THE UNIVERSITY of York

Towards the Total synthesis of Phacelocarpus-2-pyrone A:

Novel 2-pyrone chemistry

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2010

Authors Declaration

I declare that all of the work detailed within this thesis is my own, and that any material not my own is clearly referenced or acknowledged in the main body of the text. All work was conducted between October 2006 and May 2010.

Michael John Burns

1st June 2010

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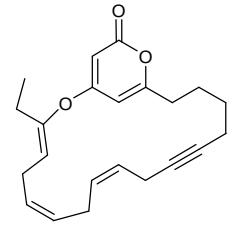
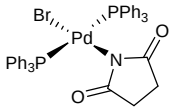
Abstract

This thesis describes the progress made towards the synthesis of the natural product phacelocarpus-2-pyrone A and the development of novel synthetic methodology for the synthesis of functionalised 2-pyrones. Initial studies focused on the synthesis of the natural product and the applications of Pd-catalysed cross-coupling reactions using the interesting palladium catalyst, *CatCat.*

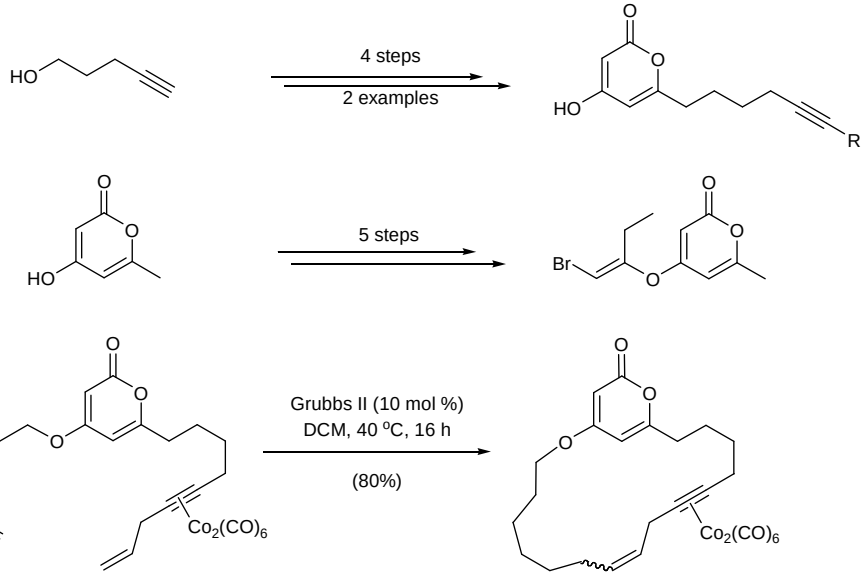


Phacelocarpus-2-pyrone A

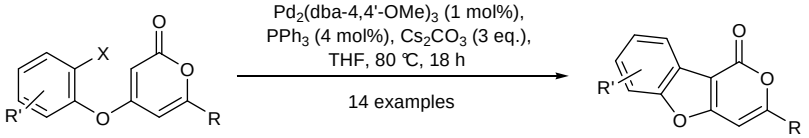


CatCat

Key findings in the studies towards the natural product include: i) the synthesis of two 6-alkyl-4-hydroxy-2-pyrone intermediates suitable for providing a synthetic platform for future work; ii) the first synthesis of a 2-pyrone bound vinyl ether; iii) the synthesis of a 19 membered macrocycle containing 2-pyrone and 1,4-en-yne functionality.



In addition, the first Pd-catalysed intramolecular C-H arylation of a 2-pyrone has been developed and applied to a number of substrates.



Abbreviations

Ac	Acetyl
Acp	Acyl carrier protein
AIBN	Azobisisobutyronitrile
app.	Apparent
aq.	Aqueous
Ar	Aryl
n-BuLi	*n*-butyl lithium
t-BuLi	*t*-butyl lithium
ca.	Circa
cat.	Catalytic
CI	Chemical Ionisation
cm^{-1}	Wavenumber
CoA	Co-enzyme A
COSY	Correlated Spectroscopy
CM	Cross metathesis
CMD	Concerted metallation-deprotonation
cp	1,3-Cyclopentadiene
d (NMR)	Doublet
δ_C	Chemical shift for ^{13}C carbon NMR spectroscopy
δ_H	Chemical shift for ^{1}H proton NMR spectroscopy
dba	*E*,*E*-Dibenzylidene acetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutyl aluminium hydride
DIC	*N*,*N'*-Diisopropylcarbodiimide
DIPEA	Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess Martin periodinane
DMSO	Dimethyl sulfoxide
dppp	1,3-*Bis*(diphenylphosphino)propane

Et	Ethyl
Ether	Diethyl ether
eq.	Equivalents
ESI	Electrospray ionisation (mass spectrometry)
FGI	Functional group interconversion
g (Prefix)	Gram
h	Hours
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear multiple quantum coherence
HRMS	High resolution mass spectrometry
Hz	Hertz
IR	Infrared (spectroscopy)
IPA	Isopropyl alcohol
J	Coupling constant in Hertz
KHMDS	Potassium hexamethyldisilazide
l	Litre
LDA	Lithium diisopropylamide
LIFDI	Liquid Injection Field Desorption/Ionisation
m (NMR)	Multiplet
m (Prefix)	Milli
M (Prefix)	Mega
Me	Methyl
mol	mole
Ms	Mesylate
MS	Mass spectroscopy
MTBD	*N*-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
mw	Microwave
m/z	Mass to charge ratio
NADP	Nicotinamide adenine dinucleotide phosphate
n (Prefix)	Nano
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
O.A.	Oxidative Addition

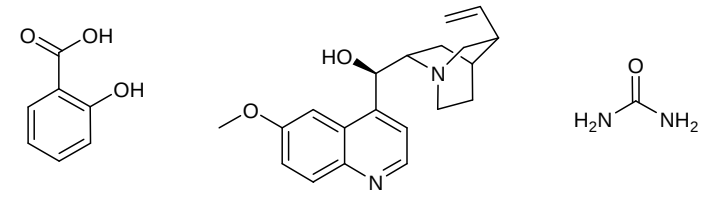
p (NMR)	Pentet
Pet ether	Petroleum ether (boiling fraction 40-60 ºC)
PFP	Pentafuorophenyl
Pin	Pinacol
Piv	Pivalate
pK_a	Acid dissociation constant
ppm	Parts per million
PTSA	*para*-Toluenesulfonic acid
q (NMR)	Quartet
RCM	Ring closing metathesis
R.E.	Reductive elimination
RSA	Retrosynthetic analysis
s (NMR)	Singlet
t (NMR)	Triplet
TBAF	Tetrabutylammonium fluoride
TBDMS	Tertiarybutyldimethylsilane
TEA	Triethylamine
Tf	Triflate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic acid anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
TMS	Trimethylsilane
Ts	Tosylate
UV	Ultra violet
Vis	Visible
µ (Prefix)	Micro

Chapter 1: Introduction

1.1 Introduction to natural products

Natural products have formed the basis of medicine for many hundreds of years. It is well documented in historical literature with examples dating back to the ancient Egyptians, who used tea brewed from willow bark to treat conditions such as fever.[1] The analgesic effect of this treatment is now known to have originated from the medicinal properties of salicylic acid (**1**), a natural product found within willow bark. Subsequently a more potent form of **1** was developed, namely acetylsalicylic acid (more commonly known as Aspirin) one of the biggest selling pharmaceutical products in today's market.[1] Other molecules can be found throughout nature which posess medicinal properties, such as quinine (**2**) (a treatment for malaria).[1]

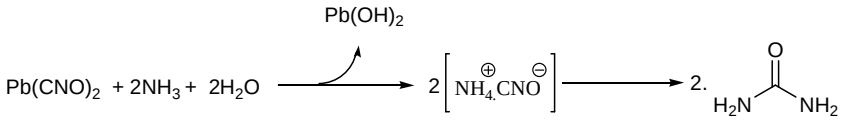
Natural products are usually in very limited supply, and in some cases as little as a few milligrams of the desired product can be isolated from a kilogram of biological material. As a result, the harvesting of natural products from nature rarely represents a feasible supply of such compounds, however the overexpression of the relevant gene in bacteria, such as *E. coli*, and subsequent fermentation can provide large scale quantities.[2] Unfortunately, the fermentation approach is not feasible for the screening of large numbers of natural products and has consequently resulted in the development of natural product synthesis as one of the key areas of research in organic synthesis. This has far ranging effects on organic chemistry, as many of these compounds require the development of new synthetic methodology.



Salicylic acid **1** | Quinine **2** | Urea **3**

Figure 1.1: Common natural products.

The total synthesis of natural products originates from Wöhler's serendipitous synthesis of urea (**3**), whilst attempting to prepare ammonium cyanate (**Scheme 1.1**).[3]



Scheme 1.1: Wöhler's synthesis of urea

Wöhler's discovery is largely considered the foundation of modern organic chemistry through disproving vitalism,[4] which previously stated that organic matter could not be created from inorganic matter. Since this discovery, the field of natural products has attracted much interest. Notably, this area has seen the award of various Nobel prizes. Arguably one of the most important prizes was awarded to E. J. Corey in 1990 for his work on natural product synthesis through the introduction of retrosynthetic analysis (RSA).[4] The use of RSA has proven to be an extremely efficient way to approach the synthesis of natural products and is now widely applied by organic chemists in the modern era.

As the demand for new therapeutically viable compounds increases, through the resistance of certain diseases to their current treatments or for conditions which have no effective treatments, scientists have continued to turn to nature as a source of inspiration. New natural products are constantly being screened for biological activity, providing starting points for the synthesis of promising biologically active targets.[5]

One of the most important attributes for these compounds is to show target selectivity. Often the most biologically active compounds also pose interesting synthetic problems, such as those possessing stereochemistry, regiochemistry and other interesting structural features (*e.g.* large ring and polycyclic ring systems). To date, there have been hundreds of succesfully synthesised natural products, many of which prove to either lack the desired level of biological activity or prove too costly to synthesise on a large scale. Fortunately, some prove to be very effective, such as cortisone (**4**) (a potent anti-inflammatory)[6] and discodermolide (**5**) (an anti-tumour agent) which has attracted alot of attention, with various analogues undergoing preclinical trials.[7]

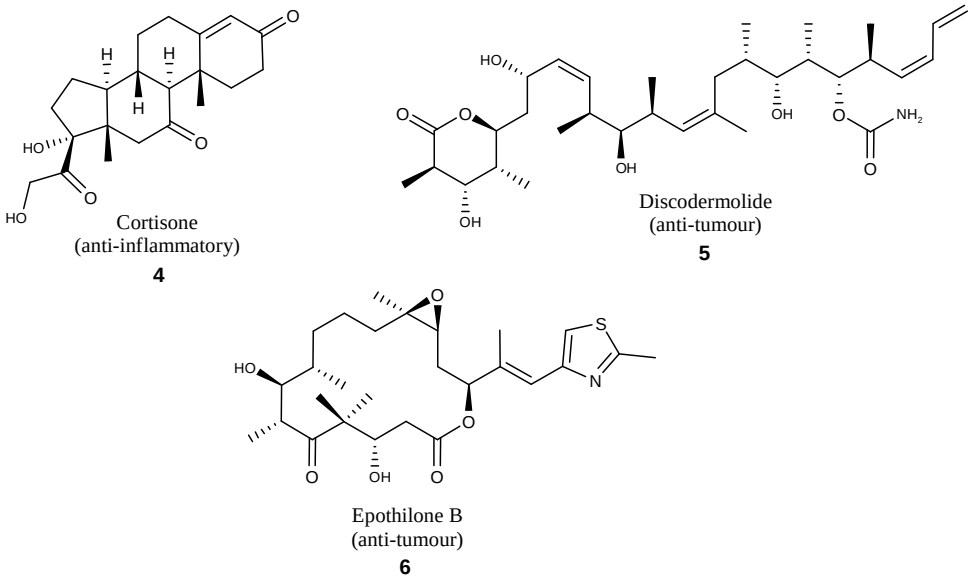


Figure 1.2: Medicinally important natural products.

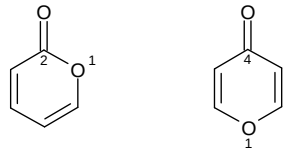
One natural product class described as being therapeutically viable are the epothilones.[8] These compounds show an interesting array of structural complexity with alkene, carbonyl and thiazole functionalities being present, as well as complex stereochemistry throughout the molecule. Significant interest was shown in this class of compounds by the group of Danishefsky *et al.*[9] who reported the first total synthesis of **6** in 1996. Due to the high level of bioactivity shown against certain cancer cell lines these compounds have continued to be studied with many hundreds of analogues having now been synthesised and biological evaluated; some derivatives are currently undergoing clinical trials.[8]

1.2 Introduction to pyrones and natural products containing the pyrone motif

There are many types of natural products which exhibit similar structural features such as polyketide chains, macrocyclic rings, saccharides and heterocycles.[10] The pyranone (or pyrone) substructure is commonly found in bacteria, plants, animals and insects. The pyrone motif often shows biological activity in the form of defence against foreign bodies. It is also found in biosynthetic precursors/intermediates and can be easily metabolised.[11] This particular facet of the pyrone ring system makes them very interesting to study as potential pharmaceutical agents.[12]

Pyrones can exist in one of two major isomeric forms, 2-pyrone and 4-pyrone (also known as α and γ pyrones, respectively) which are assigned on the position of the carbonyl

relative to the oxygen atom within the ring system (**Fig. 1.3**). The parent compounds for both types of pyrone ring system are susceptible to ring-opening by nucleophilic reagents, particularly hydroxide ions, which will predominantly attack the carbonyl position on the 2-pyrone, or in a Michael fashion in 4-pyrone.[13]

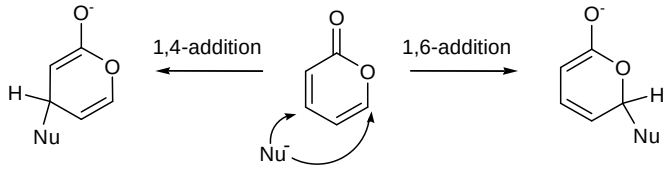


Pyran-2-one (2-Pyrone) **7**

Pyran-4-one (4-Pyrone) **8**

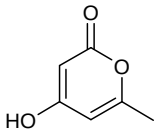
Figure 1.3: The two variations of the pyrone motif.

Due to this reactivity, 2- and 4-pyrones in nature are often found to be substituted on the ring, particularly at the positions most susceptible to nucleophilic attack. 2-Pyrones are often found to contain substituents at the C-4 and C-6 positions, the positions which can stabilise the intermediate species through resonance.

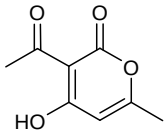


Scheme 1.2: Nucleophilic attack on 2-pyrone.

Two such examples are 4-hydroxy-6-methyl-2-pyrone (triacetic acid lactone **9**) and 3-acetyl-4-hydroxy-6-methyl-2-pyrone (tetraacetic acid lactone **10**). 4-Hydroxy-6-methyl-2-pyrone **9** is an interesting compound due to its ability to tautomerise to 4-pyrone and promote electrophilic substitution at both C-3 and C-7 positions.[14] Both of these compounds are biologically synthesised from acetic acid and are metabolised back to acetic acid *in vivo*.[15] A vital aspect in drug discovery and design is the metabolism of the test compound, but crucially one needs to know whetherby-products affect the host. The formation of this non-toxic chemical, combined with the reactivity at the C-3, -OH and C-7 positions, make these compounds an excellent starting point for the synthesis of complex natural product targets.[16,17]



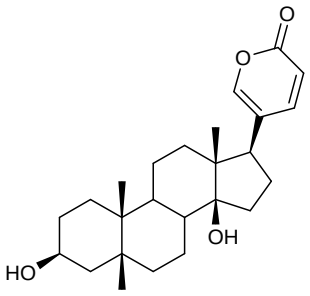
4-hydroxy-6-methyl-2-pyrone
9



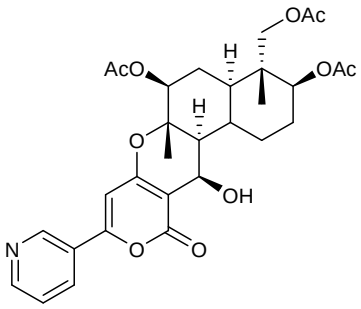
3-acetyl-4-hydroxy-6-methyl-2-pyrone
10

Figure 1.4: Simple 2-pyrones found in nature.

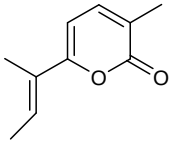
The 2-pyrone motif is found in many types of natural products such as bufadienolides (**11**), peripyrones (**12**), gibepyrones (**13**), fusapyrones (**14**) and coumarins (**15**) (**Fig. 1.5**).[10] Such examples show the extensive diversity in the size and complexity of natural products containing the 2-pyrone motif.



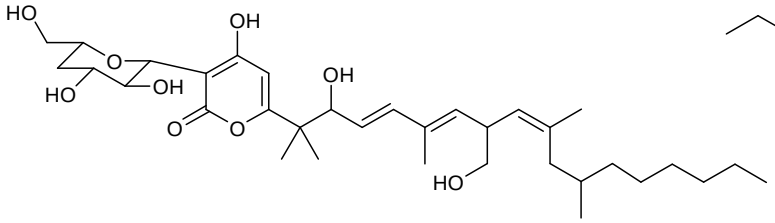
Bufalin
11



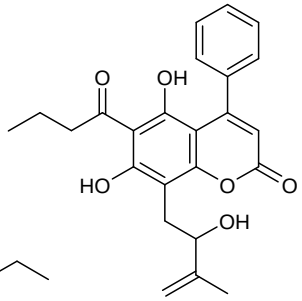
Pyripyropene A
12



Gibepyrone A
13



Fusapyrone
14



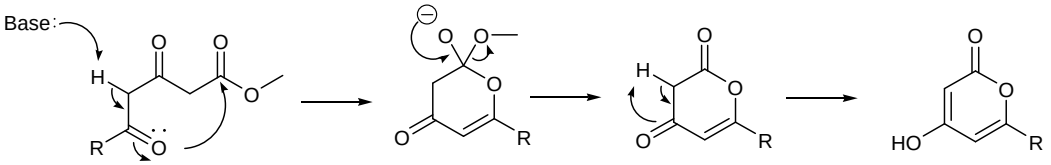
Racemosol
15

Figure 1.5: Complex 2-pyrone containing natural products.

The structural diversity shown by 2-pyrone-containing natural products is mirrored through their biological effects, *e.g.* as anti-bacterials, anti-fungals, agents acting against Alzheimer's disease, HIV, cholesterol-lowering and cancer treatments. The biological activity in all of these examples is thought to be as a result of enzyme inhibition.[18,19, 20, 21, 22]

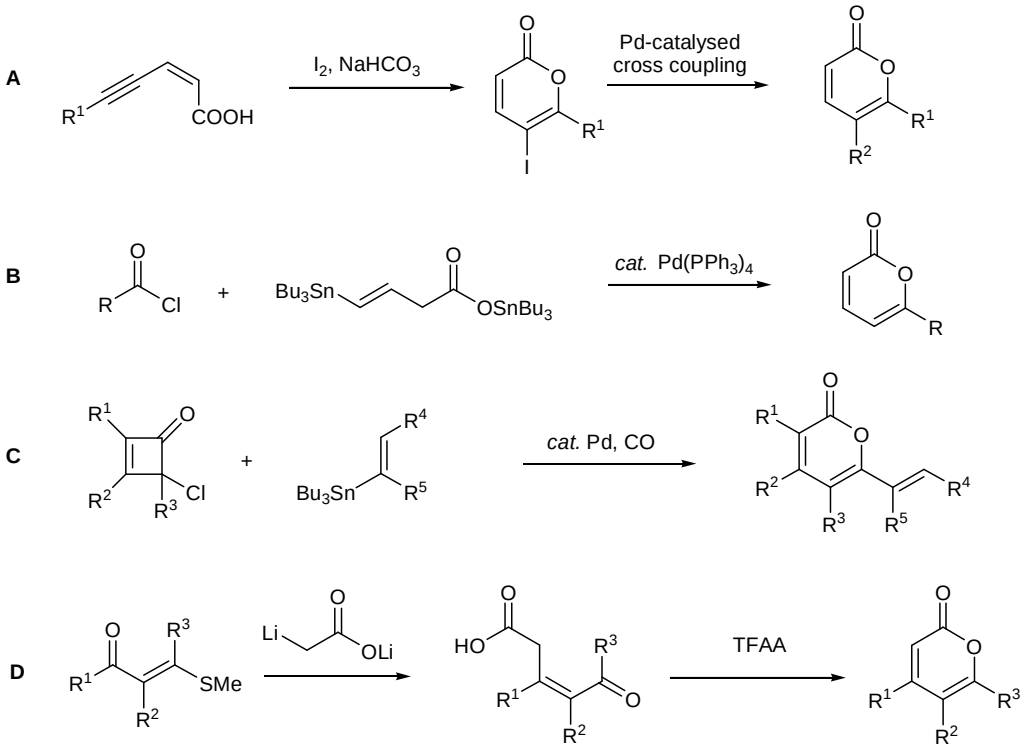
Due to the biological effects of 2-pyrone-containing natural products, it is understandable that they have been the source of study for many years, and subsequently a number of synthetic routes have been developed in order to access the 2-pyrone motif.

4-Hydroxy-6-alkyl-2-pyrones are commonly obtained *via* a biomimetic synthesis using a polyketide chain **(Scheme 1.3)**. Treatment of the appropriately substituted 3,5-diketo ester with a suitable base generates the desired 2-pyrone.



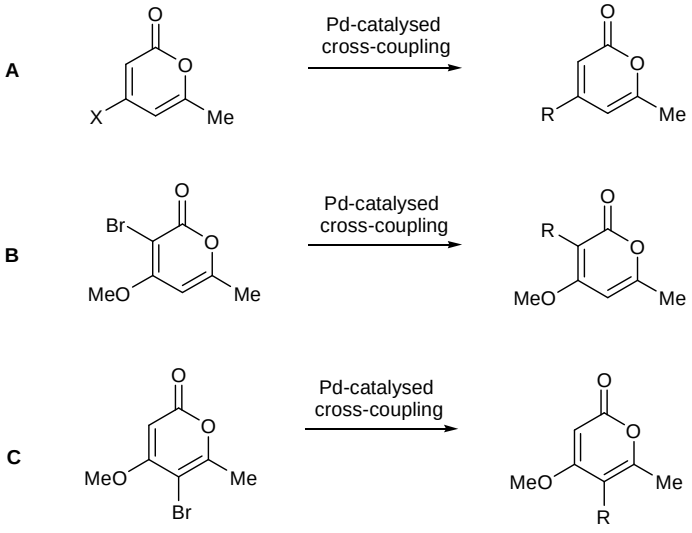
Scheme 1.3: Biomimetic route to 4-hydroxy-6-alkyl-2-pyrones.

Many other synthetic routes to 2-pyrones have utilised novel methodology involving both organic and organometallic pathways. Transition metals have been shown to be highly useful for the formation of 2-pyrones, with palladium proving particularly popular. In 2001, Bellina *et al*. showed that 5,6-difunctionalised 2-pyrones were easily accessible through the reaction of ene-ynoic acids with iodine, followed by either Stille or Negishi cross-coupling (**Scheme 1.4-A**).[23,24] Parrain *et al.* improved upon the use of Stille reactions in 2-pyrone formation, where 2-pyrones could be formed in a one step reaction of an acyl chloride with a distannane (**Scheme 1.4-B**).[25] Another interesting stille based approach was that of Liebeskind and Wang who demonstrated Pd-catalysed carbonylative cross-couplings of chlorinated cyclobutenones with various stannanes, which then underwent rearrangement to form the 2-pyrone motif (**Scheme 1.4-C**).[26] Other innovative approaches have focused on more traditional organic methods to generate the 2-pyrone moiety, such as that of Dieter and Fishpaugh who in 1987 utilised vinyl thiol ethers to create 2-pyrones showing excellent functional group diversity (**Scheme 1.4-D**).[27]



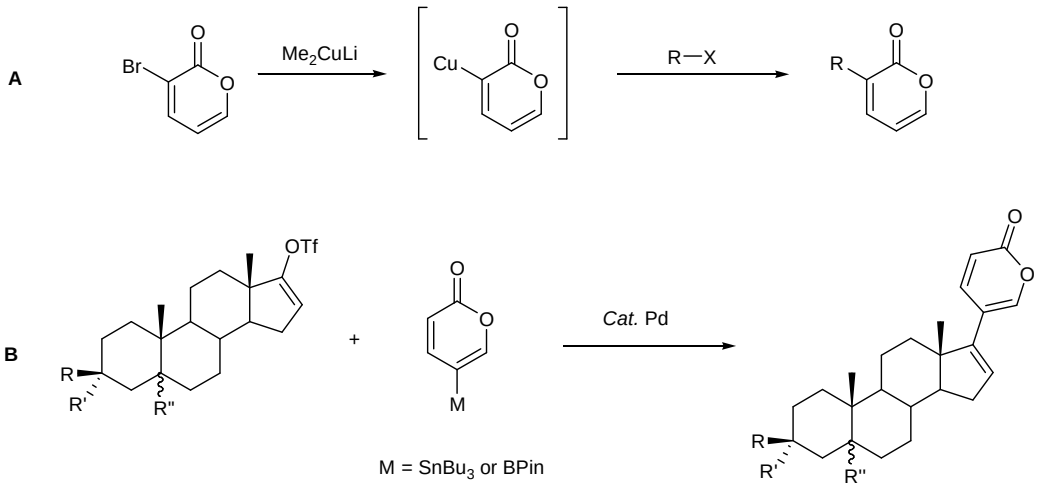
Scheme 1.4: Examples of organometallic and organic syntheses of 2-pyrones

Palladium-catalysed reactions utilising 2-pyrones has been widely studied. In addition to the examples shown in Scheme 1.4, work by Fairlamb and co-workers has shown that halides or *pseudo*-halides derived from **9** are able to undergo a number of Pd-catalysed reactions including Suzuki, Sonogashira and Negishi cross-couplings (**Scheme 1.5-A)**.[28] In addition, the C-3 and C-5 positions are easily halogenated and the subsequent C-X bond can participate in a multitude of Pd-catalysed reactions (**Scheme 1.5-B/C**).[29, 30]



Scheme 1.5: Cross-coupling reactions of halogenated 2-pyrones.

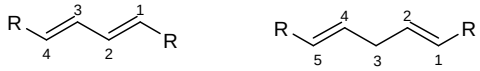
The examples given in Scheme **1.5** rely on the 2-pyrone providing the organohalide derivative for Pd-catalysed cross-couplings, however it is also possible for the 2-pyrone to provide the organometallic derivative. One of the first organometallic 2-pyrone derivatives synthesised was the cuprio-pyrone devised by Posner and co-workers as an effective nucleophile.[31] More recent work has shown the 2-pyrone can support stannane and boronate functionality for Pd-catalysed cross-couplings, as shown by Liu and Meinwald and also Gravett *et al*. in their respective approaches to the bufadienolides (**Scheme 1.6**).[32, 33]



Scheme 1.6: A) Posner's cuprio-pyrone; B) Cross-coupling approaches to bufadienolides

1.3 Introduction to skipped dienes and natural products containing the skipped diene motif

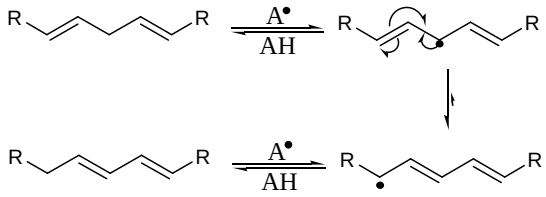
A diene is a structural motif that contains two alkenes, which can be separated by any number of other atoms. The most common is a 1,3-diene, whereby two alkenes are positioned such that only a single bond separates them. In this instance the two π-systems are able to overlap to form an extended conjugated system through the delocalisation of electrons through the extended π-system. The delocalisation results in the formation of a degree of double bond character in the single bond, thus making it a stronger bond and more stable to a variety of conditions. Another common form is the 1,4- or 'skipped' diene, where two single bonds separate the alkenes and prevent conjugation.[34]



1,3-diene 1,4-diene

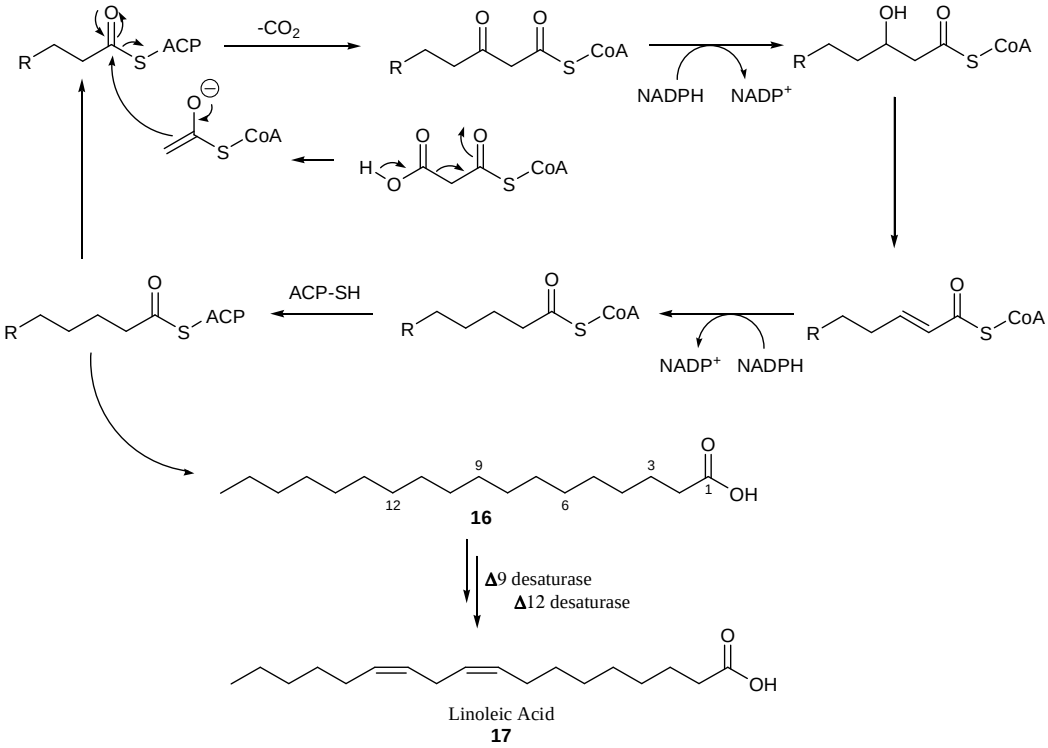
Figure 1.6: Two common diene motifs.

Though relatively stable to most conditions, skipped dienes are particularly vulnerable to oxidation. For example, radical formation can occur at the central carbon allowing a facile rearrangement of the skipped diene to form the more stable 1,3-conjugated form. Upon termination of the radical the more stable 1,3-diene will always be preferred (**Scheme 1.7**).[35]



Scheme 1.7: Radical rearrangement of a skipped diene

The skipped 1,4-diene motif is regularly observed in natural products despite this instability with the most prevalent occurence being within the long hydrocarbon chains of fatty acids. One example is the essential fatty acid, linoleic acid (**17**) which is biosynthesised via a polyketide extension reduction pathway,[36] to give octadecanoic acid (**16**), which then undergoes successive desaturation by Δ9 and Δ12 desaturases to give **16 (Scheme 1.8)**. [37,38]



Scheme 1.8: Biosynthesis of Linoleic Acid (**17**)

Linoleic acid is a vital precursor to many bioactive natural products including arachidonic acid (**18**),[39] epilachnadiene (**19**)[40] and isoprostanes (**20**)[41] which all maintain the enzymatically acquired skipped 1,4-diene **(Fig. 1.7)**.

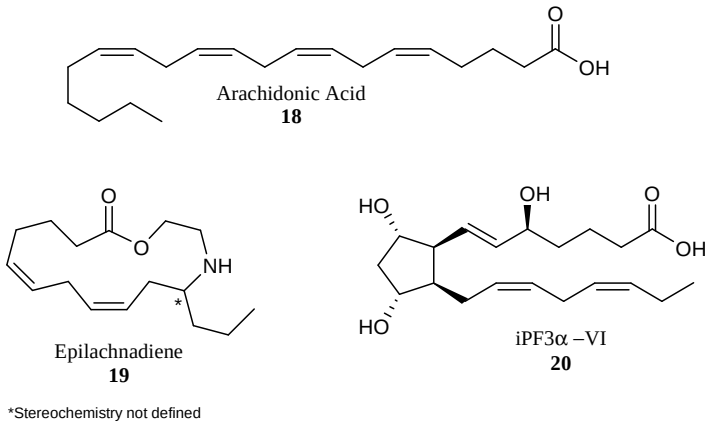
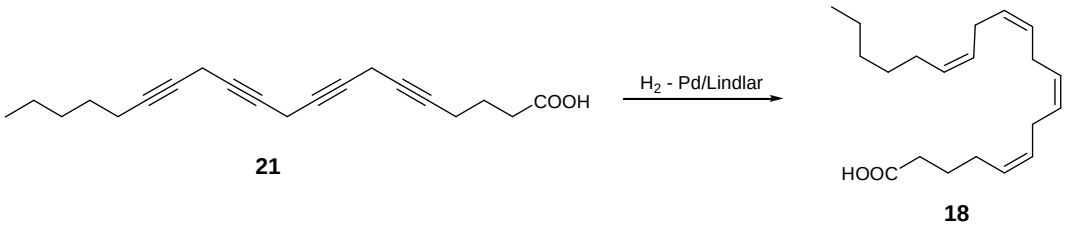


Figure 1.7: Skipped 1,4-diene containing natural products.

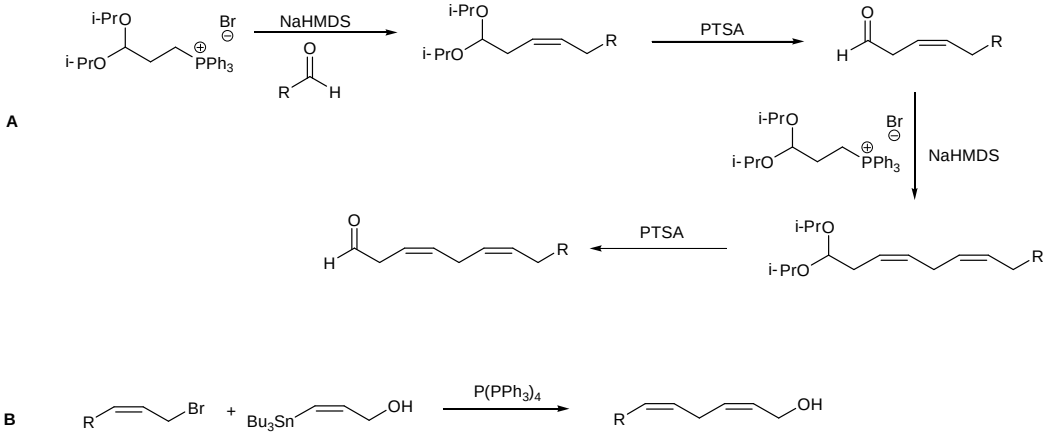
Skipped 1,4-diene containing natural products are known to be involved in many important biological functions such as cell signalling, control of inflammation, anti-asthmatic,[42] anti-predatorial,[43] and anti-diabetic.[25] The laboratory synthesis of this motif has therefore been subject to synthetic studies for over four decades. Due to the long-term instability of these compounds, the skipped 1,4-diene motif is often generated towards the end of the synthesis, with a simple motif used instead, which is stable to various conditions and leads to facile access of the alkenes required.

Alkynes are stable to a number of chemical environments and can easily be protected by a dicobalt(0) hexacarbonyl motif.[44] The selective hydrogenation of alkynes to *cis*-alkenes by Lindlar catalyst[45] provides a straightforward method for introduction of the alkene functionality. The use of the alkynyl strategy was exemplified by Osbond *et al*. in 1959 during the total synthesis of arachidonic acid (**18**) **(Scheme 1.9)**.[46] The iterative use of propargylic units to generate the 1,4-alkyne motif was complemented by a final step hydrogenation of four alkynes to generate **18**.



Scheme 1.9: Osbond's approach to **18**

The use of other transition metals in the selective hydrogenation of alkynes are also known using copper,[47] nickel[48] and titanium.[49] Other approaches have utilised methods which give access to the skipped diene directly, employing the repetitive use of the Wittig reaction, as usedby Santelli *et al.*[50] (**Scheme 1.10-A**), or the Stille cross-coupling of vinyl stannanes with allylic halides as utilised by Badone *et al*. (**Scheme 1.10-B**).[51]



Scheme 1.10: Various syntheses of the skipped diene motif.

1.4 Introduction to palladium catalysis in natural product synthesis

The use of transition metals, particularly palladium,[52] has become increasingly popular in the synthesis of natural products, with recent examples such as Takahashi's synthesis of dysiherbaine (**22**),[53] and Jacobsen's synthesis of the γ-pyrone aureothin (**23**) (**Fig. 1.8**).[54]

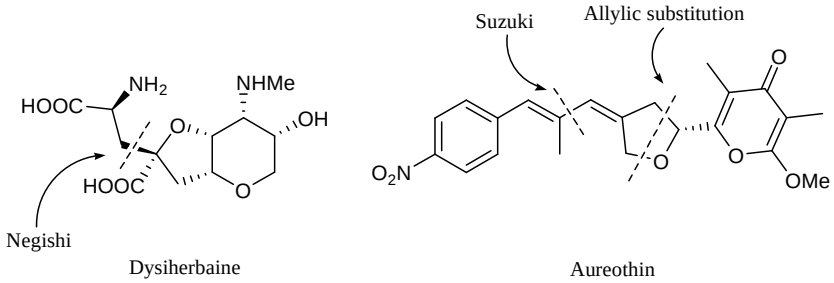
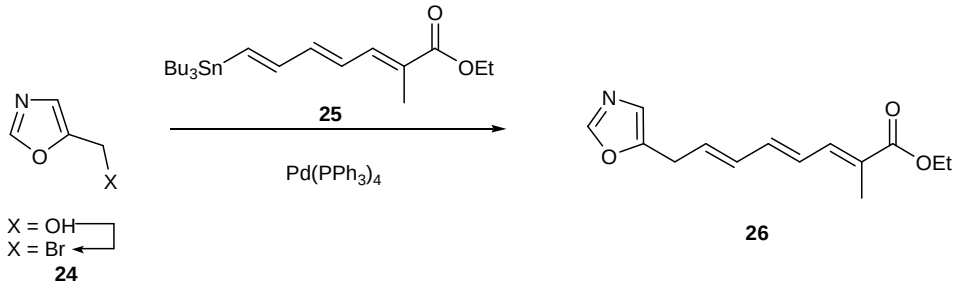


Figure 1.8: Use of Pd catalysed cross-coupling reactions in natural product synthesis.

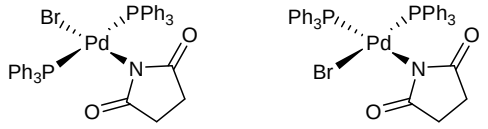
Palladium's ability to catalytically mediate various transformations, increasingly centred around C-C bond formation, making it an essential tool for the modern day organic chemist. The conditions required for catalysis can vary extensively, depending on both the reaction and the palladium complex (including surrounding ligands) being employed. One

of the most commonly employed palladium catalysts is [$Pd(PPh_3)_4$], although in recent times the importance of the mono-ligated species "$Pd(PPh_3)_n$" (n = 1) has become more understood and led to the development of many palladium complexes in a search to identify more catalytically active species for any given reaction.[55]



Scheme 1.11: Stille reaction used in a study of the inthomycins.

During a synthetic study towards the inthomycins by the groups of Fairlamb and Taylor, it was observed that a Stille cross-coupling reaction would only proceed when the preceeding bromination of **24** was performed using NBS and PPh_3 in CH_2Cl_2.[56] If the bromination was performed using CBr_4 as an alternative source of bromine then the consequent Stille coupling failed unless trace of amounts of NBS were added to the crude bromide (**24**) material (**Scheme 1.11**). This was attributed to the oxidative addition of NBS to palladium(0) and led to the discovery of a novel catalyst species for certain coupling reactions. The *cis*-succinimido palladium(II) complex (*cis*-**27**) was later shown to be highly efficient for the Stille cross-coupling of both benzylic and allylic bromides under relatively mild conditions and therefore could be a suitable catalyst for use in the synthesis of molecules containing sensitive functionality.[57] The *cis*-complex can be isomerised to the *trans*-complex (known colloquially as "*CatCat*") by simple heating in toluene.



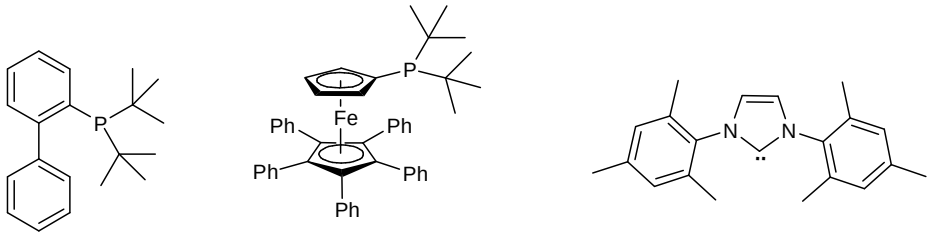
trans-**27** *(CatCat)* *cis*-**27**

Bromobis(triphenylphosphine)(*N*-succinimide)palladium(II)

Figure 1.9: A novel palladium (II) precatalyst.

To date, relatively little work has been carried out in order to ascertain the efficiency of the precatalyst in other Pd-catalysed coupling processes, such as Negishi, Suzuki and Buchwald-Hartwig cross-couplings. This project was set up to consider the use

of various palladium catalysts towards the synthesis of a phacelocarpus 2-pyrone, including simple precatalysts such as **27**, but also more complex catalyst systems possessing ligands such as those reported by Buchwald[58] (**28**) Hartwig[59] (**29**) and the phosphine free *N*-heterocyclic carbene (**30**)[60], which will be used in combination with other palladium precursor sources, *e.g.* $Pd_2(MeO\text{-}dba)_3$ or $Pd(OAc)_2$ (**Fig. 1.10**).[61]

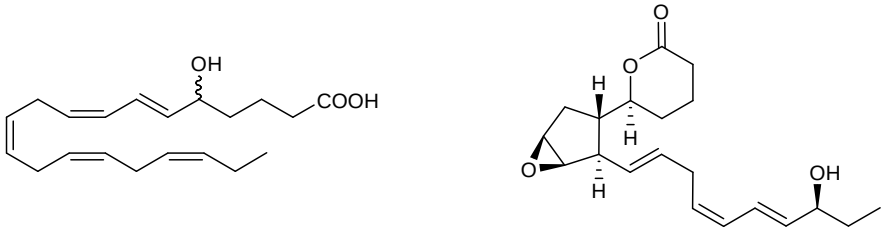


28 **29** (Q-Phos) **30**

Figure 1.10: Alternative ligands for palladium catalysts.

1.5 Introduction to the Phacelocarpus pyrones

Considering approximately two thirds of the earth is covered by water it comes as no surprise that many natural products are found from the abundance of life in the world's oceans, seas and lakes, with over 17,000 different marine natural products reported since 1965.[62] The area of marine natural products is split into several categories based on the microorganism from which the natural products were isolated, which include algae (red, green and brown), sponges and molluscs to name just a few. As of 2002, red algae accounted for approximately 6% of the natural products isolated from marine organisms, many of which have been found to contain brominated polyphenols and terpenes.[16,63] The presence of multiple alkenes is also notable in many of the structures including the oxylipins (**31**) and eicosanoids (**32**), where the alkenes are found to occur in both isomeric forms (*E/Z*), and also in conjugated (1,3) and non-conjugated (1,4) systems.



Oxylipin **31**

Agardilactone (Eicosanoid) **32**

Figure 1.11: Alkene-rich marine natural products isolated from red algae.

The skipped 1,4-diene motif was also discovered in a unique type of natural product isolated from the Australian marine red alga *Phacelocarpus Labillardieri* by Kazlauskas *et al.*[64] Further studies of the alga by Shin *et al.*[65] and Murray *et al.*[66] has resulted in the discovery of nine unique 2- and 4-pyrone macrocycles (*e.g.* **33-38**) each containing the 1,4-skipped alkene motif. These structures also contain an important motif whereby the macrocycle is completed through a vinyl ether found in both *E* and *Z* isomers. Although the vinyl ether motif is well known in natural products,[67] pyronyl vinyl ethers are a novel substructure seen only in the phacelocarpus pyrones.

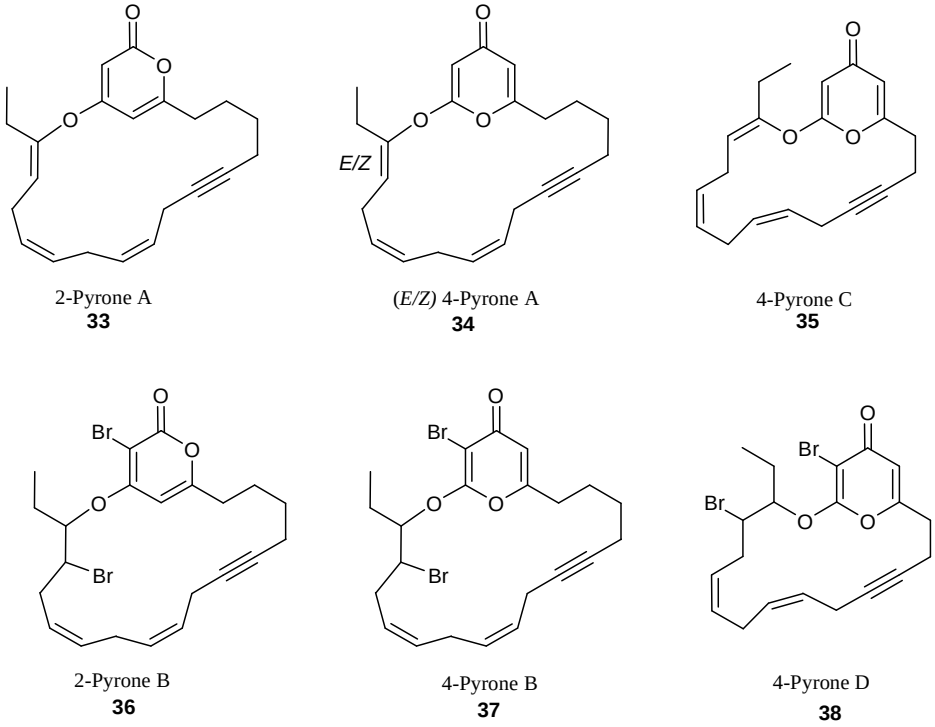
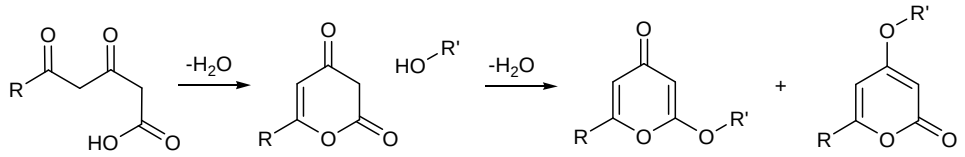


Figure 1.12: Macrocyclic 2- and 4-pyrones isolated from *Phacelocarpus Labillardieri*.[64,65,66]

Crude extracts of the alga have proven to exhibit neuromuscular inhibition, exciting interest amongst chemists due to the unique structure of these compounds. Seven out of the nine isolated pyrone macrocycles contain the 4-pyrone motif, with the remaining two being 2-pyrone analogues. Due to the presence of both 2- and 4-pyrones, the likely biological pathway originates from the cyclisation of a 3,5-diketo acid, followed by an enzymatic reaction with an alcohol to yield one of the two regioisomers, depending on which position the alcohol attacks (**Scheme 1.12**). Should the alcohol in question be tethered to the other

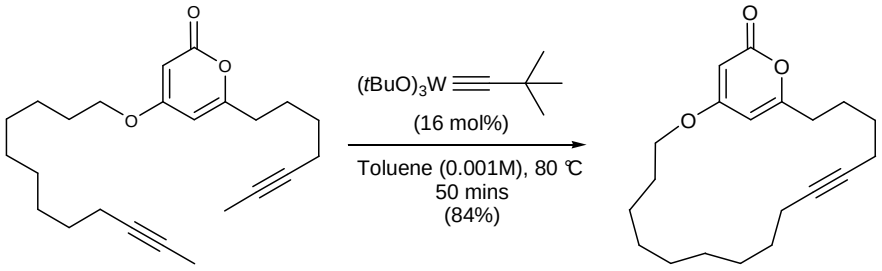
side of the ketolactone intermediate, then the formation of the 2-pyrone and the macrocyclisation can potentially occur in a single step.



Scheme 1.12: Proposed biosynthesis of 2- and 4-pyrones.

Previous work within the group has focused on the synthesis of various 2-pyrones using Pd-mediated cross-coupling reactions and the determination of their biological activity.[18, 68, 69] The phacelocarpus-2-pyrones offer a chance to further develop cross-coupling methodologies and apply them in the synthesis of intricate and challenging molecules.

To date the only studies towards **33** have been performed by Fürstner and co-workers, where they utilised alkyne metathesis in order to generate the desired macrocycle (**Scheme 1.13**).[70] Although the macrocyclisation proceeds well, the approach utilised by Fürstner was solely for the generation of the macrocycle, and does not address the additional alkenes present in the desired product, which are likely to complicate the macrocyclisation, possibly through additional ene-yne side reactions occurring.[71]



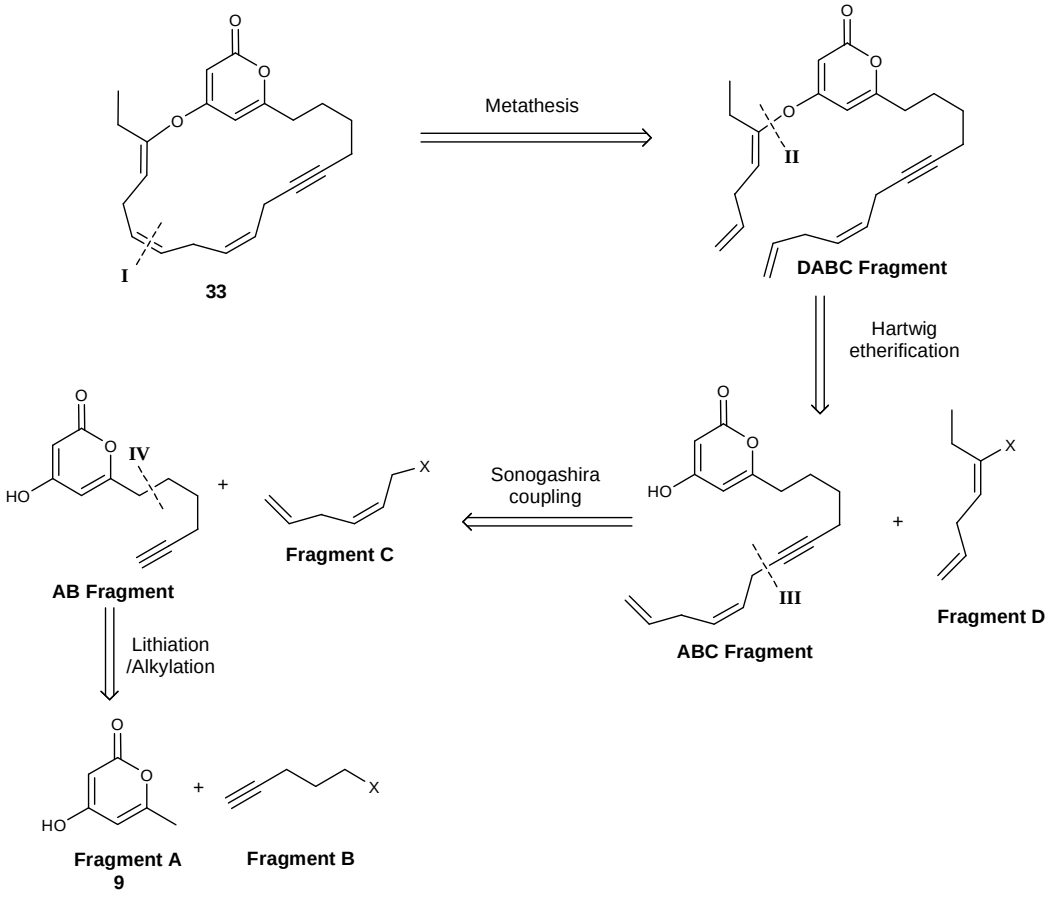
Scheme 1.13: Fürstner's approach to macrocycle formation.

1.6 Retrosynthetic analysis of phacelocarpus-2-pyrone A

The proposed RSA of **33** (**Scheme 1.14**) is centred on breaking down the compound into smaller fragments at points of functionality in order to piece the molecule together in a convergent manner. The RSA of **33** consists of four main disconnections to give four unique fragments. Fragment **A** (**9**) is a commercially available material, making

this the ideal point from which to start a forward synthesis. Fragments **B** and **C** are known in the literature, whereas fragment **D** is unknown and will require a novel synthesis.

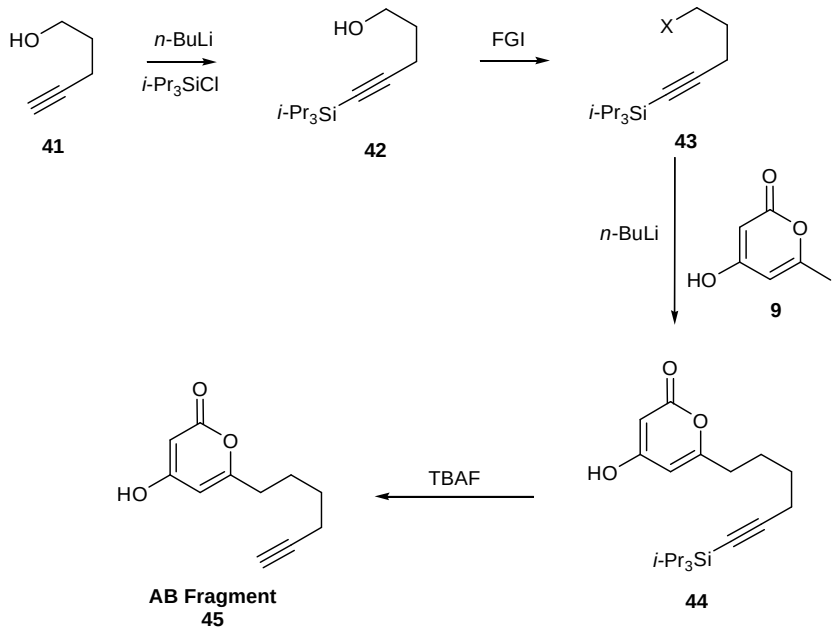
It is envisaged that Pd-catalysed reactions such as the Sonogashira cross-coupling and Hartwig etherification will be incorporated into the synthetic route, however the development of current methodologies may be required for their efficient application.



Scheme 1.14: RSA of 2-pyrone **33.**
(Note: Fragment nomenclature throughout defined by clockwise combination of individual fragments)

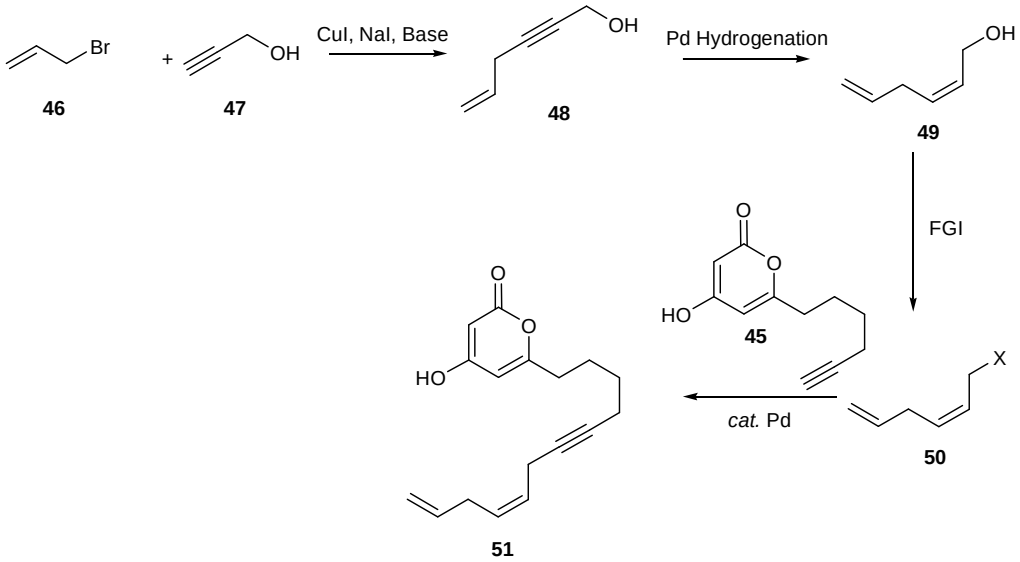
1.7 Proposed forward synthesis of phacelocarpus-2-pyrone A

The initial coupling of fragments A and B utilizes synthetic methodology developed by Zhang *et al.*[10] whereby the 2-pyrone **9** is lithiated at the C-7 position followed by alkylation using an alkyl electrophile. In order for fragment B to react by the correct path, in the presence of *n*-butyllithium, the terminal alkyne needs to protected as a silane (**Scheme 1.15**).



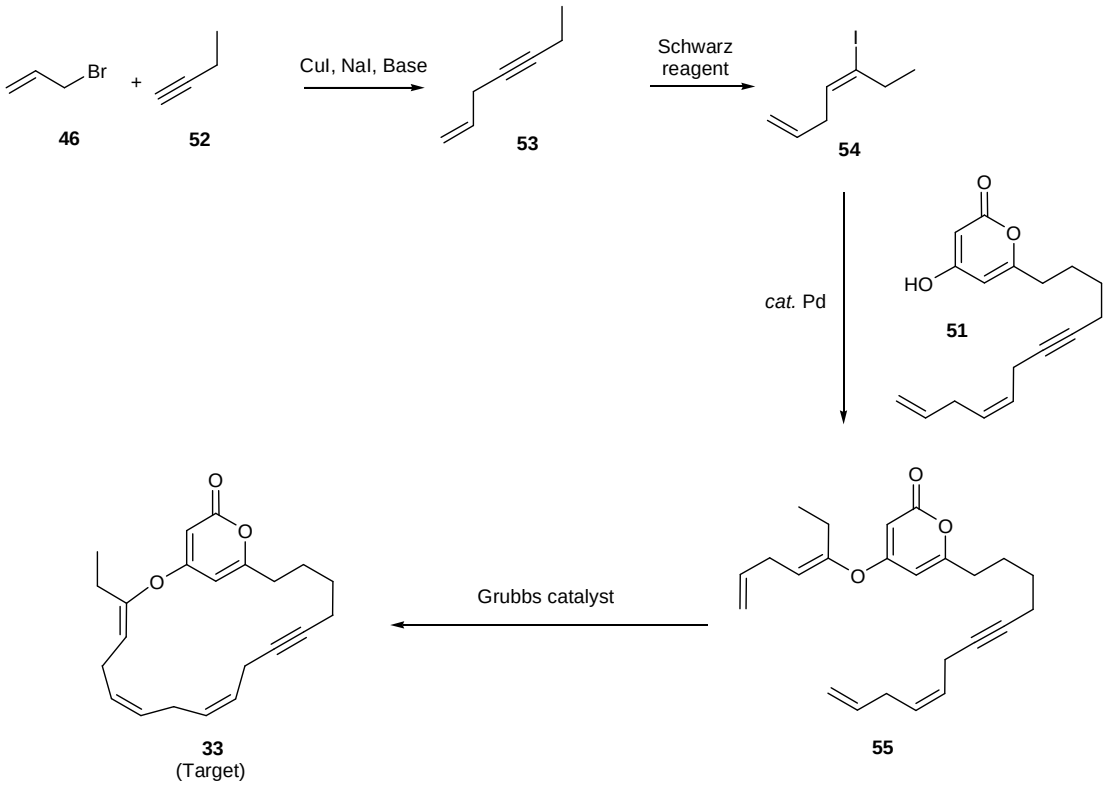
Scheme 1.15: Proposed synthetic route to **45**.

The synthesis of fragment C (**50**) can be envisaged from the known reaction of the highly active allyl bromide (**46**) with propargyl alcohol (**47**) *via* the formation of an organocuprate derived from the terminal alkyne.[72] Selective alkyne hydrogenation of the enyne **48** in the presence of a surface catalyst, such as Lindlar catalyst, would ensure the *cis*-stereochemistry of the central alkene resulting in 1,4-diene **49**. Conversion of **49** to a halide (or *pseudo*-halide) would produce the desired fragment for Sonogashira cross-coupling to **45** in as few as three steps (**Scheme 1.16**).



Scheme 1.16: Proposed synthesis of **51**.

The formation of the vinyl ether poses one of the greatest challenges in the proposed synthetic route due to the potential difficulty associated with the preparation of the fragment D. In order for a Pd-catalysed cross-coupling to be carried out, a vinyl halide precursor would need to be formed. It is likely that this compound would be highly unstable, although recent work by Yu and Jin has found a route to the synthesis of α-halo vinyl ethers.[73] The use of a pseudohalide such as a tosyl group could allow the formation of the desired fragment **55** through the increased stability that this group may provide. The final step of the proposed synthesis would be a macrocyclisation using an metathesis catalyst such as Grubbs' 1st or 2nd generation catalysts.[74] The important factor to consider in this step would be the selective generation of the *cis*-alkene to form the natural product **33** (**Scheme 1.17**).



Scheme 1.17: Proposed synthesis of **55** and **33**.

1.8 Aims and objectives

The overall aim of the work detailed in this thesis is the development of the first synthetic route towards the macrocyclic 2-pyrone **33**. Incorporated into this aim is the desire to develop novel methodology for the synthesis of highly functionalised 2-pyrone derivatives and exploit any interesting observations (*e.g.* C-H activation).

In Chapter 2 we will investigate a methodology towards the total synthesis of **33**. As a part of this work a number of objectives will be followed, namely;

- Extend the use of *CatCat* in Suzuki cross-coupling processes, particularly towards more difficult benzylic and allylic substrates.
- Explore cross-coupling strategies in the synthesis of **33**.
- Extend the lithiation chemistry of 6-alkyl-2-pyrones.
- Develop a vinyl ether synthesis involving the 2-pyrone motif possesing a suitable handle for further manipulations.
- Evaluate alkene metathesis as a macrocyclisation strategy for 2-pyrones.
- Formally identify all novel and known compounds (Chapter 4).

In Chapter 3 we will investigate a novel intramolecular Pd catalysed C-H functionalisation, observed during the course of work towards **33**. As a part of this work a number of objectives will be followed, namely;

- Develop the use of palladium to perform an intramolecular cyclisation
- Extend optimised synthetic methodology to a range of substrates.
- Assess the limitations of the reaction.
- Investigate potential reaction intermediates involved in the catalytic cycle.
- Formally identify all novel and known compounds (Chapter 5).

Chapter 2: Synthetic studies towards phacelocarpus-2-pyrone A

2.1 Suzuki-Miyaura cross-couplings

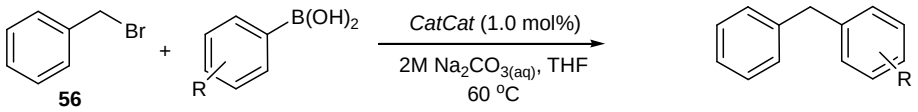
One of the key aims towards the synthesis of **33** is the formation of a 1,4-skipped diene, which can be envisaged through a Suzuki cross-coupling reaction of allylic and vinylic substrates. Whilst this type of cross-coupling has been previously reported, there are limited reports of simple efficient catalytic systems which can perform this type of transformation.[75]

2.1.1 Suzuki-Miyaura cross-couplings of benzyl bromides with aryl boronic acids

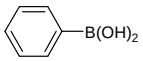
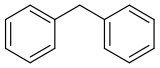
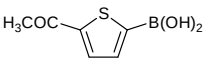
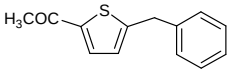
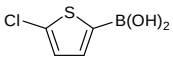
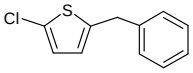
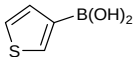
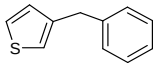
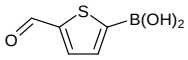
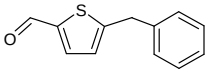
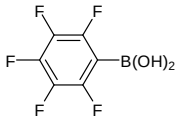
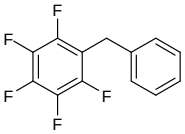
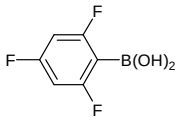
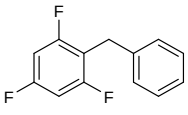
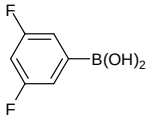
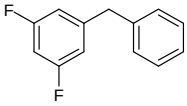
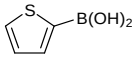
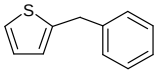
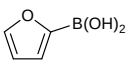
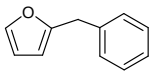
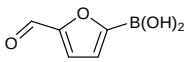
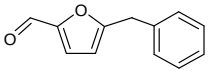
Preliminary studies focused on the Suzuki-Miyaura cross-coupling reactions of various arylboronic acids with benzyl bromides using *CatCat*, namely [*trans*-Pd(Br)*N*-Succ(PPh_3)$_2$] (**27**), as the precatalyst. The primary aim of this section of work was to investigate the use of heteroaromatic components, and evaluate the efficacy of *CatCat*. Stille couplings of organostannanes are reported to be mediated well by *CatCat*, particularly for benzylic and allylic bromides,[76] whereas Suzuki-Miyaura cross-coupling reactions remain unreported. The results from these experiments are shown in Table 2.1.

The results of this study demonstrate that *CatCat* is a useful catalyst for the Suzuki-Miyaura coupling of several thiophene boronic acid substrates with benzyl bromides. The fluorinated boronic acids **67** and **69** proved to be difficult substrates for the reaction, with the poor reactivity attributed to the steric influence of the *ortho*-substitution.

Table 2.1: Yields for Suzuki-Miyaura cross-couplings using *CatCat*.

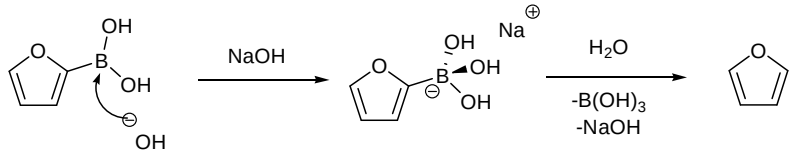


56

Entry	Aryl boronic acids	Products	Time (h)	Av. Yield (%)*
1	 **57**	 **58**	2	88
2	 **59**	 **60**	4	78
3	 **61**	 **62**	4	78
4	 **63**	 **64**	4	93
5	 **65**	 **66**	4	60
6†	 **67**	 **68**	5	5
7	 **69**	 **70**	5	0
8	 **71**	 **72**	5	69
9	 **73**	 **74**	4	91
10‡	 **75**	 **76**	5	0
11‡	 **77**	 **78**	5	0

* Yields based on an average of two runs.
† The reaction was carried out at 80 ºC.
‡ These reactions have since been successful using a different batch of **75** and **77**

Throughout the course of these reactions one of the common problems encountered was the hydrodeborylation of the organoboronic acid (**Scheme 2.1**). This was particularly noticeable with the furan derivatives although further studies within the group showed that coupling occurs when using a different batch of 2-furanboronic acid. This indicates that hydrodeborylation may be occurring as a result of moisture in the air prior to the reaction, as opposed to during the reaction.[77]

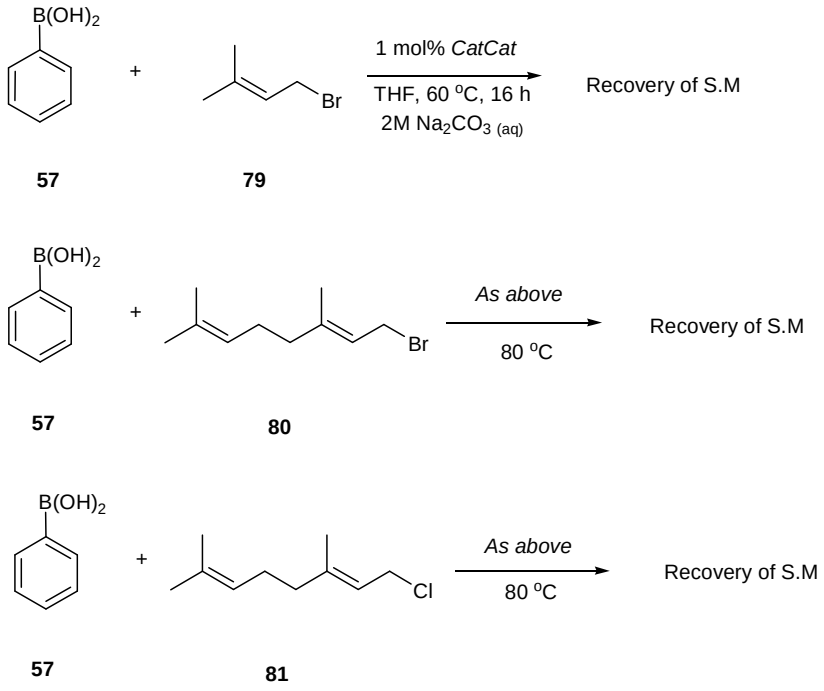


Scheme 2.1: Hydrodeborylation of 2-furanboronic acid.

2.1.2 Suzuki-Miyaura cross-couplings of prenyl and terpenyl substrates

The coupling of the prenyl (**79**) and geranyl (**80**/**81**) halides (**Scheme 2.2**) were attempted to test a system more similar to the natural product, allowing an assessment to be made as to the feasibility of using this type of coupling process in the synthesis of the natural product. Unfortunately, preliminary results indicated that the allylic bromides are a poor substrate for the Suzuki-Miyaura cross-couplings, which stands in contrast to the high reactivity observed with the same substrates in the Stille reaction (reaction with organostannanes). [76]

The high reactivity of allylic and benzylic bromides in the Stille coupling, compared to high reactivity towards benzylic substrates and low reactivity of allylic substrates in the Suzuki-Miyaura coupling could indicate the possibility of a different mechanism for *CatCat* in these apparently similar reactions. Alternatively, the rate of transmetallation could be slowed in the presence of the allylic substrate. Finally, the presence of aqueous base may be hydrolysing the allylic bromides into the allylic alcohols under the reaction conditions.

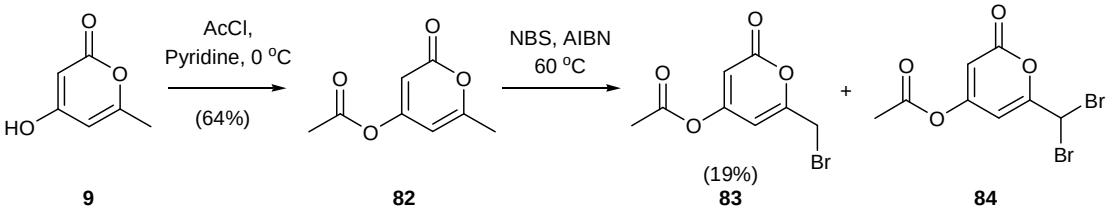


Scheme 2.2: Couplings of terpenyl substrates.

2.2 Studies towards the total synthesis of phacelocarpus-2-pyrone A[65,78]

2.2.1 Alkylation/ lithiation strategy to AB fragment

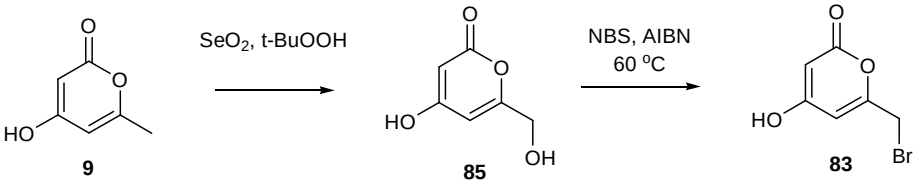
The originally proposed route to the AB fragment (**45**) was *via* the synthesis of a brominated 2-pyrone for use in a Negishi type reaction with fragment B (**43**). The results shown below correlate to the most selective route to the brominated 2-pyrone (**83**) (**Scheme 2.3**), with the major problem being the formation of the unwanted dibrominated product (**84**).



Scheme 2.3: Synthetic route to 6-(bromomethyl)-2-pyrone **83**.

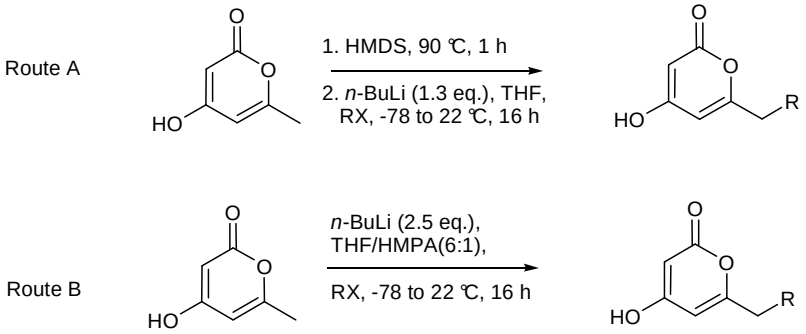
Suzuki *et al.*[79] reported an alternative method (**Scheme 2.4**) which avoids this problem by employing a SeO_2 oxidation to form a primary alcohol on the C-6-methyl

group (**85**), with subsequent conversion of this newly formed primary allylic alcohol to an allylic bromide. The results reported show a slightly improved yield, however an alternative strategy has recently been developed which may offer a synthetic advantage.



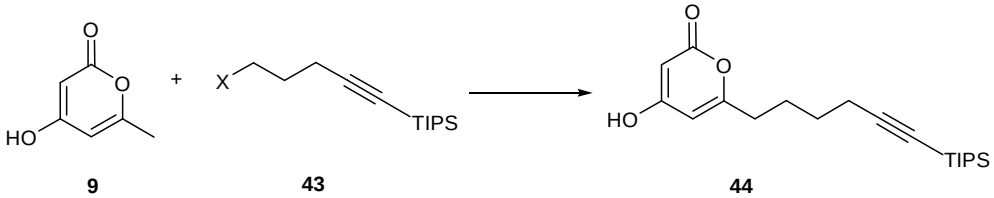
Scheme 2.4: Suzuki's approach to **83**.

Recent work by Swidorski *et al.* has shown that the direct addition of organohalides to unprotected 4-hydroxy-6-methyl-2-pyrone can be selective for the methyl group.[80,81] The implications of this novel methodology for the natural product synthesis are important, as no alterations to the commercially available 2-pyrone **9** would be required, thereby circumventing the formation of the problematic bromide. In the reports by Swidorski *et al.* two synthetic routes were examined (**Scheme 2.5**).



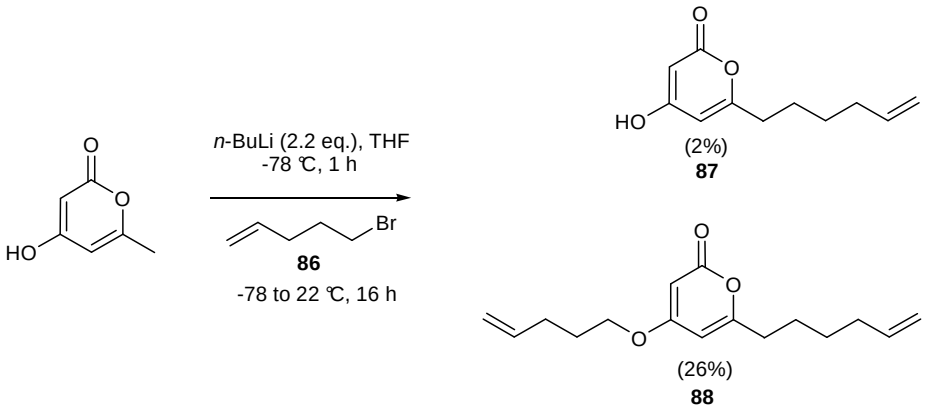
Scheme 2.5: Routes to direct alkylation of 4-hydroxy-6-methyl-2-pyrone

Route A relies on an assumed complete TMS protection of the C-4-hydroxy group, followed by selective monolithiation at the methyl position, electrophilic organohalide attack and removal of the TMS group upon work-up. Route B uses the introduction of HMPA to stabilise a dilithiated intermediate, and was found to be a more effective procedure.



Scheme 2.6: Proposed route to AB fragment.

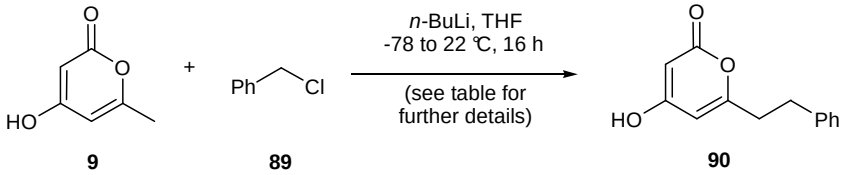
Studies focused on the possibility of using this chemistry for the initial coupling step in the natural product synthesis (**Scheme 2.6**). Preliminary results came from the coupling of various allylic and alkyl halides to 4-hydroxy-6-methyl-2-pyrone, however poor yields of the desired products were obtained with a major problem being double addition onto both the hydroxyl and methyl positions (**Scheme 2.7**).



Scheme 2.7: Initial results from alkylation/ lithiation studies.

The extent of this problem, though not discussed in the literature,[17] led to attempts to reproduce the literature results (**Table 2.2**).

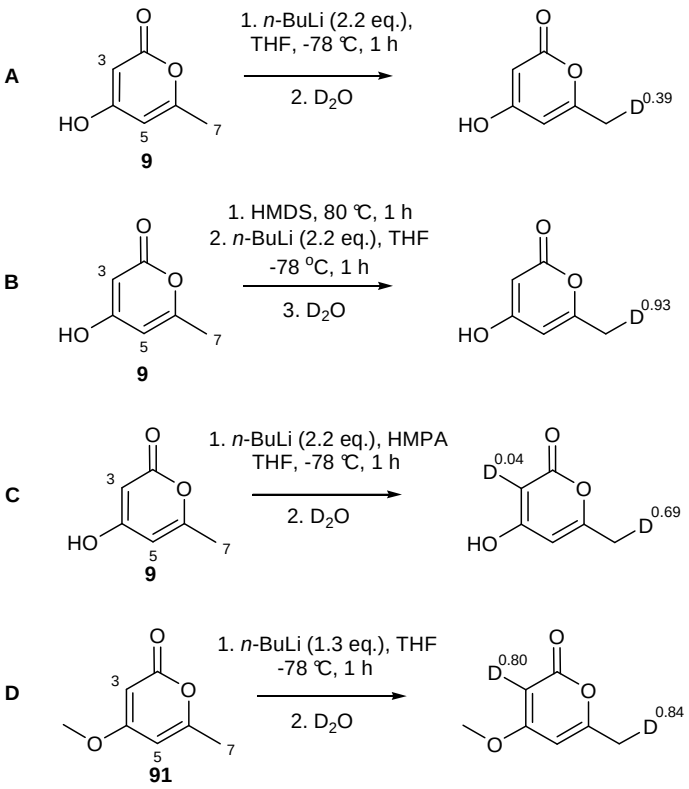
Table 2.2: Repetition of literature procedure for lithiation/ alkylation of **9**.



HMDS	eq. of *n*-BuLi	Additive	Yield (%)	Lit. Yield (%)[17]
10 eq.	1.0	None	13	-
None	2.2	None	7	-
None	2.2	HMPA	15	80

The literature result for the direct addition of benzyl chloride was 80%, almost six times higher than the yields achieved here. The formation of the double addition product was still visible in these cases, and for this reason the addition to the 4-methoxy-6-methyl-2-pyrone **91** was attempted, to remove the interference of the hydroxyl group. Unfortunately, no product was isolated in this case.

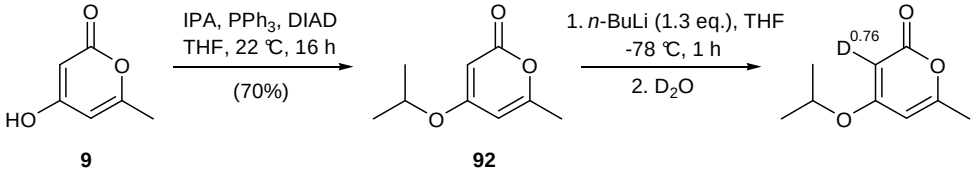
In order to better understand these reactions, research was directed into finding where the majority of lithiation was occurring under the conditions used, through deuteration studies on both the hydroxyl and methoxyl systems (**Scheme 2.8**). Preliminary results showed that the C-5 position of the 2-pyrone underwent no lithiation, allowing levels of deuteration to be calculated by proton integrations correlated to this position on the 2-pyrone ring (by ^{1}H NMR spectroscopy).



Scheme 2.8: Deuteration study of **9** and **91**
(yields not recorded; generally high recovery of material).

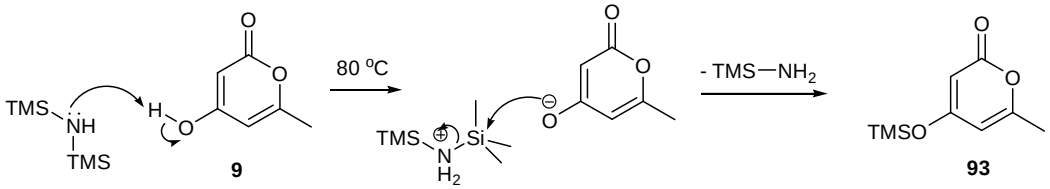
The initial study was towards the dilithiation without any additives, resulting in limited evidence of C-7 functionalisation, with only 39% deuterium incorporation (**Scheme 2.8-A**). The use of an *in situ* silylation using HMDS followed by monolithiation resulted in excellent deuterium incorporation (**Scheme 2.8-B**). The use of Swidorski's optimised conditions, with HMPA additive to stabilise the dilithiated intermediate, resulted in reasonable deuterium incorporation at C-7, but also some incorporation at the undesired C-3 position (**Scheme 2.8-C**). A methyl derivative **91** was also subjected to mono-lithiation conditions, however, increased lithiation is apparent at the C-3 position (**Scheme 2.8-D**).

These findings show that although lithiation does occur at the C-7 position, further lithiation is apparent. In further studies, an isopropyl derivative (**92**) was tested to prevent lithiation occurring at the C-3 position through increased steric bulk. This approach showed that lithiation still occurred at the C-3 position (**Scheme 2.9**).



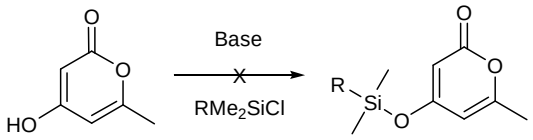
Scheme 2.9: Deuteration study of a hindered 2-pyrone.

The deuteration study indicated that the electronics of the 2-pyrone ring are sufficiently changed by the introduction of an alkoxy group, resulting in a reduction in the lithiation selectivity towards C-7. In the original direct alkylations (**Scheme 2.4**), it was suggested that the HMDS in route A was acting as a silylating agent prior to lithiation. Although there is no mechanism suggested for this transformation, it is possible that the relatively high acidity of the 2-pyrone hydroxyl group leads to the formation of an ammonium salt when combined with the lone pair of the nitrogen in HMDS. The ammonium salt can then act as the protecting group itself, or form the silyloxy species due to the high temperatures employed, with loss of the more volatile TMS amine.



Scheme 2.10: Silyl protection of **9** using HMDS.

The HMDS procedure does not appear to affect the selectivity for the alkoxy derivatives, but increases the level of lithiation occurring at the C-7 position (**Scheme 2.8**). This led to attempts to isolate a silylated 2-pyrone. Despite various bases and water free work-up procedures being employed, no successful silylations were achieved (starting material recovered in all cases- See Appendix 1.1). It is suspected that any silylations that may be occurring are rapidly hydrolysed upon isolation, through trace amounts of water found in the atmosphere.



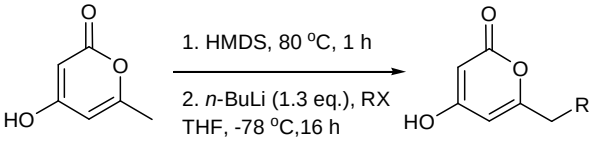
9

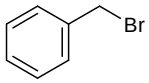
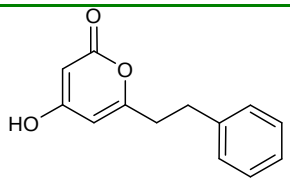
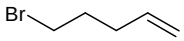
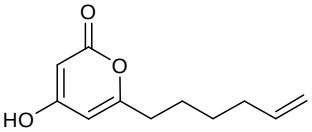
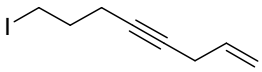
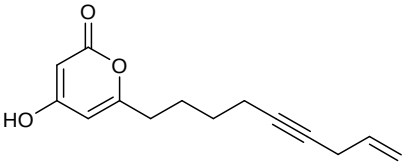
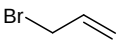
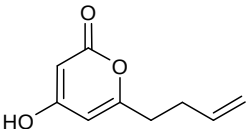
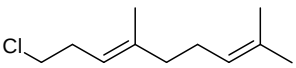
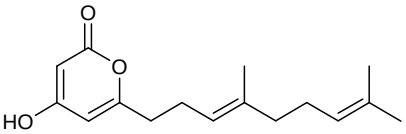
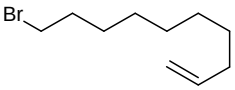
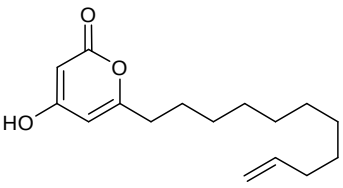
Scheme 2.11: Silylation of 4-hydroxy-6-methyl-2-pyrone (**9**).

Following these results, work returned to the use of HMDS for which the best deuteration results were observed. As these results showed, the problem was not with the extent of lithiation, but with the resulting alkylation. It was found that an increase in the amount of organohalide gives more efficient alkylation, without an increase in the generation of the unwanted dialkylated product, though still not to the level described within the literature.

The lithiation/ alkylation procedure was tested against a range of different electrophiles, with respectable yields observed throughout (**Table 2.3**). In particular, the synthesis of **95** is important due to the pentyne motif observed, which is also present in the natural product. Whilst the yield of **95** is relatively low, these results still represent an acceptable level to apply to the natural product system.

Table 2.3: Results of lithiation/ alkylations of various organohalides.



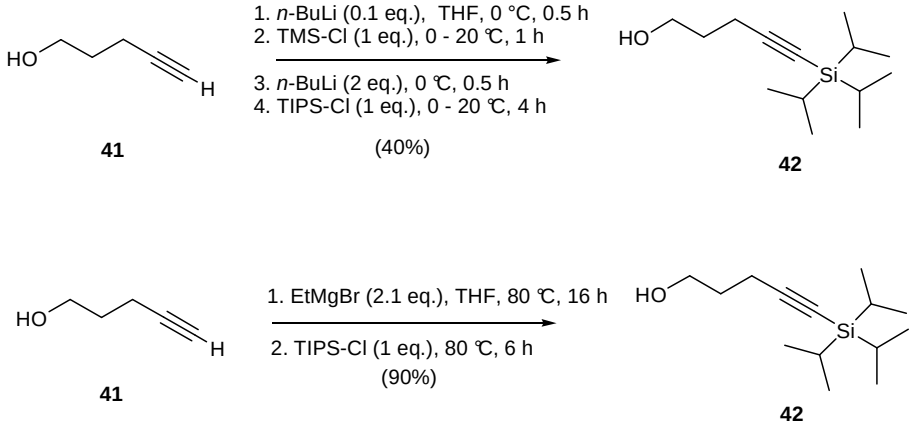
Organohalide (RX)	eq. of RX	Product	Yield (%)
 **56**	2.3	 **90**	40
 **86**	2.3	 **87**	49
 **94**	1.4*	 **95**	32
 **45**	2.3	 **96**	53
 **81**	2.3	 **97**	36
 **98**	1.0*	 **99**	17

* Equivalents of RX limited due to availability.

2.2.2 Synthesis of fragment B

The synthesis of fragment B for coupling to the 2-pyrone has also been studied. Starting from the commercially available 1-hydroxy-pent-4-yne (**41**), TIPS protection, followed by halogenation of the alkyl alcohol, should lead to the desired product in two or three steps.

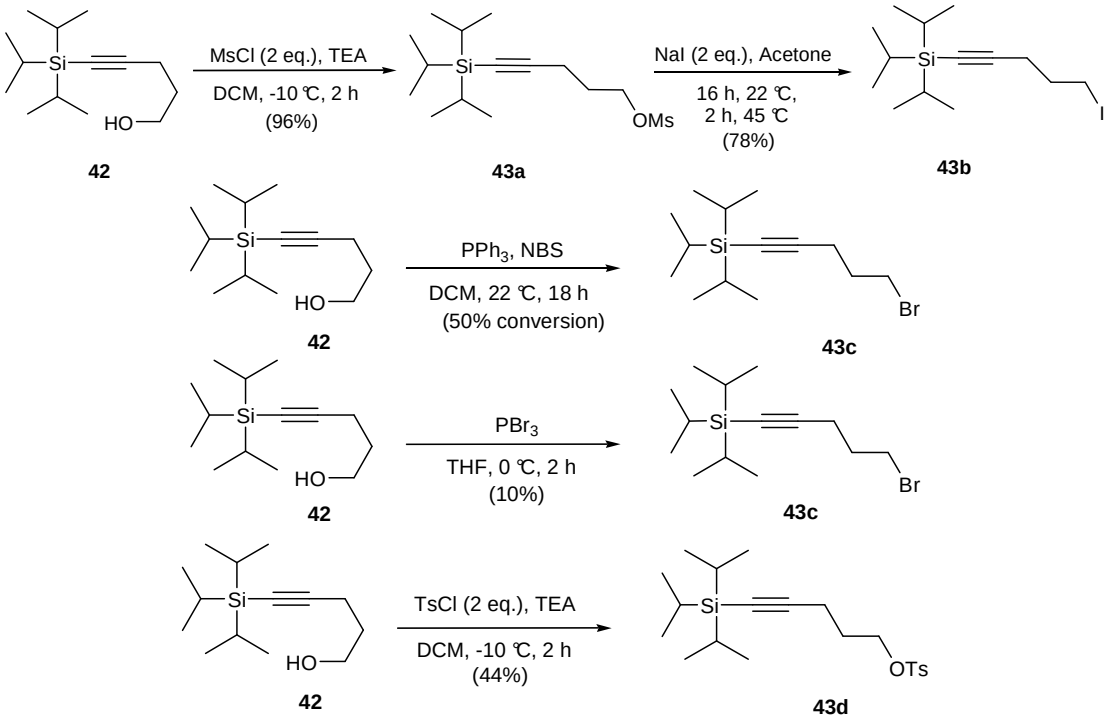
The TIPS protection of the alkyne **41** is known in literature through one of two routes,[82,83] both of which require initial protection of the alcohol (**Scheme 2.12**). The original route is through initial TMS protection of the alcohol, followed by TIPS protection of the terminal alkyne. Alternatively, the higher yielding route involves the reaction of two equivalents of a Grignard reagent, followed by addition of TIPSCl, which gives **42** in excellent yield.



Scheme 2.12: TIPS protection of 1-hydroxy-pent-4-yne.

The halogenation of **42** proved more problematic – three different synthetic routes were attempted. Mesylation (**42→43a**), followed by reaction with NaI, proved successful. However, 1-(triisopropyl)silyl-5-iodo-1-pentyne **43b** has proven to be sensitive to light and silica-gel, causing problems with purification. Further studies have focused on the formation of the 1-(triisopropyl)silyl-5-bromo-1-pentyne **43c**. Two classical brominating reagents have been employed: PBr_3 and PPh_3/NBS. Unfortunately due to the acidic nature of PBr_3 generating trace quantities of H_3PO_4, silyl deprotection of **42** occurred, whereas the use of PPh_3/NBS led to only 50% conversion. The use of the bromide for the alkylation step was therefore deemed as unacceptable due to the inefficiency of the bromination step. Therefore the tosylated pentyne (**43d**) was also synthesised to provide an additional option,

whereby the use of either the mesylate or tosylate can be used as a *pseudo*-halide leaving group for the lithiation/alkylation step.

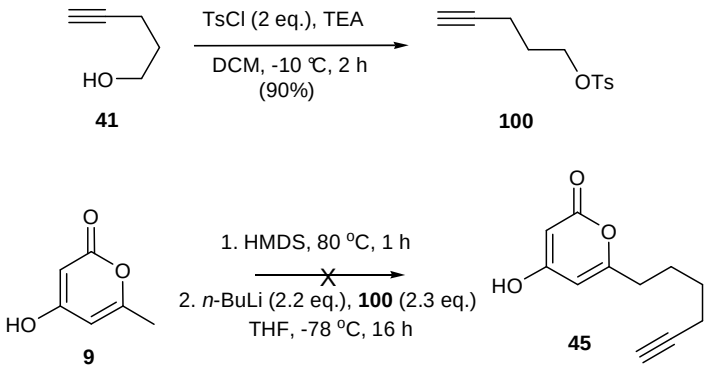


Scheme 2.13: Halogenation of TIPS protected fragment B.

2.2.3 Synthesis of AB fragment

In order to synthesise the AB fragment *via* the lithiation/alkylation route discussed above, the terminal alkyne was protected to prevent deprotonation of the alkyne in the presence of *n*-butyl lithium. Should this occur then it would severely hamper the desired reaction. However, should deprotonation of the alkyne not occur under the reaction conditions, the use of the TIPS protection can be avoided. To test whether the lithiation/alkylation of **9** would occur in the presence of an unprotected alkyne, model substrate **100** was prepared.

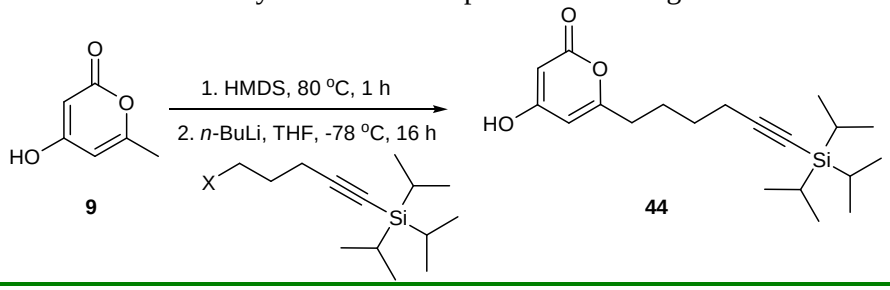
Due to the low molecular weight of the unprotected pentyne **41**, it was decided that the use of tosylate would aid the isolation and handling of this compound. Tosylation of **41** proceeded under standard conditions to give **100** in 90% yield. As expected the use of **100** in the lithiation/alkylation reaction with **9** proved unsuccessful.



Scheme 2.14: Synthesis and use of tosylate **100**.

Although the tosylate was used in this case instead of a halide, it is suggested that the cause of the failure was due to the free alkyne as opposed to an issue with the tosyl group. Due to the poor bromination of the TIPS protected alkyne **41** and the instability of the iodo compound **43b**, the lithiation/alkylation of **9** was attempted using both the mesylate **43a** and tosylate **43d** (as *pseudo*-halides). Unfortunately, in both cases this reaction proved unsuccessful, indicating that the leaving group is important for the reaction. Consequently, the iodo compound **43b**, generated *via* a Finkelstein reaction from the mesylate **43a**, was used immediately after its formation without any purification. The reaction proceeded in good yield despite fewer equivalents of organohalide being employed, affording the desired TIPS protected AB fragment **44** (**Table 2.4**).

Table 2.4: Synthesis of TIPS protected AB fragment **44**.



X	Eq. of organohalide	Yield (%)
OMs	2.3	0
OTs	2.3	0
I	1.7*	70

* Equivalents of organohalide limited due to availability.

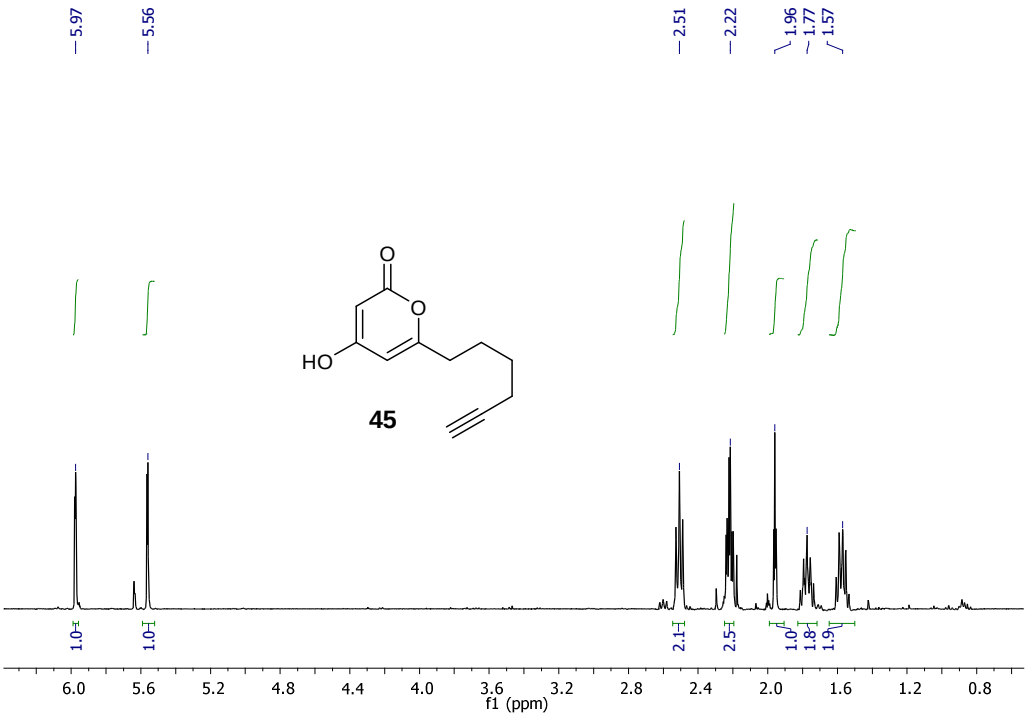
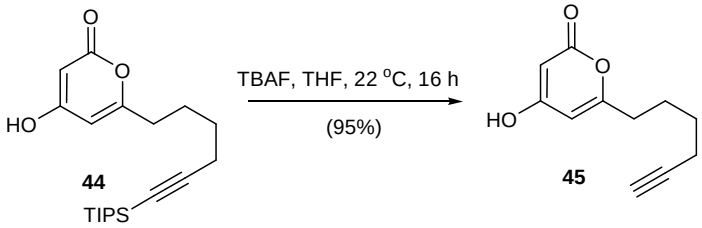


Figure 2.1: ^{1}H NMR spectrum of AB fragment **45** (400 MHz, $CDCl_3$).

The synthesis of the desired AB fragment was achieved by desilylation of **44** using TBAF in THF at 22 ºC to afford **45**. Initial attempts using one equivalent of TBAF led to no desilylation occurring, but increasing the amount to three equivalents led to deprotection in 95% yield, affording fragment AB (**45**) in approximately 60% overall yield from five linear steps.



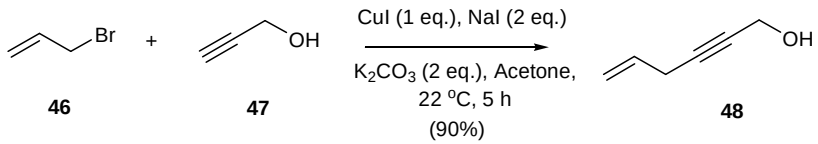
44 **45**

Scheme 2.15: Deprotection of **44** to afford **45**.

The ^{1}H NMR spectrum of **45** is shown in **Figure 2.1**. This confirms the structure of the desired product, despite the presence of trace impurities. The chemical shifts of the 2-pyrone proton signals at δ 5.98 and 5.57 remain largely unchanged in comparison to the signals observed in the starting material. However, the singlet methyl group has disappeared and replaced by a triplet signal (δ 2.51), confirming that alkylation has occurred at the C-7 position. The sharp triplet signal with a small *J* coupling (~2 Hz) at δ 1.95 also confirms the presence of a terminal alkyne proton.

2.2.4 Synthesis of fragment C (49)

One of the most important aspects in the synthesis of fragment C is the introduction of the 1,4-skipped alkene motif and the *cis*-geometry of the internal double bond. One method of introducing a *cis*-alkene would be *via* a selective hydrogenation of an internal alkyne using a heterogeneous catalyst such as Lindlar catalyst or a zinc-copper couple.[84] The precursor for the hydrogenation was synthesised via the reaction of allyl bromide **46** and propargyl alcohol **47**, incorporating the *in situ* formation of a organocuprate and allylic iodide. The reaction proceeded in excellent yield to afford the desired product **48** for the next hydrogenation step (**Scheme 2.16**).

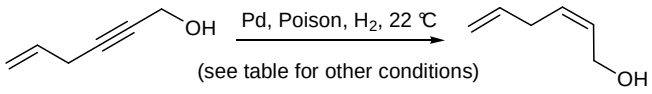


46 **47** **48**

Scheme 2.16: Synthesis of fragment C precursor.

The hydrogenation of **48** to form the *cis*-alkene was attempted under a variety of conditions, without further hydrogenation of either of the alkene motifs. The use of Lindlar catalyst for selective alkyne hydrogenation is well documented and studies were focused on the use of this as the catalyst (**Table 2.5**).[85]

Table 2.5: Hydrogenation studies of hex-5-ene-2-yn-1-ol **48**.

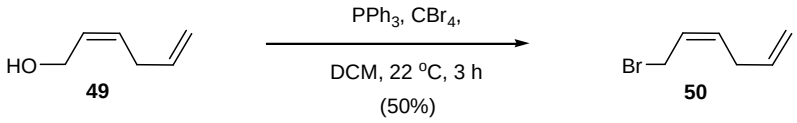


48 **49**

Entry	Solvent	Time (h)	Catalyst	Cat. mol%	Poison	Poison. mol%	Hydrogenation of alkyne (%)
1	MeOH	3	Lindlar	1	Quinoline	10	0
2	MeOH	5	Lindlar	1	Quinoline	2	8
3	Hexane	5	Lindlar	1	Quinoline	1	6
4	MeOH	5	Lindlar	1	Quinoline	1	30
5	MeOH	16	Lindlar	1	Quinoline	1	25
6	MeOH	16	Pd/C	1	Quinoline	1	>99 *
7	MeOH	16	Lindlar	1	-	-	0
8	MeOH	5	Lindlar	1	Pyridine	1	25
9	MeOH	3	Lindlar	4	Quinoline	4	50
10	**MeOH**	**16**	**Lindlar**	**5**	**Quinoline**	**5**	**>99**

* Complete hydrogenation of both alkenes and alkynes was observed.

The hydrogenation studies of **48** first examined the use of low mol% catalyst utilising quinoline as a catalyst poison, however despite varying the quantities of poison and solvent (Entries 1-4) limited hydrogenation had occurred. Moving to a more active Pd/C as a more active surface catalyst led to complete hydrogenation of all unsaturated bonds (Entry 6). After extensive studies, the use of 5 mol% Lindlar Catalyst with an equal amount of Quinoline over 16 hours proved to be the most effective (Entry 10). The completion of fragment C was achieved by an Appel reaction[86] of **49** to give bromide **50** in modest yield (S**cheme 2.17**).



Scheme 2.17: Appel bromination of **49**.

Though successful, this reaction would be expected to proceed in much higher yield.[87] One possible problem associated with this system is the possible formation of both a primary and secondary bromide, dependant upon the point of attack of the incoming bromide anion.

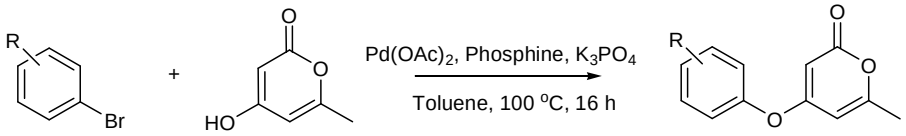
2.2.5 Buchwald-Hartwig etherifications

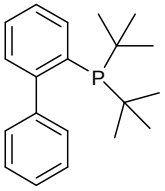
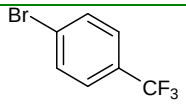
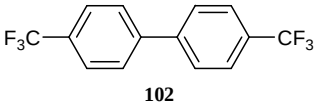
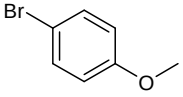
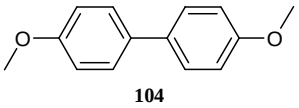
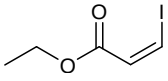
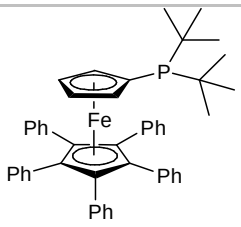
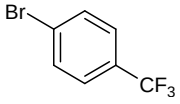
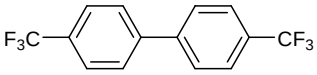
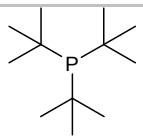
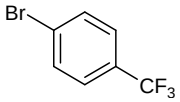
The preliminary focus on the left hand side of the macrocycle was the introduction of the novel vinyl ether motif seen in this class of natural product. The initial RSA suggested the use of Buchwald-Hartwig etherification chemistry, however in order to generate the desired vinyl ether, a new synthetic methodology was required.

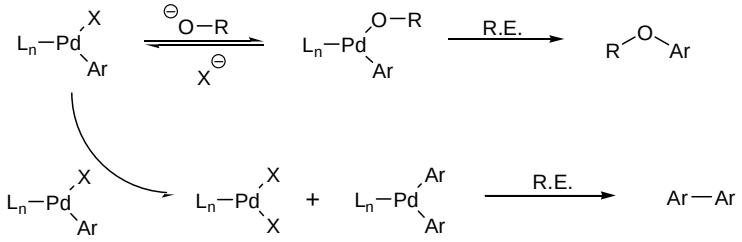
Buchwald-Hartwig etherifications have been the focus of extensive study, although limited to those of mono and biaryl systems.[88, 89] The nature of the reaction dictates the use of extremely active and often sterically bulky phosphines is required in order to promote the reductive elimination. Initial studies focused on trying to generate an aryl-pyronyl ether in order to generate methodology which could then be transferred to the natural product system (**Table 2.6**).

The results of these reactions indicated that the 4-hydroxy-6-methyl-2-pyrone **9** is not sufficiently nucleophilic for these reactions to occur. In a Pd-catalysed cross-coupling, the reactive intermediate formed after oxidative addition can react in one of two ways. Primarily (and desired) is transmetallation which occurs *via* the exchange of a nucleophile with the halide. However, if the rate of exchange is too slow, the Pd intermediate can undergo halide-aryl exchange/scrambling.[90] The resulting "$LPd(Ar)_2$" complex can then reductively eliminate to yield homocoupled product (**Scheme 2.18**). The "PdX_2" intermediate will be reduced under the reaction conditions to also give Pd(0) by a path which has not been defined.

Table 2.6: Buchwald-Hartwig etherification results



Entry	Phosphine	Organohalide	Product	Yield (%)
1	 **28**	 **101**	 **102**	70
2		 **103**	 **104**	85
3		 **105**	No Product.	-
4	 **29 (Q-Phos)**	 **101**	 **102**	82
5	 **106**	 **101**	No Product	-



Scheme 2.18: Homocoupling in palladium cross-coupling

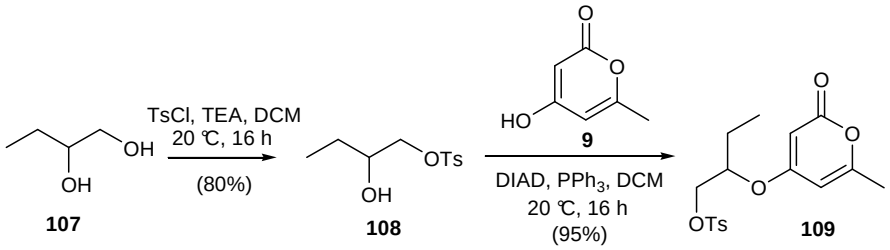
The product of oxidative addition is usually short-lived, with transmetalation occurring rapidly in the presence of a suitable nucleophile; homocoupling can be minimised by the use of low palladium concentrations (halide-aryl exchange/scrambling could also occur via dimer complexes). [91] If a poor nucleophile is used, the Pd(II) oxidative

addition intermediate experiences a longer lifetime and consequently the reaction with another Pd(II) intermediate becomes possible. The results detailed in **Table 2.6** indicate that the coupling partners in this case are incompatible. Although these reactions do not work with the 2-pyrone possessing a 4-hydroxy group, it is possible to convert 4-hydroxy-6-methyl-2-pyrone **9** into 4-bromo-6-methyl-2-pyrone **106** and then use various phenols as the coupling partners. Unfortunately, despite the successful use of 4-bromo-6-methyl-2-pyrone **106** in various cross-couplings by Fairlamb *et al.*,[Error! Bookmark not defined.] this methodology is not feasible for the synthesis of the natural product due to the required coupling partner. So, in the synthesis of phacelocarpus 2-pyrones, the coupling partner required would be an enol which would be found predominately as a ketone, the more stable tautomer.

2.2.6 Synthesis of functionalised vinyl ethers

The failure of Hartwig etherification reactions with regards to the synthesis of pyronyl ethers rendered the originally planned RSA obsolete. In order for a new RSA to be prepared, it is logical to first identify a suitable method for the introduction of the vinyl ether.

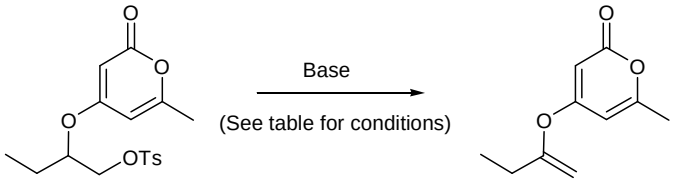
An alternative route is *via* the introduction of a suitable moiety which could then be functionalised further. One suitable motif is a terminal vinyl ether which could be used to undergo cross metathesis or an intermolecular Heck reaction. Two vinyl ethers were synthesised to develop methodology for these reactions; a natural product analogue (**110**) and also a simple vinyl ether with no substituents (**113**). Compound **109** was synthesised through the selective tosylation of butane-1,2-diol (**107**), followed by a Mitsunobu reaction with 4-hydroxy-6-methyl-2-pyrone (**9**) (**Scheme 2.19**).



Scheme 2.19: Synthesis of **109**.

The resultant product was subjected to various elimination conditions, utilising organic bases such as MTBD and DBU to avoid hydroxide-mediated decomposition of the 2-pyrone, to generate the desired product **110** (**Table 2.7**). Initial studies using MTBD as the organic base showed no elimination (entry 1), however, with the addition of NaI the reaction gave a reasonable yield (entries 2 and 3). Changing the base to DBU resulted in an excellent yield (entry 4). Further variations in time and temperature failed to give rise to any improvement in yield. (entries 5-9).

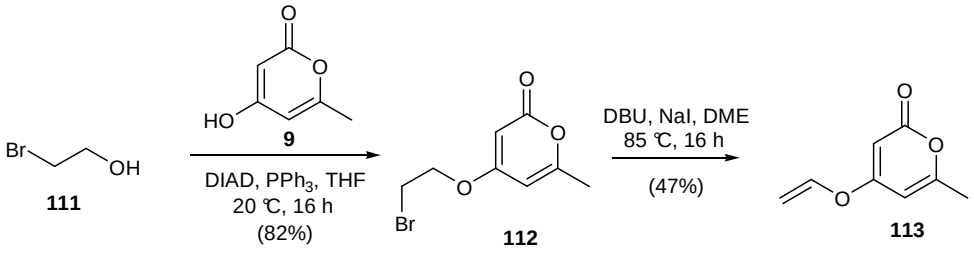
Table 2.7: Tosylate elimination reaction optimisation.



109 **110**

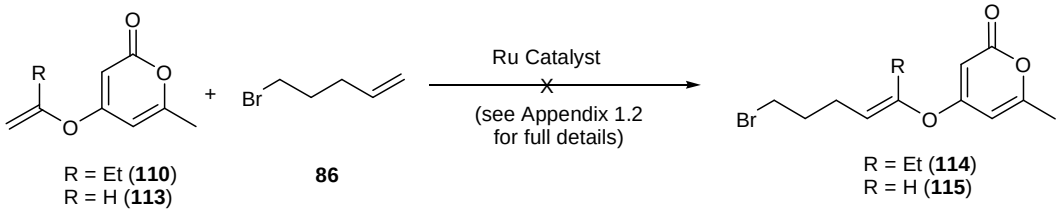
Entry	Solvent	Base	eq. NaI	Temp (°C)	Time (h)	Yield (%)
1	Toluene	MTBD	-	85	16	0
2	Toluene	MTBD	3	85	16	52
3	DME	MTBD	3	85	16	40
4	**DME**	**DBU**	**3**	**85**	**16**	**89**
5	Acetone	DBU	3	50	16	49
6	DME	DBU	3	85	3	30
7	DME	DBU	3	8	48	0
8	DME	DBU	3	85	4	50
9	Acetone	DBU	3	8	48	0

The vinyl analogue (**113**), which does not contain the ethyl side chain featured in the natural product, was subsequently obtained *via* the same route except commercially available 2-bromoethanol was utilised. In the final elimination reaction, the conditions utilised yielded a much lower quantity of product (S**cheme 2.20**). This has since been attributed to the formation of the vinyl ether in good yield, followed by the degradation of the product under the conditions employed.



Scheme 2.20: Synthesis of **111**

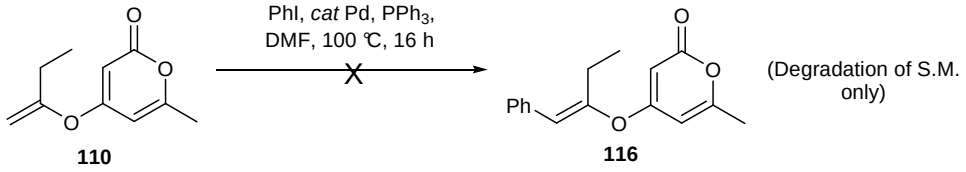
Compounds **110** and **113** were then screened unsuccessfully against a range of cross-metathesis conditions utilising various catalysts, temperatures and solvents (**Scheme 2.21**).



Scheme 2.21: Cross metathesis reactions of **110** and **113**.

The electron deficient nature of the vinyl ether, combined with the 1,1-disubstituted motif of **110**, results in poor viability towards cross-coupling despite the use of high temperatures and the most active catalysts.[92]

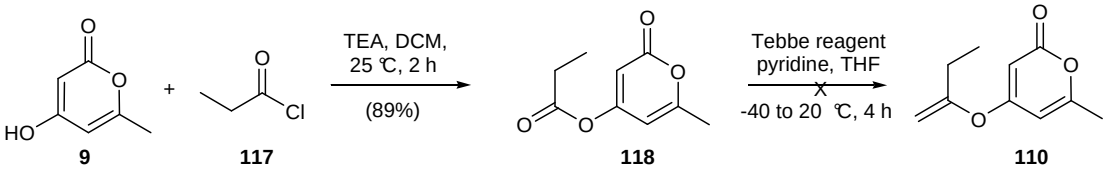
Due to the poor reactivity of the substrates in the alkene metathesis reaction, compound **110** was subsequently tested towards an intermolecular Heck reaction with iodobenzene (**Scheme 2.22**). Previous work by Nilsson *et al*. showed that vinyl ethers are susceptible to Heck reactions, particularly at the electron rich position adjacent to the oxygen atom although secondary reactions also occurred at the terminal positions once the α-position was blocked.[93] Similar conditions were adopted for the synthesis **108**, utilising various sources of catalytic Pd at high temperatures. However, no reaction at the vinyl ether was observed and most of the starting material was found to have decomposed.



Scheme 2.22: Heck reactions of **110**.

Although this reaction cannot be applied to the total synthesis, the degradation of the vinyl ether motif above 100 °C gives an insight into the stability of the natural product, and allows any routes demanding high temperatures to be ruled out of any future synthesis.

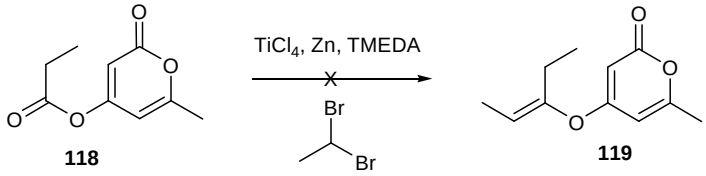
During the synthesis of alkene **110**, an alternative route was studied *via* a two step process. Initially, the 4-hydroxy-6-methyl-2-pyrone **9** was reacted with propionyl chloride **117** to generate **118**, which could subsequently undergo a Tebbe reaction to give **110** (**Scheme 2.23**).



9 **117** **118** **110**

Scheme 2.23: Tebbe route to **110.**

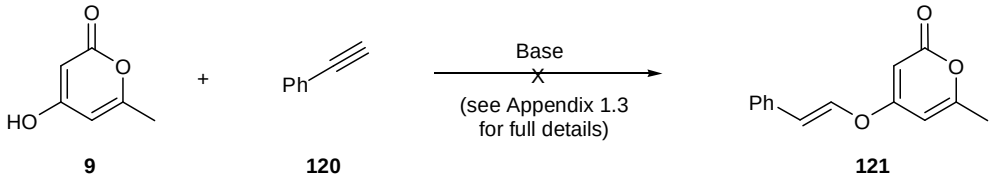
Although Tebbe conditions proved unsuccessful, work by Takai *et al*. showed that 1,1-dibromo alkanes were able to undergo a modified Tebbe reaction to generate functionalised vinyl ethers, with good selectivity towards esters.[94] This reaction was attempted to discover if the reaction presented a feasible route to functionalised vinyl ethers. Unfortunately no selectivity towards the external ester was observed, and degradation of the starting material proved to be prolific (**Scheme 2.24**).



118 **119**

Scheme 2.24: Modified Tebbe reaction.

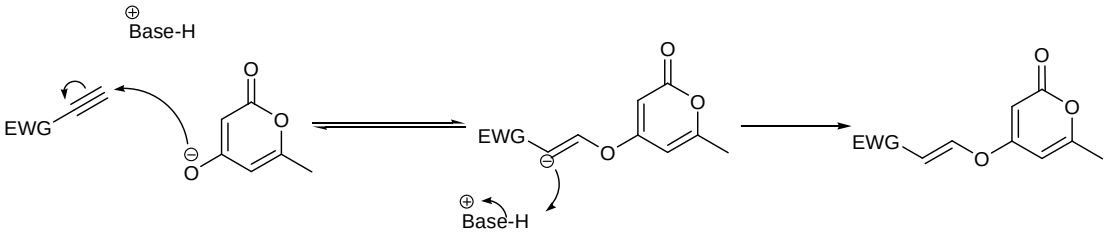
The poor reactivity of the terminal alkenes suggested the need to develop a vinyl ether which would provide a better handle for further reactions. Work by Zhou *et al.* reported that under basic conditions, relatively acidic alcohols such as phenols can act as nucleophiles towards terminal alkynes to generate vinyl ethers.[95] The use of this type of chemistry can be envisaged in the synthesis of the natural product. Preliminary investigations focused on screening phenyl acetylene **120** against various bases to develop conditions which would be compatible with 4-hydroxy-6-alkyl-2-pyrones (**Scheme 2.25**).



9 **120** **121**

Scheme 2.25: Nucleophilic addition of **9** into **120**.

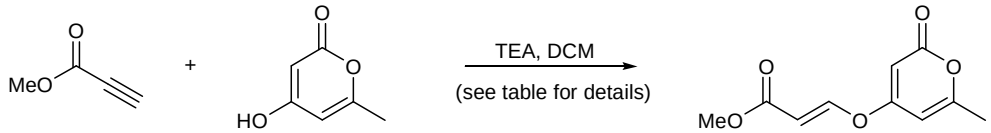
The reaction of **9** with **120** proved to be unsuccessful despite the use of a range of organic and inorganic bases, high temperatures and extended reaction times. The most likely reason for poor reactivity is due to the nature of the intermediate when using phenyl acetylene (**120**). The deprotonated alcohol attacks the alkyne, which subsequently abstracts the proton back from the conjugate base to generate the alkene. However the choice of EWG is important due to the reversible nature of the initial attack (**Scheme 2.26**). If the carbanion intermediate is not stabilised then the equilibrium of the first step will lie far to the left and very little reaction will occur.



Scheme 2.26: Mechanism for the addition of **9** to a terminal alkyne.

Although an aromatic ring is able to stabilise the carbanion to an extent, it appears the intermediate requires a much greater degree of stabilisation. In order to greatly stabilise a carbanion, a mesomeric form must be available whereby the charge is transferred to a more electrophilic atom. The choice of substrate for this reaction was an alkynoate. The reaction could then be expected to proceed in a Michael type reaction to form an allenolate intermediate which places the charge on the oxygen and greatly improves the chance of reaction. This reaction quickly proved to be successful under both thermal and microwave conditions, with an optimum yield obtained after 16 hours at reflux (**Table 2.8**).

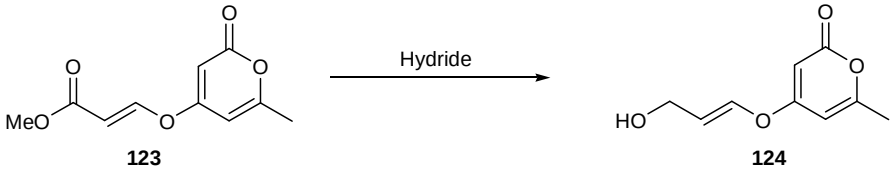
Table 2.8: Optimisation of the synthesis of **121**.



122 **9** **123**

Entry	Temperature (°C)	Time (h)	Yield (%)
1	20	2	48
2	20	16	63
3	**45**	**16**	**82**
4	80 (mw)	0.5	67

The ester group present in **123** also presents a useful handle for further steps. Hydride reduction of the ester would present allylic alcohol **124** (**Scheme 2.28**).



123 **124**

Scheme 2.27: Possible transformation of **121** to allylic alcohol **122**.

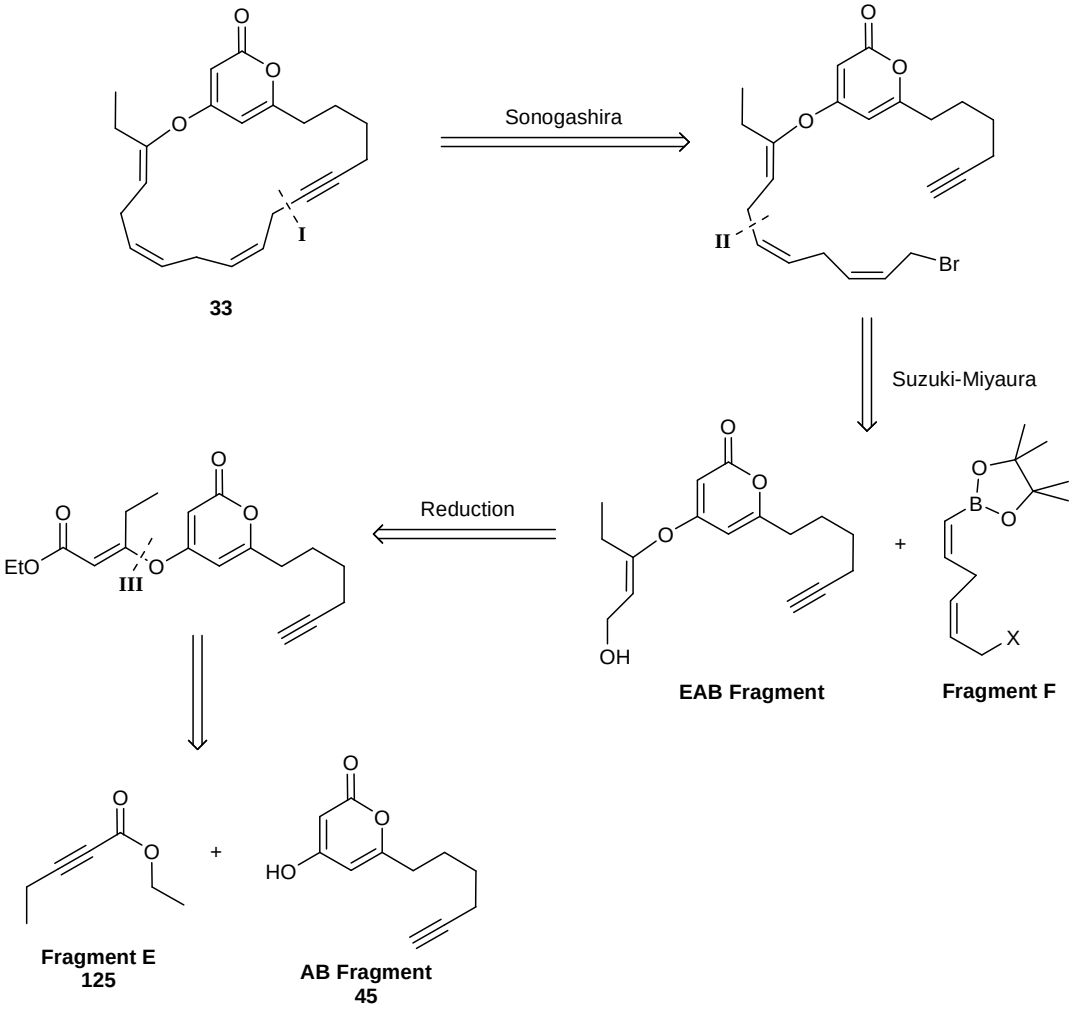
The generation of an allylic alcohol (**124**) would then be suitable to be used directly in a Suzuki cross-coupling with a vinyl boronic acid, as reported by Tsukamoto *et al.* or alternatively can be converted into an allylic halide for use in further Pd-catalysed cross-couplings.[96] The incorporation of this sub-unit can now provide a platform to re-evaluate the original RSA.

2.3 Revised RSA and synthesis

2.3.1 Revised RSA

The revised RSA utilises most of the same disconnections as were suggested originally, and also involves the same AB fragment (**45**) previously synthesised. The key difference is the incorporation of the allylic/vinylic coupling generated by disconnection **II** (**Scheme 2.28**) and the resulting fragment **E** formed as a result of the Michael addition previously shown to provide a means of forming the vinyl ether. The appropriate coupling partner to perform both a Sonogashira reaction and a vinylic/allylic coupling can now be

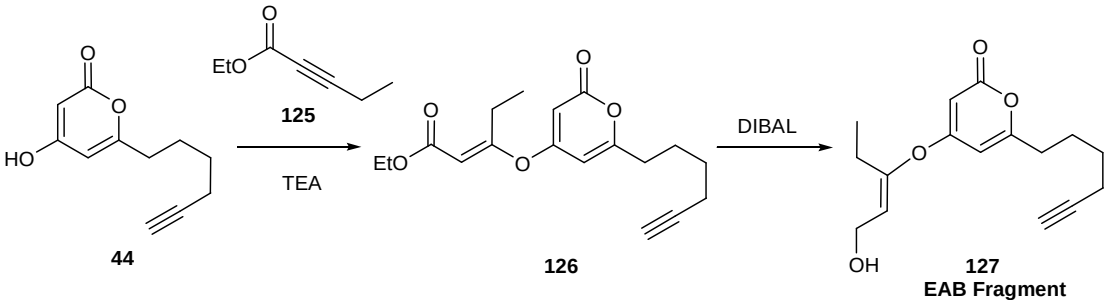
envisaged as the novel fragment **F**, which would contain all of the *cis*-alkenes required in the natural product.



Scheme 2.28: Revised RSA of **33**.

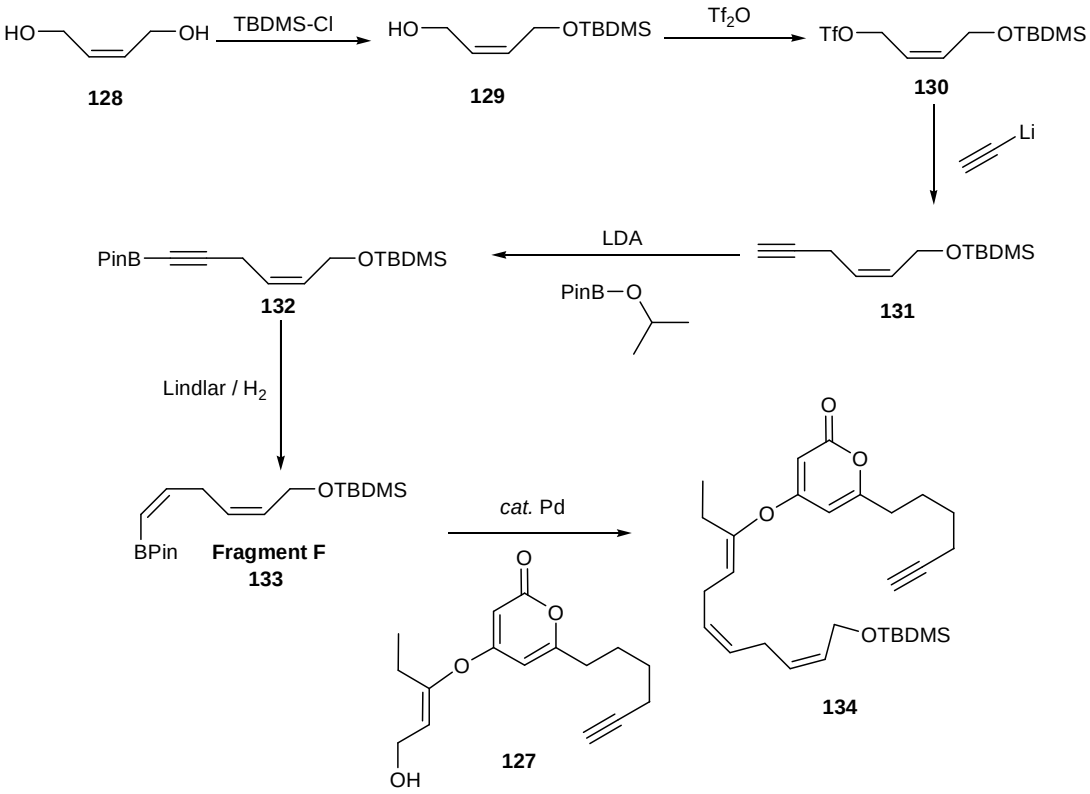
A proposed forward synthesis will now utilise the previously synthesised **AB** fragment (**45**) in a Michael addition onto the commercially available alkynoate **127**, followed by hydride reduction to the allylic alcohol **127**, generating the advanced **EAB** fragment. The original example of a Michael addition of a 4-hydroxy-6-methyl-2-pyrone (**9**) to an alkynoate was performed on a terminal alkyne, however the natural product requires the inclusion of an ethyl side chain. In order to include this side chain, it is necessary for the Michael addition to be performed on alkynoate **125** which already contains the desired ethyl unit (**Scheme 2.29**). The addition of this ethyl side chain will sterically restrict the access of the nucleophilic 2-pyrone to the alkyne in order for the

reaction to occur, and as a result will require development of the original methodology to account for the increased complexity.



Scheme 2.29: Proposed synthesis of the advanced **EAB** fragment (**127**).

The next step would require the cross-coupling of **127** with the novel fragment **F**. The synthesis of fragment **F** can be envisaged *via* a five step procedure to form the desired vinyl boronic acid pinacol ester **133** (**Scheme 2.30**).



Scheme 2.30: Proposed forward synthesis and use of fragment F.

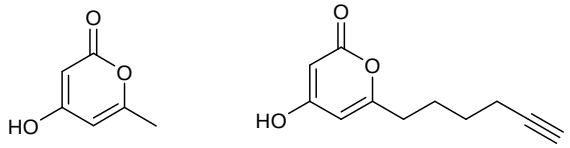
The Pd-catalysed reaction with the allylic alcohol dictates that the additional allylic group on fragment **F** cannot be either a halide or acetate due to their receptivity towards

Pd(0). The choice of a silyl protected alcohol allows a simple deprotection followed by conversion to triflate or halide for the macrocyclisation.

2.3.2 Synthesis of EA and EAB fragments

The steric influence of the 6-alkyl chain required for the natural product, increases the complexity of the Michael addition. It is therefore important to optimise the conditions with simple analogues such as **9** as opposed to wasting valuable intermediates. An important factor in the choice of analogue is that the chemical environment of the reacting group mimics that of the parent compound as closely as possible. In this case, the most important factor is the pK_a of the alcohol, although steric influence may also play a part.

The mechanism of this reaction requires deprotonation of the alcohol, so it is important that the pK_a of the two alcohols are similar. Using pK_a prediction software it is possible to compare the two 2-pyrones to assess the suitability of the chosen mimic. Although the prediction software cannot be assumed to be entirely accurate, it is possible to compare known values to judge the error. The prediction shows that the extended aliphatic chain has little influence on the acidity of the alcohol, which combined with the large difference between the pK_a of protonated bases such as HN^+Et_3 indicates that **9** is a suitable analogue on this occasion.



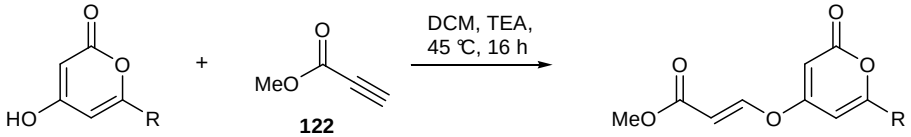
pK_a (calc.)= 5.03
Actual (H_2O) = 4.94
9

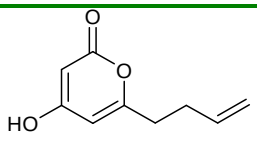
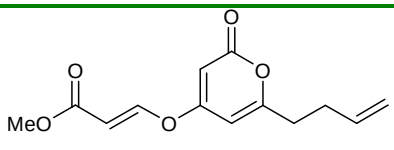
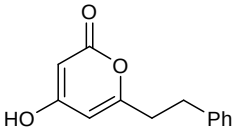
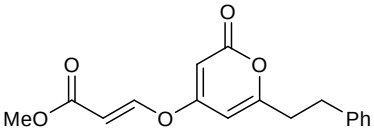
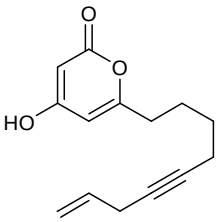
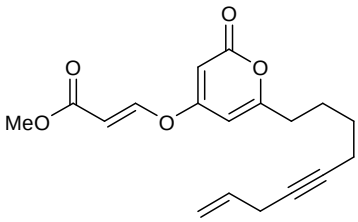
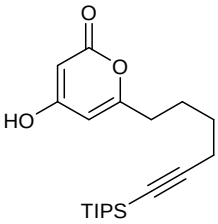
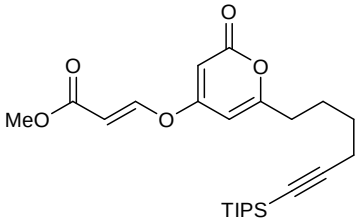
pK_a (calc.)= 5.12
45

Figure 2.2: pK_a predictions of alcohol in compounds **9** and **45**.[97]

The effect of C-6 functionalisation on the pK_a of 4-hydroxy-2-pyrones appears to be minimal when functionalisation is limited to non-conjugated systems. At this point, the benchmark reaction with methyl propiolate (**122**) was tested against various C-6 functionalised 4-hydroxy-2-pyrones (**Table 2.9**).

Table 2.9: Michael additions of C-6 functionalised 4-hydroxy-2-pyrones with **122**.

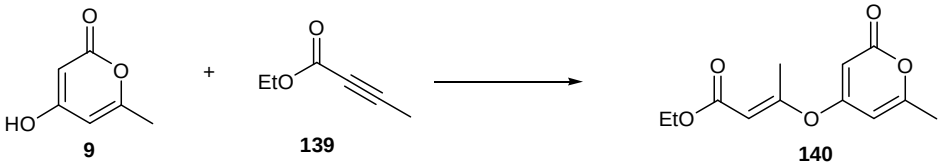


Entry	Starting Material	Product	Yield (%)
1	 **96**	 **135**	86
2	 **90**	 **136**	68
3	 **95**	 **137**	64
4	 **44**	 **138**	82

The reaction proceeded well with all of the variations, but particularly encouraging is the 82% yield of **135**, which can be seen as an ethyl side chain deficient analogue of the advanced **EAB** fragment **126**. Now with the confirmation that C-6 modified 4-hydroxy-2-pyrones will react in a similar fashion to the simpler system utilising **9**, the incorporation of the ethyl side chain must be addressed.

Preliminary investigations into the Michael addition of **9** onto an internal alkyne utilised a methyl side chain as opposed to the desired ethyl side chain in order to first generate conditions for the slightly simpler system.

Table 2.10: Optimisation of Michael addition between **9** and **139.**



9 **139** **140**

Entry	Solvent	Base	Eq. Base	Additive	Mol % Additive	Temp (ºC)	Time (h)	Yield (%)
1	DCM	TEA	1	-	-	40	1	0
2	DCM	TEA	1	-	-	80 (mw)	1	~1
3	DCM	DBU	2	-	-	90 (mw)	1	4
4	THF	DBU	1	BF_3	20	90 (mw)	2	18*
5	DCM	DBU	1	BF_3	20	80 (mw)	2	6*
6	THF	DBU	1	BF_3	20	80 (mw)	2	24*
7	THF	TEA	1	BF_3	20	80 (mw)	2	5*
8	THF	DBU	1	$Yb(OTf)_3$	20	80 (mw)	2	13
9	THF	DBU	1	BF_3	20	70	16	22*
10	THF	DBU	1	BF_3	6	80 (mw)	2	19*
11	THF	DBU	1	B^iPr_3	20	80 (mw)	2	17
12	DCM	TEA	1	CuI	10	80 (mw)	1	29
13	THF	DBU	1	CuI	10	40	16	29
14	THF	DBU	1	CuI	10	80 (mw)	2	26
15	THF	DBU	0.1	CuI	10	80 (mw)	3	0
16	THF	DBU	0.2	CuI	10	80 (mw)	6	30
17	**THF**	**DBU**	**0.66**	**CuI**	**10**	**80 (mw)**	**0.5**	**43**
18	THF	DBU	0.66	CuI	10	40	16	7
19	THF	DBU	0.66	CuI / B^iPr_3	10 / 20	80 (mw)	0.5	9
20	THF	NaH	1	-	-	20	5	0
21	THF	NaH	1	-	-	40	5	0
22	THF	NaH	1	-	-	70	5	0
23	THF	NaH	1	CuI	10	70	5	0

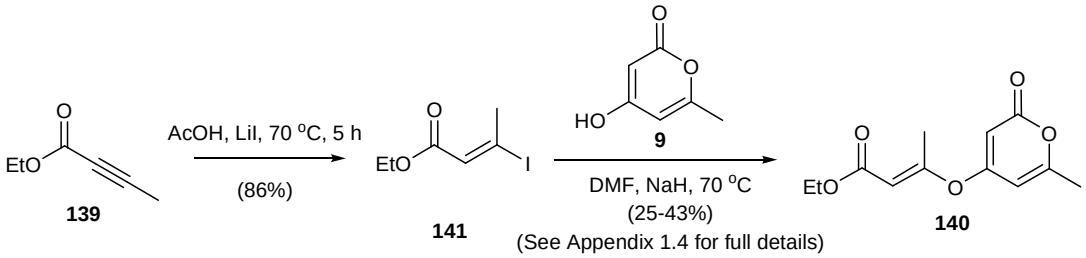
* Large amounts of 2-pyrone degradation observed

As expected, the use of an internal alkyne severely affects the reactivity of the 4-hydroxy-2-pyrone towards the alkyne. Utilising the same conditions as previously used for the terminal alkyne yielded no product. The rationale for the lack of reactivity was attributed to a combination of the restricted access to the alkyne, but also a poor nucleophilic character displayed by the 2-pyrone. By altering the base to the stronger and more bulky DBU, the degree of charge formed on the 2-pyrone **9** is increased, due to the increased distance between itself and the counterion. The nucleophilicity would now be enhanced, however this again proved to be too little to affect a substantial increase in yield (entry 3).

The use of additives in Michael additions is well documented, most commonly using a Lewis acid to activate the carbonyl and subsequently withdraw electron density from the point of nucleophilic attack.[98] The introduction of BF_3 as a Lewis acid greatly improved the reaction yield, however large amounts of 2-pyrone degradation was also noticeable (entries 4-7, 9-10). The use of weaker Lewis acids such as B^iPr_3 and $Yb(OTf)_3$ promoted the reaction to a lesser degree, although the amount of 2-pyrone degradation was noticeably smaller (entries 8 and 11). The use of Lewis acids to remove electron density from the alkyne shows that this is a feasible way of increasing reactivity. Copper(I) iodide is known to bind to alkynes, and is used in the Sonogashira cross-coupling for this purpose.[99] In binding to the alkyne the copper(I) removes electron density, thereby making it more susceptible to electrophilic attack. The use of copper(I) iodide as an alternative to a Lewis acid was then tested and was shown to increase the yield under similar conditions (entries 12-14).

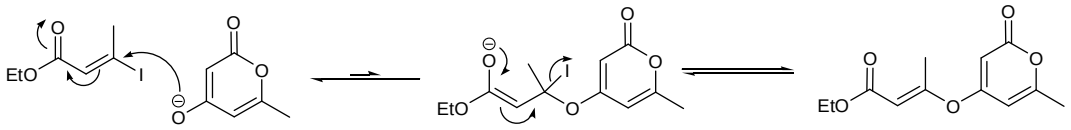
The high polarity of 2-pyrone **9** means that it is often only partially soluble in organic solvents such as DCM and THF until an organic base is introduced. On repetition of these reactions, it was noted that complete solubility occurred at precisely 0.66 equivalents of base. The use of sub-stoichiometric quantities of base was then tested and proved that the observed solubility point was also the optimum amount of base, culminating in a yield of 43% (Entry 17).

The yield of 43% represented a vast improvement, however for use in the natural product synthesis a yield above 60% would be desirable. The introduction of the same vinyl ether motif is also accessible *via* a substitution reaction utilising a vinyl iodide or triflate such as **141**.



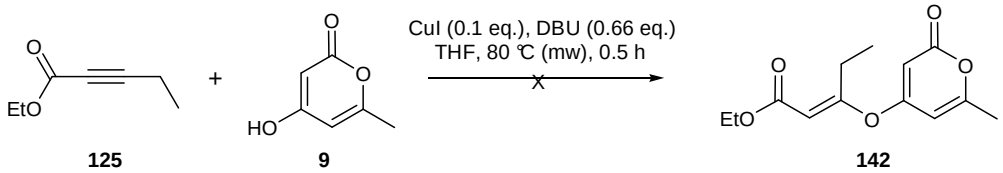
Scheme 2.31: Synthesis of **140** *via* vinyl iodide **141.**

The coupling of 2-pyrone **9** and organoiodide **141** proceeded poorly despite the use of a variety of solvents, bases, temperatures and extended reaction times (**Scheme 2.31**). The reaction would only proceed in the presence of an iodide trap such as $AgNO_3$, affording the desired product in a variable yield. The major problem with this reaction is the reversibility of each step, and the generation of a quaternary centred intermediate. The quaternary intermediate can eliminate either the iodide or the 2-pyrone, however due to the large steric bulk of the 2-pyrone, the initial addition is unlikely to occur. The 2-pyrone is also able to delocalise the charge throughout the molecule making it more stable and thus a better leaving group than the iodide (**Scheme 2.32**).



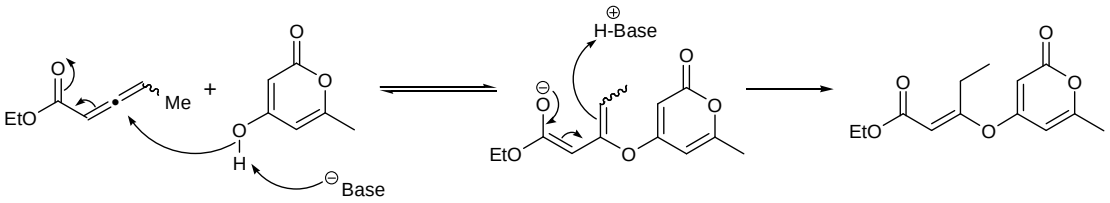
Scheme 2.32: Substitution reaction mechanism.

The addition of silver nitrate to irreversibly bind any free iodide made it possible to slowly drive the reaction forwards and generate the desired product, however the reaction proved to be unreliable and results varied. The best result obtained using this approach only matched the 43% achieved through the direct Michael addition to the alkynoate. The more challenging ethyl 3-pentynoate (**125**) was subjected to the optimised Michael conditions in order to generate the required ethyl side chain present in the natural product. Unfortunately, this proved to further reduce the activity and no product formation was observed.



Scheme 2.33: Michael addition of **9** into **125**.

The inclusion of the ethyl side chain is seen to shut down all reactivity, most likely due to the inaccessibility of the alkyne towards the incoming nucleophilic 4-hydroxy-2-pyrone (**Scheme 2.33**). In order to try and increase the accessibility of the desired β-carbon it was hypothesised that using an allenoate may provide a better platform for addition, with the β-carbon now at the centre of the more accessible allene and therefore more susceptible to nucleophilic attack. The intermediate formed can be envisaged to then react in one of two ways; firstly by re-eliminating the 2-pyrone, or alternatively by rearrangement and subsequently abstracting the proton from the conjugate base at the γ-carbon to generate the desired product (**Scheme 2.34**). Despite the equilibrium for the first step, the formation of the product would likely be an irreversible reaction and therefore drive the reaction forwards.

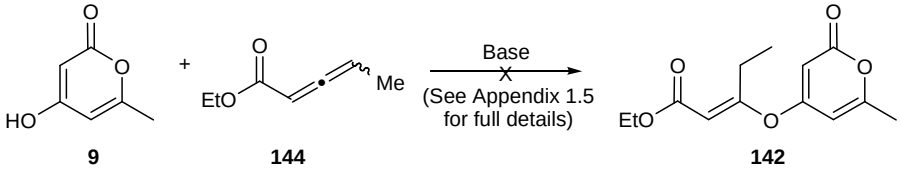


Scheme 2.34: Proposed reaction pathway for nucleophilic attack of an allenoate.

Allenoate **144** was prepared *via* a one pot-two step Wittig/elimination reaction of phosphorane **143** with propionyl chloride (**117**), to generate the desired product and also the alkynoate **125** in similar yield (**Scheme 2.35**).

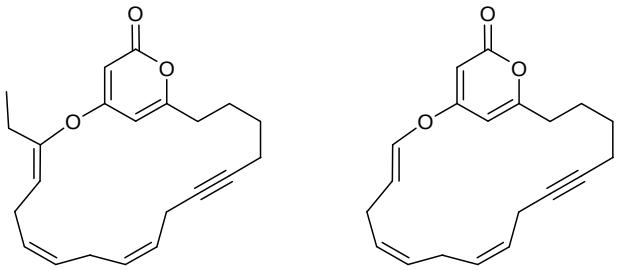
Scheme 2.35: Synthesis of **144**.

The subsequent reaction of **9** with allenoate **144** does not occur at all, with complete recovery of **9**, despite the use of elevated temperatures and a Lewis acid additive to encourage the initial step of the reaction (**Scheme 2.36**).



Scheme 2.36: Michael Addition of **9** with allenoate **144**.

At this point the synthesis of an ethyl side chain deficient analogue (**145**) of the natural product was considered to test the feasibility of the remaining steps in the proposed synthesis.

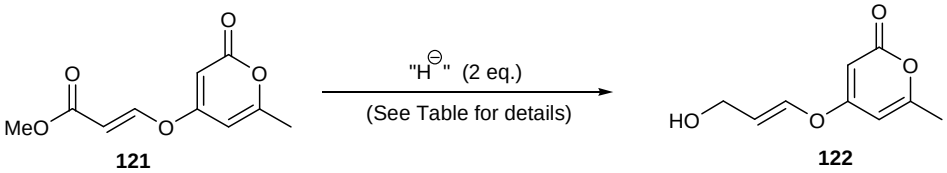


33 (Target) **145 (Analogue)**

Figure 2.3: Natural product **33** and modified analogue **145**.

The next step in the proposed synthesis involves the hydride reduction of the α,β-unsaturated ester into the allylic alcohol. The results of the hydride reduction of **123** are shown in **Table 2.11**.

Table 2.11: Hydride reduction of **123**.



121 **122**

Entry	Hydride Source	Solvent	Temperature	Yield
1	$LiAlH_4$	Ether	-78 °C	0*
2	**DIBAL-H**	**DCM**	**-78 °C**	**30***
3	DIBAL-H	Ether	-78 °C	17*
4	L-Selectride	THF	-78 °C	0†
5	$NaBH_4$	Ether	-20 °C	0†

*Complete consumption of **121** observed by TLC analysis.

†Reaction yielded >95% 4-hydroxy-6-methyl-2-pyrone **9.**

The hydride reduction of **123** gave low yields with a number of hydride sources with varying degrees of strength. It is noticeable that within the structure of **123** there are three positions at which hydride is able to attack (**Fig. 2.4**). Firstly, when utilising softer sources of hydride such as selectride and borohydride, the desired product was not formed.

Instead, the leaving group properties of the 2-pyrone encourage Michael substitution through hydride attack at the β-carbon and subsequent elimination of the 2-pyrone.

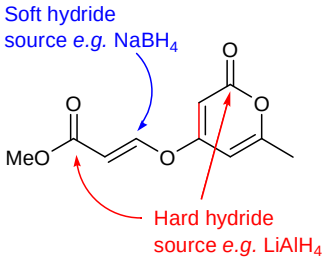
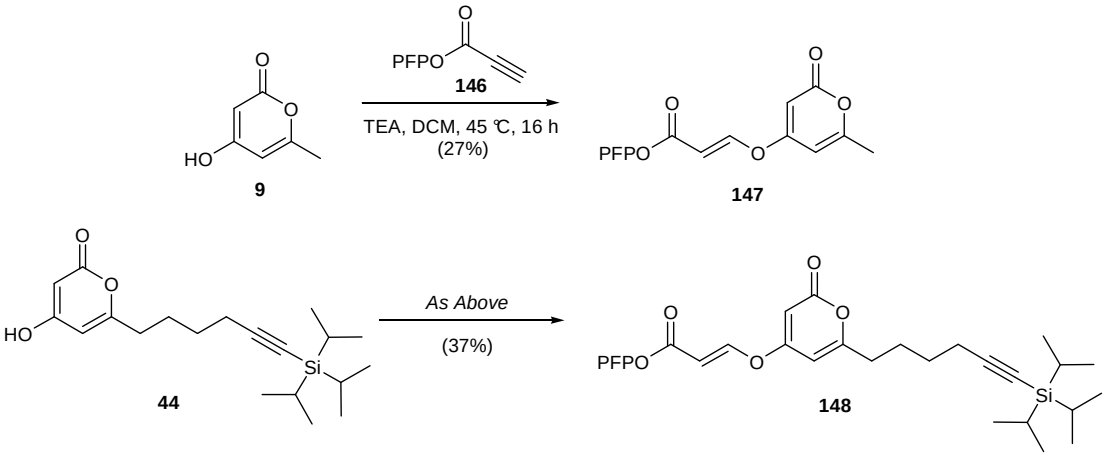


Figure 2.4: Sites of hydride attack on **123**.

Alternatively, when using harder sources of hydride such as $LiAlH_4$ and DIBAL-H the hydride attacks the carbonyl positions of both the unsaturated ester and the 2-pyrone. The subsequent 30% yield observed using can be attributed to a near statistical distribution of products where each equivalent of hydride has reacted unselectively .

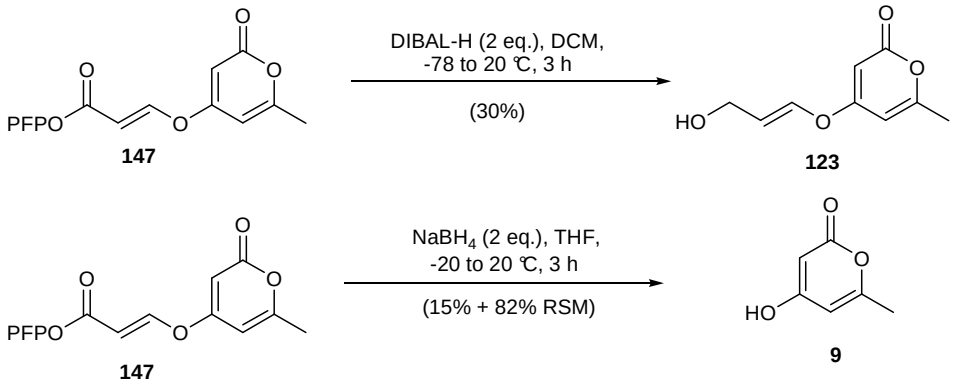
In order to improve the selectivity of the reduction, the reactivity of the ester and 2-pyrone carbonyls need to be better differentiated. One way of approaching this is to provide a better leaving group than methoxide to encourage a more facile attack from a weaker hydride source. The use of fluorinated esters is known to promote hydride reduction,[100] and with this in mind, pentafluorophenyl (PFP) propiolate (**146**) was utilised in the Michael addition with both compounds **9** and **44** (**Scheme 2.37**).



Scheme 2.37: Michael additions of **9** and **44** with fluorinated ester **146**.

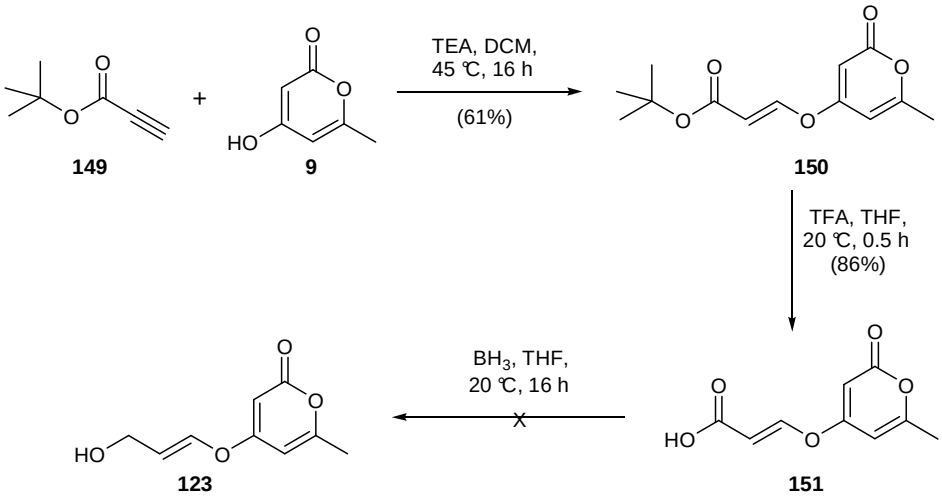
The yields of the Michael addition appear to be heavily influenced by the ester. In this case, the PFP ester proves to be a relatively poor match for the addition of 4-hydroxy-6-methyl-2-pyrone derivatives. However, despite the lower yields in the Michael addition,

it is important to test whether the variation of the ester affects the subsequent hydride reduction. The PFP ester **147** was subjected to both DIBAL-H and $NaBH_4$, though in each case the yields mimicked those seen previously with the methyl ester derivative **123** (**Scheme 2.38**).



Scheme 2.38: Hydride reduction of **147**.

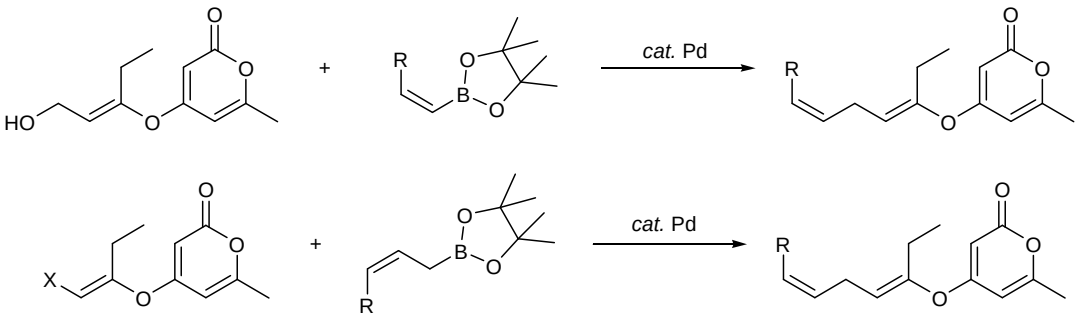
The continued poor selectivity for the reduction of the α,β-unsaturated ester *versus* the 2-pyrone suggest that this approach is not appropriate for this system. In order to differentiate better it is feasible that a BH_3 reduction of an acid would allow complete selectivity in the formation of the allyl alcohol. The Michael addition was then performed using *tert*-butyl propiolate **149** with **9** to yield **150** in a respectable 61% yield. Subsequent treatment of **150** with TFA to yield the desired acid **151**, however the following BH_3 reduction of the acid failed to generate any allyl alcohol **123** (**Scheme 2.39**).



Scheme 2.39: Hydride free approach to **123**.

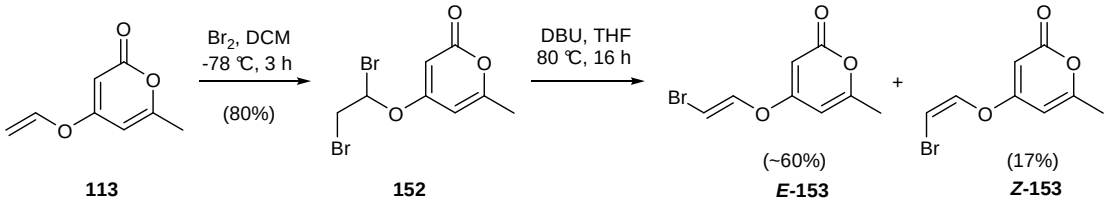
The ^{1}H NMR spectroscopic analysis of crude material from the borane reduction shows the absence of the alkene signals from the α,β-unsaturated ester, suggesting that hydroboration of the alkene has occurred in preference to the reduction of the acid. No conclusive proof was isolated from the crude reaction mixture.

The continuing poor selectivity shown in generating a 2-pyrone bound allyl functionality suitable for cross-coupling indicates that the current synthetic strategy is flawed. However, the possibility of cross-coupling vinylic and allylic groups to generate the skipped 1,4-diene motif allows two different approaches to be studied, with the pyronyl substrate able to provide the allylic or vinylic unit. The current study has shown that the 2-pyrone fragment does not easily provide access to the allylic fragment, however it is possible that the 2-pyrone can instead provide the vinylic substrate for cross-coupling (**Scheme 2.40**).



Scheme 2.40: Two Pd-mediated approaches to a skipped 1,4-diene.

In order to test the feasibility of using the 2-pyrone bound vinyl halide for cross-coupling, a simple analogue was developed. The earlier synthesised **113** was treated with bromine to generate a dibromide (**152**) which subsequently underwent an elimination reaction to generate the vinyl bromides *E*/*Z*-**153** (**Scheme 2.41**).



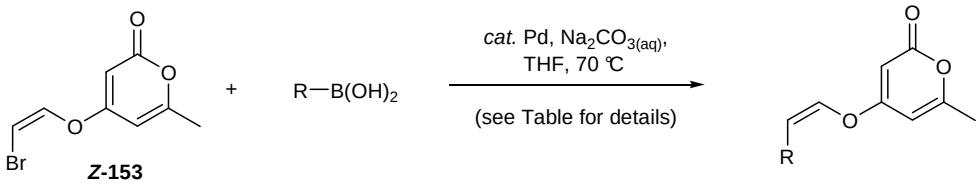
Scheme 2.41 Synthesis of vinyl bromide **153**.

The synthesis of vinyl bromide **153** is not an efficient route due to the lack of stereo-selectivity observed. The initial bromination works in good yield, however the C-3 position of the 2-pyrone core is also susceptible to attack from bromine, and it was noted

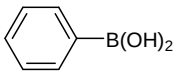
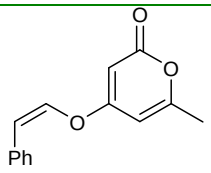
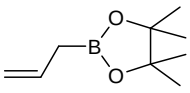
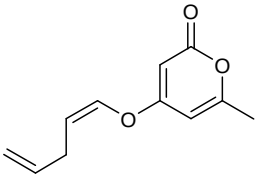
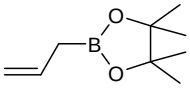
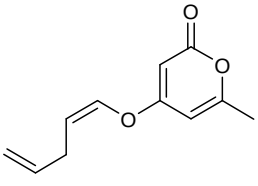
(*via* ^{1}H NMR) that some material was brominated at this position, although no isolation was possible due to the decomposition of all material on silica. As a result, the impurity was carried forwards into the elimination reaction. The elimination reaction works well with selective elimination of the secondary bromide to yield both *cis* and *trans*-isomers of the desired vinyl bromide. Unfortunately, the desired bromide *E*-**153** was never isolated cleanly, due to the presence of a second inseparable product. The identity of this impurity has not been proven, although the mass spectrum of the mixture showed only one ion present (*m/z* = 231/233), indicating an elemental composition identical to that of *E*-**153**. It is suspected that the impurity stems from the C-3 brominated material carried through from the initial bromination reaction.

Although no tests could be run on *E*-**153**, the *cis*-bromide (*Z*-**153**) was isolated and subjected to Suzuki reaction conditions (**Table 2.12**).

Table 2.12: Suzuki cross-couplings of vinyl bromide *Z*-**153** with boronic acids.



***Z*-153**

Boronic acid	Pd source	Mol% Pd	Product	Time (h)	Yield (%)
 **57**	$Pd_2(dba)_3$ / PPh_3	5	 **154**	2	60
 **155**	$Pd_2(dba)_3$ / PPh_3	5	 **156**	4	10
 **155**	*CatCat* *E*-**27**	5	 **156**	4	59

In each reaction it was noted that complete retention of stereochemistry occurred. The natural product **33** requires *trans* stereochemistry at the vinyl ether, however the retention of stereochemistry from the unfavoured *cis*-adduct *Z*-**153** indicates that the reaction will always proceed with retention of stereochemistry.

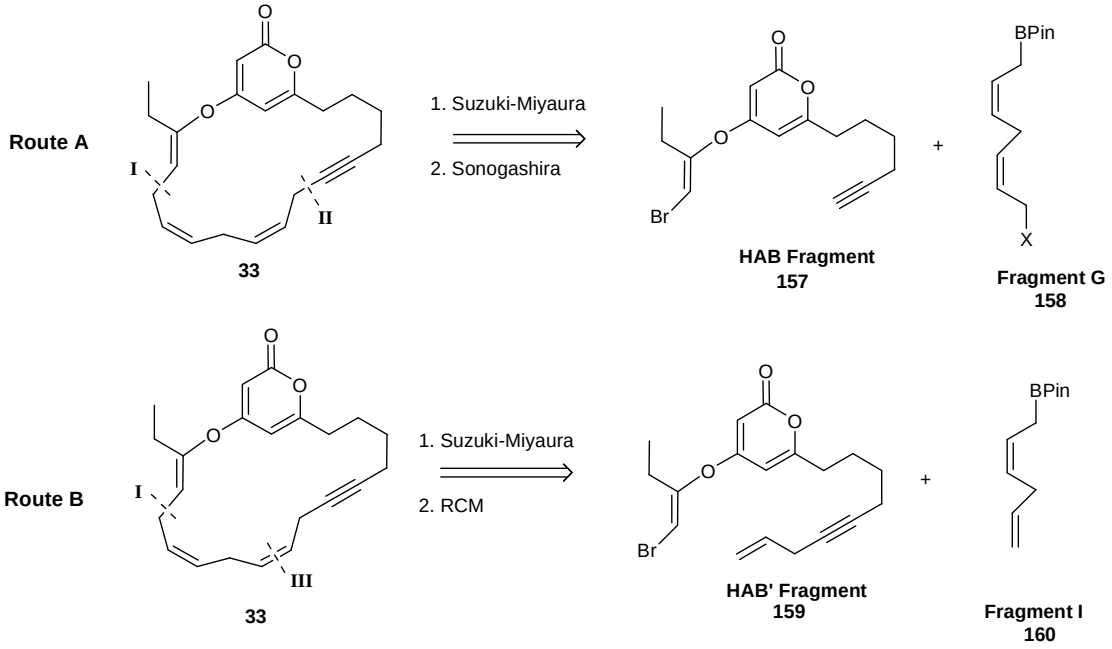
The success of utilising vinyl bromide *Z*-**153** in Suzuki cross-couplings to generate skipped 1,4-dienes, particularly using the previously studied palladium complex *E*-**27**, now offers a second route to forming the problematic left hand side of the natural product.

2.3 Further revised RSA and forward synthesis

2.3.1 Revised RSA

The new disconnection occurs adjacent to the vinyl ether, reversing the vinylic and allylic positions seen in the previous route and generates fragment **G** (**158**) and the advanced **HAB** (**157**) fragment.

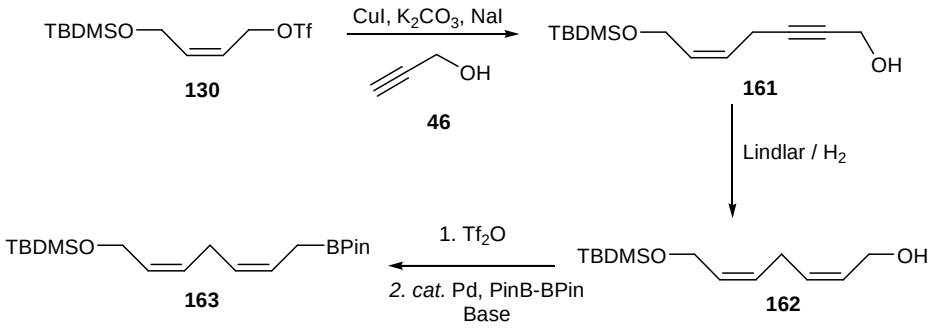
In addition to this RSA the alternative macrocycle forming disconnection can be made across a double bond to yield the two fragments **HAB′** (**159**) and **I** (**160**), suitable for RCM. Both of these routes can easily be followed in parallel (**Scheme 2.42**).



Scheme 2.42: Disconnections for routes A and B.

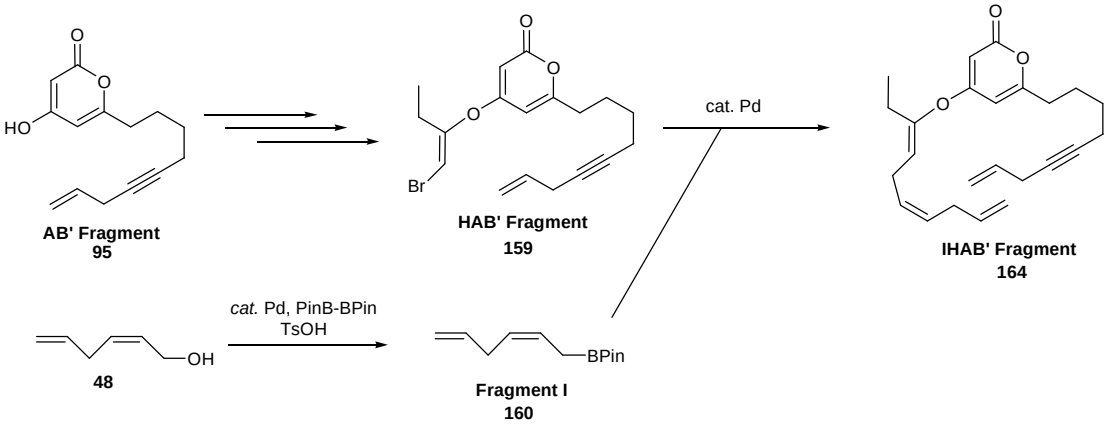
(Note: Fragments containing B′ refer to the 1,4-enyne system)

The revised synthesis for route **A** requires the synthesis of novel fragment **G** (**158**) which can easily be accessed *via* a similar route to that of fragment **F** (**133**). By utilising the intermediate **130**, the reaction with propargyl alcohol in the presence of copper(I) iodide and base will generate **161** (**Scheme 2.43**). The reaction of **161** with Lindlar catalyst will then generate allylic alcohol **162** which can be converted to the boronic acid pinacol ester *via* conversion to a halide or triflate followed by a Miyaura borylation to generate a silyl protected fragment **G** (**163**).[101]



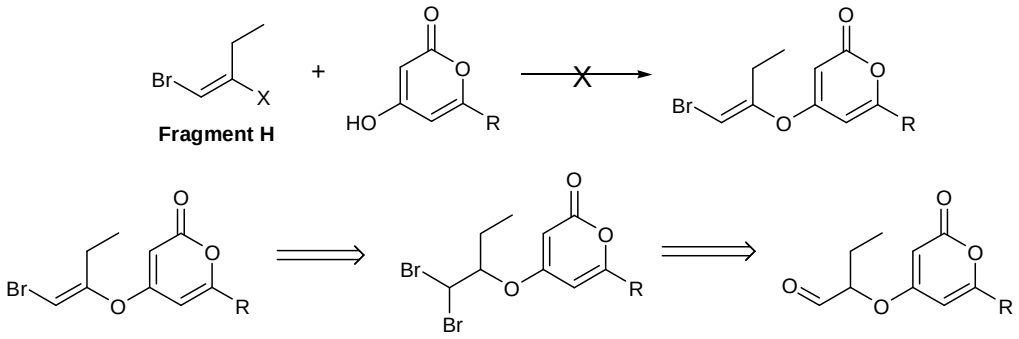
Scheme 2.43: Proposed synthesis of fragment **G.**

The revised synthesis for route **B** can utilise the previously synthesised **AB′** fragment (**95**) thereby circumventing the requirement for a silyl protection of the terminal alkyne. Conversion to the proposed **HAB′** fragment (**159**) and subsequent reaction with fragment **I** (**160**) would rapidly generate a substrate suitable for ring closing metathesis. Fragment **I** (**160**) can be accessed utilising allylic borylation methodology, developed by Aggarwal and co-workers, with the previously synthesised compound **48** (**Scheme 2.44**).[102]



Scheme 2.44: Proposed synthesis of **HAB′** fragment**.**

The generation of the vinyl bromide will present the largest challenge for the synthesis *via* the new route, as fragment **H** is not available directly, but will be accessed *via* various transformations once bound to the 2-pyrone (**Scheme 2.45**). The preliminary studies will focus on generating a 2-pyrone-bound aldehyde. The aldehyde can then be converted to a 1,1-dibromide which will subsequently undergo an elimination reaction to generate the desired vinyl bromide.

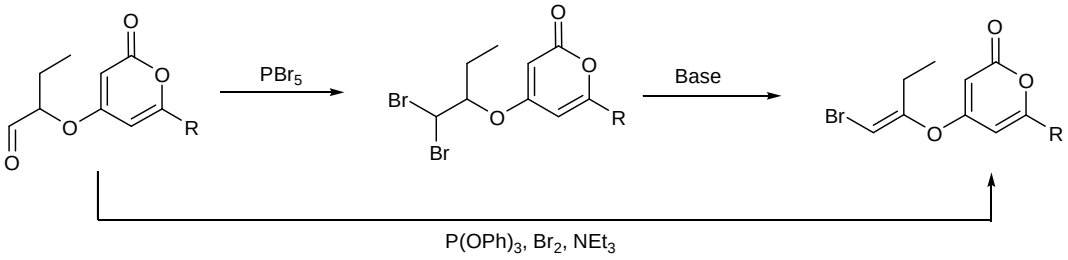


Scheme 2.45: RSA of vinyl halide.

2.5.2 Synthesis of the HA fragment (176)

The synthesis of the HAB fragment (**157**) will first rely on adequate methodology developed on the simpler HA fragment.

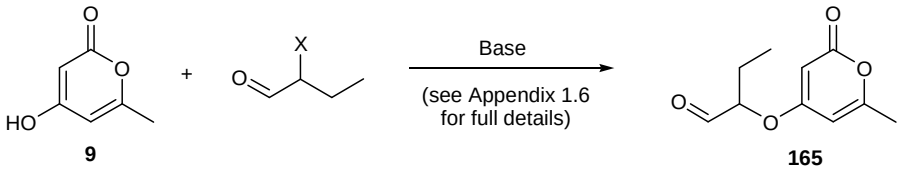
The planned synthesis of the HA fragment requires the formation of an aldehyde bound to the 2-pyrone. Once the aldehyde is incorporated, it is possible to convert the carbonyl to a dibromide, with subsequent elimination of one bromide to generate the desired vinyl bromide. Alternatively, it is possible to use the conditions discussed by Spaggiari *et al.* to generate the vinyl bromide directly (**Scheme 2.46**).[103]



Scheme 2.46: Conversion of an aldehyde to a vinyl bromide.

There is literature precedent for the introduction of alkyl groups onto the alcohol of **9** through a simple substitution reaction with alkyl bromides.[104] A substitution reaction of α-halobutyraldehyde with **9** was attempted to create the desired aldehyde, although this

proved to be unsuccessful under various conditions, with none of the desired product formed (**Scheme 2.47**).



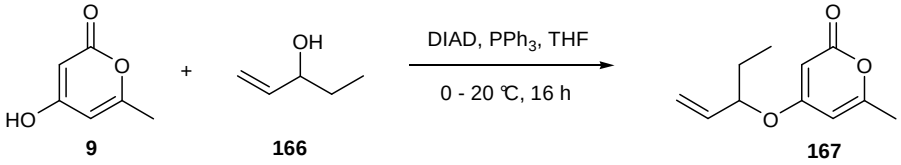
9 **165**

Scheme 2.47: Substitution reaction of **9** with α-halobutyraldehyde.

Initial attempts focused on using organic bases to assist the substitution reaction, however a quantitative amount of **9** was always recovered. The poor reactivity was attributed to an elimination reaction of the α-halobutyraldehyde occurring in preference to the substitution reaction. In order to prevent this side reaction, sodium hydride was used to pre-form a 2-pyrone salt which would be unable to act as a base to perform the elimination reaction. Unfortunately, this proved ineffective and no product was formed despite extended reaction times.

Previous work with 4-hydroxy-6-methyl-2-pyrone (**9**) had provided excellent yields when subjected to Mitsunobu conditions, and the introduction of the aldehyde was therefore planned *via* a Mitsunobu reaction of 1-penten-3-ol with 4-hydroxy-6-methyl-2-pyrone, followed by an ozonolysis of the terminal alkene to generate the desired aldehyde.

Table 2.13: Mitsunobu reactions of **9** and **164.**



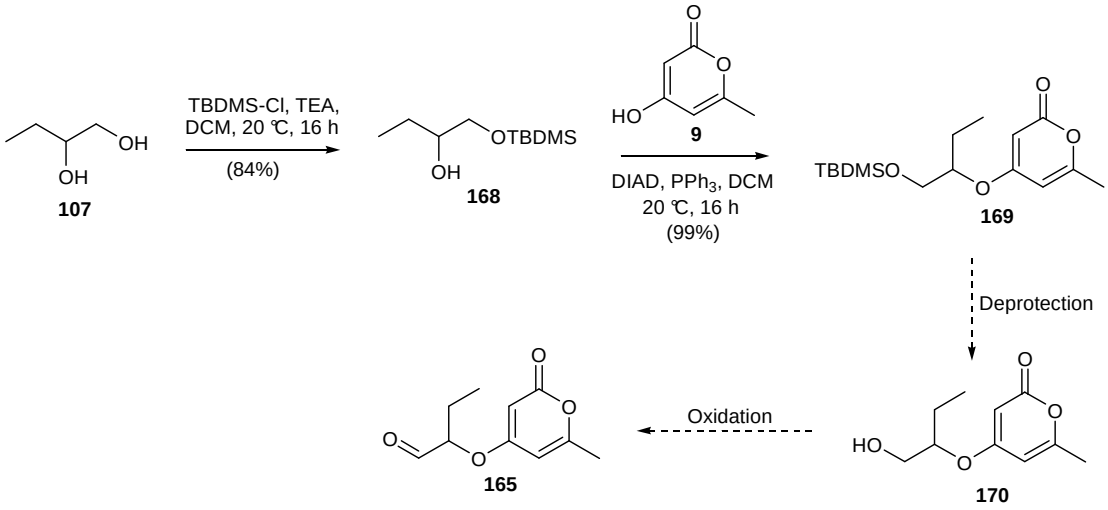
9 **166** **167**

Eq. of PPh_3/DIAD/**164**	Yield (%)
1.0	12
1.5	17 – 32*
2.0	28

*Reaction yield varied across five runs.

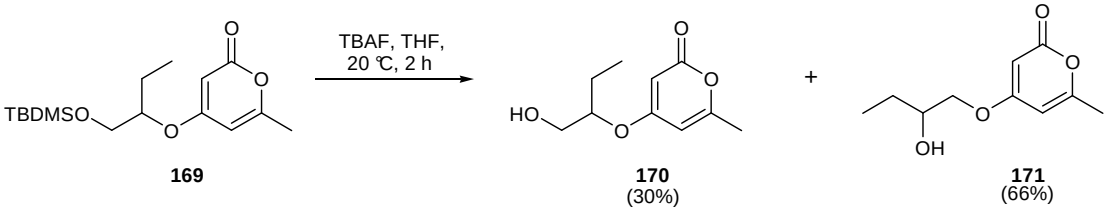
1-Penten-3-ol (**166**) proved to be a poor substrate for the reaction with variable yields obtained, and no yields of an adequate level have been achieved. In each case, large quantities of unreacted **9** were recovered.

Previous work with 1,2-butanediol had shown it was possible to selectively protect the primary alcohol and then utilise the secondary alcohol for Mitsunobu coupling to **9 (Scheme 2.19)**. By utilising the same methodology, a new approach to the aldehyde was suggested (**Scheme 2.48**).



Scheme 2.48: Proposed route to **165.**

The first two steps of the reaction proceeded in excellent yields to generate a silyl protected alcohol (**169**). It was then predicted that a simple deprotection and oxidation would lead directly to the desired aldehyde **165**. The initial deprotection strategy was to use TBAF as a source of fluoride. The deprotection step gave excellent conversion, however upon isolation, two products had been generated. The ^{1}H NMR spectroscopic analysis confirmed that a rearrangement of the diol had occurred under the conditions used (**Scheme 2.49**).



Scheme 2.49: TBAF deprotection of **169**.

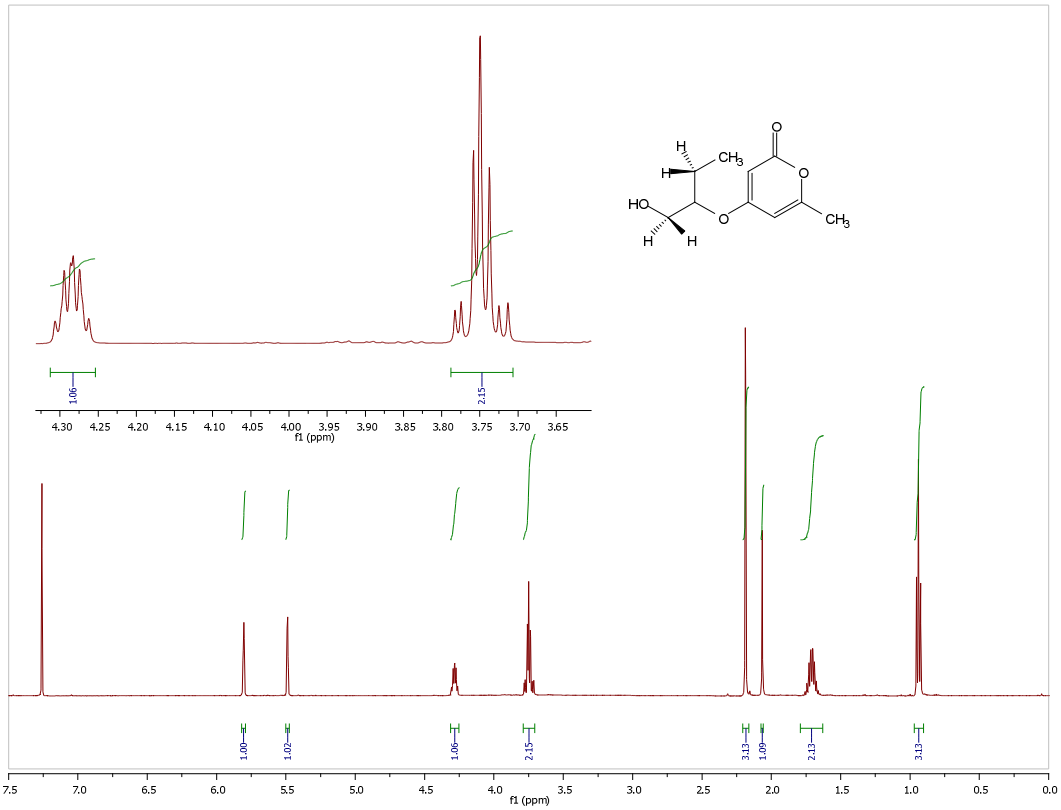


Figure 2.5: ^{1}H NMR spectrum of **171** with emphasis of the diagnostic peaks.

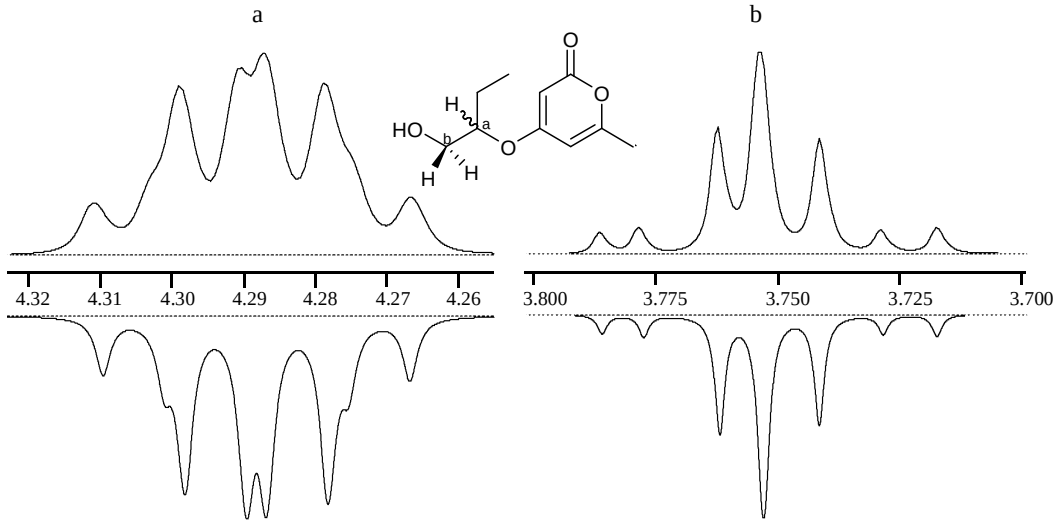


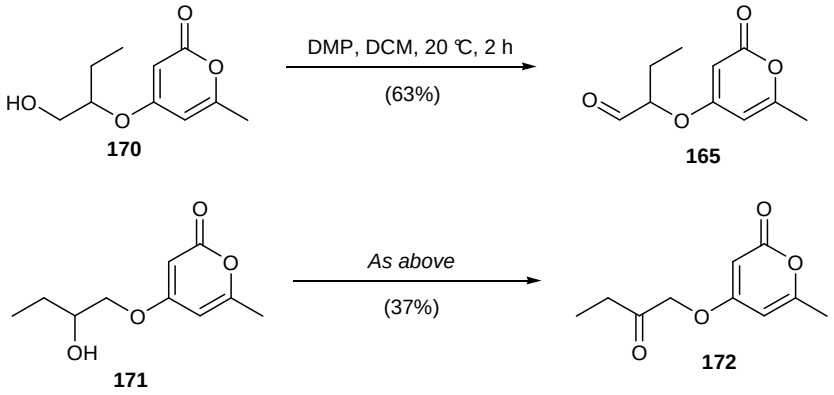
Figure 2.6: Overlay of observed ^{1}H NMR (top) and gNMR simulation (bottom) signals for diagnostic peaks of **171**.

The ^{1}H NMR spectra of the two products differ only very slightly, however the key diagnostic signals are those directly adjacent to the alcohols on the 1,2-butanediol. The electron-withdrawing effect of the 2-pyrone means that the protons on the carbon adjacent to the 2-pyrone ring will be more deshielded than those adjacent to the hydroxyl group. In the case of the TBAF deprotection, the major product showed two multiplet signals observed at δ ~3.7 and ~3.9 correlating to one and two protons, respectively. This corresponds with the shifts expected for **171**. The multiplets can be explained due to the presence of the chiral centre adjacent to the alcohol. The two protons in an adjacent CH_2 group are no longer equivalent, and as such will couple to each other and also the adjacent CH, thereby introducing increased complexity in the ^{1}H NMR spectrum of **170**.

The minor product also produced an interesting ^{1}H NMR spectrum. The two diagnostic signals were observed at chemical shifts of δ 3.75 and δ 4.3 corresponding to two and one protons' respectively. The single proton is now the more deshielded proton and therefore adjacent to the 2-pyrone as in **170**. This proton is also discernible as an indistinct quartet of doublets, indicating that three of the four adjacent protons have equivalent coupling values. The apparent multiplet corresponding to the 'CH_2OH' group can be seen as an overlapping of the two diastereotopic protons, each a doublet of doublets, which as a result leads to the second order effects observed (**Fig. 2.5**).

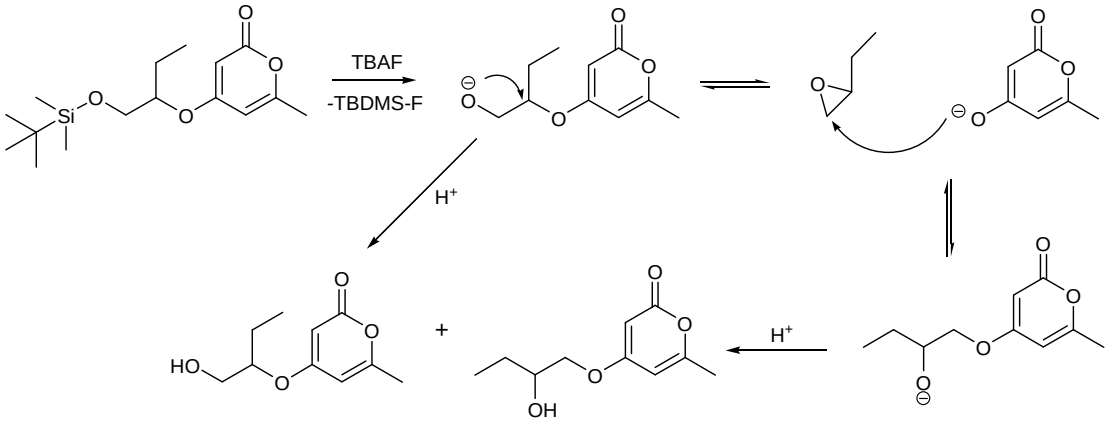
By utilising the NMR simulation program 'gNMR' developed by P. Budzelaar, it is possible to simulate the observed second order effects and designate the individual peaks and coupling constants with confidence.[105] In this case, the signals observed for the two protons adjacent to the alcohol at δ3.75, correspond to $^{3}J_{HH}$ couplings of 4.1 and 5.9 Hz to the proton at the chiral centre, and also a $^{2}J_{HH}$ coupling of 12.1 Hz between each other. The gNMR simulation of these peaks supports this assignment (**Fig. 2.6**).

The assigned structures of **170** and **171** were subsequently confirmed by oxidation, using Dess-Martin periodinane to generate the aldehyde and ketone, respectively (**Scheme 2.50**).



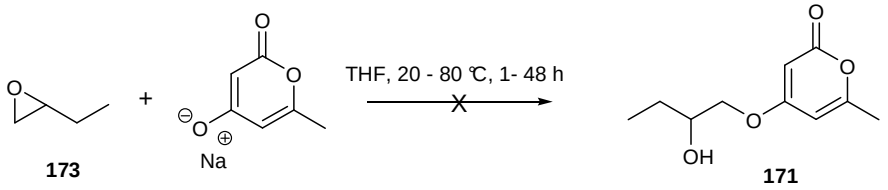
Scheme 2.50: Oxidations of **170** and **171**.

The general mechanism for TBAF deprotection is for the insertion of fluoride to create a silyl fluoride and oxide counter ion which becomes protonated upon work-up. However, due to the strong electron-withdrawing effect of the 2-pyrone motif in **169**, it is feasible that the oxide is able to eliminate the 2-pyrone to create an epoxide. Upon nucleophilic attack of the 2-pyrone on the epoxide, the terminal carbon would now be the most accessible, resulting in the undesired **171** (**Scheme 2.51**).



Scheme 2.51: Deprotection/Rearrangement of **169** in presence of TBAF.

The most surprising aspect of this rearrangement is that given the lack of nucleophilic character observed with **9** in previous experiments, none of the free 2-pyrone was isolated. In order to probe this reaction mechanism, 1,2-epoxybutane (**173**) was treated with the sodium salt of **9** and subjected to prolonged reaction times and increased temperatures (**Scheme 2.52**).

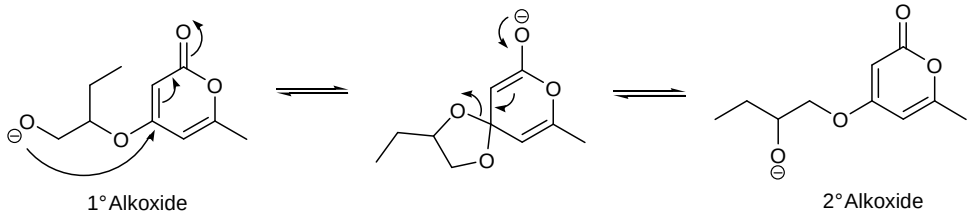


173 **171**

Scheme 2.52: Attempted synthesis of **171** from nucleophilc reaction of **9** with **173**.

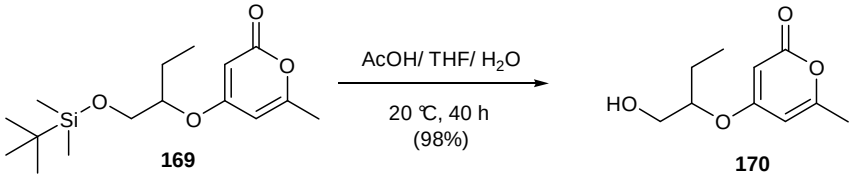
In each case no reaction was observed, indicating one of two scenarios. Either the proposed mechanism is incorrect, or the presence of the large sterically bulky tetrabutyl ammonium counter ion increases the nucleophilicity of the 2-pyrone.

Alternatively, the alkoxide ion could undergo a conjugate addition into the 2-pyrone ring to form an acetal intermediate. The resulting ring opening would generate the two products in equilibrium, with the formation of the undesired secondary alcohol likely to be favoured (**Scheme 2.53**).



Scheme 2.53: Alternative rearrangement pathway.

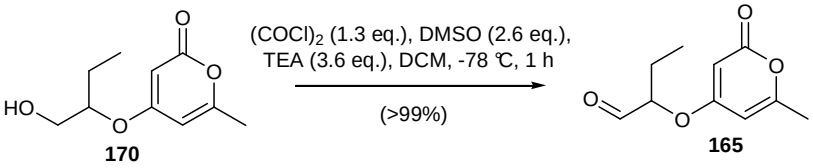
In order to avoid the rearrangement, acidic conditions were tested and quickly proved to be very effective, providing an efficient route to the free alcohol (**Scheme 2.54**).



169 **170**

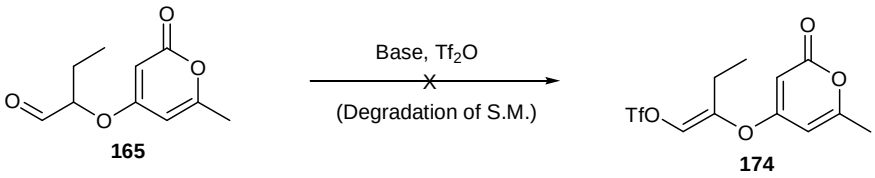
Scheme 2.54: Acidic deprotection of **169**.

The next step towards the synthesis of the vinyl halide was the oxidation to an aldehyde. Using DMP has been shown to be an adequate method for the oxidation, however trace amounts of aromatic impurities were consistently found in the product, which proved to be unstable to silica gel chromatography. Subsequent testing showed that a Swern oxidation gave quantitative yields of **165** in high purity (**Scheme 2.55**).



Scheme 2.55: Swern oxidation of **170**.

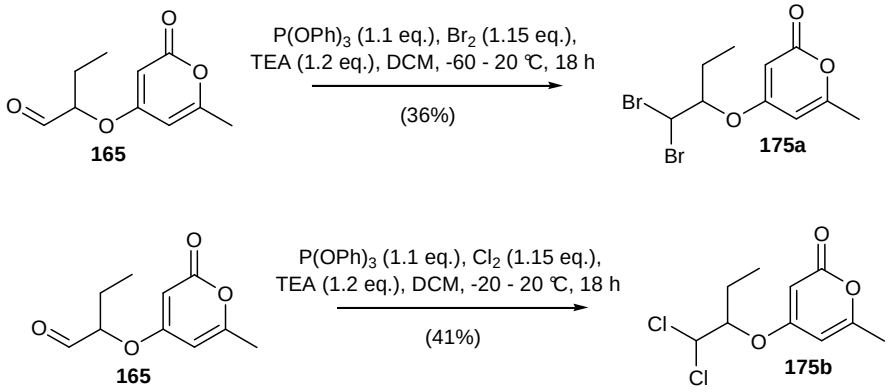
The initially proposed two step synthesis of the vinyl halide *via* the synthesis of a 1,1-dihalo-intermediate can potentially be circumvented using a suitable *pseudo*-halide such as a triflate. The use of vinyl triflates in cross-coupling reactions is well documented, with the triflates often accessed through the reaction of a suitable carbonyl with base and a source of triflate such as triflic anhydride.[106] Aldehyde **165** was subsequently treated with various bases and triflic anhydride to generate the desired vinyl triflate (**174**).



Scheme 2.56: Synthesis of vinyl triflate **172**.

The triflation of **165** proved to be unsuccessful with degradation of the 2-pyrone seen despite a variety of conditions (**Scheme 2.56**). It is likely that trace amounts of triflic acid in the reaction could have mediated the degradation of the 2-pyrone.

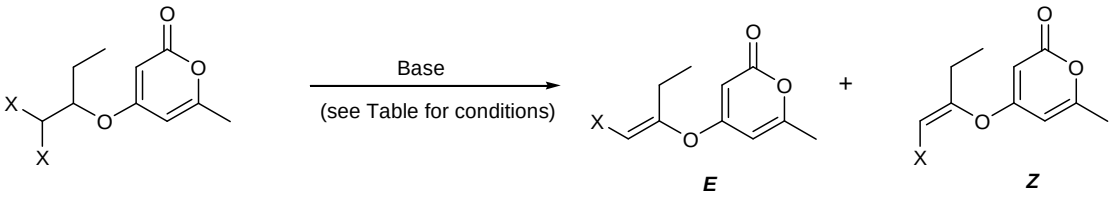
The alternative synthesis of the vinyl halide utilises methodology developed by Spaggiari *et al.* whereby an aldehyde can be converted into a 1,1-dihalide under relatively mild conditions.[103] Treatment of the resulting dihalide with base will generate the desired vinyl halides suitable for cross-coupling. Treatment of **165** under these conditions gave access to dibromo and dichloro adducts **175a** and **175b**, respectively, in relatively low yields (**Scheme 2.57**).



Scheme 2.57: Synthesis of dihalides **175a** and **175b**.

Dihalides **175a** and **175b** were subjected to a variety of elimination conditions, with the results shown in **Table 2.14**.

Table 2.14: Elimination reactions of **175a** and **175b**.



X = Br (**175a**)
Cl (**175b**)

X = Br (***E/Z*-176a**)
Cl (***E/Z*-176b**)

Entry	X	Base	Solvent	Time	Temperature	Yield (%)	*E:Z* Ratio*
1	Br	DBU	THF	24 h	80 ℃	93	41 : 59
2	Br	DBU	THF	24 h	70 ℃	>99	36 : 64
3	Br	DBU	Dioxane	18 h	100 ℃	68	31 : 69
4	Br	Ag_2CO_3	THF	24 h	70 ℃	0	-
5	Br	Ag_2CO_3	THF	24 h	100 ℃ (μλ)	0	-
6	Br	KHMDS	THF	18 h	-78 - 20 ℃	0	-
7	Cl	DBU	THF	24 h	80 ℃	0	-
8	Cl	DBU	THF	24 h	90 ℃	9	44 : 56

*Ratio established from isolated yields.

The initial elimination of HBr from **175a** resulted in the formation of both isomers of **176a** (entry 1), with the undesired *Z*-isomer favoured. Reduction of the reaction temperature to promote formation of the kinetic product resulted in the ratio shifting

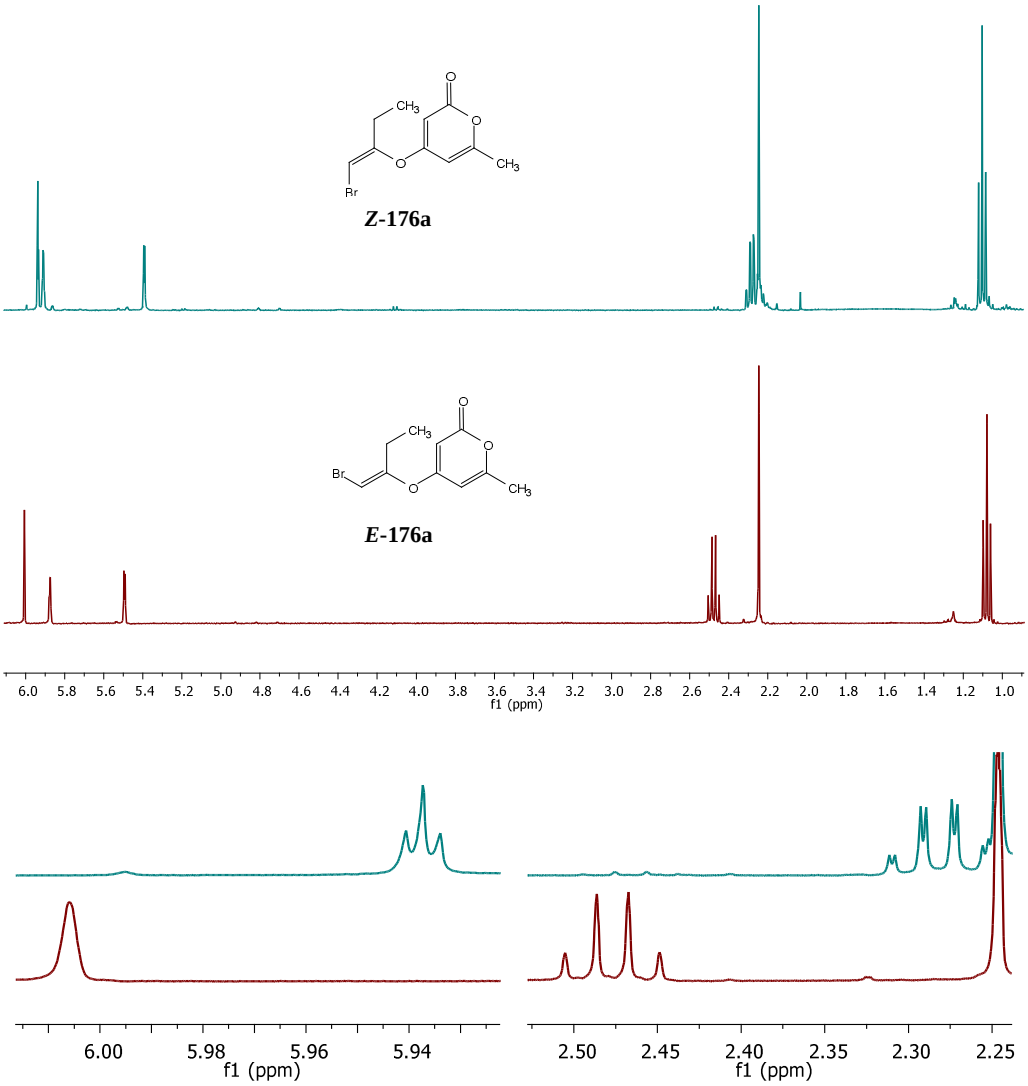
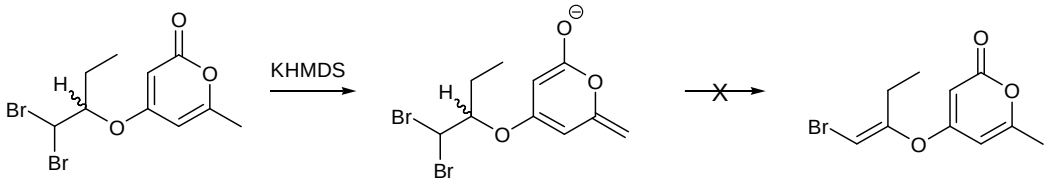


Figure 2.7: Overlay of ^{1}H NMR sprectra for *Z* and *E* isomers of **176a** (a), with emphasis of the alkene (b) and CH_2 (c) signals.

slightly more towards the *Z*-isomer (entry 2), however when utilising a higher reaction temperature to promote formation of the thermodynamic product, it was observed that the ratio of products has now shifted dramatically in favour of the *Z*-isomer (entry 3). It must be noted however that the yields drop towards higher temperatures, whilst no starting material is recovered, indicating that product degradation is a significant problem. It is a distinct possibility that at higher temperatures formation of the *E*-isomer is preferred, however due to the high temperatures, degradation of the *E*-isomer occurs quicker resulting in a distorted isomeric ratio. The use of relatively weak organic bases, such as DBU, are likely to enforce an E2 pathway for the reaction, however, by using stronger bases to generate a deprotonated intermediate the reaction can be shifted towards an $E1_{CB}$ type mechanism which may affect the isomeric ratio obtained. Unfortunately, the use of stronger inorganic bases such as KHMDS resulted in no observed reaction (entries 4,5 and 6). A possible explanation for this is the relatively acidic protons at C-7 of **175a**. In the presence of DBU, the elimination proceeds via a concerted deprotonation and elimination of bromide, whereby the strength of the base is insufficient to deprotonate any position of the molecule directly. However, when using KHMDS, it is now sufficiently basic to deprotonate the most acidic position of the molecule. On this occasion, the C-7 position would appear to be the most likely, forming the extended enolate and thereby shutting down the elimination pathway (**Scheme 2.58**).



Scheme 2.58: Possible explanation for lack of elimination when using KHMDS.

In the absence of any adjacent protons to the alkene in **174**, it is not possible to determine stereochemistry through the magnitude of the alkene-alkene $^{3}J_{HH}$ values. However, study of the two isomers indicates that the longer $^{4}J_{HH}$ allylic couplings are only present in one of the isomeric forms, allowing distinction of the isomers through these differences (**Fig. 2.7**).

Literature precedent suggests that the $^{4}J_{HH}$ allylic couplings are promoted when the alkene proton is located *cis* to the relevant allylic protons.[107] Further to this, it was noted in the isolation papers of the phacelocarpus macrocycles that some derivatives exhibited the allylic coupling, however in the case of **33**, no such coupling was observed. Complete

assignment of the stereochemistry was confirmed through NOESY correlations which were observed between the alkene and CH_2 in ***Z*-176a**, but were absent in ***E*-176a** (**Fig. 2.9**).

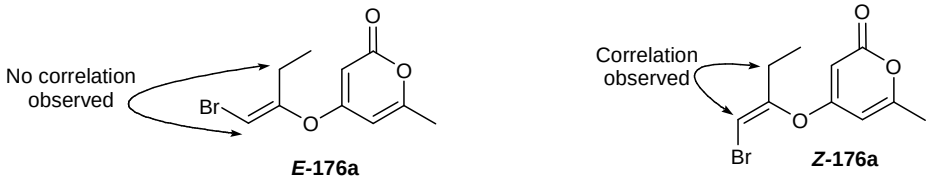


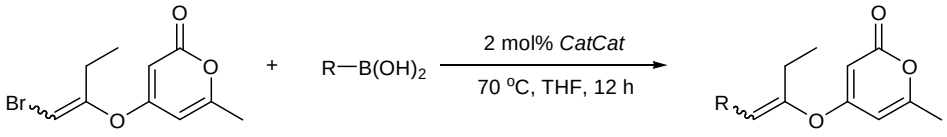
Figure 2.8: Observed NOESY correlations of ***E/Z*-174**.

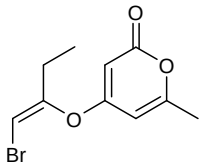
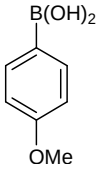
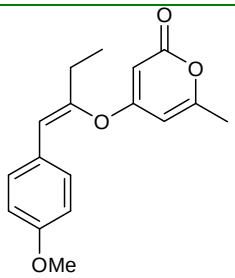
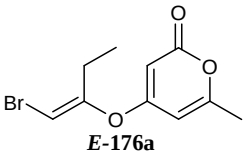
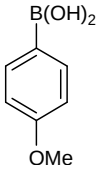
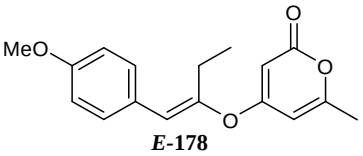
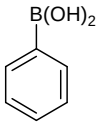
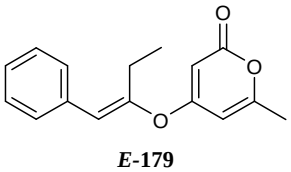
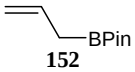
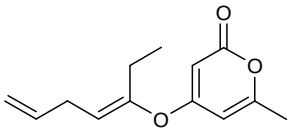
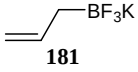
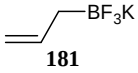
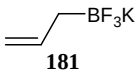
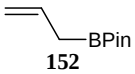
2.4.3 Cross-coupling reactions involving the HA fragment (176a)

The most important step in the current synthetic pathway is the synthesis of the 1,4-skipped diene *via* a vinylic / allylic coupling reaction. The vinyl bromides ***E/Z*-176a** were subjected to Suzuki reactions utilising the previously described methodology. The results are shown in **Table 2.15**.

The initial Suzuki reactions worked well on both isomers of **176a** when using highly active organoboronic acids (**177** and **57**), proving the activity of the vinyl bromide is sufficient for palladium catalysed cross-coupling. It is noticeable that as the stable aryl boronic acid partner is exchanged for a less active coupling partner, such as the allyl boronates, the reactivity declines rapidly. The poor reactivity of allyl BPin (**152**) can be attributed to the rapid hydrolysis of the pinacol ester into the allyl boronic acid in the presence of aqueous base, which subsequently degrades due to the slow transmetalation step. The use of stable BF_3K salts instead of the boronic acids, pioneered by Molander,[108] allows for the reaction of more sensitive reagents which may be prone to degradation. The use of **181** in the Suzuki reaction continues to show poor reactivity, despite changing to the stronger cesium carbonate base. To avoid the problems associated with hydrolysis of allyl pinacolborane, the reaction was carried out in the absence of water, resulting in a respectable 41% yield of the desired 1,4-skipped diene product (***E*-180**).

Table 2.15: Suzuki couplings of *E/Z*-**176a** with organoboronic acids.

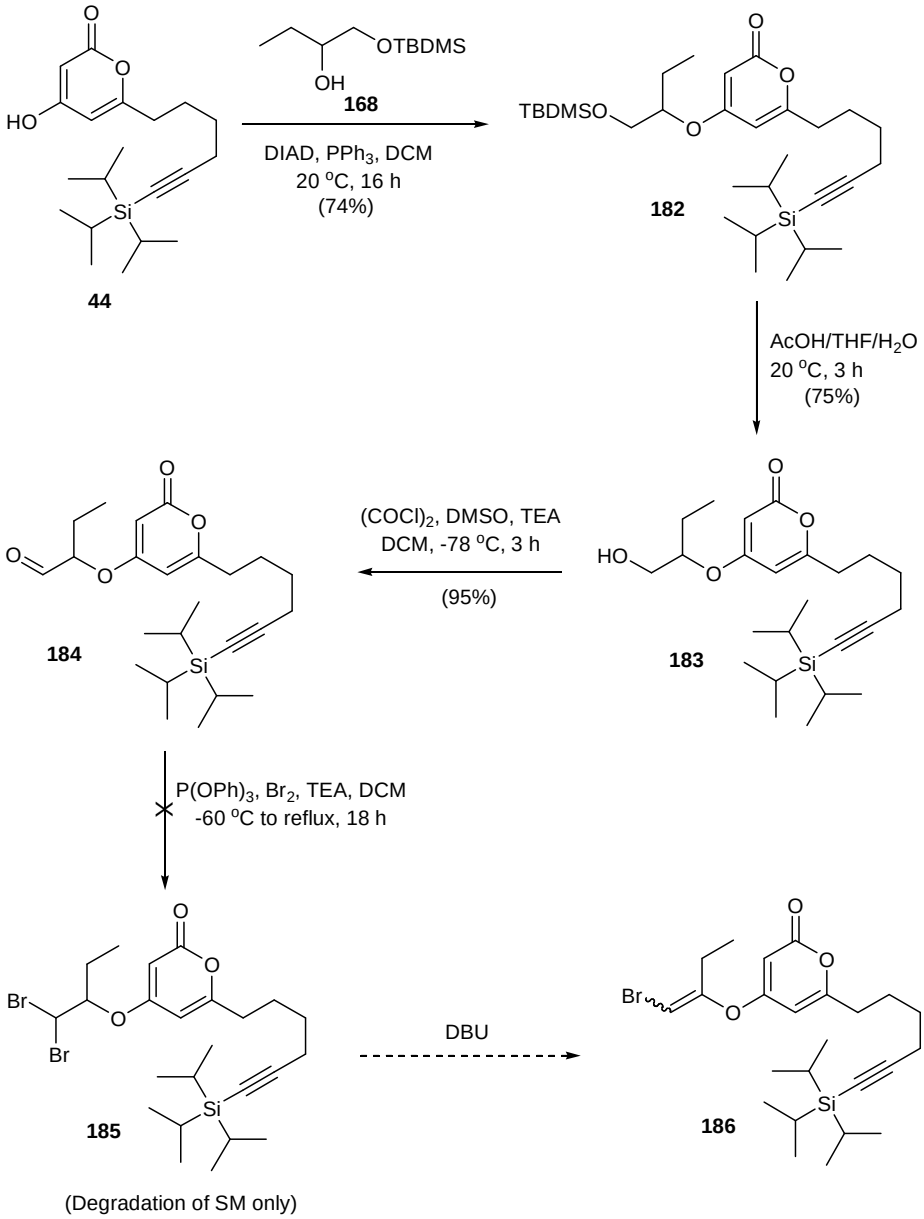


Entry	Vinyl bromide	Boronic acid	Base*	Products	Yield (%)
1	 ***Z*-176a**	 **177**	$Na_2CO_{3(aq)}$	 ***Z*-178**	68
2	 ***E*-176a**	 **177**	$Na_2CO_{3(aq)}$	 ***E*-178**	98
3	***E*-176a**	 **57**	$Na_2CO_{3(aq)}$	 ***E*-179**	61
4	***E*-176a**	 **152**	$Na_2CO_{3(aq)}$	 ***E*-180**	0
5	***E*-176a**	 **181**	$Na_2CO_{3(aq)}$	***E*-180**	0
6	***E*-176a**	 **181**	$Cs_2CO_{3(aq)}$	***E*-180**	0
7	***E*-176a**	 **181**	Cs_2CO_3	***E*-180**	0
8	***E*-176a**	 **152**	Cs_2CO_3	***E*-180**	41

* 2M aqueous solutions or 3 equivalents of anhydrous base were used in all cases

2.4.4 Synthesis of the HAB (157) and HAB′ (159) fragments

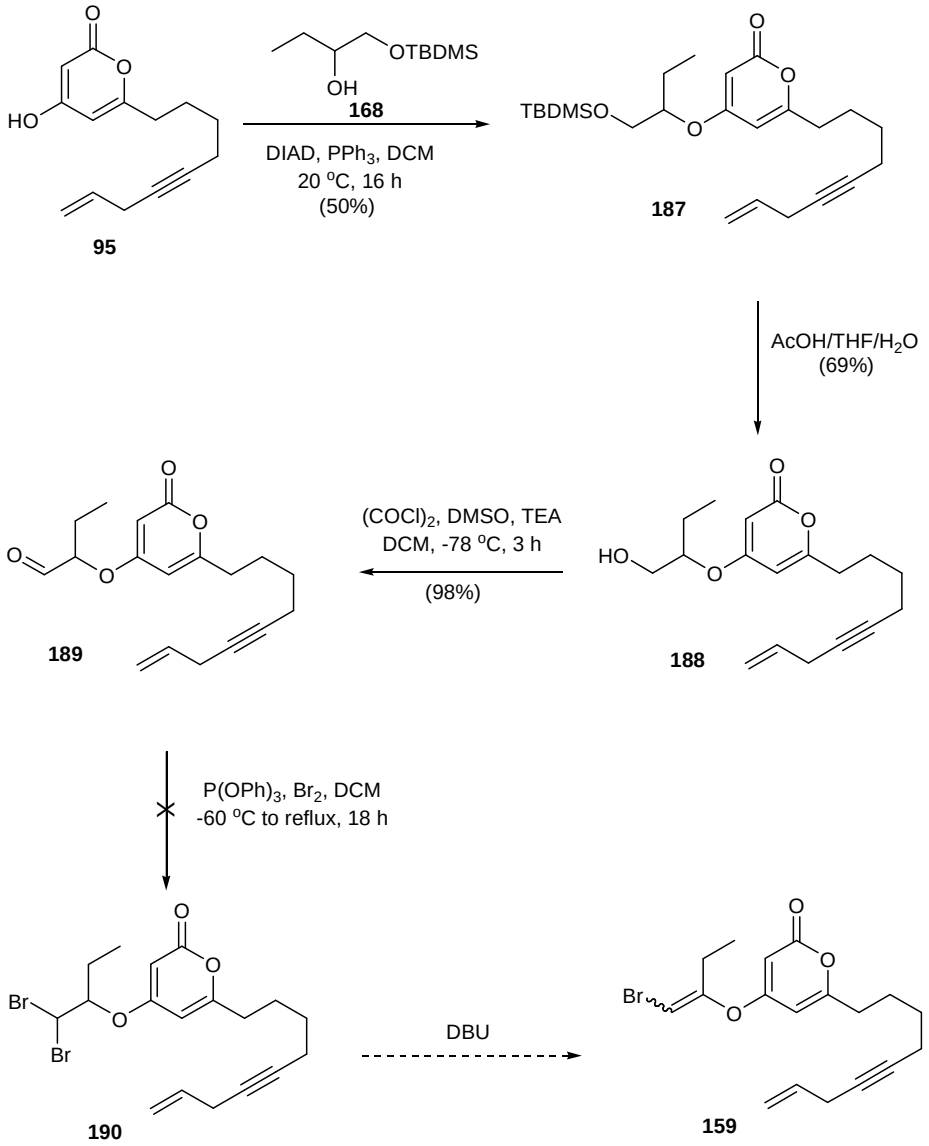
The synthetic methodology developed towards the HA fragment (**176a**) was applied to the synthetic routes A (**Scheme 2.59**) and B (**Scheme 2.60**) suggested in **Scheme 2.43**.



Scheme 2.59: Synthetic route A

The initial incorporation of the protected alcohol **168**, deprotection and oxidation to **184** proceeded with a respectable 53% yield (over the three steps). The subsequent dibromination failed with complete degradation of the starting material observed (TLC and

^{1}H NMR). The same synthetic pathway was applied to the synthesis of the HAB′ fragment (**159**) with a similar result.

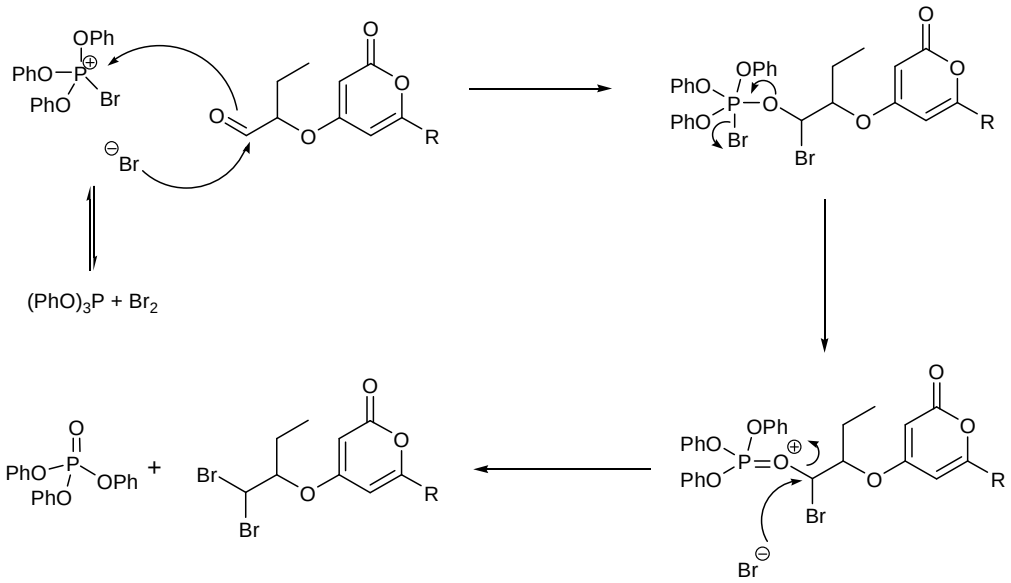


Scheme 2.60: Synthetic route B

The poor conversion to the dibromides in each of the real systems attempted was disappointing. The only significant difference between the test substrate **165** and the real systems, **184** and **189**, is the presence of the alkyne. The use of bromine in the synthesis of the dibromides **185**/**190** could contribute to the degradation of the starting materials.

The mechanism involves an initial equilibrium forming between the bromine and phosphate to generate a bromophosphonium ion and the reactive bromide ion which attacks the carbonyl. However, in the presence of non-aromatic alkenes/alkynes, a

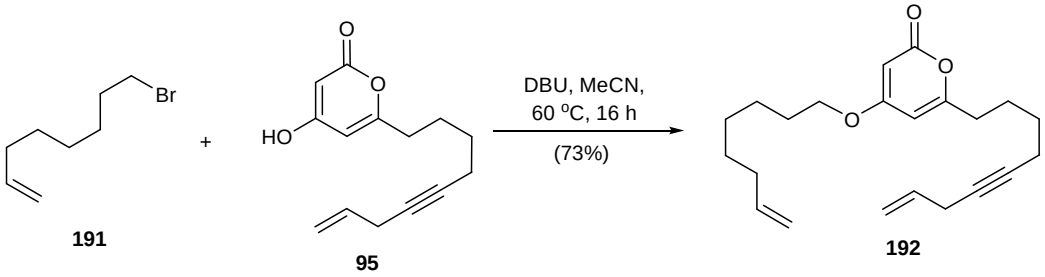
competing reaction pathway is formed whereby the bromine can react rapidly with the points of unsaturation. The dibromination of the aldehyde is a slow reaction, whereas C-3 bromination of 2-pyrones is known to be extremely rapid,[109] as is the bromination of alkynes.[110] In this instance the equilibrium of the intitial step will drive the reaction away from the desired dibromide compound.



Scheme 2.61: Proposed mechanism for dibromination.

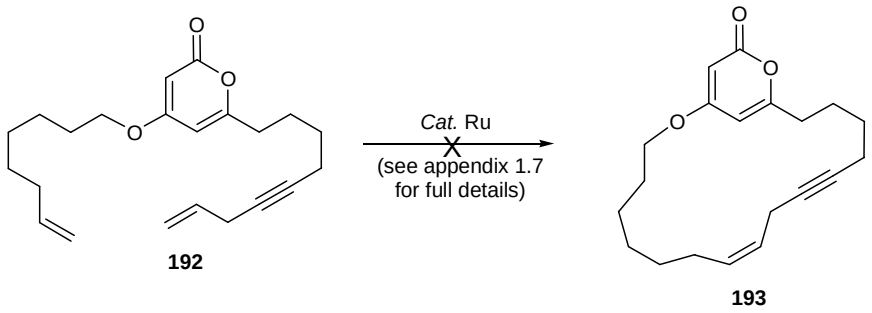
2.5 Synthesis of macrocyclic 2-pyrones

The proposed method of forming the macrocycle in route B is through ring closing alkene metathesis. In order to test the feasibility of this method a simple analogue was rapidly prepared through the reaction of 8-bromo-1-octene (**191**) with **95** under basic conditions to generate **192** (**Scheme 2.62**).



Scheme 2.62: Synthesis of **192**.

The analogue **192** was subsequently subjected to various metathesis conditions, however, no cyclised product was observed utilising a variety of conditions (**Scheme 2.63**).



Scheme 2.63: Ring closing metathesis of **192**.

The results from **Scheme 2.63** suggest that RCM is not compatible with this system. The likelihood is that the linearity of the alkyne is preventing the two alkenes being orientated in the correct manner for alkene metathesis to occur.

Recent work by Young *et al*. has shown that in medium-sized ring systems it is possible to enhance RCM compatibility of 1,4-enynes through the protection of the alkyne with $Co_2(CO)_8$.[111] The dicobalt hexacarbonyl protection enforces a significant change in the hybridisation of the alkyne. As the unprotected alkyne the orbitals are in an sp-hybridised state, allowing no rotation out of the plane. However, upon formation of the dicobalt hexacarbonyl adduct, the alkyne now assumes a tetrahedral sp_3-hybridised geometry about which there is a much greater degree of flexibility available (**Fig. 2.9**).

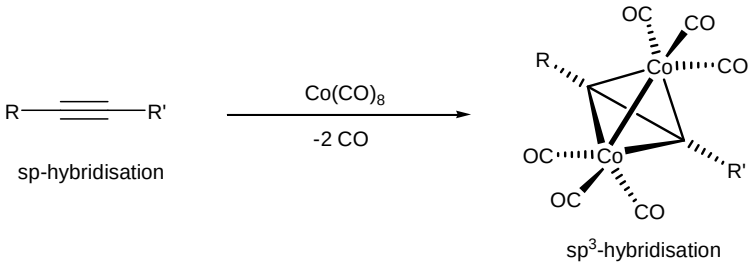


Figure 2.9: Alkyne-dicobalt hexacarbonyl compound.

The same methodology was applied to **192** which facilitates a greater degree of rotation for the macrocyclisation. The protection of the alkyne proceeds well under mild conditions, with the following RCM now proceeding in excellent yield (**Scheme 2.64**).

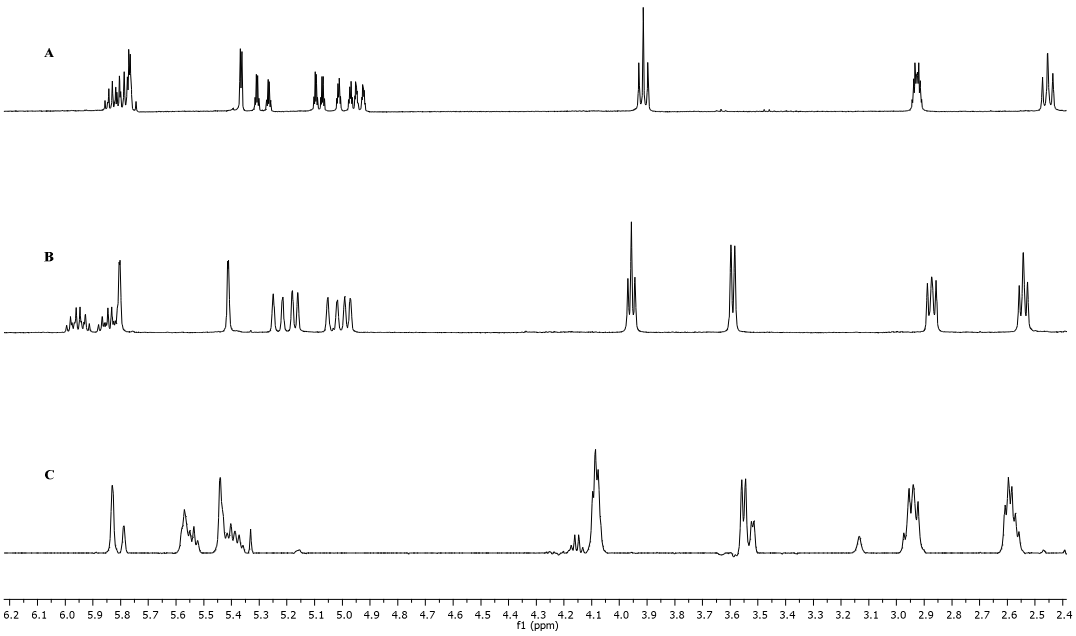


Figure 2.10: ^{1}H NMR spectra (500 MHz, $CDCl_3$) of a) **192**, b) **194**, c) **195**

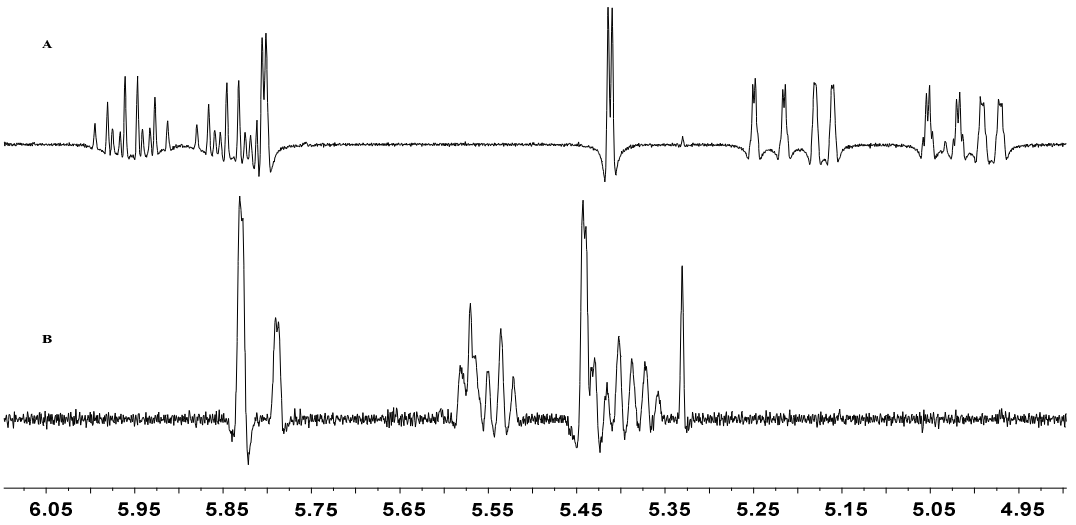
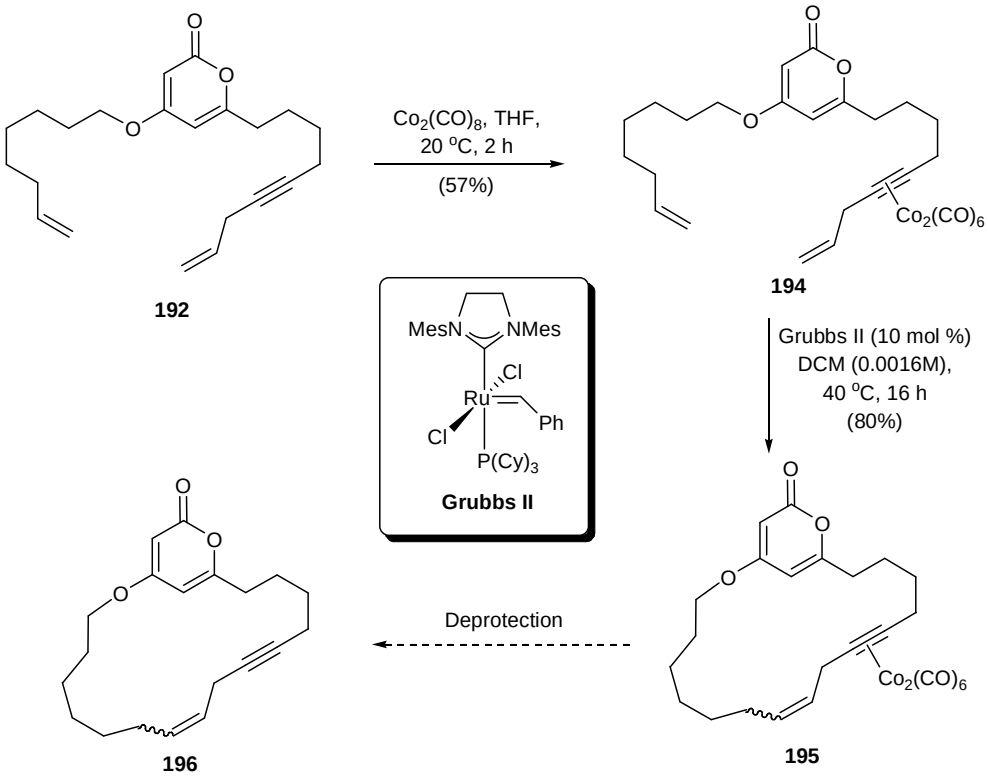


Figure 2.11: ^{1}H NMR spectra (500 MHz, $CDCl_3$) of a) **194** and b) **195** (Sine bell apodisation applied to raw FID)



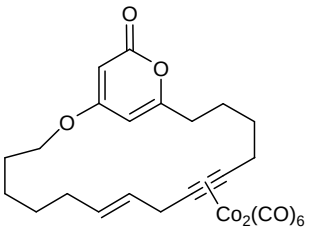
Scheme 2.64: Synthesis of macrocycle **195**.

On inspection of the ^{1}H NMR spectroscopic data for **195**, the presence of two 2-pyrone species are observed, indicating one of two possibilities. It is possible that both *cis* and *trans*-isomers of the alkene are present. Alternatively, it is equally plausible that decomposition of the dicobalt complex **195** is leading to the formation of the deprotected macrocycle **193**.

The ^{1}H NMR spectra of **192** (**Fig. 2.10-A**) shows the presence of four terminal alkene protons and two overlapping internal C-H alkenes in addition to the two 2-pyrone signals. Upon formation of the dicobalt complex **194** (**Fig. 2.10-B**) the internal alkenes become distinct. A downfield shift of the CH_2 centred in the 1,4-enyne motif, observed as a doublet at δ 3.55. Following macrocyclisation to **195** (**Fig. 2.10-C**), the four terminal alkenes have been removed, however two products in a 2:1 ratio are observed from the integrals of the two 2-pyrone signals and the CH_2 doublet signal at δ 3.55. Interestingly, the alkene signals for the major and minor products do not differ sufficiently to interpret the signals separately using standard processing methods.

Applying Sine bell apodisation to the raw NMR data obtained for **194** and **195** generates spectra with increased resolution between overlapping signals (**Fig. 2.11-A** and

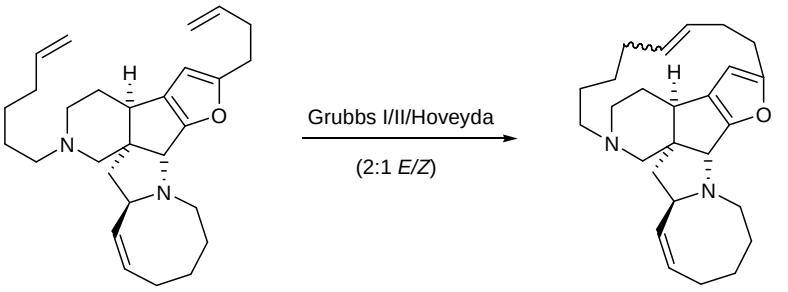
2.11-B, respectively), allowing for improved characterisation of the key alkene signals. The first alkene at δ 5.40 represents a doublet of triplets with $^{3}J_{HH}$ values of 15.0 Hz and 7.5 Hz, respectively. Analysis of the second alkene at δ 5.55 is more difficult. However, it is possible to assign the signal as a doublet of triplets with $^{3}J_{HH}$ values of 15.0 Hz and 7.0 Hz, respectively, with an additional impurity overlapping. The major component of **195** can be assigned with confidence as ***E*-195** (**Fig. 2.12**).



***E*-195**

Figure 2.12: Major component of **195**.

The interpretation of the ^{1}H NMR spectra suggests that there is only one isomer (*E*-**195**) present in the product, as a mixture would be expected to generate a complex multiplet or two additional signals corresponding to the *cis*-alkene protons. The most important factor in identifying the *cis*-isomer would be the identification of a suitable *J* value or alternatively an NOE correlation between the relevant protons. Unfortunately, a *J* value is not discernible due to the more prominent signals from ***E*-195**, and the NOESY spectra proved inconclusive. The formation of mixed isomers in large ring sized macrocylisations formed through ring closing metathesis has been well documented, which supports the evidence for the *cis*-isomer.[112] Of particular note are the selectivity problems encountered in the various syntheses of nakadomarin A **197**, whereby the final RCM is noted to generate both *E*- and *Z*- isomers in a ratio of 2:1 in all cases (**Scheme 2.66**).[113]



196

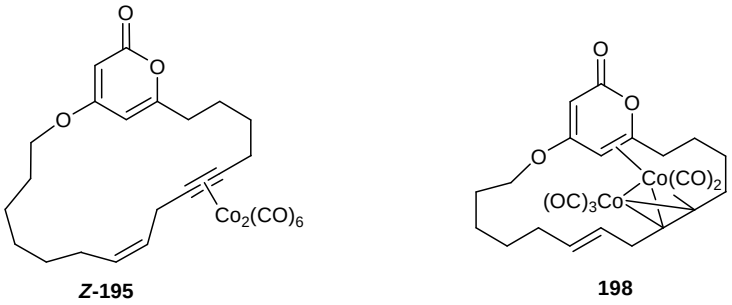
197
(-)-Nakadomarin A

Scheme 2.65: RCM approach to Nakadomarin A

The alternative explanation for the minor product as a deprotection of the dicobalt complex would also appear inaccurate. Upon complexation of dicobalt hexacarbonyl to **192**, the signals for the CH_2 group centred in the 1,4-enyne motif shifted further downfield. It can be assumed that a similar shift upfield would be expected upon removal of the protecting group, however the minor product clearly indicates the CH_2 signal remains close to the major product, and thus the cobalt complex must still be intact. Mass spectrometry supports this interpretation due to the absence of the correct mass for the deprotected macrocycle.

The degradation of dicobalt hexacarbonyl complexes has been well documented, with the loss of CO as a key fragment in their degradation.[114] The mass spectrum of **195** shows the presence of degradation peaks whereby loss of 1, 3 or 4 CO units has occurred. Whilst the presence of these peaks would be expected from pure product, it is possible that partial degradation of the dicobalt complex accounts for the minor product observed. The co-ordination of alkynyl dicobalt hexacarbonyl complexes to alkenes *via* the loss of CO has been widely shown to be a key step in the Pauson-Khand reaction.[115] It is therefore conceivable that the minor product could contain the alkene and alkyne linked cobalt complex **198.** This assignment would account for the small change in the chemical shifts observed for the C-3-H and C-5-H 2-pyrone signals. The two possibilities for the minor component in the RCM of **194** have been suggested as *Z*-**195** and **198** (**Fig. 2.13**), however upon inspection of the IR data for *E*-**195**, only three bands are observed in CO region (2086, 2043 and 2012 cm^{-1}), consistent with the presence of an alkyne bound $Co_2(CO)_6$. The IR spectrum of **198** would be expected to exhibit additional bands due to the unsymmetrical nature of the cobalt complex, whereas *Z*-**195** should exhibit the same bands as *E*-**195**.

Whilst definitive proof has yet to be obtained, the identity of the minor compenent from the RCM of **194** is attributed to *Z*-**195**. The key details in the assignment are the presence of only three distinct bands in the IR data and the minimal shifts in the NMR signals.

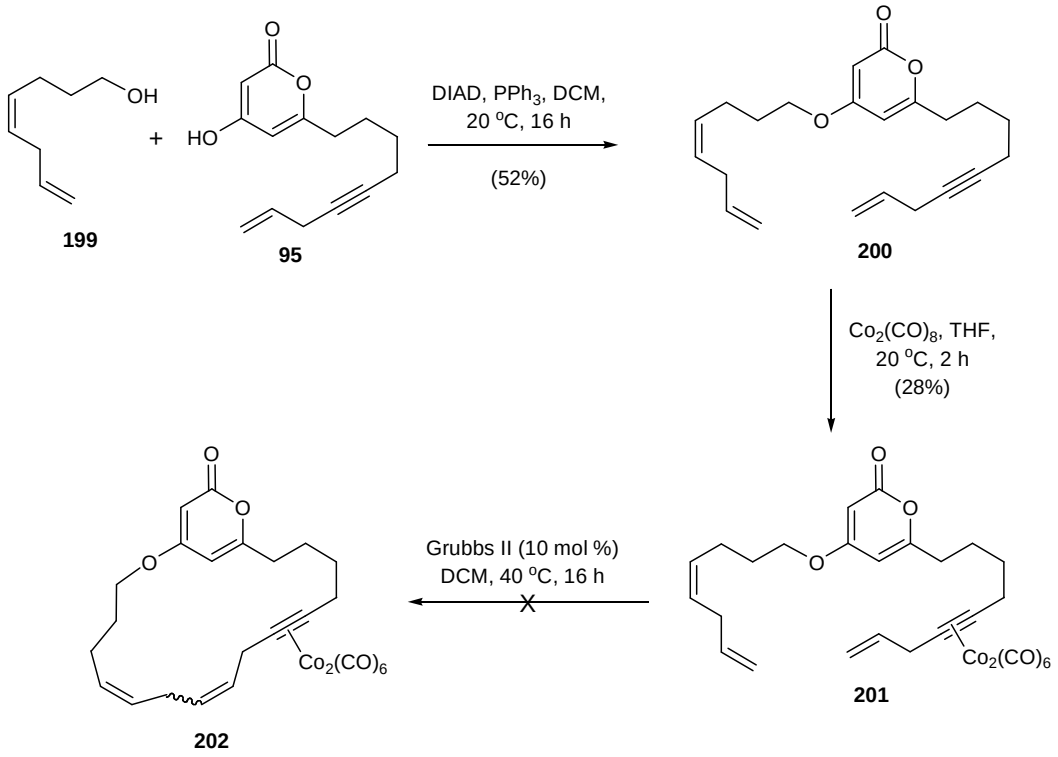


***Z*-195** **198**

Figure 2.13: Possible minor components from RCM of **194**.

The desired macrocycles can now be acquired through the oxidative deprotection of the dicobalt hexacarbonyl group. The choice of oxidant needs careful consideration for a number of reasons. The use of strong oxidants, such as CAN, may jeopardise the 1,4-enyne motif which could be converted into the 1,3-enyne in the event of radical formation, or alternatively, in the presence of elevated temperatures, an inter/intra-molecular Pauson-Khand reaction may occur.

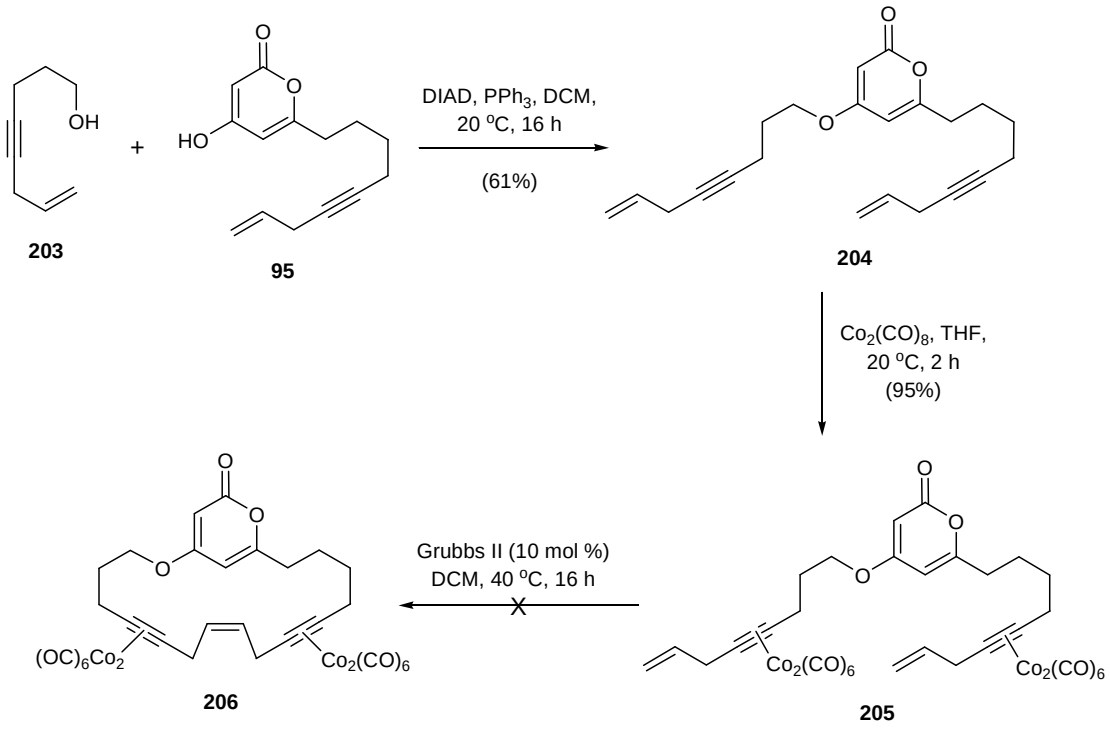
The formation of macrocycle **195** is an important result as it shows RCM is a suitable means of macrocycle formation, however it is also important that the ring closing methodology is able to accommodate further complexity in the left hand chain which would require two additional alkenes for the formation of **33**. Prior work towards the vinyl ether has shown it to be unreactive towards metathesis, although the additional alkene within the chain could potentially become involved in the metathesis and disrupt the formation of the desired product. However, the presence of the two terminal alkenes should dictate that the ruthenium catalyst reacts preferentially at these positions. The competitive RCM reaction was subsequently tested (**Scheme 2.66**).



Scheme 2.66: Synthesis and RCM of **201**.

The synthesis of triene **201** was achieved in modest yield through the Mitsunobu reaction of **95** with diene **199** and alkyne protection of the resulting triene **200**. The RCM reaction failed to yield the desired macrocycle **202** indicating that the internal alkene unit must be masked in order for the reaction to become a suitable means of macrocycle formation in the real system.

There are a number of methods available to mask alkenes, with perhaps the most widely utilised method being the alkyne, allowing stereoselective hydrogenation to give the formation of the desired alkene isomer. The presence of an alkyne has already been shown to inhibit macrocyclisation, yet further protection of the alkyne enabled the ensuing macrocyclisation to occur. In order to test the viability of a doubly protected diyne system, a simple test substrate was synthesised (**Scheme 2.66**).



Scheme 2.67: Synthesis and RCM of **205**.

The RCM of doubly alkyne protected diyne system **205** proved to be unsuccessful. Although the reaction failed, it is not a definitive failure towards the natural product formation. The presence of dicobalt hexacarbonyl units in close vicinity to the terminal alkynes on both arms could be providing too much steric bulk to allow the formation of the metathesis intermediate required for the formation of the desired product (**Scheme 2.68**).

Scheme 2.68: Proposed reaction intermediates in the RCM of **203**.

2.6 Conclusions and Future work

2.6.1 Conclusions

Throughout the course of the studies towards **33**, the important features required for the synthesis have been identified. The most important factor that has been addressed is the synthesis of the novel vinyl ether motif. Whilst the originally proposed Buchwald-Hartwig etherification strategy proved to be inadequate, alternative methods proved to be effective at installing the motif. The use of 4-hydroxy-2-pyrones as nucleophilic partners has been of key importance to the installation of functionalised side chains through Mitsunobu and Michael addition reactions. The stability of the vinyl ether motif has also been observed to be relatively poor, with degradation occurring above 100 °C.

The most important results from the studies towards **33** are: a) the successful synthesis **44** and **95** as suitable fragments for future syntheses; b) the synthesis of vinyl bromide **176a** and the subsequent successful Suzuki reactions of both isomers; and c) the utilisation of a dicobalt hexacarbonyl protected alkyne to enable the formation of the 19 membered macrocycle **195**.

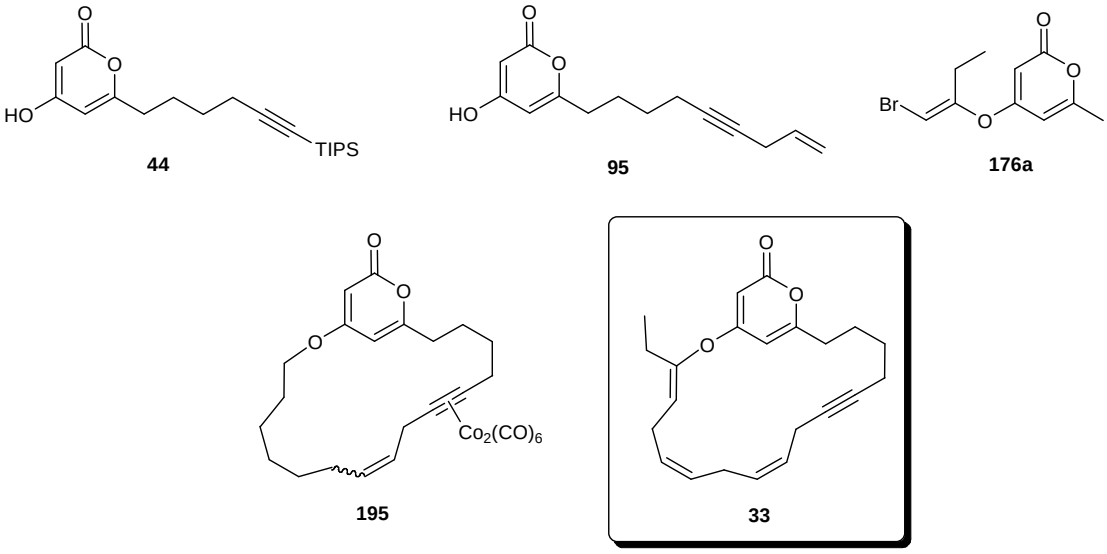
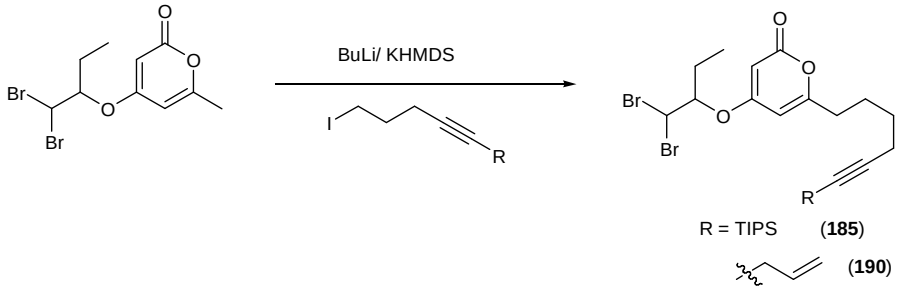


Figure 2.14: Key structures from studies towards **33.**

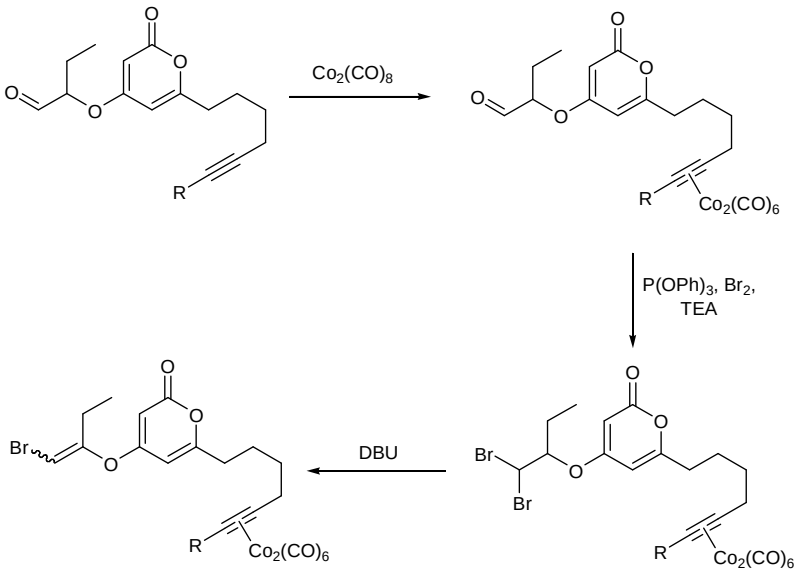
2.6.2 Future Work

The unsuccessful attempt to generate the advanced 1,1-dibromides **184** and **189** presents a problem in the planned synthesis, however future studies can contemplate one of two solutions to this problem. The elimination reaction of dibromide **175a** to generate the vinyl bromide **176a** did not occur in the presence of strong inorganic bases, such as KHMDS. The low reactivity was attributed to deprotonation at the C-7 position, which is desirable for alkylation at this position. This would allow formation of the previously synthesised dibromide **172** followed by the subsequent lithiation/ potassiation and alkylation with a suitable alkyl iodide (**Scheme 2.69**).



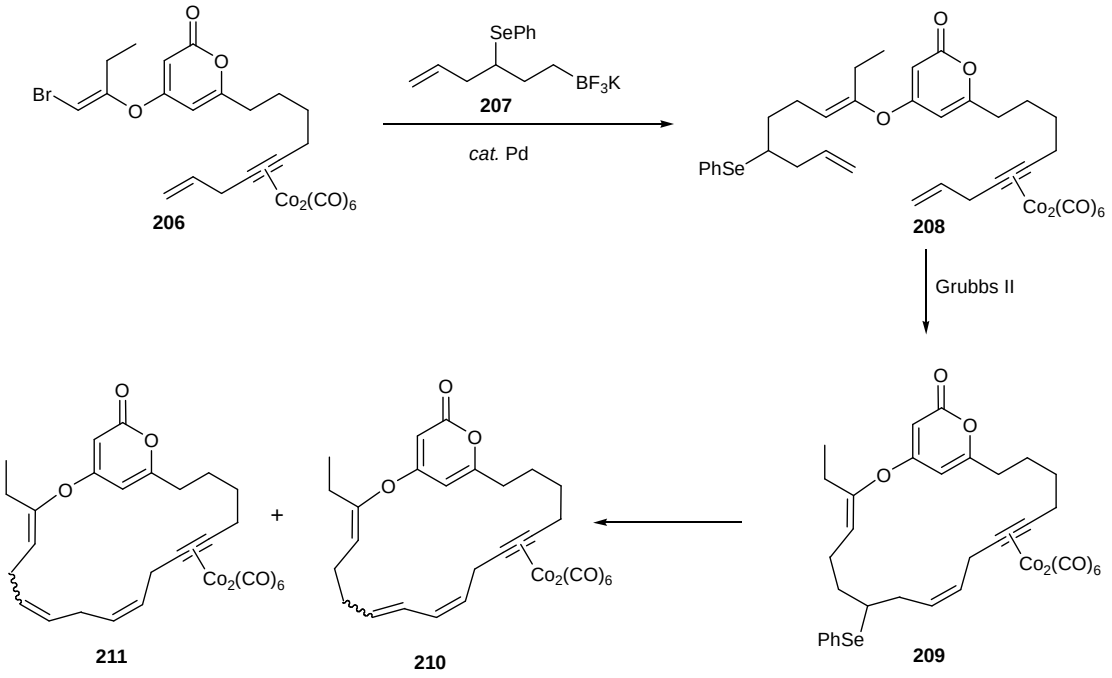
Scheme 2.69: Metallation strategy to advanced dibromides.

Alternatively, the problem of the alkyne can be circumvented *via* the introduction of an alkyne protecting group such as, $Co_2(CO)_6$ prior to the dibromination reaction. The protecting $Co_2(CO)_6$ group may then be carried forward into the potential RCM reactions (**Scheme 2.70**).



Scheme 2.70: Alkyne protection strategy to vinyl bromides.

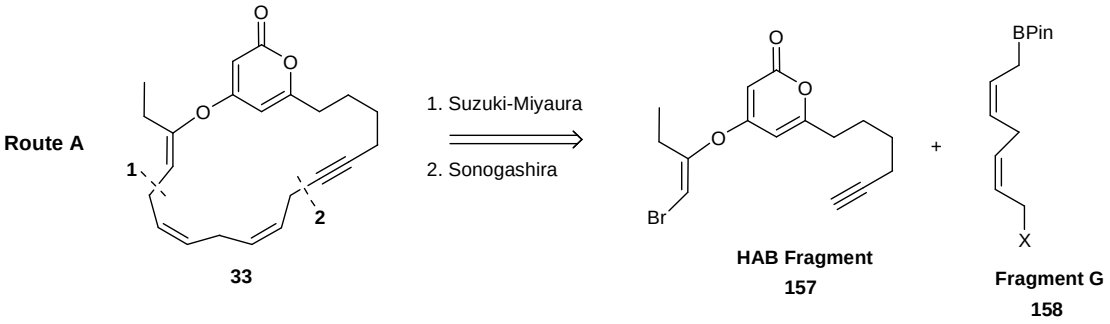
The ring-closing methodology developed so far is still at an early stage. Despite the successful macrocycle formation in the presence of a dicobalt protected alkyne, further work is necessary to assess the full capability of this reaction. The failure of the triene and doubly protected alkyne derivatives suggest that the desired macrocycle substrate can only accommodate the presence of one bulky dicobalt complex, and yet the additional alkene will require accessing at a later stage. A possible solution to this is the incorporation of a masked alkene which would allow macrocyclisation to occur and subsequent alkene formation to generate the natural product.



Scheme 2.71: Masked alkene strategy to promote RCM.

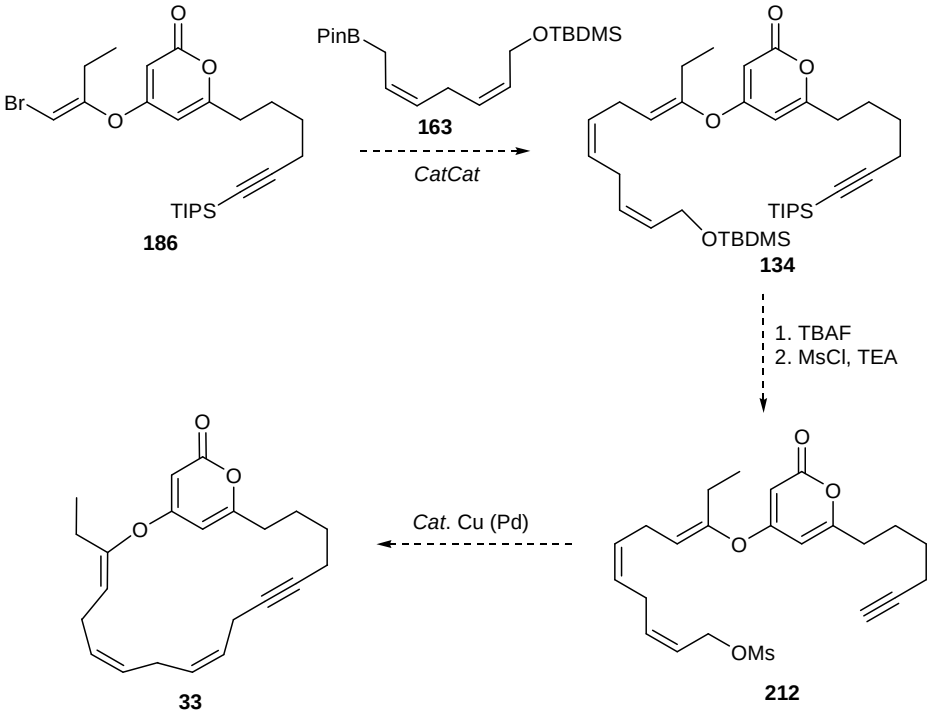
The formation of the desired *cis*-alkene as one of the final steps creates problems with selectivity. In **Scheme 2.71** it is suggested that a phenyl selenide would act as a suitable masked alkene, however the resulting elimination would generate two possible regioisomers, each with stereoisomers likely.

As a result of the poor selectivity these strategies suggest, the previously suggested route **A** would appear to be the more logical choice for selective ring-closing methodology.



Scheme 2.71: Sonogashira focused disconnections.

The formation of the macrocycle would now be reliant upon Sonogashira or copper mediated allylation reactions. The suitability of this macrocycle formation strategy will require ample testing, and the required fragment **G** will require synthesis. The proposed forward synthesis now requires the Suzuki coupling of **185** with **159**, removal of both silyl protecting groups and suitable functionalisation of the ensuing allyl alcohol, which would present an advanced intermediate suitable for macrocyclisation. The natural product would then be completed *via* the relevant alkynyl-allyl coupling reaction.

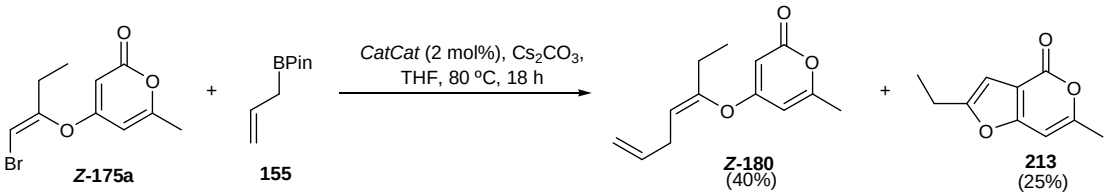


Scheme 2.72: Proposed forward synthesis of **33**.

3. Intramolecular C-H arylation of 2-Pyrones

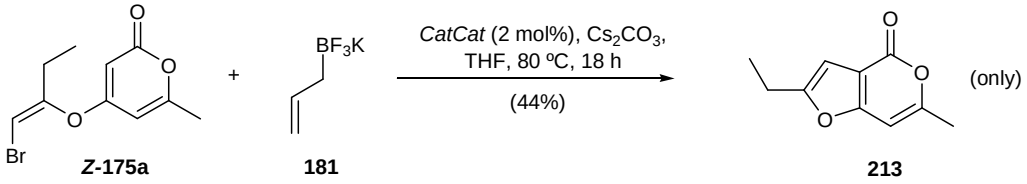
3.1 Reaction discovery and optimisation

In the course of the studies towards phacelocarpus-2-pyrone A an integral reaction in the desired route focused on a proposed Suzuki cross-coupling of allyl boronate **155** with vinyl bromide **175a**. In the course of reaction screening it was noted that the Suzuki cross-coupling of ***Z*-175a** led to the identification of a second reaction product, namely furopyrone **213** formed in 25% yield (**Scheme 3.1**).



Scheme 3.1: Intramolecular C-H functionalisation-initial discovery.

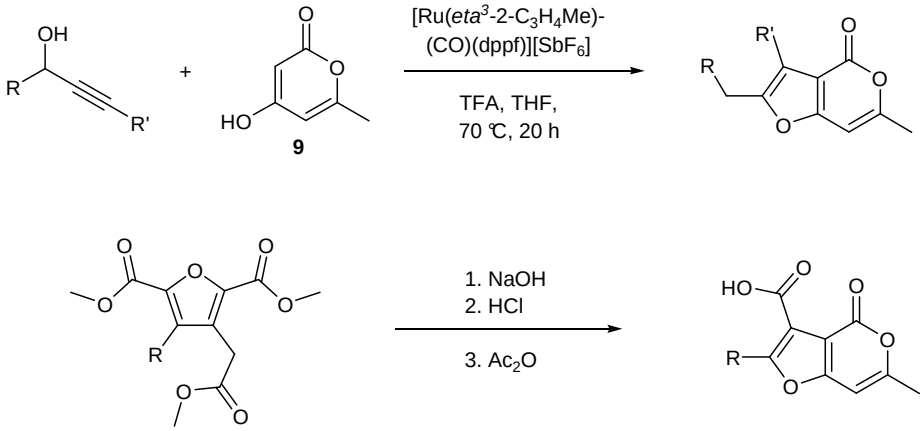
The low yield of **180** was attributed to the low stability and reactivity of the allyl pinacolborane **155**. Recent work by Molander and co-workers has shown that the more stable potassium trifluoroborate salts of boronic acids are adequate substitutes for boronic acids.[108] The Suzuki cross-coupling of ***Z*-175a** was subsequently attempted utilising potassium allyltrifluoroborate **181** as an alternative to allyl pinacol borane.



Scheme 3.2: Selective intramolecular C-H functionalisation of ***Z*-175a**.

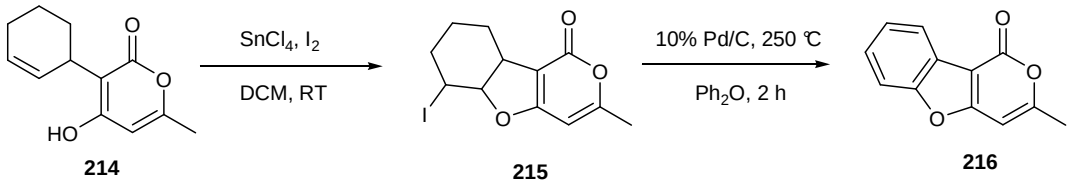
The use of **181** as an alternative source of allyl boronic acid resulted in a complete shut-down of the Suzuki reaction pathway giving an improved 44% yield of **213**. The reason for this is likely to be in part due to the absence of water. Molander and co-workers have recently shown that the presence of trace water is needed for the potassium trifluoroborate salts to be an effective boronic acid substitute.[116] The synthesis of **213** represents the first Pd-catalysed C-H functionalisation of a 2-pyrone.

The synthesis of furopyrones has been well documented, with two reported syntheses (**Scheme 3.3**) as good examples. The first was reported by Cadierno *et al.*,[117] which utilises the reaction of a propargylic alcohol with 4-hydroxy-6-methyl-2-pyrone (**9**) in the presence of a cationic ruthenium catalyst. The reaction utilises **9** in a propargylic substitution-cyclisation process. The second example, highlighted from the work of Cabarès *et al.*,[118] requires the prior formation of a tetra-substituted furan derivative and subsequent formation of the furopyrone. The reaction is limited by the accessibility of the substituted furans, however the direct product of the reaction provides a carboxylic acid as a useful handle for further manipulation.



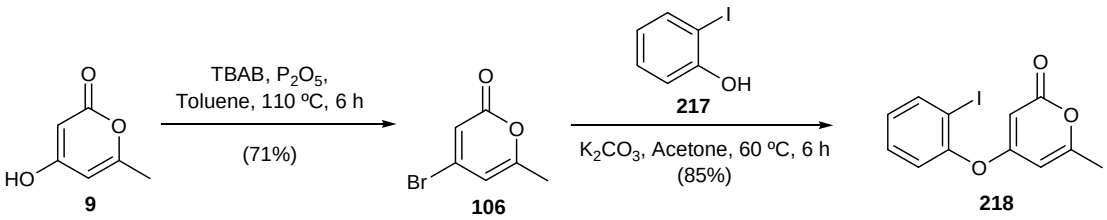
Scheme 3.3: Known synthetic routes to furopyrones.

The routes highlighted in **Scheme 3.3** are limited however, as they do not allow the incorporation of an additional fused ring into the system to create a benzofuropyrone. The synthesis of benzofuropyrones has received little attention, with only one reported pathway to date. Majumdar and co-workers have synthesised a variety of structures featuring a tricyclic system containing the benzofuran motif, including benzofuropyrone **216**. However, the reaction is limited as the final step requires very high temperatures (250 °C) to affect elimination and subsequent dehydrogenation to the benzene ring (**Scheme 3.4**).[119]



Scheme 3.4: Majumdar's synthesis of **216**.

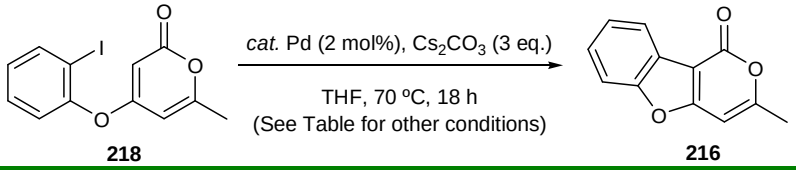
In order to further develop the unique transformation observed in **Scheme 3.2**, a model aromatic analogue was synthesised in two steps from 4-hydroxy-6-methyl-2-pyrone **9** (**Scheme 3.5**).



Scheme 3.5: Synthesis of **216**.

The cyclisation of **218** was screened with a variety of Pd sources, bases and additives to optimise the formation of cyclised product **216**. The results of the optimisation of the intramolecular cyclisation are shown in **Table 3.1**.

Table 3.1: Optimisation of cyclisation conditions.



Entry	Catalyst	Additive	Yield (%)
1	CatCat	**155** (2 eq.)	49*
2	CatCat	**181** (1 eq.)	57
3	CatCat	**181** (0.1 eq.)	69
4	CatCat	$AgBF_4$ (1 eq.)	6†
5	CatCat	PivOH (0.3 eq.)	41
6	$Pd(OAc)_2$	PivOH (0.3 eq.)	31
7	$Pd_2(dba)_3$	PPh_3 (4 mol%)	74
8	**Pd_2(dba-4,4′-OMe)$_3$**	**PPh_3 (4 mol%)**	**79**
9	Pd_2(dba-4,4′-OMe)$_3$	PPh_3 (4 mol%)	77‡
10	Pd_2(dba-4,4′-OMe)$_3$	PPh_3 (4 mol%)/ PivOH (0.3 eq.)	45

*A 42% yield of the Suzuki product is also observed.

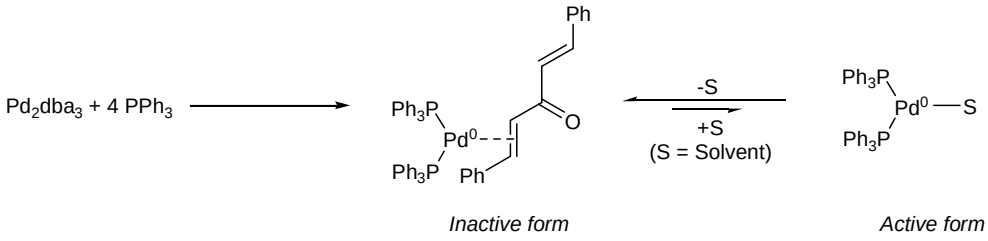
† Reaction left for 72 h in the dark.

‡ Using K_3PO_4 instead of Cs_2CO_3.

Initial studies with *CatCat* and the two allyl boronate reagents correlate well with the original observations detailed in S**cheme 3.2** where more stable boronates resulted in a higher yield for the intramolecular cyclisation (**entries 1** and **2**) under anhydrous conditions. It was suggested that the boronate could be acting in one of two ways. Firstly, it could act as a reducing agent for the palladium(II) precatalyst generating the active palladium(0) species, or alternatively, the boronate could be influencing the reaction in another capacity.

Catalytic quantities of **181** proved to further increase the yield of **216**, whereas utilising $AgBF_4$ as a boron alternative limited the reaction, indicating that **181** is acting as a reductant (**entries 3** and **4**). Recent work by Fagnou and co-workers has shown that a combination of $Pd(OAc)_2$, pivalic acid and caesium carbonate proves to be an efficient catalytic system for C-H functionalisation of various heteroaromatic systems,[120] however the inclusion of pivalic acid with either *CatCat* or $Pd(OAc)_2$ proved ineffective for the synthesis of **216** (**entries 5** and **6**).

The results so far point to the formation of $Pd^0(PPh_3)_2$ which is sufficiently active to perform the cyclisation. A common route to access $Pd^0(PPh_3)_2$ is through the reaction of Pd_2dba_3 with PPh_3 (Ratio $Pd:PPh_3$ = 1:2). The application of this methodology towards **216** proves to be effective, with an improved 74% yield obtained (**entries 7**). Work by Jutand and co-workers has shown that the presence of dba in the reaction has a profound effect on the formation of the active catalyst, with the dba forming a dynamic equilibrium between active catalyst and a stabilised form whereby the alkene from dba binds η^2 to the palladium(0) centre.[121] This interaction limits the amount of active catalyst found within the reaction, while also stabilising the highly reactive catalyst to prevent rapid catalyst degradation.



Scheme 3.6: dba stabilisation of palladium (0).

Work by Fairlamb and co-workers has shown that by influencing the electronic nature of the dba alkene, through functionalisation of the aryl group, it is possible to alter the equilibrium and therefore affect the quantity of active catalyst formed in the

reaction.[122,123] The most useful catalyst from this work, Pd_2(dba-4,4′-MeO)$_3$, proved to be effective in the intramolecular cyclisation of **218** yielding an improved 79% of **216** (**entry 8**), conditions which will be utilised in all further reactions to assess the substrate scope.

The intramolecular cyclisation reactions can functionalise two positions of the 2-pyrone, with C-3 and C-5 being equidistant from the aryl iodide and both being available for attack. The ^{1}H-NMR spectroscopic data suggests that the reaction occurs exclusively at the C-3 position, with an observable $^4J_{HH}$ coupling observed between protons at C-5 and C-7. Conclusive proof of this assignment was obtained through a single crystal X-ray diffraction study of **216** (**Fig. 3.1**).

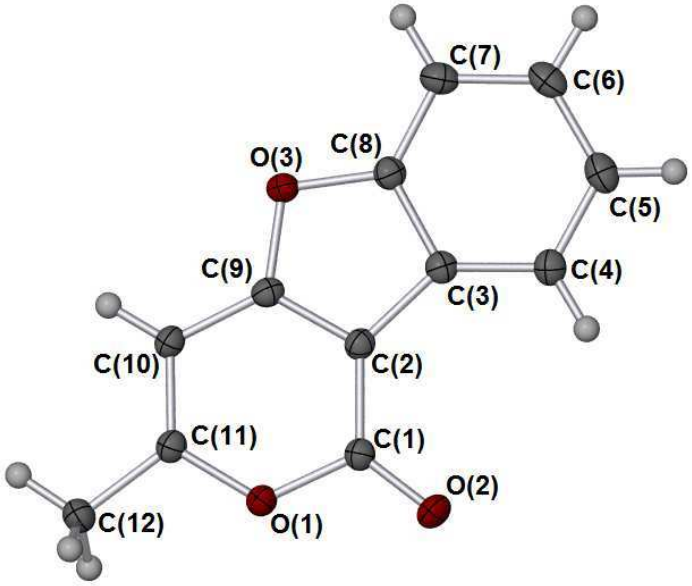
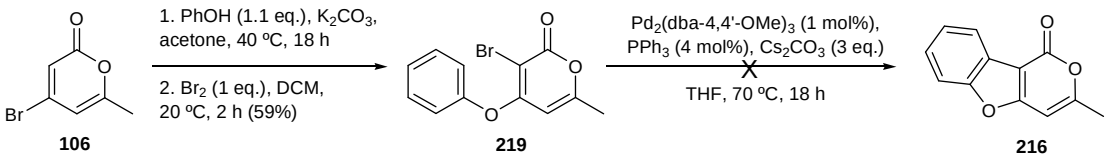


Figure 3.1: Crystal structure of **216** (Arbitrary numbering used). Selected bond lengths (Å): C(2)-C(3) 1.443, C(2)-C(9) 1.374, C(3)-C(8) 1.398. Selected bond angles: C(1)-C(2)-C(3) 133.18, C(2)-C(3)-C(4) 136.20, C(1)-C(2)-C(9) 120.00, C(2)-C(9)-O(3) 111.95.

The intramolecular reaction utilises an aryl halide and reacts at the C-3 position of the 2-pyrone, however it is also conceivable that the reaction may utilise a 4-halo-2-pyrone and react with an aryl C-H to generate the same product.

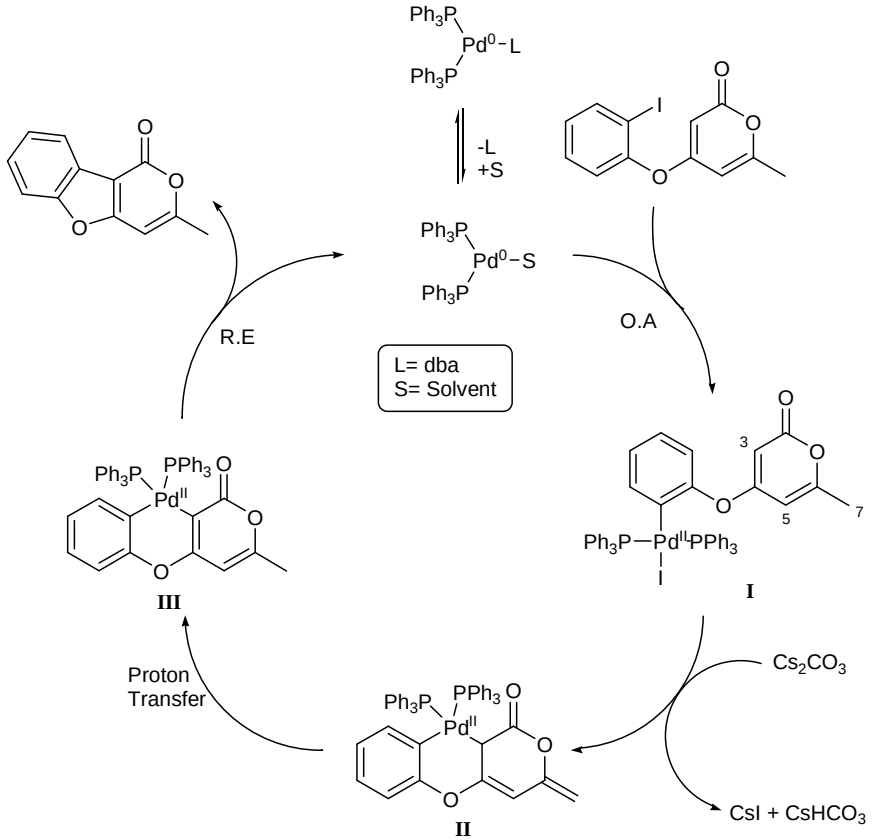


Scheme 3.7: Alternative intramolecular cyclisation.

The intramolecular reaction with **219** fails to generate any of the desired cyclisation product **216**, with starting material degradation the only notable pathway (**Scheme 3.7**). The reaction pathway is therefore highly dependant upon the inherent activity of the 2-pyrone.

3.2 Reaction scope

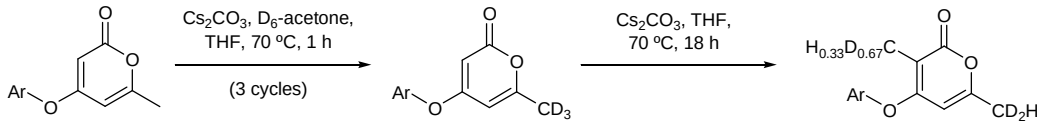
Previous work with 6-alkyl-2-pyrones (Chapter 2) has shown that the protons at C-7 are commonly the most acidic. The presence of base in the reaction media therefore point towards deprotonation at C-7 playing a crucial role in the reaction mechanism, from which a suitable mechanistic pathway can be proposed (**Scheme 3.8**).



Scheme 3.8: Preliminary proposed catalytic cycle.

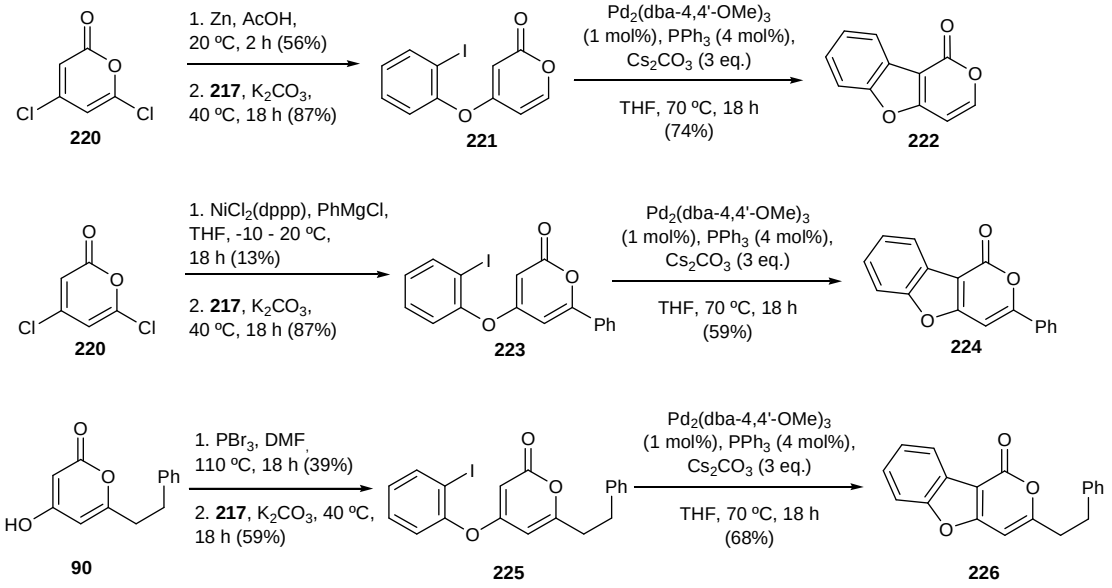
The proposed mechanism (S**cheme 3.8**) is dependant upon proton transfer between C-7 and C-3 under the reaction conditions. To test the suspected acidity of C-7 and the ensuing proton transfer required for the proposed mechanism, the starting material **218** was subjected to basic conditions in the presence of a deuterium transfer agent (acetone-d_6). ^{1}H

NMR spectroscopic analysis of the resulting product showed total incorporation of deuterium at the C-7 position. Upon treatment of the deuterated starting material **218** with Cs_2CO_3 in anhydrous THF, it was noted that the deuterium equilibrates between C-3 and C-7, thereby confirming that proton transfer is possible under the reaction conditions (**Scheme 3.9**). The reaction also confirms the requirement of a palladium catalyst for cyclisation to occur. The outcome is also consistent with Dr. L. R. Marrison in his PhD studies on the Sonogashira cross-couplings of 3-bromo-4-alkoxy-6-methyl-2-pyrones.[124]



Scheme 3.9: Deuterium transfer study of **218**.

The proposed mechanism (**Scheme 3.8**) also suggests that in the absence of any acidic protons at C-7 then the reaction would either cease entirely or require higher temperatures to attain comparable yields. In order to test the importance of the C-7 protons, a number of C-6 functionalised analogues were synthesised (**Scheme 3.10**). Firstly, a proto-C-6 derivative (**221**) was synthesised through a C-6 selective zinc reduction of **220**, followed by a conjugated nucleophilic displacement with **217** to afford **221** in 49% over the two steps. The second analogue, phenyl-C-6 derivative **223**, was synthesised through a low temperature Kumada coupling of **220** with PhMgCl, followed by a conjugated nucleophilic displacement with **217** to afford **223** in 11% over the two steps. The final analogue was synthesised *via* bromination of **90** and a conjugated nucleophilic displacement of the resulting bromide with **215** to afford **225** in 23% over the two steps.



Scheme 3.10: Synthesis and cyclisation of **221**, **223** and **225**.

Subjecting the parent system **221** to the intramolecular cyclisations yielded **222** in a 74% yield, with regioselectively confirmed through a single crystal X-ray diffraction study (**Fig. 3.2**). The subsequent cyclisations of **223** and **225** proved to be very efficient yielding **224** and **226** in yields of 59% and 68%, respectively. These findings suggest that although the presence of the acidic C-7 proton may be affecting the mechanistic pathway, the reaction is not entirely dependant upon their presence. The reaction mechanism will be further discussed later in this chapter.

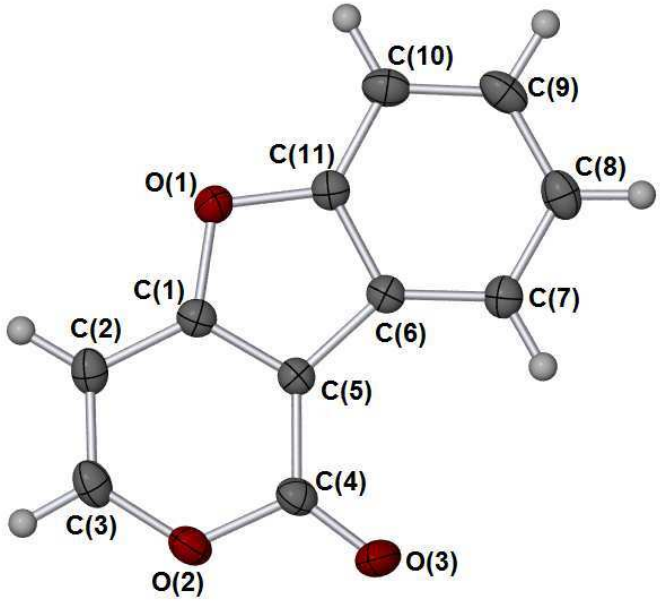
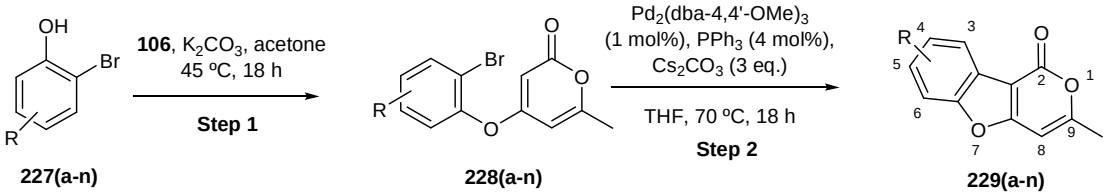


Figure 3.2: X-ray structure of **222** (Arbitrary numbering used). Selected bond lengths (Å): C(5)-C(6) 1.441, C(5)-C(1) 1.371, C(6)-C(11) 1.398. Selected bond angles: C(4)-C(5)-C(6) 132.45, C(4)-C(5)-C(1) 120.67, C(5)-C(6)-C(7) 135.78, C(5)-C(1)-O(1) 111.94.

Following the optimisation of relatively mild conditions for the cyclisation, and subsequent testing of various C-6 substituted analogues, the influence of the aromatic component was explored. This was tested through the synthesis and subsequent cyclisation of various analogues derived from 2-bromo-phenols. The results are collected in Table 4.2.

The reaction appears to be sensitive to the nature of the electronic effects of the aromatic substituents. Steric effects appear less important, as good yields are observed with substituents present in the 6-position (**entries 2**, **4** and **8**). The most important contribution to the reaction yield appears to be the stability of the starting material under the reaction conditions. In most examples, the yields after 18 hours appear to be limited by how rapidly 2-pyrone degradation has occurred, as no additional starting material or products are observed.

Table 3.2: Intramolecular cyclisations



227(a-n) 228(a-n) 229(a-n)

Entry	R	Yield Step 1 (%) (228 a-n)	Yield Step 2 (%) (229 a-n)
1	4-Me (a)	96	72
2	4,6-$(Me)_2$ (b)	37	79
3	4-*t*-Bu (c)	66	71
4	4,6-(*t*-$Bu)_2$ (d)	28[*]	71
5	4-Ph (e)	90	44 (56)[†]
6	4-OMe (f)	90	65 (93)[†]
7	5-OMe (g)	53	67
8	5,6-$(OMe)_2$ (h)	17	32
9	4-O($C_6H_5O_2$) (i)	49	16
10	4-F (j)	87	30
11	5-F (k)	88	24 (31)[†]
12	4-Cl (ℓ)	97	28
13	4-Br (m)	71	0
14	4-CF_3 (n)	90	11

[*] Reaction conditions: **106**, NaH, THF, 70 °C, 18 h.

[†] Numbers in brackets refer to the calculated yield based on recovered starting material following flash column chromatography.

It would be expected that with the methoxy functionality *para* to the bromide, as in **228g** (**entry 7**), reactivity would be enhanced, however the yield is limited due to the degradation of the starting material, whereas with the methoxy *meta* to the bromide we observe a comparable yield except with unreacted **228f** also recovered (**entry 6**). In this instance, the degradation is much slower and the yield is more reliant upon the receptivity of the substrate to cyclisation. The reaction appears to be unreceptive towards the presence of additional aryl halide functionality, with limited reactivity for fluoride adducts **228j** and **228k** (**entries 10** and **11**), chloride adduct **228ℓ** (**entry 12**) and no reactivity for the

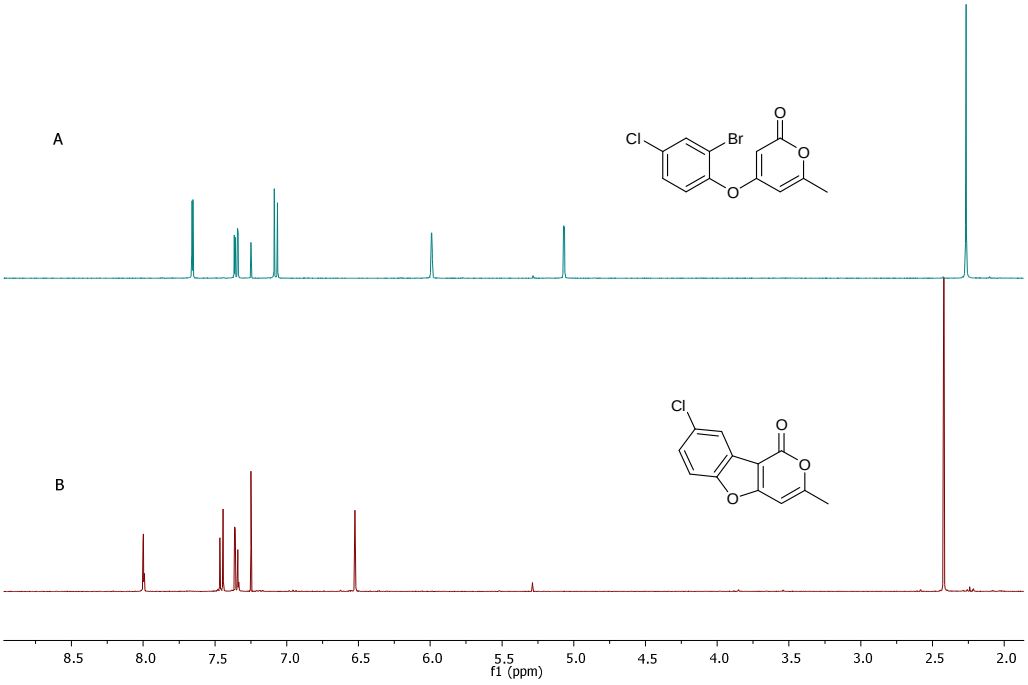
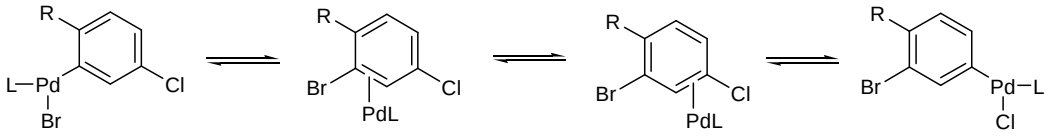


Figure 3.3: Representative example to show the ^{1}H-NMR (400 MHz, $CDCl_3$) spectral changes observed from starting material to product (**228**ℓ→**229**ℓ)

bromine adduct **228m** (**entry 13**). The low reactivity of the bromide can be attributed to competitive oxidative addition between the two aryl bromide bonds. The intramolecular arylation appears to be a slow reaction, therefore in the presence of a second bromide the palladium is likely to be moving between positions and unable to cyclise as a result. The poor reactivity of the fluoride/chloride adducts **228j, 228k** and **228ℓ** is a little more surprising. It is well established that the oxidative addition of palladium into aryl chlorides/fluorides requires phosphines which are more electron rich than triphenylphosphine, so competitive oxidative addition should not be affecting the reactivity. However, it is possible that in the presence of multiple C-X bonds, the palladium is able to migrate around the system once oxidative addition has occurred at the most active C-X bond. [125,126]



Scheme 3.11: Possible migration of Pd into C-Cl bond.

Throughout the series of benzofuropyrones synthesised, there are notable changes in the NMR spectroscopic data, allowing for accurate identification of the products. The most important changes are those in the 2-pyrone C-H signals. The ^{1}H-NMR spectra of the starting materials consistently show the C-3 and C-5 2-pyrone C-H signals at δ~5.1 and δ~6.0 respectively. Following arylation, the 2-pyrone C-5 signal is shifted significantly to δ~6.5, indicating the 2-pyrone motif is now significantly more aromatic (**Fig. 3.3**). The regioselectivity is subsequently determined through the presence of a $^{4}J_{HH}$ coupling between the CH_3 and the C-5 protons from the 2-pyrone.

Additionally, the IR spectroscopic data shows a 2-pyrone C=O stretching frequency at ~1700 cm^{-1} for the starting materials, whereas the cyclised products routinely show a shift of ~20 cm^{-1} to higher wavenumbers. The change in frequency to a higher wavenumber is consistent for systems with increased conjugation.[127]

Further X-ray diffraction studies have confirmed the regioselectivity for compounds **229j** and **229k** (**Fig. 3.4**).

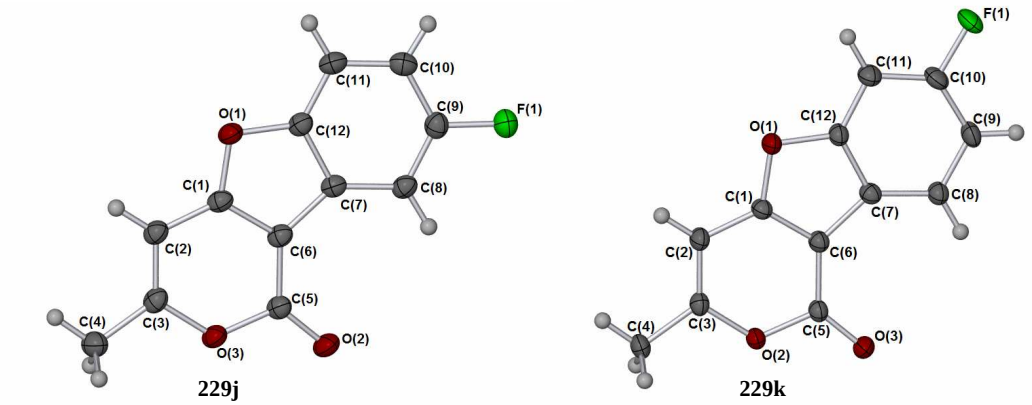
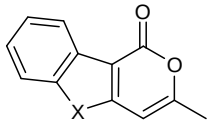


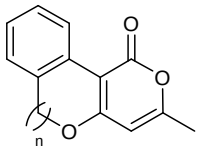
Figure 3.4: X-ray structures of **229j** and **229k** (Arbitrary numbering used). Selected bond lengths **229j** (Å): C(6)-C(7) 1.440, C(6)-C(1) 1.379, C(7)-C(12) 1.401. Selected bond angles **229j**: C(5)-C(6)-C(7) 133.35°, C(5)-C(6)-C(1) 119.94°, C(6)-C(7)-C(8) 136.17°, C(6)-C(1)-O(1) 112.02°. Selected bond lengths **229k** (Å): C(6)-C(7) 1.446, C(6)-C(1) 1.367, C(7)-C(12) 1.396. Selected bond angles **229k**: C(5)-C(6)-C(7) 133.34°, C(5)-C(6)-C(1) 119.98°, C(6)-C(7)-C(8) 136.20°, C(6)-C(1)-O(1) 112.14°.

Thus far, the importance of the 2-pyrone and aryl moieties has been tested. The final area of importance is the link between the aryl group and the 2-pyrone, whereby all reactions so far have generated a furan ring. It is conceivable that the same reaction methodology could be utilised to generate other 6:5:6 ring systems (*e.g.* benzothiophenylpyrones) or alternatively generate different sized ring systems (*e.g.* 6:6:6).



X = S, N-R, C

6:5:6 ring systems

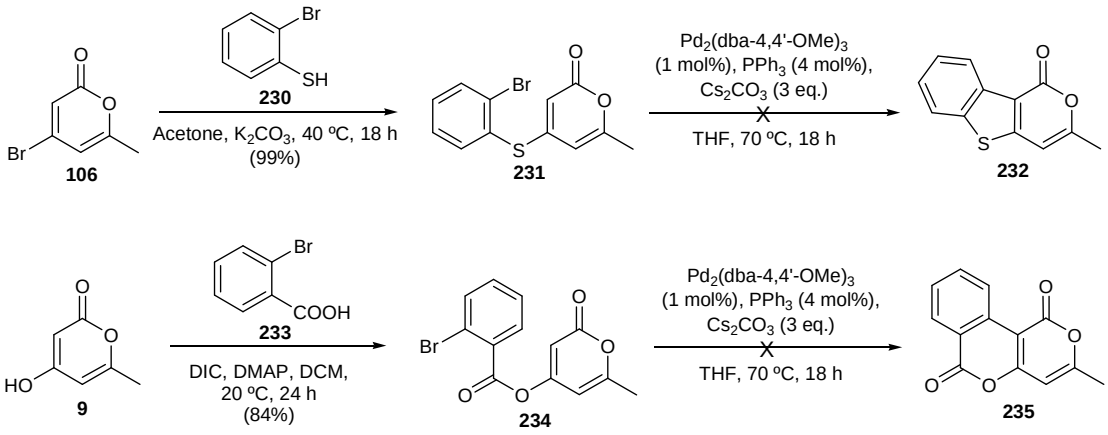


6:(5+n):6 ring systems

Figure 3.5: Alternative ring systems.

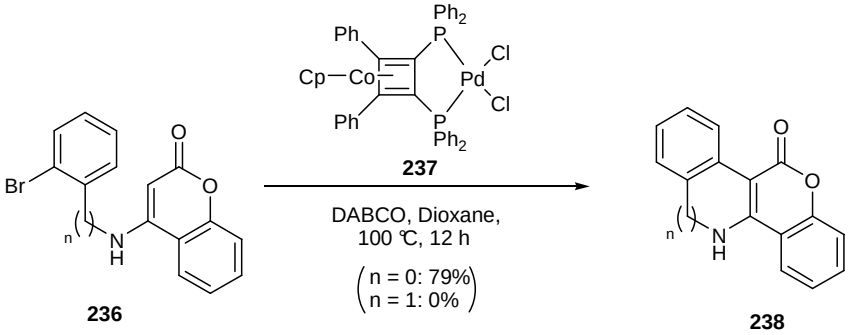
In order to probe the importance of the central ring, two suitable substrates were prepared.

The reaction of the thiophene derivative **231** failed to deliver any of the cyclisation product **232**. The cause of this is potentially due to ligand effects from the sulphur. It is possible that following oxidative addition the sulphur coordinates to palladium in any subsequent steps, thereby shutting down the catalytic cycle. This effect has not been investigated further.



Scheme 3.11: Synthesis of alternative ring systems.

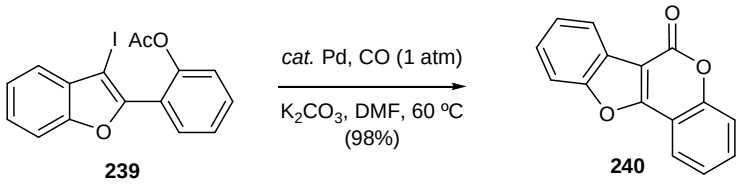
The synthesis of ester **234** was chosen as a cyclisation precursor due to the absence of any saturated positions, allowing a close mimic of the original system regarding a fully conjugated ring system. However, upon treatment with the cyclisation conditions no product was observed with complete degradation of the starting material occurring. The failure to form a 6:6:6 ring system mirrors the findings by Chang *et al.* whereby the formation of a coumarin derived 6:5:6:6 occurred in good yield when utilising their rather complex Pd precatalyst, whereas no product was observed when trying to form the 6:6:6:6 system.[128] Whilst the reactions performed by Chang *et al.* conform with the observations seen here; the authors offer no insight into the reasons they screened the reaction with the complex precatalyst **237** or the reason for the failure of the 6:6:6 system. The reaction was described as an intramolecular Heck reaction, although no proposed mechanism was put forward and no other reactions were performed.



Scheme 3.12: Chang's 'intramolecular Heck' reaction.

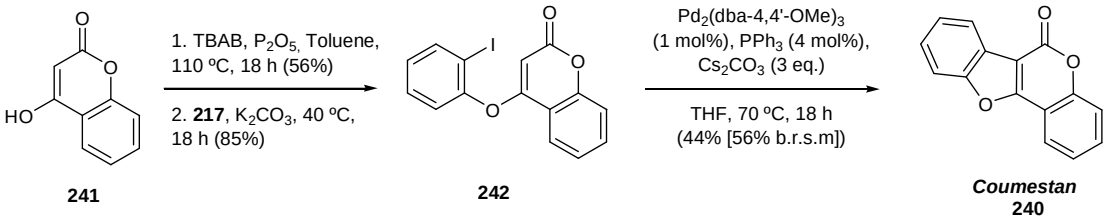
The intramolecular cyclisation reaction methodology was subsequently applied to the synthesis of the natural product coumestan.[129] The synthesis of coumestan has been

achieved on many occasions, most notably the rapid synthesis by Larock and co-workers, utilising a Pd-catalysed carbonylation to install the '2-pyrone' motif (**Scheme 3.13**).[130]



Scheme 3.13: Larock's synthesis of coumestan.

The application of the intramolecular cyclisation to the synthesis of coumestan allowed rapid access to the natural product from the commercially available 4-hydroxy coumarin (**241**). Bromination of the coumarin followed by a conjugated nucleophilic displacement reaction with 2-iodophenol (**217**) gave access to the cyclisation precursor **242**. Subsequent cyclisation of **242** gave rise to a respectable 44% yield of coumestan (**240**), with an overall unoptimised yield of 21% over three steps (**Scheme 3.14**). The three step synthesis of coumestan compares unfavourably with Larock's synthesis which accessed the natural product with an overall yield of 90% from three linear steps. However, cost analysis of the key reagents used by the two routes indicates a much more favourable outcome for the intramolecular arylation with a cost of ~£4/g compared to Larock's synthesis which costs ~£18/g.[131]



Scheme 3.14: Synthesis of coumestan (**240**).

3.3 Stoichiometric studies

To gain further insight into the reaction mechanism, a series of stoichiometric studies were performed.

The complex $[Pd^0(PPh_3)_2(\eta^2\text{-dba-4,4′-OMe})]$ is presumed to be the initial Pd^0 species formed in the reaction. Preparation and characterisation of this intermediate was performed *in situ* by the reaction of $Pd_2(\text{dba-4,4′-OMe})_3$ and PPh_3 (ratio Pd:P = 1:2) in D_8-

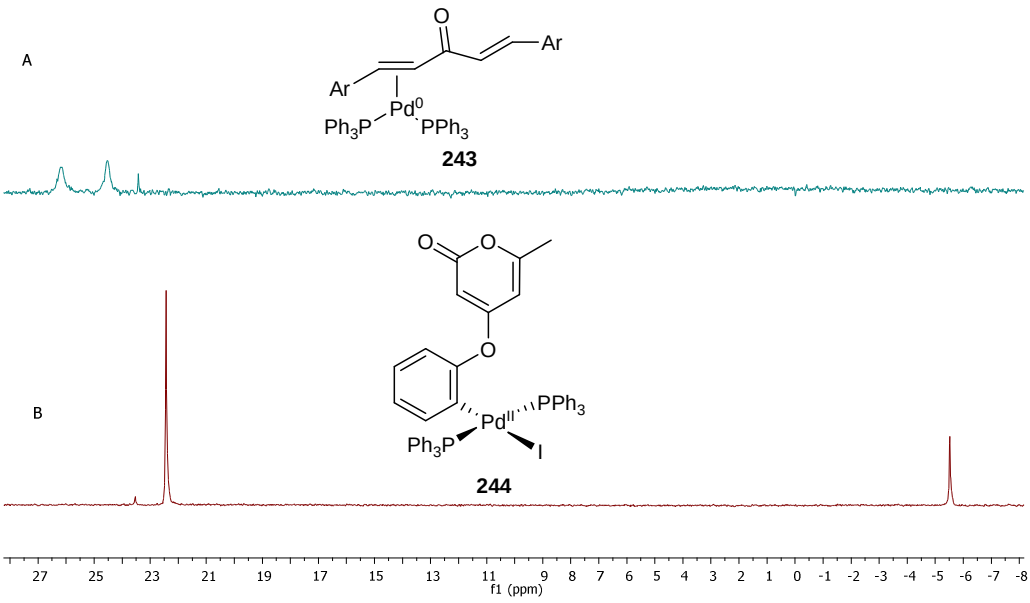
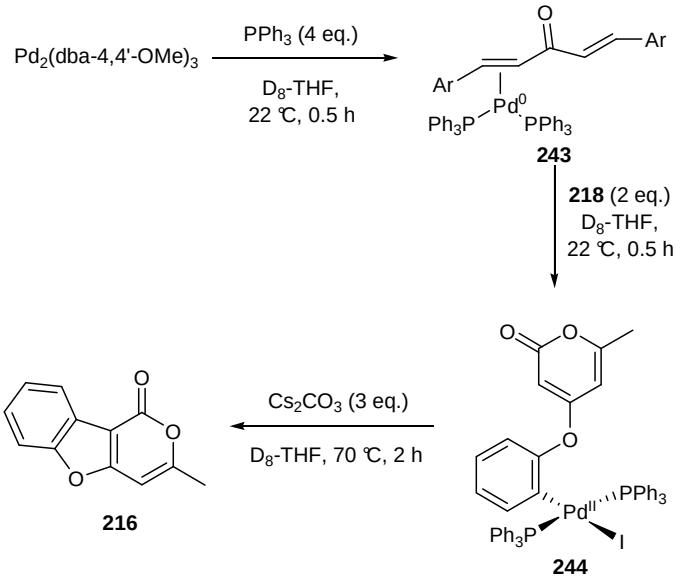


Figure 3.6: ^{31}P-NMR (700 MHz, THF-d_8) spectra of **243** and **244**.

(Spectra shown at approx. same intensity)

THF (**Scheme 3.15**). Addition of 2 equivalents of aryl iodide **218** resulted in quantitative conversion to the oxidative addition product **244** when monitored by ^{1}H NMR. Treatment of the oxidative addition product with Cs_2CO_3 at 70 °C for 2 hours results in quantitative conversion to the cyclised product **216**.



Scheme 3.15: NMR scale synthesis of **216**.

The 283 MHz ^{31}P-NMR spectrum of **243** (**Fig. 3.6-A**) shows two broad signals at δ 24.5 and 26.2 ($\Delta\nu_{1/2}$ = 60 Hz) corresponding to exchanging phosphines, as observed by Jutand and Fairlamb, and an additional peak at δ 23.4 corresponding to a small quantity of $(O)PPh_3$.[61] Following the addition of aryl iodide **218** the 283 Mhz ^{31}P-NMR spectrum exhibits a sharp singlet at δ 22.4 indicitive of a *trans*-Pd^{II} complex (**Fig. 3.6-B**). Additional peaks are seen at δ 23.4 and -5.5 corresponding to $(O)PPh_3$ and free PPh_3, respectively.

The presence of (dba-4,4′-OMe) and PPh_3 in stoichiometric quantities serves to complicate the aromatic region of the ^{1}H-NMR spectrum. However, Pd^{II} complexes are known to be air stable, and as such the oxidative addition product was isolated as both the proto- and deuteron- PPh_3 adducts (**Scheme 3.16**).

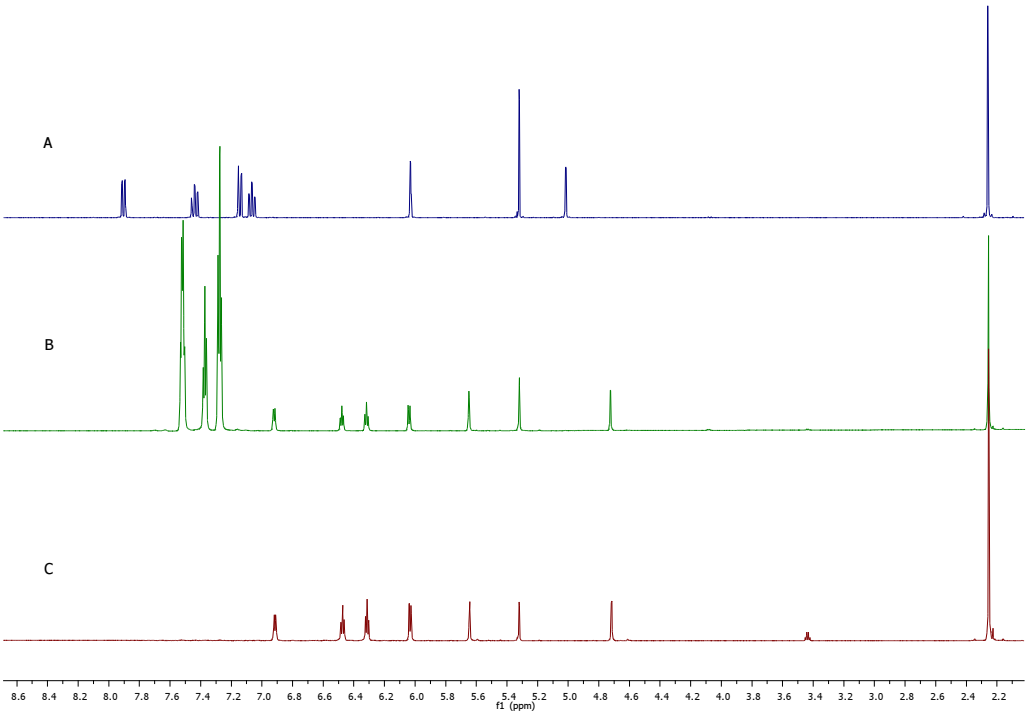
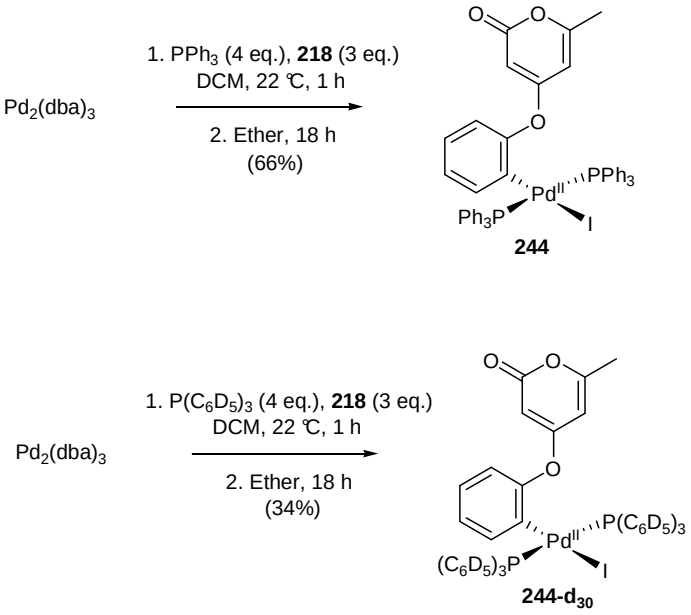


Figure 3.7: ^{1}H-NMR (700 MHz, DCM-d_2) of (a) **216**, (b) **244** and (c) **244-d_{30}**.



Scheme 3.16: Preparative synthesis of **244** and **244-d_{30}**.

The ^{1}H-NMR spectrum of the intermediate shows a substantial shift of the aromatic signals, however ^{1}H-^{1}H COSY and ^{1}H-^{31}P HMQC were able to confirm the signals associated with the 2-pyrone as those at δ 4.72 and 5.65 (**Fig 3.7**).

Crystals of **244** (obtained from DCM/Ether) were analysed by single crystal X-ray diffraction. The X-ray diffraction data confirms the structure of **244** (**Fig. 3.8**), with a distorted square planar geometry observed at the palladium centre. The key angles between P-Pd-P and C-Pd-I are observed to be 169.0° and 169.2° respectively. The distorted geometry relieves any steric interference between the bulky phosphino and aryl components. The distortion of bulky [Pd^{II}(I)R(PPh_3)$_2$] complexes has been previously reported, but note in **244** are the near identical angles observed which is unique.[132, 133, 134]

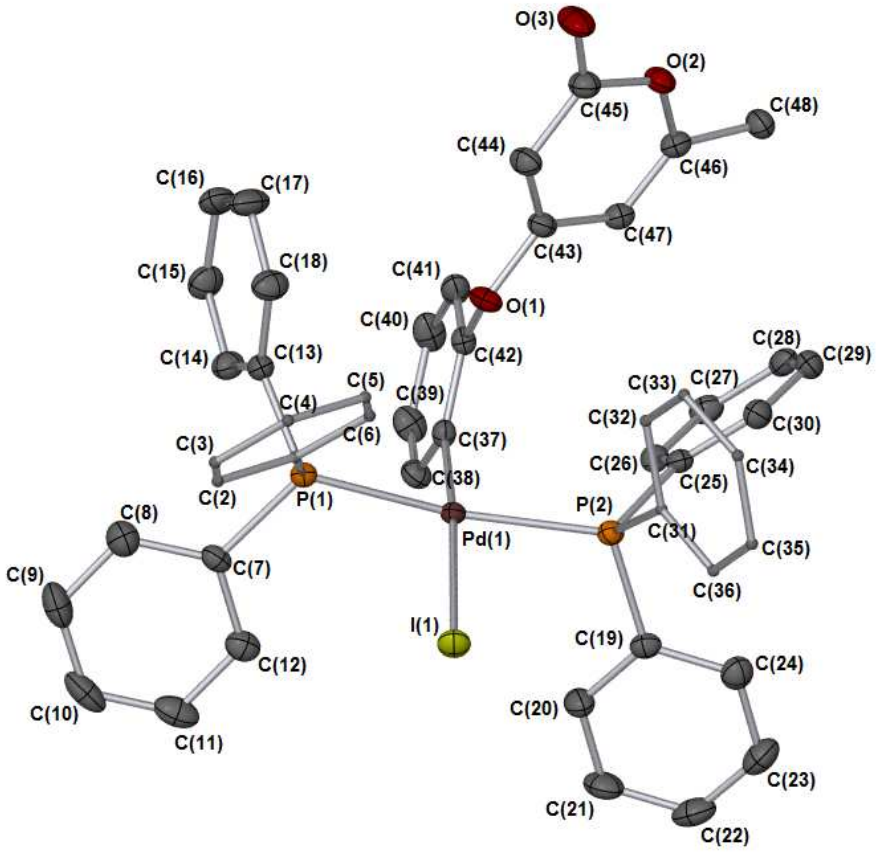
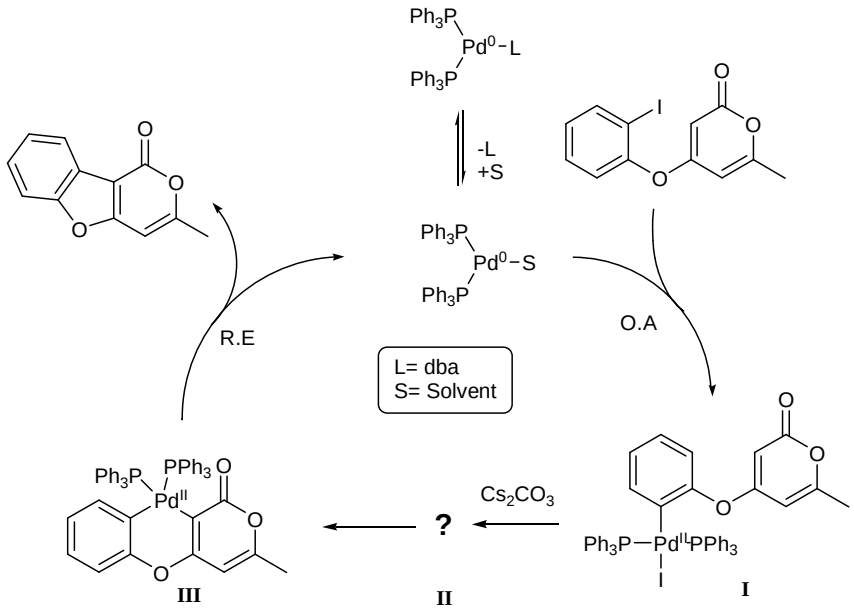


Figure 3.8: X-ray structure of **244** (Arbitrary numbering used). Selected bond lengths (Å): C(37)-Pd(1) 2.014, I(1)-Pd(1) 2.664, P(1)-Pd(1) 2.316, P(2)-Pd(1) 2.326. Selected bond angles: C(37)-Pd(1)-I(1) 169.21°, P(1)-Pd(1)-P(2) 169.03°.

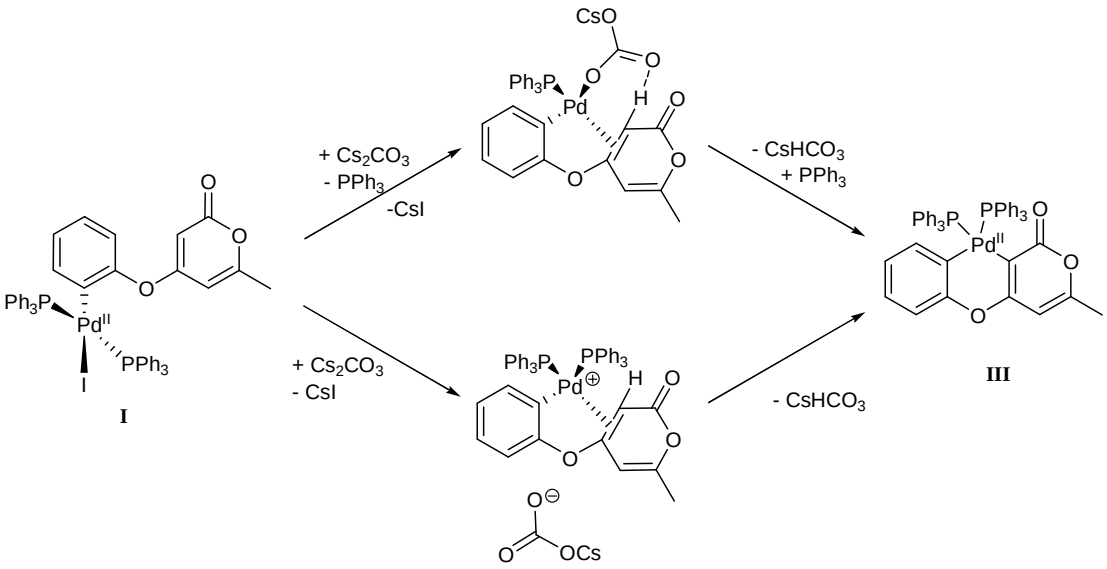


Scheme 3.17: Known intermediates in the catalytic cycle.

The initial step in the catalytic cycle has been shown to be the oxidative addition into the aryl iodide bond to give **244**. It can also be assumed that the final structure required for the catalytic cycle is the palladacycle **III** (**Scheme 3.17**) which can reductively eliminate to give the desired product **216** and regenerate the active Pd^0 catalyst. The intermediate steps (**II**) between these two crucial stages are however more difficult to envisage.

It is known that 2-pyrones are capable of binding to metal centres and conceivably could coordinate to the Pd^{II} through the alkene adjacent to C-3 of the 2-pyrone in a similar manner to dba, thereby activating the C-H bond.[135] Assuming this interaction, there are two possible routes through to **III** which can be taken. The first approach involves a neutral palladium centre which loses phosphine and co-ordinates the 2-pyrone, in conjunction with transmetallation of the iodide for the carbonate. The ensuing intermediate then rapidly undergoes an intramolecular concerted metallation deprotonation (CMD), akin to the mechanisms reported independently by Fagnou and Echavarren (**Scheme 3.18**).[120, 136]

Alternatively the mechanism could involve a cationic Pd^{II} intermediate, whereby loss of CsI generates the palladium cation stabilised by the carbonate anion. Subsequent intermolecular deprotonation of the activated C3-H by the carbonate would lead to the reductive elimination precursor **III**.



Scheme 3.18: Potential reaction pathways.

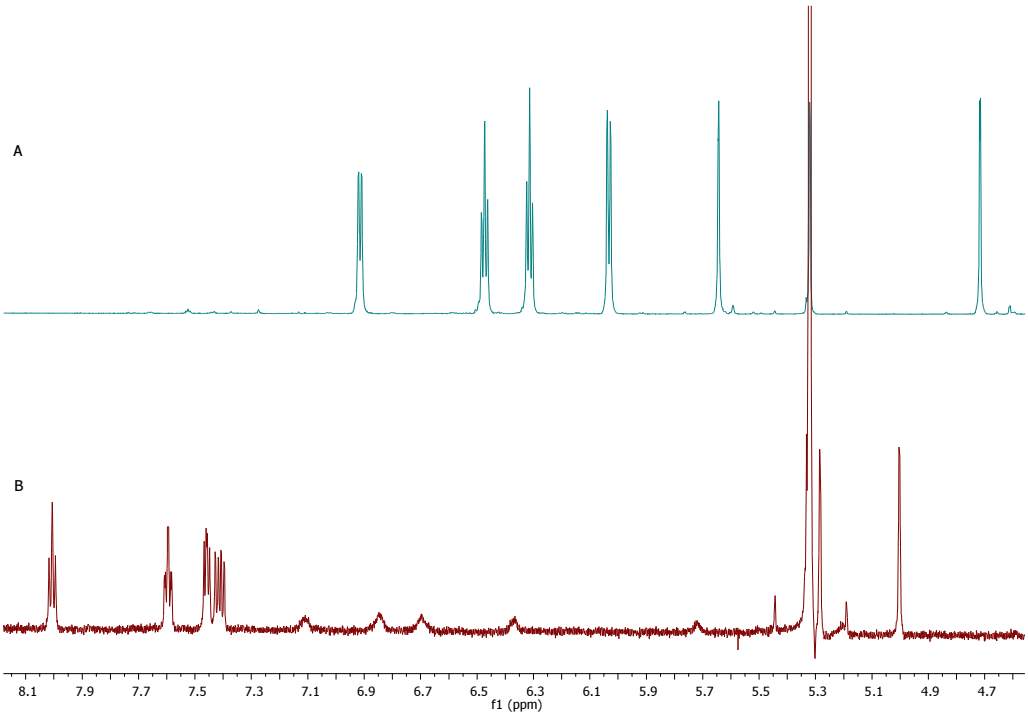
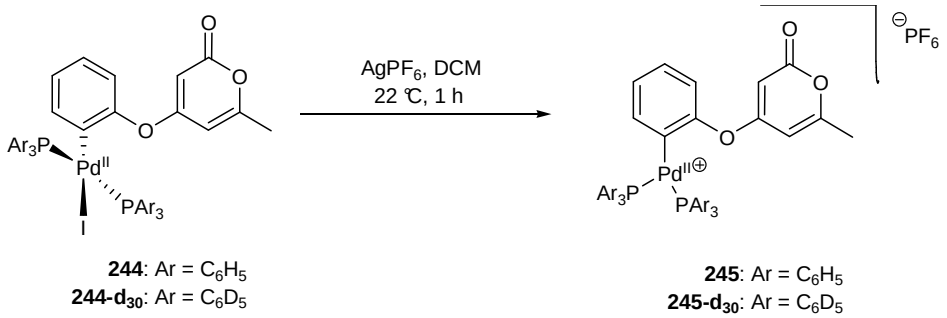


Figure 3.9: ^{1}H-NMR (700 MHz, DCM-d_2) of (a) **244-d_{30}** and (b) **248**.

To try and elucidate the reactive pathway, **244** and **244-d$_{30}$** were treated with a silver salt ($AgPF_6$) containing a non-coordinating anion. Subsequent removal of the silver iodide by filtration generated the palladium cations **245** and **245-d$_{30}$** (**Scheme 3.19**).



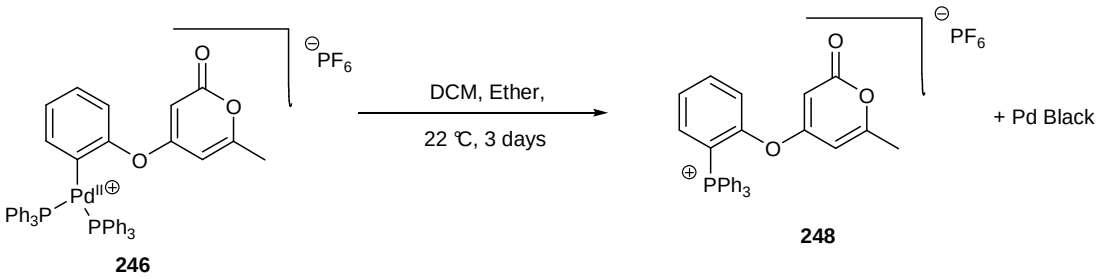
244: Ar = C_6H_5
244-d$_{30}$: Ar = C_6D_5

245: Ar = C_6H_5
245-d$_{30}$: Ar = C_6D_5

Scheme 3.19: Synthesis of cationic Pd^{II} complexes **245** and **245-d$_{30}$**.

The ^{1}H-NMR spectrum of **245-d$_{30}$** shows a significant change in the chemical shifts of the 2-pyrone signals from δ 4.72 (C-3) and 5.65 (C-5) in **244-d$_{30}$** to δ 4.41 (C-3) and 4.73 (C-5) in the cationic complex **245-d$_{30}$** (**Fig. 3.9**). However, further spectroscopic techniques, including ^{13}C, ^{1}H-^{31}P HMQC and ^{1}H-^{13}C HMQC, failed to show any significant evidence for the formation of 2-pyrone-Pd interactions (C=C or C-H agostic or anagostic[137]).

The reaction was subsequently tested utilising Ag_2CO_3 in the reaction to generate the cation in the presence of the carbonate base, however monitoring the reaction *via* ^{1}H-NMR spectroscopy showed no reactivity. The lack of reactivity under these conditions suggests that the mechanism does not follow a cationic pathway, an observation which was subsequently supported by the crystallisation of the PF_6^- derived intermediate **245**. Upon layering the NMR sample (in DCM-d_2) of **245** with ether, the formation of white crystalline needles were observed following 24 hours in the dark. Single crystal X-ray diffraction studies revealed that the cationic species formed has undergone a Pd to P transfer to generate **246** (**Scheme 3.20/ Fig. 3.10**). Whilst this type of transformation has been reported,[138,139] the formation of **246** under such mild conditions indicates that under the intramolecular arylation conditions, which require elevated temperatures to occur, this pathway will be kinetically and thermodynamically preferred to the cyclisation and thus the pathway is unlikely to involve cationic palladium(II) intermediates.



Scheme 2.20: Synthesis of **248**.

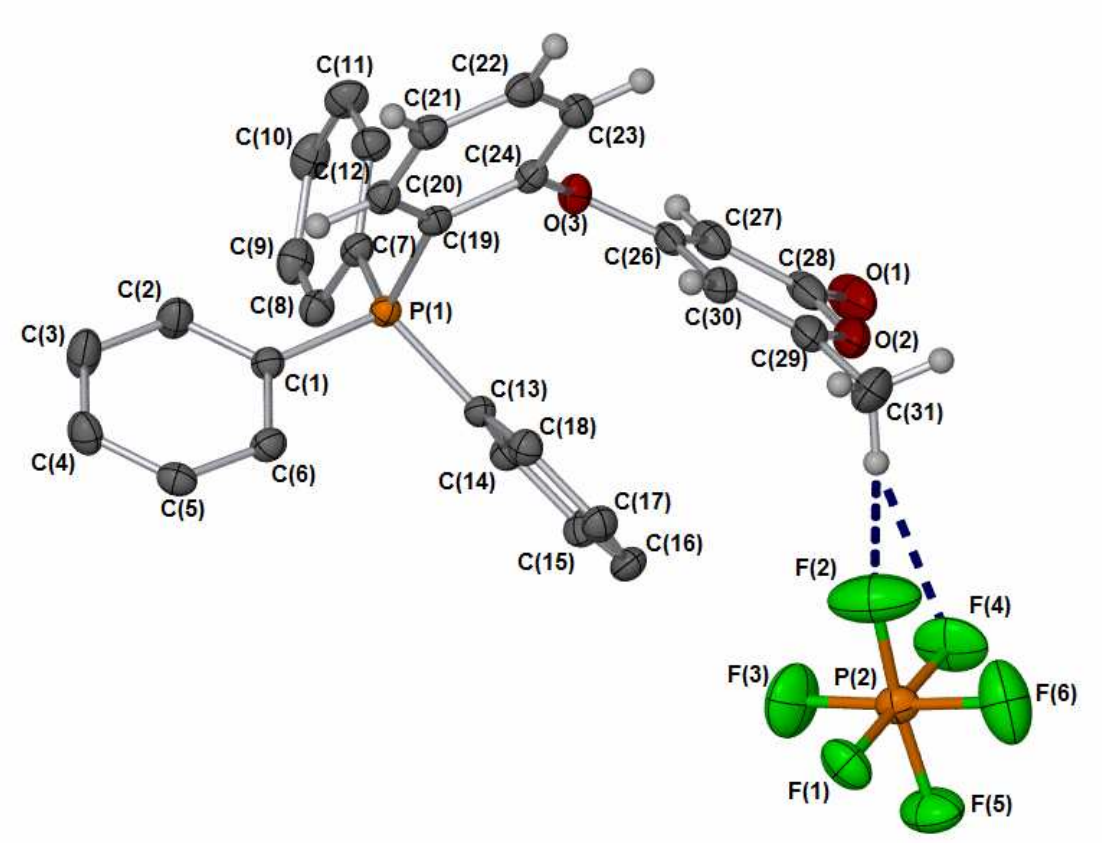
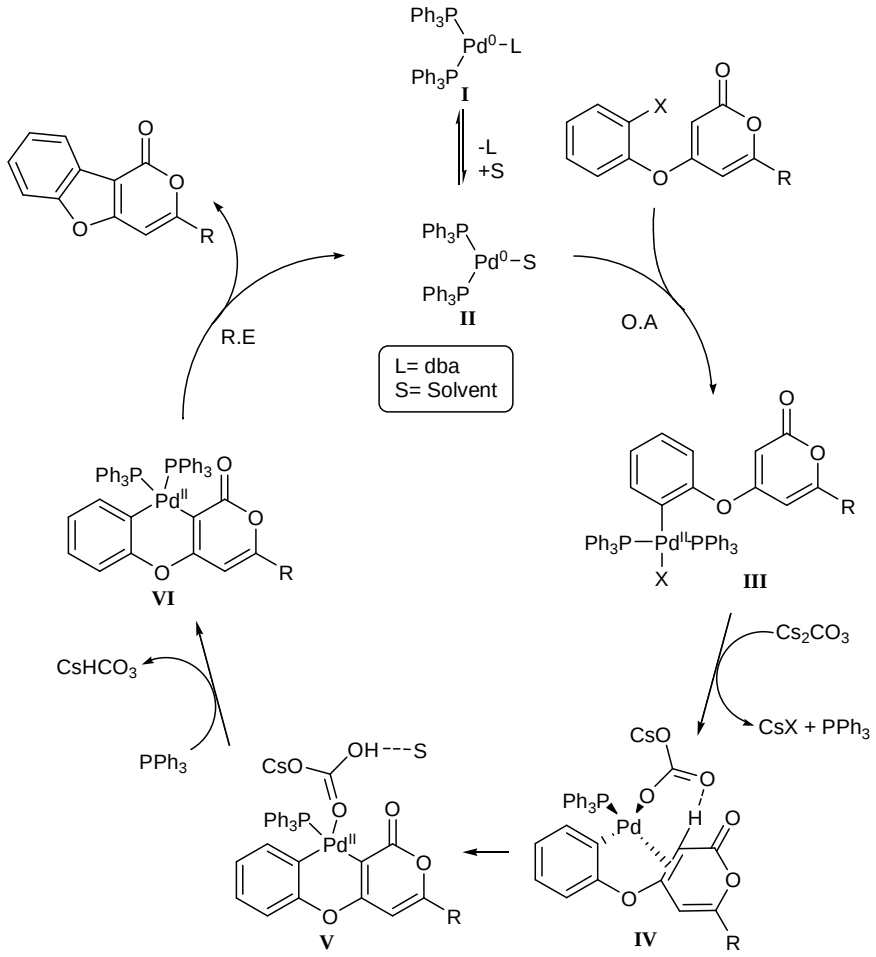


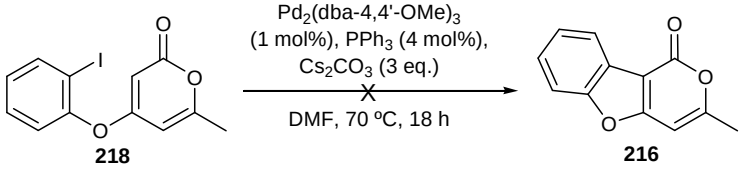
Figure 3.10: Crystal structure of **248**.

Whilst further study is required at this stage to determine the mechanism, it seems likely that the mechanism involving neutral Pd^{II} intermediates and a CMD process is preferred (**Scheme 3.21**). The key step in the mechanism is the concerted metallation and deprotonation between intermediates **IV** and **V**, which is promoted by solvation of the subsequent acid.



Scheme 3.21: Proposed mechanism for intramolecular arylation.

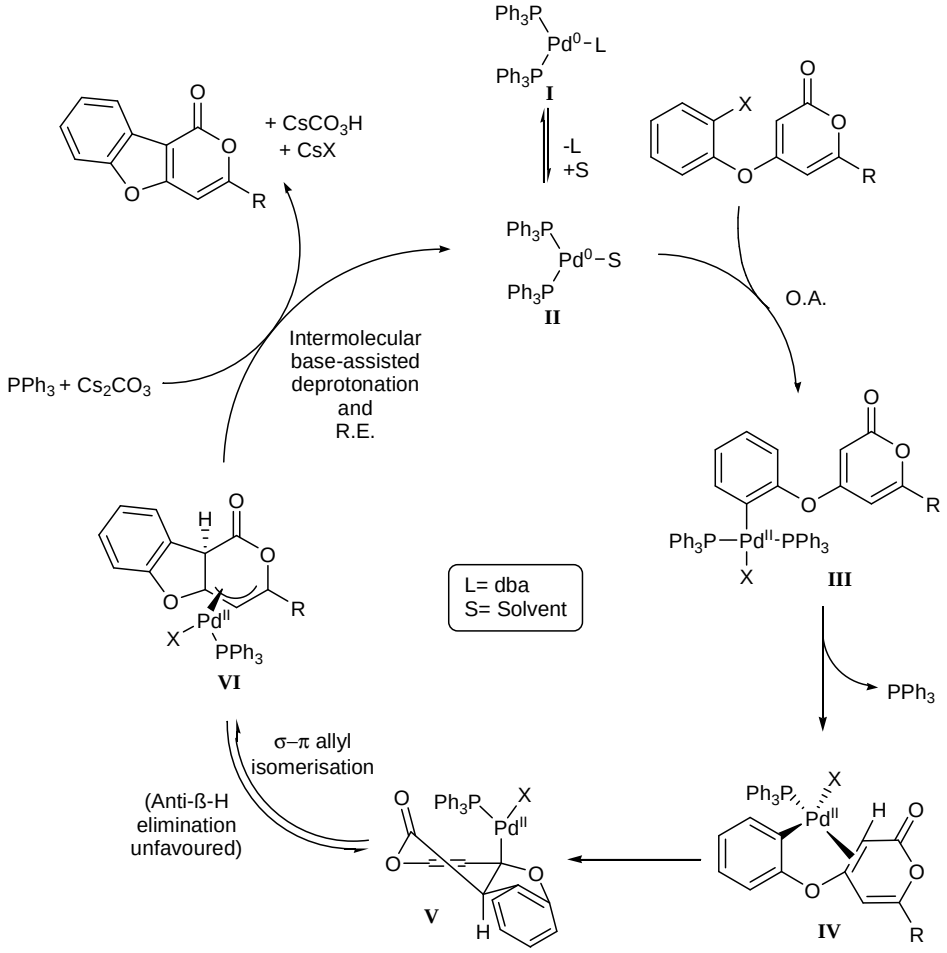
Most of the reported CMD processes reported to date have utilised highly polar solvents, such as DMF and DMA, to promote this transition.[120, 136] The use of THF in the intramolecular C-H functionalisation could partially solvate the intermediate **VI**, however not as much as DMF or DMA, and therefore it would be expected that if the reaction proceeds *via* the CMD pathway the change to one of these solvents would enhance the reaction yields. The intramolecular C-H functionalisation of **218** was subsequently attempted in DMF (**Scheme 3.22**).



218 **216**

Scheme 3.22: Intramolecular arylation of **218** in DMF.

The intramolecular arylation fails to generate any of the desired product **216**, when the more polar DMF is used as solvent instead of THF. This result suggests that the actual reaction mechanism does not undergo a CMD pathway as previously suspected. It was earlier noted during optimisation conditions (**Table 3.1**), that the inclusion of pivalic acid as an additive restricted the formation of **216**, which is also consistent with a non-CMD pathway. It therefore seems likely that the CMD process is not involved in the intramolecular arylation. Previous work by Chang and co-workers suggested a 'Heck-like' mechanism in their synthesis of Coumestan (**Scheme 3.12**); however they offered no mechanism to support their rationale. The 'Heck-like' mechanism is so far still a possibility in the intramolecular arylation reaction, however there are also problems associated with this mechanism.



Scheme 3.23: 'Heck-like' mechanism for the intramolecular arylation.

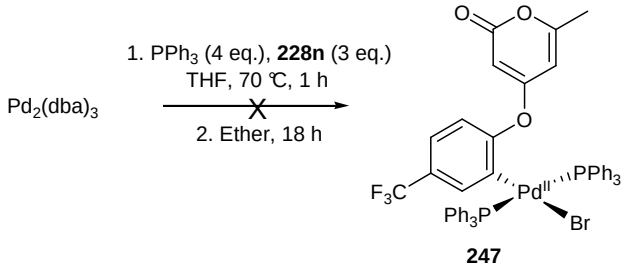
The 'Heck-like' mechanism, shown in **Scheme 3.23**, involves the same initial steps **I-III** as for the CMD mechanism. However, instead of forming a 6:6:6 palladacyclic

intermediate, loss of a phosphine leads to intermediate **IV**, where the Pd^{II} co-ordinates to the alkene of the 2-pyrone. The Pd^{II}-Ar subsequently undergoes a *syn*-insertion into the 2-pyrone alkene thereby generating the C-Ar bond in this process to form intermediate **V**. The desired product is subsequently formed *via* β-H elimination, however due to the *syn*-insertion the β-H is located *anti* to the palladium and an internal rotation is impossible due to the rigid cyclic framework. As a result, the palladium is likely to shift to the more stable π-allyl intermediate **VI**, before undergoing inter-molecular β-H elimination and R.E. to regenerate the active Pd^0 catalyst **II**. The mechanism proposed above requires base for the final regeneration of the Pd^0 catalyst, it must also be noted that the solubility of Cs_2CO_3 in THF is very low, and therefore will not easily participate in the inter-molecular base assisted deprotonation.[140]

At this point neither the 'Heck-like' or CMD mechanisms is without problems. The most likely pathway based on the results obtained is the 'Heck-like' mechanism. It should be noted that halide-carbonate exchange may be required prior to the base-assisted deprotonation/ R.E. to facilitate product formation. Clearly further study is necessary to support the exact mechanism.

The poor reactivity of electron-withdrawing substituents was further investigated by attempting the stoichiometric intramolecular arylation of the CF_3-substituted derivative **228n**.

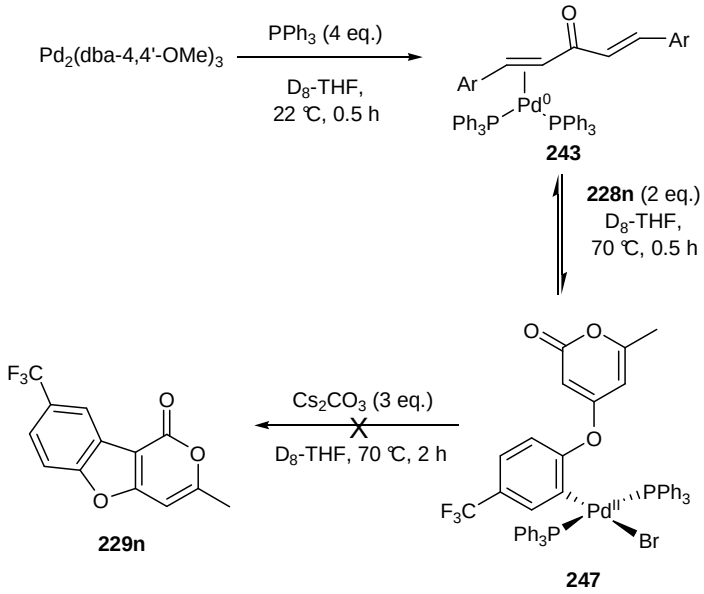
Initial preparative scale synthesis of the O.A. product (**III**) from **228n** was performed in THF at 70 °C. As expected, the solution became a bright yellow colour indicative of the formation of a palladium(II) species. Following removal of THF *in vacuo* and crystallisation from ether, the formation of dark purple crystals was observed. Single crystal X-ray diffraction of the crystals confirmed the identity of the crystals to be Pd_2dba_3. Assuming the oxidative addition had occurred, the recovery of Pd_2dba_3 indicates that the O.A. step is reversible.



247

Scheme 3.22: Preparation of **247**.

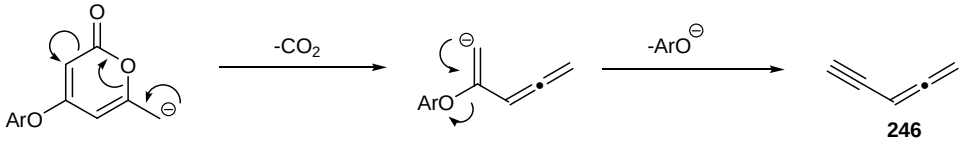
To assess whether O.A. had occurred, the reaction was subsequently performed on an NMR scale (**Scheme 3.23**). The reaction is observed to undergo O.A. to generate a *trans*-palladium(II) complex, confirmed by ^{1}H and ^{31}P NMR spectroscopy. Following 2 hours at 70 °C in the presence of Cs_2CO_3 the reaction had not proceeded. Moreover, the O.A. was observed to have reversed, regenerating the dba stabilised active catalyst **243**, identifiable *via* two broad singlets in the ^{31}P NMR spectrum at δ 26.8 and 25.2 (Δν½ 42 Hz).[60]



Scheme 3.23: NMR scale Synthesis of **229n**.

The poor yields for the more electron-withdrawing substituents can therefore be attributed to the poor conversion from the O.A. products through to the R.E. precursor, due to competitive reversal of the O.A. under reaction conditions. It is important to note that the reversal of the O.A. is not the only limitation of the reaction, as in most cases no starting material is recovered after the reaction period. Degradation pathways are therefore an important limitation in the intamolecular arylation reaction. The synthesis of electron deficient systems was limited due to the poor nucleophilic character of other functionalised phenols containing substituents such as nitro and formyl groups. The presence of electron deficient substituents therefore increases the leaving group potential of the phenoxy group. Following deprotonation at the C-7 position of the 2-pyrone, it is conceivable that loss of ArO^- is a major step in the degradation pathway, consistent with the poor recovery of starting materials with electron deficient substituents. A possible mechanism to enable the loss of ArO^- involves the initial loss of CO_2, and generates the highly unsaturated product

248 (**Scheme 3.24)**. The low molecular mass and high degree of unsaturation in **248** would suggest that it is likely to be lost as a gas or undergo polymerisation under the reaction conditions.



Scheme 3.24: Possible degradation pathway of starting materials under basic conditions.

3.4 Conclusion and Future work

3.4.1 Conclusion

During the course of studies towards **33** the first catalytic C-H functionalisation of a 2-pyrone has been identified and the reaction developed further. Optimised conditions have been applied to a wide variety of substrates to yield 15 different benzofuropyrones in yields varying from 11-79%. Whilst good yields are observed with alkyl substrates, the reaction proceeds poorly with electron deficient functionality and appears to be limited by the rate of degradation of the starting materials. In addition, the catalytic cycle has been investigated and the initial step confirmed as oxidative addition from a Pd^0 source to give a distorted square planar complex. The possibility of a cationic reaction pathway has also been disproved due to a competing Pd to P transfer at room temperature.

3.4.2 Future work

The future work in this area can develop in a number of ways. Further mechanistic studies are required to determine an absolute mechanism for the intramolecular arylation. In addition to the mechanism, further study of the reaction scope is required. Although the formation of a thiophene derivative was unsuccessful, further development and testing could give rise to nitrogen and carbon containing derivatives, whilst the variation in the size of the central ring is also largely untested. Another potential area to develop is the application to 2-pyridinone analogues which should be analogous to the 2-pyrone systems so far studied.

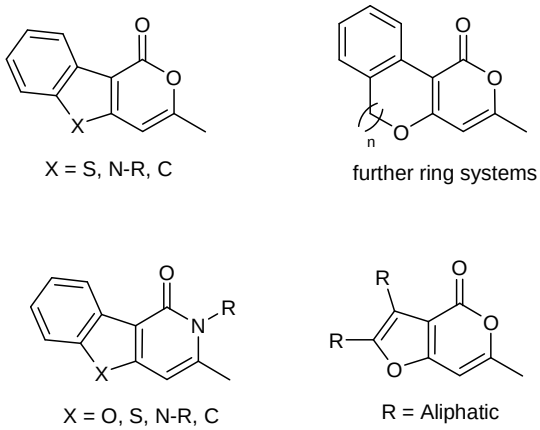
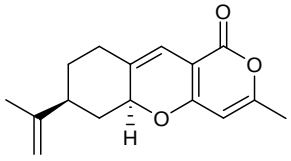


Figure 3.11: Development potential for intramolecular arylation reaction.

Finally, the development of more vinyl halide systems such as ***E*-175a**, from which the reaction was discovered, need to be probed more extensively which could allow rapid access to a large series of compounds, such as **249**, identified by Hua et al. to have excellent bio-activity and a potentially important role in the treatment and prevention of Alzheimer's disease.[141]



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Chapter 4: Natural product experimental

4.1 General Details

Reagents were purchased from either Sigma Aldrich or Alfa Aesar and used directly unless otherwise stated. Dry THF, toluene and diethyl ether were distilled over sodium wire using benzophenone indicator and stored over a potassium mirror. Dry acetone was distilled over drierite®, MeOH was distilled over magnesium turnings and triethylamine was dried over KOH. All other solvents were dried utilising a chromasolv® solvent column. Nitrogen gas was oxygen free and dried immediately before use via passage through sodium hydroxide pellets and silica. Argon and hydrogen were administered directly via balloon. All carefully additions were performed using a syringe pump unless otherwise stated within the text. Filtrations were performed under gravity with fluted filter papers unless otherwise stated within the text.

All TLC analysis was performed using Merck 5554 aluminium backed silica plates and visualised using UV light (254 nm), an aqueous solution of potassium permanganate, or an ethanol based solution of *p*-anisaldehyde. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Jeol ECX400 or Jeol ECS400 spectrometer operating at 400 and 100 MHz respectively, a Bruker 500 spectrometer operating at 500 and 126 MHz respectively. All column chromatography was performed using flash silica-gel with the solvent systems specified within the text.

Mass spectrometry was performed on a Bruker daltronics micrOTOF spectrometer, with < 5 ppm error recorded for all HRMS samples. IR was performed on a Jasco FTIR 4100 spectrometer using an ATR attachment. Melting point analyses were performed on a Stuart SMP3 melting point apparatus, using a temperature ramp of 3 °C/minute.

4.2 General procedures

4.2.1 Suzuki cross-coupling reactions (General Procedure A)

A solution of arylboronic acid (0.58 mmol, 1 eq.), organohalide (0.58 mmol, 1 eq.) and palladium precatalyst **27** (0.0058 mmol, 1 mol %) were stirred in THF (2 ml) under nitrogen at 60 °C for 10 minutes. To this solution aqueous 2M Na_2CO_3 (1 ml) was added and the reaction stirred for up to 5 hours at 60 °C. The solution was allowed to cool to 22 °C, diluted with ether (3 ml), and the organic layer separated. The aqueous layer was then

extracted with ether (3 × 3 ml) and the combined organic extracts washed with brine, dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The product was then purified by flash column chromatography on silica gel eluting with hexanes/EtOAc.

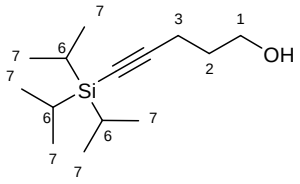
4.2.2 Lithiation/alkylations of 4-hydroxy-6-methyl-2-pyrone (General Procedure B)

4-Hydroxy-6-methyl-2-pyrone **9** (1 mmol, 1 eq.) was heated under nitrogen in HMDS (3 ml) to 80 °C for 1 hour. The solution was allowed to cool and the HMDS removed under vacuum. THF (3 ml) was then added and the solution cooled to -78 °C at which point *n*-BuLi (2.5M in hexanes) (1.25 mmol, 1.25 eq.) was added carefully over 15 minutes, and the solution stirred for 1 hour. The alkyl halide (1.7-2.3 mmol, 1.7-2.3 eq.) was then added over 10 minutes and the solution allowed to warm gradually to 20 °C and stirred for 16h. The reaction was quenched with 6M HCl until the pH ≈ 2 and the solvent removed *in vacuo*. The residue was taken up in ethyl acetate (5 ml), washed twice in brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude brown residue which was purified by flash column chromatography on silica eluting with MeOH 3% in DCM.

4.3 Characterisation data for known and novel compounds

All known compounds are indicated with a reference following the compound title. Compounds without a reference are therefore novel and have been characterised accordingly.

5-Triisopropylsilyl-4-pentyn-1-ol (42)[82,142]



Route A

To a stirred solution of 4-pentyn-1-ol **41** (1.06 g, 12.6 mmol, 1 eq.) in THF (50 ml) under nitrogen at 0 °C was added n-BuLi (2.5M in hexanes) (0.596 ml, 1.26 mmol, 0.1 eq.) carefully over 30 minutes. The solution was allowed to warm to 22 °C over 30 minutes, and chlorotrimethylsilane (1.36 g, 12.6 mmol, 1 eq.) added carefully over 1 hour. The solution was stirred for one hour at 22 °C, then cooled to 0 °C and n-BuLi (2.5M in

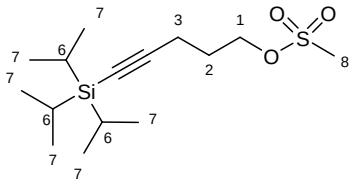
hexanes) (5.96 ml, 12.6 mmol, 1 eq.) added carefully over 30 minutes. The solution was stirred for 30 minutes at 0 °C then warmed to 22 °C and stirred for a further hour. Chlorotriisopropylsilane (2.48 g, 12.9 mmol, 1.02 eq.) was added and the solution stirred at 22 °C for 16 hours. The reaction was quenched with 2M HCl (20 ml) and the product extracted with ether (3 × 17 ml). The combined organic extracts were then concentrated *in vacuo* and dissolved in methanol (50 ml). Potassium hydroxide (0.504 g, 9.0 mmol, 0.74 eq.) was then added and the solution stirred for 2 hours at 22 °C. The solution was neutralized with drops of 2M HCl and the solvent removed *in vacuo*. The residue was taken up in water (25 ml) and extracted with ether (3 × 20 ml), then the combined organic extracts washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was then distilled under reduced pressure (108 °C, 3 mmHg) to afford the title compound as a colourless oil (1.21 g, 40%).

Route B

To a solution of pentyn-1-ol **41** (8.6 mmol, 1 eq.) in THF (16 ml) under argon was added ethyl magnesium bromide (3M in ether) (6 ml, 18 mmol, 2.1 eq.) over 30 minutes. The solution was refluxed for 16 hours then cooled to 22 °C and a solution of chlorotriisopropylsilane (1.66 g, 8.6 mmol, 1 eq.) in THF (8 ml) added slowly over 10 minutes. The reaction mixture was then refluxed for a further 6 hours, then quenched by slow addition into 2M HCl (15 ml) and the organic layer separated. The aqueous layer was then washed with ether (3 × 25 ml) and the combined organic extracts washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was then distilled under reduced pressure (b.p. 108 °C, 3 mmHg) to afford the title compound as a colourless oil (1.85 g, 90%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 3.75 (t, *J = 6.0* Hz, 2H, C^1H_2), 2.28-2.31 (m, 2H, C^2H_2), 1.73-1.77 (m, 2H, C^3H_2), 0.98-1.01 (m, 21H, C^6H/C^7H_3); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 108.4, 81.1, 61.9, 31.2, 18.3, 16.2, 10.9; **MS** (ESI) *m/z* (rel.%): 241 [MH^+] (100), 215 (4), 198 (12), 175 (5), 157 (19); **HRMS** (ESI) calculated for $C_{14}H_{29}OSi$ [MH^+]: 241.1982, found: 241.1985.

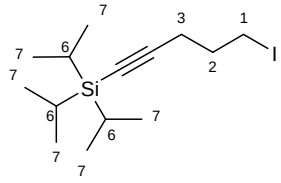
5-Trisopropylsilyl-1-methanesulfonyloxypent-4-yne (43a)[76]



To a solution of **42** (7.2 g, 30 mmol, 1 eq.) and triethylamine (4.55 g, 45 mmol, 1.5 eq.) in DCM (60 ml) under nitrogen at -10 °C, was added methanesulfonylchloride (6.87 g, 60 mmol, 2 eq.). The reaction was quenched with ice cold water (7.5 ml) and separated. The organic layer was then washed with cold 2M HCl (45 ml), sat. $NaHCO_3$ (45 ml) and brine (45 ml). The organic extracts were then dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford a pale yellow oil (10.2 g, quant.) which was used without further purification.

^{1}H-NMR (400 MHz, *$CDCl_3$*): 4.38 (t, *J* = 6.4 Hz, 2H, C^1H_2), 3.02 (s, 3H, C^8H_3), 2.43 (t, *J* = 6.4 Hz, 2H, C^3H_2), 1.97 (p, *J* = 6.4 Hz, 2H, C^2H_2), 1.03-1.07 (m, 21H, C^6H/C^7H_3); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 106.3, 82.2, 68.6, 37.3, 28.4, 18.7, 16.2, 11.3; **MS** (ESI) *m/z* (rel.%): 341 [MNa^+] (100), 272 (4), 209 (76), 181 (36), 157 (30); **HRMS** (ESI) calculated for $C_{15}H_{30}O_3SSi$ [MNa^+]: 341.1577, found: 341.1577.

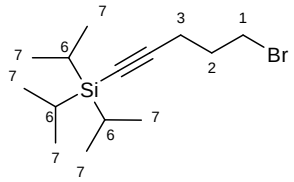
5-Triisopropylsilyl-1-iodopent-4-yne (43b)[76]



A solution of **43a** (10.2 g, 30 mmol, 1 eq.) and NaI (13.5 g, 90 mmol, 3 eq.) in acetone (300 ml) were stirred for 16 hours under argon at 20 °C, then refluxed for 2 hours. The solution was allowed to cool before being filtered, the filtrate was concentrated *in vacuo* taken up in pentane (5 × 5 ml), filtered and solvent removed *in vacuo* to afford the title compound as a pale yellow oil (8.2 g, 78.1%), which was used immediately without further purification.

^{1}H-NMR (400 MHz, *$CDCl_3$*): 3.34 (t, *J* = 6.7 Hz, 2H, C^1H_2), 2.40 (t, *J* = 6.7 Hz, 2H, C^3H_2), 2.00 (p, *J* = 6.7 Hz, 2H, C^2H_2), 1.00-1.08 (m, 21H, C^6H/C^7H_3); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 106.1, 81.5, 31.9, 20.6, 18.4, 11.0, 5.1; **MS** (ESI) *m/z* (rel.%): 351 [MH^+] (100).

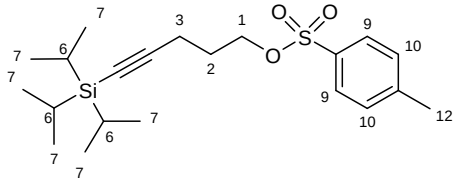
5-Triisopropylsilyl-1-bromopent-4-yne (43c)



To a solution of **42** (500 mg, 2.1 mmol, 1 eq.) in THF (4 ml) under nitrogen at 0 °C, was added PBr_3 (226 mg, 0.83 mmol, 0.4 eq.) carefully over 10 minutes. The solution was stirred for 1 hour at 0 °C, then allowed to warm to 22 °C and stirred for a further 2 hours. The reaction was quenched with 1M $NaHCO_3$ until pH ≈ 7 and the aqueous layer extracted with ether (3 × 3 ml) and the combined organic extracts washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was then purified by column chromatography on silica-gel (using hexanes) and visualized by *p*-anisaldehyde stain, to afford a pale yellow oil (63 mg, 10%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 3.77 (t, *J* = 5.8 Hz, 2H, C^1H_2), 2.37 (t, *J* = 6.8 Hz, 2H, C^3H_2), 1.73-1.82 (m, 2H, C^2H_2), 0.99-1.07 (m, 21H, C^6H/ C^7H_3); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 106.6, 99.9, 81.6, 32.5, 30.9, 18.6, 11.2; **MS** (ESI) *m/z* (rel.%): 223 (40), 209 (15), 195 (8); **HRMS**: not available due to loss of Br under ESI conditions.

5-Triisopropylsilyl-1-toluenesulfonyloxypent-4-yne (43d)

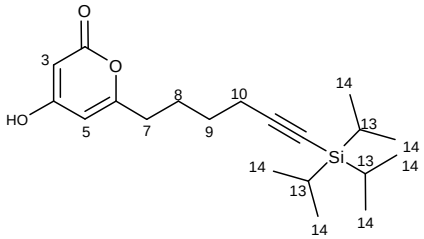


To a solution of **42** (240 mg, 1 mmol, 1 eq.) and triethylamine (151 mg, 1.5 mmol, 1.5 eq.) in DCM (2 ml) under nitrogen at -10 °C, was added toluenesulfonylchloride (381 mg, 2 mmol, 2 eq.). The reaction was quenched with ice cold water (1.5 ml) and separated. The organic layer was then washed with cold 2M HCl (1.5 ml), sat. $NaHCO_3$ (1.5 ml) and brine (1.5 ml). The organic extracts were then dried over Na_2SO_4, filtered and concentrated *in vacuo* purified by flash column chromatography (pet. ether) to afford a pale yellow oil (857 mg, 43.5%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 7.78 (d, *J* = 8.2 Hz, 2H, C^9H), 7.33 (d, *J* = 8.2 Hz, 2H, $C^{10}H$), 4.14 (t, *J* = 6.6 Hz, 2H, C^1H_2), 2.43 (s, 3H, $C^{12}H_3$), 2.31 (t, *J* = 6.6 Hz, 2H, C^3H_2), 1.85 (p, *J* = 6.6 Hz, 2H, C^2H_2), 0.96-1.00 (m, 21H, C^6H/C^7H_3); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 145.1, 133.2, 130.1, 128.1, 106.5, 81.6, 69.0, 28.0, 21.3, 18.2, 15.8, 10.8; **MS**

(ESI) *m/z* (rel.%): 417 [MNa^+] (100), 395 (24), 329 (15), 285 (79), 257 (11), 157 (13); **HRMS** (ESI) calculated for $C_{21}H_{34}NaO_3SSi$ [MNa^+]: 417.1890, found: 417.1888.

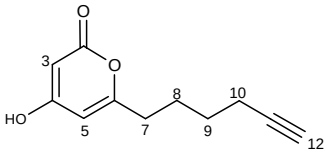
3.5.6 4-Hydroxy-6-(6-triisopropylsilyl-hex-5-yne)-2-pyrone (44)



Prepared according to General Procedure B using **9** (126 mg, 1 mmol, 1 eq.) and **43b** (550 mg, 1.6 mmol, 1.6 eq.) to afford the title compound as a yellow oil (239 mg, 69%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 5.93 (d, *J* = 2.1 Hz, 1H, C^5H), 5.54 (d, *J* = 2.1 Hz, 1H, C^3H), 2.47 (t, *J* = 7.5 Hz, 2H, C^7H), 2.24 (t, *J* = 6.9 Hz, 2H, $C^{10}H$), 1.74-1.84 (m, 2H, C^8H), 1.53-1.62 (m, 2H, C^9H), 0.97-1.01 (m, 21H, $C^{13}H$/ $C^{14}H_3$); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 172.3, 167.9, 166.8, 107.9, 101.3, 89.9, 80.9, 53.4, 33.0, 27.9, 25.6, 18.6, 11.2**;** **MS** (ESI) *m/z* (rel.%): 349 [MH^+] (100), 307 (8), 255 (3), 167 (4); **HRMS** (ESI) calculated for $C_{20}H_{33}O_3Si$ [MH^+]: 349.2193, found: 349.2189; **IR** (DCM, cm^{-1}): 3684, 2944, 2865, 2169, 1693, 1613, 1572, 1462.

4-Hydroxy-6-(hex-5-yne)-2-pyrone (45)

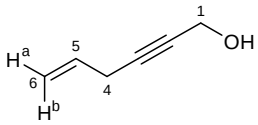


A solution of **44** (80 mg, 0.23 mmol, 1 eq.) and TBAF (1M in THF) (0.69 ml, 0.69 mmol, 3 eq.) in THF (1 ml) was stirred under nitrogen at 22 °C for 16 hours. The reaction was quenched with 2M HCl (1 ml) and the product extracted with ether (3 × 3 ml) then concentrated *in vacuo*. The resulting product was purified by flash column chromatography on silica-gel, eluting with 1% MeOH in DCM, to afford the title compound as a waxy yellow solid (32.3 mg, 73%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 5.97 (d, *J* = 1.9 Hz, 1H, C^5H), 5.56 (d, *J* = 1.9 Hz, 1H, C^3H), 2.50 (t, *J* = 7.57 Hz, 2H, C^7H_2), 2.21 (dt, *J* = 6.91 Hz, 2H, $C^{10}H_2$), 1.95 (t, *J = 2.5* Hz, 1H, $C^{12}H$), 1.74 – 1.81 (m, 2H, C^9H), 1.56 (p, *J = 7.4* Hz, 2H, C^8H); **^{13}C- NMR** (100 MHz, *$CDCl_3$*): 172.1, 167.8, 166.6, 101.3, 89.9, 83.6, 68.8, 33.1, 27.5, 25.6, 18.0; **MS**

(ESI) *m/z* (rel.%): 191 [MH^+] (83), 147 (100); **HRMS** (ESI) calculated for $C_{11}H_{11}O_3$ [M^+]: 191.0714, found: 191.0719; **IR** (DCM, cm^{-1}): 3304, 2928, 1702, 1693, 1639, 1453, 1365.

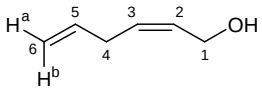
Hex-5-en-2-yn-1-ol (48)[137, 72]



Propargyl alcohol **47** (5.6 g, 100 mmol, 1 eq.) was stirred under nitrogen in acetone (400 ml) at 22 °C. Allyl bromide **46** (14.5 g, 120 mmol, 1.2 eq.) was then added, followed by CuI (19.1 g, 100 mmol, 1 eq.), NaI (30.0 g, 200 mmol, 2 eq.) and K_2CO_3 (27.6 g, 200 mmol, 2 eq.). The solution was stirred for 16 hours before being quenched with 1N HCl (120 ml), diluted with water (500 ml) and stirred for 10 minutes. The mixture was then filtered through Celite™ and the filtrate extracted with ether (5 × 120 ml). The combined organic extracts were then dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude product, which was purified by Kuhglrohr distillation under reduced pressure (b.p. 100 °C, 6 mmHg) to afford the title compound as a colourless oil (9.5 g, 99%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 5.78 (ddt, *J* = 17.0, 10.0, 5.4 Hz, 1H, C^5H), 5.28 (ddt, *J* = 17.0, 1.7, 1.7 Hz, 1H, C^6H^b), 5.09 (ddt, *J* = 10.0, 1.7, 1.7 Hz, 1H, C^6H^a), 4.26 (t, *J* = 2.2 Hz, 2H, C^1H_2), 2.95-3.00 (m, 2H, C^4H_2), 2.19 (s, 1H, OH); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 132.2, 116.2, 82.76, 80.6, 51.1, 23.0; **MS** (EI) *m/z* (rel.%): 95 [M^+] (62), 81 (100), 77 (24), 67 (32), 53 (22)

(*2Z*)-Hexa-2,5-dien-1-ol (49)[143]

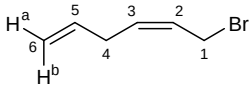


A stirred solution of **48** (480 mg, 5 mmol, 1 eq.), quinoline (32 mg, 0.25 mmol, 0.05 eq.) and Lindlar catalyst (520 mg, 5 mol % palladium) in methanol (5 ml) was stirred under a hydrogen atmosphere at 22 °C for 5 hours. The solution was then filtered through Celite™ and concentrated *in vacuo*, then the crude material was purified by flash column chromatography (15% EtOAc in hexanes) and visualized by *p*-anisaldehyde stain, to give an colourless oil (378mg, 77%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 5.80 (ddt, *J* = 17.1, 10.1, 6.2 Hz, 1H, C^5H), 5.66 (dtt, *J* = 10.8, 6.6, 1.5 Hz, 1H, C^3H), 5.57 (dtt, *J* = 10.8, 6.5, 1.3 Hz, 1H, C^2H), 5.04 (ddt, 17.1, 1.7, 1.7 Hz, 1H, C^6H^b), 5.00 (ddt, 10.1, 1.7, 1.7 Hz, 1H, C^6H^a), 4.21 (dd, *J* = 6.6, 1.5 Hz, 1H,

C^1H_2), 2.80-2.92 (m, 2H, C^4H_2); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 136.41, 129.86, 129.69, 115.26, 60.50, 31.67; **MS** (EI) *m/z* (rel.%): 97 [M^+] (25), 83 (12), 80 (100), 70 (14), 67 (42), 57 (93), 54 (41), 43 (17), 41 (73), 39 (73).

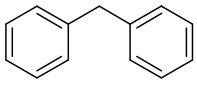
(*2Z*)-1-Bromohexa-2,5-diene (50)[144]



To a stirred solution of CBr_4 (1.99 g, 6 mmol, 1.2 eq.) and PPh_3 (1.57 g, 6 mmol, 1.2 eq.) in DCM (10 ml), under nitrogen at 22 °C, was added **49** (490 mg, 5 mmol, 1 eq.) carefully. The solution was stirred for 4 hours then the solvent removed and the crude material passed through a silica plug, eluting with ether. Concentration *in vacuo* afforded the title compound as a yellow oil (403 mg, 50%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 5.76-5.87 (m, 2H, C^5H/ C^2H), 5.63 (dtt, *J* = 10.5, 7.6, 0.8 Hz, 1H, C^3H), 5.08 (ddt, *J* = 17.1, 1.7, 1.7 Hz, 1H, C^6H^b), 5.04 (ddt, *J* = 10.0, 1.7, 1.7 Hz, 1H, C^6H^a), 3.99 (d, *J* = 8.3 Hz, 2H, C^1H_2), 2.90 (m, 2H, C^4H_2); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 135.3, 132.5, 126.3, 115.8, 31.0, 26.8; **MS** (EI) *m/z* (rel.%): 81 [MH^+-Br] (100), 53 (30), 41 (34).

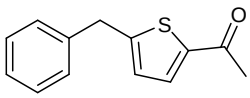
Diphenylmethane (58)[145]



Prepared according to General Procedure A using **56** (70 mg, 0.41 mmol, 1 eq.) and **57** (50 mg, 0.41 mmol, 1 eq.) to afford the title compound as a pale yellow oil (88 mg, 88%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 7.32-7.28 (m, 4H), 7.23-7.19 (m, 6H), 4.00 (s, 2H); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 141.1, 128.9, 128.4, 126.0, 41.9; **MS** (EI) *m/z* (rel.%): 168 [MH^+] (100), 152 (19), 91 (22).

2-Benzyl-5-acetylthiophene (60)[146]

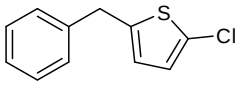


Prepared according to General Procedure A using **56** (70 mg, 0.41 mmol, 1 eq.) and **59** (70 mg, 0.41 mmol, 1 eq.) to afford the title compound as a pale yellow oil (103 mg, 82%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 7.53 (d, *J* = 3.8 Hz, 1H), 7.33 (tt, *J* = 7.2, 1.4 Hz, 2H), 7.28-7.23 (m, 3H), 6.83 (dt, *J* = 3.8, 0.8 Hz, 1H), 4.16 (s, 2H), 2.50 (s, 3H); **^{13}C-NMR** (100

MHz, *CDCl$_3$*): 190.5, 153.9, 142.8, 138.9, 132.8, 128.7, 128.5, 126.8, 126.3, 36.6, 26.4; **MS** (EI) *m/z* (rel.%): 216 [MH$^+$] (87), 201 (100), 173 (60), 129 (27).

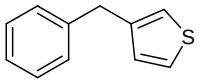
2-Benzyl-5-chlorothiophene (62)[147]



Prepared according to General Procedure A using **56** (70 mg, 0.41 mmol, 1 eq.) and **61** (66.4 mg, 0.41 mmol, 1 eq.) to afford the title compound as a pale yellow oil (102 mg, 84%).

^{1}H-NMR (400 MHz, *CDCl$_3$*): 7.36-7.30 (m, 2H), 7.28-7.22 (m, 3H), 6.73 (dd, *J* = 3.7, 1.8 Hz, 1H), 6.58 (d, *J* = 3.7 Hz, 1H), 4.06 (s, 2H); **^{13}C-NMR** (100 MHz, *CDCl$_3$*): 142.9, 139.5, 128.6, 128.5, 127.9, 126.7, 125.7, 124.3, 36.4; **MS** (EI) *m/z* (rel.%): 208 [MH$^+$] (67), 173 (100), 131 (25).

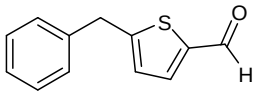
3-Benzylthiophene (64)[148]



Prepared according to General Procedure A using **56** (70 mg, 0.41 mmol, 1 eq.) and **63** (52.5 mg, 0.41 mmol, 1 eq.) to afford the title compound as a pale yellow oil (99 mg, 96%).

^{1}H-NMR (400 MHz, *CDCl$_3$*): 7.33-7.29 (m, 2H), 7.26 (dd, *J* = 4.9, 3.1 Hz, 1H), 7.24-7.20 (m, 3H), 6.94-6.91 (m, 2H), 4.00 (s, 2H); **^{13}C-NMR** (100 MHz, *CDCl$_3$*):141.5, 140.6, 128.7, 128.45, 128.43, 126.1, 125.6, 121.2, 36.5; **MS** (EI) *m/z* (rel.%): 174 [MH$^+$] (100), 97 (48).

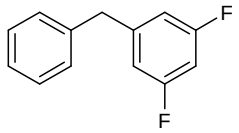
2-Benzyl-5-formylthiophene (66)[149]



Prepared according to General Procedure A using **56** (70 mg, 0.41 mmol, 1 eq.) and **65** (64 mg, 0.41 mmol, 1 eq.) to afford the title compound as a yellow oil (70 mg, 60%).

^{1}H-NMR (400 MHz, *CDCl$_3$*): 9.81 (s, 1H), 7.61 (d, *J* = 3.8 Hz, 1H), 7.34 (tt, *J* = 8.0, 1.7 Hz, 2H), 7.29-7.23 (m, 3H), 6.91 (dt, *J* = 3.7, 0.8 Hz, 1H), 4.19 (s, 2H); **^{13}C-NMR** (100 MHz, *CDCl$_3$*): 182.7, 155.8, 142.4, 138.7, 136.9, 128.8, 128.7, 127.1, 126.6, 36.9; **MS** (EI) *m/z* (rel.%): 202 [MH$^+$] (100), 173 (92), 129 (20).

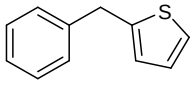
1-Benzyl-3,5-difluorobenzene (72)



Prepared according to General Procedure A using **56** (100 mg, 0.58 mmol, 1 eq.) and **71** (92.4 mg, 0.58 mmol, 1 eq.) to afford the title compound as a colourless oil (82 mg, 69%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 7.33 (tt, *J* = 8.2, 1.6 Hz, 2H), 7.25 (tt, *J* = 6.2, 1.4 Hz, 1H), 7.20-7.17 (m, 2H), 6.74-6.68 (m, 2H), 6.65 (tt, *J* = 9.0, 2.3 Hz, 1H), 3.96 (s, 2H); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 163.0 (dd, *JC-F* = 248.0, 12.9 Hz), 145.0 (t, *JC-F* = 8.9 Hz), 139.4, 128.9, 128.7, 126.6, 111.6 (dd, *JC-F* = 18.4, 6.5 Hz), 101.6 (t, *JC-F* = 25.4 Hz), 41.6 (t, *JC-F* = 1.9 Hz); **^{19}F NMR** (376 MHz, *$CDCl_3$*): -110.3 (m, 2F); **MS** (EI) *m/z* (rel.%): 204 [MH^+] (100), 183 (36), 127 (8), 91 (19); **HRMS** (EI) calculated for $C_{13}H_{10}F_2$ [MH^+]: 204.0751, found: 204.0752; **IR** (neat, cm^{-1}): 3086, 3063, 3030, 1624, 1596, 1495, 1461, 1452, 1322, 1116, 991, 972, 844, 757, 701, 684.

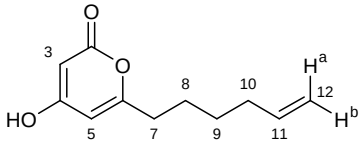
2-Benzylthiophene (74)[153]



Prepared according to General Procedure A using **56** (70 mg, 0.41 mmol, 1 eq.) and **73** (52.5 mg, 0.41 mmol, 1 eq.) to afford the title compound as a pale yellow oil (91 mg, 90%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 7.43-7.38 (m, 2H), 7.36-7.31 (m, 3H), 7.23 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.02 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.90 (dd, *J* = 3.4, 1.2 Hz, 1H), 4.25 (s, 2H); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 144.0, 140.3, 128.53, 128.48, 126.7, 126.4, 125.1, 123.9, 36.0; **MS** (EI) *m/z* (rel.%): 174 [MH^+] (100), 97 (44).

4-Hydroxy-6-(hex-5-ene)-2-pyrone (87)[150]

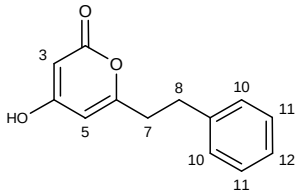


Prepared according to General Procedure B using **9** (126 mg, 1 mmol, 1 eq.) and **86** (342 mg, 2.3 mmol, 2.3 eq.) to afford the title compound as a yellow oil (95 mg, 49%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 5.98 (s, 1H, C^5H), 5.76 (ddt, *J* = 17.0, 10.2, 7.1 Hz, 1H, $C^{11}H$), 5.58 (s, 1H, C^3H), 4.99 (ddt, *J* = 17.0, 2.0, 2.0 Hz, 1H, $C^{12}H^a$), 4.94 (ddt, *J* = 10.2,

2.0, 1.2 Hz, 1H, $C^{12}H^{b}$), 2.48 (t, *J* = 7.5 Hz, 2H, $C^{7}H_2$), 2.02-2.08 (m ,2H, $C^{8}H_2$), 1.60-1.69 (m, 2H, $C^{10}H_2$), 1.39-1.48 (m, 2H, $C^{9}H_2$); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 172.49, 168.21, 167.10, 138.11, 114.92, 101.32, 89.81, 33.46, 33.25, 28.07, 26.06; **MS** (ESI) *m/z* (rel.%): 195 [MH^+] (100); **HRMS** (ESI) calculated for $C_{11}H_{15}O_3$ [M^+]: 195.1016, found: 195.1011.

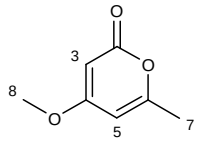
4-Hydroxy-6-(2-phenylethyl)-2-pyrone (90)[17]



Prepared according to General Procedure B using **9** (126 mg, 1 mmol, 1 eq.) and **56** (373 mg, 2.3 mmol, 2.3 eq.) to afford the title compound as a yellow solid (85 mg, 40%).

Mpt: 134-135 °C (lit. 137-138 °C); **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 7.32-7.14 (m, 5H, $C^{10}H$/ $C^{11}H$/ $C^{12}H$), 5.92 (d, *J* = 2.1 Hz, 1H, $C^{5}H$), 5.57 (d, *J* = 2.1 Hz, 1H, $C^{3}H$), 2.96 (dd, *J* = 8.8, 6.8 Hz, 2H, $C^{7}H_2$), 2.78 (dd, *J* = 8.8, 6.8 Hz, 2H, $C^{8}H_2$); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 172.24, 167.94, 165.87, 139.50, 128.54, 128.15, 126.43, 101.72,89.94, 35.36, 32.70**;** **MS** (ESI) *m/z* (rel.%): 217 [MH^+] (100); **HRMS** (ESI) calculated for $C_{13}H_{13}O_3$ [M^+]: 217.0859, found: 217.0865.

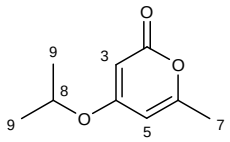
4-Methoxy-6-methyl-2-pyrone (91)[151]



To a stirred suspension of 4-hydroxy-6-methyl-2-pyrone **9** (5.29 g, 42 mmol, 1 eq.) and potassium carbonate (17.4 g, 126 mmol, 3 eq.) in acetone (80 ml), was added dimethyl sulphate (5.29 g, 42 mmol, 1 eq.). The solution was then refluxed (48 °C) for 48 hours, allowed to cool and filtered through Celite^{TM}. The filtrate was concentrated *in vacuo* and recrystallised from pet. ether to afford a white crystalline powder (4.75 mg, 81%).

Mpt: 87-88 °C (lit. 87-88 °C); **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 5.76 (d, *J* = 2.2 Hz, 1H, $C^{5}H$), 5.39 (d, *J* = 2.2 Hz, 1H, $C^{3}H$), 3.77 (s, 3H, $C^{8}H_3$), 2.18 (s, 3H, $C^{7}H_3$); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 171.4, 165.1, 162.1, 100.4, 87.4, 55.9, 19.9; **MS** (ESI) *m/z* (rel.%): 141 [MH^+] (100)

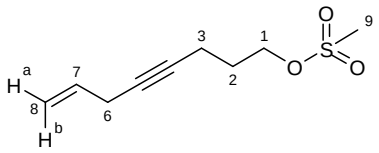
4-Isopropyloxy-6-methyl-2-pyrone (92)



To a stirred solution of 4-hydroxy-6-methyl-2-pyrone **9** (1.89 g, 15 mmol, 1 eq.), triphenylphosphine (5.89 g, 22.5 mmol, 1.5 eq.) and isopropyl alcohol (1.35 g, 22.5 mmol, 1.5 eq.), in THF (90 ml) under nitrogen at ambient temperature, was added DIAD (4.54 g, 22.5 mmol, 1.5 eq.) carefully. The solution was then stirred for 16 hours and the solvent removed *in vacuo*, then the product purified by flash column chromatography (20% EtOAc in hexanes) to afford a white crystalline solid (1.76 g, 70%).

Mpt: 49-51 °C; **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 5.71 (m, 1H, C^5H), 5.35 (d, *J* = 2.2 Hz, 1H, C^3H), 4.49 (sept., *J* = 6.1 Hz, 1H, C^8H), 2.18 (s, 3H, C^7H_3), 1.32 (d, *J* = 6.1 Hz, 6H, C^9H_3); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 169.41, 165.15, 161.85, 100.96, 87.81, 71.37, 21.23; **MS** (ESI) *m/z* (rel.%): 169 [MH^+] (100). **HRMS** (ESI) calculated for $C_9H_{12}O_3Na$ [M^+]: 191.0679, found: 191.0682; **IR** (DCM, cm^{-1}): 2984, 2937, 1733, 1651, 1562, 1467, 1376, 1321.

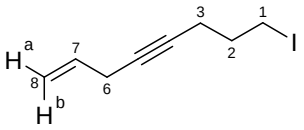
1-Iodooct-7-en-4-yne (94) (*via* 1-(methanesulfonyloxy)oct-7-en-4-yne)[137]



To a solution of oct-7-en-5-yn-1-ol (**203**) (12.4 g, 100 mmol, 1 eq.) and TEA (20.8 g, 150 mmol, 1.5 eq.) in DCM (800 ml) under nitrogen at 20 °C, was added methanesulfonylchloride (22.9 g, 200 mmol, 2 eq.). The reaction was quenched with ice cold water (150 ml) and separated. The organic layer was then washed with cold 2M HCl (150 ml), sat. $NaHCO_3$ (150 ml) and brine (150 ml). The organic extracts were then dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a pale yellow oil (20.2 g, >99%) which was used without further purification.

^{1}H- NMR (400 MHz, *$CDCl_3$*): 5.81 (ddt, *J* = 16.9, 10.0, 5.3 Hz, 1H, C^7H), 5.23 (dd, *J* =16.9, 1.7 Hz, 1H, C^8H^a), 5.10 (dd, *J* =10.0, 1.7 Hz, 1H, C^8H^b), 4.35 (t, *J* = 6.4 Hz, 2H, C^1H_2), 3.02 (s, 3H, C^9H_3), 2.91-2.95 (m, 2H, C^6H_2), 2.36 (tt, *J* =6.4, 2.5 Hz, 2H, C^3H_2), 1.94 (p, *J* = 6.4 Hz, 2H, C^2H_2); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 133.4, 116.2, 80.7, 78.7,

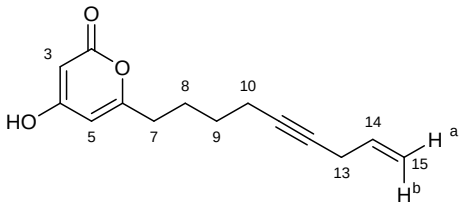
69.1, 37.6, 28.7, 23.4, 15.4; **MS** (ESI) *m/z* (rel.%): 203 [MH^+] (100); **IR** (neat, cm^{-1}): 2943, 2866, 2172, 1464, 1427, 1360, 1185, 971.



A solution of 1-(methanesulfonyloxy)oct-7-en-4-yne (20.2 g, 100 mmol, 1 eq.) and NaI (45 g, 300 mmol, 3 eq.) was stirred in acetone (300 ml) for 72 hours under nitrogen, and then refluxed for 2 hours. The solution was allowed to cool then filtered and the filtrate concentrated *in vacuo*. The crude product was then taken up in hexane (3 × 40 ml) filtered and reduced *in vacuo* to afford a pale yellow oil (17.4 g, 74.5%), which was used immediately without further purification.

^{1}H- NMR (400 MHz, *$CDCl_3$*): 5.81 (ddt, *J* = 16.9, 10.0, 5.3 *Hz*, 1H, C^7H), 5.30 (ddt, *J* =16.9, 1.7, 1.7 Hz, 1H, C^8H^a), 5.10 (ddt, *J* = 10.0, 1.7, 1.7 Hz, 1H, C^8H^b), 3.31 (t, *J* = 6.7 Hz, 2H, C^1H_2), 2.93 (m, 2H, C^6H_2), 2.34 (tt, *J* = 6.7, 2.4 Hz, 2H, C^3H_2), 1.99 (p, *J* = 6.7 Hz, 2H, C^2H_2); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 133.50, 116.15, 80.77, 78.35, 32.86, 23.49, 20.25, 5.90; **MS** (EI) *m/z* (rel.%): 234 [MH^+] (33), 206 (21), 155 (10), 127 (8), 105 (9), 91 (45), 79 (100), 65 (10), 51 (25), 39 (23); **IR** (neat, cm^{-1}): 2945, 2865, 2173, 1463, 1427, 1364, 1220, 1177.

4-Hydroxy-6-(non-8-en-5-ynyl)-2-pyrone (95)

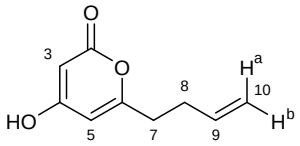


Prepared according to General Procedure B using **9** (126 mg, 1 mmol, 1 eq.) and **94** (330 mg, 1.4 mmol, 1.4 eq.) to afford the title compound as a yellow oil (74 mg, 32%).

^{1}H- NMR (400 MHz, *$CDCl_3$*): 6.00 (d, *J*= 2.1 Hz, 1H, C^5H), 5.83 (ddt, *J* = 17.0, 10.0, 5.3 Hz, 1H, $C^{14}H$), 5.58 (d, *J*= 2.1 Hz, 1H, C^3H), 5.28 (ddt, *J* = 17.0, 1.8, 1.8 Hz, 1H, $C^{15}H^b$), 5.08 (ddt, *J* = 10.0, 1.8, 1.8 Hz, 1H, $C^{15}H^a$), 2.91-2.94 (m, 2H, $C^{13}H_2$), 2.51 (t, *J = 7.6*, 2H, C^7H_2), 2.22 (tt, *J* = 7.0, 2.4 Hz, 2H, $C^{10}H_2$), 1.72-1.80 (m, 2H, C^8H_2) 1.51-1.58 (m, 2H, C^9H_2); **^{13}C- NMR** (100 MHz, *$CDCl_3$*) 172.6, 168.2, 166.9, 133.2, 133.2, 115.7, 115.7, 101.5, 89.9, 81.8, 33.2, 28.1, 25.7, 23.1, 18.4; **MS** (ESI) *m/z* (rel.%):233 [MH^+] (100), 255

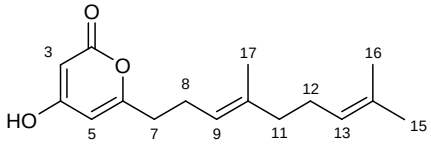
[MNa^+] (19); **HRMS** (ESI) calculated for $C_{14}H_{17}O_3$ [M^+]: 233.1172, found: 233.1178; **IR** (neat, cm^{-1}): 3083, 2939, 2619, 1694, 1568, 1492, 1445, 1364, 1250, 1142, 993.

4-Hydroxy-6-(but-3-en)-2-pyrone (96)[147]



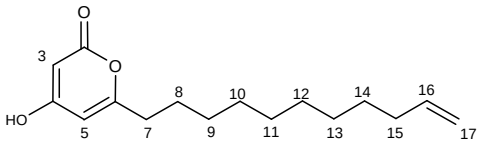
Prepared according to General Procedure B using **9** (126 mg, 1 mmol, 1 eq.) and **45** (363 mg, 2.3 mmol, 2.3 eq.) to afford the title compound as a waxy yellow solid (88 mg, 50%). **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 6.01 (d, *J* = 1.9 Hz, 1H, C^5H), 5.77 (ddt, *J* = 17.1, 10.1, 6.8 Hz, 1H, C^9H), 5.58 (d, *J* = 1.9 Hz, 1H, C^3H), 5.05 (ddt, *J* = 17.1, 1.5, 1.5 Hz, 1H, $C^{10}H^a$), 5.01 (dtd, *J* = 10.1, 3.3, 1.5 Hz, 1H, $C^{10}H^b$), 2.57 (t, *J* = 7.5 Hz, 2H, C^7H_2), 2.35-2.41 (m, 2H, C^8H); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 172.70, 168.38, 166.28, 135.94, 116.45, 101.85, 90.02, 33.04, 30.62**; MS** (ESI) *m/z* (rel.%): 167 [MH^+] (100); **HRMS** (ESI) calculated for $C_9H_{11}O_3$ [MH^+]: 167.0703, found: 167.0704.

4-Hydroxy-6-(4,8-dimethylnona-3,7-dien)-2-pyrone (97)



Prepared according to General Procedure B using **9** (126 mg, 1 mmol, 1 eq.) and **81** (395 mg, 2.3 mmol, 2.3 eq.) to afford the title compound as a dark yellow oil (95 mg, 36%). **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 5.95 (d, *J* = 2.1 Hz, 1H, C^5H), 5.57 (d, *J* = 2.1 Hz, 1H, C^3H), 5.06 (m, 2H, C^9H/ $C^{13}H$), 2.49 (t, *J* = 7.4 Hz, 2H, C^7H), 2.33 (dd, *J* = 14.6, 6.7 Hz, 2H, $C^{12}H_2$), 2.04 (dd, *J* = 14.6, 6.7 Hz, 2H, $C^{11}H_2$), 1.95 (d, *J* = 7.4 Hz, 2H, C^8H_2), 1.66 (d, *J* = 0.9 Hz, 3H, $C^{17}H_3$), 1.58 (s, 6H, $C^{15}H_3$/ $C^{16}H_3$); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 172.03, 167.71, 166.70, 137.39, 131.52, 124.02, 121.52, 101.23, 99.89, 89.84, 39.58, 33.80, 26.56, 25.66, 17.67, 16.00**; MS** (ESI) *m/z* (rel.%): 263 [MH^+] (100); **HRMS** (ESI) calculated for $C_{16}H_{23}O_3$ [MH^+]: 263.1642, found: 263.1632; **IR** (neat, cm^{-1}): 3373, 2968, 2927, 2621, 1673, 1574, 1439, 1376, 1254, 1150, 997.

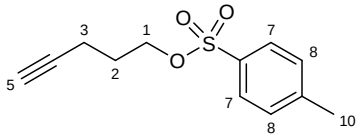
4-Hydroxy-6-(undec-10-en)-2-pyrone (99)[152]



Prepared according to General Procedure B using **9** (504 mg, 4 mmol, 1 eq.) and **98** (876 mg, 4 mmol, 1 eq.) to afford the title compound as a yellow oil (45 mg, 17%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 5.95 (d, *J* = 1.8 Hz, 1H, $C^{5}H$), 5.73 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, $C^{16}H$), 5.58 (d, *J* = 1.8 Hz, 1H, $C^{3}H$), 4.92 (m, 2H, $C^{17}H_2$), 2.38 (tt, *J* = 9.00, 5.50 Hz, 2H), 2.01 (m, 4H), 1.58 (m, 6H), 1.31 (m, 6H); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 178.41, 172.07, 167.23, 138.96, 113.90, 99.23, 89.60, 81.39, 33.55, 29.17, 29.14, 28.97, 28.84, 28.69, 28.66, 26.42; **MS** (EI) *m/z* (rel.%): 265 [MH^+] (100).

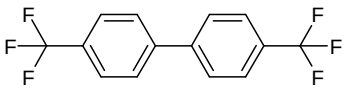
1-Toluenesulfonyloxypent-4-yne (100)[153]



To a solution of 4-pentyn-1-ol (0.42 g, 5 mmol, 1 eq.) and TEA (0.75 g, 7.5 mmol, 1.5 eq.) in DCM (20 ml) under nitrogen at -10 °C, was added toluenesulfonylchloride (1.9 g, 10 mmol, 2 eq.). The reaction was quenched with ice cold water (7.5 ml) and separated. The organic layer was then washed with cold 2M HCl (7.5 ml), sat. $NaHCO_3$ (7.5 ml) and brine (7.5 ml). The organic extracts were then dried over Na_2SO_4, filtered, concentrated *in vacuo* purified *via* flash column chromatography (hexanes) to afford a pale yellow oil (1.07g, 90%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 7.79 (d, *J* = 8.4 Hz, 2H, $C^{7}H$), 7.35 (d, *J* = 8.4 Hz, 2H, $C^{8}H$), 4.14 (t, *J* = 6.1 Hz, 2H, $C^{1}H_2$), 2.45 (s, 3H, $C^{10}H_3$), 2.26 (dt, *J* = 6.7, 2.7 Hz, 2H, $C^{3}H_2$), 2.04 (s, 1H, $C^{5}H$), 1.85 (t, *J* = 6.7 Hz, 2H, $C^{2}H_2$); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 144.91, 133.01, 129.95, 128.03, 82.20, 69.52, 68.82, 27.80, 21.74, 14.79; **MS** (ESI) *m/z* (rel.%): 261 [MNa^+] (100), 228 (8), 173 (9), 157 (9); **HRMS** (ESI) calculated for $C_{12}H_{14}NaO_3S$ [MNa^+]: 261.0556, found: 261.0566.

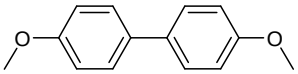
4,4'-Bis-trifluoromethyl-biphenyl (102)[154]



A solution of **9** (152 mg, 1.2 mmol, 1.2 eq.), **101** (225 mg, 1 mmol, 1 eq.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 2 mol%), K_3PO_4 (424 mg, 2 mmol, 2 eq.) and **28** (8.9 mg, 0.03 mmol, 3 mol%) in toluene (2 ml) was heated at 100 °C under nitrogen for 24 hours. The solution was allowed to cool and filtered through Celite™, then concentrated *in vacuo* to afford the crude product which was purified by flash column chromatography (hexanes) to afford a white powder (218 mg, 70%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 7.63 (dd, *J* = 8.8, 0.7 Hz, 4H), 7.49 (dd, *J* = 8.8, 0.7 Hz, 4H): **MS** (ESI) *m/z* (rel.%): 313 [MNa^+] (100).

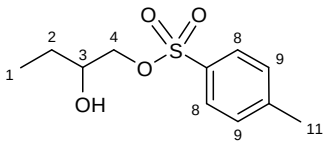
4,4'-Dimethoxy-biphenyl (104)[1540]



A solution of **9** (152 mg, 1.2 mmol, 1.2 eq.), **103** (187 mg, 1 mmol, 1 eq.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 2 mol%), K_3PO_4 (424 mg, 2 mmol, 2 eq.) and **28** (8.9 mg, 0.03 mmol, 3 mol%) in toluene (2 ml) was heated at 100 °C under nitrogen for 24 hours. The solution was allowed to cool and filtered through Celite™, then concentrated *in vacuo* to afford the crude product which was purified by flash column chromatography (hexanes) to afford a white powder (200 mg, 85%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 7.38 (d, *J* = 9.1 Hz, 4H), 6.78 (d, *J* = 9.1 Hz, 4H), 3.37 (s, 6H); **MS** (ESI) *m/z* (rel.%): 237 [MNa^+] (100).

1-Toluenesulfonyloxybutan-1-ol (108)[137, 155]

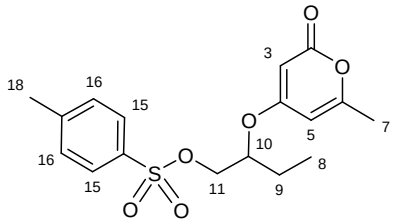


A solution of toluenesulfonyl chloride (51.5 g, 270 mmol, 1 eq.), TEA (54.6 g, 405 mmol, 1.5 eq.) and butane-1,2-diol (36.5 g, 540 mmol, 2 eq.) under nitrogen in DCM (800 ml), was stirred at 20 °C for 16 h. The reaction was then quenched with ice cold water (550 ml) and the aqueous layer removed. The organic layer was then washed sequentially with ice

cold 2M HCl (550 ml), sat. $NaHCO_3$ (550 ml) and brine (550 ml). The organic phase was then dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude material. The product was purified *via* flash column chromatography (10% EtOAc in toluene) to afford a white crystalline powder (53g, 80%).

Mpt: 59-61 °C (lit. 59-60 °C); **^{1}H- NMR** (400 MHz, *$CDCl_3$*): 7.80 (d, *J = 8.1* Hz, 2H, C^8H), 7.35 (d, *J = 8.1* Hz, 2H, C^9H), 4.05 (dd, *J = 10.1, 3.1* Hz, 1H, C^4H), 3.90 (dd, *J =7.1, 10.1* Hz, 1H, C^4H), 3.77 (qd, *J = 7.1, 3.1* Hz, 1H, C^3H), 2.45 (s, 3H, $C^{11}H_3$), 1.51-1.44 (m, 2H, C^2H_2), 0.93 (t, *J = 7.5* Hz, 3H, C^1H_3); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 145.02, 132.78, 129.92, 127.94, 73.62, 70.79, 25.75, 21.62, 9.56; **MS** (ESI) *m/z* (rel.%): 245 [MH^+] (72), 227 (13), 173 (21); **IR** (neat, cm^{-1}): 3536, 2968, 2881, 1598, 1456, 1359, 1161, 1097, 963.

4-(1-Toluenesulfonyloxybutyl-2-oxy)-6-methyl-2-pyrone (109)[137]

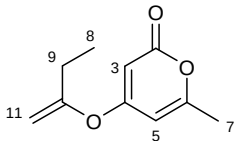


4-Hydroxy-6-methyl-2-pyrone **9** (13.87 g, 110 mmol, 1 eq.), **108** (40.3 g, 165 mmol, 1.5 eq.) and triphenylphosphine (43.3 g, 165 mmol, 1.5 eq.) were dissolved in THF (380 ml) under nitrogen at 0 °C. DIAD (33.4 g, 165 mmol, 1.5 eq.) was then added carefully over 30-40 minutes to prevent the generation of excess heat. The reaction was stirred for 16 h at 20 °C and then the solvent removed *in vacuo*. Phosphine oxide was removed from the product by dissolving the product in ether (200 ml), and vacuum filtration to remove the solid oxide. The ether was then removed in vacuo and the crude product purified by flash column chromatography (10-40% EtOAc in heptane), to afford the title compound as a white crystalline solid.

Mpt: 96-98 °C; **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 7.73 (d, *J = 7.5* Hz, 2H, $C^{15}H$), 7.31 (d, *J = 7.5* Hz, 2H, $C^{16}H$), 5.64 (m, 1H, C^5H), 5.22 (d, *J = 2.1* Hz, 1H, C^3H) 4.33-4.28 (m, 1H, $C^{10}H$), 4.16-4.07 (m, 2H, $C^{11}H_2$), 2.42 (s, 3H, $C^{18}H_3$), 2.15 (s, 3H, C^7H_3), 1.68 (p, *J = 7.5* Hz, 2H, C^9H_2), 0.93 (t, *J = 7.5* Hz, 3H, C^8H_3); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 169.2, 164.6, 162.4, 145.3, 130.0, 127.9, 100.5, 88.4, 68.8, 60.4, 23.1, 21.7, 19.8, 14.2, 9.0; **MS** (ESI) *m/z* (rel.%): 375 [MNa^+] (100), 353 [MH^+] (80), 281 (7), 227 (20); **HRMS** (ESI)

calculated for $C_{17}H_{21}O_6S$ [MH^+]: 353.1053, found: 353.1062; **IR** (DCM, cm^{-1}): 3062, 2979, 2883, 1713, 1652, 1598, 1436, 1365, 1243, 1178, 1096.

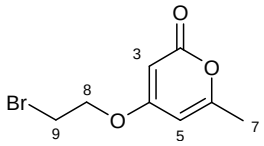
4-(But-1-en-2-yloxy)-6-methyl-2-pyrone (110)[137]



A solution of **109** (26.1 g, 74 mmol, 1 eq.), NaI (33.3 g, 222 mmol, 3 eq.) and DBU (22.5 g, 148 mmol, 2 eq.) in DME (720 ml) was refluxed under argon for 16 hours. The reaction was allowed to cool then quenched by addition of water (800 ml) and the product extracted with ether (3 × 800 ml). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash column chromatography (20-40% Ether in pet. ether) to afford the title compound as a a colourless oil (13.3g, 89%).

Rf = 0.3 (40% Ether); **^{1}H- NMR** (400 MHz, *$CDCl_3$*): 5.87 (dq, *J* = 2.0, 0.9 Hz, 1H, C^5H), 5.52 (dq, *J* = 2.0, 0.6 Hz, 1H, C^3H), 4.80 (dt, *J* = 2.0, 1.3 Hz, 1H, $C^{11}H$), 4.70 (dt, *J* = 2.0, 0.6 Hz, 1H, $C^{11}H$), 2.22 (dd, *J* = 0.9, 0.6 Hz, 3H, C^7H_3), 2.19 (qdd, *J* = 7.4, 0.9, 0.6 Hz, 2H, C^9H_2), 0.98 (t, *J* = 7.4 Hz, 3H, C^8H_3); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 168.9, 164.4, 162.8, 159.18, 100.2, 99.86, 90.3, 25.3, 19.6, 10.7; **MS** (ESI) *m/z* (rel.%): 181 [MH^+] (100), 127 (31); **HRMS** (ESI) calculated for $C_{10}H_{13}O_3$ [MH^+]: 181.0859, found: 181.0864; **IR** (neat, cm^{-1}): 3093, 2974, 2941, 2923, 2884, 1739, 1648, 1566, 1448, 1406, 1320, 1230, 1188, 1136, 1033, 997.

4-(2-Bromoethoxy)-6-methyl-2-pyrone (112)[137]

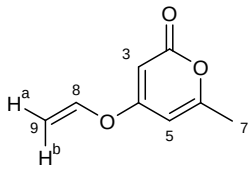


4-Hydroxy-6-methyl-2-pyrone **9** (12.6 g, 100 mmol, 1 eq.), 2-bromoethanol (18.7 g, 150 mmol, 1.5 eq.) and triphenylphosphine (39.3 g, 150 mmol, 1.5 eq.) were dissolved in THF (380 ml) under nitrogen at 0 °C. DIAD (30.3 g, 150 mmol, 1.5 eq.) was then added carefully over 30-40 minutes to prevent the formation of excess heat. The reaction was stirred for 16 h at 20 °C and then the solvent removed *in vacuo*. Phosphine oxide was removed from the product by dissolving the product in ether (200 ml), and vacuum filtration to remove the solid oxide. The ether was then removed *in vacuo* and the crude

product purified *via* flash column chromatography (10-40% EtOAc in heptane) to afford the title compound as a pale yellow crystalline solid (19.1 g, 82%).

Mpt: 66-68 °C; **^{1}H- NMR** (400 MHz, *$CDCl_3$*): 5.83 (m, 1H, C^5H), 5.37 (d, *J* = 2.0 Hz, 1H, C^3H), 4.26 (t, *J* = 6.0 Hz, 2H, C^8H_2), 3.61 (t, *J* = 6.0 Hz, 2H, C^9H_2), 2.21 (s, 3H, C^7H_3); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 169.7, 164.5, 162.5, 100.1, 88.1, 77.3, 77.0, 76.7, 68.0, 27.1, 19.8; **MS** (ESI) *m/z* (rel.%): 235 [^{81}Br-MH^+] (84), 233 [^{79}Br-MH^+] (100); **HRMS** (ESI) calculated for $C_8H_9{}^{79}BrO_3Na$: 254.9627, found: 254.9622; **IR** (DCM, cm^{-1}): 3059, 1716, 1653, 1571, 1448, 1418, 1377, 1251, 1184, 1145 cm^{-1}.

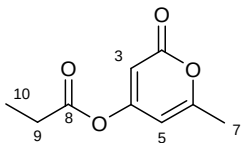
4-(Vinyloxy)-6-methyl-2-pyrone (113)[137]



A solution of **112** (18.0 g, 77 mmol, 1 eq.), NaI (34.7 g, 232 mmol, 3 eq.) and DBU (23.5 g, 154 mmol, 2 eq.) in DME (720 ml) was refluxed under argon for 16 hours. The reaction was allowed to cool then quenched by addition of water (800 ml) and the product extracted with ether (3 × 800 ml). The combined organic extracts were dried over $MgSO_4$, concentrated *in vacuo* and purified *via* flash column chromatography (20-40% Ether in pet ether) to afford the title compound as a crystalline white powder (5.5 g, 46.6%).

Mpt: 43-45 °C; **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 6.53 (dd, *J* = 13.5, 5.9 Hz, 1H, C^8H), 5.84 (d, *J* = 2.0 Hz, 1H, C^3H), 5.49 (d, *J* = 1.9 Hz, 1H, C^5H), 5.03 (dd, *J* = 13.5, 2.0 Hz, 2H, C^9H^b), 4.77 (dd, *J* = 5.9, 2.0 Hz, 2H, C^9H^a), 2.23 (s, 3H, C^7H_3); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 168.2, 164.0, 163.1, 143.6, 101.4, 99.5, 89.9, 19.8; **MS** (ESI) *m/z* (rel.%): 175 [MNa^+] (100), 153 [MH^+] (2); **HRMS** (ESI) calculated for $C_8H_8O_3Na$ [M^+]: 175.0366, found: 175.0373; **IR** (DCM, cm^{-1}): 3672, 3060, 1731, 1641, 1573, 1448, 1411, 1235, 1185, 1142.

6-Methyl-4-propionyl-2-pyrone (118)[137]

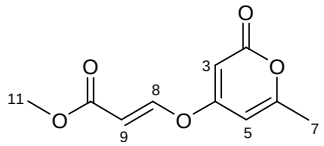


To a stirred solution of 4-hydroxy-6-methy-2-pyrone **9** (1.01 g, 8 mmol, 1 eq.) and TEA (3.34 g, 24 mmol, 3 eq.) in DCM (24 ml), was added propionyl chloride (0.81 g, 8.8 mmol,

1.1 eq.) at 20 °C. The solution was stirred for 2 hours then quenched by addition of water (15 ml) and the DCM separated and concentrated *in vacuo*. The crude product was then purified *via* flash column chromatography (20% EtOAc in pet ether) to afford the title compound as a colourless oil (1.3 g, 89%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 5.91 (d, *J = 1.1* Hz, 1H, C^5H), 5.86 (d, *J = 1.1* Hz, 1H, C^3H), 2.45 (q, *J = 7.5* Hz, 2H, C^9H_2), 2.14 (s, 3H, C^7H_3), 2.14 (t, *J = 7.5* Hz, 3H, $C^{10}H_3$); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 170.86, 164.02, 163.59, 101.67, 101.01, 53.90, 28.12, 20.28, 8.89; **MS** (ESI) *m/z* (rel.%): 183 [MH^+] (100); **HRMS** (ESI) calculated for $C_9H_{10}O_4Na$ [M^+]: 205.0471, found: 205.0478; **IR** (neat, cm^{-1}): 3097, 2986, 2945, 1772, 1739, 1648, 1571, 1447, 1398, 1352, 1317, 1218, 1110.

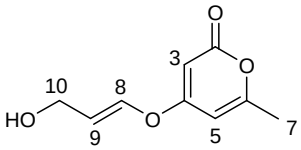
Methyl 3-(6-methyl-2-pyronyl-4-oxy)-acrylate (123)[137]



4-Hydroxy-6-methyl-2-pyrone **9** (9.45 g, 75 mmol, 1 eq.), TEA (7.58 g, 75 mmol, 1 eq.) and methyl propiolate (7.57 g, 90 mmol, 1.2 eq) were refluxed in DCM (250 ml) for 16 hours. The solvent was then removed *in vacuo* and the product purified by column chromatography (20% EtOAc in hexanes) to afford a yellow crystalline powder (12.85 g, 82%).

Mpt: 129-130 °C; **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 7.67 (d, *J* = 12.0 Hz, 1H, C^8H), 5.91 (d, *J* = 2.2 Hz, 1H, C^5H), 5.85 (d, *J* = 12.0 Hz, 1H, C^9H), 5.65 (d, *J* = 2.2 Hz, 1H, C^3H), 3.78 (s, 3H, $C^{11}H_3$), 2.27 (s, 3H, C^7H_3); **^{13}C- NMR** (100 MHz, *$CDCl_3$*); 167.2, 165.9, 164.2, 163.3, 152.5, 107.7, 99.1, 92.1, 48.8, 20.1; **MS** (ESI) *m/z* (rel.%): 233 [MNa^+] (100), 177 (5); **HRMS** (ESI) calculated for $C_{10}H_{10}O_5Na$ [M^+]: 233.0420, found: 233.0429; **IR** (DCM, cm^{-1}): 3061, 2953, 1723, 1644, 1576, 1447, 1406, 1258, 1186, 1101.

4-(3-Hydroxy-propenyloxy)-6-methyl-2-pyrone (124)

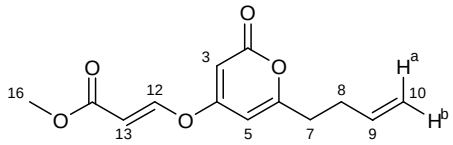


A solution of **123** (210 mg, 1 mmol, 1 eq.) was dissolved in DCM (3 ml) under nitrogen. DIBAL (1M in DCM) (2 ml, 2 mmol, 2 eq.) was then added at -40 °C, and the solution

allowed to warm up to -20 °C over 1 hour. The solution was then transferred to a flask containing aqueous Rochelle's salt (15 ml, 20% w/w) and stirred for 3 hours. The aqueous layer was then separated and washed with DCM (3 × 5 ml) and the combined organic extracts dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The crude product was then purified *via* flash column chromatography (50% EtOAc in hexanes) to afford a yellow powder (49 mg, 27%).

^{1}H- NMR (400 MHz, *$CDCl_3$*): 6.63 (dt, *J* = 12.0, 1.5 Hz, 1H, C^8H), 5.85 (dq, *J* = 2.2, 0.7 Hz, 1H, C^5H), 5.75 (dt, *J* = 12.0, 6.4 Hz, 1H, C^9H), 5.53 (d, *J* =2.2 Hz, 1H, C^3H), 4.22 (dd, *J* = 6.4, 1.5 Hz, 2H, $C^{10}H_2$), 2.23 (d, *J* = 0.7 Hz, 3H, C^7H_3); **^{13}C- NMR** (100 MHz, *$CDCl_3$*); 168.6, 164.5, 163.2, 140.0, 117.5, 99.8, 90.1, 59.0, 20.0; **MS** (ESI) *m/z* (rel.%): 205 [MNa^+] (100), 133 (9); **HRMS** (ESI) calculated for $C_9H_{10}O_4Na$ [M^+]: 205.0471, found: 205.0478; **IR** (DCM, cm^{-1}): 3683, 3603, 3056, 2927, 1716, 1650, 1570, 1448, 1409.

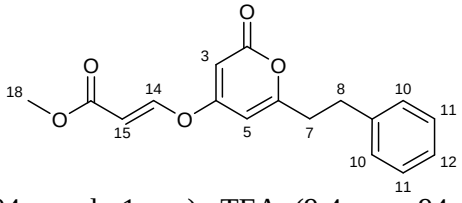
Methyl 3-(6-(but-3-enyl)-2-pyronyl-4-oxy)-acrylate (135)



2-pyrone **96** (14 mg, 84 μmol, 1 eq.), TEA (8 mg, 84 μmol, 1 eq.) and methyl propiolate (7 mg, 84 μmol, 1 eq.) were stirred in DCM (1 ml) for at 45 °C for 16 hours. The solvent was then removed *in vacuo* and the product purified *via* flash column chromatography (20% EtOAc in hexanes) to afford a yellow crystalline powder (18.1 mg, 86%).

^{1}H-NMR (500 MHz, *$CDCl_3$*): 7.67 (d, *J* = 12.1 Hz, 1H, $C^{12}H$), 5.90 (d, *J* = 2.1 Hz, 1H, C^5H), 5.84 (d, *J* = 12.1 Hz, 1H, $C^{13}H$), 5.78 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 1H, C^9H), 5.65 (d, *J* = 2.1 Hz, 1H, C^3H), 5.08 (ddt, *J* = 17.0, 1.5, 1.5 Hz, 1H, $C^{10}H^a$), 5.05 (ddt, *J* = 10.1, 1.5, 1.5 Hz, 1H, $C^{10}H^b$), 3.77 (s, 3H, $C^{16}H_3$), 2.60 (t, *J* = 7.9 Hz, 2H, C^7H_2), 2.41-2.45 (m, 2H, C^8H_2); **^{13}C-NMR** (101 MHz, *$CDCl_3$*): 167.1, 166.8, 165.9, 163.3, 152.5, 135.7, 116.6, 107.7, 98.8, 92.3, 51.8, 33.2, 30.5; **MS** (ESI) *m/z* (rel.%): 251 [MH^+] (100); **HRMS** (ESI) calculated for $C_{13}H_{15}O_5$: 251.0914, found: 251.0917; **IR** ($CHCl_3$, cm^{-1}): 3077, 2955, 2362, 1722, 1639, 1574, 1415, 1325, 1223, 1163, 1099.

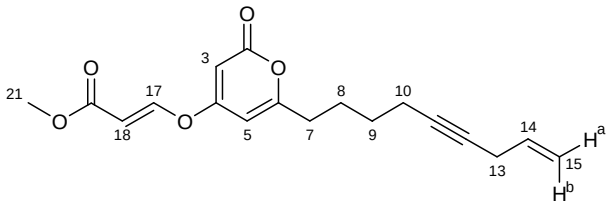
Methyl 3-(6-(2-phenylethyl)-2-pyronyl-4-oxy)-acrylate (136)



2-pyrone **90** (20.4 mg, 94 μmol, 1 eq.), TEA (9.4 mg, 94 μmol, 1 eq.) and methyl propiolate (8.7 mg, 100 μmol, 1.1 eq.) were stirred in DCM (1 ml) for at 45 °C for 16 hours. The solvent was then removed *in vacuo* and the product purified *via* flash column chromatography (20% EtOAc in hexanes) to afford a yellow crystalline powder (19.3 mg, 68%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 7.65 (d, *J* = 12.1 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 7.19 – 7.15 (m, 2H), 5.84 (dt, *J* = 2.3, 0.7 Hz, 1H), 5.82 (d, *J* = 12.1 Hz, 1H), 5.66 (d, *J* = 2.3 Hz, 1H), 3.77 (s, 3H), 2.99 (t, *J* = 7.8 Hz, 2H), 2.81 (td, *J* = 7.7, 0.7 Hz, 2H); **^{13}C-NMR** (101 MHz, *$CDCl_3$*): 167.1, 166.5, 166.0, 163.5, 152.5, 139.6, 128.8, 128.4, 126.7, 107.8, 99.2, 92.5, 52.0, 35.8, 32.9; **MS** (ESI) *m/z* (rel.%): 301 [MH^+] (100); **HRMS** (ESI) calculated for $C_{17}H_{17}O_5$: 301.1071, found: 301.1069; **IR** ($CHCl_3$, cm^{-1}): 3019, 2363, 1721, 1641, 1573, 1416, 1101, 670.

Methyl 3-(6-(non-8-en-5-ynyl)-2-pyronyl-4-oxy)-acrylate (137)

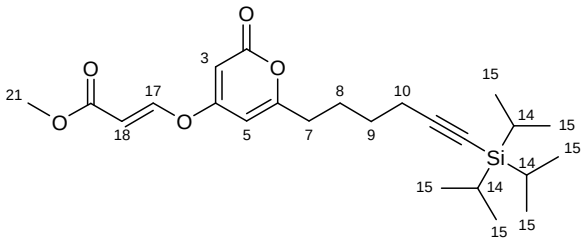


2-pyrone **95** (33.3 mg, 143 μmol, 1 eq.), TEA (15 mg, 143 μmol, 1 eq.) and methyl propiolate (12.1 mg, 144 μmol, 1.01 eq.) were stirred in DCM (1 ml) for at 45 °C for 16 hours. The solvent was then removed *in vacuo* and the product purified *via* flash column chromatography (20% EtOAc in hexanes) to afford a waxy yellow powder (28.9 mg, 64%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 7.68 (d, *J* = 12.0 Hz, 1H, $C^{17}H$), 5.92 (dt, *J* = 2.3, 0.7 Hz, 1H, $C^{5}H$), 5.85 (d, *J* = 12.0 Hz, 1H, $C^{18}H$), 5.82 (ddt, *J* =16.9, 10.0, 5.3 Hz, 1H, $C^{14}H$), 5.66 (d, *J* = 2.3 Hz, 1H, $C^{3}H$), 5.29 (ddt, *J* = 16.9, 1.8, 1.8 Hz, 1H, $C^{15}H^{b}$), 5.09 (ddt, *J* = 10.0, 1.8, 1.8 Hz, 1H, $C^{15}H^{a}$), 3.77 (s, 3H, $C^{21}H_3$), 2.91 – 2.96 (m, 2H, $C^{13}H_2$), 2.53 (dt, *J* = 7.6, 0.7 Hz, 2H, $C^{7}H_2$), 2.24 (tt, *J* = 2.4, 6.9 Hz, 2H, $C^{10}H_2$), 1.74 – 1.83 (m, 2H, $C^{8}H_2$), 1.51 – 1.62 (m, 2H, $C^{9}H_2$); **^{13}C-NMR** (101 MHz, *$CDCl_3$*): 167.5, 167.1, 166.0, 163.5,

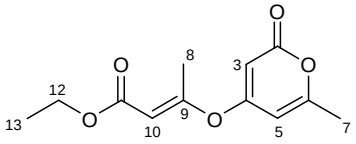
152.4, 133.2, 115.7, 107.7, 99.9, 98.6, 92.1, 81.7, 51.9, 33.4, 28.1, 25.7, 23.1, 18.4; **MS** (ESI) *m/z* (rel.%): 339 [MNa^+] (63), 317 [MH^+] (100), 210 (7), 180 (7); **HRMS** (ESI) calculated for $C_{18}H_{21}O_5$ [MH^+]: 317.1384, found: 317.1379; **IR** (neat, cm^{-1}): 3091, 2947, 2160, 1710, 1636, 1567, 1415, 1221, 1098, 823.

Methyl 3-(6-(6-triisopropylsilyl-hex-5-ynyl)-2-pyronyl-4-oxy)-acrylate (138)



2-pyrone **44** (100 mg, 287 μmol, 1 eq.), TEA (29 mg, 287 μmol, 1 eq.) and methyl propiolate (24.2 mg, 288 μmol, 1.01 eq.) were stirred in DCM (1 ml) for at 45 °C for 16 hours. The solvent was then removed *in vacuo* and the product purified *via* flash column chromatography (20% EtOAc in hexanes) to afford a waxy yellow powder (102 mg, 82%). **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 7.68 (d, *J* = 12.0 Hz, 1H, $C^{17}H$), 5.90 (d, *J* = 2.3 Hz, 1H, C^5H), 5.84 (d, *J* = 12.0 Hz, 1H, $C^{18}H$), 5.65 (d, *J* = 2.3 Hz, 1H, C^3H), 3.77 (s, 3H, $C^{21}H_3$), 2.53 (t, *J* = 7.5 Hz, 2H, C^7H_2), 2.30 (t, *J* = 6.9 Hz, 2H, $C^{10}H_2$), 1.77 – 1.86 (m, 2H, C^8H_2), 1.54 – 1.63 (m, 2H, C^9H_2), 1.00 – 1.08 (m, 21H, $C^{14}H/C^{15}H_3$); **^{13}C-NMR** (101 MHz, *$CDCl_3$*): 167.5, 167.1, 165.9, 163.4, 152.4, 107.8, 107.7, 98.5, 92.1, 81.0, 51.8, 33.2, 27.8, 25.5, 19.4, 18.6, 11.2; **MS** (ESI) *m/z* (rel.%): 455 [MNa^+] (100), 433 [MH^+] (51), 399 (5), 377 (3), 326 (4), 289 (12), 267 (8), 242 (10), 217 (7), 180 (4); **HRMS** (ESI) calculated for $C_{24}H_{36}NaO_5Si$ [MNa^+]: 455.2224, found: 455.2213; **IR** ($CHCl_3$, cm^{-1}): 3023, 2956, 2866, 2362, 1721, 1641, 1574, 1418, 1215, 1101.

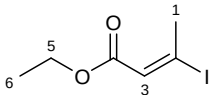
Ethyl 3-(6-methyl-2-pyronyl-4-oxy)-but-2-enoate (140)



A solution of 4-hydroxy-6-methyl-2-pyrone **9** (126 mg, 1 mmol, 1 eq.), ethyl 3-butynoate **137** (134 mg, 1.2 mmol, 1.2 eq.), DBU (100 mg, 0.66 mmol, 0.66 eq.), and CuI (19 mg, 0.1 mmol, 10 mol%) in THF (2 ml) was heated under nitrogen at 80 °C in a microwave for 30 minutes. The solvent was removed *in vacuo* and the product purified by column chromatography (30% EtOAc in hexanes) to afford a waxy yellow solid (102 mg, 42.8%).

Rf = 0.43 (40% EtOAc in hexanes); **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 5.87 (dq, *J* = 2.0, 0.8 Hz, 1H, $C^{5}H$), 5.57 (dq, *J* = 2.0, 0.6 Hz, 1H, $C^{3}H$), 5.52 (q, *J* = 0.9 Hz, 1H, $C^{10}H$), 4.19 (q, *J* = 7.1 Hz, 2H, $C^{12}H_2$), 2.38 (d, *J* = 0.9 Hz, 3H, $C^{8}H_3$), 2.26 (dd, *J* = 0.8, 0.6 Hz, 3H, $C^{7}H_3$), 1.29 (t, *J* = 7.1 Hz, 3H, $C^{13}H_3$); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 167.2, 165.8, 165.6, 163.9, 107.5, 100.1, 94.4, 79.9, 60.4, 20.1, 17.4, 14.2; **MS** (ESI) *m/z* (rel.%): 261 [MNa^+] (100), 177 (2), 153 (4); **HRMS** (ESI) calculated for $C_{12}H_{14}O_5Na$ [M^+]: 261.0733, found: 261.0738; **IR** (DCM, cm^{-1}): 3018, 2919, 2871, 2774, 1729, 1643, 1556, 1384, 1335, 1168.

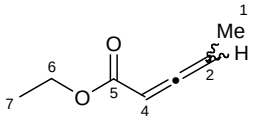
Ethyl 3-iodobut-2-enoate (141)[156]



A solution of ethyl 3-butynoate **139** (2.24 g, 20 mmol, 1 eq.) and LiI (2.95 g, 22 mmol, 1.1 eq.) in AcOH (3 ml) was heated to 70 °C for 5 hours then allowed to cool to 20 °C. Water (10 ml) and EtOAc (15 ml) were added and the organic layer separated then washed with water (10 ml), sat. $NaHCO_3$ (10 ml), and brine (10 ml). The organic layer was concentrated *in vacuo* and flushed through a silica plug (5% EtOAc in hexanes) then concentrated *in vacuo* to afford a red oil (4.14 g, 86%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 6.26 (s, 1H, $C^{3}H$), 4.21 (q, *J* = 7.1 Hz, 2H, $C^{5}H_2$) , 2.71 (s, 3H, $C^{1}H_3$), 1.28 (t, *J* = 7.1 Hz, 3H, $C^{7}H_3$); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 164.3, 125.5, 113.2, 60.2, 21.0, 14.1; **MS** (ESI) *m/z* (rel.%): 262 [MNa^+] (100), 135 (8).

Ethyl penta-2,3-dienoate (144)[157]

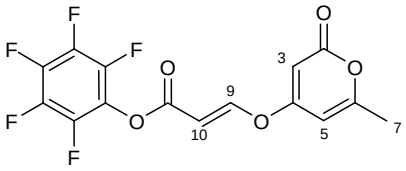


To a stirred solution of ethyl (triphenylphosphoranylidene) acetate **143** (3.48 g, 10 mmol, 1 eq.) in DCM (35 ml) at 22 °C was added TEA (1.11 g, 11 mmol, 1.1 eq.) and the solution stirred for 10 minutes. Propionyl chloride (925 mg, 10 mmol, 1 eq.) was added carefully over 15 minutes and the reaction stirred at 22 °C for 18 h. The solvent was removed *in vacuo* and the residue taken up in ether (20 ml) then filtered. The filtrate was concentrated *in vacuo* and purified by column chromatography (0-5% EtOAc in hexanes).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 5.60 – 5.48 (m, 2H, $C^{4}H/C^{2}H$), 4.15 (q, *J* = 7.1 Hz, 2H, $C^{6}H_2$), 1.74 (dd, *J* = 7.2, 3.3 Hz, 3H, $C^{1}H_3$), 1.24 (t, *J* = 7.1 Hz, 3H, $C^{7}H_3$); **^{13}C-NMR** (100

MHz, *CDCl*$_3$): 212.8, 168.9, 90.1, 87.6, 60.7, 25.9, 14.1; **MS** (ESI) *m/z* (rel.%): 127 [MH$^+$] (100).

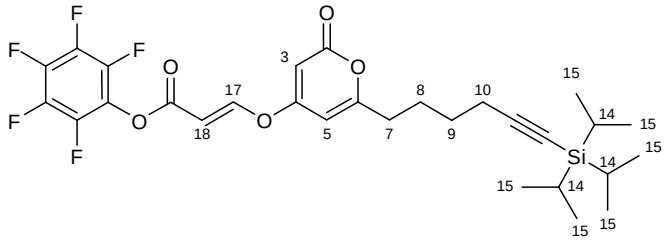
Pentafluorophenyl 3-(6-methyl-2-pyronyl-4-oxy)-acrylate (147)



2-pyrone **9** (54.5 mg, 430 µmol, 1 eq.), TEA (43.4 mg, 430 µmol, 1 eq.) and pentafluorophenyl propiolate **146** (204 mg, 860 µmol, 2 eq.) were stirred in DCM (1 ml) at 45 °C for 16 hours. The solvent was then removed *in vacuo* and the product purified *via* flash column chromatography (20% EtOAc in hexanes) to afford a yellow crystalline powder (102 mg, 82%).

Mpt: 102-105 °C; **^{1}H-NMR** (400 MHz, *CDCl*$_3$): 7.93 (d, *J* = 12.0 Hz, 1H, C^{9}H), 6.05 (d, *J* = 12.0 Hz, 1H, C^{9}H), 5.96 (dq, *J* = 2.2, 0.9 Hz, 1H, C^{5}H), 5.74 (d, *J* = 2.2 Hz, 1H, C^{3}H), 2.29 (t, *J* = 0.9 Hz, 3H, C^{5}H$_3$); **^{13}C-NMR** (101 MHz, *CDCl*$_3$): 166.7, 164.7, 163.1, 161.5, 155.9, 104.3, 98.9, 92.9, 20.2; **^{19}F-NMR** (376 MHz, *CDCl*$_3$): -152.30 – -152.41 (m, 2F), -157.31 (t, *J* = 21.7, 1F), -161.82 – -161.99 (m, 2F); **MS** (ESI) *m/z* (rel.%): 380 [MNa$^+$] (52), 363 [MH$^+$] (100), 301 (14), 279 (26); **HRMS** (ESI) calculated for $C_{15}H_8F_5O_5$ [MH$^+$]: 363.0286, found: 363.0299; **IR** (neat, cm^{-1}): 3106, 2916, 2160, 1731, 1641, 1577, 1516, 1280, 1227, 1185, 997.

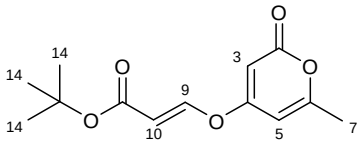
Pentafluorophenyl 3-(6-(6-triisopropylsilyl-hex-5-ynyl)-2-pyronyl-4-oxy)-acrylate (148)



2-pyrone **44** (105 mg, 301 µmol, 1 eq.), TEA (30 mg, 301 µmol, 1 eq.) and pentafluorophenyl propiolate **146** (71.2 mg, 301 µmol, 1 eq.) were stirred in DCM (1 ml) for at 45 °C for 16 hours. The solvent was then removed *in vacuo* and the product purified *via* flash column chromatography (20% EtOAc in hexanes) to afford a waxy yellow powder (65.7 mg, 37%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 7.94 (d, *J* = 12.0 Hz, 1H, $C^{17}H$), 6.06 (d, *J* = 12.0 Hz, 1H, $C^{18}H$), 5.97 (d, *J* = 2.3 Hz, 1H, $C^{5}H$), 5.75 (d, *J* = 2.3 Hz, 1H, $C^{3}H$), 2.57 (t, *J* = 7.6 Hz, 2H, $C^{7}H_2$), 2.32 (t, *J* = 6.9 Hz, 2H, $C^{10}H_2$), 1.79 – 1.89 (m, 2H, $C^{8}H_2$), 1.55 – 1.66 (m, 2H, $C^{9}H_2$), 1.01 – 1.09 (m, 21H, $C^{14}H/C^{15}H_3$); **^{13}C-NMR** (101 MHz, *$CDCl_3$*): 168.1, 166.8, 163.2, 161.5, 155.8, 107.8, 104.3, 98.3, 93.0, 81.1, 33.3, 27.8, 25.5, 19.4, 18.6, 11.2; **^{19}F-NMR** (376 MHz, *$CDCl_3$*): -152.22 – -152.50 (m, 2F), -157.29 (t, *J* = 21.7, 1F), -161.75 – -162.06 (m, 2F); **MS** (ESI) *m/z* (rel.%): 607 [MNa^+] (79), 471 (53), 284 (74), 247 (100), 225 (20); **HRMS** (ESI) calculated for $C_{29}H_{33}F_5NaO_5Si$ [MNa^+]: 607.1910, found: 607.1925; **IR** (neat, cm^{-1}): 3093, 2946, 2865, 2167, 1717, 1637, 1571, 1517, 1181, 1005.

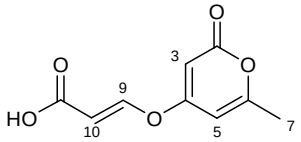
***tert*-Butyl 3-(6-methyl-2-pyronyl-4-oxy)-acrylate (150)**



2-pyrone **9** (100 mg, 0.79 mmol, 1.25 eq.), TEA (101 mg, 1 mmol, 1.6 eq.) and *tert*-butyl propiolate **149** (80 mg, 0.63 mmol, 1 eq.) were stirred in DCM (1 ml) for at 45 °C for 16 hours. The solvent was then removed *in vacuo* and the product purified *via* flash column chromatography (20% EtOAc in hexanes) to afford a yellow crystalline powder (98 mg, 61%).

Mpt: 60-62 °C; **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 7.54 (d, *J* = 12.0 Hz, 1H), 5.90 (d, *J* = 2.2 Hz, 1H), 5.74 (d, *J* = 12.0 Hz, 1H), 5.63 (d, *J* = 2.2 Hz, 1H), 2.25 (s, 3H), 1.48 (s, 9H); **^{13}C-NMR** (101 MHz, *$CDCl_3$*): 167.3, 164.7, 164.0, 163.6, 151.5, 110.0, 99.3, 91.8, 81.3, 28.1, 20.1; **MS** (ESI) *m/z* (rel.%): 275 [MNa^+] (34), 253 [MH^+] (100), 197 (8); **HRMS** (ESI) calculated for $C_{13}H_{17}O_5$: 253.1071, found: 253.1068; **IR** (neat, cm^{-1}): 3082, 2980, 2160, 1720, 1696, 1658, 1623, 1561, 1235, 1149, 1091, 845.

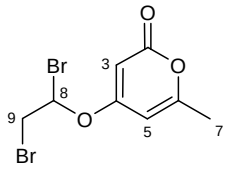
3-(6-Methyl-2-pyronyl-4-oxy)-acrylic acid (151)



A solution of **150** (46 mg, 0.18 mmol, 1 eq.) in THF (1 ml) and TFA (1 ml) was stirred at 22 °C for 30 minutes. The solution was filtered and the solid washed with DCM (3 ml) to afford the desired product as a white powder (30 mg, 86%).

Mpt: degrades > 142 °C; **^{1}H-NMR** (500 MHz, *$CDCl_3$/MeOD*): 7.63 (d, *J* = 12.0 Hz, 1H), 5.91 (d, *J* = 2.2 Hz, 1H), 5.74 (d, *J* = 12.0 Hz, 1H), 5.62 (d, *J* = 2.2 Hz, 1H), 2.21 (s, 3H); **MS** (ESI) *m/z* (rel.%): 219 [MNa^+] (33), 197 [MH^+] (100), 141 (15), 102 (13); **HRMS** (ESI) calculated for $C_9H_9O_5$: 197.0444, found: 197.0449; **IR** (neat, cm^{-1}): 3093, 2161, 2025, 1977, 1722, 1644, 1575, 1324, 1236, 1191, 1166, 1142, 1096, 982, 832.

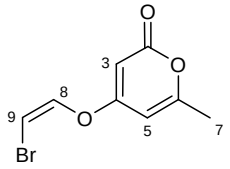
4-(1,2-Dibromoethoxy)-6-methyl-2-pyrone (152)



To a solution of **113** (1.52 g, 10 mmol, 1 eq.) in DCM (10 ml) under nitrogen at -78 °C, was added Br_2 (1.6 g, 10 mmol, 1 eq.) in DCM (5 ml) over 15 minutes. The solution was allowed to warm to 20 °C over 3 hours, the solvent and unreacted bromine was subsequently removed *in vacuo* to afford the crude product as a light brown powder (2.96 g, 95%). The crude material was used without further purification due to degradation upon silica.

^{1}H-NMR (400 MHz, *$CDCl_3$*): 5.88 (m, 1H, C^5H), 5.72 (d, *J* = 2.0 Hz, 1H, C^3H), 4.07-4.01 (m, 1H, C^8H), 3.93-4.00 (m, 2H, C^9H), 2.26 (s, 3H, C^7H_3); **MS** (ESI) *m/z* (rel.%): 315 [^{81}Br/^{81}Br-MH^+] (41), 313 [^{81}Br/^{79}Br-MH^+] (92), 311 [^{79}Br/^{79}Br-MH^+] (45); **HRMS** (ESI) calculated for $C_8H_8{}^{79}Br_2O_3Na$: 332.87, found: 332.9; **IR** (DCM, cm^{-1}): 3103, 3059, 2926, 1726, 1650, 1631, 1542, 1444, 1388, 1231, 1172, 1069.

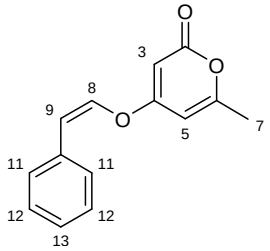
(*Z*)-4-(1-bromovinyloxy)-6-methyl-2-pyrone (*Z*-153)



A solution of **152** (3.12 g, 10 mmol, 1 eq.) and DBU (1.68 g, 20 mmol, 2 eq.) in THF (40 ml) was refluxed under argon for 16 hours. The reaction allowed to cool then quenched by addition of water (80 ml) and the product extracted from ether (3 × 80 ml). The combined organic extracts were dried over $MgSO_4$, concentrated *in vacuo* and purified *via* flash column chromatography (20-40 % Ether in pet ether) to afford a brown powder (401 mg, 17.4%).

Rf = 0.3 (40% Ether); **^{1}H-NMR** (400 MHz, *$CDCl_3$*): (400 MHz, *$CDCl_3$*): 7.03 (d, *J* = 4.4 Hz, 1H, C^8H), 5.97 (m, 1H, C^5H), 5.91 (d, *J* = 4.4 Hz, 1H, C^9H), 5.72 (d, *J* = 2.0 Hz, 1H, C^3H), 2.26 (s, 3H, C^7H_3); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 167.5, 163.8, 163.7, 139.9, 99.5, 95.1, 90.7, 20.0; **MS** (ESI) *m/z* (rel.%): 231 [MH^+] (63), 233 (61); **HRMS** (ESI) calculated for $C_8H_7{}^{79}BrO_3Na$ [MNa^+]: 252.9471, found: 252.9472; **IR** (DCM, cm^{-1}): 2960, 2928, 1717, 1640, 1572, 1447, 1408, 1317, 1234, 1139, 1055.

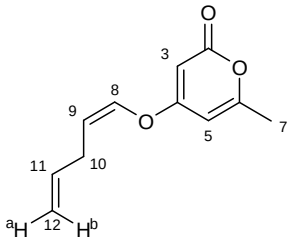
(*Z*)-6-Methyl-4-(styrenyloxy)-2-pyrone (154)



A solution of Pd_2dba_3 (22.9 mg, 0.025 mmol, 5 mol%) and triphenylphosphine (13.1 mg, 0.05 mmol, 10 mol%) in dry THF(1.2ml) was stirred at 40 °C under argon for 20 minutes. A solution of phenylboronic acid (122 mg, 1 mmol, 2 eq.) and organohalide ***Z*-153** (116 mg, 0.5 mmol, 1 eq.) in THF (0.4ml) was then added and the mixture heated to 70 °C for 15 minutes. 2M Na_2CO_3 (0.8 ml) was then added and the mixture stirred at 70 °C for 2 hours. The reaction was allowed to cool then diluted with ether (3ml) and the organic layer removed. The aqueous layer was then washed with ether (2 x 3 ml) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was then purified *via* flash column chromatography (20% EtOAc in heptane) to afford an orange crystalline solid (68 mg, 59.6%).

Rf = 0.12 (20% EtOAc in heptane); **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 7.53 (d, *J* = 7.6 Hz, 2H, $C^{11}H$), 7.35 (t, *J* = 7.6 Hz, 2H, $C^{12}H$), 7.30 (d, *J* = 7.6 Hz, 1H, $C^{13}H$), 6.54 (d, *J* = 6.8 Hz, 1H, $C^{8}H$), 5.99 (m, 1H, $C^{5}H$), 5.89 (d, *J* = 6.8 Hz, 1H, $C^{9}H$), 5.64 (d, *J* = 1.7 Hz, 1H, $C^{3}H$), 2.23 (s, 3H, $C^{7}H_3$); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 168.1, 164.1, 163.4, 136.6, 133.1, 129.1, 128.5, 127.9, 115.7, 99.7, 90.5, 20.0; **MS** (ESI) *m/z* (rel.%): 229 [MH^+] (100); **HRMS** (ESI) calculated for $C_{14}H_{12}O_3Na$ [MNa^+]: 251.0679, found: 251.0685; **IR** (DCM, cm^{-1}): 3064, 3027, 2926, 2854, 1718, 1648, 1571, 1447, 1391, 1320, 1235, 1174, 1140, 1050.

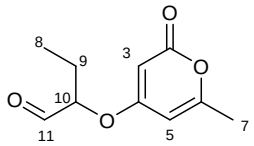
(Z)-6-Methyl-4-(penta-Z-1,4-dienyloxy)-2-pyrone (155)



A solution of allylboronic acid pinacol ester (168 mg, 1.0 mmol, 2 eq.), organohalide ***Z*-153** (116 mg, 0.5 mmol, 1 eq.) and palladium complex **27** (20 mg, 0.025 mmol, 5 mol %) were stirred in THF (1.6 ml) under nitrogen at 70 ℃ for 10 minutes. To this solution aqueous 2M Na_2CO_3 (0.8 ml) was added and the reaction stirred for up to 5 hours at 70 ℃. The solution was allowed to cool to 20 ℃ diluted with ether (3 ml), and the organic layer separated. The aqueous layer was then extracted with ether (3 × 3 ml) and the combined organic extracts washed with brine, dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The product was then purified *via* flash column chromatography (20% EtOAc in hexanes) to afford an orange oil (53.8 mg, 56%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 6.37 (dt, *J* = 6.8, 1.4 Hz, 1H, $C^{8}H$), 5.88 (m, 1H, $C^{5}H$), 5.80 (ddt, *J* = 17.0, 10.2, 6.2 Hz, 1H, $C^{11}H$), 5.50 (d, *J* = 1.9 Hz, 1H, $C^{3}H$), 5.15 (td, *J* = 7.5, 6.0 Hz, 1H, $C^{9}H$), 5.07 (dq, *J* = 17.0, 1.6 Hz, 1H, $C^{12}H^{b}$), 5.02 (dd, *J* = 10.2, 1.6 Hz, 1H, $C^{12}H^{a}$), 2.92-2.87 (m, 2H, $C^{10}H_2$), 2.24 (s, 3H, $C^{7}H_3$); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 168. 6, 164.4, 163.1, 137.1, 135.2, 115.6, 115.6, 99.8, 89.9, 28.2, 19.9; **MS** (ESI) *m/z* (rel.%): 193 [MH^+] (100); **HRMS** (ESI) calculated for $C_{11}H_{12}O_3Na$ [MNa^+]: 215.0679, found: 215.0680; **IR** (neat, cm^{-1}): 3082, 2962, 2925, 1699, 1645, 1566, 1450, 1413, 1324, 1254, 1146, 1054, 998.

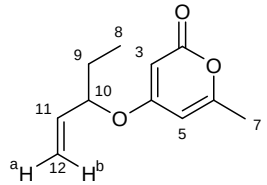
2-(6-Methyl-2-pyron-4-yloxy)-butyraldehyde (165)



To a solution of oxalyl chloride (826 mg, 6.5 mmol, 1.3 eq.) in DCM (15 ml) at -78 °C was added DMSO (1.01 g, 13 mmol, 2.6 eq.) in DCM (15 ml) carefully over 15 minutes. The reaction was stirred for 30 minutes at -78 °C then a solution of **170** (990 mg, 5 mmol, 1 eq.) in DCM (15 ml) was added carefully over 20 minutes and the reaction stirred for a further 30 minutes at -78 °C. Triethylamine (1.80 g, 18 mmol, 3.6 eq.) was added over 15 minutes and the reaction stirred for 1 h at -78 °C then allowed to warm to ambient temperature. The solvent was removed *in vacuo* and the residue taken up in ether then passed through a silica plug, eluting with ether. The solvent was then removed *in vacuo* to afford the desired product as a colourless oil (978 mg, >99%).

^{1}H-NMR (400 MHz, $CDCl_3$): 9.57 (d, *J* = 1.2 Hz, 1H, $C^{11}H$), 5.88 (d, *J*= 2.1 Hz, 1H, $C^{5}H$), 5.23 (d, *J* = 2.1 Hz, 1H, $C^{3}H$), 4.47 (ddd, *J* = 7.0, 5.4, 1.2 Hz, 1H, $C^{10}H$), 2.22 (s, 3H, $C^{7}H_3$), 1.85-2.00 (m, 2H, $C^{9}H_2$), 1.03 (t, *J* = 7.4 Hz, 3H, $C^{8}H_3$); **^{13}C-NMR** (100 MHz, *$CDCl_3$*); 198.4, 169.4, 164.4, 163.0, 100.3, 89.1, 82.9, 23.0, 20.0, 9.1; **IR** (DCM, cm^{-1}): 3608, 3376, 3061, 2965, 1710, 1650, 1566, 1450, 1413, 1322, 1244, 1146, 1093.

6-Methyl-4-(pent-1-en-3-yloxy)-2-pyrone (167)

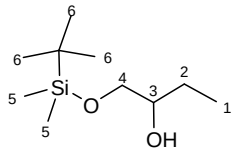


4-hydroxy-6-methyl-2-pyrone **9** (504 mg, 4 mmol, 1 eq.), 3-hydroxypent-1-ene (516 mg, 6 mmol, 1.5 eq.) and triphenylphosphine (1.57 g, 6 mmol, 1.5 eq.) were dissolved in THF (8 ml) under nitrogen at 0 °C. DIAD (1.21 g, 6 mmol, 1.5 eq.) was then added carefully over 15 minutes. The reaction was stirred for 16 h at 20 °C and then the solvent removed *in vacuo*. The crude product was purified *via* flash column chromatography (10-40% EtOAc in hexanes) to afford a pale yellow oil (130 mg, 17%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 5.77 (m, 1H, $C^{5}H$), 5.70 (ddd, *J* = 17.3, 10.7, 6.5 Hz, 1H, $C^{11}H$), 5.35 (d, *J* = 2.2 Hz, 1H, $C^{3}H$), 5.26 (dt, *J* = 10.7, 1.0 Hz, 1H, $C^{12}H^{a}$), 5.22 (dt, *J* = 17.4, 1.0 Hz, 1H, $C^{12}H^{b}$), 4.50 (q, *J* = 6.5 Hz, 1H, $C^{10}H$), 2.17 (s, 3H, $C^{7}H_3$), 1.72 (m, 2H, $C^{9}H_2$), 0.93 (t, *J* = 7.44 Hz, 3H, $C^{8}H_3$); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 169.9, 165.3, 162.2,

135.3, 118.3, 101.1, 89.4, 81.3, 28.1, 20.0, 9.4; **MS** (ESI) *m/z* (rel.%): 217 [MNa^+] (100), 157 (4), 122 (2); **HRMS** (ESI) calculated for $C_{11}H_{14}O_3Na$ [MNa^+]: 217.0835, found: 217.0844; **IR** (neat, cm^{-1}): 3086, 2971, 2936, 2879, 1731, 1650, 1563, 1450, 1319, 1243.

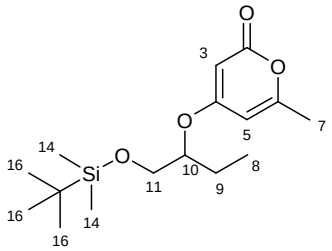
1-(*tert*-Butyl-dimethyl-silanyloxy)-butan-2-ol (168)



A solution of *tert*-butyl-dimethylsilyl chloride (3.01 g, 20 mmol, 1 eq.), TEA (4.04 g, 40 mmol, 2 eq.) and butane-1,2-diol (2.70 g, 30 mmol, 1.5 eq.) under nitrogen in DCM (25 ml), was stirred at 20 °C for 16 h. The reaction was then quenched with ice cold water (15 ml) and the aqueous layer removed. The organic layer was then washed with brine (15 ml) and dried over $MgSO_4$ then concentrated *in vacuo* to afford the crude material. The product was purified *via* flash column chromatography (40% EtOAc in toluene) to afford a colourless oil (3.43 g, 84.1%).

^{1}H-NMR (400 MHz, $CDCl_3$): 3.63 (dd, *J* = 9.7, 3.3 Hz, 1H, C^4H), 3.55 (ddt, *J* = 10.5, 7.2, 3.3 Hz, 1H, C^4H), 3.39 (dd, *J* = 9.7, 7.2 Hz, 1H, C^3H), 1.40-1.48 (m, 2H, C^2H_2), 0.95 (t, *J* = *7.5* Hz, 3H, C^1H_3), 0.89 (s, 9H, C^6H_3), 0.07 (s, 6H, C^5H_3); **^{13}C-NMR** (100 MHz, *$CDCl_3$*); 73.3, 67.0, 26.0, 21.7, 18.4, 10.0, -5.3, -5.3; **MS** (ESI) *m/z* (rel.%): 205 [MH^+] (100); **IR** (neat, cm^{-1}): 3406, 2955, 2929, 2858, 1462, 1253, 1092, 834, 774.

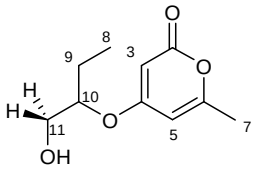
4-[1-(*tert*-Butyl-dimethyl-silanyloxymethyl)-propoxy]-6-methyl-2-pyrone (169)



4-Hydroxy-6-methyl-2-pyrone (504 mg, 4 mmol, 1 eq.), alcohol **168** (1.22 g, 6 mmol, 1.5 eq.) and triphenylphosphine (1.57 g, 6 mmol, 1.5 eq.) were dissolved in DCM (8 ml) under nitrogen at 0 °C. DIAD (1.21 g, 6 mmol, 1.5 eq.) was then added carefully over 15 minutes. The reaction was stirred for 16 h at 20 °C and then the solvent removed *in vacuo*. The crude product was purified *via* flash column chromatography (20% EtOAc in hexanes) to afford a colourless oil (1.23 g, 98.4%).

Rf = 0.56 (20% EtOAc); **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 5.71 (dq, *J*= 1.9, 0.8 Hz, 1H, C^5H), 5.36 (d, *J* = 1.9 Hz, 1H, C^3H), 4.17 (p, *J* = 5.4 Hz, 1H, $C^{10}H$), 3.66 (s, 1H, $C^{11}H$), 3.64 (d, *J* = 1.3 Hz, 1H, $C^{11}H$), 2.11-2.15 (m, 3H, C^7H_3), 1.53-1.69 (m, 2H, C^9H_2), 0.87 (t, *J* = 7.5 Hz, 3H, C^8H_3), 0.79 (s, 9H, $C^{16}H_3$), -0.03 (s, 3H, $C^{14}H_3$), -0.04 (s, 3H, $C^{14}H_3$); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 170.5, 165.3, 162.1, 100.9, 88.4, 80.9, 63.8, 25.8, 23.4, 19.8, 18.2, 9.5, -5.4, -5.4; **MS** (ESI) *m/z* (rel.%): 335 [MNa^+] (100), 313 [MH^+] (2); **HRMS** (ESI) calculated for $C_{16}H_{28}O_4NaSi$ [M^+]: 335.1649, found: 335.1640; **IR** (neat, cm^{-1}): 2929, 2883, 2857, 1736, 1651, 1563, 1450, 1414, 1320, 1249, 1139, 1036, 1001.

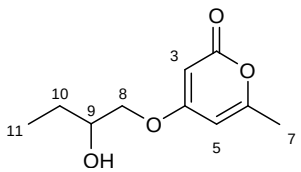
4-(1-Hydroxymethyl-propoxy)-6-methyl-2-pyrone (170)



A solution of **169** (11.0 g, 35.3 mmol, 1 eq.) in THF (20 ml), water (20 ml) and acetic acid (60 ml) was stirred for 16 hours at 20 °C. The solution was concentrated *in vacuo* and the resulting product was purified *via* flash column chromatography (2-4% MeOH in DCM) to afford a pale yellow oil (6.98 g, >99%).

Rf = 0.21 (5% MeOH in DCM); **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 5.80 (dq, *J* = 2.2, 0.8 Hz, 1H, C^5H), 5.46 (d, *J* = 2.2 Hz, 1H, C^3H), 4.28 (tdd, *J* = 5.9, 5.9, 4.1 Hz, 1H, $C^{10}H$), 3.81 (dd, *J* = 12.1, 4.1 Hz, 1H, $C^{11}H$), 3.68 (dd, *J* = 12.1, 5.9 Hz, 1H, $C^{11}H$), 2.18 (q, *J* = 0.8 Hz, 3H, C^7H_3), 2.07 (s, 1H, OH), 1.66-1.74 (m, 2H, C^9H_2), 0.93 (t, *J* = 7.5 Hz, 3H, C^8H_3); **^{13}C-NMR** (100 MHz, *$CDCl_3$*) 170.5, 165.6, 162.5, 101.2, 88.7, 81.2, 63.4, 23.2, 20.0, 9.6; **MS** (ESI) *m/z* (rel.%): 221 [MNa^+] (100), 199 [MH^+] (6), 133; **HRMS** (ESI) calculated for $C_{10}H_{14}O_4Na$ [M^+]: 221.0784, found: 221.0790;

4-(2-Hydroxy-butoxy)-6-methyl-2-pyrone (171)

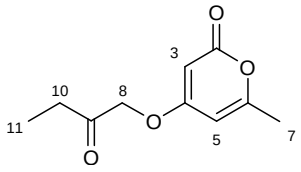


To a solution of **169** (936 mg, 3 mmol, 1 eq.) in THF (10 ml) was added TBAF (1M in THF) (3 ml, 3 mmol, 1 eq.) at 20 °C. The solution was stirred for 2 hours then quenched with 2M HCl (3 ml) and the product extracted with ether (3 × 10 ml). The combined organic extracts were then concentrated in *vacuo* and the resulting product was purified *via*

flash column chromatography (5% MeOH in DCM) to afford a colourless oil (392 mg, 66%).

Rf = 0.35 (5% MeOH in DCM); **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 5.80 (d, *J* = 2.2 Hz, 1H, $C^{5}H$), 5.39 (d, *J* = 2.2 Hz, 1H, $C^{3}H$), 3.82-3.93 (m, 2H, $C^{8}H$), 3.71-3.74 (m, 1H, $C^{9}H$), 2.19 (s, 3H, $C^{7}H_3$), 1.53-1.61 (m, 2H, $C^{10}H_2$), 1.00 (t, *J* = 7.5 Hz, 3H, $C^{11}H_3$); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 170.5, 165.1, 162.4, 100.5, 88.2, 72.5, 70.8, 26.2, 22.0, 19.9, 9.8: **MS** (ESI) *m/z* (rel.%): 221 [MNa^+] (100), 199 [MH^+] (6), 133; **HRMS** (ESI) calculated for $C_{10}H_{14}O_4Na$ [MNa^+]: 221.0784, found: 221.0790; **IR** (neat, cm^{-1}): 3325, 2928, 2884, 2857, 1705, 1651, 1565, 1463, 1361, 1253, 1049, 835, cm^{-1}.

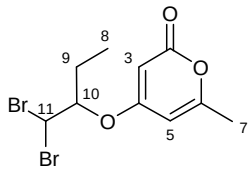
6-Methyl-4-(2-oxo-butoxy)-2-pyrone (172)



A solution of **171** (99 mmg, 0.5 mmol, 1 eq.) and Dess-Martin periodinane (212 mg, 0.5 mmol, 1 eq.) in DCM (1 ml) was stirred at 20 °C under nitrogen for 2 hours. The reaction was quenched by addition of sat. $NaHCO_3$ solution (10 ml) and sodium thiosulfate (120 mg) and stirred until the precipitate had disappeared (*ca.* 10 mins). The organic layer was separated and the aqueous layer extracted with DCM (5 ml). The combined organic extracts were washed with brine (5 ml) and dried over $MgSO_4$, then concentrated *in vacuo*. The crude product was then flushed through a silica plug eluting with 5% MeOH in DCM to afford a yellow oil (34 mg, 34.7%).

Rf = 0.61 (5% MeOH in DCM); **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 5.87 (d, *J* = 2.2 Hz, 1H, $C^{5}H$), 5.24 (d, *J* = 2.2 Hz, 1H, $C^{3}H$), 4.55 (s, 2H, $C^{8}H$), 2.49 (q, *J* = 7.3 Hz, 1H, $C^{10}H$), 2.20 (s, 3H, $C^{7}H_3$), 1.10 (t, *J* = 7.3 Hz, 3H, $C^{11}H_3$); **^{13}C-NMR** (100 MHz, *$CDCl_3$*): 204.0, 169.5, 164.5, 162.8, 100.1, 88.4, 71.8, 32.4, 19.9, 7.0; **MS** (ESI) *m/z* (rel.%): 219 [MNa^+] (100), 197 [MH^+] (5), 172 (3); **HRMS** (ESI) calculated for $C_{10}H_{12}O_4Na$ [MNa^+]: 219.0628, found: 219.0636; **IR** (DCM, cm^{-1}): 3666, 2956, 2930, 2856, 1713, 1650, 1570, 1453, 1411, 1321, 1250, 1096.

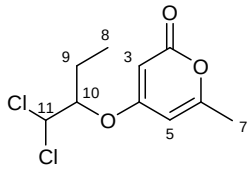
4-(1-Dibromomethyl-propoxy)-6-methyl-2-pyrone (175a)



To a stirred solution of triphenyl phosphite (748 mg, 2.4 mmol, 1.1 eq.) in DCM (10 ml) under argon at -60 °C, was added Br_2 (405 mg, 2.53 mmol, 1.15 eq.) carefully over 10 minutes. Anhydrous TEA (267 mg, 2.64 mmol, 1.2 eq.) was then added carefully over 10 minutes, followed by the carefully addition aldehyde **165** (430 mg, 2.2 mmol, 1 eq.) in DCM (1 ml) over 5 minutes. The reaction was maintained at -60 °C for 30 minutes then allowed to warm slowly to ambient temperature over 18 hours, followed by heating to reflux for a further 2 hours. The solvent was removed *in vacuo* and the reaction mixture purified *via* flash column chromatography (20% EtOAc in pet ether) to afford a white crystalline solid (265 mg, 36%).

Rf = 0.16 (20% EtOAc in pet ether); Mpt: 99-100 °C; **^{1}H-NMR** (500 MHz, *$CDCl_3$*): 5.86 (dq, *J* = 2.3, 0.8 Hz, 1H, C^5H), 5.83 (d, *J* = 4.1 Hz, 1H, $C^{10}H$), 5.43 (d, *J* = 2.3, 1H, C^3H), 4.45 (td, *J* = 8.0, 4.1 Hz, 1H, $C^{11}H$), 2.22 (app. s, 3H, C^7H_3), 2.07 – 1.86 (m, 2H, C^9H_2), 1.01 (t, *J* = 7.5 Hz, 3H, C^8H_3); **^{13}C-NMR** (126 MHz, *$CDCl_3$*): 169.5, 164.5, 163.0, 100.4, 88.8, 82.4, 71.2, 22.9, 19.9, 9.3; **MS** (ESI) *m/z* (rel.%): 343 [^{81}Br/^{81}Br -MH^+] (44), 341 [^{79}Br/^{81}Br -MH^+] (100), 339 [^{79}Br/^{79}Br -MH^+] (45); **HRMS** (ESI) calculated for $C_{10}H_{13}{}^{79}Br_2O_3$: 338.9226, found: 338.9223; **IR** (neat, cm^{-1}): 3079, 3017, 2976, 2942, 2159, 1703, 1646, 1558, 1443, 1409, 1248, 1230, 1145, 996, 829.

4-(1-Dichloromethyl-propoxy)-6-methyl-2-pyrone (175b)

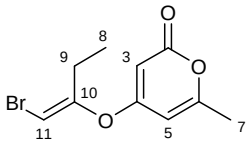


To a stirred solution of triphenyl phosphite (748 mg, 2.4 mmol, 1.1 eq.) in DCM (10 ml) under argon at -20 °C, was bubbled Cl_2 until the solution turned yellow. Additional triphenyl phosphite (~10 mg) was then added carefully until the yellow colouration disappeared. Anhydrous TEA (267 mg, 2.64 mmol, 1.2 eq.) was then added carefully over 10 minutes, followed by the carefully addition aldehyde **165** (430 mg, 2.2 mmol, 1 eq.) over 5 minutes. The reaction was maintained at -20 °C for 30 minutes then allowed to warm slowly to ambient temperature over 18 hours, followed by heating to reflux for a

further 2 hours. The solvent was removed *in vacuo* and the reaction mixture purified *via* flash column chromatography (20% EtOAc in pet ether) to afford a white crystalline solid (228 mg, 41%).

Mpt: 84-85 °C; **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 5.87 (qd, *J* = 2.2, 0.8 Hz, 1H, $C^{5}H$), 5.79 (d, *J* = 3.8 Hz, 1H, $C^{11}H$), 5.41 (d, *J* = 2.2 Hz, 1H, $C^{3}H$), 4.40 (dt, *J* = 7.8, 3.8 Hz, 1H, $C^{10}H$), 2.23 (d, *J* = 0.8 Hz, 3H, $C^{7}H_3$), 1.89 – 2.10 (m, 2H, $C^{9}H_2$), 1.01 (t, *J* = 7.5 Hz, 3H, $C^{8}H_3$); **^{13}C-NMR** (101 MHz, *$CDCl_3$*): 169.4, 164.6, 163.0, 100.5, 88.8, 82.6, 43.7, 24.4, 19.9, 9.5; **MS** (ESI) *m/z* (rel.%): 255 [^{37}Cl/^{37}Cl-MH^+] (10), 253 [^{37}Cl/^{35}Cl-MH^+] (65), 251 [^{37}Cl/^{37}Cl-MH^+] (100); **HRMS** (ESI) calculated for $C_{10}H_{13}{}^{35}Cl_2O_3$: 251.0236, found: 251.0239; **IR** (DCM, cm^{-1}): 2978, 2883, 1714, 1652, 1568, 1448, 1411, 1322, 1257, 1241, 1181, 1145, 1037, 1004.

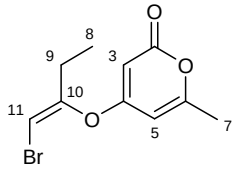
4-(*E*-1-Bromomethylene-propoxy)-6-methyl-2-pyrone (*E*-176a)



A solution of dibromide **175a** (340 mg, 1 mmol, 1 eq.) and DBU (304 mg, 2 mmol, 2 eq.) in THF (3 ml) was stirred at 70 °C for 24 hours. The solvent was then removed *in vacuo* and the reaction mixture purified *via* flash column chromatography (20% EtOAc in pet ether) to afford a pale yellow oil (94 mg, 36%).

^{1}H-NMR (500 MHz, *$CDCl_3$*): 6.00 (s, 1H, $C^{11}H$), 5.87 (dq, *J* = 2.2, 0.9 Hz, 1H, $C^{5}H$), 5.49 (d, *J* = 2.2 Hz, 1H, $C^{3}H$), 2.48 (q, *J* = 7.5 Hz, 2H, $C^{9}H_2$), 2.25 (d, *J* = 0.8 Hz, 3H, $C^{7}H_3$), 1.08 (t, *J* = 7.6 Hz, 3H, $C^{8}H_3$); **^{13}C-NMR** (126 MHz, *$CDCl_3$*): 169.9, 168.5, 163.6, 163.5, 100.1, 99.8, 89.9, 24.4, 20.0, 7.9; **MS** (ESI) *m/z* (rel.%): 283 [^{81}Br-MNa^+] (42), 281 [^{79}Br-MNa^+] (42), 261 [^{81}Br-MH^+] (98), 259 [^{79}Br-MH^+] (100); **HRMS** (ESI) calculated for $C_{10}H_{12}{}^{79}BrO_3$: 258.9964, found: 258.9964; **IR** ($CHCl_3$, cm^{-1}): 2916, 2848, 2158, 1732, 1716, 1652, 1568, 1456, 1226, 1172, 1128, 996, 818, 719.

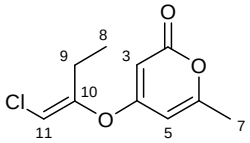
4-(*Z*-1-Bromomethylene-propoxy)-6-methyl-2-pyrone (*Z*-176a)



A solution of dibromide **175a** (340 mg, 1 mmol, 1 eq.) and DBU (304 mg, 2 mmol, 2 eq.) in THF (3 ml) was stirred at 70 °C for 24 hours. The solvent was then removed *in vacuo* and the reaction mixture purified *via* flash column chromatography (20% EtOAc in pet ether) to afford a pale yellow oil (167 mg, 65%).

^{1}H-NMR (500 MHz, *$CDCl_3$*): 5.95 (t, *J* = 1.3 Hz, 1H, $C^{11}H$), 5.92 (dq, *J* = 2.2, 0.8 Hz, 1H, $C^{5}H$), 5.40 (dq, *J* = 2.2, 0.5 Hz, 1H, $C^{3}H$), 2.29 (qd, *J* = 7.5, 1.3 Hz, 2H, $C^{9}H_2$), 2.25 (dd, *J* = 0.8, 0.5 Hz, 3H, $C^{7}H_3$), 1.11 (t, *J* = 7.5 Hz, 3H, $C^{8}H_3$); **^{13}C-NMR** (126 MHz, *$CDCl_3$*): 169.0, 164.3, 163.5, 155.0, 99.5, 97.9, 91.0, 23.3, 20.0, 10.4; **MS** (ESI) *m/z* (rel.%): 283 [^{81}Br-MNa^+] (42), 281 [^{79}Br-MNa^+] (42), 261 [^{81}Br-MH^+] (98), 259 [^{79}Br-MH^+] (100); **HRMS** (ESI) calculated for $C_{10}H_{12}{}^{79}BrO_3$: 258.9964, found: 258.9964; **IR** (neat, cm^{-1}): 3089, 2975, 2939, 1712, 1642, 1565, 1446, 1405, 1221, 1174, 1138, 998, 819.

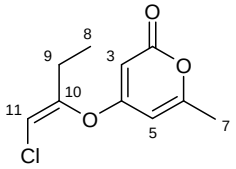
4-(*E*-1-Chloromethylene-propoxy)-6-methyl-2-pyrone (*E*-176b)



A solution of dichloride **175b** (187 mg, 0.75 mmol, 1 eq.), NaI (337 mg, 2.25 mmol, 3 eq.) and DBU (227 mg, 1.5 mmol, 2 eq.) in DME (5 ml) was stirred at 90 °C for 24 hours. The solvent was then removed *in vacuo* and the reaction mixture purified *via* flash column chromatography (20% EtOAc in pet ether) to afford a pale yellow oil (6 mg, 4%).

^{1}H-NMR (500 MHz, *$CDCl_3$*): 5.98 (s, 1H, $C^{11}H$), 5.88 (dq, *J* = 2.2, 0.9 Hz, 1H, $C^{5}H$), 5.48 (dq, *J* = 2.2, 0.5 Hz, 1H, $C^{3}H$), 2.46 (q, *J* = 7.5 Hz, 2H, $C^{9}H_2$), 2.24 – 2.25 (m, 3H, $C^{7}H_3$), 1.08 (t, *J* = 7.5 Hz, 3H, $C^{8}H_3$); **^{13}C-NMR** (126 MHz, *$CDCl_3$*): 169.3, 164.3, 163.5, 154.2, 110.6, 99.5, 90.8, 21.6, 20.0, 10.4; **MS** (ESI) *m/z* (rel.%): 217 [^{37}Cl-MH^+] (33), 215 [^{35}Cl-MH^+] (100); **HRMS** (ESI) calculated for $C_{10}H_{12}{}^{35}ClO_3$: 215.0469, found: 215.0477.

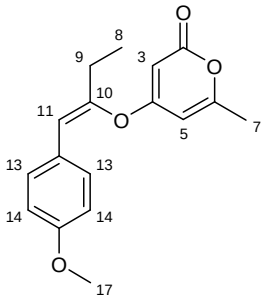
4-(*Z*-1-Chloromethylene-propoxy)-6-methyl-2-pyrone (*Z*-176b)



A solution of dichloride **175b** (187 mg, 0.75 mmol, 1 eq.), NaI (337 mg, 2.25 mmol, 3 eq.) and DBU (227 mg, 1.5 mmol, 2 eq.) in DME (5 ml) was stirred at 90 °C for 24 hours. The solvent was then removed *in vacuo* and the reaction mixture purified *via* flash column chromatography (20% EtOAc in pet ether) to afford a pale yellow oil (8 mg, 5%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 5.91 (dq, *J* = 2.1, 0.8 Hz, 1H, $C^{5}H$), 5.86 (t, *J* = 1.4 Hz, 1H, $C^{11}H$), 5.40 (d, *J* = 2.1 Hz, 1H, $C^{3}H$), 2.27 (qd, *J* = 7.4, 1.4 Hz, 2H, $C^{9}H_2$), 2.25 (d, *J* = 0.8 Hz, 3H, $C^{7}H_3$), 1.10 (t, *J* = 7.4 Hz, 3H, $C^{8}H_3$); **^{13}C-NMR** (126 MHz, *$CDCl_3$*): 169.3, 164.3, 163.5, 154.2, 110.6, 99.5, 90.8, 21.6, 20.0, 10.4; **MS** (ESI) *m/z* (rel.%): 217 [^{37}Cl-MH^+] (33), 215 [^{35}Cl-MH^+] (100); **HRMS** (ESI) calculated for $C_{10}H_{12}{}^{35}ClO_3$: 215.0469, found: 215.0477; **IR** ($CHCl_3$, cm^{-1}): 2979, 2362, 1712, 1651, 1570, 1405, 1227, 1178, 907, 732.

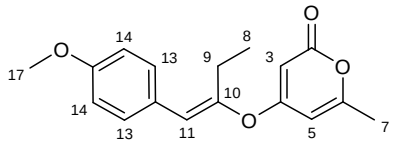
4-[1-(*Z*-4-Methoxy-benzylidene)-propoxy]-6-methyl-2-pyrone (*Z*-178)



Prepared according to General Procedure A using ***Z*-176a** (20 mg, 77 μmol, 1 eq.), **177** (24 mg, 158 μmol, 2 eq.) and *CatCat* (**27**) (1.2 mg, 1.5 μmol, 2 mol%) to afford the title compound as a pale yellow oil (15 mg, 68%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 7.23 – 7.27 (m, 2H, $C^{13}H$), 6.77 – 6.82 (m, 2H, $C^{14}H$), 5.97 (t, *J* = 1.0 Hz, 1H, $C^{11}H$), 5.93 (dq, *J* = 2.1, 0.9 Hz, 1H, $C^{5}H$), 5.46 (dq, *J* = 2.1, 0.5 Hz, 1H, $C^{3}H$), 3.77 (s, 3H, $C^{17}H_3$), 2.31 (qd, *J* = 7.4, 1.0 Hz, 2H, $C^{9}H_2$), 2.23 (dd, *J* = 0.9, 0.5 Hz, 3H, $C^{7}H_3$), 1.14 (t, *J* = 7.4 Hz, 3H, $C^{8}H_3$); **^{13}C-NMR** (101 MHz, *$CDCl_3$*): 168.0, 164.7, 163.3, 158.8, 149.6, 129.6, 126.0, 115.7, 113.9, 99.7, 90.4, 55.2, 26.4, 20.1, 11.5; **MS** (ESI) *m/z* (rel.%): 287 [MH^+] (100); **HRMS** (ESI) calculated for $C_{17}H_{19}O_4$: 287.1278, found: 287.1274; **IR** (neat, cm^{-1}): 2967, 2935, 2838, 1721, 1647, 1606, 1564, 1510, 1446, 1405, 1252, 1224, 1175, 1135, 1031, 820.

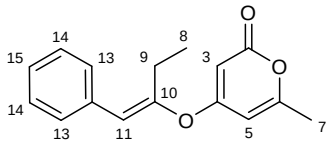
4-[*E*-1-(4-Methoxy-benzylidene)-propoxy]-6-methyl-2-pyrone (*E*-178)



Prepared according to General Procedure A using ***E*-176a** (20 mg, 77 µmol, 1 eq.), **177** (24 mg, 158 µmol, 2 eq.) and *CatCat* (**27**) (1.2 mg, 1.5 µmol, 2 mol%) to afford the title compound as a pale yellow oil (21.5 mg, 98%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 7.15 – 7.19 (m, 2H, $C^{13}H$), 6.88 – 6.92 (m, 2H, $C^{14}H$), 6.20 (s, 1H, $C^{11}H$), 5.93 (dq, *J* = 2.2, 0.9 Hz, 1H, $C^{5}H$), 5.60 (d, *J* = 2.2 Hz, 1H, $C^{3}H$), 3.82 (s, 3H, $C^{17}H_3$), 2.48 (q, *J* = 7.5 Hz, 2H, $C^{9}H_2$), 2.25 (d, *J* = 0.9 Hz, 3H, $C^{7}H_3$), 1.12 (t, *J* = 7.5 Hz, 3H, $C^{8}H_3$); **^{13}C-NMR** (101 MHz, *$CDCl_3$*): 167.0, 164.9, 163.1, 158.9, 152.3, 129.6, 126.3, 118.9, 114.0, 100.1, 90.3, 55.3, 22.6, 20.0, 11.5; **MS** (ESI) *m/z* (rel.%): 287 [MH^+] (100); **HRMS** (ESI) calculated for $C_{17}H_{19}O_4$: 287.1278, found: 287.1274; **IR** (neat, cm^{-1}): 2973, 2934, 2838, 1723, 1645, 1607, 1563, 1511, 1446, 1404, 1249, 1227, 1174, 1133, 821.

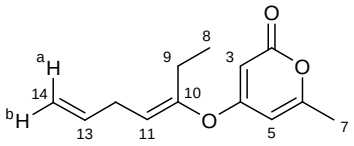
4-[*E*-1-benzylidene-propoxy]-6-methyl-2-pyrone (*E*-179)



Prepared according to General Procedure A using ***E*-176a** (15 mg, 57.7 µmol, 1 eq.), **57** (19 mg, 158 µmol, 2.7 eq.) and *CatCat* (**27**) (1.2 mg, 1.5 µmol, 3 mol%) to afford the title compound as a pale yellow oil (15 mg, 68%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 7.37 (t, *J* = 7.2 Hz, 2H, $C^{14}H$), 7.30 (t, *J* = 7.2 Hz, 1H, $C^{15}H$), 7.24 (d, *J* = 7.2 Hz, 2H, $C^{13}H$), 6.27 (s, 1H, $C^{11}H$), 5.94 (m, 1H, $C^{5}H$), 5.62 (d, *J* = 2.2 Hz, 1H, $C^{3}H$), 2.49 (q, *J* = 7.5, 2H, $C^{9}H_2$), 2.26 (s, 3H, $C^{7}H_3$), 1.13 (t, *J* = 7.5, 3H, $C^{8}H_3$); **^{13}C-NMR** (101 MHz, *$CDCl_3$*): 169.8, 164.9, 163.2, 153.6, 134.0, 129.6, 128.6, 128.4, 127.4, 124.6, 120.2, 120.2, 119.3, 100.1, 90.5, 22.6, 20.0, 11.5; **MS** (ESI) *m/z* (rel.%): 257 [MH^+] (100); **HRMS** (ESI) calculated for $C_{16}H_{17}O_3$: 257.1172, found: 257.1180; **IR** (neat, cm^{-1}): 3060, 2976, 2937, 1721, 1645, 1563, 1489, 1447, 1406, 1227, 1190, 1133, 924, 692.

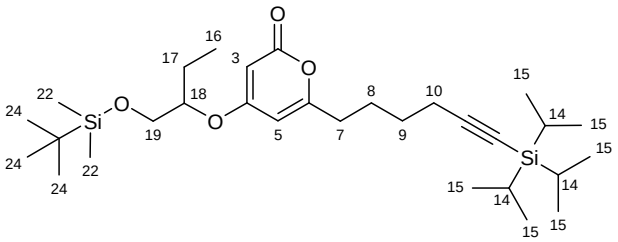
4-(1-Ethyl-penta-*E*-1,4-dienyloxy)-6-methyl-2-pyrone (*E*-180)



A solution of ***E*-176a** (23 mg, 89 μmol, 1 eq.), **152** (30 mg, 178 μmol, 2 eq.), Cs_2CO_3 (87 mg, 266 μmol, 3 eq.) and *CatCat* (**35**) (1.4 mg, 1.8 μmol, 2 mol%) in THF (1 ml) was stirred under nitrogen at 70 °C for 18 h, then quenched by the addition of water (1 ml) and EtOAc (1 ml). The organic layer was separated and the organic layer extracted with EtOAc (3 × 1 ml), then the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography (20% EtOAc in pet ether) of the crude material afforded the title compound as a pale yellow oil (8 mg, 41%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 5.87 (dq, *J* = 2.2, 0.8 Hz, 1H, C^5H), 5.79 (ddt, *J* = 17.0, 10.3, 6.0 Hz, 1H, $C^{13}H$), 5.48 (d, *J* = 2.2 Hz, 1H, C^3H), 5.20 (t, *J* = 7.8 Hz, 1H, $C^{11}H$), 5.07 (app. dq, *J* = 17.0, 1.6 Hz, 1H, $C^{14}H^a$), 5.03 (app. dq, *J* = 10.3, 1.6 Hz, 1H, $C^{14}H^b$), 2.81 (m, 2H, $C^{12}H_2$), 2.26 (q, *J* = 7.5 Hz, 2H, C^9H_2), 2.23 (d, *J* = 0.8 Hz, 3H, C^7H_3), 1.04 (t, *J* = 7.5 Hz, 3H, C^8H_3); **^{13}C-NMR** (101 MHz, *$CDCl_3$*): 168.8, 164.9, 163.1, 151.3, 135.3, 114.1, 99.8, 95.6, 89.5, 29.4, 25.3, 20.0, 11.1; **MS** (ESI) *m/z* (rel.%): 243 [MNa^+] (28), 221[MH^+] (100), 201 (6), 179 (28), 127 (4); **HRMS** (ESI) calculated for $C_{13}H_{17}O_3$: 221.1172, found: 221.1175.

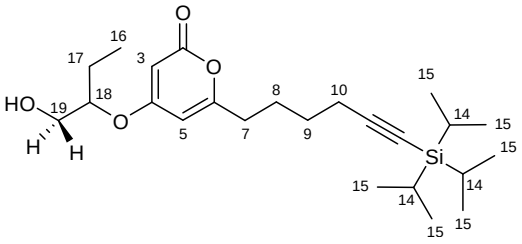
4-[1-(*tert*-Butyl-dimethyl-silanyloxymethyl)-propoxy]-6-(6-triisopropylsilyl-hex-5-ynyl)-2-pyrone (182)



2-pyrone **44** (550 mg, 1.58 mmol, 1 eq.), alcohol **168** (484 mg, 2.37 mmol, 1.5 eq.) and triphenylphosphine (621 mg, 2.37 mmol, 1.5 eq.) were dissolved in DCM (5 ml) under nitrogen at 0 °C. DIAD (479 mg, 2.37 mmol, 1.5 eq.) was then added carefully over 15 minutes. The reaction was stirred for 16 h at 20 °C and then the solvent removed *in vacuo*. The crude product was purified *via* flash column chromatography (20% EtOAc in hexanes) to afford a colourless oil (628 mg, 75%).

^{1}H-NMR (500 MHz, *$CDCl_3$*): 5.77 (d, *J* = 2.3 Hz, 1H, $C^{5}H$), 5.44 (d, *J* = 2.3 Hz, 1H, $C^{3}H$), 4.23 (p, *J* = 5.5 Hz, 1H, $C^{18}H$), 3.68-3.74 (m, 2H, $C^{19}H_2$), 2.47 (t, *J* = 7.5 Hz, 2H, $C^{7}H_2$), 2.29 (t, *J* = 6.9 Hz, 2H, $C^{10}H_2$), 1.76-1.83 (m, 2H, $C^{8}H_2$), 1.62-1.75 (m, 2H, $C^{17}H_2$), 1.54-1.61 (m, 2H, $C^{9}H_2$), 0.97-1.08 (m, 21H, $C^{14}H$/ $C^{15}H_2$), 0.94 (t, *J* = 7.5 Hz, 3H, $C^{16}H_3$), 0.86 (s, 9H, $C^{24}H_3$), 0.03 (s, 3H, $C^{22}H_3$), 0.02 (s, 3H, $C^{22}H_3$); **^{13}C-NMR** (126 MHz, *$CDCl_3$*): 170.4, 165.4, 165.4, 108.4, 100.3, 88.5, 80.8, 77.2, 63.7, 32.9, 27.9, 25.7, 25.6, 23.3, 19.5, 18.6, 18.2, 11.2, 9.4, -5.4, -5.5; **MS** (ESI) *m/z* (rel.%): 557 [MNa^+] (19), 535 [MH^+] (100), 413 (11), 391 (39); **HRMS** (ESI) calculated for $C_{30}H_{55}O_4Si_2$ [MH^+]: 535.3633, found: 535.3648.

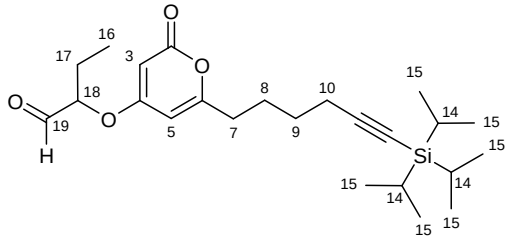
4-(1-Hydroxymethyl-propoxy)-6-(6-triisopropylsilyl-hex-5-ynyl)-2-pyrone (183)



A solution of **182** (584 mg, 1.09 mmol, 1 eq.) in THF (2 ml), water (1 ml) and acetic acid (3 ml) was stirred for 16 hours at 20 °C. The solution was concentrated *in vacuo* and the resulting product was purified *via* flash column chromatography (2-4% MeOH in DCM) to afford a pale yellow oil (343 mg, 75%).

^{1}H-NMR (500 MHz, *$CDCl_3$*): 5.79 (d, *J* = 2.0 Hz, 1H, $C^{5}H$), 5.44 (d, *J* = 2.0 Hz, 1H, $C^{3}H$), 4.28 (app.qd, *J* = 6.0, 3.5 Hz, 1H, $C^{18}H$), 3.81 (dd, *J* = 12.0, 3.5 Hz, 1H, $C^{19}H_2$), 3.76 (dd, *J* = 12.0, 6.0 Hz, 1H, $C^{19}H_2$), 2.48 (t, *J* = 7.5 Hz, 2H, $C^{7}H_2$), 2.29 (t, *J* = 6.9 Hz, 2H, $C^{10}H_2$), 1.77-1.84 (m, 2H, $C^{8}H_2$), 1.70-1.76 (m, 2H, $C^{17}H_2$), 1.55-1.63 (m, 2H, $C^{9}H_2$), 0.99 – 1.09 (m, 21H, $C^{14}H$/ $C^{15}H_3$), 0.96 (t, *J* = 7.5 Hz, 3H, $C^{16}H_3$): **^{13}C-NMR** (126 MHz, *$CDCl_3$*): 169.9, 165.7, 165.0, 108.1, 100.1, 88.7, 80.9, 80.8, 63.3, 33.0, 27.9, 25.6, 22.8, 19.5, 18.6, 11.3, 9.4; **MS** (ESI) *m/z* (rel.%): 443 [MNa^+] (15), 535 [MH^+] (100); **HRMS** (ESI) calculated for $C_{24}H_{41}O_4Si$ [MH^+]: 421.2769, found: 421.2771; **IR** (neat, cm^{-1}): 3405, 2941, 2864, 2171, 1696, 1645, 1560, 1462, 1426, 1244, 1140, 1061, 995, 882, 818.

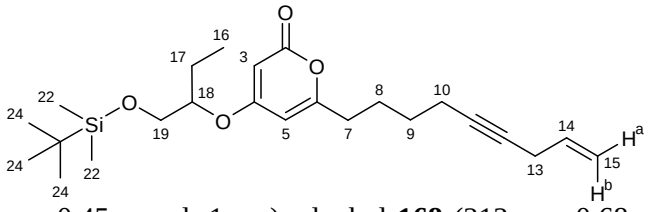
2-(6-(6-triisopropylsilanyl-hex-5-ynyl)-2-pyron-4-yloxy)-butyraldehyde (184)



To a solution of oxalyl chloride (826 mg, 6.5 mmol, 1.3 eq.) in DCM (15 ml) at -78 °C was added DMSO (1.01 g, 13 mmol, 2.6 eq.) in DCM (15 ml) carefully over 15 minutes. The reaction was stirred for 30 minutes at -78 °C then a solution of **183** (990 mg, 5 mmol, 1 eq.) in DCM (15 ml) was added carefully over 20 minutes and the reaction stirred for a further 30 minutes at -78 °C. TEA (1.80 g, 18 mmol, 3.6 eq.) was added over 15 minutes and the reaction stirred for 1 h at -78 °C then allowed to warm to ambient temperature. The solvent was removed *in vacuo* and the residue taken up in ether then passed through a silica plug, eluting with ether. The solvent was then removed *in vacuo* to afford the desired product as a colourless oil (978 mg, >99%)

^{1}H-NMR (400 MHz, *D_2-DCM*): 9.57 (d, *J* = 1.4 Hz, 1H, $C^{19}H$), 5.89 (dt, *J* = 2.3, 0.7 Hz, 1H, $C^{5}H$), 5.19 (d, *J* = 2.2 Hz, 1H, $C^{3}H$), 4.51 (ddd, *J* = 6.9, 5.4, 1.3 Hz, 1H, $C^{18}H$), 2.50 (td, *J* = 7.4, 0.7 Hz, 2H, $C^{7}H_2$), 2.30 (t, *J* = 6.9 Hz, 2H, $C^{10}H_2$), 2.00 – 1.85 (m, 2H, $C^{8}H_2$), 1.84 – 1.75 (m, 2H, $C^{17}H_2$), 1.64 – 1.56 (m, 2H, $C^{9}H_2$), 1.27 – 1.22 (m, 3H, $C^{14}H$), 1.11 – 0.99 (m, 21H, $C^{16}H_3$/ $C^{15}H_3$); **^{13}C-NMR** (101 MHz, *D_2-DCM*): 199.0, 169.8, 166.8, 164.4, 108.9, 99.9, 89.5, 83.4, 81.2, 41.6, 33.6, 28.5, 26.2, 23.4, 19.9, 18.9, 11.8, 9.3; **MS** (ESI) *m/z* (rel.%): 419 [MH^+] (100): **HRMS** (ESI) calculated for $C_{24}H_{39}O_4Si$: 419.2612, found: 419.2618.

4-[1-(*tert*-Butyl-dimethyl-silanyloxymethyl)-propoxy]-6-(non-8-en-5-ynyl)-2-pyrone (187)

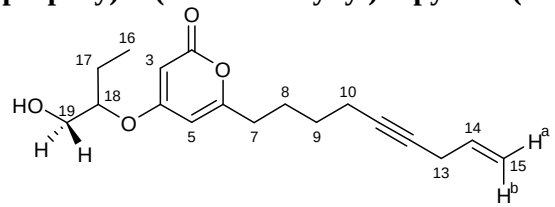


2-pyrone **95** (105 mg, 0.45 mmol, 1 eq.), alcohol **168** (212 mg, 0.68 mmol, 1.5 eq.) and triphenylphosphine (178 mg, 0.68 mmol, 1.5 eq.) were dissolved in DCM (2 ml) under nitrogen at 0 °C. DIAD (137 mg, 0.68 mmol, 1.5 eq.) was then added carefully over 15 minutes. The reaction was stirred for 16 h at 20 °C and then the solvent removed *in vacuo*.

The crude product was purified *via* flash column chromatography (20% EtOAc in hexanes) to afford a colourless oil (93 mg, 49.5%).

^{1}H-NMR (500 MHz, *$CDCl_3$*): 5.81 (ddt, *J* = 16.9, 10.0, 5.3 Hz, 1H, $C^{14}H$), 5.76 (d, *J* = 2.2 Hz, 1H, $C^{5}H$), 5.42 (d, *J* = 2.2 Hz, 1H, $C^{3}H$), 5.28 (ddt, *J* = 16.9, 1.8, 1.8 Hz, 1H, $C^{15}H^{b}$), 5.08 (ddt, *J* = 10.0, 1.8, 1.8 Hz, 1H, $C^{15}H^{a}$), 4.22 (p, *J* = 5.5 Hz, 1H, $C^{18}H$), 3.69-3.72 (m, 2H, $C^{19}H_2$), 2.90-2.94 (m, 2H, $C^{13}H_2$), 2.45 (t, *J* = 5.5 Hz, 2H, $C^{7}H_2$), 2.22 (tt, *J* = 7.0, 2.4 Hz, 2H, $C^{10}H_2$), 1.72-1.80 (m, 2H, $C^{8}H_2$), 1.62-1.71 (m, 2H, $C^{17}H_2$), 1.51-1.58 (m, 2H, $C^{9}H_2$), 0.94 (t, *J* = 7.5 Hz, 3H, $C^{16}H_3$), 0.86 (s, 9H, $C^{24}H_3$), 0.03 (s, 3H, $C^{22}H_3$), 0.02 (s, 3H, $C^{22}H_3$); **^{13}C-NMR** (126 MHz, *$CDCl_3$*): 170.3, 165.3, 165.2, 133.2, 115.6, 100.3, 88.6, 81.8, 80.8, 63.7, 33.1, 28.1, 25.7, 23.4, 23.1, 21.9, 20.4, 18.5, 18.2, 9.4, -5.4, -5.5; **MS** (ESI) *m/z* (rel.%): 441 [MNa^+] (60), 419 [MH^+] (100), 391 (9); **HRMS** (ESI) calculated for $C_{24}H_{39}O_4Si$ [MH^+]: 419.2612, found: 419.2620; **IR** (neat, cm^{-1}): 2930, 2857, 1733, 1652, 1559, 1472, 1419, 1241, 1107, 1005, 837.

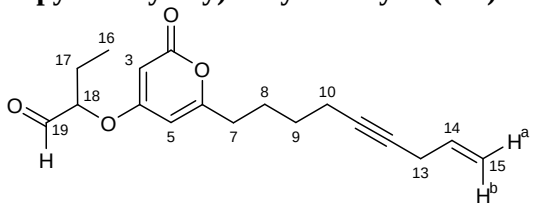
4-(1-Hydroxymethyl-propoxy)-6-(non-8-en-5-ynyl)-2-pyrone (188)



A solution of **187** (30 mg, 71 µmol, 1 eq.) in THF (1 ml), water (0.5 ml) and acetic acid (2 ml) was stirred for 16 hours at 20 °C. The solution was concentrated *in vacuo* and the resulting product was purified *via* flash column chromatography (2-4% MeOH in DCM) to afford a pale yellow oil (15 mg, 69%).

^{1}H-NMR (500 MHz, *$CDCl_3$*): 5.77-5.85 (m, 2H, $C^{14}H$/ $C^{5}H$), 5.46 (d, *J* = 2.2 Hz, 1H, $C^{3}H$), 5.28 (ddt, *J* = 16.9, 1.8, 1.8 Hz, 1H, $C^{15}H^{b}$), 5.08 (ddt, *J* = 10.0, 1.8, 1.8 Hz, 1H, $C^{15}H^{a}$), 4.22 (tdd, *J* = 6.0, 6.0, 3.7 Hz, 1H, $C^{18}H$), 3.80 (dd, *J* = 12.1, 3.7 Hz, 1H, $C^{19}H_2$), 3.75 (dd, *J* = 12.1, 6.0 Hz, 1H, $C^{19}H_2$), 2.91-2.95 (m, 2H, $C^{13}H_2$), 2.46 (t, *J* = 7.6 Hz, 2H, $C^{7}H_2$), 2.23 (tt, *J* = 7.0, 2.4 Hz, 2H, $C^{10}H_2$), 2.08 (s, 1H, OH), 1.70-1.80 (m, 4H, $C^{8}H_2$/ $C^{17}H_2$), 1.52-1.59 (m, 2H, $C^{9}H_2$), 0.96 (t, *J* = 7.5 Hz, 3H, $C^{16}H_3$); **^{13}C-NMR** (126 MHz, *$CDCl_3$*): 170.2, 165.8, 165.4, 133.4, 115.8, 100.5, 88.9, 82.0, 81.1, 63.4, 33.3, 28.3, 25.9, 23.3, 23.1, 18.7, 9.6, 1.2; **MS** (ESI) *m/z* (rel.%): 305[MH^+] (100), 293 (8), 279 (5), 247 (8), 101 (7); **HRMS** (ESI) calculated for $C_{18}H_{25}O_4$ [MH^+]: 305.1747, found: 305.1735; **IR** (neat, cm^{-1}): 3419, 2937, 2880, 1700, 1645, 1560, 1433, 1335, 1246, 1143, 1061, 1020, 916, 818, 668.

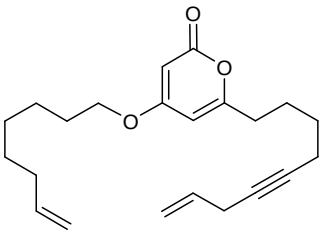
2-(6-(non-8-en-5-ynyl)-2-pyron-4-yloxy)-butyraldehyde (189)



To a solution of oxalyl chloride (16.3 mg, 129 μmol, 1.3 eq.) in DCM (1 ml) at -78 °C was added DMSO (20.1 mg, 258 μmol, 2.6 eq.) in DCM (1 ml) carefully over 15 minutes. The reaction was stirred for 30 minutes at -78 °C then a solution of **188** (30.0 mg, 99 μmol, 1 eq.) in DCM (1 ml) was added carefully over 20 minutes and the reaction stirred for a further 30 minutes at -78 °C. TEA (36 mg, 357 μmol, 3.6 eq.) was added over 15 minutes and the reaction stirred for 1 h at -78 °C then allowed to warm to ambient temperature. The solvent was removed *in vacuo* and the residue taken up in ether then passed through a silica plug, eluting with ether. The solvent was then removed *in vacuo* to afford the desired product as a colourless oil (29.2 mg, 98%).

^{1}H-NMR (400 MHz, $CDCl_3$): 9.59 (d, J = 1.5 Hz, 1H, $C^{19}H$), 5.90 (d, J = 2.3 Hz, 1H, C^5H), 5.82 (ddt, J = 17.0, 10.0, 5.4 Hz, 1H, $C^{14}H$), 5.30 (ddt, J = 17.0, 1.8, 1.8 Hz, 1H, $C^{15}H^b$), 5.23 (d, J = 2.3 Hz, 1H, C^3H), 5.10 (ddt, J = 10.0, 1.8, 1.8 Hz, 1H, $C^{15}H^a$), 4.48 (ddd, J = 7.1, 5.4, 1.5 Hz, 1H, $C^{18}H$), 2.96 – 2.93 (m, 2H, $C^{13}H_2$), 2.50 (t, J = 7.5 Hz, 2H, C^7H_2), 2.30 – 2.20 (m, 2H, $C^{10}H_2$), 2.00 – 1.89 (m, 2H, $C^{17}H_2$), 1.84 – 1.71 (m, 2H, C^8H_2), 1.61 – 1.53 (m, 2H, C^9H_2), 1.05 (t, J = 7.4 Hz, 3H, $C^{16}H_3$); **MS** (ESI) *m/z* (rel.%): 303 [MH^+] (100); **HRMS** (ESI) calculated for $C_{18}H_{23}O_4$: 303.1591, found: 303.1585.

6-(Non-8-en-5-ynyl)-4-(oct-7-enyloxy)-2-pyrone (192)

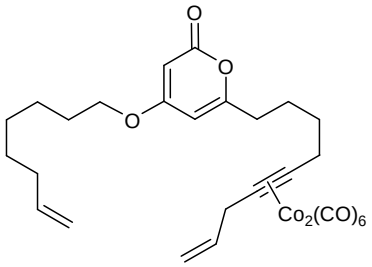


A solution of 2-pyrone **95** (11.0 mg, 47 μmol, 1 eq.), 8-bromo-1-octene (18.1 mg, 95 μmol, 2 eq.) and DBU (14.4 mg, 95 μmol, 2 eq.) in MeCN (1 ml), was stirred at 80 °C for 16 hours. The reaction mixture was cooled and the solvent removed *in vacuo*, and the crude product purified *via* flash column chromatography (40% ether in pet ether) to afford the title compound as a pale yellow oil (11.8 mg, 72.8%).

^{1}H-NMR (500 MHz, $CDCl_3$): 5.75 – 5.86 (m, 3H), 5.37 (d, J = 2.2 Hz, 1H), 5.29 (ddt, J = 17.0, 1.9, 1.9 Hz, 1H), 5.09 (ddt, J = 10.0, 1.7, 1.7 Hz, 1H), 5.00 (ddt, J = 17.1, 2.1, 1.6 Hz,

1H), 4.94 (ddt, *J* = 10.2, 2.1, 1.2 Hz, 1H), 3.92 (t, *J* = 6.5 Hz, 2H), 2.91 – 2.95 (m, 2H), 2.46 (t, *J* = 7.5 Hz, 2H), 2.23 (tt, *J* = 7.0, 2.4 Hz, 2H), 2.02 – 2.09 (m, 2H), 1.72 – 1.80 (m, 4H), 1.51 – 1.59 (m, 2H), 1.33 – 1.45 (m, 6H); **^{13}C-NMR** (126 MHz, *$CDCl_3$*): 170.6, 165.2, 165.1, 138.8, 133.2, 115.7, 114.4, 100.0, 87.9, 81.9, 77.2, 68.8, 33.6, 33.1, 28.7, 28.6, 28.4, 28.1, 25.7, 25.7, 23.1, 18.5; **MS** (ESI) *m/z* (rel.%): 365 [MNa^+] (50), 343 [MH^+] (60), 301 (17), 259 (100), 237 (75); **HRMS** (ESI) calculated for $C_{22}H_{31}O_3$: 343.2268, found: 343.2272; **IR** (DCM, cm^{-1}): 2930, 1717, 1700, 1652, 1559, 1245, 810.

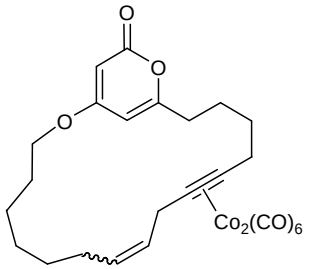
Hexacarbonyl{μ_2-[6-(non-8-en-5-ynyl)-4-(oct-7-enyloxy)-2-pyrone]} **dicobalt (0) (194)**



A solution of **192** (9.0 mg, 26.3 µmol, 1 eq.) and $Co_2(CO)_6$ (9.9 mg, 28.9 µmol, 1.1 eq.) in THF (1 ml) was stirred under argon at 20 °C for 2 hours. The reaction mixture was then purified *via* flash column chromatography (30% ether in pet ether) to afford the title compound as a red/brown oil (9.0 mg, 57%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 5.92 (ddt, *J* = 17.0, 10.0, 7.1 Hz, 1H), 5.81 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 1H), 5.77 (d, *J* = 2.2 Hz, 1H), 5.38 (d, *J* = 2.2 Hz, 1H), 5.20 (ddt, *J* = 17.0, 1.2, 1.2 Hz, 1H), 5.14 (ddt, *J* = 10.0, 1.2, 1.2 Hz, 1H), 5.00 (ddt, *J* = 17.0, 1.8, 1.8 Hz, 1H), 4.95 (ddt, *J* = 10.1, 1.8, 1.8 Hz, 1H), 3.92 (t, *J* = 6.5 Hz, 2H), 3.56 (d, *J* = 7.1 Hz, 2H), 2.84 (dd, *J* = 8.0, 7.5 Hz, 2H), 2.51 (t, *J* = 7.5 Hz, 2H), 2.06 (q, *J* = 7.0 Hz, 2H), 1.79 – 1.86 (m, 2H), 1.73 – 1.79 (m, 2H), 1.64 – 1.72 (m, 2H), 1.33 – 1.46 (m, 6H); **^{13}C-NMR** (101 MHz, *$CDCl_3$*): 170.6, 165.0, 164.8, 138.8, 135.4, 117.3, 114.4, 110.0, 100.2, 98.4, 88.0, 68.9, 38.2, 33.6, 33.4, 30.8, 29.7, 28.7, 28.6, 28.4, 26.5, 25.6; **MS** (ESI) *m/z* (rel.%): 651 [MNa^+] (60), 629 [MH^+] (55), 580 (17), 545 (100), 517 (47), 489 (19), 461 (20), 413 (56), 391 (54), 365 (56), 343 (98); **HRMS** (ESI) calculated for $C_{28}H_{31}Co_2O_9$: 629.0627, found: 629.0628.

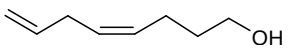
Hexacarbonyl{μ_2-[2,19-Dioxa-bicyclo[16.3.1]docosa-1(21),9,18(22)-trien-12-yn-20-one]} dicobalt (0) (195)



A solution of **194** (4.0 mg, 8.0 μmol, 1 eq.) and Grubbs (2nd Gen.) catalyst (1.4 mg, 1.6 μmol, 20 mol%) in DCM (5 ml) were stirred under nitrogen at 40 °C for 24 hours. The excess solvent was removed *in vacuo* and the crude material purified *via* flash column chromatography (DCM) to afford the title compound as a red/brown oil (3.8 mg, 79.6%) with a 70:30 mixture of isomers.

^{1}H-NMR (500 MHz, *$CDCl_3$*): 5.83 (d, *J* = 1.7 Hz, 0.7H), 5.79 (d, *J* = 1.6 Hz, 0.3H), 5.55 (dt, *J* = 15.0, 7.0 Hz, 1H), 5.44 (d, *J* = 1.7 Hz, 0.7H), 5.43 (d, *J* = 1.6 Hz, 0.3H), 5.40 (dt, *J* = 15.0, 7.5 Hz, 1H), 4.09 – 4.03 (m, 2H), 3.55 (d, *J* = 7.5 Hz, 1.4H), 3.52 (d, *J* = 5.8 Hz, 0.6H), 2.91 (dd, *J* = 16.6, 9.2 Hz, 2H), 2.63 – 2.51 (m, 2H), 1.98 (q, *J* = 6.1 Hz, 2H), 1.89 – 1.81 (m, 2H), 1.78 – 1.71 (m, 2H), 1.65 – 1.60 (m, 2H), 1.51 – 1.38 (m, 4H); **^{13}C-NMR** (126 MHz, *$CDCl_3$*): 170.5, 170.3, 165.2, 132.9, 128.2, 100.9, 100.8, 88.9, 88.2, 88.1, 38.6, 35.3, 33.0, 31.1, 30.5, 29.9, 27.5, 26.5, 24.5, 22.9; **MS** (ESI) *m/z* (rel.%): 601 [MH^+] (12), 491 (8), 413 (36), 391 (45), 297 (100), 281 (12); **HRMS** (ESI) calculated for $C_{26}H_{27}Co_2O_9$: 601.0314, found: 601.0313; **IR** (DCM, cm^{-1}): 2916, 2849, 2086, 2043, 2012, 1734, 1559, 1243, 1132.

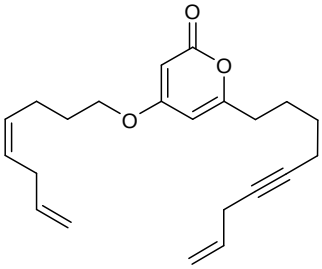
Octa-*Z*-4,7-dien-1-ol (199)[158]



To a 100 ml flask containing $PdCl_2$ (14 mg, 0.08 mmol, 8 mol%) and $NaBH_4$ (304 mg, 8 mmol, 8 eq.) under argon, was added PEG-200 (19.9 g) over 15 minutes. DCM (12 ml) was added followed by **203** (124 mg, 1 mmol, 1 eq.) in one portion. The solution was subsequently cooled to -10 °C and allowed to warm to ambient temperature over 2 hours. The reaction was quenched by the addition of water (30 ml) and the organic layer separated. The aqueous layer was then extracted with DCM (3 × 12 ml) and the combined organic extracts concentrated *in vacuo*, then purified *via* flash column chromatography (15% EtOAc in pet ether) to afford the title compound as a colourless oil (66 mg, 52.3%).

^{1}H-NMR (500 MHz, *$CDCl_3$*): 5.81 (ddt, *J* = 17.1, 10.1, 6.2 Hz, 1H), 5.49 – 5.36 (m, 2H), 5.03 (ddd, *J* = 17.1, 3.6, 1.7 Hz, 1H), 4.97 (ddd, *J* = 10.1, 3.4, 1.7 Hz, 1H), 3.63 (t, *J* = 6.5 Hz, 2H), 2.81 (dd, *J* = 13.0, 7.2 Hz, 2H), 2.16 – 2.08 (m, 2H), 1.67 – 1.58 (m, 2H); **^{13}C-NMR** (126 MHz, *$CDCl_3$*): 136.9, 130.2, 127.4, 114.6, 62.4, 32.4, 31.4, 23.4; **MS** (ESI) *m/z* (rel.%): 127 [MH^+] (40), 109 (29), 101 (62), 79 (100); **HRMS** (ESI) calculated for $C_8H_{15}O$: 127.1117, found: 127.1115; **IR** (neat, cm^{-1}): 3342, 2931, 2870, 1434, 1347, 1057, 909.

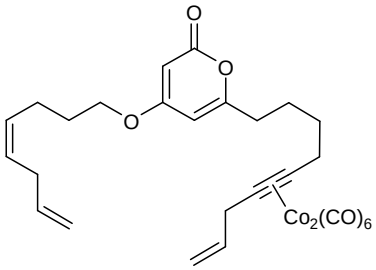
6-(Non-8-en-5-ynyl)-4-(octa-*Z*-4,7-dienyloxy)-2-pyrone (200)



2-pyrone **92** (33 mg, 142 μmol, 1 eq.), alcohol **199** (27 mg, 213 μmol, 1.5 eq.) and triphenylphosphine (56 mg, 213 μmol, 1.5 eq.) were dissolved in DCM (1 ml) under nitrogen at 0 °C. DIAD (43 mg, 213 μmol, 1.5 eq.) was then added carefully over 15 minutes. The reaction was stirred for 16 h at 20 °C and then the solvent removed *in vacuo*. The crude product was purified *via* flash column chromatography (20% EtOAc in hexanes) to afford a colourless oil (25 mg, 52%).

^{1}H-NMR (500 MHz, *$CDCl_3$*): 5.94 (d, *J* = 2.1 Hz, 1H), 5.74 – 5.86 (m, 2H), 5.52 – 5.41 (m, 2H), 5.40 (d, *J* = 2.1 Hz, 1H), 5.29 (ddt, *J* = 17.0, 1.7, 1.7 Hz, 1H), 5.09 (ddt, *J* = 10.0, 1.7, 1.7 Hz, 1H), 5.02 (ddt, *J* = 17.1, 3.4, 1.7 Hz, 1H), 4.98 (ddt, *J* = 10.2, 3.4, 1.6 Hz, 1H), 3.94 (t, *J* = 6.4 Hz, 2H), 2.91 – 2.96 (m, 2H), 2.74 – 2.83 (m, 2H), 2.15 – 2.27 (m, 4H), 1.89 – 2.06 (m, 2H), 1.80 – 1.88 (m, 2H), 1.56 – 1.71 (m, 4H); **^{13}C-NMR** (126 MHz, *$CDCl_3$*): 170.2, 166.1, 164.2, 136.6, 128.9, 128.8, 128.5, 115.7, 114.9, 100.1, 88.7, 81.6, 77.5, 68.2, 48.0, 33.1, 31.4, 31.1, 28.2, 23.2, 23.1, 14.4; **MS** (ESI) *m/z* (rel.%): 363 [MNa^+] (23), 341 [MH^+] (36), 329 (69), 307 (100); **HRMS** (ESI) calculated for $C_{22}H_{29}O_3$: 341.2111, found: 341.2114.

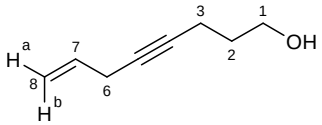
Hexacarbonyl{μ_2-[6-(non-8-en-5-ynyl)-4-(octa-*Z*-4,7-dienyloxy)-2-pyrone]} dicobalt (0) (201)



A solution of **200** (10.0 mg, 29 μmol, 1 eq.) and $Co_2(CO)_6$ (15 mg, 44 μmol, 1.5 eq.) in THF (1 ml) was stirred under argon at 20 °C for 2 hours. The reaction mixture was then purified *via* flash column chromatography (30% ether in pet ether) to afford the title compound as a red/brown oil (5.0 mg, 27.8%).

^{1}H-NMR (500 MHz, $CDCl_3$): 5.97 (d, *J* = 2.1 Hz, 1H), 5.96 – 5.87 (m, 1H), 5.83 – 5.74 (m, 1H), 5.53 – 5.42 (m, 2H), 5.40 (d, *J* = 2.2 Hz, 1H), 5.20 (d, *J* = 16.9 Hz, 1H), 5.14 (d, *J* = 9.9 Hz, 1H), 5.06 – 5.00 (m, 1H), 5.00 – 4.96 (m, 1H), 3.96 – 3.90 (m, 4H), 3.55 (d, *J* = 7.1 Hz, 2H), 2.84 (t, *J* = 8.0 Hz, 2H), 2.79 (t, *J* = 5.7 Hz, 1H), 2.25 – 2.15 (m, 4H), 1.87 – 1.81 (m, 4H); **MS** (ESI) *m/z* (rel.%): 627 [MH^+] (3), 589 (12), 533 (6), 505 (5), 409 (19), 387 (23), 329 (53), 307 (100), 282 (41), 235 (42); **HRMS** (ESI) calculated for $C_{28}H_{29}Co_2O_9$: 627.0470, found: 627.0465; **IR** (DCM, cm^{-1}): 2930, 2087, 2046, 2014, 1733, 1717, 1700, 1652, 1559.

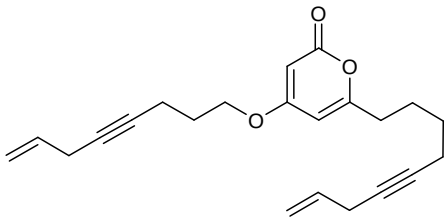
Oct-7-en-4-yn-1-ol (203)[159]



In a 3 L round bottom flask was added pent-4-yn-1-ol (14.97 g, 178 mmol, 1 eq.), allyl bromide (25.9 g, 214 mmol, 1.2 eq.), NaI (53.4 g, 356 mmol, 2 eq.), CuI (34.0 g, 178 mmol, 1 eq.) and K_2CO_3 (49.1 g, 356 mmol, 2 eq.) in acetone (700 ml). The flask was flushed with nitrogen and the mixture stirred for 16 hours at 20 °C, then filtered through celite and further quenched by the addition of 1N HCl (200 ml). Ether (200 ml) was added and the phases separated. The aqueous phase was then extracted using ether (4 x 200 ml) and the combined organic extracts washed with sat. brine solution (400 ml), dried over $MgSO_4$ and concentrated *in vacuo*. This afforded a dark orange oil and a white solid (NaI). These were separated via filtration with pet ether as eluent, and the solution once again concentrated *in vacuo* to afford the crude product which was purified *via* flash column chromatography (20% EtOAc in Heptane) to give a colourless oil (15.1 g, 68.5%).

^{1}H- NMR (400 MHz, *$CDCl_3$*): 5.81 (ddt, *J* = 16.9, 10.0, 5.3Hz, 1H, $C^{7}H$), 5.29 (ddt, *J* =16.9, 1.7, 1.7 Hz, 1H, $C^{8}H^{a}$), 5.09 (ddt, *J* =10.0, 1.7, 1.7 Hz, 1H, $C^{8}H^{b}$), 3.76 (t, *J* = 6.4 Hz, 2H, $C^{1}H_2$), 2.93 (m, 2H, $C^{6}H_2$), 2.32 (tt, *J* = 6.4, 2.4 Hz, 2H, $C^{3}H_2$), 1.76 (p, *J* = 6.4 Hz, 2H, $C^{2}H_2$); **^{13}C- NMR** (100 MHz, *$CDCl_3$*): 133.2, 115.7, 96.4, 81.8, 62.0, 31.6, 23.1, 15.4; **MS** (ESI) *m/z* (rel.%): 125 [MH^+] (100); **IR** (neat, cm^{-1}): 3359, 2946, 1641, 1421, 1056, 991, 915.

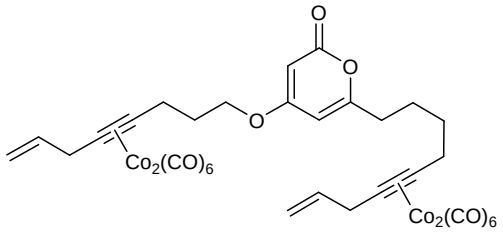
6-(Non-8-en-5-ynyl)-4-(oct-7-en-4-ynyloxy)-2-pyrone (204)



2-pyrone **95** (55 mg, 237 µmol, 1 eq.), alcohol **203** (44 mg, 355 µmol, 1.5 eq.) and triphenylphosphine (93 mg, 355 µmol, 1.5 eq.) were dissolved in DCM (1 ml) under nitrogen at 0 °C. DIAD (72 mg, 355 µmol, 1.5 eq.) was then added carefully over 15 minutes. The reaction was stirred for 16 h at 20 °C and then the solvent removed *in vacuo*. The crude product was purified *via* flash column chromatography (20% EtOAc in hexanes) to afford a colourless oil (59.3 mg, 61%).

^{1}H-NMR (500 MHz, *$CDCl_3$*): 5.76 – 5.87 (m, 3H), 5.41 (d, *J* = 2.2 Hz, 1H), 5.29 (ddt, *J* = 16.9, 1.8, 1.8 Hz, 1H), 5.28 (ddt, *J* = 16.9, 1.8, 1.8 Hz, 1H), 5.09 (app. dp, *J* = 10.0, 1.8 Hz, 2H), 4.05 (t, *J* = 6.2 Hz, 2H), 2.91 – 2.95 (m, 4H), 2.46 (t, *J* = 7.5 Hz, 2H), 2.37 (tt, *J* = 6.8, 2.4 Hz, 2H), 2.23 (tt, *J* = 7.0, 2.4 Hz, 2H), 1.96 (p, *J* = 6.6 Hz, 2H), 1.72 – 1.80 (m, 2H), 1.51 – 1.59 (m, 2H); **^{13}C-NMR** (126 MHz, *$CDCl_3$*): 170.5, 165.3, 165.1, 133.2, 133.0, 115.8, 115.77, 100.0, 88.1, 81.9, 80.5, 78.0, 67.2, 62.0, 33.1, 28.1, 27.8, 25.7, 23.1, 23.0, 18.5, 15.3; **MS** (ESI) *m/z* (rel.%): 339 [MH^+] (48), 333 (69), 313 (100); **HRMS** (ESI) calculated for $C_{22}H_{27}O_3$: 339.1955, found: 339.1949; **IR** (neat, cm^{-1}): 2939, 1700, 1642, 1564, 1436, 1249, 914, 733.

Bis[hexacarbonyl{μ_2-[6-(non-8-en-5-ynyl)-4-(oct-7-en-4-ynyloxy)-2-pyrone]} dicobalt(0)] (205)



A solution of **204** (15.0 mg, 44 μmol, 1 eq.) and $Co_2(CO)_6$ (33.4 mg, 97 μmol, 2.2 eq.) in THF (1 ml) was stirred under argon at 20 °C for 2 hours. The reaction mixture was then purified *via* flash column chromatography (20% EtOAc in pet ether) to afford the title compound as a red/brown oil (38.0 mg, 95%).

^{1}H-NMR (400 MHz, *$CDCl_3$*): 5.93 (br. s, 2H), 5.81 (s, 1H), 5.41 (s, 1H), 5.15 (br. s, 4H), 4.07 (br. s, 2H), 3.57 (br. s, 4H), 2.96 (br. s, 2H), 2.84 (br. s, 2H), 2.53 (br. s, 2H), 2.12 (br. s, 2H), 1.83 (br. s, 2H), 1.68 (br. s, 2H); **^{13}C-NMR** (101 MHz, *$CDCl_3$*): 170.5, 165.2, 165.0, 135.6, 135.4, 117.6, 117.5, 106.8, 100.3, 98.5, 97.4, 97.3, 88.3, 68.1, 38.3, 38.3, 33.5, 33.5, 30.9, 30.6, 30.3, 26.6; **MS** (ESI) *m/z* (rel.%): 933 [MNa^+] (100), 911 [MH^+] (12); **HRMS** (ESI) calculated for $C_{34}H_{26}Co_4NaO_{15}$: 932.8492, found: 932.8484; **IR** (neat, cm^{-1}): 2933, 2088, 2044, 2013, 1734, 1700, 1653, 1569, 1437, 1248.

Chapter 5: Intramolecular arylation characterisation

5.1 General Details

Reagents were purchased from either Sigma Aldrich or Alfa Aesar and used directly unless otherwise stated. Solvents were dried according to standard procedures prior to use and stored under nitrogen. Nitrogen gas was oxygen free and dried immediately before use via passage through sodium hydroxide pellets and silica. Argon and hydrogen were administered directly via balloon. The substructure *2H*-pyran-2-one is henceforth referred to in the text as 2-pyrone.

Where commercially unavailable, 2-bromophenols were synthesised from the reaction of the corresponding phenol with Br_2.[160]

All TLC analysis was performed using Merck 5554 aluminium backed silica plates and visualised using UV light (254 nm), an aqueous solution of potassium permanganate, or an ethanol based solution of *p*-anisaldehyde. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Jeol ECX400 spectrometer operating at 400 and 100 MHz respectively, a Bruker 500 spectrometer operating at 500 and 126 MHz respectively, or a Bruker 700 MHz spectrometer operating at 700 and 176 MHz respectively. All column chromatography was performed using flash silica-gel with the solvent systems specified within the text.

5.2 General procedures

5.2.1 Synthesis of 4-(2-haloaryloxy)-2-pyrones (General Procedure A)

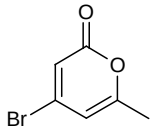
A solution of 4-Bromo-6-methyl-2-pyrone (1 eq.), 2-halophenol (1.1 eq.), and K_2CO_3 (1.5 eq.) in acetone (4 ml/mmol) was stirred at 60 °C for 16 hours. The reaction was quenched by addition of water and ethyl acetate, and the layers separated. The aqueous layer was extracted 3 times using ethyl acetate and the combined organic extracts dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (10-30 % EtOAc in hexanes).

5.2.2 Intramolecular C-H arylation (General Procedure B)

A solution of aryl halide (1 eq.), Cs_2CO_3 (3 eq.), PPh_3 (4 mol%) and $Pd_2(dba\text{-}4,4'\text{-}OMe)_3$ (1 mol%) in THF (4 ml/mmol) was stirred under nitrogen at 70 °C for 18 hours. The reaction was allowed to cool to ambient temperature and quenched by addition of water and ethyl acetate, and the layers separated. The aqueous layer was extracted 3 times using ethyl acetate and the combined organic extracts dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (10-30 % EtOAc in hexanes).

5.3 Characterisation data

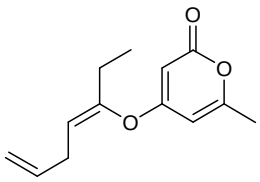
4-Bromo-6-methyl-2-pyrone (106)[161]



A 2 L 3 neck flask containing **9** (14.9 g, 119 mmol, 1 eq.), P_2O_5 (40.4 g, 284 mmol, 2.4 eq.) and TBAB (42.0 g, 130 mmol, 1.1 eq.) in toluene (1 L) was equipped with a condenser and a mechanical stirrer. The reaction mixture was then heated to reflux for 8 hours whilst stirring then allowed to cool to ambient temperature. The toluene was decanted off, and the viscous black residue was extracted with toluene (3 × 400 ml). The combined organic fractions were concentrated *in vacuo* and recrystallisation (toluene) afforded the title compound as pale orange crystals (15.9 g, 70.7%).

Mpt: 73-74 °C (lit. 73-74 °C)[167]; **^{1}H-NMR** (400 MHz, $CDCl_3$): 6.43 (dq, *J* = 1.7, 0.8 Hz, 1H), 6.18 (dq, *J* = 1.7, 0.8 Hz, 1H), 2.23 (t, *J* = 0.8 Hz, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 162.0, 160.6, 141.1, 114.6, 108.4, 19.7; **MS** (ESI) *m/z* (rel.%): 191 [^{81}Br-MH$^+$] (100), 189 [^{79}Br-MH$^+$] (98).

4-{[(1*Z*)-1-Ethyl-1,4-pentadienyl]oxy}-6-methyl-2-pyrone (180)

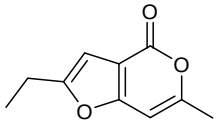


A solution of 4-{[(*Z*)-2-Bromo-1-ethyl-1-ethenyl]oxy}-6-methyl-2-pyrone ***Z*-176a** (20 mg, 0.077 mmol, 1 eq.), Cs_2CO_3 (75.3 mg, 0.231 mmol, 3 eq.), Allyl boronic acid pinacol ester

(25.9 mg, 0.154 mmol, 2 eq.) and **27** (1.2 mg, 0.0015 mmol, 2 mol%) in THF (1 ml) was stirred under nitrogen at 70 °C for 18 hours. The reaction was allowed to cool to ambient temperature and quenched by addition of water (1 ml) and ethyl acetate (2 ml), and the layers separated. The aqueous layer was extracted using ethyl acetate (3 × 2 ml) and the combined organic extracts dried over $MgSO_4$, concentrated in *vacuo* and purified by flash column chromatography (10-20 % EtOAc in hexanes) to afford the product as a colourless oil (6.8 mg, 40.0%).

Rf = 0.42 (20% EtOAc in hexanes); **^{1}H-NMR** (500 MHz, $CDCl_3$): 5.87 (s, 1H), 5.73 (ddt, *J* = 17.0, 10.1, 6.3 Hz, 1H), 5.40 (s, 1H), 5.14 (t, *J* = 7.3 Hz, 1H), 5.01 (dd, *J* = 17.0, 1.2 Hz, 1H), 4.99 (dd, *J* = 10.1, 1.2 Hz, 1H), 2.66 (dd, *J* = 6.3, 7.3 Hz, 2H), 2.23 (s, 3H), 2.18 (q, *J* = 7.3 Hz, 2H), 1.06 (t, *J* = 7.3 Hz, 3H); **^{13}C-NMR** (126 MHz, $CDCl_3$): 168.8, 164.9, 163.1, 151.3, 135.3, 114.1, 99.8, 95.6, 89.5, 29.4, 25.3, 20.0, 11.1; **MS** (ESI) *m/z* (rel.%): 243 [MNa^+] (28), 221[MH^+] (100), 201 (6), 179 (28), 127 (4); **HRMS** (ESI) calculated for $C_{13}H_{17}O_3$: 221.1172, found: 221.1175; **IR** (neat): 3084, 2975, 2938, 1700, 1643, 1560, 1448, 1407, 1225, 1177, 1139, 1037, 994, 917, 822 cm^{-1}.

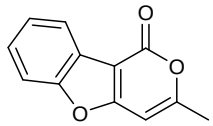
4-Ethyl-7-methyl-furo[3,2-*c*]-2-pyrone (213)



The title compound was prepared according to General Procedure B, on a 0.108 mmol scale, to afford the product as a yellow oil (9.2 mg, 47.9%).

Rf = 0.42 (20% EtOAc in hexanes); **^{1}H-NMR** (500 MHz, $CDCl_3$): 6.43 (q, *J* = 0.9 Hz, 1H), 6.36 (t, *J* = 1.1 Hz, 1H), 2.72 (dq, *J* = 7.5, 1.1 Hz, 2H), 2.32 (d, *J* = 0.9 Hz, 3H), 1.28 (t, *J* = 7.5 Hz, 3H); **^{13}C-NMR** (126 MHz, $CDCl_3$): 161.0, 160.1, 159.6, 158.8, 115.6, 109.2, 101.3, 21.3, 20.1, 11.8; **MS** (ESI) *m/z* (rel.%): 201 [MNa^+] (22), 179 [MH^+] (100); **HRMS** (ESI) calculated for $C_{10}H_{11}O_3$: 179.0703, found: 179.0700; **IR** (neat): 3099, 2976, 2922, 1734, 1622, 1593, 1574, 1459, 1381, 1258, 1027, 966, 918, 814, 764 cm^{-1}.

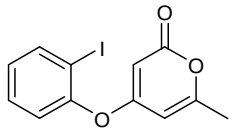
9-Methyl-benzofuro[3,2-*c*]-2-pyrone (216)[119]



The title compound was prepared according to General Procedure B, on a 0.25 mmol scale, to afford the product as a yellow solid (39.6 mg, 79.2%).

Mpt: 188-190 °C (lit. 226-228°C)[114]; **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.01 – 8.06 (m, 1H), 7.52 – 7.58 (m, 1H), 7.39 – 7.44 (m, 2H), 6.54 (q, *J* = 0.9 Hz, 1H), 2.43 (d, *J* = 0.9 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 164.5, 162.9, 159.5, 154.9, 126.1, 124.9, 122.9, 121.4, 111.5, 103.7, 95.9, 20.6; **MS** (ESI) *m/z* (rel.%): 223 [MNa^+] (16), 201 [MH^+] (100); **HRMS** (ESI) calculated for $C_{12}H_9O_3$: 201.0546, found: 201.0549; **IR** (neat): 3101, 2919, 1719, 1614, 1572, 1445, 1251, 1187, 971, 934, 816, 748 cm^{-1}

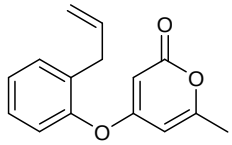
4-(2-Iodophenoxy)-6-methyl-2-pyrone (218)



The title compound was prepared according to General Procedure A, on a 10 mmol scale, to afford the product as a white solid (2.77g, 84.5%).

Mpt: 71-73 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.86 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.40 (td, *J* = 7.9, 1.5 Hz, 1H), 7.09 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.03 (td, *J* = 7.9, 1.5 Hz, 1H), 6.02 (dq, *J* = 2.3, 1.0 Hz, C^5H, 1H), 5.05 (d, *J* = 2.3, C^3H, 1H), 2.26 (d, *J* = 1.0 Hz, C^7H_3, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 169.5, 164.3, 163.6, 152.2, 140.3, 130.1, 128.3, 122.3, 99.7, 91.2, 89.6, 20.1; **MS** (ESI) *m/z* (rel.%): 351 [MNa^+] (100), 329 [MH^+] (97); **HRMS** (ESI) calculated for $C_{12}H_9INaO_3$: 350.9489, found: 350.9484; **IR** (neat): 3806, 1697, 1636, 1559, 1437, 1398, 1223, 820, 764 cm^{-1}.

4-(2-Allyl-phenoxy)-6-methyl-2-pyrone

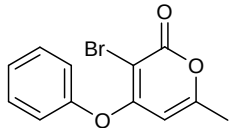


A solution of 4-(2-iodophenoxy)-6-methyl-2-pyrone (82 mg, 0.25 mmol, 1 eq.), Cs_2CO_3 (244 mg, 0.75 mmol, 3 eq.), Allyl boronic acid pinacol ester (84 mg, 0.5 mmol, 2 eq.) and (*E*)-$PdBr(PPh_3)_2$(N-succ) (4 mg, 0.005 mmol, 2 mol%) in THF (2 ml) was stirred under

nitrogen at 70 °C for 18 hours. The reaction was allowed to cool to ambient temperature and quenched by addition of water (1 ml) and ethyl acetate (2 ml), and the layers separated. The aqueous layer was extracted using ethyl acetate (3 × 2 ml) and the combined organic extracts dried over $MgSO_4$, concentrated in *vacuo* and purified by flash column chromatography (10-20 % EtOAc in hexanes) to afford the product as a colourless oil (25.6mg, 42.3%).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.14 – 7.25 (m, 3H), 6.93 (m, 1H), 5.92 (d, 2.2 Hz, 1H), 5.79 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.04 (d, *J* = 2.2 Hz, 1H), 4.93 – 5.02 (m, 2H), 3.19 (d, *J* = 6.6 Hz, 2H), 2.20 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 170.5, 164.6, 163.4, 150.2, 135.4, 132.2, 131.1, 128.1, 126.8, 121.5, 116.7, 99.7, 90.6, 33.9, 20.0; **MS** (ESI) *m/z* (rel.%): 265 [MNa^+] (14), 243 [MH^+] (100); **HRMS** (ESI) calculated for $C_{15}H_{15}O_3$: 243.1016, found: 243.1014; **IR** (neat): 3078, 2921, 1725, 1641, 1565, 1487, 1445, 1402, 1320, 1227, 1178, 1134, 982, 820, 768 cm^{-1}.

3-Bromo-6-methyl-4-phenoxy-2-pyrone (219)

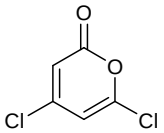


A solution of **106** (189 mg, 1 mmol, 1 eq.), PhOH (103 mg, 1.1 mmol, 1.1 eq) and K_2CO_3 (207 mg, 1.5 mmol, 1.5 eq.) in acetone (3 ml) was heated to 60 °C for 16 h. The reaction was quenched by addition of water (2 ml) and ethyl acetate (3 ml), and the layers separated. The aqueous layer was extracted with ethyl acetate (3 × 3 ml) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was taken up in $CHCl_3$ (10 ml) and Br_2 (160 mg, 1 mmol, 1 eq.) was added carefully. The solution was stirred at 20 °C for 2 h then quenched by the addition of sat. $Na_2SO_{2(aq)}$ (5 ml) and the solution stirred for a further 10 minutes. The organic layer was separated, dried over Na_2SO_4, then filtered and concentrated *in vacuo*. Purification *via* column chromatography (20% EtOAc in pet ether) afforded the title compound as a white crystalline solid (166 mg, 59%).

Mpt: 122-123 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.47 – 7.41 (m, 2H), 7.33 – 7.28 (m, 1H), 7.10 – 7.05 (m, 2H), 5.60 (q, *J* = 0.9 Hz, 1H), 2.15 (d, *J* = 0.9 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 165.5, 162.3, 160.9, 152.8, 130.3, 126.5, 120.8, 97.5, 90.8, 20.0; **MS** (ESI) *m/z* (rel.%): 283 [^{81}Br-MH^+] (100), 281 [^{79}Br-MH^+] (96), 182 (5), 180 (5); **HRMS** (ESI)

calculated for $C_{12}H_{10}{}^{79}BrO_3$: 280.9808, found: 280.9809; **IR** (neat): 3051, 2159, 1725, 1640, 1534, 1487, 1379, 1315, 1228, 993, 927 766 cm^{-1}.

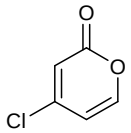
4,6-Dichloro-2-pyrone (220)[162]



A 3-neck flask (100 ml) was fitted with a magnetic stirrer, a condenser with bubbler, gas inlet adapter and a funnel. PCl_5 (6.44 g, 30.9 mmol, 1.03 eq.) was added followed by dimethyl 1,3-acetonedicarboxylate (5.22 g, 30 mmol, 1 eq.). Nitrogen gas was bubbled through the solution and the solution heated to 50 °C for 30 minutes. The reaction was quenched by pouring the cooled reaction mixture onto ice (30 g). The flask was rinsed with a DCM/Water mix (30 ml, 1:1) and the combined solutions separated. The aqueous layer was extracted with DCM (3 × 10 ml) and the combined organic extracts concentrated *in vacuo*. An aqueous solution of 20% HCl (31 ml) was then added and the reaction heated to reflux for 2.5 h. The water was removed *in vacuo* and the residue taken up in ether (30 ml) then dried over calcium chloride. Filtration of the solution and concentration *in vacuo* gave a dark orange solid. A round bottom flask was charged with PCl_5 (6.44 g, 30.9 mmol, 1.03 eq.) and the orange solid added in one portion. The mixture was maintainerd at 0 °C until the solid mixture liquefied. The red solution was then stirred at ambient temperature (20 °C) for 1 hour and a further 15 minutes at 100 °C. The solution was allowed to cool to ambient temperature and DCM (30 ml) added. The solution was subsequently washed with water (2 × 30 ml) and organic portion filtered through celite. The filtrate was neutralised by slow addition of sat. $NaHCO_{3(aq.)}$ (~10 ml) with vigorous stirring. The organic layer was separated and dried over Na_2SO_4, then filtered and concentrated *in vacuo*. Purification *via* column chromatography (DCM) afforded the title compound as a white crystalline solid (0.99 g, 20%).

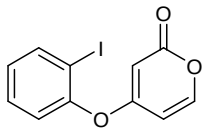
Mpt: 43-44 °C (lit. 43-45 °C)[169]; **^{1}H-NMR** (400 MHz, $CDCl_3$): 6.30 (d, *J* = 1.7 Hz, 1H), 6.30 (d, *J* = 1.7 Hz, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 158.4, 152.1, 150.3, 111.1, 106.6; **MS** (ESI) *m/z* (rel.%): 169 [^{37}Cl/^{37}Cl-MH^+] (11), 167 [^{37}Cl/^{35}Cl-MH^+] (66), 165 [^{35}Cl/^{35}Cl-MH^+] (100).

4-(2-iodophenoxy)-2-pyrone (221) *via* 4-Chloro-2-pyrone [162]



To a solution of **219** (330 mg, 2 mmol, 1 eq.) in AcOH (2 ml) was added Zn dust (156 mg, 2.4 mmol, 1.2 eq.) and the reaction stirred for 48 h at 20°C. The solution was filtered and the excess AcOH removed *in vacuo*. The residue was taken up in DCM (10 ml) and water (3 ml), then neutralised by the addition of solid K_2CO_3 (100 mg). The layers were separated and the aqueous layer extracted with DCM (3 × 3 ml). The combined organic extracts were dried over Na_2SO_4, then filtered and concentrated *in vacuo* to afford the title compound as an off white powder (145 mg, 56%).

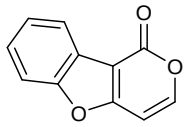
^{1}H-NMR (400 MHz, $CDCl_3$): 7.44 (dd, *J* = 5.6, 0.9 Hz, 1H), 6.40 (dd, *J* = 2.0, 0.9 Hz, 1H), 6.28 (dd, *J* = 5.6, 2.0 Hz, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 160.1, 151.3, 150.8, 114.7, 109.0; **MS** (ESI) *m/z* (rel.%): 133 [^{37}Cl-MH$^+$] (31), 131 [^{35}Cl-MH$^+$] (100); **HRMS** (ESI) calculated for $C_5H_4{}^{35}ClO_2$: 130.9894, found: 130.9894.



A solution of 4-chloro-2-pyrone (125 mg, 0.96 mmol, 1 eq.), 2-iodophenol (253 mg, 1.15 mmol, 1.2 eq.), and K_2CO_3 (264 mg, 1.9 mmol, 2 eq.) in acetone (5 mL) was stirred at 60 °C for 16 hours. The reaction was quenched by addition of water (2 mL) and ethyl acetate (5 mL), and the layers separated. The aqueous layer was extracted using ethyl acetate (3 × 5 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc in hexanes) afforded the title compound as a white solid (260.2 mg, 86.5%).

Mpt: 92-93 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.89 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.50 (dd, *J* = 5.8, 0.7 Hz, 1H), 7.42 (ddd, *J* = 8.1, 7.5, 1.5 Hz, 1H), 7.12 (dd, *J* = 8.1, 1.5, 1H), 7.05 (ddd, *J* = 7.9, 7.5, 1.5 Hz, 1H), 6.27 (dd, *J* = 5.8, 2.4 Hz, 1H), 5.20 (dd, *J* = 2.4, 0.7 Hz, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 168.4, 163.5, 152.5, 152.1, 140.4, 130.2, 128.4, 122.3, 102.8, 94.2, 89.5; **MS** (ESI) *m/z* (rel.%): 337 [MNa$^+$] (15), 315 [MH$^+$] (100); **HRMS** (ESI) calculated for $C_{11}H_8IO_3$: 314.9513, found: 314.9516; **IR** (neat): 3087, 1700, 1633, 1556, 1434, 1328, 1218, 1195, 1158, 1054, 881, 821, 770 cm^{-1}.

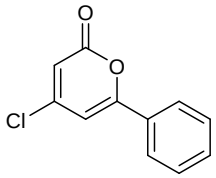
Benzofuro[3,2-*c*]-2-pyrone (222)



The title compound was prepared according to General Procedure B, on a 0.25 mmol scale, to afford the product as a white solid (34.6 mg, 74.4%).

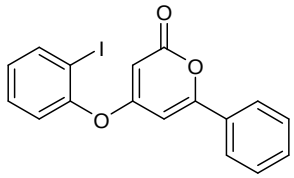
R_f = 0.33 (20% EtOAc in hexanes); Mpt: 149-150 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.09 (m, 1H), 7.65 (d, *J* = 5.7 Hz, 1H), 7.60 (m, 1H), 7.42 – 7.49 (m, 2H), 6.81 (d, *J* = 5.7 Hz, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 162.7, 159.1, 155.0, 151.5, 126.7, 125.1, 122.7, 121.7, 111.6, 106.5, 98.9; **MS** (ESI) *m/z* (rel.%): 209 [MNa^+] (39), 187 [MH^+] (100); **HRMS** (ESI) calculated for $C_{11}H_7O_3$: 187.0390, found: 187.0389; **IR** (neat): 3102, 1717, 1607, 1558, 1448, 1431, 1219, 1171, 1012, 926, 844, 783, 746 cm^{-1}.

4-(2-iodophenoxy)-6-phenyl-2-pyrone (223) *via* 4-Chloro-6-phenyl-2-pyrone



To a solution of 4,6-dichloro-2-pyrone **220** (330 mg, 2 mmol, 1 eq.) and $NiCl_2(PPh_3)_2$ (21.7 mg, 0.04 mmol, 2 mol%) in THF (4 mL) under nitrogen at 20 °C, was added 2.0 M PhMgBr in THF (1 mL, 2 mmol, 1 eq.). The reaction was then stirred at 20 °C for 24 hours then quenched by the addition of water (2 mL) and EtOAc (5 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 × 5 mL). The combined organic extracts were concentrated *in vacuo* and purified by flash column chromatography (10% EtOAc in hexanes) to afford a white crystalline solid (62.7 mg, 15.2%).

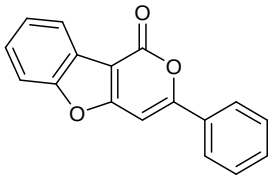
Mpt: 103-105 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.79 – 7.86 (m, 2H), 7.44 – 7.54 (m, 3H), 6.70 (d, *J* = 1.7 Hz, 1H), 6.35 (d, *J* = 1.7 Hz, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 160.6, 160.5, 151.9, 131.7, 130.2, 129.1, 125.9, 111.8, 103.6; **MS** (ESI) *m/z* (rel.%): 231 [^{37}Cl-MNa^+] (14), 229 [^{35}Cl-MNa^+] (49), 209 [^{37}Cl-MH^+] (31), 207 [^{35}Cl-MH^+] (100); **HRMS** (ESI) calculated for $C_{11}H_8{}^{35}ClO_2$:207.0207, found: 207.0209; **IR** (neat): 3079, 1721, 1706, 1612, 1537, 1494, 1451, 1364, 1328, 1235, 1149, 1088, 1050, 859, 813, 776 cm^{-1}.



A solution of 4-Chloro-6-phenyl-2-pyrone (50.0 mg, 0.24 mmol, 1 eq.), 2-iodophenol (64 mg, 0.29 mmol, 1.2 eq.), and K_2CO_3 (50 mg, 0.36 mmol, 1.5 eq.) in acetone (1 mL) was stirred at 60 °C for 16 hours. The reaction was quenched by addition of water (1 mL) and ethyl acetate (3 mL), and the layers separated. The aqueous layer was extracted using ethyl acetate (3 × 3 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc in hexanes) afforded the title compound as a white solid (77.6 mg, 82.9%).

Mpt: 155-157 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.91 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.84 – 7.89 (m, 2H), 7.47 – 7.52 (m, 3H), 7.44 (ddd, *J* = 8.1, 7.4, 1.5 Hz, 1H), 7.17 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.07 (ddd, *J* = 8.0, 7.4, 1.5 Hz, 1H), 6.70 (d, *J* = 2.1 Hz, 1H), 5.20 (d, *J* = 2.1 Hz, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 169.6, 163.7, 161.5, 152.4, 140.4, 131.3, 130.9, 130.2, 128.0, 128.4, 125.8, 122.4, 97.3, 92.2, 89.7; **MS** (ESI) *m/z* (rel.%): 413 [MNa^+] (34), 391 [MH^+] (100); **HRMS** (ESI) calculated for $C_{17}H_{12}IO_3$:390.9826, found: 390.9820; **IR** (neat): 3093, 2962, 1698, 1629, 1555, 1402, 1257, 1218, 1173, 1020, 808, 766 cm^{-1}.

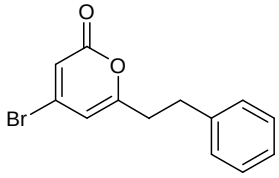
9-Phenyl-benzofuro[3,2-*c*]-2-pyrone (224)



The title compound was prepared according to General Procedure B, on a 0.13 mmol scale, to afford the product as a yellow solid (20.0 mg, 58.8%).

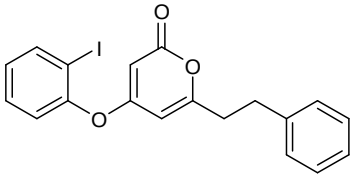
^{1}H-NMR (400 MHz, $CDCl_3$): 8.09 (m, 1H), 7.93 – 7.98 (m, 2H), 7.60 (m, 1H), 7.49 – 7.53 (m, 3H), 7.43 – 7.47 (m, 2H), 7.18 (s, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 164.4, 160.8, 158.7, 155.3, 131.4, 131.1, 129.1, 126.4, 125.9, 125.1, 122.9, 121.6, 111.5, 104.7, 93.2; **MS** (ESI) *m/z* (rel.%): 263 [MH^+] (100), 251 (28), 159 (26), 149 (15); **HRMS** (ESI) calculated for $C_{17}H_{11}O_3$:263.0703, found: 263.0706; **IR** (neat): 3090, 2161, 1721, 1560, 1537, 1446, 1382, 1021, 746, 687 cm^{-1}.

4-(2-iodophenoxy)-6-phenethyl-2-pyrone (225) *via* 4-Bromo-6-phenethyl-2-pyrone



To a solution of 4-hydroxy-6-phenethyl-2-pyrone **90** (100 mg, 0.46 mmol, 1 eq.) in DMF (1 ml) under nitrogen, was added carefully PBr_3 (502 mg, 1.85 mmol, 4 eq.) over 10 minutes. The reaction was then stirred at 80 °C for 18 hours and allowed to cool to ambient temperature, then DMF was removed under high vacuum and water (2 ml) and Et_2O (5 ml) added. The organic layer was separated and the aqueous layer extracted with Et_2O (5 × 5 ml) then the combined organic extracts dried over $MgSO_4$ and concentrated in *vacuo* to give the crude product. Purification via flash column chromatography (10% EtOAc in hexanes) gave the title compound as a yellow oil. (50.3 mg, 39.2%).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.20 – 7.26 (m, 2H), 7.17 (m, 1H), 7.07 – 7.11 (m, 2H), 6.39 (d, *J* = 1.6 Hz, 1H), 6.05 (d, *J* = 1.6 Hz, 1H), 2.90 (t, *J* =7.9 Hz, 2H), 2.70 (t, *J* = 7.9 Hz, 2H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 164.3, 160.6, 141.0, 139.4, 128.6, 128.2, 126.6, 115.1, 108.2, 35.4, 32.8; **MS** (ESI) *m/z* (rel.%): 303 [^{81}Br-MNa$^+$] (57), 301 [^{79}Br-MNa$^+$] (58), 281 [^{81}Br-MH$^+$] (96), 279 [^{79}Br-MH$^+$] (100); **HRMS** (ESI) calculated for $C_{13}H_{12}{}^{79}BrO_2$: 279.0015, found: 279.0010;

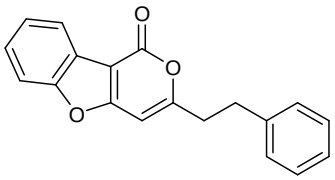


A solution of 4-Bromo-6-phenethyl-2-pyrone (45.0 mg, 0.16 mmol, 1 eq.), 2-iodophenol (40 mg, 0.18 mmol, 1.1 eq.), and K_2CO_3 (33 mg, 0.24 mmol, 1.5 eq.) in acetone (1 mL) was stirred at 60 °C for 16 hours. The reaction was quenched by addition of water (1 mL) and ethyl acetate (3 mL), and the layers separated. The aqueous layer was extracted using ethyl acetate (3 × 3 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc in hexanes) afforded the product as a yellow solid (39.4 mg, 58.9%).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.87 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.40 (ddd, *J* = 8.1, 7.4, 1.5 Hz, 1H), 7.27– 7.34 (m, 2H), 7.23 (m, 1H), 7.17– 7.21 (m, 2H), 7.08 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.04 (td, *J* = 1.5, 7.8, 1H), 5.95 (d, *J* = 2.2 Hz, 1H), 5.08 (d, *J* = 2.2 Hz, 1H), 2.98– 3.06 (m, 2H), 2.79– 2.88 (m, 2H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 169.3, 165.9, 164.3,

152.3, 140.3, 139.7, 130.1, 128.6, 128.3, 128.3, 126.5, 122.3, 99.7, 91.6, 89.6, 35.7, 32.9; **MS** (ESI) *m/z* (rel.%): 441 [MNa^+] (16), 419 [MH^+] (100); **HRMS** (ESI) calculated for $C_{19}H_{16}IO_3$: 419.0139, found: 419.0130; **IR** (DCM): 3065, 3030, 2932, 1724, 1643, 1571, 1497, 1329, 1269, 1262, 1227, 1131, 1022 cm^{-1}.

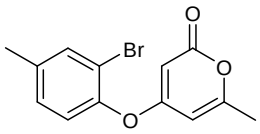
9-Phenethyl-benzofuro[3,2-*c*]-2-pyrone (226)



The title compound was prepared according to General Procedure B, on a 0.071 mmol scale, to afford the product as a yellow solid (16.3 mg, 68.2%).

R_f = 0.58 (20% EtOAc in hexanes); Mpt: 130-132 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.01 – 8.08 (m, 1H), 7.51 – 7.58 (m, 1H), 7.38 – 7.45 (m, 2H), 7.27 – 7.33 (m, 2H), 7.25 – 7.18 (m, 3H), 6.46 (t, *J* = 0.7 Hz, 1H), 3.09 (dd, *J* = 8.5, 6.4 Hz, 2H), 2.94 – 2.99 (m, 2H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 165.2, 164.2, 155.0, 139.7, 128.7, 128.3, 126.5, 126.2, 125.0, 122.9, 121.4, 111.5, 104.0, 99.9, 95.9, 36.3, 33.3; **MS** (ESI) *m/z* (rel.%): 313 [MNa^+] (44), 291 [MH^+] (100); **HRMS** (ESI) calculated for $C_{19}H_{15}O_3$: 291.1016, found: 291.1011; **IR** (neat): 3085, 3057, 2921, 1727, 1612, 1571, 1447, 1186, 1029, 970, 937, 817, 750, 701 cm^{-1}.

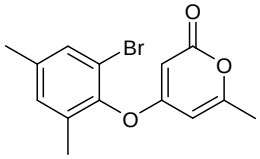
4-(2-bromo-4-methyl-phenoxy)-6-methyl-2-pyrone (228a)



The title compound was prepared according to General Procedure A, on a 1 mmol scale, to afford the product as a white solid (283.5 mg, 96.1%).

Mpt: 64-65 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.46 (d, *J* = 1.5 Hz, 1H), 7.15 (dd, *J* = 1.5, 8.1 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.00 (dq, *J* = 2.2, 0.9 Hz, 1H), 5.08 (d, *J* = 2.2, 1H), 2.36 (s, 3H), 2.26 (d, *J* = 0.9 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 169.8, 164.4, 163.5, 147.0, 138.3, 134.4, 129.7, 122.6, 115.4, 99.6, 90.9, 20.6, 20.0; **MS** (ESI) *m/z* (rel.%): 297 [^{81}Br-MH^+] (98), 295 [^{79}Br-MH^+] (100); **HRMS** (ESI) calculated for $C_{13}H_{12}{}^{79}BrO_3$: 294.9964, found: 294.9972; **IR** (neat): 3072, 1726, 1648, 1561, 1488, 1449, 1395, 1316, 1239, 1128, 850, 830 cm^{-1}.

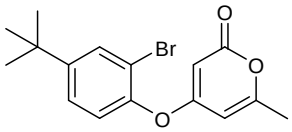
4-(2-bromo-4,6-dimethyl-phenoxy)-6-methyl-2-pyrone (228b)



The title compound was prepared according to General Procedure A, on a 4 mmol scale, to afford the product as a white solid (454 mg, 36.8%).

Mpt: 138-142 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.27 (m, 1H), 7.00 (m, 1H), 6.02 (dq, *J* = 2.0, 0.9 Hz, 1H), 5.02 (d, *J* = 2.0 Hz, 1H), 2.31 (app. t, *J* = 0.7 Hz, 3H), 2.27 (d, *J* = 0.9, 3H), 2.14 (app. t, *J* = 0.6 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 169.0, 164.6, 163.6, 145.3, 137.9, 132.0, 131.8, 131.4, 115.7, 99.4, 90.1, 20.6, 20.1, 16.4; **MS** (ESI) *m/z* (rel.%): 333 [^{81}Br-MNa^+] (17), 331 [^{79}Br-MNa^+] (18), 311 [^{81}Br-MH^+] (97), 309 [^{79}Br-MH^+] (100); **HRMS** (ESI) calculated for $C_{14}H_{14}{}^{79}BrO_3$: 309.0121, found: 309.0119; **IR** (neat): 3074, 2922, 1699, 1640, 1563, 1445, 1400, 1220, 1203, 1134, 981, 828 cm^{-1}.

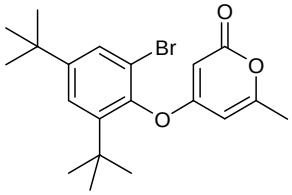
4-(2-bromo-4-*tert*-butyl-phenoxy)-6-methyl-2-pyrone (228c)



The title compound was prepared according to General Procedure A, on a 2 mmol scale, to afford the product as a white solid (442 mg, 65.6%).

Mpt: 148-149 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.60 (d, *J* = 2.2 Hz, 1H), 7.35 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.00 (d, *J* = 2.0 Hz, 1H), 5.06 (d, *J* = 2.0 Hz, 1H), 2.25 (s, 3H), 1.30 (s, 9H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 169.8, 164.4, 163.4, 151.7, 146.8, 131.0, 126.2, 122.4, 115.3, 99.6, 90.7, 34.7, 31.1, 20.0; **MS** (ESI) *m/z* (rel.%): 361 [^{81}Br-MNa^+] (20), 359 [^{79}Br-MNa^+] (22), 339 [^{81}Br-MH^+] (96), 337 [^{79}Br-MH^+] (100); **HRMS** (ESI) calculated for $C_{16}H_{18}{}^{79}BrO_3$: 337.0434, found: 337.0425; **IR** (neat): 3089, 2955, 1707, 1644, 1567, 1491, 1440, 1403, 1225, 1132, 1047, 979, 858, 822 cm^{-1}.

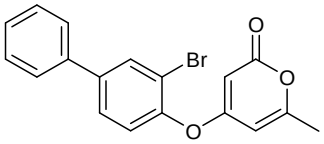
4-(2-bromo-4,6-di-*tert*-butyl-phenoxy)-6-methyl-2-pyrone (228d)



To a solution of 2-bromo-4,6-di-*tert*-butylphenol (285 mg, 1 mmol, 1 eq.) under nitrogen in THF (2 ml) was added NaH (24 mg, 1 mmol, 1eq.) in one portion. The solution was stirred at 25 °C for 1 hour then 4-bromo-6-methyl-2-pyrone (189 mg, 1 mmol, 1 eq.) was added and the solution stirred at 60 °C for 16 hours. The reaction was allowed to cool to ambient temperature and quenched by the addition of water (1 ml). The solution was then extracted by EtOAc (3 × 3 ml) and the combined organic extracts dried over $MgSO_4$, concentrated in vacuo to afford the crude product. Purification by flash column chromatography (15% EtOAc in hexanes) afforded the title compound as a white solid (108.4mg, 27.6%).

Mpt: 108-110 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.45 (d, *J* = 2.3 Hz, 1H), 7.38 (d, *J* = 2.3 Hz, 1H), 5.99 (s, 1H), 5.05 (s, 1H), 2.27 (s, 3H), 1.31 (s, 9H), 1.30 (s, 9H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 169.7, 164.6, 163.5, 150.5, 145.2, 143.5, 129.1, 124.3, 117.2, 99.7, 91.7, 35.6, 34.8, 31.2, 30.6, 20.1; **MS** (ESI) *m/z* (rel.%): 417 [^{81}Br-MNa^{+}] (17), 415 [^{79}Br-MNa^{+}] (17), 395 [^{81}Br-MH^{+}] (100), 393 [^{79}Br-MH^{+}] (98); **HRMS** (ESI) calculated for $C_{20}H_{26}{}^{79}BrO_3$: 393.1060, found: 393.1055; **IR** (neat): 2959, 1719, 1649, 1566, 1438, 1401, 1223, 1128, 979, 852, 826 cm^{-1}.

4-(2-bromo-4-phenyl-phenoxy)-6-methyl-2-pyrone (228e)

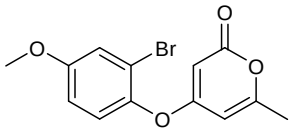


The title compound was prepared according to General Procedure A, on a 2 mmol scale, to afford the product as a white solid (646 mg, 90.4%).

Mpt: 125-127 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.86 (d, *J* = 2.2 Hz, 1H), 7.57 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.53 – 7.56 (m, 2H), 7.44 – 7.49 (m, 2H), 7.40 (m, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 6.05 (dq, *J* = 2.2, 0.8 Hz, 1H), 5.17 (dd, *J* = 2.2, 0.5 Hz, 1H), 2.29 (dd, *J* = 0.8, 0.5 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 169.6, 164.4, 163.6, 148.5, 141.6, 138.5, 132.6, 129.0, 128.2, 127.8, 127.1, 123.2, 116.2, 99.5, 91.1, 20.1; **MS** (ESI) *m/z* (rel.%): 381 [^{81}Br-MNa^{+}] (14), 379 [^{79}Br-MNa^{+}] (14), 359 [^{81}Br-MH^{+}] (98), 357 [^{79}Br-MH^{+}] (100); **HRMS**

(ESI) calculated for $C_{18}H_{14}{}^{79}BrO_3$: 357.0121, found: 357.0117; **IR** (neat): 3060, 1717, 1692, 1644, 1566, 1474, 1402, 1227, 1132, 1044, 982, 858, 817, 769, 738, 698 cm^{-1}.

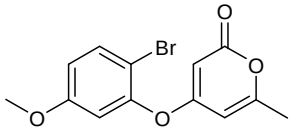
4-(2-bromo-4-methoxy-phenoxy)-6-methyl-2-pyrone (228f)



The title compound was prepared according to General Procedure A, on a 1 mmol scale, to afford the product as a white solid (279.3 mg, 89.8%).

Mpt: 98-99 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.15 (d, *J* = 2.9 Hz, 1H), 7.04 (d, *J* = 8.9 Hz, 1H), 6.88 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.00 (d, *J* = 2.2 Hz, 1H), 5.08 (d, *J* = 2.2 Hz, 1H), 3.81 (s, 3H), 2.26 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 170.1, 164.5, 163.4, 158.2, 142.9, 123.3, 118.8, 116.1, 114.8, 99.5, 90.8, 55.9, 20.0; **MS** (ESI) *m/z* (rel.%): 335 [^{81}Br-MNa^+] (99), 333 [^{79}Br-MNa^+] (100), 313 [^{81}Br-MH^+] (93), 311 [^{79}Br-MH^+] (311); **HRMS** (ESI) calculated for $C_{13}H_{12}{}^{79}BrO_4$: 310.9913, found: 310.9909; **IR** (neat): 3193, 3087, 1726, 1647, 1569, 1491, 1446, 1403, 1211, 1133, 1018, 982, 841, 805, 779 cm^{-1}.

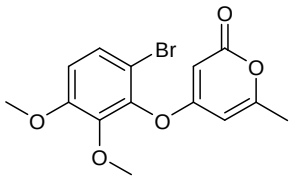
4-(2-bromo-5-methoxy-phenoxy)-6-methyl-2-pyrone (228g)



The title compound was prepared according to General Procedure A, on a 3 mmol scale, to afford the product as a white solid (492 mg, 52.7%).

Mpt: 103-106 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.15 (d, *J* = 2.9 Hz, 1H), 7.04 (d, *J* = 8.9 Hz, 1H), 6.88 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.00 (d, *J* = 2.2 Hz, 1H), 5.08 (d, *J* = 2.2 Hz, 1H), 3.81 (s, 3H), 2.26 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 170.1, 164.5, 163.4, 158.2, 142.9, 123.3, 118.8, 116.1, 114.8, 99.5, 90.8, 55.9, 20.0; **MS** (ESI) *m/z* (rel.%): 335 [^{81}Br-MNa^+] (68), 333 [^{79}Br-MNa^+] (70), 313 [^{81}Br-MH^+] (100), 311 [^{79}Br-MH^+] (100); **HRMS** (ESI) calculated for $C_{13}H_{12}{}^{79}BrO_4$: 310.9913, found: 310.9909; **IR** (neat): 3066, 1709, 1645, 1566, 1483, 1441, 1399, 1314, 1236, 1199, 1137, 1018, 991, 858, 836 cm^{-1}.

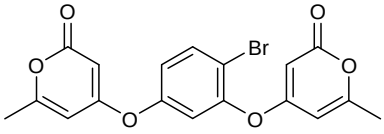
4-(6-bromo-2,3-dimethoxy-phenoxy)-6-methyl-2-pyrone (228h)



The title compound was prepared according to General Procedure A, on a 2 mmol scale, to afford the product as a white solid (116 mg, 17.0%).

Mpt: 127-129 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.29 (d, *J* = 9.0 Hz, 1H), 6.78 (d, *J* = 9.0 Hz, 1H), 6.01 (dq, *J* = 2.2, 0.9 Hz, 1H), 5.14 (dq, *J* = 0.4, 2.2 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 2.27 (dd, *J* = 0.9, 0.4 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 169.2, 164.5, 163.5, 153.4, 143.2, 142.7, 127.3, 111.5, 107.1, 99.3, 90.8, 61.3, 56.3, 20.1; **MS** (ESI) *m/z* (rel.%): 365 [^{81}Br-MNa^+] (17), 363 [^{79}Br-MNa^+] (18), 343 [^{81}Br-MH^+] (97), 341 [^{79}Br-MH^+] (100); **HRMS** (ESI) calculated for $C_{14}H_{14}{}^{79}BrO_5$: 341.0019, found: 341.0012; **IR** (neat): 3095, 2945, 1702, 1623, 1561, 1529, 1443, 1219, 1137, 1081, 983, 841, 818 cm^{-1}.

1-Bromo-2,4-bis(6-methyl-2-pyronyl-4-oxy)-benzene (228i)

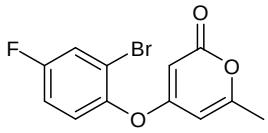


A solution of 4-Bromo-6-methyl-2-pyrone (756 mg, 4 mmol, 2 eq.), 2-bromoresorcinol (378 mg, 2 mmol, 1 eq.), and K_2CO_3 (690 mg, 5 mmol, 2.5 eq.) in acetone (4 ml/mmol) was stirred at 60 °C for 16 hours. The reaction was quenched by addition of water and ethyl acetate, and the layers separated. The aqueous layer was extracted 3 times using ethyl acetate and the combined organic extracts dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (10-30 % EtOAc in hexanes) to afford the title compound as a white crystalline solid (395 mg, 48.8%).

Mpt: 143-146 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.72 (d, *J* = 8.7 Hz, 1H), 6.97 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.93 (d, *J* = 2.7 Hz, 1H), 6.02 (dq, *J* = 2.2, 0.9 Hz, 1H), 5.95 (dq, *J* = 2.2, 0.9 Hz, 1H), 5.27 (d, *J* = 2.2 Hz, 1H), 5.11 (d, *J* = 2.2 Hz, 1H), 2.28 (d, *J* = 0.9 Hz, 3H), 2.27 (d, *J* = 0.9 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 169.5, 168.9, 164.0, 164.0, 163.9, 152.4, 150.4, 135.3, 120.8, 116.4, 113.3, 99.4, 99.3, 91.7, 91.3, 30.9, 20.1, 20.1; **MS** (ESI) *m/z* (rel.%): 429 [^{81}Br-MNa^+] (97), 427 [^{79}Br-MNa^+] (100), 407 [^{81}Br-MH^+] (90), 405 [^{79}Br-MH^+] (90); **HRMS** (ESI) calculated for $C_{18}H_{13}{}^{79}BrNaO_6$: 426.9788, found:

426.9794; **IR** (neat): 3058, 1722, 1644, 1584, 1565, 1473, 1444, 1399, 1315, 1264, 1227, 1179, 1140, 982, 856, 812 cm^{-1}.

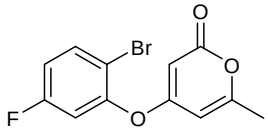
4-(2-Bromo-4-fluoro-phenoxy)-6-methyl-2-pyrone (228j)



The title compound was prepared according to General Procedure A, on a 1 mmol scale, to afford the product as a white solid (260 mg, 87.1%).

Mpt: 112-113 °C; **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 7.41 (ddd, *J* = 7.5, 2.5, 0.7 Hz, 1H), 7.15 – 7.08 (m, 2H), 6.01 (dq, *J* = 0.8, 2.1 Hz, 1H), 5.06 (d, *J* = 2.1 Hz, 1H), 2.28 (d, *J* = 0.8 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 169.53, 163.75, 162.8 (d, *J* = 273.1 Hz), 158.97, 145.7 (d, *J* = 3.6 Hz), 123.9 (d, *J* = 9.0 Hz), 121.3 (d, *J* = 26.0 Hz), 116.5 (d, *J* = 10.2 Hz), 116.1 (d, *J* = 23.3 Hz), 99.40, 90.98, 20.09; **^{19}F-NMR** (376 MHz, $CDCl_3$): -112.45 (td, *J* = 7.5, 5.4 Hz); **MS** (ESI) *m/z* (rel.%): 301 [^{81}Br-MH^+] (97), 299 [^{79}Br-MH^+] (100); **HRMS** (ESI) calculated for $C_{12}H_9{}^{79}BrFO_3$: 298.9714, found: 298.9714; **IR** (neat): 3065, 1731, 1651, 1568, 1480, 1443, 1402, 1246, 1182, 1134, 980, 851, 827, 783 cm^{-1}.

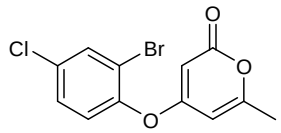
4-(2-Bromo-5-fluoro-phenoxy)-6-methyl-2-pyrone (228k)



The title compound was prepared according to General Procedure A, on a 1 mmol scale, to afford the product as a white solid (262 mg, 87.7%).

Mpt: 120-122 °C; **^{1}H-NMR** (400 MHz, *$CDCl_3$*): 7.62 (dd, *J* = 8.9, 5.7 Hz, 1H), 6.97 (ddd, *J* = 8.9, 7.7, 2.9, 1H), 6.92 (dd, *J* = 8.4, 2.9 Hz, 1H), 6.01 (dq, *J* = 2.1, 0.8 Hz, 1H), 5.10 (d, *J* = 2.1 Hz, 1H), 2.28 (d, *J* = 0.7 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 169.0, 164.1, 163.9,162.2 (d, *J* = 251.2 Hz), 150.0 (d, *J* = 10.6 Hz), 134.8 (d, *J* = 9.0 Hz), 115.5 (d, *J* = 22.2 Hz), 111.2 (d, *J* = 24.9 Hz), 110.59 (d, *J* = 4.2 Hz), 99.3, 91.3, 20.1; **^{19}F-NMR** (376 MHz, $CDCl_3$): -110.01 (td, *J* = 8.0, 5.7 Hz); **MS** (ESI) *m/z* (rel.%): 301 [^{81}Br-MH^+] (97), 299 [^{79}Br-MH^+] (100); **HRMS** (ESI) calculated for $C_{12}H_9BrFO_3$: 298.9714, found: 298.9711; **IR** (neat): 3063, 2923, 2855, 1726, 1644, 1563, 1453, 1401, 1233, 1166, 1134, 995, 947, 851, 808 cm^{-1}.

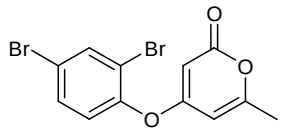
4-(2-Bromo-4-chloro-phenoxy)-6-methyl-2-pyrone (228ℓ)



The title compound was prepared according to General Procedure A, on a 2 mmol scale, to afford the product as a white solid (611 mg, 96.8%).

Mpt: 114-115 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.67 (d, *J* = 2.4 Hz, 1H), 7.36 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.00 (d, *J* = 2.2 Hz, 1H), 5.08 (d, *J* = 2.2 Hz, 1H), 2.28 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 169.2, 164.1, 163.8, 148.1, 133.8, 132.9, 129.3, 123.9, 116.7, 99.3, 91.1, 20.1; **MS** (ESI) *m/z* (rel.%): 319 [^{37}Cl/^{81}Br -MH$^+$] (23), 317 [^{35}Cl/^{81}Br, ^{37}Cl/^{79}Br-MH$^+$] (100), 315 [^{35}Cl/^{79}Br -MH$^+$] (77); **HRMS** (ESI) calculated for $C_{12}H_9{}^{79}Br^{35}ClO_3$: 314.9418, found: 314.9414; **IR** (neat): 3091, 3063, 1726, 1647, 1564, 1470, 1446, 1401, 1234, 1131, 1090, 979, 849, 813 cm^{-1}.

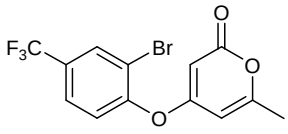
4-(2,4-Dibromo-phenoxy)-6-methyl-2-pyrone (228m)



The title compound was prepared according to General Procedure A, on a 2 mmol scale, to afford the product as a white solid (514 mg, 71.4%).

Mpt: 114-115 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.81 (d, *J* = 2.3 Hz, 1H), 7.51 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 6.00 (dq, *J* = 2.2, 0.9 Hz, 1H), 5.08 (d, *J* = 2.2 Hz, 1H), 2.28 (d, *J* = 0.9 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 169.1, 164.1, 163.8, 148.6, 136.6, 132.3, 124.3, 120.33, 117.0, 99.3, 91.1, 20.1; **MS** (ESI) *m/z* (rel.%): 363 [^{81}Br /^{81}Br -MH$^+$] (45), 361 [^{79}Br /^{81}Br,] (100), 359 [^{79}Br /^{79}Br-MH$^+$] (46); **HRMS** (ESI) calculated for $C_{12}H_9{}^{79}Br_2O_3$: 358.8913, found: 358.8911; **IR** (neat): 3204, 1731, 1647, 1566, 1535, 1468, 1445, 1402, 1235, 1194, 1132, 982, 852, 814 cm^{-1}.

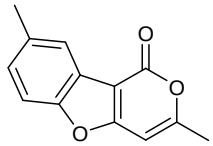
4-(2-Bromo-4-(trifluoromethyl)-phenoxy)-6-methyl-2-pyrone (228n)



The title compound was prepared according to General Procedure A, on a 0.5 mmol scale, to afford the product as a white solid (166.4 mg, 95.3%).

Mpt: 91-93 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.93 (dq, *J* = 2.2, 0.7 Hz, 1H), 7.65 (ddq, *J* = 8.4, 2.2, 0.7 Hz, 1H), 7.26 (dq, *J* =8.4, 0.8 Hz, 1H), 6.02 (dq, *J* = 2.3, 0.9 Hz, 1H), 5.07 (dq, *J* = 2.3, 0.6 Hz, 1H), 2.27 (dd, *J* = 0.9, 0.6 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 168.8, 164.1, 163.9, 152.1, 131.6 (q, *J* = 3.7 Hz), 130.3 (q, *J* = 33.9 Hz), 127.7 (q, *J* = 3.6 Hz), 126.4 (q, *J* = 3.5 Hz), 123.6, 116.6, 99.3, 91.4, 20.1; **^{19}F-NMR** (376 MHz, $CDCl_3$): -62.38 (s); **MS** (ESI) *m/z* (rel.%): 351 [^{81}Br-MH^+] (96), 349 [^{79}Br-MH^+] (100), 282 (7), 271 (12); **HRMS** (ESI) calculated for $C_{13}H_9{}^{79}BrF_3O_3$: 348.9682, found: 348.9685; **IR** (neat): 3086, 2960, 2159, 1721, 1646, 1607, 1568, 1511, 1446, 1405, 1320, 1245, 1119, 1075, 982, 818 cm^{-1}.

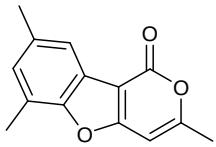
4,9-Dimethyl-benzofuro[3,2-*c*]-2-pyrone (229a)



The title compound was prepared according to General Procedure B, on a 0.25 mmol scale, to afford the product as a yellow solid (38.4 mg, 71.8%).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.82 (dq, *J* = 1.9, 0.7 Hz, 1H), 7.41 (d, *J* = 8.4, 1H), 7.20 (ddq, *J* = 8.4, 1.9, 0.7 Hz, 1H), 6.51 (q, *J* = 0.9, 1H), 2.47 (app. t, *J* = 0.7 Hz, 3H), 2.41 (d, *J* = 0.9 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 164.6, 162.6, 159.7, 153.3, 134.8, 127.2, 122.8, 121.2, 110.9, 103.5, 96.0, 21.3, 20.6; **MS** (ESI) *m/z* (rel.%): 237 [MNa^+] (40), 215 [MH^+] (100); **HRMS** (ESI) calculated for $C_{13}H_{11}O_3$ [MH^+]: 215.0703, found: 215.0706; **IR** (neat): 3088, 2921, 1727, 1615, 1571, 1450, 1190, 1037, 971, 941, 821, 795, 773 cm^{-1}.

4,6,9-Trimethyl-benzofuro[3,2-*c*]-2-pyrone (229b)

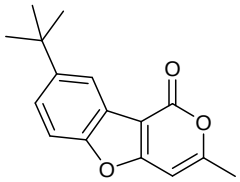


The title compound was prepared according to General Procedure B, on a 0.25 mmol scale, to afford the product as a yellow solid (44.8 mg, 78.6%).

R_f = 0.43 (20% EtOAc in hexanes); Mpt: 149-150 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.65 (s, 1H), 7.02 (s, 1H), 6.52 (s, 1H), 2.50 (s, 3H), 2.44 (s, 3H), 2.41 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 164.3, 162.4, 159.8, 152.4, 134.8, 128.5, 122.4, 121.1, 118.6, 103.8, 96.0, 21.2, 20.6, 14.9; **MS** (ESI) *m/z* (rel.%): 251 [MNa^+] (16), 229 [MH^+] (100); **HRMS** (ESI)

calculated for $C_{14}H_{13}O_3$: 229.0859, found: 229.0858; **IR** (neat): 3097, 2924, 1731, 1621, 1572, 1446, 1287, 1222, 1180, 1033, 970, 939, 842, 798, 736 cm^{-1}.

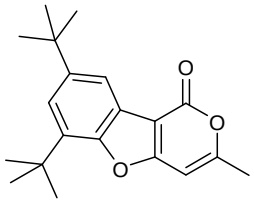
4-*tert*-Butyl-9-methyl-benzofuro[3,2-*c*]-2-pyrone (229c)



The title compound was prepared according to General Procedure B, on a 0.25 mmol scale, to afford the product as a yellow solid (44.9 mg, 70.2%).

R_f = 0.50 (20% EtOAc in hexanes); Mpt: 119-120 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.03 (app. t, *J* = 1.3 Hz, 1H), 7.46 (app. d, *J* = 1.3 Hz, 2H), 6.52 (q, *J* = 0.8 Hz, 1H), 2.42 (d, *J* = 0.8 Hz, 3H), 1.40 (s, 9H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 164.7, 162.6, 159.7, 153.1, 148.4, 123.9, 122.6, 117.8, 110.7, 103.8, 96.0, 35.0, 31.8, 20.6; **MS** (ESI) *m/z* (rel.%): 279 [MNa^+] (6), 257 [MH^+] (100); **HRMS** (ESI) calculated for $C_{16}H_{17}O_3$: 257.1172, found: 257.1176; **IR** (neat): 2964, 1732, 1626, 1570, 1459, 1192, 1030, 968, 932, 889, 824, 787 cm^{-1}.

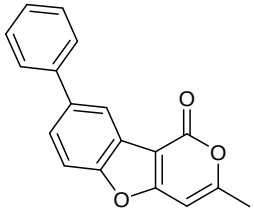
4,6-Di-*tert*-butyl-9-methyl-benzofuro[3,2-*c*]-2-pyrone (229d)



The title compound was prepared according to General Procedure B, on a 0.16 mmol scale, to afford the product as a yellow solid (35.4 mg, 70.9%).

R_f = 0.64 (20% EtOAc in hexanes); Mpt: 144-147 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.90 (d, *J* = 2.0 Hz, 1H), 7.37 (d, *J* = 2.0 Hz, 1H), 6.56 (q, *J* = 0.9 Hz, 1H), 2.42 (d, *J* = 0.9 Hz, 3H), 1.51 (s, 9H), 1.40 (s, 9H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 163.9, 162.1, 159.8, 151.5, 148.1, 134.1, 123.0, 120.8, 115.6, 103.7, 96.1, 35.1, 34.5, 31.8, 29.9, 20.6; **MS** (ESI) *m/z* (rel.%): 335 [MNa^+] (18), 313 [MH^+] (100); **HRMS** (ESI) calculated for $C_{20}H_{23}O_3$: 313.1798, found: 313.1791; **IR** (neat): 2954, 1737, 1619, 1569, 1365, 1243, 1226, 1064, 971, 874, 815, 752 cm^{-1}.

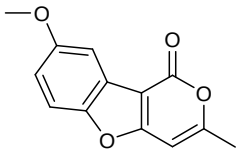
4-Phenyl-9-methyl-benzofuro[3,2-*c*]-2-pyrone (229e)



The title compound was prepared according to General Procedure B, on a 0.25 mmol scale, to afford recovered starting material (19.5 mg, 21.8%) and the product as a yellow solid (30.0 mg, 43.5% [55.6% b.r.s.m]).

R_f = 0.36 (20% EtOAc in hexanes); Mpt: 211-213 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.24 (dd, *J* = 1.9, 0.7 Hz, 1H), 7.68 – 7.65 (m, 2H), 7.65 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.60 (dd, *J* = 8.6, 0.7 Hz, 1H), 7.44 – 7.49 (m, 2H), 7.38 (m, 1H), 6.56 (q, *J* = 0.8 Hz, 1H), 2.44 (d, *J* = 0.8 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 165.0, 163.1, 154.5, 140.6, 138.7, 128.8, 127.5, 127.4, 125.6, 123.5, 119.7, 111.6, 103.8, 99.9, 95.9, 20.7; **MS** (ESI) *m/z* (rel.%): 299 [MNa^+] (8), 277 [MH^+] (100); **HRMS** (ESI) calculated for $C_{18}H_{13}O_3$: 277.0859, found: 277.0862; **IR** (neat): 3055, 2921, 1733, 1625, 1575, 1443, 1242, 1196, 1030, 968, 930, 887, 829, 805, 775, 762, 703, 682 cm^{-1}.

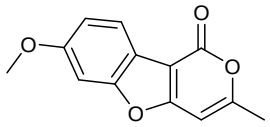
4-Methoxy-9-methyl-benzofuro[3,2-*c*]-2-pyrone (229f)



The title compound was prepared according to General Procedure B, on a 0.25 mmol scale, to afford recovered starting material (24 mg, 30.8%) and the product as a yellow solid (37.1 mg, 64.5% [93% b.r.s.m]).

R_f = 0.31 (20% EtOAc in hexanes); Mpt: 155-157 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.48 (d, *J* = 2.6 Hz, 1H), 7.43 (d, *J* = 9.0 Hz, 1H), 6.98 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.51 (q, *J* = 0.9 Hz, 1H), 3.90 (s, 3H), 2.42 (d, *J* = 0.9 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 164.9, 162.6, 159.7, 157.5, 149.6, 123.6, 115.1, 112.1, 103.9, 103.2, 96.0, 56.0, 20.6; **MS** (ESI) *m/z* (rel.%): 253 [MNa^+] (45), 231 [MH^+] (100); **HRMS** (ESI) calculated for $C_{13}H_{11}O_4$ [MH^+]: 231.0652, found: 231.0651; **IR** (neat): 3095, 2958, 1728, 1631, 1619 1572, 1461, 1436, 1274, 1226, 1177, 1023, 965, 937, 848, 813, 786, 771 cm^{-1}.

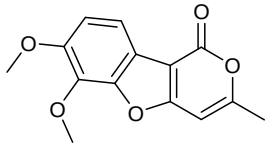
5-Methoxy-9-methyl-benzofuro[3,2-*c*]-2-pyrone (229g)



The title compound was prepared according to General Procedure B, on a 0.5 mmol scale, to afford the product as a yellow solid (76.7 mg, 66.7%).

R_f = 0.29 (20% EtOAc in hexanes); Mpt: 172-173 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.88 (d, *J* = 8.6 Hz, 1H), 7.07 (d, *J* = 2.2 Hz, 1H), 7.01 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.51 (q, *J* = 0.9, 1H), 3.88 (s, 3H), 2.41 (d, *J* = 0.9 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 164.0, 161.7, 159.7, 159.2, 156.1, 121.5, 115.9, 113.0, 103.8, 96.7, 95.9, 55.8, 20.5; **MS** (ESI) *m/z* (rel.%): 253 [MNa^+] (100), 231 [MH^+] (87); **HRMS** (ESI) calculated for $C_{13}H_{10}NaO_4$ [MNa^+]: 253.0471, found: 253.0469; **IR** (neat): 3095, 1715, 1569, 1496, 1270, 1137, 1110, 1036, 973, 939, 834, 801 cm^{-1}.

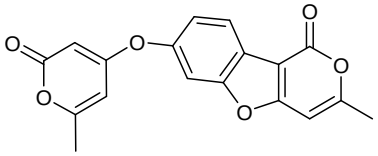
5,6-Dimethoxy-9-methyl-benzofuro[3,2-*c*]-2-pyrone (229h)



The title compound was prepared according to General Procedure B, on a 0.25 mmol scale, to afford the product as a yellow solid (20.5 mg, 31.5%).

R_f = 0.19 (20% EtOAc in hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.61 (d, *J* = 8.5 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.53 (q, *J* = 0.8 Hz, 1H), 4.15 (s, 3H), 3.95 (s, 3H), 2.41 (d, *J* = 0.8 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 164.3, 162.2, 159.6, 150.5, 147.1, 147.0, 118.0, 114.7, 110.8, 103.8, 95.9, 61.3, 57.0, 20.6; **MS** (ESI) *m/z* (rel.%): 283 [MNa^+] (8), 261 [MH^+] (100); **HRMS** (ESI) calculated for $C_{14}H_{13}O_5$: 261.0757, found: 261.0753; **IR** (neat): 3104, 2947, 1731, 1623, 1574, 1504, 1444, 1403, 1269, 1229, 1074, 1001, 971, 950, 801 cm^{-1}.

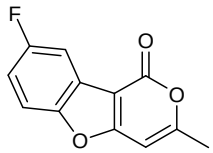
5-(6-methyl-2-pyronyl-4-oxy)-9-methyl-benzofuro[3,2-*c*]-2-pyrone (229i)



The title compound was prepared according to General Procedure B, on a 0.5 mmol scale, to afford the product as a yellow solid (26 mg, 16%).

Mpt: degrades > 215 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.05 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 2.1 Hz, 1H), 7.16 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.57 (d, *J* = 0.9 Hz, 1H), 6.00 (dd, *J* = 2.2, 0.9 Hz, 1H), 5.23 (d, *J* = 2.2 Hz, 1H), 2.45 (d, *J* = 0.9 Hz, 3H), 2.28 (d, *J* = 0.9 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 170.7, 165.5, 163.6, 163.5, 159.1, 157.9, 155.0, 150.6, 122.3, 121.4, 118.5, 105.3, 103.4, 99.9, 99.7, 95.8, 91.3, 20.7, 20.1; **MS** (ESI) *m/z* (rel.%): 347 [MNa^+] (98), 325 [MH^+] (100); **HRMS** (ESI) calculated for $C_{18}H_{13}O_6$: 325.0707, found: 325.0701; **IR** (neat): 3100, 1726, 1649, 1615, 1570, 1445, 1400, 1319, 1255, 1168, 1135, 1032, 982, 944, 819 cm^{-1}.

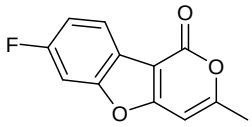
4-Fluoro -9-methyl-benzofuro[3,2-*c*]-2-pyrone (229j)



The title compound was prepared according to General Procedure B, on a 0.25 mmol scale using 2.5 mol% Pd_2(dba-4,4′-OMe)$_3$ and 10 mol% PPh_3, to afford the product as a yellow solid (22.5 mg, 41.3%).

R_f = 0.37 (20% EtOAc in hexanes); Mpt: 207-208 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.70 (dd, *J* = 8.1, 2.7 Hz, 1H), 7.48 (dd, *J* = 9.0, 3.9 Hz, 1H), 7.12 (app. td, *J* = 9.0, 2.7 Hz, 1H), 6.53 (q, *J* = 0.8 Hz, 1H), 2.43 (d, *J* = 0.8 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 165.71, 163.54, 160.3 (d, *J* = 242.1 Hz), 159.08, 151.0 (d, *J* = 1.3 Hz), 124.10 (d, *J* = 11.6 Hz), 113.65 (d, *J* = 26.4 Hz), 112.27 (d, *J* = 9.6 Hz), 107.49 (d, *J* = 26.5 Hz), 103.76 (d, *J* = 3.6 Hz), 95.85, 20.69; **^{19}F-NMR** (376 MHz, $CDCl_3$): -117.03 (ddd, *J* = 9.0, 8.1, 3.9 Hz); **MS** (ESI) *m/z* (rel.%): 241 [MNa^+] (67), 219 [MH^+] (100); **HRMS** (ESI) calculated for $C_{12}H_8FO_3$:219.0452, found: 241.0449; **IR** (neat): 3090, 2922, 1728, 1613, 1571, 1449, 1243, 1211, 1130, 1031, 972, 856, 797, 769 cm^{-1}.

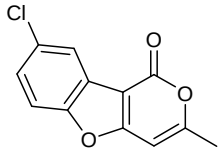
5-Fluoro -9-methyl-benzofuro[3,2-*c*]-2-pyrone (229k)



The title compound was prepared according to General Procedure B, on a 0.25 mmol scale, to afford recovered starting material (13.2 mg) and the product as a yellow solid (13.2 mg, 24.2%)

^{1}H-NMR (400 MHz, $CDCl_3$): 7.96 (dd, *J* = 8.6, 5.4 Hz, 1H), 7.28 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.17 (ddd, *J* = 9.4, 8.6, 2.3 Hz, 1H), 6.54 (q, *J* = 0.8 Hz, 1H), 2.43 (d, *J* = 0.8 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 165.1, 163.87 (d, *J* = 233.1 Hz), 162.8, 159.3, 154.93 (d, *J* = 13.5 Hz), 121.77 (d, *J* = 10.0 Hz), 119.10 (d, *J* = 2.0 Hz), 113.11 (d, *J* = 23.8 Hz), 99.78 (d, *J* = 27.4 Hz) 99.4, 95.8, 20.6; **^{19}F-NMR** (376 MHz, $CDCl_3$): -113.48 (td, *J* = 9.0, 5.4 Hz); **MS** (ESI) *m/z* (rel.%): 241 [MNa^+] (77), 219 [MH^+] (100); **HRMS** (ESI) calculated for $C_{12}H_8FO_3$: 298.9714, found: 298.9711; **IR** ($CHCl_3$): 1731, 1615, 1573, 1496, 1276, 947, 651 cm^{-1}.

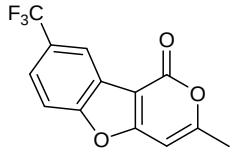
4-Chloro-9-methyl-benzofuro[3,2-*c*]-2-pyrone (229ℓ)



The title compound was prepared according to General Procedure B, on a 0.25 mmol scale, to afford the product as a yellow solid (19.5 mg, 33.3%).

R_f = 0.33 (20% EtOAc in hexanes); Mpt: 191-193 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.01 (dd, *J* = 2.2, 0.5 Hz, 1H), 7.47 (dd, *J* = 8.8, 0.5 Hz, 1H), 7.36 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.53 (q, *J* = 0.8 Hz, 1H), 2.43 (d, *J* = 0.8 Hz, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 165.4, 163.7, 158.9, 153.2, 130.8, 126.3, 124.3, 121.0, 112.4, 103.2, 95.8, 20.7; **MS** (ESI) *m/z* (rel.%): 259 [^{37}Cl-MNa^+] (10), 257 [^{35}Cl-MNa^+] (38), 237 [^{37}Cl-MH^+] (31), 235 [^{35}Cl-MH^+] (100); **HRMS** (ESI) calculated for $C_{12}H_8{}^{35}ClO_3$: 235.0156, found: 235.0156; **IR** (neat): 3093, 2923, 1737, 1627, 1570, 1438, 1258, 1194, 1030, 967, 928, 811, 797 cm^{-1}.

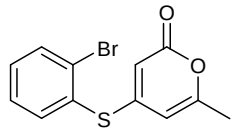
4-(Trifluoromethyl)-9-methyl-benzofuro[3,2-*c*]-2-pyrone (229n)



The title compound was prepared according to General Procedure B, on a 0.25 mmol scale, to afford the product as a yellow solid (7.1 mg, 10.6%).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.34 (dt, *J* = 1.5, 0.7 Hz, 1H), 7.70 – 7.63 (m, 2H), 6.59 (d, *J* = 0.8 Hz, 1H), 2.46 (d, *J* = 0.8 Hz, 3H); **^{19}F-NMR** (376 MHz, $CDCl_3$): -61.11 (d, J = 5.2 Hz); **MS** (ESI) *m/z* (rel.%): 269 [MH^+] (100), 249 (24), 215 (15), 126 (82), 84 (44); **HRMS** (ESI) calculated for $C_{13}H_8F_3O_3$: 269.0420, found: 269.0430; **IR** (neat): 2953, 2923, 2853, 1743, 1575, 1458, 1319, 1266, 1164, 1119, 1050, 970, 818 cm^{-1}.

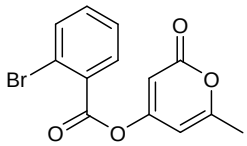
4-(2-Bromo-phenylsulfanyl)-6-methyl-2-pyrone (231)



The title compound was prepared according to General Procedure A, on a 1 mmol scale, to afford the product as a yellow solid (296 mg, >99%).

Mpt: 75-79 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.76 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.64 (dd, *J* = 7.6, 2.0, 1H), 7.41 (td, *J* = 7.6, 1.7 Hz, 1H), 7.36 (td, *J* = 7.6, 2.0 Hz, 1H), 5.86 (dq, *J* = 1.6, 0.9 Hz, 1H), 5.36 (d, *J* = 1.6, 1H), 2.21 (app. s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 161.5, 160.9, 158.2, 137.9, 134.4, 132.3, 130.7, 128.8, 128.3, 103.9, 102.6, 19.9; **MS** (ESI) *m/z* (rel.%): 299 [^{81}Br-MH^+] (100), 297 [^{79}Br-MH^+] (98); **HRMS** (ESI) calculated for $C_{12}H_{10}{}^{79}BrO_2S$: 296.9579, found: 296.9583; **IR** (neat): 3096, 1702, 1623, 1529, 1442, 1313, 1218, 1027, 981, 822, 749 cm^{-1}.

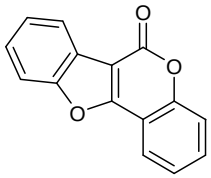
2-Bromo-benzoic acid (6-methyl-2-pyron-4-yl) ester (234)



To a solution of **9** (252 mg, 2 mmol, 2 eq.), 2-Bromo-benzoic acid (201 mg, 1 mmol, 1 eq.) and DMAP (6.6 mg, 0.05 mmol, 5 mol%) in DCM (3 ml) at 22 °C was added DIC (139 mg, 1.1 mmol, 1.1 eq.) carefully over 15 minutes. The reaction was stirred at 22 °C for 24

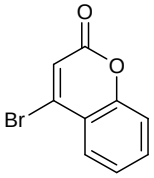
h and the solvent removed *in vacuo*. Purification *via* column chromatography (20% EtOAc in pet ether) afforded the title compound as a white crystalline solid (260 mg, 84.1%).
Mpt: 99-100 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.95 (m, 1H), 7.75 (m, 1H), 7.43 – 7.48 (m, 2H), 6.18 (d, *J* = 2.0 Hz, 1H), 6.13 (dq, *J* = 2.0, 0.8 Hz, 1H), 2.31 (d, *J* = 0.8 Hz, 2H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 163.5, 163.1, 161.9, 154.2, 135.0, 134.1, 132.2, 129.5, 127.5, 122.8, 101.4, 101.2, 20.2; **MS** (ESI) *m/z* (rel.%): 311 [^{81}Br-MH^+] (93), 309 [^{79}Br-MH^+] (100); **HRMS** (ESI) calculated for $C_{12}H_{10}{}^{79}BrO_2S$: 308.9757, found: 308.9755; **IR** (neat): 3093, 1726, 1638, 1565, 1432, 1234, 1208, 1143, 1124, 1069, 1011, 962, 849, 732 cm^{-1}.

Benzofuro[3,2-*c*]coumarin (Coumestan)(240)[130]



The title compound was prepared according to General Procedure B, on a 0.25 mmol scale, to afford recovered starting material (19.6 mg, 21.5%) and the product as a yellow solid (26.0 mg, 44.1% [56% b.r.s.m]).
Mpt: 178-180 °C (lit. 179-180°C)[125]; **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.14 (m, 1H), 8.03 (ddd, *J* = 7.8, 1.6, 0.4 Hz, 1H), 7.67 (m, 1H), 7.60 (m, 1H), 7.51 (m, 1H), 7.46 – 7.49 (m, 2H), 7.42 (m, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 156.0, 158.1, 155.5, 153.7, 131.9, 126.8, 125.2, 124.6, 123.4, 121.9, 117.5, 112.6, 111.7, 105.9; **MS** (ESI) *m/z* (rel.%): 237 [MH^+] (100), 211 (24); **HRMS** (ESI) calculated for $C_{15}H_9O_3$: 237.0546, found: 237.0543;

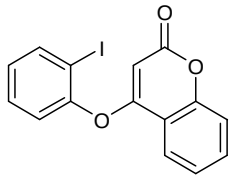
4-(2-Iodophenoxy)-coumarin (242) *via* 4-Bromo-coumarin[161]



A 250 ml 3 neck flask containing 4-hydroxycoumarin **241** (1.49 g, 9.2 mmol, 1 eq.), P_2O_5 (3.13 g, 22.1 mmol, 2.4 eq.) and TBAB (3.26 g, 10.1 mmol, 1.1 eq.) in toluene (100 ml) was equipped with a condenser and a mechanical stirrer. The reaction mixture was then heated to reflux for 8 hours whilst stirring then allowed to cool to ambient temperature. The toluene was decanted off, and the viscous black residue was extracted with toluene (3

× 40 ml). The combined organic fractions were concentrated *in vacuo* and recrystallisation (toluene) afforded the title compound as pale orange crystals (1.16 g, 56%).

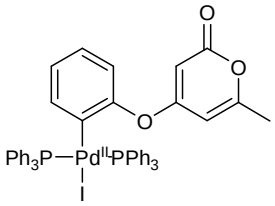
Mpt: 92-93 °C (lit. 87-89 °C)[161]; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.83 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.59 (ddd, *J* = 8.3, 7.4, 1.6 Hz, 1H), 7.38 – 7.30 (m, 2H), 6.85 (s, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 158.6, 152.4, 141.4, 133.1, 128.0, 124.9, 119.5, 118.9, 116.9; **MS** (ESI) *m/z* (rel.%): 227 [^{81}Br-MH$^+$] (100), 225 [^{79}Br-MH$^+$] (98); **HRMS** (ESI) calculated for $C_9H_6{}^{79}BrO_2$: 224.9546, found: 224.9550.



A solution of 4-Bromo-coumarin (225 mg, 1 mmol, 1 eq.), 2-iodophenol (220 mg, 1 mmol, 1 eq.), and K_2CO_3 (276 mg, 2 mmol, 2 eq.) in acetone (3 ml) was stirred at 60 °C for 16 hours. The reaction was allowed to cool to ambient temperature and quenched by addition of water (2 ml) and ethyl acetate (4 ml), and the layers separated. The aqueous layer was extracted using ethyl acetate (3 × 4 ml) and the combined organic extracts dried over $MgSO_4$, concentrated in *vacuo* and purified by flash column chromatography (10-20 % EtOAc in hexanes) to afford the product as a white solid (310 mg, 85.1%).

Mpt: 154-155 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.09 (d, *J* = 7.5 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 2H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 5.31 (s, 1H); **^{13}C-NMR** (126 MHz, $CDCl_3$): 164.9, 162.4, 153.7, 152.3, 140.5, 132.9, 130.3 128.5, 124.3, 123.3, 122.4, 116.9, 115.1, 93.8, 89.7; **MS** (ESI) *m/z* (rel.%): 387 [MNa$^+$] (16), 365 [MH$^+$] (100); **HRMS** (ESI) calculated for $C_{15}H_{10}IO_3$: 364.9669, found: 364.9678; **IR** (neat): 3067, 1714, 1623, 1608, 1568, 1380, 1227, 1177, 1088, 929, 752 cm^{-1}.

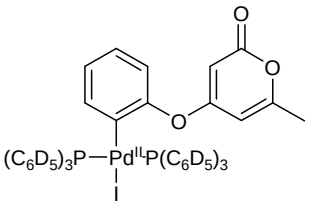
***trans*-[Pd{C_6H_4O-2-($C_6H_5O_2$)}I(PPh_3)$_2$] (244)**



A solution of Pd_2dba_3 (30 mg, 33 μmol, 1eq.), and PPh_3 (34 mg, 132 μmol, 4 eq.) in DCM (20 ml) was stirred under nitrogen at ambient temperature for 15 minutes, followed by the addition of 4-(2-iodophenoxy)-6-methyl-2-pyrone (32.8 mg, 99 μmol, 3 eq.). The solution

was then allowed to stir for 1 hour at ambient temperature. The DCM was removed *in vacuo* to afford an orange oil which was subsequently taken up in Et_2O (5 ml) and allowed to crystallise for 16 hours. The solution was then filtered and the crystals washed with Et_2O (5 ml), then dried under high vacuum to afford a yellow crystalline solid (63 mg, 65.6%). **^{1}H-NMR** (700 MHz, CD_2Cl_2): 7.52 (dd, *J* = 12.4, 5.5 Hz, 12H), 7.37 (t, *J* = 7.5 Hz, 6H), 7.28 (t, *J* = 7.5 Hz, 12H), 6.92 (ddd, *J* = 7.5, 3.5, 1.9 Hz, 1H), 6.48 (t, *J* = 7.5 Hz, 1H), 6.32 (t, *J* = 7.5 Hz, 1H), 6.04 (ddd, *J* = 7.5, 2.4, 1.2 Hz, 1H), 5.65 (dd, *J* = 1.0, 2.0, 1H), 4.72 (d, *J* = 1.9, 1H), 2.26 (app. s, 3H); **^{13}C-NMR** (176 MHz, CD_2Cl_2): 169.1, 164.4, 163.3, 153.4, 149.9, 138.8, 135.5, 132.7, 130.6, 128.3, 125.5, 124.2, 119.7, 100.4, 91.4, 20.6; **^{31}P-NMR** (283 MHz, CD_2Cl_2): 21.23; **MS** (LIFDI) *m/z* (rel.%): 958 [M^+] (100);

***trans*-[Pd{C_6H_4O-2-($C_6H_5O_2$)}I{$P(C_6D_5)_3$}$_2$] (244-d_{30})**



A solution of Pd_2dba_3 (30 mg, 33 μmol, 1 eq.), and D_{15}- PPh_3 (36 mg, 132 μmol, 4 eq.) in CH_2Cl_2 (20 mL) was stirred under nitrogen at ambient temperature for 15 minutes, followed by the addition of 4-(2-iodophenoxy)-6-methyl-2-pyrone (32.8 mg, 99 μmol, 3 eq.). The solution was then allowed to stir for 1 hour at ambient temperature. The CH_2Cl_2 was removed *in vacuo* to afford an orange oil which was subsequently taken up in Et_2O (5 mL) and allowed to crystallise for 16 hours. The solution was then filtered and the crystals washed with Et_2O (5 mL), then dried under high vacuum to afford a yellow crystalline solid (23 mg, 35.3%). ^{1}H-NMR (700 MHz, CD_2Cl_2): 6.92 (ddd, *J* = 7.5, 3.5, 1.9 Hz, 1H), 6.48 (t, *J* = 7.5 Hz, 1H), 6.32 (t, *J* = 7.5 Hz, 1H), 6.04 (ddd, *J* = 7.5, 2.4, 1.2 Hz, 1H), 5.65 (dd, *J* = 1.0, 2.0, 1H), 4.72 (d, *J* = 1.9, 1H), 2.26 (app. s, 3H); ^{31}P-NMR (283 MHz, CD_2Cl_2): 21.23; ^{31}P-NMR (283 MHz, D_8-THF): 22.44.

Attempted synthesis of a cationic derivative of 245

The neutral Pd^{II} complex **244** (41.3 mg, 43 μmol, 1 eq.) was reacted with $AgPF_6$ (10.9 mg, 43 μmol, 1 eq.) in CD_2Cl_2 (1 mL) at ambient temperature in a dry box for 1 hour in the dark. The reaction was then filtered through a pad of Celite^{TM}, and NMR

spectroscopy showed that a new cationic complex was formed along with an additional new species (presumed to be **246**). (Selected data) ^{1}H NMR (700 MHz, CD_2Cl_2): 7.93 (t, *J* = 7.9 Hz, 1H), 7.52 (td, *J* = 7.4, 2.2 Hz, 1H), 7.38 (dd, *J* = 8.1, 5.5 Hz, 1H), 7.33 (ddd, *J* = 14.3, 7.9, 1.4 Hz, 1H), 5.20 (d, *J* = 2.0 Hz, 1H), 4.92 (d, *J* = 2.0 Hz, 1H), 1.98 (s, 3H); ^{31}P NMR (162 MHz, CD_2Cl_2): 39.02 (br. s, Δν ½ 46 Hz), 22.09 (s), -143.88 (hept, *J* = 710 Hz). Layering the CH_2Cl_2 solution with Et_2O and storing room temperature in the dark for two weeks gave crystals suitable for X-ray diffraction study. Rather curiously, it was found that the "C_6H_4O-2-($C_6H_5O_2$)" group from the cationic Pd^{II} species had undergone Pd→P transfer forming [P{C_6H_4O-2-($C_6H_5O_2$)}Ph_3]PF_6 (**248**), which was accompanied by significant Pd black formation.

Reaction of 244 with Cs_2CO_3 to give product 216

A solution of Pd_2 (dba-4,4′-OMe)$_3$ (3.6 mg, 3.3 μmol, 1 eq.), and PPh_3 (3.4 mg, 13.2 μmol, 4 eq.) in D_8-THF (1 mL) was stirred in a dry box at ambient temperature for 15 minutes, followed by the addition of 4-(2-iodophenoxy)-6-methyl-2-pyrone **218** (4.2 mg, 13.2 μmol, 4 eq.). The solution was then allowed to stir for 1 hour at ambient temperature and the Pd^{II} intermediate confirmed by NMR. Cs_2CO_3 (6.6 mg, 20 μmol, 6 eq.) was added and the solution heated to 70 °C for 2 hours. The solution was cooled to ambient temperature and filtered. The ^{1}H NMR spectrum showed quantitative formation of **218a**.

Synthesis of *trans*-[Pd{C_6H_3-5-CF_3-O-2-($C_6H_5O_2$)}Br(PPh_3)$_2$] (247) and attempted reaction with Cs_2CO_3

From Pd_2(dba-H)$_3$: A solution of Pd_2(dba)$_3$ (30 mg, 33 μmol, 1 eq.), and PPh_3 (34 mg, 132 μmol, 4 eq.) in THF (20 mL) was stirred under a N_2 atmosphere for 15 minutes, giving an orange solution which is Pd(η^2-dba-H)(PPh_3)$_2$. 4-(2-Bromo-4-(trifluoromethyl)-phenoxy)-6-methyl-2-pyrone **228n** (46.0 mg, 132 μmol, 2 eq.) was then added and the solution was allowed to stir for 1 hour at 70 °C. The THF was removed *in vacuo* to afford an orange oil which was subsequently taken up in Et_2O (5 mL), and allowed to slowly crystallize over 16 hours. A mixture of purple, orange and yellow crystals were formed. X-ray crystallographic analysis identified the purple crystals as Pd_2(dba-H)$_3$ (as disordered isomers). The orange and yellow crystals were

not identified. From Pd_2(dba-4,4′-OMe)$_3$: In a dry box, a solution of Pd_2 (dba-4,4′-OMe)$_3$ (3.6 mg, 3.3 μmol, 1 eq.), and PPh_3 (3.4 mg, 13.2 μmol, 4 eq.) in D_8-THF (1 mL) was stirred at ambient temperature for 15 minutes, giving an dark orange solution which is Pd(η^2-dba-4,4′-OMe)(PPh_3)$_2$. 4-(2-Bromo-4-(trifluoromethyl)-phenoxy)-6-methyl-2-pyrone **228n** (2.3 mg, 6.6 μmol, 2 eq.) was then added. The solution was then allowed to stir for 1 hour at 70 °C and the Pd^{II} complex characterized by NMR spectroscopy. Selected Data: ^{1}H-NMR (400 MHz, D_8-THF): 7.59 – 7.54 (m, 12H), 7.35 – 7.30 (m, 6H), 7.26 – 7.22 (m, 12H), 6.67 (d, *J* = 8.5 Hz, 1H), 6.15 (d, *J* = 8.5 Hz, 1H), 6.03 (s, 1H), 5.69 (d, *J* = 2.2 Hz, 1H), 4.65 (d, *J* = 2.2 Hz, 1H), 2.24 (s, 3H); ^{31}P-NMR (162 MHz, D_8-THF): 24.46 (s). Cs_2CO_3 (13.2 mg, 40 μmol, 12 eq.) was then added to the yellow/orange solution, which was heated to 70 °C for 2 hours. The solution was allowed to cool to ambient temperature and filtered through Celite™. ^{1}H NMR spectroscopic analysis of the filtrate showed no formation of the cyclised product **229n**. The ^{31}P NMR spectrum showed degradation of the Pd^{II} complex at δ 24.46 (s), and a new species, identified as [Pd^0(η^2-dba-4-OMe)(PPh_3)$_2$] **9**. ^{31}P-NMR (162 MHz, D_8-THF): 26.8 (br. s, Δν½ 42 Hz), 25.2 (br. s, Δν½ 42 Hz).

6 References

1 Diarmuid, J. *Aspirin: The Remarkable Story of a Wonder Drug*, **2005**, *Bloomsbury*.

2 Willits, M. G.; Giovanni, M.; Prata, R. T. N.; Kramer, C. M.; De Luca, V.; Steffens, J. C.; Graser, G. *Phytochemistry* **2004**, *65*, 31-41.

3 Wohler, F. *Ann. Chim. Phys.* **1828**, *37*, 330-334.

4 Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed*. **2000**, *39*, 44-122.

5 Hou, Y.; Harinantenaina, L. *Curr. Med. Chem.* **2008**, *17*, 1191-1219.

6 Woodward R. B.; Patchett A. A.; Barton D. H. R.; Ives D. A. H.; Kelly R. B. *J. Am. Chem. Soc*. **1954,** *76*, 2852-2853.

7 Smith, A. B.; Freeze, B. S. *Tetrahedron* **2008**, *64*, 261-298.

8 Nicolaou, K. C.; Ritzen, A.; Namoto, K. *Chem. Commun.* **2001**, 1523-1535.

9 Balog, A.; Meng, D.; Kamenecka, T.; Bertinato, P.; Su, D.S.; Sorensen, E.J.; Danishefsky, S.J. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2801-2803.

10 McGlacken, G. P.; Fairlamb, I. J. S. *Nat. Prod. Rep.* **2005**, *22*, 369-385.

11 Hatch, M. S.; Brown, W. M.; Deck, J. A.; Hunsaker, L. A.; Deck, L. M.; Vander Jagt, D. L. *Biochim. Biophys. Acta* **2002**, *1596*, 381-391.

12 Lacy, A.; O'Kennedy, R. *Curr. Pharm. Des.* **2004,** *10*, 3797-3811.

13 Collie, J. N.; Wilsmore, N. T. M. *J. Chem. Soc.* **1896**, 293-304.

14 De March, P.; Moreno-Manas, M.; Pleixats, R.; Roca, J. C. *J. Heterocycl. Chem.* **1984**, *21*, 1369-1370.

15 Cyr, T. D.; Poultonc, G. A. *Can. J. Chem.* **1982**, *60***,** 133-137.

16 Swidorski, J. J.; Wang, J.; Hsung, R. P. *Org. Lett.* **2006**, *8*, 777-780.

17 Zhang, X.; McLaughlin, M.; Lizeth, R.; Munoz, P.; Hsung, R. P.; Wang, J.; Swidorski, J. *Synthesis* **2007**, *5*, 749-753.

18 Fairlamb, I. J. S.; Marrison, L. R.; Dickinson, J. M.; Lu, F. J.; Schmidt, J. P. *Bioorg. Med. Chem.* **2004**, *12*, 4285-4299.

19 Penning, G. M. *Arch. Gerontol. Geriatr.* **2001**, *33*, 13-28.

20 Hagen, S.; Vara Prasad, J. V. N.; Tait, B. D. *Adv. Med. Chem.* **2000**, *5*, 159-195.

21 Cho, K. M.; Kim, W. G.; Lee, C. K.; Sterner, O. *J. Antibiot.* **2003**, *56*, 351-357.

22 Altmann, K. H.; Gertsch, J. G. *Nat. Prod. Rep.* **2007**, *24*, 327-357.

23 Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron Lett.* **2001**, *42*, 2859-2863.

24 Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **2001**, *57*, 2857-2870.

25 Thibonnet, J.; Abarbri, M.; Parrain, J. L.; Duchene, A. *J. Org. Chem.* **2002**, *67*, 3941-3944.

26 Liebeskind, L. S.; Wang, J. *Tetrahedron* **1993**, *49*, 5461-5470.

27 Dieter, R. K.; Fishpaugh, J. R. *J. Org. Chem.* **1988**, *53*, 2031-2046.

28 Fairlamb, I. J. S.; Marrison, L. R.; Dickinson, J. M.; Lu, F. J.; Schmidt, J. P. *Bioorg. Med. Chem*. **2004**, *12*, 4285-4299.

29 Cerezo, S.; Moreno-Mafias, M.; Pleixats, R. *Tetrahedron* **1998**, *54*, 7813-7818.

30 Marrison, L. R.; Dickinson, J. M.; Fairlamb, I. J. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2667–2671.

31 Posner, G. H.; Harrison, W.; Wettlaufer, D. G. *J. Org. Chem.* **1985**, *50*, 5041–5044.

32 Liu, Z.; Meinwald, J. *J. Org. Chem.* **1996**, *61*, 6693-6699.

33 Gravett, E. C.; Hilton, P. J.; Jones, K.; Romero, F. *Tetrahedron Lett.* **2001**, *42*, 9081-9084.

34 McMurry, J. *Organic Chemistry – 5th Edition*, **1999**, *Brooks/Cole.*

35 Porter, N. A.; Caldwell, S. E.; Mills, K. A. *Lipids* **1995**, *30*, 277-290.

36 Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380-416.

37 Fauconnot, L.: Buist, P. H. *J. Org. Chem.* **2001**, *66*, 1210-1215.

38 Horrobin, D. *Am. J. Clin. Nutr.* **1993**, *57*, 732-737.

39 Durand, S.; Parrain, J. L.; Santelli, M. *J. Chem. Soc., Perkin Trans., 1* **2000**, 253-273.

40 Rao, B. V.; Kumar, V. S. *Tetrahedron Lett.* **1995**, *36*, 147-150.

41 Saha, G.; Basu, M. K.; Kim, S.; Jung, Y. J.; Adiyaman, Y.; Adiyaman, M.; Powell, W. S.; FitzGerald, G. A.; Rokach, J. *Tetrahedron Lett.* **1999**, *40*, 7179-7183.

42 Samuelsson, B.; Dahlen, S. E.; Lindgren, J. A.; Rouzer, C. A.; Serhan, C. N. *Science* **1987**, *237*, 1171-1176.

43 King, A. G.; Meinwald, J. *Chem. Rev.* **1996**, *96*, 1105-1122.

44 Nicholas, K. M.; Pettit, R. *Tetrahedron Lett.* **1971**, *37*, 3475-3478.

45 Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446-448.

46 Osbond, J. M.; Philipott, P. G.; Wickens, J. C. *J. Chem. Soc.* **1961**, 2779-2787.

47 Daeuble, J. F.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 2397-2400.

48 Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226-2230.

49 Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203-3206.

50 Viala, J.; Santelli, M. *J. Org. Chem.* **1988**, *53*, 6121-6123.

51 Badone, D.; Pagliarin, R.; Sisti, M.; Tavecchia, P. *Org. Prep. Proced. Int.* **1989**, *21*, 629-636.

52 Negishi, E. *J. Organomet. Chem.* **2002**, *653*, 34-40.

53 Takahashi, K.; Matsumura, T.; Ishihara, J.; Hatakeyama, S. *Chem. Commun.* **2007,** 4158-4166.

54 Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 641-643.

55 Beeby, A.; Bettington, S.; Fairlamb, I. J. S.; Goeta, A. E.; Kapdi, A. R.; Niemelä, E. H.; Thompson, A. L. *New J. Chem*. **2004**, *28*, 600-605.

56 Crawforth, C. M.; Burling, S.; Fairlamb, I. J. S.; Taylor, R. J. K.; Whitwood, A. C. *Chem. Commun.* **2003,** 2194-2195.

57 Crawforth, C. M.; Fairlamb, I. J. S.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 461-465.

58 Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461-1473.

59 Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. *J. Am. Chem. Soc.* **2000,** *122*, 10718-10719.

60 Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 2229-2231.

61 Macé, Y.; Kapdi, A. R.; Fairlamb, I. J. S.; Jutand, A. *Organometallics* **2006**, *25*, 1795-1800.

62 Blunt, J. W.; Copp, B. R.; Hu, W. P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rev.* **2007**, *24*, 31-86.

63 Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rev.* **2004**, *21*, 1-49.

64 Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Blackman, A. J. *Aust. J. Chem.* **1982**, *35*, 113-120.

65 Shin, S.; Paul, V. J.; Fenical, W. *Tetrahedron Lett.* **1986**, *27*, 5189-5192.

66 Murray, L.; Currie, G.; Capon, R. J. *Aust. J. Chem.* **1995**, *48*, 1485-1489.

67 Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671-719.

68 Marrison, L. R.; Dickinson, J. M.; Fairlamb, I. J. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2667-2671.

69 Fairlamb, I. J. S.; Lee, A. F.; Loe-Mie, F.; Niemelä, E. H.; O'Brien, C. T.; Whitwood, A. C. *Tetrahedron* **2005**, *61*, 9827-9838.

70 Song, D.; Blond, G.; Fürstner, A. *Tetrahedron* **2003**, *59*, 6899-6904.

71 Diver, S. T.; Giessert, A. J. *Chem Rev.* **2004**, *104*, 1317-1382.

72 Villalva-Servin, N. P.; Laurent, A.; Fallis A. G. *Can. J. Chem* **2004**, *82*, 227-239.

73 Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2000**, *122*, 9840-9841.

74 Grubbs, R. H. *Handbook of Metathesis*, **2003,** *Wiley-VCH*.

75 Miyaura, N.; Yano, T.; Suzuki, A. *Tetrahedron Lett*. **1980**, *21*, 2865-2868.

76 Burling, S.; Crawforth, C. M.; Fairlamb, I. J. S.; Kapdi, A. R.; Taylor, R. J. K.; Whitwood, A. C. *Tetrahedron.* **2005**, *61*, 9736-9751.

77 Molander, G. A.; Canturk, B.; Kennedy L. E. *J. Org. Chem.* **2009**, *74*, 973-980.

78 Blackman, A. J.; Bremner, J. B.; Paano, A. M.; Skerratt, J. H.; and Swann, M. L., *Aust. J. Chem*. **1990**, *43*, 1133-1136.

79 Suzuki, E.; Hamajima, R.; Inoue, S. *Synthesis* **1975**, 192-194.

80 Swidorski, J. J.; Wang, J.; Hsung, R. P. *Org Lett.* **2006**, *8*, 777-780.

81 Zhang, X.; McLaughlin, M.; Lizeth, R.; Muñoz, P.; Hsung, R. P.; Wang, J.; Swidorski, J. *Synthesis* **2007**, 749-753.

82 Begley, M. J.; Pattenden, G.; Robertson, G. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1085-1094.

83 Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773-775.

84 Johnstone, R. A. W.; Wilby, A. H.; Entwistle, I. D. *Chem. Rev.* **1985,** *85*, 129-170.

85 Lindlar, H.; Dubuis, R. *Org. Synth. Coll.* **1973**, *vol. 5*, 880.

86 Appel, R. *Angew. Chem. Int. Ed.* **1975**, *14*, 801-811.

87 Abele, E.; Lukevics, E. *Org. Prep. Proced. Int.* **1999**, *31*, 359-377.

88 Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202-12206.

89 Muzart, J. *Tetrahedron* **2005**, *61*, 5955-6008.

90 Amatore, C.; Jutand, A.; Périchon, J.; Rollin, Y. *Monatsh. Chem.* **2000,** *131*, 1293-1304.

91 Jutand, A.; Mosleh, A. *J. Org. Chem.* **1997**, *62*, 261-274.

92 Chatterjee, A. K.; Choi, T.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.

93 Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217-8225.

94 Okazoe, T.; Takai, K.; Oshima, K.; Utimoto K. *J. Org. Chem.* **1987**, *52*, 4410-4412.

95 Zhou, Q.-F.; Yang, F.; Guo, Q.-X.; Xue, S. *Synlett* **2007**, 215-218.

96 Tsukamoto, H.; Uchiyama, T.; Suzuki, T.; Kondo, Y. *Org. Biomol. Chem.* **2008**, *6*, 3005-3013.

97 pKa predictions performed using ACD PhysChem softwate.

98 Suga, H.; Takemoto, H.; Kakehi, A. *Heterocycles* **2007**, *71*, 361-371.

99 Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467-4470.

100 Papavassilopoulou, E.; Christofis, P.; Terzoglou, D.; Moutevelis-Minakakis, P. *Tetrahedron lett.* **2007**, *48*, 8323-8325.

101 Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001-8006.

102 Dutheuil, G.; Selander, N.; Szabó, K. J.; Aggarwal, V. K. *Synthesis*, **2008**, 2293-2297.

103 Spaggiari, A.; Vaccari, D.; Davoli, P.; Torre, G.; Prati, F. *J. Org. Chem.* **2007**, *72*, 2216-2219.

104 Obata, T.; Shimo, T.; Yasutake, M.; Shinmyozu, T.; Kawaminami, M.; Yoshida, R.; Somekawa, K. *Tetrahedron*, **2001**, *57*, 1531-1541.

105 gNMR v5, Adept Scientific plc. Amor Way, Letchworth, Herts, SG6 1ZA, UK, 2003.

106 Occhiato, E. G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2001,** *66*, 2459-2465.

107 Rummen, F. H. A.; de Haan, J. W. *Org. Mag. Res.* 2005, *2*, 351-355.

108 Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275-286.

109 Wiley, R.; Esterle, J. *J. Org. Chem.* **1957**, *22*, 1257-1259.

110 Schmid, G. H.; Modro, A.; Yates, K. *J. Org. Chem.* **1980**, *45*, 665–667.

111 Young, D. G. J.; Burlison, J. A.; Peters, U. *J. Org. Chem.* **2003**, *68*, 3494-3497.

112 Grubbs, R. H.; S. J. Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446-452.

113 Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632-16633. (and references cited therein)

114 Atkin, A. J.; Williams, S.; Sawle, P.; Motterlini, R.; Lynam, J. M.; Fairlamb, I. J. S. *Dalton Trans.* **2009**, 3653-3656.

115 Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32-42.

116 Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393-396.

117 Cadierno, V.; Díez, J.; Gimeno, J.; Nebra, N. *J. Org. Chem.* **2008**, *73*, 5852-5858.

118 Cabarès, J.; Mavoungou-Gomès, L. *Bull. Soc. Chim Fr.* **1987**, *2*, 339.

119 Majumdar, K. C.; Biswas, A.; Mukhopadhyay, P. P. *Synth. Commun.* **2007**, *37*, 2881-2890.

120 Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826-1834.

121 Amatore, C.; Jutand, A.; Khalil, F.; M'Barki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168-3178.

122 Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435-4438.

123 Amatore, C.; Jutand, A. *Coord. Chem. Rev.* **1998**, *178*, 511-528.

124 L. R. Marrison, Ph.D. Thesis, MMU, Manchester, UK, 1998.

125 Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047-1062.

126 Zhao, J.; Campo, M.; Larock, R. C. *Angew. Chem.* **2005**, *117*, 1907-1909.

127 Williams, D. H.; Fleming, I. *Spectroscopic methods in organic chemistry*, **1995**, *McGraw-Hill Higher Education*.

128 Chang, C.-P.; Pradiuldi, S. V.; Hong, F.-E. *Inorg. Chem. Commun.* **2009**, *12*, 596-599.

129 Harborne, J. B.; Mabry, T. J.; Mabry, H. *The Flavanoids*, **1975,** *Chapman and Hall.*

130 Yao, T.; Yue, D.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 9985-9989.

131 Cost evaluation based on prices from Sigma-Aldrich Catalogue 2009/2010.

132 Vicente, J.; Abad, J.-A.; Frankland, A. D.; Ramírez de Arellano, M. C. *Chem. Eur. J.* **1999**, *5*, 3066-3079.

133 Watanabe, T.; Arai, S.; Nishida, A. *Synlett* **2004**, 907-909.

134 Taher, D.; Walfort, B.; Lang, H. *Inorg. Chim. Acta* **2006**, *359*, 1899-1906.

135 Fairlamb, I. J. S.; Lynam, J. M.; Moulton, B. E.; Taylor, I. E.; Duhme-Klair, A.-K.; Sawle, P.; Motterlini, R. *Dalton Trans.* **2007**, 3603-3605.

136 Pascual, S.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Tetrahedron* **2008**, *64*, 6021-6029.

137 Yao, W.; Eisenstein, O.; Crabtree, R. H. *Inorg. Chim. Acta* **1997**, *254*, 105-111.

138 Heck, R. F. *Pure & Appl. Chem.* **1978**, *50*, 691-701.

139 Migita, T.; Nagai, T.; Kiuchi, K.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2869-2870.

140 Analysis by Special Metals Division, Chemetall GmbH, Trakehner Straβe, D-60487, Frankfurt AM Main, Germany.

141 Hua, D. H.; Huang, X.; Tamura, M.; Chen, Y.; Woltkamp, M.; Jin, L. W.; Perchellet, E. M.; Perchellet, J. P.; Chiang, P. K.; Namatame, I.; Tomoda, H. *Tetrahedron* **2003**, *59*, 4795-4803.

142 Work carried out at Merck-Schering, Newhouse, Lanarkshire

143 Moret, E.; Desponds, O.; Schlosser, M. *J. Organomet. Chem.* **1991**, *409*, 83-91.

144 Vig, O. P.; Sharma, M. L.; Bhanot, R. K.; Malik, N. *Indian J. Chem. B* **1981**, *11*, 970-971.

145 McLaughlin, M. *Org. Lett.* **2005**, *7*, 4875-4878.

146 Lapointe, D.; Fagnou, K. *Org. Lett.* **2009,** *11*, 4160-4163.

147 Bowles, T.; Jones, R.; Porter, A. E. A.; Rechka, J. A.; Rzepa, H. S.; Williams, D. J. *J. Chem. Soc. Perkin Trans. I*, **1988**, 1023-1028.

148 Zhang, S.; Marshall, D.; Liebeskind, L. S. *J. Org. Chem.* **1999**, *64*, 2796-2804.

149 Carpenter, A. J.; Chadwick, D. J. *Tetrahedron* **1985**, *41*, 3803-3812.

150 Shimo, T.; Ueda, S.; Somekawa, K. *J. Heterocyclic Chem.* **1994**, 31, 387-390.

151 Beak, P.; Abelson, H. *J. Org. Chem.* **1962**, *27*, 3715-3716.

152 Kanazawa, T.; Ohkawa, Y.; Kuda, T.; Minobe, Y.; Tani, T.; Nishizawa, M. *Chem. Pharm. Bull.* **1997**, *45*, **6**, 1046-1051.

153 Edwards, G. L.; Muldoon, C. A.; Sinclair, D. J. *Tetrahedron* **1996**, *52*, 7779-7788.

154 Ma, N.; Zhu, Z.; Wu, Y. *Tetrahedron* **2007**, *63*, 4625-4629.

155 Bonini, C.; Federici, C.; Rossi, L.; Righi, G. *J. Org. Chem.* **1995**, *60*, 4803-4812.

156 Romero, D. L.; Manninen P. R.; Han, F.; Romero, A. G. *J. Org. Chem.* **1999**, *64*, 4980-4984.

157 Lang, W. R.; Hansen, H.-J *Org. Synth.* **1990**, *7*, 232.

158 Alexakis, A.; Cahiez, G.; Normant, J. F. *Synthesis* **1979**, *10*, 826-830.

159 Pirrung, F. O. H.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Schoemaker, H. E. *Tetrahedron* **1994**, *50*, 12415-12442.

155 R. F. Clark, T. Zhang, X. Wang, R. Wang, X. Zhang, H. S. Camp, B. A. Beutal, H. L. Sham, Y. G. Gu, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1961-1965.

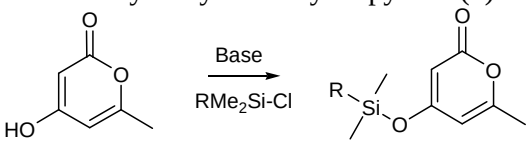
161 Jung, M. E.; Allen, D. A. *Org. Lett.* **2009,** *11*, 757-760.

162 Afarinkia, K.; Bearpark, M. J.; Ndibwam A. *J. Org. Chem.* **2003**, *68*, 7158-7166.

Chapter 6- Appendices

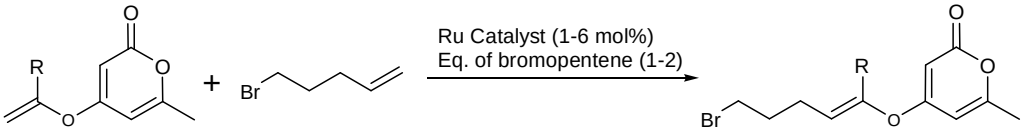
Appendix 1: Reaction optimisation tables

Appendix 1.1: Silylation of 4-hydroxy-6-methyl-2-pyrone (**9**).



Entry	R	Base	Temp (°C)	Yield (%)
1	Me	TEA	22	No Reaction
2	Me	NaH	22	No Reaction
3	Me	K_2CO_3	22	No Reaction
4	^{t}Bu	K_2CO_3	22	No Reaction
5	^{t}Bu	K_2CO_3	60	No Reaction

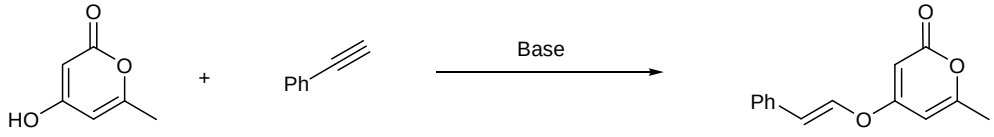
Appendix 1.2: Cross metathesis reaction of **110** and **113**.



Entry	R	Solvent	Temperature (°C)	eq. Of alkene	Catalyst	Mol% catalyst	Yield (%)[†]
1	Et	DCM	30	1.5	Grubbs II	3	0
2	Et	DCM	20	1	Grubbs II	1	0
3	Et	DCM	20	2	Grubbs II	1	0
4	Et	DCM	20	1	Grubbs II	5	0
5	Et	DCM	20	2	Grubbs II	5	0
6	Et	DCM	40	1	Grubbs II	1	0
7	Et	DCM	40	2	Grubbs II	1	0
8	Et	DCM	40	1	Grubbs II	5	0
9	Et	DCM	40	2	Grubbs II	5	0
10	H	DCM	20	2	Grubbs II	6	0
11	H	DCM	40	2	Grubbs II	6	0
12	H	$CHCl_3$	55	2*	Grubbs II	6	Trace
13	H	$CHCl_3$	55	2*	Hoveyda-Grubbs	6	0
14	H	Toluene	80	2*	Grubbs II	6	0

[*] Alkene changed to 6-hydroxyhex-1-ene
[†] Recovered starting material observed in all cases

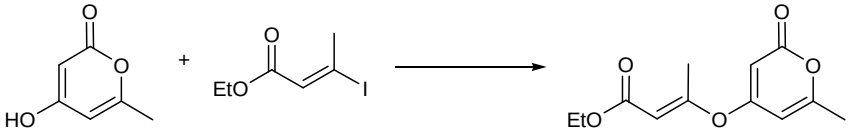
Appendix 1.3: Screening of conditions for the synthesis of **121**.



9 **120** **121**

Entry	Base	eq. Base	eq. Phenyl acetylene	Solvent	Temperature (°C)	Yield (%)
1	DMAP	0.2	1.0	DCM	20	SM recovered
2	DMAP	0.2	1.1	DCM	40	SM recovered
3	KOH	2	1.1	DCM	40	SM recovered
4	DIPEA	2	1.1	DCM	40	SM recovered
5	TEA	2	1.1	DCM	40	SM recovered
6	K_2CO_3	2	1.1	DCM	40	SM recovered
7	DMAP	0.2	1.1	THF	75	SM recovered
8	KOH	2	1.1	THF	75	SM recovered
9	DIPEA	2	1.1	THF	75	SM recovered
10	TEA	2	1.1	THF	75	SM recovered
11	K_2CO_3	2	1.1	THF	75	SM recovered
12	TEA	2	2.2	DCM	100 (µwave)	Degradation of SM
13	TEA	2	2.2	DCM	140 (µwave)	Degradation of SM

Appendix 1.4: Substitution reactions of **9** and **141.**

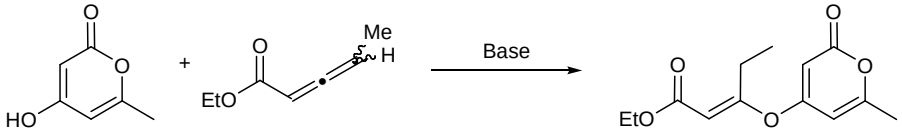


9 **141** **140**

Entry	Solvent	Base	Eq. Base	Temperature (°C)	Additive	Yield **139** (%)
1	DCM	TEA	1	20	-	SM Recovered
2	DCM	TEA	1	40	-	SM Recovered
3	DCM	TEA	1.5	40	-	SM Recovered
4	DCM	LiH	1	20	-	SM Recovered
5	DCM	LiH	1	40	-	SM Recovered
6	THF	NaH	1	25	-	SM Recovered
7	THF	NaH	1	70	-	SM Recovered
8	Acetone	K_2CO_3	1	25	-	SM Recovered
9	Acetone	K_2CO_3	1	45	-	SM Recovered
10	THF	NaH	1	70	$AgNO_3$	SM Recovered
11	DMF*	NaH	1	25	$AgNO_3$	SM Recovered
12	DMF*	NaH	1	50	$AgNO_3$	25 – 43

* Pyrone-Sodium salt preformed in THF prior to solvation in DMF

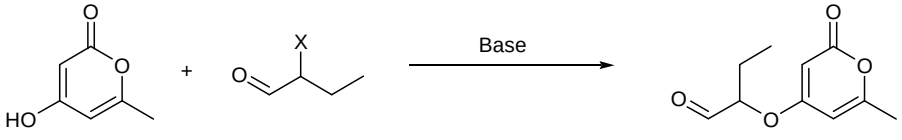
Appendix 1.5: Michael addition reactions of **9** and **142**.



9 **144** **142**

Entry	Solvent	Base	Eq. of Base	Temperature (°C)	Additive	Yield **144** (%)
1	DCM	TEA	1	20	-	SM Recovered
2	DCM	TEA	1	40	-	SM Recovered
3	DCM	TEA	1	80 (μwave)	-	SM Recovered
4	DCM	DBU	1	40	-	SM Recovered
5	DCM	DBU	1	80 (μwave)	-	SM Recovered
6	DCM	DBU	1	40	$Yb(OTf)_3$ (10 mol%)	SM Recovered
7	DCM	DBU	1	80 (μwave)	$Yb(OTf)_3$ (10 mol%)	SM Recovered

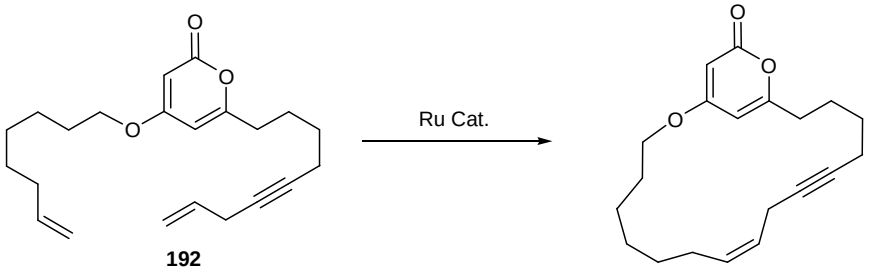
Appendix 1.6: Substitution reactions of α-halobutyraldehydes with **9**.



9 **165**

Entry	X	Base	Solvent	Yield (%)
1	Br	TEA	THF	-
2	Br	DBU	THF	-
3	Cl	TEA	THF	-
4	Cl	DBU	THF	-
5	Cl	NaH	THF	-

Appendix 1.7: Ring Closing metathesis of **192**.



192 **193**

Entry	Catalyst	Solvent†	Temperature	Time	Yield
1	Grubbs I	DCM	40 °C	48 h	0%*
2		DCM	40 °C	48 h	0%*
3	Grubbs II	Chloroform	60 °C	48 h	0%*
4		Toluene	100 °C	48 h	0%
5		DCM	40 °C	48 h	0%*
6	Hoveyda-Grubbs II	Chloroform	60 °C	48 h	0%*
7		Toluene	100 °C	48 h	0%

* Starting material recovered.

† Reactions run at a concentration of 0.0016 M.

Appendix 2: X-ray diffraction details for all compounds.

Compound reference	ijf0925m (**216**)	ijf0934m (**222**)	ijf0930 (**229j**)	ijf0931 (**229k**)	ijf0936m (**244**)	ijf1002m (**248**)
Chemical formula	$C_{12}H_8O_3$	$C_{11}H_6O_3$	$C_{12}H_7FO_3$	$C_{12}H_7FO_3$	$C_{48}H_{39}IO_3P_2Pd$	$C_{30}H_{24}O_3P{\bullet}(F_6P_1)_{0.98}{\bullet}(I)_{0.02}$
Formula Mass	200.18	186.16	218.18	218.18	959.03	608.43
Crystal system	Triclinic	Monoclinic	Triclinic	Triclinic	Monoclinic	Triclinic
a/Å	7.1467(5)	11.1190(16)	3.7437(3)	3.7597(2)	10.2109(5)	7.8107(8)
b/Å	7.3546(5)	8.2091(12)	6.3700(7)	6.1644(4)	11.8937(6)	13.2530(14)
c/Å	9.3252(6)	18.856(3)	19.0219(19)	19.6660(11)	34.1332(17)	14.2579(15)
α/°	69.7600(10)	90.00	91.665(9)	92.543(5)	90.00	97.040(2)
β/°	81.8920(10)	105.787(2)	90.858(7)	90.715(5)	93.0340(10)	104.389(2)
γ/°	75.2200(10)	90.00	93.699(8)	90.125(5)	90.00	104.932(2)
Unit cell volume/Å^3	443.91(5)	1656.2(4)	452.42(8)	455.30(5)	4139.5(4)	1353.6(2)
Temperature/K	120(2)	110(2)	120(2)	120(2)	110(2)	110(2)
Space group	$P\bar{1}$	*C2/c*	$P\bar{1}$	$P\bar{1}$	*P2(1)/n*	$P\bar{1}$
No. of formula units per unit cell, *Z*	2	8	2	2	4	2
No. of reflections measured	6084	8041	7806	4447	55989	13874
No. of independent reflections	2211	2057	1688	1706	10290	6661
R_{int}	0.0124	0.0175	0.0390	0.0286	0.0494	0.0235
Final R_1 values ($I > 2\sigma(I)$)	0.0352	0.0373	0.0480	0.0477	0.0330	0.0490
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.1005	0.0970	0.1249	0.1335	0.0684	0.1227
Final R_1 values (all data)	0.0366	0.0443	0.0574	0.0514	0.0456	0.0719
Final $wR(F^2)$ values (all data)	0.1023	0.1024	0.1316	0.1382	0.0730	0.1367
CCDC number	764708	764709	773153	773154	764710	764711

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Simple Palladium(II) Precatalyst for Suzuki–Miyaura Couplings: Efficient Reactions of Benzylic, Aryl, Heteroaryl, and Vinyl Coupling Partners

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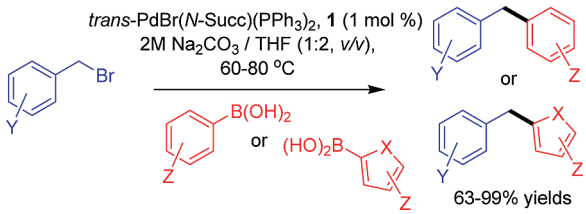
ABSTRACT



***trans*-PdBr(*N*-Succ)(PPh$_3$)$_2$ (1) is a universally effective precatalyst for Suzuki–Miyaura cross-couplings of benzylic halides with aryl- or heteroarylboronic acids. Substituted aryl halides and halogenated cyclic enones can be cross-coupled with aryl- or vinylboronic acids in excellent yields. Catalyst recycling is also demonstrated.**

Pd^0-catalyzed C−C bond-forming processes have attracted considerable attention in many applied research fields, including target-directed synthesis.[1,2] Significant effort has been placed on the development of new catalyst systems for a diverse array of coupling partners, particularly aryl components. The majority of new catalysts possess an electron-rich donor ligand, e.g., X-Phos,[3] or an *N*-heterocyclic carbene ligand,[4] including the excellent PEPPSI catalysts,[5] or utilize palladacycles.[6] While such catalysts are extremely versatile for many substrates, especially aryl/heteroaryl chlorides and alkyl halides, the coupling of benzylic halides with organoboronic acids has been little studied[7] and has unexplored potential.[8] Their generic use in Suzuki−Miyaura cross-couplings, to give diarylmethanes, is relatively rare, particularly compared to aryl halides. In the 1990s, it was reported that successful benzylic halide couplings were reliant on the use of excess organoboronic acid (1.5−2 equiv).[9] Molander and co-workers[10] recently developed a valuable synthetic protocol using potassium organotrifluoroborates as the nucleophilic boron coupling partner. The precatalyst, $PdCl_2(dppf)\cdot CH_2Cl_2$ (2 mol %), exhibited the highest catalytic performance (S-Phos and X-Phos, more activated

(1) *Metal-catalyzed Cross-coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004.

(2) *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1.

(3) Nguyen, H.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818 and references cited therein.

(4) Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431.

(5) O'Brien, C. J.; Kantchev, E. A. B.; Hadei, N.; Valente, C.; Chass, G. A.; Nasielski, J. C.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem.−Eur. J.* **2006**, *12*, 4743, and references cited therein.

(6) Bedford, R. B. *Chem. Commun.* **2003**, 1787.

(7) For use of palladacycles, with *n*-Bu$_4$NBr as a stoichiometric additive, in reactions of benzylic halides and arylboronic acids, see: (a) Botella, L.; Nájera, C. *J. Organomet. Chem.* **2002**, *663*, 46. (b) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *J. Org. Chem.* **2002**, *67*, 5588.

(8) Two other approaches to diarylmethanes have been reported. See: (a) Vanier, C.; Lorgé, F.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1679. (b) Nakao, Y.; Ebata, S.; Chen, J.; Imanaka, H.; Hiyama, T. *Chem. Lett.* **2007**, *36*, 606. For cross-coupling of an in situ generated organoborane with a substituted benzyl chloride, see: Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1994**, *59*, 6501.

(9) (a) Nobre, S. M.; Monteiro, A. L. *Tetrahedron Lett.* **2004**, *45*, 8225. (b) Chahen, L.; Doucet, H.; Santelli, M. *Synlett* **2003**, *11*, 1668. (c) Chodhury, S.; Georghiou, P. *Tetrahedron Lett.* **1999**, *40*, 7599.

(10) Molander, G. A.; Elia, M. D. *J. Org. Chem.* **2006**, *71*, 9198.

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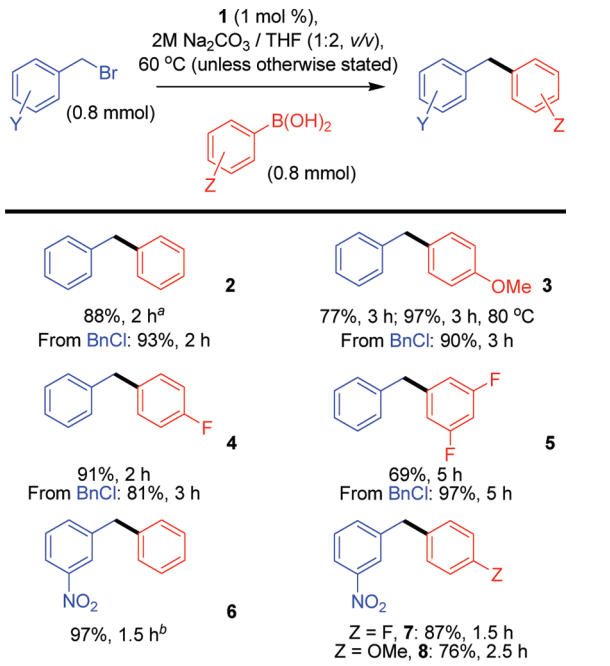
ligands, were *not as good* for this specific transformation); a THF/H_2O solvent mixture and Cs_2CO_3 (3 equiv) base were preferred. Kuwano and Yokogi reported that benzylic acetates can be used in Suzuki−Miyaura cross-couplings using a catalyst system composed of DPEphos−[Pd(η^3-C_3H_5)Cl]$_2$.[11] Given the considerable interest in diarylmethanes in medicinal chemistry[12] and in view of the efficiency of the Pd^{II} complex PdBr(*N*-Succ)(PPh_3)$_2$ (**1**) (Sigma-Aldrich; Cat. No. 643742) in Stille cross-couplings of allylic and benzylic halides with organostannanes, we envisaged that efficient Suzuki−Miyaura cross-couplings of benzylic substrates[13] could be achieved using this simple Pd source.[14] PPh_3 is a strong enough activating ligand for benzylic substrates. The imidate anion[15] is also likely to play an important role in the global catalyst efficacy. Our findings using precatalyst **1**[16] in Suzuki−Miyaura cross-couplings of benzylic halides with organoboronic acids are thus reported herein. Other tricky cross-couplings are presented, in addition to a valuable recycling protocol.

The initial benchmark was the reaction of substituted benzylic halides with an equivalent amount of substituted arylboronic acids using 1 mol % of **1**, in a mixture of 2 M Na_2CO_3 and THF (1:2, v/v) at 60 °C (Scheme 1). Under these simple conditions, a library of cross-coupled products could be formed efficiently. For example, benzyl bromide effectively reacted with phenylboronic acid to give diphenylmethane **2** in 88% yield after 2 h. The catalyst loading may be lowered to 0.01 mol %, which after 20 h gave an 81% yield (turnover number of 8100). The incorporation of substituents onto the aryl group of the boronic acid (*Z* = 4-OMe, 4-F, and 3,5-F) was also possible, giving high yields of the corresponding cross-coupled products (**3**−**5**, respectively). Where the yield dropped slightly for **3**, it could be improved by heating to 80 °C. Benzyl chlorides can also be used (at 80 °C). 3-Nitrobenzyl bromide reacts with various organoboronic acids to give cross-coupled products in very good yields (*Z* = H, 4-F, and 4-OMe, **6**−**8**). In a reaction with $PhB(OH)_2$, the catalyst loading was once again lowered to 0.01 mol % (>99% conversion in 20 h; TON = ∼10 000), exemplifying the stability and longevity of the catalyst system.[17]

Scheme 1. Cross-Coupling of Benzyl Halides and Arylboronic Acids (Isolated Yields Given)[c]



[a] Using 0.01 mol % of **1**, 81% (20 h). [b] Using 0.01 mol % of **1**, >99% (20 h). [c]All BnCl couplings were run at 80 °C.

Heteroarylboronic acids are also coupled effectively with benzylic halides (Scheme 2). For example, thiophene-2-boronic acid couples with BnBr to give **9** in 91% yield. Other thiopheneboronic acids (*Z* = 5-Cl, 5-acetyl) participate well in these reactions affording **10** and **11** in ∼80% yields for both BnBr and BnCl. For 5-formylthiophene-2-boronic acid, a small amount of protodeborylation was observed (∼10%). Thiophene-3-boronic acid reacts equally well with BnBr and BnCl to give **13** in 93% and 91% yields, respectively. Coupling of furan-2-boronic acid[18] with BnBr and 3-methoxybenzyl bromide was possible, giving the coupled products **14** and **15** in excellent yields (94% and >99%, respectively). Organotrifluoroborates[19] can be used as replacements for the organoboronic acid coupling components. However, under our reaction conditions, there is no real advantage over related organoboronic acids in terms of yields and reaction times.

(11) Kuwano, R.; Yokogi, M. *Chem. Commun.* **2005**, 5899.

(12) (a) McPhail, K. L.; Rivett, D. E. A.; Lack, D. E.; Davies-Coleman, M. T. *Tetrahedron* **2000**, *56*, 9391. (b) Long, Y.-Q.; Jiang, X.-H.; Dayam, R.; Sachez, T.; Shoemaker, R.; Sei, S.; Neamati, N. *J. Med. Chem.* **2004**, *47*, 2561.

(13) Benzylic carbonates have been employed in Suzuki−Miyaura cross-couplings. See: Kuwano, R.; Yokogi, M. *Org. Lett.* **2005**, *7*, 945.

(14) (a) Crawforth, C. M.; Burling, S.; Fairlamb, I. J. S.; Taylor, R. J. K.; Whitwood, A. C. *Chem. Commun.* **2003**, 2194. (b) Crawforth, C. M.; Fairlamb, I. J. S.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 461. (c) Burling, S.; Crawforth, C. M.; Fairlamb, I. J. S.; Kapdi, A. R.; Taylor, R. J. K.; Whitwood, A. C. *Tetrahedron* **2005**, *61*, 9736. Note that *cis*-**1** was used in these studies. The commerical source of PdBr(*N*-Succ)(PPh_3)$_2$ has a *trans*-geometry. This material was used in all of the examples presented in this paper.

(15) (a) Fairlamb, I. J. S.; Kapdi, A. R.; Lynam, J. M.; Taylor, R. J. K.; Whitwood, A. C. *Tetrahedron* **2004**, *60*, 5711. (b) Chaignon, N. M.; Fairlamb, I. J. S.; Kapdi, A. R.; Taylor, R. J. K.; Whitwood, A. C. *J. Mol. Catal. A: Chem.* **2004**, *219*, 191. (c) Serrano, J. L.; Fairlamb, I. J. S.; Sánchez, G.; García, L.; Pérez, J.; Vives, J.; López, G.; Crawforth, C. M.; Taylor, R. J. K. *Eur. J. Inorg. Chem.* **2004**, 2706. (d) Crawforth, C. M.; Fairlamb, I. J. S.; Kapdi, A. R.; Serrano, J. L.; Taylor, R. J. K.; Sanchez, G. *Adv. Synth. Catal.* **2006**, *348*, 405. (e) Young, G. L.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 3797. (f) Fairlamb, I. J. S.; Taylor, R. J. K.; Serrano, J. L.; Sanchez, G. *New J. Chem.* **2006**, *30*, 1685.

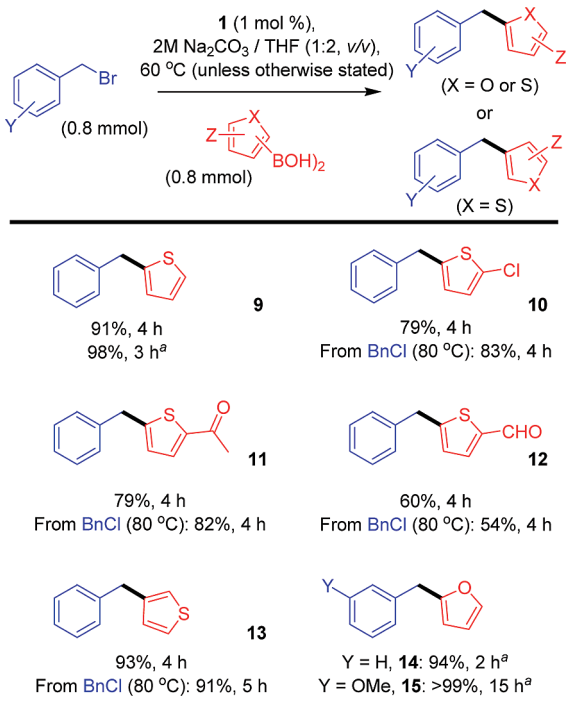
(16) In ref 15a, we reported that Pd(*N*-Succ)$_2$(PPh_3)$_2$ is an effective precatalyst for Suzuki−Miyaura cross-couplings of aryl halides with arylboronic acids. The coupling of 4-nitrobromobenzene with phenylboronic acid was tested with *cis*-**1** as the precatalyst in this paper. For this specific example, *cis*-**1** was less effective than Pd(*N*-Succ)$_2$(PPh_3)$_2$. Since this report, it has emerged that couplings of this aryl halide, and related compounds, can be complicated by electron-transfer processes, making it a poor benchmark substrate for screening catalysts/precatalysts.

(17) For selected examples given in Schemes 1 and 2, Pd(*N*-Succ)$_2$(PPh_3)$_2$ has been tested (see Supporting Information). Precatalyst **1** compares well with Pd(*N*-Succ)$_2$(PPh_3)$_2$; it is clear that both are useful precatalysts for coupling benzylic halide components in this reaction.

(18) Commercial sources of furan-2-boronic acid and thiophene-2-boronic acid were found to degrade at 25 °C in the presence of moisture.

(19) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49.

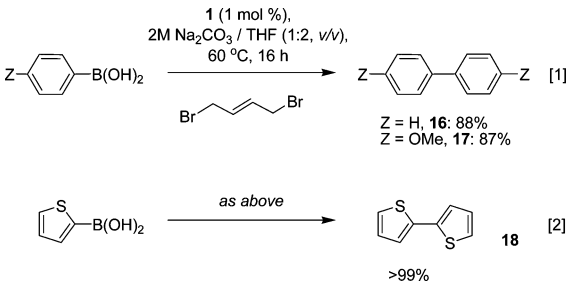
Scheme 2. Heteroaryl Couplings (Isolated Yields Given)



[a] 1.5 equiv of the organoboronic acid required.

In contrast to benzylic halides, allylic halides do not react so readily with organoboronic acids under the standard reaction conditions.[20] Only where an activated arylboronic acid is used was any coupled product detected (see Supporting Information). Interestingly, *E*-1,4-dibromo-but-2-ene can be used as an oxidant in homocoupling reactions of the organoboronic acids affording biaryls in high yield (Scheme 3). For example, $PhB(OH)_2$ and 4-methoxyphenylboronic

Scheme 3. Facile Homocoupling Using *E*-1,4-Dibromo-but-2-ene as the Oxidant (Isolated Yields Given)

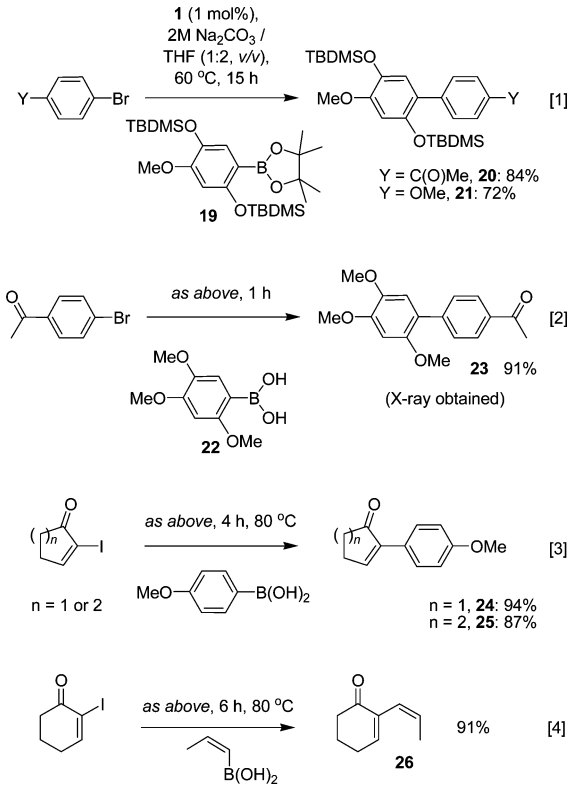


acid gave homocoupled products **16** and **17** in 88% and 87% yields, respectively. Thiophene-2-boronic acid homocouples more effectively, affording **18** in quantitative yield. The product selectivity and yields compare favorably against equivalent reactions using air as the oxidant.[21]

(20) For Suzuki−Miyaura cross-couplings using allylic halides, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1998**, *576*, 147, and references cited therein.

In view of the versatility of **1** with benzylic substrates, its reactivity toward awkward aryl coupling partners was also explored.[22] More demanding arylboron reagents (**19** and **22**), susceptible to protodeborylation, effectively cross-couple with aryl bromides (Scheme 4, reactions 1 and 2). For

Scheme 4. Other Cross-Coupling Reactions (Isolated Yields Given)



example, in eq 1, the sterically cumbersome arylboronic acid **19** couples well with two aryl bromides (Y = C(O)Me, **20** in 84% yield; Z = OMe, **21** in 72% yield). The less-hindered, but as electron-releasing, 2,4,5-trimethoxyphenylboronic acid **22** is also a useful nucleophilic coupling partner (eq 2), revealing the highly oxygenated biaryl product **23** (X-ray structure determined). Furthermore, both 2-iodocyclopent-2-enone and 2-iodocyclohex-2-enone react with 4-methoxyphenylboronic acid to give **24** and **25** in 94% and 87% yields, respectively (eq 3). Finally, *Z*-prop-1-enylboronic acid reacts well with 2-iodocyclohex-2-enone to give **26** in 91% yield, providing a useful synthon for further manipulation.

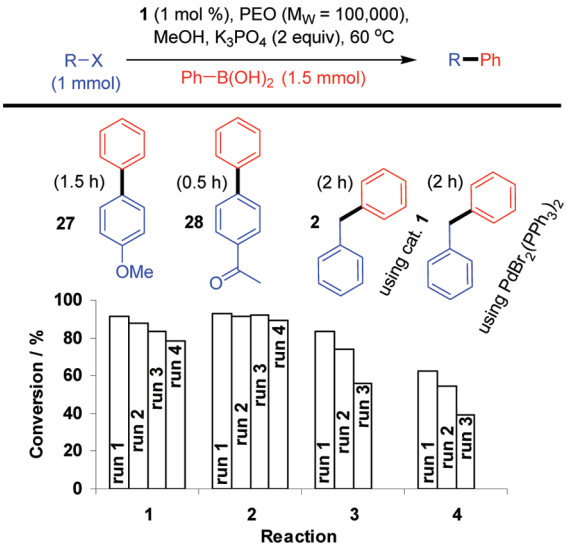
Catalyst recycling has been evaluated using a procedure modified from that originally reported by Monteiro and coworkers for $Pd(OAc)_2/PPh_3$[23] and used by our group with palladacycles,[24] using a poly(ethylene oxide) (PEO) solid

(21) For use of O_2 (air) as an oxidant in homocoupling of organoboronic acids, see: (a) Smith, C. A.; Campi, E. M.; Jackson, R.; Marcuccio, S.; Naeslund, C. G. M.; Deacon, G. B. *Synlett* **1997**, 131. (b) Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087. (c) Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829.

(22) Many monosubstituted aryl bromides and arylboronic acids effectively cross couple in good yields using the generic reaction conditions.

support[25] in methanol. At the end of the reaction, the product is extracted into a nonpolar phase, with the Pd catalyst remaining in the polar phase. The polar phase is then recharged with new reactants, allowing the Pd source to be reused (Scheme 5).

Scheme 5. Catalyst Recycling (Conversions by GC)



For example, coupling of 4-methoxyphenyl bromide with PhB(OH)$_2$ leads to good yields of **27**, in short reaction times, over several runs (reaction 1). No appreciable loss of catalytic activity is seen over four runs for an activated aryl substrate (to give **28**, reaction 2). For BnBr and PhB(OH)$_2$ cross-coupling, to give **2**, recycling is possible, but the conversions slowly deteriorate over three runs (reaction 3). However, the yields are consistently higher using **1** than for PdBr$_2$(PPh$_3$)$_2$ (reaction 4). The recycling study demonstrates that catalyst stability and longevity are assisted by the succinimidate anion in **1**.

In summary, **1** is shown to be a universal precatalyst for the Suzuki−Miyaura cross-coupling of benzylic bromides with aryl and heteroarylboronic acids. For the examples tested, catalyst loading can be significantly reduced (from 1 mol % to 0.01 mol %), allowing high TONs to be attained. The synthetic protocol reported in this paper complements the report by Molander and co-workers.[10] For the examples listed here, lower palladium loadings may be employed using the inexpensive base, Na_2CO_3. Moreover, the ratio of benzyl halide to organoboronic acid is 1:1 (in the majority of cases), improving substantially on previous protocols using excess organoboronic acid.[9] Also, **1** is an effective but *simple* precatalyst for aryl cross-couplings and offers good catalyst recyclability on a PEO solid support. Mechanistic studies on cross-coupling processes mediated by **1**, and related precatalysts, will be reported in due course.

Acknowledgment. We are grateful to the EPSRC for funding (EP/D078776/1) and the Royal Society and Astra-Zeneca (Dr. D. M. Hollinshead) for an unrestricted research award (to I.J.S.F). Dr. C. M. Crawforth (University of York, U.K.) is thanked for preliminary experiments. We thank the referees for their informative comments about this study and related work.

Supporting Information Available: Full experimental procedures, characterization (including spectroscopic data), and literature references to novel and known compounds, respectively. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702291R

(23) Nobre, S. M.; Wolke, S. I.; da Rosa, R. G.; Monteiro, A. L. *Tetrahedron Lett.* **2004**, *45*, 6527. PEO with a molecular weight of 100 000 was employed in this study.

(24) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F.; Sánchez, G.; López, G.; Serrano, J. L.; García, L.; Pérez, J.; Pérez, E. *Dalton Trans.* **2004**, 3970.

(25) PEO acts as an organic stabilizer for in situ formed palladium colloids/nanoparticles (formed by degradation of the palladium(II) precatalyst), produced by aggregation of palladium(0).

Pd-catalysed regioselective C-H functionalisation of 2-pyrones†

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First published on the web Xth XXXXXXXXX 200X
DOI: 10.1039/b000000x

In memory of Professor Keith Fagnou (Ottawa University, Canada).

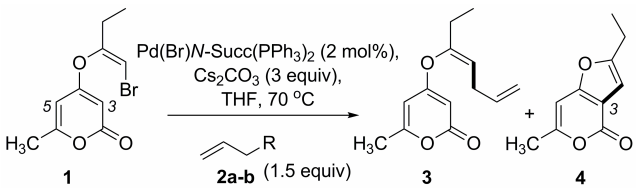
A new synthetic methodology for the catalytic C-H functionalisation of 2-pyrones is described which proceeds regioselectively at the C3 position, mirroring the observed regioselectivity in 6π-electocyclisation / oxidative aromatisation reactions of related compounds. Insight into the reaction mechanism is provided, with support for a neutral palladium(II) pathway. Cationic palladium(II) complexes possessing 2-pyrones are unstable and readily undergo Pd^{II}→P transfer at ambient temperature resulting in phosphonium salt formation (and Pd^0L_n species).

Introduction

Functionalised 2-pyrones (2*H*-pyran-2-ones) have attracted considerable interest as medicinal agents, natural products, fluorescent derivatives, and synthetic intermediates.[1] Classical cross-coupling reactions (*e.g.* Negishi,[2] Stille[3] and Suzuki-Miyaura[4] and others[5]) provide convenient access to these targets. However, there is strict requirement for the 2-pyrone to be appropriately prefunctionalised, either as the organometallic 'nucleophilic' component or the halide/pseudohalide 'electrophilic' component. It has been argued[6] that a more efficient process would involve the union of two reaction components possessing C-H and C-X bonds, respectively. For several heteroaromatic compounds, this has been possible, and indeed some very efficient methods have been developed.[7] However, surprisingly there are no reported catalytic methods involving the C-H functionalisation of 2-pyrones.[8] We are engaged in the development of innovative synthetic methods geared towards 2-pyrones and their metal complexes.[9] We report herein the intramolecular Pd-catalysed C-H functionalisation of 2-pyrones, which is regioselective.

Results and Discussion

During synthetic studies toward phacelocarpus pyrone A[10] we were interested in the Suzuki-Miyaura cross-coupling of **1** with allylborane reagents **2a-b** to give **3** using *trans*-Pd(Br)*N*-Succ$(PPh_3)_2$ as the catalytic Pd source (Scheme 1), a precatalyst that has been previously developed by our research groups for use in Stille and Suzuki cross-couplings.[11]



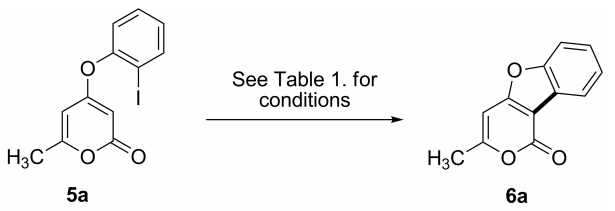
R	3 / %	4 / %
Bpin (**2a**)	40	25
BF_3K (**2b**)	0	47

Scheme 1 Suzuki-Miyaura cross-couplings of **1**.

As expected the reaction of **1** with pinacol allylboronate **2a** gave **3** in 40% yield. However, we were very surprised to observe the regioselective formation of cyclised product **4** was also found to occur. An otherwise identical reaction of potassium allyltrifluoroborate **2b** gave **4** exclusively in 47% yield. The absence of **3** in this reaction is attributed to a slower transmetallation step (**2a** is more reactive than **2b** under the anhydrous reaction conditions used). The *trans*-Pd(Br)*N*-Succ$(PPh_3)_2$ is likely acting as a precatalyst under the reaction conditions (Pd^{II}→Pd^0 mediated by **2a-b** and/or Cs_2CO_3). Further support for a Pd^0-mediated reaction was gained by substituting *trans*-Pd(Br)*N*-Succ$(PPh_3)_2$ with an active Pd^0 catalyst system {Pd_2(dba-4-OMe)$_3$/PPh_3 (Pd:P = 1:2)}, in the absence of **2a-b**, which gave **4** in 48% yield.[12]

Additional experiments on model substrate **5a** to give **6a**, a compound which is of medicinal and synthetic interest,[13] highlight that *trans*-Pd(Br)*N*-Succ$(PPh_3)_2$ is a precatalyst, requiring a sub-stoichiometric amount of **2b** (relative to **5a**) to facilitate Pd^{II} reduction (Table 1; compare entries 1-3). The best yield for cyclised product **6a** using allylBF_3K was 69% yield (entry 3). Other additives such as $AgBF_4$ or pivalic acid (PivOH) proved ineffective (entries 4 and 5). For the latter, a lower yield was obtainined with $Pd(OAc)_2$ as the catalytic source of Pd (entry 6). Using $Pd_2(dba)_3$/PPh_3 as the catalyst system with no additive gave **6a** in 74% yield (entry 7).

Table 1 Other reaction conditions screened in the regioselective C-H functionalisation of **5a**.[a]



Entry	Catalyst	Additive	Yield / %[b]
1	*trans*-Pd(Br)*N*-Succ(PPh_3)$_2$	AllylBPin (2 eq.)	49[c]
2	"	AllylBF_3K (1 eq.)	57
3	"	AllylBF_3K (0.1 eq.)	69
4	"	$AgBF_4$ (1 eq.)	6†
5	"	PivOH (0.3 eq.)	41
6	$Pd(OAc)_2$	PivOH (0.3 eq.)	31
7	$Pd_2(dba)_3$	PPh_3 (4 mol%)	74
8	Pd_2(dba-4-OMe)$_3$	"	79
9[e]	"	"	77
10	"	PPh_3 (4 mol%)/ PivOH (0.3 eq.)	45

[a] Other reaction conditions: THF, 70 °C, 18 h (unless other stated).

[b] Isolated yield following flash chromatography on silica gel.

[c] A 42% yield of the Suzuki product is also observed.

[d] Reaction left for 72 h in the dark.

[e] Using K_3PO_4 as base instead of Cs_2CO_3.

With the {Pd_2(dba-4-OMe)$_3$/PPh_3} system a 79% yield was attained (entry 8). This same reaction can be conducted using K_3PO_4 instead of Cs_2CO_3, giving a 77% yield of **6a** (entry 9). Finally, addition of pivalic acid to the best catalyst system, resulted in a lowering of the reaction yield of **6a** (entry 10).

The regioselectivity (for C3-H) for products **4** and **6a** was confirmed by ^{1}H NMR spectroscopy (C5-H exhibiting a $^4J_{HH}$ coupling with the C6 methyl group). However, conclusive evidence for the structure of **6a** was gained by a single crystal X-ray diffraction study (Fig. 1).

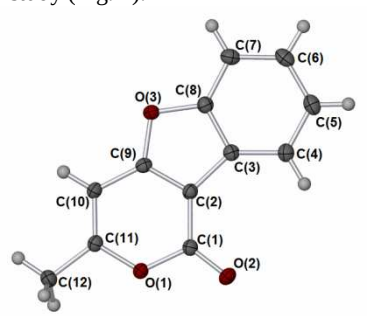
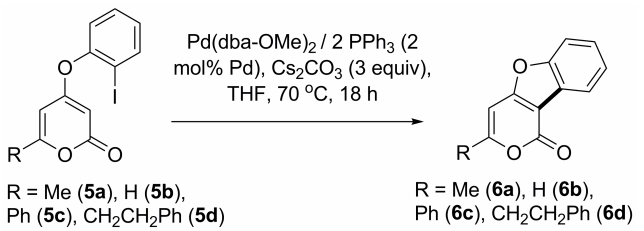


Figure 1 Structure of **6a** (X-ray diffraction; arbitrary numbering used).

Control experiments confirm that catalytic Pd and Cs_2CO_3 base is required for C-H functionalisation. In principle, the C6-methyl group could be playing a role, as previous studies[14] have shown that the C6-methyl group and C3-H share similar acidities. Therefore we have evaluated three different 2-pyrones in addition to **5a** (Table 1). Subjecting a 2-pyrone without a C6-methyl group (**5b**) to the best conditions (entry 8, Table 1) gave compound **6b** regioselectively (confirmed by X-ray studies, see ESI) in 74% yield (entry 2), comparing well with the yield for **6a** (entry 1). Other C6-substituted 2-pyrones **5c** and **5d** gave **6c** and **6d**, respectively in 59% and 68% yields (entries 3 and 4).

Table 2 On the importance of the C6-substituent.



Entry	R	Yield / %[a]
1	Me (**6a**)	79
2	H (**6b**)	74
3	Ph (**6c**)	59
4	CH_2CH_2Ph (**6d**)	68

[a] Isolated yield following flash chromatography on silica gel.

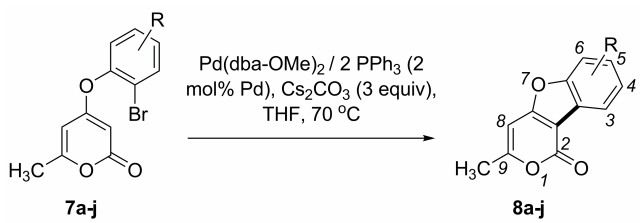
These findings indicate that the C6-methyl could be affecting these reactions, but it is not essential for the reaction to take place.

Having identified a mild set of reaction conditions and tested different C6-substituents, we next sought to understand how the reaction was affected by aromatic substituents. The synthesis of the substrates for these reactions was generally achieved in two steps by a K_2CO_3-mediated reaction of the appropriately substituted 2-bromophenol with 4-bromo-6-methyl-2-pyrone to give **7a-j** (see ESI for complete details).[15] Due to the availability of 2-halophenols, we found it more convenient to prepare the bromides. Pleasingly, the direct C-H functionalisation is feasible using bromide-containing substrates (**7a-j** → **8a-j**, Table 3). Substrates possessing methoxy-, methyl- and *t*-butyl-substituents effectively participate well in these reactions (**7a-f**, entries 1-6). The yield is modest for **8g**, possessing a 4-phenyl group (entry 7). Perhaps surprisingly, the presence of fluoro-substituents in **7h-i** to give **8h-i**, respectively, also leads to a lowering of the reaction yield (entries 8-9).‡

The most dramatic effect was seen with a 4-trifluoromethyl-substituent in **7j** (entry 10) where the yield for **8j** drops off significantly. The following relative order is therefore established based on the yields[16] of the reaction (H ≈ Me ≥ *t*-Bu > 4- or 5-OMe > 4-Ph > 4-F ≈ 5-F > 4-CF_3. The issue for the electron-withdrawing substituents appears to be related to 2-pyrone decomposition under the reaction conditions. The 'arylalkoxide' leaving group ability, from the initial oxidative addition intermediate (*vide infra*), could account for this outcome.

The low yield for **8j** is supported by a further example, where a substrate possessing an additional 2-pyrone moiety gives a low product yield (**7k→8k**, Scheme 3). This 2-pyrone 'substituent' is electron-withdrawing and unlikely to interfere in the cyclisation.

Table 3 Aromatic substituent effects.



7a-j 8a-j

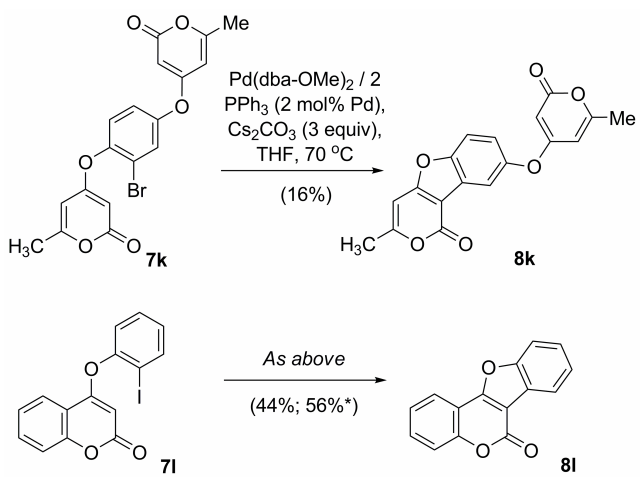
Entry	R	Yield / %[a]
1	4-OMe (**8a**)	65
2	5-OMe (**8b**)	67
3	4-Me (**8c**)	73
4	4,6-$(Me)_2$ (**8d**)	79
5	4-*t*-Bu (**8e**)	71
6	4,6-$(t\text{-Bu})_2$ (**8f**)	71
7	4-Ph (**8g**)	44
8	4-F (**8h**)[b]	30[c]
9	5-F (**8i**)[b]	24
10	4-CF_3 (**8j**)	11

[a] Isolated yield following chromatography on silica gel.

[b] Structures supported by X-ray diffraction analysis (See ESI).

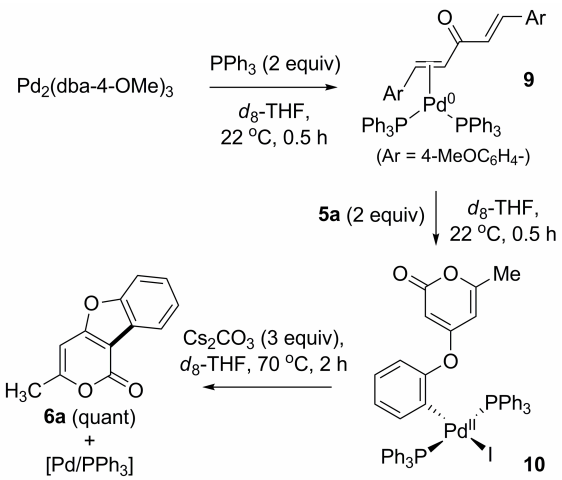
[c] A 41% yield was obtained using 5 mol% Pd.

In a separate example, we were able to show that a coumarin-derived substrate **7l** cyclised under the reaction conditions to give benzofuro[3,2-*c*]coumarin **8l**, which is better known as as the natural compound, coumestan (Scheme 2).[17]



Scheme 2 Other substrates evaluated under the general reaction conditions (* yield is based on recovered **7l**, after chromatography on silica gel).

Stoichiometric studies. To gain insight into the reaction mechanism a series of stoichiometric experiments were conducted. The complex, $[Pd^0(\eta^2\text{-dba-4-OMe})(PPh_3)_2]$ **9**, presumed to be the initial Pd^0 species formed in the reaction, was prepared and characterized *in situ* by the reaction of $Pd_2(dba\text{-}4\text{-}OMe)_3$ with PPh_3 (ratio of Pd:P = 1:2) in d_8-THF at 25 ºC (Scheme 3).



Scheme 3 Stoichiometric NMR spectroscopic experiments.

Two broad phosphorus signals corresponding to exchanging PPh_3 ligands in **9** were observed (δ 26.18 (s) and 24.52 (s), 283 MHz).[18] Addition of 2 equivalents of **5a** to **9** (in a dry box at 22 ºC) resulted in quantitative conversion into *trans*-$[Pd\{C_6H_4O\text{-}2\text{-}(C_6H_5O_2)\}I(PPh_3)_2]$ **10** (the oxidative addition product). The ^{31}P NMR spectrum of **10** in d_8-THF exhibits a singlet at δ 22.44. The ^1H NMR spectrum (700 MHz) of **10** exhibits significant upfield chemical shifts for the 2-pyrone C3-H and C5-H protons when compared to **5a** (in both CD_2Cl_2 and d_8-THF). By the same method (*vide supra*) $[Pd^0(\eta^2\text{-dba-4-OMe})\{P(C_6D_6)_3\}_2]$ and **10**-$\{P(C_6D_5)_3\}_2$ were prepared and these showed that the upfield proton signals were associated with the 2-pyrone group (confirmed also by 2D ^1H-^1H COSY and ^1H-^{31}P HMQC experiments; see Supporting Information). Crystals of **10** (from CD_2Cl_2) were analysed by X-ray diffraction (Fig. 2). The X-ray data indicates that the complex exhibits a distorted square planar *trans*-geometry (P1-Pd-P2 angle = 169.03(2)º; I-Pd-C angle = 169.21(7)º). Whilst this type of distortion has been observed in previously reported X-ray diffraction studies involving $Pd^{II}(I)R(PPh_3)_2$ complexes,[19] the angles P1-Pd-P2 (in the range 172.39-174.41º) and I-Pd-C (in the range 166.03-176.50º) are significantly different.[20] The finding that the P1-Pd-P2 and I-Pd-C angles in **10** are near identical is unique.

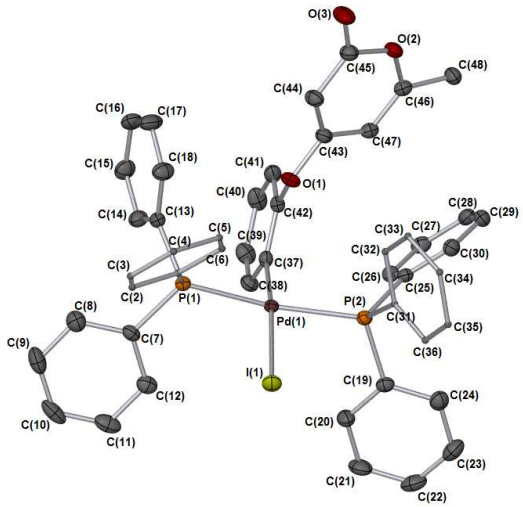
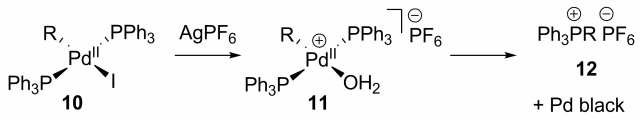


Figure 2 Structure of *trans*-[Pd{C_6H_4O-2-($C_6H_5O_2$)}I(PPh_3)$_2$] **10** by X-ray diffraction; arbitrary numbering used. Selected bond lengths (Å): C(37)-Pd(1) 2.014(2), I(1)-Pd(1) 2.6641(3), P(1)-Pd(1) 2.3157(7), P(2)-Pd(1) 2.3258(7).



Scheme 4 Decomposition of **11**; R = {C_6H_4O-2-($C_6H_5O_2$)}.

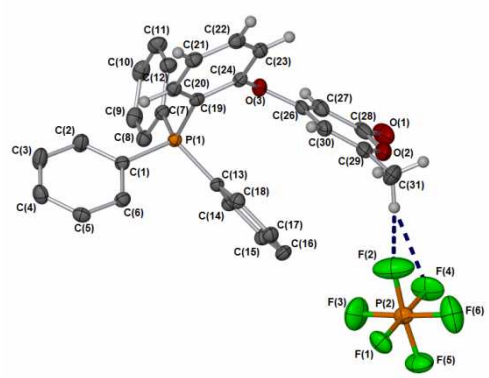


Figure 3 Structure of **12** by X-ray diffraction; arbitrary numbering used. Dotted lines show H-bonds between the CH_3 and PF_6 groups.

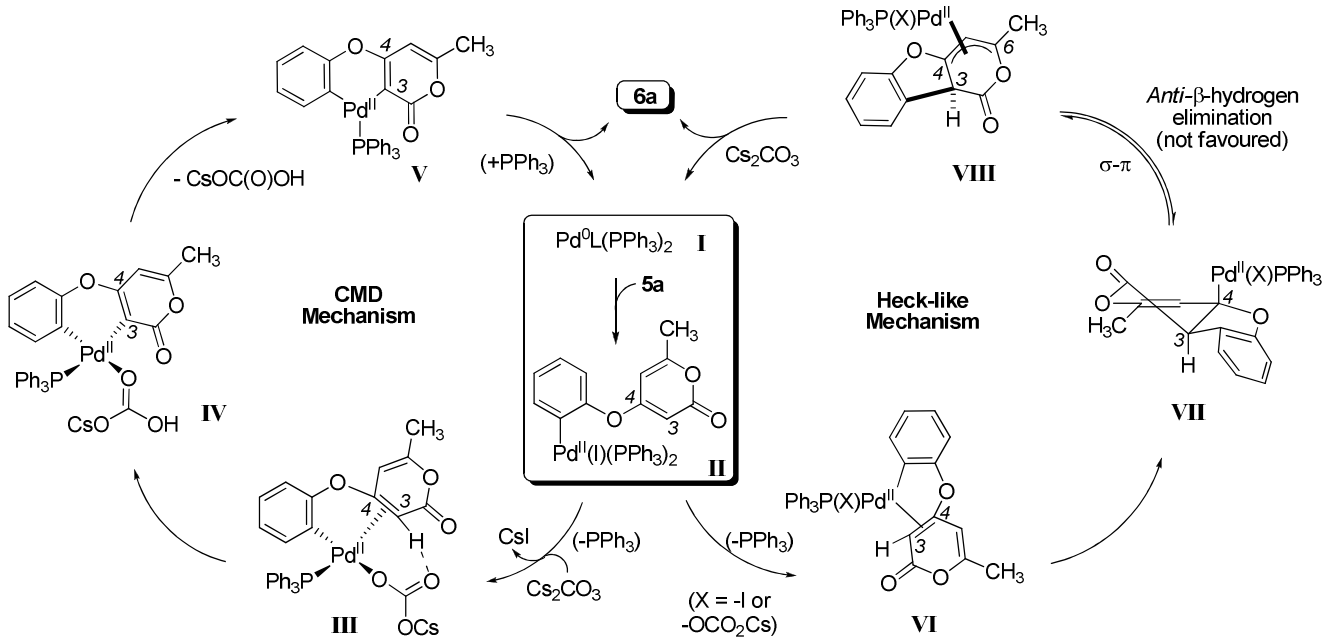
Treatment of **10** with Cs_2CO_3 (3 equiv.) (with 1.5 equiv. of dba-4-OMe ligand) in d_8-THF and heating to 70 ºC for 2 h gave product **6a** in quantitative conversion (Scheme 4). No other Pd^{II} intermediates were observed by NMR spectroscopy (note: the dba-OMe ligand was consumed under the reaction conditions – the -CH=CH- motif was no longer visible by ^{1}H NMR spectroscopy, although the exact structure of the degraded dba-OMe ligand remains unknown.

The presence of electron-withdrawing groups has a profound effect on the catalytic reaction. A further stoichiometric reaction, identical to that detailed above with **5a**, shows that the reaction (oxidative addition) of **7j** and [Pd^0(η^2-dba-4-OMe)(PPh_3)$_2$] **9** is a reversible process (see experimental section), both in the presence and absence of Cs_2CO_3. Slow deposition of Pd^0 black is observed. Catalyst and substrate decomposition is thus an issue for substrates possessing electron-withdrawing substituents.

We postulated cationic Pd^{II} species as potential reaction intermediates. Thus, whilst **10** did not react with Ag_2CO_3 in CD_2Cl_2, the cationic Pd^{II} complex **11** was formed quantitatively (NMR) by reaction of **10** with $AgPF_6$ in CD_2Cl_2 at ambient temperature (Scheme 4). ^{1}H NMR spectra show no evidence of a 2-pyrone secondary interaction (either a C=C[21] or C-H agostic[22] or anagostic[23]). Layering a CD_2Cl_2 solution of **11** with diethyl ether (in the dark at 18 ºC) gave crystals suitable for an X-ray diffraction study (Figure 3). Rather curiously, it was found that the "C_6H_4O-2-($C_6H_5O_2$)" group from **11** had undergone Pd→P transfer forming [P{C_6H_4O-2-($C_6H_5O_2$)}Ph_3]PF_6 **12**, which was accompanied by Pd black formation. Phosphonium salt formation has been observed previously by others, notably by Heck in early studies on the alkenylation of aryl halides.[24]

Proposed mechanism. The facile decomposition event (**11→12**) obviates a reaction mechanism involving cationic Pd^{II} species at elevated reaction temperatures. Therefore based on our findings, we propose that the mechanism involves neutral Pd intermediates (Scheme 6). There are two clear mechanistic possibilities – a Concerted Metallation Deprotonation (CMD) mechanism[25] or Heck-like mechanism.[26] For both, the first committed step is oxidative addition of the C-I bond in **5a** (as a representative substrate) to Pd^0 (**I**) to give **II** (complex **10**). It is important to point out that initially formed complex **9** will be in an endergonic/unfavourable equilibrium with the more reactive Pd^0(S)(PPh_3)$_2$ species, releasing free dba-4-OMe (not shown in this scheme).[18] This ligand is almost certainly consumed slowly under the reaction conditions, akin to the stoichiometric experiments detailed above. Therefore, any controlling effect of dba-type ligands[12] in this reaction is minimal {Pd_2(dba-4-OMe)$_3$ was only marginally superior to Pd_2(dba-H)$_3$ in the catalytic reaction of **5a→6a**}.

For the CMD mechanism (catalytic cycle on the left, Scheme 5), one needs to form intermediate **IV**, setting up reductive elimination to regenerate the Pd^0 catalyst species and product **6a**. Whilst it is conceivable that the Cs_2CO_3 can deprotonate the C3-proton in **10** intermolecularly, we show here an iodide/carbonate metathesis followed by an intramolecular base-assisted CMD process (via **III**). The formation of **IV** requires the loss of CsO(CO)OH (solvent-assisted?). With 14-electron Pd^{II} intermediate **V** formed, reductive elimination to give both **I** and product **6a** ought to be facile. Going against this mechanism is the result given in Table 1 (entry 10). If a CMD mechanism is operative, then we would anticipate that pivalic acid[25a,27] would accelerate the step **III→IV**. This is not the case.



Scheme 5 Possible reaction mechanisms for the C-H functionalisation reaction.

The preferred C3-H over C5-H regioselectivity can be primarily explained by the significantly different acidities of these two positions. However, one also needs to consider the Pd-C bond strengths of both the C3- and C5-products before drawing firm conclusions. Of particular note is the finding that the regiochemical outcome mirrors 6π-electrocyclisation/oxidative aromatic reactions of phenylethenyl-2-pyrone derivatives to give benzo[*h*]indeno[1,2-*f*]isochromenes.[28] In that chemistry, unfavourable 6π-electrocyclisation at C5-H results in ketene generation and 2-pyrone ring-opening.

In terms of the Heck-like mechanism (catalytic cycle on the right, Scheme 5), loss of PPh_3 from **II** will generate intermediate **VI** (which is similar to **III**). Migratory insertion (carbopalladation) then generates **VII**. However, there is an apparent problem in the next step to give product **6a** and "$(PPh_3)Pd(X)H$". In the absence of other neighbouring β-hydrogens, the *anti*-stereochemical relationship of the "$Pd^{II}(X)PPh_3$" group and C3-H proton is a problem for β-hydrogen elimination (*syn*-elimination being preferred).[29] We believe that it is more likely that **VII** isomerises to the π-allyl species **VIII**.[30] Intermolecular base-assisted deprotonation can then take place at either C3-H or the C6-methyl group. For the latter, as the 2-pyrone can be considered semi-aromatic, tautomerisation is facile. Whilst other Heck-like mechanisms may be considered, *e.g.* involving cationic Pd^{II} or Pd^{IV} species,[31a] we believe they are ruled out because phosphonium salt formation is facile from the cationic complex derived from **5a** (**11**). An alternative mechanistic possibility is the SEAr type reaction pathway.[31c] The pronounced aromatic substituent effects, particularly the deliterous effect of electron-withdrawing groups on the aromatic moieties in substrates, 4-F (**7h**), 5-F (**7i**) and 4-CF_3 (**7h**), could indicate that positive charge is developed in the transition state intermediate(s), where the 4-oxygen would be expected to play a key stabilizing role. However, extensive decomposition is observed for these substrates, so firm conclusions cannot be drawn.

Finally, a comment about the reaction solvent, THF. Whilst this solvent is sufficiently polar to stabilise charged / highly polar intermediates, previous studies[32] which support a CMD mechanism involve highly polar solvents such as DMF or DMA. Furthermore, Cs_2CO_3 is only sparingly soluble in THF (0.023 mmols/L at 25 ºC) and its concentration is quasi-constant and low.[33] Finally, under the best conditions for **5a** →**6a** (entry 8, Table 1) replacing THF with DMF results in no observable product formation.[34]

Conclusions

In summary, we have developed the first catalytic C-H functionalisation synthetic method for 2-pyrones[35] which is completely regioselective for the C3 position. The presence of a C6-methyl group could assist reactions of **7a-j**. However, the successful cyclisation of **6b-d** confirms that the C-H functionalisation process is not dependent on it. Our preliminary mechanistic studies show that cationic Pd^{II} species are unlikely intermediates and that characterised neutral Pd^{II} complex **10** gives organic product **6a** quantitatively. Further studies (both experimental and theoretical) to determine the mechanism of this C-H functionalisation reaction are ongoing in our laboratories.

Experimental Section

General details:

Reagents were purchased from either Sigma Aldrich or Alfa Aesar and used directly unless otherwise stated. Solvents were dried according to standard procedures prior to use and stored under nitrogen. Nitrogen gas was oxygen free and dried

immediately before use via passage through sodium hydroxide pellets and silica. All TLC analysis was performed using Merck 5554 aluminium backed silica plates and visualised using UV light (254 nm), an aqueous solution of potassium permanganate, or an ethanol based solution of *p*-anisaldehyde. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Jeol ECX400 spectrometer operating at 400 and 100 MHz respectively, or a Bruker 500 spectrometer operating at 500 and 126 MHz, respectively. All column chromatography was performed using flash silica gel eluting with an appropriate solvent system. Preparative details and characterisation data for the starting materials detailed in this paper, in addition to representative NMR spectra of the cyclisation products, can be found in the E.S.I. file.

General procedure for the direct C-H functionalisation of 2-pyrones:

A solution of aryl halide (1 eq.), Cs_2CO_3 (3 eq.), PPh_3 (4 mol%) and Pd_2(dba-4-OMe)$_3$ (2 mol% Pd) in THF (4 mL/mmol) was stirred under nitrogen at 70 ºC for 18 h. The reaction was allowed to cool to ambient temperature and quenched by water (8 mL per mmol) and ethyl acetate added (12 mL per mmol), and the layers separated. The aqueous layer was back-extracted with ethyl acetate (2x12mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude products were purified by flash column chromatography on silica gel (10-30 % EtOAc in hexanes).

4-{[(1*Z*)-1-Ethyl-1,4-pentadienyl]oxy}-6-methyl-2-pyrone (3)

A solution of 4-{[(*Z*)-2-bromo-1-ethyl-1-ethenyl]oxy}-6-methyl-2-pyrone (20 mg, 0.077 mmol, 1 eq.), Cs_2CO_3 (75.3 mg, 0.231 mmol, 3 eq.), allyl boronic acid pinacol ester (25.9 mg, 0.154 mmol, 2 eq.) and *trans*-Pd(Br)*N*-succ$(PPh_3)_2$ (1.2 mg, 0.0015 mmol, 2 mol%) in THF (1 mL) was stirred under nitrogen at 70 °C for 18 hours. The reaction was allowed to cool to ambient temperature and quenched by addition of water (1 mL) and ethyl acetate (2 mL), and the layers separated. The aqueous layer was extracted using ethyl acetate (3 × 2 mL) and the combined organic extracts dried over $MgSO_4$, concentrated in *vacuo* and purified by flash column chromatography (10-20 % EtOAc in hexanes) to afford the product as a colourless oil (6.8 mg, 40.0%). Rf = 0.42 (20% EtOAc in hexanes); ^{1}H-NMR (500 MHz, $CDCl_3$): 5.87 (s, 1H), 5.73 (ddt, *J* = 17.0, 10.1, 6.3 Hz, 1H), 5.40 (s, 1H), 5.14 (t, *J* = 7.3 Hz, 1H), 5.01 (dd, *J* = 17.0, 1.2 Hz, 1H), 4.99 (dd, *J* = 10.1, 1.2 Hz, 1H), 2.66 (dd, *J* = 6.3, 7.3 Hz, 2H), 2.23 (s, 3H), 2.18 (q, *J* = 7.3 Hz, 2H), 1.06 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): 168.8, 164.9, 163.1, 151.3, 135.3, 114.1, 99.8, 95.6, 89.5, 29.4, 25.3, 20.0, 11.1; MS (ESI) *m/z* (rel.%): 243 [MNa^+] (28), 221[MH^+] (100), 201 (6), 179 (28), 127 (4); HRMS (ESI) calculated for $C_{13}H_{17}O_3$: 221.1172, found: 221.1175; IR (neat): 3084, 2975, 2938, 1700, 1643, 1560, 1448, 1407, 1225, 1177, 1139, 1037, 994, 822 cm^{-1}.

4-Ethyl-7-methyl-furo[3,2-*c*]-2-pyrone (4)

The title compound was prepared according to the General Procedure, on a 0.108 mmol scale, to afford the product as a yellow oil (9.2 mg, 47.9%). R_f = 0.42 (20% EtOAc in hexanes); ^{1}H-NMR (500 MHz, $CDCl_3$): 6.43 (q, *J* = 0.9 Hz, 1H), 6.36 (t, *J* = 1.1 Hz, 1H), 2.72 (dq, *J* = 7.5, 1.1 Hz, 2H), 2.32 (d, *J* = 0.9 Hz, 3H), 1.28 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): 161.0, 160.1, 159.6, 158.8, 115.6, 109.2, 101.3, 21.3, 20.1, 11.8; MS (ESI) *m/z* (rel.%): 201 [MNa^+] (22), 179 [MH^+] (100); HRMS (ESI) calculated for $C_{10}H_{11}O_3$: 179.0703, found: 179.0700; IR (neat): 3099, 2976, 2922, 1734, 1622, 1593, 1574, 1459, 1381, 1258, 1027, 966, 918, 814, 764 cm^{-1}.

9-Methyl-benzofuro[3,2-*c*]-2-pyrone (6a)

The title compound was prepared according to the General Procedure, on a 0.25 mmol scale, to afford the product as a yellow solid (39.6 mg, 79.2%). M.p. 188-190 ºC; ^{1}H-NMR (400 MHz, $CDCl_3$): 8.01 – 8.06 (m, 1H), 7.52 – 7.58 (m, 1H), 7.39 – 7.44 (m, 2H), 6.54 (q, *J* = 0.9 Hz, 1H), 2.43 (d, *J* = 0.9 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): 164.5, 162.9, 159.5, 154.9, 126.1, 124.9, 122.9, 121.4, 111.5, 103.7, 95.9, 20.6; MS (ESI) *m/z* (rel.%): 223 [MNa^+] (16), 201 [MH^+] (100); HRMS (ESI) calculated for $C_{12}H_9O_3$: 201.0546, found: 201.0549; IR (neat): 3101, 2919, 1719, 1614, 1572, 1445, 1251, 1187, 971, 934, 816, 748 cm^{-1}.

Benzofuro[3,2-*c*]-2-pyrone (6b)

The title compound was prepared according to the General Procedure, on a 0.25 mmol scale, to afford the product as a white solid (34.6 mg, 74.4%). R_f = 0.33 (20% EtOAc in hexanes). M.p. 149-150 ºC; ^{1}H-NMR (400 MHz, $CDCl_3$): 8.09 (m, 1H), 7.65 (d, *J* = 5.7 Hz, 1H), 7.60 (m, 1H), 7.42 – 7.49 (m, 2H), 6.81 (d, *J* = 5.7 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): 162.7, 159.1, 155.0, 151.5, 126.7, 125.1, 122.7, 121.7, 111.6, 106.5, 98.9; MS (ESI) *m/z* (rel.%): 209 [MNa^+] (39), 187 [MH^+] (100); HRMS (ESI) calculated for $C_{11}H_7O_3$: 187.0390, found: 187.0389; IR (neat): 3102, 1717, 1607, 1558, 1448, 1431, 1219, 1171, 1012, 926, 844, 783, 746 cm^{-1}.

9-Phenyl-benzofuro[3,2-*c*]-2-pyrone (6c)

The title compound was prepared according to the General Procedure, on a 0.13 mmol scale, to afford the product as a yellow solid (20.0 mg, 58.8%). ^{1}H-NMR (400 MHz, $CDCl_3$): 8.09 (m, 1H), 7.93 – 7.98 (m, 2H), 7.60 (m, 1H), 7.49 – 7.53 (m, 3H), 7.43 – 7.47 (m, 2H), 7.18 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): 164.4, 160.8, 158.7, 155.3, 131.4, 131.1, 129.1, 126.4, 125.9, 125.1, 122.9, 121.6, 111.5, 104.7, 93.2; MS (ESI) *m/z* (rel.%): 263 [MH^+] (100), 251 (28), 159 (26), 149 (15); HRMS (ESI) calculated for $C_{17}H_{11}O_3$:263.0703, found: 263.0706; IR (neat): 3090, 2161, 1721, 1560, 1537, 1446, 1382, 1021, 746, 687 cm^{-1}.

9-Phenethyl-benzofuro[3,2-*c*]-2-pyrone (6d)

The title compound was prepared according to the General Procedure, on a 0.071 mmol scale, to afford the product as a yellow solid (16.3 mg, 68.2%). R_f = 0.58 (20% EtOAc in hexanes). M.p. 130-132 ºC ^{1}H-NMR (400 MHz, $CDCl_3$): 8.01 – 8.08 (m, 1H), 7.51 – 7.58 (m, 1H), 7.38 – 7.45 (m, 2H), 7.27 – 7.33 (m, 2H), 7.25 – 7.18 (m, 3H), 6.46 (t, *J* = 0.7 Hz, 1H), 3.09 (dd, *J* = 8.5, 6.4 Hz, 2H), 2.94 – 2.99 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$): 165.2, 164.2, 155.0, 139.7, 128.7, 128.3,

126.5, 126.2, 125.0, 122.9, 121.4, 111.5, 104.0, 99.9, 95.9, 36.3, 33.3; MS (ESI) *m/z* (rel.%): 313 [MNa^+] (44), 291 [MH^+] (100); HRMS (ESI) calculated for $C_{19}H_{15}O_3$: 291.1016, found: 291.1011; IR (neat): 3085, 3057, 2921, 1727, 1612, 1571, 1447, 1186, 1029, 970, 937, 817, 750, 701 cm^{-1}.

4-Methoxy-9-methyl-benzofuro[3,2-*c*]-2-pyrone (8a)

The title compound was prepared according to the General Procedure, on a 0.25 mmol scale, to afford recovered starting material (24 mg, 30.8%) and the product as a yellow solid (37.1 mg, 64.5% [93% based on recovery of halo-starting material]). R_f = 0.31 (20% EtOAc in hexanes); M.p. 155-157 ºC; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.48 (d, *J* = 2.6 Hz, 1H), 7.43 (d, *J* = 9.0 Hz, 1H), 6.98 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.51 (q, *J* = 0.9 Hz, 1H), 3.90 (s, 3H), 2.42 (d, *J* = 0.9 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): 164.9, 162.6, 159.7, 157.5, 149.6, 123.6, 115.1, 112.1, 103.9, 103.2, 96.0, 56.0, 20.6; MS (ESI) *m/z* (rel.%): 253 [MNa^+] (45), 231 [MH^+] (100); HRMS (ESI) calculated for $C_{13}H_{11}O_4$ [MH^+]: 231.0652, found: 231.0651; IR (neat): 3095, 2958, 1728, 1631, 1619 1572, 1461, 1436, 1274, 1226, 1177, 1023, 965, 937, 848, 813, 786, 771 cm^{-1}.

5-Methoxy-9-methyl-benzofuro[3,2-*c*]-2-pyrone (8b)

The title compound was prepared according to the General Procedure, on a 0.5 mmol scale, to afford the product as a yellow solid (76.7 mg, 66.7%). R_f = 0.29 (20% EtOAc in hexanes). M.p. 172-173 ºC; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.88 (d, *J* = 8.6 Hz, 1H), 7.07 (d, *J* = 2.2 Hz, 1H), 7.01 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.51 (q, *J* = 0.9, 1H), 3.88 (s, 3H), 2.41 (d, *J* = 0.9 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): 164.0, 161.7, 159.7, 159.2, 156.1, 121.5, 115.9, 113.0, 103.8, 96.7, 95.9, 55.8, 20.5; MS (ESI) *m/z* (rel.%): 253 [MNa^+] (100), 231 [MH^+] (87); HRMS (ESI) calculated for $C_{13}H_{10}NaO_4$ [MNa^+]: 253.0471, found: 253.0469; IR (neat): 3095, 1715, 1569, 1496, 1270, 1137, 1110, 1036, 973, 939, 834, 801 cm^{-1}.

4,9-Dimethyl-benzofuro[3,2-*c*]-2-pyrone (8c)

The title compound was prepared according to the General Procedure, on a 0.25 mmol scale, to afford the product as a yellow solid (38.4 mg, 71.8%). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.82 (dq, *J* = 1.9, 0.7 Hz, 1H), 7.41 (d, *J* = 8.4, 1H), 7.20 (ddq, *J* = 8.4, 1.9, 0.7 Hz, 1H), 6.51 (q, *J* = 0.9, 1H), 2.47 (app. t, *J* = 0.7 Hz, 3H), 2.41 (d, *J* = 0.9 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): 164.6, 162.6, 159.7, 153.3, 134.8, 127.2, 122.8, 121.2, 110.9, 103.5, 96.0, 21.3, 20.6; MS (ESI) *m/z* (rel.%): 237 [MNa^+] (40), 215 [MH^+] (100); HRMS (ESI) calculated for $C_{13}H_{11}O_3$ [MH^+]: 215.0703, found: 215.0706; IR (neat): 3088, 2921, 1727, 1615, 1571, 1450, 1190, 1037, 971, 941, 821, 795, 773 cm^{-1}.

4,6,9-Trimethyl-benzofuro[3,2-*c*]-2-pyrone (8d)

The title compound was prepared according to the General Procedure, on a 0.25 mmol scale, to afford the product as a yellow solid (44.8 mg, 78.6%). R_f = 0.43 (20% EtOAc in hexanes); M.p. 149-150 ºC; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.65 (s, 1H), 7.02 (s, 1H), 6.52 (s, 1H), 2.50 (s, 3H), 2.44 (s, 3H), 2.41 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): 164.3, 162.4, 159.8, 152.4, 134.8, 128.5, 122.4, 121.1, 118.6, 103.8, 96.0, 21.2, 20.6, 14.9; MS (ESI) *m/z* (rel.%): 251 [MNa^+] (16), 229 [MH^+] (100); HRMS (ESI) calculated for $C_{14}H_{13}O_3$: 229.0859, found: 229.0858; IR (neat): 3097, 2924, 1731, 1621, 1572, 1446, 1287, 1222, 1180, 1033, 970, 939, 842, 798, 736 cm^{-1}.

4-*tert*-Butyl-9-methyl-benzofuro[3,2-*c*]-2-pyrone (8e)

The title compound was prepared according to the General Procedure, on a 0.25 mmol scale, to afford the product as a yellow solid (44.9 mg, 70.2%). R_f = 0.50 (20% EtOAc in hexanes); M.p. 119-120 ºC; ^{1}H-NMR (400 MHz, $CDCl_3$): 8.03 (app. t, *J* = 1.3 Hz, 1H), 7.46 (app. d, *J* = 1.3 Hz, 2H), 6.52 (q, *J* = 0.8 Hz, 1H), 2.42 (d, *J* = 0.8 Hz, 3H), 1.40 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): 164.7, 162.6, 159.7, 153.1, 148.4, 123.9, 122.6, 117.8, 110.7, 103.8, 96.0, 35.0, 31.8, 20.6; MS (ESI) *m/z* (rel.%): 279 [MNa^+] (6), 257 [MH^+] (100); HRMS (ESI) calculated for $C_{16}H_{17}O_3$: 257.1172, found: 257.1176; IR (neat): 2964, 1732, 1626, 1570, 1459, 1192, 1030, 968, 932, 889, 824, 787 cm^{-1}.

4,6-Di-*tert*-butyl-9-methyl-benzofuro[3,2-*c*]-2-pyrone (8f)

The title compound was prepared according to the General Procedure, on a 0.16 mmol scale, to afford the product as a yellow solid (35.4 mg, 70.9%). R_f = 0.64 (20% EtOAc in hexanes); M.p. 144-147 ºC; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.90 (d, *J* = 2.0 Hz, 1H), 7.37 (d, *J* = 2.0 Hz, 1H), 6.56 (q, *J* = 0.9 Hz, 1H), 2.42 (d, *J* = 0.9 Hz, 3H), 1.51 (s, 9H), 1.40 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): 163.9, 162.1, 159.8, 151.5, 148.1, 134.1, 123.0, 120.8, 115.6, 103.7, 96.1, 35.1, 34.5, 31.8, 29.9, 20.6; MS (ESI) *m/z* (rel.%): 335 [MNa^+] (18), 313 [MH^+] (100); HRMS (ESI) calculated for $C_{20}H_{23}O_3$: 313.1798, found: 313.1791; IR (neat): 2954, 1737, 1619, 1569, 1365, 1243, 1226, 1064, 971, 874, 815, 752 cm^{-1}.

4-Phenyl-9-methyl-benzofuro[3,2-*c*]-2-pyrone (8g)

The title compound was prepared according to the General Procedure, on a 0.25 mmol scale, to afford recovered starting material (19.5 mg, 21.8%) and the product as a yellow solid (30.0 mg, 43.5% [55.6% based on recovery of halo-starting material]). R_f = 0.36 (20% EtOAc in hexanes); M.p. 211-213 ºC; ^{1}H-NMR (400 MHz, $CDCl_3$): 8.24 (dd, *J* = 1.9, 0.7 Hz, 1H), 7.68 – 7.65 (m, 2H), 7.65 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.60 (dd, *J* = 8.6, 0.7 Hz, 1H), 7.44 – 7.49 (m, 2H), 7.38 (m, 1H), 6.56 (q, *J* = 0.8 Hz, 1H), 2.44 (d, *J* = 0.8 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): 165.0, 163.1, 154.5, 140.6, 138.7, 128.8, 127.5, 127.4, 125.6, 123.5, 119.7, 111.6, 103.8, 99.9, 95.9, 20.7; MS (ESI) *m/z* (rel.%): 299 [MNa^+] (8), 277 [MH^+] (100); HRMS (ESI) calculated for $C_{18}H_{13}O_3$: 277.0859, found: 277.0862; IR (neat): 3055, 2921, 1733, 1625, 1575, 1443, 1242, 1196, 1030, 968, 930, 887, 829, 805, 775, 762, 703, 682 cm^{-1}.

4-Fluoro-9-methyl-benzofuro[3,2-*c*]-2-pyrone (8h)

The title compound was prepared according to the General Procedure, on a 0.25 mmol scale using 2.5 mol% Pd_2(dba-4,4′-OMe)$_3$ and 10 mol% PPh_3, to afford the product as a yellow solid (22.5 mg, 41.3%). R_f = 0.37 (20% EtOAc in hexanes); M.p. 207-208 ºC; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.70 (dd, *J* = 8.1, 2.7 Hz, 1H), 7.48 (dd, *J* = 9.0, 3.9 Hz, 1H), 7.12 (app. td, *J* = 9.0, 2.7 Hz, 1H), 6.53 (q, *J* = 0.8 Hz, 1H), 2.43

(d, J = 0.8 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): 165.71, 163.54, 160.3 (d, J = 242.1 Hz), 159.08, 151.0 (d, J = 1.3 Hz), 124.10 (d, J = 11.6 Hz), 113.65 (d, J = 26.4 Hz), 112.27 (d, J = 9.6 Hz), 107.49 (d, J = 26.5 Hz), 103.76 (d, J = 3.6 Hz), 95.85, 20.69; ^{19}F-NMR (376 MHz, $CDCl_3$): -117.03 (ddd, J = 9.0, 8.1, 3.9 Hz); MS (ESI) *m/z* (rel.%): 241 [MNa^+] (67), 219 [MH^+] (100); HRMS (ESI) calculated for $C_{12}H_8FO_3$:219.0452, found: 241.0449; IR (neat): 3090, 2922, 1728, 1613, 1571, 1449, 1243, 1211, 1130, 1031, 972, 856, 797, 769 cm^{-1}.

5-Fluoro-9-methyl-benzofuro[3,2-*c*]-2-pyrone (8i)

The title compound was prepared according to the General Procedure, on a 0.25 mmol scale, to afford recovered starting material (13.2 mg) and the product as a yellow solid (13.2 mg, 24.2%). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.96 (dd, J = 8.6, 5.4 Hz, 1H), 7.28 (dd, J = 8.5, 2.3 Hz, 1H), 7.17 (ddd, J = 9.4, 8.6, 2.3 Hz, 1H), 6.54 (q, J = 0.8 Hz, 1H), 2.43 (d, J = 0.8 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): 165.1, 163.87 (d, J = 233.1 Hz), 162.8, 159.3, 154.93 (d, J = 13.5 Hz), 121.77 (d, J = 10.0 Hz), 119.10 (d, J = 2.0 Hz), 113.11 (d, J = 23.8 Hz), 99.78 (d, J = 27.4 Hz) 99.4, 95.8, 20.6; ^{19}F-NMR (376 MHz, $CDCl_3$): -113.48 (td, J = 9.0, 5.4 Hz); MS (ESI) *m/z* (rel.%): 241 [MNa^+] (77), 219 [MH^+] (100); HRMS (ESI) calculated for $C_{12}H_8FO_3$: 298.9714, found: 298.9711; IR ($CHCl_3$): 1731, 1615, 1573, 1496, 1276, 947, 651 cm^{-1}.

4-(Trifluoromethyl)-9-methyl-benzofuro[3,2-*c*]-2-pyrone (8j)

The title compound was prepared according to the General Procedure, on a 0.25 mmol scale, to afford the product as a yellow solid (7.1 mg, 10.6%). ^{1}H-NMR (400 MHz, $CDCl_3$): 8.34 (dt, J = 1.5, 0.7 Hz, 1H), 7.70 – 7.63 (m, 2H), 6.59 (d, J = 0.8 Hz, 1H), 2.46 (d, J = 0.8 Hz, 3H); ^{19}F-NMR (376 MHz, CDCl3): -61.11 (d, J = 5.2 Hz); MS (ESI) *m/z* (rel.%): 269 [MH^+] (100), 249 (24), 215 (15), 126 (82), 84 (44); HRMS (ESI) calculated for $C_{13}H_8F_3O_3$: 269.0420, found: 269.0430; IR (neat): 2953, 2923, 2853, 1743, 1575, 1458, 1319, 1266, 1164, 1119, 1050, 970, 818 cm^{-1}.

5-(6-Methyl-2-pyronyl-4-oxy)-9-methyl-benzofuro[3,2-*c*]-2-pyrone (8k)

The title compound was prepared according to the General Procedure, on a 0.5 mmol scale, to afford the product as a yellow solid (26 mg, 16%). M.p. >215 ºC (decomp.); ^{1}H-NMR (400 MHz, $CDCl_3$): 8.05 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 2.1 Hz, 1H), 7.16 (dd, J = 8.4, 2.1 Hz, 1H), 6.57 (d, J = 0.9 Hz, 1H), 6.00 (dd, J = 2.2, 0.9 Hz, 1H), 5.23 (d, J = 2.2 Hz, 1H), 2.45 (d, J = 0.9 Hz, 3H), 2.28 (d, J = 0.9 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): 170.7, 165.5, 163.6, 163.5, 159.1, 157.9, 155.0, 150.6, 122.3, 121.4, 118.5, 105.3, 103.4, 99.9, 99.7, 95.8, 91.3, 20.7, 20.1; MS (ESI) *m/z* (rel.%): 347 [MNa^+] (98), 325 [MH^+] (100); HRMS (ESI) calculated for $C_{18}H_{13}O_6$: 325.0707, found: 325.0701; IR (neat): 3100, 1726, 1649, 1615, 1570, 1445, 1400, 1319, 1255, 1168, 1135, 1032, 982, 944, 819 cm^{-1}.

Benzofuro[3,2-*c*]coumarin (Coumestan) (8l)

The title compound was prepared according to the General Procedure, on a 0.25 mmol scale, to afford recovered starting material (19.6 mg, 21.5%) and the product as a yellow solid (26.0 mg, 44.1% [56% b.r.s.m]). M.p. 178-180 ºC; ^{1}H-NMR (400 MHz, $CDCl_3$): 8.14 (m, 1H), 8.03 (ddd, J = 7.8, 1.6, 0.4 Hz, 1H), 7.67 (m, 1H), 7.60 (m, 1H), 7.51 (m, 1H), 7.46 – 7.49 (m, 2H), 7.42 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): 156.0, 158.1, 155.5, 153.7, 131.9, 126.8, 125.2, 124.6, 123.4, 121.9, 117.5, 112.6, 111.7, 105.9; MS (ESI) *m/z* (rel.%): 237 [MH^+] (100), 211 (24); HRMS (ESI) calculated for $C_{15}H_9O_3$: 237.0546, found: 237.0543;

***trans*-[Pd{C_6H_4O-2-($C_6H_5O_2$)}I(PPh_3)$_2$] (10)**

A solution of Pd_2dba_3 (30 mg, 33 µmol, 1 eq.), and PPh_3 (34 mg, 132 µmol, 4 eq.) in CH_2Cl_2 (20 mL) was stirred under nitrogen at ambient temperature for 15 minutes (giving complex **9**) followed by the addition of 4-(2-iodophenoxy)-6-methyl-2-pyrone (32.8 mg, 99 µmol, 3 eq.). The solution was then allowed to stir for 1 hour at ambient temperature. The CH_2Cl_2 was removed *in vacuo* to afford an orange oil which was subsequently dissolved in Et_2O (5 mL) and stored at room temperature for 16 hours, affording yellow crystals. The solution was then filtered and the crystals washed with Et_2O (5 mL), then dried under high vacuum to afford a yellow crystalline solid (63 mg, 65.6%). ^{1}H-NMR (700 MHz, CD_2Cl_2): 7.52 (dd, J = 12.4, 5.5 Hz, 12H), 7.37 (t, J = 7.5 Hz, 6H), 7.28 (t, J = 7.5 Hz, 12H), 6.92 (ddd, J = 7.5, 3.5, 1.9 Hz, 1H), 6.48 (t, J = 7.5 Hz, 1H), 6.32 (t, J = 7.5 Hz, 1H), 6.04 (ddd, J = 7.5, 2.4, 1.2 Hz, 1H), 5.65 (dd, J = 1.0, 2.0, 1H), 4.72 (d, J = 1.9, 1H), 2.26 (app. s, 3H); ^{13}C-NMR (176 MHz, CD_2Cl_2): 169.1, 164.4, 163.3, 153.4, 149.9, 138.8, 135.5, 132.7, 130.6, 128.3, 125.5, 124.2, 119.7, 100.4, 91.4, 20.6; ^{31}P-NMR (283 MHz, CD_2Cl_2): 21.23; MS (LIFDI) *m/z* (rel.%): 958 (100). Calculated for $C_{48}H_{39}IO_3P_2Pd$: C = 60.11, H = 4.10, Found: C = 59.90, H = 4.07.

***trans*-[Pd{C_6H_4O-2-($C_6H_5O_2$)}I{$P(C_6D_5)_3$}$_2$]**

A solution of Pd_2dba_3 (30 mg, 33 µmol, 1 eq.), and D_{15}- PPh_3 (36 mg, 132 µmol, 4 eq.) in CH_2Cl_2 (20 mL) was stirred under nitrogen at ambient temperature for 15 minutes, followed by the addition of 4-(2-iodophenoxy)-6-methyl-2-pyrone (32.8 mg, 99 µmol, 3 eq.). The solution was then allowed to stir for 1 hour at ambient temperature. The CH_2Cl_2 was removed *in vacuo* to afford an orange oil which was subsequently taken up in Et_2O (5 mL) and allowed to crystallise for 16 hours. The solution was then filtered and the crystals washed with Et_2O (5 mL), then dried under high vacuum to afford a yellow crystalline solid (23 mg, 35.3%). ^{1}H-NMR (700 MHz, CD_2Cl_2): 6.92 (ddd, J = 7.5, 3.5, 1.9 Hz, 1H), 6.48 (t, J = 7.5 Hz, 1H), 6.32 (t, J = 7.5 Hz, 1H), 6.04 (ddd, J = 7.5, 2.4, 1.2 Hz, 1H), 5.65 (dd, J = 1.0, 2.0, 1H), 4.72 (d, J = 1.9, 1H), 2.26 (app. s, 3H); ^{31}P-NMR (283 MHz, CD_2Cl_2): 21.23; ^{31}P-NMR (283 MHz, D_8-THF): 22.44.

Attempted synthesis of a cationic derivative of 10

The neutral Pd^{II} complex 10 (41.3 mg, 43 µmol, 1 eq.) was reacted with $AgPF_6$ (10.9 mg, 43 µmol, 1 eq.) in CD_2Cl_2 (1 mL) at ambient temperature in a dry box for 1 hour in the dark. The reaction was then filtered through a pad of Celite^{TM}, and NMR spectroscopy showed that a new cationic complex was formed along with an additional new species (presumed

to be **12**). (Selected data) ^{1}H NMR (700 MHz, CD_2Cl_2): 7.93 (t, *J* = 7.9 Hz, 1H), 7.52 (td, *J* = 7.4, 2.2 Hz, 1H), 7.38 (dd, *J* = 8.1, 5.5 Hz, 1H), 7.33 (ddd, *J* = 14.3, 7.9, 1.4 Hz, 1H), 5.20 (d, *J* = 2.0 Hz, 1H), 4.92 (d, *J* = 2.0 Hz, 1H), 1.98 (s, 3H); ^{31}P NMR (162 MHz, CD_2Cl_2): 39.02 (br. s, Δν ½ 46 Hz), 22.09 (s), -143.88 (hept, *J* = 710 Hz). Layering the CH_2Cl_2 solution with Et_2O and storing room temperature in the dark for two weeks gave crystals suitable for X-ray diffraction study. Rather curiously, it was found that the "C_6H_4O-2-($C_6H_5O_2$)" group from the cationic Pd^{II} species had undergone Pd→P transfer forming [P{C_6H_4O-2-($C_6H_5O_2$)}Ph_3]PF_6 (**12**), which was accompanied by significant Pd black formation.

Reaction of 10 with Cs_2CO_3 to give product 6a

A solution of Pd_2(dba-4,4′-OMe)$_3$ (3.6 mg, 3.3 μmol, 1 eq.), and PPh_3 (3.4 mg, 13.2 μmol, 4 eq.) in D_8-THF (1 mL) was stirred in a dry box at ambient temperature for 15 minutes, followed by the addition of 4-(2-iodophenoxy)-6-methyl-2-pyrone (4.2 mg, 13.2 μmol, 4 eq.). The solution was then allowed to stir for 1 hour at ambient temperature and the Pd^{II} intermediate confirmed by NMR spectroscopy. Cs_2CO_3 (6.6 mg, 20 μmol, 6 eq.) was added and the solution heated to 70 °C for 2 hours. The solution was cooled to ambient temperature and filtered. The ^{1}H NMR spectrum showed quantitative formation of **6a**.

Synthesis of *trans*-[Pd{C_6H_3-5-CF_3-O-2-($C_6H_5O_2$)}Br(PPh_3)$_2$] and attempted reaction with Cs_2CO_3

From Pd_2(dba-H)$_3$: A solution of Pd_2(dba)$_3$ (30 mg, 33 μmol, 1 eq.), and PPh_3 (34 mg, 132 μmol, 4 eq.) in THF (20 mL) was stirred under a N_2 atmosphere for 15 minutes, giving an orange solution which is Pd(η^2-dba-H)(PPh_3)$_2$. 4-(2-Bromo-4-(trifluoromethyl)-phenoxy)-6-methyl-2-pyrone (46.0 mg, 132 μmol, 2 eq.) was then added and the solution was allowed to stir for 1 hour at 70 °C. The THF was removed *in vacuo* to afford an orange oil which was subsequently taken up in Et_2O (5 mL), and allowed to slowly crystallize over 16 hours. A mixture of purple, orange and yellow crystals were formed. X-ray crystallographic analysis identified the purple crystals as Pd_2(dba-H)$_3$ (as disordered isomers). The orange and yellow crystals were not identified. From Pd_2(dba-4,4′-OMe)$_3$: In a dry box, a solution of Pd_2 (dba-4,4′-OMe)$_3$ (3.6 mg, 3.3 μmol, 1 eq.), and PPh_3 (3.4 mg, 13.2 μmol, 4 eq.) in D_8-THF (1 mL) was stirred at ambient temperature for 15 minutes, giving an dark orange solution which is Pd(η^2-dba-4,4′-OMe)(PPh_3)$_2$. 4-(2-Bromo-4-(trifluoromethyl)-phenoxy)-6-methyl-2-pyrone 7**j** (2.3 mg, 6.6 μmol, 2 eq.) was then added. The solution was then allowed to stir for 1 hour at 70 °C and the Pd^{II} complex characterized by NMR spectroscopy. Selected Data: ^{1}H-NMR (400 MHz, D_8-THF): 7.59 – 7.54 (m, 12H), 7.35 – 7.30 (m, 6H), 7.26 – 7.22 (m, 12H), 6.67 (d, *J* = 8.5 Hz, 1H), 6.15 (d, *J* = 8.5 Hz, 1H), 6.03 (s, 1H), 5.69 (d, *J* = 2.2 Hz, 1H), 4.65 (d, *J* = 2.2 Hz, 1H), 2.24 (s, 3H); ^{31}P-NMR (162 MHz, D_8-THF): 24.46 (s). Cs_2CO_3 (13.2 mg, 40 μmol, 12 eq.) was then added to the yellow/orange solution, which was heated to 70 °C for 2 hours. The solution was allowed to cool to ambient temperature and filtered through Celite^{TM}. ^{1}H NMR spectroscopic analysis of the filtrate showed no formation of the cyclised product **8j**. The ^{31}P NMR spectrum showed degradation of the Pd^{II} complex at δ 24.46 (s), and a new species, identified as [Pd^0(η^2-dba-4-OMe)(PPh_3)$_2$] **9**. ^{31}P-NMR (162 MHz, D_8-THF): 26.8 (br. s, Δν½ 42 Hz), 25.2 (br. s, Δν½ 42 Hz).

Details of Crystallographic Analysis Diffraction data were collected at 110 K on a Bruker Smart Apex diffractometer with Mo-Kα radiation (λ = 0.71073 Å) using a SMART CCD camera. Diffractometer control, data collection and initial unit cell determination was performed using "SMART".[36] Frame integration and unit-cell refinement software was carried out with "SAINT+".[37] Absorption corrections were applied by SADABS (v2.10, Sheldrick). Structures were solved by direct methods using SHELXS-97[3] and refined by full-matrix least squares using SHELXL-97. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using a "riding model" and included in the refinement at calculated positions. Important X-ray details are collected in Table 4 (shown below), including CCDC numbers.

Table 4 X-ray diffraction details for all compounds.

Compound reference	ijf0925m (**6a**)	ijf0934m (**6b**)	ijf0930 (**8h**)	ijf0931 (**8i**)	ijf0936m (**10**)	ijf1002m (**12**)
Chemical formula	$C_{12}H_8O_3$	$C_{11}H_6O_3$	$C_{12}H_7FO_3$	$C_{12}H_7FO_3$	$C_{48}H_{39}IO_3P_2Pd$	$C_{30}H_{24}O_3P\bullet(F_6P_1)_{0\cdot98}\bullet(I)_{0\cdot02}$
Formula Mass	200.18	186.16	218.18	218.18	959.03	608.43
Crystal system	Triclinic	Monoclinic	Triclinic	Triclinic	Monoclinic	Triclinic
a/Å	7.1467(5)	11.1190(16)	3.7437(3)	3.7597(2)	10.2109(5)	7.8107(8)
b/Å	7.3546(5)	8.2091(12)	6.3700(7)	6.1644(4)	11.8937(6)	13.2530(14)
c/Å	9.3252(6)	18.856(3)	19.0219(19)	19.6660(11)	34.1332(17)	14.2579(15)
α/°	69.7600(10)	90.00	91.665(9)	92.543(5)	90.00	97.040(2)
β/°	81.8920(10)	105.787(2)	90.858(7)	90.715(5)	93.0340(10)	104.389(2)
γ/°	75.2200(10)	90.00	93.699(8)	90.125(5)	90.00	104.932(2)
Unit cell volume/Å^3	443.91(5)	1656.2(4)	452.42(8)	455.30(5)	4139.5(4)	1353.6(2)
Temperature/K	120(2)	110(2)	120(2)	120(2)	110(2)	110(2)
Space group	$P\bar{1}$	*C2/c*	$P\bar{1}$	$P\bar{1}$	*P2(1)/n*	$P\bar{1}$
No. of formula units per unit cell, *Z*	2	8	2	2	4	2
No. of reflections measured	6084	8041	7806	4447	55989	13874
No. of independent reflections	2211	2057	1688	1706	10290	6661
R_{int}	0.0124	0.0175	0.0390	0.0286	0.0494	0.0235
Final R_1 values ($I > 2\sigma(I)$)	0.0352	0.0373	0.0480	0.0477	0.0330	0.0490
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.1005	0.0970	0.1249	0.1335	0.0684	0.1227
Final R_1 values (all data)	0.0366	0.0443	0.0574	0.0514	0.0456	0.0719
Final $wR(F^2)$ values (all data)	0.1023	0.1024	0.1316	0.1382	0.0730	0.1367
CCDC number	764708	764709	773153	773154	764710	764711

Notes and references

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† Electronic Supplementary Information (ESI) is available for this paper: [Representative NMR spectra of the compounds detailed in this paper are included in addition to the experimental details for the starting material syntheses]. See DOI: 10.1039/b000000x/

‡ Single crystal X-ray structures of both **8h** and **8i** have been determined (see E.S.I. file).

1 For leading reviews on 2-pyrone medicinal applications and natural products, see: a) J. M. Dickinson, *Nat. Prod. Rep.*, 1993, **10**, 71-98; b) G. P. McGlacken and I. J. S. Fairlamb, *Nat. Prod. Rev.*, 2005, **22**, 369-385; for synthetic uses of 2-pyrones, see: c) K. Afarinkia, V. Vinader, T. D. Nelson and G. H. Posner, *Tetrahedron*, 1992, **48**, 9111-9171; (d) B. T. Woodard and G. H. Posner, 'Recent advances in Diels-Alder cycloadditions of 2-pyrones', In Advances in Cycloaddition; JAI Press: Greenwich, 1999; Vol. 5, p 47; For recent synthetic applications, see: e) P. M. Delaney, D. L. Browne, H. Adams, A. Plant and J. P. A. Harrity, *Tetrahedron*, 2008, **64**, 866-873; f) E. Gomez-Bengoa, M. D. Helm, A. Plant and J. P. A. Harrity, *J. Am. Chem. Soc.*, 2007, **129**, 2691-2699; g) P. M. Delaney, J. E. Moore and J. P. A. Harrity, *Chem. Commun.*, 2006, 3323-3325.

2 I. J. S. Fairlamb, L. R. Marrison, J. M. Dickinson, F.-J. Lu and J.-P. Schmidt, *Bioorg. Med. Chem.*, 2004, **12**, 4285-4299.

3 a) W.-K. Kim, H.-J. Kim and C.-G. Cho, *J. Am. Chem. Soc.*, 2003, **125**, 14288-14289; b) J.-H. Lee, W.-S. Kim, Y. Y. Lee and C.-G. Cho, *Tetrahedron Lett.*, 2002, **43**, 5779-5782.

4 K. M. Ryu, A. K. Gupta, J. W. Han, C. H. Oh and C.-G. Cho, *Synlett*, 2004, 2197-2199.

5 Other cross-couplings, see: a) P. A. Amaral, N. Gouault, M. Le Roch, V. L. Eifler-Lima and M. David, *Tetrahedron Lett.*, 2008, **49**, 6607-6609; b) I. J. S. Fairlamb, C. T. O'Brien, Z. Lin and K. C. Lam, *Org. Biomol. Chem.*, 2006, **4**, 1213-1216; c) F. Bellina, A. Carpita, L. Mannocci and R. Rossi, *Eur. J. Org. Chem.*, 2004, 2610-2619; d) J.-H. Lee, J.-S. Park and C.-G. Cho, *Org. Lett.*, 2002, **4**, 1171-1173;

6 Representative key reviews, see: a) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792-9826; b) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173-1193; c) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174-238; d) T. Satoh and M. Miura, *Chem. Lett.*, 2007, **36**, 200-205; e) L.-C. Campeau and K. Fagnou, *Chem. Commun.*, 2006, 1253-1264.

7 Selected papers from the Pd catalysis field, see: a) S. A. Ohnmacht, A. J. Culshaw and M. F. Greaney, *Org. Lett.*, 2010, **12**, 224-226; b) B.-J. Li, S.-L. Tian, Z. Fang and Z.-J. Shi, *Angew. Chem. Int. Ed.*, 2008, **47**, 1115-1118; c) E. F. Flegeau, M. E. Popkin and M. F. Greaney, *Org. Lett.*, 2008, **10**, 2717-2720; d) N. Lebrasseur and I. Larrosa, *J. Am. Chem. Soc.*, 2008, **130**, 2926-2927; e) D. R. Stuart and K. Fagnou, *Science*, 2007, **316**, 1172-1175; f) D. R. Stuart, E. Villemure and K. Fagnou, *J. Am. Chem. Soc.*, 2007, **129**, 12072-12073.

8 a) X. Zhang, M. McLaughlin, R. L. P. Muñoz, R. P. Hsung, J. Wang and J. Swidorski, *Synthesis*, 2007, **5**, 749-753; b) J. J. Swidorski, J. Wang and R. P. Hsung, *Org. Lett.*, 2006, **8**, 777-779; For other innovative syntheses, see: c) I.-J. Shin, E. S. Choi and C. G. Cho, *Angew. Chem. Int. Ed.*, 2007, **46**, 2303-2305, and references cited therein.

9 I. J. S. Fairlamb, J. M. Lynam, B. E. Moulton, I. E. Taylor, A.-K. Duhme-Klair, P. Sawle and R. Motterlini, *Dalton Trans.*, 2007, 3603-3605.

10 L. Murray, G. Currie and R. J. Capon, *Aust. J. Chem.*, 1995, **48**, 1485-1489, and references cited therein.

11 a) I. J. S. Fairlamb, P. Sehnal and R. J. K. Taylor, *Synthesis*, 2009, 508-510; b) M. J. Burns, I. J. S. Fairlamb, A. R. Kapdi, P. Sehnal and R. J. K. Taylor, *Org. Lett.*, 2007, **9**, 5397-5400. Recently, this precatalyst was found to highly effective for the benzylation of *N*-Boc indole boronic acids, see: c) A. M. Kearney, A. Landry-Bayle and L. Gomez, *Tetrahedron Lett.*, 2010, **51**, 2281-2283.

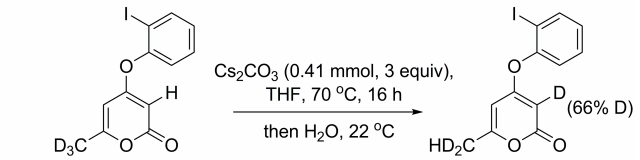
12 a) I. J. S. Fairlamb, *Org. Biomol. Chem.*, 2008, **6**, 3645-3656; b) I. J. S. Fairlamb, A. R. Kapdi, A. F. Lee, G. P. McGlacken, F. Weissburger, A. H. M. de Vries and L. Schmieder-van de Vondervoort, *Chem.–Eur. J.*, 2006, **12**, 8750-8761; c) I. J. S. Fairlamb, A. R. Kapdi and A. F. Lee, *Org. Lett.*, 2004, **6**, 4435-4438; d) L. Firmansjah and G. C. Fu, *J. Am. Chem. Soc.*, 2007, **129**, 11340-11341.

13 a) K. C. Majumdar, S. Ghosh, *Monatshefte für Chemie*, 2002, **133**, 1317-1323; b) K. C. Majumdar, A. Biswas and P. P. Mukhopadhyay, *Synth. Commun.*, 2007, 2881-2890.

14 L. R. Marrison, Ph.D. Thesis, MMU, Manchester, UK, 1998.

15 2-Bromophenols possessing electron-withdrawing groups such as nitrile or formyl were reluctant to participate in nucleophilic displacement of the bromide in 4-bromo-6-methyl-2-pyrone.

16 The recorded isolated yields mirror the conversions determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures.
17 In The Flavanoids, J. B. Harborne, T. J. Mabry and H. Mabry Eds., 1975, Chapman and Hall, London. The synthesis of this compound has attracted much attention, most recently in: T. Yao, D. Yue, R. C. Larock, *J. Org. Chem.*, 2005, **70**, 9985-9989.
18 Y. Macé, A. R. Kapdi, I. J. S. Fairlamb and A. Jutand, *Organometallics*, 2006, **25**, 1785-1800, and references cited therein.
19 The Cambridge Crystallographic Database (November 2009 release) was searched using the generic formula, "trans-[Pd(I)C*(PPh_3)$_2$] where C* is any carbon-based group bonded directly to Pd.
20 Representative P-Pd-P and I-Pd-C angles from the X-ray data available (e.s.d.s not specified here): a) I-Pd-C 167.36º; P-Pd-P 174.17º, see: J. Vicente, J.-A. Abad, A. D. Frankland and M. C. Ramírez de Arellano, *Chem.-Eur. J.*, 1999, **5**, 3066-3075; b) I-Pd-C 166.03º; P-Pd-P 174.41º, see: T. Watanabe, S. Arai and A. Nishida, *Synlett*, 2004, 907-909; c) Structure A - I-Pd-C 168.30º; P-Pd-P 174.02º, Structure B I-Pd-C 176.50º; P-Pd-P 172.39º, see: D. Taher, B. Walfort and H. Lang, *Inorg. Chim. Acta*, 2006, **359**, 1899-1906.
21 Representative papers detailing "C=C" Pd-π interactions, see: a) D. B. G. Williams and M. L. Shaw, *Tetrahedron*, 2007, **63**, 1624-1629; b) H. Zhang, X. Luo, K. Wongkhan, H. Duan, Q. Li, L. Zhu, J. Wang, A. S. Batsanov, J. A. K. Howard, T. B. Marder and A. Lei, *Chem. Eur. J.*, 2009, **15**, 3823-382; c) X. Luo, H. Zhang, H. Duan, Q. Liu, L. Zhu, T. Zhang and A. Lei, *Org. Lett.*, 2007, **9**, 4571-4574.
22 a) M. Brookhart, M. L. H. Green and L. Wong, *Prog. Inorg. Chem.* 1988, **36**, 1-124; b) R. H. Crabtree and D. G. Hamilton, *Adv. Organomet. Chem.* 1988, **28**, 299-338.
23 a) M. Brookhart, M. L. H. Green and G. Parkin, *Proc. Natl. Acad. Sci.*, 2007, **104**, 6908-6914; b) W. Yao, O. Eisenstein and R. H. Crabtree, *Inorg. Chim. Acta.*, 1997, **254**, 105-111; c) W. I. Sundquist, D. P. Bancroft and S. J. Lippard, *J. Am. Chem. Soc.*, 1990, **112**, 1590-1596.
24 R. F. Heck, *Pure & Appl. Chem.*, 1978, **50**, 691-701.
25 a) B. Liégault, D. Lapointe, L. Caron, A. Vlassova and K. Fagnou, *J. Org. Chem.*, 2009, **74**, 1826-1834; b) S. Pascual, P. de Mendoza, A. A. C. Braga, F. Maseras and A. M. Echavarren, *Tetrahedron*, 2008, **64**, 6021-6029; c) D. L. Davies, S. M. A. Donald and S. A. Macgregor, *J. Am. Chem. Soc.*, 2005, **127**, 13754-13755.
26 In The Mizoroki-Heck Reaction, Ed. M. Oestreich, John Wiley & Sons, Hoboken, 2009, ISBN 978-0470033944.
27 Some caution is necessary here as it has been reported that an intermolecular base-assisted deprotonation can take place (in the presence of bidentate phosphine ligands), see ref. 25b. For monodentate ligands, it was not possible to distinguish between inter- and intra-molecular base-assisted deprotonation reactions. Relevant references: a) D. García-Cuadrado, A. A. C. Braga, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc.*, 2006, **128**, 1066-1067; b) D. García-Cuadrado, P. De Mendoza, A. A. C. Braga, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc.*, 2007, **129**, 6880-6886.
28 B. E. Moulton, H. Dong, C. T. O'Brien, S. B. Duckett, Z. Lin and I. J. S. Fairlamb, *Org. Biomol. Chem.*, 2008, **6**, 4523-4532.
29 This pathway has been proposed previously, see: a) M. Toyata, A. Ilangovan, R. Okamoto, T. Masaki, M. Arakawa and M. Ihara, *Org. Lett.*, 2002, **4**, 4293-4296; b) E. J. Hennessy, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 12084-12085. However, it is unlikely that *anti*-β-hydrogen elimination occurs (in the absence of *syn*-β-hydrogens); c) L.-C. Campeau, M. Parisien, A. Jean and K. Fagnou, *J. Am. Chem. Soc.*, 2006, **128**, 581-590. Also see refs. 30 and 31.
30 B. Glover, K. A. Harvey, B. Liu, M. J. Sharp and M. F. Tymoschenko, *Org. Lett.*, 2003, **5**, 301-304.
31 a) C. C. Hughes and D. Trauner, *Angew. Chemie. Int. Ed.*, 2002, **41**, 1569-1572. For a general review of Pd^{IV} intermediates in catalytic reactions, see: b) P. Sehnal, R. J. K. Taylor and I. J. S. Fairlamb, *Chem. Rev.*, 2010, **110**, 824-889. For a general review on direct arylation mechanisms and synthetic applications, see: c) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174-238.
32 DMA and DMF are commonly used solvents for direct arylation, see references 6a, 25a-b, and those references cited therein.
33 Analysis by Special Metals Division, Chemetall GmbH, Trakehner Straße 3, D-60487, Frankfurt AM Main, Germany. Selectively deuterated substrate **5a**-{C6-CD_3} was subjected to the reaction conditions in the absence of catalytic Pd (see below).



5a-{C6-CD_3} ($H_{0.3}D_{2.7}$; 90%D)
(0.14 mmol)

Deuterium exchange was observed but no cyclisation occurred. We suspect that C3-H is directly deprotonated by Cs_2CO_3 and then quenched by the C6-methyl group. As Cs_2CO_3 is only sparingly soluble in THF, its concentration is quasi-constant and very low {of the total quantity of Cs_2CO_3 added in this experiment ~0.0056% is in solution at 25 ºC, see ref. 33) allowing the reaction to be quenched by H_2O without significantly perturbing the H/D balance.
34 During the submission of this paper, we ran two reactions of **5a→6a** where THF was replaced by DMF under otherwise identical conditions to those given in entry 8, Table 1. In both cases, no product formation was observed.
35 During the final preparative stages of this manuscript we found a report on a 'Heck-like' reaction of a coumarin containing a tethered aromatic bromide. Whilst the reaction requires a higher temperature (100 ºC) and unique Pd precatalyst containing a 1,2-cyclobutadiene-substituted CpCoCb diphosphine ligand, it operates in dioxane solvent with DABCO as the base, see: C.-P. Chang, S. V. Pradiuldi and F.-E. Hong, *Inorg. Chem. Commun.*, 2009, **12**, 596-598. No further mechanistic details were provided in this paper (vis-à-vis CMD versus Heck-like reaction pathways).
36 Smart diffractometer control software (v5.625), Bruker-AXS, Bruker AXS GmbH, Karlsruhe, Germany.
37 Saint+ (v6.22) Bruker AXS, Bruker AXS GmbH, Karlsruhe, Germany.
38 G. M. Sheldrick, SHELXS-97, Program for the Solution of Crystal Structures, Universität Göttingen, 1997.

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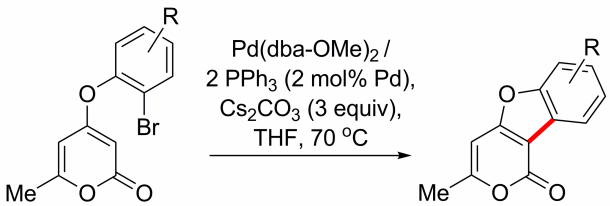
Graphical Abstract



The development of catalytic C-H functionalisation reactions for 2-pyrones provides rapid and efficient entry into fused furanopyrone products, regioselectively.