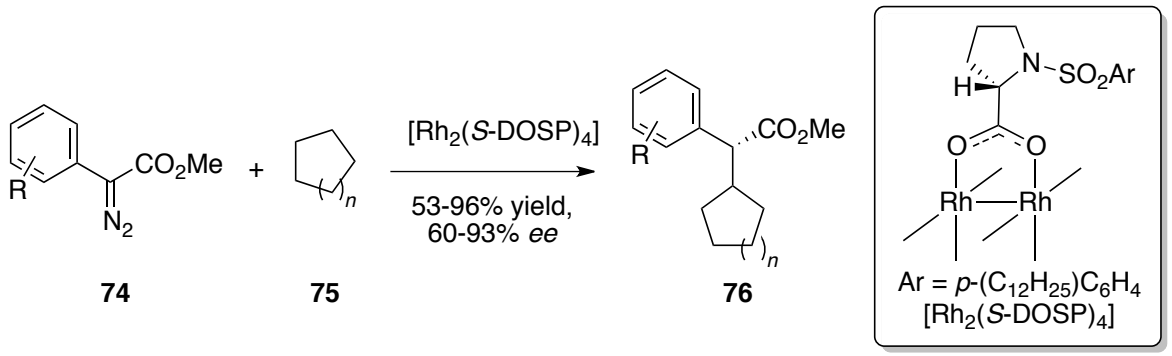
Figure 8: Amino acid-derived rhodium(II) carboxylate catalysts.

McKervey was the first to develop a series of rhodium(II) *N*-benzenesulfonyl protected prolinate catalysts,[54] with $Rh_2(BSP)_4$ found to be the most promising. Good levels of enantiocontrol could be obtained for the intramolecular C–H insertions of α-diazopropriophenones **72** (Scheme 17).



Scheme 17: McKervey's asymmetric intramolecular C–H insertion reactions of α-diazopropriophenones.

More than any other research group, it is the work of Davies *et al*. that has driven the field of the donor/acceptor diazocarbonyls, following the development of various proline-derived catalysts including Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-TBSP)$_4$.[55] These catalysts were found to provide exceptional levels of enantioselectivity for the intermolecular reactions of donor/acceptor diazocarbonyls, particularly using aryl- and vinyldiazocarbonyl compounds. For example, aryldiazoacetates **74** performed well for the C–H insertion of cycloalkanes **75**, yielding products **76** in good yields and *ee* (Scheme 18). Their effectiveness is believed to be due to the C–H insertion process occurring through a late-transition state,[40] hence the enantiopure ligands can efficiently transfer chirality to the products.[22]

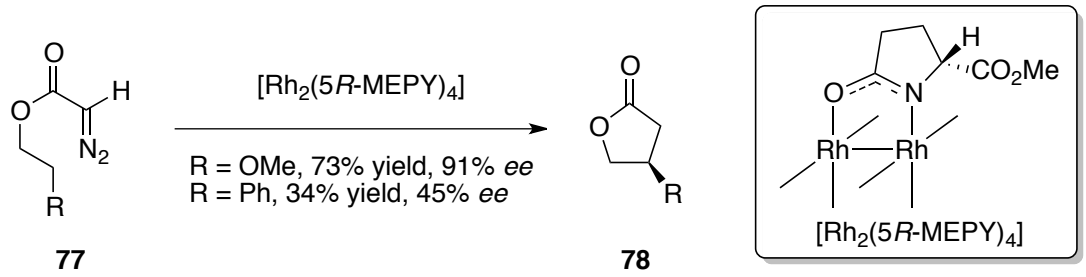


Scheme 18: Davies' asymmetric intermolecular C–H insertion reactions of aryldiazoacetates.

Since these innovative findings, the use of aryl- and vinyldiazocarbonyl compounds has been extended to many other intermolecular C–H insertions reactions including; α-heteroatom sites (e.g. oxygen- and nitrogen-containing heterocycles),[56] allylic sites,[57] benzylic sites[58] and formed the basis for the synthesis many natural product/bioactive targets.[59]

1.2.4.2. Acceptor Carbenoids

The field of acceptor-substituted carbenoids has been dominated by the work of Doyle and co-workers. This species of diazo compound was found to be active towards decomposition by rhodium(II) carboxylate and carboxamidate catalysts, however it is the latter that provided more controlled reactivity and induced higher levels of selectivity.[37,51] Following the success of achiral carboxamidate catalysts, Doyle began studying the use of chiral catalysts, leading to the development of $Rh_2(5R\text{-MEPY})_4$. The intramolecular C–H insertion of diazoacetates **77** leading to lactones **78** was found to be particularly effective with $Rh_2(5R\text{-MEPY})_4$ for insertion adjacent to heteroatoms. However, when tested on benzylic C–H bonds the yields and enantioselectivity decreased (Scheme 19).



Scheme 19: Doyle's asymmetric intramolecular C–H insertion reactions of diazoacetates.

Further systematic studies revealed additional classifications of carboxamidate catalysts that were more amenable to benzylic and non-stabilised C–H insertion reactions (Figure 9).

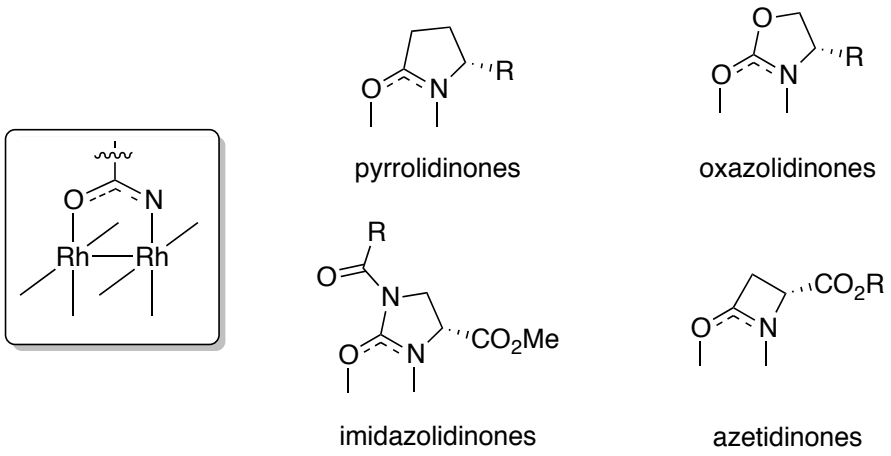
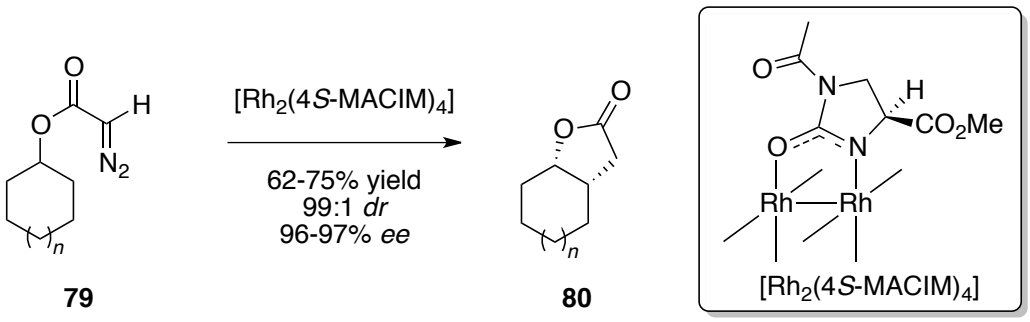


Figure 9: Rhodium(II) carboxamidate catalysts for intramolecular C–H insertions of acceptor-substituted diazo compounds.

For example, the imidazolidinone catalyst $Rh_2(4S\text{-MACIM})_4$ was shown to deliver excellent asymmetric induction for the formation of *cis*-bicyclic lactones **80** from cyclohexanol-derived diazo compounds **79** (Scheme 20).[60]



Scheme 20: Doyle's asymmetric intramolecular C–H insertion reactions of diazoacetates.

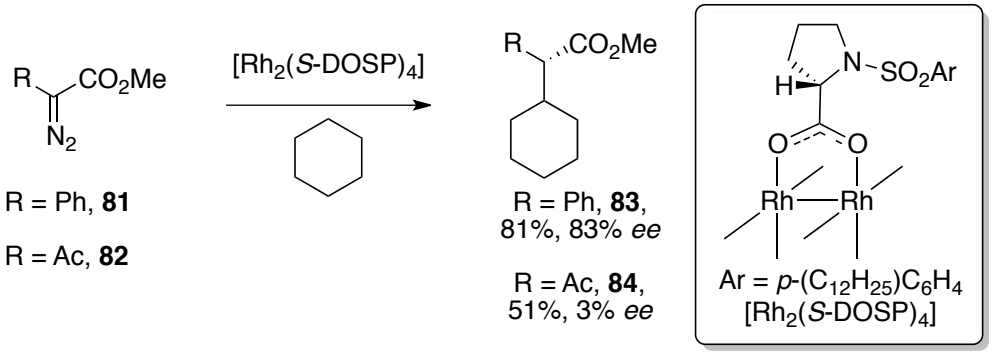
These catalysts remain widely used for asymmetric intramolecular C–H insertions of acceptor-substituted diazocarbonyls. Their use has been extended to the reactions of allylic[61] and aromatic[62] C–H bonds, the formation of lactams[63] as well as natural products.[64]

Unlike donor/acceptor diazocarbonyl compounds, the acceptor diazocarbonyls have been shown to be less effective for asymmetric intermolecular C–H insertion reactions. The higher reactivity of the intermediate carbenoid often leads to indiscriminate reactions leading to multiple products including carbenoid dimerisation.[22,65] For these more reactive species the benefits of intramolecular reactions, i.e. entropic factors leading to the formation of 5-membered rings, seems to be essential for good enantioselectivity to be obtained.[66]

1.2.4.3. Acceptor/Acceptor Carbenoids

The third class of diazo compound contains two acceptor groups. These species are the most stable to diazo decomposition due to the stabilising effect of the acceptor groups. As such, more active catalysts, i.e. rhodium(II) carboxylates, are required to form the reactive carbenoid.[33,67] Once formed, this class of carbenoid is by far the most reactive with the acceptor groups now destabilising the electrophilic carbenoid. This extreme reactivity often leads to less controlled reactions with reduced chemo-, regio- and stereoselectivity, perhaps accounting for the relatively underexplored asymmetric reactions of these species. Common side-reactions of acceptor/acceptor carbenoids are carbene dimerisation and extraneous water O–H insertion. This can be reduced by slow addition of the diazo species to a dilute rhodium(II) solution and with vigorous drying, respectively.[64]

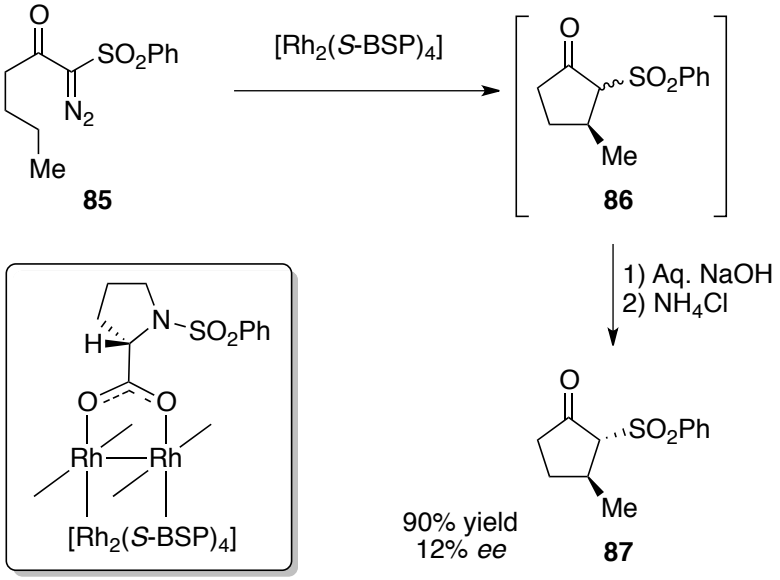
The intermolecular reactions of acceptor/acceptor diazo carbenoids are in many ways analogous to those of acceptor diazocarbenoids; the absence of intramolecular driving forces leads to unselective reactions and lack of stereocontrol. This was demonstrated by Davies when comparing the reaction of donor/acceptor-diazo compound **81** with acceptor/acceptor-diazo compound **82**. Using the Rh_2(*S*-DOSP)$_4$ catalyst for the reaction with cyclohexane generated C–H insertion products **83** and **84** in 81% yield, 83% *ee* and 51% yield, 3% *ee*, respectively (Scheme 21).[55]



Scheme 21: Davies' asymmetric intermolecular C–H insertion reactions of aryldiazoacetates and diazoacetoacetates.

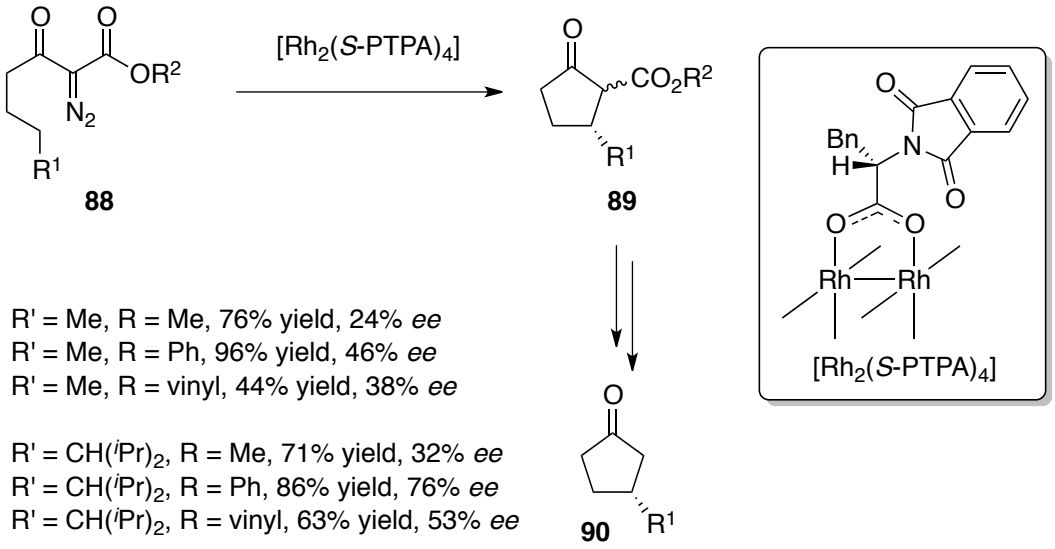
As with acceptor-substituted carbenoids, the acceptor/acceptor compounds have also found their niche in the field of intramolecular C–H insertions. There are many examples of racemic C–H insertions catalysed by rhodium(II) carboxylates for the formation of cyclopentanones,[52] γ-lactams and γ-lactones.[37,68] In line with the general trend observed by Taber there is overwhelming preference for the formation of 5-membered rings.

The first example of an asymmetric intramolecular C–H insertion of an acceptor/acceptor diazocarbonyl was reported by McKervey in 1990.[69] Treatment of α-diazo-β-ketosulfone **85** with Rh_2(*S*-BSP)$_4$, previously developed within the group, delivered cyclopentanone **86** as a mixture of diastereomers. In order to determine *ee* more easily the acidic centre was epimerised, generating cyclopentanone **87** in good yield but with just 12% *ee* (Scheme 22).



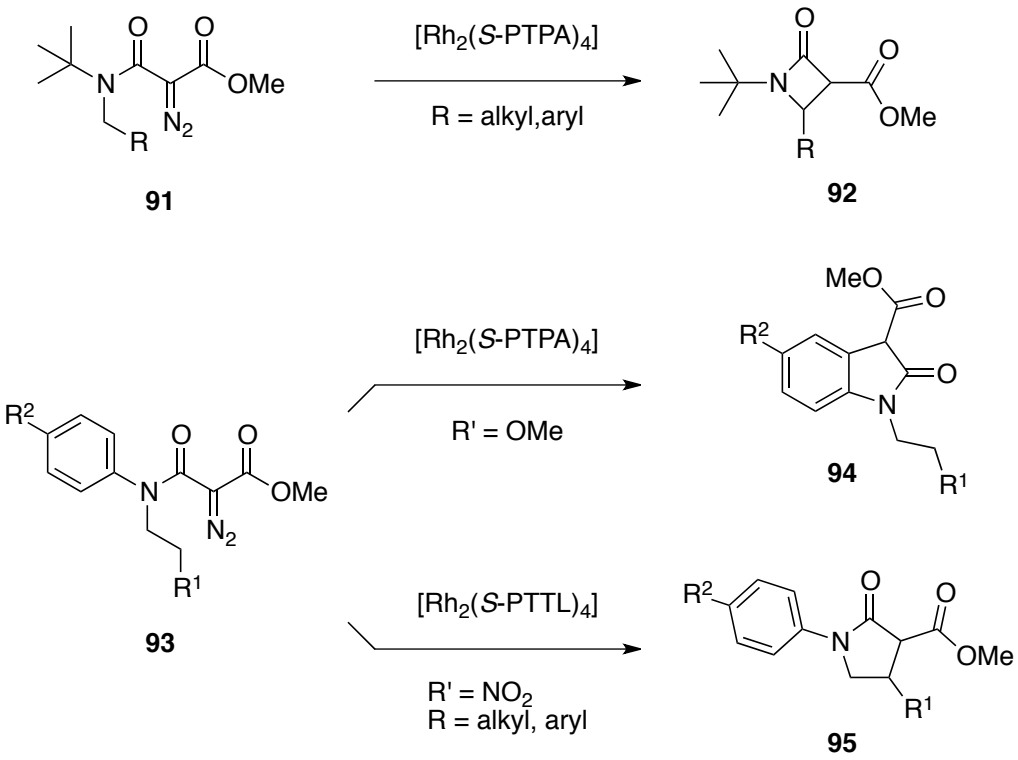
Scheme 22: McKervey's pioneering studies into asymmetric intramolecular C–H insertion reactions of acceptor/acceptor diazo compounds.

α-Diazo-β-ketoesters have been much more extensively studied, with Ikegami and co-workers providing some of the first insights.[70] Their studies focussed instead on an *N*-phthaloyl protected amino acid carboxylate catalyst, Rh_2(*S*-PTPA)$_4$ for the C–H insertions of diazo compounds **88** to cyclopentanones **89**, as shown in Scheme 23. Low *ee* was initially observed for methyl esters yet, by switching to a more bulky ester group, the *ee* was found to increase substantially. Other notable observations include the low temperature (0 °C) at which these reactions were performed as well as enhanced yields for insertion into benzylic sites compared to alkyl or allylic C–H bonds. The *ee* were determined following hydrolysis and decarboxylation to cyclopentanones **90**.



Scheme 23: Ikegami's asymmetric intramolecular C–H insertion reactions of α-diazo-β-ketoesters.[53a]

The asymmetric intramolecular C–H insertion of α-diazoacetoacetamides has also been extensively studied. The nitrogen atom provides a suitable handle for protecting group manipulation, which has enabled divergent reaction pathways to be selectively accessed. For example, substitution of the nitrogen atom with ^{t}Bu, as in amide **91**, allows for the selective formation of β-lactams **92**, even when γ-lactams are possible, in excellent yields and good *ee*, as shown in Scheme 24.[71] In contrast, when *N*-phenyl substituents are employed, as in amide **93**, divergent pathways can be accessed dependent upon the chiral catalyst used and substrate functional groups; Rh_2(*S*-PTPA)$_4$ generated indolin-2-ones **94** whereas Rh_2(*S*-PTTL)$_4$ furnished γ-lactams **95** in good yield and *ee*.[72]



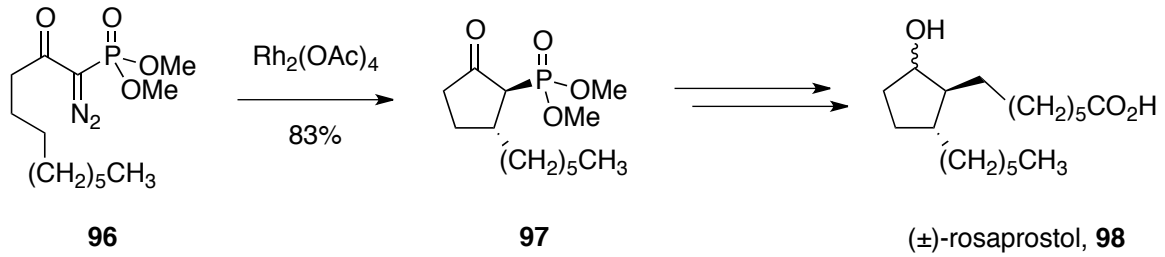
Scheme 24: Hashimoto's divergent intramolecular C–H insertion reactions of α-diazoacetoacetamides affording β-, γ-lactams and indolin-2-ones.[53a]

To the best of our knowledge, after a thorough examination of the literature, there are no reported examples of asymmetric induction for the intramolecular C–H insertion reactions of α-diazocarbonylacetates that afford γ-lactone products.

1.2.4.4. α-Diazophosphonocarbonyls

Prior to this work, the rhodium(II)-catalysed intramolecular C–H insertion reactions of α-diazophosphonocarbonyls was a relatively underexplored area. Of those examples published in the literature, there are 3 main groupings; α-diazophosphonoketones, α-diazophosphonoacetamides and α-diazophosphonoacetates.

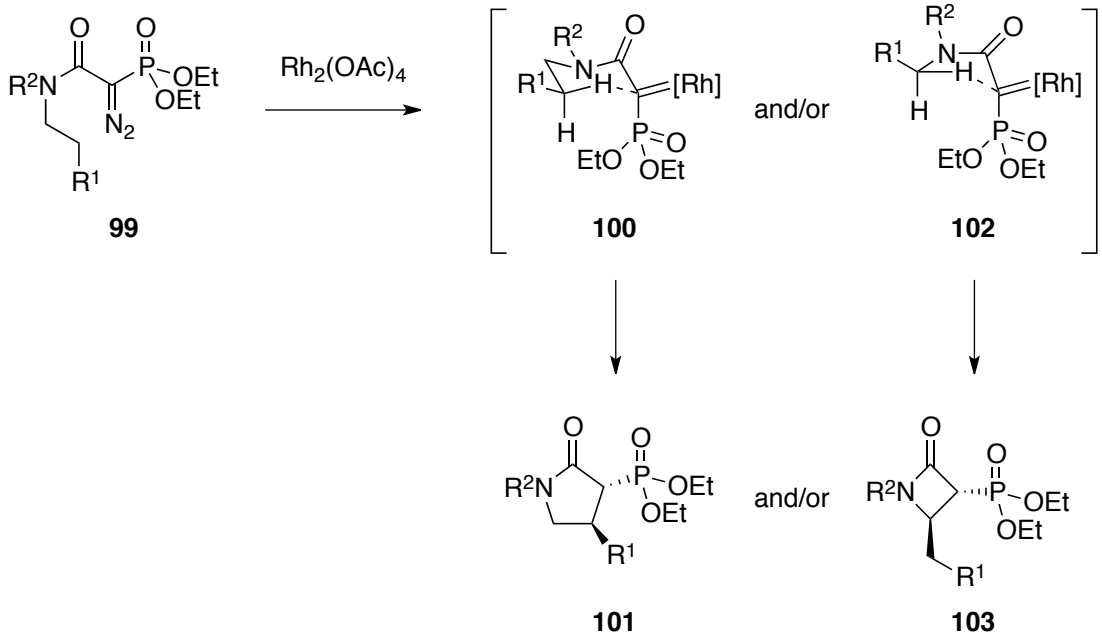
The earliest example of this class of C–H insertion was reported by Sturtz in 1987 for the synthesis of cyclopentanones from α-diazophosphonoketones, with Wolff rearrangements the major side-reaction.[73] Mikołajczyk again reported the use of α-diazophosphonoketones in 1989 as part of the total synthesis of (±)-sarkomycin,[74] as well as in 1998 for the total synthesis of (±)-rosaprostol (Scheme 25).[75]



96 **97** (±)-rosaprostol, **98**

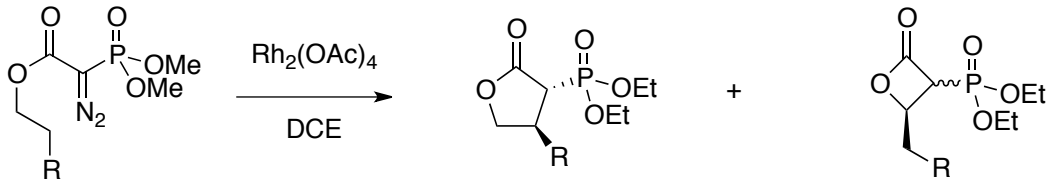
Scheme 25: Mikołajczy's intramolecular C–H insertion reaction of an α-diazophosphonoketone towards the synthesis of (±)-rosaprostol.

The use of α-diazophosphonoacetamides for the synthesis of lactams has primarily been investigated by Afonso and co-workers. Their first report came in 2003 in which β- and γ-lactams could be selectively formed by variation of substituents to exploit electronic effects and steric effects.[76] They reasoned that the phosphonate group was sufficiently bulky as to favour the formation of 5-membered rings with a *trans*-configuration (Scheme 26). This work was extended by use of chiral rhodium(II) carboxylates, including Rh_2(*S*-DOSP)$_4$, Rh_2(*S*-TBSP)$_4$ and Rh_2(*S*-PTPA)$_4$, generating the products in good yields, but with poor *ee*.[77] The group performed additional studies[78] culminating in the use of water as an alternative to chlorinated solvents.[79] Remarkably, the product of water O–H insertion was only observed in the absence of $Rh_2(OAc)_4$. A series of novel unprotected amino acid-derived rhodium(II) catalysts was also developed, displaying improved *ee* with water as the solvent.[80]



Scheme 26: Afonso's model for *trans*-selectivity in β- and γ- lactam products of the intramolecular C–H insertion reactions of α-diazophosphonoacetamides.

The only reported example of an intramolecular C–H insertion of α-diazophosphonoacetates **104** also came from Afonso and co-workers.[76] They observed a mixture of β- and γ-lactone products **105**–**110** in moderate yields (Scheme 27).



104

105, R = H, 0%
106, R = Me, 32%
107, R = Me, Me, 24%

trans-**108**, R = H, 30%
trans:cis-**109** (1.4:1) R = Me, 28%
cis-**110**, R = Me, Me, 30%

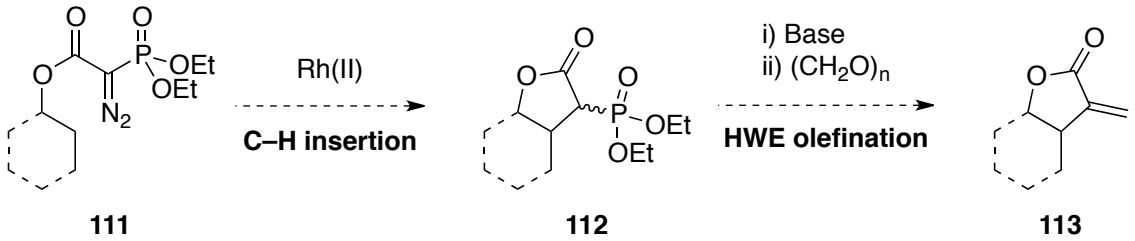
Scheme 27: Afonso's intramolecular C–H insertion reactions of α-diazo (diethoxyphosphoryl)acetates.

There are various other reports utilising α-diazophosphonoacetates, however they focus on intramolecular cyclopropanations[81] and O–H insertions.[82]

1.3 Project Background and Aims

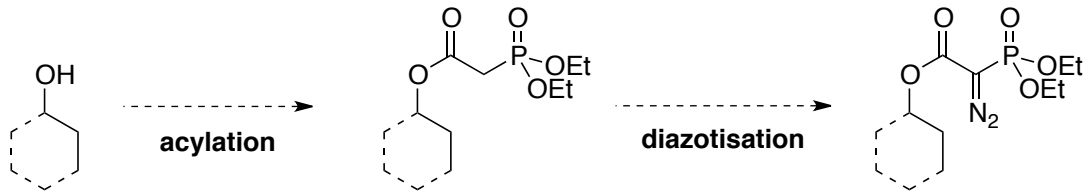
A variety of synthetic approaches towards α-methylene-γ-butyrolactones have been described, including both lactonisation and methylenation based routes. Two approaches previously developed within the Taylor group, as discussed earlier, detailed a telescoped Michael addition/olefination sequence. Excellent selectivity and yields could be obtained, yet synthesis of the γ-hydroxy unsaturated carbonyl compound starting materials was not trivial.

Whilst all of these routes have their merits, it was hoped that a more facile route to the α-methylene-γ-butyrolactone framework could be developed. It was envisaged that by use of a C–H insertion reaction, the lactone ring may be formed by reaction with a C–H bond normally considered completely unreactive; hence, the α-methylene-γ-butyrolactone target molecules could be rapidly generated from relatively simple starting materials. As such, it was contemplated that the lactone ring may be formed *via* an intramolecular rhodium(II)-catalysed C–H insertion of α-diazophosphonoacetates **111**. As has been observed for many existing literature examples, the formation of 5-membered rings was expected to predominate for the intramolecular process, with γ-lactone **112** the desired product. Taking advantage of related Taylor group precedent, a subsequent Horner–Wadsworth–Emmons olefination should deliver the α-methylene-γ-butyrolactone framework **113** (Scheme 28).



Scheme 28: Proposed intramolecular Rh(II)-catalysed C–H insertion and HWE olefination of α-diazophosphonoacetates towards α-methylene-γ-butyrolactones.

In line with previous Taylor group methodologies it was hoped that following individual optimisation, these two steps could be combined as part of a more efficient telescoped procedure, avoiding the need for isolation and purification of the α-phosphonolactone intermediate. To the best of our knowledge, such a tandem sequence is without precedent. The requisite α-diazophosphonoacetate functional group ought to be readily accessible in just 2 steps by an acylation and diazotisation from alcohols **114** (Scheme 29), thus increasing the generality of the procedure.



114 **115** **111**

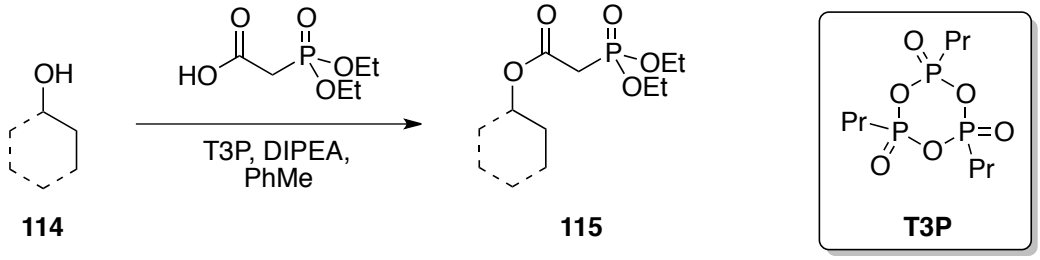
Scheme 29: Proposed 2-step synthesis of α-diazophosphonoacetates from alcohols.

Following the establishment of a reliable procedure, it was planned to demonstrate the efficacy of the procedure through the synthesis of natural products and other biologically active compounds.

Chapter 2 – Rhodium(II)-catalysed C–H insertion/olefination methodology

2.1 Preparation of diazo precursors

The studies began with the preparation of the α-diazo(diethoxyphosphoryl)acetates from alcohols using a two-step esterification and Regitz diazo transfer sequence. The coupling of alcohols with acids is a well-established process with an extensive list of conditions including, amongst others, Mitsunobu coupling (DEAD, PPh_3), Steglich (DCC, DMAP) and Fischer (acid catalysis) reactions. The Taylor group has previously taken advantage of a less well-known cyclic coupling agent known as propylphosphonic anhydride (T3P), and it was decided to exploit this method in this work (Scheme 30).[83]



114 **115**

Scheme 30: T3P-mediated esterification.

T3P has many advantages over other commonly used coupling agents including, being non-toxic, non-sensitising and easy to handle. In addition the by-product of the reaction, a water-soluble phosphate, can be readily removed by a simple aqueous workup, meaning column chromatography is usually not required. Thus, the reaction of a series of alcohols with the commercially-available diethylphosphonoacetic acid (DEPAA) **31** using T3P and DIPEA generated α-(diethoxyphosphoryl)acetates **116a**–**161a** in >95% yield in most cases. Substrates with greater steric hindrance, such as tertiary alcohols (cf. phosphonate **128a**), were met with greater difficulty. The mechanism of the process is shown in Scheme 31, and the range of products formed in Figure 10.

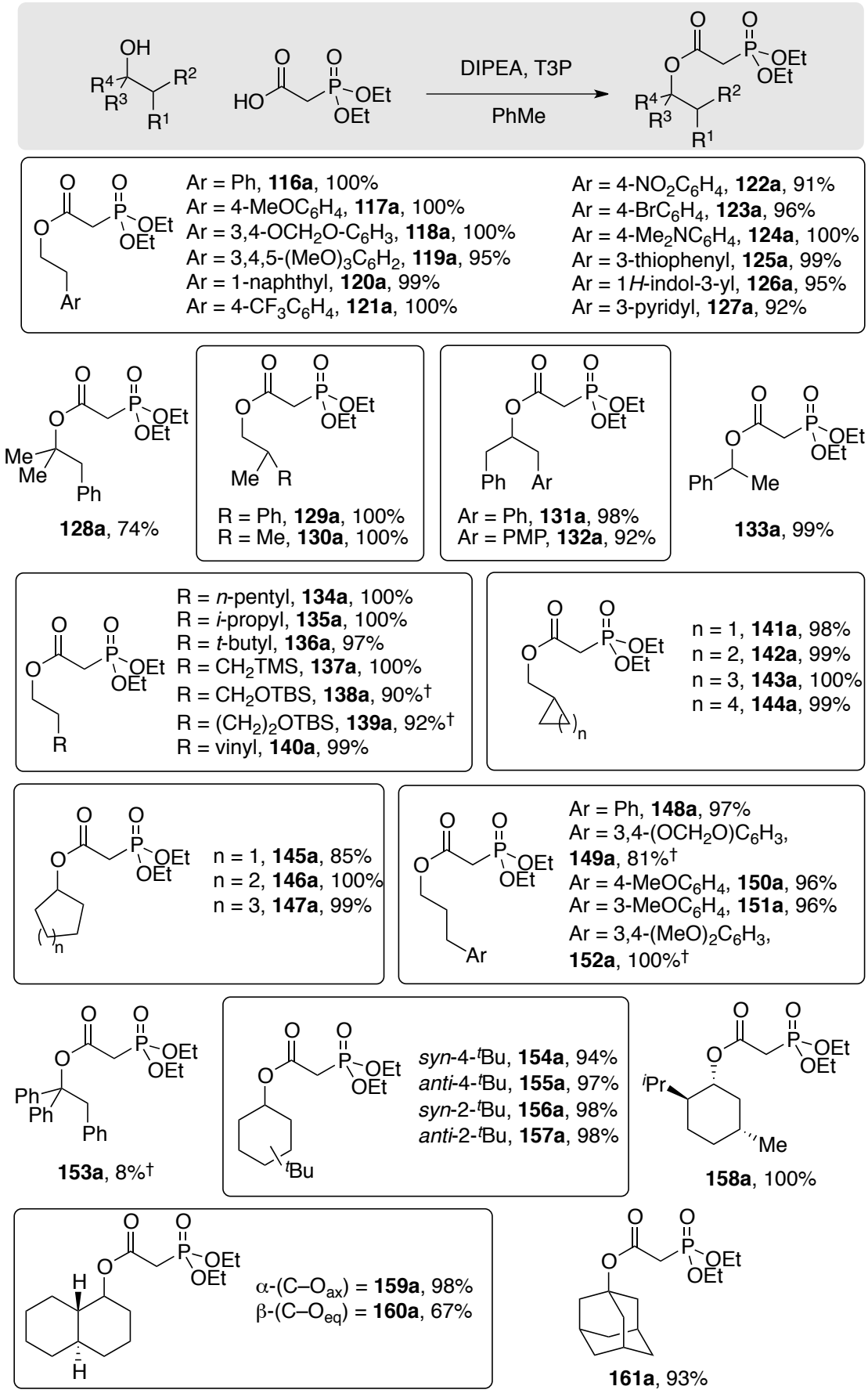
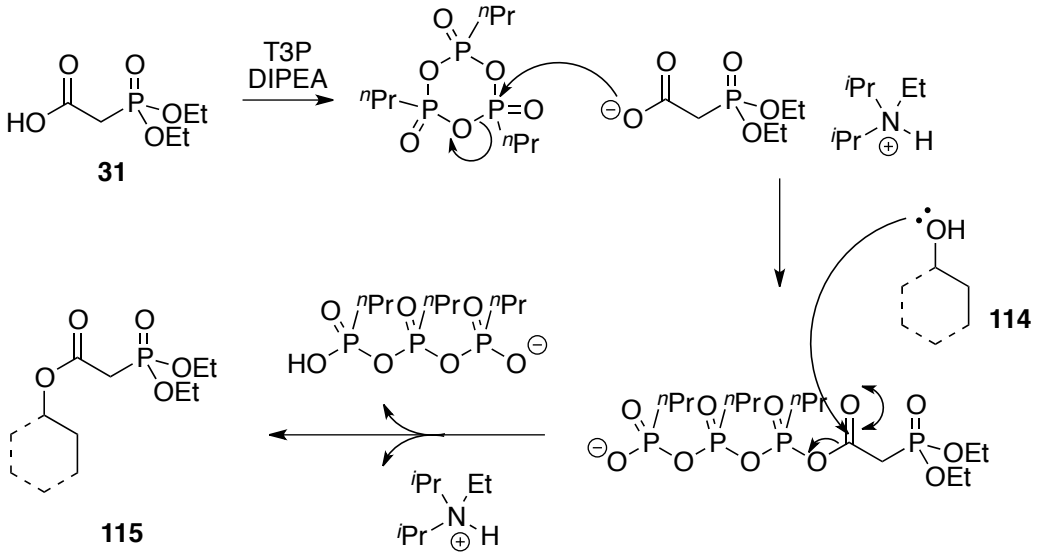


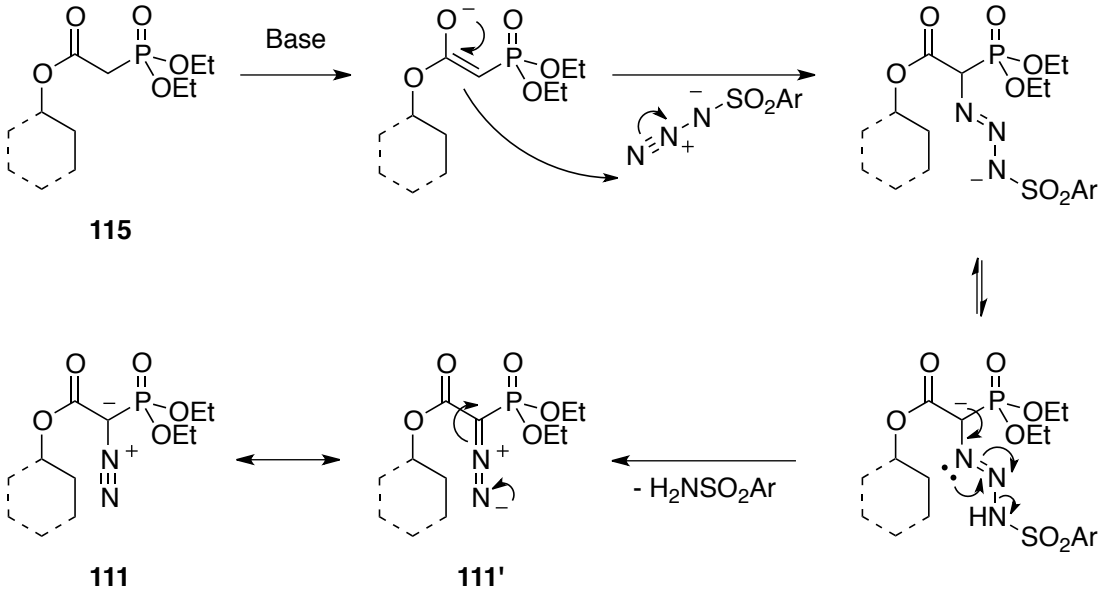
Figure 10: Range of products synthesised *via* T3P-mediated esterification.

† Yield given as part of a multistep process.



Scheme 31: Mechanism of T3P-mediated coupling of DEPAA **31** and alcohol **114**.

There are many possible routes to form diazo carbonyl compounds, including dehydrogenation of hydrazones and diazotisation of amines.[84] However, the most popular choice, particularly for doubly activated methylene compounds such as α-(diethoxyphosphoryl)acetates **115**, is using the Regitz diazo transfer using azides.[33,85] The mechanism of the process is shown in Scheme 32.[86]



Scheme 32: Mechanism of the base-mediated diazo transfer from arylsulfonyl azide.

The most commonly employed azides for the diazo transfer are electron deficient sulfonyl azides, many of which are commercially-available (Figure 11).

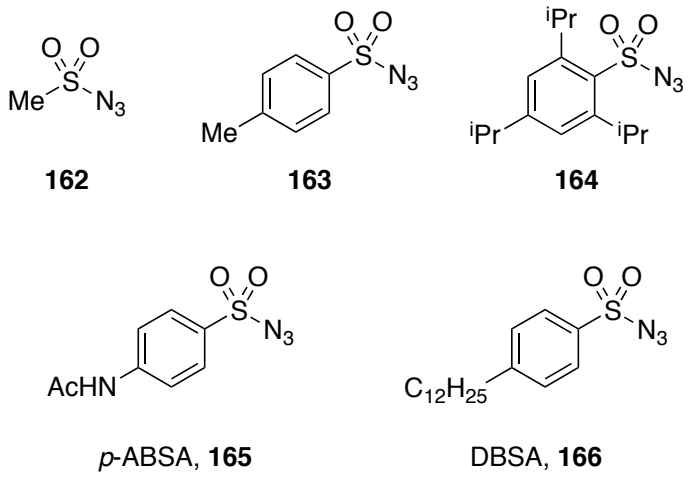


Figure 11: Sulfonyl azides available form commercial sources.*

Historically, tosyl azide **163** was the most popular option for Regitz diazo transfer reactions, however more recently alternatives have been shown to possess lower thermal and shock sensitivity making them more attractive from a safety viewpoint.[87] In addition to a lower propensity towards explosion, these newer derivatives also produce sulfonamide side-products that can be more readily separated form the desired diazo compound, particularly if the diazo compound is crystalline. Both mesyl and tosyl azide **162** and **163** have high shock sensitivities whereas azide **164** is more stable but relatively expensive. *p*-Acetamidobenzenesulfonyl azide (*p*-ABSA) **165** shows no shock sensitivity, is low cost and offers greater ease of removal, often by trituration.[88] *p*-Dodecylsufonyl azide (DBSA) **166** has also been shown to possess favourable properties; the liquid sulfonamide product offers ease of removal as well as providing a non-polar handle for column chromatography separation. This is particularly useful for very polar diazo compounds in which co-elution with the sulfonamide side-product becomes a problem. *p*-ABSA **165** was selected as the azide for the diazotisation of the α-(diethoxyphosphoryl)acetates, except in cases where undesired co-elution occured, in which DBSA **166** was employed.

Following the T3P-mediated esterification, the α-(diethoxyphosphoryl)acetates **116a**–**161a** were treated under basic conditions in the presence of an azide **165** or **166**, undergoing a diazo transfer reaction affording α-diazo(diethoxyphosphoryl)acetates **116b**–**161b**. The range of products formed using this method are shown in Figure 12.

* Each of the azides shown are available from commercial sources, e.g. Sigma Aldrich, with the exception of mesyl azide **162** which is not available due to safety reasons.

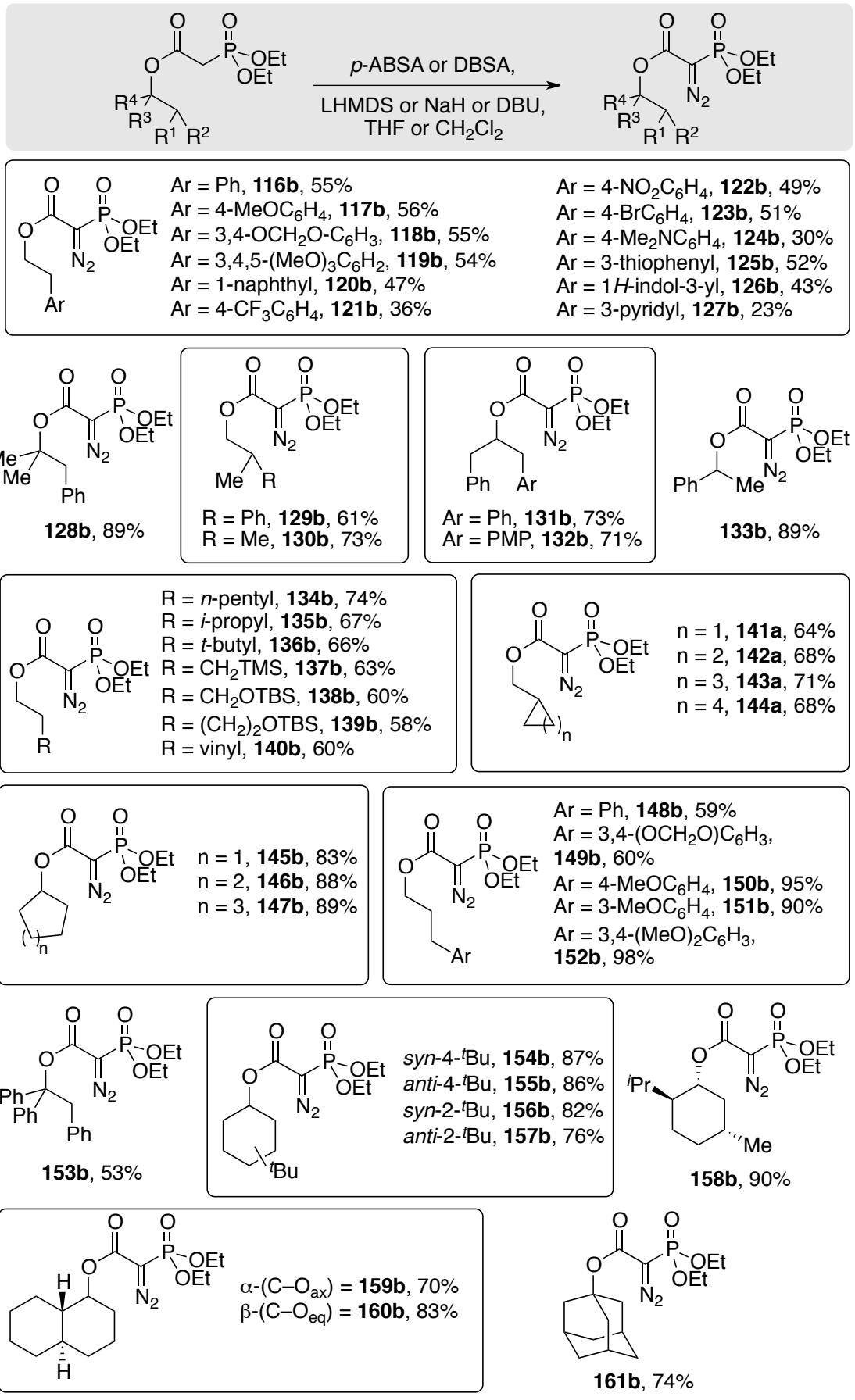
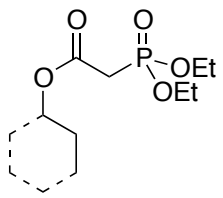


Figure 12: Range of products synthesised *via* Regitz diazo transfer reaction.

α-Diazo(diethoxyphosphoryl)acetates are typically obtained as transparent yellow oils and are stable for a period of several months when stored at room temperature under an atmosphere of air. Diazo compounds **111** are UV active and less polar than their parent phosphonates **115**, which are not UV active in the absence of other chromophores; as such, they are readily identifiable by TLC analysis. Purification by column chromatography is facile except when there is co-elution with by-products of the sulfonyl azide diazotisation reagent. No issues associated with instability or decomposition of the azide reagents or diazo products were observed, with no special handling precautions required. The typical spectroscopic data for α-(diethoxyphosphoryl)acetates **115** and α-diazo(diethoxyphosphoryl)acetates **111** are shown in Figure 13.



115

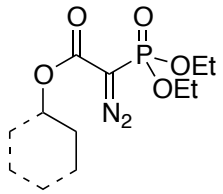
Key characterisation data for α-(diethoxyphosphoryl)acetates 115

^{1}H NMR: δ(PCH_2) ≈ 3.00 (d, $^{2}J_{HP}$ ≈ 21.6) ppm

^{13}C NMR: δ(PCH$_2$) ≈ 34.2 (d, $^{1}J_{CP}$ ≈ 134) ppm
δ(C=O) ≈ 165.0 (d, $^{2}J_{CP}$ ≈ 6.0) ppm

^{31}P NMR: δ ≈ 20.0 ppm

ν(C=O) ≈ 1700–1740 cm^{-1}



111

Key characterisation data for α-diazo(diethoxyphosphoryl)acetates 111

^{13}C NMR: δ(PCN) ≈ 53.5 (d, $^{1}J_{CP}$ ≈ 228) ppm
δ(C=O) ≈ 163.0 (d, $^{2}J_{CP}$ ≈ 12.0) ppm

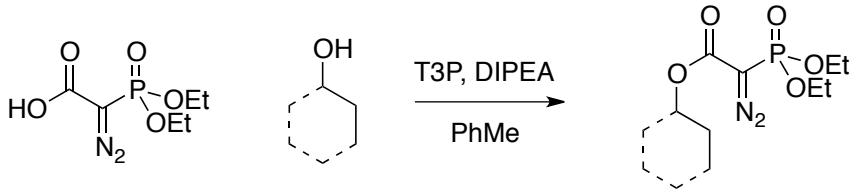
^{31}P NMR: δ ≈ 11.0 ppm

ν(C=O) ≈ 1670–1710 cm^{-1}
ν(N_2) ≈ 2100–2130 cm^{-1}

Figure 13: Typical spectroscopic data for α-(diethoxyphosphoryl)acetates **115** and α-diazo(diethoxyphosphoryl)acetates **111**.

2.1.1. Studies towards an alternative homologated coupling agent

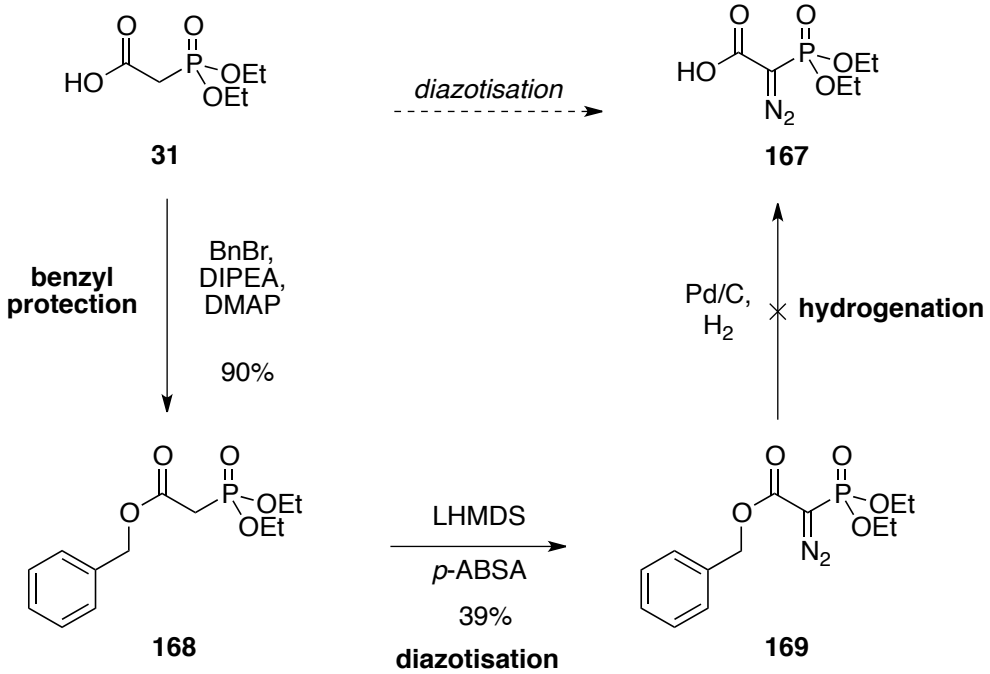
The above route towards α-diazo(diethoxyphosphoryl)acetates **111** involves an esterification followed by a diazotisation. It was considered whether this could be reduced to a single step, improving overall efficiency, if pre-diazotised acid **167** could be prepared and used in the coupling reaction (Scheme 33).



167 **114** **111**

Scheme 33: Proposed one-step synthesis of α-diazo(diethoxyphosphoryl)acetates.

The synthesis of acid **167** was envisaged *via* a protection/diazotisation/deprotection sequence (Scheme 34).



Scheme 34: Proposed preparation of homologated acid **167**.

Firstly benzyl protection of DEPAA **31** furnished ester **168** in excellent yield but the subsequent diazotisation to generate diazoester **169** was low yielding. Unfortunately, the diazotised acid **167** was not generated upon hydrogenation of diazoester **169**. A series of side-products resulting from decarboxylation and/or loss of nitrogen were the only observed compounds (Figure 14).

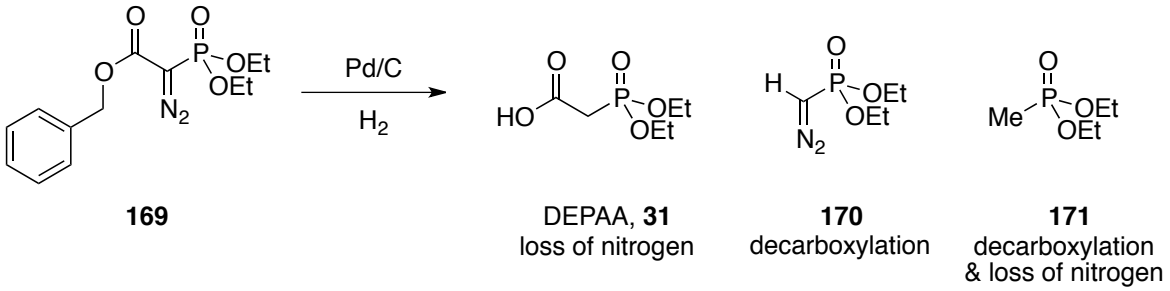
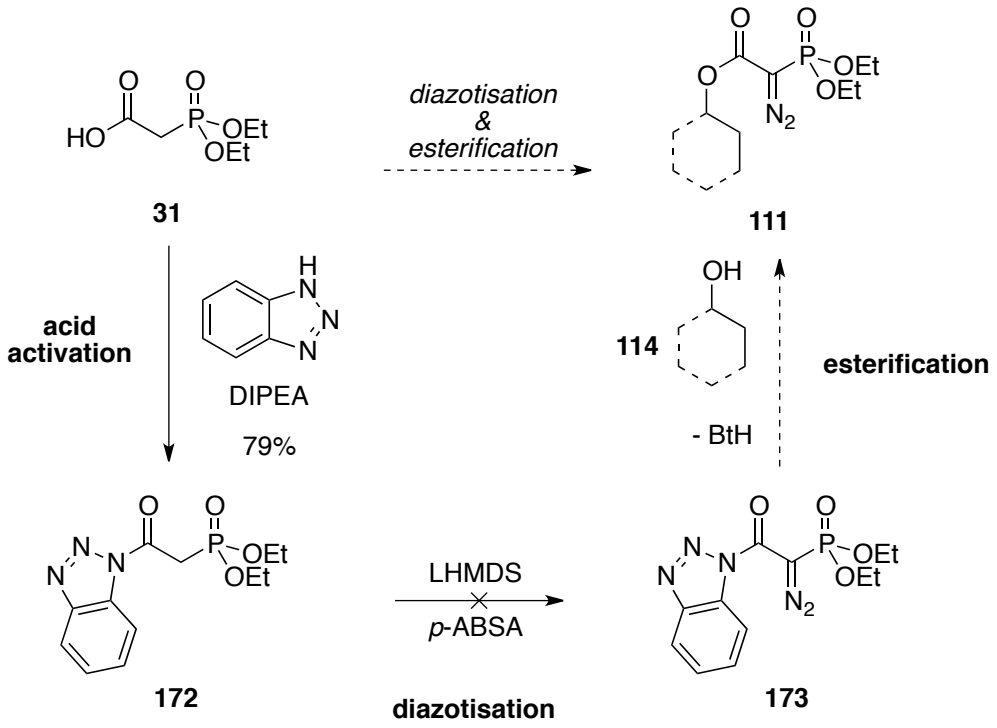


Figure 14: Attempted hydrogenation of diazoester **169**.

An alternative route was proposed in which benzotriazole-activated acid **172** would be diazotised. This product could then be treated with alcohols to directly afford α-diazo(diethoxyphosphoryl)acetates **111**. Whilst amide **172** was obtained in good yield, the diazotisation to provide diazo compound **173** was unsuccessful, leading to the decomposition of ester **172** (Scheme 35).



Scheme 35: Second proposed route, towards α-diazo(diethoxyphosphoryl)acetates **111**.

With the two-step procedure already providing good to excellent yields of the α-diazo (diethoxyphosphoryl)acetates no further investigations were conducted on this route.

2.2 Initial Studies on the insertion process

2.2.1. Rhodium(II)-catalysed C–H insertion

The first objective of the C–H insertion/olefination methodology was to optimise the two steps separately prior to developing a telescoped sequence.† A substrate with general structure **111**, shown in Figure 15, possesses two sites capable of undergoing C–H insertion, one affording the desired γ-lactone and the other the β-lactone regioisomer. It was hoped that the γ-lactone would predominate, in line with previous Rh(II)-catalysed C–H insertion observations.

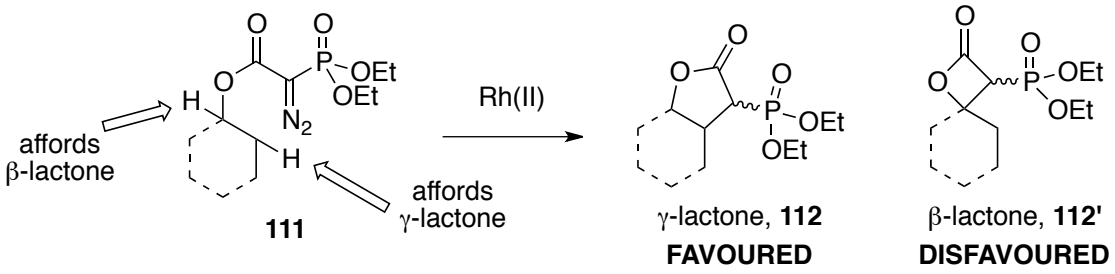


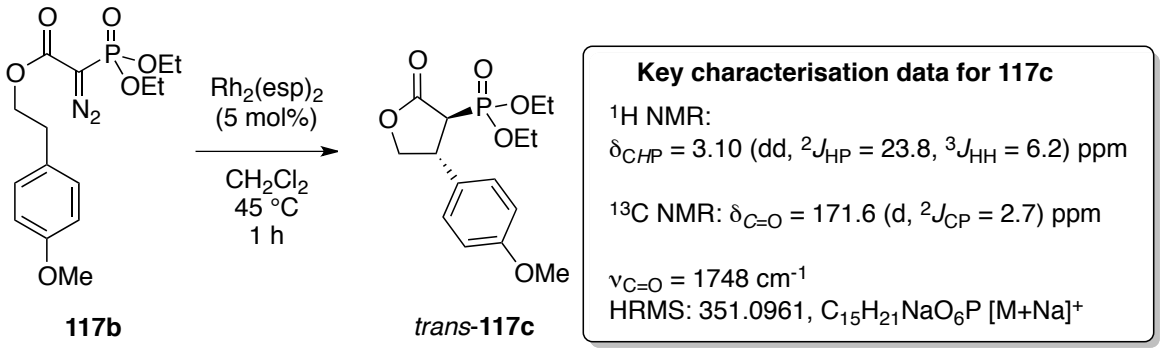
Figure 15: Possible C–H insertion products from Rh(II)-catalysed diazo decomposition.

The investigation into the C–H insertion began by treating *p*-methoxyphenyl derivative **117b** with a series of rhodium(II) catalysts. The substrate was selected on the basis that the electron-rich aryl unit would both increase the nucleophilicity of the C–H bond and stabilise the build up of +ve charge during the C–H insertion. As discussed earlier, rhodium(II) carboxylates are the catalysts of choice for acceptor/acceptor-substituted diazo compounds due to the greater reactivity towards diazo decomposition.

Initially, diazo substrate **117b** was treated with 5 mol% of $Rh_2(esp)_2$ in CH_2Cl_2 at 45 °C for 1 hour (Scheme 36). All of the starting material was consumed and analysis of the ^1H NMR spectra of the unpurified reaction mixture revealed two compounds, each possessing diagnostic signals; 3.10 (dd, J = 23.8, J = 6.2) ppm and 3.38 (dd, J = 24.0, J = 8.7) ppm. The signals are consistent with a proton α to the phosphorus (which produces the large coupling constant observed), however this signal could be expected in both the γ- and β-lactone products. After purification by silica column chromatography a single product was isolated in 64% yield, with just one of these diagnostic

† A telescoped process is one in which multiple reactions are performed without purification — in a single reaction vessel (one-pot), if required — with sequential addition of reagents.
A tandem process is one in which all of the required reagents are added at the beginning of a multi-reaction transformation.

signals, the dd at δ = 3.10 ppm, remaining. Analysis of its spectral data confirmed that the product was the desired γ-lactone. It is believed that the isolated compound is the *trans*-diastereomer based on thermodynamic considerations and that the other product observed in the crude ^{1}H NMR spectrum was the *cis*-isomer, which epimerised during chromatography.



Scheme 36: Rhodium(II)-catalysed intramolecular C–H insertion of α-diazo (diethoxyphosphoryl)acetate **117b**, showing key characteristic data for product **117c**.

In order to confirm the proposed *trans*-assignment, the ^{1}H-^{1}H coupling constants were analysed by comparisons with similar compounds. Literature data for the coupling constant ($^{3}J_{H2\text{-}H3}$, Figure 16) demonstrated that values between 8–11 Hz indicates a *trans*-relationship and 4–6 Hz a *cis*-relationship.[89] The value observed for $^{3}J_{H2\text{-}H3}$ in **117c** is 6.2 Hz. The proximity of this value to the *cis*- and *trans*-boundaries meant that a definitive assignment could not be made.

Confirmation of the *trans*-assignment was therefore sought using X-ray single crystal analysis, however lactone **117c** was isolated as an oil. As such unsubstituted phenyl analogue **116c**, which is a crystalline solid, was synthesised under similar conditions. A single crystal X-ray structure was obtained (Figure 16) and, as expected, was that of the *trans*-diastereomer. The similarity of the $^{3}J_{H2\text{-}H3}$ coupling constants of **117c** (6.2 Hz) and **116c** (5.9 Hz) was the basis for the *trans*-assignment of **117c**.

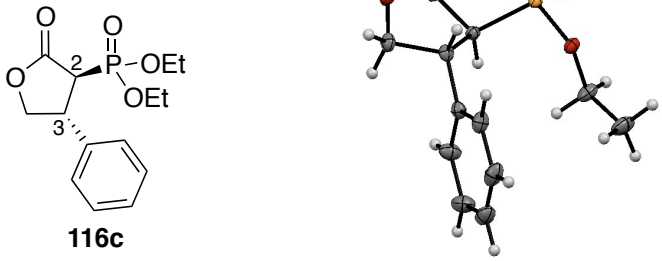


Figure 16: Single crystal X-ray structure of **116c** (CCDC: 980606). Thermal ellipsoids set to 50% probability, shown in Olex2.

Attention then turned to screening other Rh(II) carboxylate catalysts to test the C–H insertion (Figure 17).

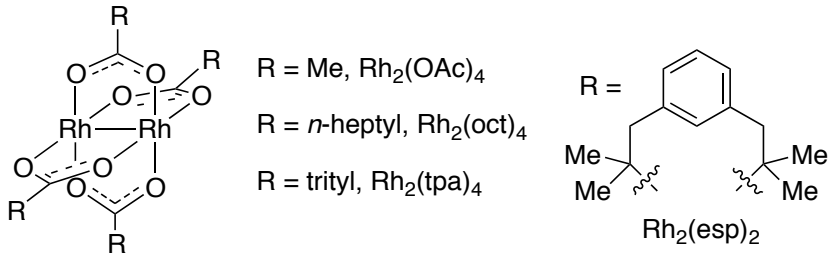
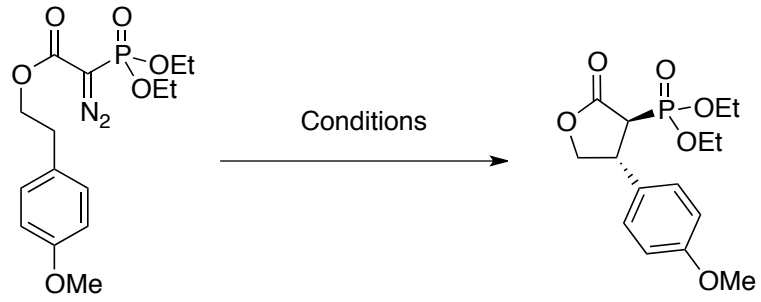


Figure 17: Commercially available rhodium(II) carboxylate catalysts.

Each catalyst was initially run with a loading of 5 mol% in CH_2Cl_2 at 45 °C for 24 h, with the reaction run in a round-bottom flask fitted with a reflux condenser (Table 3, Entries 1–4). The two least bulky catalysts, $Rh_2(OAc)_4$ and $Rh_2(oct)_4$, led to the highest yields. A reduction in catalyst loading did not change the outcome to any significant degree (Entry 5). More significantly, a 10-fold decrease in concentration led to just 30% of the γ-lactone being isolated (Entry 6). The major product **117d**, isolated in 51% yield, is the result of the carbenoid insertion into the O–H bond of water (Figure 18). This presumably occurred due to a greater quantity of expeditious water in the additional CH_2Cl_2 solvent and emphasised that the reaction must be kept under strictly anhydrous conditions. As such, the set-up changed from a large round-bottom flask to a smaller oven-dried sealable tube flushed with argon.

The original reactions were then repeated under the new conditions. No improvement was observed with $Rh_2(OAc)_4$ (Entries 7–8), but with $Rh_2(oct)_4$ there was a significant increase in isolated yield of lactone **117c** (Entries 9–11), especially so with a reduced catalyst loading of 2 mol%. This set of conditions (Entry 11) was chosen as optimal for investigations into reaction scope of the telescoped sequence, discussed later.

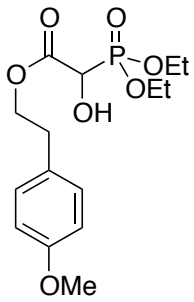
Table 3: Screening of rhodium(II) carboxylate catalysts for C–H insertion reactions of α-diazo(diethoxyphosphoryl)acetate **117b**.



117b **117c**

Entry	Rh(II) catalyst	Loading (mol%)	Conc[n] (mL/mmol)	Conditions[a]	Time (h)	Yield of 117c (%)
1	$Rh_2(oct)_4$	5	20	A	24	66
2	$Rh_2(OAc)_4$	5	20	A	24	74
3	$Rh_2(tpa)_4$	5	20	A	24	59
4	$Rh_2(esp)_2$	5	20	A	24	57
5	$Rh_2(oct)_4$	2	20	A	24	70
6	$Rh_2(oct)_4$	2	200	A	24	30[b]
7	$Rh_2(OAc)_4$	5	20	B	23	77
8	$Rh_2(OAc)_4$	2	20	B	23	71
9	$Rh_2(oct)_4$	5	20	B	6.5	80
10	$Rh_2(oct)_4$	10	20	B	4	87
11	**$Rh_2(oct)_4$**	**2**	**20**	**B**	**23**	**89**

[a] General Conditions: **117b** (0.200 mmol), CH_2Cl_2, 45 °C, time (h); Conditions A = 25 mL round-bottom flask, reflux condenser; Conditions B = 10 mL oven-dried sealable tube, argon atmosphere; [b] **117d**, 51% isolated.



117d

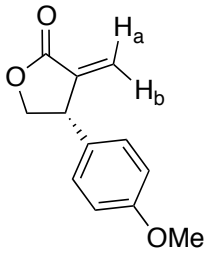
Key characterisation data for 117d

^{1}H NMR: δ_{OH} = 3.25 (broad singlet) ppm,
δ_{CHP} = 4.52 (d, J = 15.7) ppm
^{13}C NMR: δ_{COH} = 68.8 (d, J = 154.8) ppm
ν_{O-H} = 3272 cm^{-1}
HRMS: 369.1064, $C_{15}H_{23}NaO_7P$ $[M+Na]^+$

Figure 18: Alcohol product **117d** arising from water O–H bond insertion, showing key characteristic data.

2.2.2. Horner–Wadsworth–Emmons Olefination

With an optimal set of conditions for the C–H insertion in hand attention turned to the Horner–Wadsworth–Emmons (HWE) reaction. Previous work within the Taylor group on TIMO methodology also utilised the HWE reaction.[17-18] As such, similar conditions were employed, using KOBu-*t* as base and paraformaldehyde as the trapping agent (Table 4). α-Phosphonolactone **117c** was selected to test the HWE reaction, affording α-methylene-γ-butyrolactone **117e**, with the key characterisation data shown in Figure 19.



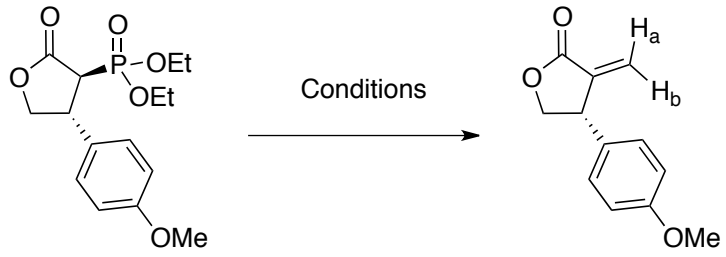
117e

Key characterisation data for 117e

^{1}H NMR: δ_{Hb} = 5.46 (d, *J* = 2.7) ppm,
δ_{Ha} = 6.36 (d, *J* = 3.0) ppm
^{13}C NMR: $\delta_{C=O}$ = 170.2 ppm
$\nu_{C=O}$ = 1740 cm^{-1}, $\nu_{C=C}$ = 1587 cm^{-1}
HRMS: 227.0688, $C_{12}H_{12}NaO_3$ $[M+Na]^+$

Figure 19: α-Methylene-γ-butyrolactone product **117e** showing key characteristic data.

Table 4: Optimisation of HWE olefination for α-phosphonolactone **117c**.



117c *rac*-**117e**

Entry	Solvent	KOBu-*t* (Equiv.)	$(CH_2O)_n$ (Equiv.)	Yield of 117e (%)
1	CH_2Cl_2	0.9	10	56
2	THF	0.9	10	56
3	CH_2Cl_2	1.0	5	68
4	CH_2Cl_2	1.0	2	75
5	**CH_2Cl_2**	**1.2**	**5**	**82**

General Conditions: i) **117c** (~0.200 mmol), CH_2Cl_2, KOBu-*t*, 0 °C, 30 mins; ii) $(CH_2O)_n$, −78–0 °C, 2 h;

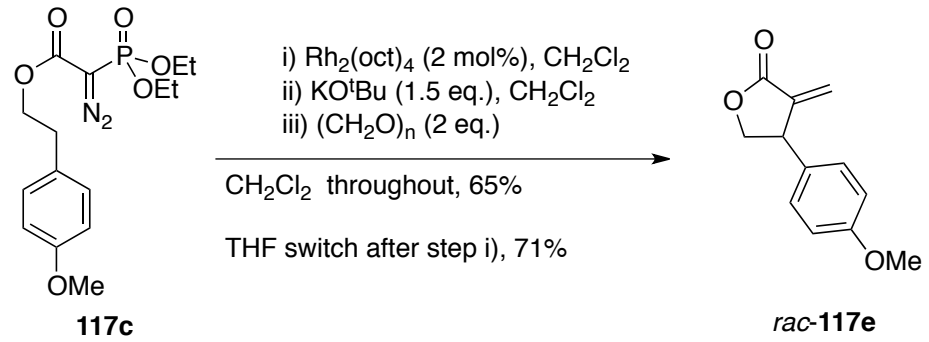
Variation of the solvent from CH_2Cl_2 to THF had no impact on the isolated yield of lactone **117e** (Entries 1–2). Previous studies within the Taylor group found that a sub-stoichiometric quantity of base was optimal due to the high base-sensitivity of the α-methylene-γ-butyrolactone products,[17a]

but it was found that during the reaction of α-phosphonolactone **117c** there was no product degradation in the presence of excess base. In fact a small excess of base and a reduction in the equivalents of paraformaldehyde gave rise to higher reaction yields (Entries 3–5).

2.2.3. Telescoped C–H insertion/olefination process

It was envisioned that the two steps discussed above could be combined into a telescoped one-pot process, given that the only side-product of the C–H insertion reaction is nitrogen gas. In doing so the efficiency of the procedure may be improved with a reduction in the number of purification steps and amount of solvent used.

Having demonstrated the tolerance of the HWE olefination to CH_2Cl_2 and THF, each was trialled for the combined one-pot C–H insertion olefination sequence (Scheme 37). The process was implemented by taking the unpurified C–H insertion reaction mixture and performing the HWE olefination. Using CH_2Cl_2 throughout gratifyingly gave the α-methylene lactone **117e** in 65% yield. Yet, when the solvent was switched to THF after the C–H insertion (by evaporation of the CH_2Cl_2), the reaction was cleaner and gave an improved yield of 71% of lactone **117e**.



117c *rac*-**117e**

Scheme 37: One-pot C–H insertion/olefination sequence.

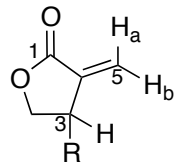
Given the ease with which the solvent can be switched (simply concentrate *in vacuo* then redissolve in THF) these conditions were taken forward for examination of the reaction scope.

2.3 One-pot C–H insertion/olefination sequence; scope & limitations

2.3.1. Benzylic systems

With an optimised set of conditions in hand the telescoped one-pot procedure was applied to a series of α-diazo(diethoxyphosphoryl)acetates to investigate steric, electronic and selectivity effects. The first series of substrates tested contained benzylic C–H insertion sites, which benefit from stabilisation of positive charge build up during the transition state. It was reasoned that more electron-rich aromatic rings would favour the C–H insertion more so than electron-deficient systems due to greater charge stabilisation. As such, the effect of electronic changes on the C–H insertions were investigated by manipulation of substituents on the aromatic ring (Figure 21).

Most examples were tested using the optimised conditions but some substrates performed better using modified conditions involving changes in the quantity of base or temperature of the HWE olefination reaction. As expected, each of the reactions furnished solely the γ-lactone products, with none of the β-lactone regioisomers observed. All products were fully characterised, with diagnostic data shown in Figure 20. The α-methylene protons H-5a and 5b are very distinguishable and observed as sharp doublets with a small coupling constant. The $^{2}J_{HH}$ geminal coupling and corresponding COSY correlations are, in general, not observed. The coupling constant arises from $^{4}J_{HH}$ with the proton H-3. The significantly downfield shift of H-5a is due to the deshielding effect of the proximal carbonyl. The ^{13}C NMR shift and IR stretch of the carbonyl group are observed at values as would be typically expected.



Key characterisation data for α-methylene-γ–butyrolactones

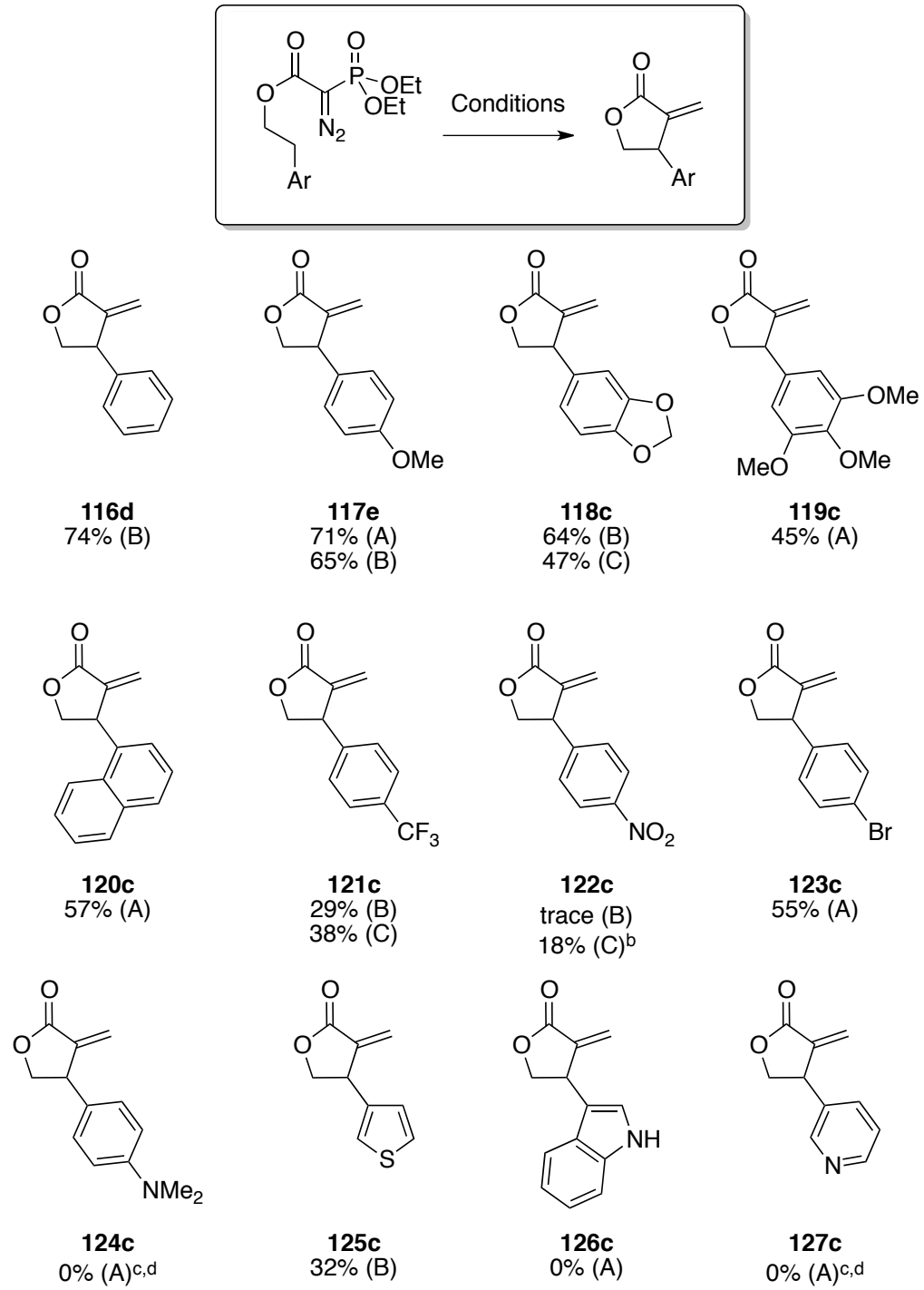
^{1}H NMR: $\delta_{5a} \approx 6.30–6.45$ (d, $^{4}J_{HH} \approx 3.0$) ppm

$\delta_{5b} \approx 5.45–5.60$ (d, $^{4}J_{HH} \approx 2.7$) ppm

^{13}C NMR: $\delta_{C=O} = 169–171$ ppm

$\nu_{C=O} = 1740–1765$ cm^{-1}

Figure 20: Diagnostic data for a general α-methylene-γ-butyrolactone.



116d
74% (B)

117e
71% (A)
65% (B)

118c
64% (B)
47% (C)

119c
45% (A)

120c
57% (A)

121c
29% (B)
38% (C)

122c
trace (B)
18% (C)[b]

123c
55% (A)

124c
0% (A)[c,d]

125c
32% (B)

126c
0% (A)

127c
0% (A)[c,d]

Figure 21: One-pot C–H insertion/olefination sequence for substrates with α-aryl C–H insertion sites, with isolated yields shown. Conditions[a] given in parentheses.

[a] Conditions A: (i) $Rh_2(oct)_4$ (2 mol %), CH_2Cl_2 (0.05 M), 45 °C, 20 h; (ii) Remove CH_2Cl_2 *in vacuo*, add THF, (iii) KOBu-*t* (1.2 or 1.5 equiv.), 0 to −78 °C; (iv) $(CH_2O)_n$ (2 equiv.), −78 to RT.

Conditions B: (i) $Rh_2(oct)_4$ (2 mol %), CH_2Cl_2 (0.05 M), 45 °C, 20 h; (ii) KOBu-*t* (1.2 or 1.5 equiv.), 0 to −78 °C; (iv) $(CH_2O)_n$ (2 equiv.), −78 to 0 °C.

Conditions C: (i) $Rh_2(oct)_4$ (5 mol %), CH_2Cl_2 (0.05 M), 45 °C, 20 h; (ii) KOBu-*t* (0.9 equiv.), 0 to −78 °C; (iv) $(CH_2O)_n$ (10 equiv.), −78 to 0 °C.

[b] $Rh_2(esp)_2$ used in place of $Rh_2(oct)_4$. [c] No HWE performed. [d] Starting material recovered.

Unsubstituted phenyl substrate **116b** afforded the desired lactone **116d** in good yield. Interestingly the more electron-rich systems **117e**, **118c** and **119c** were not obtained in greater yields as first expected. In fact, the reverse trend was observed in that the more electron-rich the system was, the lower the isolated yield became. It is possible that the increasing number of heteroatoms present in the substrates has a detrimental effect during the rhodium(II)-catalysed C–H insertion, possibly by competing side-reactions. Naphthyl derivative **120c** was also obtained in good yield.

Electron-poor derivatives were then examined. As anticipated, the most electron-deficient *p*-CF_3- and *p*-NO_2-substrates **121b** and **122b** afforded the lactones **121c** and **122c** respectively, in low yields. Competing side-reactions may account for the reduced yield of desired product. The less electron-deficient *p*-Br-substrate **123b** afforded lactone **123c** in good yield, making the methodology more attractive for further derivatisation, e.g. for use in cross-coupling reactions.

Dimethylaniline **124b** was the only *para*-substituted system tested to afford none of the desired product. In this case, the C–H insertion did not proceed, with all starting material recovered. This was to be expected based on reports that Lewis basic compounds are able to deactivate rhodium(II) catalysts by coordination to one of the vacant sites.[28,29b]

Heteroaromatic substrates were then examined. Thiophene **125b** did afford the desired lactone **125c**, albeit in low yield. Indole derivative **126b** did undergo the C–H insertion based on TLC and ^{1}H NMR analysis of the reaction mixture, however the HWE reaction was unsuccessful with decomposition observed. As with the dimethylaniline substrate **124b**, pyridine **127b** did not undergo the C–H insertion, again with complete recovery of starting material. Interestingly an immediate colour change from the characteristic green to deep red was observed upon addition of **127b** to a solution of the Rh(II) catalyst (Figure 22).

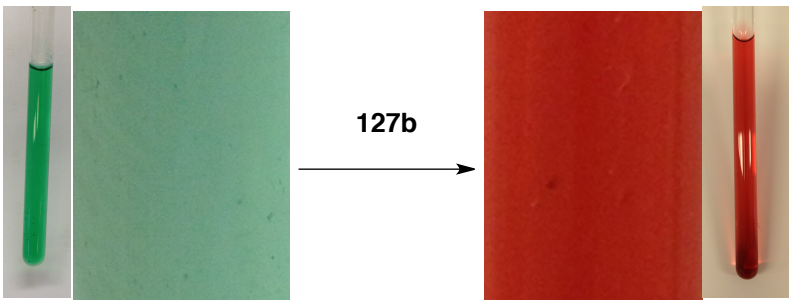


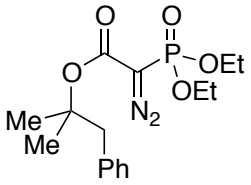
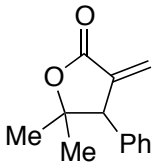
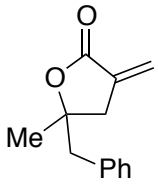
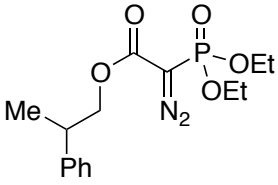
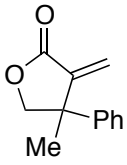
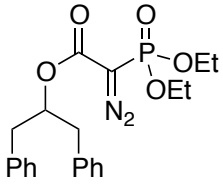
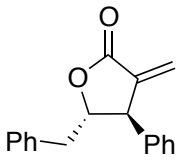
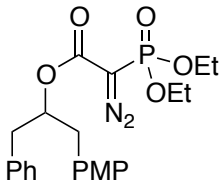
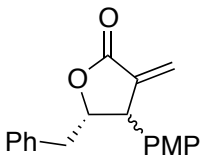
Figure 22: Colour change of rhodium(II) catalyst from green to red on addition of **127b**.

The initial studies above demonstrated that α-diazo(diethoxyphosphoryl)acetates with benzylic C–H insertion sites do readily undergo C–H insertions. As expected electron-rich aromatic systems are, in general, favoured for the stabilisation of +ve charge. However, there are notable examples in which the presence of coordinating heteroatoms reduce the isolated yield of the lactone product or suppress the C–H insertion reaction.

Focus then turned to examining more substituted systems with competing C–H insertion sites (Table 5). Dimethylphenyl substrate **128b** possesses two C–H insertions sites, one benzylic and one primary. As with related literature precedent it was expected that the benzylic site would be favoured over the primary site based on electronic considerations. Unfortunately, both of the possible products were isolated with the benzylic insertion product **128c** slightly favoured over the compound **128d** (Entry 1). This result did, however, represent the highest yielding example thus far. Diazo compound **129b**, which possesses a tertiary benzylic site, also worked well under the conditions to generate lactone **129c**, possessing a quaternary centre (Entry 2).

Diphenyl substrate **131b** gave the desired product **131c** in excellent yield and pleasingly as a single diastereomer (Entry 3). It was hoped that by differentiating two benzylic sites one might be preferred over the other. As such, a competition experiment was designed by variation of the substituents on the phenyl rings, making one site more electron-rich, and therefore more biased towards C–H insertion than the other. Hence, *p*-methoxyphenyl analogue **132c** was synthesised. It was anticipated that the C–H insertion would take place preferentially at the more electron-rich benzylic site, α- to the PMP. Under the one-pot conditions it was found that this was indeed the case with the product **132c** being formed in preference to the regioisomer **132d** (Entry 4), but unlike the unsubstituted dibenzyl product **131c** there was a loss of diastereoselectivity (1.6:1). In line with previously examined electron-rich substrates there was a small drop in isolated yield. The assignment of the regioselectivity was based on HMBC correlations (Figure 23). The observed correlations could only be present in regioisomer **132c** and not in isomer **132d**.

Table 5: One-pot C–H insertion/olefination sequence for substrates with α-aryl C–H insertion sites.[a]

Entry	Diazo Compound	Product(s)	Isolated Yield, %
1	 **128b**	 **128c**  **128d**	89 (A) 1.45:1 (**128c**:**128d**)
2	 **129b**	 **129c**	59 (A)
3	 **131b**	 **131c**	84 (B)
4	 **132b**	 **132c**	65 (B) *dr* 1.6:1

[a] Conditions A: (i) $Rh_2(oct)_4$ (2 mol %), CH_2Cl_2 (0.05 M), 45 °C, 20 h; (ii) Remove CH_2Cl_2 *in vacuo*, add THF, (iii) KOBu-*t* (1.2 or 1.5 equiv.), 0 to −78 °C; (iv) $(CH_2O)_n$ (2 equiv.), −78 to RT. Conditions B: (i) $Rh_2(oct)_4$ (2 mol %), CH_2Cl_2 (0.05 M), 45 °C, 20 h; (ii) KOBu-*t* (1.2 equiv.), 0 to −78 °C; (iv) $(CH_2O)_n$ (2 equiv.), −78 to 0 °C.

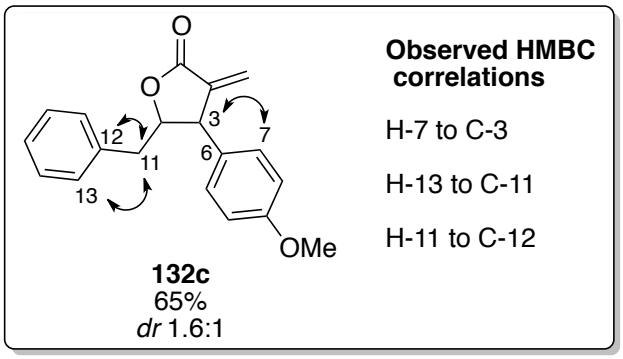


Figure 23: Observed HMBC correlations of lactone **132c**.

2.3.2. Non-benzylic systems

As discussed earlier, previous literature precedent shows that C–H insertion can occur with aliphatic C–H bonds even if not stabilised by aryl groups.[49] As such, *n*-heptanol derived diazo compound **134b** was subject to the one-pot conditions (Figure 24) yielding the desired γ-lactone **134c** in good yield with no observed regioisomeric side-products, further expanding the scope of the reaction.

The effect of steric hindrance close to the C–H insertion site was examined by installation of *i*-Pr and *t*-Bu groups in substrates **135b** and **136b** respectively. As anticipated, when subject to the one-pot conditions the increasing steric hindrance led to a decrease in isolated yield of the desired products **135c** and **136c** respectively. It is believed the increased steric hindrance leads to undesired side-reactions.

Dimethyl substrate **130b**, which possesses a tertiary C–H insertion site, reacted cleanly under the one-pot conditions, yet the desired lactone product **130c** was obtained in a disappointing 23% yield, although this may be accounted for by the product's volatility.

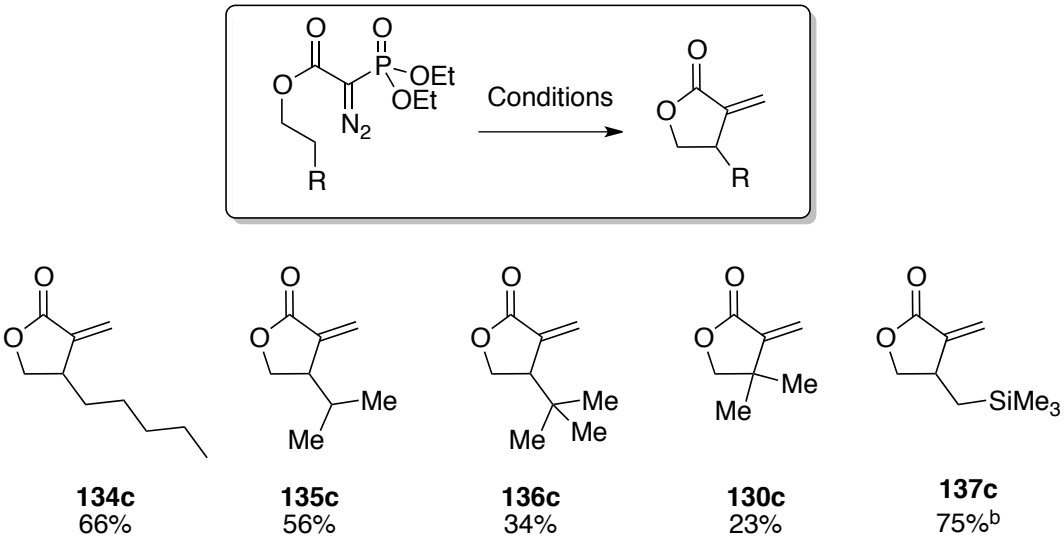


Figure 24: One-pot C–H insertion/olefination sequence for substrates with non-benzylic secondary C–H insertion sites.[a]

[a] (i) $Rh_2(oct)_4$ (2 mol %), CH_2Cl_2, 45 °C, 20 h; (ii) Remove CH_2Cl_2 *in vacuo*, add THF, KOBu-*t* (1.2 or 1.5 equiv.), 0 to −78 °C; (iii) $(CH_2O)_n$ (2 equiv.), −78 to 0 °C. [b] Warmed to RT for HWE.

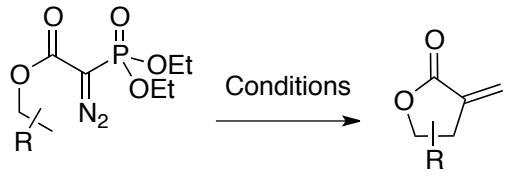
It was hoped that installation of a silyl group β- to the C–H insertion site would allow stabilisation of the positive charge, *via* the β-silicon effect, without the associated steric hindrance. Pleasingly TMS diazo derivative **137b** worked well under the one-pot conditions affording the desired lactone **137c** in very good yield.

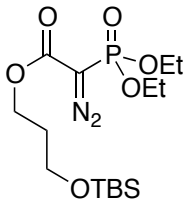
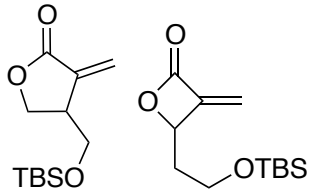
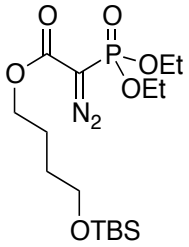
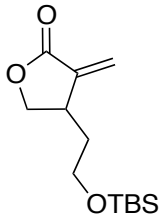
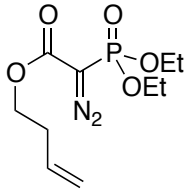
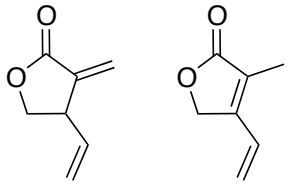
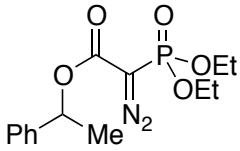
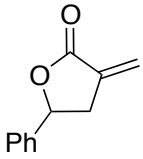
The installation of oxygen functionality α- to the C–H insertion site was seen as of particular importance given the substructure is present in over 3000 natural products. The TBS protected alcohol derivative **138b** was prepared from 1,3-propanediol. When subjected to the one-pot conditions, two products were isolated; the desired γ-lactone **138c** as well as the regioisomeric β-lactone **138d**, both in poor yield (Table 6, Entry 1). The formation of the β-lactone and low isolated yields may be accounted for by the steric hindrance of the TBS protecting group. If the C–H insertion sites are relatively inaccessible, competing reactions may take place given the high reactivity of the rhodium carbenoid. This conjecture is somewhat supported in that moving the OTBS functionality one methylene unit further away from the C–H insertion site, as in compound **139b**, both increases isolated yield and sees just a single γ-lactone product **139c** observed (Entry 2).

Substrate **140b** was prepared as an interesting chemoselectivity test, as it contains two reaction sites. Reaction of the carbenoid with the allylic C–H bond would generate a γ-lactone whereas reaction with the olefin would generate an oxabicyclo[4.1.0]heptan-2-one, the product of cyclopropanation. Typically, 5-membered ring products predominate in intramolecular rhodium(II)-catalysed C–H insertions, as such, the γ-lactone was expected to be formed selectively. Following reaction of diazo **140b** with $Rh_2(oct)_4$ (Entry 3), a single product was observed by TLC analysis. Completion of the one-pot process revealed two compounds **140c** and **140d**, each arising from C–H insertion, with no evidence of a cyclopropanation product. The major product had the structure of desired lactone **140c** and interestingly the second was the product of olefin isomerisation. This is favourable as it brings the vinyl substituent into conjugation. No other products were isolated to account for the low yield.

C–H insertion into primary C–H bonds is known to be disfavoured, but it was considered whether it may be still be possible due the high reactivity of the acceptor/acceptor carbenoid. Substrate **133b**, which possesses a primary C–H bond was synthesised, and on treatment under the standard Rh(II) conditions decomposition was observed with no starting material, C–H insertion or other products observed by ^{1}H NMR analysis.

Table 6: One-pot C–H insertion/olefination sequence for substrates with non-benzylic secondary C–H insertion sites.[a]

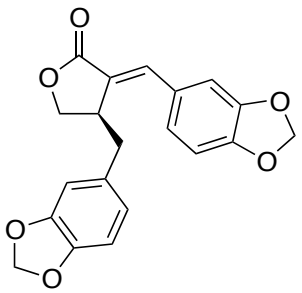


Entry	Diazo Compound	Product(s)	Isolated Yield, %
1	 **138b**	 **138c** **138d**	18 (**138c**) 16 (**138d**)[b]
2	 **139b**	 **139c**	49[b]
3	 **140b**	 **140c** **140d**	38 (**140c**) 9 (**140d**)[b]
4	 **133b**	 **133c**	0[c]

[a] (i) $Rh_2(oct)_4$ (2 mol %), CH_2Cl_2, 45 °C, 20 h; (ii) Remove CH_2Cl_2 *in vacuo*, add THF, KOBu-*t* (1.2 or 1.5 equiv.), 0 to −78 °C; (iii) $(CH_2O)_n$ (2 equiv.), −78 to 0 °C. [b] Warmed to RT for HWE. [c] No HWE performed.

2.3.2.1. β-Benzyl-substituted systems

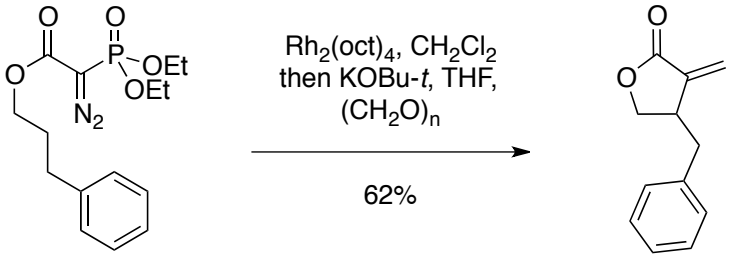
α-Methylene/alkylidene-γ-butyrolactones containing β-benzylic groups are prevalent in Nature. Many of these compounds possess benzene rings with varying degrees of oxygenation. For example, the 3,4-methylenedioxy framework is particularly common in Nature, as found in the natural product savinin **174** (Figure 25).



savinin, **174**

Figure 25: α-Methylene-γ-butyrolactone natural product, savinin **174**.

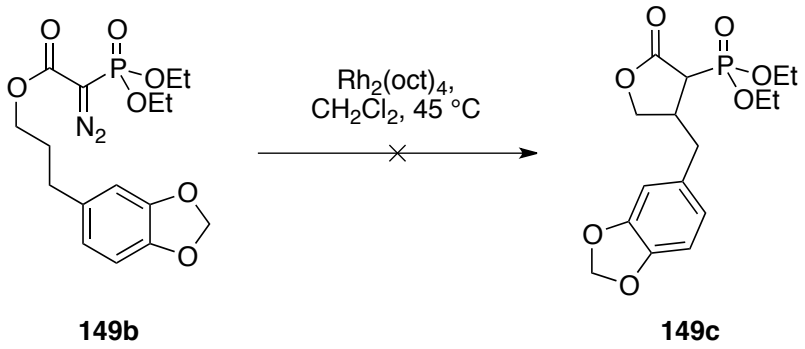
Access to this general framework was seen as an important extension of the current methodology, and as such a series of α-diazo(diethoxyphosphoryl)acetates were prepared and subjected to the one-pot C–H insertion olefination conditions. Firstly, the unsubstituted system **148b** was treated under the standard conditons (Scheme 38), generating γ-lactone **148c** in good yield, with no β or δ-lactone products observed.



148b **148c**

Scheme 38: One-pot C–H insertion/olefination sequence for substrate **148b**.

Given this successful result, the 3,4-methylenedioxy substrate **149b**, the precursor to savinin **174**, was then tested (Scheme 39). On addition of $Rh_2(oct)_4$ to a solution of diazo compound **149b** a deep orange/brown was observed instead of the usual green colour. ^{1}H NMR and TLC analysis indicated the starting material had not been consumed and that diazo decomposition had not occurred. None of the desired C–H insertion product **149c** was observed.



Scheme 39: Attempted C–H insertion reaction of 3,4-methylenedioxy substrate **149b**.

This result was puzzling given that both the unsubstituted substrate **148b** and methylenedioxy substrate **118b**, tested earlier, were successful in the one-pot sequence (Figure 26).

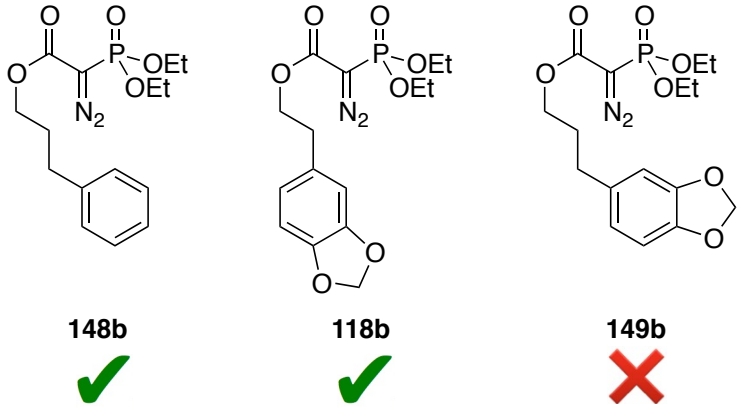
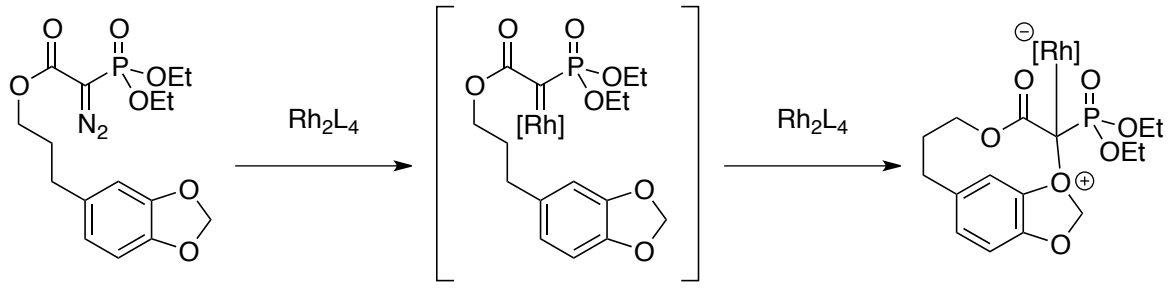


Figure 26: Comparison of C–H insertion reaction outcomes for α-diazo (diethoxyphosphoryl)acetates **148b**, **118b** and **149b**.

Given the dramatic colour change of the solution from green to red/brown, in the case of diazo compound **149b**, it was considered whether this may be due competing coordination of the oxygen lone pairs to the vacant sites on the rhodium catalyst, deactivating it towards diazo decomposition. This, however, seemed unlikely based on the earlier result of diazo compound **118b**, which also possesses the 3,4-methylenedioxy framework. This compound contains one methylene unit less in the tether, yet worked well under the standard conditions, remaining green during the rhodium(II) addition, thus implying that the presence of oxygen atoms in the substrate is not in itself a detrimental factor.

This led to consideration of an alternative explanation: it could be that diazo decomposition is occurring to a small extent but, instead of undergoing C–H insertion the lone pairs from the oxygen atom are coordinating to the carbenoid centre, shutting down the catalytic cycle and rendering the catalyst inert. The small amount of starting material consumed and the appearance of a

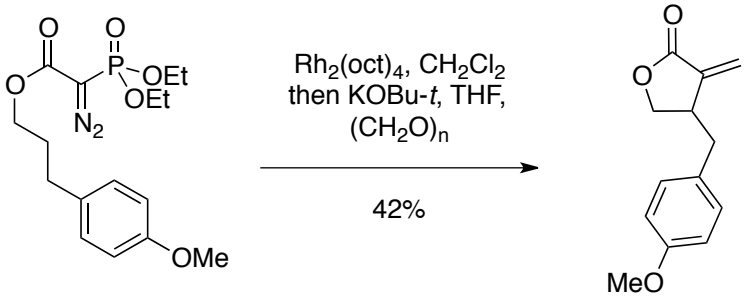
decomposition product may not be observable using ^{1}H NMR spectroscopy given the low catalyst loading. It is thought that the increased flexibility may be conferred by the additional methylene unit in the tether potentially enabling coordination of the *meta*-oxygen lone pairs to the carbenoid centre, resulting in a non-productive pathway, as shown in Scheme 40.



149b **149d** **149e**

Scheme 40: Proposed unproductive pathway following the formation of carbenoid **149d**.

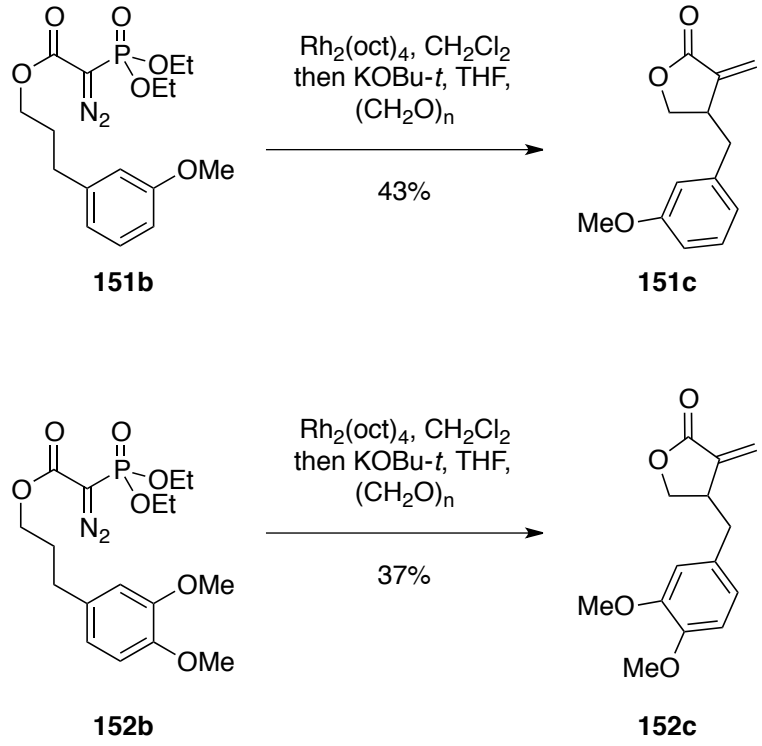
In an effort to further explore this possibility it was hoped that by removing the *meta*-oxygen this coordination would no longer be possible. As such, 4-methoxy derivative **150b** was synthesised and as anticipated successfully generated lactone **150c**, albeit in moderate yield (Scheme 41).



150b **150c**

Scheme 41: One-pot C–H insertion/olefination sequence for diazo compound **150b**.

As controls, the 3-methoxy and 3,4-dimethoxy derivatives **151b** and **152b** were also synthesised and subjected to the one-pot C–H insertion olefination conditions (Scheme 42). Remarkably, each substrate was also successful, again in moderate but unoptimised yield.



151b **151c**

152b **152c**

Scheme 42: One-pot C–H insertion/olefination sequence for diazo compounds **151b** and **152b**.

This again required the anomalous result of 3,4-methylenedioxy substrate **149b** to be reconsidered. It seems that the conformational flexibility provided by the length of the tether is an important factor, but this alone does not fully account for the observed result. It is possible that the methylene unit joining the oxygen atoms in substrate **149b**, changes the alignment of the oxygen lone pair, thus restricting conjugation into the aromatic ring, thereby making the lone pairs more available for coordination to the carbenoid centre.

The above substrates have been shown to work successfully in general, although the isolated yields are low. This complements the earlier results, which also showed reduced yields for oxygenated benzene rings. The reason for this is not known but likely stems from the oxygen lone pairs, leading to competing side-reactions and the formation of by-products.

2.3.2.2. Spirocyclic fused rings

Focus then turned to disubstituted non-benzylic systems possessing tertiary C–H bonds, which generate spirocyclic α-methylene-γ-butyrolactones (Figure 27). α-Diazo(diethoxyphosphoryl)acetates **141b**, **142b**, **143b** and **144b** were prepared and subjected to the standard one-pot C–H insertion/olefination conditions. Pleasingly, the spiro-butyl, -pentyl and -hexyl products **142c**, **143c** and **144c** were obtained in good yields, but unfortunately the spiropropyl product **141c** was not formed, with decomposition observed.

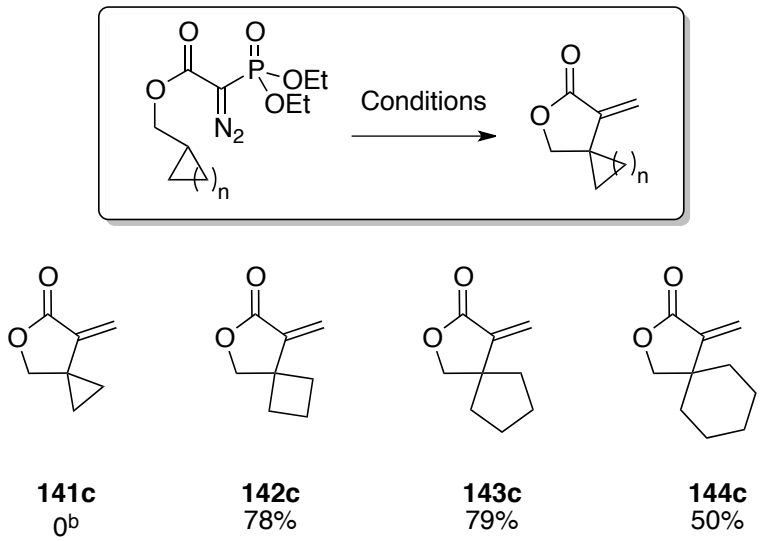
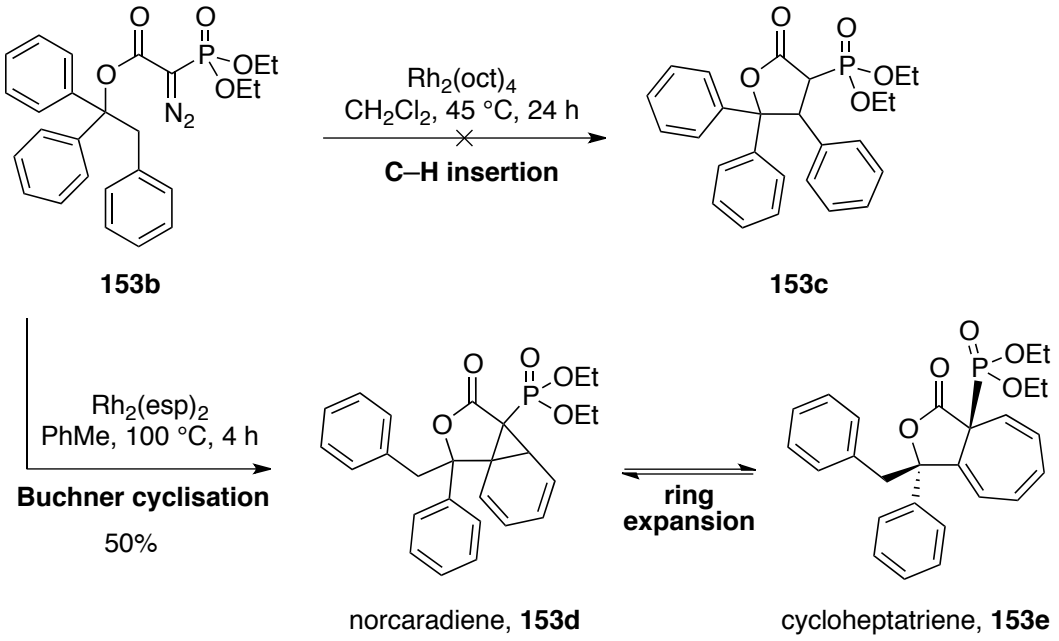


Figure 27: One-pot C–H insertion/olefination sequence for α-diazo(diethoxyphosphoryl)-acetates affording spirocyclic α-methylene-γ-butyrolactones.[a]

[a] (i) $Rh_2(oct)_4$ (2 mol %), CH_2Cl_2, 45 °C, 20 h; (ii) Remove CH_2Cl_2 *in vacuo*, add THF, KOBu-*t* (1.2 or 1.5 equiv.), 0 to −78 °C; (iii) $(CH_2O)_n$ (2 equiv.), −78 °C to RT. [b] No HWE performed.

2.3.3. Buchner cyclisation

The reaction of triphenyl diazo compound **153b** with $Rh_2(oct)_4$ under the standard conditions did not afford any of the desired C–H insertion product **153c**, with a trace amount of an unknown side-product and starting material being recovered (Scheme 43). Switching to toluene and replacing the catalyst with the more stable[90] $Rh_2(esp)_2$ with heating at 100 °C for 4 h saw complete consumption of the starting material and formation of the same unknown product in an unoptimised 50% yield. Analysis of the ^{1}H NMR data indicated the substrate had undergone a Buchner ring expansion; the carbene undergoes cyclopropanation with one of the aromatic rings affording norcaradiene **153d**, which may be in equilibrium with cycloheptatriene **153e**. As with Rh(II)-catalysed C–H insertions, the formation of 5-membered rings is favoured, hence the cyclopropanation occurs with one of the phenyl groups α to the oxygen.



Scheme 43: Rh(II)-catalysed Buchner ring expansion of diazo **153b**.

The Buchner ring expansion was first observed by Buchner and Curtius in 1885.[91] It is an intramolecular cyclopropanation between a carbene and an aromatic π-system. A lot of energy is required for the Buchner ring expansion to occur because the aromaticity of the benzene ring is broken. There have since been many examples of the Buchner ring expansion using rhodium-stabilised carbenoids,[92] as well as a thorough review.[93]

After the cyclopropanation, the bicyclo[4.1.0]heptane (norcaradiene) **153d** can undergo a thermally-allowed reversible electrocyclic ring-opening to the cycloheptatriene **153e**. In solution the norcaradiene and cycloheptatriene forms typically equilibrate. In the solid state one form may predominate, usually determined by substitution patterns and the effect of electronic and steric interactions. This topic has been well reviewed[93] and a summary is given below.

The cyclopropane possesses an occupied anti-bonding HOMO orbital, located in the C1–C6 bond. Substitution at C-7 with π-acceptor groups such as –CN, $–CO_2R$, $–P(O)(OR)_2$ and –CHO, withdraws electron density away from the anti-bonding HOMO orbital, shortening the bond, thus giving it more bonding character and hence stabilising the norcaradiene form. Cyclopropanes are known to be weak π-donors, but were found to favour the norcaradiene form, along with σ-donor substituents. Conversely, when C-7 is substituted with σ-acceptor groups, such as $–CF_3$, the norcaradiene form is destabilised, favouring the cycloheptatriene form (Figure 28).

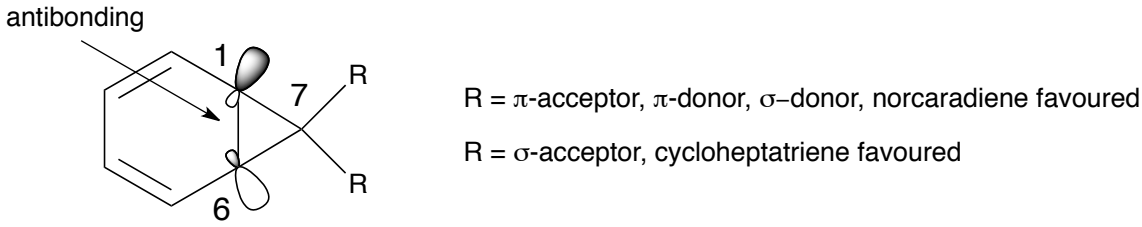


Figure 28: Electronic effect of substituents on norcaradiene/cycloheptatriene equilibrium.

From this analysis it would be expected that the equilibrium between **153d** and **153e** would lie towards norcaradiene **153d**, due to the two π-acceptors. Given that the two possible compounds were expected to possess similar ^{1}H NMR spectra and may be equilibrating in solution, a single crystal X-ray structure was obtained (Figure 29).

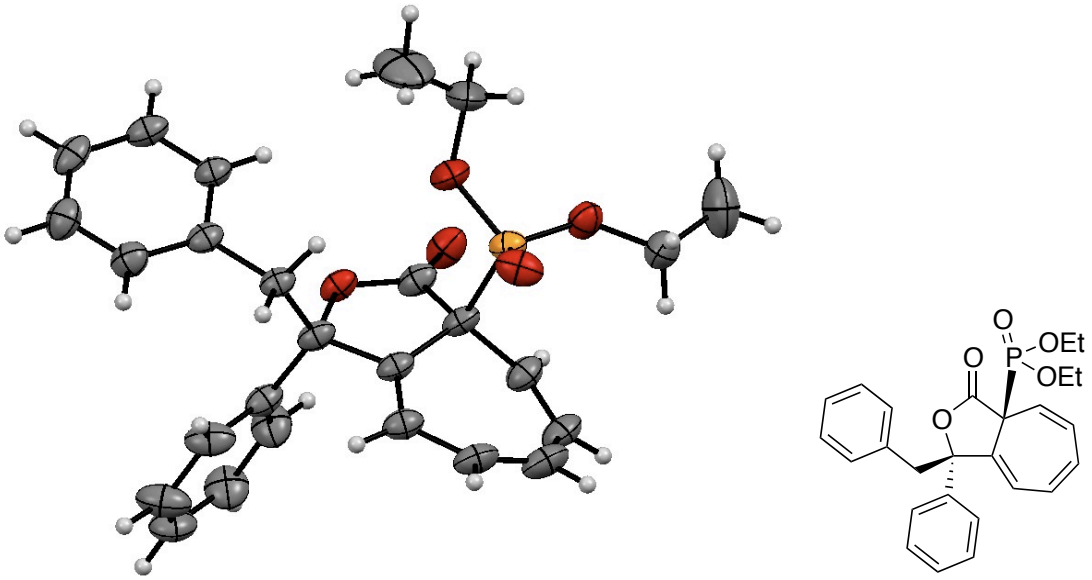
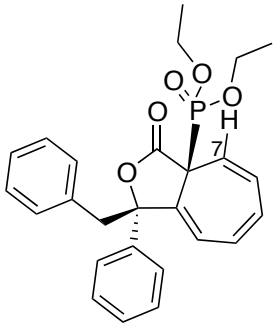


Figure 29: Single crystal X-ray structure of cycloheptatriene **153e** (CCDC: 1013524).[‡] Thermal ellipsoids set to 50% probability, shown in Olex2.

Contrary to expectations, the cycloheptatriene **153e** was the only compound observed. The predominance of the norcaradiene may only apply when in solution, with the more crystalline cycloheptatriene being favoured in the solid state. Alternatively, steric effects arising from the bulky phenyl and phosphonate functionalities may override the electronic bias towards the norcaradiene.

[‡] The crystal exhibited complete disorder of the entire molecule. The molecule was modelled in two positions with refined occupancies of 0.8902:0.1098(18). The two forms are related by an approximate inversion about a plane defined by the P=O and C=O vectors. Only the major form is shown. Full details can be found *via* The Cambridge Crystallographic Data Centre.

Given the single crystal X-ray structure revealed the cycloheptatriene form, the ^{1}H NMR spectrum was assigned as such, with the key assignments shown in Figure 30. The presence of five proton signals in the δ = 5.30 – 6.40 ppm region adds weight to the argument that the cycloheptatriene is predominant as only four signals might be expected in this region for the norcaradiene form. The signal at δ = 5.31 ppm was assigned to H-7 with one coupling to the adjacent proton and the other to the phosphorus atom.



153e

Key ^{1}H NMR data for 153e

δ_{CHH} = 3.65 (1 H, d, *J* = 14.6) ppm
δ_{CHH} = 4.11 (1 H, d, *J* = 14.6) ppm
$\delta_{PCCH\text{-}7}$ = 5.31 (1 H, dd, *J* = 10.0, *J* = 6.3) ppm
$\delta_{C=CH}$ = 6.15–6.22 (2 H, m) ppm
$\delta_{C=CH}$ = 6.27–6.36 (2 H, m) ppm

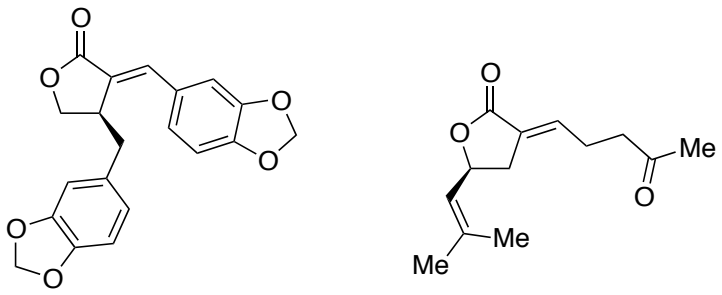
Figure 30: Key ^{1}H NMR data for cycloheptatriene **153e**.

The ^{13}C NMR data were also intriguing. The key signal, at C-7, should provide conclusive evidence of which form is favoured; in the norcaradiene it is sp^3 hybridised whereas in the cycloheptatriene it is sp^2 hybridised. Yet no clear resonance could be assigned to C-7 until careful analysis of the ^{1}H-^{13}C HSCQ spectrum revealed an extremely weak signal at δ = 119.1 ppm. The chemical shift of this resonance seems to clearly indicate the cycloheptatriene form is favoured. The low strength of the signal is puzzling given that the carbon is tertiary. However, coupling with the nearby phosphorus atom would halve the signal intensity, yet a simple doublet is not observed.

This result represents an interesting example of the Buchner ring expansion, contradicting the expected models, which predict the norcaradiene form should predominate over the cycloheptatriene.

2.3.4. Variation of the aldehyde: α-Alkylidene-γ-butyrolactones

In addition to α-methylene-γ-butyrolactones the one-pot methodology can be used to synthesise α-alkylidene/arylidene-γ-butyrolactones. This class of compounds also features prominently in Nature, for example, in compounds like heteroplexisolide E[94] and savinin[95] (Figure 31).



savinin, **174** Heteroplexisolide E, **175**

Figure 31: α-Alkylidene/arylidene-γ-butyrolactone natural products.

Simply by replacing the paraformaldehyde with aliphatic or aromatic aldehydes it is possible to gain access to α-alkylidene/arylidene-γ-butyrolactones in good yields (Figure 32). In all cases a mixture of *E*- and *Z*-isomers was obtained, with a propensity towards the *Z*-isomer in most cases. HWE reactions tend to provide *E* isomers. A combination of the tertiary phosphonate and the proximity of the β-position substitution likely disfavours the formation of the *E*-isomer.

The *p*-OMe diazo substrate **117b** was selected in order to test a range of aldehydes using the one-pot conditions (Figure 32). As expected, electron-deficient aldehydes performed best, with 4-nitrobenzaldehyde affording the desired product **176** at 0 °C. In each of the other cases the HWE reactions were warmed to RT affording products **178**–**182**, while electron-rich piperonal required heating to reflux in order to obtain product **177**. One aromatic and one aliphatic aldehyde were then screened against a range of α-diazo(diethoxyphosphoryl)acetates, **116b**, **134b** and **143b**, generally affording the desired products **183**–**188** in good yield. All products were fully characterised.

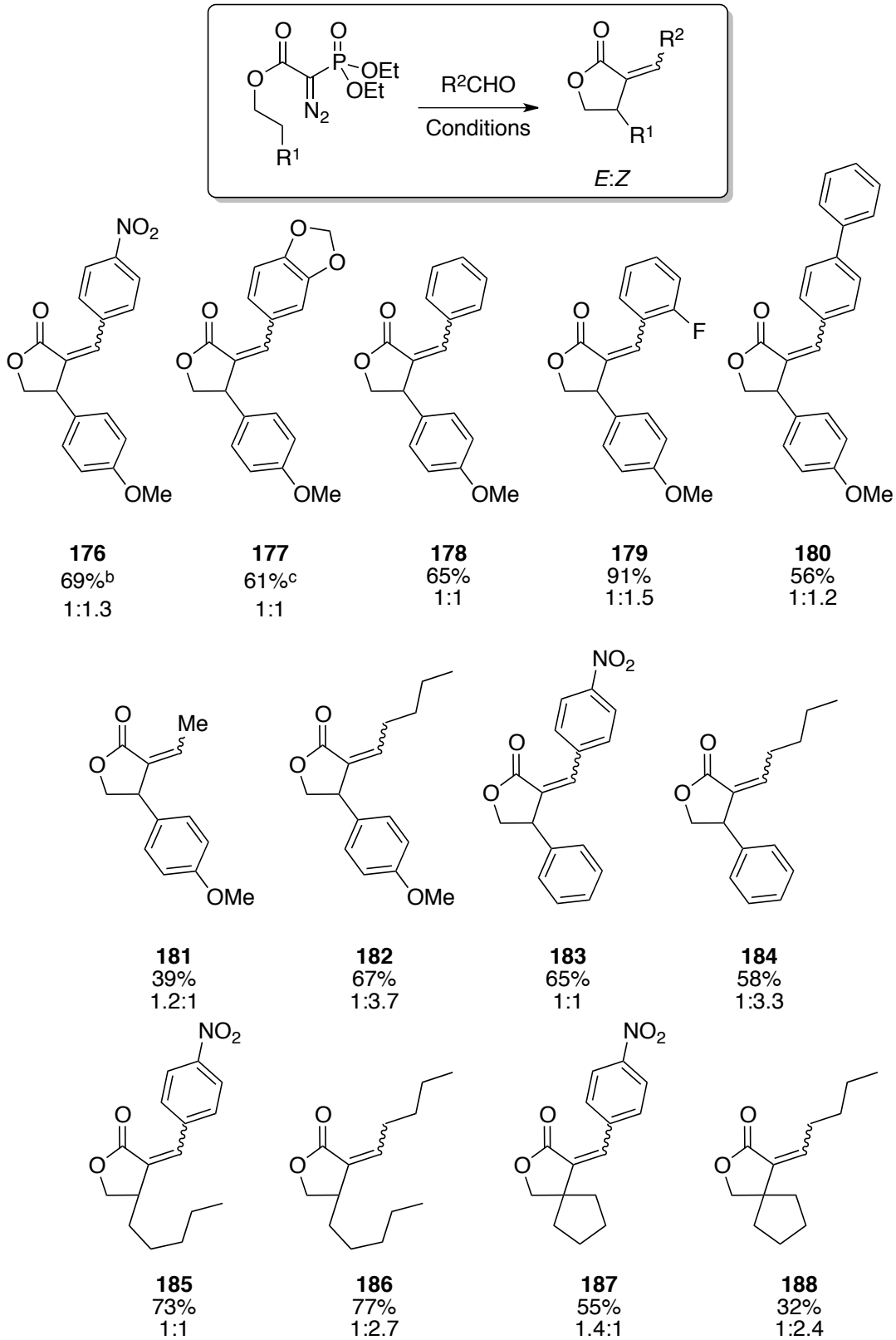


Figure 32: One-pot C–H insertion/olefination sequence using alkyl and aryl aldehydes.[a]

[a] (i) $Rh_2(oct)_4$ (2 mol %), CH_2Cl_2, 45 °C, 20 h; (ii) Remove CH_2Cl_2 *in vacuo*, add THF, KOBu-*t* (1.5 equiv.), 0 to −78 °C; (iii) RCHO (2 equiv.), −78 °C to RT. *Z*-isomer shown in products. [b] HWE was performed at 0 °C. [c] HWE was performed at reflux.

2.4 Asymmetric studies

The ability to synthesise a range of α-methylene-γ-butyrolactones using an efficient one-pot process has been demonstrated. However, with many examples of enantio-induction using chiral Rh(II) catalysts in the literature,[22] and a wide range of these catalysts available, it seemed logical to test the methodology in order to gain access to enantio-enriched α-methylene-γ-butyrolactones.

As discussed earlier, to the best of our knowledge, there are no literature examples of asymmetric induction for the intramolecular C–H insertion reactions of α-diazocarbonylacetates that afford γ-lactone products. The work of Gois *et al*. exhibits the only examples of asymmetric induction of acceptor/acceptor diazo compounds that contain phosphonate groups. Their work on α-diazophosphonoacetamides with various rhodium(II) carboxylates generated lactam products in good yields but poor *ee*.

The one-pot conditions were applied to substrate **117b** using Rh_2(*S*-DOSP)$_4$, one of the most common Rh(II) carboxylate catalysts used for asymmetric C–H insertions (Figure 33).

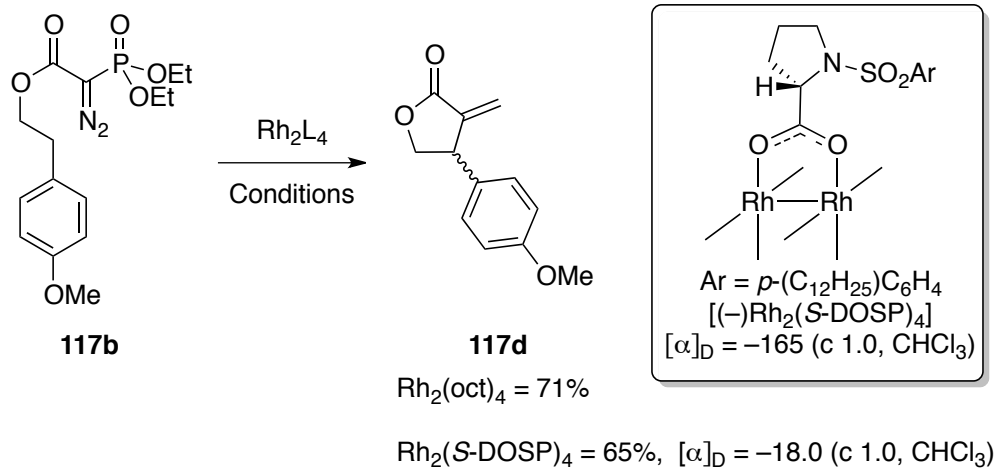


Figure 33: Rh_2(*S*-DOSP)$_4$ catalysed C–H insertion of an α-diazo(diethoxyphosphoryl)-acetate.

The desired product **117d** was formed in good yield, comparable with those using $Rh_2(oct)_4$. Following column chromatography purification, the specific rotation of the 'enriched' sample was measured, giving $[\alpha]_D = -18.0$. This result was of the same sign as the catalyst, so was treated with caution. Nevertheless attempts were made to separate the enantiomers on a non-enriched sample using chiral HPLC techniques. Unfortunately, despite screening a variety of different column types and eluting conditions no clear separation of the enantiomers was observed.

Further attempts were made to determine the *ee* using ^{1}H NMR spectroscopy by utilising a chiral shift reagent in order to generate distinguishable diastereomeric complexes. Firstly the racemic sample of lactone **117d** was tested by adding Eu(hfc)$_3$ (30 mol%) to the sample. The peaks in the ^{1}H NMR spectra were shifted downfield relative to the undoped sample, but no peak separation was observed (Figure 34). A further increase in loading of the europium reagent increased the downfield shifting but also introduced peak broadening, such that the *ee* could not be determined.

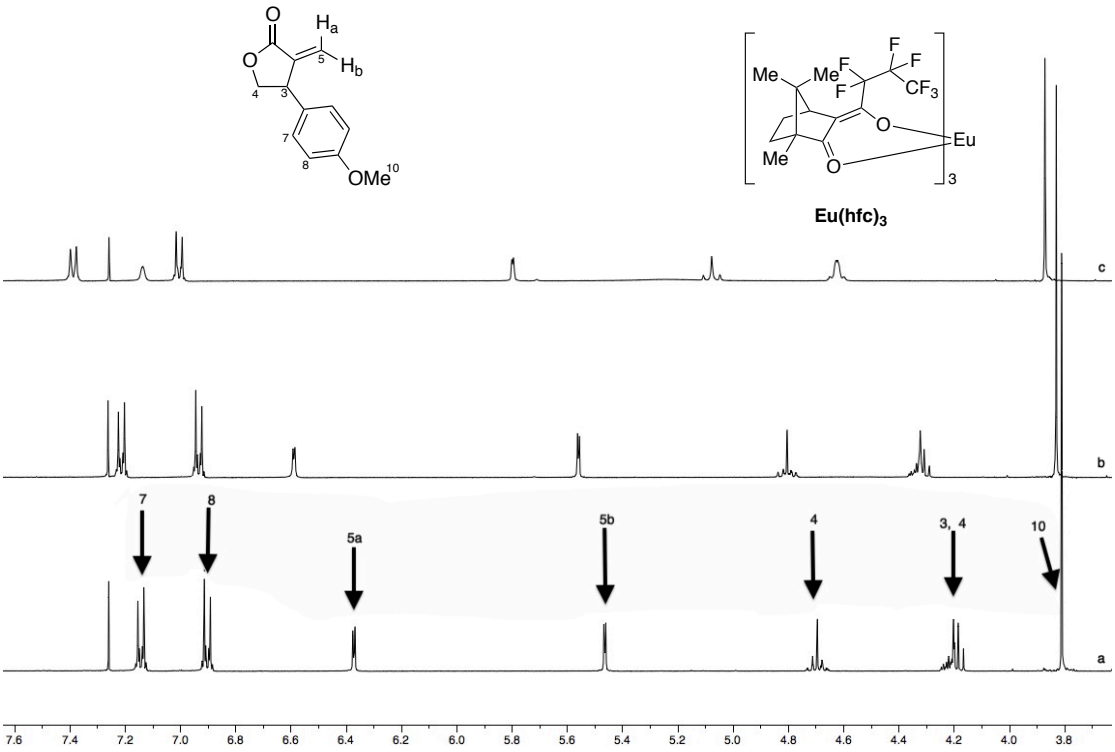


Figure 34: ^{1}H NMR spectra of racemic **117d** (above, left) with various quantities of Eu(hfc)$_3$ (above, right); a) No additive, b) 0.3 eq. of Eu(hfc)$_3$, c) 0.56 eq. of Eu(hfc)$_3$.

Another technique that has previously been used to determine the *ee* of γ-butyrolactones is by the addition of enantiopure 1-(9-anthryl)-2,2,2-trifluoroethanol (known as Pirkle's alcohol). The binding of Pirkle's alcohol through the oxygen atoms of the lactone creates diastereomeric complexes (Figure 35)[96] "causing predictable differences in shielding that occur for the two configurations of the lactone".[97] Differentiation of the diastereomeric complexes becomes possible and should be observed in both the ^{1}H and ^{13}C NMR spectra.

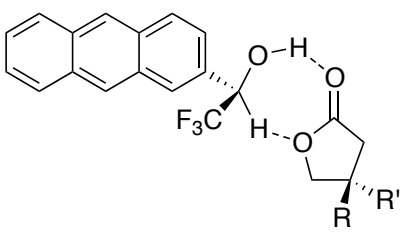


Figure 35: Binding mode of (*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol with a γ-lactone.

The addition of Pirkle's alcohol to both the racemic and enantioenriched lactone **117d** did produce a splitting of the peaks in both the ^{1}H (Figure 36) and ^{13}C NMR spectra (Figure 37). The ^{1}H NMR spectra (Figure 36, spectra b and c) show that on addition of (*R*)-Pirkle's alcohol to the γ-lactone there is splitting of the peaks, corresponding to the two diastereomeric complexes. Comparison of spectrum b (racemic **117d**) with spectrum c ('enriched' **117d**) shows that there is negligible difference indicating that there is little to no *ee* for the enriched sample. Unfortunately the peaks are not well defined enough to obtain an accurate *ee*.

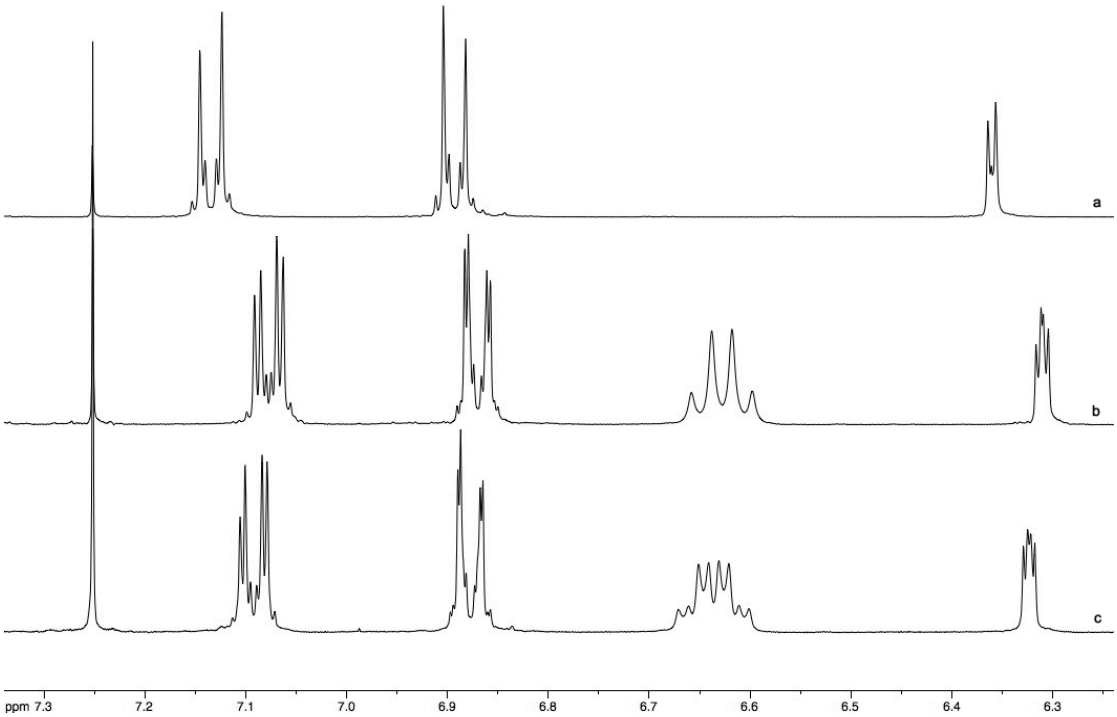


Figure 36: ^{1}H NMR spectra of: a) racemic **117d** with no additive, b) racemic **117d** with 2 eq. (*R*)-Pirkle's alcohol, c) 'enriched' **117d** with 2 eq. (*R*)-Pirkle's alcohol.

The ^{13}C NMR spectrum (Figure 37) of the enriched sample containing (*R*)-Pirkle's alcohol also induced peak splitting, but of only one peak, corresponding to the carbonyl carbon. The peaks were insufficiently separated for an accurate *ee* determination by integration.

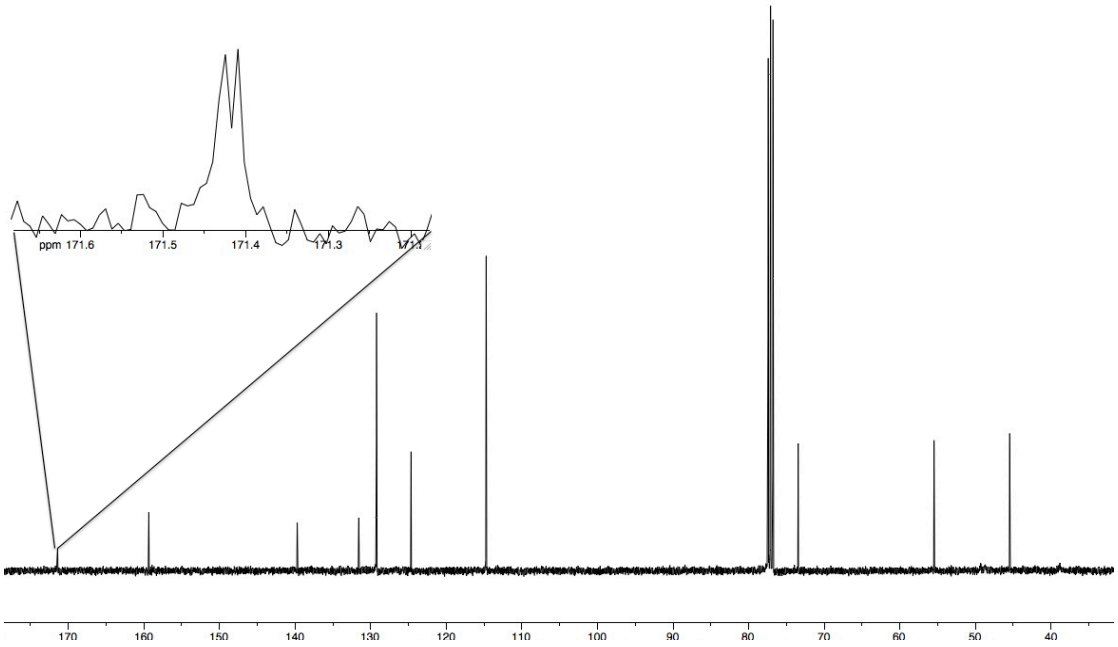


Figure 37: ^{13}C NMR spectrum of enantiomerically enriched **117d** with 2 eq. (*R*)-Pirkle's alcohol.

Despite the good yield with the chiral Rh(II) carboxylate catalyst it appears that there is little to no *ee* imparted. Further work with alternative catalysts, for example the *N*-phthaloyl-protected, amino acid-derived rhodium(II) carboxylates used by Ikegami,[70] e.g. Rh_2(*S*-PTPA)$_4$ may be required to induce any enantioselectivity. However, a prerequisite to any further studies is an effective method for the determination of *ee*.

2.5 Synthesis of biologically relevant α-methylene-γ-butyrolactones

One of the principal aims of this project was to apply use the one-pot Rh(II)-catalysed C–H insertion/HWE olefination methodology as a platform to generate products with a relatively high level of complexity from simple, readily accessible starting materials. The total synthesis of two natural products, cedarmycins A and B, as well as a bioactive MRSA inhibitor is described.

2.5.1. (±) Cedarmycins A and B

Two related antibiotics, cedarmycins A and B, **189** and **190** (Figure 38) were identified in 2001 by Furumai *et al*. after isolation from a cultured broth of the genus *Streptomyces* strain TP-A0456.[98] The butyrolactone metabolites were isolated from the plant of *Cryptomeria Japonica* (Japanese cedar) in Toyama, Japan. The group's biological studies centred on comparisons to the well-known antifungal drug amphotericin B **191**,[99] also isolated from *Streptomyces*. They discovered that both cedarmycins exhibited their most potent activity against *Candida glabrata*, a yeast strain, with cedarmycin A in particular showing similar activity to amphotericin B (MIC = 0.40 μg/mL). Both compounds also exhibited weak activity against a broad range of other bacteria and yeasts.

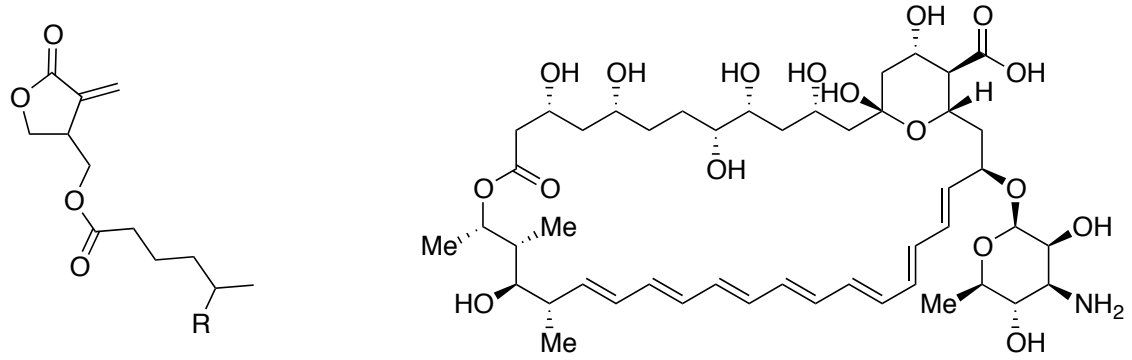


Figure 38: Structure of cedarmycins A and B and amphotericin B.

The structures of cedarmycins A and B were elucidated with typical spectroscopic techniques; both natural products were found to possess a specific rotation, yet the absolute configuration of both compounds were not determined.

Prior to this research there are no published works reporting the synthesis of cedarmycin A **189** and to date there has been only one published synthesis of cedarmycin B **190**, by Xu *et al*. in 2009.[100] Their route focused on the use of an intermolecular Barbier reaction to install the primary alcohol

functionality in compound **194**, which can undergo a simple acylation to directly afford cedarmycin B **190** (Figure 39).

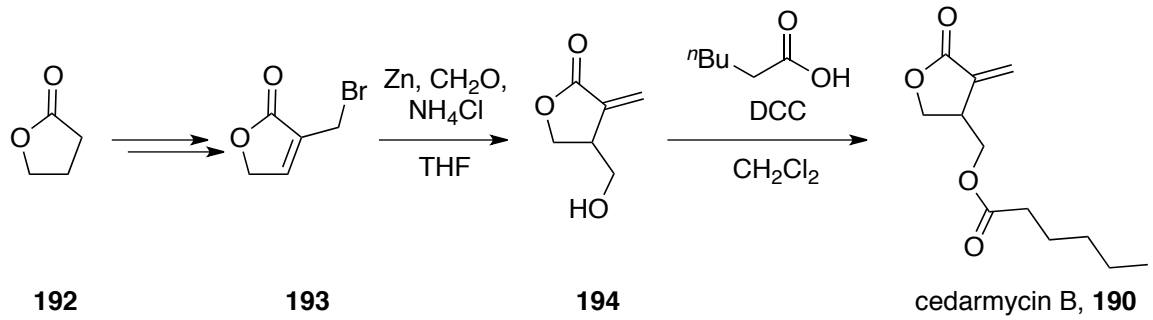


Figure 39: Xu's synthesis of (±)-cedarmycin B.

At 7 steps and 8% overall yield the route is relatively concise, but a lot of manipulation is required to install relatively simple functional groups. Furthermore, given the simplicity of the final step, *O*-acylation, it seemed unusual for the group not to have synthesised cedarmycin A also.

2.5.1.1. Synthesis of (±)-cedarmycins A and B

The synthesis of both cedarmycins A and B seemed attainable using the one-pot C–H insertion/olefination methodology, requiring C–H insertion into a methylene site with no apparent chemoselectivity issues. The retrosynthetic analysis of cedarmycins A and B (Figure 40) shows that the substrates should be readily accessible starting from propane-1,3-diol, and so the planned route to cedarmycins A and B using the novel one-pot C–H insertion/olefination methodology should be shorter than the original synthesis completed by Xu.

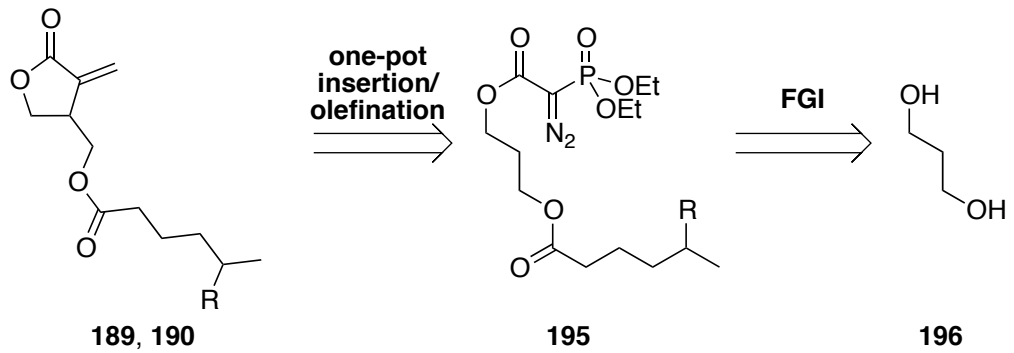


Figure 40: Retrosynthetic analysis of cedarmycins A and B.

First, mono-acetylation of propane-1,3,diol **196** furnished alcohol **197**, which under the standard T3P coupling conditions afforded phosphonate **198** (Figure 41).

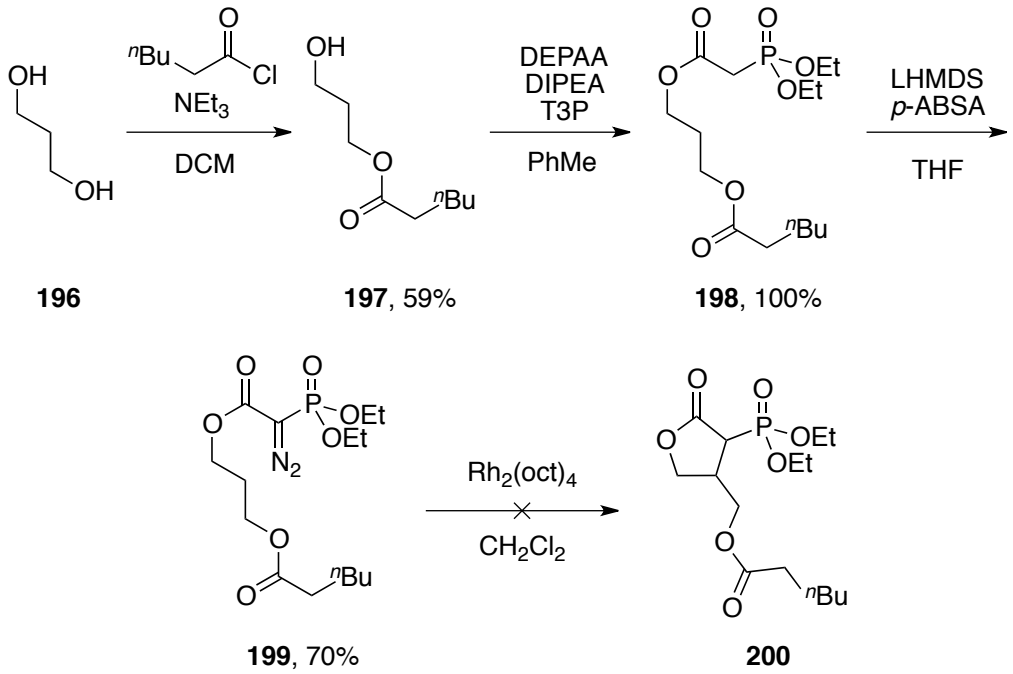


Figure 41: Attempted direct synthesis of cedarymcin B by C–H insertion.

Diazotisation generated diazo compound **199** in 41% yield over 3 steps. However, on treatment with $Rh_2(oct)_4$, decomposition of the diazo starting material occurred based on TLC analysis, but the desired C–H insertion to generate product **200** did not take place. A complex mixture of decomposition products was observed. The methodology studies showed that the insertion reaction is tolerant to many functional groups, but it appears in this case that the presence of an ester α to the insertion site may have a detrimental effect, possibly by coordination of the oxygen lone pair to the carbenoid centre.[101]

The above failed attempt to synthesise cedarmycin B led to a reconsideration of the route, instead necessitating a late stage installation of the hexanoyl functionality. This method would require prior protection of the alcohol functionality in order for the C–H insertion step to take place.

During the methodology studies into the one-pot C–H insertion/olefination sequence, TBS-protected lactone **138c** was successfully synthesised in 18% yield, alongside the β-lactone **138d** in 16% yield (Table 6, Entry 1). Nevertheless, the regioisomers were separable by column chromatography, and thus γ-lactone **138c** was taken forward for the synthesis of cedarmycins A and B (Figure 42).

Treatment of lactone **138c** with TBAF furnished known alcohol **194** in good yield with the Michael acceptor still intact. To conclude, treatment of the alcohol with the corresponding acid chlorides provided (±)-cedarmycins A **189** and B **190** in good yields. The observed spectroscopic data were

in full accord with those reported in the isolation publication (see Appendix I for comparison tables and spectra).[98] This represents the first reported synthesis of (±)-cedarmycin A **189**.

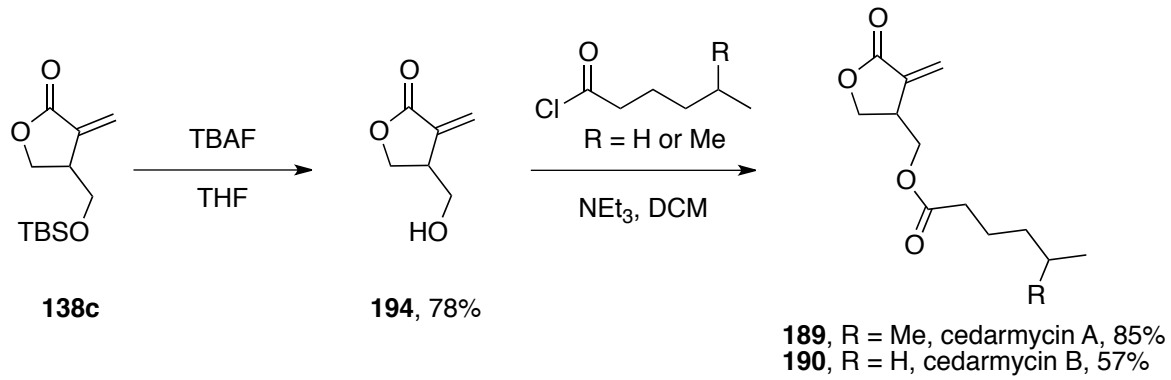


Figure 42: Synthesis of (±)-cedarmycins A and B.

These total syntheses have highlighted some limitations of the C–H insertion methodology. The presence of ester functionality as well as steric hindrance in proximity to the reactive carbenoid centre has been shown to be detrimental, leading to competing processes. Despite the low yield and lack of selectivity in the C–H insertion steps, the overall route is marginally shorter than that previously reported.

2.5.2. Staphylococcus aureus (MRSA) virulence inhibitors

In 2014 Sieber *et al*. identified a collection of α-methylene-γ-butyrolactones (Figure 43) which possess significant activity against methicillin-resistant *Staphylococcus aureus* (MRSA);[102] a lack of novel and effective antibiotics as well as rising concerns about the 'antibiotic apocalypse' due to multidrug resistant bacteria were cited as reasons behind their research. They reasoned that bacterial growth could be attenuated by targeting virulence factors contributing to the growth of the bacteria. One such virulence factor is a protein called α-hemolysin, a toxin released by the *Staphylococcus aureus* bacterium.

As is most commonly the case, the reactivity of the α-methylene-γ-butryolactone stems from the α,β-unsaturated ester functional group reacting with cysteine residues in proteins. The modification of these residues in DNA binding proteins reduced their DNA affinity, hindering the transcription of α-hemolysin. The compounds were also found to reduce the invasion efficiency of the bacterium. The four compounds shown in Figure 43 were tested against *S. aureus* strains. Compounds **203** and **204** exhibited IC_{50} values for hemolytic activity of 4 μM and 2 μM, respectively.

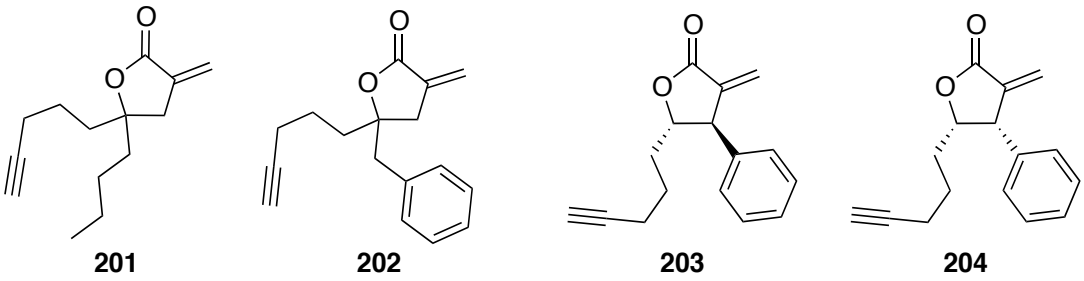


Figure 43: α-Methylene-γ-butyrolactones screened for inhibition of *S. aureus*.

The α-methylene-γ-butyrolactones were designed with the same core structure with differing side chains but all possessing terminal alkynes for later modification in order to be identified in protein profiling studies (by click chemistry with functionalised azides). Sieber's route focused on the use of a Reformatsky reaction to directly afford the α-methylene-γ-butyrolactone moiety. The route began with a Wittig olefination with benzaldehyde to generate α,β-unsaturated ester **206**, followed by an allylic bromination affording the Reformatsky precursor **207**. Treatment of compound **207** with zinc and 5-hexynal delivered diastereomeric lactones **203** and **204**.

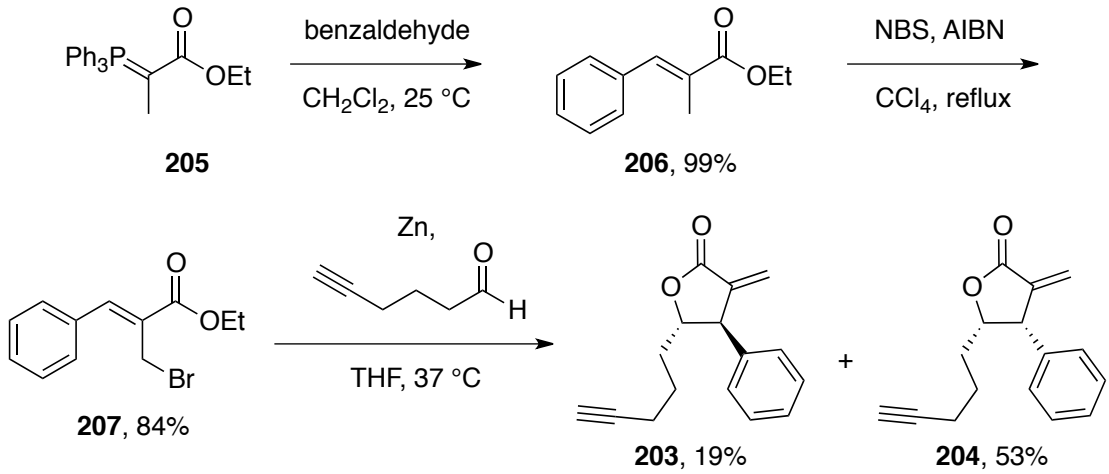


Figure 44: Sieber's synthesis of α-methylene-γ-butyrolactone MRSA inhibitors.

Lactone **203** was identified as a suitable target for the one-pot C–H insertion/olefination methodology, with retrosynthetic analysis shown in Figure 45. The *trans*-diastereomer **203** was expected to be favoured, but accompanying formation of *cis*-diastereomer **204** could be expected based on earlier results. The other targets identified in the studies, lactones **201** and **202**, were deemed unsuitable for the one-pot C–H insertion/olefination methodology as they would require selective C–H insertion into a primary site over two secondary sites.

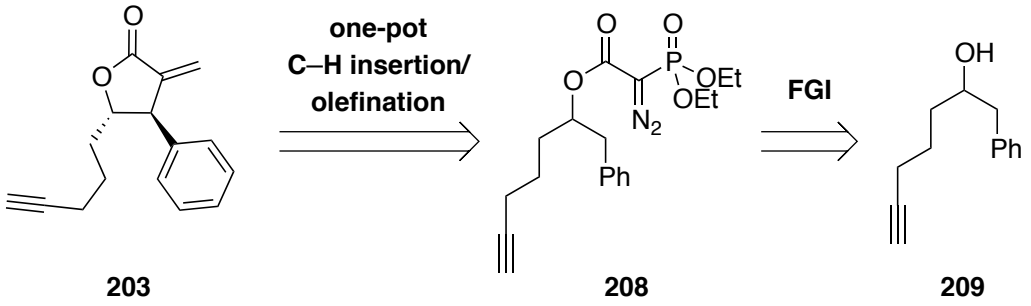


Figure 45: Retrosynthetic analysis of MRSA virulence inhibitor **203**.

Whilst the one-pot conditions were expected to work well on substrate **208** based on observations from the methodology scoping studies, it did present a regioselectivity issue. There are two possible C–H insertion sites β to the oxygen but it was expected that the desired insertion site, the benzylic position, would be favoured over the non-benzylic site due to greater stabilisation of positive charge in the transition state.

The synthesis began with the formation of Weinreb amide **211** from commercial acid **210**, followed by addition of a single equivalent of benzylmagnesium chloride to generate ketone **212**. Sodium borohydride reduction to the alcohol **209** followed by the customary acylation and diazotization procedures furnished α-diazo(diethoxyphosphoryl)acetate **208** in excellent yield. This was then

reacted under the standard one-pot C–H insertion/olefination conditions. As anticipated, the reaction yielded the desired α-methylene-γ-butyrolactone **203** along with the undesired regioisomer **214**, in 49% and 19% yields, respectively. Notably, the reaction was diastereoselective for the *trans*-isomer **203**. During the biological studies by Seiber the *trans*-lactone **203** was found to be markedly more potent for the inhibition of *S. aureus* than the *cis*-isomer **204**. The observed spectroscopic data were in full accord with those reported by Sieber.[102]

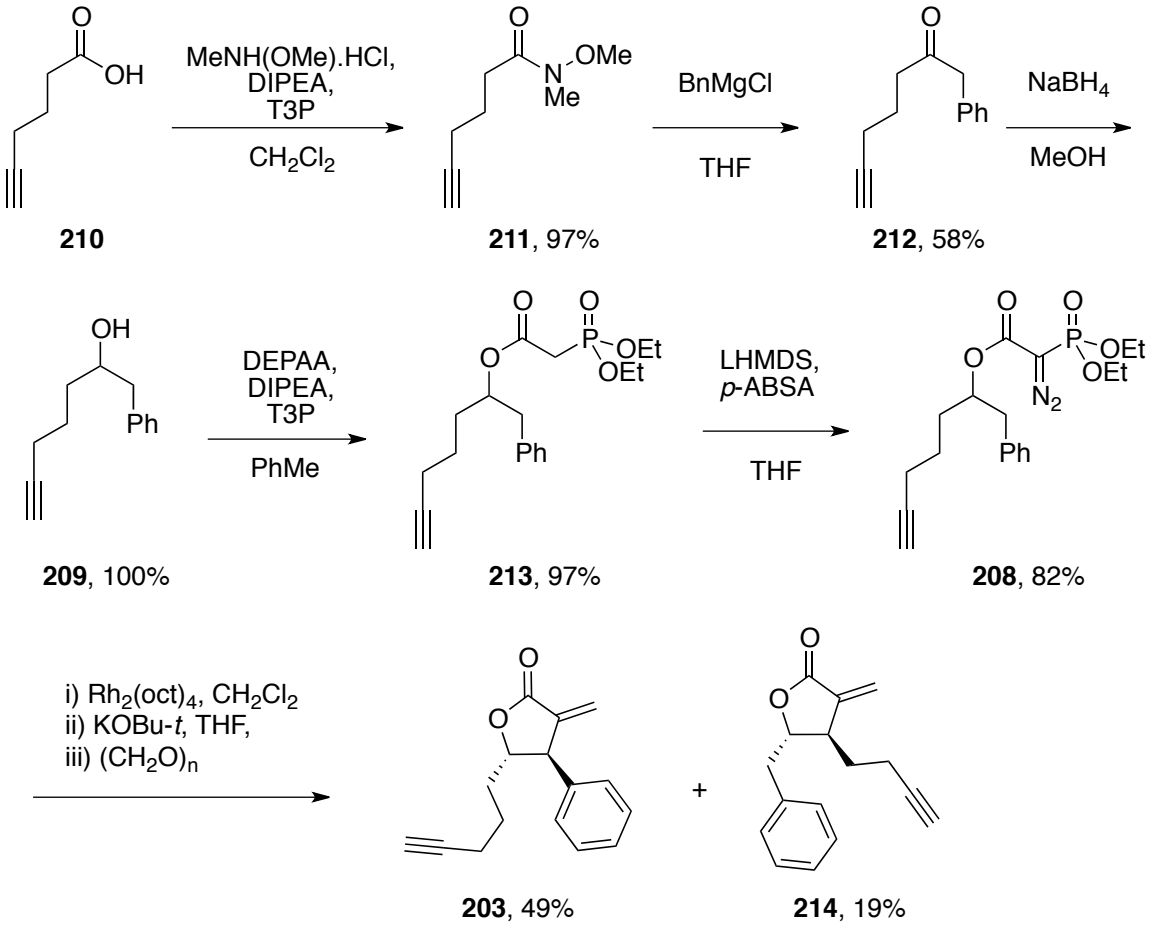


Figure 46: Synthesis of *S. aureus* inhibitor **203**.

2.6 Conclusion

A one-pot procedure for the efficient conversion of α-diazophosphonoacetates into α-methylene-γ-butyrolactones has been developed. The transformation incorporates a C–H insertion reaction of otherwise inert C–H bonds for the selective formation of γ-lactones. A subsequent Horner–Wadsworth–Emmons olefination concludes the one-pot process, circumventing the need to isolate and purify the intermediate α-phosphonolactone. A variety of α-methylene-γ-butyrolactones have been synthesised, having explored the effects of electronic and steric modifications. Excellent yields were obtained for insertion into both benzylic and non-stabilised C–H bonds, with the almost exclusive formation of γ-lactone products. The reaction was extended to the use of aldehydes other than formaldehyde, enabling the synthesis of α-alkylidene-γ-butyrolactones.

It is anticipated that this methodology will be of significant value to the synthetic community. The one-pot C–H insertion/olefination sequence is a highly selective process, reacting with C–H bonds typically considered unreactive, generating α-methylene-γ-butyrolactones in excellent yields. Additionally, the requisite α-diazophosphonoacetate functional group can be readily installed in just two steps from alcohols by way of a T3P-mediated esterification and Regitz diazo transfer reaction, enabling the efficient synthesis of substrates. The use of just 2 mol% of $Rh_2(oct)_4$ and broad substrate scope make the methodology attractive for wide-spread implementation in natural product and small molecule synthesis.

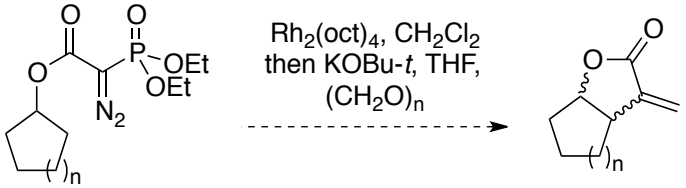
The methodology was applied to the synthesis of two antibacterial natural products, (±)-cedarmycins A and B, the former of which is the first reported synthesis. Additionally, a *Staphylococcus aureus* inhibitor was successfully synthesised in an efficient sequence, with complete *trans*-diastereoselectivity.

Selected research described in this Chapter is contained within published articles (see Appendix III and IV).[103]

Chapter 3 – Synthesis of conformationally restricted α-methylene-γ-butyrolactones

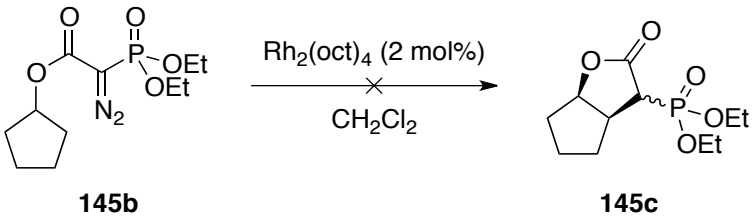
3.1 Introduction

Following the successful C–H insertion reactions of a variety of non-stabilised aliphatic α-diazo(diethoxyphosphoryl)acetates, the methodology was extended to bicyclic lactones. These systems are amongst the most important in relation to naturally occurring compounds; sesquiterpene lactones, as discussed earlier, are the largest family of naturally occurring α-methylene-γ-butyrolactone natural products. All of the sesquiterpene sub-classes are cyclic, comprising 5,5-, 6,5-, or 7,5-fused bicyclic lactone frameworks. As such, simple cycloalkanol systems were prepared in order to examine the potential of the one-pot C–H insertion/olefination methodology for the synthesis of bicyclic α-methylene-γ-butyrolactones. The diazo derivatives of cyclopentanol **145b**, cyclohexanol **146b** and cycloheptanol **147b**, were expected to deliver the 5,5-, 6,5-, and 7,5-, fused bicyclic lactones, respectively (Scheme 44).



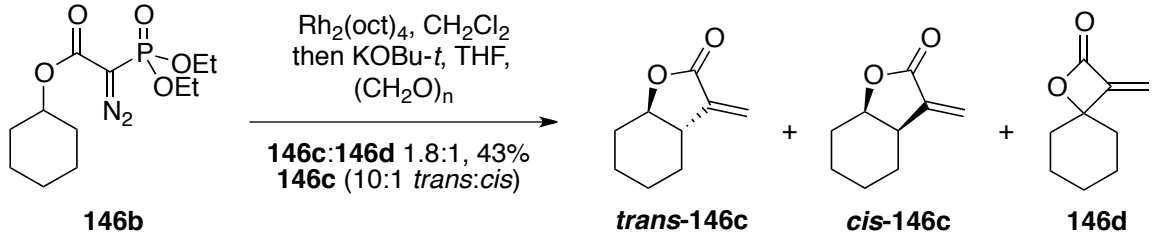
Scheme 44: Proposed synthesis of bicyclic α-methylene-γ-butyrolactones using the one-pot C–H insertion/olefination sequence.

Firstly, 5-membered derivative **145b** was treated with $Rh_2(oct)_4$ (Scheme 45), but unfortunately only decomposition was observed based on TLC analysis, with no evidence for the formation of **145c**. This was unexpected given that related literature precedent saw successful C–H insertions take place, although these examples were either with α-diazo(cyclopentylmethylketo)acetates[52] or acceptor-substituted carbenoids.[104]



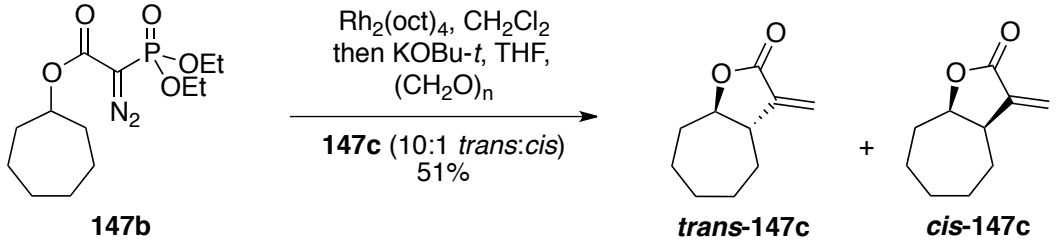
Scheme 45: Attempted C–H insertion reaction cyclopentanol derivative **145b**.

The cyclohexanol derivative **146b** performed better under the one-pot C–H insertion olefination sequence (Scheme 46), but three products were isolated; the *cis*- and *trans*-fused 5,6-bicylic lactone **146c** (10:1 *trans*:*cis*) were obtained, as well as a smaller quantity of spirocyclic β-lactone **146d**. It is unclear why the overall isolated yield is so low, but given the number of products isolated is seems likely that other undesired side-reactions are taking place. The mixture of products likely arises due to the flexible nature of the cyclohexane ring, which can undergo ring-flipping. As such, the prochiral C–H bonds become difficult to distinguish and so a mixture of C–H insertion products is observed.



Scheme 46: One-pot C–H insertion/olefination sequence for cyclohexanol derivative **146b**.

More pleasingly, the cycloheptanol derivative **147b** (Scheme 47) formed solely the γ-lactone **147c** in good yield, albeit as a mixture of isomers (3.5:1 *trans*:*cis*), which were identified by comparison with literature data.[105]



Scheme 47: One-pot C–H insertion/olefination sequence for cycloheptanol derivative **147b**.

Studies performed by Taber, Doyle and others into intramolecular C–H insertions have identified the preference for rhodium carbenoids to react with equatorially aligned C–H bonds in cyclohexane-based systems;[43,60,106] for example, menthyl α-diazoacetoacetate **215** selectively forms γ-lactone **216** when treated with $Rh_2(OAc)_4$ (Figure 47).[51] In these examples various substituent effects led to a bias towards one conformer by differentiating the axial and equatorial C–H bonds leading to high levels of diastereoselectivity. One reason cited for the equatorial selectivity of the insertion reaction is steric effects; axial C–H insertion would invoke unfavourable 1,3-diaxial interactions.[107]

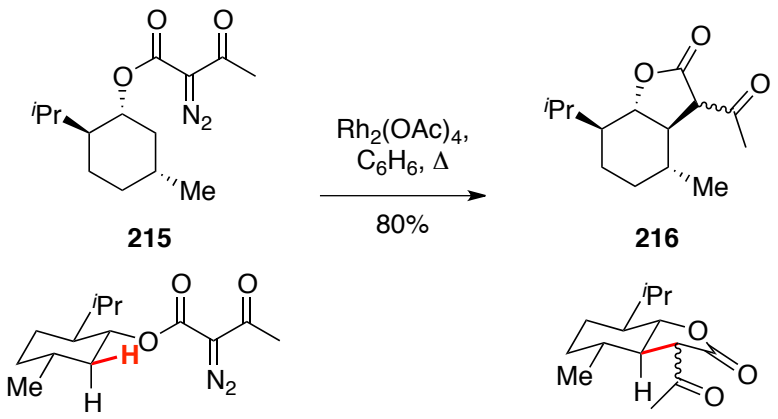
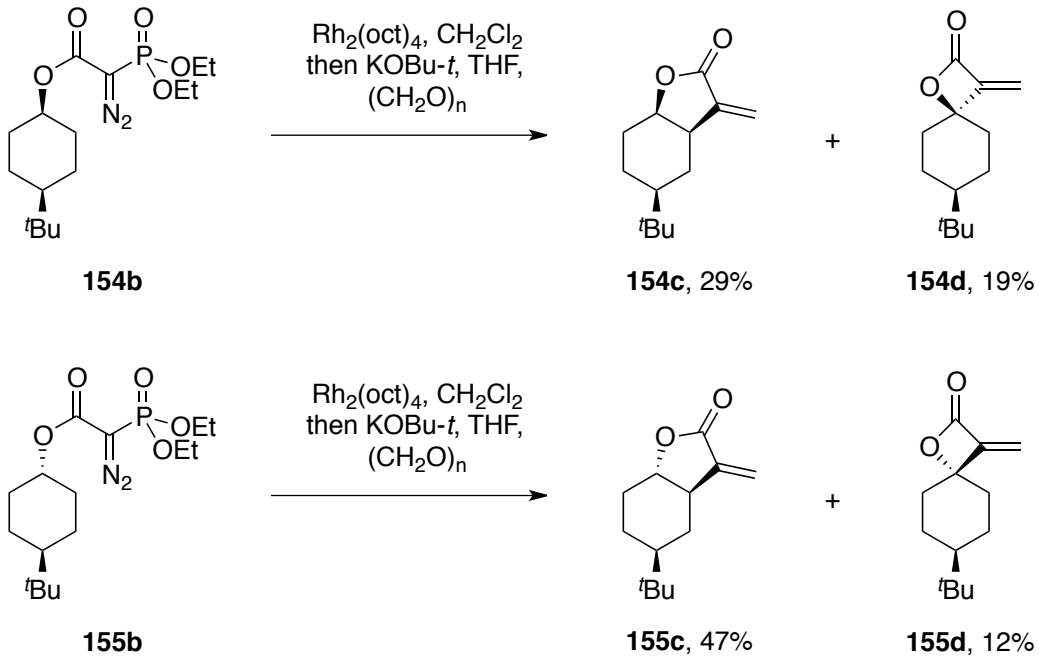


Figure 47: Doyle's diastereoselective intramolecular equatorial C–H insertion.[51]

3.2 Conformationally restricted α-diazo(diethoxyphosphoryl)acetates

This observed selectivity led to a re-examination of cyclohexanol-derived systems. It was anticipated that simply restricting the conformation of the cyclohexane ring by substitution with so-called locking groups would distinguish the C–H insertion sites and deliver diastereoselective reactions with fewer by-products and improved yields. The 6-membered systems were selected, given the preference for chair conformations. As such, a series of *tert*-butyl cyclohexanol derivatives were prepared and subjected to the standard one-pot C–H insertion/olefination sequence.

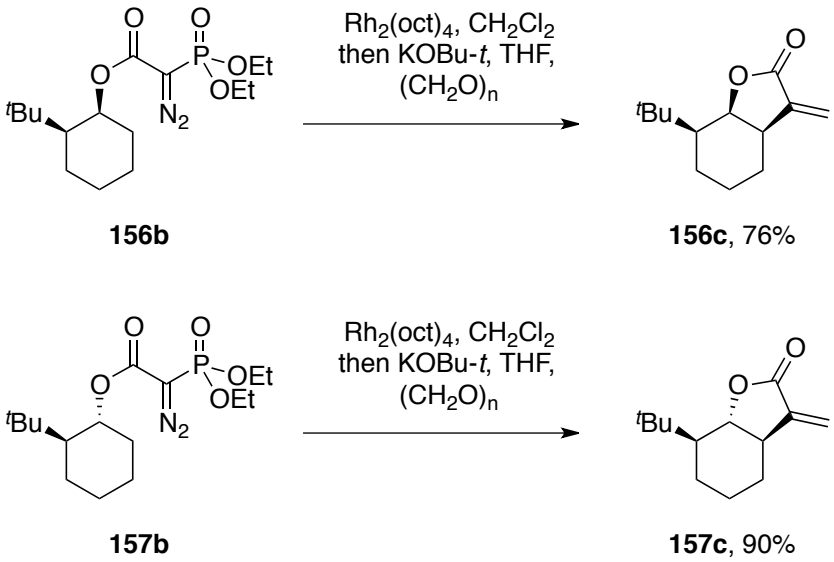
Firstly, the 4-*tert*-butyl-cyclohexanol systems **154b** and **155b** were prepared. The functionalised tether in *syn*-diazo compound **154b** is fixed in an axial orientation meaning that only equatorial C–H insertion is possible, whereas for *anti*-diazo compound **155b** the pendant functional group is equatorial with the potential for both axial and equatorial C–H insertion, and therefore chemoselectivity. Each substrate was subjected to the standard one-pot sequence and two products were identified in each case; a γ- and β-lactone (Scheme 48). As hoped, each γ-lactone, **154c** and **155c**, was identified as resulting solely from equatorial C–H insertion. The concurrent formation of separable β-lactones **154d** and **155d** was disappointing, however, the overall isolated yields were moderately improved compared to the unsubstituted cyclohexane systems.



Scheme 48: One-pot C–H insertion/olefination sequence for 4-*tert*-butyl-cyclohexanol derivatives **154b** and **155b**.

The earlier studies demonstrated that steric effects could have a profound influence on the selectivity of the C–H insertion reactions often leading to different product distributions. It was postulated that by bringing the *tert*-butyl group closer to the pendant functional group (and C–H insertion site) the unwanted β-lactone formation might be disfavoured. As a consequence the 2-*tert*-butyl-cyclohexanol derivatives **156b** and **157b** were prepared and treated under the standard one-pot C–H insertion/olefination conditions (Scheme 49).

Gratifyingly, a single product was observed from the reaction of each diazo compound; the γ-lactones derived from equatorial C–H insertion, **156c** and **157c**, respectively, were obtained in excellent yields. Neither of the corresponding β-lactones were observed. In these cases the benefit of the *tert*-butyl group appears to be twofold: locking the conformation of the cyclohexane ring and providing a steric barrier to competing β-lactone formation.



156b **156c**, 76%

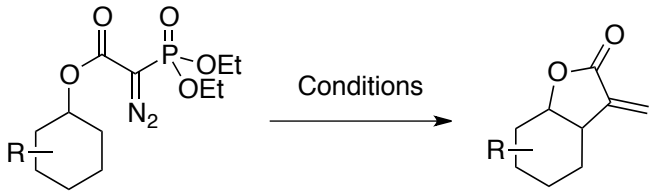
157b **157c**, 90%

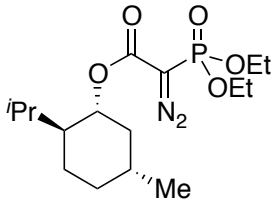
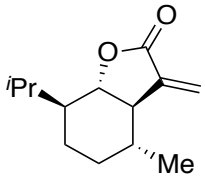
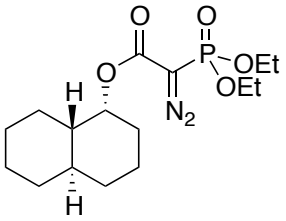
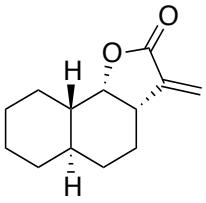
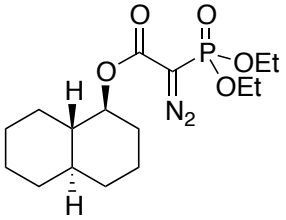
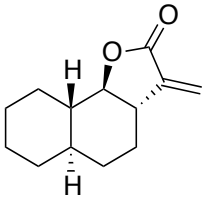
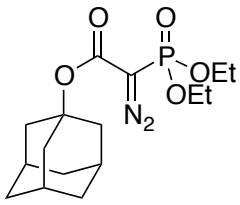
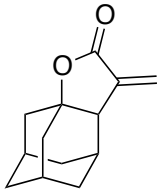
Scheme 49: One-pot C–H insertion/olefination sequence for 2-*tert*-butyl-cyclohexanol derivatives **156b** and **157b**.

This steric effect was then further examined by the preparation of additional diazo substrates derived from menthol and decalinol, each possessing substitution in the 2-position (Table 7). Menthol derivative **158b** delivered the desired diastereomer, lactone **158c**, in good yield when subject to the one-pot conditions. Similarly the two *trans*-decalinol derivatives, **159b** and **160b** afforded their corresponding γ-equatorial C–H insertion products **159c** and **160c**, respectively, again in good yield. As a final example adamantane-derived diazo compound **161b** was synthesised and when treated under the standard one-pot conditions delivered the γ-lactone **161c**, the only possible product, in excellent yield.

From these results it became apparent that restricted conformation was an important feature for diastereoselective intramolecular C–H insertions, with steric influences playing a significant role in minimising competing β-lactone formation. The above examples illustrated that substitution in the 2-positon, relative to the pendant functional group, disfavoured β-lactone formation. As an extension, substitution at the 3-position was investigated to discover the degree to which steric effects play a role.

Table 7: One-pot C–H insertion/olefination sequence for conformationally restricted cyclohexyl α-diazo(diethoxyphosphoryl)acetates.

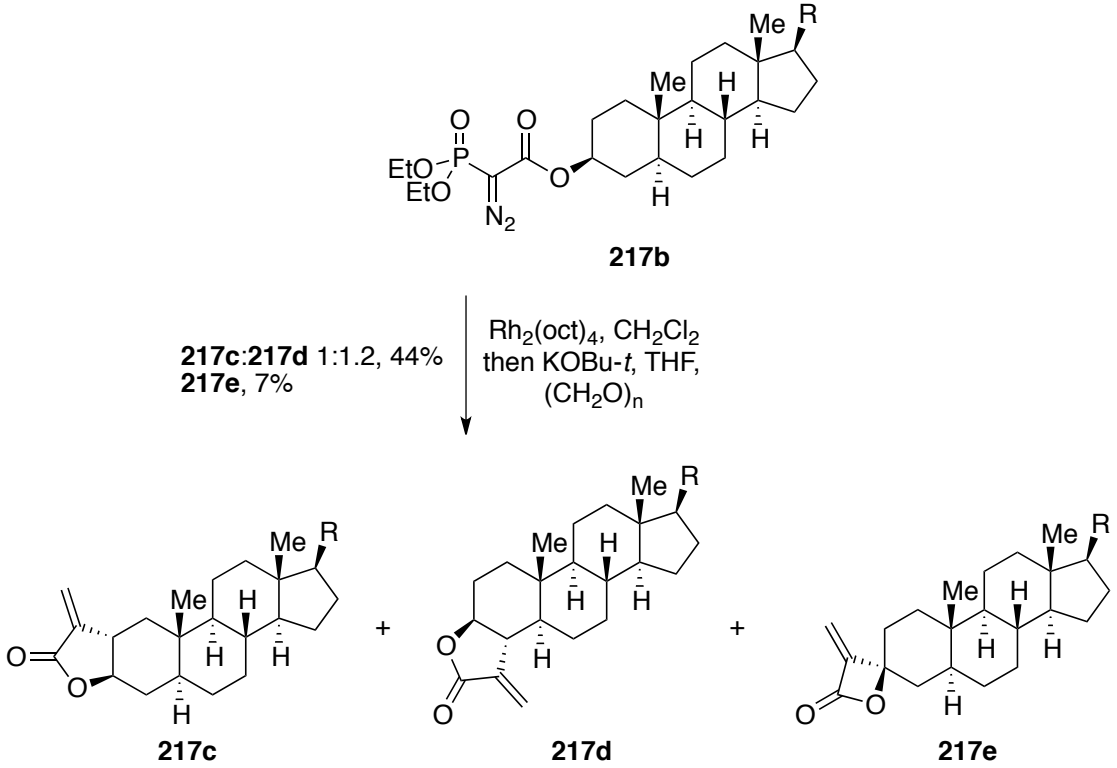


Entry	Diazo Compound	Product	Isolated Yield, %
1	 **158b**	 **158c**	73
2	 **159b**	 **159c**	68
3	 **160b**	 **160c**	64
4	 **161b**	 **161c**	79

Conditions: (i) $Rh_2(oct)_4$ (2 mol %), CH_2Cl_2, 45 °C, 20 h; (ii) Remove CH_2Cl_2 *in vacuo*, add THF, KOBu-*t* (1.2 or 1.5 equiv.), 0 to −78 °C; (iii) $(CH_2O)_n$ (2 equiv.), −78 °C to RT.

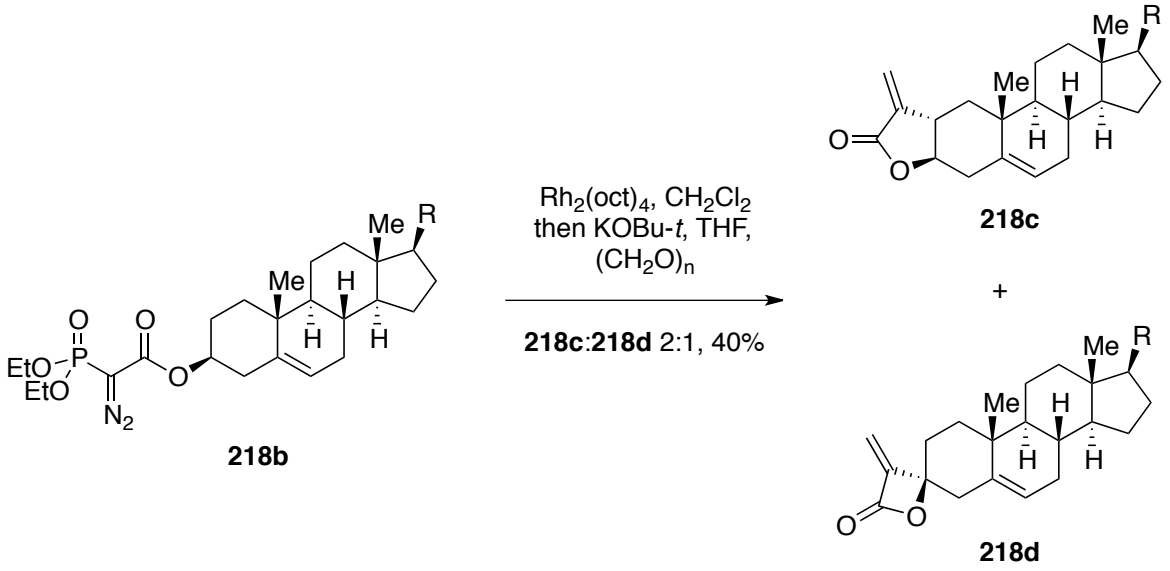
3.2.1. Steroidal α-diazo(diethoxyphosphoryl)acetates

Next, in order to further explore synthetic potential, a series of steroid-derived diazo compounds were prepared and subjected to the standard one-pot C–H insertion/olefination conditions. Firstly, cholestanol derivative **217b** led to a mixture of three products; an inseperable mixture of γ-lactones **217c** and **217d**, each arising from equatorial C–H insertion and β-lactone **217e**, which was separable from the γ-lactones (Scheme 50). Despite the lack of regioselectivity, this result demonstrated that substitution as remote as the 3-position (relative to the functionalised tether) is insufficient to fully impede β-lactone formation.



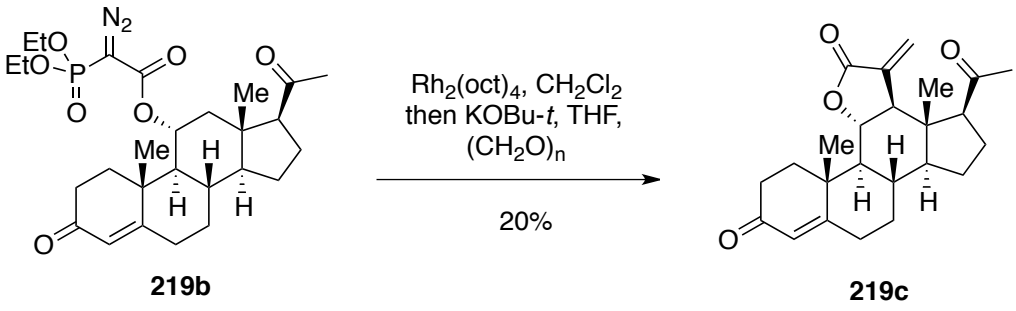
Scheme 50: One-pot C–H insertion/olefination sequence for cholestanol derivative **217b**. R = (*R*)-6-methylheptan-2-yl.

Similarly, the cholesterol-derived system **218b** (Scheme 51), delivered a small amount of the undesired β-lactone **218d**, but a single, separable γ-lactone product **218c** was obtained. These observations correspond to similar investigations performed by Doyle with cholestanol and cholesterol derivatives,[106b] but no explanation was provided on the formation of a single γ-regioisomer from the cholesterol system. This result is curious in that allylic or benzylic C–H bonds are typically favoured for C–H insertion over non-stabilised C–H bonds.



Scheme 51: One-pot C–H insertion/olefination sequence for cholesterol derivative **218b**. R = (*R*)-6-methylheptan-2-yl.

To conclude, a final steroid-based system with substitution at the 2-position (relative to the functional tether) was investigated in order to reaffirm the theory regarding proximity of the steric influence in reference to β-lactone formation. The diazo compound **219b**, derived from 11α-hydroxyprogesterone, was prepared and pleasingly generated the desired pentacyclic lactone **219c** as the single product, albeit in a disappointing yield (Scheme 52). An increased temperature (65 °C) was required in order to drive the C–H insertion reaction to completion, possibly due to the extreme steric hindrance surrounding the insertion site.



Scheme 52: One-pot C–H insertion/olefination sequence for 11α-hydroxyprogesterone derivative **219b**.

In summary, by installation of appropriate functionality on the cyclohexane ring, the outcome of the one-pot C–H insertion/olefination, in terms of product distribution, stereoselectivity and yield, can be improved. The following principles were identified:

- As previously observed, restricting the conformation of the cyclohexane ring biases the C–H insertion to equatorial sites, reducing undesired reactions hence improving yields.
- Installation of a sterically hindering group in the 2-position relative to the functional tether eliminates β-lactone formation; but 3- or 4-substitution does not confer the same effect.

3.3 Applications to eudesmanolide natural product synthesis

3.3.1. Introduction

The next progression was to apply these findings to natural product targets. Sesquiterpene lactones constitute the vast majority of naturally occurring α-methylene-γ-butyrolactones.[1,6] These structures are constructed from three isoprene units and possess a variety of configurational isomers and oxidation patterns, but almost all are cyclic. As discussed earlier, these sesquiterpene lactones can be subdivided into a series of smaller classes based on their structural arrangement, one of which are known as eudesmanolides; this class is characterised by a 6,6,5-tricyclic, γ-lactone framework **220** as shown in Figure 48 alongside some examples of *trans*-annelated natural products.[108]

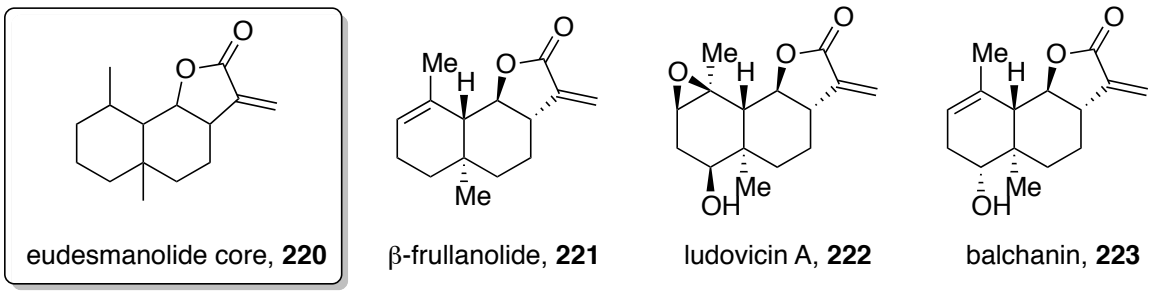
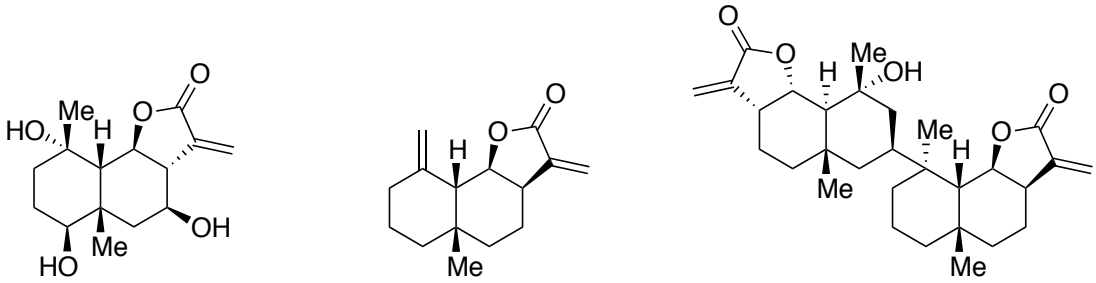


Figure 48: Eudesmanolide core framework with examples of *trans*-annelated natural products.

Eudesmanolides containing a *cis*-fused decalin core are rare but there are some examples; melanolepin B **224**,[109] eudesmadiene-12,6-olide **225**[110] and muscicolide B **226** amongst others.[111] The assignment of the *cis*-ring junction of the decalin core is ordinarily based on the ^{13}C NMR shift for the ring junction methyl group, which appears more downfield in *cis*-systems than *trans*.



melanolepin B, **224** eudesmadiene-12,6-olide, **225** muscicolide B, **226**

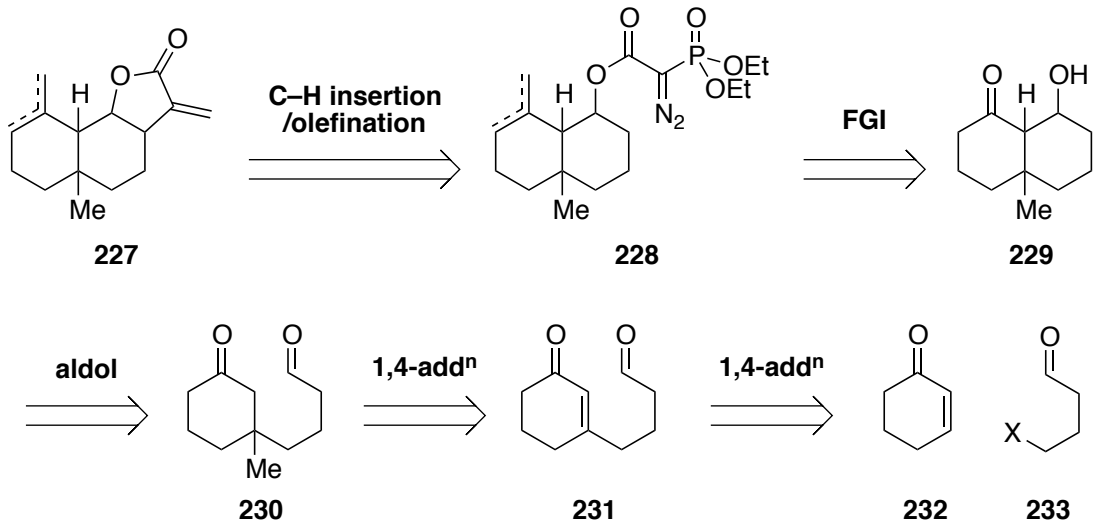
Figure 49: Examples of *cis*-annelated eudesmanolide natural products.

3.3.2. Synthesis of eudesmanolide natural product frameworks

Results from the extended methodology studies included two decalin-derived diazo compounds **159b** and **160b** (Table 7, Entries 2–3), which when subjected to the one-pot C–H insertion/olefination sequence generated the same core 6,6,5-tricyclic scaffold as eudesmanolides. As such, the possibility of utilising the one-pot C–H insertion/olefination methodology to synthesise eudesmanolide natural products was conceived.

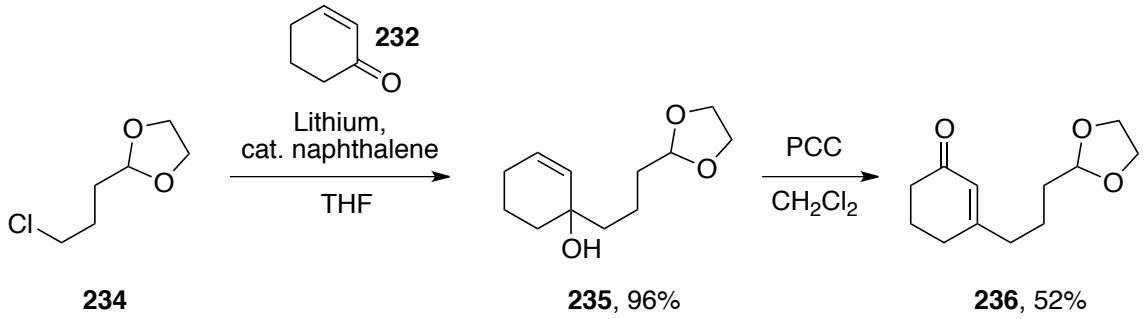
At the outset, no particular eudesmanolide natural product was targeted; instead a general approach to a *cis*- or *trans*-decalin framework, that could later be modified, was visualised. The decalin substrates, used during the earlier methodology studies, are two carbon atoms short of the eudesmanolide core. This necessitated the installation of the quaternary ring-junction methyl group, and the exocyclic carbon atom, before commencing these studies. It was anticipated that neither of these modifications would have a detrimental effect on the diastereoselectivity of the C–H insertion reaction as they will not introduce additional conformational flexibility.

The retrosynthetic strategy towards the generalised eudesmanolide **227** is shown in Scheme 53. The tricyclic eudesmanolide framework should be accessible using the one-pot C–H insertion/olefination methodology as the key step from diazo compound **228**. This will be derived from β-hydroxyketone **229** following FGI of the ketone. It is envisaged that the β-hydroxyketone **229** should be generated by intramolecular aldol addition from keto-aldehyde **230**. Installation of the quaternary methyl unit, by conjugate addition into enone **231**, will necessitate prior protection of the aldehyde functionality. The enone **231** may be derived from an overall conjugate addition of an alkyl halide **233** to readily available cyclohexenone **232**.



Scheme 53: Retrosynthetic strategy towards the generalized eudesmanolide framework **227**.

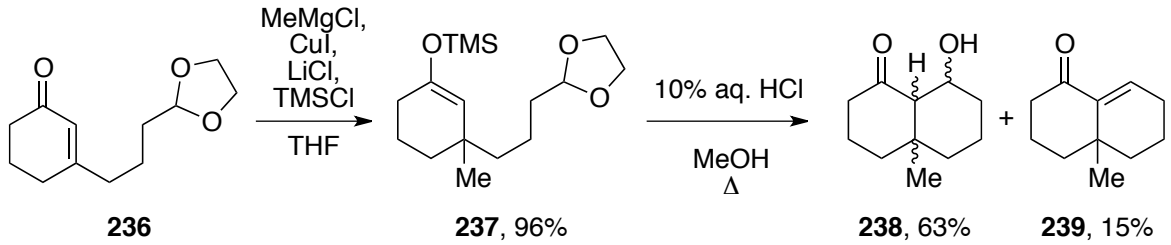
Initial efforts focussed on the synthesis of ketoaldehyde **231**, albeit with the aldehyde functionality protected as an acetal. As such, the 1,2-additon of chloride **234** to cyclohexenone **232** was attempted by formation of the Grignard reagent. Unfortunately this was met with difficulty and as an alternative, a lithium naphthalenide catalysed 1,2-addition was implemented,[112] delivering allylic alcohol **235** in near quantitative yield (Scheme 54). A subsequent PCC-mediated oxidative rearrangement furnished enone **236** in 52% yield.



Scheme 54: Synthesis of enone **236** *via* a catalytic lithium naphthalenide addition/oxidation sequence.

With enone **236** in hand, the installation of the quaternary methyl group *via* a 1,4-addition of a methyl organometallic reagent was investigated. A series of attempts were made using the traditional lower-order Gilman reagent (Me_2CuLi generated from MeLi and CuI) but unfortunately were not met with success. A procedure developed from literature precedent was applied, utilising catalytic CuI, MeMgCl and TMSCl as an *in situ* quench.[113] Pleasingly this generated the 1,4-adduct **237** in near quantitative yield with no requirement for column chromatography purification (Scheme 55). Given the high acid lability of both the silyl enol ether and acetal functionalities, substrate **237** was simply refluxed in the presence of aqueous acid in order to execute a double-

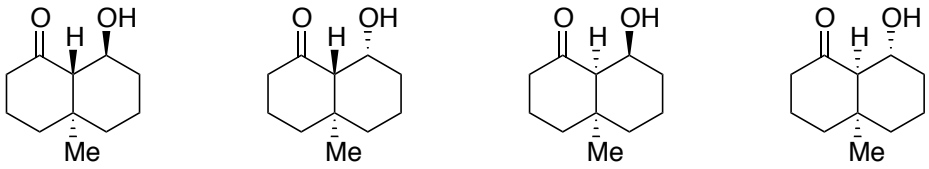
deprotection and aldol cyclisation in one step. An analogous reaction performed by Tanaka in 2001 was reported to generate a single diastereomer of β-hydroxyketone **238**, but the relative stereochemistry was not specified.[114] We were pleased to also observe the same single diastereomer of the β-hydroxyketone **238**, in addition to some of the dehydrated enone **239**, with all spectral data found to be in accord with those reported by Tanaka.



236 **237**, 96% **238**, 63% **239**, 15%

Scheme 55: Synthesis of β-hydroxyketone **238** *via* aldol cyclisation.

The spectral data of β-hydroxyketone **238** was analysed in order to identify the relative stereochemistry; with 3 stereocentres present there are 4 possible diastereomers **238a–d**, as shown in Figure 50.



238a **238b** **238c** **238d**

Figure 50: The four possible diastereomers of β-hydroxyketone **238**.

The most distinguishable feature of the ^{1}H NMR spectrum was the resonance associated with the proton β to the carbonyl: δ_H = 4.00 (1 H, app. tt, J = 10.5, J = 5.1) ppm. The two large coupling constants indicate the presence of two contiguous *trans*-diaxial proton arrangements. This can only arise from two diastereomers, **238a** and **238d**, as shown by the highlighted protons in Figure 51. The other two diastereomers can therefore be ruled out.

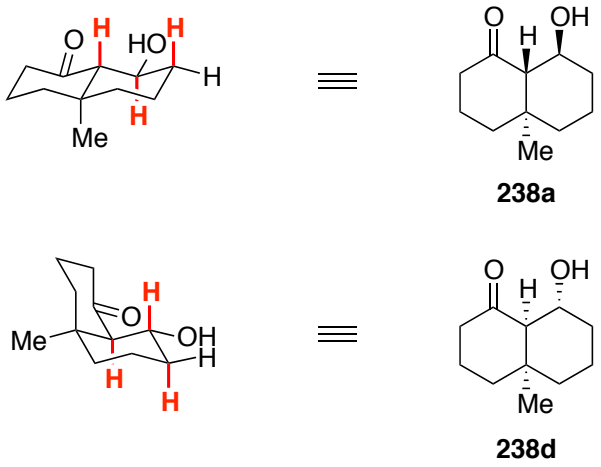
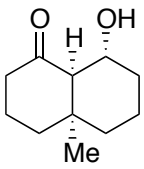


Figure 51: Comparison of β-hydroxyketone diastereomers based on ^{1}H NMR *J* values. The *trans*-diaxial arrangements are shown in red.

The differentiation of *trans*-decalin **238a** from *cis*-decalin **238d** was more challenging, but was achieved by comparing the ^{13}C NMR chemical shifts of the ring junction methyl groups, with those previously reported for related compounds.[115] *Cis*-decalins with this core structure typically generate chemical shift ca. $\delta_C \approx 27$ ppm, whereas *trans*-decalins produce a more upfield shift ca. $\delta_C \approx 17$ ppm. The observed chemical shift of this carbon is $\delta_C = 27.7$ ppm, strongly inferring a *cis*-6,6-ring junction and therefore that β-hydroxyketone **238d** is the sole product (Figure 52). This was somewhat surprising, as under the reaction conditions we expected the *trans*-decalin to predominate, on thermodynamic grounds.



238d

Key characterisation data for β-hydroxyketone 238d

^{1}H NMR: δ_{HOCH} = 4.00 (1 H, app. tt, *J* = 10.5, *J* = 5.1) ppm

^{13}C NMR: δ_{Me} = 27.7 ppm

Figure 52: Key spectroscopic data for β-hydroxyketone **238d**.

With *cis*-decalin **238d** in-hand it was decided to target eudesmanolide natural products containing the *cis*-decalin core. A literature search revealed two relatively simple compounds with the eudesmanolide core and possessing no additional oxidation. The C–H bond to be inserted using the one-pot C–H insertion/olefination procedure is in the requisite equatorial position; as such, it was hoped their synthesis could be readily accomplished. The two structures in question were isolated as part of a series of eudesmanolides reported by Dominguez *et al*. in 1985 and assigned as novel natural products morifolins A and B, **240** and **241**, respectively. However, a later publication by Herz in 2004 shed doubt upon the original assignments, instead suggesting their data were identical to that of two diastereomeric natural products that had been previously isolated by Bohlmann in

1983. Herz proposed that the structures of lactones **240** and **241** were in fact the natural products isocritonilide **242** and critonilide **243**, respectively (Figure 53).

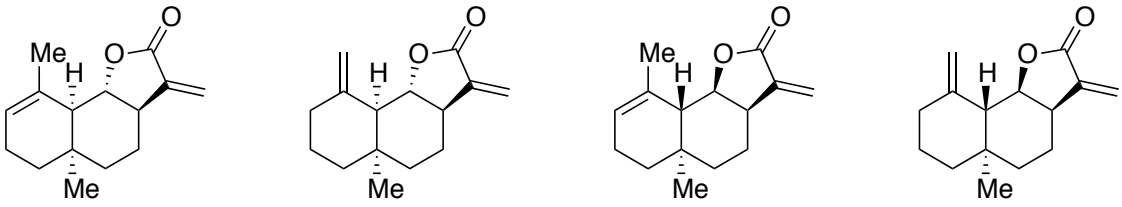
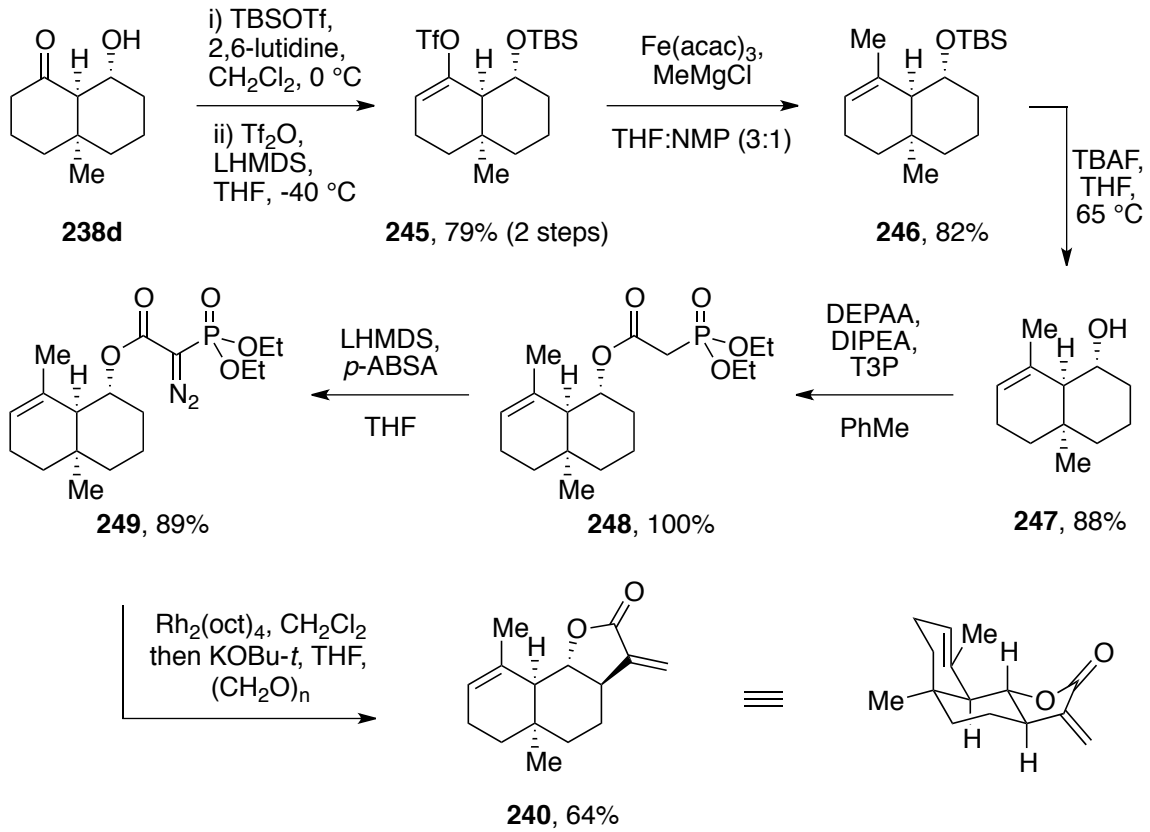


Figure 53: Assigned structures of morifolins A, B and their proposed true identities, isocritonilide and critonilide, respectively.

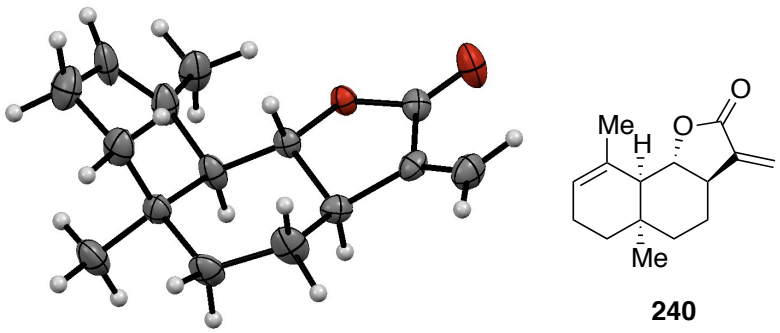
The lack of clarity over the matter stems from the insufficient data provided in the Dominguez publication, which contains partial ^{1}H NMR, IR and MS but no ^{13}C or 2D correlation NMR. Given that the one-pot C–H insertion/olefination methodology had thus far only be trialled on *trans*-decalins it was seen as an interesting opportunity to explore the applicability of *cis*-decalins whilst also clearing up confusion in the literature. As such the structures assigned to morifolins A and B, **240** and **241**, were targeted.

3.3.3. Synthesis of proposed structure of morifolin A

Morifolin A **240**, containing the endocyclic alkene was targeted first of all, beginning with silyl ether protection of β-hydroxyketone **238d**, delivering ketone **244** (not shown) which was then converted into the vinyl triflate **245** under kinetic conditions (LHMDS, Tf_2O, –40 °C) (Scheme 56). Interestingly, thermodynamic vinyl triflate-forming conditions (DTBMP, Tf_2O, RT) were unsuccessful in this case. Following literature precedent,[116] an iron-catalysed cross-coupling of vinyl triflate **245** with MeMgCl furnished the desired endocyclic alkene **246** in excellent yield. Subsequent desilylation, acylation and diazotisation proved facile, affording diazo **249** in 78% yield over 3 steps. We were now in a position to investigate the C–H insertion/olefination sequence on a cis-decalin and were delighted to observe a single product from the reaction under the standard conditions affording the desired equatorial insertion product **240** in 64% yield. In accord with the *trans*-decalin model substrates, no β-lactone or axial C–H insertion products were observed. The structure of lactone **240** was proved unambiguously following acquisition of an X-ray single crystal structure (Figure 54).



Scheme 56: Synthesis of the proposed structure of morifolin A, lactone **240**.

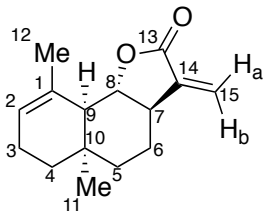


240

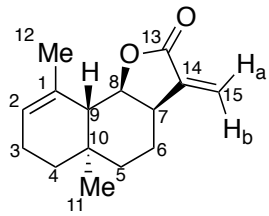
Figure 54: Single crystal X-ray structure of lactone **240** (CCDC: 1421158). Thermal ellipsoids set to 50% probability, shown in Olex2.

On comparison of the data obtained for lactone **240** with those provided by Dominguez[117] there was a discrepancy in the ^{1}H NMR data (Table 8), corroborating Herz's[118] theory that the structure assigned to morifolin A **240** was in error and that the correct structure is most likely that of isocritonilide **242**.[119] No ^{13}C NMR data were provided by Dominguez.

Table 8: Comparison of the ^{1}H NMR data ($CDCl_3$) of synthetic lactone **240**, 'isolated morifolin A' **240** and isocritonilide **242**.



240

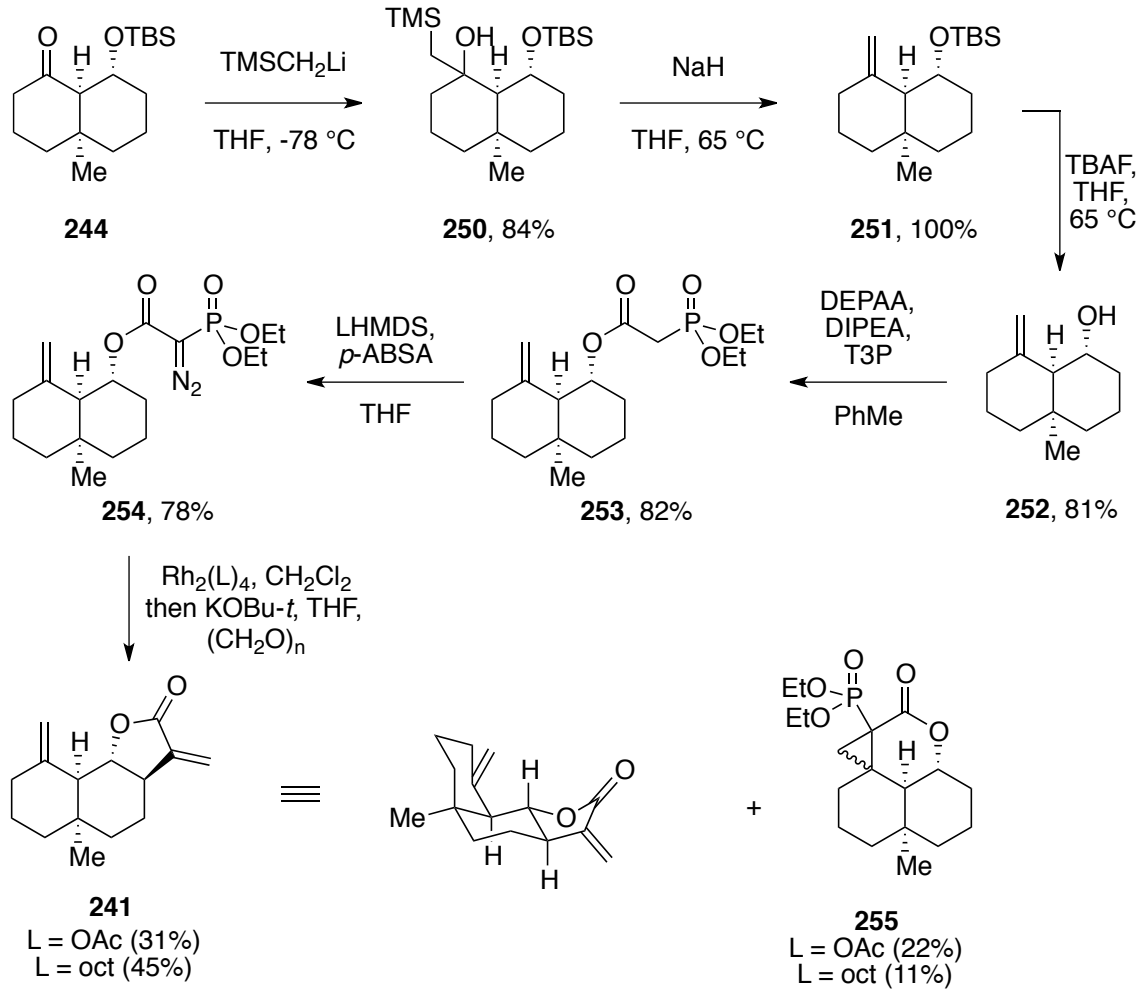


242

Assignment	Data for synthetic lactone 240 (400 MHz)	Data for 'isolated' morifolin A 240 (200 MHz)[117]	Data for isocritonilide 242 (270 MHz)[119a]
11	0.98 (4 H, m)	0.82 (3 H, s)	0.86 (3 H, s)
12	1.83–1.86 (4 H, m)	1.81 (3 H, s)	1.85 (3 H, s)
7	2.45–2.53 (1 H, m)	3.24 (1 H, m)	3.28 (1 H, ddddd, J = 7.5, J = 5.0, J = 3.5, J = 3.5, J = 3.0)
8	3.73 (1 H, app. t, J = 10.9)	4.58 (1 H, dd, J = 11.2, J = 11.0)	4.61 (1 H, dd, J = 11.0, J = 7.5)
2	5.39–5.43 (1 H, m)	5.38 (1 H, m)	5.42 (1 H, br. s)
15b	5.39 (1 H, d, J = 3.1)	5.50 (1 H, d, J = 3.2)	5.53 (1 H, d, J = 3.5)
15a	6.06 (1 H, d, J = 3.3)	6.25 (1 H, d, J = 3.5)	6.28 (1 H, d, J = 3.5)

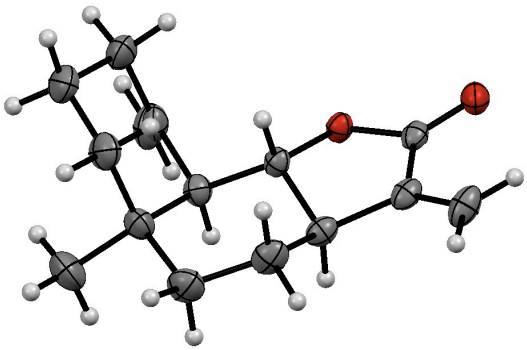
3.3.4. Synthesis of proposed structure of morifolin B

The synthesis of the *exo*-methylene analogue morifolin B **241** commenced with common precursor ketone **244** (Scheme 57). Its treatment with (trimethylsilyl)methyl lithium cleanly afforded 1,2-adduct **250** before a base-mediated Peterson olefination generated exocyclic alkene **251**. Again, desilylation, acylation and diazotisation were performed without complication, delivering the key diazo compound **254** in 52% yield over 3 steps. Upon submission to the standard one-pot C–H insertion/olefination sequence, the desired γ-lactone **256** was synthesised with complete regio- and diastereoselectivity, albeit in a disappointing 31% yield. Isolation of cyclopropanation side-product **255**, resulting from the proximity of the alkene to the pendant carbenoid, in 22% yield provided some explanation for the relatively low yield of γ-lactone **241**. Interestingly, we found that by changing the catalyst to the less-bulky $Rh_2(OAc)_4$, the yield of γ-lactone **241** could be improved to 45%, with just 11% of the cyclopropane side-product **255**.



Scheme 57: Synthesis of the proposed structure of morifolin B, lactone **241**.

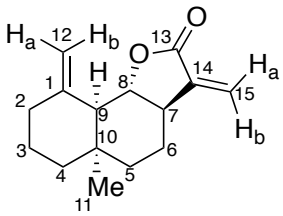
The ^{1}H NMR data for lactone **241** conflicted with those of morifolin B provided by Dominguez (Table 9).[117] Again, the acquisition of a single crystal X-ray structure (Figure 55) unambiguously proved the identity of lactone **241**, thus indicating that the structure assigned to morifolin B was in error and that the true structure is likely that of critonilide **243**,[119] as proposed by Herz.[118] No ^{13}C NMR data were provided by Dominguez.



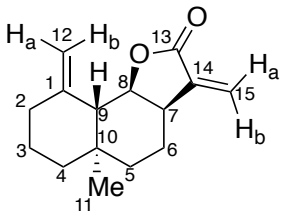
241

Figure 55: Single crystal X-ray structure of lactone **241** (CCDC: 1421154). Thermal ellipsoids set to 50% probability, shown in Olex2.

Table 9: Comparison of the ^{1}H NMR data ($CDCl_3$) of synthetic lactone **241**, 'isolated morifolin B' **241** and critonilide **243**.



241



243

Assignment	Data for synthetic lactone 241 (400 MHz)	Data for 'isolated' morifolin B 241 (200 MHz)[117]	Data for critonilide 243 (270 MHz)[119a]
11	1.00 (3 H, s)	0.75 (3 H, s)	0.79 (3 H, s)
9	2.09–2.23 (3 H, m)	1.63 (1 H, d, J = 11.2)	1.67 (1 H, br. d, J = 11.0)
8	4.11 (1 H, app. t, J 11.1)	4.77 (1 H, dd, J = 11.2, J = 10.3)	4.81 (1 H, dd, J = 11.0, J = 7.5)
7	2.45 (1 H, app. tq, J 11.1, J 3.2)	3.24 (1 H, m)	3.28 (1 H, ddddd, J = 7.5, J = 5.0, J = 3.5, J = 3.5, J = 3.0)
12a	4.80 (1 H, app. t, J 1.8)	4.75 (1 H, d, J = 1.0)	4.79 (1 H, br. s)
12b	4.88 (1 H, app. t, J 2.0)	4.91 (1 H, d, J = 1.0)	4.95 (1 H, br. s)

3.3.5. Synthesis of α-Cyclocostunolide

Following the synthesis of lactones **240** and **241**, attention returned to the synthesis of a *trans*-decalin derived natural product *via* the same methodology. Two simple examples, α- and β-cyclocostunolide **256** and **257**, respectively, each possess a *trans*-decalin core (Figure 56). Additonally, the C–C bond that would be formed using the one-pot C–H insertion/olefination sequence is equatorially aligned in each compound, therefore suitable for the methodology. β-Cyclocostunolide **257** contains the exocyclic alkene functionality that introduced chemoselectivity issues for diazo compound **254**. As such, α-cyclocostunolide **256**, containing an endocyclic alkene, was selected as a suitable target.

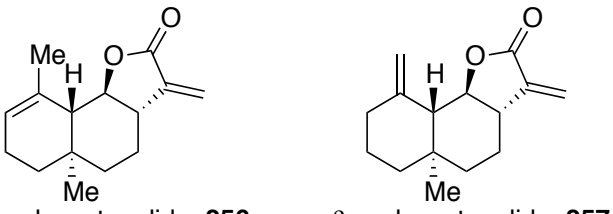
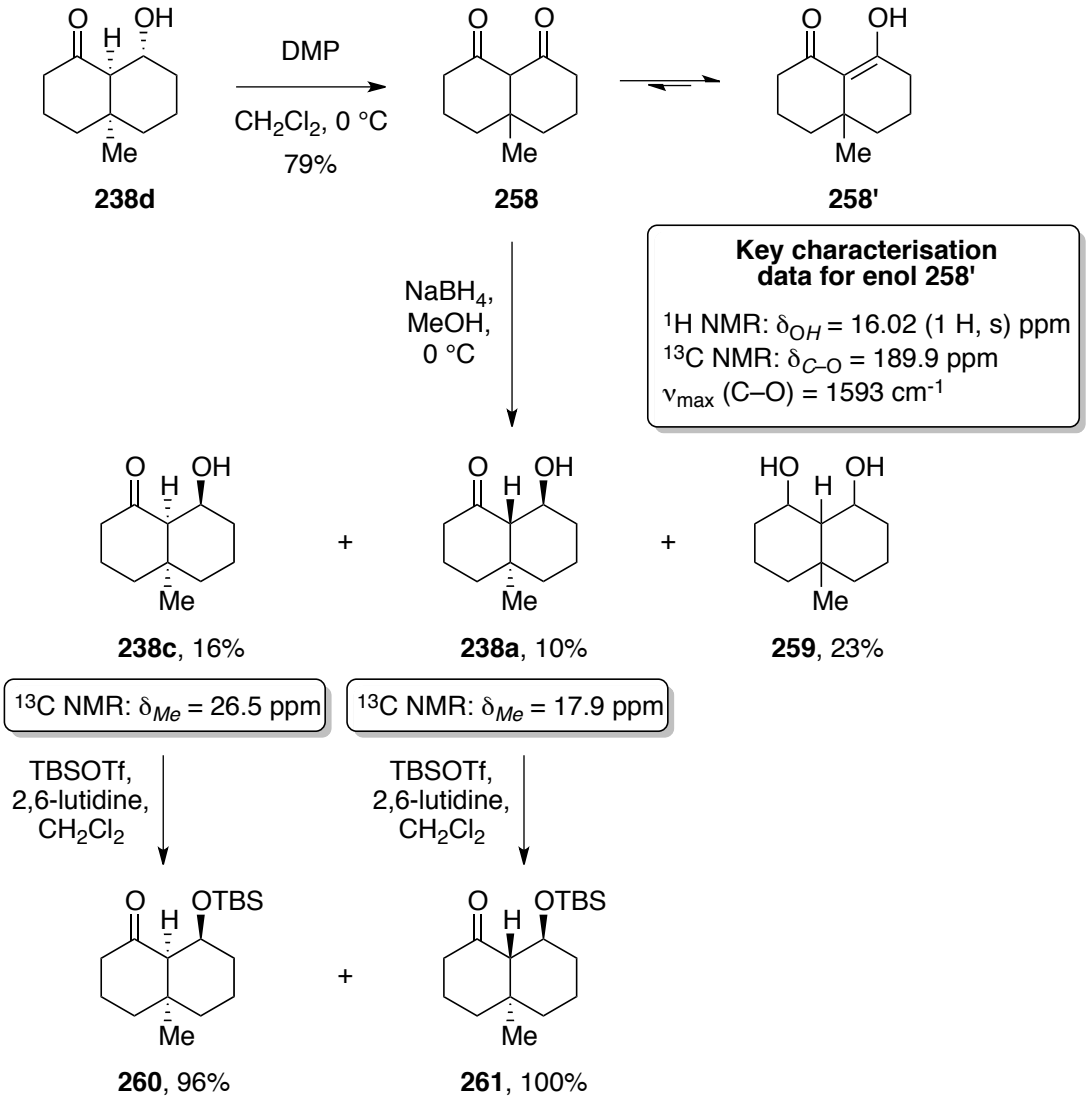


Figure 56: *trans*-Annelated eudesmanolide natural products, α- and β-cyclocostunolide.

Unfortunately, all attempts to directly isomerise *cis*-decalin **238d**, already in-hand, to the more thermodynamically stable *trans*-decalin **238a** were unsuccessful. Instead, a simple oxidation-reduction sequence of β-hydroxyketone **238d** was envisioned. Treatment with DMP delivered diketone **258**, which was found to exist primarily as the keto-enol tautomer **258'**, as demonstrated by the spectroscopic data (Scheme 58). Following slow addition of $NaBH_4$ to a solution of diketone **258** in MeOH, a mixture of products was observed by TLC analysis. Separation by column chromatography allowed these compounds to be identified as β-hydroxyketones **238a** and **238c** and complex mixture of diastereomers of over-reduction product **259**, albeit in low overall yield. The determination of *cis*- or *trans*-geometry at the ring junction was again carried out using the ^{13}C NMR chemical shifts of the quaternary methyl groups. For β-hydroxyketone **238c** the signal is observed at δ_C = 26.5 ppm, whereas for β-hydroxyketone **238a** it is observed at δ_C = 17.9 ppm, thus indicating that they are *cis*- and *trans*-decalins respectively. Each β-hydroxyketone was protected as the TBS ether; the *cis*-decalin **260** was obtained as an oil, whereas the *trans*-decalin **261** was sufficiently crystalline to obtain a single crystal X-ray structure (Figure 57), confirming the proposed framework.



Scheme 58: Oxidation-reduction sequence for the synthesis of β-hydroxyketones **238a** and **238c**.

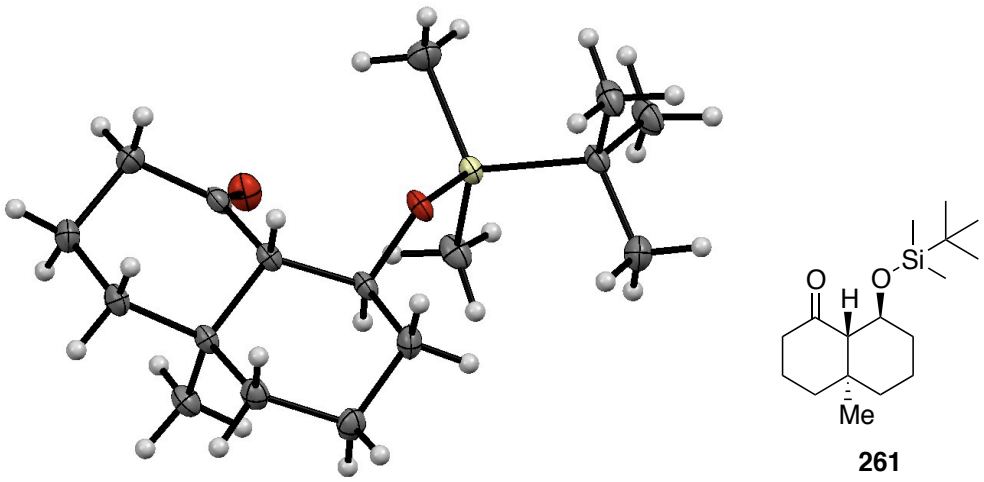
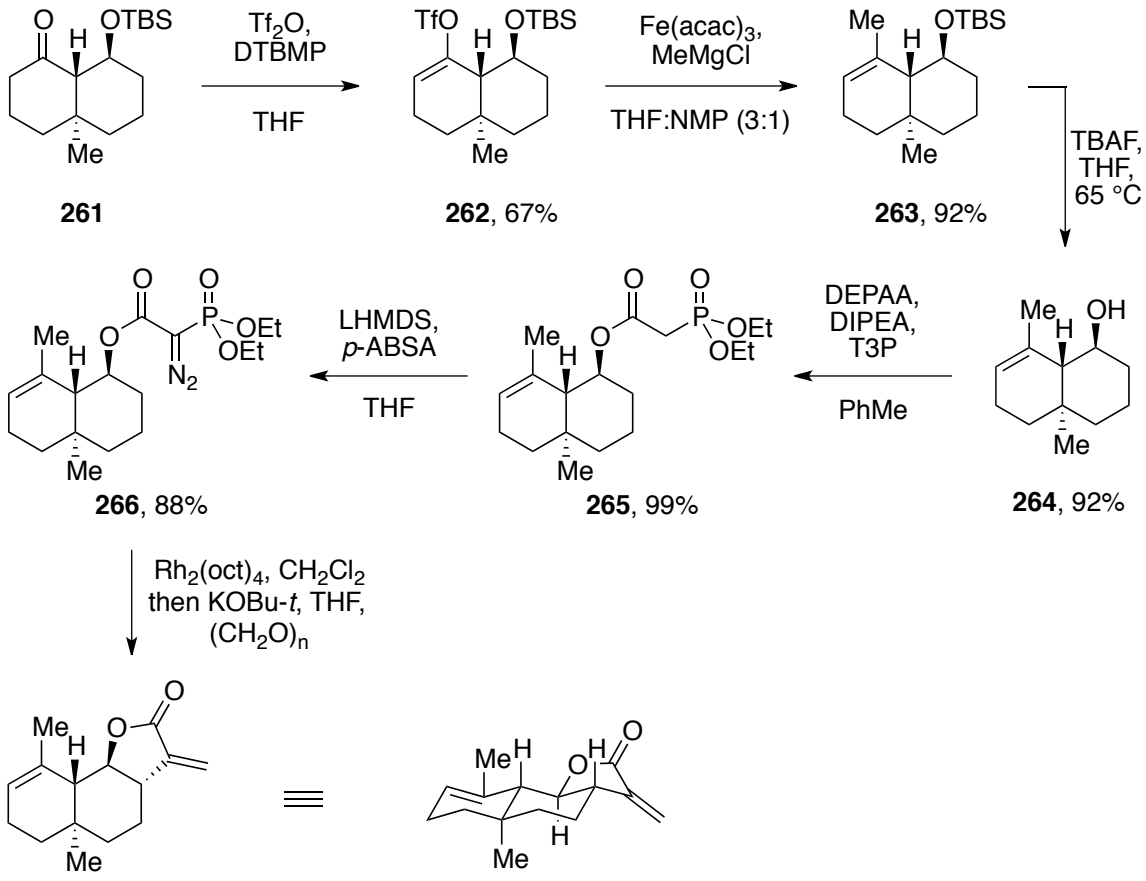


Figure 57: Single crystal X-ray structure of *trans*-decalin **261** (CCDC: 1421164). Thermal ellipsoids set to 50% probability, shown in Olex2.

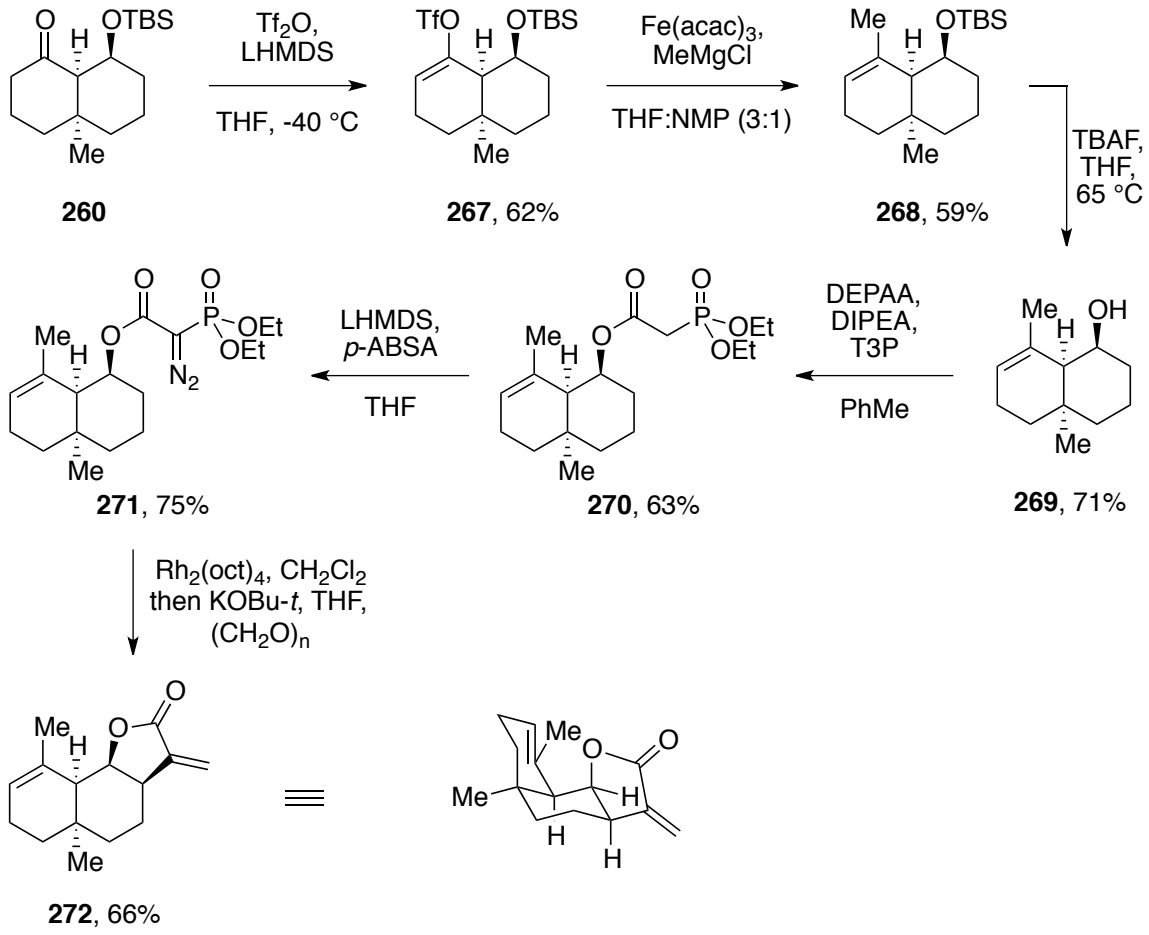
Following the sequence developed earlier, *trans*-decalinone **261** was converted into vinyl triflate **262** in 67% yield, but this time requiring thermodynamic conditions as the kinetic conditions, used earlier, were unsuccessful (Scheme 59). These results demonstrate a general trend for vinyl triflate formation in that *cis*-decalinones require kinetic conditions whereas *trans*-decalinones require thermodynamic conditions.

Conversion of vinyl triflate **262** into endocyclic alkene **263** proceeded in 92% yield. The customary desilylation, acylation and diazotisation were performed without complication, affording diazo compound **266** in 80% yield over 3 steps. With the key diazo precursor in hand, the one-pot C–H insertion/olefination procedure was applied. We were delighted to observe α-cyclocostunolide **256** as the single product from the reaction in reasonable yield. All of the observed data correlated with those published in the literature (see Appendix I for comparison tables and spectra).[120]



Scheme 59: Synthesis of α-cyclocostunolide **256**.

To conclude, *cis*-decalinone **260**, prepared earlier, was also subjected to the synthetic sequence, firstly being transformed into vinyl triflate **267** under kinetic conditions in 62% yield (Scheme 60). Successive iron-catalysed cross coupling, desilylation, acylation and diazotisation successfully delivered diazo **271** in a moderate yield over 4 steps. Once again we were pleased to observe a single diastereomeric product, novel lactone **272**, in 66% yield from the standard one-pot C–H insertion/olefination sequence. Given the large number of related natural products it is possible that lactone **272** may be found to occur naturally, in due course.



Scheme 60: Synthesis of lactone **272**.

3.4 Conclusion

The one-pot C–H insertion/olefination methodology has been successfully applied to a series of conformationally restricted cyclohexane derived diazo compounds. The differentiation of the equatorial and axial C–H bonds through conformational restriction has enabled the diastereoselective synthesis of a range of bicyclic α-methylene-γ-butyrolactones. The effect of conformationally restricting functional groups has been shown to not only modify the conformation of the cyclohexane rings, but also to provide a steric barrier to β-lactone side-product formation.

The one-pot C–H insertion/olefination procedure was then extended to a series of more complex derivatives in order to generate eudesmanolide natural product frameworks. Two *cis*-decalin derived lactones **240** and **241** were synthesised, clarifying ambiguity within previous literature regarding their identity. The eudesmanolide natural product α-cyclocostunolide **256** has also been also synthesised.

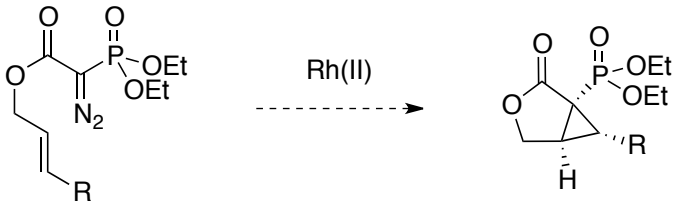
The exceptional levels of diastereoselectivity observed for the reactions of conformationally restricted α-diazophosphonoacetates complements existing literature precedent for related systems and should serve as a valuable synthetic tool for further applications in natural product and target based syntheses.

Selected results described in this Chapter are contained within recently published articles (see Appendix V).[121]

Chapter 4 – Rhodium(II)-catalysed cyclopropanations of allylic α-diazo(diethoxyphosphoryl)acetates

4.1 Introduction

Following the development of the rhodium(II)-catalysed C–H insertion reactions of α-diazophosphonoacetates, it was envisioned that this work could be extended to encompass the rhodium(II)-catalysed cyclopropanation of allylic α-diazophosphonoacetates, shown in Scheme 61.



Scheme 61: Proposed rhodium(II)-catalysed cyclopropanation of allylic α-diazophosphonoacetates **273** to generate α-phosphoryl-3-oxabicyclo[3.1.0]hexanones **274**.

The α-phosphoryl-3-oxabicyclo[3.1.0]hexanone products **274** are members of a compound class known as donor-acceptor cyclopropanes and are seen as privileged structures due to the presence of the two electron-withdrawing substituents which create a push-pull effect with polarisation of the C–C bond.[122] This distinctive zwitterionic relationship enables a wide variety of reactions to take place including: ring-openings, cycloadditions and rearrangements (Figure 58).[123]

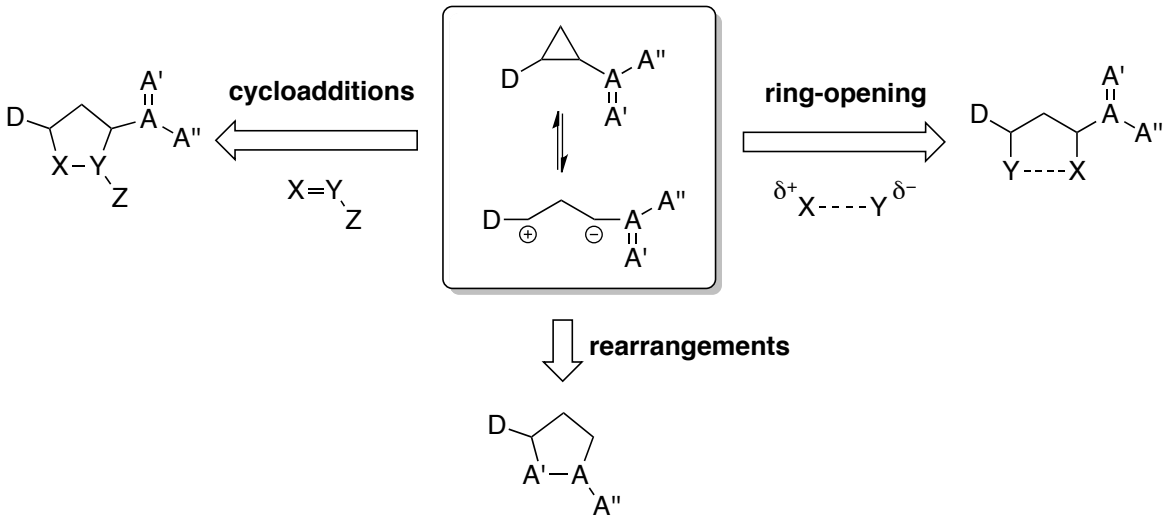
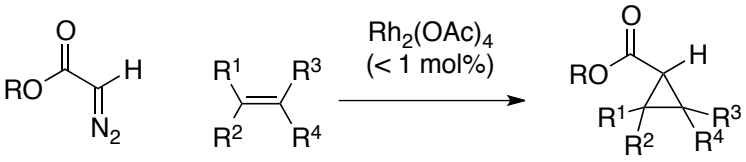


Figure 58: Modes of reactivity for donor-acceptor cyclopropanes.[123]

4.2 Rhodium(II)-catalysed cyclopropanations

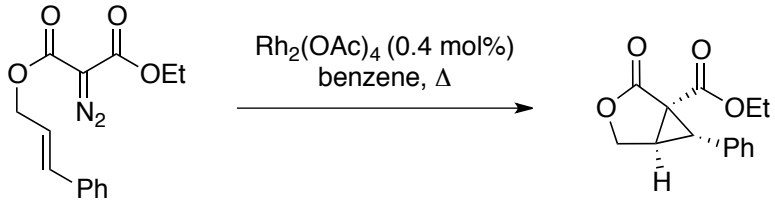
One of the first examples of a rhodium(II)-catalysed cyclopropanation was reported in 1976 by Teyssié and co-workers.[124] This work focussed on the intermolecular reactions of acceptor-substituted diazocarbaronyl compounds with simple olefins (Scheme 62).



275 **276** **277**
10 examples,
24-98% yield

Scheme 62: Teyssié's intramolecular rhodium(II)-catalysed cyclopropanations.

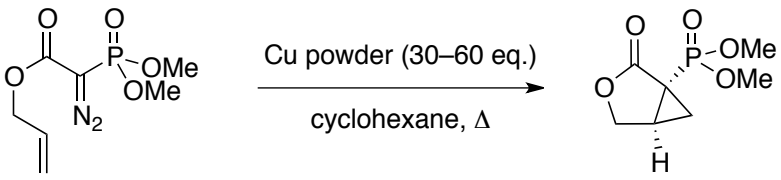
Intramolecular rhodium(II)-catalysed cyclopropanations were first reported in 1985 by Kametani *et al*., as shown in Scheme 63.[125]



278 **279**, 67%

Scheme 63: Kametani's intramolecular rhodium(II)-catalysed cyclopropanation.

To the best of our knowledge there are just 3 published examples of intramolecular cyclopropanations of α-diazophosphonoacetates; these examples are contained within one report, by Vandewalle, which was published in 1984 (one of these examples shown in Scheme 64).[81a] The reactions were performed using copper metal (30–60 eq.) to generate the intermediate carbenoid, with $Rh_2(OAc)_4$ stated to be ineffective as a catalyst for the same transformation.



280 **281**, 67%

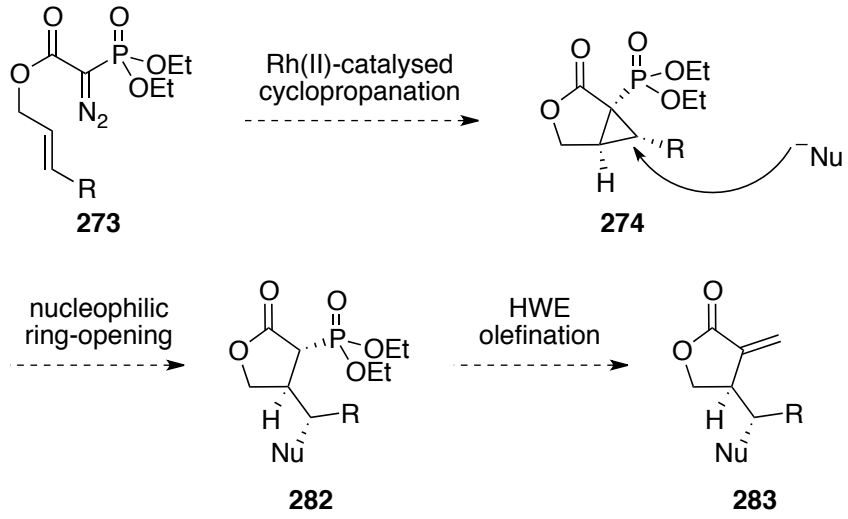
Scheme 64: Copper-mediated cyclopropanation of α-diazophosphonoacetates.

4.3 Aims and Objectives

It was envisaged that α-phosphoryl-3-oxabicyclo[3.1.0]hexanones could be prepared *via* a rhodium(II)-catalysed intramolecular cyclopropanation reaction of allylic α-diazophosphonoacetates. It was then planned to explore the scope of the reaction and demonstrate the effectiveness of the procedure through the synthesis of α-methylene-γ-butyrolactone natural products.

Following the synthesis of the α-phosphoryl-3-oxabicyclo[3.1.0]hexanone **274** a transformation such as a ring-opening reaction, would generate phosphonolactones **282**, which could then be exploited in a HWE olefination to deliver the α-methylene-γ-butyrolactone framework **283** (Scheme 65).

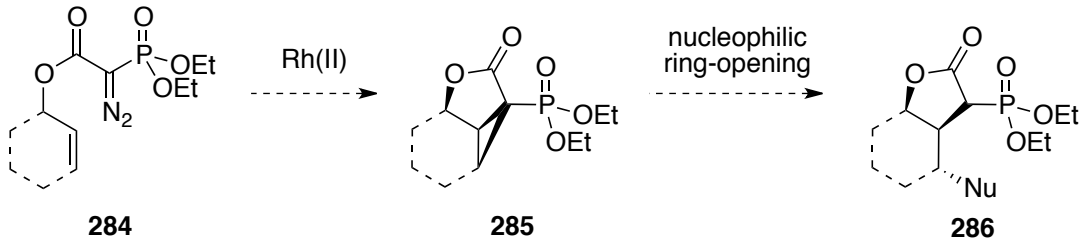
While this process would deliver the same type of products as the previously described C–H insertion methodology, a number of advantages to this cyclopropanation procedure were identified at the outset. Given that the cyclopropanation reaction is a cheletropic process,[126] the olefin geometry preinstalled in the α-diazo(diethoxyphosphoryl)acetate precursors **273** should be transferred directly to the cyclopropane product **274**, with just a single diastereomer expected. In the case of a subsequent nucleophilic ring-opening reaction, the stereochemical information should then be inverted during an S_N2 process; therefore the ability to control olefin geometry at the sp^2 hybridised site in diazo compound **273** could be directly transferred to an sp^3 centre in the ring-opened product **283**.



Scheme 65: Stereoselectivity transfer *via* rhodium(II)-catalysed cyclopropanation/nucleophilic ring-opening sequence.

The cyclopropanation reaction results in the formation of two new C–C bonds, which must be on the same face. This provides a significant advantage over the C–H insertion reaction, in which a single C–C bond is formed, because it bestows a greater degree of diastereocontrol. For example, in the cyclopropanation of cyclic diazo precursors **284**, the tricyclic product **285** should form the diastereomer in which two new C–C bonds are on the same face as the C–O bond, as shown in Scheme 66. This is based on consideration of the least strained diastereomer, which is thought to be *cis*-diasteromer **285**. A subsequent nucleophilic ring-opening reaction would selectively deliver a *cis*-fused bicyclic lactone product **286**.

This is a major advantage over the C–H insertion methodology, developed earlier, in which conformational restriction was found to be essential in order to furnish bicyclic rings diastereoselectively.

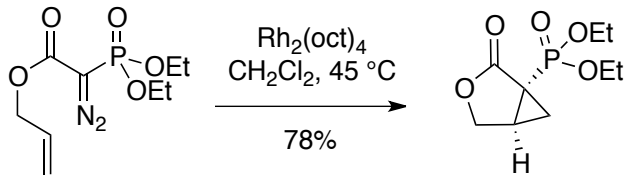


284 **285** **286**

Scheme 66: Selective formation of *cis*-bicyclic lactones *via* rhodium(II)-catalysed cyclopropanation/nucleophilic ring-opening sequence.

4.4 Scope and Limitations

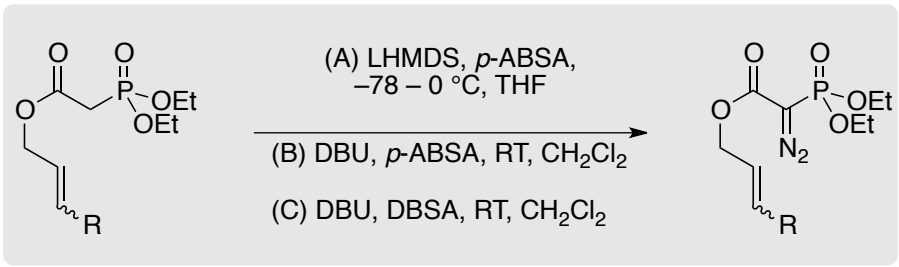
Our initial effort foccussed on the reaction of allyl alcohol-derived diazo compound **287b**, which was treated with 2 mol% of $Rh_2(oct)_4$ in CH_2Cl_2 at 45 °C for 16 hours. Pleasingly, a single product was obtained and identified as the desired cyclopropane **287c** in 78% yield. All spectroscopic data were consistent with those found in the literature.[127] This result was interesting as earlier studies, performed by Vandewalle,[81a] stated that the rhodium(II)-catalysed intramolecular cyclopropanation of α-diazophosphonolactones was ineffective.

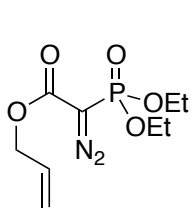


287b **287c**

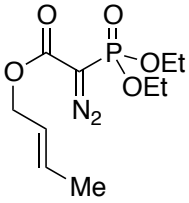
Scheme 67: Rhodium(II)-catalysed intramolecular cyclopropanation of allyl α-diazo(diethoxyphosphoryl)acetate **287c** forming bicyclic lactone **287b**.

Accordingly, several allylic α-diazo(diethoxyphosphoryl)acetates were prepared in order to fully examine the scope of the cyclopropanation reaction. It was observed that our standard diazotisation conditions (LHMDS, −78 °C–RT, then addition of azide), developed for the C–H insertion methodology, led to poor yields of the allylic α-diazo(diethoxyphosphoryl)acetates in some cases, with the major by-product being the allylic alcohol, resulting from hydrolysis. Thankfully, it was found that adding DBU to a pre-mixed solution of the α-(diethoxyphosphoryl)acetate and azide substantially improved the yields (Scheme 68). Additionally, the purification process was much more facile than the previous procedure, simply requiring the reaction mixture to be filtered through a pad of Celite and silica, followed by chromatographic purification of the filtrate.

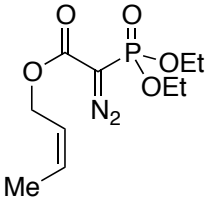




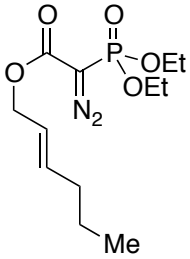
287b
43% (A)
83% (C)



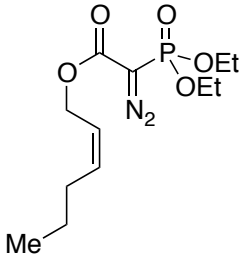
288b
54% (A)



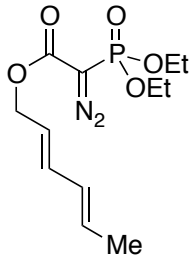
289b (4:1 *Z*:*E*)
43% (A)



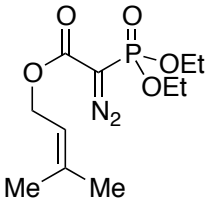
290b
54% (A)



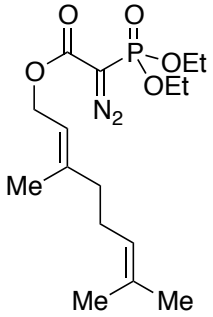
291b
75% (A)



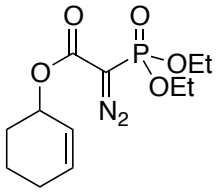
292b
75% (C)



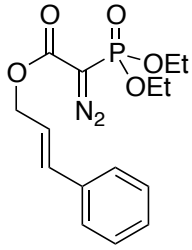
293b
85% (C)



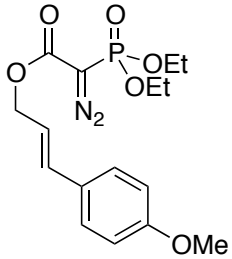
294b
63% (B)



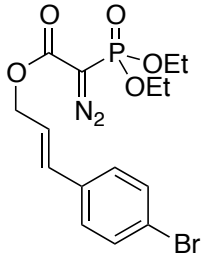
295b
75% (B)



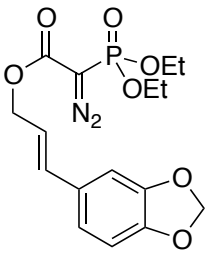
296b
42% (A)



297b
75% (C)



298b
87% (C)

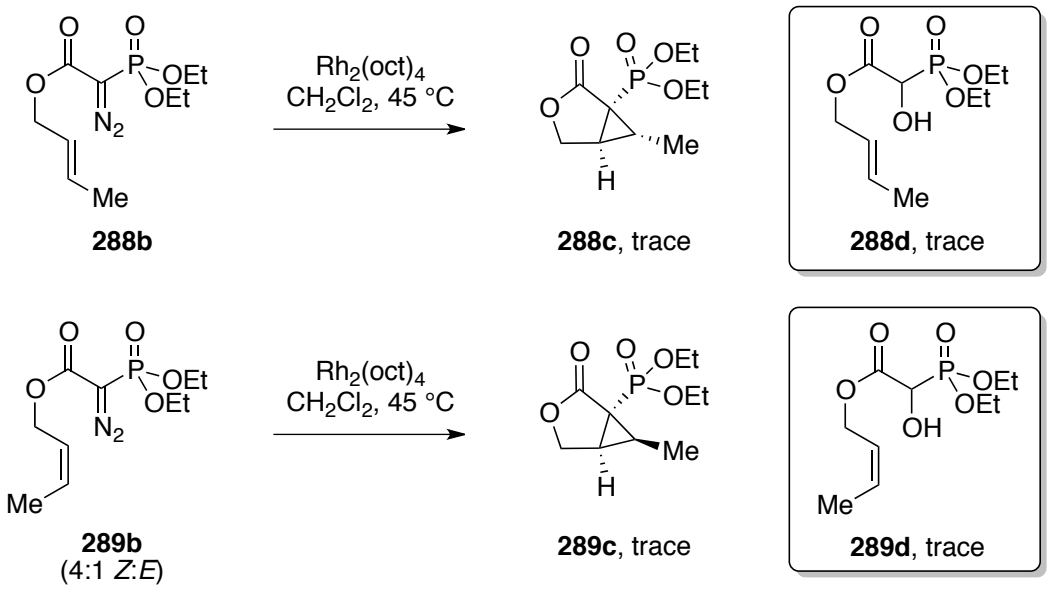


299b
46% (A)

Scheme 68: Diazotisation of allylic α-phosphorylacetates.

4.4.1. Aliphatic-substituted systems

Our first efforts focussed on the use of olefins with aliphatic groups. Disappointingly, in the case of both *E*- and *Z*- (4:1 *Z*:*E dr*) crotyl alcohol-derived diazo compounds **288b** and **289b**, the starting material was not fully consumed following treatment with $Rh_2(oct)_4$. Using ^{1}H NMR analysis of the unpurified reaction mixture, a trace amount of the desired cyclopropanes **288c** and **289c** was observed,[§] alongside the water O–H insertion products **288d** and **289d**, respectively (Scheme 69), but none of the compounds were isolated for full characterisation.

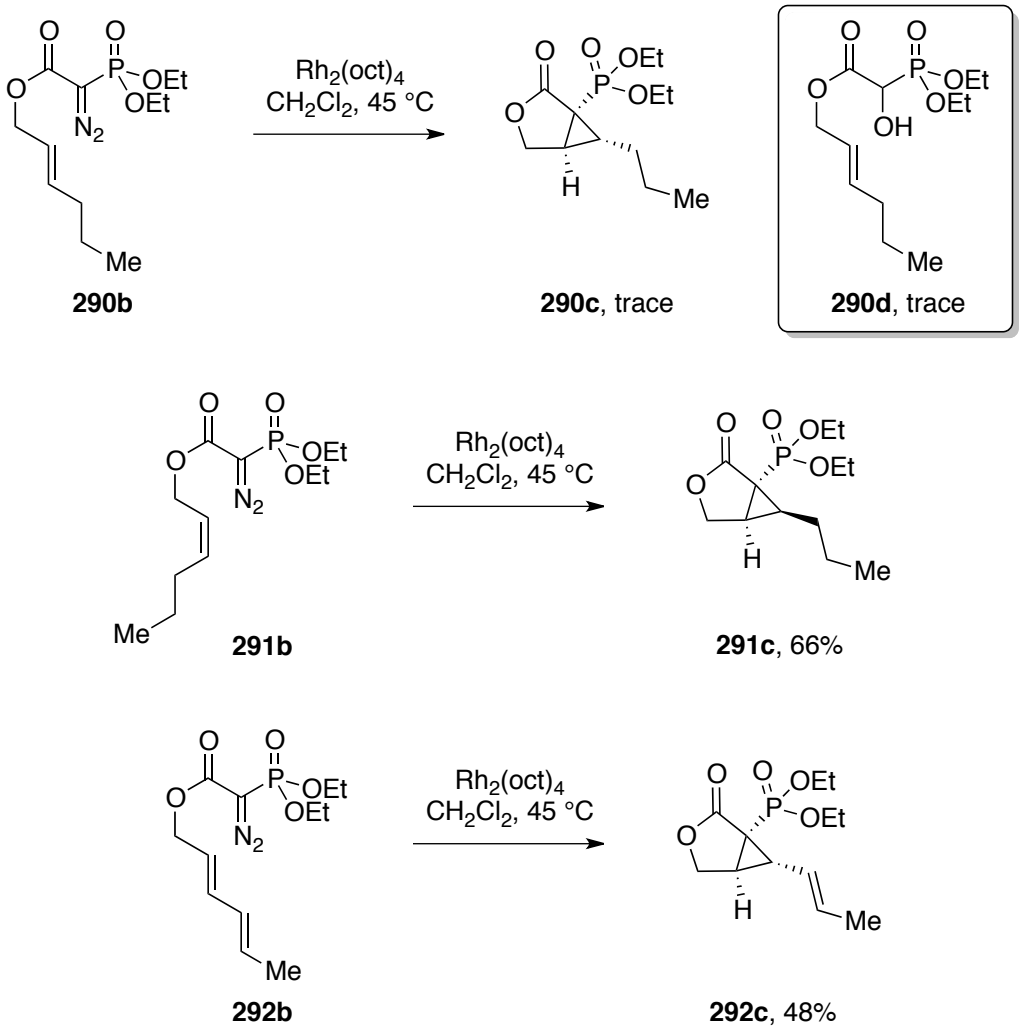


Scheme 69: Rhodium(II)-catalysed diazo decomposition of crotyl derivatives **288b** and **289b**.

Next, *E*- and *Z*-hexenol derivatives **290b** and **291b** were prepared and treated with $Rh_2(oct)_4$ (Scheme 70). Similarly to the previous crotyl examples, *E*-derivative **290b** was not fully consumed, with the desired cyclopropane **290c** again formed alongside the corresponding water O–H insertion product **290d**.[**] In contrast, the *Z*-derivative **291b** reacted well under the same conditions, with complete consumption of starting material, affording cyclopropane **291c** as the sole product in 66% isolated yield, which was fully characterised. Lower steric hindrance may favour addition to the *Z*-olefin. Interestingly, *E*-diene substrate **292b** furnished allyl cyclopropane **292c** in 48% yield under the same conditions, indicating that the incorporation of additional unsaturation is beneficial to the cyclopropanation process, offering *E*-olefins enhanced reactivity, possibly through additional charge stabilisation.

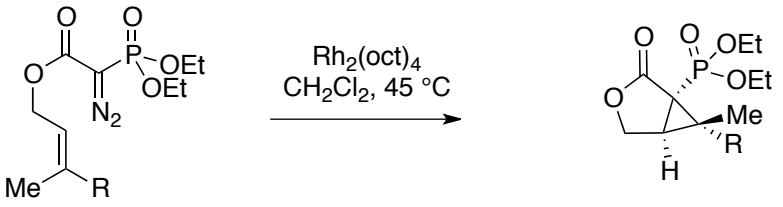
[§] Diagnostic ^{1}H NMR signals: **288c**, δ = 2.53 (dt, *J* = 10.2, *J* = 5.0, C*H*CH$_2$O); **288d**, δ = 4.51 (dd, *J* = 15.8, *J* = 6.7, OC*H*P); **289c**, δ = 2.67 (ddd, *J* = 11.4, *J* = 7.6, *J* = 5.1, C*H*CH$_2$O); **289d**, δ = 4.50 (dd, *J* = 8.9, *J* = 7.0, OC*H*P).

[**] Diagnostic ^{1}H NMR signals: **290c**, δ = 2.53 (dt, *J* = 10.3, *J* = 5.0, C*H*CH$_2$O); **290d**, δ = 4.51 (dd, *J* = 15.8, *J* = 6.8, OC*H*P).



Scheme 70: Rhodium(II)-catalysed diazo decomposition of hexenol-derivatives **290b**–**292b**.

Trisubstituted aliphatic substrates **293b**, derived from prenol, and **294b**, derived from geraniol, delivered the desired cyclopropanes **293c** and **294c**, respectively, in good yields and as single diastereomers (Scheme 71). It is thought that the additional substitution makes the olefin more electron-rich and hence more nucleophilic, leading to improved yields of the desired cyclopropanes and reduced by-product formation. The increased substitution may also enable greater stabilisation of the positive charge than the disubstituted olefins, potentially proceeding through a more S_N1-like process (i.e. not cheletropic). However, given that single diastereomers were obtained, the cyclopropanation still appears to be concerted.

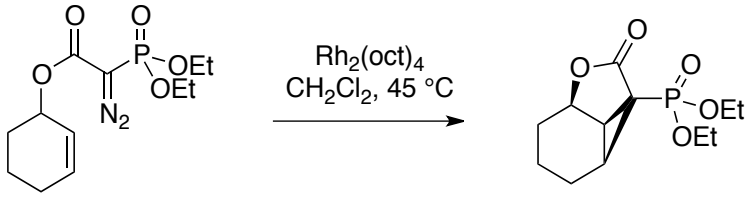


R = Me, **293b**
R = $(CH_2)_2CHCMe_2$, **294b**

R = Me, **293c**, 58%
R = $(CH_2)_2CHCMe_2$, **294c**, 64%

Scheme 71: Rhodium(II)-catalysed diazo decomposition of prenol and geraniol derivatives **293b** and **294b**.

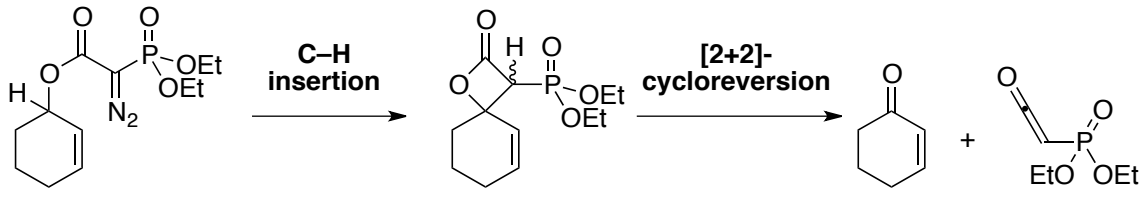
One of the key aims at the outset of this work was to synthesise *cis*-fused bicyclic α-methylene-γ-butyrolactones *via* tricyclic phosphonates. As such, 2-cyclohexen-1-ol diazo derivative **295b** was prepared and treated with $Rh_2(oct)_4$. Pleasingly, the desired tricyclic product **295c** was formed, albeit in a disappointing 24% yield (Scheme 72).



295b **295c**, 24%

Scheme 72: Rhodium(II)-catalysed diazo decomposition of cyclohexenol derivative **295b**.

The major by-product, observed by ^1H NMR analysis of the unpurified reaction mixture, was cyclohexenone **232**. This is believed to arise from an initial C–H insertion reaction to form a β-lactone **295d**,[128] which may then undergo a [2+2]-cycloreversion reaction, forming cyclohexenone **232** and a phosphonoketene **300**, which undergoes further reactions (Scheme 73). Given that the C–H bond in question is both allylic and α- to a heteroatom it therefore is not unreasonable that this appears to be a significant competing pathway for this class of diazo compound.

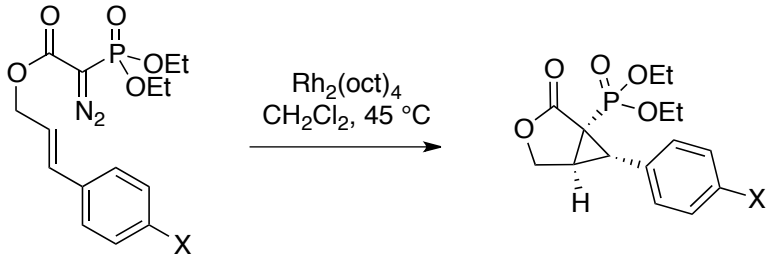


295b **295d** **232** **300**

Scheme 73: Proposed competing C–H insertion leading to β-lactone **295d** and subsequent [2+2]-cycloreversion to cyclohexenone **232**.

4.4.2. Aromatic-substituted systems

Next, the procedure was extended to the use of cinnamyl alcohol-derived diazo compounds **296b–298b** (Scheme 74). Pleasingly, each of these substrates delivered the respective cyclopropanes **296c–298c**, with complete diastereocontrol and in good to excellent yield.

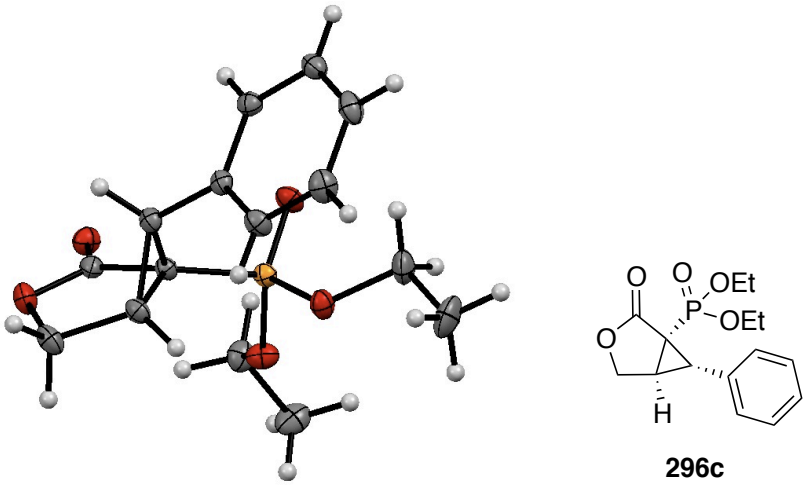


X = H, **296b**
X = OMe, **297b**
X = Br, **298b**

X = H, **296c**, 79%
X = OMe, **297c**, 53%
X = Br, **298c**, 74%

Scheme 74: Rhodium(II)-catalysed intramolecular cyclopropanation of cinnamyl α-diazo(diethoxyphosphoryl)acetates **296b**–**298b** forming bicyclic lactones **296c**–**298c**.

The relative configuration of cyclopropane **296c** was confirmed following the acquisition of a single crystal X-ray structure (Figure 59), and it is assumed that **297c** and **298c** have the same configuration based on similar diagnostic ^{1}H NMR signals.[††]



296c

Figure 59: Single crystal X-ray structure of cyclopropane **296c** (CCDC: 1465173). Thermal ellipsoids set to 50% probability, shown in Olex2.

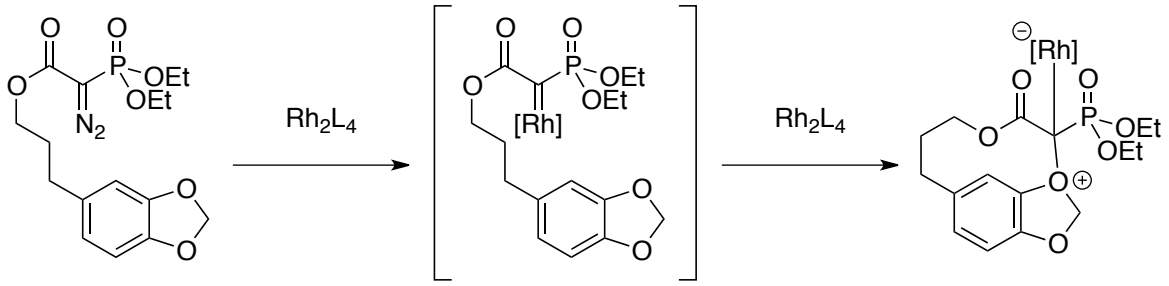
[††] Diagnostic ^{1}H NMR signals:

296c, δ = 2.81 (app. t, *J* = 6.1, C*H*Ar), δ = 3.30 (app. dt, *J* = 10.6, *J* = 5.2, C*H*CH$_2$O),

297c, δ = 2.73 (app. t, *J* = 6.1, C*H*Ar), δ = 3.24 (app. dt, *J* = 10.6, *J* = 5.2, C*H*CH$_2$O),

298c, δ = 2.71 (app. t, *J* = 6.0, C*H*Ar), δ = 3.24 (app. dt, *J* = 10.7, *J* = 5.2, C*H*CH$_2$O),

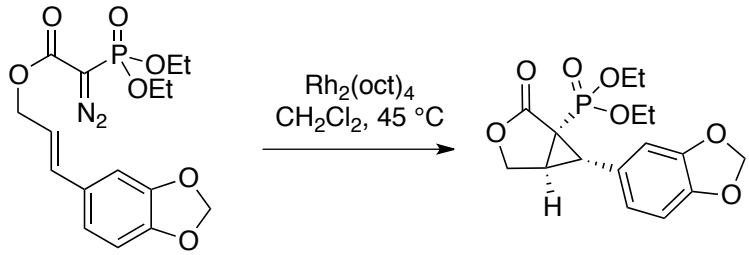
Following the success of these reactions it was decided to investigate cinnamyl derivatives that contain a 3,4-methylenedioxy unit, as this substructure is found in many natural products. The saturated substrate investigated during the C–H insertion methodology studies, compound **149b**, was unsuccessful (Chapter 2, Scheme 39). It is thought that the oxygen lone pairs coordinate to the carbenoid centre, leading to an unproductive pathway (Scheme 75). It is proposed that the introduction of unsaturation will confer additional rigidity in the molecule, minimising the coordination of the oxygen lone pairs to the carbenoid, enabling the desired reaction to occur.



149b **149d** **149e**

Scheme 75: Proposed unproductive pathway following the formation of carbenoid **149d**.

Pleasingly, on reaction of diazo compound **299b** under the standard $Rh_2(oct)_4$ conditions, the desired bicyclic lactone **299c** was generated in excellent yield and with complete diastereoselectivity (Scheme 76). It was hoped that this compound could be further elaborated for the synthesis of α-methylene-γ-butyrolactone natural products containing the 3,4-methylenedioxy framework, the synthesis of which will be discussed later, in Section 4.6.



299b **299c**, 73%

Scheme 76: Rhodium(II)-catalysed intramolecular cyclopropanation of 3,4-methylenedioxycinnamyl diazo compounds **299b**.

4.5 Ring-opening reactions of cyclopropanes

The opening of cyclopropane rings can be performed by many different types of reactions and in the case of donor/acceptor cyclopropanes (such as the α-phosphoryl-[3.1.0]-bicyclic lactones being studied here) there is the possibility of performing cycloadditions,[129] rearrangements and direct ring-opening reactions including nucleophilic, electrophilic and reductive methods. There are many examples of nucleophilic ring-openings using sulfur,[130] nitrogen,[131] oxygen,[132] carbon[131,133] and halogen[134] nucleophiles. Additionally, there have been various instances demonstrating reductive ring-openings using lithium in ammonia,[135] samarium diiodide,[136] and other reductants.[137]

In fused bicyclic systems, steric and electronic factors govern the selectivity of nucleophilic and reductive ring-opening reactions, which often proceed with excellent regioselectivity with respect to which of the cyclopropane bonds is broken. For example, in the case of π-stabilised bicylic cyclopropane systems such as compound **301**, Figure 60, the selectivity of this process is determined by the degree of orbital overlap of the cyclopropane C–C bond with the π-system of the adjacent carbonyl unit. The bond possessing the greatest degree of orbital overlap is that which is broken.[138] In the case of model system **301** a nucleophilic ring-opening would see attack at one of the cyclopropane carbons β- to the carbonyl group, with electrons flowing towards the π-system. As such, bonds 'a' or 'b' could be broken, resulting in cyclopentanone **302** or cyclohexanone **303**, respectively. In the majority of cases discussed within the literature, only bond 'a' is broken due to it having greater overlap with the carbonyl π* orbital, making the process regioselective. This selectivity has been observed in many of the aforementioned literature examples, as well as in ring-opening reactions of aziridines.[139] There have, however, been some recent examples in which the selectivity has been switched, with 6-membered rings formed in preference.[133b]

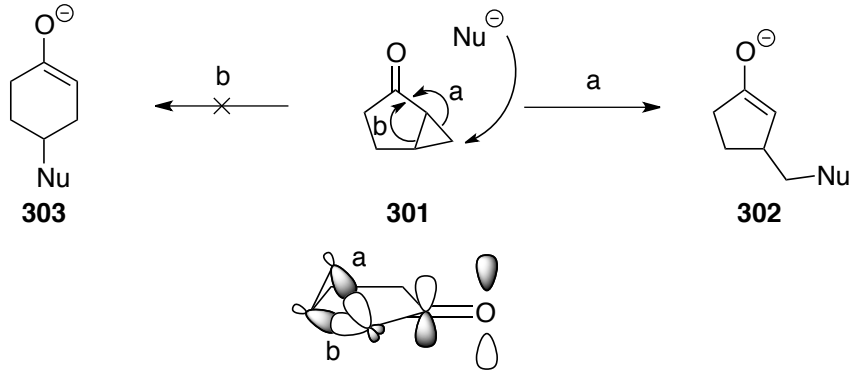
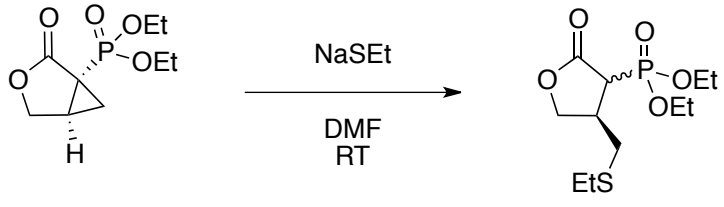


Figure 60: Orbital interactions responsible for high regioselectivity in ring-opening reactions of carbonyl-containing bicyclic rings, showing C–C σ* and C=O π* orbitals.

4.5.1. Initial studies into the ring-opening reactions of α-phosphoryl-3-oxabicyclo[3.1.0]hexanones

Initial efforts for the ring-opening reactions of α-phosphoryl-3-oxabicyclo[3.1.0]hexanone focussed on nucleophilic ring-openings of the 'unsubstituted' compound **287c**. Pleasingly, treatment with sodium ethanethiolate delivered the desired ring-opened γ-lactone product **304** in an unoptimised 37% yield (Scheme 77), with complete diastereoselectivity, although the relative configuration could not be proven definitively based on the coupling constants (which were discussed earlier in Chapter 2, page 39). The reaction was also completely regioselective, with attack at cyclopropane CH_2 leading to just a single C–C bond being broken.



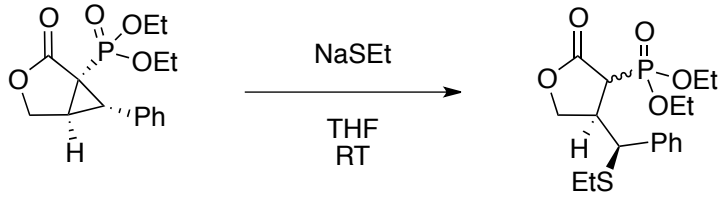
287c **304**, 37%

Key ^{1}H NMR data for compound 304

δ_{CHP} = 3.05 (1 H, dd, $^2J_{HP}$ = 24.6, $^3J_{HH}$ = 4.9) ppm

Scheme 77: Thiolate ring-opening of bicyclic lactone **287c**.

Pleasingly, the reaction of phenyl-substituted bicyclic lactone **296c** with sodium ethanethiolate also furnished the desired product **305**, although in just 19% isolated yield, but with excellent regio- and diastereocontrol (Scheme 78).



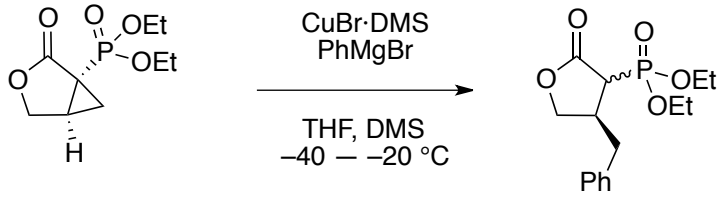
296c **305**, 19%

Key ^{1}H NMR data for compound 305

δ_{CHP} = 2.89 (1 H, dd, $^2J_{HP}$ = 24.6, $^3J_{HH}$ = 3.0) ppm

Scheme 78: Thiolate ring-opening of bicyclic lactone **296c**.

Next, the use of carbon nucleophiles was investigated. The formation of the cuprate from phenylmagnesium bromide was necessary (the Grignard by itself led to 1,2-addition), generating the desired product **306** in good yield (Scheme 79). This substrate is already accessible using the C–H insertion methodology, but demonstrates the potential for forming ring-opened products, which may be useful for more complex systems.



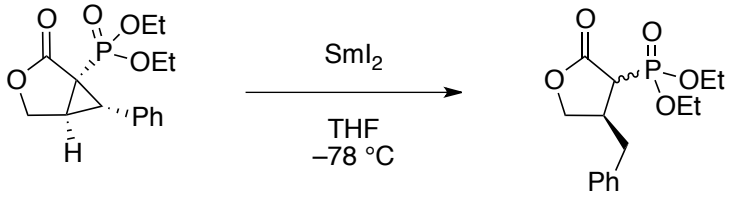
287c **306**, 63%

Key ^{1}H NMR data for compound 306

δ_{CHP} = 2.83 (1 H, dd, $^2J_{HP}$ = 23.9, $^3J_{HH}$ = 4.5) ppm

Scheme 79: Organocuprate ring-opening of bicyclic lactone **287c**.

Attention then turned to reductive ring-openings, which were first attempted using samarium(II) iodide;[136] the treatment of phenyl-substituted cyclopropane **296c** with a freshly prepared solution of SmI_2 afforded lactone **306** in moderate unoptimised yield, but with complete regio- and diastereoselectivity (Scheme 80).



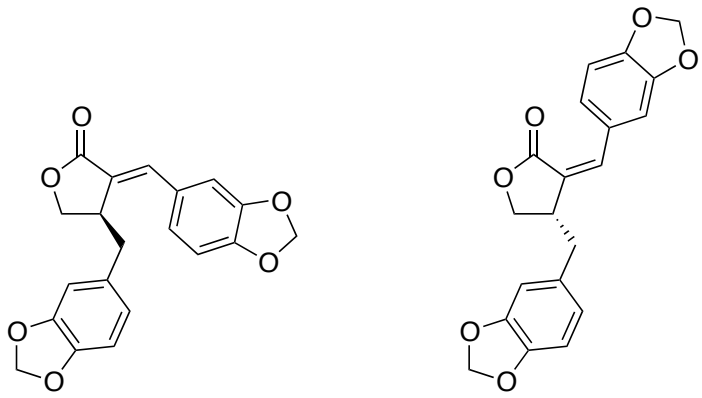
296c **306**, 48%

Scheme 80: Samarium(II) iodide-mediated reductive ring-opening of cyclopropane **296c**.

These initial studies have demonstrated the propensity of α-phosphoryl-3-oxabicyclohexanones to undergo a variety of reactions, clearly exhibiting regioselective C–C bond breaking in ring-opening reactions. Initial studies into the development of a one-pot ring-opening/HWE reaction for the direct formation of α-methylene-γ-butyrolactones have proven challenging.

4.6 Natural product targets: (±)-savinin and (±)-gadain

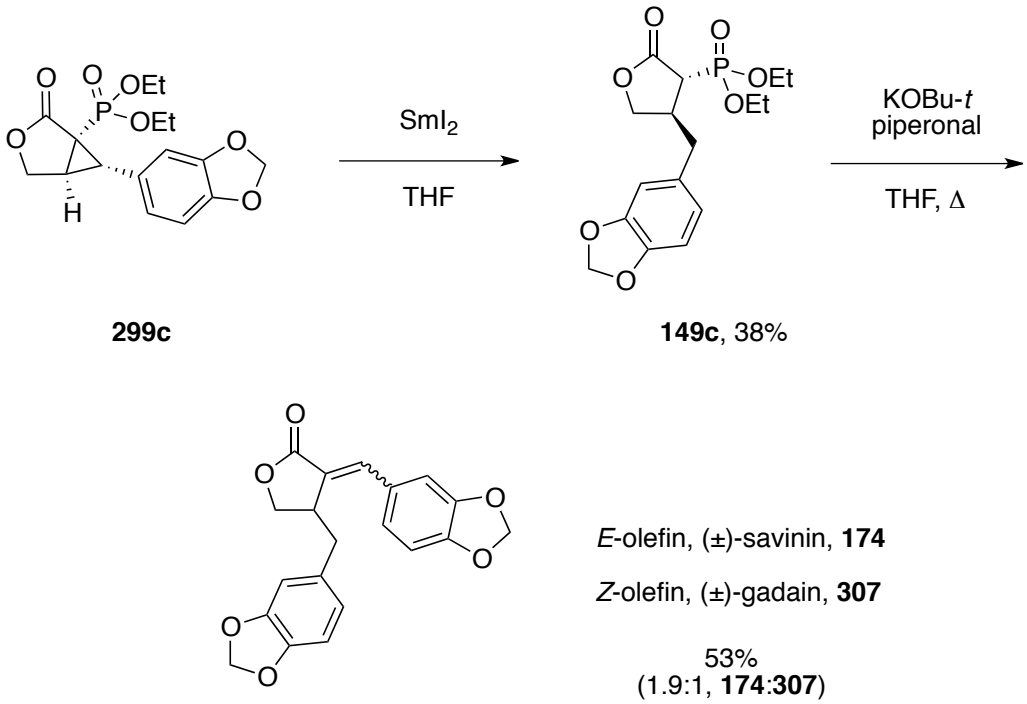
Following the successful synthesis of bicyclic lactone **299c**, which contains the 3,4-methylenedioxyphenyl unit, the synthesis of isomeric natural products savinin **174** (*E*-isomer, also known as hibalactone) and gadain **307** (*Z*-isomer, also known as isohibalactone), shown in Figure 61, were attempted. The isolation of (−)-savinin was first reported in 1953 by Hartwell,[95] although a thorough NMR assignment was not made until 1990.[140] Studies have since revealed cytoxicity[140] as well as insecticidal[141] and antiviral[142] activities. (+)-Gadain was isolated separately in 1984 and found to isomerise to (+)-savinin in acidic solution.[143] The synthesis of savinin and gadain has been performed previously, but not *via* cyclopropane intermediates.[141,144]



(–)-savinin, **174** (+)-gadain, **307**

Figure 61: Isomeric α-alkylidene-γ-butyrolactone natural products, (−)-savinin **174** and (+)-gadain **307**.

It was anticipated that treatment of the bicyclic lactone **299c** with SmI_2 would deliver the ring-opened phosphonolactone **149c**, which could not be accessed using the C–H insertion methodology earlier (Chapter 2, Scheme 39). Gratifyingly, treatment of cyclopropane **299c** with freshly prepared SmI_2 generated the desired γ-lactone **149c** in 38% yield, as a single diastereomer. Using conditions established during the earlier methodology studies, an HWE olefination was performed on lactone **149c** delivering a separable mixture of (±)-savinin **174** and (±)-gadain **307**, in an overall 53% yield (1.9:1 **174**:**307**). The data for both natural products is in agreement with those found in the literature (see Appendix I for comparison tables and spectra).[141] Isomerisation of gadain to savinin, the *E*-isomer, can be performed according to literature precedent.[141,144a]



Scheme 81: Synthesis of (±)-savinin and (±)-gadain.

4.7 Natural product targets: (±)-peperomin E

4.7.1. Introduction

Peperomins E and F, **308** and **309**, respectively, were identified by Govindachari *et al*. in 1998 following isolation from *Peperomia dindigulensis*, a succulent herb.[145] Their structures, shown in Figure 62, were elucidated using typical spectroscopic techniques. Their absolute configuration was assigned by comparing their optical rotatory dispersion to that of peperomins A and C, which have known absolute stereochemistry.

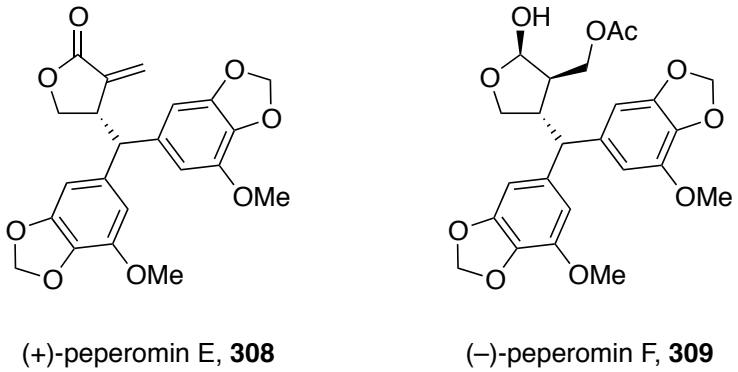


Figure 62: Lignan natural products peperomins E and F.

Peperomin E has been shown to possess a variety of biological activities including: antifeedant-activity,[145] cytotoxicity,[146] inhibition of malignant lung tumour cells (IC_{50} = 1.93 μM),[147] anti-angiogenic activity,[148] inhibition of cancer cell lines[149] and anti-inflammatory activity.[150]

To the best of our knowledge, prior to this research, there have been no reported syntheses of peperomin E. Three other lignans from the peperomin family: A, C and D, (**310**, **311** and **312** respectively), have been previously synthesised, however.[151] Peperomin A is a saturated analogue of peperomin E, whilst peperomins C and D are also saturated, they have different substitution patterns on the aromatic rings (Figure 63).

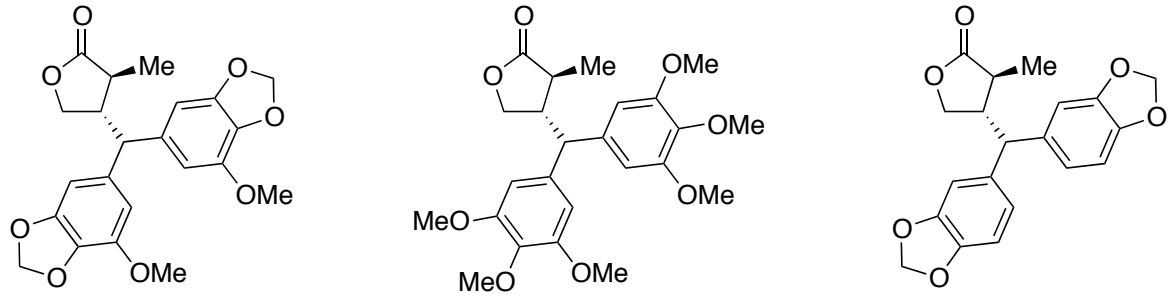
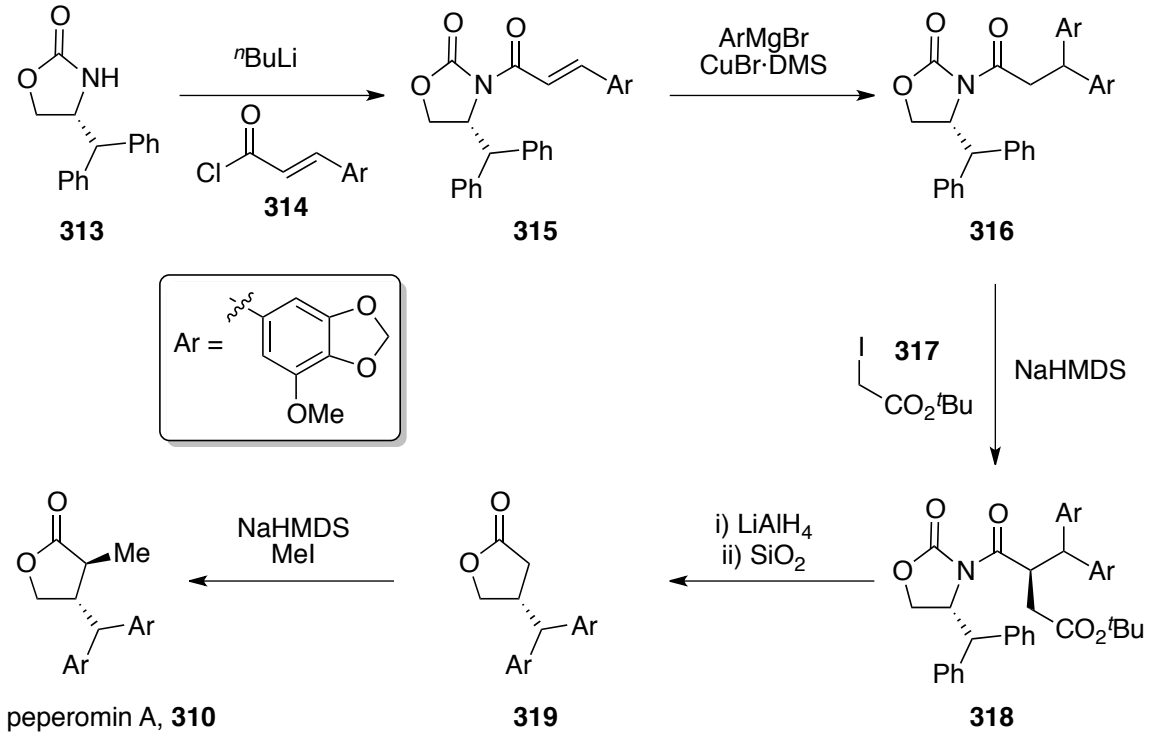


Figure 63: Lignan natural products peperomins A, C and D.

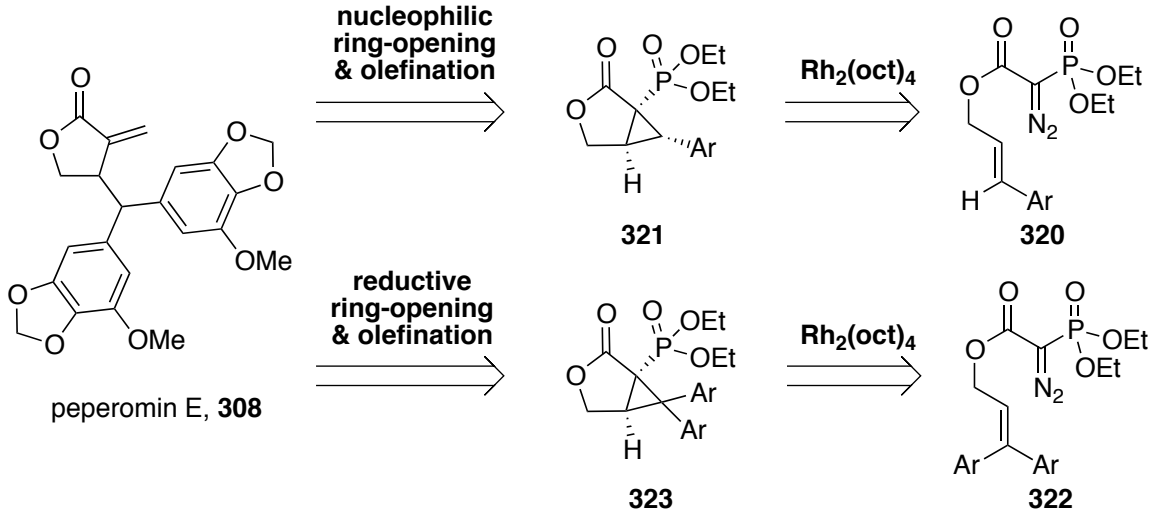
Peperomin A (and C, D) has been synthesised previously and enantioselectively using a chiral oxazolidinone auxiliary **313**. Firstly, cinnamoyl-derived auxiliary **315**, containing one of the requisite aryl units, was prepared. This was followed by installation of the second aryl unit *via* a copper-catalysed 1,4-addition of the corresponding Grignard reagent. As the aryl units are identical there were no diastereoselectivity issues. Next, enolate formation and trapping with iodide **317**, delivered the desired α,γ-dicarbonyl compound **318** with excellent *de*. Reduction and cyclisation generated γ-lactone **319** in good yield. The synthesis of peperomin A **310** was completed following installation of the exocyclic methyl group in excellent *de*. Peperomins C and D were prepared by similar routes.



Scheme 82: First asymmetric total synthesis of (+)-peperomins A by Sibi and co-workers.

4.7.2. Retrosynthetic Analysis

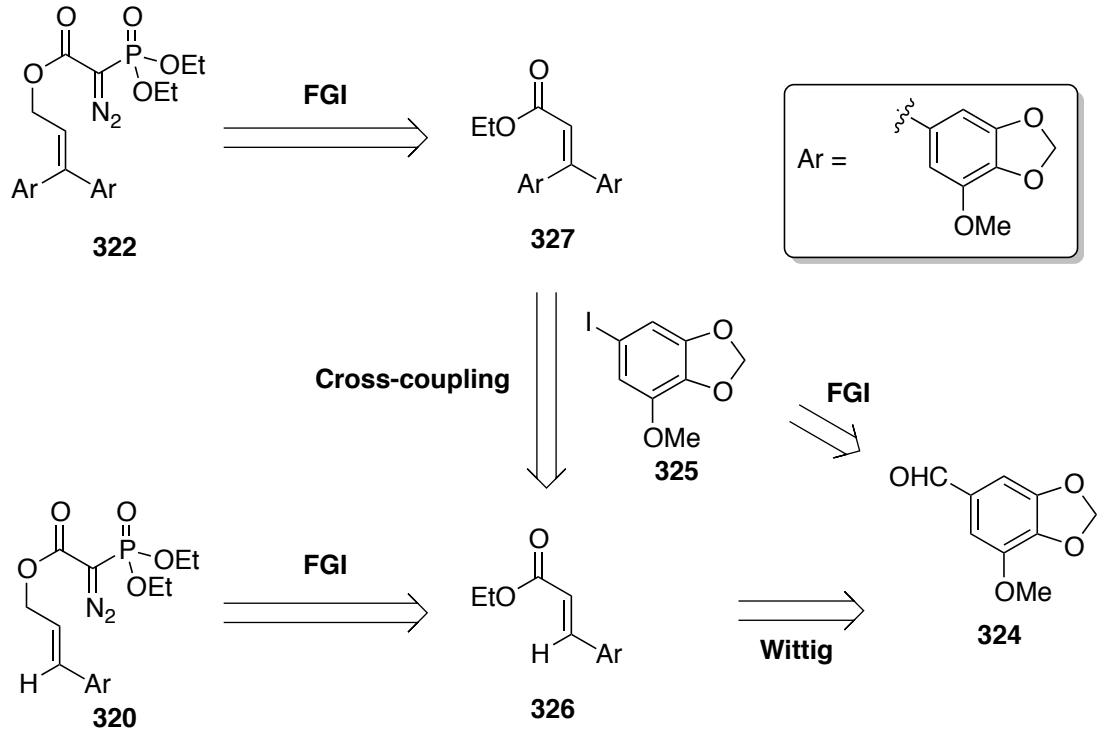
Two possible retrosynthetic strategies for (±)-peperomin E **308** were conceived (Scheme 83): one requiring a nucleophilic ring-opening of tertiary cyclopropane **321** and the other a reductive ring-opening of quaternary cyclopropane **323**.



Scheme 83: Retrosynthetic analyses for peperomin E. Ar = 3-methoxy-4,5-methylenedioxybenzene.

From the above retrosynthetic analyses it is clear that the two diazo substrates **321** and **323** are structurally related, and it was hoped that both would be accessible in order to attempt each route, although the latter approach was initially selected on the basis that the reductive ring-opening had already been successfully performed on related systems.

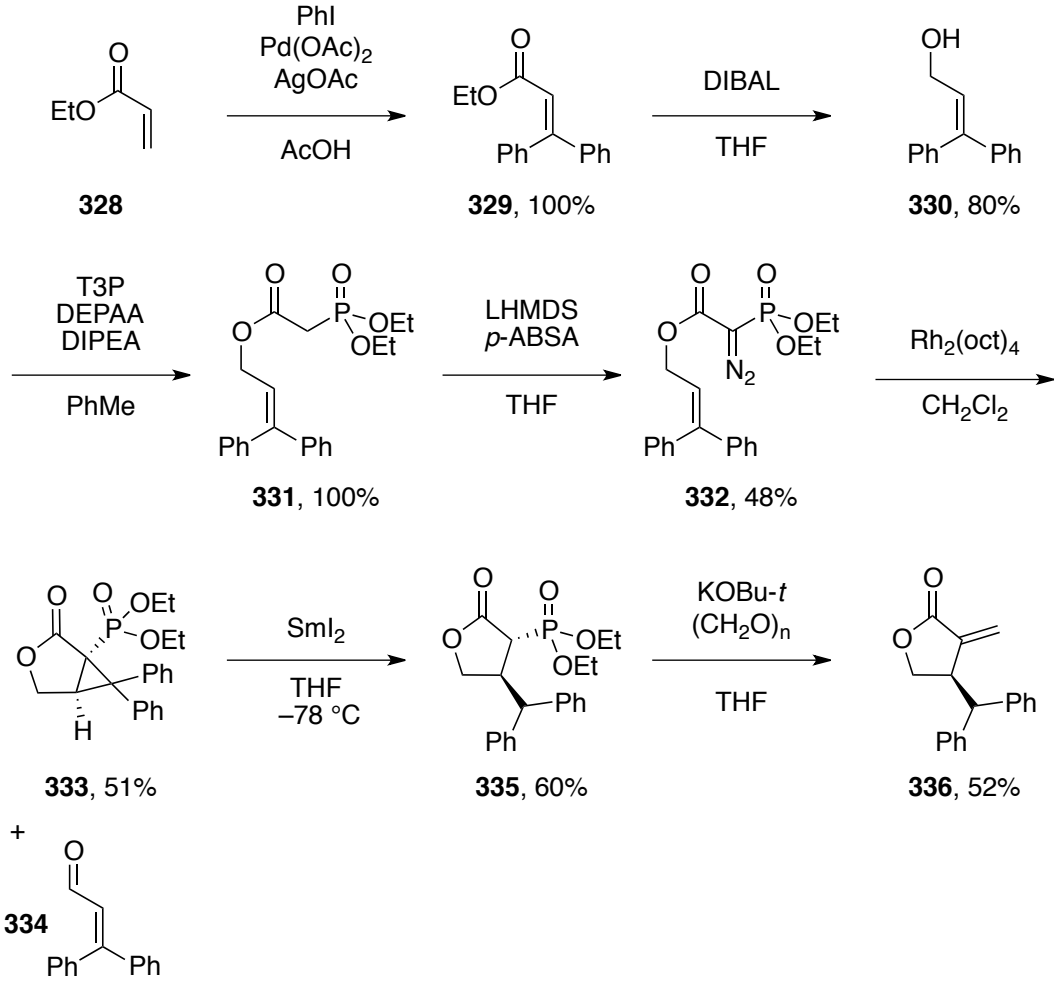
The retrosynthetic approach to diazo compounds **320** and **322** is shown in Scheme 84. It was envisaged that both diazo compounds could be derived from cinnamate **326** as a common precursor. Diarylacrylate **327** could be constructed *via* a cross-coupling reaction between cinnamate **326** and aryl iodide **325**, which each in turn could originate from the same commercially-available aldehyde **324**.



Scheme 84: Retrosynthetic strategy for diazo compounds **320** and **322**.

4.7.3. Model studies

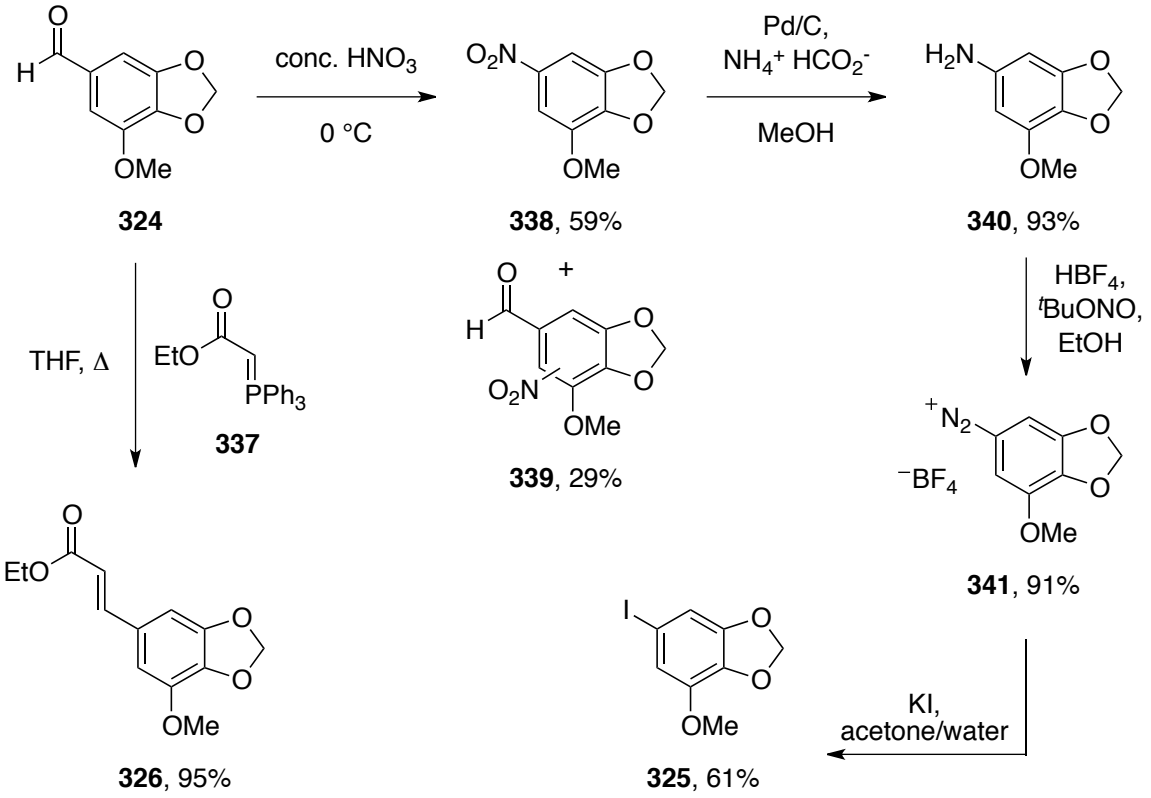
Prior to attempting the synthesis of the natural product target, it was decided to test an unsubstituted-phenyl analogue as a model system to confirm that the proposed synthesis of the extremely sterically hindered cyclopropane was achievable. Accordingly, diphenylacrylate **329** was prepared by utilising a double Heck arylation of ethyl acrylate **328**, as reported by Chen and co-workers.[152] Subsequent DIBAL reduction, acylation and diazotisation generated key substrate **332**, which was then subjected to the standard $Rh_2(oct)_4$ conditions, and pleasingly, furnished the desired quaternary cyclopropane **333**, in 51% isolated yield (Scheme 85). The modest yield was attributed to the formation of aldehyde **334**, which was considered to arise from β-lactone formation and subsequent a [2+2]-cycloreversion reaction, as proposed earlier (see Scheme 73). Cyclopropane **333** was then taken forward and reacted with SmI_2 in THF, delivering phosphonolactone **335**. To conclude, a HWE olefination generated the analogue of peperomin E, α-methylene-γ-butyrolactone **336**, as a fully characterised product in a reasonable unoptimised yield.



Scheme 85: Model studies for peperomin E.

4.7.4. Total synthesis of (±)-peperomin E

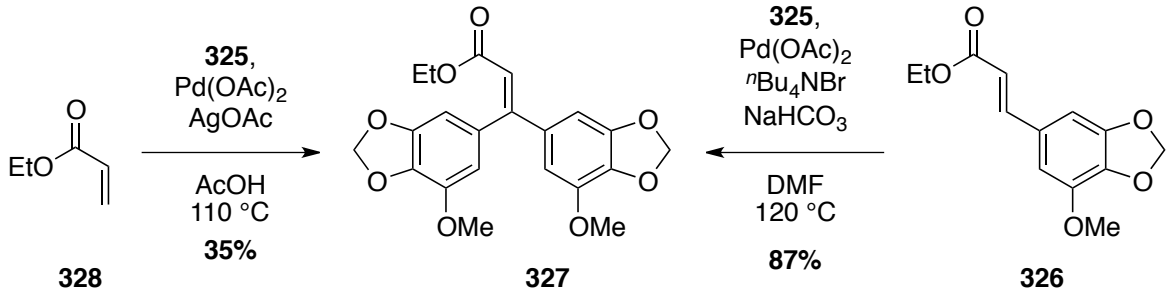
Having completed the model studies, the synthesis of peperomin E commenced with the efficient synthesis of cinnamate **326**, *via* Wittig olefination with (carbethoxymethylene)triphenylphosphorane **337** and aldehyde **324**. The synthesis of iodide **325** then began by treating aldehyde **324** with concentrated nitric acid,[153] delivering the desired nitrobenzene **338** *via* nitrodeformylation. Penta-substituted nitrobenzene side-product **339** was also isolated. The desired tetra-substituted nitrobenzene was then reduced with Pd on carbon in the presence of ammonium formate delivering aniline **340**,[154] before diazotisation with *tert*-butyl nitrite and fluoroboric acid generated aryldiazonium salt **341**.[155] Diazonium salts can be tailored to be less thermally sensitive by utilising tetrafluoroborate counterions,[156] but even so, the salt was swiftly treated with KI, completing the synthesis of aryl iodide **325**.



Scheme 86: Divergent synthesis of cinnamate **326** and iodide **325** from aldehyde **324**.

With iodide **325** and cinnamate **326** in-hand, the cross-coupling was investigated. Two Heck approaches were available to us: 1) diarylation of ethyl acrylate **328** or 2) monoarylation of cinnamate **326**. Both were performed to assess the most efficient route (Scheme 87). The palladium-catalysed double Heck reaction was tested first, using conditions developed by Chen *et al.*,[152] and this delivered the desired diarylacrylate **327**, albeit in a modest 35% yield. In contrast,

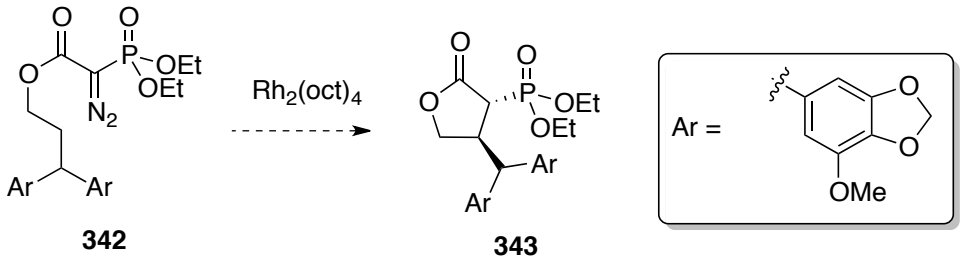
the monoarylation of cinnamate **326** using conditions, developed by Moreno-Mañas,[157] also using iodide **325**, supplied diarylacrylate **327** in a much more practical 87% yield.



Scheme 87: Alternative approaches to diarylacrylate **327**.

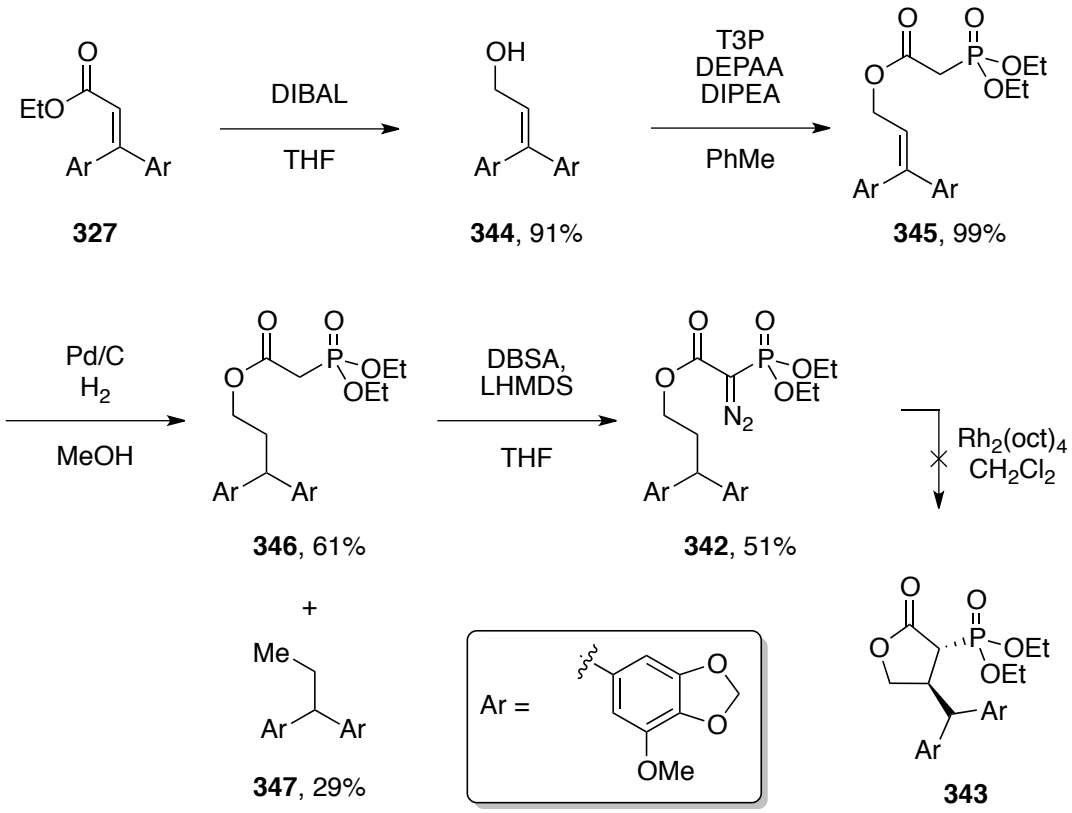
4.7.4.1. Alternative C–H insertion route

Prior to attempting the cyclopropanation route, we decided that an alternative approach, using the C–H insertion methodology developed earlier, could first be attempted, given that we had a sufficient quantity of diarylacrylate **327** in-hand. This route (Scheme 88) was speculative, as previous attempts to incorporate the 3,4-methylenedioxybenzene group were unsuccessful.



Scheme 88: Proposed C–H insertion route towards peperomin E *via* phosphonate **343.**

Following the preparation of diarylacrylate **327**, a simple DIBAL reduction and T3P-mediated acylation afforded phosphonate **345**, which was then was reduced under a hydrogen atmosphere using Pd on carbon, forming saturated phosphonate **346** in 61% yield (Scheme 89). Unfortunately, side-product **347** was formed in 29% yield, arising from an unforeseen π-allyl formation, β-hydride elimination and olefin reduction sequence. Even so, the diazotisation of phosphonate **346** successfully generated the key diazo compound **342** in 51% yield. Following treatment of diazo compound **342** with $Rh_2(oct)_4$ in CH_2Cl_2 for 18 h, the solution had turned from the characteristic green colour to a red-brown. As anticipated, the desired C–H insertion product **343** was not observed by either TLC or ^1H NMR analysis, however, the starting material did remain. Evidently, the presence of the 3,4-methylenedioxy units appears to be detrimental to the catalytic process, probably due to coordination of the oxygen lone pairs to the rhodium carbenoid.



327 **344**, 91% **345**, 99%

346, 61% **342**, 51%

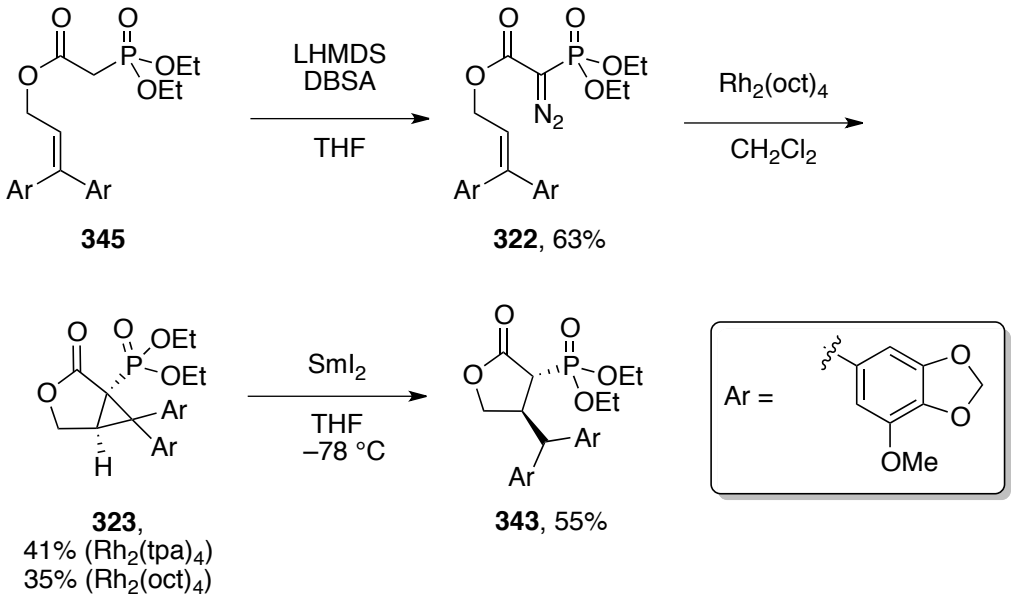
\+

347, 29% **343**

Scheme 89: Attempted synthesis of peperomin E *via* a C–H insertion approach.

4.7.4.2. Cyclopropanation route

Continuing with the originally designed cyclopropanation route, phosphonate **345** was diazotised, furnishing diazo compound **322** in excellent yield. We were then in a position to test the key rhodium(II)-catalysed cyclopropanation step. The treatment of diazo compound **322** under the standard $Rh_2(oct)_4$ conditions delivered the desired bicyclic lactone **323**, although in just 35% yield. A modest improvement could be made, with a 41% isolated yield, by switching to the more bulky $Rh_2(tpa)_4$ catalyst. Then, samarium(II) iodide-mediated reductive ring-opening delivered the monocyclic lactone **343** in good yield.



345

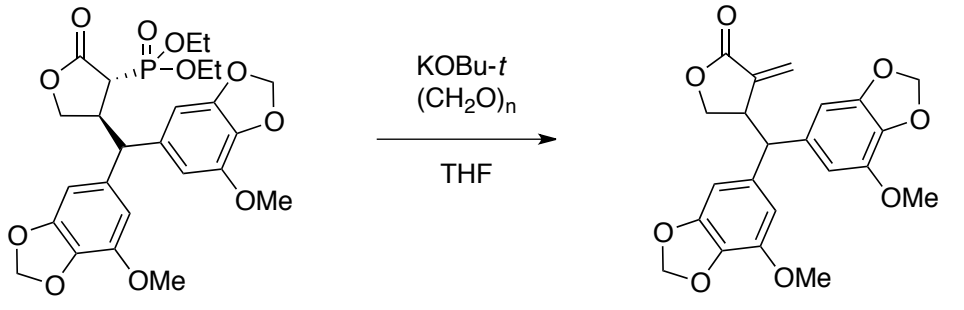
322, 63%

323,
41% ($Rh_2(tpa)_4$)
35% ($Rh_2(oct)_4$)

343, 55%

Scheme 90: Preparation of diazo precursor **322** for the Rh(II)-catalysed cyclopropanation and Sm(II) iodide-mediated ring-opening steps towards peperomin E.

Finally, a facile HWE olefination of phosphonate **343** afforded (±)-peperomin E **308** in excellent yield (Scheme 91), completing its first known synthesis. Spectroscopic data were in accord with those reported in the isolation paper (see Appendix I for comparison tables and spectra).[145]



343

(±)-peperomin E, **308**, 87%

Scheme 91: Horner–Wadsworth–Emmons olefination delivering (±)-peperomin E **308**.

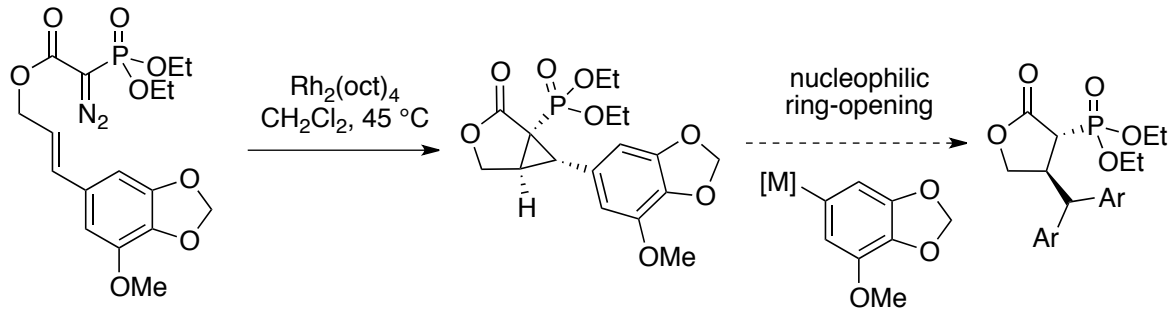
4.8 Conclusions

A simple procedure has been developed for the efficient synthesis of α-phosphoryl-3-oxabicyclo[3.1.0]hexanones, the first successful examples of a rhodium(II)-catalysed cyclopropanation route to this class of compound. A variety of aliphatic and aromatic substituted systems were prepared, exploring the effects of substitution on reaction outcome. As hoped, these systems have been shown to perform well in ring-opening reactions, in line with other donor-acceptor substituted cyclopropanes. The nucleophilic and reductive ring-opening reactions have thus far generated products with complete regio- and diastereoselectivity.

The methodology was successfully applied to the synthesis of three α-methylene-γ-butyrolactone natural products: (±)-savinin **174**, (±)-gadain **307** and notably, the first total synthesis of (±)-peperomin E **308**.

4.9 Future Work

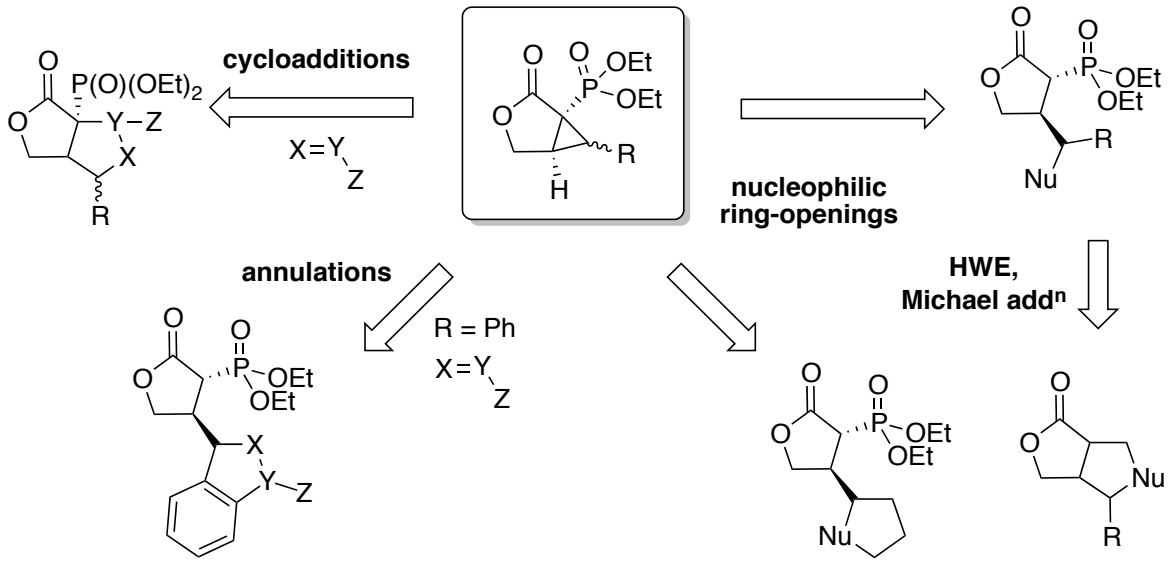
Following the successful synthesis of peperomin E *via* the reductive ring-opening of quaternary bicyclic lactone **323**, a natural extension of the work would be to perform the synthesis using the second proposed route; the nucleophilic ring-opening of tertiary cyclopropane **321**, discussed earlier (see, Scheme 83). Preliminary work towards this goal was performed with the requisite bicyclic lactone **321** synthesised from diazo compound **320** in good yield (Scheme 92). An ensuing ring-opening with the corresponding aryl unit would afford γ-lactone **343**, completing the formal synthesis, but there was insufficient time to complete this sequence.



Scheme 92: Rhodium(II)-catalysed cyclopropanation and proposed nucleophilic ring-opening route towards peperomin E.

The development of general methodology for the nucleophilic ring-opening reactions of α-phosphoryl-3-oxabicyclo[3.1.0]hexanones with a variety of nucleophiles including carbon, oxygen,

nitrogen and sulfur would also be valuable. The phosphonate functional group provides a useful synthetic handle for the installation of olefins, potentially expanding the range of heterocyclic products that could be prepared. The push-pull nature of the donor-acceptor moiety also allows the possibility of performing cycloadditions and annulations (Scheme 93). These reactions need not be limited to bicyclic lactones, with the synthesis of the analogous cyclopentanones and γ-lactams also appearing to be feasible.



Scheme 93: Proposed elaboration of α-phosphoryl-3-oxabicyclo[3.1.0]hexanones.

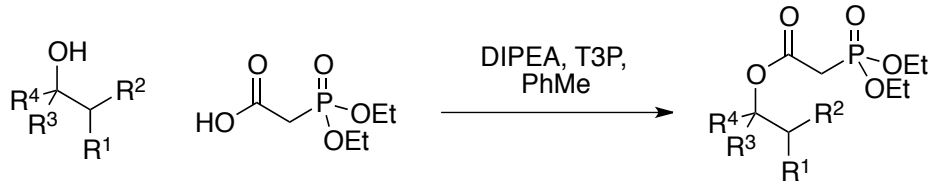
In addition to the above proposed work, the scope of the rhodium(II)-catalysed cyclopropanation reaction could be further examined for the purpose of identifying additional synthetically valuable frameworks. Furthermore, in line with previous precedent within the Taylor group, the development of tandem processes and combining multiple aspects of these reactions would also serve to increase the impact of these procedures, with the development of a one-pot ring-opening and HWE olefination procedure for the synthesis of α-methylene-γ-butyrolactones, being the ultimate goal.

Chapter 5 – Experimental

5.1 General Experimental Details

Except where stated, all reagents were purchased from commercial sources and used without further purification. Except where stated, all experimental procedures were carried out under an atmosphere of argon or nitrogen. Anhydrous CH_2Cl_2, toluene and DMF were obtained from an Innovative Technology Inc. PureSolv® solvent purification system. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl immediately before use. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer, operating at 400 MHz, 100 MHz and 162 MHz respectively. All spectral data were acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peak, δ_H 7.26 and δ_C 77.0 for $CDCl_3$, δ_H 2.50 and δ_C 39.5 for DMSO-d_6 and δ_H 7.16 and δ_C 128.1 for benzene-d_6 was used as a reference. Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.1 Hz. The multiplicity abbreviations used are: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Signal assignment was achieved by analysis of DEPT, COSY, NOESY, HMBC and HSQC experiments where required. Spectra were processed using 'iNMR' software which can be obtained free of charge online. Infrared (IR) spectra were recorded on either a ThermoNicolet IR-100 spectrometer with NaCl plates as a thin film dispersed from either CH_2Cl_2 or $CDCl_3$, or a PerkinElmer UATR Two spectrometer. Mass-spectra were obtained by the University of York Mass Spectrometry Service, using electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using Gallenkamp apparatus and are uncorrected. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. Flash column chromatography was carried out using slurry packed Fluka silica gel (SiO_2), 35–70 μm, 60 Å, under a light positive pressure, eluting with the specified solvent system. No issues associated with instability or decomposition of the azide reagents or diazo products were observed, with no special handling precautions required. Numbering schemes for compounds refer to NMR assignments not to compound naming.

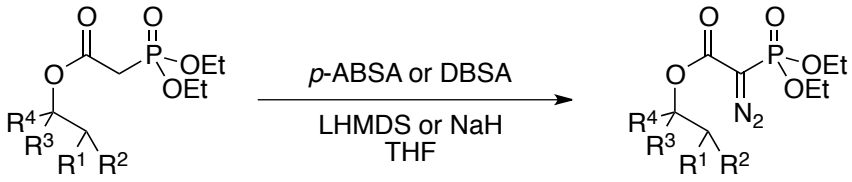
General procedure A: Esterifications using T3P



A **DEPAA** **B**

To a stirred solution of alcohol **A** (8.00 mmol) in toluene (40 mL) under an atmosphere of argon, was added sequentially DEPAA (8.40 mmol, 1.05 eq.), DIPEA (20.8 mmol, 2.6 eq.) and T3P (10.4 mmol, 1.3 eq., 50% w/w solution in EtOAc/THF). The solution was stirred at RT for 1–4 h after which time it was diluted with water (50 mL) and extracted with EtOAc (3 × 100 mL) followed by sequential washing of the combined organic extracts with 10% aq. HCl (50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL). The organic extract was then dried over $MgSO_4$ and concentrated *in vacuo*, affording the α-(diethoxyphosphoryl)acetate product **B**, which was used without further purification.

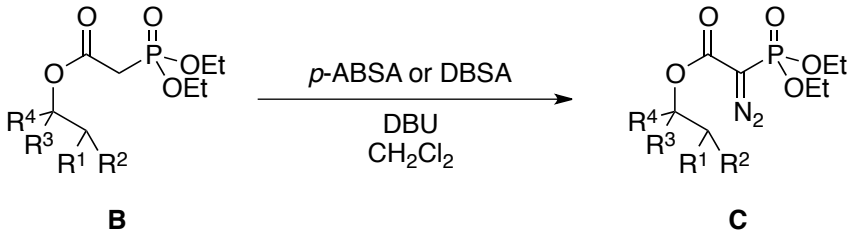
General procedure B: Diazotisation reactions using LHMDS or NaH



B **C**

To a stirred solution of α-(diethoxyphosphoryl)acetate **B** (5.0 mmol) in THF (25 mL, 5 mL/mmol), cooled to −78 °C under an atmosphere of argon, was added LHMDS (6.0 mmol, 1.2 eq., 1.0 M solution in THF) or NaH (6.0 mmol, 1.2 eq., 60% dispersion in mineral oil). The solution was allowed to warm at RT and stirred for 10 mins, after which time *p*-ABSA or DBSA (6.0 mmol, 1.2 eq.) was added to the solution. After stirring for 1 h at RT the mixture was diluted with diethyl ether (100 mL) and water (25 mL) prior to extraction with diethyl ether (3 × 50 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (2 × 25 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the α-diazo(diethoxyphosphoryl)acetate product **C**.

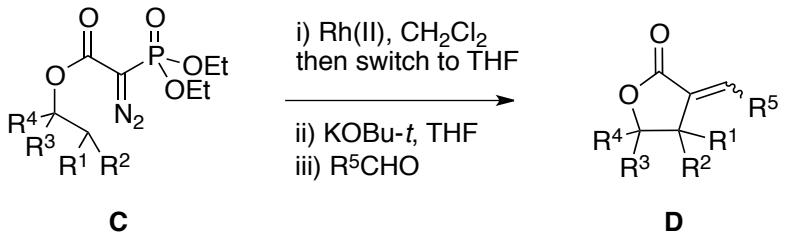
General procedure C: Diazotisation reactions using DBU



B **C**

To a stirred solution of α-(diethoxyphosphoryl)acetate **B** (5.0 mmol) and *p*-ABSA or DBSA (7.5 mmol, 1.5 eq.) in CH_2Cl_2 (50 mL, 10 mL/mmol) cooled to 0 °C under an atmosphere of argon, was added DBU (7.5 mmol, 1.5 eq.) dropwise. The solution was stirred overnight with warming at RT, after which time the mixture was filtered through a pad of Celite and silica. The filtrate was concentrated *in vacuo* then purified by column chromatography affording the α-diazo(diethoxyphosphoryl)acetate product **C**.

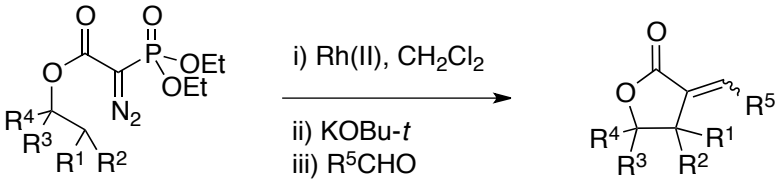
General procedure D: One-pot Rh(II)-catalysed C-H insertion/olefination (CH_2Cl_2 with THF switch)



C **D**

To an oven dried sealable tube containing α-diazo(diethoxyphosphoryl)acetate **C** (0.200 mmol) flushed with argon was added CH_2Cl_2 (4.0 mL) followed by $Rh_2(oct)_4$ or $Rh_2(esp)_2$ (2 or 5 mol%). The solution was stirred at 45 °C for 20 h and then concentrated *in vacuo*. The residue was diluted with THF (4.0 mL) and cooled to 0 °C prior to the addition of KOBu-*t* (0.9, 1.2 or 1.5 equiv.) which was stirred at 0 °C for 60 mins and then cooled to −78 °C. Aldehyde (2.0, 5.0 or 10.0 equiv.) was added to the solution and stirred for 15 mins at −78 °C and a further 2 h at either 0 °C, RT or reflux. The solution was quenched with sat. aq. NH_4Cl (10 mL) and then diluted with CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous extracted with EtOAc (2 × 20 mL). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromatography affording the α-methylene/alkylidene-γ-butyrolactone product **D**.

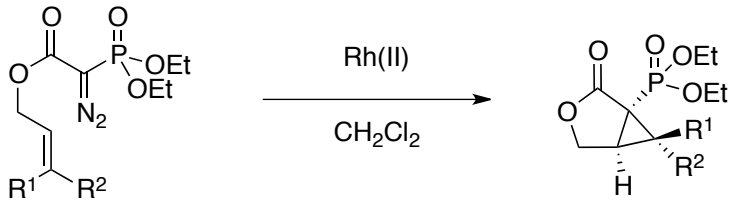
General procedure E: One-pot Rh(II)-catalysed C-H insertion/olefination (CH_2Cl_2)



C **D**

To an oven dried sealable tube containing α-diazo(diethoxyphosphoryl)acetate **C** (0.200 mmol) flushed with argon was added CH_2Cl_2 (4.0 mL) followed by $Rh_2(oct)_4$ or $Rh_2(esp)_2$ (2 or 5 mol%). The solution was stirred at 45 °C for 20 h. The solution was cooled to 0 °C prior to the addition of KOBu-*t* (0.9, 1.2 or 1.5 equiv.) which was stirred at 0 °C for 60 mins and then cooled to −78 °C. Aldehyde (2.0, 5.0 or 10.0 equiv.) was added to the solution and stirred for 15 mins at −78 °C and a further 2 h at either 0 °C, RT or reflux. The solution was quenched with sat. aq. NH_4Cl (10 mL) and then diluted with CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromatography affording the α-methylene/alkylidene-γ-butyrolactone product **D**.

General procedure F: Rh(II)-catalysed cyclopropanation

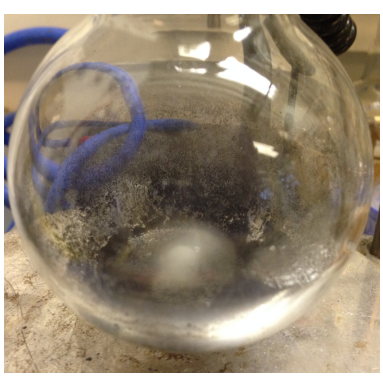


E **F**

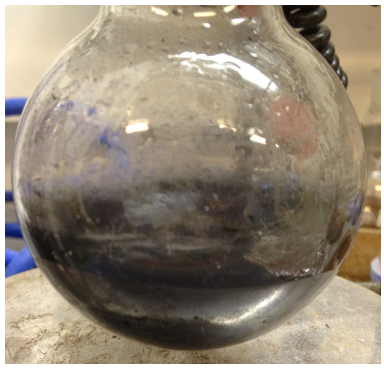
To an oven dried sealable tube containing α-diazo-α-(dialkoxyphosphoryl)acetate **E** (0.200 mmol) flushed with argon was added CH_2Cl_2 (4.0 mL) followed by $Rh_2(oct)_4$ (2 mol%). The solution was stirred at 45 °C for 20 h and then concentrated *in vacuo*. The residue was purified by column chromatography affording the 3-oxabicyclo[3.1.0]hexan-2-one product **F**.

Preparation of samarium(II) iodide in THF (~0.1 M)

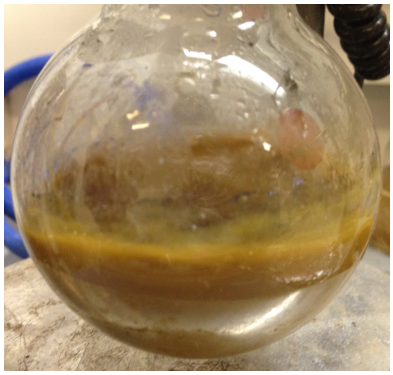
To an oven dried 100 mL one-neck RBF equipped with oven dried Teflon-coated magnetic stirrer bar, was added samarium metal (825 mg, 6.50 mmol, 99.9% REO (Rare Earth Oxide basis), powder, Strem). [The samarium appeared as silvery/grey and metallic at this point.] The flask was tightly sealed with a suba-seal and wrapped in Parafilm®, then purged with argon (balloon) for 10 mins. This was stirred under a positive pressure of argon and stirred at medium to high speed for 16 h. [The samarium appeared as a fine black powder at this point (**A**).] THF (22.5 mL) was added, followed by iodine (698 mg, 2.75 mmol) dissolved in THF (5 mL). [The solution immediately turned from a black suspension to an orange/brown suspension (**B**).] The suba-seal was again wrapped with Parafilm® and stirring was continued for 2 h. [The mixture turned from orange/brown to green then to dark blue, almost black, typically within the first 5–15 mins (**C**–**F**).] The solution of SmI_2 (~0.1 M) was allowed to settle prior to use.
See images below for colour changes.



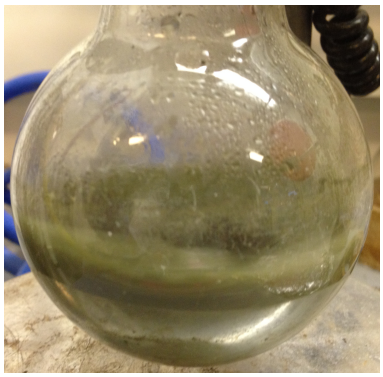
A



B

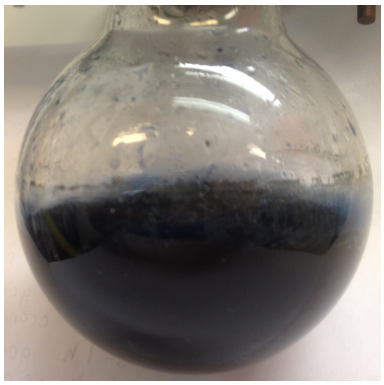


C



D

E



F

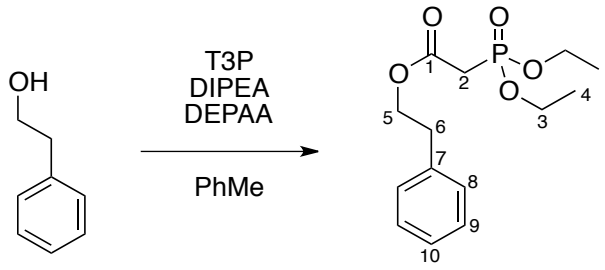
5.2 Reaction procedures and compound characterisations

5.2.1. Chapter 2

5.2.1.1. Preparation of α-methylene-γ-butyrolactones

Experimental procedures and full characterisation data are provided for all novel compounds. Literature compounds are not reported, but were prepared according to the available procedures, where provided, or adapted from similar procedures.

Phenethyl 2-(diethoxyphosphoryl)acetate (116a)

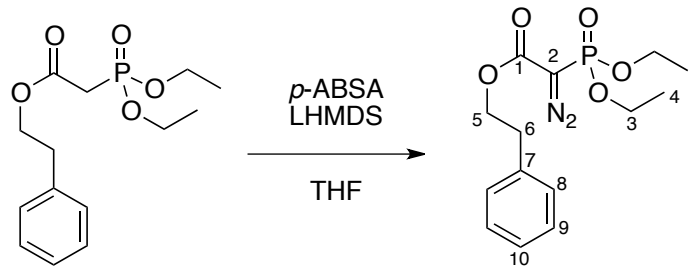


116 **116a**

Synthesised using general procedure A with phenethyl alcohol **116** (977 mg, 8.00 mmol), toluene (40 mL), DEPAA (1.35 mL, 8.40 mmol), DIPEA (3.62 mL, 20.8 mmol) and T3P (6.62 g, 10.4 mmol, 50% w/w solution in EtOAc) affording the *title compound* **116a** as a yellow oil (2.40 g, 100%). No further purification was required; R_f 0.34 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2984s, 1738s, 1269m, 1052m, 1025m; δ_H (400 MHz, $CDCl_3$) 1.31 (6 H, td, J = 7.1, J = 0.5, H-4), 2.96 (2 H, t, J = 7.2, H-6), 2.96 (2 H, d, J = 21.6, H-2), 4.13 (4 H, dq, J = 8.3, J = 7.1, H-3), 4.35 (2 H, t, J = 7.2, H-5), 7.20–7.25 (3 H, m, H-8/9,10), 7.28–7.33 (2 H, m, H-8/9); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.2, C-4), 34.3 (d, J = 134.3, C-2), 34.8 (C-6), 62.6 (d, J = 6.4, C-3), 66.0 (C-5), 126.6 (C-10), 128.5 (C-9), 128.8 (C-8), 137.4 (C-7), 165.7 (d, J = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.2; HRMS (ESI^+): Found: 323.1020; $C_{14}H_{21}NaO_5P$ (MNa^+) Requires 323.1019 (–0.3 ppm error), Found: 301.1200; $C_{14}H_{22}O_5P$ (MH^+) Requires 301.1199 (–0.1 ppm error).

Lab notebook reference: MGL/02/55

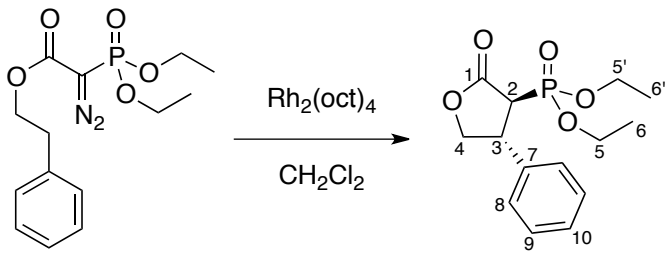
Phenethyl 2-diazo-2-(diethoxyphosphoryl)acetate (116b)



116a **116b**

Synthesised using general procedure B with phenethyl 2-(diethoxyphosphoryl)acetate **116a** (2.39 g, 7.96 mmol), THF (40 mL), LHMDS (9.55 mL, 9.55 mmol, 1.0 M solution in THF) and *p*-ABSA (2.29 g, 9.55 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **116b** as a golden yellow oil (1.42 g, 55%); R_f 0.48 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2984m, 2925m, 2129s, 1709s, 1280s, 1022s; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, J = 7.1, J = 0.7, H-4), 2.97 (2 H, t, J = 6.9, H-6), 4.04–4.23 (4 H, m, H-3), 4.41 (2 H, t, J = 6.9, H-5), 7.19–7.26 (3 H, m, H-8/9,10), 7.28–7.34 (2 H, m, H-8/9); δ_C (100 MHz, $CDCl_3$) 16.0 (d, J = 6.9, C-4), 35.0 (C-6), 53.8 (d, J = 226.7, C-2), 63.5 (d, J = 5.9, C-3), 65.9 (C-5), 126.6 (C-10), 128.4 (C-9), 128.8 (C-8), 137.2 (C-7), 163.2 (d, J = 12.3, C-1); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI$^+$): Found: 349.0921; $C_{14}H_{19}N_2NaO_5P$ (MNa^+) Requires 349.0929 (2.4 ppm error), Found: 327.1100; $C_{14}H_{20}N_2O_5P$ (MH^+) Requires 327.1110 (3.2 ppm error).
Lab notebook reference: MGL/01/03, 02/56

Diethyl ((3*SR*,4*RS*)-2-oxo-4-phenyltetrahydrofuran-3-yl)phosphonate (116c)



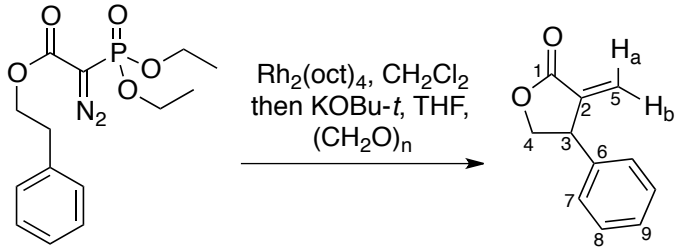
116b **116c**

To an oven dried sealable tube containing phenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **116b** (51 mg, 0.160 mmol) flushed with argon was added CH_2Cl_2 (3.2 mL) followed by $Rh_2(oct)_4$ (6.1 mg, 7.8 μmol). The solution was stirred at 45 °C for 23 h. Concentration *in vacuo* and purification by column chromatography (1:1 petrol:EtOAc) afforded the *title compound* **116c** as a colourless oil that crystallised on standing (24 mg, 51%); R_f 0.25 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1}

2984w, 2912w, 1775s, 1253w, 1205m; m.p. 73–77 °C; δ_H (400 MHz, $CDCl_3$) 1.26 (3 H, td, *J* = 7.1, *J* = 0.5, H-6/6'), 1.31 (3 H, td, *J* = 7.1, *J* = 0.5, H-6/6'), 3.16 (1 H, dd, *J* = 23.8, *J* = 5.9, H-2), 4.00–4.26 (5 H, m, H-3,5,5'), 4.35 (1 H, dd, *J* = 9.1, *J* = 5.1, H-4), 4.77 (1 H, dd, *J* = 9.1, *J* = 7.8, H-4), 7.23–7.27 (2 H, m, H-8), 7.28–7.33 (1 H, m, H-10), 7.34–7.39 (2 H, m, H-9); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.2, C-6/6'), 16.3 (d, *J* = 6.1, C-6/6'), 43.5 (d, *J* = 2.1, C-3), 47.2 (d, *J* = 140.4, C-2), 63.1 (d, *J* = 6.9, C-5/5'), 63.8 (d, *J* = 6.6, C-5/5'), 73.7 (d, *J* = 6.8, C-4), 126.7 (C-8), 128.0 (C-10), 129.2 (C-9), 140.2 (d, *J* = 7.9, C-7), 171.6 (d, *J* = 2.9, C-1); δ_P (162 MHz, $CDCl_3$) 19.8; HRMS (ESI^+): Found: 321.0855; $C_{14}H_{19}NaO_5P$ (MNa^+) Requires 321.0862 (2.4 ppm error), Found: 299.1035; $C_{14}H_{20}O_5P$ (MH^+) Requires 299.1043 (2.5 ppm error).
Lab notebook reference: MGL/01/04, 01/05

Note: The ^{1}H NMR data of compound **116c** match those reported[158] with the exception of the H-3 resonance: 4.00−4.26 (5 H, m, H-3,5a,5b) [lit. 3.65 (dd, J = 6.5 Hz, $^3J_{PH}$ = 6.0 Hz, 1H, H-3)]. In view of the fact that the X-ray structure of **116c** was solved it seems likely that there is an error in the previously reported data.

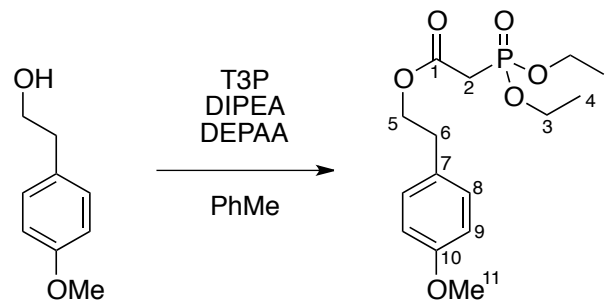
(*SR*)-3-Methylene-4-phenyldihydrofuran-2(3*H*)-one (116d)



116b **116d**

Synthesised using general procedure E with phenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **116b** (71 mg, 0.218 mmol), CH_2Cl_2 (4.4 mL), $Rh_2(oct)_4$ (3.4 mg, 4.4 μmol), KOBu-*t* (29.3 mg, 0.262 mmol) and paraformaldehyde (13.1 mg, 0.436 mmol). Purification by column chromatography (5:1 petrol:EtOAc) afforded the title compound as a colourless oil (28 mg, 74%); R_f 0.52 (4:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2919s, 1763s, 1108s, 1018s; δ_H (400 MHz, $CDCl_3$) 4.21–4.31 (2 H, m, H-3,4), 4.68–4.77 (1 H, m, H-4), 5.49 (1 H, d, *J* = 2.7, H-5b), 6.39 (1 H, d, *J* = 3.1, H-5a), 7.21–7.25 (2 H, m, H-7), 7.29–7.34 (1 H, m, H-9), 7.35–7.41 (2 H, m, H-8); δ_C (100 MHz, $CDCl_3$) 45.6 (C-3), 72.7 (C-4), 124.0 (C-5), 127.8 (C-7/8/9), 127.8 (C-7/8/9) 129.2 (C-7/8/9), 138.8 (C-2/6), 139.5 (C-2/6), 170.1 (C-1); HRMS (ESI^+): Found: 197.0571; $C_{11}H_{10}NaO_2$ (MNa^+) Requires 197.0578 (3.6 ppm error), Found: 175.0752; $C_{11}H_{11}O_2$ (MH^+) Requires 175.0759 (3.8 ppm error).
Lab notebook reference: MGL/03/03, 01/10
Obtained data in accord with reported literature.[159]

4-Methoxyphenethyl 2-(diethoxyphosphoryl)acetate (117a)

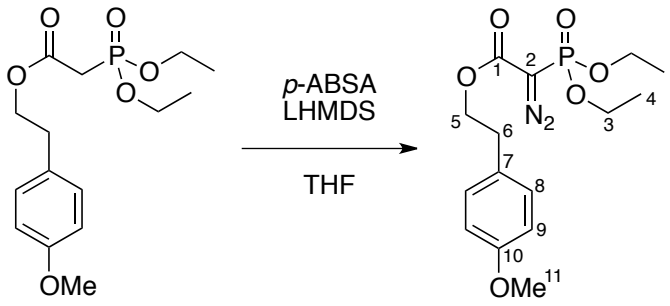


117 **117a**

Synthesised using general procedure A with 4-methoxyphenethyl alcohol **117** (3.00 g, 19.7 mmol), toluene (100 mL), DEPAA (3.32 mL, 20.7 mmol), DIPEA (8.93 mL, 51.3 mmol) and T3P (16.3 g, 25.6 mmol, 50% w/w solution in THF) affording the *title compound* **117a** as a yellow oil (6.53 g, 100%). No further purification was required; R_f 0.21 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 3419w, 2937s, 1709s, 1491m, 1229s, 1098w, 1011s, 955w; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, J = 7.1, J = 0.5, H-4), 2.89 (2 H, t, J = 7.2, H-6), 2.95 (2 H, d, J = 21.6, H-2), 3.78 (3 H, s, H-11), 4.13 (4 H, dq, J = 8.2, J = 7.1, H-3), 4.31 (2 H, t, J = 7.2, H-5), 6.84 (2 H, d, J = 8.7, H-9), 7.14 (2 H, d, J = 8.7, H-8); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.3, C-4), 34.0 (C-6), 34.3 (d, J = 134.2, C-2), 55.2 (C-11), 62.6 (d, J = 6.2, C-3), 66.2 (C-5), 113.9 (C-9), 129.4 (C-7), 129.8 (C-8), 158.7 (C-10), 165.9 (d, J = 6.3, C-1); δ_P (162 MHz, $CDCl_3$) 20.3; HRMS (ESI^+): Found: 353.1117; $C_{15}H_{23}NaO_6P$ (MNa^+) Requires 353.1124 (2.2 ppm error), Found: 331.1302; $C_{15}H_{24}O_6P$ (MH^+) Requires 331.1305 (0.9 ppm error).

Lab notebook reference: MGL/01/16

4-Methoxyphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate (117b)

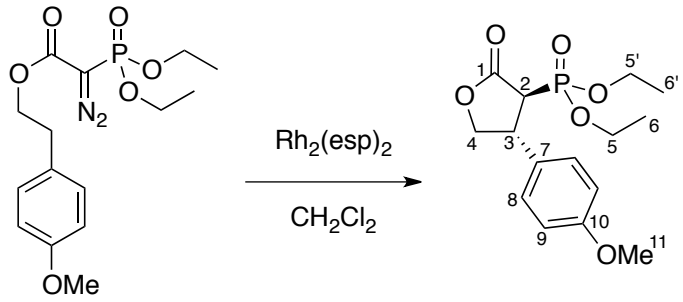


117a **117b**

Synthesised using general procedure B with 4-methoxyphenethyl 2-(diethoxyphosphoryl)acetate **117a** (3.30 g, 10.0 mmol), THF (50 mL), LHMDS (12.0 mL, 12.0 mmol, 1.0 M solution in THF) and *p*-ABSA (2.88 g, 12.0 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **117b** as a pale yellow oil (2.00 g, 56%); R_f 0.43 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 3434m, 2939s, 2794s, 2097s, 1682s, 1491m, 1261m, 1230w, 1007w, 964w; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, *J* = 7.1, *J* = 0.8, H-4), 2.90 (2 H, t, *J* = 6.9, H-6), 3.78 (3 H, s, H-11), 4.04–4.22 (4 H, m, H-3), 4.36 (2 H, t, *J* = 6.9, H-5), 6.83 (2 H, d, *J* = 8.8, H-9), 7.12 (2 H, d, *J* = 8.8, H-8); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* = 6.9, C-4), 34.2 (C-6), 53.7 (d, *J* = 226.0, C-2), 55.2 (C-11) 63.5 (d, *J* = 5.6, C-3), 66.1 (C-5), 113.9 (C-9), 129.2 (C-7), 129.8 (C-8), 158.3 (C-10), 163.2 (d, *J* = 12.2, C-1); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI$^+$): Found: 379.1011; $C_{15}H_{21}N_2NaO_6P$ (MNa^+) Requires 379.1029 (4.8 ppm error), Found: 357.1196; $C_{15}H_{22}N_2O_6P$ (MH^+) Requires 357.1210 (4.0 ppm error).

Lab notebook reference: MGL/01/18

Diethyl ((3*SR*,4*RS*)-4-(4-methoxyphenyl)-2-oxotetrahydrofuran-3-yl)phosphonate (117c)

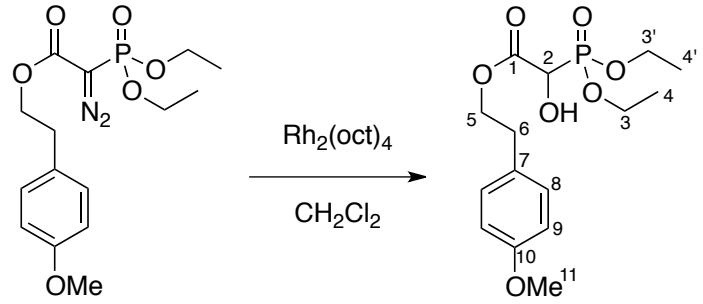


117b **117c**

To an oven dried sealable tube containing 4-methoxyphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **117b** (62 mg, 0.174 mmol) flushed with argon was added CH_2Cl_2 (3.5 mL) followed by $Rh_2(esp)_2$ (11.0 mg, 14.0 μmol). The solution was stirred at 45 °C for 23 h. Concentration *in vacuo* and purification by column chromatography (1:1 petrol:EtOAc) afforded the *title compound* **117c** as a colourless oil (67 mg, 64%); R_f 0.26 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 3412s, 2937s, 2870s, 2796w, 1748s, 1588w, 1493m, 1233m, 1162w, 1011m, 959w; δ_H (400 MHz, $CDCl_3$) 1.25 (3 H, td, J = 7.1, J = 0.5, H-6/6'), 1.30 (3 H, td, J = 7.1, J = 0.5, H-6/6'), 3.10 (1 H, dd, J = 23.8, J = 6.2, H-2), 3.78 (3 H, s, H-11), 3.95–4.24 (5 H, m, H-3,5), 4.28 (1 H, dd, J = 9.1, J = 5.3, H-4), 4.72 (1 H, dd, J = 9.1, J = 7.8, H-4), 6.87 (2 H, d, J = 8.7, H-9), 7.15 (2 H, d, J = 8.7, H-8); δ_C (100 MHz, $CDCl_3$) 16.2 (d, J = 6.2, C-6/6'), 16.3 (d, J = 6.2, C-6/6'), 42.7 (d, J = 2.2, C-3), 47.3 (d, J = 140.4, C-2), 55.3 (C-11), 62.9 (d, J = 6.8, C-5/5'), 63.7 (d, J = 6.4, C-5/5'), 73.8 (d, J = 7.0, C-4), 114.5 (C-9), 127.7 (C-8), 132.0 (d, J = 7.8, C-7), 159.1 (C-10), 171.6 (d, J = 2.7, C-1); δ_P (162 MHz, $CDCl_3$) 19.9; HRMS (ESI^+): Found: 351.0961; $C_{15}H_{21}NaO_6P$ (MNa^+) Requires 351.0968 (1.9 ppm error), Found: 329.1160; $C_{15}H_{22}O_6P$ (MH^+) Requires 329.1149 (−3.6 ppm error).

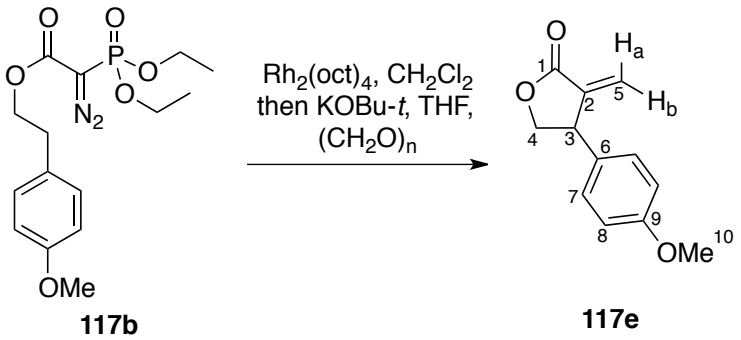
Lab notebook reference: MGL/01/19

4-Methoxyphenethyl 2-(diethoxyphosphoryl)-2-hydroxyacetate (117d)



To a solution of 4-methoxyphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **117b** (75.0 mg, 0.210 mmol) in CH_2Cl_2 (40 mL) in a 100 mL rbf, fitted with a reflux condenser flushed with argon was added $Rh_2(oct)_4$ (3.3 mg, 4.2 μmol). The solution was stirred at 45 °C for 24 h. Concentration *in vacuo* and purification by column chromatography (1:2 petrol:EtOAc) afforded the *title compound* **117d** as a colourless oil (37 mg, 51%); R_f 0.17 (1:2 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 3272br, 2983w, 2845w, 1748s, 1613w, 1514s, 1246s, 1178w, 1101m, 1023s, 975m; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, t, *J* = 7.1, H-4,4'), 2.95 (2 H, t, *J* = 7.2, H-6), 3.25 (1 H, br s, O*H*), 3.78 (3 H, s, H-11), 4.11–4.23 (4 H, m, H-3), 4.44 (2 H, t, *J* = 7.2, H-5), 4.52 (1 H, d, *J* = 15.7, H-2), 6.84 (2 H, d, *J* = 8.7, H-9), 7.15 (2 H, d, *J* = 8.7, H-8); δ_C (100 MHz, $CDCl_3$) 16.4 (d, *J* = 5.9, C-4,4'), 34.0 (C-6), 55.2 (C-11), 63.5 (d, *J* = 6.8, C-3/3'), 63.8 (d, *J* = 6.8, C-3/3'), 67.3 (C-5), 68.8 (d, *J* = 154.8, C-2), 114.0 (C-9), 128.9 (C-7), 129.9 (C-8), 158.5 (C-10), 169.5 (C-1); δ_P (162 MHz, $CDCl_3$) 16.1; HRMS (ESI^+): Found: 369.1064; $C_{15}H_{23}NaO_7P$ (MNa^+) Requires 369.1074 (2.5 ppm error).
Lab notebook reference: MGL/02/50B

(*SR*)-4-(4-Methoxyphenyl)-3-methylenedihydrofuran-2(3*H*)-one (117e)

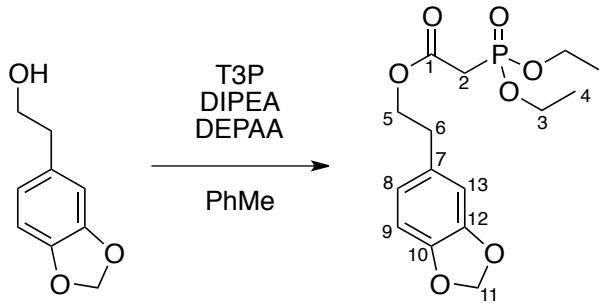


Synthesised using general procedure D with 4-methoxyphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **117b** (68 mg, 0.191 mmol), CH_2Cl_2 (3.8 mL), $Rh_2(oct)_4$ (3.0 mg, 3.8

μmol), THF (3.8 mL), KOBu-*t* (32.1 mg, 0.287 mmol) and paraformaldehyde (11.5 mg, 0.382 mmol). Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound* **117e** as a colourless oil (30 mg, 71%); R_f 0.30 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3456s, 2914m, 2872s, 2795s, 1740s, 1587m, 1491s, 1273w, 1233m, 1163w, 1094w, 1016w, 821w; δ_H (400 MHz, $CDCl_3$) 3.81 (3 H, s, H-10), 4.16–4.24 (2 H, m, H-3,4), 4.64–4.74 (1 H, m, H-4), 5.46 (1 H, d, *J* = 2.7, H-5b), 6.36 (1 H, d, *J* = 3.0, H-5a), 6.90 (2 H, d, *J* = 8.7, H-8), 7.14 (2 H, d, *J* = 8.7, H-7); δ_C (100 MHz, $CDCl_3$) 45.0 (C-3), 55.3 (C-10), 72.9 (C-4), 114.5 (C-8), 123.7 (C-5), 129.0 (C-7) 131.3 (C-6), 139.1 (C-2), 159.1 (C-9), 170.2 (C-1); HRMS (ESI$^+$): Found: 227.0688; $C_{12}H_{12}NaO_3$ (MNa^+) Requires 227.0679 (–4.3 ppm error).

Lab notebook reference: MGL/03/94, 01/20

2-(1,3-Benzodioxol-5-yl)ethyl 2-(diethoxyphosphoryl)acetate (118a)

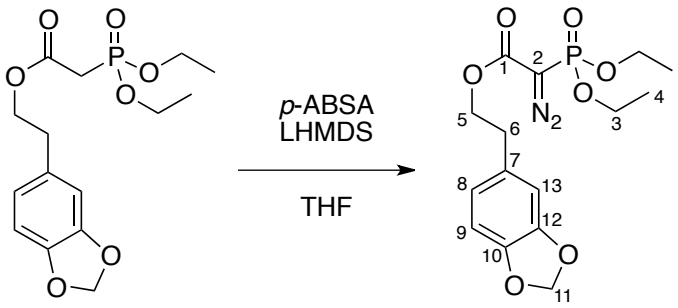


118 **118a**

Synthesised using general procedure A with 2-(1,3-benzodioxol-5-yl)ethanol **118** (1.31 g, 7.85 mmol), toluene (40 mL), DEPAA (1.33 mL, 8.25 mmol), DIPEA (3.56 mL, 20.4 mmol) and T3P (6.50 g, 10.2 mmol, 50% w/w solution in EtOAc) affording the *title compound* **118a** as an orange oil (2.69 g, 100%). No further purification was required; R_f 0.35 (1:2 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2938s, 2865s, 1710s, 1468m, 1230s, 1013m; δ_H (400 MHz, $CDCl_3$) 1.31 (6 H, td, *J* = 7.1, *J* = 0.4, H-4), 2.86 (2 H, t, *J* = 7.1, H-6), 2.94 (2 H, d, *J* = 21.6, H-2), 4.13 (4 H, dq, *J* = 8.3, *J* = 7.1, H-3), 4.28 (2 H, t, *J* = 7.1, H-5), 5.91 (2 H, s, H-11), 6.65 (1 H, dd, *J* = 7.9, *J* = 1.7, H-8), 6.71 (1 H, d, *J* = 1.7, H-13), 6.72 (1 H, d, *J* = 7.9, H-9); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.2, C-4), 34.3 (d, *J* = 134.3, C-2), 34.6 (C-6), 62.6 (d, *J* = 6.2, C-3), 66.1 (C-5), 100.8 (C-11), 108.2 (C-9), 109.2 (C-13), 121.8 (C-8), 131.1 (C-7), 146.2 (C-10), 147.6 (C-12), 165.7 (d, *J* = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.2; HRMS (ESI$^+$): Found: 367.0908; $C_{15}H_{21}NaO_7P$ (MNa^+) Requires 367.0917 (2.5 ppm error), Found: 345.1090; $C_{15}H_{22}O_7P$ (MH^+) Requires 345.1098 (2.2 ppm error).

Lab notebook reference: MGL/01/34

2-(1,3-Benzodioxol-5-yl)ethyl 2-diazo-2-(diethoxyphosphoryl)acetate (118b)

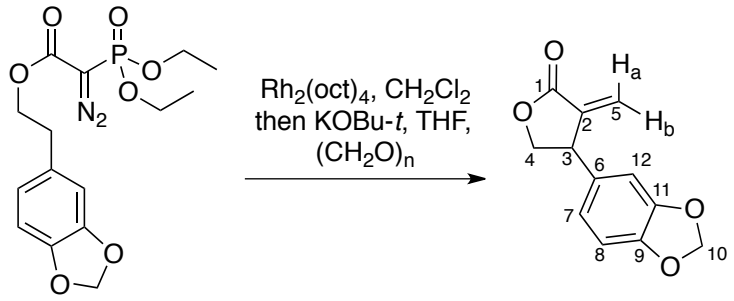


118a **118b**

Synthesised using general procedure B with 2-(1,3-benzodioxol-5-yl)ethyl 2-(diethoxyphosphoryl)acetate **118a** (3.44 g, 10.00 mmol), THF (50 mL), LHMDS (12.0 mL, 12.0 mmol, 1.0 M solution in THF) and *p*-ABSA (2.88 g, 12.0 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **118b** as a yellow oil (2.02 g, 55%); R_f 0.38 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2939s, 2098s, 1683s, 1468w, 1262s, 1229w, 1008m; δ_H (400 MHz, $CDCl_3$) 1.33 (6 H, td, J = 7.1, J = 0.8, H-4), 2.87 (2 H, t, J = 6.9, H-6), 4.06–4.24 (4 H, m, H-3), 4.34 (2 H, t, J = 6.9, H-5), 5.92 (2 H, s, H-11), 6.64 (1 H, dd, J = 7.9, J = 1.7, H-8), 6.70 (1 H, d, J = 1.7, H-13), 6.73 (1 H, d, J = 7.9, H-9); δ_C (100 MHz, $CDCl_3$) 16.1 (d, J = 6.9, C-4), 34.8 (C-6), 53.9 (d, J = 227.3, C-2), 63.6 (d, J = 5.5, C-3), 66.1 (C-5), 100.9 (C-11), 108.3 (C-9), 109.3 (C-13), 121.8 (C-8), 131.0 (C-7), 146.3 (C-10), 147.7 (C-12), 163.3 (d, J = 12.3, C-1); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI^+): Found: 393.0807; $C_{15}H_{19}N_2NaO_7P$ (MNa^+) Requires 393.0822 (3.9 ppm error), Found: 371.1000; $C_{15}H_{20}N_2O_7P$ (MH^+) Requires 371.1003 (0.8 ppm error).

Lab notebook reference: MGL/01/35

(*SR*)-4-(1,3-Benzodioxol-5-yl)-3-methylenedihydrofuran-2(3*H*)-one (118c)

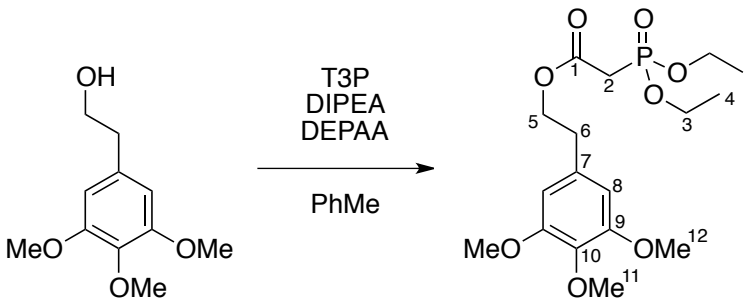


118b **118c**

Synthesised using general procedure E with 2-(1,3-benzodioxol-5-yl)ethyl 2-diazo-2-(diethoxyphosphoryl)acetate **118b** (79 mg, 0.213 mmol), CH_2Cl_2 (4.2 mL), $Rh_2(oct)_4$ (3.3 mg, 4.3 μmol), KOBu-*t* (28.7 mg, 0.256 mmol) and paraformaldehyde (12.8 mg, 0.426 mmol). Purification by column chromatography (4:1 petrol:EtOAc) afforded the *title compound* **118c** as a white solid (30 mg, 64%); R_f 0.47 (2:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2873s, 1737s, 1481w, 1466m, 1229s, 1022m; δ_H (400 MHz, $CDCl_3$) 4.14–4.23 (2 H, m, H-3,4), 4.64–4.72 (1 H, m, H-4), 5.50 (1 H, d, *J* = 2.7, H-5b), 5.97 (2 H, s, H-10), 6.39 (1 H, dd, *J* = 3.0, H-5a), 6.68 (1 H, d, *J* = 1.8, H-12), 6.69 (1 H, dd, *J* = 7.8, *J* = 1.8, H-7), 6.79 (1 H, d, *J* = 7.8, H-8); δ_C (100 MHz, $CDCl_3$) 45.5 (C-3), 72.7 (C-4), 101.3 (C-10), 107.8 (C-12), 108.6 (C-8), 121.5 (C-7), 124.0 (C-5), 133.1 (C-6), 138.8 (C-2), 147.2 (C-9), 148.4 (C-11), 170.1 (C-1); HRMS (ESI^+): Found: 241.0482; $C_{12}H_{10}NaO_4$ (MNa^+) Requires 241.0471 (–4.3 ppm error), Found: 219.0657; $C_{12}H_{11}O_4$ (MH^+) Requires 219.0652 (–2.5 ppm error).

Lab notebook reference: MGL/03/04, 01/39, 01/40

3,4,5-Trimethoxyphenethyl 2-(diethoxyphosphoryl)acetate (119a)

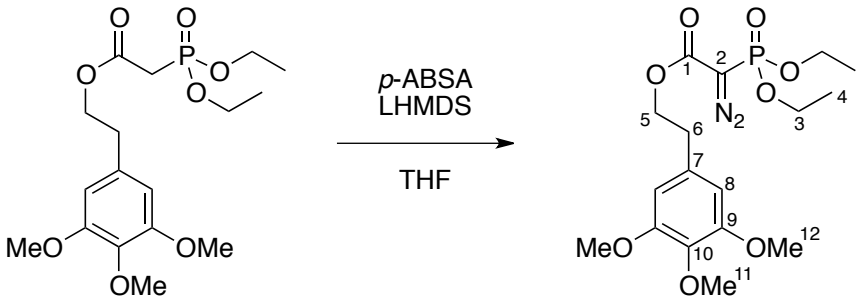


119 **119a**

Synthesised using general procedure A with 2-(3,4,5-trimethoxyphenyl)ethanol **119** (205 mg, 0.966 mmol), toluene (4.80 mL), DEPAA (0.16 mL, 1.01 mmol), DIPEA (0.44 mL, 2.51 mmol) and T3P (0.80 g, 1.26 mmol, 50% w/w solution in THF) affording the *title compound* **119a** as a yellow oil (360 mg, 95%). No further purification was required; R_f 0.10 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2939w, 2841w, 1733s, 1590s, 1508m, 1459m, 1422m, 1852w, 1238s, 1154w, 1123s, 1047w, 1018s, 967s, 827m, 778m; δ_H (400 MHz, $CDCl_3$) 1.28–1.31 (6 H, m, H-4), 2.88 (2 H, t, J = 7.2, H-6), 2.94 (2 H, d, J = 21.5, H-2), 3.79 (3 H, s, H-11), 3.82 (6 H, s, H-12), 4.07–4.15 (4 H, m, H-3), 4.32 (2 H, t, J = 7.2, H-5), 6.41 (2 H, s, H-8); δ_C (100 MHz, $CDCl_3$) 16.2 (d, J = 6.2, C-4), 34.2 (d, J = 134.3, C-2), 35.2 (C-6), 56.0 (C-12), 60.7 (C-11), 62.6 (d, J = 6.3, C-3), 65.9 (C-5), 105.7 (C-8), 132.9 (C-7), 136.6 (C-10), 153.1 (C-9), 165.7 (d, J = 6.0, C-1); δ_P (162 MHz, $CDCl_3$) 20.2; HRMS (ESI$^+$): Found: 413.1351; $C_{17}H_{27}NaO_8P$ (MNa^+) Requires 413.1336 (−3.6 ppm error), Found: 391.1528; $C_{17}H_{28}O_8P$ (MH^+) Requires 391.1516 (−2.9 ppm error).

Lab notebook reference: MGL/05/11S

3,4,5-Trimethoxyphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate (119b)



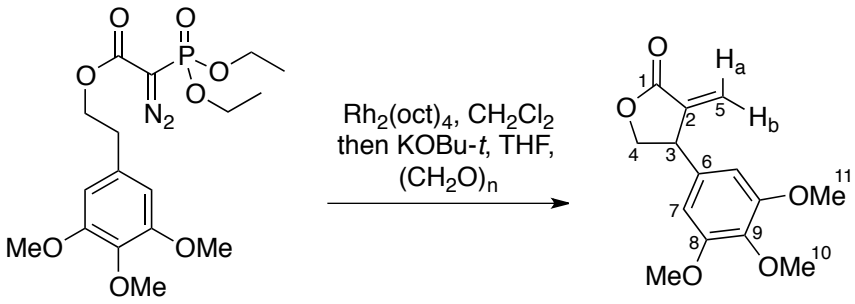
119a **119b**

Synthesised using general procedure B with 3,4,5-trimethoxyphenethyl 2-(diethoxyphosphoryl)acetate **119a** (350 mg, 0.90 mmol), THF (4.5 mL), LHMDS (1.08 mL, 1.08

mmol, 1.0 M solution in THF) and *p*-ABSA (259 mg, 1.08 mmol). Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **119b** as a yellow oil (202 mg, 54%); R_f 0.21 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2983w, 2940w, 2841w, 2125s, 1704s, 1590s, 1508m, 1459s, 1422m, 1389m, 1352w, 1274s, 1238s, 1155w, 1124s, 1012s, 977s, 815m, 745m, 589m, 559m; δ_H (400 MHz, $CDCl_3$) 1.29 (6 H, td, *J* = 7.1, *J* = 0.7, H-4), 2.87 (2 H, t, *J* = 6.9, H-6), 3.77 (3 H, s, H-11), 3.80 (6 H, s, H-12), 4.02–4.19 (4 H, m, H-3), 4.36 (2 H, t, *J* = 6.9, H-5), 6.38 (2 H, s, H-8); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* = 6.9, C-4), 35.4 (C-6), 53.5 (d, *J* = 227.1, C-2), 55.9 (C-12), 60.6 (C-11), 63.5 (d, *J* = 5.6, C-3), 65.9 (C-5), 105.6 (C-8), 132.8 (C-7), 136.6 (C-10), 153.1 (C-9), 163.1 (d, *J* = 12.5, C-1); δ_P (162 MHz, $CDCl_3$) 10.4; HRMS (ESI$^+$): Found: 439.1234; $C_{17}H_{25}N_2NaO_8P$ (MNa^+) Requires 439.1241 (1.6 ppm error), Found: 417.1423; $C_{17}H_{26}N_2O_8P$ (MH^+) Requires 417.1421 (–0.3 ppm error).

Lab notebook reference: MGL/05/11

3-Methylene-4-(3,4,5-trimethoxyphenyl)dihydrofuran-2(3*H*)-one (119c)

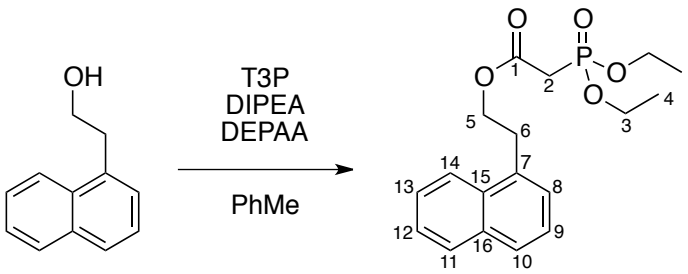


119b **119c**

Synthesised using general procedure D with 3,4,5-trimethoxyphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **119b** (77 mg, 0.185 mmol), CH_2Cl_2 (3.7 mL), $Rh_2(oct)_4$ (2.9 mg, 3.7 μmol), THF (3.7 mL), KOBu-*t* (31.1 mg, 0.278 mmol) and paraformaldehyde (11.1 mg, 0.370 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **119c** as a colourless oil (22 mg, 45%); R_f 0.26 (2:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2937w, 1763s, 1660w, 1591m, 1509m, 1461m, 1425m, 1347w, 1242m, 1124s, 1013m; δ_H (400 MHz, $CDCl_3$) 3.83 (3 H, s, H-10), 3.84 (6 H, s, H-11), 4.17–4.24 (2 H, m, H-3,4), 4.68–4.75 (1 H, m, H-4), 5.56 (1 H, d, *J* = 2.6, H-5b), 6.40–6.41 (3 H, m, H-5a,7); δ_C (100 MHz, $CDCl_3$) 45.9 (C-3), 56.2 (C-11), 60.8 (C-10), 72.7 (C-4), 104.7 (C-7), 124.3 (C-5), 135.2 (C-6), 137.4 (C-9), 138.5 (C-2), 153.7 (C-8), 170.1 (C-1); HRMS (ESI$^+$): Found: 287.0892; $C_{14}H_{16}NaO_5$ (MNa^+) Requires 287.0890 (–0.5 ppm error), Found: 265.1071; $C_{14}H_{17}O_5$ (MH^+) Requires 265.1071 (–0.1 ppm error).

Lab notebook reference: MGL/05/25

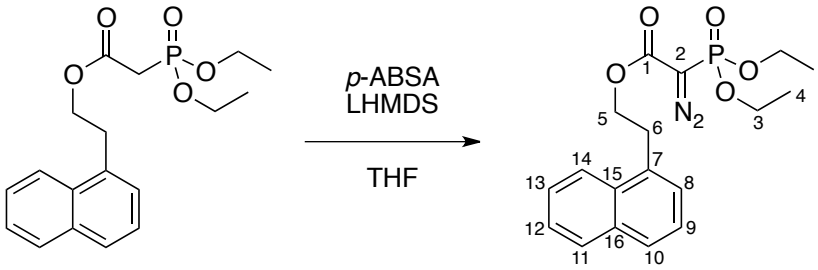
2-(Naphthalen-1-yl)ethyl 2-(diethoxyphosphoryl)acetate (120a)



120 **120a**

Synthesised using general procedure A with 2-(naphthalen-1-yl)ethanol **120** (861 mg, 5.00 mmol), toluene (25 mL), DEPAA (0.84 mL, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in THF) affording the *title compound* **120a** as a yellow oil (1.74 g, 99%). No further purification was required; R_f 0.20 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2982w, 1735s, 1598w, 1510w, 1496w, 1445w, 1395w, 1257s, 1163w, 1113m, 1048w, 1019s, 965s, 838w, 798w, 777s, 731s, 696m; δ_H (400 MHz, $CDCl_3$) 1.31 (6 H, t, *J* = 7.1, H-4), 2.97 (2 H, d, *J* = 21.6, H-2), 3.44 (2 H, t, *J* = 7.5, H-6), 4.10–4.17 (4 H, m, H-3), 4.48 (2 H, t, *J* = 7.5, H-5), [7.36–7.43 (2 H, m), 7.47–7.56 (2 H, m), 7.75–7.77 (1 H, m), 7.85–7.87 (1 H, m), 8.07–8.09 (1 H, m) (H-8,9,10,11,12,13,14)]; δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.2, C-4), 32.0 (C-6), 34.3 (d, *J* = 134.2, C-2), 62.6 (d, *J* = 6.2, C-3), 65.4 (C-5), [123.4, 125.4, 125.6, 126.2, 127.0, 127.5, 128.8 (C-8,9,10,11,12,13,14)], [131.9, 133.2, 133.8 (C-7,15,16)], 165.8 (d, *J* = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.3; HRMS (ESI^+): Found: 373.1171; $C_{18}H_{23}NaO_5P$ (MNa^+) Requires 373.1175 (1.2 ppm error), Found: 351.1353; $C_{18}H_{24}O_5P$ (MH^+) Requires 351.1356 (0.9 ppm error).
Lab notebook reference: MGL/05/15S

2-(Naphthalen-1-yl)ethyl 2-diazo-2-(diethoxyphosphoryl)acetate (120b)

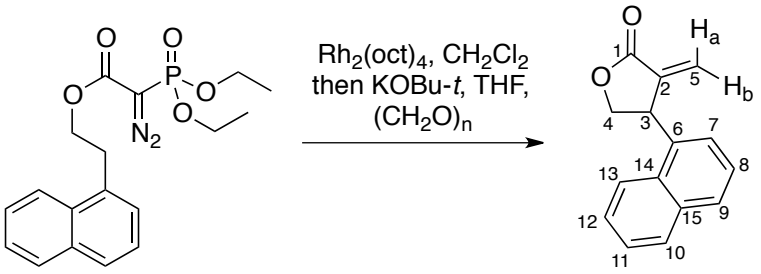


120a **120b**

Synthesised using general procedure B with 2-(naphthalen-1-yl)ethyl 2-(diethoxyphosphoryl)acetate **120a** (1.70 g, 4.85 mmol), THF (24 mL), LHMDS (5.82 mL, 5.82 mmol, 1.0 M solution in THF) and *p*-ABSA (1.40 g, 5.82 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **120b** as a yellow oil (859 mg, 47%); R_f 0.41 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2984w, 2127s, 1708s, 1597w, 1511w, 1445w, 1388w, 1279s, 1215s, 1164w, 1095w, 1020s, 978m, 799m, 778m, 745w; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, J = 7.1, J = 0.8, H-4), 3.45 (2 H, t, J = 7.2, H-6), 4.04–4.22 (4 H, m, H-3), 4.55 (2 H, t, J = 7.2, H-5), [7.35–7.43 (2 H, m), 7.47–7.57 (2 H, m), 7.76–7.78 (1 H, m), 7.85–7.88 (1 H, m), 8.06–8.08 (1 H, m) (H-8,9,10,11,12,13,14)]; δ_C (100 MHz, $CDCl_3$) 16.1 (d, J = 6.9, C-4), 32.2 (C-6), 53.5 (d, J = 226.9, C-2), 63.6 (d, J = 5.9, C-3), 65.5 (C-5), [123.4, 125.4, 125.7, 126.3, 127.1, 127.6, 128.8 (C-8,9,10,11,12,13,14)], [131.9, 133.1, 133.8 (C-7,15,16)], 163.2 (d, J = 12.2, C-1); δ_P (162 MHz, $CDCl_3$) 10.5; HRMS (ESI^+): Found: 399.1075; $C_{18}H_{21}N_2NaO_5P$ (MNa^+) Requires 399.1080 (1.2 ppm error), Found: 377.1257; $C_{18}H_{22}N_2O_5P$ (MH^+) Requires 377.1261 (0.9 ppm error).

Lab notebook reference: MGL/05/15

3-Methylene-4-(naphthalen-1-yl)dihydrofuran-2(3*H*)-one (120c)

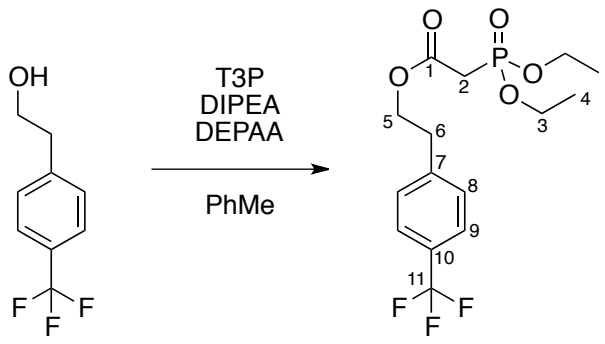


120b **120c**

Synthesised using general procedure D with 2-(naphthalen-1-yl)ethyl 2-diazo-2-(diethoxyphosphoryl)acetate **120b** (82 mg, 0.218 mmol), CH_2Cl_2 (4.4 mL), $Rh_2(oct)_4$ (3.4 mg, 4.4 μmol), THF (4.4 mL), KOBu-*t* (36.7 mg, 0.327 mmol) and paraformaldehyde (13.1 mg, 0.436 mmol). Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **120c** as a colourless oil (28 mg, 57%); R_f 0.45 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3050w, 2918w, 1759s, 1662w, 1598w, 1511w, 1398m, 1261w, 1230w, 1111s, 1022m, 948w, 802m, 780s; δ_H (400 MHz, $CDCl_3$) 4.36 (1 H, dd, J = 9.0, J = 6.3, H-4), 4.89 (1 H, app. t, J = 9.0, H-4), 5.03–5.08 (1 H, m, H-3), 5.60 (1 H, d, J = 2.7, H-5b), 6.51 (1 H, d, J = 3.0, H-5a), [7.38–7.40 (1 H, m), 7.47 (1 H, app. t, J = 7.7), 7.53–7.60 (2 H, m), 7.81–7.88 (2 H, m), 7.91–7.95 (1 H, m) (H-7,8,9,10,11,12,13)]; δ_C (100 MHz, $CDCl_3$) 41.6 (C-3), 72.0 (C-4), 124.5 (C-5), [122.6, 125.0, 125.5, 126.1, 126.7, 128.5, 129.3 (C-7,8,9,10,11,12,13)], [131.0, 134.2, 135.6, 137.6 (C-2,6,14,15)], 170.4 (C-1); HRMS (ESI^+): Found: 247.0728; $C_{15}H_{12}NaO_2$ (MNa^+) Requires 247.0730 (0.5 ppm error), Found: 225.0902; $C_{15}H_{13}O_2$ (MH^+) Requires 225.0910 (3.6 ppm error).

Lab notebook reference: MGL/05/31

4-Trifluoromethylphenethyl 2-(diethoxyphosphoryl)acetate (121a)

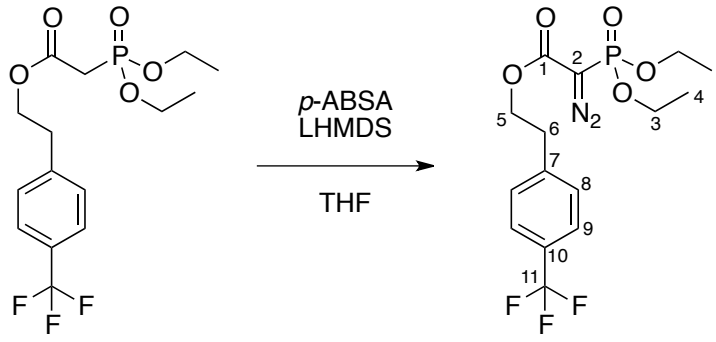


121 **121a**

Synthesised using general procedure A with 4-trifluoromethylphenethyl alcohol **121** (497 mg, 2.61 mmol), toluene (10 mL), DEPAA (0.44 mL, 2.74 mmol), DIPEA (1.19 mL, 6.80 mmol) and T3P (2.16 g, 3.40 mmol, 50% w/w solution in EtOAc) affording the *title compound* **121a** as a yellow oil (963 mg, 100%). No further purification was required; R_f 0.19 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2940s, 2890w, 1712s, 1307m, 1251m, 1146w, 1099m, 1007m, 956w; δ_H (400 MHz, $CDCl_3$) 1.30 (6 H, td, J = 7.1, J = 0.5, H-4), 2.94 (2 H, d, J = 21.6, H-2), 3.02 (2 H, t, J = 6.8, H-6), 4.11 (4 H, dq, J = 8.8, J = 7.1, H-3), 4.37 (2 H, t, J = 6.8, H-5), 7.35 (2 H, d, J = 8.0, H-8), 8.17 (2 H, d, J = 8.0, H-9); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.2, C-4), 34.3 (d, J = 134.4, C-2), 34.7 (C-6), 62.7 (d, J = 6.2, C-3), 65.3 (C-5), 125.4 (q, J = 3.7, C-9), 126.9 (q, J = 271.1, C-11), 129.2 (C-8), 129.7 (q, J = 32.5, C-10), 141.7 (C-7), 165.7 (d, J = 6.1, C-1); δ_F (376 MHz, $CDCl_3$) −62.4; δ_P (162 MHz, $CDCl_3$) 20.1; HRMS (ESI^+): Found: 391.0878; $C_{15}H_{20}F_3NaO_5P$ (MNa^+) Requires 391.0893 (3.7 ppm error), Found: 369.1064; $C_{15}H_{21}F_3O_5P$ (MH^+) Requires 369.1073 (2.5 ppm error).

Lab notebook reference: MGL/03/10, 01/21

4-Trifluoromethylphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate (121b)

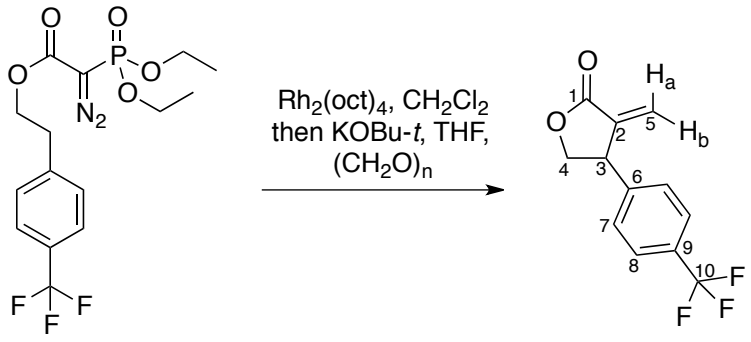


121a **121b**

Synthesised using general procedure B with 4-trifluoromethylphenethyl 2-(diethoxyphosphoryl)acetate **121a** (1.00 g, 2.72 mmol), THF (14 mL), LHMDS (3.30 mL, 3.30 mmol, 1.0 M solution in THF) and *p*-ABSA (785 mg, 3.26 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **121b** as a pale yellow oil (386 mg, 36%); R_f 0.44 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2941s, 2099s, 1686s, 1308m, 1262m, 1147w, 1106w, 1051w, 1006w; δ_H (400 MHz, $CDCl_3$) 1.31 (6 H, td, J = 7.1, J = 0.8, H-4), 3.03 (2 H, t, J = 6.7, H-6), 4.03–4.21 (4 H, m, H-3), 4.43 (2 H, t, J = 6.7, H-5), 7.34 (2 H, d, J = 8.0, H-8), 7.56 (2 H, d, J = 8.0, H-9); δ_C (100 MHz, $CDCl_3$) 16.1 (d, J = 6.8, C-4), 34.9 (C-6), 53.9 (d, J = 228.8, C-2), 63.6 (d, J = 5.6, C-3), 65.3 (C-5), 125.4 (q, J = 3.8, C-9), 124.1 (q, J = 271.9, C-11), 129.1 (q, J = 32.3, C-10), 129.3 (C-8), 141.5 (C-7), 163.3 (d, J = 11.6, C-1); δ_F (376 MHz, $CDCl_3$) −62.4; δ_P (162 MHz, $CDCl_3$) 10.4; HRMS (ESI^+): Found: 417.0779; $C_{15}H_{18}F_3N_2NaO_5P$ (MNa^+) Requires 417.0798 (4.5 ppm error), Found: 395.0964; $C_{15}H_{19}F_3N_2O_5P$ (MH^+) Requires 395.0978 (3.7 ppm error).

Lab notebook reference: MGL/01/26

(*SR*)-3-Methylene-4-(4-(trifluoromethyl)phenyl)dihydrofuran-2(3*H*)-one (121c)

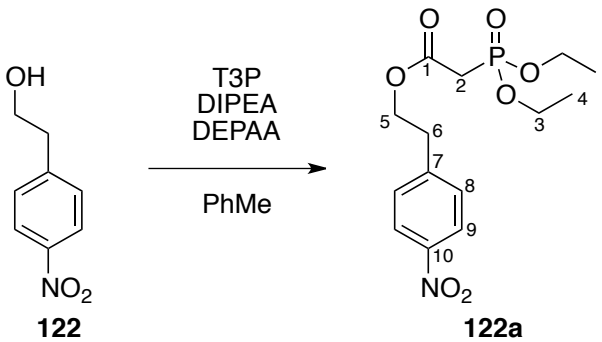


121b **121c**

Synthesised using general procedure E with 4-trifluoromethylphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **121b** (64 mg, 0.162 mmol), CH_2Cl_2 (1.6 mL), $Rh_2(oct)_4$ (6.3 mg, 8.1 μmol), KOBu-*t* (16.4 mg, 0.146 mmol) and paraformaldehyde (48.6 mg, 1.62 mmol). Purification by column chromatography (5:1 petrol:EtOAc) afforded the *title compound* **121c** as a colourless oil (15 mg, 38%); R_f 0.59 (2:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2875w, 1741s, 1307s, 1097m, 1053w; δ_H (400 MHz, $CDCl_3$) 4.24 (1 H, dd, J = 9.0, J = 7.1, H-4), 4.33–4.38 (1 H, m, H-3), 4.75 (1 H, app. t, J = 9.0, H-4), 5.50 (1 H, d, J = 2.9, H-5b), 6.44 (1 H, d, J = 2.9, H-5a), 7.37 (2 H, d, J = 8.0, H-7), 7.65 (2 H, d, J = 8.0, H-8); δ_C (100 MHz, $CDCl_3$) 45.3 (C-3), 72.2 (C-4), 123.8 (q, J = 272.2, C-10), 124.7 (C-5), 126.2 (q, J = 3.8, C-8), 128.3 (C-7), 130.2 (q, J = 32.1, C-9), 138.1 (C-2), 143.7 (C-6), 169.6 (C-1); δ_F (376 MHz, $CDCl_3$) −62.6; HRMS (ESI^+): Found: 265.0447; $C_{12}H_9F_3NaO_2$ (MNa^+) Requires 265.0447 (0.0 ppm error).

Lab notebook reference: MGL/02/63, 03/33

4-Nitrophenethyl 2-(diethoxyphosphoryl)acetate (122a)



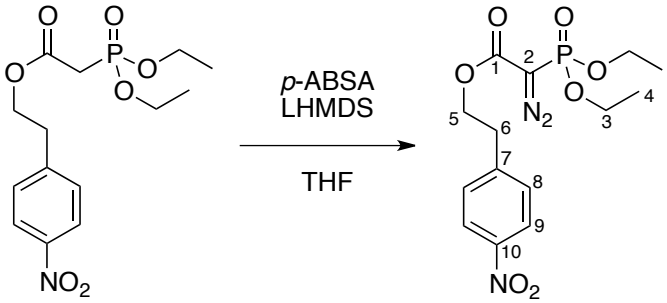
122 **122a**

Synthesised using general procedure A with 4-nitrophenethyl alcohol **122** (2.50 g, 15.0 mmol), toluene (78 mL), DEPAA (2.52 mL, 15.7 mmol), DIPEA (6.80 mL, 38.9 mmol) and T3P (12.4 g,

19.4 mmol, 50% w/w solution in THF) affording the *title compound* **122a** as an orange oil (4.72 g, 91%). No further purification was required; R_f 0.12 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2936s, 1712s, 1577m, 1495s, 1371m, 1325m, 1249m, 1145w, 1095m, 1009m, 955w, 842w; δ_H (400 MHz, $CDCl_3$) 1.31 (6 H, t, *J* = 7.1, H-4), 2.94 (2 H, d, *J* = 21.6, H-2), 3.08 (2 H, t, *J* = 6.7, H-6), 4.13 (4 H, dq, *J* = 8.3, *J* = 7.1, H-3), 4.39 (2 H, t, *J* = 6.7, H-5), 7.41 (2 H, d, *J* = 8.8, H-8), 8.17 (2 H, d, *J* = 8.8, H-9); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.2, C-4), 34.3 (d, *J* = 134.6, C-2), 34.7 (C-6), 62.7 (d, *J* = 6.2, C-3), 64.9 (C-5), 123.7 (C-9), 129.8 (C-8), 145.3 (C-7/10), 146.9 (C-7/10), 165.6 (d, *J* = 6.0, C-1); δ_P (162 MHz, $CDCl_3$) 20.0; HRMS (ESI$^+$): Found: 368.0875; $C_{14}H_{20}NNaO_7P$ (MNa^+) Requires 368.0870 (−1.3 ppm error), Found: 346.1055; $C_{14}H_{21}NO_7P$ (MH^+) Requires 346.1050 (−1.3 ppm error).

Lab notebook reference: MGL/01/11

4-Nitrophenethyl 2-diazo-2-(diethoxyphosphoryl)acetate (122b)

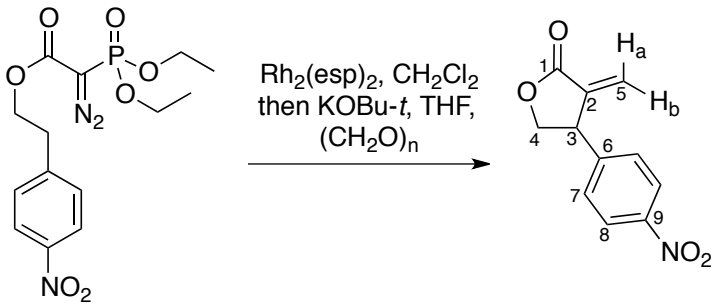


122a **122b**

Synthesised using general procedure B with 4-nitrophenethyl 2-(diethoxyphosphoryl)acetate **122a** (212 mg, 0.614 mmol), THF (3.0 mL), LHMDS (0.740 mL, 0.740 mmol, 1.0 M solution in THF) and *p*-ABSA (177 mg, 0.737 mmol). Purification by column chromatography (1:1 petrol:EtOAc) afforded the *title compound* **122b** as a colourless oil (111 mg, 49%); R_f 0.53 (1:2 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2099s, 1681s, 1497s, 1326s, 1261s, 1006m; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, *J* = 7.1, *J* = 0.8, H-4), 3.09 (2 H, t, *J* = 6.6, H-6), 4.05–4.23 (4 H, m, H-3), 4.45 (2 H, t, *J* = 6.6, H-5), 7.40 (2 H, d, *J* = 8.8, H-8), 8.18 (2 H, d, *J* = 8.8, H-9); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* = 6.8, C-4), 34.9 (C-6), 53.8 (d, *J* = 228.4, C-2), 63.6 (d, *J* = 5.7, C-3), 64.9 (C-5), 123.7 (C-9), 129.8 (C-8), 145.1 (C-7/10), 146.9 (C-7/10), 163.2 (d, *J* = 12.2, C-1); δ_P (162 MHz, $CDCl_3$) 10.3; HRMS (ESI$^+$): Found: 394.0762; $C_{14}H_{18}N_3NaO_7P$ (MNa^+) Requires 394.9775 (3.2 ppm error), Found: 372.0956; $C_{14}H_{19}N_3O_7P$ (MH^+) Requires 372.0955 (−0.2 ppm error).

Lab notebook reference: MGL/01/15

(*SR*)-3-Methylene-4-(4-nitrophenyl)dihydrofuran-2(3*H*)-one (122c)

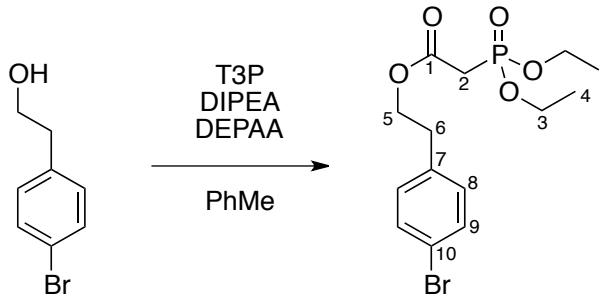


122b **122c**

Synthesised using general procedure E with 4-nitrophenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **122b** (37 mg, 0.100 mmol), CH_2Cl_2 (2.0 mL), $Rh_2(esp)_2$ (3.8 mg, 5.0 μmol), KOBu-*t* (10.1 mg, 0.090 mmol) and paraformaldehyde (30.0 mg, 0.997 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **122c** as a colourless oil (4 mg, 18%); R_f 0.58 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2878s, 2809s, 1737s, 1575w, 1496m, 1327m, 1092w, 1004w, 843w; δ_H (400 MHz, $CDCl_3$) 4.27 (1 H, dd, J = 9.1, J = 6.8, H-4), 4.39–4.45 (1 H, m, H-3), 4.78 (1 H, app. t, J = 9.1, H-4), 5.53 (1 H, d, J = 2.7, H-5b), 6.48 (1 H, d, J = 3.1, H-5a), 7.44 (2 H, d, J = 8.8, H-7), 8.26 (2 H, d, J = 8.8, H-8); δ_C (100 MHz, $CDCl_3$) 45.2 (C-3), 71.9 (C-4), 124.5 (C-8), 125.1 (C-5), 128.8 (C-7), 137.7 (C-2), 147.0 (C-6/9), 147.6 (C-6/9), 169.2 (C-1); HRMS (ESI^+): Found: 242.0427; $C_{11}H_9NNaO_4$ (MNa^+) Requires 242.0424 (–1.5 ppm error), Found: 220.0614; $C_{11}H_{10}NO_4$ (MH^+) Requires 220.0604 (–4.5 ppm error).

Lab notebook reference: MGL/01/17

4-Bromophenethyl 2-(diethoxyphosphoryl)acetate (123a)



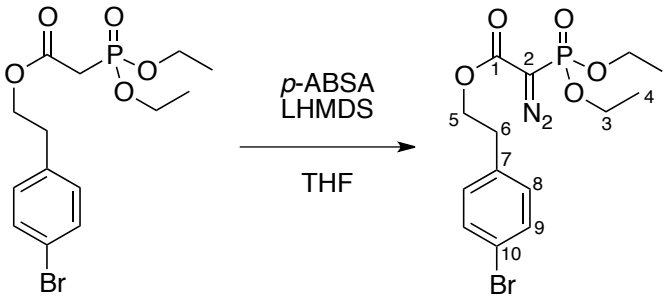
123 **123a**

Synthesised using general procedure A with 2-(4-bromophenyl)ethanol **123** (1.01 g, 5.00 mmol), toluene (25 mL), DEPAA (0.84 mL, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in THF) affording the *title compound* **123a** as a yellow oil (1.80 g,

96%). No further purification was required; R_f 0.23 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2982w, 1735s, 1489m, 1443w, 1393w, 1256s, 1163w, 1114m, 1049w, 1020s, 964s, 804m; δ_H (400 MHz, $CDCl_3$) 1.29 (6 H, td, *J* = 7.1, *J* = 0.5, H-4), 2.89 (2 H, t, *J* = 6.9, H-6), 2.92 (2 H, d, *J* = 21.6, H-2), 4.06–4.13 (4 H, m, H-3), 4.30 (2 H, t, *J* = 6.9, H-5), 7.08 (2 H, d, *J* = 8.5, H-8/9), 7.39 (2 H, d, *J* = 8.5, H-8/9); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.2, C-4), 34.2 (d, *J* = 134.3, C-2), 34.2 (C-6), 62.6 (d, *J* = 6.2, C-3), 65.5 (C-5), 120.4 (C-10), 130.6 (C-8/9), 131.5 (C-8/9), 136.4 (C-7), 165.6 (d, *J* = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.1; HRMS (ESI$^+$): Found: 401.0124; $C_{14}H_{20}{}^{79}BrNaO_5P$ (MNa^+) Requires 401.0124 (–0.1 ppm error), Found: 379.0303; $C_{14}H_{21}{}^{79}BrO_5P$ (MH^+) Requires 379.0304 (0.4 ppm error).

Lab notebook reference: MGL/05/08S

4-Bromophenethyl 2-diazo-2-(diethoxyphosphoryl)acetate (123b)

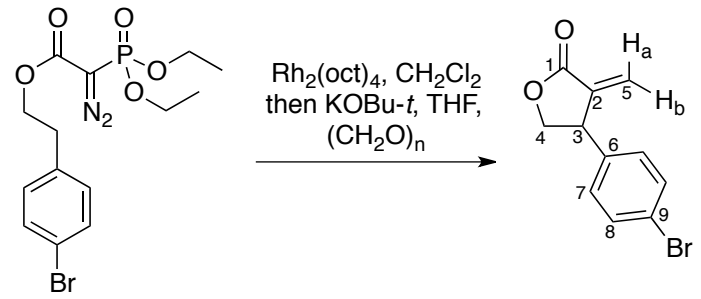


123a **123b**

Synthesised using general procedure B with 4-bromophenethyl 2-(diethoxyphosphoryl)acetate **123a** (1.78 g, 4.69 mmol), THF (24 mL), LHMDS (5.63 mL, 5.63 mmol, 1.0 M solution in THF) and *p*-ABSA (1.35 g, 5.63 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **123b** as a yellow oil (969 mg, 51%); ν_{max} (thin film)/cm^{-1} 2983w, 2129s, 1708s, 1489w, 1384w, 1279s, 1216w, 1164w, 1094w, 1022s, 979m, 815w, 596w, 560w; δ_H (400 MHz, $CDCl_3$) 1.30 (6 H, td, *J* = 7.1, *J* = 0.8, H-4), 2.90 (2 H, t, *J* = 6.7, H-6), 4.02–4.19 (4 H, m, H-3), 4.36 (2 H, t, *J* = 6.7, H-5), 7.07 (2 H, d, *J* = 8.5, H-8), 7.40 (2 H, d, *J* = 8.5, H-9); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* = 6.8, C-4), 34.5 (C-6), 53.8 (d, *J* = 228.5, C-2), 63.5 (d, *J* = 5.8, C-3), 65.4 (C-5), 120.5 (C-10), 130.6 (C-8), 131.5 (C-9), 136.2 (C-7), 163.1 (d, *J* = 12.3, C-1); δ_P (162 MHz, $CDCl_3$) 10.4; HRMS (ESI$^+$): Found: 427.0038; $C_{14}H_{18}{}^{79}BrN_2NaO_5P$ (MNa^+) Requires 427.0029 (–2.2 ppm error), Found: 405.0224; $C_{14}H_{19}{}^{79}BrN_2O_5P$ (MH^+) Requires 405.0209 (–3.7 ppm error).

Lab notebook reference: MGL/05/08

4-(4-Bromophenyl)-3-methylenedihydrofuran-2(3*H*)-one (123c)

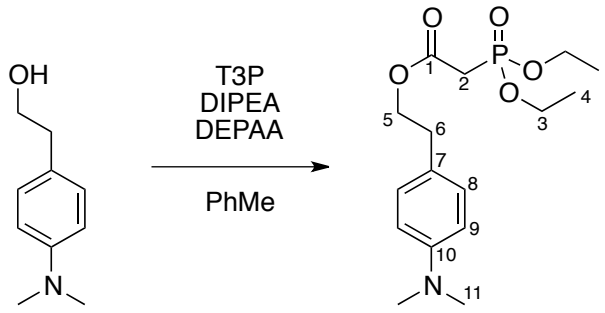


123b **123c**

Synthesised using general procedure D with 4-bromophenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **123b** (90 mg, 0.222 mmol), CH_2Cl_2 (4.4 mL), $Rh_2(oct)_4$ (3.5 mg, 4.4 μmol), THF (4.4 mL), KOBu-*t* (37.4 mg, 0.333 mmol) and paraformaldehyde (13.3 mg, 0.444 mmol). Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound* **123c** as a pale yellow oil (31 mg, 55%); R_f 0.40 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2972w, 2913w, 1761s, 1666w, 1590w, 1489m, 1412m, 1274w, 1231m, 1107s, 1010s, 947w, 825s; δ_H (400 MHz, $CDCl_3$) 4.17–4.27 (2 H, m, H-3,4), 4.71 (1 H, app. t, J = 8.4, H-4), 5.48 (1 H, d, J = 2.7, H-5b), 6.39 (1 H, d, J = 3.0, H-5a), 7.11 (2 H, d, J = 8.5, H-7), 7.50 (2 H, d, J = 8.5, H-8); δ_C (100 MHz, $CDCl_3$) 45.1 (C-3), 72.3 (C-4), 121.8 (C-2/6/9), 124.3 (C-5), 129.5 (C-7), 132.3 (C-8), 138.3 (C-2/6/9), 138.5 (C-2/6/9), 169.8 (C-1); HRMS (ESI^+): Found: 274.9679; $C_{11}H_9{}^{79}BrNaO_2$ (MNa^+) Requires 274.9678 (−0.4 ppm error), Found: 252.9859; $C_{11}H_{10}{}^{79}BrO_2$ (MH^+) Requires 252.9859 (−0.1 ppm error).

Lab notebook reference: MGL/05/21

4-(Dimethylamino)phenethyl 2-(diethoxyphosphoryl)acetate (124a)

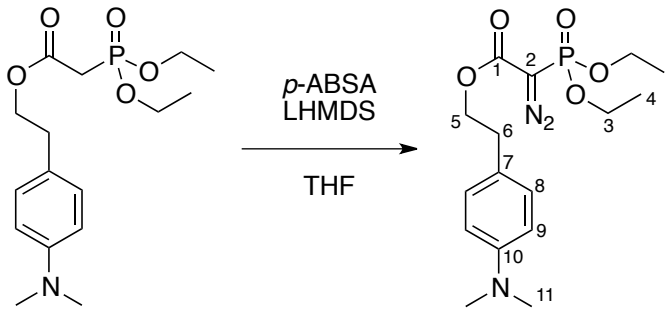


124 **124a**

Synthesised using general procedure A with 4-(*N*,*N*-dimethylamino)phenethyl alcohol **124** (835 mg, 5.05 mmol), toluene (25 mL), DEPAA (0.85 mL, 5.31 mmol), DIPEA (2.29 mL, 13.1 mmol) and T3P (4.18 g, 6.57 mmol, 50% w/w solution in EtOAc) affording the *title compound* **124a** as an orange oil (1.77 g, 100%). No further purification was required; R_f 0.44 (1:2 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2988w, 1733s, 1522s, 1258s, 1114w, 1019s; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, *J* = 7.1, *J* = 0.5, H-4), 2.86 (2 H, t, *J* = 7.3, H-6), 2.91 (6 H, s, H-11), 2.96 (2 H, d, *J* = 21.5, H-2), 4.14 (4 H, dq, *J* = 8.2, *J* = 7.1, H-3), 4.29 (2 H, t, *J* = 7.3, H-5), 6.69 (2 H, d, *J* = 8.7, H-9), 7.10 (2 H, d, *J* = 8.7, H-8); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.4, C-4), 33.9 (C-6), 34.3 (d, *J* = 134.2, C-2), 40.7 (C-11), 62.6 (d, *J* = 6.2, C-3), 66.5 (C-5), 112.8 (C-9), 125.1 (C-7), 129.5 (C-8), 149.5 (C-10), 165.8 (d, *J* = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI$^+$): Found: 366.1444; $C_{16}H_{26}NNaO_5P$ (MNa^+) Requires 366.1441 (–0.8 ppm error), Found: 344.1616; $C_{16}H_{27}NO_5P$ (MH^+) Requires 344.1621 (1.7 ppm error).

Lab notebook reference: MGL/02/33

4-(Dimethylamino)phenethyl 2-diazo-2-(diethoxyphosphoryl)acetate (124b)

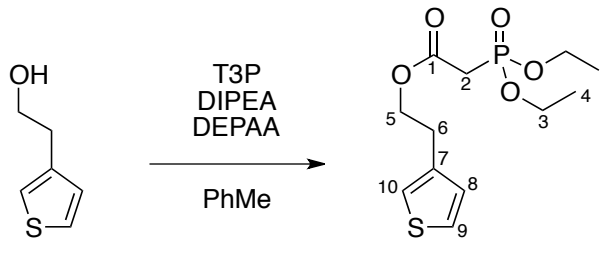


124a **124b**

Synthesised using general procedure B with 4-(dimethylamino)phenethyl 2-(diethoxyphosphoryl)acetate **124a** (1.03 g, 3.00 mmol), THF (15 mL), LHMDS (3.60 mL, 3.60 mmol, 1.0 M solution in THF) and *p*-ABSA (865 mg, 3.60 mmol). Purification by column chromatography (3:1 petrol:EtOAc) afforded the *title compound* **124b** as a yellow oil (327 mg, 30%); R_f 0.48 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2985w, 2128s, 1704s, 1616w, 1523m, 1277s, 1020s; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, J = 7.1, J = 0.6, H-4), 2.85 (2 H, t, J = 7.0, H-6), 2.90 (6 H, s, H-11), 4.04–4.21 (4 H, m, H-3), 4.33 (2 H, t, J = 7.0, H-5), 6.67 (2 H, d, J = 8.7, H-9), 7.06 (2 H, d, J = 8.7, H-8); δ_C (100 MHz, $CDCl_3$) 15.9 (d, J = 6.9, C-4), 34.0 (C-6), 40.5 (C-11), 53.4 (d, J = 226.5, C-2), 63.4 (d, J = 5.8, C-3), 66.3 (C-5), 112.6 (C-9), 124.8 (C-7), 129.4 (C-8), 149.3 (C-10), 163.1 (d, J = 12.3, C-1); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI$^+$): Found: 392.1338; $C_{16}H_{24}N_3NaO_5P$ (MNa^+) Requires 392.1346 (1.9 ppm error), Found: 370.1520; $C_{16}H_{25}N_3O_5P$ (MH^+) Requires 370.1526 (1.8 ppm error).

Lab notebook reference: MGL/02/54

2-(Thiophen-3-yl)ethyl 2-(diethoxyphosphoryl)acetate (125a)



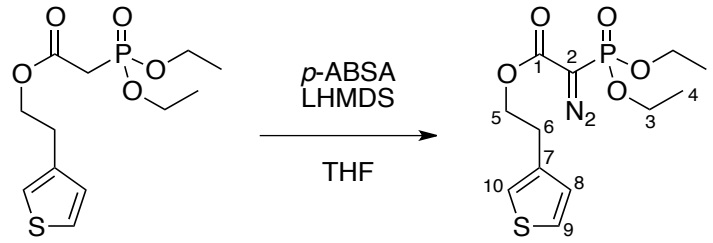
125 **125a**

Synthesised using general procedure A with 2-(thiophen-3-yl)ethanol **125** (1.03 g, 8.00 mmol), toluene (40 mL), DEPAA (1.35 mL, 8.40 mmol), DIPEA (3.62 mL, 20.8 mmol) and T3P (6.62 g, 10.4 mmol, 50% w/w solution in EtOAc) affording the *title compound* **125a** as a yellow oil (2.41 g,

99%). No further purification was required; R_f 0.33 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2983w, 1734s, 1393w, 1258s, 1115w, 1049w, 1020s, 968s; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, *J* = 7.1, *J* = 0.5, H-4), 2.97 (2 H, d, *J* = 21.6, H-2), 3.00 (2 H, t, *J* = 6.9, H-6), 4.14 (4 H, dq, *J* = 8.3, *J* = 7.1, H-3), 4.35 (2 H, td, *J* = 6.9, *J* = 0.5, H-5), 6.98 (1 H, dd, *J* = 4.9, *J* = 1.3, H-8), 7.06 (1 H, ddt, *J* = 3.0, *J* = 1.3, *J* = 0.9, H-10), 7.27 (1 H, dd, *J* = 4.9, *J* = 3.0, H-9); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.4, C-4), 29.4 (C-6), 34.3 (d, *J* = 134.4, C-2), 62.7 (d, *J* = 6.5, C-3), 65.4 (C-5), 121.7 (C-10), 125.6 (C-9), 128.2 (C-8), 137.6 (C-7), 165.8 (d, *J* = 6.2, C-1); δ_P (162 MHz, $CDCl_3$) 20.2; HRMS (ESI$^+$): Found: 329.0582; $C_{12}H_{19}NaO_5PS$ (MNa^+) Requires 329.0583 (0.4 ppm error), Found: 307.0768; $C_{12}H_{20}O_5PS$ (MH^+) Requires 307.0764 (−1.6 ppm error).

Lab notebook reference: MGL/03/01

2-(Thiophen-3-yl)ethyl 2-diazo-2-(diethoxyphosphoryl)acetate (125b)

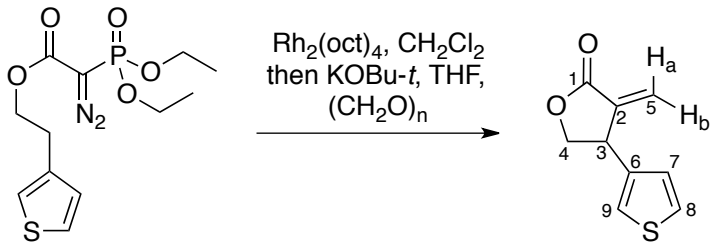


125a **125b**

Synthesised using general procedure B with 2-(thiophen-3-yl)ethyl 2-(diethoxyphosphoryl)acetate 1**25a** (1.53 g, 5.00 mmol), THF (25 mL), LHMDS (6.00 mL, 6.00 mmol, 1.0 M solution in THF) and *p*-ABSA (1.44 g, 6.00 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **125b** as a yellow oil (871 mg, 52%); R_f 0.43 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2989w, 2126s, 1703s, 1274s, 1017s, 977m; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, *J* = 7.1, *J* = 0.8, H-4), 2.99 (2 H, t, *J* = 6.8, H-6), 4.05–4.22 (4 H, m, H-3), 4.39 (2 H, t, *J* = 6.8, H-5), 6.95 (1 H, dd, *J* = 4.9, *J* = 1.3, H-8), 7.03 (1 H, ddt, *J* = 2.9, *J* = 1.3, *J* = 0.7, H-10), 7.25 (1 H, dd, *J* = 4.9, *J* = 2.9, H-9); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* = 6.9, C-4), 29.5 (C-6), 53.8 (d, *J* = 228.2, C-2), 63.5 (d, *J* = 5.6, C-3), 65.3 (C-5), 121.7 (C-10), 125.6 (C-9), 128.1 (C-8), 137.4 (C-7), 163.3 (d, *J* = 12.2, C-1); δ_P (162 MHz, $CDCl_3$) 10.5; HRMS (ESI$^+$): Found: 355.0488; $C_{12}H_{17}N_2NaO_5PS$ (MNa^+) Requires 355.0488 (0.1 ppm error), Found: 333.0671; $C_{12}H_{18}N_2O_5PS$ (MH^+) Requires 333.0669 (−0.8 ppm error).

Lab notebook reference: MGL/03/09

(*SR*)-3-Methylene-4-(thiophen-3-yl)dihydrofuran-2(3*H*)-one (125c)

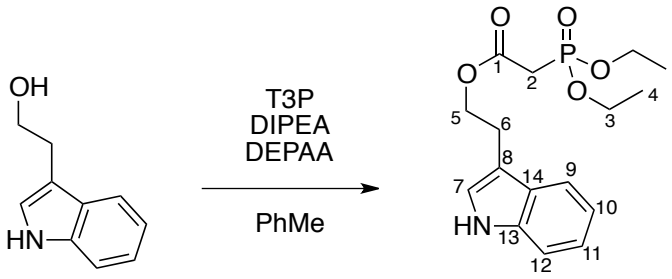


125b **125c**

Synthesised using general procedure E with 2-(thiophen-3-yl)ethyl 2-diazo-2-(diethoxyphosphoryl)acetate **125b** (69 mg, 0.208 mmol), CH_2Cl_2 (4.2 mL), $Rh_2(oct)_4$ (3.2 mg, 4.2 μmol), KOBu-*t* (28.0 mg, 0.250 mmol) and paraformaldehyde (12.5 mg, 0.416 mmol). Purification by column chromatography (5:1 petrol:EtOAc) afforded the *title compound* **125c** as a colourless oil (12 mg, 32%); R_f 0.59 (2:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 3110w, 2910w, 1761s, 1404w, 1250m, 1109m, 1018m; δ_H (400 MHz, $CDCl_3$) 4.23 (1 H, dd, *J* = 8.9, *J* = 7.3, H-4), 4.38–4.44 (1 H, m, H-3), 4.68 (1 H, app. t, *J* = 8.9, *J* = 8.9, H-4), 5.56 (1 H, d, *J* = 2.8, H-5b), 6.38 (1 H, d, *J* = 3.1, H-5a), 6.95 (1 H, dd, *J* = 5.0, *J* = 1.4, H-7), 7.15 (1 H, ddd, *J* = 3.0, *J* = 1.4, *J* = 0.5, H-9), 7.38 (1 H, dd, *J* = 5.0, *J* = 3.0, H-8); δ_C (100 MHz, $CDCl_3$) 41.0 (C-3), 71.9 (C-4), 122.6 (C-9), 123.8 (C-5), 126.1 (C-7), 127.4 (C-8), 138.1 (C-2), 139.4 (C-6), 170.0 (C-1); HRMS (ESI$^+$): Found: 203.0134; $C_9H_8NaO_2S$ (MNa^+) Requires 203.0137 (1.4 ppm error).

Lab notebook reference: MGL/03/12

2-(1*H*-Indol-3-yl)ethyl 2-(diethoxyphosphoryl)acetate (126a)



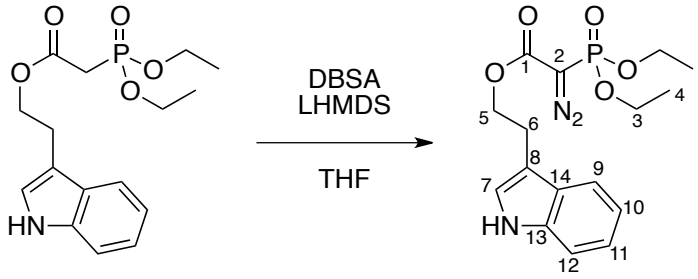
126 **126a**

Synthesised using general procedure A with 3-(2-hydroxyethyl)indole **126** (806 mg, 5.00 mmol), toluene (25 mL), DEPAA (0.84 mL, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in EtOAc) affording the *title compound* **126a** as a pale yellow oil (1.62 g, 95%). No further purification was required; R_f 0.12 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3269br, 2983w, 1733s, 1457w, 1441w, 1392w, 1340w, 1244s, 1163w, 1113m, 1019s,

969s, 787w, 767w, 737s; δ_H (400 MHz, $CDCl_3$) 1.31 (6 H, t, *J* = 7.1, H-4), 2.98 (2 H, d, *J* = 21.5, H-2), 3.11 (2 H, t, *J* = 7.2, H-6), 4.10–4.18 (4 H, m, H-3), 4.41 (2 H, t, *J* = 7.2, H-5), 7.06 (1 H, d, *J* = 2.3, H-7), 7.10–7.14 (1 H, m, H-10/11), 7.17–7.21 (1 H, m, H-10/11), 7.35–7.37 (1 H, m, H-9/12), 7.60–7.62 (1 H, m, H-9/12), 8.40 (1 H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.2, C-4), 24.5 (C-6), 34.3 (d, *J* = 134.3, C-2), 62.7 (d, *J* = 6.2, C-3), 65.6 (C-5), 111.2 (C-9/12), 111.3 (C-8), 118.5 (C-9/12), 119.3 (C-10/11), 121.9 (C-10/11), 122.3 (C-7), 127.3 (C-14), 136.2 (C-13), 165.8 (d, *J* = 6.0, C-1); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI^+): Found: 362.1130; $C_{16}H_{22}NNaO_5P$ (MNa^+) Requires 363.1128 (–0.7 ppm error), Found: 340.1309; $C_{16}H_{23}NO_5P$ (MH^+) Requires 340.1308 (–0.1 ppm error).

Lab notebook reference: MGL/05/36S

2-(1*H*-Indol-3-yl)ethyl 2-diazo-2-(diethoxyphosphoryl)acetate (126b)

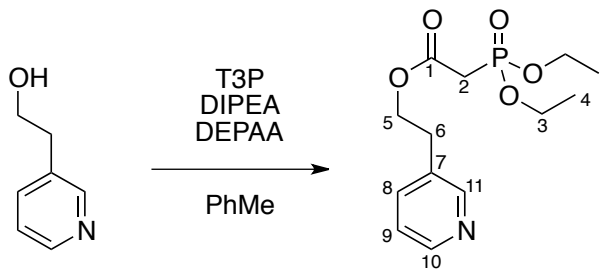


126a **126b**

Synthesised using general procedure B with 2-(1*H*-indol-3-yl)ethyl 2-(diethoxyphosphoryl)acetate **126a** (598 mg, 1.76 mmol), THF (9.0 mL), LHMDS (2.11 mL, 2.11 mmol, 1.0 M solution in THF) and DBSA (0.71 mL, 2.22 mmol). Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **126b** as a yellow oil (276 mg, 43%); R_f 0.23 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3410w, 3280br, 2984w, 2929w, 2126s, 1702s, 1457w, 1387w, 1275s, 1163w, 1096m, 1018s, 980m, 742s; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, *J* = 7.1, *J* = 0.5, H-4), 3.14 (2 H, t, *J* = 7.1, H-6), 4.05–4.26 (4 H, m, H-3), 4.48 (2 H, t, *J* = 7.1, H-5), 7.05 (1 H, d, *J* = 2.2, H-7), 7.11–7.15 (1 H, m, H-10/11), 7.17–7.22 (1 H, m, H-10/11), 7.35–7.37 (1 H, m, H-9/12), 7.60–7.62 (1 H, m, H-9/12), 8.47 (1 H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* = 6.9, C-4), 24.8 (C-6), 53.5 (d, *J* = 228.2, C-2), 63.6 (d, *J* = 5.8, C-3), 65.7 (C-5), 111.1 (C-8), 111.2 (C-9/12), 118.4 (C-9/12), 119.3 (C-10/11), 121.9 (C-10/11), 122.3 (C-7), 127.2 (C-14), 136.1 (C-13), 163.3 (d, *J* = 12.4, C-1); δ_P (162 MHz, $CDCl_3$) 10.7; HRMS (ESI^+): Found: 388.1028; $C_{16}H_{20}N_3NaO_5P$ (MNa^+) Requires 388.1033 (1.2 ppm error), Found: 366.1208; $C_{16}H_{21}N_3O_5P$ (MH^+) Requires 366.1213 (1.6 ppm error).

Lab notebook reference: MGL/05/36

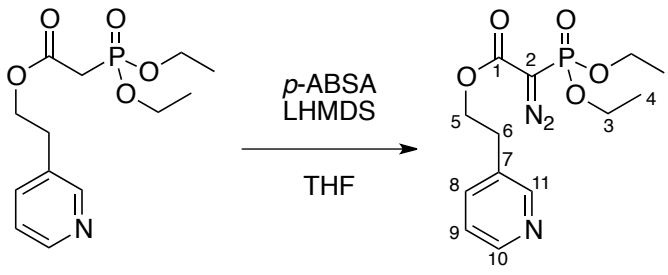
2-(Pyridin-3-yl)ethyl 2-(diethoxyphosphoryl)acetate (127a)



127 **127a**

Synthesised using general procedure A with 2-(pyridin-3-yl)ethanol **127** (2.00 g, 16.2 mmol), toluene (80 mL), DEPAA (2.74 mL, 17.1 mmol), DIPEA (7.35 mL, 42.2 mmol) and T3P (13.4 g, 21.1 mmol, 50% w/w solution in EtOAc) affording the *title compound* **127a** as a yellow oil (4.49 g, 92%). No further purification was required; R_f 0.44 (10:1 CH_2Cl_2:MeOH); ν_{max} (thin film)/cm^{-1} 2938s, 2887w, 1711s, 1468m, 1249s, 1100w, 1034w, 1010m, 957w; δ_H (400 MHz, $CDCl_3$) 1.31 (6 H, td, J = 7.1, J = 0.5, H-4), 2.95 (2 H, d, J = 21.6, H-2), 2.97 (2 H, t, J = 6.8, H-6), 4.13 (4 H, dq, J = 8.3, J = 7.1, H-3), 4.36 (2 H, t, J = 6.8, H-5), 7.25 (1 H, ddd, J = 7.8, J = 4.8, J = 0.8, H-9), 7.60 (1 H, ddd, J = 7.8, J = 2.3, J = 1.7, H-8), 8.48–8.51 (2 H, m, H-10,11); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.1, C-4), 32.1 (C-6), 34.3 (d, J = 134.3, C-2), 62.7 (d, J = 6.5, C-3), 65.2 (C-5), 123.5 (C-9), 133.1 (C-7), 136.5 (C-8), 148.0 (C-10), 150.1 (C-11), 165.7 (d, J = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.0; HRMS (ESI^+): Found: 324.0976; $C_{13}H_{20}NNaO_5P$ (MNa^+) Requires 324.0971 (1.5 ppm error), Found: 302.1140; $C_{13}H_{21}NO_5P$ (MH^+) Requires 302.1152 (3.9 ppm error).
Lab notebook reference: MGL/02/10

2-(Pyridin-3-yl)ethyl 2-diazo-2-(diethoxyphosphoryl)acetate (127b)

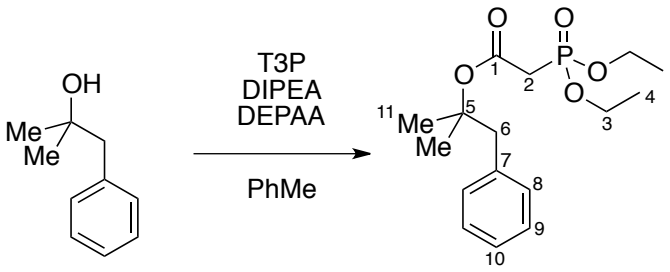


127a **127b**

Synthesised using general procedure B with 2-(pyridin-3-yl)ethyl 2-(diethoxyphosphoryl)acetate **127a** (2.00 g, 6.64 mmol), THF (35 mL), LHMDS (7.97 mL, 7.97 mmol, 1.0 M solution in THF) and *p*-ABSA (1.91 g, 7.97 mmol). Purification by column chromatography (7% MeOH in CH_2Cl_2) afforded the *title compound* **127b** as a yellow oil (497 mg, 23%); R_f 0.44 (7% MeOH in CH_2Cl_2); ν_{max} (thin film)/cm^{-1} 2939s, 2098s, 1684s, 1262s, 1104w, 1078w, 1008s, 964w; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, J = 7.1, J = 0.8, H-4), 2.98 (2 H, t, J = 6.7, H-6), 4.05–4.22 (4 H, m, H-3),

4.41 (2 H, t, J = 6.7, H-5), 7.24 (1 H, ddd, J = 7.8, J = 4.8, J = 0.7, H-9), 7.56 (1 H, ddd, J = 7.8, J = 2.3, J = 1.7, H-8), 8.47–8.51 (2 H, m, H-10,11); δ_C (100 MHz, $CDCl_3$) 15.8 (d, J = 6.9, C-4), 32.0 (C-6), 53.5 (d, J = 226.1, C-2), 63.3 (d, J = 5.8, C-3), 65.0 (C-5), 123.1 (C-9), 132.7 (C-7), 136.1 (C-8), 147.9 (C-10), 149.9 (C-11), 162.9 (d, J = 12.1, C-1); δ_P (162 MHz, $CDCl_3$) 10.4; HRMS (ESI^+): Found: 350.0876; $C_{13}H_{18}N_3NaO_5P$ (MNa^+) Requires 350.0876 (0.1 ppm error), Found: 328.1052; $C_{13}H_{19}N_3O_5P$ (MH^+) Requires 328.1057 (1.6 ppm error).
Lab notebook reference: MGL/02/11

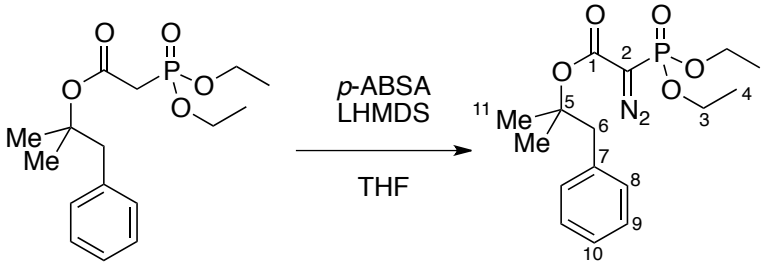
2-Methyl-1-phenylpropan-2-yl 2-(diethoxyphosphoryl)acetate (128a)



128 **128a**

Synthesised using general procedure A with 2-methyl-1-phenyl-2-propanol **128** (2.20 mL, 14.3 mmol), toluene (70 mL), DEPAA (2.41 mL, 15.0 mmol), DIPEA (6.45 mL, 37.1 mmol) and T3P (11.8 g, 18.5 mmol, 50% w/w solution in EtOAc) affording the *title compound* **128a** as a yellow oil (3.45 g, 74%); R_f 0.28 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2937s, 2889m, 1703s, 1241m, 1094w, 1037m; δ_H (400 MHz, $CDCl_3$) 1.31 (6 H, td, J = 7.1, J = 0.4, H-4), 1.46 (6 H, s, H-11), 2.89 (2 H, d, J = 21.5, H-2), 3.06 (2 H, s, H-6), 4.12 (4 H, dq, J = 8.3, J = 7.1, H-3), 7.17–7.30 (5 H, m, H-8,9,10); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.2, C-4), 25.6 (C-11), 35.6 (d, J = 133.8, C-2), 46.6 (C-6), 62.4 (d, J = 6.3, C-3), 83.9 (C-5), 126.5 (C-10), 127.9 (C-9), 130.6 (C-8), 136.9 (C-7), 165.0 (d, J = 6.2, C-1); δ_P (162 MHz, $CDCl_3$) 21.0; HRMS (ESI^+): Found: 351.1321; $C_{16}H_{25}NaO_5P$ (MNa^+) Requires 351.1332 (3.0 ppm error).
Lab notebook reference: MGL/02/20

2-Methyl-1-phenylpropan-2-yl 2-diazo-2-(diethoxyphosphoryl)acetate (128b)

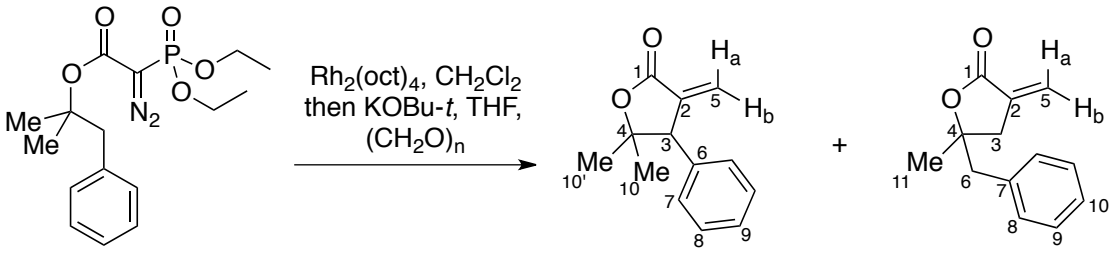


128a **128b**

Synthesised using general procedure B with 2-methyl-1-phenylpropan-2-yl 2-(diethoxyphosphoryl)acetate **128a** (2.00 g, 6.10 mmol), THF (31 mL), LHMDS (7.31 mL, 7.31 mmol, 1.0 M solution in THF) and *p*-ABSA (1.76 g, 7.31 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **128b** as a yellow oil (1.92 g, 89%); R_f 0.56 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2937m, 2095s, 1672s, 1268m, 1008m; δ_H (400 MHz, $CDCl_3$) 1.31 (6 H, td, J = 7.1, J = 0.8, H-4), 1.50 (6 H, s, H-11), 3.09 (2 H, s, H-6), 4.03–4.21 (4 H, m, H-3), 7.15–7.18 (2 H, m, H-8), 7.21–7.30 (3 H, m, H-9,10); δ_C (100 MHz, $CDCl_3$) 16.1 (d, J = 7.0, C-4), 26.2 (C-11), 46.6 (C-6), 54.2 (d, J = 227.4, C-2), 63.4 (d, J = 5.9, C-3), 84.7 (C-5), 126.6 (C-10), 128.0 (C-9), 130.5 (C-8), 136.6 (C-7), 162.6 (d, J = 12.4, C-1); δ_P (162 MHz, $CDCl_3$) 11.3; HRMS (ESI$^+$): Found: 377.1230; $C_{16}H_{23}N_2NaO_5P$ (MNa^+) Requires 377.1237 (1.8 ppm error).

Lab notebook reference: MGL/02/23

(*SR*)-5,5-Dimethyl-3-methylene-4-phenyldihydrofuran-2(3*H*)-one (128c) and (*SR*)-5-Benzyl-5-methyl-3-methylenedihydrofuran-2(3*H*)-one (128d)



128b **128c** **128d**

Synthesised using general procedure D with 2-methyl-1-phenylpropan-2-yl 2-diazo-2-(diethoxyphosphoryl)acetate **128b** (71 mg, 0.200 mmol), CH_2Cl_2 (4.0 mL), $Rh_2(oct)_4$ (3.1 mg, 4.0 μmol), THF (4.0 mL), KOBu-*t* (33.7 mg, 0.300 mmol) and paraformaldehyde (12.0 mg, 0.400 mmol). The HWE was performed at RT. Purification by column chromatography (8:1

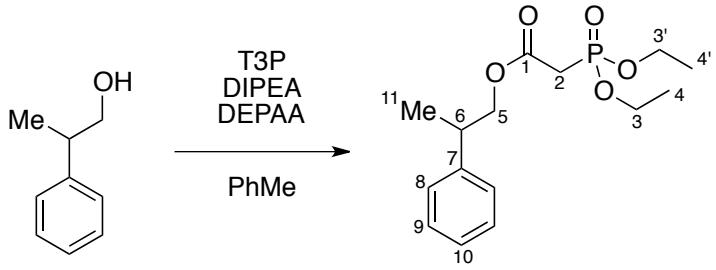
petrol:EtOAc) afforded a mixture of the *title compound*s (**128c**:**128d** 1.45:1), as a colourless oil (36 mg, 89%).

Small quantities of each compound were isolated separately for characterisation purposes.

Data for **128c**; R_f 0.63 (4:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2979w, 1763s, 1257m, 1089m; δ_H (400 MHz, $CDCl_3$) 1.02 (3 H, s, H-10/10'), 1.56 (3 H, s, H-10/10'), 4.04 (1 H, dd, *J* = 3.3, *J* = 3.0, H-3), 5.57 (1 H, d, *J* = 3.0, H-5b), 6.48 (1 H, d, *J* = 3.3, H-5a), 7.20–7.23 (2 H, m, H-7/8), 7.31–7.40 (3 H, m, H-7/8,9); δ_C (100 MHz, $CDCl_3$) 25.0 (C-10/10'), 28.0 (C-10/10'), 57.1 (C-3), 85.5 (C-4), 123.9 (C-5), 127.9 (C-9), 128.7 (C-7/8), 129.2 (C-7/8), 136.5 (C-6), 139.2 (C-2), 169.8 (C-1); HRMS (ESI^+): Found: 203.1067; $C_{13}H_{15}O_2$ (MH^+) Requires 203.1067 (0.0 ppm error).

Data for **128d**; R_f 0.46 (4:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2979w, 2928w, 1757s, 1481w, 1276m, 1055w; δ_H (400 MHz, $CDCl_3$) 1.43 (3 H, s, H-11), 2.63 (1 H, ddd, *J* = 16.8, *J* = 2.8, *J* = 2.5, H-3), 2.90 (1 H, ddd, *J* = 16.8, *J* = 2.8, *J* = 2.5, H-3), 2.88–3.03 (3 H, m, H-3,6), 5.46 (1 H, app. t, *J* = 2.5, H-5b), 6.07 (1 H, app. t, *J* = 2.8, H-5a), 7.19–7.32 (5 H, m, H-8,9,10); δ_C (100 MHz, $CDCl_3$) 27.1 (C-11), 38.6 (C-3), 46.8 (C-6), 83.2 (C-4), 121.7 (C-5), 127.0 (C-10), 128.4 (C-9), 130.6 (C-8), 135.3 (C-2/7), 135.5 (C-2/7), 169.8 (C-1); HRMS (ESI^+): Found: 203.1066; $C_{13}H_{15}O_2$ (MH^+) Requires 203.1067 (0.3 ppm error).
Lab notebook reference: MGL/03/87, 02/25

2-Phenylpropyl 2-(diethoxyphosphoryl)acetate (129a)



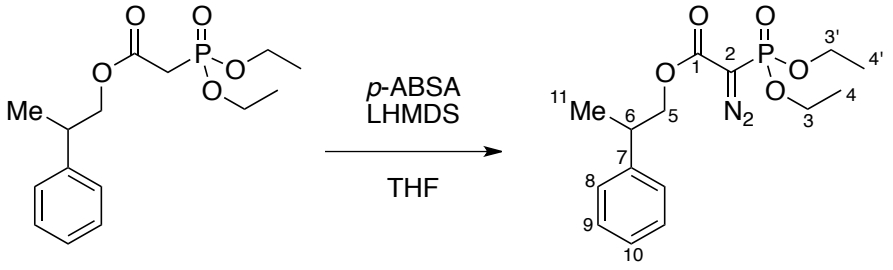
129 **129a**

Synthesised using general procedure A with 2-phenyl-1-propanol **129** (2.00 g, 14.9 mmol), toluene (75 mL), DEPAA (2.51 mL, 15.6 mmol), DIPEA (6.75 mL, 38.7 mmol) and T3P (12.3 g, 19.4 mmol, 50% w/w solution in EtOAc) affording the *title compound* **129a** as a dark orange oil (4.67 g, 100%). No further purification was required; R_f 0.25 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2936s, 1710s, 1252s, 1036w, 1009m; δ_H (400 MHz, $CDCl_3$) 1.30 (3 H, td, *J* = 7.1, *J* = 0.5, H-4/4'), 1.31 (3 H, td, *J* = 7.1, *J* = 0.5, H-4/4'), 1.30 (3 H, d, *J* = 7.0, H-11), 2.94 (2 H, d, *J* = 21.6, H-2), 3.12 (1 H, dqd, *J* = 7.4, *J* = 7.0, *J* = 6.8, H-6), 4.06–4.16 (4 H, m, H-3,3'), 4.19 (1 H, dd, *J* = 10.8, *J*

= 7.4, H-5), 4.27 (1 H, dd, J = 10.8, J = 6.8, H-5), 7.20–7.25 (3 H, m, H-8,10), 7.28 (2 H, m, H-9); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.2, C-4,4'), 18.0 (C-11), 34.2 (d, J = 134.1, C-2), 38.8 (C-6), 62.6 (d, J = 6.2, C-3), 70.4 (C-5), 126.7 (C-10), 127.3 (C-8), 128.5 (C-9), 142.8 (C-7), 165.8 (d, J = 6.2, C-1); δ_P (162 MHz, $CDCl_3$) 20.3; HRMS (ESI^+): Found: 337.1189; $C_{15}H_{23}NaO_5P$ (MNa^+) Requires 337.1175 (–3.9 ppm error).

Lab notebook reference: MGL/02/21

2-Phenylpropyl 2-diazo-2-(diethoxyphosphoryl)acetate (129b)

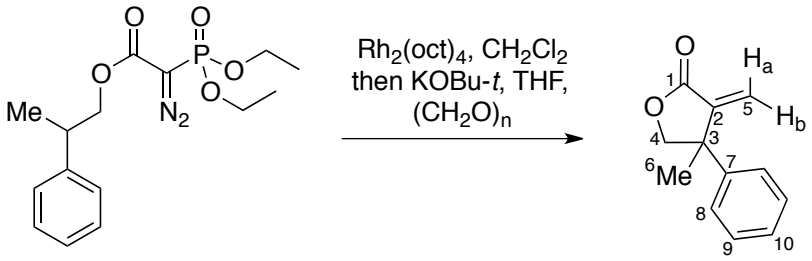


129a **129b**

Synthesised using general procedure B with 2-phenylpropyl 2-(diethoxyphosphoryl)acetate **129a** (2.00 g, 6.36 mmol), THF (32 mL), LHMDS (7.64 mL, 7.64 mmol, 1.0 M solution in THF) and *p*-ABSA (1.83 g, 7.64 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **129b** as a yellow oil (1.33 g, 61%); R_f 0.35 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2983w, 2125s, 1700s, 1390w, 1272s, 1015s; δ_H (400 MHz, $CDCl_3$) 1.24–1.28 (9 H, m, H-4,11), 3.08 (1 H, app. sex., J = 7.0, H-6), 3.95–4.14 (4 H, m, H-3), 4.20 (1 H, dd, J = 10.7, J = 6.9, H-5/5'), 4.28 (1 H, dd, J = 10.7, J = 7.1, H-5/5'), 7.15–7.19 (3 H, m, H-8,10), 7.23–7.28 (2 H, m, H-9); δ_C (100 MHz, $CDCl_3$) 15.8 (d, J = 6.9, C-4), 17.5 (C-11), 38.7 (C-6), 53.6 (d, J = 226.7, C-2), 63.2 (d, J = 5.9, C-3), 70.0 (C-5), 126.5 (C-10), 127.0 (C-8), 128.2 (C-9), 142.4 (C-7), 163.0 (d, J = 11.9, C-1); δ_P (162 MHz, $CDCl_3$) 10.5; HRMS (ESI^+): Found: 363.1081; $C_{15}H_{21}N_2NaO_5P$ (MNa^+) Requires 363.1080 (–0.2 ppm error), Found: 341.1261; $C_{15}H_{22}N_2O_5P$ (MH^+) Requires 341.1261 (0.0 ppm error).

Lab notebook reference: MGL/02/24

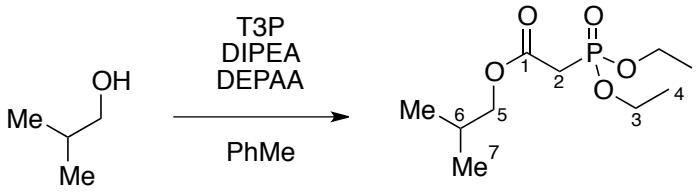
(*SR*)-4-Methyl-3-methylene-4-phenyldihydrofuran-2(3*H*)-one (129c)



129b **129c**

Synthesised using general procedure D with 2-phenylpropyl 2-diazo-2-(diethoxyphosphoryl)acetate **129b** (73 mg, 0.215 mmol), CH_2Cl_2 (4.3 mL), $Rh_2(oct)_4$ (3.3 mg, 4.3 μmol), THF (4.3 mL), KOBu-*t* (39.4 mg, 0.323 mmol) and paraformaldehyde (12.9 mg, 0.430 mmol). Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound* **129c** as a colourless oil (24 mg, 59%); R_f 0.33 (8:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2922w, 1761s, 1661w, 1496w, 1446w, 1406w, 1291w, 1253w, 1211w, 1103m, 1012m, 949w, 816w, 765w, 700m; δ_H (400 MHz, $CDCl_3$) 1.67 (3 H, s, H-6), 4.26 (1 H, d, J = 9.0, H-4), 4.52 (1 H, d, J = 9.0, H-4), 5.53 (1 H, s, H-5b), 6.42 (1 H, s, H-5a), 7.27–7.39 (5 H, m, H-8,9,10); δ_C (100 MHz, $CDCl_3$) 26.1 (C-6), 46.8 (C-3), 79.5 (C-4), 123.0 (C-5), 126.2 (C-8/9/10), 127.3 (C-8/9/10), 128.8 (C-8/9/10), 143.5 (C-7), 144.1 (C-2), 170.3 (C-1); HRMS (ESI$^+$): Found: 211.0738; $C_{12}H_{12}NaO_2$ (MNa^+) Requires 211.0730 (−3.8 ppm error), Found: 189.0911; $C_{12}H_{13}O_2$ (MH^+) Requires 189.0910 (−0.4 ppm error).
Lab notebook reference: MGL/03/95

2-Methylpropyl 2-(diethoxyphosphoryl)acetate (130a)



130 **130a**

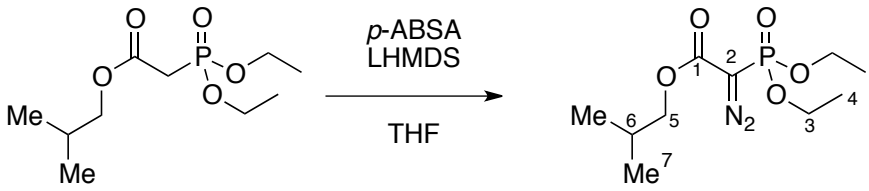
Synthesised using general procedure A with 2-methylpropanol **130** (593 mg, 8.00 mmol), toluene (40 mL), DEPAA (1.35 mL, 8.40 mmol), DIPEA (3.62 mL, 20.8 mmol) and T3P (6.62 g, 10.4 mmol, 50% w/w solution in EtOAc) affording the title compound **130a** as a yellow oil (2.02 g, 100%). No further purification was required; R_f 0.24 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2965m, 1735s, 1394w, 1265s, 1117w, 1052w, 1024s; δ_H (400 MHz, $CDCl_3$) 0.94 (6 H, d, J = 6.7, H-7), 1.32 (6 H, t, J = 7.1, H-4), 1.95 (1 H, app. nonet, J = 6.7, H-6), 2.97 (2 H, d, J = 21.6, H-2),

3.92 (2 H, d, J = 6.7, H-5), 4.17 (4 H, dq, J = 8.3, J = 7.1, H-3); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.5, C-4), 19.0 (C-7), 27.6 (C-6), 34.3 (d, J = 134.0, C-2), 62.6 (d, J = 6.2, C-3), 71.6 (C-5), 165.9 (d, J = 6.4, C-1); δ_P (162 MHz, $CDCl_3$) 20.5; HRMS (ESI^+): Found: 275.1018; $C_{10}H_{21}NaO_5P$ (MNa^+) Requires 275.1019 (0.3 ppm error), Found: 253.1202; $C_{10}H_{22}O_5P$ (MH^+) Requires 253.1199 (−1.1 ppm error).

Lab notebook reference: MGL/03/16

Obtained data in accord with reported literature.[76]

2-Methylpropyl 2-diazo-2-(diethoxyphosphoryl)acetate (130b)



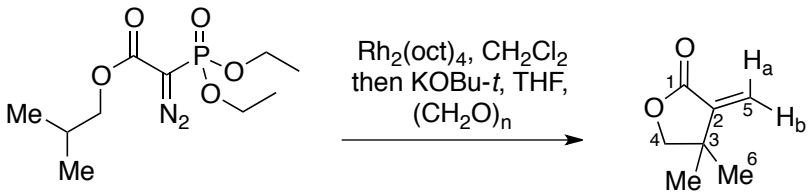
130a **130b**

Synthesised using general procedure B with 2-methylpropyl 2-(diethoxyphosphoryl)acetate **130a** (2.02 g, 8.00 mmol), THF (40 mL), LHMDS (9.60 mL, 9.60 mmol, 1.0 M solution in THF) and *p*-ABSA (2.31 g, 9.60 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the title compound **130b** as a pale yellow oil (1.62 g, 73%); R_f 0.50 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2966m, 2127s, 1702s, 1276s, 1115w, 1019s, 978m; δ_H (400 MHz, $CDCl_3$) 0.89 (6 H, d, J = 6.7, H-7), 1.31 (6 H, td, J = 7.1, J = 0.8, H-4), 1.91 (1 H, app. nonet, J = 6.7, J = 6.6, H-6), 3.93 (2 H, d, J = 6.6, H-5), 4.06–4.22 (4 H, m, H-3); δ_C (100 MHz, $CDCl_3$) 16.0 (d, J = 6.9, C-4), 18.7 (C-7), 27.7 (C-6), 53.7 (d, J = 227.9, C-2), 63.4 (d, J = 5.7, C-3), 71.5 (C-5), 163.4 (d, J = 11.9, C-1); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI^+): Found: 301.0913; $C_{10}H_{19}N_2NaO_5P$ (MNa^+) Requires 301.0924 (3.5 ppm error), Found: 279.1104; $C_{10}H_{20}N_2O_5P$ (MH^+) Requires 279.1104 (0.2 ppm error).

Lab notebook reference: MGL/03/21

Obtained data in accord with reported literature.[76]

4,4-Dimethyl-3-methylenedihydrofuran-2(3*H*)-one (130c)



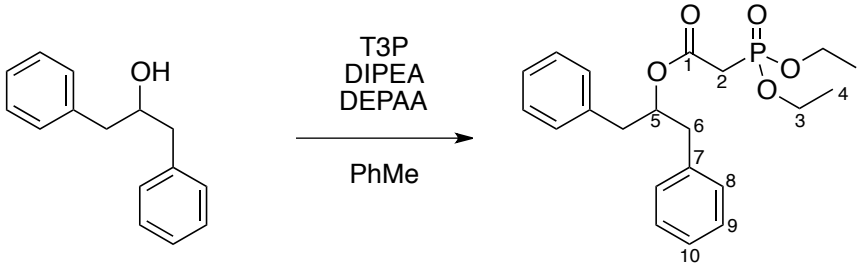
130b **130c**

Synthesised using general procedure D with 2-methylpropyl 2-diazo-2-(diethoxyphosphoryl)acetate **130b** (85 mg, 0.305 mmol), CH_2Cl_2 (6.1 mL), $Rh_2(oct)_4$ (3.4 mg, 6.1 μmol), KOBu-*t* (41.1 mg, 0.366 mmol) and paraformaldehyde (18.3 mg, 0.610 mmol). Purification by column chromatography (8:1 hexane:EtOAc) afforded the title compound **130c** as a colourless oil (9 mg, 23%); R_f 0.39 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2966w, 2929w, 1760s, 1668w, 1464w, 1410w, 1371w, 1294m, 1169w, 1107m, 1014m; δ_H (400 MHz, $CDCl_3$) 1.26 (6 H, s, H-6), 4.03 (2 H, s, H-4), 5.54 (1 H, s, H-5b), 6.20 (1 H, s, H-5a); δ_C (100 MHz, $CDCl_3$) 26.9 (C-6), 38.9 (C-3), 78.3 (C-4), 119.9 (C-5), 144.7 (C-2), 170.8 (C-1); HRMS (ESI$^+$): Found: 127.0758; $C_7H_{11}O_2$ (MH^+) Requires 127.0754 (−3.6 ppm error).

Lab notebook reference: MGL/03/42

Obtained data in accord with reported literature.[160]

1,3-Diphenylpropan-2-yl 2-(diethoxyphosphoryl)acetate (131a)



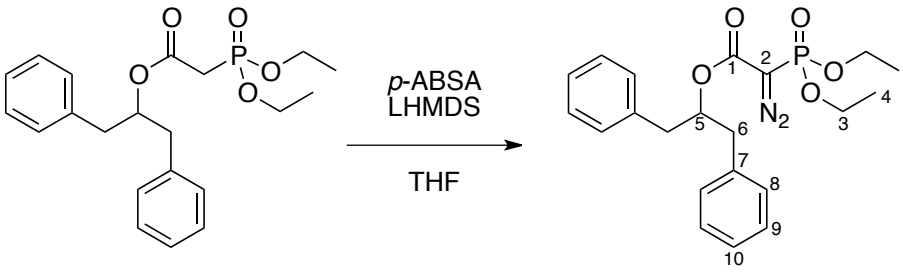
131 **131a**

Synthesised using general procedure A with 1,3-diphenylpropan-2-ol **130** (2.50 g, 11.8 mmol), toluene (60 mL), DEPAA (2.00 mL, 12.4 mmol), DIPEA (5.30 mL, 30.6 mmol) and T3P (9.74 g, 15.3 mmol, 50% w/w solution in EtOAc) affording the *title compound* **131a** as a yellow oil (4.48 g, 98%). No further purification was required; R_f 0.26 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2938s, 2883s, 1708s, 1249s, 1097w, 1036w, 1011m, 955w; δ_H (400 MHz, $CDCl_3$) 1.29 (6 H, td, J = 7.1, J = 0.5, H-4), 2.82–2.96 (4 H, m, H-6), 2.87 (2 H, d, J = 21.5, H-2), 4.01–4.11 (4 H, m, H-3), 5.31–5.39 (1 H, m, H-5), 7.18–7.24 (6 H, m, H-8,10), 7.26–7.31 (4 H, m, H-9); δ_C (100 MHz, $CDCl_3$)

16.3 (d, J = 6.2, C-4), 34.3 (d, J = 134.4, C-2), 39.5 (C-6), 62.5 (d, J = 6.2, C-3), 76.8 (C-5), 126.5 (C-10), 128.3 (C-9), 129.4 (C-8), 137.1 (C-7), 165.2 (d, J = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.3; HRMS (ESI^+): Found: 413.1472; $C_{21}H_{27}NaO_5P$ (MNa^+) Requires 413.1488 (3.9 ppm error), Found: 391.1661; $C_{21}H_{28}O_5P$ (MH^+) Requires 391.1669 (1.9 ppm error).

Lab notebook reference: MGL/01/25

1,3-Diphenylpropan-2-yl 2-diazo-2-(diethoxyphosphoryl)acetate (131b)

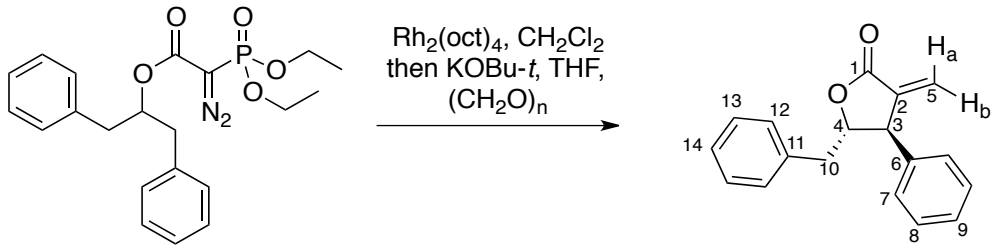


131a **131b**

Synthesised using general procedure B with 1,3-diphenylpropan-2-yl 2-(diethoxyphosphoryl)acetate **131a** (1.00 g, 2.56 mmol), THF (13 mL), LHMDS (3.07 mL, 3.07 mmol, 1.0 M solution in THF) and *p*-ABSA (739 mg, 3.07 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **131b** as a yellow oil (778 mg, 73%); R_f 0.62 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2939m, 2096s, 1683s, 1257s, 1009m; δ_H (400 MHz, $CDCl_3$) 1.25 (6 H, td, J = 7.1, J = 0.7, H-4), 2.91 (4 H, d, J = 6.6, H-6), 3.88–4.10 (4 H, m, H-3), 4.45 (1 H, quin., J = 6.6, H-5), 7.17–7.25 (6 H, m, H-8,10), 7.26–7.37 (4 H, m, H-9); δ_C (100 MHz, $CDCl_3$) 16.0 (d, J = 7.0, C-4), 40.1 (C-6), 54.0 (d, J = 226.5, C-2), 63.5 (d, J = 5.5, C-3), 76.7 (C-5), 126.6 (C-10), 128.4 (C-9), 129.4 (C-8), 137.0 (C-7), 163.2 (d, J = 12.2, C-1); δ_P (162 MHz, $CDCl_3$) 10.5; HRMS (ESI^+): Found: 439.1382; $C_{21}H_{25}N_2NaO_5P$ (MNa^+) Requires 439.1393 (2.7 ppm error), Found: 417.1565; $C_{21}H_{26}N_2O_5P$ (MH^+) Requires 417.1574 (2.0 ppm error).

Lab notebook reference: MGL/01/27

(4*RS*,5*SR*)-5-Benzyl-3-methylene-4-phenyldihydrofuran-2(3*H*)-one (131c)

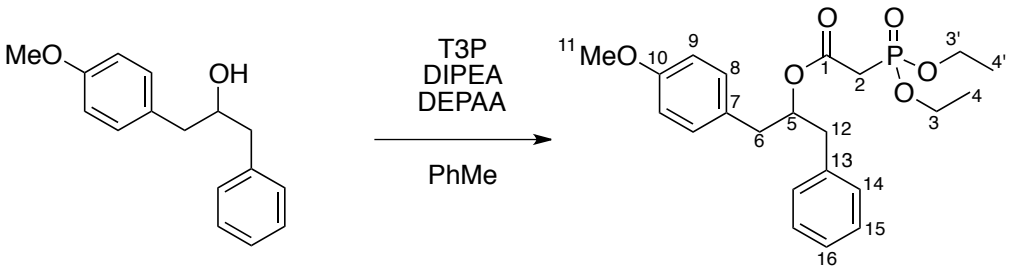


131b **131c**

Synthesised using general procedure E with 1,3-diphenylpropan-2-yl 2-diazo-2-(diethoxyphosphoryl)acetate **131b** (81 mg, 0.195 mmol), CH_2Cl_2 (3.9 mL), $Rh_2(oct)_4$ (3.0 mg, 3.9 μmol), KOBu-*t* (26.3 mg, 0.234 mmol) and paraformaldehyde (11.7 mg, 0.390 mmol). Purification by column chromatography (5:1 petrol:EtOAc) afforded the *title compound* **131c** as a colourless oil (43 mg, 84%); R_f 0.52 (6:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2877s, 2807w, 1738s, 895m, 721m; δ_H (400 MHz, $CDCl_3$) 3.03 (1 H, dd, *J* = 14.5, *J* = 6.7, H-10), 3.11 (1 H, dd, *J* = 14.5, *J* = 4.6, H-10), 3.86 (1 H, ddd, *J* = 7.4, *J* = 3.2, *J* = 2.9, H-3), 4.67 (1 H, ddd, *J* = 7.4, *J* = 6.7, *J* = 4.6, H-4), 5.36 (1 H, dd, *J* = 2.9, H-5b), 6.33 (1 H, dd, *J* = 3.2, H-5a), 7.12–7.14 (2 H, m, Ar*H*), 7.22–7.37 (8 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 39.8 (C-10), 51.0 (C-3), 85.2 (C-4), 123.7 (C-5), [127.0, 127.8, 128.3, 128.5, 129.1, 129.7 (C-7/8/9/12/13/14)], 135.5 (C-2/6/11), 138.8 (C-2/6/11), 140.0 (C-2/6/11), 169.5 (C-1); HRMS (ESI$^+$): Found: 287.1048; $C_{18}H_{16}NaO_2$ (MNa^+) Requires 287.1043 (–2.1 ppm error), Found: 265.1229; $C_{18}H_{17}O_2$ (MH^+) Requires 265.1223 (–2.4 ppm error).

Lab notebook reference: MGL/03/06, 01/32, 01/37

1-(4-Methoxyphenyl)-3-phenylpropan-2-yl 2-(diethoxyphosphoryl) acetate (132a)



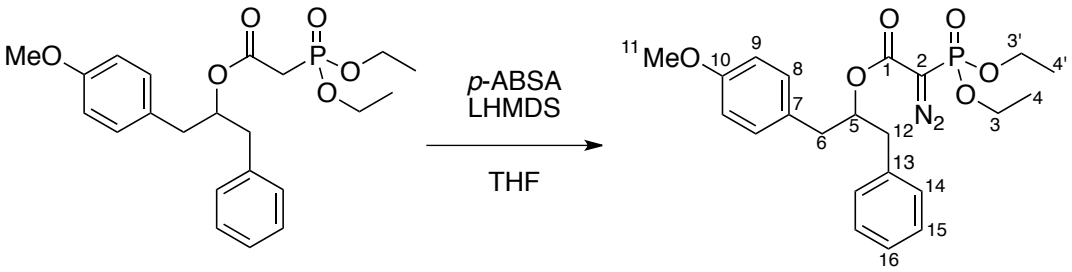
132 **132a**

Synthesised using general procedure A with 1-(4-methoxyphenyl)-3-phenylpropan-2-ol **132** (530 mg, 2.19 mmol), toluene (15 mL), DEPAA (0.370 mL, 2.30 mmol), DIPEA (0.99 mL, 5.69 mmol) and T3P (1.81 g, 2.84 mmol, 50% w/w solution in EtOAc) affording an orange oil (972 mg) as crude. Purification by column chromatography (1:1 petrol:EtOAc) afforded the *title compound*

132a as a colourless oil (850 mg, 92%); R_f 0.26 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2937s, 2872s, 1708s, 1490m, 1231s, 1012s; δ_H (400 MHz, $CDCl_3$) 1.27–1.31 (6 H, m, H-4,4'), 2.75–2.93 (4 H, m, H-6,12), 2.87 (2 H, d, *J* = 21.5, H-2), 3.79 (3 H, s, H-11), 4.02–4.13 (4 H, m, H-3,3'), 5.25–5.33 (1 H, m, H-5), 6.82 (2 H, d, *J* = 8.7, H-9), 7.12 (2 H, d, *J* = 8.7, H-8), 7.17–7.24 (3 H, m, H-14,16), 7.25–7.31 (2 H, m, H-15); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.1, C-4), 34.3 (d, *J* = 134.5, C-2), 38.7 (C-6), 39.5 (C-12), 55.2 (C-11), 62.3 (d, *J* = 6.3, C-3), 77.2 (C-5), 113.8 (C-9), 126.5 (C-16), 128.4 (C-15), 129.1 (C-7), 129.4 (C-14), 130.4 (C-8), 137.2 (C-13), 158.3 (C-10), 165.2 (d, *J* = 6.0, C-1); δ_P (162 MHz, $CDCl_3$) 20.3; HRMS (ESI$^+$): Found: 443.1587; $C_{22}H_{29}NaO_6P$ (MNa^+) Requires 443.1594 (1.7 ppm error), Found: 421.1787; $C_{22}H_{30}O_6P$ (MH^+) Requires 421.1775 (–3.0 ppm error).

Lab notebook reference: MGL/01/54

1-(4-Methoxyphenyl)-3-phenylpropan-2-yl 2-diazo-2-(diethoxyphosphoryl) acetate (132b)

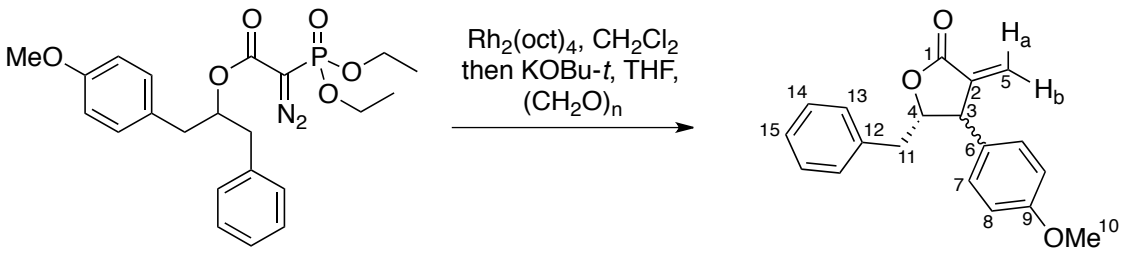


132a **132b**

Synthesised using general procedure B with 1-(4-methoxyphenyl)-3-phenylpropan-2-yl 2-(diethoxyphosphoryl) acetate **132a** (828 mg, 1.97 mmol), THF (10 mL), LHMDS (2.36 mL, 2.36 mmol, 1.0 M solution in THF) and *p*-ABSA (568 mg, 2.36 mmol). Purification by column chromatography (1:1 petrol:EtOAc) afforded the *title compound* **132b** as a yellow oil (621 mg, 71%); R_f 0.40 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2939s, 2889w, 2094s, 1683s, 1490m, 1258s, 1231w, 1009s; δ_H (400 MHz, $CDCl_3$) 1.26 (6 H, td, *J* = 7.1, *J* = 0.8, H-4/4'), 2.86 (2 H, d, *J* = 6.5, H-6), 2.90 (2 H, d, *J* = 6.9, H-12), 3.78 (3 H, s, H-11), 3.89–4.00 (2 H, m, H-3/3'), 4.01–4.12 (2 H, m, H-3/3'), 5.37 (1 H, m, H-5), 6.82 (2 H, d, *J* = 8.7, H-9), 7.10 (2 H, d, *J* = 8.7, H-8), 7.16–7.24 (3 H, m, H-14,16), 7.25–7.31 (2 H, m, H-15); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* = 6.9, C-4/4'), 16.1 (d, *J* = 6.9, C-4/4'), 39.2 (C-6), 40.0 (C-12), 53.2 (d, *J* = 232.8, C-2), 55.1 (C-11), 63.5 (d, *J* = 5.4, C-3/3'), 76.8 (C-5), 113.8 (C-9), 126.6 (C-16), 128.4 (C-15), 128.9 (C-7), 129.3 (C-14), 130.3 (C-8), 137.0 (C-13), 158.3 (C-10), 162.5 (d, *J* = 12.7, C-1); δ_P (162 MHz, $CDCl_3$) 10.5; HRMS (ESI$^+$): Found: 469.1485; $C_{22}H_{27}N_2NaO_6P$ (MNa^+) Requires 469.1499 (2.9 ppm error), Found: 447.1680; $C_{22}H_{28}N_2NaO_6P$ (MH^+) Requires 447.1679 (–0.2 ppm error).

Lab notebook reference: MGL/01/55

5-Benzyl-4-(4-methoxyphenyl)-3-methylenedihydrofuran-2(3*H*)-one (132c)

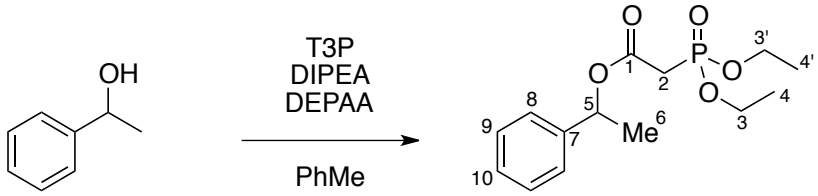


132b **132c**

Synthesised using general procedure E with 1-(4-methoxyphenyl)-3-phenylpropan-2-yl 2-diazo-2-(diethoxyphosphoryl) acetate **132b** (95 mg, 0.213 mmol), CH_2Cl_2 (4.2 mL), $Rh_2(oct)_4$ (3.3 mg, 4.3 μmol), KOBu-*t* (28.7 mg, 0.256 mmol) and paraformaldehyde (12.8 mg, 0.426 mmol). The HWE was performed at 0 °C. Purification by column chromatography (8:1 petrol:EtOAc) afforded the *title compound* **132c** as an inseparable mixture of diastereomers A:B (1.6:1) as a colourless oil (41 mg, 65%); R_f 0.71 (2:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2937w, 1764s, 1513m, 1251m, 1131w, 1032w; δ_H (400 MHz, $CDCl_3$) 2.91–3.12 (2 H, m, H-11A,B), 3.78–3.85 (4 H, m, H-3A,B, H-10A,B), 4.58–4.65 (2 H, m, H-4A,B), 5.34–5.35 (1 H, m, H-5b(A,B)), 6.30–6.31 (1 H, m, H-5a(A,B)), 6.83 (2 H, d, J = 8.7, H-8B), 6.88 (2 H, d, J = 8.7, H-8A), 7.05 (2 H, d, J = 8.7, H-7A), 7.14 (2 H, d, J = 8.7, H-7B), 7.12–7.38 (5 H, m, H-13/14/15(A,B)); δ_C (100 MHz, $CDCl_3$) 38.7 (C-11B), 39.6 (C-11A), 50.4 (C-3A), 50.8 (C-3B), 55.2 (C-10B), 55.3 (C-10A), 85.3 (C-4B), 85.4 (C-4A), 114.0 (C-8B), 114.5 (C-8A), 123.5 (C-5A), 123.6 (C-5B), [127.0, 127.4, 127.8, 128.3, 128.5, 129.1, 129.4, 129.7, 130.5, 130.8 (C-6/7/13/14/15(A/B))], 135.6 (C-12A), 138.9 (C-12B), 140.1 (C-2B), 140.3 (C-2A), 158.6 (C-9B), 159.1 (C-9A), 169.6 (C-1B), 169.6 (C-1A); HRMS (ESI^+): Found: 317.1144; $C_{19}H_{18}NaO_3$ (MNa^+) Requires 317.1148 (1.2 ppm error), Found: 295.1326; $C_{19}H_{19}O_3$ (MH^+) Requires 295.1329 (0.8 ppm error).

Lab notebook reference: MGL/03/07, 02/28

1-Phenylethyl 2-(diethoxyphosphoryl)acetate (133a)

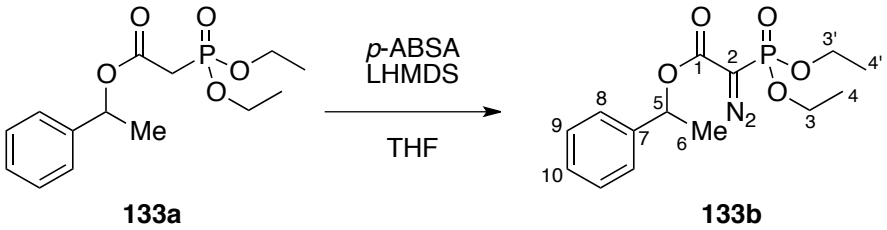


133 **133a**

Synthesised using general procedure A with 1-phenylethanol **133** (0.60 mL, 5.00 mmol), toluene (25 mL), DEPAA (0.84 mL, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in EtOAc) affording the *title compound* **133a** as a pale orange oil (1.48 g, 99%). No further purification was required; R_f 0.31 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2983w, 2933w, 1731s, 1496w, 1452w, 1393w, 1259s, 1208w, 1163w, 1113m, 1048w, 1019s, 960s, 888w, 836w, 795w, 761m, 699s; δ_H (400 MHz, $CDCl_3$) 1.26 (3 H, td, *J* = 7.1, *J* = 0.4, H-4/4'), 1.29 (3 H, td, *J* = 7.1, *J* = 0.4, H-4/4'), 1.56 (3 H, d, *J* = 6.6, H-6), 2.97 (2 H, d, *J* = 21.6, H-2), 4.05–4.16 (4 H, m, H-3,3'), 5.92 (1 H, q, *J* = 6.6, H-5), 7.26–7.38 (5 H, m, H-8,9,10); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.3, C-4/4'), 16.2 (d, *J* = 6.3, C-4/4'), 21.9 (C-6), 34.6 (d, *J* = 133.7, C-2), 62.6 (d, *J* = 6.2, C-3/3'), 62.6 (d, *J* = 6.2, C-3/3'), 73.6 (C-5), 126.1 (C-8/9), 128.0 (C-10), 128.4 (C-8/9), 140.9 (C-7), 165.0 (d, *J* = 6.3, C-1); δ_P (162 MHz, $CDCl_3$) 20.3; HRMS (ESI$^+$): Found: 323.1017; $C_{14}H_{21}NaO_5P$ (MNa^+) Requires 323.1019 (0.6 ppm error), Found: 301.1198; $C_{14}H_{22}O_5P$ (MH^+) Requires 301.1199 (0.6 ppm error).

Lab notebook reference: MGL/05/05S

1-Phenylethyl 2-diazo-2-(diethoxyphosphoryl)acetate (133b)

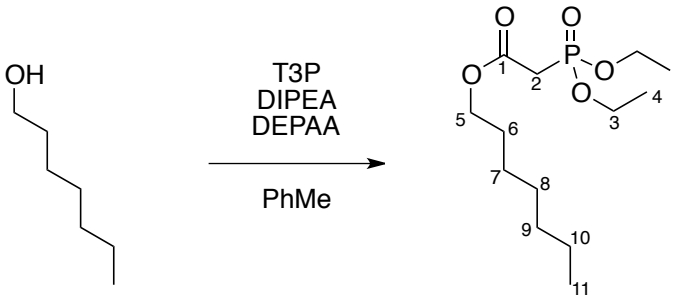


133a **133b**

Synthesised using general procedure B with 1-phenylethyl 2-(diethoxyphosphoryl)acetate **133a** (1.43 g, 4.76 mmol), THF (24 mL), LHMDS (5.71 mL, 5.71 mmol, 1.0 M solution in THF) and *p*-ABSA (1.37 g, 5.71 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **133b** as a yellow oil (1.38 g, 89%); R_f 0.56 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2984w, 2129s, 1700s, 1496w, 1453w, 1332w, 1275s, 1209w, 1164w, 1115w, 1019s, 979m, 797w, 762w, 746w, 700m, 588m, 553m; δ_H (400 MHz, $CDCl_3$) 1.28–1.33 (6 H, m, H-4,4'),

1.57 (3 H, d, J = 6.6, H-6), 4.05–4.24 (4 H, m, H-3,3'), 5.98 (1 H, q, J = 6.6, H-5), 7.27–7.36 (5 H, m, H-8,9,10); δ_C (100 MHz, $CDCl_3$) 16.0 (d, J = 7.0, C-4/4'), 16.0 (d, J = 7.0, C-4/4'), 22.3 (C-6), 54.2 (d, J = 224.3, C-2), 63.5 (d, J = 5.5, C-3/3'), 63.5 (d, J = 5.9, C-3/3'), 73.8 (C-5), 125.9 (C-8/9), 128.0 (C-10), 128.5 (C-8/9), 140.9 (C-7), 162.8 (d, J = 11.8, C-1); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI^+): Found: 349.0919; $C_{14}H_{19}N_2NaO_5P$ (MNa^+) Requires 349.0924 (1.4 ppm error).
Lab notebook reference: MGL/05/05

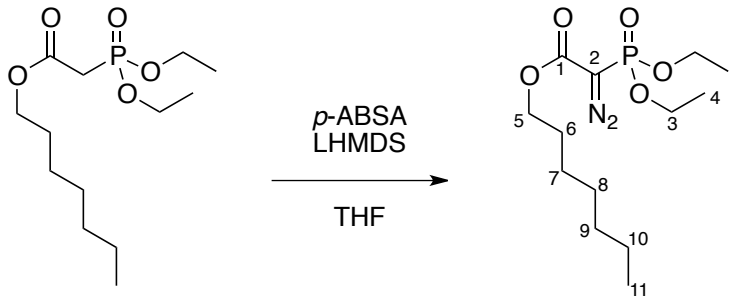
Heptyl 2-(diethoxyphosphoryl)acetate (134a)



134 **134a**

Synthesised using general procedure A with 1-heptanol **134** (930 mg, 8.00 mmol), toluene (40 mL), DEPAA (1.35 mL, 8.40 mmol), DIPEA (3.62 mL, 20.8 mmol) and T3P (6.62 g, 10.4 mmol, 50% w/w solution in EtOAc) affording the *title compound* **134a** as a yellow oil (2.36 g, 100%). No further purification was required; R_f 0.38 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2959w, 2931m, 2859w, 1738s, 1393w, 1267s, 1116w, 1053w, 1025s; δ_H (400 MHz, $CDCl_3$) 0.84 (3 H, t, J = 6.7, H-11), 1.19–1.35 (8 H, m, H-7,8,9,10), 1.31 (6 H, td, J = 7.1, J = 0.2, H-4), 1.61 (2 H, app. quin., J = 7.3, H-6), 2.93 (2 H, d, J = 21.6, H-2), 4.09 (2 H, br t, J = 6.8, H-5), 4.14 (4 H, dq, J = 8.4, J = 7.1, H-3); δ_C (100 MHz, $CDCl_3$) 14.0 (C-11), 16.2 (d, J = 6.2, C-4), 22.5 (C-10), 25.6 (C-7), 28.4 (C-6), 28.8 (C-8), 31.6 (C-9), 34.3 (d, J = 134.2, C-2), 62.5 (d, J = 6.2, C-3), 65.6 (C-5), 165.8 (d, J = 6.2, C-1); δ_P (162 MHz, $CDCl_3$) 20.5; HRMS (ESI^+): Found: 317.1486; $C_{13}H_{27}NaO_5P$ (MNa^+) Requires 317.1488 (0.6 ppm error), Found: 295.1675; $C_{13}H_{28}O_5P$ (MH^+) Requires 295.1669 (–2.2 ppm error).
Lab notebook reference: MGL/03/17

Heptyl 2-diazo-2-(diethoxyphosphoryl)acetate (134b)

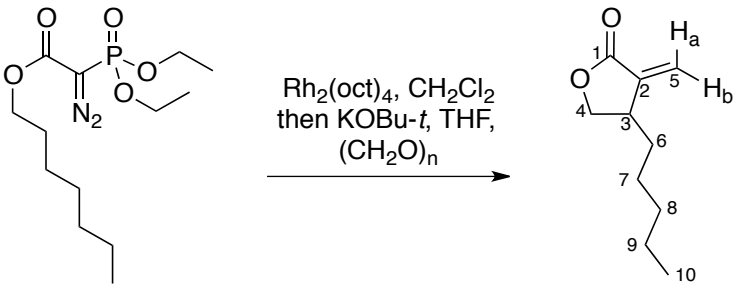


134a **134b**

Synthesised using general procedure B with heptyl 2-(diethoxyphosphoryl)acetate **134a** (2.36 g, 8.00 mmol), THF (40 mL), LHMDS (9.60 mL, 9.60 mmol, 1.0 M solution in THF) and *p*-ABSA (2.31 g, 9.60 mmol). Purification by column chromatography (3:1 petrol:EtOAc) afforded the *title compound* **134b** as a pale yellow oil (1.50 g, 74%); R_f 0.65 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2931m, 2859w, 2127s, 1705s, 1280s, 1023s, 978m; δ_H (400 MHz, $CDCl_3$) 0.81 (3 H, t, J = 7.0, H-11), 1.15–1.32 (8 H, m, H-7,8,9,10), 1.29 (6 H, td, J = 7.1, J = 0.8, H-4), 1.59 (2 H, app. quin., J = 7.2, H-6), 4.04–4.20 (6 H, m, H-3,5); δ_C (100 MHz, $CDCl_3$) 13.8 (C-11), 16.0 (d, J = 6.9, C-4), 22.4 (C-10), 25.5 (C-7), 28.5 (C-6), 28.6 (C-8), 31.5 (C-9), 53.6 (d, J = 226.9, C-2), 63.4 (d, J = 5.9, C-3), 65.6 (C-5), 163.3 (d, J = 12.2, C-1); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI$^+$): Found: 343.1390; $C_{13}H_{25}N_2NaO_5P$ (MNa^+) Requires 343.1393 (1.0 ppm error), Found: 321.1576; $C_{13}H_{26}N_2O_5P$ (MH^+) Requires 321.1574 (–0.6 ppm error).

Lab notebook reference: MGL/03/22

(*SR*)-3-Methylene-4-pentyldihydrofuran-2(3*H*)-one (134c)

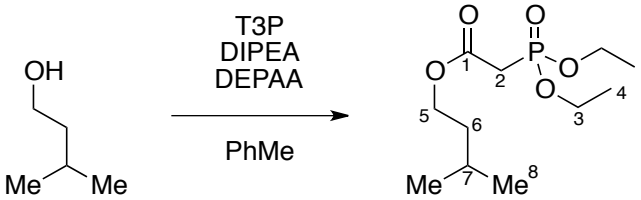


134b **134c**

Synthesised using general procedure D with heptyl 2-diazo-2-(diethoxyphosphoryl)acetate **134b** (78 mg, 0.244 mmol), CH_2Cl_2 (4.9 mL), $Rh_2(oct)_4$ (3.8 mg, 4.9 μmol), THF (4.9 mL), KOBu-*t*

(32.9 mg, 0.293 mmol) and paraformaldehyde (14.7 mg, 0.488 mmol). Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound* **134c** as a pale yellow oil (27 mg, 66%); R_f 0.46 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2957w, 2929m, 2859w, 1763s, 1405w, 1268m, 1112m, 1009w; δ_H (400 MHz, $CDCl_3$) 0.87–0.90 (3 H, m, H-10), 1.24–1.38 (6 H, m, H-7, 8, 9), 1.45–1.54 (1 H, m, H-6), 1.64–1.73 (1 H, m, H-6), 3.03 (1 H, app. ttt, J = 8.5, J = 5.6, J = 2.6, H-3), 3.97 (1 H, dd, J = 9.0, J = 5.6, H-4), 4.45 (1 H, app. t, J = 8.5, H-4), 5.59 (1 H, d, J = 2.6, H-5b), 6.25 (1 H, d, J = 2.6, H-5a); δ_C (100 MHz, $CDCl_3$) 13.9 (C-10), 22.4 (C-9), 26.0 (C-7), 31.6 (C-8), 33.7 (C-6), 38.8 (C-3), 71.2 (C-4), 121.7 (C-5), 138.5 (C-2), 170.9 (C-1); HRMS (ESI$^+$): Found: 191.1040; $C_{10}H_{16}NaO_2$ (MNa$^+$) Requires 191.1043 (1.4 ppm error).
Lab notebook reference: MGL/03/40, 39

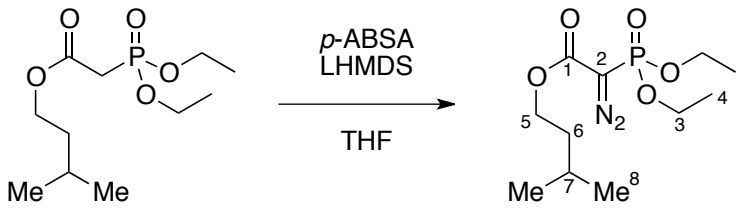
3-Methylbutyl 2-(diethoxyphosphoryl)acetate (135a)



135 **135a**

Synthesised using general procedure A with 3-methyl-1-butanol **135** (882 mg, 10.0 mmol), toluene (50 mL), DEPAA (1.69 mL, 10.5 mmol), DIPEA (4.53 mL, 26.0 mmol) and T3P (8.27 g, 13.0 mmol, 50% w/w solution in EtOAc) affording the *title compound* **135a** as an orange oil (2.67 g, 100%). No further purification was required; R_f 0.28 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2960w, 1735s, 1466w, 1392w, 1261s, 1116m, 1021s, 969m; δ_H (400 MHz, $CDCl_3$) 0.90 (6 H, d, J = 6.6, H-8), 1.33 (6 H, td, J = 7.1, J = 0.4, H-4), 1.52 (2 H, app. q, J = 6.9, H-6), 1.63–1.76 (1 H, m, H-7), 2.94 (2 H, d, J = 21.6, H-2), 4.12–4.19 (6 H, m, H-3,5); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.2, C-4), 22.3 (C-8), 24.8 (C-7), 34.3 (d, J = 134.2, C-2), 37.1 (C-6), 62.6 (d, J = 6.2, C-3), 64.2 (C-5), 165.9 (d, J = 6.2, C-1); δ_P (162 MHz, $CDCl_3$) 20.5; HRMS (ESI$^+$): Found: 289.1356; $C_{11}H_{23}NaO_5P$ (MNa$^+$) Requires 289.1175 (–1.9 ppm error), Found: 267.1356; $C_{11}H_{24}O_5P$ (MH$^+$) Requires 267.1356 (0.0 ppm error).
Lab notebook reference: MGL/03/47

3-Methylbutyl 2-diazo-2-(diethoxyphosphoryl)acetate (135b)

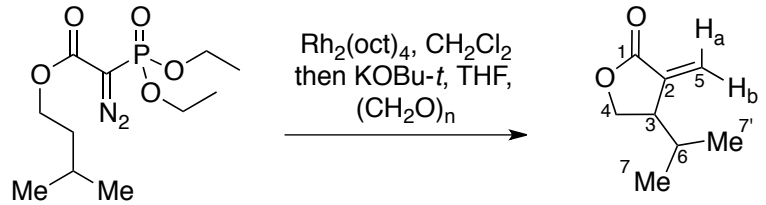


135a **135b**

Synthesised using general procedure B with 3-methylbutyl 2-(diethoxyphosphoryl)acetate **135a** (1.60 g, 6.00 mmol), THF (30 mL), LHMDS (7.20 mL, 7.20 mmol, 1.0 M solution in THF) and *p*-ABSA (1.73 g, 7.20 mmol). Purification by column chromatography (5:1 hexane:EtOAc) afforded the *title compound* **135b** as a pale yellow oil (1.18 g, 67%); R_f 0.65 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2960w, 2125s, 1701s, 1389w, 1272s, 1215w, 1164w, 1116w, 1091w, 1016s, 977m; δ_H (400 MHz, $CDCl_3$) 0.91 (6 H, d, *J* = 6.6, H-8), 1.35 (6 H, td, *J* = 7.1, *J* = 0.8, H-4), 1.54 (2 H, app. q, *J* = 6.8, H-6), 1.62–1.75 (1 H, m, H-7), 4.10–4.26 (4 H, m, H-3), 4.22 (2 H, t, *J* = 6.8, H-5); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* = 6.9, C-4), 22.2 (C-8), 24.8 (C-7), 37.2 (C-6), 53.5 (d, *J* = 228.2, C-2), 63.4 (d, *J* = 5.7, C-3), 64.1 (C-5), 163.3 (d, *J* = 12.0, C-1); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI$^+$): Found: 315.1084; $C_{11}H_{21}N_2NaO_5P$ (MNa^+) Requires 315.1080 (−1.2 ppm error), Found: 293.1263; $C_{11}H_{22}N_2O_5P$ (MH^+) Requires 293.1261 (−0.7 ppm error).

Lab notebook reference: MGL/03/51

(*SR*)-4-Isopropyl-3-methylenedihydrofuran-2(3*H*)-one (135c)



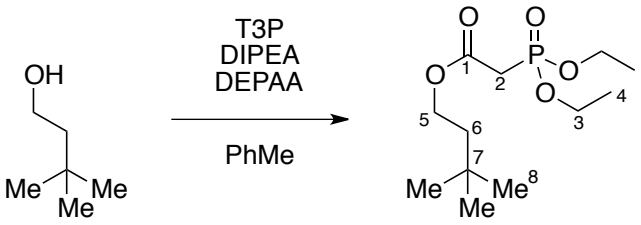
135b **135c**

Synthesised using general procedure D with 3-methylbutyl 2-diazo-2-(diethoxyphosphoryl)acetate **135b** (56 mg, 0.191 mmol), CH_2Cl_2 (3.8 mL), $Rh_2(oct)_4$ (3.0 mg, 3.8 μmol), THF (3.8 mL), KOBu-*t* (25.7 mg, 0.229 mmol) and paraformaldehyde (11.5 mg, 0.382 mmol). Purification by column chromatography (8:1 pentane:diethyl ether) afforded the *title compound* **135c** as a colourless oil (15 mg, 56%); R_f 0.30 (8:1 pentane:diethyl ether); ν_{max} (thin film)/cm^{-1} 2963m, 1762s, 1409w, 1267w, 1117m, 1039w, 979w; δ_H (400 MHz, $CDCl_3$) 0.92 (3 H, d, *J* = 6.8, H-7/7'), 0.95 (3 H, d, *J* = 6.8,

H-7/7'), 1.87–1.99 (1 H, m, H-6), 2.93–2.99 (1 H, m, H-3), 4.16 (1 H, dd, J = 9.3, J = 4.0, H-4), 4.35 (1 H, dd, J = 9.3, J = 8.1, H-4), 5.62 (1 H, d, J = 2.2, H-5b), 6.34 (1 H, d, J = 2.5, H-5a); δ_C (100 MHz, $CDCl_3$) 17.7 (C-7/7'), 19.1 (C-7/7'), 31.4 (C-6), 44.6 (C-3), 68.3 (C-4), 123.1 (C-5), 136.9 (C-2), 171.2 (C-1); HRMS (ESI^+): Found: 163.0722; $C_8H_{12}NaO_2$ (MNa^+) Requires 163.0730 (4.9 ppm error).

Lab notebook reference: MGL/03/58

3,3-Dimethylbutyl 2-(diethoxyphosphoryl)acetate (136a)

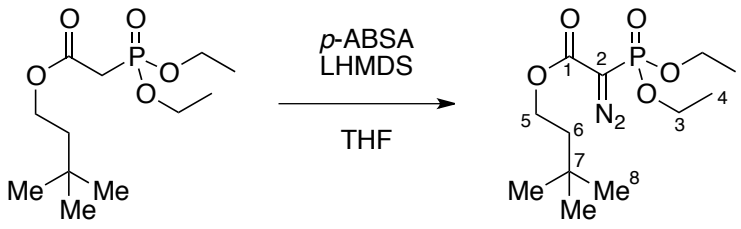


136 **136a**

Synthesised using general procedure A with 3,3-dimethyl-1-butanol **136** (1.02 g, 10.0 mmol), toluene (50 mL), DEPAA (1.69 mL, 10.5 mmol), DIPEA (4.53 mL, 26.0 mmol) and T3P (8.27 g, 13.0 mmol, 50% w/w solution in EtOAc) affording the *title compound* **136a** as an orange oil (2.70 g, 97%). No further purification was required; R_f 0.41 (1:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2958w, 2870w, 1736s, 1478w, 1396w, 1261s, 1116m, 1023s, 971m; δ_H (400 MHz, $CDCl_3$) 0.92 (9 H, s, H-8), 1.33 (6 H, td, J = 7.1, J = 0.5, H-4), 1.57 (2 H, t, J = 7.7, H-6), 2.94 (2 H, d, J = 21.6, H-2), 4.12–4.19 (6 H, m, H-3,5); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.3, C-4), 29.5 (C-8), 29.6 (C-7), 34.3 (d, J = 134.3, C-2), 41.5 (C-6), 62.6 (d, J = 6.3, C-3), 63.4 (C-5), 165.9 (d, J = 6.0, C-1); δ_P (162 MHz, $CDCl_3$) 20.5; HRMS (ESI^+): Found: 303.1323; $C_{12}H_{25}NaO_5P$ (MNa^+) Requires 303.1332 (3.0 ppm error), Found: 281.1505; $C_{12}H_{26}O_5P$ (MH^+) Requires 281.1512 (2.7 ppm error).

Lab notebook reference: MGL/03/48

3,3-Dimethylbutyl 2-diazo-2-(diethoxyphosphoryl)acetate (136b)

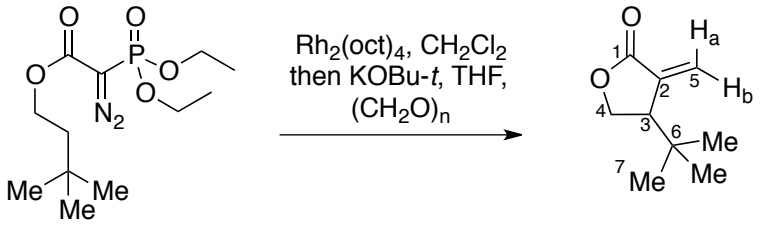


136a **136b**

Synthesised using general procedure B with 3,3-dimethylbutyl 2-(diethoxyphosphoryl)acetate **136a** (1.68 g, 6.00 mmol), THF (30 mL), LHMDS (7.20 mL, 7.20 mmol, 1.0 M solution in THF) and *p*-ABSA (1.73 g, 7.20 mmol). Purification by column chromatography (3:1 hexane:EtOAc) afforded the *title compound* **136b** as a pale yellow oil (1.22 g, 66%); R_f 0.49 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2959m, 2880w, 2125s, 1702s, 1276s, 1216w, 1164w, 1119w, 1095w, 1016s, 976m; δ_H (400 MHz, $CDCl_3$) 0.89 (9 H, s, H-8), 1.31 (6 H, td, J = 7.1, J = 0.8, H-4), 1.54 (2 H, t, J = 7.4, H-6), 4.06–4.22 (4 H, m, H-3), 4.21 (2 H, t, J = 7.4, H-5); δ_C (100 MHz, $CDCl_3$) 16.0 (d, J = 6.9, C-4), 29.4 (C-8), 29.6 (C-7), 41.6 (C-6), 53.5 (d, J = 228.5, C-2), 63.3 (C-5), 63.4 (d, J = 5.6, C-3), 163.3 (d, J = 12.3, C-1); δ_P (162 MHz, $CDCl_3$) 10.7; HRMS (ESI$^+$): Found: 329.1223; $C_{12}H_{23}N_2NaO_5P$ (MNa^+) Requires 329.1237 (4.1 ppm error), Found: 307.1409; $C_{12}H_{24}N_2O_5P$ (MH^+) Requires 307.1417 (2.8 ppm error).

Lab notebook reference: MGL/03/52

(*SR*)-4-(*tert*-Butyl)-3-methylenedihydrofuran-2(3*H*)-one (136c)



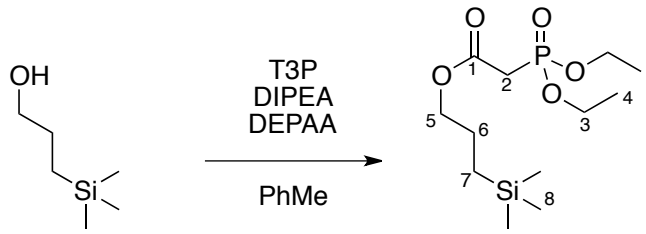
136b **136c**

Synthesised using general procedure D with 3,3-dimethylbutyl 2-diazo-2-(diethoxyphosphoryl)acetate **136b** (58 mg, 0.189 mmol), CH_2Cl_2 (3.8 mL), $Rh_2(oct)_4$ (3.0 mg, 3.8 μmol), THF (3.8 mL), KOBu-*t* (25.5 mg, 0.227 mmol) and paraformaldehyde (11.4 mg, 0.378 mmol). Purification by column chromatography (8:1 pentane:diethyl ether) afforded the *title compound* **136c** as a colourless oil (10 mg, 34%); R_f 0.24 (8:1 pentane:diethyl ether); ν_{max} (thin film)/cm^{-1} 2962m, 1765s, 1492w, 1401w, 1364w, 1274m, 1250w, 1119m, 1041w, 969w, 822w; δ_H

(400 MHz, $CDCl_3$) 0.94 (9 H, s, H-7), 2.74–2.78 (1 H, m, H-3), 4.26–4.34 (2 H, m, H-4), 5.66 (1 H, dd, *J* = 1.9, *J* = 0.7, H-5b), 6.38 (1 H, d, *J* = 2.1, H-5a); δ_C (100 MHz, $CDCl_3$) 26.3 (C-7), 33.5 (C-6), 49.1 (C-3), 67.8 (C-4), 124.5 (C-5), 136.2 (C-2), 171.3 (C-1); HRMS (ESI^+): Found: 177.0878; $C_9H_{14}NaO_2$ (MNa^+) Requires 177.0886 (4.7 ppm error), Found: 155.1063; $C_9H_{15}O_2$ (MH^+) Requires 155.1067 (2.6 ppm error).

Lab notebook reference: MGL/03/60

3-(Trimethylsilyl)propyl 2-(diethoxyphosphoryl)acetate (137a)

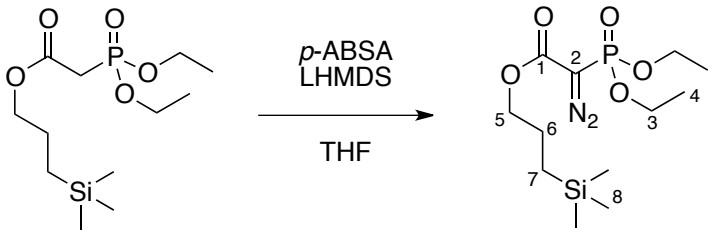


137 **137a**

Synthesised using general procedure A with 3-(trimethylsilyl)-1-propanol **137** (882 mg, 10.0 mmol), toluene (50 mL), DEPAA (1.69 mL, 10.5 mmol), DIPEA (4.53 mL, 26.0 mmol) and T3P (8.27 g, 13.0 mmol, 50% w/w solution in EtOAc) affording the *title compound* **137a** as an orange oil (3.11 g, 100%). No further purification was required; R_f 0.48 (1:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2953w, 1735s, 1394w, 1248s, 1116m, 1021s, 969m; δ_H (400 MHz, $CDCl_3$) −0.03 (9 H, s, H-8), 0.45–0.50 (2 H, m, H-7), 1.32 (6 H, td, *J* = 7.1, *J* = 0.4, H-4), 1.57–1.65 (2 H, m, H-6), 2.94 (2 H, d, *J* = 21.6, H-2), 4.07 (2 H, t, *J* = 7.0, H-5), 4.11–4.19 (4 H, m, H-3); δ_C (100 MHz, $CDCl_3$) −1.9 (C-8), 12.2 (C-7), 16.3 (d, *J* = 6.2, C-4), 23.1 (C-6), 34.3 (d, *J* = 134.1, C-2), 62.6 (d, *J* = 6.2, C-3), 68.1 (C-5), 165.8 (d, *J* = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.5; HRMS (ESI^+): Found: 333.1251; $C_{12}H_{27}NaO_5PSi$ (MNa^+) Requires 333.1258 (2.1 ppm error), Found: 311.1432; $C_{12}H_{28}O_5PSi$ (MH^+) Requires 311.1438 (1.9 ppm error).

Lab notebook reference: MGL/03/49

3-(Trimethylsilyl)propyl 2-diazo-2-(diethoxyphosphoryl)acetate (137b)

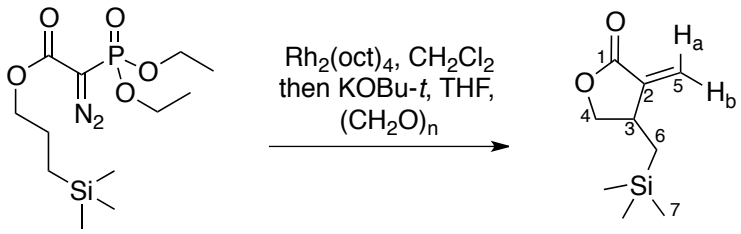


137a **137b**

Synthesised using general procedure B with 3-(trimethylsilyl)propyl 2-(diethoxyphosphoryl)acetate **137a** (1.86 g, 6.00 mmol), THF (30 mL), LHMDS (7.20 mL, 7.20 mmol, 1.0 M solution in THF) and *p*-ABSA (1.73 g, 7.20 mmol). Purification by column chromatography (3:1 hexane:EtOAc) afforded the *title compound* **137b** as a pale yellow oil (1.26 g, 63%); R_f 0.65 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2953w, 2126s, 1702s, 1276s, 1249w, 1216w, 1165w, 1119w, 1092w, 1020s, 977m; δ_H (400 MHz, $CDCl_3$) 0.04 (9 H, s, H-8), 0.44–0.48 (2 H, m, H-7), 1.33 (6 H, td, J = 7.1, J = 0.8, H-4), 1.57–1.65 (2 H, m, H-6), 4.08–4.24 (4 H, m, H-3), 4.12 (2 H, t, J = 7.0, H-5); δ_C (100 MHz, $CDCl_3$) −1.8 (C-8), 12.3 (C-7), 16.2 (d, J = 6.9, C-4), 23.4 (C-6), 53.9 (d, J = 228.0, C-2), 63.6 (d, J = 5.6, C-3), 68.3 (C-5), 163.5 (d, J = 12.1, C-1); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI$^+$): Found: 359.1151; $C_{12}H_{25}N_2NaO_5PSi$ (MNa^+) Requires 359.1163 (3.3 ppm error), Found: 337.1332; $C_{12}H_{26}N_2O_5PSi$ (MH^+) Requires 337.1343 (3.2 ppm error).

Lab notebook reference: MGL/03/53

(*SR*)-3-Methylene-4-((trimethylsilyl)methyl)dihydrofuran-2(3*H*)-one (137c)



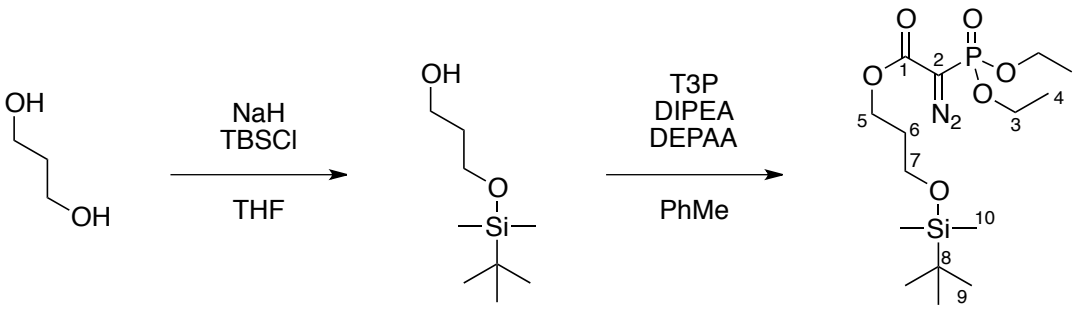
137b **137c**

Synthesised using general procedure D with 3-(trimethylsilyl)propyl 2-diazo-2-(diethoxyphosphoryl)acetate **137b** (61 mg, 0.197 mmol), CH_2Cl_2 (4.0 mL), $Rh_2(oct)_4$ (3.1 mg, 3.9 μmol), THF (4.0 mL), KOBu-*t* (33.2 mg, 0.296 mmol) and paraformaldehyde (11.8 mg, 0.394 mmol). Purification by column chromatography (8:1 petrol:EtOAc) afforded the *title compound* **137c** as a colourless oil (27 mg, 75%); R_f 0.33 (8:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2955w,

2898w, 1768s, 1403w, 1251s, 1109m, 1017m, 841s, 693w; δ_H (400 MHz, $CDCl_3$) 0.06 (9 H, s, H-7), 0.73 (1 H, dd, *J* = 14.8, *J* = 10.9, H-6), 1.08 (1 H, dd, *J* = 14.8, *J* = 3.8, H-6), 3.05–3.14 (1 H, m, H-3), 3.80 (1 H, dd, *J* = 8.7, *J* = 7.6, H-4), 4.49 (1 H, app. t, *J* = 8.6, H-4), 5.58 (1 H, d, *J* = 2.8, H-5b), 6.24 (1 H, d, *J* = 3.1, H-5a); δ_C (100 MHz, $CDCl_3$) –0.98 (C-7), 20.8 (C-6), 35.9 (C-3), 72.7 (C-4), 120.8 (C-5), 141.1 (C-2), 170.8 (C-1); HRMS (ESI^+): Found: 207.0807; $C_9H_{16}NaO_2Si$ (MNa^+) Requires 207.0812 (2.4 ppm error), Found: 185.0986; $C_9H_{17}O_2Si$ (MH^+) Requires 185.0992 (3.6 ppm error).

Lab notebook reference: MGL/03/62,82

3-((*tert*-Butyldimethylsilyl)oxy)propyl 2-(diethoxyphosphoryl)acetate (138a)

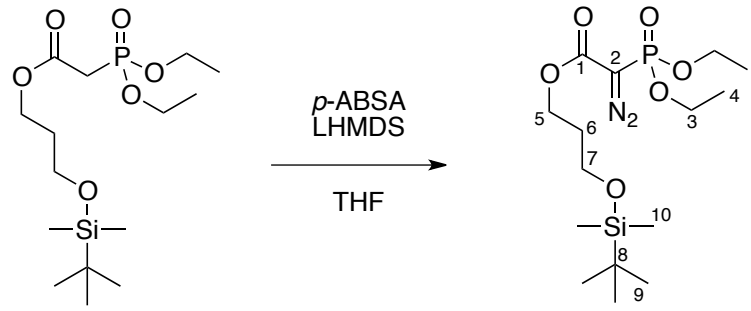


196 **138** **138a**

To a solution of NaH (60% dispersion in mineral oil) (480 mg, 12.0 mmol) in THF (20 mL) cooled to 0 °C was added 1,3-propanediol **196** (0.80 mL, 11.0 mmol) dropwise over 5 mins. The solution was allowed to warm at RT and stirred for 30 mins after which TBSCl (1.51 g, 10.0 mmol) was added then stirred at RT for 1 h. The solution was diluted with water (25 mL), extracted with diethyl ether (2 × 25 mL), washed with brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude alcohol **138**, which was treated under the conditions of general procedure A with toluene (50 mL), DEPAA (1.69 mL, 10.5 mmol), DIPEA (4.53 mL, 26.0 mmol) and T3P (8.27 g, 13.0 mmol, 50% w/w solution in EtOAc) affording the *title compound* **138a** as a yellow oil (3.32 g, 90% over 2 steps); R_f 0.22 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2956w, 2930m, 2857w, 1738s, 1473w, 1392w, 1258s, 1100m, 1054w, 1025s, 970m, 836s, 777m; δ_H (400 MHz, $CDCl_3$) 0.04 (6 H, s, H-10), 0.88 (9 H, s, H-9), 1.34 (6 H, t, *J* = 7.1, H-4), 1.85 (2 H, tt, *J* = 6.5, *J* = 6.0, H-6), 2.96 (2 H, d, *J* = 21.6, H-2), 3.69 (2 H, t, *J* = 6.0, H-7), 4.13–4.20 (4 H, m, H-3), 4.24 (2 H, t, *J* = 6.5, H-5); δ_C (100 MHz, $CDCl_3$) –5.4 (C-10), 16.3 (d, *J* = 6.2, C-4), 18.2 (C-8), 25.8 (C-9), 31.7 (C-6), 34.3 (d, *J* = 134.3, C-2), 59.2 (C-7), 62.6 (d, *J* = 6.3, C-3), 62.6 (C-5), 165.8 (d, *J* = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI^+): Found: 391.1691; $C_{15}H_{33}NaO_6PSi$ (MNa^+) Requires 391.1676 (–3.8 ppm error), Found: 369.1859; $C_{15}H_{34}O_6PSi$ (MH^+) Requires 369.1857 (–0.5 ppm error).

Lab notebook reference: MGL/04/01

3-((*tert*-Butyldimethylsilyl)oxy)propyl 2-diazo-2-(diethoxyphosphoryl) acetate (138b)

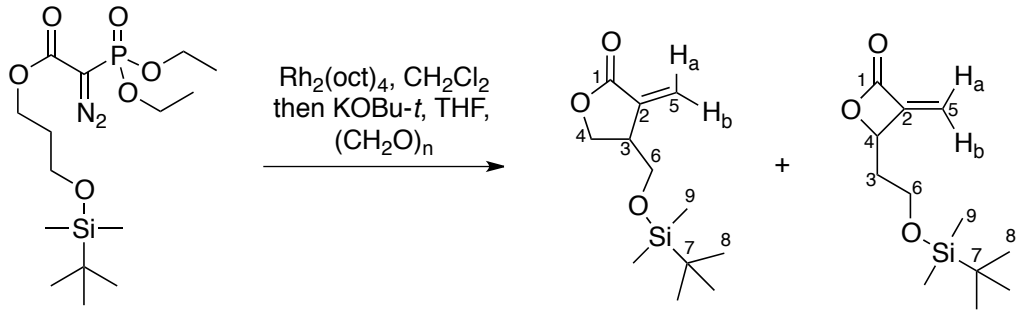


138a **138b**

Synthesised using general procedure B with 3-((*tert*-butyldimethylsilyl)oxy)propyl 2-(diethoxyphosphoryl) acetate **138a** (2.21 g, 6.00 mmol), THF (30 mL), LHMDS (7.20 mL, 7.20 mmol, 1.0 M solution in THF) and *p*-ABSA (1.73 g, 7.20 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **138b** as a yellow oil (1.42 g, 60%); R_f 0.30 (2:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2964w, 2931w, 2866w, 2128s, 1707s, 1474w, 1395w, 1281s, 1097m, 1024s, 838m, 777w; δ_H (400 MHz, $CDCl_3$) −0.05 (6 H, s, H-10), 0.79 (9 H, s, H-9), 1.26 (6 H, td, J = 7.1, J = 0.8, H-4), 1.77 (2 H, tt, J = 6.4, J = 6.0, H-6), 3.69 (2 H, t, J = 6.0, H-7), 4.02–4.17 (4 H, m, H-3), 4.24 (2 H, t, J = 6.4, H-5); δ_C (100 MHz, $CDCl_3$) −5.7 (C-10), 15.9 (d, J = 6.9, C-4), 18.0 (C-8), 25.6 (C-9), 31.6 (C-6), 53.5 (d, J = 230.0, C-2), 58.8 (C-7), 62.4 (C-5), 63.3 (d, J = 5.9, C-3), 163.1 (d, J = 11.6, C-1); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI$^+$): Found: 417.1590; $C_{15}H_{31}N_2NaO_6PSi$ (MNa^+) Requires 417.1581 (−2.1 ppm error), Found: 395.1768; $C_{15}H_{32}N_2O_6PSi$ (MH^+) Requires 395.1762 (−1.7 ppm error).

Lab notebook reference: MGL/04/03

4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-methylenedihydrofuran-2(3*H*)-one (138c) and 4-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3-methyleneoxetan-2-one (138d)



138b **138c** **138d**

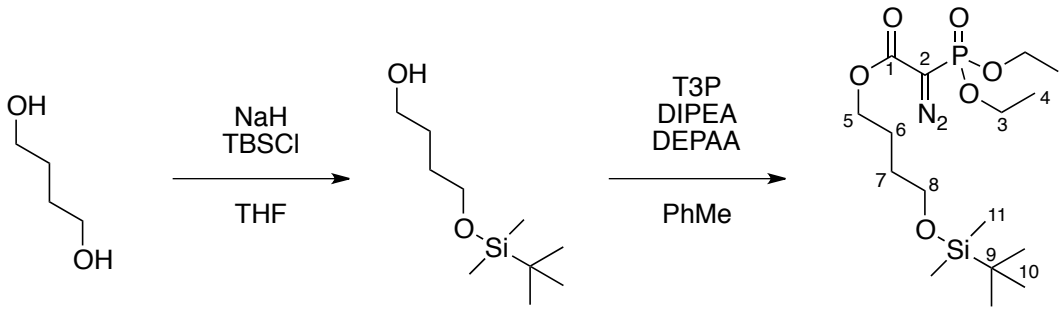
Synthesised using general procedure D with 3-((*tert*-butyldimethylsilyl)oxy)propyl 2-diazo-2-(diethoxyphosphoryl)acetate **138b** (83 mg, 0.210 mmol), CH_2Cl_2 (4.2 mL), $Rh_2(oct)_4$ (3.3 mg, 4.2 μmol), THF (4.2 mL), KOBu-*t* (35.3 mg, 0.315 mmol) and paraformaldehyde (12.6 mg, 0.420 mmol). Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound*s 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methylenedihydrofuran-2(3*H*)-one **138c** as a colourless oil (9 mg, 18%) and 4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-methyleneoxetan-2-one **138d** as a colourless oil (8 mg, 16%).

Data for **138c**; R_f 0.49 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2955m, 2930m, 2857m, 1766s, 1663w, 1472m, 1408w, 1362w, 1258m, 1115s, 1039m, 1004m, 940w, 837s, 815w, 778m; δ_H (400 MHz, $CDCl_3$) 0.05 (3 H, s, H-9), 0.05 (3 H, s, H-9), 0.88 (9 H, s, H-8), 3.20–3.27 (1 H, m, H-3), 3.65 (1 H, dd, J = 9.9, J = 7.2, H-6), 3.72 (1 H, dd, J = 9.9, J = 5.9, H-6), 4.21 (1 H, dd, J = 9.3, J = 4.3, H-4), 4.42 (1 H, dd, J = 9.3, J = 8.2, H-4), 5.69 (1 H, d, J = 2.2, H-5b), 6.31 (1 H, d, J = 2.5, H-5a); δ_C (100 MHz, $CDCl_3$) −5.6 (C-9), −5.5 (C-9), 18.2 (C-7), 25.7 (C-8), 41.2 (C-3), 64.8 (C-6), 68.4 (C-4), 123.2 (C-5), 135.6 (C-2), 170.6 (C-1); HRMS (ESI^+): Found: 265.1223; $C_{12}H_{22}NaO_3Si$ (MNa^+) Requires 265.1230 (2.7 ppm error), Found: 243.1406; $C_{12}H_{23}O_3Si$ (MH^+) Requires 243.1411 (1.9 ppm error).

Data for **138d**; R_f 0.60 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2955m, 2930m, 2858m, 1826s, 1472w, 1408w, 1362w, 1257m, 1208w, 1099s, 1049m, 946w, 834s, 778m; δ_H (400 MHz, $CDCl_3$) 0.07 (3 H, s, H-9), 0.07 (3 H, s, H-9), 0.90 (9 H, s, H-8), 2.00–2.09 (2 H, m, H-3), 3.80 (2 H, app. dd, J = 6.6, J = 5.2, H-6), 5.16 (1 H, app. ddt, J = 7.5, J = 5.7, J = 1.8, H-4), 5.47 (1 H, app. t, J = 1.7, H-5b), 5.93 (1 H, app. t, J = 1.9, H-5a); δ_C (100 MHz, $CDCl_3$) −5.5 (C-9), −5.4 (C-9), 18.3 (C-7), 25.9 (C-8), 36.5 (C-3), 58.6 (C-6), 77.1 (C-4), 115.3 (C-5), 146.4 (C-2), 163.6 (C-1); HRMS

(ESI$^+$): Found: 265.1227; $C_{12}H_{22}NaO_3Si$ (MNa^+) Requires 265.1230 (1.3 ppm error), Found: 243.1402; $C_{12}H_{23}O_3Si$ (MH^+) Requires 243.1411 (3.8 ppm error).
Lab notebook reference: MGL/04/05

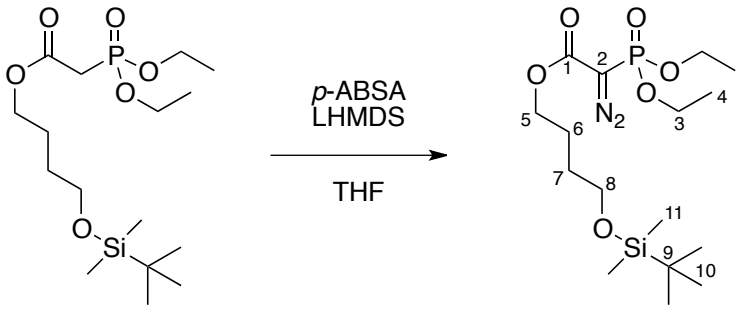
4-((*tert*-Butyldimethylsilyl)oxy)butyl 2-(diethoxyphosphoryl)acetate (139a)



S1 **139** **139a**

To a solution of NaH (60% dispersion in mineral oil) (240 mg, 6.00 mmol) in THF (10 mL) cooled to 0 °C was added 1,4-butanediol **S1** (0.44 mL, 5.50 mmol) dropwise over 5 mins. The solution was allowed to warm at RT and stirred for 30 mins after which TBSCl (754 mg, 5.00 mmol) was added then stirred at RT for 1 h. The solution was diluted with water (25 mL), extracted with diethyl ether (2 × 25 mL), washed with brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude alcohol **139**, which was treated under the conditions of general procedure A with toluene (25 mL), DEPAA (0.84 mL, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in THF) affording the *title compound* **139a** as a yellow oil (1.76 g, 92% over 2 steps). No further purification was required; R_f 0.43 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2955w, 2929w, 2857w, 1737s, 1472w, 1391w, 1255s, 1164w, 1097s, 1052w, 1023s, 968s, 892w, 834s, 774s; δ_H (400 MHz, $CDCl_3$) 0.01 (6 H, s, H-11), 0.85 (9 H, s, H-10), 1.31 (6 H, td, J = 7.1, J = 0.5, H-4), 1.51–1.58 (2 H, m, H-7), 1.65–1.72 (2 H, m, H-6), 2.93 (2 H, d, J = 21.6, H-2), 3.60 (2 H, t, J = 6.2, H-8), 4.10–4.17 (6 H, m, H-3,5); δ_C (100 MHz, $CDCl_3$) −5.4 (C-11), 16.3 (d, J = 6.2, C-4), 18.2 (C-9), 25.1 (C-6), 25.8 (C-10), 28.9 (C-7), 34.2 (d, J = 134.2, C-2), 62.4 (C-8), 62.6 (d, J = 6.4, C-3), 65.5 (C-5), 165.8 (d, J = 6.2, C-1); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI$^+$): Found: 405.1833; $C_{16}H_{35}NaO_6PSi$ (MNa^+) Requires 405.1833 (0.0 ppm error), Found: 383.2010; $C_{16}H_{36}O_6PSi$ (MH^+) Requires 383.2013 (0.8 ppm error).
Lab notebook reference: MGL/05/12S

4-((*tert*-Butyldimethylsilyl)oxy)butyl 2-diazo-2-(diethoxyphosphoryl)acetate (139b)

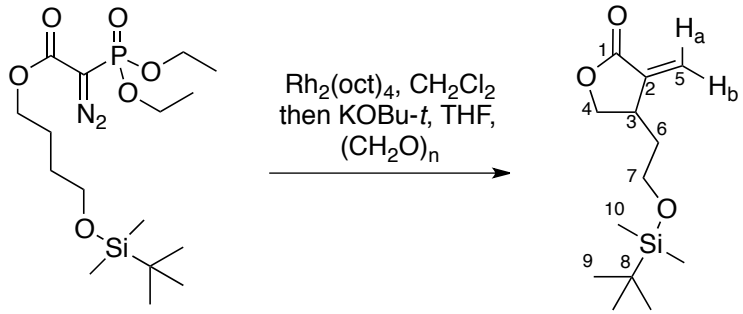


139a **139b**

Synthesised using general procedure B with 4-((*tert*-butyldimethylsilyl)oxy)butyl 2-(diethoxyphosphoryl)acetate **139a** (1.70 g, 4.44 mmol), THF (22 mL), LHMDS (5.33 mL, 5.33 mmol, 1.0 M solution in THF) and *p*-ABSA (1.28 g, 5.33 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **139b** as a yellow oil (1.05 g, 58%); R_f 0.74 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2954w, 2930w, 2857w, 2126s, 1703s, 1473w, 1389w, 1275s, 1257w, 1164w, 1095s, 1019s, 977s, 892w, 834s, 813w, 774s, 746w, 662w, 589m, 560m; δ_H (400 MHz, $CDCl_3$) –0.05 (6 H, s, H-11), 0.79 (9 H, s, H-10), 1.26 (6 H, td, J = 7.1, J = 0.8, H-4), 1.45–1.52 (2 H, m, H-7), 1.61–1.68 (2 H, m, H-6), 3.54 (2 H, t, J = 6.2, H-8), 4.02–4.18 (6 H, m, H-3,5); δ_C (100 MHz, $CDCl_3$) –5.6 (C-11), 15.9 (d, J = 6.9, C-4), 18.0 (C-9), 25.2 (C-6), 25.7 (C-10), 28.7 (C-7), 53.5 (d, J = 227.3, C-2), 62.2 (C-8), 63.3 (d, J = 6.0, C-3), 65.4 (C-5), 163.2 (d, J = 11.9, C-1); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI$^+$): Found: 431.1748; $C_{16}H_{33}N_2NaO_6PSi$ (MNa^+) Requires 431.1738 (–2.4 ppm error), Found: 409.1928; $C_{16}H_{34}N_2O_6PSi$ (MH^+) Requires 409.1918 (–2.4 ppm error).

Lab notebook reference: MGL/05/12

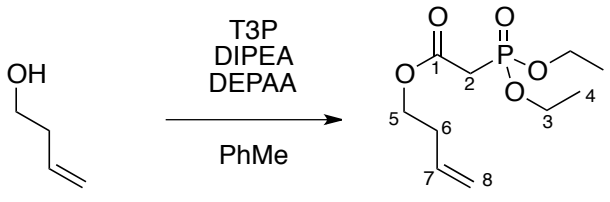
4-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3-methylenedihydrofuran-2(3*H*)-one (139c)



139b **139c**

Synthesised using general procedure D with 4-((*tert*-butyldimethylsilyl)oxy)butyl 2-diazo-2-(diethoxyphosphoryl)acetate **139b** (87 mg, 0.213 mmol), CH_2Cl_2 (4.2 mL), $Rh_2(oct)_4$ (3.3 mg, 4.2 mol), THF (4.2 mL), KOBu-*t* (35.9 mg, 0.320 mmol) and paraformaldehyde (12.8 mg, 0.426 mmol). Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **139c** as a colourless oil (27 mg, 49%); R_f 0.50 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2954m, 2929m, 2857m, 1767s, 1472w, 1257s, 1103s, 1020m, 940w, 836s, 777m; δ_H (400 MHz, $CDCl_3$) 0.05 (3 H, s, H-10), 0.05 (3 H, s, H-10), 0.89 (9 H, s, H-9), 1.72 (1 H, dddd, J = 14.0, J = 9.1, J = 7.5, J = 5.1, H-6), 1.91 (1 H, app. ddt, J = 14.0, J = 5.7, J = 4.9, H-6), 3.17–3.26 (1 H, m, H-3), 3.65–3.76 (2 H, m, H-7), 4.07 (1 H, dd, J = 9.1, J = 6.1, H-4), 4.51 (1 H, dd, J = 9.1, J = 8.4, H-4), 5.60 (1 H, d, J = 2.6, H-5b), 6.27 (1 H, d, J = 2.9, H-5a); δ_C (100 MHz, $CDCl_3$) −5.5 (C-10), −5.5 (C-10), 18.2 (C-8), 25.8 (C-9), 36.3 (C-6), 36.8 (C-3), 60.5 (C-7), 71.7 (C-4), 121.7 (C-5), 138.4 (C-2), 170.8 (C-1); HRMS (ESI^+): Found: 279.1393; $C_{13}H_{24}NaO_3Si$ (MNa^+) Requires 279.1387 (2.1 ppm error), Found: 257.1573; $C_{13}H_{25}O_3Si$ (MH^+) Requires 257.1567 (2.2 ppm error).
Lab notebook reference: MGL/05/26

But-3-en-1-yl 2-(diethoxyphosphoryl)acetate (140a)



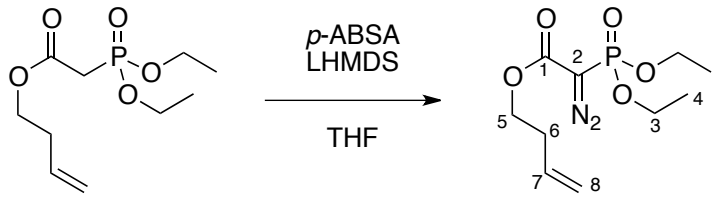
140 **140a**

Synthesised using general procedure A with but-3-en-1-ol **140** (0.43 mL, 5.00 mmol), toluene (25 mL), DEPAA (0.84 mL, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in EtOAc) affording the *title compound* **140a** as a pale yellow oil (1.24 g, 99%).

No further purification was required; R_f 0.20 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2983w, 1735s, 1643w, 1445w, 1393w, 1257s, 1163w, 1115m, 1049w, 1019s, 964s, 839w, 782w, 733w; δ_H (400 MHz, $CDCl_3$) 1.33 (6 H, td, *J* = 7.1, *J* = 0.4, H-4), 2.40 (2 H, app. qt, *J* = 6.8, *J* = 1.4, H-6), 2.96 (2 H, d, *J* = 21.6, H-2), 4.12–4.20 (6 H, m, H-3,5), 5.05–5.14 (2 H, m, H-8), 5.78 (1 H, ddt, *J* = 17.1, *J* = 10.3, *J* = 6.8, H-7); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.2, C-4), 32.8 (C-6), 34.2 (d, *J* = 134.3, C-2), 62.6 (d, *J* = 6.3, C-3), 64.6 (C-5), 117.4 (C-8), 133.6 (C-7), 165.8 (d, *J* = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.3; HRMS (ESI^+): Found: 273.0868; $C_{10}H_{19}NaO_5P$ (MNa^+) Requires 273.0862 (–2.2 ppm error), Found: 251.1048; $C_{10}H_{20}O_5P$ (MH^+) Requires 251.1043 (–2.0 ppm error).

Lab notebook reference: MGL/05/06S

But-3-en-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (140b)

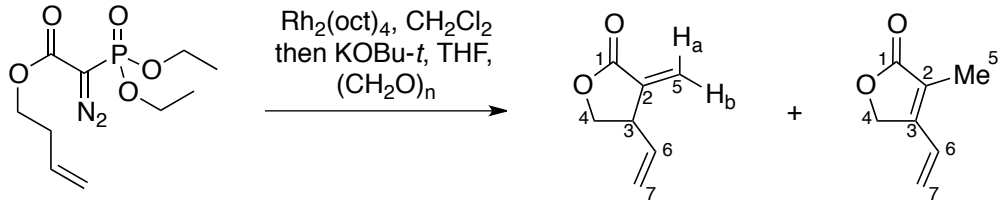


140a **140b**

Synthesised using general procedure B with but-3-en-1-yl 2-(diethoxyphosphoryl)acetate **140a** (1.20 g, 4.80 mmol), THF (24 mL), LHMDS (5.76 mL, 5.76 mmol, 1.0 M solution in THF) and *p*-ABSA (1.38 g, 5.76 mmol). Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **140b** as a yellow oil (790 mg, 60%);R_f 0.43 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2984w, 2126s, 1702s, 1643w, 1445w, 1384w, 1276s, 1164w, 1117w, 1092w, 1019s, 978s, 797m, 746m; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, *J* = 7.1, *J* = 0.8, H-4), 2.38 (2 H, app. qt, *J* = 6.7, *J* = 1.3, H-6), 4.07–4.23 (6 H, m, H-3,5), 5.03–5.11 (2 H, m, H-8), 5.74 (1 H, ddt, *J* = 17.1, *J* = 10.3, *J* = 6.7, H-7); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* = 6.9, C-4), 33.0 (C-6), 53.7 (d, *J* = 226.3, C-2), 63.5 (d, *J* = 5.9, C-3), 64.5 (C-5), 117.5 (C-8), 133.4 (C-7), 163.3 (d, *J* = 12.1, C-1); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI^+): Found: 299.0768; $C_{10}H_{17}N_2NaO_5P$ (MNa^+) Requires 299.0767 (–0.1 ppm error), Found: 277.0952; $C_{10}H_{18}N_2O_5P$ (MH^+) Requires 277.0948 (–1.5 ppm error).

Lab notebook reference: MGL/05/06

(*SR*)-3-Methylene-4-vinyldihydrofuran-2(3*H*)-one (140c) and 3-Methyl-4-vinylfuran-2(5*H*)-one (140d)



140b **140c** **140d**

Synthesised using general procedure D with but-3-en-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate **140b** (58 mg, 0.210 mmol), CH_2Cl_2 (4.2 mL), $Rh_2(oct)_4$ (3.3 mg, 4.2 μmol), THF (4.2 mL), KOBu-*t* (35.3 mg, 0.315 mmol) and paraformaldehyde (12.6 mg, 0.420 mmol). Purification by column chromatography (8:1 pentane:diethyl ether) afforded the title compounds 3-methylene-4-vinyldihydrofuran-2(3*H*)-on **140c** as a colourless oil (10 mg, 38%) and 3-methyl-4-vinylfuran-2(5*H*)-one **140d** as a colourless oil (2.3 mg, 9%).

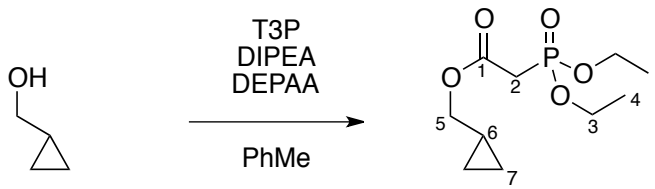
Data for **140c**;[161] R_f 0.54 (4:1 pentane:diethyl ether); ν_{max} (thin film)/cm^{-1} 2965, 2919, 2851, 1766, 1238, 1112; δ_H (400 MHz, $CDCl_3$) 3.68–3.76 (1 H, m, H-3), 4.02 (1 H, dd, J = 9.1, J = 7.4, H-4), 4.53 (1 H, app. t, J = 9.0, H-4), 5.23–5.28 (2 H, m, H-7), 5.62 (1 H, d, J = 2.8, H-5b), 5.71 (1 H, ddd, J = 16.6, J = 10.4, J = 8.2, H-6), 6.33 (1 H, d, J = 3.2, H-5a); δ_C (100 MHz, $CDCl_3$) 44.0 (C-3), 70.0 (C-4), 119.2 (C-7), 123.4 (C-5), 135.0 (C-6), 137.0 (C-2), 170.1 (C-1); HRMS (ESI^+): Found: 147.0411; $C_7H_8NaO_2$ (MNa^+) Requires 147.0417 (3.5 ppm error).

Data for **140d**;[162] R_f 0.29 (4:1 pentane:diethyl ether); ν_{max} (thin film)/cm^{-1} 2925, 2855, 1752, 1663, 1432, 1337, 1208, 1077, 1045; δ_H (400 MHz, $CDCl_3$) 1.94 (3 H, s, H-5), 4.88–4.89 (2 H, m, H-4), 5.49–5.56 (2 H, m, H-7), 6.72 (1 H, dd, J = 17.8, J = 11.0, H-6); δ_C (100 MHz, $CDCl_3$) 8.8 (C-5), 69.2 (C-4), 121.0 (C-7), 124.3 (C-2), 126.9 (C-6), 152.0 (C-3), 178.1 (C-1); HRMS (ESI^+): Found: 147.0417; $C_7H_8NaO_2$ (MNa^+) Requires 147.0417 (–0.4 ppm error), Found: 125.0598; $C_7H_9O_2$ (MH^+) Requires 125.0597 (–0.7 ppm error).

Lab notebook reference: MGL/05/20

Obtained data in accord with reported literature.[161-162]

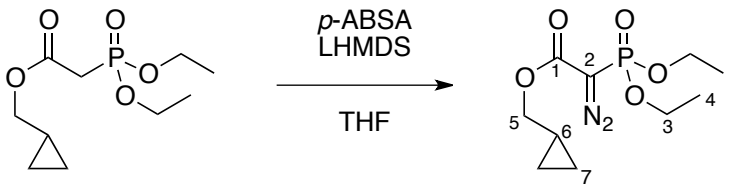
Cyclopropylmethyl 2-(diethoxyphosphoryl)acetate (141a)



141 **141a**

Synthesised using general procedure A with cyclopropylmethanol **141** (0.41 mL, 5.00 mmol), toluene (25 mL), DEPAA (0.84 mL, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in THF) affording the *title compound* **141a** as a yellow oil (1.23 g, 98%). No further purification was required; R_f 0.23 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2984w, 1731s, 1446w, 1394w, 1369w, 1346w, 1257s, 1164w, 1115m, 1049w, 1018s, 966s, 943w, 889w, 839m; δ_H (400 MHz, $CDCl_3$) 0.27–0.31 (2 H, m, H-7), 0.55–0.59 (2 H, m, H-7), 1.09–1.20 (1 H, m, H-6), 1.34 (6 H, t, *J* = 7.1, H-4), 2.98 (2 H, d, *J* = 21.5, H-2), 3.97 (2 H, d, *J* = 7.3, H-5), 4.14–4.21 (4 H, m, H-3); δ_C (100 MHz, $CDCl_3$) 3.3 (C-7), 9.6 (C-6), 16.3 (d, *J* = 6.4, C-4), 34.4 (d, *J* = 134.2, C-2), 62.7 (d, *J* = 6.3, C-3), 70.3 (C-5), 165.9 (d, *J* = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI$^+$): Found: 273.0862; $C_{10}H_{19}NaO_5P$ (MNa^+) Requires 273.0862 (0.1 ppm error), Found: 251.1047; $C_{10}H_{20}O_5P$ (MH^+) Requires 251.1043 (–1.6 ppm error).
Lab notebook reference: MGL/05/14S

Cyclopropylmethyl 2-diazo-2-(diethoxyphosphoryl)acetate (141b)



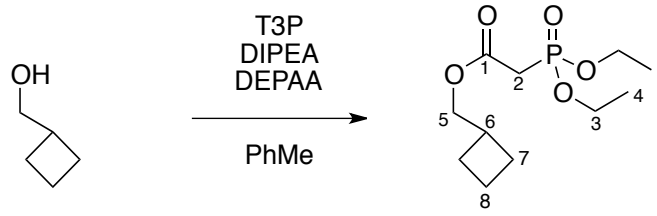
141a **141b**

Synthesised using general procedure B with cyclopropylmethyl 2-(diethoxyphosphoryl)acetate **141a** (1.20 g, 4.80 mmol), THF (24 mL), LHMDS (5.75 mL, 5.75 mmol, 1.0 M solution in THF) and *p*-ABSA (1.38 g, 5.75 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **141b** as a yellow oil (850 mg, 64%); R_f 0.43 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2986w, 2908w, 2125s, 1700s, 1446w, 1394w, 1348m, 1275s, 1216w, 1164w, 1115w, 1082w, 1018s, 977w, 958s, 796m, 746m, 590m, 560m; δ_H (400 MHz, $CDCl_3$) 0.25–0.29 (2 H, m, H-7), 0.52–0.57 (2 H, m, H-7), 1.07–1.17 (1 H, m, H-6), 1.33 (6 H, t, *J* = 7.1, H-4), 4.01 (2

H, d, J = 7.3, H-5), 4.10–4.25 (4 H, m, H-3); δ_C (100 MHz, $CDCl_3$) 3.2 (C-7), 9.8 (C-6), 16.1 (d, J = 6.9, C-4), 53.9 (d, J = 226.8, C-2), 63.6 (d, J = 5.6, C-3), 70.3 (C-5), 163.5 (d, J = 12.2, C-1); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI^+): Found: 299.0771; $C_{10}H_{17}N_2NaO_5P$ (MNa^+) Requires 299.0767 (–1.4 ppm error), Found: 277.0958; $C_{10}H_{18}N_2O_5P$ (MH^+) Requires 277.0948 (–3.7 ppm error).

Lab notebook reference: MGL/05/14

Cyclobutylmethyl 2-(diethoxyphosphoryl)acetate (142a)

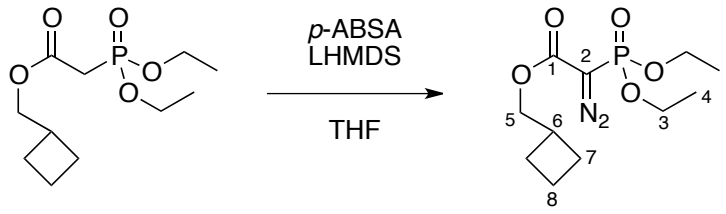


142 **142a**

Synthesised using general procedure A with cyclobutylmethanol **142** (0.47 mL, 5.00 mmol), toluene (25 mL), DEPAA (0.84 mL, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in THF) affording the *title compound* **142a** as a yellow oil (1.31 g, 99%). No further purification was required; R_f 0.22 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2980w, 2941w, 1733s, 1445w, 1393w, 1334w, 1259s, 1163w, 1115m, 1049w, 1019s, 964s, 838m, 783m, 609m; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, J = 7.1, J = 0.5, H-4), 1.71–1.96 (4 H, m, H-7,8), 2.00–2.08 (2 H, m, H-7), 2.61 (1 H, app. heptet, J = 7.4, H-6), 2.95 (2 H, d, J = 21.6, H-2), 4.08–4.19 (6 H, m, H-3,5); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.2, C-4), 18.3 (C-8), 24.6 (C-7), 33.9 (C-6), 34.3 (d, J = 133.8, C-2), 62.6 (d, J = 6.2, C-3), 69.2 (C-5), 165.9 (d, J = 6.2, C-1); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI^+): Found: 287.1033; $C_{11}H_{21}NaO_5P$ (MNa^+) Requires 287.1019 (–5.0 ppm error).

Lab notebook reference: MGL/05/13S

Cyclobutylmethyl 2-diazo-2-(diethoxyphosphoryl)acetate (142b)

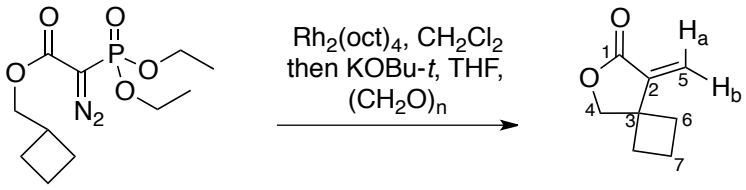


142a **142b**

Synthesised using general procedure B with cyclobutylmethyl 2-(diethoxyphosphoryl)acetate **142a** (1.28 g, 4.84 mmol), THF (24 mL), LHMDS (5.81 mL, 5.81 mmol, 1.0 M solution in THF) and *p*-ABSA (1.40 g, 5.81 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **142b** as a brown oil (949 mg, 68%); R_f 0.50 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2981w, 2942w, 2869w, 2125s, 1700s, 1445w, 1391w, 1335w, 1276s, 1216w, 1164w, 1117w, 1095w, 1019w, 977m, 797m, 747m, 590m, 560m; δ_H (400 MHz, $CDCl_3$) 1.34 (6 H, td, J = 7.1, J = 0.8, H-4), 1.72–1.97 (4 H, m, H-7,8), 1.99–2.08 (2 H, m, H-7), 2.57–2.68 (1 H, m, H-6), 4.09–4.25 (6 H, m, H-3,5); δ_C (100 MHz, $CDCl_3$) 16.1 (d, J = 7.0, C-4), 18.3 (C-8), 24.5 (C-7), 34.0 (C-6), 53.8 (d, J = 228.6, C-2), 63.5 (d, J = 5.9, C-3), 69.2 (C-5), 163.6 (d, J = 12.0, C-1); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI$^+$): Found: 313.0917; $C_{11}H_{19}N_2NaO_5P$ (MNa^+) Requires 313.0924 (2.1 ppm error), Found: 291.1097; $C_{11}H_{20}N_2O_5P$ (MH^+) Requires 291.1104 (2.5 ppm error).

Lab notebook reference: MGL/05/13

8-Methylene-6-oxaspiro[3.4]octan-7-one (142c)



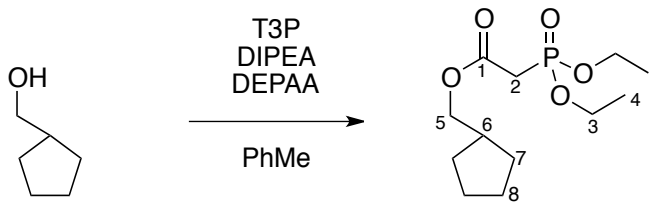
142b **142c**

Synthesised using general procedure D with cyclobutylmethyl 2-diazo-2-(diethoxyphosphoryl)acetate **142b** (59 mg, 0.203 mmol), CH_2Cl_2 (4.0 mL), $Rh_2(oct)_4$ (3.2 mg, 4.1 μmol), THF (4.0 mL), KOBu-*t* (34.2 mg, 0.305 mmol) and paraformaldehyde (12.2 mg, 0.406 mmol). Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **142c** as a colourless oil (22 mg, 78%); R_f 0.42 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2935w, 1760s, 1662w, 1408w, 1296m, 1117m, 1005m, 942w, 814w; δ_H (400 MHz, $CDCl_3$) 1.95–2.04 (2

H, m, H-7), 2.18–2.30 (4 H, m, H-6), 4.32 (2 H, s, H-4), 5.80 (1 H, s, H-5b), 6.26 (1 H, s, H-5a); δ_C (100 MHz, $CDCl_3$) 15.3 (C-7), 34.5 (C-6), 44.5 (C-3), 78.1 (C-4), 119.9 (C-5), 143.1 (C-2), 169.8 (C-1); HRMS (ESI^+): Found: 161.0571; $C_8H_{10}NaO_2$ (MNa^+) Requires 161.0573 (1.5 ppm error), Found: 139.0748; $C_8H_{11}O_2$ (MH^+) Requires 139.0754 (3.9 ppm error).

Lab notebook reference: MGL/05/29

Cyclopentylmethyl 2-(diethoxyphosphoryl)acetate (143a)

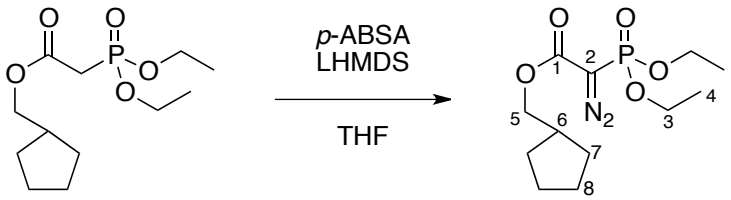


143 **143a**

Synthesised using general procedure A with cyclopentanemethanol **143** (1.00 g, 10.0 mmol), toluene (50 mL), DEPAA (1.69 mL, 10.5 mmol), DIPEA (4.53 mL, 26.0 mmol) and T3P (8.27 g, 13.0 mmol, 50% w/w solution in EtOAc) affording the *title compound* **143a** as an orange oil (2.78 g, 100%). No further purification was required; R_f 0.27 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2964s, 2872w, 1736s, 1450w, 1395w, 1271s, 1116m, 1026s, 976m; δ_H (400 MHz, $CDCl_3$) 1.19–1.29 (2 H, m, H-7), 1.32 (6 H, td, J = 7.1, J = 0.4, H-4), 1.48–1.64 (4 H, m, H-8), 1.69–1.78 (2 H, m, H-7), 2.20 (1 H, app. heptet, J = 7.5, H-6), 2.95 (2 H, d, J = 21.6, H-2), 4.00 (2 H, d, J = 7.2, H-5), 4.11–4.19 (4 H, m, H-3); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.2, C-4), 25.2 (C-8), 29.2 (C-7), 34.2 (d, J = 134.1, C-2), 38.4 (C-6), 62.6 (d, J = 6.2, C-3), 69.4 (C-5), 165.9 (d, J = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.5; HRMS (ESI^+): Found: 301.1185; $C_{12}H_{23}NaO_5P$ (MNa^+) Requires 301.1175 (–3.1 ppm error), Found: 279.1362; $C_{12}H_{24}O_5P$ (MH^+) Requires 279.1356 (–2.4 ppm error).

Lab notebook reference: MGL/03/70

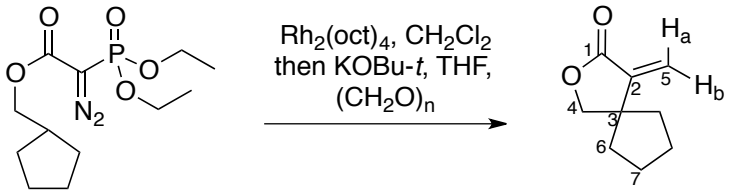
Cyclopentylmethyl 2-diazo-2-(diethoxyphosphoryl)acetate (143b)



143a **143b**

Synthesised using general procedure B with cyclopentylmethyl 2-(diethoxyphosphoryl)acetate **143a** (1.39 g, 5.00 mmol), THF (25 mL), LHMDS (6.00 mL, 6.00 mmol, 1.0 M solution in THF) and *p*-ABSA (1.44 g, 6.00 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **143b** as a pale yellow oil (1.08 g, 71%); R_f 0.61 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2956m, 2872w, 2128s, 1702s, 1389w, 1279s, 1022s, 978m; δ_H (400 MHz, $CDCl_3$) 1.18–1.27 (2 H, m, H-7), 1.33 (6 H, td, J = 7.1, J = 0.8, H-4), 1.46–1.63 (4 H, m, H-8), 1.68–1.76 (2 H, m, H-7), 2.19 (1 H, app. heptet, J = 7.5, H-6), 4.06 (2 H, d, J = 7.1, H-5), 4.08–4.24 (4 H, m, H-3); δ_C (100 MHz, $CDCl_3$) 16.1 (d, J = 6.9, C-4), 25.2 (C-8), 29.1 (C-7), 38.5 (C-6), 53.7 (d, J = 226.5, C-2), 63.5 (d, J = 5.9, C-3), 69.4 (C-5), 163.5 (d, J = 12.1, C-1); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI$^+$): Found: 327.1068; $C_{12}H_{21}N_2NaO_5P$ (MNa^+) Requires 327.1080 (3.8 ppm error), Found: 305.1258; $C_{12}H_{22}N_2O_5P$ (MH^+) Requires 305.1261 (1.0 ppm error).
Lab notebook reference: MGL/03/77

4-Methylene-2-oxaspiro[4.4]nonan-3-one (143c)



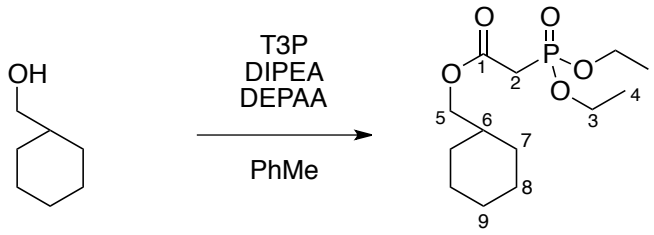
143b **143c**

Synthesised using general procedure D with cyclopentylmethyl 2-diazo-2-(diethoxyphosphoryl)acetate **143b** (68 mg, 0.223 mmol), CH_2Cl_2 (4.4 mL), $Rh_2(oct)_4$ (3.5 mg, 4.7 μmol), THF (4.4 mL), KOBu-*t* (37.5 mg, 0.335 mmol) and paraformaldehyde (13.4 mg, 0.446 mmol). Purification by column chromatography (8:1 petrol:EtOAc) afforded the *title compound* **143c** as a colourless oil (27 mg, 79%); R_f 0.55 (4:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2957m, 2872w, 1765s, 1456w, 1414w, 1286w, 1112m, 1021w, 1000w; δ_H (400 MHz, $CDCl_3$) 1.68–1.87 (8 H, m, H-6,7), 4.11 (2 H, s, H-4), 5.54 (1 H, s, H-5b), 6.19 (1 H, s, H-5a); δ_C (100 MHz, $CDCl_3$)

24.5 (C-7), 39.3 (C-6), 49.9 (C-3), 78.2 (C-4), 119.6 (C-5), 143.6 (C-2), 171.1 (C-1); HRMS (ESI^+): Found: 175.0729; $C_9H_{12}NaO_2$ (MNa^+) Requires 175.0730 (0.4 ppm error), Found: 153.0911; $C_9H_{13}O_2$ (MH^+) Requires 153.0910 (–0.4 ppm error).

Lab notebook reference: MGL/03/81,80

Cyclohexylmethyl 2-(diethoxyphosphoryl)acetate (144a)

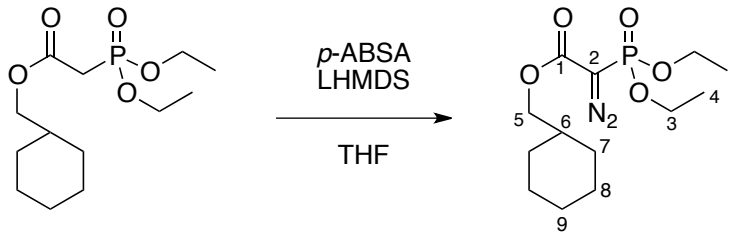


144 **144a**

Synthesised using general procedure A with cyclohexanemethanol **144** (569 mg, 4.98 mmol), toluene (50 mL), DEPAA (0.84 mL, 5.23 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.12 g, 6.47 mmol, 50% w/w solution in EtOAc) affording the *title compound* **144a** as a yellow oil (1.44 g, 99%). No further purification was required; R_f 0.53 (EtOAc); ν_{max} (thin film)/cm^{-1} 2927s, 2854m, 1737s, 1269s, 1053w, 1026s; δ_H (400 MHz, $CDCl_3$) 0.86–0.96 (2 H, m, H-6/7/8/9), 1.04–1.24 (3 H, m, H-6/7/8/9), 1.28 (6 H, t, J = 7.1, H-4), 1.54–1.70 (6 H, m, H-6/7/8/9), 2.91 (2 H, d, J = 21.6, H-2), 3.89 (2 H, d, J = 6.6, H-5), 4.07–4.14 (4 H, m, H-3); δ_C (100 MHz, $CDCl_3$) 16.2 (d, J = 6.2, C-4), 25.5 (C-7/8/9), 26.1 (C-7/8/9), 29.3 (C-7/8/9), 34.1 (d, J = 134.2, C-2), 36.8 (C-6), 62.5 (d, J = 6.2, C-3), 70.5 (C-5), 165.7 (d, J = 6.2, C-1); δ_P (162 MHz, $CDCl_3$) 20.5; HRMS (ESI^+): Found: 315.1338; $C_{13}H_{25}NaO_5P$ (MNa^+) Requires 315.1332.

Note: This compound was synthesised by another person.

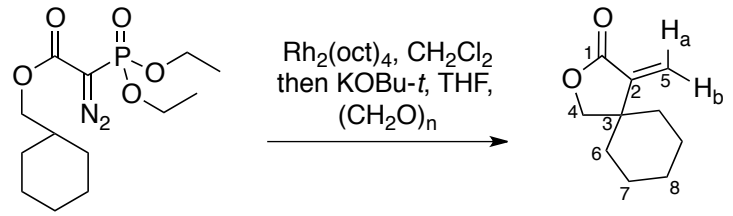
Cyclohexylmethyl 2-diazo-2-(diethoxyphosphoryl)acetate (144b)



144a **144b**

Synthesised using general procedure B with cyclohexylmethyl 2-(diethoxyphosphoryl)acetate **144a** (597 mg, 1.98 mmol), THF (25 mL), NaH (95.0 mg, 2.37 mmol, 60% dispersion in mineral oil) and *p*-ABSA (1.44 g, 6.00 mmol). Purification by column chromatography (3:1 petrol:EtOAc) afforded the *title compound* **144b** as a yellow oil (410 mg, 68%); R_f 0.85 (EtOAc); ν_{max} (thin film)/cm^{-1} 2930s, 2131s, 1705s, 1280s, 1024s; δ_H (400 MHz, $CDCl_3$) 0.93–1.04 (2 H, m, H-6/7/8/9), 1.11–1.30 (3 H, m, H-6/7/8/9), 1.36 (6 H, td, J = 7.1, J = 0.8), 1.55–1.77 (6 H, m, H-6/7/8/9), 4.01 (2 H, d, J = 6.5, H-5), 4.11–4.27 (4 H, m, H-3); δ_C (100 MHz, $CDCl_3$) 16.0 (d, J = 7.1, C-4), 25.5 (C-7/8/9), 26.2 (C-7/8/9), 29.3 (C-7/8/9), 37.1 (C-6), 53.7 (d, J = 227.4, C-2), 63.5 (d, J = 5.6, C-3), 70.6 (C-5), 163.5 (d, J = 12.0, C-1); δ_P (162 MHz, $CDCl_3$) 10.9; HRMS (ESI$^+$): Found: 341.1228; $C_{13}H_{23}N_2NaO_5P$ (MNa^+) Requires 341.1237.
Note: This compound was synthesised by another person.

4-Methylene-2-oxaspiro[4.5]decan-3-one (144c)

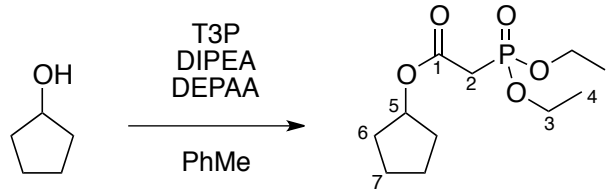


144b **144c**

Synthesised using general procedure D with cyclohexylmethyl 2-diazo-2-(diethoxyphosphoryl)acetate **144b** (57 mg, 0.179 mmol), CH_2Cl_2 (3.6 mL), $Rh_2(oct)_4$ (2.8 mg, 3.6 μmol), THF (3.6 mL), KOBu-*t* (30.2 mg, 0.269 mmol) and paraformaldehyde (10.8 mg, 0.358 mmol). Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **144c** as a colourless oil (15 mg, 50%); R_f 0.63 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2926m, 2854w, 1759s, 1661w, 1451m, 1407w, 1305m, 1254m, 1113s, 1013s, 943m, 815m; δ_H (400 MHz, $CDCl_3$) 1.24–1.75 (10 H, m, H-6,7,8), 4.15 (2 H, s, H-4), 5.54 (1 H, s, H-5b), 6.22 (1 H, s, H-5a);

δ_C (100 MHz, $CDCl_3$) 22.5 (C-7), 25.0 (C-8), 36.2 (C-6), 42.4 (C-3), 75.3 (C-4), 120.7 (C-5), 144.4 (C-2), 171.3 (C-1); HRMS (ESI^+): Found: 189.0891; $C_{10}H_{14}NaO_2$ (MNa^+) Requires 189.0886 (–2.8 ppm error), Found: 167.1065; $C_{10}H_{15}O_2$ (MH^+) Requires 167.1067 (1.1 ppm error).
Lab notebook reference: MGL/05/33

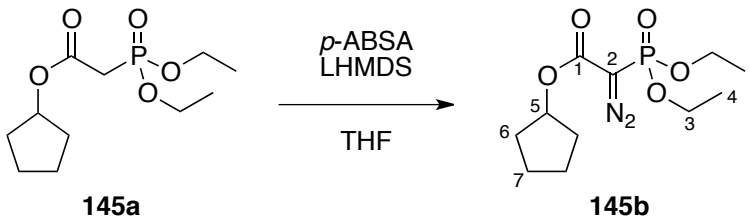
Cyclopentyl 2-(diethoxyphosphoryl)acetate (145a)



145 **145a**

Synthesised using general procedure A with cyclopentanol **145** (0.45 mL, 5.00 mmol), toluene (25 mL), DEPAA (0.84 mL, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in THF) affording the *title compound* **145a** as a yellow oil (1.12 g, 85%). No further purification was required; R_f 0.24 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2974m, 2874w, 1730s, 1443w, 1393w, 1368w, 1259s, 1165m, 1114m, 1050w, 1019s, 966s, 839m, 780m; δ_H (400 MHz, $CDCl_3$) 1.34 (6 H, td, J = 7.1, J = 0.4, H-4), 1.54–1.90 (8 H, m, H-6,7), 2.92 (2 H, d, J = 21.6, H-2), 4.16 (4 H, dq, J = 8.1, J = 7.1, H-3), 5.20 (1 H, tt, J = 5.6, J = 2.7, H-5); δ_C (100 MHz, $CDCl_3$) 16.2 (d, J = 6.2, C-4), 23.6 (C-7), 32.4 (C-6), 34.5 (d, J = 133.5, C-2), 62.5 (d, J = 6.2, C-3), 78.4 (C-5), 165.5 (d, J = 6.2, C-1); δ_P (162 MHz, $CDCl_3$) 20.7; HRMS (ESI^+): Found: 287.1020; $C_{11}H_{21}NaO_5P$ (MNa^+) Requires 287.1019 (–0.4 ppm error), Found: 265.1201; $C_{11}H_{22}O_5P$ (MH^+) Requires 265.1199 (–0.5 ppm error).
Lab notebook reference: MGL/05/10S

Cyclopentyl 2-diazo-2-(diethoxyphosphoryl)acetate (145b)



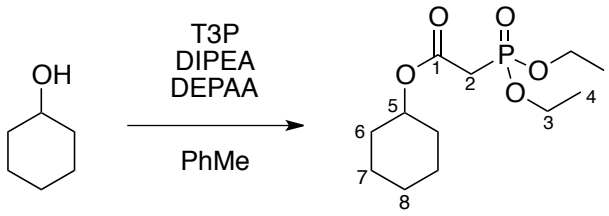
145a **145b**

Synthesised using general procedure B with cyclopentyl 2-(diethoxyphosphoryl)acetate **145a** (1.10 g, 4.16 mmol), THF (21 mL), LHMDS (5.00 mL, 5.00 mmol, 1.0 M solution in THF) and *p*-ABSA (1.20 g, 5.00 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **145b** as a yellow oil (1.00 g, 83%); R_f 0.54 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1}

2972m, 2875w, 2125s, 1696s, 1478w, 1443w, 1393w, 1321w, 1274s, 1218w, 1165m, 1121m, 1089w, 1018s, 977m, 959m, 796m, 749m; δ_H (400 MHz, $CDCl_3$) 1.29 (6 H, td, *J* = 7.1, *J* = 0.8, H-4), 1.49–1.86 (8 H, m, H-6,7), 4.04–4.19 (4 H, m, H-3), 5.21 (1 H, tt, *J* = 5.6, *J* = 2.7, H-5); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* = 7.0, C-4), 23.4 (C-7), 32.6 (C-6), 53.8 (d, *J* = 227.0, C-2), 63.3 (d, *J* = 5.6, C-3), 78.6 (C-5), 163.0 (d, *J* = 11.7, C-1); δ_P (162 MHz, $CDCl_3$) 10.9; HRMS (ESI^+): Found: 313.0930; $C_{11}H_{19}N_2NaO_5P$ (MNa^+) Requires 313.0924 (–2.0 ppm error), Found: 291.1111; $C_{11}H_{20}N_2O_5P$ (MH^+) Requires 291.1104 (–2.1 ppm error).

Lab notebook reference: MGL/05/10

Cyclohexyl 2-(diethoxyphosphoryl)acetate (146a)

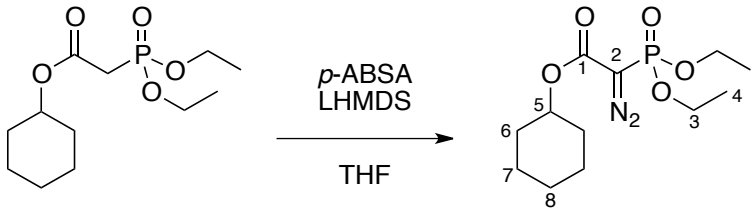


146 **146a**

Synthesised using general procedure A with cyclohexanol **146** (1.59 g, 15.9 mmol), toluene (80 mL), DEPAA (2.68 mL, 16.7 mmol), DIPEA (7.19 mL, 41.3 mmol) and T3P (13.1 g, 20.6 mmol, 50% w/w solution in EtOAc) affording the *title compound* **146a** as a dark orange oil (4.43 g, 100%). No further purification was required; R_f 0.33 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2985w, 2937s, 2862m, 1729s, 1258s, 1114w, 1016s, 964s; δ_H (400 MHz, $CDCl_3$) 1.16–1.52 (6 H, m, H-6/7/8), 1.30 (6 H, td, *J* = 7.1, *J* = 0.5, H-4), 1.65–1.73 (2 H, m, H-6/7/8), 1.77–1.84 (2 H, m, H-6/7/8), 2.90 (2 H, d, *J* = 21.6, H-2), 4.12 (4 H, dq, *J* = 8.4, *J* = 7.1, H-3), 4.76 (1 H, tt, *J* = 8.7, *J* = 4.2, H-5); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.2, C-4), 23.5 (C-7), 25.2 (C-8), 31.3 (C-6), 34.5 (d, *J* = 133.4, C-2), 62.4 (d, *J* = 6.3, C-3), 73.9 (C-5), 165.1 (d, *J* = 6.4, C-1); δ_P (162 MHz, $CDCl_3$) 20.6; HRMS (ESI^+): Found: 301.1162; $C_{12}H_{23}NaO_5P$ (MNa^+) Requires 301.1175 (4.3 ppm error), Found: 279.1345; $C_{12}H_{24}O_5P$ (MH^+) Requires 279.1356 (4.0 ppm error).

Lab notebook reference: MGL/02/43

Cyclohexyl 2-diazo-2-(diethoxyphosphoryl)acetate (146b)

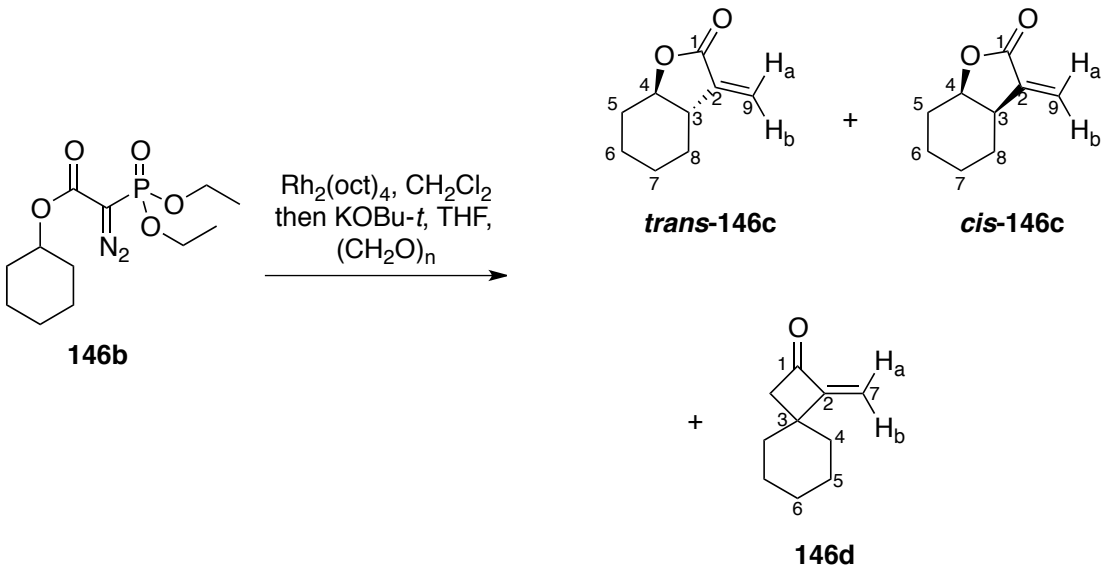


146a **146b**

Synthesised using general procedure B with cyclohexyl 2-(diethoxyphosphoryl)acetate **146a** (2.78 g, 10.0 mmol), THF (50 mL), LHMDS (12.0 mL, 12.0 mmol, 1.0 M solution in THF) and *p*-ABSA (2.88 g, 12.0 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **146b** as a pale yellow oil (2.68 g, 88%);R_f 0.50 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2990w, 2937s, 2864m, 2124s, 1694s, 1279s, 1260s, 1115w, 1013s, 976s; δ_H (400 MHz, $CDCl_3$) 1.18–1.50 (6 H, m, H-6/7/8), 1.31 (6 H, td, *J* = 7.1, *J* = 0.8, H-4), 1.64–1.71 (2 H, m, H-6/7/8), 1.77–1.82 (2 H, m, H-6/7/8), 4.06–4.22 (4 H, m, H-3), 4.84 (1 H, tt, *J* = 8.4, *J* = 4.1, H-5); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* = 7.2, C-4), 23.2 (C-7), 25.1 (C-8), 31.4 (C-6), 53.8 (d, *J* = 228.0, C-2), 63.4 (d, *J* = 5.7, C-3), 74.0 (C-5), 162.8 (d, *J* = 11.8, C-1); δ_P (162 MHz, $CDCl_3$) 10.9; HRMS (ESI^+): Found: 327.1082; $C_{12}H_{21}N_2NaO_5P$ (MNa^+) Requires 327.1010 (−0.6 ppm error), Found: 305.1263; $C_{12}H_{22}N_2O_5P$ (MH^+) Requires 305.1261 (−0.6 ppm error).

Lab notebook reference: MGL/02/62

3-Methylene-1-oxaspiro[3.5]nonan-2-one (146d), (3a*SR*,7a*RS*)-3-Methylenehexahydrobenzofuran-2(3*H*)-one (*trans*-146c) and (3a*RS*,7a*RS*)-3-Methylenehexahydrobenzofuran-2(3*H*)-one (*cis*-146c)



Synthesised using general procedure E with cyclohexyl 2-diazo-2-(diethoxyphosphoryl)acetate **146b** (84 mg, 0.276 mmol), CH_2Cl_2 (5.4 mL), $Rh_2(oct)_4$ (4.3 mg, 0.006 mmol), KOBu-*t* (37.2 mg, 0.331 mmol) and paraformaldehyde (16.6 mg, 0.552 mmol). Purification by column chromatography (20:1 hexane:EtOAc) afforded the *title compound*s (**146d** ***trans*-146c**:***cis*-146c** 6:10:1) (18 mg, 43%); HRMS (ESI^+): Found: 175.0726; $C_9H_{12}NaO_2$ (MNa^+) Requires 175.0730 (1.9 ppm error), Found: 153.0914; $C_9H_{13}O_2$ (MH^+) Requires 153.0910 (–2.5 ppm error).

Small quantities of each compound were isolated separately for characterisation purposes.

Data for **146d**;[163] R_f 0.70 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2937, 2861, 1814, 1450, 1177, 1107, 1011; δ_H (400 MHz, $CDCl_3$) 1.41–1.96 (10 H, m, H-4,5,6), 5.41 (1 H, d, *J* = 1.9, H-9b), 5.80 (1 H, d, *J* = 1.9, H-9a); δ_C (100 MHz, $CDCl_3$) 23.0, 24.6, 34.5, 87.2, 113.0, 150.1, 163.8.

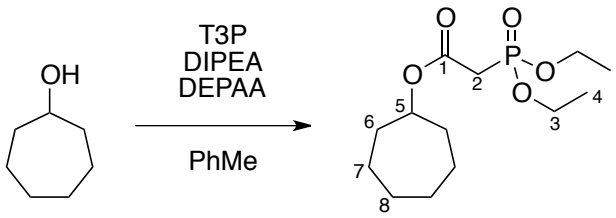
Data for ***trans*-146c**;[164] R_f 0.65 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2940, 2864, 1770, 1251, 1132, 1026, 996; δ_H (400 MHz, $CDCl_3$) [1.32–1.44 (3 H, m), 1.57–1.67 (1 H, m), 1.83–1.87 (1 H, m), 1.95–1.98 (1 H, m), 2.11–2.15 (1 H, m), 2.24–2.29 (1 H, m), 2.37–2.44 (1 H, m) H-3,5,6,7,8)], 3.71 (1 H, ddd, *J* = 11.5, *J* = 10.8, *J* = 3.7, H-4), 5.38 (1 H, d, *J* = 3.1, H-9b), 6.06 (1 H, d, *J* = 3.3, H-9a); δ_C (100 MHz, $CDCl_3$) 24.0, 24.8, 25.8, 30.4, 48.9, 83.1, 117.1, 139.6, 170.7.

Data for ***cis*-146c**;[164] R_f 0.57 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2936, 2864, 1763, 1263, 1127, 965; δ_H (400 MHz, $CDCl_3$) 1.31–1.94 (8 H, m, H-5,6,7,8), 2.99–3.05 (1 H, m, H-3), 4.52–4.56 (1 H, m, H-4), 5.51 (1 H, d, *J* = 2.3, H-9b), 6.20 (1 H, d, *J* = 2.5, H-9a); δ_C (100 MHz, $CDCl_3$) 20.5, 21.1, 26.3, 28.9, 39.6. 76.9, 119.8, 139.9, 171.0.

Lab notebook reference: MGL/03/32

Obtained data in accord with reported literature.[163, 164]

Cycloheptyl 2-(diethoxyphosphoryl)acetate (147a)

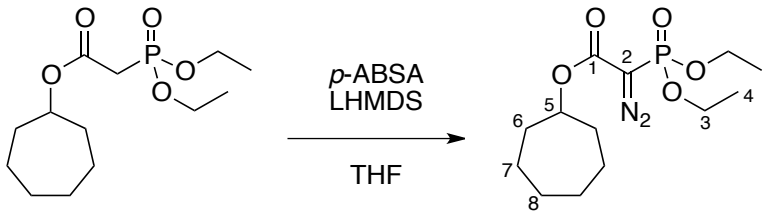


147 **147a**

Synthesised using general procedure A with cycloheptanol **147** (571 mg, 5.00 mmol), toluene (25 mL), DEPAA (0.84 mL, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in THF) affording the *title compound* **147a** as a colourless oil (1.45 g, 99%). No further purification was required; R_f 0.31 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2982w, 2929m, 2861w, 1728s, 1446w, 1394w, 1266s, 1113m, 1051w, 1021s, 969s; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, *J* = 7.1, *J* = 0.5, H-4), 1.35–1.69 (10 H, m, H-6/7/8), 1.85–1.92 (2 H, m, H-6/7/8), 2.91 (2 H, d, *J* = 21.5, H-2), 4.10–4.18 (4 H, m, H-3), 4.95 (1 H, tt, *J* = 8.3, *J* = 4.3, H-5); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.5, C-4), 22.7 (C-6/7/8), 28.2 (C-6/7/8), 33.5 (C-6/7/8), 34.6 (d, *J* = 133.5, C-2), 62.5 (d, *J* = 6.2, C-3), 76.5 (C-5), 165.1 (d, *J* = 6.2, C-1); δ_P (162 MHz, $CDCl_3$) 20.7; HRMS (ESI$^+$): Found: 293.1502; $C_{13}H_{26}O_5P$ (MH^+) Requires 293.1512 (3.5 ppm error).

Lab notebook reference: MGL/05/45

Cycloheptyl 2-diazo-2-(diethoxyphosphoryl)acetate (147b)

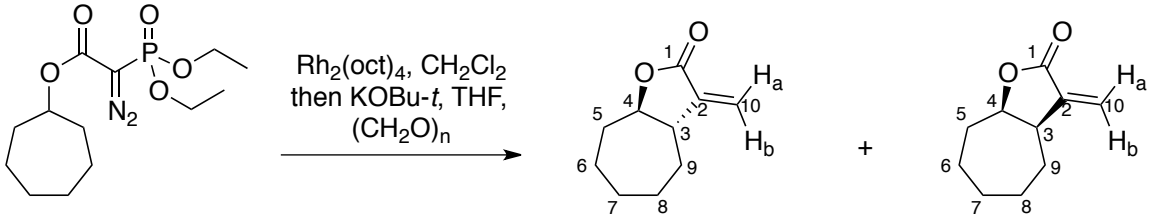


147a **147b**

Synthesised using general procedure B with cycloheptyl 2-(diethoxyphosphoryl)acetate **147a** (1.40 g, 4.79 mmol), THF (24 mL), LHMDS (5.75 mL, 5.75 mmol, 1.0 M solution in THF) and *p*-ABSA (1.38 g, 5.75 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **147b** as a yellow oil (1.35 g, 89%); R_f 0.52 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2987w, 2930m, 2861w, 2125s, 1694s, 1446w, 1369w, 1322w, 1270s, 1215w, 1164w, 1120m, 1015s, 961s, 885w, 974m, 746s, 590s, 555s; δ_H (400 MHz, $CDCl_3$) 1.26 (6 H, td, J = 7.1, J = 0.8, H-4), 1.31–1.66 (10 H, m, H-6/7/8), 1.77–1.85 (2 H, m, H-6/7/8), 4.01–4.17 (4 H, m, H-3), 4.96 (1 H, tt, J = 8.1, J = 4.2, H-5); δ_C (100 MHz, $CDCl_3$) 15.8 (d, J = 7.0, C-4), 22.4 (C-6/7/8), 27.9 (C-6/7/8), 33.5 (C-6/7/8), 53.7 (d, J = 227.0, C-2), 63.2 (d, J = 6.0, C-3), 76.5 (C-5), 162.7 (d, J = 11.9, C-1); δ_P (162 MHz, $CDCl_3$) 10.9; HRMS (ESI$^+$): Found: 341.1226; $C_{13}H_{23}N_2NaO_5P$ (MNa^+) Requires 341.1237 (3.1 ppm error), Found: 319.1410; $C_{13}H_{24}N_2O_5P$ (MH^+) Requires 319.1417 (2.4 ppm error).

Lab notebook reference: MGL/05/47

(3a*SR*,8a*RS*)-3-Methyleneoctahydro-2*H*-cyclohepta[*b*]furan-2-one (*trans*-147c) and (3a*RS*,8a*RS*)-3-Methyleneoctahydro-2*H*-cyclohepta[*b*]furan-2-one (*cis*-147c)



147b ***trans*-147c** ***cis*-147c**

Synthesised using general procedure D with cycloheptyl 2-diazo-2-(diethoxyphosphoryl)acetate **147b** (72 mg, 0.226 mmol), CH_2Cl_2 (4.5 mL), $Rh_2(oct)_4$ (3.5 mg, 4.5 μmol), THF (4.5 mL), KOBu-*t* (38.0 mg, 0.339 mmol) and paraformaldehyde (13.6 mg, 0.452 mmol). Purification by column

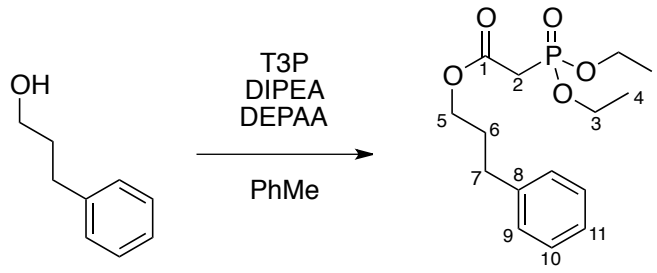
chromatography (4:1 hexane:EtOAc) afforded the *title compound*s (***trans*-147c**:***cis*-147c** 3.5:1) (19 mg, 51%).

A small quantity of the major (***trans*-147c**) compound was separated for characterisation. The minor (***cis*-147c**) compound was characterised from a mixture.

Data for ***trans*-147c**;[105a,165] Colourless oil; R_f 0.50 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2929, 2861, 1761, 1667, 1454, 1400, 1313, 1262, 1246, 998; δ_H (400 MHz, $CDCl_3$) 1.40–1.82 (8 H, m, H-5,6,7,8,9), 2.12–2.20 (1 H, m, H-9), 2.33–2.42 (1 H, m, H-5), 2.73–2.81 (1 H, m, H-3), 4.15 (1 H , ddd, J = 10.6, J = 9.3, J = 4.4, H-4), 5.46 (1 H, d, J = 3.2, H-10b), 6.18 (1 H, d, J = 3.5, H-10a); δ_C (100 MHz, $CDCl_3$) 25.1, 25.3, 27.3, 28.0, 33.0, 45.6, 83.3, 119.6, 141.0, 170.5; HRMS (ESI$^+$): Found: 189.0889; $C_{10}H_{14}NaO_2$ (MNa^+) Requires 189.0886 (–1.8 ppm error), Found: 167.1063; $C_{10}H_{15}O_2$ (MH^+) Requires 167.1067 (2.4 ppm error).

Data for ***cis*-147c**;[105b] R_f 0.43 (4:1 hexane:EtOAc); δ_H (400 MHz, $CDCl_3$) 1.17–1.97 (9 H, m, H-5,6,7,8,9), 2.03–2.09 (1 H, m, H-5), 3.19–3.27 (1 H, m, H-3), 4.71 (1 H , ddd, J = 10.6, J = 8.6, J = 3.6, H-4), 5.55 (1 H, d, J = 2.7, H-10b), 6.27 (1 H, d, J = 3.1, H-10a); δ_C (100 MHz, $CDCl_3$) 24.2, 27.4, 30.6, 31.2, 31.8, 43.1, 82.3, 122.0, 140.3, 170.4.
Lab notebook reference: MGL/05/48
Obtained data in accord with reported literature.[105]

3-Phenylpropyl 2-(diethoxyphosphoryl)acetate (148a)



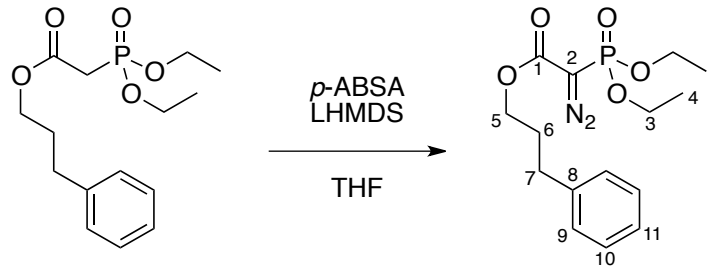
148 **148a**

Synthesised using general procedure A with 3-phenyl-1-propanol **148** (1.36 g, 10.0 mmol), toluene (50 mL), DEPAA (2.49 mL, 15.5 mmol), DIPEA (4.53 mL, 26.0 mmol) and T3P (8.27 g, 13.0 mmol, 50% w/w solution in EtOAc), with heating to 80 °C for 2 h, affording the *title compound* **148a** as a yellow oil (3.04 g, 97%). No further purification was required; R_f 0.23 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2983w, 1734s, 1455w, 1393w, 1266m, 1116w, 1050w, 1020s; δ_H (400 MHz, $CDCl_3$) 1.34 (6 H, t, J = 7.1, H-4), 1.93–2.01 (2 H, m, H-6), 2.70 (2 H, t, J = 7.7, H-7), 2.96 (2 H, d, J = 21.6, H-2), 4.13–4.21 (6 H, m, H-3,5), 7.16–7.29 (5 H, m, H-8,9,10); δ_C

(100 MHz, $CDCl_3$) 16.3 (d, J = 6.2, C-4), 30.0 (C-6), 31.9 (C-7), 34.3 (d, J = 133.9, C-2), 62.6 (d, J = 6.5, C-3), 64.8 (C-5), 126.0 (C-11), 128.4 (C-9/10), 128.4 (C-9/10), 141.0 (C-8), 165.8 (d, J = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.5; HRMS (ESI^+): Found: 337.1166; $C_{15}H_{23}NaO_5P$ (MNa^+) Requires 337.1175 (2.9 ppm error), Found: 315.1349; $C_{15}H_{24}O_5P$ (MH^+) Requires 315.1356 (2.2 ppm error).

Lab notebook reference: MGL/03/46

3-Phenylpropyl 2-diazo-2-(diethoxyphosphoryl)acetate (148b)

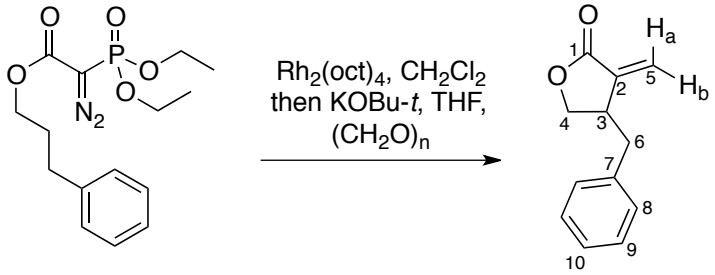


148a **148b**

Synthesised using general procedure B with 3-phenylpropyl 2-(diethoxyphosphoryl)acetate **148a** (1.89 g, 6.00 mmol), THF (30 mL), LHMDS (7.20 mL, 7.20 mmol, 1.0 M solution in THF) and *p*-ABSA (1.73 g, 7.20 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **148b** as a pale yellow oil (1.18 g, 59%); R_f 0.45 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2984w, 2128s, 1702s, 1390w, 1275s, 1216w, 1164w, 1122w, 1098w, 1017s, 978m; δ_H (400 MHz, $CDCl_3$) 1.34 (6 H, td, J = 7.1, J = 0.8, H-4), 1.93–2.01 (2 H, m, H-6), 2.68 (2 H, t, J = 7.6, H-7), 4.10–4.26 (6 H, m, H-3,5), 7.13–7.19 (3 H, m, H-9,11), 7.24–7.28 (2 H, m, H-10); δ_C (100 MHz, $CDCl_3$) 16.0 (d, J = 6.9, C-4), 30.1 (C-6), 31.8 (C-7), 53.7 (d, J = 228.2, C-2), 63.4 (d, J = 5.7, C-3), 64.7 (C-5), 126.0 (C-11), 128.2 (C-9/10), 128.3 (C-9/10), 140.7 (C-8), 163.3 (d, J = 12.1, C-1); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI^+): Found: 363.1066; $C_{15}H_{21}N_2NaO_5P$ (MNa^+) Requires 363.1080 (4.0 ppm error), Found: 341.1251; $C_{15}H_{22}N_2O_5P$ (MH^+) Requires 341.1261 (2.8 ppm error).

Lab notebook reference: MGL/03/50

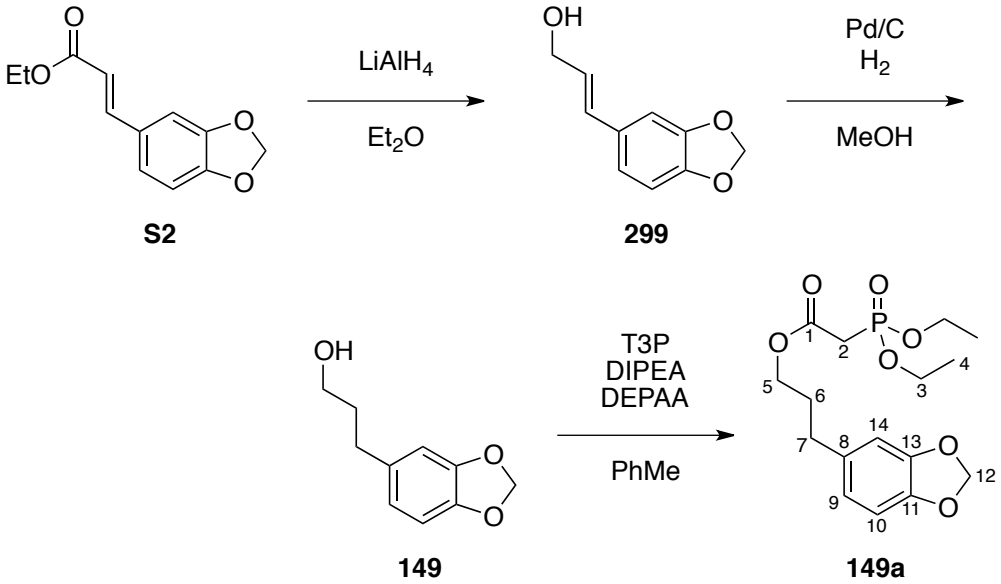
(*SR*)-4-Benzyl-3-methylenedihydrofuran-2(3*H*)-one (148c)



148b **148c**

Synthesised using general procedure D with 3-phenylpropyl 2-diazo-2-(diethoxyphosphoryl)acetate **148b** (73 mg, 0.215 mmol), CH_2Cl_2 (4.3 mL), $Rh_2(oct)_4$ (3.3 mg, 4.3 μmol), THF (4.3 mL), KOBu-*t* (29.0 mg, 0.258 mmol) and paraformaldehyde (12.9 mg, 0.430 mmol). Purification by column chromatography (8:1 petrol:EtOAc) afforded the *title compound* **148c** as a colourless oil (25 mg, 62%); R_f 0.29 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2912w, 1760s, 1661w, 1497w, 1455w, 1406w, 1268m, 1116m, 999m; δ_H (400 MHz, $CDCl_3$) 2.81 (1 H, dd, *J* = 13.8, *J* = 8.9, H-6), 2.98 (1 H, dd, *J* = 13.8, *J* = 6.9, H-6), 3.33–3.42 (1 H, m, H-3), 4.07 (1 H, dd, *J* = 9.2, *J* = 5.2, H-4), 4.34 (1 H, dd, *J* = 9.2, *J* = 8.0, H-4), 5.43 (1 H, d, *J* = 2.3, H-5b), 6.27 (1 H, d, *J* = 2.6, H-5a), 7.16–7.19 (2 H, m, H-8), 7.24–7.28 (1 H, m, H-10), 7.30–7.35 (2 H, m, H-9); δ_C (100 MHz, $CDCl_3$) 39.9 (C-6), 40.1 (C-3), 70.6 (C-4), 122.7 (C-5), 126.9 (C-10), 128.7 (C-8/9), 128.9 (C-8/9), 137.4 (C-2/7), 137.5 (C-2/7), 170.7 (C-1); HRMS (ESI^+): Found: 211.0721; $C_{12}H_{12}NaO_2$ (MNa^+) Requires 211.0730 (4.1 ppm error), Found: 189.0902; $C_{12}H_{13}O_2$ (MH^+) Requires 189.0910 (4.4 ppm error).
Lab notebook reference: MGL/03/54,57

3-(1,3-Benzodioxol-5-yl) 2-(diethoxyphosphoryl)acetate (149a)

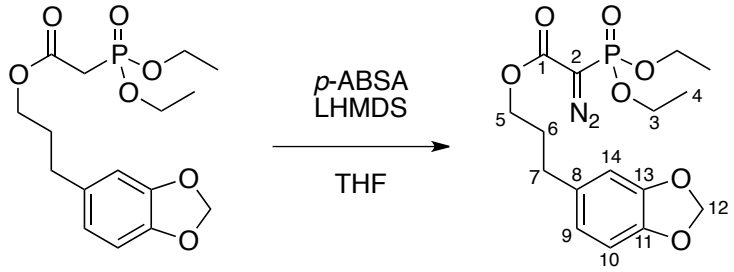


To powdered $LiAlH_4$ (1.516 g, 30.5 mmol) under argon was added ether (120 mL) *via* cannula whilst being cooled to 0 °C. A solution of (*E*)-ethyl 3-(1,3-benzodioxol-5-yl)acrylate **S2** (1.68 g, 7.63 mmol) in ether (20 mL) was added dropwise *via* cannula to the suspension over 5 mins and stirred at 0 °C for 1 h then at RT for 30 mins. The suspension was quenched at 0 °C dropwise with water (1.5 mL) followed by 15% aq. NaOH (1.5 mL) and again with water (4.5 mL) then stirred for 30 mins at RT. The solution was filtered through a pad of Celite and washed with ether (50 mL). The filtrate was concentrated *in vacuo* affording the allylic alcohol **299**, which was used without further purification. To a solution of alcohol **299** in methanol (30 mL) was added palladium on carbon (10% wt. % loading, 100 mg). The flask was purged 4 times with argon then 4 times with hydrogen. The mixture was stirred at RT for 16 h. The mixture was filtered through a pad of Celite and washed with methanol (50 mL). The filtrate was concentrated *in vacuo* to afford the saturated alcohol **149**, which was used without further purification. Using general procedure A with alcohol **149**, toluene (40 mL), DEPAA (1.29 mL, 8.01 mmol), DIPEA (3.46 mL, 19.8 mmol) and T3P (6.31 g, 9.92 mmol, 50% w/w solution in EtOAc) afforded the *title compound* **149a** as a colourless oil (2.21 g, 81% over 3 steps); R_f 0.28 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm-1 2988w, 1735s, 1511s, 1493m, 1450w, 1246s, 1116w, 1024s, 970m; δ_H (400 MHz, $CDCl_3$) 1.34 (6 H, td, J = 7.1, J = 0.5, H-4), 1.88–1.96 (2 H, m, H-6), 2.62 (2 H, t, J = 7.6, H-7), 2.97 (2 H, d, J = 21.6, H-2), 4.11–4.21 (6 H, m, H-3,5), 5.91 (2 H, s, H-12), 6.61–6.63 (1 H, m, H-9), 6.66–6.67 (1 H, m, H-14), 6.72 (1 H, d, J = 7.8, H-10); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.2, C-4), 30.3 (C-6), 31.6 (C-7), 34.3 (d, J = 134.2, C-2), 62.7 (d, J = 6.3, C-3), 64.6 (C-5), 100.8 (C-12), 108.2 (C-10), 108.8 (C-14), 121.2 (C-9), 134.8 (C-8), 145.8 (C-11/13), 147.6 (C-11/13), 165.8 (d, J = 6.2, C-1); δ_P (162 MHz, $CDCl_3$)

20.5; HRMS (ESI^+): Found: 381.1061; $C_{16}H_{23}NaO_7P$ (MNa^+) Requires 381.1074 (3.3 ppm error), Found: 359.1245; $C_{16}H_{24}O_7P$ (MH^+) Requires 359.1254 (2.6 ppm error).

Lab notebook reference: MGL/03/73, 67, 68

3-(1,3-Benzodioxol-5-yl)propyl 2-diazo-2-(diethoxyphosphoryl)acetate (149b)

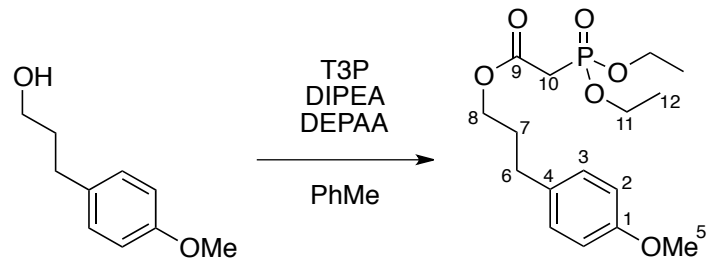


149a **149b**

Synthesised using general procedure B with 3-(1,3-benzodioxol-5-yl)propyl 2-(diethoxyphosphoryl)acetate **149a** (2.09 g, 5.83 mmol), THF (29 mL), LHMDS (7.00 mL, 7.00 mmol, 1.0 M solution in THF) and *p*-ABSA (1.68 g, 7.00 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **149b** as a pale yellow oil (1.35 g, 60%); R_f 0.66 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2984w, 2130s, 1704s, 1504w, 1490m, 1390w, 1280s, 1246w, 1099w, 1020s, 978w; δ_H (400 MHz, $CDCl_3$) 1.35 (6 H, td, J = 7.1, J = 0.7, H-4), 1.88–1.95 (2 H, m, H-6), 2.60 (2 H, t, J = 7.5, H-7), 4.10–4.26 (6 H, m, H-3,5), 5.90 (2 H, s, H-12), 6.59 (1 H, dd, J = 7.9, J = 1.7, H-9), 6.64 (1 H, d, J = 1.7, H-14), 6.70 (1 H, d, J = 7.9, H-10); δ_C (100 MHz, $CDCl_3$) 16.1 (d, J = 6.9, C-4), 30.4 (C-6), 31.5 (C-7), 53.8 (d, J = 228.5, C-2), 63.5 (d, J = 5.6, C-3), 64.6 (C-5), 100.7 (C-12), 108.1 (C-10), 108.7 (C-14), 121.0 (C-9), 134.5 (C-8), 145.8 (C-11/13), 147.6 (C-11/13), 163.3 (d, J = 12.0, C-1); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI^+): Found: 407.0967; $C_{16}H_{21}N_2NaO_7P$ (MNa^+) Requires 407.0979 (2.9 ppm error), Found: 385.1147; $C_{16}H_{22}N_2O_7P$ (MH^+) Requires 385.1159 (3.1 ppm error).

Lab notebook reference: MGL/03/76

3-(4-Methoxyphenyl)propyl 2-(diethoxyphosphoryl)acetate (150a)

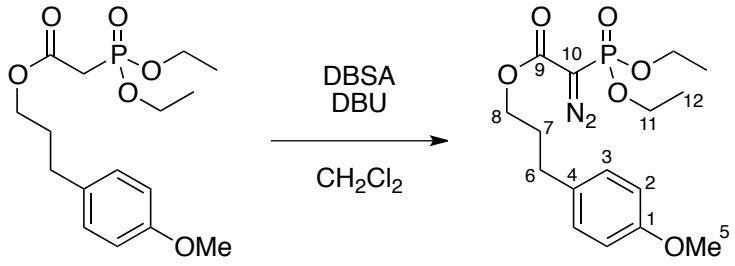


150 **150a**

Synthesised using general procedure A with 3-(4-methoxyphenyl)propan-1-ol **150** (831 mg, 5.00 mmol), toluene (25.0 mL), DEPAA (1.03 g, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in EtOAc) affording the *title compound* **150a** as a yellow oil (1.66 g, 96%); R_f 0.09 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2982w, 1733s, 1612w, 1513s, 1243s, 1177m, 1114m, 1019s, 964s, 834m, 813m, 783w; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, t, *J* = 7.1, H-12), 1.88–1.95 (2 H, m, H-7), 2.62 (2 H, t, *J* = 7.6, H-6), 2.95 (2 H, d, *J* = 21.6, H-10), 3.75 (3 H, s, H-5), 4.10–4.19 (6 H, m, H-8,11), 6.80 (2 H, d, *J* = 8.7, H-2), 7.07 (2 H, d, *J* = 8.7, H-3); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.4, C-12), 30.2 (C-7), 30.9 (C-6), 34.2 (d, *J* = 134.1, C-10), 55.1 (C-5), 62.5 (d, *J* = 6.3, C-11), 64.7 (C-8), 113.7 (C-2), 129.2 (C-3), 132.9 (C-4), 157.8 (C-1), 165.7 (d, *J* = 6.1, C-9); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI$^+$): Found: 367.1286; $C_{16}H_{25}NaO_6P$ (MNa^+) Requires 367.1281 (–1.4 ppm error).

Lab notebook reference: MGL/08/14

3-(4-Methoxyphenyl)propyl 2-diazo-2-(diethoxyphosphoryl)acetate (150b)



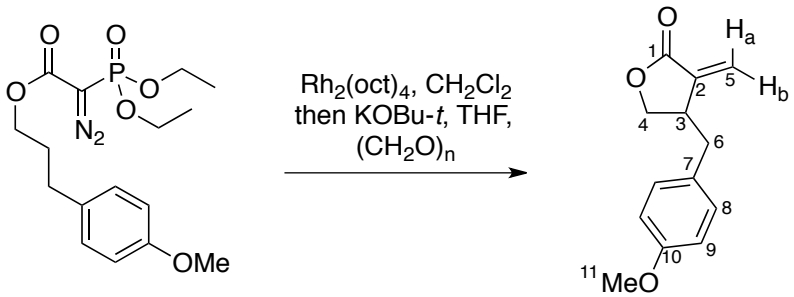
150a **150b**

Synthesised using general procedure C with 3-(4-methoxyphenyl)propyl 2-(diethoxyphosphoryl)acetate **150a** (1.66 g, 4.82 mmol), DBSA (2.42 mL, 7.23 mmol), DBU (1.08 mL, 7.23 mmol) and CH_2Cl_2 (48.0 mL). Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **150b** as a pale yellow oil (1.70 mg, 95%); R_f 0.57 (1:4 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2985w, 2128s, 1702s, 1613w, 1513s, 1389w, 1276s, 1246s,

1018s, 978m, 813m, 746m, 591m, 560m; δ_H (400 MHz, $CDCl_3$) 1.36 (6 H, td, J = 7.1, J = 0.8, H-12), 1.91–1.98 (2 H, m, H-7), 2.63 (2 H, t, J = 7.6, H-6), 3.78 (3 H, s, H-5), 4.11–4.27 (6 H, m, H-8,11), 6.82 (2 H, d, J = 8.7, H-2), 7.08 (2 H, d, J = 8.7, H-3); δ_C (100 MHz, $CDCl_3$) 16.1 (d, J = 7.3, C-12), 30.4 (C-7), 30.9 (C-6), 54.0 (d, J = 226.6, C-10), 55.1 (C-5), 63.5 (d, J = 5.9, C-11), 64.8 (C-8), 113.8 (C-2), 129.2 (C-3), 132.7 (C-4), 157.9 (C-1), 163.3 (d, J = 12.3, C-9); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI^+): Found: 393.1196; $C_{16}H_{23}N_2NaO_6P$ (MNa^+) Requires 393.1186 (–2.6 ppm error).

Lab notebook reference: MGL/08/18

4-(4-Methoxybenzyl)-3-methylenedihydrofuran-2(3*H*)-one (150c)

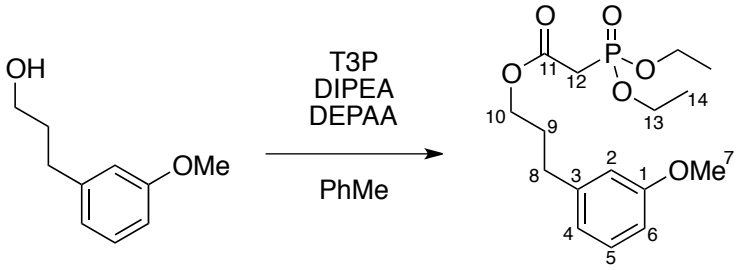


150b **150c**

Synthesised using general procedure D with 3-(4-methoxyphenyl)propyl 2-diazo-2-(diethoxyphosphoryl)acetate **150b** (78 mg, 0.211 mmol), CH_2Cl_2 (4.2 mL), $Rh_2(oct)_4$ (3.3 mg, 4.2 μmol), THF (4.2 mL), KOBu-*t* (28.4 mg, 0.253 mmol) and paraformaldehyde (12.7 mg, 0.422 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **150c** as a colourless oil (20 mg, 43%); R_f 0.53 (2:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2912w, 1760w, 1611m, 1513s, 1301m, 1248s, 1179m, 1114s, 1033m, 815m; δ_H (400 MHz, $CDCl_3$) 2.75 (1 H, dd, J = 13.9, J = 8.8, H-6), 2.90 (1 H, dd, J = 13.9, J = 7.0, H-6), 3.28–3.36 (1 H, m, H-3), 3.80 (3 H, s, H-11), 4.05 (1 H, dd, J = 9.2, J = 5.1, H-4), 4.33 (1 H, dd, J = 9.2, J = 8.1, H-4), 5.42 (1 H, d, J = 2.3, H-5b), 6.26 (1 H, d, J = 2.6, H-5a), 6.85 (2 H, d, J = 8.6, H-9), 7.09 (2 H, d, J = 8.6, H-8); δ_C (100 MHz, $CDCl_3$) 39.0 (C-6), 40.3 (C-3), 55.2 (C-11), 70.6 (C-4), 114.1 (C-9), 122.7 (C-5), 129.4 (C-7), 129.9 (C-8), 137.6 (C-2), 158.5 (C-10), 170.7 (C-1); HRMS (ESI^+): Found: 241.0827; $C_{13}H_{14}NaO_3$ (MNa^+) Requires 241.0835 (3.5 ppm error).

Lab notebook reference: MGL/08/31

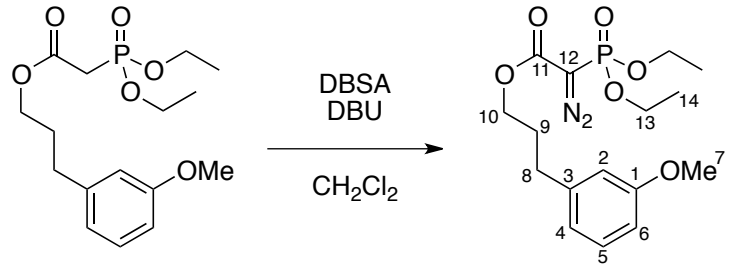
3-(3-Methoxyphenyl)propyl 2-(diethoxyphosphoryl)acetate (151a)



151 **151a**

Synthesised using general procedure A with 3-(3-methoxyphenyl)propan-1-ol **151** (831 mg, 5.00 mmol), toluene (25.0 mL), DEPAA (1.03 g, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in EtOAc) affording the *title compound* **151a** as a yellow oil (1.66 g, 96%); R_f 0.09 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2982w, 1736s, 1601w, 1585w, 1489w, 1392w, 1262s, 1154w, 1117w, 1025s, 970s; δ_H (400 MHz, $CDCl_3$) 1.33 (6 H, t, *J* = 7.1, H-14), 1.92–2.00 (2 H, m, H-9), 2.67 (2 H, t, *J* = 7.7, H-8), 2.96 (2 H, d, *J* = 21.6, H-12), 3.78 (3 H, s, H-7), 4.13–4.20 (6 H, m, H-10,13), 6.72–6.77 (3 H, m, H-2,4,6), 7.16–7.21 (1 H, m, H-5); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.5, C-14), 29.9 (C-9), 31.9 (C-8), 34.2 (d, *J* = 133.8, C-12), 55.0 (C-7), 62.6 (d, *J* = 6.6, C-13), 64.7 (C-10), 111.2 (C-2/4/6), 114.2 (C-2/4/6), 120.7 (C-2/4/6), 129.3 (C-5), 142.6 (C-3), 159.6 (C-1), 165.8 (d, *J* = 6.1, C-11); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI$^+$): Found: 367.1272; $C_{16}H_{25}NaO_6P$ (MNa^+) Requires 367.1281 (2.5 ppm error).
Lab notebook reference: MGL/08/13

3-(3-Methoxyphenyl)propyl 2-diazo-2-(diethoxyphosphoryl)acetate (151b)



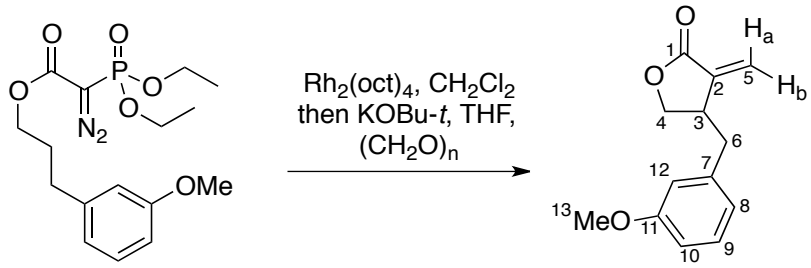
151a **151b**

Synthesised using general procedure C with 3-(3-methoxyphenyl)propyl 2-(diethoxyphosphoryl)acetate **150a** (1.66 g, 4.82 mmol), DBSA (2.42 mL, 7.23 mmol), DBU (1.08 mL, 7.23 mmol) and CH_2Cl_2 (48.0 mL). Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **151b** as a pale yellow oil (1.61 g, 90%); R_f 0.57 (1:4

hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2983w, 2127s, 1701s, 1602m, 1584m, 1489m, 1455m, 1389m, 1273s, 1015s, 976s, 780m, 745m, 590m, 559m; δ_H (400 MHz, $CDCl_3$) 1.36 (6 H, td, *J* = 7.1, *J* = 0.7, H-14), 1.94–2.01 (2 H, m, H-9), 2.67 (2 H, t, *J* = 7.6, H-8), 3.78 (3 H, s, H-7), 4.11–4.27 (6 H, m, H-10,13), 6.71–6.77 (3 H, m, H-2,4,6), 7.20 (1 H, app. t, *J* = 7.8, H-5); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* = 6.9, C-14), 30.0 (C-9), 31.8 (C-8), 53.9 (d, *J* = 226.6, C-12), 55.0 (C-7), 63.5 (d, *J* = 6.2, C-13), 64.8 (C-10), 111.1 (C-2/4/6), 114.2 (C-2/4/6), 120.6 (C-2/4/6), 129.34 (C-5), 142.3 (C-3), 159.6 (C-1), 163.3 (d, *J* = 12.1, C-11); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI$^+$): Found: 393.1177; $C_{16}H_{23}N_2NaO_6P$ (MNa^+) Requires 393.1186 (2.2 ppm error).

Lab notebook reference: MGL/08/17

4-(3-Methoxybenzyl)-3-methylenedihydrofuran-2(3*H*)-one (151c)

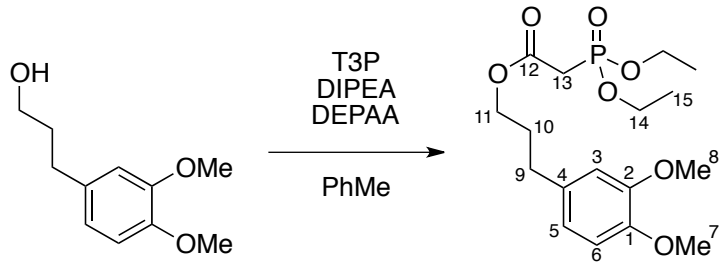


151b **151c**

Synthesised using general procedure D with 3-(3-methoxyphenyl)propyl 2-diazo-2-(diethoxyphosphoryl)acetate **151b** (77 mg, 0.208 mmol), CH_2Cl_2 (4.2 mL), $Rh_2(oct)_4$ (3.2 mg, 4.2 μmol), THF (4.2 mL), KOBu-*t* (28.0 mg, 0.250 mmol) and paraformaldehyde (12.5 mg, 0.416 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **151c** as a colourless oil (20 mg, 44%); R_f 0.52 (2:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2915w, 1762s, 1601w, 1490w, 1262s, 1154w, 1116m, 1040m; δ_H (400 MHz, $CDCl_3$) 2.77 (1 H, dd, *J* = 13.8, *J* = 9.0, H-6), 2.96 (1 H, dd, *J* = 13.8, *J* = 6.8, H-6), 3.33–3.42 (1 H, m, H-3), 3.80 (3 H, s, H-13), 4.06 (1 H, dd, *J* = 9.2, *J* = 5.2, H-4), 4.35 (1 H, dd, *J* = 9.2, *J* = 8.0, H-4), 5.47 (1 H, d, *J* = 2.4, H-5b), 6.28 (1 H, d, *J* = 2.7, H-5a), 6.71–6.72 (1 H, m, H-12), 6.77 (1 H, br. d, *J* = 7.5, H-8/10), 6.79 (1 H, dd, *J* = 8.3, *J* = 2.5, H-8/10), 7.23 (1 H, app. t, *J* = 7.9, H-9); δ_C (100 MHz, $CDCl_3$) 40.0 (C-6), 40.1 (C-3), 55.3 (C-13), 70.7 (C-4), 112.1 (C-8/10), 114.9 (C-12), 121.3 (C-8/10), 122.8 (C-5), 129.9 (C-9), 137.7 (C-2/7), 139.1 (C-2/7), 159.9 (C-11), 170.8 (C-1); HRMS (ESI$^+$): Found: 241.0846; $C_{13}H_{14}NaO_3$ (MNa^+) Requires 241.0835 (–4.5 ppm error).

Lab notebook reference: MGL/08/30

3-(3,4-Dimethoxyphenyl)propyl 2-(diethoxyphosphoryl)acetate (152a)

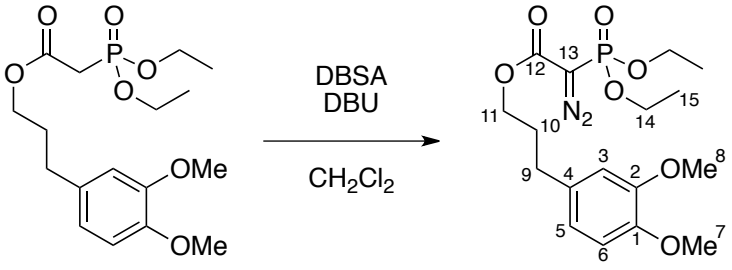


152 **152a**

Synthesised using general procedure A with 3-(3,4-dimethoxyphenyl)propan-1-ol **152** (981 mg, 5.00 mmol), toluene (25.0 mL), DEPAA (1.03 g, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in EtOAc) affording the *title compound* **152a** as a yellow oil (1.87 g, 100%); R_f 0.09 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2936w, 1732s, 1515s, 1465m, 1257s, 1236w, 1157m, 1140m, 1116m, 1019s, 965s; δ_H (400 MHz, $CDCl_3$) 1.31 (6 H, td, *J* = 7.1, *J* = 0.4, H-15), 1.89–1.96 (2 H, m, H-10), 2.62 (2 H, t, *J* = 7.6, H-9), 2.95 (2 H, d, *J* = 21.6, H-13), 3.82 (3 H, s, H-7/8), 3.84 (3 H, s, H-7/8), 4.11–4.18 (6 H, m, H-11,14), 6.68–6.77 (3 H, m, H-3,5,6); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.4, C-15), 30.2 (C-10), 31.4 (C-9), 34.2 (d, *J* = 134.0, C-13), 55.7 (C-7/8), 55.8 (C-7/8), 62.5 (d, *J* = 6.7, C-14), 64.7 (C-11), 111.1 (C-3/5/6), 111.5 (C-3/5/6), 120.1 (C-3/5/6), 133.5 (C-4), 147.2 (C-1/2), 148.7 (C-1/2), 165.7 (d, *J* = 6.4, C-12); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI$^+$): Found: 397.1392; $C_{17}H_{27}NaO_7P$ (MNa^+) Requires 397.1387 (−1.4 ppm error).

Lab notebook reference: MGL/08/12

3-(3,4-Dimethoxyphenyl)propyl 2-diazo-2-(diethoxyphosphoryl)acetate (152b)

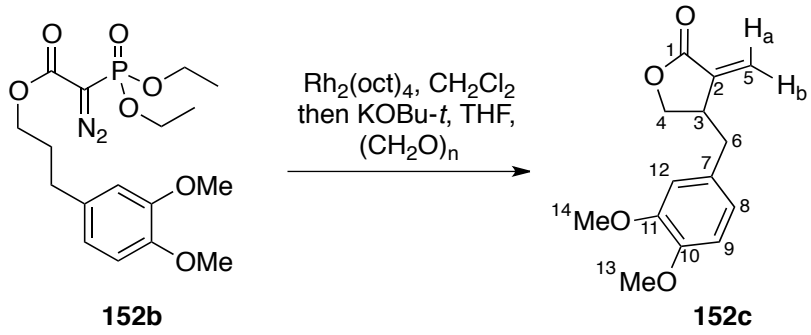


152a **152b**

Synthesised using general procedure C with 3-(3,4-dimethoxyphenyl)propyl 2-(diethoxyphosphoryl)acetate **152a** (1.87 g, 5.00 mmol), DBSA (2.42 mL, 7.25 mmol), DBU (1.08 mL, 7.25 mmol) and CH_2Cl_2 (50.0 mL). Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **152b** as a pale yellow oil (1.97 mg, 98%); R_f 0.53 (1:4

hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2936w, 2127s, 1701s, 1515s, 1465w, 1274s, 1260s, 1156w, 1015s, 976s, 799m, 731s, 589s, 558s; δ_H (400 MHz, $CDCl_3$) 1.36 (6 H, td, *J* = 7.1, *J* = 0.8, H-15), 1.93–2.00 (2 H, m, H-10), 2.64 (2 H, t, *J* = 7.6, H-9), 3.85 (3 H, s, H-7/8), 3.87 (3 H, s, H-7/8), 4.12–4.28 (6 H, m, H-11,14), 6.69–6.80 (3 H, m, H-3,5,6); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* = 7.2, C-15), 30.3 (C-10), 31.3 (C-9), 53.7 (d, *J* = 229.3, C-13), 55.6 (C-7/8), 55.7 (C-7/8), 63.5 (d, *J* = 6.1, C-14), 64.7 (C-11), 111.1 (C-3/5/6), 111.5 (C-3/5/6), 120.0 (C-3/5/6), 133.2 (C-4), 147.2 (C-1/2), 148.7 (C-1/2), 163.2 (d, *J* = 12.5, C-12); δ_P (162 MHz, $CDCl_3$) 10.7; HRMS (ESI$^+$): Found: 423.1275; $C_{17}H_{25}N_2NaO_7P$ (MNa^+) Requires 423.1292 (3.9 ppm error).
Lab notebook reference: MGL/08/16

4-(3,4-Dimethoxybenzyl)-3-methylenedihydrofuran-2(3*H*)-one (152c)

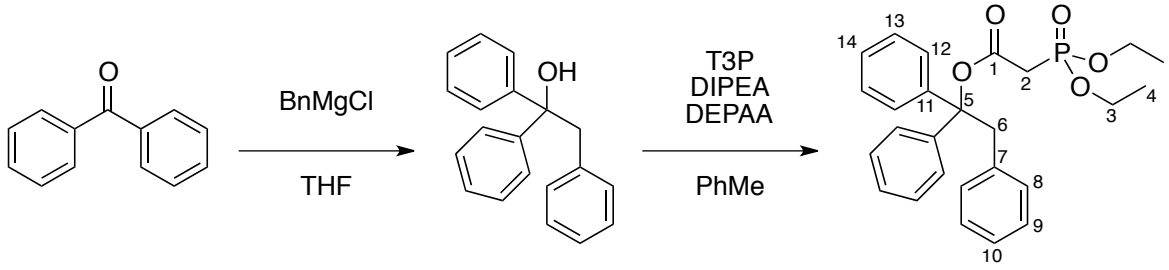


152b **152c**

Synthesised using general procedure D with 3-(3,4-dimethoxyphenyl)propyl 2-diazo-2-(diethoxyphosphoryl)acetate **152b** (86 mg, 0.215 mmol), CH_2Cl_2 (4.3 mL), $Rh_2(oct)_4$ (3.4 mg, 4.3 μmol), THF (4.3 mL), KOBu-*t* (29.0 mg, 0.258 mmol) and paraformaldehyde (12.9 mg, 0.430 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **152c** as a colourless oil (20 mg, 37%); R_f 0.26 (2:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2911w, 2836w, 1759s, 1590m, 1515s, 1465m, 1260s, 1157m, 1141m, 1115m, 1026m; δ_H (400 MHz, $CDCl_3$) 2.75 (1 H, dd, *J* = 13.9, *J* = 8.8, H-6), 2.90 (1 H, dd, *J* = 13.9, *J* = 7.0, H-6), 3.29–3.38 (1 H, m, H-3), 3.86 (3 H, s, H-13/14), 3.86 (3 H, s, H-13/14), 4.06 (1 H, dd, *J* = 9.2, *J* = 5.0, H-4), 4.34 (1 H, dd, *J* = 9.2, *J* = 8.0, H-4), 5.43 (1 H, d, *J* = 2.3, H-5b), 6.26 (1 H, d, *J* = 2.6, H-5a), 6.68 (1 H, d, *J* = 2.0, H-12), 6.71 (1 H, dd, *J* = 8.1, *J* = 2.0, H-8), 6.81 (1 H, d, *J* = 8.1, H-9); δ_C (100 MHz, $CDCl_3$) 39.6 (C-6), 40.3 (C-3), 55.8 (2 C, C-13,14), 70.5 (C-4), 111.2 (C-9), 111.9 (C-12), 120.9 (C-12), 122.7 (C-5), 129.9 (C-7), 137.5 (C-2), 147.9 (C-10/11), 149.0 (C-10/11), 170.7 (C-1); HRMS (ESI$^+$): Found: 271.0950; $C_{14}H_{16}NaO_4$ (MNa^+) Requires 271.0941 (−3.3 ppm error).
Lab notebook reference: MGL/08/29

5.2.1.1. Buchner cyclisation

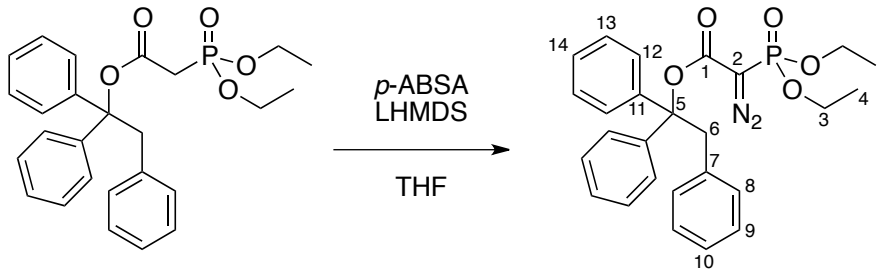
1,1,2-Triphenylethyl 2-(diethoxyphosphoryl)acetate (153a)



S3 **153** **153a**

The procedure for the Grignard addition was followed according to the literature procedure.[166]
To benzylmagnesium chloride solution (20 mL, 40 mmol, 2.0 M in THF) cooled to 0 °C under an atmosphere of argon, was added benzophenone **S3** (5.47 g, 30 mmol). After 2 h stirring at RT a further addition of benzylmagnesium chloride (10 mL, 20 mmol) was made. The suspension was stirred overnight at RT. The suspension was quenched with sat. aq. NH_4Cl. The organic layer was removed and the aqueous extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product **153** as a white powder (9.03 g). A portion of the crude material (3.35 g) was treated under the conditions of general procedure A with toluene (60 mL), DEPAA (2.06 mL, 12.8 mmol), DIPEA (5.52 mL, 31.7 mmol) and T3P (10.1 g, 15.8 mmol, 50% w/w solution in EtOAc). Purification by column chromatography (1:2 petrol:EtOAc) afforded the *title compound* **153a** as a colourless oil (389 mg, 8% over 2 steps); R_f 0.25 (1:2 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2937s, 1711s, 1251s, 1218w, 1012s; δ_H (400 MHz, $CDCl_3$) 1.25 (6 H, td, *J* = 7.1, *J* = 0.3, H-4), 2.94 (2 H, d, *J* = 21.5, H-2), 4.02–4.13 (6 H, m, H-3,6), 6.60–6.65 (2 H, m, Ar*H*), 7.06–7.18 (3 H, m, Ar*H*), 7.20–7.35 (10 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.3, C-4), 35.2 (d, *J* = 134.4, C-2), 42.7 (C-6), 62.4 (d, *J* = 6.2, C-3), 87.6 (C-5), 126.3 (C-12/13), 126.4 (C-10), 127.1 (C-14), 127.5 (C-8/9), 127.8 (C-12/13), 130.4 (C-8/9), 135.3 (C-7), 143.9 (C-11), 163.8 (d, *J* = 6.4, C-1); δ_P (162 MHz, $CDCl_3$) 20.3; HRMS (ESI^+): Found: 475.1636; $C_{26}H_{29}NaO_5P$ (MNa^+) Requires 475.1645 (1.8 ppm error).
Lab notebook reference: MGL/01/61,63

1,1,2-Triphenylethyl 2-diazo-2-(diethoxyphosphoryl)acetate (153b)

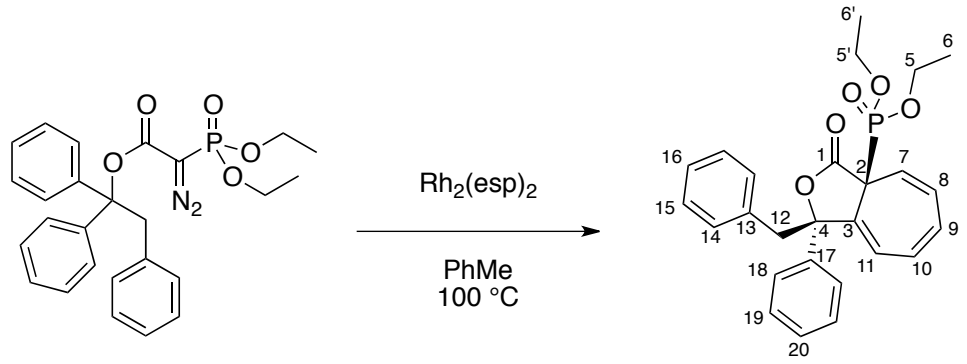


153a **153b**

Synthesised using general procedure B with 1,1,2-triphenylethyl 2-(diethoxyphosphoryl)acetate **153a** (308 mg, 0.681 mmol), THF (3.4 mL), LHMDS (0.82 mL, 0.82 mmol, 1.0 M solution in THF) and *p*-ABSA (196 mg, 0.82 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **153b** as a white crystalline solid (171 mg, 53%); R_f 0.77 (1:2 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2938w, 2884w, 2100s, 1675s, 1264s, 1219w, 1005m; m.p. 68–72 °C; δ_H (400 MHz, $CDCl_3$) 1.19 (6 H, td, J = 7.1, J = 0.7, H-4), 3.81–3.93 (2 H, m, H-3), 4.03–4.13 (2 H, m, H-3), 4.14 (2 H, s, H-6), 6.61–6.65 (2 H, m, Ar*H*), 7.06–7.18 (3 H, m, Ar*H*), 7.22–7.34 (10 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 15.9 (d, J = 7.6, C-4), 43.3 (C-6), 55.2 (d, J = 227.8, C-2), 63.1 (d, J = 5.4, C-3), 88.3 (C-5), 126.1 (C-12/13), 126.5 (C-10), 127.2 (C-14), 127.5 (C-8/9), 128.0 (C-12/13), 130.3 (C-8/9), 135.3 (C-7), 144.1 (C-11), 162.2 (d, J = 10.2, C-1); δ_P (162 MHz, $CDCl_3$) 11.0; HRMS (ESI^+): Found: 501.1527; $C_{26}H_{27}N_2NaO_5P$ (MNa^+) Requires 501.1550 (4.5 ppm error).

Lab notebook reference: MGL/02/05

Diethyl ((1*SR*,3a*SR*)-1-benzyl-3-oxo-1-phenyl-3,3a-dihydro-1*H*-cyclohepta[*c*]furan-3a-yl)phosphonate (153e)



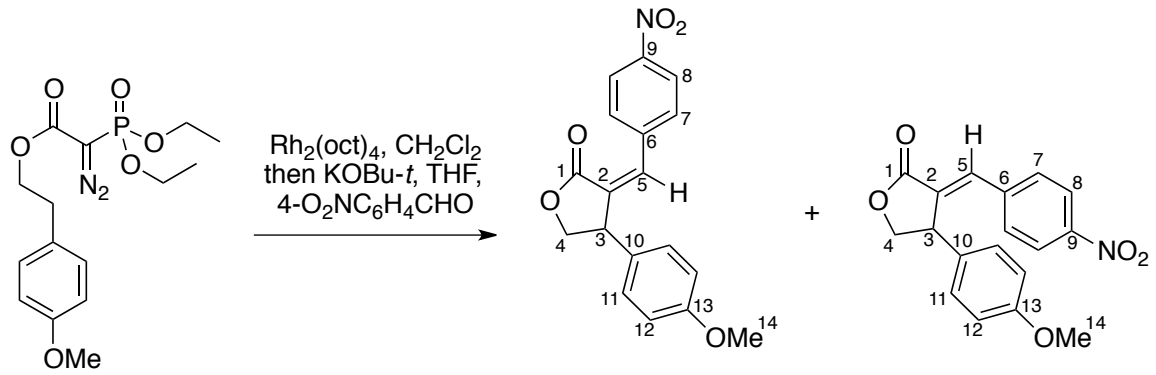
153b **153e**

To a solution of 1,1,2-triphenylethyl 2-diazo-2-(diethoxyphosphoryl)acetate **153b** (47 mg, 0.098 mmol) in toluene (5 mL) flushed with argon was added $Rh_2(esp)_2$ (3.7 mg, 4.9 μmol). The mixture was stirred at 100 °C for 4 h. Concentration *in vacuo* and purification by column chromatography (1:1 petrol:EtOAc) afforded the *title compound* **153e** as an off-white solid (22 mg, 50%); R_f 0.22 (1:1 petrol:EtOAc); m.p. 92–95 °C; ν_{max} (thin film)/cm^{-1} 2936w, 1744s, 1230m, 1034w, 1009m; δ_H (400 MHz, $CDCl_3$) 1.35 (3 H, td, *J* = 7.1, *J* = 0.4, H-6/6'), 1.38 (3 H, td, *J* = 7.1, *J* = 0.4, H-6/6'), 3.65 (1 H, d, *J* = 14.6, H-12), 4.10–4.28 (4 H, m, H-5,5'), 4.11 (1 H, d, *J* = 14.6, H-12), 5.31 (1 H, dd, *J* = 10.0, *J* = 6.3, H-7), 6.15–6.22 (2 H, m, 2 × C*H*), 6.27–6.36 (2 H, m, 2 × C*H*), 7.09–7.16 (5 H, m, H-Ar*H*), 7.19–7.30 (3 H, m, Ar*H*), 7.32–7.36 (2 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 16.4 (d, *J* = 5.6, C-6/6'), 16.7 (d, *J* = 5.3, C-6/6'), 45.6 (C-12), 56.0 (d, *J* = 145.2, C-2), 63.8 (d, *J* = 7.5, C-5/5'), 64.4 (d, *J* = 7.3, C-5/5'), 90.0 (d, *J* = 3.8, C-4), 119.1 (C-7), 124.2 (d, *J* = 7.2, C-8/11), 125.6 (Ar*C*H), 126.6 (C-9/10/16/20), 127.7 (C-9/10/16/20), 127.8 (Ar*C*H), 128.4 (Ar*C*H), 128.5 (d, *J* = 7.4, C-8/11), 129.0 (C-9/10/16/20), 129.9 (C-9/10/16/20), 130.7 (Ar*C*H), 134.4 (C-3), 135.0 (C-13), 141.3 (C-17), 172.7 (d, *J* = 3.6, C-1); δ_P (162 MHz, $CDCl_3$) 17.3; HRMS (ESI$^+$): Found: 473.1477; $C_{26}H_{27}NaO_5P$ (MNa^+) Requires 473.1488 (2.5 ppm error), Found: 451.1660; $C_{26}H_{28}O_5P$ (MNa^+) Requires 451.1669 (2.1 ppm error).

5.2.1.2. α-Alkylidene-γ-butyrolactones

Note: The assignment of *Z*- and *E*-configurations for α-alkylidene/arylidene-γ-butyrolactones is based on literature data for similar compounds.[167] The isomers can be readily distinguished by comparison of the alkylidene proton, which is more downfield in the *E*-isomer (adjacent to the carbonyl).

(*SR*,*E*)-4-(4-Methoxyphenyl)-3-(4-nitrobenzylidene)dihydrofuran-2(3*H*)-one (*E*-176) and (*SR*,*Z*)-4-(4-Methoxyphenyl)-3-(4-nitrobenzylidene) dihydrofuran-2(3*H*)-one (*Z*-176)



Synthesised using general procedure D with 4-methoxyphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **117b** (70 mg, 0.196 mmol), CH_2Cl_2 (4.0 mL), $Rh_2(oct)_4$ (3.1 mg, 3.9 μmol), THF (4.0 mL), KOBu-*t* (33.0 mg, 0.294 mmol) and 4-nitrobenzaldehyde (59.2 mg, 0.392 mmol). The HWE was performed at 0 °C. Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compounds* as an inseparable mixture of (*E*) and (*Z*) isomers (***E*-176**:***Z*-176** 1:1.3), as an orange oil (44 mg, 69%); R_f 0.40 (2:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2971w, 2916w, 2838w, 1752s, 1599s, 1513s, 1344s, 1248m, 1177m, 1031m; HRMS (ESI^+): Found: 348.0850; $C_{18}H_{15}NNaO_5$ (MNa^+) Requires 348.0842 (−2.3 ppm error).

The two isomers were characterized from the mixture.

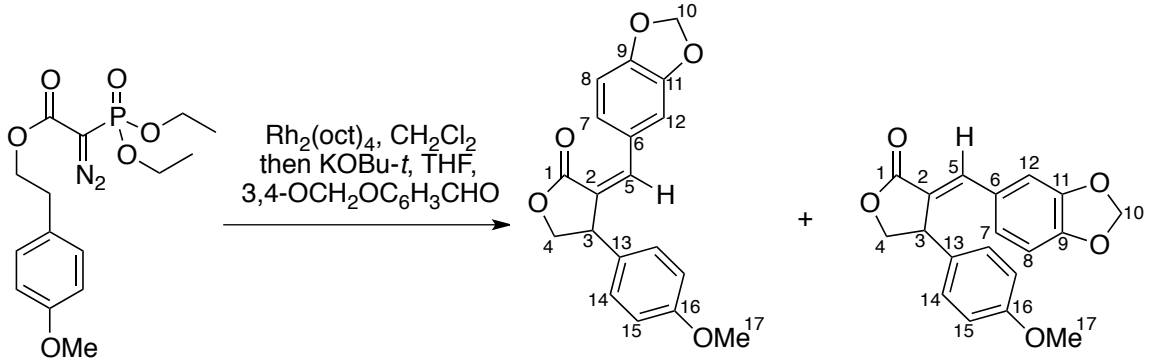
Data for ***E*-176**; δ_H (400 MHz, $CDCl_3$) 3.76 (3 H, s, H-14), 4.29 (1 H, dd, *J* = 8.8, *J* = 3.4, H-4), 4.56 (1 H, ddd, *J* = 8.0, *J* = 3.4, *J* = 2.5, H-3), 4.74 (1 H, dd, *J* = 8.8, *J* = 8.0, H-4), 6.83 (2 H, d, *J* = 8.8, H-12), 7.09 (2 H, d, *J* = 8.8, H-11), 7.47 (2 H, d, *J* = 8.8, H-7), 7.81 (1 H, d, *J* = 2.5, H-5), 8.09 (2 H, d, *J* = 8.8, H-8); δ_C (100 MHz, $CDCl_3$) 43.8 (C-3), 55.4 (C-14), 74.2 (C-4), 115.0 (C-12),

123.8 (C-8), 128.1 (C-11), 131.1 (C-7), 131.5 (C-2), 131.6 (C-10), 136.2 (C-5), 139.6 (C-6), 147.9 (C-9), 159.3 (C-13), 171.7 (C-1).

Data for ***Z*-176**; δ_H (400 MHz, $CDCl_3$) 3.83 (3 H, s, H-14), 4.33 (1 H, dd, *J* = 8.4, *J* = 8.1, H-4), 4.40 (1 H, ddd, *J* = 8.4, *J* = 8.1, *J* = 2.8, H-3), 4.74 (1 H, app. t, *J* = 8.4, *J* = 8.4, H-4), 6.69 (1 H, d, *J* = 2.8, H-5), 6.95 (2 H, d, *J* = 8.8, H-12), 7.23 (2 H, d, *J* = 8.8, H-11), 7.87 (2 H, d, *J* = 8.8, H-7), 8.17 (2 H, d, *J* = 8.8, H-8); δ_C (100 MHz, $CDCl_3$) 48.3 (C-3), 55.5 (C-14), 72.6 (C-4), 114.9 (C-12), 123.3 (C-8), 129.5 (C-11), 130.8 (C-2), 131.4 (C-7), 133.6 (C-10), 138.3 (C-5), 139.4 (C-6), 147.8 (C-9), 159.5 (C-13), 168.2 (C-1).

Lab notebook reference: MGL/03/11, 04/15

(*SR*,*Z*)-3-(1,3-Benzodioxol-5-ylmethylene)-4-(4-methoxyphenyl) dihydrofuran-2(3*H*)-one (*Z*-177) and (*SR*,*E*)-3-(1,3-Benzodioxol-5-ylmethylene)-4-(4-methoxyphenyl)dihydrofuran-2(3*H*)-one (*E*-177)



117b ***Z*-177** ***E*-177**

Synthesised using general procedure D with 4-methoxyphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **117b** (70 mg, 0.196 mmol), CH_2Cl_2 (4.0 mL), $Rh_2(oct)_4$ (3.1 mg, 3.9 μmol), THF (4.0 mL), KOBu-*t* (33.0 mg, 0.294 mmol) and piperonal (58.9 mg, 0.392 mmol). The HWE was performed at reflux. Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound*s as mixture of (*Z*) and (*E*) isomers (***Z*-177**:***E*-177** 1.2:1), as an orange oil (36 mg, 56%).

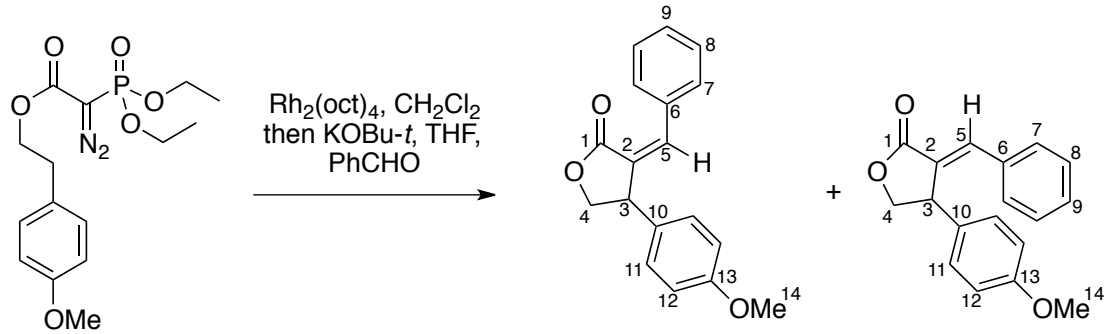
Small quantities of each compound were isolated separately for characterisation purposes.

Data for ***Z*-177**; R_f 0.33 (4:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2907w, 1743s, 1611m, 1513s, 1489w, 1448m, 1248s, 1158s, 1073m, 1036s, 930w; δ_H (400 MHz, $CDCl_3$) 3.82 (3 H, s, H-17), 4.26 (1 H, dd, *J* = 8.4, *J* = 7.8, H-4), 4.34 (1 H, app. td, *J* = 8.1, *J* = 2.4, H-3), 4.68 (1 H, app. t, *J* = 8.4, H-4), 5.99 (2 H, s, H-10), 6.52 (1 H, d, *J* = 2.4, H-5), 6.76 (1 H, d, *J* = 8.2, H-8), 6.92 (2 H, d, *J*

= 8.7, H-15), 7.15 (1 H, dd, *J* = 8.2, *J* = 1.7, H-7), 7.21 (2 H, d, *J* = 8.7, H-14), 7.82 (1 H, d, *J* = 1.7, H-12); δ_C (100 MHz, $CDCl_3$) 48.4 (C-3), 55.3 (C-17), 72.6 (C-4), 101.4 (C-10), 107.8 (C-8), 110.9 (C-12), 114.6 (C-15), 126.7 (C-2), 127.2 (C-7), 128.0 (C-6), 129.4 (C-14), 132.2 (C-13), 141.6 (C-5), 147.6 (C-11), 149.1 (C-9), 159.1 (C-16), 169.1 (C-1); HRMS (ESI^+): Found: 347.0873; $C_{19}H_{16}NaO_5$ (MNa^+) Requires 347.0890 (4.8 ppm error), Found: 325.1065; $C_{19}H_{17}O_5$ (MH^+) Requires 325.1071 (1.6 ppm error).

Data for ***E*-177**; R_f 0.26 (4:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2908w, 1744s, 1644m, 1611m, 1511s, 1491w, 1448m, 1341w, 1263m, 1218m, 1172s, 1036s, 927w; δ_H (400 MHz, $CDCl_3$) 3.78 (3 H, s, H-17), 4.26 (1 H, dd, *J* = 8.7, *J* = 2.7, H-4), 4.49–4.52 (1 H, m, H-3), 4.68 (1 H, dd, *J* = 8.7, *J* = 7.9, H-4), 5.94 (1 H, d, *J* = 1.3, H-10), 5.95 (1 H, d, *J* = 1.3, H-10), 6.73 (1 H, d, *J* = 8.1, H-8), 6.80 (1 H, d, *J* = 1.8, H-12), 6.86 (2 H, d, *J* = 8.7, H-15), 6.93 (1 H, dd, *J* = 8.1, *J* = 1.8, H-7), 7.14 (2 H, d, *J* = 8.7, H-14), 7.70 (1 H, d, *J* = 2.1, H-5); δ_C (100 MHz, $CDCl_3$) 43.6 (C-3), 55.3 (C-17), 74.0 (C-4), 101.5 (C-10), 108.6 (C-8), 109.6 (C-12), 114.7 (C-15), 124.3 (C-2/6), 127.0 (C-7), 127.9 (C-2/6), 128.0 (C-14), 132.6 (C-13), 139.0 (C-5), 148.0 (C-9/11), 149.3 (C-9/11), 158.9 (C-16), 172.9 (C-1); HRMS (ESI^+): Found: 347.0873; $C_{19}H_{16}NaO_5$ (MNa^+) Requires 347.0890 (4.8 ppm error), Found: 325.1066; $C_{19}H_{17}O_5$ (MH^+) Requires 325.1071 (1.5 ppm error).
Lab notebook reference: MGL/03/74,88

(*SR*,*Z*)-3-Benzylidene-4-(4-methoxyphenyl)dihydrofuran-2(3*H*)-one (*Z*-178) and (*SR*,*E*)-3-Benzylidene-4-(4-methoxyphenyl)dihydrofuran-2(3*H*)-one (*E*-178)



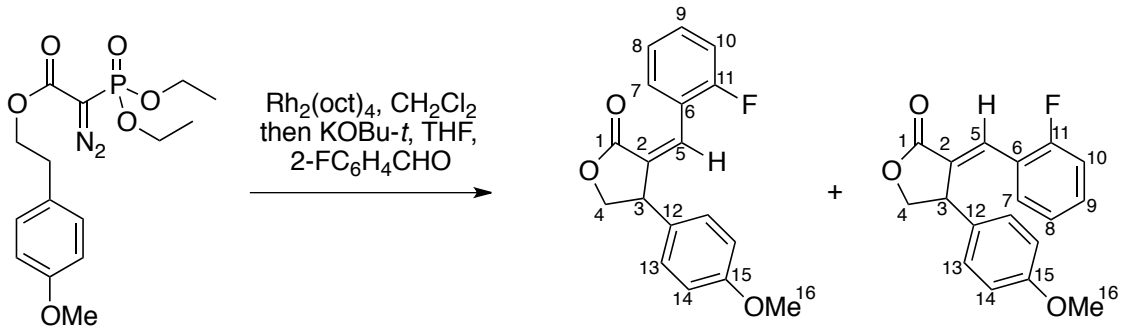
Synthesised using general procedure D with 4-methoxyphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **117b** (66 mg, 0.185 mmol), CH_2Cl_2 (3.9 mL), $Rh_2(oct)_4$ (2.9 mg, 3.7 μmol), THF (3.9 mL), KOBu-*t* (31.0 mg, 0.278 mmol) and freshly distilled benzaldehyde (37.6 μL, 0.370 mmol). The HWE was performed at RT. Purification by column chromatography (8:1 petrol:EtOAc) afforded the *title compound*s as mixture of (*Z*) and (*E*) isomers (***Z*-178**:***E*-178** 1:1), as a pale yellow oil (34 mg, 65%).

Small quantities of each compound were isolated separately for characterisation purposes.

Data for ***Z*-178**; R_f 0.33 (4:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2887m, 2869m, 1724s, 1490s, 1229m, 1136m; δ_H (400 MHz, $CDCl_3$) 3.83 (3 H, s, H-14), 4.28 (1 H, dd, *J* = 8.5, *J* = 7.8, H-4), 4.37 (1 H, ddd, *J* = 8.5, *J* = 7.8, *J* = 2.7, H-3), 4.71 (1 H, dd, *J* = 8.5, *J* = 8.5, H-4), 6.67 (1 H, d, *J* = 2.7, H-5), 6.94 (2 H, d, *J* = 8.7, H-12), 7.23 (2 H, d, *J* = 8.7, H-11), 7.31–7.39 (3 H, m, H-8,9), 7.79–7.83 (2 H, m, H-7); δ_C (100 MHz, $CDCl_3$) 48.2 (C-3), 55.3 (C-14), 72.4 (C-4), 114.6 (C-12), 128.1 (C-8), 129.1 (C-2), 129.4 (C-11), 129.7 (C-9), 130.8 (C-7), 131.9 (C-10), 133.4 (C-6), 141.7 (C-5), 159.2 (C-13), 168.8 (C-1); HRMS (ESI^+): Found: 303.0979; $C_{18}H_{16}NaO_3$ (MNa^+) Requires 303.0992 (4.1 ppm error), Found: 281.1183; $C_{18}H_{17}O_3$ (MH^+) Requires 281.1172 (–3.8 ppm error).

Data for ***E*-178**; R_f 0.25 (4:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2877m, 1724s, 1488s, 1228m, 1153m; δ_H (400 MHz, $CDCl_3$) 3.77 (3 H, s, H-14), 4.29 (1 H, dd, *J* = 8.7, *J* = 2.7, H-4), 4.56 (1 H, ddd, *J* = 7.9, *J* = 2.7, *J* = 2.2, H-3), 4.69 (1 H, dd, *J* = 8.7, *J* = 7.9, H-4), 6.84 (2 H, d, *J* = 8.8, H-12), 7.14 (2 H, d, *J* = 8.8, H-11), 7.26–7.31 (3 H, m, H-8,9), 7.33–7.37 (2 H, m, H-7), 7.81 (1 H, d, *J* = 2.2, H-5); δ_C (100 MHz, $CDCl_3$) 43.6 (C-3), 55.3 (C-14), 74.1 (C-4), 114.6 (C-12), 126.8 (C-2), 128.0 (C-11), 128.7 (C-8), 130.0 (C-9), 130.6 (C-7), 132.6 (C-10), 133.6 (C-6), 139.2 (C-5), 158.9 (C-13), 172.7 (C-1); HRMS (ESI^+): Found: 303.0998; $C_{18}H_{16}NaO_3$ (MNa^+) Requires 303.0992 (–2.0 ppm error), Found: 281.1167; $C_{18}H_{17}O_3$ (MH^+) Requires 281.1172 (1.9 ppm error).
Lab notebook reference: MGL/03/89

(*SR*,*Z*)-3-(2-Fluorobenzylidene)-4-(4-methoxyphenyl)dihydrofuran-2(3*H*)-one (*Z*-179) and (*SR*,*E*)-3-(2-Fluorobenzylidene)-4-(4-methoxyphenyl) dihydrofuran-2(3*H*)-one (*E*-179)



117b ***Z*-179** ***E*-179**

Synthesised using general procedure D with 4-methoxyphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **117b** (71 mg, 0.199 mmol), CH_2Cl_2 (4.0 mL), $Rh_2(oct)_4$ (3.1 mg, 4.0 μmol), THF (4.0 mL), KOBu-*t* (33.5 mg, 0.299 mmol) and 2-fluorobenzaldehyde (41.6 μL, 0.398 mmol). The HWE was performed at RT. Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound*s as mixture of (*Z*) and (*E*) isomers (***Z*-179**:***E*-179** 1.5:1), as a colourless oil (54 mg, 91%).

Small quantities of each compound were isolated separately for characterisation purposes.

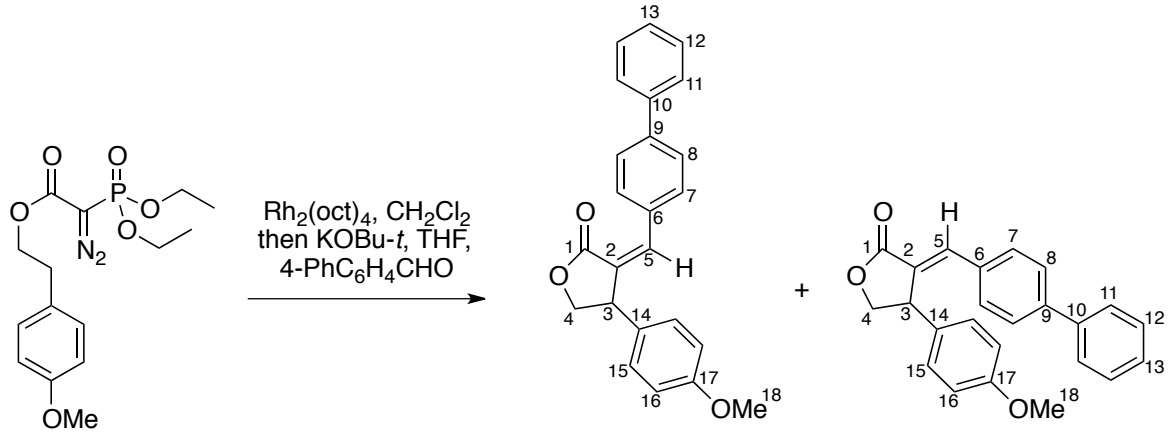
Data for ***Z*-179**; R_f 0.40 (4:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2919m, 2842w, 1757s, 1611m, 1514s, 1484m, 1456w, 1371w, 1249s, 1160m, 1107m, 1072w, 1025m, 833w, 754m; δ_H (400 MHz, $CDCl_3$) 3.83 (3 H, s, H-16), 4.28 (1 H, dd, *J* = 8.7, *J* = 7.8, H-4), 4.36–4.41 (1 H, m, H-3), 4.71 (1 H, app. t, *J* = 8.7, H-4), 6.86 (1 H, d, *J* = 2.1, H-5), 6.94 (2 H, d, *J* = 8.7, H-14), 7.00–7.05 (1 H, m, H-10), 7.14 (1 H, app. td, *J* = 7.7, *J* = 1.0, H-8), 7.23 (2 H, d, *J* = 8.7, H-13), 7.29–7.35 (1 H, m, H-9), 8.01 (1 H, app. td, *J* = 7.7, *J* = 1.6, H-7); δ_C (100 MHz, $CDCl_3$) 47.9 (C-3), 55.3 (C-16), 72.5 (C-4), 114.6 (C-14), 115.1 (d, *J* = 22.0, C-10), 121.4 (d, *J* = 12.3, C-6), 123.6 (d, *J* = 3.8, C-7/8/9), 129.3 (C-13), 131.4 (C-2/12), 131.4 (d, *J* = 8.7, C-7/8/9), 131.5 (C-2/12), 131.7 (d, *J* = 1.5, C-7/8/9), 133.0 (d, *J* = 5.4, C-5), 159.2 (C-15), 160.4 (d, *J* = 251.0, C-11), 168.5 (C-1); HRMS (ESI^+): Found: 321.0886; $C_{18}H_{15}FNaO_3$ (MNa^+) Requires 321.0897 (3.6 ppm error), Found: 299.1071; $C_{18}H_{16}FNaO_3$ (MNa^+) Requires 299.1078 (2.4 ppm error).

Data for ***E*-179**; R_f 0.27 (4:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2922m, 2852w, 1752s, 1649m, 1611m, 1581w, 1512s, 1486m, 1458w, 1351w, 1302w, 1248s, 1211s, 1174s, 1154w, 1100w, 1064w, 1032s, 832w, 808w, 792w, 758s; δ_H (400 MHz, $CDCl_3$) 3.75 (3 H, s, H-16), 4.24 (1 H, dd,

J = 8.7, *J* = 3.7, H-4), 4.50–4.54 (1 H, m, H-3), 4.71 (1 H, app. t, *J* = 8.4, H-4), 6.79 (2 H, d, *J* = 8.7, H-14), 6.92–6.96 (1 H, m, H-7/8/9), 6.98–7.03 (1 H, m, H-10), 7.08 (2 H, d, *J* = 8.7, H-13), 7.15–7.20 (1 H, m, H-7/8/9), 7.22–7.28 (1 H, m, H-7/8/9), 7.99 (1 H, d, *J* = 2.4, H-5); δ_C (100 MHz, $CDCl_3$) 43.8 (C-3), 55.2 (C-16), 74.0 (C-4), 114.5 (C-14), 115.7 (d, *J* = 22.1, C-10), 121.8 (d, *J* = 12.1, C-6), 123.9 (d, *J* = 3.7, C-7/8/9), 128.2 (C-13), 129.4 (C-2), 130.1 (d, *J* = 2.2, C-7/8/9), 130.9 (d, *J* = 5.4, C-5), 131.6 (d, *J* = 8.8, C-7/8/9), 132.0 (C-12), 158.8 (C-15), 161.2 (d, *J* = 253.4, C-11), 172.0 (C-1); HRMS (ESI^+): Found: 321.0887; $C_{18}H_{15}FNaO_3$ (MNa^+) Requires 321.0897 (3.4 ppm error), Found: 299.1074; $C_{18}H_{16}FNaO_3$ (MNa^+) Requires 299.1078 (1.2 ppm error).

Lab notebook reference: MGL/03/92

(*SR*,*Z*)-3-([1,1'-Biphenyl]-4-ylmethylene)-4-(4-methoxyphenyl) dihydrofuran-2(3*H*)-one (*Z*-180) and (*SR*,*E*)-3-([1,1'-Biphenyl]-4-ylmethylene)-4-(4-methoxyphenyl)dihydrofuran-2(3*H*)-one (*E*-180)



Synthesised using general procedure D with 4-methoxyphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **117b** (70 mg, 0.196 mmol), CH_2Cl_2 (4.0 mL), $Rh_2(oct)_4$ (3.1 mg, 3.9 μmol), THF (4.0 mL), KOBu-*t* (33.0 mg, 0.294 mmol) and 4-biphenylcarboxyaldehyde (71.4 mg, 0.392 mmol). The HWE was performed at RT. Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound*s as mixture of (*Z*) and (*E*) isomers (***Z*-180**:***E*-180** 1:1), as a pale yellow oil (43 mg, 61%).

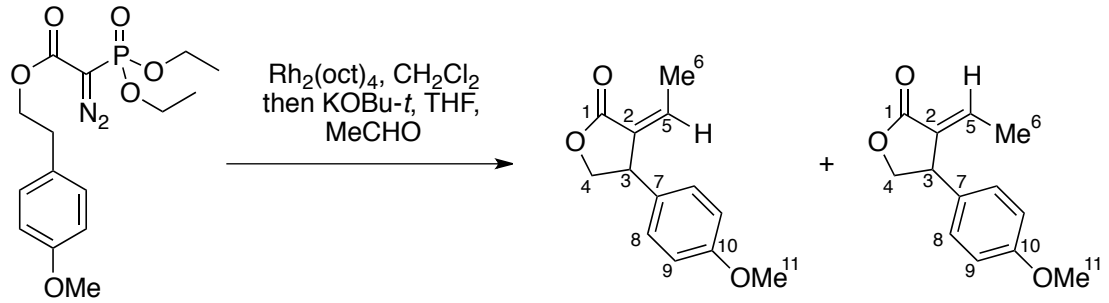
Small quantities of each compound were isolated separately for characterisation purposes.

Data for ***Z*-180**; R_f 0.37 (4:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2928m, 1749s, 1638m, 1611m, 1513s, 1487m, 1464w, 1416w, 1371m, 1305w, 1248s, 1179w, 1155s, 1115w, 1074m, 1030s, 915w, 834m; δ_H (400 MHz, $CDCl_3$) 3.83 (3 H, s, H-18), 4.30 (1 H, app. t, *J* = 8.2, H-4), 4.39 (1 H,

app. td, J = 8.2, J = 2.6, H-3), 4.72 (1 H, app. t, J = 8.6, H-4), 6.69 (1 H, d, J = 2.6, H-5), 6.95 (2 H, d, J = 8.7, H-16), 7.24 (2 H, d, J = 8.7, H-15), 7.34–7.38 (1 H, m, H-13), 7.42–7.46 (2 H, m, H-12), 7.58–7.62 (4 H, m, H-8,11), 7.92 (2 H, d, J = 8.4, H-7); δ_C (100 MHz, $CDCl_3$) 48.4 (C-3), 55.3 (C-18), 72.5 (C-4), 114.6 (C-16), 126.7 (C-8/11), 127.1 (C-8/11), 127.7 (C-13), 128.8 (C-12), 128.9 (C-2), 129.4 (C-15), 131.5 (C-7), 132.0 (C-6), 132.4 (C-14), 140.3 (C-10), 141.2 (C-5), 142.4 (C-9), 159.2 (C-17), 168.9 (C-1); HRMS (ESI^+): Found: 379.1294; $C_{24}H_{20}NaO_3$ (MNa^+) Requires 379.1305 (2.9 ppm error).

Data for ***E*-180**; R_f 0.29 (4:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 3030w, 2970w, 2934w, 2915w, 2836w, 1749s, 1645m, 1607m, 1511s, 1487w, 1360w, 1248s, 1170s, 1033m, 834m, 766m, 698w; δ_H (400 MHz, $CDCl_3$) 3.77 (3 H, s, H-18), 4.30 (1 H, dd, J = 8.6, J = 2.7, H-4), 4.60 (1 H, ddd, J = 7.9, J = 2.7, J = 2.1, H-3), 4.71 (1 H, dd, J = 8.6, J = 7.9, H-4), 6.86 (2 H, d, J = 8.7, H-16), 7.17 (2 H, d, J = 8.7, H-15), 7.33–7.37 (1 H, m, H-13), 7.40–7.45 (4 H, m, H-7/8/11/12), 7.50–7.56 (4 H, m, H-7/8/11/12), 7.85 (1 H, d, J = 2.1, H-5); δ_C (100 MHz, $CDCl_3$) 43.8 (C-3), 55.4 (C-18), 74.2 (C-4), 114.8 (C-16), 126.6 (C-2/6/9/10/14), 127.1 (C-7/8/11/12), 127.4 (C-7/8/11/12), 128.0 (C-13), 128.2 (C-15), 129.0 (C-7/8/11/12), 131.3 (C-7/8/11/12), 132.6 (C-2/6/9/10/14), 132.7 (C-2/6/9/10/14), 138.9 (C-5), 140.0 (C-2/6/9/10/14), 142.8 (C-2/6/9/10/14), 159.0 (C-17), 172.8 (C-1); HRMS (ESI^+): Found: 357.1489; $C_{24}H_{21}O_3$ (MH^+) Requires 357.1485 (−1.1 ppm error).
Lab notebook reference: MGL/03/90

(*SR*,*Z*)-3-Ethylidene-4-(4-methoxyphenyl)dihydrofuran-2(3*H*)-one (*Z*-181) and (*SR*,*E*)-3-Ethylidene-4-(4-methoxyphenyl)dihydrofuran-2(3*H*)-one (*E*-181)



117b ***Z*-181** ***E*-181**

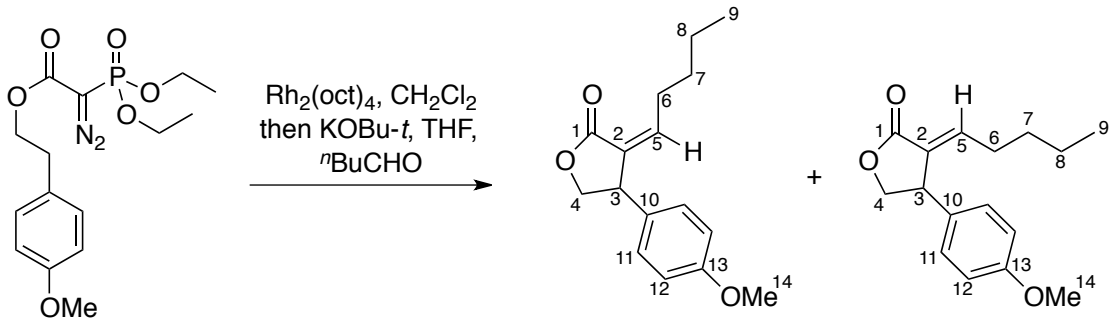
Synthesised using general procedure D with 4-methoxyphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **117b** (71 mg, 0.199 mmol), CH_2Cl_2 (4.0 mL), $Rh_2(oct)_4$ (3.1 mg, 4.0 μmol), THF (4.0 mL), KOBu-*t* (33.5 mg, 0.299 mmol) and acetaldehyde (22.0 μL, 0.398 mmol). The HWE was performed at RT. Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound*s as mixture of (*Z*) and (*E*) isomers (***Z*-181**:***E*-181** 1:1.2), as a colourless oil (17 mg, 39%).

Small quantities of each compound were isolated separately for characterisation purposes.

Data for ***Z*-181**; R_f 0.33 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2913w, 1752s, 1672w, 1612w, 1514s, 1441w, 1352w, 1305w, 1280w, 1249s, 1207w, 1180m, 1114m, 1021m; δ_H (400 MHz, $CDCl_3$) 2.18 (3 H, dd, *J* = 7.4, *J* = 2.5, H-6), 3.81 (3 H, s, H-11), 4.12–4.19 (2 H, m, H-3,4), 4.57–4.64 (1 H, m, H-4), 6.05 (1 H, qd, *J* = 7.4, *J* = 2.4, H-5), 6.89 (2 H, d, *J* = 8.8, H-9), 7.13 (2 H, d, *J* = 8.8, H-8); δ_C (100 MHz, $CDCl_3$) 13.9 (C-6), 46.3 (C-3), 55.3 (C-11), 72.6 (C-4), 114.4 (C-9), 129.1 (C-8), 130.0 (C-2), 132.3 (C-7), 140.9 (C-5), 159.0 (C-10), 170.0 (C-1); HRMS (ESI^+): Found: 241.0832; $C_{13}H_{14}NaO_3$ (MNa^+) Requires 241.0835 (1.4 ppm error), Found: 219.1008; $C_{13}H_{15}O_3$ (MH^+) Requires 219.1016 (3.7 ppm error).

Data for ***E*-181**; R_f 0.23 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2917w, 1756s, 1675w, 1611w, 1512s, 1464w, 1372w, 1304w, 1246s, 1218m, 1179m, 1132w, 1023s; δ_H (400 MHz, $CDCl_3$) 1.63 (3 H, dd, *J* = 7.3, *J* = 1.8, H-6), 3.80 (3 H, s, H-11), 4.18 (1 H, dd, *J* = 8.9, *J* = 4.7, H-4), 4.22–4.27 (1 H, m, H-3), 4.67 (1 H, app. t, *J* = 8.8, H-4), 6.87 (2 H, d, *J* = 8.7, H-9), 6.99 (1 H, qd, *J* = 7.3, *J* = 2.6, H-5), 7.11 (2 H, d, *J* = 8.7, H-8); δ_C (100 MHz, $CDCl_3$) 15.3 (C-6), 42.5 (C-3), 55.3 (C-11), 73.7 (C-4), 114.4 (C-9), 128.2 (C-8), 130.3 (C-2), 133.1 (C-7), 138.8 (C-5), 158.8 (C-10), 171.1 (C-1); HRMS (ESI^+): Found: 241.0836; $C_{13}H_{14}NaO_3$ (MNa^+) Requires 241.0835 (–0.5 ppm error), Found: 219.1010; $C_{13}H_{15}O_3$ (MH^+) Requires 219.1016 (2.8 ppm error).
Lab notebook reference: MGL/04/20

(*SR*,*Z*)-4-(4-Methoxyphenyl)-3-pentylidenedihydrofuran-2(3*H*)-one (*Z*-182) and (*SR*,*E*)-4-(4-Methoxyphenyl)-3-pentylidenedihydrofuran-2(3*H*)-one (*E*-182)



Synthesised using general procedure D with 4-methoxyphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **117b** (69 mg, 0.194 mmol), CH_2Cl_2 (4.0 mL), $Rh_2(oct)_4$ (3.0 mg, 3.9 μmol), THF (4.0 mL), KOBu-*t* (32.7 mg, 0.291 mmol) and valeraldehdye (41.3 μL, 0.388 mmol). The HWE was performed at RT. Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound*s as mixture of (*E*) and (*Z*) isomers (***Z*-182**:***E*-182** 1:3.7), as a colourless oil (34 mg, 67%).

Small quantities of each compound were isolated separately for characterisation purposes.

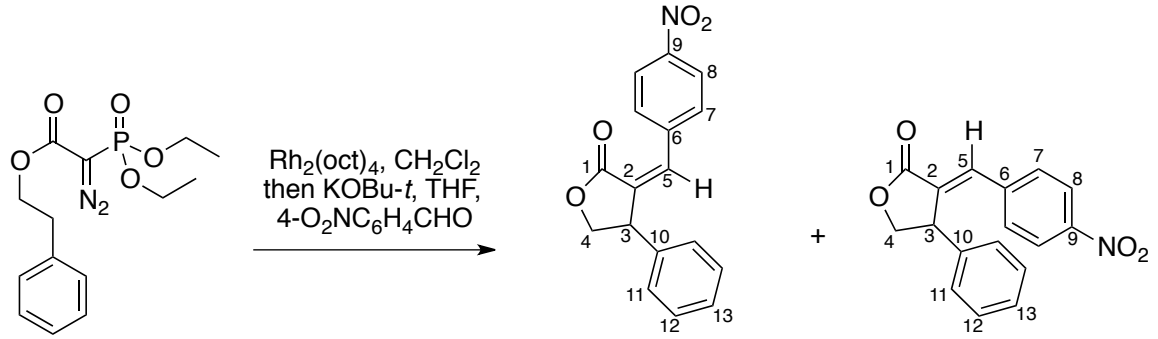
Data for ***Z*-182**; R_f 0.42 (4:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2958m, 2929m, 2859w, 1754s, 1668w, 1612w, 1514s, 1465w, 1372w, 1249m, 1177m, 1127m, 1028m, 833w; δ_H (400 MHz, $CDCl_3$) 0.88 (3 H, t, *J* = 7.2, H-9), 1.25–1.42 (4 H, m, H-7,8), 2.66–2.81 (2 H, m, H-6), 3.81 (3 H, s, H-14), 4.13–4.19 (2 H, m, H-3,4), 4.58–4.64 (1 H, m, H-4), 5.96 (1 H, app. td, *J* = 7.8, *J* = 2.3, H-5), 6.90 (2 H, d, *J* = 8.8, H-12), 7.13 (2 H, d, *J* = 8.8, H-11); δ_C (100 MHz, $CDCl_3$) 13.9 (C-9), 22.3 (C-8), 27.2 (C-6), 31.1 (C-7), 46.3 (C-3), 55.3 (C-14), 72.6 (C-4), 114.4 (C-12), 129.0 (C-2), 129.1 (C-11), 132.3 (C-10), 146.6 (C-5), 159.0 (C-13), 169.9 (C-1); HRMS (ESI^+): Found: 283.1299; $C_{16}H_{20}NaO_3$ (MNa^+) Requires 283.1305 (2.0 ppm error), Found: 261.1473; $C_{16}H_{21}O_3$ (MH^+) Requires 261.1485 (4.8 ppm error).

Data for ***E*-182**; R_f 0.33 (4:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2930s, 1759s, 1673w, 1612w, 1513s, 1465w, 1249s, 1180m, 1029m, 832w; δ_H (400 MHz, $CDCl_3$) 0.77 (3 H, t, *J* = 7.2, H-9), 1.12–1.34 (4 H, m, H-7,8), 1.87–2.02 (2 H, m, H-6), 3.80 (3 H, s, H-14), 4.16–4.25 (2 H, m, H-3,4), 4.67 (1 H, app. t *J* 8.4, H-4), 6.86 (2 H, d, *J* = 8.7, H-12), 6.90 (1 H, app. td, *J* = 7.7, *J* = 2.5, H-5), 7.11 (2 H, d, *J* = 8.7, H-11); δ_C (100 MHz, $CDCl_3$) 13.7 (C-9), 22.3 (C-8), 29.2 (C-6), 30.0 (C-7), 42.6 (C-3), 55.3 (C-14), 73.7 (C-4), 114.4 (C-12), 128.2 (C-11), 129.2 (C-2), 133.6 (C-10),

144.2 (C-5), 158.8 (C-13), 171.3 (C-1); HRMS (ESI^+): Found: 283.1309; $C_{16}H_{20}NaO_3$ (MNa^+) Requires 283.1305 (−1.7 ppm error), Found: 261.1484; $C_{16}H_{21}O_3$ (MH^+) Requires 261.1485 (0.6 ppm error).

Lab notebook reference: MGL/03/93

(*SR*,*Z*)-3-(4-Nitrobenzylidene)-4-phenyldihydrofuran-2(3*H*)-one (*Z*-183) and (*SR*,*E*)-3-(4-Nitrobenzylidene)-4-phenyldihydrofuran-2(3*H*)-one (*E*-183)



Synthesised using general procedure D with phenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **116b** (75 mg, 0.230 mmol), CH_2Cl_2 (4.6 mL), $Rh_2(oct)_4$ (3.6 mg, 4.6 μmol), THF (4.6 mL), KOBu-*t* (38.7 mg, 0.345 mmol) and 4-nitrobenzaldehyde (69.5 mg, 0.460 mmol). The HWE was performed at 0 °C. Purification by column chromatography (10:1 hexane:EtOAc) afforded the *title compound*s as mixture of (*Z*) and (*E*) isomers (***Z*-183**:***E*-183** 1:1) (44 mg, 65%).

Small quantities of each compound were isolated separately for characterisation purposes.

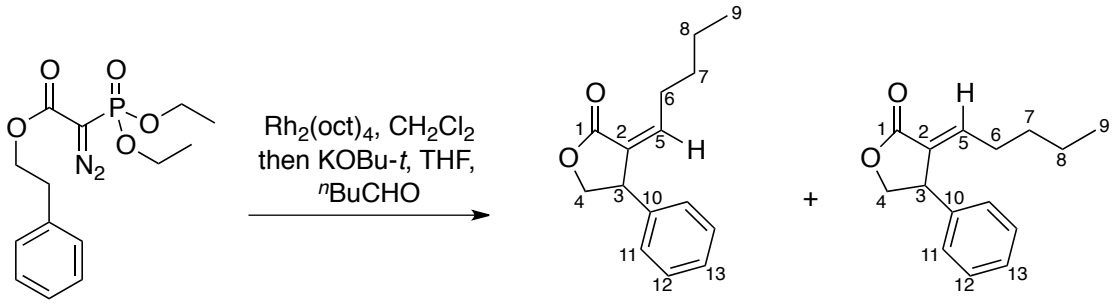
Data for ***Z*-183**; Pale yellow oil; R_f 0.40 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2920w, 1754s, 1597w, 1518s, 1345s, 1161s, 1074w, 1023w; δ_H (400 MHz, $CDCl_3$) 4.39 (1 H, app. t, J = 8.0, H-4), 4.45 (1 H, app. td, J = 7.8, J = 2.7, H-3), 4.78 (1 H, app. t, J = 8.4, H-4), 6.72 (1 H, d, J = 2.7, H-5), 7.30–7.32 (2 H, m, H-11/12), 7.35–7.39 (1 H, m, H-13), 7.41–7.46 (2 H, m, H-11/12), 7.88 (2 H, d, J = 8.9, H-7), 8.19 (2 H, d, J = 8.9, H-8); δ_C (100 MHz, $CDCl_3$) 48.8 (C-3), 72.4 (C-4), 123.2 (C-8), 128.2 (C-11/12), 128.2 (C-13), 129.5 (C-11/12), 131.3 (C-7), 133.2 (C-2/6/10), 138.5 (C-5), 139.2 (C-2/6/10), 139.3 (C-2/6/10), 147.8 (C-9), 168.0 (C-1); HRMS (ESI^+): Found: 318.0749; $C_{17}H_{13}NNaO_4$ (MNa^+) Requires 318.0737 (−3.8 ppm error).

Data for ***E*-183**; Pale yellow oil; R_f 0.32 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2923w, 2854w, 1755s, 1691w, 1653w, 1598m, 1518s, 1343s, 1300w, 1226m, 1173s, 1021w; δ_H (400 MHz, $CDCl_3$) 4.33 (1 H, dd, J = 8.9, J = 3.5, H-4), 4.61 (1 H, app. dt, J = 8.1, J = 3.0, H-3), 4.78 (1 H, app. t, J =

8.5, H-4), 7.17–7.19 (2 H, m, H-11/12), 7.24–7.34 (3 H, m, H-11/12,13), 7.45 (2 H, d, J = 8.8, H-7), 7.84 (1 H, d, J = 2.4, H-5), 8.08 (2 H, d, J = 8.8, H-8); δ_C (100 MHz, $CDCl_3$) 44.5 (C-3), 73.8 (C-4), 123.6 (C-8), 127.0 (C-11/12), 128.0 (C-13), 129.5 (C-11/12), 130.8 (C-7), 131.4 (C-2/6/10), 136.3 (C-5), 139.6 (C-2/6/10), 139.6 (C-2/6/10), 147.9 (C-9), 171.4 (C-1); HRMS (ESI^+): Found: 318.0746; $C_{17}H_{13}NNaO_4$ (MNa^+) Requires 318.0737 (−2.8 ppm error).

Lab notebook reference: MGL/05/38

(*SR*,*Z*)-3-Pentylidene-4-phenyldihydrofuran-2(3*H*)-one (*Z*-184) and (*SR*,*E*)-3-Pentylidene-4-phenyldihydrofuran-2(3*H*)-one (*E*-184)



116b ***Z*-184** ***E*-184**

Synthesised using general procedure D with phenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **116b** (73 mg, 0.224 mmol), CH_2Cl_2 (4.5 mL), $Rh_2(oct)_4$ (3.5 mg, 4.5 μmol), THF (4.5 mL), KOBu-*t* (37.7 mg, 0.336 mmol) and valeraldehyde (44.8 μL, 0.448 mmol). The HWE was performed at reflux. Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound*s as mixture of (*Z*) and (*E*) isomers (***Z*-184**:***E*-184** 3.3:1) (29 mg, 56%).

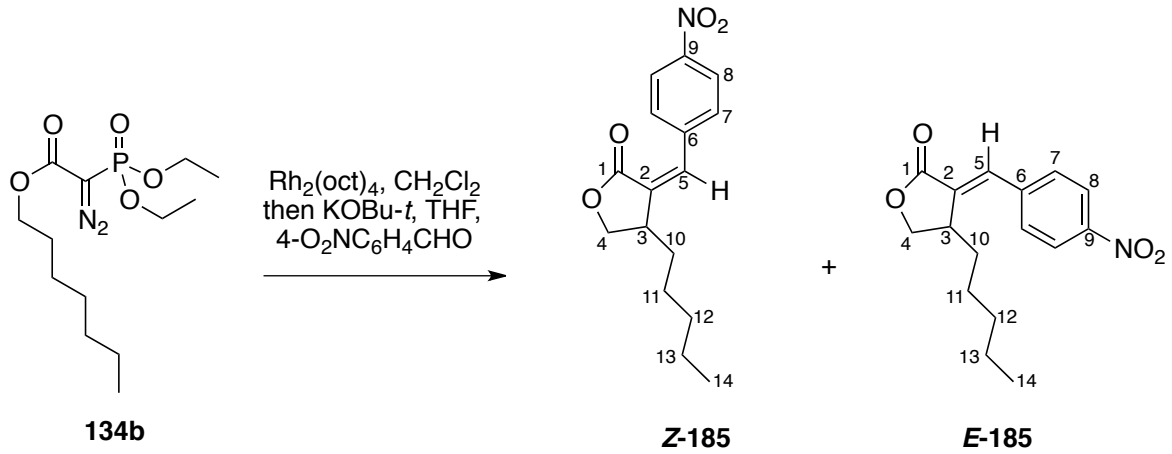
Small quantities of each compound were isolated separately for characterisation purposes.

Data for ***Z*-184**; Pale yellow oil; R_f 0.53 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2957m, 2928m, 2871w, 1755s, 1667w, 1455w, 1373w, 1175m, 1127m, 1025s; δ_H (400 MHz, $CDCl_3$) 0.88 (3 H, t, J = 7.1, H-9), 1.25–1.43 (4 H, m, H-7,8), 2.66–2.82 (2 H, m, H-6), 4.18–4.24 (2 H, m, H-3,4), 4.61–4.67 (1 H, m, H-4), 5.99 (1 H, td, J = 7.8, J = 2.2, H-5), 7.20–7.23 (2 H, m, H-11), 7.28–7.32 (1 H, m, H-13), 7.34–7.39 (2 H, m, H-12); δ_C (100 MHz, $CDCl_3$) 13.8 (C-9), 22.3 (C-8), 27.2 (C-6), 31.1 (C-7), 46.9 (C-3), 72.5 (C-4), 127.6 (C-13), 128.0 (C-11), 128.8 (C-12), 129.1 (C-2/10), 140.7 (C-2/10), 146.9 (C-5), 169.8 (C-1); HRMS (ESI^+): Found: 253.1188; $C_{15}H_{18}NaO_2$ (MNa^+) Requires 253.1199 (4.5 ppm error), Found: 231.1380; $C_{15}H_{19}O_2$ (MH^+) Requires 231.1380 (−0.2 ppm error).

Data for ***E*-184**; Pale yellow oil; R_f 0.44 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2957m, 2928s, 2858m, 1759s, 1672w, 1456w, 1378w, 1184m, 1026m; δ_H (400 MHz, $CDCl_3$) 0.76 (3 H, t, J = 7.2,

H-9), 1.10–1.33 (4 H, m, H-7,8), 1.88–2.01 (2 H, m, H-6), 4.20–4.29 (2 H, m, H-3,4), 4.70 (1 H, app. t, J = 8.2, H-4), 6.92 (1 H, td, J = 7.7, J = 2.3, H-5), 7.19–7.21 (2 H, m, H-11), 7.26–7.29 (1 H, m, H-13), 7.31–7.36 (2 H, m, H-12); δ_C (100 MHz, $CDCl_3$) 13.6 (C-9), 22.2 (C-8), 29.2 (C-6), 29.9 (C-7), 43.4 (C-3), 73.5 (C-4), 127.2 (C-11), 127.4 (C-13), 129.0 (C-2/10), 129.1 (C-12), 141.7 (C-2/10), 144.3 (C-5), 171.2 (C-1); HRMS (ESI^+): Found: 253.1187; $C_{15}H_{18}NaO_2$ (MNa^+) Requires 253.1199 (4.9 ppm error), Found: 231.1376; $C_{15}H_{19}O_2$ (MH^+) Requires 231.1380 (1.7 ppm error).
Lab notebook reference: MGL/05/39

(*SR*,*Z*)-3-(4-Nitrobenzylidene)-4-pentyldihydrofuran-2(3*H*)-one (*Z*-185) and (*SR*,*E*)-3-(4-Nitrobenzylidene)-4-pentyldihydrofuran-2(3*H*)-one (*E*-185)



Synthesised using general procedure D with heptyl 2-diazo-2-(diethoxyphosphoryl)acetate **134b** (68 mg, 0.212 mmol), CH_2Cl_2 (4.2 mL), $Rh_2(oct)_4$ (3.3 mg, 4.2 μmol), THF (4.2 mL), KOBu-*t* (35.7 mg, 0.318 mmol) and 4-nitrobenzaldehyde (62.6 mg, 0.424 mmol). The HWE was performed at 0 °C. Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound*s as mixture of (*Z*) and (*E*) isomers (***Z*-185**:***E*-185** 1:1) (42 mg, 68%).

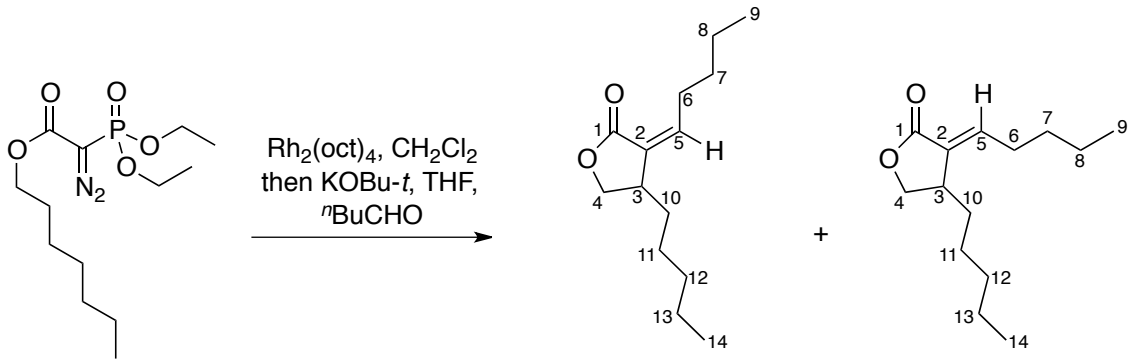
Small quantities of each compound were isolated separately for characterisation purposes.

Data for ***Z*-185**; Yellow oil; R_f 0.46 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2928m, 2857m, 1752s, 1651w, 1597m, 1518s, 1466w, 1378w, 1344s, 1175s, 1112w; δ_H (400 MHz, $CDCl_3$) 0.91 (3 H, t, J = 7.0, H-14), 1.25–1.45 (6 H, m, H-11,12,13), 1.57–1.68 (1 H, m, H-10), 1.73–1.82 (1 H, m, H-10), 3.15–3.22 (1 H, m, H-3), 4.09 (1 H, dd, J = 8.9, J = 5.1, H-4), 4.52 (1 H, dd, J = 8.9, J = 7.7, H-4), 6.93 (1 H, d, J = 2.2, H-5), 7.89 (2 H, d, J = 8.8, H-7), 8.21 (2 H, d, J = 8.8, H-8); δ_C (100 MHz, $CDCl_3$) 14.0 (C-14), 22.5 (C-13), 26.0 (C-11), 31.7 (C-12), 34.1 (C-10), 42.0 (C-3), 70.8 (C-4), 123.2 (C-8), 131.1 (C-7), 133.0 (C-2), 136.1 (C-5), 139.7 (C-6), 147.6 (C-9), 168.6 (C-1);

HRMS (ESI^+): Found: 312.1210; $C_{16}H_{19}NNaO_4$ (MNa^+) Requires 312.1206 (–0.6 ppm error), Found: 290.1392; $C_{16}H_{20}NO_4$ (MH^+) Requires 290.1387 (–1.6 ppm error).

Data for ***E*-185**; Pale yellow solid; R_f 0.41 (4:1 hexane:EtOAc); m.p. 114–117 °C; ν_{max} (thin film)/cm^{-1} 2929m, 2858m, 1754s, 1598m, 1520s, 1344s, 1225m, 1183s, 1112w; δ_H (400 MHz, $CDCl_3$) 0.86 (3 H, t, *J* = 7.0, H-14), 1.18–1.42 (6 H, m, H-11,12,13), 1.50–1.67 (2 H, m, H-10), 3.53–3.60 (1 H, m, H-3), 4.28 (1 H, dd, *J* = 9.1, *J* = 2.0, H-4), 4.45 (1 H, ddd, *J* = 9.1, *J* = 7.0, *J* = 0.7, H-4), 7.56 (1 H, d, *J* = 2.1, H-5), 7.67 (2 H, d, *J* = 8.8, H-7), 8.29 (2 H, d, *J* = 8.8, H-8); δ_C (100 MHz, $CDCl_3$) 13.0 (C-14), 22.4 (C-13), 26.4 (C-11), 31.4 (C-12), 32.4 (C-10), 38.1 (C-3), 70.7 (C-4), 124.1 (C-8), 130.3 (C-7), 133.4 (C-2), 133.8 (C-5), 140.3 (C-6), 147.8 (C-9), 171.6 (C-1); HRMS (ESI^+): Found: 312.1205; $C_{16}H_{19}NNaO_4$ (MNa^+) Requires 312.1206 (0.4 ppm error), Found: 290.1388; $C_{16}H_{20}NO_4$ (MH^+) Requires 290.1387 (–0.3 ppm error).
Lab notebook reference: MGL/05/01

(*SR*,*Z*)-4-Pentyl-3-pentylidenedihydrofuran-2(3*H*)-one (*Z*-186) and (*SR*,*E*)-4-Pentyl-3-pentylidenedihydrofuran-2(3*H*)-one (*E*-186)



134b ***Z*-186** ***E*-186**

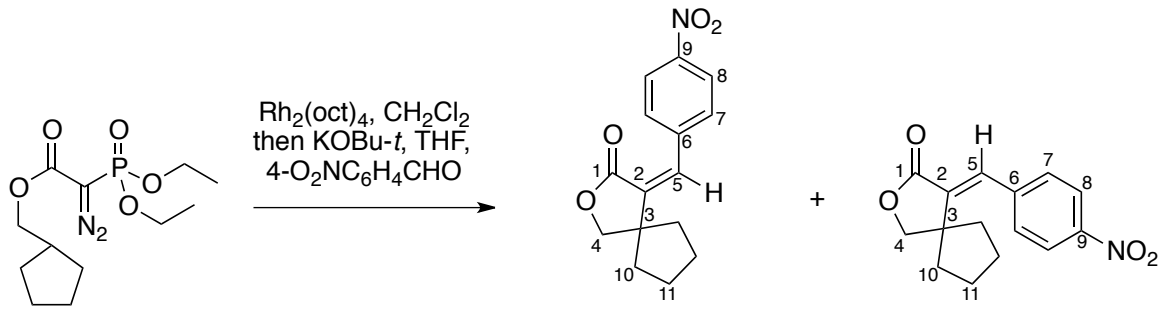
Synthesised using general procedure D with heptyl 2-diazo-2-(diethoxyphosphoryl)acetate **134b** (67 mg, 0.209 mmol), CH_2Cl_2 (4.2 mL), $Rh_2(oct)_4$ (3.3 mg, 4.2 μmol), THF (4.2 mL), KOBu-*t* (35.2 mg, 0.314 mmol) and valeraldehyde (45.0 μL, 0.418 mmol). The HWE was performed at RT. Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound*s as mixture of (*Z*) and (*E*) isomers (***Z*-186**:***E*-186** 2.7:1) (36 mg, 77%).
Small quantities of each compound were isolated separately for characterisation purposes.

Data for ***Z*-186**; Colourless oil; R_f 0.75 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2957s, 2928s, 2858s, 1754s, 1668m, 1466m, 1378m, 1185m, 1127s, 1027s; δ_H (400 MHz, $CDCl_3$) 0.87–0.92 (6 H, m, H-9,14), 1.24–1.49 (11 H, m, H-7,8,10,11,12,13), 1.56–1.65 (1 H, m, H-10), 2.69–2.75 (2 H, m, H-6), 2.88–2.97 (1 H, m, H-3), 3.92 (1 H, dd, *J* = 8.8, *J* = 5.3, H-4), 4.37 (1 H, dd, *J* = 8.8, *J* =

7.9, H-4), 6.12 (1 H, td, J = 7.7, J = 1.6, H-5); δ_C (100 MHz, $CDCl_3$) 13.9 (C-9/14), 14.0 (C-9/14), 22.3 (C-8), 22.5 (C-13), 25.9 (C-11), 27.1 (C-6), 31.3 (C-7), 31.7 (C-12), 34.2 (C-10), 40.1 (C-3), 70.8 (C-4), 128.3 (C-2), 144.1 (C-5), 170.5 (C-1); HRMS (ESI^+): Found: 247.1670; $C_{14}H_{24}NaO_2$ (MNa^+) Requires 247.1669 (−0.7 ppm error), Found: 225.1857; $C_{14}H_{25}O_2$ (MH^+) Requires 225.1849 (−3.6 ppm error).

Data for ***E*-186**; Colourless oil; R_f 0.66 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2961s, 2930s, 2859m, 1760s, 1676m, 1466m, 1380w, 1193m, 1021m; δ_H (400 MHz, $CDCl_3$) 0.87–0.94 (6 H, m, H-9,14), 1.22–1.57 (12 H, m, H-7,8,10,11,12,13), 2.15–2.28 (2 H, m, H-6), 3.04–3.10 (1 H, m, H-3), 4.12 (1 H, dd, J = 9.1, J = 2.2, H-4), 4.31 (1 H, dd, J = 9.1, J = 7.3, H-4), 6.73 (1 H, td, J = 7.7, J = 2.0, H-5); δ_C (100 MHz, $CDCl_3$) 13.8 (C-9/14), 14.0 (C-9/14), [22.4, 22.5, 26.1, 29.4, 30.7, 31.7, 34.2 (C-6,7,8,10,11,12,13)], 37.1 (C-3), 70.8 (C-4), 129.8 (C-2), 141.5 (C-5), 171.7 (C-1); HRMS (ESI^+): Found: 247.1666; $C_{14}H_{24}NaO_2$ (MNa^+) Requires 247.1669 (1.1 ppm error), Found: 225.1851; $C_{14}H_{25}O_2$ (MH^+) Requires 225.1849 (−1.0 ppm error).
Lab notebook reference: MGL/05/02

(*SR*,*Z*)-4-(4-Nitrobenzylidene)-2-oxaspiro[4.4]nonan-3-one (*Z*-187) and (*SR*,*E*)-4-(4-Nitrobenzylidene)-2-oxaspiro[4.4]nonan-3-one (*E*-187)



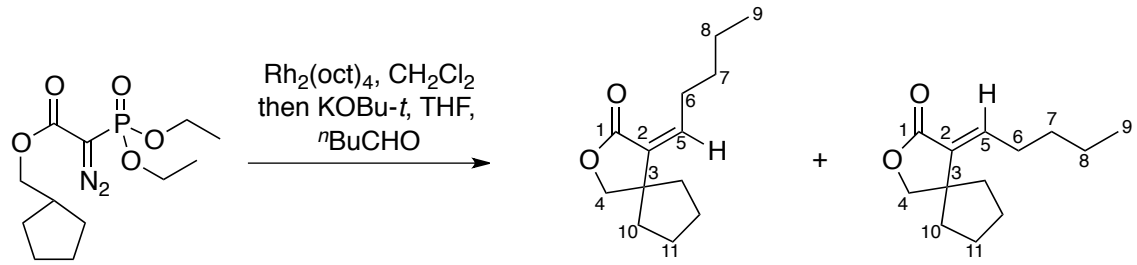
143b ***Z*-187** ***E*-187**

Synthesised using general procedure D with cyclopentylmethyl 2-diazo-2-(diethoxyphosphoryl)acetate **143b** (61 mg, 0.200 mmol), CH_2Cl_2 (4.0 mL), $Rh_2(oct)_4$ (3.1 mg, 4.0 μmol), THF (4.0 mL), KOBu-*t* (33.7 mg, 0.300 mmol) and 4-nitrobenzaldehyde (60.5 mg, 0.400 mmol). The HWE was performed at 0 °C. Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compounds* as an inseparable mixture of (*Z*) and (*E*) isomers (***Z*-187**:***E*-187** 1:1.4), as a white solid (30 mg, 55%); R_f 0.32 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2959w, 2874w, 1755s, 1646w, 1597m, 1518s, 1492w, 1453w, 1344s, 1257w, 1227w, 1201w, 1160m, 1096m, 1023m, 910w, 851m; δ_H (400 MHz, $CDCl_3$) 1.61–1.96 (16 H, m, H-10*E* and *Z*,11*E* and *Z*), 4.04 (3 H, s, H-4*E*), 4.16 (3 H, s, H-4*Z*), 6.87 (1 H, s, H-5*Z*), 7.52 (2 H, dd, J = 8.9, J = 0.6,

H-7*E*), 7.65 (1 H, s, H-5*E*), 7.86 (2 H, dd, *J* = 8.9, *J* = 0.5, H-7*Z*), 8.19 (2 H, d, *J* = 8.9, H-8*Z*), 8.25 (2 H, d, *J* = 8.9, H-8*E*); δ_C (100 MHz, $CDCl_3$) 24.6 (C-11*E*/*Z*), 25.3 (C-11*E*/*Z*), 37.1 (C-10*E*), 39.3 (C-10*Z*), 50.3 (C-3*E*), 52.5 (C-3*Z*), 77.5 (C-4*Z*), 79.4 (C-4*E*), 123.1 (C-8*Z*), 123.5 (C-8*E*), 130.0 (C-7*E*), 131.1 (C-7*Z*), 134.0 (C-5*Z*), 134.3 (C-5*E*), 136.6 (C-2*E*), 137.3 (C-2*Z*), 139.8 (C-6*Z*), 140.9 (C-6*E*), 147.5 (C-9*E*/*Z*), 147.6 (C-9*E*/*Z*), 168.9 (C-1*Z*), 171.9 (C-1*E*); HRMS (ESI^+): Found: 296.0899; $C_{15}H_{15}NNaO_4$ (MNa^+) Requires 296.0893 (–1.8 ppm error), Found: 274.1082; $C_{15}H_{16}NO_4$ (MH^+) Requires 274.1074 (–2.9 ppm error).

Lab notebook reference: MGL/05/03

(*SR*,*Z*)-4-Pentylidene-2-oxaspiro[4.4]nonan-3-one (*Z*-188) and (*SR*,*E*)-4-Pentylidene-2-oxaspiro[4.4]nonan-3-one (*E*-188)



143b **Z-188** **E-188**

Synthesised using general procedure D with cyclopentylmethyl 2-diazo-2-(diethoxyphosphoryl)acetate **143b** (63 mg, 0.207 mmol), CH_2Cl_2 (4.2 mL), $Rh_2(oct)_4$ (3.2 mg, 4.1 μmol), THF (4.2 mL), KOBu-*t* (34.8 mg, 0.311 mmol) and valeraldehyde (44.0 μL, 0.414 mmol). The HWE was performed at reflux. Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound*s as mixture of (*Z*) and (*E*) isomers (***Z*-188**:***E*-188** 2.4:1) (14 mg, 32%).

Small quantities of each compound were isolated separately for characterisation purposes.

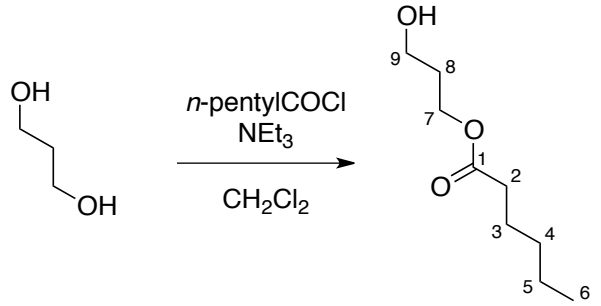
Data for ***Z*-188**; Colourless oil; R_f 0.67 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2956m, 2929w, 2871m, 1752s, 1665m, 1453m, 1370m, 1164w, 1128w, 1105m, 1025s; δ_H (400 MHz, $CDCl_3$) 0.91 (3 H, t, *J* = 7.2, H-9), 1.24–1.46 (4 H, m, H-7,8), 1.62–1.81 (8 H, m, H-10,11), 2.72 (2 H, app. q, *J* = 7.4, H-6), 4.02 (2 H, s, H-4), 6.08 (1 H, t, *J* = 7.7, H-5); δ_C (100 MHz, $CDCl_3$) 13.9 (C-9), 22.3 (C-7/8), 24.5 (C-10/11), 26.9 (C-6), 31.4 (C-7/8), 39.2 (C-10/11), 50.8 (C-3), 77.7 (C-4), 132.8 (C-2), 141.9 (C-5), 170.1 (C-1); HRMS (ESI^+): Found: 231.1354; $C_{13}H_{20}NaO_2$ (MNa^+) Requires 231.1356 (0.6 ppm error), Found: 209.1536; $C_{13}H_{21}O_2$ (MH^+) Requires 209.1536 (–0.2 ppm error).

Data for ***E*-188**; Colourless oil; R_f 0.54 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2956s, 2934s, 2872s, 1758s, 1668m, 1455m, 1383w, 1362w, 1164w, 1028s; δ_H (400 MHz, $CDCl_3$) 0.93 (3 H, t, *J* = 7.1, H-9), 1.20–2.00 (12 H, m, H-7,8,10,11), 2.29 (2 H, app. q, *J* = 7.5, H-6), 4.00 (2 H, s, H-4), 6.70 (1 H, t, *J* = 8.0, H-5); δ_C (100 MHz, $CDCl_3$) 13.8 (C-9), 22.5 (C-7/8), 25.5 (C-10/11), 27.7 (C-6), 31.0 (C-7/8), 38.6 (C-10/11), 48.8 (C-3), 79.8 (C-4), 132.5 (C-2), 141.6 (C-5), 171.4 (C-1); HRMS (ESI$^+$): Found: 231.1352; $C_{13}H_{20}NaO_2$ (MNa^+) Requires 231.1356 (1.4 ppm error), Found: 209.1537; $C_{13}H_{21}O_2$ (MH^+) Requires 209.1536 (–0.3 ppm error).

Lab notebook reference: MGL/05/37

5.2.1.3. Cedarmycins A and B

3-Hydroxypropyl hexanoate (197)



196 **197**

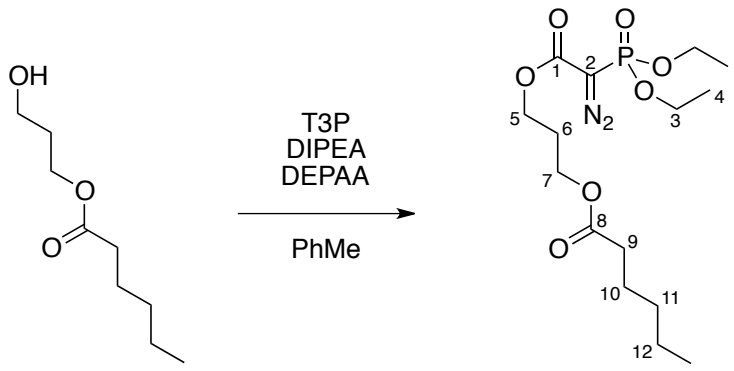
Prepared according to the literature procedure.[168]

To a solution of 1,3-propanediol (10.8 mL, 150 mmol) and triethylamine (31.4 mL, 225 mmol) in CH_2Cl_2 (100 mL) was added a solution of hexanoyl chloride (14.0 mL, 100 mmol) in CH_2Cl_2 (50 mL) over 2 h. The solution was stirred at RT for a further 4 h and then concentrated *in vacuo*. Purification by column chromatography (2:1 petrol:EtOAc) afforded the title compound **197** as a colourless liquid (10.3 g, 59%); R_f 0.37 (2:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 3426, 2957, 2931, 2873, 1734, 1247, 1171, 1052; δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, t, *J* = 7.0, H-6), 1.25–1.37 (4 H, m, H-4,5), 1.59–1.66 (2 H, m, H-3), 1.87 (2 H, app. quin., *J* = 6.1, H-8), 1.93 (1 H, br t, *J* = 5.7, O*H*), 2.31 (2 H, t, *J* = 7.6, H-2), 3.69 (2 H, app. q, *J* = 5.8, H-9), 4.24 (2 H, t, *J* = 6.1, H-7); δ_C (100 MHz, $CDCl_3$) 13.9, 22.3, 24.6, 31.3, 31.8, 34.3, 59.2, 61.1, 174.4; HRMS (ESI$^+$): Found: 197.1142; $C_9H_{18}NaO_3$ (MNa^+) Requires 197.1148 (2.9 ppm error).

Lab notebook reference: MGL/03/63

Obtained data in accord with reported literature.[168]

3-(2-(Diethoxyphosphoryl)acetoxy)propyl hexanoate (198)

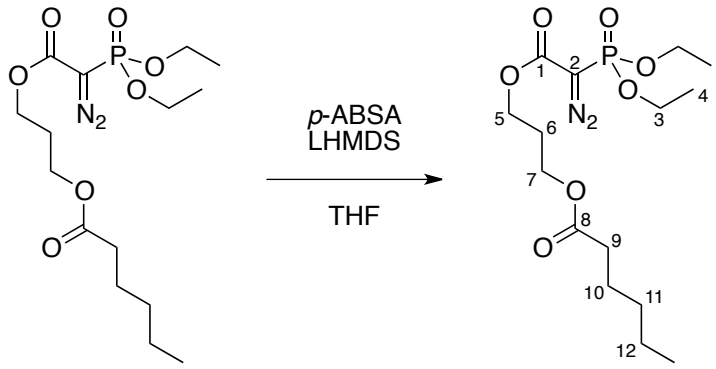


197 **198**

Synthesised using general procedure A with 3-hydroxypropyl hexanoate **197** (1.74 g, 10.0 mmol), toluene (50 mL), DEPAA (1.69 mL, 10.5 mmol), DIPEA (4.53 mL, 26.0 mmol) and T3P (8.27 g, 13.0 mmol, 50% w/w solution in EtOAc) affording the *title compound* **198** as an orange oil (3.55 g, 100%). No further purification was required; R_f 0.30 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2960w, 2929w, 2866w, 1736s, 1459w, 1393w, 1268s, 1170m, 1114m, 1024s, 970m; δ_H (400 MHz, $CDCl_3$) 0.88 (3 H, t, *J* = 7.0, H-13), 1.23–1.36 (4 H, m, H-11,12), 1.33 (6 H, td, *J* = 7.1, *J* = 0.5, H-4), 1.58–1.64 (2 H, m, H-10), 1.98 (2 H, app. quin., *J* = 6.3, H-6), 2.28 (2 H, t, *J* = 7.6, H-9), 2.96 (2 H, d, *J* = 21.6, H-2), 4.12–4.23 (8 H, m, H-3,5,7); δ_C (100 MHz, $CDCl_3$) 13.9 (C-13), 16.3 (d, *J* = 6.2, C-4), 22.3 (C-12), 24.6 (C-10), 27.9 (C-6), 31.2 (C-11), 34.1 (C-9), 34.2 (d, *J* = 134.2, C-2), 60.5 (C-7), 62.1 (C-5), 62.7 (d, *J* = 6.2, C-3), 165.7 (d, *J* = 6.2, C-1), 173.7 (C-8); δ_P (162 MHz, $CDCl_3$) 20.2; HRMS (ESI$^+$): Found: 375.1525; $C_{15}H_{29}NaO_7P$ (MNa^+) Requires 375.1543 (4.7 ppm error), Found: 353.1712; $C_{15}H_{30}O_7P$ (MH^+) Requires 353.1724 (3.3 ppm error).

Lab notebook reference: MGL/03/65

3-(2-Diazo-2-(diethoxyphosphoryl)acetoxy)propyl hexanoate (199)

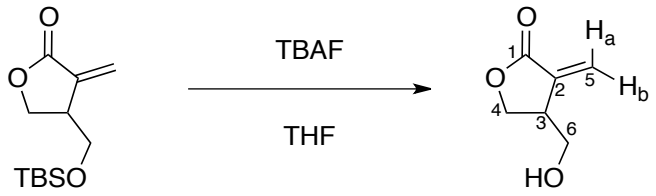


198 **199**

Synthesised using general procedure B with 3-(2-(diethoxyphosphoryl)acetoxy)propyl hexanoate **198** (1.76 g, 5.00 mmol), THF (25 mL), LHMDS (6.00 mL, 6.00 mmol, 1.0 M solution in THF) and *p*-ABSA (1.44 g, 6.00 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **199** as a pale yellow oil (1.32 g, 70%); R_f 0.50 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2960m, 2933m, 2873w, 2127s, 1735w, 1703s, 1458w, 1392w, 1276s, 1214w, 1167m, 1097w, 1016s, 976m; δ_H (400 MHz, $CDCl_3$) 0.82 (3 H, t, *J* = 7.0, H-13), 1.18–1.30 (4 H, m, H-11,12), 1.29 (6 H, td, *J* = 7.1, *J* = 0.8, H-4), 1.51–1.58 (2 H, m, H-10), 1.93 (2 H, app. quin., *J* = 6.3, H-6), 2.22 (2 H, t, *J* = 7.6, H-9), 4.04–4.23 (8 H, m, H-3,5,7); δ_C (100 MHz, $CDCl_3$) 13.7 (C-13), 16.0 (d, *J* = 6.9, C-4), 22.1 (C-12), 24.4 (C-10), 27.9 (C-6), 31.1 (C-11), 34.0 (C-9), 53.8 (d, *J* = 227.5, C-2), 60.2 (C-7), 62.0 (C-5), 63.5 (d, *J* = 5.6, C-3), 163.1 (d, *J* = 12.0, C-1), 173.5 (C-8); δ_P (162 MHz, $CDCl_3$) 10.5; HRMS (ESI$^+$): Found: 401.1430; $C_{15}H_{27}N_2NaO_7P$ (MNa^+) Requires 401.1448 (4.5 ppm error), Found: 379.1611; $C_{15}H_{28}N_2O_7P$ (MH^+) Requires 379.1629 (4.7 ppm error).

Lab notebook reference: MGL/03/75

(*SR*)-4-(Hydroxymethyl)-3-methylenedihydrofuran-2(3*H*)-one (194)



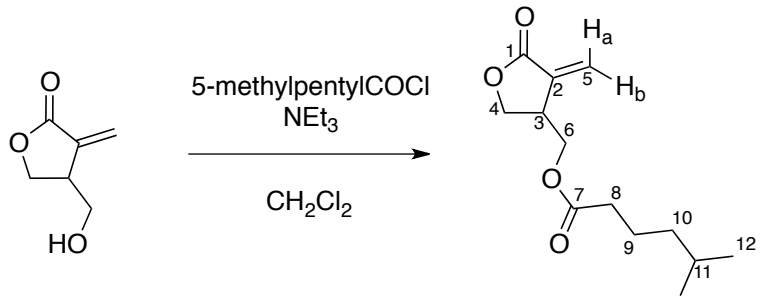
138c **194**

To a solution of 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methylenedihydrofuran-2(3*H*)-one **138c** (29 mg, 0.120 mmol) in THF (0.6 mL) cooled to 0 °C under an atmosphere of argon, was added TBAF (144 μL, 0.144, 1.0 M in THF) dropwise. The solution was stirred at 0 °C for 1 h then quenched with sat. aq. NH_4Cl (10 mL) and extracted with diethyl ether (2 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (1:2 hexane:EtOAc) afforded the *title compound* **194** as a pale yellow oil (12 mg, 78%); R_f 0.29 (1:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3417br, 2924m, 1756s, 1407w, 1268m, 1120m, 1017m, 816m; δ_H (400 MHz, $CDCl_3$) 3.26–3.34 (1 H, m, H-3), 3.76–3.78 (2 H, m, H-6), 4.27 (1 H, dd, J = 9.4, J = 4.5, H-4), 4.47 (1 H, dd, J = 9.4, J = 8.2, H-4), 5.75 (1 H, d, J = 2.3, H-5b), 6.36 (1 H, d, J = 2.6, H-5a); δ_C (100 MHz, $CDCl_3$) 40.9 (C-3), 64.1 (C-6), 68.2 (C-4), 123.6 (C-5), 135.2 (C-2), 170.4 (C-1); HRMS (ESI^+): Found: 151.0360; $C_6H_8NaO_3$ (MNa^+) Requires 151.0366 (3.5 ppm error).

Lab notebook reference: MGL/04/22

Obtain data in accord with reported literature.[100]

Cedarmycin A (189)



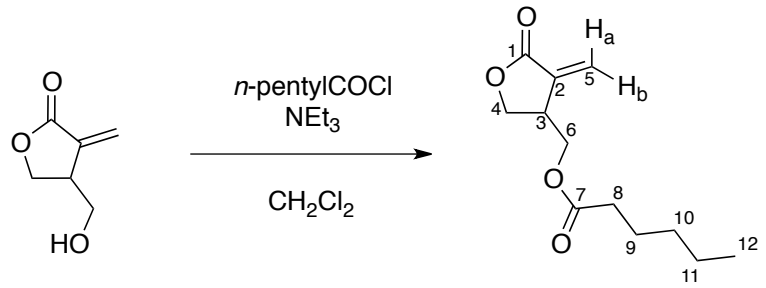
194 cedarmycin A, **189**

To a solution of 4-(hydroxymethyl)-3-methylenedihydrofuran-2(3*H*)-one **194** (5 mg, 0.039 mmol) and triethylamine (8.2 μL, 0.059 mmol) in CH_2Cl_2 (0.20 mL) was added 5-methylhexanoyl chloride (10 μL). After 2 h additional 5-methylhexanoyl chloride (10 μL) was added and stirred for 16 h. The solution was quenched with sat. aq. NH_4Cl (1 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **189** as a colourless oil (6 mg, 85%); R_f 0.75 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2956m, 2871w, 1768s, 1739s, 1468w, 1252w, 1170m, 1115m, 1019w; δ_H (400 MHz, $CDCl_3$) 0.88 (6 H, d, J = 6.6, H-12), 1.15–1.21 (2 H, m, H-10), 1.51–1.65 (3 H, m, H-9,11), 2.31 (2 H, t, J = 7.6, H-8), 3.39–3.47 (1 H, m, H-3), 4.16 (1 H, dd, J = 11.2, J = 7.3, H-6), 4.18 (1 H, dd, J = 9.4, J = 4.9, H-4), 4.25 (1 H, dd, J = 11.2, J = 5.6, H-6), 4.48 (1 H, dd, J = 9.4, J = 8.4, H-4), 5.76 (1 H, d, J = 2.3, H-5b), 6.39 (1 H, d, J = 2.7, H-5a); δ_C (100 MHz, $CDCl_3$) 22.4 (C-12), 22.7 (C-9), 27.7 (C-11), 34.3 (C-8), 38.0 (C-3), 38.3 (C-10), 64.7 (C-6), 68.1 (C-4), 124.2 (C-5), 134.5 (C-2), 169.8 (C-1), 173.5 (C-7); HRMS (ESI^+): Found: 263.1251; $C_{13}H_{20}NaO_4$ (MNa^+) Requires 263.1254 (1.2 ppm error).

Lab notebook reference: MGL/04/24

Obtain data in accord with reported literature.[98,100]

Cedarmycin B (190)



194 cedarmycin B, **190**

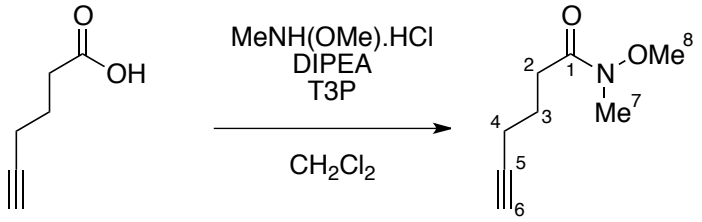
To a solution of 4-(hydroxymethyl)-3-methylenedihydrofuran-2(3*H*)-one **194** (3 mg, 0.023 mmol) and triethylamine (4.8 μL, 0.035 mmol) in CH_2Cl_2 (0.12 mL) was added hexanoyl chloride (3.9 μL, 0.035 mmol). The solution was stirred at RT for 10 mins then quenched with sat. aq. NH_4Cl (1 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **190** as a colourless oil (3 mg, 57%); R_f 0.76 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2959m, 2936m, 2864w, 1768s, 1738s, 1270w, 1246w, 1168m, 1115m, 1018w; δ_H (400 MHz, $CDCl_3$) 0.90 (3 H, t, *J* = 7.0, H-12), 1.25–1.36 (4 H, m, H-10,11), 1.62 (2 H, app. quin., *J* = 7.5, H-9), 2.32 (2 H, t, *J* = 7.5, H-8), 3.39–3.47 (1 H, m, H-3), 4.16 (1 H, dd, *J* = 11.2, *J* = 7.3, H-6), 4.18 (1 H, dd, *J* = 9.4, *J* = 4.9, H-4), 4.25 (1 H, dd, *J* = 11.2, *J* = 5.6, H-6), 4.48 (1 H, dd, *J* = 9.4, *J* = 8.4, H-4), 5.76 (1 H, d, *J* = 2.4, H-5b), 6.38 (1 H, d, *J* = 2.7, H-5a); δ_C (100 MHz, $CDCl_3$) 13.9 (C-12), 22.3 (C-11), 24.5 (C-9), 31.2 (C-10), 34.0 (C-8), 38.1 (C-3), 64.7 (C-6), 68.1 (C-4), 124.1 (C-5), 134.5 (C-2), 169.8 (C-1), 173.5 (C-7); HRMS (ESI^+): Found: 249.1099; $C_{12}H_{18}NaO_4$ (MNa^+) Requires 249.1097 (−0.8 ppm error).

Lab notebook reference: MGL/04/11

Obtain data in accord with reported literature.[98,100]

5.2.1.4. Staphyloccous aureus inhibitor

_N_-Methoxy-_N_-methylhex-5-ynamide (211)



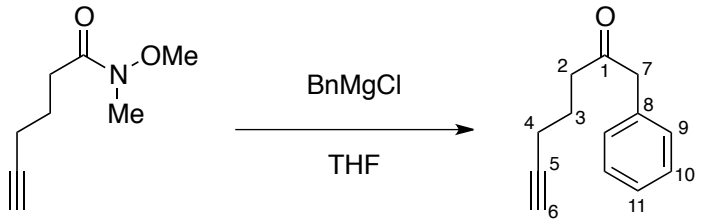
210 **211**

To a solution of 5-hexynoic acid **210** (2.24 g, 20.0 mmol) in CH_2Cl_2 (50 mL) was added sequentially *N*,*O*-dimethylhydroxylamine hydrochloride (2.15 g, 22.0 mmol) and DIPEA (10.5 mL, 60.0 mmol) and T3P (19.1 g, 30.0 mmol, 50% w/w solution in EtOAc). The solution was stirred at RT for 1 h. The reaction was quenched with 10% aq. HCl (25 mL). The phases were separated and the organic washed with 2M NaOH (25 mL) and brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* **211** as colourless oil (3.00 g, 97%). No further purification was required; R_f 0.70 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 3291m, 2940m, 2117w, 1656s, 1417m, 1386m, 1179m, 1108m, 994s; δ_H (400 MHz, $CDCl_3$) 1.81 (2 H, app. quin., J = 7.2, H-3), 1.93 (1 H, t, J = 2.7, H-6), 2.24 (2 H, td, J = 6.9, J = 2.7, H-4), 2.53 (2 H, t, J = 7.3, H-2), 3.14 (3 H, s, H-7) 3.66 (3 H , s, H-8); δ_C (100 MHz, $CDCl_3$) 17.8 (C-4), 23.0 (C-3), 30.3 (C-2), 32.0 (C-7), 61.1 (C-8), 68.8 (C-6), 83.7 (C-5), 173.7 (C-1); HRMS (ESI^+): Found: 178.0847; $C_8H_{13}NNaO_2$ (MNa^+) Requires 178.0838 (−5.0 ppm error), Found: 156.1021; $C_8H_{14}NO_2$ (MH^+) Requires 156.1019 (−1.0 ppm error).

Lab notebook reference: MGL/04/50

Obtained data in accord with reported literature.[169]

1-Phenylhept-6-yn-2-one (212)

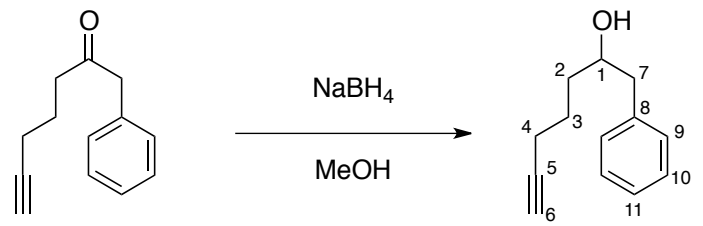


211 **212**

To a solution of *N*-methoxy-*N*-methylhex-5-ynamide **211** (1.24 g, 8.00 mmol) in THF (40 mL) cooled to −78 °C was added was added benzylmagnesium chloride (8.0 mL, 16.0 mmol, 2 M in THF). The solution was warmed to 0 °C and stirred for 30 mins then quenched with sat. aq. NH_4Cl (50 mL). The phases were separated and the aqueous extracted with diethyl ether (3 × 50 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (8:1 petrol:EtOAc) afforded the *title compound* **212** as a colourless oil (860 mg, 58%); R_f 0.55 (8:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 3292m, 2940m, 2120w, 1709s, 1496m, 1454m, 1366m, 1092m; δ_H (400 MHz, $CDCl_3$) 1.77 (2 H, app. quin., *J* = 7.0, H-3), 1.93 (1 H, t, *J* = 2.7, H-6), 2.19 (2 H, td, *J* = 6.9, *J* = 2.7, H-4), 2.61 (2 H, t, *J* = 7.2, H-2), 3.70 (2 H, s, H-7), 7.19–7.22 (2 H, m, H-9), 7.25–7.29 (1 H, m, H-11), 7.31–7.33 (2 H, m, H-10); δ_C (100 MHz, $CDCl_3$) 17.6 (C-4), 22.2 (C-3), 40.3 (C-2), 50.2 (C-7), 69.0 (C-6), 83.5 (C-5), 127.0 (C-11), 128.7 (C-10), 129.4 (C-9), 134.1 (C-8), 207.7 (C-1); HRMS (ESI$^+$): Found: 209.0932; $C_{13}H_{14}NaO$ (MNa^+) Requires 209.0937 (2.6 ppm error), Found: 187.1110; $C_{13}H_{15}O$ (MH^+) Requires 187.1117 (3.9 ppm error).

Lab notebook reference: MGL/04/51

1-Phenylhept-6-yn-2-ol (209)



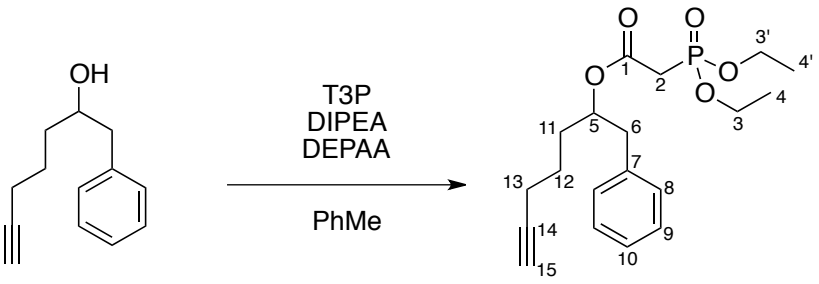
212 **209**

To a solution of 1-phenylhept-6-yn-2-one **212** (840 mg, 4.51 mmol) in MeOH (21 mL) cooled to 0 °C under an atmosphere of argon, was added $NaBH_4$ (512 mg, 13.5 mmol) in 4 portions over 15 mins. The solution was stirred at RT for 3 h then quenched with sat. aq. $NaHCO_3$ (4 mL) and

concentrated *in vacuo*. The resulting white residue was dissolved in CH_2Cl_2 (15 mL) and water (15 mL). The organic was separated and the aqueous extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* **209** as a colourless oil (852 mg, 100%). No further purification was required; R_f 0.48 (4:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 3406br, 3296s, 3028w, 2937s, 2871w, 2120w, 1496m, 1454m, 1084m, 1031w, 998w, 747m, 701s; δ_H (400 MHz, $CDCl_3$) 1.52 (1 H, s, O*H*), 1.56–1.81 (4 H, m, H-2,3), 1.96 (1 H, t, *J* = 2.7, H-6), 2.22–2.26 (2 H, m, H-4), 2.66 (1 H, dd, *J* = 13.6, *J* = 8.6, H-7), 2.85 (1 H, dd, *J* = 13.6, *J* = 4.2, H-7), 7.20–7.26 (3 H, m, H-9,11), 7.30–7.35 (2 H, m, H-10); δ_C (100 MHz, $CDCl_3$) 18.4 (C-4), 24.7 (C-3), 35.7 (C-2), 44.1 (C-7), 68.5 (C-6), 72.2 (C-1), 84.3 (C-5), 126.5 (C-11), 128.6 (C-10), 129.4 (C-9), 138.3 (C-8); HRMS (ESI$^+$): Found: 211.1093; $C_{13}H_{16}NaO$ (MNa^+) Requires 211.1093 (0.0 ppm error).

Lab notebook reference: MGL/04/52

1-Phenylhept-6-yn-2-yl 2-(diethoxyphosphoryl)acetate (213)

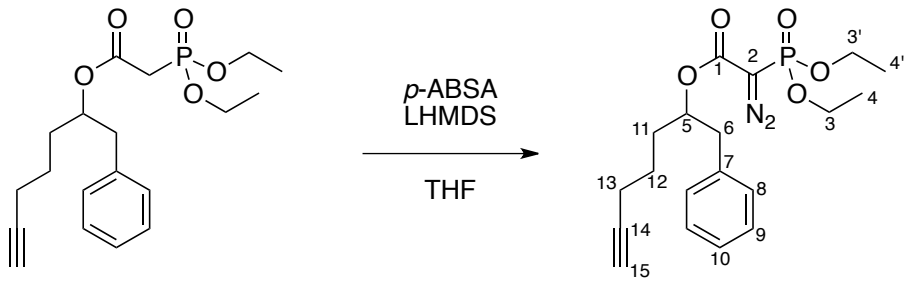


209 **213**

Synthesised using general procedure A with 1-phenylhept-6-yn-2-ol **209** (846 mg, 4.49 mmol), toluene (22.5 mL), DEPAA (0.76 mL, 4.72 mmol), DIPEA (2.03 mL, 11.7 mmol) and T3P (3.71 g, 5.84 mmol, 50% w/w solution in EtOAc) affording the *title compound* **213** as a yellow oil (1.60 g, 97%). No further purification was required; R_f 0.29 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 3291w, 2983w, 2932w, 1732s, 1496w, 1455w, 1393w, 1264s, 1164w, 1114w, 1050w, 1023s, 970s; δ_H (400 MHz, $CDCl_3$) 1.30 (3 H, td, *J* = 7.1, *J* = 0.4, H-4/4'), 1.31 (3 H, td, *J* = 7.1, *J* = 0.4, H-4/4'), 1.46–1.71 (4 H, m, H-11,12), 1.89 (1 H, t, *J* = 2.7, H-15), 2.13–2.16 (2 H, m, H-13), 2.77–2.96 (4 H, m, H-2,6), 4.08–4.16 (4 H, m, H-3,3'), 5.08–5.14 (1 H, m, H-5), 7.16–7.21 (3 H, m, H-8,10), 7.24-7.28 (2 H, m, H-9); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.6, C-4), 18.0 (C-13), 24.0 (C-12), 32.2 (C-11), 34.3 (d, *J* = 134.2, C-2), 40.3 (C-6), 62.5 (d, *J* = 6.2, C-3), 68.6 (C-15), 75.6 (C-5), 83.6 (C-14), 126.5 (C-10), 128.3 (C-9), 129.3 (C-8), 136.9 (C-7), 165.3 (d, *J* = 6.2, C-1); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI$^+$): Found: 389.1499; $C_{19}H_{27}NaO_5P$ (MNa^+) Requires 389.1488 (–2.7 ppm error), Found: 367.1674; $C_{19}H_{27}O_5P$ (MH^+) Requires 367.1669 (–1.4 ppm error).

Lab notebook reference: MGL/04/53

1-Phenylhept-6-yn-2-yl 2-diazo-2-(diethoxyphosphoryl)acetate (208)

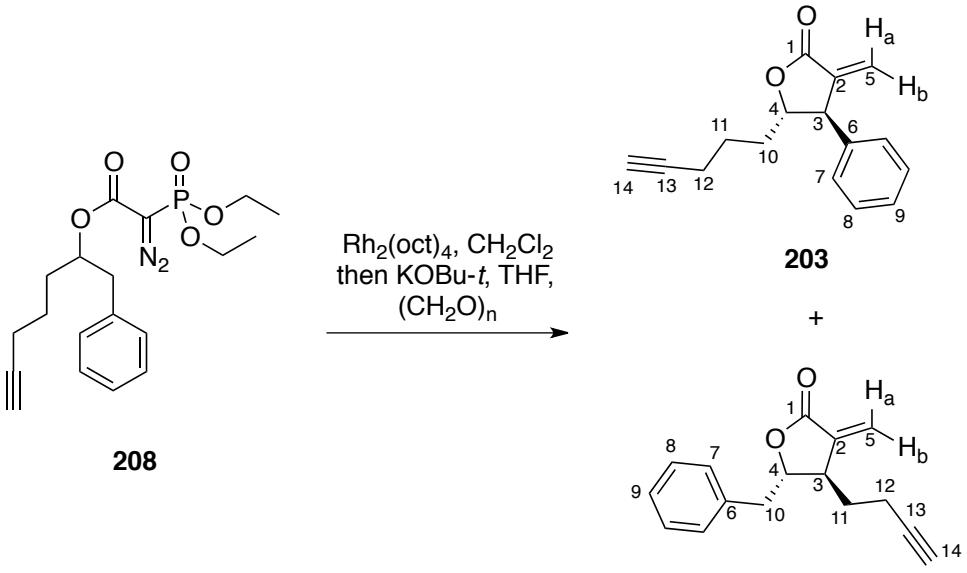


213 **208**

Synthesised using general procedure B with 1-phenylhept-6-yn-2-yl 2-(diethoxyphosphoryl)acetate **213** (1.47 g, 4.00 mmol), THF (20 mL), LHMDS (4.80 mL, 4.80 mmol, 1.0 M solution in THF) and *p*-ABSA (1.15 g, 4.80 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **208** as a yellow oil (1.29 g, 82%); R_f 0.27 (2:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3294w, 2984w, 2934w, 2126s, 1698s, 1455w, 1392w, 1366w, 1271s, 1216w, 1164w, 1121w, 1016s, 976s; δ_H (400 MHz, $CDCl_3$) 1.31 (3 H, td, *J* = 7.1, *J* = 0.7, H-4/4'), 1.33 (3 H, td, *J* = 7.1, *J* = 0.7, H-4/4'), 1.52–1.79 (4 H, m, H-11,12), 1.94 (1 H, t, *J* = 2.6, H-15), 2.20 (2 H, td, *J* = 7.0, *J* = 2.6, H-13), 2.85–2.95 (2 H, m, H-6), 3.96–4.22 (4 H, m, H-3,3'), 5.19–5.25 (1 H, m, H-5), 7.19–7.31 (5 H, m, H-8,9,10); δ_C (100 MHz, $CDCl_3$) 15.9 (d, *J* = 6.8, C-4/4'), 16.0 (d, *J* = 6.8, C-4/4'), 17.9 (C-13), 24.0 (C-12), 32.5 (C-11), 40.4 (C-6), 53.5 (d, *J* = 226.6, C-2), 63.3 (d, *J* = 5.7, C-3/3'), 63.4 (d, *J* = 5.7, C-3/3'), 68.7 (C-15), 75.6 (C-5), 83.4 (C-14), 126.4 (C-10), 128.2 (C-9), 129.2 (C-8), 136.7 (C-7), 162.7 (d, *J* = 12.0, C-1); δ_P (162 MHz, $CDCl_3$) 10.7; HRMS (ESI$^+$): Found: 415.1398; $C_{19}H_{25}N_2NaO_5P$ (MNa^+) Requires 415.1393 (−1.2 ppm error), Found: 393.1579; $C_{19}H_{26}N_2O_5P$ (MH^+) Requires 393.1574 (−1.3 ppm error).

Lab notebook reference: MGL/04/54

(4*RS*,5*SR*)-3-Methylene-5-(pent-4-yn-1-yl)-4-phenyldihydrofuran-2(3*H*)-one (203) and (4*RS*,5*SR*)-5-Benzyl-4-(but-3-yn-1-yl)-3-methylenedihydrofuran-2(3*H*)-one (214)



Synthesised using general procedure D with 1-phenylhept-6-yn-2-yl 2-diazo-2-(diethoxyphosphoryl)acetate **208** (70 mg, 0.178 mmol), CH_2Cl_2 (3.6 mL), $Rh_2(oct)_4$ (2.8 mg, 3.6 μmol), THF (3.6 mL), KOBu-*t* (30.0 mg, 0.267 mmol) and paraformaldehyde (10.7 mg, 0.356 mmol). Purification by column chromatography (10:1 hexane:EtOAc) afforded the *title compound*s **203** (21 mg, 49%) and **214** (8 mg, 19%) both as a colourless oils.

Data for **203**; R_f 0.52 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3291w, 2928w, 2117w, 1764s, 1455w, 1284w, 1230m, 1132m; δ_H (400 MHz, $CDCl_3$) 1.55–1.65 (1 H, m, H-11), 1.73–1.96 (4 H, m, H-10,11,14), 2.22 (2 H, td, *J* = 6.8, *J* = 2.7, H-12), 3.79 (1 H, app. dt, *J* = 7.5, *J* = 3.2, H-3), 4.40 (1 H, app. td, *J* = 7.9, *J* = 4.1, H-4), 5.40 (1 H, d, *J* = 2.9, H-5b), 6.36 (1 H, d, *J* = 3.3, H-5a), 7.19–7.22 (2 H, m, H-7/8), 7.30–7.35 (1 H, m, H-9), 7.36–7.41 (2 H, m, H-7/8); δ_C (100 MHz, $CDCl_3$) 18.1 (C-12), 24.2 (C-11), 33.6 (C-10), 52.6 (C-3), 69.0 (C-14), 83.4 (C-13), 84.9 (C-4), 123.8 (C-5), 127.9 (C-9), 128.3 (C-7/8), 129.2 (C-7/8), 138.9 (C-6), 140.2 (C-2), 169.6 (C-1); HRMS (ESI$^+$): Found: 263.1038; $C_{16}H_{16}NaO_2$ (MNa^+) Requires 263.1043 (1.7 ppm error), Found: 241.1219; $C_{16}H_{17}O_2$ (MH^+) Requires 241.1223 (1.8 ppm error).
Obtained data in accord with reported literature.[102]

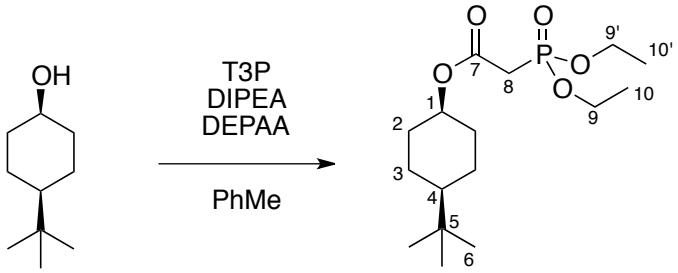
Data for **214**; R_f 0.42 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3288w, 2924m, 2117w, 1761s, 1454w, 1268m, 1135m; δ_H (400 MHz, $CDCl_3$) 1.70–1.76 (2 H, m, H-11), 2.00 (1 H, t, *J* = 2.7, H-14), 2.17–2.23 (2 H, m, H-12), 2.92–3.05 (3 H, m, H-3,10), 4.45–4.49 (1 H, m, H-4), 5.61 (1 H, d,

J = 2.2, H-5b), 6.25 (1 H, d, J = 2.5, H-5a), 7.21–7.36 (5 H, m, H-7,8,9); δ_C (100 MHz, $CDCl_3$) 15.4 (C-12), 32.5 (C-11), 41.7 (C-10), 42.0 (C-3), 69.9 (C-14), 82.4 (C-13), 82.9 (C-4), 123.1 (C-5), 127.1 (C-9), 128.7 (C-8), 129.6 (C-7), 135.4 (C-6), 138.1 (C-2), 169.8 (C-1); HRMS (ESI^+): Found: 263.1043; $C_{16}H_{16}NaO_2$ (MNa^+) Requires 263.1043 (0.0 ppm error), Found: 241.1222; $C_{16}H_{17}O_2$ (MH^+) Requires 241.1223 (0.3 ppm error).

5.2.2. Chapter 3

5.2.2.1. Conformationally restricted systems

syn-4-(_tert_-Butyl)cyclohexyl 2-(diethoxyphosphoryl)acetate (154a)

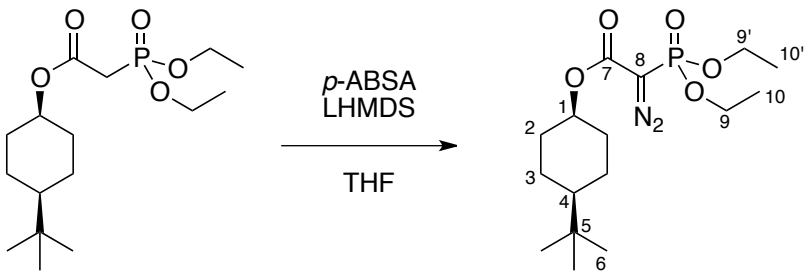


154 **154a**

Synthesised using general procedure A with *syn*-4-(tert-butyl)cyclohexanol **154** (285 mg, 1.82 mmol), toluene (9.3 mL), DEPAA (381 mg, 1.94 mmol), DIPEA (0.84 mL, 4.81 mmol) and T3P (1.53 g, 2.41 mmol, 50% w/w solution in EtOAc) affording the *title compound* **154a** as a yellow oil (575 mg, 94%). No further purification was required; R_f 0.21 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2945s, 1731s, 1446m, 1393m, 1363m, 1267s, 1108s, 1051w, 1022s, 965s; δ_H (400 MHz, $CDCl_3$) 0.84 (9 H, s, H-6), 1.00 (1 H, tt, J = 12.0, J = 3.0), 1.23–1.35 (8 H, m), 1.41–1.50 (2 H, m), 1.55–1.59 (2 H, m), 1.91–1.98 (2 H, m), 2.96 (2 H, d, J = 21.5, H-8), 4.12–4.20 (4 H, m, H-9,9'), 5.05 (1 H, quin., J = 2.8, H-1); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.5, C-10,10'), 21.6 (CH_2), 27.4 (C-6), 30.4 (CH_2), 32.4 (C-5), 34.7 (d, J = 133.4, C-8), 47.5 (C-4), 62.5 (d, J = 6.1, C-9,9'), 70.9 (C-1), 165.3 (d, J = 6.6, C-7); δ_P (162 MHz, $CDCl_3$) 20.9; HRMS (ESI^+): Found: 357.1814; $C_{16}H_{31}NaO_5P$ (MNa^+) Requires 357.1801 (–3.4 ppm error).

Lab notebook reference: MGL/06/62

syn-4-(_tert_-Butyl)cyclohexyl 2-diazo-2-(diethoxyphosphoryl)acetate (154b)

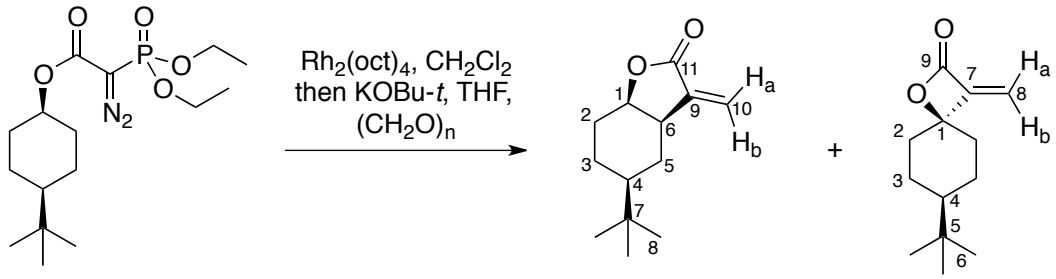


154a **154b**

Synthesised using general procedure B with *syn*-4-(tert-butyl)cyclohexyl 2-(diethoxyphosphoryl)acetate **154a** (540 mg, 1.61 mmol), THF (8.0 mL), LHMDS (1.94 mL, 1.94 mmol, 1.0 M solution in THF) and *p*-ABSA (466 mg, 1.94 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **154b** as a yellow oil (505 mg, 87%); R_f 0.51 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2946s, 2128s, 1694s, 1479m, 1446m, 1361s, 1287s, 1269s, 1104s, 1017s, 975s, 793s, 747s, 590s, 560s; δ_H (400 MHz, $CDCl_3$) 0.83 (9 H, s, H-6), 1.01 (1 H, tt, J = 12.0, J = 3.0), 1.21–1.35 (8 H, m), 1.42–1.52 (2 H, m), 1.55–1.59 (2 H, m), 1.89–1.96 (2 H, m), 4.08–4.24 (4 H, m, H-9,9'), 5.12 (1 H, quin., J = 2.7, H-1); δ_C (100 MHz, $CDCl_3$) 16.1 (d, J = 7.0, C-10,10'), 21.4 (CH_2), 27.3 (C-6), 30.6 (CH_2), 32.4 (C-5), 47.3 (C-4), 54.1 (d, J = 228.0, C-8), 63.3 (d, J = 6.0, C-9,9'), 71.2 (C-1), 162.9 (d, J = 12.0, C-7); δ_P (162 MHz, $CDCl_3$) 11.3; HRMS (ESI^+): Found: 383.1714; $C_{16}H_{29}N_2NaO_5P$ (MNa^+) Requires 383.1706 (–1.9 ppm error).

Lab notebook reference: MGL/06/64

(3a*RS*,5*SR*,7a*RS*)-5-(*tert*-Butyl)-3-Methylenehexahydrobenzofuran-2(3*H*)-one (154c) and *syn*-7-(*tert*-Butyl)-3-Methylene-1-oxaspiro[3.5]nonan-2-one (154d)



154b **154c** **154d**

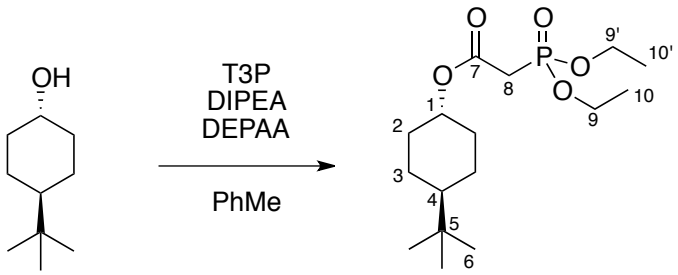
Synthesised using general procedure D with *syn*-4-(*tert*-butyl)cyclohexyl 2-diazo-2-(diethoxyphosphoryl)acetate **154b** (72 mg, 0.200 mmol), CH_2Cl_2 (4.0 mL), $Rh_2(oct)_4$ (3.1 mg, 4.0 μmol), THF (4.0 mL), KOBu-*t* (33.7 mg, 0.300 mmol) and paraformaldehyde (12.0 mg, 0.400

mmol). Purification by column chromatography (10:1 hexane:EtOAc) afforded the *title compounds* **154c** (12 mg, 29%) and **154d** (8 mg, 19%).

Data for **154c**; white solid; R_f 0.24 (8:1 hexane:EtOAc); m.p. 48–51 °C; ν_{max} (thin film)/cm^{-1} 2952s, 1763s, 1359m, 1259s, 1181s, 1124s, 1100s, 990s, 964s, 917m; δ_H (400 MHz, $CDCl_3$) 0.84 (9 H, s, H-8), 0.94–1.42 (3 H, m, H-3,4,5), 1.61–1.70 (2 H, m, H-2,3), 1.77–1.82 (1 H, m, H-5), 2.26 (1 H, dq, *J* = 15.3, *J* = 3.4, H-2), 2.86–2.92 (1 H, m, H-6), 4.43 (1 H, q, *J* = 3.9, H-1), 5.53 (1 H, s, H-10b), 6.08 (1 H, s, H-10a); δ_C (100 MHz, $CDCl_3$) 20.6 (C-3), 27.2 (C-8), 27.9 (C-2), 30.2 (C-5), 32.4 (C-7), 41.0 (C-6), 44.9 (C-4), 76.2 (C-1), 119.6 (C-10), 142.7 (C-9), 171.1 (C-11); HRMS (ESI$^+$): Found: 231.1363; $C_{13}H_{20}NaO_2$ (MNa^+) Requires 231.1356 (–3.3 ppm error), Found: 209.1538; $C_{13}H_{21}O_2$ (MH^+) Requires 209.1536 (–0.9 ppm error).

Data for **154d**; white solid; R_f 0.36 (8:1 hexane:EtOAc); m.p. 111–114 °C; ν_{max} (thin film)/cm^{-1} 2960s, 1797s, 1438w, 1366m, 1160m, 1091m, 952m, 796m; δ_H (400 MHz, $CDCl_3$) 0.88 (9 H, s, H-6), 1.08 (1 H, tt, *J* = 12.2, *J* = 2.9, H-4), 1.25–1.42 (2 H, m, H-3), 1.70–1.81 (4 H, m, H-2,3), 2.01–2.08 (2 H, m, H-2), 5.31 (1 H, d, *J* = 1.9, H-8b), 5.81 (1 H, d, *J* = 1.9, H-8a); δ_C (100 MHz, $CDCl_3$) 23.0 (C-3), 27.4 (C-6), 32.5 (C-5), 34.5 (C-2), 46.7 (C-4), 87.3 (C-1), 112.9 (C-8), 149.8 (C-7), 164.0 (C-9); HRMS (ESI$^+$): Found: 231.1352; $C_{13}H_{20}NaO_2$ (MNa^+) Requires 231.1356 (1.4 ppm error).
Lab notebook reference: MGL/06/67

anti-4-(*tert*-Butyl)cyclohexyl 2-(diethoxyphosphoryl)acetate (155a)



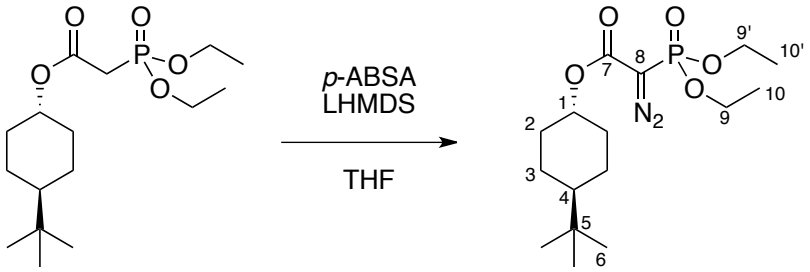
155 **155a**

Synthesised using general procedure A with *anti*-4-(tert-butyl)cyclohexanol **155** (1.56 g, 10.0 mmol), toluene (50 mL), DEPAA (2.06 g, 10.5 mmol), DIPEA (4.52 mL, 26.0 mmol) and T3P (8.27 g, 13.0 mmol, 50% w/w solution in EtOAc) affording the *title compound* **155a** as a yellow oil (3.23 g, 97%). No further purification was required; R_f 0.21 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2947s, 2866m, 1730s, 1451w, 1394m, 1366m, 1260s, 1113m, 1019s, 966s; δ_H (400 MHz, $CDCl_3$) 0.82 (9 H, s, H-6), 0.92–1.12 (3 H, m), 1.26–1.36 (8 H, m), 1.75–1.81 (2 H, m), 1.98–2.04 (2 H, m), 2.91 (2 H, d, *J* = 21.6, H-8), 4.10–4.17 (4 H, m, H-9,9'), 4.65 (1 H, tt, *J* = 11.3,

J = 4.5, H-1); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.1, C-10,10'), 25.3 (CH_2), 27.5 (C-6), 31.8 (CH_2), 32.2 (C-5), 34.7 (d, J = 133.6, C-8), 46.9 (C-4), 62.5 (d, J = 6.1, C-9,9'), 75.0 (C-1), 165.3 (d, J = 5.8, C-7); δ_P (162 MHz, $CDCl_3$) 20.6; HRMS (ESI^+): Found: 357.1790; $C_{16}H_{31}NaO_5P$ (MNa^+) Requires 357.1801 (3.1 ppm error), Found: 335.1970; $C_{16}H_{32}O_5P$ (MH^+) Requires 335.1982 (3.5 ppm error).

Lab notebook reference: MGL/06/63

anti-4-(*tert*-Butyl)cyclohexyl 2-diazo-2-(diethoxyphosphoryl)acetate (155b)

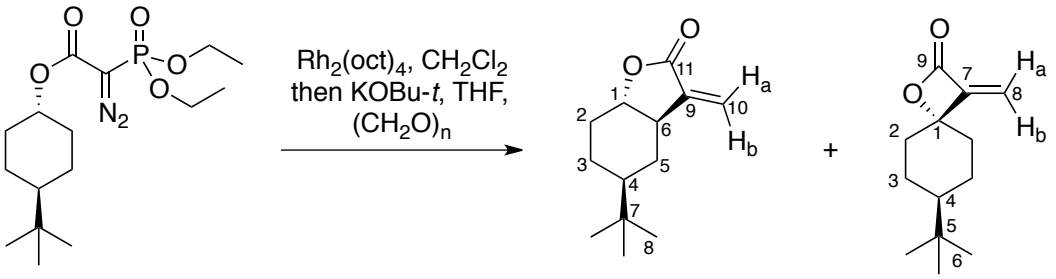


155a **155b**

Synthesised using general procedure B with *anti*-4-(tert-butyl)cyclohexyl 2-(diethoxyphosphoryl)acetate **155a** (3.22 g, 9.63 mmol), THF (48 mL), LHMDS (11.6 mL, 11.6 mmol, 1.0 M solution in THF) and *p*-ABSA (2.78 g, 11.6 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **155b** as a yellow oil (2.99 g, 86%); R_f 0.51 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2949s, 2866m, 2126s, 1698s, 1453w, 1363w, 1279s, 1020s, 977m; δ_H (400 MHz, $CDCl_3$) 0.83 (9 H, s, H-6), 0.94–1.14 (3 H, m), 1.27–1.37 (8 H, m), 1.76–1.84 (2 H, m), 2.00–2.06 (2 H, m), 4.07–4.25 (4 H, m, H-9,9'), 4.72 (1 H, tt, J = 11.3, J = 4.5, H-1); δ_C (100 MHz, $CDCl_3$) 15.7 (d, J = 7.3, C-10,10'), 24.9 (CH_2), 27.1 (C-6), 31.7 (CH_2), 31.8 (C-5), 46.5 (C-4), 53.4 (d, J = 226.5, C-8), 63.1 (d, J = 6.3, C-9,9'), 74.8 (C-1), 162.5 (d, J = 12.3, C-7); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI^+): Found: 383.1711; $C_{16}H_{29}N_2NaO_5P$ (MNa^+) Requires 383.1706 (–1.2 ppm error).

Lab notebook reference: MGL/06/65

(3a*RS*,5*SR*,7a*SR*)-5-(*tert*-Butyl)-3-Methylenehexahydrobenzofuran-2(3*H*)-one (155c) and *anti*-7-(*tert*-Butyl)-3-Methylene-1-oxaspiro[3.5]nonan-2-one (155d)



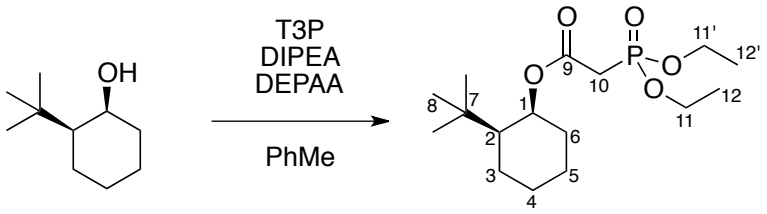
155b **155c** **155d**

Synthesised using general procedure D with *anti*-4-(*tert*-butyl)cyclohexyl 2-diazo-2-(diethoxyphosphoryl)acetate **155b** (73 mg, 0.203 mmol), CH_2Cl_2 (4.0 mL), $Rh_2(oct)_4$ (3.2 mg, 4.1 μmol), THF (4.0 mL), KOBu-*t* (34.2 mg, 0.305 mmol) and paraformaldehyde (12.2 mg, 0.406 mmol). Purification by column chromatography (10:1 hexane:EtOAc) afforded the *title compounds* **155c** (20 mg, 47%) and **155d** (5 mg, 12%).

Data for **155c**; colourless oil; R_f 0.36 (8:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2954s, 2870m, 1772s, 1395m, 1366m, 1251s, 1132s, 1079m, 1034m, 1019s, 993m; δ_H (400 MHz, $CDCl_3$) 0.91 (9 H, s, H-8), 1.06–1.34 (3 H, m, H-3,4,5), 1.62 (1 H, qd, *J* = 11.9, *J* = 3.7, H-2), 1.98–2.04 (1 H, m, H-3), 2.18 (1 H, dq, *J* = 12.5, *J* = 3.7, H-5), 2.29 (1 H, dq, *J* = 11.5, *J* = 3.7, H-2), 2.41 (1 H, tq, *J* = 11.1, *J* = 3.2, H-6), 3.65 (1 H, td, *J* = 11.1, *J* = 3.7, H-1), 5.39 (1 H, d, *J* = 3.1, H-9b), 6.06 (1 H, d, *J* = 3.2, H-9a); δ_C (100 MHz, $CDCl_3$) 25.0 (C-3), 26.4 (C-5), 27.7 (C-8), 30.1 (C-2), 32.6 (C-7), 47.1 (C-4), 48.7 (C-6), 83.2 (C-1), 116.9 (C-10), 139.8 (C-9), 171.0 (C-11); HRMS (ESI^+): Found: 231.1362; $C_{13}H_{20}NaO_2$ (MNa^+) Requires 231.1356 (–2.7 ppm error), Found: 209.1532; $C_{13}H_{21}O_2$ (MH^+) Requires 209.1536 (1.8 ppm error).

Data for **155d**; white needles; R_f 0.45 (8:1 hexane:EtOAc); m.p. 69–73 °C; ν_{max} (thin film)/cm^{-1} 2969s, 2872w, 1820s, 1368m, 1193m, 1087m, 1024m, 959m, 857m, 808m; δ_H (400 MHz, $CDCl_3$) 0.90 (9 H, s, H-6), 0.94–1.46 (3 H, m, H-3,4), 1.87–1.99 (4 H, m, H-2,3), 2.04–2.12 (2 H, m, H-2), 5.49 (1 H, d, *J* = 1.8, H-8b), 5.80 (1 H, d, *J* = 1.8, H-8a); δ_C (100 MHz, $CDCl_3$) 25.0 (C-3), 27.5 (C-6), 32.3 (C-5), 35.0 (C-2), 46.3 (C-4), 87.1 (C-1), 113.2 (C-8), 150.1 (C-7), 163.5 (C-9); HRMS (ESI^+): Found: 231.1352; $C_{13}H_{20}NaO_2$ (MNa^+) Requires 231.1356 (1.5 ppm error).
Lab notebook reference: MGL/06/68

(1*SR*,2*SR*)-2-(*tert*-Butyl)cyclohexyl 2-(diethoxyphosphoryl)acetate (156)

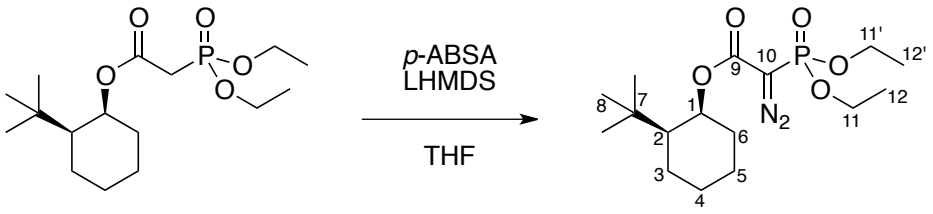


156 **156a**

Synthesised using general procedure A with (1*SR*,2*SR*)-2-(*tert*-butyl)cyclohexanol **156** (1.56 g, 10.0 mmol), toluene (50 mL), DEPAA (2.06 g, 10.5 mmol), DIPEA (4.52 mL, 26.0 mmol) and T3P (8.27 g, 13.0 mmol, 50% w/w solution in EtOAc) affording the *title compound* **156a** as a pink oil (3.28 g, 98%). No further purification was required; R_f 0.33 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2938s, 2868m, 1728s, 1447m, 1396m, 1366m, 1262s, 1115m, 1051w, 1020s, 966s; δ_H (400 MHz, $CDCl_3$) 0.83 (9 H, s, H-8), 1.09 (1 H, ddd, J = 12.4, J = 3.5, J = 2.0), 1.14–1.34 (8 H, m), 1.40–1.62 (4 H, m), 1.73–1.80 (1 H, m), 1.90–1.97 (1 H, m), 2.83–2.98 (2 H, m, H-10), 4.08–4.16 (4 H, m, H-11,11'), 5.24–5.27 (1 H, m, H-1); δ_C (100 MHz, $CDCl_3$) 16.1 (d, J = 6.7, C-12/12'), 16.1 (d, J = 6.7, C-12/12'), 20.2 (CH_2), 22.0 (CH_2), 26.3 (CH_2), 28.3 (C-8), 31.1 (CH_2), 32.4 (C-7), 34.6 (d, J = 134.4, C-10), 49.8 (C-2), 62.3 (app. t, J = 6.5, C-11,11'), 72.6 (C-1), 165.0 (d, J = 6.3, C-9); δ_P (162 MHz, $CDCl_3$) 20.7; HRMS (ESI$^+$): Found: 357.1791; $C_{16}H_{31}NaO_5P$ (MNa^+) Requires 357.1801 (2.9 ppm error).

Lab notebook reference: MGL/06/69

(1*SR*,2*SR*)-2-(*tert*-Butyl)cyclohexyl 2-diazo-2-diethoxyphosphoryl)acetate (156b)



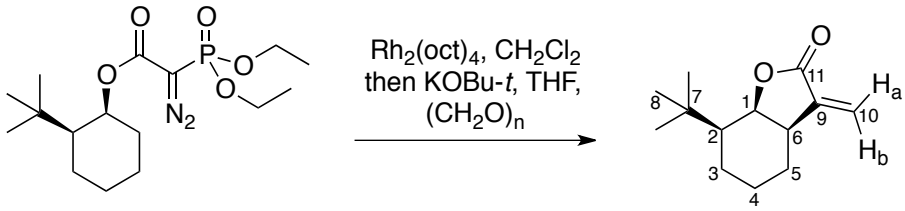
156a **156b**

Synthesised using general procedure B with (1*SR*,2*SR*)-2-(*tert*-butyl)cyclohexyl 2-(diethoxyphosphoryl)acetate **156a** (1.67 g, 5.00 mmol), THF (25 mL), LHMDS (6.00 mL, 6.00 mmol, 1.0 M solution in THF) and *p*-ABSA (1.44 g, 6.00 mmol). Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **156b** as a yellow oil (1.47 g, 82%); R_f 0.63 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2939s, 2868m, 2125s, 1693s, 1480m, 1447m, 1368m, 1277s, 1269s, 1222m, 1018s, 976m; δ_H (400 MHz, $CDCl_3$) 0.84 (9 H, s, H-8),

1.10–1.49 (12 H, m), 1.57–1.64 (1 H, m), 1.74–1.82 (1 H, m), 1.86–1.93 (1 H, m), 4.05–4.23 (4 H, m, H-11,11'), 5.40–5.43 (1 H, m, H-1); δ_C (100 MHz, $CDCl_3$) 16.0 (d, J = 7.2, C-12/12'), 16.0 (d, J = 7.5, C-12/12'), 20.3 (CH_2), 21.9 (CH_2), 26.4 (CH_2), 28.3 (C-8), 31.7 (CH_2), 32.4 (C-7), 50.2 (C-2), 54.0 (d, J = 226.6, C-10), 63.3 (d, J = 5.9, C-11/11'), 63.4 (d, J = 5.9, C-11/11'), 72.6 (C-1), 162.5 (d, J = 12.1, C-9); δ_P (162 MHz, $CDCl_3$) 11.2; HRMS (ESI^+): Found: 383.1690; $C_{16}H_{29}N_2NaO_5P$ (MNa^+) Requires 383.1706 (4.3 ppm error).

Lab notebook reference: MGL/06/72

(3a*RS*,7*SR*,7a*RS*)-7-(*tert*-Butyl)-3-methylenehexahydrobenzofuran-2(3*H*)-one (156c)

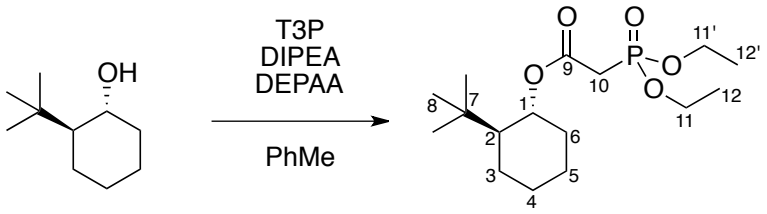


156b **156c**

Synthesised using general procedure D with (1*SR*,2*SR*)-2-(*tert*-butyl)cyclohexyl 2-diazo-2-diethoxyphosphoryl)acetate **156b** (75 mg, 0.208 mmol), CH_2Cl_2 (4.2 mL), $Rh_2(oct)_4$ (3.2 mg, 4.2 μmol), THF (4.2 mL), KOBu-*t* (35.0 mg, 0.312 mmol) and paraformaldehyde (12.5 mg, 0.416 mmol). Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **156c** as a white solid (39 mg, 90%); R_f 0.49 (4:1 hexane:EtOAc); m.p. 57–60 °C; ν_{max} (thin film)/cm^{-1} 2944s, 2866m, 1762s, 1669w, 1366m, 1261s, 1175m, 1145s, 1117s, 1078m, 962s, 945m, 896m, 818m; δ_H (400 MHz, $CDCl_3$) 1.00 (9 H, s, H-8), 1.15–1.34 (4 H, m), 1.65–1.79 (3 H, m), 2.81–2.86 (1 H, m), 4.58–4.60 (1 H, m, H-1), 5.49 (1 H, d, J = 0.8, H-10b), 6.05 (1 H, d, J = 0.8, H-10a); δ_C (100 MHz, $CDCl_3$) 20.2 (C-3/4/5), 23.8 (C-3/4/5), 28.3 (C-8), 28.5 (C-3/4/5), 32.9 (C-7), 41.5 (C-2/6), 48.1 (C-2/6), 78.0 (C-1), 119.1 (C-10), 141.9 (C-9), 171.4 (C-11); HRMS (ESI^+): Found: 231.1361; $C_{13}H_{20}NaO_2$ (MNa^+) Requires 231.1356 (–2.5 ppm error), Found: 209.1538; $C_{13}H_{21}O_2$ (MH^+) Requires 209.1536 (–0.9 ppm error).

Lab notebook reference: MGL/06/75

(1*RS*,2*SR*)-2-(*tert*-Butyl)cyclohexyl 2-(diethoxyphosphoryl)acetate (157a)

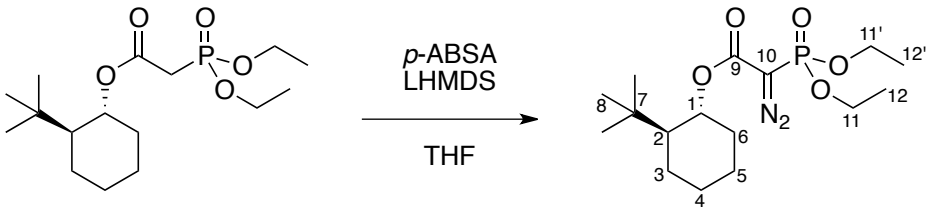


157 **157a**

Synthesised using general procedure A with (1*RS*,2*SR*)-2-(*tert*-butyl)cyclohexanol **157** (1.56 g, 10.0 mmol), toluene (50 mL), DEPAA (2.06 g, 10.5 mmol), DIPEA (4.52 mL, 26.0 mmol) and T3P (8.27 g, 13.0 mmol, 50% w/w solution in EtOAc) affording the *title compound* **157a** as a yellow oil (3.27 g, 98%). No further purification was required; R_f 0.31 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2937s, 2865m, 1727s, 1479m, 1449m, 1396m, 1368m, 1263s, 1164w, 1113s, 1051w, 1022s, 967s, 835m, 780m; δ_H (400 MHz, $CDCl_3$) 0.86 (9 H, s, H-8), 0.90–1.41 (11 H, m), 1.60–1.67 (2 H, m), 1.80–1.86 (1 H, m), 1.94–1.99 (1 H, m), 2.81–2.95 (2 H, m, H-10), 4.09–4.16 (4 H, m, H-11,11'), 4.72 (1 H, td, J = 10.2, J = 4.5, H-1); δ_C (100 MHz, $CDCl_3$) 16.2 (d, J = 6.4, C-12,12'), 24.4 (CH_2), 25.7 (CH_2), 26.6 (CH_2), 28.9 (C-8), 32.7 (C-7), 32.8 (CH_2), 34.8 (d, J = 134.9, C-10), 50.1 (C-2), 62.4 (d, J = 6.7, C-11/11'), 62.5 (d, J = 6.7, C-11/11'), 76.8 (C-1), 165.0 (d, J = 6.0, C-9); δ_P (162 MHz, $CDCl_3$) 20.6; HRMS (ESI$^+$): Found: 357.1785; $C_{16}H_{31}NaO_5P$ (MNa^+) Requires 357.1801 (4.6 ppm error), Found: 335.1989; $C_{16}H_{32}O_5P$ (MH^+) Requires 335.1982 (–2.3 ppm error).

Lab notebook reference: MGL/06/70

(1*RS*,2*SR*)-2-(*tert*-Butyl)cyclohexyl 2-diazo-2-diethoxyphosphoryl)acetate (157b)



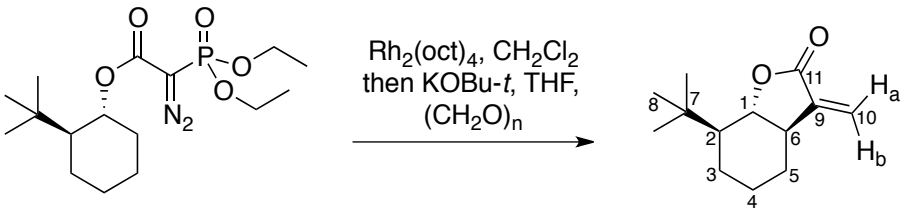
157a **157b**

Synthesised using general procedure B with (1*RS*,2*SR*)-2-(*tert*-butyl)cyclohexyl 2-(diethoxyphosphoryl)acetate **157a** (1.67 g, 5.00 mmol), THF (25 mL), LHMDS (6.00 mL, 6.00 mmol, 1.0 M solution in THF) and *p*-ABSA (1.44 g, 6.00 mmol). Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **157b** as a yellow oil (1.37 g, 76%); R_f 0.60 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2936s, 2865m, 2122s, 1698s, 1478m,

1449m, 1395w, 1367m, 1319w, 1272s, 1220s, 1164w, 1130w, 1108w, 1018s, 976s, 951s, 817s, 795s, 743s; δ_H (400 MHz, $CDCl_3$) 0.82–1.40 (20 H, m), 1.61–1.67 (2 H, m), 1.81–1.87 (1 H, m), 1.92–1.96 (1 H, m), 4.04–4.23 (4 H, H-11,11'), 4.84 (1 H, td, *J* = 10.1, *J* = 4.5, H-1); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* = 7.4, C-12,12'), 24.4 (CH_2), 25.5 (CH_2), 26.6 (CH_2), 28.8 (C-8), 32.8 (C-7), 33.4 (CH_2), 50.3 (C-2), 53.8 (d, *J* = 227.2, C-10), 63.4 (d, *J* = 5.9, C-11/11'), 63.5 (d, *J* = 5.9, C-11/11'), 76.6 (C-1), 162.4 (d, *J* = 13.0, C-9); δ_P (162 MHz, $CDCl_3$) 10.9; HRMS (ESI^+): Found: 383.1705; $C_{16}H_{29}N_2NaO_5P$ (MNa^+) Requires 383.1706 (0.4 ppm error).

Lab notebook reference: MGL/06/73

(3a*RS*,7*SR*,7a*SR*)-7-(*tert*-Butyl)-3-methylenehexahydrobenzofuran-2(3*H*)-one (157c)

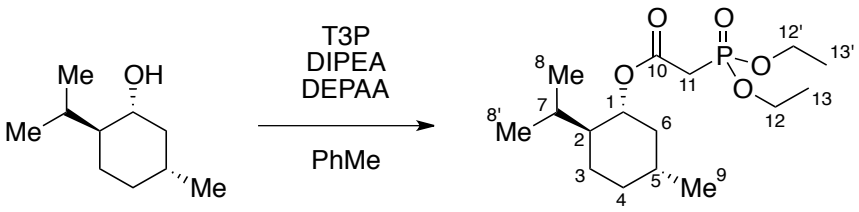


157b **157c**

Synthesised using general procedure D with (1*RS*,2*SR*)-2-(*tert*-butyl)cyclohexyl 2-diazo-2-diethoxyphosphoryl)acetate **157b** (75 mg, 0.208 mmol), CH_2Cl_2 (4.2 mL), $Rh_2(oct)_4$ (3.2 mg, 4.2 μmol), THF (4.2 mL), KOBu-*t* (35.0 mg, 0.312 mmol) and paraformaldehyde (12.5 mg, 0.416 mmol). Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **157c** as a yellow oil (33 mg, 76%); R_f 0.57 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2938s, 2868m, 1770s, 1447w, 1408w, 1367m, 1255m, 1239s, 1151s, 1127s, 1081m, 1032m, 1009s, 995s, 933m; δ_H (400 MHz, $CDCl_3$) 0.97 (9 H, s, H-8), 1.05–1.16 (1 H, m, H-3), 1.22–1.32 (1 H, m, H-5), 1.41 (1 H, app. qt, *J* = 13.1, *J* = 4.0, H-4), 1.56–1.64 (1 H, m, H-2), 1.85–1.96 (2 H, m, H-3,4), 2.06–2.12 (1 H, m, H-5), 2.49 (1 H, app. tq, *J* = 10.8, *J* = 3.4, H-6), 3.63 (1 H, app. t, *J* = 10.6, H-1), 5.37 (1 H, d, *J* = 3.1, H-10b), 6.06 (1 H, d, *J* = 3.3, H-10a); δ_C (100 MHz, $CDCl_3$) 25.2 (C-4), 26.0 (C-5), 26.4 (C-3), 28.1 (C-8), 32.6 (C-7), 49.0 (C-6), 51.5 (C-2), 85.4 (C-1), 117.2 (C-10), 139.3 (C-9), 170.8 (C-11); HRMS (ESI^+): Found: 231.1356; $C_{13}H_{20}NaO_2$ (MNa^+) Requires 231.1356 (0.0 ppm error).

Lab notebook reference: MGL/06/76

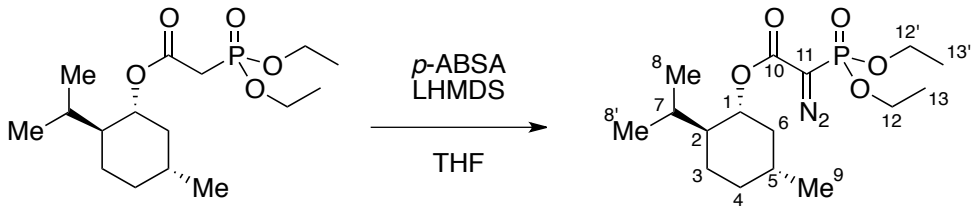
(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(diethoxyphosphoryl)acetate (158a)



158 **158a**

Synthesised using general procedure A with L-menthol **158** (781 mg, 5.00 mmol), toluene (25 mL), DEPAA (1.03 g, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in EtOAc) affording the *title compound* **158a** as a colourless oil (1.67 g, 100%). No further purification was required; R_f 0.44 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2955s, 2931s, 2870m, 1728s, 1456m, 1390m, 1369m, 1264s, 1114m, 1052w, 1023s, 966s; δ_H (400 MHz, $CDCl_3$) 0.73 (3 H, d, J = 6.9), 0.82–1.07 (9 H, m), 1.14–1.52 (8 H, m), 1.63–1.69 (2 H, m), 1.91–2.02 (2 H, m), 2.92 (2 H, d, J = 21.7, H-11), 4.10–4.18 (4 H, m, H-12,12'), 4.70 (1 H, app. td, J = 10.9, J = 4.4, H-1); δ_C (100 MHz, $CDCl_3$) 16.0 (CH_3), 16.2 (d, J = 6.0, C-13,13'), 20.7 (CH_3), 21.9 (CH_3), 23.1 (CH_2), 25.7 (CH), 31.3 (CH), 34.1 (CH_2), 34.5 (d, J = 133.3, C-11), 40.6 (CH_2), 46.8 (CH), 62.5 (app. t, J = 5.8, C-12,12'), 75.6 (C-1), 165.3 (d, J = 6.3, C-10); δ_P (162 MHz, $CDCl_3$) 20.7; HRMS (ESI$^+$): Found: 357.1801; $C_{16}H_{31}NaO_5P$ (MNa^+) Requires 357.1801 (0.2 ppm error).
Lab notebook reference: MGL/06/54

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-diazo-2-(diethoxyphosphoryl)acetate (158b)



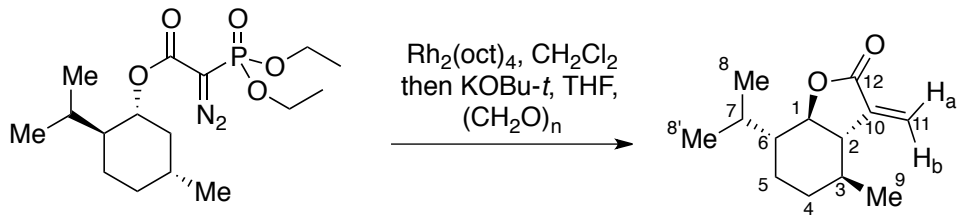
158a **158b**

Synthesised using general procedure B with (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-(diethoxyphosphoryl)acetate **158a** (1.64 g, 4.90 mmol), THF (25.0 mL), LHMDS (5.90 mL, 5.90 mmol, 1.0 M solution in THF) and *p*-ABSA (1.41 g, 5.90 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **158b** as a yellow solid (1.59 g, 90%); R_f 0.67 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2956s, 2127s, 1697s, 1457m, 1369m, 1275s, 1119m, 1021s, 980s, 957s; δ_H (400 MHz, $CDCl_3$) 0.75 (3 H, d, J = 7.0), 0.80–1.08 (9 H, m),

1.32–1.52 (8 H, m), 1.64–1.70 (2 H, m), 1.81–1.92 (1 H, m), 1.99–2.04 (1 H, m), 4.07–4.25 (4 H, m, H-12,12'), 4.77 (1 H, app. td, J = 10.9, J = 4.4, H-1); δ_C (100 MHz, $CDCl_3$) 16.0 (CH_3), 16.0 (d, J = 6.9, C-13,13'), 16.1 (CH_3), 20.7 (CH_3), 21.9 (CH_3), 23.2 (CH_2), 26.1 (CH), 31.4 (CH), 34.0 (CH_2), 41.0 (CH_2), 47.1 (CH), 53.8 (d, J = 223.2, C-11), 63.4 (d, J = 5.7, C-12,12'), 75.9 (C-1), 163.1 (d, J = 11.4, C-10); δ_P (162 MHz, $CDCl_3$) 10.9; HRMS (ESI^+): Found: 383.1718; $C_{16}H_{29}N_2NaO_5P$ (MNa^+) Requires 383.1706 (−3.1 ppm error).

Lab notebook reference: MGL/06/61

(3a*R*,4*R*,7*S*,7a*S*)-7-Isopropyl-4-methyl-3-methylenehexahydrobenzofuran-2(3*H*)-one (158c)

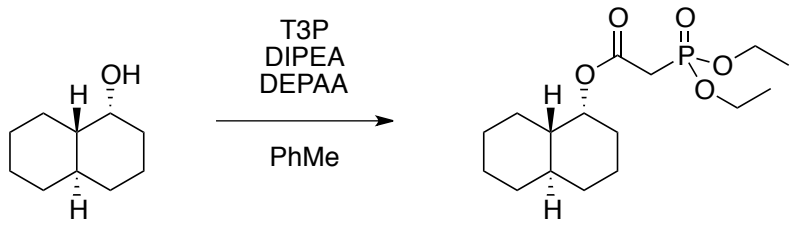


158b **158c**

Synthesised using general procedure D with (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-diazo-2-(diethoxyphosphoryl)acetate **158b** (71 mg, 0.197 mmol), CH_2Cl_2 (4.0 mL), $Rh_2(oct)_4$ (3.1 mg, 3.9 μmol), THF (4.0 mL), KOBu-*t* (33.2 mg, 0.296 mmol) and paraformaldehyde (11.8 mg, 0.394 mmol). Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound* **158c** as a colourless oil (30 mg, 73%); R_f 0.41 (8:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2958m, 1766s, 1462m, 1388w, 1249s, 1133s, 1042s, 980s; δ_H (400 MHz, $CDCl_3$) 0.88 (3 H, d, J = 7.0, H-8/8'), 0.94 (3 H, d, J = 7.0, H-8/8'), 1.02–1.34 (5 H, m), 1.62–1.82 (4 H, m), 1.99 (1 H, hept.d, J = 7.0, J = 3.4, H-7), 2.19 (1 H, app. tt, J = 10.5, J = 3.1, H-2), 3.60 (1 H, app. t, J = 10.7, H-1), 5.63 (1 H, d, J = 3.0, H-11b), 6.09 (1 H, d, J = 3.2, H-11a); δ_C (100 MHz, $CDCl_3$) 17.6 (C-8/8'), 19.3 (C-9), 19.9 (C-8/8'), 24.5 (C-4/5), 28.1 (C-7), 33.5 (C-3), 35.4 (C-4/5), 46.8 (C-6), 53.9 (C-2), 84.0 (C-1), 118.3 (C-11), 139.6 (C-10), 171.0 (C-12); HRMS (ESI^+): Found: 231.1354; $C_{13}H_{20}NaO_2$ (MNa^+) Requires 231.1356 (0.8 ppm error), Found: 209.1532; $C_{13}H_{21}O_2$ (MH^+) Requires 209.1536 (1.8 ppm error).

Lab notebook reference: MGL/06/66

(1*RS*,4a*RS*,8a*SR*)-Decahydronaphthalen-1-yl 2-(diethoxyphosphoryl)acetate (159a)

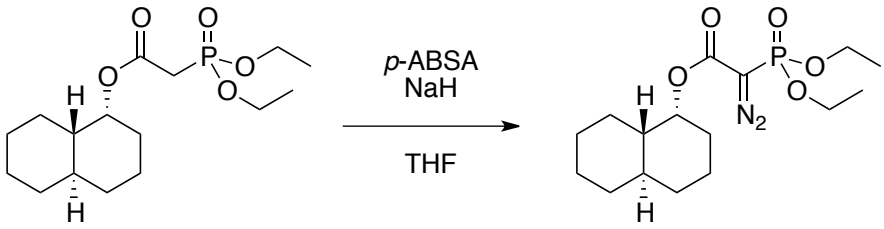


159 **159a**

Synthesised using general procedure A with (1*RS*,4a*RS*,8a*SR*)-decahydronaphthalen-1-ol **159** (201 mg, 1.30 mmol), toluene (10 mL), DEPAA (0.22 mL, 1.37 mmol), DIPEA (0.60 mL, 3.38 mmol) and T3P (1.08 g, 1.70 mmol, 50% w/w solution in EtOAc) affording the *title compound* **159a** as a yellow oil (425 mg, 98%). No further purification was required; R_f 0.54 (3:7 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2982, 2924, 2853, 1731, 1448, 1394, 1263, 1114, 1021, 960; δ_H (400 MHz, $CDCl_3$) 0.79–1.95 (22 H, m), 2.94–3.00 (2 H, m), 4.13–4.20 (4 H, m), 4.93–4.96 (1 H, m); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.3), 16.3 (d, *J* = 6.3), 20.4, 26.2, 26.4, 29.1, 30.6, 33.4, 34.2, 34.6 (d, *J* = 134.0), 36.3, 45.7, 62.5 (d, *J* = 6.3), 75.0, 165.4 (d, *J* = 6.8); δ_P (162 MHz, $CDCl_3$) 20.9; HRMS (ESI$^+$): Found: 355.1638; $C_{16}H_{29}NaO_5P$ (MNa^+) Requires 355.1645 (1.9 ppm error), Found: 333.1818; $C_{16}H_{30}O_5P$ (MH^+) Requires 333.1825 (2.2 ppm error).

Note: This compound was synthesised by Mariantonietta D'Acunto.

(1*RS*,4a*RS*,8a*SR*)-Decahydronaphthalen-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (159b)



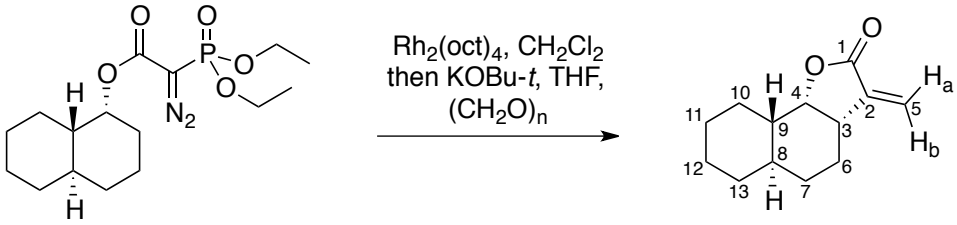
159a **159b**

Synthesised using general procedure B with (1*RS*,4a*RS*,8a*SR*)-decahydronaphthalen-1-yl 2-(diethoxyphosphoryl)acetate **159a** (475 mg, 1.43 mmol), THF (9.0 mL), NaH (68.6 mg, 1.72 mmol, 60% dispersion in mineral oil) and *p*-ABSA (412 mg, 1.72 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **159b** as a yellow oil (350 mg, 68%); R_f 0.80 (3:7 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2927, 2857, 2126, 1698, 1448, 1290, 1277, 1118, 1023, 981; δ_H (400 MHz, $CDCl_3$) 0.87–1.97 (22 H, m), 4.11–4.29 (4 H, m), 5.02–5.04 (1 H, m); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* = 6.9), 16.1 (d, *J* = 6.9), 20.3, 26.1, 26.3, 29.2, 30.8, 33.3,

34.0, 36.3, 45.7, 54.0 (d, J = 227.6), 63.2 (d, J = 5.5), 63.2 (d, J = 5.4), 75.3, 163.3 (d, J = 11.1); δ_P (162 MHz, $CDCl_3$) 11.6; HRMS (ESI^+): Found: 381.1556; $C_{16}H_{27}N_2NaO_5P$ (MNa^+) Requires 381.1550 (–1.7 ppm error), Found: 359.1731; $C_{16}H_{30}N_2O_5P$ (MH^+) Requires 359.1730 (–0.2 ppm error).

Note: This compound was synthesised by Mariantonietta D'Acunto.

(3a*SR*,5a*RS*,9a*SR*,9b*SR*)-3-Methylenedecahydronaphtho[1,2-*b*]furan-2(9b*H*)-one (159c)



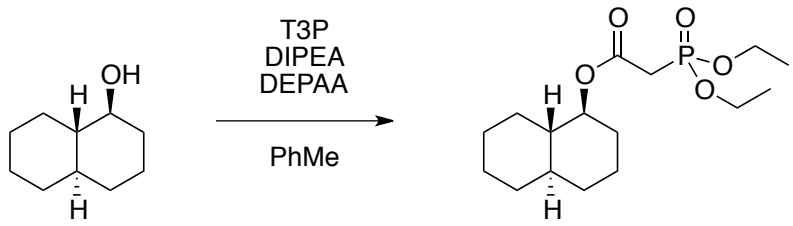
159b **159c**

Synthesised using general procedure D with (1*RS*,4a*RS*,8a*SR*)-decahydronaphthalen-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate **159b** (82 mg, 0.229 mmol), CH_2Cl_2 (4.6 mL), $Rh_2(oct)_4$ (3.6 mg, 4.6 μmol), THF (4.6 mL), KOBu-*t* (38.5 mg, 0.344 mmol) and paraformaldehyde (13.8 mg, 0.458 mmol). Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **159c** as a colourless oil (32 mg, 68%); R_f 0.56 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2923s, 2854m, 1761s, 1447w, 1260s, 1144s, 1117m, 1081m, 949m; δ_H (400 MHz, $CDCl_3$) 0.89–1.06 (2 H, m), 1.18–1.35 (5 H, m), 1.46–1.85 (7 H, m), 2.84–2.90 (1 H, m, H-3), 4.25 (1 H, dd, J = 4.6, J = 2.6, H-4), 5.49 (1 H, d, J = 1.0, H-5b), 6.04 (1 H, d, J = 1.1, H-5a); δ_C (100 MHz, $CDCl_3$) 26.0 (CH_2), 26.7 (CH_2), 28.7 (CH_2), 28.8 (CH_2), 31.0 (CH_2), 33.7 (CH_2), 34.9 (C-8/9), 40.8 (C-3), 43.8 (C-8/9), 80.6 (C-4), 119.1 (C-5), 142.5 (C-2), 171.0 (C-1); HRMS (ESI^+): Found: 229.1207; $C_{13}H_{18}NaO_2$ (MNa^+) Requires 229.1199 (–3.4 ppm error), Found: 207.1384; $C_{13}H_{19}O_2$ (MH^+) Requires 207.1380 (–2.0 ppm error).

Lab notebook reference: MGL/05/35

Obtained data in accord with reported literature.[165]

(1*SR*,4a*RS*,8a*SR*)-Decahydronaphthalen-1-yl 2-(diethoxyphosphoryl)acetate (160a)

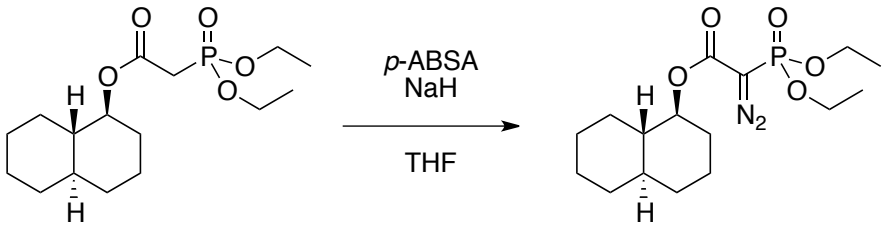


160 **160a**

Synthesised using general procedure A with (1*SR*,4a*RS*,8a*SR*)-decahydronaphthalen-1-ol **160** (271 mg, 1.76 mmol), toluene (15 mL), DEPAA (0.30 mL, 1.85 mmol), DIPEA (0.82 mL, 4.60 mmol) and T3P (1.46 g, 2.30 mmol, 50% w/w solution in EtOAc) affording the *title compound* **160a** as a yellow oil (390 mg, 67%). No further purification was required; R_f 0.36 (3:7 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2983, 2921, 2855, 1730, 1447, 1394, 1264, 1114, 1023, 963; δ_H (400 MHz, $CDCl_3$) 0.78–2.02 (22 H, m), 2.93 (2 H, d, J = 21.7), 4.11–4.18 (4 H, m), 4.50 (1 H, app. td, J = 10.3, J = 4.4); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.6), 16.3 (d, J = 6.3), 23.7, 25.8, 26.1, 28.7, 31.9, 33.0, 33.8, 34.5 (d, J = 133.7), 41.2, 47.2, 62.5 (d, J = 6.2), 62.5 (d, J = 6.2), 78.6, 165.5 (d, J = 6.6); δ_P (162 MHz, $CDCl_3$) 20.8; HRMS (ESI$^+$): Found: 355.1648; $C_{16}H_{29}NaO_5P$ (MNa^+) Requires 355.1645 (–0.8 ppm error), Found: 333.1830; $C_{16}H_{30}O_5P$ (MH^+) Requires 333.1825 (–1.3 ppm error).

Note: This compound was synthesised by Mariantonietta D'Acunto.

(1*SR*,4a*RS*,8a*SR*)-Decahydronaphthalen-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (160b)



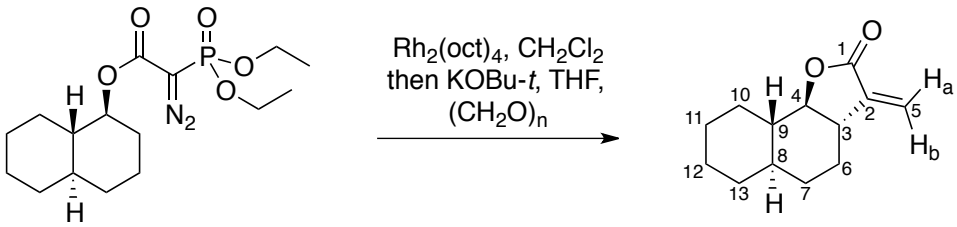
160a **160b**

Synthesised using general procedure B with (1*SR*,4a*RS*,8a*SR*)-decahydronaphthalen-1-yl 2-(diethoxyphosphoryl)acetate **160a** (390 mg, 1.17 mmol), THF (7.0 mL), NaH (56.2 mg, 1.40 mmol, 60% dispersion in mineral oil) and *p*-ABSA (337 mg, 1.40 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **160b** as a yellow oil (330 mg, 78%); R_f 0.67 (3:7 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2983, 2925, 2853, 2132, 1697, 1448, 1344, 1275, 1120, 1019, 978; δ_H (400 MHz, $CDCl_3$) 0.84–2.05 (22 H, m), 4.10–4.27 (4 H, m), 4.58 (1 H,

app. td, J = 10.2, J = 4.2); δ_C (100 MHz, $CDCl_3$) 16.0 (d, J = 7.1), 16.0 (d, J = 7.1), 23.6, 25.7, 26.0, 28.7, 32.2, 32.9, 33.4, 41.2, 47.4, 53.8 (d, J = 226.6), 63.4 (d, J = 5.7), 79.1, 163.3 (d, J = 12.0); δ_P (162 MHz, $CDCl_3$) 11.0; HRMS (ESI^+): Found: 381.1532; $C_{16}H_{27}N_2NaO_5P$ (MNa^+) Requires 381.1550 (4.7 ppm error), Found: 359.1718; $C_{16}H_{30}N_2O_5P$ (MH^+) Requires 359.1730 (3.4 ppm error).

Note: This compound was synthesised by Mariantonietta D'Acunto.

(3a*SR*,5a*RS*,9a*SR*,9b*RS*)-3-Methylenedecahydronaphtho[1,2-*b*]furan-2(9b*H*)-one (160c)



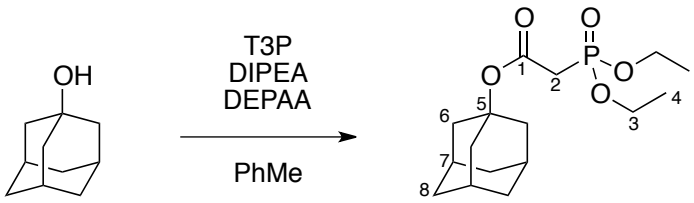
160b **160c**

Synthesised using general procedure D with (1*SR*,4a*RS*,8a*SR*)-decahydronaphthalen-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate **160b** (79 mg, 0.221 mmol), CH_2Cl_2 (4.4 mL), $Rh_2(oct)_4$ (3.4 mg, 4.4 μmol), THF (4.4 mL), KOBu-*t* (37.2 mg, 0.332 mmol) and paraformaldehyde (13.3 mg, 0.442 mmol). Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **160c** as a white solid (29 mg, 64%); R_f 0.72 (4:1 hexane:EtOAc); m.p. 80–83 °C (lit.[165] 75–77 °C); ν_{max} (thin film)/cm^{-1} 2924s, 2852m, 1766s, 1672w, 1449m, 1256m, 1241m, 1125m, 990m, 967m; δ_H (400 MHz, $CDCl_3$) 0.98–1.46 (8 H, m), 1.65–1.77 (4 H, m), 2.08–2.13 (2 H, m), 2.43–2.51 (1 H, m, H-3), 3.44 (1 H, app. t, J = 10.6, H-4), 5.36 (1 H, d, J = 3.1, H-5b), 6.04 (1 H, d, J = 3.3, H-5a); δ_C (100 MHz, $CDCl_3$) 25.1 (CH_2), 25.2 (CH_2), 26.1 (CH_2), 29.0 (CH_2), 32.6 (CH_2), 32.8 (CH_2), 41.6 (C-8), 47.0 (C-9), 48.6 (C-3), 86.7 (C-4), 117.0 (C-5), 139.9 (C-2), 171.0 (C-1); HRMS (ESI^+): Found: 229.1203; $C_{13}H_{18}NaO_2$ (MNa^+) Requires 229.1199 (−1.6 ppm error), Found: 207.1380; $C_{13}H_{19}O_2$ (MH^+) Requires 207.1380 (0.0 ppm error).

Lab notebook reference: MGL/05/34

Obtained data in accord with reported literature.[165]

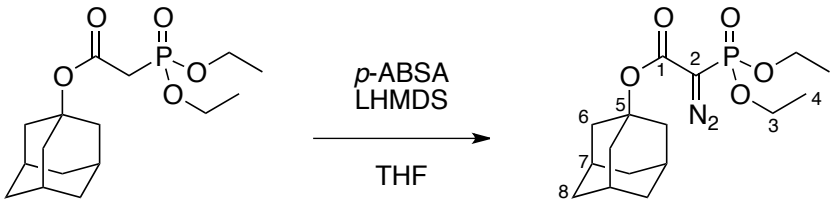
Adamantan-1-yl 2-(diethoxyphosphoryl)acetate (161a)



161 **161a**

Synthesised using general procedure A with adamantan-1-ol **161** (761 mg, 5.00 mmol), toluene (25 mL), DEPAA (0.84 mL, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in THF) affording the *title compound* **161a** as a colourless oil (1.53 g, 93%). No further purification was required; R_f 0.30 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2981w, 2910s, 2853w, 1728s, 1584w, 1457w, 1393w, 1369w, 1355w, 1321w, 1259s, 1164w, 1103m, 1049w, 1020s, 967s, 890m, 836w, 814w; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, J = 7.1, J = 0.5, H-4), 1.57–1.69 (6 H, m, H-8), 2.09–2.14 (9 H, m, H-6,7), 2.85 (2 H, d, J = 21.4, H-2), 4.10–4.18 (4 H, m, H-3); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.2, C-4), 30.7 (C-7), 35.7 (d, J = 132.8, C-2), 36.0 (C-8), 41.1 (C-6), 62.4 (d, J = 6.2, C-3), 82.0 (C-5), 164.5 (d, J = 6.3, C-1); δ_P (162 MHz, $CDCl_3$) 21.2; HRMS (ESI$^+$): Found: 353.1489; $C_{16}H_{27}NaO_5P$ (MNa^+) Requires 353.1488 (–0.2 ppm error), Found: 331.1668; $C_{16}H_{28}O_5P$ (MH^+) Requires 331.1669 (0.2 ppm error).
Lab notebook reference: MGL/05/09S

Adamantan-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (161b)



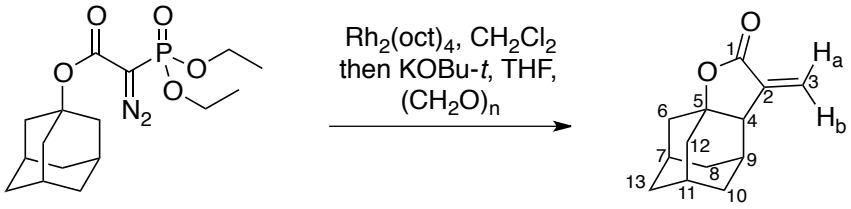
161a **161b**

Synthesised using general procedure B with adamantan-1-yl 2-(diethoxyphosphoryl)acetate **161a** (1.51 g, 4.57 mmol), THF (23 mL), LHMDS (5.48 mL, 5.48 mmol, 1.0 M solution in THF) and *p*-ABSA (1.32 g, 5.48 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **161b** as a white solid (1.21 g, 74%); R_f 0.63 (1:1 hexane:EtOAc); m.p. 51–54 °C; ν_{max} (thin film)/cm^{-1} 2912s, 2855w, 2125s, 1697s, 1457w, 1321m, 1269s, 1219w, 1164w, 1122w, 1023s, 966m; δ_H (400 MHz, $CDCl_3$) 1.30 (6 H, td, J = 7.1, J = 0.8, H-4), 1.60–1.61 (6 H, m, H-8), 2.07–2.15 (9 H, m, H-6,7), 4.05–4.20 (4 H, m, H-3); δ_C (100 MHz, $CDCl_3$) 16.0 (d, J =

6.8, C-4), 30.7 (C-7), 35.9 (C-8), 41.4 (C-6), 53.9 (d, J = 228.4, C-2), 63.3 (d, J = 5.6, C-3), 82.9 (C-5), 162.0 (d, J = 12.0, C-1); δ_P (162 MHz, $CDCl_3$) 11.3; HRMS (ESI^+): Found: 379.1384; $C_{16}H_{25}N_2NaO_5P$ (MNa^+) Requires 379.1393 (2.5 ppm error), Found: 357.1567; $C_{16}H_{26}N_2O_5P$ (MH^+) Requires 357.1574 (2.0 ppm error).

Lab notebook reference: MGL/05/09

6-Methylene-4-oxatetracyclo[6.3.1.1^{3,10}.0^{3,7}]tridecan-5-one (161c)

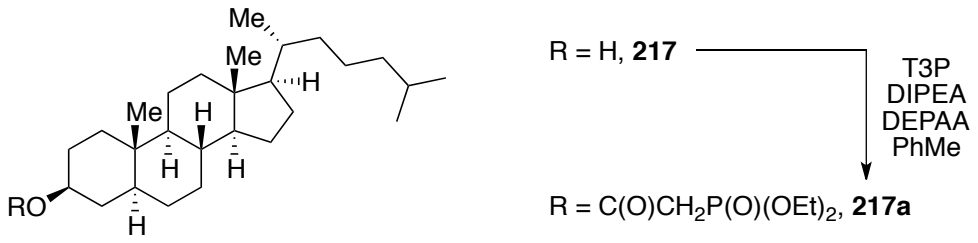


161b **161c**

Synthesised using general procedure D with adamantan-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate **161b** (75 mg, 0.210 mmol), CH_2Cl_2 (4.2 mL), $Rh_2(oct)_4$ (3.3 mg, 4.2 μmol), THF (4.2 mL), KOBu-*t* (35.3 mg, 0.315 mmol) and paraformaldehyde (12.6 mg, 0.420 mmol). Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **161c** as a white solid (34 mg, 79%); R_f 0.47 (4:1 hexane:EtOAc); m.p. 88–90 °C; ν_{max} (thin film)/cm^{-1} 2921s, 2856m, 1967w, 1764s, 1675w, 1451w, 1279w, 1262m, 1242w, 1211m, 1151m, 1042s, 949s; δ_H (400 MHz, $CDCl_3$) [1.57–1.89 (8 H, m), 1.99–2.15 (3 H, m), 2.30–2.35 (1 H, m) (H-6,7,8,10,11,12,13)], 2.44–2.48 (1 H, m, H-9), 2.81–2.84 (1 H, m, H-4), 5.36 (1 H, d, J = 3.2, H-5b), 6.14 (1 H, d, J = 3.4, H-5a); δ_C (100 MHz, $CDCl_3$) 29.2 (C-9), 29.2 (C-6/8/10/12/13), 29.6 (C-7/11), 30.9 (C-7/11), [35.8, 37.6, 39.8, 41.1 (C-6/8/10/12/13)], 53.5 (C-4), 80.4 (C-5), 117.4 (C-3), 138.6 (C-2), 170.8 (C-1); HRMS (ESI^+): Found: 227.1050; $C_{13}H_{16}NaO_2$ (MNa^+) Requires 227.1043 (−3.5 ppm error), Found: 205.1230; $C_{13}H_{17}O_2$ (MH^+) Requires 205.1223 (−3.2 ppm error).

Lab notebook reference: MGL/05/22

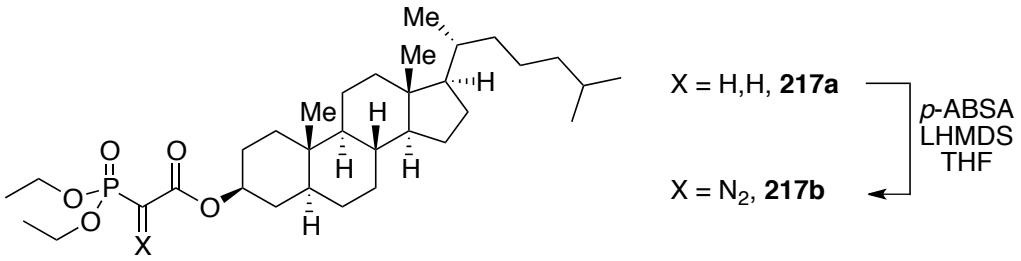
5-α-Cholestan-3-β-yl 2-(diethoxyphosphoryl)acetate (217a)



Synthesised using general procedure A with 5-α-cholestan-3-β-ol **217** (1.94 g, 5.00 mmol), toluene (25 mL), DEPAA (1.03 g, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in EtOAc) affording the *title compound* **217a** as a white solid (2.78 g, 98%). No further purification was required; R_f 0.25 (1:1 hexane:EtOAc); m.p. 102–105 °C; ν_{max} (thin film)/cm^{-1} 2935s, 2915s, 2867m, 2851m, 1734s, 1469m, 1385m, 1282s, 1258s, 1201s, 1115s, 1047m, 1029s, 969s; δ_H (400 MHz, $CDCl_3$) 0.64 (3 H, s), 0.81 (3 H, s), 0.85 (3 H, d, *J* = 6.6), 0.86 (3 H, d, *J* = 6.6), 0.89 (3 H, d, *J* = 6.5), 0.96–1.84 (36 H, m), 1.95 (1 H, dt, *J* = 12.5, *J* = 3.3), 2.93 (2 H, d, *J* = 21.6), 4.13–4.20 (4 H, m), 4.74 (1 H, tt, *J* = 11.0, *J* = 5.3); δ_C (100 MHz, $CDCl_3$) 12.0 (CH_3), 12.2 (CH_3), 16.3 (d, *J* = 5.9, CH_3), 18.6 (CH_3), 21.2 (CH_2), 22.5 (CH_3), 22.8 (CH_3), 23.8 (CH_2), 24.2 (CH_2), 27.3 (CH_2), 28.0 (CH), 28.2 (CH_2), 28.5 (CH_2), 31.9 (CH_2), 33.8 (CH_2), 34.6 (d, *J* = 133.7, CH_2), 35.4 (C), 35.4 (CH), 35.8 (CH), 36.1 (CH_2), 36.7 (CH_2), 39.5 (CH_2), 39.9 (CH_2), 42.5 (C), 44.6 (CH), 54.2 (CH), 56.2 (CH), 56.4 (CH), 62.6 (d, *J* = 5.9, CH_2), 75.1 (CH), 165.4 (d, *J* = 6.2, C); δ_P (162 MHz, $CDCl_3$) 20.6; HRMS (ESI$^+$): Found: 589.3980; $C_{33}H_{59}NaO_5P$ (MNa^+) Requires 589.3992 (2.0 ppm error).

Lab notebook reference: MGL/06/49

5-α-Cholestan-3-β-yl 2-diazo-2-(diethoxyphosphoryl)acetate (217b)

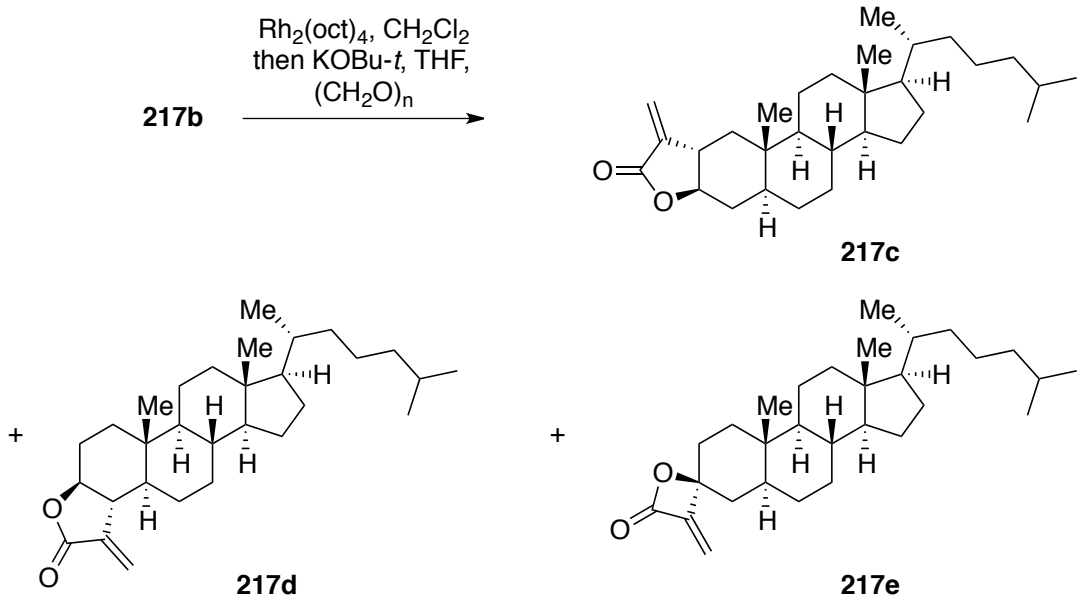


Synthesised using general procedure B with 5-α-cholestan-3-β-yl 2-(diethoxyphosphoryl)acetate **217a** (2.75 g, 4.85 mmol), THF (24.3 mL), LHMDS (5.82 mL, 5.82 mmol, 1.0 M solution in THF) and *p*-ABSA (1.40 g, 5.82 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **217b** as a white solid (2.38 g, 83%); R_f 0.70 (1:1 hexane:EtOAc); m.p. 95–98 °C; ν_{max} (thin film)/cm^{-1} 2932s, 2867w, 2129s, 1698s, 1469w, 1375w, 1331w, 1289s,

1119m, 1023s, 978m; δ_H (400 MHz, $CDCl_3$) 0.64 (3 H, s), 0.81 (3 H, s), 0.85 (3 H, d, *J* = 6.6), 0.85 (3 H, d, *J* = 6.6), 0.88 (3 H, d, *J* = 6.5), 0.95–1.86 (36 H, m), 1.95 (1 H, dt, *J* = 12.5, *J* = 3.2), 4.10–4.26 (4 H, m), 4.79 (1 H, tt, *J* = 11.0, *J* = 5.3); δ_C (100 MHz, $CDCl_3$) 12.0 (CH_3), 12.2 (CH_3), 16.1 (d, *J* = 7.1, CH_3), 18.6 (CH_3), 21.2 (CH_2), 22.5 (CH_3), 22.8 (CH_3), 23.8 (CH_2), 24.2 (CH_2), 27.6 (CH_2), 28.0 (CH), 28.2 (CH_2), 28.5 (CH_2), 31.9 (CH_2), 34.1 (CH_2), 35.4 (C), 35.4 (CH), 35.8 (CH), 36.1 (CH_2), 36.7 (CH_2), 39.5 (CH_2), 39.9 (CH_2), 42.3 (C), 44.6 (CH), 53.7 (d, *J* = 225.5, C), 54.1 (CH), 56.2 (CH), 56.3 (CH), 63.6 (d, *J* = 5.8, CH_2), 75.5 (CH), 163.0 (d, *J* = 11.9, C); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI^+): Found: 615.3875; $C_{33}H_{57}N_2NaO_5P$ (MNa^+) Requires 615.3897 (3.6 ppm error).

Lab notebook reference: MGL/06/53

(1*R*,3a*S*,3b*R*,5a*S*,6a*R*,9a*S*,10a*S*,10b*S*,12a*R*)-10a,12a-Dimethyl-9-methylene-1-((*R*)-6-methylheptan-2-yl)hexadecahydro-1*H*-cyclopenta[7,8]phenanthro[2,3-*b*]furan-8(2*H*)-one (217c), (3a*S*,5a*R*,5b*S*,7a*R*,8*R*,10a*S*,10b*S*,12a*S*,12b*R*)-5a,7a-Dimethyl-1-methylene-8-((*R*)-6-methylheptan-2-yl)hexadecahydro-1*H*-cyclopenta[7,8]phenanthro[2,1-*b*]furan-2(12b*H*)-one (217d), (2'*S*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-Dimethyl-3'-methylene-17-((*R*)-6-methylheptan-2-yl)hexadecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-oxetan]-4'-one (217e)



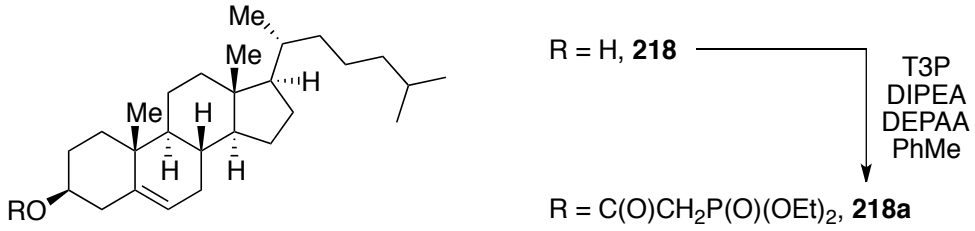
Synthesised using general procedure D with 5-α-cholestan-3-β-yl 2-diazo-2-(diethoxyphosphoryl)acetate **217b** (116 mg, 0.196 mmol), CH_2Cl_2 (3.9 mL), $Rh_2(oct)_4$ (3.1 mg, 3.9 μmol), THF (3.9 mL), KOBu-*t* (33.0 mg, 0.294 mmol) and paraformaldehyde (11.8 mg, 0.392 mmol). Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compounds* **217e** (6 mg, 7%) along with an inseparable mixture of compounds **217c** and **217d** (38 mg, 44%).

Note: The γ-regioisomers were isolated as an inseparable 1.18:1 mixture A:B, however the β-regioisomer could be separated for characterisation purposes.

Data for **217c** and **217d**; white solid; R_f 0.51 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2932s, 2867s, 1773s, 1713m, 1466m, 1383m, 1234m, 1128m, 1001m, 910m, 732s; δ_H (400 MHz, $CDCl_3$) 0.63–2.13 (86 H, m, A, B), 2.22–2.42 (2 H, m, A,B), 2.49 (1 H, tt, *J* = 10.6, *J* = 3.0, A), 2.61 (1 H, tq, *J* = 11.5, *J* = 3.0, B), 3.66–3.74 (2 H, m, A,B), 5.32 (1 H, d, *J* = 3.0, B), 5.62 (1 H, d, *J* = 3.0, A), 6.03 (1 H, d, *J* = 3.2, B), 6.10 (1 H, d, *J* = 3.2, A); δ_C (100 MHz, $CDCl_3$) 11.4, 12.0, 12.1, 13.7, 14.2, 18.6, 21.3, 21.4, 22.5, 22.8, 23.8, 24.1, 24.2, 26.2, 28.0, 28.2, 28.2, 28.6, 28.9, 31.4, 31.7, 32.0, 33.1, 34.9, 35.3, 35.4, 35.6, 35.7, 36.1, 36.1, 37.7, 37.8, 38.2, 38.5, 39.5, 39.8, 42.2, 42.5, 42.6, 44.5, 44.7, 45.8, 46.4, 46.7, 48.1, 53.7, 54.0, 54.2, 56.2, 56.2, 56.2, 56.3, 83.3, 83.4, 116.1, 118.8, 139.7, 140.3, 170.9, 171.2; HRMS (ESI$^+$): Found: 463.3535; $C_{30}H_{48}NaO_2$ (MNa^+) Requires 463.3547 (2.4 ppm error).

Data for **217e**; yellow gum; R_f 0.59 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2931s, 2869s, 1832s, 1467m, 1382m, 1198m, 837m; δ_H (400 MHz, $CDCl_3$) 0.64–2.13 (46 H, m), 5.54 (1 H, d, *J* = 1.8), 5.78 (1 H, d, *J* = 1.8); δ_C (100 MHz, $CDCl_3$) 11.5 (CH_3), 12.1 (CH_3), 18.6 (CH_3), 21.3 (CH_2), 22.5 (CH_3), 22.8 (CH_3), 23.8 (CH_2), 24.2 (CH_2), 28.0 (CH), 28.2 (CH_2), 28.5 (CH_2), 30.8 (CH_2), 31.8 (CH_2), 35.4 (C), 35.4 (CH), 35.8 (CH), 36.1 (CH_2), 36.5 (CH_2), 37.2 (CH_2), 39.5 (CH_2), 39.9 (CH_2), 42.6 (C), 44.7 (CH), 54.3 (CH), 56.3 (CH), 56.4 (CH), 87.2 (C), 112.9 (CH_2), 150.4 (C), 163.7 (C); HRMS (ESI$^+$): Found: 463.3540; $C_{30}H_{48}NaO_2$ (MNa^+) Requires 463.3547 (1.5 ppm error).
Lab notebook reference: MGL/06/57

Cholesteryl 2-(diethoxyphosphoryl)acetate (218a)

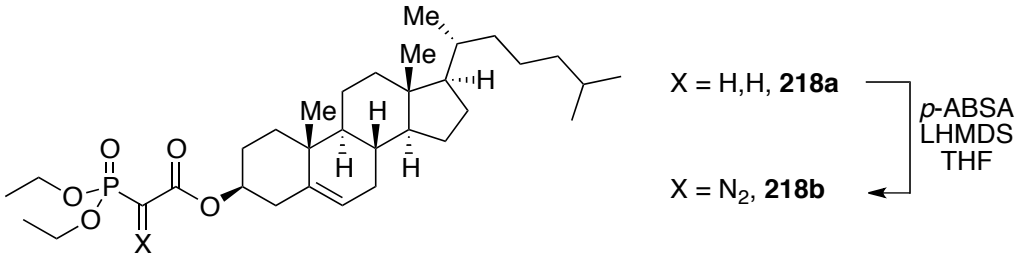


Synthesised using general procedure A with cholesterol **218** (1.00 g, 2.59 mmol), toluene (13 mL), DEPAA (533 mg, 2.72 mmol), DIPEA (1.17 mL, 6.73 mmol) and T3P (2.14 g, 3.37 mmol, 50% w/w solution in EtOAc) affording the *title compound* **218a** as a yellow solid (1.46 g, 100%). No further purification was required; R_f 0.36 (1:1 hexane:EtOAc); m.p. 75–77 °C; ν_{max} (thin film)/cm^{-1} 2934s, 2868w, 1733s, 1467m, 1368w, 1271s, 1115s, 1051m, 1024s, 967s; δ_H (400 MHz, $CDCl_3$) 0.66 (3 H, s), 0.82–1.66 (39 H, m), 1.77–2.02 (5 H, m), 2.34 (2 H, d, *J* = 7.6), 2.94 (2 H, d, *J* =

21.6), 4.13–4.20 (4 H, m), 4.65 (1 H, dtd, J = 11.9, J = 8.1, J = 3.9), 5.37 (1 H, d, J = 3.6); δ_C (100 MHz, $CDCl_3$) 11.8 (CH_3), 16.3 (d, J = 6.4, CH_3), 18.7 (CH_3), 19.3 (CH_3), 21.0 (CH_2), 22.5 (CH_3), 22.8 (CH_3), 23.8 (CH_2), 24.2 (CH_2), 27.6 (CH_2), 28.0 (CH), 28.2 (CH_2), 31.8 (CH), 31.8 (CH_2), 34.6 (d, J = 133.6, CH_2), 35.7 (CH), 36.1 (CH_2), 36.5 (C), 36.9 (CH_2), 37.9 (CH_2), 39.5 (CH_2), 39.7 (CH_2), 42.3 (C), 49.9 (CH), 56.1 (CH), 56.6 (CH), 62.6 (d, J = 6.3, CH_2), 75.3 (CH), 122.9 (CH), 139.3 (C), 165.2 (d, J = 6.7, C); δ_P (162 MHz, $CDCl_3$) 20.6; HRMS (ESI^+): Found: 587.3830; $C_{33}H_{57}NaO_5P$ (MNa^+) Requires 587.3836 (1.0 ppm error).

Lab notebook reference: MGL/06/47

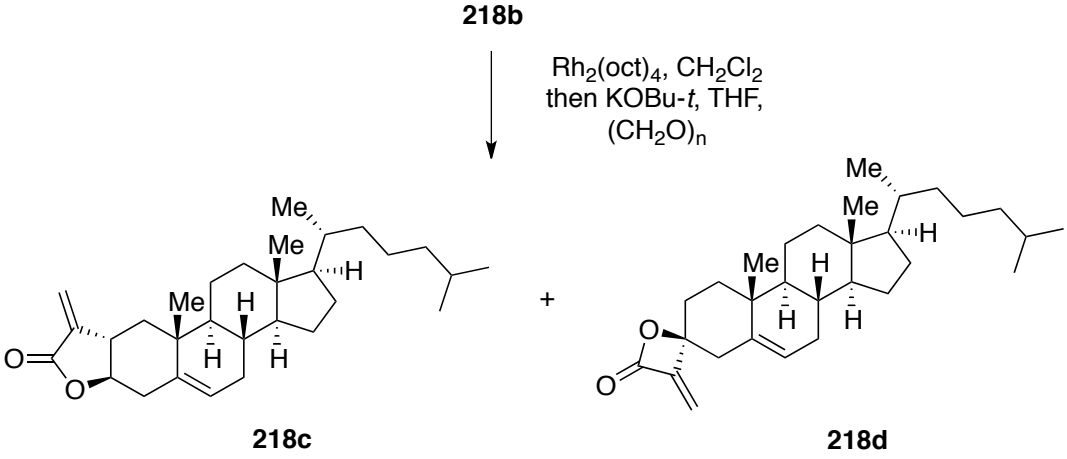
Cholesteryl 2-diazo-2-(diethoxyphosphoryl)acetate (218b)



Synthesised using general procedure B with cholesteryl 2-(diethoxyphosphoryl)acetate **218a** (1.37 g, 2.43 mmol), THF (12 mL), LHMDS (2.91 mL, 2.91 mmol, 1.0 M solution in THF) and *p*-ABSA (699 mg, 2.91 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **218b** as a yellow gum (890 mg, 62%); R_f 0.70 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2935s, 2868w, 2128s, 1698s, 1468w, 1369w, 1279s, 1121m, 1022s, 976m; δ_H (400 MHz, $CDCl_3$) 0.67 (3 H, s), 0.82–2.02 (44 H, m), 2.28–2.39 (2 H, m), 4.11–4.26 (4 H, m), 4.70 (1 H, tdd, J = 10.8, J = 6.4, J = 4.4), 5.37 (1 H, d, J = 5.1); δ_C (100 MHz, $CDCl_3$) 11.8 (CH_3), 16.1 (d, J = 6.8, CH_3), 18.7 (CH_3), 19.3 (CH_3), 21.0 (CH_2), 22.5 (CH_3), 22.8 (CH_3), 23.8 (CH_2), 24.2 (CH_2), 27.9 (CH_2), 28.0 (CH), 28.2 (CH_2), 31.8 (CH), 31.9 (CH_2), 35.7 (CH), 36.1 (CH_2), 36.5 (C), 36.9 (CH_2), 38.2 (CH_2), 39.5 (CH_2), 39.7 (CH_2), 42.3 (C), 49.9 (CH), 53.8 (d, J = 225.9, C), 56.1 (CH), 56.6 (CH), 63.5 (d, J = 5.8, CH_2), 75.6 (CH), 123.1 (CH), 139.2 (C), 162.9 (d, J = 12.3, C); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI^+): Found: 613.3721; $C_{33}H_{55}N_2NaO_5P$ (MNa^+) Requires 613.3741 (3.2 ppm error).

Lab notebook reference: MGL/06/52

(1*R*,3b*S*,6a*R*,9a*S*,10a*R*,10b*S*,12a*R*)-10a,12a-Dimethyl-9-methylene-1-((*R*)-6-methylheptan-2-yl)-3,3a,3b,4,6,6a,9,9a,10,10a,10b,11,12,12a-tetradecahydro-1*H*-cyclopenta[7,8]phenanthro[2,3-*b*]furan-8(2*H*)-one (218c), (2'*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-3'-methylene-17-((*R*)-6-methylheptan-2-yl)-1,2,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-oxetan]-4'-one (218d)



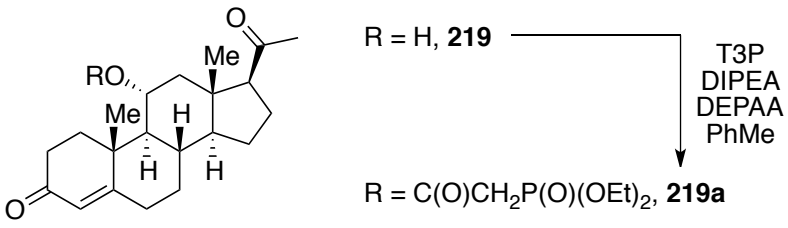
Synthesised using general procedure D with cholesteryl 2-diazo-2-(diethoxyphosphoryl)acetate **218b** (118 mg, 0.200 mmol), CH_2Cl_2 (4.0 mL), $Rh_2(oct)_4$ (3.1 mg, 4.0 μmol), THF (4.0 mL), KOBu-*t* (33.7 mg, 0.300 mmol) and paraformaldehyde (12.0 mg, 0.400 mmol). Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compounds* **218c**:**218d** (2:1) (35 mg, 40%).

Small quantities of each compound were isolated separately for characterisation purposes.

Data for **218c**; white solid; R_f 0.69 (1:1 hexane:EtOAc); m.p. 104–109 °C; ν_{max} (thin film)/cm^{-1} 2935s, 2866m, 1778s, 1462m, 1382m, 1254m, 1132s, 1000s, 926m, 813m; δ_H (400 MHz, $CDCl_3$) 0.69 (3 H, s), 0.83–1.62 (32 H, m), 1.79–1.89 (1 H, m), 1.99–2.07 (2 H, m), 2.19 (1 H, dd, J = 12.7, J = 3.4), 2.55–2.64 (2 H, m), 2.68–2.76 (1 H, m), 3.61 (1 H, td, J = 10.8, J = 5.7), 5.37 (1 H, d, J = 3.0), 5.51 (1 H, d, J = 5.3), 6.07 (1 H, d, J = 3.2); δ_C (100 MHz, $CDCl_3$) 11.9 (CH_3), 18.7 (CH_3), 20.6 (CH_3), 21.1 (CH_2), 22.5 (CH_3), 22.8 (CH_3), 23.8 (CH_2), 24.2 (CH), 28.0 (CH), 28.2 (CH_2), 31.7 (CH), 31.8 (CH_2), 35.8 (CH), 36.1 (CH_2), 38.1 (CH_2), 38.3 (CH_2), 38.4 (C), 39.5 (CH_2), 39.6 (CH_2), 42.3 (C), 44.6 (CH), 50.1 (CH), 56.1 (CH), 56.6 (CH), 82.8 (CH), 117.1 (CH_2), 126.1 (CH), 137.8 (C), 139.8 (C), 170.8 (C); HRMS (ESI$^+$): Found: 461.3387; $C_{30}H_{46}NaO_2$ (MNa^+) Requires 461.3390 (0.6 ppm error).

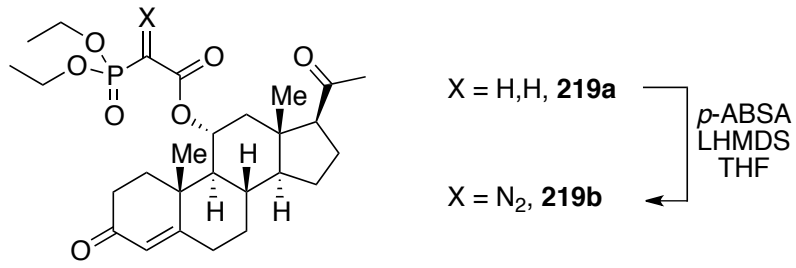
Data for **218d**; yellow gum; R_f 0.79 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2933s, 1821s, 1465m, 1378m, 1260m, 1191m, 1086m, 1034m, 908s, 806s, 731s; δ_H (400 MHz, $CDCl_3$) 0.70–2.33 (42 H, m), 2.92–2.97 (1 H, m), 5.34 (1 H, d, J = 1.3), 5.44–5.46 (1 H, m), 5.74 (1 H, d, J = 1.3); δ_C (100 MHz, $CDCl_3$) 11.8 (CH_3), 18.7 (CH_3), 18.8 (CH_3), 21.1 (CH_2), 22.5 (CH_3), 22.8 (CH_3), 23.8 (CH_2), 24.3 (CH), 28.0 (CH), 28.2 (CH_2), 31.0 (CH_2), 31.8 (CH_2), 32.0 (CH_2), 35.8 (CH), 36.1 (C), 36.6 (CH_2), 36.8 (CH_2), 39.5 (CH_2), 39.6 (CH_2), 41.4 (CH_2), 42.3 (C), 50.3 (CH), 56.1 (CH), 56.6 (CH), 86.9 (C), 113.8 (CH_2), 124.5 (CH), 138.2 (C), 148.9 (C), 163.5 (C); HRMS (ESI$^+$): Found: 461.3377; $C_{30}H_{46}NaO_2$ (MNa^+) Requires 461.3390 (2.9 ppm error).
Lab notebook reference: MGL/06/56

11-α-(2-(Diethoxyphosphoryl)acetoxy)progesterone (219a)



Synthesised using general procedure A with 11α-hydroxyprogesterone **219** (1.26 g, 3.81 mmol), toluene (19 mL), DEPAA (785 mg, 4.00 mmol), DIPEA (1.73 mL, 9.91 mmol) and T3P (3.15 g, 4.96 mmol, 50% w/w solution in EtOAc) affording the *title compound* **219a** as a pale yellow solid (1.92 g, 99%). No further purification was required; R_f 0.16 (1:8 hexane:EtOAc); m.p. 108–111 °C; ν_{max} (thin film)/cm^{-1} 2971s, 2938s, 1729s, 1703s, 1670s, 1613w, 1447w, 1391m, 1358m, 1267s, 1115m, 1048m, 1024s, 969s; δ_H (400 MHz, $CDCl_3$) 0.72 (3 H, s), 1.08–1.36 (12 H, m), 1.46–1.53 (2 H, m), 1.59–1.77 (3 H, m), 1.85–2.06 (3 H, m), 2.09 (3 H, s), 2.16–2.45 (6 H, m), 2.55 (1 H, t, J = 9.1), 2.85–2.99 (2 H, m), 4.13–4.21 (4 H, m), 5.28 (1 H, app. td, J = 10.6, J = 5.1), 5.75 (1 H, s); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 16.4 (d, J = 6.7, 2 × CH_3), 18.1 (CH_3), 22.9 (CH_2), 24.2 (CH_2), 31.3 (CH_3), 31.5 (CH_2), 33.3 (CH_2), 34.0 (CH_2), 35.0 (d, J = 134.9, CH_2), 35.0 (CH), 36.6 (CH_2), 39.7 (C), 43.7 (C), 44.9 (CH_2), 54.8 (CH), 55.3 (CH), 62.7 (app. t, J = 6.3, 2 × CH_2), 62.9 (CH), 72.3 (CH), 124.9 (CH), 165.0 (d, J = 5.9, C), 169.1 (C), 199.2 (C), 208.2 (C); δ_P (162 MHz, $CDCl_3$) 20.0; HRMS (ESI$^+$): Found: 531.2484; $C_{27}H_{41}NaO_7P$ (MNa^+) Requires 531.2482 (–0.3 ppm error), Found: 509.2663; $C_{27}H_{42}O_7P$ (MH^+) Requires 509.2663 (0.0 ppm error).
Lab notebook reference: MGL/06/71

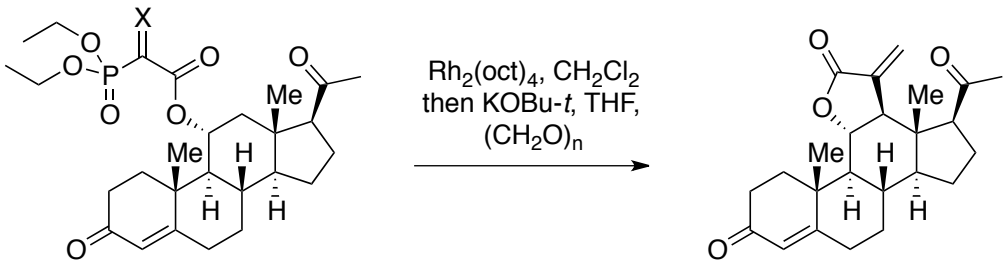
11-α-(2-Diazo-2-(diethoxyphosphoryl)acetoxy)progesterone (219b)



Synthesised using general procedure B with 11-α-(2-(diethoxyphosphoryl)acetoxy)progesterone **219a** (970 mg, 1.91 mmol), THF (9.5 mL), LHMDS (2.29 mL, 2.29 mmol, 1.0 M solution in THF) and *p*-ABSA (550 g, 2.29 mmol). Purification by column chromatography (1:20 hexane:EtOAc) afforded the *title compound* **219b** as a pale yellow solid (747 mg, 73%); R_f 0.28 (1:20 hexane:EtOAc); m.p. 143–146 °C; ν_{max} (thin film)/cm^{-1} 2968s, 2934s, 2129s, 1702s, 1674s, 1446w, 1391w, 1276s, 1219w, 1164w, 1120w, 1020s, 978m, 949m; δ_H (400 MHz, $CDCl_3$) 0.73 (3 H, s), 1.09–1.38 (12 H, m), 1.45–1.54 (2 H, m), 1.60–2.00 (6 H, m), 2.10 (3 H, s), 2.15–2.46 (6 H, m), 2.53 (1 H, t, *J* = 9.0), 4.09–4.28 (4 H, m), 5.40 (1 H, app. td, *J* = 10.6, *J* = 5.2), 5.75 (1 H, s); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 16.1 (d, *J* 6.6, CH_3), 16.2 (d, *J* 6.6, CH_3), 18.0 (CH_3), 22.9 (CH_2), 24.2 (CH_2), 31.3 (CH_3), 31.5 (CH_2), 33.2 (CH_2), 33.9 (CH_2), 34.9 (CH), 36.5 (CH_2), 39.7 (C), 43.7 (C), 45.5 (CH_2), 54.6 (d, *J* 224.4, C), 54.6 (CH), 55.4 (CH), 62.8 (CH), 63.5 (d, *J* 5.8, CH_2), 63.7 (d, *J* 5.8, CH_2), 72.1 (CH), 124.9 (CH), 162.5 (d, *J* 12.9, C), 168.8 (C), 198.8 (C), 208.2 (C); δ_P (162 MHz, $CDCl_3$) 10.4; HRMS (ESI$^+$): Found: 557.2388; $C_{27}H_{39}N_2NaO_7P$ (MNa^+) Requires 557.2387 (−0.2 ppm error), Found: 535.2560; $C_{27}H_{40}N_2O_7P$ (MH^+) Requires 535.2568 (1.5 ppm error).

Lab notebook reference: MGL/06/77

(1*S*,3a*S*,3b*S*,9a*R*,9b*S*,9c*S*,12a*R*,12b*R*)-1-Acetyl-9a,12b-dimethyl-12-methylene-3,3a,4,5,8,9,9a,9b,9c,12,12a,12b-dodecahydro-1*H*-cyclopenta[1,2]phenanthro[4,3-b]furan-7,11(2*H*,3b*H*)-dione (219c)



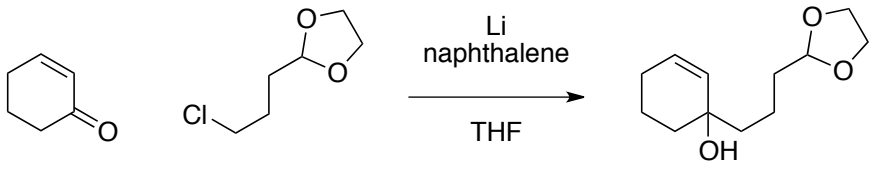
219b **219c**

Synthesised using general procedure D with 11-α-(2-diazo-2-(diethoxyphosphoryl)acetoxy)progesterone **219b** (107 mg, 0.200 mmol), CH_2Cl_2 (4.0 mL), $Rh_2(oct)_4$ (3.1 mg, 4.0 mol), THF (4.0 mL), KOBu-*t* (33.7 mg, 0.300 mmol) and paraformaldehyde (12.0 mg, 0.400 mmol). Purification by column chromatography (1:4 hexane:EtOAc) afforded the *title compound* **219c** as a pale yellow solid (18 mg, 24%); R_f 0.69 (EtOAc); m.p. 152–156 °C; ν_{max} (thin film)/cm^{-1} 2940m, 2878w, 1767s, 1706s, 1666s, 1616w, 1417w, 1353m, 1250m, 1236m, 1170m, 1134m, 1049m, 975m, 734m; δ_H (400 MHz, $CDCl_3$) 0.73–2.75 (26 H, m), 4.16 (1 H, app. t, J = 10.8), 5.41 (1 H, d, J = 2.9), 5.76 (1 H, s), 6.18 (1 H, d, J = 3.1); δ_C (100 MHz, $CDCl_3$) 10.1 (CH_3), 17.9 (CH_3), 23.8 (CH_2), 27.5 (CH_2), 30.6 (CH_2), 32.8 (CH_2), 33.0 (CH_3), 33.8 (CH_2), 34.4 (CH), 36.9 (CH_2), 38.8 (C), 45.6 (C), 56.4 (CH), 58.3 (CH), 58.8 (CH), 60.2 (CH), 79.1 (CH), 120.9 (CH_2), 125.3 (CH), 135.7 (C), 168.1 (C), 170.0 (C), 199.4 (C), 211.4 (C); HRMS (ESI^+): Found: 405.2025; $C_{24}H_{30}NaO_4$ (MNa^+) Requires 405.2036 (2.9 ppm error).

Lab notebook reference: MGL/06/79

5.2.2.3. Eudesmanolide frameworks

1-(3-(1,3-Dioxolan-2-yl)propyl)cyclohex-2-enol (235)



232 **234** **235**

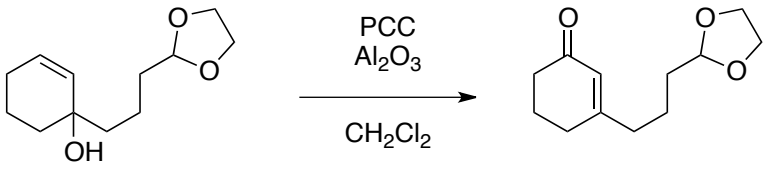
Procedure developed based on literature precedent.[112] Lithium naphthalenide could be effectively prepared using literature precedent.[170]

Lithium naphthalenide was prepared from freshly chopped lithium wire (333 mg, 48.0 mmol) and naphthalene (103 mg, 0.80 mmol) in dry THF (33 mL) under an atmosphere of argon,. The dark green mixture was cooled to –78 °C and neat 2-(3-chloropropyl)-1,3-dioxolane **234** (3.31 g, 22.0 mmol) was added over 5 mins during which time the mixture turned light green then colourless. The mixture was stirred at –78 °C for 1 h. To the now yellow solution was added freshly distilled neat 2-cyclohexen-1-one **232** (1.92 g, 20.0 mmol) dropwise over 5 mins and stirred for 16 h with warming at RT. The mixture was diluted with sat. aq. NH_4Cl (200 mL) and extracted with EtOAc (2 × 250 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the *title compound* **235** as a colourless oil (4.00 g, 94%), which was used without further purification; R_f 0.30 (2:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3447, 2933, 2872, 1704, 1408, 1140, 1031, 941, 733; δ_H (400 MHz, $CDCl_3$) 1.40–2.09 (12 H, m), 3.83–3.98 (4 H, m), 4.86 (1 H, t, J = 4.8), 5.62 (1 H, d, J = 10.0), 5.80 (1 H, ddd, J = 10.0, J = 4.5, J = 2.9); δ_C (100 MHz, $CDCl_3$) 18.2, 19.0, 25.2, 34.3, 35.3, 42.1, 64.8, 69.6, 104.5, 130.0, 132.6; HRMS (ESI^+): Found: 235.1311; $C_{12}H_{20}NaO_3$ (MNa^+) Requires 235.1305 (–2.5 ppm error).

Lab notebook reference: MGL/05/90

Obtained data in accord with those reported in the literature.[114]

3-(3-(1,3-Dioxolan-2-yl)propyl)cyclohex-2-enone (236)



235 **236**

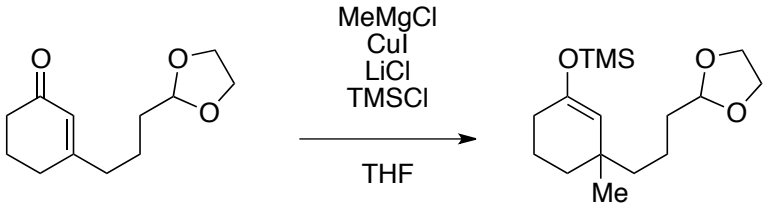
Prepared according to the literature procedure.[114]

To a suspension of PCC (4.31 g, 20.0 mmol) and Al_2O_3 (4.08 g, 40.0 mmol) in CH_2Cl_2 (50 mL) cooled to 0 °C was added 1-(3-(1,3-dioxolan-2-yl)propyl)cyclohex-2-enol **235** (2.12 g, 10.0 mmol) and stirred at RT for 1 h. The mixture was filtered through a pad of Celite and silica. The filtrate was concentrated *in vacuo* and purified by column chromatography (1:1 hexane:EtOAc) to afford the title compound **236** as a pale yellow oil (1.11 g, 52%); R_f 0.40 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2948, 2874, 1665, 1623, 1130, 1041; δ_H (400 MHz, $CDCl_3$) 1.59–1.70 (4 H, m), 1.98 (2 H, app. quin., J = 6.5), 2.24–2.29 (4 H, m), 2.35 (2 H, t, J = 6.7), 3.83–3.97 (4 H, m), 4.86 (1 H, t, J = 3.9), 5.88 (1 H, s); δ_C (100 MHz, $CDCl_3$) 21.2, 22.7, 29.5, 33.2, 37.3, 37.7, 64.9, 104.0, 125.8, 165.9, 199.8; HRMS (ESI^+): Found: 233.1153; $C_{12}H_{18}NaO_3$ (MNa^+) Requires 233.1148 (–2.2 ppm error), Found: 211.1336; $C_{12}H_{19}O_3$ (MNa^+) Requires 211.1329 (–3.6 ppm error).

Lab notebook reference: MGL/05/92

Obtained data in accord with reported literature.[114]

((3-(3-(1,3-Dioxolan-2-yl)propyl)-3-methylcyclohex-1-en-1-yl)oxy)trimethylsilane (237)



236 **237**

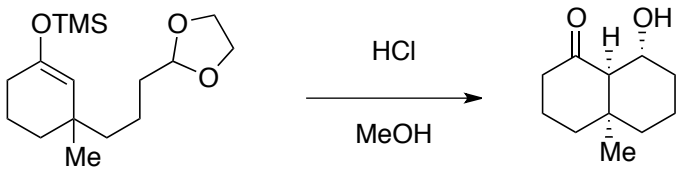
Procedure developed based on literature precedent.[113]

LiCl (90.0 mg, 2.12 mmol) and CuI (202 mg, 1.06 mmol) were thoroughly heat-dried under vacuum then dissolved in dry THF (106 mL) under an atmosphere of argon, at RT. The solution was cooled to –40 °C at which time 3-(3-(1,3-dioxolan-2-yl)propyl)cyclohex-2-enone **236** (4.46 g, 21.2 mmol) and freshly distilled TMSCl (2.96 mL, 23.3 mmol) were added and the solution stirred

for 10 mins. MeMgCl (10.6 mL, 31.8 mmol, 3.0 M solution in THF) was added dropwise over 5 mins and stirred at –40 °C for 45 mins. The reaction mixture was then poured onto sat. aq. NH_4Cl (300 mL) and extracted with EtOAc (3 × 300 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* **237** as a yellow oil (6.18 g, 98%), which was used without further purification; R_f 0.81 (2:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2951s, 2871m, 1662s, 1363s, 1251s, 1204m, 1192m, 1132s, 964m, 884s, 839s; δ_H (400 MHz, $CDCl_3$) 0.17 (9 H, s, H-13), 0.94 (3 H, s, H-12), 1.22–1.43 (6 H, m), 1.58–1.72 (4 H, m), 1.82–2.02 (2 H, m), 3.80–4.00 (4 H, m, H-11), 4.65 (1 H, s, H-2), 4.84 (1 H, t, J = 4.8, H-10); δ_C (100 MHz, $CDCl_3$) 0.3 (C-13), 18.9 (CH_2), 19.6 (CH_2), 27.9 (C-12), 29.9 (CH_2), 34.5 (CH_2), 34.6 (C-3), 34.7 (CH_2), 43.4 (CH_2), 64.8 (C-11), 104.7 (C-10), 114.6 (C-2), 149.2 (C-1); HRMS (ESI^+): Found: 321.1846; $C_{16}H_{30}NaO_3Si$ (MNa^+) Requires 321.1856 (3.2 ppm error), Found: 299.2031; $C_{16}H_{31}O_3Si$ (MH^+) Requires 299.2037 (1.9 ppm error).

Lab notebook reference: MGL/05/93, 06/04, 06/82

(4a*SR*,8*RS*,8a*RS*)-8-Hydroxy-4a-methyloctahydronaphthalen-1(2*H*)-one (238d)



237 **238d**

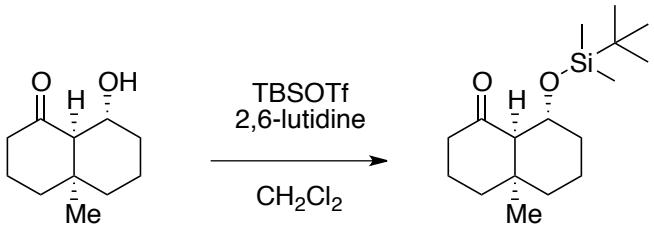
Procedure Developed based on literature precedent.[114]

To a solution of ((3-(3-(1,3-dioxolan-2-yl)propyl)-3-methylcyclohex-1-en-1-yl)oxy)trimethylsilane **237** (298 mg, 1.00 mmol), in MeOH (3.0 mL) was added 10% aq. HCl (1.6 mL) and refluxed at 80 °C for 1 h. The reaction mixture was neutralised by sat. aq. $NaHCO_3$ and concentrated *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography afforded the title compound **238d** as a brown solid (119 mg, 65%); R_f 0.32 (1:1 hexane:EtOAc); m.p. 52–55 °C; ν_{max} (thin film)/cm^{-1} 3406, 2931, 2870, 1702, 1048; δ_H (400 MHz, $CDCl_3$) 0.93 (3 H, s), 1.10–1.25 (3 H, m), 1.50 (1 H, dtd, J = 13.8, J = 3.3, J = 1.1), 1.60–1.67 (2 H, m), 1.71–2.10 (6 H, m), 2.26 (1 H, ddq, J = 14.5, J = 4.8, J = 1.7), 2.53 (1 H, ddd, J = 14.5, J = 13.3, J = 7.3), 4.00 (1 H, app. tt, J = 10.5, J = 5.1); δ_C (100 MHz, $CDCl_3$) 19.8 (CH_2), 22.1 (CH_2), 27.7 (CH_3), 29.8 (CH_2), 35.0 (CH_2), 37.1 (CH_2), 38.5 (CH_2), 39.4 (C), 67.4 (CH), 69.6 (CH), 215.0 (CO); HRMS (ESI^+): Found: 205.1204; $C_{11}H_{18}NaO_2$ (MNa^+) Requires 205.1199 (–2.2 ppm error), Found: 183.1382; $C_{11}H_{19}O_2$ (MH^+) Requires 183.1380 (–1.6 ppm error).

Lab notebook reference: MGL/05/94, 06/05

Obtained data in accord with reported literature.[114]

(4a*SR*,8*RS*,8a*RS*)-8-((*tert*-Butyldimethylsilyl)oxy)-4a-methyloctahydronaphthalen-1(2*H*)-one (244)

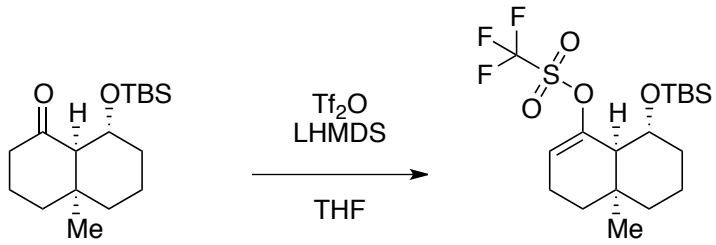


238d **244**

To a solution of (4a*SR*,8*RS*,8a*RS*)-8-hydroxy-4a-methyloctahydronaphthalen-1(2*H*)-one **238d** (273 mg, 1.50 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added 2,6-lutidine (0.44 mL, 3.75 mmol) then TBSOTf (0.38 mL, 1.65 mmol). The solution was stirred at 0 °C for 1 h then quenched with NH_4Cl (50 mL) and the organic fraction separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic fractions dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **244** as a white crystalline solid (440 mg, 99%); R_f 0.67 (4:1 hexane:EtOAc); m.p. 55–58 °C; ν_{max} (thin film)/cm^{-1} 2929s, 2857s, 1713s, 1472w, 1462m, 1252s, 1089s, 832s, 774s; δ_H (400 MHz, $CDCl_3$) −0.01 (3 H, s), 0.03 (3 H, s), 0.82 (9 H, s), 0.94 (3 H, s), 1.10–1.29 (3 H, m), 1.45 (1 H, dtd, J = 13.7, J = 3.8, J = 0.7), 1.53–1.67 (2 H, m), 1.80–2.04 (5 H, m), 2.18 (1 H, dddd, J = 13.7, J = 4.6, J = 3.1, J = 1.5), 2.46 (1 H, ddd, J = 13.5, J = 12.7, J = 6.7), 4.12 (1 H, app. td, J = 9.9, J = 4.2); δ_C (100 MHz, $CDCl_3$) −4.9 (CH_3), −3.8 (CH_3), 17.9 (C), 19.7 (CH_2), 22.6 (CH_2), 25.6 (CH_3), 27.9 (CH_3), 31.2 (CH_2), 35.1 (CH_2), 37.9 (CH_2), 38.3 (CH_2), 39.6 (C), 67.0 (CH), 70.5 (CH), 212.7 (C); HRMS (ESI^+): Found: 319.2055; $C_{17}H_{32}NaO_2Si$ (MNa^+) Requires 319.2064 (2.8 ppm error), Found: 297.2232; $C_{17}H_{33}O_2Si$ (MH^+) Requires 297.2244 (4.1 ppm error).

Lab notebook reference: MGL/06/11,28

(4a*SR*,8*RS*,8a*RS*)-8-((*tert*-Butyldimethylsilyl)oxy)-4a-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl trifluoromethanesulfonate (245)

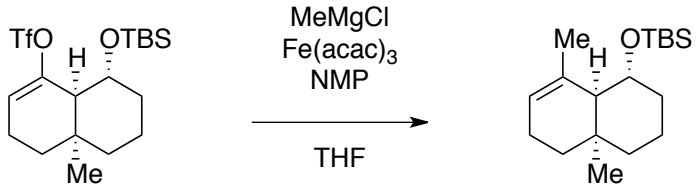


244 **245**

To a solution of (4a*SR*,8*RS*,8a*RS*)-8-((*tert*-butyldimethylsilyl)oxy)-4a-methyloctahydronaphthalen-1(2*H*)-one **244** (720 mg, 2.43 mmol) in THF (12.2 mL) cooled to –40 °C under an atmosphere of argon, was added LHMDS (7.28 mL, 7.28 mmol, 1.0 M solution in THF) dropwise. The solution was stirred at –40 °C for 1 h then trifluoromethanesulfonic anhydride (1.23 mL, 7.28 mmol) was added dropwise. The solution was stirred at –40 °C for 20 mins then quenched by addition of water (25 mL). The mixture was extracted with diethyl ether (3 × 50 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (40:1 hexane:diethyl ether) afforded the *title compound* **245** as a colourless oil (835 mg, 80%); R_f 0.77 (8:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2931s, 2858m, 1416s, 1246s, 1205s, 1144s, 1116m, 1082m, 1028m, 934m, 874m, 836s, 775m, 628m, 601s; δ_H (400 MHz, $CDCl_3$) 0.02 (3 H, s), 0.03 (3 H, s), 0.88 (9 H, s), 1.02–1.08 (4 H, m), 1.25–1.49 (4 H, m), 1.57–1.64 (1 H, m), 1.68–1.81 (2 H, m), 1.97 (1 H, d, J = 8.5), 2.24–2.29 (2 H, m), 3.69 (1 H, td, J = 9.3, J = 3.7), 5.68 (1 H, t, J = 3.9); δ_C (100 MHz, $CDCl_3$) –4.8 (CH_3), –4.9 (CH_3), 17.9 (C), 19.3 (CH_2), 21.5 (CH_2), 25.8 (CH_3), 26.9 (CH_3), 28.0 (CH_2), 35.4 (CH_2), 35.7 (C), 38.1 (CH_2), 52.9 (CH), 74.3 (CH), 117.7 (CH), 118.5 (q, J = 319.9, C), 151.9 (C); HRMS (ESI^+): Found: 451.1546; $C_{18}H_{31}F_3NaO_4SSi$ (MNa^+) Requires 451.1557 (2.4 ppm error), Found: 429.1737; $C_{18}H_{32}F_3O_4SSi$ (MH^+) Requires 429.1737 (0.1 ppm error).

Lab notebook reference: MGL/07/30

***tert*-Butyl(((1*RS*,4a*SR*,8a*SR*)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)oxy)dimethylsilane (246)**



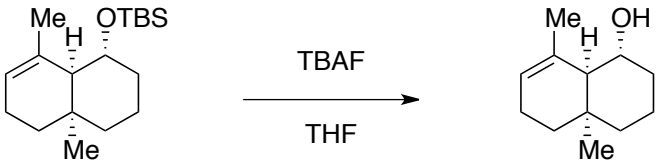
245 **246**

Prepared according to a modified literature procedure.[116]

To a solution of (4a*SR*,8*RS*,8a*RS*)-8-((*tert*-butyldimethylsilyl)oxy)-4a-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl trifluoromethanesulfonate **245** (355 mg, 0.828 mmol) in THF (1.24 mL) and NMP (3.31 mL) under an atmosphere of argon, was added $Fe(acac)_3$ (322 mg, 0.911 mmol). The solution was cooled to −25 °C and methylmagnesium chloride (2.76 mL, 8.28 mmol, 3.0 M solution in THF) was added dropwise. The orange solution was stirred at −25 °C for 1 h then quenched by careful addition of sat. aq. NH_4Cl (25 mL). The mixture was extracted with diethyl ether (3 × 25 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (hexane) afforded the *title compound* **246** as a colourless oil (201 mg, 82%); R_f 0.45 (hexane); ν_{max} (thin film)/cm^{-1} 2928s, 2858s, 1462m, 1373m, 1251s, 1095m, 1071s, 1041s, 921s, 860m, 834s, 773s; δ_H (400 MHz, $CDCl_3$) 0.01 (3 H, s), 0.03 (3 H, s), 0.87–0.95 (12 H, m), 1.19–1.55 (7 H, m), 1.69–1.79 (5 H, m), 1.98–2.15 (2 H, m), 3.61 (1 H, app. td, J = 9.6, J = 3.8), 5.24–5.30 (1 H, m); δ_C (100 MHz, $CDCl_3$) −4.6 (CH_3), −4.5 (CH_3), 18.1 (C), 19.9 (CH_2), 23.0 (CH_2), 26.0 (CH_3), 26.4 (CH_3), 27.4 (CH_3), 28.0 (CH_2), 34.0 (C), 36.4 (CH_2), 39.0 (CH_2), 54.1 (CH), 75.8 (CH), 120.1 (CH), 136.6 (C); HRMS (ESI^+): Found: 317.2265; $C_{18}H_{34}NaOSi$ (MNa^+) Requires 317.2271 (2.0 ppm error).

Lab notebook reference: MGL/07/34,37

(1*RS*,4a*SR*,8a*SR*)-4a,8-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-ol (247)

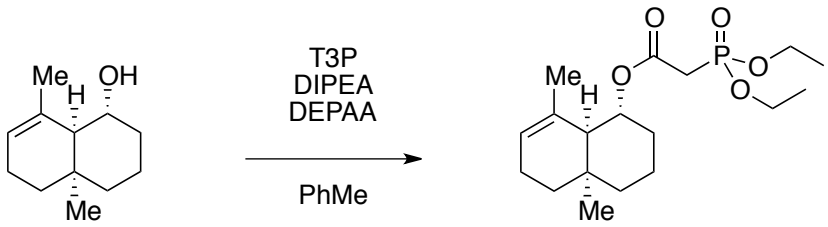


246 **247**

To a solution of *tert*-butyl(((1*RS*,4a*SR*,8a*SR*)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)oxy)dimethylsilane **246** (321 mg, 1.09 mmol) in THF (5.5 mL) under an atmosphere of argon, at RT was added TBAF (5.45 mL, 5.00 mmol, 1.0 M in THF). The solution was refluxed for 1 h, allowed to cool at RT, then quenched by addition of water (25 mL). The aqueous layer was extracted with diethyl ether (3 × 25 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound* **247** as a white solid (172 mg, 88%); R_f 0.39 (8:1 hexane:EtOAc); m.p. 65–67 °C; ν_{max} (thin film)/cm^{-1} 3337br, 2924s, 2863s, 2842s, 1450s, 1373m, 1353m, 1180w, 1133w, 1080m, 1061s, 1027s, 1008s, 854s, 804s; δ_H (400 MHz, $CDCl_3$) 0.86–0.91 (4 H, m), 1.21–1.31 (2 H, m), 1.37–1.56 (5 H, m), 1.69–1.77 (1 H, m), 1.85–1.91 (4 H, m), 2.04–2.08 (2 H, m), 3.56 (1 H, ddd, *J* = 11.2, *J* = 9.7, *J* = 4.3), 5.34–5.37 (1 H, m); δ_C (100 MHz, $CDCl_3$) 20.1 (CH_2), 23.1 (CH_2), 26.5 (CH_3), 27.0 (CH_3), 27.1 (CH_2), 34.0 (C), 36.6 (CH_2), 39.7 (CH_2), 54.6 (CH), 75.6 (CH), 120.9 (CH), 135.9 (C); HRMS (ESI$^+$): Found: 203.1405; $C_{12}H_{20}NaO$ (MNa^+) Requires 203.1406 (0.5 ppm error).

Lab notebook reference: MGL/07/38

(1*RS*,4a*SR*,8a*SR*)-4a,8-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl 2-(diethoxyphosphoryl)acetate (248)



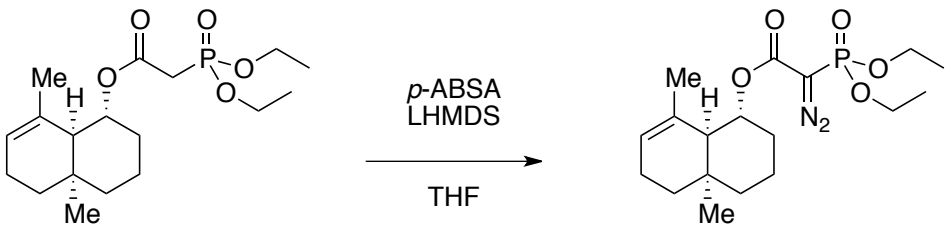
247 **248**

Synthesised using general procedure A with (1*RS*,4a*SR*,8a*SR*)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-ol **247** (145 mg, 0.804 mmol), toluene (4.0 mL), DEPAA (166 mg, 0.844 mmol), DIPEA (0.36 mL, 2.09 mmol) and T3P (665 mg, 1.05 mmol, 50% w/w solution in THF)

affording the *title compound* **248** as a yellow oil (288 mg, 100%). No further purification was required; R_f 0.33 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2978w, 2931s, 2869m, 1731s, 1450m, 1393m, 1375m, 1261s, 1111s, 1051s, 1020s, 967s; δ_H (400 MHz, $CDCl_3$) 0.89–0.97 (4 H, m), 1.23–1.36 (8 H, m), 1.41–1.58 (3 H, m), 1.68 (1 H, d, J = 9.9), 1.72–1.80 (4 H, m), 1.96–2.13 (3 H, m), 2.86–3.01 (2 H, m), 4.13–4.21 (4 H, m), 4.82 (1 H, app. td, J = 10.4, J = 4.2), 5.32–5.37 (1 H, m); δ_C (100 MHz, $CDCl_3$) 16.2 (d, J = 5.7, CH_3), 16.3 (d, J = 5.7, CH_3), 19.4 (CH_2), 22.8 (CH_2), 25.4 (CH_3), 26.9 (CH_3), 27.4 (CH_2), 31.9 (CH_2), 34.0 (C), 34.6 (d, J = 135.1, CH_2), 38.9 (CH_2), 50.5 (CH), 62.5 (app. t, J = 5.3, 2 × CH_2), 79.2 (CH), 122.0 (CH), 134.0 (C), 165.2 (d, J = 5.8, C); δ_P (162 MHz, $CDCl_3$) 20.5; HRMS (ESI$^+$): Found: 381.1802; $C_{18}H_{31}NaO_5P$ (MNa^+) Requires 381.1801 (–0.1 ppm error), Found: 359.1981; $C_{18}H_{32}O_5P$ (MH^+) Requires 359.1982 (0.1 ppm error).

Lab notebook reference: MGL/07/41

(1*RS*,4a*SR*,8a*SR*)-4a,8-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl 2-diazo-2-diethoxyphosphoryl)acetate (249)

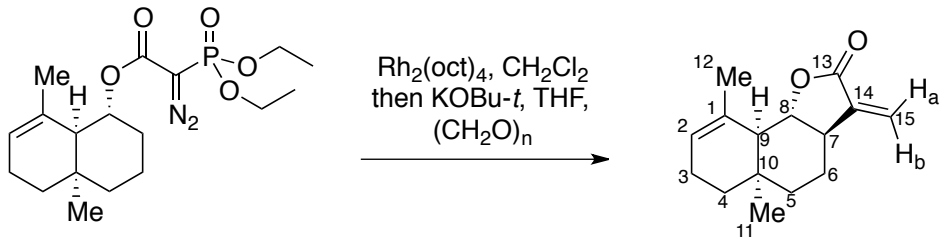


248 **249**

Synthesised using general procedure B with (1*RS*,4a*SR*,8a*SR*)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl 2-diethoxyphosphoryl)acetate **248** (279 mg, 0.778 mmol), THF (3.9 mL), LHMDS (0.93 mL, 0.934 mmol, 1.0 M solution in THF) and *p*-ABSA (224 mg, 0.934 mmol). Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **249** as a pale yellow oil (265 mg, 89%); R_f 0.63 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2932s, 2870w, 2124s, 1705s, 1451w, 1376w, 1286s, 1273s, 1022s, 980m; δ_H (400 MHz, $CDCl_3$) 0.91–0.99 (4 H, m), 1.24–1.38 (8 H, m), 1.43–1.60 (3 H, m), 1.68–1.79 (5 H, m), 1.92–2.15 (3 H, m), 4.10–4.28 (4 H, m), 4.95 (1 H, app. td, J = 10.2, J = 4.2), 5.35–5.39 (1 H, m); δ_C (100 MHz, $CDCl_3$) 16.0 (d, J = 7.2, 2 × CH_3), 19.3 (CH_2), 22.8 (CH_2), 25.1 (CH_3), 26.9 (CH_3), 27.6 (CH_2), 32.3 (CH_2), 34.1 (C), 38.7 (CH_2), 50.6 (CH), 53.7 (d, J = 227.8, C), 63.4 (d, J = 5.8, CH_2), 63.5 (d, J = 5.8, CH_2), 79.1 (CH), 122.4 (CH), 133.6 (C), 162.7 (d, J = 12.5, C); δ_P (162 MHz, $CDCl_3$) 11.0; HRMS (ESI$^+$): Found: 407.1704; $C_{18}H_{29}N_2NaO_5P$ (MNa^+) Requires 407.1706 (0.5 ppm error).

Lab notebook reference: MGL/07/42

(3a*RS*,5a*RS*,9a*SR*,9b*RS*)-5a,9-Dimethyl-3-methylene-3a,4,5,5a,6,7,9a,9b-octahydronaphtho[1,2-*b*]furan-2(3*H*)-one (240)

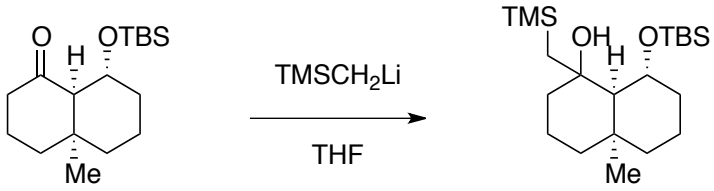


249 **240**

Synthesised using general procedure D with (1*RS*,4a*SR*,8a*SR*)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl 2-diazo-2-diethoxyphosphoryl)acetate **249** (72 mg, 0.187 mmol), CH_2Cl_2 (3.7 mL), $Rh_2(oct)_4$ (2.9 mg, 3.7 μmol), THF (3.7 mL), KOBu-*t* (31.5 mg, 0.281 mmol) and paraformaldehyde (11.2 mg, 0.374 mmol). Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound* **240** as a white crystalline solid (28 mg, 64%); R_f 0.33 (8:1 hexane:EtOAc); m.p. 63–66 °C; ν_{max} (thin film)/cm^{-1} 2931m, 2871w, 1771s, 1451m, 1378m, 1278m, 1244s, 1081m, 1127s, 1014s, 980s; δ_H (400 MHz, $CDCl_3$) 0.98–1.04 (4 H, m), 1.42–1.77 (4 H, m), 1.83–1.86 (4 H, m, H-9,12), 1.93–1.97 (1 H, m, H-6), 2.06–2.12 (2 H, m), 2.45–2.53 (1 H, m, H-7), 3.73 (1 H, app. t, *J* = 10.9, H-8), 5.39 (1 H, d, *J* = 3.1, H-15b), 5.39–5.43 (1 H, m, H-2), 6.06 (1 H, d, *J* = 3.3, H-15a); δ_C (100 MHz, $CDCl_3$) 21.8 (C-6), 22.8 (C-3), 24.7 (C-12), 26.7 (C-11), 27.9 (C-4), 34.9 (C-10), 40.2 (C-5), 49.2 (C-7), 50.5 (C-9), 87.4 (C-8), 117.3 (C-15), 121.1 (C-2), 133.4 (C-1), 139.3 (C-14), 170.9 (C-13); HRMS (ESI^+): Found: 255.1355; $C_{15}H_{20}NaO_2$ (MNa^+) Requires 255.1356 (0.2 ppm error), Found: 233.1545; $C_{15}H_{21}O_2$ (MH^+) Requires 233.1536 (–4.0 ppm error).

Lab notebook reference: MGL/07/43

(4a*SR*,8*RS*,8a*RS*)-8-((*tert*-Butyldimethylsilyl)oxy)-4a-methyl-1-((trimethylsilyl)methyl)decahydronaphthalen-1-ol (250)

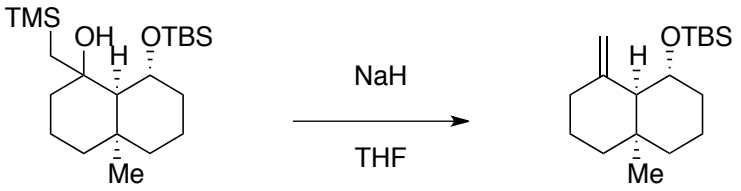


244 **250**

To a solution of (trimethylsilyl)methyllithium (4.63 mL, 4.63 mmol, 1.0 M in pentane) cooled to −78 °C under an atmosphere of argon, was added dropwise *via* cannula a solution of (4a*SR*,8*RS*,8a*RS*)-8-((*tert*-butyldimethylsilyl)oxy)-4a-methyloctahydronaphthalen-1(2*H*)-one **244** (458 mg, 1.54 mmol) in THF (2.5 mL) pre-cooled to −78 °C. The solution was stirred at −78 °C for 30 mins and then at RT for 1 h. The solution was quenched by careful addition of water (10 mL) and stirred for 10 mins. The aqueous layer was extracted with diethyl ether (3 × 25 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (20:1 hexane:EtOAc) afforded the *title compound* **250** as a colourless oil (497 mg, 84%); R_f 0.58 (8:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2928s, 2857m, 1462m, 1361w, 1249s, 1056m, 1027s, 1005m, 862m, 836s, 772s; δ_H (400 MHz, $CDCl_3$) 0.05 (3 H, s), 0.06 (3 H, s), 0.07 (9 H, s), 0.89 (9 H, s), 0.92–1.00 (2 H, m), 1.12 (3 H, s), 1.16–1.97 (14 H, m), 4.33–4.36 (1 H, m); δ_C (100 MHz, $CDCl_3$) −4.6 (CH_3), −4.2 (CH_3), 0.6 (CH_3), 16.9 (CH_2), 17.6 (CH_2), 17.9 (C), 25.8 (CH_3), 32.0 (CH_3), 32.3 (CH_2), 33.1 (C), 33.8 (CH_2), 34.2 (CH_2), 42.0 (CH_2), 42.7 (CH_2), 56.4 (CH), 69.1 (CH), 74.7 (C); HRMS (ESI^+): Found: 407.2754; $C_{21}H_{44}NaO_2Si_2$ (MNa^+) Requires 407.2772 (4.3 ppm error).

Lab notebook reference: MGL/06/42,29,33,90

tert-Butyldimethyl(((1*RS*,4a*RS*,8a*RS*)-4a-methyl-8-methylenedecahydronaphthalen-1-yl)oxy)silane (251)

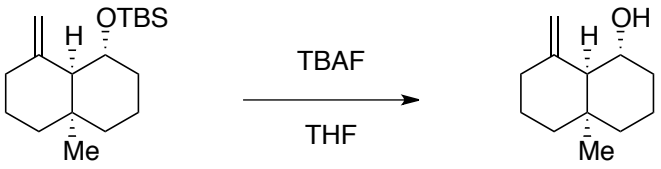


250 **251**

Sodium hydride was purified by washing with hexane and drying *in vacuo* immediately prior to the reaction.

To a suspension of sodium hydride (827 mg, 20.7 mmol) in THF (6.5 mL) under an atmosphere of argon, was added *via* cannula a solution of (4a*SR*,8*RS*,8a*RS*)-8-((*tert*-butyldimethylsilyl)oxy)-4a-methyl-1-((trimethylsilyl)methyl)decahydronaphthalen-1-ol **250** (497 mg, 1.29 mmol) in THF (3 mL). The mixture was heated to reflux and stirred for 4 h then cooled at RT. The mixture was carefully poured into sat. aq. NH_4Cl (100 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* affording the *title compound* **251** as a yellow oil (385 mg, 100%). No further purification was required; R_f 0.88 (8:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2929s, 2856m, 1650w, 1461m, 1362m, 1248s, 1096s, 1082s, 1055m, 919m, 888s, 833s, 772s; δ_H (400 MHz, $CDCl_3$) –0.03 (3 H, s), 0.01 (3 H, s), 0.84 (9 H, s), 0.89 (3 H, s), 0.91–0.97 (1 H, m), 1.16–1.28 (2 H, m), 1.37 (1 H, app. dtd, J = 13.5, J = 3.2, J = 1.6), 1.44–1.67 (4 H, m), 1.70–1.78 (2 H, m), 1.92 (1 H, app. ddtd, J = 12.5, J = 4.7, J = 3.2, J = 1.6), 2.00–2.13 (2 H, m), 3.76 (1 H, ddd, J = 10.8, J = 10.0, J = 4.6), 4.66 (1 H, app. dd, J = 2.8, J = 1.2), 4.76 (1 H, app. t, J = 2.1); δ_C (100 MHz, $CDCl_3$) –4.8 (CH_3), –4.1 (CH_3), 18.1 (C), 20.0 (CH_2), 23.3 (CH_2), 25.9 (CH_3), 28.4 (CH_3), 31.0 (CH_2), 31.3 (CH_2), 36.0 (C), 36.4 (CH_2), 40.1 (CH_2), 60.0 (CH), 68.9 (CH), 112.0 (CH_2), 146.4 (C); HRMS (ESI^+): Found: 317.2267; $C_{18}H_{34}NaOSi$ (MNa^+) Requires 317.2271 (1.4 ppm error).
Lab notebook reference: MGL/06/43,36,91

(1*RS*,4a*RS*,8a*RS*)-4a-Methyl-8-methylenedecahydronaphthalen-1-ol (252)

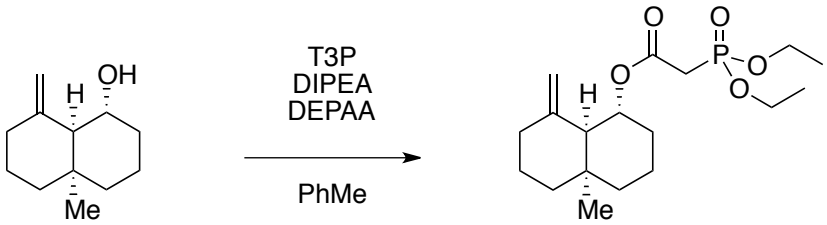


251 **252**

To a solution of *tert*-butyldimethyl(((1*RS*,4a*RS*,8a*RS*)-4a-methyl-8-methylenedecahydronaphthalen-1-yl)oxy)silane **251** (85 mg, 0.289 mmol) in THF (1.5 mL) under an atmosphere of argon, at RT was added TBAF (1.44 mL, 1.44 mmol, 1.0 M in THF). The solution was refluxed for 1 h, allowed to cool at RT, then quenched by addition of water (10 mL). The aqueous layer was extracted with diethyl ether (3 × 25 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound* **252** as a pale yellow oil (42 mg, 81%); R_f 0.31 (8:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3431br, 3068w, 2933s, 2867s, 1646m, 1450s, 1264w, 1159w, 1064s, 1049s, 1022m, 1011m, 896s; δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, s), 0.97 (1 H, app. dddt, J = 13.3, J = 3.9, J = 2.6, J = 1.3), 1.11–1.27 (2 H, m), 1.39–1.80 (8 H, m), 2.03–2.18 (3 H, m), 3.70 (1 H, ddd, J = 11.0, J = 10.2, J = 4.4), 4.78 (1 H, app. t, J = 2.2), 4.91 (1 H, app. t, J = 2.1); δ_C (100 MHz, $CDCl_3$) 19.7 (CH_2), 22.7 (CH_2), 28.3 (CH_3), 30.2 (CH_2), 30.8 (CH_2), 33.6 (CH_2), 35.7 (C), 39.9 (CH_2), 60.2 (CH), 67.1 (CH), 112.8 (CH_2), 146.9 (C); HRMS (ESI^+): Found: 203.1400; $C_{12}H_{20}NaO$ (MNa^+) Requires 203.1406 (3.3 ppm error).

Lab notebook reference: MGL/06/37,45,97

(1*RS*,4a*RS*,8a*RS*)-4a-Methyl-8-methylenedecahydronaphthalen-1-yl 2-(diethoxyphosphoryl)acetate (253)



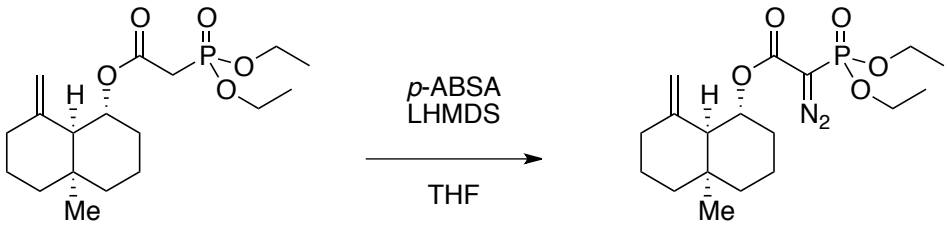
252 **253**

Synthesised using general procedure A with (1*RS*,4a*RS*,8a*RS*)-4a-methyl-8-methylenedecahydronaphthalen-1-ol **252** (108 mg, 0.600 mmol), toluene (3.0 mL), DEPAA (124 mg, 0.630 mmol), DIPEA (0.27 mL, 1.56 mmol) and T3P (496 mg, 0.780 mmol, 50% w/w solution

in THF) affording the *title compound* **253** as a yellow oil (176 mg, 82%). No further purification was required; R_f 0.14 (2:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2978w, 2932s, 2869w, 1731s, 1648w, 1445w, 1393w, 1267s, 1113m, 1051w, 1024s, 965s; δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, s), 0.94–1.00 (1 H, m), 1.16–1.66 (13 H, m), 1.78 (1 H, td, J = 13.5, J = 4.6), 1.85 (1 H, d, J = 10.8), 1.96–2.07 (2 H, m), 2.13–2.22 (1 H, m), 2.83 (1 H, dd, J = 21.4, J = 14.5), 2.90 (1 H, dd, J = 21.4, J = 14.5), 4.09–4.17 (4 H, m), 4.62 (1 H, app. t, J = 2.0), 4.73 (1 H, app. t, J = 2.3), 5.15 (1 H, app. td, J = 11.2, J = 4.5); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.5, 2 × CH_3), 19.7 (CH_2), 22.7 (CH_2), 28.0 (CH_3), 30.3 (CH_2), 30.7 (CH_2), 31.8 (CH_2), 34.2 (d, J = 134.6, CH_2), 36.3 (C), 39.6 (CH_2), 56.8 (CH), 62.5 (app. t, J = 5.7, 2 × CH_2), 72.0 (CH), 112.0 (CH_2), 145.8 (C), 165.1 (d, J = 5.9, C); δ_P (162 MHz, $CDCl_3$) 20.7; HRMS (ESI$^+$): Found: 381.1783; $C_{18}H_{31}NaO_5P$ (MNa^+) Requires 381.1801 (4.7 ppm error).

Lab notebook reference: MGL/06/51

(1*RS*,4a*RS*,8a*RS*)-4a-Methyl-8-methylenedecahydronaphthalen-1-yl 2-diazo-2-diethoxyphosphoryl)acetate (254)

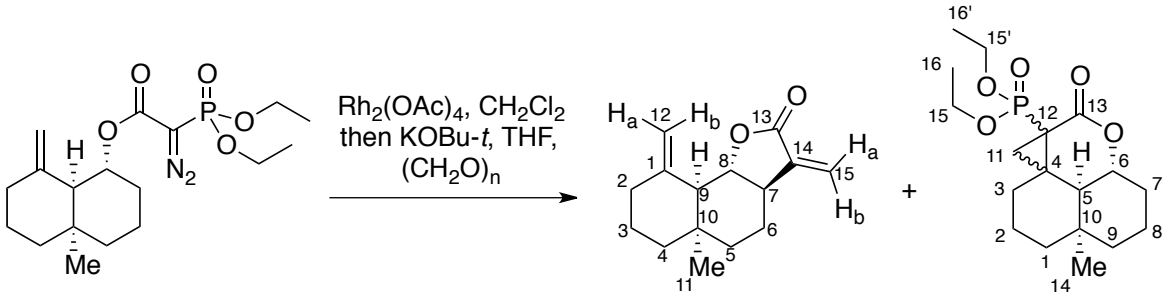


253 **254**

Synthesised using general procedure B with (1*RS*,4a*RS*,8a*RS*)-4a-methyl-8-methylenedecahydronaphthalen-1-yl 2-diethoxyphosphoryl)acetate **253** (175 mg, 0.488 mmol), THF (2.5 mL), LHMDS (0.59 mL, 0.585 mmol, 1.0 M solution in THF) and *p*-ABSA (141 mg, 0.585 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **254** as a colourless oil (146 mg, 78%); R_f 0.28 (2:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2982w, 2934s, 2870m, 2124s, 1703s, 1445w, 1361w, 1289w, 1273s, 1218m, 1161m, 1120w, 1021s, 978s; δ_H (400 MHz, $CDCl_3$) 0.91 (3 H, s), 0.96–1.02 (1 H, m), 1.17–1.67 (13 H, m), 1.78 (1 H, td, J = 13.5, J = 4.6), 1.86 (1 H, d, J = 10.8), 1.98–2.09 (2 H, m), 2.16–2.25 (1 H, m), 4.03–4.24 (4 H, m), 4.64 (1 H, app. t, J = 2.1), 4.74 (1 H, app. t, J = 2.3), 5.22 (1 H, app. td, J = 11.2, J = 4.5); δ_C (100 MHz, $CDCl_3$) 16.1 (app. t, J = 7.6, 2 × CH_3), 19.8 (CH_2), 22.7 (CH_2), 28.0 (CH_3), 30.3 (CH_2), 30.7 (CH_2), 32.1 (CH_2), 36.4 (C), 39.5 (CH_2), 53.0 (d, J = 225.1, C), 57.2 (CH), 63.4 (d, J = 5.5, CH_2), 63.5 (d, J = 5.7, CH_2), 72.2 (CH), 111.9 (CH_2), 146.1 (C), 162.6 (d, J = 12.4, C); δ_P (162 MHz, $CDCl_3$) 11.0; HRMS (ESI$^+$): Found: 385.1884; $C_{18}H_{30}N_2O_5P$ (MH^+) Requires 385.1887 (0.7 ppm error).

Lab notebook reference: MGL/06/55, 06/39, 07/13

(3a*RS*,5*aRS*,9a*RS*,9b*RS*)-5a-Methyl-3,9-dimethylenedecahydronaphtho[1,2-b]furan-2(9b*H*)-one (241) and Diethyl ((3a*RS*,3a^1*SR*,6a*RS*)-6a-methyl-2-oxododecahydrobenzo[*de*]cyclopropa[*c*]chromen-1a-yl)phosphonate (255)



254 **241** **255**

Synthesised using general procedure D with (1*RS*,4a*RS*,8a*RS*)-4a-methyl-8-methylenedecahydronaphthalen-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate **254** (77 mg, 0.200 mmol), CH_2Cl_2 (4.0 mL), $Rh_2(OAc)_4$ (1.8 mg, 4.0 μmol), THF (4.0 mL), KOBu-*t* (33.7 mg, 0.300 mmol) and paraformaldehyde (12.0 mg, 0.400 mmol). Purification by column chromatography (8:1 hexane:EtOAc → 1:4 hexane:EtOAc) afforded the *title compounds* **241** as a white crystalline solid (21 mg, 45%) and **255** as a pale yellow oil (8 mg, 11%).

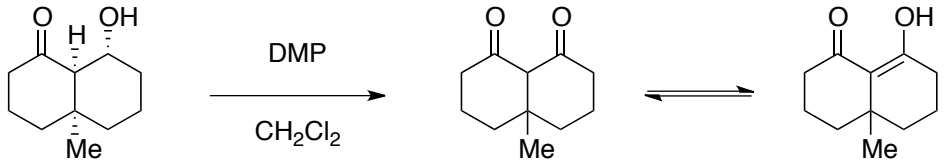
Data for **241**: R_f 0.39 (4:1 hexane:EtOAc); m.p. 66–68 °C; ν_{max} (thin film)/cm^{-1} 2932s, 2869w, 1770s, 1650w, 1456m, 1378m, 1247s, 1171m, 1131s, 1024s, 991s, 964m, 936m, 892m; δ_H (400 MHz, $CDCl_3$) 1.00 (3 H, s, H-15), 1.07 (1 H, dddt, *J* = 13.6, *J* = 3.9, *J* = 2.6, *J* = 1.3, H-1), 1.42–1.71 (5 H, m, H-2,8,9), 1.77 (1 H, td, *J* = 13.6, *J* = 4.6, H-1), 1.96–2.02 (1 H, m, H-8), 2.09–2.23 (3 H, m, H-3,5), 2.45 (1 H, app. tq, *J* = 11.1, *J* = 3.2, H-7), 4.11 (1 H, app. t, *J* = 11.1, H-6), 4.80 (1 H, app. t, *J* = 1.8, H-14a), 4.88 (1 H, app. t, *J* = 2.0, H-14b), 5.40 (1 H, d, *J* = 3.0, H-12b), 6.07 (1 H, d, *J* = 3.2, H-12a); δ_C (100 MHz, $CDCl_3$) 21.9 (C-8), 22.9 (C-2), 27.6 (C-15), 30.0 (C-3), 31.7 (C-1), 37.3 (C-10), 40.0 (C-9), 48.8 (C-7), 55.9 (C-5), 80.6 (C-6), 112.7 (C-14), 117.3 (C-12), 139.8 (C-11), 144.0 (C-4), 170.6 (C-13); HRMS (ESI$^+$): Found: 255.1362; $C_{15}H_{20}NaO_2$ (MNa^+) Requires 255.1356 (–2.5 ppm error), Found: 233.1541; $C_{15}H_{21}O_2$ (MH^+) Requires 233.1536 (–2.2 ppm error).

Data for **255**: R_f 0.33 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2980w, 2934s, 2868m, 1735s, 1452s, 1392w, 1375w, 1317m, 1296m, 1249s, 1208s, 1051m, 1031s, 971s; δ_H (400 MHz, $CDCl_3$) 0.58 (1 H, d, *J* = 9.8, H-5), 1.07–1.14 (4 H, m), 1.20–1.68 (15 H, m), 1.80 (1 H, dd, *J* = 17.5, *J* = 4.8, H-11), 1.85–1.93 (1 H, m), 2.05–2.08 (1 H, m), 2.13–2.22 (1 H, m, H-7), 4.09–4.34 (4 H, m, H-15,15'), 4.47 (1 H, ddd, *J* = 10.9, *J* = 9.9, *J* = 5.7, H-6); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.8, C-16/16'), 16.3 (d, *J* = 6.6, C-16/16'), 18.4 (C-2/8), 19.6 (C-2/8), 24.5 (d, *J* = 182.9, C-12), 26.4 (d,

J = 4.8, C-3), 26.7 (d, *J* = 3.9, C-3), 29.1 (C-14), 29.6 (d, *J* = 3.2, C-11), 31.6 (C-7), 32.1 (C-1/9), 34.3 (C-10), 40.2 (C-1/9), 55.4 (d, *J* = 2.0, C-5), 62.4 (d, *J* = 7.4, C-15/15'), 63.2 (d, *J* = 5.7, C-15/15'), 78.4 (C-6), 168.3 (d, *J* = 6.0, C-13); δ_P (162 MHz, $CDCl_3$) 21.6; HRMS (ESI^+): Found: 379.1635; $C_{18}H_{29}NaO_5P$ (MNa^+) Requires 379.1645 (2.7 ppm error), Found: 357.1817; $C_{18}H_{30}O_5P$ (MH^+) Requires 357.1825 (2.2 ppm error).

Lab notebook reference: MGL/07/14, 06/40, 06/58

4a-Methylhexahydronaphthalene-1,8(2*H*,8a*H*)-dione (258)



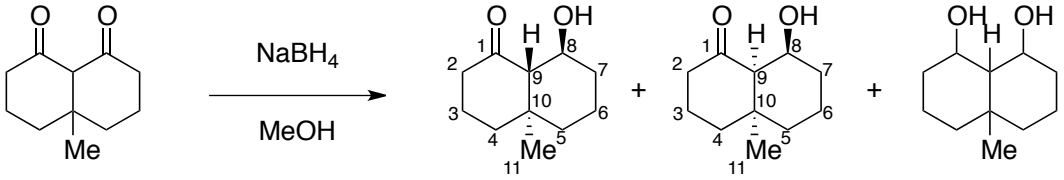
238d **258** **258'**

To a solution of (4a*SR*,8*RS*,8a*RS*)-8-hydroxy-4a-methyloctahydronaphthalen-1(2*H*)-one **238d** (182 mg, 1.00 mmol) in CH_2Cl_2 (10 mL), cooled to 0 °C was added DMP (467 mg, 1.10 mmol). The solution was stirred for 15 mins at 0 °C and then for 30 mins at RT after which a mixture of 1:1 sat. aq. $NaHCO_3$: sat. aq. $Na_2S_2O_3$ (50 mL) and CH_2Cl_2 (50 mL) was added and stirred vigourously for 1 h. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **258** as a yellow solid (142 mg, 79%); N.B. The product appears as two spots by TLC, a major (less polar) and minor (more polar); R_f 0.94 (major), 0.71 (minor) (2:1 hexane:EtOAc); m.p. 50–53 °C; ν_{max} (thin film)/cm^{-1} 2940s, 1593s, 1457m, 1407m, 1336w, 1248m, 1168w, 1081w, 1038w, 962m, 829m; δ_H (400 MHz, $CDCl_3$) 1.03 (3 H, s), 1.37 (2 H, td, *J* = 13.4, *J* = 4.0), 1.54 (2 H, dt, *J* = 13.0, *J* = 3.4), 1.69–1.77 (2 H, m), 1.87–1.99 (2 H, m), 2.28–2.43 (4 H, m), 16.02 (1 H, s); δ_C (100 MHz, $CDCl_3$) 17.1, 26.7, 32.1, 32.8, 37.4, 114.4, 189.9; HRMS (ESI^+): Found: 203.1036; $C_{11}H_{16}NaO_2$ (MNa^+) Requires 203.1043 (3.1 ppm error), Found: 181.1215; $C_{11}H_{17}O_2$ (MH^+) Requires 181.1223 (4.7 ppm error).

Lab notebook reference: MGL/06/87

Note: The spectroscopic data suggests the enol form **258'** predominates.

(4a*SR*,8*SR*,8a*SR*)-8-Hydroxy-4a-methyloctahydronaphthalen-1(2*H*)-one (238a) and (4a*SR*,8*SR*,8a*RS*)-8-Hydroxy-4a-methyloctahydronaphthalen-1(2*H*)-one (238c)



258 **238a** **238c** **258**

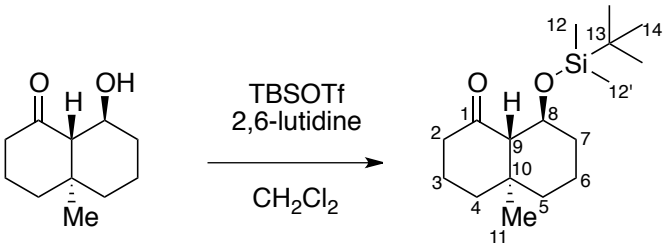
To a solution of 4a-methylhexahydronaphthalene-1,8(2*H*,8a*H*)-dione **258** (2.04 g, 11.3 mmol) in MeOH (57 mL) cooled to 0 °C under an atmosphere of argon, was added $NaBH_4$ (470 mg, 12.4 mmol) in small portions over 1 h. The solution was stirred at 0 °C for 1 h then quenched with sat. aq. $NaHCO_3$ (25 mL) and concentrated *in vacuo*. To the resulting white residue was added CH_2Cl_2 (50 mL) and water (50 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (1:1 hexane:diethyl ether → EtOAc) affording the *title compounds* **238a** (216 mg, 10%) and **238c** (333 mg, 16%) in addition to mixed **238a** and **238c** (202 mg, 10%) and diol **258** (478 mg, 23%).

Data for **238a**: Colourless oil, R_f 0.61 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3554br, 2931s, 1699s, 1458m, 1384m, 1275m, 1178m, 1087m, 1056s, 1038m, 936w; δ_H (400 MHz, $CDCl_3$) 0.80 (3 H, s, H-11), 1.17–1.36 (2 H, m), 1.41–1.47 (1 H, m), 1.49–1.67 (4 H, m), 1.82–2.02 (3 H, m), 2.12 (1 H, d, *J* 9.8, H-9), 2.25–2.36 (2 H, m), 3.17 (1 H, s, O*H*), 3.94 (1 H, app. td, *J* 10.6, *J* 4.5, H-8); δ_C (100 MHz, $CDCl_3$) 17.9 (C-11), 19.8 (CH_2), 22.2 (CH_2), 32.9 (CH_2), 39.7 (CH_2), 40.2 (CH_2), 40.8 (C-10), 41.4 (CH_2), 64.5 (C-9), 65.5 (C-8), 214.7 (C-1); HRMS (ESI^+): Found: 205.1206; $C_{11}H_{18}NaO_2$ (MNa^+) Requires 205.1199 (–3.4 ppm error).

Data for **238c**: Colourless oil, R_f 0.68 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3420br, 2937s, 1692s, 1458m, 1421m, 1380w, 1321m, 1267m, 1233m, 1189w, 1141w, 1057s; δ_H (400 MHz, $CDCl_3$) 0.97–1.02 (1 H, m), 1.07 (3 H, s, H-11), 1.34 (1 H, td, *J* 13.0, 4.2), 1.46–1.71 (5 H, m), 1.80–1.93 (3 H, m), 2.19–2.33 (2 H, m), 2.45–2.46 (1 H, m, H-9), 3.70–3.81 (2 H, m, H-8, O*H*); δ_C (100 MHz, $CDCl_3$) 20.3 (CH_2), 21.2 (CH_2), 26.5 (C-11), 31.1 (CH_2), 31.8 (CH_2), 39.2 (CH_2), 40.8 (C-10), 42.3 (CH_2), 59.2 (C-9), 68.4 (C-8), 216.0 (C-1); HRMS (ESI^+): Found: 205.1192; $C_{11}H_{18}NaO_2$ (MNa^+) Requires 205.1199 (3.5 ppm error).

Lab notebook reference: MGL/07/12,15

(4a*SR*,8*SR*,8a*SR*)-8-((*tert*-Butyldimethylsilyl)oxy)-4a-methyloctahydronaphthalen-1(2*H*)-one (261)

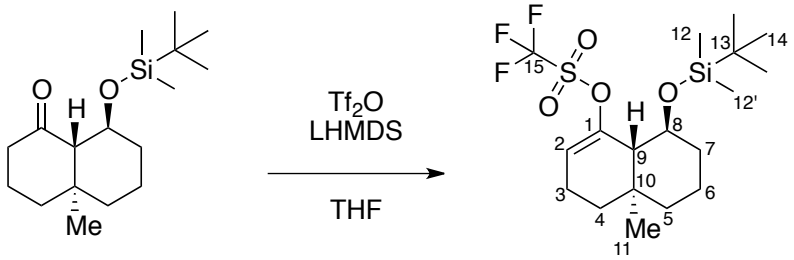


238a **261**

To a solution of (4a*SR*,8*SR*,8a*SR*)-8-hydroxy-4a-methyloctahydronaphthalen-1(2*H*)-one **238a** (205 mg, 1.12 mmol) in CH_2Cl_2 (11.2 mL) at 0 °C was added 2,6-lutidine (0.33 mL, 2.80 mmol) then TBSOTf (0.28 mL, 1.24 mmol). The solution was stirred at 0 °C for 1 h then quenched with NH_4Cl (50 mL) and the organic fraction separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic fractions dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **261** as a white crystalline solid (1.12 g, 100%); R_f 0.24 (20:1 hexane:EtOAc); m.p. 36–39 °C; ν_{max} (thin film)/cm^{-1} 2925s, 2853s, 1714s, 1470m, 1381m, 1358m, 1242s, 1142m, 1094s, 1077s, 1031m, 1004m, 940m, 901m, 830s, 779s, 666m; δ_H (400 MHz, benzene-d_6) 0.28 (3 H, s, H-12/12'), 0.38 (3 H, s, H-12/12'), 0.57 (3 H, s, H-11), 0.90–1.44 (17 H, m), 1.48–1.61 (1 H, m), 1.87–1.95 (2 H, m), 2.09–2.15 (2 H, m), 4.01–4.07 (1 H, m, H-8); δ_C (100 MHz, benzene-d_6) –4.3 (C-12/12'), –4.1 (C-12/12'), 17.7 (C-11), 18.4 (C-13), 20.2 (CH_2), 23.6 (CH_2), 26.4 (C-14), 36.3 (CH_2), 40.2 (CH_2), 40.9 (CH_2), 41.8 (C-10), 42.5 (CH_2), 64.8 (C-9), 65.7 (C-8), 208.6 (C-1); HRMS (ESI^+): Found: 319.2062; $C_{17}H_{32}NaO_2Si$ (MNa^+) Requires 319.2064 (0.5 ppm error), Found: 297.2244; $C_{17}H_{33}O_2Si$ (MH^+) Requires 297.2244 (0.0 ppm error).

Lab notebook reference: MGL/07/40

(4a*SR*,8*SR*,8a*SR*)-8-((*tert*-Butyldimethylsilyl)oxy)-4a-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl trifluoromethanesulfonate (262)

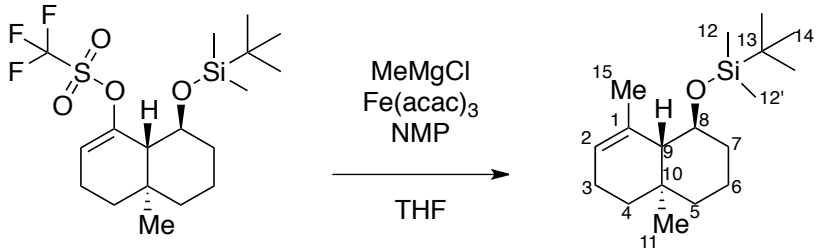


261 **262**

To a solution of (4a*SR*,8*SR*,8a*SR*)-8-((*tert*-butyldimethylsilyl)oxy)-4a-methyloctahydronaphthalen-1(2*H*)-one **261** (95 mg, 0.320 mmol) and trifluoromethanesulfonic anhydride (64.0 μL, 0.384 mmol) in CH_2Cl_2 (1.6 mL) at RT under an atmosphere of argon, was added 2,6-di-*tert*-butyl-4-methylpyridine (99 mg, 0.480 mmol) in one portion. The suspension was stirred for 2 h at RT then concentrated *in vacuo*. The residue was taken up in hexane (25 mL), filtered and washed with hexane (3 × 25 mL). The solution was concentrated *in vacuo*. Purification by column chromatography (20:1 hexane:EtOAc) afforded the *title compound* **262** as a yellow oil (92 mg, 67%); R_f 0.55 (20:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2930m, 2856m, 1669w, 1416s, 1245m, 1198s, 1142s, 1079s, 1032m, 1005w, 974m, 940m, 894m, 857m, 833s, 776s, 602s; δ_H (400 MHz, $CDCl_3$) 0.09 (3 H, s, H-12/12'), 0.10 (3 H, s, H-12/12'), 0.89–0.93 (12 H, m, H-11,14), 1.19–1.46 (5 H, m), 1.55–1.73 (2 H, m), 2.00–2.06 (1 H, m), 2.11–2.38 (3 H, m), 3.94 (1 H, app. td, J = 10.3, J = 4.3, H-8), 5.70–5.73 (1 H, m, H-2); δ_C (100 MHz, $CDCl_3$) −4.2 (C-12/12'), −3.2 (C-12/12'), 16.9 (C-11), 18.4 (C-13), 20.2 (CH_2), 21.1 (CH_2), 26.4 (C-14), 36.8 (CH_2), 36.9 (C-10), 38.3 (CH_2), 38.7 (CH_2), 52.9 (C-9), 69.2 (C8), 118.8 (q, J = 321.6, C-15), 119.1 (q, J = 1.7, C-2), 151.0 (C-1); HRMS (ESI^+): Found: 451.1545; $C_{18}H_{31}F_3NaO_4SSi$ (MNa^+) Requires 451.1557 (2.5 ppm error), Found: 429.1732; $C_{18}H_{32}F_3O_4SSi$ (MH^+) Requires 429.1737 (1.2 ppm error).

Lab notebook reference: MGL/07/47

tert-Butyl(((1*SR*,4a*SR*,8a*RS*)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)oxy)dimethylsilane (263)



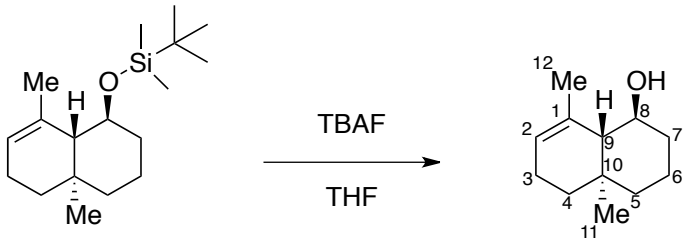
262 **263**

Prepared according to a modified literature procedure.[116]

To a solution of (4a*SR*,8*SR*,8a*SR*)-8-((*tert*-butyldimethylsilyl)oxy)-4a-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl trifluoromethanesulfonate **262** (154 mg, 0.359 mmol) in THF (0.54 mL) and NMP (1.44 mL) under an atmosphere of argon, was added $Fe(acac)_3$ (139 mg, 0.395 mmol). The solution was cooled to −25 °C and methylmagnesium chloride (1.20 mL, 3.59 mmol, 3.0 M solution in THF) was added dropwise. The orange solution was stirred at −25 °C for 1 h then quenched by careful addition of sat. aq. NH_4Cl (25 mL). The mixture was extracted with diethyl ether (3 × 25 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (hexane) afforded the *title compound* **263** as a colourless oil (97 mg, 92%); R_f 0.50 (hexane); ν_{max} (thin film)/cm^{-1} 2927s, 2855m, 1461m, 1378w, 1362w, 1255s, 1119m, 1069s, 1006w, 946w, 884s, 832s, 772s, 666m; δ_H (400 MHz, $CDCl_3$) 0.06 (3 H, s, H-12/12'), 0.09 (3 H, s, H-12/12'), 0.80 (3 H, s, H-11), 0.90 (9 H, s, H-14), 1.11–1.66 (7 H, m), 1.82–1.84 (3 H, m, H-15), 1.89–2.12 (4 H, m), 3.79 (1 H, app. td, J = 10.3, J = 4.7, H-8), 5.28–5.32 (1 H, m, H-2); δ_C (100 MHz, $CDCl_3$) −3.5 (C-12/12'), −2.8 (C-12/12'), 16.8 (C-11), 18.3 (C-13), 20.3 (CH_2), 22.9 (CH_2), 25.5 (C-15), 26.7 (C-14), 34.9 (C-10), 38.6 (CH_2), 38.7 (CH_2), 40.1 (CH_2), 53.5 (C-9), 70.7 (C-8), 122.5 (C-2), 135.9 (C-1); HRMS (ESI$^+$): Found: 317.2261; $C_{18}H_{34}NaOSi$ (MNa^+) Requires 317.2271 (3.3 ppm error).

Lab notebook reference: MGL/07/48

(1*SR*,4a*SR*,8a*RS*)-4a,8-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-ol (264)

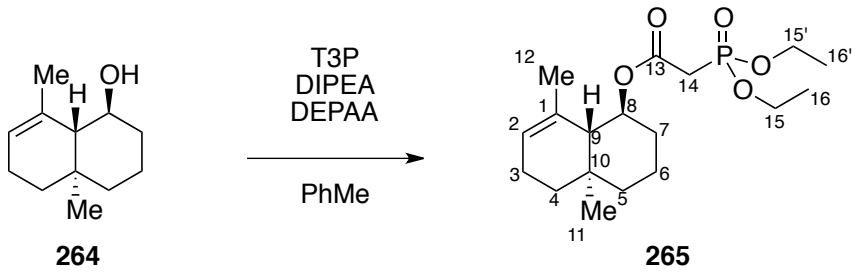


263 **264**

To a solution of *tert*-butyl(((1*SR*,4a*SR*,8a*RS*)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)oxy)dimethylsilane **263** (90 mg, 0.306 mmol) in THF (1.5 mL) under an atmosphere of argon, at RT was added TBAF (1.53 mL, 1.53 mmol, 1.0 M in THF). The solution was refluxed for 1 h, allowed to cool at RT, then quenched by addition of water (25 mL). The aqueous layer was extracted with diethyl ether (3 × 25 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound* **264** as a white solid (51 mg, 92%); R_f 0.27 (8:1 hexane:EtOAc); m.p. 59–61 °C; ν_{max} (thin film)/cm^{-1} 3350br, 2910s, 2848s, 1446s, 1375m, 1352m, 1267m, 1163m, 1079m, 1058s, 1018s, 933s, 8966m, 843m; δ_H (400 MHz, $CDCl_3$) 0.79 (3 H, s, H-11), 1.10–1.44 (6 H, m), 1.54–1.70 (2 H, m), 1.77–1.82 (1 H, m, H-9), 1.88 (3 H, s, H-12), 1.95–2.12 (3 H, m), 3.95 (1 H, app. td, J = 10.4, J = 4.4, H-8), 5.31–5.35 (1 H, m, H-2); δ_C (100 MHz, $CDCl_3$) 16.6 (C-11), 20.2 (CH_2), 23.0 (CH_2), 24.6 (C-12), 34.8 (C-10), 38.2 (CH_2), 38.2 (CH_2), 40.0 (CH_2), 53.5 (C-9), 69.3 (C-8), 123.3 (C-2), 134.8 (C-1); HRMS (ESI$^+$): Found: 203.1403; $C_{12}H_{20}NaO$ (MNa^+) Requires 203.1406 (1.7 ppm error).

Lab notebook reference: MGL/07/49

(1*SR*,4a*SR*,8a*RS*)-4a,8-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl 2-(diethoxyphosphoryl)acetate (265)

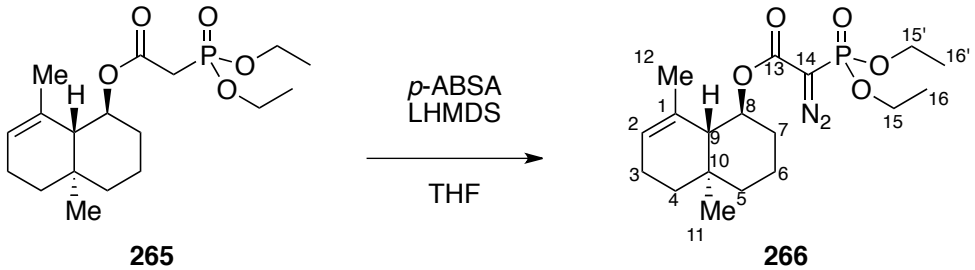


264 **265**

Synthesised using general procedure A with (1*SR*,4a*SR*,8a*RS*)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-ol **264** (49 mg, 0.272 mmol), toluene (1.4 mL), DEPAA (56 mg, 0.285 mmol), DIPEA (0.12 mL, 0.707 mmol) and T3P (225 mg, 0.354 mmol, 50% w/w solution in THF) affording the *title compound* **265** as a yellow oil (97 mg, 99%). No further purification was required; R_f 0.39 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2928s, 1729s, 1444m, 1393w, 1261s, 1208w, 1163w, 1114m, 1051w, 1021s, 967s, 823m, 783m; δ_H (400 MHz, $CDCl_3$) 0.81 (3 H, s, H-11), 1.11–1.71 (16 H, m), 1.93–2.14 (4 H, m), 2.82–2.97 (2 H, m, H-14), 4.10–4.18 (4 H, m, H-15,15'), 4.90 (1 H, app. td, *J* = 11.0, *J* = 4.9, H-8), 5.29–5.33 (1 H, m, H-2); δ_C (100 MHz, $CDCl_3$) 16.2–16.3 (3 C, m, C-11,16,16'), 19.7 (CH_2), 22.7 (CH_2), 23.4 (C-12), 33.2 (CH_2), 34.8 (d, *J* = 135.1, C-14), 34.9 (C-10), 38.0 (CH_2), 39.5 (CH_2), 49.3 (C-9), 62.5 (d, *J* = 6.4, C-15/15'), 62.5 (d, *J* = 6.4, C-15/15'), 74.1 (C-8), 123.7 (C-2), 133.2 (C-1), 165.3 (d, *J* = 5.8, C-13); δ_P (162 MHz, $CDCl_3$) 20.5; HRMS (ESI$^+$): Found: 381.1806; $C_{18}H_{31}NaO_5P$ (MNa^+) Requires 381.1801 (–1.1 ppm error), Found: 359.1977; $C_{18}H_{32}O_5P$ (MH^+) Requires 359.1982 (1.3 ppm error).

Lab notebook reference: MGL/07/50

(1*SR*,4a*SR*,8a*RS*)-4a,8-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl 2-diazo-2-diethoxyphosphoryl)acetate (266)

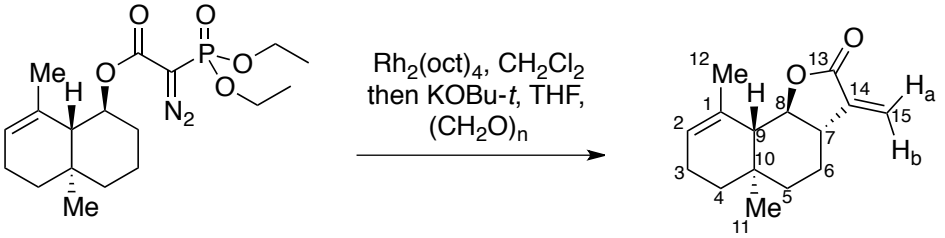


265 **266**

Synthesised using general procedure B with (1*SR*,4a*SR*,8a*RS*)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl 2-diethoxyphosphoryl)acetate **265** (96 mg, 0.268 mmol), THF (1.34 mL), LHMDS (0.32 mL, 0.321 mmol, 1.0 M solution in THF) and *p*-ABSA (77 mg, 0.321 mmol). Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **266** as a pale yellow oil (91 mg, 88%); R_f 0.74 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2929m, 2122s, 1697s, 1445m, 1368m, 1318w, 1297w, 1270s, 1163w, 1017s, 977m, 957m, 804s, 743s, 590s, 553s; δ_H (400 MHz, $CDCl_3$) 0.80 (3 H, s, H-11), 1.10–1.71 (16 H, m), 1.92–2.12 (4 H, m), 4.04–4.24 (4 H, m, H-15,15'), 4.98 (1 H, app. td, J = 11.0, J = 5.0, H-8), 5.30–5.33 (1 H, m, H-2); δ_C (100 MHz, $CDCl_3$) 16.0 (C-16/16'), 16.1 (C-16/16'), 16.3 (C-11), 19.7 (CH_2), 22.7 (CH_2), 23.0 (C-12), 33.8 (CH_2), 35.0 (C-10), 37.9 (CH_2), 39.4 (CH_2), 49.4 (C-9), 54.0 (d, J = 229.1, C-14), 63.4 (d, J = 5.7, C-15/15'), 63.6 (d, J = 5.9, C-15/15'), 74.2 (C-8), 123.8 (C-2), 132.9 (C-1), 162.7 (d, J = 12.2, C-13); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI$^+$): Found: 407.1716; $C_{18}H_{29}N_2NaO_5P$ (MNa^+) Requires 407.1706 (−2.3 ppm error).

Lab notebook reference: MGL/07/51

(3a*SR*,5a*RS*,9a*RS*,9b*SR*)-5a,9-Dimethyl-3-methylene-3a,4,5,5a,6,7,9a,9b-octahydronaphtho[1,2-*b*]furan-2(3*H*)-one (α-cyclocostunolide) (256)



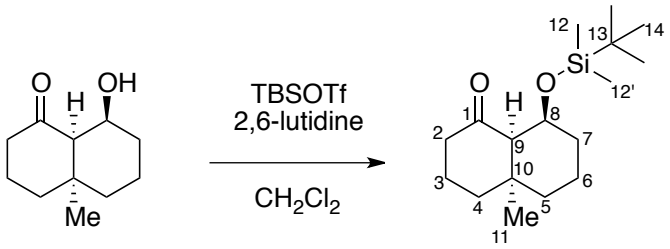
266 α-cyclocostunolide, **256**

Synthesised using general procedure D with (1*SR*,4a*SR*,8a*RS*)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl 2-diazo-2-diethoxyphosphoryl)acetate **266** (90 mg, 0.234 mmol), CH_2Cl_2 (4.7 mL), $Rh_2(oct)_4$ (3.6 mg, 4.7 μmol), THF (4.7 mL), KOBu-*t* (39.4 mg, 0.351 mmol) and paraformaldehyde (14.1 mg, 0.468 mmol). Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound* **256** as a white crystalline solid (28 mg, 52%); R_f 0.38 (8:1 hexane:EtOAc); m.p. 80–82 °C (lit.[171] 83–84 °C); ν_{max} (thin film)/cm^{-1} 2920s, 2851m, 1771s, 1445w, 1377w, 1344w, 1286w, 1249s, 1220w, 1132m, 1118m, 1076w, 1046w, 1014w, 982m; δ_H (400 MHz, $CDCl_3$) 0.90 (3 H, s, H-11), 1.21–1.74 (6 H, m), 1.83 (3 H, s, H-12), 1.97–2.18 (2 H, m), 2.34 (1 H, d, *J* = 11.2, H-9), 2.52 (1H, app. tq, *J* = 11.2, *J* = 3.5, H-7), 3.86 (1 H, app. t, *J* = 11.0, H-8), 5.35–5.38 (2 H, m, H-2,15b), 6.05 (1 H, d, *J* = 3.2, H-15a); δ_C (100 MHz, $CDCl_3$) 17.4 (C-11), 21.5 (C-6), 22.8 (C-3), 23.7 (C-12), 35.9 (C-10), 37.7 (C-4), 39.2 (C-5), 51.2 (C-9), 51.5 (C-9), 82.2 (C-8), 116.4 (C-15), 122.4 (C-2), 133.0 (C-1), 139.4 (C-14), 171.0 (C-13); HRMS (ESI$^+$): Found: 255.1360; $C_{15}H_{20}NaO_2$ (MNa^+) Requires 255.1356 (−1.7 ppm error).

Lab notebook reference: MGL/07/52

Obtained data in accord with reported literature.[120,171]

(4a*SR*,8*SR*,8a*RS*)-8-((*tert*-Butyldimethylsilyl)oxy)-4a-methyloctahydronaphthalen-1(2*H*)-one (260)

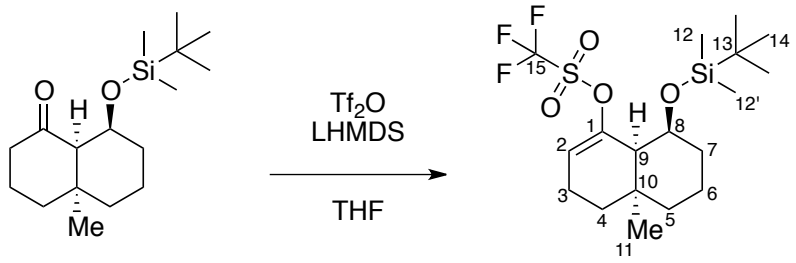


238c **260**

To a solution of (4a*SR*,8*SR*,8a*RS*)-8-hydroxy-4a-methyloctahydronaphthalen-1(2*H*)-one **238c** (316 mg, 1.73 mmol) in CH_2Cl_2 (17.3 mL) at 0 °C was added 2,6-lutidine (0.50 mL, 4.33 mmol) then TBSOTf (0.44 mL, 1.91 mmol). The solution was stirred at 0 °C for 1 h then quenched with NH_4Cl (50 mL) and the organic fraction separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic fractions dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **260** as a pale yellow oil (491 mg, 96%); R_f 0.20 (20:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2951m, 2930s, 2856s, 1699s, 1471m, 1462m, 1383m, 1255s, 1226m, 1172m, 1150m, 1060m, 1033s, 973s, 961s, 900s, 836s, 775s, 688m; δ_H (400 MHz, benzene-d_6) −0.09 (3 H, s, H-12/12'), −0.04 (3 H, s, H-12/12'), 0.73 (3 H, s, H-11), 0.81–1.41 (14 H, m), 1.57–1.68 (3 H, m), 1.84 (1 H, qt, J = 13.1, J = 3.3), 1.94–1.96 (1 H, m, H-9), 2.33–2.56 (3 H, m), 4.02 (1 H, app. q, J = 3.2, H-8); δ_C (100 MHz, benzene-d_6) −5.0 (C-12/12'), –4.9 (C-12/12'), 16.3 (CH_2), 18.1 (C-13), 20.7 (CH_2), 26.1 (C-14), 29.5 (C-11), 31.7 (CH_2), 33.8 (CH_2), 35.4 (C-10), 39.6 (CH_2), 40.6 (CH_2), 61.7 (C-9), 69.9 (C-8), 212.3 (C-1); HRMS (ESI^+): Found: 319.2068; $C_{17}H_{32}NaO_2Si$ (MNa^+) Requires 319.2064 (−1.4 ppm error), Found: 297.2249; $C_{17}H_{33}O_2Si$ (MH^+) Requires 297.2244 (-1.5 ppm error).

Lab notebook reference: MGL/07/39

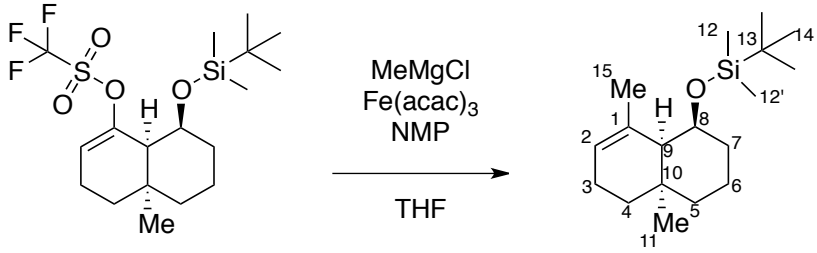
(4a*SR*,8*SR*,8a*RS*)-8-((*tert*-Butyldimethylsilyl)oxy)-4a-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl trifluoromethanesulfonate (267)



260 **267**

To a solution of (4a*SR*,8*SR*,8a*RS*)-8-((*tert*-butyldimethylsilyl)oxy)-4a-methyloctahydronaphthalen-1(2*H*)-one **260** (325 mg, 1.10 mmol) in THF (5.5 mL) cooled to −40 °C under an atmosphere of argon, was added LHMDS (3.29 mL, 3.29 mmol, 1.0 M solution in THF) dropwise. The solution was stirred at −40 °C for 1 h then trifluoromethanesulfonic anhydride (0.55 mL, 3.29 mmol) was added dropwise. The solution was stirred at −40 °C for 20 mins then quenched by addition of water (25 mL). The mixture was extracted with diethyl ether (3 × 50 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (hexane) afforded the *title compound* **267** as a colourless oil (291 mg, 62%); R_f 0.74 (20:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2931m, 2857s, 1416s, 1246s, 1205s, 1143s, 1074s, 1042s, 990m, 977m, 939m, 908m, 878s, 837s, 802m, 776m, 604m; δ_H (400 MHz, $CDCl_3$) −0.02 (3 H, s, H-12/12'), 0.02 (3 H, s, H-12/12'), 0.84–0.94 (13 H, m), 1.26–1.40 (3 H, m), 1.51–1.59 (1 H, m), 1.74–1.86 (2 H, m), 1.94 (1 H, d, J = 3.1, H-9), 2.12–2.32 (3 H, m), 4.11 (1 H, app. q, J = 2.8, H-8), 5.75–5.77 (1 H, m, H-2); δ_C (100 MHz, $CDCl_3$) −5.5 (C-12/12'), −4.9 (C-12/12'), 15.4 (CH_2), 17.8 (C-13), 21.6 (CH_2), 25.7 (C-14), 28.0 (CH_2), 28.2 (C-11), 33.2 (CH_2), 33.7 (C-10), 39.9 (CH_2), 50.2 (C-9), 65.9 (C-8), 118.5 (q, J = 320.2, C-15), 119.2 (C-2), 149.0 (C-1); HRMS (ESI^+): Found: 451.1541; $C_{18}H_{31}F_3NaO_4SSi$ (MNa^+) Requires 451.1557 (3.4 ppm error).
Lab notebook reference: MGL/07/55

***tert*-Butyl(((1*SR*,4a*SR*,8a*SR*)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)oxy)dimethylsilane (268)**

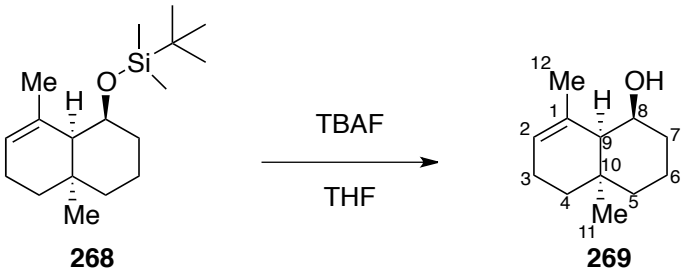


Prepared according to a modified literature procedure.[116]

To a solution of (4a*SR*,8*SR*,8a*RS*)-8-((*tert*-butyldimethylsilyl)oxy)-4a-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl trifluoromethanesulfonate **267** (270 mg, 0.630 mmol) in THF (0.95 mL) and NMP (2.52 mL) under an atmosphere of argon, was added $Fe(acac)_3$ (245 mg, 0.693 mmol). The solution was cooled to −25 °C and methylmagnesium chloride (2.10 mL, 6.30 mmol, 3.0 M solution in THF) was added dropwise. The orange solution was stirred at −25 °C for 1 h then quenched by careful addition of sat. aq. NH_4Cl (25 mL). The mixture was extracted with diethyl ether (3 × 25 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (hexane) afforded the *title compound* **268** as a colourless oil (110 mg, 59%); R_f 0.93 (hexane); ν_{max} (thin film)/cm^{-1} 2928s, 2855w, 1446m, 1378m, 1251s, 1153s, 1079s, 1060s, 1040s, 977s, 907s, 834s, 798s, 772s, 679m; δ_H (400 MHz, $CDCl_3$) −0.04 (3 H, s, H-12/12'), 0.00 (3 H, s, H-12/12'), 0.77–0.89 (13 H, m), 1.23–1.49 (5 H, m), 1.63–1.65 (3 H, m, H-15), 1.74–1.88 (2 H, m), 1.98–2.04 (2 H, m), 2.28–2.35 (1 H, m), 4.06 (1 H, app. q, J = 2.7, H-8), 5.37–5.39 (1 H, m, H-2); δ_C (100 MHz, $CDCl_3$) −5.2 (C-12/12'), −4.7 (C-12/12'), 16.1 (CH_2), 18.0 (C-13), 22.5 (C-15), 23.3 (CH_2), 25.7 (C-14), 28.6 (CH_2), 28.8 (C-11), 31.9 (C-10), 34.4 (CH_2), 40.8 (CH_2), 51.5 (C-9), 67.2 (C-8), 122.6 (C-2), 131.9 (C-1); HRMS ($APCI^+$): Found: 295.2443; $C_{18}H_{35}OSi$ (MH^+) Requires 295.2452 (2.9 ppm error).

Lab notebook reference: MGL/07/56

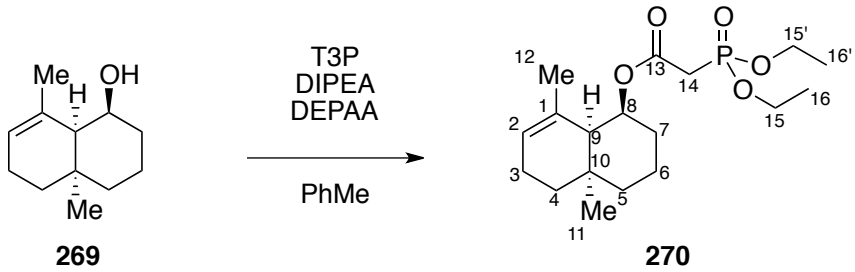
(1*SR*,4a*SR*,8a*SR*)-4a,8-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-ol (269)



268 **269**

To a solution of *tert*-butyl(((1*SR*,4a*SR*,8a*SR*)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)oxy)dimethylsilane **268** (99 mg, 0.336 mmol) in THF (1.68 mL) under an atmosphere of argon, at RT was added TBAF (1.68 mL, 1.68 mmol, 1.0 M in THF). The solution was refluxed for 24 h, allowed to cool at RT, then quenched by addition of water (25 mL). The aqueous layer was extracted with diethyl ether (3 × 25 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound* **269** as a colourless oil (43 mg, 71%); R_f 0.45 (8:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3354br, 2929s, 2871s, 2842s, 1448s, 1389m, 1377m, 1342w, 1255s, 1199w, 1162m, 1072m, 1012s, 963s, 949s, 831s; δ_H (400 MHz, $CDCl_3$) 0.80 (3 H, s, H-11), 0.87–0.92 (1 H, m), 1.22–1.86 (10 H, m), 1.97–2.17 (4 H, m), 3.98 (1 H, app. q, J = 3.0, H-8), 5.65–5.68 (1 H, m, H-2); δ_C (100 MHz, $CDCl_3$) 15.8 (CH_2), 21.9 (C-12), 22.8 (CH_2), 28.4 (CH_2), 28.5 (C-11), 31.3 (C-10), 31.6 (CH_2), 40.4 (CH_2), 51.2 (C-9), 65.3 (C-8), 125.1 (C-2), 132.3 (C-1); HRMS (ESI^+): Found: 203.1406; $C_{12}H_{20}NaO$ (MNa^+) Requires 203.1406 (0.0 ppm error).
Lab notebook reference: MGL/07/58

(1*SR*,4a*SR*,8a*SR*)-4a,8-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl 2-(diethoxyphosphoryl)acetate (270)



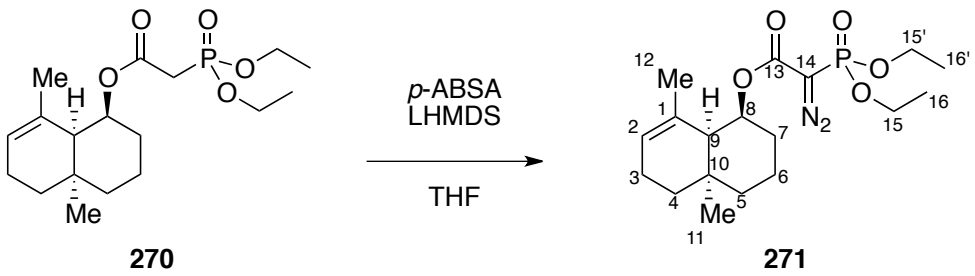
269 **270**

Synthesised using general procedure A with (1*SR*,4a*SR*,8a*SR*)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-ol **269** (21 mg, 0.116 mmol), toluene (0.58 mL), DEPAA (24 mg, 0.122 mmol), DIPEA (0.05 mL, 0.302 mmol) and T3P (96 mg, 0.151 mmol, 50% w/w solution in THF).

Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **270** as a pale yellow oil (26 mg, 63%); R_f 0.38 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2929m, 1732s, 1448m, 1393w, 1261s, 1113w, 1021s, 968s, 813m; δ_H (400 MHz, $CDCl_3$) 0.83–0.91 (4 H, m), 1.24–1.54 (9 H, m), 1.58 (1 H, d, *J* = 2.6, H-9), 1.62–1.64 (3 H, m, H-12), 1.67–1.92 (2 H, m), 1.98–2.16 (3 H, m), 2.79–2.94 (2 H, m, H-14), 4.10–4.18 (4 H, m, H-15,15'), 5.32 (1 H, app. q, *J* = 3.1, H-8), 5.38–5.41 (1 H, m, H-2); δ_C (100 MHz, $CDCl_3$) 16.2–16.3 (2 C, m, C-16,16'), 16.4 (CH_2), 22.3 (C-12), 22.8 (CH_2), 28.0 (CH_2), 28.3 (C-11), 30.4 (CH_2), 31.6 (C-10), 34.5 (d, *J* = 134.5, C-14), 40.0 (CH_2), 49.4 (C-9), 62.4 (d, *J* = 6.5, C-15/15'), 62.5 (d, *J* = 6.5, C-15/15'), 70.4 (C-8), 122.9 (C-2), 131.1 (C-1), 164.8 (d, *J* = 6.1, C-13); δ_P (162 MHz, $CDCl_3$) 20.9; HRMS (ESI$^+$): Found: 381.1802; $C_{18}H_{31}NaO_5P$ (MNa^+) Requires 381.1801 (–0.3 ppm error), Found: 359.1975; $C_{18}H_{32}O_5P$ (MH^+) Requires 359.1982 (2.0 ppm error).

Lab notebook reference: MGL/07/59

(1*SR*,4a*SR*,8a*SR*)-4a,8-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl 2-diazo-2-diethoxyphosphoryl)acetate (271)

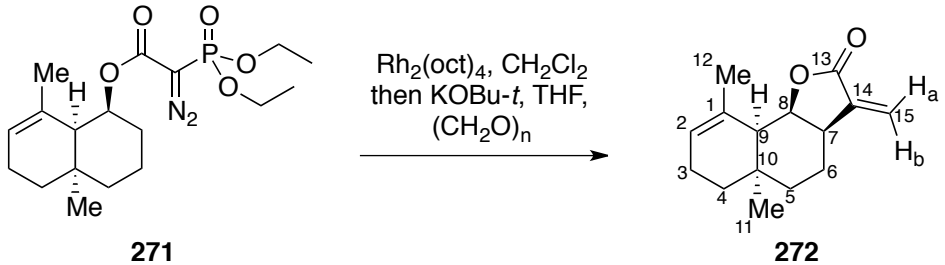


270 **271**

Synthesised using general procedure B with (1*SR*,4a*SR*,8a*SR*)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl 2-diethoxyphosphoryl)acetate **270** (26 mg, 72.5 μmol), THF (0.36 mL), LHMDS (0.09 mL, 87.1 μmol, 1.0 M solution in THF) and *p*-ABSA (20.9 mg, 87.1 μmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **271** as a pale yellow solid (21 mg, 75%); R_f 0.67 (1:1 hexane:EtOAc); m.p. 65–68 °C; ν_{max} (thin film)/cm^{-1} 2932m, 2123s, 1706s, 1448w, 1368w, 1271s, 1217w, 1021s, 977m; δ_H (400 MHz, $CDCl_3$) 0.86 (3 H, s, H-11), 0.89–0.93 (1 H, m), 1.17–1.55 (9 H, m), 1.61–1.72 (5 H, m), 1.89–2.12 (3 H, m), 4.06–4.25 (4 H, m, H-15,15'), 5.39–5.43 (2 H, m, H-2,8); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* = 7.4, C-16/16'), 16.1 (d, *J* = 6.7, C-16/16'), 16.3 (CH_2), 22.3 (C-12), 22.8 (CH_2), 28.0 (CH_2), 28.3 (C-11), 30.7 (CH_2), 31.6 (C-10), 40.0 (CH_2), 49.5 (C-9), 52.9 (d, *J* = 226.5, C-14), 63.4 (d, *J* = 5.7, C-15/15'), 63.6 (d, *J* = 5.7, C-15/15'), 70.5 (C-8), 122.9 (C-2), 131.2 (C-1), 162.6 (d, *J* = 13.1, C-13); δ_P (162 MHz, $CDCl_3$) 11.3; HRMS (ESI$^+$): Found: 407.1707; $C_{18}H_{29}N_2NaO_5P$ (MNa^+) Requires 407.1706 (–0.2 ppm error).

Lab notebook reference: MGL/07/60

(3a*RS*,5a*RS*,9a*SR*,9b*SR*)-5a,9-Dimethyl-3-methylene-3a,4,5,5a,6,7,9a,9b-octahydronaphtho[1,2-*b*]furan-2(3*H*)-one



271 **272**

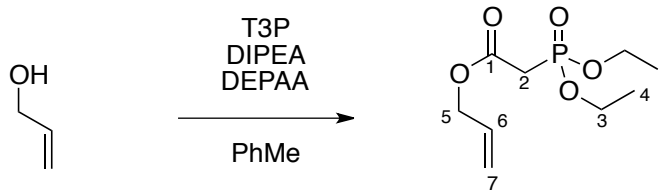
Synthesised using general procedure D with (1*SR*,4a*SR*,8a*SR*)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl 2-diazo-2-diethoxyphosphoryl)acetate **271** (20 mg, 52.0 μmol), CH_2Cl_2 (1.04 mL), $Rh_2(oct)_4$ (0.8 mg, 1.04 μmol), THF (1.04 mL), KOBu-*t* (8.8 mg, 78.0 μmol) and paraformaldehyde (3.1 mg, 104 μmol). Purification by column chromatography (8:1 hexane:EtOAc) afforded the *title compound* **272** as a pale yellow oil (8 mg, 66%); R_f 0.36 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2928s, 2865w, 1759s, 1452w, 1402w, 1380w, 1346w, 1263m, 1156w, 1143m, 1130m, 1080m, 957m; δ_H (400 MHz, $CDCl_3$) 0.91 (3 H, s, H-11), 1.05–1.09 (1 H, m), 1.21-1.81 (9 H, m), 2.00–2.09 (2 H, m), 3.00–3.06 (1 H, m, H-7), 4.74 (1 H, dd, J = 6.1, J = 3.8, H-8), 5.57–5.59 (2 H, m, H-2,15b), 6.19 (1 H, d, J = 1.6, H-15a); δ_C (100 MHz, $CDCl_3$) 22.1 (C-12), 22.5 (C-3), 24.9 (C-6), 27.1 (C-11), 30.4 (C-10), 30.7 (C-4), 35.8 (C-5), 39.7 (C-7), 46.5 (C-9), 76.9 (C-8), 121.0 (C-15), 124.3 (C-2), 129.5 (C-1), 142.0 (C-14), 170.6 (C-13); HRMS (ESI^+): Found: 255.1359; $C_{15}H_{20}NaO_2$ (MNa^+) Requires 255.1356 (−1.3 ppm error), Found: 233.1536; $C_{15}H_{21}O_2$ (MH^+) Requires 233.1536 (−0.1 ppm error).

Lab notebook reference: MGL/07/64

5.2.3. Chapter 4

5.2.3.1. Rhodium(II)-catalysed cyclopropanations

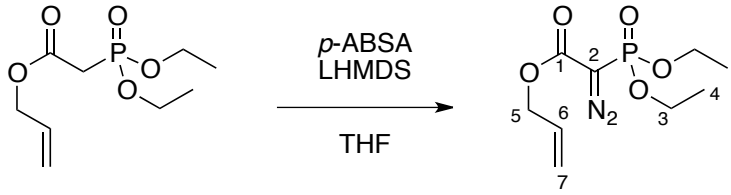
Allyl 2-(diethoxyphosphoryl)acetate (287a)



287 **287a**

Synthesised using general procedure A with allyl alcohol **287** (1.16 g, 20.0 mmol), toluene (100 mL), DEPAA (3.38 mL, 21.0 mmol), DIPEA (9.06 mL, 52.0 mmol) and T3P (16.5 g, 26.0 mmol, 50% w/w solution in EtOAc) affording the *title compound* **287a** as an orange oil (4.63 g, 98%). No further purification was required; R_f 0.26 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2985w, 1738s, 1394w, 1261s, 1117w, 1050w, 1023s, 971m; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, J = 7.1, J = 0.5, H-4), 2.98 (2 H, d, J = 21.6, H-2), 4.12–4.19 (4 H, m, H-3), 4.61–4.64 (1 H, m, H-5), 5.24 (1 H, app. dq, J = 10.4, J = 1.3, H-7a), 5.35 (1 H, app. dq, J = 17.2, J = 1.5, H-7b), 5.90 (2 H, ddt, J = 17.2, J = 10.4, J = 5.7, H-6); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.2, C-4), 34.2 (d, J = 134.3, C-2), 62.7 (d, J = 6.2, C-3), 66.1 (C-5), 118.7 (C-7), 131.5 (C-6), 165.5 (d, J = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.1; HRMS (ESI$^+$): Found: 259.0708; $C_9H_{17}NaO_5P$ (MNa^+) Requires 259.0706 (−0.8 ppm error), Found: 237.0890; $C_9H_{18}O_5P$ (MH^+) Requires 237.0886 (−1.6 ppm error).
Lab notebook reference: MGL/03/26

Allyl 2-diazo-2-(diethoxyphosphoryl)acetate (287b)



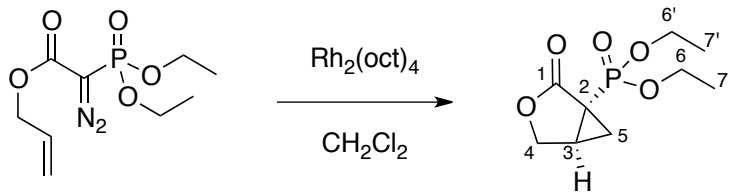
287a **287b**

Synthesised using general procedure C with 3-(4-methoxyphenyl)propyl 2-(diethoxyphosphoryl)acetate **287a** (2.19 g, 9.27 mmol), DBSA (4.89 g, 13.9 mmol), DBU (2.08 mL, 13.9 mmol) and CH_2Cl_2 (93.0 mL). Purification by column chromatography (2:1 petrol:EtOAc) affording the *title compound* **287b** as a pale yellow oil (2.02 g, 83%); R_f 0.43 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2992w, 2932w, 2129s, 1707s, 1368w, 1276s, 1020s, 983m; δ_H

(400 MHz, $CDCl_3$) 1.33 (6 H, td, *J* = 7.1, *J* = 0.8, H-4), 4.09–4.25 (4 H, m, H-3), 4.67 (1 H, app. dt, *J* = 5.6, *J* = 1.4, H-5), 5.24 (1 H, app. dq, *J* = 10.5, *J* = 1.3, H-7a), 5.32 (1 H, app. dq, *J* = 17.2, *J* = 1.5, H-7b), 5.89 (2 H, ddt, *J* = 17.2, *J* = 10.5, *J* = 5.6, H-6); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* = 6.9, C-4), 53.9 (d, *J* = 226.1, C-2), 63.6 (d, *J* = 5.6, C-3), 65.9 (C-5), 118.7 (C-7), 131.4 (C-6), 163.1 (d, *J* = 12.0, C-1); δ_P (162 MHz, $CDCl_3$) 10.4; HRMS (ESI^+): Found: 285.0603; $C_9H_{15}N_2NaO_5P$ (MNa^+) Requires 285.0611 (2.9 ppm error), Found: 263.0792; $C_9H_{16}N_2O_5P$ (MH^+) Requires 263.0791 (–0.2 ppm error).

Lab notebook reference: MGL/08/32

Diethyl ((1*RS*,5*SR*)-2-oxo-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate (287c)



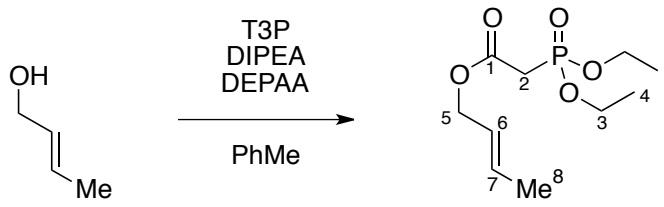
287b **287c**

Synthesised using general procedure F with allyl 2-diazo-2-(diethoxyphosphoryl)acetate **287b** (600 mg, 2.29 mmol), CH_2Cl_2 (17 mL) and $Rh_2(oct)_4$ (35.6 mg, 0.046 mmol). Purification by column chromatography (1:20 hexane:EtOAc) afforded the title compound **287c** as a dark yellow oil (417 mg, 78%); R_f 0.30 (1:8 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2986w, 2920w, 2838w, 1764s, 1376w, 1271w, 1243m, 1015s; δ_H (400 MHz, $CDCl_3$) 1.18–1.22 (1 H, m, H-5), 1.27 (3 H, td, *J* = 7.1, *J* = 0.5, H-7/7'), 1.29 (3 H, td, *J* = 7.1, *J* = 0.5, H-7/7'), 1.76 (1 H, ddd, *J* = 15.2, *J* = 7.8, *J* = 4.7, H-5), 2.58–2.65 (1 H, m, H-3), 4.07–4.18 (5 H, m, H-4, 6,6'), 4.28 (1 H, dd, *J* = 9.5, *J* = 4.7, H-4); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* = 6.0, C-7,7'), 17.3 (d, *J* = 3.0, C-5), 22.5 (d, *J* = 207.0, C-2), 24.3 (d, *J* = 1.4, C-3), 63.0 (d, *J* = 6.2, C-6/6'), 63.0 (d, *J* = 6.2, C-6/6'), 67.5 (d, *J* = 2.5, C-4), 171.5 (d, *J* = 10.6, C-1); δ_P (162 MHz, $CDCl_3$) 17.9; HRMS (ESI^+): Found: 257.0552; $C_9H_{15}NaO_5P$ (MNa^+) Requires 257.0549 (–1.2 ppm error), Found: 235.0737; $C_9H_{16}O_5P$ (MH^+) Requires 235.0730 (–3.0 ppm error).

Lab notebook reference: MGL/03/28B

Obtained data in accord with reported literature.[127]

(*E*)-But-2-en-1-yl 2-(diethoxyphosphoryl)acetate (288a)

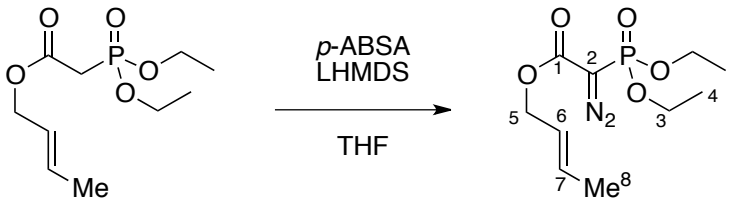


288 **288a**

Synthesised using general procedure A with 2-buten-1-ol **288** (2.16 g, 30.0 mmol), toluene (150 mL), DEPAA (5.06 mL, 31.5 mmol), DIPEA (13.6 mL, 78.0 mmol) and T3P (24.8 g, 39.0 mmol, 50% w/w solution in EtOAc) affording the *title compound* **288a** as an orange oil (7.41 g, 99%). No further purification was required; R_f 0.29 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2983w, 1737s, 1446w, 1394w, 1266s, 1164w, 1115m, 1052m, 10234, 968s; δ_H (400 MHz, $CDCl_3$) 1.33 (6 H, t, *J* = 7.1, H-4), 1.70–1.72 (3 H, m, H-8), 2.96 (2 H, d, *J* = 21.5, H-2), 4.12–4.20 (4 H, m, H-3), 4.56 (2 H, d, *J* = 6.6, H-5), 5.54–5.62 (1 H, m, H-6), 5.77 –5.86 (1 H, m, H-7); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.2, C-4), 17.7 (C-8), 34.3 (d, *J* = 134.3, C-2), 62.7 (d, *J* = 6.3, C-3), 66.2 (C-5), 124.5 (C-6), 132.0 (C-7), 165.6 (d, *J* = 6.2, C-1); δ_P (162 MHz, $CDCl_3$) 20.3; HRMS (ESI$^+$): Found: 273.0872; $C_{10}H_{19}NaO_5P$ (MNa^+) Requires 273.0862 (–3.5 ppm error), Found: 251.1039; $C_{10}H_{20}O_5P$ (MH^+) Requires 251.1043 (1.4 ppm error).

Lab notebook reference: MGL/04/49

(*E*)-But-2-en-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (288b)

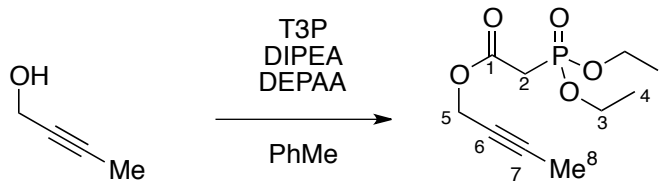


288a **288b**

Synthesised using general procedure B with (*E*)-but-2-en-1-yl 2-(diethoxyphosphoryl)acetate **288a** (2.50 g, 10.0 mmol), THF (50 mL), LHMDS (12.0 mL, 12.0 mmol, 1.0 M solution in THF) and *p*-ABSA (2.88 g, 12.0 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **288b** as a yellow oil (1.50 g, 54%); R_f 0.57 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2984w, 2126s, 1704s, 1446w, 1376w, 1274s, 1215w, 1164w, 1113w, 1090w, 1020s, 970m; δ_H (400 MHz, $CDCl_3$) 1.34 (6 H, t, *J* = 7.1, *J* = 0.7, H-4), 1.70–1.72 (3 H, m, H-8), 4.10–4.25 (4 H, m, H-3), 4.59–4.62 (2 H, m, H-5), 5.52–5.61 (1 H, m, H-6), 5.76–5.85 (1 H, m, H-7); δ_C

(100 MHz, $CDCl_3$) 16.1 (d, J = 6.9, C-4), 17.7 (C-8), 53.7 (d, J = 228.3, C-2), 63.6 (d, J = 5.9, C-3), 66.2 (C-5), 124.5 (C-6), 132.1 (C-7), 163.2 (d, J = 12.2, C-1); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI^+): Found: 299.0776; $C_{10}H_{17}N_2NaO_5P$ (MNa^+) Requires 299.0767 (–2.9 ppm error).
Lab notebook reference: MGL/04/60

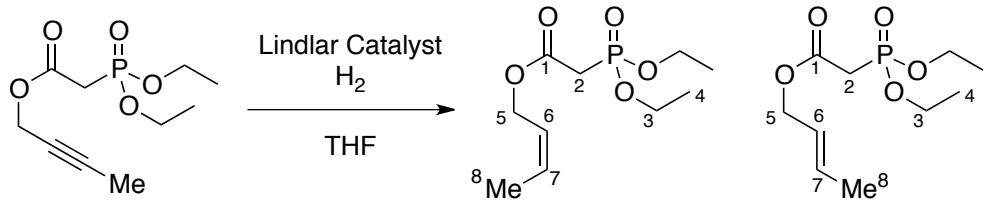
But-2-yn-1-yl 2-(diethoxyphosphoryl)acetate (S5)



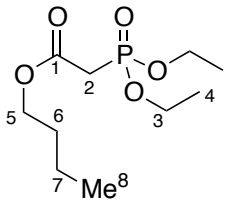
S4 **S5**

Synthesised using general procedure A with 2-butyn-1-ol **S4** (1.40 g, 20.0 mmol), toluene (100 mL), DEPAA (3.38 mL, 21.0 mmol), DIPEA (9.06 mL, 52.0 mmol) and T3P (16.5 g, 26.0 mmol, 50% w/w solution in EtOAc) affording the *title compound* **S5** as an orange oil (4.89 g, 99%). No further purification was required; R_f 0.32 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2985w, 2242w, 1742s, 1444w, 1394w, 1370w, 1266s, 1161w, 1113m, 1050w, 1023s, 973s, 838w; δ_H (400 MHz, $CDCl_3$) 1.34 (6 H, td, J = 7.1, J = 0.5, H-4), 1.84 (3 H, t, J = 2.4, H-8), 2.90 (2 H, d, J = 21.5, H-2), 4.14–4.21 (4 H, m, H-3), 4.68–4.70 (2 H, m, H-5); δ_C (100 MHz, $CDCl_3$) 3.6 (C-8), 16.3 (d, J = 6.4, C-4), 34.1 (d, J = 134.3, C-2), 53.8 (C-5), 62.8 (d, J = 6.2, C-3), 72.5 (C-57, 83.6 (C-6), 165.3 (d, J = 6.0, C-1); δ_P (162 MHz, $CDCl_3$) 19.7; HRMS (ESI^+): Found: 249.0890; $C_{10}H_{18}O_5P$ (MH^+) Requires 249.0886 (–1.4 ppm error).
Lab notebook reference: MGL/04/77

(*Z*)-But-2-en-1-yl 2-(diethoxyphosphoryl)acetate (289a), (*E*)-But-2-en-1-yl 2-(diethoxyphosphoryl)acetate (288a) and Butyl 2-(diethoxyphosphoryl)acetate (S6)



S5 **289a** **288a**



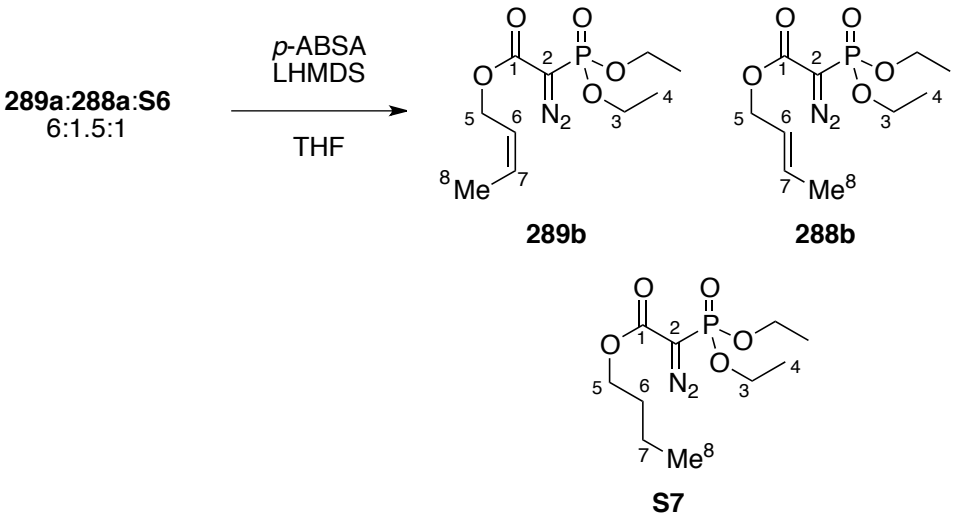
S6

To a solution of but-2-yn-1-yl 2-(diethoxyphosphoryl)acetate **S5** (4.88 g, 19.7 mmol) in MeOH (200 mL) under an argon atmosphere was added Lindlar catalyst (400 mg). The flask was purged 4 times with argon then 4 times with hydrogen and stirred for 2 h. The mixture was filtered through a pad of Celite and washed with CH_2Cl_2 (200 mL). The filtrate was concentrated *in vacuo* to afford the *title compound*s as an inseparable mixture (**289a**:**288a**:**S6** 6:1.5:1) as a yellow oil (4.62 g, 94%); R_f 0.29 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2983w, 2934w, 1733w, 1445w, 1394w, 1257s, 1113m, 1049w, 1018s, 963s, 838m, 781m; δ_H (400 MHz, $CDCl_3$) 0.92 (3 H, t, *J* = 7.4, H-8sat), 1.27–1.72 (28 H, m, H-(4*Z*,*E*,sat),(6sat),(7sat),(8*Z*,*E*)), 2.93–2.99 (6 H, m, H-2*Z*,*E*,sat), 4.11–4.15 (14 H, m, H-(3*Z*,*E*,sat),(5sat)), 4.54–4.56 (2 H, m, H-5*E*), 4.68–4.70 (2 H, m, H-5*Z*), 5.50–5.61 (2 H, m, H-7*Z*,*E*), 5.68–5.85 (2 H, m, H-6*Z*,*E*); δ_C (100 MHz, $CDCl_3$) 13.1, 13.6, 16.2, 16.3, 17.7, 18.9, 30.5, 33.6, 33.6, 34.9, 35.0, 61.1, 62.6, 62.6, 62.7, 62.7, 62.7, 65.4, 66.2, 123.6, 124.5, 130.1, 132.0, 165.7, 165.7, 165.9; δ_P (162 MHz, $CDCl_3$) 20.3, 20.3, 20.5; HRMS (ESI$^+$): **289a** and **288a**: Found: 273.0860; $C_{10}H_{19}NaO_5P$ (MNa^+) Requires 273.0862 (0.9 ppm error), Found: 251.1039; $C_{10}H_{20}O_5P$ (MH^+) Requires 251.1043 (1.6 ppm error); **S6**: Found: 275.1009; $C_{10}H_{21}NaO_5P$ (MNa^+) Requires 275.1019 (3.5 ppm error), Found: 253.1190; $C_{10}H_{22}O_5P$ (MH^+) Requires 253.1199 (3.7 ppm error).

Lab notebook reference: MGL/04/78

Note: NMR assignment labels; *Z* = **289a**, *E* = **288a**, sat = **S6**.

(*Z*)-But-2-en-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (289b), (*E*)-But-2-en-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (288b) and Butyl 2-diazo-2-(diethoxyphosphoryl)acetate (S7)

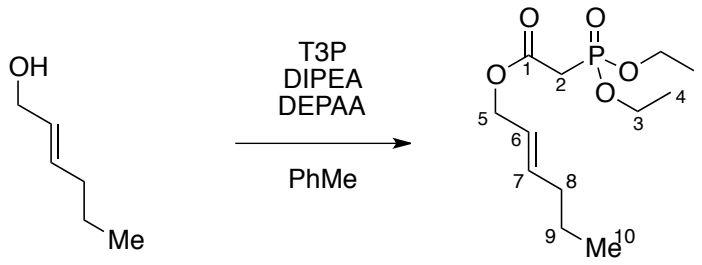


Synthesised using general procedure B with (*Z*)-but-2-en-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (**289a**), (*E*)-but-2-en-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (**288a)** and butyl 2-diazo-2-(diethoxyphosphoryl)acetate (**S6**) as a 6:1.5:1 mixture (2.50 g, 10.0 mmol), THF (50 mL), LHMDS (12.0 mL, 12.0 mmol, 1.0 M solution in THF) and *p*-ABSA (2.88 g, 12.0 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compounds* as an inseparable mixture (**289b**:**288b**:**S7** 4.8:1.2:1) as an orange oil (1.19 g, 43%); R_f 0.57 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2984w, 2124s, 1800s, 1445w, 1381w, 1350w, 1271s, 1214w, 1164w, 1112w, 1015s, 975s, 796m, 743s, 588s, 555s; δ_H (400 MHz, $CDCl_3$) 0.87 (3 H, t, *J* = 7.4, H-8sat), 1.23–1.67 (28 H, m, H-(4*Z*,*E*,sat),(6sat),(7sat),(8*Z*,*E*)), 4.04–4.21 (14 H, m, H-(3*Z*,*E*,sat),(5sat)), 4.54–4.56 (2 H, m, H-5*E*), 4.68–4.70 (2 H, m, H-5*Z*), 5.44–5.55 (2 H, m, H-7*Z*,*E*), 5.64–5.79 (2 H, m, H-6*Z*,*E*); δ_C (100 MHz, $CDCl_3$) 13.2, 13.6, 16.1, 16.2, 17.8, 19.0, 30.7, 52.6, 52.6, 52.6, 54.8, 54.9, 61.1, 63.6, 63.6, 63.7, 65.5, 66.2, 123.6, 124.6, 130.4, 132.1, 163.2, 163.3, 163.4, 163.5, 163.6; δ_P (162 MHz, $CDCl_3$) 10.5, 10.5, 10.7; HRMS (ESI$^+$): **289b** and **288b**: Found: 299.0760; $C_{10}H_{17}N_2NaO_5P$ (MNa^+) Requires 299.0767 (2.4 ppm error), Found: 277.0945; $C_{10}H_{18}N_2O_5P$ (MH^+) Requires 277.0948 (0.9 ppm error); **S7**: Found: 301.0915; $C_{10}H_{19}N_2NaO_5P$ (MNa^+) Requires 301.0924 (2.8 ppm error), Found: 279.1099; $C_{10}H_{20}N_2O_5P$ (MH^+) Requires 279.1104 (1.8 ppm error).

Lab notebook reference: MGL/04/92

Note: NMR assignment labels; *Z* = **289b**, *E* = **288b**, sat = **S7**.

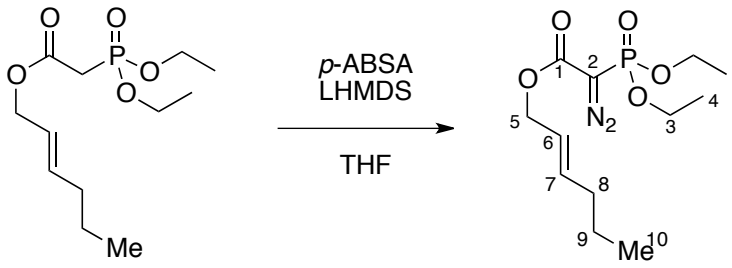
(*E*)-Hex-2-en-1-yl 2-(diethoxyphosphoryl)acetate (290a)



290 **290a**

Synthesised using general procedure A with (*E*)-hex-2-en-1-ol **290** (3.00 g, 30.0 mmol), toluene (150 mL), DEPAA (5.06 mL, 31.5 mmol), DIPEA (13.6 mL, 78.0 mmol) and T3P (24.8 g, 39.0 mmol, 50% w/w solution in EtOAc) affording the *title compound* **290a** as a yellow oil (8.34 g, 100%). No further purification was required; R_f 0.34 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2961m, 2933m, 2872w, 1738s, 1445w, 1393w, 1267s, 1164w, 1115m, 1052m, 1025s, 971s, 839w, 783w; δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, t, *J* = 7.4, H-10), 1.31–1.45 (8 H, m, H-4,9), 2.00–2.05 (2 H, m, H-8), 2.97 (2 H, d, *J* = 21.5, H-2), 4.13–4.20 (4 H, m, H-3), 4.58 (2 H, d, *J* = 6.5, H-5), 5.56 (1 H, dtt, *J* = 15.3, *J* = 6.5, *J* = 1.4, H-6), 5.79 (1 H, dtt, *J* = 15.3, *J* = 6.9, *J* = 1.2, H-7); δ_C (100 MHz, $CDCl_3$) 13.6 (C-10), 16.3 (d, *J* = 6.2, C-4), 22.0 (C-9), 34.3 (d, *J* = 134.3, C-2), 34.3 (C-8), 62.7 (d, *J* = 6.3, C-3), 66.3 (C-5), 123.3 (C-6), 137.0 (C-7), 165.6 (d, *J* = 6.2, C-1); δ_P (162 MHz, $CDCl_3$) 20.3; HRMS (ESI$^+$): Found: 301.1183; $C_{12}H_{23}NaO_5P$ (MNa^+) Requires 301.1175 (–2.7 ppm error), Found: 279.1365; $C_{12}H_{24}O_5P$ (MH^+) Requires 279.1356 (–3.3 ppm error).
Lab notebook reference: MGL/04/63

(*E*)-Hex-2-en-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (290b)



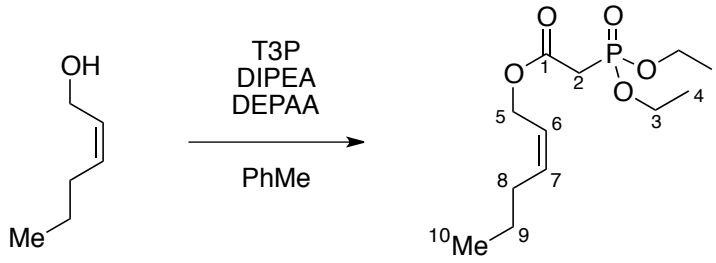
290a **290b**

Synthesised using general procedure B with (*E*)-hex-2-en-1-yl 2-(diethoxyphosphoryl)acetate **290a** (2.78 g, 10.0 mmol), THF (50 mL), LHMDS (12.0 mL, 12.0 mmol, 1.0 M solution in THF) and *p*-ABSA (2.88 g, 12.0 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded

the *title compound* **290b** as a yellow oil (1.64 g, 54%); R_f 0.55 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2961w, 2933w, 2125s, 1703s, 1445w, 1380w, 1273s, 1215w, 1164w, 1114w, 1019s, 974s, 797w, 745m, 590m, 560m; δ_H (400 MHz, $CDCl_3$) 0.88 (3 H, t, *J* = 7.4, H-10), 1.31–1.43 (8 H, m, H-4,9), 1.99–2.05 (2 H, m, H-8), 4.10–4.25 (4 H, m, H-3), 4.62 (2 H, app. dq, *J* = 6.5, *J* = 1.0, H-5), 5.54 (1 H, dtt, *J* = 15.3, *J* = 6.5, *J* = 1.4, H-6), 5.78 (1 H, dtt, *J* = 15.3, *J* = 6.9, *J* = 1.2, H-7); δ_C (100 MHz, $CDCl_3$) 13.5 (C-10), 16.1 (d, *J* = 7.1, C-4), 21.9 (C-9), 34.2 (C-8), 53.6 (d, *J* = 225.1, C-2), 63.6 (d, *J* = 6.0, C-3), 66.3 (C-5), 123.3 (C-6), 137.2 (C-7), 163.2 (d, *J* = 12.2, C-1); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI$^+$): Found: 327.1095; $C_{12}H_{21}N_2NaO_5P$ (MNa^+) Requires 327.1080 (–4.3 ppm error).

Lab notebook reference: MGL/04/70

(*Z*)-Hex-2-en-1-yl 2-(diethoxyphosphoryl)acetate (291a)

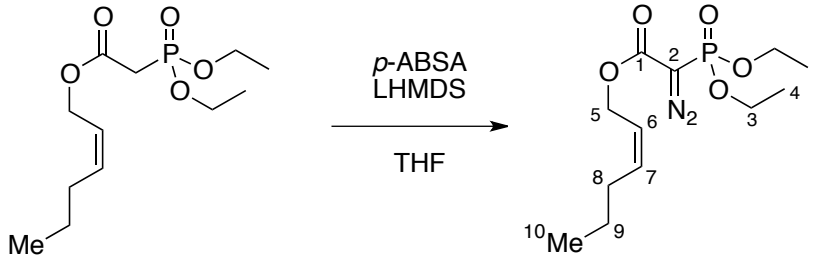


291 **291a**

Synthesised using general procedure A with (*Z*)-hex-2-en-1-ol **291** (2.16 g, 21.6 mmol), toluene (110 mL), DEPAA (3.65 mL, 22.7 mmol), DIPEA (9.78 mL, 56.2 mmol) and T3P (17.8 g, 28.0 mmol, 50% w/w solution in THF) affording the *title compound* **291a** as a yellow oil (1.87 g, 79%). No further purification was required; R_f 0.70 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2963m, 2933m, 2874w, 1738s, 1460w, 1394w, 1267s, 1115m, 1056m, 1026s, 971s, 842w, 782w; δ_H (400 MHz, $CDCl_3$) 0.90 (3 H, t, $^3J_{HH}$ 7.4, H-10), 1.32–1.44 (8 H, m, H-4,9), 2.05–2.11 (2 H, m, H-8), 2.97 (2 H, d, $^2J_{HP}$ 21.5, H-2), 4.13–4.21 (4 H, m, H-3), 4.69 (2 H, dd, $^3J_{HH}$ 6.9, H-5), 5.54 (1 H, dtt, $^3J_{HH}$ 10.9, $^3J_{HH}$ 6.9, $^4J_{HH}$ 1.4, H-6), 5.66 (1 H, dtt, $^3J_{HH}$ 10.9, $^3J_{HH}$ 7.5, $^4J_{HH}$ 1.2, H-7); δ_C (100 MHz, $CDCl_3$) 13.6 (C-10), 16.3 (d, $^3J_{CP}$ 6.2, C-4), 22.5 (C-9), 29.5 (C-8), 34.3 (d, $^1J_{CP}$ 134.3, C-2), 61.4 (C-5), 62.7 (d, $^2J_{CP}$ 6.2, C-3), 122.8 (C-6), 135.6 (C-7), 165.7 (d, $^2J_{CP}$ 6.2, C-1); δ_P (162 MHz, $CDCl_3$) 20.3; HRMS (ESI$^+$): Found: 301.1181; $C_{12}H_{23}NaO_5P$ (MNa^+) Requires 301.1175 (–1.8 ppm error), Found: 279.1361; $C_{12}H_{24}O_5P$ (MH^+) Requires 279.1356 (–2.0 ppm error).

Note: This compound was synthesised by William P. Unsworth.

(*Z*)-Hex-2-en-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (291b)

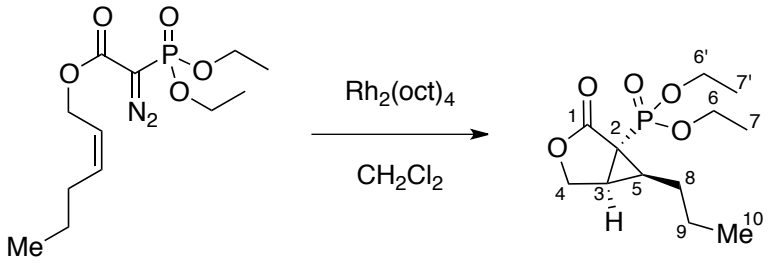


291a **291b**

Synthesised using general procedure B with (*Z*)-hex-2-en-1-yl 2-(diethoxyphosphoryl)acetate **291a** (385 mg, 1.38 mmol), THF (50 mL), NaH (66.4 mg, 1.66 mmol, 60% dispersion in mineral oil). and *p*-ABSA (399 mg, 1.66 mmol). Purification by column chromatography (3:1 petrol:EtOAc) afforded the *title compound* **291b** as a yellow oil (315 mg, 75%); R_f 0.52 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2962w, 2128s, 1709s, 1445w, 1361w, 1279s, 1164w, 1023s, 978m; δ_H (400 MHz, $CDCl_3$) 0.88 (3 H, t, *J* = 7.4, H-10), 1.30–1.43 (8 H, m, H-4,9), 2.07 (2 H, qd, *J* = 7.4, *J* = 1.3, H-8), 4.09–4.25 (4 H, m, H-3), 4.72–4.74 (2 H, m, H-5), 5.52 (1 H, dtt, *J* = 10.9, *J* = 6.9, *J* = 1.5, H-6), 5.65 (1 H, dtt, *J* = 10.9, *J* = 7.6, *J* = 1.3, H-7); δ_C (100 MHz, $CDCl_3$) 13.5 (C-10), 16.1 (d, *J* = 6.9, C-4), 22.4 (C-9), 29.4 (C-8), 53.8 (d, *J* = 227.5, C-2), 61.3 (C-5), 63.6 (d, *J* = 6.0, C-3), 122.8 (C-6), 136.0 (C-7), 163.3 (d, *J* = 12.3, C-1); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI^+): Found: 327.1087; $C_{12}H_{21}N_2NaO_5P$ (MNa^+) Requires 327.1080 (–2.1 ppm error), Found: 305.1262; $C_{12}H_{22}N_2O_5P$ (MH^+) Requires 305.1261 (–0.5 ppm error).

Note: This compound was synthesised by William P. Unsworth.

Diethyl ((1*RS*,5*SR*,6*SR*)-2-oxo-6-propyl-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate (291c)

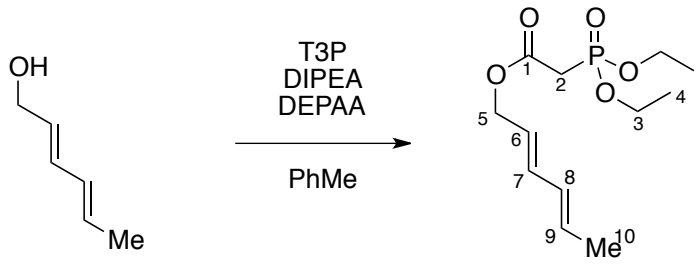


291b **291c**

Synthesised using general procedure F with (*Z*)-hex-2-en-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate **291b** (212 mg, 0.697 mmol), CH_2Cl_2 (7.0 mL) and $Rh_2(oct)_4$ (10.8 mg, 13.9 μmol). Purification by column chromatography (1:10 hexane:EtOAc) afforded the *title compound* **291c** as a pale yellow oil (128 mg, 66%); R_f 0.15 (1:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2963w, 2934w, 2874w, 1764s, 1468w, 1371w, 1254m, 1197w, 1164w, 1130w, 1022s, 976m; δ_H (400 MHz, $CDCl_3$) 0.97 (3 H, t, *J* = 7.1, H-10), 1.29–1.56 (10 H, m, H-7/7',8,9), 2.02–2.11 (1 H, m, H-5), 2.70 (1 H, dddd, *J* = 11.2, *J* = 8.0, *J* = 5.4, *J* = 0.9, H-3), 4.13–4.29 (5 H, m, H-4/4',6,6'), 4.42 (1 H, dd, *J* = 10.0, *J* = 5.4, H-4/4'); δ_C (100 MHz, $CDCl_3$) 13.7 (C-10), 16.3 (d, *J* = 6.1, C-7/7'), 16.3 (d, *J* = 6.1, C-7/7'), 21.9 (C-9), 24.9 (C-8), 28.1 (d, *J* = 2.3, C-5), 28.1 (d, *J* = 203.3, C-2), 29.5 (d, *J* = 2.5, C-3), 63.1 (d, *J* = 6.3, C-6/6'), 63.2 (d, *J* = 6.2, C-6/6'), 64.6 (d, *J* = 3.0, C-4), 170.5 (d, *J* = 10.0, C-1); δ_P (162 MHz, $CDCl_3$) 18.8; HRMS (ESI^+): Found: 299.1026; $C_{12}H_{21}NaO_5P$ (MNa^+) Requires 299.1019 (–2.5 ppm error), Found: 277.1212; $C_{12}H_{22}O_5P$ (MH^+) Requires 277.1199 (–4.5 ppm error).

Lab notebook reference: MGL/04/89

(2*E*,4*E*)-Hexa-2,4-dien-1-yl 2-(diethoxyphosphoryl)acetate (292a)

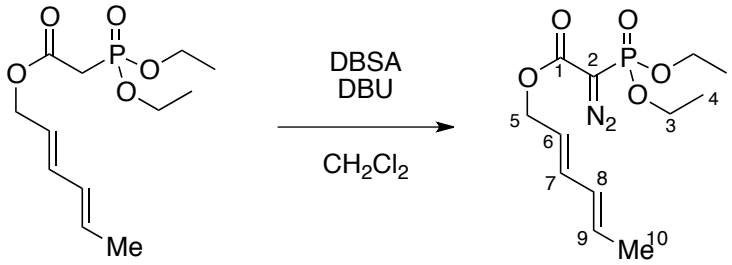


292 **292a**

Synthesised using general procedure A with (2*E*,4*E*)-hexa-2,4-dien-1-ol **292** (491 mg, 5.00 mmol), toluene (25.0 mL), DEPAA (1.03 mL, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in EtOAc) affording the *title compound* **292a** as an orange oil (1.36 g, 98%). No further purification was required; R_f 0.26 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2984w, 2934w, 1735s, 1444w, 1393w, 1258s, 1112s, 1020s, 965s; δ_H (400 MHz, $CDCl_3$) 1.31 (6 H, t, *J* = 7.1, H-4), 1.73 (3 H, d, *J* = 6.7, H-10), 2.95 (2 H, d, *J* = 21.5, H-2), 4.14 (4 H, app. quin., *J* = 7.5, H-3), 4.61 (2 H, d, *J* = 6.7, H-5), 5.58 (1 H, dt, *J* = 15.2, *J* = 6.7, H-6), 5.73 (1 H, dq, *J* = 15.2, *J* = 6.7, H-9), 6.01 (1 H, ddd, *J* = 15.2, *J* = 10.5, *J* = 1.2, H-8), 6.24 (1 H, dd, *J* = 15.2, *J* = 10.5, H-7); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.6, C-4), 18.1 (C-10), 34.3 (d, *J* = 134.2, C-2), 62.6 (d, *J* = 6.6, C-3), 65.9 (C-5), 122.8 (C-6), 130.2 (C-8), 131.6 (C-9), 135.4 (C-7), 165.5 (d, *J* = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.2; HRMS (ESI$^+$): Found: 299.1026; $C_{12}H_{21}NaO_5P$ (MNa^+) Requires 299.1019 (−2.4 ppm error).

Lab notebook reference: MGL/08/76

(2*E*,4*E*)-Hexa-2,4-dien-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (292b)



292a **292b**

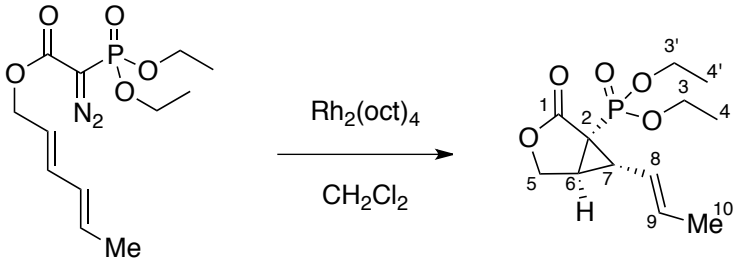
Synthesised using general procedure C with (2*E*,4*E*)-hexa-2,4-dien-1-yl 2-(diethoxyphosphoryl)acetate **292a** (1.36 g, 4.92 mmol), DBSA (2.47 g, 7.38 mmol), DBU (1.10 mL, 7.38 mmol) and CH_2Cl_2 (49.0 mL). Purification by column chromatography (2:1

hexane:EtOAc) afforded the *title compound* **292b** as a yellow oil (1.54 g, 75%); R_f 0.43 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2985w, 2127s, 1705s, 1445w, 1375w, 1274s, 1113m, 1020s, 797m, 745m, 590m, 561m; δ_H (400 MHz, $CDCl_3$) 1.34 (6 H, td, *J* = 7.1, *J* = 0.7, H-4), 1.75 (3 H, dd, *J* = 6.7, *J* = 1.0, H-10), 4.09–4.25 (4 H, m, H-3), 4.68 (2 H, d, *J* = 6.7, H-5), 5.60 (1 H, dt, *J* = 15.2, *J* = 6.7, H-6), 5.75 (1 H, dq, *J* = 15.2, *J* = 6.7, H-9), 6.00–6.07 (1 H, m, H-8), 6.26 (1 H, dd, *J* = 15.2, *J* = 10.5, H-7); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* = 7.1, C-4), 18.1 (C-10), 63.6 (d, *J* = 5.9, C-3), 66.0 (C-5), 122.8 (C-6), 130.2 (C-8), 131.8 (C-9), 135.6 (C-7), 163.2 (d, *J* = 12.6, C-1); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI$^+$): Found: 325.0930; $C_{12}H_{19}N_2NaO_5P$ (MNa^+) Requires 325.0924 (–1.9 ppm error).

Lab notebook reference: MGL/08/82

Note: C-2 not observed in ^{13}C NMR spectrum.

Diethyl ((1*RS*,5*SR*,6*RS*)-2-oxo-6-((*E*)-prop-1-en-1-yl)-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate (292c)

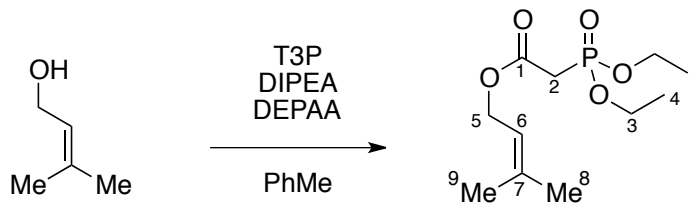


292b **292c**

Synthesised using general procedure F with (2*E*,4*E*)-hexa-2,4-dien-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate **292b** (68.6 mg, 0.250 mmol), CH_2Cl_2 (5.0 mL) and $Rh_2(oct)_4$ (4.0 mg, 5.0 μmol). Purification by column chromatography (1:10 hexane:EtOAc) afforded the *title compound* **292c** as a pale yellow oil (33 mg, 48%); R_f 0.34 (EtOAc); ν_{max} (thin film)/cm^{-1} 2983w, 1767s, 1370w, 1276m, 1246s, 1157m, 1025s, 971s, 590m; δ_H (400 MHz, $CDCl_3$) 1.32 (3 H, t, *J* = 7.1, H-4/4'), 1.33 (3 H, t, *J* = 7.1, H-4/4'), 1.72 (3 H, dd, *J* = 6.5, *J* = 1.6, H-10), 2.17 (1 H, ddd, *J* = 9.4, *J* = 6.0, *J* = 5.3, H-7), 2.73 (1 H, app. dt, *J* = 10.3, *J* = 5.0, H-6), 4.14–4.22 (4 H, m, H-3,3'), 4.27 (1 H, dd, *J* = 9.4, *J* = 3.0, H-5), 4.34 (1 H, dd, *J* = 9.4, *J* = 4.6, H-5), 5.60 (1 H, ddq, *J* = 15.3, *J* = 9.4, *J* = 1.6, H-8), 5.80 (1 H, dq, *J* = 15.3, *J* = 6.5, H-9); δ_C (100 MHz, $CDCl_3$) 16.2 (C-4/4'), 16.3 (C-4/4'), 17.9 (C-10), 29.5 (d, *J* = 202.7, C-2), 30.3 (C-6), 34.6 (d, *J* = 2.8, C-7), 62.8 (d, *J* = 6.5, C-3/3'), 63.1 (d, *J* = 6.4, C-3/3'), 67.7 (d, *J* = 2.9, C-5), 124.3 (d, *J* = 4.8, C-8), 130.8 (C-9), 171.7 (d, *J* = 9.1, C-1); δ_P (162 MHz, $CDCl_3$) 16.5; HRMS (ESI$^+$): Found: 297.0866; $C_{12}H_{19}NaO_5P$ (MNa^+) Requires 297.0862 (–1.1 ppm error), Found: 275.1044; $C_{12}H_{20}O_5P$ (MH^+) Requires 275.1043 (–0.3 ppm error).

Lab notebook reference: MGL/08/90

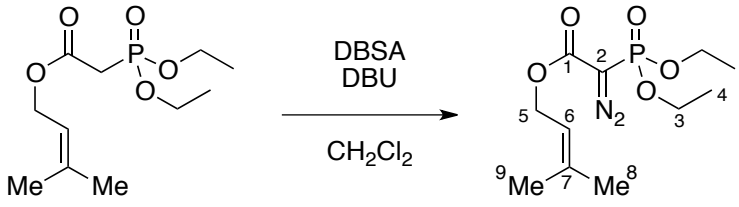
3-Methyl-but-2-en-1-yl 2-(diethoxyphosphoryl)acetate (293a)



293 **293a**

Synthesised using general procedure A with 3-methyl-but-2-en-1-ol **293** (431 mg, 5.00 mmol), toluene (25.0 mL), DEPAA (1.03 mL, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in EtOAc) affording the *title compound* **293a** as a yellow oil (1.25 g, 95%). No further purification was required; R_f 0.24 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2982m, 2933w, 1734s, 1445w, 1392w, 1264s, 1113m, 1051w, 1029s, 968s; δ_H (400 MHz, $CDCl_3$) 1.33 (6 H, t, *J* = 7.1, H-4), 1.70 (3 H, s, H-8/9), 1.74 (3 H, s, H-8/9), 2.95 (2 H, d, *J* = 21.5, H-2), 4.12–4.19 (4 H, m, H-3), 4.62 (2 H, d, *J* = 7.3, H-5), 5.31–5.36 (1 H, m, H-6); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.7, C-4), 18.0 (C-8/9), 25.7 (C-8/9), 34.3 (d, *J* = 134.5, C-2), 62.4 (C-5), 62.6 (d, *J* = 6.6, C-3), 118.0 (C-6), 139.7 (C-7), 165.8 (d, *J* = 6.5, C-1); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI$^+$): Found: 287.1021; $C_{11}H_{21}NaO_5P$ (MNa^+) Requires 287.1019 (–0.9 ppm error).
Lab notebook reference: MGL/08/87-1

3-Methyl-but-2-en-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (293b)



293a **293b**

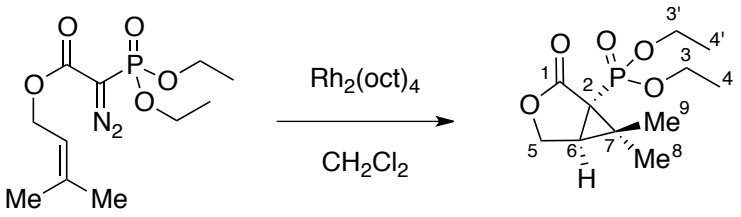
Synthesised using general procedure C with 3-methyl-but-2-en-1-yl 2-(diethoxyphosphoryl)acetate **293a** (1.24 g, 4.69 mmol), DBSA (2.35 g, 7.04 mmol), DBU (1.05 mL, 7.04 mmol) and CH_2Cl_2 (47.0 mL). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **293b** as a pale yellow oil (1.15 g, 85%); R_f 0.39 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2983m, 2933w, 2124s, 1700s, 1445w, 1374w, 1271s, 1110w, 1016s, 976s, 746s, 588s, 556s; δ_H (400 MHz, $CDCl_3$) 1.34 (6 H, t, *J* = 7.1, H-4), 1.70 (3 H, s, H-8/9), 1.74 (3 H, s, H-8/9), 4.09–4.25 (4 H, m, H-3), 4.68 (2 H, d, *J* = 7.3, H-5), 5.29–5.35 (1 H, m, H-6); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* = 7.3, C-4), 18.0 (C-8/9), 25.7 (C-8/9), 62.4 (C-5), 63.6 (d, *J* = 5.9, C-3), 118.0

(C-6), 139.9 (C-7), 163.4 (d, J = 12.7, C-1); δ_P (162 MHz, $CDCl_3$) 10.7; HRMS (ESI^+): Found: 313.0928; $C_{11}H_{19}N_2NaO_5P$ (MNa^+) Requires 313.0924 (–1.4 ppm error).

Lab notebook reference: MGL/08/87-2

Note: C-2 not observed in ^{13}C NMR spectrum.

Diethyl ((1*SR*,5*SR*)-6,6-dimethyl-2-oxo-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate (293c)

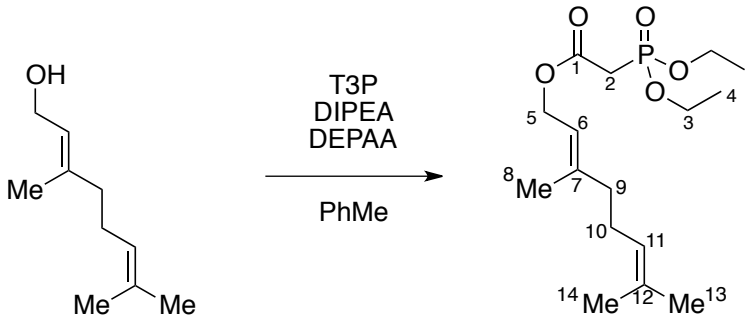


293b **293c**

ynthesised using general procedure F with 3-methyl-but-2-en-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate **293b** (74.0 mg, 0.255 mmol), CH_2Cl_2 (5.1 mL) and $Rh_2(oct)_4$ (4.0 mg, 5.1 μmol). Purification by column chromatography (1:10 hexane:EtOAc) afforded the *title compound* **293c** as a pale yellow oil (39 mg, 58%); R_f 0.27 (EtOAc); ν_{max} (thin film)/cm^{-1} 2985w, 1764s, 1389w, 1364w, 1260s, 1181s, 1052s, 1025s, 995s, 971s, 591m; δ_H (400 MHz, $CDCl_3$) 1.24 (3 H, s, H-8/9), 1.32 (3 H, t, J = 7.1, H-4/4'), 1.35 (3 H, t, J = 7.1, H-4/4'), 1.50 (3 H, s, H-8/9), 2.58 (1 H, dd, J = 12.2, J = 5.3, H-6), 4.12–4.27 (5 H, m, H-3,3',5), 4.38 (1 H, dd, J = 10.0, J = 5.3, H-5); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.2, C-4/4'), 16.3 (d, J = 6.8, C-4/4'), 16.5 (C-8/9), 21.6 (d, J = 4.8, C-8/9), 30.0 (d, J = 2.8, C-7), 33.9 (d, J = 197.6, C-2), 36.3 (d, J = 3.8, C-6), 62.6 (d, J = 6.5, C-3/3'), 62.9 (d, J = 6.8, C-3/3'), 65.2 (d, J = 2.9, C-5), 171.4 (d, J = 9.8, C-1); δ_P (162 MHz, $CDCl_3$) 18.6; HRMS (ESI^+): Found: 285.0865; $C_{11}H_{19}NaO_5P$ (MNa^+) Requires 285.0862 (–1.1 ppm error), Found: 263.1043; $C_{11}H_{20}O_5P$ (MH^+) Requires 263.1043 (–0.2 ppm error).

Lab notebook reference: MGL/08/92

(*E*)-3,7-Dimethylocta-2,6-dien-1-yl 2-(diethoxyphosphoryl)acetate (294a)

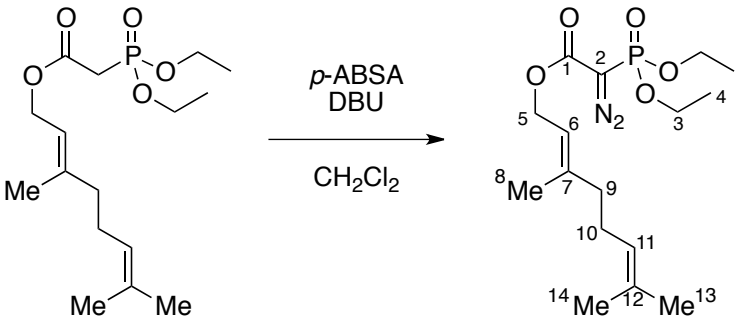


294 **294a**

Synthesised using general procedure A with geraniol **294** (771 mg, 5.00 mmol), toluene (25.0 mL), DEPAA (1.03 mL, 5.25 mmol), DIPEA (2.26 mL, 13.0 mmol) and T3P (4.14 g, 6.50 mmol, 50% w/w solution in EtOAc) affording the *title compound* **294a** as an orange oil (1.65 g, 99%). No further purification was required; R_f 0.27 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2980w, 2928w, 1735s, 1444w, 1391w, 1263s, 1112m, 1051w, 1025s, 966s; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, t, J = 7.1, H-4), 1.58 (3 H, s, H-13/14), 1.67 (3 H, d, J = 0.9, H-13/14), 1.69 (3 H, d, J = 0.9, H-8), 2.00–2.09 (4 H, m, H-9,10), 2.96 (2 H, d, J = 21.5, H-2), 4.16 (4 H, app. quin., J = 7.4, H-3), 4.64 (2 H, d, J = 7.2, H-5), 5.04–5.08 (1 H, m, H-11), 5.31–5.36 (1 H, m, H-6); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J = 6.6, C-4), 16.4 (C-8), 17.6 (C-13/14), 25.6 (C-13/14), 26.2 (C-10), 34.3 (d, J = 134.2, C-2), 39.5 (C-9), 62.4 (C-5), 62.6 (d, J = 6.2, C-3), 117.7 (C-6), 123.6 (C-11), 131.9 (C-7/12), 142.9 (C-7/12), 165.8 (d, J = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI^+): Found: 355.1644; $C_{16}H_{29}NaO_5P$ (MNa^+) Requires 355.1645 (0.3 ppm error).

Lab notebook reference: MGL/08/59

(*E*)-3,7-Dimethylocta-2,6-dien-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (294b)

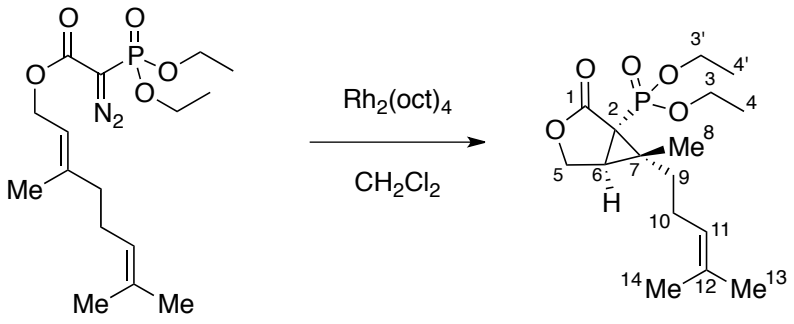


294a **294b**

Synthesised using general procedure C with (*E*)-3,7-dimethylocta-2,6-dien-1-yl 2-(diethoxyphosphoryl)acetate **294a** (1.65 g, 4.96 mmol), *p*-ABSA (1.79 g, 7.45 mmol), DBU (1.11 mL, 7.45 mmol) and CH_2Cl_2 (50.0 mL). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **294b** as a yellow oil (1.12 g, 63%); R_f 0.56 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2981w, 2915w, 2124s, 1701s, 1444w, 1378w, 1273s, 1021s, 975s, 797m, 744m, 588m, 559m; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, td, J = 7.1, J = 0.8, H-4), 1.56 (3 H, s, H-13/14), 1.64 (3 H, d, J = 1.0, H-13/14), 1.68 (3 H, d, J = 1.1, H-8), 1.98–2.08 (4 H, m, H-9,10), 4.08–4.23 (4 H, m, H-3), 4.68 (2 H, d, J = 7.2, H-5), 5.01–5.05 (1 H, m, H-11), 5.28–5.32 (1 H, m, H-6); δ_C (100 MHz, $CDCl_3$) 16.0 (d, J = 6.9, C-4), 16.4 (C-8), 17.5 (C-13/14), 25.5 (C-13/14), 26.1 (C-10), 39.4 (C-9), 53.5 (d, J = 227.1, C-2), 62.3 (C-5), 63.5 (d, J = 5.9, C-3), 117.6 (C-6), 123.5 (C-11), 131.8 (C-7/12), 143.0 (C-7/12), 163.3 (d, J = 12.6, C-1); δ_P (162 MHz, $CDCl_3$) 10.7; HRMS (ESI^+): Found: 381.1549; $C_{16}H_{27}N_2NaO_5P$ (MNa^+) Requires 381.1550 (0.3 ppm error).

Lab notebook reference: MGL/08/61

Diethyl ((1*SR*,5*SR*,6*RS*)-6-methyl-6-(4-methylpent-3-en-1-yl)-2-oxo-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate (294c)

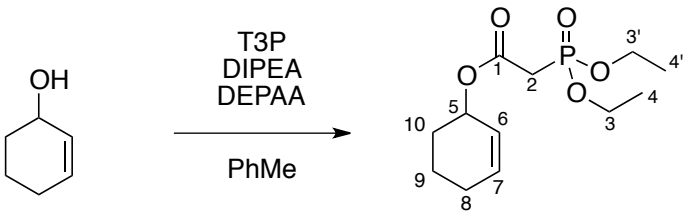


294b **294c**

Synthesised using general procedure F with (*E*)-3,7-dimethylocta-2,6-dien-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate **294b** (71.7 mg, 0.200 mmol), CH_2Cl_2 (4.0 mL) and $Rh_2(oct)_4$ (3.1 mg, 4.0 μmol). Purification by column chromatography (2:1 → 1:1 hexane:EtOAc) afforded the *title compound* **294c** as a pale yellow oil (42 mg, 64%); R_f 0.20 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2977w, 2912w, 1764s, 1445w, 1391w, 1366w, 1255s, 1172s, 1051s, 1023s, 993m, 970m, 597m; δ_H (400 MHz, $CDCl_3$) 1.24 (3 H, d, *J* = 0.6, H-8), 1.33 (3 H, t, *J* = 7.1, H-4/4'), 1.36 (3 H, t, *J* = 7.1, H-4/4'), 1.60 (3 H, s, H-13/14), 1.65 (3 H, d, *J* = 0.5, H-13/14), 1.76–1.93 (2 H, m, H-9), 2.03–2.12 (1 H, m, H-10), 2.17–2.26 (1 H, m, H-10), 2.59 (1 H, ddd, *J* = 12.5, *J* = 5.3, *J* = 0.5, H-6), 4.11–4.29 (5 H, m, H-3,3',5), 4.40 (1 H, dd, *J* = 10.0, *J* = 5.3, H-5), 5.05–5.10 (1 H, m, H-11); δ_C (100 MHz, $CDCl_3$) 13.4 (C-8), 16.3 (C-4/4'), 16.3 (C-4/4'), 17.6 (C-13/14), 25.3 (C-10), 25.6 (C-13/14), 33.8 (d, *J* = 1.9, C-7), 34.2 (d, *J* = 198.2, C-2), 34.4 (d, *J* = 4.2, C-9), 35.7 (d, *J* = 3.6, C-6), 62.6 (d, *J* = 6.6, C-3/3'), 63.0 (d, *J* = 6.6, C-3/3'), 65.2 (d, *J* = 2.1, C-5), 123.2 (C-11), 132.2 (C-12), 171.4 (d, *J* = 9.6, C-1); δ_P (162 MHz, $CDCl_3$) 18.8; HRMS (ESI^+): Found: 353.1493; $C_{16}H_{27}NaO_5P$ (MNa^+) Requires 353.1488 (−1.2 ppm error), Found: 331.1668; $C_{16}H_{28}O_5P$ (MH^+) Requires 331.1669 (0.1 ppm error).

Lab notebook reference: MGL/08/62

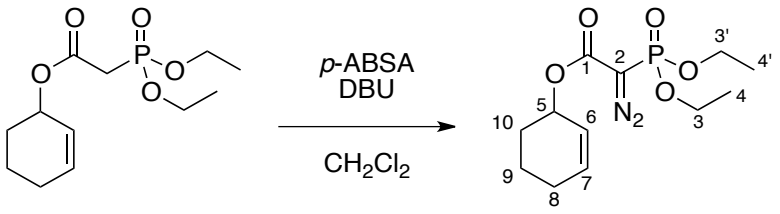
Cyclohex-2-en-1-yl 2-(diethoxyphosphoryl)acetate (295a)



295 **295a**

Synthesised using general procedure A with cyclohex-2-en-1-ol **295** (481 mg, 4.90 mmol), toluene (24.5 mL), DEPAA (1.01 mL, 5.15 mmol), DIPEA (2.22 mL, 12.7 mmol) and T3P (4.05 g, 6.37 mmol, 50% w/w solution in EtOAc) affording the *title compound* **295a** as an orange oil (1.26 g, 93%). No further purification was required; R_f 0.23 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2937s, 1730s, 1394w, 1270s, 1113m, 1050m, 1025s, 968s; δ_H (400 MHz, $CDCl_3$) 1.29–1.33 (6 H, m, H-4,4'), 1.55–1.64 (1 H, m), 1.66–1.77 (2 H, m), 1.79–1.87 (1 H, m), 1.91–2.10 (2 H, m), 2.93 (2 H, d, *J* = 21.5, H-2), 4.10–4.17 (4 H, m, H-3,3'), 5.25–5.29 (1 H, m, H-5), 5.67 (1 H, ddt, *J* = 10.1, *J* = 3.8, *J* = 2.0, H-6), 5.94 (1 H, m, H-7); δ_C (100 MHz, $CDCl_3$) 16.2 (2C, d, *J* = 6.8, C-4,4'), 16.3 (C-8/9/10), 24.7 (C-8/9/10), 28.0 (C-8/9/10), 34.5 (d, *J* = 133.4, C-2), 62.5 (2C, d, *J* = 6.4, C-3,3'), 69.2 (C-5), 124.9 (C-6), 133.1 (C-7), 165.5 (d, *J* = 6.6, C-1); δ_P (162 MHz, $CDCl_3$) 20.5; HRMS (ESI^+): Found: 299.1018; $C_{12}H_{21}NaO_5P$ (MNa^+) Requires 299.1019 (0.1 ppm error).
Lab notebook reference: MGL/08/56

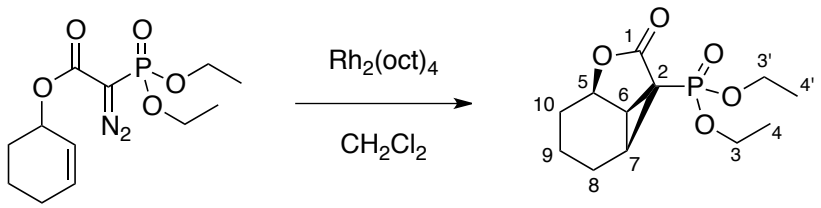
Cyclohex-2-en-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (295b)



Synthesised using general procedure C with cyclohex-2-en-1-yl 2-(diethoxyphosphoryl)acetate **295a** (1.26 g, 4.56 mmol), *p*-ABSA (1.64 g, 6.84 mmol), DBU (1.02 mL, 6.84 mmol) and CH_2Cl_2 (46.0 mL). Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **295b** as a yellow oil (1.04 g, 75%); R_f 0.49 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2984w, 2939w, 2124s, 1694s, 1270s, 1118m, 1016s, 976s, 908m, 794m, 747m, 588m, 557m; δ_H (400 MHz, $CDCl_3$) 1.31 (3 H, td, J = 7.1, J = 0.8, H-4/4'), 1.32 (3 H, td, J = 7.1, J = 0.8, H-4/4'), 1.56–1.78 (3 H, m), 1.80–1.88 (1 H, m), 1.91–2.10 (2 H, m), 4.07–4.23 (4 H, m, H-3,3'), 5.29–5.33 (1 H, m, H-5), 5.69 (1 H, ddt, J = 10.1, J = 3.9, J = 2.0, H-6), 5.94 (1 H, m, H-7); δ_C (100 MHz, $CDCl_3$) 16.0–16.2 (2C, m, C-4,4'), 16.4 (C-8/9/10), 24.7 (C-8/9/10), 28.2 (C-8/9/10), 53.8 (d, J = 224.3, C-2), 63.4–63.5 (2C, m, C-3,3'), 69.4 (C-5), 124.9 (C-6), 133.3 (C-7), 163.1 (d, J = 12.4, C-1); δ_P (162 MHz, $CDCl_3$) 10.7; HRMS (ESI^+): Found: 325.0932; $C_{12}H_{19}N_2NaO_5P$ (MNa^+) Requires 325.0924 (–2.5 ppm error).

Lab notebook reference: MGL/08/57

Diethyl ((2a^1*SR*,2b*SR*,5a*RS*)-2-oxooctahydrocyclopropa[*cd*]benzofuran-2a-yl)phosphonate (295c)



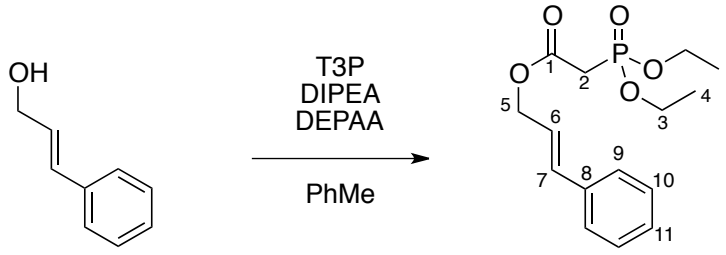
295b **295c**

Synthesised using general procedure F with cyclohex-2-en-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate **295b** (60 mg, 0.200 mmol), CH_2Cl_2 (4.0 mL) and $Rh_2(oct)_4$ (3.1 mg, 4.0 μmol). Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **295c** as a pale yellow oil (13 mg, 24%); R_f 0.10 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2952w, 1759s, 1252m, 1161m, 1023s, 970s, 586m; δ_H (400 MHz, $CDCl_3$) 1.35 (3 H, t, J

= 7.0, H-4/4'), 1.37 (3 H, td, *J* = 7.0, H-4/4'), 1.44–1.66 (3 H, m), 1.73–1.81 (1 H, m), 1.87–1.95 (1 H, m), 2.10–2.27 (2 H, m, H-7,8/9), 2.79 (1 H, ddd, *J* = 11.7, *J* = 7.9, *J* = 6.0, H-6), 4.15–4.28 (4 H, m, H-3,3'), 4.93 (1 H, app. dt, *J* = 5.7, *J* = 2.7, H-5); δ_C (100 MHz, $CDCl_3$) 14.1 (C-9), 16.3 (d, *J* = 6.1, C-4,4'), 17.7 (d, *J* = 2.8, C-8), 24.4 (d, *J* = 1.9, C-10), 24.6 (d, *J* = 1.8, C-7), 29.3 (d, *J* = 200.1, C-2), 29.3 (d, *J* = 3.7, C-6), 63.1–63.2 (m, C-3,3') 72.5 (d, *J* = 4.8, C-5), 171.0 (d, *J* = 9.5, C-1); δ_P (162 MHz, $CDCl_3$) 18.9; HRMS (ESI^+): Found: 297.0857; $C_{12}H_{19}NaO_5P$ (MNa^+) Requires 297.0862 (1.8 ppm error).

Lab notebook reference: MGL/08/60

Cinnamyl 2-(diethoxyphosphoryl)acetate (296a)

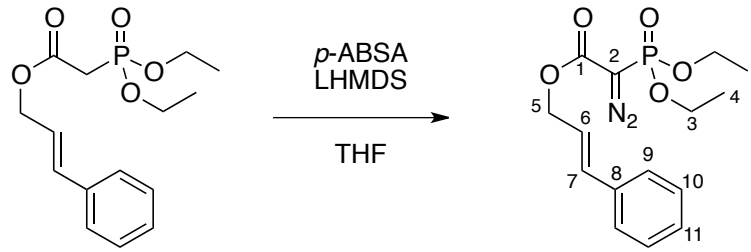


296 **296a**

Synthesised using general procedure A with cinnamyl alcohol **296** (4.03 g, 30.0 mmol), toluene (150 mL), DEPAA (5.06 mL, 31.5 mmol), DIPEA (13.6 mL, 78.0 mmol) and T3P (24.8 g, 39.0 mmol, 50% w/w solution in EtOAc) affording the *title compound* **296a** as a yellow oil (7.14 g, 76%). No further purification was required; R_f 0.23 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2984w, 1737s, 1449w, 1393w, 1264s, 1163w, 1114m, 1050m, 1023s, 968s; δ_H (400 MHz, $CDCl_3$) 1.33 (6 H, t, *J* = 7.0, H-4), 3.01 (2 H, d, *J* = 21.6, H-2), 4.13–4.21 (4 H, m, H-3), 4.80 (2 H, dd, *J* = 6.5, *J* = 1.2, H-5), 6.27 (1 H, dt, *J* = 15.9, *J* = 6.5, H-6), 6.68 (1 H, d, *J* = 15.9, H-7), 7.24–7.28 (1 H, m, H-11), 7.30–7.34 (2 H, m, H-10), 7.36–7.39 (2 H, m, H-9); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.2, C-4), 34.3 (d, *J* = 134.2, C-2), 62.7 (d, *J* = 6.5, C-3), 66.0 (C-5), 122.4 (C-6), 126.6 (C-9), 128.1 (C-11), 128.6 (C-10), 134.7 (C-7), 136.0 (C-8), 165.6 (d, *J* = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.2; HRMS (ESI^+): Found: 335.1027; $C_{15}H_{21}NaO_5P$ (MNa^+) Requires 335.1019 (–2.4 ppm error), Found: 313.1197; $C_{15}H_{22}O_5P$ (MH^+) Requires 313.1199 (0.7 ppm error).

Lab notebook reference: MGL/04/48

Cinnamyl 2-diazo-2-(diethoxyphosphoryl)acetate (296b)

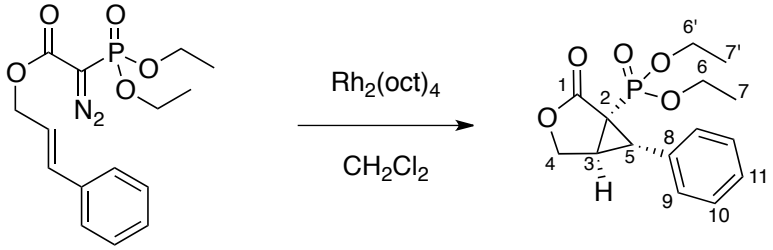


296a **296b**

Synthesised using general procedure B with cinnamyl 2-(diethoxyphosphoryl)acetate **296a** (3.12 g, 10.0 mmol), THF (50 mL), LHMDS (12.0 mL, 12.0 mmol, 1.0 M solution in THF) and *p*-ABSA (2.88 g, 12.0 mmol). Purification by column chromatography (2:1 petrol:EtOAc) afforded the *title compound* **296b** as a yellow oil (1.41 g, 42%); R_f 0.50 (1:1 petrol:EtOAc); ν_{max} (thin film)/cm^{-1} 2985w, 2128s, 1707s, 1496w, 1449w, 1380w, 1275s, 1214w, 1164w, 1120w, 1020s, 975m; δ_H (400 MHz, $CDCl_3$) 1.36 (6 H, t, *J* = 7.1, *J* = 0.8, H-4), 4.11–4.29 (4 H, m, H-3), 4.86 (2 H, dd, *J* = 6.5, *J* = 1.3, H-5), 6.28 (1 H, dt, *J* = 15.9, *J* = 6.5, H-6), 6.68 (1 H, d, *J* = 15.9, H-7), 7.25–7.40 (5 H, m, H-9,10,11); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* = 6.9, C-4), 53.9 (d, *J* = 227.3, C-2), 63.7 (d, *J* = 5.6, C-3), 66.0 (C-5), 122.4 (C-6), 126.6 (C-9), 128.2 (C-11), 128.6 (C-10), 134.9 (C-7), 135.9 (C-8), 163.2 (d, *J* = 11.8, C-1); δ_P (162 MHz, $CDCl_3$) 10.5; HRMS (ESI$^+$): Found: 361.0928; $C_{15}H_{19}N_2NaO_5P$ (MNa^+) Requires 361.0924 (−1.0 ppm error).

Lab notebook reference: MGL/04/59

Diethyl ((1*RS*,5*SR*,6*SR*)-2-oxo-6-phenyl-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate (296c)



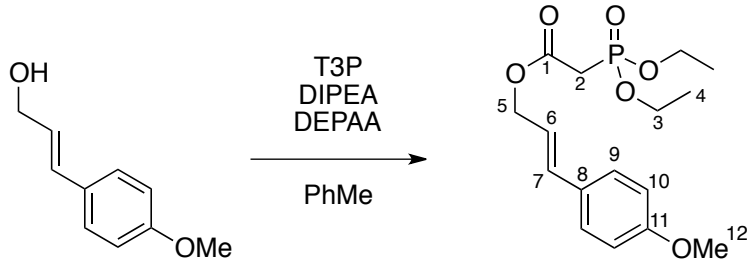
296b **296c**

To an oven dried 50 mL rbf containing cinnamyl 2-diazo-2-(diethoxyphosphoryl)acetate **296b** (676 mg, 2.00 mmol) flushed with argon was added CH_2Cl_2 (20 mL) followed by $Rh_2(oct)_4$ (31.1 mg, 0.04 mmol). The solution was stirred at 45 °C for 18 h. Concentration *in vacuo* and purification by

column chromatography (1:10 hexane:EtOAc) afforded the *title compound* **296c** as a pale yellow solid (490 mg, 79%); R_f 0.15 (1:2 hexane:EtOAc); m.p. 79–81 °C; ν_{max} (thin film)/cm^{-1} 2989w, 2909w, 1762s, 1369w, 1251m, 1200w, 1163w, 1098w, 1049w, 1013s, 971s; δ_H (400 MHz, $CDCl_3$) 1.07 (3 H, td, *J* = 7.1, *J* = 0.5, H-7/7'), 1.21 (3 H, t, *J* = 7.1, H-7/7'), 2.81 (1 H, app. t, *J* = 6.1, H-5), 3.30 (1 H, app. dt, *J* = 10.6, *J* = 5.2, H-3), 3.80 (2 H, dq, *J* = 8.2, *J* = 7.1, H-6/6'), 3.88–4.08 (2 H, m, H-6/6'), 4.41 (1 H, dd, *J* = 9.3, *J* = 2.8, H-4), 4.51 (1 H, dd, *J* = 9.3, *J* = 4.7, H-4), 7.26–7.39 (5 H, m, H-9,10,11); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* = 6.3, C-7/7'), 16.2 (d, *J* = 5.9, C-7/7'), 28.1 (C-3), 31.5 (d, *J* = 206.1, C-2), 34.9 (d, *J* = 3.0, C-5), 62.5 (d, *J* = 6.1, C-6/6'), 62.8 (d, *J* = 6.6, C-6/6'), 68.0 (d, *J* = 2.4, C-4), 128.0 (C-11), 128.1 (C-10), 129.4 (C-9), 131.7 (d, *J* = 4.8, C-8), 171.9 (d, *J* = 10.1, C-1); δ_P (162 MHz, $CDCl_3$) 15.3; HRMS (ESI$^+$): Found: 333.0861; $C_{15}H_{19}NaO_5P$ (MNa^+) Requires 333.0862 (0.4 ppm error), Found: 311.1035; $C_{15}H_{20}O_5P$ (MH^+) Requires 311.1043 (2.5 ppm error).

Lab notebook reference: MGL/04/67,61

(*E*)-3-(4-Methoxyphenyl)allyl 2-(diethoxyphosphoryl)acetate (297a)

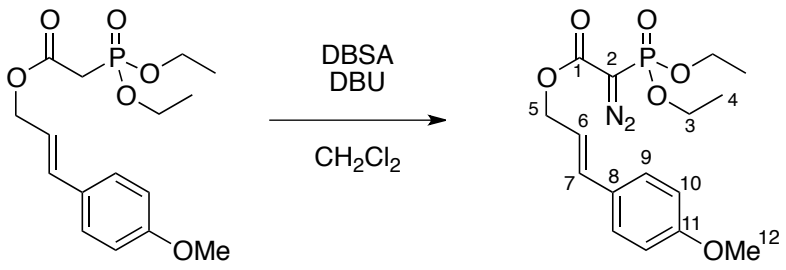


297 **297a**

Synthesised using general procedure A with (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol **297** (1.37 g, 8.34 mmol), toluene (41.7 mL), DEPAA (1.72 g, 8.76 mmol), DIPEA (3.78 mL, 21.7 mmol) and T3P (6.90 g, 10.8 mmol, 50% w/w solution in EtOAc) affording the *title compound* **297a** as an orange oil (2.79 g, 98%). No further purification was required; R_f 0.20 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2983w, 1733s, 1607m, 1512s, 1247s, 1176m, 1114m, 1023s, 966s, 841m; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, t, *J* = 7.1, H-4), 3.00 (2 H, d, *J* = 21.5, H-2), 3.80 (3 H, s, H-12), 4.13–4.20 (4 H, m, H-3), 4.77 (2 H, d, *J* = 6.7, H-5), 6.14 (1 H, dt, *J* = 15.8, *J* = 6.7, H-6), 6.62 (1 H, d, *J* = 15.8, H-7), 6.85 (2 H, d, *J* = 8.3, H-10), 7.31 (2 H, d, *J* = 8.3, H-9); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.6, C-4), 34.3 (d, *J* = 134.2, C-2), 55.2 (C-12), 62.7 (d, *J* = 6.7, C-3), 66.3 (C-5), 114.0 (C-10), 120.0 (C-6), 127.8 (C-9), 128.7 (C-8), 134.5 (C-7), 160.0 (C-11), 165.7 (d, *J* = 6.5, C-1); δ_P (162 MHz, $CDCl_3$) 20.2; HRMS (ESI$^+$): Found: 365.1129; $C_{16}H_{23}NaO_6P$ (MNa^+) Requires 365.1124 (–1.2 ppm error).

Lab notebook reference: MGL/08/74

(*E*)-3-(4-Methoxyphenyl)allyl 2-diazo-2-(diethoxyphosphoryl)acetate (297b)



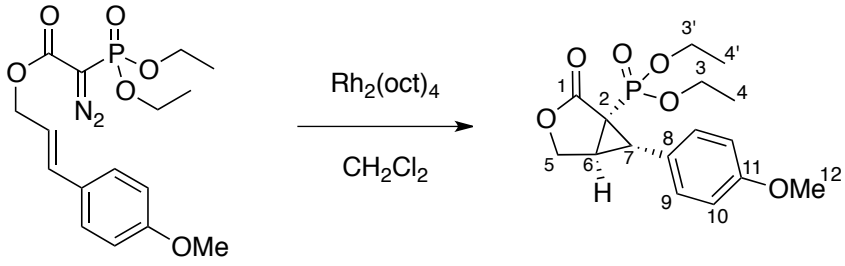
297a **297b**

Synthesised using general procedure C with (*E*)-3-(4-methoxyphenyl)allyl 2-(diethoxyphosphoryl)acetate **297a** (2.79 g, 8.15 mmol), DBSA (4.09 mL, 12.2 mmol), DBU (1.82 mL, 12.2 mmol) and CH_2Cl_2 (81.5 mL). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **297b** as a yellow oil (2.26 g, 75%); R_f 0.37 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2985w, 2127s, 1704s, 1607m, 1512s, 1273s, 1250s, 1176w, 1020s, 975s; δ_H (400 MHz, $CDCl_3$) 1.35 (6 H, td, *J* = 7.1, *J* = 0.8, H-4), 3.80 (3 H, s, H-12), 4.11–4.27 (4 H, m, H-3), 4.82 (2 H, dd, *J* = 6.7, *J* = 1.2, H-5), 6.14 (1 H, dt, *J* = 15.8, *J* = 6.7, H-6), 6.62 (1 H, d, *J* = 15.8, H-7), 6.85 (2 H, d, *J* = 8.7, H-10), 7.32 (2 H, d, *J* = 8.7, H-9); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* = 6.9, C-4), 55.2 (C-12), 63.7 (d, *J* = 6.1, C-3), 66.3 (C-5), 114.0 (C-10), 120.0 (C-6), 127.9 (C-9), 128.6 (C-8), 134.7 (C-7), 159.7 (C-11), 163.2 (d, *J* = 12.8, C-1); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI^+): Found: 391.1032; $C_{16}H_{21}N_2NaO_6P$ (MNa^+) Requires 391.1029 (–0.6 ppm error).

Lab notebook reference: MGL/08/80

Note: C-2 not observed in ^{13}C NMR spectrum.

Diethyl ((1*RS*,5*SR*,6*SR*)-6-(4-methoxyphenyl)-2-oxo-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate (297c)

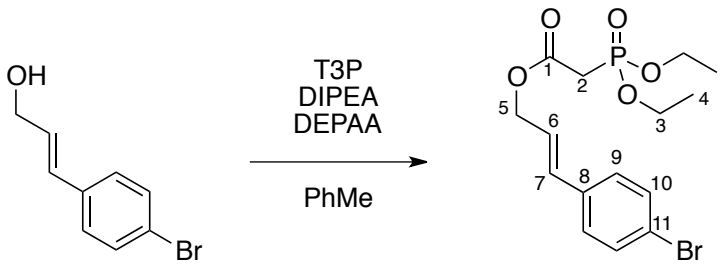


297b **297c**

Synthesised using general procedure F with (*E*)-3-(4-methoxyphenyl)allyl 2-diazo-2-(diethoxyphosphoryl)acetate **297b** (85 mg, 0.250 mmol), CH_2Cl_2 (5.0 mL) and $Rh_2(oct)_4$ (4.0 mg, 5.0 μmol). Purification by column chromatography (EtOAc) afforded the *title compound* **297c** as a pale yellow oil (45 mg, 53%); R_f 0.23 (EtOAc); ν_{max} (thin film)/cm^{-1} 2982w, 1764s, 1613w, 1518m, 1370w, 1294w, 1249s, 1182m, 1052m, 1020s, 983s, 820m; δ_H (400 MHz, $CDCl_3$) 1.09 (3 H, td, *J* = 7.1, *J* = 0.4, H-4/4'), 1.20 (3 H, t, *J* = 7.1, H-4/4'), 2.73 (1 H, app. t, *J* = 6.1, H-7), 3.24 (1 H, app. dt, *J* = 10.6, *J* = 5.2, H-6), 3.76 (3 H, s, H-12), 3.77–4.06 (4 H, m, H-3/3'), 4.36 (1 H, dd, *J* = 9.3, *J* = 2.8, H-5), 4.46 (1 H, dd, *J* = 9.3, *J* = 4.7, H-5), 6.83 (2 H, d, *J* = 8.8, H-10), 7.26 (2 H, d, *J* = 8.8, H-9); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* = 6.6, C-4/4'), 16.2 (d, *J* = 6.0, C-4/4'), 28.3 (C-6), 31.6 (d, *J* = 206.2, C-2), 34.6 (d, *J* = 3.2, C-7), 55.2 (C-12), 62.5 (d, *J* = 6.6, C-3/3'), 62.8 (d, *J* = 6.8, C-3/3'), 68.0 (d, *J* = 3.0, C-5), 113.4 (C-10), 123.5 (d, *J* = 5.6, C-8), 130.5 (C-9), 159.3 (C-11), 171.9 (d, *J* = 10.2, C-1); δ_P (162 MHz, $CDCl_3$) 15.5; HRMS (ESI^+): Found: 363.0960; $C_{16}H_{21}NaO_6P$ (MNa^+) Requires 363.0968 (2.1 ppm error), Found: 341.1140; $C_{16}H_{22}O_6P$ (MH^+) Requires 341.1149 (2.6 ppm error).

Lab notebook reference: MGL/08/88

(*E*)-3-(4-Bromophenyl)allyl 2-(diethoxyphosphoryl)acetate (298a)

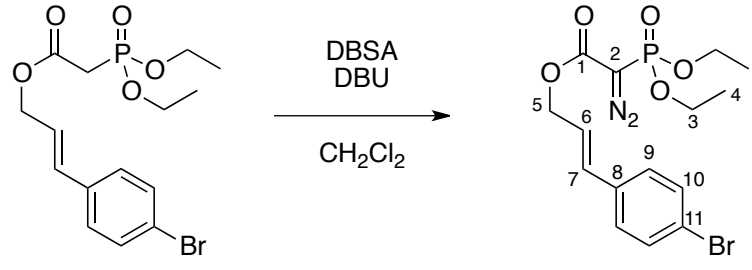


298 **298a**

Synthesised using general procedure A with (*E*)-3-(4-bromophenyl)prop-2-en-1-ol **298** (1.58 g, 7.43 mmol), toluene (37.2 mL), DEPAA (1.53 g, 7.80 mmol), DIPEA (3.36 mL, 19.3 mmol) and T3P (6.15 g, 9.66 mmol, 50% w/w solution in EtOAc) affording the *title compound* **298a** as an orange oil (2.90 g, 100%). No further purification was required; R_f 0.20 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2982w, 1736w, 1488m, 1402w, 1258s, 1114m, 1049m, 1022s, 967s, 840m, 785m; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, t, *J* = 7.1, H-4), 3.01 (2 H, d, *J* = 21.5, H-2), 4.13–4.20 (4 H, m, H-3), 4.78 (2 H, d, *J* = 6.3, H-5), 6.26 (1 H, dt, *J* = 15.9, *J* = 6.3, H-6), 6.62 (1 H, d, *J* = 15.9, H-7), 7.24 (2 H, d, *J* = 8.5, H-9/10), 7.43 (2 H, d, *J* = 8.5, H-9/10); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.6, C-4), 34.3 (d, *J* = 134.2, C-2), 62.7 (d, *J* = 6.7, C-3), 65.7 (C-5), 122.0 (C-11), 123.3 (C-6), 128.1 (C-9/10), 131.7 (C-9/10), 133.2 (C-7), 135.0 (C-8), 165.6 (d, *J* = 6.5, C-1); δ_P (162 MHz, $CDCl_3$) 20.1; HRMS (ESI$^+$): Found: 413.0130; $C_{15}H_{20}{}^{79}BrNaO_5P$ (MNa^+) Requires 413.0124 (–1.4 ppm error).

Lab notebook reference: MGL/08/75

(*E*)-3-(4-Bromophenyl)allyl 2-diazo-2-(diethoxyphosphoryl)acetate (298b)



298a **298b**

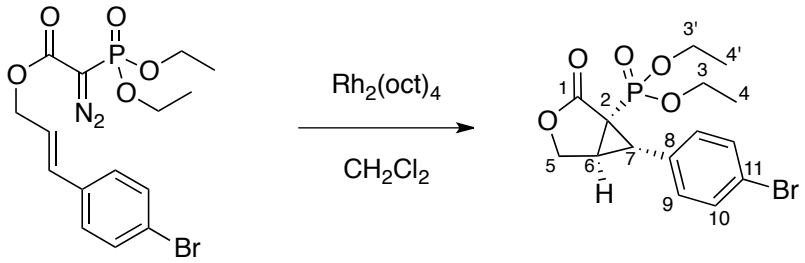
Synthesised using general procedure C with (*E*)-3-(4-bromophenyl)allyl 2-(diethoxyphosphoryl)acetate **298a** (2.90 g, 7.41 mmol), DBSA (3.72 mL, 11.1 mmol), DBU (1.66 mL, 11.1 mmol) and CH_2Cl_2 (74.1 mL). Purification by column chromatography (2:1

hexane:EtOAc) afforded the *title compound* **298b** as a yellow oil (2.69 g, 87%); R_f 0.42 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2984w, 2127s, 1705s, 1488m, 1275s, 1020s, 975s, 798w, 744w, 590w, 560w; δ_H (400 MHz, $CDCl_3$) 1.33–1.37 (6 H, m, H-4), 4.12–4.28 (4 H, m, H-3), 4.83 (2 H, dd, *J* = 6.4, *J* = 1.3, H-5), 6.26 (1 H, dt, *J* = 15.9, *J* = 6.4, H-6), 6.61 (1 H, d, *J* = 15.9, H-7), 7.24 (2 H, d, *J* = 8.5, H-9/10), 7.44 (2 H, d, *J* = 8.5, H-9/10); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 7.2, C-4), 63.8 (d, *J* = 6.1, C-3), 65.9 (C-5), 122.2 (C-11), 123.3 (C-6), 128.2 (C-9/10), 131.9 (C-9/10), 133.6 (C-7), 135.0 (C-8), 163.3 (d, *J* = 12.6, C-1); δ_P (162 MHz, $CDCl_3$) 10.5; HRMS (ESI$^+$): Found: 439.0019; $C_{15}H_{18}{}^{79}BrN_2NaO_5P$ (MNa^+) Requires 439.0029 (2.3 ppm error).

Lab notebook reference: MGL/08/81

Note: C-2 not observed in ^{13}C NMR spectrum.

Diethyl ((1*RS*,5*SR*,6*SR*)-6-(4-bromophenyl)-2-oxo-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate (298c)

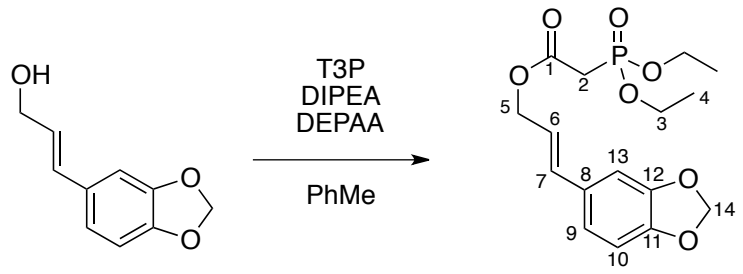


298b **298c**

Synthesised using general procedure F with (*E*)-3-(4-bromophenyl)allyl 2-diazo-2-(diethoxyphosphoryl)acetate **298b** (97 mg, 0.250 mmol), CH_2Cl_2 (5.0 mL) and $Rh_2(oct)_4$ (4.0 mg, 5.0 μmol). Purification by column chromatography (EtOAc) afforded the *title compound* **298c** as a pale yellow oil (72 mg, 74%); R_f 0.32 (EtOAc); ν_{max} (thin film)/cm^{-1} 2982w, 1768s, 1492w, 1369w, 1252m, 1053s, 1019s, 974m, 810m, 590m; δ_H (400 MHz, $CDCl_3$) 1.09 (3 H, t, *J* = 7.1, H-4/4'), 1.21 (3 H, t, *J* = 7.1, H-4/4'), 2.71 (1 H, app. t, *J* = 6.0, H-7), 3.24 (1 H, app. dt, *J* = 10.7, *J* = 5.2, H-6), 3.81–4.08 (4 H, m, H-3/3'), 4.38 (1 H, dd, *J* = 9.4, *J* = 2.8, H-5), 4.48 (1 H, dd, *J* = 9.4, *J* = 4.8, H-5), 7.22 (2 H, d, *J* = 8.5, H-9/10), 7.43 (2 H, d, *J* = 8.5, H-9/10); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* = 6.6, C-4/4'), 16.1 (d, *J* = 6.0, C-4/4'), 28.1 (C-6), 31.4 (d, *J* = 205.8, C-2), 34.0 (d, *J* = 3.7, C-7), 62.6 (d, *J* = 6.6, C-3/3'), 62.9 (d, *J* = 6.8, C-3/3'), 67.8 (d, *J* = 3.1, C-5), 122.0 (C-11), 130.9 (d, *J* = 5.7, C-8), 131.0 (C-9/10), 131.1 (C-9/10), 171.5 (d, *J* = 10.2, C-1); δ_P (162 MHz, $CDCl_3$) 15.0; HRMS (ESI$^+$): Found: 410.9970; $C_{15}H_{18}{}^{79}BrNaO_5P$ (MNa^+) Requires 410.9967 (−0.6 ppm error), Found: 389.0154; $C_{15}H_{19}{}^{79}BrO_5P$ (MH^+) Requires 389.0148 (−1.5 ppm error).

Lab notebook reference: MGL/08/89

(*E*)-3-(1,3-Benzodioxol-5-yl)allyl 2-(diethoxyphosphoryl)acetate (299a)

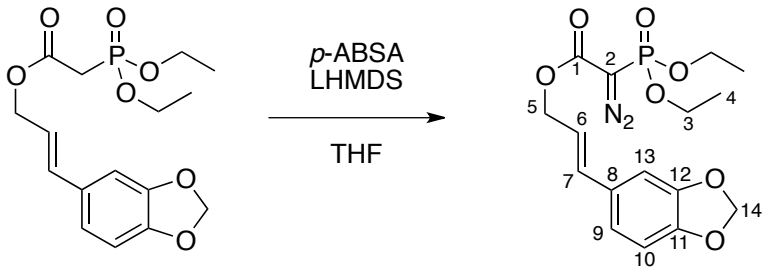


299 **299a**

Synthesised using general procedure A with (*E*)-3-(1,3-benzodioxol-5-yl)prop-2-en-1-ol **299** (1.95 g, 10.9 mmol), toluene (55 mL), DEPAA (1.85 mL, 11.5 mmol), DIPEA (4.95 mL, 28.4 mmol) and T3P (9.05 g, 14.2 mmol, 50% w/w solution in EtOAc) affording the *title compound* **299a** as a yellow oil (3.89 g, 100%). No further purification was required; R_f 0.17 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2986w, 2908w, 1733s, 1654w, 1607w, 1504m, 1491m, 1446m, 1398w, 1354w, 1248s, 1195w, 1164w, 1021s, 965s; δ_H (400 MHz, $CDCl_3$) 1.32 (6 H, t, *J* = 7.1, *J* = 0.4, H-4), 2.99 (2 H, d, *J* = 21.5, H-2), 4.12–4.20 (4 H, m, H-3), 4.75 (2 H, dd, *J* = 6.6, *J* = 1.0, H-5), 5.95 (2 H, s, H-14), 6.09 (1 H, dt, *J* = 15.8, *J* = 6.6, H-6), 6.58 (1 H, d, *J* = 15.8, H-7), 6.74 (1 H, d, *J* = 8.0, H-10), 6.81 (1 H, dd, *J* = 8.0, *J* = 1.6, H-9), 6.91 (1 H, d, *J* = 1.6, H-13); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.2, C-4), 34.3 (d, *J* = 134.2, C-2), 62.7 (d, *J* = 6.2, C-3), 66.1 (C-5), 101.1 (C-14), 105.7 (C-13), 108.3 (C-10), 120.5 (C-6), 121.5 (C-9), 130.4 (C-8), 134.5 (C-7), 147.7 (C-11/12), 148.0 (C-11/12), 165.6 (d, *J* = 6.1, C-1); δ_P (162 MHz, $CDCl_3$) 20.2; HRMS (ESI$^+$): Found: 379.0920; $C_{16}H_{21}NaO_7P$ (MNa^+) Requires 379.0917 (–0.8 ppm error).

Lab notebook reference: MGL/04/65

(*E*)-3-(1,3-Benzodioxol-5-yl)allyl 2-diazo-2-(diethoxyphosphoryl)acetate (299b)

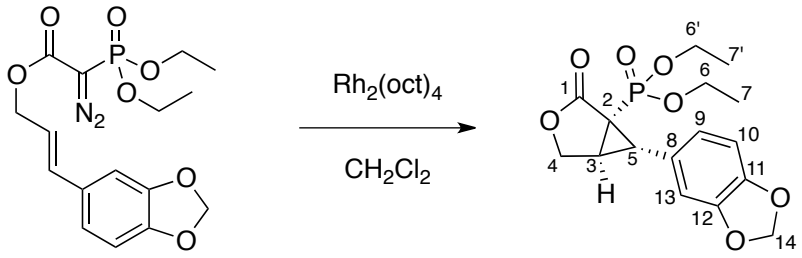


299a **299b**

Synthesised using general procedure B with purification by column chromatography (1:1 hexane:EtOAc) affording the *title compound* as a pale yellow solid (1.71 g, 46%); R_f 0.36 (1:1

hexane:EtOAc); m.p. 71–75 °C ν_{max} (thin film)/cm^{-1} 2985w, 2129s, 1703s, 1504m, 1491m, 1446m, 1383w, 1355w, 1274s, 1250s, 1164w, 1101w, 1019s, 975m, 862w, 797m, 745m, 590m, 560m; δ_H (400 MHz, $CDCl_3$) 1.36 (6 H, t, *J* = 7.1, *J* = 0.8, H-4), 4.12–4.28 (4 H, m, H-3), 4.82 (2 H, dd, *J* = 6.6, *J* = 1.3, H-5), 5.96 (2 H, s, H-14), 6.10 (1 H, dt, *J* = 15.8, *J* = 6.6, H-6), 6.59 (1 H, d, *J* = 15.8, H-7), 6.76 (1 H, d, *J* = 8.0, H-10), 6.82 (1 H, dd, *J* = 8.0, *J* = 1.7, H-9), 6.92 (1 H, d, *J* = 1.7, H-13); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* = 6.9, C-4), 53.9 (d, *J* = 229.3, C-2), 63.7 (d, *J* = 5.6, C-3), 66.1 (C-5), 101.2 (C-14), 105.7 (C-13), 108.3 (C-10), 120.5 (C-6), 121.6 (C-9), 130.3 (C-8), 134.8 (C-7), 147.8 (C-11/12), 148.1 (C-11/12), 163.2 (d, *J* = 12.2, C-1); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI$^+$): Found: 405.0820; $C_{16}H_{19}N_2NaO_7P$ (MNa^+) Requires 405.0822 (0.4 ppm error).
Lab notebook reference: MGL/04/75

Diethyl ((1*RS*,5*SR*,6*SR*)-6-(1,3-benzodioxol-5-yl)-2-oxo-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate (299c)

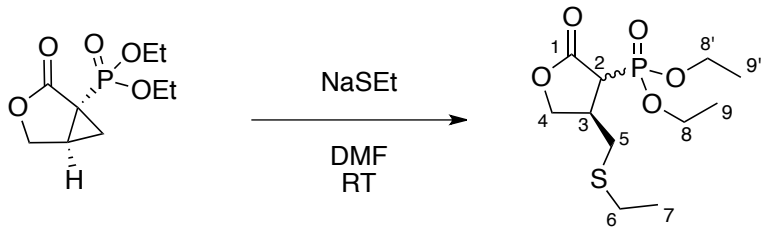


299b **299c**

Synthesised using general procedure F with (*E*)-3-(1,3-benzodioxol-5-yl)allyl 2-diazo-2-(diethoxyphosphoryl)acetate **299b** (68 mg, 0.178 mmol), CH_2Cl_2 (3.6 mL) and $Rh_2(oct)_4$ (2.8 mg, 3.6 μmol). Purification by column chromatography (1:10 hexane:EtOAc) afforded the *title compound* **299c** as a pale yellow solid (46 mg, 73%); R_f 0.17 (1:2 hexane:EtOAc); m.p. 96–99 °C; ν_{max} (thin film)/cm^{-1} 2980m, 2910m, 1754s, 1500m, 1489m, 1447m, 1395w, 1371m, 1311m, 1233s, 1214w, 1180w, 1098w, 1014s, 832m, 807m, 585s; δ_H (400 MHz, $CDCl_3$) 1.15 (3 H, t, *J* = 7.1, H-7/7'), 1.24 (3 H, t, *J* = 7.1, H-7/7'), 2.74 (1 H, app. t, *J* = 6.1, H-5), 3.21 (1 H, app. dt, *J* = 10.7, *J* = 5.2, H-3), 3.89–4.12 (4 H, m, H-6,6'), 4.38 (1 H, dd, *J* = 9.3, *J* = 2.8, H-4), 4.48 (1 H, dd, *J* = 9.3, *J* = 4.7, H-4), 5.94 (2 H, s, H-14), 6.75 (1 H, d, *J* = 7.9, H-10), 6.81–6.84 (2 H, m, H-9,13); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* = 6.5, C-7/7'), 16.3 (d, *J* = 6.0, C-7/7'), 28.4 (C-3), 31.5 (d, *J* = 205.7, C-2), 34.9 (d, *J* = 3.0, C-5), 62.6 (d, *J* = 6.1, C-6/6'), 62.9 (d, *J* = 6.6, C-6/6'), 68.0 (d, *J* = 2.4, C-4), 101.2 (C-14), 107.9 (C-10), 109.8 (C-9/13), 123.0 (C-9/13), 125.3 (d, *J* = 5.1, C-8), 147.4 (C-11/12), 147.4 (C-11/12), 171.8 (d, *J* = 10.2, C-1); δ_P (162 MHz, $CDCl_3$) 15.4; HRMS (ESI$^+$): Found: 377.0750; $C_{16}H_{19}NaO_7P$ (MNa^+) Requires 377.0761 (2.8 ppm error), Found: 355.0925; $C_{16}H_{20}O_7P$ (MH^+) Requires 355.0941 (4.4 ppm error).
Lab notebook reference: MGL/04/81

5.2.3.2. Ring-openings

Diethyl ((4*SR*)-4-((ethylthio)methyl)-2-oxotetrahydrofuran-3-yl)phosphonate (304)

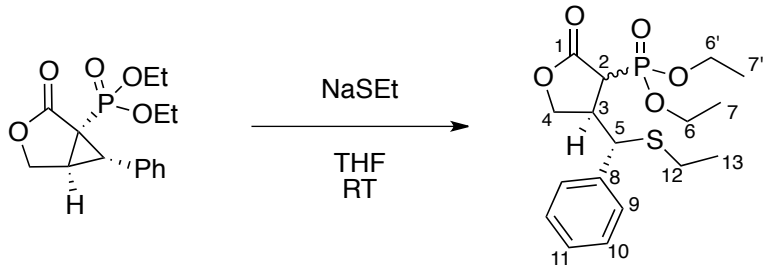


287c **304**

To a solution of diethyl ((1*RS*,5*SR*)-2-oxo-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate **287c** (47.0 mg, 0.201 mmol) in DMF (1 mL) was added sodium ethanethiolate (20.3 mg, 0.241 mmol). The solution was stirred at RT for 2 h then quenched with sat. aq. NH_4Cl (10 mL) and the aqueous layer separated. The organic layer was washed with water (2 × 10 mL) and dried over $MgSO_4$. Concentration *in vacuo* and purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **304** as a colourless oil (22 mg, 37%); R_f 0.44 (1:8 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2979w, 2915w, 2838w, 1772s, 1251m, 1160w, 1047w, 1021s, 971m; δ_H (400 MHz, $CDCl_3$) 1.25 (3 H, t, *J* = 7.4, H-7), 1.34 (3 H, td, *J* = 7.1, *J* = 0.6, H-9/9'), 1.36 (3 H, td, *J* = 7.1, *J* = 0.6, H-9/9'), 2.55 (2 H, q, *J* = 7.4, H-6), 2.68 (1 H, ddd, *J* = 13.4, *J* = 7.8, *J* = 0.8, H-5), 2.74 (1 H, dd, *J* = 13.4, *J* = 7.8, H-5), 2.99–3.11 (1 H, m, H-3), 3.05 (1 H, dd, *J* = 24.6, *J* = 4.9, H-2), 4.13 (1 H, dd, *J* = 9.2, *J* = 4.1, H-4), 4.16–4.26 (4 H, m, H-8,8'), 4.56 (1 H, dd, *J* = 9.2, *J* = 6.9, H-4); δ_C (100 MHz, $CDCl_3$) 14.6 (C-7), 16.3 (d, *J* = 6.1, C-9/9'), 16.3 (d, *J* = 6.1, C-9/9'), 25.9 (C-6), 34.7 (d, *J* = 10.1, C-5), 37.6 (d, *J* = 2.2, C-3), 44.2 (d, *J* = 141.1, C-2), 63.0 (d, *J* = 6.8, C-8/8'), 63.7 (d, *J* = 6.8, C-8/8'), 71.7 (d, *J* = 5.7, C-4), 171.4 (d, *J* = 3.2, C-1); δ_P (162 MHz, $CDCl_3$) 20.1; HRMS (ESI^+): Found: 319.0730; $C_{11}H_{21}NaO_5PS$ (MNa^+) Requires 319.0740 (3.0 ppm error).

Lab notebook reference: MGL/03/31

Diethyl ((4*SR*)-4-((*SR*)-(ethylthio)(phenyl)methyl)-2-oxotetrahydrofuran-3-yl)phosphonate (305)

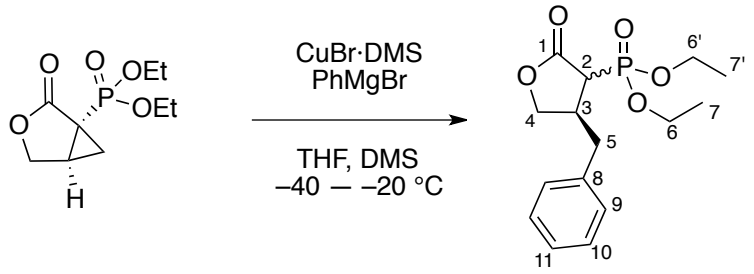


296c **305**

To a solution of diethyl ((1*RS*,5*SR*,6*SR*)-2-oxo-6-phenyl-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate **296c** (62 mg, 0.200 mmol) in THF (1.0 mL) was added sodium ethanethiolate (33.6 mg, 0.400 mmol). The solution was stirred at RT for 18 h then quenched with sat. aq. NH_4Cl (10 mL), diluted with diethyl ether (10 mL) and the aqueous layer separated. The aqueous layer was extracted once with diethyl ether (10 mL) then the combined organic extracts were washed with water (2 × 10 mL) and dried over $MgSO_4$. Concentration *in vacuo* and purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **305** as a colourless oil (14 mg, 19%); R_f 0.28 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2978m, 2928m, 1773s, 1453w, 1254s, 1151m, 1048m, 1023s, 972m, 702w; δ_H (400 MHz, $CDCl_3$) 1.14 (3 H, t, *J* = 7.4, H-13), 1.25–1.32 (6 H, m, H-7,7'), 2.33 (2 H, q, *J* = 7.4, H-12), 2.89 (1 H, dd, *J* = 24.6, *J* = 3.0, H-2), 3.17–3.27 (1 H, m, H-3), 3.84 (1 H, d, *J* = 9.7, H-5), 3.93–4.18 (4 H, m, H-6,6'), 4.53 (1 H, dd, *J* = 9.4, *J* = 6.7, H-4), 4.67 (1 H, dd, *J* = 9.4, *J* = 2.5, H-4), 7.27–7.37 (5 H, m, H-9,10,11); δ_C (100 MHz, $CDCl_3$) 14.3 (C-13), 16.2 (d, *J* = 6.5, C-7/7'), 16.3 (d, *J* = 6.5, C-7/7'), 25.3 (C-12), 43.5 (C-3), 43.9 (d, *J* = 136.2, C-2), 52.1 (d, *J* = 12.3, C-5), 62.9 (d, *J* = 7.3, C-6/6'), 63.8 (d, *J* = 6.8, C-6/6'), 70.6 (d, *J* = 3.3, C-4), 128.0 (C-11), 128.3 (C-9/10), 128.9 (C-9/10), 139.4 (C-8), 171.4 (d, *J* = 4.2, C-1); δ_P (162 MHz, $CDCl_3$) 19.4; HRMS (ESI^+): Found: 395.1065; $C_{17}H_{25}NaO_5PS$ (MNa^+) Requires 395.1053 (−3.0 ppm error), Found: 373.1243; $C_{17}H_{26}O_5PS$ (MH^+) Requires 373.1233 (−2.6 ppm error).

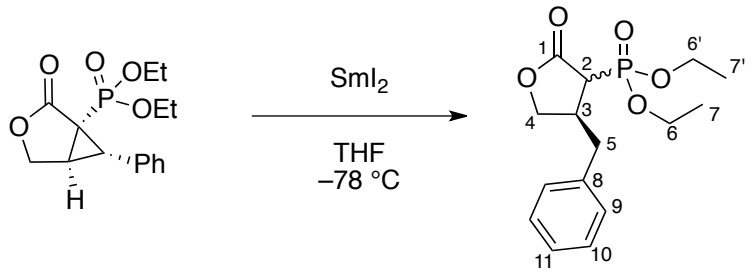
Lab notebook reference: MGL/08/98B

Diethyl ((4*SR*)-4-benzyl-2-oxotetrahydrofuran-3-yl)phosphonate (306)



287c **306**

Cuprate method: To a stirred solution of CuBr·DMS (61.7 mg, 0.300 mmol) in THF (0.6 mL) and DMS (0.2 mL) at −40 °C was added phenylmagnesium bromide (0.2 mL, 0.600 mmol, 3.0 M solution in diethyl ether). The solution was stirred for 20 mins with warming to −20 °C. A solution of diethyl ((1*RS*,5*SR*)-2-oxo-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate **287c** (52 mg, 0.222 mmol) in THF (0.6 mL) was added *via* cannula over 5 mins. After stirring the solution for 2 h at RT the reaction was quenched with sat. aq. NH_4Cl (5 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (1:2 hexane:EtOAc) afforded the *title compound* **306** as a pale yellow oil (44 mg, 63%).



296c **306**

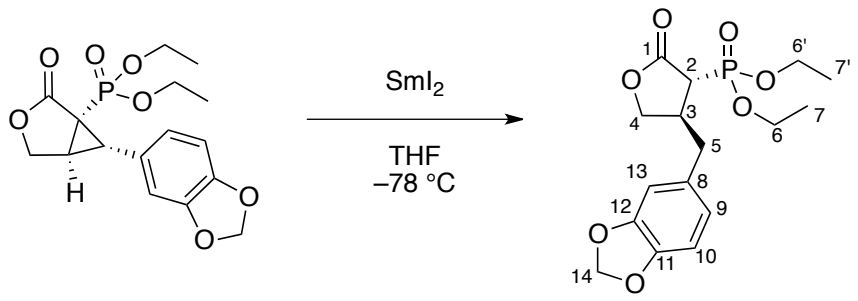
SmI_2 method: To a solution of freshly prepared SmI_2 (2.00 mL, 0.200 mmol, ~0.1 M in THF) in an oven dried sealable tube at −78 °C under an atmosphere of argon, was added a solution of diethyl ((1*RS*,5*SR*,6*SR*)-2-oxo-6-phenyl-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate **296c** (31 mg, 0.100 mmol) in THF (0.5 mL). The solution was stirred at −78 °C for 5 mins then quenched with sat. aq. NH_4Cl (5 mL) and then allowed to warm at RT. The mixture was diluted with water (5 mL) and extrated with diethyl ether (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (1:2 hexane:EtOAc) afforded the *title compound* **306** as a pale yellow oil (15 mg, 48%).

Data for **306**: R_f 0.52 (1:4 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2983w, 2915w, 1771s, 1497w, 1479w, 1455w, 1381w, 1252m, 1206w, 1160m, 1047w, 1020s, 972s, 753m, 703m; δ_H (400 MHz, $CDCl_3$) 1.29–1.33 (6 H, m, H-7,7'), 2.81 (1 H, dd, *J* = 13.8, *J* = 8.6, H-5), 2.83 (1 H, dd, *J* = 23.9, *J* = 4.5, H-2), 2.93 (1 H, dd, *J* = 13.8, *J* = 7.1, H-5), 3.11–3.24 (1 H, m, H-3), 3.99–4.29 (5 H, m, H-4,6,6'), 4.45 (1 H, dd, *J* = 9.1, *J* = 6.9, H-4), 7.15–7.18 (2 H, m, H-9/10), 7.23–7.27 (1 H, m, H-11), 7.29–7.34 (2 H, m, H-9/10); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.1, C-7/7'), 16.3 (d, *J* = 6.1, C-7/7'), 39.3 (d, *J* = 2.6, C-3), 39.3 (d, *J* = 10.1, C-5), 44.5 (d, *J* = 139.5, C-2), 62.9 (d, *J* = 6.8, C-6/6'), 63.6 (d, *J* = 6.8, C-6/6'), 71.8 (d, *J* = 5.0, C-4), 127.0 (C-11), 128.8 (C-9/10), 129.0 (C-9/10), 137.2 (C-8), 171.7 (d, *J* = 3.6, C-1); δ_P (162 MHz, $CDCl_3$) 20.0; HRMS (ESI$^+$): Found: 335.1030; $C_{15}H_{21}NaO_5P$ (MNa^+) Requires 335.1019 (–3.4 ppm error), Found: 313.1205; $C_{15}H_{22}O_5P$ (MH^+) Requires 313.1199 (–1.7 ppm error).

Lab notebook reference: MGL/04/68, 07/83

5.2.3.3. Savinin and Gadain

Diethyl ((3*RS*,4*SR*)-4-(benzo[*d*][1,3]dioxol-5-ylmethyl)-2-oxotetrahydrofuran-3-yl)phosphonate (149c)



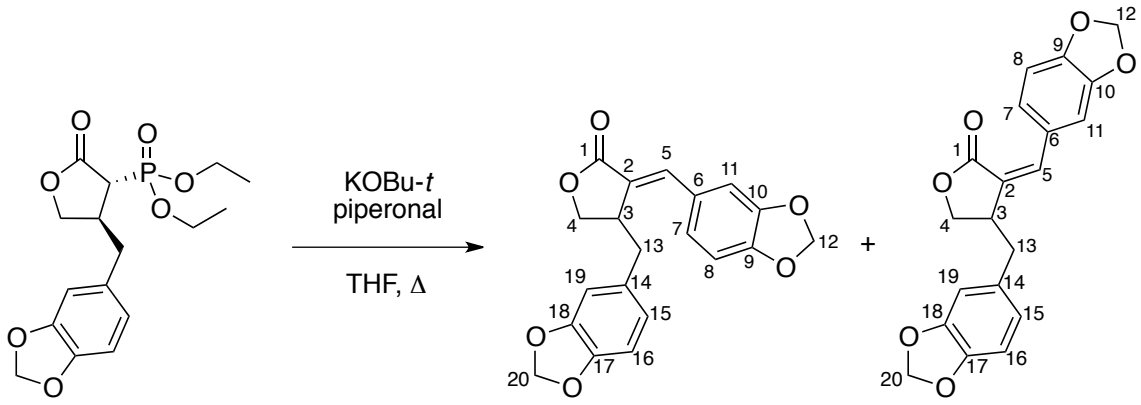
299c **149c**

To a solution of freshly prepared SmI_2 (4.00 mL, 0.400 mmol, ~0.1 M in THF) in an oven dried sealable tube at −78 °C under an atmosphere of argon, was added a solution of diethyl ((1*RS*,5*SR*,6*SR*)-6-(1,3-benzodioxol-5-yl)-2-oxo-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate **299c** (70.9 mg, 0.200 mmol) in THF (1.0 mL). The solution was stirred at −78 °C for 30 mins then quenched with sat. aq. NH_4Cl (1.70 mL) and then allowed to warm at RT. The mixture was diluted with water (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (1:4 hexane:EtOAc) afforded the *title compound* **149c** as a yellow oil (27 mg, 38%); R_f 0.55 (EtOAc); ν_{max} (thin film)/cm^{-1} 2983w, 2910w, 1768s, 1503w, 1490s, 1443m, 1245s, 1196m, 1149m, 1018s, 971s, 809w, 549w; δ_H (400 MHz, $CDCl_3$) 1.33 (6 H, t, *J* = 7.1, H-7,7'),

2.69–2.87 (3 H, m, H-2,5), 3.04–3.16 (1 H, m, H-3), 4.04–4.22 (5 H, m, H-4,6,6'), 4.44 (1 H, dd, *J* = 9.1, *J* = 6.9, H-4), 5.94 (2 H, s, H-14), 6.60 (1 H, dd, *J* = 7.9, *J* = 1.4, H-9), 6.65 (1 H, d, *J* = 1.4, H-13), 6.74 (1 H, d, *J* = 7.9, H-10); δ_C (100 MHz, $CDCl_3$) 16.3 (app. t, *J* = 6.4, C-7/7'), 39.0 (d, *J* = 10.0, C-5), 39.3 (d, *J* = 3.0, C-3), 44.5 (d, *J* = 139.9, C-2), 62.9 (d, *J* = 7.3, C-6/6'), 63.7 (d, *J* = 7.0, C-6/6'), 71.7 (d, *J* = 5.3, C-4), 101.1 (C-14), 108.4 (C-13), 109.1 (C-10), 122.2 (C-9), 130.8 (C-8), 146.6 (C-11/12), 148.0 (C-11/12), 171.7 (d, *J* = 3.8, C-1); δ_P (162 MHz, $CDCl_3$) 20.1; HRMS (ESI^+): Found: 379.0923; $C_{16}H_{21}NaO_7P$ (MNa^+) Requires 379.0917 (–1.6 ppm error), Found: 357.1100; $C_{16}H_{22}O_7P$ (MH^+) Requires 357.1098 (–0.8 ppm error).

Lab notebook reference: MGL/08/96

(*RS*,*E*)-4-(benzo[*d*][1,3]dioxol-5-ylmethyl)-3-(benzo[*d*][1,3]dioxol-5-ylmethylene)dihydrofuran-2(3*H*)-one ((±)-savinin) (174) and (*RS*,*Z*)-4-(benzo[*d*][1,3]dioxol-5-ylmethyl)-3-(benzo[*d*][1,3]dioxol-5-ylmethylene)dihydrofuran-2(3*H*)-one ((±)-gadain) (307)



299c savinin, **174** gadain, **307**

To a solution of diethyl ((3*RS*,4*SR*)-4-(benzo[*d*][1,3]dioxol-5-ylmethyl)-2-oxotetrahydrofuran-3-yl)phosphonate **149c** (59 mg, 0.166 mmol) in THF (3.3 mL) at 0 °C was added KOBu-*t* (27.9 mg, 0.248 mmol). The solution was stirred at 0 °C for 60 mins, after which, piperonal (49.8 mg, 0.332 mmol) was added to the solution, which was refluxed for 2 h. After cooling at RT, the solution was quenched with sat. aq. NH_4Cl (10 mL). The organic layer was separated and the aqueous extracted with EtOAc (2 × 10 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (5:1 hexane:EtOAc → 3:1 hexane:EtOAc) afforded the title compounds as mixture (**174**:**307** 1.9:1) (31 mg, 53%).

Small quantities of each compound were isolated separately for characterisation purposes.

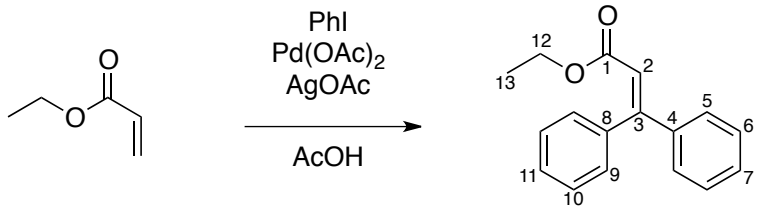
Data for savinin, **174**; White solid; R_f 0.20 (4:1 hexane:EtOAc); m.p. 127–129 °C (lit.[95] 146.4–148.4 °C); ν_{max} (thin film)/cm^{-1} 2908m, 1744s, 1646m, 1503s, 1490s, 1447s, 1341m, 1250s, 1214s, 1180s, 1037s, 927m, 810w; δ_H (400 MHz, $CDCl_3$) 2.59 (1 H, dd, *J* = 14.2, *J* = 10.1, H-13), 2.99 (1 H, dd, *J* = 14.2, *J* = 4.5, H-13), 3.71–3.77 (1 H, m, H-3), 4.22–4.29 (2 H, m, H-4), 5.93 (1 H, d, *J* = 1.4, H-20), 5.94 (1 H, d, *J* = 1.4, H-20), 6.05 (2 H, s, H-12), 6.64 (1 H, dd, *J* = 7.8, *J* = 1.6, H-15), 6.67 (1 H, d, *J* = 1.6, H-19), 6.74 (1 H, d, *J* = 7.8, H-16), 6.88 (1 H, d, *J* = 8.1, H-8), 7.05 (1 H, d, *J* = 1.7, H-11), 7.08 (1 H, dd, *J* = 8.1, *J* = 1.7, H-7), 7.50 (1 H, d, *J* = 1.9, H-5); δ_C (100 MHz, $CDCl_3$) 37.5 (C-13), 39.9 (C-3), 69.5 (C-4), 101.0 (C-20), 101.7 (C-12), [108.5, 108.6, 108.8, 109.2 (C-8,11,16,19)], 122.2 (C-15), 125.8 (C-2), 126.1 (C-7), 128.2 (C-6), 131.5 (C-14), 137.5 (C-5), 146.5 (C-17/18), 147.9 (C-17/18), 148.3 (C-9/10), 149.2 (C-9/10), 172.6 (C-1); HRMS (ESI^+): Found: 375.0833; $C_{20}H_{16}NaO_6$ (MNa^+) Requires 375.0839 (1.5 ppm error), Found: 353.1019; $C_{20}H_{17}O_6$ (MH^+) Requires 353.1020 (0.3 ppm error).
Obtained data in accord with reported literature.[95,140-141]

Data for gadain, **307**; White solid; R_f 0.26 (4:1 hexane:EtOAc); m.p. 136–139 °C (lit.[143] 145 °C); ν_{max} (thin film)/cm^{-1} 2906w, 1741s, 1634w, 1600w, 1503s, 1488s, 1446s, 1246s, 1171s, 1083s, 1037s, 928s, 810m; δ_H (400 MHz, $CDCl_3$) 2.78 (1 H, dd, *J* = 13.8, *J* = 8.9, H-13), 2.91 (1 H, dd, *J* = 13.8, *J* = 6.9, H-13), 3.29 (1 H, app. dtdd, *J* = 8.9, *J* = 7.1, *J* = 3.8, *J* = 1.7, H-3), 4.10 (1 H, dd, *J* = 9.1, *J* = 3.8, H-4), 4.32 (1 H, dd, *J* = 9.1, *J* = 7.3, H-4), 5.95 (1 H, d, *J* = 1.4, H-20), 5.96 (1 H, d, *J* = 1.4, H-20), 6.00 (2 H, s, H-12), 6.59 (1 H, d, *J* = 1.7, H-5), 6.62 (1 H, dd, *J* = 7.9, *J* = 1.7, H-15), 6.69 (1 H, d, *J* = 1.7, H-19), 6.76 (1 H, d, *J* = 7.9, H-16), 6.79 (1 H, d, *J* = 8.1, H-8), 7.15 (1 H, dd, *J* = 8.1, *J* = 1.7, H-7), 7.74 (1 H, d, *J* = 1.7, H-11); δ_C (100 MHz, $CDCl_3$) 40.7 (C-13), 44.2 (C-3), 69.8 (C-4), 101.0 (C-20), 101.4 (C-12), 107.9 (C-8), 108.4 (C-16), 109.3 (C-19), 110.7 (C-11), 122.3 (C-15), 125.2 (C-2), 126.9 (C-7), 127.9 (C-6), 131.4 (C-14), 140.4 (C-5), 146.5 (C-17/18), 147.6 (C-17/18), 147.9 (C-9/10), 149.0 (C-9/10), 169.3 (C-1); HRMS (ESI^+): Found: 375.0843; $C_{20}H_{16}NaO_6$ (MNa^+) Requires 375.0839 (–1.2 ppm error), Found: 353.1027; $C_{20}H_{17}O_6$ (MH^+) Requires 353.1020 (–2.0 ppm error).
Obtained data in accord with reported literature.[143]

Lab notebook reference: MGL/08/100

5.2.3.4. Peperomin E

Ethyl 3,3-diphenylacrylate (329)



328 **329**

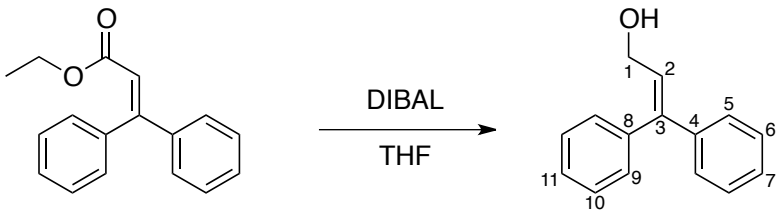
Prepared according to a modified literature procedure.[152]

To a suspension of AgOAc (2.59 g, 15.5 mmol) and $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) in AcOH (15 mL) was added iodobenzene (1.73 mL, 15.5 mmol) and ethyl acrylate **328** (0.54 mL, 5.00 mmol). The mixture was stirred under an atmosphere of argon, at 110 °C for 6 h then allowed cool at RT and diluted with EtOAc (20 mL). The mixture was filtered through a pad of Celite, washed with EtOAc (200 mL) and the filtrate concentrated *in vacuo*. Purification by column chromatography (15:1 hexane:EtOAc) afforded the title compound **329** as a yellow oil (1.26 g, 100%); R_f 0.26 (15:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2980, 1722, 1618, 1446, 1369, 1264, 1164, 1038, 771, 697; δ_H (400 MHz, $CDCl_3$) 1.12 (3 H, t, *J* = 7.1, H-13), 4.06 (2 H, q, *J* = 7.1, H-12), 6.37 (1 H, s, H-2), 7.20–7.24 (2 H, m, Ar*H*), 7.29–7.40 (8 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.0, 60.0, 117.5, 127.8, 128.1, 128.3, 128.3, 129.1, 129.4, 139.0, 140.8, 156.5, 166.1; MS (ESI^+): 275.10 (MNa^+), 253.12 (MH^+).

Lab notebook reference: MGL/04/82

Obtained data in accord with reported literature.[152]

3,3-Diphenylprop-2-en-1-ol (330)

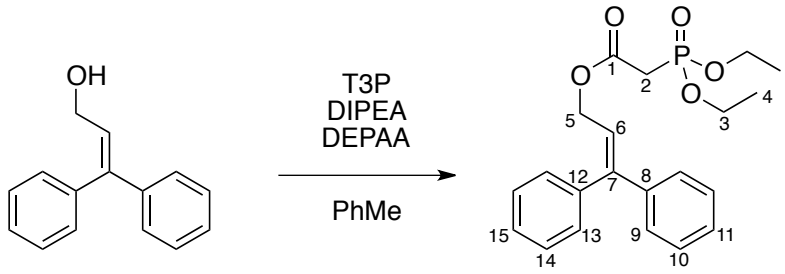


329 **330**

To a solution of ethyl 3,3-diphenylacrylate **329** (1.33 g, 5.27 mmol) in THF (19 mL) cooled to −78 °C was added dropwise DIBAL (21.1 mL, 21.1 mmol, 1.0 M in hexane) and stirred for 2 h. The solution was quenched with water (15 mL) dropwise and stirred for 30 mins at RT before being filtered through a pad of Celite and silica and washed with diethyl ether (500 mL). The filtrate was

concentrated *in vacuo*. Purification by column chromatography (4:1 hexane:EtOAc) afforded the title compound **330** as a white solid (886 mg, 80%); R_f 0.33 (4:1 hexane:EtOAc); m.p. 60–62 °C (lit.[172] 61–63 °C); ν_{max} (thin film)/cm^{-1} 3325, 3056, 3024, 1598, 1494, 1444, 1074, 1013, 758, 692; δ_H (400 MHz, $CDCl_3$) 1.50 (1 H, br s, O*H*), 4.23 (2 H, d, *J* = 6.9, H-1), 6.26 (1 H, t, *J* = 6.9, H-2), 7.16–7.19 (2 H, m, Ar*H*), 7.24–7.40 (8 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 60.7, 127.4, 127.5, 127.6, 127.6, 128.2, 128.2, 129.7, 139.0, 141.8, 144.2; MS (ESI$^+$): 249.07 (MK$^+$), 233.09 (MNa$^+$).
Lab notebook reference: MGL/04/83
Obtained data in accord with reported literature.[172-173]

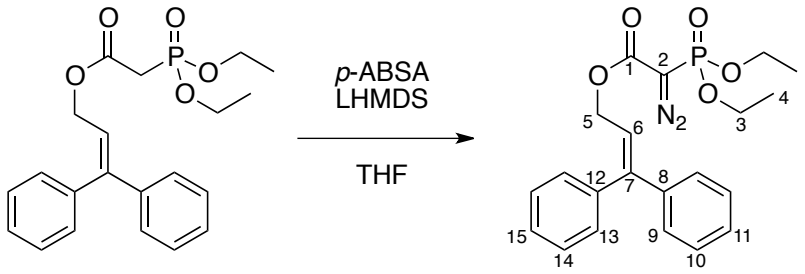
3,3-Diphenylallyl 2-(diethoxyphosphoryl)acetate (331)



330 **331**

Synthesised using general procedure A with 3,3-diphenylprop-2-en-1-ol (862 mg, 4.10 mmol), toluene (20.5 mL), DEPAA (0.69 mL, 4.30 mmol), DIPEA (1.86 mL, 10.7 mmol) and T3P (3.40 g, 5.33 mmol, 50% w/w solution in EtOAc) affording the *title compound* **331** as an orange oil (1.59 g, 100%). No further purification was required; R_f 0.26 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2983w, 1736s, 1445w, 1265s, 1113m, 1025s, 969m, 774m, 702m; δ_H (400 MHz, $CDCl_3$) 1.33 (6 H, t, *J* = 7.1, *J* = 0.5, H-4), 3.00 (2 H, d, *J* = 21.5, H-2), 4.13–4.21 (4 H, m, H-3), 4.71 (2 H, d, *J* = 7.1, H-5), 6.18 (1 H, t, *J* = 7.1, H-6), 7.16–7.19 (2 H, m, H-9/10/11/13/14/15), 7.23–7.40 (8 H, m, H-9/10/11/13/14/15); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* = 6.3, C-4), 34.5 (d, *J* = 134.2, C-2), 62.7 (d, *J* = 6.2, C-3), 63.7 (C-5), 121.5 (C-6), [127.7, 127.9, 127.9, 128.2, 128.3, 129.7 (C-9,10,11,13,14,15)], [138.4, 141.4, 147.0 (C-7,8,12)], 165.7 (d, *J* = 6.3, C-1); δ_P (162 MHz, $CDCl_3$) 20.2; HRMS (ESI$^+$): Found: 411.1325; $C_{21}H_{25}NaO_5P$ (MNa$^+$) Requires 411.1332 (1.8 ppm error).
Lab notebook reference: MGL/04/84

3,3-Diphenylallyl 2-diazo-2-(diethoxyphosphoryl)acetate (332)

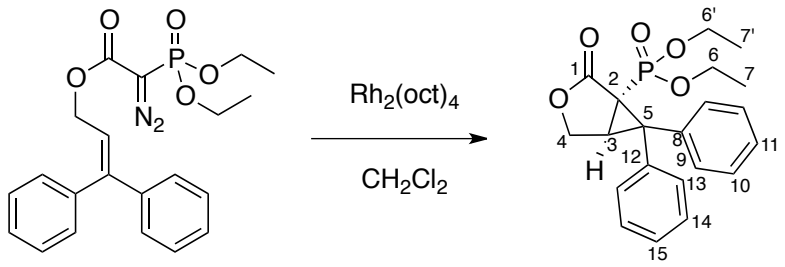


331 **332**

Synthesised using general procedure B with 3,3-diphenylallyl 2-(diethoxyphosphoryl)acetate **331** (1.59 g, 4.10 mmol), THF (20.5 mL), LHMDS (4.92 mL, 4.92 mmol, 1.0 M solution in THF) and *p*-ABSA (1.18 g, 4.92 mmol). Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **332** as a yellow oil (823 g, 48%); R_f 0.52 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2984w, 2126s, 1703s, 1494w, 1444w, 1377w, 1348w, 1271s, 1214w, 1163w, 1117w, 1099w, 1017s, 976s, 796m, 729s, 699s, 585s, 558s; δ_H (400 MHz, $CDCl_3$) 1.35 (6 H, t, J = 7.1, J = 0.8, H-4), 4.12–4.28 (4 H, m, H-3), 4.77 (2 H, d, J = 7.2, H-5), 6.19 (1 H, t, J = 7.2, H-6), 7.16–7.19 (2 H, m, H-9/10/11/13/14/15), 7.22–7.39 (8 H, m, H-9/10/11/13/14/15); δ_C (100 MHz, $CDCl_3$) 15.9 (d, J = 6.9, C-4), 53.5 (d, J = 227.1, C-2), 63.3 (C-5), 63.4 (d, J = 5.7, C-3), 121.1 (C-6), [127.4, 127.7, 127.8, 128.0, 128.1, 129.3 (C-9,10,11,13,14,15)], [138.1, 141.0, 147.1 (C-7,8,12)], 162.9 (d, J = 12.2, C-1); δ_P (162 MHz, $CDCl_3$) 10.5; HRMS (ESI^+): Found: 437.1242; $C_{21}H_{23}N_2NaO_5P$ (MNa^+) Requires 437.1237 (−1.1 ppm error).

Lab notebook reference: MGL/04/85

Diethyl ((1*SR*,5*SR*)-2-oxo-6,6-diphenyl-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate (333)

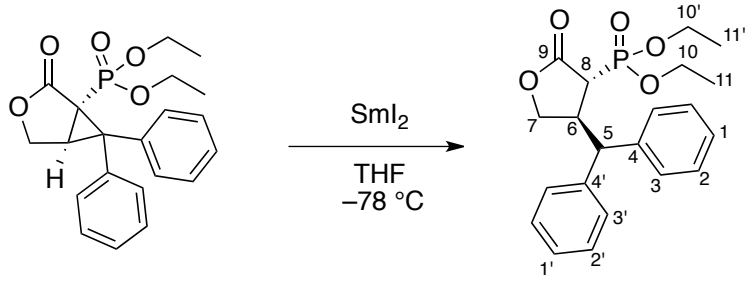


332 **333**

Synthesised using general procedure F with 3,3-diphenylallyl 2-diazo-2-(diethoxyphosphoryl)acetate **332** (78 mg, 0.188 mmol), CH_2Cl_2 (3.8 mL) and $Rh_2(oct)_4$ (2.9 mg, 3.8 μmol). Purification by column chromatography (1:10 hexane:EtOAc) afforded the *title compound* **333** as a pale yellow oil (38 mg, 51%); R_f 0.18 (1:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2982w, 2908w, 1761s, 1600w, 1495w, 1474w, 1449w, 1388w, 1365w, 1252m, 1221w, 1195w, 1162w, 1071w, 1054s, 1019s, 973m, 710m; δ_H (400 MHz, $CDCl_3$) 1.11 (3 H, t, *J* = 7.1, H-7/7'), 1.22 (3 H, t, *J* = 7.1, H-7/7'), 3.53 (1 H, dd, *J* = 12.3, *J* = 5.3, H-3), 3.68 (1 H, ddq, *J* = 10.2, *J* = 9.5, *J* = 7.1, H-6/6'), 3.89–3.99 (1 H, m, H-6/6'), 4.04–4.13 (2 H, m, H-6/6'), 4.27 (1 H, ddd, *J* = 9.9, *J* = 2.8, *J* = 0.7, H-4/4'), 4.54 (1 H, dd, *J* = 9.9, *J* = 5.3, H-4/4'), 7.16–7.34 (6 H, m, H-9/10/11/13/14/15), 7.42–7.50 (4 H, m, H-9/10/11/13/14/15); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.1, C-7/7'), 16.2 (d, *J* = 6.3, C-7/7'), 33.7 (d, *J* = 3.2, C-3), 37.3 (d, *J* = 203.9, C-2), 46.5 (d, *J* = 2.5, C-5), 62.4 (d, *J* = 6.2, C-6/6'), 63.4 (d, *J* = 6.5, C-6/6'), 65.4 (d, *J* = 2.5, C-4), [127.6, 128.0, 128.4, 128.6, 129.1, 129.3 (C-9/10/11/13/14/15)], 136.5 (C-8/12), 138.7 (d, *J* = 4.6, C-8/12), 171.3 (d, *J* = 10.4, C-1); δ_P (162 MHz, $CDCl_3$) 16.1; HRMS (ESI$^+$): Found: 409.1172; $C_{21}H_{23}NaO_5P$ (MNa^+) Requires 409.1175 (0.9 ppm error), Found: 387.1352; $C_{21}H_{24}O_5P$ (MH^+) Requires 387.1356 (0.9 ppm error).

Lab notebook reference: MGL/04/86

Diethyl ((3*RS*,4*SR*)-4-benzhydryl-2-oxotetrahydrofuran-3-yl)phosphonate (335)

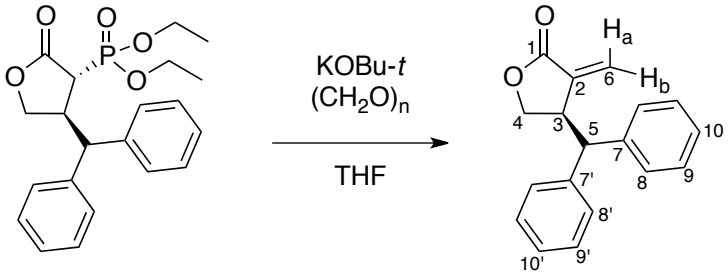


333 **335**

To a solution of freshly prepared SmI_2 (1.70 mL, 0.170 mmol, ~0.1 M in THF) in an oven dried sealable tube at −78 °C under an atmosphere of argon, was added a solution of diethyl ((1*SR*,5*SR*)-2-oxo-6,6-diphenyl-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate **333** (33 mg, 0.085 mmol) in THF (0.5 mL). The solution was stirred at −78 °C for 5 mins then quenched with sat. aq. NH_4Cl (1.70 mL) and then allowed to warm at RT. The mixture was diluted with water (5 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **335** as a yellow oil (20 mg, 60%); R_f 0.29 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2982w, 1770s, 1493w, 1453m, 1251s, 1152s, 1046m, 1019s, 971s, 749m, 705s; δ_H (400 MHz, $CDCl_3$) 1.29 (3 H, t, *J* = 7.1, H-11/11'), 1.31 (3 H, t, *J* = 7.1, H-11/11'), 2.84 (1 H, d, *J* = 24.6, H-8), 3.69 (1 H, ddd, *J* = 17.3, *J* = 11.9, *J* = 5.7, H-6), 3.83–4.20 (6 H, m, H-5,7,10,10'), 4.55 (1 H, dd, *J* = 9.4, *J* = 6.1, H-7), 7.19–7.33 (10 H, m, H-1,1',2,2',3,3'); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.7, C-11/11'), 16.3 (d, *J* = 6.5, C-11/11'), 42.1 (d, *J* = 3.0, C-6), 44.8 (d, *J* = 133.1, C-8), 54.5 (d, *J* = 13.5, C-5), 63.0 (d, *J* = 7.0, C-10/10'), 63.8 (d, *J* = 6.9, C-10/10'), 70.7 (C-7), [127.2, 127.2, 127.9, 128.2, 129.0, 129.1 (C-1/1'/2/2'/3/3')], 141.0 (C-4/4'), 141.5 (C-4/4'), 171.9 (d, *J* = 5.0, C-9); δ_P (162 MHz, $CDCl_3$) 19.5; HRMS (ESI^+): Found: 411.1338; $C_{21}H_{25}NaO_5P$ (MNa^+) Requires 411.1332 (−1.6 ppm error), Found: 389.1519; $C_{21}H_{26}O_5P$ (MH^+) Requires 389.1512 (−1.7 ppm error).

Lab notebook reference: MGL/07/94

4-Benzhydryl-3-methylenedihydrofuran-2(3*H*)-one (336)



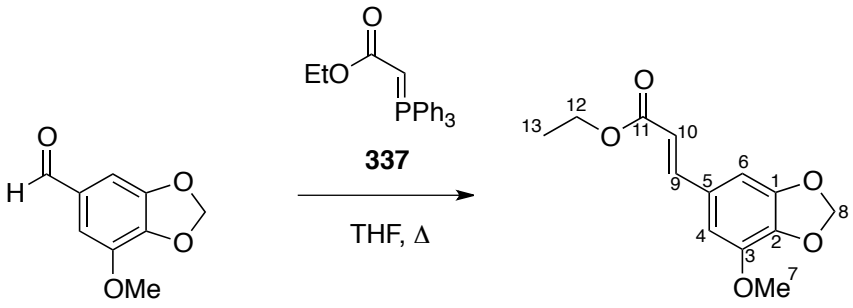
335 **336**

To a solution of diethyl ((3*RS*,4*SR*)-4-benzhydryl-2-oxotetrahydrofuran-3-yl)phosphonate **335** (20 mg, 51.5 μmol) in THF (0.25 mL) at 0 °C was added KOBu-*t* (8.7 mg, 0.772 mmol). The solution was stirred at 0 °C for 60 mins and then cooled to −78 °C. Paraformaldehyde (3.1 mg, 0.103 mmol) was added to the solution and stirred for 15 mins at −78 °C and a further 2 h at RT. The solution was quenched with sat. aq. NH_4Cl (10 mL). The organic layer was separated and the aqueous extracted with EtOAc (2 × 10 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (4:1 hexane:EtOAc) afforded the title compound **336** as a pale yellow oil (7 mg, 52%); R_f 0.35 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2023w, 1759s, 1656w, 1494m, 1451m, 1401m, 1262s, 1114s, 1030m, 813m, 748s, 703s, 611s; δ_H (400 MHz, DMSO-d6) 3.82–3.87 (1 H, m), 4.05–4.10 (1 H, m), 4.26–4.35 (2 H, m), 4.65 (1 H, d, *J* = 1.4), 5.88 (1 H, d, *J* = 1.8), 7.18–7.23 (2 H, m), 7.29–7.33 (4 H, m), 7.42–7.46 (4 H, m);[174] δ_H (400 MHz, $CDCl_3$) 3.88–4.02 (3 H, m, H-3,4,5), 4.33 (1 H, dd, *J* = 9.2, *J* = 7.1, H-4), 4.75 (1 H, d, *J* = 1.9, H-6b), 6.09 (1 H, d, *J* = 2.1, H-6a), 7.20–7.34 (10 H, m, H-8,8',9,9',10,10'); δ_C (100 MHz, $CDCl_3$) 42.3 (C-3), 55.5 (C-5), 69.8 (C-4), 124.7 (C-6), [127.2, 127.2, 127.7, 128.3, 128.8, 129.1 (C-8,8',9,9',10,10')], 136.0 (C-2), 141.5 (C-7/7'), 141.6 (C-7/7'), 170.9 (C-1); HRMS (ESI^+): Found: 287.1044; $C_{18}H_{16}NaO_2$ (MNa^+) Requires 287.1043 (−0.5 ppm error), Found: 265.1225; $C_{18}H_{17}O_2$ (MH^+) Requires 265.1223 (−0.6 ppm error).

Lab notebook reference: MGL/07/94/2

Obtained data in accord with reported literature.[174]

(*E*)-Ethyl 3-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)acrylate (326)



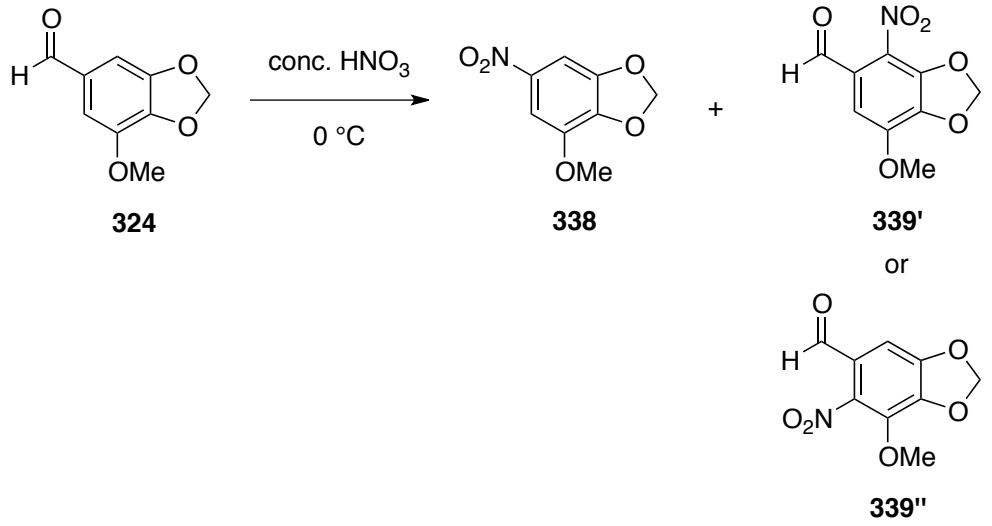
324 **326**

To a solution of 5-methoxypiperonal **324** (5.17 g, 28.7 mmol) in THF (86 mL) was added (carbethoxymethylene)triphenylphosphorane **337** (12.0 g, 34.4 mmol) and refluxed for 16 h. Concentration *in vacuo* and purification by column chromatography (4:1 hexane:EtOAc) afforded the title compound **326** as a crystalline white solid (6.78 g, 95%); R_f 0.46 (4:1 hexane:EtOAc); m.p. 65–68 °C (lit.[175] 76 °C); ν_{max} (thin film)/cm^{-1} 2996w, 2975w, 2908w, 1702s, 1622s, 1593s, 1511s, 1431s, 1324m, 1281s, 1171s, 1137s, 1093s, 1038s, 996s, 925s, 846s, 819s, 594s, 477s; δ_H (400 MHz, $CDCl_3$) 1.31 (3 H, t, *J* = 7.1, H-13), 3.90 (3 H, s, H-8), 4.23 (2 H, q, *J* = 7.1, H-12), 5.99 (2 H, s, H-7), 6.25 (1 H, d, *J* = 15.9, H-10), 6.68 (1 H, d, *J* = 1.4, H-4/6), 6.72 (1 H, d, *J* = 1.4, H-4/6), 7.54 (1 H, d, *J* = 15.9, H-9); δ_C (100 MHz, $CDCl_3$) 14.3 (C-13), 56.5 (C-7), 60.4 (C-12), 101.2 (C-4/6), 101.9 (C-8), 109.0 (C-4/6), 116.6 (C-10), 129.2 (C-1/2/3/5), 137.2 (C-1/2/3/5), 143.6 (C-1/2/3/5), 144.2 (C-9), 149.2 (C-1/2/3/5), 167.0 (C-11); HRMS (ESI$^+$): Found: 273.0731; $C_{13}H_{14}NaO_5$ (MNa^+) Requires 273.0733 (0.8 ppm error).

Lab notebook reference: MGL/07/80

Obtained data in accord with reported literature.[175]

4-Methoxy-6-nitrobenzo[*d*][1,3]dioxole (338) and 5-Iodo-7-methoxy-4-nitrobenzo[*d*][1,3]dioxole (339') or 6-Iodo-4-methoxy-5-nitrobenzo[*d*][1,3]dioxole (339'')



324 **338** **339'** or **339''**

Prepared according to a modified literature procedure.[176]

To a stirred flask containing concentrated nitric acid (70% solution, 100 mL) cooled to 0 °C was added 5-methoxypiperonal **324** (10.81 g, 60.0 mmol) portionwise over 2 h. After a further 1 h the yellow mixture was poured onto ice water (1 L) to precipitate a pale yellow solid, which was collected by suction filitration and washed with water (3 × 100 mL). Purification by column chromatography (7:1 hexane:EtOAc) afforded the title compound **338** (6.92 g, 59%) along with compound **339'** or **339''** (3.96 g, 29%).

Data for **338**; Pale yellow solid; R_f 0.45 (4:1 hexane:EtOAc); m.p. 130–132 °C (lit.[177] 145–146 °C); ν_{max} (thin film)/cm^{-1} 3109w, 1645m, 1521s, 1491s, 1451m, 1435m, 1347s, 1316s, 1218m, 1198m, 1112s, 1090m, 970m, 918m, 861m, 770m, 742m; δ_H (400 MHz, DMSO-d_6) 3.93 (3 H, s, OCH_3), 6.24 (2 H, s, OCH_2O), 7.53 (1 H, d, J = 2.2, ArH), 7.62 (1 H, d, J = 2.2, ArH); δ_H (400 MHz, $CDCl_3$) 3.96 (3 H, s, OCH_3), 6.14 (2 H, s, OCH_2O), 7.42 (1 H, d, J = 2.1, ArH), 7.56 (1 H, d, J = 2.1, ArH); δ_C (100 MHz, $CDCl_3$) 56.8, 99.0, 103.3, 104.9, 141.1, 142.8, 142.9, 148.7; HRMS (ESI$^+$): Found: 220.0218; $C_8H_7NNaO_5$ (MNa$^+$) Requires 220.0216 (–0.6 ppm error).

Data for **339'**/**339''**; Yellow solid; R_f 0.19 (4:1 hexane:EtOAc); m.p. 105–108 °C; ν_{max} (thin film)/cm^{-1} 2952w, 16988s, 1622m, 1593s, 1523s, 1484s, 1451m, 1418s, 1357s, 1300s, 1231m, 1151m, 1092s, 1047m, 1020s, 956m, 893s, 864s, 793m, 787m, 762m, 669m, 627m; δ_H (400 MHz, $CDCl_3$) 4.09 (3 H, s, OCH_3), 6.17 (2 H, s, OCH_2O), 7.03 (1 H, s, ArH), 9.73 (1 H, s, CHO); δ_C (100 MHz, $CDCl_3$) 60.9, 102.0, 103.5, 123.2 (2 C), 136.0, 141.8, 150.6, 185.1; HRMS (ESI$^+$): Found:

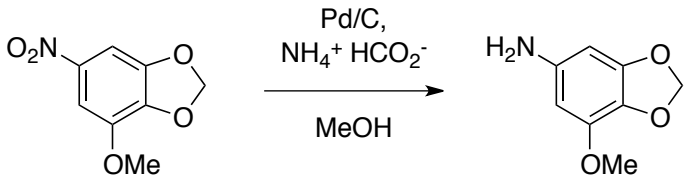
248.0172; $C_9H_7NNaO_6$ (MNa^+) Requires 248.0166 (–2.6 ppm error), Found: 226.0353; $C_9H_8NO_6$ (MH^+) Requires 226.0346 (–3.2 ppm error).

Lab notebook reference: MGL/07/33

NMR data in accord with reported literature.[178]

Note: The correct regioisomer of compound **339** could not be determined; as such, it is assigned as either compound **339'** or **339''**.

7-Methoxybenzo[*d*][1,3]dioxol-5-amine (340)



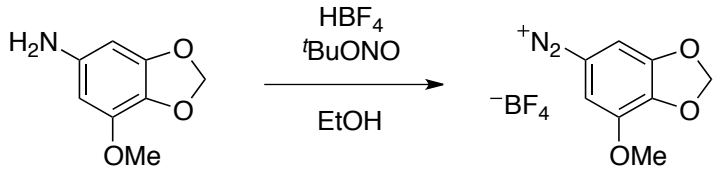
338 **340**

To a suspension of 4-methoxy-6-nitrobenzo[*d*][1,3]dioxole **338** (6.86 g, 34.8 mmol) in MeOH (174 mL) under an atmosphere of argon, was added ammonium formate (11.0 g, 174.0 mmol) and palladium on carbon (10% wt. % loading, 1.74 g). The solution was stirred for 16 h then filtered through a pad of Celite and washed with MeOH (100 mL). The filtrate was concentrated *in vacuo*. The residue was diluted with brine (250 mL) and extracted with EtOAc (2 × 250 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (1:1 hexane:EtOAc) afforded the title compound **340** as an off-white solid (5.41 g, 93%); R_f 0.45 (1:1 hexane:EtOAc); m.p. 75–76 °C (lit.[154] 85–86 °C); ν_{max} (thin film)/cm^{-1} 3397, 3312, 3210, 2886, 1640, 1508, 1459, 1183, 1144, 1087, 1037, 958, 924, 802, 703, 618; δ_H (400 MHz, DMSO-d_6) 3.71 (3 H, s, OCH_3), 4.83 (2 H, br. s, NH_2), 5.75 (2 H, s, OCH_2O), 5.82 (1 H, d, J = 2.0, ArH), 5.86 (1 H, d, J = 2.0, ArH); δ_H (400 MHz, $CDCl_3$) 3.49 (2 H, br. s br. s, NH_2), 3.84 (3 H, s, OCH_3), 5.85 (2 H, s, OCH_2O), 5.86 (1 H, d, J = 2.0, ArH), 5.96 (1 H, d, J = 2.0, ArH); δ_C (100 MHz, $CDCl_3$) 56.4, 91.0, 94.3, 100.8, 128.0, 142.1, 143.9, 149.3; HRMS (ESI^+): Found: 169.0657; $C_8H_{10}NO_3$ (MNa^+) Requires 168.0655 (–0.8 ppm error).

Lab notebook reference: MGL/07/19,22,35

Obtained data in accord with reported literature.[154]

7-Methoxybenzo[*d*][1,3]dioxole-5-diazonium tetrafluoroborate (341)



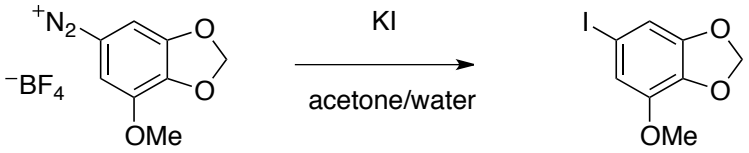
340 **341**

Procedure developed from literature precedent.[155]

To a solution of 7-methoxybenzo[*d*][1,3]dioxol-5-amine **340** (5.22 g, 31.2 mmol) in ethanol (10.3 mL), cooled to 0 °C was added an aqueous solution of HBF_4 (50% w/w, 11.0 g, 62.5 mmol) followed by *tert*-butyl nitrite (7.43 mL, 62.5 mmol) dropwise. The solution was stirred for 1 h after which diethyl ether (50 mL) was added, forming a precipitate. The solution was filtered and the solid washed with diethyl ether (3 × 100 mL). The solid was dried *in vacuo*, affording the *title compound* **341** as a yellow solid (7.57 g, 91%). No further purification was required. R_f 0.00 (1:1 hexane:EtOAc); m.p. decomposes at 126 °C; ν_{max} (thin film)/cm^{-1} 3119w, 2257s, 1624m, 1587m, 1495s, 1454s, 1442s, 1308s, 1240s, 1223m, 1114s, 1072s, 1023s, 962m, 854s, 522m; δ_H (400 MHz, DMSO-d_6) 3.94 (3 H, s, OCH_3), 6.45 (2 H, s, OCH_2O), 7.95 (1 H, d, J = 2.0, Ar*H*), 8.29 (1 H, d, J = 2.0, Ar*H*); δ_C (100 MHz, DMSO-d_6) 57.5, 104.1, 105.9, 106.5, 116.2, 143.2, 148.0, 148.9; HRMS (ESI^+): Found: 179.0447; $C_8H_7N_2O_3$ (MNa^+) Requires 179.0451 (2.1 ppm error).

Lab notebook reference: MGL/07/36

6-Iodo-4-methoxybenzo[*d*][1,3]dioxole (325)

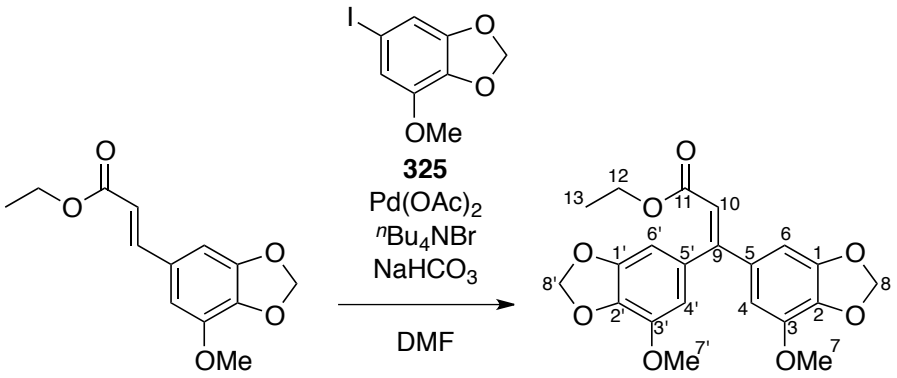


341 **325**

To a solution of KI (10.4 g, 62.5 mmol) in water (187 mL) and acetone (125 mL) was added 7-methoxybenzo[*d*][1,3]dioxole-5-diazonium tetrafluoroborate **341** (7.57 g, 28.3 mmol) over 15 mins. The mixture was stirred for 1 h and the acetone removed *in vacuo*. The residue was extracted with diethyl ether (3 × 250 mL). The combined organic extracts were washed with sat. aq. $Na_2S_2O_3$ (250 mL) then water (250 mL) then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (8:1 hexane:EtOAc) afforded the title compound **325** as white crystals (4.78 g, 61%); R_f 0.63 (4:1 hexane:EtOAc); m.p. 55–58 °C (lit.[179] 71–72 °C); ν_{max}

(thin film)/cm^{-1} 3098, 2939, 2893, 2775, 1623, 1483, 1443, 1414, 1288, 1230, 1175, 1097, 1031, 966, 928, 811, 764, 709, 564; δ_H (400 MHz, $CDCl_3$) 3.85 (3 H, s, OC*H*$_3$), 5.94 (2 H, s, OC*H*$_2$O), 6.81–6.82 (2 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 56.6, 82.0, 101.7, 111.6, 116.8, 135.7, 144.4, 149.4; HRMS (ESI$^+$): Found: 277.9441; $C_8H_7IO_3$ (MNa^+) Requires 277.9434 (–2.3 ppm error).
Lab notebook reference: MGL/07/36, 05/72

Ethyl 3,3-bis(7-methoxybenzo[*d*][1,3]dioxol-5-yl)acrylate (327)



326 **327**

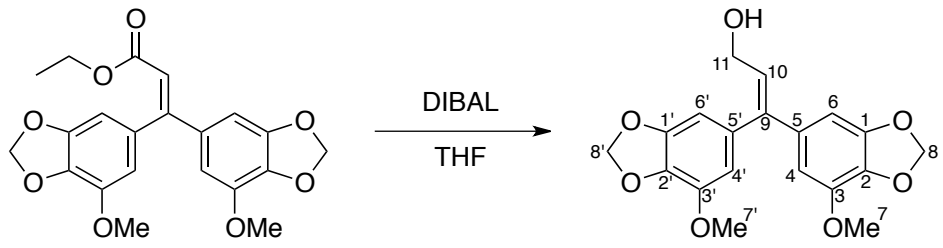
Procedure developed from literature precedent.[157]

To an oven dried sealable tube was added (*E*)-ethyl 3-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)acrylate **326** (500 mg, 2.00 mmol), 6-iodo-4-methoxybenzo[*d*][1,3]dioxole **325** (834 mg, 3.00 mmol), TBAB (709 mg, 2.20 mmol), $NaHCO_3$ (420 mg, 5.00 mmol), $Pd(OAc)_2$ (44.9 mg, 0.20 mmol) and DMF (5 mL). The tube was sealed and flushed with argon then heated at 120 °C for 16 h. The mixture was cooled at RT, diluted with water (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 hexane:EtOAc) affording the *title compound* **327** as an orange oil that later crystallised (695 mg, 87%); R_f 0.22 (4:1 hexane:EtOAc); m.p. 72–76 °C; ν_{max} (thin film)/cm^{-1} 2976w, 2939w, 2900w, 1715s, 1627s, 1600m, 1506s, 1426s, 1377s, 1290m, 1222s, 1171m, 1112s, 1083s, 1044s, 968m, 929s, 844s, 730s; δ_H (400 MHz, $CDCl_3$) 1.16 (3 H, t, *J* = 7.1, H-13), 3.84 (6 H, app. s, H-7,7'), 4.07 (2 H, q, *J* = 7.1, H-12), 5.97 (2 H, s, H-8/8'), 5.99 (2 H, s, H-8/8'), 6.18 (1 H, s, H-10), 6.36 (1 H, d, *J* = 1.3, H-4/4'/6/6'), 6.38 (1 H, d, *J* = 1.3, H-4/4'/6/6'), 6.48 (1 H, d, *J* = 1.5, H-4/4'/6/6'), 6.51 (1 H, d, *J* = 1.5, H-4/4'/6/6'); δ_C (100 MHz, $CDCl_3$) 14.0 (C-13), 56.5 (C-7/7'), 56.7 (C-7/7'), 59.9 (C-12), 101.5 (C-8/8'), 101.8 (C-8/8'), 102.2 (C-4/4'/6/6'), 103.8 (C-4/4'/6/6'), 108.7 (C-4/4'/6/6'), 109.0 (C-4/4'/6/6'), 116.2 (C-10), 132.9 (C-5/5'), 132.9 (C-5/5'), 135.3 (C-1/1'/2/2'), 135.4 (C-5/5'), 136.5 (C-1/1'/2/2'), 143.1 (C-3/3'), 143.1 (C-3/3'), 148.3 (C-1/1'/2/2'), 148.8 (C-1/1'/2/2'), 155.5 (C-9), 165.9 (C-11); HRMS (ESI$^+$): Found: 423.1048; $C_{21}H_{20}NaO_8$ (MNa^+)

Requires 423.1050 (0.5 ppm error), Found: 401.1220; $C_{21}H_{21}O_8$ (MH^+) Requires 401.1231 (2.8 ppm error).

Lab notebook reference: MGL/07/85

3,3-Bis(7-methoxybenzo[*d*][1,3]dioxol-5-yl)prop-2-en-1-ol (344)

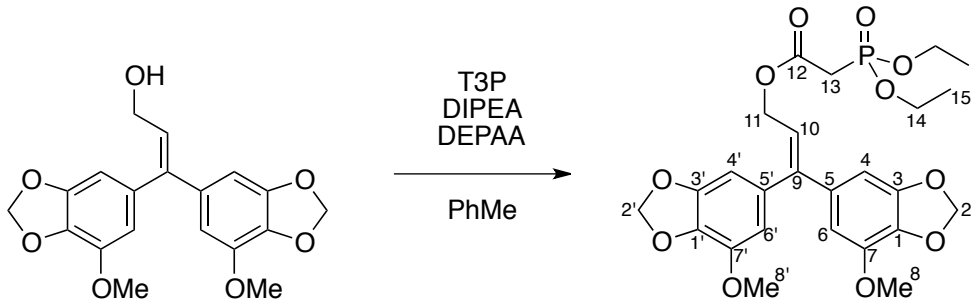


327 **344**

To a solution of ethyl 3,3-bis(7-methoxybenzo[*d*][1,3]dioxol-5-yl)acrylate **327** (1.32 g, 3.30 mmol) in THF (16 mL) cooled to −78 °C was added dropwise DIBAL (6.60 mL, 6.60 mmol, 1.0 M in hexane) and stirred for 2 h. The solution was quenched with water (15 mL) dropwise and stirred for 30 mins at RT before being filtered through a pad of Celite and washed with diethyl ether (500 mL). The filtrate was concentrated *in vacuo*. Purification by column chromatography (4:1 hexane:EtOAc) afforded the *title compound* **344** as a yellow gum (1.08 g, 91%); R_f 0.31 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3360br, 2889w, 1626s, 1505s, 1447w, 1424s, 1376m, 1191m, 1153m, 1085s, 1042s, 967m, 928s, 844s, 728s; δ_H (400 MHz, $CDCl_3$) 2.15 (1 H, br. s, O*H*), 3.80 (3 H, s, H-7/7'), 3.82 (3 H, s, H-7/7'), 4.16 (2 H, d, *J* = 6.8, H-11), 5.91 (2 H, s, H-8/8'), 5.95 (2 H, s, H-8/8'), 6.04 (1 H, t, *J* = 6.8, H-10), 6.31 (1 H, d, *J* = 1.4, H-4/4'/6/6'), 6.31 (1 H, d, *J* = 1.4, H-4/4'/6/6'), 6.41 (1 H, d, *J* = 1.5, H-4/4'/6/6'), 6.42 (1 H, d, *J* = 1.5, H-4/4'/6/6'); δ_C (100 MHz, $CDCl_3$) 56.4 (C-7/7'), 56.5 (C-7/7'), 60.4 (C-11), 101.4 (2 C, C-8,8'), [101.8, 103.8, 107.5, 109.1 (C-4/4'/6/6')], 126.5 (C-10), [133.1, 134.5, 134.8, 136.5, 142.9, 143.1, 143.2, 148.4, 148.5 (C-1,1',2,2',3,3',5,5',9)]; HRMS (ESI^+): Found: 381.0938; $C_{19}H_{18}NaO_7$ (MNa^+) Requires 381.0945 (1.7 ppm error).

Lab notebook reference: MGL/07/86

3,3-Bis(7-methoxybenzo[*d*][1,3]dioxol-5-yl)allyl 2-(diethoxyphosphoryl)acetate (345)

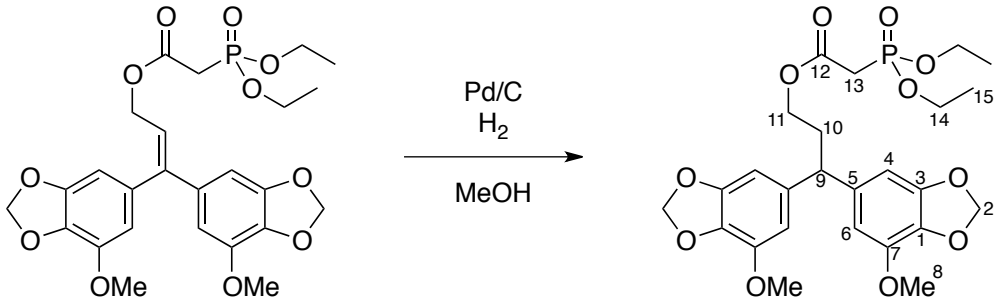


344 **345**

Synthesised using general procedure A with 3,3-bis(7-methoxybenzo[*d*][1,3]dioxol-5-yl)prop-2-en-1-ol **344** (973 mg, 2.72 mmol), toluene (13.6 mL), DEPAA (559 mg, 2.85 mmol), DIPEA (1.23 mL, 7.07 mmol) and T3P (2.25 g, 3.54 mmol, 50% w/w solution in THF) affording the *title compound* **345** as a yellow oil (1.45 g, 99%); R_f 0.26 (1:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2984w, 2936w, 2902w, 1733s, 1626s, 1507s, 1426s, 1262s, 1160m, 1107s, 1042s, 1020s, 965s, 929m, 839s, 728s; δ_H (400 MHz, $CDCl_3$) 1.29 (6 H, td, J = 7.1, J = 0.4, H-15), 2.95 (2 H, d, J = 21.5, H-13), 3.81 (3 H, s, H-8/8'), 3.83 (3 H, s, H-8/8'), 4.09–4.17 (4 H, m, H-14), 4.65 (2 H, d, J = 7.2, H-11), 5.91 (2 H, s, H-2/2'), 5.96 (2 H, s, H-2/2'), 5.98 (1 H, t, J = 7.2, H-10), 6.31 (1 H, d, J = 1.4, H-4/4'/6/6'), 6.33 (1 H, d, J = 1.4, H-4/4'/6/6'), 6.39 (1 H, d, J = 1.6, H-4/4'/6/6'), 6.41 (1 H, d, J = 1.6, H-4/4'/6/6'); δ_C (100 MHz, $CDCl_3$) 16.2 (d, J = 6.6, C-15), 34.2 (d, J = 134.2, C-13), 56.5 (C-8/8'), 56.5 (C-8/8'), 62.6 (d, J = 6.5, C-14), 63.6 (C-11), 101.4 (2 C, C-2,2'), [101.9, 103.8, 107.7, 109.2 (C-4/4'/6/6')], 120.5 (C-10), [132.5, 134.8, 135.2, 136.0, 143.0, 143.2, 146.2, 148.6, 148.6 (C-1,1',3,3',5,5',7,7',9)], 165.5 (d, J = 6.5, C-12); δ_P (162 MHz, $CDCl_3$) 20.2; HRMS (ESI$^+$): Found: 559.1348; $C_{25}H_{29}NaO_{11}P$ (MNa^+) Requires 559.1340 (−1.5 ppm error).

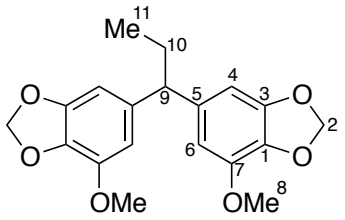
Lab notebook reference: MGL/07/87

3,3-Bis(7-methoxybenzo[*d*][1,3]dioxol-5-yl)propyl 2-(diethoxyphosphoryl)acetate (346) and 6,6'-(Propane-1,1-diyl)bis(4-methoxybenzo[*d*][1,3]dioxole) (347)



345 **346**

+



347

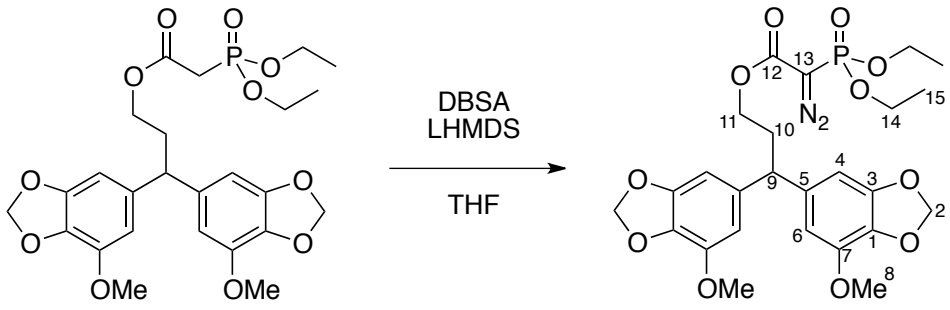
To a solution of 3,3-bis(7-methoxybenzo[*d*][1,3]dioxol-5-yl)allyl 2-(diethoxyphosphoryl)acetate **345** (457 mg, 0.852 mmol) in methanol (4.26 mL) was added palladium on carbon (10% wt. % loading, 17 mg). The flask was purged 4 times with argon then 4 times with hydrogen. The mixture was stirred at RT for 16 h. The mixture was filtered through a pad of Celite and washed with methanol (50 mL) and the filtrate concentrated *in vacuo*. Purification by column chromatography (1:2 hexane:EtOAc) afforded the *title compounds* **346** (280 mg, 61%) and **347** (86 mg, 29%).

Data for **346**; Yellow oil; R_f 0.21 (1:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2982w, 2940w, 2905w, 1733s, 1632s, 1507s, 1449m, 1430s, 1266s, 1193s, 1128s, 1091s, 1019s, 964s, 929w, 834s; δ_H (400 MHz, $CDCl_3$) 1.30 (6 H, t, *J* = 7.1, H-15), 2.24 (2 H, app. q, *J* = 7.2, H-10), 2.94 (2 H, d, *J* = 21.6, H-13), 3.85 (6 H, s, H-8), 3.87 (1 H, t, *J* = 7.9, H-9), 4.05 (2 H, t, *J* = 6.5, H-11), 4.14 (4 H, dq, *J* = 8.3, *J* = 7.1, H-14), 5.88 (4 H, s, H-2), 6.37 (2 H, d, *J* = 1.4, H-4/6), 6.38 (2 H, d, *J* = 1.4, H-4/6); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.1, C-15), 34.2 (d, *J* = 133.6, C-13), 34.2 (C-10), 46.9 (C-9), 56.6 (C-8), 62.6 (d, *J* = 6.4, C-14), 63.6 (C-11), 101.2 (C-2), 101.4 (C-4/6), 107.3 (C-4/6), [133.6, 138.3, 143.3, 148.9 (C-1,3,5,7)], 165.5 (d, *J* = 5.9, C-12); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI$^+$): Found: 561.1503; $C_{25}H_{31}NaO_{11}P$ (MNa^+) Requires 561.1496 (–1.1 ppm error).

Data for **347**; Yellow oil; R_f 0.86 (1:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2961w, 2933w, 2874w, 1632s, 1506s, 1449s, 1428s, 1366w, 1312m, 1193s, 1133s, 1092s, 1043s, 930s; δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, t, *J* = 7.3, H-11), 1.95 (2 H, app. quin., *J* = 7.4, H-10), 3.58 (1 H, t, *J* = 7.8, H-9), 3.88 (6 H, s, H-8), 5.91–5.92 (4 H, m, H-2) 6.39 (2 H, d, *J* = 1.3, H-4/6), 6.42 (2 H, d, *J* = 1.3, H-4/6); δ_C (100 MHz, $CDCl_3$) 12.7 (C-11), 28.8 (C-10), 53.1 (C-9), 56.6 (C-8), 101.2 (C-2), 101.6 (C-4/6), 107.3 (C-4/6), [133.4, 139.8, 143.3, 148.8 (C-1,3,5,7)]; HRMS (ESI$^+$): Found: 367.1149; $C_{19}H_{20}NaO_6$ (MNa^+) Requires 367.1152 (0.7 ppm error).

Lab notebook reference: MGL/07/88

3,3-Bis(7-methoxybenzo[*d*][1,3]dioxol-5-yl)propyl 2-diazo-2-(diethoxyphosphoryl)acetate (342)

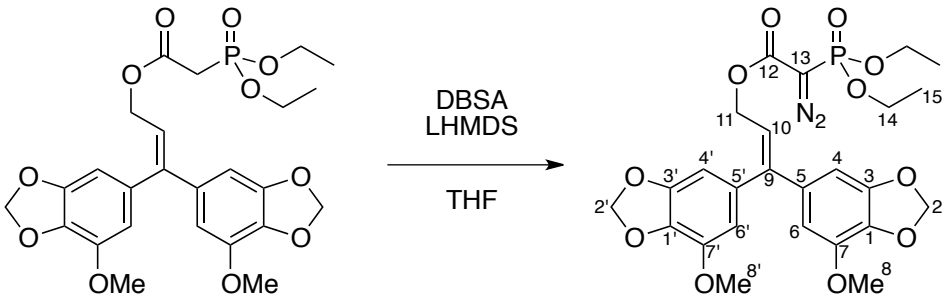


346 **342**

Synthesised using general procedure B with 3,3-bis(7-methoxybenzo[*d*][1,3]dioxol-5-yl)propyl 2-(diethoxyphosphoryl)acetate **346** (278 mg, 0.516 mmol), THF (2.58 mL), LHMDS (0.620 mL, 0.620 mmol, 1.0 M solution in THF) and DBSA (0.21 mL, 0.620 mmol). Purification by column chromatography (1:2 hexane:EtOAc) afforded the *title compound* **342** as a yellow oil (147 mg, 51%); R_f 0.70 (1:4 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2982w, 2941w, 2906w, 2129s, 1704s, 1633s, 1508m, 1451m, 1431m, 1369w, 1279s, 1194m, 1131s, 1092s, 1041s, 1019s, 977m; δ_H (400 MHz, $CDCl_3$) 1.36 (6 H, td, *J* = 7.1, *J* = 0.7, H-15), 2.27 (2 H, app. q, *J* = 7.2, H-10), 3.85 (1 H, t, *J* = 7.8, H-9), 3.87 (6 H, s, H-8), 4.11–4.27 (6 H, m, H-11,14), 5.92 (4 H, s, H-2), 6.37 (2 H, d, *J* = 1.4, H-4/6), 6.39 (2 H, d, *J* = 1.4, H-4/6); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.8, C-15), 34.5 (C-10), 47.2 (C-9), 53.7 (d, *J* = 231.7, C-13), 56.8 (C-8), 63.6 (d, *J* = 5.7, C-14), 63.9 (C-11), 101.5 (C-2), 101.5 (C-4/6), 107.4 (C-4/6), [133.8, 138.3, 143.4, 149.1 (C-1,3,5,7)], 163.2 (d, *J* = 11.8, C-12); δ_P (162 MHz, $CDCl_3$) 10.7; HRMS (ESI$^+$): Found: 587.1406; $C_{25}H_{29}N_2NaO_{11}P$ (MNa^+) Requires 587.1401 (–0.8 ppm error).

Lab notebook reference: MGL/07/89

3,3-Bis(7-methoxybenzo[*d*][1,3]dioxol-5-yl)allyl 2-diazo-2-(diethoxyphosphoryl)acetate (322)

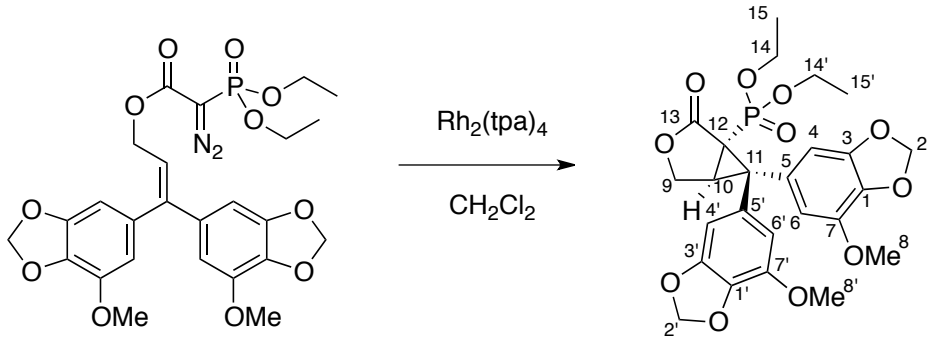


345 **322**

Synthesised using general procedure B with 3,3-bis(7-methoxybenzo[*d*][1,3]dioxol-5-yl)allyl 2-(diethoxyphosphoryl)acetate **345** (996 mg, 1.86 mmol), THF (9.30 mL), LHMDS (2.23 mL, 2.23 mmol, 1.0 M solution in THF) and DBSA (0.75 mL, 2.23 mmol). Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **322** as a yellow oil (665 mg, 63%); R_f 0.27 (1:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2984w, 2943w, 2905w, 2129s, 1703s, 1627s, 1507s, 1427s, 1275s, 1162m, 1108m, 1094m, 1044s, 1020s, 970s, 932m; δ_H (400 MHz, $CDCl_3$) 1.34 (6 H, td, J = 7.1, J = 0.6, H-15), 3.84 (3 H, s, H-8/8'), 3.86 (3 H, s, H-8/8'), 4.08–4.27 (4 H, m, H-14), 4.74 (2 H, d, J = 7.2, H-11), 5.95 (2 H, s, H-2/2'), 5.99 (2 H, s, H-2/2'), 6.01 (1 H, t, J = 7.2, H-10), 6.34–6.35 (2 H, m, H-4/4'/6/6'), 6.42 (1 H, d, J = 1.6, H-4/4'/6/6'), 6.43 (1 H, d, J = 1.6, H-4/4'/6/6'); δ_C (100 MHz, $CDCl_3$) 16.1 (2 C, d, J = 6.9, C-15), 53.6 (d, J = 228.1, C-13), 56.6 (C-8/8'), 56.7 (C-8/8'), 63.6–63.7 (3C, m, C-11,14), 101.6 (2 C, C-2,2'), [102.1, 103.9, 107.9, 109.2 (C-4/4'/6/6')], 120.3 (C-10), [132.5, 135.0, 135.4, 136.0, 143.1, 143.4, 146.9, 148.7, 148.8 (C-1,1',3,3',5,5',7,7',9)], 163.3 (d, J = 12.7, C-12); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI^+): Found: 585.1240; $C_{25}H_{27}N_2NaO_{11}P$ (MNa^+) Requires 585.1245 (0.7 ppm error).

Lab notebook reference: MGL/07/91

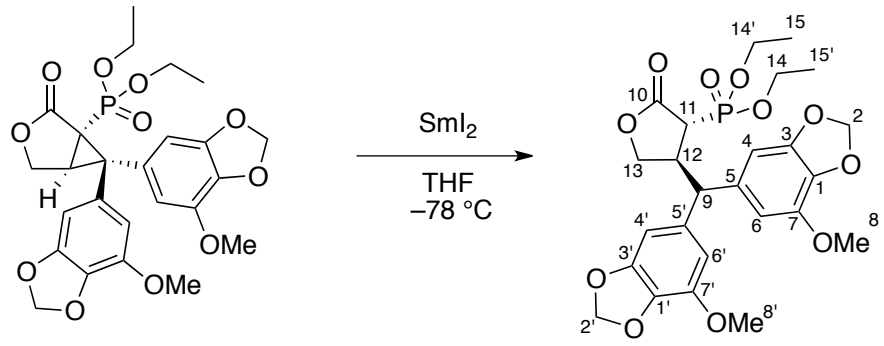
Diethyl ((1*SR*,5*SR*)-6,6-bis(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-2-oxo-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate (323)



322 **323**

Synthesised using general procedure F with 3,3-bis(7-methoxybenzo[*d*][1,3]dioxol-5-yl)allyl 2-diazo-2-(diethoxyphosphoryl)acetate **322** (368 mg, 0.654 mmol), CH_2Cl_2 (13.1 mL) and $Rh_2(tpa)_4$ (18.8 mg, 13.1 μmol). Purification by column chromatography (1:4 hexane:EtOAc → EtOAc) afforded the *title compound* **323** as an off-white solid (153 mg, 44%); R_f 0.24 (1:4 hexane:EtOAc); m.p. 81–84 °C; ν_{max} (thin film)/cm^{-1} 2926w, 1758s, 1632s, 1507m, 1429s, 1364m, 1240s, 1192s, 1155m, 1093s, 1042s, 1015s, 968s, 929m, 728s; δ_H (400 MHz, $CDCl_3$) 1.14 (3 H, t, *J* = 7.1, H-15/15'), 1.27 (3 H, t, *J* = 7.1, H-15/15'), 3.36 (1 H, dd, *J* = 12.5, *J* = 4.8, H-10), 3.69–3.81 (1 H, m, H-14/14'), 3.88 (3 H, s, H-8/8'), 3.89 (3 H, s, H-8/8'), 3.91–4.01 (1 H, m, H-14/14'), 4.06–4.23 (2 H, m, H-14/14'), 4.28 (1 H, dd, *J* = 9.9, *J* = 2.2, H-9), 4.50 (1 H, dd, *J* = 9.9, *J* = 5.3, H-9), 5.89–5.93 (4 H, m, H-2,2'), 6.51 (1 H, br. s, H-4/4'/6/6'), 6.60–6.61 (2 H, m, H-4/4'/6/6'), 6.72 (1 H, d, *J* = 1.6, H-4/4'/6/6'); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.1, C-15/15'), 16.3 (d, *J* = 6.5, C-15/15'), 34.5 (d, *J* = 4.0, C-10), 37.8 (d, *J* = 203.9, C-12), 46.4 (d, *J* = 2.8, C-11), 56.7 (C-8/8'), 56.7 (C-8/8'), 62.3 (d, *J* = 6.5, C-14/14'), 63.5 (d, *J* = 6.9, C-14/14'), 65.5 (d, *J* = 3.5, C-9), 101.5 (C-2/2'), 101.6 (C-2/2'), [102.4, 102.9, 108.1, 109.3 (C-4/4'/6/6')], 130.6 (d, *J* = 1.8, C-5/5'), 133.2 (d, *J* = 5.5, C-5/5'), [134.6, 135.0, 143.1, 143.9, 148.7, 149.2 (C-1/1'/3/3'/7/7')], 171.2 (d, *J* = 10.5, C-13); δ_P (162 MHz, $CDCl_3$) 16.2; HRMS (ESI$^+$): Found: 557.1169; $C_{25}H_{27}NaO_{11}P$ (MNa^+) Requires 557.1183 (2.5 ppm error), Found: 535.1362; $C_{25}H_{28}O_{11}P$ (MH^+) Requires 535.1364 (0.2 ppm error). Lab notebook reference: MGL/07/96,92

Diethyl ((3*RS*,4*SR*)-4-(bis(7-methoxybenzo[*d*][1,3]dioxol-5-yl)methyl)-2-oxotetrahydrofuran-3-yl)phosphonate (343)

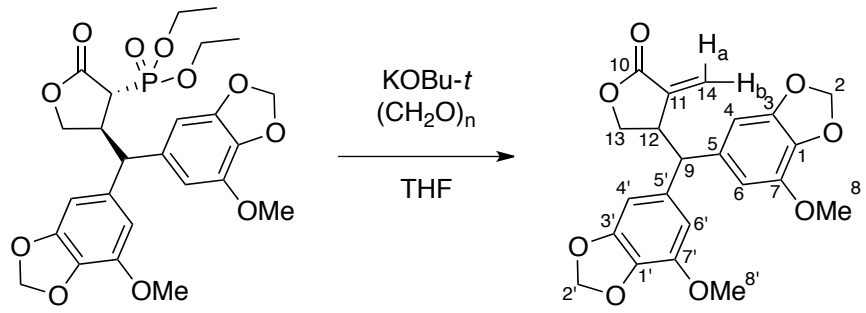


323 **343**

To an oven dried sealable tube containing SmI_2 (10.6 mL, 1.06 mmol, ~0.1 M solution in THF) under an atmosphere of argon, atmosphere and cooled to −78 °C was added dropwise a solution of diethyl ((1*SR*,5*SR*)-6,6-bis(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-2-oxo-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate **323** (142 mg, 0.266 mmol) in THF (2.66 mL). The mixture was stirred at −78 °C for 10 mins then quenched by addition of sat. aq. NH_4Cl (5 mL) and allowed to warm at RT. The biphasic mixture was extracted with EtOAc (3 × 25 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (1:2 hexane:EtOAc) afforded the *title compound* **343** as a white solid (78 mg, 55%); R_f 0.44 (1:2 hexane:EtOAc); m.p. 59–62 °C; ν_{max} (thin film)/cm^{-1} 2981w, 2909w, 1770s, 1633s, 1508s, 1451s, 1433s, 1370m, 1316s, 1248s, 1197m, 1156m, 1132m, 1091s, 1042s, 1021s, 968s, 731s; δ_H (400 MHz, $CDCl_3$) 1.31 (3 H, t, *J* = 7.1, H-15/15'), 1.31 (3 H, t, *J* = 7.1, H-15/15'), 2.84 (1 H, d, *J* = 24.5, H-11), 3.44–3.53 (1 H, m, H-12), 3.61 (1 H, d, *J* = 12.4, H-9), 3.88 (3 H, s, H-8/8'), 3.90 (3 H, s, H-8/8'), 3.99–4.21 (5 H, m, H-13,14,14'), 4.49 (1 H, dd, *J* = 9.4, *J* = 6.0, H-13), 5.90–5.92 (4 H, m, H-2,2'), 6.37 (1 H, d, *J* = 1.4, H-4/4'/6/6'), 6.41 (1 H, d, *J* = 1.4, H-4/4'/6/6'), 6.45 (1 H, d, *J* = 1.3, H-4/4'/6/6'), 6.46 (1 H, d, *J* = 1.3, H-4/4'/6/6'); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* = 6.5, C-15/15'), 16.2 (d, *J* = 6.2, C-15/15'), 42.1 (d, *J* = 2.6, C-12), 44.8 (d, *J* = 133.0, C-11), 54.2 (d, *J* = 13.9, C-9), 56.7 (C-8/8'), 56.8 (C-8/8'), 63.1 (d, *J* = 7.0, C-14/14'), 63.7 (d, *J* = 7.1, C-14/14'), 70.6 (C-13), 101.2 (C-4/4'/6/6'), 101.4 (C-2/2'), 101.5 (C-2/2'), 101.9 (C-4/4'/6/6'), 107.6 (C-4/4'/6/6'), 107.9 (C-4/4'/6/6'), 134.2 (C-1/1'/3/3'), 134.3 (C-1/1'/3/3'), 135.3 (C-5/5'), 136.2 (d, *J* = 1.8, C-5/5'), 143.6 (C-7/7'), 143.6 (C-7/7'), 149.2 (C-1/1'/3/3'), 149.4 (C-1/1'/3/3'), 171.7 (d, *J* = 5.4, C-10); δ_P (162 MHz, $CDCl_3$) 19.7; HRMS (ESI$^+$): Found: 559.1329; $C_{25}H_{29}NaO_{11}P$ (MNa^+) Requires 559.1340 (1.8 ppm error).

Lab notebook reference: MGL/08/06

(±)-Peperomin E (308)



343 peperomin E, **308**

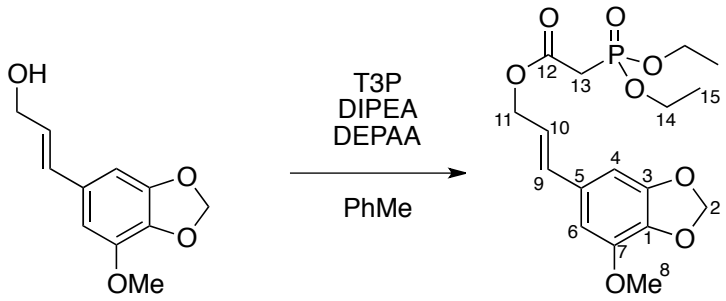
To a solution of diethyl ((3*RS*,4*SR*)-4-(bis(7-methoxybenzo[*d*][1,3]dioxol-5-yl)methyl)-2-oxotetrahydrofuran-3-yl)phosphonate **343** (66 mg, 0.123 mmol) in THF (2.5 mL) cooled to 0 °C under an argon atmosphere was added KOBu-*t* (16.6 mg, 0.148 mmol). The solution was stirred for 30 mins after which paraformaldehyde (18.5 mg, 0.615 mmol) was added in one portion. The mixture was stirred for 30 mins at 0°C then 1 h at RT then quenched by addition of sat. aq. NH_4Cl (5 mL). The mixture was extracted with EtOAc (3 × 25 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (2:1 hexane:EtOAc) afforded the title compound **308** as a white crystalline solid (44 mg, 87%); R_f 0.68 (1:1 hexane:EtOAc); m.p. 56–59 °C (lit.[145] 140 °C); ν_{max} (thin film)/cm^{-1} 2903w, 1760s, 1633s, 1508s, 1451s, 1432s, 1363m, 1315s, 1195s, 1130s, 1092s, 1042s, 927m, 730m; δ_H (400 MHz, $CDCl_3$) 3.66 (1 H, d, *J* = 11.6, H-9), 3.75 (1 H, app. dddt, *J* = 11.6, *J* = 7.7, *J* = 4.4, *J* = 2.2, H-12), 3.88 (3 H, s, H-8/8'), 3.89 (3 H, s, H-8/8'), 3.98 (1 H, dd, *J* = 9.5, *J* = 4.4, H-13), 4.32 (1 H, dd, *J* = 9.5, *J* = 7.7, H-13), 4.93 (1 H, d, *J* = 2.0, H-14b), 5.93–5.95 (4 H, m, H-2,2'), 6.14 (1 H, d, *J* = 2.3, H-14a), 6.36 (1 H, d, *J* = 1.5, H-4/4'/6/6'), 6.38 (1 H, d, *J* = 1.5, H-4/4'/6/6'), 6.45 (1 H, d, *J* = 1.5, H-4/4'/6/6'), 6.46 (1 H, d, *J* = 1.5, H-4/4'/6/6'); δ_C (100 MHz, $CDCl_3$) 42.4 (C-12), 55.3 (C-9), 56.8 (C-8/8'), 56.9 (C-8/8'), 69.7 (C-13), 101.1 (C-4/4'/6/6'), 101.5 (2C, C-2,2'), 101.5 (C-4/4'/6/6'), 107.9 (C-4/4'/6/6'), 108.3 (C-4/4'/6/6'), 124.9 (C-14), 134.2, 134.3, 135.8, 136.0, 136.1, 143.4 (C-7/7'), 143.6 (C-7/7'), 149.2, 149.5, 170.7 (C-10); HRMS (ESI$^+$): Found: 435.1050; $C_{22}H_{20}NaO_8$ (MNa^+) Requires 435.1050 (0.1 ppm error).

Lab notebook reference: MGL/08/09

Obtained data in accord with reported literature.[145]

Note: Obtained melting point does not match the literature value.

(*E*)-3-(7-Methoxybenzo[*d*][1,3]dioxol-5-yl)allyl 2-(diethoxyphosphoryl)acetate (S9)

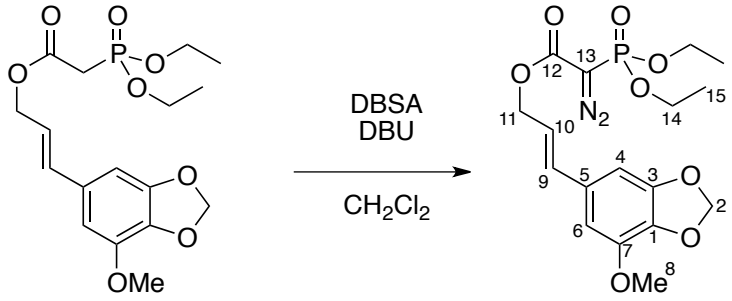


S8 **S9**

Synthesised using general procedure A with (*E*)-3-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)prop-2-en-1-ol **S8** (1.92 g, 9.22 mmol), toluene (46.1 mL), DEPAA (1.90 g, 9.68 mmol), DIPEA (4.18 mL, 24.0 mmol) and T3P (7.62 g, 12.0 mmol, 50% w/w solution in toluene) affording the *title compound* **S9** as a yellow oil (3.56 g, 100%); R_f 0.33 (1:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2983w, 1733s, 1626s, 1509s, 1430s, 1259s, 1199s, 1136m, 1092m, 1041w, 1021s, 965s; δ_H (400 MHz, $CDCl_3$) 1.30 (6 H, t, *J* = 7.1, H-15), 2.98 (2 H, d, *J* = 21.5, H-13), 3.87 (3 H, s, H-8), 4.11–4.18 (4 H, m, H-14), 4.74 (2 H, dd, *J* = 6.6, *J* = 1.0, H-11), 5.94 (2 H, s, H-2), 6.09 (1 H, dt, *J* = 15.8, *J* = 6.6, H-10), 6.51 (1 H, d, *J* = 1.5, H-4/6), 6.53 (1 H, br. d, *J* = 15.8, H-9), 6.58 (1 H, d, *J* = 1.5, H-4/6); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* = 6.3, C-15), 34.2 (d, *J* = 134.3, C-13), 56.4 (C-8), 62.6 (d, *J* = 6.5, C-14), 65.9 (C-11), 100.1 (C-4/6), 101.5 (C-2), 106.9 (C-4/6), 121.0 (C-10), 130.9 (C-1/3/5/7), 134.5 (C-9), 135.3 (C-1/3/5/7), 143.4 (C-1/3/5/7), 149.0 (C-1/3/5/7), 165.5 (d, *J* = 6.1, C-12); δ_P (162 MHz, $CDCl_3$) 20.2; HRMS (ESI^+): Found: 409.1018; $C_{17}H_{23}NaO_8P$ (MNa^+) Requires 409.1023 (1.2 ppm error).

Lab notebook reference: MGL/08/04

(*E*)-3-(7-Methoxybenzo[*d*][1,3]dioxol-5-yl)allyl 2-diazo-2-(diethoxyphosphoryl)acetate (320)

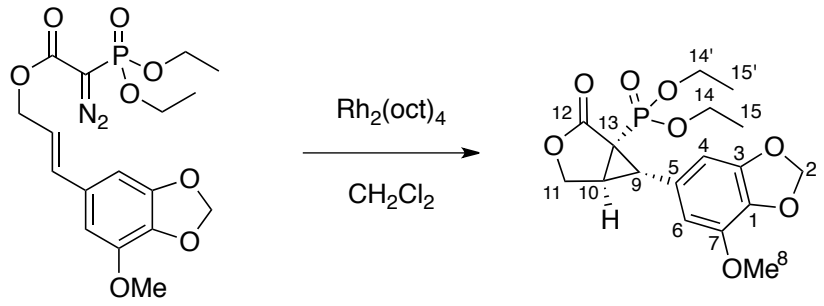


S9 **320**

To a solution of (*E*)-3-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)allyl 2-(diethoxyphosphoryl)acetate **S9** (386 mg, 1.00 mmol) and DBSA (422 mg, 1.5 mmol) in CH_2Cl_2 (10.0 mL), cooled to 0 °C under an argon atmosphere was added DBU (0.22 mL, 1.50 mmol) dropwise. The solution was allowed to warm to RT and stirred for 2 h. Concentration *in vacuo* and purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **320** as a pale yellow oil (397 mg, 96%); R_f 0.29 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2984w, 2940w, 2907w, 2127s, 1702s, 1625m, 1509m, 1430m, 1270s, 1199m, 1092m, 1015s, 965s, 813m, 743m, 589m, 560m; δ_H (400 MHz, $CDCl_3$) 1.35 (6 H, t, *J* 7.1, H-15), 3.89 (3 H, s, H-8), 4.11–4.27 (4 H, m, H-14), 4.81 (2 H, d, *J* 6.6, H-11), 5.96 (2 H, s, H-2), 6.11 (1 H, dt, *J* 15.7, *J* 6.6, H-10), 6.52 (1 H, d, *J* 1.2, H-4/6), 6.55 (1 H, br. d, *J* 15.7, H-9), 6.60 (1 H, d, *J* 1.2, H-4/6); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* 7.1, C-15), 53.8 (d, *J* 225.8, C-13), 56.5 (C-8), 63.7 (d, *J* 5.9, C-14), 66.0 (C-11), 100.2 (C-4/6), 101.6 (C-2), 107.0 (C-4/6), 121.0 (C-10), 130.8 (C-1/3/5/7), 134.8 (C-9), 135.5 (C-1/3/5/7), 143.5 (C-1/3/5/7), 149.1 (C-1/3/5/7), 163.2 (d, *J* 12.4, C-12); δ_P (162 MHz, $CDCl_3$) 10.5; HRMS (ESI^+): Found: 435.0917; $C_{17}H_{21}N_2NaO_8P$ (MNa^+) Requires 435.0928 (2.5 ppm error).

Lab notebook reference: MGL/08/11

Diethyl ((1*RS*,5*SR*,6*SR*)-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-2-oxo-3-oxabicyclo[3.1.0]hexan-1-yl)phosphonate (321)



320 **321**

Synthesised using general procedure F with (*E*)-3-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)allyl 2-diazo-2-(diethoxyphosphoryl)acetate **320** (80 mg, 0.194 mmol), CH_2Cl_2 (3.9 mL) and $Rh_2(oct)_4$ (3.0 mg, 3.9 μmol). Purification by column chromatography (1:4 hexane:EtOAc → EtOAc) afforded the *title compound* **321** as a yellow solid (48 mg, 64%); R_f 0.14 (1:4 hexane:EtOAc); m.p. 95–97 °C; ν_{max} (thin film)/cm^{-1} 2982w, 2909w, 1762s, 1634m, 1514m, 1432m, 1370m, 1249m, 1195m, 1140m, 1093m, 1017s, 971s, 812m, 589m; δ_H (400 MHz, $CDCl_3$) 1.16 (3 H, t, *J* = 7.1, H-15/15'), 1.21 (3 H, t, *J* = 7.1, H-15/15'), 2.73 (1 H, app. t, *J* = 6.0, H-9), 3.17 (1 H, app. dt, *J* = 10.6, *J* = 5.2, H-10), 3.88 (3 H, s, H-8), 3.91–4.09 (4 H, m, H-14/14'), 4.37 (1 H, dd, *J* = 9.4, *J* = 2.8, H-11), 4.47 (1 H, dd, *J* = 9.4, *J* = 4.7, H-11), 5.94 (1 H, d, *J* = 1.4, H-2), 5.94 (1 H, d, *J* = 1.4, H-2), 6.51 (1 H, d, *J* = 1.0, H-4/6), 6.61 (1 H, d, *J* = 1.0, H-4/6); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* = 6.2, C-15/15'), 16.2 (d, *J* = 6.2, C-15/15'), 28.7 (C-10), 31.6 (d, *J* = 206.1, C-13), 35.0 (d, *J* = 3.3, C-9), 56.5 (C-8), 62.5 (d, *J* = 6.2, C-14/14'), 63.0 (d, *J* = 6.7, C-14/14'), 68.0 (d, *J* = 3.0, C-11), 101.5 (C-2), 103.4 (C-4/6), 109.3 (C-4/6), 126.1 (d, *J* = 5.6, C-5), 135.0 (C-1/3/7), 143.1 (C-1/3/7), 148.4 (C-1/3/7), 171.8 (d, *J* = 10.5, C-12); δ_P (162 MHz, $CDCl_3$) 15.5; HRMS (ESI$^+$): Found: 407.0860; $C_{17}H_{21}NaO_8P$ (MNa^+) Requires 407.0866 (1.5 ppm error), Found: 385.1040; $C_{17}H_{22}O_8P$ (MH^+) Requires 385.1047 (1.8 ppm error).

Lab notebook reference: MGL/08/23

Appendices

Appendix I: Natural product NMR spectra and literature comparison tables

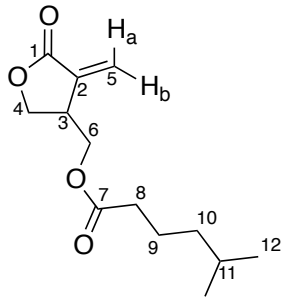
Cedarmycin A

Table 10: Comparison table of the ^{1}H NMR data of the natural (δ_H ref)[98] and synthetic (δ_H obs) cedarmycin A **189**.

^{1}H NMR data of cedarmycin A ($CDCl_3$)				
Label	**δ_H ref[98] (400 MHz)**		**δ_H obs (400 MHz)**	
12	0.89	6 H, d, J = 6.6	0.88	6 H, d, J = 6.6
10	1.19	2 H, m	1.15–1.21	2 H, m
9,11	1.55	1 H, m	1.51–1.65	3 H, m
	1.62	2 H, m		
8	2.31	2 H, t, J = 7.6	2.31	2 H, t, J = 7.6
3	3.43	1 H, m	3.39–3.47	1 H, m
6	4.18	1 H, dd, J = 11.2, J = 7.3	4.16	1 H, dd, J = 11.2, J = 7.3
4	4.19	1 H, dd, J = 9.4, J = 5.1	4.18	1 H, dd, J = 9.4, J = 4.9
6	4.25	1 H, dd, J = 10.9, J = 5.6	4.25	1 H, dd, J = 11.2, J = 5.6
4	4.48	1 H, dd, J = 9.6, J = 8.5	4.48	1 H, dd, J = 9.4, J = 8.4
5b	5.76	1 H, d, J = 2.4	5.76	1 H, d, J = 2.3
5a	6.39	1 H, d, J = 2.7	6.39	1 H, d, J = 2.7

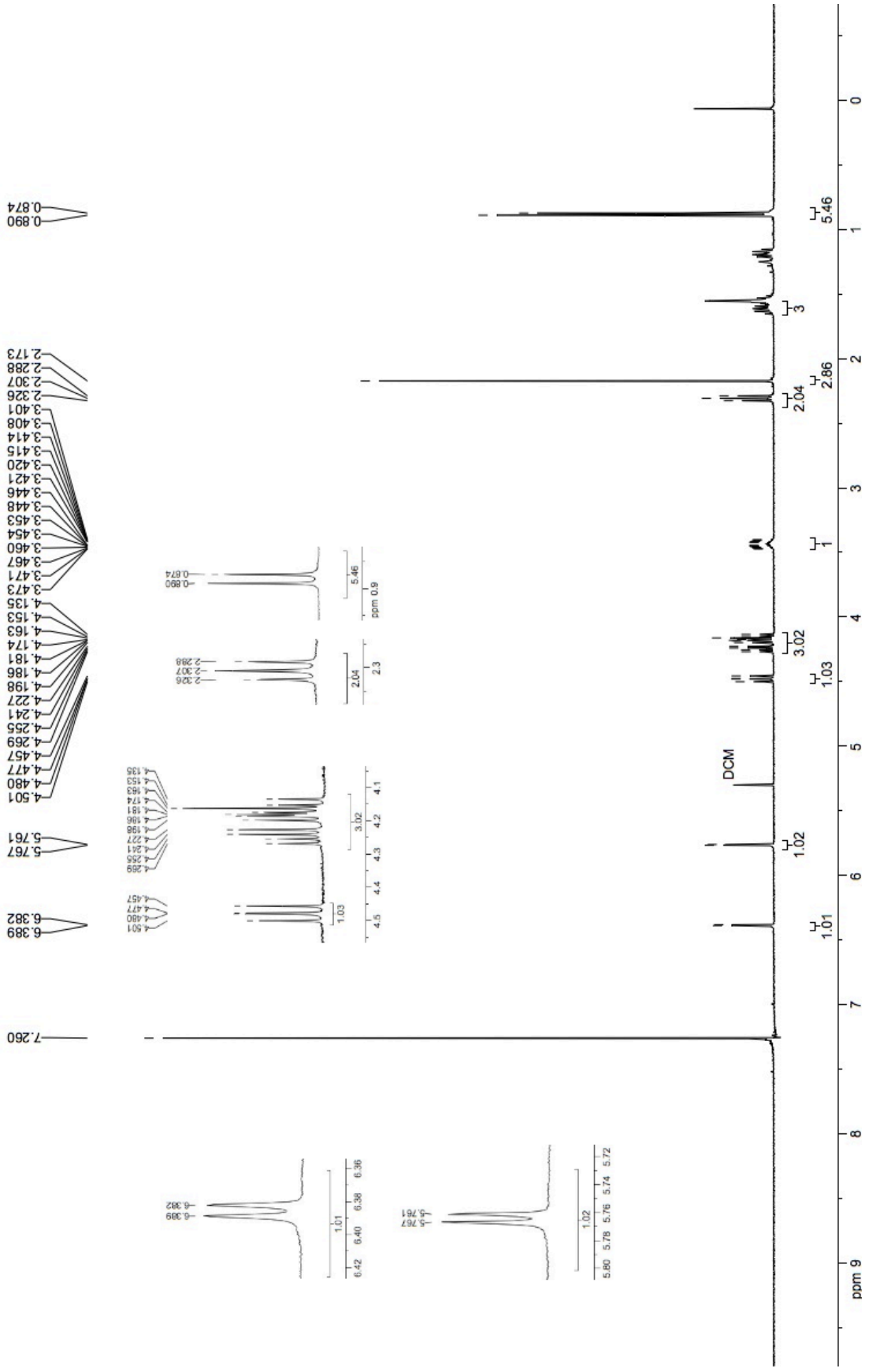
Table 11: Comparison table of the ^{13}C NMR data of the natural (δ_C ref)[98] and synthetic (δ_C obs) cedarmycin A **189**.

^{13}C NMR data of cedarmycin A ($CDCl_3$)			
Label	**δ_C ref[98] (100 MHz)**	**δ_C obs (100 MHz)**	**$\Delta\delta_C$**
12	22.5	22.4	–0.1
9	22.8	22.7	–0.1
11	27.7	27.7	0.0
8	34.3	34.3	0.0
3	38.1	38.0	–0.1
10	38.3	38.3	0.0
6	64.7	64.7	0.0
4	68.1	68.1	0.0
5	124.1	124.2	+0.1
2	134.6	134.5	–0.1
1	169.8	169.8	0.0
7	173.5	173.5	0.0

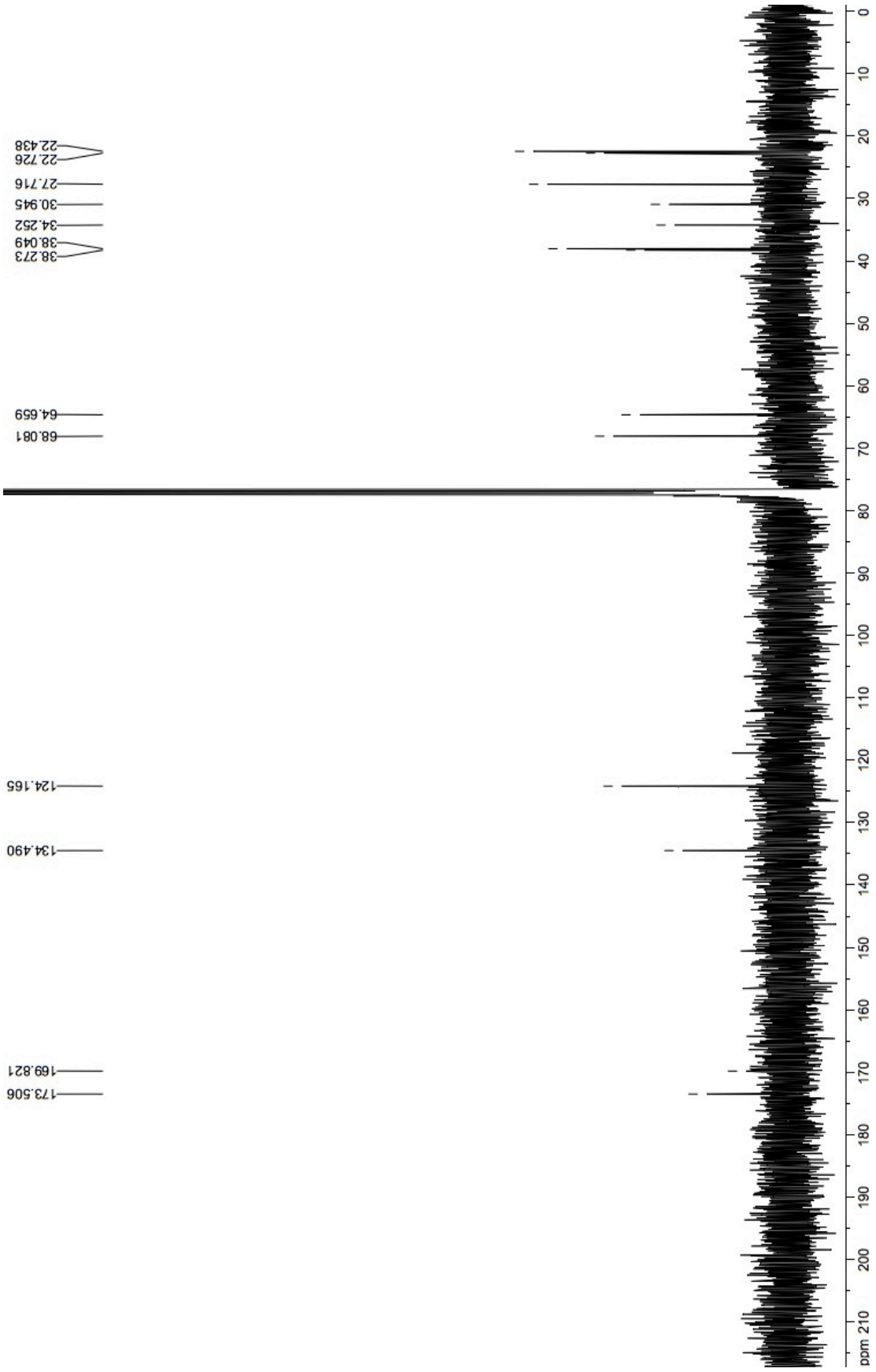


cedarmycin A, **189**

^{1}H NMR spectrum of Cedarmycin A 189 (400 MHz, $CDCl_3$)



^{13}C NMR spectrum of Cedarmycin A 189 (100 MHz, $CDCl_3$)



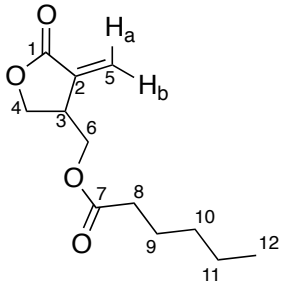
Cedarmycin B

Table 12: Comparison table of the ^{1}H NMR data of the natural (δ_H ref)[98] and synthetic (δ_H obs) cedarmycin B **190**.

^{1}H NMR data of cedarmycin B ($CDCl_3$)				
Label	**δ_H ref[98] (400 MHz)**		**δ_H obs (400 MHz)**	
12	0.90	3 H, t, J = 7.1	0.90	3 H, t, J = 7.0
10,11	1.32	4 H, m	1.25–1.36	4 H, m
9	1.62	2 H, quin., J = 7.6	1.62	2 H, app. quin., J = 7.5
8	2.34	2 H, t, J = 7.8	2.32	2 H, t, J = 7.5
3	3.43	1 H, m	3.39–3.47	1 H, m
6	4.18	1 H, dd, J = 11.2, J = 7.3	4.16	1 H, dd, J = 11.2, J = 7.3
4	4.19	1 H, dd, J = 9.4, J = 5.2	4.18	1 H, dd, J = 9.4, J = 4.9
6	4.25	1 H, dd, J = 11.2, J = 5.6	4.25	1 H, dd, J = 11.2, J = 5.6
4	4.48	1 H, dd, J = 9.4, J = 8.3	4.48	1 H, dd, J = 9.4, J = 8.4
5b	5.76	1 H, d, J = 2.2	5.76	1 H, d, J = 2.4
5a	6.39	1 H, d, J = 2.7	6.38	1 H, d, J = 2.7

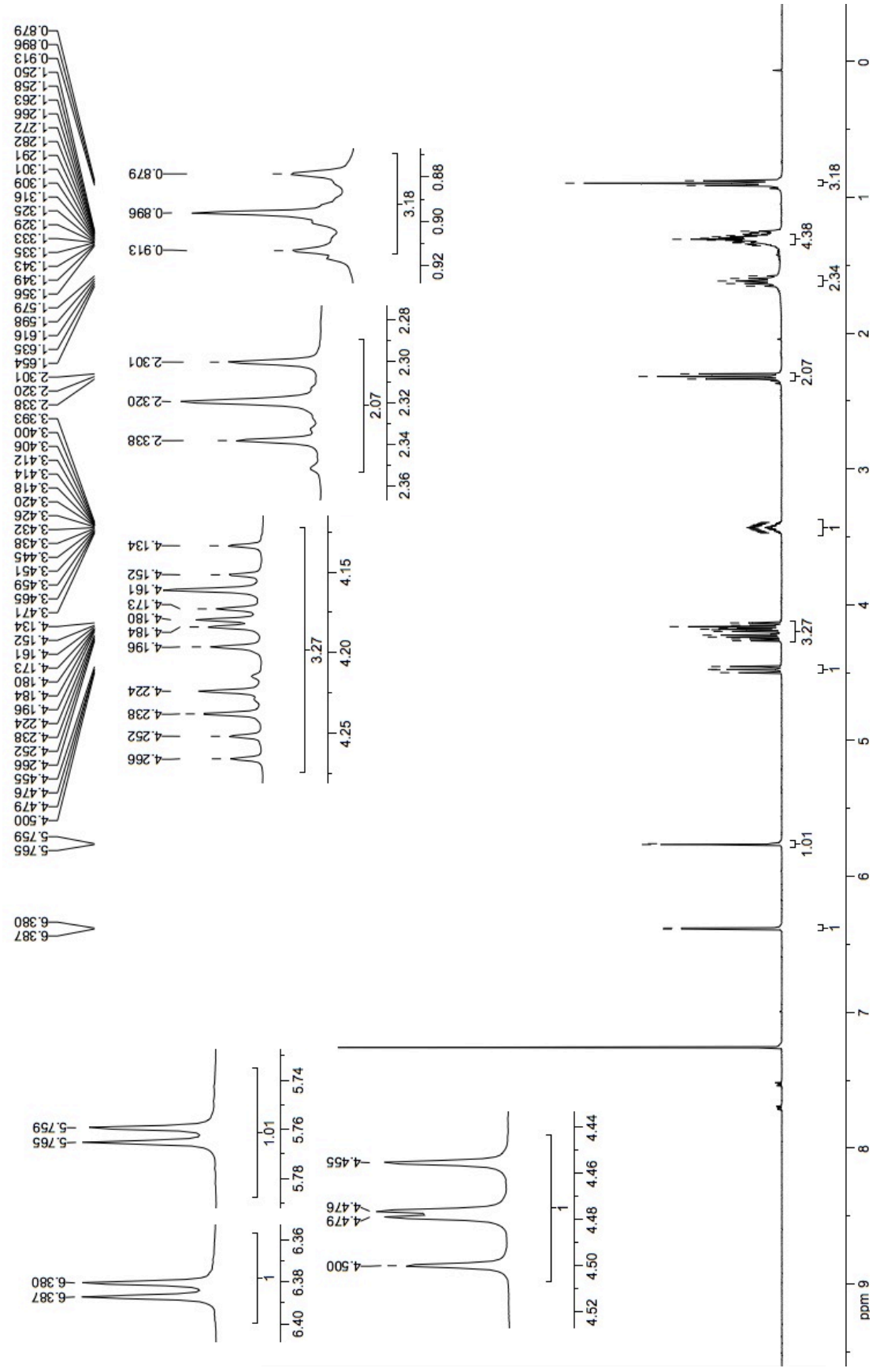
Table 13: Comparison table of the ^{13}C NMR data of the natural (δ_C ref)[98] and synthetic (δ_C obs) cedarmycin B **190**.

^{13}C NMR data of cedarmycin B ($CDCl_3$)			
Label	**δ_C ref[98] (100 MHz)**	**δ_C obs (100 MHz)**	**$\Delta\delta_C$**
12	13.9	13.9	0.0
11	22.3	22.3	0.0
9	24.6	24.5	–0.1
10	31.3	31.2	–0.1
8	34.0	34.0	0.0
3	38.1	38.1	0.0
6	64.7	64.7	0.0
4	68.1	68.1	0.0
5	124.1	124.1	0.0
2	134.6	134.5	–0.1
1	169.9	169.8	–0.1
7	173.5	173.5	0.0

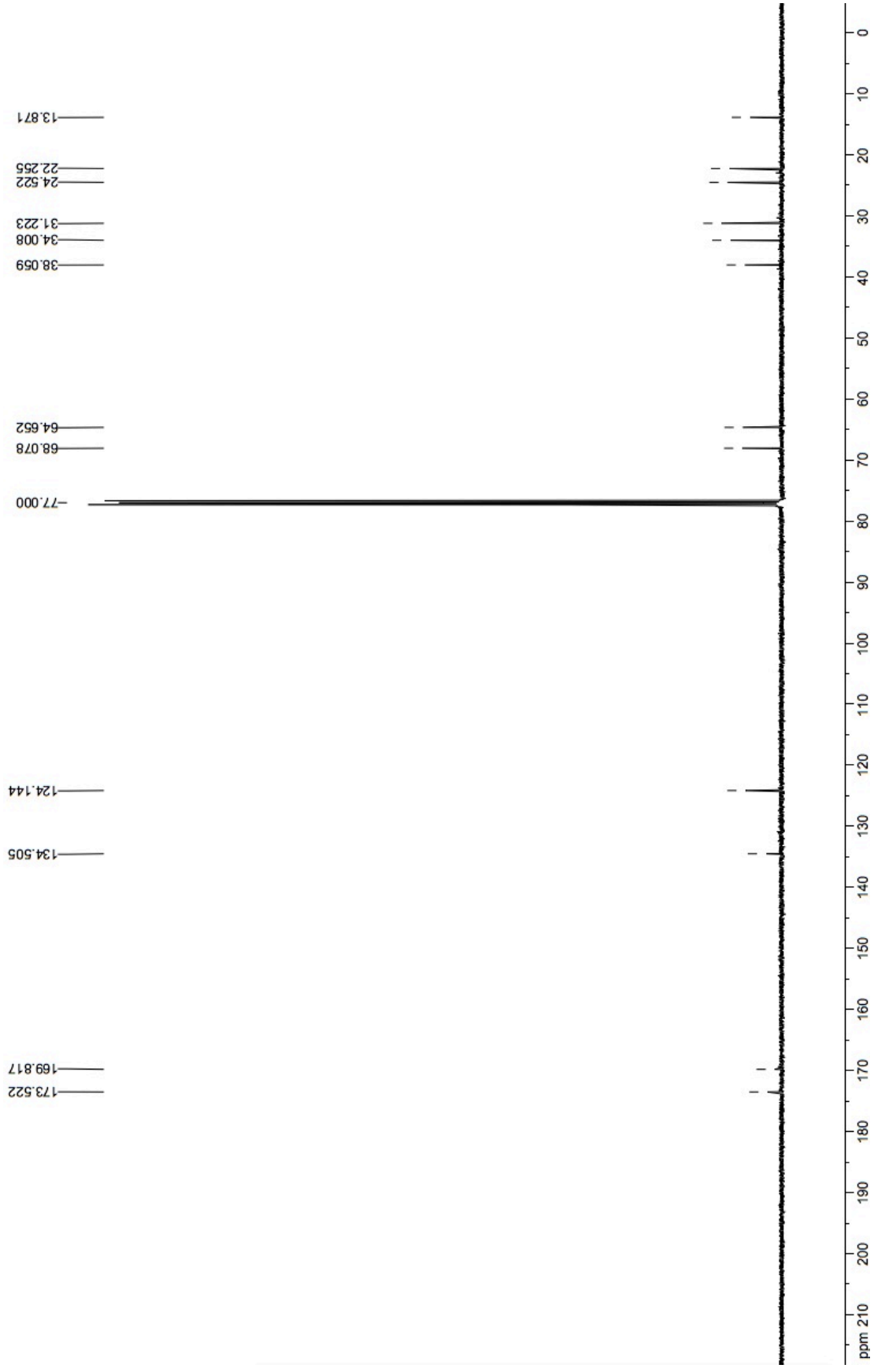


cedarmycin B, **190**

^{1}H NMR spectrum of Cedarmycin B 190 (400 MHz, $CDCl_3$)



^{13}C NMR spectrum of Cedarmycin B 190 (100 MHz, $CDCl_3$)



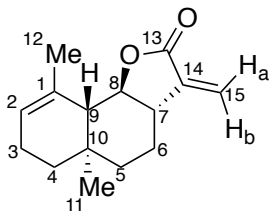
α-Cyclocostunolide

Table 14: Comparison table of the ^{1}H NMR data of the natural (δ_H ref)[120b] and synthetic (δ_H obs) α-cyclocostunolide **256**.

^{1}H NMR data of (±)-α-cyclocostunolide ($CDCl_3$)				
Label	**δ_H ref[120b] (100 MHz)**		**δ_H obs (400 MHz)**	
11	0.90	1 H, s	0.90	1 H, s
12	1.84	1 H, s	1.83	1 H, s
8	3.87	1 H, t, *J* = 11.0	3.87	1 H, t, *J* = 11.0
15b, 2	5.38	2 H, d, *J* 3.0	5.38	2 H, d, *J* 3.1
15a	6.05	1 H, d, *J* 3.0	6.05	1 H, d, *J* 3.2

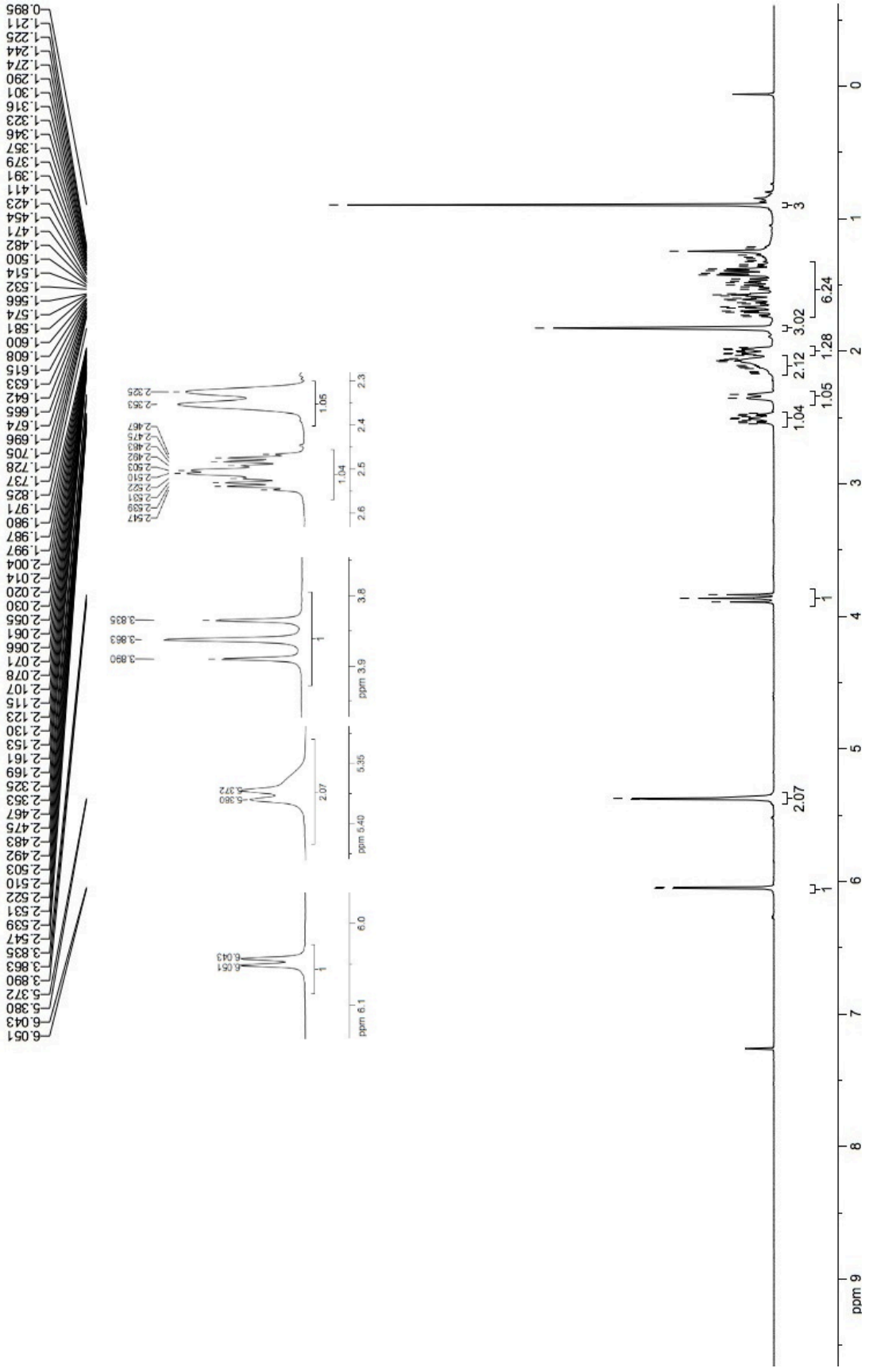
Table 15: Comparison table of the ^{13}C NMR data of the natural (δ_C ref)[120a] and synthetic (δ_C obs) α-cyclocostunolide **256**.

^{13}C NMR data of (±)-α-cyclocostunolide ($CDCl_3$)			
Label	**δ_C ref[120a] (25.2 MHz)**	**δ_C obs (100 MHz)**	**$\Delta\delta_C$**
11	17.4	17.4	0.0
6	21.5	21.5	0.0
3	22.9	22.8	–0.1
12	23.7	23.7	0.0
10	36.0	35.9	–0.1
4	37.8	37.7	–0.1
5	39.2	39.2	0.0
7	51.2	51.2	0.0
9	51.3	51.5	+0.2
8	82.1	82.2	+0.1
15	116.3	116.4	+0.1
2	122.3	122.4	+0.1
1	132.9	133.0	+0.1
14	139.3	139.4	+0.1
13	170.8	171.0	+0.2

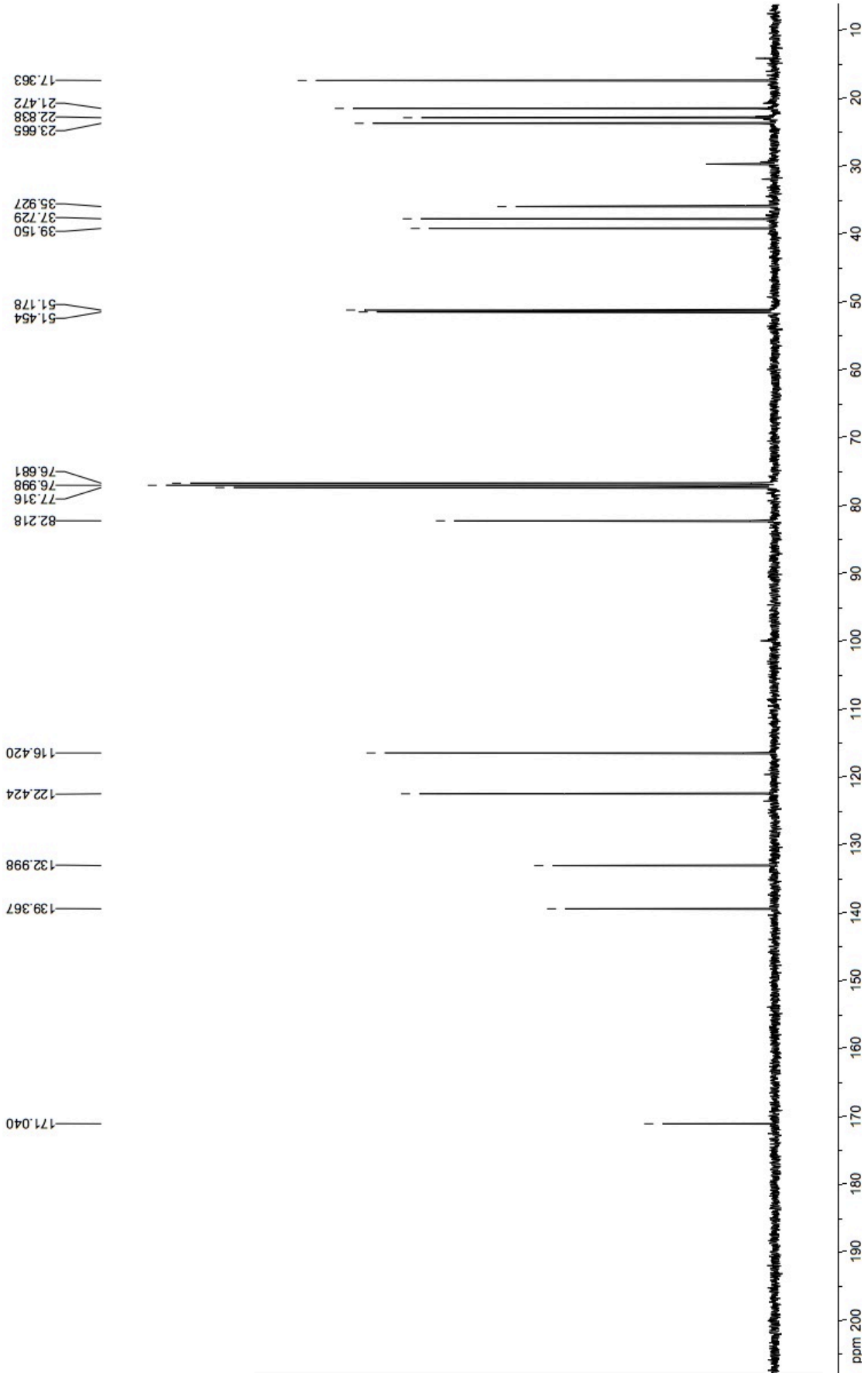


α-cyclocostunolide, **256**

^{1}H NMR spectrum of α-cyclocostunolide 256 (400 MHz, $CDCl_3$)



^{13}C NMR spectrum of α-cyclocostunolide 256 (100 MHz, $CDCl_3$)



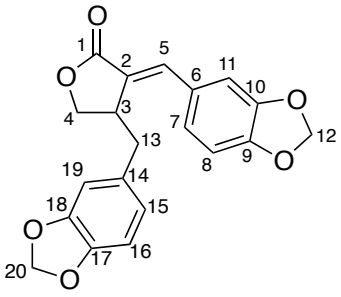
(±)-Savinin

Table 16: Comparison table of the ^{1}H NMR data of the natural (δ_H ref)[141] and synthetic (δ_H obs) savinin **174**.

^{1}H NMR data of savinin ($CDCl_3$)				
Label	**δ_H ref[141] (400 MHz)**		**δ_H obs (400 MHz)**	
13	2.60	1 H, dd, J = 14.6, J = 10.4	2.59	1 H, dd, J = 14.2, J = 10.1
	3.00	1 H, dd, J = 14.6, J = 5.0	2.99	1 H, dd, J = 14.2, J = 4.5
3	3.73	1 H, m	3.71–3.77	1 H, m
4	4.21–4.26	2 H, m	4.22–4.29	2 H, m
20	5.93	2 H, s	5.93	1 H, d, J = 1.4
			5.94	1 H, d, J = 1.4
12	6.04	2 H, s	6.05	2 H, s
15	6.62–6.75	3 H, m	6.64	1 H, dd, J = 7.8, J = 1.6
19			6.67	1 H, d, J = 1.6
16			6.74	1 H, d, J = 7.8
8	6.88	1 H, d, J = 8.5	6.88	1 H, d, J = 8.1
11	7.04–7.09	2 H, m	7.05	1 H, d, J = 1.7
7			7.08	1 H, dd, J = 8.1, J = 1.7
5	7.49	1 H, s	7.50	1 H, d, J = 1.9

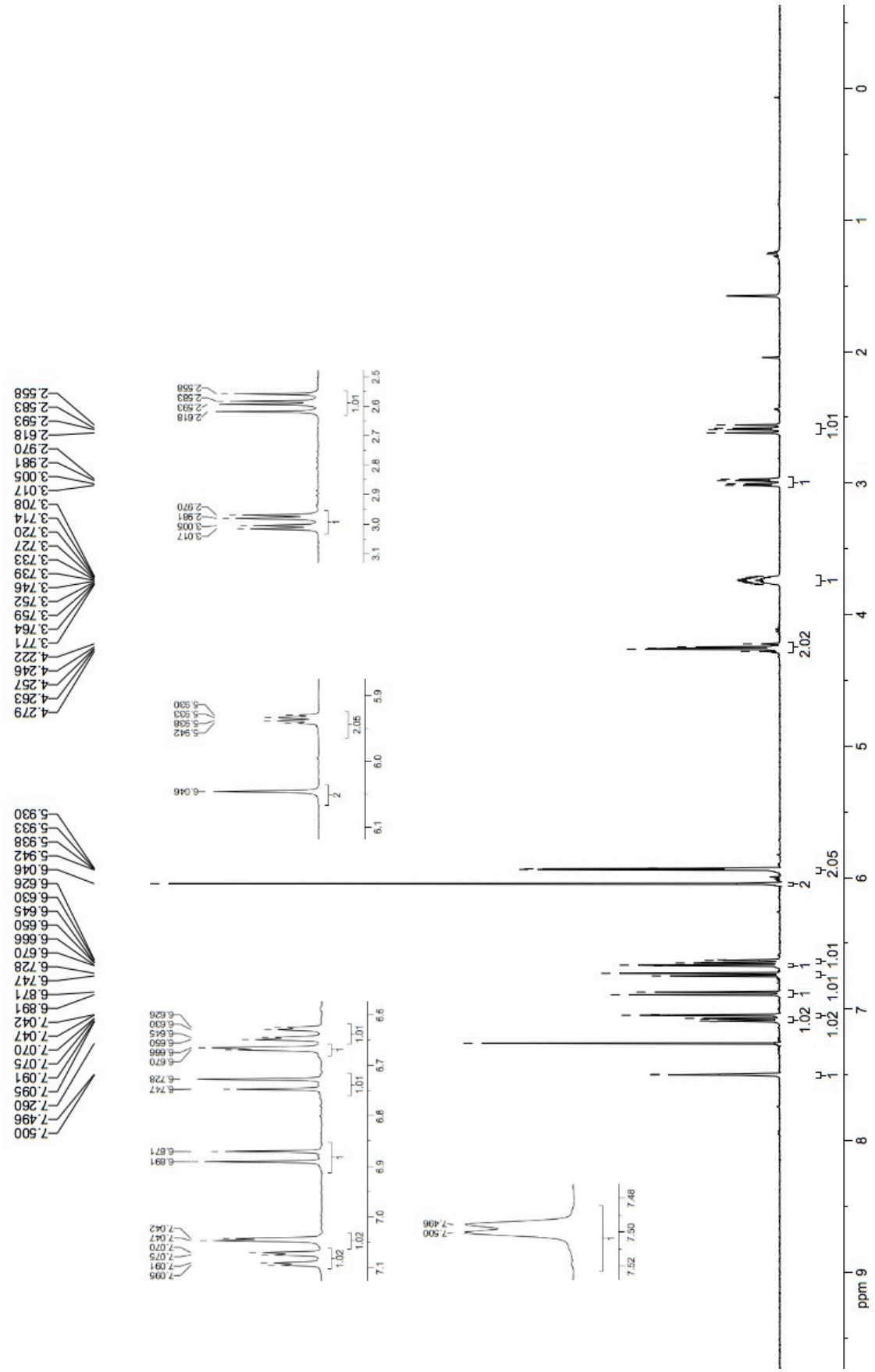
Table 17: Comparison table of the ^{13}C NMR data of the natural (δ_C ref)[140] and synthetic (δ_C obs) savinin **174**.

^{13}C NMR data of savinin ($CDCl_3$)				
Label ref	**δ_C ref[140] (100 MHz)**	**Label obs**	**δ_C obs (100 MHz)**	**$\Delta\delta_C$**
13	37.4	13	37.5	+0.1
3	39.8	3	39.9	+0.1
4	69.4	4	69.5	+0.1
20	101.0	20	101.0	0.0
12	101.7	12	101.7	0.0
8	108.4	8, 11, 16, 19	108.5	+0.1
11	108.6		108.6	0.0
16	108.7		108.8	+0.1
19	109.1		109.2	+0.1
15	122.0	15	122.2	+0.2
2	125.7	2	125.8	+0.1
7	126.0	7	126.1	+0.1
6	128.1	6	128.2	+0.1
14	131.4	14	131.5	+0.1
5	137.2	5	137.5	+0.3
17	146.4	17, 18	146.5	+0.1
18	147.8		147.9	+0.1
10	148.2	9,10	148.3	+0.1
9	149.1		149.2	+0.1
1	172.5	1	172.6	+0.1

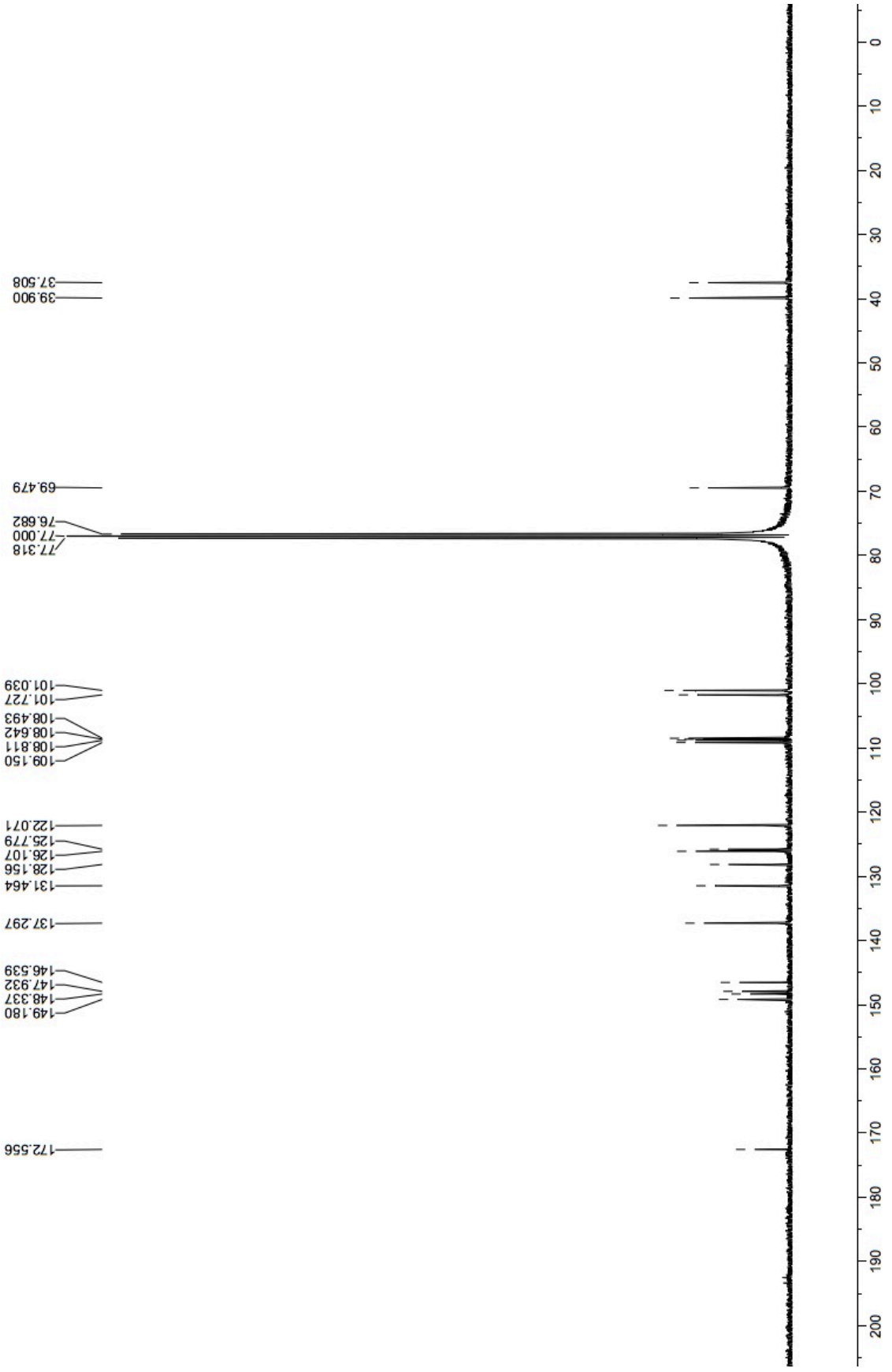


savinin, **174**

^{1}H NMR spectrum of Savinin 174 (400 MHz, $CDCl_3$)



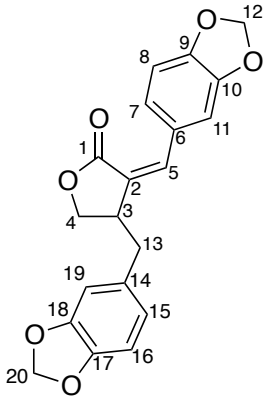
^{13}C NMR spectrum of Savinin 174 (400 MHz, $CDCl_3$)



(±)-Gadain

Table 18: Comparison table of the ^{1}H NMR data of the natural (δ_H ref)[143] and synthetic (δ_H obs) gadain **307**.

^{1}H NMR data of gadain ($CDCl_3$)					
Label ref	**δ_H ref[143] (300 MHz)**		**Label obs**	**δ_H obs (400 MHz)**	
13	2.82	1 H, dd, J = 16.8, J = 10.8	13	2.78	1 H, dd, J = 13.8, J = 8.9
	2.92	1 H, dd, J = 16.8, J = 8.4		2.91	1 H, dd, J = 13.8, J = 6.9
3	3.31	1 H, m	3	3.29	1 H, app. dtdd, J = 8.9, J = 7.1, J = 3.8, J = 1.7
4	4.12	1 H, dd, J = 10.8, J = 4.8	4	4.10	1 H, dd, J = 9.1, J = 3.8
	4.34	1 H, dd, J = 10.8, J = 8.4		4.32	1 H, dd, J = 9.1, J = 7.3
12, 20	5.96	1 H, dd, J = 3.0, J = 1.4	20	5.95	1 H, d, J = 1.4
				5.96	1 H, d, J = 1.4
	6.00	2 H, s	12	6.00	2 H, s
5	6.59	1 H, d, J = 1.6	5	6.59	1 H, d, J = 1.7
15	6.77	1 H, dd, J = 8.0, J = 1.5	15	6.62	1 H, dd, J = 7.9, J = 1.7
19	6.70	1 H, d, J = 1.5	19	6.69	1 H, d, J = 1.7
16	6.66	1 H, d, J = 8.0	16	6.76	1 H, d, J = 7.9
8	6.80	1 H, d, J = 8.0	8	6.79	1 H, d, J = 8.1
7	7.17	1 H, dd, J = 8.0, J = 1.5	7	7.15	1 H, dd, J = 8.1, J = 1.7
11	7.75	1 H, d, J = 1.5	11	7.74	1 H, d, J = 1.7



gadain, **307**

^{1}H NMR spectrum of Gadain 307 (400 MHz, $CDCl_3$)

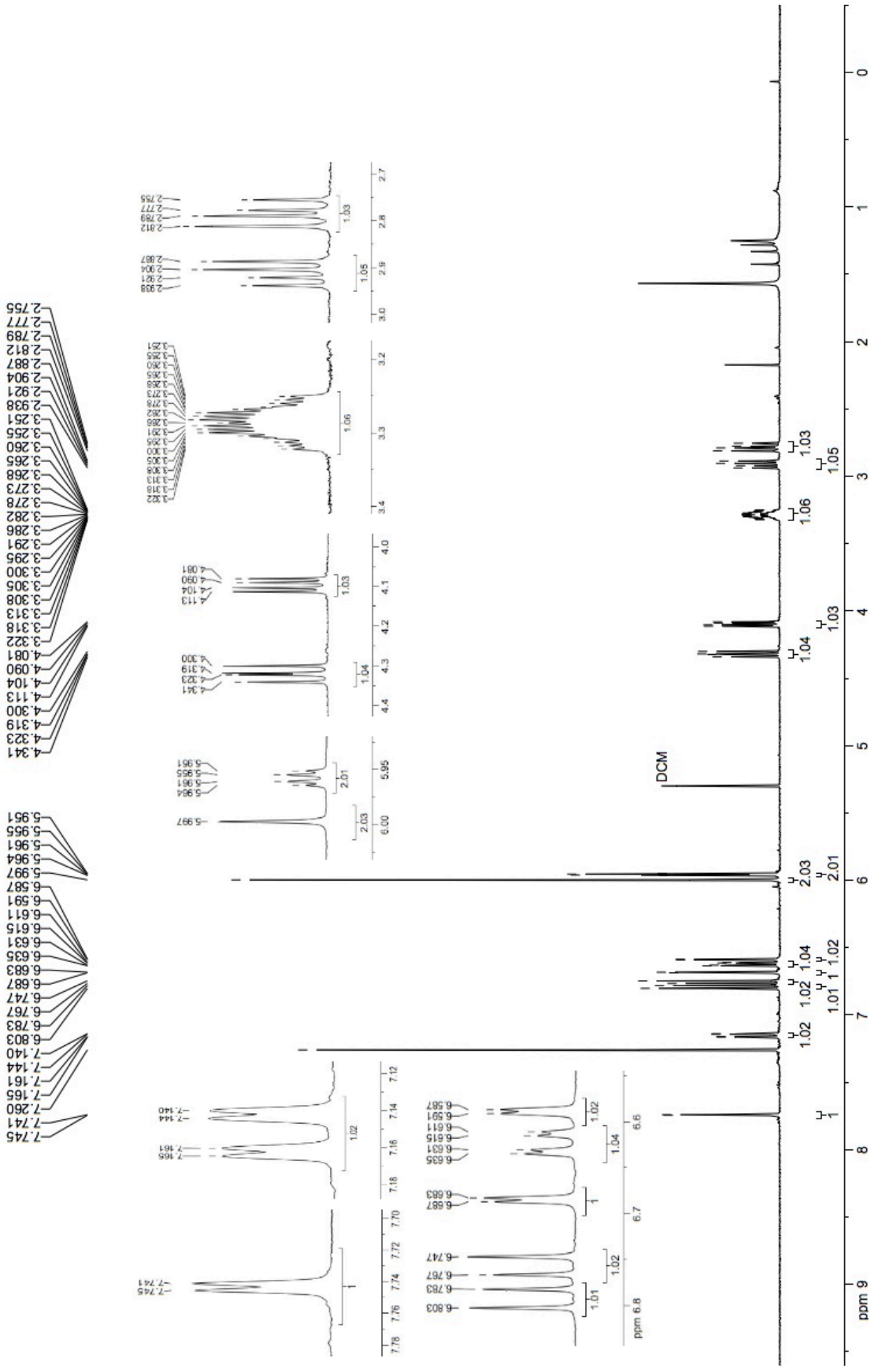
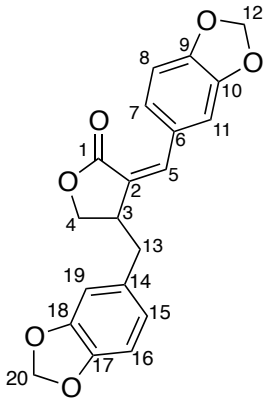


Table 19: Comparison table of the ^{13}C NMR data of the natural (δ_C ref)[143] and synthetic (δ_C obs) gadain **307**.

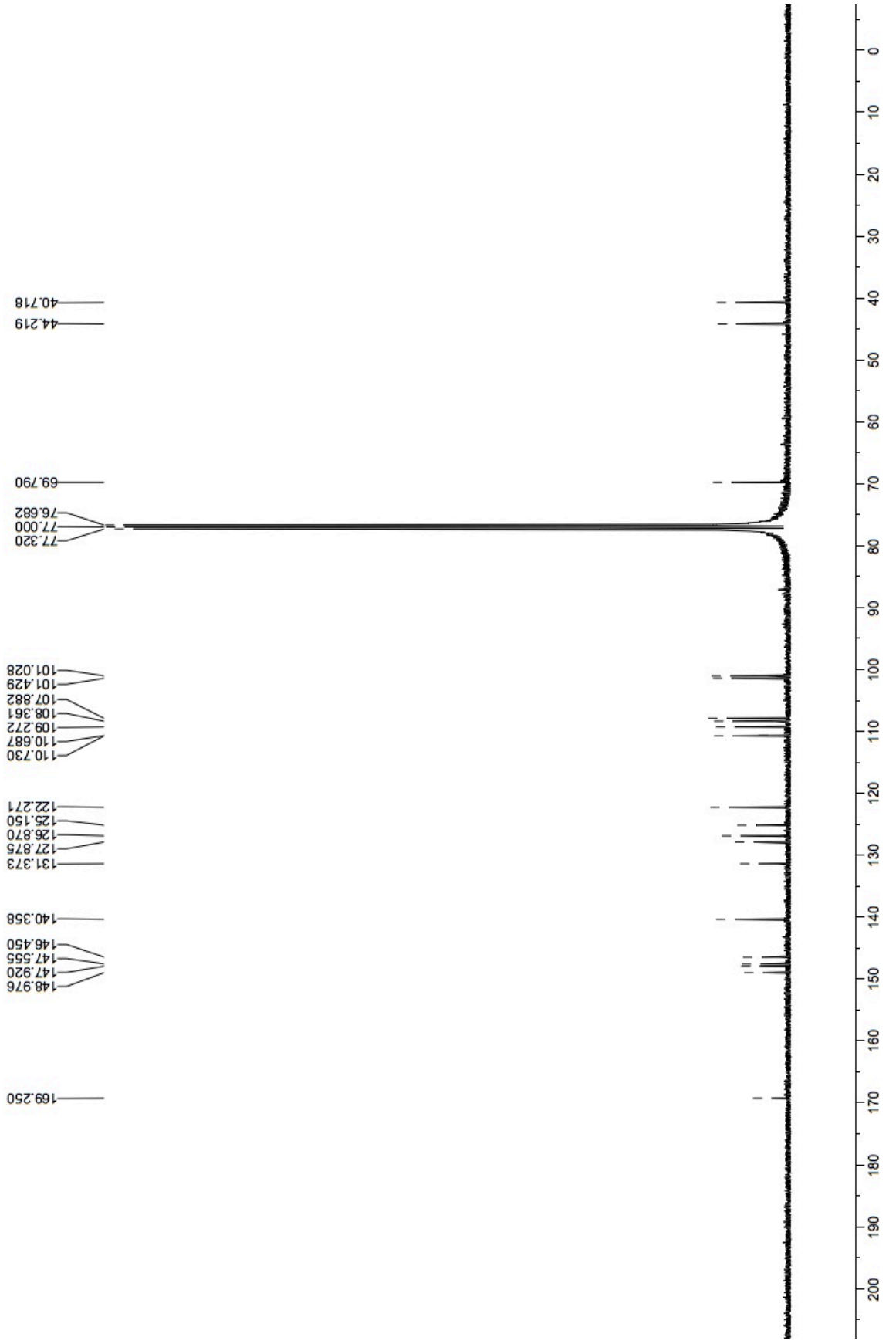
^{13}C NMR data of gadain ($CDCl_3$)				
Label ref	**δ_C ref[143] (100 MHz)**	**Label obs**	**δ_C obs (100 MHz)**	**$\Delta\delta_C$**
13	40.7	13	40.7	0.0
3	44.2	3	44.2	0.0
4	69.8	4	69.8	0.0
12, 20	101.0	20	101.0	0.0
	101.4	12	101.4	0.0
19	107.9	8	107.9	0.0
11	108.4	16	108.4	0.0
16	109.3	19	109.3	0.0
8	110.3	11	110.7	+0.4
15	122.7	15	122.3	–0.4
7	125.2	2	125.2	0.0
2	126.9	7	126.9	0.0
14	127.9	6	127.9	0.0
6	131.4	14	131.4	0.0
5	140.3	5	140.4	+0.1
18	146.5	17, 18	146.5	0.0
17	147.6		147.6	0.0
10	147.9	9,10	147.9	0.0
9	149.0		149.0	0.0
1	169.3	1	169.3	0.0

Note: Whilst the observed data points match extremely well with the reference data points, there is a discrepancy in the assignment of the peaks in the ^{13}C NMR spectra, despite a complete agreement of the assignments in the ^{1}H NMR spectra.



gadain, **307**

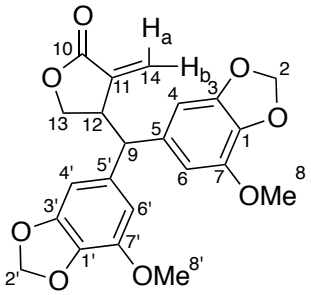
^{13}C NMR spectrum of Gadain 307 (400 MHz, $CDCl_3$)



(±)-Peperomin E

Table 20: Comparison table of the ^{1}H NMR data of the natural (δ_H ref)[145] and synthetic (δ_H obs) (±)-peperomin E **308**.

^{1}H NMR data of (±)-Peperomin E ($CDCl_3$)				
Label	**δ_H ref[145] (200 MHz)**		**δ_H obs (400 MHz)**	
9	3.65	1 H, d, *J* = 11.5	3.66	1 H, d, *J* = 11.6
12	3.70	1 H, m	3.75	1 H, ddddd, *J* = 11.6, *J* = 7.7, *J* = 4.4, *J* = 2.3, *J* = 2.0
8/8’	3.88	3 H, s	3.88	3 H, s
8/8’	3.89	3 H, s	3.89	3 H, s
13	3.99	1 H, dd, *J* = 9.4, *J* = 4.1,	3.98	1 H, dd, *J* = 9.5, *J* = 4.4,
13	4.32	1 H, dd, *J* = 9.4, *J* = 7.3,	4.32	1 H, dd, *J* = 9.5, *J* = 7.7,
14b	4.94	1 H, d, *J* = 1.7	4.93	1 H, d, *J* = 2.0
2,2’	5.92	4 H, s	5.93–5.95	4 H, m
14a	6.15	1 H, d, *J* = 2.0	6.14	1 H, d, *J* = 2.3
4/4’/6/6’	6.37	1 H, d, *J* = 1.5	6.36	1 H, d, *J* = 1.5
4/4’/6/6’	6.43	1 H, d, *J* = 1.5	6.38	1 H, d, *J* = 1.5
4/4’/6/6’	6.50	1 H, d, *J* = 1.5	6.45	1 H, d, *J* = 1.5
4/4’/6/6’	6.60	1 H, d, *J* = 1.5	6.46	1 H, d, *J* = 1.5



peperomin E, **308**

^{1}H NMR spectrum of peperomin E 308 (400 MHz, $CDCl_3$)

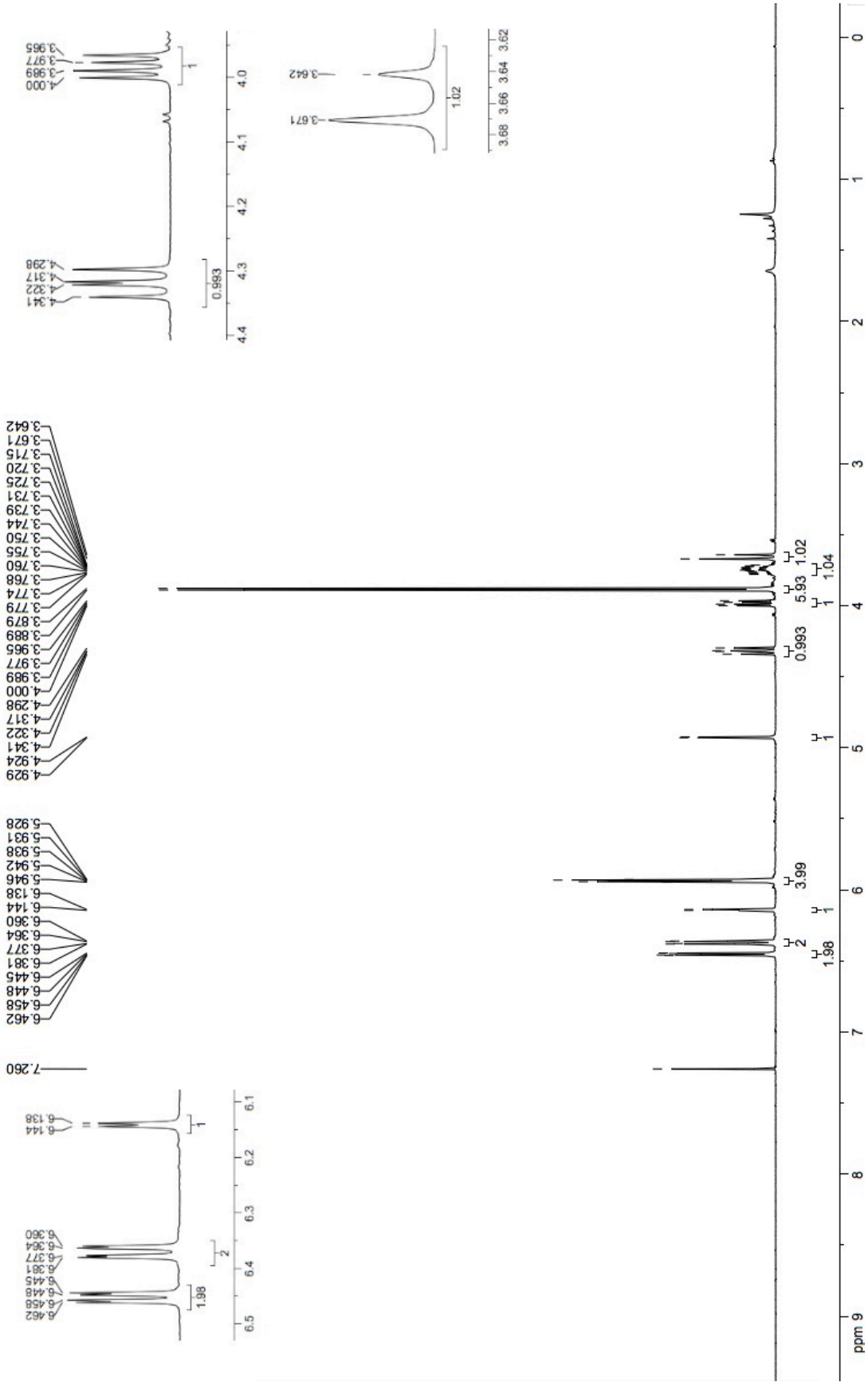
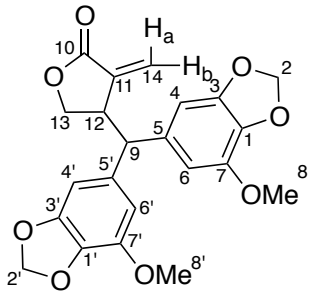


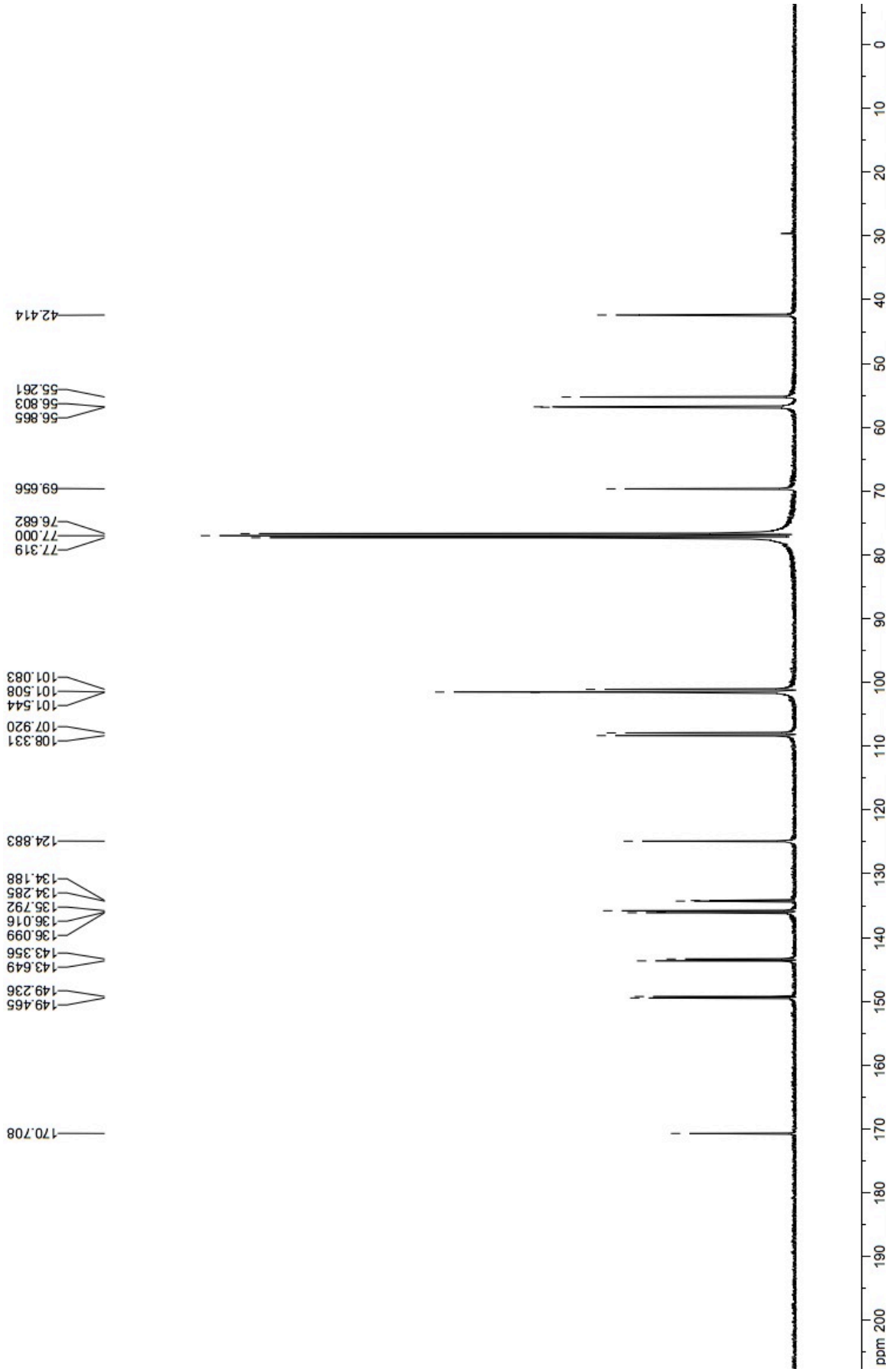
Table 21: Comparison table of the ^{13}C NMR data of the natural (δ_C ref)[145] and synthetic (δ_C obs) (±)-peperomin E **308**.

^{13}C NMR data of (±)-Peperomin E ($CDCl_3$)				
Label ref[120a]	**δ_C ref[145] (50 MHz)**	**Label obs**	**δ_C obs (100 MHz)**	**$\Delta\delta_C$**
12	42.4	12	42.4	0.0
9	55.3	9	55.3	0.0
8/8’	56.8	8/8’	56.8	0.0
8/8’	56.9	8/8’	56.9	0.0
13	69.6	13	69.7	+0.1
4/4’	101.5	4/4’/6/6’	101.1	–0.4
2,2’	102.0	2,2’ (2 C)	101.5	–0.5
4/4’	101.5	4/4’/6/6’	101.5	0.0
6/6’	108.4	4/4’/6/6’	107.9	–0.5
6/6’	108.8	4/4’/6/6’	108.3	–0.5
14	125.2	14	124.9	–0.3
5,5’ (2 C)	134.3	1/1’/3/3’/5/5’/11	134.2	0.0
		1/1’/3/3’/5/5’/11	134.3	
11	135.8	1/1’/3/3’/5/5’/11	135.8	0.0
1/1’	136.0	1/1’/3/3’/5/5’/11	136.0	0.0
1/1’	136.1	1/1’/3/3’/5/5’/11	136.1	0.0
7/7’	143.4	7/7’	143.4	0.0
7/7’	143.6	7/7’	143.6	0.0
3/3’	149.2	1/1’/3/3’/5/5’/11	149.2	0.0
3/3’	149.5	1/1’/3/3’/5/5’/11	149.5	0.0
10	170.7	10	170.7	0.0



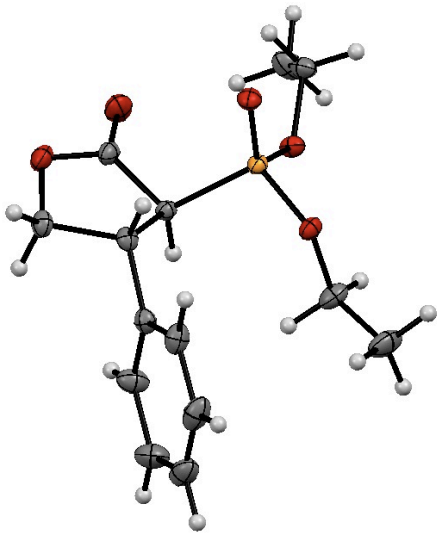
peperomin E, **308**

^{13}C NMR spectrum of peperomin E 308 (100 MHz, $CDCl_3$)



Appendix II: Crystallographic data

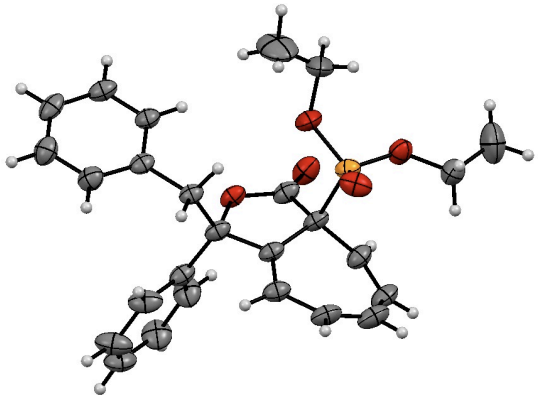
Compound 116c



CCDC Number	980606
Identification code	rjkt1212
Empirical formula	$C_{14}H_{19}O_5P$
Formula weight	298.26
Temperature/K	110.00(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	10.12764(18)
b/Å	8.97571(13)
c/Å	15.9855(3)
α/°	90.00
β/°	94.4074(16)
γ/°	90.00
Volume/Å^3	1448.83(4)
Z	4
ρ_{calc}g/cm^3	1.367
μ/mm^{-1}	0.206
F(000)	632.0
Crystal size/mm^3	0.225 × 0.1634 × 0.0635
2Θ range for data collection/°	6.08 to 64.4
Index ranges	$-15 \leq h \leq 13$, $-13 \leq k \leq 13$, $-23 \leq l \leq 23$
Reflections collected	13784
Independent reflections	4681[R(int) = 0.0270]
Data/restraints/parameters	4681/0/183
Goodness-of-fit on F^2	1.037
Final R indexes [I>=2σ (I)]	R_1 = 0.0362, wR_2 = 0.0894
Final R indexes [all data]	R_1 = 0.0431, wR_2 = 0.0953
Largest diff. peak/hole / e Å^{-3}	0.40/-0.358

The crystal was grown by evaporation of diethyl ether layered on chloroform inside a standard NMR tube.

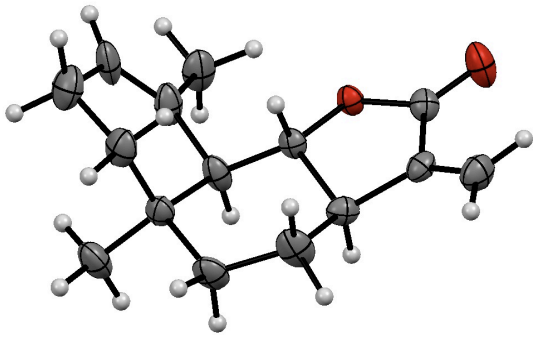
Compound 153e



CCDC Number	1013524
Identification code	rjkt1306
Empirical formula	$C_{26}H_{27}O_5P$
Formula weight	450.45
Temperature/K	110.00(10)
Crystal system	triclinic
Space group	P-1
a/Å	9.5981(5)
b/Å	11.0011(9)
c/Å	12.4360(9)
α/°	68.604(7)
β/°	72.191(5)
γ/°	79.237(6)
Volume/Å^3	1159.82(14)
Z	2
ρ_{calc}g/cm^3	1.290
μ/mm^{-1}	0.153
F(000)	476.0
Crystal size/mm^3	0.2995 × 0.1557 × 0.0689
2Θ range for data collection/°	5.74 to 60.06
Index ranges	$-13 \leq h \leq 12$, $-14 \leq k \leq 15$, $-17 \leq l \leq 12$
Reflections collected	10694
Independent reflections	6704[R(int) = 0.0282]
Data/restraints/parameters	6704/18/446
Goodness-of-fit on F^2	1.043
Final R indexes [I>=2σ (I)]	R_1 = 0.0719, wR_2 = 0.1760
Final R indexes [all data]	R_1 = 0.1018, wR_2 = 0.1993
Largest diff. peak/hole / e Å^{-3}	0.63/-0.35

The crystal was grown by evaporation of diethyl ether layered on chloroform inside a standard NMR tube.

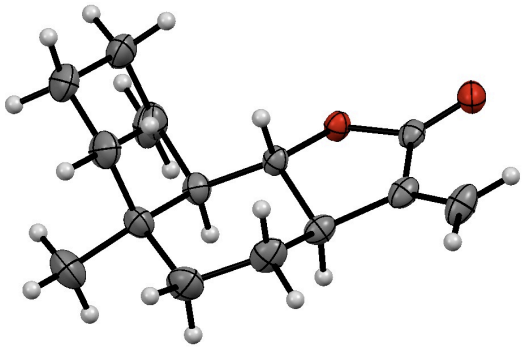
Compound 240



CCDC Number	1421158
Identification code	rjkt1516
Empirical formula	$C_{15}H_{18}O_2$
Formula weight	230.29
Temperature/K	132(30)
Crystal system	triclinic
Space group	P-1
a/Å	7.4631(4)
b/Å	8.1068(4)
c/Å	10.7071(5)
α/°	89.047(4)
β/°	89.710(4)
γ/°	89.044(4)
Volume/Å^3	647.61(6)
Z	2
ρ_{calc}g/cm^3	1.181
μ/mm^{-1}	0.608
F(000)	248.0
Crystal size/mm^3	0.2239 × 0.1846 × 0.0284
Radiation	CuKα (λ = 1.54181)
2Θ range for data collection/°	8.26 to 142.02
Index ranges	-8 ≤ h ≤ 9, -9 ≤ k ≤ 7, -12 ≤ l ≤ 13
Reflections collected	4954
Independent reflections	2399 [R_{int} = 0.0157, R_{sigma} = 0.0212]
Data/restraints/parameters	2399/1/176
Goodness-of-fit on F^2	1.030
Final R indexes [I>=2σ (I)]	R_1 = 0.0395, wR_2 = 0.1082
Final R indexes [all data]	R_1 = 0.0439, wR_2 = 0.1122
Largest diff. peak/hole / e Å^{-3}	0.27/-0.19

The crystal was grown by evaporation of diethyl ether layered on chloroform inside a standard NMR tube.

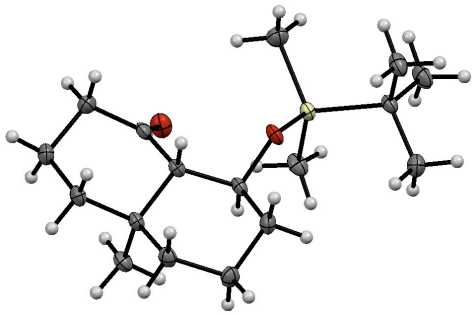
Compound 241



CCDC Number	1421154
Identification code	rjkt1506
Empirical formula	$C_{15}H_{20}O_2$
Formula weight	232.31
Temperature/K	110.05(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	6.95182(16)
b/Å	12.2280(3)
c/Å	30.5046(6)
α/°	90
β/°	95.654(2)
γ/°	90
Volume/Å^3	2580.47(10)
Z	8
ρ_{calc}g/cm^3	1.196
μ/mm^{-1}	0.611
F(000)	1008.0
Crystal size/mm^3	0.1215 × 0.081 × 0.0366
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.794 to 134.144
Index ranges	$-8 \leq h \leq 7$, $-10 \leq k \leq 14$, $-32 \leq l \leq 36$
Reflections collected	8613
Independent reflections	4600 [R_{int} = 0.0192, R_{sigma} = 0.0302]
Data/restraints/parameters	4600/0/309
Goodness-of-fit on F^2	1.039
Final R indexes [I>=2σ (I)]	R_1 = 0.0487, wR_2 = 0.1285
Final R indexes [all data]	R_1 = 0.0633, wR_2 = 0.1362
Largest diff. peak/hole / e Å^{-3}	0.35/-0.21

The crystal was grown by evaporation of diethyl ether layered on chloroform inside a standard NMR tube.

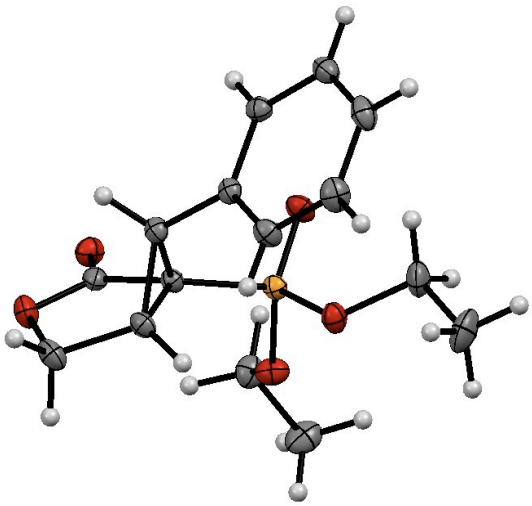
Compound 261



CCDC Number	1421164
Identification code	rjkt1515
Empirical formula	$C_{17}H_{32}O_2Si$
Formula weight	296.51
Temperature/K	110.05(10)
Crystal system	monoclinic
Space group	C2/c
a/Å	23.0721(10)
b/Å	6.5804(2)
c/Å	26.2324(11)
α/°	90
β/°	117.509(5)
γ/°	90
Volume/Å^3	3532.4(3)
Z	8
ρ_{calc}g/cm^3	1.115
μ/mm^{-1}	1.161
F(000)	1312.0
Crystal size/mm^3	0.1481 × 0.0793 × 0.0664
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.6 to 134.142
Index ranges	$-27 \leq h \leq 27$, $-5 \leq k \leq 7$, $-31 \leq l \leq 30$
Reflections collected	9587
Independent reflections	3146 [R_{int} = 0.0255, R_{sigma} = 0.0246]
Data/restraints/parameters	3146/0/187
Goodness-of-fit on F^2	1.043
Final R indexes [I>=2σ (I)]	R_1 = 0.0349, wR_2 = 0.0925
Final R indexes [all data]	R_1 = 0.0386, wR_2 = 0.0961
Largest diff. peak/hole / e Å^{-3}	0.34/-0.29

The crystal was grown by evaporation of the hexane solution which was left standing in a round-bottom flask.

Compound 296c



CCDC Number	1465173
Identification code	rjkt1408
Empirical formula	$C_{15}H_{19}O_5P$
Formula weight	310.27
Temperature/K	110.05(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	12.11290(15)
b/Å	10.43581(14)
c/Å	11.94338(15)
α/°	90
β/°	90.0578(13)
γ/°	90
Volume/Å^3	1509.74(3)
Z	4
ρ_{calc}g/cm^3	1.365
μ/mm^{-1}	0.201
F(000)	656.0
Crystal size/mm^3	0.2985 × 0.1689 × 0.1447
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.178 to 60.064
Index ranges	-17 ≤ h ≤ 17, -14 ≤ k ≤ 13, -16 ≤ l ≤ 16
Reflections collected	13086
Independent reflections	4207 [R_{int} = 0.0209, R_{sigma} = 0.0210]
Data/restraints/parameters	4207/0/197
Goodness-of-fit on F^2	1.080
Final R indexes [I>=2σ (I)]	R_1 = 0.0328, wR_2 = 0.0859
Final R indexes [all data]	R_1 = 0.0368, wR_2 = 0.0886
Largest diff. peak/hole / e Å^{-3}	0.39/-0.34

The crystal was grown by evaporation of diethyl ether layered on chloroform inside a standard NMR tube.

Organic LETTERS

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A One-Pot C−H Insertion/Olefination Sequence for the Formation of α-Alkylidene-γ-butyrolactones

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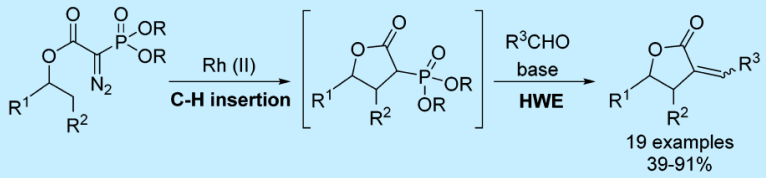
Supporting Information



ABSTRACT: A one-pot C−H insertion/olefination sequence for the conversion of α-diazo-α-(dialkoxyphosphoryl)acetates into α-alkylidene-γ-butyrolactones is reported. The key C−H insertion process is achieved using a catalytic amount of a dirhodium carboxylate catalyst, using operationally simple conditions. The size and electronic properties of the attached substituents were found to influence the regio- and diastereoselectivity of the process. The utility of the process is demonstrated by the synthesis of a known *Staphylococcus aureus* (MRSA) virulence inhibitor.

α-Alkylidene-γ-butyrolactones are found in a vast number of important bioactive natural products; remarkably, approximately 3% of all known natural products contain this structural motif (*e.g.*, **1**−**5**, Figure 1).[1]

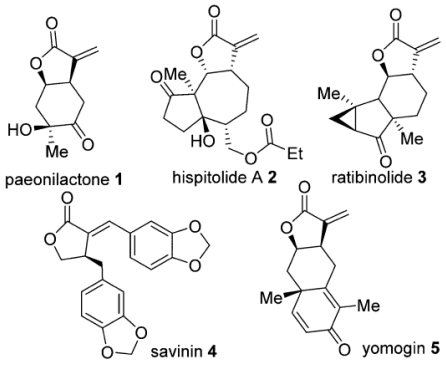


Figure 1. α-Alkylidene-γ-butyrolactone natural products.

A number of methods for the synthesis of α-alkylidene-γ-butyrolactones have been reported,[1,2] most commonly involving initial lactone formation followed by methylenation, e.g. via aldol-type processes. However, many of the reported procedures are either impractical or low yielding due to problems handling the relatively sensitive products and/or the length of the synthetic routes. Previous work in our own laboratory[3] aimed to redress this via the application of telescoped reaction processes.[4] We first reported a telescoped intramolecular Michael/olefination (TIMO)[3] sequence which enabled the construction of α-alkylidene-γ-butyrolactones, in good overall yields, from phosphonates (**6**) derived from γ-hydroxy unsaturated carbonyl compounds.[5] This reaction is initiated by deprotonation and intramolecular Michael addition, to generate an intermediate anion (**7**). An aldehyde may then be added directly to the reaction mixture, resulting in Horner−Wadsworth−Emmons-type (HWE) olefination (Scheme 1), furnishing product **8**. We subsequently showed[3c,d] that acylated phosphoranes, prepared *in situ* by the reaction of functionalized alcohols (**9**) with Bestmann's ylide,[6] react similarly, thus incorporating an additional synthetic step into the telescoped sequence (Scheme 1).

Both procedures are relatively simple to perform experimentally and give good yields of the desired products. However, a notable drawback of both methods is that three functional groups (an alcohol, an alkene, and a carbonyl group) are necessary for the desired reactions to take place, which reduces the generality of the methodology in cases where the starting material synthesis is not trivial. The strategy reported herein is based on an efficient rhodium-catalyzed C−H activation process,[7] which is used in place of the Michael addition in the TIMO sequence. Using this method, the starting material synthesis is simplified dramatically, so that simple, unfunctionalized alcohol derivatives (**10**) may be used as precursors to α-alkylidene-γ-butyrolactones. In addition, Michael acceptors are no longer required, thus increasing the generality of the process.

To the best of our knowledge, only three examples (contained in a single report)[8] of the rhodium-catalyzed C−H insertion of α-diazo-α-(dialkoxyphosphoryl)acetates[9] are known and these reactions were reported to furnish mixtures

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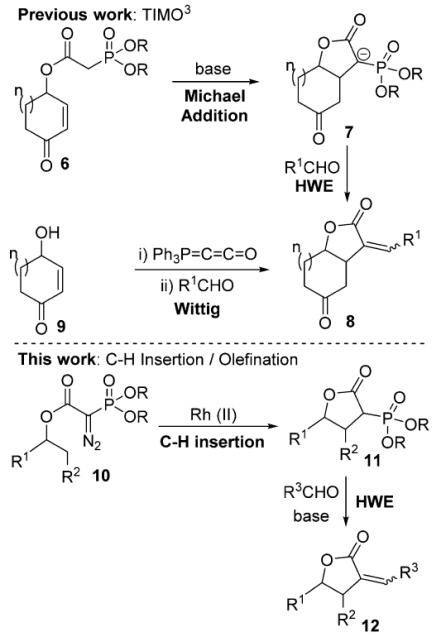
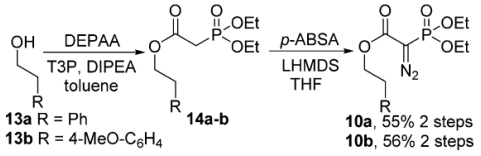
Scheme 1. One-Pot C−H Insertion/Olefination Compared with Previous Michael Addition Methodology



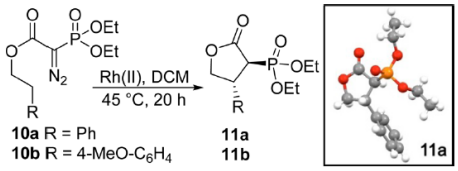
of β- and γ-lactones in moderate/low yield. Related α-diazo-α-(dialkoxyphosphoryl)acetamides are also known to react similarly, but in this case there is a stronger bias toward formation of the β-lactam C−H insertion product.[8,10] Note that the HWE reactions of the C−H insertion products were not examined in any of these reports. A desire to avoid β-lactone formation directed our decision to use substrates **10a** and **10b** to test the key C−H insertion reaction; rhodium(II) carbenoids are highly electrophilic and typically insert preferentially into electron-rich C−H bonds,[7] and thus it was expected that the use of benzylic substrates would expedite the desired γ-lactone formation. The requisite substrates were made in two steps from alcohols **13a** and **13b** via coupling with diethyl phosphonoacetic acid (DEPAA) using propyl phosphonic anhydride (T3P)[11] and *N*,*N*-diisopropylethylamine (DIPEA), followed by a Regitz diazo-transfer reaction (Scheme 2).[12]

Scheme 2. Formation of Diazophosphonates 10a and 10b



Pleasingly, both substrates reacted with 5 mol % of $Rh_2(esp)_2$ in DCM at 45 °C to generate γ-lactones **11a** and **11b** as single regio- and diastereoisomers (Table 1, entries 1−2). The structural assignment of compound **11a** is supported by X-ray crystallography (see Supporting Information).[13,14] Additional optimization experiments (entries 3−12) examined the catalyst choice and its loading, the reaction concentration, and the reaction vessel, revealing that heating the substrate **10b** in an

Table 1. Optimization of Rhodium-Catalyzed C−H Insertion of Diazophosphonates 10a and 10b



entry	sub.	Rh(II) catalyst	catalyst loading [mol %]	DCM (mL/mmol)	yield (%)
1	**10a**	$Rh_2(esp)_2$	5	20	64[a]
2	**10b**	$Rh_2(esp)_2$	5	20	57[a]
3	**10b**	$Rh_2(OAc)_4$	5	20	74[a]
4	**10b**	$Rh_2(oct)_4$	5	20	66[a]
5	**10b**	$Rh_2(tpa)_4$	5	20	59[a]
6	**10b**	$Rh_2(oct)_4$	2	20	70[a]
7	**10b**	$Rh_2(oct)_4$	2	200	30[a,c]
8	**10b**	$Rh_2(OAc)_4$	5	20	77[b]
9	**10b**	$Rh_2(OAc)_4$	2	20	71[b]
10	**10b**	$Rh_2(oct)_4$	10	20	87[b]
11	**10b**	$Rh_2(oct)_4$	5	20	80[b]
12	**10b**	$Rh_2(oct)_4$	2	20	89[b]

[a]Heated at 45 °C in a round-bottom flask fitted with reflux condenser and argon balloon for 20 h. [b]Heated at 45 °C in an oven-dried sealable tube flushed with argon for 20 h. [c]A 51% yield of the product of water insertion [4-methoxyphenethyl 2-(diethoxyphosphoryl)-2-hydroxy-acetate (**15**)] was also isolated in this instance.

oven-dried sealable tube at 45 °C for 20 h with 2 mol % of $Rh_2(oct)_4$ in DCM at a concentration of 20 mL/mmol afforded lactone **11b** in the highest isolated yield (89%, entry 12).

With optimized C−H insertion conditions in hand, attention switched to performing the HWE olefination. As the only byproduct of the cyclization is nitrogen gas, it was expected that this step could be performed in the same reaction vessel without workup or purification. This was achieved by cooling the crude reaction mixture and directly adding KOBu-*t* (1.2−1.5 equiv), followed by paraformaldehyde (2 equiv). In some cases a solvent switch (DCM to THF) was made prior to the HWE reaction. Scoping studies were performed on a range of α-diazo-α-(dialkoxyphosphoryl)acetates **10a**−**10l** (which were synthesized as described in Scheme 2) to generate α-methylene-γ-butyrolactones **12a**−**12l** (Table 2).

The two-step, one-pot telescoped sequence works well using benzylic substrates **10a**−**10c**; cyclization using the optimized C−H insertion conditions followed by treatment with KOBu-*t* (1.2 equiv), then paraformaldehyde (2 equiv), resulted in the formation of α-methylene-γ-butyrolactones **12a**−**12c** in good overall yield (Table 2, entries 1−4). The use of more than 1 equiv of base is noteworthy, as related HWE reactions are known to proceed better with substoichiometric amounts of base.[3,15] Compound **10d** reacted smoothly (entries 5−6), demonstrating that insertion into sterically hindered tertiary C−H bonds is viable. There is also scope for the construction of lactones with a high level diastereocontrol; the reaction of dibenzyl substrate **10e** resulted in the formation of lactone **12e** as a single *trans*-diastereoisomer in excellent overall yield (entry 7). Furthermore, remarkable levels of regiocontrol have been demonstrated; the C−H insertion reaction of unsymmetrical dibenzyl substrate **10f** took place exclusively α- to the 4-MeO−C_6H_4 group,[16] clearly highlighting the strong proclivity of such rhodium(II) carbenoids to insert into electron-rich C−H bonds

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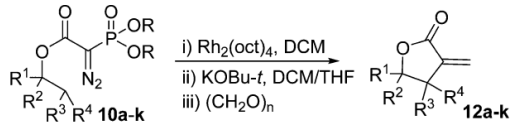
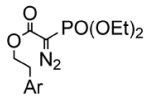
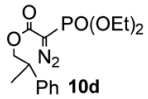
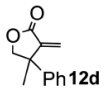
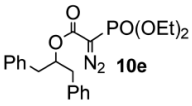
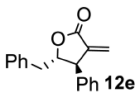
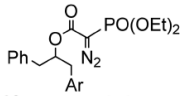
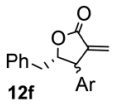
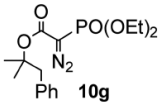
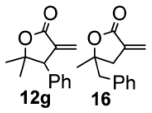
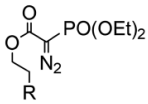
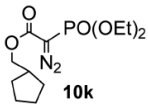
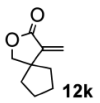
Table 2. One-Pot C−H Insertion/Olefination Sequence for the Formation of α-Methylene-γ-butyrolactones



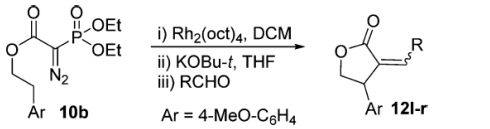
entry	diazo compound	product	yield (%)
			
1	**10a** Ar = Ph	**12a**	74[a]
2	**10b** Ar = 4-MeO-C_6H_4	**12b**	65[a]
3	**10b**	**12b**	71[a,b,c]
4	**10c** Ar = 3,4-OCH_2O-C_6H_3	**12c**	64[a]
5			51[a,b]
6	**10d**	**12d**	59[a,b,c]
7	 **10e**	 **12e**	84[a]
8	 **10f** Ar = 4-MeO-C_6H_4	 **12f**	65[a] (1.6:1)
9	 **10g**	 **12g** **16**	89[a,b,c] (1.45:1)
			
10	**10h** R = *n*-pentyl	**12h**	66[a,b]
11	**10i** R = CH_2Ph	**12i**	62[a,b]
12	**10j** R = CH_2TMS	**12j**	75[a,b,c]
13	 **10k**	 **12k**	79[a,b,c]

[a](i) 2 mol % $Rh_2(oct)_4$, DCM, 45 °C, 20 h; (ii) 1.2 equiv of KOBu-*t*, 0 to −78 °C; (iii) 2 equiv of $(CH_2O)_n$, −78 to 0 °C. [b]Solvent switched from DCM to THF before the HWE. [c]HWE was done with 1.5 equiv of KOBu-*t* and was warmed to rt.

(entry 8). This furnished lactone **12f** in good overall yield, albeit without the high level of diastereocontrol observed during the formation of its analogue **12e**. Substrate **10g** underwent cyclization and olefination in in excellent overall yield but resulted in the formation of a 1.45:1 mixture of the desired product **12g** and its regioisomer **16**, in which C−H insertion has taken place on one of the methyl groups (entry 9). The partial formation of lactone **16** was somewhat surprising given the stereoelectronic bias for insertion into electron-rich C−H bonds, but this is likely to be a result of reduced steric hindrance in the C−H insertion step. Until this point, the formation of lactones **12a−g** all involved electronically favorable C−H insertion into benzylic C−H bonds (*vide supra*). Pleasingly, this assistance to the cyclization is by no means essential; substrates **10h−10j**, which are derived from simple aliphatic alcohols, were all compatible with the two-step sequence, affording lactones **12h−12j** in comparable yields to those of the preceding benzylic substrates (entries 10−12). Crucially, there was no evidence for the formation of *β*- or *δ*-lactone products in any of these reactions. Finally, the reaction of cyclopentyl substrate **10k** generated spirocyclic lactone **12k** in very good overall yield (entry 13).

α-Alkylidene-*γ*-butyrolactones may also be accessed using the same procedure (Table 3). A range of aromatic aldehydes can be used instead of paraformaldehyde in the telescoped two-step, one-pot procedure. The olefination proceeds smoothly at rt when electron-neutral and -deficient benzaldehyde derivatives are used (entries 1−4), but the reaction required heating at reflux when electron-rich piperonal was used (entry 5). In all cases the desired lactones **12l−12p** were obtained in good to excellent overall yield. Aliphatic aldehydes are also compatible, as evidenced by the formation of lactones **12q−12r** (entries 6−7).

Table 3. One-Pot C−H Insertion/Olefination Sequence for the Formation of α-Alkylidene-γ-butyrolactones



entry	R	product	*E*:*Z*	yield (%)
1	Ph	**12l**	1:1	65[a]
2	4-NO_2-C_6H_4	**12m**	1:1.3	69[a,b]
3	2-F-C_6H_4	**12n**	1:1.5	91[a]
4	4-Ph-C_6H_4	**12o**	1:1	61[a]
5	3,4-OCH_2O-C_6H_3	**12p**	1:1.2	56[a,c]
6	CH_3	**12q**	1.2:1	39[a]
7	*n*-butyl	**12r**	1:3.7	67[a]

[a](i) 2 mol % $Rh_2(oct)_4$, DCM, 45 °C, 20 h; (ii) THF; (iii) 1.2 equiv of KOBu-*t*, 0 to −78 °C; (iv) 2 equiv of RCHO, −78 °C to rt. [b]HWE at 0 °C. [c]HWE at reflux.

This method would appear to have great potential in target synthesis, and as a simple demonstration, the synthesis of lactone **17** was completed (Scheme 3). This was the most potent compound found in a recent study of *Staphylococcus aureus* (MRSA) virulence inhibitors.[17] Along with other related *α*-alkylidene-*γ*-butyrolactones, it works by binding covalently to the cysteine residues of several binding proteins involved in *α*-hemolysin expression and, thus, represents a highly promising treatment of antibiotic-resistant *S. aureus* strains. The synthesis commenced by the conversion of commercially available acid **18** into ketone **19** via its Weinreb amide. Subsequent reduction and conversion into the *α*-diazo-*α*-(dialkoxyphosphoryl)acetate

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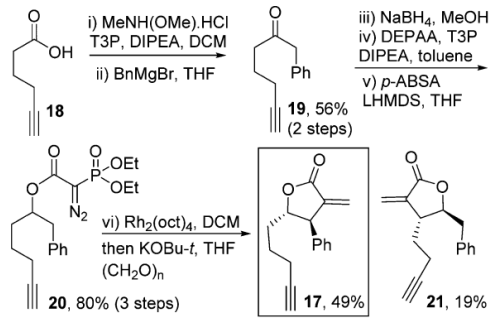
Scheme 3. Synthesis of *S. aureus* Virulence Inhibitor 17



in the usual way furnished precursor **20**. The synthesis was then completed using the standard one-pot C−H insertion/HWE protocol; the desired product **17** was isolated in 49% yield, along with 19% of the regioisomeric lactone **21**. The high level of diastereoselectivity (all *trans*) is noteworthy, as the corresponding *cis*-isomer was found to be a significantly less potent inhibitor.[17]

Rhodium(II) carbenoids have therefore been used to convert alcohol derivatives into a range of α-alkylidene-γ-butyrolactones, via a one-pot C−H insertion/olefination sequence in good overall yields.[18] The convenient starting material synthesis and the mild, straightforward experimental conditions should prove valuable in both academic and industrial research settings.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, spectral data, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) The NMR data of compound **11a** match those reported with the exception of the H-3 resonance: 4.00−4.26 (5 H, m, H-3, 2 × CH_2) [lit. 3.65 (dd, $^3J_{HH}$ = 6.5 Hz, $^3J_{PH}$ = 6.0 Hz, 1H, H-3)]. In view of the fact that the X-ray structure of **11a** was solved it seems likely that there is an error in the previously reported data. Krawczyk, H.; Wasek, K.; Kedzia, J.; Wojciechowski, J.; Wolf, W. M. *Org. Biomol. Chem.* **2008**, *6*, 308.
(15) This has been attributed to the instability of α-methylene-γ-butyrolactones with respect to the base, but in this study, the use of 0.9 equiv of KOBu-*t* led to a lower overall yield in all cases.
(16) The assignment of regioisomer **12f** is supported by HMBC correlation data: H-7 to C-3, H-13 to C-11, H-11 to C-12, no correlation between H-11 and C-6 (see Supporting Information).
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(18) Efforts to develop an asymmetric variant of this reaction using chiral rhodium(II) catalysts are ongoing and will be reported in due course.

Appendix IV: Tetrahedron 2015, 71, 7107–7123

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α-Alkylidene-γ-butyrolactone synthesis via one-pot C–H insertion/olefination: substrate scope and the total synthesis of (±)-cedarmycins A and B

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Dedicated to the memory of Alan Katritzky: inspirational giant of heterocyclic chemistry, collaborator and friend

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ABSTRACT

A system for the synthesis of α-alkylidene-γ-butyrolactones via a one-pot C–H insertion/olefination sequence is described. The process is based on the rhodium catalysed C–H insertion reaction of α-diazo-α-(diethoxyphosphoryl)acetates. The mild reaction conditions, operational simplicity and ready availability of starting materials are all key features. A wide range of successful reaction systems are reported (41 examples) highlighting the generality of the method. The application of this method in the total synthesis of the natural products (±)-cedarmycins A and B is also described.

1. Introduction

The synthesis of α-alkylidene-γ-butyrolactones has captured the interest of synthetic chemists for many years[1] and remains an extremely important endeavour today.[2] One reason for the sustained high level of interest in this field is that a vast number of natural products have been isolated containing this structural motif (α-methylene-γ-butyrolactones are particularly prominent) and this area has been well reviewed.[3] Much of the reported synthetic methodology was developed with such targets in mind, and has facilitated many completed total syntheses. In addition, there is significant interest in the biological activity of α-alkylidene-γ-butyrolactones: this stems from the fact that they are typically very good Michael acceptors, in particular for cysteine residues, thus imparting broad therapeutic potential and the capability to modulate a range of biological processes.[4]

Our research group became interested in the synthesis of α-alkylidene-γ-butyrolactones as part of a research program to develop improved synthetic procedures using tandem/telescoped reaction sequences.[5] In particular a method for α-alkylidene-γ-butyrolactone synthesis based on an intramolecular Michael addition of a phosphonate[6] followed by olefination, either via a Horner–Wadsworth–Emmons (HWE)[6a,b] or Wittig-type olefination.[6c,d] These telescoped intramolecular Michael/olefination protocols (TIMO) enable functionalised hydroxy-enone derivatives to be converted into alkylidene-γ-butyrolactones in one-pot, in good overall yield (e.g., **1**→**3**, Scheme 1).[6] More recently, we reported a modified version of this protocol in which the key C–C bond is installed via a rhodium(II) catalysed C–H insertion reaction of a diazo-phosphonate, before performing the olefination via HWE olefination in the same way (**4**→**6**, Scheme 1).[7]

A key advantage of the new C–H insertion methodology is the comparative simplicity of the requisite starting materials. Unfunctionalised alcohol derivatives can be used in place of the hydroxyl-enone derivatives required for the TIMO reaction, which greatly increases the generality and synthetic potential of this method. The key C–H insertion step utilises a small amount of a relatively benign, air-stable rhodium(II) carboxylate and furthermore, by using a transition metal catalyst to effect this transformation, the

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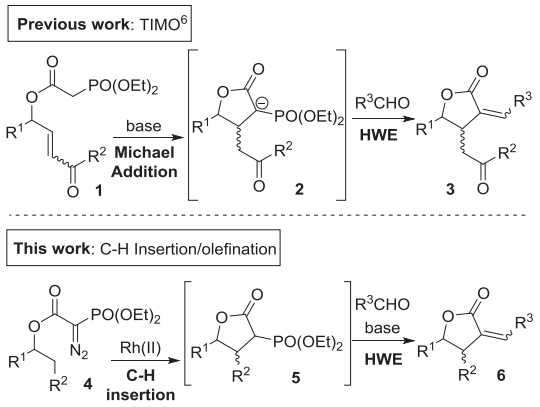


Scheme 1. Telescoped approaches to α-alkylidene-γ-butyrolactones.

possibility of developing an asymmetric variant is introduced.[8] In a recent preliminary communication[7] in this area we described the optimisation of the key procedure, initial scoping studies and the application of the methodology towards the synthesis of a *Staphylococcus aureus* (MRSA) virulence inhibitor (**7**, Fig. 1).[2g,7] Herein we report significantly expanded substrate scope results and discuss the strengths and limitations of the methodology along with some stereochemical, regiochemical and stereoelectronic aspects. The successful application of this methodology towards the first total synthesis of the natural product (±)-cedarmycin A (**8a**), as well as the synthesis of closely related (±)-cedarmycin B (**8b**), is also described.[9]

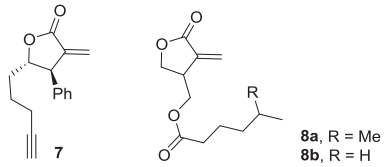
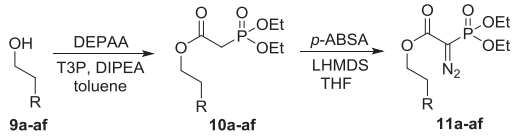


Fig. 1. MSRA inhibitor **7** and (±)-cedarmycins A and B.

2. Results and discussion

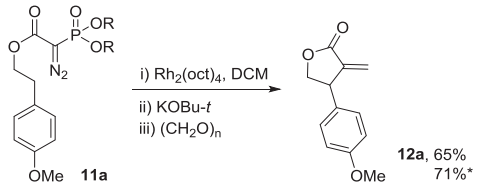
The requisite diazophosphonate substrates **11a**–**af** were made in two steps from alcohols **9a**–**af**. The alcohols were first coupled with diethyl phosphonoacetic acid (DEPAA) using propyl phosphonic anhydride (T3P)[10] and *N*,*N*-diisopropylethylamine (DIPEA); we have found T3P to be an excellent coupling reagent for a variety of applications[5c,e,11] and in the majority of cases the esters **10a**–**af** were formed in excellent yields (usually >95%) and required no purification other than aqueous work-up (Scheme 2). This was followed by a Regitz diazo-transfer reaction to furnish the required diazophosphonates, typically in good unoptimised yield (23–89%).[12] Note that LHMDS was used as the base for these transformations as, in our hands, it generally afforded higher yields



Scheme 2. Formation of diazophosphonates.

of the diazo product than more common procedures, in which either sodium hydride, KOBu-*t* or triethylamine are typically used.[13]

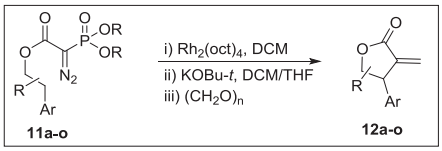
Initial efforts focused on the reactions of homobenzyl alcohol derivatives, along with their heteroaromatic analogues. This was because related rhodium carbenoids are reported to undergo C–H insertion preferentially into electron-rich positions (e.g., benzylic C–H bonds).[14] The formation of unwanted four-membered ring side products was considered to be a genuine concern during this process, based on literature precedent for similar transformations,[13a,15] and hence these substrates, which were expected to be biased towards the formation of the desired five-membered ring γ-lactones, were chosen in order to probe the key reaction. Optimisation experiments were first performed using diazophosphonate **11a** (Scheme 3). It was found that the C–H insertion reaction worked best when performed at 45 °C for 20 h using 2 mol % of $Rh_2(oct)_4$ in DCM.[7] Conditions for the HWE olefination were based on those developed as part of the TIMO reaction sequence described above;[6] minor modifications made were to increase the number of equivalents of KOBu-*t* (from 0.9 up to 1.2–1.5 equiv) and to reduce the excess of paraformaldehyde used (from typically 5 equiv down to 2). The use of more than 1 equiv of base is noteworthy as related HWE reactions are known to proceed better with substoichiometric amounts of base.[6,17] Given that nitrogen gas is the only byproduct formed during the C–H insertion step, it was predicted that these two steps could be performed in the one-pot without work-up or purification. Indeed, this proved to be the case; the most straightforward procedure is performed by conducting the C–H insertion step in DCM as described above, before cooling the crude reaction mixture and directly adding KOBu-*t* (1.2–1.5 equiv), followed by paraformaldehyde (2 equiv). When applied to diazophosphonate **11a**, this telescoped one-pot sequence resulted in the formation of α-methylene-γ-butyrolactone **12a** in 65% overall yield (Scheme 3). It was later found that performing a solvent switch (DCM to THF) between the C–H insertion and HWE steps, led to a small increase in yield to 71%. HWE reactions are most commonly performed in ethereal solvents rather than chlorinated, and this most likely accounts for the observed improvement.[16] Note that no further manipulation was performed during this solvent switch; the DCM was simply removed under vacuum and THF was added back into the same reaction vessel, before the HWE reaction was completed as described above.

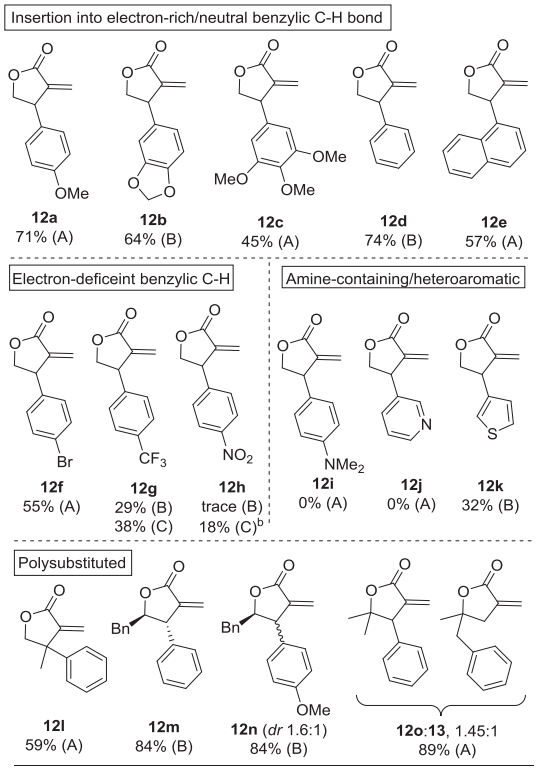


Scheme 3. Formation of α-methylene-γ-butyrolactone **12a**. *A solvent switch (DCM to THF) was performed following step (i).

These conditions were then applied to a range of homobenzyl alcohol derivatives, as well as some heteroaromatic variants (Table 1). Electron-rich/neutral benzene derivatives generally react well in the two-step telescoped procedure, furnishing α-methylene-γ-butyrolactones **12a**–**e** in moderate to good yields (45–74%). As already discussed, related rhodium carbenoids are reported to insert preferentially into electron-rich C–H bonds, hence electron-deficient benzene derivatives were expected to be poorer substrates in comparison. Pleasingly, substitution with a *para*-bromo group appears not to significantly impair the reaction as product **12f** was formed in reasonable yield (55%) under the standard conditions; the incorporation of a bromo-substituent in this example is

Table 1
One-pot C–H insertion/olefination sequence for the formation of α-methylene-γ-butyrolactones: aromatic substrates[a]





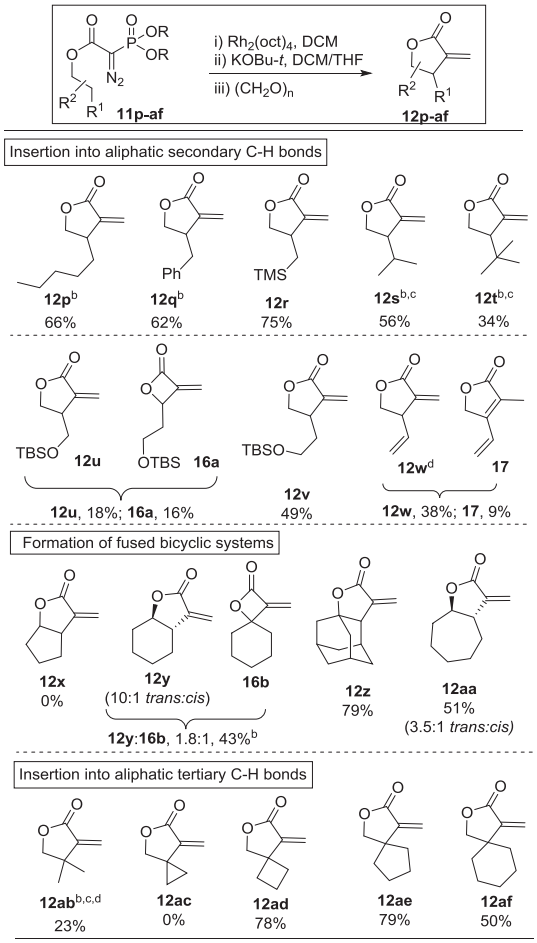
[a] Conditions (A) i) 2 mol % $Rh_2(oct)_4$, DCM (0.1 M), 45 °C, 20 h; ii) Remove DCM *in vacuo* then add THF; iii) 1.5 equiv KOBu-*t*, 0 °C to –78 °C; iv) 2 equiv $(CH_2O)_n$, –78 °C to RT. (B) i) 2 mol % $Rh_2(oct)_4$, DCM (0.1 M), 45 °C, 20 h; ii) 1.2 equiv KOBu-*t*, 0 °C to –78 °C; iii) 2 equiv $(CH_2O)_n$, –78 °C to 0 °C. (C) i) 5 mol % $Rh_2(oct)_4$, DCM (0.1 M), 45 °C, 20 h; ii) 0.9 equiv KOBu-*t*, 0 °C to –78 °C; iii) 10 equiv $(CH_2O)_n$, –78 °C to 0 °C.

[b] $Rh_2(esp)_2$ used in place of $Rh_2(oct)_4$.

important as it should facilitate the installation of additional functionality (e.g., in cross-coupling reactions). The yield does drop when a more strongly electron withdrawing trifluoromethyl group is present (**12g**, 29%) and decreases further in the case of *para*-nitro-substituted product (**12h**). In these two examples the yield was increased marginally by using a higher catalyst loading and a greater excess paraformaldehyde, but the overall yields remained relatively low. Thus, a trend is revealed, whereby the isolated yields of products **12f**–**h** decrease as the electron withdrawing ability of the *para*-substituent increases. Nonetheless, the fact that some product was isolated in all of these electronically diverse systems is positive. Indeed, the only homobenzylic substrate that failed to react at all was the *para*-dimethylamine-substituted system (**11i**→**12i**); this result is not at all that surprising, given that Lewis basic residues capable of coordinating to the vacant axial sites of the dirhodium(II) carboxylates are known to deactivate the catalyst.[18,19] Pyridine nitrogen atoms also appear to be incompatible (0% conversion for **11j**→**12j**), presumably for the same reason. Sulfur heteroatoms are better tolerated as evidenced by the formation of thiophene derivative **12k**, albeit in modest yield.

Substrates with additional substitution were next examined (Table 1, **12l**–**o**). Compound **12l** was generated in good yield under the standard conditions, demonstrating that insertion into sterically hindered tertiary C–H bonds can take place (for other examples, see Table 2, **12ab**–**af**). The conversion of dibenzyl substrate

Table 2
One-pot C–H insertion/olefination sequence for the formation of α-methylene-γ-butyrolactones: aliphatic substrates[a]



[a] Conditions i) 2 mol % $Rh_2(oct)_4$, DCM (0.1 M), 45 °C, 20 h; ii) Remove DCM *in vacuo* then add THF; iii) 1.5 equiv KOBu-*t*, 0 °C to –78 °C; iv) 2 equiv $(CH_2O)n$, –78 °C to RT.

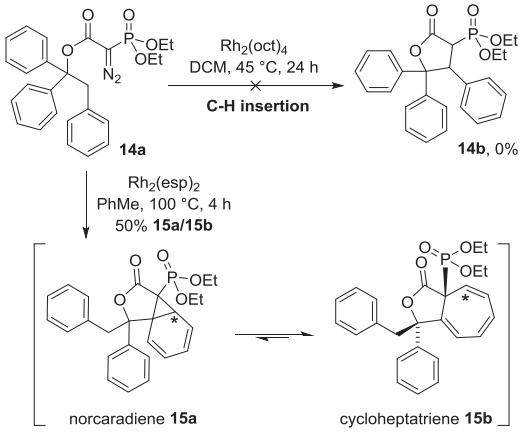
[b] HWE performed at 0 °C

[c] 1.2 equiv KOBu-*t* used.

[d] The comparatively low yield is this case may result from the high volatility of the product

11m into lactone **12m** is noteworthy as it proceeds with excellent diasterocontrol, furnishing compound **12m** as single trans-diastereoisomer in excellent overall yield. Excellent regiocontrol was also observed during the formation of the related product **12n**; in this example, the C–H insertion reaction of unsymmetrical starting material **11n** took place exclusively α-to the 4-MeO-C_6H_4 group,[20] further highlighting the preference for insertion into electron-rich C–H bonds. The reaction of dimethylated substrate **11o** also proceeded in excellent overall yield, but gave a 1.45:1 mixture of the desired product **12o** and its regioisomer **13**, in which insertion into one of the methyl C–H bonds has taken place. The partial formation of lactone **13** highlights the importance of steric factors on the key C–H insertion step. On electronic grounds, the formation of product **12o** is expected, but it appears likely that an interplay between electronic factors and steric hindrance in the C–H insertion step results in the partial formation of isomer **13** in this case. Indeed, the C–H insertion step was found to be sensitive to steric effects in a number of other examples (see later, Table 2), which is reasonable, considering the combined bulk of phosphonate group and the intermediate rhodium carbenoid.

The reaction of the triphenyl substrate **14a**, which did not proceed as planned, is an interesting example (Scheme 4). In this case, treating diazo compound **14a** under our standard C–H insertion conditions resulted in almost complete recovery of the starting material and the formation of a trace amount of an unknown side product, which was not the expected lactone **14b**. To generate a larger amount of this product, in order to confirm its structure, compound **14a** was heated to 100 °C using the more stable catalyst $Rh_2(esp)_2$ in place of $Rh_2(oct)_4$; this led to the complete consumption of the starting material and the isolation of the same product (**15**) in 50% yield, which was assigned as a rapidly equilibrating mixture of two tautomers, norcaradiene **15a** and cycloheptatriene **15b**. This reaction pathway (known as the Buchner reaction) proceeds via cyclopropanation of one of the phenyl rings, followed by reversible electrocyclic ring opening/closing. Rhodium carbenoid mediated variants of this reaction are well-known,[21] and the ratio of the two components in any mixture is dependent on the substituents present.[21c] In this case the equilibrium is biased towards the cycloheptatriene tautomer, as evidenced by the high NMR chemical shifts (δ_H 5.31, δ_C 119.0 in $CDCl_3$) of the position labelled (*) in Scheme 4.[21c] In the solid phase, the product appears to exist exclusively in the cycloheptatriene form **15b**, as the single diastereoisomer shown: this assignment is supported by X-ray crystallographic data (Fig. 2).[22]



Scheme 4. Buchner cyclisation of diazo compound **14a**.

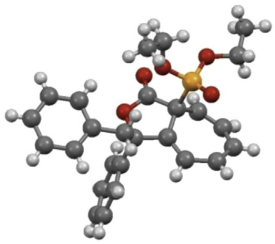


Fig. 2. X-ray crystal structure of cycloheptatriene **15b**.

Attention then turned to the synthesis of α-methylene-γ-butyrolactones from non-aromatic precursors (Table 2). For the reasons described above,[13a,15] it was considered that attempting to direct the rhodium catalysed C–H insertion into less reactive, non-benzylic C–H bonds may lead to competing side reactions (e.g., the formation of β- and/or δ-lactones). However, we are pleased to report that in most cases, efficient α-methylene-γ-butyrolactone synthesis can be achieved. For example, lactones **12p**–**r** were all generated using the standard two-step sequence, with no evidence for the formation of competing β- or δ-lactone products in any of these reactions. The sensitivity of the C–H insertion step to steric factors was highlighted above and further evidence for this can be found in the syntheses of lactones **12s** and **12t**; the desired α-methylene-γ-butyrolactone products were isolated in both cases, but the yields were lower than those of substrate **12p**–**r**, seemingly decreasing in line with the steric bulk of the substituent α-to the C–H insertion site. A similar trend was observed during the syntheses of homologues **12u** and **12v**. The lower homologue **12u** was formed in low yield, along with a significant amount of β-lactone side product **16a**. However, the higher homologue **12v**, in which the bulky OTBS group is more remote from the C–H insertion site, was formed in a much more respectable yield (49%), with no evidence of β-lactone formation. The formation of lactone **12w**, via insertion into an allylic C–H bond, is noteworthy as cyclopropanation may have been expected to compete with C–H insertion in this case. Pleasingly, no evidence for the formation of the alternative cyclopropane product was observed, although a small amount of known butenolide **17**,[23] which presumably forms via isomerisation of the methylene alkene of **12w**, was also isolated.

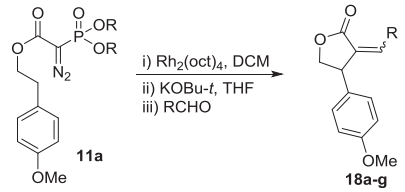
Next, attention turned to the synthesis of bicyclic ring scaffolds (**12x**–**aa**). Unfortunately the cyclopentane-fused bicyclic product **12x** was not formed under the standard reaction conditions, which instead furnished a complex mixture of unidentified products. The analogous cyclohexane-fused product proceeded better, although the C–H insertion was not as regioselective as most other examples, generating a mixture of γ-lactone and β-lactone products (**12y**/**16b** 1.8:1). More positively, the α-methylene-γ-butyrolactone **12y** was formed with very good diasterocontrol; a 10:1 trans/cis ratio of the two possible fused ring systems was observed, with C–H insertion taking place predominantly into the equatorial C–H bond. The process worked extremely well for the formation of adamantanol-derived lactone **12z**, which was formed in very good yield over the two-step sequence (79%). Lactone **12aa**, which is derived from cycloheptanol, was also formed in good yield, with reasonable diastereoselectivity (trans/cis 3.5:1), with no evidence of β-lactone formation. This example is likely to be important in target synthesis, given that α-methylene-γ-butyrolactone scaffolds based on fused five- and seven-membered rings of this type are particularly prevalent in nature.[3]

γ-Lactone products formed via insertion into tertiary C–H bonds typically proceed well. First, known lactone **12ab**[24] was formed via insertion into an *iso*-butyl C–H bond. Note that the

isolated yield in this case was low (23%) but that no side products or starting material were detected in the crude ^{1}H NMR spectra for this reaction; the poor yield is likely to be a result of the high volatility of the product. We then went on to examine the formation of spirocyclic products **12ac**–**af**. Attempts to form the spirocyclic cyclopropane adduct **12ac** failed under the standard conditions, but pleasingly the analogous four-, five- and six-membered ring variants all furnished the desired products **12ad**–**af** in good overall yields (50–79%).

As described in our previous communication,[7] α-alkylidene-γ-butyrolactones may also accessed using the same procedure (Table 3). Diazophosphonate **11a** can treated under the standard conditions for C–H insertion, before performing the HWE step using a range of aromatic and aliphatic aldehydes in place of paraformaldehyde, affording products **18a**–**g** as mixtures of *E*- and *Z*-isomers in fair to excellent overall yield (36–91%).

Table 3
One-pot C–H insertion/olefination sequence for the formation of α-alkylidene-γ-butyrolactones from **11a**[a]



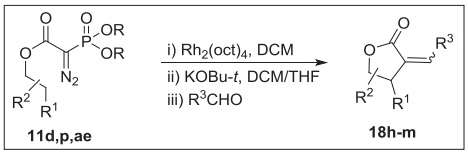
Entry	R	Product	*E*/*Z*	Yield (%)
1	Ph	**18a**	1:1	65
2	4-NO_2–C_6H_4	**18b**[b]	1:1.3	69
3	2-F–C_6H_4	**18c**	1:1.5	91
4	4-Ph–C_6H_4	**18d**	1:1	61
5	3,4-OCH_2O–C_6H_3	**18e**[c]	1:1.2	56
6	CH_3	**18f**	1.2:1	39
7	*n*-Butyl	**18g**	1:3.7	67

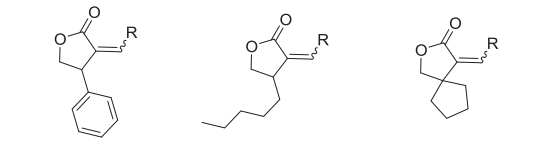
[a] Conditions: (i) 2 mol % $Rh_2(oct)_4$, DCM (0.1 M), 45 °C, 20 h; (ii) remove DCM in vacuo then add THF; (iii) 1.5 equiv KOBu-*t*, 0 °C to −78 °C; (iv) 2 equiv RCHO, −78 °C to rt.
[b] HWE was performed at 0 °C.
[c] HWE was performed at reflux.

We have since gone on to show that three other diazophosphonates (**11d**, **11p**, **11ae**) can also be used to furnish alkylidene-γ-butyrolactones (Table 4). The substrates chosen include one benzylic, one aliphatic and one spirocyclic system and each was reacted with an aromatic and aliphatic aldehyde, to demonstrate the generality of the methodology. As above, the products **18h**–**m** were formed as mixtures of *E*- and *Z*-isomers, with partial diastereoselectivity for the *Z*-isomer in some cases, typically in good overall yields (32–77%). Note that all of these examples are unoptimised and were performed using the standard reaction conditions, with the exception of lactone **18m**. In this case, the HWE reaction did not proceed at room temperature (as indicated by TLC analysis) hence this step was performed at reflux.

As described above, there is an abundance of biologically important compounds containing the α-alkylidene-γ-butyrolactone motif found in nature.[1–4] Future applications of this methodology in the synthesis of such natural product targets are anticipated, as demonstrated by the successful total syntheses of (±)-cedarmycins A and B (**8a** and **8b**, Scheme 5).[9] Thus, lactone **12u** (for its synthesis, see Table 2 above) was first treated with TBAF to cleave the silyl protecting group to furnish alcohol **19**, before coupling it with each of the acid chlorides **20a** and **20b** under standard conditions to complete both syntheses. Both sets of spectral data were in full

Table 4
One-pot C–H insertion/olefination sequence for the formation of α-alkylidene-γ-butyrolactones[a]



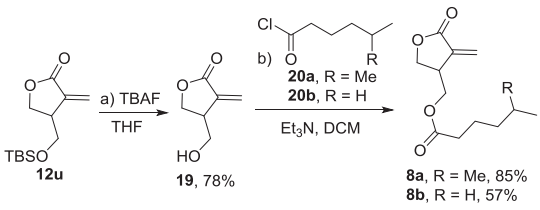


18h, R = 4-NO_2-C_6H_4 65%, *E*:Z 1:1
18i, R = *n*-butyl, 56%, *E*:Z 1:3.3

18j, R = 4-NO_2-C_6H_4 73%, *E*:Z 1:1
18k, R = *n*-butyl, 77%, *E*:Z 1:2.7

18l, R = 4-NO_2-C_6H_4 55%, *E*:Z 1.4:1
18m[b], R = *n*-butyl, 32%, *E*:Z 1:2.4

[a] Conditions (A) i) 2 mol % $Rh_2(oct)_4$, DCM (0.1 M), 45 °C, 20 h; ii) Remove DCM *in vacuo* then add THF; iii) 1.5 equiv KOBu-*t*, 0 °C to –78 °C; iv) 2 equiv $(CH_2O)_n$, –78 °C to RT.
[b] HWE was performed at reflux



Scheme 5. The total syntheses of (±)-cedarmycins A and B.

agreement with those published[9] and in the case of (±)-cedarmycin A, this is its first reported total synthesis and thus confirms the proposed structure.[25] Of course, both of these syntheses are very simple, but they do serve to highlight the relative ease with which natural product targets can be accessed from simple precursors using C–H activation chemistry.

3. Conclusion

The telescoped C–H insertion/olefination sequence described has been used to convert simple alcohol derivatives into a wide range of α-alkylidene-γ-butyrolactones, typically in good overall yield (in total, the formation of 41 distinct α-alkylidene-γ-butyrolactone products are described). The reaction conditions are mild, straightforward to perform and applicable to a wide range of substrates. Furthermore, the products themselves are biologically important, hence the methods developed are expected to be widely used by academic and industrial research groups. The application of these methods in natural product synthesis has also been demonstrated during the synthesis of (±)-cedarmycins A and B. The methodology appears to be very well suited to natural product synthesis and more complex biologically important targets are currently under investigation, the results of which will be reported in due course.

4. Experimental

4.1. General aspects

Except where stated, all reagents were purchased from commercial sources and used without further purification and all experimental procedures were carried out under an atmosphere of argon. Anhydrous CH_2Cl_2, toluene and diethyl ether were obtained from an Innovative Technology Inc. PureSolv® solvent purification system. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl immediately before use. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer, operating at 400 MHz and 100 MHz, respectively. All spectral data was acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peak, δ_H 7.26 and δ_C 77.0 for $CDCl_3$ was used as a reference. Coupling constants (J) are reported in hertz (Hz) to the nearest 0.1 Hz. The multiplicity abbreviations used are: s singlet, d doublet, t triplet, q quartet, m multiplet. Signal assignment was achieved by analysis of DEPT, COSY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on either a ThermoNicolet IR-100 spectrometer with NaCl plates as a thin film dispersed from either CH_2Cl_2 or $CDCl_3$, or a PerkinElmer UATR II spectrometer and the data are assigned as being strong (s), medium (m), weak (w) or broad (br) signals. Mass spectra (low- and high-resolution) were obtained by the University of York Mass Spectrometry Service, using electrospray ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using Gallenkamp apparatus and are uncorrected. Thin layer chromatography was carried out on Merck silica gel 60F_{254} pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. Flash column chromatography was carried out using slurry packed Fluka silica gel (SiO_2), 35–70 μm, 60 Å, under a light positive pressure, eluting with the specified solvent system. Petrol refers to petroleum ether boiling point 40–60 °C. Ether refers to diethyl ether. Experimental procedures and characterisation data for compounds **7**, **9m**, **9n**, **10a**,**b**, **10d**, **10l**–**o**, **10p**–**r**, **10ae**, **11a**,**b**, **11d**, **11l**–**o**, **11p**–**r**, **11ae**, **12a**,**b**, **12d**, **121**–**o**, **12p**–**r**, **12ae**, **13** and **18a**–**g** can be found in our previous communication.[7]

4.2. General experimental procedures

The majority of alcohols were commercially available. Alcohols **9c**,[26] **9i**,[27] **9j**[28] and **9k**[29] were prepared by $LiAlH_4$ reduction of the corresponding carboxylic acids and gave spectral data consistent with those in the literature.

*General procedure A: esterifications using T3P (**9**→**10**)*

To a stirred solution of alcohol **9** (8.00 mmol) in toluene (40 mL) under argon were added sequentially diethyl phosphonoacetic acid (1.35 mL, 8.40 mmol), DIPEA (3.62 mL, 20.8 mmol) and propyl phosphonic anhydride (6.62 g, 10.4 mmol, 50% w/w solution in ethyl acetate/THF). The solution was stirred at rt for 4 h after which time it was diluted with water (50 mL) and extracted with ethyl acetate (3×100 mL) followed by sequential washing of the combined organic extracts with 10% aq HCl (50 mL), satd aq $NaHCO_3$ (50 mL) and brine (50 mL). The organic extracts were dried over $MgSO_4$ and concentrated in vacuo, affording the α-(diethoxyphosphoryl)acetate product **10**, which was used without further purification.

*General procedure B: diazotisation reactions (**10**→**11**)*

To a stirred solution of α-(diethoxyphosphoryl)acetate **10** (5.0 mmol) in THF (25 mL), cooled to −78 °C under argon was added LHMDS (6.0 mL, 6.0 mmol, 1.0 M solution in THF). The solution was allowed to warm to rt and stirred for 10 min. 4-Acetamidobenzenesulfonylazide (1.44 g, 6.0 mmol) was added to the solution forming a suspension. After stirring for 1 h at rt the mixture was diluted with ether (100 mL) and water (25 mL) prior to extraction with ether (3×50 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (2×25 mL), dried over $MgSO_4$, concentrated in vacuo and purified by column chromatography affording the α-diazo-α-(diethoxyphosphoryl)acetate product **11**.

*General procedure C: one-pot Rh(II)-catalysed C–H insertion/HWE (**11**→**12**, DCM)*

To an oven dried sealable tube containing α-diazo-α-(dialkoxyphosphoryl)acetate **11** (0.200 mmol) flushed with argon was added DCM (4.0 mL) followed by $Rh_2(oct)_4$ or $Rh_2(esp)_2$ (2 or 5 mol %). The solution was stirred at 45 °C for 20 h. The solution was cooled to 0 °C prior to the addition of KOBu-*t* (0.9, 1.2 or 1.5 equiv), which was stirred at 0 °C for 60 min and then cooled to −78 °C. Aldehyde (2.0, 5.0 or 10.0 equiv) was added to the solution and stirred for 15 min at −78 °C and a further 2 h at either 0 °C, rt or reflux. The solution was quenched with satd aq NH_4Cl (10 mL) and then diluted with DCM (20 mL). The organic layer was separated and the aqueous extracted with EtOAc (2×20 mL). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo and purified by column chromatography affording the α-methylene/alkylidene-γ-butyrolactone product **12**.

*General procedure D: one-pot Rh(II)-catalysed C–H insertion/HWE (**11**→**12**, DCM with THF switch)*

To an oven dried sealable tube containing α-diazo-α-(dialkoxyphosphoryl)acetate **11** (0.200 mmol) flushed with argon was added DCM (4.0 mL) followed by $Rh_2(oct)_4$ or $Rh_2(esp)_2$ (2 or 5 mol %). The solution was stirred at 45 °C for 20 h and then concentrated in vacuo. The residue was diluted with THF (4.0 mL) and cooled to 0 °C prior to the addition of KOBu-*t* (0.9, 1.2 or 1.5 equiv), which was stirred at 0 °C for 60 min and then cooled to −78 °C. Aldehyde (2.0, 5.0 or 10.0 equiv) was added to the solution and stirred for 15 min at −78 °C and a further 2 h at either 0 °C, rt or reflux. The solution was quenched with satd aq NH_4Cl (10 mL) and then diluted with DCM (20 mL). The organic layer was separated and the aqueous extracted with EtOAc (2×20 mL). The organic extracts were dried over Na_2SO_4, concentrated in vacuo and purified by column chromatography affording the α-methylene/alkylidene-γ-butyrolactone product **12**.

4.3. 3,4,5-Trimethoxyphenethyl 2-(diethoxyphosphoryl)acetate (10c)

Synthesised using general procedure A affording the *title compound* as a yellow oil (360 mg, 95%); R_f 0.10 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2939w, 2841w, 1733s, 1590s, 1508m, 1459m, 1422m, 1852w, 1238s, 1154w, 1123s, 1047w, 1018s, 967s, 827m, 778m; δ_H (400 MHz, $CDCl_3$) 1.28–1.31 (6H, m), 2.88 (2H, t, J 7.2), 2.94 (2H, d, J 21.5), 3.79 (3H, s), 3.82 (6H, s), 4.07–4.15 (4H, m), 4.32 (2H, t, J 7.2), 6.41 (2H, s); δ_C (100 MHz, $CDCl_3$) 16.2 (d, J 6.2), 34.2 (d, J 134.3), 35.2, 56.0, 60.7, 62.6 (d, J 6.3), 65.9, 105.7, 132.9, 136.6, 153.1, 165.7 (d, J 6.0); δ_P (162 MHz, $CDCl_3$) 20.2; HRMS (ESI$^+$): found: 413.1351; $C_{17}H_{27}NaO_8P$ (MNa^+) requires 413.1336.

4.4. 2-(Naphthalen-1-yl)ethyl 2-(diethoxyphosphoryl)acetate (10e)

Synthesised using general procedure A affording the *title compound* as a yellow oil (1.74 g, 99%); R_f 0.20 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2982w, 1735s, 1598w, 1510w, 1496w, 1445w, 1395w, 1257s, 1163w, 1113m, 1048w, 1019s, 965s, 838w, 798w, 777s, 731s, 696m; δ_H (400 MHz, $CDCl_3$) 1.31 (6H, t, J 7.1), 2.97 (2H, d, J 21.6), 3.44 (2H, t, J 7.5), 4.10–4.17 (4H, m), 4.48 (2H, t, J 7.5), 7.36–7.43 (2H, m), 7.47–7.56 (2H, m), 7.75–7.77 (1H, m), 7.85–7.87 (1H, m), 8.07–8.09 (1H, m); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J 6.2), 32.0, 34.3 (d, J 134.2), 62.6 (d, J 6.2), 65.4, 123.4, 125.4, 125.6, 126.2, 127.0,

127.5, 128.8, 131.9, 133.2, 133.8, 165.8 (d, *J* 6.1); δ_P (162 MHz, $CDCl_3$) 20.3; HRMS (ESI^+): found: 373.1171; $C_{18}H_{23}NaO_5P$ (MNa^+) requires 373.1175.

4.5. 4-Bromophenethyl 2-(diethoxyphosphoryl)acetate (10f)

Synthesised using general procedure A affording the *title compound* as a yellow oil (1.80 g, 96%); R_f 0.23 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2982w, 1735s, 1489m, 1443w, 1393w, 1256s, 1163w, 1114m, 1049w, 1020s, 964s, 804m; δ_H (400 MHz, $CDCl_3$) 1.29 (6H, td, *J* 7.1, 0.5), 2.89 (2H, t, *J* 6.9), 2.92 (2H, d, *J* 21.6), 4.06–4.13 (4H, m), 4.30 (2H, t, *J* 6.9), 7.08 (2H, d, *J* 8.5), 7.39 (2H, d, *J* 8.5); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* 6.2), 34.2 (d, *J* 134.3), 34.2, 62.6 (d, *J* 6.2), 65.5, 120.4, 130.6, 131.5, 136.4, 165.6 (d, *J* 6.1); δ_P (162 MHz, $CDCl_3$) 20.1; HRMS (ESI^+): found: 401.0124; $C_{14}H_{20}^{79}BrNaO_5P$ (MNa^+) requires 401.0124.

4.6. 4-Trifluoromethylphenethyl 2-(diethoxyphosphoryl)acetate (10g)

Synthesised using general procedure A affording the *title compound* as a yellow oil (963 mg, 100%); R_f 0.19 (1:1 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2940s, 2890w, 1712s, 1307m, 1251m, 1146w, 1099m, 1007m, 956w; δ_H (400 MHz, $CDCl_3$) 1.30 (6H, td, *J* 7.1, 0.5), 2.94 (2H, d, *J* 21.6), 3.02 (2H, t, *J* 6.8), 4.11 (4H, dq, *J* 8.8, 7.1), 4.37 (2H, t, *J* 6.8), 7.35 (2H, d, *J* 8.0), 8.17 (2H, d, *J* 8.0); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* 6.2), 34.3 (d, *J* 134.4), 34.7, 62.7 (d, *J* 6.2), 65.3, 125.4 (q, *J* 3.7), 126.9 (q, *J* 271.1), 129.2, 129.7 (q, *J* 32.5), 141.7, 165.7 (d, *J* 6.1); δ_F (376 MHz, $CDCl_3$) −62.4; δ_P (162 MHz, $CDCl_3$) 20.1; HRMS (ESI^+): found: 391.0878; $C_{15}H_{20}F_3NaO_5P$ (MNa^+) requires 391.0893.

4.7. 4-Nitrophenethyl 2-(diethoxyphosphoryl)acetate (10h)

Synthesised using general procedure A affording the *title compound* as an orange oil (4.72 g, 91%); R_f 0.12 (1:1 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2936s, 1712s, 1577m, 1495s, 1371m, 1325m, 1249m, 1145w, 1095m, 1009m, 955w, 842w; δ_H (400 MHz, $CDCl_3$) 1.31 (6H, t, *J* 7.1), 2.94 (2H, d, *J* 21.6), 3.08 (2H, t, *J* 6.7), 4.13 (4H, dq, *J* 8.3, 7.1), 4.39 (2H, t, *J* 6.7), 7.41 (2H, d, *J* 8.8), 8.17 (2H, d, *J* 8.8); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* 6.2), 34.3 (d, *J* 134.6), 34.7, 62.7 (d, *J* 6.2), 64.9, 123.7, 129.8, 145.3, 146.9, 165.6 (d, *J* 6.0); δ_P (162 MHz, $CDCl_3$) 20.0; HRMS (ESI^+): found: 368.0875; $C_{14}H_{20}NNaO_7P$ (MNa^+) requires 368.0870 (−1.3 ppm error).

4.8. 4-(Dimethylamino)phenethyl 2-(diethoxyphosphoryl)acetate (10i)

Synthesised using general procedure A affording the *title compound* as an orange oil (1.77 g, 100%); R_f 0.44 (1:2 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2988w, 1733s, 1522s, 1258s, 1114w, 1019s; δ_H (400 MHz, $CDCl_3$) 1.32 (6H, td, *J* 7.1, *J* 0.5), 2.86 (2H, t, *J* 7.3), 2.91 (6H, s), 2.96 (2H, d, *J* 21.5), 4.14 (4H, dq, *J* 8.2, 7.1), 4.29 (2H, t, *J* 7.3), 6.69 (2H, d, *J* 8.7), 7.10 (2H, d, *J* 8.7); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* 6.4), 33.9, 34.3 (d, *J* 134.2), 40.7, 62.6 (d, *J* 6.2), 66.5, 112.8, 125.1, 129.5, 149.5, 165.8 (d, *J* 6.1); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI^+): found: 366.1444; $C_{16}H_{26}NNaO_5P$ (MNa^+) requires 366.1441.

4.9. 2-(Pyridin-3-yl)ethyl 2-(diethoxyphosphoryl)acetate (10j)

Synthesised using general procedure A affording the *title compound* as a yellow oil (4.49 g, 92%); R_f 0.44 (10:1 DCM/MeOH); ν_{max} (thin film)/cm^{-1} 2938s, 2887w, 1711s, 1468m, 1249s, 1100w, 1034w, 1010m, 957w; δ_H (400 MHz, $CDCl_3$) 1.31 (6H, td, *J* 7.1, 0.5), 2.95 (2H, d, *J* 21.6), 2.97 (2H, t, *J* 6.8), 4.13 (4H, dq, *J* 8.3, 7.1), 4.36 (2H, t, *J* 6.8), 7.25 (1H, ddd, *J* 7.8, 4.8, 0.8), 7.60 (1H, ddd, *J* 7.8, 2.3, 1.7), 8.48–8.51 (2H, m); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* 6.1), 32.1, 34.3 (d, *J* 134.3), 62.7 (d, *J* 6.5), 65.2, 123.5, 133.1, 136.5, 148.0, 150.1, 165.7 (d, *J* 6.1); δ_P (162 MHz, $CDCl_3$) 20.0; HRMS (ESI^+): found: 324.0976; $C_{13}H_{20}NNaO_5P$ (MNa^+) requires 324.0971.

4.10. 2-(Thiophen-3-yl)ethyl 2-(diethoxyphosphoryl)acetate (10k)

Synthesised using general procedure A affording the *title compound* as a yellow oil (2.41 g, 99%); R_f 0.33 (1:1 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2983w, 1734s, 1393w, 1258s, 1115w, 1049w, 1020s, 968s; δ_H (400 MHz, $CDCl_3$) 1.32 (6H, td, *J* 7.1, 0.5), 2.97 (2H, d, *J* 21.6), 3.00 (2H, t, *J* 6.9), 4.14 (4H, dq, *J* 8.3, 7.1), 4.35 (2H, td, *J* 6.9, 0.5), 6.98 (1H, dd, *J* 4.9, 1.3), 7.06 (1H, ddt, *J* 3.0, 1.3, 0.9), 7.27 (1H, dd, *J* 4.9, 3.0); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* 6.4), 29.4, 34.3 (d, *J* 134.4), 62.7 (d, *J* 6.5), 65.4, 121.7, 125.6, 128.2, 137.6, 165.8 (d, *J* 6.2); δ_P (162 MHz, $CDCl_3$) 20.2; HRMS (ESI^+): found: 329.0582; $C_{12}H_{19}NaO_5PS$ (MNa^+) requires 329.0583.

4.11. 3-Methylbutyl 2-(diethoxyphosphoryl)acetate (10s)

Synthesised using general procedure A affording the *title compound* as an orange oil (2.67 g, 100%); R_f 0.28 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2960w, 1735s, 1466w, 1392w, 1261s, 1116m, 1021s, 969m; δ_H (400 MHz, $CDCl_3$) 0.90 (6H, d, *J* 6.6), 1.33 (6H, td, *J* 7.1, 0.4), 1.52 (2H, app. q, *J* 6.9), 1.63–1.76 (1H, m), 2.94 (2H, d, *J* 21.6), 4.12–4.19 (6H, m); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* 6.2), 22.3, 24.8, 34.3 (d, *J* 134.2), 37.1, 62.6 (d, *J* 6.2), 64.2, 165.9 (d, *J* 6.2); δ_P (162 MHz, $CDCl_3$) 20.5; HRMS (ESI^+): found: 289.1356; $C_{11}H_{23}NaO_5P$ (MNa^+) requires 289.1175.

4.12. 3,3-Dimethylbutyl 2-(diethoxyphosphoryl)acetate (10t)

Synthesised using general procedure A affording the *title compound* as an orange oil (2.70 g, 97%); R_f 0.41 (1:2 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2958w, 2870w, 1736s, 1478w, 1396w, 1261s, 1116m, 1023s, 971m; δ_H (400 MHz, $CDCl_3$) 0.92 (9H, s), 1.33 (6H, td, *J* 7.1, 0.5), 1.57 (2H, t, *J* 7.7), 2.94 (2H, d, *J* 21.6), 4.12–4.19 (6H, m); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* 6.3), 29.5, 29.6, 34.3 (d, *J* 134.3), 41.5, 62.6 (d, *J* 6.3), 63.4, 165.9 (d, *J* 6.0); δ_P (162 MHz, $CDCl_3$) 20.5; HRMS (ESI^+): found: 303.1323; $C_{12}H_{25}NaO_5P$ (MNa^+) requires 303.1332.

4.13. 3-((*tert*-Butyldimethylsilyl)oxy)propyl 2-(diethoxyphosphoryl)acetate (10u)

To a solution of NaH (480 mg, 12.0 mmol, 60% dispersion in mineral oil) in THF (20 mL) cooled to 0 °C was added 1,3-propanediol (0.80 mL, 11.0 mmol) dropwise over 5 min. The solution was allowed to warm to rt and stirred for 30 min after which TBSCl (1.51 g, 10.0 mmol) was added then stirred at rt for 1 h. The solution was diluted with water (25 mL), extracted with ether (2×25 mL), washed with brine (25 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude alcohol (1.96 g) was then treated under the conditions of general procedure A affording the *title compound* as a yellow oil (3.32 g, 90% over two steps); R_f 0.22 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2956w, 2930m, 2857w, 1738s, 1473w, 1392w, 1258s, 1100m, 1054w, 1025s, 970m, 836s, 777m; δ_H (400 MHz, $CDCl_3$) 0.04 (6H, s), 0.88 (9H, s), 1.34 (6H, t, *J* 7.1), 1.85 (2H, tt, *J* 6.5, 6.0), 2.96 (2H, d, *J* 21.6), 3.69 (2H, t, *J* 6.0), 4.13–4.20 (4H, m), 4.24 (2H, t, *J* 6.5); δ_C (100 MHz, $CDCl_3$) −5.4, 16.3 (d, *J* 6.2), 18.2, 25.8, 31.7, 34.3 (d, *J* 134.3), 59.2, 62.6 (d, *J* 6.3), 62.6, 165.8 (d, *J* 6.1); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI^+): found: 391.1691; $C_{15}H_{33}NaO_6PSi$ (MNa^+) requires 391.1676.

4.14. 4-((*tert*-Butyldimethylsilyl)oxy)butyl 2-(diethoxyphosphoryl)acetate (10v)

To a solution of NaH (240 mg, 6.00 mmol, 60% dispersion in mineral oil) in THF (10 mL) cooled to 0 °C was added 1,4-butanediol (0.44 mL, 5.50 mmol) dropwise over 5 min. The solution was allowed to warm to rt and stirred for 30 min after which TBSCl (754 mg, 5.00 mmol) was added then stirred at rt for 1 h. The solution was diluted with water (25 mL), extracted with ether (2×25 mL), washed with brine (25 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude alcohol (1.20 g) was then treated under the conditions of general procedure A affording the *title compound* as a yellow oil (1.76 g, 92% over two steps); R_f 0.43 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2955w, 2929w, 2857w, 1737s, 1472w, 1391w, 1255s, 1164w, 1097s, 1052w, 1023s, 968s, 892w, 834s, 774s; δ_H (400 MHz, $CDCl_3$) 0.01 (6H, s), 0.85 (9H, s), 1.31 (6H, td, *J* 7.1, 0.5), 1.51–1.58 (2H, m), 1.65–1.72 (2H, m), 2.93 (2H, d, *J* 21.6), 3.60 (2H, t, *J* 6.2), 4.10–4.17 (6H, m); δ_C (100 MHz, $CDCl_3$) −5.4, 16.3 (d, *J* 6.2), 18.2, 25.1, 25.8, 28.9, 34.2 (d, *J* 134.2), 62.4, 62.6 (d, *J* 6.4), 65.5, 165.8 (d, *J* 6.2); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI^+): found: 405.1833; $C_{16}H_{35}NaO_6PSi$ (MNa^+) requires 405.1833.

4.15. But-3-en-1-yl 2-(diethoxyphosphoryl)acetate (10w)

Synthesised using general procedure A affording the *title compound* as a pale yellow oil (1.24 g, 99%); R_f 0.20 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2983w, 1735s, 1643w, 1445w, 1393w, 1257s, 1163w, 1115m, 1049w, 1019s, 964s, 839w, 782w, 733w; δ_H (400 MHz, $CDCl_3$) 1.33 (6H, td, *J* 7.1, 0.4), 2.40 (2H, app. qt, *J* 6.8, 1.4), 2.96 (2H, d, *J* 21.6), 4.12–4.20 (6H, m), 5.05–5.14 (2H, m), 5.78 (1H, ddt, *J* 17.1, 10.3, 6.8); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* 6.2), 32.8, 34.2 (d, *J* 134.3), 62.6 (d, *J* 6.3), 64.6, 117.4, 133.6, 165.8 (d, *J* 6.1); δ_P (162 MHz, $CDCl_3$) 20.3; HRMS (ESI^+): found: 273.0868; $C_{10}H_{19}NaO_5P$ (MNa^+) requires 273.0862.

4.16. Cyclopentyl 2-(diethoxyphosphoryl)acetate (10x)

Synthesised using general procedure A affording the *title compound* as a yellow oil (1.12 g, 85%); R_f 0.24 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2974m, 2874w, 1730s, 1443w, 1393w, 1368w, 1259s, 1165m, 1114m, 1050w, 1019s, 966s, 839m, 780m; δ_H (400 MHz, $CDCl_3$) 1.34 (6H, td, *J* 7.1, 0.4), 1.54–1.90 (8H, m), 2.92 (2H, d, *J* 21.6), 4.16 (4H, dq, *J* 8.1, 7.1), 5.20 (1H, tt, *J* 5.6, 2.7); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* 6.2), 23.6, 32.4, 34.5 (d, *J* 133.5), 62.5 (d, *J* 6.2), 78.4, 165.5 (d, *J* 6.2); δ_P (162 MHz, $CDCl_3$) 20.7; HRMS (ESI^+): found: 287.1020; $C_{11}H_{21}NaO_5P$ (MNa^+) requires 287.1019.

4.17. Cyclohexyl 2-(diethoxyphosphoryl)acetate (10y)

Synthesised using general procedure A affording the *title compound* as a dark orange oil (4.43 g, 100%); R_f 0.33 (1:1 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2985w, 2937s, 2862m, 1729s, 1258s, 1114w, 1016s, 964s; δ_H (400 MHz, $CDCl_3$) 1.16–1.52 (6H, m), 1.30 (6H, td, *J* 7.1, 0.5), 1.65–1.73 (2H, m), 1.77–1.84 (2H, m), 2.90 (2H, d, *J* 21.6), 4.12 (4H, dq, *J* 8.4, 7.1), 4.76 (1H, tt, *J* 8.7, 4.2); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* 6.2), 23.5, 25.2, 31.3, 34.5 (d, *J* 133.4), 62.4 (d, *J* 6.3), 73.9, 165.1 (d, *J* 6.4); δ_P (162 MHz, $CDCl_3$) 20.6; HRMS (ESI^+): found: 301.1162; $C_{12}H_{23}NaO_5P$ (MNa^+) requires 301.1175.

4.18. Adamantan-1-yl 2-(diethoxyphosphoryl)acetate (10z)

Synthesised using general procedure A affording the *title compound* as a colourless oil (1.53 g, 93%); R_f 0.30 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2981w, 2910s, 2853w, 1728s, 1584w, 1457w, 1393w, 1369w, 1355w, 1321w, 1259s, 1164w, 1103m, 1049w, 1020s, 967s, 890m, 836w, 814w; δ_H (400 MHz, $CDCl_3$) 1.32 (6H, td, *J* 7.1, 0.5), 1.57–1.69 (6H, m), 2.09–2.14 (9H, m), 2.85 (2H, d, *J* 21.4), 4.10–4.18 (4H, m); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* 6.2), 30.7, 35.7 (d, *J* 132.8), 36.0, 41.1, 62.4 (d, *J* 6.2), 82.0, 164.5 (d, *J* 6.3); δ_P (162 MHz, $CDCl_3$) 21.2; HRMS (ESI^+): found: 353.1489; $C_{16}H_{27}NaO_5P$ (MNa^+) requires 353.1488.

4.19. Cycloheptyl 2-(diethoxyphosphoryl)acetate (10aa)

Synthesised using general procedure A affording the *title compound* as a colourless oil (1.45 g, 99%); R_f 0.31 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2982w, 2929m, 2861w, 1728s, 1446w, 1394w, 1266s, 1113m, 1051w, 1021s, 969s; δ_H (400 MHz, $CDCl_3$) 1.32 (6H, td, *J* 7.1, 0.5), 1.35–1.69 (10H, m), 1.85–1.92 (2H, m), 2.91 (2H, d, *J* 21.5), 4.10–4.18 (4H, m), 4.95 (1H, tt, *J* 8.3, 4.3); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* 6.5), 22.7, 28.2, 33.5, 34.6 (d, *J* 133.5), 62.5 (d, *J* 6.2), 76.5, 165.1 (d, *J* 6.2); δ_P (162 MHz, $CDCl_3$) 20.7; HRMS (ESI^+): found: 293.1502; $C_{13}H_{26}O_5P$ (MH^+) requires 293.1512.

4.20. 2-Methylpropyl 2-(diethoxyphosphoryl)acetate (10ab)[15a]

Synthesised using general procedure A affording the *title compound* as a yellow oil (2.02 g, 100%); R_f 0.24 (1:1 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2965m, 1735s, 1394w, 1265s, 1117w, 1052w, 1024s; δ_H (400 MHz, $CDCl_3$) 0.94 (6H, d, *J* 6.7), 1.32 (6H, t, *J* 7.1), 1.95 (1H, app. nonet, *J* 6.7), 2.97 (2H, d, *J* 21.6), 3.92 (2H, d, *J* 6.7), 4.17 (4H, dq, *J* 8.3, 7.1); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* 6.5), 19.0, 27.6, 34.3 (d, *J* 134.0), 62.6 (d, *J* 6.2), 71.6, 165.9 (d, *J* 6.4); δ_P (162 MHz, $CDCl_3$) 20.5; HRMS (ESI^+): found: 275.1018; $C_{10}H_{21}NaO_5P$ (MNa^+) requires 275.1019.

4.21. Cyclopropylmethyl 2-(diethoxyphosphoryl)acetate (10ac)

Synthesised using general procedure A affording the *title compound* as a yellow oil (1.23 g, 98%); R_f 0.23 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2984w, 1731s, 1446w, 1394w, 1369w, 1346w, 1257s, 1164w, 1115m, 1049w, 1018s, 966s, 943w, 889w, 839m; δ_H (400 MHz, $CDCl_3$) 0.27–0.31 (2H, m), 0.55–0.59 (2H, m), 1.09–1.20 (1H, m), 1.34 (6H, t, *J* 7.1), 2.98 (2H, d, *J* 21.5), 3.97 (2H, d, *J* 7.3), 4.14–4.21 (4H, m); δ_C (100 MHz, $CDCl_3$) 3.3, 9.6, 16.3 (d, *J* 6.4), 34.4 (d, *J* 134.2), 62.7 (d, *J* 6.3), 70.3, 165.9 (d, *J* 6.1); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI^+): found: 273.0862; $C_{10}H_{19}NaO_5P$ (MNa^+) requires 273.0862.

4.22. Cyclobutylmethyl 2-(diethoxyphosphoryl)acetate (10ad)

Synthesised using general procedure A affording the *title compound* as a yellow oil (1.31 g, 99%); R_f 0.22 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2980w, 2941w, 1733s, 1445w, 1393w, 1334w, 1259s, 1163w, 1115m, 1049w, 1019s, 964s, 838m, 783m, 609m; δ_H (400 MHz, $CDCl_3$) 1.32 (6H, td, *J* 7.1, 0.5), 1.71–1.96 (4H, m), 2.00–2.08 (2H, m), 2.61 (1H, app. heptet, *J* 7.4), 2.95 (2H, d, *J* 21.6), 4.08–4.19 (6H, m); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* 6.2), 18.3, 24.6, 33.9, 34.3 (d, *J* 133.8), 62.6 (d, *J* 6.2), 69.2, 165.9 (d, *J* 6.2); δ_P (162 MHz, $CDCl_3$) 20.4; HRMS (ESI^+): found: 287.1033; $C_{11}H_{21}NaO_5P$ (MNa^+) requires 287.1019.

4.23. Cyclohexylmethyl 2-(diethoxyphosphoryl)acetate (10af)

Synthesised using general procedure A affording the *title compound* as a yellow oil (1.44 g, 99%); R_f 0.53 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2927s, 2854m, 1737s, 1269s, 1053w, 1026s; δ_H (400 MHz, $CDCl_3$) 0.86–0.96 (2H, m), 1.04–1.24 (3H, m), 1.28 (6H, t, *J* 7.1),

1.54–1.70 (6H, m), 2.91 (2H, d, *J* 21.6), 3.89 (2H, d, *J* 6.6), 4.07–4.14 (4H, m); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* 6.2), 25.5, 26.1, 29.3, 34.1 (d, *J* 134.2), 36.8, 62.5 (d, *J* 6.2), 70.5, 165.7 (d, *J* 6.2); δ_P (162 MHz, $CDCl_3$) 20.5; HRMS (ESI^+): found: 315.1338; $C_{13}H_{25}NaO_5P$ (MNa^+) requires 315.1332.

4.24. 3,4,5-Trimethoxyphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate (11c)

Synthesised using general procedure B affording the *title compound* as a yellow oil (202 mg, 54%); R_f 0.21 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2983w, 2940w, 2841w, 2125s, 1704s, 1590s, 1508m, 1459s, 1422m, 1389m, 1352w, 1274s, 1238s, 1155w, 1124s, 1012s, 977s, 815m, 745m, 589m, 559m; δ_H (400 MHz, $CDCl_3$) 1.29 (6H, td, *J* 7.1, 0.7), 2.87 (2H, t, *J* 6.9), 3.77 (3H, s), 3.80 (6H, s), 4.02–4.19 (4H, m), 4.36 (2H, t, *J* 6.9), 6.38 (2H, s); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* 6.9), 35.4, 53.5 (d, *J* 227.1), 55.9, 60.6, 63.5 (d, *J* 5.6), 65.9, 105.6, 132.8, 136.6, 153.1, 163.1 (d, *J* 12.5); δ_P (162 MHz, $CDCl_3$) 10.4; HRMS (ESI^+): found: 439.1234; $C_{17}H_{25}N_2NaO_8P$ (MNa^+) requires 439.1241.

4.25. 2-(Naphthalen-1-yl)ethyl 2-diazo-2-(diethoxyphosphoryl)acetate (11e)

Synthesised using general procedure B affording the *title compound* as a yellow oil (859 mg, 47%); ν_{max} (thin film)/cm^{-1} 2984w, 2127s, 1708s, 1597w, 1511w, 1445w, 1388w, 1279s, 1215s, 1164w, 1095w, 1020s, 978m, 799m, 778m, 745w; δ_H (400 MHz, $CDCl_3$) 1.32 (6H, td, *J* 7.1, 0.8), 3.45 (2H, t, *J* 7.2), 4.04–4.22 (4H, m), 4.55 (2H, t, *J* 7.2), 7.35–7.43 (2H, m), 7.47–7.57 (2H, m), 7.76–7.78 (1H, m), 7.85–7.88 (1H, m), 8.06–8.08 (1H, m); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* 6.9), 32.2, 53.5 (d, *J* 226.9), 63.6 (d, *J* 5.9), 65.5, 123.4, 125.4, 125.7, 126.3, 127.1, 127.6, 128.8, 131.9, 133.1, 133.8, 163.2 (d, *J* 12.2); δ_P (162 MHz, $CDCl_3$) 10.5; HRMS (ESI^+): found: 399.1075; $C_{18}H_{21}N_2NaO_5P$ (MNa^+) requires 399.1080.

4.26. 4-Bromophenethyl 2-diazo-2-(diethoxyphosphoryl)acetate (11f)

Synthesised using general procedure B affording the *title compound* as a yellow oil (969 mg, 51%); R_f 0.48 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2983w, 2129s, 1708s, 1489w, 1384w, 1279s, 1216w, 1164w, 1094w, 1022s, 979m, 815w, 596w, 560w; δ_H (400 MHz, $CDCl_3$) 1.30 (6H, td, *J* 7.1, 0.8), 2.90 (2H, t, *J* 6.7), 4.02–4.19 (4H, m), 4.36 (2H, t, *J* 6.7), 7.07 (2H, d, *J* 8.5), 7.40 (2H, d, *J* 8.5); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* 6.8), 34.5, 53.8 (d, *J* 228.5), 63.5 (d, *J* 5.8), 65.4, 120.5, 130.6, 131.5, 136.2, 163.1 (d, *J* 12.3); δ_P (162 MHz, $CDCl_3$) 10.4; HRMS (ESI^+): found: 427.0038; $C_{14}H_{18}^{79}BrN_2NaO_5P$ (MNa^+) requires 427.0029.

4.27. 4-Trifluoromethylphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate (11g)

Synthesised using general procedure B affording the *title compound* as a pale yellow oil (386 mg, 36%); R_f 0.44 (1:1 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2941s, 2099s, 1686s, 1308m, 1262m, 1147w, 1106w, 1051w, 1006w; δ_H (400 MHz, $CDCl_3$) 1.31 (6H, td, *J* 7.1, 0.8), 3.03 (2H, t, *J* 6.7), 4.03–4.21 (4H, m), 4.43 (2H, t, *J* 6.7), 7.34 (2H, d, *J* 8.0), 7.56 (2H, d, *J* 8.0); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* 6.8), 34.9, 53.9 (d, *J* 228.8), 63.6 (d, *J* 5.6), 65.3, 125.4 (q, *J* 3.8), 124.1 (q, *J* 271.9), 129.1 (q, *J* 32.3), 129.3, 141.5, 163.3 (d, *J* 11.6); δ_F (376 MHz, $CDCl_3$) −62.4; δ_P (162 MHz, $CDCl_3$) 10.4; HRMS (ESI^+): found: 417.0779; $C_{15}H_{18}F_3N_2NaO_5P$ (MNa^+) requires 417.0798.

4.28. 4-Nitrophenethyl 2-diazo-2-(diethoxyphosphoryl)acetate (11h)

Synthesised using general procedure B affording the *title compound* as a colourless oil (111 mg, 49%); R_f 0.53 (1:2 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2099s, 1681s, 1497s, 1326s, 1261s, 1006m; δ_H (400 MHz, $CDCl_3$) 1.32 (6H, td, *J* 7.1, 0.8), 3.09 (2H, t, *J* 6.6), 4.05–4.23 (4H, m), 4.45 (2H, t, *J* 6.6), 7.40 (2H, d, *J* 8.8), 8.18 (2H, d, *J* 8.8); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* 6.8), 34.9, 53.8 (d, *J* 228.4), 63.6 (d, *J* 5.7), 64.9, 123.7, 129.8, 145.1, 146.9, 163.2 (d, *J* 12.2); δ_P (162 MHz, $CDCl_3$) 10.3; HRMS (ESI^+): found: 394.0762; $C_{14}H_{18}N_3NaO_7P$ (MNa^+) requires 394.9775.

4.29. 4-(Dimethylamino)phenethyl 2-diazo-2-(diethoxyphosphoryl)acetate (11i)

Synthesised using general procedure B affording the *title compound* as a yellow oil (327 mg, 30%); R_f 0.48 (1:1 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2985w, 2128s, 1704s, 1616w, 1523m, 1277s, 1020s; δ_H (400 MHz, $CDCl_3$) 1.32 (6H, td, *J* 7.1, 0.6), 2.85 (2H, t, *J* 7.0), 2.90 (6H, s), 4.04–4.21 (4H, m), 4.33 (2H, t, *J* 7.0), 6.67 (2H, d, *J* 8.7), 7.06 (2H, d, *J* 8.7); δ_C (100 MHz, $CDCl_3$) 15.9 (d, *J* 6.9), 34.0, 40.5, 53.4 (d, *J* 226.5), 63.4 (d, *J* 5.8), 66.3, 112.6, 124.8, 129.4, 149.3, 163.1 (d, *J* 12.3); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI^+): found: 392.1338; $C_{16}H_{24}N_3NaO_5P$ (MNa^+) requires 392.1346.

4.30. 2-(Pyridin-3-yl)ethyl 2-diazo-2-(diethoxyphosphoryl) acetate (11j)

Synthesised using general procedure B affording the *title compound* as a yellow oil (497 mg, 23%); R_f 0.44 (7% MeOH in DCM); ν_{max} (thin film)/cm^{-1} 2939s, 2098s, 1684s, 1262s, 1104w, 1078w, 1008s, 964w; δ_H (400 MHz, $CDCl_3$) 1.32 (6H, td, *J* 7.1, 0.8), 2.98 (2H, t, *J* 6.7), 4.05–4.22 (4H, m), 4.41 (2H, t, *J* 6.7), 7.24 (1H, ddd, *J* 7.8, 4.8, 0.7), 7.56 (1H, ddd, *J* 7.8, 2.3, 1.7), 8.47–8.51 (2H, m); δ_C (100 MHz, $CDCl_3$) 15.8 (d, *J* 6.9), 32.0, 53.5 (d, *J* 226.1), 63.3 (d, *J* 5.8), 65.0, 123.1, 132.7, 136.1, 147.9, 149.9, 162.9 (d, *J* 12.1); δ_P (162 MHz, $CDCl_3$) 10.4; HRMS (ESI^+): found: 350.0876; $C_{13}H_{18}N_3NaO_5P$ (MNa^+) requires 350.0876.

4.31. 2-(Thiophen-3-yl)ethyl 2-diazo-2-(diethoxyphosphoryl) acetate (11k)

Synthesised using general procedure B affording the *title compound* as a yellow oil (871 mg, 52%); R_f 0.43 (1:1 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2989w, 2126s, 1703s, 1274s, 1017s, 977m; δ_H (400 MHz, $CDCl_3$) 1.32 (6H, td, *J* 7.1, 0.8), 2.99 (2H, t, *J* 6.8), 4.05–4.22 (4H, m), 4.39 (2H, t, *J* 6.8), 6.95 (1H, dd, *J* 4.9, 1.3), 7.03 (1H, ddt, *J* 2.9, 1.3, 0.7), 7.25 (1H, dd, *J* 4.9, 2.9); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* 6.9), 29.5, 53.8 (d, *J* 228.2), 63.5 (d, *J* 5.6), 65.3, 121.7, 125.6, 128.1, 137.4, 163.3 (d, *J* 12.2); δ_P (162 MHz, $CDCl_3$) 10.5; HRMS (ESI^+): found: 355.0488; $C_{12}H_{17}N_2NaO_5PS$ (MNa^+) requires 355.0488.

4.32. 3-Methylbutyl 2-diazo-2-(diethoxyphosphoryl)acetate (11s)

Synthesised using general procedure B affording the *title compound* as a pale yellow oil (1.18 g, 67%); R_f 0.65 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2960w, 2125s, 1701s, 1389w, 1272s, 1215w, 1164w, 1116w, 1091w, 1016s, 977m; δ_H (400 MHz, $CDCl_3$) 0.91 (6H, d, *J* 6.6), 1.35 (6H, td, *J* 7.1, 0.8), 1.54 (2H, app. q, *J* 6.8), 1.62–1.75 (1H, m), 4.10–4.26 (4H, m), 4.22 (2H, t, *J* 6.8); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* 6.9), 22.2, 24.8, 37.2, 53.5 (d, *J* 228.2),

63.4 (d, *J* 5.7), 64.1, 163.3 (d, *J* 12.0); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI^+): found: 315.1084; $C_{11}H_{21}N_2NaO_5P$ (MNa^+) requires 315.1080.

4.33. 3,3-Dimethylbutyl 2-diazo-2-(diethoxyphosphoryl)acetate (11t)

Synthesised using general procedure B affording the *title compound* as a pale yellow oil (1.22 g, 66%); R_f 0.49 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2959m, 2880w, 2125s, 1702s, 1276s, 1216w, 1164w, 1119w, 1095w, 1016s, 976m; δ_H (400 MHz, $CDCl_3$) 0.89 (9H, s), 1.31 (6H, td, *J* 7.1, 0.8), 1.54 (2H, t, *J* 7.4), 4.06–4.22 (4H, m), 4.21 (2H, t, *J* 7.4); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* 6.9), 29.4, 29.6, 41.6, 53.5 (d, *J* 228.5), 63.3, 63.4 (d, *J* 5.6), 163.3 (d, *J* 12.3); δ_P (162 MHz, $CDCl_3$) 10.7; HRMS (ESI^+): found: 329.1223; $C_{12}H_{23}N_2NaO_5P$ (MNa^+) requires 329.1237.

4.34. 3-((*tert*-Butyldimethylsilyl)oxy)propyl 2-diazo-2-(diethoxyphosphoryl) acetate (11u)

Synthesised using general procedure B affording the *title compound* as a yellow oil (1.42 g, 60%); R_f 0.30 (2:1 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2964w, 2931w, 2866w, 2128s, 1707s, 1474w, 1395w, 1281s, 1097m, 1024s, 838m, 777w; δ_H (400 MHz, $CDCl_3$) −0.05 (6H, s), 0.79 (9H, s), 1.26 (6H, td, *J* 7.1, 0.8), 1.77 (2H, tt, *J* 6.4, 6.0), 3.69 (2H, t, *J* 6.0), 4.02–4.17 (4H, m), 4.24 (2H, t, *J* 6.4); δ_C (100 MHz, $CDCl_3$) −5.7, 15.9 (d, *J* 6.9), 18.0, 25.6, 31.6, 53.5 (d, *J* 230.0), 58.8, 62.4, 63.3 (d, *J* 5.9), 163.1 (d, *J* 11.6); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI^+): found: 417.1590; $C_{15}H_{31}N_2NaO_6PSi$ (MNa^+) requires 417.1581.

4.35. 4-((*tert*-Butyldimethylsilyl)oxy)butyl 2-diazo-2-(diethoxyphosphoryl)acetate (11v)

Synthesised using general procedure B affording the *title compound* as a yellow oil (1.05 g, 58%); R_f 0.74 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2954w, 2930w, 2857w, 2126s, 1703s, 1473w, 1389w, 1275s, 1257w, 1164w, 1095s, 1019s, 977s, 892w, 834s, 813w, 774s, 746w, 662w, 589m, 560m; δ_H (400 MHz, $CDCl_3$) −0.05 (6H, s), 0.79 (9H, s), 1.26 (6H, td, *J* 7.1, 0.8), 1.45–1.52 (2H, m), 1.61–1.68 (2H, m), 3.54 (2H, t, *J* 6.2), 4.02–4.18 (6H, m); δ_C (100 MHz, $CDCl_3$) −5.6, 15.9 (d, *J* 6.9), 18.0, 25.2, 25.7, 28.7, 53.5 (d, *J* 227.3), 62.2, 63.3 (d, *J* 6.0), 65.4, 163.2 (d, *J* 11.9); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI^+): found: 431.1748; $C_{16}H_{33}N_2NaO_6PSi$ (MNa^+) requires 431.1738.

4.36. But-3-en-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (11w)

Synthesised using general procedure B affording the *title compound* as a yellow oil (790 mg, 60%); R_f 0.43 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2984w, 2126s, 1702s, 1643w, 1445w, 1384w, 1276s, 1164w, 1117w, 1092w, 1019s, 978s, 797m, 746m; δ_H (400 MHz, $CDCl_3$) 1.32 (6H, td, *J* 7.1, 0.8), 2.38 (2H, app. qt, *J* 6.7, 1.3), 4.07–4.23 (6H, m), 5.03–5.11 (2H, m), 5.74 (1H, ddt, *J* 17.1, 10.3, 6.7); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* 6.9), 33.0, 53.7 (d, *J* 226.3), 63.5 (d, *J* 5.9), 64.5, 117.5, 133.4, 163.3 (d, *J* 12.1); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI^+): found: 299.0768; $C_{10}H_{17}N_2NaO_5P$ (MNa^+) requires 299.0767.

4.37. Cyclopentyl 2-diazo-2-(diethoxyphosphoryl)acetate (11x)

Synthesised using general procedure B affording the *title compound* as a yellow oil (1.00 g, 83%); R_f 0.54 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2972m, 2875w, 2125s, 1696s, 1478w, 1443w, 1393w, 1321w, 1274s, 1218w, 1165m, 1121m, 1089w, 1018s, 977m, 959m, 796m, 749m; δ_H (400 MHz, $CDCl_3$) 1.29 (6H, td, *J* 7.1, 0.8), 1.49–1.86 (8H, m), 4.04–4.19 (4H, m), 5.21 (1H, tt, *J* 5.6, 2.7); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* 7.0), 23.4, 32.6, 53.8 (d, *J* 227.0), 63.3 (d, *J* 5.6), 78.6, 163.0 (d, *J* 11.7); δ_P (162 MHz, $CDCl_3$) 10.9; HRMS (ESI^+): found: 313.0930; $C_{11}H_{19}N_2NaO_5P$ (MNa^+) requires 313.0924.

4.38. Cyclohexyl 2-diazo-2-(diethoxyphosphoryl)acetate (11y)

Synthesised using general procedure B affording the *title compound* as a pale yellow oil (2.68 g, 88%); R_f 0.50 (1:1 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2990w, 2937s, 2864m, 2124s, 1694s, 1279s, 1260s, 1115w, 1013s, 976s; δ_H (400 MHz, $CDCl_3$) 1.18–1.50 (6H, m), 1.31 (6H, td, *J* 7.1, 0.8), 1.64–1.71 (2H, m), 1.77–1.82 (2H, m), 4.06–4.22 (4H, m), 4.84 (1H, tt, *J* 8.4, 4.1); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* 7.2), 23.2, 25.1, 31.4, 53.8 (d, *J* 228.0), 63.4 (d, *J* 5.7), 74.0, 162.8 (d, *J* 11.8); δ_P (162 MHz, $CDCl_3$) 10.9; HRMS (ESI^+): found: 327.1082; $C_{12}H_{21}N_2NaO_5P$ (MNa^+) requires 327.1010.

4.39. Adamantan-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate (11z)

Synthesised using general procedure B affording the *title compound* as a white solid (1.21 g, 74%); R_f 0.63 (1:1 hexane/ethyl acetate); mp 51–54 °C; ν_{max} (thin film)/cm^{-1} 2912s, 2855w, 2125s, 1697s, 1457w, 1321m, 1269s, 1219w, 1164w, 1122w, 1023s, 966m; δ_H (400 MHz, $CDCl_3$) 1.30 (6H, td, *J* 7.1, 0.8), 1.60–1.61 (6H, m), 2.07–2.15 (9H, m), 4.05–4.20 (4H, m); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* 6.8), 30.7, 35.9, 41.4, 53.9 (d, *J* 228.4), 63.3 (d, *J* 5.6), 82.9, 162.0 (d, *J* 12.0); δ_P (162 MHz, $CDCl_3$) 11.3; HRMS (ESI^+): found: 379.1384; $C_{16}H_{25}N_2NaO_5P$ (MNa^+) requires 379.1393.

4.40. Cycloheptyl 2-diazo-2-(diethoxyphosphoryl)acetate (11aa)

Synthesised using general procedure B affording the *title compound* as a yellow oil (1.35 g, 89%); R_f 0.52 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2987w, 2930m, 2861w, 2125s, 1694s, 1446w, 1369w, 1322w, 1270s, 1215w, 1164w, 1120m, 1015s, 961s, 885w, 974m, 746s, 590s, 555s; δ_H (400 MHz, $CDCl_3$) 1.26 (6H, td, *J* 7.1, 0.8), 1.31–1.66 (10H, m), 1.77–1.85 (2H, m), 4.01–4.17 (4H, m), 4.96 (1H, tt, *J* 8.1, 4.2); δ_C (100 MHz, $CDCl_3$) 15.8 (d, *J* 7.0), 22.4, 27.9, 33.5, 53.7 (d, *J* 227.0), 63.2 (d, *J* 6.0), 76.5, 162.7 (d, *J* 11.9); δ_P (162 MHz, $CDCl_3$) 10.9; HRMS (ESI^+): found: 341.1226; $C_{13}H_{23}N_2NaO_5P$ (MNa^+) requires 341.1237.

4.41. 2-Methylpropyl 2-diazo-2-(diethoxyphosphoryl)acetate (11ab)[15a]

Synthesised using general procedure B affording the *title compound* as a pale yellow oil (1.62 g, 73%); R_f 0.50 (1:1 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2966m, 2127s, 1702s, 1276s, 1115w, 1019s, 978m; δ_H (400 MHz, $CDCl_3$) 0.89 (6H, d, *J* 6.7), 1.31 (6H, td, *J* 7.1, 0.8), 1.91 (1H, app. nonet, *J* 6.7), 3.93 (2H, d, *J* 6.6), 4.06–4.22 (4H, m); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* 6.9), 18.7, 27.7, 53.7 (d, *J* 227.9), 63.4 (d, *J* 5.7), 71.5, 163.4 (d, *J* 11.9); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI^+): found: 301.0913; $C_{10}H_{19}N_2NaO_5P$ (MNa^+) requires 301.0924.

4.42. Cyclopropylmethyl 2-diazo-2-(diethoxyphosphoryl)acetate (11ac)

Synthesised using general procedure B affording the *title compound* as a yellow oil (850 mg, 64%); R_f 0.43 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2986w, 2908w, 2125s, 1700s, 1446w, 1394w, 1348m, 1275s, 1216w, 1164w, 1115w, 1082w, 1018s, 977w, 958s, 796m, 746m, 590m, 560m; δ_H (400 MHz, $CDCl_3$) 0.25–0.29

(2H, m), 0.52–0.57 (2H, m), 1.07–1.17 (1H, m), 1.33 (6H, t, *J* 7.1), 4.01 (2H, d, *J* 7.3), 4.10–4.25 (4H, m); δ_C (100 MHz, $CDCl_3$) 3.2, 9.8, 16.1 (d, *J* 6.9), 53.9 (d, *J* 226.8), 63.6 (d, *J* 5.6), 70.3, 163.5 (d, *J* 12.2); δ_P (162 MHz, $CDCl_3$) 10.6; HRMS (ESI^+): found: 299.0771; $C_{10}H_{17}N_2NaO_5P$ (MNa^+) requires 299.0767.

4.43. Cyclobutylmethyl 2-diazo-2-(diethoxyphosphoryl)acetate (11ad)

Synthesised using general procedure B affording the *title compound* as a brown oil (949 mg, 68%); R_f 0.50 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2981w, 2942w, 2869w, 2125s, 1700s, 1445w, 1391w, 1335w, 1276s, 1216w, 1164w, 1117w, 1095w, 1019w, 977m, 797m, 747m, 590m, 560m; δ_H (400 MHz, $CDCl_3$) 1.34 (6H, td, *J* 7.1, 0.8), 1.72–1.97 (4H, m), 1.99–2.08 (2H, m), 2.57–2.68 (1H, m), 4.09–4.25 (6H, m); δ_C (100 MHz, $CDCl_3$) 16.1 (d, *J* 7.0), 18.3, 24.5, 34.0, 53.8 (d, *J* 228.6), 63.5 (d, *J* 5.9), 69.2, 163.6 (d, *J* 12.0); δ_P (162 MHz, $CDCl_3$) 10.8; HRMS (ESI^+): found: 313.0917; $C_{11}H_{19}N_2NaO_5P$ (MNa^+) requires 313.0924.

4.44. Cyclohexylmethyl 2-diazo-2-(diethoxyphosphoryl)acetate (11af)

Synthesised using general procedure B with NaH (1.2 equiv, 60% dispersion in mineral oil) in place of LHMDS affording the *title compound* as a yellow oil (410 mg, 68%); R_f 0.85 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2930s, 2131s, 1705s, 1280s, 1024s; δ_H (400 MHz, $CDCl_3$) 0.93–1.04 (2H, m), 1.11–1.30 (3H, m), 1.36 (6H, td, *J* 7.1, 0.8), 1.55–1.77 (6H, m), 4.01 (2H, d, *J* 6.5), 4.11–4.27 (4H, m); δ_C (100 MHz, $CDCl_3$) 16.0 (d, *J* 7.1), 25.5, 26.2, 29.3, 37.1, 53.7 (d, *J* 227.4), 63.5 (d, *J* 5.6), 70.6, 163.5 (d, *J* 12.0); δ_P (162 MHz, $CDCl_3$) 10.9; HRMS (ESI^+): found: 341.1228; $C_{13}H_{23}N_2NaO_5P$ (MNa^+) requires 341.1237.

4.45. (*SR*)-3-Methylene-4-(3,4,5-trimethoxyphenyl)dihydrofuran-2(3*H*)-one (12c)

Synthesised using general procedure D with 3,4,5-trimethoxyphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **11c** (77 mg, 0.185 mmol), DCM (3.7 mL), $Rh_2(oct)_4$ (2.9 mg, 3.7 μmol), THF (3.7 mL), KOBu-*t* (31.1 mg, 0.278 mmol) and paraformaldehyde (11.1 mg, 0.370 mmol). The HWE was performed at rt. Purification by column chromatography (2:1 hexane/ethyl acetate) afforded the *title compound* as a colourless oil (22 mg, 45%); R_f 0.26 (2:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2937w, 1763s, 1660w, 1591m, 1509m, 1461m, 1425m, 1347w, 1242m, 1124s, 1013m; δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s), 3.84 (6H, s), 4.17–4.24 (2H, m), 4.68–4.75 (1H, m), 5.56 (1H, d, *J* 2.6), 6.40–6.41 (3H, m); δ_C (100 MHz, $CDCl_3$) 45.9, 56.2, 60.8, 72.7, 104.7, 124.3, 135.2, 137.4, 138.5, 153.7, 170.1; HRMS (ESI^+): found: 287.0892; $C_{14}H_{16}NaO_5$ (MNa^+) requires 287.0890.

4.46. (*SR*)-3-Methylene-4-(naphthalen-1-yl)dihydrofuran-2(3*H*)-one (12e)

Synthesised using general procedure D with 2-(naphthalen-1-yl)ethyl 2-diazo-2-(diethoxyphosphoryl)acetate **11e** (82 mg, 0.218 mmol), DCM (4.4 mL), $Rh_2(oct)_4$ (3.4 mg, 4.4 μmol), THF (4.4 mL), KOBu-*t* (36.7 mg, 0.327 mmol) and paraformaldehyde (13.1 mg, 0.436 mmol). The HWE was performed at rt. Purification by column chromatography (4:1 hexane/ethyl acetate) afforded the *title compound* as a colourless oil (28 mg, 57%); R_f 0.45 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 3050w, 2918w, 1759s, 1662w, 1598w, 1511w, 1398m, 1261w, 1230w, 1111s, 1022m, 948w, 802m, 780s; δ_H (400 MHz, $CDCl_3$) 4.36 (1H, dd, *J* 9.0, 6.3), 4.89 (1H, app. t, *J* 9.0), 5.03–5.08 (1H, m), 5.60 (1H, d, *J* 2.7), 6.51 (1H, d, *J* 3.0), 7.38–7.40 (1H, m), 7.47 (1H, app. t, *J* 7.7), 7.53–7.60 (2H, m), 7.81–7.88 (2H, m), 7.91–7.95 (1H, m); δ_C (100 MHz, $CDCl_3$) 41.6, 72.0, 124.5, 122.6, 125.0, 125.5, 126.1, 126.7, 128.5, 129.3, 131.0, 134.2, 135.6, 137.6, 170.4; HRMS (ESI^+): found: 247.0728; $C_{15}H_{12}NaO_2$ (MNa^+) requires 247.0730.

4.47. (*SR*)-4-(4-Bromophenyl)-3-methylenedihydrofuran-2(3*H*)-one (12f)

Synthesised using general procedure D with 4-bromophenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **11f** (90 mg, 0.222 mmol), DCM (4.4 mL), $Rh_2(oct)_4$ (3.5 mg, 4.4 μmol), THF (4.4 mL), KOBu-*t* (37.4 mg, 0.333 mmol) and paraformaldehyde (13.3 mg, 0.444 mmol). The HWE was performed at rt. Purification by column chromatography (8:1 hexane/ethyl acetate) afforded the *title compound* as a pale yellow oil (31 mg, 55%); R_f 0.40 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2972w, 2913w, 1761s, 1666w, 1590w, 1489m, 1412m, 1274w, 1231m, 1107s, 1010s, 947w, 825s; δ_H (400 MHz, $CDCl_3$) 4.17–4.27 (2H, m), 4.71 (1H, app. t, *J* 8.4), 5.48 (1H, d, *J* 2.7), 6.39 (1H, d, *J* 3.0), 7.11 (2H, d, *J* 8.5), 7.50 (2H, d, *J* 8.5); δ_C (100 MHz, $CDCl_3$) 45.1, 72.3, 121.8, 124.3, 129.5, 132.3, 138.3, 138.5, 169.8; HRMS (ESI^+): found: 274.9679; $C_{11}H_9{}^{79}BrNaO_2$ (MNa^+) requires 274.9678.

4.48. (*SR*)-3-Methylene-4-(4-(trifluoromethyl)phenyl)dihydrofuran-2(3*H*)-one (12g)

Synthesised using general procedure D with 4-trifluoromethylphenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **11g** (83 mg, 0.162 mmol), DCM (4.2 mL), $Rh_2(oct)_4$ (3.3 mg, 4.2 μmol), KOBu-*t* (28.4 mg, 0.253 mmol) and paraformaldehyde (12.7 mg, 0.422 mmol). The HWE was performed at 0 °C. Purification by column chromatography (4:1 hexane/ethyl acetate) afforded the *title compound* as a colourless oil (15 mg, 29%); R_f 0.59 (2:1 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2875w, 1741s, 1307s, 1097m, 1053w; δ_H (400 MHz, $CDCl_3$) 4.24 (1H, dd, *J* 9.0, 7.1), 4.33–4.38 (1H, m), 4.75 (1H, app. t, *J* 9.0), 5.50 (1H, d, *J* 2.9), 6.44 (1H, d, *J* 2.9), 7.37 (2H, d, *J* 8.0), 7.65 (2H, d, *J* 8.0); δ_C (100 MHz, $CDCl_3$) 45.3, 72.2, 123.8 (q, *J* 272.2), 124.7, 126.2 (q, *J* 3.8), 128.3, 130.2 (q, *J* 32.1), 138.1, 143.7, 169.6; δ_F (376 MHz, $CDCl_3$) −62.6; HRMS (ESI^+): found: 265.0447; $C_{12}H_9F_3NaO_2$ (MNa^+) requires 265.0447.

4.49. (*SR*)-3-Methylene-4-(4-nitrophenyl)dihydrofuran-2(3*H*)-one (12h)

Synthesised using general procedure C with 4-nitrophenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **11h** (37 mg, 0.100 mmol), DCM (2.0 mL), $Rh_2(esp)_2$ (3.8 mg, 5.0 μmol), KOBu-*t* (10.1 mg, 0.090 mmol) and paraformaldehyde (30.0 mg, 0.997 mmol). The HWE was performed at 0 °C. Purification by column chromatography (2:1 petrol/ethyl acetate) afforded the *title compound* as a colourless oil (4 mg, 18%); R_f 0.58 (1:1 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2878s, 2809s, 1737s, 1575w, 1496m, 1327m, 1092w, 1004w, 843w; δ_H (400 MHz, $CDCl_3$) 4.27 (1H, dd, *J* 9.1, 6.8), 4.39–4.45 (1H, m), 4.78 (1H, app. t, *J* 9.1), 5.53 (1H, d, *J* 2.7), 6.48 (1H, d, *J* 3.1), 7.44 (2H, d, *J* 8.8), 8.26 (2H, d, *J* 8.8); δ_C (100 MHz, $CDCl_3$) 45.2, 71.9, 124.5, 125.1, 128.8, 137.7, 147.0, 147.6, 169.2; HRMS (ESI^+): found: 242.0427; $C_{11}H_9NNaO_4$ (MNa^+) requires 242.0424.

4.50. (*SR*)-3-Methylene-4-(thiophen-3-yl)dihydrofuran-2(3*H*)-one (12k)

Synthesised using general procedure C with 2-(thiophen-3-yl) ethyl 2-diazo-2-(diethoxyphosphoryl)acetate **11k** (69 mg, 0.208 mmol), DCM (4.2 mL), $Rh_2(oct)_4$ (3.2 mg, 4.2 μmol), KOBu-*t* (28.0 mg, 0.250 mmol) and paraformaldehyde (12.5 mg, 0.416 mmol). The HWE was performed at 0 °C. Purification by column chromatography (5:1 petrol/ethyl acetate) afforded the *title*

compound as a colourless oil (12 mg, 32%); R_f 0.59 (2:1 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 3110w, 2910w, 1761s, 1404w, 1250m, 1109m, 1018m; δ_H (400 MHz, $CDCl_3$) 4.23 (1H, dd, *J* 8.9, 7.3), 4.38–4.44 (1H, m), 4.68 (1H, app. t, *J* 8.9), 5.56 (1H, d, *J* 2.8), 6.38 (1H, d, *J* 3.1), 6.95 (1H, dd, *J* 5.0, 1.4), 7.15 (1H, ddd, *J* 3.0, 1.4, 0.5), 7.38 (1H, dd, *J* 5.0, 3.0); δ_C (100 MHz, $CDCl_3$) 41.0, 71.9, 122.6, 123.8, 126.1, 127.4, 138.1, 139.4, 170.0; HRMS (ESI$^+$): found: 203.0134; $C_9H_8NaO_2S$ (MNa^+) requires 203.0137.

4.51. (*SR*)-4-Isopropyl-3-methylenedihydrofuran-2(3*H*)-one (12s)

Synthesised using general procedure D with 3-methylbutyl 2-diazo-2-(diethoxyphosphoryl)acetate **11s** (56 mg, 0.191 mmol), DCM (3.8 mL), $Rh_2(oct)_4$ (3.0 mg, 3.8 μmol), THF (3.8 mL), KOBu-*t* (25.7 mg, 0.229 mmol) and paraformaldehyde (11.5 mg, 0.382 mmol). The HWE was performed at 0 °C. Purification by column chromatography (8:1 pentane/ether) afforded the *title compound* as a colourless oil (15 mg, 56%); R_f 0.30 (8:1 pentane/ether); ν_{max} (thin film)/cm^{-1} 2963m, 1762s, 1409w, 1267w, 1117m, 1039w, 979w; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.8), 0.95 (3H, d, *J* 6.8), 1.87–1.99 (1H, m), 2.93–2.99 (1H, m), 4.16 (1H, dd, *J* 9.3, 4.0), 4.35 (1H, dd, *J* 9.3, 8.1), 5.62 (1H, d, *J* 2.2), 6.34 (1H, d, *J* 2.5); δ_C (100 MHz, $CDCl_3$) 17.7, 19.1, 31.4, 44.6, 68.3, 123.1, 136.9, 171.2; HRMS (ESI$^+$): found: 163.0722; $C_8H_{12}NaO_2$ (MNa^+) requires 163.0730.

4.52. (*SR*)-4-(*tert*-Butyl)-3-methylenedihydrofuran-2(3*H*)-one (12t)

Synthesised using general procedure D with 3,3-dimethylbutyl 2-diazo-2-(diethoxyphosphoryl)acetate **11t** (58 mg, 0.189 mmol), DCM (3.8 mL), $Rh_2(oct)_4$ (3.0 mg, 3.8 μmol), THF (3.8 mL), KOBu-*t* (25.5 mg, 0.227 mmol) and paraformaldehyde (11.4 mg, 0.378 mmol). The HWE was performed at 0 °C. Purification by column chromatography (8:1 pentane/ether) afforded the *title compound* as a colourless oil (10 mg, 34%); R_f 0.24 (8:1 pentane/ether); ν_{max} (thin film)/cm^{-1} 2962m, 1765s, 1492w, 1401w, 1364w, 1274m, 1250w, 1119m, 1041w, 969w, 822w; δ_H (400 MHz, $CDCl_3$) 0.94 (9H, s), 2.74–2.78 (1H, m), 4.26–4.34 (2H, m), 5.66 (1H, dd, *J* 1.9, 0.7), 6.38 (1H, d, *J* 2.1); δ_C (100 MHz, $CDCl_3$) 26.3, 33.5, 49.1, 67.8, 124.5, 136.2, 171.3; HRMS (ESI$^+$): found: 177.0878; $C_9H_{14}NaO_2$ (MNa^+) requires 177.0886.

4.53. (*SR*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-methylenedihydrofuran-2(3*H*)-one (12u) and (*SR*)-4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-methyleneoxetan-2-one (16a)

Synthesised using general procedure D with 3-((*tert*-butyldimethylsilyl)oxy)propyl 2-diazo-2-(diethoxyphosphoryl)acetate **11u** (83 mg, 0.210 mmol), DCM (4.2 mL), $Rh_2(oct)_4$ (3.3 mg, 4.2 μmol), THF (4.2 mL), KOBu-*t* (35.3 mg, 0.315 mmol) and paraformaldehyde (12.6 mg, 0.420 mmol). The HWE was performed at rt. Purification by column chromatography (8:1 hexane/ethyl acetate) afforded the *title compounds* 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methylenedihydrofuran-2(3*H*)-one **12u** (9 mg, 18%) and 4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-methyleneoxetan-2-one **16a** (8 mg, 16%) as colourless oils.

4.53.1. Data for ***12u****.* R_f 0.49 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2955m, 2930m, 2857m, 1766s, 1663w, 1472m, 1408w, 1362w, 1258m, 1115s, 1039m, 1004m, 940w, 837s, 815w, 778m; δ_H (400 MHz, $CDCl_3$) 0.05 (3H, s), 0.05 (3H, s), 0.88 (9H, s), 3.20–3.27 (1H, m), 3.65 (1H, dd, *J* 9.9, 7.2), 3.72 (1H, dd, *J* 9.9, 5.9), 4.21 (1H, dd, *J* 9.3, 4.3), 4.42 (1H, dd, *J* 9.3, 8.2), 5.69 (1H, d, *J* 2.2), 6.31 (1H, d, *J* 2.5); δ_C (100 MHz, $CDCl_3$) −5.6, −5.5, 18.2, 25.7, 41.2, 64.8, 68.4, 123.2, 135.6, 170.6; HRMS (ESI$^+$): found: 265.1223; $C_{12}H_{22}NaO_3Si$ (MNa^+) requires 265.1230.

4.53.2. Data for ***16a****.* R_f 0.60 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2955m, 2930m, 2858m, 1826s, 1472w, 1408w, 1362w, 1257m, 1208w, 1099s, 1049m, 946w, 834s, 778m; δ_H (400 MHz, $CDCl_3$) 0.07 (3H, s), 0.07 (3H, s), 0.90 (9H, s), 2.00–2.09 (2H, m), 3.80 (2H, app. dd, *J* 6.6, 5.2), 5.16 (1H, app. ddt, *J* 7.5, 5.7, 1.8), 5.47 (1H, app. t, *J* 1.7), 5.93 (1H, app. t, *J* 1.9); δ_C (100 MHz, $CDCl_3$) −5.5, −5.4, 18.3, 25.9, 36.5, 58.6, 77.1, 115.3, 146.4, 163.6; HRMS (ESI$^+$): found: 265.1227; $C_{12}H_{22}NaO_3Si$ (MNa^+) requires 265.1230.

4.54. (*SR*)-4-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3-methylenedihydrofuran-2(3*H*)-one (12v)

Synthesised using general procedure D with 4-((*tert*-butyldimethylsilyl)oxy)butyl 2-diazo-2-(diethoxyphosphoryl)acetate **11v** (87 mg, 0.213 mmol), DCM (4.2 mL), $Rh_2(oct)_4$ (3.3 mg, 4.2 mol), THF (4.2 mL), KOBu-*t* (35.9 mg, 0.320 mmol) and paraformaldehyde (12.8 mg, 0.426 mmol). The HWE was performed at rt. Purification by column chromatography (4:1 hexane/ethyl acetate) afforded the *title compound* as a colourless oil (27 mg, 49%); R_f 0.50 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2954m, 2929m, 2857m, 1767s, 1472w, 1257s, 1103s, 1020m, 940w, 836s, 777m; δ_H (400 MHz, $CDCl_3$) 0.05 (3H, s), 0.05 (3H, s), 0.89 (9H, s), 1.72 (1H, dddd, *J* 14.0, 9.1, 7.5, 5.1), 1.91 (1H, app. ddt, *J* 14.0, 5.7, 4.9), 3.17–3.26 (1H, m), 3.65–3.76 (2H, m), 4.07 (1H, dd, *J* 9.1, 6.1), 4.51 (1H, dd, *J* 9.1, 8.4), 5.60 (1H, d, *J* 2.6), 6.27 (1H, d, *J* 2.9); δ_C (100 MHz, $CDCl_3$) −5.5, −5.5, 18.2, 25.8, 36.3, 36.8, 60.5, 71.7, 121.7, 138.4, 170.8; HRMS (ESI$^+$): found: 279.1393; $C_{13}H_{24}NaO_3Si$ (MNa^+) requires 279.1387.

4.55. (*SR*)-3-Methylene-4-vinyldihydrofuran-2(3*H*)-one (12w)[30] and 3-methyl-4-vinylfuran-2(5*H*)-one (17)[23]

Synthesised using general procedure D with but-3-en-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate **11w** (58 mg, 0.210 mmol), DCM (4.2 mL), $Rh_2(oct)_4$ (3.3 mg, 4.2 μmol), THF (4.2 mL), KOBu-*t* (35.3 mg, 0.315 mmol) and paraformaldehyde (12.6 mg, 0.420 mmol). The HWE was performed at rt. Purification by column chromatography (8:1 pentane/ether) afforded the *title compounds* 3-methylene-4-vinyldihydrofuran-2(3*H*)-one **12w** as a colourless oil (10 mg, 38%) and 3-methyl-4-vinylfuran-2(5*H*)-one **17** as a colourless oil (2.3 mg, 9%).

4.55.1. Data for ***12w****.*[31] R_f 0.54 (4:1 pentane/ether); ν_{max} (thin film)/cm^{-1} 2965, 2919, 2851, 1766, 1238, 1112; δ_H (400 MHz, $CDCl_3$) 3.68–3.76 (1H, m), 4.02 (1H, dd, *J* 9.1, 7.4), 4.53 (1H, app. t, *J* 9.0), 5.23–5.28 (2H, m), 5.62 (1H, d, *J* 2.8), 5.71 (1H, ddd, *J* 16.6, 10.4, 8.2), 6.33 (1H, d, *J* 3.2); δ_C (100 MHz, $CDCl_3$) 44.0, 70.0, 119.2, 123.4, 135.0, 137.0, 170.1; HRMS (ESI$^+$): found: 147.0411; $C_7H_8NaO_2$ (MNa^+) requires 147.0417.

4.55.2. Data for ***17****.*[23] R_f 0.29 (4:1 pentane/ether); ν_{max} (thin film)/cm^{-1} 2925, 2855, 1752, 1663, 1432, 1337, 1208, 1077, 1045; δ_H (400 MHz, $CDCl_3$) 1.94 (3H, s), 4.88–4.89 (2H, m), 5.49–5.56 (2H, m), 6.72 (1H, dd, *J* 17.8, 11.0); δ_C (100 MHz, $CDCl_3$) 8.8, 69.2, 121.0, 124.3, 126.9, 152.0, 178.1; HRMS (ESI$^+$): found: 147.0417; $C_7H_8NaO_2$ (MNa^+) requires 147.0417.

4.56. 3-Methylene-1-oxaspiro[3.5]nonan-2-one (16b),[31] (3a*S*-*R*,7a*RS*)-3-methylenehexahydrobenzofuran-2(3*H*)-one (*trans*-12y)[32] and (3a*RS*,7a*RS*)-3-methylenehexahydrobenzofuran-2(3*H*)-one (*cis*-12y)[32]

Synthesised using general procedure C with cyclohexyl 2-diazo-2-(diethoxyphosphoryl)acetate **11y** (84 mg, 0.276 mmol), DCM

(5.4 mL), $Rh_2(oct)_4$ (4.3 mg, 0.006 mmol), KOBu-*t* (37.2 mg, 0.331 mmol) and paraformaldehyde (16.6 mg, 0.552 mmol). The HWE was performed at 0 °C. Purification by column chromatography (20:1 hexane/ethyl acetate) afforded the *title compounds* (18 mg, 43%) (**16b**/*trans*-**12y**/*cis*-**12y** 6:10:1); HRMS (ESI^+): found: 175.0726; $C_9H_{12}NaO_2$ (MNa^+) requires 175.0730. Small quantities of each compound were isolated separately for characterisation purposes.

4.56.1. Data for ***16b****.*[32] R_f 0.70 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2937, 2861, 1814, 1450, 1177, 1107, 1011; δ_H (400 MHz, $CDCl_3$) 1.41–1.96 (10H, m), 5.41 (1H, d, *J* 1.9), 5.80 (1H, d, *J* 1.9); δ_C (100 MHz, $CDCl_3$) 23.0, 24.6, 34.5, 87.2, 113.0, 150.1, 163.8.

*4.56.2. Data for trans-****12y****.*[33] R_f 0.65 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2940, 2864, 1770, 1251, 1132, 1026, 996; δ_H (400 MHz, $CDCl_3$) 1.32–1.44 (3H, m), 1.57–1.67 (1H, m), 1.83–1.87 (1H, m), 1.95–1.98 (1H, m), 2.11–2.15 (1H, m), 2.24–2.29 (1H, m), 2.37–2.44 (1H, m), 3.71 (1H, ddd, *J* 11.5, 10.8, 3.7), 5.38 (1H, d, *J* 3.1), 6.06 (1H, d, *J* 3.3); δ_C (100 MHz, $CDCl_3$) 24.0, 24.8, 25.8, 30.4, 48.9, 83.1, 117.1, 139.6, 170.7.

*4.56.3. Data for cis-****12y****.*[33] R_f 0.57 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2936, 2864, 1763, 1263, 1127, 965; δ_H (400 MHz, $CDCl_3$) 1.31–1.94 (8H, m), 2.99–3.05 (1H, m), 4.52–4.56 (1H, m), 5.51 (1H, d, *J* 2.3), 6.20 (1H, d, *J* 2.5); δ_C (100 MHz, $CDCl_3$) 20.5, 21.1, 26.3, 28.9, 39.6, 76.9, 119.8, 139.9, 171.0.

4.57. 6-Methylene-4-oxatetracyclo[6.3.1.1^{3,10}.0^{3,7}]tridecan-5-one (12z)

Synthesised using general procedure D with adamantan-1-yl 2-diazo-2-(diethoxyphosphoryl)acetate **11z** (75 mg, 0.210 mmol), DCM (4.2 mL), $Rh_2(oct)_4$ (3.3 mg, 4.2 μmol), THF (4.2 mL), KOBu-*t* (35.3 mg, 0.315 mmol) and paraformaldehyde (12.6 mg, 0.420 mmol). The HWE was performed at rt. Purification by column chromatography (4:1 hexane/ethyl acetate) afforded the *title compound* as a white solid (34 mg, 79%); R_f 0.47 (4:1 hexane/ethyl acetate); mp 88–90 °C; ν_{max} (thin film)/cm^{-1} 2921s, 2856m, 1967w, 1764s, 1675w, 1451w, 1279w, 1262m, 1242w, 1211m, 1151m, 1042s, 949s; δ_H (400 MHz, $CDCl_3$) 1.57–1.89 (8H, m), 1.99–2.15 (3H, m), 2.30–2.35 (1H, m), 2.44–2.48 (1H, m), 2.81–2.84 (1H, m), 5.36 (1H, d, *J* 3.2), 6.14 (1H, d, *J* 3.4); δ_C (100 MHz, $CDCl_3$) 29.2, 29.2, 29.6, 30.9, 35.8, 37.6, 39.8, 41.1, 53.5, 80.4, 117.4, 138.6, 170.8; HRMS (ESI^+): found: 227.1050; $C_{13}H_{16}NaO_2$ (MNa^+) requires 227.1043.

4.58. (3a*SR*,8a*RS*)-3-Methyleneoctahydro-2*H*-cyclohepta[*b*]furan-2-one (*trans*-12aa)[33] and (3a*RS*,8a*RS*)-3-methyleneoctahydro-2*H*-cyclohepta[*b*]furan-2-one (*cis*-12aa)[34]

Synthesised using general procedure D with cycloheptyl 2-diazo-2-(diethoxyphosphoryl)acetate **11aa** (72 mg, 0.226 mmol), DCM (4.5 mL), $Rh_2(oct)_4$ (3.5 mg, 4.5 μmol), THF (4.5 mL), KOBu-*t* (38.0 mg, 0.339 mmol) and paraformaldehyde (13.6 mg, 0.452 mmol). The HWE was performed at rt. Purification by column chromatography (4:1 hexane/ethyl acetate) afforded the *title compounds* as mixture of trans and cis isomers (*trans*-**12aa**/*cis*-**12aa** 3.5:1) (19 mg, 51%). A small quantity of the major (*trans*) compound was separated for characterisation. The minor (*cis*) compound was characterised from a mixture.

*4.58.1. Data for trans-****12aa****.*[34] Colourless oil; R_f 0.50 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2929, 2861, 1761, 1667, 1454, 1400, 1313, 1262, 1246, 998; δ_H (400 MHz, $CDCl_3$) 1.40–1.82 (8H, m), 2.12–2.20 (1H, m), 2.33–2.42 (1H, m), 2.73–2.81 (1H, m), 4.15 (1H, ddd, *J* 10.6, 9.3, 4.4), 5.46 (1H, d, *J* 3.2), 6.18 (1H, d, *J* 3.5); δ_C (100 MHz, $CDCl_3$) 25.1, 25.3, 27.3, 28.0, 33.0, 45.6, 83.3, 119.6, 141.0, 170.5; HRMS (ESI^+): found: 189.0889; $C_{10}H_{14}NaO_2$ (MNa^+) requires 189.0886.

*4.58.2. Data for cis-****12aa****.*[35] R_f 0.43 (4:1 hexane/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 1.17–1.97 (9H, m), 2.03–2.09 (1H, m), 3.19–3.27 (1H, m), 4.71 (1H, ddd, *J* 10.6, 8.6, 3.6), 5.55 (1H, d, *J* 2.7), 6.27 (1H, d, *J* 3.1); δ_C (100 MHz, $CDCl_3$) 24.2, 27.4, 30.6, 31.2, 31.8, 43.1, 82.3, 122.0, 140.3, 170.4.

4.59. 4,4-Dimethyl-3-methylenedihydrofuran-2(3*H*)-one (12ab)[24]

Synthesised using general procedure D with 2-methylpropyl 2-diazo-2-(diethoxyphosphoryl)acetate **11ab** (85 mg, 0.305 mmol), DCM (6.1 mL), $Rh_2(oct)_4$ (3.4 mg, 6.1 μmol), KOBu-*t* (41.1 mg, 0.366 mmol) and paraformaldehyde (18.3 mg, 0.610 mmol). The HWE was performed at 0 °C. Purification by column chromatography (8:1 hexane/ethyl acetate) afforded the *title compound* as a colourless oil (9 mg, 23%); R_f 0.39 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2966w, 2929w, 1760s, 1668w, 1464w, 1410w, 1371w, 1294m, 1169w, 1107m, 1014m; δ_H (400 MHz, $CDCl_3$) 1.26 (6H, s), 4.03 (2H, s), 5.54 (1H, s), 6.20 (1H, s); δ_C (100 MHz, $CDCl_3$) 26.9, 38.9, 78.3, 119.9, 144.7, 170.8; HRMS (ESI^+): found: 127.0758; $C_7H_{11}O_2$ (MH^+) requires 127.0754.

4.60. 8-Methylene-6-oxaspiro[3.4]octan-7-one (12ad)

Synthesised using general procedure D with cyclobutylmethyl 2-diazo-2-(diethoxyphosphoryl)acetate **11ad** (59 mg, 0.203 mmol), DCM (4.0 mL), $Rh_2(oct)_4$ (3.2 mg, 4.1 μmol), THF (4.0 mL), KOBu-*t* (34.2 mg, 0.305 mmol) and paraformaldehyde (12.2 mg, 0.406 mmol). The HWE was performed at rt. Purification by column chromatography (4:1 hexane/ethyl acetate) afforded the *title compound* as a colourless oil (22 mg, 78%); R_f 0.42 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2935w, 1760s, 1662w, 1408w, 1296m, 1117m, 1005m, 942w, 814w; δ_H (400 MHz, $CDCl_3$) 1.95–2.04 (2H, m), 2.18–2.30 (4H, m), 4.32 (2H, s), 5.80 (1H, s), 6.26 (1H, s); δ_C (100 MHz, $CDCl_3$) 15.3, 34.5, 44.5, 78.1, 119.9, 143.1, 169.8; HRMS (ESI^+): found: 161.0571; $C_8H_{10}NaO_2$ (MNa^+) requires 161.0573.

4.61. 4-Methylene-2-oxaspiro[4.5]decan-3-one (12af)

Synthesised using general procedure D with cyclohexylmethyl 2-diazo-2-(diethoxyphosphoryl)acetate **11af** (57 mg, 0.179 mmol), DCM (3.6 mL), $Rh_2(oct)_4$ (2.8 mg, 3.6 μmol), THF (3.6 mL), KOBu-*t* (30.2 mg, 0.269 mmol) and paraformaldehyde (10.8 mg, 0.358 mmol). The HWE was performed at rt. Purification by column chromatography (4:1 hexane/ethyl acetate) afforded the *title compound* as a colourless oil (15 mg, 50%); R_f 0.63 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2926m, 2854w, 1759s, 1661w, 1451m, 1407w, 1305m, 1254m, 1113s, 1013s, 943m, 815m; δ_H (400 MHz, $CDCl_3$) 1.24–1.75 (10H, m), 4.15 (2H, s), 5.54 (1H, s), 6.22 (1H, s); δ_C (100 MHz, $CDCl_3$) 22.5, 25.0, 36.2, 42.4, 75.3, 120.7, 144.4, 171.3; HRMS (ESI^+): found: 189.0891; $C_{10}H_{14}NaO_2$ (MNa^+) requires 189.0886.

4.62. 1,1,2-Triphenylethyl 2-diazo-2-(diethoxyphosphoryl)acetate (14a)

Procedure for Grignard addition followed according to the literature procedure.[35] To benzylmagnesium chloride solution

(20 mL, 40 mmol, 2 M in THF) cooled to 0 °C under argon was added benzophenone (5.47 g, 30 mmol). After 2 h stirring at rt a further addition of benzylmagnesium chloride (10 mL, 20 mmol) was made. The suspension was stirred overnight at rt. The suspension was quenched with satd aq NH_4Cl. The organic layer was removed and the aqueous extracted with ethyl acetate (3×25 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to afford the crude product as a white powder (9.03 g). A portion of the crude material (3.35 g) was taken forward to the following step without further purification. To a solution of the crude material in toluene (60 mL) under argon was added sequentially diethyl phosphonoacetic acid (2.06 mL, 12.8 mmol), DIPEA (5.52 mL, 31.7 mmol) and propyl phosphonic anhydride (10.1 g, 15.8 mmol, 50% w/w solution in ethyl acetate). The solution was stirred at 50 °C for 1.5 h. The solution was diluted with water (50 mL) and extracted with ethyl acetate (3×25 mL) followed by sequential washing of the combined organic extracts with 10% aq HCl (10 mL), satd aq $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo to afford and dark orange oil (4.60 g) as crude. Purification by column chromatography (1:2 petrol/ethyl acetate) afforded 1,1,2-triphenylethyl 2-(diethoxyphosphoryl)acetate as a colourless oil (389 mg, 8% over two steps); R_f 0.25 (1:2 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2937s, 1711s, 1251s, 1218w, 1012s; δ_H (400 MHz, $CDCl_3$) 1.25 (6H, td, *J* 7.1, 0.3), 2.94 (2H, d, *J* 21.5), 4.02–4.13 (6H, m), 6.60–6.65 (2H, m), 7.06–7.18 (3H, m), 7.20–7.35 (10H, m); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* 6.3), 35.2 (d, *J* 134.4), 42.7, 62.4 (d, *J* 6.2), 87.6, 126.3, 126.4, 127.1, 127.5, 127.8, 130.4, 135.3, 143.9, 163.8 (d, *J* 6.4); δ_P (162 MHz, $CDCl_3$) 20.3; HRMS (ESI^+): found: 475.1636; $C_{26}H_{29}NaO_5P$ (MNa^+) requires 475.1645. 1,1,2-Triphenylethyl 2-(diethoxyphosphoryl)acetate (308 mg, 0.681 mmol) was then treated under the conditions of general procedure B with THF (3.4 mL), LHMDS (0.82 mL, 0.82 mmol, 1.0 M solution in THF) and 4-acetamidobenzenesulfonylazide (196 mg, 0.82 mmol). Purification by column chromatography (2:1 petrol/ethyl acetate) afforded the *title compound* as a white crystalline solid (171 mg, 53%); R_f 0.77 (1:2 petrol/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2938w, 2884w, 2100s, 1675s, 1264s, 1219w, 1005m; mp 68–72 °C; δ_H (400 MHz, $CDCl_3$) 1.19 (6H, td, *J* 7.1, 0.7), 3.81–3.93 (2H, m), 4.03–4.13 (2H, m), 4.14 (2H, s), 6.61–6.65 (2H, m), 7.06–7.18 (3H, m), 7.22–7.34 (10H, m); δ_C (100 MHz, $CDCl_3$) 15.9 (d, *J* 7.6), 43.3, 55.2 (d, *J* 227.8), 63.1 (d, *J* 5.4), 88.3, 126.1, 126.5, 127.2, 127.5, 128.0, 130.3, 135.3, 144.1, 162.2 (d, *J* 10.2); δ_P (162 MHz, $CDCl_3$) 11.0; HRMS (ESI^+): found: 501.1527; $C_{26}H_{27}N_2NaO_5P$ (MNa^+) requires 501.1550.

4.63. Diethyl ((1*SR*,3a*SR*)-1-benzyl-3-oxo-1-phenyl-3,3a-dihydro-1*H*-cyclohepta[*c*]furan-3a-yl)phosphonate (15b)

To a solution of 1,1,2-triphenylethyl 2-diazo-2-(diethoxyphosphoryl)acetate **14a** (47 mg, 0.098 mmol) in toluene (5 mL) flushed with argon was added $Rh_2(esp)_2$ (3.7 mg, 4.9 μmol). The mixture was stirred at 100 °C for 4 h. Concentration in vacuo and purification by column chromatography (1:1 petrol/ethyl acetate) afforded the *title compound* as an off-white solid (22 mg, 50%); R_f 0.22 (1:1 petrol/ethyl acetate); mp 92–95 °C; ν_{max} (thin film)/cm^{-1} 2936w, 1744s, 1230m, 1034w, 1009m; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, td, *J* 7.1, 0.4), 1.38 (3H, td, *J* 7.1, 0.4), 3.65 (1H, d, *J* 14.6), 4.10–4.28 (4H, m), 4.11 (1H, d, *J* 14.6), 5.31 (1H, dd, *J* 10.0, 6.3), 6.15–6.22 (2H, m), 6.27–6.36 (2H, m), 7.09–7.16 (5H, m), 7.19–7.30 (3H, m), 7.32–7.36 (2H, m); δ_C (100 MHz, $CDCl_3$) 16.4 (d, *J* 5.6), 16.7 (d, *J* 5.3), 45.6, 56.0 (d, *J* 145.2), 63.8 (d, *J* 7.5), 64.4 (d, *J* 7.3), 90.0 (d, *J* 3.8), 119.1, 124.2 (d, *J* 7.2), 125.6, 126.6, 127.7, 127.8, 128.4, 128.5 (d, *J* 7.4), 129.0, 129.9, 130.7, 134.4, 135.0, 141.3, 172.7 (d, *J* 3.6); δ_P (162 MHz, $CDCl_3$) 17.3; HRMS (ESI^+): found: 473.1477; $C_{26}H_{27}NaO_5P$ (MNa^+) requires 473.1488.

4.64. (*SR*,*Z*)-3-(4-Nitrobenzylidene)-4-phenyldihydrofuran-2(3*H*)-one (*Z*-18h) and (*SR*,*E*)-3-(4-nitrobenzylidene)-4-phenyldihydrofuran-2(3*H*)-one (*E*-18h)

Synthesised using general procedure D with phenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **11d** (75 mg, 0.230 mmol), DCM (4.6 mL), $Rh_2(oct)_4$ (3.6 mg, 4.6 μmol), THF (4.6 mL), KOBu-*t* (38.7 mg, 0.345 mmol) and 4-nitrobenzaldehyde (69.5 mg, 0.460 mmol). The HWE was performed at 0 °C. Purification by column chromatography (10:1 hexane/ethyl acetate) afforded the *title compound*s as mixture of (*Z*) and (*E*) isomers (*Z*-**18h**/*E*-**18h** 1:1) (44 mg, 65%). Small quantities of each compound were isolated separately for characterisation purposes.

*4.64.1. Data for Z-**18h**.* Pale yellow oil; R_f 0.40 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2920w, 1754s, 1597w, 1518s, 1345s, 1161s, 1074w, 1023w; δ_H (400 MHz, $CDCl_3$) 4.39 (1H, app. t, *J* 8.0), 4.45 (1H, app. td, *J* 7.8, 2.7), 4.78 (1H, app. t, *J* 8.4), 6.72 (1H, d, *J* 2.7), 7.30–7.32 (2H, m), 7.35–7.39 (1H, m), 7.41–7.46 (2H, m), 7.88 (2H, d, *J* 8.9), 8.19 (2H, d, *J* 8.9); δ_C (100 MHz, $CDCl_3$) 48.8, 72.4, 123.2, 128.2, 128.2, 129.5, 131.3, 133.2, 138.5, 139.2, 139.3, 147.8, 168.0; HRMS (ESI^+): found: 318.0749; $C_{17}H_{13}NNaO_4$ (MNa^+) requires 318.0737.

*4.64.2. Data for E-**18h**.* Pale yellow oil; R_f 0.32 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2923w, 2854w, 1755s, 1691w, 1653w, 1598m, 1518s, 1343s, 1300w, 1226m, 1173s, 1021w; δ_H (400 MHz, $CDCl_3$) 4.33 (1H, dd, *J* 8.9, 3.5), 4.61 (1H, app. dt, *J* 8.1, 3.0), 4.78 (1H, app. t, *J* 8.5), 7.17–7.19 (2H, m), 7.24–7.34 (3H, m), 7.45 (2H, d, *J* 8.8), 7.84 (1H, d, *J* 2.4), 8.08 (2H, d, *J* 8.8); δ_C (100 MHz, $CDCl_3$) 44.5, 73.8, 123.6, 127.0, 128.0, 129.5, 130.8, 131.4, 136.3, 139.6, 139.6, 147.9, 171.4; HRMS (ESI^+): found: 318.0746; $C_{17}H_{13}NNaO_4$ (MNa^+) requires 318.0737.

4.65. (*SR*,*Z*)-3-Pentylidene-4-phenyldihydrofuran-2(3*H*)-one (*Z*-18i) and (*SR*,*E*)-3-pentylidene-4-phenyldihydrofuran-2(3*H*)-one (*E*-18i)

Synthesised using general procedure D with phenethyl 2-diazo-2-(diethoxyphosphoryl)acetate **11d** (73 mg, 0.224 mmol), DCM (4.5 mL), $Rh_2(oct)_4$ (3.5 mg, 4.5 μmol), THF (4.5 mL), KOBu-*t* (37.7 mg, 0.336 mmol) and valeraldehyde (44.8 μL, 0.448 mmol). The HWE was performed at reflux. Purification by column chromatography (8:1 hexane/ethyl acetate) afforded the *title compound*s as mixture of (*Z*) and (*E*) isomers (*Z*-**18i**/*E*-**18i** 3.3:1) (29 mg, 56%). Small quantities of each compound were isolated separately for characterisation purposes.

*4.65.1. Data for Z-**18i**.* Pale yellow oil; R_f 0.53 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2957m, 2928m, 2871w, 1755s, 1667w, 1455w, 1373w, 1175m, 1127m, 1025s; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.1), 1.25–1.43 (4H, m), 2.66–2.82 (2H, m), 4.18–4.24 (2H, m), 4.61–4.67 (1H, m), 5.99 (1H, td, *J* 7.8, 2.2), 7.20–7.23 (2H, m), 7.28–7.32 (1H, m), 7.34–7.39 (2H, m); δ_C (100 MHz, $CDCl_3$) 13.8, 22.3, 27.2, 31.1, 46.9, 72.5, 127.6, 128.0, 128.8, 129.1, 140.7, 146.9, 169.8; HRMS (ESI^+): found: 253.1188; $C_{15}H_{18}NaO_2$ (MNa^+) requires 253.1199.

*4.65.2. Data for E-**18i**.* Pale yellow oil; R_f 0.44 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2957m, 2928s, 2858m, 1759s, 1672w, 1456w, 1378w, 1184m, 1026m; δ_H (400 MHz, $CDCl_3$) 0.76 (3H, t, *J* 7.2), 1.10–1.33 (4H, m), 1.88–2.01 (2H, m), 4.20–4.29 (2H, m), 4.70 (1H, app. t, *J* 8.2), 6.92 (1H, td, *J* 7.7, 2.3), 7.19–7.21 (2H, m), 7.26–7.29 (1H, m), 7.31–7.36 (2H, m); δ_C (100 MHz, $CDCl_3$) 13.6, 22.2, 29.2, 29.9, 43.4, 73.5, 127.2, 127.4, 129.0, 129.1, 141.7, 144.3,

171.2; HRMS (ESI$^+$): found: 253.1187; $C_{15}H_{18}NaO_2$ (MNa^+) requires 253.1199.

4.66. (*SR*,*Z*)-3-(4-Nitrobenzylidene)-4-pentyldihydrofuran-2(3*H*)-one (*Z*-18j) and (*SR*,*E*)-3-(4-nitrobenzylidene)-4-pentyldihydrofuran-2(3*H*)-one (*E*-18j)

Synthesised using general procedure D with heptyl 2-diazo-2-(diethoxyphosphoryl)acetate **11p** (68 mg, 0.212 mmol), DCM (4.2 mL), $Rh_2(oct)_4$ (3.3 mg, 4.2 μmol), THF (4.2 mL), KOBu-*t* (35.7 mg, 0.318 mmol) and 4-nitrobenzaldehyde (62.6 mg, 0.424 mmol). The HWE was performed at 0 °C. Purification by column chromatography (8:1 hexane/ethyl acetate) afforded the *title compounds* as mixture of (*Z*) and (*E*) isomers (*Z*-**18j**/*E*-**18j** 1:1) (42 mg, 68%). Small quantities of each compound were isolated separately for characterisation purposes.

*4.66.1. Data for Z-**18j**.* Yellow oil; R_f 0.46 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2928m, 2857m, 1752s, 1651w, 1597m, 1518s, 1466w, 1378w, 1344s, 1175s, 1112w; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.0), 1.25–1.45 (6H, m), 1.57–1.68 (1H, m), 1.73–1.82 (1H, m), 3.15–3.22 (1H, m), 4.09 (1H, dd, *J* 8.9, 5.1), 4.52 (1H, dd, *J* 8.9, 7.7), 6.93 (1H, d, *J* 2.2), 7.89 (2H, d, *J* 8.8), 8.21 (2H, d, *J* 8.8); δ_C (100 MHz, $CDCl_3$) 14.0, 22.5, 26.0, 31.7, 34.1, 42.0, 70.8, 123.2, 131.1, 133.0, 136.1, 139.7, 147.6, 168.6; HRMS (ESI$^+$): found: 312.1210; $C_{16}H_{19}NNaO_4$ (MNa^+) requires 312.1206.

*4.66.2. Data for E-**18j**.* Pale yellow solid; R_f 0.41 (4:1 hexane/ethyl acetate); mp 114–117 °C; ν_{max} (thin film)/cm^{-1} 2929m, 2858m, 1754s, 1598m, 1520s, 1344s, 1225m, 1183s, 1112w; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.0), 1.18–1.42 (6H, m), 1.50–1.67 (2H, m), 3.53–3.60 (1H, m), 4.28 (1H, dd, *J* 9.1, 2.0), 4.45 (1H, ddd, *J* 9.1, 7.0, 0.7), 7.56 (1H, d, *J* 2.1), 7.67 (2H, d, *J* 8.8), 8.29 (2H, d, *J* 8.8); δ_C (100 MHz, $CDCl_3$) 13.0, 22.4, 26.4, 31.4, 32.4, 38.1, 70.7, 124.1, 130.3, 133.4, 133.8, 140.3, 147.8, 171.6; HRMS (ESI$^+$): found: 312.1205; $C_{16}H_{19}NNaO_4$ (MNa^+) requires 312.1206.

4.67. (*SR*,*Z*)-4-Pentyl-3-pentylidenedihydrofuran-2(3*H*)-one (*Z*-18k) and (*SR*,*E*)-4-pentyl-3-pentylidenedihydrofuran-2(3*H*)-one (*E*-18k)

Synthesised using general procedure D with heptyl 2-diazo-2-(diethoxyphosphoryl)acetate **11p** (67 mg, 0.209 mmol), DCM (4.2 mL), $Rh_2(oct)_4$ (3.3 mg, 4.2 μmol), THF (4.2 mL), KOBu-*t* (35.2 mg, 0.314 mmol) and valeraldehyde (45.0 μL, 0.418 mmol). The HWE was performed at rt. Purification by column chromatography (8:1 hexane/ethyl acetate) afforded the *title compounds* as mixture of (*Z*) and (*E*) isomers (*Z*-**18k**/*E*-**18k** 2.7:1) (36 mg, 77%). Small quantities of each compound were isolated separately for characterisation purposes.

*4.67.1. Data for Z-**18k**.* Colourless oil; R_f 0.75 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2957s, 2928s, 2858s, 1754s, 1668m, 1466m, 1378m, 1185m, 1127s, 1027s; δ_H (400 MHz, $CDCl_3$) 0.87–0.92 (6H, m), 1.24–1.49 (11H, m), 1.56–1.65 (1H, m), 2.69–2.75 (2H, m), 2.88–2.97 (1H, m), 3.92 (1H, dd, *J* 8.8, 5.3), 4.37 (1H, dd, *J* 8.8, 7.9), 6.12 (1H, td, *J* 7.7, 1.6); δ_C (100 MHz, $CDCl_3$) 13.9, 14.0, 22.3, 22.5, 25.9, 27.1, 31.3, 31.7, 34.2, 40.1, 70.8, 128.3, 144.1, 170.5; HRMS (ESI$^+$): found: 247.1670; $C_{14}H_{24}NaO_2$ (MNa^+) requires 247.1669.

*4.67.2. Data for E-**18k**.* Colourless oil; R_f 0.66 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2961s, 2930s, 2859m, 1760s, 1676m, 1466m, 1380w, 1193m, 1021m; δ_H (400 MHz, $CDCl_3$) 0.87–0.94 (6H, m), 1.22–1.57 (12H, m), 2.15–2.28 (2H, m), 3.04–3.10 (1H, m), 4.12 (1H, dd, *J* 9.1, 2.2), 4.31 (1H, dd, *J* 9.1, 7.3), 6.73 (1H, td, *J* 7.7, 2.0); δ_C (100 MHz, $CDCl_3$) 13.8, 14.0, 22.4, 22.5, 26.1, 29.4, 30.7, 31.7, 34.2, 37.1, 70.8, 129.8, 141.5, 171.7; HRMS (ESI$^+$): found: 247.1666; $C_{14}H_{24}NaO_2$ (MNa^+) requires 247.1669.

4.68. (*SR*,*Z*)-4-(4-Nitrobenzylidene)-2-oxaspiro[4.4]nonan-3-one (*Z*-18l) and (*SR*,*E*)-4-(4-nitrobenzylidene)-2-oxaspiro[4.4]nonan-3-one (*E*-18l)

Synthesised using general procedure D with cyclopentylmethyl 2-diazo-2-(diethoxyphosphoryl)acetate **11ae** (61 mg, 0.200 mmol), DCM (4.0 mL), $Rh_2(oct)_4$ (3.1 mg, 4.0 μmol), THF (4.0 mL), KOBu-*t* (33.7 mg, 0.300 mmol) and 4-nitrobenzaldehyde (60.5 mg, 0.400 mmol). The HWE was performed at 0 °C. Purification by column chromatography (8:1 hexane/ethyl acetate) afforded the *title compounds* as an inseparable mixture of (*Z*) and (*E*) isomers (*Z*-**18l**/*E*-**18l** 1:1.4), as a white solid (30 mg, 55%); R_f 0.32 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2959w, 2874w, 1755s, 1646w, 1597m, 1518s, 1492w, 1453w, 1344s, 1257w, 1227w, 1201w, 1160m, 1096m, 1023m, 910w, 851m; δ_H (400 MHz, $CDCl_3$) 1.61–1.96 (16H, m, *E*,*Z*), 4.04 (3H, s, *E*), 4.16 (3H, s, *Z*), 6.87 (1H, s, *Z*), 7.52 (2H, dd, *J* 8.9, 0.6, *E*), 7.65 (1H, s, *E*), 7.86 (2H, dd, *J* 8.9, 0.5, *Z*), 8.19 (2H, d, *J* 8.9, *Z*), 8.25 (2H, d, *J* 8.9, *E*); δ_C (100 MHz, $CDCl_3$) 24.6 (*E*/*Z*), 25.3 (*E*/*Z*), 37.1 (*E*), 39.3 (*Z*), 50.3 (*E*), 52.5 (*Z*), 77.5 (*Z*), 79.4 (*E*), 123.1 (*Z*), 123.5 (*E*), 130.0 (*E*), 131.1 (*Z*), 134.0 (*Z*), 134.3 (*E*), 136.6 (*E*), 137.3 (*Z*), 139.8 (*Z*), 140.9 (*E*), 147.5 (*E*/*Z*), 147.6 (*E*/*Z*), 168.9 (*Z*), 171.9 (*E*); HRMS (ESI$^+$): found: 296.0899; $C_{15}H_{15}NNaO_4$ (MNa^+) requires 296.0893.

4.69. (*SR*,*Z*)-4-Pentylidene-2-oxaspiro[4.4]nonan-3-one (*Z*-18m) and (*SR*,*E*)-4-pentylidene-2-oxaspiro[4.4]nonan-3-one (*E*-18m)

Synthesised using general procedure D with cyclopentylmethyl 2-diazo-2-(diethoxyphosphoryl)acetate **11ae** (63 mg, 0.207 mmol), DCM (4.2 mL), $Rh_2(oct)_4$ (3.2 mg, 4.1 μmol), THF (4.2 mL), KOBu-*t* (34.8 mg, 0.311 mmol) and valeraldehyde (44.0 μL, 0.414 mmol). The HWE was performed at reflux. Purification by column chromatography (8:1 hexane/ethyl acetate) afforded the *title compounds* as mixture of (*Z*) and (*E*) isomers (*Z*-**18m**/*E*-**18m** 2.4:1) (14 mg, 32%). Small quantities of each compound were isolated separately for characterisation purposes.

*4.69.1. Data for Z-**18m**.* Colourless oil; R_f 0.67 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2956m, 2929w, 2871m, 1752s, 1665m, 1453m, 1370m, 1164w, 1128w, 1105m, 1025s; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.2), 1.24–1.46 (4H, m), 1.62–1.81 (8H, m), 2.72 (2H, app. q, *J* 7.4), 4.02 (2H, s), 6.08 (1H, t, *J* 7.7); δ_C (100 MHz, $CDCl_3$) 13.9, 22.3, 24.5, 26.9, 31.4, 39.2, 50.8, 77.7, 132.8, 141.9, 170.1; HRMS (ESI$^+$): found: 231.1354; $C_{13}H_{20}NaO_2$ (MNa^+) requires 231.1356.

*4.69.2. Data for E-**18m**.* Colourless oil; R_f 0.54 (4:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2956s, 2934s, 2872s, 1758s, 1668m, 1455m, 1383w, 1362w, 1164w, 1028s; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.1), 1.20–2.00 (12H, m), 2.29 (2H, app. q, *J* 7.5), 4.00 (2H, s), 6.70 (1H, t, *J* 8.0); δ_C (100 MHz, $CDCl_3$) 13.8, 22.5, 25.5, 27.7, 31.0, 38.6, 48.8, 79.8, 132.5, 141.6, 171.4; HRMS (ESI$^+$): found: 231.1352; $C_{13}H_{20}NaO_2$ (MNa^+) requires 231.1356.

4.70. (*SR*)-4-(Hydroxymethyl)-3-methylenedihydrofuran-2(3*H*)-one (19)[9b]

To a solution of 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methylenedihydrofuran-2(3*H*)-one **12u** (29 mg, 0.120 mmol) in THF (0.6 mL) cooled to 0 °C under argon was added TBAF (144 μL, 0.144, 1.0 M in THF) dropwise. The solution was stirred at 0 °C for 1 h then quenched with satd aq NH_4Cl (10 mL) and extracted with ether (2×25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by column

chromatography (1:2 hexane/ethyl acetate) afforded the *title compound* as a pale yellow oil (12 mg, 78%); R_f 0.29 (1:2 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 3417br, 2924m, 1756s, 1407w, 1268m, 1120m, 1017m, 816m; δ_H (400 MHz, $CDCl_3$) 3.26–3.34 (1H, m), 3.76–3.78 (2H, m), 4.27 (1H, dd, *J* 9.4, 4.5), 4.47 (1H, dd, *J* 9.4, 8.2), 5.75 (1H, d, *J* 2.3), 6.36 (1H, d, *J* 2.6); δ_C (100 MHz, $CDCl_3$) 40.9, 64.1, 68.2, 123.6, 135.2, 170.4; HRMS (ESI$^+$): found: 151.0360; $C_6H_8NaO_3$ (MNa^+) requires 151.0366.

4.71. (±)-Cedarmycin A (8a)[9a]

*Preparation of 5-methylhexanoyl chloride **20a***: to a solution of 5-methylhexanoic acid (130.2 mg, 1.00 mmol) in DCM (2.5 mL) at 0 °C was added oxalyl chloride (253 μL, 3.00 mmol) dropwise. Stirred for 30 min at 0 °C followed by 2 h at rt then concentrated in vacuo to afford a colourless oil. To a solution of 4-(hydroxymethyl)-3-methylenedihydrofuran-2(3*H*)-one **19** (5 mg, 0.039 mmol) and triethylamine (8.2 μL, 0.059 mmol) in DCM (0.20 mL) was added 5-methylhexanoyl chloride (10 μL). After 2 h additional 5-methylhexanoyl chloride (10 μL) was added and stirred for 16 h. The solution was quenched with satd aq NH_4Cl (1 mL) and extracted with DCM (3×10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (4:1 hexane/ethyl acetate) afforded the *title compound* as a colourless oil (6 mg, 85%); R_f 0.75 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2956m, 2871w, 1768s, 1739s, 1468w, 1252w, 1170m, 1115m, 1019w; δ_H (400 MHz, $CDCl_3$) 0.88 (6H, t, *J* 6.6), 1.15–1.21 (2H, m), 1.51–1.65 (3H, m), 2.31 (2H, t, *J* 7.6), 3.39–3.47 (1H, m), 4.16 (1H, dd, *J* 11.2, 7.3), 4.18 (1H, dd, *J* 9.4, 4.9), 4.25 (1H, dd, *J* 11.2, 5.6), 4.48 (1H, dd, *J* 9.4, 8.4), 5.76 (1H, d, *J* 2.3), 6.39 (1H, d, *J* 2.7); δ_C (100 MHz, $CDCl_3$) 22.4, 22.7, 27.7, 34.3, 38.0, 38.3, 64.7, 68.1, 124.2, 134.5, 169.8, 173.5; HRMS (ESI$^+$): found: 263.1251; $C_{13}H_{20}NaO_4$ (MNa^+) requires 263.1254.

4.72. (±)-Cedarmycin B (8b)[9]

To a solution of 4-(hydroxymethyl)-3-methylenedihydrofuran-2(3*H*)-one **19** (3 mg, 0.023 mmol) and triethylamine (4.8 μL, 0.035 mmol) in DCM (0.12 mL) was added hexanoyl chloride (3.9 μL, 0.035 mmol). The solution was stirred at rt for 10 min then quenched with satd aq NH_4Cl (1 mL) and extracted with DCM (3×10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (4:1 hexane/ethyl acetate) afforded the *title compound* as a colourless oil (3 mg, 57%); R_f 0.76 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2959m, 2936m, 2864w, 1768s, 1738s, 1270w, 1246w, 1168m, 1115m, 1018w; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.0), 1.25–1.36 (4H, m), 1.62 (2H, app. quin, *J* 7.5), 2.32 (2H, t, *J* 7.5), 3.39–3.47 (1H, m), 4.16 (1H, dd, *J* 11.2, 7.3), 4.18 (1H, dd, *J* 9.4, 4.9), 4.25 (1H, dd, *J* 11.2, 5.6), 4.48 (1H, dd, *J* 9.4, 8.4), 5.76 (1H, d, *J* 2.4), 6.38 (1H, d, *J* 2.7); δ_C (100 MHz, $CDCl_3$) 13.9, 22.3, 24.5, 31.2, 34.0, 38.1, 64.7, 68.1, 124.1, 134.5, 169.8, 173.5; HRMS (ESI$^+$): found: 249.1099; $C_{12}H_{18}NaO_4$ (MNa^+) requires 249.1097.

Acknowledgements

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A selective C–H insertion/olefination protocol for the synthesis of α-methylene-γ-butyrolactone natural products†

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A regio- and stereoselective one-pot C–H insertion/olefination protocol has been developed for the late stage installation of α-methylene-γ-butyrolactones into conformationally restricted cyclohexanol-derivatives. The method has been successfully applied in the total synthesis of eudesmanolide natural product frameworks, including α-cyclocostunolide.

The selective functionalization of sp^3 centres *via* the activation of unfunctionalised C–H bonds is of much current interest,[1] given that it facilitates the synthesis of complex molecular architectures from relatively simple precursors. Over the last two decades, rhodium(II)-catalysed C–H insertions have become a mainstay in this field; an array of useful reaction modes with well-established reactivity patterns have been developed, including asymmetric variants, based on the C–H insertion of rhodium-stabilised carbenoids.[2] In particular, the donor/acceptor carbenoid systems popularised by Davies have proved to be especially valuable.[2d]

The acceptor/acceptor carbenoid class has received less attention in comparison,[3] although there are prominent exceptions.[4] A useful feature of carbenoids of this type is the fact that the additional acceptor substituent may be used as a handle for further chemical modification; this is exemplified by work published by our own group, in which a one-pot rhodium(II)-catalysed C–H insertion/Horner–Wadsworth–Emmons olefination (HWE) sequence for the conversion of α-diazo-α-(diethoxy)phosphoryl acetates **1** into α-methylene-γ-butyrolactones **2** was reported (Fig. 1a).[5] This research focused primarily on substrates with electron rich C–H bonds (*e.g.* benzylic reaction system **1**) that are well-suited to react with electrophilic carbenoids. The work described herein concerns the extension of this method to cyclohexanol derivatives (**3**, Fig. 1b). These are much more challenging substrates compared to those examined previously, as there is no electronic bias to direct the C–H insertion, but the products **4** are arguably more important given that a huge number of bioactive cyclohexane-based α-methylene-γ-butyrolactone natural products have been isolated.[6] Our aim (Fig. 1b) was to design the cyclohexane precursors so that C–H insertion (and subsequent olefination) occurs exclusively into equatorial C–H bonds,[7] to selectively form fused γ-lactones **4**. The success of this approach, and its application in the total synthesis of three natural product targets and one isomeric analogue, are described.

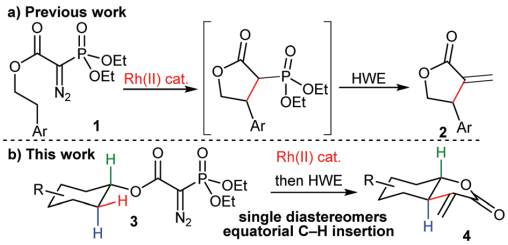

Fig. 1 C–H insertion/olefination approach to α-methylene-γ-butyrolactones.

Our only previous attempt at performing a C–H insertion/olefination of this type was not encouraging; when the diazophosphonate derivative of cyclohexanol (*i.e.* compound **3**, with R = H) was treated under the standard reaction conditions [Rh_2(oct)$_4$ (2 mol%), CH_2Cl_2, 45 °C, 16 h; (ii) KOBu-*t*, THF, −78 – 0 °C, 1 h; (iii) $(CH_2O)_n$, 0 °C – rt, 1 h][5] a diastereomeric mixture of γ-lactones, as well as some β-lactone product, was obtained (corresponding to insertion into all three of the highlighted C–H bonds in **3**) and the overall yield was low.[5b] It was postulated that the poor selectivity in this case may be related

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to the flexible nature of the substrate, and that by restricting its conformation, the regio- and stereoselectivity may be improved.

To test this idea, 4-*tert*-butyl cyclohexyl derivatives **5a** and **5b** were formed and reacted under the standard one-pot C–H insertion/olefination conditions (Fig. 2). The expectation was that the *tert*-butyl group would lock the cyclohexane scaffold in a chair conformation to better distinguish the two γ-C–H insertion sites, and improve the diastereoselectivity. Greater control was indeed observed in both cases; γ-lactones **6a** and **6b** were each isolated as single diastereoisomers, with the stereochemical outcome consistent with insertion into the equatorial C–H bonds. However, in both reactions the overall yield was relatively low, which is partly explained by the formation of β-lactone side-products **7a** and **7b** (not shown, see ESI†). Pleasingly, by moving the *tert*-butyl group closer to the C–H insertion site, a significant improvement was observed; 2-*tert*-butyl substrates **5c** and **5d** furnished α-methylene-γ-butyrolactones **6c** and **6d** respectively, with complete diastereoselectivity and a significant increase in isolated yield (76% and 90%), with no β-lactone side-products being formed in either case. The *tert*-butyl group is likely to be playing two roles in these substrates, both fixing the conformation of the cyclohexane ring and providing a steric barrier to competing β-insertion reactions. To further probe this cooperative effect, other 2-subtituted conformationally restricted systems based on menthol and decalinol (**5e**, **5f** and **5g**) were treated under the standard conditions and all afforded the expected γ-lactone products selectively (**6e**, **6f** and **6g**). It is noteworthy that in all cases, there is complete selectivity for equatorial C–H insertion, irrespective of whether the diazoester substituent itself has an equatorial (**6a**, **6c**, **6e**, **6f**) or axial (**6b**, **6d**, **6g**) configuration.

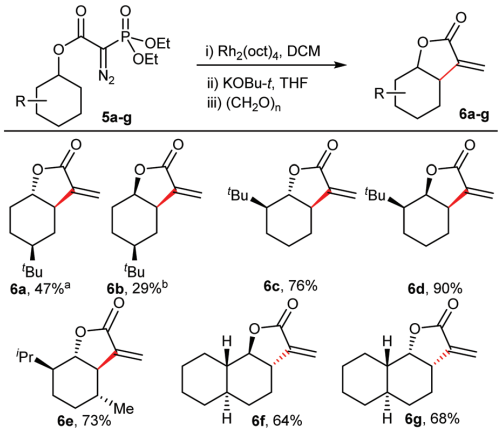


Fig. 2 C–H insertion/olefination sequence for conformationally restricted cyclohexane derivatives **5a–g**. Reaction conditions: (i) $Rh_2(oct)_4$ (2 mol%), CH_2Cl_2, 45 °C, 16 h; (ii) KOBu-*t*, THF, −78 – 0 °C, 1 h; (iii) $(CH_2O)_n$, 0 °C – rt, 1 h. Yields of isolated product. [a] β-lactone product **7a**, (12%) was also isolated; [b] β-lactone product **7b**, (19%) was also isolated.

In view of the excellent regio- and stereoselectivity observed in these reactions, attention turned to their application in natural product synthesis. Sesquiterpene lactones are the most common class of α-methylene-γ-butyrolactone found in Nature[6e,8] and selected compounds from a sub-class of this family collectively known as the eudesmanolides, are shown in Fig. 3 (**8–13**).

First, compounds **8** and **9** (labelled morifolins A and B, Fig. 3) were targeted. As the C–H insertion procedure had not previously been tested on a *cis*-decalin framework (which can potentially ring flip), they were considered to be an interesting challenge to the methodology. An additional reason for performing the synthesis of the morifolins was to clear up confusion that exists in the literature about their structural assignments. In 1985, Dominguez and co-workers isolated a series of sesquiterpene lactones, two of which were named morifolin A and B and assigned the structures **8** and **9** above.[9] However, in a 2004 publication,[10] Herz suggested that these products had been assigned incorrectly, and proposed that they were in fact identical to isocritonilide **10** and critonilide **11**, respectively, described by Bohlmann and co-workers in 1983.[11] The spectral data in the Dominguez publication were insufficient to draw a definitive conclusion, and hence it was decided to complete the total syntheses of lactones **8** and **9** to clarify the anomaly.

The synthesis began with a lithium naphthalenide mediated 1,2-addition of chloride **14** into cyclohexenone,[12] which was followed by oxidative rearrangement with PCC, furnishing α,β-unsaturated ketone **16** (Scheme 1). Next, the 1,4-addition of methylmagnesium chloride under Gilman-type conditions afforded doubly-masked keto-aldehyde **17**. This was followed by an intramolecular aldol reaction under acidic conditions, which furnished *cis*-β-hydroxyketone **18** as a single diastereoisomer, as reported in the literature.[13] Next, silyl protection of the alcohol, vinyl triflate formation and iron-catalysed cross-coupling[14] with methylmagnesium chloride furnished alkene **21** in excellent overall yield. Desilylation using TBAF followed by a T3P-mediated acylation and Regitz diazo transfer reaction, generated the key diazo substrate **24**. This was then primed to undergo the one-pot C–H insertion/olefination sequence, which was performed under the

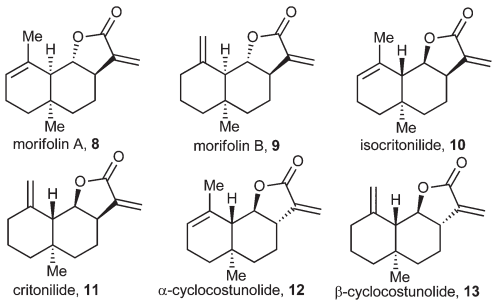
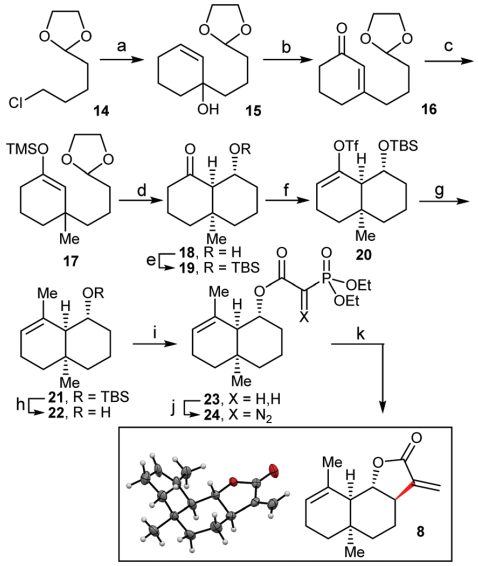
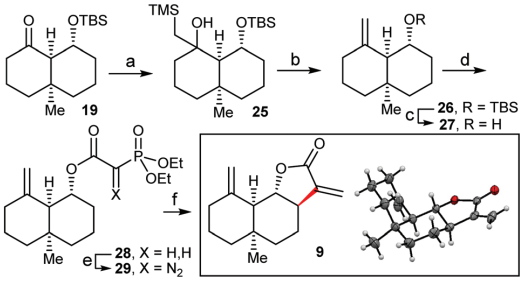


Fig. 3 Eudesmanolide natural products **8–13**.



Scheme 1 Synthesis of α-methylene-γ-butyrolactone **8**. Reagents and conditions: (a) (1) **14**, Li, naphthalene, THF, –78 °C; (2) 2-cyclohexen-1-one, –78 °C – rt, 100%; (b) PCC, Al_2O_3, CH_2Cl_2, 0 °C – rt, 52%; (c) CuI, LiCl, TMSCl, MeMgCl, THF, –78 °C – rt, 98%; (d) 10% aq. HCl, MeOH, 80 °C, 65%; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C – rt, 99%; (f) LHMDS, Tf_2O, THF, –40 °C, 80%; (g) $Fe(acac)_3$, MeMgCl, THF : NMP (1 : 3), 82%; (h) TBAF, THF, 65 °C, 88%; (i) diethylphosphonoacetic acid, DIPEA, T3P, PhMe, rt, 100%; (j) LHMDS, *p*-ABSA, THF, –78 °C – rt, 89%; (k) (1) $Rh_2(oct)_4$ (2 mol%), CH_2Cl_2, 45 °C, 16 h; (2) KOBu-*t*, THF, 0 °C, 1 h; (3) $(CH_2O)_n$, –78 °C – rt, 1 h, 64%.



Scheme 2 Synthesis of α-methylene-γ-butyrolactone **9**. Reagents and conditions: (a) $TMSCH_2Li$, THF, –78 °C, 84%; (b) NaH, THF, 65 °C, 100%; (c) TBAF, THF, 65 °C, 81%; (d) diethylphosphonoacetic acid, DIPEA, T3P, PhMe, rt, 82%; (e) LHMDS, *p*-ABSA, THF, –78 °C – rt, 78%; (f) (1) $Rh_2(OAc)_4$ (2 mol%), CH_2Cl_2, 45 °C, 16 h; (2) KOBu-*t*, THF, 0 °C, 1 h; (3) $(CH_2O)_n$, –78 °C – rt, 1 h, 45% (**9**) and 11% (**30**).

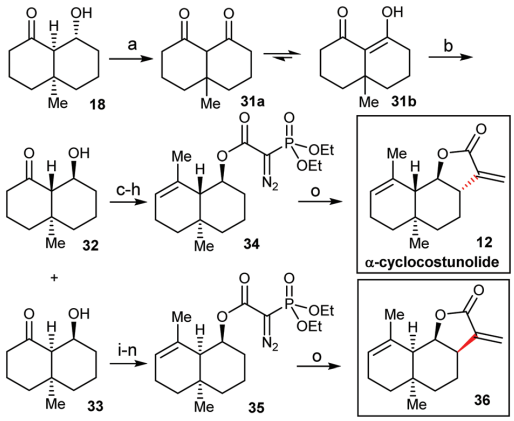
standard conditions, affording α-methylene-γ-butyrolactone **8** in 64% yield with complete stereo- and regiocontrol. The relative configuration of **8** was found to be in line with that observed in the model studies and was assigned unambiguously by X-ray crystallography.[15] With the identity of our synthetic sample **8** confirmed, its spectral data were then compared with those reported for the natural product morifolin A; significant differences between the ^{1}H NMR data of *cis*-decalin **8** and the natural product were clearly observed, thus confirming that morifolin A had indeed been incorrectly assigned. Thus it appears most likely that the natural isolated material named morifolin A **8** is in fact the same as isocritonilide **10**, as suggested previously by Herz.[10]

The synthesis of the proposed structure of morifolin B **9** started with a common intermediate from the morifolin A route, ketone **19**, which was treated with $TMSCH_2Li$ to form alcohol **25** (Scheme 2). This was followed by a base-mediated Peterson olefination to generate exocyclic alkene **26**, and subsequent desilylation, acylation and diazotization as before, to generate diazo substrate **29** in excellent overall yield. Then, $Rh_2(OAc)_4$ catalysed C–H insertion[16] and olefination in the usual way, furnished lactone **9** as a single diastereoisomer (which was again verified by X-ray crystallography),[15] along with a small amount of a cyclopropane side-product **30** (not shown, see ESI†). The ^{1}H NMR data of synthetic material **9** were again significantly different to those published for the natural product,[9] confirming that morifolin B was also incorrectly assigned in the literature. Therefore, similarly to morifolin A, it again seems most likely that the isolated material named morifolin B **9** is in fact the same as critonilide **11**, again as suggested previously by Herz.[10]

Next, attention turned to the synthesis of α-cyclocostunolide **12**,[17] a cytotoxic[18] *trans*-decalin eudesmanolide natural product with anti-trypanosomal[19] and anti-coagulant activity.[20] Its synthesis began with a two-step epimerisation of *cis*-β-hydroxyketone **18** *via* an oxidation–reduction sequence, which provided the desired *trans*-β-hydroxyketone **32**, in addition to diastereoisomeric *cis*-β-hydroxyketone **33** (Scheme 3).[21]

Then, the same sequence shown in Scheme 2 was performed on each of these β-hydroxyketones, affording diazo substrates **34** and **35** without complication. We were then pleased to isolate α-cyclocostunolide **12** as the sole product from the reaction of diazophosphonate **34** under the standard one-pot C–H insertion/olefination conditions, with its spectral data fully matching those of natural α-cyclocostunolide.[17] In addition, diastereomeric lactone **36** was also isolated from diazophosphonate **35**, and was again formed in good yield, *via* selective equatorial C–H insertion.[22]

In summary, a highly regio- and stereoselective one-pot C–H insertion/olefination protocol for the late-stage functionalisation of conformationally restricted cyclohexanol-derivatives has been developed. Exclusive formation of γ-lactones *via* insertion into equatorial C–H bonds was observed and the method was validated in natural product synthesis. Eudesmanolide sesquiterpene natural product α-cyclocostunolide **12** was synthesised in racemic form in high yield using this protocol. In addition, structures **8** and **9**, originally assigned to the natural products morifolin B and morifolin A, were prepared and it was demonstrated unambiguously that the original



Scheme 3 Synthesis of (±)-α-cyclocostunolide **12** and α-methylene-γ-butyrolactone **36**. Reagents and conditions: (a) DMP, CH_2Cl_2, 0 °C, 80%; (b) $NaBH_4$, MeOH, 0 °C, 10% (**32**), 16% (**33**); (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C – rt, 100%; (d) Tf_2O, DTBMP, CH_2Cl_2, rt, 67%; (e) $Fe(acac)_3$, MeMgCl, THF : NMP (1 : 3), 92%; (f) TBAF, THF, 65 °C, 92%; (g) diethylphosphonoacetic acid, DIPEA, T3P, PhMe, rt, 99%; (h) LHMDS, *p*-ABSA, THF, −78 °C – rt, 88%; (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C – rt, 96%; (j) LHMDS, Tf_2O, THF, −40 °C, 62%; (k) $Fe(acac)_3$, MeMgCl, THF : NMP (1 : 3), 59%; (l) TBAF, THF, 65 °C, 71%; (m) diethylphosphonoacetic acid, DIPEA, T3P, PhMe, rt, 63%; (n) LHMDS, *p*-ABSA, THF, −78 °C – rt, 75%; (o) (1) $Rh_2(oct)_4$ (2 mol%), CH_2Cl_2, 45 °C, 16 h; (2) KOBu-*t*, THF, 0 °C, 1 h; (3) $(CH_2O)_n$, −78 °C – rt, 1 h, 52% (**12** from **34**) and 66% (**36** from **35**).

structural assignments were in error. Finally, a fourth isomeric α-methylene-γ-butyrolactone **36**, which is apparently novel, was also prepared.[22] This chemistry is expected to be applicable to a variety of synthetic targets possessing the α-methylene-γ-butyrolactone motif.

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21 The relative stereochemistry of compounds **32** and **33** were assigned retrospectively based on an X-ray crystal structure of a TBS-protected derivative of **32** (**S8**); see CCDC 1421164 and the ESI† for details.

22 To the best of our knowledge, isomer **36** is novel and has not yet been found in Nature, although in view of the high number of related natural products known, it is not inconceivable that it occurs naturally.

Abbreviations

Ac	acetyl
acac	acetylacetonate
acam	acetamidate
AIBN	2,2′-azobis(2-methylpropionitrile)
app.	apparent
aq.	aqueous
Ar	aryl
Bn	benzyl
br	broad
Bu	*n*-butyl
BtH	1*H*-benzotriazole
conc.	concentrated
COSY	correlation spectroscopy
δ	chemical shift
d	doublet
DBSA	4-*n*-dodecylbenzenesulfonyl azide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DEPAA	diethylphosphonoacetic acid
DEPT	distortionless enhancement by polarisation transfer
DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
DTBMP	2,6-di-*tert*-butylmethylpyridine
EDG	electron-donating group
ee	enantiomeric excess
eq.	equivalent(s)
ESI	electrospray ionisation
esp	α,α,α',α'-tetramethyl-1,3,-benzenedipropionic acid
Et	ethyl
ether	diethyl ether
EtOAc	ethyl acetate
EWG	electron-withdrawing group
FGI	functional group interconversion
h	hour(s)
hex	*n*-hexyl
HMBC	heteronuclear multiple bond correlation
HOMO	Highest Occupied Molecular Orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
HWE	Horner–Wadsworth–Emmons
IR	infrared

J	coupling constant (Hz)
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
lit.	literature
LUMO	Lowest Unoccupied Molecular Orbital
m	*meta*
m	multiplet
M	molar
Me	methyl
min(s)	minute(s)
m.p.	melting point
MRSA	Methicillin-resistant *Staphylococcus aureus*
n	normal
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
[O]	oxidation
o/n	overnight
o	*ortho*
OAc	acetate
oct	octanoate
p	*para*
p-ABSA	4-acetamidobenzenesulfonyl azide
PCC	pyridinium chlorochromate
petrol	petroleum diethyl ether 40–60 °C
pfb	perfluorobutyrate
Ph	phenyl
PMP	4-methoxyphenyl
ppm	parts per million
Pr	*n*-propyl
q	quartet
quin.	quintet
rbf	round-bottom flask
R_f	retention factor
RT	room temperature
s	singlet
sat.	saturated
sex.	sextet
t	tertiary
t	triplet
T3P	propyl phosphonic anhydride
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEA	*N,N,N*-triethylamine
tert	tertiary
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl (triflyl)
THF	tetrahydrofuran
TIMO	telescoped intramolecular Michael/olefination
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethyl-ethane-1,2-diamine
TMS	trimethylsilyl
tpa	triphenylacetate
trityl	triphenylmethyl
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet
vis	visible

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