Studies Towards the Total Synthesis of ‘Upenamide

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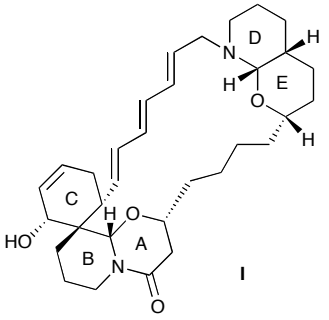
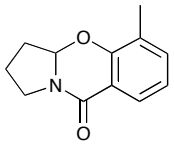
August 2011

Abstract

Synthetic studies towards the total synthesis of the macrocyclic marine alkaloid ‘upenamide (**I**) are reported. After an introduction (Chapter 1), Chapter 2 describes an extension of some methodology utilised during the total synthesis project. Both the polycyclic ABC and DE core units of ’upenamide were formed by a stannous chloride dihydrate mediated cyclisation reaction and the methodology described involves using stannous chloride dihydrate to deliver novel polycyclic heterocycles, for example **II**, **III** and **IV**.



I



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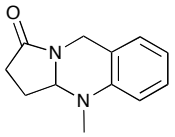

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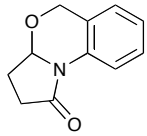
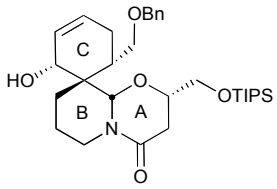


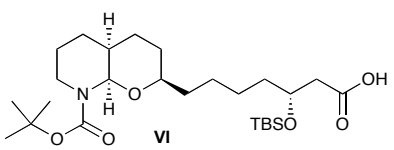
IV

In Chapter 3, a shortened synthetic route to the ABC core unit **V** is described, using a novel azide as a protected amine.



V

A route to the DE core unit **VI** was developed and is described in Chapter 4. Chapter 5 describes the coupling of the DE core unit **VI** with the ABC core unit precursor **VII**, giving the ABC and DE cores joined through the fully saturated chain in the advanced intermediate **VIII**. Chapter 5 also contains a discussion of future research needed to complete the program of research into ’upenamide.



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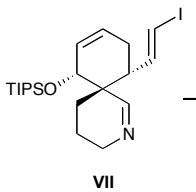

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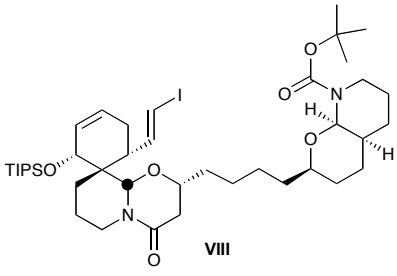

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Acknowledgments

Firstly I would like to thank Professor Richard Taylor for giving me the opportunity to work in his group. Over the last four years he has been constantly supportive and encouraging.

Thanks to my industrial sponsors AstraZeneca, especially my supervisor Louis Diorazio and Andy Godfrey who looked after me when Louis wasn't around. Thanks also to Andy Hard for his help running chiral HPLC samples, and to Ian Ashworth and Jan Cherrywell for their help with pH stat equipment while I was on placement in Macclesfield.

The Taylor group have welcomed me and provided an incredibly fun and supportive environment to work in for the time I've been here. Special thanks to Dr Will Unsworth for all his work on the 'upenamide project and reading this whole thesis with a red pen and an eagle eye, especially for wrongly used minus signs. To Dr Graeme McAllister for huge quantities of proof reading, fixing the things I broke, and being a great climbing partner over the last few years. Dr Mike Edwards for proof reading and the traditional Friday night pub trip. To the rest of the group over the years I have been here: James C, Pugh, Dan, Alessia, Alexis, Mickael, Will B, Reyhan, James D, Alan, Russ, Sandra, Rich, Cat, Phil, Dave, Johannes, Melanie, Jana, Subhrangsu, Mark, Vil and Monique. The O'Brian group have also been great next-door neighbours, thanks especially to Graeme B for the loan of a mechanical stirrer for weeks a time. Thanks to the Fairlambs, especially Mandy and Tom for use of their glovebox for KHMDS studies and a high vac line for my one oxygen sensitive reaction.

Thanks to Heather and Amanda for NMR help, Trevor, Ben and Karl for mass spectrometry services, Graeme for elemental analysis and Adrian and Rob for X-Ray crystallography. Thanks also to Mike, Val and Steve (stores) and Brian and Abby (glassblowing). Finally thanks to my family and to my boyfriend Fergus for their support.

Declaration

The research presented in this Thesis was carried out at the University of York between October 2007 and May 2010. This work is, to the best of my knowledge, original except where due reference has been made to other workers.

Katherine Gallagher
August 2010

Chapter 1 – Introduction

1.1 Introduction

'Upenamide **1** is a macrocyclic marine natural product, isolated by Jiménez *et al.* in 2000 from a branching sponge of the genus *Echinochalina,* found in the coastal waters of Indonesia.[1] The complete structural assignment could not be completed (see Section 1.2) and the authors suggested that the structure was either **1a** or its diastereoisomer **1b** (Figure 1.1).

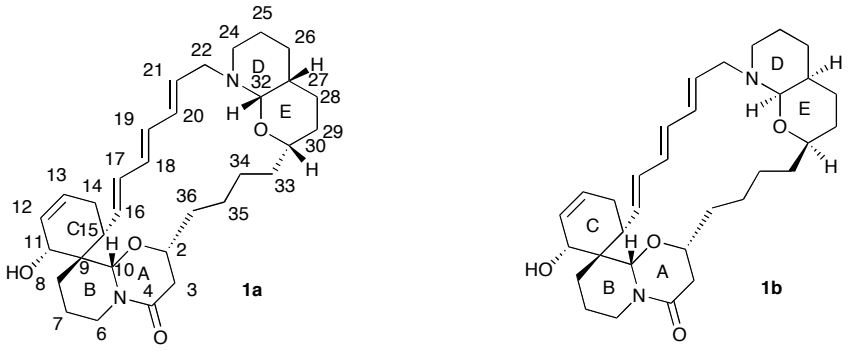


Figure 1.1 The two possible structures of 'upenamide **1**.

'Upenamide has a unique structure, with two highly functionalised hemi-aminal cores linked to form a twenty membered macrocycle by an all-*trans* triene chain and a fully saturated four carbon chain. There are eight chiral centres in the molecule, five in the tricyclic ABC core, and the remaining three found in the DE core.

The name given to this natural product is derived from the Hawaiian word *'upena*, meaning fishing net or trap. It was chosen to describe 'upenamide's meshlike structure. What appears to be an apostrophe at the beginning of the name is in fact an *okina*, or glottal stop, which is a letter in the Hawaiian alphabet.

The unique structure of 'upenamide and its scarcity (2.2 mg from 590 g of wet sponge, representing a yield of 0.00037%)[1] make it an attractive target for total synthesis.

1.2 Structural determination

1.2.1 ABC core unit

Comprehensive nOe studies allowed Jiménez *et al.* to establish the relative stereochemistry possessed by the five chiral centres contained in the ABC core unit.

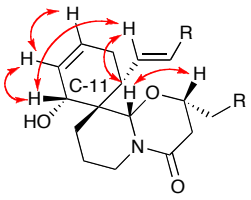


Figure 1.2 nOe correlations observed in the ABC core unit.

This was followed by Mosher's ester derivatization of the allylic alcohol present at C-11. The Mosher's ester derivatives confirmed the absolute stereochemistry of the ABC core unit.

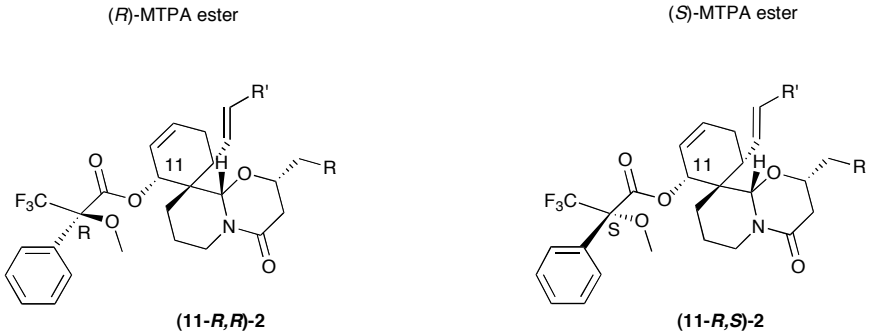


Figure 1.3 Mosher's ester derivatives of 'upenamide.

The configuration of esters **2** proposed by the Mosher's study is such that the methine CH of the chiral alcohol (i.e. H-11 in **2**) and the CF_3 group of the derivatizing agent are *syn*-periplanar to the carbonyl group, as illustrated in Figure 1.4. This results in the phenyl group eclipsing a specific region of the molecule – either L1 or L2 as labelled in Figure 1.4. The phenyl group exerts an anisotropic effect on the area of the molecule it eclipses; shielding the nuclei and moving the chemical shifts observed in the NMR spectrum upfield. The difference between the chemical shifts of specific protons in the (11-*R,S*) and (11-*R,R*) diastereoisomers is defined as $\Delta\delta_{SR} = (\delta_{RS}-\delta_{RR})$. All the protons shielded in the (*S*)-MTPA ester will have a negative $\Delta\delta_{SR}$ while those

shielded in the (*R*)-MTPA ester will have a positive $\Delta\delta_{SR}$. An examination of these numbers allows the absolute stereochemistry of the molecule to be assigned.

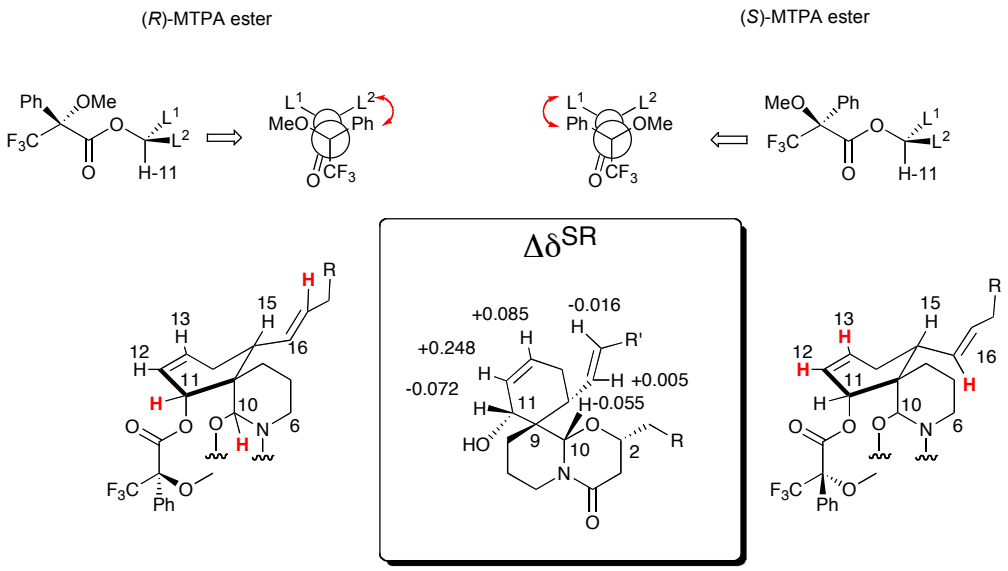


Figure 1.4 Eclipsing interactions of Mosher's ester in the ABC core unit.[1]

Thus the C-11 stereocentre was assigned as *R*, giving the ABC ring system as 2*R*, 9*S*, 10*S*, 11*R*, 15*R*.

1.2.2 DE core unit

nOe studies allowed the relative stereochemistry of the DE core unit to be determined (Figure 1.5). Reduction of the hemi-aminal and derivatisation as the MTPA ester was achieved, but no chemical shift differences were observed between the diastereoisomers produced. Thus, only the relative stereochemistry of the DE core unit is known.

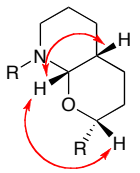


Figure 1.5 nOe correlations observed in the DE core.

1.3 Proposed biosynthesis of 'upenamide

A large number of macrocyclic diamine alkaloids have been isolated from marine sponges. To date, more than ten classes of polycyclic alkaloids have been described in the literature: saraines,[2-7] haliclamines,[8-10] xestospongins,[11-16] petrosins,[17-21] papuamines,[22] manzamines,[23-32] cyclostellettamines,[33-35] mandangamines,[36, 37] xestocyclamines,[38, 39] ircinols,[40-42] ingenamines,[34, 43-45] and halitoxins.[46-48]

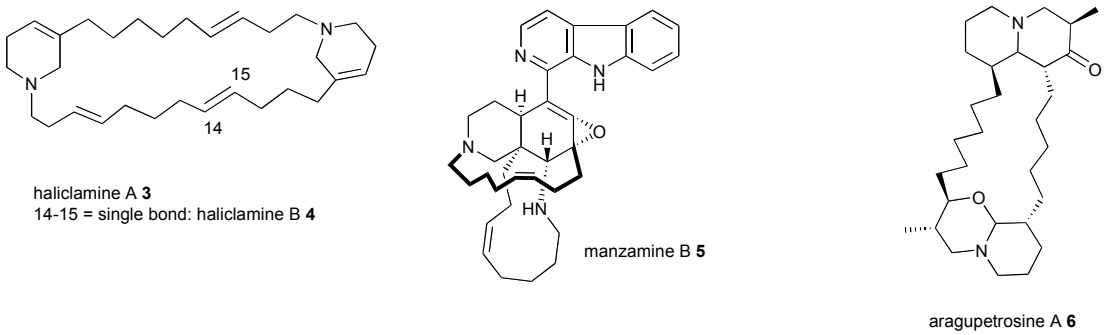
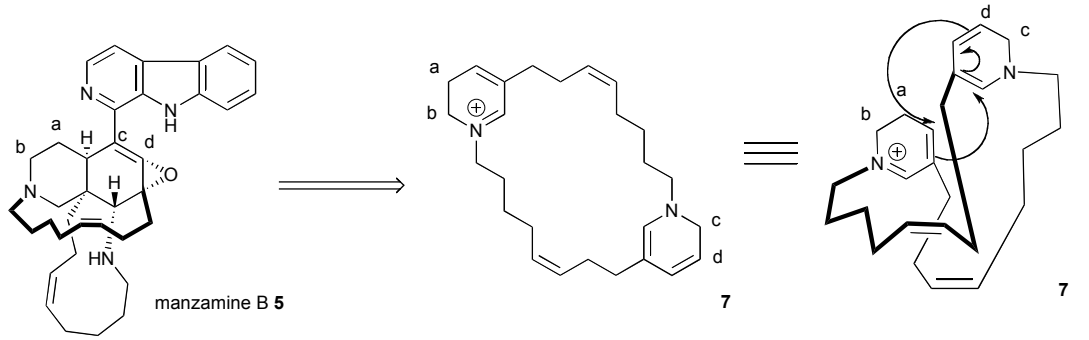


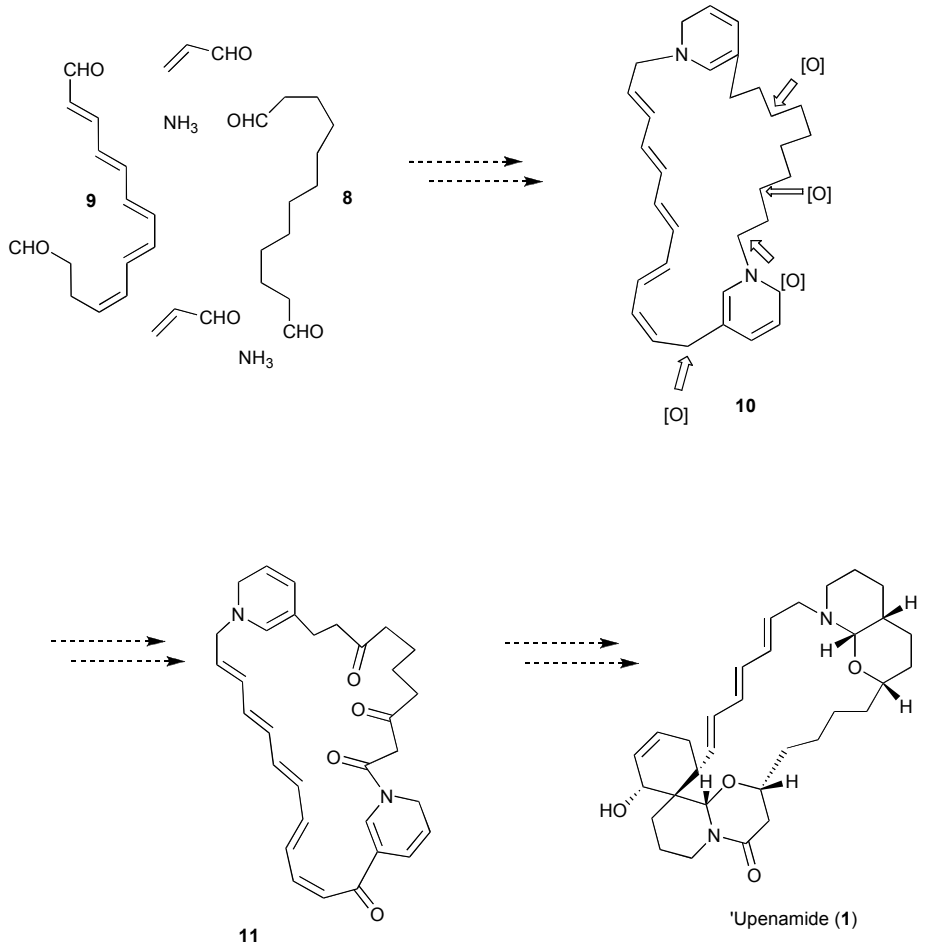
Figure 1.6 Macrocyclic diamine alkaloids.[12, 20, 27, 49]

Despite the huge structural variation between these compounds it has been proposed that all the diamine macrocyclic alkaloids described share the same biogenetic precursor.[50] The haliclamines (ie **3**, **4**) are a class of simple diamine natural products isolated from a variety of marine sponges.[49] Baldwin and Whitehead proposed *bis*-dihydropyridines, closely structurally related to the haliclamines, as intermediates in the biosynthesis of the structurally complex diamine natural product manzamine B (**5**) (Scheme 1.1). The structural similarities led to Baldwin's theory that all the diamine macrocyclic alkaloids described to date may be derived *in vivo* from *bis*-dihydropyridines.



Scheme 1.1 Baldwin's proposed bioynthesis of manzamine B: A Diels–Alder reaction between the two dihydropyridine rings constructs the octahydroisoquinoline present in the natural product.

Based on this work, Jiménez and co-workers proposed a biosynthesis of 'upenamide which begins with a hypothetical member of the haliclamine class of natural products **10** (Scheme 1.2). The formation of the hypothetical **10** is envisaged from ammonia, a three carbon unit (acrolein), a saturated dialdehyde (**8**) and an unsaturated linear dialdehyde (**9**). Enzymatic oxidations at the indicated positions would furnish intermediate **11** which then could undergo intramolecular cyclisation to afford the final 'upenamide skeleton.



Scheme 1.2 Proposed biosynthesis of 'upenamide.[1]

1.4 Biological activity

The scarcity of the natural product means the biological activity of ’upenamide is yet to be widely investigated. In preliminary bioassays, ’upenamide did not show any inhibition effects against P388, A549, and HT29 (cancerous cell lines from human leukaemia, lung carcinoma, and colon adenocarcinoma). However, it should be noted that full biological evaluation is unlikely to be possible until a synthetic route is established as very large quantities of sponge would otherwise be required.

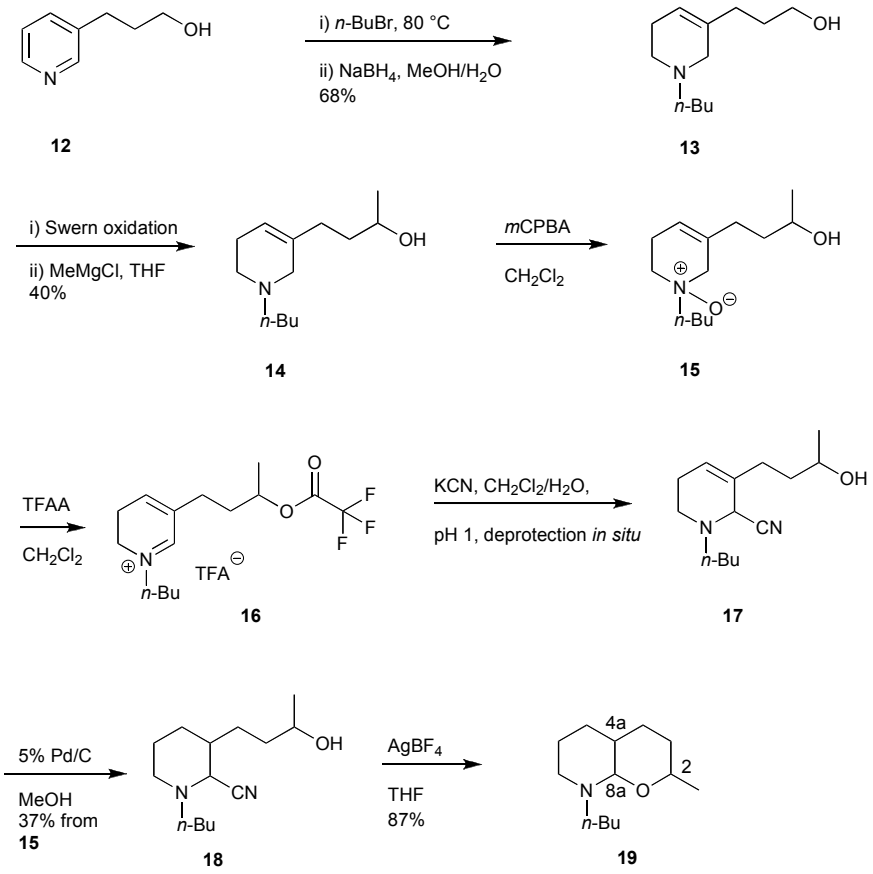
1.5 Background literature

To date there has been no total synthesis of ’upenamide, but a number of papers have been published detailing synthetic studies towards both core systems. Publications from the groups of Mons,[51] Sulikowski[52] and Taylor[53] have tackled the bicyclic DE core, while the only synthesis of the ABC core fragment comes from the Taylor group.[54] Sulikowski’s group have published the most advanced intermediate to date, with their paper describing a partial “BC” ring system coupled with the DE core.[55]

1.5.1 Mons *et al.*, DE core fragment[51]

In 2004, Mons and co-workers published their studies towards the *cis*-decalin hemi-aminal DE core unit (Scheme 1.3).[51] The route begins from pyridine **12**, which was alkylated with *n*-butyl bromide. The aromatic system was then partially reduced with sodium borohydride to provide the tertiary amine **13**. The alcohol was then oxidised under Swern conditions to provide the aldehyde, which was reacted with MeMgCl in a one-pot process. Oxidation of the tertiary amine with *m*CPBA delivered the *N*-oxide **15**. This compound was subjected to treatment with TFAA, effecting a Polonovski–Potier reaction, a mild version of the Polonovski reaction employing TFAA in the place of acetic anhydride. The iminium ion generated was subsequently reacted with cyanide and the trifluoroacetate group removed *in situ*, delivering alcohol **17**. The double bond was removed by hydrogenation over Pd/C to give amino-nitrile **18**. Treatment with silver tetrafluoroborate regenerated the iminium ion,

which then cyclised to give the desired product **19** in an inseparable mixture of diastereoisomers in a 81:3:16:trace ratio (Figure 1.7). The major diastereoisomer was tentatively assigned as the desired (2*S**, 4a*R**, 8a*S**) isomer **19a** by nOe studies.



Scheme 1.3 Mons' DE core unit synthesis. [51]

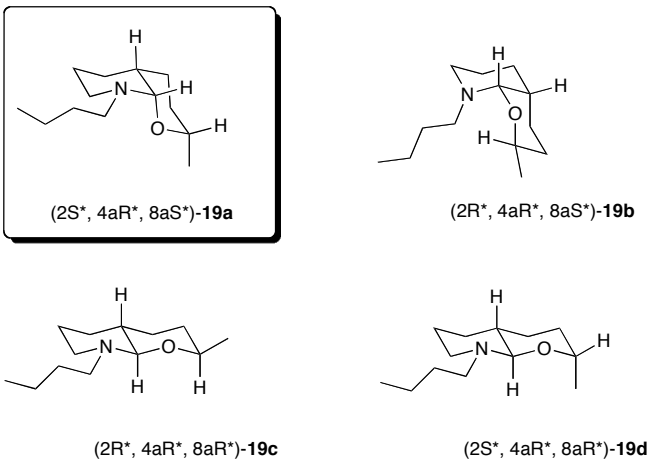
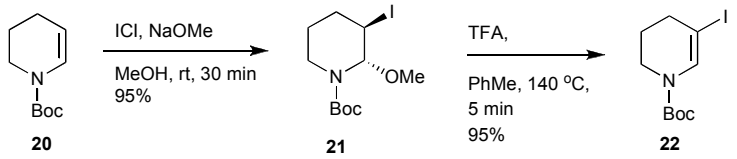


Figure 1.7 Diastereoisomers of **19** (86:3:16:trace **19a**: **19b**: **19c**: **19d**)

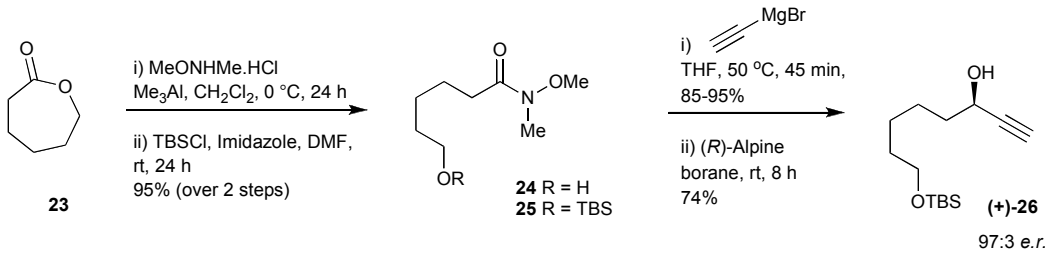
1.5.2 Sulikowski *et al.*, DE core fragment[52]

In 2005, the group of Sulikowski published a stereocontrolled route allowing access to both enantiomers of the DE core unit of 'upenamide. The initial steps of their synthesis involved the 2 step formation of the iodo-enecarbamate **22** from the enecarbamate **20** (Scheme 1.4). This was accomplished by the iodomethoxylation of **20** with ICl, which proceeded in excellent yield, without purification. Heating this product in toluene with TFA resulted in the rapid elimination of methanol to give the desired iodo-enecarbamate **22**.



Scheme 1.4 Synthesis of iodoenecarbamate **22**.

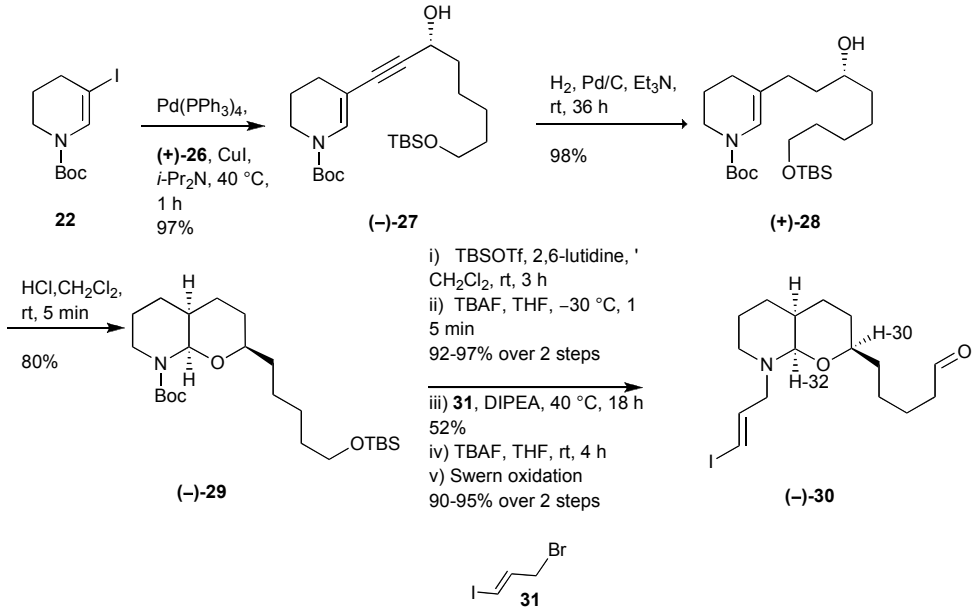
The synthesis of the alkyne coupling partner **26** (Scheme 1.5) commenced with the condensation of ε-caprolactone (**23**) with *N,O*-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminium to generate the Weinreb amide **24**. This was followed by protection of the alcohol as the TBS derivative, giving the amide **25** in excellent yield. Treatment with ethynylmagnesium bromide gave an alkynone in good to excellent yield. This alkynone was reduced with (*R*)-Alpine borane giving the desired (*R*)-isomer of propargyl alcohol **26** in good yield and excellent enantiomeric excess.



Scheme 1.5 Synthesis of propargyl alcohol **(+)-26**.

The Sonogashira coupling of iodide **22** and alkyne **(+)-26** proceeded well, delivering the enyne **(–)-27** in excellent yield (Scheme 1.6). Selective reduction of the triple bond gave the alcohol **(+)-28**, which upon treatment with acid cyclised to the hemi-aminal system **(–)-29**, with only one isomer observed. Boc-cleavage was achieved

under mild conditions by first making the TBS carbamate, then cleaving this by treatment with fluoride. Allylation of the free nitrogen, TBS cleavage and Swern oxidation gave the final product **(–)-30** as a single enantiomer.



Scheme 1.6 DE core unit synthesis.

The critical *cis*-ring fusion stereochemistry was assigned by the small coupling constant (<2 Hz) and chemical shift of the hemi-aminal proton (>4.0 ppm). The relative stereochemistry of the side chain was assigned by a nOe correlation between H-30 and H-32 (Figure 1.8).

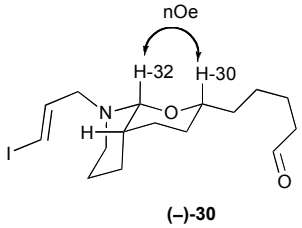


Figure 1.8 Stereochemistry assigned by nOe.

Sulikowski's observation that a single isomer was formed in the key ring formation contrasts with the result obtained by Mons, who saw a mixture of the 4 possible diastereoisomers. Sulikowski rationalises this by noting the main difference is the substituent present on the nitrogen of the 'D' ring; Mons' work has a *n*-butyl substituent while Sulikowski's compound uses a Boc protecting group (Figure 1.9). Sulikowski suggests the carbamate favours a kinetic reaction, while if the nitrogen substituent is alkyl the reaction is reversible and thus the thermodynamic mixture of

products is observed.

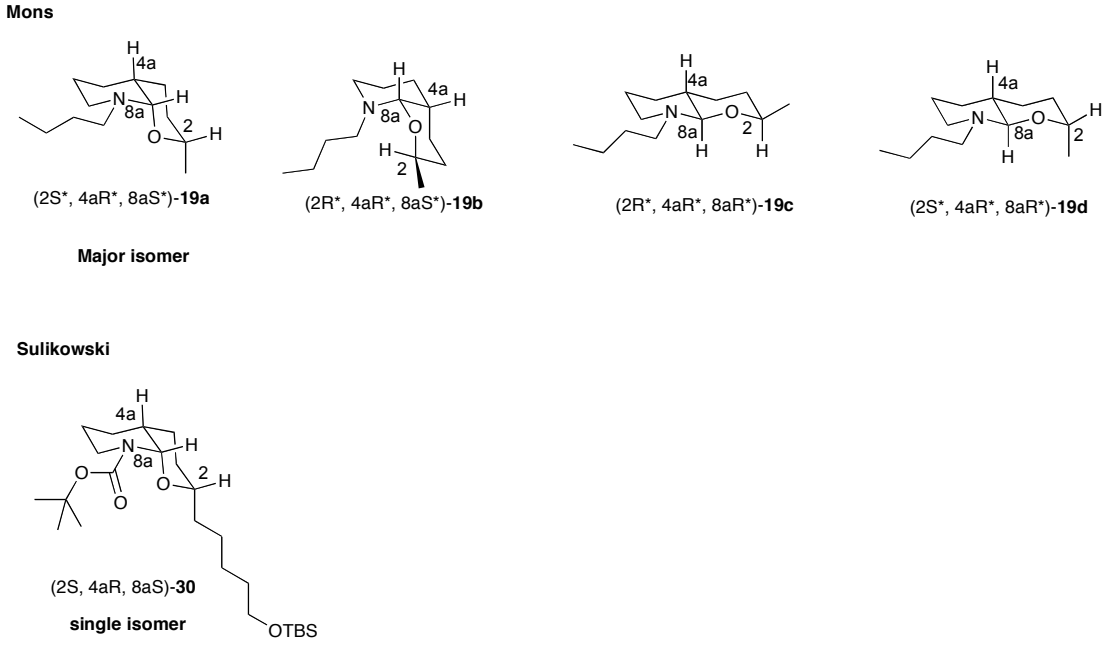
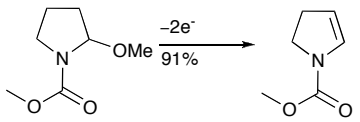


Figure 1.9 Isomers observed by Sulikowski and Mons.

Sulikowski's use of Alpine borane to effect the chiral reduction allows access to both enantiomers of the alcohol **26**. This in turn facilitates the synthesis of both enantiomers of the DE core; essential for the full structural elucidation of the natural product.

Sulikowski does not describe the synthesis of the enecarbamate starting material **20** (Scheme 1.4) stating only "prepared by electrochemical oxidation" but not specifying what the starting material for that oxidation is. Referencing Shono[56] suggests that it might formed from the corresponding α-methoxy carbamate by loss of methanol (Scheme 1.7).[56]



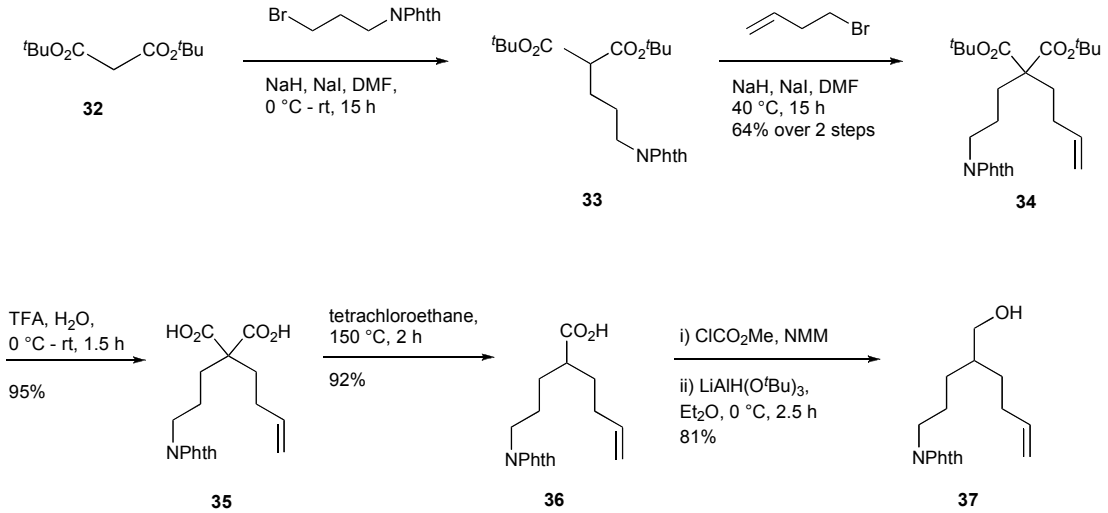
Scheme 1.7 Enecarbamate formation under electrochemical conditions.[56]

1.5.3 Taylor and Ménard-Moyon, DE core fragment[53]

In 2007 Taylor and Ménard-Moyon published two syntheses of the bicylic DE core.[53] The first synthesis was racemic and constructed both the ring systems by malonate chemistry (Schemes 1.8 and 1.9). The second synthesis detailed the elaboration of the dihydropyran **50** (Schemes 1.10 and 1.11). The chemistry of the second synthesis allowed the development an enantioselective route.

Route 1

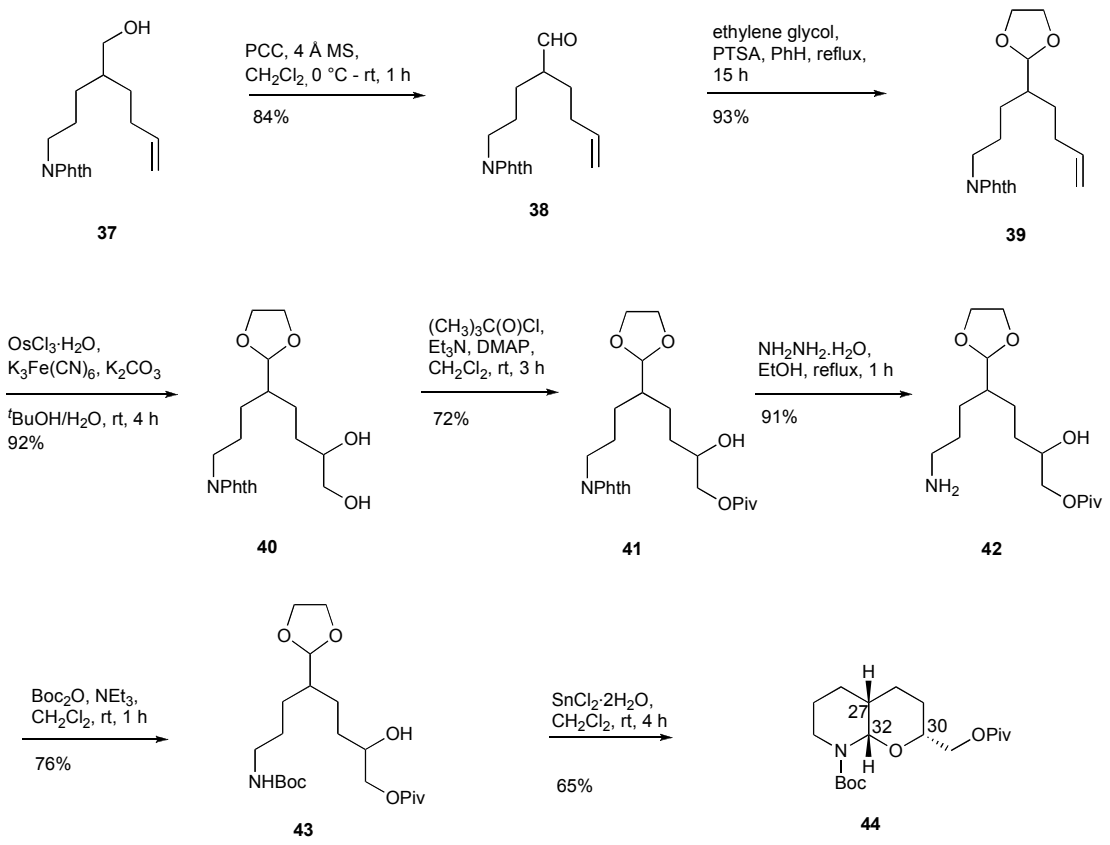
The initial steps of the first route are described in Scheme 1.8. Alkylation of di-*tert*-butyl malonate **32** with 3-bromopropylphthalimide and sodium hydride gave the phthalimide **33**. This was used unpurified in a second alkylation at elevated temperatures with 4-bromo-1-butene. This double alkylation gave the allyl adduct **34** in good yield over 2 steps. Ester hydrolysis with TFA gave the *bis*-acid **35**, which was decarboxylated at 150 °C to give the acid **36** in excellent yield. Formation of the mixed anyhyride of the acid allowed for selective reduction using lithium tri-*tert*-butoxyaluminium hydride to deliver alcohol **37**.



Scheme 1.8 Initial steps of Taylor and Ménard-Moyon's malonate-based route.

Oxidation of alcohol **37** with PCC gave the aldehyde **38** (Scheme 1.9) which was protected as the 1,3-dioxolane by refluxing under Dean–Stark conditions with *para*-toluenesulfonic acid and ethylene glycol. Dihydroxylation of actetal **39** with catalytic osmium trichloride and stoichiometric potassium ferricyanide gave the diol **40** (1:1

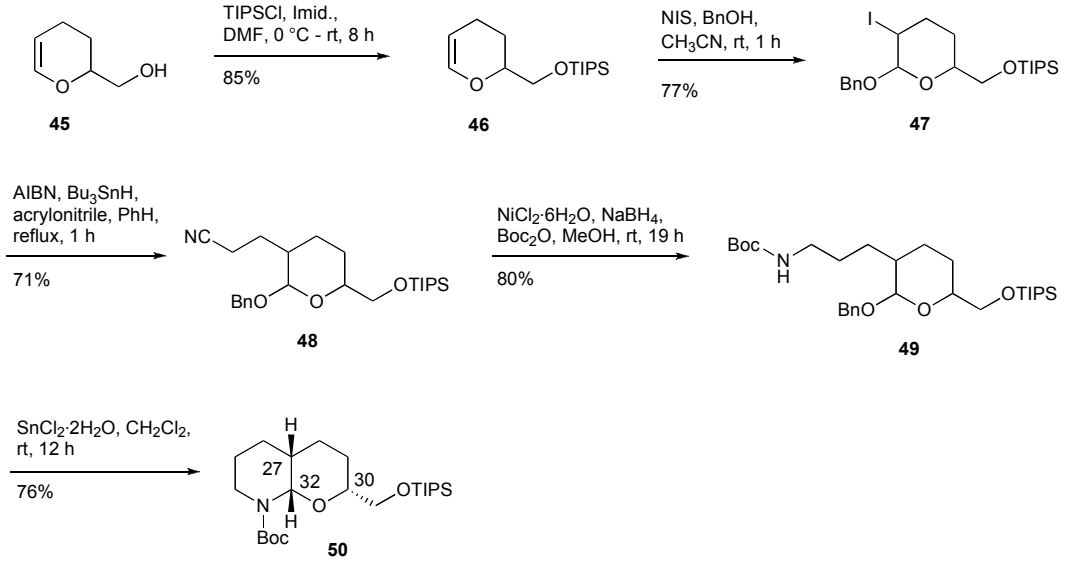
mixture of diastereoisomers). Protection of the primary alcohol as the pivaloate ester was accomplished by treatment with the acid chloride to give **41**. Deprotection of the phthalimide group with hydrazine was accomplished in good yield, giving the amine **42**. Finally Boc protection of the amine gave the cyclisation precursor **43**. On treatment of this with stannous dichloride dihydrate the bicyclic octahydropyrano[2,3-*b*]pyridine of the DE core unit was produced in a 65% yield. The cyclisation was stereoselective producing a single diastereoisomer of the hemiaminal ring. The *cis*-ring junction was once again assigned on the basis of chemical shift and small coupling constant (singlet observed) H-32. The same nOe correlation used by Sulikowski (H-32 – H-30) allowed the ring fusion stereochemistry to be assigned. Pleasingly, this was the same as present in the natural product. The route is lengthy if high yielding (11% over 12 steps) but produced a racemic product.



Scheme 1.9 Later steps of Taylor and Ménard-Moyon's malonate-based route.

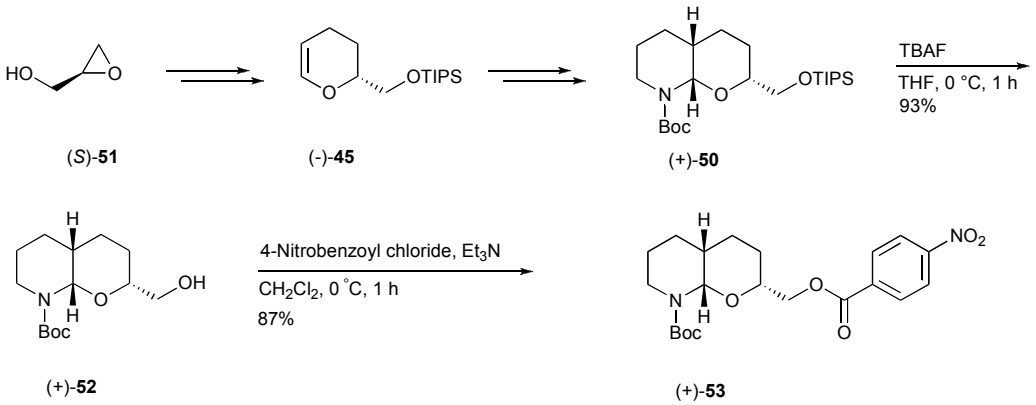
Route 2

Taylor and Ménard-Moyon's second synthesis of the DE core unit was based on the derivatisation of the commercially available dihydropyran **45**. TIPS protection furnished **46**, which was treated with NIS and benzyl alcohol to give compound **47** as a mixture of diastereoisomers. Treating this with acrylonitrile in the presence of of AIBN and tributyltin hydride in refluxing benzene gave the adduct **48** in high yield. The nitrile was reduced with nickel boride in the presence of di-*tert*-butyl dicarbonate gave the Boc-protected amine **49** in good yield. As in the previous work, the key cyclisation sequence proceeded well, once again giving the DE core unit as a single diastereoisomer. Analysis of coupling constants and nOe studies once again elucidated the relative stereochemistry of the 3 chiral centres.



Scheme 1.10 Taylor and Ménard-Moyon's second DE route.

Because the total synthesis of 'upenamide requires an enantioselective route to the DE core, Taylor prepared enantiopure **51** following a procedure by Ley *et al.* [57] The chemistry described in Schemes 1.9 and 1.10 was applied to this material, generating the DE core unit as a single enantiomer (Scheme 1.11). Derivatisation with *para*-nitrobenzoic acid gave the ester **53** and allowed confirmation of the stereochemistry by X-ray crystallography.

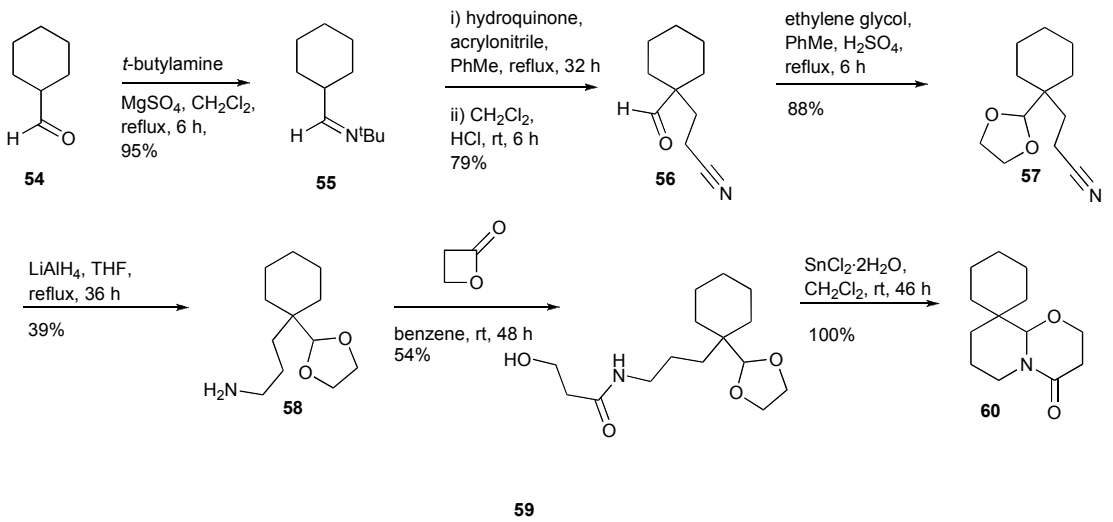


Scheme 1.11 Taylor and Ménard-Moyon's enantioselective DE synthesis.

1.5.4 Taylor and Reid, ABC core unit 1[58]

Both publications concerning the ABC core unit come from the Taylor group. The first, by Reid and Taylor, describes a stannous dichloride dihydrate mediated synthesis of the skeleton of the ABC core.[58]

Cyclohexane carboxaldehyde **54** was converted into *tert*-butyl imine **55** by treatment with *tert*-butylamine (Scheme 1.12). Imine **55** was alkylated using acrylonitrile and catalytic hydroquinone and the product hydrolysed under acidic conditions to give the desired aldehyde **56**. The aldehyde was protected as the dioxolane **57** in good yield by treatment with ethylene glycol, then the nitrile reduced with lithium aluminium hydride. The resulting amine **58** was used in a nucleophilic ring opening of β-propiolactone to furnish amide **59** in a moderate yield. Treatment of this with stannous dichloride dihydrate delivered the desired spirooxaquinolizidinone framework of the ABC core unit **60** in a quantitative yield.

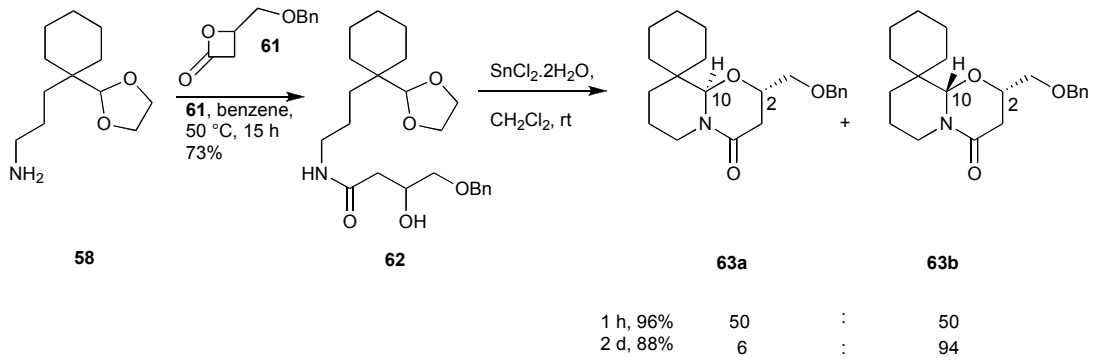


Scheme 1.12 Taylor and Reid's synthesis of the ABC skeleton.

Reid and Taylor continued their studies into the model system for the ABC core fragment by investigating substitution at C-2. This was achieved by employing a substituted β-propiolactone, allowing them to probe the stereochemical outcome of the key cyclisation reaction.

Treatment of amine **58** with racemic 4-(benzyloxymethyl)oxetan-2-one (**61**) (Scheme 1.13) gave the cyclisation precursor **62**. Treatment of this with stannous dichloride dihydrate under the conditions used to form **60** gave the desired ABC skeleton **63** in high yield, but as a 1:1 mixture of diastereoisomers. It was postulated that the cyclisation might be reversible, and thus the reaction time was extended considerably from 1 hour to 2 days. This resulted in a 94:6 ratio, in favour of **63b**, which, pleasingly, has the stereochemistry present in the natural product. The structure and stereochemistry of **63a** and **63b** were confirmed by X-Ray crystallography.

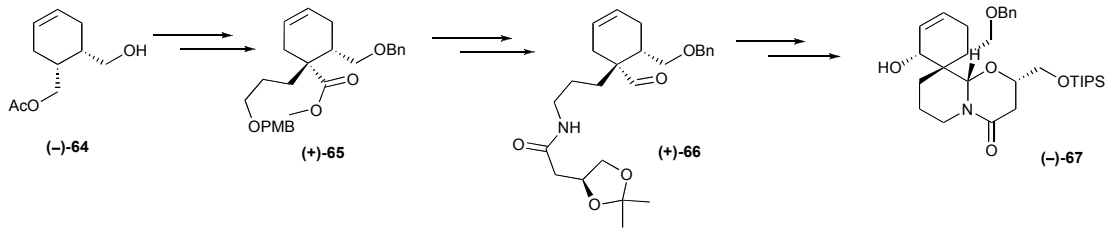
The ^{1}H NMR spectrum of **63a** and **63b** differ primarily about the chemical shift of H-2. In the 'natural' isomer **63b** H-2 has a chemical shift of δ_H 3.86 – 3.80, while in **63a** H-2 is shifted downfield to δ_H 4.29 – 4.25. In the natural product **1** H-2 has a chemical shift of δ_H 3.62. The ^{13}C NMR spectrum differs primarily about the shift of C-10, with **63b** δ_C 92.9 and **63a** δ_C 88.8. 'Upenamide has a chemical shift of δ_C 88.7.



Scheme 1.13 C-2 substituted ABC skeleton.

1.5.5 Taylor and Schmidt, ABC core unit 2[54]

In the second paper by Taylor detailing studies towards the ABC core, the first synthesis of the fully functionalised spirooxaquinolizidinone is described (Scheme 1.14).[54] An enzymatic desymmetrisation was used to provide an enantioselective route, while the key allylic oxygen was introduced by a selenium dioxide mediated allylic oxidation.



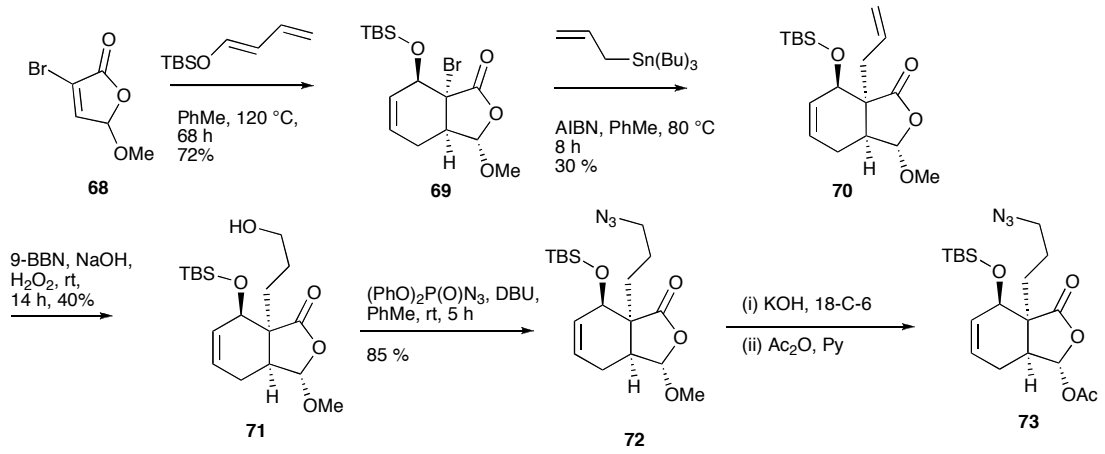
Scheme 1.14 Schmidt and Taylor's route to the fully functionalised ABC core.

Much of the work described in this Thesis is based on this chemistry, and this route will be discussed in detail in Chapter 3.

1.5.6 Sulikowski *et al.*, DE & BC core units[55]

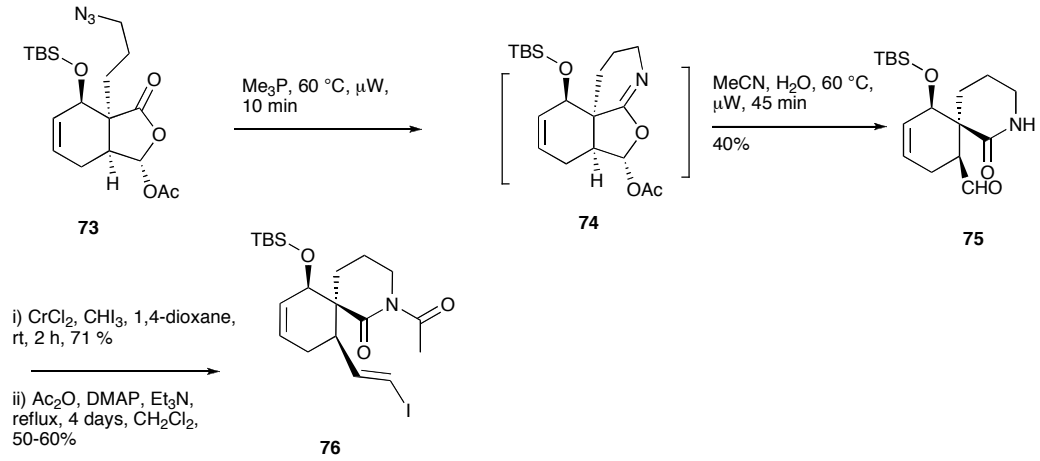
The final paper detailing studies toward 'upenamide is a second from the group of Sulikowski. It details a route to a spirocyclic compound which forms two of the three rings of the tricyclic ABC core unit of 'upenamide, and the coupling of this "BC" ring system to the DE core unit to generate an advanced intermediate.[55] The key step in the synthesis is a microwave-mediated Staudinger/ aza-Wittig/ imine hydrolysis sequence which generates the spirocyclic BC core.

From 2-bromobutenolide **68** (Scheme 1.15), a Diels–Alder reaction delivered the *endo*-adduct **69** as a single diastereoisomer. A Keck allylation introduced the required 3-carbon fragment to give **70** in a moderate yield after chromatographic separation of the mixture of isomers generated. Hydroboration of the desired isomer followed by oxidation gave alcohol **71** in good yield. The alcohol was then converted into the azide *via* treatment with DPPA, giving the azide **72** in good yield. Treatment with potassium hydroxide and acetyl chloride removed the methoxy substituent and replaced it with an acetate, generating the cyclisation precursor **73**. The methyl ester **71** had been shown to give undesired epimerisation in the following step (note, no yields given for the hydroysis or acetate protection).



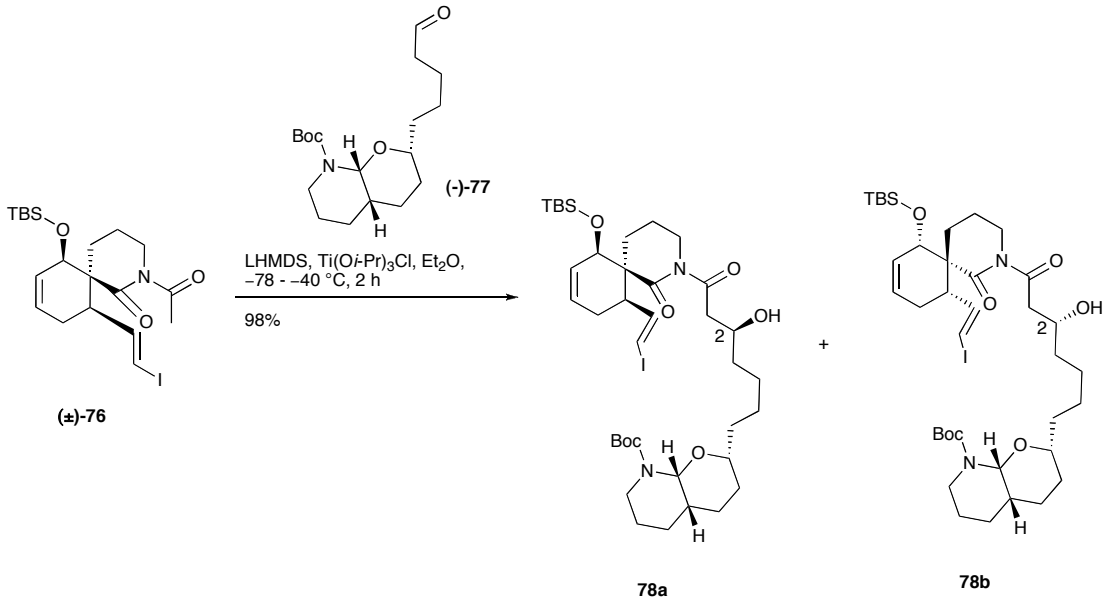
Scheme 1.15 Sulikowski's initial BC synthesis.

In the key triphenyl phosphine microwave-mediated Staudinger/ aza-Wittig/ imine hydrolysis sequence, the acetate was transformed into the spirocyclic product **75** as a single diastereoisomer but as a mixture of enantiomers (Scheme 1.16). Subsequent Takai olefination and nitrogen acylation gave the spirocyclic imide **76** in good yield.



Scheme 1.16 Later steps in Sulikowski's BC synthesis.

Sulikowski continued with the coupling of this 'BC' fragment to the DE core unit of 'upenamide[52] *via* an aldol reaction. The use of Ti(O*i*-Pr)$_3$Cl allowed the control of the stereocentre produced at the C-2 position. The racemic BC core fragment coupled with the enantiomerically pure DE core unit to give the inseparable diastereoisomers **78a** and **78b** in a 1:1 ratio.



Scheme 1.17 Coupling BC core unit to DE core.

It appears the aim of Sulikowski was to install the 'A' ring of the ABC core unit of 'upenamide as one of the final stages of the total synthesis, as the route described does not allow its introduction earlier. However, given the publication describes only the late stage intermediate it can be assumed that this has proved more difficult than anticipated.

1.6 Project aims

The ultimate aim of this project was the development of a viable, efficient synthetic route to the natural product 'upenamide. Previous studies within the group [59-61] sought to achieve this by the separate synthesis of each core system followed by uniting the cores in the macrocyclic structure of 'upenamide.

Firstly a short methodology project was planned to explore the scope of the $SnCl_2 \cdot 2H_2O$ methodology used by Taylor in both the ABC and DE core structures,[53, 54, 58] and apply it to the synthesis of a range of small heterocycles. The background to this project, and the results, are detailed in Chapter 2.

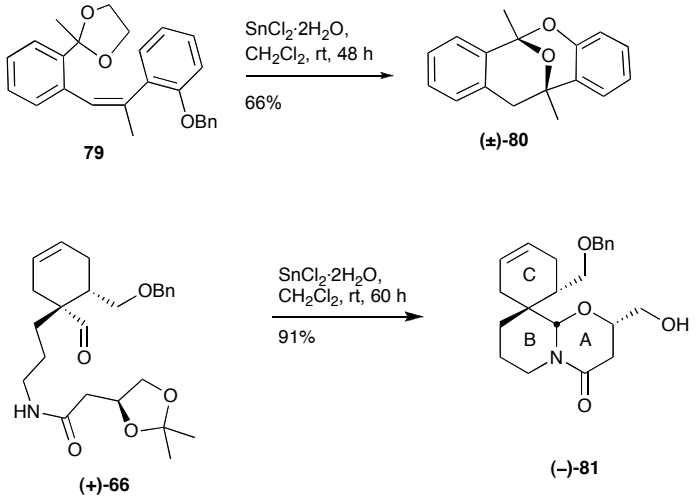
Studies on model systems by Taylor and Jean had identified possible routes for coupling the ABC and DE cores.[59] Application of this methodology to the "real system" required multi-gram quantities of both ABC and DE core structures. Thus, the major aim of the project was the modification of existing routes[52-54] to both core structures to make this possible. This would be followed by coupling studies to complete the 'upenamide synthesis.

Chapter 2 – Results and discussion 1: Novel routes to heterocyles mediated by tin (II)

2.1 Background to methodology project

Polycyclic heterocycles are considered to be "privileged structures" in the pharmaceutical and agrochemical industries,[62] and new methods for their construction are invaluable in the search for bioactive lead compounds in medicinal chemistry.

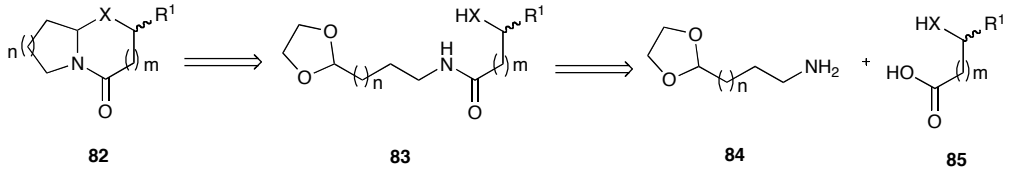
This project concerned the use of stannous dichloride dihydrate ($SnCl_2 \cdot 2H_2O$) to perform a deacetalisation-bicyclisation sequence, producing polycyclic heterocycles in a single step from simple precursors. The work was inspired by previous synthetic efforts within the group towards natural product targets. Initially the core structure of the of the HIV-1 integrase inhibitors integrastatins A and B **(±)-80** was constructed from stilbene **79** using this methodology,[63] and it was used further in the synthesis of the ABC core fragment of 'upenamide (Scheme 2.1). Treatment of the acetal precursor **(+)-66** with $SnCl_2 \cdot 2H_2O$ gave the tricyclic ABC core of 'upenamide **(–)-81** in excellent yield.[54]



Scheme 2.1 The construction of the integrastatin core and the ABC core unit of 'upenamide.[54, 63]

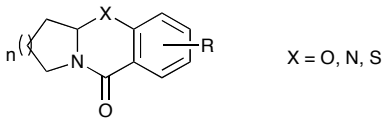
It was envisaged that this methodology could be applied to allow access to a focussed library of compounds, of the general structures **82** and **87** (Scheme 2.2).

*Route 1 - from dioxolane amine **83***



82 **83** **84** **85**

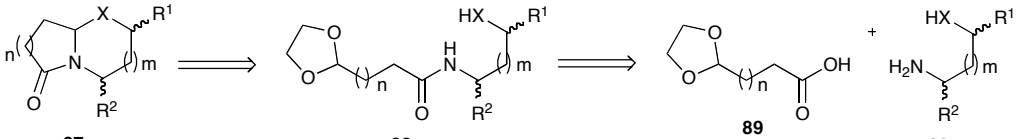
Or with an aromatic group:



X = O, N, S

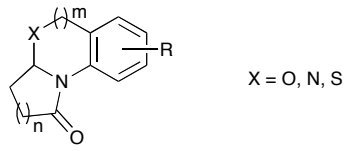
86

*Route 2 - from dioxolane acid **88***



87 **88** **89** **90**

Or with an aromatic group:



X = O, N, S

91

Scheme 2.2 Retrosynthetic analysis of heterocycles.

The $SnCl_2 \cdot 2H_2O$ methodology would allow compounds of types **82** and **86** to be accessed from an amide of the general form **83**, which in turn could be disconnected to reveal the amine **84**, to be coupled with a range of acids **85**. Compounds like **87** and **91** could be accessed from the amides of general form **88**, which can be further disconnected to reveal the dioxolane acid **89** coupled with a range of amines **90** (Scheme 2.2).

Compounds with the general structure **82** had been previously studied within the group, along with a few examples of compounds in the series **87** and a single example of the general structure **86** (Figure 2.1). A communication describing this methodology was published in 2007.[64]

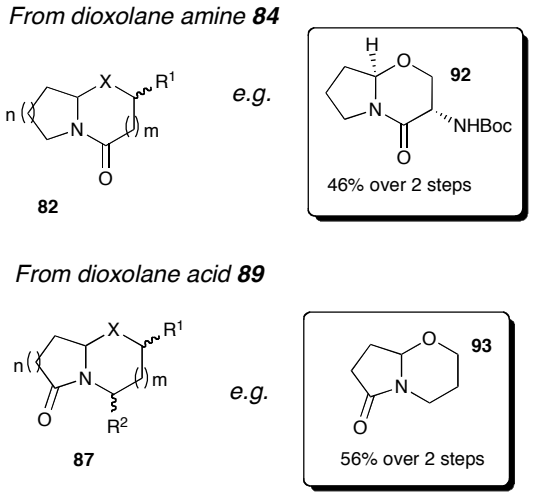
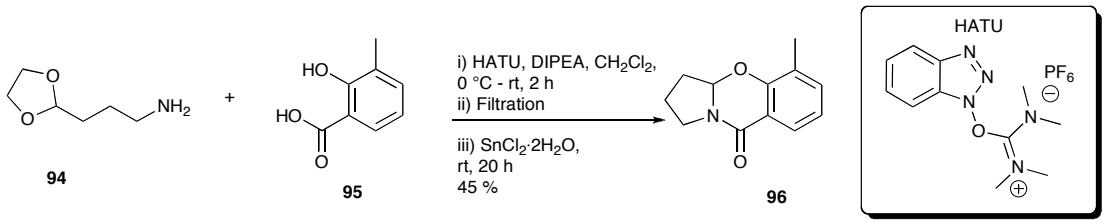


Figure 2.1 Compounds accessible from acid **89** and amine **84**.

2.2 Aims and objectives: Methodology project

The initial aim of the project was to optimise the synthesis of the aromatic product **96** (Scheme 2.3), apply these optimised conditions to a range of systems, then follow the same procedure for the series **87**. It was hoped that the results obtained would provide a greater understanding of the chemistry of these targets and allow for the publication of a full paper describing examples accessible by the application of this methodology.

The initial series worked on comprised compounds with the general structure **86**. The single example **96** had been previously synthesised, using the peptide coupling reagent HATU to form the amide bond, resulting in a moderate yield of 45% over the two steps (Scheme 2.3).[64]



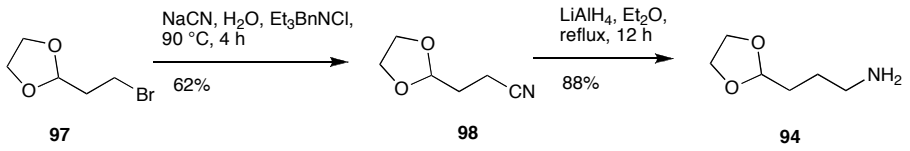
Scheme 2.3 Cayley's HATU coupling.[64]

2.3 Results

Previous work in the group suggested that the $SnCl_2 \cdot 2H_2O$ cyclisation step was generally high yielding,[63, 64] and so initial efforts concentrated on optimising the amide formation.

2.3.1 Synthesis of amine 94

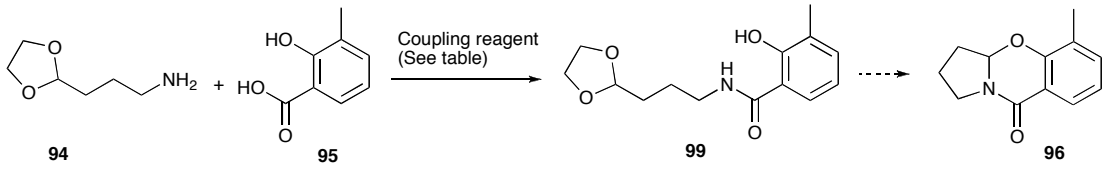
The amine **94** was synthesised according to the procedure developed by Shimizu and co-workers.[65] Commercially available 2-(2-bromoethyl)-1,3-dioxolane **97** was treated with sodium cyanide in water in the presence of a phase transfer catalyst, and the crude reaction purified by flash column chromatography to give the desired product in 62% yield (Scheme 2.4). The purified nitrile **98** was reduced with lithium aluminium hydride to afford the primary amine **94** in 88% yield. The amine **94** was >95% pure by ^{1}H NMR spectroscopy. Purification of this highly polar amine was problematic, and thus **94** was used without further purification.



Scheme 2.4 Synthesis of amine **94**.

2.3.2 Initial coupling studies

Initial optimisation was carried out on the system illustrated in Scheme 2.5 and focussed on the isolation of the intermediate amide **99**. A range of standard coupling reagents were screened.



Scheme 2.5 Coupling reaction.

Table 2.1 Amide bond formation on amine **94**.

Entry	Conditions	Yield of amide 99 and observations
1	HATU, DIPEA, CH_2Cl_2, 0 ºC - rt. * Aqueous workup.	~10% mass recovery many unidentified by-products
2	HATU, DIPEA, DMF, 0 ºC - rt* Aqueous workup.	~10% mass recovery many unidentified by-products
3	Acid chloride, CH_2Cl_2, rt. †	Trace of coupling observed, mainly recovered starting material.
4	*i*-BuOCOCl, NMP, 0 ºC - rt. §	Isolation of mixed anhydride
5	*i*-BuOCOCl, NMP, rt - 60 °C. §	Some reaction observed by ^{1}H NMR spectroscopy, but deprotection of acetal main product
6	T3P®, rt- 40 ºC. ¶	No reaction at rt. Heating resulted in deprotection of aldehyde
7	HATU, DIPEA, DMF, filtered through pad of silica. *	11% yield amide, however recovered some cyclised product **96**

*According to procedure described by Cayley *et al.*[64] (with a standard aqueous workup or DMF replacing CH_2Cl_2)

† Acid chloride formed according to the procedure described by Wu *et al.*[66]

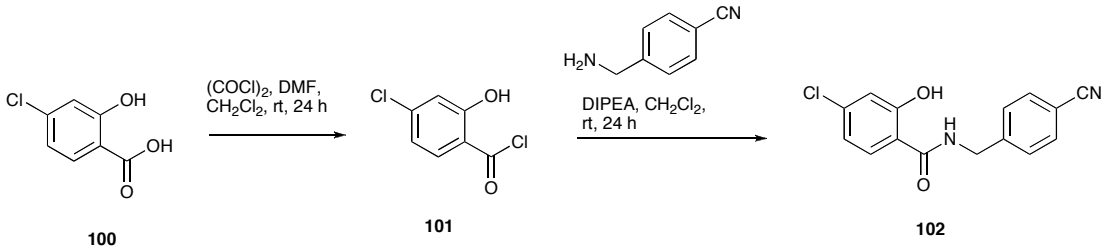
§ As described by Cayley *et al.*[64]

¶ According to the procedure described by Taylor *et al.*[67]

The single example of this type of system studied from the previous work within the group used HATU as the coupling reagent, and thus this was initially tried (Table 2.1, Entries 1 and 2), but the results observed were poor.

The literature for amide bond formation on salicylic acid derived systems suggests the use of acid chlorides as the preferred method of coupling, and that the favoured method of formation of the acid chloride is treatment with PCl_3.[68, 69] Given the difficulty of handing PCl_3[70] it was decided to prepare the acid chloride *via* another method.

The formation of an amide bond on a similar system *via* the acid chloride was described by Boxer *et al.* (Scheme 2.6).[71]

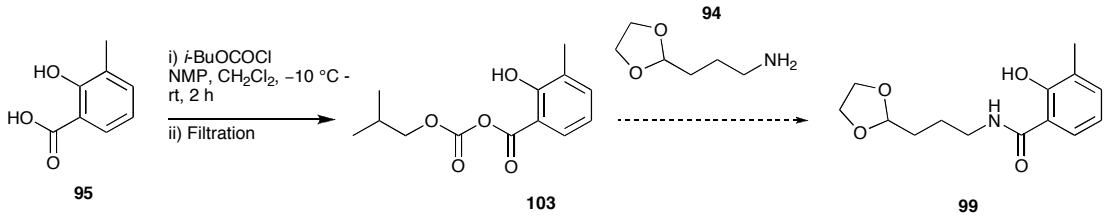


100 **101** **102**

Scheme 2.6 Amide bond formation on salicylic acid **100** (no yields reported).[71]

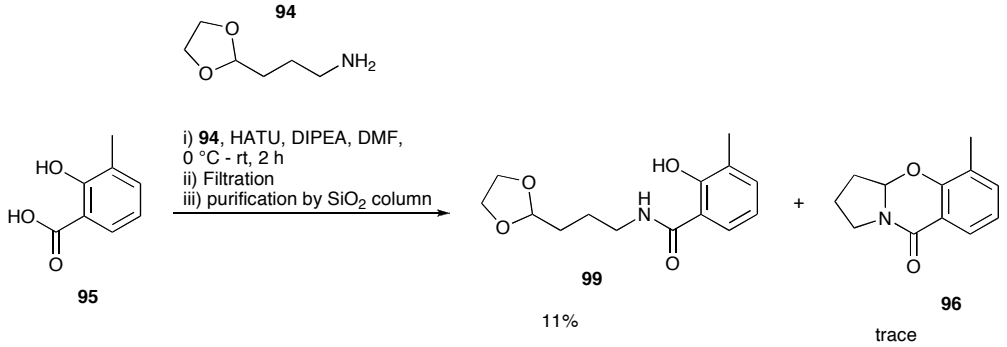
Based on this, the next coupling protocol attempted was the synthesis of the acid chloride and its displacement by amine **94** (Table 2.1, Entry 3), was unsuccessful. The acid chloride was formed by the standard procedure of thionyl chloride and pyridine (for an example see Wu *et al.*[66]), and its formation was confirmed by TLC analysis (quenching a small sample into excess MeOH yielded only the methyl ester, suggesting complete consumption of the acid). However, reaction of this activated species with amine **94** returned only the amine. It was presumed that either the amine was not nucleophilic enough to displace the chloride or the acid chloride itself was not stable.

The mixed anhydride coupling method *via* the use of *iso*butyl chloroformate (Scheme 2.7) was next attempted. However, this reaction returned the mixed anhydride **103** at rt, while heating the reaction cleaved the acetal (Entries 4 and 5, Table 2.1).



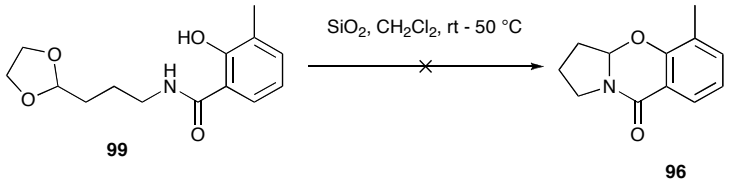
Scheme 2.7 Mixed anhydride coupling.

The final method tried was a return to the coupling reagent tried initially, HATU, but with a variation in the workup conditions (Entry 7, Table 2.1). Instead of an aqueous workup the reaction was filtered through a pad of silica to remove the HATU residues, and then concentrated and purified by column chromatography. The yield of amide **99** was still disappointingly low, although a trace of the desired cyclised product **96** was observed.



Scheme 2.8 HATU coupling gave some cyclisation.

At this point it was concluded that the intermediate amide was not stable. The cyclisation that would be effected with $SnCl_2 \cdot 2H_2O$ appeared to be taking place slowly. It seemed likely that this was occurring during the chromatographic purification, but attempts to induce this cyclisation with SiO_2 failed (Scheme 2.9).

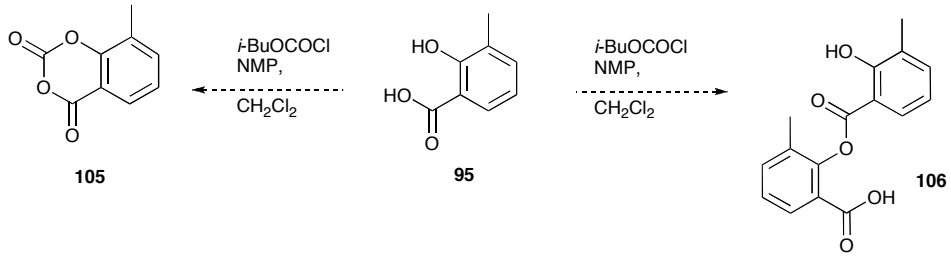


Scheme 2.9 Treatment with silica failed to induce the desired cyclisation.

2.3.3 Phenol protection

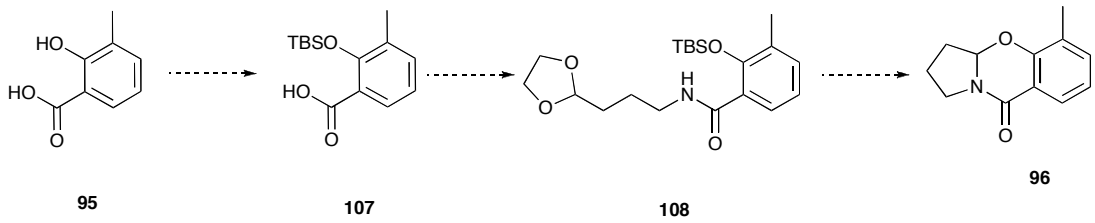
The presence of the phenol group seemed likely to be causing the problems with the amide bond formation reactions. It is possible that when the active ester or acid

chloride was formed during the coupling reaction, either another molecule containing the nucleophilic OH group is displacing it to form the ester **106**, or it was cyclising with itself to give **105** (Scheme 2.10). This could be prevented by the protection of the phenol group. If the cyclisation of the intermediate amide was the reason behind the difficulties in amide bond formation this should also be prevented.



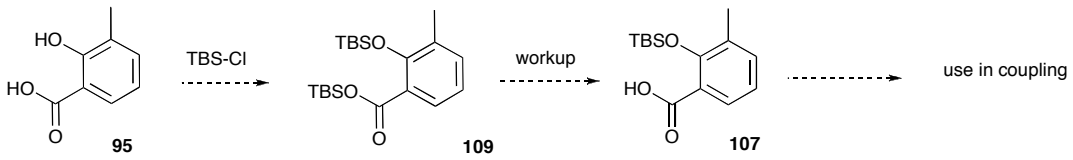
Scheme 2.10 Proposed undesired reactions of phenol **95**.

A silyl protecting group was chosen, as it was hoped that it would protect the phenol during the planned amide coupling step, and then be cleaved under the $SnCl_2 \cdot 2H_2O$ cyclisation conditions, with the stannous dichloride performing a one pot desilylation-deacetalisation-bicyclisation sequence (Scheme 2.11).



Scheme 2.11 Envisaged protected phenol coupling and cyclisation.

The silyl-protected phenol **107** was not known in the literature, but it was envisaged that it would be synthesised in a standard manner for the formation of TBS ethers: DIPEA and TBSCl. It was assumed that the TBS ester **109** would be formed first, but that it would be readily cleaved upon aqueous workup (Scheme 2.12).

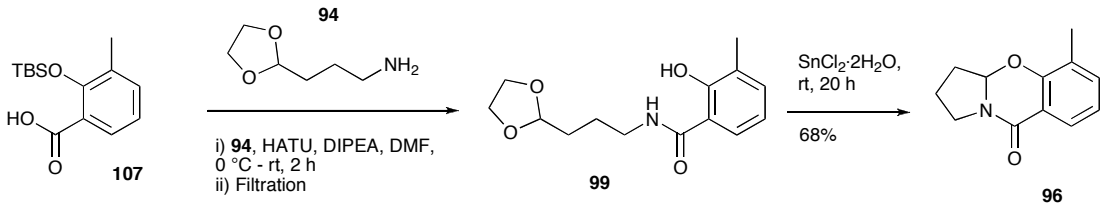


Scheme 2.12 Envisaged synthesis of protected phenol **107**.

The standard TBS protection conditions (2 eq.), however, yielded only the *bis*-protected salicylic acid derivative **109**, even after an aqueous workup. This surprising stability may simply be a steric issue – the TBS groups are in very close proximity, and the presence of a large region of very non-polar alkyl groups might prevent the approach of water to hydrolyse the silyl ester.

The desired mono-protected salicylic acid **107** could be isolated by careful treatment of **109** with either 10% citric acid (aq.), or TBAF in THF. However, **107** appeared to be unstable, even when stored at freezer temperatures (~ –18 °C). The estimated pKa of the acid proton is 3.06 (ACD labs predictor), and while there is no precedent in the literature for the deprotection of phenolic silyl ethers with acids as mild as this, there is considerable precedent for the deprotection of alkyl silyl ethers under similar conditions; formic acid (pKa 3.7[72]) has been shown to remove TBS ethers,[73] and Dowex resin, a carboxylic acid immobilised on polystyrene beads, has also been used in alkyl systems.[74]

A small amount of the TBS-protected material **107** was prepared and used immediately in the HATU mediated coupling, followed by immediate treatment with $SnCl_2 \cdot 2H_2O$ to effect cyclisation. This sequence gave a slightly higher yield of the desired heterocycle **96** (Scheme 2.13). However, analysis of the crude reaction mixture after the coupling stage indicated that the silyl protecting group had been cleaved under the coupling reaction conditions. This, combined with the difficulty in preparing the mono-protected material led to the route being abandoned.



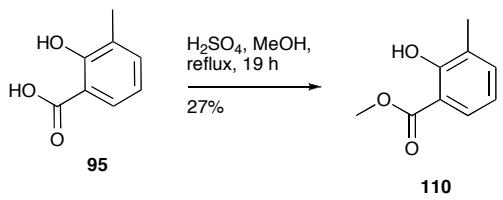
Scheme 2.13 Coupling of mono-protected **107**.

2.3.4 Direct ester displacement

It is possible to form amide bonds *via* the direct displacement of an ester by an amine[75] and this method was attempted next. Literature precedent on similar salicylic acid derived systems under both thermal[76] and microwave conditions provided encouragement.[77] Norman *et al.*[76] suggested the use of the methyl ester while Toma and co-workers suggested the use of the phenyl ester under microwave conditions.[77] It was decided to synthesise both and test them in the displacement reactions.

2.3.4.1 Synthesis of esters

The methyl ester **110** was synthesised from the corresponding acid under standard Fischer esterification conditions,[78] with catalytic H_2SO_4 in MeOH at reflux (Scheme 2.14). An acid-base workup gave ester **110** in a low but unoptimised yield of 27%.

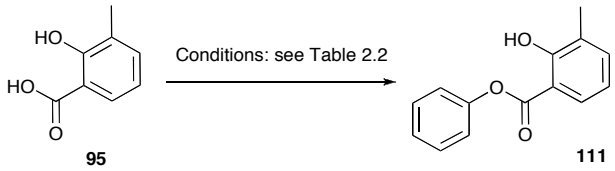


Scheme 2.14 Methyl ester formation.

The synthesis of the phenyl ester **111** proved to be more problematic, perhaps due to the lability of the desired product. Standard coupling conditions, heating with Amberlite® acidic resin and phenol, returned only starting material (Entry 1, Table 2.2).

Literature reports suggested the use of polyphosphoric acid (PPA) on similar systems.[79] It is reported that PPA acts as both a dehydrating agent and acid catalyst. Initial attempts at this reaction were promising, heating to 100 °C with excess PPA and 4 eq. of phenol in xylene gave yields in the region of 65% of the desired phenyl ester **111** after column chromatography. However, when a new bottle of PPA was used the reaction returned only starting material until the temperature reached ~50 °C, when the starting material polymerised. Attempts to 'age' the new PPA by adding water gave the same result (Entries 2 and 3, Table 2.2).

The final approach optimised for the formation of the ester bond was a return to some of the chemistry tried in making the amide bond. Work then had shown that it was possible to make the acid chloride of 3-methyl salicylic acid. Repeating this and treating the acid chloride with PhOH (2 eq.) gave a reasonable yield of the desired product **111** after chromatographic purification (Scheme 2.15) (Entry 4, Table 2.2).



95 **111**

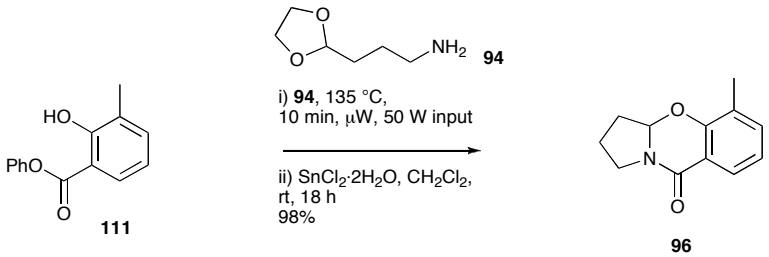
Scheme 2.15 Phenol ester formation.

Table 2.2 Phenol ester formation.

Entry	Conditions	Yield of ester 111 and observations
1	Amberlite resin, 4 eq. PhOH, neat, 80 °C, 4 h.	0%, Recovered starting material.
2	PPA (old bottle), xylene, PhOH, 100 °C, 18 h.[79]	65%
3	PPA (new bottle), xylene, 100 °C, PhOH 1 h.	0% Dark red polymeric material formed when reaction heated above 50 °C.
4	Thionyl chloride, pyridine, CH_2Cl_2, PhOH, 0 °C - rt, 30 min.	65%

2.3.4.2 Ester displacements

Both the methyl and the phenyl ester were treated under the conditions described by Toma *et al.*[77] heating neat to 135 °C for 10 minutes under microwave irradiation. The methyl ester **110** was recovered unchanged from the reaction, whilst the phenyl ester **111** was converted cleanly into the amide. With concerns about the stability of the intermediate amide, the neat reaction mixture was immediately dissolved in CH_2Cl_2, and treated with $SnCl_2 \cdot 2H_2O$ (2 eq.), to yield the desired cyclised product, in an almost quantitive yield of 98% over the two steps (Scheme 2.16).



Scheme 2.16 Phenyl ester displacement and subsequent cyclisation.

2.3.4.3 Solvent screening

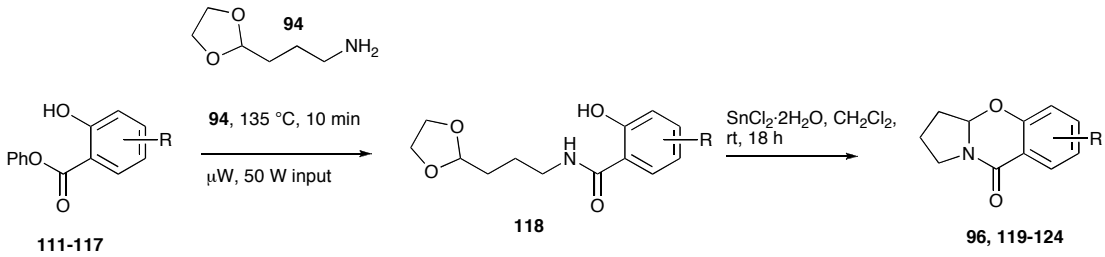
While the neat reaction protocol gave very good results it was difficult to handle the viscous, oily amine **94** on a small scale. A reaction which could be carried out under the same microwave conditions, but with the amine in solvent would make handling easier. With this aim a series of reactions in various solvents were carried out using ester **111**. The reactions were performed on the same scale as the neat reaction, and heated in the microwave to the same temperature. Each reaction was monitored by TLC for the disappearance of starting material (Table 2.3).

Table 2.3 Solvent screen for amide bond formation of phenyl ester **111** and amine **94** to give amide **96**.

Entry	Solvent	Result:
1	None (control reaction)	No starting material observed by TLC after 10 minutes. Complete conversion to **96**. 98% isolated yield of **96** after treatment with $SnCl_2 \cdot 2H_2O$.
2	Xylene	Some conversion by TLC, but mainly starting material **111** after 30 minutes.
3	Chlorobenzene	~ 50% conversion by TLC after 30 minutes.
4	Chloroform	Only trace of desired product after 30 minutes, recovered **111**.

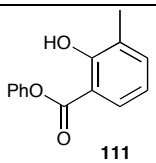
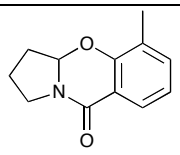
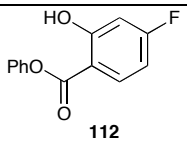
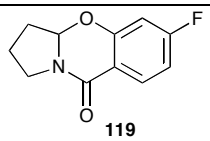
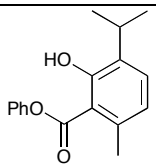
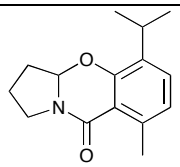
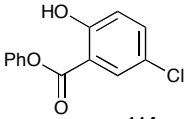
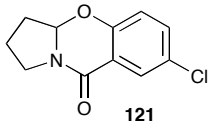
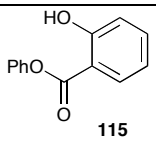
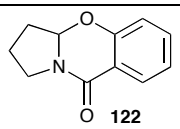
The non-polar high boiling solvent xylene (a mixture of isomers, boiling point around 140 °C) gave a disappointing result, with some conversion observed by TLC analysis. The slightly lower boiling (131 °C) but more polar chlorobenzene gave a more promising result, with approximately 50% conversion by TLC. Chloroform (boiling

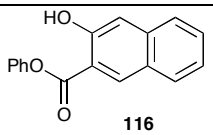
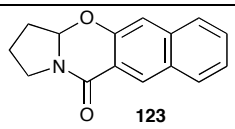
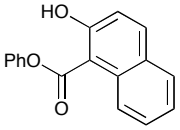
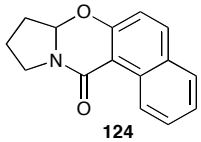
point 61 °C) resulted in only a trace of reaction, with phenyl ester **111** recovered unreacted. None of these results were comparable to the neat reaction (98% isolated yield Entry 1, Table 2.3), and so while handling the amine neat was difficult it appeared to be the most appealing of the routes studied. The methodology for forming the phenyl esters and then the displacement with the primary amine was applied to a range of compounds. The results are summarised in Table 2.4.



Scheme 2.17 General reaction for bond formation and cyclisation.

Table 2.4. Phenol ester displacement and cyclisations.

Entry	Ester	Yield of ester*	Cyclised	Yield of heterocycle
1	 **111**	65%	 **96**	98%
2	 **112**	32%	 **119**	98%
3	 **113**	45%	 **120**	84%
4	 **114**	34%	 **121**	87%
5	 **115**	commercial	 **122**	75%

6	 116	commercial	 123	65%
7	 117	commercial	 124	56%

* Prepared by treatment with thionyl chloride, pyridine, CH_2Cl_2 and PhOH.

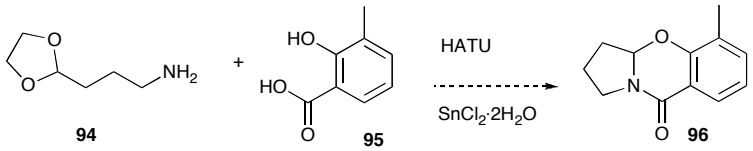
Each of the heterocyles produced had a characteristic hemi-aminal proton doublet of doublets (J 5.5 – 6.0 Hz) in the ^{1}H NMR spectrum between 5.33 and 5.65 ppm, and a hemi-aminal ^{13}C NMR signal between 88.2 and 89.1 ppm. All compounds were further characterised by mass spectrometry, high resolution mass spectrometry and IR spectroscopy.

2.3.5 Studies towards a one-pot procedure

While the purification of the intermediate amide had been kept to a minimum in these sequential reactions, the ideal situation would be a tandem process where all the reagents were charged to the flask at the beginning of the reaction.

A series of experiments were carried out to investigate this possibility. These were carried out on the HATU-mediated coupling (Scheme 2.18) and the phenyl ester displacement (Scheme 2.19).

2.3.5.1 HATU coupling



94 95 96

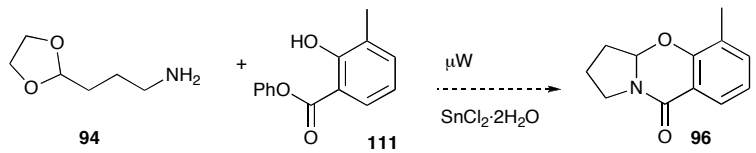
Scheme 2.18 Envisaged tandem process with HATU.

After carrying out the HATU coupling between amine **94** and acid **95**, $SnCl_2 \cdot 2H_2O$ was added in a single portion to the reaction mixture and the reaction monitored by TLC. The standard loading of 2 eq. of $SnCl_2 \cdot 2H_2O$ gave no conversion to product, and the loading was increased in increments of 2 until 10 eq. had been added. At this

point the reaction was worked up in the standard fashion, filtering through a celite pad, washing with CH_2Cl_2. After column chromatography the desired product **96** was isolated in a slightly lowered yield of 38%. It was assumed that by-products from the HATU coupling reaction formed a complex with the tin present in the reaction mixture and prevented the acetal deprotection-bicyclisation reaction occurring.

With this reasonably positive result in hand attention was turned to the true 'tandem' process: adding all the reagents at the beginning of the reaction. Disappointingly, charging the $SnCl_2 \cdot 2H_2O$ to the reaction mixture of amine **94** and acid **95** with the HATU coupling reagent resulted in the recovery of only starting materials.

2.3.5.2 Ester Displacement



Scheme 2.19 Envisaged tandem process with phenyl ester displacement.

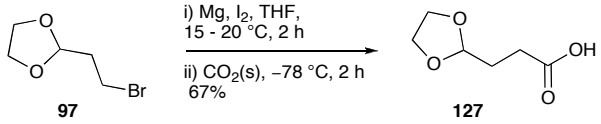
As the only byproduct of the ester displacement is phenol, it was hoped that this coupling method would allow the sequential process to become tandem. Adding 2 eq. of $SnCl_2 \cdot 2H_2O$ to the reaction mixture of amine **94** and phenyl ester **111** before subjecting it to the microwave heating required for coupling however resulted only in degradation of the starting material. It was assumed that the microwave conditions combined with the $SnCl_2 \cdot 2H_2O$ were simply too harsh for the starting material.

This concluded the work on the initial series of compounds to be investigated. The second series of compounds to be investigated also completed some work started by Cayley.[64]

2.3.6 Reversed coupling partners

2.3.6.1 Acid synthesis

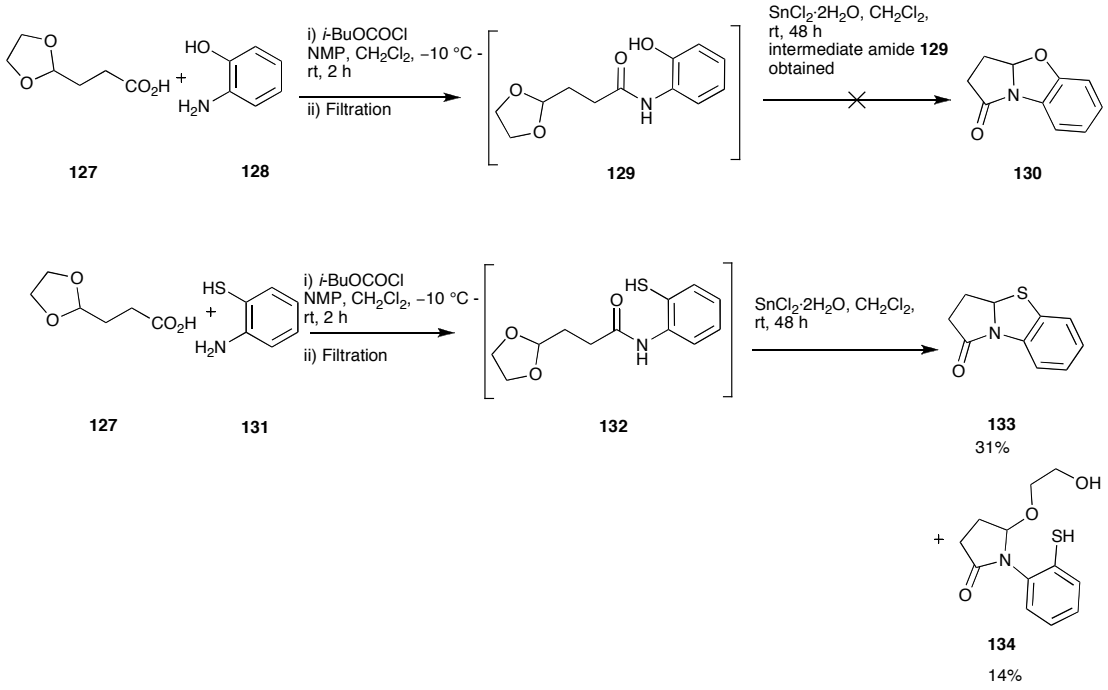
The dioxolane acid **127** was synthesised from the commercially available bromide **97** according to the procedure of Shea *et al.*[80] The Grignard reagent was formed by treatment with magnesium and catalytic iodine, then cooled, and the acid moiety installed by the addition of solid carbon dioxide. An acid-base workup gave the acid **127** in a moderate yield requiring no further purification (Scheme 2.20).



Scheme 2.20 Synthesis of acid **127**.

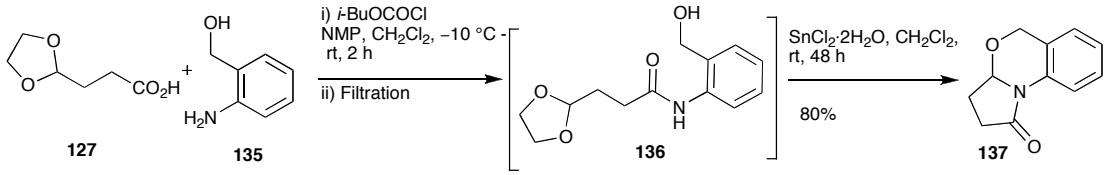
2.3.6.2 Initial series

A synthesis of the compounds illustrated in Scheme 2.21 had been investigated by Cayley. Initially attempting to form heterocycle **130**, Cayley had isolated only intermediate amide **129**. It was assumed that the 5-membered ring in **130** was too strained for the desired product to be formed. It was hoped that replacing oxygen with sulfur, to make compound **133**, would solve this problem given the longer sulfur-carbon bond length (183 pm vs 143 pm); however, a mixture of the desired compound **133** and partially cyclised **134** was isolated. It was assumed **134** was an intermediate in the formation of **133** and Cayley predicted that moving to the larger 6-membered ring of **137** would reduce ring strain and hence favour the formation of the cyclic product **137**.



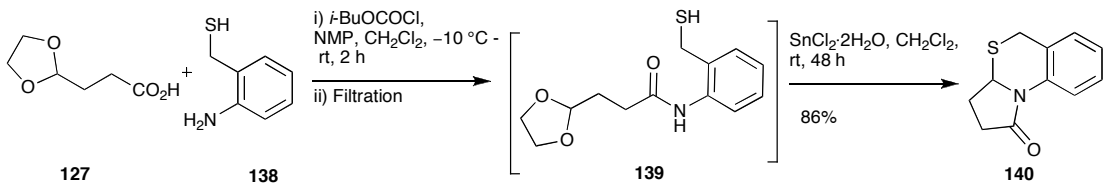
Scheme 2.21 Cayley's work on compounds derived from acid **127**.

We were pleased to observe that this was the case. Treatment of 2-aminobenzyl alcohol **135** under the standard conditions developed by Cayley[64] of *iso*butyl chloroformate amide coupling, filtration through a pad of silica, and treatment of the crude amide with $SnCl_2 \cdot 2H_2O$ gave the desired compound in a high yield of 80% over two steps (Scheme 2.22).



Scheme 2.22 Synthesis of hemi-aminal **137**.

The synthesis of the sulfur analogue of **137**, **140** also proceeded smoothly, giving the desired compound in an 86% yield (Scheme 2.23).



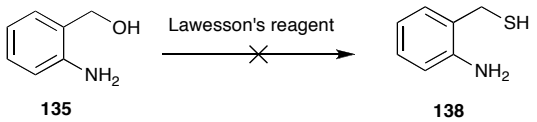
Scheme 2.23 Synthesis of thio-aminal **140**.

The hemi-aminal **137** and thio-aminal **140** each had distinctive signals for the hemi-/thio- aminal proton and carbon (δ_H=5.27 and δ_C=87.2 for the oxygen-containing **137**, and δ_H=5.04 and δ_C=60.9 for the sulfur-containing **140**). Both compounds were fully characterised by NMR spectroscopy, mass spectrometry, high resolution mass spectrometry and IR spectroscopy.

2.3.6.3 Synthesis of thiol 138

The seemingly trivial thiol **138** for the coupling illustrated in Scheme 2.35 is not commercially available. It is reported in the literature, but all references suggest a preparation described by Kitamura,[81] compromising 6 steps from the corresponding benzyl alcohol **135** and with an overall yield of less than 10%. For this reason a more facile route to prepare the starting material was required.

Lawesson's reagent is widely used for the conversion of ketones to thioketones[82] and alcohols to thiols,[83] and the first attempts made to synthesise the thiol **138** were based on the use of this reagent. However treatment of amino alcohol **135** under standard conditions (*e.g.* those described by Nishio[83] or Taylor[84]) returned no product, although all the starting material was consumed. The reaction was very messy and the isolated products appeared to consist entirely of byproducts of Lawesson's reagent. Varying the workup conditions had no effect on the reaction and the route was abandoned.

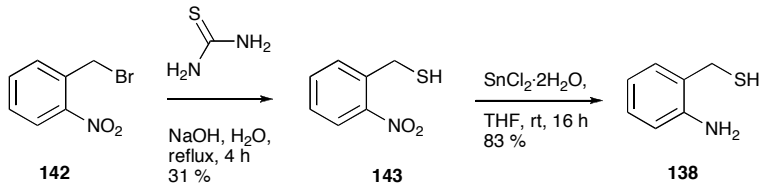


135 **138**

Scheme 2.24 Lawesson's reagent did not deliver the desired thiol **138**.

The second route investigated (Scheme 2.25) involved starting from 2-nitrobenzyl bromide (**142)**, displacing the bromine with thiourea, followed by hydrolysis of the resulting thiourea with NaOH. This sequence delivered the nitrobenzyl thiol **143** in a moderate yield. Reduction of the nitro group with tin, HCl and acetic acid (following the procedure of Kandler *et al.* described for a very similar substrate[85]) returned none

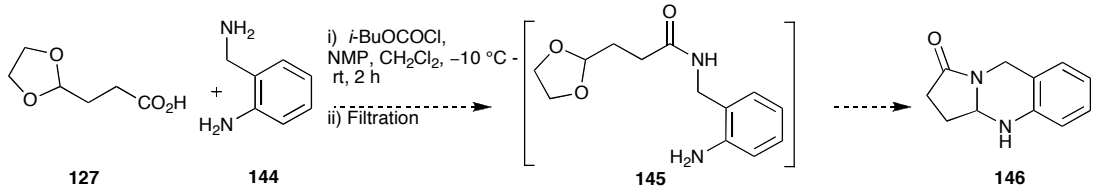
of the desired product. Treatment with $SnCl_2 \cdot 2H_2O$ in HCl (aq.) gave a similar result, but pleasingly treatment of the nitro thiol **143** with $SnCl_2 \cdot 2H_2O$ in THF gave the desired product **138** in a reasonable yield after purification by cation exchange chromatography.



Scheme 2.25 Synthesis of thiol **138**.

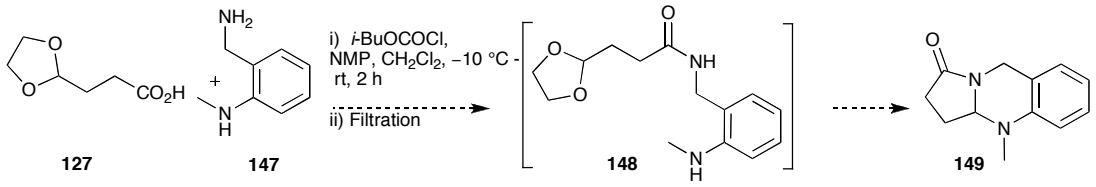
2.3.6.4 Aminal heterocycle formation

To complete the series the final example was to be an aminal-containing heterocycle of the form **146**. The free amine **144** (Scheme 2.26) however proved difficult to handle under the standard methodology used for the rest of the series. Neither the desired compound **146** or the amide **145** were isolated and it was assumed that this was due to the high polarity of the intermediate amide **145**, which is likely to have remained on the silica plug used to remove the *iso*butyl chloroformate coupling residues.



Scheme 2.26 Envisaged formation of aminal **146**.

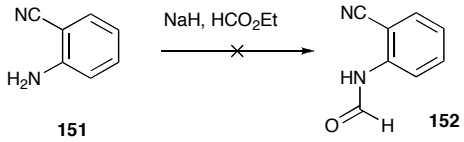
It was hoped that methylating the free amine to generate heterocycle **149** would solve this problem, and allow the methodology to be applied unchanged to this example.



Scheme 2.27 Envisaged synthesis of aminal **149**.

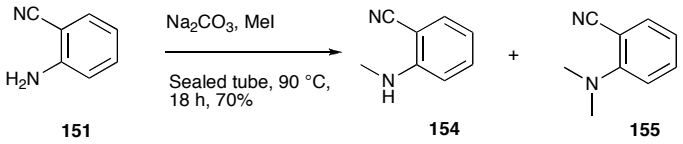
2.3.6.5 Synthesis of methylated amine 147

Initial attempts were made to synthesise methylated amine **147** *via* the initial formylation of nitrile **151** under conditions described by Hays *et al*.[86](sodium hydride, ethyl formate). TLC showed complete consumption of starting material, but ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture showed none of the desired material. No signal for the formamide proton was present, and the integration of the aromatic proton signals suggested one had been consumed in the reaction.



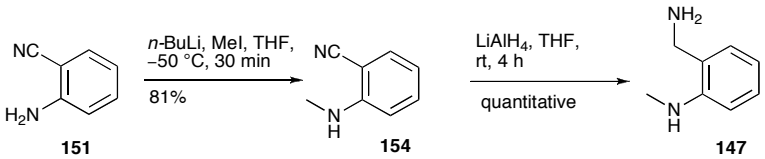
Scheme 2.28 Formylation gave an unknown product.

Attention was then focussed on direct methylation of 2-aminobenzonitrile **151**. Literature suggested that this could be achieved by heating with neat MeI and Na_2CO_3.[87] Treatment of nitrile **151** under the conditions described by Antonini *et al.* gave a mixture of the *mono*- and *di*- methylated compounds **154** and **155** in a ratio of 1:1 and a yield of 70%.



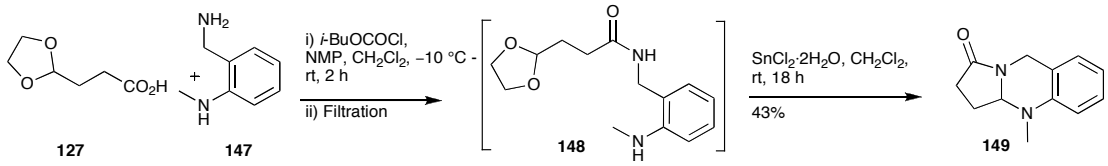
Scheme 2.29 Direct methylation resulted in a mixture of *mono*- and *di*- methylation.

Given the difficulty in separating the *mono*- and *di*- methylated products, a further method was tried. Following the procedure described by Fernandez *et al.,*[88] the amino nitrile **151** was treated with *n*-BuLi (0.45 eq.) followed by MeI. The desired product **154** was isolated in 81% yield. Reduction with $LiAlH_4$ afforded the amine **147** in a quantitive yield, requiring no further purification (Scheme 2.30).



Scheme 2.30 Synthesis of amine **147**.

Pleasingly, methylation of the amine allowed the application of the method previously described unchanged, which generated the heterocyclic product **149** in moderate yield of 43% after purification by preparative TLC.



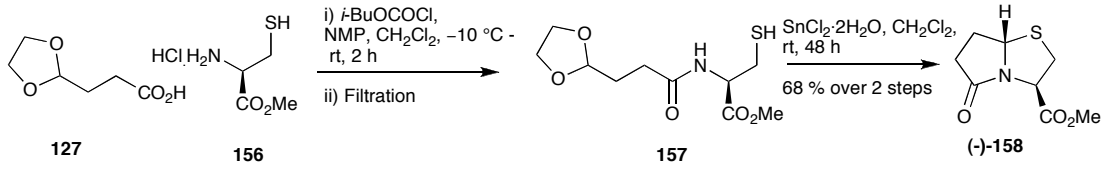
Scheme 2.31 Methylated **147** cyclised to give the desired aminal heterocycle.

The aminal **149** had distinctive hemi-aminal ^{1}H NMR (δ_H=4.56) and ^{13}C NMR signals (δ_C=71.9), and was fully characterised by NMR spectroscopy, mass spectrometry, high resolution mass spectrometry and IR spectroscopy.

2.3.6.6 Disulfide example

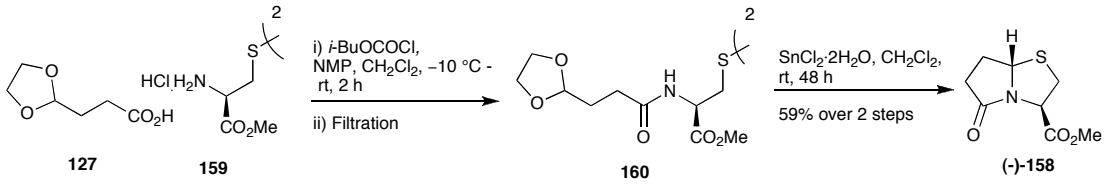
It is possible to use tin to reduce disulfide bonds (usually in combination with HCl.[89, 90]). It was hoped that the conditions developed to perform the deacetalisation-bicyclisation sequence would allow the reduction of a disulfide bond *in situ*. This would allow heterocycles such as the thio-aminal **140** to be prepared in two steps from the corresponding disulfide, with the $SnCl_2 \cdot 2H_2O$ performing a disulfide reduction-deacetalisation-bicyclisation sequence in a single pot.

Given the difficulties in synthesising **138**, the target heterocycle chosen for this study was the cysteine-derived thio-aminal **(−)-158**. This molecule had been synthesised by Cayley[64] in a reasonable yield over two steps from L-cysteine methyl ester (**156**), giving the desired compound **(−)-158** as a single diastereoisomer (Scheme 2.32). This was tentatively assigned the 3*R*,7a*S*-configuration shown, on the basis of NMR studies.[64] The methyl ester of L-cysteine (**156**) is commercially available as the disulfide.



Scheme 2.32 Cayley's synthesis of **158**.

We were delighted to observe that applying the methodology unchanged to the disulfide **159** facilitated the one-pot coupling-disulfide reduction-deacetalisation-bicyclisation smoothly in a 59% yield over the 4 steps performed, delivering the thio-aminal **(−)-158** as a single diastereoisomer{$[\alpha]_D$ −250.7 (*c* 1.25, $CHCl_3$)}. This is comparable to the yield achieved by Cayley over 3 steps.[64]



Scheme 2.33 **(−)-158** from the disulfide.

This completed the methodology project. This work was published as a full paper in Synthesis in 2008.[91] This paper is included as Appendix 1.

2.4 Conclusions

A novel tin(II) chloride dihydrate-mediated deacetalisation-bicyclisation procedure has been described for the construction of novel polycyclic heterocycles from amides possessing a pendant acetal group. The methodology developed allows access to a range of aminal, hemi-aminal and thio-aminal containing heterocycles in a two step process from easily synthesised precursors. The novel ring-fused heterocyclic systems produced have been fully characterised.

Development of a tandem process was unsuccessful, but the sequential process described is simple to carry out and gives high yields.

The small library of compounds examined for each series could easily be expanded to include more examples. If the compounds were to show any biological activity this would allow full structure-activity relationships to be established.

Chapter 3 – Results and discussion 2: Synthesis of ABC core unit

3.1 Previous work on the ABC core unit

The ABC core unit of ’upenamide is a tricyclic spirooxaquinolizidinone ring system. It has received considerable attention in the Taylor group, who reported the only synthesis of the fully functionalised core unit to date.[54] The stereochemistry of the ABC core unit is difficult to draw without overlapping bonds, so for clarity the stereochemistry of the ‘up’ hydrogen at the hemiaminal centre is abbreviated as a dot for the remainder of this Thesis.[92]

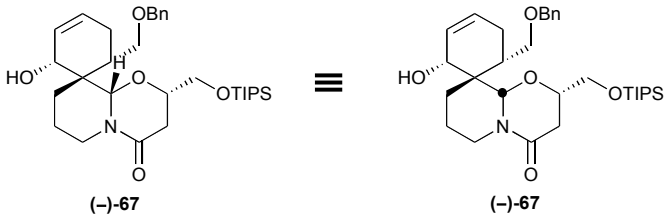
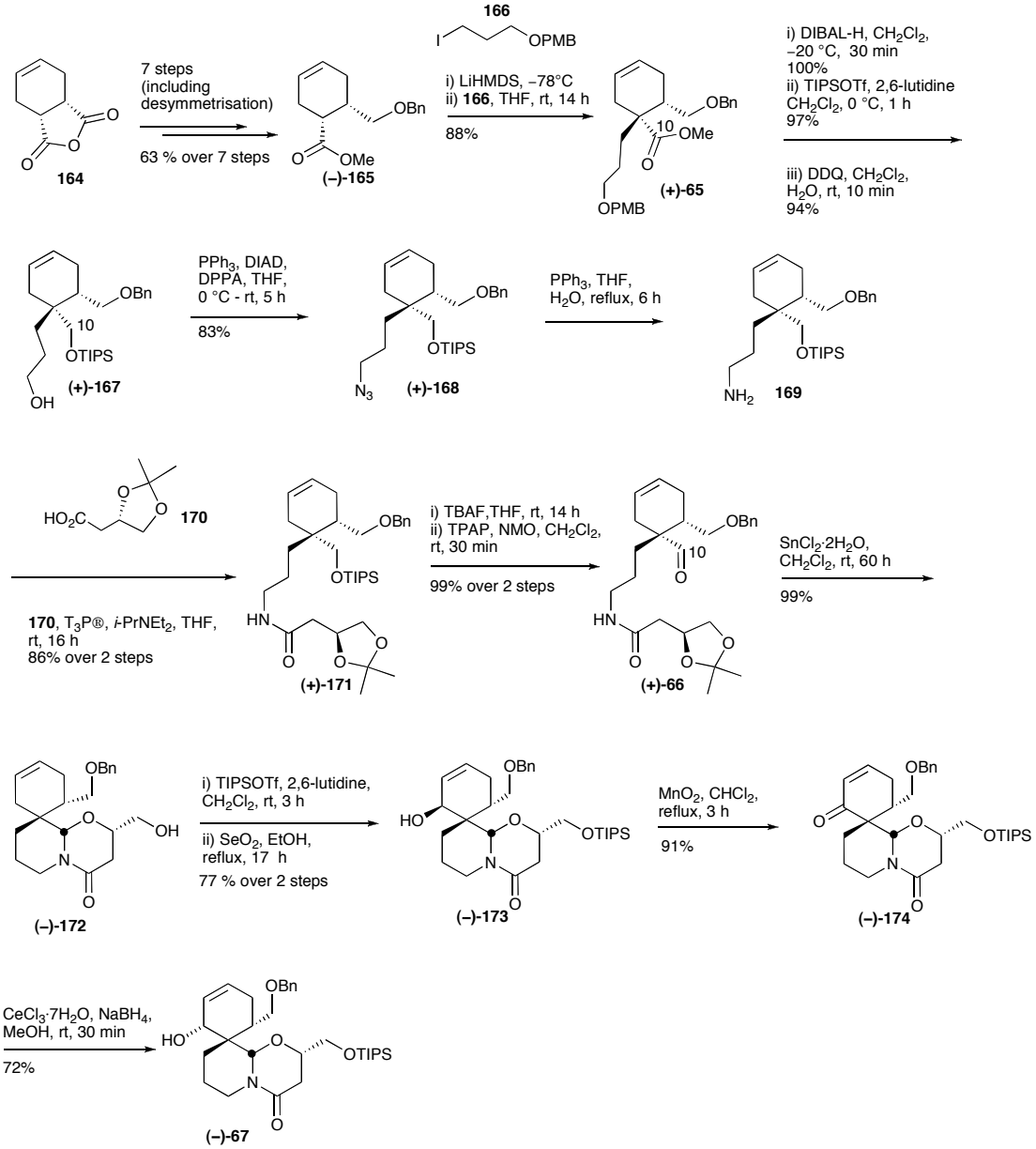


Figure 3.1 Stereochemical notation used for ABC core unit.

The synthesis of the ABC core unit by Schmidt, McAllister and Beltrán-Rodil was based on chemistry developed within the Taylor group by Reid.[58] The route is high yielding, but involves many steps, some of which are detailed in Scheme 3.1. Starting from the commercially available *meso*-anhydride **164**, seven steps including an enzymatic desymmetrisation deliver the ester **(–)-165** in an enantio-enriched form (~94% e.e.) and in high yield. The carbon atoms which will comprise the key spirocyclic six membered B-ring are installed by alkylating with the three-carbon PMB-protected iodo alcohol **166** to deliver the protected alcohol **(+)-65**. After reduction of the ester and TIPS protection of the resulting alcohol, the PMB group is removed under oxidative conditions and the alcohol **(+)-167** transformed to the azide **(+)-168** *via* a Mitsunobu reaction. Staudinger reduction of the azide **(+)-168**, coupling of the amine **169** with the carboxylic acid **170**, and finally deprotection and oxidation of the alcohol to the aldehyde give the cyclisation precursor **(+)-66**. In the key reaction, treatment of this intermediate with $SnCl_2 \cdot 2H_2O$ effects an acetal deprotection and condensation onto the resulting aldehyde to give the skeleton of the

ABC core unit **(–)-172**. TIPS protection of the primary alcohol was followed by allylic oxidation effected by selenium dioxide, installing the required allylic alcohol **(–)-173**. The stereocentre created was the opposite epimer to the natural product, and so in two final steps the alcohol was oxidised to the enone **(–)-174** using manganese dioxide, then reduced under Luche conditions to give the desired (*R*)-epimer **(–)-67**.



Scheme 3.1 Schmidt and Taylor's synthesis of the ABC core unit **(–)-67**.[54]

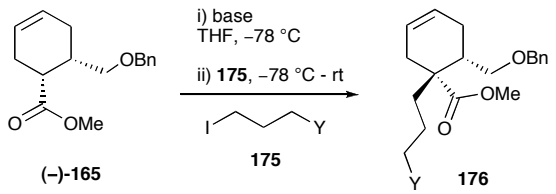
3.2 Aims and objectives: Improved synthesis of the ABC core unit

The ABC synthesis is 20 steps long but despite the length of the synthesis the yields are high (18% from commercially available starting materials). Initially the development of a shortened route, allowing easier access to the fully functionalised ABC core unit, was to be examined. Attention was first to be focussed on shortening the number of steps to install the three carbon chain aminated chain [*i.e.* **(–)-165** → **169** in fewer than six steps]. Further studies were then to be carried out to see if the reduction, protection, oxidation sequence performed on carbon 10 (**(+)-65**, **(+)-167** Scheme 3.1) could be simplified. Finally a modified synthesis of the carboxylic acid **170** employed in the amide coupling was to be investigated.

3.3 Results

3.3.1 Previous alkylation results

One of the major reasons why the published route to the ABC core unit was so long is the nature of the alkylating agent employed on ester **(–)-165**. Ideally, the amine required in the final product would be present on the three carbon chain before the alkylation, but Schmidt's route installed a protected alcohol, and then required three steps to deliver the amine present in **169**. However, previous work had shown that alkylation reactions on ester **(–)-165** with alkylating agents **175** containing a variety of protected nitrogen groups, yielded either only starting material, or gave very low yields of the desired compound. The attempted reaction is illustrated in Scheme 3.2. Alkylation with Y = OPMB was successfully optimised to give the desired compound in high yield. A selection of alkylating agents investigated is illustrated in Table 3.1.[60]

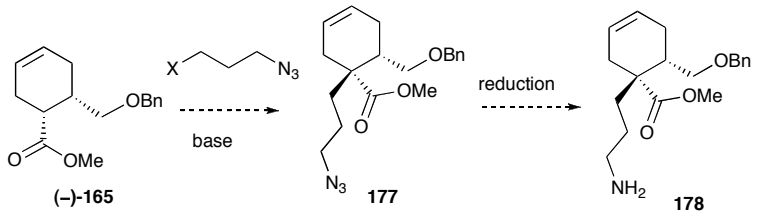


Scheme 3.2 Schmidt and McAllister's alkylation studies.[60]

Table 3.1 Schmidt and McAllister's work on alkylating ester **(–)-165**.[54]

Entry	Base	Solvent	Conditions	175, Y	Yield
1	NaHMDS	THF	–78 ˚C then rt	$N(PMB)_2$	23%
2	NaHMDS	THF	–78 ˚C then rt	$N(Allyl)_2$	-
3	NaHMDS	THF	–78 ˚C then rt	NPhth	-
4	LiHMDS	THF	–78 ˚C then rt	OPMB	88%

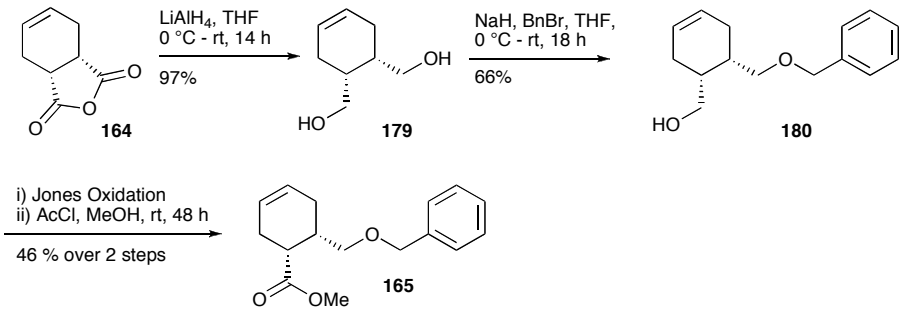
Initial studies by Jean[59] suggested that alkylation with an azide as a masked amine moiety might be successful. If this were successful, alkylation followed by Staudinger reduction would deliver amine **178** in 2 steps from the ester **(–)-165** (Scheme 3.3).



Scheme 3.3 Envisaged alkylation with azide.

3.3.2 Synthesis of a racemic system for model studies

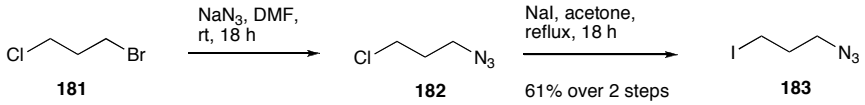
Rather than waste valuable chiral material while searching for a suitable alkylating agent a racemic synthesis of the ester **165** was developed. Following the procedure described by Schmidt,[54] the *meso*-anhydride **164** was reduced to the diol **179** in excellent yield by treatment with $LiAlH_4$ (Scheme 3.4). Mono-benzylation with sodium hydride and benzyl bromide delivered the mono-protected alcohol **180** in reasonable yield. The alcohol was then treated with Jones' reagent,[93] again following a procedure described by Schmidt,[54] to yield the carboxylic acid. Subsequent treatment with methanolic HCl delivered the desired racemic methyl ester **165**, in a moderate yield.



Scheme 3.4 Synthesis of racemic ester **165**.

3.3.3 Synthesis of iodo-azide 183

With the aim of optimising the reaction illustrated in Scheme 3.3, the iodo azide **183** was to be synthesised (X = I). This was prepared according to the procedure developed by Yao *et al*.[94] As noted by the authors, these compounds are likely to be explosive. Consequently all procedures involved in their synthesis were carried out behind blast shields, and on small scales. Following the procedure of Yao, 1-bromo-3-chloropropane **181** was treated with sodium azide in DMF to give the volatile chloro-azide **182**, which was used directly after in a Finkelstein reaction to deliver the iodo-azide **183** in a reasonable yield after aqueous workup (Scheme 3.5).



Scheme 3.5 Synthesis of azide **183**.

3.3.4 Potentially explosive nature of azide 183

As advised by Yao,[94] the azide **183** was treated at all times as though it was explosive. This explosive nature, however, was an assumption based only on its structure. In order to gain more of an understanding of the behaviour of this compound a series of tests were carried out on it by the Process Safety group at AstraZeneca, Macclesfield. The first of these was differential scanning calorimertry (DSC). DSC is a technique which measures the energy output of a substance as a function of the temperature to which it is heated. The energy output is measured in Jg^{-1}, and anything with an energy greater than 800 Jg^{-1} is considered to be a potential explosive.

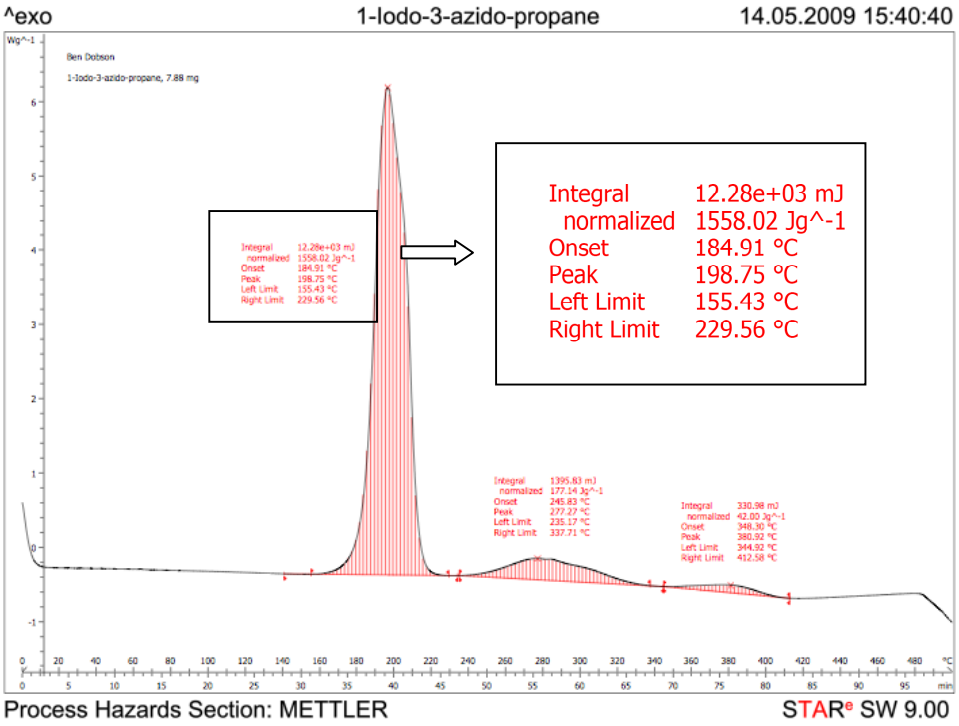


Figure 3.2 The DSC tracing for azide **183**.

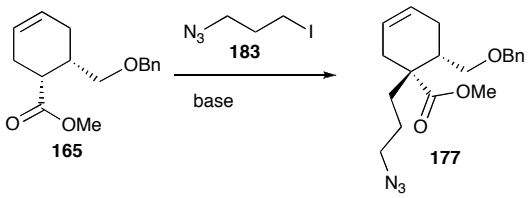
The DSC trace (Figure 3.2) suggests that if the azide were heated to ~180 °C it would decompose, giving off 1558 Jg^{-1} of energy, over the 800 Jg^{-1} suggested as the lower limit for a potential explosive. The DSC however, can give no measure of the explosive nature of the compound, only the energy it has the potential to release.

In order to determine if the high energy observed in the DSC had the potential to lead to explosion, the shock sensitivity of the compound was investigated. AstraZeneca carried out a further series of tests called Fall Hammer Testing. This involves weights being repeatedly dropped onto a small sample of the material from various heights, increasing in energy until an explosion or flame is observed and can be recorded by camera or microphone.

The results of the fall hammer testing were negative and no explosion or flame was observed. This result makes it unlikely that the material would explode under standard laboratory handling conditions, although as a precaution the azide was still handled behind a blast shield.

3.3.5 Alkylation studies

With the racemic ester **165** and azide **183** in hand, alkylation studies could begin. Attempts to optimise the alkylation reaction (Scheme 3.6) focussed on the base used to perform the deprotonation. A repeat of the reaction carried out by Jean (Entry 1, Table 3.2) treating the ester **165** with lithium hexamethyldisilylazide (LiHMDS), then quenching with the azide **183** gave the initially promising result of a 1:1.2 mixture of starting material and the desired product by ^{1}H NMR spectroscopy of the unpurified material. Column chromatography gave the desired product **177** in a 40% isolated yield, and the presence of the azide was confirmed by IR spectroscopy, with a stretching band observed at 2095 cm^{-1}.[95]



Scheme 3.6 Reaction to be optimised.

Increasing the equivalents of base to two had little effect on the isolated yield of the product, and the ^{1}H NMR spectrum of the unpurified reaction mixture suggested more side products were formed (Entry 2, Table 3.2). Increasing the loading of the azide under the same reaction conditions had the opposite effect to that desired: returning more starting material (Entry 3, Table 3.2). A change in the base from LiHMDS to lithium di*iso*propylamide (LDA), which was formed *in situ* by the treatment of di*iso*propylamine with *n*-butyl lithium, gave similar isolated yields (Table 3.2, Entries 4 and 5). Changing the cation to sodium by employing sodium hexamethyldisilylazide (NaHMDS) yielded only the starting material (Table 3.2, Entry 6). Changing the cation to potassium however, increased the yield markedly (Table 3.2, Entries 7 and 8). Using 1.1 eq. of KHMDS gave the desired product **177** in an 83% isolated yield.

Table 3.2 Changing the base in the synthesis of azide **177**.

Entry	**Base (equivs)**	**Azide (eqivs)**	**Yield of azide 177 and observations***
1	LiHMDS in THF (1 eq.)	1.1	1:1.2 Product: SM 40% yield
2	LiHMDS in THF (2 eq.)	1.1	~2:1 Product: SM 43% yield
3	LiHMDS in THF (1 eq.)	2.2	1:4 Product: SM
4	LDA made in situ (1 eq.)	1.1	1:1 by NMR 41% yield
5	LDA made in situ (2 eq.)	1.1	~2:1 Product: SM 51 % yield
6	NaHMDS in THF (1 eq.)	1.1	RSM
7	KHMDS in toluene (1 eq.)†	1	4:1 Product: SM
8	KHMDS in toluene (1.1 eq.)†	1.1	>19:1 Product: SM 83 %

* Product: SM ratios were determined by ^{1}H NMR spectroscopy.

† Supplied by Acros.

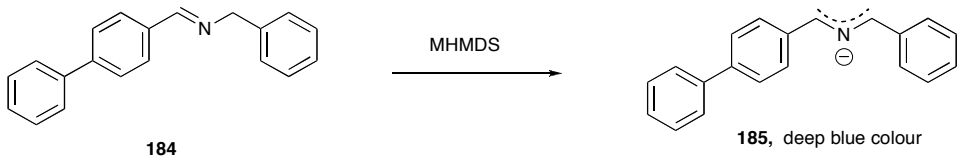
The excellent result observed by employing KHMDS was not as straightforward as appeared on first inspection. The KHMDS is supplied in toluene, while LiHMDS and NaHMDS are supplied in THF: is the increased yield observed a solvent or cation effect? A second observation was noted on attempting to repeat this reaction: KHMDS supplied by either Aldrich or Alfa Aesar gave much poorer yields than that supplied by Acros. While this reaction initially gave excellent yields it clearly required more detailed investigation.

3.3.6 Further investigations into KHMDS

It appeared the KHMDS solution supplied by Acros somehow differed from those supplied by Aldrich and Alfa Aesar. Identical reaction conditions to those employed

for the Acros material using the Aldrich or Alfa solutions resulted in lowered yields and the formation of undesired side products. A series of titrations gave some insight into the reasons behind these differences. Quenching a known volume of the KHMDS solution into water, then titrating the hydroxide generated against acid of an accurately known molarity gives a value for the total base concentration of the solution, including any hydroxide present as an impurity.

It is also possible to determine the HMDS concentration base by applying the procedure described by Duhamel *et al.*[96] Using indicator **184** (Scheme 3.7) the base is added dropwise to a known volume of butanol in xylene. The solution stays colourless until all the butanol is consumed, then the first drop of excess HMDS base deprotonates the indicator giving the anion **185** and an easily observable deep blue colour.



Scheme 3.7 HMDS titration indicator **184**.

A comparison of the total base and HMDS concentrations of the KHMDS obtained from the three different companies, illustrated in Table 3.3, gave an indication of the reasons behind the differing reactivities observed. All of the base supplied by Acros appeared to be HMDS, which the solutions supplied by Alfa and Aldrich contained significant quantities of KOH.

Table 3.3 HMDS and total base concentrations for KHMDS from different sources.

Entry	Supplier	Total base concentration	HMDS concentration
1	Acros	0.67 M	0.67 M
2	Aldrich	0.53 M	0.48 M
3	Alfa	0.82 M	0.71 M
4	Made from solid	0.25 M	0.24 M

As well as solutions of KHMDS it is possible to purchase solid KHMDS. The solid is very deliquescent and best stored and used in a glove box. The solid KHMDS gave the opportunity to investigate the effect of the mixed solvent systems generated by the commercial KHMDS in toluene.

Initially the solid was dissolved in toluene. Pleasingly, using this solution in the standard azide alkylation reaction illustrated in Scheme 3.6 gave excellent results, with yields of azide **177** comparable to those obtained using the solution purchased from Acros. Total base and Duhamel titrations confirmed there was very little KOH present in the solution produced (Entry 4, Table 3.3). Dissolving the solid in THF gave the non-commercial solution of KHMDS in THF. The solution was pale yellow, but became opaque on storage. It was possible to determine the total base of this solution by titration, but the Duhamel HMDS titration method failed for the THF solution; the end point was no longer a sharp colour change, instead the solution slowly darkened. Duhamel does not mention this, but nor does he make any attempt to titrate non-commercial THF solution of KHMDS. Using the THF solution in the azide alkyation reaction (Scheme 3.6) gave disappointing results. Analysis of the unpurified reaction mixture by ^{1}H NMR spectroscopy suggested an approximately 2:1 mixture of product: starting material, with a significant quantity of undesired side products. It was unclear if this result demonstrated the instability of the THF solution or indicated that toluene was required for the clean conversion observed with the commercial solutions of KHMDS.

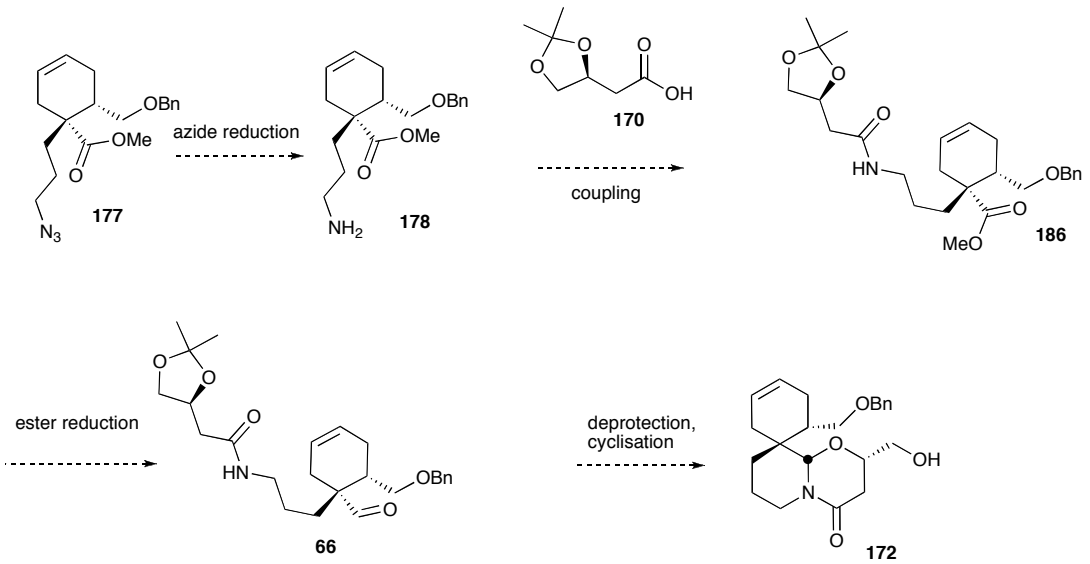
Various other modifications were made to the reaction in an attempt to understand it better. The addition of hexamethylphosphorylamide (HMPA), which is known to enhance the reactivity of KHMDS by decreasing the aggregation state, resulted in a complex mixture of products. Variations in the time the reaction was maintained at –78 °C for gave identical yields. Reverse addition, adding the ester to the base, also gave the same yield. Adding the base to a mixture of the ester and azide, removing the hold time resulted in a 1:1 mixture of starting material and product.

It seemed that a mixture of toluene and THF was required for the reaction to proceed to completion, and that KHMDS supplied as a solution from Acros was the easiest

way to ensure clean reactions. In the event of supply problems, then it was possible to buy solid KHMDS, store and weigh in a glove box, and achieve the same results.

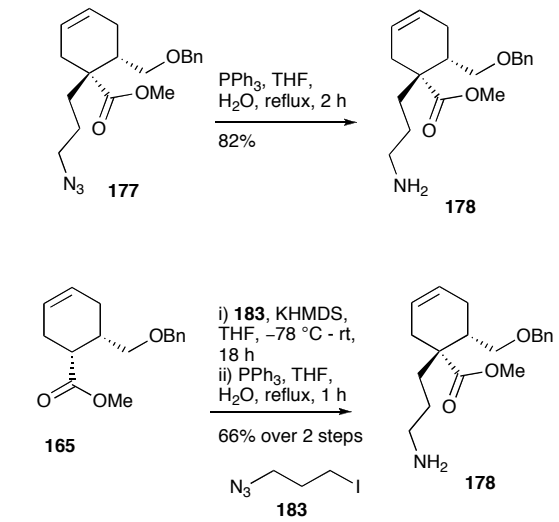
3.3.7 Reduction

With the alkylation process optimised, it was next hoped to reduce the azide **177** to generate the amino ester **178**, and then perform an amide coupling with acetal acid **170**, followed by reduction of the ester to the aldehyde and cyclisation as described by Schmidt[54] (Scheme 3.8).



Scheme 3.8 Envisaged shortened synthesis from azide **177**.

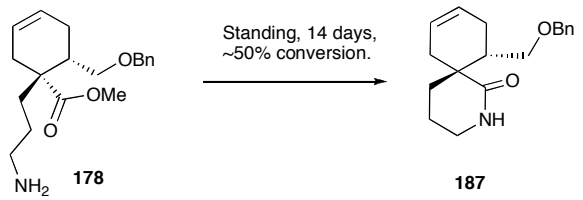
Following the procedure described by Schmidt for the classical Staudinger reduction from azide to amine,[97] good yields of amine **178** were obtained after purification by ion exchange resin (SCX column). The amine could also be purified by chromatography, but it was difficult to separate the triphenylphosphine oxide residues from the mixture. With the aim of minimising time spent handling the potentially explosive azide **183** in mind, the Staudinger reduction was tried on the unpurified reaction mixture resulting from the alkylation. This worked well, and purification by SCX allowed easy separation of any unreacted ester **165** or alkyl azide **183**, as well as triphenylphosphine (Scheme 3.9).



Scheme 3.9 Staudinger reduction and one pot alkylation-reduction procedure.

3.3.8 Stability of amine 178

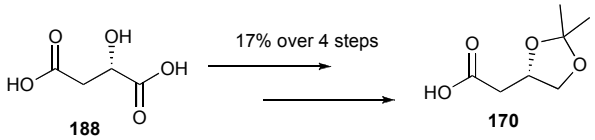
The amine **178** initially appeared stable, but on standing at room temperature the undesired spirocyclic lactam **187** was formed (Scheme 3.10). Using the amine within 2 days resolved this problem.



Scheme 3.10 Formation of undesired lactam **187**.

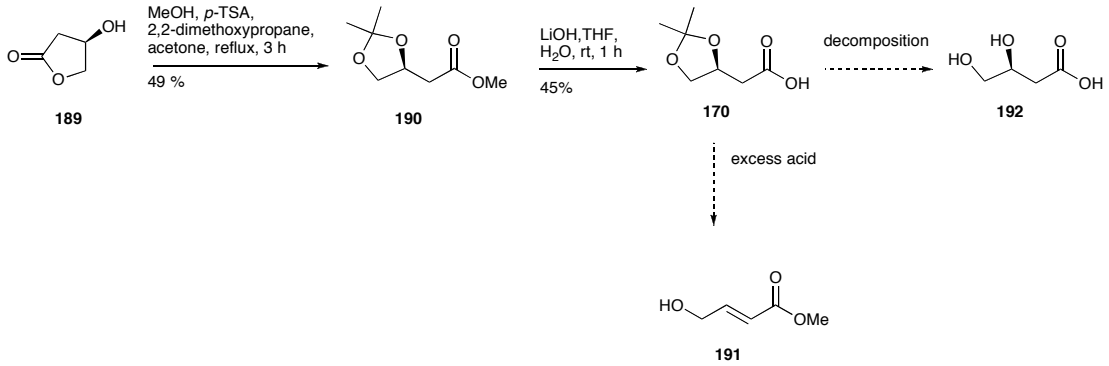
3.3.9 Acid synthesis

With the amine **178** in hand, attention was turned to the synthesis of the protected β-hydroxy acid **170** required for the amide coupling step. Schmidt[60] had prepared this in 4 steps from the commercially available diacid **188**, following a procedure described by Ley *et al*.[98]



Scheme 3.11 Schmidt's formation of acid **170**.

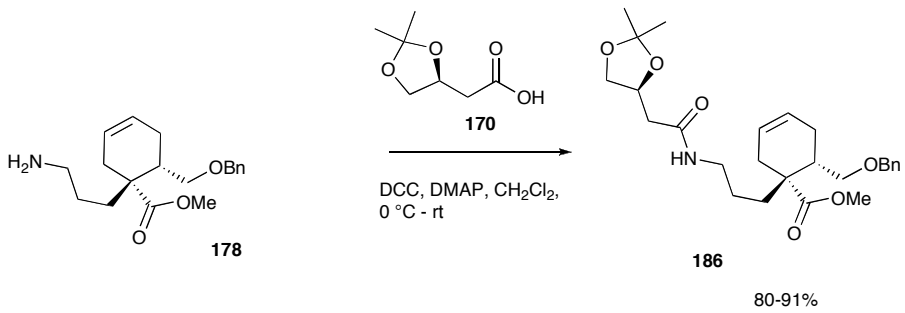
A literature search revealed a patent describing the synthesis of the same acid in a two step process from the commercially available chiral hydroxy butyrolactone **189** (Scheme 3.12).[99] Treatment of (*S*)-hydroxy butyrolactone **189** with MeOH and catalytic *p*-TSA in 2,2-dimethoxy propane and acetone gave the methyl ester **190** in moderate yield, and subsequent hydrolysis with LiOH delivered the desired acid **170**, again in moderate yield (Scheme 3.12). The ester hydrolysis is neutralised by the addition of oxalic acid, and yields were better when this was monitored by pH meter, as opposed to pH paper, as the acid was prone to β-elimination to **191** under acidic conditions. The acid was not very stable, and so was made and used on the same day. On prolonged storage the acetal appeared to deprotect and a very polar material (assumed to be the diol **192)** was isolated. Despite the modest yield (22% over two steps) this two step procedure was simpler and higher yielding than Schmidt's 17% over four steps.



Scheme 3.12 Shortened synthesis of acid **170**.

3.3.10 Amide coupling

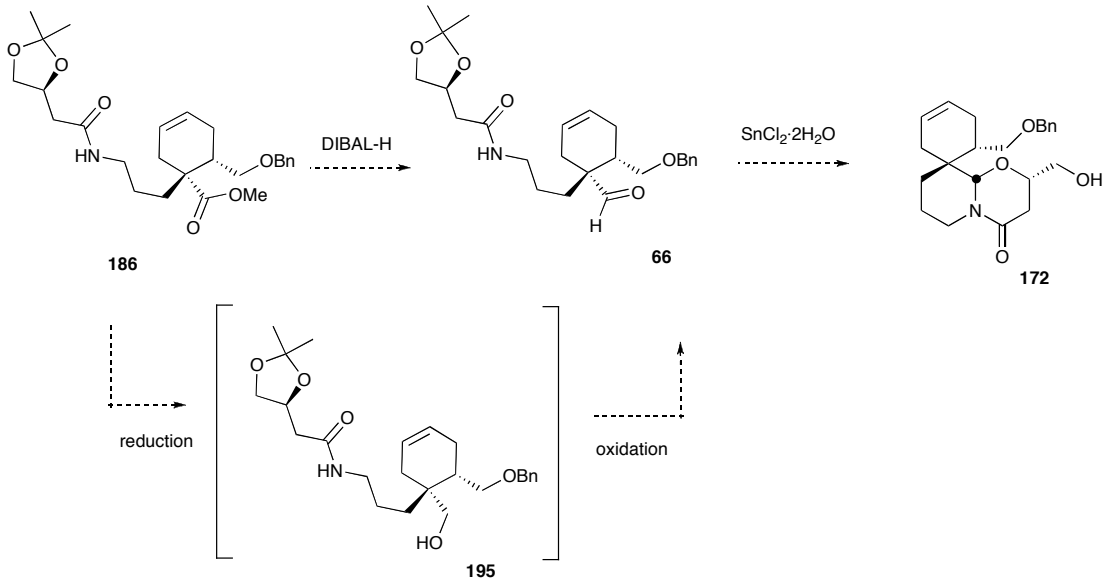
The amine **178** and acid **170** were successfully coupled employing DCC and catalytic DMAP to generate the amide **186** in excellent yield (Scheme 3.13).



Scheme 3.13 Amide coupling.

3.3.11 Ester reduction attempts

With the amide in hand the key step in the synthesis was now to reduce the ester to generate the desired aldehyde **66**. At this point the $SnCl_2 \cdot 2H_2O$ methodology described previously could be used to cyclise and generate the deoxy-ABC core unit of the target natural product. It was hoped that the ester would be directly reduced to the aldehyde by the action of di*iso*butylaluminium hydride (DIBAL-H), but if this was not possible then a reduction-oxidation sequence *via* alcohol **195** was proposed (Scheme 3.14).



Scheme 3.14 Envisaged synthesis of aldehyde **66** and its cyclisation.

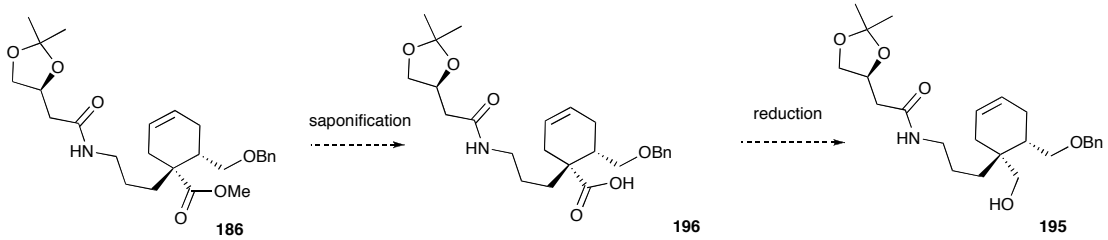
Disappointingly, after a number of attempts it appeared that the ester **186** was too sterically hindered to reduce to either the aldehyde or the alcohol. All attempts resulted in recovered starting material, followed by degradation to a very polar material, with apparent amide bond cleavage (Table 3.4).

Table 3.4 Attempts to reduce ester **186** to aldehyde **66**.

Conditions	Results
DIBAL-H, 2 eq., THF, –20 °C – rt, 18 h	Mixture of starting material **186** and degradation
DIBAL-H, 2 eq., THF, –78 °C, 1 h, then quenched at –15 °C	No reaction, recovered **186**
DIBAL-H, 3.5 eq., THF, 0 °C, 2 h	No reaction, then degradation
DIBAL-H, 4 eq., THF, –20 °C, 2 h	No reaction, then degradation
$NaBH_4$, MeOH, 65 °C, 18 h	Degradation
$LiAlH_4$, 1 eq., THF, rt, 1 h	No reaction, recovered **186**
$LiAlH_4$, 1 eq., THF, 50 °C, 2 h	No reaction, then degradation
SuperHydride 0 °C – rt, 18 h	No reaction

3.3.12 Ester Saponification

With the apparent difficulty of direct ester reduction, attention was turned to the possibility of saponification of the ester **186** to generate the acid **196**. It was hoped it would then be possible to reduce **196** (Scheme 3.15).



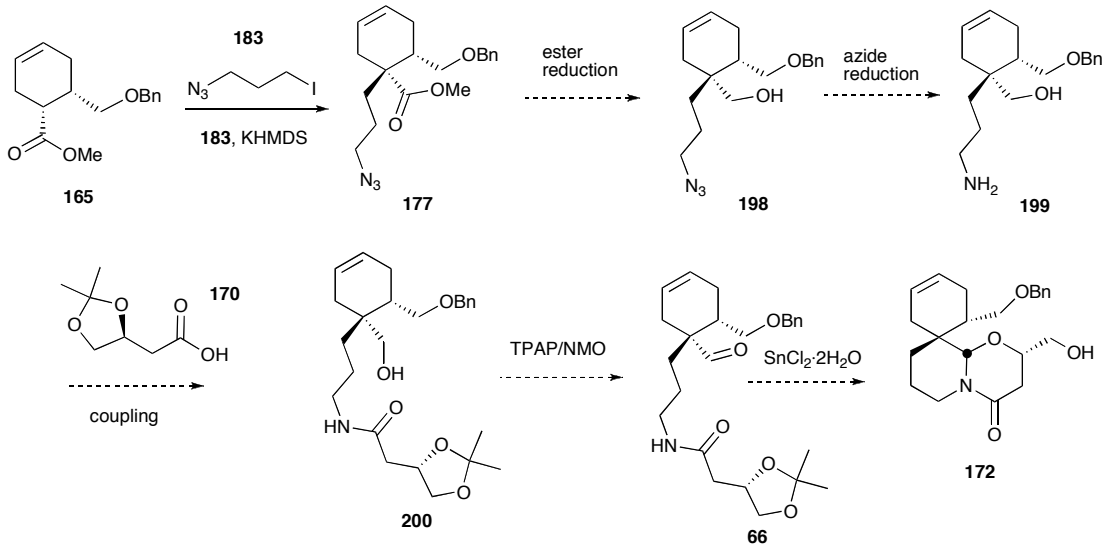
Scheme 3.15 Envisaged saponification of ester **186** to acid **196**.

Disappointingly, on exposure of the ester to saponification conditions (TMSOK, NaOH) no reaction was observed, followed by degradation if forcing conditions were employed.

At this point it was decided to attempt to reduce the ester at an earlier stage in the synthesis.

3.3.13 Proposed early reduction

After alkylation of the ester with the azide, reduction of the ester to the alcohol was envisaged, generating the hydroxy-azide **198**; then a further reduction of the azide to the amine would be attempted. It was then proposed to subject the amino alcohol **199** to a sequence of coupling, oxidation and cyclisation similar to those described earlier (Scheme 3.16).

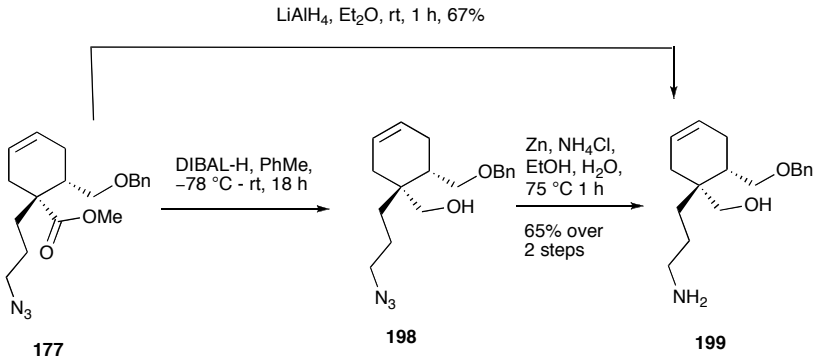


Scheme 3.16. Envisaged earlier reduction.

This sequence should deliver the alcohol **200**, which is known, after oxidation to the aldehyde **66**,[54] to cyclise to the desired spirooxaquinolizidinone system.

3.3.14 Azide and ester reduction

Reduction of **177** with DIBAL-H gave a more polar compound (Scheme 3.17), which was shown by IR spectroscopy to still contain the azide moiety (ν = 2095 cm^{-1}). Mass spectrometry confirmed the compound to be **198**. In a further step, the azide was easily reduced to the amine under the mild conditions described by Lin and co-workers using zinc and ammonium chloride[100] generating the very polar desired amino alcohol **199**.



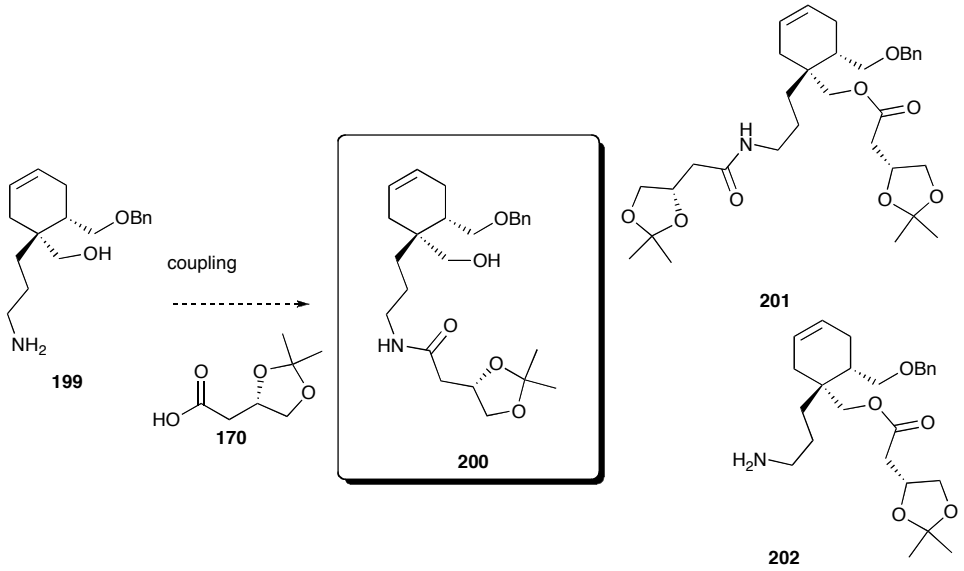
Scheme 3.17 Synthesis of amino alcohol **199**.

Pleasingly, the yield could be maintained and the sequence shortened, by reducing both the ester and azide in a single step. This was achieved with lithium aluminium hydride in diethyl ether at room temperature, and delivered the desired amino alcohol **199** in 67% yield. Workup conditions were key: aqueous workup resulted in the loss of most of the very polar **199**, as did filtration through Celite. The $LiAlH_4$ reaction could be quenched by the addition of Glauber's salt ($Na_2SO_4 \cdot 10H_2O$) which was then removed by filtration. Purification of the filtrate by SCX chromatography delivered the product **199**.

The reduction could also be conducted directly on unpurified **177** with no purification of the azide after alkylation. The trace of ester **165** remaining after the alkylation was removed by the SCX purification. The yields were comparable with the two step process, and easier to perform.

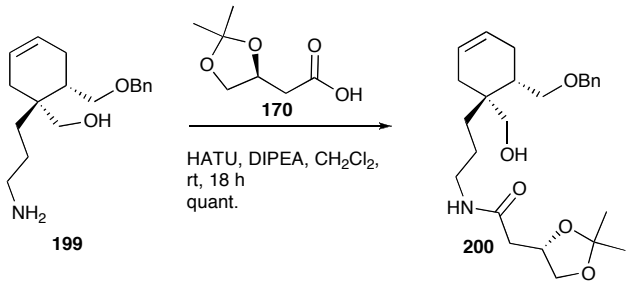
3.3.15 Amide coupling

With amino alcohol **199** in hand the next stage of the shortened synthesis was to couple this to acid **170**. This was complicated by the free alcohol in the molecule, and care was needed to minimise the formation of ester **202**, or the di-coupled compound **201**.



Scheme 3.18 Envisaged coupling of amino alcohol **199** to acid **170**, and possible byproducts.

Treatment of amino alcohol **199** with DCC and catalytic DMAP, under identical conditions to those employed in the previous synthesis (Scheme 3.13), generated the product **200** in good yield (75%), but we were unable to separate it from the DCU produced in the coupling. T3P® gave the desired compound **200** in 67% yield, but the di-coupled side product **201** was present in ~3% yield. We were pleased to observe that using HATU as the coupling reagent gave the desired product **200** in quantative yield after chromatography. The di-coupled product **201** was not observed.

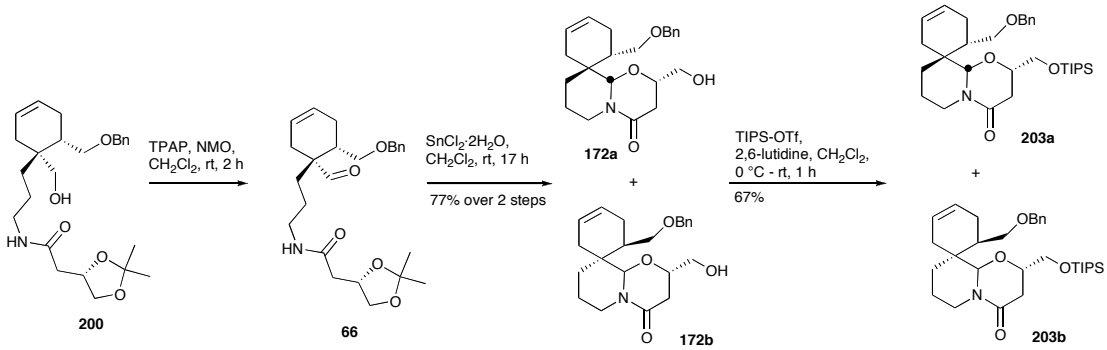


Scheme 3.19 HATU coupling of amino alcohol **199** and acid **170**.

3.3.16 Final steps in the racemic route

The final steps of the synthesis were followed according to the procedure developed by Schmidt and McAllister[54] and generated an inseparable 1:1 mixture of the known diastereoisomeric spirooxaquinolizidinones[60] **203a** and **203b**, in a good yield over 3 steps (Scheme 3.20). The diastereoisomers arise from the racemic amine **199**, coupled with the chiral acid **170**. ^{1}H NMR data was comparable to that published for **(–)-203**[54]

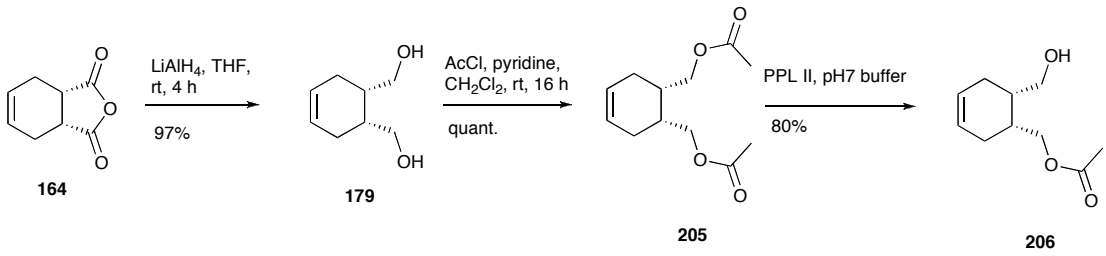
and for similar diastereoisomeric spirooxaquinolizidinones synthesised by Schmidt.[60] It was planned to use enantio-enriched material in later steps, now that the route had been optimised on the racemic system.



Scheme 3.20 Final racemic steps in the ABC synthesis.

3.3.17 Enantio-enriched synthesis

A synthesis of the enantio-enriched ester **(–)-165** was developed by Schmidt and McAllister.[54] This chemistry was repeated to generate the bisacetate **205** (Scheme 3.21) by the reduction of anhydride **164** to the diol **179** and acetate protection with acetyl chloride and pyridine. The bisacetate **205** was then treated under the desymmetristaion conditions first described by Von Langen and co-workers[101] and applied to this system by Schmidt.[54] The enzymatic hydrolysis generates AcOH, which would denature the enzyme if allowed to build up. Adding base at the beginning of the reaction would also render the enzyme inactive, and so the pH is monitored and NaOH added by an autoburette.*

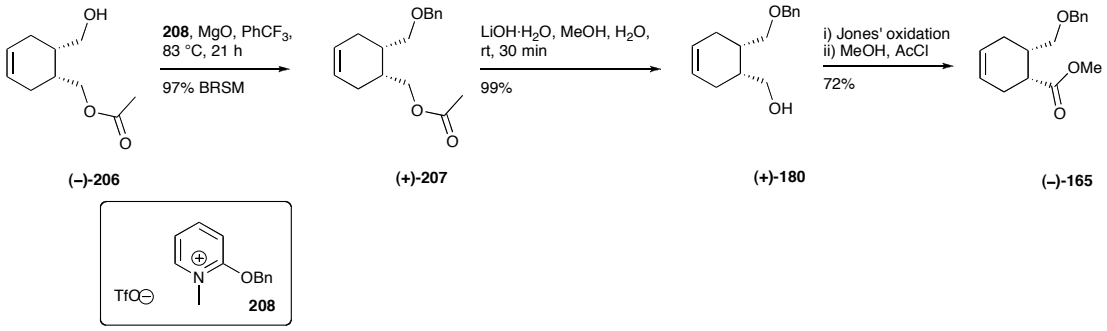


Scheme 3.21 Synthesis of acetate **206**.

The final stages of the ester synthesis were repeated exactly as described by Schmidt.[54] Benzylation under neutral conditions was achieved in good yield with Dudley's reagent.[102] This was required as the substrate had been shown to epimerise under standard basic or acidic conditions.[54] Acetate hydrolysis was followed by the

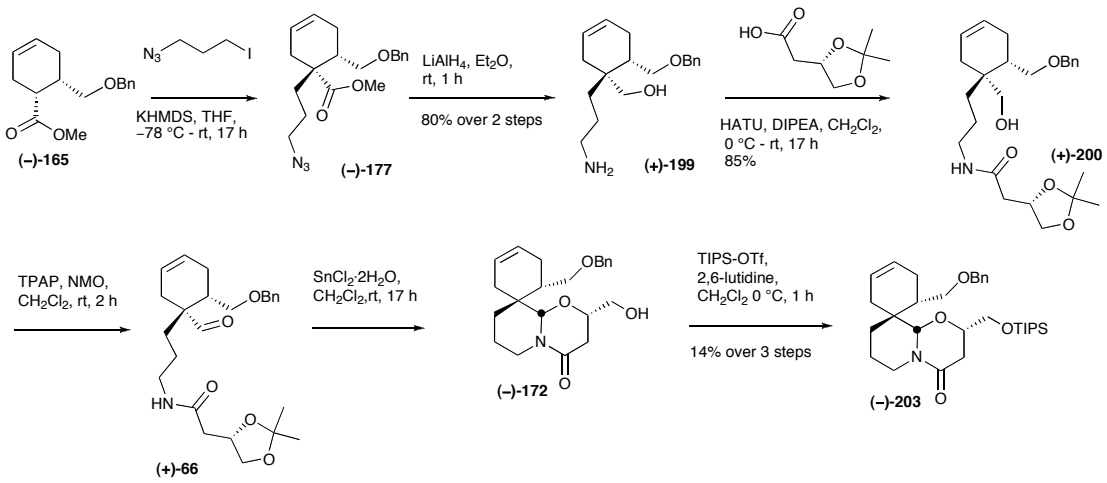
* Carried out at AstraZeneca, Macclesfield. Thanks to Ian Ashworth and Jan Cherrywell of the Process Support group at AstraZeneca for setting this equipment up.

previously described oxidation and ester formation to give ester **(–)-165** in good yield. ^{1}H NMR data of **(–)-165** was consistent with literature and $[\alpha]_D$ {$[\alpha]_D$ –14.9 (*c* 1.2, $CHCl_3$) (Lit.[54] 15.5 (*c* 1.1, $CHCl_3$)} confirmed the *e.e.* to be comparable with that obtained by Schmidt (94%).



Scheme 3.22 Synthesis of ester **(–)-165**.

The ester **(–)-165** was then subjected to the shortened synthesis developed on the racemic system (Scheme 3.23).

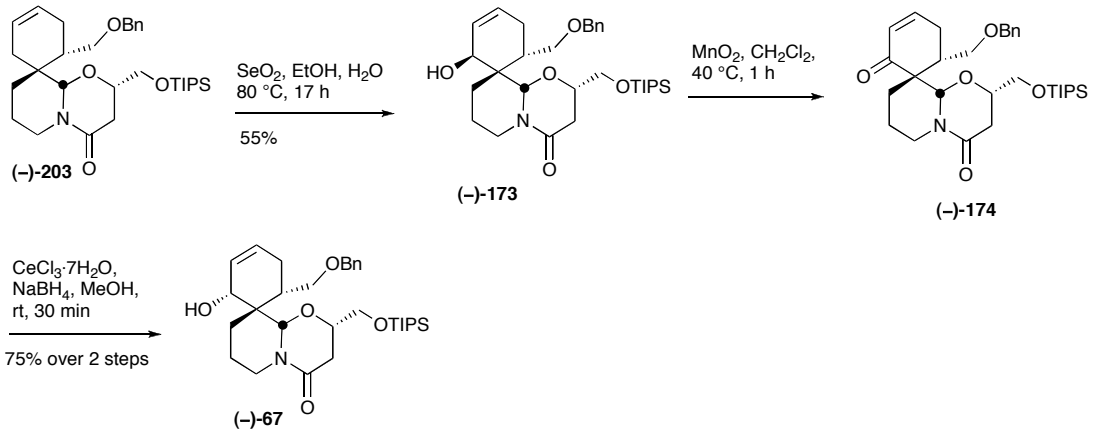


Scheme 3.23 Synthesis of chiral ABC core unit.

The alkylation, reduction and coupling reactions proceeded in yields comparable to those observed on the racemic system, and delivered the alcohol **(+)-200**. Problems were experienced with purification of the final product **(–)-203** as there was a leak in the inlet system of the purification system and some material was lost, which lowered the yield to 14% over the oxidation, cyclisation, and TIPS protection steps. NMR data for **(–)-203** matched that obtained by Schmidt.[54]

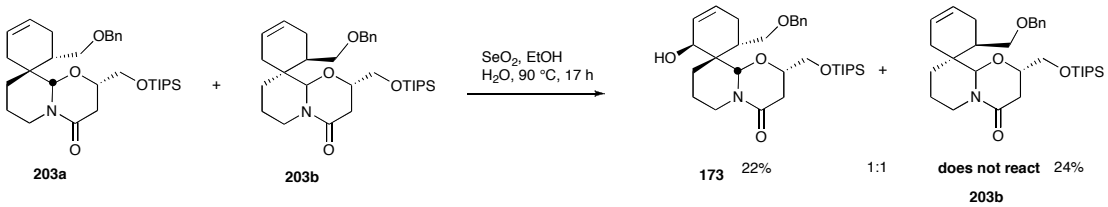
3.3.18 Allylic oxidation.

The final steps described by Schmidt[54] in the synthesis of the fully functionalised ABC core unit involved selenium dioxide mediated allylic oxidation to furnish the alcohol **173**. This was then inverted by an oxidation and Luche reduction sequence, giving the desired isomer **(–)-67**. Schmidt's work proved troublesome to repeat on the mixture of diastereoisomers **203a** and **203b** with only small amounts of oxidation being observed and mainly recovered starting materials. Pleasingly, however, the chemistry was repeated on the chiral system **(–)-203** in yields comparable to Schmidt's. The key to this chemistry lay in the ethanol used in the selenium dioxide oxidation. Initial attempts used dry ethanol, when in fact slightly wet ethanol was required. Using 95:5 ethanol: water gave the best results (Scheme 3.24). All data for **(–)-67** was in good agreement with the published data.[54]



Scheme 3.24 Allylic oxidation on the chiral ABC core unit **(–)-67**. Reactions carried out by Unsworth.

Applying these modified "wet" conditions to the racemic system **203a** and **203b** revealed a second observation: the "correct" diastereoisomer of the ABC core unit **203a** reacted under these conditions, leaving the "wrong" diastereoisomer **203b** untouched and easily removed by chromatography (Scheme 3.25).



Scheme 3.25 Allylic oxidation acts only on one isomer of ABC core unit. Reaction carried out by Unsworth.

3.4 Conclusions

A shortened synthesis of the ABC core unit of ’upenamide is described, the key step utilising an alkylating agent containing an azide as a masked amine moiety. This modification allowed the synthesis to be shortened from the published 21 steps (17% overall yield) to 16 steps (9% overall yield) and allowed easier access to large quantities of material for coupling studies. The problematic selenium dioxide mediated allylic oxidation was resolved by the use of 95:5 ethanol: water as a solvent.

Attention was now turned to synthesis of the bicyclic DE core unit.

Chapter 4 – Results and discussion 3: DE core unit

4.1 Previous work on DE core unit

The DE core unit of ’upenamide is a *cis*-fused bicyclic hemi-aminal. As discussed in the Introduction (Chapter 1), only the relative stereochemistry of the system is known. Thus, for a successful total synthesis of ’upenamide, any route developed to the DE core unit should give access to both of the possible enantiomers (Figure 4.1). A synthesis of the DE core unit was developed in the Taylor group by Ménard-Moyon,[53] but was lengthy and subsequently proved difficult to reproduce,[103] and so a new route was sought.

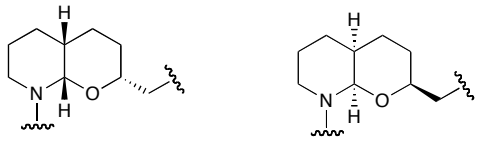
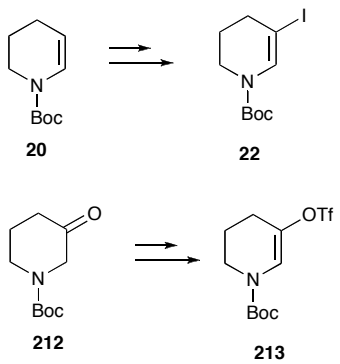


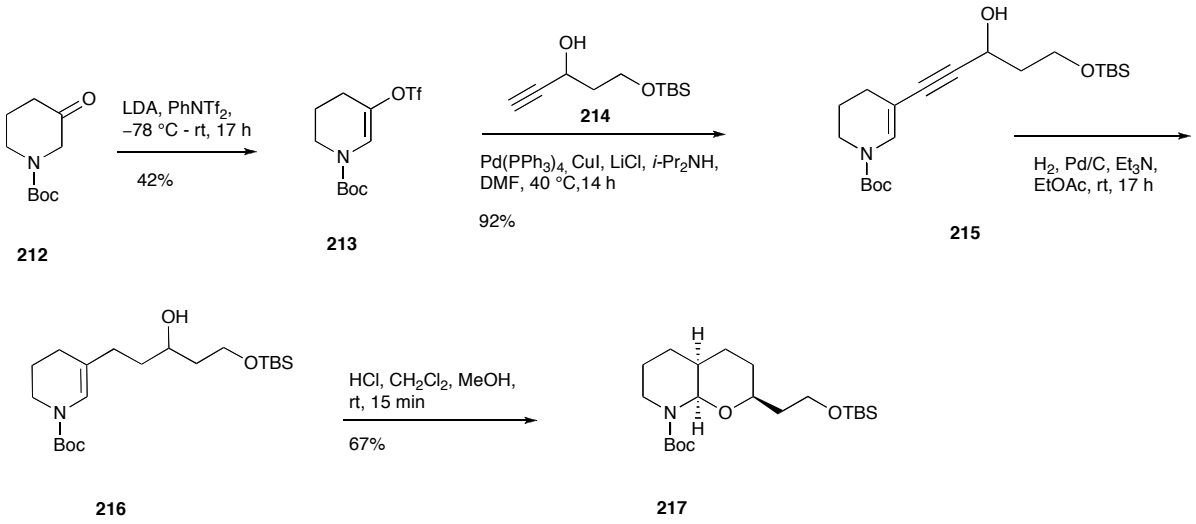
Figure 4.1 Both enantiomers of the DE core unit.

Jean developed a second route to the DE core unit,[59] based closely on the route published by Sulikowski.[52] The route described by Sulikowski begins from the ene-carbamate **20**, which he describes only as being “prepared by electrochemical oxidation,” and elaborated this to the iodide **22**. To avoid the potentially problematic undescribed electrochemistry step, Jean instead began by forming the triflate **213** from the piperidone **212** (Scheme 4.1).



Scheme 4.1 Sulikowski’s iodide and Jean’s triflate.

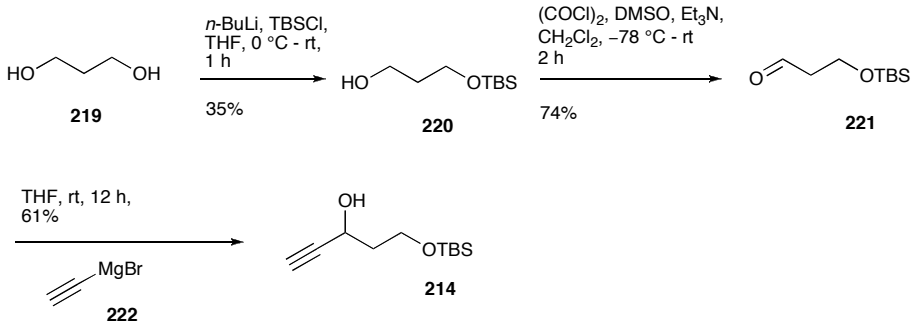
Triflate **213** was formed by treatment of piperidone **212** with LDA, and was coupled with alkyne **214** under Sonogashira coupling conditions in an analogous reaction to Sulikowski's iodide **22**. This delivered the enyne **215** in excellent yield (92%). The selective alkyne hydrogenation described by Sulikowski for the longer chain system worked well, and treatment with HCl in dichloromethane and methanol cyclised alcohol **216** to deliver the TBS-protected DE core unit **217** in good yield (Scheme 4.2).



Scheme 4.2 Jean's synthesis of the DE core unit.

As discussed in Chapter 1 (Section 1.5.2) Sulikowski observed the formation of a single isomer of the DE core unit on cyclisation effected by treatment with HCl. By analysis of the ^{1}H NMR data he assigned this as the desired *cis*-fused hemi-aminal: "The ring fusion stereochemistry was assigned based on the small constant observed between the ring fusion protons (ca. $J < 2$ Hz) and chemical shift of the hemiaminal proton ($\delta > 4.0$)."[52] Pleasingly, we also observed this in the ^{1}H NMR spectrum of **217**. As racemic alcohol **214** was used for the coupling studies the products produced were a racemic mixture of the two *cis*-fused ring products.

The alcohol **214** employed in the Sonogashira coupling was synthesised by Jean following the procedure described by Gung and co-workers.[104] Treatment of 1,3-propane diol with *n*-butyllithium and TBSCl gave the mono-protected **220**, which was subjected to Swern oxidation to deliver the aldehyde **221**. Treatment of the aldehyde **221** with ethynylmagnesium bromide **222** gave the desired alkyne **214** (Scheme 4.3).



Scheme 4.3 Synthesis of alcohol **214**.

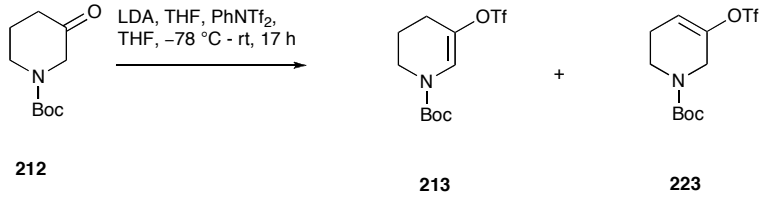
4.2 Aims and objectives: DE core unit synthesis

The first aim for this part of the project was to optimise the low yielding formation of triflate **213** (Scheme 4.2). This would be followed by the asymmetric preparation of both enantiomers of alcohol **214** (Scheme 4.2). Both enantiomers of **214** would then be used in synthesis illustrated in Figure 4.2, with the aim being to deliver both enantiomers of the DE core unit. At this stage, the later direction of the synthesis would depend on coupling strategies being developed in parallel to this work.

4.3 Results

4.3.1 Triflate formation

The yields obtained in Jean's synthesis were high, aside from the initial triflate formation step. The modest yield of **213** (Scheme 4.2) could be explained due to the uncontrolled formation of undesired regioisomer **223** (Scheme 4.4).



Scheme 4.4 Formation of triflates **213** and **223**.

In the current work investigations were carried out to determine if it was possible to improve this yield. The conditions developed by Jean involved treating the carbamate **212** with LDA (formed *in situ* from di*iso*propylamine and *n*-butyllithium), using *N*-phenyl-bis(trifluoromethanesulfonimide) ($PhNTf_2$) as the triflate source (Entry 1,

Table 4.1). The reaction was carried out at –78 ºC and allowed to warm slowly to room temperature overnight. The workup comprised concentrating the reaction, then immediately purifying by column chromatography. It seemed important to column the product quickly, as on standing it quickly turned into a dark brown material, insoluble in all solvents investigated, which was assumed to be polymeric. For this reason it was hard to quantify the amount of **223** obtained in each case, as attention was focussed on obtaining **213** and using it quickly.

Zheng and co-workers[105] claimed an 80% yield of triflate **213** and the formation of single isomer under very similar reaction conditions to those initially tried, with the only difference being that the reaction was warmed to room temperature quickly. This was tried (Entry 2, Table 4.1) but the reported result was not reproduced, in fact a lower yield was obtained, and the undesired isomer **223** was observed.

It was hoped that running the reaction in a less coordinating solvent than THF would encourage a chelation interaction between the carbamate protecting group and the metallic base, favouring removal of the α-proton. This would lead to preferential formation of the desired isomer (Figure 4.2). This was attempted by employing both diethyl ether and toluene as solvent (Entries 3 and 4, Table 4.1) but resulted in the formation of undesired side-products and lower yields. Once again the undesired isomer **223** was observed, but not quantified.

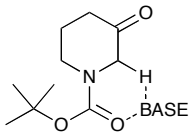


Figure 4.2 Possible chelation effect.

A total synthesis paper by Overman *et al*. described problems with triflate regioisomers in similar systems.[106] Their best results were achieved by using LiHMDS as the base, but when this was tried (Entry 5, Table 4.1) it gave a lower yield than LDA. A change in workup conditions to incorporate an aqueous workup (Entry 6, Table 4.1) then confirmed the suspicion that the product **213** is unstable to water.

Classic conditions for thermodynamic enolate formation with either triethylamine and heating[107, 108] (Entry 7, Table 4.1) or di-*tert*-butylmethylpyridine (DTBMP) and heating[109, 110] led only to decomposition, in the various solvents examined (Entries 8-11).

Finally, a less hindered version of LDA was employed: the base resulting from the treatment of diethylamine (DEA) with *n*-butyllithium. Disappointingly, however, this led only to a small increase in yield – 48% when allowed to warm to room temperature overnight, and a comparable 46% yield when quenched at –78 °C. In this case the undesired regioisomeric triflate **223** was observed but not isolated.

Table 4.1. Attempted optimisation of formation of triflate **213**

Entry	**Base**	**Solvent**	**Temp**	**Time**	**Triflate source**	**Workup**	**Yield 213**
1	LDA†	THF	–78 °C	To rt o/n	$PhNTf_2$	Concentrated	42%
2	LDA†	THF	–78 °C	To rt quickly	$PhNTf_2$	Concentrated	30%
3	LDA†	Et_2O	–78 °C	To rt o/n	$PhNTf_2$	Concentrated	24%
4	LDA†	toluene	–78 °C	To rt o/n	$PhNTf_2$	Concentrated	35%
5	LiHMDS	THF	–78 °C	To rt o/n	$PhNTf_2$	Concentrated	38%
6	LiHMDS	THF	–78 °C	To rt o/n	$PhNTf_2$	Aqueous workup (EtOAc + water)	0%
7	Et_3N	DMF	80 °C	12 h	$PhNTf_2$		0% *
8	DTBMP¶	DCE	90 °C		$PhNTf_2$	n/a	0% *
9	DTBMP¶	toluene	80 °C		$PhNTf_2$	n/a	0% *
10	DTBMP¶	CH_2Cl_2	rt		Tf_2O	n/a	0% *
11	DTBMP¶	DCE	60 °C		Tf_2O	n/a	0% *
12	DEA+*n*-BuLi	THF	–78 °C	To rt o/ns	$PhNTf_2$	Concentrated	48%
13	DEA+*n*-BuLi	THF	–78 °C	2 h	$PhNTf_2$	Quenched at –78 °C by adding NH_4Cl	46%

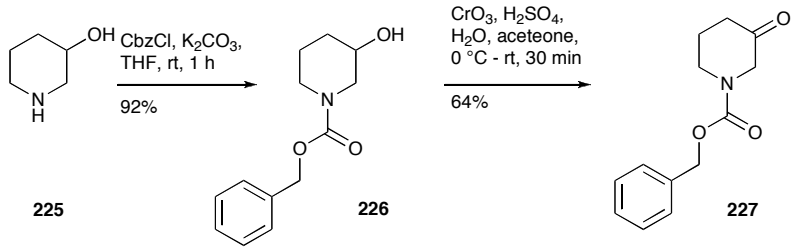
¶ 2,6-di-*tert*-butyl-4-methylpyridine.

* Decomposition was observed.

† made *in situ*

Overman[106] found that greater selectivity could be obtained in similar systems by changing the nature of the nitrogen protecting group on the piperidone to either a Cbz group or a tosyl group. Zheng[105] claimed full regioselectivity with the Cbz group.

The Cbz-protected piperidone **227** was synthesised from 3-hydroxypiperidine **225** according to the procedure described by Aitken *et al*.[111] followed by Jones oxidation[93] to the piperidone (Scheme 4.5).



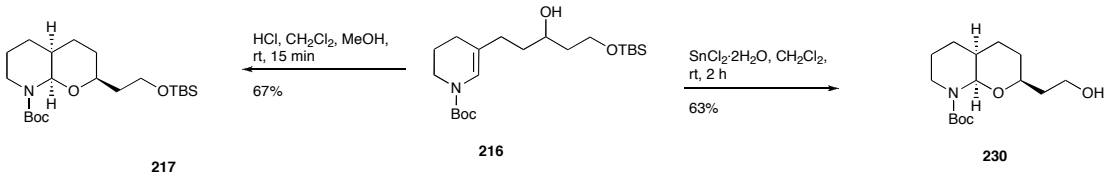
Scheme 4.5 Synthesis of Cbz-protected piperidone **227**.

With the Cbz-protected piperidone in hand, triflate formation was attempted. Disappointingly this gave lower yields than the Boc-protected compound when treated with LDA and $PhNTf_2$ (23-24%), and only decomposition on treatment with DTBMP.

At this point it was concluded that further study was not worthwhile. As this step was the first in the synthesis a low yield could be tolerated here.

4.3.2 Stannous dichloride dihydrate cyclisation

Sulikowski's HCl-mediated cyclisation conditions worked well to deliver the TBS-protected DE core unit **217**. We were delighted to observe that on applying the previously developed $SnCl_2 \cdot 2H_2O$ methodology conditions to the cyclisation precursor **216** the unprotected DE core unit **230** was produced in comparable yield to Sulikowski's HCl method (Scheme 4.6). Direct access to the free alcohol **230** without a separate deprotection step should allow for easier elaboration to the final skeleton of 'upenamide.

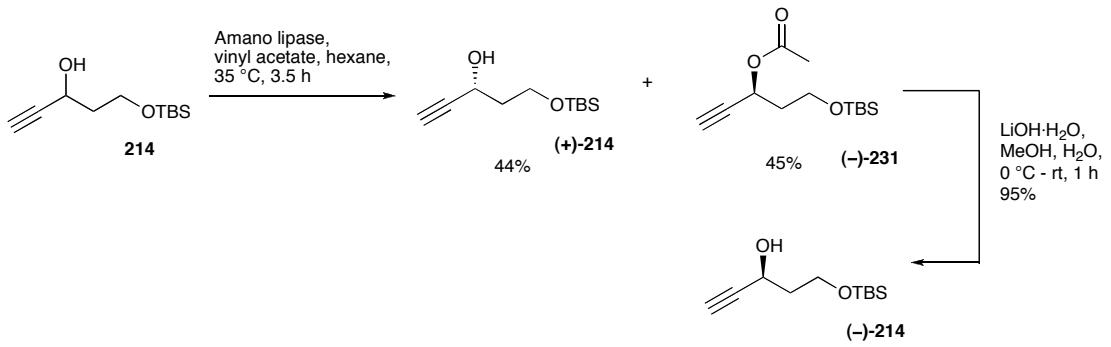


Scheme 4.6 Treatment of cyclisation precursor **216** with $SnCl_2 \cdot 2H_2O$ and HCl.

4.3.3 Synthesis of enantio-enriched alcohol 214

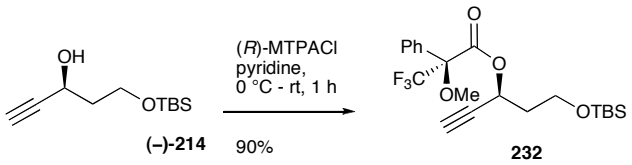
Using either enantiomer of alcohol **214** in the synthesis described in Scheme 4.2 would allow both enantiomers of the DE core unit to be produced. With a simple route to the racemic alcohol **214** in hand, and the requirement for both enantiomers, resolving the chiral material seemed an attractive option.

This resolution was achieved according to the procedure of Gung,[104] resolving alcohol **214** with lipase AK from *pseudomonas* sp. and vinyl acetate. The enzyme selectively acetylated the (*S*)-(–)-enantiomer of the alcohol, giving acetate **(–)-231** and alcohol **(*R*)-(+)-214**. Chromatographic separation, followed by hydrolysis of the acetate with lithium hydroxide gave the desired alcohols **(–)-214** and **(+)-214** in good yield (Scheme 4.7).



Scheme 4.7 Resolution of alcohol **214**.

The e.r. of **(+)-214** and **(–)-214** were determined by Mosher's ester analysis: both enantiomers were treated with (*R*)-MTPACl to generate the corresponding Mosher's ester (Scheme 4.8, Figure 4.3).



Scheme 4.8 Mosher's ester of (*S*)-**(–)-214**.

Integration of signals in the ^{19}F NMR spectrum suggested an e.r. of 93:7 for the (*S*)-compound **(–)-214**. Identical conditions generated the ester **233** from (*R*)-**(–)-214** with ^{19}F NMR suggesting an e.r. of 90:10 for the alcohol **(–)-214**.

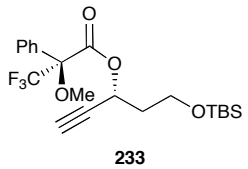
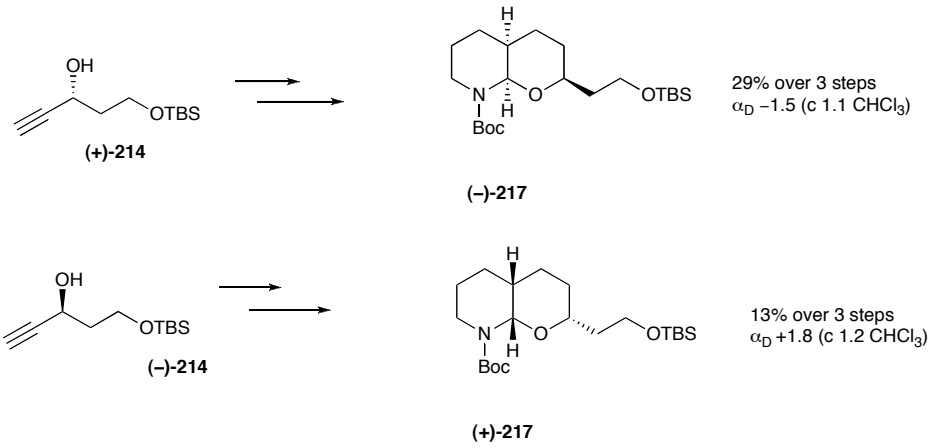


Figure 4.3 Mosher's ester of *(R)*-**(+)-214**.

4.3.4 Enantio-enriched DE synthesis

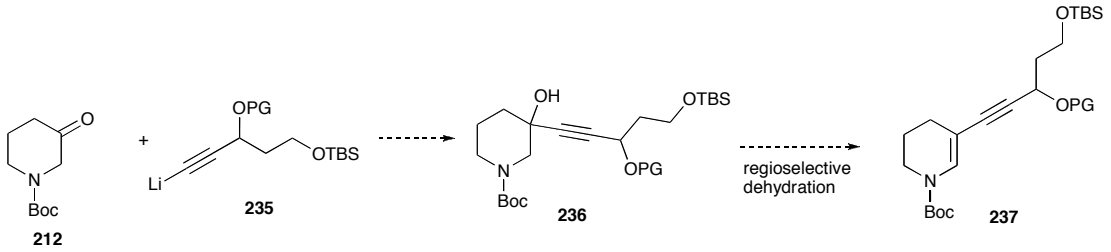
With the enantio-enriched alcohols **(–)-214** and **(+)-214** in hand the synthesis of both enantiomers of the DE core unit was straightforward. Minimal purification of the intermediate alkyne gave the best results, and the alcohols **(–)-217** and **(+)-217** were successfully synthesised (Scheme 4.9), using the conditions described in Scheme 4.2. The Sonogashira coupling was problematic in both cases – reducing the yield to 29% for the **(–)-217** and 13% for the **(+)-217**. Repeating Jean's synthesis proved this reaction to be remarkably capricious, appearing to require rigorously dry solvents, flame dried reagents and glassware for high yields. With these modifications yields were still very variable. Alternatives to the Sonogashira strategy were investigated on the short chain DE core **217** (Section 4.3.5) and later again when the extended chain DE core was investigated (see Section 4.3.9). The e.r. of **(–)-217** and **(+)-217** were not determined, but it was assumed that the 93:7 and 90:10 ratio observed in alcohols **(+)-214** and **(–)-214** were retained in the products **(–)-217** and **(+)-217**.



Scheme 4.9 Synthesis of chiral DE core units.

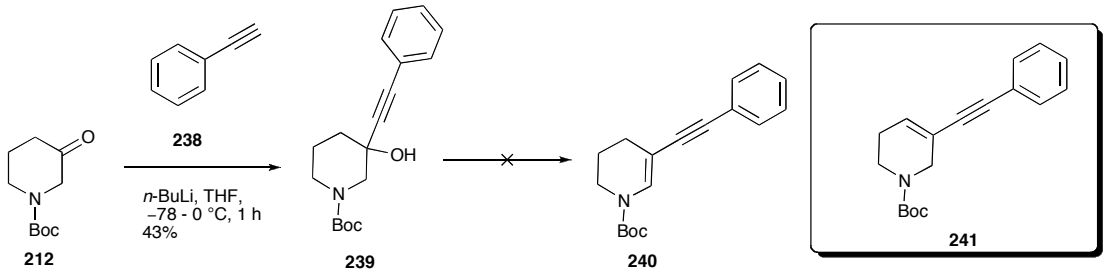
4.3.5 Alternative acetylene route

Given the regiochemistry problems encountered with the triflate formation and the capricious nature of the Sonogashira reaction an alternative sequence illustrated in Scheme 4.10 was also considered. If it were possible to react the protected piperidone **212** with the lithium acetylide **235** to afford the alcohol **236**, then regioselective dehydration would yield the desired compound **237**, potentially removing the problem of triflate regioselectivity.



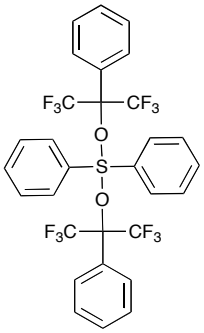
Scheme 4.10 Envisaged nucleophilic attack and dehydration sequence.

A model system utilising lithium phenylacetylide **238** formed *in situ* from phenyl acetylene and *n*-butyllithium successfully formed the alcohol **239** (Scheme 4.11).

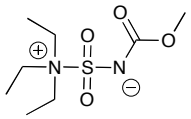


Scheme 4.11 Model system to investigate the dehydration chemistry.

Disappointingly, under all the dehydration conditions examined, the undesired isomer **241** predominated, or no reaction was observed (Table 4.2). Martin's sulfurane **242** (Figure 4.4) at 40 °C gave the most promising results, but all attempts to push the reaction to completion resulted in the isolation of only the undesired isomer in very low yield (13%). Thus, the addition – elimination route was abandoned.



242 Martin's sulfurane



243 Burgess reagent

Figure 4.4 Martin's sulfurane and Burgess reagent.

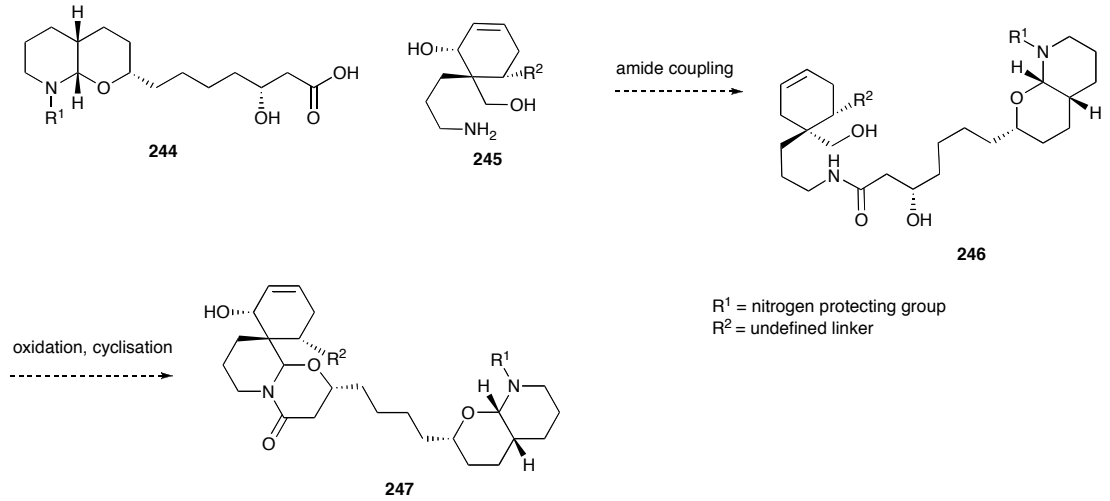
Table 4.2. Attempted elimination to alkene **240**.

Entry	Conditions	Result
1	MsCl, Et_3N, CH_2Cl_2, 0 °C - rt, 5 min, Then PhMe, DBU, rt - 100 °C	Recovered mesylate (96% yield)
2	$BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C - rt	RSM
3	Burgess Reagent **243**, PhMe, 80 °C 19 h	**241** (100% yield)
4	Burgess Reagent **243**, PhMe, rt, 19 h	RSM
5	Burgess Reagent **243**, PhMe, 40 °C, 4 h	**241**
6	Martin's Sulfurane **242**, CH_2Cl_2, rt, 2 h	No reaction
7	Martin's Sulfurane **242**, CH_2Cl_2, 40 °C, 2 h	1.3:1 **240**:**241** 20% isolated yield + RSM

4.3.6 DE core unit with an extended side chain

With the short chain DE core unit successfully completed the project began to move in a different direction. In collaboration with Dr W. Unsworth (Postdoctoral Researcher), attention was turned to an alternative route: the possibility of installing the saturated linking chain earlier in the synthesis. The idea was for the DE core unit to contain the four carbon saturated chain, and a β-hydroxy acid functionality. The β-

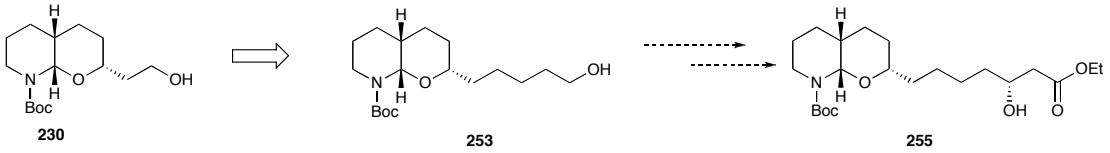
hydroxy acid moiety would, after coupling to amine **245**, oxidation and cyclisation, make up the "A" ring of the ABC system. In theory this should deliver the ABC and DE core units likened through the saturated chain (compound **247**, Scheme 4.12). The full route is described in Chapter 5.



244 **245** **246** **247**

Scheme 4.12 Envisaged coupling of long chain DE core unit to amino alcohol ABC precursor.

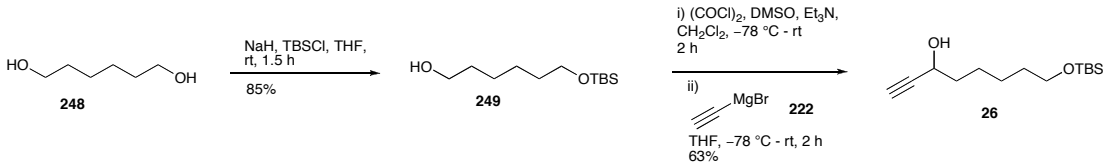
For this route to succeed a two carbon homologue of the DE core unit **230** produced previously was required. It was hoped this could then be elaborated to the β-hydroxy ester **255** (Scheme 4.13).



230 **253** **255**

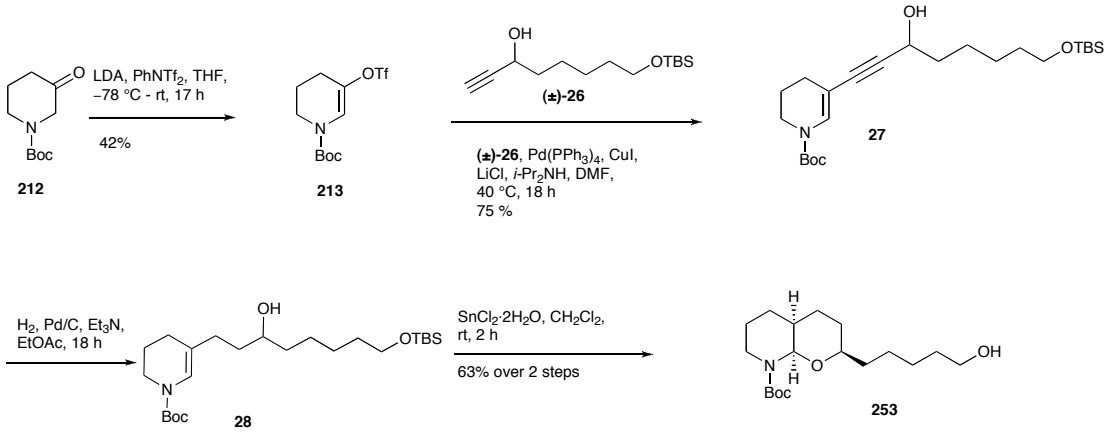
Scheme 4.13 Two carbon homologue of DE core unit **253**

The longer chain alcohol **26** required for the 2 carbon homologue of the DE core was synthesised by a modified procedure to that used by Jean on the shorter chain compound. Treatment of 1,6-hexanediol with sodium hydride and TBSCl gave the mono-protected alcohol **249** in excellent yield. Tandem Swern oxidation–Grignard reaction with ethynylmagnesium bromide **222** as described by Ireland[112] gave alcohol **26** in good yield (Scheme 4.14).



Scheme 4.14 Synthesis of alcohol **26**.

We were pleased to observe that the chemistry developed by Jean to produce the shorter chain **217** and **230** translated well to the longer chain system, and the Sonogashira and hydrogenation steps worked well (Scheme 4.15). Treating alcohol **28** produced with $SnCl_2 \cdot 2H_2O$ to effect the cyclisation to **253** delivered the deprotected compound, in good yield. The *in situ* deprotection effected by $SnCl_2 \cdot 2H_2O$ allowed for easier elaboration to install the required β-hydroxy acid without the requirement for a separate deprotection step.



Scheme 4.15 Synthesis of long chain DE core unit **253**.

The *cis*-ring fusion stereochemistry was again confirmed by ^{1}H NMR spectroscopy, with the hemi-aminal proton splitting small enough not to be observed. The hemi-aminal proton appeared as a ~ 1:1 mixture of rotamers at 5.30 and 5.10 ppm, (Figure 4.6). As the alcohol **26** employed was racemic, the product **253** was once again a racemic mixture of the *cis*-ring fused products.

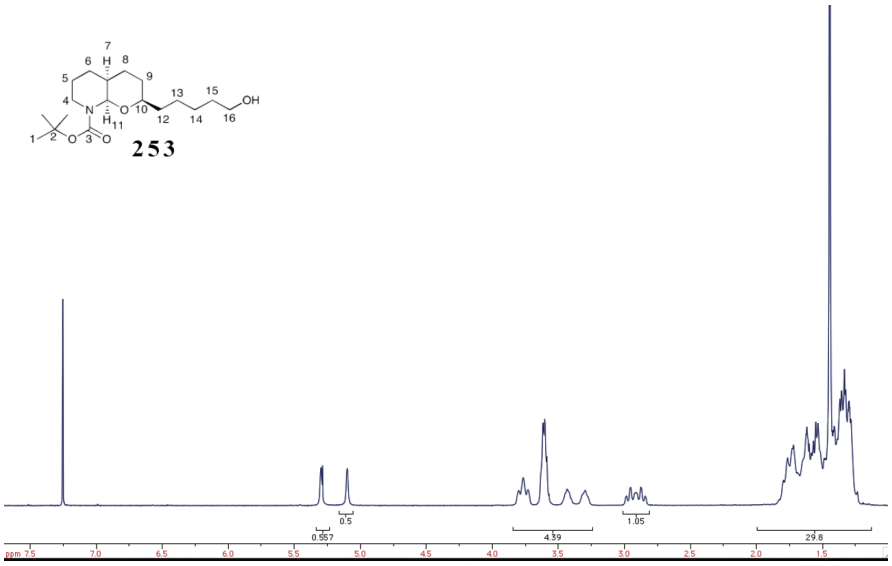
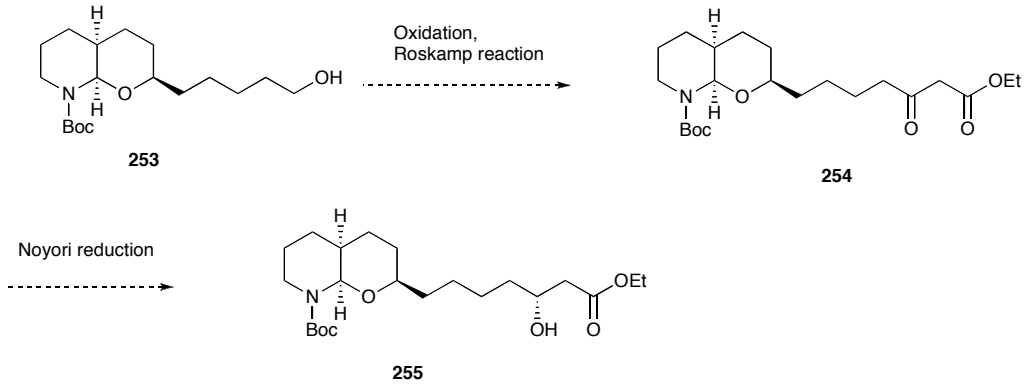


Figure 4.6 The ^{1}H NMR spectrum of alcohol **253**.

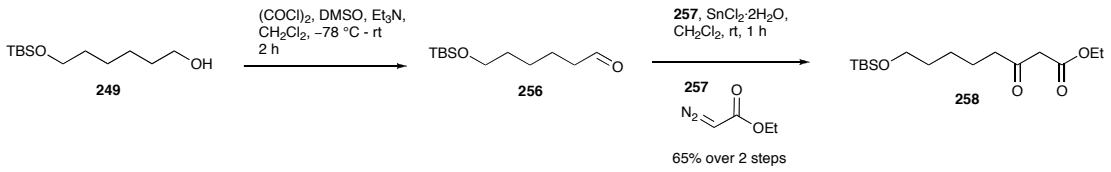
4.3.7 β-Hydroxy ester synthesis

With the alcohol **253** in hand, attention turned to modifying this to give the β-hydroxy ester **255** required for coupling. It was hoped this could be synthesised from the β-keto ester **254** by an enantioselective Noyori reduction. The β-keto ester was to be installed by a Roskamp reaction[113] on the aldehyde formed by oxidation of alcohol **253** (Scheme 4.16).



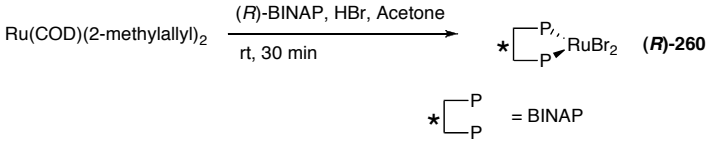
Scheme 4.16 Envisaged β-hydroxy ester synthesis.

The mono-protected diol **249** was used as a model system to investigate this sequence. Performing a Swern oxidation gave the aldehyde **256**, which was then treated with ethyl diazoacetate **257** in the presence of catalytic $SnCl_2 \cdot 2H_2O$ at rt. This performed a Roskamp reaction and delivered the β-keto ester **258** (Scheme 4.17).



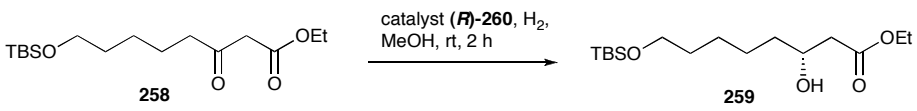
Scheme 4.17 Model system for oxidation and Roskamp sequence.

The next stage in the synthesis was the reduction of the β-keto ester to deliver a β-hydroxy ester *via* a Noyori asymmetric hydrogenation. Classical Noyori hydrogenation reactions take place at high pressures of hydrogen (100 atmospheres) and involve oxygen sensitive catalysts.[114] The high pressure hydrogenator at York is not designed for air-sensitive material, and thus the classical Noyori procedure was not practical. Genêt and co-workers[115] reported an alternative Noyori catalyst which can be used at 1 atmosphere of hydrogen and was much better suited to our needs. Thus, following the procedure of Genêt the catalyst **(*R*)-260** was synthesised from Ru(COD)(methylallyl)$_2$, (*R*)-BINAP and HBr (Scheme 4.18).



Scheme 4.18 Synthesis of Genêt's Noyori catalyst.

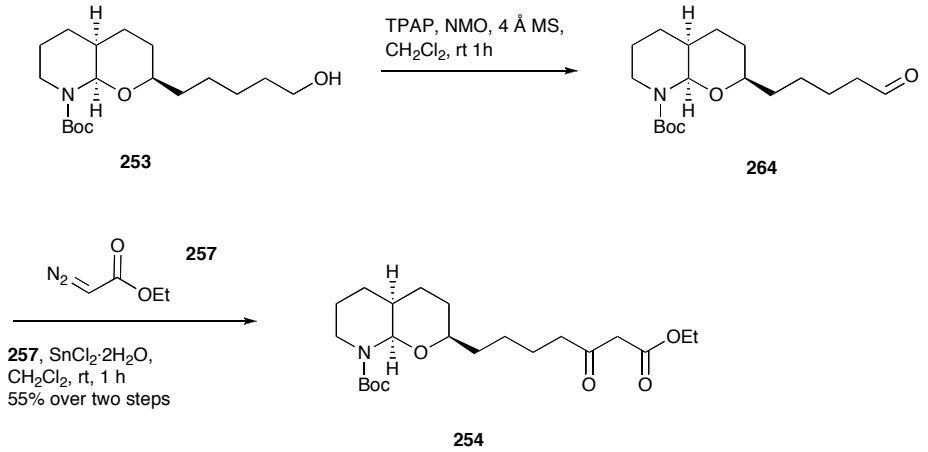
Pleasingly, the Noyori reduction using Genêt's catalyst was successful when applied to the model β-keto ester **258**, giving complete reduction to the alcohol **259** (Scheme 4.19). The e.r. of **259** was not determined but is generally high in Noyori β-keto ester reductions. This promising result meant that elaboration of the real system could now be attempted.



Scheme 4.19 Noyori reduction model system.

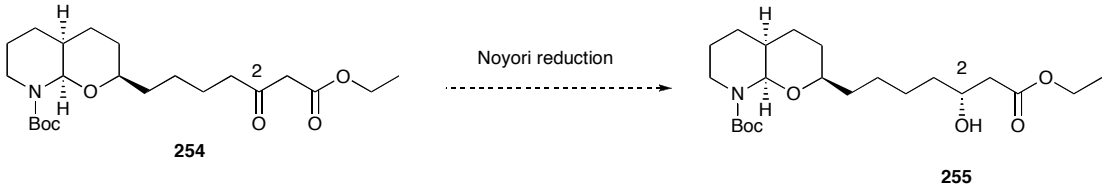
The oxidation and Roskamp conditions developed on the model system were applied to the DE core unit alcohol **253** to elaborate to the required β-keto ester. Swern oxidation gave 60% after chromatography of the aldehyde **264** but this compound

proved to be unstable on standing. Changing the oxidation method to TPAP and NMO removed the requirement for a column; **264** could instead be purified by filtration through a silica plug and used immediately in the subsequent Roskamp step which worked well, delivering the desired β-keto ester **254** in good yield (Scheme 4.20).



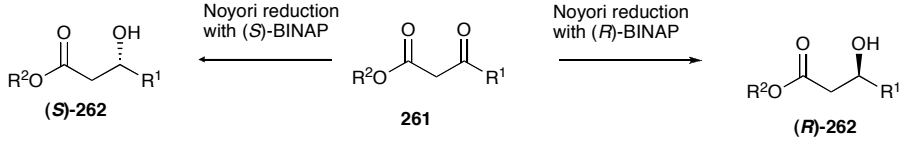
Scheme 4.20 Synthesis of β-keto ester **254**.

It was now hoped to reduce the β-keto ester **254** to the corresponding β-hydroxy ester **255** The stereocentre generated at C-2 in **255** would be incorporated into the ABC core, and was required to be of the configuration (*R*) (Scheme 4.21).



Scheme 4.21 Envisaged Noyori reduction of **254**.

The absolute stereochemistry of the product of Noyori reduction of β-keto esters to β-hydroxy esters is well established.[116] In systems like these where R^1 (**261**, Scheme 4.22) is an alkyl group (*R*)-BINAP gives the (*R*)-alcohol, while using (*S*)-BINAP would deliver the corresponding (*S*)-enantiomer.



Scheme 4.22 Stereochemical outcome of Noyori reduction.

This can be explained by the conformation the BINAP ligand adopts in the Ru-BINAP complex. Figure 4.7 shows the chiral environment around the Ru centre viewed from above, illustrating how the rigid BINAP ligand forces the phenyl rings to protrude in two quadrants. This view also demonstrates how access to one face of the structure is blocked by the naphthyl rings. In the side view in Figure 4.7 (with naphthyl rings omitted) it is clear that the protruding phenyl rings block access to two of the possible four quadrants of the accessible face. This is illustrated by the circle split into four quadrants, with the shaded areas suggesting no coordination can occur.

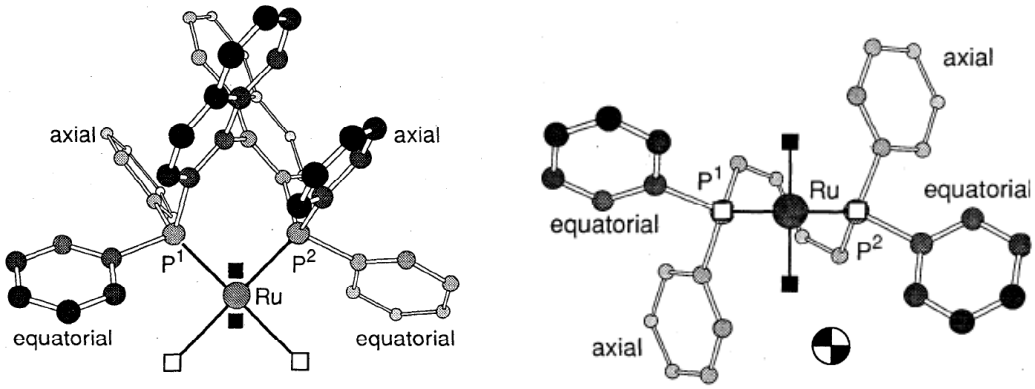


Figure 4.7 (*R*)-BINAP complexed to Ru. Figure taken from Noyori *et al.*[116]

The stereochemistry determining step is the coordination of the β-keto ester to the Ru-BINAP complex. Preferential binding of the β-keto ester occurs in order to minimise non-bonding interactions between the protruding phenyl ring and the ketone substituent. Figure 4.8 illustrates the diastereoisomeric transition states leading to the two possible enantiomeric products. **(*S*)-263**, which would lead to the (*S*)-alcohol is unlikely, as the R^1 substituent clashes with the equatorial phenyl ring. The transition state **(*R*)-263**, leading to the (*R*)-product does not suffer from this interaction and thus is favoured.

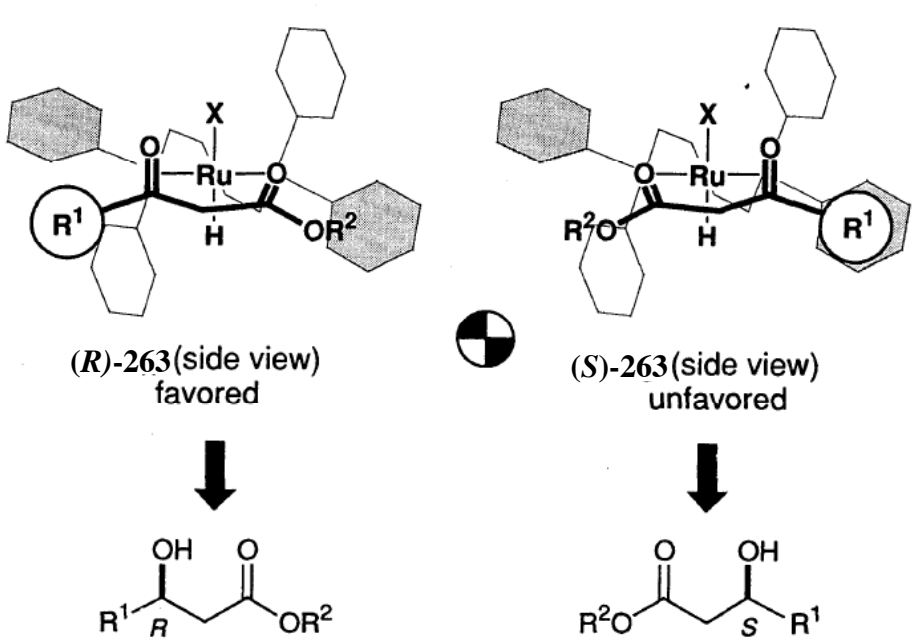
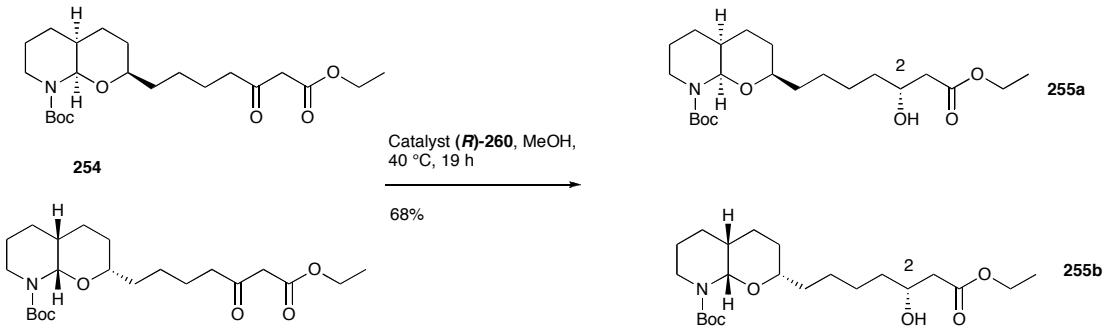


Figure 4.8 Transition states leading to enantioselective reduction. Figure taken from Noyori *et al.*[116]

With the ester **254** in hand, the Noyori reduction could now be attempted on the real system. The catalyst **(*R*)-260** described by Genêt was synthesised in an identical manner as previously, and the β-keto ester **254** was added to the Schlenk tube. The reduction appeared slow at room temperature and so, as suggested by Genêt,[115] the reaction was heated to 40 °C. This resulted in complete consumption of starting material in 19 h. The yield was reasonable after chromatography, with the racemic **254** giving an inseparable 1:1 mixture of diastereoisomers **255a** and **255b** in a 68% yield (Scheme 4.23).

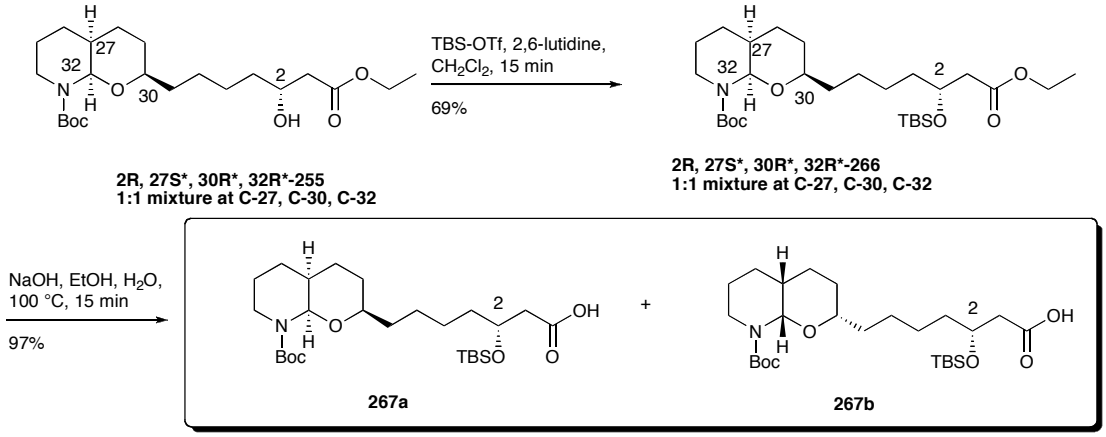


Scheme 4.23 The two enantiomers of **254** give two diastereoisomers of **255**.

The (*R*)-stereochemistry of C-2 was assumed due to the well known stereochemical outcome of the Noyori reduction of a number of closely structurally related β-keto esters.[114, 116]

4.3.8 β-Hydroxy acid synthesis

The final steps to produce allow the DE core unit suitable for coupling to the ABC precursor involved protecting the alcohol and hydrolysing the ester to reveal the carboxylic acid. These proceeded smoothly, yielding the acid **267** as an inseparable 1:1 mixture of diastereoisomers (Scheme 4.24).



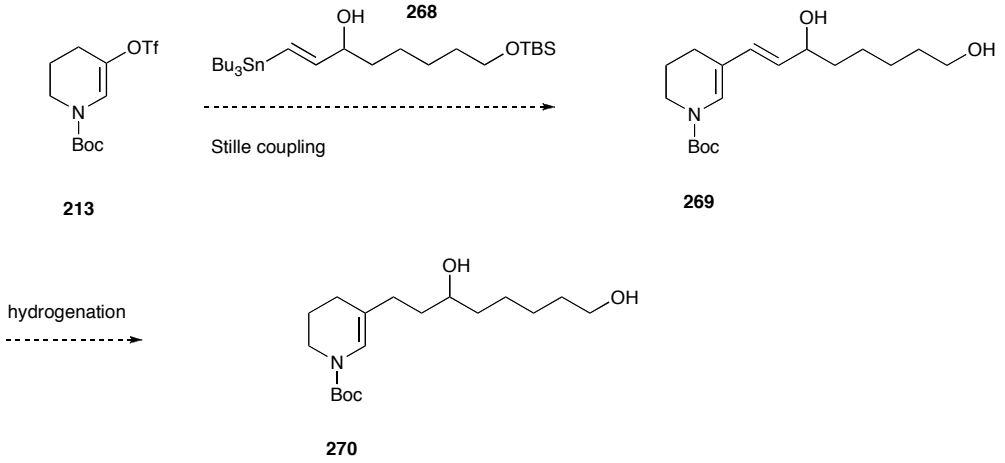
Scheme 4.24 β-hydroxy acid synthesis.

The β-hydroxy acid **267** produced was used to investigate conditions to couple the DE core unit to the ABC precursor. These investigations are described in detail in Chapter 5.

4.3.9 Stille coupling route

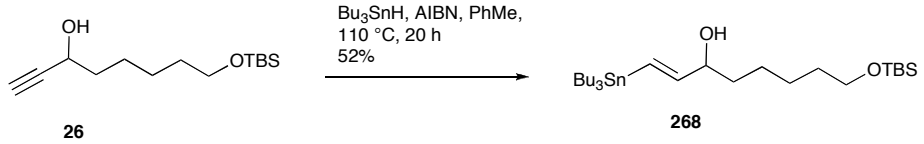
The Sonogashira coupling was generally high yielding, but was remarkably capricious, with yields sometimes dropping to around 20%. For consistently high yields the solvents had to be dry and thoroughly degassed, the $Pd(PPh_3)_4$ fresh and the lithium chloride flame-dried immediately before use. It was hoped that by replacing the Sonogashira coupling with a Stille reaction, some of these problems could be removed.

The Stille sequence would involve the treatment of the triflate **213** used previously, with the stannane **268** to give the diene **269**. Although hydrostannylation usually affords a mixture of *E/Z*-alkene isomers this would not be problematic since the subsequent step would involve alkene hydrogenation (Scheme 4.25).



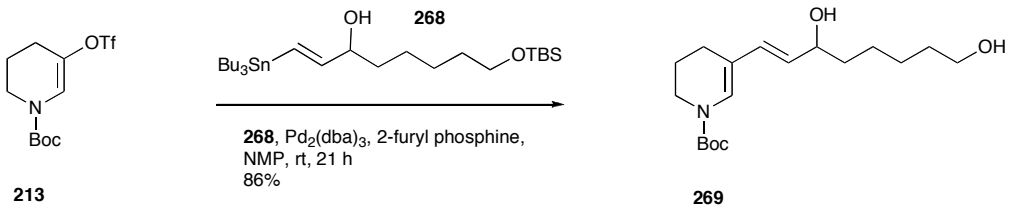
Scheme 4.25 Envisaged Stille route.

The stannane **268** was synthesised in a single step from the alkyne **26** by treatment with tributyltinhydride and AIBN (Scheme 4.26). Only the *E* isomer (J = 19.0 Hz) was isolated.



Scheme 4.26 Synthesis of stannane **268**.

The stannane **268** and triflate **213** were treated under conditions developed in the Taylor group[117] to effect the Stille reaction to **269** in good yield (Scheme 4.27). Once again only the *E*-isomer was isolated (J = 15.5 Hz). The product was contaminated with a small quantity of tin residues.

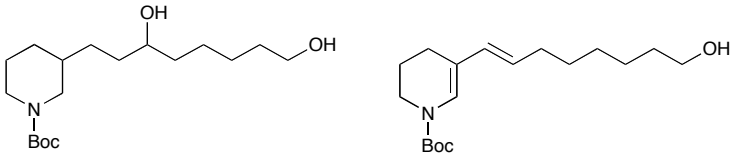


Scheme 4.27 Stille reaction to give diene **269**.

The diene **269** was subjected to the reduction conditions of palladium on carbon, ethyl acetate, triethylamine and 1 atmosphere of hydrogen which had been successfully

applied to the enyne **27** in the Sonogashira route. Disappointingly these returned only the starting material. Increasing the catalyst loading gradually (from 10% weight to 100% weight) resulted in no reaction, however on stirring for 24 h with 100% catalyst loading the over-reduced product **271** was obtained.

It was also noted that the diene **269** was prone to elimination, losing water on standing in NMR solvents at room temperature to give the compound **272** (Figure 4.9).



over reduction product **271** elimination product **272**

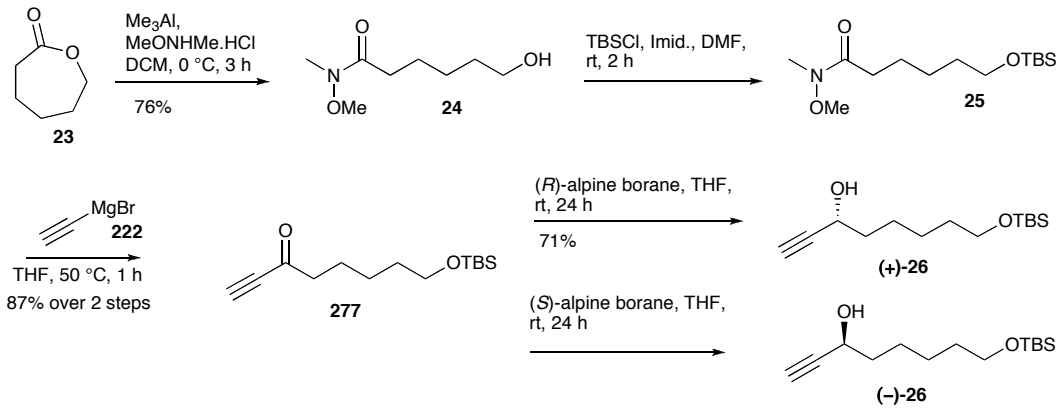
Figure 4.9 unwanted byproducts from **269**.

It was assumed that the tin residues present in the compound were poisoning the catalyst. Attempts to remove these by working the reaction up with base,[118] aqueous potassium fluoride[119] or potassium carbonate returned tin-contaminated material, as did triturating with pentane. Attempts to purify by chromatography on silica, alumina, and silica doped with potassium carbonate[120] or potassium fluoride[121] were unsuccessful, returning only the eliminated product **272**. The use of palladium hydroxide as a catalyst returned only starting material, as did increasing the temperature at which the reduction was run. Diimide reduction ($TsNH_2NH_2$ and sodium acetate) gave a complex mixture of products.

With the difficulty in reducing the double bond apparent this route was abandoned and the Sonogashira sequence (Scheme 4.14) returned to.

4.3.10 Preparation of enantio-enriched (–)-253 and (+)-253

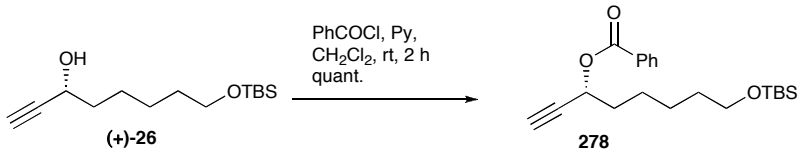
The enantio-enriched alcohol **26** was synthesised according to the procedure described by Sulikowski.[52]



Scheme 4.28 Synthesis of enantio-enriched alcohols **(+)-26** and **(–)-26**.

Treatment of ε-caprolactone **23** with *N*,*O*-dimethylhydroxylamine hydrochloride and trimethylaluminium gave the Weinreb amide **24**. TBS-protection was achieved with TBSCl and imidazole, giving the protected alcohol **25**. Treatment of this with ethynylmagnesium bromide generated the ketone **277**. Asymmetric reduction of the ketone moiety with (*R*)-Alpine borane gave the alcohol **(+)-26**, and analogously treatment of the ketone **277** with (*S*)-Alpine borane under identical conditions gave the enantiomeric alcohol **(–)-26** (Scheme 4.28).

Synthesis of the benzoate ester of **(+)-26**, **278** allowed the e.r. of the chiral reduction to be determined by chiral HPLC* (Scheme 4.29).



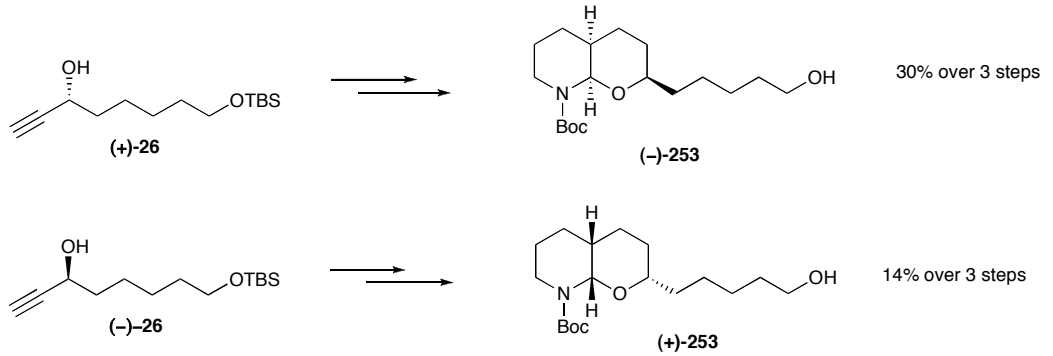
Scheme 4.29 Derivatization for chiral HPLC.

The benzoate ester **278** showed an e.r. of 93:7. This was slightly lower than that reported by Sulikowski who claimed 97:3 e.r. for the same reaction, but high enough to proceed with.

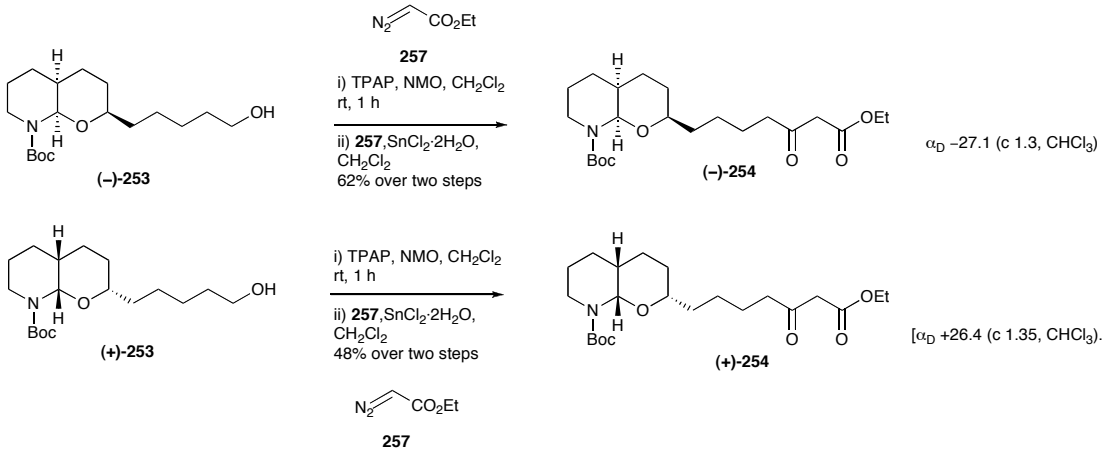
Under identical conditions to those described for the racemic alcohol (Scheme 4.15) the chiral alcohols were coupled with the triflate **213**, reduced and cyclised to give the two enantiomeric DE cores **(+)-253** and **(–)-253** (Scheme 4.29). These were further

* Column: Chiralpak IA-3. Full details in experimental Chapter 6. Thanks to Andy Hard at AstraZeneca for running the sample.

elaborated *via* a Roskamp reaction to give the enantiomeric β-keto esters **(+)-254** and **(–)-254** (Scheme 4.31).

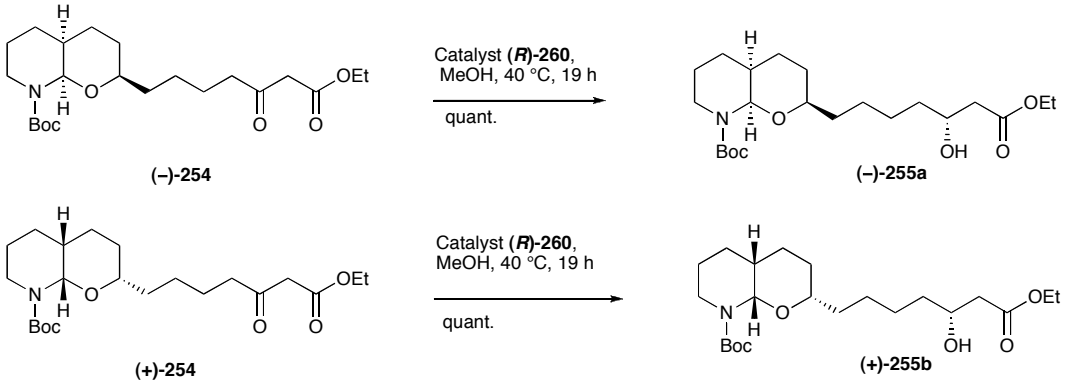


Scheme 4.30 Chiral DE cores.



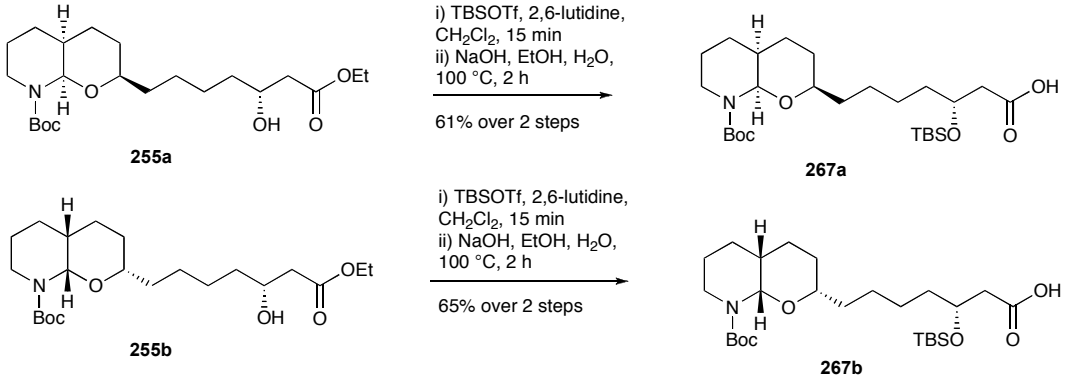
Scheme 4.31 Synthesis of chiral β-keto esters.

Each enantiomer of **254** was then treated separately under Genêt's[115] Noyori conditions to deliver the diastereoisomeric β-hydroxy esters **255a** and **255b**. Minimal purification of the Noyori reaction by filtering through a silica "plug" gave the best yields, with both products formed in quantitative yield (Scheme 4.32).



Scheme 4.32 Noyori reduction of both enantiomers of DE core unit.

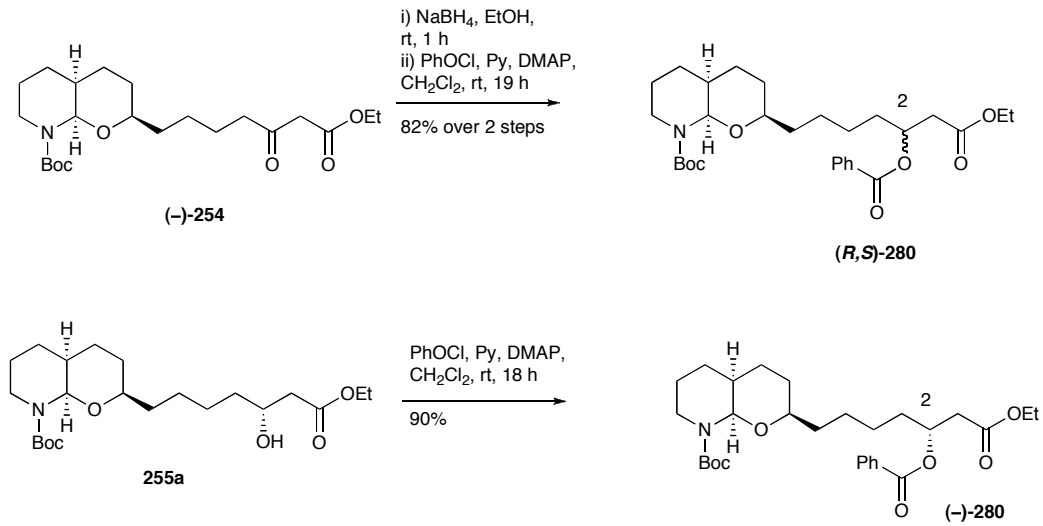
The diastereoisomeric β-hydroxy esters **255a** and **255b** were separately TBS-protected and then the ethyl ester hydrolysed to deliver both the required DE containing acids **267a** and **267b**, ready for coupling to the ABC core unit (Scheme 4.33).



Scheme 4.33 TBS protection and hydrolysis on chiral DE core units.

4.3.11 Determination of diastereoselectivity of Noyori reduction

The *d.r.* of the Noyori reductions was determined by chiral HPLC. A sample of the enantio-enriched Roskamp product **(–)-254** was reduced with $NaBH_4$, giving a 50:50 mixture of diastereoisomers at the newly formed stereogenic centre. This was converted to its benzoate ester to give UV activity and became our comparative sample. The analogous chiral benzoate ester was formed on alcohol **255a** (Scheme 4.34).



Scheme 4.34 Synthesis of UV tagged HPLC samples.

The three chiral centres in the DE core unit are all determined by the single chiral centre introduced by the Alpine borane reduction, meaning the reduction was performed on a 93:7 mixture of the two enantiomers **(–)-254** and **(+)-254** (Figure 4.10). The Noyori reduction installs another stereocentre, leading, after ester formation, to the 4 possible diastereoisomers **280a**, **280b**, **280c**, and **280d** illustrated in Figure 4.10. For the sodium borohydride reduced **(*R,S*)-280** we were expecting to see 4 peaks in an approximate ratio of 47:47:3:3 in the HPLC trace. Pleasingly this was the case, as illustrated in the trace depicted in Figure 4.11.

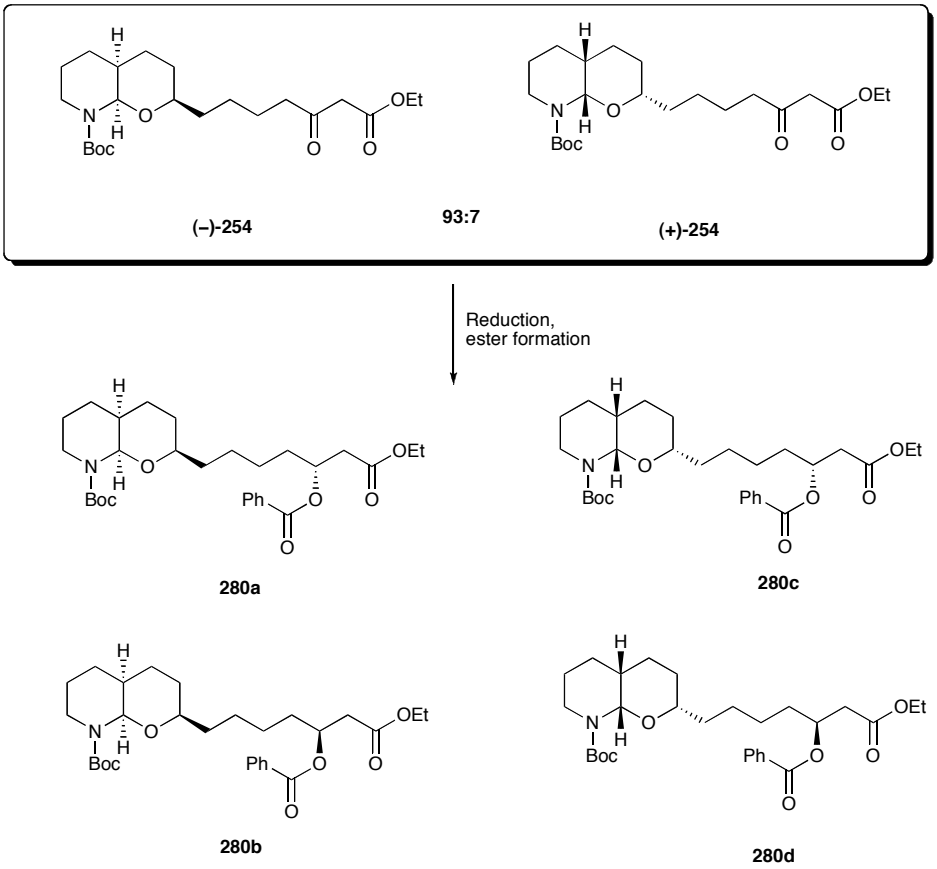
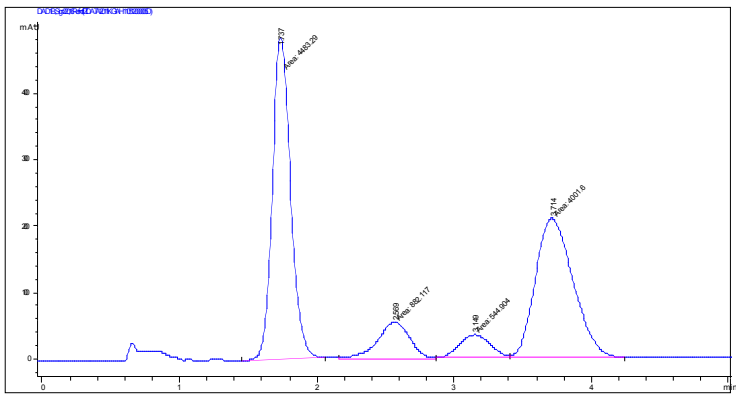


Figure 4.10 Possible diastereoisomers of **280**.

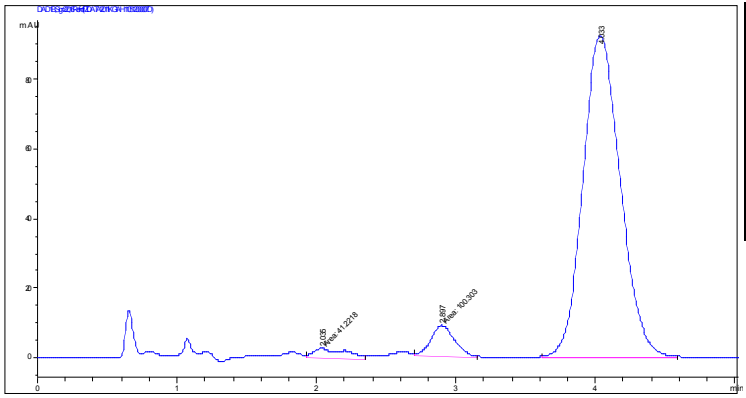


R_T	Area	Area%
1.7	4483.3	45.2%
2.6	882.1	8.9%
3.1	544.9	5.5%
3.7	4001.6	40.4%

Figure 4.11 $NaBH_4$ **280** sample HPLC trace[†]

The "chiral" sample **(–)-280** was run under the same conditions, giving the trace illustrated in Figure 4.12.

[†] Thanks to Andy Hard at AstraZeneca for running these samples. Column: Chiralpak IA-3, Full details in Experimental (Chapter 6).



R_T	Area	Area%
2.0	41.2	2.2%
2.9	100.3	5.4%
3.4	None detected	
4.0	1723.5	92.4%

Figure 4.12 **(–)-280** HPLC trace.

Peak integration gives a ratio of 92.5: 5.4: 2.1: 0. An overlay of the racemic and chiral samples confirmed the peaks corresponded to the sample compounds (Figure 4.13).

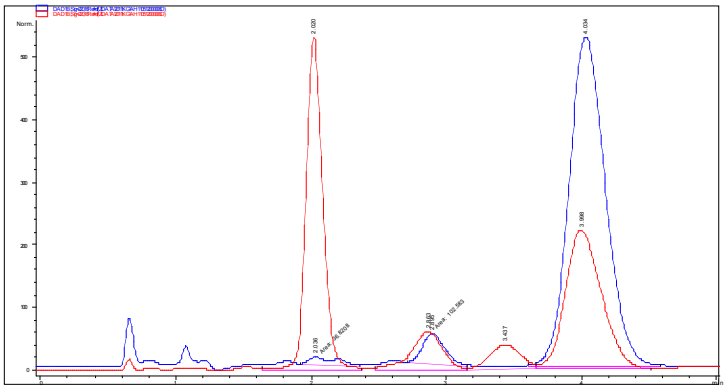
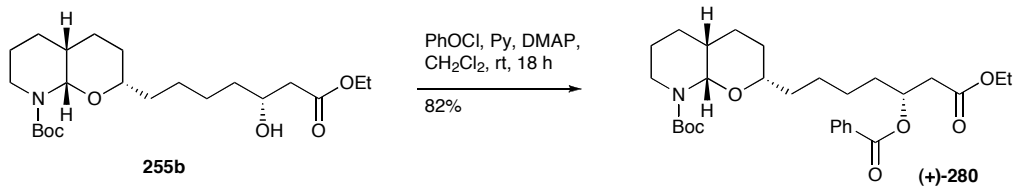


Figure 4.13 Overlay of racemic and chiral samples.

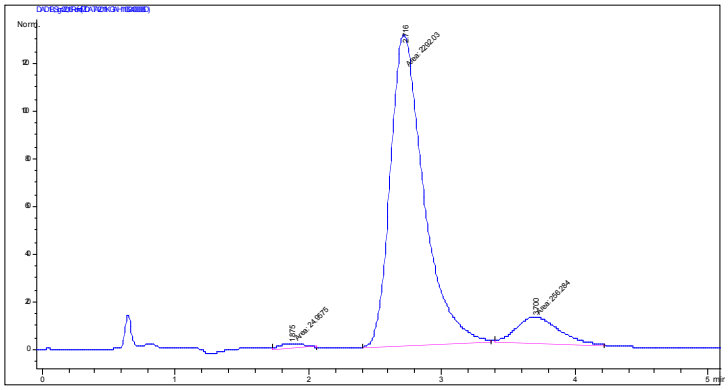
The ratio of the major peaks should be the ratio of isomers observed in the Alpine borane reduction × ratio from the Noyori reduction. As we know that the Alpine borane was 93:7 we have 0.93 × x = 0.925 – thus x = 0.99, suggesting that the Noyori reduction gave a 99:1 e.r. Integration of the minor peaks suggests slightly different ratios, however it is assumed that the error on the minor peaks would be much greater.

A benzoate ester was also formed from the diastereoisomeric Noyori reduction product **255b** (Scheme 4.33).



Scheme 4.33 Benzoate ester of **255b**.

This was subjected to the same HPLC conditions as **(–)-280**, giving the trace illustrated in Figure 4.14. The separation was not as clear as with the previous sample[‡] but the ratio of peaks was 1.0:89.1:0:10. By the same method as previously this suggested that the Noyori was 96:4 e.r. This was not as good as that observed on the previous sample, but high enough to proceed with.



R_T	Area	Area%
1.9	25	1.0%
2.7	2292	89.1%
3.2	None detected	
3.7	256.6	10.0%

Figure 4.14 HPLC trace of **(–)-280**.[§]

[‡] Possibly due to sample degradation; the machine was busy and the sample left in solution at room temperature for ~ 10 weeks before the HPLC was recorded.
[§] Chiralpak IA-3. Full details in Experimental (Chapter 6).

4.4 Conclusions

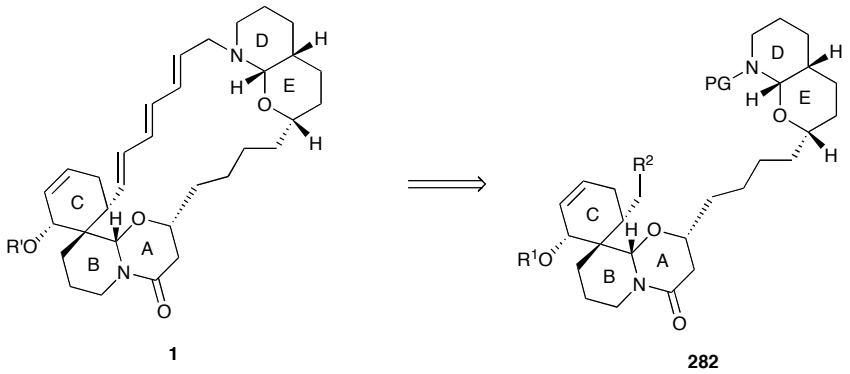
The synthesis of the original DE core unit developed by Jean was extended to enantio-enriched material **(+)-217** and **(–)-217**, and optimisation attempted on the initial triflate formation step. The same route was applied to give an enantio-enriched synthesis of both enantiomers of the redeveloped DE core unit **267**. A β-hydroxy acid moiety, which would allow coupling to the ABC core, was incorporated and the e.r. of both asymmetric steps was determined by chiral HPLC analysis. Attention then moved to the possible coupling strategies between the ABC and the DE core units as described in Chapter 5.

Chapter 5 – Results and discussion 4: Linking the ABC and DE core units

5.1 Background

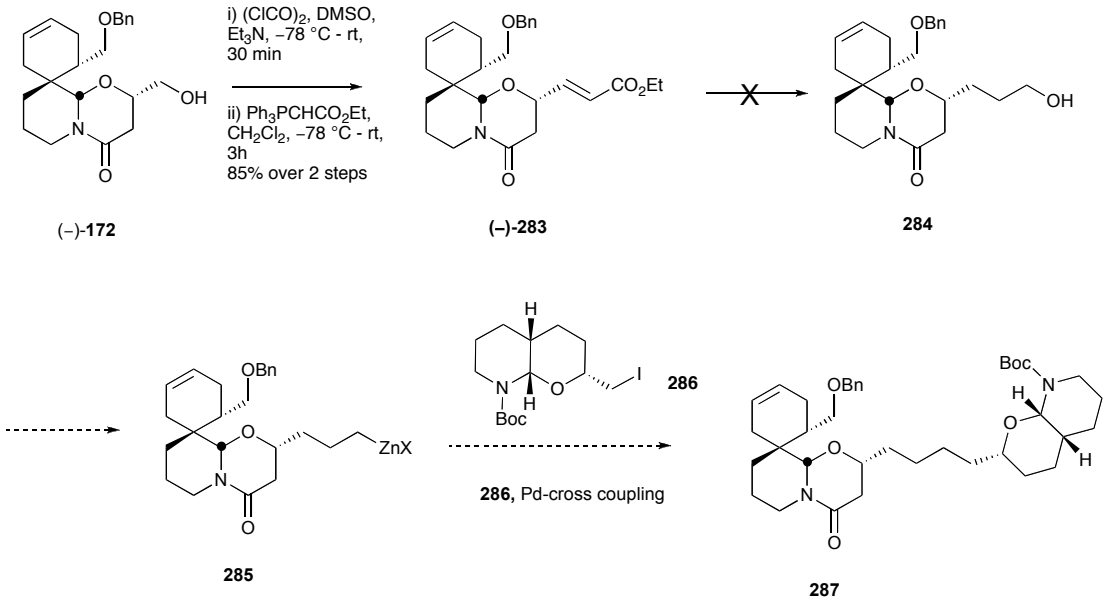
5.1.1 Schmidt's approach

The ABC and DE core units need to be linked to form the macrocycle of 'upenamide by both a fully saturated chain and an all-*trans* triene chain. It was reasoned that the fully saturated chain would be harder to form, given the plethora of double bond forming reactions available for the unsaturated chain; attention was thus initially focussed on linking the ABC and DE core units through the saturated chain, giving a target molecule of the form **282** (Scheme 5.1).



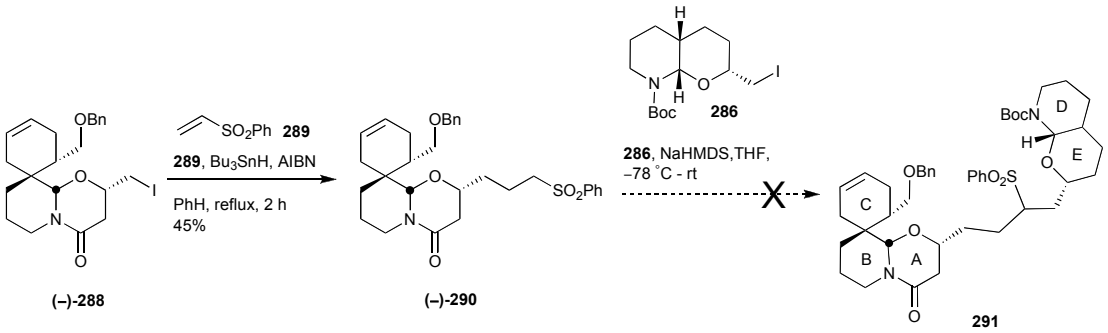
Scheme 5.1 The structure of upenamide and initial retrosynthesis.

Initial work by Schmidt[60] focussed on forming the fully saturated chain *via* a Negishi coupling, such as that reported by Organ and co-workers to couple two sp^3 hybridised alkyl centres.[122] It was possible to perform a tandem oxidation-olefination to give the unsaturated ester **(–)-283**, however, reduction to the desired alcohol **284** was unsuccessful. Schmidt had hoped to elaborate this alcohol to the zinc species **285**, then couple with the iodo-DE compound **286** (Scheme 5.2).



Scheme 5.2 Synthesis of alcohol **284** was not successful.

Later work by Schmidt concentrated on performing a similar coupling *via* sulfone **290**, which was itself synthesised by converting alcohol **(–)-172** into iodide **(–)-288** followed by a radical reaction in which the primary radical was trapped with phenyl vinyl sulfone (Scheme 5.3). Disappointingly, however, all attempts to perform the subsequent deprotonation and alkylation with the iodo-DE compound **286** were unsuccessful.

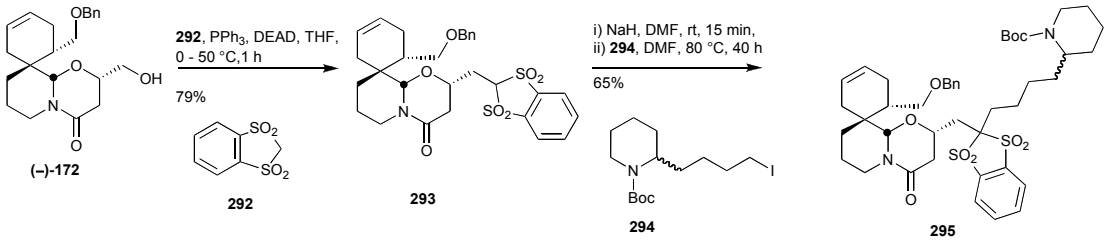


Scheme 5.3 Schmidt's attempted sulfone route.[60]

5.1.2 Jean's approach

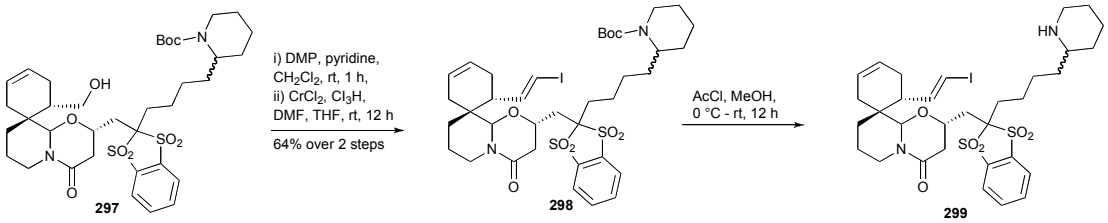
Jean focussed on a similar approach to Schmidt's sulfone strategy, employing instead the cyclic sulfone benzodithiole tetraoxide (BDT) **292**. This was first reported by Kündig and co-workers[123] who claimed that it offers higher reactivity in alkylation reactions than bis-sulfones. BDT was coupled with the ABC core unit **(–)-172** *via* a

Mitsunobu reaction, affording sulfone **293** (Scheme 5.4), which was then alkylated with the iodo compound **294** (used as a model for the DE core unit). This marked the first successful coupling of the ABC core fragment through the fully saturated linker, albeit with a simplified model DE core unit. Jean failed to remove the BDT moiety in reasonable yield at this stage but hoped to do so later, and therefore continued with the synthesis on this model system.



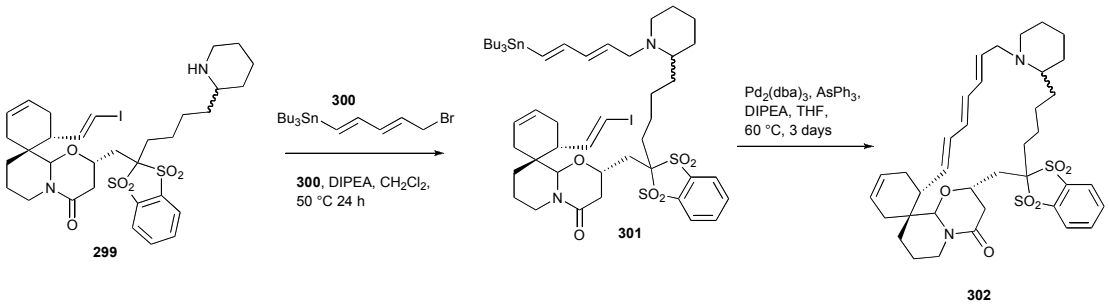
Scheme 5.4 Jean's ABC-DE model linked through saturated chain.

After protecting group manipulation, Dess–Martin oxidation and Takai olefination delivered the vinyl iodide **298**. Jean then removed the Boc group by treating with acetyl chloride in methanol to reveal the free amine of the model DE system **299** (Scheme 5.5).



Scheme 5.5 Jean's later stages

Allylation of the amine **299** with bromo-stannane **300** gave the Stille cyclisation precursor **301**. Treatment with $Pd_2(dba)_3$ and triphenylarsine generated a small quantity of the macrocycle **302**, observable only by mass spectrometry (Scheme 5.6).



Scheme 5.6 Jean's ring-closing approach.

5.2 Results

At this point Dr W. Unsworth joined the project and a new strategy involving pre-forming the saturated chain was examined. The work described below was carried out in partnership with Unsworth, with due credit being given.

5.2.1 Amino alcohol coupling partner

Given the problems encountered by Schmidt and Jean forming the fully saturated linking chain, and in particular concerns about the cleavage of the sulfone auxiliary, an alternative method for its installation was sought. Instead of assembling the saturated chain at a latter stage of the synthesis it was decided to incorporate the saturated chain into the DE core unit. It was hoped that the coupling of a suitable extended DE-containing substrate (*e.g.* **267**) to a precursor of the ABC core unit would give an intermediate amide, and following the previously described oxidation/cyclisation methodology, give the ABC and DE core units linked through the fully saturated chain (Scheme 5.7). Furthermore, with the problems encountered installing the allylic oxygen on the fully formed ABC core unit system in mind (Chapter 3), it was hoped to synthesise an ABC precursor already containing the required allylic oxygen. A route to the benzyl-protected amino alcohol **199** (Figure 5.1), described in Chapter 3, which was an intermediate on the shortened ABC synthesis, had already been developed. Thus, an oxygenated version of this, ideally containing a more advanced handle in place of the benzyl-protected alcohol to allow elaboration to the triene chain, was the target. With the Boc-protected acid **267** in hand (Chapter 4), this made the ABC precursor **303** (Figure 5.1) the next target.

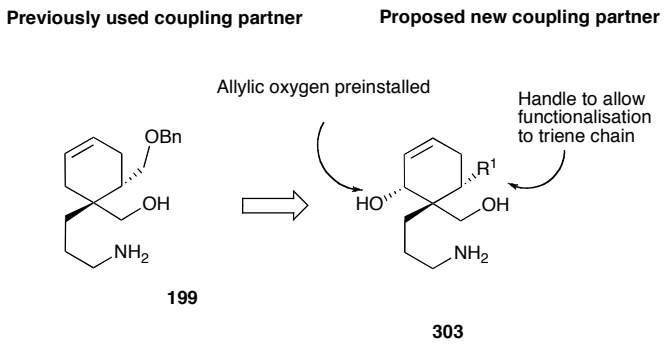
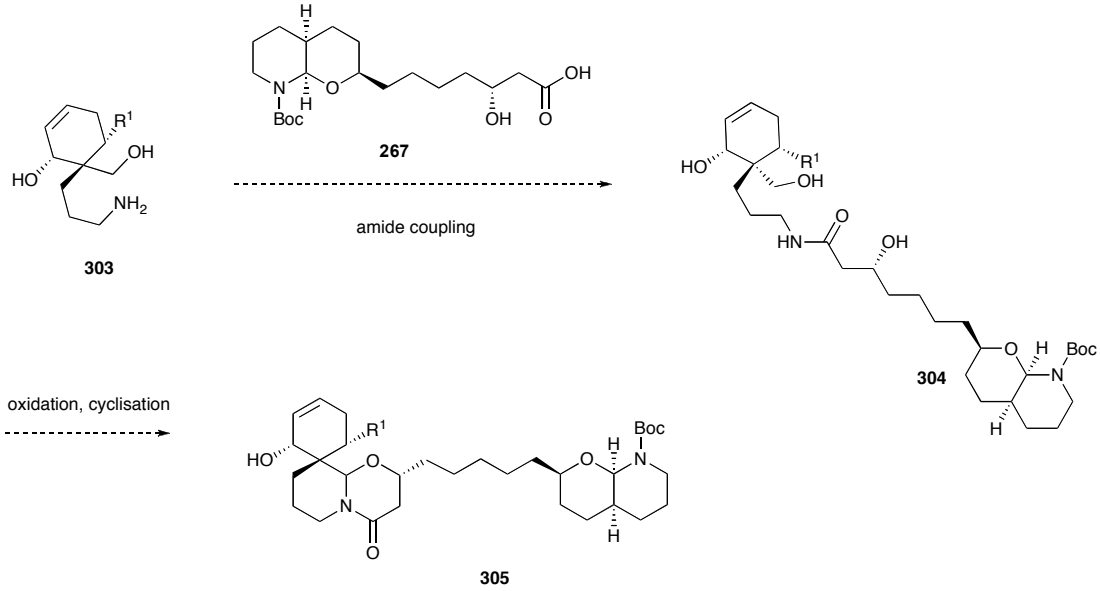


Figure 5.1 Proposed ABC precursor for coupling.

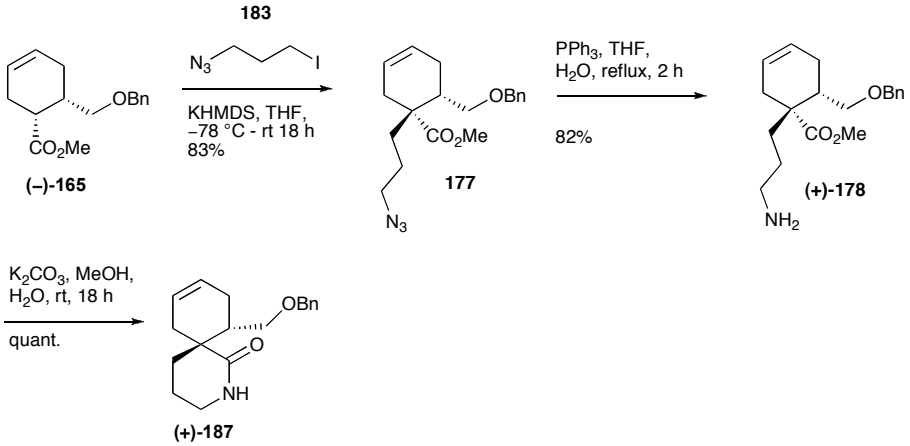


Scheme 5.7 Proposed early installation of the saturated chain.

In order to test this methodology a deoxy-version of the desired amino alcohol **303**, excluding the allylic oxygen present in the natural product, was synthesised by Unsworth with an unsaturated ester in place of the benzyl-protected alcohol. This modification was made in the hope that it would eventually allow elaboration to the triene chain more easily and avoid synthetic problems differentiating between the two similar alcohols present.

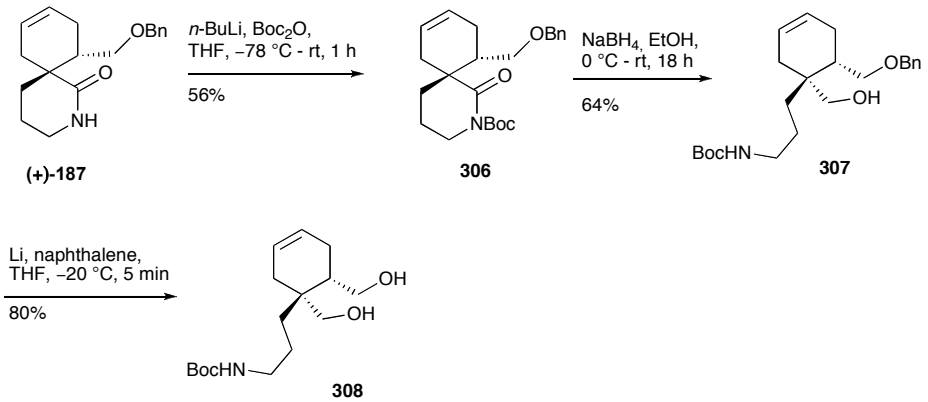
To produce the deoxy-amino alcohol coupling partner **313** Unsworth began with the synthesis of the lactam **(+)-187** (Scheme 5.8). This was originally isolated as an undesired side product resulting from the cyclisation of amino ester **(+)-178** during studies into the ABC synthesis. It was possible to promote this cyclisation by treating amino ester **(+)-178** with aqueous potassium carbonate. The procedure could be simplified by telescoping the alkylation, reduction and cyclisation reactions, without

purification at any step. This resulted in similar yields (66% over 3 steps). It was possible to purify the amine **(+)-178** by ion exchange chromatography before the cyclisation. If this was not undertaken the material was contaminated with a trace of triphenylphosphine oxide. This, however, made no difference to the later steps, and so, aside from for characterisation purposes, no purification was undertaken.



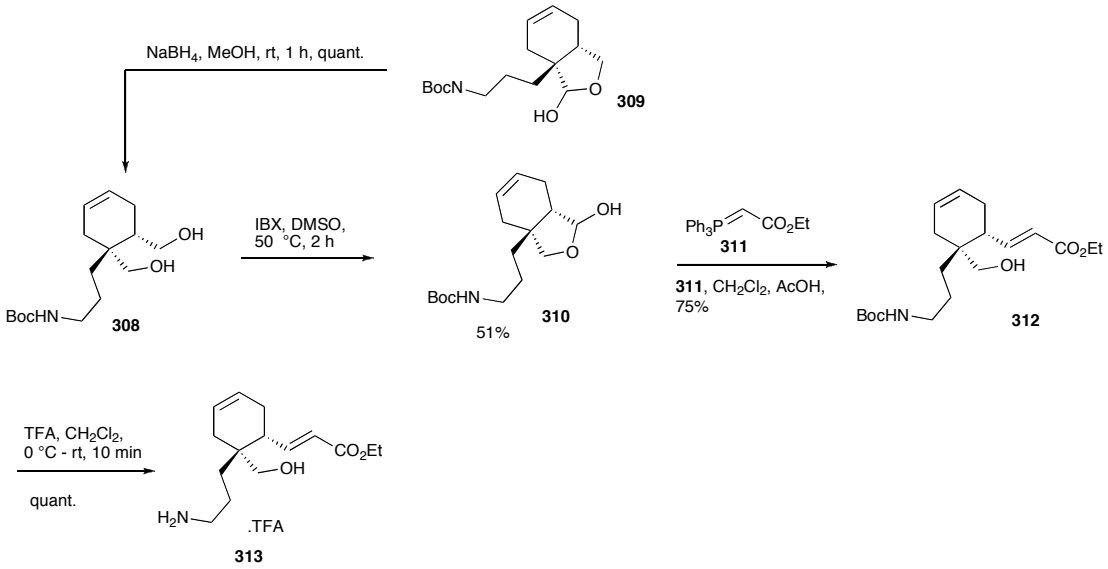
Scheme 5.8 Unsworth's lactam synthesis.

To reduce the lactam to the desired amino alcohol, an activating group was needed on the nitrogen, and so a Boc group was installed by treatment with *n*-butyllithium and di-*tert*-butyl dicarbonate (Scheme 5.9). This facilitated reductive ring-opening with sodium borohydride, delivering the benzyl-protected compound **307**. Treatment of this compound with lithium naphthalide in THF allowed cleavage of the benzyl group without reduction of the double bond, such as would be observed if hydrogenation had been employed to cleave the benzyl group.[124]



Scheme 5.9 Unsworth's synthesis of amino alcohol coupling partner **308**.

Unsworth found it very difficult to differentiate between the newly revealed alcohol and the primary alcohol present in **308** (*e.g.* TBSCl gave statistical mixtures). IBX oxidation gave some selectivity, preferentially oxidising the desired alcohol, albeit to a small degree, delivering the lactols **309** and **310** in a 2:1 ratio (Scheme 5.10). These could be separated by column chromatography, the undesired lactol reduced to recover **308**, while the desired isomer **310** was reacted in a Wittig reaction with the stabilised ylide **311** to install the unsaturated ester with complete *E* selectivity. Cleavage of the Boc group with TFA revealed the required amine **313**.



Scheme 5.10 Unsworth's synthesis of amino alcohol **313**.

Unsworth carried out initial coupling studies with a 1:1 mixture of the two diastereoisomers **267a** and **267b** (Figure 5.2). The chiral centre at C-2 would become part of the ABC core unit (of which the absolute stereochemistry was known) and was introduced using a Noyori reduction (see Chapter 4). This material was more readily accessible than the enantio-enriched version described in Chapter 4, which was retained for use later, after this coupling strategy was more fully explored.

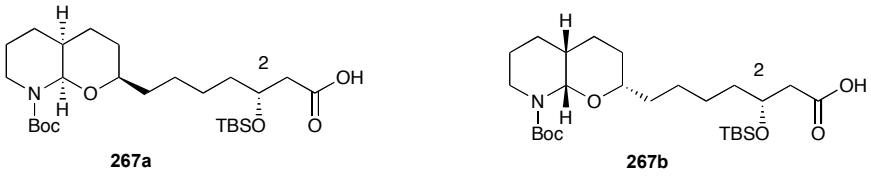
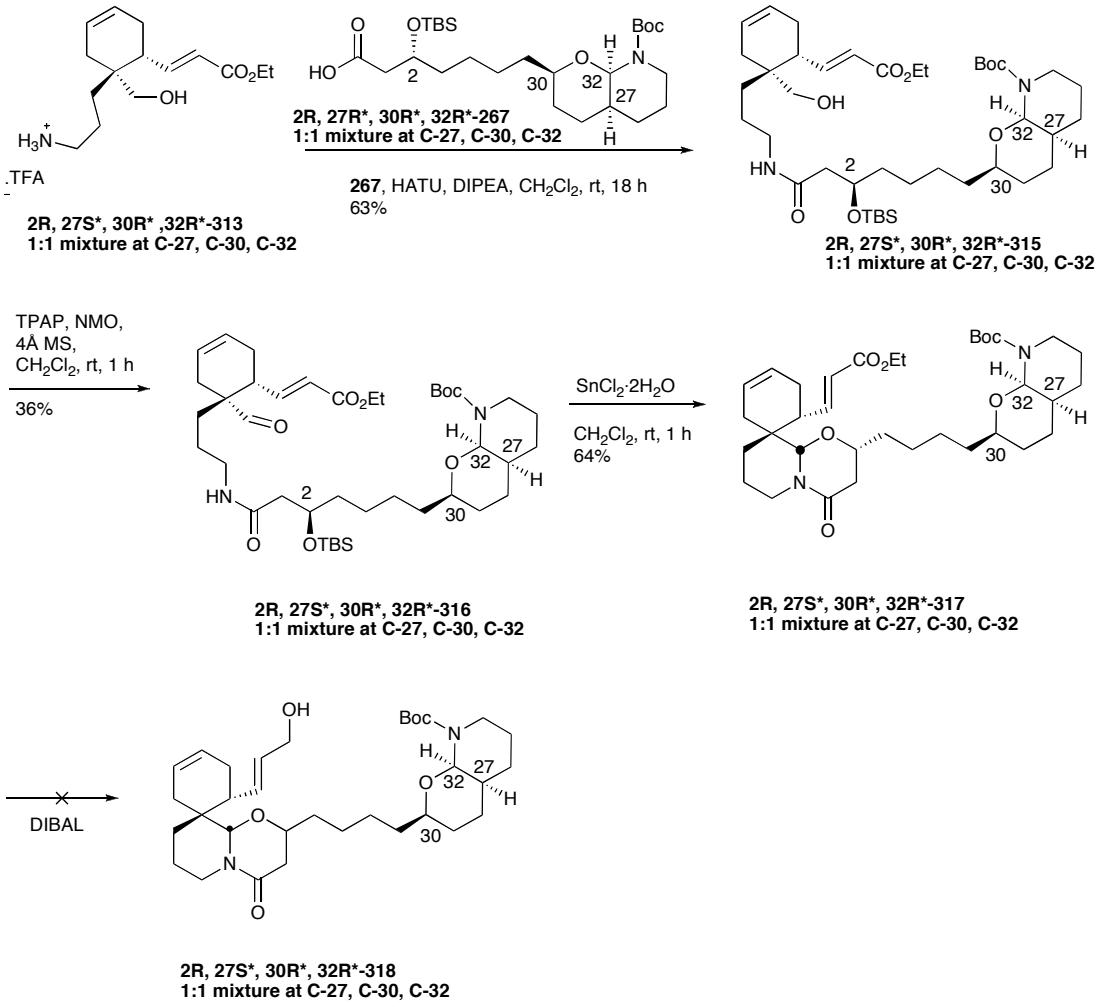


Figure 5.2 The two diastereoisomers of acid **267** coupled.

Unsworth successfully coupled amino alcohol **313** with acid **267** to deliver the amide **315** in good yield on treatment with HATU. The Ley–Griffith oxidation step also worked, albeit in a poor yield of 36%. However, in the key step this material cyclised on treatment with $SnCl_2{\cdot}2H_2O$ to give the deoxy-ABC and DE core units joined through the fully saturated chain (Scheme 5.11). Disappointingly, all attempts to reduce the unsaturated ester returned only starting material.

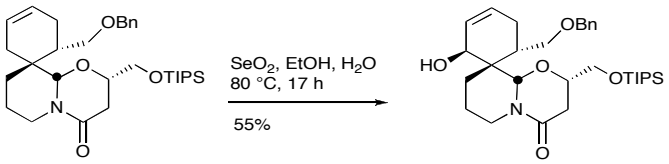


Scheme 5.11 ABC and DE core units linked through saturated chain, giving two diastereoisomers of **318**.

Despite the difficulties encountered in reducing the unsaturated ester, this was an excellent result, representing the first coupling of the deoxy-ABC core unit with the fully formed DE core unit. With this hugely encouraging result in hand, attention was now turned to the synthesis of the C-11 oxygenated system, which it was hoped would ultimately lead to the total synthesis of the natural product.

5.2.2 Oxygenated amino alcohol system

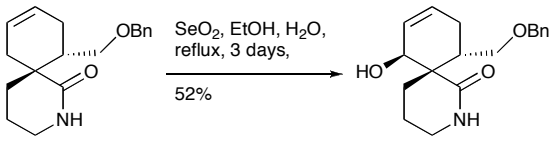
Attempts to synthesise the C-11 oxygenated variant of the amino alcohol **313** began with the attempted allylic oxidation of the lactam **(+)-187**. Compound **(+)-187** was a very different molecule to the fully formed ABC core unit **(–)-203** on which Schmidt had originally developed the selenium dioxide mediated allylic oxidation (Scheme 5.12), but shared the spirocylic, bicyclic BC core unit in common with this molecule. It was hoped they would be similar enough to allow the regioselective oxidation observed by Schmidt to occur.



(–)-203 **(–)-173**

Scheme 5.12 Schmidt's SeO_2 oxidation on the ABC core unit **(–)-203**.

We were delighted to observe this was the case, and compound **(+)-187** was oxidised by selenium dioxide (Scheme 5.13), giving a single isomer of product. X-Ray crystallography (Figure 5.3) confirmed the product of allylic oxidation on lactam **(+)-187** to be the correct regioisomer, but the undesired stereoisomer, mirroring the result obtained by Schmidt on oxidation of the ABC core unit.



(+)-187 **(+)-319**

Scheme 5.13 Allylic oxidation on lactam **(+)-187**.

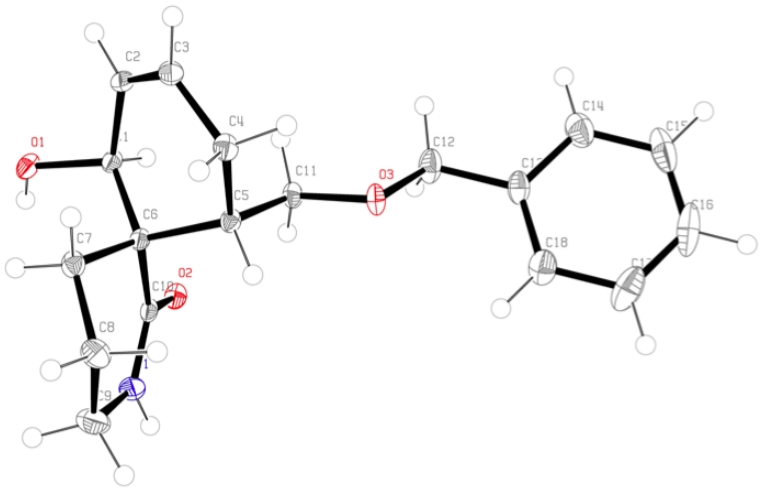
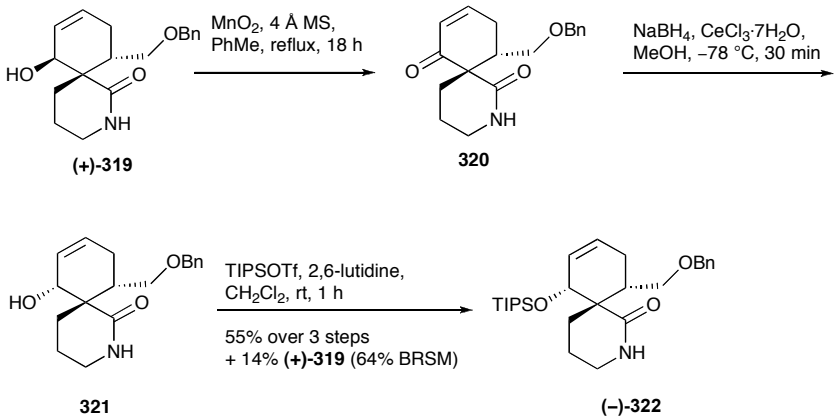


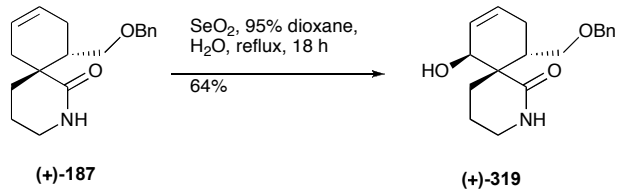
Figure 5.3 X-Ray structure of **(+)-319**.

With the oxygenated lactam **(+)-319** in hand, attention turned to inversion of the alcohol centre. Schmidt[54] achieved this on the fully formed ABC core unit by oxidation to the enone, followed by a Luche reduction. Oxidation of **(+)-319** with manganese dioxide gave the desired enone **320** and we were delighted to find Luche reduction of this material was successful, giving a 10:1 mixture of the desired product **321** to the undesired isomer **(+)-319** (Scheme 5.14). These were easily separated following TIPS protection of the alcohol; the desired product reacted to give the protected (–)-**322**, while **(+)-319** was inert under these conditions and was returned unprotected. Thus, following purification by column chromatography, the synthesis of the desired protected oxygenated lactam (–)-**322** was complete.



Scheme 5.14 Synthesis of oxygenated lactam.

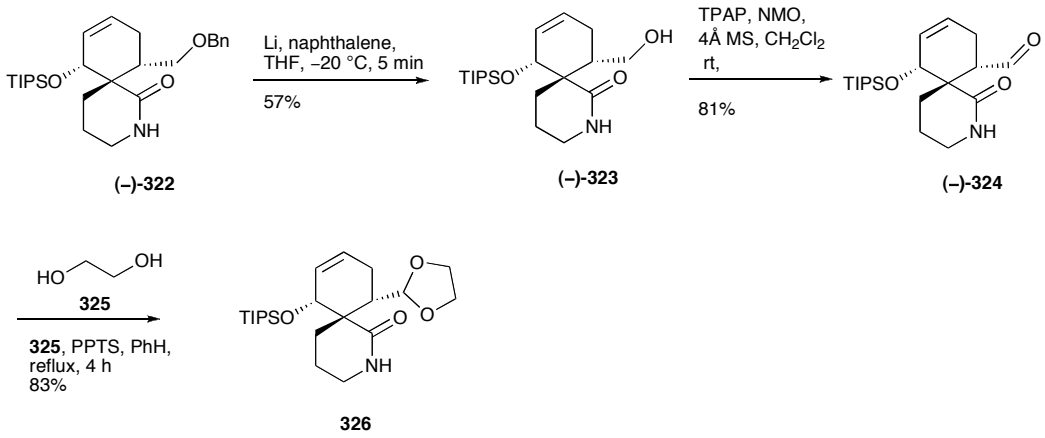
Unsworth later modified the selenium dioxide oxidation conditions; solvent screening revealed that by changing the solvent to dioxane, the yield could be increased and reaction time reduced (Scheme 5.15).



(+)-187 (+)-319

Scheme 5.15 Unsworth's modified oxidation conditions

A slight change to the to the previous route was made, with the benzyl protecting group cleaved at this stage to give alcohol **(−)-323**. The alcohol revealed was oxidised to aldehyde **(−)-324** and protected as the acetal **326** rather than the unsaturated ester used previously (Scheme 5.16). This would change the triene disconnection, but this approach had the added bonus that the acetal protecting group should be deprotected in the $SnCl_2 \cdot 2H_2O$ mediated cyclisation step to reveal the aldehyde.

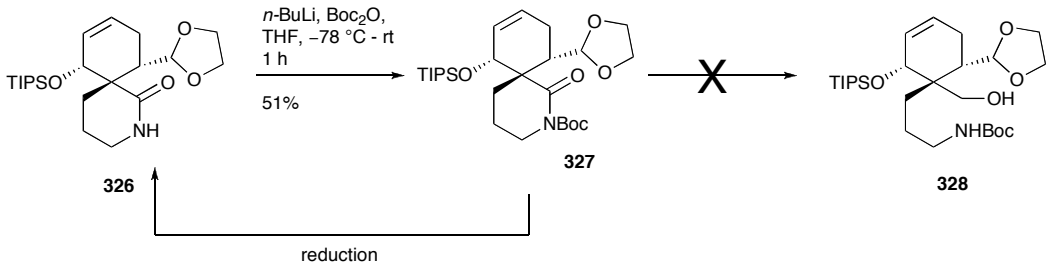


(−)-322 (−)-323 (−)-324

326

Scheme 5.16 Acetal synthesis. Carried out by Unsworth.

In an analogous manner to the deoxy-**(+)-187**, it was possible to protect the lactam nitrogen with using di-*tert*-butyl dicarbonate, to give the imide **327**. Disappointingly, all attempts to ring-open this to give the desired amino alcohol **328**, *e.g.* using SuperHydride, or lithium aluminium hydride, gave a mixture of products, primarily the lactam **326** resulting from Boc cleavage. Di*iso*butylaluminium hydride returned only starting material. The change in preference from lactam carbonyl reduction in the deoxy-system to Boc cleavage in the oxygenated system is most likely to be explained by steric hindrance. The bulky TIPS group is in close proximity to the lactam carbonyl and presumably prevents approach of the reducing agent.

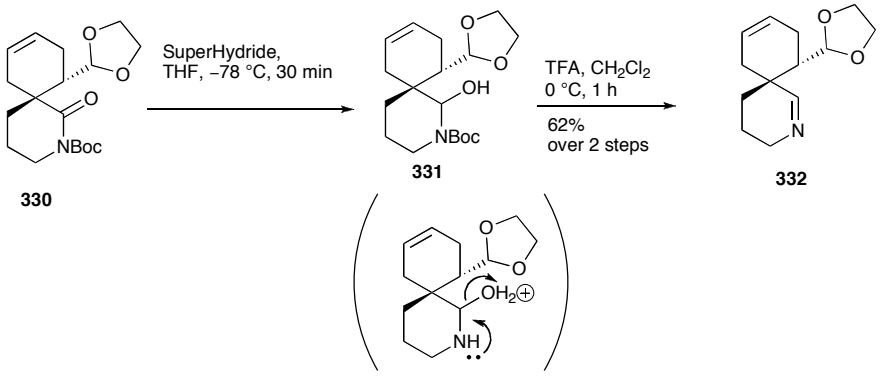


Scheme 5.17 attempted ring opening.

Making an oxygenated version of the amino alcohol coupling partner seemed to be difficult, presumably due to steric hindrance caused by the bulky TIPS protecting group, located close to the carbonyl centre. Attention turned to a different coupling strategy.

5.2.3 Imine coupling partner

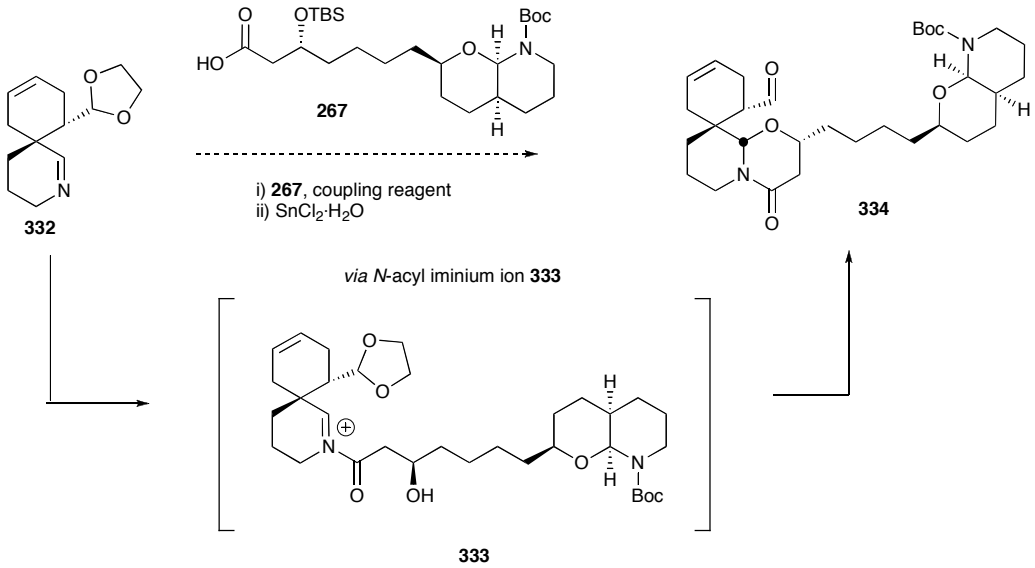
Given the problems reducing lactam **327** further studies were undertaken by Unsworth using deoxy-model compound **330**. In this case reduction was much easier, presumably due to the decreased steric hindrance, with deoxy-**330** affording the hemi-aminal **331**. It was then hoped to remove the Boc protecting group, prior to coupling with a suitable carboxylic acid derivative, but, on Boc cleavage with TFA, the compound eliminated water to give the imine **332** (Scheme 5.18).



Scheme 5.18 Imine formation.

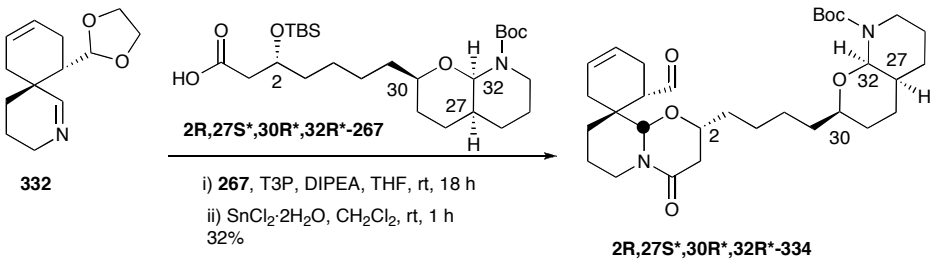
Imine **332** was surprisingly stable, and this led to the idea of using it as a coupling partner, by coupling with DE intermediate **267** to form an intermediate *N*-acyl

iminium species **333**, which following treatment with $SnCl_2 \cdot 2H_2O$, should deliver the ABC core unit **334** (Scheme 5.19).



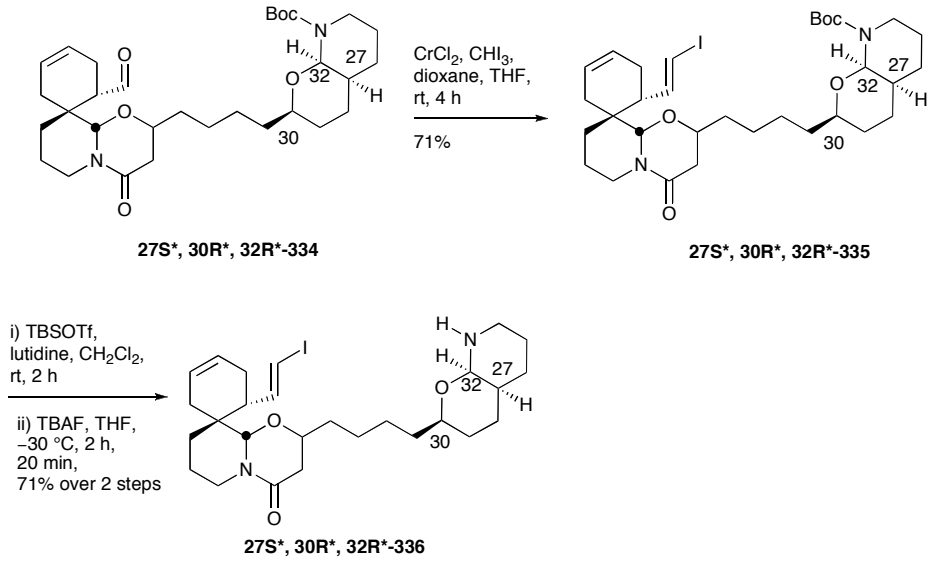
Scheme 5.19 Proposed imine coupling partner.

Pleasingly, Unsworth found the imine coupling proceeded as envisaged; treatment of imine **332** and acid **267** with the peptide coupling reagent T3P,[125] then stirring with $SnCl_2 \cdot 2H_2O$ gave the desired ABC-DE system **334**. As expected, concomitant acetal cleavage also took place to reveal the aldehyde (Scheme 5.20).



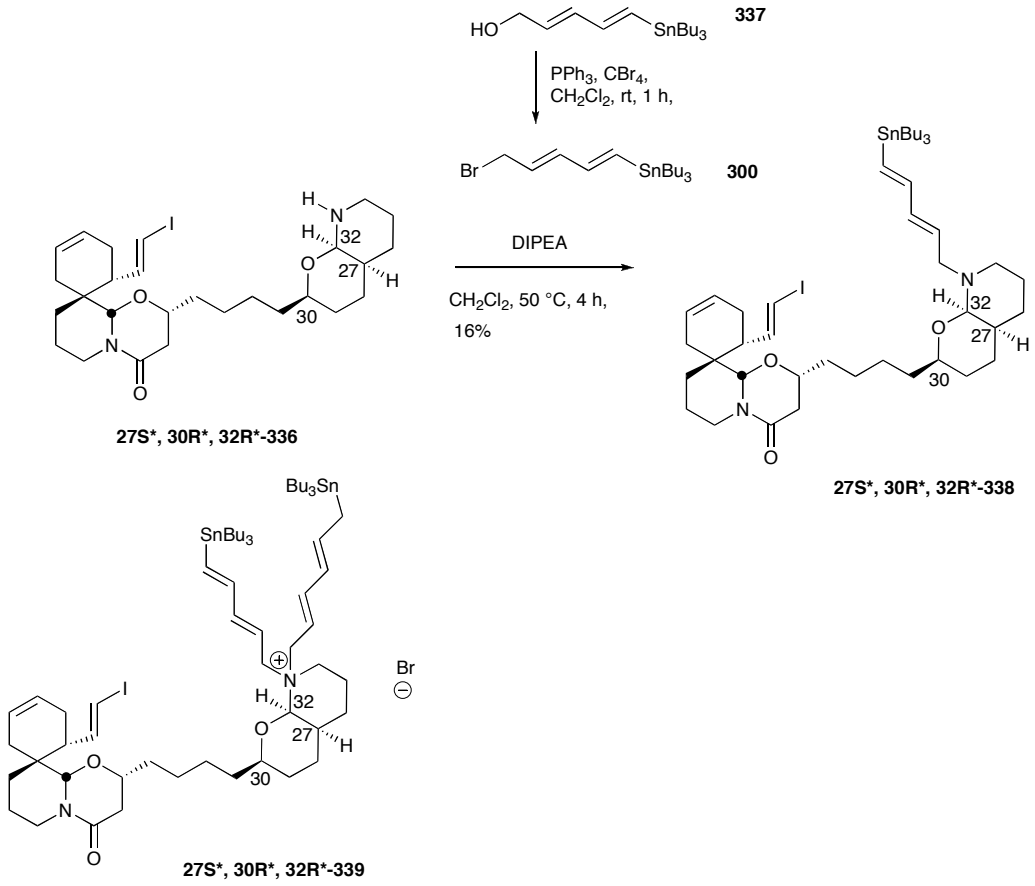
Scheme 5.20 Imine coupling. Carried out by Unsworth.

Unsworth next converted the aldehyde into **334** vinyl iodide **335** using a Takai olefination. The DE core unit is not stable to acidic conditions, and so the Boc group was removed by a basic method as used by Sulikowski; treatment of the Boc-carbamate with TBSOTf generates the corresponding TBS-carbamate, which is then cleaved with TBAF, revealing the amine **336** (Scheme 5.21).



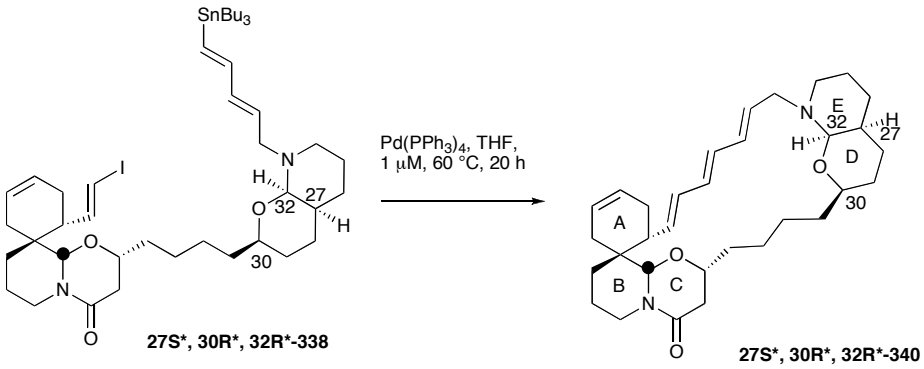
Scheme 5.21 Takai olefination and Boc deprotection. Carried out by Unsworth.

Jean[59] showed the bromide **300** to be unstable, and so in the current strategy **300** was prepared *in situ* from the alcohol **337** and used directly without workup (Scheme 5.22). The ABC-DE compound **336** was treated with this unpurified reaction mixture and DIPEA, generating a small quantity of the desired allylated product **338**. Disappointingly, the major product was the quaternary ammonium salt **339**. It was hoped that, in future, this problem would be removed by using only one equivalent of the bromide **300**, rather than the two equivalents employed in this instance.



Scheme 5.22 Allylation studies. Carried out by Unsworth.

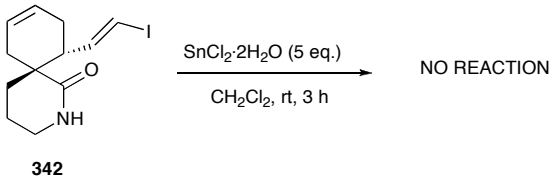
Despite the small quantity of **338** isolated it was still possible for Unsworth to perform the desired Stille ring closing by treatment of iodo-stannane **338** with $Pd(PPh_3)_4$ in THF. The scale was so small that it was possible to analyse this reaction only by mass spectrometry, but this appeared to indicate that "deoxy-'upenamide" **340** was successfully formed (Scheme 5.23).



Scheme 5.23 Ring closure giving deoxy-'upenamide. Carried out by Unsworth.

5.2.4 Oxygenated imine system

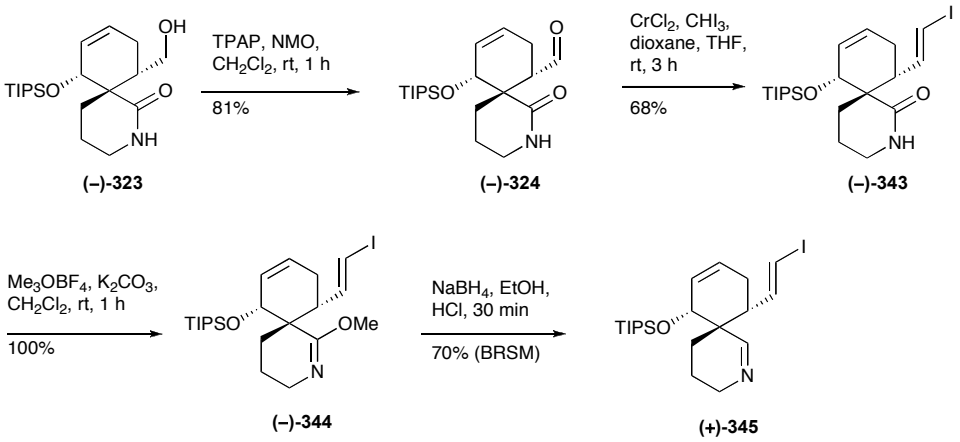
Following this hugely promising result, attention was turned to the synthesis of the oxygenated form of the imine coupling partner **332**. It was hoped to use a more advanced handle to allow the construction of the triene chain chain, replacing the acetal used in the deoxy-version, and thus limiting the number of steps the sensitive DE core unit was exposed to. A test reaction (Scheme 5.24) suggested the possibility of using a vinyl iodide as this coupling partner, as vinyl iodide **342** was stable to the $SnCl_2{\cdot}2H_2O$ mediated 'A' ring forming cyclisation conditions.



342

Scheme 5.24 Vinyl iodide stable to cyclisation conditions. Carried out by Unsworth.

Vinyl iodide containing imine **345** was synthesised starting from the alcohol **(–)-323** (synthesis described in Scheme 5.16). This was oxidised to the aldehyde **(–)-324** *via* a Ley–Griffith oxidation followed by a Takai olefination to deliver the vinyl iodide **(–)-343** (Scheme 5.25). Imidate formation with Meerwein's salt delivered the imidate **(–)-344** and then careful partial reduction with sodium borohydride gave the desired imine **(+)-345**.



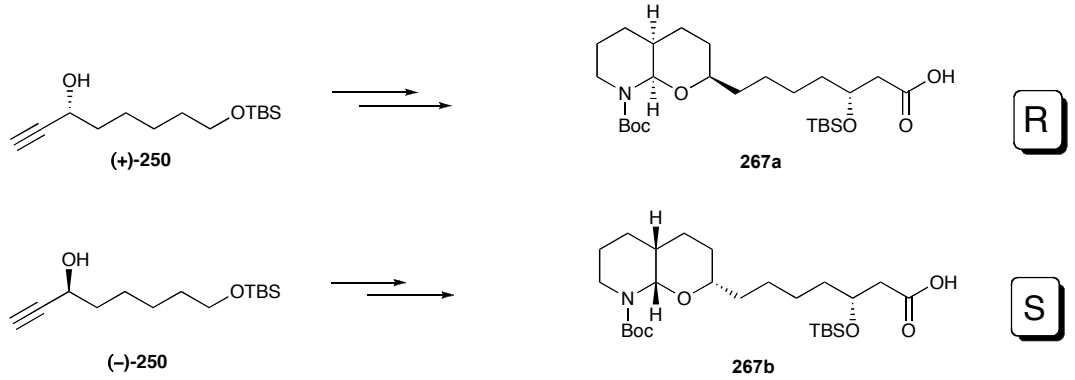
(–)-323 **(–)-324** **(–)-343**

(–)-344 **(+)-345**

Scheme 5.25 Synthesis of vinyl iodide imine.

This imine was to be coupled with acid **267** in a similar way to the coupling of deoxy-**332**. As mentioned earlier, only the relative stereochemistry of the DE core unit was

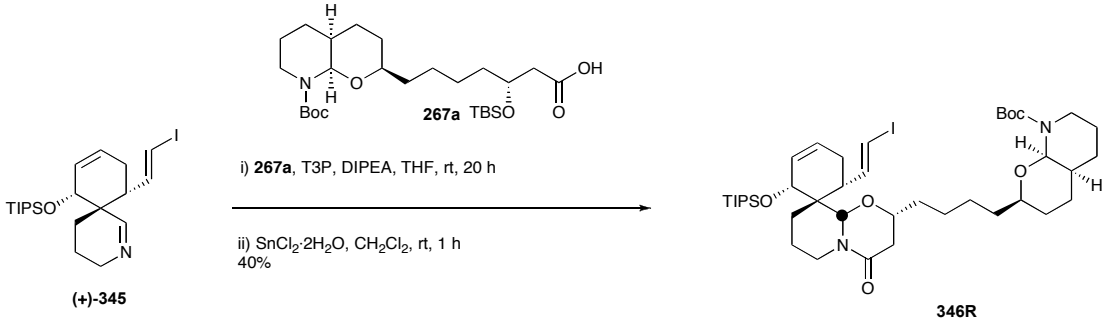
elucidated by Jiménez *et al.*[1] and thus both possible DE core units **267a** and **267b** were synthesised as described in Chapter 4. This enantio-enriched (e.r. 93:7) material was now used – giving two series of compounds. These were labelled **R** and **S**, with **R** derived from the (*R*)-alcohol **250** and **S** from the (*S*)-**250** (Scheme 5.26). According to Jiménez's assignment, one of these should result in 'upenamide.



Scheme 5.26 DE core units.

5.2.5 R Series

We were delighted to observe that the oxygenated imine compound **(+)-345** reacted very similarly to the deoxy-model system. Treatment with T3P and DIPEA promoted the coupling of **(+)-345** and acid **267a**, which was followed by cyclisation with $SnCl_2{\cdot}2H_2O$, delivering the desired coupled compound **346R** (Scheme 5.27).

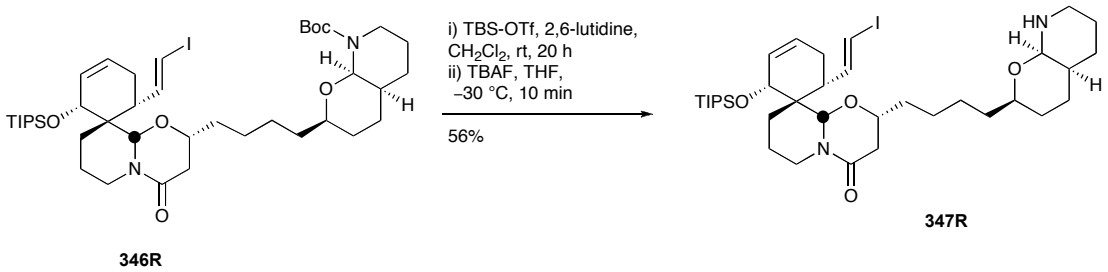


Scheme 5.27 Series R coupling.

In the key $SnCl_2.2H_2O$ cyclisation step the ABC-DE couple **346R** was formed in a >10:1 mixture of diastereoisomers with the major diastereoisomer isolable cleanly following column chromatography. It was assumed that the major diastereoisomer was as drawn, with the hemiaminal proton H-10 *syn* to H-2. This assumption was based on the work by Reid[126] and Schmidt[60] who showed that the reaction conditions

promote equilibrium of this stereocentre, and that the isomer shown is thermodynamically stable in model systems.

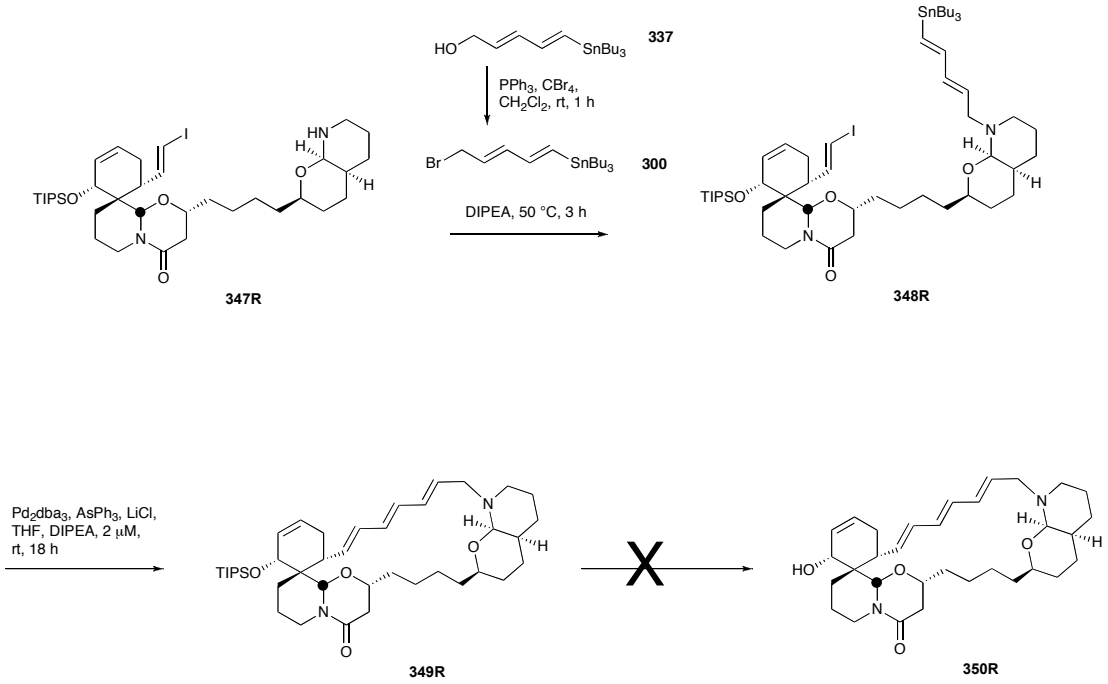
The Boc protecting group was removed under the basic conditions described previously, by forming the TBS carbamate and cleaving with TBAF (Scheme 5.28).



346R **347R**

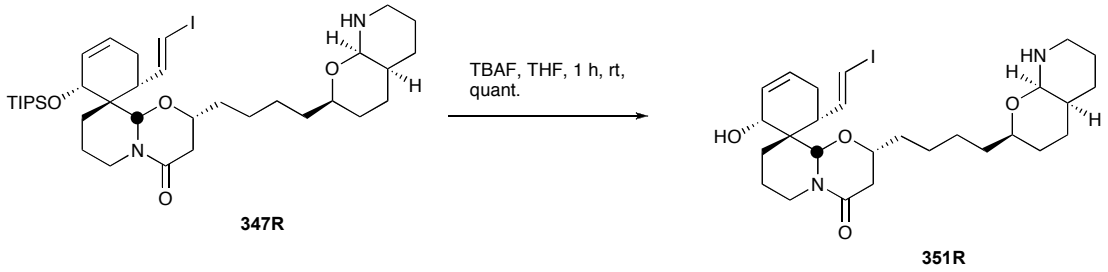
Scheme 5.28 Boc deprotection of **346R**.

Allylation of the deprotected **347R** was successful under the previously described conditions, making one equivalent of the bromide **300** *in situ* and treating with DIPEA. These conditions delivered the desired Stille cyclisation precursor **348R** (Scheme 5.29), with none of the undesired quaternary ammonium salt observed previously being isolated. Compound **348R** showed notable destannylation on storage, and so was used immediately without purification in the key ring-closing Stille reaction to deliver the TIPS-protected compound **349R**. Disappointingly, all attempts to remove the TIPS group were unsuccessful. TBAF returned the TIPS-protected **349R**, and treatment with HF·pyridine resulted in degradation, with only TIPS residues recovered. Despite this setback, this was a very exciting result, representing the first union of the fully formed ABC and DE core units in the macrocycle of ’upenamide.



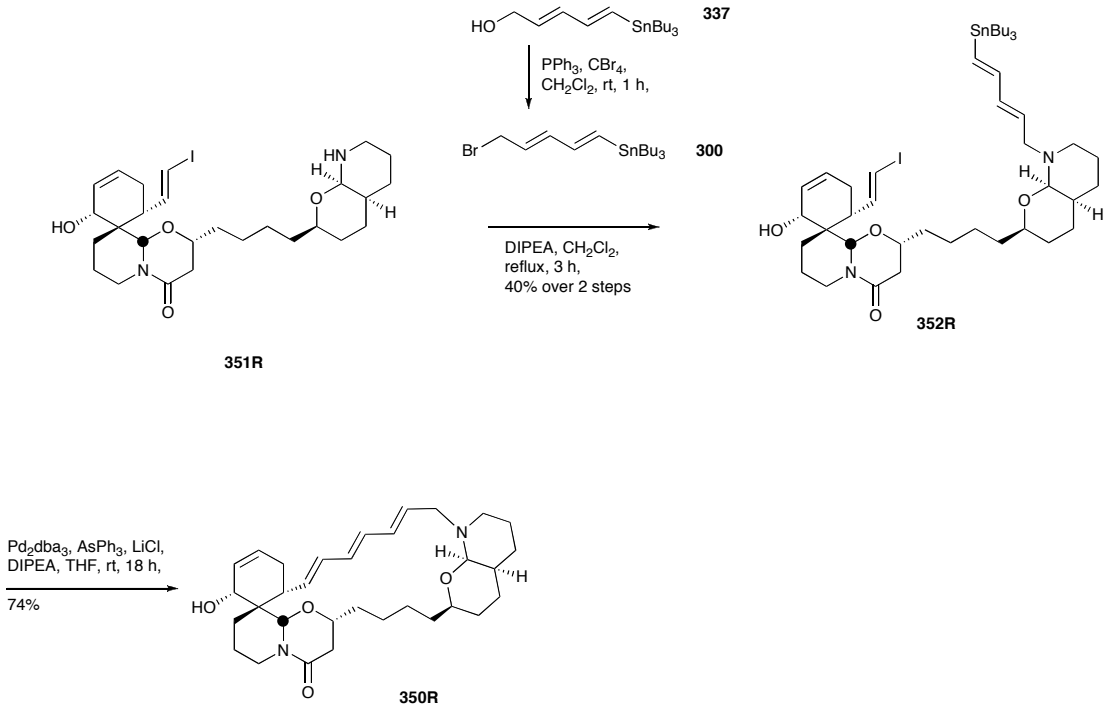
Scheme 5.29 Allyation and Stille on TIPS-protected R series. No yields reported as on a very small scale. Carried out by Unsworth.

It was assumed that the difficulties encountered attempting to remove the TIPS protecting group were due to steric hinderance in the cyclised material, and it was hoped it would be possible to remove it at an earlier stage. We were gratified to find that this was readily achieved by treating the amine **347R** obtained after hydrolysis of the Boc group with TBAF, giving the very polar amino alcohol **351R** (Scheme 5.30).



Scheme 5.30 Early TIPS deprotection. Carried out by Unsworth.

Pleasingly, amino alcohol **351R** was successfully *N*-alkylated with bromide **300** under the conditions described previously, delivering the stannane **352R**. In the key Stille reaction the material was cyclised, to deliver the desired 'R' isomer of 'upenamide (Scheme 5.31).



Scheme 5.31 The 'R' isomer of 'upenamide. Carried out by Unsworth.

The product isolated from the Stille reaction was a white film, which was insoluble in CD_3OD. This was surprising, as the isolated natural product was described with NMR data collected in deuterated methanol. The ^1H NMR spectrum of the product in $CDCl_3$ (Figure 5.4) contained the expected signals with the distinctive doublet and doublet of doublet vinyl iodide ^1H signals at $\delta_H \sim 7.2$ and 5.9 no longer present, and new alkene peaks present as a multiplet between 6.3 and 5.8. However the spectrum appeared quite different from the data described for 'upenamide by Jiménez (Figure 5.5), especially in the alkene region. It was possible this was a solvent effect, as NMR data in different solvents can vary considerably. The unexpected CD_3OD insolubility of the material isolated, combined with the inconclusive NMR data, led to the assumption that the DE stereochemistry was wrong: that the DE core unit resulting from the S-series would result in the total synthesis. Attention was thus turned to this compound.

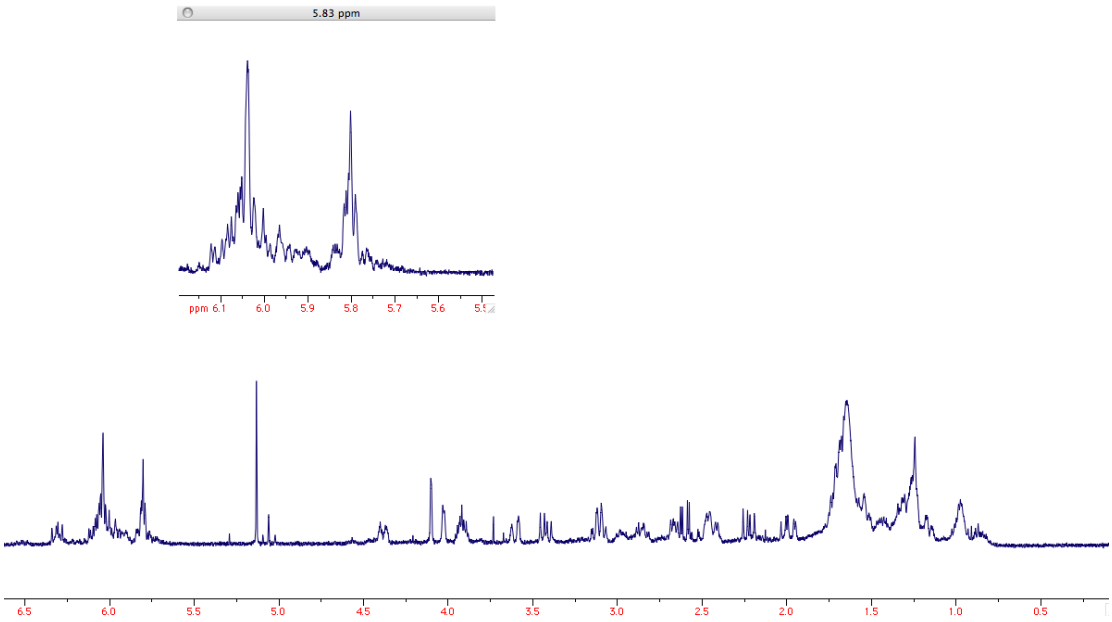


Figure 5.4 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **350R**.

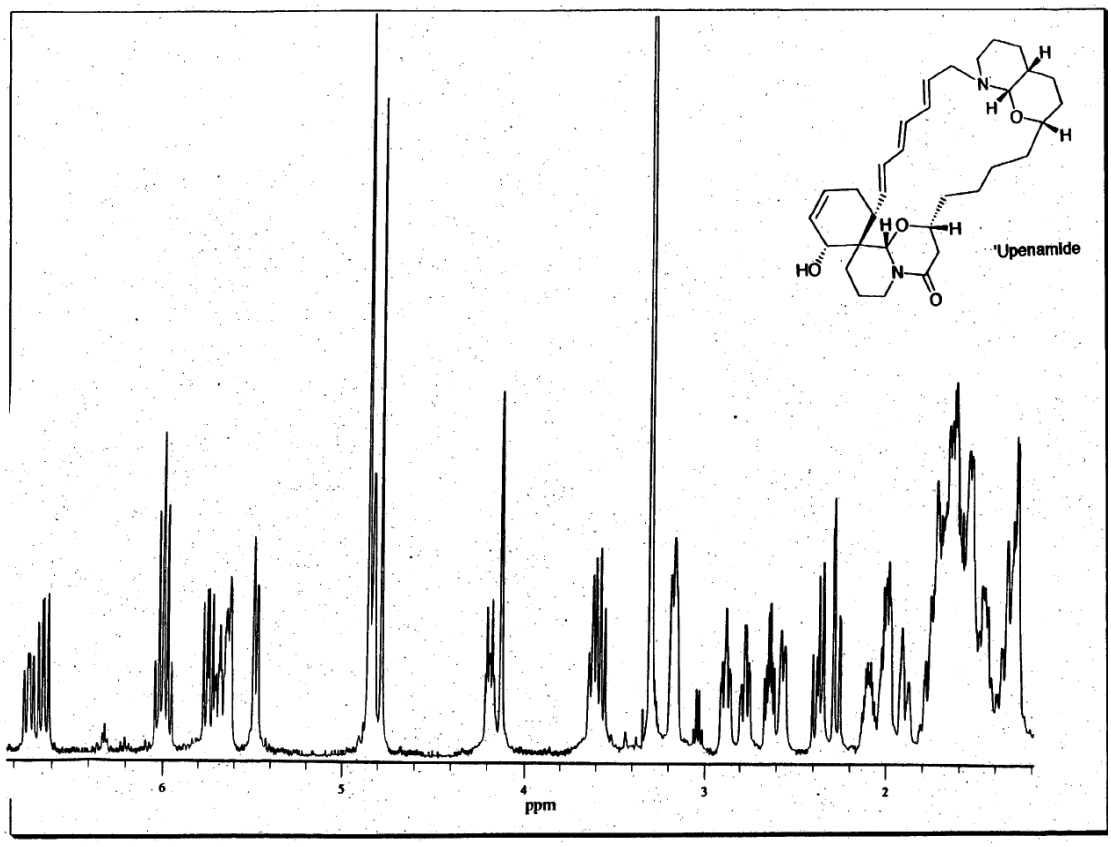
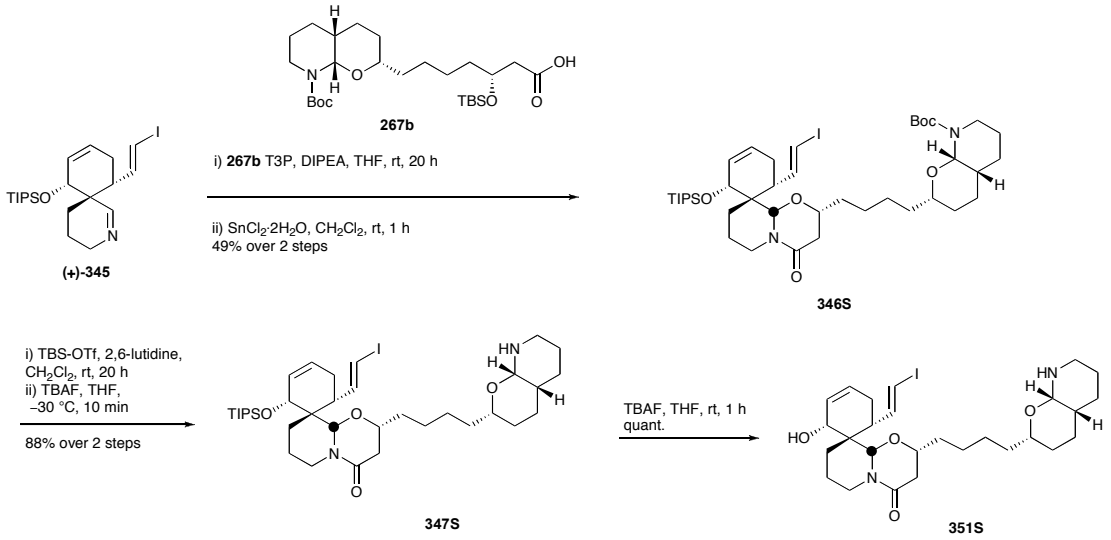


Figure 5.5 Reported ^{1}H NMR spectrum of 'upenamide.[1]

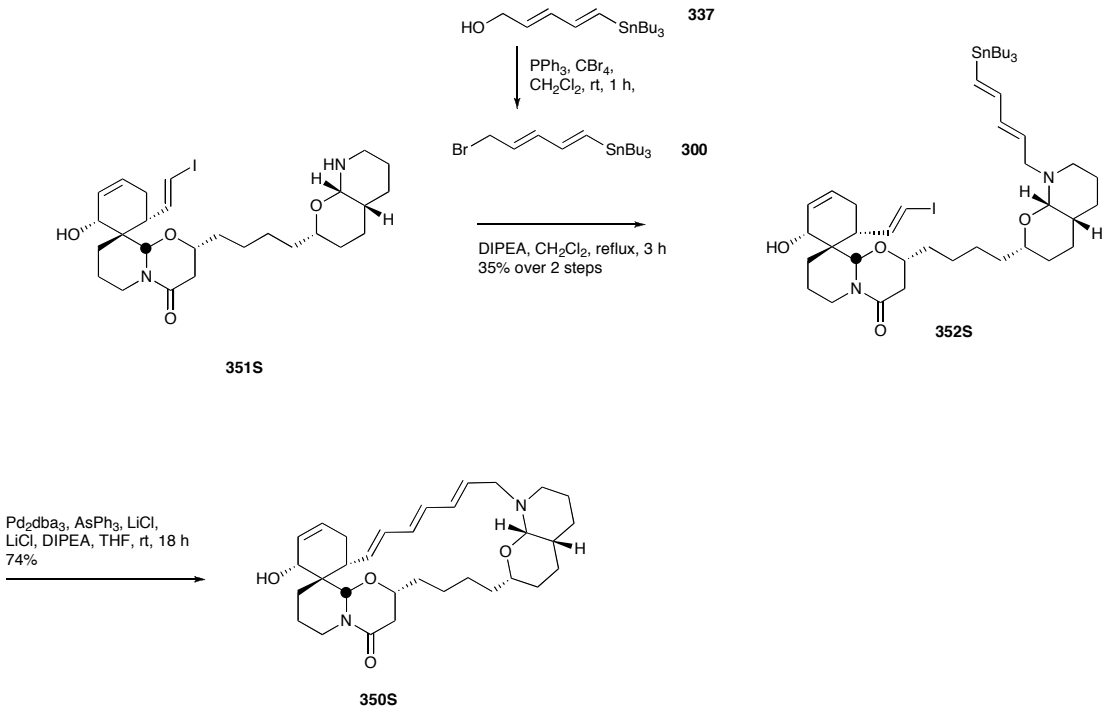
5.2.6 S Series

Coupling the imine **(+)-345** with the S-isomer of carboxylic **267b** and treating with $SnCl_2 \cdot 2H_2O$ to cyclise gave the ABC-DE compound **346S**. The Boc group was removed under the basic conditions described for the R-series delivering the amine **347S**, which was then treated with TBAF to cleave the TIPS protecting group and give the amino alcohol **351S** (Scheme 5.32).



Scheme 5.32 S-series coupling and Boc deprotection.

Amino alcohol **351S** was then allylated with bromide **300** and the Stille cyclisation performed in an identical fashion to R-series (Scheme 5.33), delivering **350S** the reported structure S diastereoisomer of ’upenamide.



Scheme 5.33 S series cyclisation. Carried out by Unsworth.

Once again, all of the data collected suggested the desired cyclised product **350S** was formed, but the ^{1}H and ^{13}C-NMR data did not match those reported by Jiménez and co-workers for the natural product. In this series, the product was soluble in CD_3OD, allowing direct comparison of the NMR data. The ^{1}H NMR spectrum is illustrated in Figure 5.6. The vinylic region (insert in Figure 5.6) is again particularly different to that of the natural product (Figure 5.7).

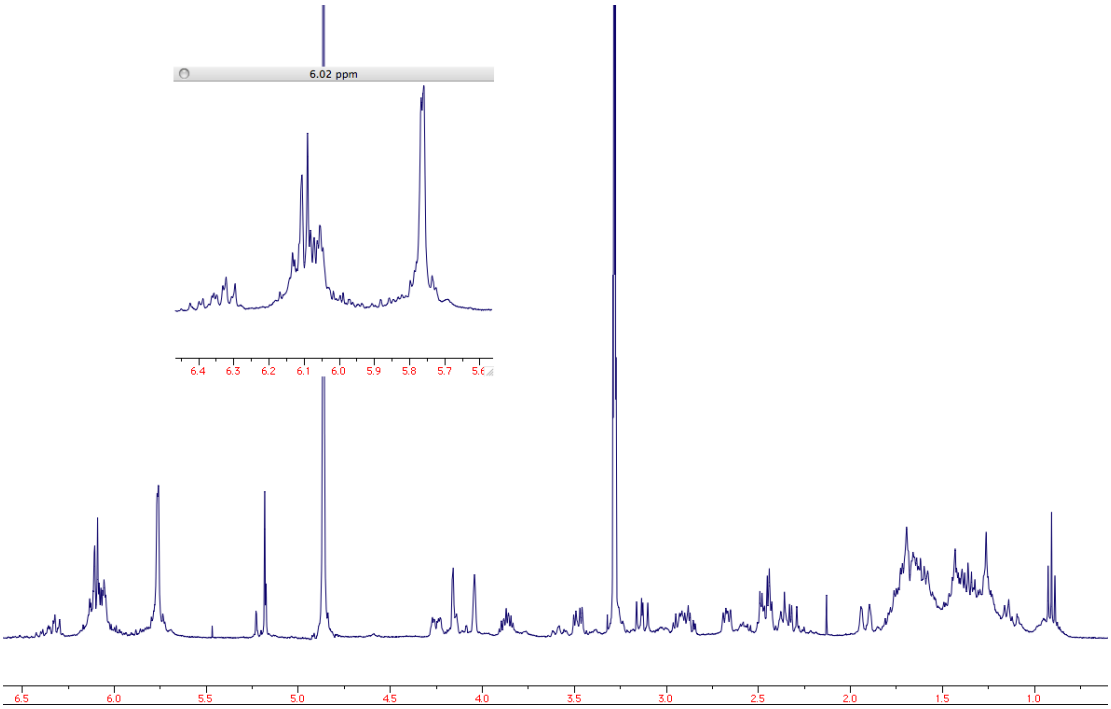


Figure 5.6 ^{1}H NMR Spectrum of **350S** (400 MHz, CD_3OD).

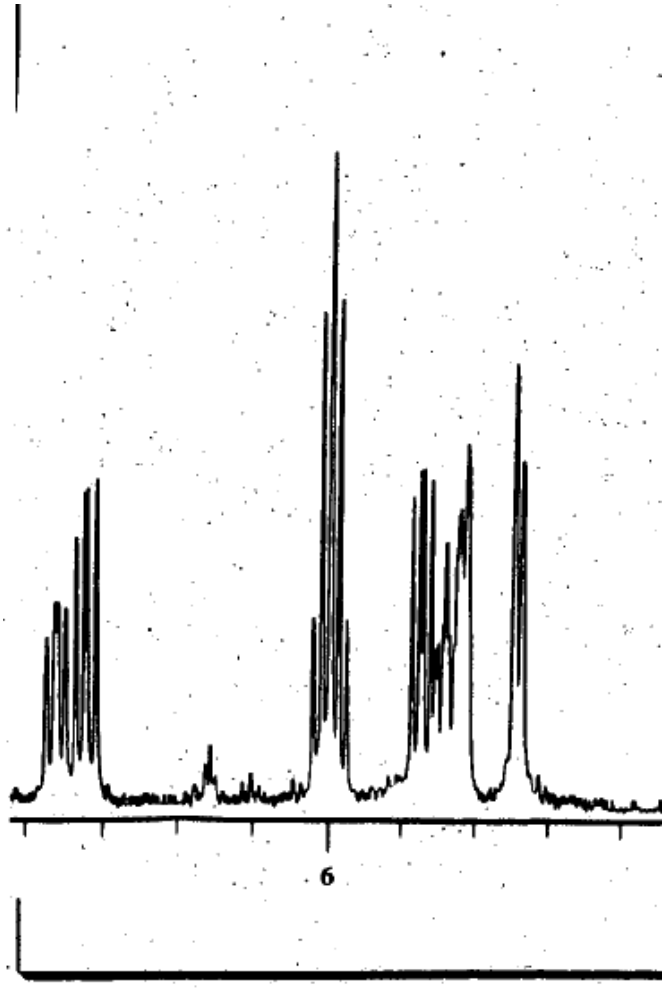
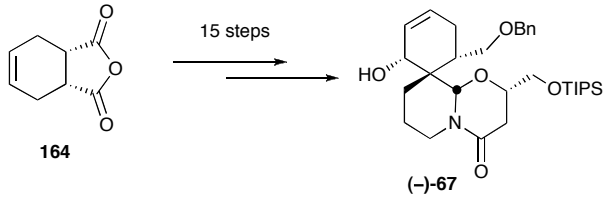


Figure 5.7 Vinylic region of isolated material.[1]

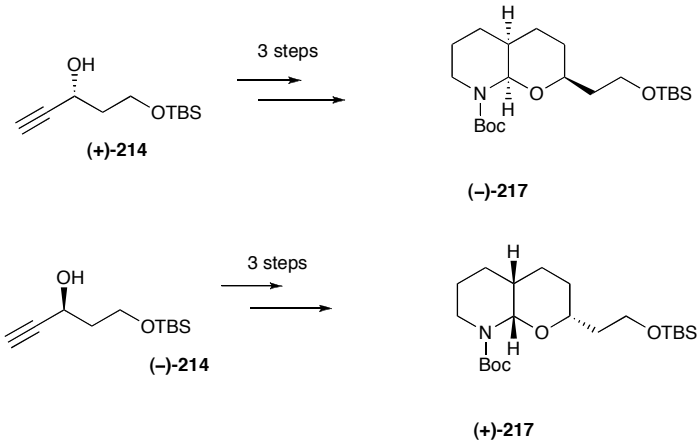
Disappointingly, neither **350R** or **350S** matched the literature data for ’upenamide described by Jiménez *et al.*[1] Investigations are ongoing to confirm the structure of both **350R** and **350S** and to confirm where the differences lie. Attempts to obtain crystallographic data for **350R** and **350S** are in progress, as this would definitively confirm the structure of the molecules synthesised.

5.3 Conclusions

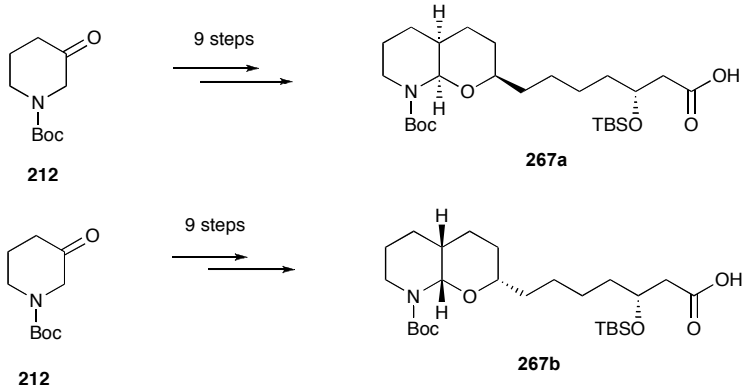
This Thesis describes a shortened route to the ABC core unit of 'upenamide **(–)-67** in 15 steps from the commercially available *meso*-anhydride **164**, a new route to both enantiomers of the DE core unit **217** from piperidone **212**. The chemistry developed to synthesise **217** was then applied to the synthesis of both enantiomers of the DE core unit incorporating the fully saturated linking chain and a β-hydroxy ester **267** moiety for coupling studies.



Scheme 5.34 Shortened synthesis of ABC core **(–)-67**.

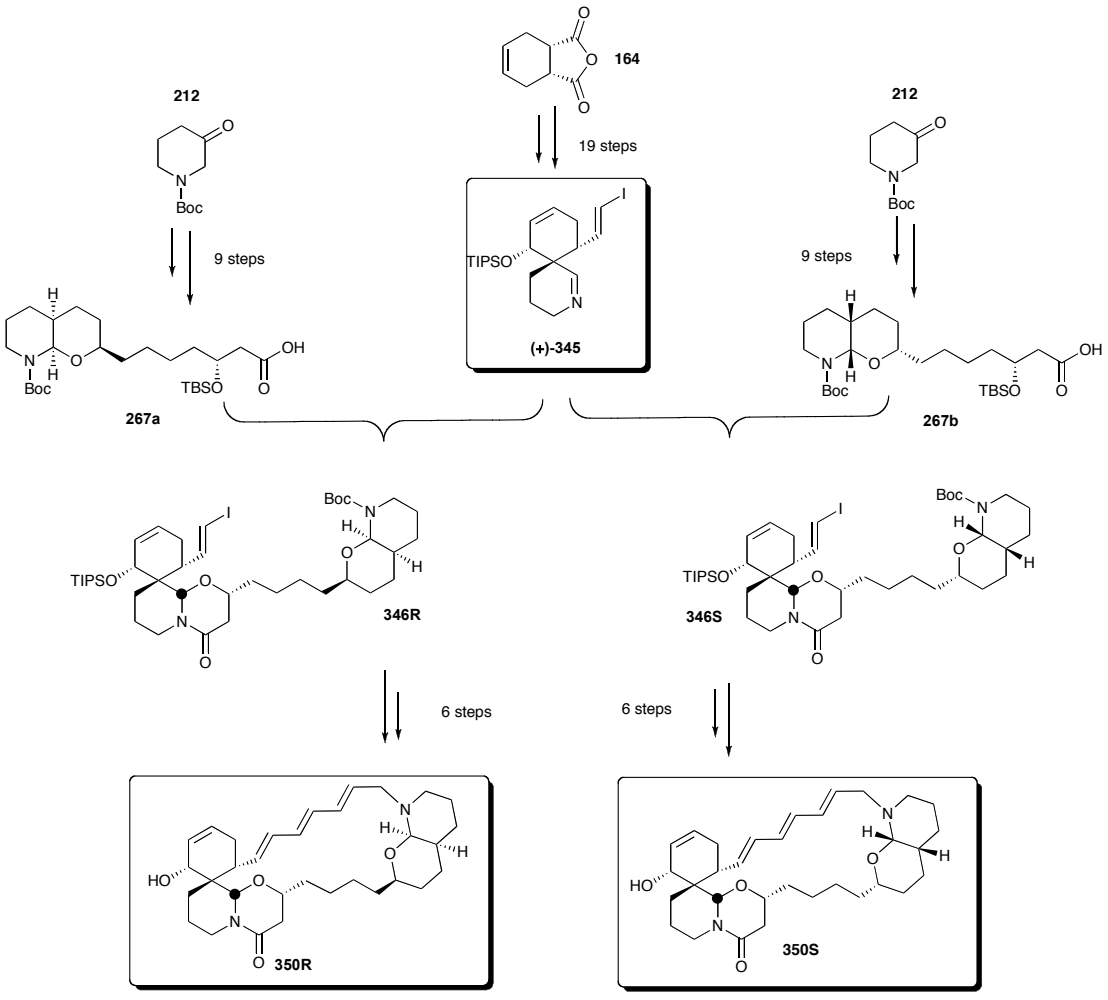


Scheme 5.35 Synthesis of both enantiomers of **217**.



Scheme 5.36 Synthesis of DE core **267** incorporating linker chain.

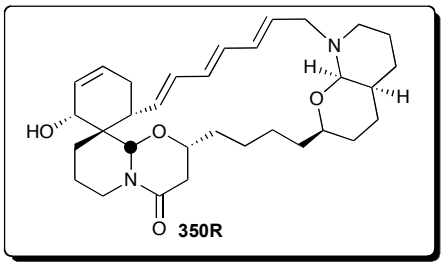
The final Chapter details attempts to join the ABC and DE core units *via* a novel tandem acyl iminium formation/$SnCl_2 \cdot 2H_2O$ mediated cyclisation, which successfully gave the ABC and DE units linked through the fully saturated chain. Further studies produced both of the reported possible structures of 'upenamide **350R** and **350S**, and attempts to confirm if either are the natural product are under way. The route described comprises a 19 step synthesis of the bicyclic BC ring-containing **267** from anhydride **164**, a 9 step synthesis of the bicyclic DE ring-containing **(+)-345** from piperidinone **212**, and a further 6 steps to couple the fragments and complete the synthesis. This represents in total a longest linear sequence of 25 steps.



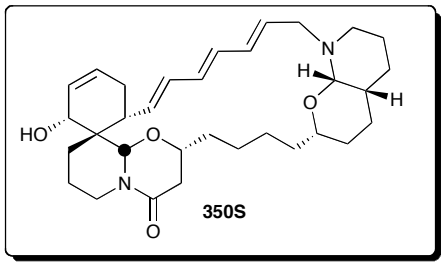
Scheme 5.37 Current route to the reported structure of 'upenamide.

5.4 Future work

The priority is to confirm the structure of the compounds **350R** and **350S**, ideally by X-ray crystallography. A thorough examination of the published isolation data has revealed no obvious weaknesses in the original structural assignment of ’upenamide. The isolation group have been contacted, however no sample of the natural product remains; but it is hoped we will be able to access the original data. Hopefully this, combined with the confirmed structure of the material synthesised, will allow us to understand the differences, and see where the discrepancies lie. If the incorrect structures have been prepared, then modifications of the route developed to allow access to the correct material will be sought. If the reported structure turns out to be incorrect, then a rethink will be required, but again, perhaps modification of the ssynthetic route described here would allow access to the correct structure of ’upenamide. These studies are ongoing in the group.



350R



350S

Chapter 6 – Experimental

Diethyl ether (Et_2O) was dried using an MBraun MPS solvent purification system. Anhydrous tetrahydrofuran (THF) was obtained by distillation over sodium benzophenone. Methanol (MeOH) was distilled from magnesium.[127] Petroleum ether (PE) refers to light petroleum ether, b.p. 40–60 ^oC. All reagents were used as supplied by the manufacturers, unless otherwise stated. Stannous chloride dihydrate was purchased from Aldrich (Cat No. 20803-5) and was used without further purification. Column chromatography was performed using Fluka silica gel 60 at a low positive pressure. Analytical thin layer chromatography was performed on aluminium sheets pre-coated with Merck silica gel 60 F_{254}, and visualised with ultraviolet light (254 nm), aqueous potassium permanganate or alcoholic vanillin solutions, as appropriate. Preparative TLC was performed on Whatman Partasil K6F pre-coated 60 Silica Gel Glass plates, and visualised with ultraviolet light (254 nm).

SCX refers to the use of prepacked Varian BondElut SCX colums (1 g, 20 g). All melting points were taken on a Gallenkamp apparatus. Proton magnetic resonance (^1H NMR) spectra were recorded at 400 MHz on a JEOL ECX 400 spectrometer or a JEOL ESC 400 spectrometer, or at 270 MHz on a JEOL ECX 270 spectrometer and are reported as follows: chemical shift δ (ppm) (number of protons, multiplicity, coupling constant *J* (Hz), assignment). The coupling constants are quoted to the nearest 0.5 Hz (s = singlet, d = doublet, t = triplet, q = quartet, quin. = quintet, m = multiplet, br = broad, app = apparent) and are reported as measured splittings on each individual resonance. The residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) was used as an internal reference. ^{13}C NMR spectra were recorded at 100 MHz on a JEOL ECX 400 spectrometer or at 125 MHz on a Bruker AV500 spectrometer. The central reference of $CDCl_3$ (δ_C = 77.0 ppm, t) was used as an internal reference. ^{19}F NMR spectra were recorded at 254 MHz on a JEOL ECX 400 spectrometer. Chemical shifts are reported in parts per million (ppm) to the nearest 0.01 ppm for ^1H and the nearest 0.1 ppm for ^{13}C and ^{19}F. Infrared spectra were carried out on a ThermoNicolet IR100 spectrometer and are recorded as a thin film between NaCl disks. Absorption maxima are reported in wavenumbers (cm^{-1}) and only selected absorbances are reported. Mass

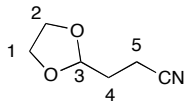
spectra and accurate mass measurements were recorded on a Micromass Autospec spectrometer.

Microwave irradiation refers to the use of a CEM 'Discovery' reactor, with reactions contained in 10 mL CEM tubes with Intellivent® caps.

All numbering of the structures below is for characterisation and does not conform to IUPAC rules.

6.1 Methodology compounds

3-[1,3]Dioxolan-2-ylpropionitrile (98)



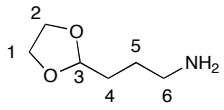
Prepared according to the procedure described by Shimizu and co-workers.[65]

To a stirred solution of sodium cyanide (1.20 g, 30.6 mmol) and benzyltriethylammonium chloride (570 mg, 2.55 mmol) in water (10 mL) was added 2-(2-bromoethyl)-1,3-dioxolane (3.00 mL, 25.5 mmol) maintaining a temperature of 20 ^{o}C with a water bath. The resulting emulsion was heated to 90 ^{o}C for 4 h then cooled, diluted with water (10 mL) and extracted with Et_2O (4 x 10 mL). The organic extracts were combined, washed with brine (20 mL) and dried over $MgSO_4$. The volatiles were removed under reduced pressure to yield the crude nitrile **98** which was purified by column chromatography. Eluting with 1:1 PE:Et_2O gave the *title compound* **98** as a clear colourless oil (2.01 g, 62%); R_f 0.20 (1:1 PE:Et_2O); δ_H (400 MHz, $CDCl_3$) 4.96 (1H, t, *J* 4.0, H-3), 3.98–3.94 (2H, m, H-1/H-2), 3.88–3.83 (2H, m, H-1/H-2), 2.44 (2H, t, *J* 7.5, H-5), 2.01 (2H, td, *J* 7.5, 4.0, H-4).

^{1}H NMR data consistent with literature.[65]

KAG/1/9

3-[1,3]Dioxolan-2-ylpropylamine (94)



Prepared according to the procedure described by Shimizu and co-workers.[65]

To a stirred slurry of $LiAlH_4$ (900 mg, 23.6 mmol) in Et_2O (40 mL) under a stream of nitrogen was added nitrile **98** (2.00 g, 15.7 mmol) in Et_2O (30 mL) at such a rate as to maintain a gentle reflux. The reaction mixture was heated to reflux for 12 h and then cooled and quenched by the careful addition of a mixture of Celite and $Na_2SO_4{\cdot}10H_2O$ (1:1) until the evolution of gas was complete (~ 5 g). The reaction was filtered, the

solids washed with Et_2O (3 x 20 mL) and the volatiles removed from the filtrate under reduced pressure to yield the *title compound* **94** as a colourless oil (1.80 g, 88%) which was used without further purification; IR ν_{max} (neat) 3627, 2930, 2868, 1602, 1408, 1139, 1036, 944; δ_H (400 MHz, $CDCl_3$) 4.78 (1H, t, *J* 4.5, H-3), 3.89–3.86 (2H, m, H-1/H-2), 3.78–3.74 (2H, m, H-1/H-2), 2.64 (2H, t, *J* 7.0, H-6), 1.64–1.44 (6H, m, H-4, H-5, NH_2); δ_C (100 MHz, $CDCl_3$) 104.4 (C-3), 64.8 (C-1, C-2), 42.0 (C-6), 31.1 (C-4), 28.1 (C-5); *m/z* (ESI) 132 (100), $[MH]^+$; [HRMS (ESI) calcd. for $C_6H_{14}NO_2$, 132.1019. Found: $[MH]^+$ 132.1025. (4.4 ppm error)].

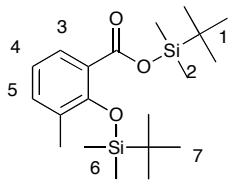
^1H NMR data consistent with literature.[65]

KAG/1/8

This reaction can also be performed in THF, using either $LiAlH_4$ solid, or as a solution in THF (commercially available), in comparable yields.

KAG/1/12, KAG/1/38

tert-Butyldimethylsilyl 2-(_tert_-butyldimethylsilyloxy)-3-methylbenzoate (109)

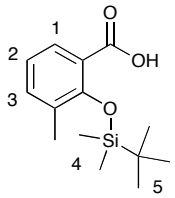


To a stirred solution of 3-methylsalicylic acid (500 mg, 3.28 mmol) and *N,N*-di*iso*propylethylamine (1.26 mL, 7.22 mmol) at 0 °C was added *tert*-butyldimethyl silyl chloride (1.14 g, 7.54 mmol) portionwise. The reaction was warmed to rt and stirred for 5 hours under an atmosphere of argon, then partitioned between CH_2Cl_2 (75 mL) and water (75 mL), the organic layer was sequentially washed with water (3 x 100 mL), aqueous $CuSO_4$ (sat., 100 mL) and water (100 mL). The organic layer was dried over $MgSO_4$ and volatiles were removed under reduced pressure to yield the crude **109** which was purified by column chromatography. Eluting with 9:1 PE:Et_2O gave the *title compound* **109** as a yellow oil (1.19 g, 96%); R_f 0.90 (1:1 PE:Et_2O); δ_H (400 MHz, $CDCl_3$) 7.56–7.53 (1H, m, H-3), 7.25 (1H, dd, *J* 7.5, 2.0, H-5), 6.87 (1H, dd, *J* 7.5, 7.4 H-4), 2.23 (3H, s, CH_3), 1.02 (9H, s, H-1), 0.99 (9H, s, H-7), 0.35 (6H, s, H-2), 0.11 (6H, s, H-6).

^1H NMR data consistent with literature.[128]

KAG/1/21

2-(*tert*-Butyldimethylsilyloxy)-3-methylbenzoic acid (107)

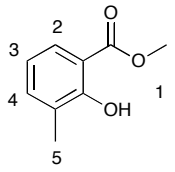


To a stirred solution of *tert*-butyldimethylsilyl 2-(*tert*-butyldimethylsilyloxy)-3-methylbenzoate **109** (200 mg, 0.526 mmol) in THF (10 mL) at 0 °C under an atmosphere of argon was added slowly TBAF (1 M in THF, 0.53 mL, 0.526 mmol). The reaction was stirred at rt for 10 minutes, then partitioned between water (10 mL) and CH_2Cl_2 (10 mL). The organic layer was washed with water (10 mL), then dried over $MgSO_4$ and volatiles removed under reduced pressure to yield the *title compound* **107** as a colourless solid (91 mg, 65%) which was used without further purification; R_f 0.88 (1:1 PE:Et_2O); δ_H (400 MHz, $CDCl_3$) 7.75 (1H, d, *J* 7.5, H-1), 7.36 (1H, d, *J* 7.5, H-3), 6.82 (1H, app t, *J* 7.5, H-2), 2.27 (3H, s, CH_3), 0.91 (9H, s, H-5), 0.10 (6H, s, H-4).

The compound decomposed to the unprotected phenol on storage (even at low temperature), and no further characterisation was obtained.

KAG/1/25

Methyl 2-hydroxy-3-methylbenzoate (110)



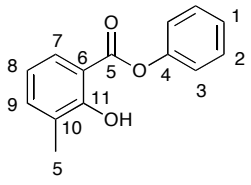
To a stirred solution of 3-methyl salicylic acid (500 mg, 3.29 mmol) **95** in MeOH (10 mL) was added conc. H_2SO_4 (1 mL), and the reaction heated to reflux for 19 h. The reaction was cooled to 0 °C and solid K_2CO_3 added portionwise until the pH of the reaction was ~ 6. The solvent was then removed under reduced pressure and the

resulting solid partitioned between water (25 mL) and CH_2Cl_2 (25 mL). The organic layer was dried over $MgSO_4$ and the volatiles removed under reduced pressure to yield the *title compound* **110** as a colourless oil (147 mg, 27%); R_f 0.80 (1:1 PE:Et_2O); δ_H (400 MHz, $CDCl_3$) 11.02 (1H, s, OH), 7.67 (1H, d, *J* 7.5, H-2), 7.30 (1H, d, *J* 7.5, H-4), 7.67 (1H, t, *J* 7.5, H-3), 3.93 (3H, s, H-1), 2.26 (3H, s, H-5).
^{1}H NMR data consistent with literature.[129]
KAG/1/24

General procedure A – preparation of phenyl esters.

To a stirred solution of carboxylic acid (1 eq.) and a catalytic amount of pyridine (2 drops) in CH_2Cl_2 (0.15 M) at 0 °C was added thionyl chloride (1 eq.) dropwise and the reaction stirred at rt for 30 minutes under an atmosphere of argon before the volatiles were removed under reduced pressure at 0 °C. The resulting gum was redissolved in CH_2Cl_2 (20 mL) at 0 °C, then phenol (2 eq.) followed by pyridine (2 eq.) added. The reactions were stirred at 0 °C for a further 30 minutes, then allowed to warm to room temperature and volatiles removed under reduced pressure. The crude products were purified by column chromatography, eluting with 97:3 → 94:6 PE:EtOAc.

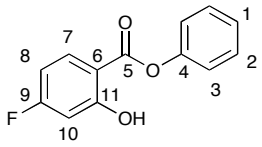
Phenyl 2-hydroxy-3-methylbenzoate (111)



3-Methyl salicylic acid (500 mg, 3.29 mmol), thionyl chloride (240 μL, 3.29 mmol), pyridine (540 μL, 6.58 mmol) and phenol (620 mg, 6.54 mmol) according to general procedure **A** gave the *title compound* **111** as a pale yellow oil (493 mg, 65%); R_f 0.25 (95:5 PE:EtOAc); IR ν_{max} (neat) 3200, 1686, 1614, 1590, 1492, 1461, 1380, 1329, 1288, 1193, 1129, 1084, 740; δ_H (400 MHz, $CDCl_3$) 10.81 (1H, s, OH), 7.97 (1H, d, *J*

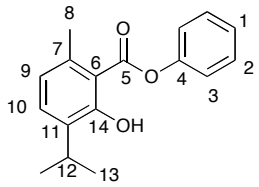
7.5, H-7), 7.51–7.47 (2H, m, H-2), 7.43 (1H, d, *J* 7.5, H-9), 7.34 (1H, t, *J* 7.5, H-1), 7.26–7.23 (2H, m, H-3), 6.91 (1H, app t, *J* 7.5, H-8), 2.34 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 169.4 (C-5), 160.6 (C-11), 150.2 (C-4), 137.2 (C-9), 129.6 (C-2), 127.8 (C-7), 126.9 (C-10), 126.3 (C-1), 121.7 (C-3), 118.8 (C-8), 111.1 (C-6), 15.7 (CH_3); *m/z* (ESI) 172 (100), 251 (20) $[MNa]^+$; [HRMS (ESI) calcd. for $C_{14}H_{12}NaO_3$, 251.0679 Found: $[MNa]^+$ 251.0679 (0.0 ppm error)].
KAG/1/43

Phenyl 4-fluoro-2-hydroxybenzoate (112)



4-Fluoro-2-hydroxybenzoic acid (500 mg, 3.21 mmol), thionyl chloride (233 μL, 3.21 mmol), pyridine (520 μL, 6.44 mmol), and phenol (606 mg, 6.44 mmol) according to general procedure **A** gave the *title compound* **112** as a white sticky solid (223 mg, 32%); m.p. 44–46 °C; R_f 0.35 (96:4 PE:EtOAc); IR ν_{max} (neat) 3403, 1654, 1507, 1476, 1455, 1388, 1341, 1263, 1138, 1121, 1965; δ_H (400 MHz, $CDCl_3$) 10.74 (1H, s, OH), 8.09 (1H, dd, $^3J_{HH}$ 9.0, $^3J_{HF}$ 7.0, H-8), 7.46 (2H, t, *J* 8.0, H-2), 7.32 (1H, t, *J* 8.0, H-1), 7.20 (2H, d, *J* 8.0, H-3), 6.75–6.79 (2H, m, H-7, H-10); δ_C (100 MHz, $CDCl_3$) 168.4 (C-5), 167.5 (d, $^1J_{CF}$ 254.0, C-9), 164.4 (d, $^3J_{CF}$ 13.0, C-11), 150.0 (C-4), 132.7 (d, $^3J_{CF}$ 12.0, C-7), 129.8 (C-2), 126.6 (C-1), 121.7 (C-3), 108.7 (d, $^4J_{CF}$ 1.5, C-6), 108.0 (d, $^4J_{CF}$ 23.0, C-8/C-10), 104.7 (d, $^4J_{CF}$ 24.0, C-8/C-10); δ_F (376 MHz, MeOD) –102.5 (ddd *J* 7.0, 7.0, 5.0); *m/z* (ESI) 125 (100) 233 (10), $[MH]^+$ [HRMS (ESI) calcd. for $C_{13}H_{10}FO_3$, 233.0608 Found: $[MH]^+$ 233.0608 (1.6 ppm error)].
KAG/1/70

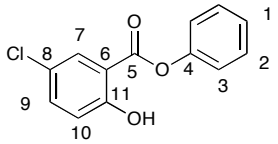
Phenyl 2-hydroxy-3-*iso*propyl-6-methylbenzoate (113)



2-Hydroxy-3-*iso*propyl-6-methylbenzoic acid (500 mg, 2.58 mmol), thionyl chloride (216 μL, 2.58 mmol), pyridine (420 μL, 5.20 mmol) and phenol (489 mg, 5.20 mmol) according to general procedure **A** gave the *title compound* **113** as a pale yellow oil (313 mg, 45%); R_f 0.23 (97:3 PE:Et_2O); IR ν_{max} (neat) 3413, 1666, 1612, 1492, 1414, 1160, 1136, 799, 637; δ_H (400 MHz, $CDCl_3$) 11.36 (1H, s, OH), 7.46 (2H, t, *J* 7.0, H-2), 7.33–7.31 (1H, m, H-1), 7.30 (1H, d, *J* 8.0, H-10), 7.21–7.18 (2H, m, H-3), 6.77 (1H, d, *J* 8.0, H-9), 3.36 (1H, sept, *J* 7.0, H-12), 2.67 (3H, s, H-8), 1.23 (6H, d, *J* 7.0, H-13); δ_C (100 MHz, $CDCl_3$) 171.2 (C-5), 161.0 (C-14), 150.0 (C-4), 138.6 (C-7), 134.9 (C-11), 131.7 (C-9/C-10/C-1), 129.8 (C-2), 122.8 (C-9/C-10/C-1), 126.5 (C-9/C-10/C-1), 121.8 (C-3), 111.1 (C-6), 26.6 (C-12), 24.3 (C-13), 22.5 (C-8); *m/z* (ESI) 271 (100), $[MH]^+$; [HRMS (ESI) calcd. for $C_{17}H_{19}O_3$, 271.1329. Found: $[MH]^+$ 271.1331 (0.9 ppm error)].

KAG/1/69

Phenyl 5-chloro-2-hydroxybenzoate (114)



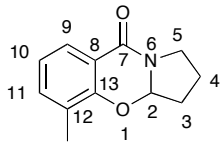
5-Chloro-2-hydroxybenzoic acid (500 mg, 2.89 mmol), thionyl chloride (211 μL, 2.89 mmol), pyridine (467 μL, 5.78 mmol) and phenol (540 mg, 5.76 mmol) according to general procedure A gave the *title compound* **114** as a white solid (363 mg, 34%); m.p. 87–89 °C; Found: C, 62.86; H, 3.71, $C_{13}H_9ClO_3$ requires C, 62.79; H, 3.65%; R_f 0.33 (95:5 PE:Et_2O); IR ν_{max} (neat) 3566, 1685, 1614, 1599, 1473, 1454, 1103, 829, 799, 756; δ_H (400 MHz, $CDCl_3$) 10.45 (1H, s, OH), 8.05 (1H, d, *J* 2.5, H-7), 7.49–7.44 (3H, m, H-9, H-2), 7.33 (1H, tt, *J* 7.5, 1.0, H-1), 7.22–7.19 (2H, m, H-3), 6.99 (1H, d, *J* 9.0, H-10); δ_C (100 MHz, $CDCl_3$) 168.1 (C-5), 160.8 (C-11), 149.9 (C-4),

126.5 (C-9), 129.8 (C-7), 129.6 (C-2), 126.7 (C-8), 124.4 (C-1), 121.6 (C-3), 119.6 (C-10), 112.8 (C-6); *m/z* (ESI) 246 (100), $[MH]^+$; [HRMS (ESI) calcd. for $C_{13}H_{10}{}^{35}ClO_3$, 249.0313. Found: $[MH]^+$ 249.0300 (1.4 ppm error)].
KAG/1/52

General procedure B – Ester displacement and cyclisations

A mixture of 3-[1,3]dioxolan-2-ylpropylamine **94** (1.3 eq.) and phenyl ester (1 eq.) in a sealed tube was heated under microwave irradiation at 135 ^oC for 10 minutes (50 W input power). The resulting gum was allowed to cool to rt, dissolved in CH_2Cl_2 (5 mL) and $SnCl_2{\cdot}2H_2O$ (2 eq.) added in a single portion. The reaction was allowed to stir at rt for 18 h whereupon it was diluted with $CHCl_3$ (5 mL), treated with K_2CO_3 (4 eq.) and stirring continued for a further 30 min. The mixture was filtered through a short pad of Celite, washing with $CHCl_3$ (3 x 10 mL). The volatiles were removed under reduced pressure and the crude products purified by column chromatography, eluting with Et_2O.

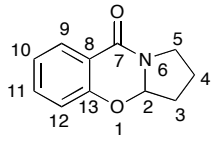
8-Methyl-1,2,3,9a-tetrahydro-9-oxa-3a-aza-cyclopenta[b]naphthalen-4-one (96)



3-[1,3]Dioxolan-2-ylpropylamine (37 mg, 0.285 mmol), phenyl 2-hydroxy-3-methylbenzoate **111** (50 mg, 0.219 mmol) and $SnCl_2 \cdot 2H_2O$ (99 mg, 0.438 mmol) according to general procedure **B** gave the *title compound* **96** as a colourless solid (70 mg, 98%); m.p. 111–113 ^oC; R_f 0.25 (Et_2O); IR ν_{max} (nujol mull) 2955, 2924, 2855, 1669, 1440, 1073; δ_H (400 MHz, $CDCl_3$) 7.76 (1H, d, *J* 7.5, H-9), 7.26 (1H, d, *J* 7.5, H-11), 6.99 (1H, app t, *J* 7.5, H-10), 5.46 (1H, app t, *J* 6.0, H-2), 3.84 (1H, dt, *J* 11.5, 7.5, H-5a), 3.61 (1H, ddd, *J* 11.5, 8.0, 5.0, H-5b), 2.49–2.39 (1H, m, H-3a), 2.33–2.24 (1H, m, H-3b), 2.23 (3H, s, Me), 2.16–2.07 (1H, m, H-4a), 1.99–1.88 (1H, m, H-4b); δ_C (100 MHz, $CDCl_3$) 161.3 (C-7), 155.5 (C-13), 134.9 (C-11), 125.8 (C-8), 125.4 (C-9), 121.9 (C-10), 119.4 (C-12), 88.2 (C-2), 44.3 (C-5), 32.0 (CH_3), 21.4 (C-3), 15.4 (C-4); *m/z* (ESI) 204 (100), $[MH]^+$; [HRMS (ESI) calcd. for $C_{12}H_{14}NO_2$, 204.1019. Found: $[MH]^+$ 204.1034 (1.7 ppm error)].

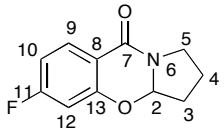
KAG/1/36

1,2,3,3a-Tetrahydro-pyrrolo[2,1,b][1,3]benzoxanin-9-one (122)



3-[1,3]Dioxolan-2-ylpropylamine **94** (80 mg, 0.607 mmol), phenyl salicylate **115** (100 mg, 0.467 mmol) and $SnCl_2 \cdot 2H_2O$ (211 mg, 0.934 mmol) according to general procedure **B** gave the *title compound* **122** as a colourless oil (69 mg, 75%); R_f 0.22 (Et_2O); IR ν_{max} (nujol mull) 2884, 1667, 1611, 1468, 1347; δ_H (400 MHz, $CDCl_3$) 7.93 (1H, dd, *J* 7.5, 1.5, H-9), 7.42 (1H, td, *J* 7.5, 2.0, H-11), 7.11 (1H, td, *J* 7.5, 1.0, H-10), 6.96 (1H, dd, *J* 7.5, 1.0, H-12), 5.50 (1H, t, *J* 6.0, H-2), 3.81–3.88 (1H, m, H-5a), 3.59–3.66 (1H, m, H-5b), 2.40–2.47 (1H, m, H-3a), 2.21–2.30 (1H, m, H-3b), 2.07–2.16 (1H, m, H-4a), 1.89–1.99 (1H, m, H-4b); δ_C (100 MHz, $CDCl_3$) 160.9 (C-7), 157.2 (C-13), 133.7 (C-11), 127.9 (C-9), 122.6 (C-10), 119.7 (C-8), 116.4 (C-12), 88.4 (C-2), 44.3 (C-5), 31.9 (C-3), 21.3 (C-4); *m/z* (ESI) 190 (100), $[MH]^+$, 212 (8) $[MNa]^+$; [HRMS (ESI) calcd. for $C_{11}H_{12}NO_2$, 190.0863. Found: $[MH]^+$ 190.0863 (0.2 ppm error)].
KAG/1/36

6-Fluoro-1,2,3,3a-tetrahydro-pyrrolo[2,1,b][1,3]benzoxanin-9-one (119)

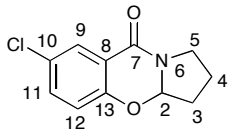


Phenyl 4-fluoro-2-hydroxybenzoate (**112**) (75 mg, 0.323 mmol), 3-[1,3]dioxolan-2-ylpropylamine **94** (55 mg, 0.419 mmol) and $SnCl_2 \cdot 2H_2O$ (146 mg, 0.646 mmol) according to general procedure **B** gave the *title compound* **119** as a colourless solid (70 mg, 98%); m.p. 79–81 ^oC; R_f 0.44 (Et_2O); IR ν_{max} (neat) 1666, 1618, 1450, 1261, 1154, 766; δ_H (400 MHz, $CDCl_3$) 7.86 (1H, dd, *J* 9.0, 7.0, H-9), 6.74 (1H, td, *J* 10.0, 2.0, H-12), 6.60 (1H, dd, *J* 10.0, 2,0, H-10), 5.45 (1H, t, *J* 6.0, H-2), 3.73–3.80 (1H, m, H-5a), 3.57–3.51 (1H, m, H-5b), 2.41–2.34 (1H, m, H-3a), 2.23–2.14 (1H, m, H-

3a), 2.09–2.01 (1H, m, H-4a), 1.94–1.84 (1H, m, H-4b); δ_C (100 MHz, $CDCl_3$) 165.9 (d, *J* 252.0, C-11), 164.6 (C-7), 158.9 (C-13), 130.0 (d, *J* 11.0, C-9), 116.2 (C-8), 110.3 (d, *J* 22.0, C-10), 104.3 (d, *J* 25.0, C-12), 88.9 (C-2), 44.3 (C-5), 31.9 (C-3), 21.3 (C-4); δ_F (376 MHz, $CDCl_3$) –103.8 (ddd, *J* 10.0, 10.0, 9.0); *m/z* (ESI) 230 (100), $[MNa]^+$; [HRMS (ESI) calcd. for $C_{11}H_{10}FNNaO_2$, 230.0588. Found: $[MNa]^+$ 230.0592 (1.9 ppm error)].

KAG/1/75

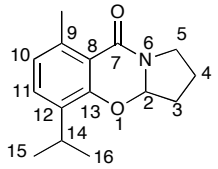
7-Chloro-1,2,3,3a-tetrahydro-pyrrolo[2,1,b][1,3]benzoxanin-9-one (121)



3-[1,3]Dioxolan-2-ylpropylamine **94** (103 mg, 0.784 mmol), phenyl 5-chloro-2-hydroxybenzoate **114** (150 mg, 0.603 mmol) and $SnCl_2{\cdot}2H_2O$ (272 mg, 1.21 mmol) according to general procedure **B** to gave the *title compound* **121** as a sticky colourless solid (125 mg, 87%), m.p. 63–64 ^oC; R_f 0.36 (Et_2O); IR ν_{max} (neat) 1669, 1609, 1451, 1413, 1346, 825, 713; δ_H (400 MHz, $CDCl_3$) 7.83 (1H, d, *J* 2.5, H-9), 7.31 (1H, dd, *J* 9.0, 3.0, H-11), 6.87 (1H, d, *J* 9.0, H-12), 5.43 (1H, t, *J* 5.5, H-2), 3.81–3.75 (1H, m, H-5), 3.59–3.53 (1H, m, H-5), 2.43–2.35 (1H, m, H-3), 2.24–2.16 (1H, m, H-3), 2.10–2.03 (1H, m, H-4), 1.95–1.86 (1H, m, H-4); δ_C (100 MHz, $CDCl_3$) 159.7 (C-7), 155.7 (C-13), 133.5 (C-9), 127.9 (C-10), 127.5 (C-11), 120.8 (C-8), 118.0 (C-12), 88.6 (C-2), 44.2 (C-5), 31.7 (C-3), 21.2 (C-4); *m/z* (ESI) 224 (100), $[MH]^+$; [HRMS (ESI) calcd. for $C_{11}H_{10}ClNaNO_2$, 246.0293. Found: $[MNa]^+$ 246.0293 (0.2 ppm error)].

KAG/1/56

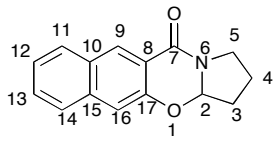
5-*iso*Propyl-8-methyl-1,2,3,3a-tetrahydro-pyrrolo[2,1,b][1,3]benzoxanin-9-one (120)



3-[1,3]Dioxolan-2-ylpropylamine **94** (60 mg, 0.457 mmol), phenyl 2-hydroxy-3-*iso*propyl-6-methylbenzoate **113** (100 mg, 0.352 mmol) and $SnCl_2{\cdot}2H_2O$ (159 mg, 0.704 mmol) according to general procedure **B** gave the *title compound* **120** as a colourless oil (81 mg, 84%); R_f 0.68 (Et_2O); IR ν_{max} (neat) 2960, 1663, 1579, 1491, 1428, 1357, 1062, 795; δ_H (400 MHz, $CDCl_3$) 7.15 (1H, d, *J* 7.5, H-11), 6.82 (1H, d, *J* 7.5, H-10), 5.33 (1H, dd, *J* 6.0, 5.0, H-2), 3.91–3.84 (1H, m, H-5), 3.55–3.49 (1H, m, H-5), 3.18 (1H, sept., *J* 7.0, H-14), 2.61 (3H, s, Me), 2.43–2.35 (1H, m, H-3), 2.29–2.21 (1H, m, H-3), 2.16–2.03 (1H, m, H-4), 1.94–1.87 (1H, m, H-4), 1.18 (3H, d, *J* 7.0, H-15/H-16), 1.15 (3H, d, *J* 7.0, H-15/H-16); δ_C (100 MHz, $CDCl_3$) 162.0 (C-7), 155.4 (C-13), 138.3 (C-9), 133.9 (C-12), 129.3 (C-11), 125.3 (C-10), 118.4 (C-8), 87.7 (C-2), 44.7 (C-5), 32.2 (C-3), 26.7 (C-14), 22.7 (C-15/C-16), 22.5 (C-15/C-16), 21.8 (C-4), 20.7 (Ar-CH_3); *m/z* (ESI) 246 (100), $[MH]^+$; [HRMS (ESI) calcd. for $C_{15}H_{20}NO_2$, 246.1489. Found: $[MH]^+$ 246.1493 (2.6 ppm error)].

KAG/1/74

1,2,3,11a-Tetrahydro-11-oxa-3a-aza-cyclopen[b]anthracen-4-one (123)

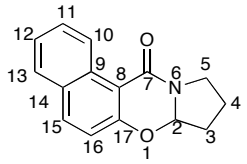


3-[1,3]Dioxolan-2-ylpropylamine **94** (65 mg, 0.494 mmol), phenyl 3-hydroxynaphthalene-2-carboxylate **116** (100 mg, 0.378 mmol) and $SnCl_2{\cdot}2H_2O$ (171 mg, 0.757 mmol) according to general procedure **B** gave the *title compound* **123** as a colourless solid (59 mg, 65%); m.p. 111–114 ^oC; R_f 0.21 (Et_2O); IR ν_{max} (neat) 1664,

1661, 1633, 1634, 1436; δ_H (400 MHz, $CDCl_3$) 8.51 (1H, s, H-9), 7.90 (1H, d, *J* 8.0, H-11), 7.73 (1H, d, *J* 8.0, H-14), 7.53–7.49 (1H, m, H-13), 7.42–7.38 (1H, m, H-12), 7.32–7.35 (1H, m, H-16), 5.54 (1H, t, *J* 6.0, H-2), 3.92–3.87 (1H, m, H-5a), 3.72–3.66 (1H, m, H-5b), 2.52–2.44 (1H, m, H-3a), 2.33–2.24 (1H, m, H-3b), 2.20–2.13 (1H, m, H-4a), 2.02–1.91 (1H, m, H-4b); δ_C (100 MHz, $CDCl_3$) 161.1 (C-7), 153.6 (C-17), 136.4 (C-10), 129.5 (C-11, C-9, C-15), 128.5 (C-13), 127.0 (C-14), 125.1 (C-12), 120.1 (C-8), 112.1 (C-16), 88.6 (C-2), 44.5 (C-5), 32.1 (C-3), 21.2 (C-4); *m/z* (ESI) 262 (100), $[MNa]^+$; [HRMS (ESI) calcd. for $C_{15}H_{13}NNaO_2$, 262.0838. Found: $[MNa]^+$ 262.0843 (0.9 ppm error)].

KAG/2/63

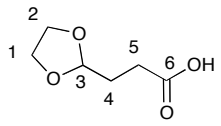
7a,8,9,10-Tetrahydro-7-oxa-10a-aza-cyclopenta[b]phenanthrene-11-one (124)



3-[1,3]Dioxolan-2-ylpropylamine **94** (64 mg, 0.492 mmol), phenyl 2-hydroxynaphthalene-1-carboxylate **117** (100 mg, 0.378 mmol) and $SnCl_2{\cdot}2H_2O$ (171 mg, 0.756 mmol) according to general procedure **B** gave the *title compound* **124** as a colourless solid (51 mg, 56%); m.p. 104–107 ^oC; R_f 0.24 (Et_2O); IR ν_{max} (neat) 1658, 1634, 1631, 1443, 763; δ_H (400 MHz, $CDCl_3$) 8.20 (1H, dd, *J* 8.5, 1.0, H-10), 7.92 (1H, d, *J* 9.0, H-16), 7.81 (1H, d, *J* 8.0, H-12), 7.59–7.49 (3H, m, H-11, H-13, H-15), 5.65 (1H, t, *J* 5.5, H-2), 3.93–3.87 (1H, m, H-5a), 3.68–3.62 (1H, m, H-5b), 2.57–2.40 (2H, m, H-3), 2.22–2.13 (1H, m, H-4a), 2.05–1.94 (1H, m, H-4b); δ_C (100 MHz, $CDCl_3$) 161.5 (C-7), 154.8 (C-17), 136.6 (C-14), 128.5 (C-12), 127.8 (C-15), 126.3 (C-11), 123.8 (C-9), 123.2 (C-16), 122.8 (C-10), 122.1 (C-13), 114.3 (C-8), 89.1 (C-2), 44.6 (C-5), 32.1 (C-3), 21.7 (C-4); *m/z* (ESI) 262 (100), $[MNa]^+$; [HRMS (ESI) calcd. for $C_{15}H_{13}NNaO_2$, 262.0838. Found: $[MNa]^+$ 262.0840 (0.2 ppm error)].

KAG/2/64.

3-[1,3]Dioxolan-2-ylpropionic acid (127).



Prepared according to the procedure described by Shea and co-workers.[80]

A solution of 2-(2-bromoethyl)-1,3-dioxolane (1.3 mL, 11.0 mmol) in THF (10 mL) along with a crystal of iodine to initiate reaction was added dropwise to a stirred suspension of magnesium turnings (0.94 g, 38.7 mmol) in THF (20 mL) at 15–20 ^{o}C, under an atmosphere of argon. The reaction mixture was stirred for 2 h before being cooled to –78 ^{o}C. A large excess of dry ice (30 g, crushed to a powder under an atmosphere of argon) was then slowly added to the reaction vessel. The resulting slurry was slowly allowed to warm to rt and stirred for 1 h. The reaction was quenched by the addition of aqueous NH_4Cl (sat., 20 mL), filtered, the volatiles removed under reduced pressure, then extracted with Et_2O (20 mL). The aqueous phase was acidified to pH 3 and extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give the *title compound* **127** as a colourless solid (1.08 g, 67%); m.p. 35–37 ^{o}C; IR ν_{max} (neat) 3450, 2963, 2892, 1711, 1412, 1140; δ_H (400 MHz, $CDCl_3$) 4.97 (1H, t, *J* 4.0, H-3), 3.99–3.95 (2H, m, H-1/H-2), 3.88–3.84 (2H, m, H-1/H-2), 2.48 (2H, t, *J* 7.5, H-5), 2.03 (2H, td, *J* 7.5, 4.0, H-4); δ_C (100 MHz, $CDCl_3$) 179.2 (C-6), 102.9 (C-3), 65.1 (C-1, C-2), 28.4 (C-4), 27.9 (C-5); *m/z* (ESI) 169 (100), $[MNa]^+$, 147 (100), $[MH]^+$; [HRMS (ESI) calcd. for $C_6H_{11}O_4$, 147.0648. Found: $[MH]^+$ 147.0652. (0.2 ppm error)].

^{1}H NMR data consistent with literature.[80]

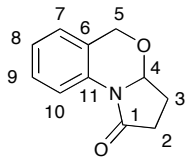
KAG/1/89

General procedure C – Mixed anhydride coupling and cyclisation.

According to the procedure developed by Cayley *et al*.[64]

*Iso*butyl chloroformate (1 eq.) was added dropwise to a stirred solution of 3-[1,3]dioxolan-2-ylpropionic acid **127** (1 eq.) and *N*-methylpiperidine (1 eq.) in CH_2Cl_2 (8 mL) at –10 ^oC (acetone-ice bath). After exactly 2 min an ice cold solution of amine (1.1 eq.) in CH_2Cl_2 (2 mL) was added dropwise and stirring continued at –10 ^oC for 1 h, then the reaction was allowed to warm to rt and stirred for a further 1 h. The solution was then filtered through a short pad of silica gel, eluting with EtOAc (3 x 10 mL) and the volatiles removed under reduced pressure. The resulting amides were redissolved in CH_2Cl_2 (5 mL), $SnCl_2{\cdot}2H_2O$ (2 eq.) added in a single portion and the reaction stirred at rt for 18–24 h. The mixture was filtered through a short pad of Celite and washed with $CHCl_3$ (3 x 15 mL). The volatiles were removed under reduced pressure and the crude products purified by column chromatography.

2,3,3a,5-Tetrahydro-*1H*-benzo[d]pyrrolo[2,1 b][1,3]oxazin-1-one (137)

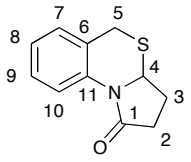


Prepared from 2-amino benzyl alcohol **135** (106 mg, 0.752 mmol) and acid **127** (100 mg, 0.684 mmol) according to general procedure **C**. The crude amide was stirred with $SnCl_2{\cdot}2H_2O$ (309 mg, 1.37 mmol) for 24 h and the crude product purified by column chromatography. Eluting with Et_2O gave the *title compound* **137** as a colourless solid (104 mg, 80%); m.p. 89–90 °C; R_f 0.38 (Et_2O); IR ν_{max} (neat) 1695, 1494, 1490, 1215, 1080; δ_H (400 MHz, $CDCl_3$) 8.30 (1H, d, *J* 8.5, Ar-H), 7.27–7.26 (1H, m, Ar-H), 7.10 (1H, td, *J* 7.5, 1.0, Ar-H), 7.02 (1H, br d, *J* 7.5, Ar-H), 5.27 (1H, dd, *J* 7.0, 5.0, H-4), 5.05 (1H, d, *J* 15.0, H-5a), 4.90 (1H, d, *J* 15.0, H-5b), 2.61–2.47 (3H, m, H-2, H-3a), 2.11–2.01 (1H, m, H-3b); δ_C (125 MHz, $CDCl_3$) 172.0 (C-1), 134.2 (ArC), 127.7 (ArCH), 124.4 (ArCH), 124.3 (ArCH), 123.8 (ArC), 119.6 (ArCH), 87.2 (C-4),

58.1 (C-5), 30.1 (C-2), 24.8 (C-3); *m/z* (ESI) 212 (100), $[MNa]^+$; [HRMS (ESI) calcd. for $C_{11}H_{11}NNaO_2$, 212.0682. Found: $[MNa]^+$ 212.0687 (2.2 ppm error)].

KAG/1/91

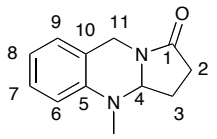
3,3a-Dihydro-*2H,5H*-pyrrolo[2,1-a][3,1]benzothiazine-1-one (140)



Prepared from (2-aminophenyl)methane thiol **138** (106 mg, 0.752 mmol) and 3-[1,3]dioxolan-2-ylpropionic acid **127** (100 mg, 0.684 mmol) according to general procedure **C**. The crude amide was stirred with $SnCl_2 \cdot 2H_2O$ (309 mg, 1.36 mmol) for 18 h and the crude product purified by column chromatography. Eluting with 97:3 CH_2Cl_2: MeOH gave the title compound, although not pure. The impure product was dissolved in MeOH and loaded onto an SCX column. Washing with MeOH then elution with 9:1 MeOH:7 N NH_3 in MeOH and concentration gave the *title compound* **140** as a pale yellow oil (105 mg, 86%); R_f 0.65 (9:1 CH_2Cl_2: MeOH); IR ν_{max} (neat) 3430, 2095, 1643, 1468, 1210, 1104; δ_H (400 MHz, $CDCl_3$) 8.25 (1H, dd, *J* 8.0, 1.0, Ar-H), 7.30 (1H, br t, *J* 8.0, Ar-H), 7.17–7.15 (1H, m, Ar-H), 7.10 (1H, br d, *J* 8.0, Ar-H), 5.05–5.02 (1H, m, H-4), 4.30 (1H, d, *J* 17.0, H-5a), 3.70 (1H, d, *J* 17.0, H-5b), 2.57–2.68 (3H, m, H-2, H-3a), 2.03–1.98 (1H, m, H-3b); δ_C (100 MHz, $CDCl_3$) 173.2 (C-1), 135.9 (ArC), 128.7 (ArCH), 127.6 (ArCH), 124.4 (ArCH), 123.5 (ArC), 122.7 (ArCH), 60.9 (C-4), 31.0 (C-5), 30.5 (C-2), 23.9 (C-3); *m/z* (ESI) 228 (100), $[MNa]^+$; [HRMS (ESI) calcd. for $C_{11}H_{11}NNaOS$, 228.0454. Found: $[MNa]^+$ 228.0459 (2.1 ppm error)].

KAG/2/48

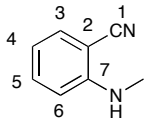
4-Methyl-3,3a,4,9-tetrahydro-*2H*-pyrrolo[2,1-b]quinazoin-1-one (149)



Prepared from 2-methylaminobenzylamine **147** (60 mg, 0.437 mmol) and 3-[1,3]dioxolan-2-ylpropionic acid **127** (58 mg, 0.397 mmol) according to general procedure **C**. The crude amide was stirred with $SnCl_2 \cdot 2H_2O$ (179 mg, 0.794 mmol) for 18 h and the crude product purified by preparative TLC. Eluting with 1:1 PE:EtOAc gave the *title compound* **149** as a colourless oil (35 mg, 43%); R_f 0.31 (1:1 PE:EtOAc); IR ν_{max} (neat) 1685, 1498, 1447, 1369, 1307, 1273, 1212; δ_H (400 MHz, $CDCl_3$) 7.16 (1H, t, *J* 7.5, Ar-H), 7.03 (1H, d, *J* 7.5, Ar-H), 6.81–6.79 (2H, m, Ar-H), 4.85 (1H, d, *J* 17.0, H-11a), 4.56 (1H, t, *J* 6.0, H-4), 4.25 (1H, d, *J* 17.0, H-11b), 2.81 (3H, s, NCH_3), 2.57–2.36 (3H, m, H-2, H-3a), 2.09–2.02 (1H, m, H-3b); δ_C (100 MHz, $CDCl_3$) 173.5 (C-1), 145.7 (ArC), 128.0 (ArCH), 126.8 (ArCH), 119.6 (ArC), 119.2 (ArCH), 113.7 (ArCH), 71.9 (C-4), 41.1 (C-11), 33.8 (NCH_3), 29.5 (C-2), 28.8 (C-3); *m/z* (ESI) 225 (100), $[MNa]^+$; [HRMS (ESI) calcd. for $C_{12}H_{14}N_2NaO$, 225.0998. Found: $[MNa]^+$ 225.1006 (3.5 ppm error)].

KAG/2/46

2-(Methylamino)benzonitrile (154)

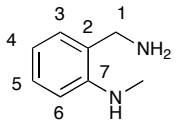


To a stirred solution of 2-aminobenzonitrile **151** (1.00 g, 8.46 mmol) in THF (30 mL) at –50 °C under an atmosphere of argon was added *n*-butyl lithium in hexane (1.45 M, 2.63 mL, 3.81 mmol) dropwise. The reaction was stirred at –50 °C for 30 minutes, then warmed to rt for 45 minutes. After recooling to –50 °C methyl iodide (237 μL, 3.81 mmol) in THF (20 mL) was added dropwise and the reaction allowed to warm to rt and stirred for 16 h. The reaction was quenched by the addition of water (50 mL), then extracted with EtOAc (50 mL). The volatiles were removed under reduced pressure to yield crude product, which was purified by column chromatography. Eluting with 4:1 PE:Et_2O gave the *title compound* **154** as a white solid (409 mg, 81%). m.p. 60–63 °C (lit 62–64 ^oC[130]); Found: C, 72.7; H, 6.15, N 21.32 $C_8H_8N_2$ requires C, 72.7; H, 6.10 N, 21.20%; R_f 0.23 (4:1 PE:Et_2O); δ_H (400 MHz, $CDCl_3$) 7.42–7.35 (2H, m, H-3, H-5), 6.68–6.62 (2H, m, H-4, H-6), 4.66 (1H, s, NH), 2.90 (3H, d, *J* 5.0, NMe).

^1H NMR data consistent with literature.[130]

KAG/2/23

2-(Aminomethyl)-*N*-methylaniline (147)

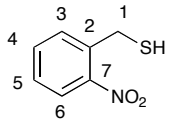


To a stirred solution of $LiAlH_4$ in THF (1.00 M, 4.52 mL, 4.52 mmol) under a stream of nitrogen was added dropwise 2-(methylamino)benzonitrile **154** (300 mg, 2.26 mmol) in THF (20 mL). The resulting solution was stirred at rt for 4 h. The reaction was quenched by the careful addition of a mixture of Celite and $Na_2SO_4 \cdot 10H_2O$ (1:1) until the evolution of gas was complete (~3 g). The slurry was then filtered and washed with Et_2O. Removal of the volatiles under reduced pressure gave the *title compound* **147** as a pale yellow oil (309 mg, 100%); IR ν_{max} (neat) 3368, 2914, 1626,

1605, 1585, 1515, 1467, 1427, 1168, 749; δ_H (400 MHz, $CDCl_3$) 7.22 (1H, t, *J* 8.0, H-5), 7.03 (1H, d, *J* 8.0, H-3), 6.64–6.67 (2H, m, H-4, H-6), 3.89 (2H, s, H-1), 2.84 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 149.1 (C-7) 128.9 (C-3/C-5), 128.7 (C-3/C-5), 128.6 (C-2), 116.3 (C-4), 109.9 (C-6), 45.5 (C-1), 30.4 (NCH_3); *m/z* (ESI) 137 (100), $[MH]^+$; [HRMS (ESI) calcd. for $C_8H_{13}N_2$, 137.1073. Found: $[MH]^+$ 137.1069 (3.1 ppm error)].

KAG/2/24

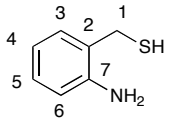
(2-Nitrophenyl)methanethiol (143)



2-Nitrobenzyl bromide **142** (500 mg, 2.33 mmol) and thiourea (177 mg, 2.33 mmol) in water (20 mL) were heated to reflux for 2 h, then NaOH (93 mg, 2.33 mmol) in water (1 mL) added and the reaction maintained at reflux for a further 2 h. After cooling to rt the pH was adjusted to 2 (monitored with pH meter) by the dropwise addition of aqueous HCl (1 M), then extracted with $CHCl_3$ (3 x 25 mL). The organic layers were combined and dried over $MgSO_4$, the volatiles were removed under reduced pressure to yield the crude product, which was purified by column chromatography. Eluting with 4:1 PE:Et_2O gave the *title compound* **143** as an orange-yellow oil (123 mg, 31%); R_f 0.43 (4:1 PE:Et_2O); IR ν_{max} (neat) 3066, 2951, 2855, 1608, 1577, 1523, 1429, 1344, 1309, 861; δ_H (400 MHz, $CDCl_3$) 8.00–7.98 (1H, m, H-6), 7.58–7.34 (3H, m, H-3, H-4, H-5), 4.00 (2H, d, *J* 8.5, H-1), 2.14 (1H, t, *J* 8.5, SH); δ_C (100 MHz, $CDCl_3$) 137.1 (C-7), 133.8 (C-6), 133.7 (C-2), 131.7 (C-4), 128.3 (C-3/C-5), 125.5 (C-3/C-5), 26.6 (C-1); *m/z* (ESI) 192 (90), $[MNa]^+$; [HRMS (ESI) calcd. for $C_7H_7NNaO_2S$, 192.0090. Found: $[MNa]^+$ 192.0099 (4.9 ppm error)].

KAG/2/30

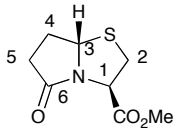
(2-(Methylamino)phenyl)methanethiol (138)



To a stirred solution of (2-nitrophenyl)methanethiol **143** (100 mg, 0.591 mmol) in THF (5 mL) under an argon atmosphere was added in a single portion $SnCl_2 \cdot 2H_2O$ (293 mg, 1.29 mmol) and the reaction stirred at rt for 16 h. The reaction was quenched by the addition of aqueous $NaHCO_3$ (sat., 3 mL) and then extracted with CH_2Cl_2 (2 x 10 mL). The resulting emulsion was filtered through a sinter, then the layers separated and the organic layer loaded onto a 1 g SCX column. The column was washed with MeOH, then the product eluted with 9:1 CH_2Cl_2: 6 N NH_3 in MeOH. Removal of the volatiles under reduced pressure gave the *title compound* **138** as a yellow oil (68 mg, 83%); IR ν_{max} (neat) 3355, 3220, 3024, 1622, 1581, 1493, 1458, 1313, 1276, 1156, 750; δ_H (400 MHz, $CDCl_3$) 7.11 (1H, td *J* 7.5, 1.5, H-5), 6.99 (1H, dd, *J* 7.5, 1.5, H-3), 6.73 (1H, td, *J* 7.5, 1.0, H-4), 6.66 (1H, dd, *J* 7.5, 1.0, H-6), 3.66 (2H, s, H-1); δ_C (100 MHz, $CDCl_3$) 145.2 (ArC), 131.6 (ArCH), 129.3 (ArCH), 120.9 (ArC), 118.7 (ArCH), 116.4 (ArCH), 40.5 (C-1); *m/z* (ESI) 277 (100), $[2M\text{-}H]^+$; [HRMS (ESI) calcd. for $C_{14}H_{17}N_2S_2$ 277.0828. Found: $[2M\text{-}H]^+$ 277.0830 (0.7 ppm error)].

KAG/2/38

Methyl *3R,8S*-5-oxohexahydropyrrolo[2, 1-*b*]thiazole-3-carboxylate ((–)-158)



Prepared from L-cysteine dimethyl ester dihydrochloride (**159**) (128 mg, 0.376 mmol) and acid **127** (100 mg, 0.684 mmol) according to general procedure **C**. The crude amide was stirred with $SnCl_2 \cdot 2H_2O$ (309 mg, 1.37 mmol) for 72 h and the crude product purified by column chromatography. Eluting with Et_2O gave the *title compound* **(–)-158** as a colourless oil (82 mg, 59% over two steps); R_f 0.20 (1:1 PE:EtOAc); δ_H (400 MHz, $CDCl_3$) 5.19 (1H, dd, *J* 7.0, 4.0, H-3), 5.08 (1H, dd, *J* 7.5,

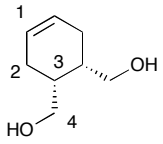
4.5, H-1), 3.73 (3H, s, CO_2Me), 3.38 (1H, dd, *J* 11.5, 7.5, H-2a), 3.33 (1H, dd, *J* 11.5, 4.5, H-2b), 2.73–2.60 (1H, m, H-5), 2.59–2.48 (2H, m, H-5, H-4a), 2.19–2.09 (1H, m, H-4b).

Data consistent with literature[64]

KAG/2/55

6.2 ABC core compounds

(1*R*,2*S*)-Cyclohex-4-ene-1,2-diyldimethanol (179)

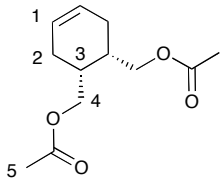


To a stirred suspension of lithium aluminium hydride (54.6 g, 1.44 mol) in THF (1.5 L) at 0 °C under an atmosphere of argon was added a solution of *cis*-1,2,3,6-tetrahydrophthalic anhydride (**164**) (100 g, 657 mmol) in THF (500 mL). Upon complete addition, the reaction mixture was allowed to warm to rt at which it was stirred for 4 h. The reaction was then cooled to 0 °C and a mixture of Celite and $Na_2SO_4 \cdot 10H_2O$ 1:1 (~300 g) was added in portions until no more gas evolution was observed. The reaction mixture was filtered and the solids washed with EtOAc (2 x 1 L). The organic phases were combined and volatiles removed under reduced pressure to yield the crude product, which was purified by column chromatography. Eluting with 7:3 PE:EtOAc→ EtOAc gave the *title compound* **179** as a colourless oil (90.7 g, 97%); R_f 0.22 (EtOAc); δ_H (400 MHz, $CDCl_3$) 5.69–5.53 (2H, t, *J* 1.5, H-1), 3.73 (2H, dd, *J* 11.0, 7.0, H-4a), 3.59 (2H, dd, *J* 11.0, 3.5, H-4b), 3.20 (2H, br s, O*H*), 2.17–2.00 (6H, m, H-2, H-3).

^{1}H-NMR data were consistent with those reported in the literature.[101]

KAG/2/15

Acetic acid (1*R*,6*S*)-6-acetoxymethyl-cyclohex-3-enylmethyl ester (205)

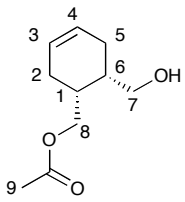


To a stirred solution of diol **179** (90.0 g, 633 mmol) in CH_2Cl_2 (1 L) at 0 °C was added pyridine (154 mL, 1.90 mol) in a single portion followed by acetyl chloride (112 mL, 1.58 mol) dropwise. The reaction was allowed to warm to rt where it was stirred for 16 h. To this was added CH_2Cl_2 (600 mL) and water (800 mL). The layers were separated and then the organic layer was washed with aqueous HCl (2 M, 2 x 400 mL) and brine (400 mL). The solvent was removed and the crude oil purified by column chromatography. Eluting with 95:5→9:1 PE:EtOAc gave the *title compound* **205** as a colourless oil (174 g, quant.) contaminated with trace acetic acid; R_f 0.19 (9:1 PE:EtOAc); δ_H (400 MHz, $CDCl_3$) 5.64–5.63 (2H, m, H-1), 4.11 (2H, dd, *J* 15.0, 9.0, H-4a), 4.03 (2H, dd, *J* 15.0, 10.0, H-4b), 2.27–2.14 (4H, m, H-2a, H-3), 2.06 (6H, s, H-5), 1.97–1.90 (2H, m, H-2b).

^{1}H NMR data consistent with literature.[60]

KAG/7/92

((1*R*,6*S*)-6-(Hydroxymethyl)cyclohex-3-enyl)methyl ethanoate ((–)-206)



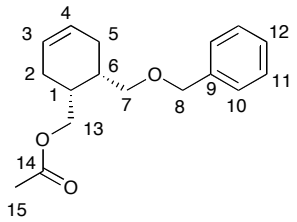
To a stirred emulsion of diacetate **205** (87.0 g, 0.385 mol) in aqueous phosphate buffer (potassium dihydrogen phosphate / disodium hydrogen phosphate, Fluka, 800 mL, pH 7) in a 2 L jacketed vessel at 25 °C was added *porcine pancreatic lipase* (PPL, Sigma Type II, 100-400 units/mg, 8.20 g). As the reaction proceeded, the pH was kept constant by the addition of aqueous NaOH (2 M) from an autoburette (pH set to 7.00). After 20 h, approximately 80 mL of NaOH solution had been added (~80% conversion). The reaction mixture was then filtered through a pad of Celite and the solids were washed with EtOAc (1 L). The filtrate was extracted with EtOAc

(2 x 1 L) and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography. Eluting with 95:5→8:2 *iso*-hexane: EtOAc gave the *title compound* **(–)-206** as a colourless oil (57.1 g, 80%); R_f 0.16 (7:3 PE:EtOAc); $[\alpha]_D$ –19.3 (*c* 2.2, $CHCl_3$) (Lit.[131] –19.0 (*c* 4.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.68–5.62 (2H, m, H-3, H-4), 4.20 (1H, dd, *J* 11.0, 6.0 Hz, H-8a), 3.96 (1H, dd, *J*, 11.0, 7.5 Hz, H-8b), 3.72–3.57 (2H, m, H-7), 2.29–2.08 (4H, m, H-2a, H-1, H-6, H-5a), 2.07 (3H, s, H-10), 2.01–1.72 (3H, m, H-2b, H-5b, OH).

^{1}H NMR data consistent with literature.[131]

KAG/7/97

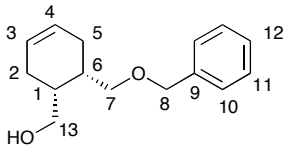
((1*R*,6*S*)-6-(Benzyloxymethyl)cyclohex-3-enyl)methyl ethanoate ((+)-207)



To a stirred solution of alcohol **(–)-206** (15.0 g, 81.5 mmol) in α,α,α-trifluorotoluene (200 mL) was added magnesium oxide (6.67 g, 32.6 mmol) and 2-benzyloxy-*N*-methylpyridinium triflate (41.0 g, 122 mmol). The resulting slurry was stirred at 83 °C for 20 h, then filtered through Celite washing with EtOAc (300 mL). The filtrate was concentrated under reduced pressure to give the crude product as a pale yellow oil, which was purified by column chromatography. Eluting with 7:3 PE:EtOAc gave the *title compound* **(+)-207** as a colourless oil (1.16 g, 72%) along with starting material **(–)-206** (3.75 g, 25%), giving a BRSM yield of 97%; R_f 0.50 (7:3 PE:EtOAc); $[\alpha]_D$ +11.0 (*c* 1.8, $CHCl_3$) (Lit.[54]+11.1(*c* 1,2, $CHCl_3$); (400 MHz, $CDCl_3$) 7.38–7.28 (5H, m, H-10, H-11, H-12), 5.67–5.60 (2H, m, H-3, H-4), 4.51 (2H, s, H-8), 4.11 (1H, dd, *J* 11.0, 5.5, H-7a), 4.01 (1H, dd, *J* 11.0, 8.0, H-7b), 3.50 (1H, dd, *J* 9.0, 6.5, H-13a), 3.41 (1H, dd, *J* 9.0, 7.0, H-13b), 2.28–1.91 (9H, m, H-1, H-2, H-5, H-6, H-15).

KAG/8/4

((1*R*S,6*SR*)-6-(Benzyloxymethyl)cyclohex-3-enyl)methanol (180)

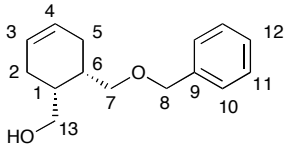


To a stirred suspension of NaH (60% in mineral oil, 2.37 g, 71.9 mmol) (washed with PE and THF before use) in THF (100 mL) at –10 °C was added dropwise (1*RS*,2*SR*)-cyclohex-4-ene-1,2-diyldimethanol (**179**) (9.30 g, 65.4 mmol) in THF (50 mL). The reaction was warmed to rt and stirred for 1 h. The reaction was then cooled to 0 °C and benzyl bromide (8.54 mL, 71.9 mmol) in THF (50 mL) added dropwise. When the addition was complete the reaction was allowed to warm to rt then stirred at rt for 18 h. The reaction was quenched by the addition of aqueous NH_4Cl (sat.,150 mL), then extracted with Et_2O (3 x 100 mL). The organic layers were combined and dried over Na_2SO_4, the volatiles removed under reduced pressure to give the *title compound* **180** as pale yellow oil (10.1 g, 66%) which required no further purification; R_f 0.24 (1:1 PE:Et_2O); δ_H (400 MHz, $CDCl_3$) 7.38–7.27 (5H, m, H-10, H-11, H-12), 5.64–5.56 (2H, m, H-3, H-4), 4.55 (1H, d, *J* 12.0, H-8a), 4.52 (1H, d, *J* 12.0, H-8b), 3.67–3.53 (3H, m, H-7a, H-13), 3.41 (1H, dd, *J* 9.5, 4.5, H-7b), 3.55 (1H, br s, OH), 2.27–1.93 (6H, m, H-1, H-2, H-5, H-6).

^{1}H-NMR Data were consistent with those reported in the literature.[132]

KAG/2/17

((1*R*,6*S*)-6-(Benzyloxymethyl)cyclohex-3-enyl)methanol ((+)-180)



To a stirred solution of acetate **(+)-207** (21.3 g, 77.7 mmol) in MeOH (300 mL) and water (150 mL) at 0 °C was added lithium hydroxide monohydrate (36.0 g, 85.8

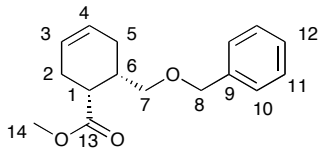
mmol). The ice-bath was removed and the reaction mixture was stirred for 45 min. The MeOH was then removed under reduced pressure and the residue partitioned between EtOAc (800 mL) and brine (800 mL). The aqueous phase was extracted using EtOAc (2 x 500 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure to give the *title compound* **(+)-180** as a colourless oil (17.9 g, 99%) which was used without any further purification; R_f 0.24 (1:1 PE:Et_2O);

Data as for racemate **±180** except

$[\alpha]_D$ +4.7 (*c* 1.2, $CHCl_3$) (Lit.[54]+3.8 (*c* 1.1, $CHCl_3$))

KAG/8/27

(1*RS*,6*SR*)-Methyl 6-(benzyloxymethyl)cyclohex-3-enecarboxylate (165)



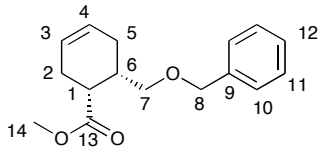
To a stirred solution of the crude alcohol **180** (6.00 g, 25.8 mmol) in acetone (100 mL) at 0 °C was added dropwise freshly prepared Jones' reagent (33.5 mmol, ~15 mL). The reaction was allowed to warm to rt, then recooled to 0 °C and *iso*-propyl alcohol (~10 mL, until the reaction remained green) was added carefully dropwise to quench excess Jones' reagent. The volatiles were removed under reduced pressure to give a green gum, which was partitioned between water (300 mL) and CH_2Cl_2 (2 x 200 mL). The organic layers were combined and dried over Na_2SO_4, and the volatiles removed under reduced pressure. The resulting oil was dissolved in MeOH (50 mL) and acetyl chloride (1.28 mL 18.1 mmol) added in a single portion. The reaction was stirred for 48 h at rt. The MeOH was removed under reduced pressure and the yellow residue dissolved in CH_2Cl_2 (100 mL) and washed twice with aqueous $NaHCO_3$ (sat., 50 mL). The organic layer was then dried over Na_2SO_4 and the volatiles removed under reduced pressure to yield the crude compound, which was purified by column chromatography. Eluting with 7:3 PE:EtOAc gave the *title compound* **165** as a colourless oil (3.10 g, 46%); R_f 0.56 (1:1 PE:Et_2O); δ_H (400 MHz, $CDCl_3$) 7.36–7.27 (5H, m, H-10, H-11, H-12), 5.67–5.60 (2H, m, H-3, H-4), 4.46 (2H, s, H-8), 3.59 (3H,

s, H-14), 3.49 (1H, dd, *J* 9.0, 5.0, H-7a), 3.42 (1H, dd, *J* 9.0, 7.0, H-7b), 2.82–2.77 (1H, m, H-1), 2.61–2.53 (1H, m, H-6), 2.36–2.19 (3H, m, H-2, H-5a), 2.11–2.04 (1H, m, H-5b).

^{1}H NMR data consistent with literature.[60]

KAG/2/89

Methyl-(1*R*,6*S*)-6-(Benzyloxymethyl)cyclohex-3-enecarboxylate ((–)-165)



Prepared according to the procedure for **±165**

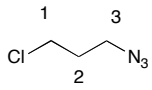
Data as for racemate **±165** except

$[\alpha]_D$ –14.9 (*c* 1.2, $CHCl_3$) (Lit.[54]–15.5 (*c* 1.1, $CHCl_3$);

KAG/4/8

The following two compounds are likely to be both explosive and volatile, and all procedures were carried out behind blast shields.

1-Azido-3-chloropropane (182)



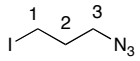
Prepared according to the procedure described by Yao and co-workers.[94]

To a stirred solution of 1-bromo-3-chloropropane **181** (5.00 g, 31.7 mmol) in DMF (40 mL) under an atmosphere of argon was added in a single portion sodium azide (2.06 g, 31.7 mmol) and stirred at rt for 18 h. The reaction was partitioned between water (75 mL) and Et_2O (75 mL) and the organic layer dried over Na_2SO_4. The volatiles were removed under reduced pressure in an ice-cooled water bath to give the *title compound* **182** as a pale orange oil. The crude product was ~ 80% pure by ^1H NMR, and was used directly in the subsequent reaction without further purification; δ_H (400 MHz, $CDCl_3$) 3.61 (2H, t, *J* 6.5, H-3), 3.48 (2H, t, *J* 7.0, H-1), 1.99 (2H, tt, *J* 7.0, 6.5 H-2).

^1H-NMR Data were consistent with those reported in the literature.[94]

KAG/2/67

1-Azido-3-iodopropane (183)



Prepared according to the procedure described by Yao and co-workers.[94]

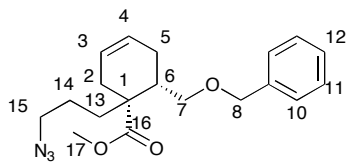
To a stirred solution of crude 1-azido-3-chloropropane (**182**) (31.7 mmol if 100%), in acetone (100 mL) was added in a single portion sodium iodide (9.52 g, 63.5 mmol), then the reaction heated to reflux for 18 h. After cooling the reaction was partitioned between water (100 mL) and EtOAc (2 x 100 mL). The organic layers were combined, dried over Na_2SO_4 and the volatiles removed under reduced pressure to yield the crude product, which was purified by column chromatography. Eluting with 9:1 PE:Et_2O gave the *title compound* **183** as a pale yellow oil (4.06 g, 61% over 2 steps from **181**); R_f 0.28 (9:1 PE:Et_2O); δ_H (400 MHz, $CDCl_3$) 3.44 (2H, t, *J* 6.0, H-3), 3.25 (2H, t, *J* 6.5, H-1), 2.04 (2H, tt, *J* 6.5, 6.0, H-2).

^{1}H-NMR Data were consistent with those reported in the literature.[94]

KAG/2/68

Later this compound was used successfully without purification. e.g. KAG/8/2

(1*RS*,6*SR*)-methyl 1-(3-azidopropyl)-6-(benzyloxymethyl)cyclohex-3-enecarboxylate (177)



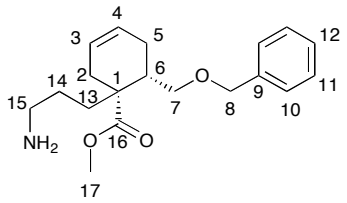
General procedure:

To a stirred solution of ester (**165**) (100 mg, 0.384 mmol), in THF (1 mL) at –78 °C was added dropwise base (see Table 3.2). After complete addition the reaction was stirred at –78 °C for 2 h, then azide **183** (88 mg, 0.422 mmol) in THF (0.5 mL) was added dropwise. The reaction was stirred at –78 °C for 15 minutes, then warmed to rt and stirred for 18 h, then partitioned between EtOAc (2 x 5 mL) and aqueous NH_4Cl

(sat., 5 mL). The organic layers were combined, and the volatiles removed under reduced pressure to yield the crude product, which was purified by column chromatography. Eluting with 9:1 PE:EtOAc gave the *title compound* **177** as a colourless oil. (Yields see Table 3.2); R_f 0.25 (1:1 PE:Et_2O); IR ν_{max} (neat) 3443, 2095, 1727, 1197, 1104, 736, 699; δ_H (400 MHz, $CDCl_3$) 7.35–7.27 (5H, m, H-10, H-11, H-12), 5.56 (2H, s, H-3, H-4), 4.42 (2H, H-8), 3.56 (3H, s, H-17), 3.34 (2H, d, *J* 7.0, H-7), 3.01-3.22 (2H, m, H-15), 2.39–2.20 (4H, m, H-2, H-5), 1.67–1.54 (4H, m, H-13, H-14, H-6), 1.40–1.31 (1H, m, H-13/H-14); δ_C (100 MHz, $CDCl_3$) 176.6 (C-16), 138.4 (C-9), 128.4 (C-11), 127.8 (C-10), 127.6 (C-12), 124.3 (C-3/C-4), 124.2 (C-3/C-4), 73.3 (C-7/C-8), 71.2 (C-7/C-8), 51.6 (C-6), 51.6 (C-1), 45.7 (C-17), 39.1 (C-2/C-5/C-14/C-15), 32.7 (C-2/C-5/C-14/C-15), 27.3 (C-2/C-5/C-14/C-15), 25.0 (C-2/C-5/C-14/C-15), 23.8 (C-2/C-5/C-14/C-15); *m/z* (ESI) 366 (100), $[MNa]^+$; [HRMS (ESI) calcd. for $C_{19}H_{25}N_3NaO_3$, 366.1788. Found: $[MNa]^+$ 366.1798 (2.6 ppm error)].

When working on the chiral series the azide was not isolated – see amine below for preparation.

(1*RS*,6*SR*)-Methyl 1-(3-aminopropyl)-6-(benzyloxymethyl)cyclohex-3-enecarboxylate (178)



To a stirred solution of azide (**177**) (400 mg, 1.16 mmol) in THF (10 mL) and water (260 μL) was added in a single portion triphenylphosphine (333 mg, 1.28 mmol). The reaction was heated to reflux for 2 h. After cooling the volatiles were removed under reduced pressure, then the crude product was purified by loading onto an SCX column. Washing with MeOH followed by eluting with 9:1 CH_2Cl_2:7 N NH_3 in MeOH in CH_2Cl_2 gave the *title compound* **178** as a colourless film (303 mg, 82%); R_f 0.48 (90:9:1 CH_2Cl_2:MeOH:NH_3); IR ν_{max} (neat) 3376, 3026, 2926, 2855, 1726, 1453, 1024, 1104, 689; δ_H (400 MHz, $CDCl_3$) 7.34–7.27 (5H, m, H-10, H-11, H-12), 5.55 (2H, t, *J* 14, H-3, H-4), 4.42 (2H, s, H-8), 3.56 (3H, s, H-17), 3.33 (2H, d, *J* 7.0, H-7), 2.63 (2H, t, *J* 7.0, H-15), 2.36–2.02 (5H, m, H-2, H-5, H-6), 1.61–1.38 (5H, m, H-13, H-14, NH_2), 1.23–1.17 (1H, m, H-14/H-13); δ_C(100 MHz, $CDCl_3$) 176.3 (C-16), 138.0 (C-9), 127.9 (C-11), 127.3 (C-10), 127.1 (C-12), 124.0 (C-3), 123.8 (C-4), 72.7 (C-7), 70.8 (C-8), 51.0 (C-17), 45.7 (C-1), 42.5 (C-15), 39.1 (C-6), 32.9 (C-13), 28.9 (C-14) 27.3 (C-2), 24.9 (C-5); *m/z* (ESI) 318 (100), $[MH]^+$; [HRMS (ESI) calcd. for $C_{19}H_{28}NO_3$, 318.2064 Found: $[MH]^+$ 318.2069 (1.4 ppm error)].

KAG/2/78

(1*R*,6*S*)-Methyl 1-(3-aminopropyl)-6-(benzyloxymethyl)cyclohex-3-enecarboxylate ((+)-178)

To a stirred solution of ester **(–)-165** (4.00 g, 15.4 mmol), in THF (37 mL) at –78 °C was added dropwise KHMDS (0.70 M in toluene, 33.0 mL, 23.1 mmol). After complete addition the reaction was stirred at –78 °C for 2 h, then azide **183** (3.90 g, 18.5 mmol) in THF (19 mL) was added dropwise. The reaction was stirred at –78 °C for 15 minutes, warmed to rt and stirred for 18 h, then partitioned between EtOAc (2

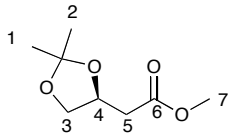
x 5 mL) and aqueous NH_4Cl (sat., 5 mL). The organic layers were combined, and the volatiles removed under reduced pressure to yield the crude azide **177**. The azide was dissolved in THF (120 mL) and water (3.15 mL) and triphenylphosphine (4.47 g, 17.0 mmol) added. The reaction was heated to reflux for 1 h, then cooled to rt, concentrated and purified by loading onto 2 x 20 g SCX columns. Washing with MeOH followed by eluting with 9:1 CH_2Cl_2:7 N NH_3 in MeOH gave the *title compound* **(+)-178** as a colourless film (3.23 g, 66% over 2 steps).

Data as for racemate **±178** except

$[\alpha]_D$ +25.7 (*c* 1.3, $CHCl_3$).

KAG/8/80 and KAG/8/81

(*S*)-2,4-*O*-*Iso*propylidine-3,4-dihydroxy butyric acid methyl ester (190)[99]



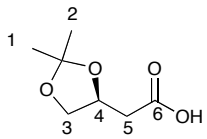
Prepared according to the procedure described in patent.[99]

(*S*)-Hydroxy butyrolactone **189** (5.00 g, 49.0 mmol), MeOH (15 mL), 2,2-dimethoxy propane (10 mL), acetone (5 mL) and *p*-TSA (466 mg, 2.71 mmol) were mixed and heated to reflux for 3 h. The reaction was quenched by the addition of aqueous $NaHCO_3$ (sat., 30 mL) and then extracted with Et_2O (3 x 50 mL). The organic layers were combined, washed with brine (3 x 40 mL), dried over Na_2SO_4, then the volatiles removed under reduced pressure to yield the crude product, which was purified by column chromatography. Eluting with 8:2 PE:Et_2O gave the *title compound* **190** as a pale yellow oil (4.16 g, 49%); R_f 0.51 (1:1 PE:Et_2O); δ_H (400 MHz, $CDCl_3$) 4.46 (1H, app quin., *J* 6.5, H-4), 4.14 (1H, dd, *J* 8.0, 6.5, H-3a), 3.70 (3H, s, H-7), 3.64 (1H, dd, *J* 8.0, 6.5, H-3b), 2.27 (1H, dd, *J* 16.0, 6.5, H-5a), 2.52 (1H, dd, *J* 16.0, 6.5, H-5b), 1.40 (3H, s, H-1/H-2), 1.34 (3H, s, H-1/H-2).

^{1}H NMR data consistent with literature.[98]

KAG/2/82

(*S*)-2,4-*O*-*Iso*propylidine-3,4-dihydroxy butyric acid (170)[99]



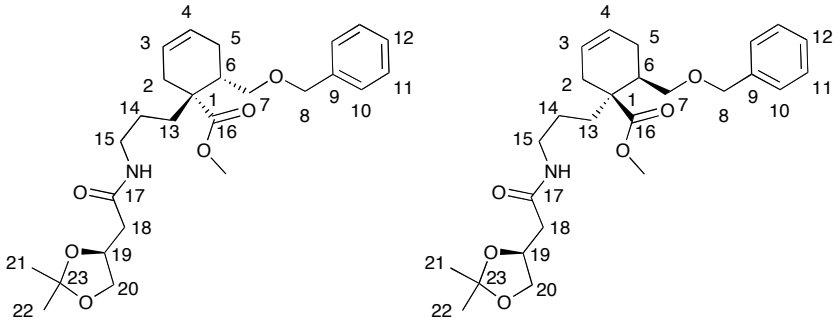
To a stirred solution of ester **190** (4.16 g, 23.9 mmol) in THF (2.4 mL) and water (12 mL) was added in a single portion lithium hydroxide monohydrate (1.00 g, 23.9 mmol) and the reaction stirred at rt for 1 hour. The pH was adjusted to 4 by the dropwise addition of aqueous oxalic acid (10%) and then extracted with Et_2O (2 x 50 mL). The organic layers were combined, dried over Na_2SO_4, then the volatiles

removed under reduced pressure to yield the *title compound* **170** as a pale yellow oil (2.03 g, 45%) which was used without further purification; R_f 0.18 (EtOAc); δ_H (400 MHz, $CDCl_3$) 4.46 (1H, app quin., *J* 6.0, H-4), 4.14 (1H, dd, *J* 8.5, 6.0, H-3a), 3.65 (1H, dd, *J* 8.5, 6.0, H-3b), 2.73 (1H, dd, *J* 16.0, 6.0, H-5a), 2.55 (1H, dd, *J* 16.0, 6.0, H-5b), 1.40 (3H, s, H-1/H-2), 1.36 (3H, s, H-1/H-2).

^{1}H NMR data consistent with literature.[133]

KAG/2/83

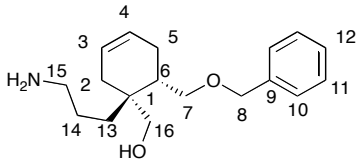
(1*R*,6*S*)-Methyl 6-(benzyloxymethyl)-1-(3-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanamido)propyl)cyclohex-3-enecarboxylate (186a) and (1*S*,6*R*)-methyl 6-(benzyloxymethyl)-1-(3-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanamido)propyl)cyclohex-3-enecarboxylate (186b)



To a stirred solution of amine **178** (65 mg, 0.205 mmol), acid **170** (40 mg, 0.250 mmol) and DMAP (3 mg, 0.0245 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C under an atmosphere of argon was added in a single portion DCC (65 mg, 0.315 mmol). The reaction was stirred at 0 °C for 10 min, then the ice bath removed and the reaction allowed to warm to rt, where it was stirred for 30 min. The reaction was filtered through a plug of SiO_2 to remove the DCU, washing with EtOAc (20 mL). The volatiles were removed under reduced pressure to yield the crude product, which was purified by column chromatography. Eluting with EtOAc gave the *title compounds* **186a** and **186b** in a 1:1 mixture as a colourless film (80 mg, 91%); R_f: 0.23 (75:25 PE:EtOAc); IR ν_{max} (neat) 3323, 3027, 2929, 1726, 1643, 1554, 1494, 1452, 1370, 1312, 1246, 1212, 1111, 1066, 736; δ_H (400 MHz, $CDCl_3$) 7.34–7.42 (5H, m, H-10, H-11, H-12), 6.04 (1H, s, NH), 5.54 (2H, s, H-3, H-4), 4.51–4.39 (3H, m, H-8, H-19),

4.11 (2H, dd, *J* 8.0, 6.0, H-20), 3.59 (3H, s, CH_3), 3.31 (2H, d, *J* 7.0, H-7), 3.19 (2H, q, *J* 6.5, H-15), 2.49–3.39 (2H, m, H-18), 2.33–2.19 (2H, m, H-5), 2.06–2.03 (2H, m, H-2), 1.67–1.57 (3H, m, H-14, H-6), 1.46 (3H, s, H-21/22), 1.35 (3H, s, H-21/22), 2.49 (2H, m, H-13); δ_C (100 MHz, $CDCl_3$) 176.8 (C-16), 170.0 (C-17), 138.4 (C-9), 128.4 (C-11), 127.8 (C-10), 127.6 (C-12), 124.4 (C-4), 124.3 (C-3), 109.5 (C-23), 73.2 (C-7), 72.6 (C-19), 71.2 (C-8), 69.2 (C-20), 51.6 (CH_3), 45.7 (C-1), 40.7 (C-15), 39.6 (C-18), 39.2 (C-6), 32.8 (C-13), 27.2 (C-2), 27.0 (C-21/C-22), 25.6 (C-21/C-22), 25.0 (C-14), 24.5 (C-5); *m/z* (ESI) 482 (100), $[MNa]^+$ 460 $[MH]^+$; [HRMS (ESI) calcd. for $C_{26}H_{37}NNaO_6$, 482.2513. Found: $[MNa]^+$ 482.2521 (1.6 ppm error)].
No difference between the diastereoisomers was observed by ^1H or ^{13}C NMR.

((1*RS*,6*SR*)-1-(3-Aminopropyl)-6-(benzyloxymethyl)cyclohex-3-enyl)methanol (199)



To a stirred solution of ester **165** (2.00 g, 7.68 mmol) in THF (20 mL) at –78 °C under an atmosphere of argon was added dropwise KHMDS in toluene (0.67 M, 13.2 mL, 8.83 mmol) The solution was stirred at –78 °C for 2 h, then azide **183** in THF (10 mL) was added dropwise and the reaction allowed to warm to rt and stirred overnight. The reaction was partitioned between water (200 mL) and EtOAc (2 x 200 mL), the organic layers combined and dried over Na_2SO_4, then the volatiles removed under reduced pressure. The resulting yellow oil was dissolved in Et_2O (20 mL) and added to a stirred solution of lithium aluminium hydride (4.0 M in Et_2O, 15.4 mL, 61.44 mmol[*]) diluted in Et_2O (20 mL). When the addition was complete the reaction was allowed to stir at room temperature for 1 h, then quenched by the portionwise addition of $Na_2SO_4 \cdot 10H_2O$[*] until no more effervescence was observed (~10 g). The solids

[*]The reaction was run with an excess of LAH as the THF contained higher than normal levels of peroxides which were quenching the reagent. This was due to a supply problem.

[*] Note: the use of Celite mixed with $Na_2SO_4 \cdot 10H_2O$ in the quench for this reaction resulted in a dramatic loss of yield. It was assumed the very polar amino alcohol stuck to the Celite.

were filtered, washed with EtOAc, then the volatiles removed under reduced pressure to yield the crude product, which was purified by SCX cartridge. Washing with MeOH, then eluting with 9:1 MeOH:7M NH_3/MeOH in gave the *title compound* **199** as a colourless oil (1.40 g, 67%); IR ν_{max} (neat) 3369, 3026, 2925, 1453, 1365, 1265, 1097, 702; δ_H (400 MHz, $CDCl_3$) 7.37–7.29 (5H, m, H-10, H-11, H-12), 5.61–5.74 (2H, m, H-3, H-4), 4.54 (1H, d, *J* 12.0, H-8a), 4.48 (1H, d, *J* 12.0, H-8b), 3.64 (1H, d, *J* 12.0, H-16a), 3.63–3.46 (2H, m, H-7), 3.23 (1H, d, *J* 12.0, H-16b), 2.67-2.68 (2H, m, H-15), 2.25–1.64 (10H, br m, H-2, H-5, H-6, H-13, NH_2, OH), 1.52–1.24 (2H, m, H-14); δ_C (100 MHz, $CDCl_3$) 137.6 (C-9), 128.6 (C-11), 128.0 (C-12), 127.9 (C-10), 125.5 (C-3), 124.9 (C-4), 73.5 (C-8), 70.9 (C-7), 64.9 (C-16), 43.0 (C-15), 39.5 (C-6), 38.7 (C-1), 33.2 (C-2), 32.0 (C-14), 26.9 (C-5), 26.7 (C-13); *m/z* (ESI) 290 (100), $[MH]^+$; [HRMS (ESI) calcd. for $C_{18}H_{28}NO_2$, 290.2115. Found: $[MH]^+$ 290.2106 (3.0 ppm error)].

KAG/4/13

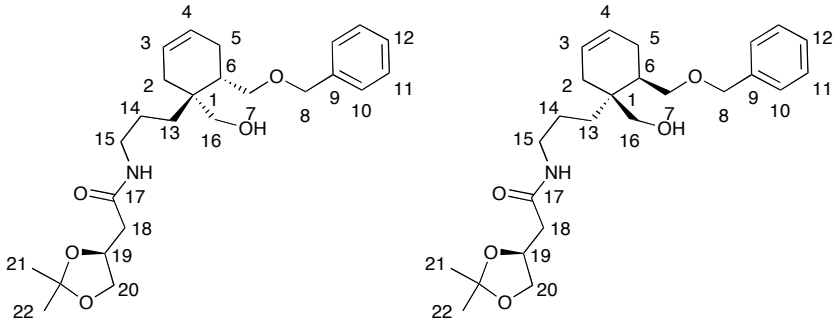
((1*R*,6*S*)-1-(3-Aminopropyl)-6-(benzyloxymethyl)cyclohex-3-enyl)methanol ((+)-199)

Was prepared according to the procedure described above, data was in accordance with the racemic material.

$[\alpha]_D$ +12.8 (*c* 1.0, $CHCl_3$).

KAG/4/46

***N*-(3-((1*R*,6*S*)-6-(Benzyloxymethyl)-1-(hydroxymethyl)cyclohex-3-enyl)propyl)-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanamide (200a) and *N*-(3-((1*S*,6*R*)-6-(benzyloxymethyl)-1-(hydroxymethyl)cyclohex-3-enyl)propyl)-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanamide (200b)**



To a stirred solution of amine **199** (1.82 g, 6.28 mmol) acid **170** (1.0 g, 6.28 mmol) in CH_2Cl_2 at 0 °C under an atmosphere of argon was added in a single portion HATU (2.39 g, 6.28 mmol). The reaction was stirred at 0 °C for 30 min, then allowed to warm to rt and stirred there overnight. The reaction was partitioned between water (150 mL) and EtOAc (150 mL), the aqueous layer washed with EtOAc (150 mL) then the organic layers combined and dried over Na_2SO_4. Removal of the volatiles under reduced pressure gave the crude product as a sticky yellow oil, which was purified by column chromatography. Eluting with 98:2 EtOAc:MeOH gave the *title compounds* **200a** and **200b** in a 1:1 mixture as a thick colourless oil (2.76 g, *quant.*) This was dried under high vacuum (~1 mbar) with stirring at 60 °C for 5 h, but still contained traces of EtOAc; R_f 0.21 (98:2 EtOAc:MeOH); δ_H (400 MHz, $CDCl_3$) 7.44–7.22 (5H, m, H-10, H-11, H-12), 6.32 (1H, br s, NH), 5.58 (1H, br d, *J* 10.0, H-4), 5.49 (1H, br d, *J* 10.0, H-3), 4.52 (1H, d, *J* 12.0, H-8a) 4.48 (1H, d, *J* 12.0, H-8b), 4.42–4.36 (1H, m, H-19), 4.11 (1H, dd, *J* 8.5, 6.0, H-20a), 3.71–3.55 (3H, m, H-7a, H-16a, H-20b),

3.51 (1H, dd, *J* 9.5, 5.0, H-7b), 3.40–3.09 (3H, m, H-16b, H-15), 2.47 (1H, dd, *J* 15.0, 7.5, H-18a), 2.39 (1H, dd, *J* 15.0, 5.5, H-18b), 2.21 (1H, ddd, *J* 18.5, 5.5, 3.0, H-5a), 2.07 (1H, brd, *J* 18.5, H-5b), 1.87–1.62 (4H, m, H-2, H-6, H-13a), 1.49 (2H, app quintet, *J* 7.0, H-14), 1.43 (3H, s, H-21/H-22), 1.36 (3H, s, H-21/H-22), 1.86–1.29 (1H, m, H-13b).

^{1}H NMR data consistent with literature.[60]

KAG/4/24

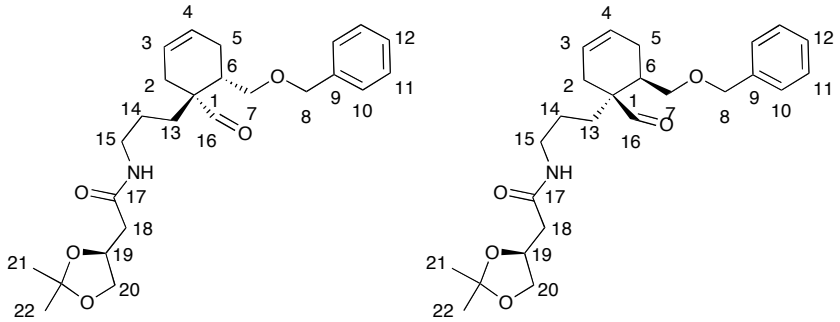
_N_-(3-((1_R_,6_S_)-6-(Benzyloxymethyl)-1-(hydroxymethyl)cyclohex-3-enyl)propyl)-2-((_S_)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanamide ((+)-200)

was prepared according to the procedure described above, data was in accordance with the racemic material.

$[\alpha]_D$ +13.4 (*c* 1.1, $CHCl_3$) (Lit.[54] +11.5 (*c* 1.1, $CHCl_3$)).

KAG/4/47

_N_-(3-((1_R_,6_S_)-6-(Benzyloxymethyl)-1-formylcyclohex-3-enyl)propyl)-2-((_S_)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanamide (66a) and _N_-(3-((1_S_,6_R_)-6-(benzyloxymethyl)-1-formylcyclohex-3-enyl)propyl)-2-((_S_)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanamide (66b)



To a stirred solution of alcohol **200** (2.00 g, 4.64 mmol) in CH_2Cl_2 (100 mL) under an atmosphere of argon were added freshly dried 4 Å molecular sieves (2.00 g). This solution was stirred for 15 min at rt, before *N*-methyl-morpholine-*N*-oxide (650 mg, 5.56 mmol) was added in a single portion, followed by tetra-*n*-propylammonium perruthenate (122 mg, 0.347 mmol). The reaction was stirred at rt for 2 h. The

reaction was filtered through a pad of silica, washing with EtOAc (100 mL) then the volatiles removed under reduced pressure to give the *title compounds* **66a** and **66b** in a 1:1 mixture as a pale brown film which was immediately used crude in the next reaction; R_f 0.48 (EtOAc); δ_H (400 MHz, $CDCl_3$) 9.57 (1H, s, H-13), 7.45–7.18 (5H, m, H-10, H-11, H-12), 6.07 (1H, br s, NH), 5.65–5.60 (2H, m, H-3, H-4), 4.44 (1H, d, *J* 12.0, H-8a), 4.39 (1H, d, *J* 12.0, H-8b), 4.40–4.38 (1H, m, H-19), 4.12 (1H, dd, *J* 8.5, 6.0, H-20a), 3.60 (1H, dd, *J* 8.5, 7.0, H-20b), 3.40–3.36 (2H, m, H-7), 3.20 (2H, dd, *J* 13.0, 7.0, H-15), 2.47 (1H, dd, *J* 15.0, 7.5, H-18a), 2.41 (1H, dd, *J* 15.0, 5.0, H-18b), 2.32–2.19 (3H, m, H-2a, H-6, H-5a), 2.08–1.95 (2H, m, H-2b, H-5b), 1.58–1.53 (2H, m, H-14), 1.50–1.43 (1H, m, H-13a), 1.42 (3H, s, H-21/H-22), 1.36 (3H, s, H-21/H-22), 1.32–1.29 (1H, m, H-13b).

^{1}H NMR data consistent with literature.[60]

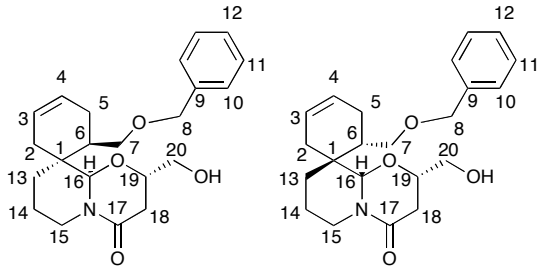
KAG/4/30

_N_-(3-((1_R_,6_S_)-6-(Benzyloxymethyl)-1-formylcyclohex-3-enyl)propyl)-2-((_S_)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanamide ((+)-66)

Was prepared according to the procedure described above, data was in accordance with the racemic material.

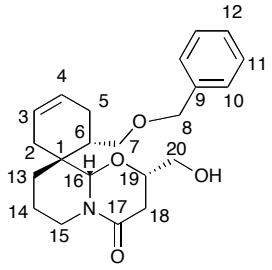
KAG/4/50

(1*R*,2'*S*,6*S*,9a'*S*)-6-(Benzyloxymethyl)-2'-(hydroxymethyl)-6',7',8',9a'-tetrahydro-2'*H*-spiro[cyclohex[3]ene-1,9'-pyrido[2,1-*b*][1,3]oxazin]-4'(3'*H*)-one (172a) and (1*S*,2'*S*,6*R*,9a'*S*)-6-(benzyloxymethyl)-2'-(hydroxymethyl)-6',7',8',9a'-tetrahydro-2'*H*-spiro[cyclohex[3]ene-1,9'-pyrido[2,1-*b*][1,3]oxazin]-4'(3'*H*)-one (172b) (1:1 mixture)



$SnCl_2 \cdot 2H_2O$ (392 mg, 1.74 mmol) was added in a single portion to the crude reaction mixture of aldehyde **66** (0.695 mmol) in CH_2Cl_2 and the reaction stirred at rt for 17 h. K_2CO_3 (1.00 g) was added in a single portion and the reaction stirred for a further 30 min at rt, before being filtered through a pad of Celite, which was washed with EtOAc (50 mL). Removal of the volatiles under reduced pressure gave the crude product, which was purified by column chromatography. Eluting with EtOAc gave the *title compounds* **172a** and **172b** in a 1:1 mixture as a sticky pale yellow oil (198 mg, 77% from **200**); R_f 0.11 (EtOAc); δ_H (400 MHz, $CDCl_3$) 7.36–7.27 (10H, m, H-10, H-10', H-11, H-11', H-12, H-12'), 5.65–5.54 (4H, m, H-3, H-3', H-4, H-4'), 4.76–4.69 (2H, m, H-15a, H-15a'), 4.71–4.68 (2H, m, H-16, H16'), 4.58–4.36 (4H, m, H-8, H-8'), 4.05 (1H, br dd, *J* 9.5, 3.5, H-7a'), 3.93 (1H, dd, *J* 10.0, 5.0, H-7a), 3.75–3.61 (4H, m, H-20a, H-20a', H-19, H-19'), 3.54–3.40 (2H, m, H-7b, 20b), 3.30 (1H, dd, *J* 12.0, 6.5, H-7b'), 3.21 (1H, t, *J* 10.0, H-20b'), 2.61–1.95 (14H, m, H-18, H-18', H-14, H-14', H-15b, H-15b', H-5, H-5'), 1.82–1.42 (10H, m, H-2, H-2', H-13, H-13', H-6, H-6').
KAG/4/28

(1*R*,2'*S*,6*S*,9a'*S*)-6-(Benzyloxymethyl)-2'-(hydroxymethyl)-6',7',8',9a'-tetrahydro-2'*H*-spiro[cyclohex[3]ene-1,9'-pyrido[2,1-*b*][1,3]oxazin]-4'(3'*H*)-one ((–)-172)



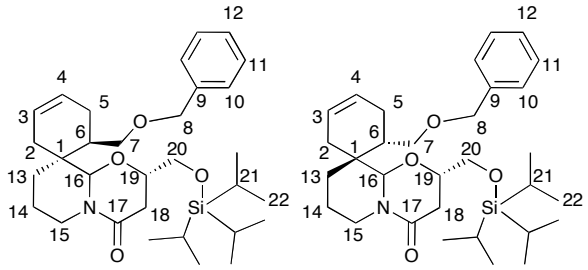
According to the procedure described for the racemic material aldehyde **(+)-66** (4.63 mmol, assuming 100% conversion) and $SnCl_2 \cdot 2H_2O$ (2.61 g, 11.6 mmol) gave the crude product which was purified by column chromatography. Eluting with 98:2 EtOAc:MeOH gave the *title compound* **(–)-172** as a pale yellow sticky oil (600 mg, 36% from **200**)[*]; R_f 0.11 (EtOAc); δ_H (400 MHz, $CDCl_3$) 7.40–7.25 (5H, m, H-10, H-11, H-12), 5.58–5.54 (2H, m, H-3, H-4), 4.72 (1H, s, H-16), 4.69–4.67 (1H, m, H-15a), 4.53 (1H, d, *J* 12.0, H-8a), 4.48 (1H, d, *J* 12.0, H-8b), 3.93 (1H, dd, *J* 10.0, 5.0, H-7a), 3.74–3.68 (1H, m, H-19), 3.62 (1H, br d, *J* 11.0, H-20a), 3.46–3.42 (1H, m, H-20b), 3.41 (1H, dd, *J* 10.0, 6.0, H-7b), 2.51 (1H, d, *J* 12.0, H-18a), 2.46 (1H, d, *J* 12.0, H-18b), 2.41–2.32 (2H, m, H-14a, H-15b), 2.26–2.21 (2H, m, H-5), 1.81–1.71 (3H, m, H-2a, H-6, H-14b), 1.56–1.46 (3H, m, H-2b, H-13).

^{1}H NMR data consistent with literature.[60]

KAG/4/52

[*] The low yield was attributed to the problems experienced with the TPAP oxidation. The chromatography conditions were changed from the racemic synthesis as the material eluted very slowly in EtOAc

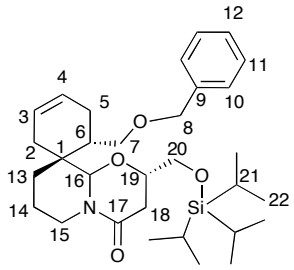
(1*S*,2'*S*,6*R*)-6-(Benzyloxymethyl)-2'-((tri*iso*propylsilyloxy)methyl)-6',7',8',9a'-tetrahydro-2'*H*-spiro[cyclohex[3]ene-1,9'-pyrido[2,1-*b*][1,3]oxazin]-4'(3'*H*)-one (203a) and (1*R*,2'*S*,6*S*)-6-(benzyloxymethyl)-2'-((tri*iso*propylsilyloxy)methyl)-6',7',8',9a'-tetrahydro-2'*H*-spiro[cyclohex[3]ene-1,9'-pyrido[2,1-*b*][1,3]oxazin]-4'(3'*H*)-one (203b)



To a stirred solution of alcohol **172** (50 mg, 0.135 mmol) in CH_2Cl_2 (1 mL) at 0 ºC was added 2,6-lutidine (47 μL, 0.402 mmol) in a single portion, followed by tri*iso*propylsilyl trifluoromethanesulfonate (50 mg, 0.162 mmol) in a single portion. The reaction was stirred at 0 °C for 5 min, then allowed to warm to rt and stirred for 1 h. The volatiles were removed under reduced pressure, then the crude product purified by column chromatography. Eluting with EtOAc gave the *title compounds* **203a** and **203b** in a 1:1 mixture of inseparable diastereoisomers as a colourless oil (47 mg, 67%); R_f 0.57 (EtOAc); δ_H (400 MHz, $CDCl_3$) 7.35–7.24 (10H, m, H-10, H-10', H-11, H-11', H-12, H-12'), 5.63–5.21 (4H, m, H-3, H-3', H-4, H-4'), 4.78–4.68 (2H, m, H-15a, H-15a'), 4.59–4.36 (6H, m, H-16, H-16', H-8, H-8'), 4.21–4.11 (1H, m, H-7a'), 4.01 (1H, dd, *J* 9.5, 4.5, H-7a), 3.72–3.44 (6H, m, H-19, H-19', H-20, H-20'), 3.36 (1H, t, *J* 9.5, H-7b), 3.23 (1H, dd, *J* 11.0, 9.5, H-7b'), 2.61–1.36 (24H, m, H-5, H-5', H-15b, H-15b', H-18, H-18', H-14, H-14', H-2, H-2', H-6, H-6', H-13, H-13'), 1.07–1.03 (42H, m, H-21, H-21', H-22, H-22').

KAG/4/38

(1*R*,2'*S*,6*S*)-6-(Benzyloxymethyl)-2'-((tri*iso*propylsilyloxy)methyl)-6',7',8',9a'-tetrahydro-2'*H*-spiro[cyclohex[3]ene-1,9'-pyrido[2,1-*b*][1,3]oxazin]-4'(3'*H*)-one ((–)-203)



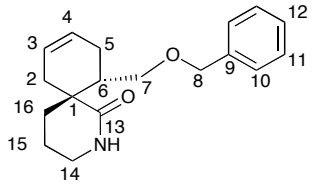
According to the procedure described for the racemic material alcohol **(–)-172** (628 mg, 1.19 mmol) gave the crude product as a yellow oil, which was purified by column chromatography. Eluting with 75:25→25:75 *iso*-hexane:EtOAc gave the *title compound* **(–)-203** as a colourless oil (360 mg, 41%)[*]; R_f 0.20 (25:75 EtOAc:*iso*-hexane); δ_H (400 MHz, $CDCl_3$) 7.36–7.25 (5H, m, H-10, H-11, H-12), 5.60–5.54 (2H, m, H-4, H-3), 4.72 (1H, dddd, *J* 13.0, 4.5, 2.0, 2.0, H-15a), 4.61 (1H, s, H-16), 4.49 (1H, d, *J* 12.0, H-8a), 4.46 (1H, d, *J* 12.0, H-8b), 4.02 (1H, dd, *J* 9.5, 4.0, H-7a), 3.74–3.68 (2H, m, H-17, H-20a), 3.64–3.60 (1H, m, H-20b), 3.37 (1H, dd, *J* 9.5, 9.5, H-7b), 2.53–2.36 (4H, m, H-5a, H-15b, H-18), 2.28 (1H, brd, *J* 18.5, H-14a), 2.15 (1H, brd, *J* 18.5 H-5b), 1.92 (1H, dd, *J* 13.5, 2.0, H-2a), 1.83–1.73 (2H, m, H-6, H-13a), 1.60–1.49 (2H, m, H-13b, H-14b), 1.40 (1H, dd, *J* 13.5, 4.5, H-2b), 1.07–1.03 (21H, m, H-21, H-22).

^{1}H NMR data consistent with literature.[60]

KAG/4/59

[*] The low yield can partly be attributed to a leak in the purification system's injection port.

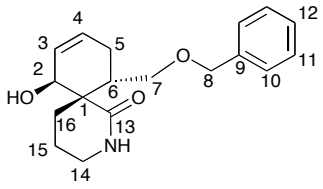
(6*R*,11*S*)-11-(benzyloxymethyl)-2-azaspiro[5.5]undec-8-en-1-one (187)



Crude amine **178** (assume 15.5 mmol) was dissolved in MeOH (320 mL) and aquous K_2CO_3 (10%, 80 mL) added. The reaction was stirred at rt for 18 h, the volatiles removed under reduced pressure and the crude product purifed by column chromatography. Eluting with 9:1→1:1 PE:EtOAc gave the *title compound* **187** as a colourless oil (1.28 g, contaminated with PPh_3); R_f 0.58 (1:1 PE:EtOAc); $[\alpha]_D$ +65.0 (*c* 1.7, $CHCl_3$); IR ν_{max} (neat) 3430, 1647, 1099; δ_H (400 MHz, $CDCl_3$) 7.25–7.18 (5H, m, H-10, H-11, H-12), 5.58–5.47 (3H, m, H-3, H-4, NH), 4.44 (1H, d, *J* 11.5, H-8a), 4.35 (1H, d, *J* 11.5, H-8b), 3.70 (1H, ddd, *J* 9.0, 2.0, 1.0, H-7a), 3.41–3.36 (1H, m, H-7b), 3.27–3.23 (2H, m, H-14), 2.76–2.68 (2H, m, H-16a, H-2a), 2.42–2.39 (1H, m, H-5a), 2.38–2.16 (3H, m, H-6, H-2b, H-16b), 1.93–1.82 (1H, m, H-15a), 1.72–1.56 (1H, m, H-5b), 1.43-1.38 (1H, m, H-15b); δ_C (100 MHz, $CDCl_3$) 180.3 (C-13), 142.6 (C-9), 132.1 (C-11), 131.4 (C-10), 131.2 (C-12), 128.3 (C-3), 127.4 (C-4), 77.0 (C-7), 74.5 (C-8), 46.1 (C-1), 45.2 (C-14), 40.7 (C-6), 35.0 (C-2), 34.6 (C-16), 27.7 (C-5), 21.4 (C-15); *m/z* (ESI) 308 (100), $[MNa]^+$; [HRMS (ESI) calcd. for $C_{18}H_{23}NNaO_2$, 308.1621 Found: $[MNa]^+$ 308.1626 (1.7 ppm error)].

KAG/8/80

(6*S*,7*S*,11*S*)-11-(benzyloxymethyl)-7-hydroxy-2-azaspiro[5.5]undec-8-en-1-one (+)-319)

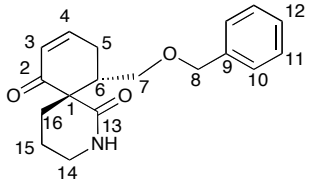


To a stirred solution of lactone **187** (2.89 g, 10.1 mmol) in EtOH (142 mL) and water (7.5 mL) was added selenium dioxide (1.34 g, 12.2 mmol). The mixture was heated to

90 °C under an atmosphere of argon for 3 days. After cooling to rt the volatiles were removed under reduced pressure and the residue purified by column chromatography. Eluting with 1:1 PE:EtOAc→EtOAc gave the *title compound* **(+)-319** as a yellow oil (1.58 g, 52%); R_f 0.21 (30% EtOAc); $[\alpha]_D$ +158.3 (*c* 0.3, $CHCl_3$); IR ν_{max} (neat) 3429, 2928, 1638, 1454, 1364, 1100, 667; δ_H (400 MHz, $CDCl_3$) 7.35–7.24 (5H, m, H-10, H-11, H-12), 5.65–5.58 (3H, m, H-3, H-4, NH), 4.91 (1H, br s, H-2), 4.50 (1H, d, *J* 11.5, H-8a), 4.42 (1H, d, *J* 11.5, H-8b), 3.38–3.71 (1H, m, H-7a), 3.48–3.32 (3H, m, H-7b, H-14), 2.38–1.56 (8H, m, H-5, H-6, H-15, H-16, OH); δ_C (100 MHz, $CDCl_3$) 175.5 (C-13), 138.4 (C-9), 128.7 (C-11), 128.4 (C-10), 127.6 (C-12), 127.5 (C-3/4), 125.9 (C-3/4), 73.3 (C-7), 70.4 (C-8), 66.6 (C-2), 47.8 (C-1), 42.1 (C-14), 37.8 (C-6), 24.3 (C-16), 22.2 (C-5), 17.8 (C-15);*m/z* (ESI) 324 (100), $[MNa]^+$ 301 (70) $[MH]^+$; [HRMS (ESI) calcd. for $C_{18}H_{24}NO_3$, 302.1751. Found: $[MH]^+$ 302.1754 (1.2 ppm error)].

KAG/8/30

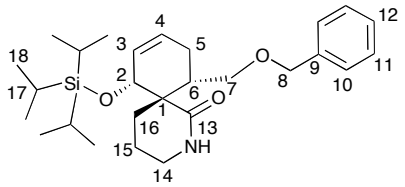
(6*S*,11*S*)-11-(Benzyloxymethyl)-2-azaspiro[5.5]undec-8-ene-1,7-dione (320)



To a stirred solution of alcohol **320** (650 mg, 2.15 mmol) in toluene (32 mL) was added freshly dried 4 Å molecular sieves (1.30 g) and manganese dioxide (1.96 g, 21.5 mmol). The reaction was heated at reflux for 18 h, then cooled to rt and filtered through a pad of Celite, washing with EtOAc (100 mL). The filtrate was concentrated to give the *title compound* **320** (648 mg, 100%) which was used without further purification; R_f 0.88 (1:1 PE:EtOAc); IR ν_{max} (neat) 3290, 3031, 2934, 2868, 1651, 1486, 1453, 1390, 1318, 1104, 737; δ_H (400 MHz, $CDCl_3$) 7.36–7.23 (5H, m, H-10, H-11, H-12), 7.01 (1H, ddd, *J* 10.0, 5.5, 3.0, H-4), 6.20 (1H, br s, NH), 6.01 (1H, ddd, *J* 10.0, 2.0, 1.5, H-3), 4.52–4.45 (2H, m, H-8), 3.73 (1H, dd, *J* 9.5, 5.0, H-7a), 3.55 (1H, dd, *J* 9.5, 8.0 H-7b), 3.30–3.15 (2H, m, H-14), 2.91–2.83 (1H, m, H-6), 2.56–2.48 (1H, m, H-5a), 2.39–2.28 (1H, m, H-16a), 2.27–2.09 (2H, m, H-15), 1.93–1.82

(1H, m, H-5b), 1.81–1.65 (1H, m, H-16b); δ_C (100 MHz, $CDCl_3$) 198.7 (C-2), 169.9 (C-13), 150.5 (C-4), 138.1 (C-9), 128.5 (C-10/C11), 127.9 (C-3), 127.8 (C-12), 127.7 (C-10/C11), 73.8 (C-8), 71.5 (C-7), 54.1 (C-1), 43.6 (C-6), 42.5 (C-14), 31.4 (C-15), 28.3 (C-5), 21.5 (C-16); *m/z* (ESI) 300 (100), $[MH]^+$ 322 (70) $[MNa]^+$; [HRMS (ESI) calcd. for $C_{18}H_{22}NO_3$, 300.1595. Found: $[MH]^+$ 300.1603 (3.0 ppm error)].
KAG/8/31

(6*S*,7*R*,11*S*)-11-(Benzyloxymethyl)-7-(tri*iso*propylsilyloxy)-2-azaspiro[5.5]undec-8-en-1-one (–)-322)



To a stirred solution of enone **320** (1.47 g, 4.91 mmol) in MeOH (120 mL) was added $CeCl_3 \cdot 7H_2O$ (1.83 g, 4.91 mmol). The reaction was stirred at rt under an atmosphere of argon for 10 min, before being cooled to –78 °C, and sodium borohydride (372 mg, 9.82 mmol) added in a single portion. The reaction was stirred for a further 30 min at –78 °C, then allowed to warm to rt. The methanol was removed under reduced pressure then the resulting slurry partitioned between CH_2Cl_2 (2 x 50 mL) and aqueous HCl (2 M, 75 mL) The layers were separated, the organic layer dried over Na_2SO_4 and the volatiles removed under reduced pressure to give the crude product **321** which was immediately dissolved in CH_2Cl_2 (25 mL) and the solution cooled to 0 °C. To this solution was added 2,6-lutidine (1.10 mL, 9.41 mmol), followed by tri*iso*propylsilyl trifluoromethanesulfonate (1.06 mL, 3.96 mmol). The reaction was allowed to warm to rt, where it was stirred for 1 h, then water (40 mL) and CH_2Cl_2 (2 x 40 mL) added. The organic layers were combined and dried over Na_2SO_4 and the volatiles removed under reduced pressure to give the crude product, which was purified by column chromatography. Eluting with 6:4 PE:EtOAc gave the *title compound* **322** as a pale brown oil (703 mg, 15% over 3 steps from **(+)-319**); R_f 0.39 (40% 6:4 PE:EtOAc); $[\alpha]_D$ –24.1 (*c* 0.3, $CHCl_3$); IR ν_{max} (neat) 3208, 3034, 2865,1666, 1463, 1390, 1365, 1312, 1116, 1013, 883; δ_H (400 MHz, $CDCl_3$) 7.25–

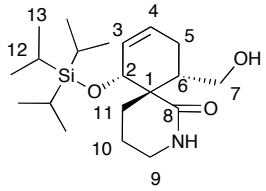
7.24 (5H, m, H-10, H-11, H-12), 5.79–5.56 (3H, m, H-3, H-4, NH), 4.46–4.40 (2H, m, H-8), 4.24 (1H, br t, *J* 3.0, H-2), 3.69 (1H, dd, *J* 9.0, 5.0, H-7a), 3.35 (1H, dd, *J* 9.0, 7.0, H-7b), 3.24–3.18 (1H, m, H-14a), 3.10–3.06 (1H, m, H-14b), 2.51–2.43 (1H, m, H-5a), 2.15–2.06 (2H, m, H-6, H-16a), 1.99–1.81 (3H, m, H-5b, H-15), 1.69–1.61 (1H, m, H-16b), 1.10–0.91 (21H, m, H-17, H-18); δ_C (100 MHz, $CDCl_3$) 171.8 (C-13), 138.6 (C-9), 128.8 (C-3/C-4), 128.4 (C-10/C-11), 128.2 (C-3/C-4), 127.5 (C-10/C-11), 127.4 (C-12), 77.8 (C-2), 73.1 (C-8), 72.6 (C-7), 45.7 (C-1), 44.5 (C-6), 42.1 (C-14), 34.6 (C-15), 29.4 (C-5), 22.5 (C-16), 18.4 (C-18), 13.5 (C-17); *m/z* (ESI) 458 (100), $[MH]^+$ 480 (20) $[MNa]^+$; [HRMS (ESI) calcd. for $C_{27}H_{44}NO_3Si$, 458.3085. Found: $[MH]^+$ 458.3086 (0.3 ppm error)].

KAG/7/68

Will Unsworth managed 55% yield over 3 steps 64% BRSM

WPU743, WPU746, WPU747.

(6*S*,7*R*,11*S*)-11-(Hydroxymethyl)-7-(tri*iso*propylsilyloxy)-2-azaspiro[5.5]undec-8-en-1-one ((–)-323)

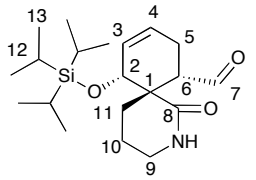


Lithium wire (560 mg, 80.2 mmol) was finely chopped and charged to a 1 L RBF, which was flushed with argon. To this was added THF (55 mL) followed by naphthalene (3.05 g, 23.8 mmol). The mixture was placed in a sonic bath for 1 h, before being cooled to –20 °C, then (6*S*,7*R*,11*S*)-11-(benzyloxymethyl)-7-(tri*iso*propylsilyloxy)-2-azaspiro[5.5]undec-8-en-1-one (**(–)-322**) (1.36 g, 2.97 mmol) in THF (15 mL) was added *via* canula. The solution was maintained at –20 °C for 5 mins (with no stirring), then quenched by the dropwise addition of aqueous NH_4Cl (sat., 100 mL). The resulting solution was extracted with EtOAc (2 x 150 mL) and then the volatiles removed to give the crude product, which was purified by column chromatography. Eluting with 35:65 PE:EtOAc→EtOAc→95:5 EtOAc:MeOH gave the *title compound* **(–)-323** as a white solid (620 mg, 57%); m.p. 135–136 °C; Found:

C, 65.0; H, 9.4, N 3.7 $C_{20}H_{57}NO_3Si$ requires C, 65.4; H, 10.1 N, 3.81%; $[\alpha]_D$ –108.2 (*c* 0.5, $CHCl_3$); R_f 0.12 (EtOAc); IR ν_{max} (neat) 3402, 2942, 2865, 1641, 1111, 682; δ_H (400 MHz, $CDCl_3$) 5.90– 5.81 (1H, m, H-4), 5.75 (1H, br s, NH), 5.71–5.64 (1H, m, H-3), 2.47–4.32 (1H, m, H-2), 4.03–3.94 (1H, m, H-7a), 3.77–3.71 (1H, m, H-7b), 3.37–3.25 (2H, m, H-9), 2.53–2.50 (2H, m, H-5), 2.19–2.11 (2H, m, H-11), 1.99–1.94 (1H, m, H-6), 1.87–1.80 (2H, m, H-10), 1.16–1.06 (21H, m, H-12, H-13); δ_C (100 MHz, $CDCl_3$) 173.5 (C-8), 128.6 (C3/C4), 128.0 (C-3/C-4), 76.2 (C-2), 64.8 (C-7), 47.3 (C-1), 45.8 (C-6), 42.2 (C-9), 33.9 (C-11), 28.7 (C-5), 22.0 (C-10), 18.3 (C-13), 13.3 (C-12); *m/z* (ESI) 368 (100), $[MH]^+$ 390 (30) $[MNa]^+$; [HRMS (ESI) calcd. for $C_{20}H_{38}NO_3Si$, 368.2615. Found: $[MH]^+$ 368.2608 (1.9 ppm error)].

KAG/8/38

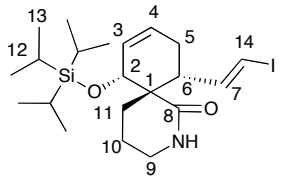
(6*S*,7*S*,11*R*)-1-Oxo-11-(tri*iso*propylsilyloxy)-2-azaspiro[5.5]undec-9-ene-7-carbaldehyde ((–)-324)



To a stirred solution of (6*S*,7*R*,11*S*)-11-(hydroxymethyl)-7-(tri*iso*propylsilyloxy)-2-azaspiro[5.5]undec-8-en-1-one **((–)-323)** (413 mg, 1.12 mmol), in CH_2Cl_2 (17 mL), were added freshly dried 4 Å molecular sieves (600 mg) and *N*-methyl-morpholine-*N*-oxide (158 mg, 1.35 mmol). The reaction was stirred at rt for 10 min, then tetra-*n*-propylammonium perruthenate (39.5 mg, 0.266 mmol) added and the reaction stirred at rt for 1 h. The reaction mixture was filtered through a plug of Celite, then concentrated to give the crude product, which was purified by column chromatography. Eluting with 85:15→1:1 PE:EtOAc gave the *title compound* **(–)-324** as a white solid (334 mg, 81%) m.p. 112–114 °C; R_f 0.42 (1:1 PE:EtOAc); $[\alpha]_D$ –78.2 (*c* 0.85, $CHCl_3$); IR ν_{max} (neat) 3205, 2941, 2865, 1703, 1658, 1492, 1462, 1413, 1326, 1088, 883; δ_H (400 MHz, $CDCl_3$) 10.30 (1H, d, *J* 4.0, H-7), 5.87 (1H, s, NH), 5.77–5.75 (2H, m, H-3, H-4), 4.48 (1H, s, H-2), 3.37–3.31 (2H, m, H-9), 2.49–2.39 (2H, m, H-6, H-5a), 2.04–1.95 (2H, m, H-10), 1.84–1.77 (1H, m, H-11a), 1.67–1.61 (1H, m, H-11b) 1.09–1.04 (21H, m, H-12, H-13); δ_C (100 MHz, $CDCl_3$) 205.1 (C-7), 173.5 (C-8), 127.6 (C3/C4), 126.4 (C3/C4), 69.8 (C-2), 52.8 (C-6), 47.2 (C-1), 42.0 (C-9), 30.7 (C-11), 27.8 (C-5), 19.3 (C-10), 18.2 (C-13), 13.1 (C-12); *m/z* (ESI) 366 (100), $[MH]^+$; [HRMS (ESI) calcd. for $C_{20}H_{36}NO_3Si$, 366.2453. Found: $[MH]^+$ 366.2461 (0.6 ppm error)].

WPU 679/680 (best yield)

(6*S*,7*R*,11*R*)-11-((*E*)-2-Iodovinyl)-7-(tri*iso*propylsilyloxy)-2-azaspiro[5.5]undec-8-en-1-one (–)-343

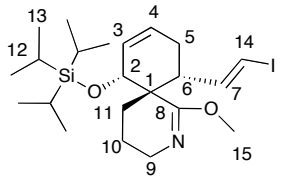


An oven dry Schlenk tube was charged with $CrCl_2$ (1.00 g, 8.14 mmol), and the contents flame dried under high vacuum. The tube was then allowed to cool and the $CrCl_2$ slurried in dry THF (3.94 mL). To this was added a solution of aldehyde **(–)-324** (297 mg, 0.814 mmol) and CH_3I (961 mg, 2.44 mmol) in dry 1,4-dioxane (23.7 mL). The reaction was stirred at rt for 3 h, then quenched by the addition of water (50 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), then dried over $MgSO_4$ and the volatiles removed under reduced pressure to give the crude product, which was purified by column chromatography. Eluting with 85:15→3:1→1:1 PE:EtOAc gave the *title compound* **(–)-343** as a colourless oil (271 mg, 68%); R_f 0.21 (3:1 PE:EtOAc); $[\alpha]_D$ –77.9 (*c* 0.50, $CHCl_3$); IR ν_{max} (neat) 2941, 2866, 1666, 1464, 1313, 1110, 961; δ_H (400 MHz, $CDCl_3$) 6.57 (1H, dd, *J* 14.5, 10.0, H-7), 6.12 (1H, d, *J* 14.5, H-14), 5.78–5.62 (3H, m, H-3, H-4, NH), 4.26–4.24 (1H, m, H-2), 3.28–3.17 (2H, m, H-9), 5.66–5.56 (1H, m, H-5a), 2.28–2.12 (2H, m, H-5a, H-6), 1.93–1.71 (4H, m, H-10, H-11) 1.09-1.04 (21H, m, H-12, H-13); δ_C (100 MHz, $CDCl_3$) 170.9 (C-8), 147.9 (C-7), 129.1 (C-3/C-4), 127.3 (C-3/C-4), 77.2 (C-2), 79.2 (C-14), 52.5 (C-6), 47.6 (C-1), 42.3 (C-9), 35.0 (C-11), 31.1 (C-5), 21.5 (C-10), 18.3 (C-13), 13.5 (C-12); *m/z* (ESI) 490 (100), $[MH]^+$, 512 (30) $[MNa]^+$; [HRMS (ESI) calcd. for $C_{21}H_{37}INO_2Si$, 490.1643. Found: $[MH]^+$ 490.1643(2.0 ppm error)].

WPU/683

Rigorously anhydrous conditions necessary, use a new ampoule of CrC_2 each time.

(6*S*,7*R*,11*R*)-11-((*E*)-2-Iodovinyl)-1-methoxy-7-(tri*iso*propylsilyloxy)-2-azaspiro[5.5]undeca-1,8-diene ((–)-344)

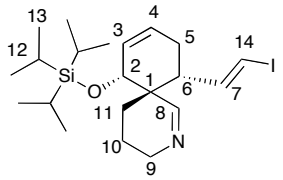


To s stirred solution of vinyl iodide **(–)-343** (435 mg, 0.889 mmol) in CH_2Cl_2 (10.9 mL) at rt were added freshly dried 4 Å molecular sieves (450 mg), then K_2CO_3 (491 mg, 3.56 mmol), followed by Meerwein's salt (394 mg, 2.67 mmol). The reaction was stirred at rt for 1 h, then diluted with CH_2Cl_2 (20 mL) and filtered through a plug of Celite, washing with CH_2Cl_2 (40 mL). The volatiles were removed under reduced pressure, giving the *title compound* **(–)-344** as a mixed salt (440 mg), which was used without further purification.

Data was collected on the free imidate by taking a small sample and performing an aqueous workup with aqueous $NaHCO_3$.

R_f 0.90 (EtOAc); $[\alpha]_D$ –40.1 (*c* 1.6, $CHCl_3$); IR ν_{max} (neat) 2941, 2865, 2360, 1650, 1463, 1112, 1064, 974; δ_H (400 MHz, $CDCl_3$) 6.30 (1H, dd, *J* 10.0, 14.0), 6.07 (1H, d, *J* 14.0, H-14), 5.68–5.58 (2H, m, H-3, H-4), 4.14–4.09 (1H, m, H-2), 3.50–3.31 (5H, m, H-9, H-15), 2.37–2.15 (2H, m, H-6, H-5a), 2.06–1.96 (1H, m, H-11a), 1.89–1.82 (1H, m, H-5b), 1.69–1.54 (3H, m, H-10, H-11b), 1.19–0.92 (21H, m, H-12, H-13); δ_C (100 MHz, $CDCl_3$) 162.3 (C-8), 148.1 (C-7), 130.0 (C-3/C-4), 126.4 (C-3/C-4), 76.3 (C-2), 75.9 (C-14), 51.7 (C-15/C-6), 51.5 (C-15/C6), 46.7 (C-9), 49.7 (C-1), 35.8 (C-11), 31.4 (C-5), 21.0 (C-10), 18.3 (C-13), 13.4 (C-12); *m/z* (ESI) 504 (100), $[MH]^+$; [HRMS (ESI) calcd. for $C_{22}H_{39}INO_2Si$, 504.1789. Found: $[MH]^+$ 504.1802 (2.6 ppm error)].
WPU/762

(6*R*,7*R*,11*R*)-11-((*E*)-2-Iodovinyl)-7-(tri*iso*propylsilyloxy)-2-azaspiro[5.5]undeca-1,8-diene (+)-345)

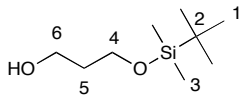


To a stirred solution of crude mixed salt **(–)-344** (553 mg, assume 1.10 mmol (100% based on lactam **(–)-343** in 95% EtOH (12 mL) at –40 °C was added $NaBH_4$ (81.2 mg, 2.20 mmol). The pH of the reaction was monitored and maintained as close to 7 as possible by the dropwise addition of aqueous HCl (1 M). After 30 min the reaction was quenched by the addition of aqueous $NaHCO_3$ (sat., 10 mL) and then extracted with CH_2Cl_2 (3 x 10 mL). Removal of the volatiles under reduced pressure gave the crude compound, which was purified by column chromatrography. Eluting with 85:15 PE:EtOAc gave the *title compound* **(+)-345** as a colourless oil (179 mg, 34%, along with 251 mg, 45% of starting material **(–)-344**)

The starting material recovered (251 mg) was recycled by resubjection to the above reduction conditions, giving a further 68 mg product and 163 mg starting material **(–)-344**. A further two cycles generated another 38.5 mg and 30 mg of **(–)-344**, giving a total of 328 mg (63% yield) of the isolated product **(+)-345** along with 57 mg of the starting imidate **(–)-344** (70% BRSM); R_f 0.70 (EtOAc); $[\alpha]_D$ +16.3 (*c* 0.90, $CHCl_3$); IR ν_{max} (neat) 2941, 2685, 1668, 1462, 1247, 1214, 1110, 1067, 883; δ_H (400 MHz, $CDCl_3$) 7.88 (1H, s, H-8), 6.59 (1H, dd, *J* 14.0, 10.0, H-7), 6.08 (1H, d, *J* 14.0, H-14), 5.77–5.70 (2H, m, H-3, H-4), 4.22–4.19 (1H, m, H-2), 3.68–3.58 (1H, m, H-9a), 3.51–3.40 (1H, m, H-9b), 2.30–2.29 (1H, m, H-6), 2.18–2.08 (2H, m, H-5), 1.99–1.82 (1H, m, H-11a), 1.67–1.54 (2H, m, H-10), 1.47–1.40 (1H, m, H-11b) 1.09–1.04 (21H, m, H-12, H-13); δ_C (100 MHz, $CDCl_3$) 164.9 (C-8), 147.6 (C-7), 129.6 (C-3/C-4), 125.8 (C-3/C-4), 75.8 (C-2/C-14), 74.1 (C-2/C-14), 50.2 (C-6), 49.3 (C-9), 42.1 (C-1), 29.0 (C-5/C-11), 28.9 (C5/C11), 19.8 (C10), 18.3 (C-12), 13.0 (C-13); *m/z* (ESI) 474 (100), $[MH]^+$; [HRMS (ESI) calcd. for $C_{21}H_{37}INOSi$, 474.1684. Found: $[MH]^+$ 474.1688 (0.3 ppm error)].
WPU/763-766

6.3 Short chain DE core compounds

3-(*tert*-Butyldimethylsilyloxy)propan-1-ol (220)

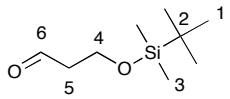


To a stirred solution of 1,3-propane diol (10.0 g, 131 mmol) in THF (50 mL) at –10 °C under an atmosphere of argon was added dropwise *n*-BuLi (2.7 M in heptane, 53.5 mL, 145 mmol). The reaction was allowed to warm to 0 °C, where it was stirred for 30 min. *tert*-Butyldimethylsilyl chloride (19.8 g, 131 mmol) in THF (25 mL) was added dropwise and the reaction allowed to warm to rt and stirred overnight. The reaction was partitioned between water (250 mL) and EtOAc (2 x 250 mL). The organic layers were combined and dried over $MgSO_4$ and the volatiles removed under reduced pressure to give the crude product as a pale yellow oil. This could be used crude, or purified by column chromatography. Eluting with 9:1→7:3 *iso*-hexane:EtOAc gave the *title compound* **220** as a pale yellow oil (8.50 g, 35%); R_f 0.23 (8:2 *iso*-hexane:EtOAc); δ_H (400 MHz, $CDCl_3$) 3.82 (2H, t, *J* 5.5, H-4), 3.79 (2H, t, *J* 5.5, H-6), 2.63 (1H, br s, OH), 1.77 (2H, app quin., *J* 5.5, H-5), 0.89 (9H, s, H-1), 0.07 (6H, s, H-3).

^{1}H NMR data consistent with literature.[134]

KAG/4/75

3-(*tert*-Butyldimethylsilyloxy)propanal (221)



To a stirred solution of oxalyl chloride (1.48 mL, 17.0 mmol) in CH_2Cl_2 (15 mL) at –78 °C under an atmosphere of argon was added DMSO (2.21 mL, 31.1 mmol) in CH_2Cl_2 (2 mL). The internal temperature was monitored and the addition rate controlled such that it remained below –60 °C. The resulting mixture was stirred at –78 °C for 10 min, then 3-(*tert*-butyldimethylsilyloxy)propan-1-ol (**220**) (2.69 g, 14.1

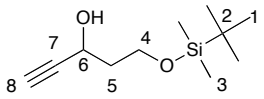
mmol) in CH_2Cl_2 (20 mL) added dropwise maintaining the internal temperature below –60 °C. The reaction was stirred at –78 °C for 1 h, before being quenched by the addition of triethylamine (9.82 mL, 70.6 mmol) and the reaction warmed to rt. The reaction was diluted with CH_2Cl_2 (150 mL) and washed with aqueous HCl (2 M, 2 x 150 mL) and water (2 x 150 mL). The organic layer was dried over $MgSO_4$ then the volatiles removed under reduced pressure to give the *title compound* **221** as a brown oil (1.91 g, 74%) which was used without further purification; R_f 0.46 (8:2 *iso*-hexane:EtOAc); δ_H (400 MHz, $CDCl_3$) 9.79 (1H, t, *J* 2.0, H-6), 3.98 (2H, t, *J* 6.0, H-4), 2.58 (2H, td, *J* 6.0, 2.0, H-5), 0.87 (9H, s, H-1), 0.05 (6H, s, H-3).

^{1}H NMR data consistent with literature.[135]

KAG/4/79

It should be noted that this compound appeared unstable at room temperature.

5-(*tert*-Butyldimethylsilyloxy)pent-1-yn-3-ol (214)



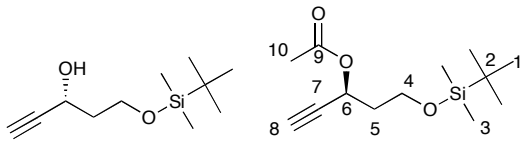
To a stirred solution of ethynylmagnesium bromide **222** (0.5 M in THF, 21.2 mL, 10.6 mmol) at 0 °C under an atmosphere of argon was added slowly 3-(*tert*-butyldimethylsilyloxy)propanal (**221**) (1.80 g, 9.63 mmol) in THF (5 mL). The reaction was stirred at 0 °C for 30 min, then allowed to warm to rt and stirred for 30 min. The reaction was quenched by the addition of aqueous $NaHCO_3$ solution (sat., 20 mL) then the THF removed under reduced pressure. The remaining yellow oil was partitioned between water (50 mL) and Et_2O (2 x 50 mL). The organic layers were combined, dried over $MgSO_4$ and the volatiles removed under reduced pressure to give the crude product as a yellow oil, which was purified by column chromatography. Eluting with 3:1 *iso*-hexane:EtOAc gave the *title compound* **214** as a yellow oil (1.25 g, 61%); R_f 0.31 (3:1 *iso*-hexane:EtOAc); δ_H (400 MHz, $CDCl_3$) 4.71–4.61 (1H, m, H-6), 4.05 (1H, ddd, *J* 10.0, 8.0, 4.0, H-4a), 3.84 (1H, ddd, *J* 10.0, 6.5, 4.0, H-4b), 3.50 (1H, br s, OH), 2.46 (1H, d, *J* 2.0, H-8), 2.01 (1H, ddt *J* 18.5, 8.0, 4.0, H-5a), 1.87 (1H, dddd, *J* 18.5, 13.0, 6.5, 4.0, H-5b), 0.89 (9H, t, *J* 3.0, H-1), 0.08 (6H, d, *J* 3.0, H-3).

KAG/4/64

^{1}H NMR data consistent with literature.[104]

This was not the most repeatable procedure for synthesis of this compound. Yields varied with polymerisation and deprotection of the TBS group observed on several occasions. When attention was turned to the synthesis of the longer chain analogue a different procedure was used (see Section 6.4 for details). If this compound was to be synthesised again we would recommend the route used for the longer chain compound.

(*R*)-5-(*tert*-Butyldimethylsilyloxy)pent-1-yn-3-ol ((+)-214) and (*S*)-5-(*tert*-butyldimethylsilyloxy)pent-1-yn-3-yl ethanoate ((−)-231)



To a stirred solution of alcohol **214** (3.00 g, 14.0 mmol) in *n*-hexane (100 mL) under an atmosphere of argon was added powdered 4 Å molecular sieves (3.60 g), followed by vinyl acetate (8.01 mL, 84.0 mmol), then Amano lipase (3.00 g). The mixture was stirred at 35 ºC, and monitored by removing 60 μL aliquots for GC. After 3.5 h the conversion reached 50%, and the reaction was filtered through a pad of Celite washing with EtOAc (150 mL). The volatiles were removed under reduced pressure to give the crude product, which was purified by column chromatography. Eluting with 8:2→ 6:4 *iso*-hexane:EtOAc gave acetate **(−)-231** as a colourless oil (1.63 g, 45%, 91% theoretical) and alcohol **(+)-214** (1.32 g, 44%, 88% theoretical).

(*R*)-5-(tert-Butyldimethylsilyloxy)pent-1-yn-3-ol (+)-214)

Data as for racemate **(±)-214** except

$[\alpha]_D$ +16.3 (*c* 8.25, $CHCl_3$) (Lit.[104] +14.8 (*c* 8.25, $CHCl_3$)).

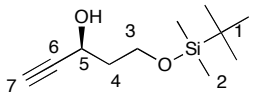
(*S*)-5-(tert-Butyldimethylsilyloxy)pent-1-yn-3-yl ethanoate ((−)-231)

R_f 0.49 (3:1 *iso*-hexane:EtOAc); δ_H (400 MHz, $CDCl_3$) 5.48 (1H, dt, *J* 7.0, 2.0, H-6), 3.79–3.69 (2H, m, H-4), 2.45 (1H, d, *J* 2.0, H-8), 2.08 (3H, s, H-10), 2.07–1.91 (2H, m, H-5), 0.89 (9H, s, H-1), 0.02 (6H, s, H-3).

KAG/4/66

^{1}H NMR data consistent with literature.[104]

(*S*)-5-(*tert*-Butyldimethylsilyloxy)pent-1-yn-3-ol ((−)-214)



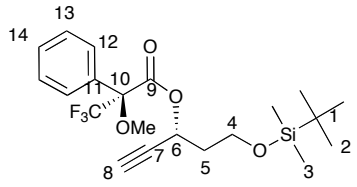
To a stirred solution of acetate **(−)-231** (1.40 g, 5.46 mmol) in MeOH (20 mL) and water (10 mL) at 0 ºC was added lithium hydroxide monohydrate (252 mg, 6.01 mmol), then the reaction allowed to warm to rt, and stirred for an hour. The reaction was partitioned between water (100 mL) and Et_2O (2 x 100 mL), the organic layers combined and dried over $MgSO_4$, then the volatiles removed under reduced pressure to give the *title compound* **(−)-214** as a colourless oil (1.12 g, 95%).

Data as for racemate **(±)-214** except

$[\alpha]_D$ −19.5 (*c* 8.25, $CHCl_3$).

KAG/4/88

(*S*)-((*R*)-5-(*tert*-Butyldimethylsilyloxy)pent-1-yn-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (233)

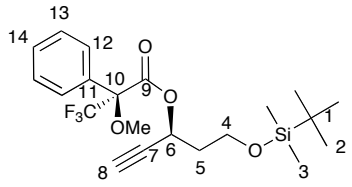


To a stirred solution of alcohol **(+)-214** (50 mg, 0.233 mmol) in pyridine (1 mL) at 0 °C under argon was added (*R*)-(–)-α-methoxy-α(trifluoromethyl)phenylacetyl chloride (56 μL, 0.299 mmol) in a single portion. The reaction was allowed to warm to rt, where it was stirred for an hour. The cloudy solution was partitioned between water (25 mL) and Et_2O (2 x 25 mL), the organic layers combined and dried over $MgSO_4$ to give the *title compound* **233** as a colourless oil (92 mg, 92 %) which was used without further purification; R_f 0.52 (4:1 *iso*-hexane:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.56–7.52 (2H, m, ArCH), 7.43–7.37 (3H, m, ArCH), 5.70 (1H, ddd, *J* 8.5, 6.5, 2.5, H-6), 3.79–3.68 (2H, m, H-3), 3.55 (3H, s, OMe), 2.50 (1H, d, *J* 2.5, H-8), 2.15–1.99 (2H, m, H-5), 0.89 (9H, s, H-1), 0.05 (6H, s, H-3); δ_C (125 MHz, $CDCl_3$) 165.7 (C-9), 132.1 (C-11), 129.7 (C-12/C-13/C-14), 128.5 (C-12/C-13/C-14), 127.7 (C-12/C-13/C-14), 126.6 (q, $^1J_{CF}$ 274, CF_3), 78.9 (C-7), 77.1 (C-10), 74.9 (C-8), 63.3 (C-6), 55.1 (OCH_3), 37.5 (C-4), 29.8 (C-5), 29.0 (C-1), 18.4 (C-2), –5.3 (C-3); δ_F (470 MHz, $CDCl_3$) –72.03 (s, minor CF_3), –72.32 (s, major CF_3).

^{19}F NMR integration indicated an d.r of 93:7, meaning an e.r of 93:7 or e.e of 86% for the precursor alcohol. The diastereoisomers were also observable in the ^1H NMR peak for the OMe group (δ= 3.55) but were closer and less accurate to integrate. The diastereoisomers were not observed by ^{13}C NMR.

KAG/4/86

(*S*)-((*S*)-5-(*tert*-Butyldimethylsilyloxy)pent-1-yn-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (232)



According to the procedure for **233**.

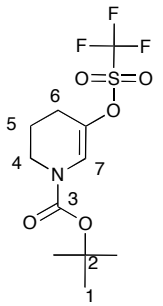
Colourless oil (90 mg, 90 %)

R_f 0.52 (4:1 *iso*-hexane:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.41–7.35 (2H, m, ArCH), 7.32–7.28 (3H, m, ArCH), 5.72 (1H, ddd, *J* 8.5, 6.5, 2.5, H-6), 3.85–3.51 (5H, m, H-4, OCH_3), 2.55 (1H, d, *J* 2.5, H-8), 2.13–1.91 (2H, m, H-5), 0.87 (9H, br t, *J* 4.0, H-1), 0.01 (6H, d, *J* 4.0, H-3); δ_C (100 MHz, $CDCl_3$) 165.7 (C-9), 132.4 (C-11), 129.8 (C-12/C-13/C-14), 128.5 (C-12/C-13/C-14), 127.4 (C-12/C-13/C-14), 125.9 (q, $^1J_{CF}$ 270, CF_3), 80.0 (C-7), 77.2 (C-10), 75.0 (C-8), 62.9 (C-6), 58.1 (OCH_3), 37.6 (C-4), 29.8 (C-5), 29.0 (C-1), 18.3 (C-2), –5.4 (C-3); δ_F (376 MHz, $CDCl_3$) –71.08 (s, major CF_3), –72.10 (s, minor CF_3).

^{19}F NMR integration indicated an d.r of 90:10, meaning an e.r. of 90:10 or a e.e. of 80% for the precursor alcohol. The diastereoisomers were not observed by ^1H or ^{13}C NMR.

KAG/4/88

tert-Butyl 5-(trifluoromethylsulfonyloxy)-3,4-dihydropyridine-1(2*H*)-carboxylate (213)



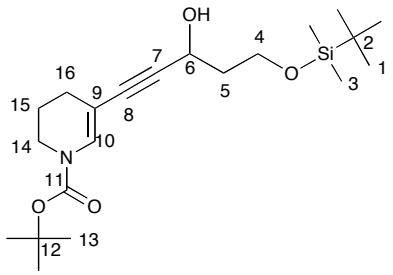
According to the procedure described by Vicart *et al*.[136]

To a stirred solution of freshly distilled di*iso*propylamine (984 μL, 7.03 mmol) in THF (15 mL) at 0 °C under an atmosphere of argon was added slowly *n*-butyl lithium (1.34 M in hexane, 5.25 mL, 7.03 mmol). The resulting solution was stirred at 0 °C for 15 min, before being cooled to –78 °C. *N*-Boc-3-piperidone (1.00 g, 5.02 mmol) in THF (3 mL) was added dropwise to this solution, and it was stirred at –78 °C for 15 min. *N*-Phenyl-bis(trifluoromethanesulfonimide) (1.79 g, 5.02 mmol) in THF (5 mL) was added dropwise, and the solution allowed to warm slowly to rt overnight. The volatiles were removed under reduced pressure, then the crude product immediately purified by column chromatography. Eluting with 92:8 PE:Et_2O gave the *title compound* **213** as a pale brown oil as a mixture of 2 rotamers (659 mg, 42%); R_f 0.59 (4:1 PE:Et_2O); δ_H (400 MHz, $CDCl_3$) 7.24, 7.09 (1H, 2 x s, H-7), 3.51 (2H, br s, H-4), 2.42 (2H, t, *J* 5.5, H-6), 1.95 (2H, app quin., *J* 5.5, H-5), 1.48 (9H, s, H-1).

^{1}H NMR data consistent with literature.[136]

KAG/7/6, KAG/5/52

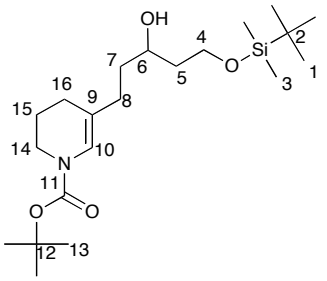
***tert*-Butyl 5-(5-(*tert*-butyldimethylsilyloxy)-3-hydroxypent-1-ynyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (125)**



To a stirred solution of triflate **213** (488 mg, 1.47 mmol) and alcohol **214** (380 mg, 1.77 mmol) in distilled di*iso*propylamine (9.60 mL) was added flame dried lithium chloride (186 mg, 4.41 mmol), copper iodide (14 mg, 0.0735 mmol) and $Pd(PPh_3)_4$ (42 mg, 0.0363 mmol) followed by dry degassed DMF (2.4 mL). The reaction was purged with argon before being heated to 45 °C for 1 h. The volatiles were removed under reduced pressure, then the residue partitioned between water (50 mL) and EtOAc (2 x 50 mL). The organic layers were combined, dried over Na_2SO_4 and the volatiles removed under reduced pressure to give the crude product as a brown oil, which was purified by column chromatography. Eluting with 7:3 PE:Et_2O gave the *title compound* **215** as a pale brown oil as a mixture of 2 rotamers (537 mg, 92%); R_f 0.37 (7:3 PE:Et_2O); IR ν_{max} (neat) 3440, 2953, 2930, 2856, 1709, 1631, 1471, 1384, 1308, 1254, 1159, 1112, 835, 776; δ_H (400 MHz, $CDCl_3$); 7.22, 7.07 (1H, 2 x s, H-10), 4.70 (1H, br s, H-6), 4.02–3.97 (1H, m, H-14a), 3.82–3.78 (1H, m, H-14b), 3.48 (2H, br s, H-4), 2.12 (2H, t, *J* 5.5, H-5), 1.99–1.76 (4H, m, H-15, H-16), 1.46 (9H, s, H-13), 0.87 (9H, s, H-1), 0.06 (6H, s, H-3); δ_C (100 MHz, $CDCl_3$) 151.7 (C-11), 131.6 (C-10), 98.4 (C-9), 87.2 (C-8), 85.6 (C-7), 81.6 (C-12), 62.5 (C-6), 61.3 (C-4), 41.1 (C-14), 39.0 (C-5), 28.3 (C-13), 26.0 (C-16), 25.9 (C-1), 21.2 (C-15), 18.2 (C-2), –5.4 (C-3); *m/z* (ESI) 396 (100), $[MH]^+$ 418 (65) $[MNa]^+$; [HRMS (ESI) calcd. for $C_{21}H_{38}NO_4Si$, 396.2565. Found: $[MH]^+$ 396.2567 (0.3 ppm error)].

KAG/3/46

tert-Butyl 5-(5-(_tert_-butyldimethylsilyloxy)-3-hydroxypentyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (216)



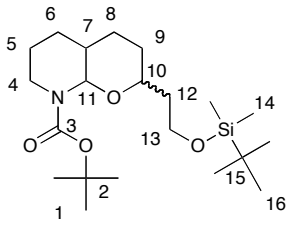
To a stirred solution of alcohol **215** (450 mg, 1.14 mmol) in EtOAc (13 mL), was added Et_3N (475 μL) followed by Pd/C (23 mg). The reaction was purged with H_2, then stirred under an atmosphere of H_2 at rt overnight. The reaction was filtered through a pad of Celite, washed with EtOAc and the volatiles removed under reduced pressure to give the *title compound* **216** as a pale brown oil, which was used immediately without further purification; R_f 0.26 (7:3 PE:Et_2O); IR ν_{max} (neat) 3467, 2930, 2857, 1700, 1472, 1395, 1365, 1316, 1158, 1092, 836; δ_H (400 MHz, $CDCl_3$) 6.65, 6.52 (1H, 2 x s, H-10), 3.89–3.75 (3H, m, H-6, H-14), 3.45–3.41 (2H, m, H-4), 2.13–2.08 (1H, m, H-15a), 2.01–1.93 (3H, m, H-5, H-15b), 1.79–1.74 (2H, m, H-7), 1.64–1.44 (4H, m, H-8, H-16), 1.45 (9H, s, H-13), 0.86 (9H, s, H-1), 0.05 (6H, s, H-3);

The ^{13}C NMR displays an ~1:1 mixture of rotamers for many signals.

δ_C (100 MHz, $CDCl_3$) 152.8, 152.4 (C-11), 120.5, 210.1 (C-10), 118.2, 117.6 (C-9), 80.3, 80.2 (C-12), 71.9, 71.8 (C-6), 62.9, 62.8 (C-4), 45.8. 42.2 (C-14), 41.2 (C-5), 38.4, 38.3 (C-7), 31.6, 31.5 (C-8), 25.9 (C-13), 25.2, 25.1 (C-16), 21.9, 21.8 (C-15), 18.2 (C-2), –5.4 (C-1), –5.5 (C-3); *m/z* (ESI) 400 (73), $[MH]^+$ 422 (100) $[MNa]^+$; [HRMS (ESI) calcd. for $C_{21}H_{41}NNaO_4Si$, 422.2697. Found: $[MNa]^+$ 422.2704 (1.6 ppm error)].

KAG/3/47

tert-Butyl 2-(2-(_tert_-butyldimethylsilyloxy)ethyl)hexahydro-2_H_-pyrano[2,3-_b_]pyridine-8(8a_H_)-carboxylate (217)



To a stirred solution of crude alcohol **216** (1.14 mmol assuming 100% conversion) in CH_2Cl_2 (19 mL) was added 183 μL of HCl (0.1 M solution of HCl in a 20:1 mixture of CH_2Cl_2: MeOH). The mixture was stirred for 5 min, then SiO_2 (900 mg) was added and the volatiles removed under reduced pressure to give a pale yellow oil, which was purified immediately by column chromatography. Eluting with 9:1→2:8 PE:Et_2O gave the *title compound* **217** as a colourless oil (219 mg, 67%); R_f 0.27 (8:2 PE:Et_2O); IR ν_{max} (neat) 3422, 2933, 2862, 1696, 1415, 1366, 1274, 1159, 1091, 1052, 987, 938, 737; δ_H (400 MHz, $CDCl_3$); 5.31, 5.11 (1H, 2 x br s, H-11), 3.81–3.46 (2H, m, H-4a, H-10), 3.68 (2H, t, *J* 6.5, H-13), 2.97–2.83 (1H, m, H-4b), 1.80–1.53 (7H, m, H-7, H-12, H-8, H-9), 1.45 (9H, s, H-1), 1.3–1.63 (4H, m, H-5, H-6), 0.87 (9H, s, H-16), 0.03 (6H, d, *J* 1.0, H-14);

The ^{13}C NMR displays an ~1:1 mixture of rotamers for many signals.

δ_C (100 MHz, $CDCl_3$) 153.4 (C-3), 82.7 (C-11), 79.8 (C-2), 74.7 (C-10), 59.9 (C-13), 39.8, 39.6 (C-4), 39.4, 39.1 (C-12), 34.0 (C-7), 28.9 (C-8/9), 28.4 (C-1), 26.4 (C-8/9), 26.1 (C-16), 28.4 (C5/6), 23.2 (C-5/6), 18.4 (C-15), –5.7 (C-14); *m/z* (ESI) 400 (25), $[MH]^+$ 422 (100) $[MNa]^+$; [HRMS (ESI) calcd. for $C_{21}H_{41}NNaO_4Si$, 422.2697. Found: $[MNa]^+$ 422.2703 (1.3 ppm error)].

KAG/3/49

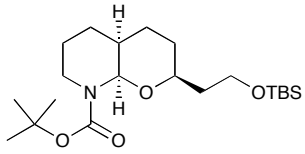
tert-Butyl 2-(2-hydroxyethyl)hexahydro-2H-pyrano[2,3-b]pyridine-8(8a_H_)-carboxylate (230)

To crude alcohol **216** (1.56 mmol assuming 100% conversion) in CH_2Cl_2 (19 mL) was added $SnCl_2{\cdot}2H_2O$ in a single portion (877 mg, 3.90 mmol). The reaction was stirred at rt for 2 h, before being filtered through a plug of Celite, washing with CH_2Cl_2 (50 mL). The filtrate was concentrated under reduced pressure, then purified by column chromatography. Eluting with 2:8 PE:Et_2O gave the *title compound* **230** as a colourless film (281 mg, 63% over 2 steps from **215**); R_f 0.41 (7:3 PE:Et_2O); IR ν_{max} (neat) 3423, 2932, 2861, 1701, 1452, 1413, 1365, 1313, 1275, 1249, 1159, 1127, 1091, 1052, 983; δ_H (400 MHz, $CDCl_3$); 5.35, 5.19 (1H, 2 x br s, H-11), 3.91–3.62 (4H, m, H-13, H-4a, H-10), 2.89 (1H, br s, H-4b), 1.85–1.60 (8H, m, H-7, H-5, H-6a, H-9, H-12), 1.45 (10H, br s, H-1, H-6b), 1.36–1.23 (2H, m, H-8);

The ^{13}C NMR displays a 1:1 mixture of rotamers for many signals.

δ_C (100 MHz, $CDCl_3$) 155.6 (C-3), 82.8, 81.7 (C-11), 78.5, 78.4 (C-10), 80.4 (C-2), 62.1, 61.6 (C-13), 40.1, 39.4 (C-4), 37.5 (C-12), 33.7 (C-7), 28.6 (C-6), 28.4 (C-1), 26.3 (C9/C5), 24.8 (C-9/C-5), 23.0 (C-8); *m/z* (ESI) 308 (100), $[MNa]^+$; [HRMS (ESI) calcd. for $C_{15}H_{27}NNaO_4$, 308.1832. Found: $[MNa]^+$ 308.1839 (2.0 ppm error)].

(2*S*,4a*S*,8a*R*)-*tert*-butyl 2-(2-(*tert*-butyldimethylsilyloxy)ethyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate ((–)-217)



According to the procedure for **(±)-217**

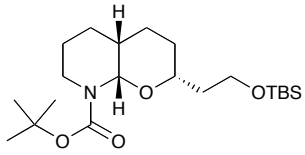
29% over 3 steps from **(+)-214**

Data as for racemate **(±)-217** except

$[\alpha]_D$ –1.5 (*c* 1.1, $CHCl_3$).

KAG/5/60

(2*R*,4a*R*,8a*S*)-*tert*-butyl 2-(2-(*tert*-butyldimethylsilyloxy)ethyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate ((+)-217)



According to the procedure for **(±)-217**

13% over 3 steps from **(**–)-**214**

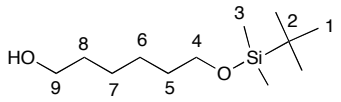
Data as for racemate **(±)-217** except

$[\alpha]_D$ +1.8 (*c* 1.2, $CHCl_3$).

KAG/5/58

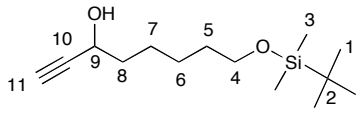
6.4 Long chain DE core compounds

6-(*tert*-Butyldimethylsilyloxy)hexan-1-ol (249)



Prepared according to the procedure described by McDougal and co-workers.[134]
To a stirred suspension of sodium hydride (10.1 g, 253 mmol) in THF (350 mL) at rt under an atmosphere of argon was added dropwise 1,6-hexane diol (30.0 g, 253 mmol) in THF (150 mL). The solution was stirred at rt under a flow of nitrogen for 45 min. *tert*-Butyldimethylsilyl chloride (38.1 g, 253 mmol) was added portionwise and the reaction stirred for a further 45 min at rt. The reaction was quenched by the addition of aqueous K_2CO_3 (10%, 200 mL) and then extracted with Et_2O (2 x 250 mL). The organic layers were combined and the volatiles removed under reduced pressure to give the *title compound* **249** as a colourless oil (49.9 g, 85%) which was used without further purification; R_f 0.42 (7:3 PE:EtOAc); δ_H (400 MHz, $CDCl_3$) 3.75–3.42 (4H, m, H-4, H-9), 1.62–1.41 (8H, m, H-5, H-6, H-7, H-8), 0.81 (9H, s, H-3), 0.03 (6H, s, H-1).
KAG/7/15

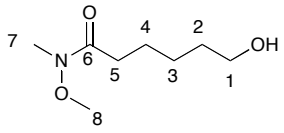
8-(*tert*-Butyldimethylsilyloxy)oct-1-yn-3-ol (26)



The telescoped Swern-Griganard reaction was carried out according to the procedure described by Ireland.[112]

To a stirred solution of oxalyl chloride (7.64 mL, 90.3 mmol) in THF (200 mL) at –78 °C was added dropwise DMSO (6.72 mL, 94.6 mmol) under a flow of nitrogen. The internal temperature was monitored and the addition rate maintained such that it did not exceed –60 °C. The solution was allowed to warm to –35 °C, then recooled to –78 °C. Alcohol **249** (20.0 g, 86.0 mmol) in THF (150 mL) was added dropwise maintaining the internal temperature below –60 °C. The reaction was allowed to warm to –35 °C, where it was stirred for 15 min. Triethylamine (60.0 mL, 430 mmol) was added in a single portion and the solution warmed to rt briefly before being recooled to –78 °C. Ethynylmagnesium bromide **222** (0.5 M in THF, 860 mL, 430 mmol) was added dropwise, then the solution warmed to rt and stirred for 2 h. The reaction was quenched by the addition of 10% NH_4OH in aqueous NH_4Cl (sat., 800 mL) then extracted with Et_2O (2 x 1 L). The organic layers were combined, dried over Na_2SO_4 and the volatiles removed under reduced pressure to yield the crude product which was purified by column chromatography. Eluting with 85:15 PE:EtOAc gave the *title compound* **26** as an orange oil (13.8 g, 63 %); R_f 0.55 (7:3 PE:EtOAc); IR ν_{max} (neat) 3310, 2931, 2858, 1470, 1388 1254, 1099, 836; δ_H (400 MHz, $CDCl_3$) 4.44 (1H, dt, *J* 6.0, 2.0, H-9), 3.56 (2H, t, *J* 6.0, H-4), 2.42 (1H, d, *J* 2.0, H-11), 1.21–1.67 (8H, m, H-5, H-6, H-7, H-8), 0.84 (9H, s, H-1), 0.01 (6H, s, H-3); δ_C (100 MHz, $CDCl_3$) 84.9 (C-10), 72.8 (C-11), 63.1 (C-4), 62.2 (C-9), 37.6 (C-8), 32.7 (C-5), 26.0 (C-1), 25.4 (C-6/7), 24.8 (C-6/7) 18.4 (C-2), –0.1 (C-3); *m/z* (ESI) 257 (100), $[MH]^+$ 279 (35) $[MNa]^+$; [HRMS (ESI) calcd. for $C_{14}H_{29}O_2Si$, 257.1931. Found: $[MH]^+$ 257.1932 (0.3 ppm error)].
KAG/6/57 (eg)

6-Hydroxy-*N*-methoxy-*N*-methylhexanamide (24)



Prepared according to the procedure described by Sulikowski and co-workers.[52]

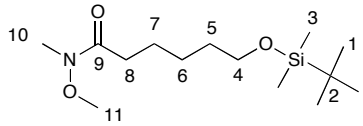
To a stirred solution of ε-caprolactone (11.4 g, 100 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (19.5 g, 200 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added trimethyl aluminium (2.0 M in hexane, 100 mL, 200 mmol) dropwise *via* canula. The reaction was stirred at 0 °C for 1 h, then quenched by portionwise addition to a stirred solution of aqueous Rochelle's salt (sat., 400 mL) (CAUTION, gas evolution). Extraction with EtOAc (2 x 500 mL) gave the *title compound* **24** as a pale yellow oil which (13.3 g, 76%) which was used without further purification; R_f 0.14 (1:1 PE:EtOAc); δ_H (400 MHz, $CDCl_3$) 3.66 (3H, s, H-8), 3.62 (2H, t, *J* 6.5, H-1), 3.16 (3H, s, H-7), 2.41 (2H, t, *J* 7.0, H-5), 1.68–1.55 (5H, m, H-2, H-4, OH), 1.44–1.37 (2H, m, H-3).

^{1}H NMR data consistent with literature.[52]

KAG/8/39

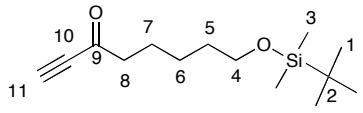
This reaction was scaled to the 100 mL bottles of Me_3Al available. Batches were processed to avoid scaling up any further.

6-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*-methylhexanamide (25)



Prepared according to the procedure described by Sulikowski and co-workers.[52]
To a stirred solution of alcohol **24** (27.0 g, 154 mmol) in DMF (55 mL) was added *tert*butyldimethylsilyl chloride (28.9 g, 192 mmol) and imidazole (26.2 g, 386 mmol). The reaction was stirred at rt for 1 h, before being partitioned between water (200 mL) and Et_2O (2 x 300 mL). The organic layer was washed with water (3 x 300 mL) and brine (300 mL), then dried and the volatiles removed under reduced pressure to give the *title compound* **25** as a pale yellow oil (45 g, 100%) which was used without further purification; R_f 0.46 (8:2 PE:EtOAc); δ_H (400 MHz, $CDCl_3$) 3.63 (3H, s, H-11), 3.56 (2H, t, *J* 6.5, H-4), 3.13 (3H, s, H-10), 2.38 (2H, t, *J* 7.5, H-8), 1.63–1.46 (4H, m, H-5, H-7), 1.37–1.30 (2H, m, H-6), 0.84 (9H, s, H-1), 0.00 (6H, s, H-3).
^1H NMR data consistent with literature.[52]
KAG/8/46

8-(*tert*-Butyldimethylsilyloxy)oct-1-yn-3-one (277)



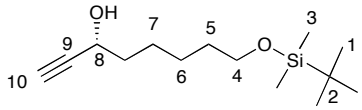
Prepared according to the procedure described by Sulikowski and co-workers.[52]
To neat Weinreb amide **25** (45.0 g, 154 mmol) was added ethynylmagnesium bromide (0.5 M in THF, 616 mL, 308 mmol). The mixture was heated to 50 °C for 1 h, cooled to rt, then partitioned between water (400 mL) and Et_2O (3 x 400 mL). The organic layers were combined, dried over Na_2SO_4, then the volatiles removed under reduced pressure to give the crude product as a brown oil, which was purified by column chromatography. Eluting with 9:1 PE:Et_2O gave the *title compound* **277** as a orange oil (20.6 g, 87% from alcohol **24**); R_f 0.37 (9:1 PE:EtOAc); δ_H (400 MHz, $CDCl_3$) 3.59 (2H, t, *J* 6.5, H-4), 3.21 (1H, s, H-11), 2.60 (2H, t, *J* 7.4, H-8), 1.68 (2H, dd, *J*

7.5. 7.5, H-7), 1.57–1.50 (2H, m, H-5), 1.41–1.34 (2H, m, H-6), 0.89 (9H, s, H-1), 0.04 (6H, s, H-3);

^{1}H NMR data consistent with literature.[52]

KAG/8/47

(*R*)-8-(*tert*-Butyldimethylsilyloxy)oct-1-yn-3-ol ((+)-26)



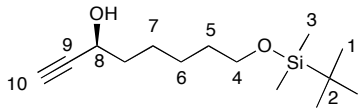
To neat stirred ketone **277** (6.00 g, 23.6 mmol) at 0 °C was added (*R*)-Alpine Borane (0.5 M in THF, 66.0 mL, 33.0 mmol). The reaction was allowed to warm to rt, where it was stirred for 48 h. The solvent was removed under reduced pressure, then the residual oil dissolved in Et_2O (150 mL) and ethanolamine (4.3 mL, 66.1 mmol) added in a single portion. The solution was stirred at rt for 1 h, then the solid formed removed by filtration. Concentration of the filtrate gave the crude product as a dark yellow oil, which was purified by column chromatography. Eluting with 9:1 PE:EtOAc gave the *title compound* **(+)-26** as a pale yellow oil (4.28 g, 71%).

Data as for racemate **(±)-26** except

$[\alpha]_D$ +5.0 (*c* 1.2, $CHCl_3$) (Lit.[52] +3.0 (*c* 1.2, $CHCl_3$)).

KAG/7/90

(*S*)-8-(*tert*-Butyldimethylsilyloxy)oct-1-yn-3-ol ((–)-26)

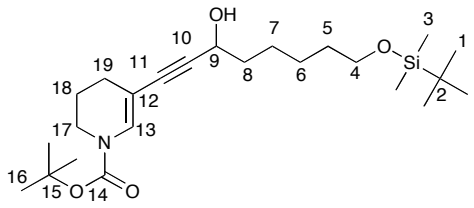


According to the procedure for **(+)-26** (*S*)-Alpine borane and ketone **277** gave the *title compound* **(–)-26** as a pale yellow oil.

Data as for racemate **(+)-26** except

$[\alpha]_D$ –2.2 (*c* 1.2, $CHCl_3$).

***tert*-Butyl 5-(8-(*tert*-butyldimethylsilyloxy)-3-hydroxyoct-1-ynyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (27)**



Alcohol **26** (4.37 g, 17.02 mmol) was added neat to triflate **213** (4.7 g, 14.2 mmol). To this mixture was added flame dried lithium chloride (1.80 g, 42.6 mmol), copper iodide (135 mg, 0.709 mmol) and $Pd(PPh_3)_4$ (410 mg, 0.355 mmol). After each addition the flask was evacuated and purged with argon. Degassed DMF (20 mL) and freshly distilled diispropylamine (84 mL) were added *via* syringe. The reaction was heated to 40 °C for 18 h. On cooling the mixture was partitioned between water (300 mL) and EtOAc (2 x 250 mL). The organic layers were combined and the volatiles removed under reduced pressure to give a black oil which was purified by column chromatography. Eluting with 7:3 PE:EtOAc gave the *title compound* **251** as a brown oil (1.49 g, 75%); R_f 0.26 (3:1 PE:EtOAc); IR ν_{max} (neat) 3423, 2930, 2857, 1708, 1632, 1468, 1385, 1308, 1254, 1159, 1102, 1047, 905; δ_H (400 MHz, $CDCl_3$) 7.25, 7.10 (1H, 2 x s, H-13), 4.47–4.50 (1H, br m, H-9), 3.60 (2H, t, *J* 6.5, H-4), 3.50 (2H, br s, H-17), 2.14 (2H, br t, *J* 6.0, H-19), 1.81–1.36 (19H, m, H-5, H-6, H-7, H-8, H-16, H-18), 0.84 (9H, s, H-1), 0.06 (6H, s, H-3); δ_C (100 MHz, $CDCl_3$) 151.7 (C-15), 131.6, 129.8 (C-13), 98.2 (C-12), 87.8 (C10/C-11/C-15), 85.5 (C10/C-11/C-15), 81.8 (C10/C-11/C-15), 63.1 (C-9), 62.9 (C-4). 41.5 (C-17), 38.0 (C-8), 32.7 (C-5), 28.2 (C-16), 26.0 (C-1), 25.9 (C-6/C-7/C-18), 25.5 (C-6/C-7/C-18), 25.0 (C-6/C-7/C-18), 21.1 (C-19), 18.5 (C-2) –5.1 (C-3); *m/z* (ESI) 420 (100) $[M\text{-}H_2O]^+$ 438 (70) $[MH]^+$; [HRMS (ESI) calcd. for $C_{24}H_{44}NO_4Si$, 438.3034. Found: $[MH]^+$ 438.3023 (2.6 ppm error)].

KAG/6/41 (eg)

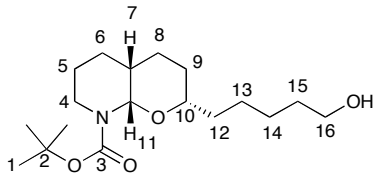
Yields for this reaction were variable (25%-91%). Key points to a high yield were:

Thorough degassing, especially of DMF

Flame drying LiCl immediately before use

Quick column with little silica – isn't so stable on standing. In later stages this material was used without purification.

(2*SR*,4a*RS*,8a*SR*)-*tert*-Butyl 2-(5-hydroxypentyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate (253)



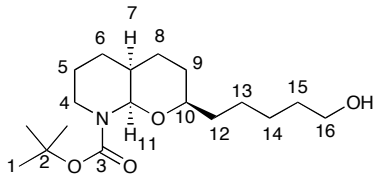
To a stirred solution of alkyne **251** (1.29 g, 2.97 mmol) in EtOAc (40 mL) was added triethylamine (1.26 mL, 9.00 mmol) followed by palladium on carbon (20% w/w, 65 mg). The was evacuated and purged with hydrogen. The reaction was stirred at rt for 18 h. The palladium was removed by filtration through a pad of Celite, washing with EtOAc (100 mL). The volatiles were removed under reduced pressure to yield *tert*-butyl 5-(8-(*tert*-butyldimethylsilyloxy)-3-hydroxyoctyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (**252**) as a pale brown oil. The oil was dissolved in CH_2Cl_2 and $SnCl_2{\cdot}2H_2O$ was added in a single portion (1.67 g, 7.43 mmol). The reaction was stirred at rt for 2 h, before being filtered through a plug of Celite, washing with CH_2Cl_2 (100 mL). The filtrate was concentrated under reduced pressure, then purified by column chromatography. Eluting with 3:7 PE:Et_2O gave the *title compound* **253** as a colourless film (330 mg, 63% over 3 steps from **27**); R_f 0.22 (4:6 PE:EtOAc); IR ν_{max} (neat) 3437, 2928, 1681, 1365, 1313, 1276, 1158, 1094, 1025, 990; δ_H (400 MHz, $CDCl_3$) 5.30, 5.10 (1H, 2 x s, H-11), 3.76 (1H, t, *J* 13.0, H-10), 3.63–3.52 (2H, m, H-16), 3.43–3.30 (1H, m, H-4a), 2.93–2.78 (1H, m, H-4b), 1.79–1.23 (26H, m, H-1, H-5, H-6, H-7, H-8, H-9, H-12, H-13, H-14, H-15);

As observed with the shorter chain compounds the ^{13}C NMR displays an ~1:1 mixture of rotamers for many signals.

δ_C (100 MHz, $CDCl_3$) 155.6, 155.1 (C-3), 82.6, 81.3 (C-11), 79.7, 79.5 (C-10), 77.6, 77.5 (C-2), 63.2, 63.5 (C-16), 39.8 (CH_2), 36.1 (CH_2), 33.9 (C-7), 32.8 (CH_2), 28.9 (CH_2), 28.3 (C-1), 26.3 (CH_2), 25.9 (CH_2), 25.3, 25.0 (CH_2), 24.7 (CH_2), 23.1 (C-5); *m/z* (ESI) 228 (100) 328 (40) $[MH]^+$ 350 (45) $[MNa]^+$; [HRMS (ESI) calcd. for $C_{18}H_{34}NO_4$, 328.2491. Found: $[MH]^+$ 257.1932 (0.3 ppm error)].

KAG/6/57

(2*R*,4a*S*,8a*R*)-*tert*-Butyl 2-(5-hydroxypentyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate ((–)-253)



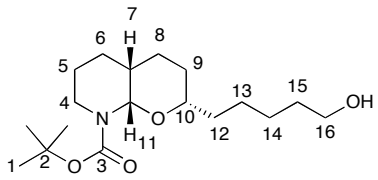
Prepared according to the procedure for **(±)-27** and **(±)-253** using enantio-enriched **(+)-250**. The intermediate alkyne was not isolated. 30% over 3 steps.

Data as for racemate **(±)-253** except

$[\alpha]_D$ –13.0 (*c* 1.2, $CHCl_3$).

KAG/8/13

(2*S*,4a*R*,8a*S*)-*tert*-Butyl 2-(5-hydroxypentyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate ((+)-253)



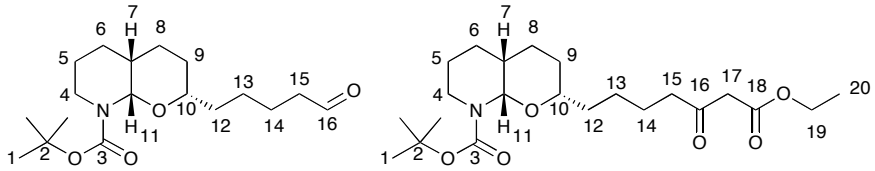
Prepared according to the procedure for **(±)-27** and **(±)-253** using enantio-enriched **(–)-250**. The intermediate alkyne was not isolated. 14% over 3 steps.

Data as for racemate **(±)-253** except

$[\alpha]_D$ +17.5 (*c* 1.4, $CHCl_3$).

KAG/8/64

(2*SR*,4a*RS*,8a*SR*)-*tert*-Butyl 2-(5-oxopentyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate (264) and (2*SR*,4a*RS*,8a*SR*)-*tert*-Butyl 2-(7-ethoxy-5,7-dioxoheptyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate (254)



To a stirred solution of alcohol **253** (310 mg, 0.948 mmol) in CH_2Cl_2 (10mL) were added freshly dried powdered 4 Å molecular sieves (600 mg), the reaction was stirred at rt under argon to 15 min, before the addition of 4-methylmorpholine *N*-oxide (134 mg, 1.14 mmol) followed by tetrapropylammonium perruthenate (25 mg, 0.0711 mmol). The reaction was stirred at rt for 1 h, then filtered through a plug of silica, washing with CH_2Cl_2. Removal of the volatiles under vacuum gave *tert*-butyl 2-(5-oxopentyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate **264** as a pale brown oil, which was used immediately as it proved unstable. To a stirred solution of aldehyde **264** (assuming 0.948 mmol) in CH_2Cl_2 (10 mL) was added $SnCl_2{\cdot}2H_2O$ (21 mg, 0.0948 mmol) and ethyl diazo acetate (120 mg, 1.05 mmol). The reaction was stirred for 1 h at rt, then filtered through a pad of Celite. Washing with CH_2Cl_2 (50 mL) gave the crude product as a yellow oil, which was purified by column chromatography. Eluting with 7:3 PE:EtOAc gave the *title compound* **254** as a sticky pale yellow oil (215 mg, 55% over 2 steps from alcohol **253**).

Aldehyde **264**

R_f 0.68 (1:1 PE:EtOAc); δ_H (400 MHz, $CDCl_3$) 9.72 (1H, s, H-16), 5.28, 5.07 (1H, 2 x s, H-11), 3.74 (1H, t, *J* 13.0, H-10), 3.47–3.23 (1H, m, H-4a), 2.79–2.98 (1H, m, H-4b), 2.38 (2H, t, *J* 6.0, H-15), 1.59–1.23 (24H, m, H-1, H-5, H-6, H-7, H-8, H-9, H-12, H-13, H-14).

KAG/7/9

β-keto ester **254**

R_f 0.48 (7:3 PE:EtOAc); IR ν_{max} (neat) 2932, 2859, 1744, 1701, 1453, 1411, 1365, 1312, 1257, 1158, 1094, 1019, 989; δ_H (400 MHz, $CDCl_3$) 5.28, 4.92 (1H, 2 x s, H-11), 4.21–4.13 (2H, m, H-19), 3.77 (1H, br t, *J* 13.0, H-10), 3.45–3.27 (3H, m, H-16,

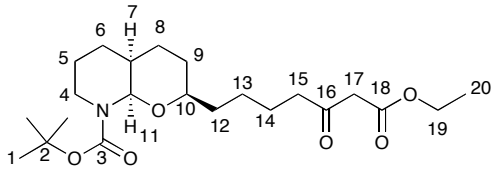
H-4a), 2.98–2.83 (1H, m, H-4b), 2.52 (2H, t, *J* 7.0, H-15), 1.80–1.15 (27H, m, H-1, H-5, H-6, H-7, H-8, H-9, H-12, H-13, H-14, H-20);

The ^{13}C NMR showed a ~1:1 mixture of rotamers

δ_C (100 MHz, $CDCl_3$) 202.8 (C-17), 167.2 (C-18), 155.5, 155.0 (C-3), 82.6, 81.3 (C-11), 79.9, 79.5 (C-10), 77.3 (C-2), 61.2 (C-19), 59.8 (C-17), 52.0 (C-15), 42.8 (CH_2), 39.8, 39.4 (C-4), 35.6 (CH_2), 33.8 (CH_2), 28.3 (C-1), 26.2 (CH_2), 25.7 (CH_2), 25.0 (CH_2), 24.6 (CH_2), 23.1 (CH_2), 23.0 (CH_2), 14.0 (CH_2); *m/z* (ESI) 312 (100), [M–Boc+H]$^+$ 434 (35) [MNa]$^+$; [HRMS (ESI) calcd. for $C_{22}H_{37}NNaO_6$, 434.2513. Found: [MNa]$^+$ 434.2507 (1.3 ppm error)].

KAG/7/10 (eg)

(2*R*,4a*S*,8a*R*)-*tert*-Butyl 2-(7-ethoxy-5,7-dioxoheptyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate ((–)-254)



Pale yellow oil. 62% over 2 steps.

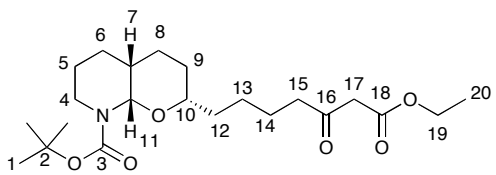
Prepared according to the procedure for **(±)-254**

Data as for racemate **(±)-254**except

$[\alpha]_D$ –27.1 (*c* 1.3, $CHCl_3$).

KAG/8/65 + KAG/8/66

(2*S*,4a*R*,8a*S*)-*tert*-Butyl 2-(7-ethoxy-5,7-dioxoheptyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate ((+)-254)



Pale yellow oil 48% over 2 steps.

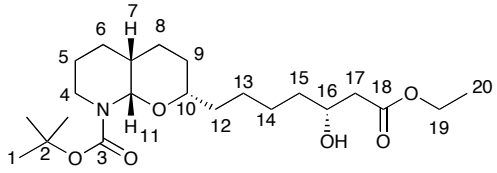
Prepared according to the procedure for **(±)-254**

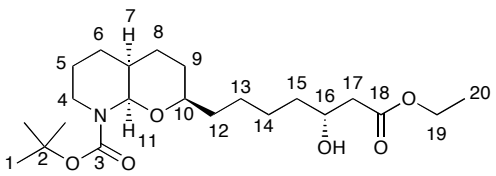
Data as for racemate **(±)-254** except

$[\alpha]_D$ +26.4 (*c* 1.35, $CHCl_3$).

KAG/8/67 + KAG/8/68

(2*S*,4a*R*,8a*S*)-*tert*-Butyl 2-((*R*)-7-ethoxy-5-hydroxy-7-oxoheptyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate (255a) and (2*R*,4a*S*,8a*R*)-*tert*-butyl 2-((*R*)-7-ethoxy-5-hydroxy-7-oxoheptyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate (255b) as a 1:1 mixture of diastereoisomers.





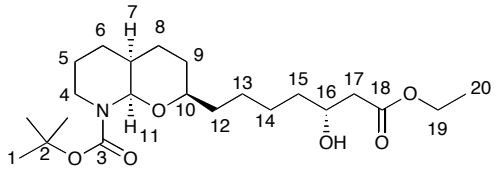
According to the procedure of Genet *et al*.[115]

Bis(2-methylallyl)(1,5-cyclooctadiene)ruthenium (I) (4 mg, 0.0125 mmol) and (*R*)-BINAP (8 mg, 0.0125 mmol) were charged to a Schlenk tube. After 3 vacuum/ argon cycles degassed acetone (2 mL) was added, followed by HBr (0.29 M in MeOH prepared from 48% aq HBr, 0.11 mL). The reaction was allowed to stir for 30 minutes at rt, then the volatiles removed under reduced pressure to give the catalyst as an oxygen-sensitive yellow-brown solid. β-Keto ester **254** was dissolved in distilled MeOH (3 mL) and added to the catalyst. The reaction was purged with hydrogen, heated to 40 °C and stirred for 19 h. After cooling the hydrogen was removed, the resulting brown oil passed though a silica pad, eluting with EtOAc (20 mL) to give the *title compounds* **255a** and **255b** as a brown oil (146 mg, 68%) which was used without further purification; R_f 0.26 (7:3 PE:EtOAc); IR ν_{max} (neat) 3481, 2933, 1735, 1704, 1412, 1366, 1313, 1248, 1160, 1031, 989; δ_H (400 MHz, $CDCl_3$) 5.27, 5.08 (1H, 2 x s, H-11), 4.13–3.98 (2H, m, H-19), 3.97–3.92 (1H, m, H-16), 3.77–3.70 (1H, m, H-10), 3.42–3.25 (1H, m, H-4a), 3.10–2.81 (2H, m, H-4b, OH), 2.48–2.32 (2H, m, H-17), 1.81–1.17 (29H, m, H-1, H-5, H-6, H-7, H-8, H-9, H-12, H-13, H-14, H-15, H-20); δ_C (100 MHz, $CDCl_3$) 172.9 (C-18), 155.1, 155.3 (C-3), 82.5, 81.9 (C-11), 79.6, 79.4 (C-10), 77.2 (C-2), 67.7 (C-16), 60.4 (C-19), 41.1 (CH_2) 39.7 (CH_2), 38.9 (CH_2), 36.2 (CH_2), 35.7, 35.6 (C-7), 33.7 (CH_2), 28.7 (CH_2), 28.1 (C-1) 26.0 (CH_2), 25.3 (CH_2), 24.5 (CH_2), 22.9 (CH_2), 20.8 (C-20); *m/z* (ESI) 314 (100), $[M\text{-Boc}+H]^+$ 414

(50) $[MH]^+$; [HRMS (ESI) calcd. for $C_{22}H_{40}NO_6$, 414.2850. Found: $[MH]^+$ 414.2841 (2.1 ppm error)].

KAG/7/11

(2*R*,4a*S*,8a*R*)-*tert*-Butyl 2-((*R*)-7-ethoxy-5-hydroxy-7-oxoheptyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate ((–)-255a)



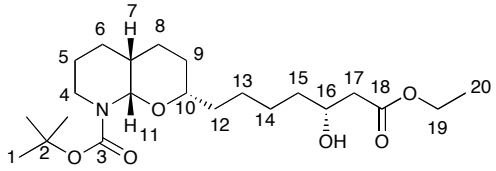
Prepared according to the procedure for **(±)-255**

Brown oil (1.08 g, 100%); R_f 0.26 (7:3 PE:EtOAc); $[\alpha]_D$ –0.1 (*c* 2.0, $CHCl_3$); IR ν_{max} (neat) 3427, 2932, 2361, 2340, 1704, 1366, 1159; δ_H (400MHz, $CDCl_3$) 5.27, 5.08 (1H, 2 x s, H-11), 4.13–3.98 (2H, m, H-19), 3.97–3.92 (1H, m, H-16), 3.77–3.70 (1H, m, H-10), 3.42–3.25 (1H, m, H-4a), 3.10–2.81 (2H, m, H-4b, OH), 2.48–2.32 (2H, m, H-17), 1.81–1.17 (29H, m, H-1, H-5, H-6, H-7, H-8, H-9, H-12, H-13, H-14, H-15, H-20); δ_C (100 MHz, $CDCl_3$) 172.9 (C-18), 155.1, 155.3 (C-3), 82.5, 81.9 (C-11), 79.6, 79.4 (C-10), 77.2 (C-2), 67.7 (C-16), 60.4 (C-19), 41.1 (CH_2) 39.7 (CH_2), 38.9 (CH_2), 36.2 (CH_2), 35.7, 35.6 (C-7), 33.7 (CH_2), 28.7 (CH_2), 28.1 (C-1) 26.0 (CH_2), 25.3 (CH_2), 24.5 (CH_2), 22.9 (CH_2), 20.8 (C-20);

m/z (ESI) 436 (100), $[M+Na]^+$ 414 (10) $[MH]^+$; [HRMS (ESI) calcd. for $C_{22}H_{40}NO_6$, 414.2856. Found: $[MH]^+$ 414.2850 (1.3 ppm error)].

KAG/8/69

(2*S*,4a*R*,8a*S*)-*tert*-Butyl 2-((*R*)-7-ethoxy-5-hydroxy-7-oxoheptyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate ((+)-255b)

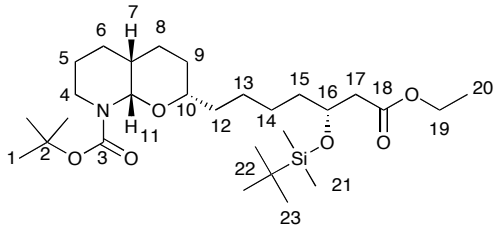


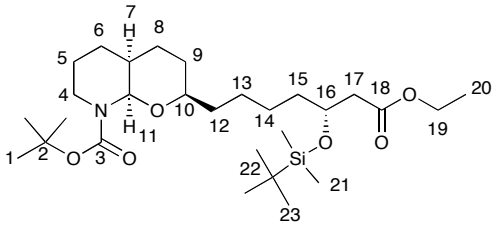
Prepared according to the procedure for **(±)-255**

Brown oil (990 mg, 100%); R_f 0.26 (7:3 PE:EtOAc); $[\alpha]_D$ +60.3 (*c* 2.0, $CHCl_3$); IR ν_{max} (neat) 3452, 2934, 2360, 2339, 1735, 17041454, 1366; δ_H (400 MHz, $CDCl_3$) 5.27, 5.08 (1H, 2 x s, H-11), 4.13–3.98 (2H, m, H-19), 3.97–3.92 (1H, m, H-16), 3.77–3.70 (1H, m, H-10), 3.42–3.25 (1H, m, H-4a), 3.10–2.81 (2H, m, H-4b, OH), 2.48–2.32 (2H, m, H-17), 1.81–1.17 (29H, m, H-1, H-5, H-6, H-7, H-8, H-9, H-12, H-13, H-14, H-15, H-20); δ_C (100 MHz, $CDCl_3$) 172.9 (C-18), 155.1, 155.3 (C-3), 82.5, 81.9 (C-11), 79.6, 79.4 (C-10), 77.2 (C-2), 67.7 (C-16), 60.4 (C-19), 41.1 (CH_2) 39.7 (CH_2), 38.9 (CH_2), 36.2 (CH_2), 35.7, 35.6 (C-7), 33.7 (CH_2), 28.7 (CH_2), 28.1 (C-1) 26.0 (CH_2), 25.3 (CH_2), 24.5 (CH_2), 22.9 (CH_2), 20.8 (C-20); *m/z* (ESI) 436 (100), $[M+Na]^+$ 414 (15) $[MH]^+$; [HRMS (ESI) calcd. for $C_{22}H_{40}NO_6$, 414.2850. Found: $[MH]^+$ 414.2857 (1.8 ppm error)].

KAG/8/72

(2*S*4a*R*,8a*S*)-*tert*-Butyl 2-((*R*)-5-(*tert*-butyldimethylsilyloxy)-7-ethoxy-7-oxoheptyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate (266a) and (2*R*,4a*S*,8a*R*)-*tert*-butyl 2-((*R*)-5-(*tert*-butyldimethylsilyloxy)-7-ethoxy-7-oxoheptyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate (266b)





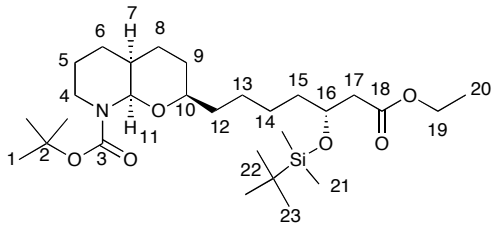
To a stirred solution of alcohol **255** (120 mg, 0.290 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C was added 2,6-lutidine (68 μL, 0.582 mmol) followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (67 μL, 0.290 mmol). The reaction was allowed to warm to rt, and stirred for 15 min before being quenched by the addition of aqueous $NaHCO_3$ (sat., 10 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL), the organic layers combined, dried over Na_2SO_4 and the volatiles removed under reduced pressure to give the crude product, which was purified by column chromatography. Eluting with 8:2 PE:EtOAc gave the *title compounds* **266a** and **266b** as a colourless film (105 mg, 69%). R_f 0.82 (8:2 PE:EtOAc); IR ν_{max} (neat) 2893, 2858, 1738, 1365, 1312, 1253, 1160, 1094, 990; δ_H (400 MHz, $CDCl_3$) 5.27, 5.08 (1H, 2 x s, H-11), 4.14–4.06 (3H, m, H-19, H-16), 3.80–3.74 (1H, m, H-10), 3.42–3.25 (1H, m, H-4a), 3.10–2.81 (1H, m, H-4b), 2.48–2.32 (2H, m, H-17), 1.81–1.17 (29H, m, H-1, H-5, H-6, H-7, H-8, H-9, H-12, H-13, H-14, H-15, H-20), 0.84 (9H, s, H-23), 0.03 (6H, d, *J* 9.0, H-21);

The ^{13}C NMR showed a ~ 1:1 mixture of rotamers for some signals.

δ_C (100 MHz, $CDCl_3$) 172.1 (C-18), 152.8, 153.1 (C-3), 82.8, 81.5 (C-11), 79.6, 79.4 (C-10), 77.7 (C-2), 69.6 (C-16), 60.4 (C-19), 42.8 (C-17), 39.9 (CH_2), 39.2 (CH_2), 37.6 (CH_2), 36.2 (CH_2), 34.1 (C-7), 29.0 (CH_2), 28.5 (C-1), 26.3 (CH_2), 25.9 (C-23), 25.2 (CH_2), 24.8 (C-22), 23.2 (CH_2), 18.1 (CH_2), 14.3 (C-20), –4.4 (C-21); *m/z* (ESI) 528 (100), $[MH]^+$ 428 (80) $[M–BocH]^+$; [HRMS (ESI) calcd. for $C_{28}H_{54}NO_6Si$, 528.3715. Found: $[MH]^+$ 528.3706 (1.7 ppm error)].

KAG/7/13 (eg)

(2*R*,4a*S*,8a*R*)-*tert*-Butyl 2-((*R*)-5-(*tert*-butyldimethylsilyloxy)-7-ethoxy-7-oxoheptyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate (266a)



Prepared according to the procedure for **266**

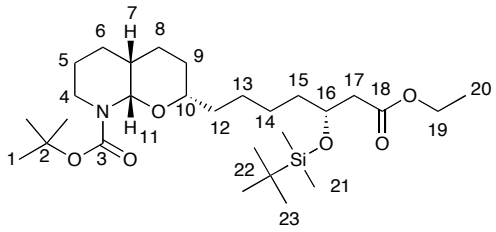
Pale yellow oil (880 mg, 83% over 2 steps from **254**); R_f 0.82 (8:2 PE:EtOAc); $[\alpha]_D$ – 21.6 (*c* 0.85, $CHCl_3$); IR ν_{max} (neat) 2930, 2857, 1736, 1704, 1463, 1410, 1365 1251, 1159, 1093, 836; δ_H (400 MHz, $CDCl_3$) 5.27, 5.08 (1H, 2 x s, H-11), 4.14–4.06 (3H, m, H-19, H-16), 3.80–3.74 (1H, m, H-10), 3.42–3.25 (1H, m, H-4a), 3.10–2.81 (1H, m, H-4b), 2.48–2.32 (2H, m, H-17), 1.81–1.17 (29H, m, H-1, H-5, H-6, H-7, H-8, H-9, H-12, H-13, H-14, H-15, H-20), 0.84 (9H, s, H-23), 0.03 (6H, d, *J* 9.0, H-21);

The ^{13}C NMR showed a ~ 1:1 mixture of rotamers for some signals.

δ_C (100 MHz, $CDCl_3$) 172.1 (C-18), 152.8, 153.1 (C-3), 82.8, 81.5 (C-11), 79.6, 79.4 (C-10), 77.7 (C-2), 69.6 (C-16), 60.4 (C-19), 42.8 (C-17), 39.9 (CH_2), 39.2 (CH_2), 37.6 (CH_2), 36.2 (CH_2), 34.1 (C-7), 29.0 (CH_2), 28.5 (C-1), 26.3 (CH_2), 25.9 (C-23), 25.2 (CH_2), 24.8 (C-22), 23.2 (CH_2), 18.1 (CH_2), 14.3 (C-20), –4.4 (C-21); *m/z* (ESI) 550 (100), $[M+Na]^+$ 528 (70) $[MH]^+$; [HRMS (ESI) calcd. for $C_{28}H_{54}NO_6Si$, 528.3715. Found: $[MH]^+$ 528.3725 (1.9 ppm error)].

KAG/8/70

(2*S*,4a*R*,8a*S*)-*tert*-Butyl 2-((*R*)-5-(*tert*-butyldimethylsilyloxy)-7-ethoxy-7-oxoheptyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate (266b)



Prepared according to the procedure for **266**

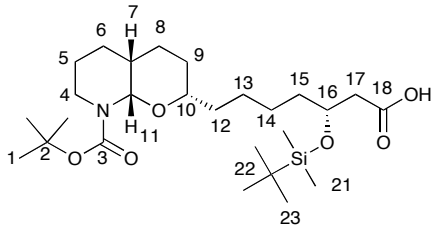
Pale yellow oil (860 mg, 74% over 2 steps from **254**); R_f 0.82 (8:2 PE:EtOAc); $[\alpha]_D$ +11.2 (*c* 1.0, $CHCl_3$); IR ν_{max} (neat) 2930, 2857, 1736, 1704, 1462, 1409, 1365, 1253, 1159, 1093; δ_H (400 MHz, $CDCl_3$) 5.27, 5.08 (1H, 2 x s, H-11), 4.14–4.06 (3H, m, H-19, H-16), 3.80–3.74 (1H, m, H-10), 3.42–3.25 (1H, m, H-4a), 3.10–2.81 (1H, m, H-4b), 2.48–2.32 (2H, m, H-17), 1.81–1.17 (29H, m, H-1, H-5, H-6, H-7, H-8, H-9, H-12, H-13, H-14, H-15, H-20), 0.84 (9H, s, H-23), 0.03 (6H, d, *J* 9.0, H-21);

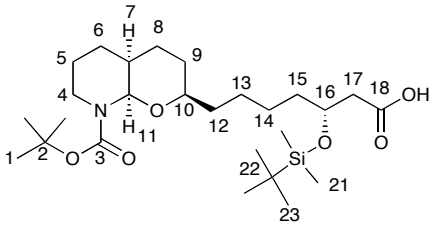
The ^{13}C NMR showed a ~ 1:1 mixture of rotamers for some signals.

δ_C (100 MHz, $CDCl_3$) 172.1 (C-18), 152.8, 153.1 (C-3), 82.8, 81.5 (C-11), 79.6, 79.4 (C-10), 77.7 (C-2), 69.6 (C-16), 60.4 (C-19), 42.8 (C-17), 39.9 (CH_2), 39.2 (CH_2), 37.6 (CH_2), 36.2 (CH_2), 34.1 (C-7), 29.0 (CH_2), 28.5 (C-1), 26.3 (CH_2), 25.9 (C-23), 25.2 (CH_2), 24.8 (C-22), 23.2 (CH_2), 18.1 (CH_2), 14.3 (C-20), –4.4 (C-21); *m/z* (ESI) 550 (100), $[M+Na]^+$ 528 (60) $[MH]^+$; HRMS (ESI) calcd. for $C_{28}H_{54}NO_6Si$, 528.3715. Found: $[MH]^+$ 528.3720 (1.0 ppm error)].

KAG/8/70

(*R*)-7-((2*S*,4a*R*,8a*S*)-8-(*tert*-Butoxycarbonyl)octahydro-2*H*-pyrano[2,3-*b*]pyridin-2-yl)-3-(*tert*-butyldimethylsilyloxy)heptanoic acid (267a) and (*R*)-7-((2*R*,4a*S*,8a*R*)-8-(*tert*-butoxycarbonyl)octahydro-2*H*-pyrano[2,3-*b*]pyridin-2-yl)-3-(*tert*-butyldimethylsilyloxy)heptanoic acid (267b)





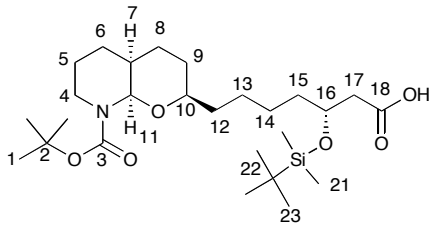
To a stirred solution of ester (105 mg, 0.199 mmol) **266** in EtOH (1 mL) was added aqueous sodium hydroxide (1 M, 0.60 mL, 0.600 mmol) and the reaction heated to 100 °C for 5 h. After cooling to rt the reaction was partitioned between water (50 mL) and EtOAc (3 x 50 mL) and the volatiles removed under reduced pressure to give the *title compounds* **267a** and **267b** as a colourless film (96 mg, 97%); R_f 0.12 (4:6 PE:EtOAc); IR ν_{max} (neat) 2931, 1707, 1390, 1366, 1254, 1160, 1093, 990; δ_H (400 MHz, $CDCl_3$) 5.31, 5.11 (1H, 2 x s, H-11), 4.14–4.04 (1H, m, H-16), 3.81–3.74 (1H, m, H-10), 3.43–3.29 (1H, m, H-4a), 3.00–2.81 (1H, m, H-4b), 2.56–2.43 (2H, m, H-17), 1.80–1.20 (26H, m, H-1, H-5, H-6, H-7, H-8, H-9, H-12, H-13, H-14, H-15), 0.87 (9H, s, H-21), 0.07 (6H, d, *J* 9.0, H-19);

The ^{13}C NMR showed a ~ 1:1 mixture of rotamers for some signals.

δ_C (100 MHz, $CDCl_3$) 176.3 (C-18), 155.2, 155.6 (C-3), 82.8, 81.6 (C-11), 80.0, 79.9 (C-10), 77.7 (C-2), 69.5 (C-16), 42.2 (C-17), 40.0 (CH_2), 39.2 (CH_2), 37.4 (CH_2), 36.0 (CH_2), 34.0 (C-7), 28.8 (CH_2), 28.4 (C-1), 26.2 (CH_2), 25.7 (C-23), 25.4 (CH_2), 25.3 (CH_2), 24.8 (C-22), 23.2 (CH_2), –4.4 (C-21); *m/z* (ESI) 500 (100), $[MH]^+$; [HRMS (ESI) calcd. for $C_{26}H_{50}NO_6Si$, 500.3402. Found: $[MH]^+$ 500.3392 (2.1 ppm error)].

KAG/7/14

(*R*)-7-((2*R*,4a*S*,8a*R*)-8-(*tert*-Butoxycarbonyl)octahydro-2*H*-pyrano[2,3-*b*]pyridin-2-yl)-3-(*tert*-butyldimethylsilyloxy)heptanoic acid (267a)



Prepared according to the procedure for **267**

Pale yellow oil (620 mg, 74%); R_f 0.12 (4:6 PE:EtOAc); $[\alpha]_D$ –15.4 (*c* 1.0, $CHCl_3$)

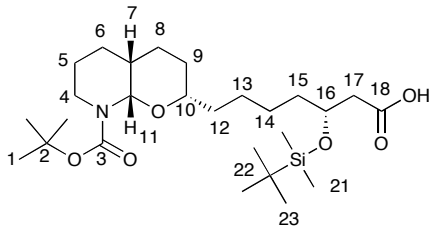
IR ν_{max} (neat) 2932, 2858, 1735, 1708, 1471, 1365, 1254, 1159, 1093; δ_H (400 MHz, $CDCl_3$) 5.31, 5.11 (1H, 2 x s, H-11), 4.14–4.04 (1H, m, H-16), 3.81–3.74 (1H, m, H-10), 3.43–3.29 (1H, m, H-4a), 3.00–2.81 (1H, m, H-4b), 2.56–2.43 (2H, m, H-17), 1.80–1.20 (26H, m, H-1, H-5, H-6, H-7, H-8, H-9, H-12, H-13, H-14, H-15), 0.87 (9H, s, H-21), 0.07 (6H, d, *J* 9.0, H-19);

The ^{13}C NMR showed a ~ 1:1 mixture of rotamers for some signals.

δ_C (100 MHz, $CDCl_3$) 176.3 (C-18), 155.2, 155.6 (C-2), 82.8, 81.6 (C-11), 80.0, 79.9 (C-10), 77.7 (C-2), 69.5 (C-16), 42.2 (C-17), 40.0 (CH_2), 39.2 (CH_2), 37.4 (CH_2), 36.0 (CH_2), 34.0 (C-7), 28.8 (CH_2), 28.4 (C-1), 25.7 (C-23), 26.2 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 24.8 (C-22), 23.2 (CH_2), –4.4 (C-21); *m/z* (ESI) 522 (100), $[M+Na]^+$ 500 (40) $[MH]^+$; HRMS (ESI) calcd. for $C_{26}H_{50}NO_6Si$, 500.3402. Found: $[MH]^+$ 500.3404 (0.5 ppm error)].

KAG/8/71

(*R*)-7-((2*S*,4a*R*,8a*S*)-8-(*tert*-Butoxycarbonyl)octahydro-2*H*-pyrano[2,3-*b*]pyridin-2-yl)-3-(*tert*-butyldimethylsilyloxy)heptanoic acid (267b)



Prepared according to the procedure for **267**

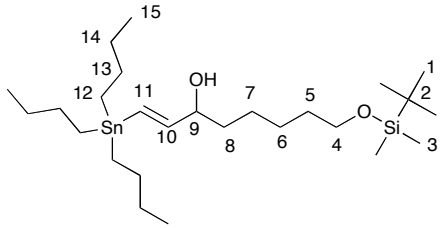
Pale yellow oil (708 mg, 88%); R_f 0.12 (4:6 PE:EtOAc); $[\alpha]_D$ +11.9 (*c* 1.7, $CHCl_3$); IR ν_{max} (neat) 2931, 2857, 1736, 1704, 1365, 1311, 1253, 1159, 1093; δ_H (400 MHz, $CDCl_3$) 5.31, 5.11 (1H, 2 x s, H-11), 4.14–4.04 (1H, m, H-16), 3.81–3.74 (1H, m, H-10), 3.43–3.29 (1H, m, H-4a), 3.00–2.81 (1H, m, H-4b), 2.56–2.43 (2H, m, H-17), 1.80–1.20 (26H, m, H-1, H-5, H-6, H-7, H-8, H-9, H-12, H-13, H-14, H-15), 0.87 (9H, s, H-21), 0.07 (6H, d, *J* 9.0, H-19);

The ^{13}C NMR showed a ~ 1:1 mixture of rotamers for some signals.

δ_C (100 MHz, $CDCl_3$) 176.3 (C-18), 155.2, 155.6 (C-2), 82.8, 81.6 (C-11), 80.0, 79.9 (C-10), 77.7 (C-2), 69.5 (C-16), 42.2 (C-17), 40.0 (CH_2), 39.2 (CH_2), 37.4 (CH_2), 36.0 (CH_2), 34.0 (C-7), 28.8 (CH_2), 28.4 (C-1), 26.2 (CH_2), 25.7 (C-23), 25.4 (CH_2), 25.3 (CH_2), 24.8 (C-22), 23.2 (CH_2), –4.4 (C-21); *m/z* (ESI) 522 (100), $[MNa]^+$ 500 (40) $[MH]^+$; [HRMS (ESI) calcd. for $C_{26}H_{50}NO_6Si$, 500.3702. Found: $[MH]^+$ 500.3414 (2.5 ppm error)].

KAG/8/74

(*E*)-8-(*tert*-Butyldimethylsilyloxy)-1-(tributylstannyl)oct-1-en-3-ol (268)

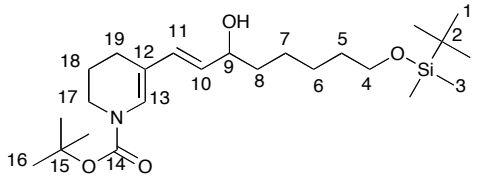


To a stirred solution of alkyne **250** (250 mg, 0.976 mmol) in toluene (10 mL) was added tributyltinhydride (392 μL, 1.46 mmol) followed by AIBN (8 mg, 0.049 mmol). The reaction was heated to 70 °C for 13 h, then cooled to rt and concentrated to a colourless oil, which was purified by column chromatography. Eluting with 9:1 PE:Et_2O gave the *title compound* **268** as a colourless oil (280 mg, 52%); R_f 0.65 (8:2 PE:Et_2O); Found: C, 56.7; H, 10.1. $C_{26}H_{56}O_2SiSn$ requires C, 57.0; H, 10.3%; IR ν_{max} (neat) 3348, 2955, 2928, 2956, 1462, 1254, 1101, 1005, 990; δ_H (400 MHz, $CDCl_3$) 6.12 (1H, dd, *J* 19.0, 1.0, H-10), 5.91 (1H, dd, *J* 19.0, 5.0, H-11), 4.09–4.02 (1H, m, H-9), 3.60 (2H, t, *J* 6.5, H-4), 1.59–1.27 (20H, m, H-5, H-6, H-7, H-8, H-13, H-14), 0.94–0.87 (24H, m, H-1, H-12, H-15) 0.02 (6H, s, H-3); δ_C (100 MHz, $CDCl_3$) 151.2 (C-10), 127.7 (C-11), 75.7 (C-9), 63.3 (C-4), 37.1 (C-8), 33.0 (C-5), 29.2 (C-13/C-14), 27.4 (C-13/C-14), 26.1 (C-1), 25.9 (C-7/C-8), 25.3 (C-7/C-8), 18.5 (C-2), 13.8 (C-15), 9.6 (C-12), –5.15 (C-3);

m/z (TOF FD+) 548.3 (100), 546.3 (75), 547.3 (47), 544.1 (40), 545.3 (34.2), 549.3 (33), 550.3 (18) 552.31 (16), 551.3 (5), 553.3 (5)

KAG/6/61

(*E*)-*tert*-Butyl 5-(8-(*tert*-butyldimethylsilyloxy)-3-hydroxyoct-1-enyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (269)



To a stirred solution of stannane **268** (710 mg, 1.29 mmol) in NMP (4 mL) was added lithium chloride (291 mg, 6.87 mmol), 2-furylphosphine (42 mg, 0.181 mmol) and Bis(dibenzylideneacetone)palladium(0) (30 mg, 0.0522 mmol). The flask was purged with argon, then triflate **213** (450 mg, 1.35 mmol) in NMP (8 mL) was added dropwise. The reaction was stirred at rt for 21 h, then partitioned between Et_2O (2 x 25 mL) and water (25 mL). The organic layers were combined, dried over Na_2SO_4 and the volatiles removed under reduced pressure to give the *title compound* **269** as a pale brown oil (517 mg, 86%) containing traces of Sn residues; R_f 0.16 (3:1 PE:Et_2O); IR ν_{max} (neat) 3451, 2930, 2857, 1705, 1644, 1472, 1390, 1318, 1254, 1159, 1104, 835; δ_H (400 MHz, $CDCl_3$) 6.97, 6.82 (1H, 2 x s, H-13), 6.16 (1H, d, *J* 15.5, H-10), 5.48–5.38 (1H, m, H-11), 4.17–4.10 (1H, m, H-9), 3.60–3.53 (5H, m, H-4, H-17, OH), 2.20–1.24 (21H, m, H-5, H-6, H-7, H-8, H-16, H-18, H-19), 0.09 (9H, s, H-1), 0.03 (6H, s, H-3); *m/z* (ESI) 422 (100), $[M\text{-}H_2O]^+$ 462 (20) $[MNa]^+$; [HRMS (ESI) calcd. for $C_{24}H_{45}NNaO_4Si$, 462.3010. Found: $[MNa]^+$ 462.3013 (0.6 ppm error)].

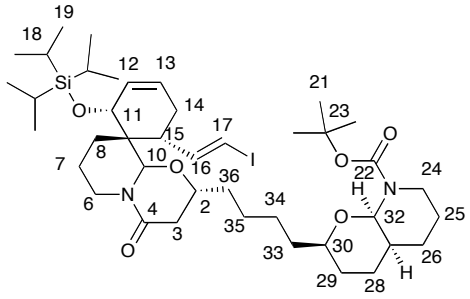
KAG/6/71

This compound eliminated water on standing, either neat or in any NMR solvents. Attempts to collect NMR data longer than ^1H experiments resulted in the observation of an unassignable mixture of the desired product and the eliminated **272**.

6.5 Coupled compounds

R DE core

(2*R*,4a*S*,8a*R*)-*tert*-Butyl 2-(4-((1*S*,2*R*,2'*R*,6*R*,9a'*R*)-6-((*E*)-2-iodovinyl)-4'-oxo-2-(tri*iso*propylsilyloxy)-3',4',6',7',8',9a'-hexahydro-2'*H*-spiro[cyclohex[3]ene-1,9'-pyrido[2,1-*b*][1,3]oxazine]-2'-yl)butyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate (346R)

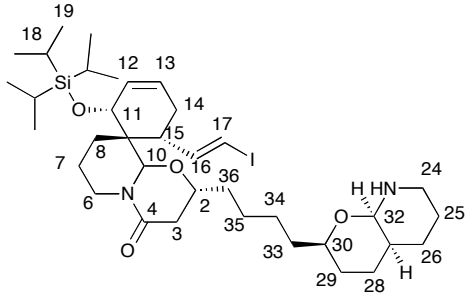


To imine **(+)-345** (145 mg, 0.306 mmol) was added carboxylic acid **267a** (184 mg, 0.367 mmol) in THF (3.2 mL). The mixture was cooled to 0 °C and DIPEA (98 uL, 0.566 mmol) added, followed by T3P 50% solution in THF (292 mg, 0.459 mmol). The reaction was allowed to warm to rt, and stirred for 20 h, before being quenched by the addition of water (5 mL). The mixture was extracted with EtOAc (3 x 10 mL), the organic layers combined, washed with brine and dried over $MgSO_4$. Removal of the volatiles under reduced pressure gave the intermediate which was dissolved in CH_2Cl_2 (3.2 mL) and $SnCl_2{\cdot}2H_2O$ (170 mg, 0.765 mmol) added. The reaction was stirred at rt for 1h, before excess K_2CO_3 was added and the solids removed by filtration. Concentration of the filtrate gave the crude compound, which was purified by flash column chromatography. Eluting with 8:2→7:3 PE:EtOAc gave the *title compound* **346R** as a pale yellow film (102 mg, 40%); R_f 0.89 (EtOAc); $[\alpha]_D$ +11.8 (*c* 0.5, $CHCl_3$); IR ν_{max} (neat) 2935, 2864, 1702, 1413, 1365, 1159, 1082, 1061, 990; δ_H (400 MHz, $CDCl_3$) 7.02 (1H, dd, *J* 14.5, 10.5, H-16), 5.97 (1H, d, *J* 10.5, H-17), 5.74 (2H, s, H-12, H-13), 5.32, 5.11 (1H, 2 x s, H-32), 5.27 (1H, s, H-10), 4.29–4.23 (2H, m, H-6a, H-11), 3.86–3.72 (2H, m, H-2, H-30), 3.47–3.30 (1H, m, H-24a), 3.00–2.85 (2H, m, H-24b, H-6b), 2.62–2.56 (2H, m, H-3a, H-15), 2.37 (1H, dd, *J* 15.5, 9.0, H-3b), 2.29–2.23 (1H, m, H-14a), 2.11–2.03 (1H, m, H-14b), 1.83–1.20 (30H, m, H-7,

H-8, H-21, H-25, H-26, H-27, H-28, H-29, H-33, H-34, H-35, H-36), 1.09–1.04 (21H, m, H-18, 19); δ_C (100 MHz, $CDCl_3$) 171.4 (C-4), 151.3, 150.9 (C-22), 148.1 (C-16), 127.2 (C-12/C-13), 127.1 (C-12/13), 82.7, 81.1 (C-32), 81.4 (C-10), 79.6 (C-30), 75.3 (C-17), 71.5 (C-2), 70.8 (C-11), 46.3 (C-15), 42.0 (C-9), 39.9 (CH_2), 39.2 (CH_2), 38.3 (CH_2), 38.2 (CH_2), 34.0 (C-27), 29.5 (C-3), 28.9 (C-23), 28.4 (C-21), 26.5-24.8 (7C, m, CH_2), 23.2 (CH_2), 20.2 (CH_2), 18.4 (C-19), 12.9 (C-18); *m/z* (ESI) 863 (100), $[MNa]^+$ 841 $[MNa]^+$; [HRMS (ESI) calcd. for $C_{41}H_{69}IN_2NaO_6Si$, 863.3862. Found: $[MNa]^+$ 863.3836 (2.9 ppm error)].

WPU 760/770

(1*S*,2*R*,2'*R*,6*R*,9a'*R*)-6-((*E*)-2-Iodovinyl)-2'-(4-((2*R*,4a*S*,8a*R*)-octahydro-2*H*-pyrano[2,3-*b*]pyridin-2-yl)butyl)-2-(tri*iso*propylsilyloxy)-6',7',8',9a'-tetrahydro-2'*H*-spiro[cyclohex[3]ene-1,9'-pyrido[2,1-*b*][1,3]oxazin]-4'(3'*H*)-one (357R)



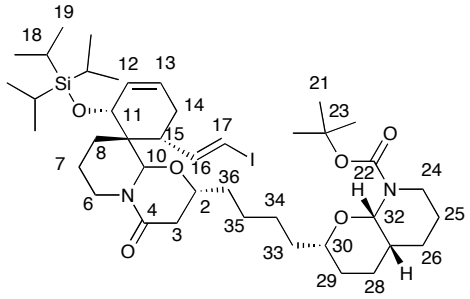
To a stirred solution of Boc-protected **346R** (102 mg, 0.121 mmol) in CH_2Cl_2 (1.7 mL) was added 2,6-lutidine (39.9 μL, 0.342 mmol) followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (52.5 μL 0.228 mmol). The reaction was stirred at rt for 20 h, then quenched by the addition of aqueous NH_4Cl (sat, 2 mL) and extracted with EtOAc (3 x 10 mL). The volatiles were removed under reduced pressure, the intermediate silyl carbamate dissolved in THF (1.70 mL), cooled to –30 °C and TBAF (0.114 mL, 0.114 mmol) added. The reaction was allowed to warm to –20 °C, then quenched by the addition of aqueous NaOH (0.5 M, 1 mL) and extracted with Et_2O. Concentration gave the crude compound, which was purified by flash column chromatography. Eluting with 94:5:1EtOAc:MeOH:Et_3N gave the *title compound* **347R** as a pale yellow oil (47 mg, 56%); R_f 0.21 (94:5:1EtOAc:MeOH:Et_3N); $[\alpha]_D$ +44.2 (*c* 1.0, CH_2Cl_2); IR ν_{max} (neat) 2934, 2863, 2360, 2340, 1681, 1081, 1062, 669; δ_H (400 MHz, C_6D_6) 7.23 (1H, dd, *J* 14.5, 10.5, H-16), 5.97 (1H, d, *J* 14.5, H-17) 5.64–5.59 (1H, m, H-12/H-13), 5.47–5.43 (1H, m, H-12/H-13), 5.37 (1H, s, H-10), 4.52–4.47 (1H, m, H-6a), 4.23–4.21 (1H, m, H-32), 4.12 (1H, br d, *J* 4.0, H-11), 3.72–3.67 (1H, m, H-2), 3.27–3.15 (2H, m, H-30, H-3a), 2.80–2.82 (1H, m, H-6a), 2.59–2.43 (4H, m, H-3b, H-15, H-24), 1.95–0.97 (45H, m, H-7, H-8, H-14, H-18, H-19, H-25, H-26, H-27, H-28, H-29, H-33, H-34, H-35, H-36, NH); δ_C (100 MHz, C_6D_6) 170.9 (C-4), 148.7 (C-16), 127.4 (C-12/C-13), 127.3 (C-12/C-13), 86.2 (C-32), 81.3 (C-10), 76.7 (C-30), 75.6 (C-17), 71.9 (C-2), 70.7 (C-11), 46.0 (C-15), 42.1 (C-9), 39.9 (C-3), 38.8 (C-24), 38.5 (C-6), 36.8 (CH_2), 35.8 (CH_2), 34.2 (C-27), 29.6 (CH_2), 29.3 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 26.3 (CH_2), 26.2 (C-8), 26.0 (C-14), 24.5 (C-25), 20.5 (C-7), 18.7 (C-19), 13.2 (C-18); *m/z* (ESI) 741 (100),

$[MH]^+$; [HRMS (ESI) calcd. for $C_{36}H_{62}IN_2O_4Si$, 741.3518. Found: $[MH]^+$ 741.3527 (1.2 ppm error)].

WPU 729/730

S DE core

(2*S*,4a*R*,8a*S*)-*tert*-butyl 2-(4-((1*S*,2*R*,2'*R*,6*R*,9a'*R*)-6-((*E*)-2-iodovinyl)-4'-oxo-2-(tri*iso*propylsilyloxy)-3',4',6',7',8',9a'-hexahydro-2'*H*-spiro[cyclohex[3]ene-1,9'-pyrido[2,1-*b*][1,3]oxazine]-2'-yl)butyl)hexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate (346S)

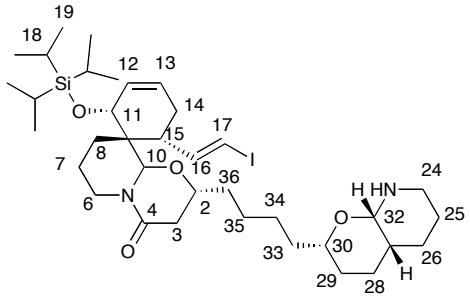


Prepared according to the procedure described for **346R**

49% over 2 steps.

$[\alpha]_D$ +34.5 (*c* 1.5, CH_2Cl_2); R_f 0.89 (EtOAc); IR ν_{max} (neat) 2936, 2965, 1698, 1414, 1365, 1159, 1082, 1062, 989;δ_H (400 MHz, $CDCl_3$) 7.02 (1H, dd, *J* 14.5, 10.5, H-16), 5.97 (1H, d, *J* 10.5, H-17), 5.74 (2H, s, H-12, H-13), 5.32, 5.11 (1H, 2 x s, H-32), 5.27 (1H, s, H-10), 4.29–4.23 (2H, m, H-6a, H-11), 3.86–3.72 (2H, m, H-2, H-30), 3.47–3.30 (1H, m, H-24a), 3.00–2.85 (2H, m, H-24b, H-6b), 2.62–2.56 (2H, m, H-3a, H-15), 2.37 (1H, dd, *J* 15.5, 9.0, H-3b), 2.29–2.23 (1H, m, H-14a), 2.11–2.03 (1H, m, H-14b), 1.83–1.20 (30H, m, H-7, H-8, H-21, H-25, H-26, H-27, H-28, H-29, H-33, H-34, H-35, H-36), 1.09–1.04 (21H, m, H-18, 19); δ_C (100 MHz, $CDCl_3$) 171.4 (C-4), 151.3, 150.9 (C-22), 148.1 (C-16), 127.2 (C-12/C-13), 127.1 (C-12/13), 82.7, 81.1 (C-32), 81.4 (C-10), 79.6 (C-30), 75.3 (C-17), 71.5 (C-2), 70.8 (C-11), 46.3 (C-15), 42.0 (C-9), 39.9 (CH_2), 39.2 (CH_2), 38.3 (CH_2), 38.2 (CH_2), 34.0 (C-27), 29.5 (C-3), 28.9 (C-23), 28.4 (C-21), 26.5-24.8 (7C, m, CH_2), 23.2 (CH_2), 20.2 (CH_2), 18.4 (C-19), 12.9 (C-18); *m/z* (ESI) 863 (100), $[MNa]^+$ 841 (25) $[MH]^+$; [HRMS (ESI) calcd. for $C_{41}H_{70}IN_2O_6Si$, 841.4042. Found: $[MH]^+$ 841.4031 (1.3 ppm error)].
WPU781, WPU 782.

(1*S*,2*R*,2'*R*,6*R*,9a'*R*)-6-((*E*)-2-iodovinyl)-2'-(4-((2*S*,4a*R*,8a*S*)-octahydro-2*H*-pyrano[2,3-*b*]pyridin-2-yl)butyl)-2-(tri*iso*propylsilyloxy)-6',7',8',9a'-tetrahydro-2'*H*-spiro[cyclohex[3]ene-1,9'-pyrido[2,1-*b*][1,3]oxazin]-4'(3'*H*)-one (347S)



Prepared according to the procedure described for **347R**

88% over 2 steps.

$[\alpha]_D$ +16.6 (*c* 1.0, CH_2Cl_2); R_f 0.21 (94:5:1EtOAc:MeOH:Et_3N); IR ν_{max} (neat) 2927, 2863, 1681, 1651, 1463, 1442, 1061, 994; δ_H (400 MHz, C_6D_6) 7.23 (1H, dd, *J* 14.5, 10.5, H-16), 5.97 (1H, d, *J* 14.5, H-17) 5.64–5.59 (1H, m, H-12/H-13), 5.47–5.43 (1H, m, H-12/H-13), 5.37 (1H, s, H-10), 4.52–4.47 (1H, m, H-6a), 4.23–4.21 (1H, m, H-32), 4.12 (1H, br d, *J* 4.0, H-11), 3.72–3.67 (1H, m, H-2), 3.27–3.15 (2H, m, H-30, H-3a), 2.80–2.82 (1H, m, H-6a), 2.59–2.43 (4H, m, H-3b, H-15, H-24), 1.95–0.97 (45H, m, H-7, H-8, H-14, H-18, H-19, H-25, H-26, H-27, H-28, H-29, H-33, H-34, H-35, H-36, NH); δ_C (100 MHz, C_6D_6) 171.1 (C-4), 148.7 (C-16), 127.4 (C-12/C-13), 127.3 (C-12/C-13), 86.2 (C-32), 81.3 (C-10), 76.2 (C-30), 75.7 (C-17), 71.9 (C-2), 70.6 (C-11), 46.0 (C-15), 42.1 (C-9), 39.9 (C-3), 38.8 (C-24), 38.5 (C-6), 36.6 (CH_2), 35.9 (CH_2), 34.3 (C-27), 29.6 (CH_2), 29.1 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.3 (CH_2), 26.2 (C-8), 25.5 (C-14), 24.5 (C-25), 20.5 (C-7), 18.7 (C-19), 13.2 (C-18); *m/z* (ESI) 679 (100), $[MH]^+$ 479 (80), 457 (70), 440 (20); [HRMS (ESI) calcd. for $C_{41}H_{67}N_4O_4Si$, 679.4865. Found: $[MH]^+$ 679.4838 (3.9 ppm error)].

WPU783, WPU787.

HPLC details.

Chiral alcohol/benzoate ester from alpine borane reduction.

HPLC details:

Sample prep: ~0.5 mg/mL in EtOH

All solvents were HPLC grade (Fisher)

Instrument: Agilent 1100 HPLC with Diode Array detector.

Column: Chiralpak IA-3 50 mm x 4.6 mm i.d. (Daicel, supplied by Chiral Technologies (Europe)

Column temperature: 20 °C

Detector wavelength: 220 nm

Injection Vol: 2 μl

Conditions: Iso-cratic; 100% iso-hexane; 1.0 mL/min.

Run-time: 20 min

Benzoate ester of Noyori prodict

Instrument: Agilent 1100 HPLC with Diode Array Detector.

Column: Chiralpak AD-3; 50mm x 4.6mm ID

Column Temp: 20 °C

Injection: 2 μl

Detector Wavelength: 220 nm (16nm bandwidth)

Mobile Phase: Isocratic; 95% Iso-Hexane (HPLC grade, Fisher); 5% Ethanol (HPLC grade, Fisher)

Run time: 30 mins (but could be cut to 5mins)

Samples prepared as ~1 mg/mL solutions in Ethanol (as above) and injected in duplicate

Appendix 1 – *Synthesis*, 2008, 3846.

Preparation of Novel Polycyclic Heterocycles Using a Tin(II) Chloride Dihydrate-Mediated Deacetalisation–Bicyclisation Sequence

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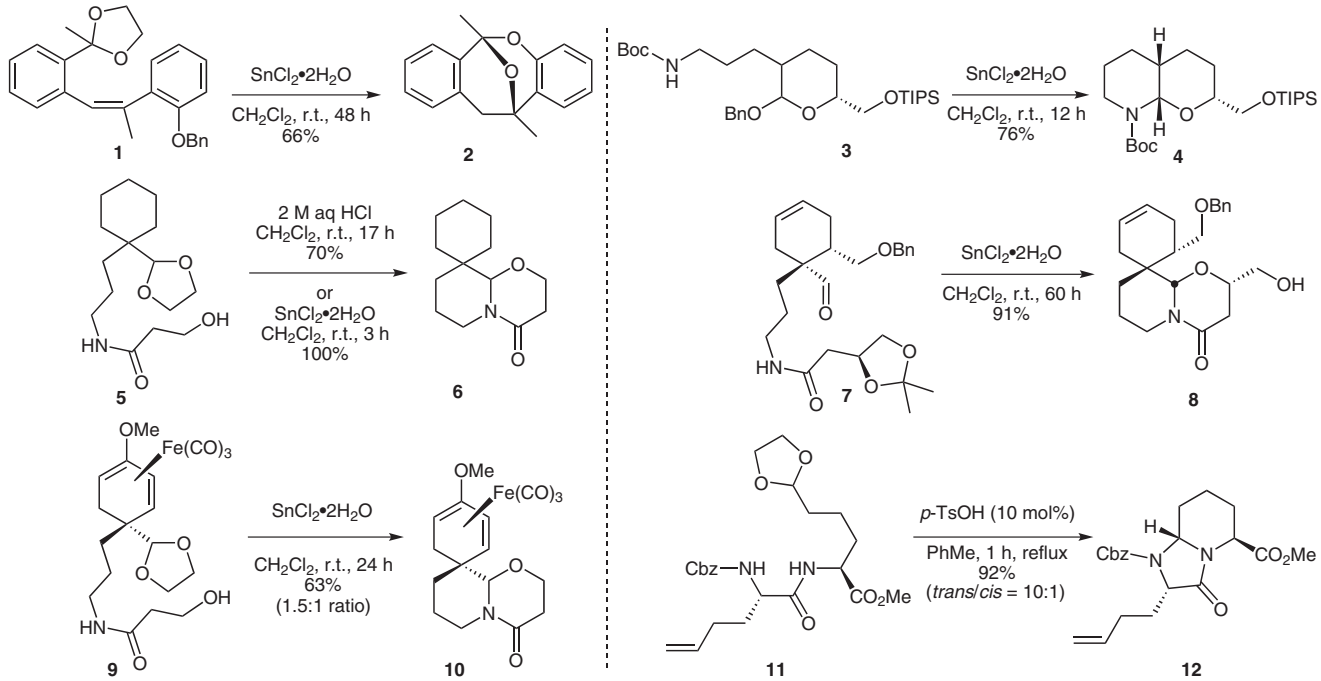
Received 12 August 2008

Abstract: Tin(II) chloride dihydrate-mediated deacetalisation–bicyclisation procedures for the construction of novel polycyclic heterocycles from amides possessing a pendant acetal group are reported. Optimisation and scoping studies are described; using this methodology, a range of known, and novel, ring-fused heterocyclic systems have been prepared, some in enantiomerically pure form.

Key words: heterocycles, tin(II) chloride dihydrate, deacetalisation, bicyclisation, tandem processes

The formation of novel polycyclic heterocycles is of great interest to the synthetic organic chemist. This interest is not purely of an academic nature but also based on the fact that polycyclic heterocycles are considered to be 'privileged structures' in the pharmaceutical and agrochemical industries.[1] Thus, new methods for the construction of such compounds with low molecular weights are invaluable in the search for bioactive lead compounds. In this paper we report the preparation of a range of polycyclic heterocyclic systems using a tin(II) chloride dihydrate ($SnCl_2{\cdot}2H_2O$) mediated deprotection–bicyclisation sequence in the key step. Tin(II) chloride is widely used as a reducing agent and as a Lewis acid catalyst[2] and, as its dihydrate, has been employed as a mild reagent for the deprotection of acetals.[3]

This research was inspired by recent natural product studies in our group which featured the use of $SnCl_2{\cdot}2H_2O$-mediated deprotection–cyclisation processes. As illustrated in Scheme 1, treatment of acetal **1** with $SnCl_2{\cdot}2H_2O$ gave the racemic [6,6,6,6]-tetracyclic core **2** of the HIV-1 integrase inhibitors integrastatins A and B via a presumed sequence of acetal deprotection, debenzylation, hemi-acetal formation, and alkene etherification.[4] More recently, in an effort directed towards the total synthesis of the macro-



Scheme 1

SYNTHESIS 2008, No. 23, pp 3846–3856
Advanced online publication: 30.10.2008
DOI: 10.1055/s-0028-1083214; Art ID: P08508SS

cyclic marine alkaloid 'upenamide,[5] it was found that $SnCl_2{\cdot}2H_2O$ can be employed in the key step for the construction of the core systems **4**,[6] **6**[7] and **8**[8] from the respective precursors **3**, **5** and **7**. The $SnCl_2{\cdot}2H_2O$ deacetalisation–bicyclisation procedure was subsequently employed by Han and Ong to prepare the iron tricarbonyl–cyclohexadiene analogue **10**,[9] thus establishing still further its mild nature and synthetic utility. It should be noted that a number of acid-catalysed deprotection–bicyclisation procedures have been reported leading to related O/N-bicyclic acetals[10] as well as to N/N-bicyclic systems.[11,12] For example (Scheme 1), in 2006, Blaauw and co-workers converted acetal **11** into bicycle **12**, which was subsequently transformed into the natural product (–)-dysibetaine PP.[11]

The generality and simplicity of the $SnCl_2{\cdot}2H_2O$ cyclisation procedures, coupled with the novelty of the heterocycles produced, encouraged us to investigate further applications of this methodology. Preliminary results were published in a recent communication.[13] We have since carried out additional optimisation and scoping studies and now present a more detailed discussion of this one-pot, tandem deprotection–bicyclisation procedure.

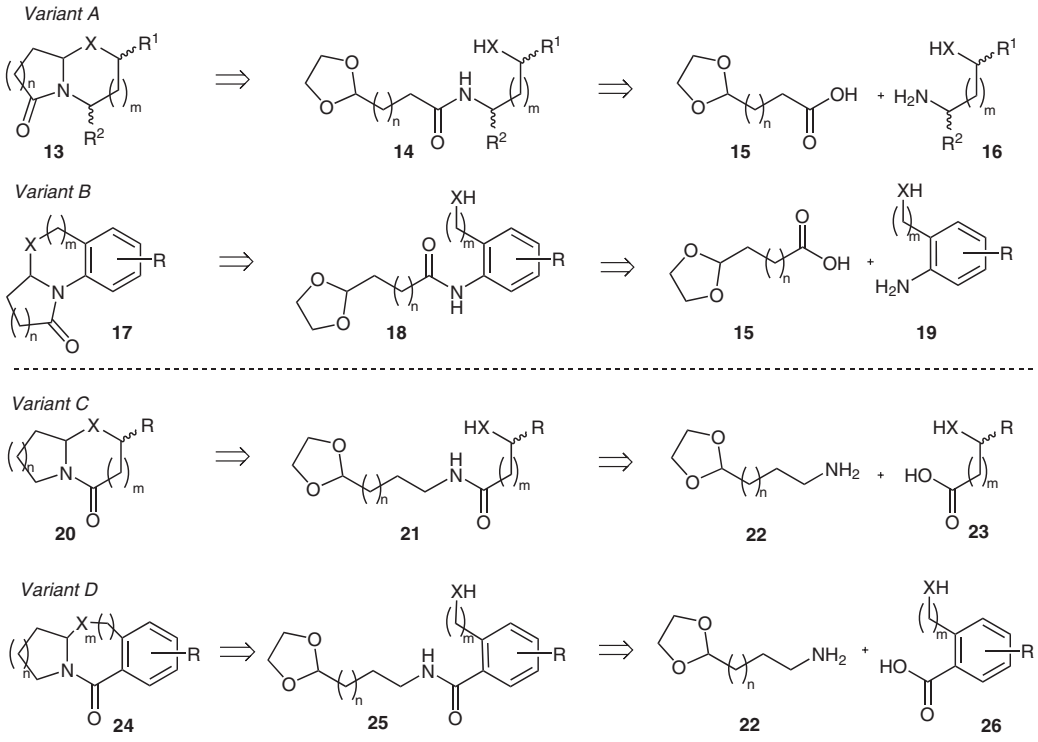
Four variants of the tandem deprotection–bicyclisation procedure were investigated and these are outlined in retrosynthetic form in Scheme 2. It was envisaged that the most useful, general coupling partners would be the dioxolane-acids **15** and the dioxolane-amines **22**. Thus, variants A and B would both utilise dioxolane-acids **15** as the coupling partner. In Variant A, bicycles **13** would be prepared from amides **14** which would in turn be prepared by coupling dioxolane-acids **15** with ω-functionalised aliphatic amines **16**. In Variant B, the benzannelated analogues, tricycles **17**, would be prepared via amides **18** from dioxolane-acids **15** with ω-functionalised aryl amines **19**.

Similarly, in Variant C, bicycles **20** would be prepared from amides **21**, which would in turn be obtained by coupling dioxolane-amines **22** with ω-functionalised aliphatic acids **23**. Variant D would then involve the preparation of the benzannelated analogues, tricycles **24**, from amides **25** derived from dioxolane-amines **22** and ω-functionalised aryl acids **26**.

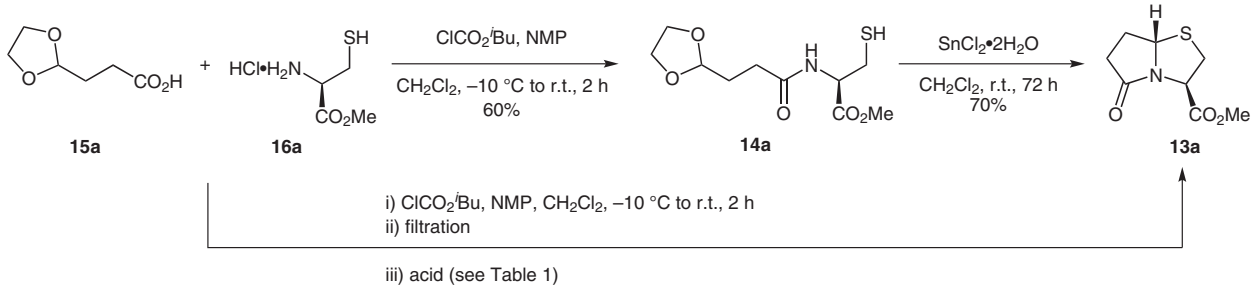
(i) Heterocycles via Variant A

Having identified four variants for the construction of novel polycyclic heterocycles by tandem deprotection–bicyclisation procedures, we initially decided to evaluate the feasibility of Variant A starting from L-cysteine methyl ester hydrochloride (**16a**; Scheme 3). Thus, coupling of the readily available dioxolane-acid **15a**[14] with amine **16a** using the mixed anhydride method gave the required amide **14a** in 60% purified yield. We were delighted to observe that treatment of amide **14a** with $SnCl_2{\cdot}2H_2O$ in dichloromethane for 72 hours gave methyl 5-oxohexahydropyrrolo[2,1-*b*]thiazole-3-carboxylate (**13a**)[15] in 70% yield. This one-pot tandem deprotection–bicyclisation process produced **13a** as a single diastereoisomer {$[\alpha]_D^{23}$ –250.7 (*c* 1.25, $CHCl_3$)}, which was tentatively assigned the (presumed thermodynamically preferred) 3*R*,7a*S*-configuration shown, on the basis of NMR studies.

Attempts to combine the two-step amide-formation–deprotection–bicyclisation sequence into a single one-pot



Scheme 2



Scheme 3

process failed. However, it was found that minimal purification (filtration through silica gel and removal of the volatiles in vacuo) of the intermediate amide **14a** prior to treatment with $SnCl_2·2H_2O$ in dichloromethane was sufficient to provide the bicycle **13a** in 68% isolated yield (as compared to the 42% overall yield for the two-step process involving purification of intermediate **14a**).

At this stage we screened a range of mineral, organic and Lewis acids in the deprotection–bicyclisation process (Table 1). In view of related cyclisation sequences, dilute hydrochloric acid[10] and *p*-TsOH·H_2O[11] were studied first (entries 1 and 2) but mixtures of products were obtained and the yields of compound **13a** were disappointing. The widely used Lewis acid, $BF_3·Et_2O$, gave a similarly low yield (entry 3), as did $SnBr_2$ and $SnCl_4$ (entries 4 and 5). Anhydrous $SnCl_2$ gave an improved yield (57%, entry 6) but the original procedure using $SnCl_2·2H_2O$ proved to be the best (68% over two steps from **15a**, entry 7). A likely rationale is that $SnCl_2·2H_2O$ slowly releases dilute hydrochloric acid to aid acetal cleavage in addition to the Lewis acidic Sn(II) to aid the bicyclisation process; this theory is supported by the fact that addition of potassium carbonate to the $SnCl_2·2H_2O$ reaction resulted in a dramatic loss of activity. However, it is noteworthy that $CuCl_2·2H_2O$, a reagent which efficiently hydrolyses acetals when used in ethanol,[16] proved to be totally ineffective in dichloromethane (entry 8).

It should be noted that the ability of tin(II) chloride to act as a reductant can also be exploited. Thus, processing of the disulfide, L-cysteine dimethyl ester dihydrochloride **27**, through the same coupling and $SnCl_2·2H_2O$ conditions via amide **28** gave the same heterocycle **13a** in 59% overall yield (Scheme 4). In the second step, the $SnCl_2·2H_2O$ is mediating the three-step disulfide reduction–deprotection–bicyclisation sequence.

Next, three further examples were explored in order to indicate the generality of the procedure (Scheme 5). Thus,

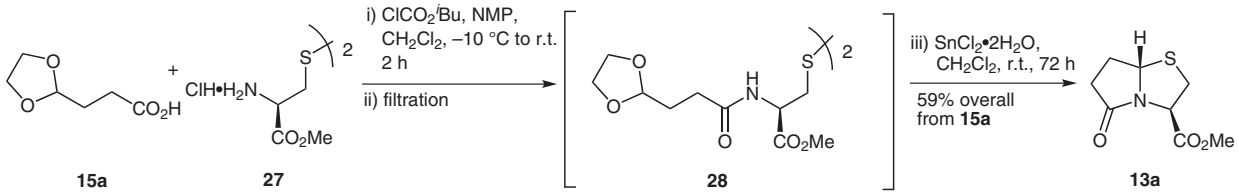
Table 1 Yields of **13a** from **15a** Using the Deprotection–Bicyclisation Process

Entry	Reagent	Solvent	Temp	Time (h)	Yield (%)
1	10% aq HCl	CH_2Cl_2	r.t.	72	39
2	*p*-TsOH·H_2O (cat)	PhMe	reflux	2	29
3	$BF_3·Et_2O$ (2 equiv)	CH_2Cl_2	r.t.	24	26
4	$SnBr_2$ (2 equiv)	CH_2Cl_2	r.t.	72	35
5	$SnCl_4$ (2 equiv)	CH_2Cl_2	r.t.	72	5
6	$SnCl_2$ (2 equiv)	CH_2Cl_2	r.t.	72	57
7	$SnCl_2·2H_2O$ (2 equiv)	CH_2Cl_2	r.t.	72	68
8	$CuCl_2·2H_2O$ (2 equiv)	CH_2Cl_2	r.t.	24	0

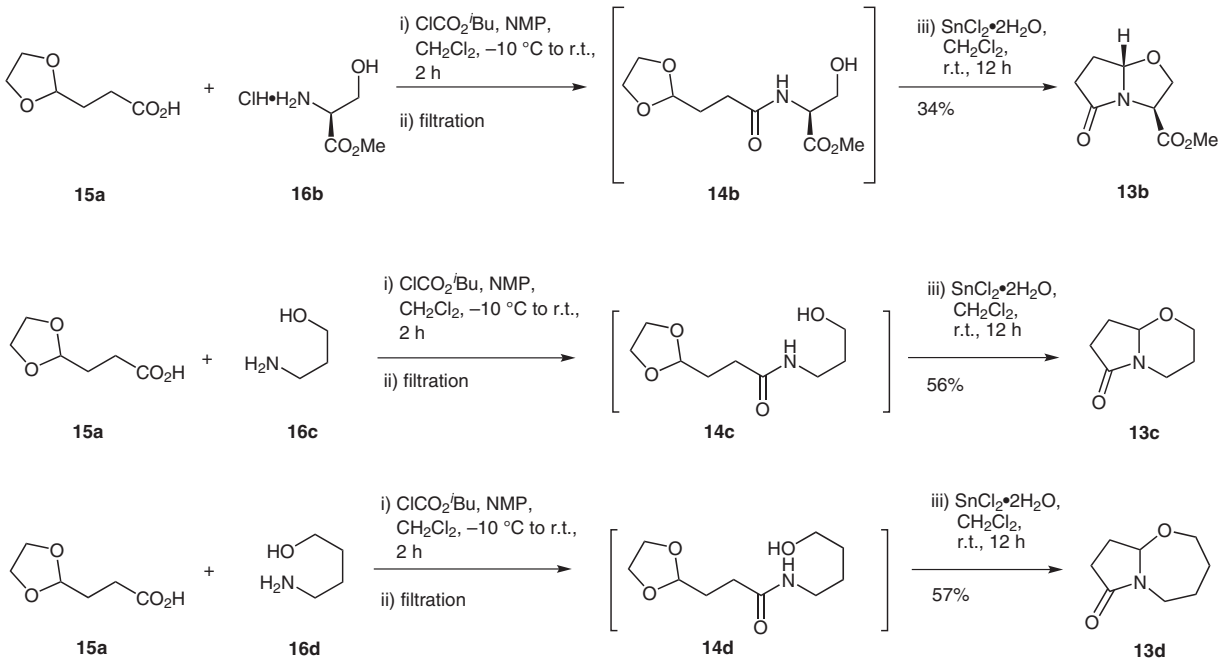
amide formation between acid **15a** and L-serine derivative **16b** followed by treatment with $SnCl_2·2H_2O$ induced the desired deacetalisation–bicyclisation reaction to give the novel heterocycle **13b** {$[\alpha]_D^{23}$ –124.3 (*c* 1.0, $CHCl_3$)} in moderate yield over the two-step process. In a similar manner, amide formation between acid **15a** and 3-aminopropanol (**16c**) followed by deacetalisation–bicyclisation gave the known heterocyclic system **13c**[17] {hemi-aminal proton: δ_H = 4.94 ppm, 1 H, dd, *J* = 6.5, 2.8 Hz; IR 1690 cm^{-1}; Lit.[17] δ_H = 4.94 ppm, 1 H, m; IR 1690 cm^{-1}}. The novel, higher homologue **13d** was then prepared from 4-aminobutanol (**16d**) in reasonable yield over the two steps.

(ii) Heterocycles via Variant B

Our attention next turned to the second combination of coupling partners outlined in Scheme 2, in which the same dioxolane-acid **15a** is coupled with ω-functionalised aryl amines **19** to generate benzannelated tricycles **17**, via amides **18**. The initial example explored was unsuccess-



Scheme 4



Scheme 5

ful: conversion of 2-aminophenol (**19a**) into amide **18a** was straightforward, but all attempts to effect the cyclisation to give **17a** failed (Scheme 6). On the assumption that this failure was due to the low nucleophilicity of the phenolic group and/or to ring strain in the product, ω-functionalised anilines **19b–d** were studied. In the case of the corresponding thiophenol **19b**, coupling again proceeded smoothly but in this example, treatment with $SnCl_2 \cdot 2H_2O$ promoted the desired deacetalisation–bicyclisation reaction to give the novel heterocycle **17b** accompanied by the cyclisation precursor **29**.

Encouraged by this partial success, we investigated the use of 2-aminobenzyl alcohol **19c** and the corresponding thiol **19d** (Scheme 6). In both cases, the coupling and deacetalisation–bicyclisation proceeded smoothly, giving the novel benzannelated heterocycles **17c** and **17d** in 80 and 86% overall yields, respectively. Finally, in a slight variation, the *N*-methylated diamine **30** was subjected to the coupling–deacetalisation–bicyclisation sequence to produce the linear tricyclic adduct **32** in 43% overall yield, further illustrating the potential of this methodology.

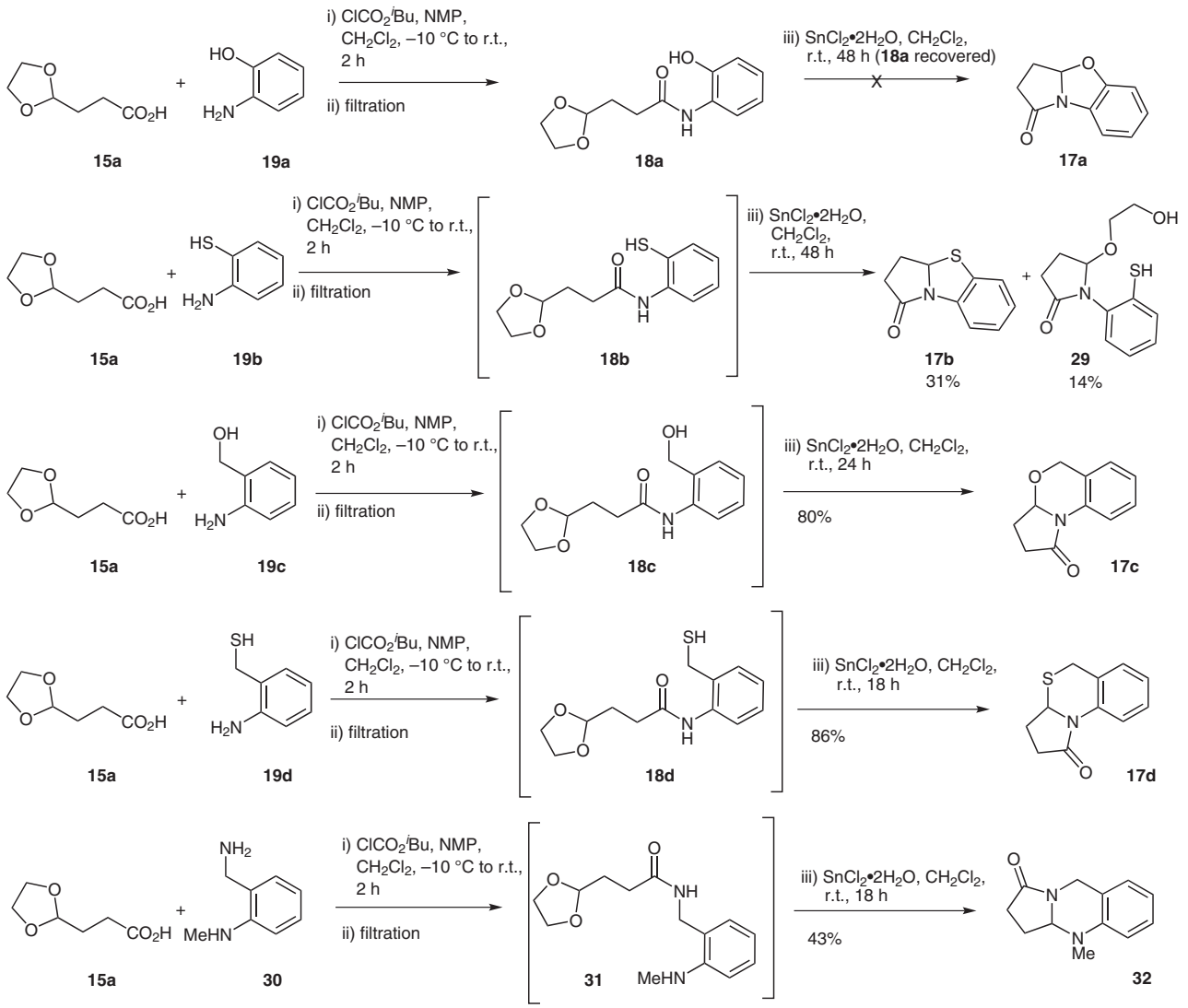
(iii) Heterocycles Via Variant C

Having established the viability of procedures utilising dioxolane-acid **15a** for heterocycle formation, we moved on to explore the potential of dioxolane-amines **22**, initially looking at their coupling with ω-functionalised aliphatic acids **23** (Scheme 7). In the initial example, amine **22a**[18] was coupled to (*R*)-mandelic acid **23a**; it was established that 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)-mediated peptide coupling was preferable to the mixed anhydride method for the formation of amide **21a**. The $SnCl_2 \cdot 2H_2O$-mediated deacetalisation–bicyclisation proceeded cleanly, if in modest yield, to give the novel bicyclo[3.3.0]octane heterocyclic products **20a** as a separable mixture of two diastereoisomers. In a similar manner, *N*-Boc-L-alanine (**23b**) was converted into an inseparable mixture of novel diazabicyclo[3.3.0]octanes **20b** (ratio established by NMR spectroscopy).[19] In both **20a** and **20b**, the major diastereoisomer was tentatively assigned by inspection of molecular models (NMR and NOE studies were uninformative). Finally in this section, amine **22a** and *N*-Boc-L-serine **23c** gave the bicyclo[4.3.0]nonane adduct **20c** as a single diastereoisomer in 46% yield {$[\alpha]_D^{22}$ +32.5 (*c* 0.95, $CHCl_3$)}.

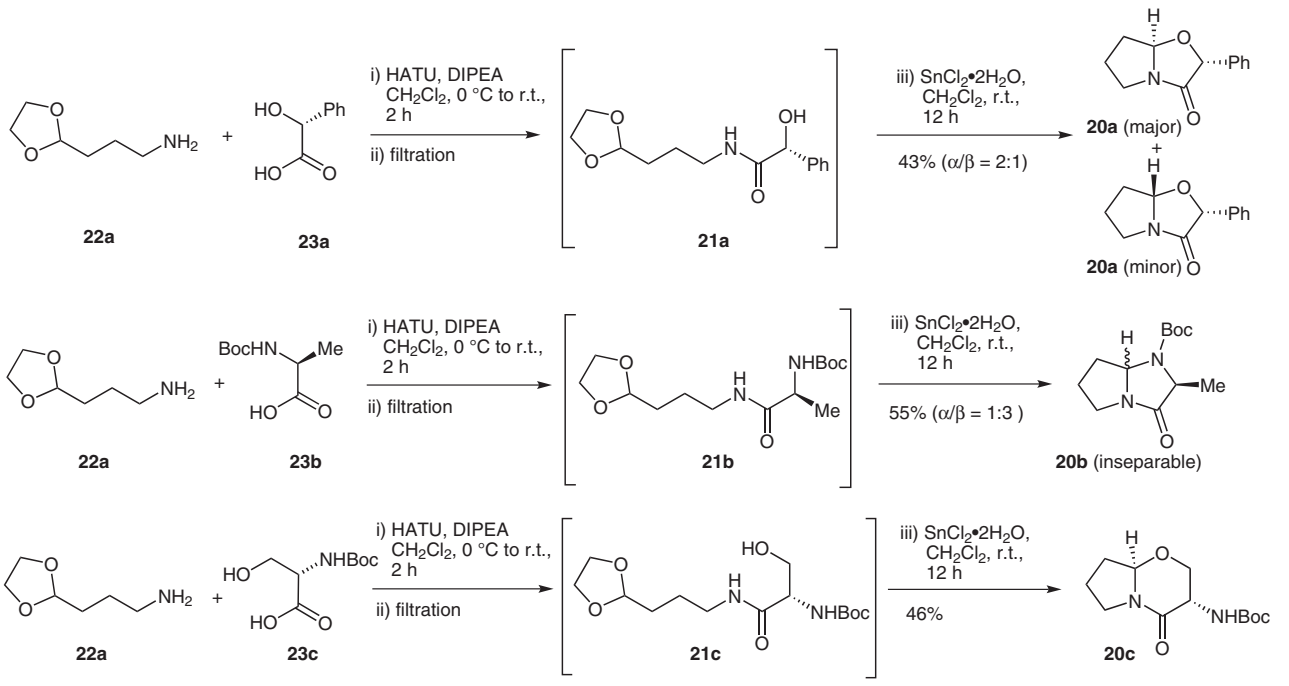
(iv) Heterocycles via Variant D

The final variant to be explored utilised dioxolane-amine **22a** and ω-functionalised aryl acids **26** (m = 0) to produce benzannelated products **24** (Scheme 8). Once again, the coupling procedure to produce the intermediate amides **25** proved problematic. Using 2-hydroxy-3-methylbenzoic acid (**26a**) to ultimately produce heterocycle **24a**, the mixed anhydride procedure ($ClCO_2{}^tBu$) gave no product and HATU gave the required product **24a** in only 45% yield. Turning to other activated acid derivatives, the acid chloride and methyl ester derived from **26a** gave only trace amounts of product **24a** after attempted coupling and treatment with $SnCl_2 \cdot 2H_2O$. However, we were delighted to find that the phenyl ester derivative **33** underwent efficient coupling to amine **22a** under microwave irradiation (MW) and deacetalisation–bicyclisation using $SnCl_2 \cdot 2H_2O$ gave the expected product **24a** in almost quantitative yield.

Attempts to develop a tandem process were unsuccessful; heating the mixture of **22a**, **33** and $SnCl_2 \cdot 2H_2O$ under microwave conditions resulted in complete degradation of the starting materials. However, a telescoped procedure

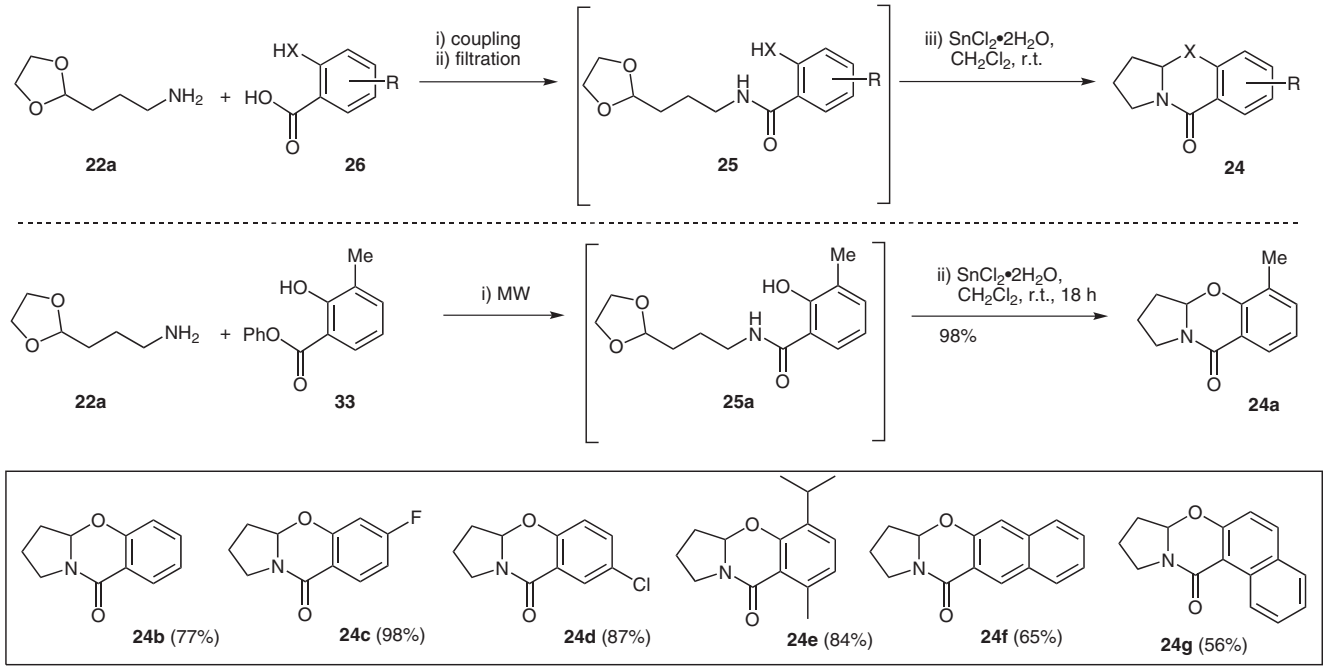


Scheme 6



Scheme 7

Synthesis 2008, No. 23, 3846–3856 © Thieme Stuttgart · New York



Scheme 8

was developed that proved to be extremely straightforward; after heating the amine and ester together neat in a microwave system, the resulting amide was then dissolved directly in dichloromethane and $SnCl_2 \cdot 2H_2O$ was added in a single portion. After stirring at room temperature, the desired heterocycles could then be isolated by flash chromatography. These conditions were then applied to a range of phenyl esters,[20] producing novel polycyclic heterocycles **24b–g** (Scheme 8). These heterocycles all show characteristic ^1H and ^{13}C NMR signals (hemi-aminal protons between δ = 5.33 and 5.65 ppm; hemi-aminal carbons at δ = 87.7–89.0 ppm; e.g. **24a**, δ_H = 5.46 ppm; δ_C = 88.4 ppm).

In summary, we have developed a mild, cheap and simple method of producing a diverse range of polycyclic heterocycles from commercially available or easily accessible starting materials using amide coupling followed by a tin(II) chloride mediated deacetalisation–bicyclisation sequence. The products, several of which have been obtained in diastereoselective processes, should be of interest both in their own right and as building blocks for the production of more complex target molecules. We are currently investigating the application of this methodology to complex natural product targets.

Et_2O was dried using an MBraun MPS solvent purification system. Anhydrous THF was obtained by distillation over sodium benzophenone. Petroleum ether (PE) refers to light petroleum ether, bp 40–60 °C. All reagents were used as supplied by the manufacturers, unless otherwise stated. $SnCl_2 \cdot 2H_2O$ was purchased from Aldrich and used without further purification. 3-[1,3]-Dioxolan-2-ylpropionic acid (**15a**) was prepared by the method of Shea and co-workers;[14] all data were in accordance with the assigned structure, and ^1H NMR data was in accordance with the literature.[14] 3-[1,3]-Dioxolan-2-ylpropylamine (**22a**) was prepared by the method of Shimizu and co-workers;[18] all data were in accordance with the assigned structure, and ^1H NMR data was in accordance with the literature.[18]

Flash column chromatography was performed using Fluka silica gel 60 at a low positive pressure. Analytical TLC was performed on aluminium sheets precoated with Merck silica gel 60 F_{254}, and visualised with ultraviolet light (254 nm), aq $KMnO_4$ or alcoholic vanillin solutions, as appropriate. Preparative TLC was performed on Whatman Partasil K6F precoated 60 Silica Gel Glass plates, and visualised under UV light (254 nm). SCX refers to prepacked Varian BondElut SCX columns (1 g). All melting points were taken on a Gallenkamp apparatus. ^1H NMR spectra were recorded at 400 MHz on a JEOL ECX 400 spectrometer or at 270 MHz on a JEOL ECX 270 spectrometer and are reported as follows: chemical shift (δ, ppm), multiplicity, coupling constant *J* (to the nearest 0.5 Hz), number of protons, assignment. Residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) or DMSO (δ_H = 2.50 ppm) was used as an internal reference. ^{13}C NMR spectra were recorded at 100 MHz on a JEOL ECX 400 spectrometer or at 125 MHz on a Bruker AV500 spectrometer. The central peak of $CDCl_3$ (δ_C = 77.0 ppm) or DMSO (δ_C = 39.4 ppm) was used as an internal reference. ^{19}F NMR spectra were recorded at 376 MHz on a JEOL ECX 400 spectrometer. Chemical shifts are reported in parts per million (ppm) to the nearest 0.01 ppm for ^1H and the nearest 0.1 ppm for ^{13}C and ^{19}F. Infrared spectra were carried out on a ThermoNicolet IR100 spectrometer and are recorded as a liquid film or a Nujol® mull between NaCl disks. Absorption maxima are reported in wavenumbers (cm^{-1}) and only selected absorbencies are reported. Mass spectra and accurate mass measurements were recorded on a Micromass Autospec spectrometer.

Microwave irradiation refers to the use of a CEM 'Discovery' reactor, with reactions contained in 10 mL CEM tubes with Intellivent® caps.

Methyl 2-(3-[1,3]Dioxolan-2-ylpropionylamino)-3-mercaptopropanoate (14a)

Isobutyl chloroformate (44 μL, 0.34 mmol) was added dropwise to a solution of acid **15a**[14] (50 mg, 0.34 mmol) and *N*-methylpiperidine (41 μL, 0.34 mmol) in CH_2Cl_2 (4 mL) at –10 °C (acetone–ice bath). After exactly 2 min, an ice-cold solution of L-cysteine methyl ester

hydrochloride (**16a**; 62 mg, 0.36 mmol) and *N*-methylpiperidine (44 μL, 0.36 mmol) in CH_2Cl_2 (1 mL) was added dropwise and stirring was continued at –10 °C for 1 h and then the reaction mixture was slowly allowed to warm to r.t. and stirred for a further 1 h. The solution was then filtered through a short pad of silica gel, washing through with EtOAc (3 × 5 mL) and the volatiles removed from the filtrate in vacuo to give the crude amide **14a**, which was used immediately in the subsequent cyclisation reaction without further purification. If so desired, the crude amide **14a** could be purified by flash column chromatography (SiO_2, EtOAc), to give the title compound **14a**.

Yield: 54 mg (60%); clear colourless oil; $[\alpha]_D^{23}$ +41.9 (*c* 1.00, $CHCl_3$); R_f = 0.40 (EtOAc).

IR (neat): 3300 (br), 2955, 2886, 1740, 1659, 1531, 1439, 1242, 1215, 1140, 1042 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (t, *J* = 9.0 Hz, 1 H, SH), 1.98–2.03 (m, 2 H, CH_2), 2.37 (t, *J* = 7.5 Hz, 2 H, CH_2C=O), 2.96 (dd, *J* = 9.0, 4.0 Hz, 2 H, C*H*$_2$SH), 3.76 (s, 3 H, CO_2CH_3), 3.82–3.87 (m, 2 H, OCH_2), 3.92–3.99 (m, 2 H, OCH_2), 4.86 (dt, *J* = 7.5, 4.0 Hz, 1 H, C*H*CO_2CH_3), 4.92 [t, *J* = 4.0 Hz, 1 H, C*H*$(OCH_2)_2$], 6.71 (br d, *J* = 7.5 Hz, 1 H, NHCO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.7, 28.9, 30.1, 52.7, 53.5, 64.9, 103.1, 170.6, 172.2.

MS (ESI): *m*/*z* (%) = 286 (20) $[M + Na]^+$, 264 (100) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{18}NO_5S$: 264.0900; found: 264.0907 (3.3 ppm error).

Methyl (3*R*,8*S*)-5-Oxohexahydropyrrolo[2,1-*b*]thiazole-3-carboxylate (13a)

*Method A: From Purified **14a***

Amide **14a** (100 mg, 0.38 mmol) was dissolved in CH_2Cl_2 (5 mL) and $SnCl_2{\cdot}2H_2O$ (0.17 g, 0.76 mmol) added. The reaction mixture was stirred for 72 h at r.t. then diluted with $CHCl_3$ (5 mL) and treated with K_2CO_3 (0.25 g, 1.8 mmol). Stirring was continued for a further 30 min then the mixture was filtered through a short pad of Celite®, washing through with $CHCl_3$ (3 × 10 mL). The filtrate was concentrated in vacuo and the crude product was purified by flash column chromatography (SiO_2, PE–EtOAc, 1:1), to give the title compound **13a**.

Yield: 53 mg (70%); clear colourless oil; $[\alpha]_D^{23}$ –250.7 (*c* 1.25, $CHCl_3$); R_f = 0.33 (PE–EtOAc, 1:1).

IR (neat): 2954, 1743, 1709, 1437, 1388, 1285, 1218, 1177 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.09–2.19 (m, 1 H, CH*H*), 2.48–2.59 (m, 2 H, CH*H*C=O, C*H*H), 2.60–2.73 (m, 1 H, C*H*HC=O), 3.33 (dd, *J* = 11.5, 4.5 Hz, 1 H CH*H*S), 3.38 (dd, *J* = 11.5, 7.5 Hz, 1 H, C*H*HS), 3.73 (s, 3 H, CO_2CH_3), 5.08 (dd, *J* = 7.5, 4.5 Hz, 1 H, C*H*CO_2CH_3), 5.19 (dd, *J* = 7.0, 4.0 Hz, 1 H, NCHS).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 31.0, 36.1, 52.7, 57.6, 66.3, 170.2, 176.3.

MS (ESI): *m*/*z* (%) = 202 (100) $[M + H]^+$, 142 (10) $[M – CO_2Me]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{12}NO_3S$: 202.0532; found: 202.0539 (3.3 ppm error).

Method B: Telescoped Procedure

Unpurified amide **14a** (see above) was redissolved in CH_2Cl_2 (5 mL). $SnCl_2{\cdot}2H_2O$ (0.17 g, 0.75 mmol) was added to this solution and the reaction mixture was stirred at r.t. for 72 h, whereupon it was diluted with $CHCl_3$ (5 mL) and then treated with K_2CO_3 (0.25 g, 1.8 mmol). Stirring was continued for a further 30 min then the mixture was filtered through a short pad of Celite®, washing through with $CHCl_3$ (3 × 10 mL). The filtrate was concentrated in vacuo and the crude product was purified by flash column chromatography (SiO_2, PE–EtOAc, 1:1), to give the title compound **13a**.

Yield: 46 mg (68% over two steps from **15a**); clear colourless oil.

*Method C: From Disulfide **27***

L-Cysteine dimethyl ester dihydrochloride (**27**; 128 mg, 0.37 mmol) and 3-[1,3]dioxolan-2-ylpropionic acid (**15a**; 100 mg, 0.68 mmol) were converted into amide **28** according to the procedure used for amide **14a** (see above). The unpurified amide **28** was then treated with $SnCl_2{\cdot}2H_2O$ (306 mg, 1.36 mmol) for 72 h following the procedure used in methods A and B above. The crude product was purified by flash column chromatography (SiO_2, Et_2O), to give the title compound **13a**.

Yield: 82 mg (59% over two steps); clear colourless oil.

Methyl (3*S*,8*S*)-5-Oxohexahydropyrrolo[2,1-b]oxazole-3-carboxylate (13b)

Prepared from L-serine methyl ester hydrochloride (**16b**; 56 mg, 0.36 mmol) and 3-[1,3]dioxolan-2-ylpropionic acid (**15a**; 50 mg, 0.34 mmol) according to the procedures described for the preparation of compound **13a**. The unpurified amide was stirred with $SnCl_2{\cdot}2H_2O$ (153 mg, 0.68 mmol) for 12 h and the crude product was purified by flash column chromatography (SiO_2, Et_2O), to yield the title compound **13b**.

Yield: 21 mg (34% over two steps); clear colourless oil; $[\alpha]_D^{23}$ –124.3 (*c* 1.0, $CHCl_3$); R_f = 0.24 (Et_2O).

IR (neat): 2956, 2921, 1719, 1403, 1279, 1212, 1173, 1007 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.06–2.17 (m, 1 H, CH*H*), 2.38–2.56 (m, 2 H, CH*H*C=O, C*H*H), 2.65–2.75 (m, 1 H, C*H*HC=O), 3.78 (s, 3 H, CO_2CH_3), 3.91 (dd, *J* = 8.5, 6.5 Hz, 1 H, CH*H*O), 4.36 (t, *J* = 8.5 Hz, 1 H, C*H*HO), 4.68 (dd, *J* = 8.5, 6.5 Hz, 1 H, C*H*CO_2CH_3), 5.20 (dd, *J* = 6.0, 2.0 Hz, 1 H, NCHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.8, 30.9, 52.7, 56.0, 69.5, 93.0, 170.6, 179.5.

MS (ESI): *m*/*z* (%) = 186 (100) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{12}NO_4$: 186.0761; found: 186.0761 (0.1 ppm error).

Tetrahydropyrrolo[2,1-*b*][1,3]oxazin-6-one (13c)

Prepared from 3-amino-1-propanol (**16c**; 55 μL, 0.71 mmol) and 3-[1,3]dioxolan-2-ylpropionic acid (**15a**; 100 mg, 0.68 mmol) according to the procedures described for the preparation of compound **13a**. The unpurified amide was stirred with $SnCl_2{\cdot}2H_2O$ (306 mg, 1.36 mmol) for 12 h, then the crude product was purified by flash column chromatography (SiO_2, MeOH–CH_2Cl_2, 5:95), to give the title compound **13c**.

Yield: 54 mg (56% over two steps); clear colourless oil; R_f = 0.46 (MeOH–CH_2Cl_2, 5:95).

IR (neat): 2960, 2864, 1690, 1451, 1277, 1076, 1053 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.44–1.50 (m, 1 H, C*H*HCNO), 1.74–1.93 (m, 2 H, CH_2), 2.22–2.39 (m, 2 H, CH*H*C=O, C*H*H), 2.45–2.54 (m, 1 H, C*H*HC=O), 3.08 (td, *J* = 13.0, 4.0 Hz, 1 H, CH*H*N), 3.71 (td, *J* = 12.0, 2.0 Hz, 1 H, CH*H*O), 4.06–4.12 (m, 1 H, C*H*HO), 4.15–4.21 (m, 1 H, C*H*HN), 4.94 (dd, *J* = 6.5, 2.5 Hz, 1 H, NCHO). Consistent with published data.[16]

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 24.7, 28.8, 38.6, 67.0, 88.0, 173.5.

MS (CI, NH_3): *m*/*z* (%) = 159 (80) $[M + NH_4]^+$, 142 (100) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_7H_{11}NO_2Na$: 164.0682; found: 164.0680 (1.3 ppm error).

Hexahydropyrrolo[2,1-*b*][1,3]oxazepin-7-one (13d)

Prepared from 4-amino-1-butanol (**16d**; 33 μL, 0.36 mmol) and 3-[1,3]dioxolan-2-ylpropionic acid (**15a**; 50 mg, 0.34 mmol) according to the procedure described for the preparation of compound **13a**.

The unpurified amide was stirred with $SnCl_2·2H_2O$ (153 mg, 0.68 mmol) for 12 h and the crude product was purified by flash column chromatography (SiO_2, MeOH–CH_2Cl_2, 5:95), to yield the title compound **13d**.

Yield: 30 mg (57% over two steps); clear colourless oil; R_f = 0.30 (MeOH–CH_2Cl_2, 5:95).

IR (neat): 2931, 1689, 1419, 1374, 1279, 1186, 1099 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.65–1.95 (m, 5 H, CH_2), 2.21–2.35 (m, 2 H, CH*H*C=O, C*H*H), 2.47–2.58 (m, 1 H, C*H*HC=O), 3.20 (ddd, *J* = 13.5, 6.5, 3.0 Hz, 1 H, CH*H*N), 3.46–3.53 (m, 1 H, CH*H*O), 3.57–3.66 (m, 1 H, C*H*HN), 3.82–3.89 (m, 1 H, C*H*HO), 5.06 (dd, *J* = 6.5, 2.5 Hz, 1 H, NCHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 26.4, 29.4, 30.9, 42.5, 68.8, 90.3, 174.8.

MS (ESI): *m*/*z* (%) = 156 (100) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{14}NO_2$: 156.1019; found: 156.1018 (0.5 ppm error).

2,3,3a,5-Tetrahydro-1*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazin-1-one (17c)

Prepared from 2-aminobenzyl alcohol (**19c**; 89 mg, 0.72 mmol) and acid **15a** (100 mg, 0.72 mmol) according to the procedure described for the preparation of compound **13a**. The crude amide was stirred with $SnCl_2·2H_2O$ (324 mg, 1.44 mmol) for 24 h and the crude product was purified by flash column chromatography (SiO_2, Et_2O), to yield the title compound **17c**.

Yield: 104 mg (80%); colourless solid; mp 89–90 °C; R_f = 0.38 (Et_2O).

IR (neat): 1695, 1494, 1490, 1215, 1080 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 2.01–2.10 (m, 1 H, C*H*HCH$_2$C=O), 2.47–2.61 (m, 3 H, CH$_2$C=O, CH*H*CH$_2$C=O), 4.90 (d, *J* = 15.0 Hz, 1 H, Ar-CH$_2$O), 5.05 (d, *J* = 15.0 Hz, 1 H, Ar-CH$_2$O), 5.27 (dd, *J* = 7.0, 5.0 Hz, 1 H, OCHN), 7.02 (br d, *J* = 7.5 Hz, 1 H, Ar-H), 7.10 (td, *J* = 7.5, 1.0 Hz, 1 H, Ar-H), 7.26–7.27 (m, 1 H, Ar-H), 8.30 (d, *J* = 8.5 Hz, 1 H, Ar-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.8, 30.1, 58.1, 87.2, 119.6, 123.8, 124.3, 124.4, 127.7, 134.2, 172.0.

MS (ESI): *m*/*z* (%) = 212 (100) $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{11}NO_2Na$: 212.0682; found: 212.0687 (2.2 ppm error).

3,3a-Dihydro-2*H*,5*H*-pyrrolo[2,1-*a*][3,1]benzothiazine-1-one (17d)

Prepared from (2-aminophenyl)methane thiol[21] (**19d**; 106 mg, 0.75 mmol) and 3-[1,3]dioxolan-2-ylpropionic acid (**15a**; 100 mg, 0.68 mmol) according to the procedure for compound **13a**. The crude amide was stirred with $SnCl_2·2H_2O$ (306 mg, 1.36 mmol) for 18 h and the crude product was partially purified by flash column chromatography (MeOH–CH_2Cl_2, 3:97). The impure product was dissolved in MeOH and loaded onto an SCX column. Washing with MeOH then elution with ~0.5M methanolic ammonia and concentration gave the title compound **17d**.

Yield: 105 mg (86%); pale-yellow oil; R_f = 0.65 (MeOH–CH_2Cl_2, 1:10).

IR (neat): 3430, 2095, 1643, 1468, 1210, 1104 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.03–2.11 (m, 1 H, C*H*H), 2.57–2.68 (m, 3 H, CH$_2$=O, CH*H*), 3.70 (d, *J* = 17.0 Hz, 1 H, ArCH$_2$N), 4.30 (d, *J* = 17.0 Hz, 1 H, ArCH$_2$), 5.02–5.05 (m, 1 H, NCHS), 7.10 (br d, *J* = 8.0 Hz, 1 H, Ar-H), 7.15–7.17 (m, 1 H, Ar-H), 7.30 (br t, *J* = 8.0 Hz, 1 H, Ar-H), 8.25 (dd, *J* = 8.0, 1.0 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 30.5, 31.0, 60.9, 122.7, 123.5, 124.4, 127.6, 128.7, 135.9, 173.2.

MS (ESI): *m*/*z* (%) = 228 (100) $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{11}NOSNa$: 228.0454; found: 228.0459 (2.1 ppm error).

4-Methyl-3,3a,4,9-tetrahydro-2*H*-pyrrolo[2,1-*b*]quinazoin-1-one (32)

Prepared from 2-methylaminobenzylamine (**30**; 60 mg, 0.43 mmol)[22] and 3-[1,3]dioxolan-2-ylpropionic acid (**15a**; 58 mg, 0.39 mmol) according to the procedure described for the preparation of compound **13a**. The crude amide was stirred with $SnCl_2·2H_2O$ (175 mg, 0.78 mmol) for 18 h and the crude product was purified by preparative TLC (EtOAc–PE, 1:1) to yield the title compound **32**.

Yield: 35 mg (43%); colourless oil; R_f = 0.31 (EtOAc–PE, 1:1).

IR (neat): 1685, 1498, 1447, 1369, 1307, 1273, 1212 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.02–2.09 (m, 1 H, C*H*HCH$_2$C=O), 2.36–2.57 (m, 3 H, CH*H*CH$_2$C=O, CH$_2$C=O), 2.81 (s, 3 H, NCH$_3$), 4.25 (d, *J* = 17.0 Hz, 1 H, ArC*H*H), 4.56 (t, *J* = 6.0 Hz, 1 H, NCHN), 4.85 (d, *J* = 17.0 Hz, 1 H, ArCH*H*), 6.79–6.81 (m, 2 H, Ar-H), 7.03 (d, *J* = 7.5 Hz, 1 H Ar-H), 7.16 (t, *J* = 7.5 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.8, 29.5, 33.8, 41.1, 71.9, 113.7, 119.2, 119.6, 126.8, 128.0, 145.7, 173.5.

MS (ESI): *m*/*z* (%) = 225 (100) $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{14}N_2ONa$: 225.0998; found: 225.1006 (3.5 ppm error).

(2*R*)-2-Phenyltetrahydropyrrolo[2,1-*b*]oxazol-3-one (20a)

A solution of 3-[1,3]dioxolan-2-ylpropylamine (**22a**; 0.10 g, 0.76 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a solution of (*R*)-(–)-mandelic acid (**23a**; 0.12 g, 0.80 mmol) and DIPEA (0.16 mL, 0.91 mmol) in CH_2Cl_2 (5 mL) at 0 °C. This was followed immediately by the portionwise addition of HATU (0.32 g, 0.84 mmol) to the reaction. The yellow solution was stirred at 0 °C for 1 h and then allowed to slowly warm to r.t. and stirred for a further 1 h. The reaction was filtered through a short pad of silica, washing through with EtOAc (3 × 10 mL). The volatiles were removed from the filtrate under reduced pressure to yield the crude amide (contaminated with tetramethylurea). The unpurified amide was redissolved in CH_2Cl_2 (8 mL), $SnCl_2·2H_2O$ (0.38 g, 1.67 mmol) was added, and the reaction mixture was stirred at r.t. for 12 h. The mixture was diluted with $CHCl_3$ (8 mL) and then treated with K_2CO_3 (0.5 g, 3.6 mmol) and stirring was continued for a further 30 min. The mixture was filtered through a short pad of Celite®, washing through with $CHCl_3$ (3 × 10 mL). The filtrate was concentrated in vacuo and the crude product was purified by flash column chromatography (SiO_2, EtOAc), to give the title compound **20a**.

Yield: 54 mg (43% over two steps); mixture of diastereoisomers [2:1, separable by careful chromatography: R_f = 0.50 (major), 0.55 (minor) (EtOAc)]; clear colourless oil.

IR (neat): 2979, 2945, 2894, 1717, 1413, 1309, 1091, 911 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of diastereoisomers) = 1.69–2.26 (m, 4 H, CH$_2$), 3.07–3.17 (m, 1 H, CH*H*N), 3.74–3.84 (m, 1 H, C*H*HN), 5.38 [s, 1 H, CHC=O (minor)], 5.45 [s, 1 H, CHC=O (major)], 5.59–5.63 [m, 1 H, NCHO (major)], 5.66–5.70 [m, 1 H, NCHO (minor)], 7.30–7.50 (m, 5 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (minor diastereoisomer given in brackets) = 24.3, (24.0), 31.50, (31.45), 43.0, (42.4), 83.7, (83.3), (94.2), 92.7, 126.9, (125.6), 128.5, (128.4), 128.7, (128.6), (136.1), 135.6, (173.6), 173.1.

MS (ESI): *m*/*z* (%) = 204 (100) $[M + H]^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}NO_2$: 204.1019; found: 204.1020 (0.5 ppm error).

tert-Butyl (2*S*)-2-Methyl-3-oxohexahydropyrrolo[1,2-*a*]imidazole-1-carboxylate (20b)

Prepared from 3-[1,3]dioxolan-2-ylpropylamine (**22a**; 0.10 g, 0.76 mmol) and *N*-Boc-L-alanine (**23b**; 0.15 g, 0.80 mmol) according to the procedure described for the preparation of compound **20a**. The crude amide was stirred with $SnCl_2{\cdot}2H_2O$ (342 mg, 1.52 mmol) for 12 h and the crude product **20b** was purified by flash column chromatography (SiO_2, EtOAc), to yield the title compound **20b** as an inseparable mixture of diastereoisomers (3:1).

Yield: 0.10 g (55% over two steps); clear colourless oil; R_f = 0.45 (EtOAc).

IR (neat): 2977, 2933, 1705, 1477, 1450, 1418, 1175, 1136, 1043 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): δ (mixture of diastereoisomers) = 1.33 [d, *J* = 7.0 Hz, 3 H, CH_3 (major)], 1.37 [d, *J* = 6.5 Hz, 3 H, CH_3 (minor)], 1.45 [s, 9 H, *t*-Bu (minor)], 1.45 [s, 9 H, *t*-Bu (major)], 1.26–1.50 (occluded m, 1 H, CH_2), 1.90–2.07 (m, 2 H, CH_2), 2.14–2.30 (m, 1 H, CH_2), 2.98–3.06 (m, 1 H, CH*H*N), 3.50–3.60 (m, 1 H, C*H*HN), 4.02 [q, *J* = 6.5 Hz, 1 H, CHC=O (minor)], 4.21 [q, *J* = 7.0 Hz, 1 H, CHC=O (major)], 5.06 [dd, *J* = 8.5, 5.5 Hz, 1 H, NCHN (major)], 5.08–5.10 [m, 1 H, NCHN (minor overlaying major diastereoisomer)].

^{13}C NMR (100 MHz, DMSO-d_6, 80 °C): δ (minor diastereoisomer given in brackets) = 17.7 (both diastereoisomers), 23.2, (23.3), 27.6, (27.61), 32.2 (both diastereoisomers), 40.9, (40.5), 56.4 (both diastereoisomers), 74.6, (74.4), 79.5, (79.3), 152.6 (both diastereoisomers), 172.3 (both diastereoisomers).

MS (ESI): *m*/*z* (%) = 263 (10) [M + Na]$^+$, 241 (100), [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{21}N_2O_3$: 241.1547; found: 241.1554 (2.9 ppm error).

tert-Butyl (3*S*,8a*R*)-(4-Oxohexahydropyrrolo[2,1-*b*][1,3]oxazin-3-yl)carbamate (20c)

Prepared from 3-[1,3]dioxolan-2-ylpropylamine (**22a**; 0.10 g, 0.76 mmol) and *N*-Boc-L-serine (**23c**; 0.16 g, 0.80 mmol) according to the procedure described for the preparation of compound **20a**. The crude amide was stirred with $SnCl_2{\cdot}2H_2O$ (342 mg, 1.52 mmol) for 12 h and the crude product **20c** was purified by flash column chromatography (SiO_2, EtOAc), to yield the title compound **20c**.

Yield: 90 mg (46% over two steps); colourless solid; single diastereoisomer; mp 104–106 °C; $[\alpha]_D^{22}$ 32.5 (*c* 0.95, $CHCl_3$); R_f = 0.30 (EtOAc).

IR (Nujol mull): 3343, 2922, 2853, 1724, 1666, 1519, 1458, 1252, 1165, 1000 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, *t*-Bu), 1.19–2.02 (m, 3 H, CH_2, C*H*HCHNO), 2.20–2.28 (m, 1 H, CH*H*CHNO), 3.35 (ddd, *J* = 11.5, 7.5, 5.5 Hz, 1 H, CH*H*N), 3.64 (dd, *J* = 13.5, 10.5 Hz, 1 H, CH*H*O), 3.82 (dt, *J* = 11.5, 7.0 Hz, 1 H, C*H*HN), 4.34–4.40 (m, 2 H, C*H*HO, CHC=O), 5.08 (t, *J* = 5.0 Hz, 1 H, NCHO), 5.53 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 28.3, 32.5, 45.0, 49.0, 68.7, 80.1, 87.0, 155.8, 166.4.

MS (ESI): *m*/*z* (%) = 257 (40) [M + H]$^+$, 201 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{21}N_2O_4$: 257.1496; found: 257.1502 (2.4 ppm error).

8-Methyl-1,2,3,9a-tetrahydro-9-oxa-3a-azacyclopenta[*b*]naphthalen-4-one (24a)

A mixture of 3-[1,3]dioxolan-2-yl-propylamine (**22a**; 37 mg, 0.28 mmol) and phenyl 2-hydroxy-3-methylbenzoate (**33**; 50 mg, 0.22 mmol) in a sealed tube, was heated under microwave irradiation at 135 °C for 10 min (50 W input power). The resulting gum was allowed to cool to r.t., dissolved in CH_2Cl_2 (5 mL) and $SnCl_2{\cdot}2H_2O$ (100 mg, 0.44 mmol) was added in a single portion. The reaction was allowed to stir at r.t. for 18 h whereupon it was diluted with $CHCl_3$ (5 mL) and then treated with K_2CO_3 (130 mg, 0.94 mmol) and stirring was continued for a further 30 min. The mixture was filtered through a short pad of Celite®, washing with $CHCl_3$ (3 × 10 mL). The filtrate was concentrated in vacuo and purified by flash chromatography (SiO_2; Et_2O) to give the title compound **24a**.

Yield: 70 mg (98%); colourless solid; mp 111–113 °C; R_f = 0.25 (Et_2O).

IR (Nujol mull): 2955, 2924, 2855, 1669, 1440, 1073 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88–1.99 (m, 1 H, NCHOCH$_2$C*H*H), 2.07–2.16 (m, 1 H, NCHOCH$_2$CH*H*), 2.23 (s, 3 H, CH_3), 2.24–2.33 (m, 1 H, NCHOC*H*H), 2.39–2.49 (m, 1 H, NCHOCH*H*), 3.61 (ddd, *J* = 11.5, 8.0, 5.0 Hz, 1 H, CONC*H*H), 3.84 (dt, *J* = 11.5, 7.5 Hz, 1 H, CONCH*H*), 5.46 (t, *J* = 6.0 Hz, 1 H, NCHO), 6.99 (t, *J* = 7.5 Hz, 1 H, Ar-H), 7.26 (d, *J* = 7.5 Hz, 1 H, Ar-H), 7.76 (dd, *J* = 7.5, 1.0 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4, 21.4, 32.0, 44.3, 88.2, 119.4, 121.9, 125.4, 125.8, 134.9, 155.5, 161.3.

MS (ESI): *m*/*z* (%) = 204 (100) [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}NO_2$: 204.1019; found: 204.1023 (1.7 ppm error).

1,2,3,3a-Tetrahydropyrrolo[2,1-*b*][1,3]benzoxanin-9-one (24b)

Prepared from 3-[1,3]dioxolan-2-ylpropylamine (**22a**; 79 mg, 0.61 mmol), phenyl salicylate (**26b**; 100 mg, 0.47 mmol) and $SnCl_2{\cdot}2H_2O$ (212 mg, 0.94 mmol) according to the procedure described for compound **24a**. Flash chromatography (SiO_2; Et_2O), yielded the title compound **24b**.[23]

Yield: 68.5 mg (75%); colourless oil; R_f = 0.22 (Et_2O).

IR (neat): 2884, 1667, 1611, 1468, 1347 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.89–1.99 (m, 1 H, NCHOCH$_2$C*H*H), 2.07–2.16 (m, 1 H, NCHOCH$_2$CH*H*), 2.21–2.30 (m, 1 H, NCHOC*H*H), 2.40–2.47 (m, 1 H, NCHOCH*H*), 3.59–3.66 (m, 1 H, CONC*H*H), 3.81–3.88 (m, 1 H, CONCH*H*), 5.50 (t, *J* = 6.0 Hz, 1 H, NCHO), 6.96 (dd, *J* = 7.5, 1.0 Hz, 1 H, Ar-H), 7.11 (td, *J* = 7.5, 1.0 Hz, 1 H, Ar-H), 7.42 (td, *J* = 7.5, 2.0 Hz, 1 H, Ar-H), 7.93 (dd, *J* = 7.5, 1.5 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 31.9, 44.3, 88.4, 116.4, 119.7, 122.6, 127.9, 133.7, 157.2, 160.9.

MS (ESI): *m*/*z* (%) = 190 (100) [M + H]$^+$, 212 (8) [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NO_2$: 190.0863; found: 190.0863 (0.2 ppm error).

6-Fluoro-1,2,3,3a-tetrahydro-pyrrolo[2,1-*b*][1,3]benzoxanin-9-one (24c)

Prepared from 3-[1,3]dioxolan-2-ylpropylamine (**22a**; 55 mg, 0.41 mmol), phenyl 4-fluoro-2-hydroxybenzoate (**26c**; 75 mg, 0.32 mmol) and $SnCl_2{\cdot}2H_2O$ (144 mg, 0.64 mmol) according to the procedure described for compound **24a**. Flash chromatography (SiO_2; Et_2O), yielded the title compound **24c**.

Yield: 70 mg (98%); colourless solid; mp 79–81 °C; R_f = 0.44 (Et_2O).

IR (neat): 1666, 1618, 1450, 1261 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84–1.94 (m, 1 H, NCHOCH$_2$C*H*H), 2.01–2.09 (m, 1 H, NCHOCH$_2$CH*H*), 2.14–2.23 (m, 1 H, NCHOC*H*H), 2.34–2.41 (m, 1 H, NCHOCH*H*), 3.51–3.57 (m, 1 H, CONC*H*H), 3.73–3.80 (m, 1 H, CONCH*H*), 5.45 (t, 1 H,

J = 6.0 Hz, NCHO), 6.60 (dd, J = 10.0, 2.0 Hz, 1 H, Ar-H), 6.74 (td, J = 10.0, 2.0 Hz, 1 H, Ar-H), 7.86 (dd, J = 7.0, 9.0 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 31.9, 44.3, 88.9, 104.3 (d, J = 25.0 Hz), 110.3 (d, J = 22.0 Hz), 116.2, 130.0 (d, J = 11.0 Hz), 158.9, 160.9, 164.6, 165.9 (d, J = 252.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.8 (ddd, J = 10.3, 10.2, 9.0 Hz).

MS (ESI): m/z (%) = 230 (100) $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{11}H_{10}NFO_2Na$: 230.0588; found: 230.0592 (1.9 ppm error).

7-Chloro-1,2,3,3a-tetrahydropyrrolo[2,1-*b*][1,3]benzoxanin-9-one (24d)

Prepared from 3-[1,3]dioxolan-2-ylpropylamine (**22a**; 120 mg, 0.60 mmol), phenyl 5-chloro-2-hydroxybenzoate (**26d**; 150 mg, 0.91 mmol) and $SnCl_2{\cdot}2H_2O$ (410 mg, 1.82 mmol) according to the procedure described for compound **24a**. Flash chromatography (SiO_2; Et_2O) yielded the title compound **24d**.

Yield: 125 mg (87%); sticky colourless solid; mp 63–64 °C; R_f = 0.36 (Et_2O).

IR (neat): 1669, 1609, 1451, 1413, 1346 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86–1.95 (m, 1 H, $NCHOCH_2CHH$), 2.03–2.10 (m, 1 H, $NCHOCH_2CHH$), 2.16–2.24 (m, 1 H, $NCHOCHH$), 2.35–2.43 (m, 1 H, $NCHOCHH$), 3.53–3.59 (m, 1 H, $CONCHH$), 3.75–3.81 (m, 1 H, $CONCHH$), 5.43 (t, J = 5.5 Hz, 1 H, NCHO), 6.87 (d, J = 9.0 Hz, 1 H, Ar-H), 7.31 (dd, J = 9.0, 3.0 Hz, 1 H, Ar-H), 7.83 (d, J = 2.5 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 31.7, 44.2, 88.6, 118.0, 120.8, 127.5, 127.9, 133.5, 155.7, 159.7.

MS (ESI): m/z (%) = 224 (100) $[M + H]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $NaC_{11}H_{10}ClNO_2$: 246.0292; found: 246.0293 (0.2 ppm error).

5-Isopropyl-8-methyl-1,2,3,3a-tetrahydropyrrolo[2,1-*b*][1,3]benzoxanin-9-one (24e)

Prepared from 3-[1,3]dioxolan-2-ylpropylamine (**22a**; 67 mg, 0.51 mmol), phenyl 2-hydroxy-3-isopropyl-6-methylbenzoate (**26e**; 100 mg, 0.30 mmol) and $SnCl_2{\cdot}2H_2O$ (135 mg, 0.60 mmol) according to the procedure described for compound **24a**. Flash chromatography (SiO_2; Et_2O) yielded the title compound **24e**.

Yield: 81 mg (84%); colourless oil; R_f = 0.68 (Et_2O).

IR (neat): 2960, 1663, 1491, 1428 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 1.18 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 1.87–1.94 (m, 1 H, $NCHOCH_2CHH$), 2.03–2.16 (m, 1 H, $NCHOCH_2CHH$), 2.21–2.29 (m, 1 H, $NCHOCHH$), 2.35–2.43 (m, 1 H, $NCHOCHH$), 2.61 (s, 3 H, CH_3), 3.18 [quint, J = 7.0 Hz, 1 H, $CH(CH_3)_2$], 3.49–3.55 (m, 1 H, $CONCHH$), 3.84–3.91 (m, 1 H, $CONCHH$), 5.33 (dd, J = 6.0, 5.0 Hz, 1 H, NCHO), 6.82 (d, J = 7.5 Hz, 1 H, Ar-H), 7.15 (d, J = 7.5 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 21.8, 22.5, 22.7, 26.7, 32.2, 44.7, 87.7, 118.4, 125.3, 129.3, 133.9, 138.3, 155.4, 162.0.

MS (ESI): m/z (%) = 246 (100) $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{20}NO_2$: 246.1489; found: 246.1493 (2.6 ppm error).

1,2,3,11a-Tetrahydro-11-oxa-3a-azacyclopenta[*b*]anthracen-4-one (24f)

Prepared from 3-[1,3]dioxolan-2-ylpropylamine (**22a**; 64 mg, 0.64 mmol), phenyl 3-hydroxynaphthalene-2-carboxylate (**26f**; 100 mg, 0.49 mmol) and $SnCl_2{\cdot}2H_2O$ (220 mg, 0.98 mmol) according to the procedure described for compound **24a**. Flash chromatography (SiO_2; Et_2O) yielded the title compound **24f**.

Yield: 59 mg (65%); colourless solid; mp 111–114 °C; R_f = 0.21 (Et_2O).

IR (neat): 1664, 1633, 1436 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91–2.02 (m, 1 H, $NCHOCH_2CHH$), 2.13–2.20 (m, 1 H, $NCHOCH_2CHH$), 2.24–2.33 (m, 1 H, $NCHOCHH$), 2.44–2.52 (m, 1 H, $NCHOCHH$), 3.66–3.72 (m, 1 H, $CONCHH$), 3.87–3.92 (m, 1 H, $CONCHH$), 5.54 (t, J = 11.0 Hz, 1 H, NCHO), 7.33 (m, 1 H, Ar-H), 7.38–7.42 (m, 1 H, Ar-H), 7.49–7.53 (m, 1 H, Ar-H), 7.73 (d, J = 8.0 Hz, 1 H, Ar-H), 7.90 (d, J = 8.0 Hz, 1 H, Ar-H), 8.51 (s, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 32.1, 44.5, 88.6, 112.1, 120.1, 125.1, 127.0, 128.5, 129.5 (3 × C), 136.4, 153.6, 161.1.

MS (ESI): m/z (%) = 262 (100) $[M + Na]^+$, 240 (30) $[M + H]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{13}NO_2Na$: 262.0838; found: 262.0843 (0.9 ppm error).

7a,8,9,10-Tetrahydro-7-oxa-10a-azacyclopenta[*b*]phenanthrene-11-one (24g)

Prepared from 3-[1,3]dioxolan-2-yl-propylamine (**22a**; 64 mg, 0.64 mmol) and phenyl 2-hydroxynaphthalene-1-carboxylate (**26g**; 100 mg, 0.49 mmol) according to the procedure described for compound **24a**. Flash chromatography (SiO_2; Et_2O) yielded the title compound **24g**.

Yield: 51 mg (56%); colourless solid; mp 104–107 °C; R_f = 0.24 (Et_2O).

IR (neat): 1658, 1443, 763 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94–2.05 (m, 1 H, $NCHOCH_2CHH$), 2.13–2.22 (m, 1 H, $NCHOCH_2CHH$), 2.40–2.57 (m, 2 H, $NCHOCH_2$), 3.62–3.68 (m, 1 H, $CONCHH$), 3.87–3.93 (m, 1 H, $CONCHH$), 5.65 (t, J = 5.5 Hz, 1 H, NCHO), 7.49–7.59 (m, 3 H, Ar-H), 7.81 (d, J = 8.0, 1.0 Hz, 1 H, Ar-H), 7.92 (d, J = 9.0 Hz, 1 H, Ar-H), 8.20 (dd, J = 8.5, 1.0 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 32.1, 44.6, 89.1, 114.3, 122.1, 122.8, 123.2, 123.8, 126.3, 127.8, 128.5, 136.6, 154.8, 161.5.

MS (ESI): m/z (%) = 362 (100) $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{13}NO_2Na$: 262.0838; found: 262.0840 (0.2 ppm error).

Acknowledgment

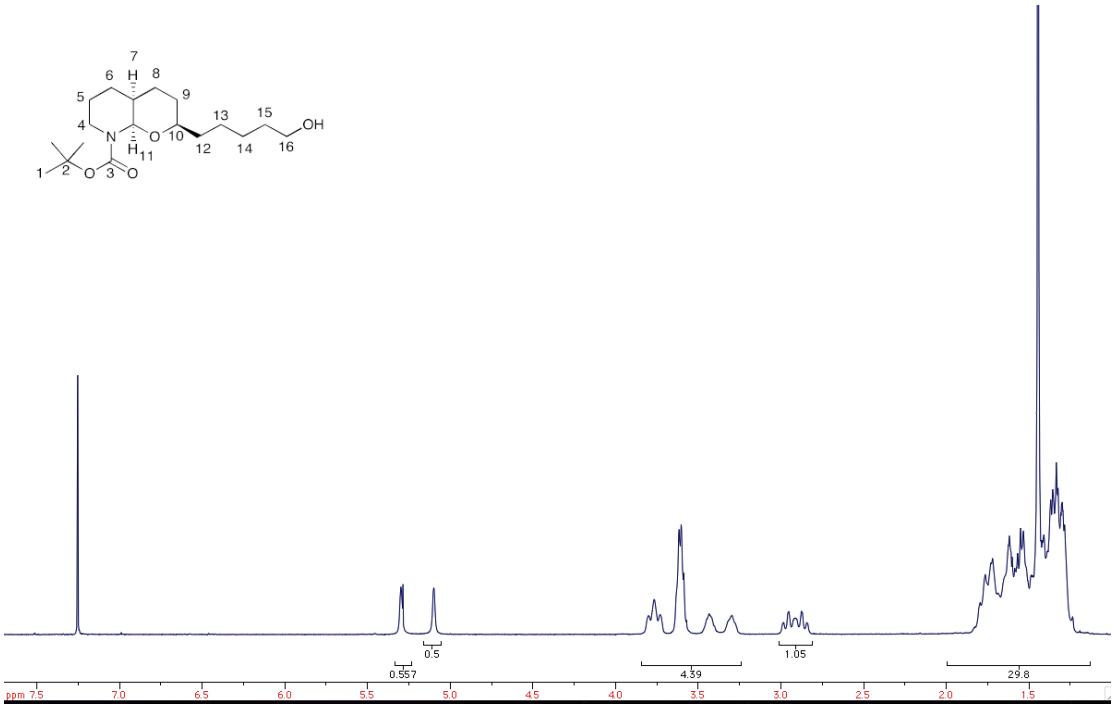
We are grateful to the University of York for studentship and PDRA support (J.P.S. and A.N.C., respectively), EPSRC Pharmasynth program for studentship (K.A.G.), AstraZeneca for further funding (J.P.S., K.A.G.) and the French Ministère des Affaires Etrangères for a Lavoisier Postdoctoral Fellowship (C.M.M.). We are also grateful to Dr Trevor Dransfield (University of York) for assistance with mass spectrometry and to Dr Rhona J. Cox (AstraZeneca) and Dr Mike Edwards (University of York) for helpful discussions.

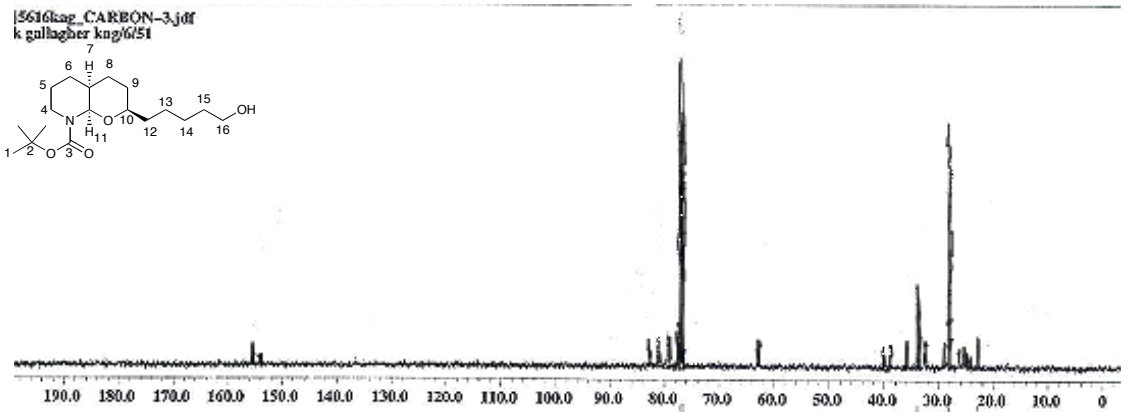
References

(1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893; and references therein.
(2) Faul, M. M. *Encyclopedia of Reagents for Organic Synthesis*, Vol. 7; Paquette, L. A., Ed.; Wiley: Chichester, **1995**, 4892.
(3) Ford, K. L.; Roskamp, E. J. *Tetrahedron Lett.* **1992**, *33*, 1135.
(4) Foot, J. S.; Giblin, G. M. P.; Taylor, R. J. K. *Org. Lett.* **2003**, *5*, 4441.

(5) Jiménez, J. I.; Goetz, G.; Mau, C. M. S.; Yoshida, W. Y.; Scheuer, P. J.; Williamson, R. T.; Kelly, M. *J. Org. Chem.* **2000**, *65*, 8465.
(6) Ménard-Moyon, C.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2007**, 3698.
(7) Reid, M.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 4181.
(8) Schmidt, J. P.; Beltrán-Rodil, S.; Cox, R. J.; McAllister, G. D.; Reid, M.; Taylor, R. J. K. *Org. Lett.* **2007**, *9*, 4041.
(9) Han, J. L.; Ong, C. W. *Tetrahedron* **2007**, *63*, 609.
(10) Winterfeld, K.; Michael, H. *Pharm. Ber. Dtsch. Pharm. Ges.* **1961**, 65.
(11) Ijzendoorn, D. R.; Botman, P. N. M.; Blaauw, R. H. *Org. Lett.* **2006**, *8*, 239.
(12) For related processes, see: (a) Mizutani, N.; Chiou, W.-H.; Ojima, I. *Org. Lett.* **2002**, *4*, 4575. (b) Armorde, S. M.; Judd, A. S.; Martin, S. F. *Org. Lett.* **2005**, *7*, 2031. (c) Vink, M. K. S.; Schortinghuis, C. A.; Mackova-Zabelinskaja, A.; Fechter, M.; Pöchlauer, P.; Castelijns, A. M. C. F.; van Maarseveen, J. H.; Hiemstra, H.; Griengl, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2003**, *345*, 483.
(13) Cayley, A. N.; Cox, R. J.; Ménard-Moyon, C.; Schmidt, J. P.; Taylor, R. J. K. *Tetrahedron Lett.* **2007**, *48*, 6556.
(14) Shea, K. J.; Wada, E. *J. Am. Chem. Soc.* **1982**, *104*, 5715.
(15) For similar systems, see: Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, *54*, 4243.
(16) (a) Iwata, M.; Ohrui, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2837. (b) Tanner, D.; Somfai, P. *Tetrahedron Lett.* **1988**, *29*, 2373.
(17) Okita, M.; Wakamatsu, T.; Mori, M.; Ban, Y. *Heterocycles* **1980**, *14*, 1089.
(18) Shimizu, M.; Ishikawa, M.; Komoda, Y.; Nakajima, T. *Chem. Pharm. Bull.* **1982**, *30*, 909.
(19) For similar systems, see: Griot, R. G.; Frey, A. J. *Tetrahedron* **1963**, *19*, 1661; see also reference 11.
(20) The phenyl esters were either commercially available (**26b**, **26f** and **26g**) or were prepared from the corresponding acids using standard conditions, see: Jeffery, E. A.; Bansal, R. K.; Andrews, L. J.; Keefer, R. M. *J. Org. Chem.* **1964**, *29*, 3365.
(21) (a) Kitamura, R. *J. Pharm. Soc. Jpn.* **1937**, *57*, 55; in practice, compound **19d** was prepared from 2-nitrobenzyl bromide according to the procedure of Leach and co-workers (ref. 21b), followed by reduction with $SnCl_2 \cdot 2H_2O$ in THF. (b) Leach, D. N.; Reiss, J. A. *J. Org. Chem.* **1978**, *43*, 2484.
(22) (a) Papot, S.; Bachmann, C.; Combaud, D.; Gesson, J. P. *Tetrahedron* **1999**, *55*, 4699; prepared via the alkylation of 2-aminobenzonitrile with *n*-BuLi and MeI (ref. 22b), then reduction with $LiAlH_4$ to afford the primary amine. (b) Barluenga, J.; Fañanás, F. J.; Sanz, R.; Fernández, Y. *Chem Eur. J.* **2002**, *8*, 2034.
(23) Bohme, H.; Boing, H. *Arch. Pharm.* **1961**, *294*, 556.

Appendix 2 – Selected NMR spectra





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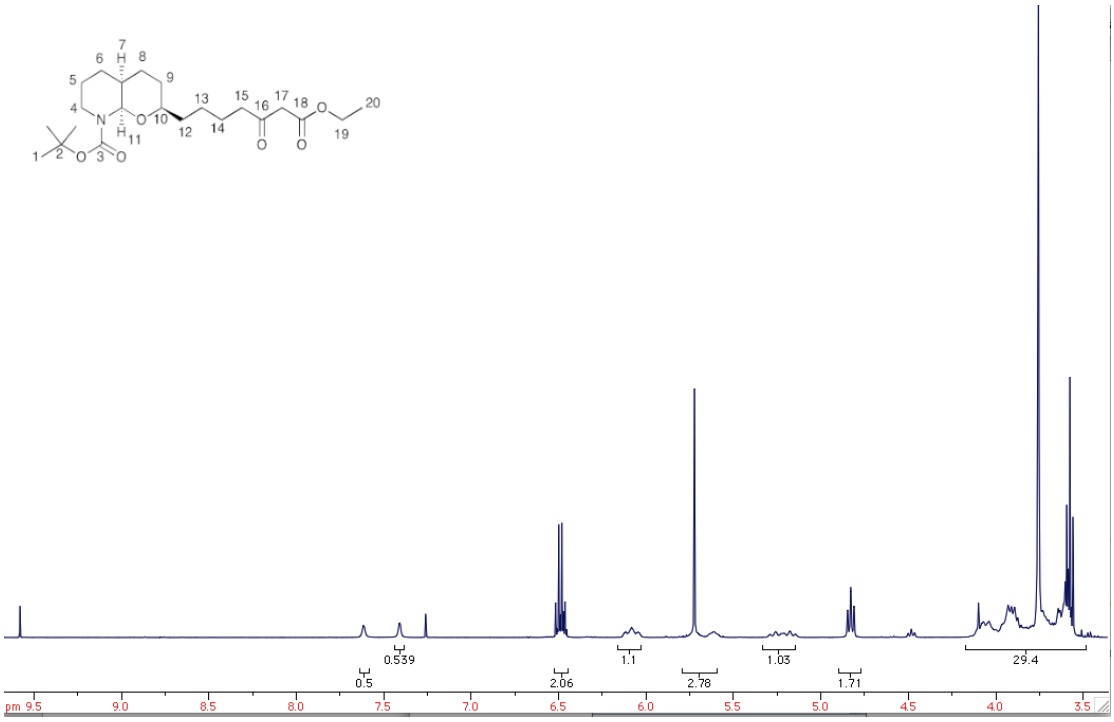
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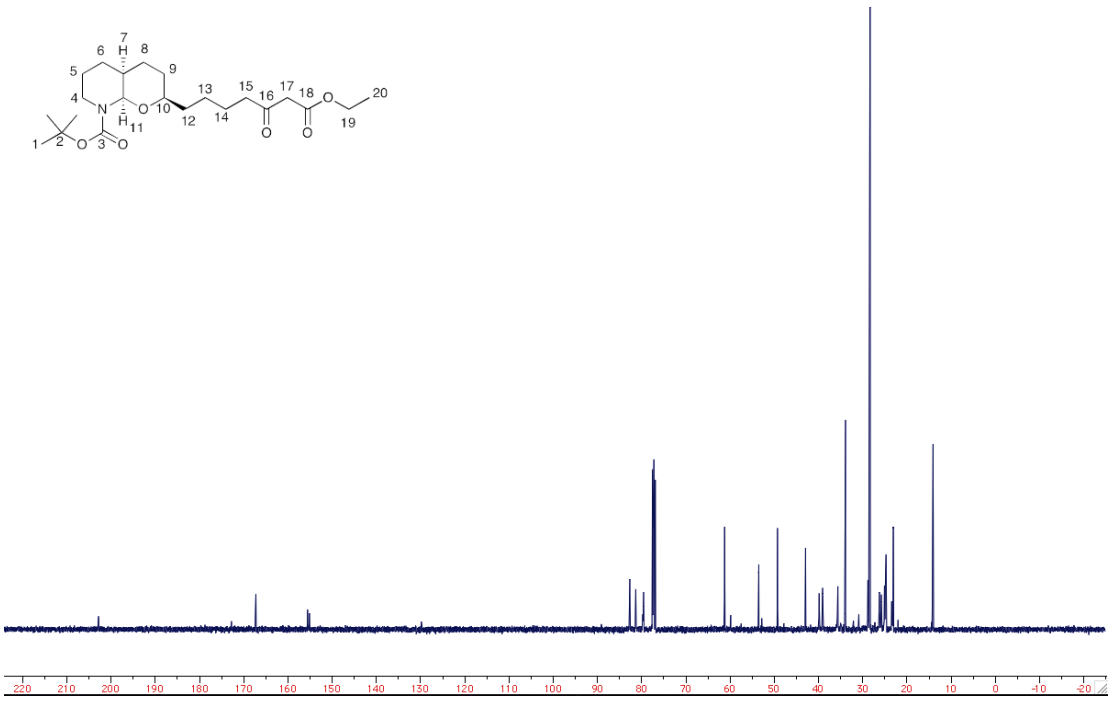
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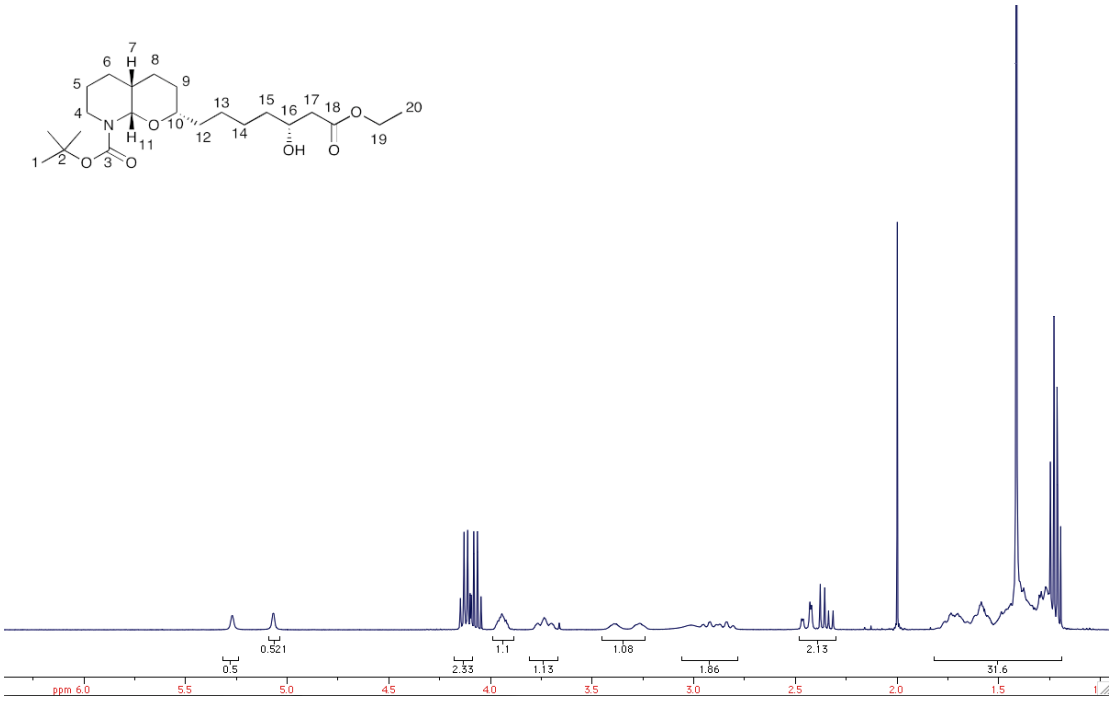
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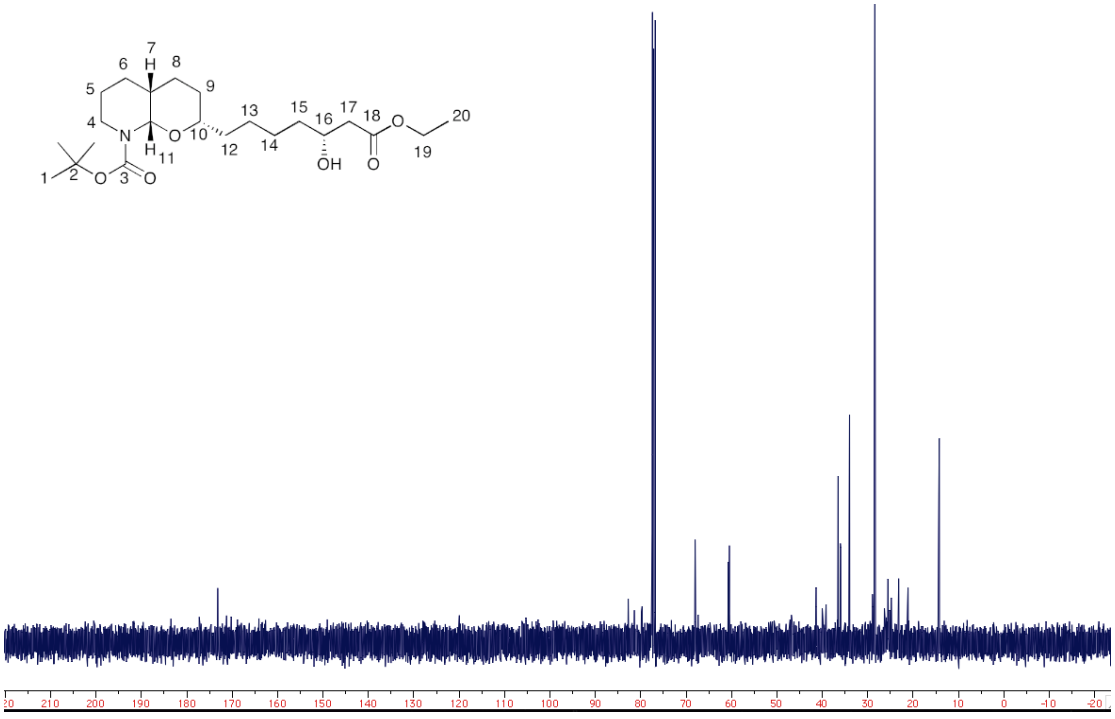
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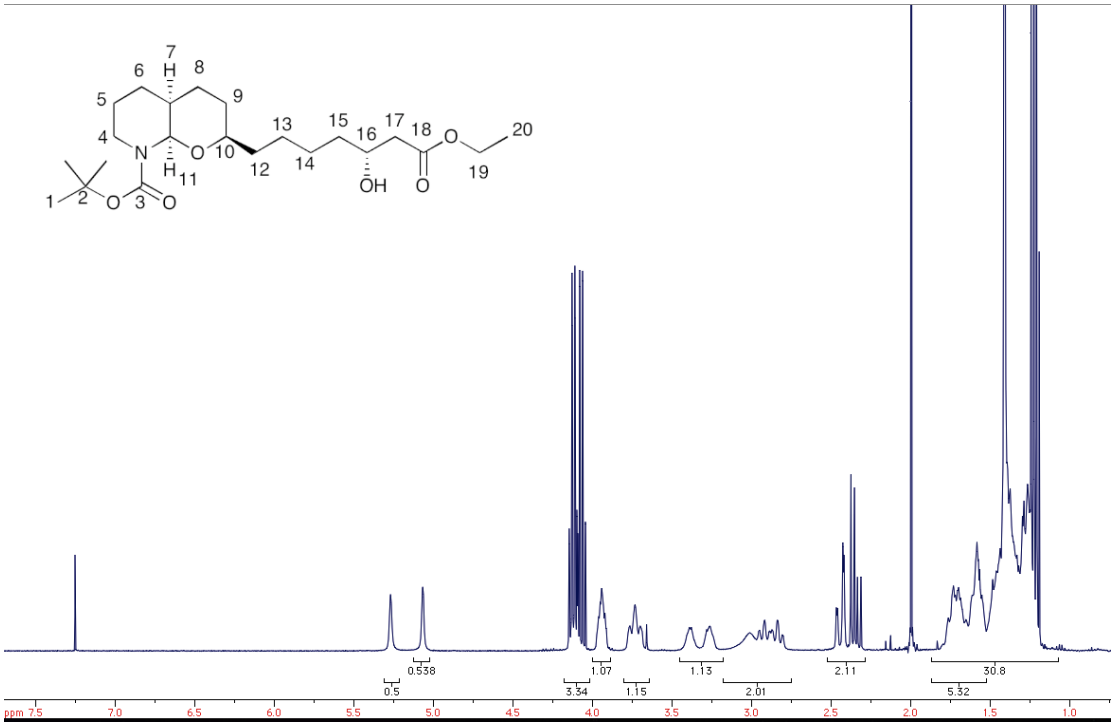
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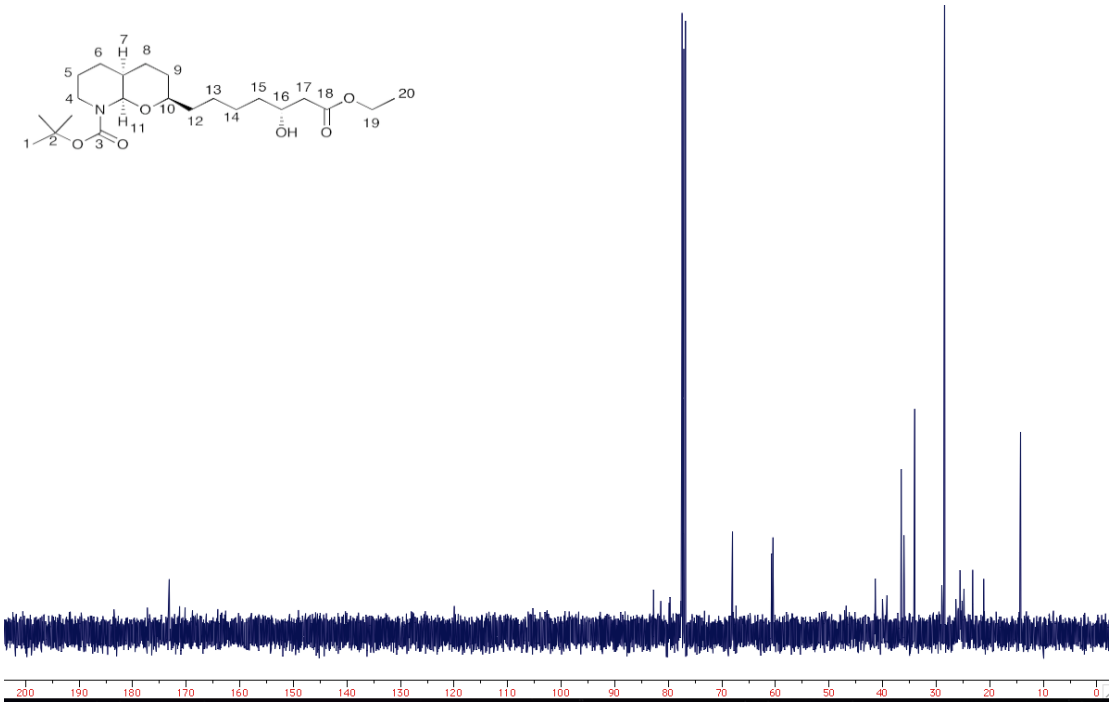
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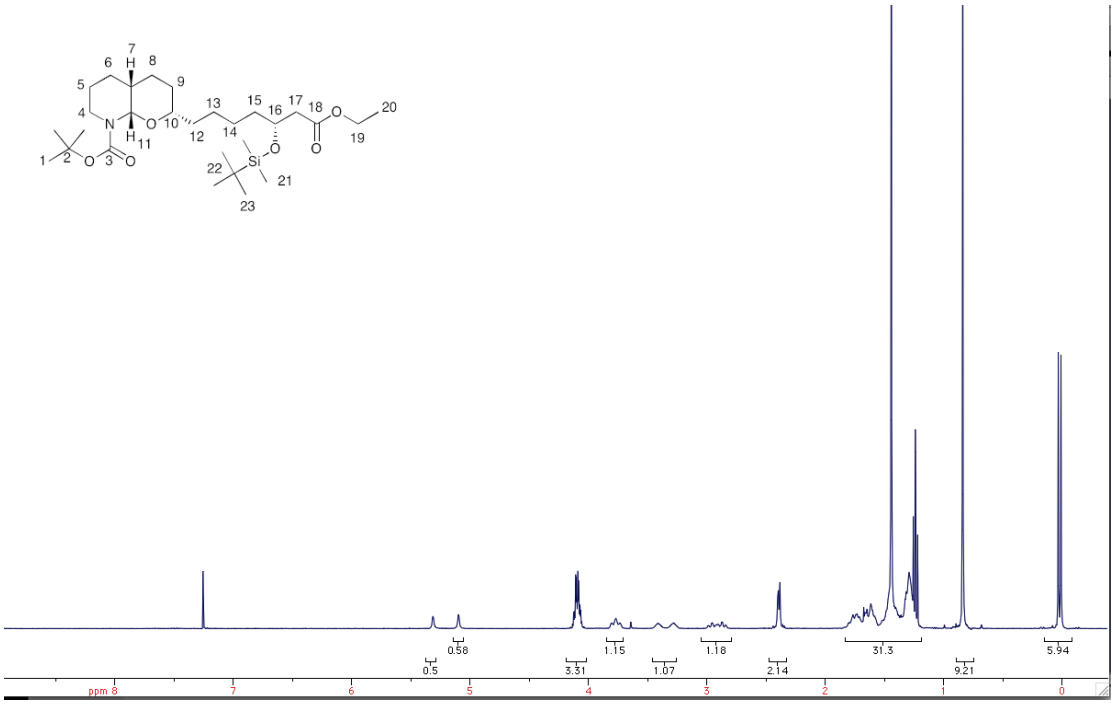
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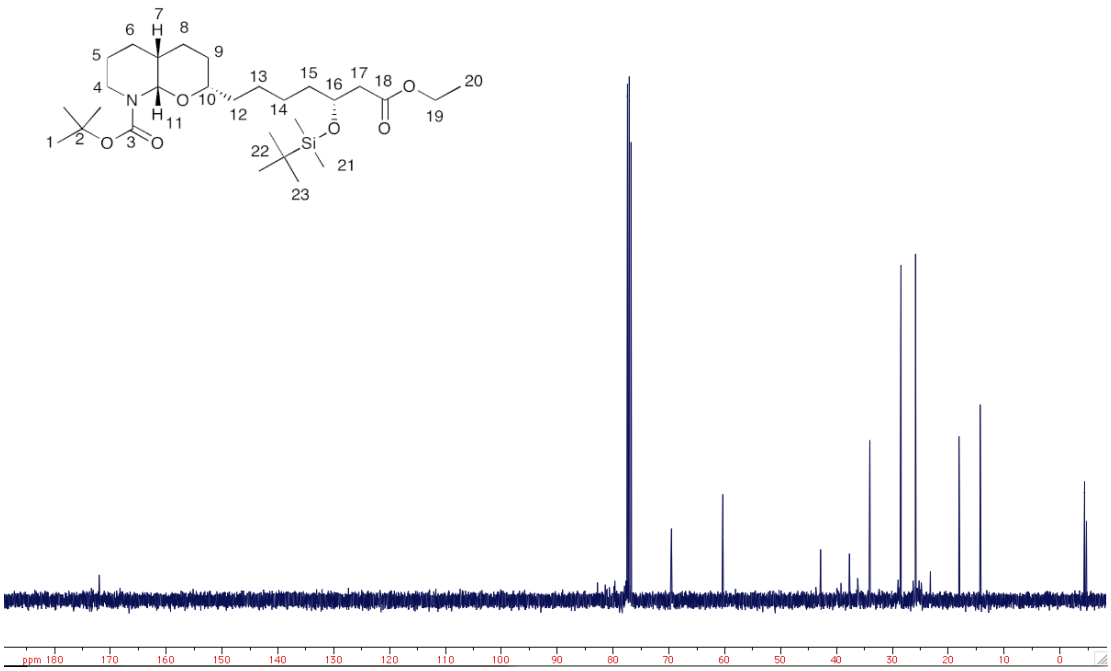
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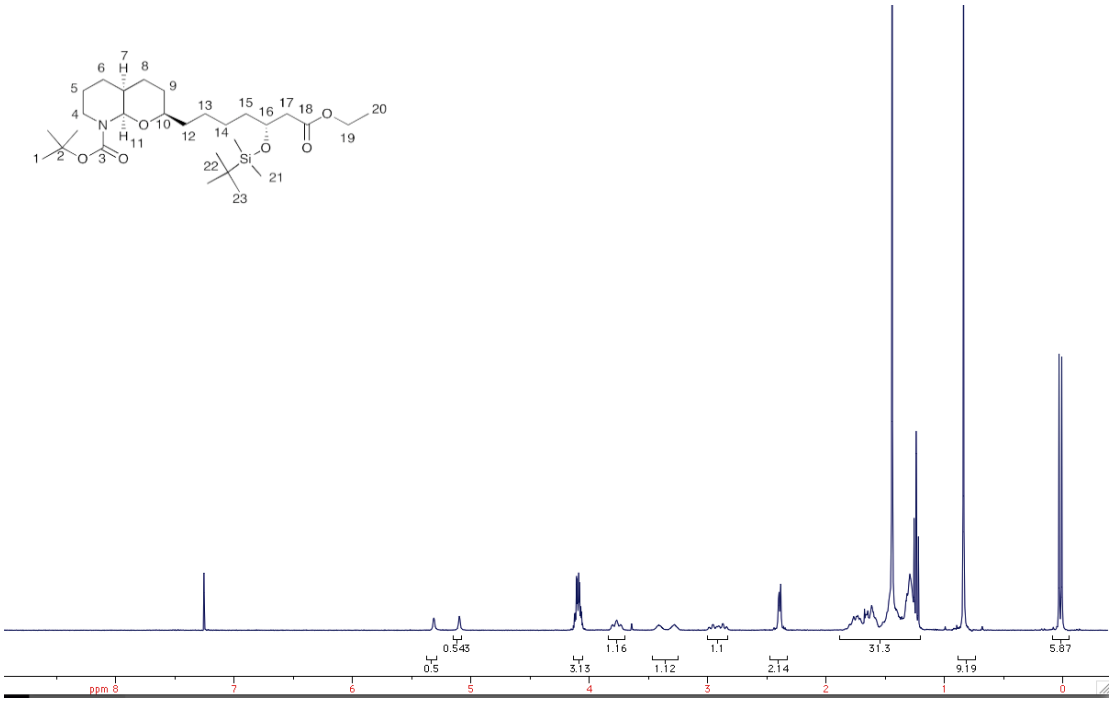
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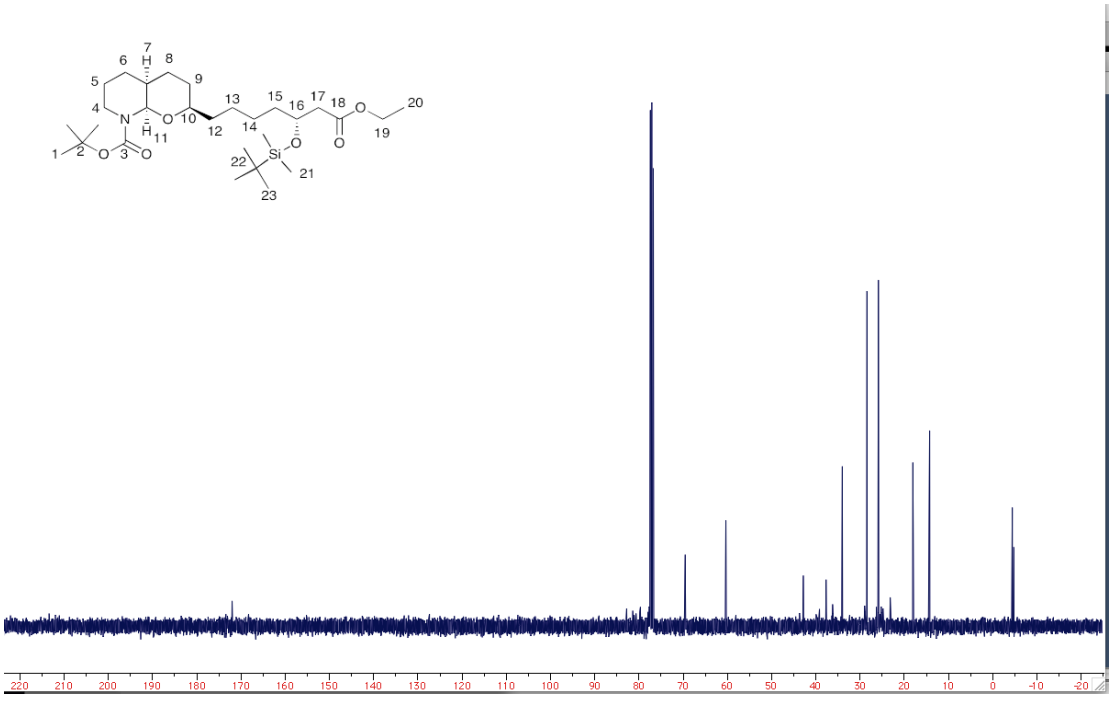
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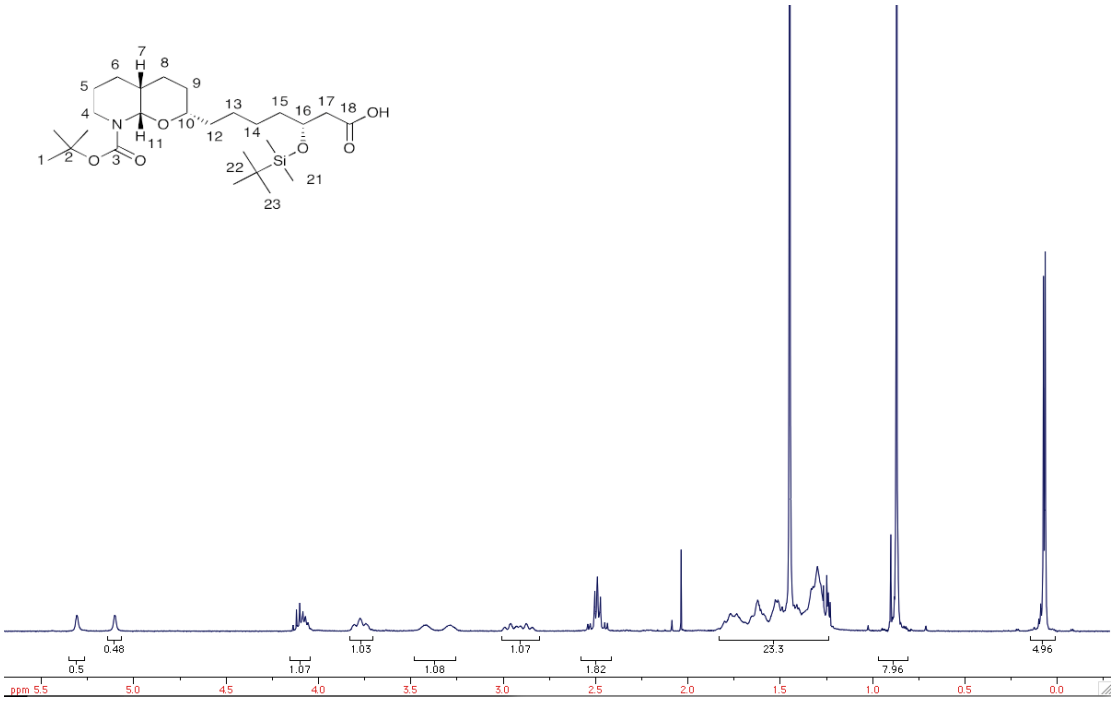
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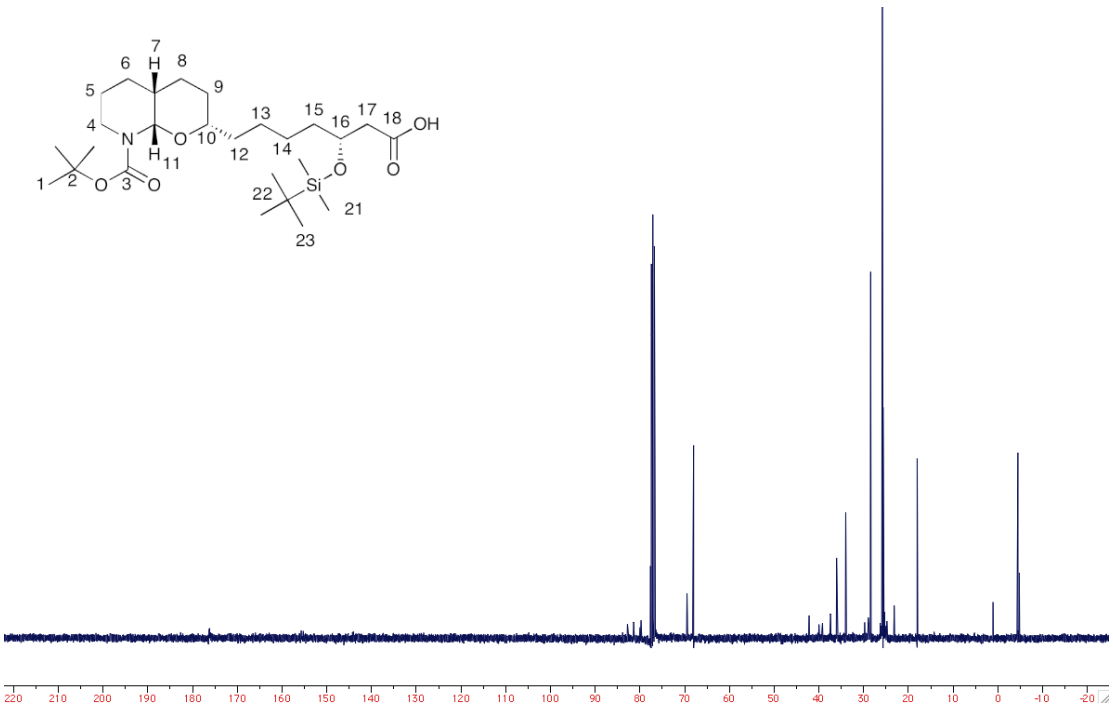
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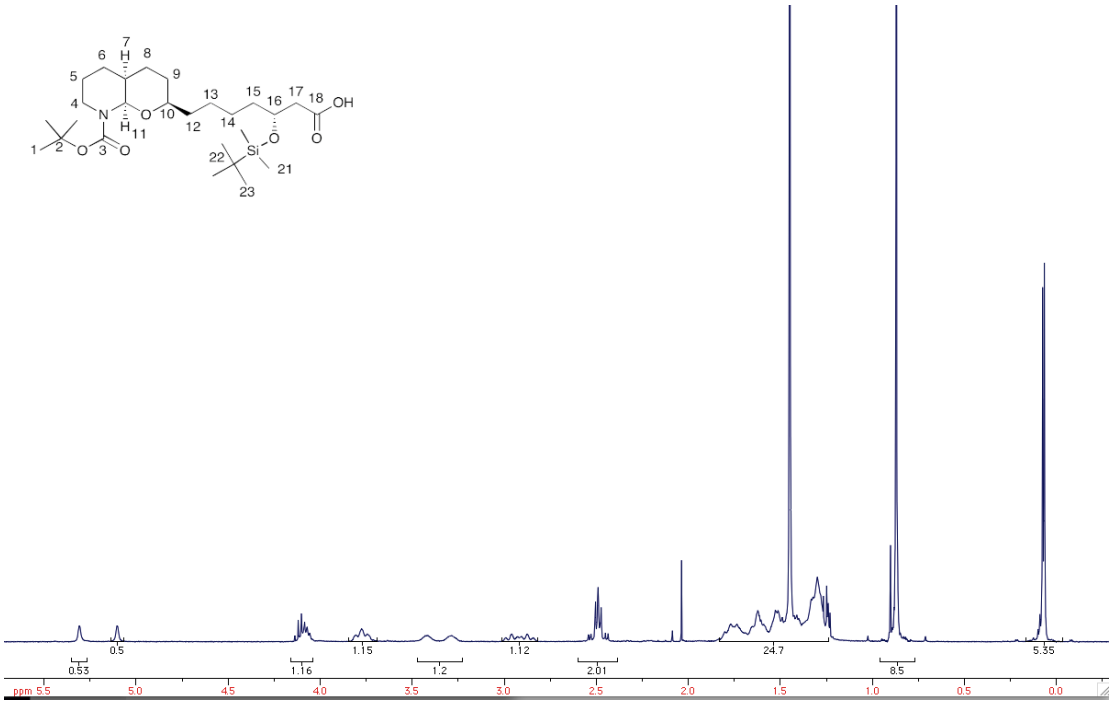
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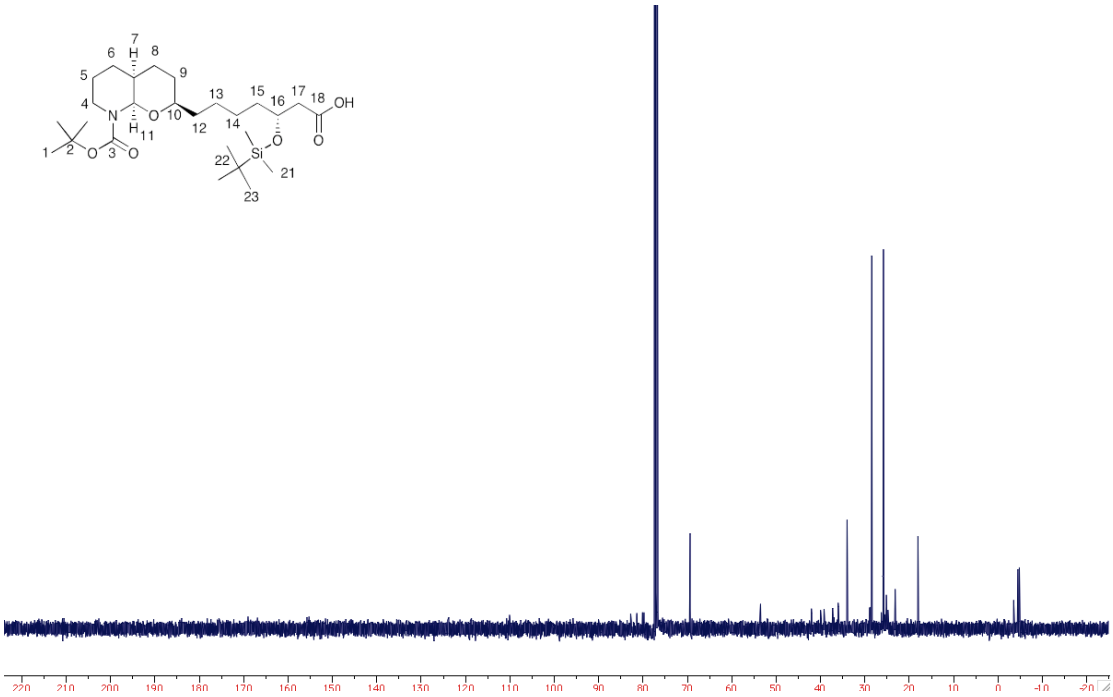
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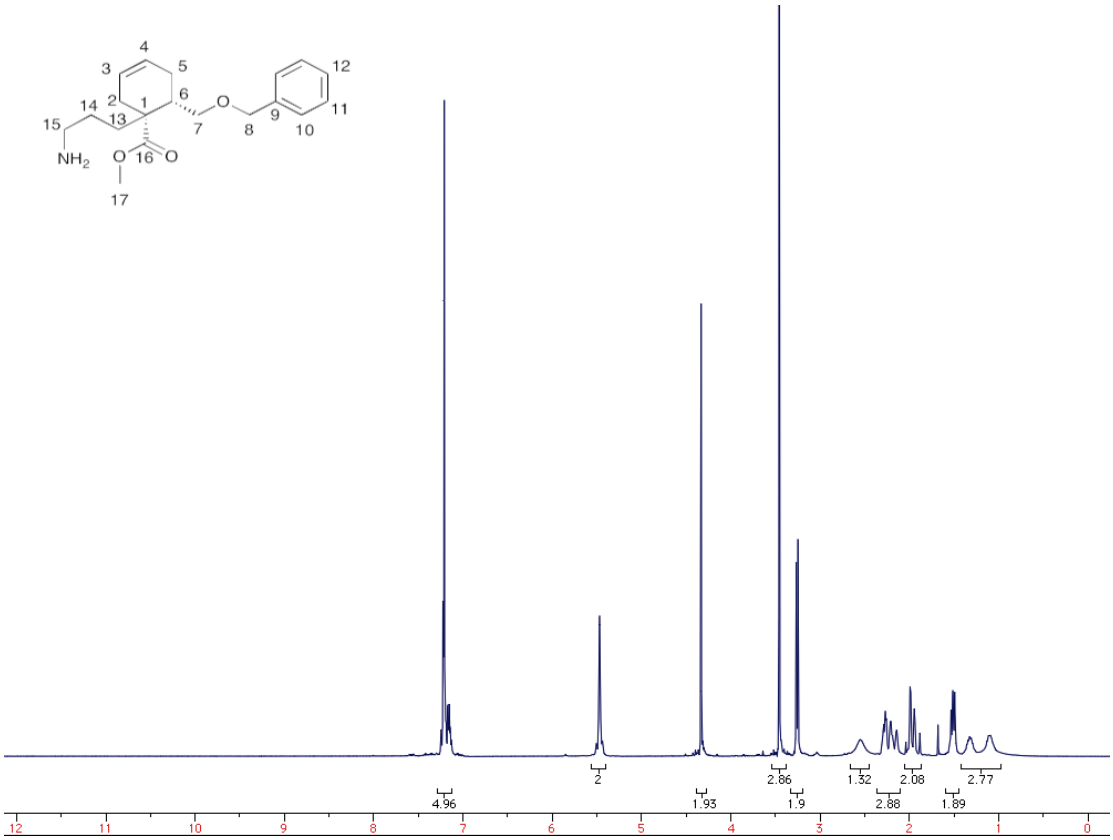
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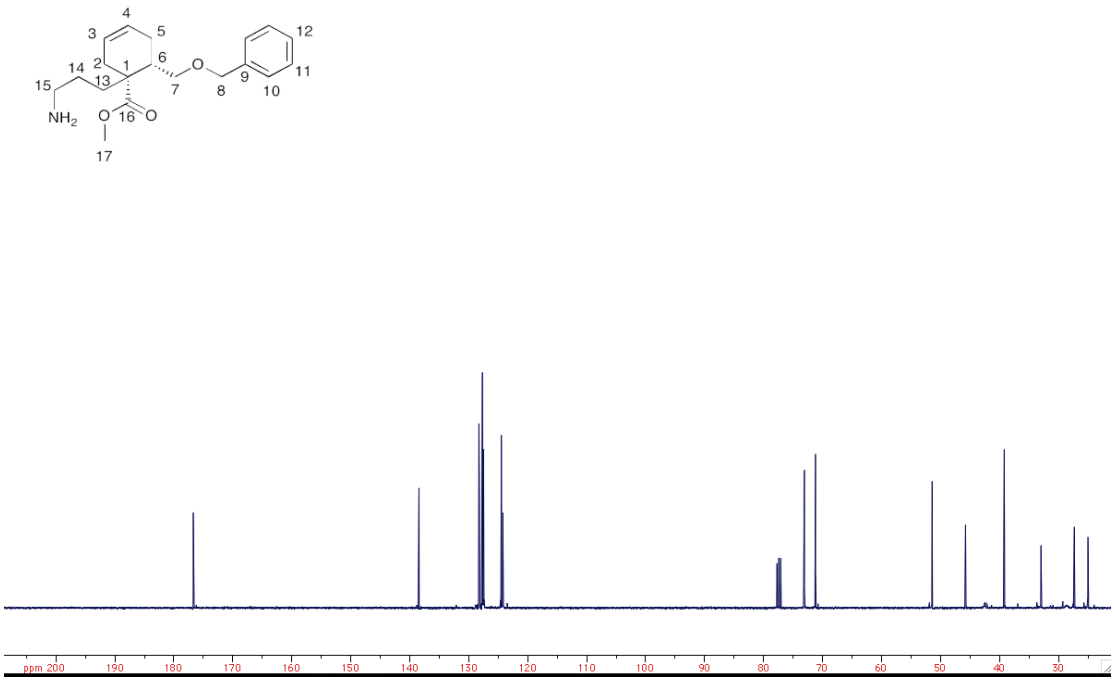

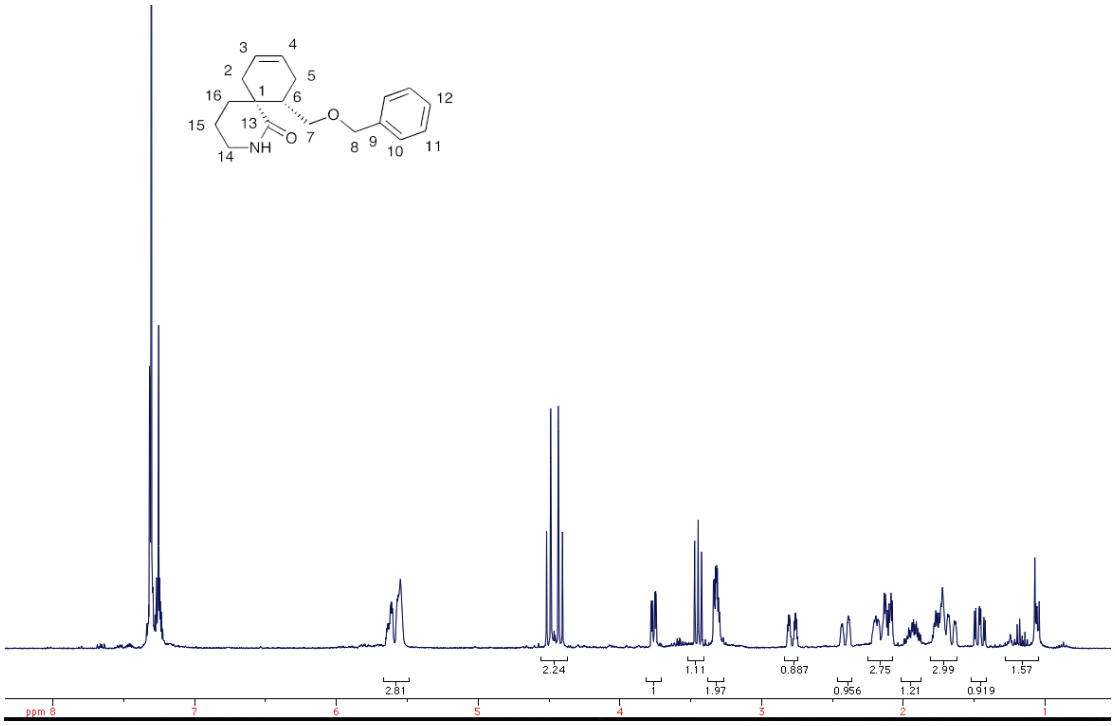
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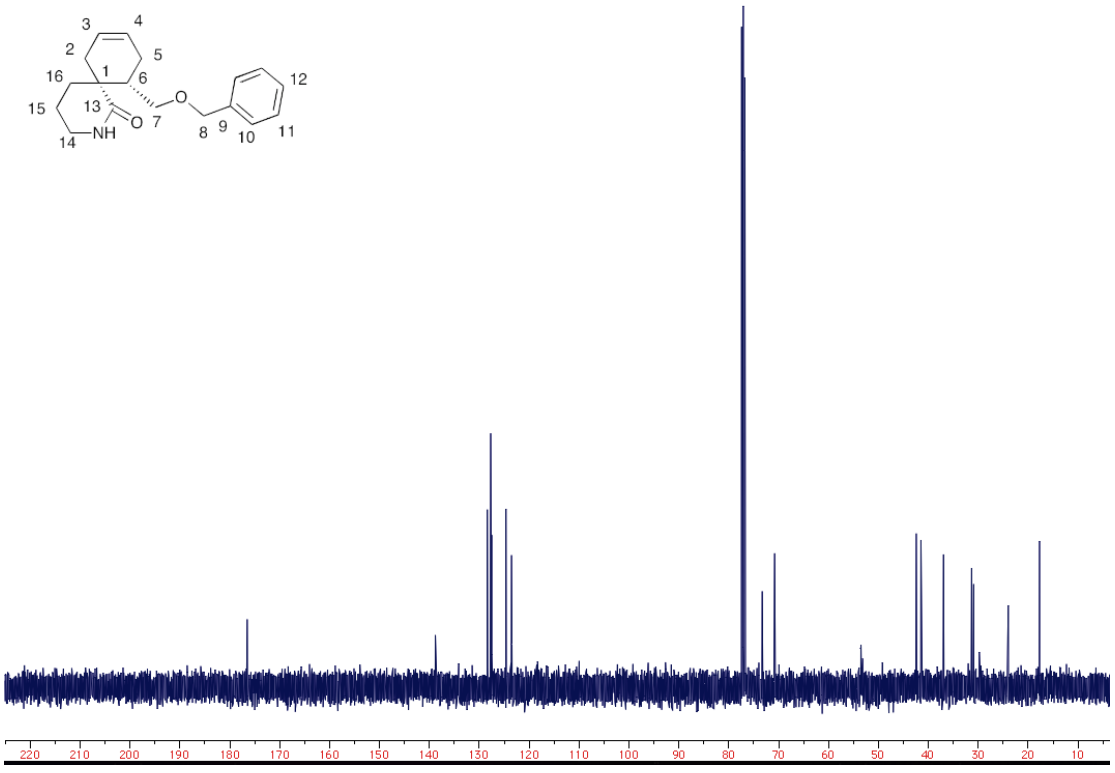
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NH
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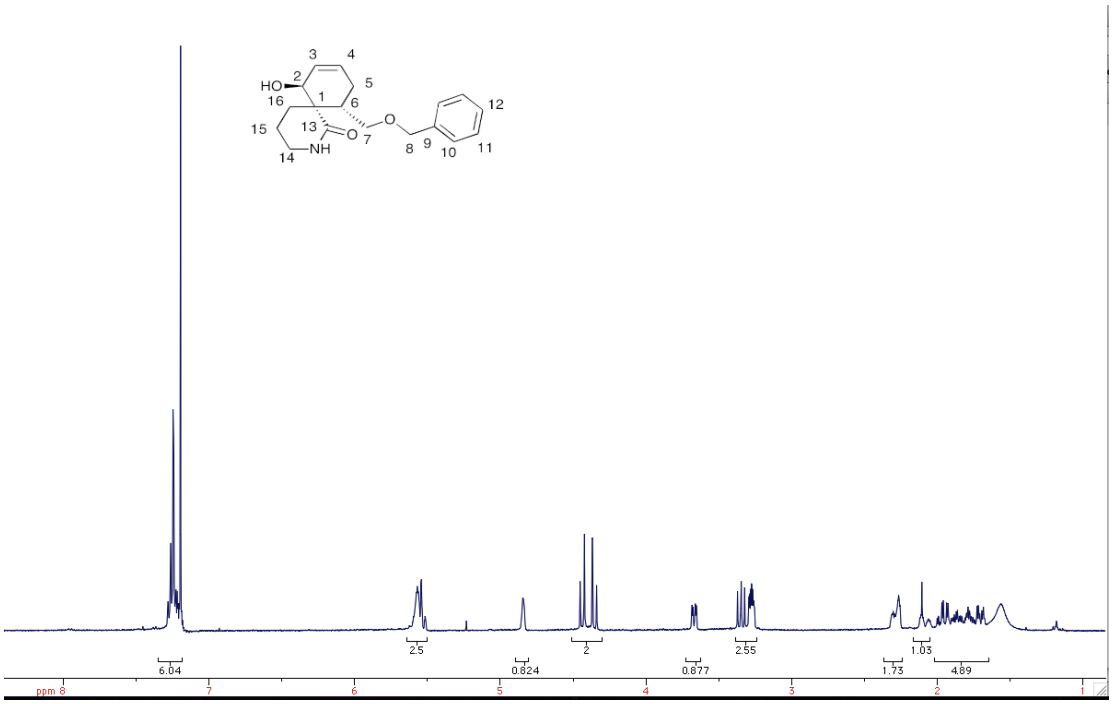
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2
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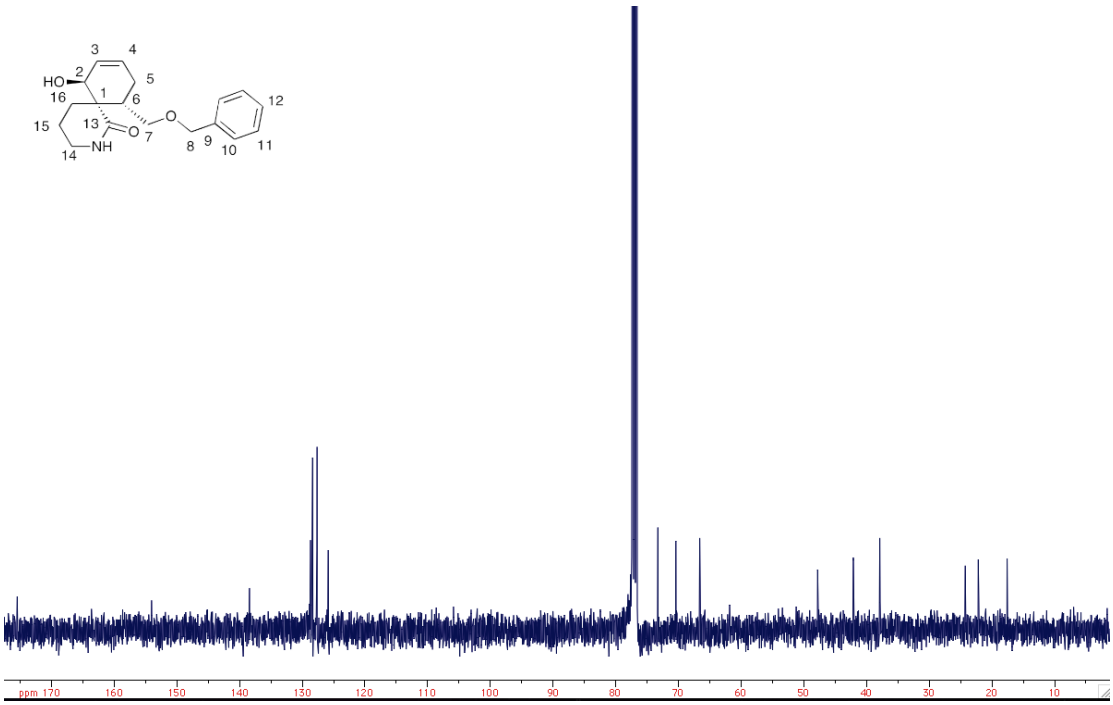
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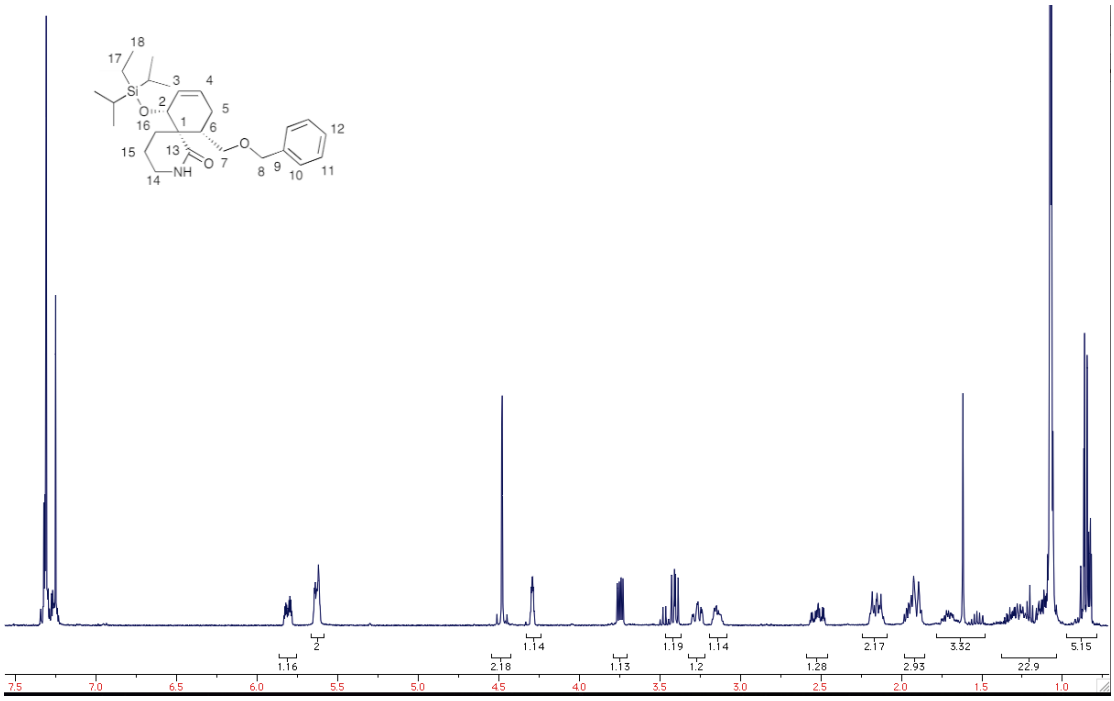
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1.14
1.13
1.19
1.14
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1.28
2.17
2.93
3.32
22.9
5.15
7.5
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3.0
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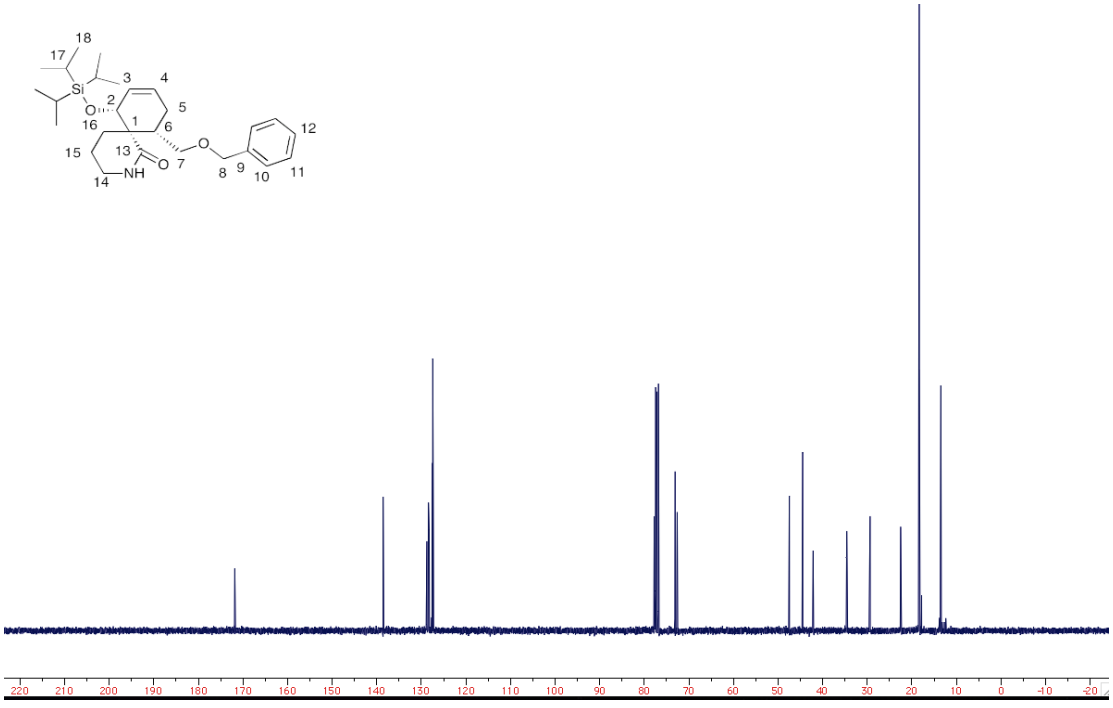
2.0
1.5
1.0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NH
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200
190
180
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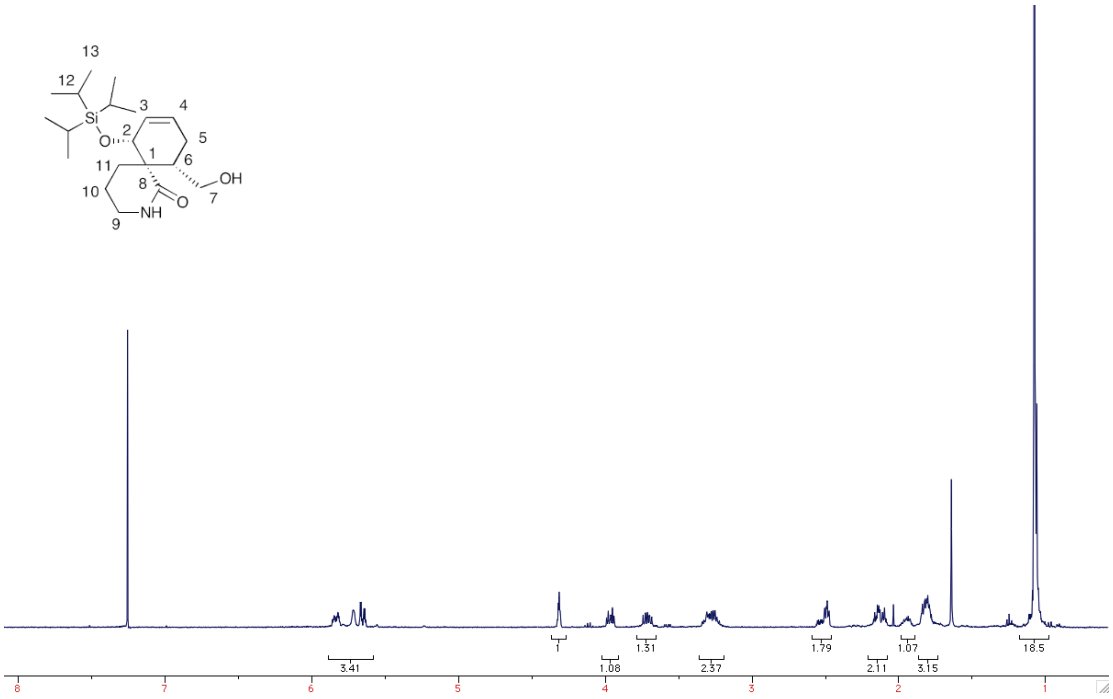
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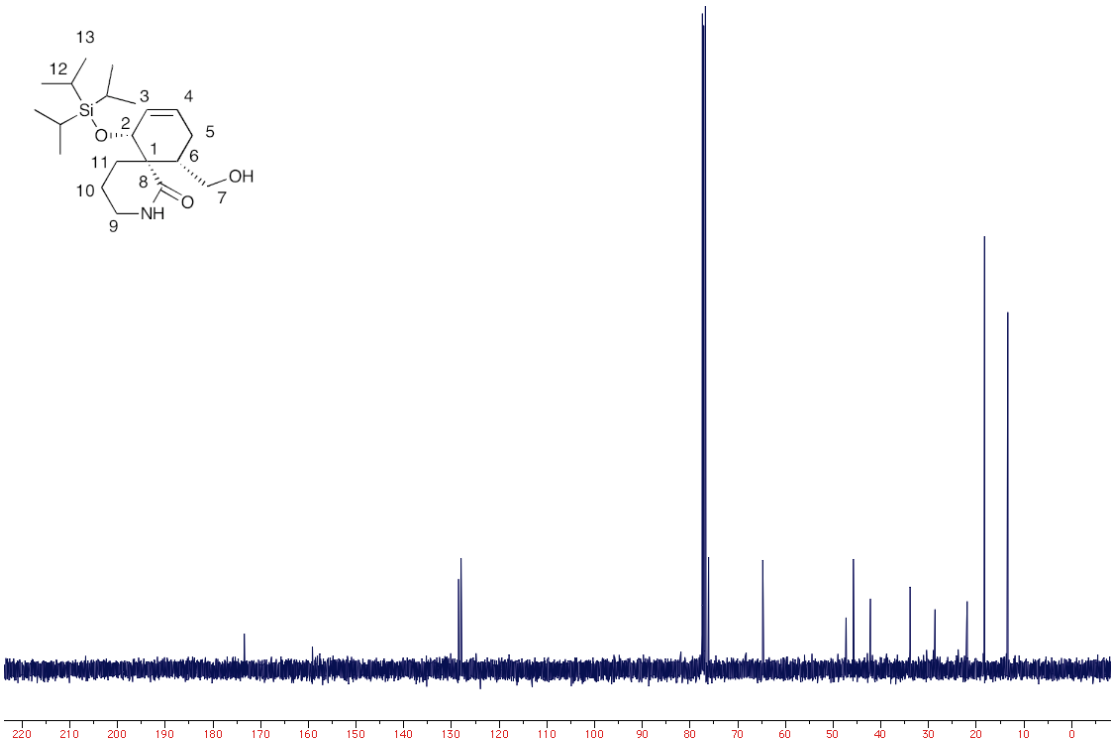
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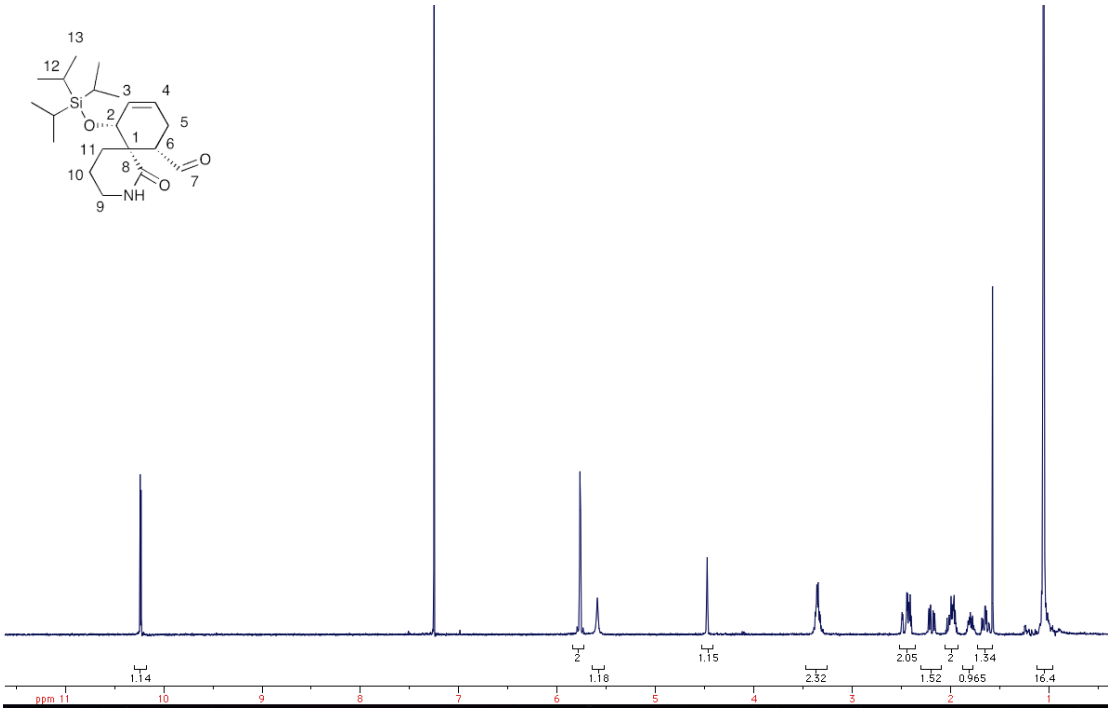
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NH
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2.32
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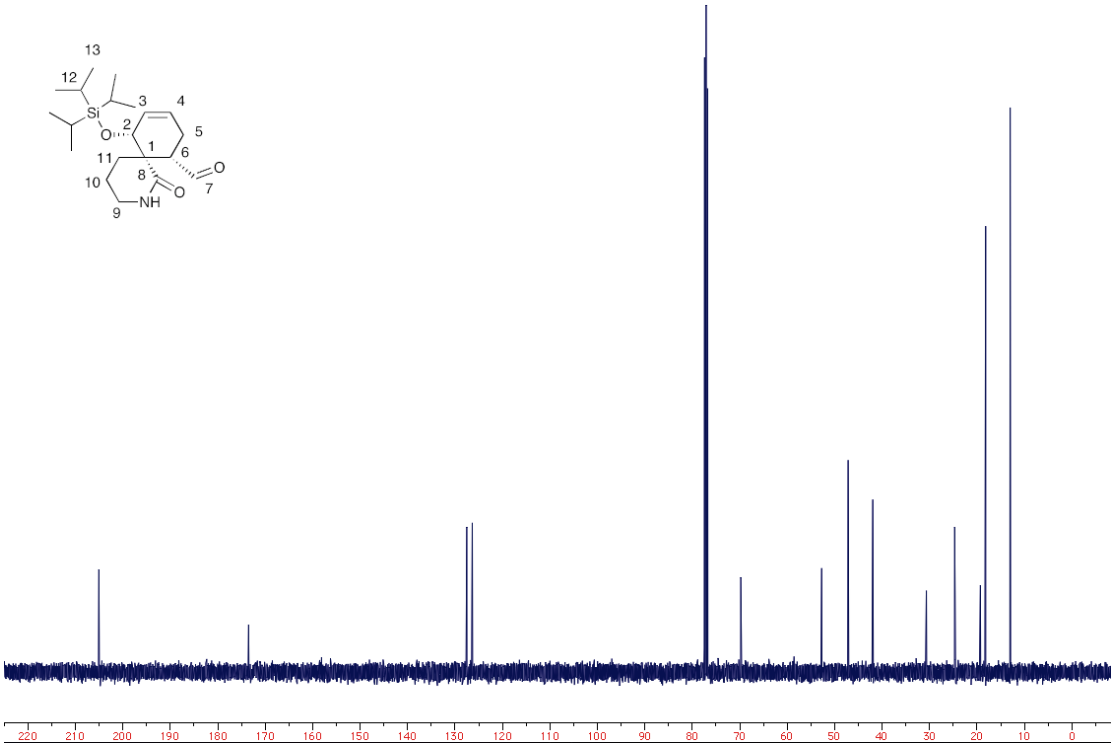
4
3
2
1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NH
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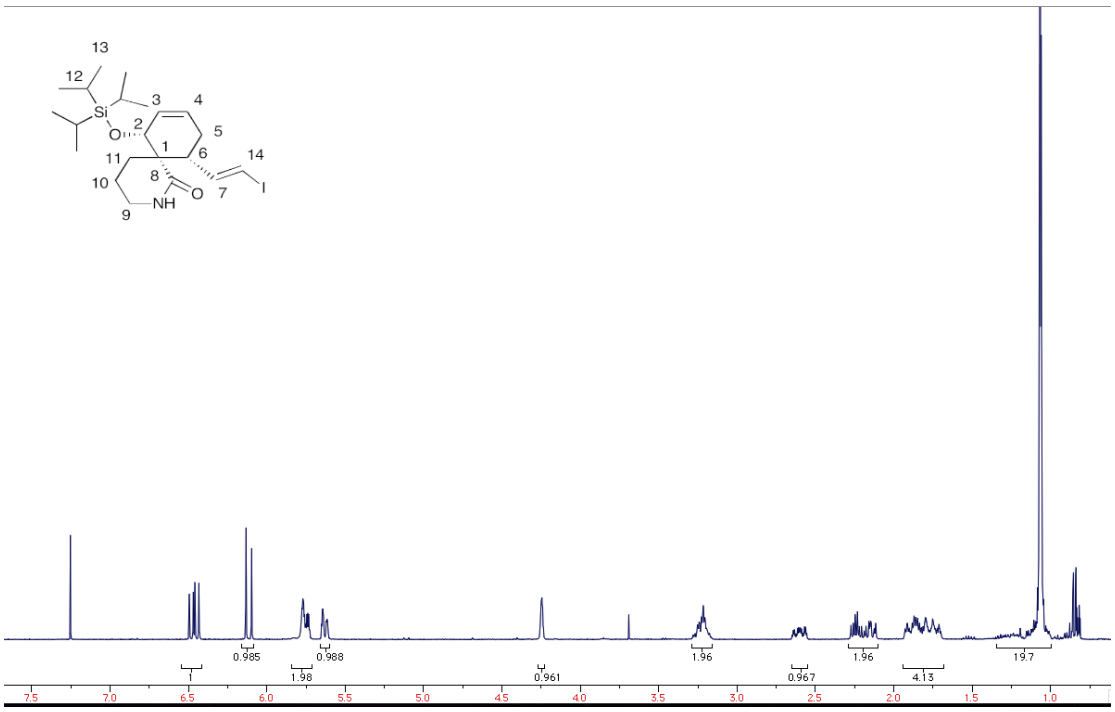
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1.98
0.961
1.96
0.967
1.96
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19.7
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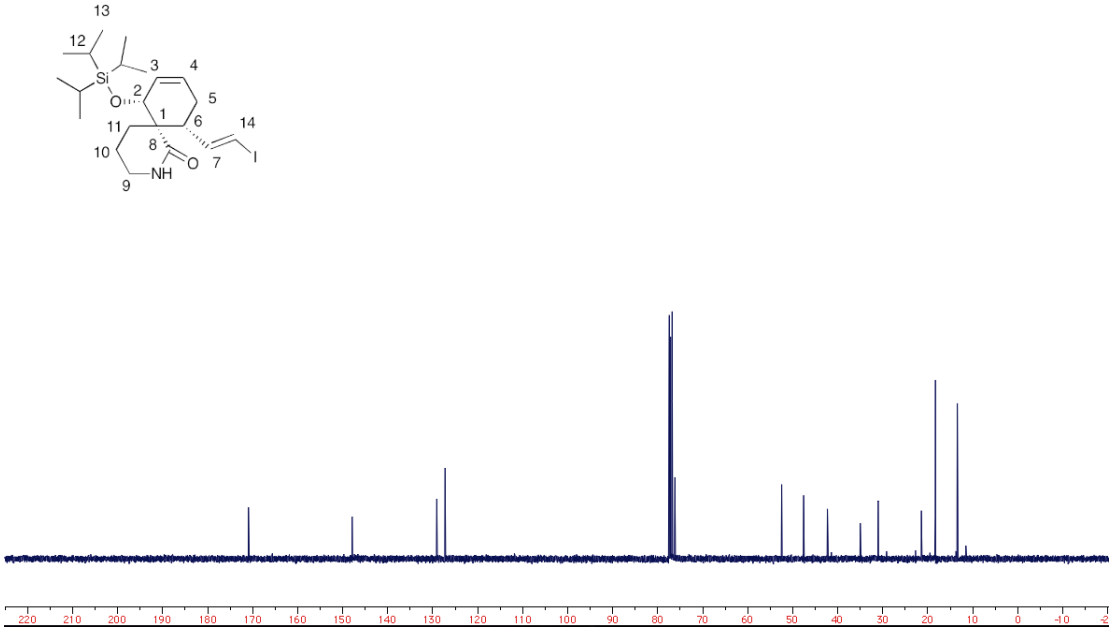
1.0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11
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NH
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200
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180
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40
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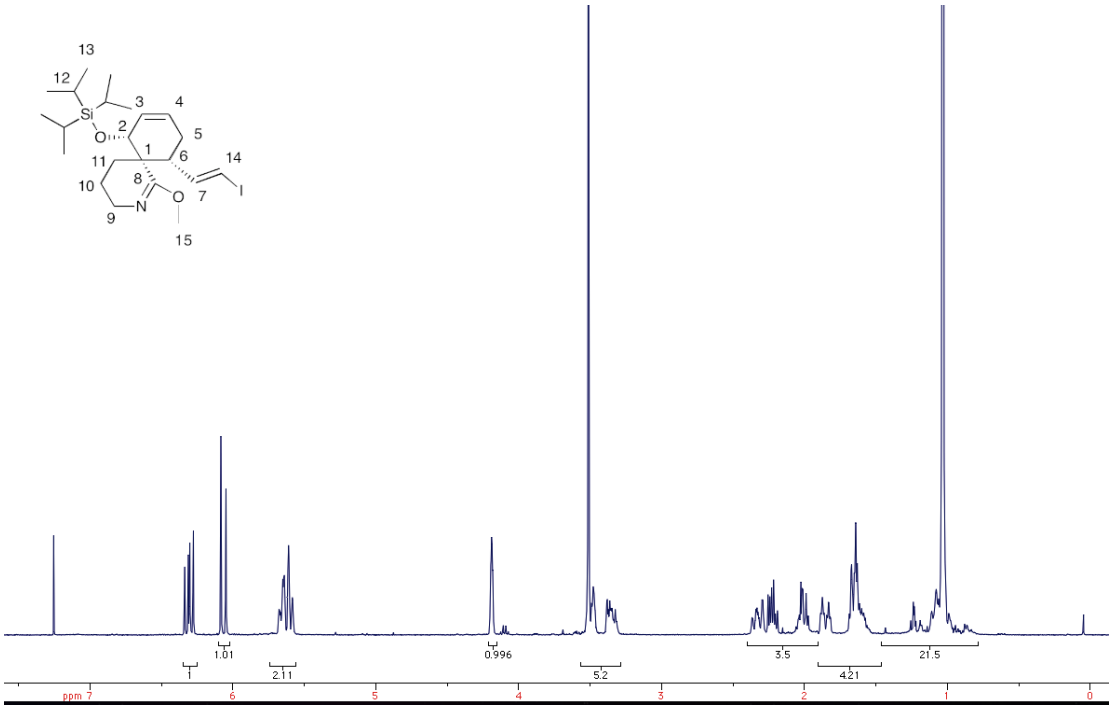
0
-10
-2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10
8
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21.5
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3
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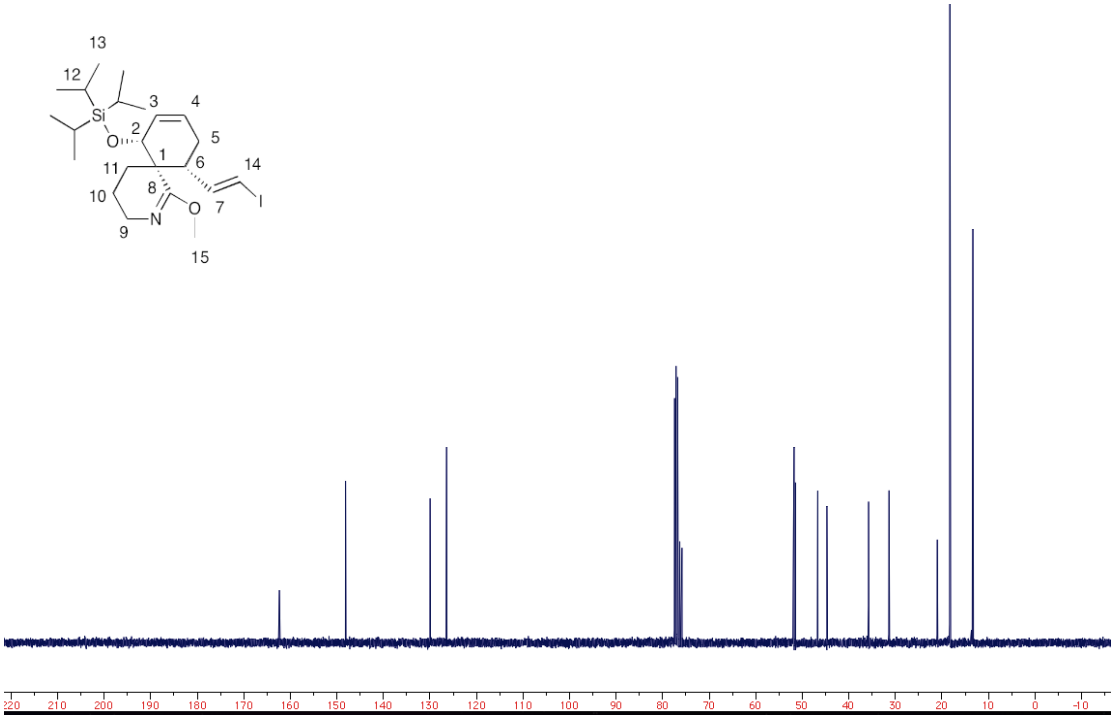
1
0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200
190
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10
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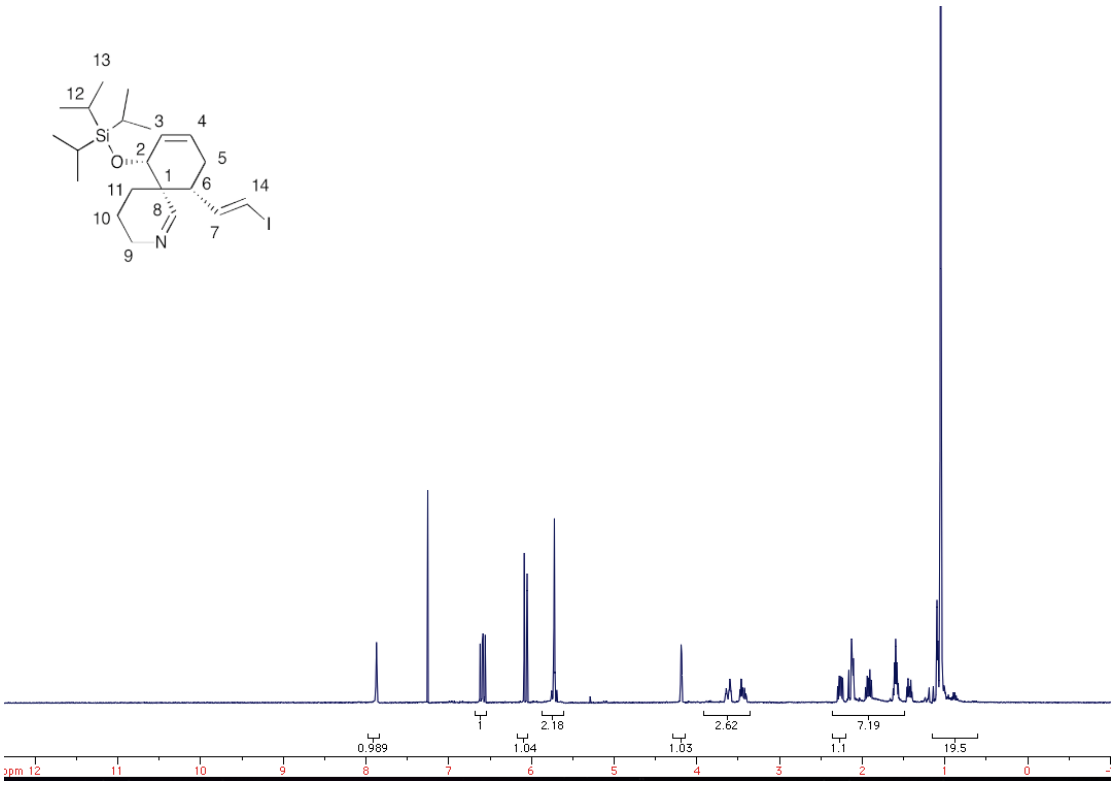
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2.18
1.03
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19.5
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7
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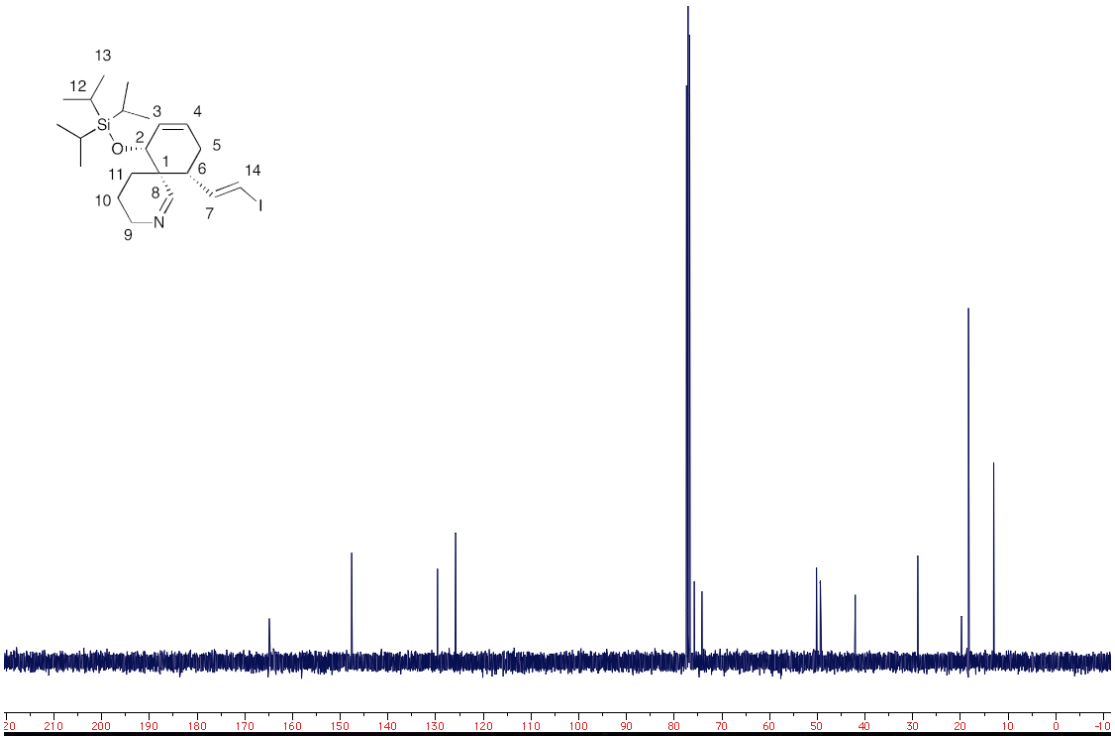
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11
6
14
8
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I
N
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220
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200
190
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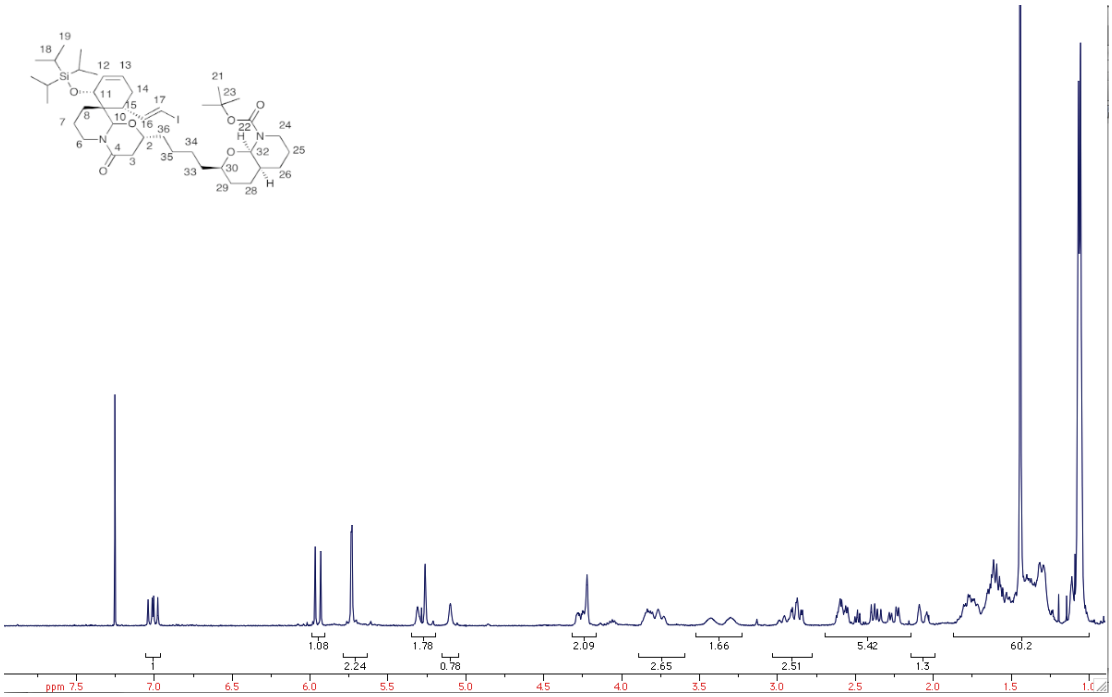
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10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2.09
2.65
1.66
2.51
5.42
1.3
60.2
ppm 7.5
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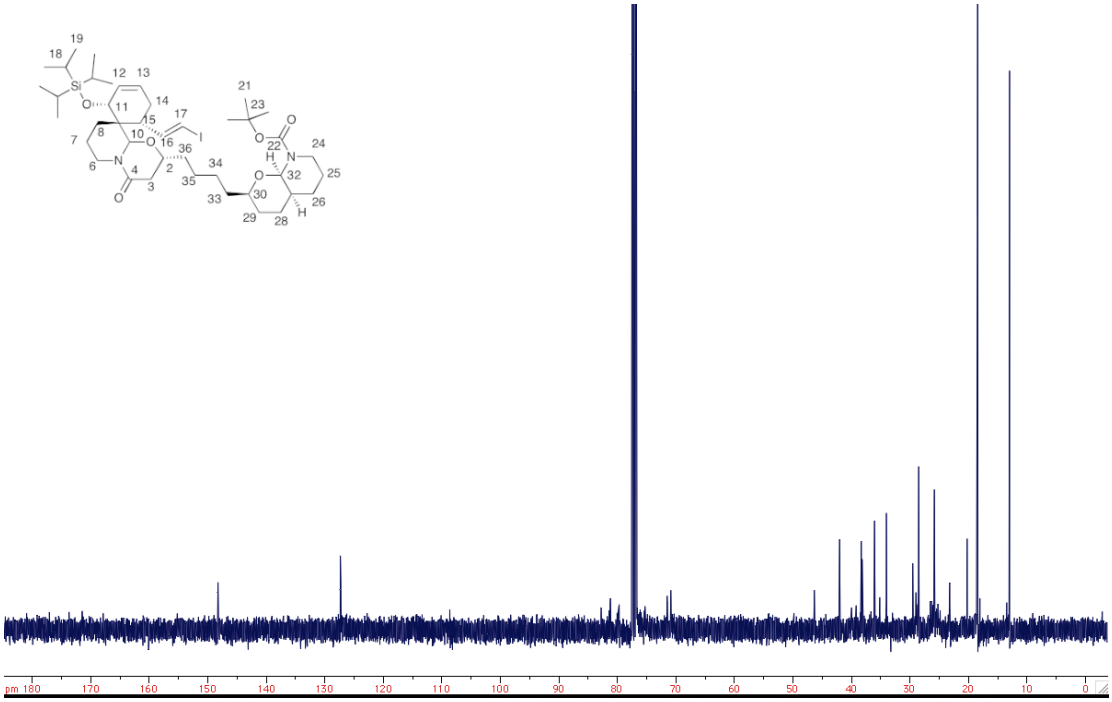
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5


pm 180
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150
140
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120
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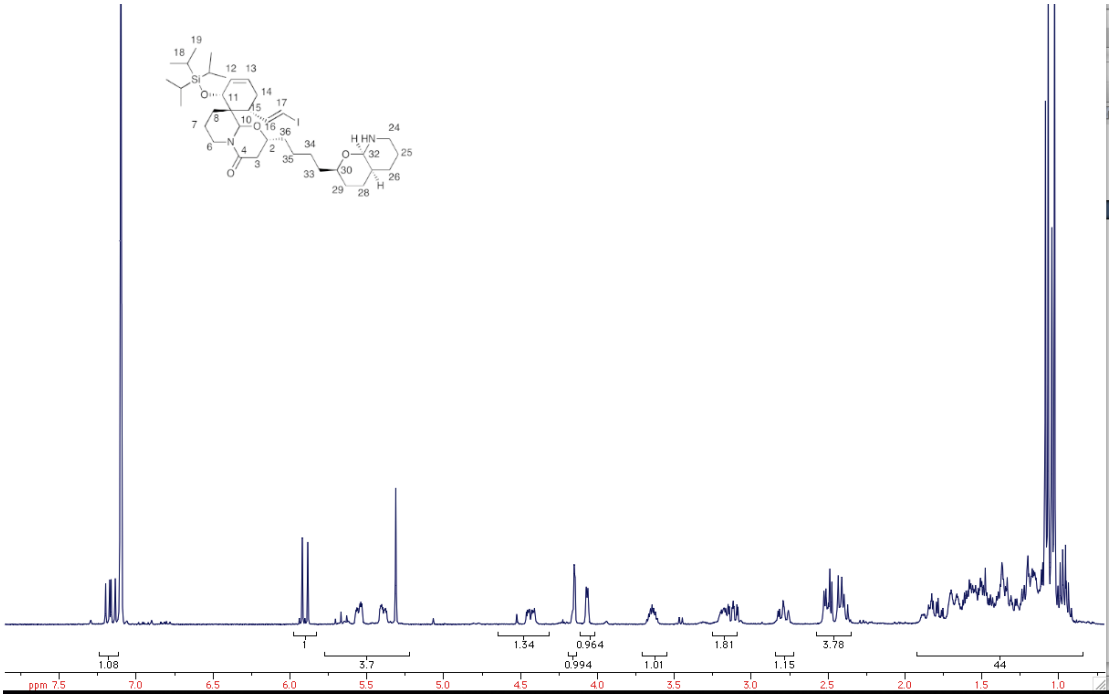
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0.994
1.01
1.81
1.15
3.78
44
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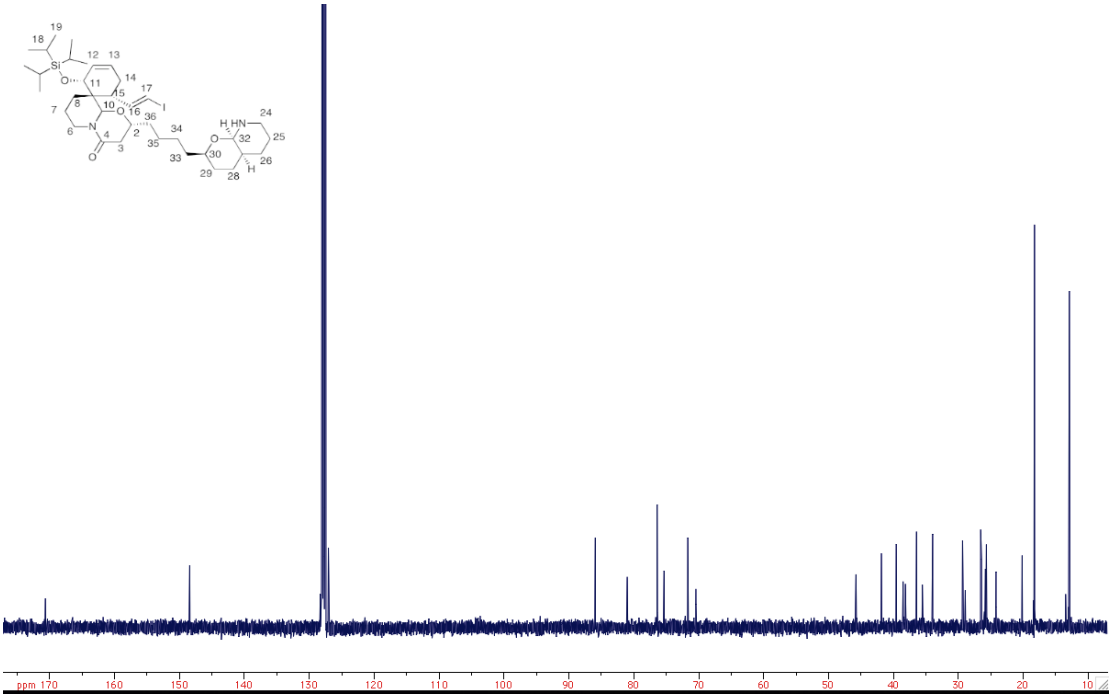
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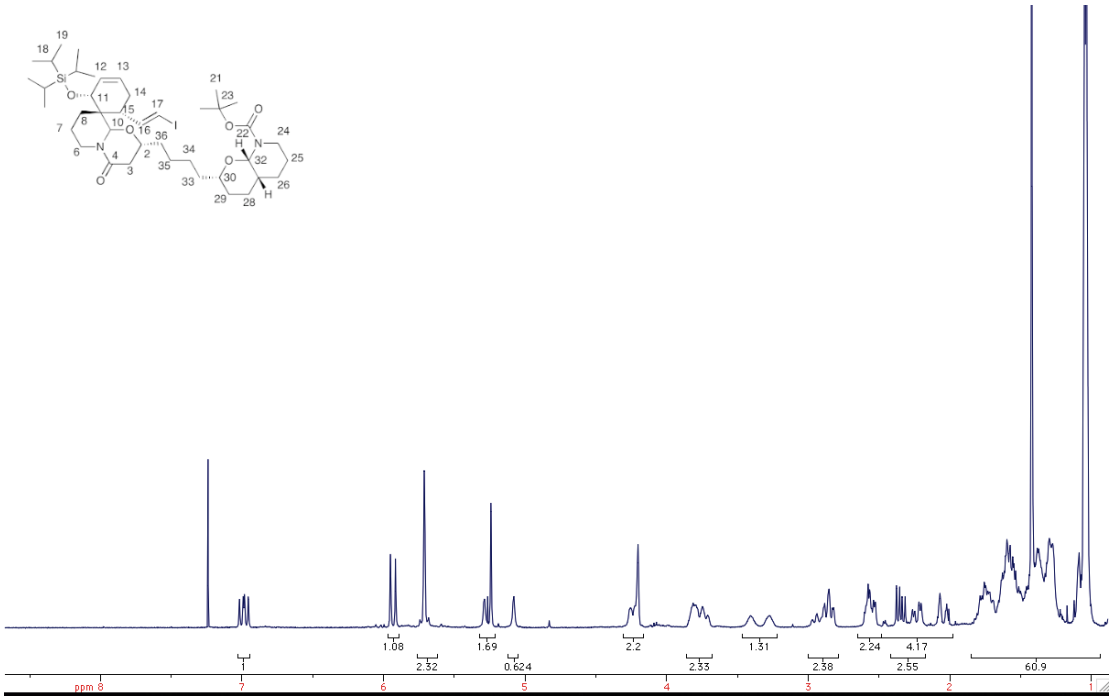
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2.33
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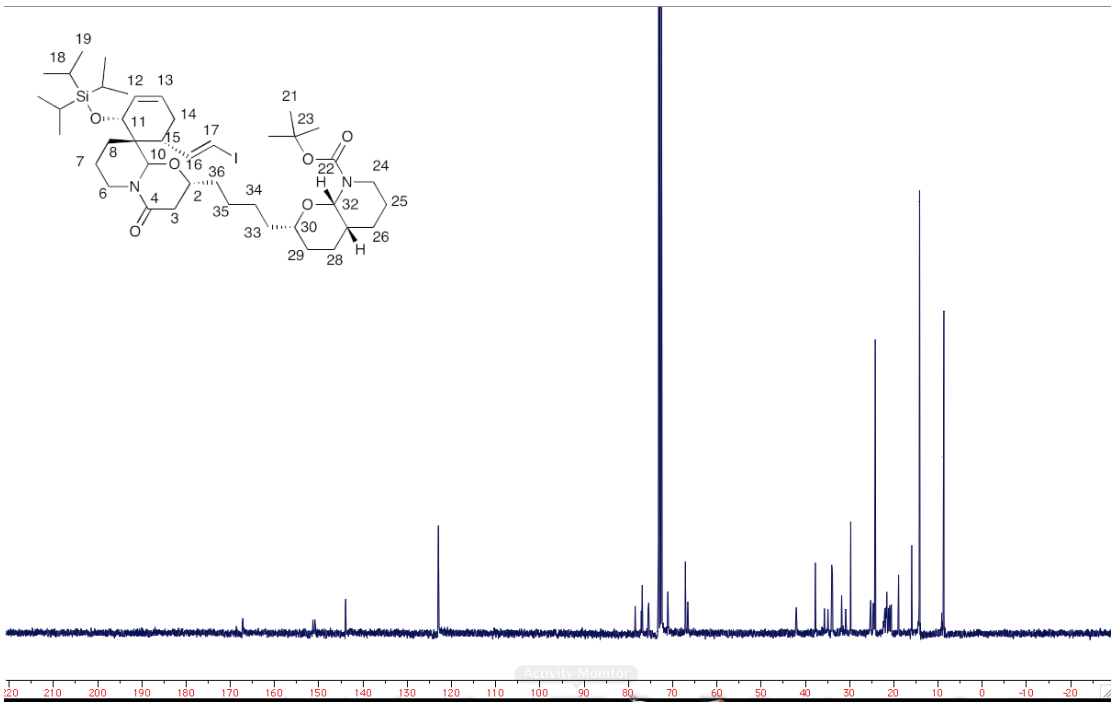
5
4
3
2
1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180
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150
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90
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50
40
30
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10
0
-10
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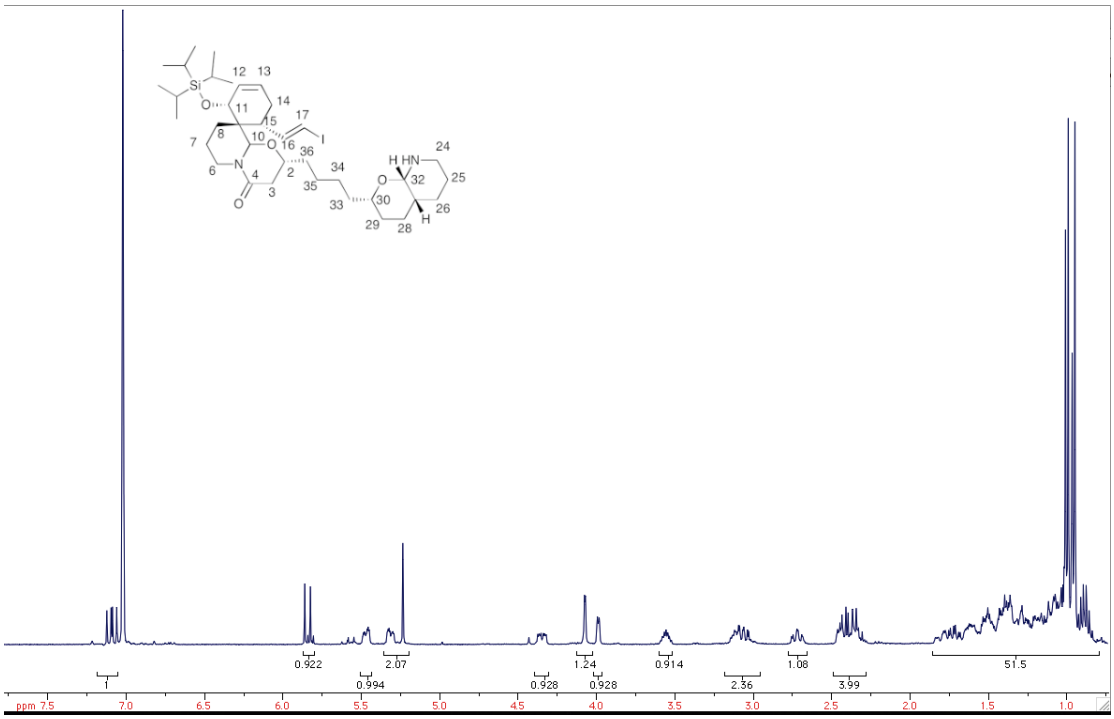
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0.928
0.914
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1.08
3.99
51.5
1
ppm 7.5
7.0
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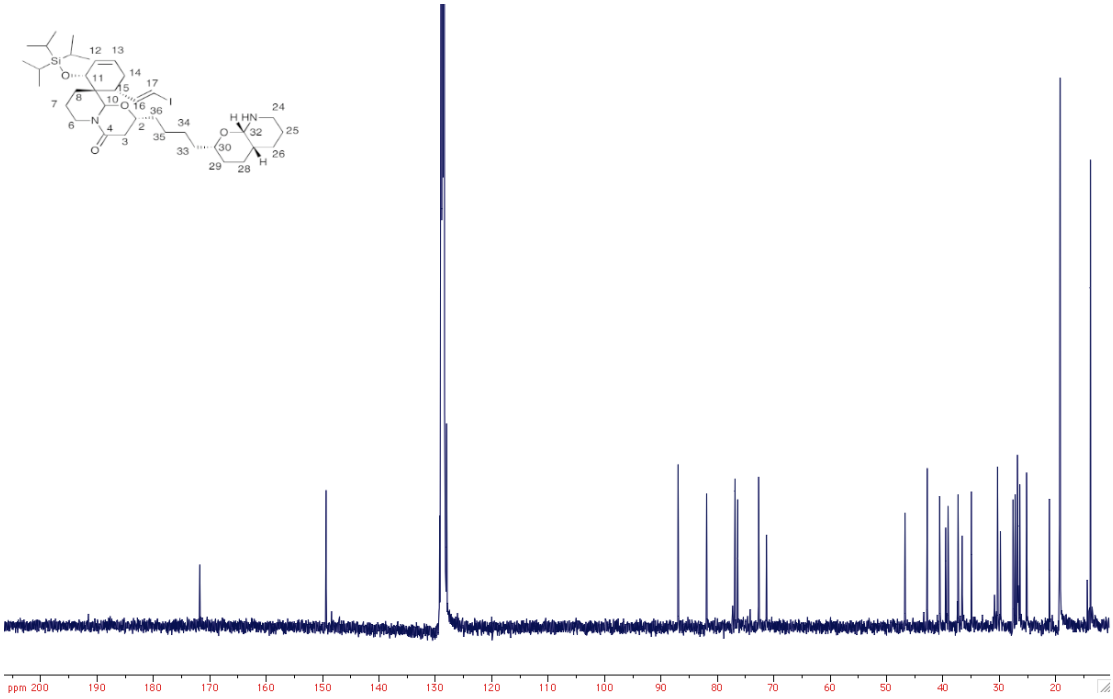
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0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190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

Appendix 3 – Crystal data for (+)-319

rjt1011

Will Unsworth
Crystal Submitted on:

Data Collected on:
16/11/2010
Structure Solved by:
Adrian Whitwood

Table 1: Crystal data and structure refinement for rjt1011

Identification code	rjt1011
Empirical formula	$C_{18}H_{23}NO_3$
Formula weight	301.37
Temperature / K	109.6
Crystal system	triclinic
Space group	P-1
a / Å, b / Å, c / Å	6.6179(4), 10.4551(6), 12.6299(8)
α/°, β/°, γ/°	66.362(6), 84.587(5), 78.614(5)
Volume / Å^3	784.69(8)
Z	2
ρ_{calc} / mg mm^{-3}	1.276
μ / mm^{-1}	0.086
F(000)	324
Crystal size / mm^3	0.1450 × 0.1366 × 0.0743
Theta range for data collection	3.1341 to 59.9252°
Index ranges	-9 ≤ h ≤ 9, -14 ≤ k ≤ 14, -17 ≤ l ≤ 17
Reflections collected	7805
Independent reflections	4152[R(int) = 0.0194]
Data/restraints/parameters	4152/0/207
Goodness-of-fit on F^2	1.064
Final R indexes [I>2σ (I)]	R_1 = 0.0430, wR_2 = 0.0987
Final R indexes [all data]	R_1 = 0.0521, wR_2 = 0.1045
Largest diff. peak/hole / e Å^{-3}	0.411/-0.231

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for rjt1011. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)

C1	-2266.8(17)	-6643.8(12)	-3231.8(9)	13.3(2)
C2	-645.4(18)	-7310.6(13)	-2315.4(10)	15.9(2)
C3	-852.0(18)	-8376.1(13)	-1309(1)	17.1(2)
C4	-2778.1(18)	-9012.5(12)	-932.9(10)	15.8(2)
C5	-4594.3(17)	-8063.5(11)	-1708.5(9)	12.9(2)
C6	-3887.0(17)	-7603.8(11)	-3009.8(9)	12.0(2)
C7	-2996.3(18)	-8905.5(12)	-3299(1)	16.0(2)
C8	-4649(2)	-9766.2(13)	-3215.8(11)	21.0(3)
C9	-6300(2)	-8872.1(14)	-4102.2(12)	24.9(3)
C10	-5777.7(17)	-6755.3(12)	-3751.8(9)	13.3(2)
C11	-5439.3(18)	-6823.9(12)	-1352.4(9)	14.8(2)
C12	-7013(2)	-6311.6(14)	200.7(12)	23.9(3)
C13	-8519(2)	-6726.9(12)	1193.0(11)	19.6(3)
C14	-8371(2)	-6380.0(16)	2132.7(12)	28.9(3)
C15	-9849(3)	-6633.2(19)	3011.3(13)	39.1(4)
C16	-11463(3)	-7263.0(17)	2970.4(14)	41.1(4)
C17	-11609(2)	-7638.7(16)	2054.3(15)	36.3(4)
C18	-10148(2)	-7362.5(14)	1159.3(12)	25.6(3)
N1	-6835.3(16)	-7425.3(12)	-4156.3(9)	18.6(2)
O1	-1242.4(13)	-6386.5(9)	-4328.1(7)	17.27(19)
O2	-6384.0(13)	-5489.2(9)	-3913.2(7)	16.10(18)
O3	-6459.5(13)	-7374.2(9)	-252.4(7)	16.88(19)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for rjt1011. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka \times b \times U_{12}]$

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
C1	10.4(5)	15.9(5)	10.8(5)	-2.8(4)	0.1(4)	-1.5(4)
C2	10.3(5)	22.5(5)	14.6(5)	-7.3(4)	-1.8(4)	-1.4(4)
C3	13.1(5)	22.2(6)	14.1(5)	-6.5(4)	-3.5(4)	1.5(4)
C4	16.3(5)	15.4(5)	11.4(5)	-2.0(4)	-1.9(4)	0.7(4)
C5	12.0(5)	13.4(5)	10.9(5)	-2.9(4)	0.4(4)	-1.4(4)
C6	10.4(5)	13.4(5)	10.2(5)	-3.3(4)	-0.5(4)	-0.3(4)
C7	14.7(5)	16.7(5)	15.8(5)	-7.0(4)	-0.4(4)	0.8(4)
C8	24.5(6)	18.7(5)	22.2(6)	-10.6(5)	-0.7(5)	-3.5(5)
C9	23.7(7)	26.6(6)	30.3(7)	-16.5(6)	-6.1(5)	-3.5(5)
C10	10.3(5)	18.0(5)	9.0(5)	-3.7(4)	1.4(4)	-1.0(4)
C11	16.0(5)	15.5(5)	10.7(5)	-3.4(4)	2.2(4)	-2.5(4)
C12	30.3(7)	20.4(6)	24.8(6)	-13.2(5)	11.7(5)	-9.4(5)
C13	23.9(6)	15.2(5)	17.4(6)	-6.7(4)	5.9(5)	-0.7(4)
C14	31.5(8)	32.3(7)	24.9(7)	-15.8(6)	1.5(6)	-0.9(6)
C15	47.8(10)	45.8(9)	19.8(7)	-15.8(7)	5.9(6)	4.1(8)

C16	46.8(10)	33.2(8)	28.0(8)	-4.6(6)	22.4(7)	0.1(7)
C17	32.3(8)	23.9(7)	46.7(9)	-9.5(6)	17.6(7)	-9.7(6)
C18	30.7(7)	20.1(6)	27.6(7)	-11.6(5)	7.9(5)	-7.0(5)
N1	13.0(5)	24.6(5)	19.1(5)	-10.1(4)	-3.9(4)	-0.1(4)
O1	11.4(4)	22.9(4)	10.1(4)	0.0(3)	-0.1(3)	-0.8(3)
O2	13.9(4)	16.5(4)	13.1(4)	-2.6(3)	-1.2(3)	1.6(3)
O3	22.0(4)	15.0(4)	12.6(4)	-5.7(3)	6.1(3)	-3.2(3)

Table 4 Bond Lengths for rjt1011.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C2	1.5063(15)	C9	N1	1.4589(17)
C1	C6	1.5422(16)	C10	N1	1.3377(16)
C1	O1	1.4302(13)	C10	O2	1.2427(14)
C2	C3	1.3294(16)	C11	O3	1.4327(13)
C3	C4	1.5034(17)	C12	C13	1.5007(17)
C4	C5	1.5364(15)	C12	O3	1.4160(16)
C5	C6	1.5689(15)	C13	C14	1.390(2)
C5	C11	1.5259(17)	C13	C18	1.3852(19)
C6	C7	1.5408(17)	C14	C15	1.386(2)
C6	C10	1.5320(15)	C15	C16	1.376(3)
C7	C8	1.5195(17)	C16	C17	1.380(3)
C8	C9	1.5195(18)	C17	C18	1.3924(19)

Table 5 Bond Angles for rjt1011.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C1	C6	C5	107.95(9)	C13	C18	C17	120.10(14)
C2	C1	C6	110.78(9)	C14	C13	C12	119.52(12)
C2	C3	C4	123.64(10)	C15	C14	C13	120.78(15)
C3	C2	C1	124.20(11)	C15	C16	C17	119.95(14)
C3	C4	C5	111.04(9)	C16	C15	C14	119.92(15)
C4	C5	C6	109.44(9)	C16	C17	C18	120.31(15)
C7	C6	C1	110.94(9)	C18	C13	C12	121.40(12)
C7	C6	C5	111.12(9)	C18	C13	C14	118.92(13)
C7	C8	C9	109.66(10)	N1	C9	C8	111.86(11)
C8	C7	C6	111.25(10)	N1	C10	C6	118.80(10)
C10	C6	C1	109.46(9)	O1	C1	C2	107.65(9)
C10	C6	C5	107.72(9)	O1	C1	C6	112.13(10)
C10	C6	C7	109.57(10)	O2	C10	C6	120.27(11)
C10	N1	C9	128.17(11)	O2	C10	N1	120.79(10)
C11	C5	C4	109.20(10)	O3	C11	C5	107.67(9)

C11	C5	C6	113.96(9)	O3	C12	C13	111.36(10)
C12	O3	C11	110.15(9)				

Table 6 Hydrogen Bonds for rjt1011.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	H1A	O1[1]	0.896(17)	2.066(17)	2.9005(13)	154.5(15)
O1	H1B	O2[2]	0.888(19)	1.797(19)	2.6825(11)	174.9(18)

[1]-1+X,+Y,+Z; [2]-1-X,-1-Y,-1-Z

Table 7 Torsion Angles for rjt1011.

A	B	C	D	Angle/°
C1	C2	C3	C4	-2.8(2)
C1	C6	C7	C8	-173.45(9)
C1	C6	C10	N1	146.79(11)
C1	C6	C10	O2	-37.54(14)
C2	C1	C6	C5	48.65(12)
C2	C1	C6	C7	-73.33(12)
C2	C1	C6	C10	165.63(10)
C2	C3	C4	C5	-13.53(17)
C3	C4	C5	C6	47.12(13)
C3	C4	C5	C11	-78.25(12)
C4	C5	C6	C1	-66.06(11)
C4	C5	C6	C7	55.80(12)
C4	C5	C6	C10	175.83(9)
C4	C5	C11	O3	-70.78(11)
C5	C6	C7	C8	66.45(12)
C5	C6	C10	N1	-96.08(12)
C5	C6	C10	O2	79.59(12)
C5	C11	O3	C12	171.49(10)
C6	C1	C2	C3	-16.01(17)
C6	C5	C11	O3	166.52(9)
C6	C7	C8	C9	62.75(13)
C6	C10	N1	C9	-7.91(18)
C7	C6	C10	N1	24.92(14)
C7	C6	C10	O2	-159.41(10)
C7	C8	C9	N1	-42.41(15)
C8	C9	N1	C10	16.65(19)
C10	C6	C7	C8	-52.47(12)
C11	C5	C6	C1	56.52(12)

C11	C5	C6	C7	178.38(9)
C11	C5	C6	C10	-61.59(12)
C12	C13	C14	C15	174.05(13)
C12	C13	C18	C17	-175.16(13)
C13	C12	O3	C11	166.02(10)
C13	C14	C15	C16	1.4(2)
C14	C13	C18	C17	0.3(2)
C14	C15	C16	C17	-0.1(2)
C15	C16	C17	C18	-1.1(2)
C16	C17	C18	C13	1.0(2)
C18	C13	C14	C15	-1.5(2)
O1	C1	C2	C3	-138.95(12)
O1	C1	C6	C5	168.94(8)
O1	C1	C6	C7	46.97(12)
O1	C1	C6	C10	-74.07(11)
O2	C10	N1	C9	176.44(12)
O3	C12	C13	C14	142.46(13)
O3	C12	C13	C18	-42.12(17)

Table 8 Hydrogen Atom Coordinates (Å×10⁴) and Isotropic Displacement Parameters (Å²×10³) for rjt1011.

Atom	*x*	*y*	*z*	U(eq)
H1	-2973	-5715	-3212	16
H2	605	-6946	-2466	19
H3	280	-8757	-799	21
H4A	-3125	-9135	-122	19
H4B	-2533	-9960	-968	19
H5	-5707	-8637	-1575	15
H7B	-2397	-8587	-4091	19
H7A	-1879	-9511	-2756	19
H8A	-5275	-10071	-2430	25
H8B	-4025	-10625	-3359	25
H9A	-5799	-8848	-4873	30
H9B	-7549	-9316	-3900	30
H11A	-4301	-6368	-1295	18
H11B	-6422	-6107	-1933	18
H12B	-7633	-5412	-416	29
H12A	-5759	-6151	465	29
H14	-7242	-5964	2173	35
H15	-9748	-6372	3641	47

H16	-12477	-7439	3573	49
H17	-12712	-8088	2034	44
H18	-10267	-7610	525	31
H1A	-8080.0(3)	-6938(17)	-4432(14)	28(4)
H1B	-2070.0(3)	-5750.0(2)	-4880(16)	41(5)

Crystal Data. $C_{18}H_{23}NO_3$, M =301.37, triclinic, a = 6.6179(4) Å, b = 10.4551(6) Å, c = 12.6299(8) Å, α = 66.362(6)°, β = 84.587(5)°, γ = 78.614(5)°, U = 784.69(8) Å^3, T = 109.6, space group P-1 (no. 2), Z = 2, μ(Mo Kα) = 0.086, 7805 reflections measured, 4152 unique (R_{int} = 0.0194) which were used in all calculations. The final $wR(F_2)$ was 0.1045 (all data)

Abbreviations

Ac	Acetyl
AIBN	Azo-*iso*-butyronitrile
aq.	Aqueous
Ar	Aryl (unspecified)
9-BBN	9-Borabicyclo[3.3.1]nonane
BINAP	(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Bn	Benzyl
Boc	*Tert*-butyloxycarbonyl
b.p.	Boiling point
br	Broad
Bu	Butyl
Cbz	Carboxybenzyl
CbzCl	Carboxybenzyl chloride
COD	*Cis,cis*-1,5-Cyclooctadiene
δ	Chemical shift
d	Doublet
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
d.e.	Diastereisomeric excess
DEA	Diethylamine
DEAD	Diethyl azodicarboxylate
DIAD	Di-*iso*-propyl azodicarboxyate
DIBAL-H	Di-*iso*-butylaluminium hydride
DIPEA	*N*,*N*-Di-*iso*-propylethylamine
DMAP	4-*N*,*N*-Dimethylaminopyridine
DMBMP	2,6-Di-*tert*-butyl-4-methylpyridine
DMF	*N*,*N*-Dimethylformamide
DMP	Dess–Martin Periodinane
DMSO	Dimethyl sulfoxide
DPPA	Diphenyl phosphoryl azide
d.r.	Diastereoisomeric ratio

DSC	Differential scanning calorimetry
e.e.	Enantiomeric excess
e.r.	Enatiomeric ratio
ESI	Electrospray ionisation
Et	Ethyl
eq.	Equivalent
ether	Diethyl ether
g	Gram(s)
h	Hour(s)
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetra-methyluronium hexafluorophosphate
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
Hz	Hertz
i	*Iso*
IBX	2-Iodoxybenzoic acid
ImH	1*H*-Imidazole
IR	Infra-red
J	Coupling constant in Hz
LDA	Lithium di-*iso*-propylamide
m	*Meta*
m	Multiplet
M	Molar
M^+	Molecular ion
*m*CPBA	*Meta*-chloroperoxybenzoic acid
Me	Methyl
min	Minute(s)
mL	Millilitre
mmol	Millimole
m.p.	Melting point
Ms	Methanesulfonyl (mesyl)
MS	Mass Spectrometry
MS	Molecular sieves

MTPA	α-Methoxy-α-(trifluoromethyl)phenylacetic acid
MTPACl	α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride
μW	Microwave
m/z	Mass to charge ratio
NIS	*N*-Iodosuccinimide
NMP	*N*-Methyl-piperidine
NMO	*N*-Methylmorpholine-*N*-oxide
NMM	*N*-Methylmorpholine
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
o	*Ortho*
p	*Para*
PCC	Pyridinium chlorochromate
PG	Protecting group (unspecified)
PE	Petroleum ether (that fraction which boils at 40-60 °C)
Ph	Phenyl
Phth	Phthaloyl
PMB	*Para*-methoxybenzyl
PPA	Polyphosphoric acid
ppm	Parts per million
PPL II	Porcine pancreas lipase type II
PPTS	Pyridinium *para*-toluenesulfonate
PTSA	*Para*-toluenesulfonic acid
Pr	Propyl
Pv	Pivaloyl
Py	Pyridine
q	Quartet
quint	Quintet
R	Alkyl group (unspecified)
R_f	Retention factor
r.s.m.	Recovered starting material
rt	Room temperature
s	Singlet
s.m.	Starting material

SCX	Strong cation exchange
t	*Tert*
t	Triplet
T3P®	Propylphosphonic anhydride
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TBSCl	*tert*-Butyldimethylsilyl chloride
TBSOTf	*tert*-Butyldimethylsilyl triflate
Tf	Trifluoromethanesulfonyl (triflate)
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	Tri-*iso*-propylsilyl
TIPSCl	Tri-*iso*-propylsilyl chloride
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPAP	Tetra-*n*-propylammonium perruthenate

References

1. J. I. Jiménez, G. Goetz, C. M. S. Mau, W. Y. Yoshida, P. J. Scheuer, R. T. Williamson and M. Kelly, *J. Org. Chem.*, 2000, **65**, 8465.
2. G. Cimino, S. de Stefano, G. Scognamiglio, G. Sodano and E. Trivellone, *Bull. Soc. Chim. Belg.*, 1986, **95**, 783.
3. G. Cimino, C. A. Mattia, L. Mazzarella, R. Puliti, G. Scognamiglio, A. Spinella and E. Trivellone, *Tetrahedron*, 1989, **45**, 3863.
4. G. Cimino, G. Scognamiglio, A. Spinella and E. Trivellone, *J. Nat. Prod.*, 1990, **53**, 1519.
5. Y.-W. Guo, A. Madaio, G. Scognamiglio, E. Trivellone and G. Cimino, *Tetrahedron*, 1996, **52**, 8341.
6. Y.-W. Guo, A. Madaio, E. Trivellone, G. Scognamiglio and G. Cimino, *Tetrahedron*, 1996, **52**, 14961.
7. Y.-W. Guo, E. Trivellone, G. Scognamiglio and G. Cimino, *Tetrahedron Lett.*, 1998, **39**, 463.
8. N. Fusetani, K. Yasumuro, S. Matsunaga and H. Hirota, *Tetrahedron Lett.*, 1989, **30**, 6891.
9. M. Jaspars, V. Pasupathy and P. Crews, *J. Org. Chem.*, 1994, **59**, 3253.
10. M. Arai, M. Sobou, C. Vilcheze, A. Baughn, H. Hashizume, P. Pruksakorn, S. Ishisa, M. Matsumoto, W. R. Jacobs and M. Kobayashi, *Bioorg. Med. Chem. Lett.*, 2008, **16**, 6732.
11. E. Jaimovich, C. Mattei, J. L. Liberona, C. Cardenas, M. Estrada, J. Barbier, C. Debitus, D. Laurent and J. Molgu, *FEBS Letters*, 2005, **579**, 2051.
12. M. Kobayashi, Y. Miyamoto and I. Kitagawa, *Chem. Pharm. Bull.*, 1989, **37**, 1676.
13. M. Nakagawa, M. Endo, N. Tanaka and L. Gen-Pei, *Tetrahedron Lett.*, 1984, **25**, 3227.
14. J.-C. Quirion, T. Sevenet, H.-P. Husson, B. Weniger and C. Debitus, *J. Nat. Prod.*, 1992, **55**, 1505.
15. M. Venkata Rami Reddy and D. J. Faulkner, *J. Nat. Prod. Lett.*, 1997, **11**, 53.
16. Y. Venkateswarlu, M. Venkata Rami Reddy and J. Venkataswara Rao, *J. Nat. Prod.*, 1994, **57**, 1283.
17. J. C. Braekman, D. Daloze, G. Cimino and E. Trivellone, *Bull. Soc. Chim. Belg.*, 1988, **97**, 519.

18. J. C. Braekman, D. Daloze, N. Defay and D. Zimmerman, *Bull. Soc. Chim. Belg.*, 1984, **93**, 941.
19. J. C. Braekman, D. Daloze, P. Macedo de Abreu, C. Piccini-Leopardi, G. Germain and M. Meerssche, *Tetrahedron Lett.*, 1982, **23**, 4277.
20. M. Kobayashi, K. Kawazoe and I. Kitagawa, *Tetrahedron Lett.*, 1989, **30**, 4149.
21. T. Venkateshwar Goud, N. Srinivasa Reddy, N. Raghavendra Swamy, T. Siva Ram and Y. Venkateswarlu, *Biol. Pharm. Bull.*, 2003, **26**, 1498.
22. B. J. Baker, P. J. Scheuer and J. N. Shoolery, *J. Am. Chem. Soc.*, 1988, **110**, 965.
23. K. V. Rao, B. D. Santarsiero, A. D. Mesecar, R. F. Schinazi, B. L. Tekwani and M. T. Hamann, *J. Nat. Prod*, 2003, **66**, 823.
24. T. Ichiba, J. M. Corgiat, P. J. Scheuer and M. Kelly-Borges, *J. Nat. Prod.*, 1994, **57**, 168.
25. T. Ichiba, R. Sakai, S. Kohmoto, G. Saucy and T. Higa, *Tetrahedron Lett.*, 1988, **29**, 3083.
26. M. Kobayashi, Y.-J. Chen, S. Aoki, Y. In and T. Ishida, *Tetrahedron*, 1995, **51**, 3727.
27. H. Nakamura, S. Deng, J. Kobayashi, Y. Ohizumi, Y. Tomotake, T. Matsuzaki and Y. Hirata, *Tetrahedron Lett.*, 1987, **28**, 621.
28. I. I. Ohtani, T. Ichiba, M. Isobe, M. Kelly-Borges and P. J. Scheuer, *J. Am. Chem. Soc.*, 1995, **117**, 10743.
29. R. Sakai, T. Higa, C. W. Jefford and G. Benardinelli, J., *J. Am. Chem. Soc.*, 1986, **108**, 6404.
30. R. Sakai, S. Kohmoto, T. Higa, C. W. Jefford and G. Benardinelli, *Tetrahedron Lett.*, 1987, **28**, 5493.
31. M. Tsuda, N. Kawasaki and J. Kobayashi, *Tetrahedron Lett.*, 1994, **35**, 4387.
32. B. Zhang, H. Ryuichi, T. Miyamoto and R. W. M. Van Soest, *Chem. Pharm. Bull*, 2008, **56**, 866.
33. N. Oku, K. Nagai, N. Shindoh, Y. Terada, R. W. M. Van Soest, S. Matsunagaa and N. Fusetania, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2617–2620.
34. J. H. H. L. de Oliveira, A. Grube, M. Kock, R. G. S. Berlinck, M. L. Macedo, A. G. Ferreira and E. Hajdu, *J. Nat. Prod*, 2004, **67**, 1685.
35. N. Fusetani, N. Asai, S. Matsunaga, K. Honda and K. Yasumuro, *Tetrahedron Lett.*, 1994, **35**, 3967.
36. F. Kong, R. J. Andersen and T. M. Allen, *J. Am. Chem. Soc.*, 1994, **116**, 6007.
37. F. Kong, E. I. Graziani and R. J. Andersen, *J. Nat. Prod*, 1998, **61** 267.
38. J. M. Rodríguez and P. Crews, *Tetrahedron Lett.*, 1994, **35**, 4719.
39. J. M. Rodríguez, B. M. Peters, L. Kurz, R. C. Schatzman, D. McCarley, L. Lou and P. Crews, *J. Am. Chem. Soc.*, 1994, **115**, 10436.

40. J. Kobayashi, M. Tsuda, N. Kawasaki, K. Matsumoto and T. Adachi, *Tetrahedron Lett.*, 1994, **35**, 4383.
41. K. Kondo, H. Shigemori, J. Kikuchi, M. Ishibashi, T. Saski and J. Kobayashi, *J. Org. Chem.*, 1992, **57**, 2480.
42. M. Tsuda, N. Kawasaki and J. Kobayashi, *Tetrahedron*, 1994, **50**, 7957.
43. F. Kong and R. J. Andersen, *Tetrahedron*, 1995, **51**, 2895.
44. F. Kong, R. J. Andersen and T. M. Allen, *Tetrahedron Lett.*, 1994, **35**, 1643.
45. F. Kong, R. J. Andersen and T. M. Allen, *Tetrahedron*, 1994, **50**, 6137.
46. M. T. Davies-Coleman, D. J. Faulkner, G. M. Dubowchik, G. P. Roth, C. Polson and C. Fairchild, *J. Org. Chem.*, 1993, **58**, 5925.
47. F. J. Schmitz, K. H. Hollenbeak and D. C. Campbell, *J. Org. Chem.*, 1978, **43**, 3916.
48. R. Talpir, A. Rudi, M. Ilan and Y. Kashman, *Tetrahedron Lett.*, 1992, **33**, 3033.
49. C. A. Volk, H. Lippert, E. Lichte and M. Köck, *Eur. J. Org. Chem.*, 2004, 3154.
50. J. E. Baldwin and R. C. Whitehead, *Tetrahedron Lett.*, 1992, **33**, 2059.
51. A. Malves Maia, S. Mons, R. Pereira de Freitas Gil and C. Marazano, *Eur. J. Org. Chem.*, 2004, 1057.
52. K. Kiewel, Z. Luo and G. A. Sulikowski, *Org. Lett.*, 2005, **7**, 5163.
53. C. Ménard-Moyon and R. J. K. Taylor, *Eur. J. Org. Chem.*, 2007, 3698.
54. J. P. Schmidt, S. Beltrán-Rodil, R. J. Cox, G. D. McAllister, M. Reid and R. J. K. Taylor, *Org. Lett.*, 2007, **9**, 4041.
55. Z. S. Luo, K. Peplowski and G. A. Sulikowski, *Org. Lett.*, 2007, **9**, 5051.
56. T. Shono, *Tetrahedron*, 1984, **40**, 811.
57. D. Lainé, M. Fujita and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1639.
58. M. Reid and R. J. K. Taylor, *Tetrahedron Lett.*, 2004, **45**, 4181.
59. M. Jean and R. J. K. Taylor, *Unpublished results*, 2008.
60. J. P. Schmidt, *PhD Thesis, University of York*, 2007.
61. C. Ménard-Moyon and R. J. K. Taylor, *Unpublished results*, 2006.
62. D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893.
63. J. S. Foot, G. M. P. Giblin and R. J. K. Taylor, *Org. Lett.*, 2003, **5**, 4441.
64. A. N. Cayley, R. J. Cox, C. Menard-Moyon, J. P. Schmidt and R. J. K. Taylor, *Tetrahedron Lett.*, 2007, **48**, 6556.
65. M. Shimizu, M. Ishikawa, Y. Komoda and T. Nakajima, *Chem. Pharm. Bull.*, 1982, **30**, 909.
66. C. Wu, E. R. Decker, N. Blok, H. Bui, T. J. You, J. Wang, A. R. Bourgoyne, V. Knowles, K. L. Berens, G. W. Holland, T. A. Brock and R. A. F. Dixon, *J. Med. Chem.*, 2004, **47**, 1969.

67. M. G. Edwards, M. N. Kenworthy, R. R. A. Kitson, M. S. Scott and R. J. K. Taylor, *Angew. Chem. Int. Ed.*, 2008, **47**, 1935.
68. *US Pat.*, 1868612, 1930.
69. *German Pat.*, 695064, 1937.
70. L. Bretherick, *Hazards in the Chemical Laboratory*, Royal Society of Chemistry, London, 1981.
71. A. T. Fafarman, L. J. Webb, J. I. Chuang and S. G. Boxer, *J. Am. Chem. Soc.*, 2006, **128**, 13356.
72. D. A. Evans, pKa table, (www.evans.harvard.edu/pdf/evans_pKa_table.pdf).
73. A. S. Kende, K. Liu, I. Kaldor, G. Dorey and K. Koch, *J. Am. Chem. Soc.*, 1995, **117**, 8258.
74. E. J. Corey, J. W. Ponder and P. Ulrich, *Tetrahedron Lett.*, 1980, **21**, 137.
75. C. J. Kibler and A. Weissberger, *Org. Syn. Coll. Vol. 3*, 1955, 108.
76. M. H. Norman, J. L. Kelley and E. B. Hollingsworth, *J. Med. Chem.*, 1993, **36**, 3417.
77. E. Veverkova, M. Meciarova, S. Toma and J. Balko, *Monatsh. Chem.*, 2003, **134**, 1215.
78. E. Fischer and A. Speier, *Chem. Ber.*, 1895, **28**, 3252.
79. A. R. Bader and A. D. Kontowicz, *J. Am. Chem. Soc.*, 1953, **75**, 5416.
80. K. J. Shea and E. Wada, *J. Am. Chem. Soc.*, 1982, **104**, 5715.
81. R. Kitamura, *J. Pharm. Soc. Jpn.*, 1937, **57**, 55.
82. J. Woolins, D; and M. S. J. Forman, *J. Chem. Soc., Dalton Trans.*, 2000, 1533.
83. T. Nishio, *J. Chem. Soc., Chem. Commun.*, 1989, 205.
84. J. E. Robinson and R. J. K. Taylor, *Chem. Commun.*, 2007, 1619.
85. J. Goerdeler and J. Kandler, *Chem. Ber.*, 1959, 1679.
86. S. J. Hays, B. W. Caprathe, J. L. Gilmore, N. Amin, M. R. Emmerling, W. Michael, R. Nadimpalli, R. Nath, K. J. Raser, D. Stafford, D. Watson, K. Wang and J. C. Jaen, *J. Med. Chem.*, 1998, **41**, 1060.
87. I. Antonini, G. G. Cristalli, P. Franchetti, M. Grifantini and S. Martelli, *J. Heterocycl. Chem.*, 1980, **17**, 155.
88. J. Barluenga, F. J. Fañanás, R. Sanz and Y. Fernández, *Chem. Eur. J.*, 2002, 2034.
89. H. P. Lankelma and A. E. Knauf, *J. Am. Chem. Soc.*, 1931, **53**, 309.
90. S. Shinkai, T. Minami, Y. Araragi and O. Manabe, *J. Chem. Soc., Perkin Trans. 2*, 1985, 503.
91. A. N. Cayley, K. A. Gallagher, C. Ménard-Moyon, J. P. Schmidt, L. J. Diorazio and R. J. K. Taylor, *Synthesis*, 2008, 3846.
92. H. Maehr, *J. Chem. Educ.*, 1985, **62**, 114.

93. K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.
94. L. Yao, B. T. Smith and J. Aube, *J. Org. Chem.*, 2004, **69**, 1720.
95. D. H. Williams and I. Fleming, *Spectroscopic Methods in Organic Chemistry* 5th edn., McGraw-Hill, London, 1995.
96. L. Duhamel and J. Plaquevent, *J. Orgmet. Chem*, 1993, **448**, 1.
97. H. Staudinger and J. Meyer, *Helv. Chim. Acta*, 1919, **2**, 635.
98. M. J. Gaunt, A. S. Jessiman, P. Orsini, H. R. Tanner, D. F. Hook and S. V. Ley, *Org. Lett.*, 2003, **5**, 4819.
99. *Korean Pat.*, 096915, 2002.
100. W. Lin, X. Zhang, Z. He, Y. Jin, L. Gong and A. Mi, *Synth. Comm.*, 2002, **32**, 3279.
101. D. J. Von Langen and R. L. Tolman, *Tetrahedron: Asymmetry*, 1997, **8**, 677.
102. K. W. C. Poon and G. B. Dudley, *J. Org. Chem.*, 2006, **71**, 3923.
103. S. Beltrán-Rodil, PhD Thesis, University of York, 2007.
104. B. W. Gung and R. M. Fox, *Tetrahedron*, 2004, **60**, 9405.
105. Q. Zheng, Y. Yang and A. R. Martin, *Tetrahedron Lett.*, 1993, **34**, 2235.
106. A. D. Brosius, L. E. Overman and L. Schwink, *J. Am. Chem. Soc.*, 1999, **121**, 700.
107. M. E. Garst, J. N. Bonfiglio, D. A. Grudoski and J. Marks, *Tetrahedron Lett.*, 1978, **30**, 2671.
108. P. Duhamel, D. Abdallah and J. M. Poirier, *Tetrahedron Lett.*, 1993, 3863.
109. S. K. Pandey, A. E. Greene and J.-F. Poisson, *J. Org. Chem*, 2007, **72**, 7769.
110. A. G. Anderson and P. J. Stang, *Org. Synth. Coll.*, 1990, **7**, 144.
111. S. J. Aitken, G. Grogan, C. S. S.-Y. Chow, N. J. Turner and S. B. Filtch, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3365.
112. R. E. Ireland and D. W. Norbeck, *J. Org. Chem.*, 1985, **50**, 2198.
113. C. R. Holmquist and E. J. Roskamp, *J. Org. Chem.*, 1989, **54**, 3258.
114. R. Noyori, T. Ohkuma and M. Kitamura, *J. Am. Chem. Soc.*, 1987, **109**, 5858.
115. J. P. Genêt, V. Ratovelomanana-Vidal, M. C. Cano de Andrade, X. Pfister, P. Guerreiro and J. Y. Lenoir, *Tetrahedron Lett.*, 1995, **36**, 4801.
116. R. Noyori, M. Tokunaga and M. Kitamura, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 36.
117. A. R. Burns, G. D. McAllister, S. E. Shanahan and R. J. K. Taylor, *Angew. Chem. Int. Ed.*, 2010, **49**, 5574.
118. P. Renaud, L. E and Q. L, *Tetrahedron Lett.*, 1998, **39**, 2123.
119. J. E. Leibner and J. Jacobus, *J. Org. Chem.*, 1979, **44**, 449.
120. D. C. Harrowven, D. P. Curran, S. L. Kostiuk, I. L. Wallis-Guy, S. Whiting, K. J. Stenning, B. Tang, E. Packard and L. Nanson, *Chem. Commun.*, 2010, 6335.
121. D. C. Harrowven and I. L. Guy, *Chem. Commun.*, 2004, 1968.

122. N. Hadei, E. A. B. Kantchev, C. J. O'Brien and M. G. Organ, *Org. Lett.*, 2005, **7**, 3805.
123. E. P. Kündig and A. F. Cunningham, *Tetrahedron*, 1988, **44**, 6855.
124. P. K. Mandal and J. S. McMurray, *J. Org. Chem.*, 2007, **72**, 6599.
125. J. K. Augustine, R. N. Atta, R. Kolathur and Boodappa, *Synlett*, 2009, 3378.
126. M. Reid, *Ph.D. Thesis, University of York*, 2006.
127. H. Lund and J. Bjerrum, *Chem. Ber.*, 1931, **64**, 210.
128. M. Malon, S. Takahashi and H. Koshino, *Tetrahedron Lett.*, 2007, **48**, 7586.
129. S. Crosignani, P. D. White and B. Linclau, *J. Org. Chem.*, 2004, **69**, 5897.
130. C. C. Yang, H. M. Tai and P. J. Sun, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2843.
131. B. Danieli, G. Lesma, M. Mauro, G. Palmisano and D. Passarella, *Tetrahedron: Asymmetry*, 1990, **1**, 793.
132. P. O'Brien and J. J. Tournayre, *Tetrahedron*, 1997, **53**, 17527.
133. F. Tavares, J. P. Lawson and A. I. Meyers, *J. Am. Chem. Soc.*, 1996, **118**, 3303.
134. P. G. McDougal, J. G. Rico, Y. I. Oh and B. D. Condon, *J. Org. Chem*, 1986, **51**, 3388.
135. R. J. Vijn, H. Hiemstra, J. J. Kok, M. Knotter and W. N. Speckamp, *Tetrahedron*, 1987, **43**, 5019.
136. N. Vicart, B. Cazes and J. Gore, *Tetrahedron*, 1996, **52**, 9101.