Methodology for the synthesis of NP25302

and other bioactive natural products

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ASLIB ABSTRACT

Methodology for the synthesis of NP25302 and other bioactive natural products

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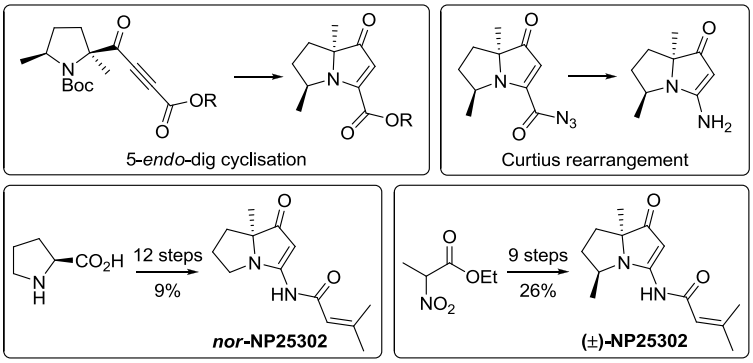
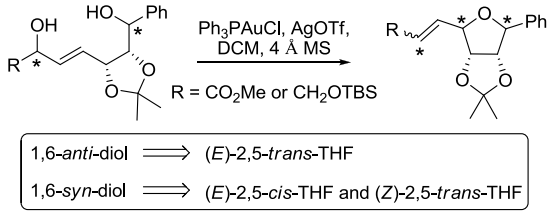
Total synthesis of the pyrrolizidine alkaloid NP25302

(+)-NP25302 is an unusual vinylogous urea containing pyrrolizidine alkaloid shown to exhibit cell adhesion inhibition. It was envisaged that this natural product could be accessed by a novel 5-*endo*-dig cyclisation to construct the pyrrolizidine core, and a Curtius rearrangement to install the vinylogous urea motif. This methodology was first tested on a model system, furnishing *nor*-NP25302 from L-proline in 12 steps and 9% overall yield. The total synthesis of (±)-NP25302 was completed in 9 steps and 26% overall yield from ethyl 2-nitropropionate using similar methodology.



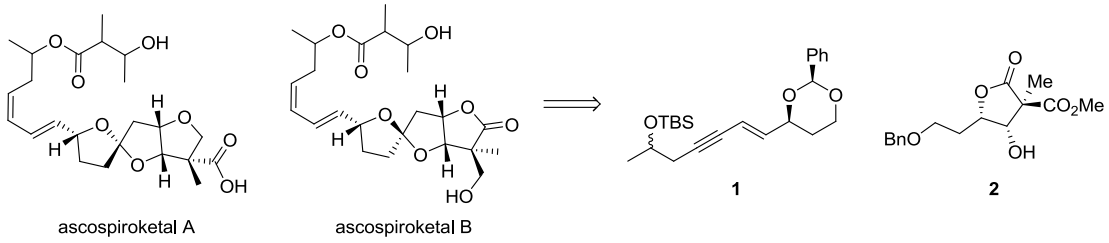
Studies into the stereospecificity of the Au(I)-catalysed cyclisation of monoallylic diols

During the synthesis of (+)-isoaltholactone in the Robertson group, the key Au(I)-catalysed cyclisation was observed to occur with some stereospecificity. Further investigations were therefore conducted into the stereochemical outcome of this reaction using stereodefined allylic alcohols, and from the combined results a mnemonic was proposed to predict the stereochemistry of the products of this reaction.



Studies into the total synthesis of ascospiroketals A and B

Investigations were conducted into the total synthesis of the recently isolated natural products ascospiroketals A and B. A second generation synthesis was used to construct advanced intermediates **1** and **2**.



Firstly, I would like to thank Dr Jeremy Robertson for giving me chance to work in the wonderful JR group, for all the help and advice over the last few years and for introducing me to Peppa Pig.

I would like to thank the incredible Dr Chris (P.) North for his incomparable proof-reading skills, much needed support and encouragement, love and accommodation. I don't think I'd have made it without you, your wisdom and your brilliant sense of humour.

Massive thanks must also be given to all the wonderful friends I've made over the years in the Robertson group! It would be impossible to write in such short space how much you've meant to me and how privileged I feel to have known you all, but I'll give it a go regardless…

Thanks to Jessie for being my original Robertson group friend, for all the fun, entertainment, super food and wine you've given me. I will miss you terribly and am sad that I will never get to live with you again, but I will be sure to still send postcards, and if you ever again drink so much tequila you need someone to be your eyes/fetch a porter/stop Jack from slapping your face, you just call!

Thanks to George for being hilarious 95% of the time, at least 50% of it intentionally. Thanks also for the other 5% - your love and friendship have been much appreciated. How proud I am of you making a new life over in Australia! (But how terribly you'll be missed!) What a shame we never got to have our biggest day…

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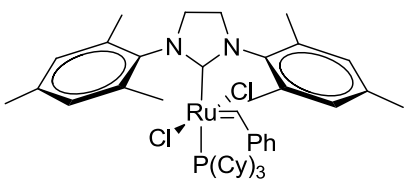
Huge thanks should go to my wonderful family for all their love and support over the last few years, and to Jackie and Dave for their support, cakes/jam/hot cross buns and coming to my aid during the dark days of the broken wrist. Thanks should also be sent across the world to all the amazing and incredible pink-book girls of the WGHS for always believing in me much more than I deserve, and much more than I ever do! You guys always understood just how much I loved chemistry. And ham. And gin.

Finally, thanks to the NMR, mass spectrometry and crystallography staff who have been immensely helpful for the last three years, and to the CRL support staff for their behind the scenes help.

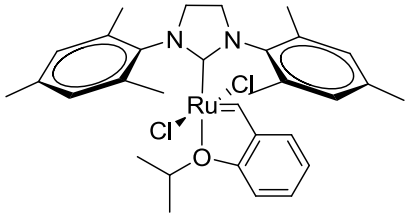
Abbreviations

Ac acetyl
app. apparent
aq. aqueous
Ar aryl (substituted aromatic ring)
9-BBN 9-borabicyclo[3.3.1]nonane
Bn benzyl
Boc *tert*-butoxycarbonyl
Bu butyl
ca. *circa*
Cbz carbobenzyloxy
conc. concentrated
COSY correlation spectroscopy
CAN cerium(IV) ammonium nitrate
cat. catalytic
CSA camphorsulfonic acid
Cy cyclohexyl
DABCO 1,4-diazabicyclo[2.2.2]octane
dba dibenzylideneacetone
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DCA 9,10-dicyanoanthracene
DCC dicyclohexylcarbodiimide
DCE 1,2-dichloroethane
DCM dichloromethane
DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD diethylazodicarboxylate
DEPT distortionless enhancement by polarisation transfer
DET diethyl tartrate
DHQ dihydroquinine
DHQD dihydroquinidine
DAIB diacetoxyiodobenzene
DIBAL diisobutylaluminium hydride
DIPEA diisopropylethylamine
DIPT diisopropyl tartrate
DMAP *N*,*N*-4-dimethylaminopyridine
DME 1,2-dimethoxyethane
DMF *N*,*N*-dimethylformamide
DMN 1,5-dimethoxynaphthalene
DMP Dess-Martin periodinane
DMSO dimethylsulfoxide
DPPA diphenylphosphoryl azide
dppf 1,1′-bis(diphenylphosphino)ferrocene
d.r. diastereomeric ratio
dtbpy 4,4-di-*tert*-butyl-2,2-bipyridine
EDA ethylenediamine
e.e. enantiomeric excess
EE ethoxyethyl
eq. equivalents
ESI electrospray ionisation
Et ethyl
EVE ethyl vinyl ether
FI field ionisation
h hour(s)
Hal halogen
HATU 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate
HMBC heteronuclear multiple bond correlation
HMPA hexamethylphosphoramide
HMQC heteronuclear multiple-quantum correlation
HSQC heteronuclear single-quantum correlation
i- *iso*
imid. imidazole
IPA isopropyl alcohol
IR infrared
J coupling constant
KHMDS potassium bis(trimethylsilyl)amide
LDA lithium diisopropylamide
LHMDS lithium bis(trimethylsilyl)amide
lit. literature
m- *meta*
M molar
m-CPBA *meta*-chloroperbenzoic acid
m/*z* mass/charge ratio

Me	methyl
mins	minute(s)
MOM	methoxymethyl
m.p.	melting point
MS	molecular sieves
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
o-	*ortho*
p-	*para*
[P]	protecting group
Ph	phenyl
PHAL	phthalazine
PHB	polyhydroxybutyrate
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PNB	*para*-nitrobenzoyl
p.p.m.	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
PTSA	*para*-toluenesulfonic acid
pyr	pyridine
quant.	quantitative
RCM	ring closing metathesis
R_f	retention factor
RT	room temperature
RVC	reticulated vitreous carbon
s-/*sec*-	secondary
SAD	Sharpless asymmetric dihydroxylation
SAE	Sharpless asymmetric epoxidation
sat.	saturated
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*para*-toluenesulfonyl
t-/*tert*-	tertiary
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TBHP	*tert*-butyl hydroperoxide
TEA	triethylamine
TFA	trifluoroacetic acid
UV	ultraviolet



Grubbs' II



Hoveyda–Grubbs' II

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1 Total synthesis of the pyrrolizidine alkaloid NP25302

1.1 Introduction

1.1.1 Pyrrolizidine Alkaloids

The pyrrolizidine 1-azabicyclo[3.3.0]octane motif consists of two fused 5-membered rings with a bridgehead nitrogen atom (**Figure 1**). Numbering is typically conducted as shown, with nitrogen at the 4 position.

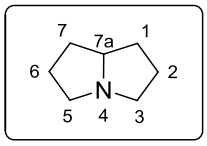


Figure 1

Pyrrolizidine alkaloids (PAs) have been isolated from an enormous range of plants all over the world, in particular the Compositae, Boraginaceae and Leguminosae plant families.[1] The first PAs to be reported were isolated from plants belonging to the genus *Senecio*, of the Compositae family; examples are shown below (**Figure 2**).[2] Over 600 PAs and PA *N*-oxides have been isolated from more than 6000 plants.

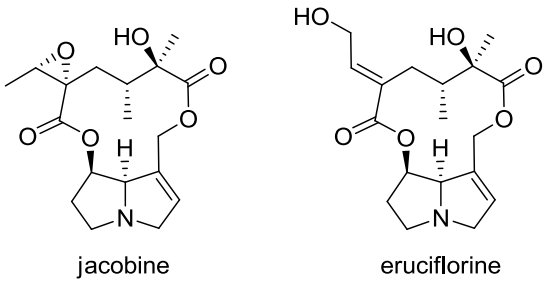
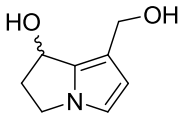


Figure 2

Investigation into the toxicological properties of the *Senecio* PAs revealed that they were the cause of a number of diseases which lead to chronic hepatic lesions.[3] This is consistent with the observation of poisoning in livestock and domestic animals which grazed on the *Senecio* plants.

The mode of toxicity of these alkaloids is well understood,[4, 5] deriving from their metabolism in the liver to the highly reactive pyrrolic dehydroalkaloid **1.1**, (**Figure 3**).[4] This metabolite reacts quickly to cross-link double DNA strands, leading to a long-lasting antimitotic effect and eventually destruction of much of the healthy liver tissue. In some instances, the reactive pyrrolic metabolite can enter the blood stream and be transported to other organs, typically the lung, or be metabolised further to give metabolites that, whilst still toxic, have a lower reactivity which allows them to circulate further and affect a wider range of organs.



1.1

Figure 3

As well as affecting livestock, PAs are also the leading plant toxins associated with disease in humans through contamination of staple foods, such as wheat and bread, honey, milk, herbal teas and herbal medicines.[4] A report published by the World Health Organisation in 1988 expressed a general concern over even low levels (1 to 4 ppm) of PAs in food sources.[6]

Despite the toxicity of many PAs, some have been found to have interesting biological activities. They are said to be distasteful to herbivores grazing on PA producing plants, hence acting as a defence mechanism for the plant,[7] and some species of butterflies and moths take the PAs from these plants to use as defense agents or pheromones.[8] For example, danaidone, danaidal and hydroxydanaidal, secreted as a pheromone by males of *Lepidoptera*, can be traced back to ingestion of monocrotaline or heliotrine (**Figure 4**).[9]

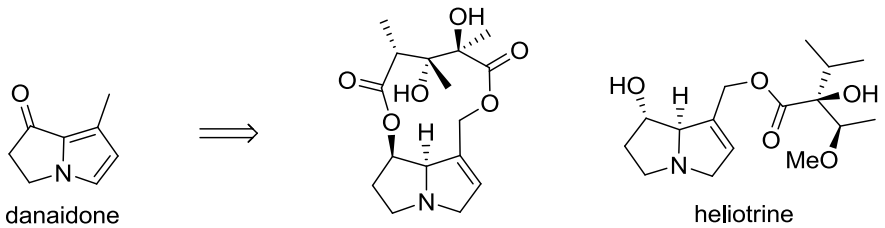


Figure 4

It has been observed that PAs transferred from male *Uthethesia ornatrix* moths to females during mating are rapidly distributed throughout the female's body, including the wings.[10] Similarly, male *Cosmosoma myrodora* moths, which acquire PAs from food plants, have been shown to donate alkaloids to females during mating, uniquely, by distribution of a layer of alkaloid laden filaments onto their mate.[11] These distributed alkaloids have been shown to provide defence against predators for both the males and for those females receiving them.

The *N*-oxides of PAs are believed to be less toxic than the corresponding free bases,[7] and are often sequestered by plants in this more polar form. Although enzymes in the gut of animals can convert these *N*-oxides back into the toxic free-base to a small extent, the *N*-oxide can be considered as detoxification products which can be excreted.[12, 13] These *N*-oxides have even shown potential as therapeutic agents in the treatment of tumours. Indicine *N*-oxide (**1.2**, **Figure 5**) was particularly successful in clinical trials at stabilising patients with advanced gastrointestinal cancer.[14]

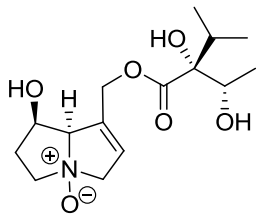


Figure 5

More recently the naturally occurring, poly-hydroxylated pyrrolizidines alexine (**1.3**),[15] casuarine (**1.4**)[16] and australine (**1.5**, **Figure 6**),[17] showed that PAs can act as effective sugar mimics.[18]

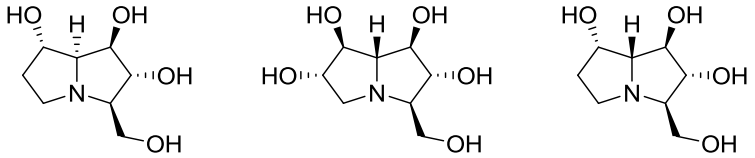


Figure 6

The wide variety of structures observed in PAs have been categorised by Hartmann and Witte (**Figure 7**).[19]

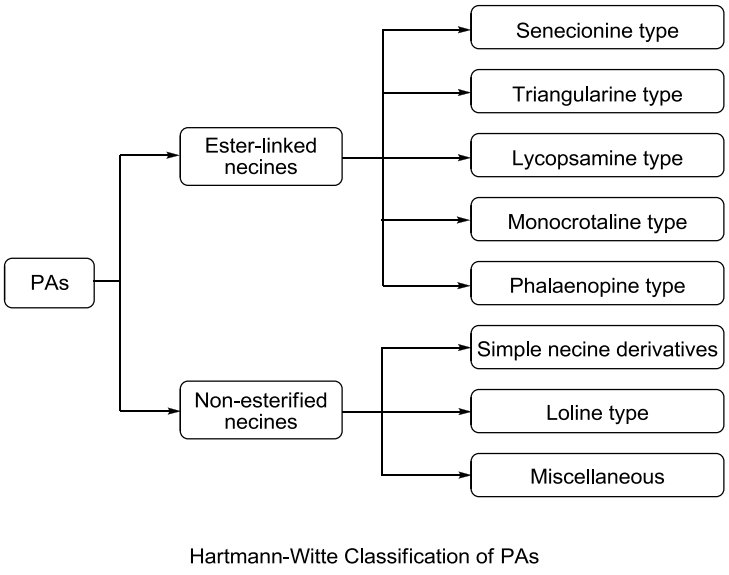


Figure 7[20]

This system splits the structures into groups that either have or lack an ester group attached to the necine base unit, the most common of these necines being shown below (**Figure 8**). The majority of naturally occurring PAs are esterified.[5]

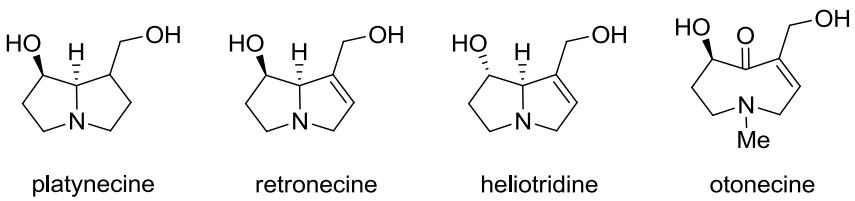
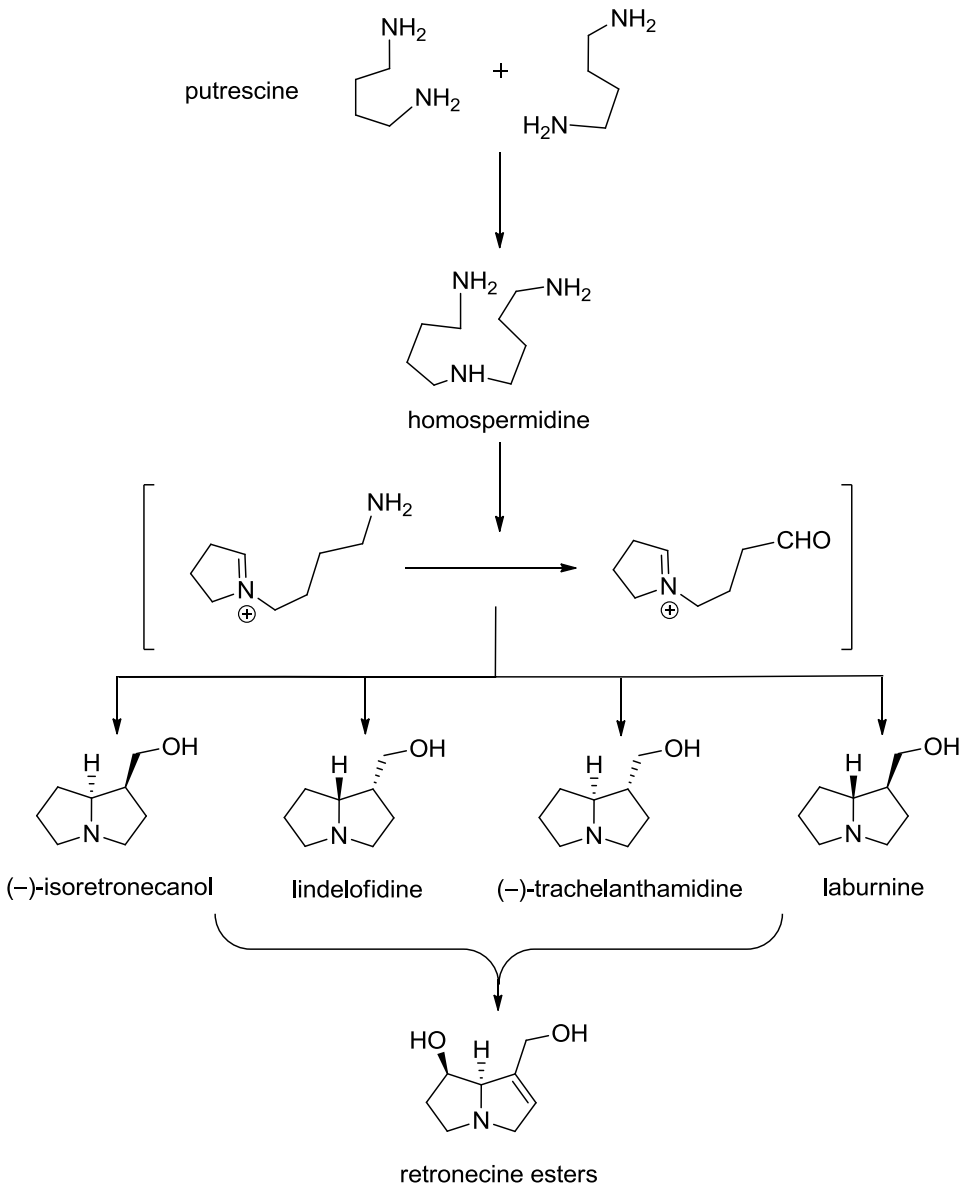


Figure 8

The biosynthesis of retronecine was initially investigated by Robins and Sweeney in 1979,[21] who concluded that these motifs were probably built up from two putrescine units. Further support for this

proposed theory was obtained *via* work undertaken mainly by Robins and Khan[22, 23] in which the plants from the *Senecio* genus were fed on ^{13}C-labelled putrescines. The pyrrolizidines biosynthesised in these plants contained two labelled carbon atoms. Studies with ^{15}N and ^{13}C labelled putrescines[24-27] showed a symmetrical intermediate species presumed to be homospermidine, which was incorporated, intact, into the pyrrolizidine product. Biomimetic experiments[28] confirmed this hypothesis and a complete biosynthetic pathway could be described (**Scheme 1**).



Scheme 1

1.1.2 Vinylogous urea containing PAs including (+)-NP25302

The vinylogous urea containing PAs are an unusual PA sub-class first reported upon the discovery of bohemamine (**1.6**, **Figure 9**).[29] Its structure, confirmed by single crystal X-ray analysis, shows a substitution pattern that differs significantly from the majority of PAs isolated previously. The key structural features include an *endo*-face C(6)-C(7) epoxide and an *N*-acyl vinylogous urea type side-chain.

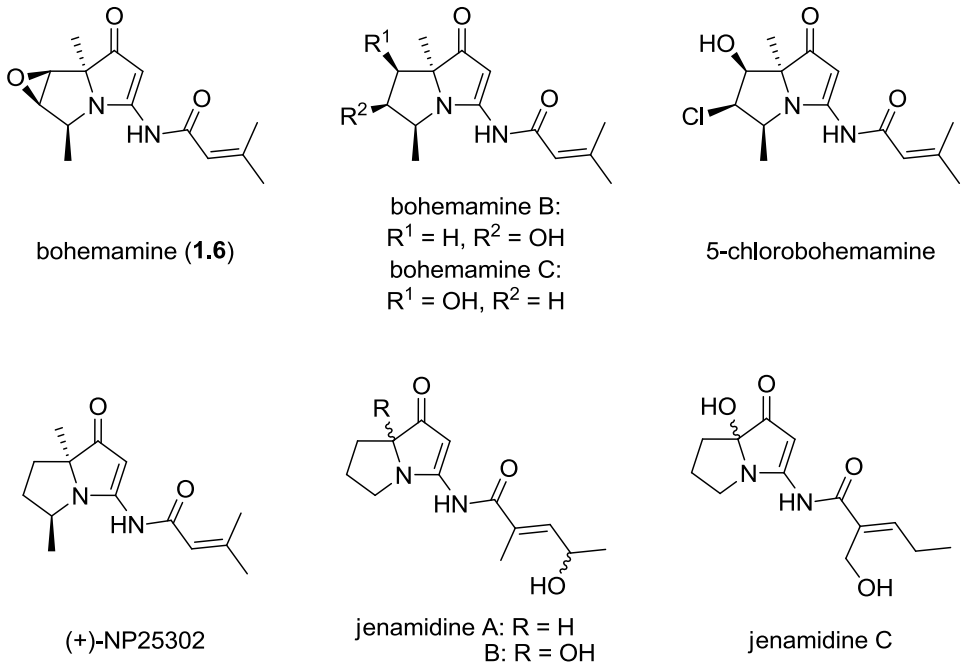


Figure 9

Since this first example, a number of similar pyrrolizidine alkaloid natural products have been described: jenamidines A, B and C,[30, 31] (+)-NP25302,[32] bohemamine B and C and a chlorinated analogue of bohemamine itself, 5-chlorobohemamine.[33]

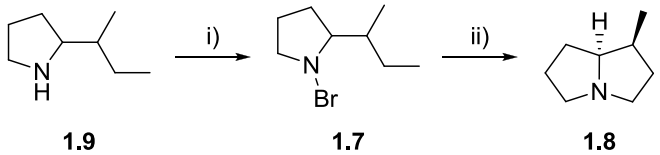
Jenamidine A was observed to inhibit the proliferation of the chronic myeloid leukemia cell line K-562, and its lack of antiproliferative activity against mouse fibroplast L-929 or cytotoxicity against HeLa cells suggested a high level of specificity.[30] Bohemamine was found to exhibit no antibiotic,

antifungal and antitumour activity,[34] but along with (+)-NP25302 was found to inhibit cell adhesion of HL-60 cells to CHO-ICAM-1 cells.[i]

1.1.3 Synthetic strategies to PAs

There are many published synthetic routes to pyrrolizidines, catalogued in regular review papers published by Robins (1984–1995)[35-46] and Liddell (1996–2002)[47-53] in *Natural Product Reports*, following on from the coverage of literature in *The Alkaloids*.

The first published synthesis of a pyrrolizidine was conducted in 1933 by Menschikoff.[54] His approach, based on the Hofmann–Löffler–Freytag reaction of *N*-bromo pyrrolidine **1.7**, gave known pyrrolizidine heliotridane (**1.8**, **Scheme 2**) in two steps from amine **1.9**.



1.9 **1.7** **1.8**

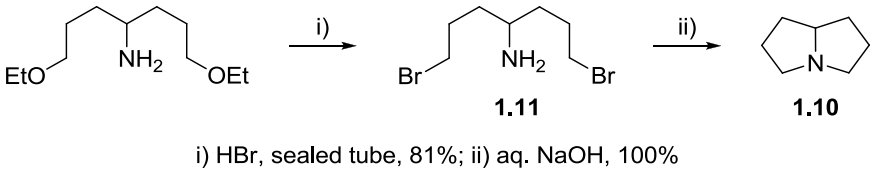
i) NaOBr; ii) H_2SO_4, Δ

Scheme 2

The majority of the later-reported routes to pyrrolizidines are also based around formation of the N-C(3) bond. However, these syntheses typically use the inherent nucleophilicity of the nitrogen to react with a suitable tethered electrophile.

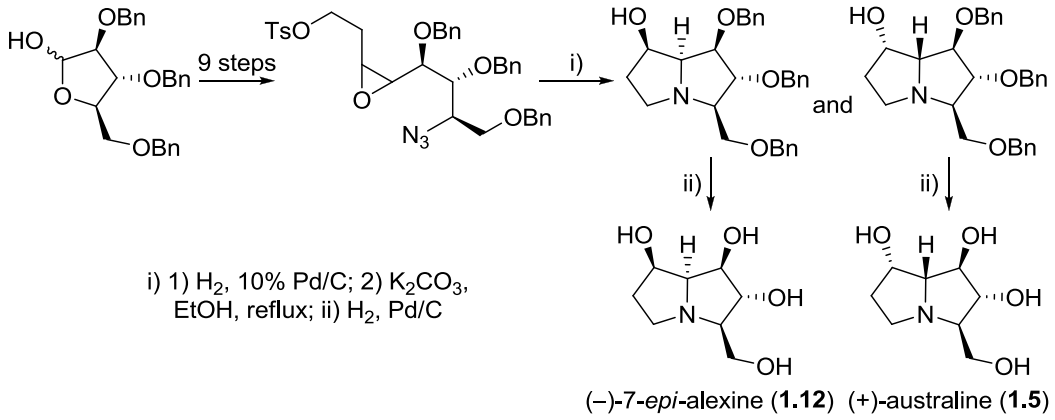
[i] The reported activity of the two compounds was similar: bohemamine showed an IC_{50} of 27.2 μg/mL and NP25302 an IC_{50} of 24.3 μg/mL. Bohemamines B, C and chlorobohemamine were not able to be assayed under the same conditions, but they showed no inhibitory activity against HCT-116 colon carcinoma; they also showed no antimicrobial activity.

Formation of the pyrrolizidine core *via* an S_N2 process is a commonly used strategy, either forming one or both of the rings in the same step. This strategy, wide in substrate scope and conducted under mild conditions, was first reported by Prelog and Heimbach in 1939 to form pyrrolizidine **1.10** from dibromoamine **1.11** (**Scheme** 3).[55]



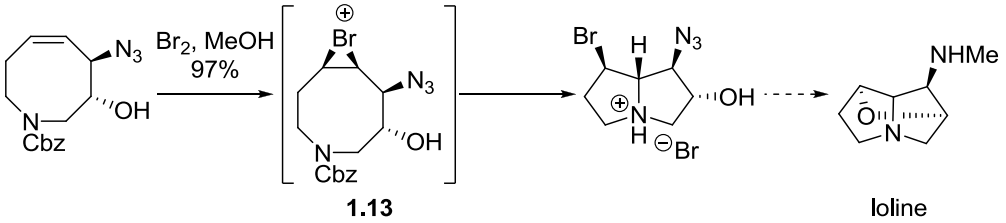
Scheme 3

More recently this strategy has been used to form much more complex structures such as (+)-australine (**1.5**) and its diastereomer (−)-7-*epi*-alexine (**1.12**, **Scheme 4**).[56] This synthesis is somewhat unusual as the amine component originated at the end of the chain, rather than lying in the middle and forming the two rings either side of it.



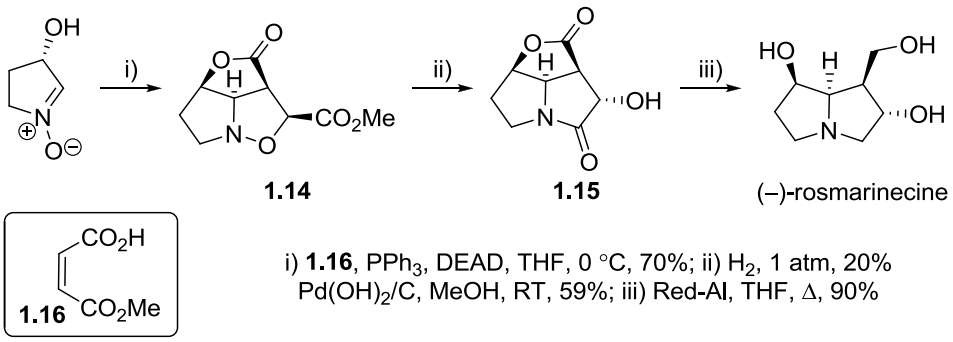
Scheme 4

Trauner *et al*. employed a transannular S_N2 ring-opening of bromonium ion **1.13** (**Scheme 5**) to create the bicyclic core structure of loline,[57] a structure that has been the subject of synthetic attempts, both successful and unsuccessful.[58-62] Only one asymmetric synthesis had previously been reported, however,[61, 62] and Trauner's synthesis, at 10 steps, was half the length of this previous route.



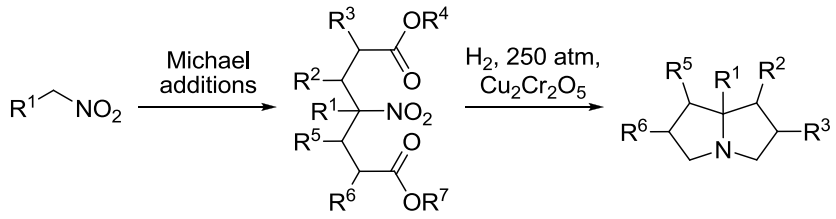
Scheme 5

Conceptually related approaches based on intramolecular addition to carbonyl substituents. can lead either to lactam products, *via* addition into ester components, or imine products from addition into aldehydes. In most cases, this is conducted under or followed by reducing conditions leading to the saturated pyrrolizidine products. For example, in Goti's 2001 synthesis of (−)-rosemarinecine,[63] isoxazolidine **1.14** was opened reductively and the resulting amino ester closed to give lactam **1.15** (**Scheme 6**). This amide functionality was then removed under more strongly reducing conditions.



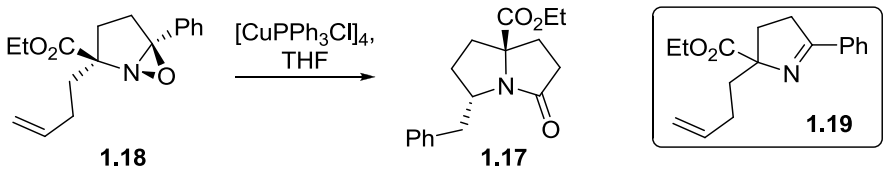
Scheme 6

The use of reductive cyclisation conditions can also allow the use of masked amines which are revealed under the hydrogenation conditions. An example of this strategy, using nitropimelates, was developed by Leonard *et al*. (**Scheme 7**).[64] This approach is of great utility due to the ease of synthesis of the nitropimelate starting materials *via* sequential Michael additions into α,β-unsaturated carbonyl compounds.



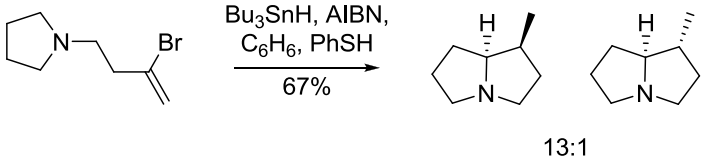
Scheme 7

Another example of this N-C(3) disconnection is *via* radical ring closure of nitrogen-centered radicals. This method was used by Black *et al*. to synthesise pyrrolizidine **1.17** from oxaziridine **1.18** (**Scheme 8**).[65] Interestingly, when the butenyl side-chain was *cis*- to the oxaziridine, only pyrrolidine **1.19** was obtained.



Scheme 8

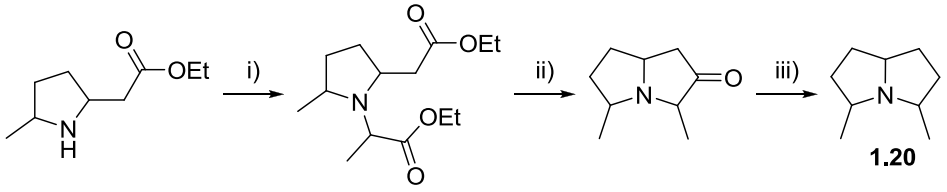
Radical cyclisation *via* C–C bond disconnections at other points around the ring system is much more common. The synthesis of (±)-heliotridane was completed within the Robertson group using such a disconnection (**Scheme 9**).[66]



Scheme 9

The majority of other common syntheses of pyrrolizidines rely on ring closure at bonds other than N-C(3) disconnection, however, it is difficult to define these many and diverse approaches as neatly. These methods are greatly dependent on the functional groups present around the bicycle, and the varied nature of these make the range of potential disconnections even more expansive. Accordingly, only a cursory selection is provided here.

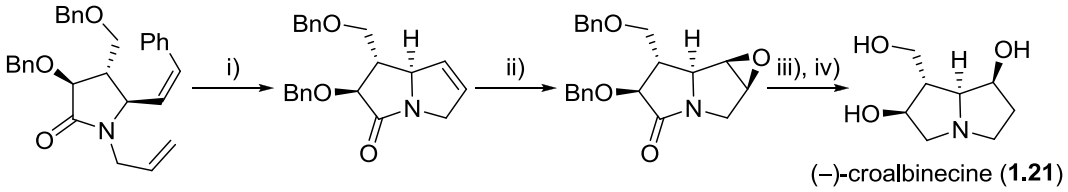
A particularly popular example of C–C bond forming cyclisation uses the Dieckmann cyclisation of pyrrolidine derivatives to form the second ring of the pyrrolizidine moiety. This method was first demonstrated in 1936 by Clemo and Metcalfe, in their synthesis of 3,5-dimethylpyrrolizidine (**1.20**, **Scheme 10**).[67] This strategy is similar to that used by Snider in his synthesis of (+)-NP25302,[68] which will be discussed later.



i) $BrCH(Me)CO_2Et$, K_2CO_3, 74%; ii) K in xylene, then HCl, Δ, 62%;
iii) $NH_2NH_2.H_2O$, NaOEt, Δ, 30%

Scheme 10

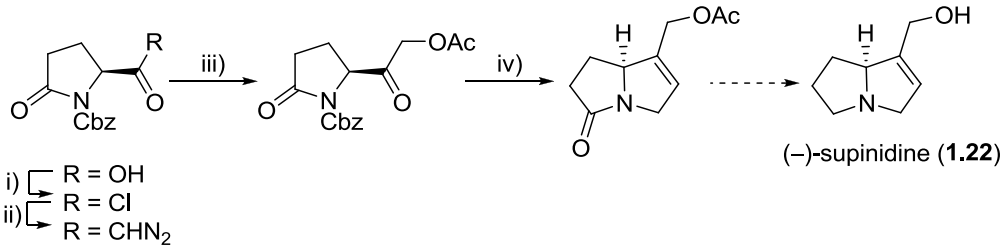
Amongst other, more common C-C bond forming strategies, there are a few unusual and less intuitive examples that deserve mention. For example, Ahn's synthesis of (−)-croalbinecine (**1.21**, **Scheme 11**) is based on ring closing metathesis to form the second ring of the bicyclic system.[69]



i) Grubbs I, PhH, 90%; ii) *m*-CPBA, $NaHCO_3$, PhH, 61%;
iii) $LiAlH_4$, THF, 65%; H_2, $Pd(OH)_2/C$, MeOH, 61%

Scheme 11

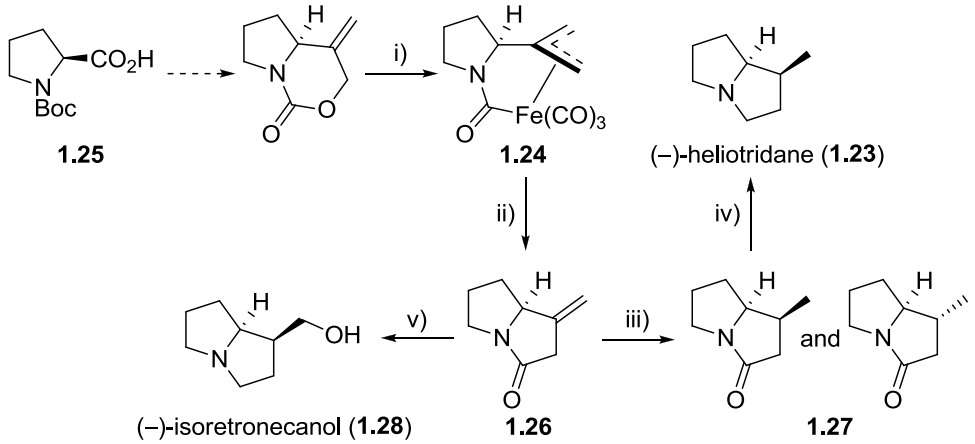
An unusual sequential conjugate addition/Wittig process formed the N-C(3) and C(1)-C(2) bonds concomitantly in Hewson's formal synthesis of (−)-supinidine (**1.22**, **Scheme 12**).[70]



i) $(COCl)_2$, THF; ii) CH_2N_2, THF, KOH 84% over two steps; iii) AcOH, Δ, 78%;
iv) 1) H_2, Pd/C, MeOH, 87%; 2) $CH_2{=}CHPPh_3{}^+Br^-$, THF, MeCN, NaH, 58%

Scheme 12

Ley and Knight used π-allyltricarbonyl iron chemistry to prepare (−)-heliotridane (**1.23**, **Scheme 13**).[71] Iron complex **1.24** was obtained from *N*-Boc proline **1.25** in good yield, and treatment of this complex with either CAN or carbon monoxide gave lactam **1.26**. Hydrogenolytic reduction gave both diastereomers of methyl lactam **1.27**, and amide reduction of the desired diastereomer gave heliotridane. Separately, lactam **1.26** could also be converted, by hydroboration and oxidation, to (−)-isoretronecanol (**1.28**).



i) $Fe_2(CO)_9$, PhH,))), 98%; ii) CAN, MeCN, –30 °C, 26% **or** CO, 305 atm, PhH, 105 °C, 80%;
iii) H_2, Pd/C, EtOAc, RT, 73%; iv) $LiAlH_4$; v) 1) BH_3, THF, Δ; 2) NaOH, H_2O_2; 3) HCl, MeOH, Δ

Scheme 13

1.1.4 Snider's synthesis of the jenamidines and (+)-NP25302

Work by Snider on the jenamidine PAs[68] (**Figure 10**) showed that the initial structural assignment of these natural products was incorrect. Re-examination of spectroscopic data from the natural product

led to the proposal of a pyrrolizidine-type core, and this structural reassignment was confirmed by the total synthesis of jenamidines A_1 (**1.29**) and A_2 (**1.30**) within the Snider group.

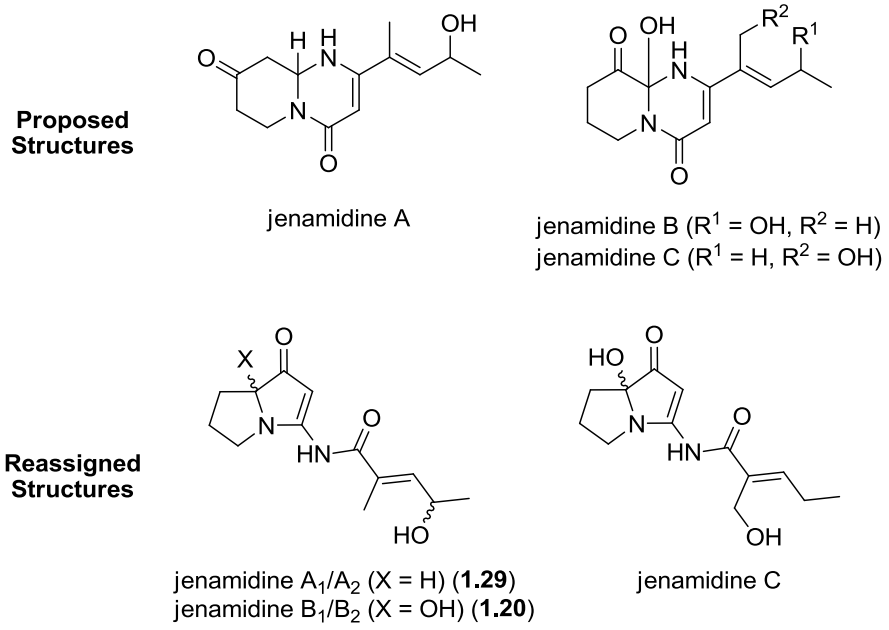
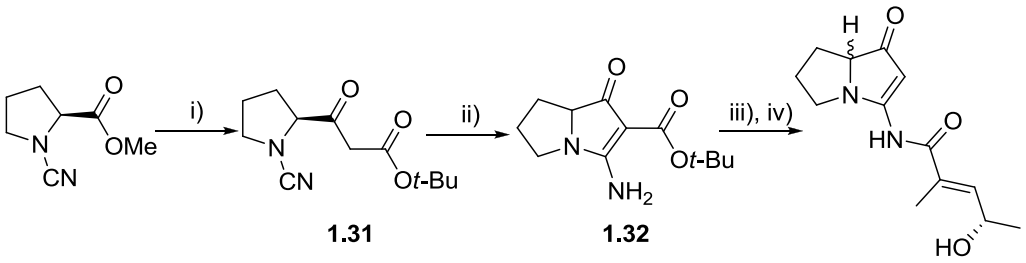
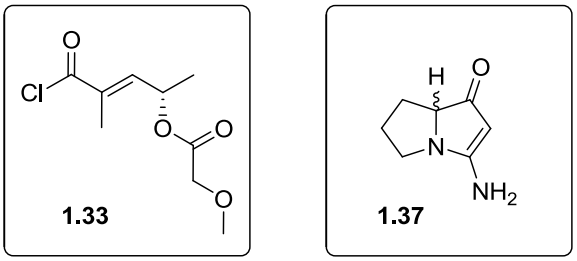


Figure 10

The key step of Snider's synthetic route was intramolecular addition of an enolate to the *N*-centred nitrile in cyanamide **1.31**, derived from (*S*)-proline, giving amine **1.32** (**Scheme** 14). This was acylated and the *tert*-butyl ester group removed to give access to the natural product as a mixture of diastereomers.

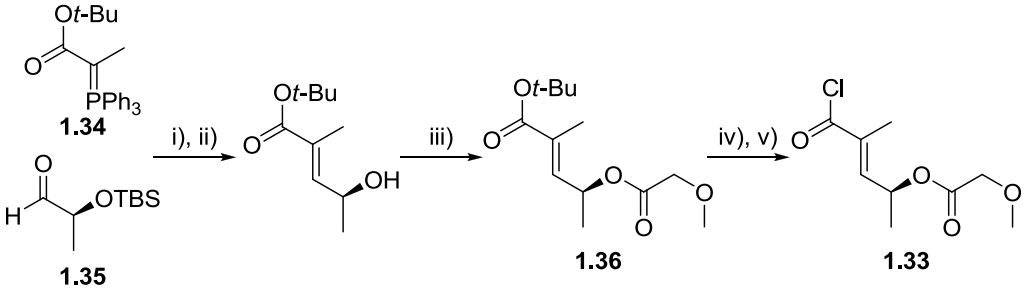


i) LDA, *t*-BuOAc, THF, –45 °C; ii) LHMDS, 25 °C, 27% over two steps;
iii) NaH, **1.33**, THF then 9:1 DCM/TFA; iv) Na_2CO_3, MeOH, 0°C, 45% over 2 steps.



Scheme 14

Formation of side-chain component **1.33** began with the Wittig reaction of ylid **1.34** and aldehyde **1.35** (**Scheme 15**), this latter coupling partner being obtained from (*S*)-lactic acid. The so-formed hydroxy ester was transformed into *tert*-butyl diester **1.36** before being converted into the acid chloride **1.33** under standard conditions.



i) DCM, 25 °C, 67%; ii) pyr.HF, THF, pyr, 99%; iii) $MeOCH_2COCl$, DMAP, pyr, THF, 99%;
iv) 9:1 DCM/TFA, 25 °C, 98%; v) $(COCl)_2$, 25 °C

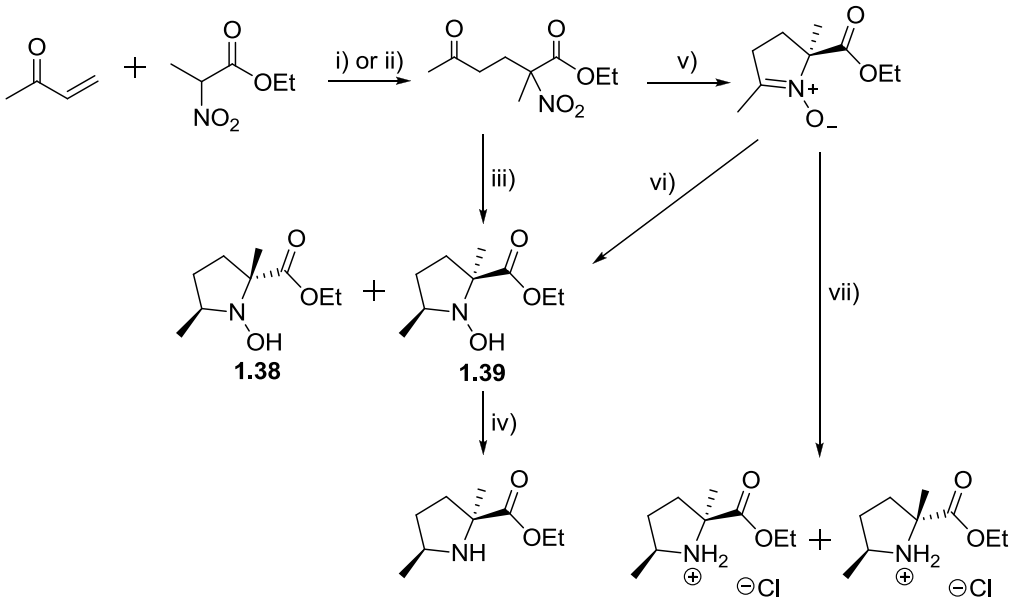
Scheme 15

Protection of the side-chain alcohol had to be carefully considered; the installed protecting group had to be stable under the conditions required to form the acid chloride, and yet deprotected under conditions mild enough that cleavage of the amide bond was avoided. Although the methoxyacetate group performed relatively badly in the coupling reaction, giving only 39% of the amide product,

deprotection with Na_2CO_3 in methanol gave 70% of the desired jenamidines, A_1 and A_2 with only 18% of the hydrolysis product, vinylogous urea **1.37**, and was found to be the best overall protecting group.

Sadly, **1.37** could not be acylated using the conditions that had been successful for **1.32** and, in the end, the highest yields were obtained by conducting the deprotection on the crude product from the previous step, giving a 45% two-step yield and only trace amounts of the amide side-product.

The group then went on to synthesise (+)-NP25302 *via* the same key cyclisation step. The required 2,2,5-trisubstituted pyrrolidine was obtained *via* a diastereoselective reductive cyclisation of ethyl 2-methyl-2-nitro-5-oxohexanoate (**Scheme 16**). This acyclic ketone was prepared as the racemate using either DABCO in DCM or $Yb(OTf)_3$ in water to couple ethyl 2-nitropropanoate with methyl vinyl ketone, a procedure reported by Feringa *et al*. in 1997.[72]

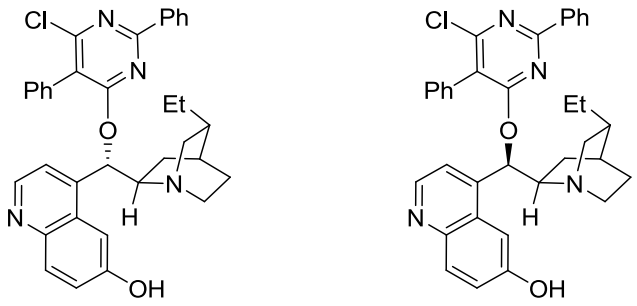


(i) $Yb(OTf)_3$, H_2O, 98%; (ii) 0.1 eq. DABCO, DCM, 5 h, 98%; (iii) 35 psi H_2, Pd/C, EtOH, Na_2SO_4, 2 h, 69% (2:1); (iv) Zn/Cu, 70 °C, 2:1 AcOH:EtOH, 63%; (v) H_2, Pd/C, EtOH, Na_2SO_4, 15 h, 99%; (vi) H_2, PtO_2, EtOH, 8 h, 100% (19:1); (vii) as vi) then 3 eq. HCl, 3.3 atm H_2, 36 h, 100% (20:1).

Scheme 16

Hydrogenation over Pd/C gave a 2:1 ratio of the *trans*-/*cis*-dimethyl hydroxylamines **1.38** and **1.39** (**Scheme 16**). Reduction of the hydroxylamines to the desired amines required more forcing conditions than expected, presumed to be due to the steric hindrance from the 2,2,5-trisubstitution pattern. This reduction procedure was improved by Snider with the addition of c. HCl (aq.) to the reaction mixture after the relatively fast formation of the oxime. This more efficient, one pot procedure furnished the amine in a 95:5 *trans*-/*cis*-dimethyl ratio, and in nearly quantitative yield.

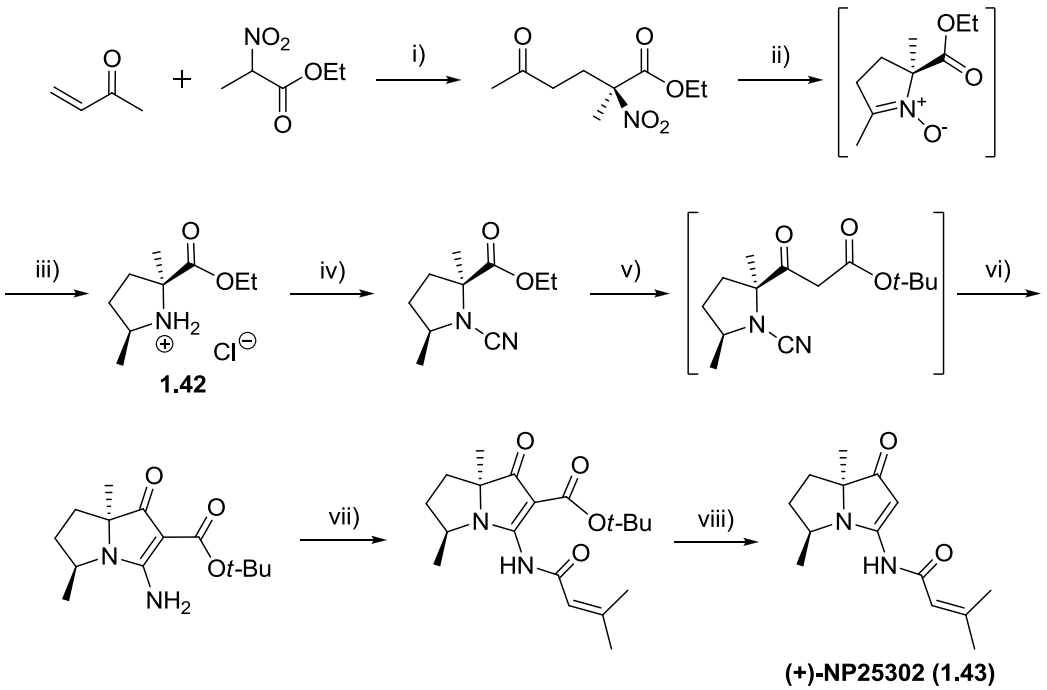
The sequence was then adapted to give enantiopure 2,5-dimethyl proline by the use of the chiral catalysts **1.40** and **1.41** (**Figure 11**)[73, 74] for the Michael addition. The stereochemistry of the two enantiopure salts obtained after the reductive cyclisation step was determined by comparison of the (*R*)- and (*S*)- Mosher amides with known data.



1.40 **1.41**

Figure 11

From hydrochloride salt (−)-**1.42** (**Scheme 17**), formed in 90% e.e. using catalyst **1.41**, (+)-NP25302 was obtained in five steps, analogous to those used in the jenamidine synthesis. The coupling partner for side-chain installation was commercially available 3-methyl-2-butenoyl chloride.



i)10 mol% **1.41**, DCM, –20 °C, 100%, 90% e.e; ii) 35 psi H_2, Pd/C, EtOH, Na_2SO_4; iii) H_2, PtO_2, EtOH then HCl, 3.3 atm H_2, 95% (and 5% *cis*-); iv) CNBr, $NaHCO_3$, EtOH, 75%; v) LDA, THF, *t*-BuOAc, -45 °C to RT; vi) tBuOK, tBuOH, 135 °C, 49%; vii) NaH, THF, 3-methyl-2-butenoyl chloride; (viii) TFA, DCM, 88% over two steps.

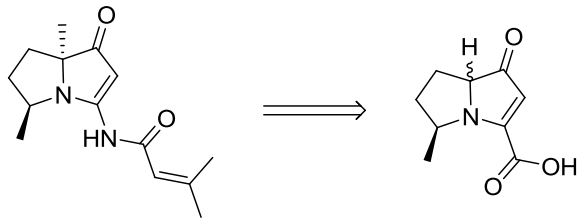
Scheme 17

Snider's first total synthesis of (+)-NP25302 (**1.43**) confirmed the absolute stereochemistry of the natural product was 4*S*,7*S*.

1.1.5 Previous work in Robertson group towards *nor*-NP25302

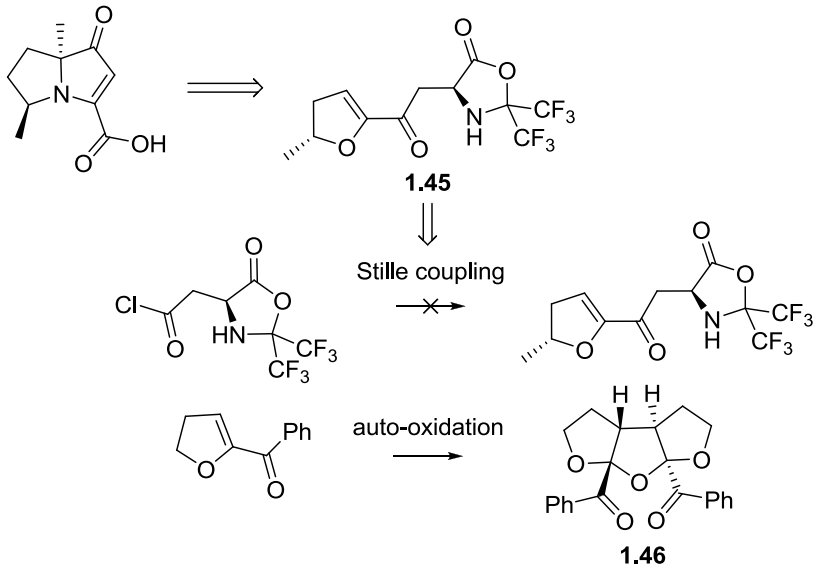
With a view to synthesising pyrrolizidine containing natural products, several pyrrolizidine forming strategies were trialled within the Robertson group.[75]

The initial retrosynthetic plan for (+)-NP25302 (**1.43**) was to incorporate the side chain moiety by means of a Curtius rearrangement, following on from work conducted in the group towards the *N*-acyl dienamine side-chain of the lituarines A–C.[76,77] Introduction of the C(7a) methyl group was to be conducted stereoselectively at a late stage in the synthesis. This left pyrrolizidine acid **1.44** (**Scheme 18**) as the required precursor, for which several methods of formation were envisaged and trialled.



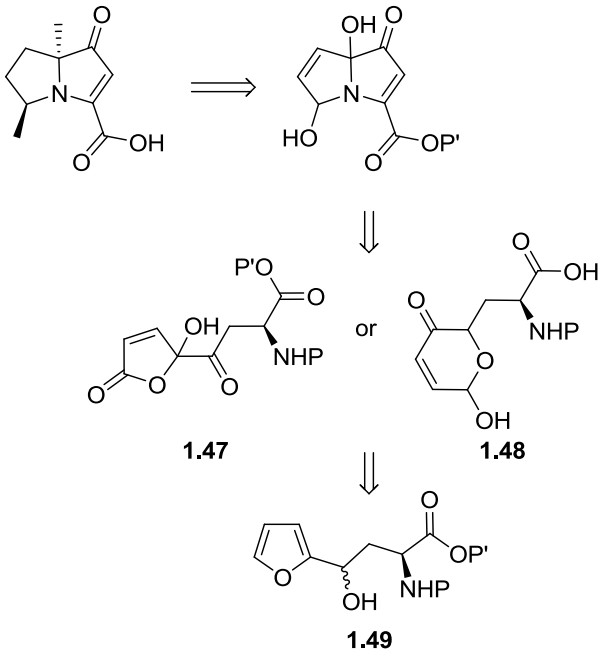
Scheme 18

The first attempts were based upon the oxidative rearrangement of acyl-dihydrofuran **1.45** (**Scheme 19**). This route was unsuccessful due to the unexpected and facile oxidative dimerisation of such precursors in model systems to give dimeric products **1.46**.[78]



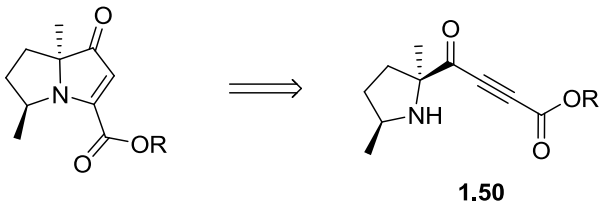
Scheme 19

This instability, as well as difficulties in forming the required dihydrofuran **1.45** *via* Stille coupling, led to attempts to work with the analogous acyl furan derivatives (**Scheme 20**). These were to be oxidised either to the hydroxy butenolide **1.47**, or to the pyranone **1.48** *via* Achmatowicz reaction[79] of α-hydroxyfuran **1.49**. Removal of the nitrogen protecting group would, it was expected, lead to cyclisation to the desired pyrrolizidine core. This route was also unsuccessful, in this case because furan precursor **1.49** was found to be strongly resistant to oxidation.



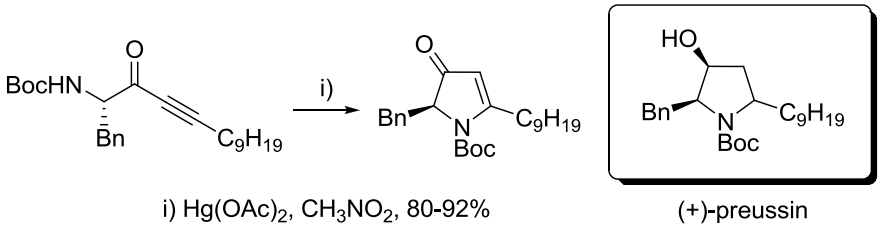
Scheme 20

The most successful conditions were found in a 5-*endo*-dig cyclisation approach, where the second ring of the pyrrolizidine was disconnected across N-C(3) to give alkyne **1.50** as the necessary precursor (**Scheme 21**).



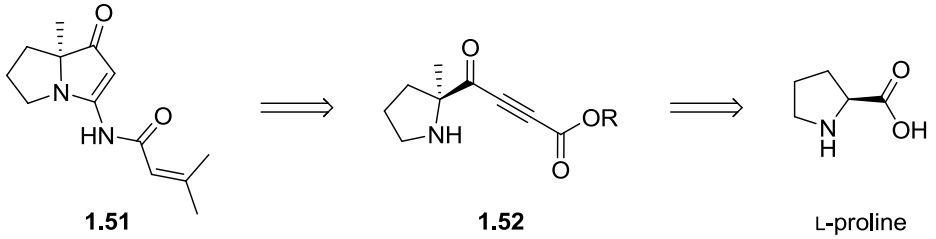
Scheme 21

This Baldwin-favoured[80] mode of cyclisation was used in one earlier natural product synthesis, that of the antifungal agent (+)-preussin (**Scheme 22**).[81] In this case the cyclisation was induced by treatment with $Hg(OAc)_2$, but there are many conditions that have been shown to effect the same type of transformation, and also to conduct 6-*endo*-dig cyclisations on analogous one-carbon homologated ynone substrates.[82] However, this cyclisation type has never previously been used to construct the pyrrolizidine core.



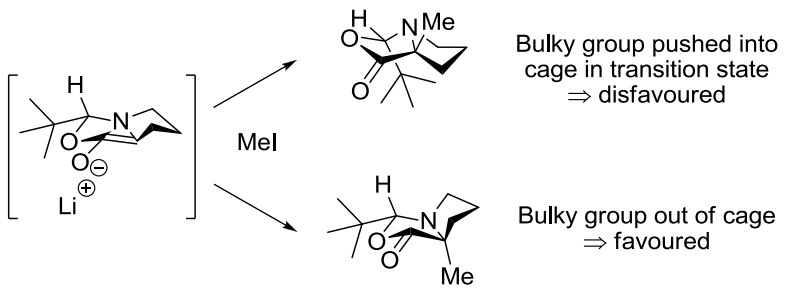
Scheme 22

In order to simplify the synthesis during the investigative stage, work began towards the C-5 unsubstituted analogue, '*nor*-NP25302' (**1.51**, **Scheme 23**).



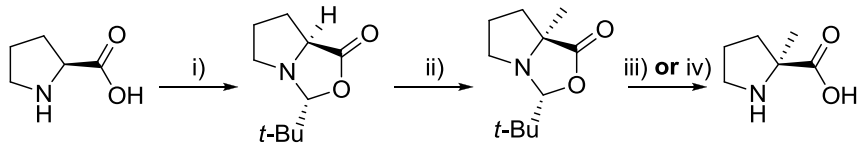
Scheme 23

The required alkyne (**1.52**) was envisaged to come from L-proline, making use of Seebach's conditions for stereoselective C-2 alkylation of proline enolates.[83] Following formation of the bicyclic oxazolidinone diastereoselectively, the enolate then alkylates on the *exo*- face, hence retaining the original stereochemistry (**Scheme 24**). The oxazolidinone component is easily cleaved under mildly acidic conditions, and Johnson *et al*. have devised an improved method[84] which avoids the ion exchange chromatography required in Seebach's original work. This 'self-regeneration of stereochemistry' *via* the use of a 'temporary' stereogenic centre has been applied to L-proline on a number of occasions, and is a useful tool in total synthesis.



Scheme 24

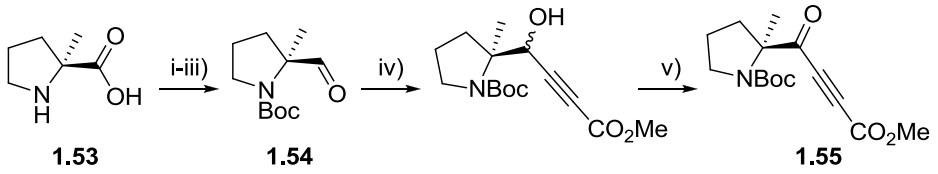
Following this protocol, (*S*)-2-methyl proline was obtained in three steps from L-proline in good yield. Both methods of oxazolidinone deprotection were successful but, for convenience, the Johnson method was preferred.



i) *t*-BuCHO, cat. TFA, pentane, reflux 3–6 d, 74%; ii) LDA, THF, –78 °C, then MeI, 95%;
iii) 3 M HCl, reflux, 1 h, then Dowex 50W × 8(H^+), 90%; iv) SiO_2, MeOH, H_2O, > 90%.

Scheme 25

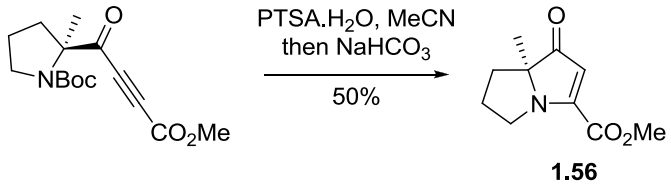
Amine **1.53** was protected as the *tert*-butyl carbamate (**Scheme 26**) under conditions developed by Johnson *et al.*, using *tert*-methylammonium hydroxide in order to enhance the solubility of the amino acid.[85] This protected amino acid was transformed under standard conditions into aldehyde **1.54**, and the alkyne component introduced by addition of lithiated methyl propiolate. Oxidation of the resulting alcohol furnished cyclisation precursor **1.55** in good yield.



i) Boc_2O, TMAH, MeCN, 100%; ii) BH_3.THF, THF, 100%; iii) DMP, DCM, 97%;
vii) *n*-BuLi, $HCCCO_2Me$, THF, –78 °C, 100%; iv) DMP, DCM, 73%.

Scheme 26

Initial attempts to effect the 5-*endo*-dig cyclisation step employed conditions for the deprotection of *N*-Boc prolines (**Scheme 27**).[86] The yield for this transformation was slightly disappointing, but due to the time constraints on this previous work, no further investigations had been conducted at the start of this project.



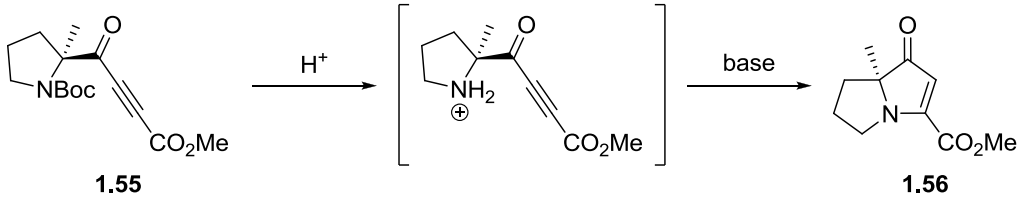
Scheme 27

Optimisation of this 5-*endo*-dig cyclisation step was, however, important in order to ensure that this was a viable and efficient method of pyrrolizidine ring synthesis. Accordingly, this project began with investigations into the cause of the relatively low yields observed for this transformation in an attempt to improve this step.

1.2 Results and Discussion

1.2.1 Studies into the 5-*endo*-dig cyclisation

It was postulated that the initial, acidic stage of the cyclisation reaction was simply removing the Boc group and that the $NaHCO_3$ was effecting the cyclisations (**Scheme 28**). Certainly, the characteristic bright yellow of these pyrrolizidine compounds was only observed upon addition of the basic reagent. It was therefore decided to split this process into its two constituent parts in order to pinpoint where material was being lost.



Scheme 28

Attempts to obtain the amine explicitly were unfortunately unsuccessful; no deprotection was observed using TFA at RT and increasing the reaction temperature led to decomposition.

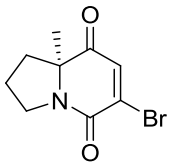
It was also possible that the low yields and mass recovery were arising from saponification of the methyl ester under the reaction conditions. Reducing the time spent stirring in base gave a small increase in yield to 59%, however, no evidence of such hydrolysis products could be observed in the crude material obtained from extensive methanol washing of the filter cake.

With no further optimisation achievable for these conditions, other reagents were trialled (**Table 1**); in particular, using reagents that might be sufficiently Lewis acidic to encourage the cyclisation process.

Reagents	**Temp**	**Product (yield/%)**
i) PTSA.H_2O, MeCN, 18 h; ii) $NaHCO_3$, $PtCl_2$ (5 mol%),[87] 4 h	RT	**1.56** (56)
i) PTSA.H_2O, MeCN, 24 h; ii) $NaHCO_3$, $SnBr_2$ (10 mol%), 4 h	RT	**1.56** (57)
Catechol boron bromide (2 eq), DCM, 18 h[88]	RT	**1.57** (50)
$Hg(OAc)_2$, $MeNO_2$, then NaCl (aq.), 18 h[81]	RT	SM only
$Hg(OAc)_2$, AcOH, then NaCl (aq.), 18 h[89]	RT	**1.56** (16)
$Hg(OCOCF_3)_2$, AcOH then NaCl (aq.), 18 h[89]	RT	**1.56** (38); **1.58** (60)
TMSOTf (3 eq.), DCM then $NaHCO_3$ (aq.), 3 h	−30 °C	**1.56** (61)

Table 1

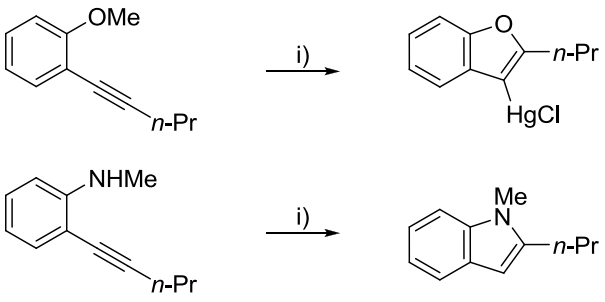
Although the majority of these gave no improvement, some interesting results were obtained. For example, application of pre-formed catechol boron bromide[90] in DCM, a reagent known to deprotect Boc groups,[88] gave brominated diketone **1.57** (**Figure 12**) as the only identifiable product.



1.57

Figure 12

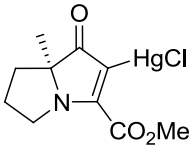
Application of conditions used in the synthesis of (+)-preussin (**Scheme 22**),[81] were unsuccessful, returning only unreacted starting material. However, changing the solvent to acetic acid, as used by Larock and Harrison in the synthesis of 3-(chloromercurio)benzofurans *via* a similar 5-*endo*-dig cyclisation (**Scheme 29**),[89] gave a small amount of the pyrrolizidine product.



i) $Hg(OAc)_2$, HOAc then NaCl (aq.)

Scheme 29

The more reactive $Hg(OCOCF_3)_2$, gave a slight improvement in yield but also furnished a significant amount of undesired organomercury species **1.58**, the chloro- substituent coming from the brine work up. This product is similar to those obtained by Larock and Harrison in cyclisation reactions using oxygen nucleophiles, although they observed no mercury incorporation in examples using nitrogen nucleophiles instead getting directly to the protonated indole products.



1.58

Figure 13

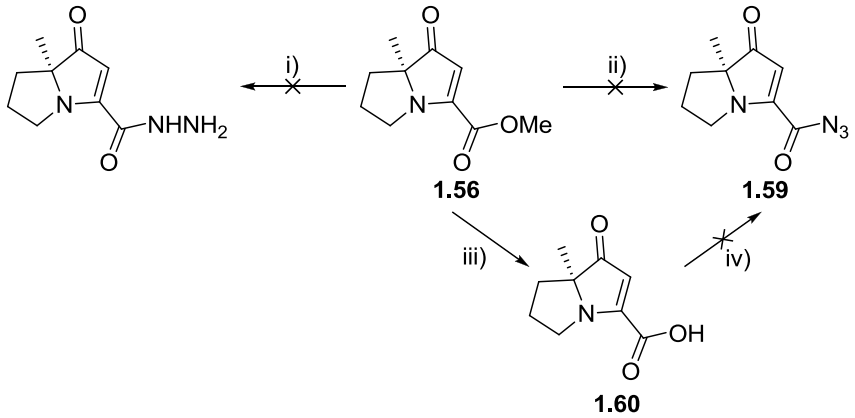
Although the mercury could be removed under reductive conditions,[91] the addition of an extra step into the synthesis was not acceptable.

The best conditions found for cyclisation of **1.55** were TMSOTf in DCM, with the reaction being allowed to warm from −30 °C until no starting material remained, and quenched with sat. aq. $NaHCO_3$. The progress of this reaction was similar to that of the original PTSA conditions, with the yellow colour developing during the basic work-up. These conditions were reproducible and gave consistent yields.

1.2.2 Acyl azide synthesis

With the small amount of material obtained from initial work on the cyclisation step, some investigations had already been undertaken into formation of the acyl azide (**1.59**, **Scheme** 30), with little success.

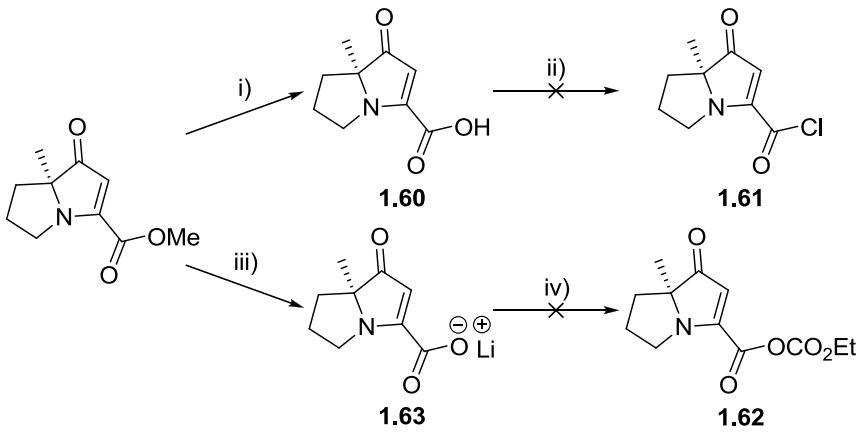
Treatment of ester **1.56** with either NH_2NH_2 or Et_2AlCl and NaN_3 had been unsuccessful, returning only unreacted starting material (**Scheme 30**). Proceeding *via* carboxylic acid **1.60** and using DPPA in toluene gave trace quantities of the desired product, but problems with the solubility of the acid in toluene or 1:1 toluene/*tert*-butanol meant that this route was not viable.



i) NH_2NH_2, MeOH; ii) Et_2AlCl, NaN_3, hexane; iii) aq. LiOH, MeCN, 42%; iv) DPPA, TEA, PhMe or 1:1 *t*-BuOH/PhMe

Scheme 30

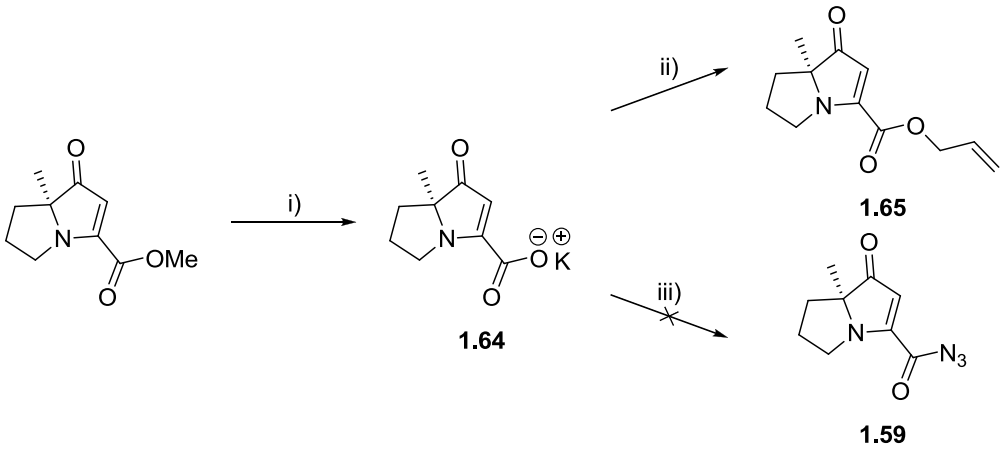
Forming the acid chloride (**1.61**) or the mixed anhydride (**1.62**) from this acid, in the hope of effecting displacement with NaN_3, was also unsuccessful (**Scheme 31**). Interestingly, when anhydride formation was attempted using ethyl chloroformate in THF, the reagent reacted with the solvent in preference to the carboxylate substrate. These results led to concerns over the reactivity of this lithium carboxylate (**1.63**), however, time constraints on this work meant that no solution had been found to this problem.



i) aq. LiOH, MeCN then H_3O^+, 42%; ii) $(COCl)_2$, DCM, DMF; iii) aq. LiOH, MeCN; iv) $ClCO_2Et$, H_2O, acetone

Scheme 31

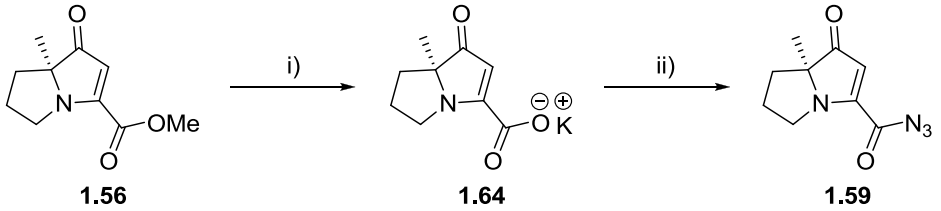
The more reactive potassium carboxylate (**1.64**) (**Scheme 32**) was prepared and its reactivity tested by reaction with allyl bromide in DMSO, pleasingly, furnishing allyl ester **1.65** in quantitative yield. However, this species was still unreactive towards ethyl chloroformate and NaN_3.



i) KOH, MeCN/H_2O, 100%; ii) CH_2=$CHCH_2Br$, DMSO, 100%;
iii) $ClCO_2Et$, NEt_3, DMAP, H_2O, acetone then NaN_3

Scheme 32

There was precedent for DPPA being used in DMF to furnish azides from carboxylic acids.[92,93] Although DPPA had failed when used in toluene, it was hoped that this more polar reaction solvent would lead to increased reactivity of the carboxylate. Application of these conditions[93] gave the desired acyl azide in poor yield, but omission of TEA from the reaction led to a significant improvement, with near quantitative conversion (**Scheme 33**).



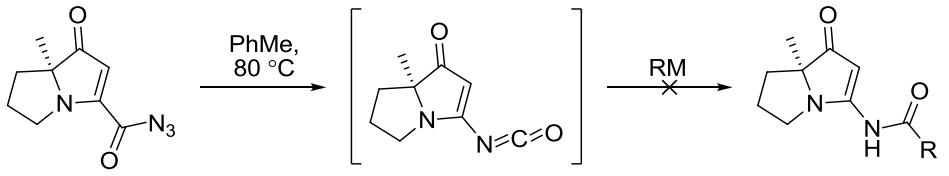
i) KOH, MeCN/H_2O, 100%; ii) DPPA, DMF, 0 °C, 95%

Scheme 33

1.2.3 Curtius rearrangement of acyl azide 1.59

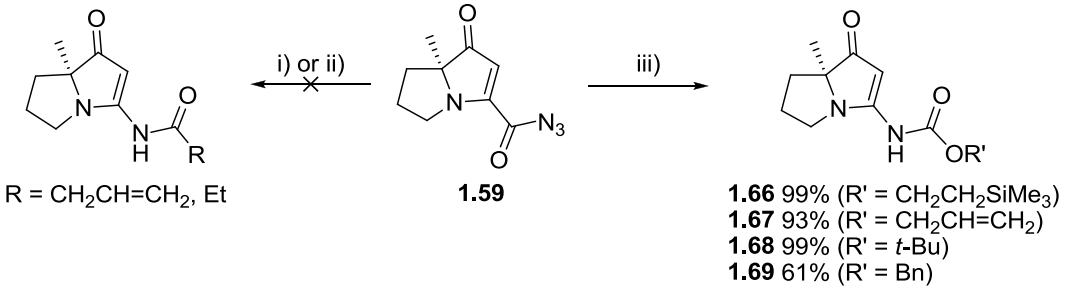
With acyl azide **1.59** obtained in good yield, attention was then turned to the second key step of the synthesis, the Curtius rearrangement (**Scheme 34**). ^{1}H NMR experiments carried out to establish the lifetime of the isocyanate intermediate found that formation of the isocyanate in the absence of any trapping agent led to rapid precipitation of an unidentifiable polymeric species. This meant that

original plans to add organometallic reagents to the pre-formed isocyanate had to be modified to use organometallic species that were compatible with the high temperatures required to form the isocyanate.



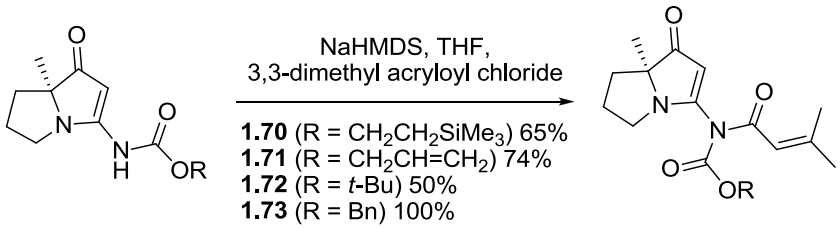
Scheme 34

Allyltributyl tin[94] and diethyl zinc[95] were both unsuccessful in this application, leading to polymeric decomposition products (**Scheme 35**). However, heating the acyl azide in the presence of a large excess of an alcohol nucleophile led to formation of carbamates **1.66–1.69**.



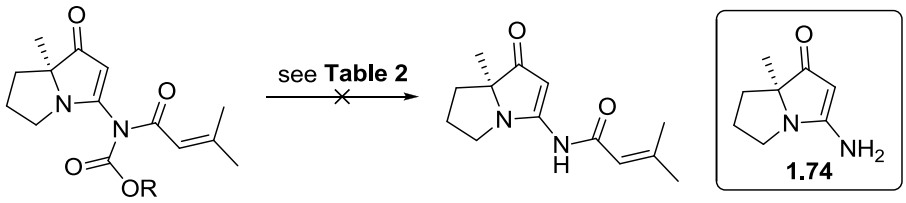
Scheme 35

It was envisaged that *nor*-NP25302 could be accessed by acylation and subsequent deprotection of these carbamate species. Indeed, acylation proved facile, giving good yields of the protected amides **1.70–1.73** (**Scheme 36**).



Scheme 36

However, deprotection of any of the acylated carbamates (**Scheme 37**) was unsuccessful under a range of conditions (**Table 2**). Typically, the result was either removal of the newly installed acyl chain in preference to the protecting group, or removal of both groups simultaneously to yield amine **1.74**.

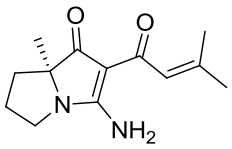


Scheme 37

SM	Conditions	Temp	Time (h)	Product (yield/%)
1.70	TBAF (3 eq), THF[96]	0 °C	0.33	**1.74** (100)
1.70	H_2SiF_6 (20% aq.), MeCN[97]	0 °C – RT	24	SM + **1.74** (45)
1.70	CsF, DMF[98]	90 °C	1	**1.75** (97)
1.70	CsF, DMF	RT	1	SM
1.70	CsF, DMF	40 °C	2	Decomposition
1.70	TFA/DCM, 1:2[99]	RT	0.5	**1.74** (100%)
1.70	TASF, DMF[100]	0 °C – RT	16	**1.74** (100%)
1.70	TFA/DCM, 1:9[68]	0 °C	0.5	SM + **1.74**
1.71	$Pd(PPh_3)_4$, PPh_3, pyrrolidine, MeCN	0 °C – RT	0.5	**1.74** (100%)
1.72	TFA/DCM, 1:9	RT	1	**1.74** (73%)
1.72	$BiCl_3$, MeCN then $NaHCO_3$[81]	RT	2	**1.74**
1.73	H_2, 10% Pd/C (1.5 eq), EtOAc/EtOH[101, 102]	RT	0.17	**1.74** (100%)
1.73	H_2, 10% Pd/C (10 mol%), EtOAc/EtOH	RT	1.5	**1.74** (100%)

Table 2

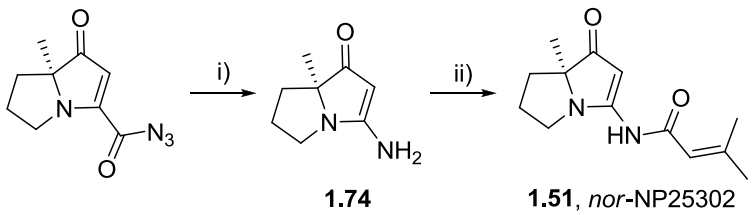
Some interesting results were obtained during attempted deprotection of Teoc protected compound **1.70** with CsF in DMF, conditions used by Igarashi *et al.* in the final step of their synthesis of quinidine.[98] At higher temperatures the carbamate protecting group was removed but the acyl chain migrated to C(2) giving isomeric pyrrolizidine **1.75** (**Figure 14**). Conducting this reaction at lower temperatures, in the hope of deprotecting the carbamate without this unwanted migration, was unsuccessful: at RT only starting material was recovered, and at 40 °C the reaction mixture decomposed, presumably due to the extended reaction time required for complete consumption of the starting material.



1.75

Figure 14

Having observed free amine **1.74** a number of times in these deprotection attempts, it was decided to access this directly and simply acylate under similar conditions to those described by Snider *et al.* in his original synthesis.[68] Conducting the Curtius rearrangement in an acidic aqueous environment[103] followed by acylation of the so-formed amine (**1.74**) finally gave access to *nor*-NP25302 (**1.51**) in good yield (**Scheme 38**).



1.74 **1.51**, *nor*-NP25302

i) AcOH (95% aq.), 120 °C, 85%; ii) NaH, THF, 3,3-dimethylacryloyl chloride, 68%

Scheme 38

Overall, this provided an efficient route to *nor*-NP25302, conducted in 12 steps and 9% overall yield from L-proline, and proved the utility of the 5-*endo*-dig cyclisation in pyrrolizidine syntheses.

1.2.4 First generation synthesis of disubstituted motif

Having demonstrated the viability of the proposed route, it was now necessary to apply this to the real system. This required an equivalent 2,2,5-trisubtituted pyrrolidine scaffold (**Figure** 15), for which few diastereoselective syntheses are available. A survey of these methods is given below.

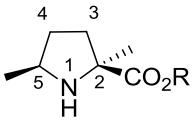
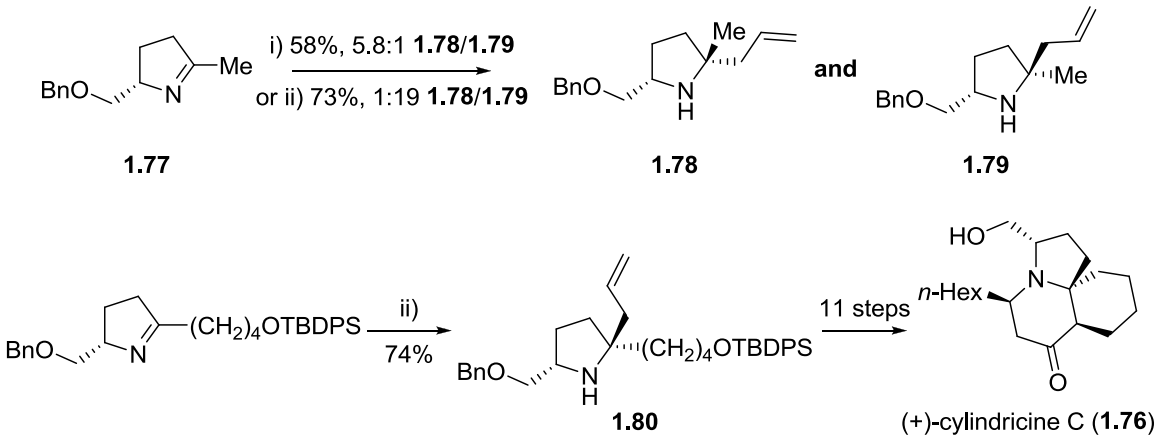


Figure 15

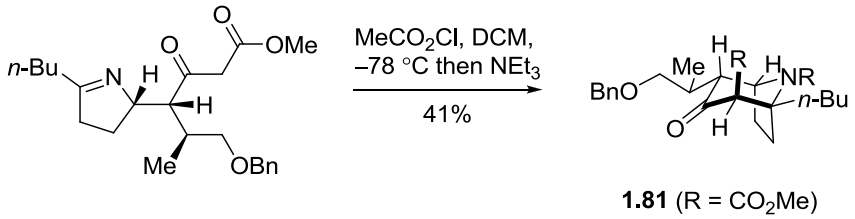
One regularly used method for the synthesis of such pyrrolidines is based around the addition of a nucleophile to a pyrroline, with addition either occurring from the less hindered face, or on the same face as any chelating groups attached to the ring. This approach was utilised in Kibayashi's synthesis of (+)-cylindricine C (**1.76**, **Scheme 39**).[104] Addition of allyl magnesium bromide to model imine **1.77** gave a 5.8:1 ratio of amines **1.78** and **1.79**, the major isomer arising from chelated delivery of the nucleophile and the minor arising from addition to the less hindered face of the ring. This selectivity was reversed by addition of a Lewis acid to the reaction, blocking any potential chelation of the benzyl ether to the Grignard reagent; when this modified procedure was applied to their real system, amine **1.80** was isolated in good yield as a single diastereomer.



i) CH_2=$CHCH_2MgBr$, THF, 0 °C; ii) CH_2=$CHCH_2MgBr$, $BF_3{\cdot}OEt_2$ (3 eq.), THF, –78 °C

Scheme 39

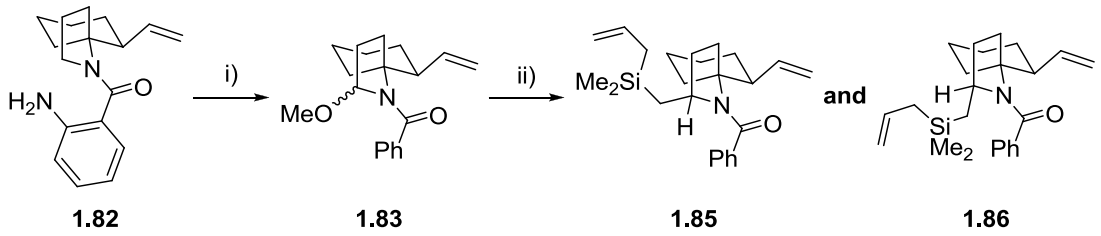
This methodology was also used in Thomas' work towards the synthesis of stemofoline,[105] an intramolecular enolate addition giving bicyclic pyrrolidine **1.81** (**Scheme 40**).



1.81 (R = CO_2Me)

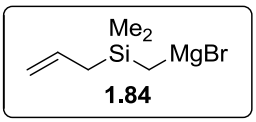
Scheme 40

A similar approach, based on addition to hemiaminal substrates and forming the imine *in situ*, was used in Weinreb's synthesis of the marine alkaloid lepadiformine (**Scheme 41**).[106] Oxidation of pyrrolidine **1.82** furnished α-methoxybenzamide **1.83** in good yield, and addition of Grignard reagent **1.84** gave a 7:1 ratio of amines **1.85** and **1.86**, the selectivity of this process again arising from the steric demands of the substrate.



1.82 **1.83** **1.85** **1.86**

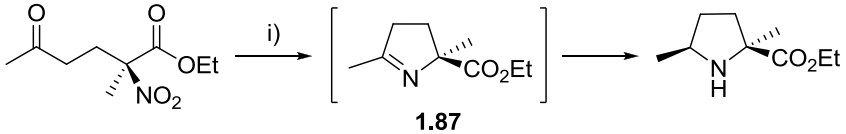
i) $NaNO_2$, HCl, CuCl, MeOH, 81%; ii) **1.84**, $CuBr_2{\cdot}SMe_2$, $BF_3{\cdot}OEt_2$, Et_2O, –78 °C → RT, 87%, 7:1 **1.85**/**1.86**



1.84

Scheme 41

This approach also bears similarity to that used by Snider in his synthesis of (+)-NP25302,[68] where imine **1.87** (**Scheme 42**) was reduced selectively on the less hindered face.

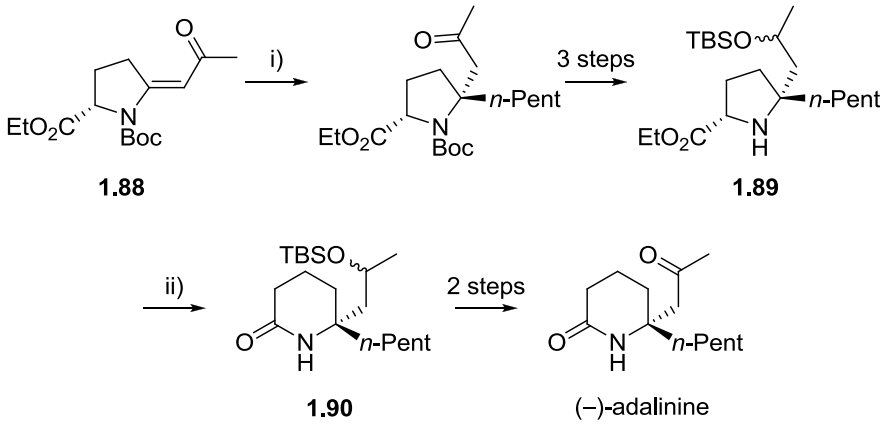


1.87

i) H_2, Pd/C, EtOH, Na_2SO_4, 99%

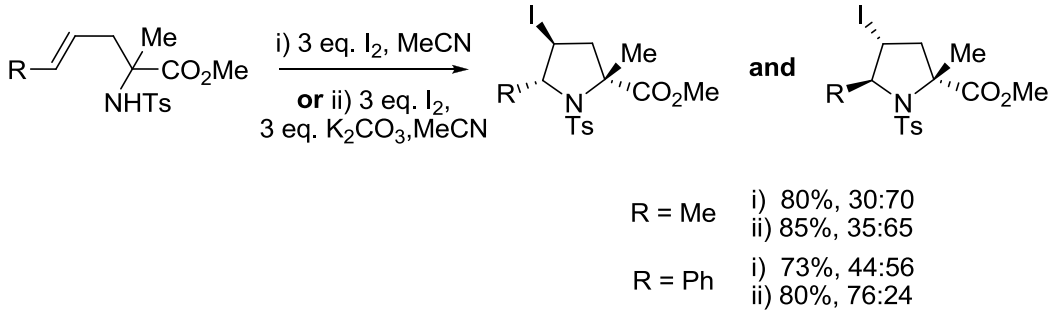
Scheme 42

A related addition process, in this case into α,β-unsaturated ketone **1.88** (**Scheme 43**) was employed by Honda during the total synthesis of (−)-adalinine.[107] Grignard addition gave selective addition to the least hindered face in good yield. Three further steps gave amino ester **1.89**, and SmI_2 mediated C–N bond cleavage furnished amide **1.90**, two steps away from the natural product.



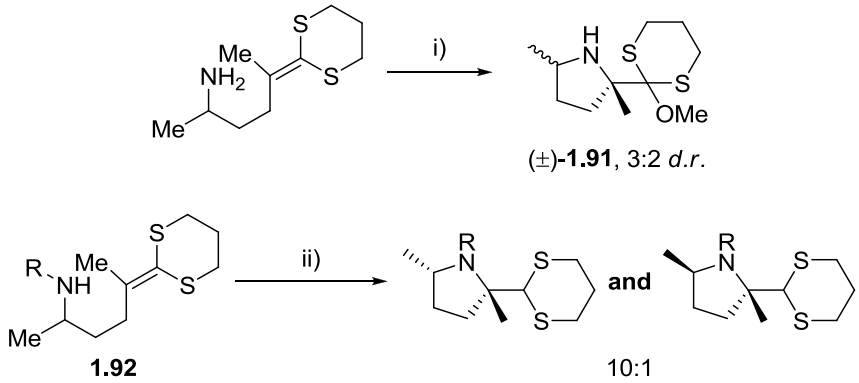
Scheme 43

N-Cyclisations are also used to form this type of structure, as in Knight's work on 5-*endo*-trig iodocyclisations (**Scheme 44**).[108] The different product ratio obtained upon addition of K_2CO_3 to the reaction is ascribed to a similar initial cyclisation in both systems, *via* a chair-like transition state, giving the *trans*-isomer, and subsequent equilibration of this product under protic conditions leading to the *cis*-product. Although this transformation tolerates high levels of substitution at the C(2) and C(5) positions, reactions on these crowded substrates tend to show little diastereoselectivity. As well as this, the iodine substituent present after the cyclisation must be removed in a separate step.



Scheme 44

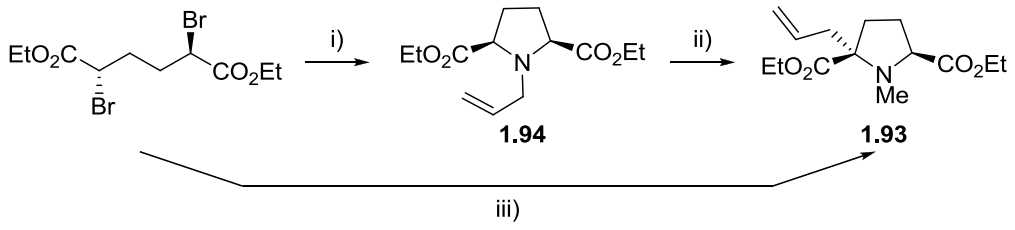
In work towards anodic coupling reactions of dithioketene acetals with amines,[109] Moeller *et al*. reported one example of a 2,2,5-trisubstituted pyrrolidine, **1.91**. Under these conditions, low diastereomeric ratios were obtained, a result that was attributed to the rapid rate of cyclisation. The same group later reported different conditions to cyclise similar substrate **1.92**[110] and, under these conditions, analogous products were obtained in a much higher *d.r*.



i) RVC anode, Pt cathode, LiOMe (0.5 eq.), MeOH, Et_4NOTs, 6 mA, 2.0 F/mol, 92%;
ii) 16% *n*-BuLi, THF, RT, R = Bn 95%, R = PMB 98%

Scheme 45

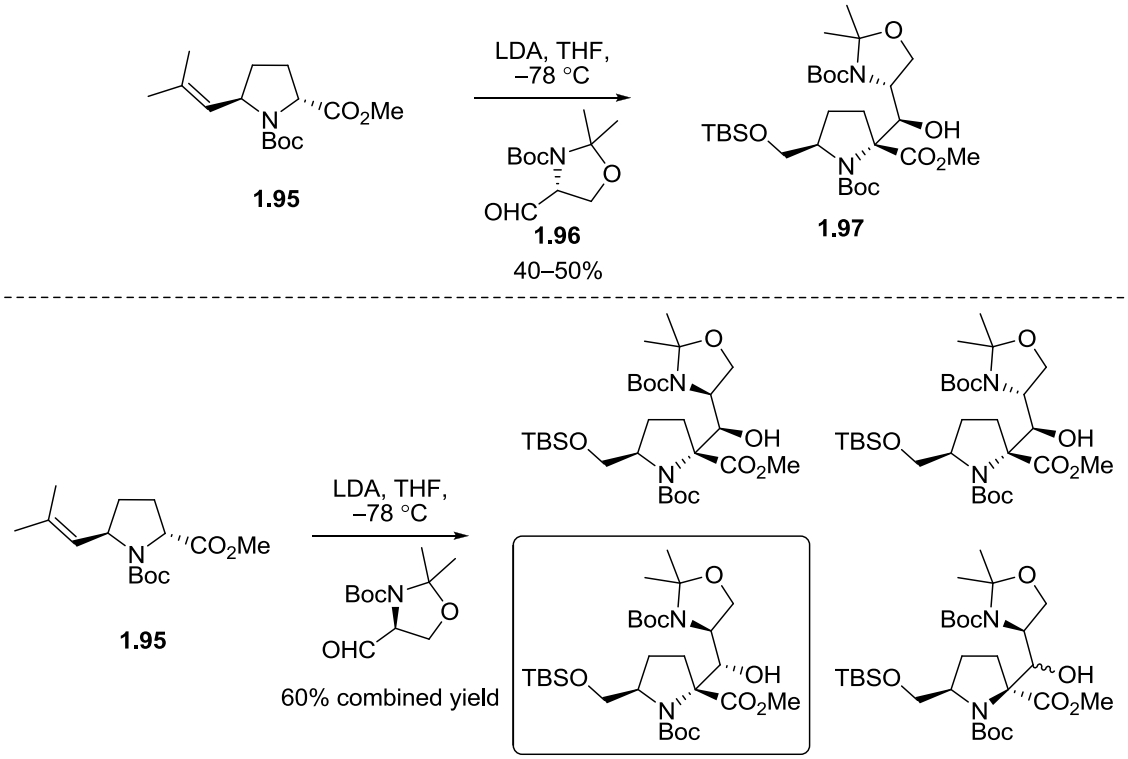
Smith and Bentley furnished pyrrolidine **1.93** by a Stevens [2,3]-sigmatropic rearrangement of *N*-allylamine **1.94** (**Scheme 46**),[111] using an external amine nucleophile to form the *cis*-2,5-disubstituted starting material. The trisubstituted pyrrolidine product was obtained as an inseparable mixture of *cis*-/*trans*- diastereomers in a 4:1 ratio (measured by GC), although only in moderate yield. These two steps were shortened to a one-pot procedure by the use of *N*-methylallylamine in the initial cyclisation step, thus avoiding the need for a separate amine quaternisation step required to promote the rearrangement.



i) allylamine, PhMe, 8 °C, 80% (3:1 *cis*-/*trans*- by GC); ii) MeI, K_2CO_3, DMF, 55 °C, 42% (4:1 *cis*-/*trans*- by GC);
iii) *N*-methylallylamine, K_2CO_3, DMF, 0 °C → RT, 58% (13:5 *cis*-/*trans*- by GC)

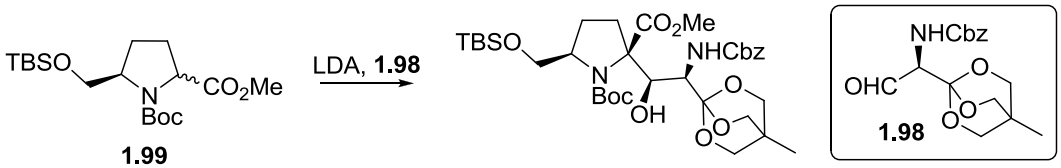
Scheme 46

Addition of pyrrolidine ester enolates to chiral aldehydes has been utilised in two separate syntheses of (−)-kaitocephalin, a natural product whose trisubstituted pyrrolidine core has been the subject of a great deal of synthetic attention. Chamberlin *et al*. found that the enolate of pyroglutamate-derived *trans*-disubstituted pyrrolidine ester **1.95** (**Scheme 47**) was able to add to (*R*)-Garner's aldehyde (**1.96**) to give alcohol **1.97** as a single diastereomer.[112] Unfortunately, when the same reaction was conducted using (*S*)-Garner's aldehyde, four diastereomeric products were obtained, the required isomer boxed, indicating a stereochemical mismatch between the two components.



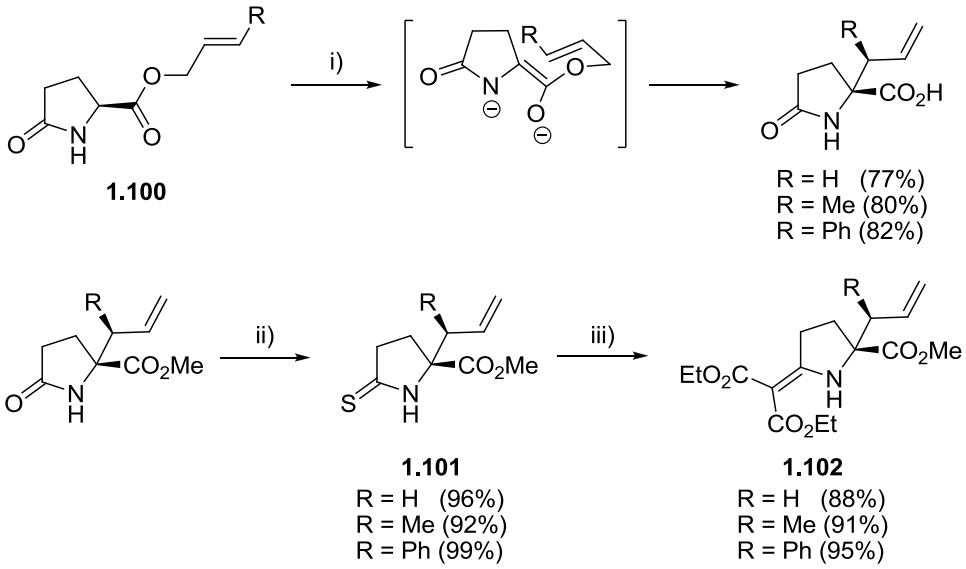
Scheme 47

Shinade and Ohfune used aldehyde **1.98** for a similar addition,[113] forming the enolate from a mixture of epimeric amino esters **1.99** (**Scheme 48**).



Scheme 48

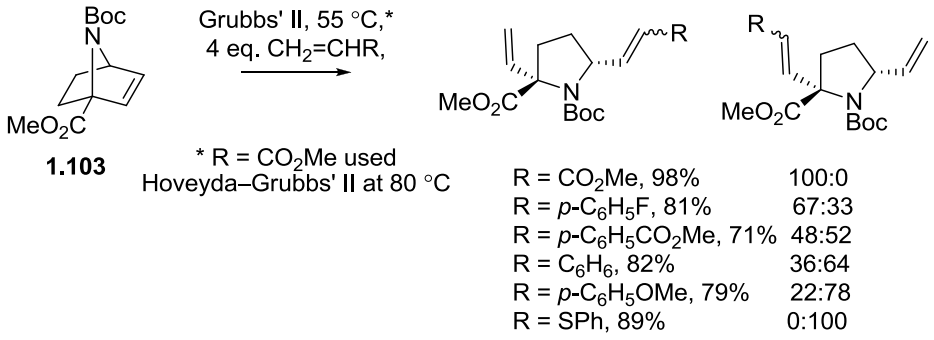
In their work towards the same natural product target, the Moloney group developed a diastereocontrolled synthesis of 2,2,5-trisubstituted pyrrolidines,[114] utilising the Ireland–Claisen rearrangement of pyroglutamic acid derived esters **1.100** (**Scheme 49**). After esterification of the resulting carboxylic acids, the C(5) carbonyl was converted, *via* Eschenmoser sulfide contraction of thioamides **1.101**, to enamines **1.102**.



i) LiHMDS, Al(*i*-OPr)$_3$, quinine, THF, –78 °C → RT; ii) Lawesson's reagent; iii) $(EtO_2C)_2CHBr$, $NaHCO_3$, Δ

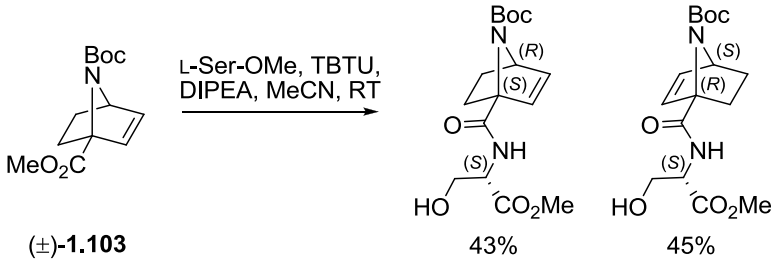
Scheme 49

Busto and Avenoza reported some unusual methodology for the synthesis of substituted pyrrolidine ring systems, *via* ring-opening methathesis/cross metathesis of azanorbornene substrates **1.103**.[115] Further work on this process led to the development of a highly regioselective process,[116] the connectivity of the product being determined by the electron density of the alkene being coupled to this bicyclic starting material (**Scheme 50**).



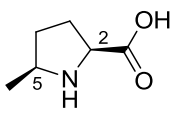
Scheme 50

More recently, this process has been developed to allow access to enantiopure quaternary prolines by first resolving the racemic norbornene **1.103** (**Scheme 51**),[117] giving two diastereomeric amides, separable by column chromatography.



Scheme 51

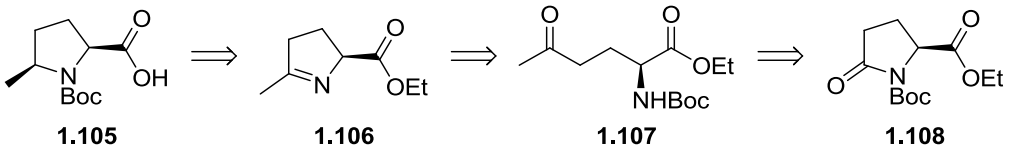
Since those approaches which were most applicable to the required dimethyl motif were only able to produce diastereomeric mixtures of products, an alternative approach was sought. Thus, the synthesis of 2,5-disubstituted amino acid **1.104** (**Figure 16**) was attempted, in the hope that the C(2) methyl group could be introduced using Seebach's methodology, analogously to the model system. Unlike many of the methods discussed, this approach would also allow incorporation of a wide variety of functional groups on the pyrrolidine ring, thus making the synthesis adaptable to other vinylogous urea-containing PAs, for example the bohemamines.



1.104

Figure 16

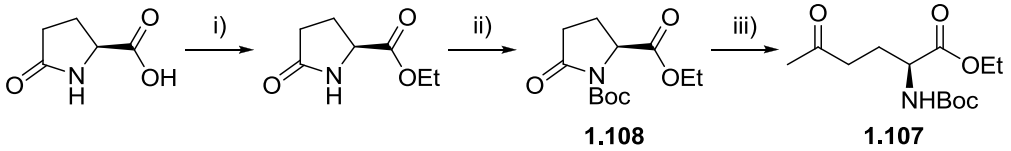
N-Protected derivative **1.105** (**Scheme 52**) was obtained *via* hydrogenation of imine **1.106**, following a sequence first reported by Pei *et al.*[118] in the synthesis of pyrrolidinyl substituted cyanopyrrolidines. Imine **1.106** came from the cyclisation of open-chain ketoester **1.107**, itself obtained from a Grignard addition into pyroglutamate derivative **1.108**.



1.105 **1.106** **1.107** **1.108**

Scheme 52

Hence, work began with formation of the ethyl ester of L-pyroglutamic acid (**Scheme 53**).[119] *N*-Protection of the amide followed by addition of methylmagnesium bromide gave open chain amino ketone **1.107** in good yield.

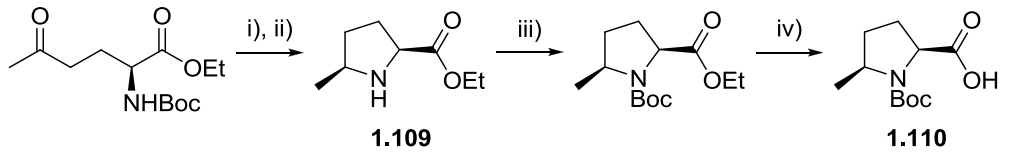


1.108 **1.107**

i) $SOCl_2$, DMF, EtOH, 90%; ii) Boc_2O, DMAP, MeCN, 90%; iii) MeMgBr, THF, –40 °C, 79%

Scheme 53

This was simultaneously deprotected and cyclised using TFA, before being reduced under hydrogenation conditions to give the desired *cis*-disubstituted amine **1.109** as a single diastereomer. Reprotection allowed saponification of the ethyl ester to be conducted efficiently and the crystallinity of this acid **1.110** allowed for single crystal X-ray analysis (**Appendix A**), confirming the relative stereochemistry of the two ring substituents.

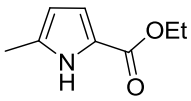


1.109 **1.110**

i) TFA, DCM; ii) H_2, 10% Pd/C, EtOH, 94% over two steps;
iii) Boc_2O, DMAP, DCM, TEA, 66%; iv) LiOH, EtOH then HCl, 99%

Scheme 54

In some larger scale attempts at the saponification (*ca*. 10 g), small quantities of pyrrole **1.111** (**Figure 17**) were identified, interestingly with the ethyl ester still intact. The structure of this unexpected byproduct was also confirmed by single crystal X-ray analysis (**Appendix B**).

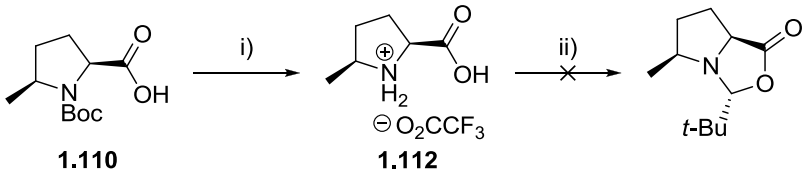


1.111

Figure 17

1.2.5 Oxazolidinone formation and attempted alkylation

Analogously to the model system, formation and alkylation of the bicyclic oxazolidinone was envisaged, following removal of the nitrogen protecting group. Boc deprotection to give the amino acid salt **1.112** was conducted using TFA (**Scheme 55**) which was also required in catalytic amounts in the next proposed step. Disappointingly, the *tert*-butyl oxazolidinone could not be formed from this amino acid salt.

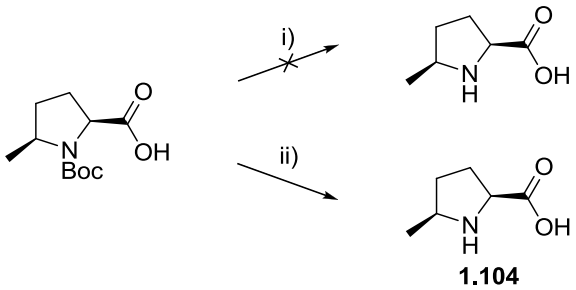


1.110 **1.112**

i) TFA, DCM; ii) *t*-BuCHO, TFA, pentane, Δ

Scheme 55

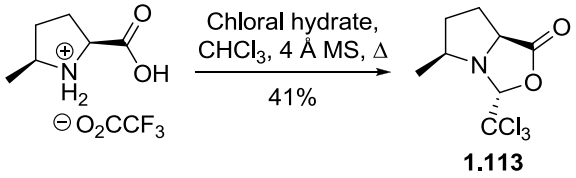
These *tert*-butyl oxazolidinones are known to be relatively air- and moisture-sensitive and the extra steric demands of the C(5) methyl group could potentially have further destabilised this moeity. However, it was also conceivable that the stoichiometric amounts of TFA present in the reaction mixture caused decomposition of the product *in situ* and so alternative methods of removing the Boc group were investigated. Thermal deprotection[120] led to a polymeric mixture of products, but conducting this reaction at slightly reduced temperatures in the presence of silica[121] gave 70% of the free amino acid **1.104** (**Scheme 56**). However, this result was not reproducible and, due to concurrent research showing more promise, was not further investigated.



i) 185 °C; ii) SiO_2, PhMe, reflux

Scheme 56

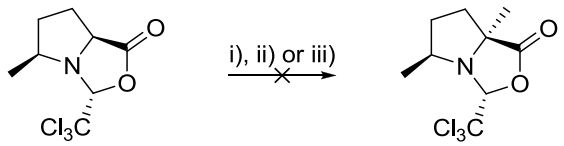
The analogous trichloro-oxazolidinones are reportedly more stable[122] and indeed this bicyclic species was obtained in reasonable yield using chloral hydrate in chloroform refluxing through Soxhlet apparatus containing 4 Å molecular sieves (**Scheme 57**).[123] This reaction was particularly sensitive to the amount of TFA present and extensive drying of the starting material was necessary to achieve optimal and reproducible yields of the desired product.



Scheme 57

The crystalline nature of oxazolidinone **1.113** allowed a single crystal X-ray structure to be obtained (**Appendix C**), confirming the *cis*- relationship of the C(2) and C(5) substituents and from this it is possible to see how the position of the *endo*- C(5) methyl may cause steric destabilisation.

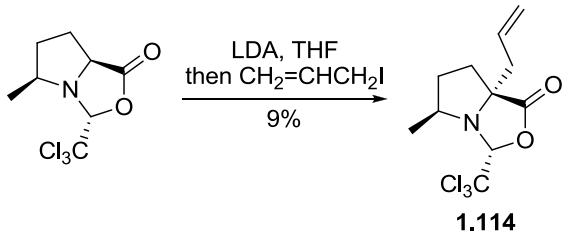
Alkylation of this motif proved elusive; use of LDA and methyl iodide, as in the model system,[75] simply returned starting material, even when excess LDA was used or the reaction warmed (**Scheme 58**). The combination of LDA and additional *n*-BuLi was also unsuccessful.



i) 1 eq. *i*-Pr_2NH, 1 eq. *n*-BuLi, THF, –78 °C then MeI; ii) 3 eq. *i*-Pr_2NH, 3 eq. *n*-BuLi, –78 °C then MeI; iii) 1 eq. *i*-Pr_2NH, 1 eq. *n*-BuLi, THF, –78 °C then *n*-BuLi → –30 °C then MeI

Scheme 58

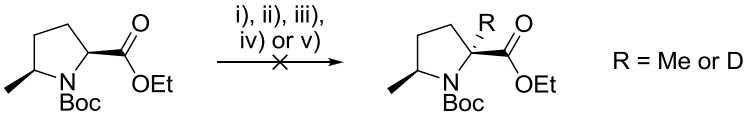
Use of allyl iodide as the alkylating agent gave a small amount of allylated product **1.114** (**Scheme 59**), a result that could not be optimised either by changing the base to the more reactive KH or by addition of HMPA to the reaction, both of which resulted in decomposition.



1.114

Scheme 59

Due to the difficulty of formation and alkylation of these oxazolidinone compounds, alkylation of the simple disubstituted amine was attempted. It was hoped that the electrophile would approach preferentially from the face opposite to the C(5) methyl group to give the desired *trans*-dimethyl product.[124] Unfortunately no reaction was observed using LDA, NaHMDS or NaH with methyl iodide (**Scheme 60**). Deuteration experiments also failed on this substrate.

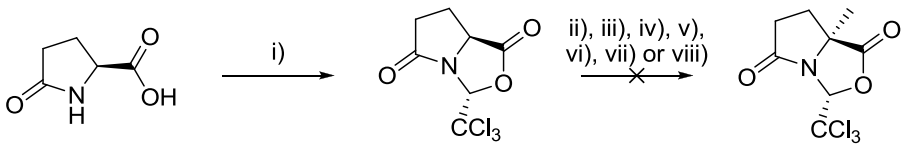


i) 2.2 eq. *i*-Pr_2NH, 2.2 eq. *n*-BuLi, THF, –78 °C then MeI; ii) NaHMDS, THF, –78 °C then MeI; iii) 1 eq. *i*-Pr_2NH, 1 eq. *n*-BuLi, THF, –78 °C then AcOD; iv) 1 eq. *i*-Pr_2NH, 1 eq. *n*-BuLi, THF, –78 °C then *n*-BuLi then MeI; v) NaH, THF, 0 °C then MeI;

Scheme 60

Since installation of the C(2) methyl at this late stage had been unsuccessful an alternative strategy was investigated, installing this before the C(5) methyl was in place. To this end, the previously reported oxazolidinone of L-pyroglutamic acid **1.115** was formed using chloral hydrate and catalytic

PTSA in toluene, under Dean–Stark conditions (**Scheme 61**).[125] This reaction was low yielding, especially on a small scale, and the highest yields (25%) were obtained when conducting this reaction on a 5 g scale.



1.115

i) chloral hydrate, PhMe, PTSA.H_2O, Δ, Dean–Stark, 25%; ii) LiHMDS, THF, –78 °C then MeI; iii) LiHMDS, THF, –78 °C then BnBr; iv) *i*-Pr_2NH, *n*-BuLi, THF, –78 °C then BnBr; v) KHMDS, PhMe, –78 °C then BnBr; vi) KHMDS, PhMe, –40 °C → –25 °C then BnBr; vii) KHMDS, 18-crown-6, DMF/THF, –78 °C then BnBr, → RT; viii) KH, THF, 0 °C then MeOTf

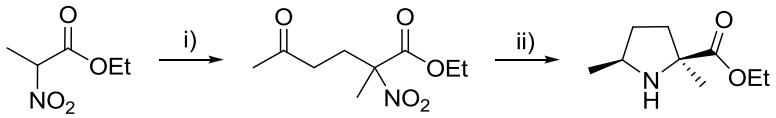
Scheme 61

Alkylation was again unsuccessful on this substrate[126] and could not be conducted even under forcing conditions, either using KHMDS and 18-crown-6[127] or KH and methyl triflate[128] (**Scheme 61**).

1.2.6 Second generation synthesis of disubstituted motif

The lack of success in alkylating these disubstituted oxazolidinones led to the investigation of alternative strategies. The previously discussed route, used by Snider in his synthesis of (+)-NP25302,[68] gave rapid access to amino ester **1.117** with the requisite relative stereochemistry.

Hydrogenation of nitro ketone **1.116**, formed by the conjugate addition of ethyl nitropropionate to methyl vinyl ketone, gave amine (±)-**1.117** in good yield. This reduction was observed to be completely diastereoselective, giving quantitative conversion to the required 2,5-*trans*-dimethyl pyrrolidine motif. The diastereoselectivity of this process was proved by single crystal X-ray crystallography of the hydrochloride salt of amine **1.117** (**Appendix D**).

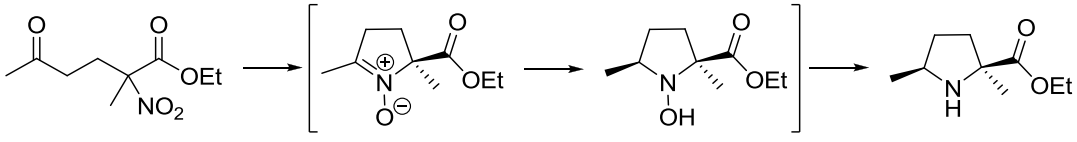


i) DABCO, methyl vinyl ketone, DCM, 100%; ii) H_2, Pd/C, Na_2SO_4, EtOH, 98%

Scheme 62

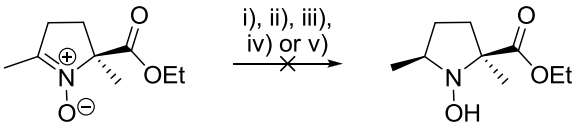
This complete diastereoselectivity was not observed in either Feringa's[125] or Snider's[67] synthesis of this amine, with a small proportion of the *cis*- product being obtained in both these previous attempts. However, in a modification to their procedures, it was found that the hydrogenation step could be conducted in one pot with no addition of acid required. In fact, in our hands, Snider's conditions, adding HCl to the reaction mixture after formation of the oxime, led to decomposition products.

The reduction was found to be somewhat capricious, with different catalyst batches requiring enormously differing reaction times, from 16 h up to 20 days, to give complete conversion. The reaction was invariably quick to form nitrone **1.118** (**Scheme 63**), but it seemed that reduction of this to either hydroxylamine **1.39** or desired amine **1.117** was significantly slower. In fact, reactions could be stopped early and the recovered under-reduced products successfully resubmitted to the reaction conditions, generally reducing the overall reaction times required for complete conversion to amine **1.117**.



Scheme 63

Other methods[129] of reducing this intermediate nitrone were investigated (**Scheme 64**), unfortunately with no success.

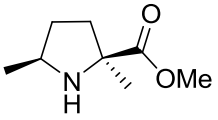


(±)-**118** (±)-**39**

i) $LiAlH_4$, ether, 0 °C → RT; ii) $TiCl_4$, $NaBH_4$, L-tartaric acid, MeOH, pH 7 then HCl;
iii) $NaBH_3CN$, MeOH, pH 2–3; iv) $NaBH_4$, EtOH, 0 °C; v) H-cube, Pd/C, 40 °C → 75 °C

Scheme 64

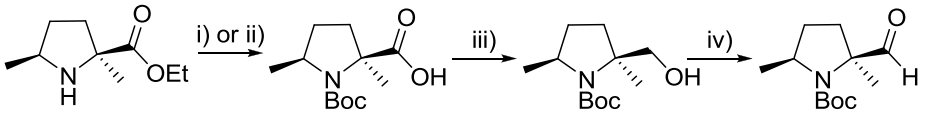
Reductions conducted in methanol led to the production of varying quantities of the volatile methyl ester **1.119** (**Figure 18**), arising from transesterification under the reaction conditions.



(±)-**1.119**

Figure 18

From the ethyl ester, conversion to the aldehyde (**1.120**) was conducted simply, by either of two, similarly efficient methods (**Scheme 65**). Although Boc protection was successful under the same conditions used for the model system, these conditions led to lower isolated yields of the protected amino ester (70%).



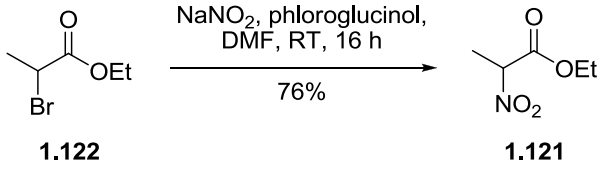
1.117 (±)-**1.120**

i) a) Boc_2O, DMAP, MeCN, 90%; b) LiOH, MeOH, 65 °C, 87%; ii) a) LiOH, MeOH, 65 °C;
b) Boc-ON, NEt_3, dioxane, H_2O, 69% over two steps; iii) BH_3.THF, THF, 100%; iv) DMP, DCM, 100%

Scheme 65

Overall, this gave a short and efficient route to aldehyde **1.120** from nitro propionate **1.121**. On a large scale, the economy of this route was improved by starting from ethyl 2-bromopropionate (**1.122**), a

significantly cheaper starting material.[ii] This was converted directly to the required nitropropionate in one step (**Scheme 66**).[130]

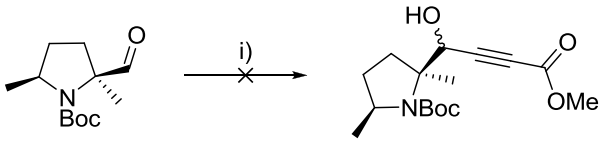


1.122 **1.121**

Scheme 66

1.2.7 Addition into the aldehyde

The addition of methyl propiolate to the aldehyde proved problematic. It is known that lithiated methyl propiolate has a tendency to polymerise at temperatures above −78 °C, but at these low temperatures no significant addition was observed (**Scheme 67**). The significantly reduced reactivity of the C(5) methylated aldehyde could, again, be linked to increased steric congestion.

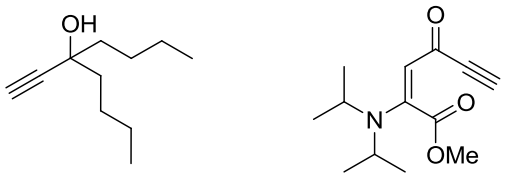


i) *n*-BuLi, $HCCCO_2Me$, THF

Scheme 67

Allowing the temperature of the reaction to warm even slightly above −78 °C resulted in the formation of alcohol **1.123** (**Figure 19**), arising from addition of the base to the methyl propiolate. Using a bulkier base (LDA) gave a similar outcome, with formation of vinylogous amide **1.124**, whose identity was confirmed by single crystal X-ray analysis, preceeding addition to our aldehyde. Changing to ethyl propiolate, hoping to slow the rate of addition to the ester, gave no improvement.

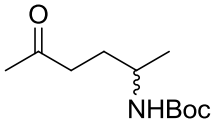
[ii] Ethyl 2-nitropropionate costs £16.30 for 1 g; ethyl 2-bromopropionate costs £16.80 for 100 g. (Sigma-Aldrich, Oct. 2011)



1.123 **1.124**

Figure 19

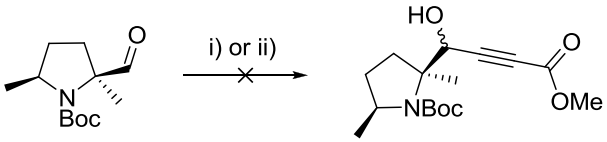
Small quantites (~10%) of ketone **1.125** (**Figure 20**) were also isolated from these reaction, presumably arising from decarbonylation of **1.120** and hydrolysis of the resulting imine. This result echoes similar observations made previously during addition to the unsubstituted aldehyde in the synthesis of *nor*-NP25302.[75]



1.125

Figure 20

In an attempt to slow these undesired side-reactions the addition was conducted at lower temperature, in the presence of Lewis acidic $BF_3{\cdot}OEt_2$ to encourage addition (**Scheme 68**).[131] This also gave no addition product, only returning starting material.

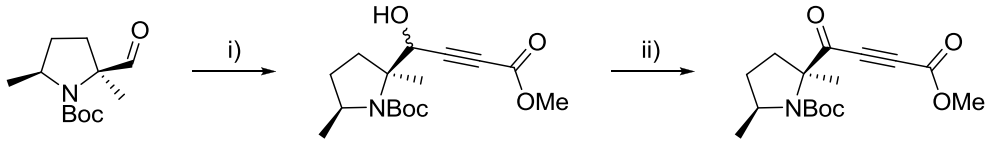


i) $HCCCO_2Me$, $BF_3{\cdot}Et_2O$, THF, –85 °C;
ii) $HCCCO_2Me$, TMSOTf, *i*-Pr_2NEt, $ZnBr_2$, Et_2O, RT then H_3O^+

Scheme 68

Following a procedure developed by Wade Downey *et al*,[132] TMSOTf was used in conjunction with $ZnBr_2$ to attempt addition of the zinc acetylide to our aldehyde. Despite this having been used for the addition of ethyl propiolate to aldehydes in the original paper, the reaction was unsuccessful when applied to aldehyde **1.120** and gave only a low mass recovery of starting material with no identifiable products.

On a small scale, addition of TMSCl to the reaction mixture allowed isolation of low yields of alcohol **1.126** (**Scheme 69**). However, this result could not be improved upon, even with large excesses of the organolithium reagent. This alcohol could be oxidised, analogously to the model system, but low yields for the formation of **1.126** meant that this route was not pursued further.



1.126

i) BuLi, $HCCCO_2Me$, TMSCl, THF, –78 °C, 19%; ii) DMP, DCM, 0 °C → RT, 62%

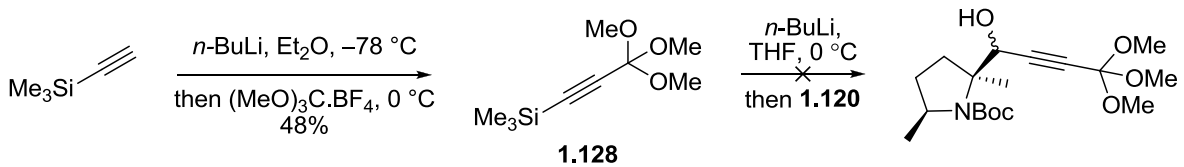
Scheme 69

Attempts to form acid chloride **1.127** (**Scheme 70**),[75] to furnish a more reactive electrophile, were also unsuccessful, simply returning the acid starting material.

1.127

Scheme 70

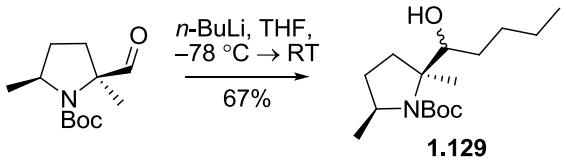
To avoid undesired addition into the propiolate ester carbonyl, an orthoester analogue of methyl propiolate (**1.128**, **Scheme 71**) was prepared, following a procedure for the formation of the corresponding ethyl orthoester developed by Baldwin *et al.*[133] The air and moisture sensitive tetrafluoroborate salt required for this transformation was formed by careful addition of $BF_3{\cdot}OEt_2$ to a solution of tetramethyl orthocarbonate in rigorously dried ether, followed by repeated washing of the salt with dry pentane and ether under argon. The white crystalline product was used immediately in the next step, but unsuccessfully.



1.128

Scheme 71

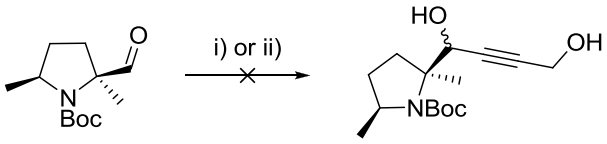
To better understand the reaction conditions required for addition to the aldehyde, and also to eliminate the possibility that the lack of reactivity was coming from some problem in formation of the lithiated alkyne, the simple addition of *n*-BuLi was attempted. A good yield of alcohol **1.129** (**Scheme 72**) was achieved by allowing the reaction to warm from −78 °C to RT overnight, with starting material still being present at −20 °C, after 6 hours.



Scheme 72

Since it appeared that addition to the aldehyde was possible at higher temperatures, it was hoped that addition of a suitable propargyl alcohol derivative would provide a solution, anticipating that these unoxidised propiolate equivalents would be significantly more stable at temperatures above −78 °C. The side-chain of the addition products would then be oxidised either immediately, or after the cyclisation step.

Addition of propargyl alcohol itself into the aldehyde was unsuccessful (**Scheme 73**), almost certainly due to the insolubility of the dianion in the reaction solvent even in the presence of TMEDA.

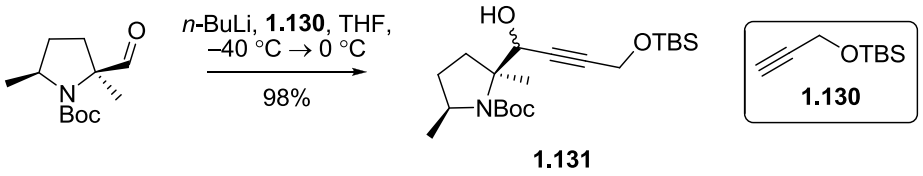


i) propargyl alcohol, *n*-BuLi, THF, 0 °C → RT;
ii) propargyl alcohol, *n*-BuLi, THF, TMEDA, 0 °C → RT

Scheme 73

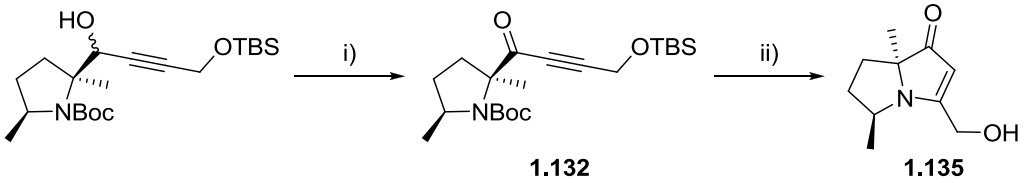
Pleasingly, using the TBS protected derivative **1.130**,[134] addition into aldehyde **1.120** was effected in good yield, giving the two separable diastereomeric alcohols **1.131** (**Scheme 74**) in a 4:1 ratio (calculated by ^{1}H NMR analysis of the crude reaction mixture). The yield of this reaction was optimised to afford near quantitative conversion by conducting the initial deprotonation step at −40 °C

and warming the reaction mixture quickly to 0 °C before immediate addition of a solution of **1.120** in THF.



Scheme 74

The crude mixture obtained from this addition could be oxidised without compromising the overall two-step yield for this process (**Scheme 75**) and cyclisation of ynone **1.132** was conducted in good yield using the previously developed TMSOTf mediated cyclisation conditions. For this substrate, the PTSA monohydrate conditions led to recovery of a small proportion of the starting material, with the majority of the material decomposing under the reaction conditions.



Scheme 75

Interestingly, deprotection of the silyl protecting group was also observed during this transformation, although on some occasions small quantities of the cyclised TBS ether (**1.133**, **Figure 21**) were obtained.

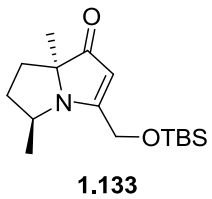
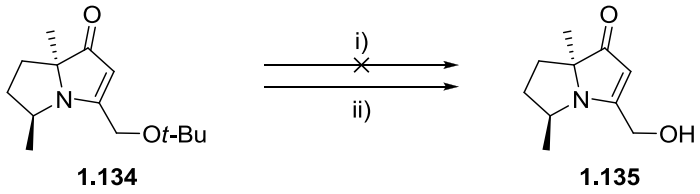


Figure 21

In some cases, another product, **1.134** (**Scheme 76**), was observed in this reaction, resulting from *tert*-butyl transfer from the Boc group to the free hydroxyl. This ether could not be deprotected under

standard conditions which, instead, caused decomposition; however, catalytic TFA in DCM did furnish deprotected alcohol **1.135**, although only in relatively low yield.



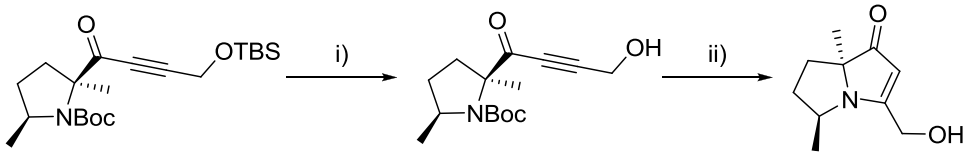
1.134 **1.135**

i) $CeCl_3 \cdot 7H_2O$, NaI, MeCN, 70 °C; ii) cat. TFA, DCM, 0 °C → RT, 40%

Scheme 76

Attempts were made to reduce the amount of this undesired side-product by including cation scavengers such as anisole, triethylsilane or 1,2-ethanedithiol. These modifications gave no observable improvement, and the inclusion of 1,2-ethanediol led to complete inhibition of the cyclisation reaction, returning only starting material.

The unwanted side-products **1.133** and **1.134** were produced in varying amounts and with no apparent predictability, reducing the reliability of this transformation. Removing the TBS protecting group prior to conducting the cyclisation led to reproducibly good yields of pyrrolizidine **1.135**, with no evidence of any other products in the crude mixture (**Scheme** 77). The use of TBAF to cleave the silyl ether simply led to decomposition of the starting material; however, HF in pyridine furnished keto alcohol **1.136** in quantitative yield.



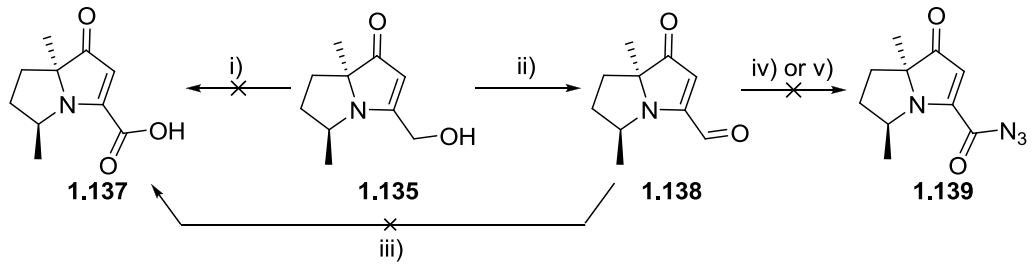
1.136 **1.135**

i) HF.pyridine, THF, RT, 100%; ii) TMSOTf, DCM, –30 °C → 0 °C, 78%

Scheme 77

Having constructed the required pyrrolizidine core, attention now turned to the oxidation of the pendant hydroxyl and subsequent conversion of this to the acyl azide. A number of conditions to effect this initial oxidation were screened.

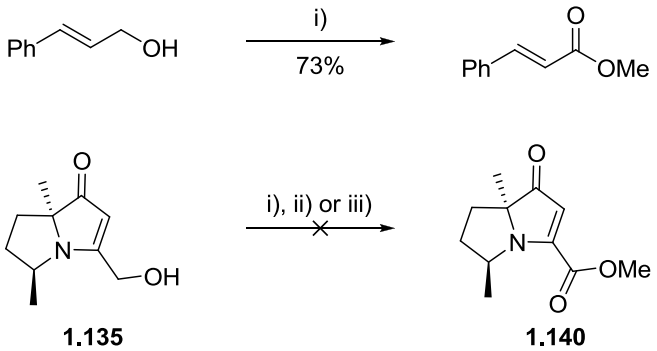
Direct oxidation of alcohol **1.135** to acid **1.137** was unsuccessful using CrO_3[135] (**Scheme 78**) with extensive decomposition being seen. It was found that oxidation to aldehyde **1.138** could be achieved using DMP in DCM, however the product could only ever be obtained in moderate yield. This could perhaps be due to the instability of the aldehyde, with its rapid decomposition being observed when stored neat. Attempts to further oxidise this aldehyde to the corresponding acid[136] were unsuccessful, as were attempts to form the acyl azide **1.139** directly.[137]



i) CrO_3, H_2SO_4, acetone, 0 °C; ii) DMP, DCM, 0 °C → RT, 46%; iii) $NaClO_2$, 2-methyl-2-butene, *t*-BuOH, H_2O, pH 3.6 phosphate buffer; iv) MnO_2, NaN_3, THF; v) MnO_2, NaN_3, THF, 50 °C

Scheme 78

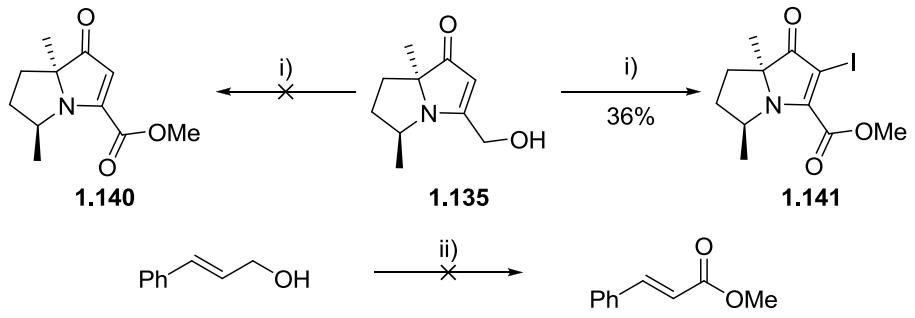
Test reactions using NaCN and MnO_2 in methanol, as developed by Corey,[138] were successful in transforming cinnamyl alcohol to methyl cinnamate in good yield (**Scheme 79**) but these conditions were unsuccessful when applied to pyrrolizidine alcohol **1.135**, causing decomposition instead. This transformation was also unsuccessful using I_2 and DAIB in methanol,[139] and a similar conversion using *N*-hydroxysuccinimide with DAIB[140] was also unsuccessful, with starting material being returned in both cases.



i) NaCN, AcOH, MnO_2, MeOH; ii) DAIB, I_2, MeOH;
iii) DAIB, *N*-hydroxysuccinimide, EtOAc, 0 °C → RT

Scheme 79

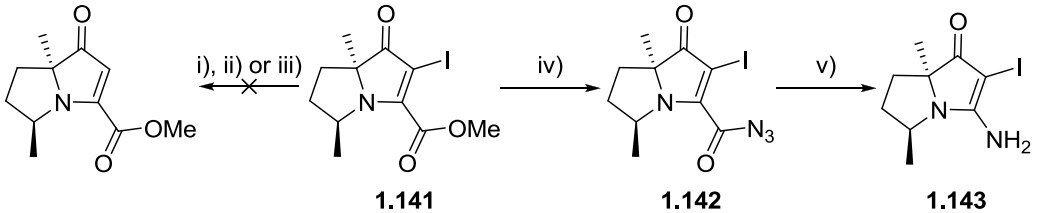
Attempts to form ester **1.140** using I_2 in methanol with K_2CO_3[141] were unsuccessful (**Scheme** 80); although the desired oxidation was observed, this was accompanied by iodination at C(2) to yield iodide **1.141**. It has been reported previously that these vinylogous urea species are susceptible to deprotonation of the C(2) position[75] and hence a modified set of reaction conditions, without K_2CO_3, were attempted on a test system. Unfortunately, no reaction at all was observed in the absence of the base.



i) I_2, K_2CO_3, MeOH, 70 °C; ii) I_2, MeOH, 70 °C

Scheme 80

Deiodination of **1.141** was attempted using NaI in methanol and PPh_3 in methanol,[142] but neither set of conditions gave any reaction (**Scheme 81**). Instead, this iodinated material was taken through the previously described synthetic sequence to give acyl azide **1.142** which was then transformed to amine **1.143**. The low yields obtained for these steps meant that there was insufficient material to obtain a clean sample of amine **1.143**, or to conduct the acylation reaction.

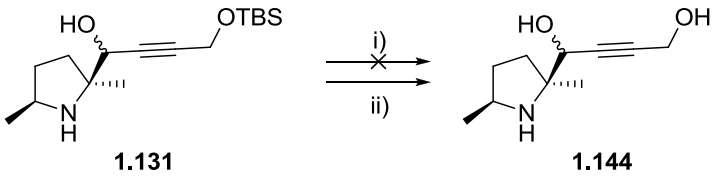


i) NaI (10 eq.), MeOH; ii) NaI (10 eq.), MeOH, Δ; iii) PPh_3, MeOH;
iv) 1) KOH, MeCN, H_2O; 2) DPPA, DMF, 0 °C, 21%; v) AcOH (95% aq.), Δ, 15%

Scheme 81

As oxidation of the cyclised species was proving difficult, attempts were made to oxidise the alkyne derivatives obtained from addition to aldehyde **1.120**. It was also hoped that it would be possible to oxidise both alcohol functionalities under the same conditions, improving the efficiency of the

synthesis. To that end, silyl ether **1.131** was deprotected with TBAF to give diol **1.144** (**Scheme 82**). Suprisingly, this transformation could not be achieved using fluorosilicic acid, these conditions causing decomposition of the material.

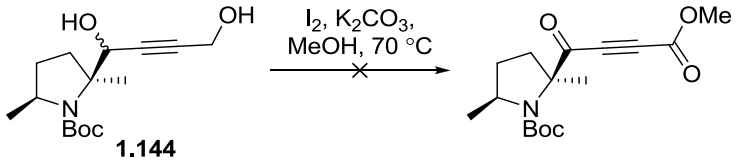


1.131 **1.144**

i) H_2SiF_6, MeCN; ii) TBAF, THF, 0 °C, 100%

Scheme 82

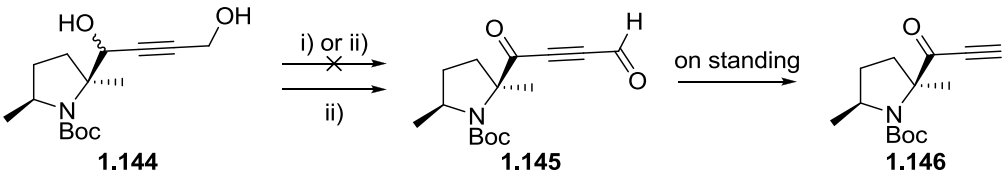
Direct oxidation of the diol to the methyl ester could not be achieved when using the I_2-mediated conditions[141] which had previously given the C(2)-iodinated pyrrolizidine **1.141**. When applied to diol **1.144**, only starting material was recovered from the reaction (**Scheme** 83).



1.144

Scheme 83

Diol **1.144** did not react with MnO_2,[143] and decomposed upon exposure to PDC[144] (**Scheme** 84); however, aldehyde **1.145** could be synthesised in quantitative yield using DMP. This ketoaldehyde decomposed on standing, decarbonylating to give crystals of unsubstituted alkyne **1.146**, the structure of which was confirmed by single crystal X-ray analysis. (**Appendix E**).



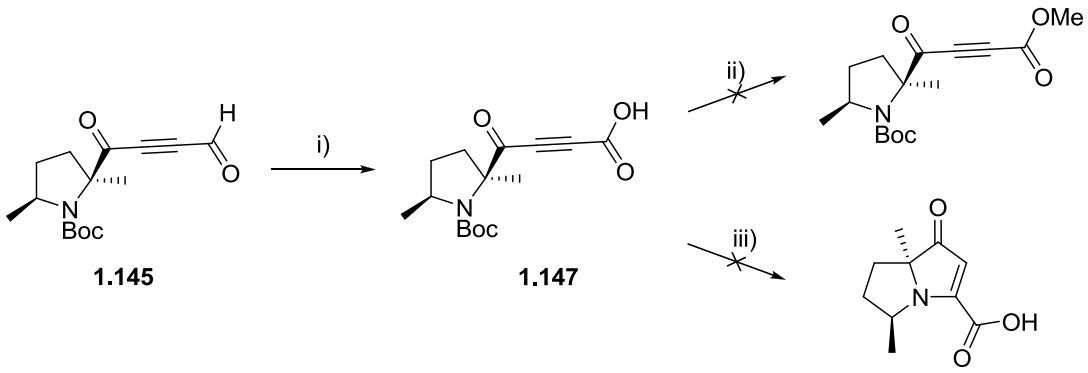
1.144 **1.145** **1.146**

i) MnO_2, DCM; ii) PDC, DMF; iii) DMP, DCM, 0 °C, 100%

Scheme 84

Immediate reaction of aldehyde **1.145** under oxidative conditions[145] furnished acid **1.146** (**Scheme 85**), although the reaction proved temperamental with a wide range of yields being obtained. This route

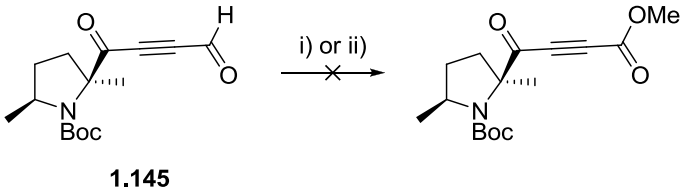
was ultimately unsuccessful as the acid could neither be converted to the methyl ester[146] nor cyclised to give the corresponding pyrrolizidine.



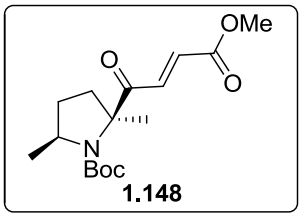
i) $NaH_2PO_4 \cdot H_2O$, $NaClO_2$, *t*-BuOH, H_2O, 2-methyl-2-butene, –5 °C, 0–100%;
ii) $TMSCHN_2$, PhMe, MeOH, RT; iii) TMSOTf, –30 °C → RT

Scheme 85

Oxidation of aldehyde **1.145** to the methyl ester was also unsuccessful (**Scheme 86**); treatment with Oxone® in methanol[147] returned unreacted starting material, and application of Corey's conditions[138] instead gave alkene **1.148** as the only identifiable product, in 71% yield.



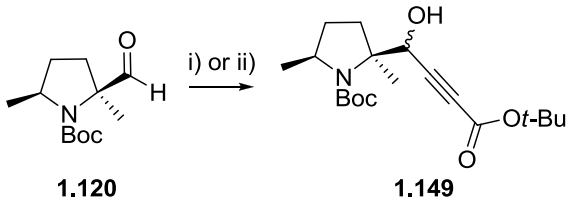
i) Oxone®, MeOH, RT; ii) NaCN, AcOH, MnO_2, MeOH, RT, 12 h



Scheme 86

Due to the lack of success observed in this strategy, further work was conducted into the addition of other propiolate nucleophiles to aldehyde **1.120**. Pleasingly, the lithiated species generated from *tert*-butyl propiolate was found to add into aldehyde **1.120** smoothly under the conditions used for protected propargyl alcohol derivative **1.130** (**Scheme 87**). Although trace amounts of *n*-BuLi addition product **1.123** were obtained, the reaction gave reasonable yields of alcohol **1.149**, as a separable

mixture of diastereomers in a 8:1 ratio. However, LHMDS was found to be a more successful base for this reaction, giving an improved yield of the addition product and a much cleaner crude reaction mixture.

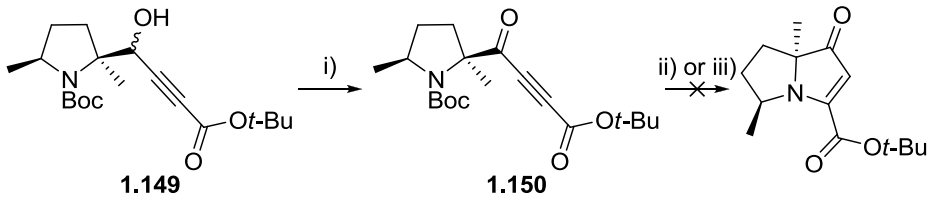


1.120 **1.149**

i) $HCCCO_2t$-Bu, *n*-BuLi, THF, 71%; ii) $HCCCO_2t$-Bu, LHMDS, THF, 90%

Scheme 87

Alcohol **1.149** could be oxidised to afford cyclisation precursor **1.150** (**Scheme 88**), but this species did not form the corresponding pyrrolizidine under either the TMSOTf or PTSA mediated cyclisation conditions, possibly due to facile removal of the acid sensitive *tert*-butyl group under the reaction conditions.

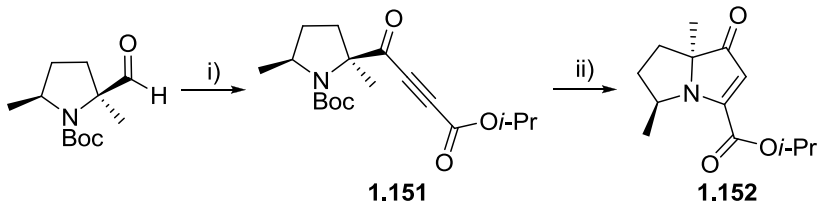


1.149 **1.150**

i) DMP, DCM, 100%; ii) TMSOTf, DCM, –30 °C → 0 °C; iii) PTSA·H_2O, MeCN then $NaHCO_3$

Scheme 88

Pleasingly, switching to *iso*-propyl propiolate gave ynone **1.151**, which was cyclised efficiently to give the desired pyrrolizidine ester **1.152** (**Scheme 89**). The synthetic sequence from aldehyde **1.120** to pyrrolizidine **1.152** was improved when the mixture of alcohols obtained from propiolate addition was not purified prior to oxidation.



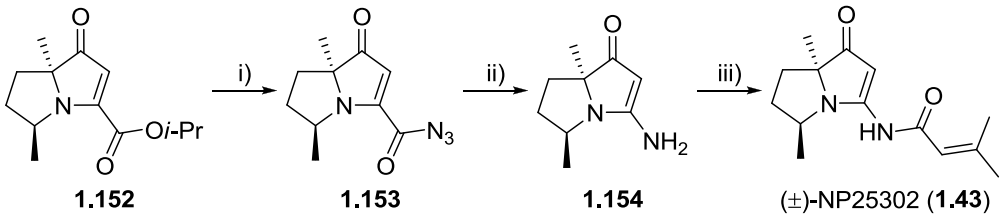
i) 1) HCCCO$_2$*i*-Pr, LHMDS, THF; 2) DMP, DCM, 88% over 2 steps;
ii) TMSOTf, DCM, –30 °C → 0 °C, 63%

Scheme 89

The reactions of methyl and ethyl propiolate with aldehyde **1.120** were also tested under these optimised conditions, but no addition was observed and these reactions resulted in complex product mixtures.

1.2.8 Conversion to the azide and amine, and acylation to give NP25302

Acyl azide **1.153** was readily obtained using similar conditions to those used in the synthesis of *nor*-NP25302 and the Curtius rearrangement in aqueous acetic acid furnished vinylogous amide **1.154** which was acylated in good yield. However, the ^{1}H and ^{13}C NMR spectra did not correlate with those previously published for (+)-NP25302, leading to uncertainty over the identity of our final compound.

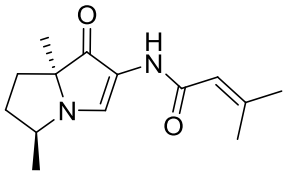


i) 1) KOH, MeCN/H$_2$O; 2) DPPA, DMF, 0 °C, 95% over 2 steps; ii) AcOH, 120 °C, 90%;
iii) NaH, 3,3-dimethylacryloyl chloride, THF, 71%

Scheme 90

The relative stereochemistry across the pyrrolidine ring was believed to be correct, as proved by single crystal X-ray structures obtained of the HCl salt of amino ester **1.117** (**Appendix D**) and correlation of the ^{1}H and ^{13}C NMR spectra of this known intermediate with previously published data. However, there were conceivable connectivity issues. First, the cyclisation of the amino-ynone could have proceeded *via* a 4-*exo*-dig cyclisation mode rather than a 5-*exo*-dig. Although HMBC NMR

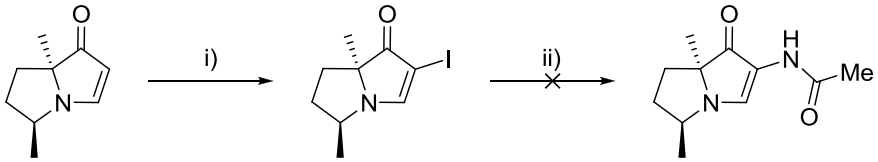
experiments seemed to confirm the correct connectivity, this evidence was not completely unambiguous and no crystal structures of intermediates after the cyclisation step had been obtained. A second potential problem could be formation of an undesired rearrangement product during the Curtius step. In order to rule out the latter suggestion, the synthesis of the isomeric C(2) substituted pyrrolizidine **1.155** (**Figure 22**) was attempted.



1.155

Figure 22

Based on the ease of C(2) iodination observed previously, attempts were made to obtain C(2)-iodo pyrrolizidine **1.156** from unsubstituted pyrrolizidine **1.157,** anticipating that this could be subsequently coupled with a suitable amide. NMR scale experiments using *N*-iodosuccinimide in methanol (**Scheme 91**) appeared to show the formation of iodide **1.156** (based on ^{1}H NMR and HRMS analysis[iii]), but introduction of the C(2) amide group, under conditions used by Charette *et al*. on a similar vinylogous amide in their synthesis of barrenazines A and B,[148] was unsuccessful.



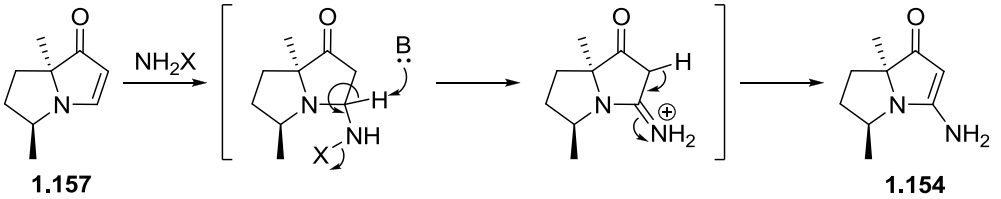
1.157 **1.156**

i) NIS, d_4-MeOH, 0 °C → RT; ii) CuI, DMEDA, $MeCONH_2$, Cs_2CO_3, PhMe, 90 °C

Scheme 91

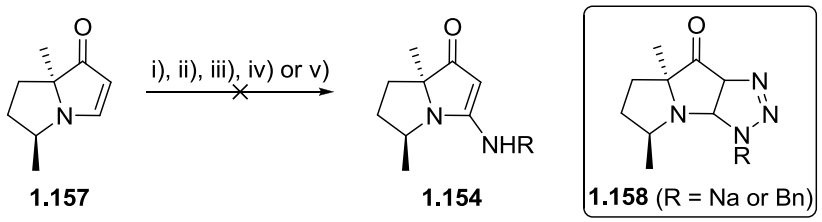
In parallel with attempts to synthesise isomer **1.155** explicitly, another route to the desired C(3)-amino scaffold was also investigated. This route was based around a conjugate addition-elimination process to transform unsubstituted pyrrolizidine **1.157** directly to vinylogous amide **1.154** (**Scheme 92**).

[iii] HRMS found 299.9858, $C_9H_{12}INNaO$ (MNa^+) requires 299.9856



Scheme 92

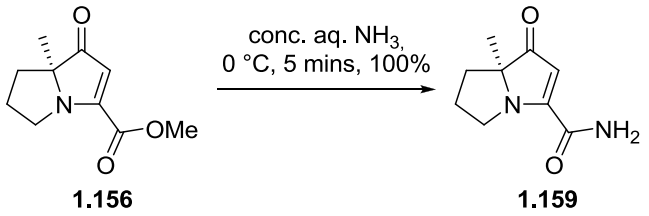
Initial attempts, on an NMR scale, used hydroxylamine hydrochloride in methanol (**Scheme** 93), warming from RT to 70 °C over a number of hours, but under these conditions no reaction was observed. It was hoped that the reaction of our susbtrate with a suitable azide species would lead to the same amide product **1.154**, potentially *via* cyclic intermediate **1.158**. NaN_3 in benzene, with or without catalytic CuI, gave none of the desired product, and using benzyl azide under similar conditions, hoping to obtain the benzylated amide was also unsuccessful. Conducting this reaction in deuterated DCM in the presence of TMSOTf gave no identifiable product.



i) $NH_2OH.HCl$ (aq.), d_4-MeOH, RT → 70 °C; ii) NaN_3, d_6-PhH, sealed tube, 100 °C; iii) NaN_3, CuI, d_6-PhH, sealed tube, 100 °C; iv) BnN_3, d_6-PhH, sealed tube, 100 °C; v) BnN_3, TMSOTf, d_2-DCM

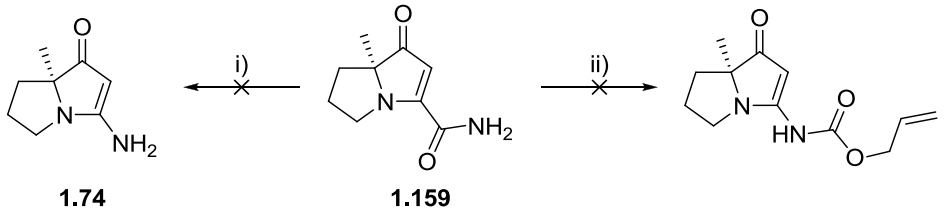
Scheme 93

Alongside these investigations, a Hofmann degradation process was tested on the model *nor*-NP25302 system, as a potential alternative to the Curtius rearrangement. Amide 1.159 (**Scheme 94**) was obtained in quantitative yield *via* the rapid reaction of ester 1.56 with aq. NH_3. The crystalline nature of this amide allowed for single crystal X-ray analysis (**Appendix F**), clearly showing the desired 5,5-fused ring system and lending some support to the NMR-based assertions that the cyclisation step had indeed proceeded in a 5-*endo*-dig fashion.



Scheme 94

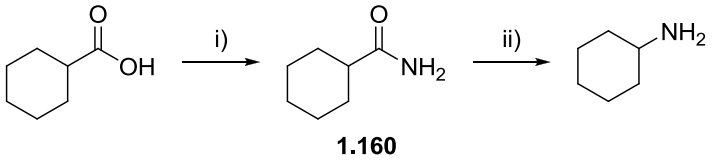
However, application of [bis(trifluoroacetoxy)iodo]benzene (PIFA) to amide 1.159 in acetonitrile149 simply caused decomposition of the starting material and the attempted trapping of the isocyanate formed on exposure to DAIB with allyl alcohol150 was also unsuccessful (**Scheme 95**).



i) PIFA, MeCN, H_2O, RT; ii) DAIB, CH_2=$CHCH_2OH$, PhMe, 4Å MS, 60 °C

Scheme 95

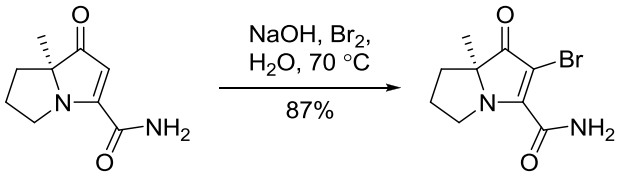
PIFA is known to be relatively unstable, and reports suggest that the freshly made reagent is much more effective in such transformations. Indeed, freshly prepared reagent, obtained from reaction of DAIB with freshly distilled TFA,[149] proved very successful when applied to a test system cycohexane carboxamide (**1.160**, **Scheme 96**). Despite this, no improvement was observed in the Hofmann rearrangement of amide **1.159**.



i) $SOCl_2$, 50 °C then NH_3 (aq.), 10 °C, 40%; ii) PIFA, MeCN, H_2O, 93%

Scheme 96

More conventional Hofmann degradation conditions, using Br_2 under basic conditions (**Scheme 97**),[151] did not cause the desired rearrangement, but did result in bromination at the C(2) position, giving an 87% yield of bromoamide **1.161**.



Scheme 97

1.2.9 Concentration and acidity effects on NMR spectra

In parallel with these investigations, work had been ongoing to repeat the original synthetic sequence. This led to the observation that the NMR (both ^{1}H and ^{13}C) spectra of several intermediates obtained under seemingly identical conditions showed some variation. It had also been noted that spectra of the same batch of product differed when the concentration of compound in the NMR sample was altered and on changing between suppliers of deuterated chloroform. This was also found to be true for samples of final product **1.43** and so a more quantitative measurement of this variation was sought.

In contact with Professor Snider regarding the possibility of obtaining samples of his synthetic (+)-NP25302, he also suggested that, due to the relative basicity of the vinylogous urea functionality, the pH of the NMR chloroform may be important, and that addition of solid K_2CO_3 may lead to a spectrum that better matched their published data.

In order to set a standard from which to work, deuterated chloroform was first passed through a short plug of basic alumina. Gratifyingly, under these conditions the peaks were stabilised for samples of a similar concentration. From this base point, NMR spectra of the final compound upon successive additions of TFA (0.1 eq. aliquots) were obtained. This gave a noticeable difference in the spectra, with almost every peak moving to some extent upon acidification (**Figure 23**) and after addition of 1 equivalent of TFA, our peaks were getting close in p.p.m. to those previously reported.

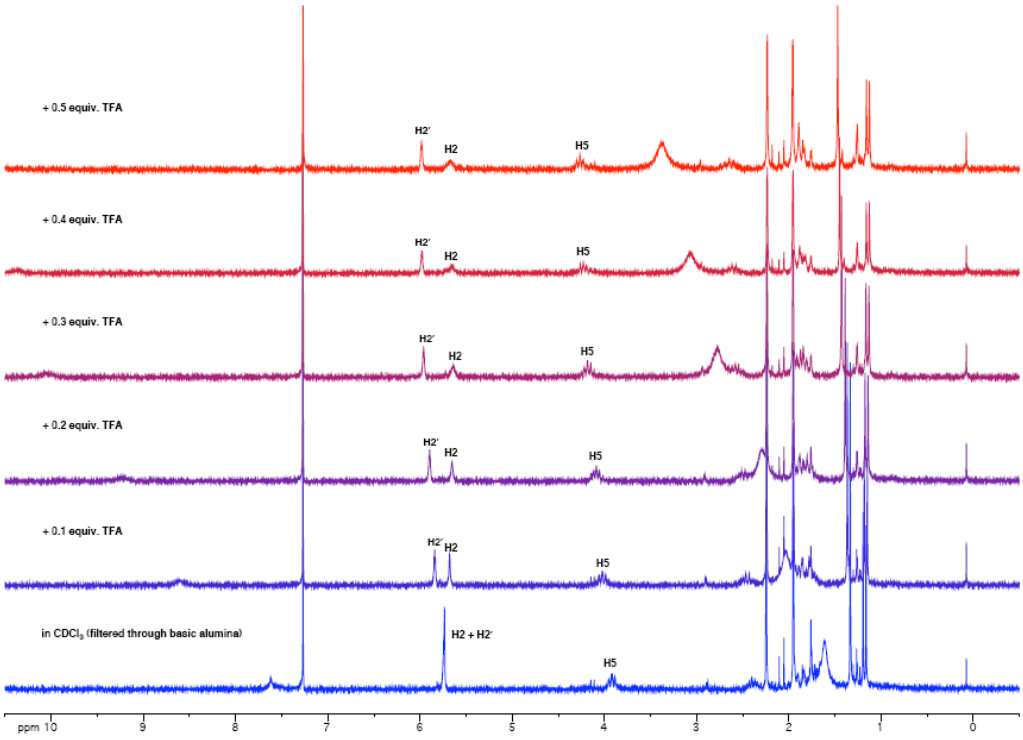


Figure 23 – pH dependence of the ^{1}H NMR spectrum of 1.43

Fortuitously, during these NMR experiments, the formation of fine, needle-like crystals was observed at the top of the sample. Single crystal X-ray analysis of these crystals (**Figure 24** with TFA counterion removed for clarity, **Appendix G**) found them to be the TFA salt of the final compound, and from these crystals it was possible to confirm that final compound **1.43** was indeed the correct structure, and that the connectivity and relative stereochemistry were also correct.

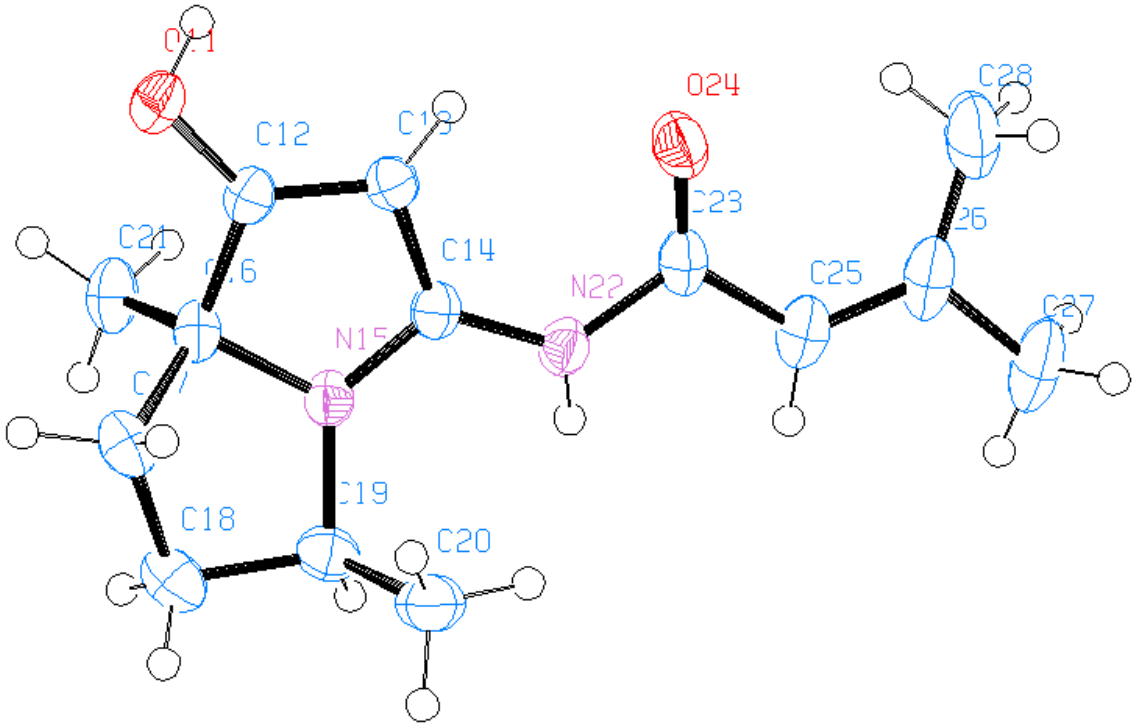


Figure 24 – X-ray crystal structure of compound 1.43

Although attempts to run small scale NMR experiments on this particular crystal, in order to prove that it was representative of the sample as a whole, were unsuccessful, the crystal structure, coupled with the large variations observed in the NMR spectra of this compound as the concentration or pH were altered, are enough to be sure that the synthesis of NP25302 has been completed successfully.

1.3 Conclusions

This project sought to synthesise (+)-NP25302 using two key steps: a 5-*endo*-dig cyclisation to furnish the core motif, and a Curtius rearrangement to install the side-chain. Although modifications had to be made to the exact nature of the intended Curtius rearrangement, both steps were successfully included in the total synthesis of this pyrrolizidine natural product.

The total synthesis of *nor*-NP25302, a model system designed to test out this novel methodology, was completed, following on from previous work within the Robertson group. Using information gathered from this study, the total synthesis of the natural product NP25302 was completed in 9 linear steps, and 26% overall yield.

Through this synthesis, the viability of the 5-*endo*-dig cyclisation as a route to pyrrolizidine containing structures has been demonstrated, and some degree of generality in this method has been shown.

The variability of NMR spectra of compounds of this type upon changes in the concentration and pH dependence has been highlighted, and a method of standardising such spectra has been discussed.

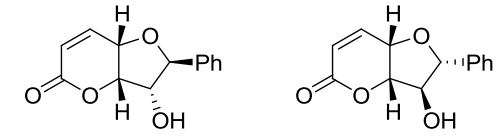
Finally, the first single crystal X-ray structure of the natural product NP25302 has been successfully obtained.

2 Studies into the stereospecificity of the gold-catalysed cyclisation of hydroxy-alkenes

2.1 Introduction

2.1.1 (+)-Isoaltholactone

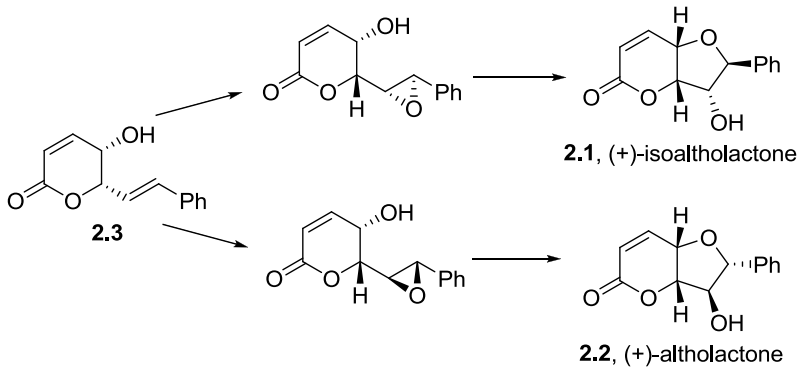
(+)-Isoaltholactone (**2.1**) (**Figure 25**) was isolated in 1990 from the combined extracts of *Goniothalamus malayanus*, *Goniothalamus montanus* and *Goniothalamus tapis*.[1] It is one of a large number of styryl lactone natural products isolated from the genus *Goniothalamus* which exhibit a diverse range of structural motifs and biological activities.[2] (+)-Isoaltholactone is a diastereoisomer of (+)-altholactone (**2.2**), a natural product previously isolated from an unnamed *Polyalthia* species[3, 4] which differs in the absolute stereochemistry at two contiguous centres around the THF ring.



2.1, (+)-isoaltholactone **2.2**, (+)-altholactone

Figure 25

This observation can be explained biosynthetically by the potential for epoxidation on either face of proposed styryl lactone intermediate **2.3**, 5-hydroxygoniothalamin (**Scheme** 98).[1]

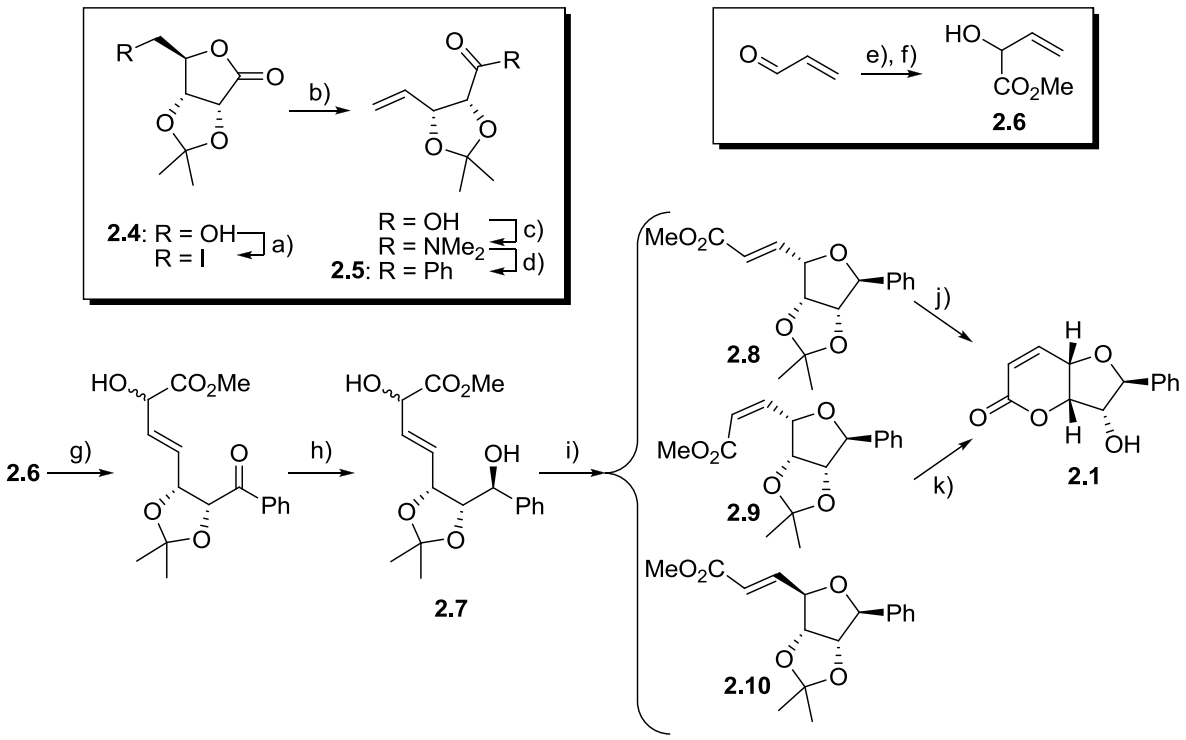


Scheme 98

Biological testing of these isomers revealed that (+)-isoaltholactone shows selective cytotoxicity towards HT-29 colon cancer cells,[5] and (+)-altholactone exhibits a variety of biological activities: an antiproliferative effect on breast cancer cells,[6] toxicity towards P388 cells[4] and induction of apoptosis in HL-60 cells.[7]

2.1.2 Previous work towards (+)-isoaltholactone

The synthesis of (+)-isoaltholactone was recently completed within the Robertson group, taking nine steps from D-ribonolactone (**2.4**, **Scheme 99**). This compares favourably with previously published syntheses,[8-17] and differs from the majority in that it starts with formation of the THF ring; the majority of syntheses start by constructing the chiral δ-lactone component and there are only two reported examples in which the chiral THF fragment is formed first.[13, 17]



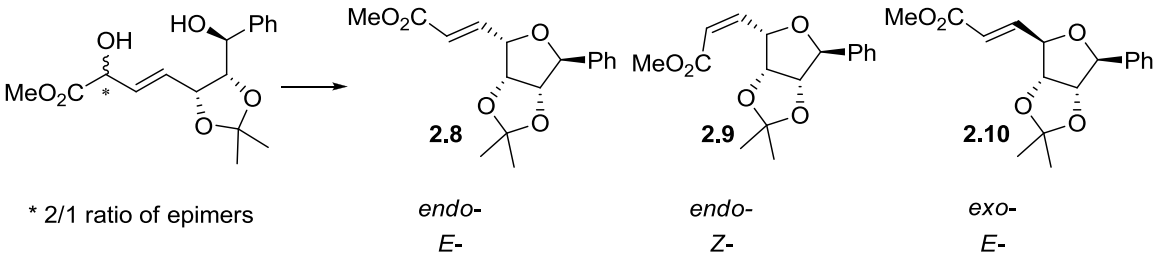
a) PPh_3, imidazole, I_2, PhMe, 70 °C, 86%; b) *t*-BuLi, THF, –78 °C, 92%; c) $HNMe_2$, DIPEA, HATU, DMF, RT, 65%; d) PhMgBr, THF, 0 °C, 68%; e) Ac_2O, NaCN, PhMe, –10 °C, 85%; f) MeOH, $SOCl_2$, ∆, 43%; g) Grubbs II, **2.5**, DCM, ∆, 72%; h) L-selectride, THF, –78 °C, 69%; i) Ph_3PAuCl, AgOTf, 4 Å MS, DCM, 87%; j) 1) TsOH, MeOH, ∆; 2) NaOH, *i*-PrOH 3) 2,4,6-trichlorobenzoyl chloride, pyridine, 34%; k) 1) TsOH, MeOH; 2) benzene,))); 3) $(MeO)_2CH_2$, acetone, MeOH, 87% from **2.9**

Scheme 99

The key step of this synthesis was the gold-catalysed cyclisation of diol **2.7** (**Scheme 99**), based on work originally reported by Aponick *et al.*[18, 19] Over the course of these studies, it became apparent that this cyclisation might be stereospecific. Cyclisation precursor **2.7** was synthesised as a mixture of epimers at the α-position of the ester, with a *dr* of 2:1 but the absolute stereochemistry of the major and minor components was unknown.

From this diol three diastereomeric THF products were obtained, the relative ratios of which could be fitted into either a 2:1 ratio of *E*-/*Z*- double bonds or a 2:1 ratio of *endo*-/*exo*- epimers at the newly formed stereogenic centre on the THF ring (**Scheme 100**). This led to speculation as to whether one of these outcomes was determined by the stereochemistry of the α-hydroxyl and, if so, which. It was also of

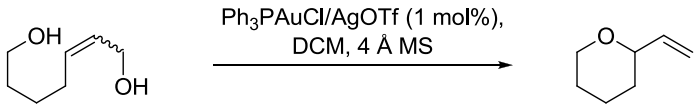
interest with regards to possible improvements in the total synthesis since only two of the THF products were of the appropriate stereochemistry to be taken forward to make (+)-isoaltholactone (**Scheme** 99), and only one of these (**2.9**) could be transformed without first isomerising the double bond. A better understanding of the providence of this desired product could lead to reduced wastage in the cyclisation step.



Scheme 100

2.1.3 Developments in Au-catalysed cyclisation onto alkenes

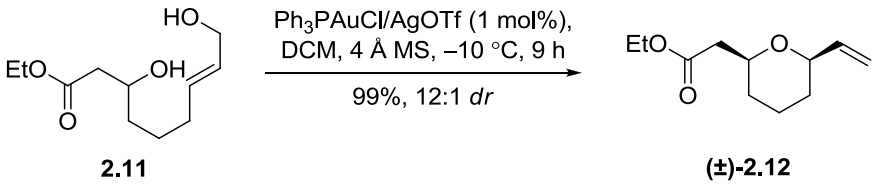
Gold-catalysed activation of alkenes is relatively limited in precedent, with activation of allenes and alkynes being found more frequently.[20] Recent work by Aponick *et al.*[18] has shown that formation of the THP moiety can be effected readily using a gold(I) source in the presence of silver triflate (**Scheme 101**).



Scheme 101

The reaction conditions developed in this study avoid the high temperatures and long reaction times typical of previously reported examples of alkene activation, and the use of gold catalysis to conduct this type of process also gives greater functional group tolerance than similar processes using classical Lewis or Brønsted acids, which usually require relatively harsh, acidic conditions. For example, cyclisation of

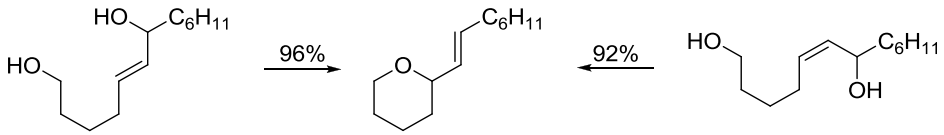
aldol product **2.11** under these conditions gave high yields of THP **2.12** with no elimination observed (**Scheme 102**).



2.11 **(±)-2.12**

Scheme 102

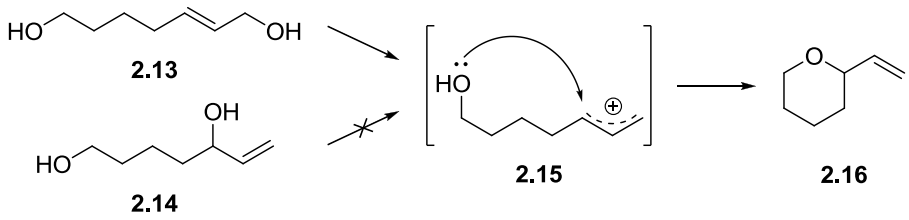
This cyclisation process is generally found to occur with high levels of diastereoselectivity, the major diastereomer having the two groups across the ring *cis*-disposed to one another and the newly formed alkene having exclusively *E*- stereochemistry, regardless of the alkene geometry in the starting allylic alcohol (**Scheme 103**).



Conditions: $Ph_3PAuCl/AgOTf$ (1 mol%), DCM, 4 Å MS, RT, 40 min

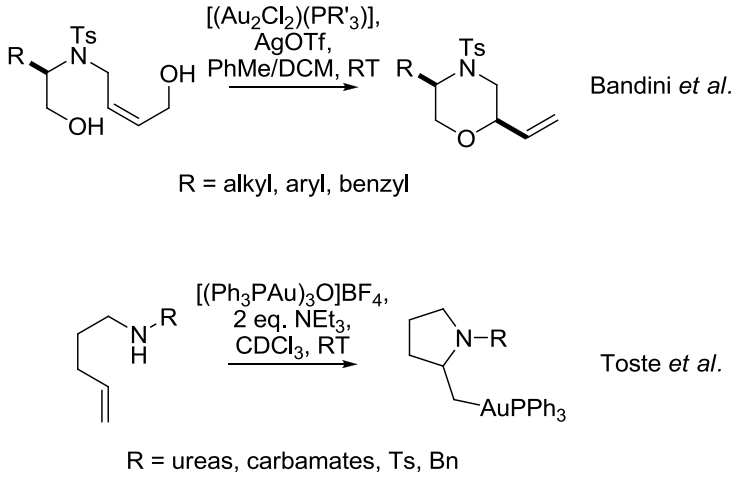
Scheme 103

The reaction was initially postulated to proceed *via* either an S_N2' mechanism or a cationic process. The latter of these was discounted by studies conducted in the initial work by Aponick: were the process to proceed *via* an allylic cation then, in principle, diols **2.13** and **2.14** should both give the same cyclised product, **2.16**, from the same cationic intermediate, **2.15** (**Scheme** 104).[18] This was found not to be the case, however, and diol **2.14** was, in fact, found to be inert under the standard cyclisation conditions, and even under more forcing conditions using either higher temperatures or the more oxophilic Au(III) species, $AuCl_3$. Aponick also suggested a third potential mechanism consisting of a discrete hydroxyauration step followed by elimination of a hydroxyl-gold species to yield the alkene product.



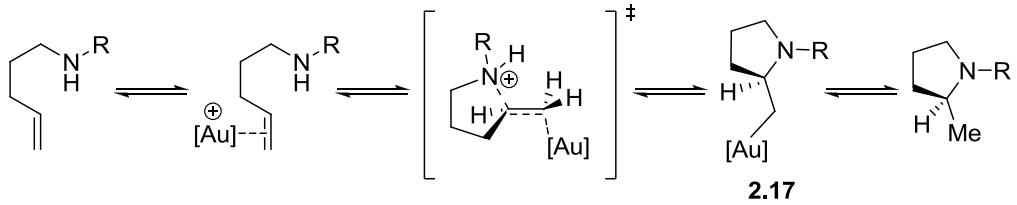
Scheme 104

This gold-catalysed cyclisation has since been extended in scope by Bandini *et al.*[21] to include cyclisations of amine nucleophiles onto allylic alcohols (**Scheme 105**), and, more recently, similar procedures have been developed by Toste *et al.* to allow cyclisation of nitrogen nucleophiles onto unactivated alkenes.[22]



Scheme 105

During these investigations by Toste, there was further discussion of the possibility of a mechanism proceeding *via* initial addition of the nucleophile and the electrophilic gold species across the alkene followed by protodeauration (**Scheme 106**). This mechanistic suggestion bears similarity to early work using mercury salts to conduct similar transformations,[23] where an organomercurial product was often obtained and the mercury removed in a separate step. and also to procedures carried out with other late transition metals, namely platinum[24-26] and palladium.[27]

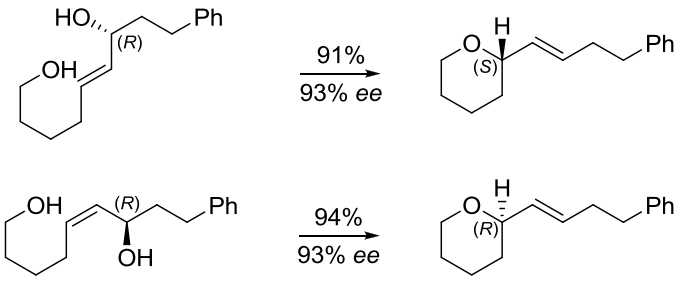


2.17

Scheme 106

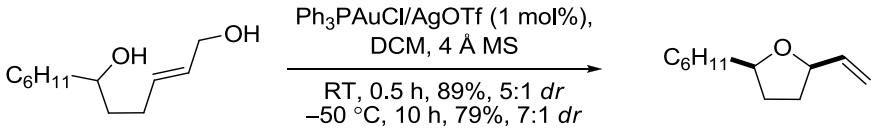
Toste *et al.* succeeded in obtaining single crystal X-ray structures of some aminoauration products of type **2.17**,[22] potentially providing some support to the possibility of this *anti*-addition mechanism in the gold-catalysed cyclisation of nitrogen-based nucleophiles onto these unactivated alkenes. However, difficulties in conducting the second, protodeauration step make it problematic to reconcile with the rapid rate of reaction observed in the catalytic process.

More recently, Aponick has published investigations into the chirality transfer of stereochemistry from the starting allylic alcohol centre to the newly formed allylic C-O bond in the formation of THP rings.[28] In this case, it was possible to form either enantiomer in good *ee* by either keeping the stereochemistry at the allylic alcohol the same and changing the geometry of the starting alkene, or *vice versa* (**Scheme 107**). The alkene geometry in the product was, as earlier reported, always found to be *E*-.



Scheme 107

Throughout all of these studies there has never been a consideration of the stereochemical outcome of THF synthesis by this method, the only example of this transformation being one example in the initial work by Aponick (**Scheme 108**).[19] Hence, no further information was available on the likely stereochemical outcomes of this reaction on our substrate (**Scheme 100**).



Scheme 108

2.1.4 Project Aims

The aim of our work in this area was therefore to investigate the stereospecificity of this cyclisation process in the context of THF synthesis and examine the stereochemical control exerted by the stereochemistry of the allylic alcohol in particular. It was hoped that this may give some further insight into the mechanism of this process, and potentially provide a method to gain access to the THF moiety in a stereodefined sense.

2.2 Results and Discussion

2.2.1 Synthesis of the first cyclisation precursor

Hydroxy-vinyl acetate moiety **2.6** (**Figure 26**) has not been reported as a single enantiomer, possibly because racemisation is rapid. It was also found to be impossible to separate the two diastereomeric cross metathesis products (**2.18**) chromatographically, or the products of the L-selectride reduction (**2.7**).

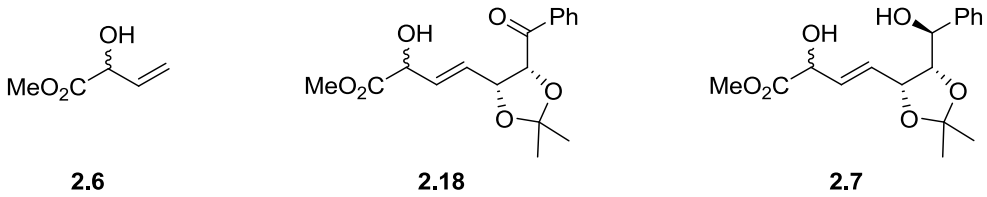
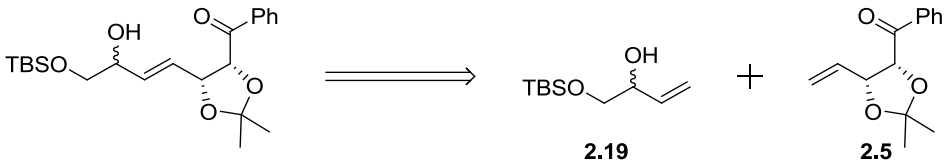


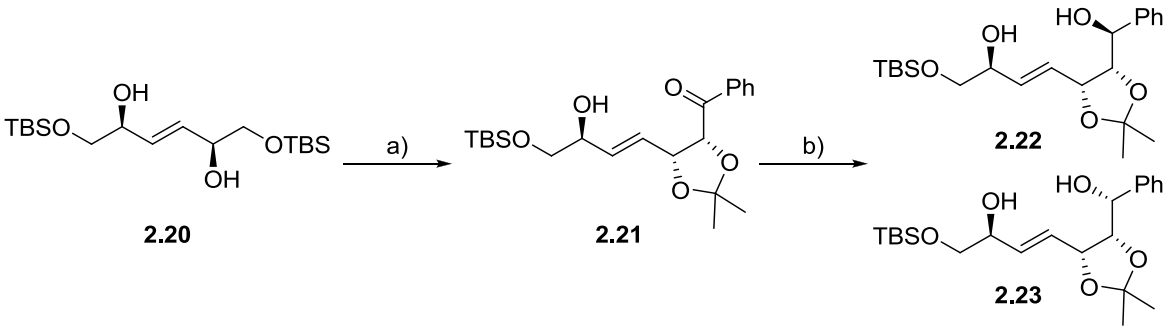
Figure 26

Hence, it was decided to synthesise an ester equivalent that would avoid this undesired racemisation, namely silyl ether **2.19** (**Scheme 109**). This would be taken forward by cross metathesis with ketone **2.5**, the latter being the same component used in the total synthesis of (+)-isoaltholactone.



Scheme 109

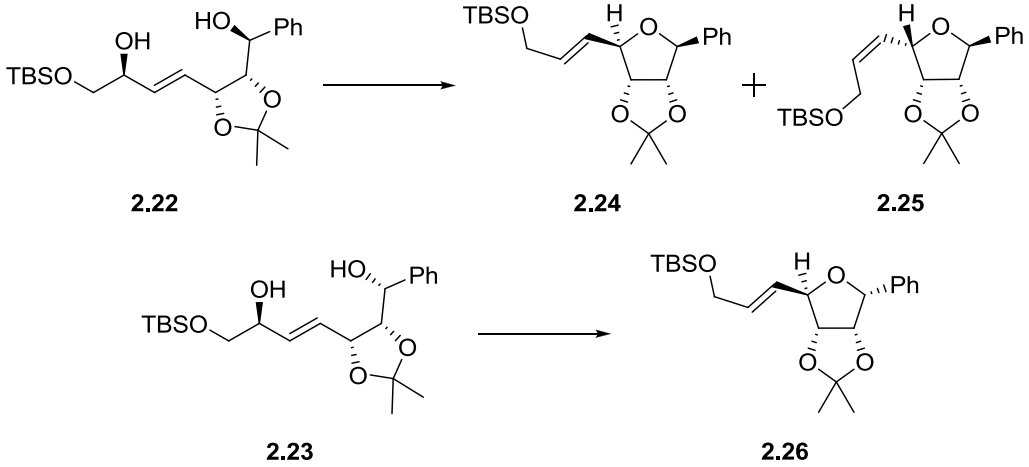
We had in hand a supply of allylic alcohol dimer **2.20** (**Scheme 110**), obtained in four steps from D-mannitol,[29] and, since the monomer itself underwent rapid and reversible dimerisation under cross metathesis reaction conditions,[29] this dimer could be used as an equivalent to the (*S*)-enantiomer of allylic alcohol monomer **2.19** in the cross metathesis step. Indeed, cross metathesis using Hoveyda–Grubbs II in DCM at 50 °C gave the desired product (**2.21**) in 97% yield. This was reduced under the previously developed L-selectride conditions[30] to give (*S*,*S*) diol **2.22** in 87% yield, along with a small amount (12%) of the (*S*,*R*) isomer **2.23**.



a) Hoveyda–Grubbs II, **2.5**, DCM, 50 °C, 3 h, 97%; b) L-selectride, THF, –78 °C, 1 h, 99%, 7.2:1 **2.22**/**2.23**

Scheme 110

This inseparable mixture was then subjected to the standard cyclisation conditions furnishing three isomeric THF compounds (**Scheme 111**), two of which corresponded to the (*S*,*S*) configured starting material and one to the (*S*,*R*) isomer. The two compounds obtained from the major diol component were obtained in an approximately 2:1 ratio, the major product being *endo*-*Z*- product **2.25**.

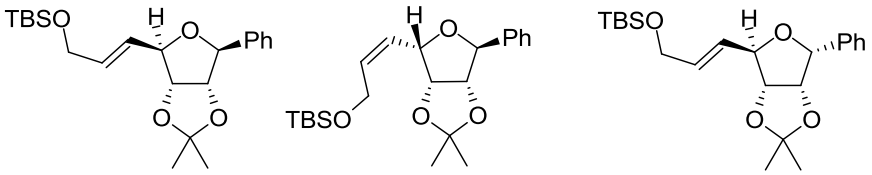


Conditions: 10 mol% Ph_3PAuCl, AgOTf, 4 Å MS, DCM, dark, 74% total (**2.24** 19%, **2.25** 42%, **2.26** 13%)

Scheme 111

The alkene geometry of these cyclisation products was readily assigned on the basis of ^3J H NMR coupling constants (**Figure 27**). The *endo*-/*exo*- nature of the side chain in **2.24** and **2.25** was assigned by analogy to a series of similar compounds prepared previously within the Robertson group.[29] This previous research showed that in compounds of this type with an *endo*- side chain, the C*H*Ph resonance is generally

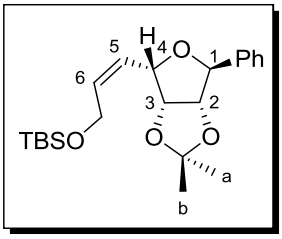
found at *ca*. 5.2 p.p.m., appearing as a broad singlet, whereas compounds with an *exo*- side chain show a distinct doublet at *ca*. 4.9 p.p.m. for the same proton. This trend seemed to play out in our examples, and also analogously in the slightly dissimilar derivative **2.26**.



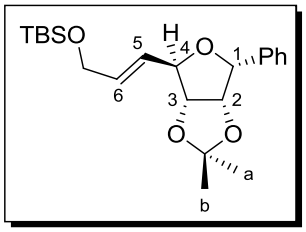
^3J for CH=CH	15.5 Hz	11.5 Hz	15.6 Hz
δ C*H*Ph	4.90, d, *J* 5.0 Hz	5.23, s	4.93, d, *J* 4.0 Hz

Figure 27

These initial assignments were also later confirmed by NOE experiments conducted on diastereomers **3.25** and **3.26** (**Figure 28**).



	H^1	**H^2**	**H^3**	**H^4**	**H^5**	**H^6**	**Me^a**	**Me^b**	**Ph**
H^1	-	S	X	X	X	X	S	X	S
H^2	S	-	S	W	X	X	X	S	S
H^{3,4}	W	S	-	-	S	X	X	S	S



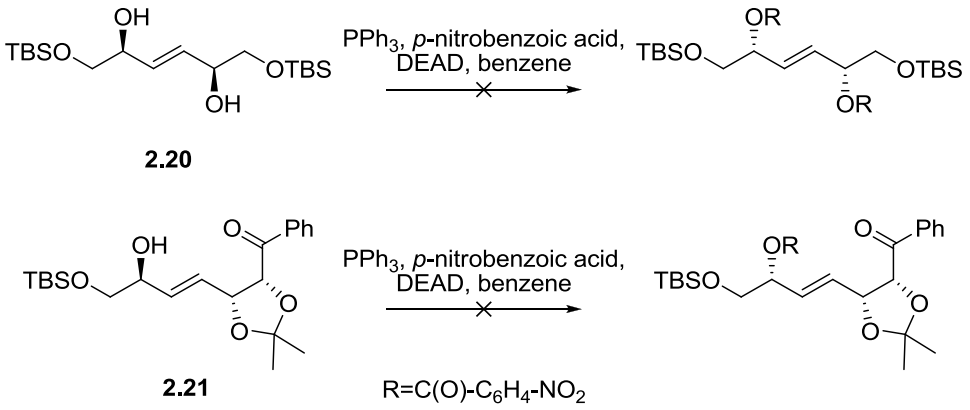
	H^1	**H^2**	**H^3**	**H^4**	**H^5**	**H^6**	**Me^a**	**Me^b**	**Ph**
H^1	-	S	W	X	S	S	X	X	S
H^2	S	-	S	X	X	X	X	S	W
H^3	W	S	-	W	S	W	X	S	X
H^4	X	X	W	-	S	S	W	X	VW

S = strong, W = weak, VW = very weak, X = absent

Figure 28

2.2.2 Synthesis of the second cyclisation precursor

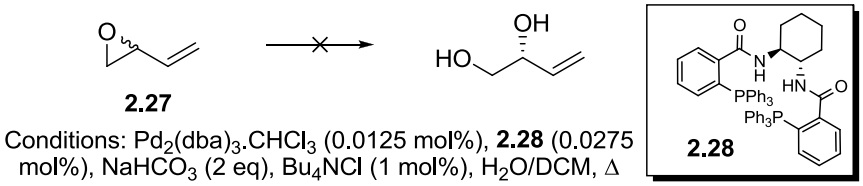
The synthesis of the epimeric cyclisation precursor was not as simple as anticipated and a number of potential routes were tested before a successful option was found. The first strategy was simply to conduct a double Mitsunobu reaction[31] on the D-mannitol derived dimer **2.20** used previously (**Scheme 112**). However, under the conditions described by Martin *et al.*[32] for inversion of sterically hindered secondary alcohols, this was unsuccessful and the diol merely decomposed. The same conditions were applied to cross metathesis product **2.21** but a similar result was obtained.



Scheme 112

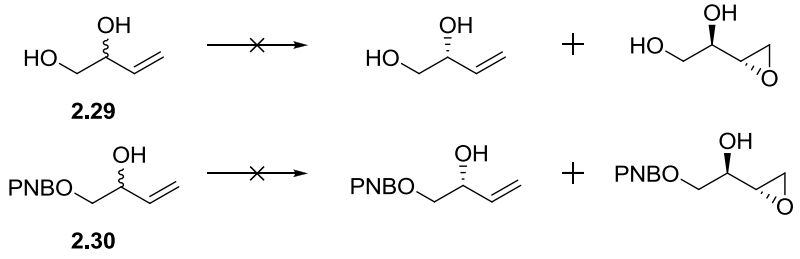
In 1999, Trost and McEachern reported a procedure for the palladium catalysed, dynamic kinetic asymmetric transformation of 3,4-epoxy-1-butene (**2.27**, **Scheme 113**) into (2*R*)-3-butene-1,2-diol using chiral bis-phosphine ligand **2.28**.[33] This was a relatively difficult substrate to work with since it was prone to oligomerisation under the reaction conditions. However, in 2004, Cheeseman *et al.* reported an improved, scaleable and robust route to the same diol product.[34] Despite following these modified conditions, we were unable to conduct this transformation successfully and found that the small quantities of product we were able to obtain had, in fact, no observable optical rotation.[iv, 35]

[iv] lit. reported $[\alpha]_D^{25}$ = +40 ° (c = 4.6 in chloroform)[35]



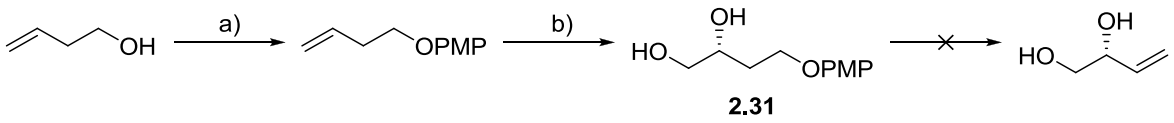
Scheme 113

The next strategy was based on kinetic resolution of diol **2.29** (**Scheme 114**) using epoxidation conditions designed to epoxidise the undesired, (*S*)-enantiomer preferentially.[36] Sharpless' procedure for asymmetric dihydroxylation was applied to racemic diol **2.29** but, again, the product obtained had no observable optical rotation. Similar conditions were applied to monoprotected diol **2.30**,[37] in the hope that this choice of protecting group would allow the product to be easily extracted and potentially crystalline, allowing recrystallisation to improve the *ee*. For example, Sharpless reported that use of the PNB protecting group for *in situ* protection of crotyl- and prenyl-derived epoxides formed by this SAE reaction can lead to products with 100% *ee* after just one recrystallisation.[36, 38] On our substrate, however, these resolution attempts failed due to lack of reactivity.



Scheme 114

It was hoped that subjecting diol **2.31** (**Scheme 115**) to strongly basic conditions would lead to elimination of *p*-methoxyphenol and give access to the desired allylic alcohol.[42] The PMP group was chosen since this would provide a relatively good leaving group in the elimination step. Diol **2.31** was obtained in two steps from buten-3-ol but stirring this diol with DBU in DMSO simply led to decomposition of the starting material with no olefinic peaks identifiable in the ^{1}H NMR spectrum of the crude product.

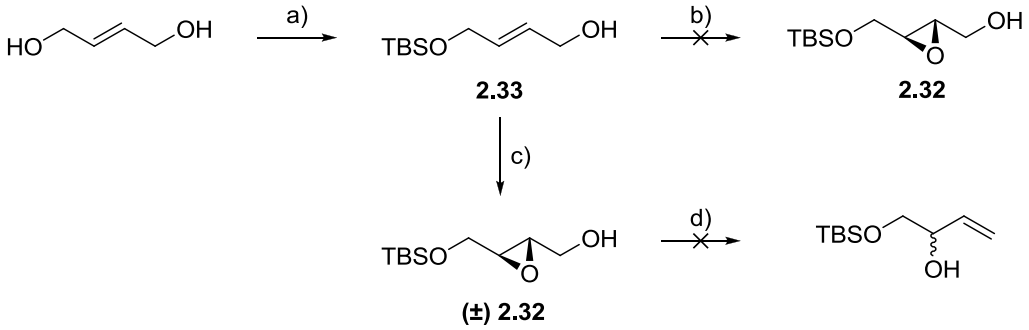


2.31

a) PMPOH, PPh_3, DEAD, THF, Δ, 90%; b) AD-mix β, *t*-BuOH, H_2O, 99%.

Scheme 115

A final, unsuccessful, attempt was based around phosphorus mediated deoxygenation of epoxide **2.32** (**Scheme 116**), using a procedure developed by Li *et al*.[43] Li's work was based on similar, earlier work by Dorta *et al.*[44] which was unfortunately restricted to the synthesis of tertiary allylic alcohols. To that end, monoprotected diol **2.33** was synthesised from butenediol in 95% yield.[38] Although this could not be readily epoxidised asymmetrically using Sharpless' method,[39] racemic epoxidation with vanadyl acetylacetonate and *tert*-butyl hydrogen peroxide in DCM[40] gave epoxide **2.32** in 65% yield. However, subjecting this epoxide to the deoxygenation conditions gave a complex mixture in which no product could be identified.

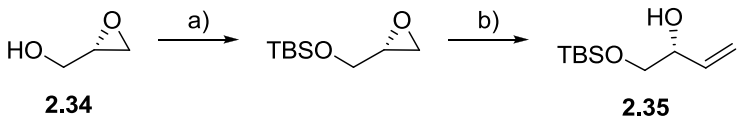


2.33 **2.32** **(±) 2.32**

a) NaH, TBSCl, THF, 95%; b) Ti(*i*-OPr)$_4$, L-(+)-diethyltartrate, *t*-BuOOH, DCM, 4 Å MS, –20 – 0 °C; c) $VO(acac)_2$, *t*-BuOOH, DCM, 65%; d) PPh_3, I_2, pyridine, Et_2O/MeCN, 0 °C then H_2O, 38 °C

Scheme 116

A solution to this synthetic problem was eventually found in an addition-elimination reaction of trimethylsulfonium iodide into epoxide **2.34** (**Scheme 117**), a procedure originally developed by Alcaraz *et al*.[41] Under these conditions, allylic alcohol **2.35** was obtained conveniently from (*S*)-glycidol in 68% yield over two steps.

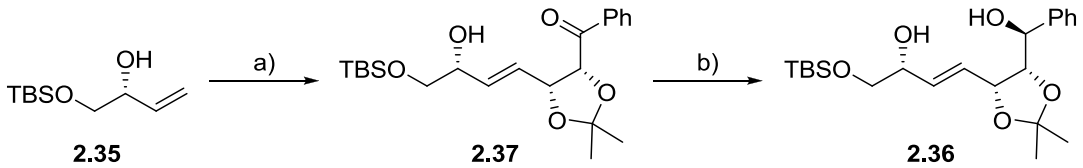


2.34 **2.35**

a) TBSCl, imidazole, DMF, 95%; b) $Me_3S^{\oplus}I^{\ominus}$, BuLi, THF, 72%

Scheme 117

With the desired substrate in hand, efforts were continued toward cyclisation precursor **2.36** (**Scheme 118**), using the methodology developed previously. Hence, ketone **2.37** was obtained in 80% yield and was reduced using L-selectride to give (*R*,*S*) diol **2.36** with no observable contamination from the benzylic epimer.

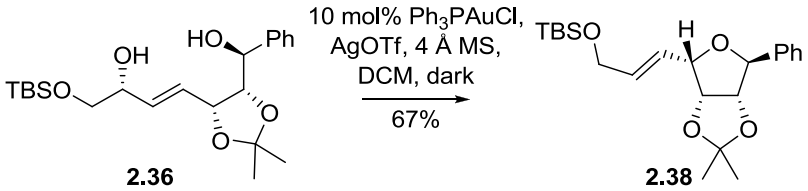


2.35 **2.37** **2.36**

a) Hoveyda–Grubbs II, **2.5**, DCM, 50 °C, 1.5 h, 80%; b) L-selectride, THF, –78 °C, 1 h, 60%

Scheme 118

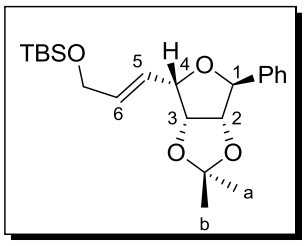
Subjecting this stereodefined diol to the standard cyclisation conditions led, in this case, to a single diastereomer of the THF product, showing *endo*-*E*- stereochemistry (**Scheme 119**).



2.36 **2.38**

Scheme 119

The stereochemistry of this cyclised product was assigned analogously to those obtained from the epimeric cyclisation precursor with NOE correlations again backing up initial conclusions based on ^{1}H NMR chemical shifts and ^{3}J coupling patterns (**Figure 29**).



	H^1	H^2	H^3	H^4	H^5	H^6	Me^a	Me^b	Ph
H^1	-	S	X	VW	VW	VW	S	X	S
H^2	S	-	S	W	X	X	X	S	S
H^3	VW	S	-	S	W	W	X	S	W
H^4	VW	W	S	-	S	S	X	X	S

S = strong, W = weak, VW = very weak, X = absent

Figure 29

2.2.3 Consideration of the cyclisation results

The combination of these cyclisation outcomes, summarized below (**Figure 30**), show some interesting results. Specifically, although these fit the general stereochemical model published by Aponick *et al.*,[28] our results give the first examples of *Z*- alkenes being formed in this reaction. It is also apparent from our results that a difference in the configuration of the incoming alcohol can alter the stereochemistry of the product, and therefore that the stereochemical outcome of the reaction does not depend entirely on the stereochemistry of the alkene and allylic alcohol.

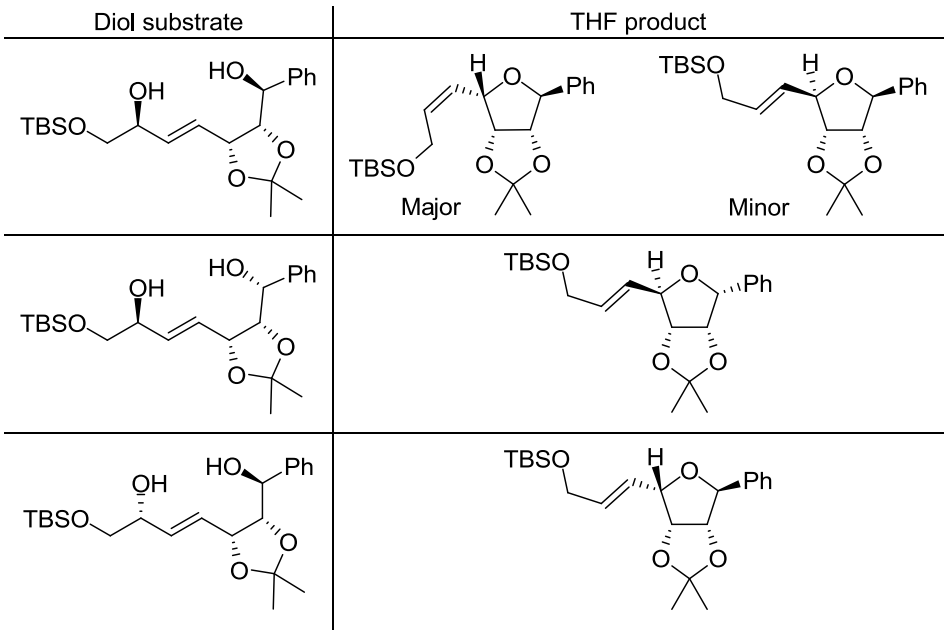


Figure 30

A model placing the metal species loosely coordinated to both hydroxyls and mediating an overall *syn*-S_N2' process gives a workable mnemonic to predict product stereochemistry (**Figure** 31).

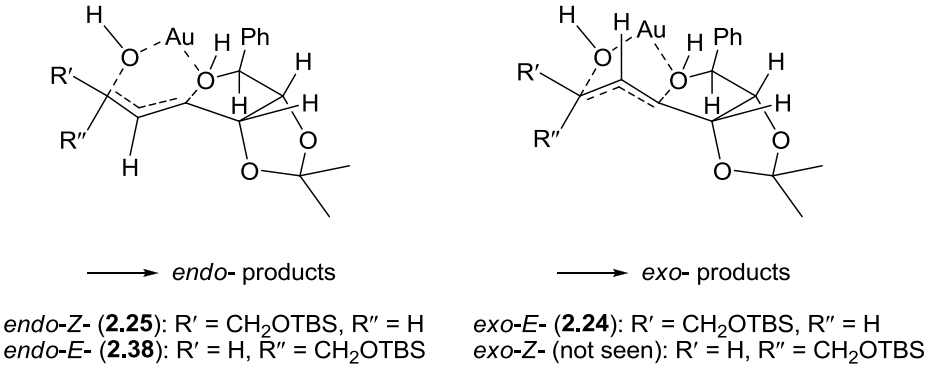


Figure 31

Although this general model can be established from our findings, this study is by no means exhaustive and it is difficult to reach any firm conclusions from these results alone. Certainly, any simple model based on the stereochemistry of the allylic alcohol alone fails to predict the observed results accurately, and it is obviously necessary to consider the stereochemistry of other components of the molecule.

By consideration of these results, it is also possible to draw some conclusions about the providence of the three THF products obtained in the original (+)-isoaltholactone synthesis (**Figure 32**). Using these models we can infer that THF derivative **3.8** came from the (*R*)-configured allylic alcohol **3.39**, and diastereomers **3.9** and **3.10** from the (*S*)-configured allylic alcohol **3.40**. We can also conclude, therefore, that this (*S*)-allylic alcohol must have been the major component in the epimeric mixture.

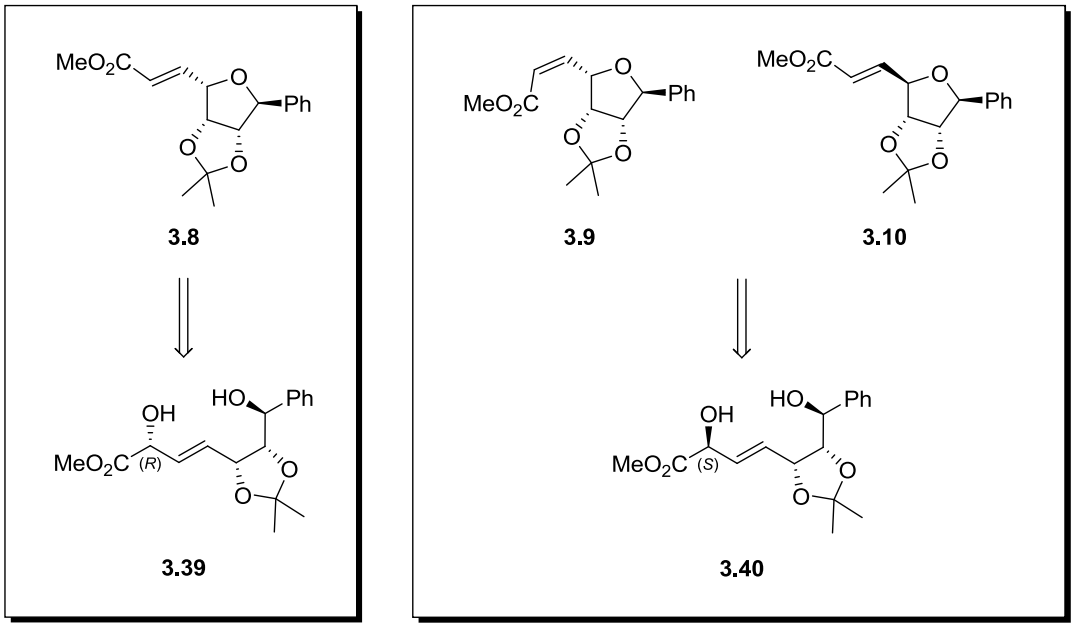


Figure 32

2.3 Further Work

With only a small selection of examples, it is impossible to provide conclusive answers about the mechanistic and stereochemical origin of these results. A wider survey is required to provide these answers, however time constraints have meant that an extensive study has not been conducted. It would also be important to check these results under conditions that more closely match those used in Aponick's work, to allow a more direct comparison of the studies.

The lack of previous examples of Au(I)-catalysed THF formation reported means that a more detailed study of this process would be of general interest to the scientific community, potentially leading to the development of a useful synthesis of chiral THF derivatives from more easily obtained stereodefined diol precursors and providing a complementary method to those involving other late transition metals. The development of such a reaction would be of particular interest considering the large number of natural product targets that contain this motif.

It may also be of interest to study the outcome of similar reactions using different intramolecular nucleophiles, for example nitrogen, to further gain understanding of this process and expand the scope of this potentially useful transformation.

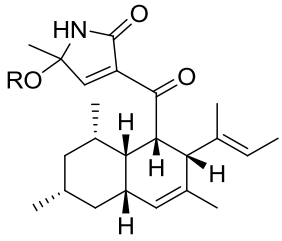
3 STUDIES INTO THE TOTAL SYNTHESIS OF ASCOSPIROKETALS A AND B

3.1 Introduction

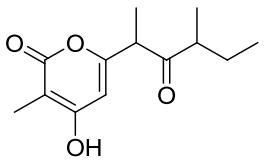
3.1.1 Ascospiroketals A and B

Over the last decade, König *et al.*, have conducted investigations into the secondary metabolites obtained from the fungus *Ascochyta salicorniae*, an algal endophyte isolated from the marine green alga *Ulva* sp. obtained from the North Sea. Cultivation of this fungus has shown that it is able to produce a variety of polyketides and alkaloids.

Initial studies[1] identified the unusual tetramic acid derivatives ascosalipyrrolidinones A and B (**Figure 33**), along with the polyketide metabolite ascosalipyrone and three other previously identified natural products. Ascosalipyrrolidinone A showed potent antiplasmodial activity against the malaria-causing parasite *Plasmodium falciparum* as well as antimicrobial activity. Ascosalipyrone exhibited no such activity and ascosalipyrrolidinone B was isolated in insufficient quantities to allow for testing.



ascosalipyrrolidinone A: R = *n*-Bu
ascosalipyrrolidinone B: R = Me



ascosalipyrone

Figure 33

An OSMAC approach (One Strain-MAny Compounds)[2] to cultivation of the same species led to isolation of five more metabolites of polyketide origin,[3] two new polyketide-derived lactones, epimeric ascolactones A and B (**Figure 34**), and known metabolites hyalopyrone, ascochitine, ascochital and

ascosalipyrone. These were identified as potential protein phosphatase inhibitors using *in silico* screening studies with PASS software (Prediction of Activity Spectra for Substances) but testing of these six polyketides against a broad range of both eukaryotic and prokaryotic protein phosphotases found that all but ascochitine were weak or inactive phosphatase inhibitors.

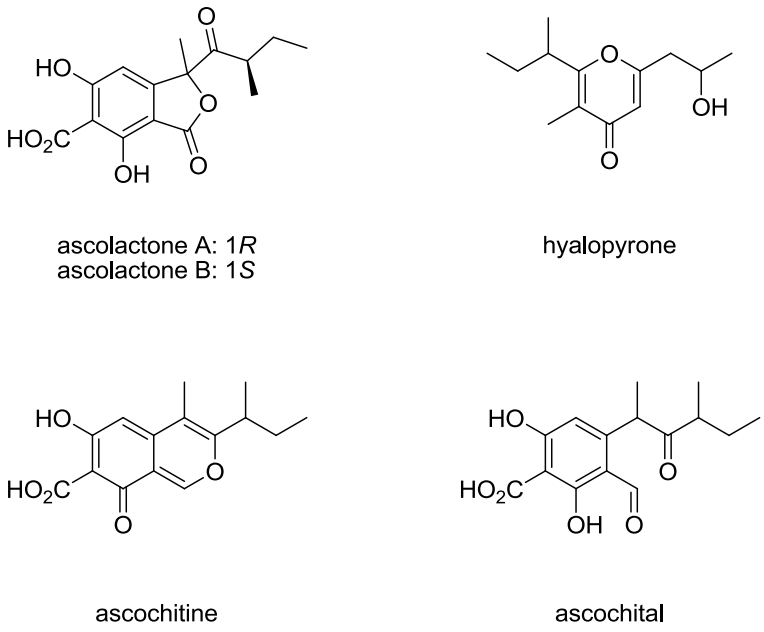


Figure 34

More recently, the group reported two additional compounds from this fungal strain, the ascospiroketals A and B (**Figure 35**).[4] The structures of these metabolites were idenitified using EI-MS, IR and NMR analysis, relying heavily on assignments made in HMBC and NOE experiments. Unfortunately, although the relative configuration of the rigid tricyclic core was able to be assigned confidently, the stereochemistry of the ester side-chain was not easily established *via* these methods, and degradation studies were also unsuccessful due to inseparability of the two enantiomers of 3-hydroxy-2-methyl-butanoic acid used as reference compounds by either chiral GC-MS or HPLC.

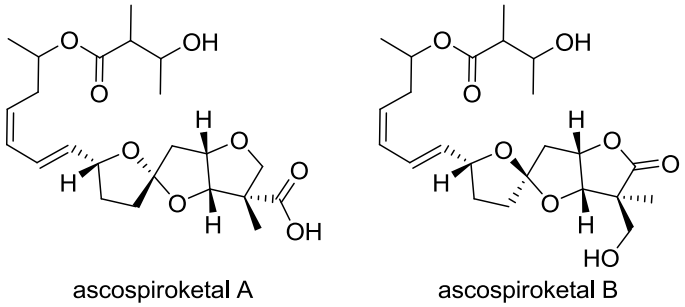


Figure 35

The proposed structures of these natural products bear some resemblance to the well-known natural products cephalosporolides E and F (**Figure 36**), but show significant differences in the substitution pattern around the tricyclic core.

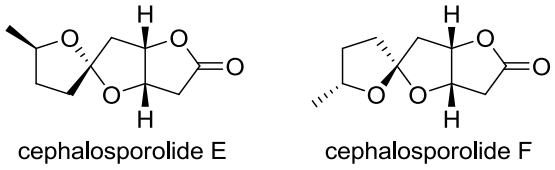


Figure 36

Structurally, the ascospiroketals are quite different from any previously reported natural products. A fused THF, spiroketal-containing tricyclic core structure similar to that observed in ascospiroketal A has been reported in the brominated acetogenins isolated from *Laurencia* species (**Figure 37**).[5, 6]

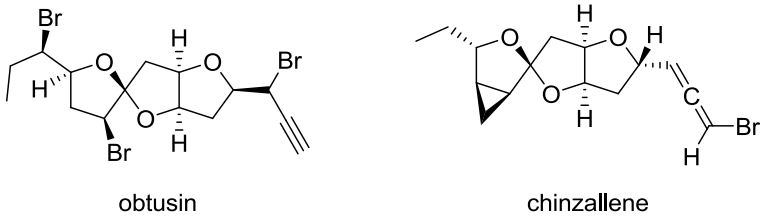


Figure 37

The fused γ-butyrolactone motif observed in ascospiroketal B has only previously been observed in the cephalosporolides E and F, although these spiroketals do not bear the same, or any, substitution at the C(2)

position. The substitution pattern of this γ-butyrolactone motif is particularly unusual, with only one other example known in the literature: secondary metabolites of the leupyrrin family,[7] isolated from the *Sorangium cellulosum* myxobacterial strain, exhibit the same substitution pattern in the C(1)–C(4) section of their macrocyclic structure.

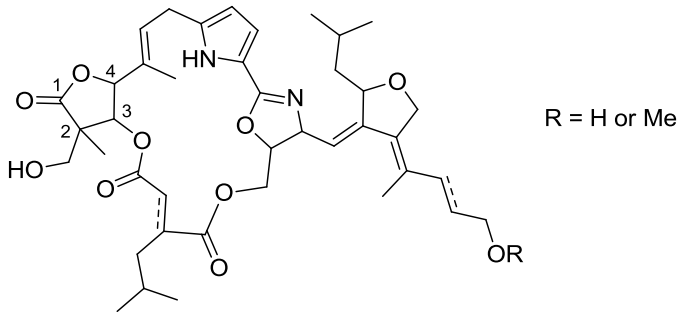


Figure 38

The presence of these unusual structural features make the ascospiroketals an interesting target for synthesis and the necessity for identification of the side-chain stereochemistry is also a tractable synthetic problem. Since the biological activity of the ascospiroketals has not yet been investigated, it would also be interesting to see whether they exhibit any similar activity to those metabolites obtained from the same marine fungus, or whether their unusual structure leads them to show any unique activity.

3.1.2 Retrosynthetic analysis

It was envisaged that the structure of the ascospiroketals A and B could be broken down into three components (**Figure 39**): bicycles **3.1** and **3.2**, diene **3.3** and acid **3.4**. This approach also allowed for the possibility of coupling with the four possible stereoisomers of **3.4** to correctly identify the relative stereochemistry of the natural products, with all four isomers of **3.4** being easily accessed *via* diastereoselective aldol reactions using methodology developed by Mukaiyama[8] and Evans.[9] Introduction of this side-chain could be achieved *via* either an ester coupling reaction or a Mitsunobu reaction,[10] allowing easy access to both potential C(15) epimers.

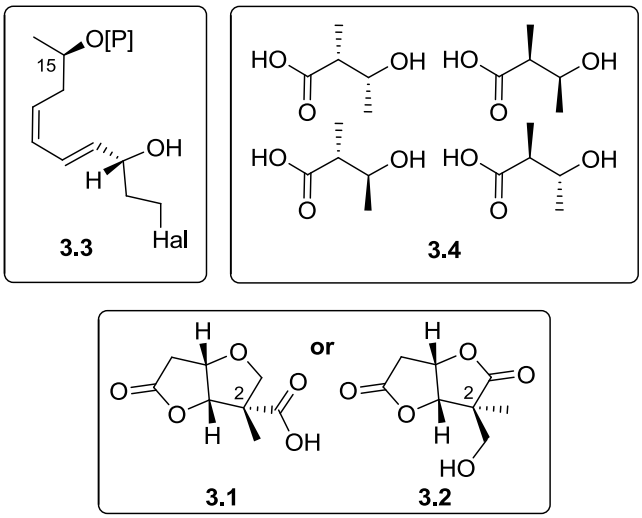
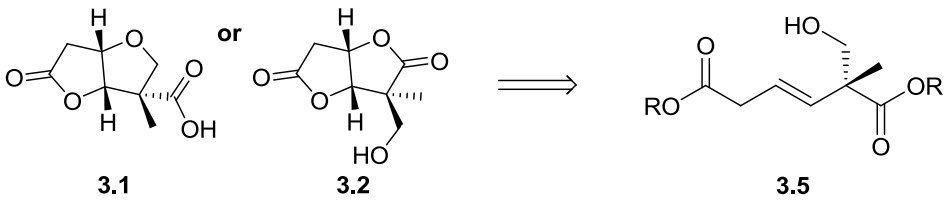


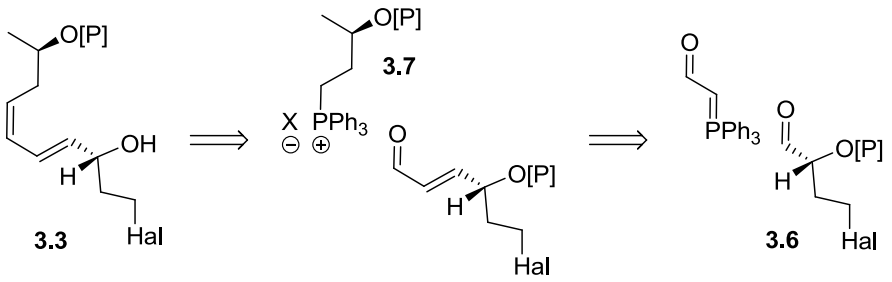
Figure 39

It was also envisaged that it would be possible to interconvert the two bicyclic components **3.1** and **3.2** since they exhibit the same absolute stereochemistry at the C(2) position. These could then be most easily furnished by a Sharpless Asymmetric Dihydroxylation (SAD)[11] reaction on a suitable *trans*-β-hydromuconic acid derivative (**3.5**, **Scheme 120**) and *in situ*[12] cyclisation to give dilactone **3.2**. This would then be isomerised to give dilactone **3.1**.



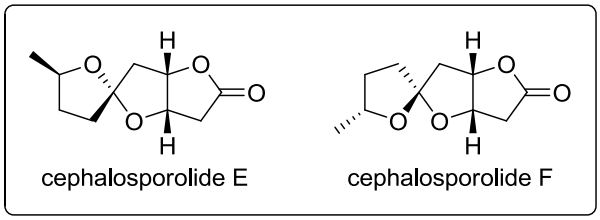
Scheme 120

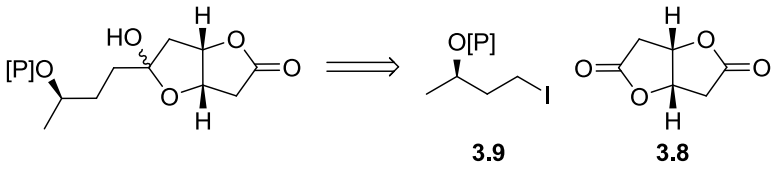
Diene **3.3** could be constructed using a number of possible strategies, the simplest of these being a Horner-Wadsworth-Emmons reaction[13] on aldehyde **3.6** followed by a Wittig reaction[14] on the resultant α,β-unsaturated aldehyde using phosphonium salt **3.7** (**Scheme 121**). Other possibilities include metal coupling reactions to attach the two alkene units, reactions which would be especially useful due to the high levels of stereospecificity with respect to the starting alkene geometry.



Scheme 121

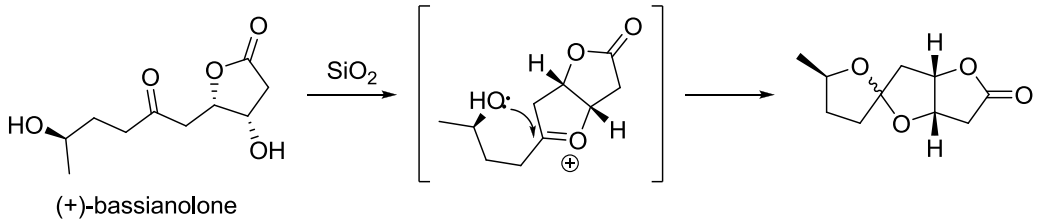
Since the most challenging part of this strategy would be the selective monoaddition of the organolithium to the bicyclic component, the methodology would first be tested on the cephalosporolides E and F (**Scheme 122**). These less complex natural products could be considered to arise from unsubstituted dilactone **3.8** and iodoalkane **3.9**, derived from commercially available (*R*)-1,3-butanediol.





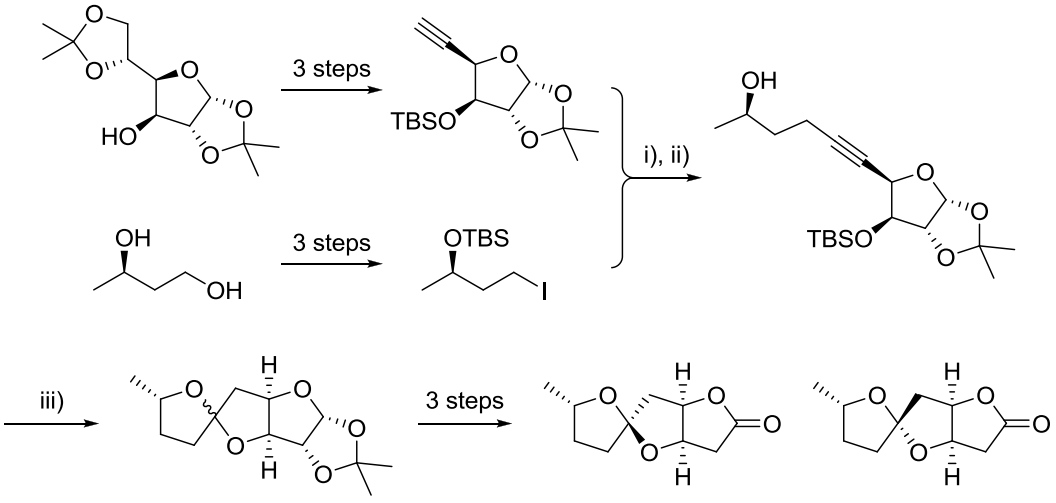
Scheme 122

Despite being isolated in 1985,[15] the cephalosporolides E and F were not obtained synthetically until 2005, when it was shown that the antimicrobial natural product (+)-bassianolone, isolated from *Beauveria bassiana*,[16] could be converted to a diastereomeric mixture of cephalosporolides E and F by treatment with silica (**Scheme 123**). (+)-Bassianolone is considered to be the linear biological precursor to the two spiroketal natural products.



Scheme 123

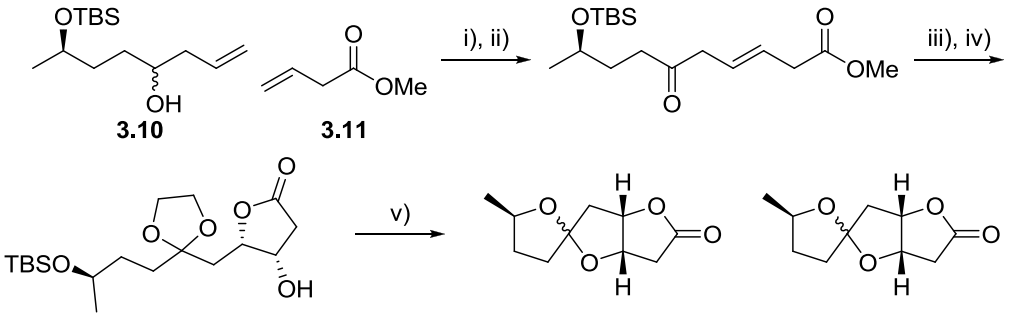
Although the relative stereochemistry of the cephalosporolides E and F had been determined at the time of isolation, the absolute stereochemistry had not and was first determined by asymmetric synthesis of the two enantiomers of the natural products, achieved by a Pd-mediated alkenediol cyclo-isomerisaton (**Scheme 124**).[17] The absolute stereochemistry of the products was derived from the chiral pool starting materials.



i) *n*-BuLi, HMPA, THF, –40 °C, 68%; ii) TBAF, THF, 89%; iii) $Cl_2Pd(CH_3CN)_2$, MeCN, 62%

Scheme 124

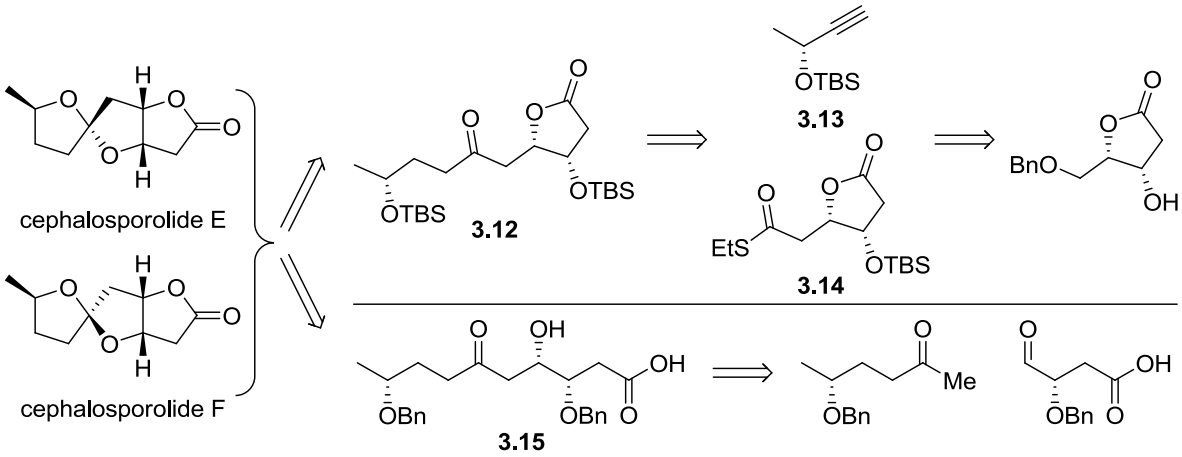
More recently, the cephalosporolides E and F were synthesised by cross metathesis of alkenes **3.10** and **3.11** (**Scheme 125**),[18] with subsequent acetal protection and dihydroxylation furnishing a mixture of the two separable diastereomers.



i) Grubbs' II, DCM, Δ, 82% (5:1 *E*-/*Z*-); ii) IBX, EtOAc, Δ, 89%; iii) $(CH_2OH)_2$, PTSA, PhH, Δ, 77%; iv) K_3FeCN_6, K_2CO_3, $MeSO_4NH_2$, $(DHQ)_2PHAL$, $K_2OsO_4{\cdot}2H_2O$, *t*-BuOH, H_2O, 0 °C, 70%; v) 2 M HCl, MeOH or PTSA, MeOH

Scheme 125

A similar sequence was attempted by the Brimble group, with cross metathesis and cyclisation giving access to lactone **3.12** (**Scheme 126**).[19] Unfortunately, addition of alkyne **3.13** to thioester **3.14** was prohibitively low yielding and this strategy had to be modified. The total synthesis of the cephalosporolides E and F was eventually achieved using a Mukaiyama aldol reaction to construct syn diol **3.15**.



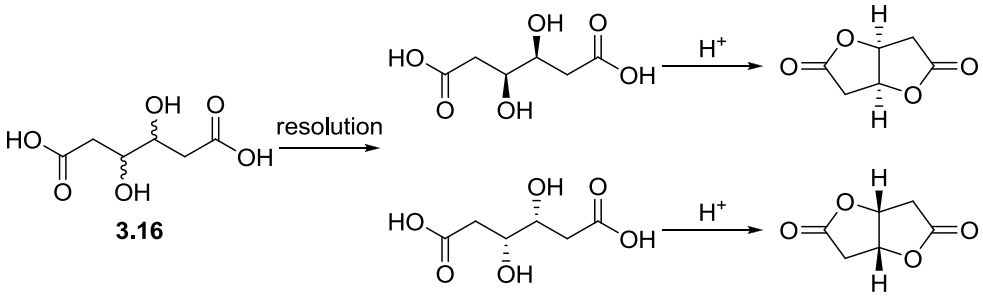
Scheme 126

None of these previously reported syntheses had attempted to conduct alkylation on the preformed dilactone core (**3.8**, **Scheme 122**), a strategy which, if successful, would lead to a short and efficient linear sequence to the cephalosporolides E and F.

3.1.3 Previous syntheses of the dilactone core

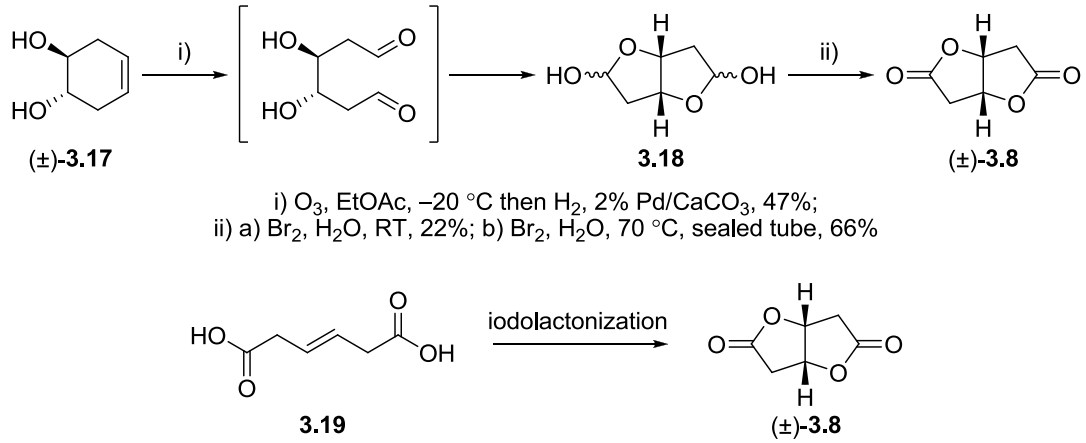
Unsubstituted lactone core (**3.8**) has been prepared previously, but few of these syntheses furnished the dilactone core as a single enantiomer.

Chronologically, the first synthesis was achieved by resolution of precursor **3.16** by recrystallisation of its strychnine salt, and subsequent cyclisation under acidic conditions (**Scheme 127**).[20]



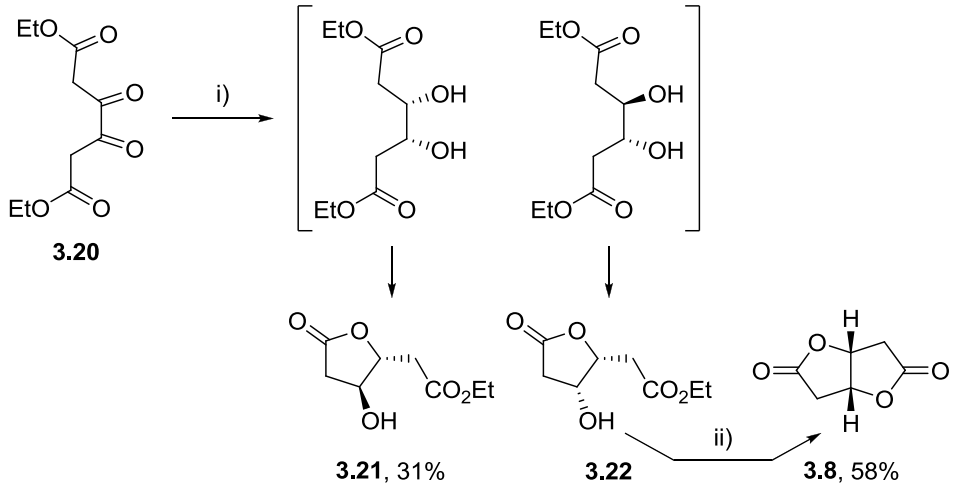
Scheme 127

From that early work until 2000, no further syntheses of this fragment as a single enantiomer were published. Two racemic syntheses were however reported (**Scheme 128**), the first using oxidative cleavage of alkene **3.17** to give dilactol **3.18**,[21] and the second furnishing dilactone **3.8** in one step by iodolactonisation of diacid **3.19**.[22]



Scheme 128

The first of the more recent asymmetric syntheses was conducted by asymmetric reduction of diketone **3.20** (**Scheme 129**). The first cyclisation occurred during the reduction to give hydroxylactones **3.21** and **3.22**, the *trans*- product arising from the *syn*- diol and the *cis*- lactone from the *trans*- diol. Cyclisation of this cis-hydroxylactone under acidic conditions gave (*R*,*R*)-dilactone **3.8** in 89% *e.e.*[23]

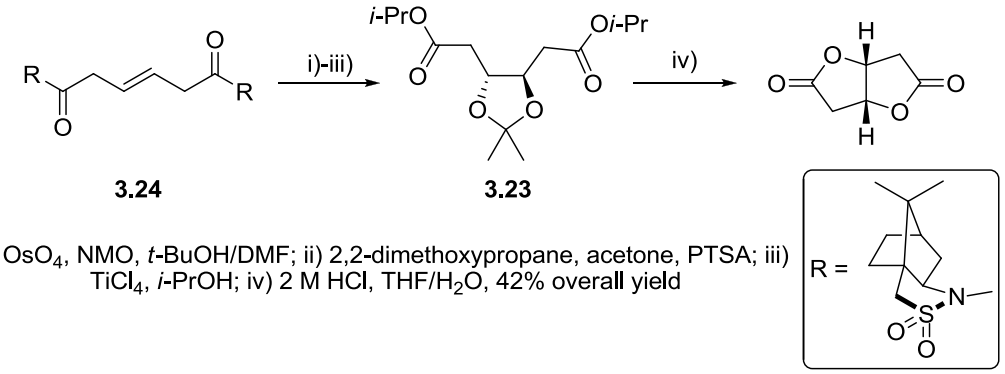


i) $RuCl_2$[(*S*)-BINAP](*p*-cymene), H_2 (100 atm), EtOH, 65 °C, 16 h; ii) PTSA, PhMe, Δ

Scheme 129

A second synthesis also obtained the (*R*,*R*) enantiomer by acidic cyclisation, in this case of isopropyl ester **3.23** (**Scheme 130**).[24] This protected diol was obtained by dihydroxylation of alkene **3.24**, the enantioselectivity of this process being induced by the camphor-sulfonamide auxiliaries. However, this

sequence was relatively low yielding and any attempts to improve it only led to a drop in the *e.e.* of the product.

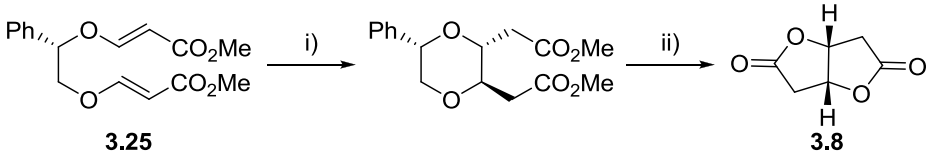


3.24 **3.23**

i) OsO_4, NMO, *t*-BuOH/DMF; ii) 2,2-dimethoxypropane, acetone, PTSA; iii) $TiCl_4$, *i*-PrOH; iv) 2 M HCl, THF/H_2O, 42% overall yield

Scheme 130

Pandey *et al.* reported the synthesis of the (*R*,*R*)-dilactone using diastereoselective photo-cyclisation of diene **3.25** (**Scheme 131**).[25] Removal of the madelate-derived auxiliary gave dilactone **3.8** in good yield.

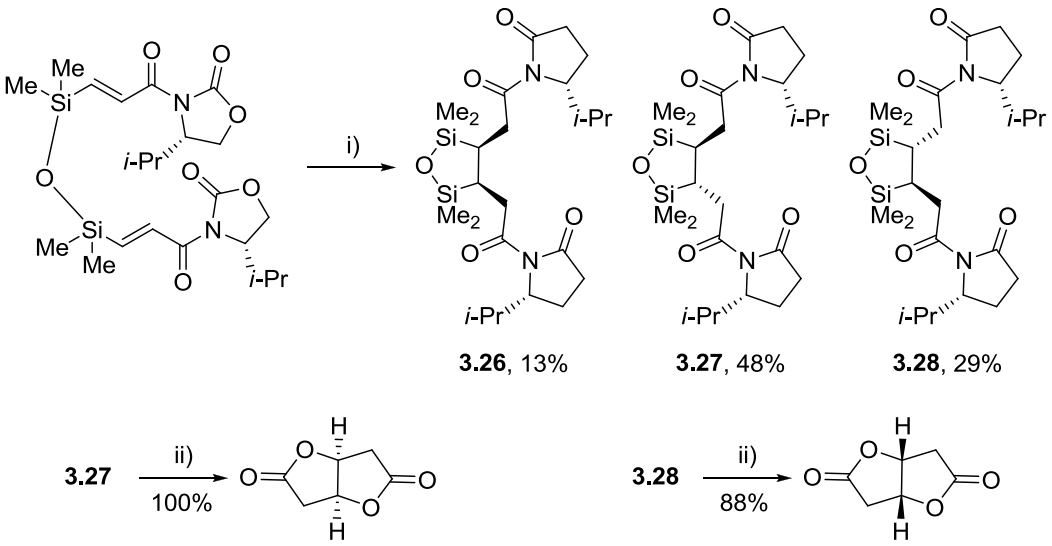


3.25 **3.8**

i) hν, DMN, DCA, ascorbic acid, DMF/*i*-PrOH/H_2O, 88%; ii) BBr_3, DCM, 98%

Scheme 131

The most recent synthesis also utilises a diene cyclisation reaction, in this case mediated by magnesium, to give silyl ether **3.26**−**3.28** (**Scheme 132**).[26] The absolute stereochemistry of this product was controlled by the chiral oxazolidinone auxiliaries and the diastereomeric products could be separated chromatographically. The two *trans*- isomers **3.27** and **3.28** were subjected to Fleming−Tamao oxidation[27, 28] and acid catalysed cyclisation to yield the enantiomers of dilactone **3.8** in good yield.



i) Mg, TMSCl, DMF, 0 °C; ii) 1) 30% H_2O_2, KHF_2, THF/MeOH; 2) H_3O^+ then PTSA, THF, 55 °C

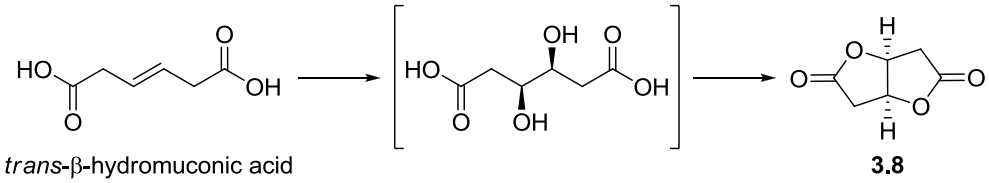
Scheme 132

The published syntheses suffer from lengthy procedures or low overall yields, or impractical procedures. This project began with an investigation into an efficient and scalable route to (*S*,*S*)-dilactone **3.8**, to be used as the starting point for the total synthesis of the cephalosporolides E and F.

3.2 Results and Discussion

3.2.1 Synthesis of the unsubstituted dilactone core

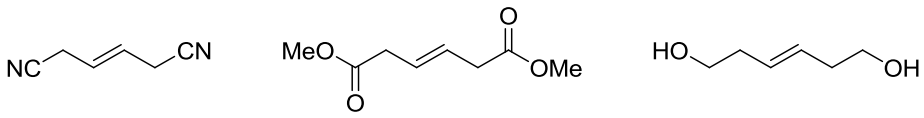
Initial investigations sought to effect SAD on *trans*-β-hydromuconic acid derivatives and cyclisation to give the required product **3.8** (**Scheme 133**).



trans-β-hydromuconic acid **3.8**

Scheme 133

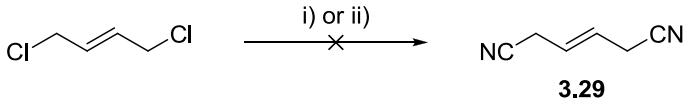
Three appropriate alkenes were identified, namely dinitrile **3.29**, diester **3.30** and diol **3.31** (**Figure 40**), the latter of which would require oxidation before dihydroxylation.



3.29 **3.30** **3.31**

Figure 40

Dinitrile **3.29** could not be accessed from *trans*-1,4-dichlorobut-2-ene by double displacement with NaCN in DMF,[29] either at RT or on warming to 50 °C (**Scheme 134**).

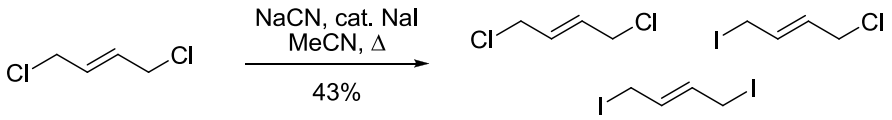


3.29

i) NaCN, DMF, 0 °C → RT; ii) NaCN, DMF, 50 °C

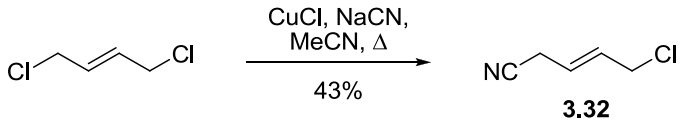
Scheme 134

Using NaCN in conjunction with NaI as a nucleophilic catalyst[30] was also unsuccessful, instead furnishing a mixture of starting material and mono- and diiodo- substituted material (**Scheme 135**, ca. 5:1 overall ratio of chloro- to iodo- substitution observed by ^{1}H NMR analysis).



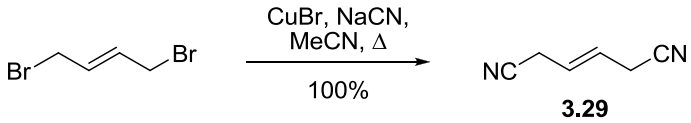
Scheme 135

Introduction of CuCl to the reaction mixture (**Scheme 136**)[31] led to formation of monosubstituted nitrile **3.32** in moderate yield, with recovered starting material accounting for the mass balance.



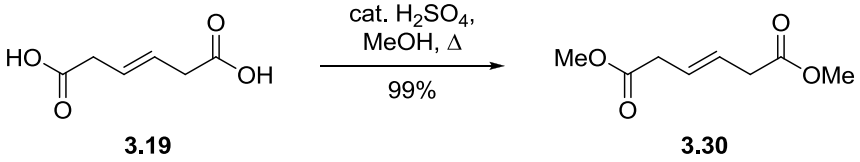
Scheme 136

Pleasingly, application of analogous conditions to the more reactive *trans*-1,4-dibromo-2-butene (**Scheme 137**), gave a quantitative conversion to desired dinitrile **3.29**.



Scheme 137

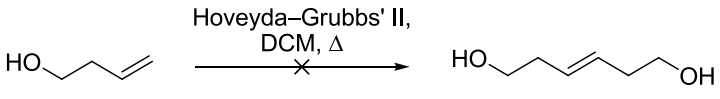
The second substrate, diester **3.30**, was obtained by acid-catalysed esterification of *trans*-β-hydromuconic acid (**3.19**, **Scheme 138**).[32]



3.19 **3.30**

Scheme 138

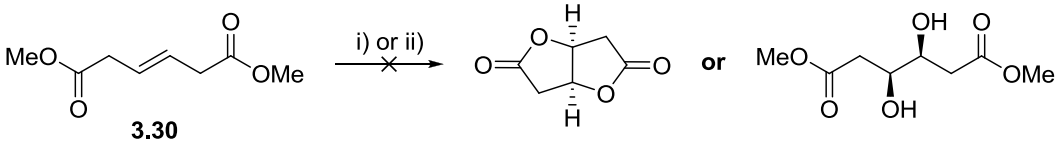
Attempts to form diol **3.31** by metathesis of 3-buten-1-ol (**3.33**, **Scheme 139**), led to complex mixtures. The observation of aldehydic peaks in the ^{1}H NMR spectrum of the crude product suggested competitive oxidation of the free alcohol was complicating the reaction.



3.33 **3.31**

Scheme 139

With two suitable substrates in hand, investigations began into the SAD reaction. AD-mix α[33] was applied to diester **3.30** at RT (**Scheme 140**), but even after extended reaction times, only starting material was recovered. Addition of extra $(DHQ)_2PHAL$ ligand, hoping to speed up any potential reaction, provided no improvement. In order to check the viability of this reaction, racemic dihydroxylation conditions were applied to the substrate, but unfortunately application of 'Upjohn' conditions[34] also gave no reaction, even upon addition of further quantities of the osmium species.



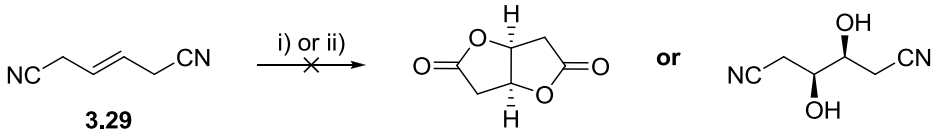
3.30

i) AD-mix α, $CH_3SO_2NH_2$, H_2O, *t*-BuOH; ii) OsO_4, NMO, acetone, H_2O, 0 °C → RT

Scheme 140

Similar behaviour was observed using dinitrile substrate **3.29** (**Scheme 141**), with application of the AD-mix conditions returning starting material along with some evidence of decomposition products. Use of

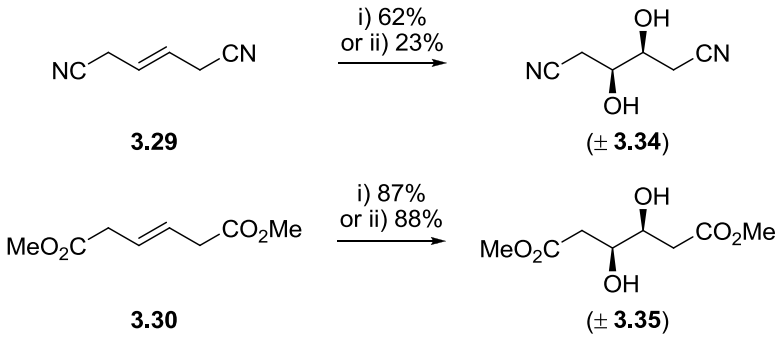
'super AD-mix', as applied in Armstrong's synthesis of (+)-zaragozic acid C,[35] gave no improvement and simply increased the level of decomposition observed.



i) AD-mix α, $CH_3SO_2NH_2$, H_2O, *t*-BuOH;
ii) AD-mix α, $CH_3SO_2NH_2$, $(DHQ)_2PHAL$, OsO_4, H_2O, *t*-BuOH

Scheme 141

Instead, racemic dihydroxylation was attempted using catalytic $RuCl_3$ with $NaIO_4$ as the stoichiometric reoxidant.[36] This gave good conversion to diols **3.34** and **3.35** (**Scheme 142**), with no cyclisation of either substrate being observed under the reaction conditions, despite the presence of H_2SO_4. The reaction was extremely rapid, taking less than 5 minutes at 0 °C, and this, combined with the biphasic nature of the reaction meant that on larger scales increased amounts of over-oxidation and decomposition products were observed. Hence, the largest scale on which this reaction could be conducted successfully was approximately 100 mg.

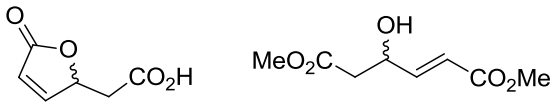


i) $RuCl_3$, $NaIO_4$, H_2SO_4, EtOAc, MeCN, H_2O;
ii) $K_2OsO_2(OH)_4$, NMO, citric acid, *t*-BuOH, H_2O

Scheme 142

A more robust procedure was found in Sharpless' modification of the racemic dihydroxylation conditions,[37] using citric acid as a ligand to effectively stabilise the osmium(VI) species, allowing for a

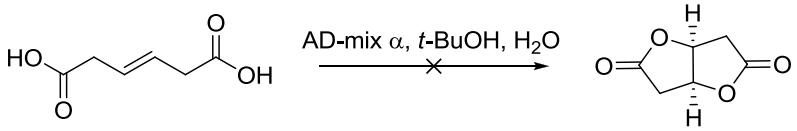
higher catalyst turnover and faster reaction rate. This reaction furnished the corresponding diols controllably for both substrates (**Scheme 142**), although there was a significant drop for yield for dinitrile diol **3.34** under these conditions compared to small scale reactions using the ruthenium based conditions. Again, no *in situ* cyclisation was observed for the dinitrile, however under these conditions some cyclisation was observed for the diester substrate, as well as elimination products **3.36** and **3.37** (**Figure** 41). These products were formed in small but variable yields, the quantities increasing with reaction time.



3.37 **3.38**

Figure 41

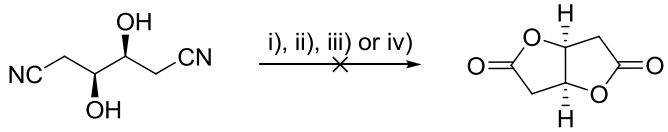
Finally, asymmetric dihydroxylation with AD-mix α was attempted on *trans*-β-hydromuconic acid itself (**3.19**, **Scheme 143**), although with little success, with no identifiable products or intermediates being obtained from this reaction.



3.19

Scheme 143

The cyclisation of racemic diols **3.34** and **3.35** to the dilactone **3.8** (**Scheme 144**) was then investigated, initial work being focused on dinitrile **3.34**. Basic hydrolysis conditions were unsuccessful and attempts to conduct a Pinner reaction[38] using HCl gas,[39] followed by hydrolysis of the formed imidate were equally disappointing. This was presumed to be due to low solubility of the starting material in the solvent (benzene) and other solvents were tested. Changing to dioxane gave trace amounts of the desired product, but in methanol decomposition predominated.

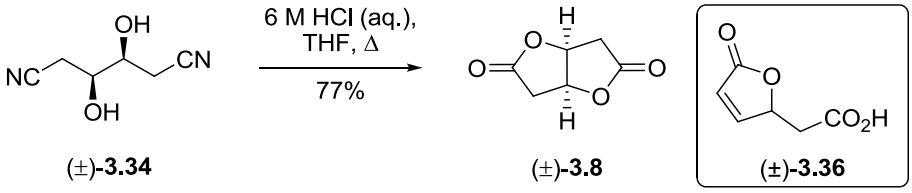


(±)-**3.34** (±)-**3.8**

i) NaOH (40% aq.), Δ; ii) HCl (g), benzene; iii) HCl (g), dioxane; iv) HCl (g), methanol

Scheme 144

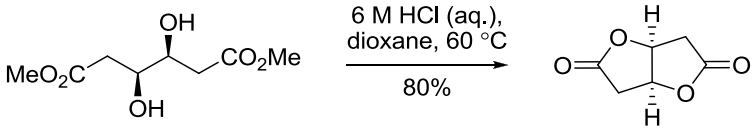
Pleasingly, acidic hydrolysis using 6 M HCl in THF at reflux (**Scheme 145**)[40] furnished the dilactone in good yields. This was accompanied by elimination product **3.36**, as observed previously during the dihydroxylation of diester **3.30** (**Figure 41**).



(±)-**3.34** (±)-**3.8** (±)-**3.36**

Scheme 145

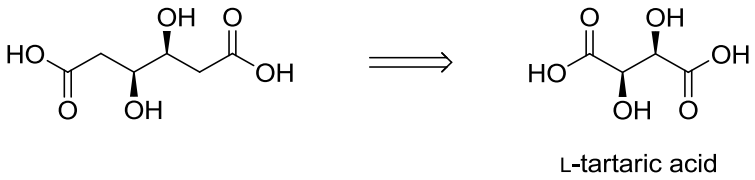
Based on this successful cyclisation, similar reactions were carried out on diester **3.35**, in this case conducting the reaction in dioxane at 60 °C (**Scheme 146**). This led to dilactone **3.8** in similar yield, although the formation of **3.36** was again observed.



(±)-**3.35** (±)-**3.8**

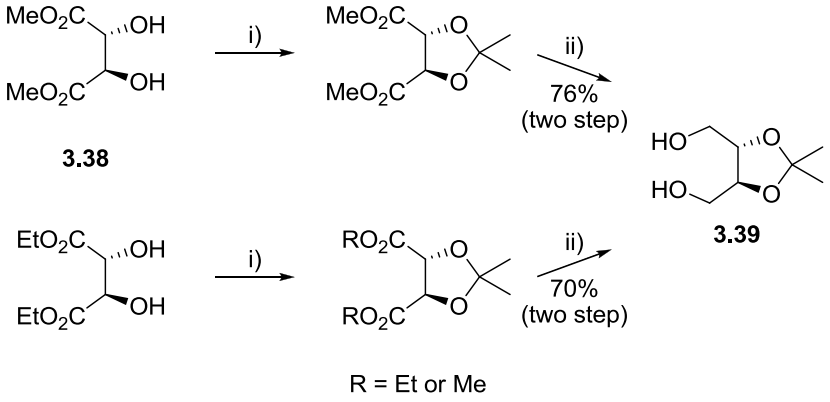
Scheme 146

A parallel investigation was conducted into a slightly longer sequence from tartaric acid (**Scheme 147**), aimed to take advantage of the in-built stereochemistry of this cheap chiral pool starting material.



Scheme 147

Acetonide protection of dimethyl-L-tartrate (**3.38**, **Scheme 148**) followed by reduction of the crude mixture afforded diol **3.39** in 76% yield.[41] This sequence could be repeated using the significantly cheaper diethyl-L-tartrate[v] and the first-formed mixture of acetonide-protected dimethyl-, diethyl- and mixed esters were reduced without problem to give a 70% overall yield of diol **3.39**.

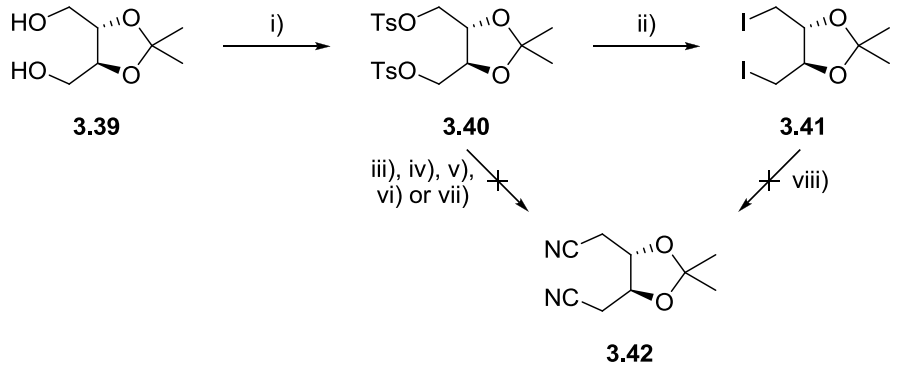


Scheme 148

With diol **3.39** in hand, efforts were made to convert this to the desired dinitrile. Bistosylate **3.40** was synthesised in good yield,[42] and this could readily be transformed to diiodide **3.41**.[43] Substitution with NaCN could not be achieved on either the bistosylate or the diiodide; presumably the lower nucleophilicity of ^{-}CN relative to I^{-} leaves it unable to attack this deactivated position. The majority of conditions tested, in a variety of solvents,[40, 44] gave no observable reaction, and heating bistosylate **3.40** in DMSO in the presence of excess NaCN resulted in decomposition of the starting material. Addition of

[v] Dimethyl-L-tartrate costs £31.40 for 25 g; diethyl-L-tartrate costs £21.30 for 100 g. (Sigma-Aldrich, Oct. 2011)

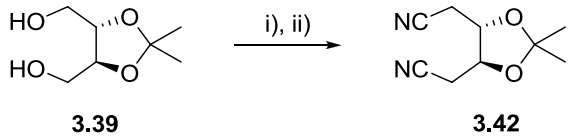
copper salts to the halide displacement reaction, successful in the formation of dinitrile **3.29**, had little effect.



i) TsCl, TEA, DCM, 93%; ii) NaI, acetone, Δ, 99%; iii) NaCN, DMF, 140 °C;
iii) NaCN, DMF, 160 °C; v) NaCN, DMSO, 80 °C; vi) NaCN, acetone, sealed tube, 80 °C;
vii) NaCN, MeCN, sealed tube, Δ; viii) CuCl, NaCN, MeCN, Δ

Scheme 149

In the end, the low susceptibility of this position to substitution meant that a much more reactive leaving group had to be used. Accordingly, the bistriflate was prepared using conditions used regularly within the Fleet group for similar displacements in carbohydrate substrates,[45] where substitution reactions are typically difficult due to the large number of oxygen atoms present in these compounds. Indeed, the triflate group could be displaced using NaCN in DMF, the reaction giving improved yields of **3.42** when initial addition of the cyanide nucleophile was conducted at 0 °C, presumably slowing decomposition of the relatively unstable starting material.



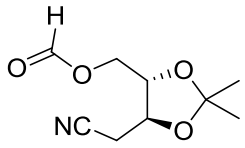
i) Tf_2O, DCM, pyridine, –40 °C; ii) NaCN, DMF, 0 °C → RT, 36% over two steps

Scheme 150

Although the crude material isolated from the triflate formation reaction was relatively clean (87%, determined by ^1H NMR spectroscopy), rapid decomposition was observed when this compound was

stored neat, and purification on silica led to poor mass recovery. In fact, this two-step process was improved by immediate dissolution in DMF of the residue obtained from evaporation of the extraction solvents and conducting the second step immediately. On a large scale, some decomposition was observed during evaporation of the DCM extracts at the end of the triflation step, and this was avoided by addition of DMF before removal of the DCM, thus providing the starting material for the displacement step already in the reaction solvent.

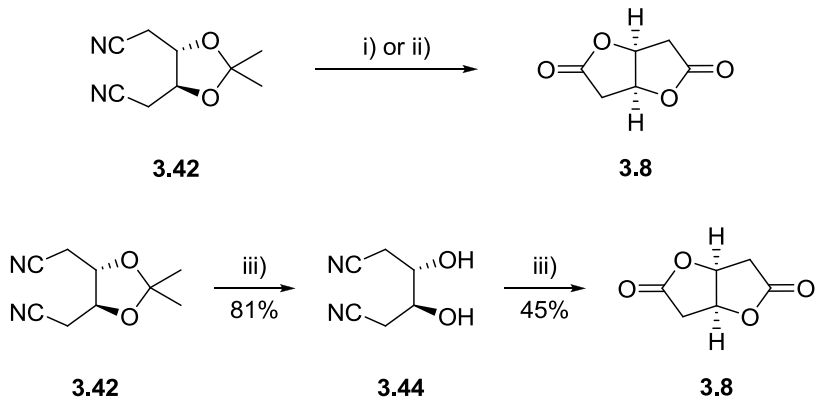
The low yields obtained for this capricious process could not be improved upon, and decomposition of the unstable bistriflate seemed unavoidable. As well as this, undesired formate side-product **3.43** was produced in varying quantities; the yield of this species increased as the scale of the reaction increased.



3.43

Figure 42

With enantiomerically pure dinitrile **3.42** in hand, the cyclisation could be tested. Using the same conditions as for dinitrile diol **3.34**, hydrochloric acid in THF, a moderate yield of dilactone **3.8** was obtained (**Scheme 151**), again accompanied by butenolide **3.36**. Dilactone **3.8** was also obtained, albeit in lower yield, with dioxane as the solvent,[46] and in methanol, no cyclisation occurred at all, with only acetonide removal occurring to furnish **3.44** in 81% yield. Resubmission of this diol to the reaction conditions provided dilactone **3.8**, again contaminated with butenolide **3.36**.



i) 6 M HCl, THF Δ, 16 h, 58%; ii) 25% aq. HCl, dioxane, 50 °C → Δ, 2 h, 25%; iii) 6 M HCl, methanol, Δ, 16 h

Scheme 151

Reducing the reaction temperature of the cyclisation reaction in methanol, in an attempt to avoid elimination proved unsuccessful. At room temperature, the starting material disappeared slowly but was not converted to the dilactone product, instead providing an unidentifiable mixture of products. At 40 °C, despite rapid acetonide deprotection, no cyclisation was observed.

This route was two steps longer than the original plan, but the ready availability and low cost of the starting material relative to that of *trans*-β-hydromuconic acid,[vi] makes this a competitive route, even considering the low yields. The availability of both enantiomers of tartaric acid allows access to both enantiomers of the dilactone core.

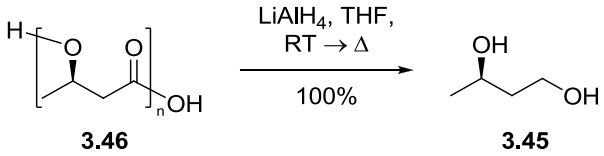
[vi] *trans*-β-Hydromuconic acid costs £88.00 for 10 g; L-tartaric acid costs £12.20 for 100 g. (Sigma-Aldrich, Oct. 2011)

3.2.2 Synthesis of side chain for cephalosporolides

The side-chain of cephalosporolides E and F was envisaged to arise from conversion of the terminal hydroxyl of (*R*)-1,3-butanediol (**3.45**, **Scheme 152**) to an appropriate halide from which an organometallic nucleophile could be obtained.

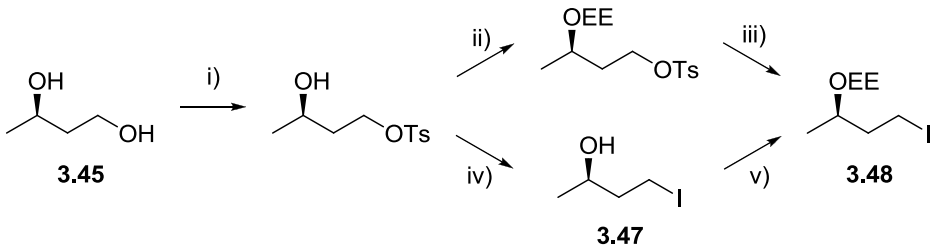
Scheme 152

(*R*)-1,3-Butanediol is commercially available but relatively expensive and instead was prepared from cheap polymer PHB (**3.46**, **Scheme 153**).[47]



Scheme 153

Monotosylation of this diol was achieved in reasonable yield (**Scheme 154**),[48] with only a small amount (4%) of the bistosylate being isolated. The monotosylate could be either be protected and then converted to the iodide, or converted immediately to the terminal iodide **3.47** with subsequent protection to give the required side-chain component (**3.48**), the latter process being slightly more effiecient. The ethoxyethyl (EE) protecting group was chosen on the basis that it would be removable under relatively mild acidic conditions, yet stable under the basic conditions planned for the organometallic addition into the dilactone core.



i) TsCl, py, – 25 °C, 69%; ii) PPTS, EVE, DCM, 0 °C, 100%; iii) NaI, acetone, dark, 67%; iv) NaI, acetone, dark, 100%; v) PPTS, EVE, DCM, 0 °C, 77%

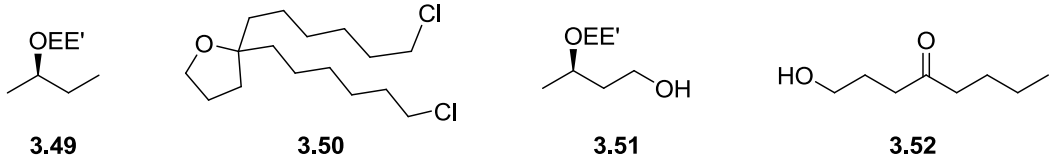
Scheme 154

3.2.3 Alkylation attempts

With the required components in hand, work began on attempts to couple the two fragments, initially following Negishi's procedure for lithiation of primary alkyl iodides,[49] using γ-butyrolactone as a test electrophile (**Table 3**). With protected alcohol **3.48** no product was obtained, alkane **3.49** (**Figure 43**) being the only isolable product (entries 1 and 2). Addition of 1-iodoheptane was also unsuccessful, in this case heptanol was obtained in near quantitative yield (entry 3). Addition of LiCl to the reaction mixture, reported to help break up aggregated lithium species in this type of reaction,[50] did not result in addition to the lactone, and, again, heptanol was the major product obtained from the reaction (entry 4). Addition of TMSCl again gave no product and did not stop formation of the heptanol side-product but did return some unreacted lactone starting material (entry 5). Some success was obtained using 6-chloro-1-iodohexane, although only double addition product **3.50** was observed (entry 6). Mono-addition product (**Figure 43**) was observed when using *n*-BuLi as the nucleophile (entry 8), following a procedure published by Umani-Ronchi and Savoia[51] to form hydroxyketones from lactones, furnishing hydroxyketone **3.52** in good yield, in a 9:2 ratio of open chain/cyclised isomers (determined by ^{1}H NMR spectroscopy). Addition was not observed using Knochel and Fleming's procedure for alkoxide directed iodine-magnesium exchange at sp^{3} centres, forming cyclic Grignard reagents from 1,3- and 1,4- displaced hydroxyiodides (entry 9).[52]

	Iodide	Conditions	Solvent	T /(°C)	Result
1	**3.48**	2.1 eq. *t*-BuLi	ether	−78 → RT → −78	trace **3.49**
2	**3.48**	2.1 eq. *t*-BuLi	ether	−78	trace **3.49**
3	1-iodoheptane	2.1 eq. *t*-BuLi	ether	−78 → RT	98% heptanol
4	1-iodoheptane	2.1 eq. *t*-BuLi, LiCl	ether	−78 → RT	95% heptanol
5	1-iodoheptane	2.1 eq. *t*-BuLi, TMSCl	ether	−78 → RT	rec. SM
6	6-chloro-1-iodohexane	2.1 eq. *t*-BuLi	ether	−78	25% **3.50**
7	**3.48**	2.1 eq. *t*-BuLi	ether	−78	alcohol **3.51**
8	-	1 eq. *n*-BuLi	ether	−90 → −10	79% **3.52**
9	**3.47**	1.1 eq. *i*-PrMgCl then 2.1 eq. *n*-BuLi	ether	−78	No isolable products

Table 3



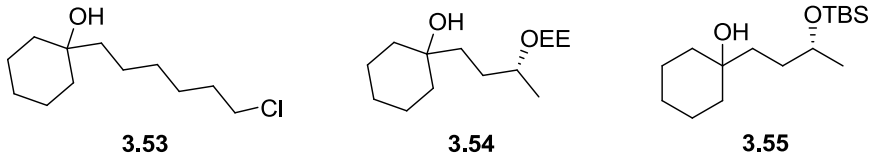
3.49 **3.50** **3.51** **3.52**

Figure 43

Since addition to γ-butyrolactone was proving difficult, addition into cyclohexanone was instead attempted (**Table 4**). This was much more successful, with addition of the organolithium reagents giving the corresponding tertiary alcohol products **3.53**−**3.55** (**Figure** 44) reliably, in moderate yield (entries 1−3). However, small amounts of the corresponding alcohols were obtained in this process, analogously to previous reactions. Application of Knochel and Fleming's procedure[52] was still unsuccessful on this electrophile (entries 4 and 5).

	Iodide	Conditions	Solvent	T /(°C)	Result
1	6-chloro-1-iodohexane	2.1 eq. *t*-BuLi	ether	−78	65% **3.53**
2	**3.48**	2.1 eq. *t*-BuLi	ether	−78	89% **3.54**
3	**3.59**	2.1 eq. *t*-BuLi	ether	−78	79% **3.55**
4	**3.47**	1.1 eq. *i*-PrMgCl then 2.1 eq. *n*-BuLi	ether	−78	No isolable products
5	**3.47**	3.1 eq. *t*-BuLi	ether	−78	No isolable products

Table 4



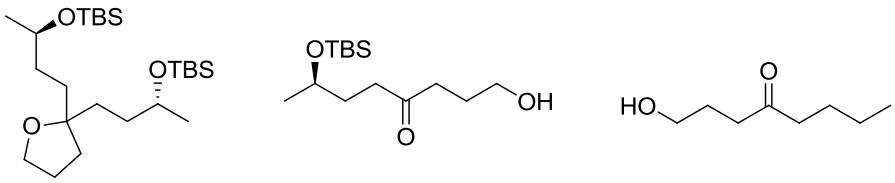
3.53 **3.54** **3.55**

Figure 44

Having proved that a reactive organolithium reagent could be formed from the side-chain iodide, efforts were again made to conduct addition to γ-butyrolactone (**Table 5**). Under Negishi's conditions only traces of the double addition product **3.56** (**Figure 45**) were seen, with no evidence of mono-addition. At cooler temperatures, using *n*-BuLi to form the organometallic, the desired product **3.57** was obtained, but was accompanied by addition of *n*-BuLi itself.

	Iodide	Conditions	Solvent	T /(°C)	Result
1	**3.59**	2.1 eq. *t*-BuLi	ether	−78	trace **3.56**
2	**3.59**	1 eq. *n*-BuLi	ether	−90	46% **3.57** and 24% **3.52**

Table 5



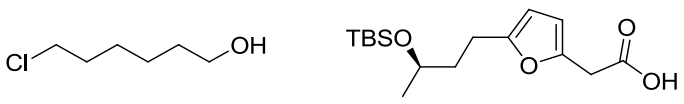
3.56 **3.57** **3.52**

Figure 45

Brief attempts were made to add into the real dilactone system **3.8** (**Table 6**). The poor results obtained from these reactions were attributed to the extremely low solubility of dilactone, but despite screening alternative solvents and additives none of the desired product or recovered starting material was obtained, the only isolable product being small quantities of alcohol **3.58** (**Figure 46**, entries 1−3). Addition of *n*-BuLi was also unproductive (entries 4 and 5). At cooler temperatures, addition of iodide **3.59** to the dilactone was observed, but was unfortunately accompanied by rearrangement of the product to furan product **3.60** (**Figure 46**, entries 6 and 7).

	Iodide	Conditions	Solvent	T /(°C)	Result
1	6-chloro-1-iodohexane	2.1 eq. *t*-BuLi	ether	−78	**3.58**
2	6-chloro-1-iodohexane	2.1 eq. *t*-BuLi, HMPA	ether	−78	**3.58**
3	6-chloro-1-iodohexane	2.1 eq. *t*-BuLi, THF	ether	−78	**3.58**
4	-	1 eq. *n*-BuLi	ether	−78	**3.58**
5	-	1 eq. *n*-BuLi	THF	−78	**3.58**
6	**3.59**	2.1 eq. *t*-BuLi	ether	−78 → −90	furan **3.60**
7	**3.59**	2.1 eq. *t*-BuLi	DME	−78 → −90	furan **3.60**

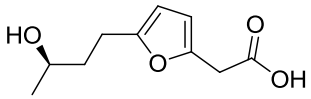
Table 6



3.58 **3.60**

Figure 46

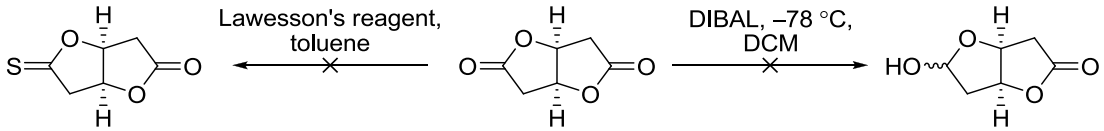
This furan product is a protected version of known metabolite **3.61** (**Figure 47**), isolated from *Beauveria bassiana* along with (+)-bassianolone (**Scheme 123**) and the cephalosporolides E and F,[16] and from *Cordyceps militaris* BCC 2816, also along with the cephalosporolides E and F.[53]



3.61

Figure 47

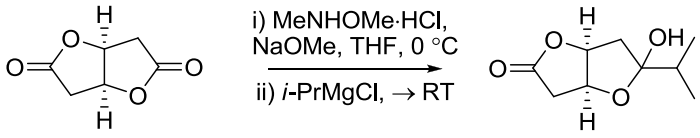
In order to achieve some differentiation between the two carbonyl functionalities, and increase the reactivity of one relative to the other, mono-reduction to the lactol **3.62** was attempted using DIBAL (**Scheme 155**). Unfortunately, this was unsuccessful, as was the use of Lawesson's reagent to form thioester **3.63**.



3.63 (±)-**3.8** **3.62**

Scheme 155

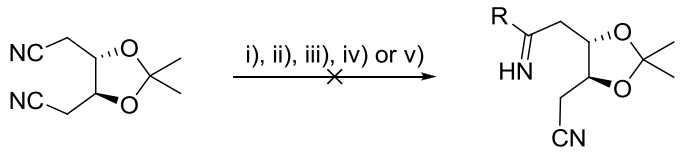
Formation of the Weinreb amide of dilactone **3.8** (**Scheme 156**), followed by Grignard addition was also attempted, using a procedure reported by Xu *et al*. for addition to similar lactone substrates.[54] This reaction was sadly unsuccessful, leading to decomposition of the dilactone starting material.



(±)-**3.8**

Scheme 156

Instead, an alternative strategy, adding organometallics to dinitrile **3.42** before cyclisation, was attempted (**Scheme 157**). Reactions conducted in ether[55] suffered due to precipitation of the reagents and thus mainly returned unreacted starting material. Although using THF as the reaction solvent solved this problem, the reactions were still unsuccessful, leading instead to the formation of decomposition products. Addition of the organocerium reagent generated from transmetallation with methyllithium,[56] hoping that this would be more nucleophilic, also failed.



3.42 R = Et, *i*-Pr or Me

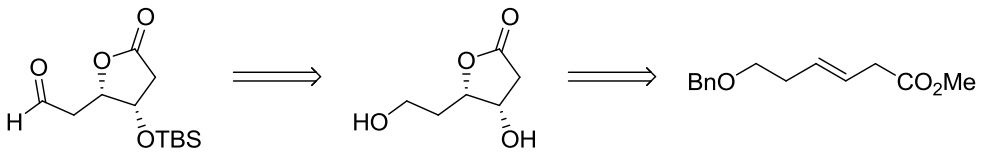
i) *i*-PrMgCl, Et_2O, PhH, 0 °C → RT; ii) EtMgBr, Et_2O, RT → 35 °C T; iii) *i*-PrMgCl, THF, 0 °C → RT; iv) EtMgBr, THF, 0 °C → RT; v) $CeCl_3$, MeI, THF, 40 °C → 160 °C

Scheme 157

Since addition into the dilactone or related systems was proving difficult, an alternative strategy was investigated.

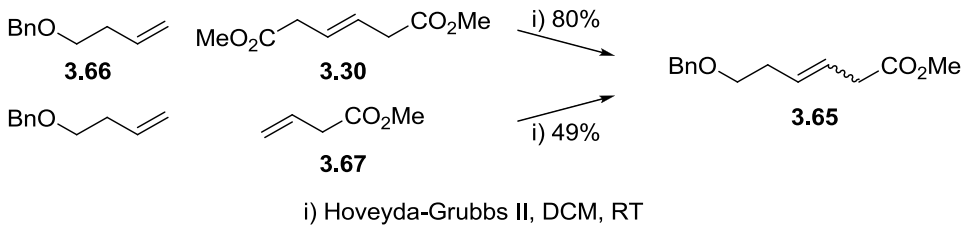
3.2.4 Second generation synthesis of the unsubstituted lactone core

It was envisaged that formation of aldehyde **3.64** (**Scheme 158**) would allow easier differentiation between the two reactive sites and more successful installation of the side-chain component. Following work conducted as part of Brimble's first generation synthesis of the cephalosporolides (**Scheme 126**),[19] along with Paterson's previously published synthesis of this motif,[57] lactone **3.64** was to be obtained by SAD of alkene **3.65** followed by deprotection and oxidation of the primary alcohol to reveal the aldehyde electrophile.



Scheme 158

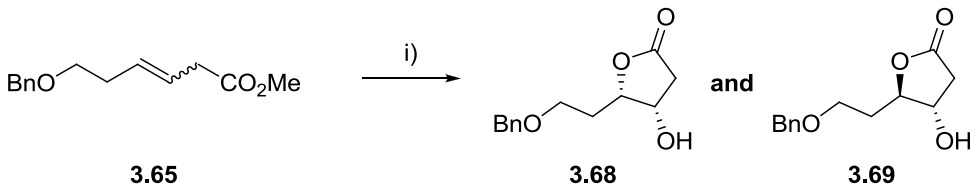
The sythesis began with cross metathesis of benzyl ether **3.66** and ester dimer **3.30** (**Scheme** 159). Although the original work[57] used the ester monomer **3.67** in large excess, it was found that the cross metathesis reaction worked in higher yield when the dimer was used (80% *vs* 49%). Furthermore, this monomer was more expensive and attempts to synthesis it from the slightly cheaper 3-butenoic acid were unsuccessful.[vii] Alkene **3.65** was thus obtained as an inseparable mixture of *E*-/*Z*- isomers in a 9:2 ratio, as determined by ^{1}H NMR spectroscopy.



Scheme 159

The SAD reaction was carried out on this material giving a mixture of the desired diastereomer of lactone **3.68** as well as undesired diastereomer **3.69** derived from the *Z*-alkene starting material (**Scheme 160**).

[vii] Methyl 3-butenoate costs £57.30 for 1 g; *trans*-β-hydromuconic acid costs £88.00 for 10 g; 3-butenoic acid costs £57.30 for 25 g. (Sigma-Aldrich, Oct. 2011)

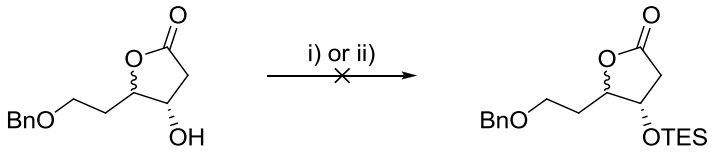


3.65 **3.68** **3.69**

i) AD-mix α, *t*-BuOH, H_2O, RT, 60 h, 91% combined yield

Scheme 160

In their synthesis of the cephalosporolides E and F, Brimble *et al.* note that undesired elimination of TBSOH was occurring with their lactone substrates during the addition reaction. It was envisaged that changing the protecting group from TBS to TES may reduce the rate of this elimination process, as the smaller protecting group would reduce bulk around the lactone ring, one of the potential driving forces for this type of process. Unfortunately, TES protection of the alcohol was unsuccessful (**Scheme 161**), even when adding large excesses of imidazole to promote the reaction.[58] In each case complete recovery of the starting material was observed.

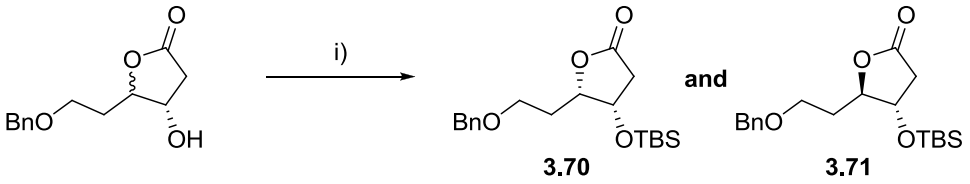


i) TESCl, imidazole (1.15 eq.), DMF; ii) TESCl, imidazole (5.15 eq.), DMF

Scheme 161

Although the two diastereomeric lactones were previously inseparable, following TBS- protection, the two lactones could be separated by careful flash chromatography. Silyl protection under standard conditions, using TBSCl,[19] was never able to give complete conversion to the protected product, however, using TBSOTf, the separable silyl ethers **3.70** and **3.71** could be obtained in good yield in just 10 minutes (**Scheme 162**). This reagent is known to be particularly effective at protecting hindered, secondary alcohols where TBSCl fails. This reaction was not successful under standard conditions, using 2,6-lutidine,[59] with these conditions giving very low conversion to the protected alcohol, along with traces of

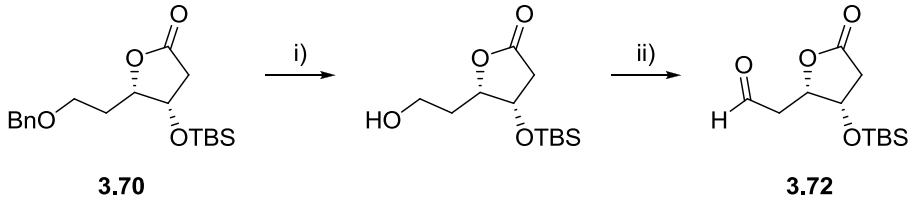
the butenolide elimination product. This competing dehydration process was noted by Chamberlin *et al*. in their synthesis of 9-(*S*)-dihydroerythronolide A seco acid[60] and was overcome by the use of di-*tert*-butylpyridine instead of 2,6-lutidine.



i) TBSOTf, di-*tert*-butylpyridine, DCM, 0 °C, 75% **3.70** and 13% **3.71**

Scheme 162

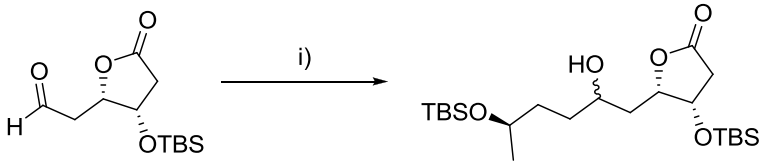
The orthogonal protection of the two alcohol functionalities allowed for selective removal of benzyl protecting group (**Scheme 163**). Oxidation of the revealed hydroxyl group gave aldehyde **3.72** in good yield *via* a robust synthetic sequence.



i) H_2, 10% Pd/C, EtOH, 88%; ii) DMP, DCM, 0 °C → RT, 98%

Scheme 163

With the desired electrophile in hand, addition into the aldehyde was investigated. Addition of the alkyllithium formed from **3.59** could indeed be achieved to give **3.73** (**Scheme 164**), although only in very poor yield which, due to time constraints, has not been optimised.

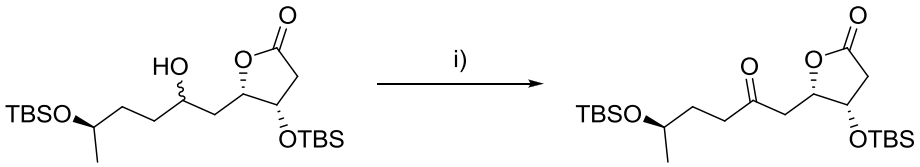


3.72 **3.73**

i) *t*-BuLi, **3.59**, ether, –78 °C → –90 °C, 10%

Scheme 164

Oxidation of this small amount of material to lactone **3.74** could be achieved under standard conditions (**Scheme 165**).

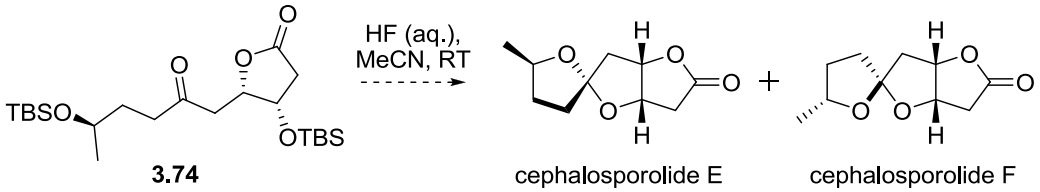


3.73 **3.74**

i) DMP, DCM, 0 °C → RT, 78%

Scheme 165

This lactone corresponds to the protected version of previously mentioned natural product (+)-bassianolone (**Scheme 123**). From here, all that remained in order to obtain the cephalosporolides E and F was global deprotection and cyclisation, theoretically achievable in just one step although the chosen conditions needed to avoid undesired elimination to give the α,β-unsaturated lactone. Hence, aqueous HF was used (**Scheme 166**).



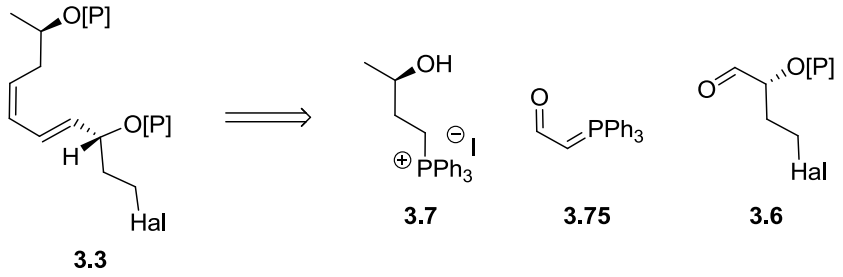
3.74 cephalosporolide E cephalosporolide F

Scheme 166

The desired product could be observed by TLC and mass spectrometry but, unfortunately, insufficient amounts of material were obtained for this result to be confirmed by ^{1}H NMR spectroscopy. Again, due to time constraints, this synthetic route could not be repeated in order to obtain more material, and in any case this would be better done after optimisation of the organometallic addition step.

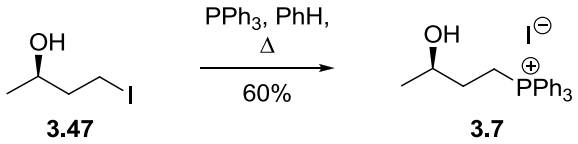
3.2.5 1st generation synthesis of the ascospiroketal side-chain

The first synthetic strategy for the ascospiroketal side-chain was a sequence based on sequential Wittig type olefinations. Thus, side-chain **3.3** could be broken down further into three components: chiral aldehyde **3.6**, butanol derived phosphonium salt **3.7**, and linker **3.75**.



Scheme 167

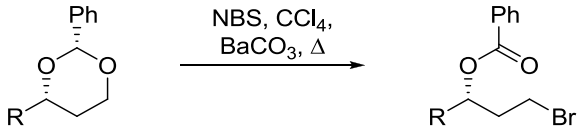
With linker **3.75**, (triphenylphosphoranylidene)acetaldehyde, commercially available, and the butan-3-ol derived phosphonium salt obtained in one step from previously synthesised iodoalcohol **3.47** (**Scheme 168**), synthetic efforts were turned towards the third component, chiral aldehyde fragment **3.6**.



Scheme 168

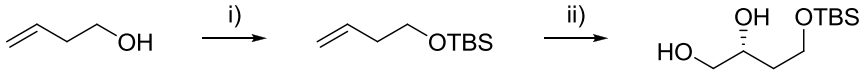
The need to install a terminal halide, potentially late on in the synthesis, as well as the need for protection of an alcohol situated 3 carbons away from this terminal position, led to the use of a benzylidene acetal

protecting group. Acting as a diol protecting group for the majority of the synthesis, this group would have the added advantage of selective cleavage using the Hanessian reaction[61] giving direct access to the terminal bromide whilst leaving the secondary alcohol protected as the benzoyl ester (**Scheme 169**).



Scheme 169

Triol **3.76** was initially synthesised using a SAD reaction of TBS protected butenol **3.77**.

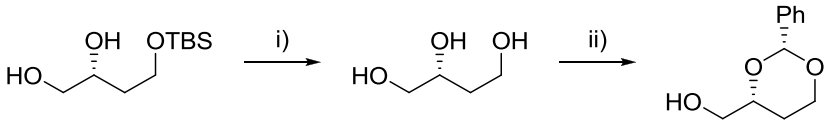


3.77 **3.76**

i) TBSCl, imidazole, DMF, 100%; ii) AD-mix β, *t*-BuOH, H_2O, 82%

Scheme 170

The TBS group could be cleaved[62] to give triol **3.78** which was taken on crude to the acetal protection step.



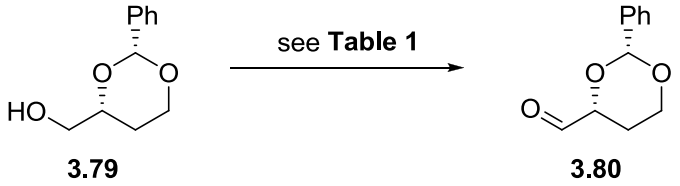
3.76 **3.78** **3.79**

i) 3:2, AcOH/H_2O, RT; ii) $PhCH(OMe)_2$, CSA, DCM then NEt_3, 86% over two steps

Scheme 171

Unfortunately, the observed optical rotations of both triol **3.78** and acetal **3.79** were lower than those previously reported for these compounds.[63, 64] Mosher's ester anaysis of diol **3.76** indicated a disappointing 62% *d.r.*, in agreement with the poor optical rotations observed for these compounds. Presumably this low enantiopurity arises from poor selectivity in the SAD reaction, something that has been previously reported for terminal alkenes,[65, 66] in particular those with relatively short chain lengths.[67]

With the protected alcohol in hand, work began into oxidation of this substrate to the aldehyde. Previous reports for this transformation[68-72] made use of the Swern oxidation conditions,[73, 74] and the varied range of conditions employed to effect this transformation implied that the reaction should be relatively robust. This was, however, not found to be the case and in our hands oxidation attempts mainly resulted in decomposition to an unidentified polymeric product (**Scheme 172**, **Table 7**). Having checked the condition of our reagents (test oxidation of octanol under standard conditions gave 92% conversion to octanal), we applied the same standard Swern conditions to our substrate, unfortunately with no success.



3.79 **3.80**

Scheme 172

DMSO (eq.)	$(COCl)_2$ (eq.)	Temperature (°C)	NEt_3 (eq.)	Result
4.8	2.2	−60 °C → −15 °C	5.0	SM + decomposition
2.2	1.1	−23 °C	5.0	SM
15	7.5	−23 °C	34	**3.80** + decomposition
2.2	1.1	−23 °C	5.0	SM + **3.80**

Table 7

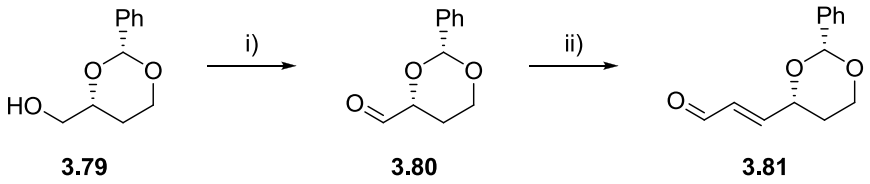
Other conditions screened for this oxidation were mostly unsuccessful (**Table 8**). Conditions that did lead to any aldehyde formation, however, resulted in similar decomposition, leading us to believe that the product was inherently unstable, rather than this decomposition being an artefact of a particular set of

reaction conditions. Any purification attempts led to loss of the material, and if crude aldehyde was left to stand, even in the freezer, it would decompose completely over a very short time.

Reagents	Temperature	Result
SO_3.pyridine, DMSO, NEt_3[75]	0 °C	Impure **3.80**
SO_3.pyridine, DMSO, NEt_3[76]	−10 °C → RT	SM
Solid supported SO_3.pyridine, DMSO, NEt_3	0 °C	SM
DMP, DCM	0 °C → RT	SM
DMP, pyridine, DCM[77]	RT	9:1 SM/**3.80**
PDC, DMF, 4 Å MS[77]	RT	SM
NCS, DMS, PhMe then NEt_3[78]	−25 °C → RT	SM + decomposition

Table 8

Some success was achieved by immediate Wittig reaction of the crude oxidation product,[79] leading to α,β-unsaturated aldehdyde **3.81** in a moderate two-step yield (40%) (**Scheme 173**).

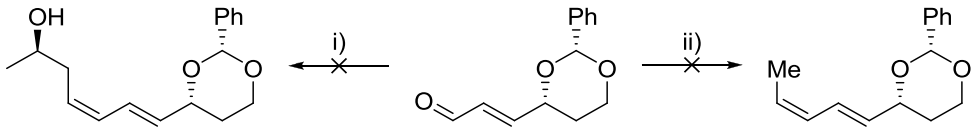


3.79 **3.80** **3.81**

i) SO_3.pyridine, DMSO, NEt_3, DCM; ii) PPh_3CHCHO, MeCN, Δ

Scheme 173

Having coupled two of the required components, all that remained was to conduct the Wittig reaction with previously synthesised phosphonium salt **3.7** (**Scheme 174**). Unfortunately, using conditions previously employed for the Wittig reaction of this same phosphonium salt,[80] the two components could not be coupled.



3.81

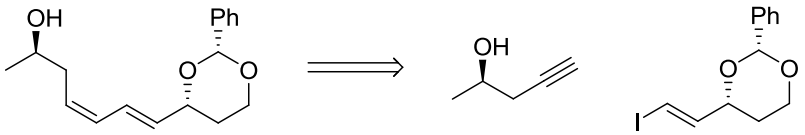
i) **3.7**, NaH, THF, RT then *n*-BuLi then aldehyde;
ii) $EtPPh_3Br$, *n*-BuLi, THF, RT then aldehyde, –78 °C

Scheme 174

A test reaction, coupling aldehyde **3.81** with a simpler Wittig reagent[81] was also unsuccessful (**Scheme 174**), and this, coupled with the observation that the only previous example of a Wittig reaction on this aldehyde substrate (**3.81**) proceeded selectively to afford the *E*- alkene, even with an unstabilised ylid,[82] led to the abandonment of this route and concentration of efforts into other synthetic strategies.

3.2.6 Second generation synthesis of the ascospiroketal side-chain

The second route undertaken to the side-chain was based around the Sonogashira coupling[83] of vinyl iodide **3.82** and alkyne **3.83** (**Scheme 175**). A subsequent Lindlar reduction[84] would hopefully give access the desired diene component, with the requisite alkene geometry.

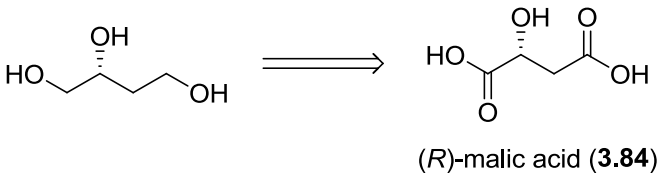


3.83 **3.82**

Scheme 175

Although there were a number of options available for the synthesis of vinyl iodide **3.82** the majority of these proceeded *via* aldeyde **3.80** and so further investigations were made into a more robust method to obtain this fragment. The poor *e.e.* of the product obtained from the SAD reaction of terminal alkene **3.77** also meant that we needed an alternative synthetic route to the triol precursor.

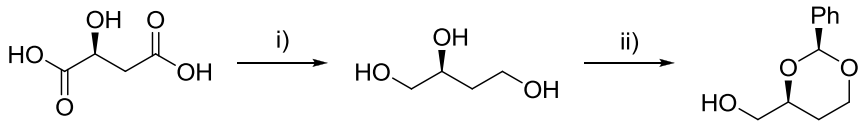
The majority of previous syntheses of the protected triol began with reduction of malic acid (**3.84**, **Scheme 176**), allowing an unambiguous synthesis of either enantiomer. This methodology was first tested on the significantly cheaper, naturally occurring (*S*)-enantiomer of malic acid,[viii] allowing investigations into the troublesome Swern oxidation to be conducted on a larger scale.



(*R*)-malic acid (**3.84**)

Scheme 176

Reduction of (*S*)-malic acid was conducted in quantitative yield (**Scheme 177**)[85] and protection of triol **3.85** was conducted as previously described to give alcohol **3.86** (**Scheme 177**). Oxidation of this substrate was found to be similarly difficult to the attempts on the SAD derived alcohol, putting aside worries that the problems experienced were simply related to an unwanted contaminant that would not have been present in the alcohol used in the previously published syntheses.



(*S*)-malic acid **3.85** **3.86**

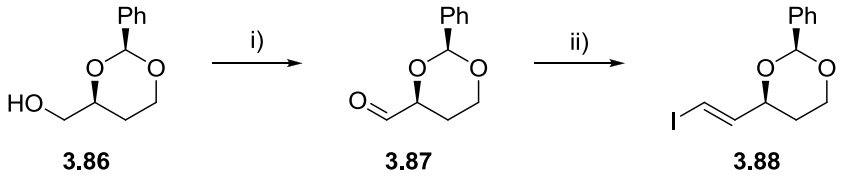
i) $BH_3.SMe_2$, $B(OMe)_3$, THF, 0 °C → RT; ii) $PhCH(OMe)_2$, CSA (cat.), DCM, 78% over two steps

Scheme 177

In the hope of slowing any undesired decomposition, oxidation was attempted using the lowest temperature conditions previously reported in the literature (**Scheme 178**). Gratifyingly, these conditions[68] gave good yields of aldehyde of sufficient purity to be used in the next step. These conditions were found

[viii] (*R*)-malic acid costs £43.10 for 5 g; (*S*)-malic acid costs £40.50 for 100 g. (Sigma-Aldrich, Oct. 2011)

to give consistently good yields and were robust enough to be conducted on synthetically useful amounts (800 mg, 4.1 mmol) with no observable drop in the yield or purity of the product.



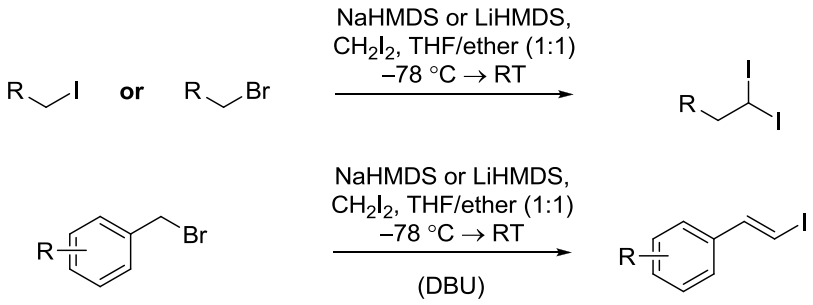
3.86 **3.87** **3.88**

i) DMSO, $(COCl)_2$, NEt_3, DCM, –60 °C; ii) CHI_3, $CrCl_2$, THF, dark, 30% over two steps

Scheme 178

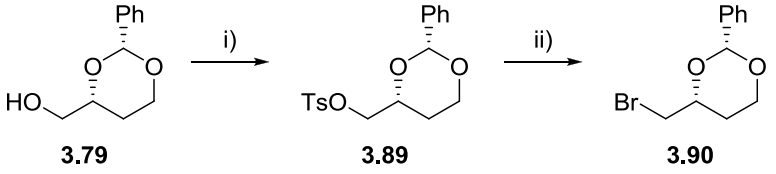
Having finally identified a reliable route to aldehyde **3.87**, formation of the vinyl iodide required for the cross coupling reaction was investigated. Pleasingly, using the aldehyde immediately in a Takai olefination[86] reaction furnished vinyl iodide **3.88** in a 3.6:1 ratio of separable *E*-/*Z*- isomers (as measured by ^{1}H NMR spectroscopy) (**Scheme 178**). This iodide was found to be stable to purification by flash chromatography and withstood storage in the freezer over relatively long time periods. Although the two-step yield for this conversion was low, this is comparable to literature yields for reactions proceeding *via* this unstable aldehyde component. However, parallel investigations were conducted into synthesising this vinyl iodide by other methods, hoping to obtain this component in higher yield by avoiding aldehyde **3.87**.

Charette *et al*. recently reported the synthesis of one carbon homologated *gem*-diiodoalkanes from alkyl bromides or iodides using lithiated diiodomethane (**Scheme 179**).[87] In the presence of excess base, elimination of HI across this newly formed bond was observed, leading to vinyl iodide products. The procedure was later extended for benzyl halides to give reliable conversion to the vinyl iodide products directly.[88]



Scheme 179

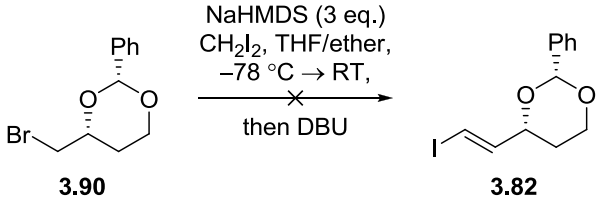
It was hoped that a combination of these conditions, using excess base in the reaction, would give access to vinyl iodide **3.82** from the corresponding alkyl halide. Hence, tosylate **3.89** was prepared from alcohol **3.79**[89] (**Scheme 180**) and displacement of the tosylate gave bromide **3.90**.[90]



i) TsCl, NEt_3, DCM, 99%; ii) LiBr, $NaHCO_3$, DMF, 90 °C, 70%

Scheme 180

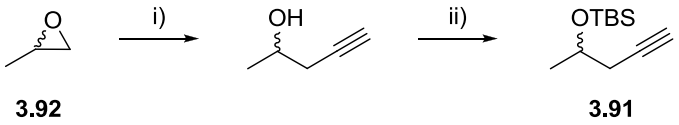
Unfortunately, application of Charette's conditions to this alkyl bromide was not successful in yielding either the vinyl iodide product or the homologated *gem*-diiodide (**Scheme 181**), and only starting material could be recovered. Time constraints prevented any further investigations into this alternative strategy.



Scheme 181

With one coupling partner in hand, attention was turned to the second. Alkyne **3.91** was synthesised from propylene oxide (**3.92**) by addition of lithium acetylide EDA complex[91] and subsequent protection[92]

(**Scheme 182**). Again, the relative cost of the enantiopure material compared to this racemic material led us to test this methodology on the racemic material first.

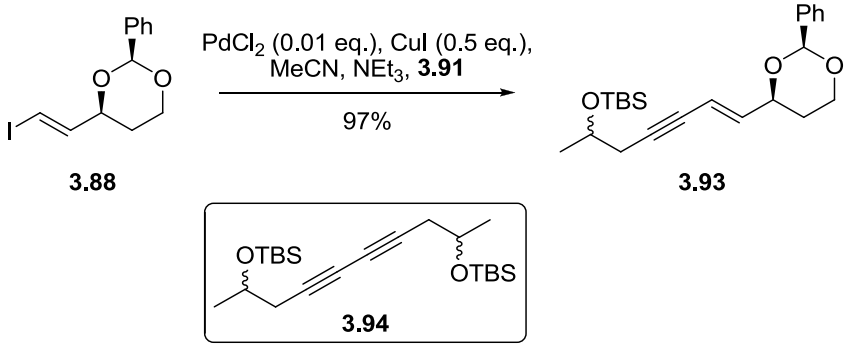


3.92 **3.91**

i) HCCLi.EDA, DMSO, 0 °C → RT; ii) TBSCl, imidazole, DCM, MeCN, 52% over two steps

Scheme 182

Gratifyingly, the Sonogashira coupling of these two components[93] worked well and enyne **3.93** was obtained in good yield (**Scheme 183**). Despite, due to the volatility of the alkyne component, being unable to extensively de-gas our reaction solutions, only a trace amount of the Glaser coupled[94] side-product (**3.94**) was observed.



3.88 **3.93** **3.94**

Scheme 183

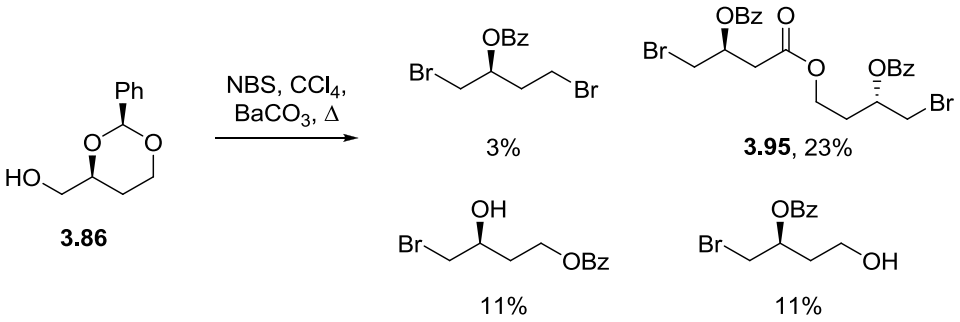
Owing to the success of this synthetic sequence, alkyne **3.94** and alcohol **3.79** (from (*R*)-malic acid) bearing the correct stereochemistry were synthesised, analogously to the test systems (**Figure 48**).

3.94 **3.79**

Figure 48

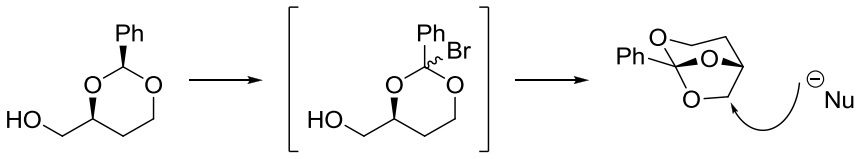
At this stage it was difficult to decide the best order for the next two steps to be conducted on the Sonogashira product **3.93** – Lindlar reduction of the enyne, or Hanessian reaction of the benzylidene acetal. Concerns over the susceptibility of the acetal protecting group to reduction under the hydrogenation conditions suggested conducting the Hanessian reaction first, but there were also concerns over the reactivity of the unsaturated bonds in the presence of NBS.

In order to minimise the potential for reaction of the enyne moiety, the time-scale of this deprotection reaction was tested using acetal protected triol **3.86**, providing some interesting results (**Scheme 184**).



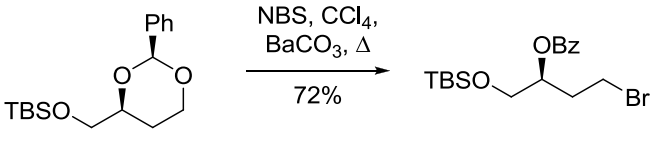
Scheme 184

Although the desired reaction had taken place, the presence of the free hydroxyl had altered the reaction path, possibly due to formation of a 5,6-fused cage structure, preferentially opened at the terminal position of the 5 membered ring (**Scheme 185**). Oxidation product **3.95** was also isolated as the major product.



Scheme 185

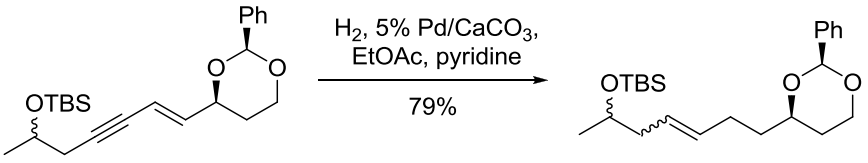
Although interesting, this reaction was not useful for identification of the reaction timescale. Hence, the same reaction was conducted on silyl protected derivative **3.96**, and in this case the Hanessian reaction proceeded smoothly to give bromide **3.97** in four hours (**Scheme 186**).



3.96 **3.97**

Scheme 186

Investigations into the Lindlar reduction[93] showed that the reaction was very catalyst dependent. Long reaction times with certain bottles of catalyst gave complete recovery of the starting enyne, whereas 45 min exposure to one particular bottle resulted in good yield of over-reduced product **3.98**. Unfortunately, the double bond geometry could not be identified using ^{1}H NMR spectroscopy. Shorter reaction times gave a mixture of singly and doubly reduced products, as well as returned starting material.



3.93 **3.98**

Scheme 187

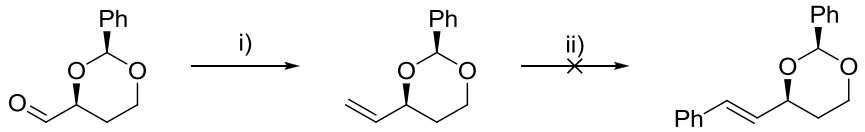
Conducting the reaction in the presence of large quantities of allyl alcohol, simply using 5% Pd/C as the catalyst gave no reduction after 15 mins, and after 1 h overreduction was again observed. Time constraints restricted any further investigation into this reduction.

As an alternative, a Heck reaction[95, 96] of alkene **3.99** with vinyl iodide **3.100** (**Figure 49**) was considered, since this would give the correct alkene geometry without requiring further manipulation.

3.99 **3.100**

Figure 49

Accordingly, alkene **3.100** was obtained by Wittig reaction[97] of aldehyde **3.87**. A test reaction using phenyl iodide as the coupling partner was run, using conditions employed by Kirschning for the Heck reaction of a similarly protected allylic alcohol. These conditions used Jeffery's modifications[98] of the original Heck reaction to allow successful coupling of allylic alcohol substrates whilst avoiding undesired side-reactions observed under standard Heck conditions. However, in our hands this coupling reaction was unsuccessful, with no reaction of alkene **3.100** being observed.

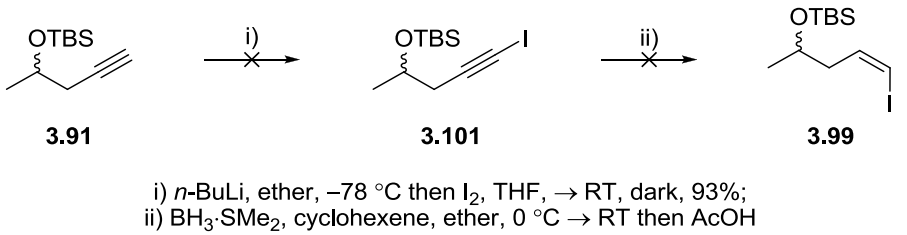


3.87 **3.100**

i) $MePPh_3Br$, *n*-BuLi, THF, 0 °C → RT, 91%; ii) PhI, Cs_2CO_3, Bu_4NBr, $Pd(OAc)_2$, NEt_3, DMF, RT → 45 °C

Scheme 188

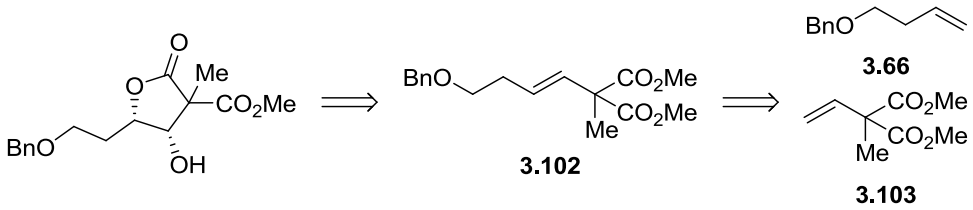
Iodide **3.101** was synthesised[99] in good yield from alkyne **3.91** (**Scheme 189**), but could not be converted to vinyl iodide **3.99** following a procedure used for hydroboration of a similar substrate by Pearson in his work towards the homoerythrina alkaloids,[100] the reaction leading to low mass recovery of decomposition products. Although other options were available for this transformation, for example diimide reduction,[101] time constraints again meant that no further investigation was possible.



Scheme 189

3.2.7 Synthesis of the substituted lactone core

It was envisaged that the two isomeric lactone cores of the ascospiroketals could be obtained from the cyclisation of diester alkene precursor **3.102** (**Scheme 190**), using a similar SAD reaction and *in-situ* cyclisation to that used to construct the core of the cephalosporolides. This alkene would come from the cross metathesis of components **3.66** and **3.103**.

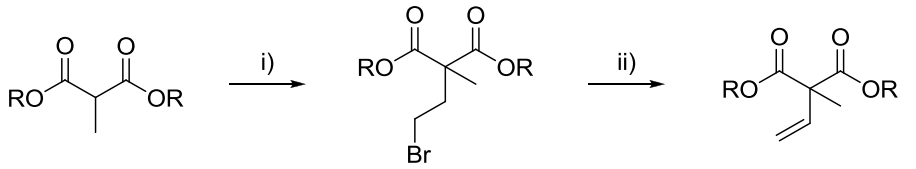


Scheme 190

Asymmetric dihydroxylation of this alkene would theoretically give two epimeric products, hopefully separable by chromatography. These could then be modified to give the desired lactone cores, and the side-chain manipulated analogously to the unsubtituted case to give the aldehyde electrophile required for coupling.

To this end, alkene **3.103** was synthesised in two steps from commercially available malonate **3.104** (**Scheme 191**). This work was based on that of Bunce and Burns who used this strategy to alkylate mixed malonate substrates, eliminating HBr to give vinylated products.[102] This procedure could be conducted on

either the dimethyl- or diethyl- methylmalonates (**3.104** or **3.105**), with the initial alkylation reaction being lower yielding for the ethyl ester. This result echoes observations in the original paper where bulkier substrates slowed the rate of this substitution reaction.



3.105 R = Et
3.104 R = Me

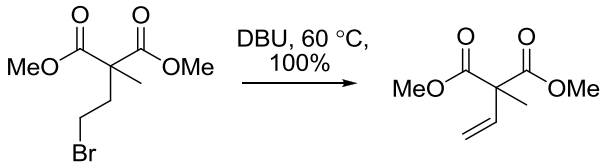
3.106 R = Et 43%
3.107 R = Me 89%

3.108 R = Et 33%
3.103 R = Me 15%

i) NaH, DMF, $BrCH_2CH_2Br$; ii) DBU, 75 °C

Scheme 191

The yield of this elimination process was somewhat lower than expected, and the lack of any other products or apparent decomposition indicated that this may be simply due to loss of material in the work up. This was eventually put down to the unexpected volatility of these vinyl malonates, in particular dimethyl malonate **3.103**. Significantly improved yields were obtained by slightly decreasing the reaction temperature and extracting with ether rather than ethyl acetate (**Scheme 192**).

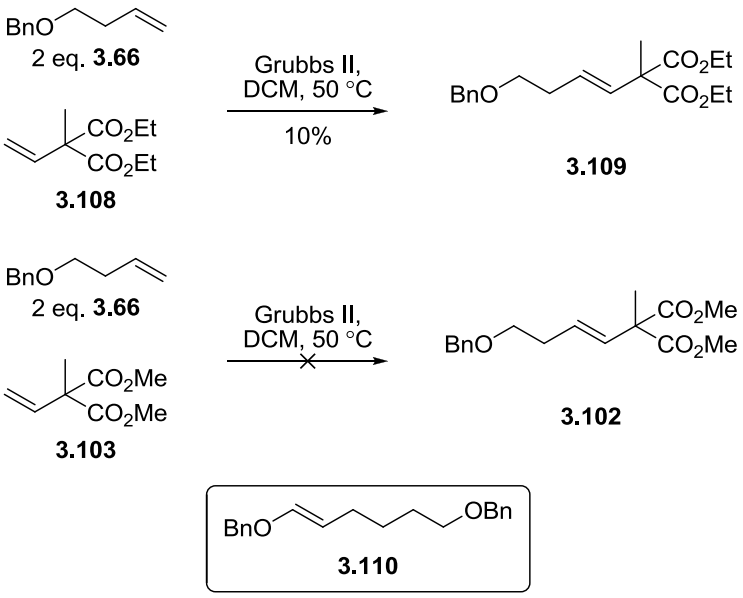


3.107 **3.103**

Scheme 192

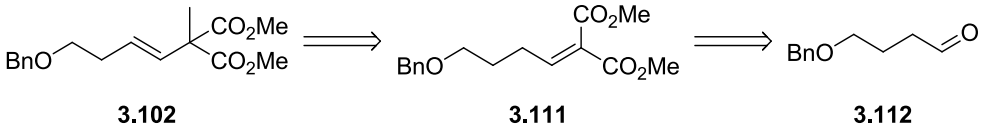
Having obtained this alkene, the intended cross metathesis was tested, using the same coupling partner (**3.66**) as for the unsubstituted system. Grubbs' II catalyst at 50 °C in DCM, using diethyl malonate **3.108**, gave a small amount (10%) of product **3.109** after 2 h at reflux. Changing to Hoveyda-Grubbs II gave no product, only returning the diester component along with benzylated enol ether **3.110**, derived from dimerisation and isomerisation of the benzyl ether starting material. Repeating the initial reaction, using

Grubbs II, with the dimethyl ester component gave none of the desired product, the major product again being enol ether **3.110** along with unreacted starting material. Conducting the reaction in toluene, allowing a much higher reaction temperature, still gave no isolated product, simply giving near quantitative conversion of benzyl ether **3.66** to dimerisation-isomerisation product **3.110**.



Scheme 193

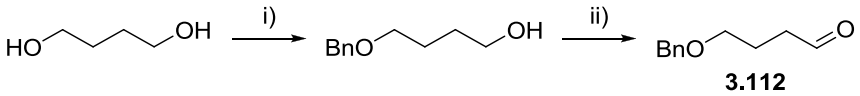
Although there was potential for improvement of this cross metathesis step, for example using relay metathesis[103-105] to overcome the slow reaction rate presumably arising from the sterically hindered nature of this diester metathesis partner, in the interests of time an alternative synthesis of alkene **3.102** was devised. This route was based around the deconjugative alkylation of alkylidene malonate **3.111** (**Scheme 194**), with **3.111** being obtained from the Knoevenagel condensation of aldehyde **3.112** with dimethyl malonate.



3.102 **3.111** **3.112**

Scheme 194

The sequence began with monoprotection of 1,4-butanediol using benzyl bromide and TBAI (**Scheme 195**)[106] and oxidation under Swern conditions gave aldehyde **3.112**.

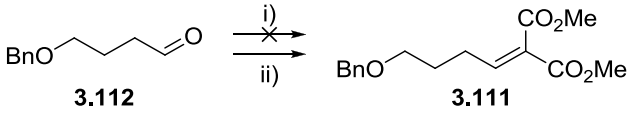


3.112

i) 2.1 eq. NaH, THF, 0 °C then 1.1 eq. BnBr, TBAI, RT, 54%;
ii) DMSO, $(COCl)_2$, DCM, –78 °C then NEt_3, 76%

Scheme 195

Knoevenagel condensation under classical conditions, using piperidine and acetic acid in benzene (**Scheme 196**),[107] gave very little of the desired product and returned mainly unreacted starting material. However, the use of catalytic proline in DMSO[108] furnished diester **3.111**.

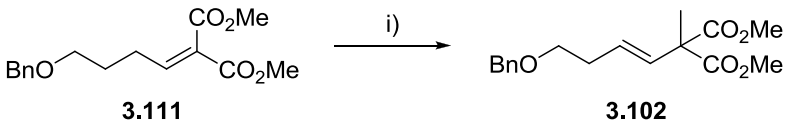


3.112 **3.111**

i) dimethylmalonate, piperidine, AcOH, PhH, Δ;
ii) dimethyl malonate, L-proline, DMSO, RT, 66%

Scheme 196

The deconjugative alkylation could be conducted in moderate yield using LDA and methyl iodide, with DMPU to aid solubility (**Scheme 197**).[109]

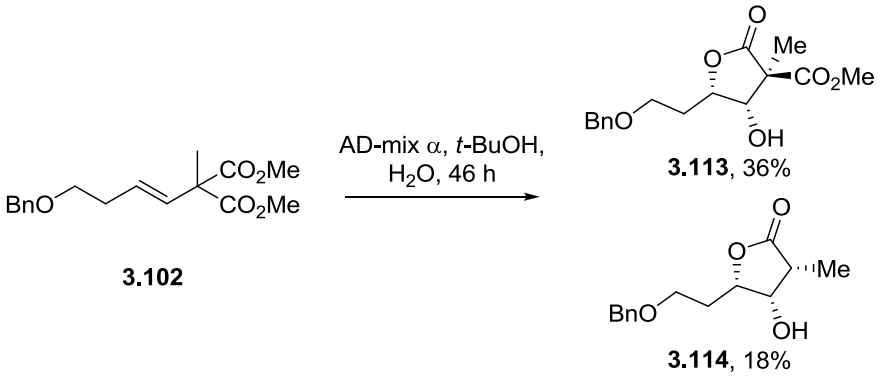


3.111 **3.102**

i) LDA, THF, DMPU, –78 °C then MeI, → RT, 58%

Scheme 197

With material in hand, investigations into the SAD reaction were initiated. Subjection of alkene **3.102** to the asymmetric dihydroxylation conditions gave some conversion to the desired lactone product **3.113** (**Scheme 198**), albeit very slowly. However, this was also accompanied by formation of decarboxylated product **3.114**, potentially formed in response to the steric crowding around the lactone ring.



3.102

3.113, 36%

3.114, 18%

Scheme 198

It appeared that both products had been formed as single diastereomers, and NOE experiments were conducted in order to confirm this, also hoping to identify which stereoisomers had been synthesised. NOE studies on **3.114** were relatively clear, allowing conclusive assignment of the C(3) stereochemistry based on strong correlations between the C(5), C(4) and C(3) protons (**Figure 50**). Although a weak correlation between C(4)H and the methyl group was observed, explainable by short internuclear distances even when these groups are *trans*- disposed, no correlation was observed between the C(5) proton and the methyl group as would be expected were these two groups in a *syn*- relationship.

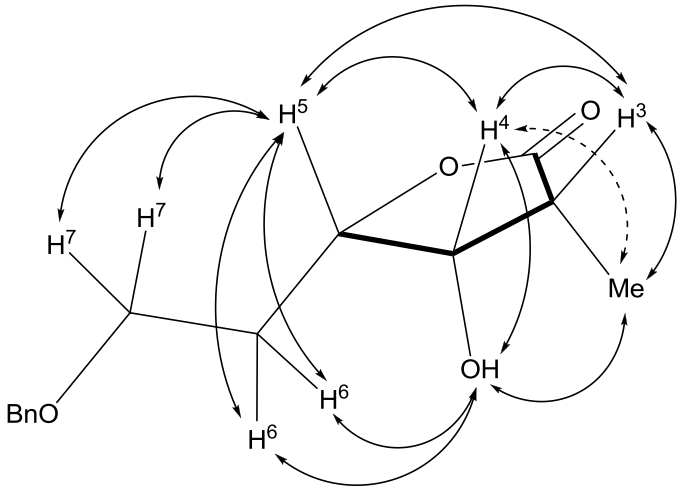


Figure 50

Assigning the stereochemistry of the quaternary C(3) centre in lactone **3.113** was more difficult, but this was determined to be (*R*)- based on the heteronuclear coupling constant between H(4) and the ester carbonyl (^3J = 3.4 Hz) implying that these groups were *cis*- disposed to one another, along with the absence of an HMBC cross-peak between H(4) and the methyl group, implying these groups were *trans*- to one another. This conclusion was corroborated by a weak NOE correlation between C(5) proton and the ester methyl group, with no correlation at all observed between the C(5) proton and the methyl group (**Figure 51**). The weak nature of this C(5)H to ester correlation can be explained by distances of greater than 4 Å being measured in the lowest energy conformations of this molecule, as calculated by molecular modelling studies (using Schrodinger Maestro). These modelling experiments could also be used to explain the strong correlation observed between the C(4) proton and the methyl group; despite their location on opposite faces of the lactone ring, the distance between these two atoms is approximately 3 Å in all of the low energy conformations measured.

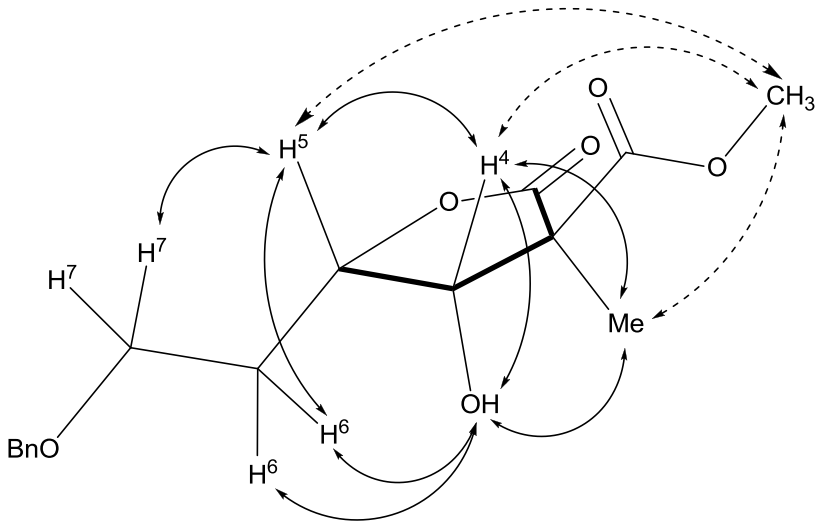
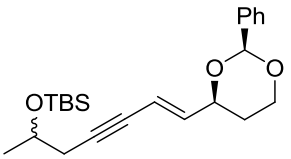


Figure 51

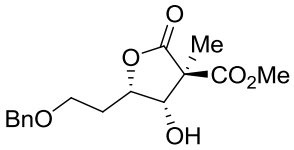
The formation of this undesired side-product in similar yield to our desired product unfortunately made the use of the SAD reaction to form this lactone potentially problematic. Although these reaction conditions may be able to be modified such that this side-reaction is avoided and the lactone can be formed in a synthetically useful yield, time constraints have currently prevented such investigations.

3.3 Conclusions and further work

Investigations into the total synthesis of the ascospiroketals A and B have led to the production of advanced intermediates **3.93** and **3.113** (**Figure 52**), a few steps away from the natural products.



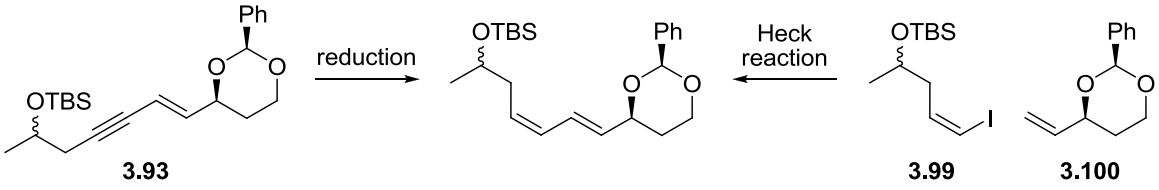
3.93



3.113

Figure 52

In order to complete this total synthesis, further work needs to be conducted on the reduction of diene side-chain component **3.93** (**Scheme 199**), either by continuing with the Lindlar reduction strategy and finding conditions that avoid over-reduction of the enyne moiety, or by investigating alternative methods used for similar enyne reductions such as hydroboration[110] or Zn-mediated reduction.[111-113] If this strategy proves unsuccessful, it may be necessary to find an alternative to the Sonogashira coupling that avoids the need to conduct this reduction step, for example by revisiting the Heck reaction of fragments **3.99** and **3.100**.

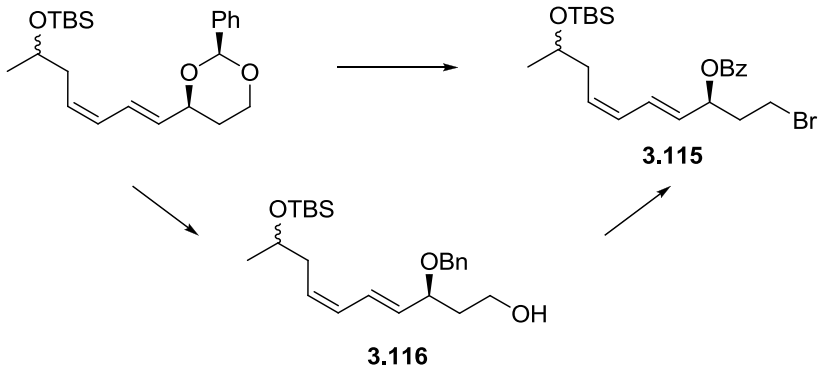


3.93 **3.99** **3.100**

Scheme 199

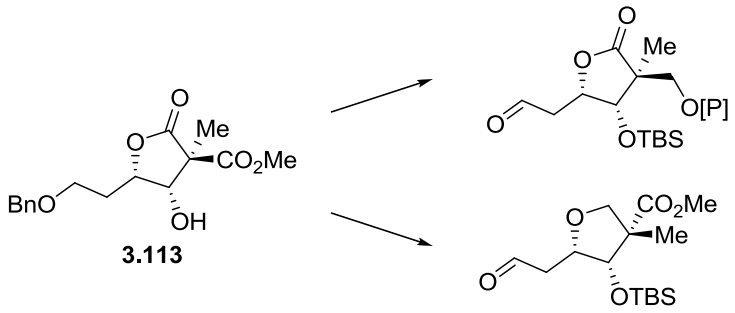
It will also be necessary to successfully convert the benzylidene acetal to terminal bromide **3.115** (**Scheme 200**), either by continuing work on the Hannesian reaction, perhaps looking at alternative conditions to conduct the same transformation,[114, 115] or by reduction to the mono-protected diol **3.116**,[116-119] in which the unprotected primary alcohol could be converted to a halide in a separate step. After identification of a

successful route to side-chain fragment **3.115**, this work must then be completed on the correct isomers, using intermediates **3.94** and **3.79** (**Figure 48**) already synthesised.



Scheme 200

Further work is also needed to transform lactone **3.113** to the aldehyde electrophiles required for coupling with the side-chain component (**Scheme 201**). Along with completion of these two fragments, work must also be conducted to improve the coupling reaction between the lactone aldehyde and side-chain iodide fragments.



Scheme 201

Once completed, this methodology could be used to synthesise a number of other spiroketal natural products with similar core motifs, for example the penisporolides A and B (**Figure** 53), isolated from *Penicillium* sp. in 2007.[120]

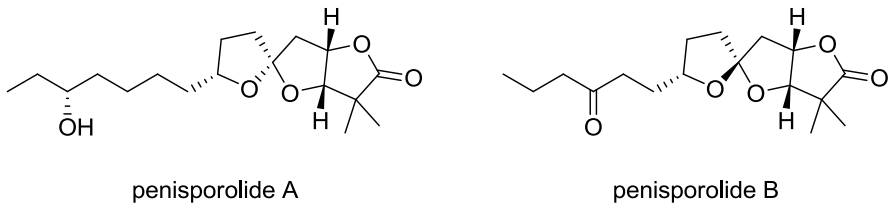


Figure 53

These spiroketal natural products could come from similar disconnections to the ascospiroketals and cephalosporolides, requiring alkene ester **3.117** (**Figure 54**), the ethyl ester of which has been previously synthesised *via* a similar deconjugative alkylation strategy to that used in this project,[121] and either diol **3.118** or γ-hydroxyketone **3.119**. This latter component could be envisaged to arise from addition of a suitable organometallic into known lactone **3.120**,[122-125] perhaps *via* the corresponding Weinreb amide.[126]

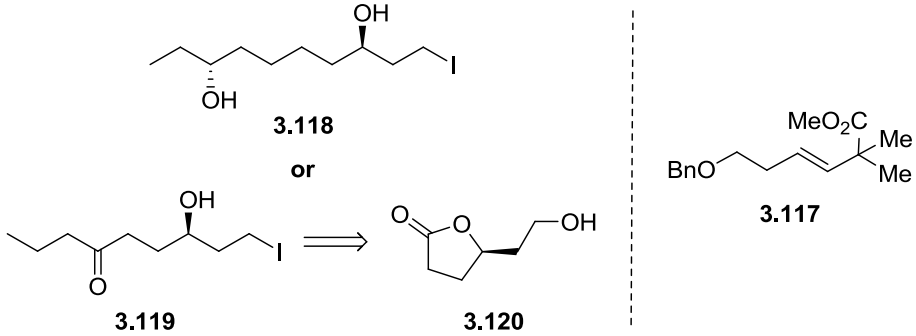
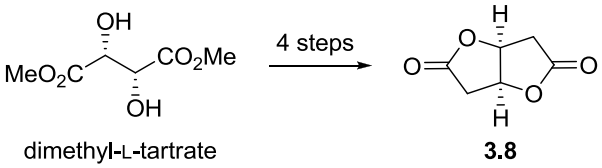


Figure 54

Whilst time constraints meant that completion of the total synthesis of ascospiroketals A and B was not possible, this project has been successful in providing a short and practical route to dilactone **3.8** (**Scheme 202**), a useful synthetic fragment that has been the subject of a number of previous synthetic attempts. This route has the advantage of being able to provide either enantiomer of this dilactone in an enantiopure fashion, making use of chiral pool starting materials.



dimethyl-L-tartrate **3.8**

Scheme 202

GENERAL EXPERIMENTAL

CHROMATOGRAPHY: Thin layer chromatography (TLC) was performed using Merck aluminium backed DC 60 F_{254} 0.2 mm precoated plates. Product spots were visualised by the quenching of UV fluorescence (λ_{max} 254 nm) then stained and heated using anisaldehyde, phosphomolybdic acid or potassium permanganate as appropriate. Retention factors (R_f) are reported with the solvent system used in parentheses, graduated solvent systems are indicated with an arrow.

Flash column chromatography was carried out on Merck 60 silica gel (particle size 40-63 μm) with the solvent system used in parentheses. The general method was adapted from the procedure reported by Still and co-workers.[1]

MELTING POINTS: Melting points were determined using a Griffin melting point apparatus and are uncorrected.

POLARIMETRY: Optical rotations were determined using a Perkin-Elmer 241 polarimeter at a wavelength of 589 nm and are quoted in units 10^{-1} deg cm^2 g^{-1}. Concentrations are quoted in g/100 mL.

INFRARED SPECTROSCOPY: Infrared spectra were either recorded on a Bruker Tensor 27 Fourier Transform spectrometer, and samples were prepared either as a thin film between NaCl plates, pressed into a KBr disc, or places directly onto a diamond ATR module. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}) and are described as s (strong), m (medium), w (weak) or br (broad).

NMR SPECTRA: Proton (^1H) and carbon (^{13}C) spectra were recorded on a Bruker AV 200 (200/50 MHz), Bruker AV 400 (400/125 MHz) or a Bruker AV 500 (500/125 MHz) spectrometer. Chemical shifts (δ_H/δ_C) are quoted in ppm downfield of tetramethylsilane with residual solvent as the internal standard. Assignments were made on the basis of chemical shifts, coupling constants, COSY, DEPT, HMQC, HMBC and HSQC data and comparison with the spectra of similar compounds, as well as NOE

experiments where appropriate. Resonances are described as s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). Coupling constants (*J*) are given in Hz and are rounded to the nearest 0.5 Hz. Labels H and H′ refer to diastereotopic protons attached to the same carbon and impart no stereochemical information. Fluorine (^{19}F) NMR spectra were recorded on a Brucker AV 400 (376.5 MHz) spectrometer. Chemical shifts (δ_F) are reported in parts per million (ppm) downfield of trichlorofluoromethane.

MASS SPECTRA: Low resolution mass spectra were recorded on a Fisons Platform spectrometer (ESI). High resolution mass spectra (HRMS) were recorded using a Bruker Daltronics microTOF spectrometer by Robin Proctor or James McCullagh at the Chemistry Research Laboratory. *m/z* values are reported in Daltons with percentage abundances in parentheses. High resolution values are calculated to four decimal places from the molecular formula and all obtained values are within a tolerance of 5 ppm.

SOLVENTS AND REAGENTS: Solvents and commercially available reagents were dried and purified before use where appropriate using standard procedures.[2] Ether (diethyl ether), DCM, THF, methanol and toluene were obtained dry and oxygen free from Grubbs' solvent stills, having been passed through an activated alumina column under argon. Acetonitrile and dimethylformamide were distilled over CaH_2 under reduced pressure and stored over 4 Å molecular sieves; trimethylsilyl chloride, benzene and pyridine were distilled over CaH_2 and stored over 4 Å molecular sieves. Dimethylsulfoxide was distilled by fractional distillation, the first 20% being discarded, and stored over 4 Å molecular sieves. Triethylamine and diisopropylamine were distilled from and stored over KOH. Petrol refers to the fraction of light petroleum ether which boils in the range 30-40 °C.

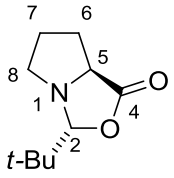
REACTIONS: For reactions requiring anhydrous conditions, experiments were carried out in oven-dried glassware under an inert argon atmosphere.

1. W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

2. D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, Pergamon Press, 3rd Edition.

EXPERIMENTAL FOR CHAPTER 1

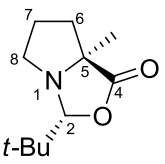
(*2R*, 5*S*)-2-*tert*-Butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (1.162)



Trimethylacetaldehyde (69.8 g, 810 mmol) and TFA (720 μL, 9.56 mmol) were added to a suspension of L-proline (18.7 g, 162 mmol) stirring in pentane (478 mL) and the mixture heated to reflux for 3 d under Dean-Stark conditions. The resulting clear solution was concentrated *in vacuo* to afford **1.162** which was stored, without further purification, under argon in the fridge until required (18.9 g, 64%).

$[\alpha]_D^{25}$ –39.2 (c 2.4, $CHCl_3$); [lit. reported $[\alpha]_D^{25}$ –24.7 (c 2.4 $CHCl_3$)];[1] δ_H (400 MHz, $CDCl_3$) 0.91 (9H, s, C(C**H**$_3$)$_3$), 1.61–1.74 (1H, m, C(7)**H**H′), 1.74–1.88 (1H, m, C(7)H**H′**), 1.96–2.07 (1H, m, C(6)**H**H′), 2.08–2.20 (1H, m, C(6)H**H′**), 2.79 (1H, dt, *J* 10.5, 6.5, C(8)**H**H′), 3.19 (1H, td, *J* 10.5, 6.5, C(8)H**H′**), 3.79 (1H, dd, *J* 9.0, 4.5 Hz C(5)**H**), 4.51 (1H, s, C(2)**H**); δ_C (100 MHz, $CDCl_3$) 24.1 (C(**C**H$_3$)$_3$), 25.1 (**C**(7)H$_2$), 29.6 (**C**(6)H$_2$), 37.4 (**C**(CH$_3$)$_3$), 58.3 (**C**(8)H$_2$), 62.8 (**C**(5)H), 108.1 (**C**(2)H), 178.0 (**C**(4)). Data as reported.[2]

(2*R*, 5*S*)-2-*tert*-Butyl-5-methyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (1.163)

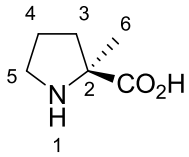


n-Butyllithium (1.6 M in hexanes, 68.1 mL, 109.0 mmol) was added to a stirred solution of diisopropylamine (15.3 mL, 109.0 mmol) in THF (95 mL) at –78 °C and the mixture was allowed to warm to RT over 30 min. This solution was re-cooled to –78 °C and added *via* cannula to a solution of

bicycle **1.162** (19.0 g, 103.8 mmol) in THF (570 mL) over 20 mins. The resulting solution was stirred at –78 °C for 45 mins before iodomethane (7.11 mL, 114.2 mmol) was passed through a short plug of neutral alumina under a stream of argon and added to the reaction mixture over 10 mins. The reaction mixture was allowed to warm to 0 °C over a period of 3 h before being quenched with NH_4Cl (sat. aq., 300 mL). The layers were separated and the organic layer washed successively with Na_2CO_3 (sat. aq., 200 mL) and brine (sat. aq., 200 mL). The aqueous layers were extracted with ethyl acetate (2 × 200 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo* to yield **1.163** as a brown oil (14.0 g, 69%).

$[\alpha]_D^{25}$ –12.5 (c 0.7, $CHCl_3$); [lit. reported $[\alpha]_D^{25}$ –29.8 (c 0.7 $CHCl_3$)][1]; δ_H (400 MHz, $CDCl_3$) 0.89 (9H, s, C(C**H₃**)₃, 1.36 (3H, s, C(5)C**H₃**), 1.58–2.26 (4H, C(6)**H₂** and C(7)**H₂**), 2.71–2.91 (1H, m, C(8)**H**H′), 3.00–3.20 (1H, m, C(8)H**H′**), 4.25 (1H, s, C(2)**H**); δ_C (100 MHz, $CDCl_3$) 24.0 (C(**C**H_3)₃), 25.3, 25.4 (**C**(6)H_2 and **C**(7)H_2), 36.3 (**C**$(CH_3)_3$), 38.6 (C(5)**C**H_3), 57.8 (**C**(8)H_2), 68.7 (**C**(5)CH_3), 105.8 (**C**(2)H), 179.0 (**C**(4)). Data as reported.[2]

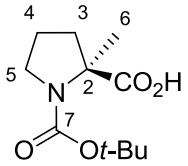
(*S*)-2-Methylproline (1.53)



Silica gel (15 g) was added to a solution of bicycle **1.163** (13.9 g, 70.6 mmol) in methanol (160 mL) and water (24.5 mL) and the suspension stirred at RT for 24 h. The reaction was then filtered, dried *in vacuo* and the crude residue recrystallised from hot 2:1 ethyl acetate/methanol to yield compound **1.53** as a white solid (6.42 g, 70%).

$[\alpha]_D^{21}$ –64.1 (c 0.75, CH_3OH), [lit. reported $[\alpha]_D^{25}$ –71.1 to –72.1 (c 1.00 CH_3OH)];[3] δ_H (400 MHz, D_2O) 1.45 (3H, s, C(6)**H₃**), 1.74-2.26 (4H, m, C(3)**H₂** and C(4)**H₂**), 3.16-3.33 (2H, m, C(5)**H₂**); δ_C (100 MHz, D_2O) 21.7 (**C**(6)H_3), 23.6 (**C**(4)H_2), 36.0 (**C**(3)H_2), 45.8 (**C**(5)H_2), 71.1 (**C**(2)), 177.7 (**C**O_2H). Data as reported.[3]

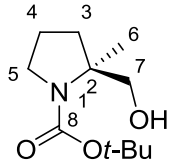
(*S*)-1-(*tert*-Butoxycarbonyl)-2-methylpyrrolidine-2-carboxylic acid (1.164)



A mixture of (*S*)-2-methylproline (**1.53**) (1.00 g, 7.74 mmol) and tetramethylammonium hydroxide pentahydrate (1.40 g, 7.74 mmol) in acetonitrile (45 mL) was stirred at RT until a homogeneous solution had formed, at which point di-*tert*-butyl dicarbonate (2.67 mL, 11.6 mmol) was added and the stirring continued for 48 h at which point further di-*tert*-butyl dicarbonate (0.89 mL, 3.87 mmol) was added and the reaction stirred for a further 8 h. The resulting mixture was concentrated *in vacuo* and the residue partitioned between water (100 mL) and ether (100 mL). The aqueous layer was washed with ether (100 mL), acidified to pH 3 with solid citric acid and then extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water (200 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give compound **1.164**, as a mixture of rotamers, as a colourless oil (1.86 g, 100%).

δ_H (400 MHz, $CDCl_3$, major rotamer) 1.40 (9H, s, C(C**H**$_3$)$_3$), 1.50 (3H, s, C(6)**H**$_3$), 1.77-2.00 (3H, m, C(4)**H**$_2$ and C(3)**H**H′), 2.20-2.32 (1H, m, C(3)H**H′**), 3.38-3.63 (2H, m, C(5)**H**$_2$), 10.50 (CO_2**H**); δ_C (100 MHz, $CDCl_3$, major rotamer) 22.9 (**C**(4)H_2), 23.5 (**C**(6)H_3), 28.0 (C(**C**H_3)$_3$), 39.7 (**C**(3)H_2), 47.5 (**C**(5)H_2), 64.3 (**C**(2)), 80.8 (**C**(CH_3)$_3$), 153.1 (**C**(7)), 169.9 (**C**O_2H). Data as reported.[4]

(*S*)-*tert*-Butyl 2-(hydroxymethyl)-2-methylpyrrolidine-1-carboxylate (1.165)

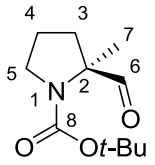


BH_3·THF (1.0 M in THF, 8.61 mL, 8.61 mmol) was added dropwise over 1 h to a stirred solution of acid **1.164** (1.79 g, 7.83 mmol) in THF (46 mL). The reaction was then heated at a gentle reflux for

1 h, cooled to RT and concentrated *in vacuo* to yield compound **1.165** as a colourless oil (1.70 g, 100%).

$[\alpha]_D^{21}$ –9.7 (c 0.6, $CHCl_3$); [lit.reported $[\alpha]_D^{21}$ –10.3 (c 0.6, $CHCl_3$)];[2] δ_H (500 MHz, $CDCl_3$) 1.36 (3H, s, C(6)**H$_3$**), 1.46 (9H, s, C(C**H$_3$**)$_3$), 1.63-1.70 (2H, m, C(3)**H$_2$**), 1.72-1.92 (2H, m, C(4)**H$_2$**). 3.26-3.35 (1H, m, C(5)**H**H′), 3.46-3.54 (1H, m, C(5)H**H′**), 3.54-3.72 (2H, m, C(7)**H$_2$**), 5.30 (1H, app. d, *J* 9.5 Hz, O**H**); δ_C (125 MHz, $CDCl_3$) 20.3 (**C**(6)H_3), 21.7 (**C**(4)H_2), 28.3 (C(**C**H_3)$_3$), 37.5 (**C**(3)H_2), 48.5 (**C**(5)H_2), 64.7 (**C**(2)), 70.7 (**C**(7)H_2), 79.9 (**C**$(CH_3)_3$), 156.0 (**C**(8)). Data as reported.[2]

(*S*)-*tert*-Butyl 2-formyl-2-methylpyrrolidine-1-carboxylate (1.54)

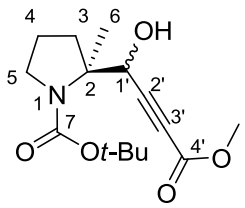


To a stirred solution of alcohol **1.165** (1.60 g, 7.45 mmol) in DCM (88 mL) at 0 °C was added Dess–Martin periodinane (4.86 g, 10.9 mmol). The mixture was allowed to warm to RT, stirred for 6 h then diluted with ether (100 mL). The mixture was poured onto NaOH solution (1.3 M aq., 200 mL) and stirred for 15 min. The layers were separated and the organic layer was washed successively with NaOH (1.3 M aq., 60 mL) and NaCl solution (sat. aq., 60 mL), dried ($MgSO_4$) and evaporated *in vacuo* to yield aldehyde **1.54**, in a 2:1 ratio of rotamers (as determined by ^{1}H NMR), as a yellow oil that was used without further purification (1.55 g, 97%).

$[\alpha]_D^{21}$ –38.4 (c 0.41, $CHCl_3$); [lit. reported $[\alpha]_D^{21}$ –38.5 (c 0.41, $CHCl_3$)];[2] δ_H (500 MHz, $CDCl_3$) **Major rotamer**: 1.37 (3H, s, C(7)**H$_3$**), 1.40 (9H, s, C(C**H$_3$**)$_3$), 1.58-1.71 (1H, m, C(3)**H**H′), 1.87-2.02 (3H, m, C(3)H**H′** and C(4)**H$_2$**), 3.41-3.67 (2H, m, C(5)**H$_2$**), 9.32 (1H, s, C**H**O); **Minor rotamer**: 1.41 (3H, s,C(7)**H$_3$**), 1.44 (9H, s, C(C**H$_3$**)$_3$), 1.58-1.71 (1H, m, C(3)**H**H′), 1.87-2.02 (3H, m, C(3)H**H′** and C(4)**H$_2$**), 3.41-3.67 (2H, m, C(5)**H$_2$**), 9.40 (1H, s, C**H**O); δ_C (125 MHz, $CDCl_3$) **Major rotamer**: 18.7 (**C**(7)H_3), 22.7 (**C**(4)H_2), 28.2 (C(**C**H_3)$_3$, 35.4 (**C**(3)H_2), 47.4 (**C**(5)H_2), 68.2 (**C**(2)), 80.8 (**C**$(CH_3)_3$),

153.2 (**C**(8)), 199.6 (**C**(6)); **Minor rotamer**: 17.9 (**C**(7)H_3), 23.6 (**C**(4)H_2), 28.4 (C(**C**H_3)$_3$), 34.4 (**C**(3)H_2), 47.4 (**C**(5)H_2), 68.4 (**C**(2)), 80.1 (**C**(CH_3)$_3$), 154.0 (**C**(8)), 200.2 (**C**(6)). Data as reported.[2]

(*S*)-*tert*-Butyl 2-(1-hydroxy-4-methoxy-4-oxobut-2-ynyl)-2-methylpyrrolidine-1-carboxylate (1.166)

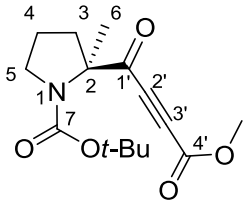


n-Butyllithium (1.6 M in hexanes, 3.87 mL, 6.20 mmol) was added dropwise to a solution of methyl propiolate (0.55 mL, 6.20 mmol) in THF (15.6 mL) at –78 °C. The resulting solution was stirred for 1 h, before adding a solution of aldehyde **1.54** (1.10 g, 5.16 mmol) in THF (44 mL) *via* cannula over 20 min. The reaction mixture was stirred for 3 h at –78 °C then quenched with NH_4Cl (sat. aq., 60 mL). The mixture was warmed to RT and the layers separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL) and the combined organic layers washed with brine (sat. aq., 60 mL) and dried ($MgSO_4$). Evaporation *in vacuo* gave alcohol **1.166**, in a 1.4:1 ratio of separable diastereomers (as determined by ^{1}H NMR analysis), as a yellow oil whichcould be used without further purification (1.53 g, 100%).

δ_H (400 MHz, $CDCl_3$) **Major diastereomer**: 1.39 (3H, s, C(6)**H$_3$**), 1.45 (9H, s, C(C**H$_3$**)$_3$), 1.65-2.04 (4H, m, C(3)**H$_2$** and C(4)**H$_2$**), 3.25-3.38 (1H, m, C(5)**H**H′), 3.54-3.62 (1H, m, C(5)H**H′**), 3.75 (3H, s, OC**H$_3$**), 4.34 (1H, d, *J* 11.0 Hz, C(1′)**H**), 6.67 (1H, d, *J* 11.0 Hz, O**H**); **Minor diastereomer**: 1.44 (9H, s, C(C**H$_3$**)$_3$), 1.47 (3H, s, C(6)**H$_3$**), 1.69-1.94 (3H, m, C(3)**H**H′ and C(4)**H$_2$**), 1.95-2.07 (1H, m, C(3)H**H′**), 3.27-3.41 (1H, m, C(5)**H**H′), 3.50-3.61 (1H, m, C(5)H**H′**), 3.75 (3H, s, OC**H$_3$**), 4.73 (1H, s, C(1′)**H**), 6.23 (1H, br s, O**H**); δ_C (100 MHz, $CDCl_3$) **Major Diastereomer**: 21.1 (**C**(6)H_3), 22.0 (**C**(4)H_2), 28.4 (C(**C**H_3)$_3$), 38.0 (**C**(3)H_2), 49.4 (**C**(5)H_2), 52.6 (O**C**H_3), 67.1 (**C**(2)), 69.7 (**C**(1′)H), 76.0 (**C**≡C), 80.9 (**C**(CH_3)$_3$), 87.0 (C≡**C**), 153.7 (**C**(7)), 156.4 (**C**(4′)); **Minor diastereomer**: 18.5

(**C**(6)H_3), 21.8 (**C**(4)H_2), 28.4 (C(**C**H_3)$_3$), 38.1 (**C**(3)H_2), 49.2 (**C**(5)H_2), 52.7 (O**C**H_3), 67.2 (**C**(2)), 70.4 (**C**(1′)H), 75.8 (**C**≡C), 80.8 (**C**(CH_3)$_3$), 86.7 (C≡**C**), 153.8 (**C**(7)), 156.2 (**C**(4′)). Data as reported.[2]

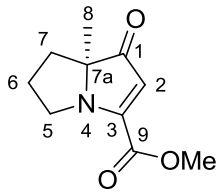
(*S*)-*tert*-Butyl 2-(4-methoxy-4-oxobut-2-ynoyl)-2-methylpyrrolidine-1-carboxylate (1.55)



Dess–Martin periodinane (3.77 g, 8.83 mmol) was added to a solution of alcohol **1.166** (1.75 g, 5.89 mmol) in DCM (109 mL) at 0 °C. The mixture was allowed to warm to RT and stirred for 18 h before being diluted with ether (100 mL), poured into NaOH solution (1.3 M aq., 100 mL) and stirred for 15 min. The layers were separated and the organic layer was washed successively with NaOH solution (1.3 M aq., 100 mL), brine (sat. aq., 100 mL) dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash column chromatography (5:1, petrol/ethyl acetate) gave ketone **1.55**, as a mixture of rotamers, as a yellow oil (1.26 g, 73%).

$[\alpha]_D^{22}$ –57.6 (c 0.45, $CHCl_3$); [lit. reported $[\alpha]_D^{21}$ –58.4 (c 0.45, $CHCl_3$)][2]; δ_H (500 MHz, $CDCl_3$, **Major rotamer**: 1.43 (9H, s, C(C**H$_3$**)$_3$), 1.46 (3H, s, C(6)**H$_3$**), 1.79-1.86 (1H, m, C(3)**H**H′), 1.90-2.06 (2H, m, C(4)**H$_2$**), 2.18-2.28 (1H, m, C(3)H**H′**), 3.45-3.71 (2H, m, C(5)**H$_2$**), 3.82 (3H, s, OC**H$_3$**); δ_C (125 MHz, $CDCl_3$) **Major (M) and minor (m) rotamers**: 19.5 (**C**(6)H_3, m), 20.3 (**C**(6)H_3, M), 22.9 (**C**(4)H_2, M), 23.8 (**C**(4)H_2, m), 28.1 (C(**C**H_3)$_3$, M), 28.4 (C(**C**H_3)$_3$, m), 36.8 (**C**(3)H_2, m), 40.0 (**C**(3)H_2, M), 47.6 (**C**(5)H_2, M), 47.7 (**C**(5)H_2, m), 53.2 (O**C**H_3, m), 53.3 (O**C**H_3, M), 70.0 (**C**(2), M), 70.2 (**C**(2), m), 77.5, 78.7, 79.9, 80.3, 80.5 and 81.5 (**C**(CH_3)$_3$, **C**(2′) and **C**(3′), M and m), 152.4, 152.6, 152.8 and 153.9 (**C**(7) and **C**(4′), both), 186.8 (**C**(1′), m), 186.8 (**C**(1′), M). Data as reported.[5]

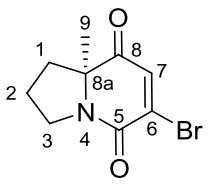
(*S*)-Methyl 7a-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizine-3-carboxylate (1.56)



Ester **1.55** (50 mg, 0.17 mmol) was dissolved in DCM (1.7 mL) and the solution cooled to −30 °C before trimethylsilyl trifluoromethanesulfonate (92 µL, 0.51 mmol) was added and the reaction mixture allowed to warm to 0 °C over 3 h. $NaHCO_3$ (sat. aq., 5 mL) was added and the reaction extracted with DCM (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 3:2, petrol/ether) gave ester **1.56** as a bright yellow oil (20 mg, 61%).

R_f 0.28 (petrol/ethyl acetate, 3:1); $[\alpha]_D^{23}$ +476.0 (c 0.55, $CHCl_3$); [lit. reported $[\alpha]_D^{21}$ +491.1 (c 0.55, $CHCl_3$)];[2] δ_H (500 MHz, $CDCl_3$) 1.35 (3H, s, C(8)**H$_3$**), 1.75-1.82 (2H, m, C(7)**H$_2$**), 1.99-2.09 (2H, m, C(6)**H$_2$**), 3.43 (1H, app. dt, *J* 11.5, 7.5 Hz, C(5)**H**H′), 3.59 (1H, ddd, *J* 11.5, 7.5, 5.0 Hz, C(5)H**H′**), 3.91 (3H, s, OC**H$_3$**), 5.80 (1H, s, C(2)**H**); δ_C (125 MHz, $CDCl_3$) 22.1 (**C**(8)H_3), 27.3 (**C**(6)H_2), 31.8 (**C**(7)H_2), 48.7 (**C**(5)H_2), 52.8 (O**C**H_3), 77.3 (**C**(7a)), 109.1 (**C**(2)H), 162.0 (**C**(9)), 166.2 (**C**(3)), 208.3 (**C**(1)). Data as reported.[2]

(*S*)-6-Bromo-8a-methyl-1,2,3,8a-tetrahydroindolizine-5,8-dione (1.57)

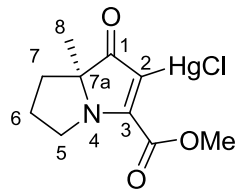


Acetylenic ketone **1.55** (50 mg, 0.17 mmol) was dissolved in DCM (0.68 mL) and stirred at RT under argon. A solution of 2-bromocatechol borane (67.6 mg, 0.34 mmol) in DCM (1.7 mL) was added *via* cannula over 30 min and the reaction stirred at RT for 16 h before being quenched with water (5 mL) and the resulting mixture stirred for 20 mins. The reaction was then diluted with DCM (5 mL) and

washed with NaOH (10% aq., 2 × 5 mL) and brine (5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, DCM) gave *bromide* **1.57** as on off-white solid (20 mg, 50%).

R_f 0.26 (3:1, ether/petrol); m.p. 132 °C; $[\alpha]_D^{25}$ +47.0 (c 1.0 in $CHCl_3$); ν_{max} (KBr disc)/cm^{-1} 3441br, 3056w, 2965m, 2929m, 1682s, 1654s, 1579s, 1422m, 1374w, 1336w, 1285m, 1263s, 1145s, 1061m, 1014m, 878m, 805s; δ_H (500 MHz, $CDCl_3$) 1.46 (3H, s, C(9)**H₃**), 2.03-2.18 (4H, m, C(1)**H₂** and C(2)**H₂**), 3.68-3.74 (1H, m, C(3)**H**H′), 3.82-3.91 (1H, m, C(3)H**H′**), 7.02 (1H, s, C(7)**H**); δ_C (125 MHz, $CDCl_3$) 20.3 (**C**(2)H_2), 26.1 (**C**(9)H_3), 34.1 (**C**(1)H_2), 46.2 (**C**(3)H_2), 70.8 (**C**(8a)), 134.8 (**C**(7)H), 142.6 (**C**(6)), 155.2 (**C**(5)), 196.3 (**C**(8)); HRMS (FI^+) found 242.9889; $C_9H_{10}{}^{79}BrNO_2$ (M^+) requires 242.9895.

(*S*)-[3-(methoxycarbonyl)-7a-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-2-yl]mercury(II) chloride (1.58)

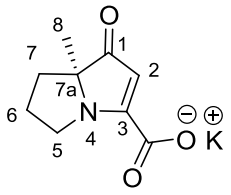


A solution of ester **1.55** (100 mg, 0.34 mmol) in acetic acid (0.75 mL) was added *via* cannula to a stirring slurry of mercury(II) trifluoroacetate (145 mg, 0.34 mmol) in acetic acid (0.25 mL). The reaction was stirred for 16 h before being cooled to 0 °C and quenched with brine and extracted with ethyl acetate (2 × 15 mL) and chloroform (2 × 15 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 2:3, petrol/ether) gave *pyrrolizidine* **1.56** (40 mg, 60%) and pyrrolizidine **1.58** (25 mg, 38%), both as yellow oils.

R_f 0.12 (2:3, petrol/ether); m.p. 206 °C; $[\alpha]_D^{25}$ **–**25.2 (c 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.48 (3H, s, C(8)**H₃**), 1.94-2.14 (3H, m, C(7)**H**H′ and C(6)**H₂**), 2.28-2.38 (1H, m, C(7)H**H′**), 3.58-3.78 (2H, m, C(5)**H₂**), 3.87 (3H, s, CO_2C**H₃**); δ_C (100 MHz, $CDCl_3$) 21.5 (**C**(8)H_2), 23.5 (**C**(7)H_3), 34.2 (**C**(6)H_2),

46.9 (**C**(5)H_2), 53.1 (CO_2**C**H_3), 66.9 (**C**(2)), 146.8 and 149.3 (**C**(3) and **C**O_2CH_3), 193.0 (**C**(1)); HRMS (FI+) found 431.0258; $C_{10}H_{12}ClHgNO_3$ (M^+) requires 431.0212.

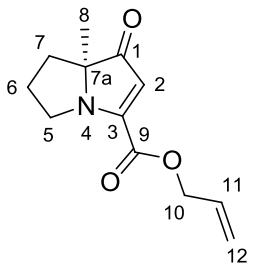
Potassium (*S*)-7a-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizine-3-carboxylate (1.64)



Ester **1.56** (100 mg, 0.51 mmol) was dissolved in acetonitrile (3.5 mL) and water (3.5 mL) and KOH (31.4 mg, 0.56 mmol) was added. The reaction mixture was stirred for 2 h and then evaporated *in vacuo* to give *carboxylate* **1.64** as an orange oil (113 mg, 100%).

δ_H (200 MHz, MeOD) 1.36 (3H, s, C(8)**H₃**), 1.71-1.82 (2H, m, C(7)**H₂**), 2.10-2.30 (2H, m, C(6)**H₂**), 3.52-3.65 (2H, m, C(5)**H₂**), 5.31 (1H, C(2)**H**).

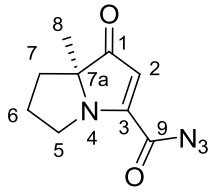
(*S*)-Allyl 7a-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizine-3-carboxylate (1.65)



Allyl bromide (14.3 μL, 0.17 mmol) was added to a stirred solution of potassium carboxylate **1.64** (25 mg, 0.11 mmol) in DMSO (0.12 mL). The reaction was stirred at RT under argon for 16 h before being quenched with water (5 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 3:2, petrol/ether) furnished *allyl ester* **1.65** as a brown liquid (24.4 mg, 100%).

R_f 0.09 (3:2, petrol/ether); $[\alpha]_D^{23}$ +319 (c 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2360s, 2345s, 1710m, 1685m, 1560m, 1250m, 1221m, 1091w; δ_H (500 MHz, $CDCl_3$) 1.34 (3H, s, C(8)**H$_3$**), 1.74-1.80 (2H, m, C(7)**H$_2$**), 1.98-2.21 (2H, m, C(6)**H$_2$**), 3.37-3.45 (1H, m, C(5)**H**H′), 3.54-3.62 (1H, m, C(5)H**H′**), 4.72-4.83 (2H, m, C(10)**H**$_2$), 5.32 (1H, dm, *J* 10.5 Hz, C(12)**H**), 5.40 (1H, dm, *J* 16.0 Hz, C(12)**H**), 5.81 (1H, s, C(2)**H**), 5.91-6.02 (1H, m, C(11)**H**); δ_C (125 MHz, $CDCl_3$) 22.1 (**C**(8)H_3), 27.3 (**C**(6)H_2), 31.8 (**C**(7)H_2), 48.7 (**C**(5)H_2), 66.6 (**C**(10)H_2), 76.7 (**C**(7a)), 109.1 (**C**(2)H), 119.6 (**C**(12)H_2), 130.9 (**C**(11)H), 161.2 (**C**(3)), 166.3 (**C**(9)), 208.3 (**C**(1)); *m/z* (ESI^+) 102 (70%), 222 (100, MH^+), 285 (24), 454 (78), 492 (75), 804 (60); HRMS found 222.1119; $C_{12}H_{16}NO_3$ (MH^+) requires 222.1125.

(*S*)-7a-Methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizine-3-carbonyl azide (1.59)



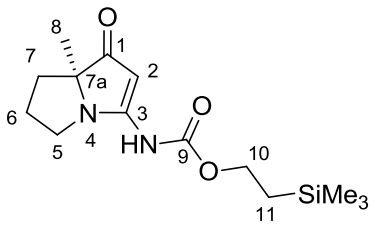
DPPA (49.1 μL, 0.23 mmol) was added to a solution of carboxylate **1.64** (50 mg, 0.23 mmol) in DMF (0.69 mL) at 0 °C and the resulting dark yellow solution was stirred at 0 °C for 3 h. The reaction was quenched with water (5 mL) and diluted with ether (5 mL), the layers were separated and the aqueous layer washed with ethyl acetate (3 × 10 mL). The combined organic layers were washed with $NaHCO_3$ (sat. aq., 20 mL), brine (sat. aq., 20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 1:1, petrol/ether) furnished *acyl azide* **1.59** as a bright yellow liquid (45 mg, 95%).

R_f 0.23 (1:1, ether/petrol); $[\alpha]_D^{23}$ +616 (c 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3418br, 2972w, 2148m, 1683br, 1489br, 1198m, 951w, 795w; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, s, C(8)**H$_3$**), 1.71-1.79 (C(7)**H$_2$**), 1.97-2.07 (1H, m, C(6)**H**H′), 2.09-2.20 (1H, m, C(6)H**H′**), 3.33-3.44 (1H, m, C(5)**H**H′), 3.52-3.62 (1H, m, C(5)H**H′**), 5.81 (1H, s, C(2)**H**); δ_C (100 MHz, $CDCl_3$) 22.1 (**C**(8)H_3), 27.3 (**C**(6)H_2), 31.4 (**C**(7)H_2), 48.8 (**C**(5)H_2), 77.4 (**C**(7a)), 110.0 (**C**(2)H), 166.2 (**C**(3)), 167.7 (**C**(9)), 208.4 (**C**(1)); m/z (ESI^+) 196 (88%), 259 (49), 328 (100); HRMS data unobtainable.

General procedure for isocyanate trapping and carbamate formation:

Azide **1.59** (10–90 mg, 0.05–0.44 mmol) was dissolved in toluene (6.9 mL/mmol) and the appropriate alcohol (15 eq, 0.75–6.6 mmol) added. The reaction mixture was heated to 80 °C under argon and stirred for 1 h before being cooled and washed with $NaHCO_3$ (sat. aq., 10 mL/mmol). The aqueous layer was extracted with ethyl acetate (3 × 10 mL/mmol) and the combined organic layers washed with brine (20 mL/mmol), dried ($MgSO_4$) and evaporated *in vacuo*.

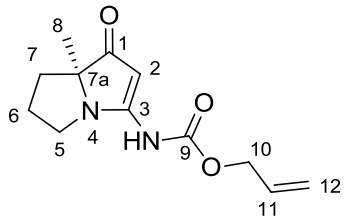
(*S*)-2-(Trimethylsilyl)ethyl 7a-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-3-ylcarbamate (1.66)



On a 0.12 mmol scale, with 2-trimethylsilylethanol as the trapping agent, *carbamate* **1.66** was obtained as an off-white, powdery solid (36 mg, 99%) after purification by flash chromatography (SiO_2, ethyl acetate).

R_f 0.27 (ethyl acetate); m.p. 192 °C; $[\alpha]_D^{18}$ +118.8 (c 1.0 in $CHCl_3$); ν_{max} (KBr disc)/cm^{-1} 3220w, 2957m, 2902m, 1749s, 1634s, 1581m, 1512s, 1407m, 1366w, 1336w, 1252m, 1217s, 1104m, 1071m, 935w, 863m, 837m; δ_H (500 MHz, $CDCl_3$) 0.04 (9H, s, Si(C**H₃**)$_3$), 0.98-1.12 (2H, m, C(11)**H₂**), 1.30 (3H, s, C(8)**H₃**), 1.62-1.88 (2H, m, C(7)**H₂**), 1.91-2.21 (2H, m, C(6)**H₂**), 3.12-3.42 (2H, m, C(5)**H₂**), 4.18-4.35 (2H, m, C(10)**H₂**), 5.56 (1H, s, C(2)**H**), 8.17-8.46 (1H, br, N**H**); δ_C (125 MHz, $CDCl_3$) –1.6 (Si(**C**H_3)$_3$), 17.6 (**C**(11)H_2), 22.4 (**C**(8)H_3), 26.8 (**C**(6)H_2), 32.0 (**C**(7)H_2), 47.9 (**C**(5)H_2), 65.1 (**C**(10)H_2), 73.9 (**C**(7a)), 90.6 (**C**(2)H), 152.1 (**C**(9)), 169.8 (**C**(3)), 204.5 (**C**(1)); *m/z* ($ES\Gamma^-$) 295.2 (100%, $[M–H]^-$); HRMS found 297.1632; $C_{14}H_{25}N_2O_3Si$ (MH^+) requires 297.1629.

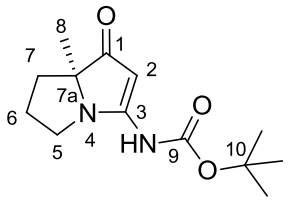
(*S*)-Allyl 7a-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-3-ylcarbamate (1.67)



On a 0.24 mmol scale, with allyl alcohol as the trapping agent, *carbamate* **1.67** was obtained as a yellow solid (52 mg, 93%) after purification by flash chromatography (SiO_2, ethyl acetate).

R_f 0.20 (ethyl acetate); m.p. 150 °C; $[\alpha]_D^{25}$ +80.1 (c 1.0 in $CHCl_3$); ν_{max} (KBr disc)/cm^{-1} 3442br, 3195w, 2966m, 1751s, 1630s, 1583m, 1511s, 1406m, 1368m, 1335w, 1217s, 1105, 799m; δ_H (500 MHz, $CDCl_3$) 1.32 (3H, s, C(8)**H$_3$**), 1.69-1.84 (2H, m, C(7)**H$_2$**), 1.97-2.16 (2H, m, C(6)**H$_2$**), 3.19-3.25 (1H, m, C(5)**H**H′), 3.32-3.38 (1H, m, C(5)H**H′**), 4.67-4.70 (2H, m, C(10)**H$_2$**), 5.28 (1H, d, *J* 10.5 Hz, C(12)**H**H′), 5.36 (1H, d, *J* 17.0 Hz, C(12)H**H′**), 5.56 (1H, s, C(2)**H**), 5.88-5.97 (1H, m, C(11)**H**), 8.34-8.51 (1H, br s, N**H**); δ_C (125 MHz, $CDCl_3$) 22.3 (**C**(8)H_3), 26.7 (**C**(6)H_2), 31.7 (**C**(7)H_2), 47.9 (**C**(5)H_2), 67.0 (**C**(10)H_2), 74.0 (**C**(7a)), 90.7 (**C**(2)H), 119.3 (**C**(12)H_2), 131.4 (**C**(11)H), 151.6 (**C**(3)), 169.6 (**C**(9)), 204.5 (**C**(1)); *m/z* (ESI^+) 237 (71%, MH^+), 300 (65), 473 (80, M_2H^+), 495 (100, M_2Na^+), 589 (62), 731 (31); HRMS found 259.1053; $C_{12}H_{16}N_2O_3Na$ (MNa^+) requires 259.1046.

(*S*)-*tert*-Butyl 7a-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-3-ylcarbamate (1.68)

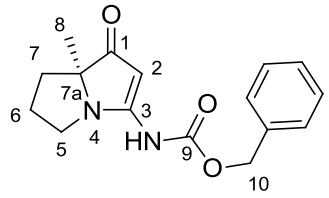


On a 0.077 mmol scale, with tert-butanol as the trapping agent, *carbamate* **1.68** was obtained as a pale brown oil (19.8 mg, 99%) after purification by flash chromatography (SiO_2, ethyl acetate).

R_f 0.13 (ethyl acetate); $[\alpha]_D^{21}$ +72.7 (c 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2973br, 1745s, 1629s, 1572s, 1502br, 1404m, 1367m, 1335w, 1308w, 1234s, 1152s, 917w, 885w, 797br; δ_H (400 MHz,

$CDCl_3$) 1.30 (3H, s, C(8)**H₃**), 1.52 (9H, s, (C(C**H₃**)$_3$), 1.66-1.87 (2H, m, C(7)**H₂**), 1.96-2.17 (2H, m, C(6)**H₂**), 3.13-3.22 (1H, m, C(5)**H**H′), 3.27-3.35 (1 H, m, C(5)H**H′**), 5.49 (1H, s, C(2)**H**), 7.14 (1H, br, N**H**); δ_C (100 MHz, $CDCl_3$) 22.5 (**C**(8)H_3), 26.8 (**C**(6)H_2), 28.0 (C(**C**H_3)$_3$), 32.1 (**C**(7)H_2), 47.8 (**C**(5)H_2), 73.7 (**C**(7a)), 82.4 (**C**(10)), 90.5 (**C**(2)H), 149.8 (**C**(3)), 152.8 (**C**(9)), 204.3 (**C**(1)); *m/z* (ESI^+) 253 (51, MH^+), 311 (100, $[M+MeCN+NH_4]^+$), 577 (26); HRMS found 275.1360; $C_{13}H_{20}N_2O_3Na$ (MNa^+) requires 275.1366.

(*S*)-Benzyl 7a-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-3-ylcarbamate (1.69)



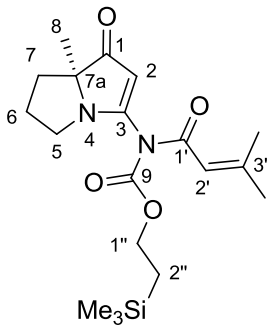
On a 0.17 mmol scale, with benzyl alcohol as the trapping agent, *carbamate* **1.69** was obtained as an off-white powder (30 mg, 61%) after purification by flash chromatography (SiO_2, ether).

R_f 0.13 (ethyl acetate); m.p. 124 °C; $[\alpha]_D^{25}$ +56.9 (c 1.0 in $CHCl_3$); ν_{max} (KBr disc)/cm^{-1} 2970m, 2925s, 2860m, 1749m, 1630m, 1602w, 1511s, 1475w, 1405w, 1350w, 1261s, 1210s, 1185w, 1103s, 1025m, 799s, 700m; δ_H (500 MHz, $CDCl_3$) 1.31 (3H, s, C(8)**H₃**), 1.69-1.84 (2H, m, C(7)**H₂**), 1.96-2.15 (2H, m, C(6)**H₂**), 3.11-3.17 (1H, m, C(5)**H**H′), 3.26-3.31 (1H, m, C(5)H**H′**), 5.23 (2H, s, C(10)**H₂**), 5.57 (1H, s, C(2)**H**), 7.19 (1H, s, N**H**), 7.27 (1H, s, **Ar**), 7.37-7.41 (4H, m, **Ar**); δ_C (125 MHz, $CDCl_3$) 22.7 (**C**(8)H_3), 26.8 (**C**(6)H_2), 32.0 (**C**(7)H_2), 47.8 (**C**(5)H_2), 68.5 (**C**(10)H_2), 74.0 (**C**(7a)), 91.2 (**C**(2)H), 128.6 (3 × Ar **C**H), 134.7 (Ar **C**), 151.2 (**C**(3)), 168.7 (**C**(9)), 204.3 (**C**(1)); m/z (ESI^+) 287 (46%, MH^+), 573 (100, M_2H^+); HRMS found 287.1387; $C_{16}H_{19}N_2O_3$ (MH^+) requires 287.1390.

General procedure for acylation of carbamates:

Carbamates **1.66–1.69** (20–50 mg, 0.067–0.17 mmol) were dissolved in THF (8.0 mL/mmol) and stirred at −78 °C under argon. NHMDS (1M in THF, 67–169 µL, 0.067–0.169 mmol) was added dropwise and the reaction stirred for 30 min before 3,3-dimethylacryloyl chloride (8.2–20.6 µL, 0.074–0.186 mmol) was added and stirring continued at −78 °C. After 5 h the reaction mixture was passed through a silica plug and the filtrate evaporated *in vacuo*.

(*S*)-2-(Trimethylsilyl)ethyl 7a-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-3-yl(3-methylbut-2-enoyl)carbamate (1.70)

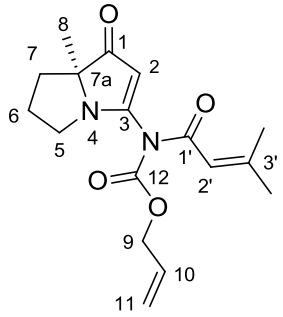


On a 0.17 mmol scale, *carbamate* **1.70** was obtained as a white oil (41.1 mg, 64%) after purification by flash chromatography (SiO_2, ether/petrol, 3:1).

R_f 0.12 (3:2, ether/petrol); $[\alpha]_D^{23}$ +7.5 (c 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3419br, 3107s, 2958s, 2854m, 2360m, 2341m, 1759s, 1673s, 1644s, 1603s, 1483m, 1410m, 1376m, 1257s, 1214s, 1171s, 1112s, 1089s, 1053s, 928m, 860s, 838s, 802s; δ_H (500 MHz, $CDCl_3$) 0.05 (9H, s, Si(C**H$_3$**)$_3$), 1.06-1.12 (2H, m, C(2′′)**H$_2$**), 1.39 (3H, s, C(8)**H$_3$**), 1.56-1.66 (1H, m, C(7)**H**H′), 1.81-1.87 (1H, m, C(7)H**H′**), 2.00 (3H, s, C(3′)C**H$_3$**), 2.24 (3H, s, C(3′)C**H$_3$**), 2.25-2.37 (2H, m, C(6)**H$_2$**), 3.34-3.41 (1H, m, C(5)**H**H′), 3.67-3.75 (1H, m, C(5)H**H′**), 4.15-4.22 (2H, m, C(1′′)**H$_2$**), 5.82 (1H, s, C(2′)**H**), 6.92 (1H, s, C(2)**H**); δ_C (125 MHz, $CDCl_3$) −1.5 (Si(**C**H$_3$)$_3$), 17.6 (**C**(2′′)H$_2$), 20.7 (**C**(8)H$_3$), 21.3 and 27.8 (2 × C(3′)**C**H$_3$ and **C**(6)H$_2$), 32.9 (**C**(7)H$_2$), 43.6 (**C**(5)H$_2$), 63.3 (**C**(1′′)H$_2$), 72.1 (**C**(7a)), 103.8 (**C**(2)H), 113.8 (**C**(2′)H), 161.1, 163.0, 163.5, 169.3 and 172.4 (**C**(1), **C**(3), **C**(1′), **C**(9) and **C**(3′)); *m/z* (ESI^+)

379 (65%, MH^+), 757 (100, M_2H^+), 779 (35, M_2Na^+); HRMS found 379.2041; $C_{19}H_{31}N_2O_4Si$ (MH^+) requires 379.2048.

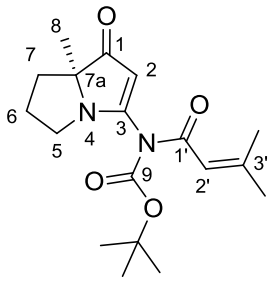
(*S*)-Allyl 7a-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-3-yl(3-methylbut-2-enoyl)carbamate (1.71)



On a 0.085 mmol scale, *carbamate* **1.71** was obtained as a colourless oil (20 mg, 74%) after purification by flash chromatography (SiO_2, ether).

R_f 0.26 (ether); $[\alpha]_D^{18}$ +4.8 (c 0.5 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2978br, 1758s, 1680s, 1601s, 1445m, 1377m, 1346m, 1255s, 1153s, 1090s, 1052s, 927s, 855w; δ_H (500 MHz, $CDCl_3$) 1.40 (3H, s, C(8)**H$_3$**), 1.59-1.65 (1H, m, C(7)**H**H′), 1.85 (1H, ddd, *J* 12.5, 7.0, 2.0 Hz, C(7)H**H′**), 2.01 (3H, d, *J* 1.5 Hz, C(3′)C**H$_3$**), 2.25 (3H, d, *J* 1.5 Hz, C(3′)C**H$_3$**), 2.26-2.39 (2H, m, C(6)**H$_2$**), 3.39 (1H, ddd, *J* 12.5, 9.0, 4.0 Hz, C(5)**H**H′), 3.72 (1H, dt, *J* 12.5, 8.5 Hz, C(5)H**H′**), 4.58-4.67 (2H, m, C(9)**H$_2$**), 5.20 (1H, ddd, *J* 10.5, 3.0, 1.5 Hz, C(11)**H**H′), 5.34 (1H, dq, *J* 17.0, 1.5 Hz, C(11)H**H′**), 5.82 (1H, app. quin., *J* 1.5 Hz, C(2′)**H**), 6.01 (1H, ddt, *J* 17.0, 10.5, 6.0 Hz, C(10)**H**), 6.95 (1H, s, C(2)**H**); δ_C (125 MHz, $CDCl_3$) 20.8 (C(3′)**C**H_3), 21.2 (**C**(8)H_3), 26.7 (C(3′)**C**H_3 and **C**(6)H_2), 32.8 (**C**(7)H_2), 43.5 (**C**(5)H_2), 66.2 (**C**(9)H_2), 72.1 (**C**(7a)), 103.8 (**C**(2)H), 113.8 (**C**(2′)H), 117.5 (**C**(11)H_2), 133.3 (**C**(10)H), 161.1 (**C**(12)), 162.5 (**C**(3)), 163.6 (**C**(3′)), 169.5 (**C**(1′)), 172.8 (**C**(1)); *m/z* (ESI^+) 237 (14%), 319 (100, MH^+), 320 (40), 377 (31), 637 (25, M_2H^+); HRMS found 319.1652; $C_{17}H_{23}N_2O_4$ (MH^+) requires 319.1652.

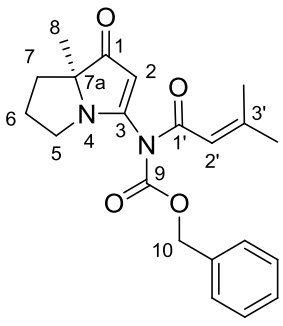
(*S*)-*tert*-Butyl 7a-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-3-yl(3-methylbut-2-enoyl)carbamate (1.72)



On a 0.099 mmol scale, *carbamate* **1.72** was obtained as a colourless oil (17 mg, 50%) after purification by flash chromatography (SiO_2, ether).

R_f 0.42 (ethyl acetate); $[\alpha]_D^{20}$ +45.3 (c 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3346br, 3203br, 2973br, 2381m, 1749s, 1635br, 1297br, 1152br, 800br; δ_H (400 MHz, $CDCl_3$) 1.36 (3H, s, C(8)**H$_3$**), 1.51 (9H, s, C(C**H$_3$**)$_3$), 1.52-1.63 (1H, m, C(7)**H**H′), 1.82 (1H, ddd, *J* 12.0, 6.5, 2.0 Hz, C(7)H**H′**), 1.99 (3H, d, *J* 1.0 Hz, C(3′)C**H$_3$**), 2.20-2.36 (2H, m, C(6)**H$_2$**), 2.23 (3H, d, *J* 1.0 Hz, C(3′)C**H$_3$**), 3.36 (1H, ddd, *J* 12.0, 8.5, 3.5 Hz, C(5)**H**H′), 3.67 (1H, dt, *J* 12.0, 8.5 Hz, C(5)H**H′**), 5.80 (1H, part resolved sept, *J* 1.0 Hz, C(2′)**H**), 6.87 (1H, s, C(2)**H**); δ_C (100 MHz, $CDCl_3$) 20.8 (C(3′)**C**H_3), 21.3 (**C**(8)H_3), 27.80 (**C**(6)H_2), 27.83 (C(3′)**C**H_3), 28.2 (C(**C**H_3)$_3$), 32.9 (**C**(7)H_2), 43.7 (**C**(5)H_2), 72.0 (**C**(7a)), 79.0 (**C**$(CH_3)_3$), 103.8 (**C**(2)H), 113.9 (**C**(2′)H), 161.2, 162.0 and 163.4 (**C**(3), **C**(9) and **C**(3′)), 168.9 (**C**(1′)), 171.9 (**C**(1)); HRMS found 357.1789; $C_{18}H_{26}N_2NaO_4$ (MNa^+) requires 357.1785.

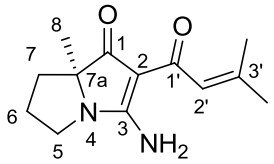
(*S*)-Benzyl 7a-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-3-yl(3-methylbut-2-enoyl)carbamate (1.73)



On a 0.105 mmol scale, *carbamate* **1.73** was obtained as a colourless oil (37 mg, 96%) after purification by flash chromatography (SiO_2, petrol/ether, 1:1).

R_f 0.46 (ether); $[\alpha]_D^{21}$ +11.7 (c 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2977br, 1758s, 1676s, 1601br, 1446m, 1375m, 1345m, 1255br, 1152br, 1089s, 926m, 883w, 855br, 799w, 752m, 699m; δ_H (400 MHz, $CDCl_3$) 1.38 (3H, s, C(8)**H$_3$**), 1.53-1.64 (1H, m, C(7)**H**H′), 1.79-1.86 (1H, m, C(7)H**H′**), 1.99 (3H, s, C(3′)C**H$_3$**), 2.22-2.38 (5H, m, C(3′)C**H$_3$** and C(6)**H$_2$**), 3.33-3.41 (1H, m, C(5)**H**H′), 3.64-3.74 (1H, m, C(5)H**H′**), 5.11-5.21 (2H, m, C(10)**H$_2$**), 5.80 (1H, s, C(2′)**H**), 6.95 (1H, s, C(2)**H**), 7.23-7.36 (3H, m, **Ar**), 7.39-7.44 (2H, m, **Ar**); δ_C (100 MHz, $CDCl_3$) 20.8 (C(3′)**C**H_3), 21.2 (**C**(8)H_3), 27.8 (C(3′)**C**H_3), 27.9 (**C**(6)H_2), 32.8 (**C**(7)H_2), 43.5 (**C**(5)H_2), 67.1 (**C**(10)H_2), 72.2 (**C**(7a)), 103.8 (**C**(2)H), 113.8 (**C**(2′)H), 127.7, 128.27 and 128.33 (Ar **C**H), 137.0 (Ar **C**), 161.1 (**C**(3′)), 162.6 (**C**(3)), 163.7 (**C**(9)), 169.5 (**C**(1′)), 172.9 (**C**(1)); *m/z* (ESI^+) 287 (15%), 369 (100, MH^+), 370 (71), 737 (78, M_2H^+), 738 (71), 739 (10), 759 (68, M_2Na^+), 760 (16); HRMS found 391.1622; $C_{21}H_{24}N_2O_4Na$ (MNa^+) requires 391.1628.

(*S*)-3-Amino-7a-methyl-2-(3-methylbut-2-enoyl)-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-1-one (1.75)

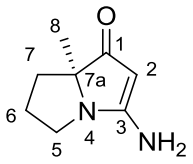


Caesium fluoride (40.2 mg, 0.27 mmol) was added to a solution of carbamate **1.70** (20 mg, 0.053 mmol) in DMF (0.5 mL). The mixture was heated to 90 °C under argon and stirred for 1 h before being cooled to RT. Methanol (0.5 mL) was added and the solution concentrated *in vacuo*. The residue was diluted in ether (2 mL), filtered and the filtrate evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 9:1, ethyl acetate/methanol) gave *amine* **1.75** as an off-white, waxy solid (12 mg, 97%).

R_f 0.20 (3:1, ethyl acetate/petrol); m.p. 152 °C decomposition; $[\alpha]_D^{23}$ –2.4 (c 1.0 in $CHCl_3$); ν_{max} (KBr disc)/cm^{-1} 3287m, 2970m, 2925s, 2820m, 1591s, 1516s, 1464m, 1374m, 1338w, 1261s, 1232w, 1090s,

1032s, 869m, 803s; δ_H (500 MHz, $CDCl_3$) 1.33 (3H, s, C(8)**H$_3$**), 1.63-1.70 (1H, m, C(7)**H**H′), 1.78-1.84 (1H, m, C(7)H**H′**), 1.95 (3H, m, C(3′)C**H$_3$**), 2.10-2.18 (1H, m, C(6)**H**H′), 2.19 (3H, m, C(3′)C**H$_3$**), 2.21-2.27 (1H, m, C(6)H**H′**), 3.28-3.35 (1H, m, C(5)**H**H′), 3.40-3.46 (1H, m, C(5)H**H′**), 5.61 (1H, br s, **NH**H′), 7.16-7.19 (1H, m, C(2′)**H**), 9.39 (1H, br s, NH**H′**); δ_C (125 MHz, $CDCl_3$) 21.1 (C(3′)**C**H_3), 21.8 (**C**(8)H_3), 26.5 (**C**(6)H_2), 28.0 (C(3′)**C**H_3), 31.8 (**C**(7)H_2), 45.6 (**C**(5)H_2), 74.5 (**C**(7a)), 98.9 (**C**(2)), 123.5 (**C**(2′)H), 153.1 (**C**(3′)) 173.2 (**C**(3)), 187.6 (**C**(1′)), 195.9 (**C**(1)); *m/z* (ESI^-) 233.2 (100%, $[M–H]^-$), 234.1 (28); HRMS found 235.1438; $C_{13}H_{19}N_2O_2$ (MH^+) requires 235.1441.

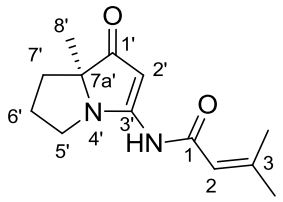
(*S*)-3-Amino-7a-methyl-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-1-one (1.74)



Azide **1.59** (20 mg, 0.10 mmol) was dissolved in AcOH (95% aq., 0.83 mL) and heated at reflux under argon for 40 min before being cooled to RT and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 17:3, ethyl acetate/methanol) provided *amine* **1.74** as an off-white, waxy solid (12.5 mg, 85%).

R_f 0.18 (17:3, ethyl acetate/methanol); m.p. 42 °C; $[\alpha]_D^{25}$ +12.0 (c 1.0 in $CHCl_3$); ν_{max} (KBr disc)/cm^{-1} 3418br, 2964m, 1684m, 1608m, 1550m, 1458m, 1262s, 1099s, 1024s, 802s; δ_H (500 MHz, $CDCl_3$) 1.34 (3H, s, C(8)**H$_3$**), 1.69-1.84 (2H, m, C(7)**H$_2$**), 2.00-2.18 (2H, m, C(6)**H$_2$**), 3.18-3.31 (2H, m, C(5)**H$_2$**), 4.52 (1H, s, C(2)**H**), 4.87 (2H, br, N**H$_2$**); δ_C (125 MHz, $CDCl_3$) 22.6 (**C**(8)H_3), 27.1 (**C**(6)H_2), 32.2 (**C**(7)H_2), 46.8 (**C**(5)H_2), 75.5 (**C**(7a)), 83.7 (**C**(2)H), 174.7 (**C**(3)), 201.1 (**C**(1)); *m/z* (ESI^+) 153.1 (52%, MH^+), 216.1 (50), 242.3 (29), 305.2 (35), 327.2 (59, M_2Na^+), 471.3 (100, M_3Na^+); HRMS found 175.0845; $C_8H_{12}N_2ONa$ (MNa^+) requires 175.0842.

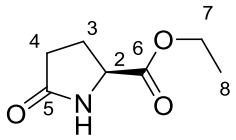
(*S*)-3-Methyl-*N*-(7a-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-3-yl)but-2-enamide (1.51)



Sodium hydride (60% dispersion in mineral oil, 5.8 mg, 0.14 mmol) was added to a solution of amine **1.74** (12.5 mg, 0.082 mmol) in THF (1.4 mL). The resultant slurry was stirred for 10 min at RT before a solution of 3,3-dimethylacryloyl chloride (9.1 μL, 82 μmol) in THF (1.4 mL) was added *via* cannula and the reaction mixture stirred for a further 30 min. The reaction was quenched with water (1 mL), extracted with DCM (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, ethyl acetate) gave *target compound* **1.51** as a white solid (13.1 mg, 68%).

R_f 0.13 (ethyl acetate); m.p. 162 °C; $[\alpha]_D^{20}$ +75.2 (c 1.0 in $CHCl_3$); ν_{max} (KBr disc)/cm^{-1} 3421br, 3184br, 2927br, 1714m, 1623s, 1572m, 1496br, 1398w, 1366w, 1333w, 1261w, 1227m, 1134s, 1042m, 847m, 791br; δ_H (500 MHz, $CDCl_3$) 1.33 (3H, s, C(8′)**H₃**), 1.80-1.87 (1H, ddd, *J* 12.5, 6.6, 5.5 Hz, C(7′)**H**H′), 1.80-1.87 (1H, m, C(7′)H**H′**), 1.95 (3H, d, *J* 1.0 Hz, C(3)C**H₃**), 1.93-2.13 (2H, m, C(6′)**H₂**), 2.24 (3H, d, *J* 1.0 Hz, C(3)C**H₃**), 3.16 (2H, app. dt, *J* 10.5, 7.5 Hz, C(5′)**H**H′), 3.33 (2H, ddd, *J* 10.5, 7.0, 5.5 Hz, C(5′)H**H′**), 5.74 (1H, s, C(2′)**H**), 5.77 (1H, sept, *J* 1.0 Hz, C(2)**H**), 7.59 (1H, br s, N**H**); δ_C (100 MHz, $CDCl_3$) 20.5 (C(3)**C**H_3), 22.6 (**C**(8′)H_3), 26.7 (**C**(6′)H_2), 27.7 (C(3)**C**H_3), 32.2 (**C**(7′)H_2), 48.2 (**C**(5′)H_2), 73.4 (**C**(7a′)), 92.2 (**C**(2′)H), 117.0 (**C**(2)H), 159.1 (**C**(3)), 163.5 (**C**(3′)), 168.7 (**C**(1)), 205.1 (**C**(1′)); *m/z* (ESI^+) 153 (8%, $[M\text{-}COCHC(CH_3)_2]H^+$), 235 (91, MH^+), 293 (100, $[M+MeCN+NH_4^+]$), 491 (54, M_2Na^+); HRMS found 257.1264; $C_{13}H_{18}N_2O_2Na$ (MNa^+) requires 257.1260.

(*S*)-Ethyl 5-oxopyrrolidine-2-carboxylate (1.167)

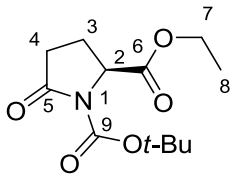


Thionyl chloride (1.36 mL, 18.6 mmol) was added dropwise to a solution of DMF (20 mL) and L-pyroglutamic acid (1.0 g, 7.75 mmol) in ethanol (5.9 mL) stirring at −15 °C. The reaction was warmed to RT over 16 h before being passed through a silica plug and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, ethyl acetate) gave ethyl ester **1.167** as a white crystalline solid (1.1 g, 90%).

On a larger scale (100 g) the crude product was taken through to the next step without purification.

m.p. 51 °C [lit. reported 48-50 °C];[6] $[\alpha]_D^{24}$ +3.4 (c 1.0 in EtOH) [lit. reported $[\alpha]_D^{20}$ +2.4 (c 10.0 in EtOH)][6]; δ_H (500 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.0 Hz, C(8)**H$_3$**), 2.19-2.26 (1H, m, C(3)**H**H′), 2.30-2.42 (2H, m, C(3)H**H′** and C(4)**H**H′), 2.48-2.52 (1H, m, C(4)H**H′**), 4.19-4.25 (3H, m, C(2)**H** and C(7)**H$_2$**), 6.39 (1H, br, N**H**); δ_C (125 MHz, $CDCl_3$) 14.1 (**C**(8)H_3), 24.8 (**C**(3)H_2), 29.2 (**C**(4)H_2), 55.4 (**C**(2)H), 61.6 (**C**(7)H_2), 172.0 (**C**(6)), 177.8 (**C**(5)). NMR data as reported.[6]

(*S*)-1-*tert*-Butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate (1.108)

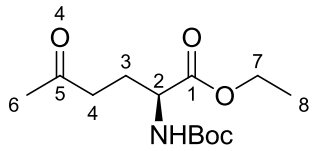


DMAP (65.8 mg, 0.54 mmol) and di-*tert*-butyl dicarbonate (1.36 mL, 5.93 mmol) were added to a solution of amide **1.167** (850 mg, 5.39 mmol) in acetonitrile (14.1 mL) and the reaction stirred for 2 h at RT. The reaction mixture was concentrated *in vacuo* and the residue dissolved in ether (15 mL) and $KHSO_4$ (1M aq., 15 mL). The layers were separated and the organic layer washed with further $KHSO_4$

(1M aq., 15 mL), $NaHCO_3$ (sat. aq., 15 mL) and brine (15 mL), dried and evaporated *in vacuo* to give ester **1.108** as a white solid (1.25 g, 90%).

m.p. 52 °C [lit. reported 53-54 °C][7]; $[\alpha]_D^{20}$ −35.3 (c 1.0 in methanol) [lit. reported $[\alpha]_D^{20}$ −39.8 (c 0.5 in methanol)][7]; δ_H (500 MHz, $CDCl_3$) **Major rotamer**: 1.30 (3H, t, *J* 7.0 Hz, C(8)**H$_3$**), 1.50 (9H, s, C(C**H$_3$**)$_3$), 2.00-2.06 (1H, m, C(3)**H**H′), 2.27-2.37 (1H, m, C(4)**H**H′), 2.51 (1H, app. dd, *J* 9.5, 4.0 Hz, C(3)H**H′**), 2.61 (1H, app. t, *J* 10.0 Hz, C(4)H**H′**), 4.24 (2H, q, *J* 7.0 Hz, C(7)**H$_2$**), 4.60 (1H, dd, *J* 9.5, 3.0 Hz, C(2)**H**); **Minor rotamer**: 1.30 (3H, t, *J* 7.0 Hz, C(8)**H$_3$**), 1.50 (9H, s, C(C**H$_3$**)$_3$), 2.00-2.06 (1H, m, C(3)**H**H′), 2.27-2.37 (1H, m, C(4)**H**H′), 2.47 (1H, app. dd, *J* 9.5, 3.5 Hz, C(3)H**H′**), 2.65 (1H, app. t, *J* 10.0 Hz, C(4)H**H′**), 4.24 (2H, q, *J* 7.0 Hz, C(7)**H$_2$**), 4.60 (1H, dd, *J* 9.5, 3.0 Hz, C(2)**H**); δ_C (125 MHz, $CDCl_3$) 14.2 (**C**(8)H_3), 21.5 (**C**(3)H_2), 27.9 (C(**C**H_3)$_3$), 31.1 (**C**(4)H_2), 58.9 (**C**(2)H), 61.6 (**C**(7)H_2), 83.5 (**C**$(CH_3)_3$), 149.3 (**C**(9)), 171.3 (**C**(6)), 173.3 (**C**(5)). NMR data as reported.[7]

(*S*)-Ethyl 2-(*tert*-butoxycarbonylamino)-5-oxohexanoate (1.107)



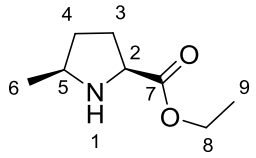
Methyl magnesium bromide (3.0 M in ether, 1.94 mL, 5.83 mmol) was slowly added to a solution of amide **1.108** (1.25 g, 4.86 mmol) in THF (3.25 mL) stirring at −40 °C. The reaction was stirred for 2 h before being warmed to −20 °C and kept in the freezer overnight. The reaction was then quenched with NH_4Cl (sat. aq., 10 mL) followed by HCl (1 M aq., 10 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 1:1, petrol/ether) gave amino ester **1.107** as a colourless liquid (1.05 g, 79%).

On a larger scale (100 g) the crude material was taken on to the next step without purification.

δ_H (500 MHz) 1.28 (3H, t, *J* 7.0 Hz, C(8)**H$_3$**), 1.44 (9H, s, C(C**H$_3$**)$_3$), 1.88 (1H, dtd, *J* 14.5, 8.0, 6.0 Hz, C(3)**H**H′), 2.09-2.15 (1H, m, C(3)H**H′**), 2.16 (3H, s, C(6)**H$_3$**), 2.51 (1H, ddd, *J* 18.0, 8.0, 6.5 Hz, C(4)**H**H′), 2.59 (1H, app. dt, *J* 18.0, 7.5 Hz, C(4)H**H′**), 4.19 (2H, q, *J* 7.0 Hz, C(7)**H$_2$**), 4.22-4.28 (1H,

br s, C(2)**H**), 5.08-5.13 (1H, br s, N**H**); δ_C (125 MHz) 14.1 (**C**(8)H_3), 26.6 (**C**(3)H_2), 28.3 (C(**C**H_3)$_3$), 30.1 (**C**(6)H_3), 39.4 (**C**(4)H_2), 52.9 (**C**(2)H), 61.5 (**C**(7)H_2), 79.9 (**C**(CH_3)$_3$), 155.5 (N**C**=O), 172.3 (**C**(1)), 207.5 (**C**(5)). NMR data as reported.[8]

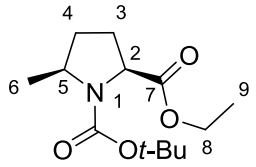
(2*S*,5*S*)-Ethyl 5-methylpyrrolidine-2-carboxylate (1.109)



Amino ester **1.107** (17.6 g, 64.4 mmol)) was dissolved in DCM (26.3 mL), and TFA (26.3 mL) was added dropwise. The reaction was stirred at RT under argon for 3 h then evaporated to dryness. The residue was dissolved in ethanol (228 mL) and 10% palladium on carbon (2.13 g) was added. The flask was purged several times with Argon, then evacuated and filled with hydrogen. The reaction mixture was stirred under a balloon of hydrogen for 24 h before being filtered through celite and eluted with chloroform and the filtrate evaporated to dryness *in vacuo* to give *amine* **1.109** as a pale yellow oil (9.5 g, 94%). An analytical sample was purified by flash chromatography (SiO_2, 9:1, ethyl acetate/methanol) for characterisation.

$[\alpha]_D^{25}$ −14.0 (c 1.0 in methanol); ν_{max} (thin film)/cm^{-1} 3461br, 2986w, 1746m, 1679s, 1441m, 1306w, 1206s, 1135s, 840w, 800m, 723m; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.0 Hz, C(9)**H$_3$**), 1.49 (3H, d, *J* 6.5 Hz, C(6)**H$_3$**), 1.62-1.74 (1H, m, C(4)**H**H′), 2.18-2.31 (2H, m, C(3)**H**H′ and C(4)H**H′**), 2.38-2.50 (1H, m, C(3)H**H′**), 3.85-3.94 (1H, m, C(5)**H**), 4.27 (2H, q, *J* 7.0 Hz, C(8)**H$_2$**), 4.48 (1H, dd, *J* 9.0, 4.5 Hz, C(2)**H**); δ_C (100 MHz, $CDCl_3$) 13.7 (**C**(9)H_3), 17.4 (**C**(6)H_3), 28.3 (**C**(3)H_2), 31.1 (**C**(4)H_2), 57.4 (**C**(5)H), 59.4 (**C**(2)H), 63.4 (**C**(8)H_2), 169.7 (**C**(7)); *m/z* (ESI^+) 144 (43%), 147 (48), 158 (47, MH^+), 187 (46), 198 (31), 399 (74), 402 (100), 413 (60); HRMS found 180.1002; $C_8H_{15}NO_2Na$ (MNa^+) requires 180.0995.

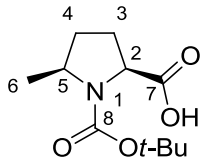
(2*S*,5*S*)-1-*tert*-Butyl 2-ethyl 5-methylpyrrolidine-1,2-dicarboxylate (1.168)



TEA (16.8 mL, 121 mmol), DMAP (370 mg, 3.02 mmol) and di-*tert*-butyl dicarbonate (15.3 mL, 66 mmol) were added slowly to a solution of amine **1.109** (9.5 g, 60.4 mmol) in DCM (133 mL). The reaction was stirred at RT for 16 h before being quenched with HCl (1 M aq., 200 mL). The organic layer was separated, washed with further HCl (150 mL) and brine (150 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give carbamate **1.168** as a pale yellow liquid (10.2 g, 66%).

$[\alpha]_D^{25}$ −37.5 (c 1.45 in methanol) [lit. reported $[\alpha]_D^{25}$ −35.8 (c 1.45 in methanol)];[8] δ_H (500 MHz, $CDCl_3$) 1.25-1.50 (15H, m, C(6)**H$_3$**, C(9)**H$_3$** and C(C**H$_3$**)$_3$), 1.59-1.68 (1H, m, C(4)**H**H′), 1.95-2.08 (2H, m, C(4)H**H′** and C(3)**H**H′), 2.12-2.23 (1H, m, C(3)H**H′**), 3.89-4.09 (1H, m, C(5)**H**), 4.13-4.36 (3H, m, C(2)**H** and C(8)**H$_2$**); δ_C (125 MHz, $CDCl_3$) **Major rotamer**: 14.2 (**C**(9)H_3), 19.8 (**C**(6)H_3), 28.3 (C(**C**H_3)$_3$), 28.4 (**C**(3)H_2), 31.7 (**C**(4)H_2), 60.3 (**C**(5)H), 60.8 (**C**(8)H_2), 65.9 (**C**(2)H), 79.7 (**C**(CH_3)$_3$), 153.4 (N**C**=O), 173.5 (**C**(7)); **Minor rotamer**: 15.3 (**C**(9)H_3), 20.6 (**C**(6)H_3), 28.3 (C(**C**H_3)$_3$), 28.9 (**C**(3)H_2), 32.5 (**C**(4)H_2), 60.1 (**C**(5)H), 60.8 (**C**(8)H_2), 65.9 (**C**(2)H), 79.7 (**C**(CH_3)$_3$), 154.2 (N**C**=O), 173.2 (**C**(7)). NMR data as reported.[8]

(2*S*,5*S*)-1-(*tert*-Butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid (1.110)



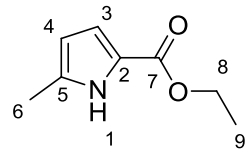
Ester **1.168** (5.0 g, 19.4 mmol) was dissolved in ethanol (20.4 mL) and LiOH (1.7 M aq., 19.4 mL) and stirred at RT for 4 h before removal of solvent *in vacuo*. The residue was diluted in ether (30 mL)

and water (30 mL), the layers separated and the organic layer discarded. The aqueous layer was acidified (1 M HCl) and extracted with ethyl acetate (3 × 30 mL). The combined ethyl acetate layers were dried ($MgSO_4$) and evaporated *in vacuo* to yield the acid **1.110** as a white crystalline solid (4.4g, 99%).

m.p. 81 °C; $[\alpha]_D^{25}$ –76.3 (c 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, s, C(6)**H$_3$**), 1.36-1.51 (9H, m, C(C**H$_3$**)$_3$), 1.58-1.69 (1H, m, C(4)**H**H′), 1.96-2.29 (3H, m, C(3)**H$_2$** and C(4)H**H′**), 3.84-4.10 (1H, m, C(5)**H**), 4.16-4.41 (1H, m, C(2)**H**), 10.55-10.94 (1H, br, CO_2**H**); δ_C (100 MHz, $CDCl_3$) **Both rotamers**: 19.8 and 20.6 (**C**(6)H_3), 27.3 and 28.9 (**C**(3)H_2), 28.4 (C(**C**H_3)$_3$), 31.8 and 32.5 (**C**(4)H_2), 54.1 and 54.5 (**C**(5)H), 60.1 (**C**(2)H), 80.1 and 81.0 (**C**$(CH_3)_3$), 153.5 and 155.8 (**C**(8)), 176.6 and 179.3 (**C**(7)). NMR data as reported.[9]

Crystal structure obtained (see **Appendix A**).

Ethyl 5-methyl-1H-pyrrole-2-carboxylate (1.111)

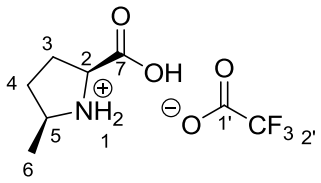


In larger scale attempts to obtain acid **1.110** (≥10g) a second compound was obtained in the ether extraction and identified as compound **1.111** (obtained as a brown crystalline solid, 540 mg, 9%).

δ_H (400 MHz, $CDCl_3$) 1.36 (3H, t, *J* 7.0 Hz, C(9)**H$_3$**), 2.32 (3H, s, C(6)**H$_3$**), 4.31 (2H, q, *J* 7.0 Hz, C(8)**H$_2$**), 5.96 (1H, m, C(4)**H**), 6.82 (1H, m, C(3)**H**), 9.14 (1H, br, N**H**); δ_C (100 MHz, $CDCl_3$) 13.1 (**C**(6)H_3), 14.5 (**C**(9)H_3), 60.0 (**C**(8)H_2), 108.9 (**C**(3)H), 116.0 (**C**(4)H), 121.4 (**C**(2)), 133.7 (**C**(5)), 161.3 (**C**(7)). Data as reported.[10]

Crystal structure obtained (see **Appendix B**).

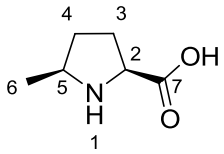
(2*S*,5*S*)-2-carboxy-5-methylpyrrolidinium 2,2,2-trifluoroacetate (1.112)



TFA (5.9 mL, 77.1 mmol) was added to acid **1.110** (500 mg, 2.20 mmol) dissolved in DCM (4.0 mL) and the reaction stirred for ten minutes at RT. The reaction was evaporated to dryness *in vacuo* to give *TFA salt* **1.112** as a brown oil (535 mg, 100%).

ν_{max} (thin film)/cm^{-1} 3420br, 2950br, 1679br, 1415m, 1329m, 1202s, 1138s, 837m, 801m, 722m; δ_H (400 MHz, $CDCl_3$) 1.46 (3H, d, *J* 6.5 Hz, C(6)**H$_3$**), 1.65-1.77 (1H, C(4)**H**H′), 2.21-2.33 (2H, m, C(4)H**H′** and C(3)**H**H′), 2.36-2.49 (1H, m, C(3)H**H′**), 3.77 (1H, dq, *J* 16.0, 6.5 Hz, C(5)**H**), 4.42 (1H, dd, *J* 9.5, 6.5 Hz, C(2)**H**); δ_C (100 MHz, $CDCl_3$) 16.3 (**C**(6)H$_3$), 27.6 (**C**(3)H$_2$), 30.7 (**C**(4)H$_2$), 57.3 (**C**(5)H), 59.7 (**C**(2)H), 115.0 (q, *J* 284.5 Hz, **C**(2′)H), 160.1 (q, *J* 38.5 Hz, **C**(1′)H), 170.5 (**C**(7)); δ_F (377 MHz, $CDCl_3$) −76.8; *m/z* (ESI$^+$) 130 (39%, [M−CF_3CO_2]$^+$), 147 (42, MNH_4^+), 357 (34), 374 (100), 413 (88), 443 (40); HRMS data unobtainable.

(2*S*,5*S*)-5-Methylpyrrolidine-2-carboxylic acid (1.104)

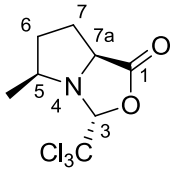


Acid **1.110** (100 mg, 0.44 mmol) was dissolved in toluene (8.7 mL) and silica (2.18 g) was added. The slurry was heated at reflux for 18 h and then cooled to RT before being filtered through celite with DCM/MeOH (9:1, 200 mL). The filtrate was evaporated *in vacuo* to give amino acid **1.104** (40 mg, 70%).

δ_H (500 MHz, D_2O) 1.42 (3H, d, *J* 6.5 Hz, C(6)**H$_3$**), 1.59-1.68 (1H, m, C(4)**H**H′), 2.12-2.19 (1H, m, C(4)H**H′**), 2.22-2.33 (2H, m, C(3)**H$_2$**), 3.69 (1H, dq, *J* 16.0, 6.5 Hz, C(5)**H**), 4.02 (1H, dd, *J* 9.0, 5.0

Hz, C(2)**H**); δ_C (125 MHz, D_2O) 17.9 (**C**(6)H_3), 30.2 (**C**(3)H_2), 32.5 (**C**(4)H_2), 58.2 (**C**(5)H), 62.8 (**C**(2)H), 174.4 (**C**(7)). Data as reported.[11]

(3*R*,5*S*,7a*S*)-5-Methyl-3-(trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (1.113)

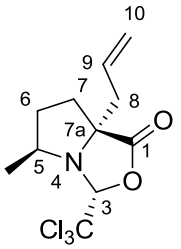


Chloral hydrate (546 mg, 3.3 mmol) was added to a solution of amino acid salt **1.112** (530 mg, 2.18 mmol) in chloroform (2.5 mL) and the resulting mixture refluxed with a soxhlet condenser containing 4 Å MS. After 16 h the reaction mixture was cooled, washed with water (10 mL) and the aqueous layer was extracted with chloroform (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), evaporated *in vacuo* and the residue passed through a plug of silica and eluted with to yield *bicycle* **1.113** as a white crystalline solid (230 mg, 41%).

R_f 0.68 (ether); m.p. 86 °C; $[\alpha]_D^{22}$ +23.1 (c 1.0 in $CHCl_3$); ν_{max} (KBr disc)/cm^{-1}2980m, 1794s, 1586br, 1465m, 1388m, 1327m, 1293m, 1263m, 1188s, 1172s, 1128s, 1084s, 1030m, 1004s, 948s, 895s, 809s, 773s, 742s, 647s; δ_H (500 MHz, $CDCl_3$) 1.32-1.35 (1H, m, C(6)**H**H′), 1.38 (3H, d, *J* 7.0 Hz, C(5)C**H**$_3$), 2.05 (1H, app. dq, *J* 12.5, 5.5 Hz, C(6)H**H′**), 2.18-2.23 (2H, m, C(7)**H**$_2$), 3.59-3.66 (1H, m, C(5)**H**), 4.23 (1H, dd, *J* 7.0, 5.5 Hz, C(7a)**H**), 5.51 (1H, s, C(3)**H**); δ_C (125 MHz, $CDCl_3$) 16.2 (C(5)**C**H_3), 29.1 (**C**(6)H_2), 33.3 (**C**(7)H_2), 60.2 (**C**(5)H), 62.8 (**C**(7a)H), 96.4 (**C**(3)H), 101.4 (**C**Cl_3), 176.3 (**C**(1)); *m/z* (ESI^+) 130 (43%), 152 (68), 258 (40, MH^+), 280 (100, MNa^+), 314 (49), 410 (70), 539 (56); HRMS found 279.9667; $C_8H_{10}Cl_3NNaO_2$ (MNa^+) requires 279.9669.

Crystal structure obtained (see **Appendix C**).

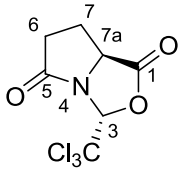
(3*R*,5*S*,7a*R*)-7a-Allyl-5-methyl-3-(trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3*H*)-one (1.114)



tert-Butyllithium (1.7 M in pentane, 455 µL, 0.77 mmol) was added to a solution of diisopropylamine (115 µL, 0.82 mmol) in THF (0.35 mL) at −78 °C. The mixture was stirred for 50 mins before being added to a solution of oxazolidinone **1.113** (100 mg, 0.39 mmol) in THF (2.0 mL) stirring at −78 °C and the resulting solution was warmed to −30 °C. After 30 mins allyl iodide (74.9 µL, 0.82 mmol) was added and the reaction stirred for 2 h 30. The reaction was quenched with water (5 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (sat. aq., 20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 8:1 petrol/ether) gave *allylated oxizolidinone* **1.114** as a clear oil (10 mg, 9%).

R_f 0.44 (4:1, petrol/ether); $[\alpha]_D^{26}$ −17.0 (c 0.5 in $CHCl_3$)**;** ν_{max} (thin film) 2963s, 2917m, 2850w, 1788w, 1413w, 1261s, 1020br, 932w, 799s, 668m; δ_H (500 MHz, $CDCl_3$) 1.28-1.32 (1H, m, C(6)**H**H′), 1.44 (3H, d, *J* 7.0 Hz, C(5)C**H₃**), 1.92-1.98 (1H, m, C(6)H**H′**), 2.03-2.10 (1H, m, C(7)**H**H′), 2.13-2.18 (1H, m, C(7)H**H′**), 2.58 (1H, dd, *J* 14.0, 8.5 Hz, C(8)**H**H′), 2.76 (1H, ddt, *J* 14.0, 6.0, 1.5 Hz, C(8)H**H′**), 3.36-3.44 (1H, m, C(5)**H**), 5.18-5.23 (2H, m, C(10)**H₂**), 5.96 (1H, s, C(3)**H**), 5.80-5.96 (1H, m, C(9)**H**); δ_C (125 MHz, $CDCl_3$) 16.1 (C(5)**C**H_3), 33.5 (**C**(6)H_2), 36.0 (**C**(7)H_2), 41.3 (**C**(8)H_2), 61.9 (**C**(5)H), 71.4 (**C**(7a)), 94.8 (**C**(3)H), 101.1 (**C**Cl_3), 119.9 (**C**(10)H_2), 132.1 (**C**(9)H), 177.3 (**C**(1)); m/z (ESI^+) 320 (100%, MNa^+), 352 (42, [M+MeOH+Na^+]), 616 (54), 765 (48); HRMS found 319.9982; $C_{11}H_{14}Cl_3NNaO_2$ (MNa^+) requires 319.9982.

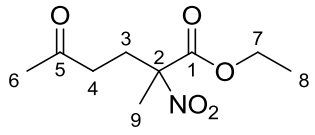
(3*R*,7a*S*)-3-(Trichloromethyl)dihydropyrrolo[1,2-c]oxazole-1,5(3*H*,6*H*)-dione (1.115)



To a solution of L-pyroglutamic acid (5.0 g, 38.7 mmol) in toluene (116 mL) was added chloral hydrate (9.61 g, 58.1 mmol) and PTSA monohydrate (206 mg, 1.08 mmol). The resulting slurry was stirred and heated vigorously under Dean-Stark conditions for 20 h. The resulting brown slurry was then filtered (hot) and the filtrate evaporated *in vacuo*. The residue was washed with hot ethyl acetate (50 mL) and the mixture left to cool before being filtered to obtain **1.115** as white crystals (2.45 g, 25%).

$[\alpha]_D^{26}$ +36.5 (c 2.0 in C_6H_6); [lit. reported +43.5 (c 2.0 in C_6H_6)];[12] δ_H (400 MHz, $CDCl_3$) 2.25-2.36 (1H, m, C(7)**H**H′), 2.56 (1H, ddd, *J* 16.5, 9.0, 1.5 Hz, C(6)**H**H′), 2.67-2.77 (1H, m, C(7)H**H′**), 2.87 (ddd, *J* 16.5, 11.5, 10.0 Hz, C(6)H**H′**), 4.71 (1H, t, *J* 8.5 Hz, C(7a)**H**), 6.08 (1H, s, C(3)**H**); δ_C (100 MHz, $CDCl_3$) 24.6 (**C**(7)H_2), 31.9 (**C**(6)H_2), 56.8 (**C**(7a)H), 76.7 (**C**Cl_3), 92.4 (**C**(3)H), 171.9 (**C**(1)), 178.9 (**C**(5)). Data as reported.[12]

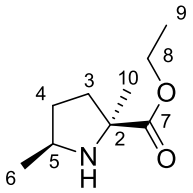
Ethyl 2-methyl-2-nitro-5-oxohexanoate (1.116)



Ethyl-2-nitropropionate (3.54 mL, 27.2 mmol) and DABCO (305 mg, 2.72 mmol) were stirred in DCM (40 mL) at RT for 10 min before methyl vinyl ketone (5.58 mL, 68.8 mmol) was added. The reaction mixture was stirred for 5 h at RT under argon and then filtered through a silica plug with ether. The filtrate was evaporated *in vacuo* to provide nitro ketone **1.116** as a colourless oil (5.91 g, 100%).

δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.0 Hz, C(8)**H₃**), 1.78 (3H, s, C(9)**H₃**), 2.17 (3H, s, C(6)**H₃**), 2.38-2.59 (4H, m, C(3)**H₂** and C(4)**H₂**), 4.27 (2H, q, *J* 7.0 Hz, C(7)**H₂**); δ_C (100 MHz, $CDCl_3$) 13.8 (**C**(8)H_3), 22.0 (**C**(9)H_3), 30.0 (**C**(6)H_3), 30.2 (**C**(4)H_2), 37.9 (**C**(3)H_2), 63.0 (**C**(7)H_2), 91.8 (**C**(2)), 167.1 (**C**(1)), 205.8 (**C**(5)). Data as reported.[13]

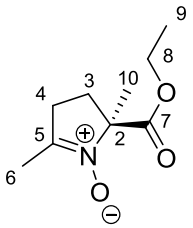
(2*SR*,5*SR*)-Ethyl 2,5-dimethylpyrrolidine-2-carboxylate (1.117)



Nitro ester **1.116** (100 mg, 0.46 mmol) was dissolved in ethanol (2.3 mL) and Na_2SO_4 (69 mg, 0.48 mmol) and palladium on carbon (5%, 98 mg, 0.046 mmol) were added. The flask was purged several times with argon, then evacuated and filled with hydrogen. The reaction was stirred under an atmosphere of hydrogen for 72 h and monitored by ^{1}H NMR. The reaction mixture was then filtered through a celite pad with chloroform and the filtrate evaporated *in vacuo* to furnish amine **1.117** as a yellow oil (77 mg, 98%).

δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.5 Hz, C(6)**H$_3$**), 1.18-1.22 (1H, m, C(4)**H**H′), 1.25 (3H, t, *J* 7.0 Hz, C(9)**H$_3$**), 1.35 (3H, s, C(10)**H**$_3$), 1.69 (1H, ddd, *J* 12.5, 10.0, 7.5 Hz, C(3)**H**H′), 1.90 (1H, dddd, *J* 12.5, 7.5, 6.0, 3.5 Hz, C(4)H**H′**), 2.22 (1H, ddd, *J* 12.5, 8.0, 3.5 Hz, C(3)H**H′**), 2.30-2.40 (1H, br, N**H**), 3.20-3.29 (1H, m, C(5)**H**), 4.16 (2H, q, *J* 7.0 Hz, C(8)**H$_2$**); δ_C (100 MHz, $CDCl_3$) 14.1 (**C**(9)H_3), 16.7 (**C**(10)H_3), 18.9 (**C**(6)H_3), 26.1 (**C**(4)H_2), 31.3 (**C**(3)H_2), 58.3 (**C**(5)H), 60.8 (**C**(8)H_2), 69.7 (**C**(2)), 175.5 (**C**(7)). Data as reported.[13]

(2*SR*)-(Ethoxycarbonyl)-2,5-dimethyl-3,4-dihydro-2H-pyrrole 1-oxide (1.118)

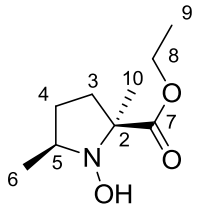


Nitro ester **1.116** (1.00 g, 4.60 mmol) was dissolved in ethanol (23 mL) and Na_2SO_4 (690 mg, 4.86 mmol) and palladium on carbon (5%, 980 mg, 0.46 mmol) were added. The flask was purged several times with argon, then evacuated and filled with hydrogen. The reaction was stirred under an

atmosphere of hydrogen for 2 h and monitored by ^{1}H NMR. The reaction mixture was then filtered through a celite pad with chloroform and the filtrate evaporated *in vacuo* to furnish oxime **1.118** as a colourless oil (852 mg, 100%).

δ_H (400 MHz, $CDCl_3$) 1.20-1.25 (3H, m, C(9)**H$_3$**), 1.64-1.65 (3H, m, C(10)**H$_3$**), 1.91-2.01 (1H, m, C(3)**H**H′), 2.03-2.05 (3H, m, C(6)**H$_3$**), 2.34-2.43 (1H, m, C(3)H**H′**), 2.55-2.66 (1H, m, C(4)**H**H′), 2.68-2.79 (1H, m, C(4)H**H′**), 4.08-4.27 (2H, m, C(8)**H$_2$**); δ_C (100 MHz, $CDCl_3$) 13.0 (**C**(6)H_3), 14.0 (**C**(9)H_3), 21.0 (**C**(10)H_3), 30.3 (**C**(3)H_2 and **C**(4)H_2) , 62.0 (**C**(8)H_2), 78.7 (**C**(2)), 144.9 (**C**(5)), 170.5 (**C**(7)). Data as reported.[13]

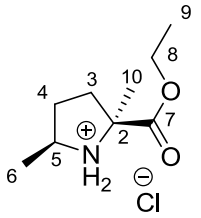
(2*SR*,5*SR*)-Ethyl 1-hydroxy-2,5-dimethylpyrrolidine-2-carboxylate (1.39)



Hydroxylamine **1.39** could be observed in the reduction of ester **1.117** if the reaction was not left to go to completion.

δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.0 Hz, C(6)**H$_3$**), 1.23-1.28 (3H, m, C(9)**H$_3$**), 1.33 3H, s, C(10)**H$_3$**), 1.34-1.41 (1H, m, C(4)**H**H′), 1.74 (1H, ddd, *J* 13.0, 10.0, 5.5 Hz, C(3)**H**H′), 1.83-1.95 (1H, m, C(4)H**H′**), 2.07-2.15 (1H, m, C(3)H**H′**), 3.01-3.11 (1H, m, C(5)**H**), 4.10-4.12 (2H, m, C(8)**H$_2$**), 5.28-5.39 (1H, br, O**H**); δ_C (100 MHz, $CDCl_3$) 14.2 (**C**(9)H_3), 20.9 (**C**(6)H_3), 26.7 (**C**(10)H_3), 34.6 (**C**(4)H_2), 38.5 (**C**(3)H_2), 54.6 (**C**(5)H), 61.2 (**C**(8)H_2), 65.9 (**C**(2)), 177.6 (**C**(7)). Data as reported.[13]

(2*SR*,5*SR*)-2-(Ethoxycarbonyl)-2,5-dimethylpyrrolidinium chloride (1.117·HCl)

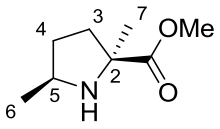


The *hydrochloride salt* **1.117** was obtained in small quantities during some hydrogenation attempts.

m.p. 138 °C; ν_{max} (KBr disc/cm^{-1}) 3430br, 2913br, 2520s, 1748s, 1465s, 1427m, 1395m, 1368s, 1288br, 1241s, 1192m, 1145s, 1114s, 1059m, 1016s, 853w, 803m, 764m; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.0 Hz, C(9)**H$_3$**), 1.53 (3H, d, *J* 6.5 Hz, C(6)**H$_3$**), 1.55-1.64 (1H, m, C(4)**H**H′), 1.83 (3H, s, C(10)**H$_3$**), 2.00-2.10 (1H, m, C(3)**H**H′), 2.20 (1H, dtd, *J* 13.5, 7.0, 2.5 Hz, C(4)H**H′**), 2.41 (1H, ddd, *J* 13.0, 7.0, 2.5 Hz, C(3)H**H′**), 4.04-4.15 (1H, m, C(5)**H**), 4.28 (2H, q, *J* 7.0 Hz, C(8)**H$_2$**); δ_C (100 MHz, $CDCl_3$) 14.0 (**C**(9)H_3), 18.4 (**C**(6)H_3), 21.7 (**C**(10)H_3), 31.5 (**C**(4)H_2), 36.4 (**C**(3)H_2), 56.5 (**C**(5)H), 63.2 (**C**(8)H_2), 69.0 (**C**(2)), 171.4 (**C**(7)); *m/z* (ESI$^+$) 172 (100%, [M−Cl]$^+$); HRMS found 172.1333; $C_9H_{18}NO_2$ ([M−Cl]$^+$) requires 172.1332.

Crystal structure obtained (see **Appendix D**)

(2*SR*,5*SR*)-Methyl 2,5-dimethylpyrrolidine-2-carboxylate (1.119)

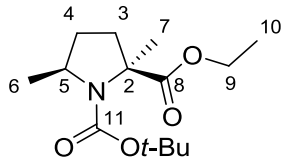


When the hydrogenation step was conducted in methanol, *methyl ester* **1.119** was obtained in varying quantities. A sample was purified by flash chromatography (SiO_2, 1:1, petrol/ether) for characterisation.

R_f 0.21 (1:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2962br, 1730s, 1450br, 1270m, 1146br, 914w, 733s; δ_H (500 MHz) 1.19 (3H, d, *J* 6.5 Hz, C(6)**H$_3$**), 1.38 (3H, s, C(7)**H$_3$**), 1.71 (1H, ddd, *J* 12.5, 10.5,

7.5 Hz, C(3)**H**H′), 1.88-2.00 (3H, m, C(4)$\mathbf{H_2}$ and N**H**), 2.24 (1H, ddd, *J* 12.5, 8.0, 3.0 Hz, C(3)**H**H′), 3.23-3.32 (1H, m, C(5)**H**), 3.73 (1H, s, $CO_2C\mathbf{H_3}$); δ_C (125 MHz) 20.9 (**C**(6)H_3), 26.6 (**C**(7)H_3), 34.6 (**C**(4)H_2), 38.5 (**C**(3)H_2), 52.4 ($CO_2\mathbf{C}H_3$) 54.6 (**C**(5)H), 65.9 (**C**(2)), 178.1 ($\mathbf{C}O_2CH_3$); *m*/*z* (ESI^+) 180 (MNa^+, 56%), 360 (M_2Na^+, 100), 528 (84); HRMS found 180.0993; $C_{14}H_{21}NO_3$ requires 180.0995.

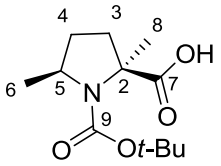
(2*SR*,5*SR*)-1-*tert*-Butyl 2-ethyl 2,5-dimethylpyrrolidine-1,2-dicarboxylate (1.169)



DMAP (13.4 mg, 0.11 mmol) and di-*tert*-butyl dicarbonate (278 µL, 1.21 mmol) were added to a solution of amine **1.117** (190 mg, 1.10 mmol) in acetonitrile (2.81 mL) and the resulting solution stirred for 1 h at RT before further di-*tert*-butyl dicarbonate (1.37 µL, 0.65 mmol) was added. The reaction mixture was stirred for another 30 min and then filtered through a silica plug first with petrol (50 mL) to remove impurities, and then with ether (100 mL) to give *protected amine* **1.169** as a colourless oil (267 mg, 90%).

R_f 0.55 (1:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2982br, 1790s, 1734s, 1466m, 1372s, 1230br, 1146s, 1058s, 933w, 896w, 861m, 738m; δ_H (400 MHz, $CDCl_3$) **Major and minor rotamers:** 1.25-1.35 (6H, m, C(6)$\mathbf{H_3}$ and C(10)$\mathbf{H_3}$), 1.49 (3H, s, C(7)$\mathbf{H_3}$), 1.52 (9H, s, C($C\mathbf{H_3}$)$_3$), 1.62-1.70 (1H, m, C(4)**H**H′), 1.86-1.94 (1H, m, C(3)**H**H′), 2.09-2.23 (1H, m, C(4)H**H′**), 2.27-2.41 (1H, m, C(3)H**H′**), 4.08-4.17 (1H, m, C(5)**H**), 4.20 (2H, q, *J* 7.5 Hz, C(9)$\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) **Major rotamer**: 14.0 (**C**(10)H_3), 20.0 (**C**(6)H_3), 20.4 (**C**(7)H_3), 27.4 (C($\mathbf{C}H_3$)$_3$), 30.6 (**C**(4)H_2), 36.2 (**C**(3)H_2), 56.0 (**C**(5)H), 61.5 (**C**(9)H_2), 66.8 (**C**(2)), 84.5 (**C**(CH_3)$_3$), 147.6 (**C**(11)), 173.2 (**C**(8)); **Minor rotamer**: 13.9 (**C**(10)H_3), 18.2 (**C**(6)H_3), 22.6 (**C**(7)H_3), 27.4 (C($\mathbf{C}H_3$)$_3$), 29.7 (**C**(4)H_2), 37.5 (**C**(3)H_2), 56.2 (**C**(5)H), 61.6 (**C**(9)H_2), 66.6 (**C**(2)), 84.4 (**C**(CH_3)$_3$), 147.3 (**C**(11)), 173.6 (**C**(8)); HRMS data unobtainable.

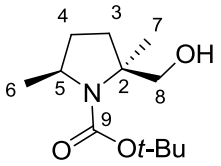
(2*SR*,5*SR*)-1-(*tert*-Butoxycarbonyl)-2,5-dimethylpyrrolidine-2-carboxylic acid (1.170)



Lithium hydroxide (1.7 M aq., 0.15 mL), was added to a solution of ester **1.169** (100 mg, 0.37 mmol) in methanol (0.16 mL) and the reaction heated at reflux for 16 h before being diluted in ether (5 mL) and water (5 mL). The aqueous layer was separated, acidified to pH 4 with HCl (1 M aq.) and extracted with ethyl acetate (3 × 10 mL). The combined ethyl acetate layers were dried ($MgSO_4$) and evaporated *in vacuo* to give *acid* **1.170** as a colourless oil (77 mg, 87%).

R_f 0.62 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 3469 br, 2976s, 1698s, 1456w, 1389s, 1246w, 1167m, 1087m, 1041w, 992w, 939w, 854w, 773w, 700w; δ_H (200 MHz) 1.17-1.28 (3H, m, C(6)**H$_3$**), 1.36-1.53 (12H, m, C(8)**H$_3$** and C(C**H$_3$**)$_3$), 1.56-1.61 (1H, m, C(4)**H**H′), 1.82-1.85 (1H, m, C(3)**H**H′), 2.07-2.11 (1H, m, C(4)H**H′**), 2.28-2.50 (1H, m, C(3)H**H′**), 3.90-4.19 (1H, m, C(5)**H**), 10.19-10.93 (1H, br s, CO_2**H**); δ_C (125 MHz) **Major and minor rotamers:** 18.9 and 20.3 (**C**(6)H_3), 21.8 and 22.0 (**C**(8)H_3), 28.4 and 29.9 (C(**C**H_3)$_3$), 29.7 (**C**(4)H_2), 35.7 and 37.4 (**C**(3)H_2), 54.8 and 55.6 (**C**(5)H), 65.4 and 67.0 (**C**(2)), 80.3 and 81.4 (**C**(CH_3)$_3$), 152.7 and 155.7 (**C**(9)), 177.0 and 180.7 (**C**(7)); *m/z* (ESI^-) 242 (89%, $[M-H]^-$), 507 (100), 772 (66); HRMS found 242.1397; $C_{12}H_{20}NO_4$ ($[M-H]^-$) requires 242.1398.

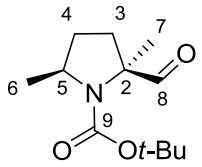
(2*SR*,5*SR*)-*tert*-Butyl 2-(hydroxymethyl)-2,5-dimethylpyrrolidine-1-carboxylate (1.171)



BH_3.THF (1 M, 320 µL, 0.32 mmol) was added slowly to a solution of acid **1.170** (70 mg, 0.29 mmol) in THF (1.72 mL) and the resulting mixture heated to reflux for 2 h before being evaporated *in vacuo* to furnish *alcohol* **1.171** as a colourless oil (67 mg, 100%).

R_f 0.30 (1:1, ether/petrol); ν_{max} (thin film)/cm^{-1} 3388br, 2972s, 1663s, 1456s, 1456m, 1394s, 1256w, 1174m, 1135m, 1077m, 852w, 774w; δ_H (400 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.0 Hz, C(6)**H$_3$**), 1.22 (3H, s, C(8)**H$_3$**), 1.36 (9H, s, C(C**H$_3$**)$_3$), 1.48 (1H, dd, *J* 12.5, 7.0 Hz, C(3)**H**H′), 1.64-2.05 (3H, m, C(3)H**H′** and C(4)**H$_2$**), 3.52 (2H, br, C(8)**H$_2$**), 3.82-3.93 (1H, m, C(5)**H**), 5.52 (1H, br, O**H**); δ_C (100 MHz, $CDCl_3$) 19.6 (**C**(7)H_3), 20.9 (**C**(6)H_3), 23.8 and 29.1 (**C**(4)H_2), 28.4 (C(**C**H_3)$_3$), 30.8 and 34.7 (**C**(3)H_2), 55.3 (**C**(5)H), 65.4 (**C**(2)), 67.3 and 71.6 (**C**(8)H_2), 79.8 (**C**(CH_3)$_3$), 155.7 (**C**(9)); *m/z* (ESI^+) 252 (23%, MNa^+), 288 (100, [M+MeCN+NH_4^+]), 481 (45, M_2Na^+), 755 (19); HRMS found 252.1561; $C_{12}H_{23}NO_3Na$ (MNa^+) requires 252.1570.

(2*SR*,5*SR*)-*tert*-Butyl 2-formyl-2,5-dimethylpyrrolidine-1-carboxylate (1.120)

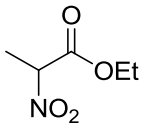


Alcohol **1.171** (100 mg, 0.44 mmol) was dissolved in DCM (8 mL) and stirred at 0 °C. DMP (278 mg, 0.66 mmol) was added and the reaction stirred for 30 min before being allowed to warm to RT and stirred for a further 1 h 30 mins. The mixture was then diluted with ether (10 mL) and poured onto sodium hydroxide (1.3 M aq., 10 mL), stirred for 15 mins and the layers separated. The organic layer was washed with sodium hydroxide (1.3 M aq., 10 mL), brine (sat. aq., 10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 4:1, petrol/ether) furnished *aldehyde* **1.120** as a colourless liquid (99 mg, 100%).

R_f 0.27 (3:2, ether/petrol); ν_{max} (thin film)/cm^{-1} 2975s, 1741s, 1699br, 1457w, 1382br, 1255w, 1167m, 1131w, 1077m, 1042w, 872w, 773w; δ_H (500 MHz, $CDCl_3$) **Major rotamer**: 1.25 (3H, d, *J* 6.5 Hz, C(6)**H$_3$**), 1.36 (3H, s, C(7)**H$_3$**), 1.40 (9H, s, (C(C**H$_3$**)$_3$)), 1.49-1.57 (1H, m, C(3)**H**H′), 1.60-1.68 (1H, m, C(4)**H**H′), 1.93-2.07 (1H, m, C(3)H**H′**), 2.12-2.25 (1H, m, C(4)H**H′**), 4.11-4.18 (1H, m, C(5)**H**), 9.28 (1H, s, C(8)**H**); **Minor rotamer**: 1.22 (3H, d, *J* 6.5 Hz, C(6)**H$_3$**), 1.39 (3H, s, C(7)**H$_3$**), 1.46 (9H, s, C(C**H$_3$**)$_3$), 1.49-1.57 (1H, m, C(3)**H**H′), 1.60 1.68 (1H, m, C(4)**H**H′), 1.93-2.07 (1H, m, C(3)H**H′**),

2.12-2.25 (1H, m, C(4)H**H′**), 3.97-4.04 (1H, m, C(5)**H**), 9.35 (1H, s, C(8)**H**); δ_C (125 MHz, $CDCl_3$) **Major rotamer**: 18.3 (**C**(7)H_3), 20.1 (**C**(6)H_3), 28.4 (C(**C**H_3)$_3$), 29.7 (**C**(4)H_2), 32.4 (**C**(3)H_2), 54.4 (**C**(5)H), 69.3 (**C**(2)), 80.8 (**C**(CH_3)$_3$), 152.9 (**C**(9)), 200.2 (**C**(8)H); **Minor rotamer**: 17.9 (**C**(7)H_3), 21.0 (**C**(6)H_3), 28.6 (C(**C**H_3)$_3$), 30.9 (**C**(4)H_2), 31.2 (**C**(3)H_2), 54.0 (**C**(5)H), 69.4 (**C**(2)), 80.1 (**C**(CH_3)$_3$), 153.8 (**C**(9)), 200.7 (**C**(8)H); *m/z* (ESI^+) 286 (100, $[M+NH_4+MeCN]^+$); HRMS found 250.1410; $C_{12}H_{21}NO_3Na$ (MNa^+) requires 250.1414.

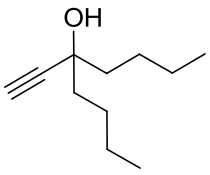
Ethyl 2-nitropropionate (1.121)



Ethyl-2-bromopropionate (10.9 g, 60 mmol) was added to a stirred solution of sodium nitrite (7.20 g, 104 mmol) and phloroglucinol (6.60 g, 52 mmol) in DMF (120 mL). The reaction was stirred for 16 h before being quenched by pouring onto ice water (240 mL) and extracted with ethyl acetate (4 × 100 mL). The combined organic layers were washed with $NaHCO_3$ (sat. aq., 200 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was redissolved in ether (200 mL) and washed with water (3 × 100 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give 2-nitropropionate (**1.121**) as a colourless liquid (6.7 g, 76%).

δ_H (200 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.0 Hz, $CO_2CH_2C\mathbf{H_3}$), 1.80 (3H, d, *J* 7.0 Hz, $C\mathbf{H_3}$), 4.30 (2H, q, *J* 7.0 Hz, $CO_2C\mathbf{H_2}CH_3$), 5.20 (1H, q, *J* 7.0 Hz, C**H**NO_2). Data as reported.[14]

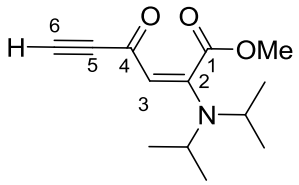
5-Ethynylnonan-5-ol (1.123)



Attempted alkylations with both methyl propiolate and ethyl propiolate resulted in isolation of significant quantities of unwanted addition product **1.123**.

R_f 0.50 (4:1, petrol/ether); δ_H (500 MHz, $CDCl_3$) 0.94 (6H, t, *J* 7.5 Hz, C(1)**H$_3$** and C(9)**H$_3$**), 1.36 (4H, sext., *J* 7.5 Hz, C(3)**H$_2$** and C(7)**H$_2$**), 1.43-1.54 (4H, m, C(2)**H$_2$** and C(8)**H$_2$**), 1.63-1.68 (4H, m, C(4)**H$_2$** and C(6)**H$_2$**), 1.91 (1H, s, O**H**), 2.44 (1H, s, ≡C**H**); δ_C (125 MHz, $CDCl_3$) 14.0 (**C**(1)H_3 and **C**(9)H_3), 22.8 and 26.3 (**C**(2)H_2 and **C**(8)H_2, **C**(3)H_2 and **C**(7)H_2), 41.6 (**C**(4)H_2 and **C**(6)H_2), 71.1 (**C**(5)), 72.1 (C≡**C**H), 87.0 (**C**≡CH). Data as reported.[15]

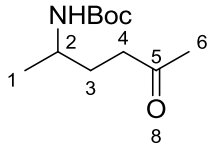
(*E*)-Methyl 2-(diisopropylamino)-4-oxohex-2-en-5-ynoate (1.124)



In attempts to form alkyne **1.126** (below) using LDA, *alkyne* **1.124** was isolated as a white crystalline solid (37 mg from 43 μL of methyl propiolate, 35%).

R_f 0.33 (3:2 petrol/ethyl acetate); m.p. 152 °C; ν_{max} (KBr disc)/cm^{-1} 3220m, 2981br, 2090m, 1732s, 1611m, 1506br, 1398s, 1341s, 1224s, 1186m, 1159m, 1122s, 752br; δ_H (400 MHz, $CDCl_3$) 1.33 (12H, m, 2 × NCH(C**H$_3$**)$_2$), 2.90 (1H, s, C(6)**H**), 3.73 (2H, sept, *J* 7.0 Hz, 2 × NC**H**), 3.91 (3H, s, CO_2C**H$_3$**), 5.38 (1H, s, C(3)**H**); δ_C (100 MHz, $CDCl_3$) 20.0 (NCH(**C**H_3)$_2$), 53.3 (CO_2**C**H_3), 55.0 (N**C**H(CH_3)$_2$), 73.8 (C≡**C**H), 84.2 (**C**≡CH), 97.1 (**C**(3)H), 152.8 (**C**(2)), 165.8 (**C**(1)), 170.3 (**C**(4)); *m/z* (ESI^+) 238 (MH^+, 52%), 260 (MNa^+, 33), 339 (70), 481 (63), 497 (M_2Na^+, 94), 498 (100); HRMS (ESI^+) found 260.1259; $C_{13}H_{19}NNaO_3$ (MNa^+) requires 260.1257.

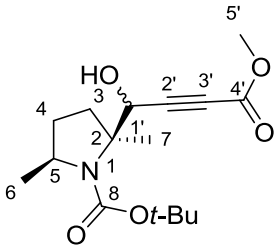
***tert*-Butyl 5-oxohexan-2-ylcarbamate (1.125)**



n-BuLi (188 μL, 1.6 M in hexanes, 0.30 mmol) was added to a solution of methyl propiolate (27 μL, 0.30 mmol) in THF (2.13 mL) and the mixture stirred for 45 min at −78 °C before being added to a solution of aldehyde **1.120** (57 mg) in THF (0.76 mL), precooled to −78 °C. The reaction mixture was stirred for 2 h 30 mins at −78 °C and then left to warm to RT over 16 h before being quenched with ammonium chloride (sat. aq., 5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (sat. aq., 15 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 3:1, petrol/ether) gave *amino ketone* **1.125** as a colourless liquid (10 mg, 19%).

R_f 0.09 (3:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 3354br, 2976s, 1712s, 1522s, 1454m, 1366s, 1249m, 1172s, 1074m, 854w, 780w; δ_H (500 MHz, $CDCl_3$) 1.13 (3H, d, *J* 6.5 Hz, C(1)**H$_3$**), 1.44 (9H, s, C(C**H$_3$**)$_3$), 1.60-1.66 (1H, m, C(3)**H**H′), 1.68-1.77 (1H, m, C(3)H**H′**), 2.15 (3H, s, C(6)**H$_3$**), 2.48-2.53 (2H, m, C(4)**H$_2$**), 3.63 (1H, br, C(2)**H**), 4.33 (1H, br, N**H**); δ_C (125 MHz, $CDCl_3$) 22.3 (**C**(1)H_3), 28.4 (C(**C**H_3)$_3$), 30.0 (**C**(6)H_3), 31.0 (**C**(3)H_2), 40.4 (**C**(4)H_2), 46.2 (**C**(2)H), 79.1 (**C**$(CH_3)_3$), 155.5 (NH**C**=O), 208.6 (**C**(5)); *m/z* (ESI$^+$) 238 (16%, MNa^+), 274 (34, [M+MeCN+NH_4^+]), 453 (71, M_2Na^+), 597 (100); HRMS found 238.1422; $C_{11}H_{21}NNaO_3$ (MNa^+) requires 238.1414.

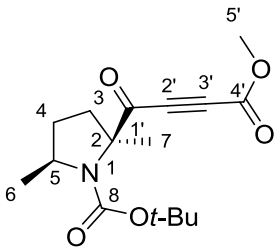
(2*SR*,5*SR*)-*tert*-Butyl 2-(1-hydroxy-4-methoxy-4-oxobut-2-ynyl)-2,5-dimethylpyrrolidine-1-carboxylate (1.126)



n-Butyllithium (1.6 M in hexanes, 144 µL, 0.23 mmol) was added to a solution of methyl propiolate (20.7 µL, 0.23 mmol) in THF (2 mL) stirring at −78 °C. After 15 mins aldehyde **1.120** (50 mg, 0.22 mmol) in THF (1 mL) was added dropwise *via* cannula over 5 mins, followed immediately by trimethylsilyl chloride (30.7 µL, 0.24 mmol). After 1 h the reaction was warmed, diluted in ether (5 mL) and quenched with water (5 mL). The layers were separated and the organic layer was washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 4:1→3:1 petrol/ether) gave *alcohol* **1.126** as a yellow oil (14 mg, 19%).

R_f 0.42 (3:2, petrol/ether); ν_{max} (thin film)/cm^{-1} 3283br, 2975w, 2361w, 2341w, 1718s, 1660m, 1399s, 1251s, 1170m, 1136w, 1099w, 1077w, 1044w; δ_H (500 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.5 Hz, C(6)**H$_3$**), 1.36 (3H, s, C(7)**H$_3$**), 1.47 (9H, s, C(C**H$_3$**)$_3$), 1.49-1.54 (1H, m, C(4)**H**H′), 1.59-1.69 (1H, m, C(3)**H**H′), 2.05-2.17 (2H, m, C(3)H**H′** and C(4)H**H′**), 3.75 (3H, s, C(5′)**H$_3$**), 4.01 (1H, app. quin., *J* 6.5 Hz, C(5)**H**), 4.39 (1H, d, *J* 11.0 Hz, C(1′)**H**), 6.78 (1H, d, *J* 11.0 Hz, O**H**); δ_C (125 MHz, $CDCl_3$) 20.2 (**C**(7)H_3), 20.5 (**C**(6)H_3), 28.3 (C(**C**H_3)$_3$), 28.6 (**C**(4)H_2), 35.2 (**C**(3)H_2), 52.6 (**C**(5′)H_3), 55.6 (**C**(5)H), 68.4 (**C**(2)), 69.3 (**C**(1′)H), 76.2 (**C**≡C), 80.7 (**C**(CH_3)$_3$), 87.7 (C≡**C**), 153.8 and 156.0 (C(4′) and C(8)); *m/z* (ESI^+) 256 (42%), 312 (MH^+, 27), 334 (MNa^+, 51) 370 ([M +MeCN+NH_4]$^+$, 25), 413 (93), 645 (M_2Na^+, 100); HRMS (ESI^+) found 334.1625; $C_{16}H_{25}NNaO_5$ (MNa^+) requires 334.1625.

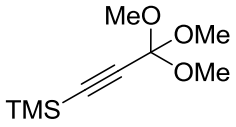
(2*SR*,5*SR*)-*tert*-Butyl 2-(4-methoxy-4-oxobut-2-ynoyl)-2,5-dimethylpyrrolidine-1-carboxylate (1.172)



DMP (27 mg, 0.063 mmol) was added to a solution of alcohol **1.126** (13 mg, 0.042 mmol) in DCM (0.78 mL) stirring at 0 °C. After 30 mins the reaction was warmed to RT and allowed to stir for 3 h before being diluted in ether (3 mL) and sodium hydroxide (1.3 M, 3 mL). The mixture was stirred for 15 mins, the layers separated and the aqueous layer extracted with ether (5 mL). The organic layers were washed with sodium hydroxide (1.3 M, 5 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, chloroform) gave *ketone* **1.172** (8 mg, 62%).

R_f 0.25 (chloroform); ν_{max} (thin film)/cm^{-1} 2975br, 1725s, 1698s, 1460m, 1388s, 1261s, 1169m, 1106m, 973w; δ_H (500 MHz, $CDCl_3$) **Major (M) and minor (m) rotamers**: 1.31-1.34 (6H, m, C(6)**H$_3$** M and m), 1.43 (12H, m, C(7)**H$_3$** M and C(C**H$_3$**)$_3$ M), 1.47 (3H, s, C(7)**H$_3$** m), 1.48 (9H, s, C(C**H$_3$**)$_3$ m), 1.63-1.73 (4H, m, C(4)**H**H′ M and m and C(3)**H**H′ M and m), 2.14-2.27 (3H, m, C(3)H**H′** m and C(4)H**H′** M and m), 2.34 (1H, td, *J* 12.5, 6.5 Hz, C(3)H**H′** M), 3.81 (3H, s, C(5′)**H$_3$** m), 3.83 (3H, s, C(5′)**H$_3$** M), 4.04 (1H, q, *J* 6.5 Hz, C(5)**H** m), 4.17 (1H, dq, *J* 7.5, 6.5 Hz, C(5)**H** M); δ_C (125 MHz, $CDCl_3$) 18.5 (**C**(7)H_3 m), 19.6 (**C**(7)H_3 M and **C**(6)H_3 M), 20.4 (**C**(6)H_3 m), 28.1 (C(**C**H_3)$_3$ M), 28.4 (C(**C**H_3)$_3$ m), 30.0 (**C**(4)H_2 M), 31.1 (**C**(4)H_2 m), 33.7 (**C**(3)H_2 m), 35.0 (**C**(3)H_2 M), 53.1 (**C**(5′)H_3 m), 53.3 (**C**(5′)H_3 M), 54.3 (**C**(5)H m), 54.8 (**C**(5)H M), 71.2 (**C**(2) M), 71.4 (**C**(2) m), 78.6, 80.1, 80.4, 80.5 and 81.4 (**C**(2′), **C**(3′) and **C**(CH_3)$_3$ M and m), 152.3 (**C**(4′) M), 152.4 (**C**(4′) m), 152.6 (**C**O_2*t*-Bu m), 153.6 (**C**O_2*t*-Bu M), 187.3 (**C**(1′) m), 187.6 (**C**(1′) M); *m/z* (ESI^+) 332 (M_2Na^+, 35%), 411 (32), 641 (M_2Na^+, 100); HRMS (ESI+) found 332.1472; $C_{16}H_{23}NNaO_5$ (MNa^+) requires 332.1468.

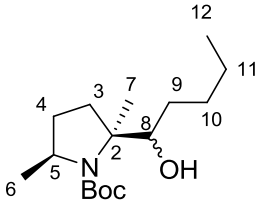
Trimethyl(3,3,3-trimethoxyprop-1-ynyl)silane (1.128)



A solution of $BF_3{\cdot}OEt_2$ (1.40 mL, 11.0 mmol) in ether (1.47 mL) was added *via* a dropping funnel to a solution of tetramethyl orthocarbonate (980 μL, 7.34 mmol) in ether (5.90 mL) stirring at 0 °C. The reaction was stirred at this temperature for 20 mins then allowed to warm to RT and stirred for 3 h. The mixture was filtered under argon, washing with dry pentane/ether (2:1, 5 × 15 mL). The solid was cooled to −78 °C and a solution of premixed trimethylsilyl acetylene (519 μL, 3.67 mmol) and *n*-BuLi (2.30 mL, 1.6 M in hexanes, 3.67 mmol) in ether (5.3 mL), which had been stirred at 0 °C for 1 h, was added *via* cannula. After 1 h at −78 °C the reaction was warmed to RT over 30 mins and then quenched with Na_2CO_3 (sat. aq., 10 mL). The aqueous layer was extracted with ether (2 × 20 mL) and the combined organic phases dried ($MgSO_4$) and evaporated *in vacuo* to give *orthoester* **1.128** as a colourless oil (357 mg, 48%).

R_f 0.09 (3:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2692br, 2838s, 1719m, 1440br, 1252br, 1107br, 1041s, 1001s, 846br, 762s; δ_H (500 MHz, $CDCl_3$) 0.14-0.20 (9H, m, 3 × SiC**H$_3$**), 3.32 (9H, s, 3 × C(OC**H$_3$**); δ_C (125 MHz, $CDCl_3$) −0.4 (3 × Si**C**H_3), 50.7 (3 × O**C**H_3), 89.9 and 96.7 (**C**≡**C**), 109.6 (**C**$(OCH3)_3$); *m/z* (ESI^+) 171 (47%), 225 (MNa^+, 45), 303 (67), 335 (100), 343 (65), 427 (M_2Na^+, 49), 545 (72), 663 (74); HRMS found 225.0917; $C_{19}H_{18}NaO_3Si$ (MNa^+) requires 225.0915.

(2*SR*,5*SR*)-*tert*-Butyl 2-(1-hydroxypentyl)-2,5-dimethylpyrrolidine-1-carboxylate (1.129)

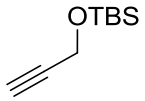


n-Butyllithium (1.6 M in hexanes, 76 μL, 0.12 mmol) was added to a solution of aldehyde **1.120** (25 mg, 0.11 mmol) in THF (0.25 mL) stirring at –78 °C and the resultant mixture was allowed to

warm to RT over 16 h. The reaction was then quenched with ammonium choride solution (sat. aq., 1.5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic phrases were dried ($MgSO_4$) and evaporated *in vacuo* to give *alcohol* **1.129** as a brown oil (21 mg, 67%).

ν_{max} (thin film)/cm^{-1} 3349br, 2967s, 2874s, 1741w, 1689s, 1665s, 1456m, 1392s, 1324w, 1257m 1173s, 1139m, 1099s, 1069s, 1034m, 876w, 853w, 806w; δ_H (500 MHz, $CDCl_3$) **Major and minor isomers:** 0.92 (6H, td, *J* 7.0, 2.0 Hz, C(12)**H₃** M and m), 1.10-1.43 (18H, m, C(6)**H₃**, C(9)**H₂**, C(10)**H₂** and C(11)**H₂** M and m), 1.46 (18H, s, C(C**H₃**)₃ M and m), 1.58 (10H, m, C(3)**H**H′, C(4)**H**H′ and C(7)**H₃** M and m), 1.78-2.13 (4H, m, C(3)H**H′** and C(4)H**H′** M and m), 3.46-4.66 (2H, m, C(8)**H** M and m), 3.97-4.09 (2H, m, C(5)**H** M and m), 6.63 (2H, s, O**H** M and m); δ_C (125 MHz, $CDCl_3$) **Major:** 14.1 (**C**(12)H_3), 16.6 (**C**(6)H_3), 21.0 (**C**(7)H_3), 22.9 (**C**(9)H_2, **C**(10)H_2 and **C**(11)H_2), 28.5 (C(**C**H_3)$_3$), 28.9 (**C**(4)H_2), 35.5 (**C**(3)H_2), 55.5 (**C**(5)H), 68.7 (**C**(2)), 80.1 (**C**(8)H), 80.2 (**C**$(CH_3)_3$), 156.4 (**C**=O); *m/z* (ESI^+) 286 (MH^+, 30%), 308 (MNa^+, 44), 386 (44), 593 (M_2Na^+, 100); HRMS (ESI+) found 308.2193; $C_{16}H_{31}NNaO_3$ (MNa^+) requires 308.2196.

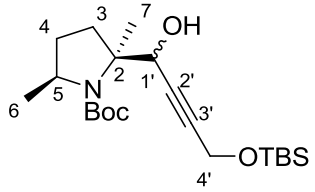
***tert*-Butyldimethyl(prop-2-ynyloxy)silane (1.130)**



Propargyl alcohol (5.19 mL, 89.0 mmol) was added dropwise to a stirring suspension of sodium hydride (60% wt in mineral oil, 3.57 g, 89.0 mmol) in THF (310 mL). The slurry was stirred for 45 mins and then *tert*-butyldimethylsilyl chloride (13.4 g, 89.0 mmol) was added. The reaction was stirred for 2 h before being carefully quenched with water (50 mL) and extracted with ether (3 × 70 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give silyl ether **1.130** as a colourless liquid (11.6 g, 100%).

δ_H (500 MHz, $CDCl_3$) 0.13-0.15 (6H, m, Si(C**H₃**)$_2$), 0.91-0.93 (9H, m, SiC(C**H₃**)$_3$), 2.38-2.41 (1H, m, C≡C**H**), 4.31-4.33 (2H, m, OC**H₂**); δ_C (125 MHz, $CDCl_3$) −5.2 (Si(**C**H_3)$_2$), 18.3 (Si**C**$(CH_3)_3$), 25.7 (SiC(**C**H_3)$_3$), 51.5 (O**C**H_2), 72.8 (C≡**C**H), 82.4 (**C**≡CH). Data as reported.[16]

(2*SR*,5*SR*)-*tert*-Butyl 2-[4-(*tert*-butyldimethylsilyloxy)-1-hydroxybut-2-ynyl]-2,5-dimethylpyrrolidine-1-carboxylate (1.131)



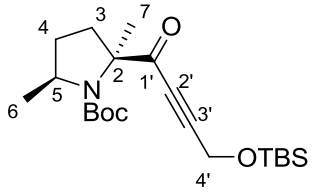
Silyl ether **1.130** (493 µL, 2.42 mmol) was dissolved in THF (0.85 mL) and cooled to −40 °C. *n*-Butyllithium (1.6 M in hexanes, 1.51 mL, 2.42 mmol) was added dropwise and the reaction stirred for 20 mins before being warmed to 0 °C and a solution of aldehyde **X** (550 mg, 2.42 mmol) in THF (1 mL) added *via cannula*. After 3 h the reaction was quenched with ammonium chloride solution (sat. aq., 10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 6:1, petrol/ether) gave *alcohol* **1.131**, as a separable mixture of diastereomers in a 4:1 ratio (as determined by ^{1}H NMR analysis) (combined yield 940 mg, 98%).

Major Diastereomer: R_f 0.20 (6:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 3345br, 2970s, 1666s, 1396s, 1256m, 1174m, 1142s, 1077m, 838s, 776m; δ_H (500 MHz, $CDCl_3$) 0.09 (6H, s, Si(C**H**$_3$)$_2$), 0.89 (9H, s, SiC(C**H**$_3$)$_3$), 1.21 (3H, d, *J* 6.5 Hz, C(6)**H**$_3$), 1.36 (3H, s, C(7)**H**$_3$), 1.46 (9H, s, C(C**H**$_3$)$_3$), 1.56-1.67 (1H, m, C(3)**H**H′), 1.93-2.11 (2H, m, C(4)**H**$_2$), 2.13-2.22 (1H, m, C(3)H**H′**), 4.00 (1H, app. quin., *J* 6.5 Hz, C(5)**H**), 4.31-4.36 (3H, m, C(4′)**H**$_2$ and C(1′)**H**), 6.41 (1H, d, *J* 7.0 Hz, O**H**); δ_C (125 MHz, $CDCl_3$) −5.2 (2 × SiC**H**$_3$), 14.1 (Si**C**(CH$_3$)$_3$), 18.3 (**C**(7)H$_3$), 20.6 (**C**(6)H$_3$), 25.8 (SiC(**C**H$_3$)$_3$), 28.5 (C(**C**H$_3$)$_3$), 29.7 (**C**(4)H$_2$), 35.1 (**C**(3)H$_2$), 51.7 (**C**H$_2$OTBS), 55.6 (**C**(5)H), 68.6 (**C**(2)), 69.2 (**C**(1′)H), 80.1 (**C**≡C), 83.1 (O**C**(CH$_3$)$_3$), 84.3 (C≡**C**), 155.8 (**C**=O); *m/z* (ESI$^+$) 398 (MH$^+$, 17%), 420 (MNa$^+$, 49), 436 (MK$^+$, 54), 817 (M$_2$Na$^+$, 78), 833 (M$_2$K$^+$, 100); HRMS (ESI$^+$) found 420.2533; $C_{21}H_{39}NNaO_4Si$ (MNa$^+$) requires 420.2541.

Minor Diastereomer: R_f 0.14 (6:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 3412br, 2931br, 1691m, 1390s, 1259m, 1086br, 837m; δ_H (500 MHz, $CDCl_3$) 0.07 (6H, s, Si(C**H**$_3$)$_2$), 0.91 (9H, s, SiC(C**H**$_3$)$_3$), 1.13 (3H, d, *J* 6.0 Hz, C(6)**H**$_3$), 1.42 (3H, s, C(7)**H**$_3$), 1.46 (10H, m, C(C**H**$_3$)$_3$ and C(4)**H**H′), 1.78-1.85 (1H,

m, C(4)H**H′**), 1.96-2.10 (2H, m, C(3)$\mathbf{H_2}$), 4.01-4.08 (1H, m, C(5)**H**), 4.35 (2H, s, C$\mathbf{H_2}$OTBS), 4.54 (1H, br s, C**H**OH), 6.56 (1H, br s, O**H**); δ_C (125 MHz, $CDCl_3$) −5 2 (Si(**C**H_3)$_3$), 17.2 (**C**(2)H_3), 18.3 (Si**C**$(CH_3)_3$), 21.0 (**C**(6)H_3), 25.8 (SiC(**C**H_3)$_3$), 28.5 (C(**C**H_3)$_3$), 29.7 (**C**(4)H_2), 36.2 (**C**(3)H_2), 51.8 (**C**(4′)H_2OTBS), 56.2 (**C**(5)H), 68.6 (**C**(2)), 72.5 (**C**(1′)H), 80.5 (**C**≡C), 82.7 (**C**$(CH_3)_3$), 83.9 (C≡**C**), 156.2 (**C**=O); *m/z* (ESI^+) 342 (41%), 398 (MH^+, 44), 420 (MNa^+, 78), 499 (81), 703 (94), 743 (48), 801 (53), 810 (95), 817 (M_2Na^+, 100); HRMS (ESI+) found 420.2534; $C_{21}H_{39}NO_4SiNa$ (MNa^+) requires 420.2541.

(2*SR*,5*SR*)-*tert*-Butyl 2-[4-(*tert*-butyldimethylsilyloxy)but-2-ynoyl]-2,5-dimethylpyrrolidine-1-carboxylate (1.132)

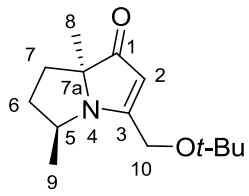


Alcohol **1.131** (414 mg, 1.04 mmol) was dissolved in DCM (12.4 mL) and cooled to 0 °C. DMP (487mg, 1.15 mmol) was added and the reaction stirred at 0 °C for 30 mins, then RT for 16 h before being diluted in ether (15 mL) and sodium hydroxide solution (1.3 M aq., 15 mL). After 15 mins stirring at RT the layers were separated and the aqueous phase extracted with ether (2 × 15 mL). The combined organic phases were washed with sodium hydroxide (1.3 M aq., 15 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give *ketone* **1.132** as a 2:1 mixture of rotamers (as determined by ^{1}H NMR analysis) (410 mg, 100%).

R_f 0.37 (9:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2930br, 1693s, 1464w, 1380s, 1258m, 1173m, 1132m, 1093m, 838m, 780w; δ_H (500 MHz, $CDCl_3$) **Major (M) and minor (m) rotamers**: 0.07-0.10 (12H, m, 4 × SiC$\mathbf{H_3}$ M and m), 0.89 (18H, m, SiC(C$\mathbf{H_3}$)$_3$ M and m), 1.31-1.35 (6H, m, C(6)$\mathbf{H_3}$ M and m), 1.41-1.49 (24H, m, C(C$\mathbf{H_3}$)$_3$ and C(7)$\mathbf{H_3}$ M and m), 1.61-1.69 (4H, m, C(3)**H**H′ and C(4)**H**H′ M and m), 2.10-2.23 (2H, m, C(4)H**H′** M and m), 2.24-2.39 (2H, m, C(3)H**H′** M and m), 4.02 (1H, app. quin., *J* 6.5 Hz, C(5)**H** m), 4.15 (1H, dq, *J* 7.0, 6.5 Hz, C(5)**H** M), 4.42 (2H, s, C(4′)$\mathbf{H_2}$OTBS m), 4.43

(2H, s, C(4′)$\mathbf{H_2}$OTBS M); δ_C (125 MHz, $CDCl_3$) −5.43, −5.41, −5.40 and −5.37 (2 × Si(**C**H_3) M and m), 18.7 (**C**(7)H_3 m), 19.7 (**C**(7)H_3 M), 19.9 (**C**(6)H_3 M), 20.6 (**C**(6)H_3 m), 25.7 (SiC(**C**H_3)$_3$ M and m), 28.4 (SiC(**C**H_3)$_3$ M and m), 30.1 (**C**(4)H_2 M), 31.1 (**C**(4)H_2 m), 34.3 (**C**(3)H_2 m), 35.4 (**C**(3)H_2 M), 51.4 (**C**(4′)H_2OTBS M and m), 54.4 (**C**(5)H m), 54.8 (**C**(5)H M), 71.1 (**C**(2) M) 71.3 (**C**(2) m), 79.8 (**C**≡C m), 80.6 (**C**≡C M), 81.5 (O**C**$(CH_3)_3$ M), 81.8 (O**C**$(CH_3)_3$ m), 89.6 (C≡**C** m), 90.5 (C≡**C** M), 152.6 (**C**O_2*t*-Bu M), 153.4 (**C**O_2*t*-Bu m), 188.7 (**C**(1′) m), 188.9 (**C**(1′) M); *m/z* (ESI^+) 293 (52%), 296 (71), 418 (MNa^+, 70), 454 ([M+MeCN+NH_4^+], 28), 497 (42), 645 (82), 696 (100), 813 (M_2Na^+, 100); HRMS (ESI^+) found 418.2385; $C_{21}H_{37}NNaO_4Si$ (MNa^+) requires 418.2384.

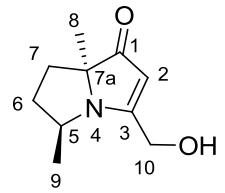
(5*SR*,7a*SR*)-3-(*tert*-Butoxymethyl)-5,7a-dimethyl-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-1-one (1.134)



Ether **1.134** was isolated in varying quantities during attempts to furnish alcohol **1.135** from silyl ether **1.132**.

R_f 0.50 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2974m, 1643s, 1525w, 1465m, 1347w, 1257br, 1173s, 1125m, 1037m; δ_H (500 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.5 Hz, C(9)$\mathbf{H_3}$), 1.26 (9H, s, C(C$\mathbf{H_3}$)$_3$), 1.33 (3H, s, C(8)$\mathbf{H_3}$), 1.69-1.85 (3H, m, C(6)**H**H′ and C(7)$\mathbf{H_2}$), 2.43-2.53 (1H, m, C(6)H**H′**), 4.01 (1H, quin. d, *J* 6.5, 1.5 Hz, C(5)**H**), 4.23 (1H, d, *J* 15.5 Hz, C(10)**H**H′), 4.37 (1H, d, *J* 15.5 Hz, C(10)H**H′**), 5.31 (1H, s, C(2)**H**); δ_C (125 MHz, $CDCl_3$) 19.6 (**C**(9)H_3), 24.0 (**C**(8)H_3), 27.4 (C(**C**H_3)$_3$), 27.6 (**C**(7)H_2), 36.1 (**C**(6)H_2), 54.1 (**C**(5)H), 59.4 (**C**(10)H_2), 74.4 (**C**$(CH_3)_3$), 76.7 (**C**(7a)), 103.8 (**C**(2)H), 179.2 (**C**(3)), 206.4 (**C**(1)); *m/z* (ESI^+) 238 (MH^+, 56%), 260 (MNa^+, 72), 292 ([M+MeOH+Na^+], 40), 475 (M_2H^+, 38), 481 (68), 498 (100), 650 (41); HRMS (ESI^+) found 260.1622; $C_{14}H_{23}NNaO_2$ (MNa^+) requires 260.1621.

(5*S*,7a*S*)-3-(Hydroxymethyl)-5,7a-dimethyl-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-1-one (1.135)

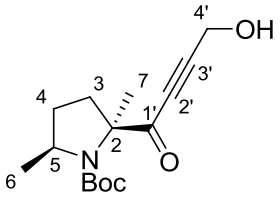


Method A: Ketone **1.132** (40 mg, 0.10 mmol) was dissolved in DCM (1.0 mL) and the solution cooled to −30 °C before trimethylsilyl trifluoromethanesulfonate (55.0 μL, 0.30 mmol) was added and the reaction mixture allowed to warm to 0 °C over 3 h. Sodium bicarbonate (sat. aq., 5 mL) was added and the reaction extracted with ethyl acetate (5 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, ethyl acetate) gave *alcohol* **1.135** as a bright yellow oil (16 mg, 88%).

Method B: TFA (one drop) was added to a solution of ether **1.134** (30 mg, 0.13 mmol) in DCM (0.5 mL) stirring at 0 °C. After 1 h further TFA (9.4 μL, 0.13 mmoL) was added and the reaction stirred for 2 h before being evaporated *in vacuo*. The residue was dissolved in DCM (5 mL), neutralized with $NaHCO_3$ and the aqueous layer extracted with DCM (2 × 5 mL). The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo* to give *alcohol* **1.135** as a bright yellow oil (10 mg, 44%).

R_f 0.13 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 3375br, 2968m, 1640s, 1447s, 1261m, 1096m, 780m; δ_H (500 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.5 Hz, C(9)**H$_3$**), 1.33 (3H, s, C(8)**H$_3$**), 1.68-1.74 (1H, m, C(7)**H**H′), 1.78-1.88 (2H, m, C(7)H**H′** and C(6)**H**H′), 1.86-1.94 (1H, br s, O**H**), 2.43-2.52 (1H, m, C(6)H**H′**), 4.00 (1H, quin. d, *J* 6.5, 2.5 Hz, C(5)**H**), 4.48 (1H, d, *J* 16.0 Hz, C(10)**H**H′), 4.66 (1H, d, *J* 16.0 Hz, C(10)H**H′**), 5.34 (1H, s, C(2)**H**); δ_C (125 MHz, $CDCl_3$) 19.4 (**C**(9)H_3), 24.0 (**C**(8)H_3), 27.9 (**C**(7)H_2), 36.2 (**C**(6)H_2), 54.2 (**C**(5)H), 60.1 (**C**(10)H_2), 77.2 (**C**(7a)), 103.6 (**C**(2)H), 179.8 (**C**(3)), 206.7 (**C**(1)); *m/z* (ESI^+) 182 (MH^+, 42%), 204 (MNa^+, 63), 236 (41), 385 (M_2Na^+, 100), 592 (39), 799 (61); HRMS (ESI+) found 204.0993; $C_{10}H_{15}NNaO_2$ (MNa^+) requires 204.0995.

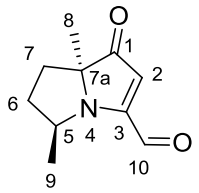
(2*SR*,5*SR*)-*tert*-Butyl 2-(4-hydroxybut-2-ynoyl)-2,5-dimethylpyrrolidine-1-carboxylate (1.136)



Ketone **1.132** (50 mg, 0.13 mmol) was dissolved in THF (0.6 mL) and cooled to 0 °C. Fluorosilicic acid (19 μL) was added and the reaction stirred at 0 °C for 5 mins before being quenched with $NaHCO_3$ (sat. aq., 5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (sat. aq., 10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 2:1, petrol/ether) gave *alcohol* **1.136** as a colourless oil, in a 2:1 ratio of rotamers (as determined by ^1H NMR analysis) (36 mg, 100%).

R_f 0.36 (1:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 3432br, 2976br, 2218w, 1686s, 1393br, 1258m, 1171m, 1132m, 1077m, 1042m, 943w; δ_H (500 MHz, $CDCl_3$**) Major rotamer**: 1.33 (3H, d, *J* 6.5 Hz, C(6)**H$_3$**), 1.40 (9H, s, C(C**H$_3$**)$_3$), 1.45 (3H, s, C(7)**H$_3$**), 1.61-1.69 (2H, m, C(3)**H**H′ and C(4)**H**H′), 2.11-2.22 (1H, m, C(4)H**H′**), 2.33 (1H, td, *J* 13.0, 7.0 Hz, C(3)H**H′**), 2.51-2.70 (1H, br s, O**H**), 4.14 (1H, app. quin., *J* 6.5 Hz, C(5)**H**), 4.40 (2H, s, C(4′)**H$_2$**); **Minor rotamer**: 1.31 (3H, d, *J* 6.5 Hz, C(6)**H$_3$**), 1.40 (9H, s, C(C**H$_3$**)$_3$), 1.45 (3H, s, C(7)**H$_3$**), 1.61-1.69 (2H, m, C(3)**H**H′ and C(4)**H**H′), 2.11-2.22 (1H, m, C(4)H**H′**), 2.25 (1H, td, *J* 13.0, 6.5 Hz, C(3)H**H′**), 2.51-2.70 (1H, br s, O**H**), 4.02 (1H, app. quin., *J* 6.5 Hz, C(5)**H**), 4.37 (2H, d, *J* 3.0 Hz, C(4′)**H$_2$**); δ_C (125 MHz, $CDCl_3$) 18.8 (**C**(7)H_3 m), 19.6 (**C**(7)H_3), 19.8 (**C**(6)H_3 M), 20.4 (**C**(6)H_3 m), 28.2 (C(**C**H_3)$_3$ M), 28.4 (C(**C**H_3)$_3$ m), 30.1 (**C**(4)H_2 M), 31.0 (**C**(4)H_2 m), 34.3 (**C**(3)H_2 m), 35.3 (**C**(3)H_2 M), 50.6 (**C**(4′)H_2 M and m), 54.5 (**C**(5)H m), 54.9 (**C**(5)H M), 71.3 (**C**(2) M and m), 80.1, 80.9, 82.2, 82.4, 89.5 and 90.3 (**C**≡**C** M and m and **C**$(CH_3)_3$ M and m), 152.9 (**C**=O M), 153.5 (**C**=O m), 188.9 (**C**(1′) M and m); *m/z* (ESI^+) 304 (MNa^+, 72%), 457 (59), 519 (67), 585 (M_2Na^+, 100), 641 (97); HRMS (ESI^+) found 304.1516; $C_{15}H_{23}NNaO_4$ (MNa^+) requires 304.1519.

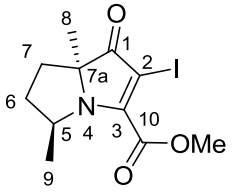
(5*SR*,7a*SR*)-5,7a-Dimethyl-1-oxo-5,6,7,7a-tetrahydro-1H-pyrrolizine-3-carbaldehyde (1.138)



Alcohol **1.135** (20.0 mg, 0.11 mmol) was dissolved in DCM (2.02 mL) at 0 °C and DMP (51.6 mg, 0.12 mmol) was added. The reaction was stirred at 0 °C for 30 mins and then RT for 1 h. The reaction was diluted in ether (5 mL), quenched with sodium hydroxide solution (1.3 M, 5 mL) and stirred for 15 mins. The layers were then separated and the aqueous layer extracted with ethyl acetate (4 × 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give *aldehyde* **1.138** as a bright yellow oil. Aldehyde **1.138** was stored in solution, since it was found to decompose readily if kept neat.

R_f 0.60 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 3384w, 2970m, 1680br, 1465br, 1079m, 800m; δ_H (500 MHz, $CDCl_3$) 1.02 (3H, d, *J* 6.5 Hz, C(9)**H$_3$**), 1.34 (3H, s, C(8)**H$_3$**), 1.75-1.90 (3H, m, C(7)**H$_2$** and C(6)**H**H′), 2.41-2.49 (1H, m, C(6)H**H′**), 4.13 (1H, quin. d, *J* 6.5, 1.5 Hz, C(5)**H**), 5.97 (1H, s, C(2)**H**), 9.97 (1H, s, C(10)**H**); δ_C (125 MHz, $CDCl_3$) 20.1 (**C**(9)H_3), 24.3 (**C**(8)H_3), 27.7 (**C**(7)H_2), 35.4 (**C**(6)H_2), 54.8 (**C**(5)H), 78.3 (**C**(7a)), 115.6 (**C**(2)H), 168.0 (**C**(3)), 187.3 (**C**(10)H), 209.5 (**C**(1)); *m/z* (ESI^+) 212 ($[M+MeOH+H]^+$, 32%), 234 ($[M+MeOH+Na]^+$, 67), 266 (48), 309 (38), 445 ($[(M+MeOH)_2+Na]^+$, 100), 624 (56); HRMS (ESI^+) found 234.1097; $C_{10}H_{13}NNaO_2$ ($[M+MeOH+Na]^+$) requires 234.1101.

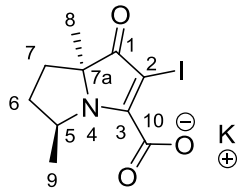
(5*SR*,7a*SR*)-Methyl 2-iodo-5,7a-dimethyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizine-3-carboxylate (1.141)



I_2 (190 mg, 0.75 mmol) and K_2CO_3 (104 mg, 0.75 mmol) were added to a solution of alcohol **1.135** (45 mg, 0.25 mmol) in methanol (0.14 mL). The reaction mixture was then stirred at 70 °C under argon for 16 h before being cooled to 0 °C and quenched with sodium thiosulphate (sat. aq., 1.3 mL). The reaction mixture was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers were washed with brine (sat. aq., 10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, ether) gave *iodoester* **1.141** as a bright yellow oil (30 mg, 36%).

R_f 0.75 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2972br, 1737s, 1688s, 1512w, 1438br, 1229br, 1135m, 1095m, 795w; δ_H (500 MHz, $CDCl_3$) 1.09 (3H, d, *J* 7.0 Hz, C(9)**H$_3$**), 1.37 (3H, s, C(8)**H$_3$**), 1.75-1.92 (3H, m, C(6)**H**H′ and C(7)**H$_2$**), 2.37-2.46 (1H, m, C(6)H**H′**), 3.97 (3H, s, OC**H$_3$**), 4.11 (1H, quin. d, *J* 7.0, 3.0 Hz, C(5)**H**); δ_C (125 MHz, $CDCl_3$) 19.7 (**C**(9)H_3), 24.4 (**C**(8)H_3), 28.7 (**C**(7)H_2), 35.0 (**C**(6)H_2), 53.0 (O**C**H_3), 56.3 (**C**(5)H), 72.5 (**C**(2)), 75.3 (**C**(7a)), 162.5 (**C**(10)), 164.8 (**C**(3)), 203.8 (**C**(1)); *m/z* (ESI^+) 336 (MH^+, 77%), 358 (MNa^+, 76), 390 (26), 567 (33), 693 (M_2Na^+, 100), 748 (62); HRMS (ESI^+) found 357.9907; $C_{11}H_{14}INNaO_3$ (MNa^+) requires 357.9911.

Potassium (5*SR*,7a*SR*)-2-iodo-5,7a-dimethyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizine-3-carboxylate (1.173)

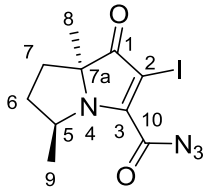


Potassium hydroxide (6.7 mg, 0.12 mmol) was added to a solution of ester **1.141** (36 mg, 0.11 mmol) in acetonitrile (0.74 mL) and water (0.74 mL). The reaction mixture was stirred for 1 h before being evaporated *in vacuo* to give *carboxylate salt* **1.173** as a yellow oil which was reacted on without further purification.

δ_H (500 MHz, CD_3OD) 1.11 (3H, d, *J* 6.5 Hz, C(9)**H$_3$**), 1.19 (3H, s, C(8)**H$_3$**), 1.56-1.75 (3H, m, C(6)**H**H′ and C(7)**H$_2$**), 2.34-2.43 (1H, m, C(6)H**H′**), 3.94 (1H, quin. d, *J* 6.5, 1.5 Hz, C(5)**H**); δ_C (125

MHz, CD_3OD) 18.2 (**C**(9)H_3), 24.4 (**C**(8)H_3), 28.0 (**C**(7)H_2), 35.8 (**C**(6)H_2), 54.9 (**C**(5)H), 76.8 (**C**(2) and **C**(7a)), 167.8 (**C**(10)), 175.4 (**C**(3)), 205.8 (**C**(1)).

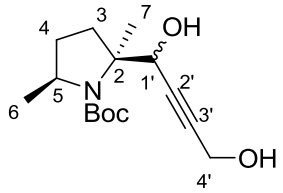
(5*SR*,7a*SR*)-2-Iodo-5,7a-dimethyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizine-3-carbonyl azide (1.142)



Carboxylate **1.173** (39.0 mg, 0.11 mmol) was dissolved in DMF (0.33 mL) and cooled to 0 °C before diphenylphosphoryl azide (23.7 µL, 0.11 mmol) was added. The reaction was stirred for 2 h 30 mins then quenched with water (1 mL) and diluted in ether (3 mL). The layers were separated, the aqueous layer extracted with ethyl acetate (2 × 5 mL) and the combined organic layers washed with sodium bicarbonate (sat. aq., 5 mL) and brine (sat. aq., 5 mL) before being dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography gave *acyl azide* **1.142** as a bright yellow oil (8 mg, 21%).

R_f 0.21 (ether); ν_{max} (thin film)/cm^{-1} 3363br, 2969w, 2360w, 2149w, 1694m, 1615m, 1531m, 1445m, 1260w, 1164br, 1131w, 800w; δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* 6.5 Hz, C(9)**H$_3$**), 1.36 (3H, s, C(8)**H$_3$**), 1.78-1.92 (3H, m, C(7)**H$_2$** and C(6)**H**H′), 2.41-2.48 (1H, m, C(6)H**H′**), 4.18 (1H, quin. d, *J* 6.5, 2.0 Hz, C(5)**H**); δ_C (125 MHz, $CDCl_3$) 20.3 (**C**(9)H_3), 24.6 (**C**(8)H_3), 28.4 (**C**(7)H_2), 34.9 (**C**(6)H_2), 56.4 (**C**(5)H), 75.1 (**C**(2)), 75.7 (**C**(7a)), 164.1 (**C**(10)), 168.5 (**C**(3)), 203.9 (**C**(1)); *m/z* (ESI^+) 293 (42%), 315 (96), 389 (MNa^+, 76), 607 (100), 661 (84), 715 (M_2Na^+, 66); HRMS not found.

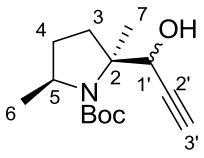
(2*SR*,5*SR*)-*tert*-Butyl 2-(1,4-dihydroxybut-2-ynyl)-2,5-dimethylpyrrolidine-1-carboxylate (1.144)



TBAF (1M in THF, 1.57 mL, 1.57 mmol) was added dropwise to a solution of alcohol **1.131** (566 mg, 1.43 mmol, major isomer obtained from addition reaction) in THF (11.1 mL) stirring at 0 °C. Afer 15 mins the reaction was quenched with water (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with ammonium chloride (15 mL) and brine (sat. aq., 15 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 3:2, petrol/ether) gave diol **1.144** as a colourless oil (410 mg, 100%).

R_f 0.25 (3:2, ether/petrol); ν_{max} (thin film)/cm^{-1} 3382br, 2974s, 1661s, 1400br, 1255w, 1173m, 1142m, 1099m, 1076m, 1036br; δ_H (500 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.5 Hz, C(6)**H$_3$**), 1.36 (3H, s, C(7)**H$_3$**), 1.47 (10H, m, C(C**H$_3$**)$_3$ and C(4)**H**H′), 1.52-1.65 (2H, m, C(3)**H**H′ and CH_2O**H**), 2.02-2.20 (2H, m, C(3)H**H′** and C(4)H**H′**), 4.02 (1H, quin., *J* 6.5 Hz, C(5)**H**), 4.28 (2H, app. t, *J* 2.0 Hz, C(4′)**H$_2$**), 4.34 (1H, br s, C(1′)**H**), 6.57 (1H, br s, CHO**H**); δ_C (125 MHz, $CDCl_3$) 20.3 (**C**(7)H_3), 20.4 (**C**(6)H_3), 28.4 (C(**C**H_3)$_3$), 28.6 (**C**(4)H_2), 35.1 (**C**(3)H_2), 51.2 (**C**(4′)H_2), 55.5 (**C**(5)H), 69.2 (**C**(1′)H), 80.3, 82.8 and 85.8 (**C**≡**C** and **C**$(CH_3)_3$), 155.9 (**C**=O); *m/z* (ESI^+) 306 (MNa^+, 100), 589 (M_2Na^+, 99); HRMS (ESI^+) found 306.1676; $C_{15}H_{25}NNaO_4$ (MNa^+) requires 306.1676.

(2*SR*,5*SR*)-*tert*-Butyl 2-(1-hydroxyprop-2-ynyl)-2,5-dimethylpyrrolidine-1-carboxylate (1.174)

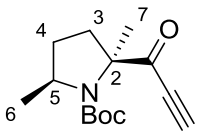


Lithium acetylide ethylene diamine complex (46 mg, 0.50 mmol) was added to a solution of aldehyde **1.120** (75 mg, 0.32 mmol) in THF (2.5 mL) stirring at RT. After 6 h 30 mins the reaction was

quenched with water (10 mL) and extracted with ether (2 × 15 mL). The combined organic phases were washed with brine (sat. aq., 10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 5:1, petrol/ether) gave *alcohol* **1.174** as a colourless oil (65 mg, 80%).

R_f 0.16 (5:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 3312br, 2972br, 1664br, 1396s, 1260m, 1172br, 1078br; δ_H (500 MHz) 1.21 (3H m, d, *J* 6.5 Hz, C(6)**H$_3$**), 1.36 (3H, s, C(7)**H$_3$**), 1.47 (9H, s, C(C**H$_3$**)$_3$), 1.56-1.65 (2H, m, C(3)**H**H′ and C(4)**H**H′), 1.97-2.24 (2H, C(3)H**H′** and C(4′)H**H′**), 2.36 (1H, d, *J* 2.0 Hz, C(3′)**H**), 4.01 (1H m, app. quin., *J* 6.5 Hz, C(5)**H**), 4.31 (1H, d, *J* 10.0 Hz, C(1′)**H**), 6.56 (1H, d, *J* 10.0 Hz, O**H**); δ_C (125 MHz) 20.3 and 22.3 (**C**(6)H_3 and **C**(7)H_3), 28.4 (C(**C**H_3)$_3$), 29.7 (**C**(4)H_2), 35.0 (**C**(3)H_2), 55.5 (**C**(5)H), 69.1 (**C**(1′)H), 72.7 (**C**(3′)H), 77.2 (**C**(2)), 80.3 (**C**(CH_3)$_3$), 83.4 (**C**(2′)), 155.9 (**C**O_2*t*-Bu); *m*/*z* (ESI^+) 276 (MNa^+, 94%), 503 (86), 529 (M_2Na^+, 100); HRMS (ESI^+) found 276.1570; $C_{14}H_{23}NNaO_3$ (MNa^+) requires 276.1570.

(2*SR*,5*SR*)-*tert*-Butyl 2,5-dimethyl-2-propioloylpyrrolidine-1-carboxylate (1.146)



Method A: Upon standing, aldehyde **X** was found to decarbonylate, yielding alkyne **1.146**.

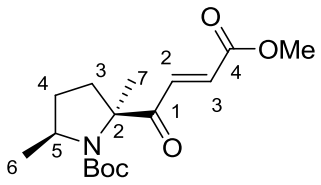
Method B: Alcohol **1.174** (65.0 mg, 0.26 mmol) was dissolved in DCM (4.7 mL) and cooled to 0 °C. DMP (218 mg, 0.51 mmol) was added and the reaction stirred at 0 °C for 30 mins before being warmed to RT. After 2 h, the reaction mixture was diluted in ether (10 mL) and quenched with NaOH solution (1.3 M aq., 10 mL). The mixture was stirred for 15 mins before the layers were separated and the organic layer was washed with NaOH solution (1.3 M aq., 5 mL), water (5 mL) and brine (sat. aq., 5 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give *ketone* **1.146** as a colourless oil, in a 1.6:1 ratio of rotamers (as determined by ^{1}H NMR analysis) (64 mg, 100%).

R_f 0.17 (4:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2976br, 2091m, 1692s, 1387br, 1256w, 1171br, 1095m; δ_H (500 MHz) **Major (M) and minor (m) rotamers**: 1.32 (3H, d, *J* 6.5 Hz, C(6)**H$_3$** m), 1.34

(3H, d, *J* 6.5 Hz, C(6)**H$_3$** M), 1.41 (10H, app. s, C(7)**H$_3$** and C(C**H$_3$**)$_3$ M), 1.45-1.46 (10H, m, C(7)**H$_3$** and C(C**H$_3$**)$_3$ M), 1.60-1.71 (4H, m, C(3)**H**H′ and C(4)**H**H′ M and m), 2.12-2.30 (3H, m, C(3)H**H′** m and C(4)H**H′** M and m), 2.35 (1H, td, *J* 13.0, 6.5 Hz, C(3)H**H′** M), 3.05 (1H, s, C≡C**H** m), 3.13 (1H, s, C≡C**H** M), 4.03 (1H, app. quin., *J* 6.5 Hz, C(5)**H** m), 4.16 (1H, dq, *J* 7.0, 6.5 Hz, C(5)**H** M); δ_C (125 MHz) 18.6 (**C**(7)H$_2$ m), 19.6 (**C**(7)H$_2$ M), 19.7 (**C**(6)H$_2$ M), 20.4 (**C**(6)H$_2$ m), 28.2 (C(**C**H$_3$)$_3$ M), 28.5 (C(**C**H$_3$)$_3$ m), 30.1 (**C**(4)H$_2$ M), 31.1 (**C**(4)H$_2$ m), 34.0 (**C**(3)H$_2$ m), 35.2 (**C**(3)H$_2$ M), 54.4 (**C**(5)H m), 54.7 (**C**(5)H M), 71.2 (**C**(2) M), 71.3 (**C**(2) m), 78.0, 78.9, 79.5, 79.7, 80.6 and 80.9 (**C**≡**C** and **C**(CH$_3$)$_3$ M and m), 152.6 (**C**O$_2$*t*-Bu M), 153.5 (**C**O$_2$*t*-Bu m), 188.5 (**C**=O m), 188.7 (**C**=O M); *m*/*z* (ESI$^+$) 274 (MNa$^+$, 72%), 353 (40), 525 (M$_2$Na$^+$, 100), 585 (59), 625 (74); HRMS (ESI$^+$) found 274.1413; $C_{14}H_{21}NNaO_3$ (MNa$^+$) requires 274.1414.

Crystal structure obtained (see **Appendix E**).

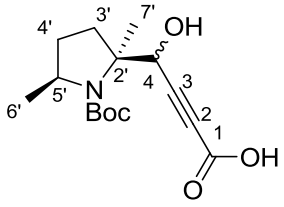
(2*SR*,5*SR*)-*tert*-Butyl 2-[(*E*)-4-methoxy-4-oxobut-2-enoyl]-2,5-dimethylpyrrolidine-1-carboxylate (1.148)



Sodium cyanide (18.6 mg, 0.38 mmol), manganese oxide (85% activated, 154 mg, 1.51 mmol) and acetic acid (6.2 µL, 0.11 mmol) were added to a solution of aldehyde **1.145** (20 mg, 0.072 mmol) in methanol (0.3 mL) and the resultant solution was stirred at RT for 20 mins before the reaction mixture was evaporated *in vacuo* with the evaporated gases being quenched by bubbling through sodium hydroxide solution (1M aq.). The residue was redissolved in water (2 mL), extracted with ether (5 × 3 mL) and the organic layers were dried (MgSO$_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO$_2$, 4:1, petrol/ether) gave *ester* **1.148** as a pale yellow oil, in a 1.5:1 ratio of rotamers (as determined by ^{1}H NMR analysis) (16 mg, 71%).

R_f 0.60 (1:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2975br, 1737s, 1697s, 1437m, 1388s, 1229br, 1169m, 1089w, 1063m, 1034m; δ_H (500 MHz, $CDCl_3$) **Major (M) and minor (m) rotamers**: 1.22 (3H, d, *J* 6.5 Hz, C(6)**H**$_3$ m), 1.29 (3H, d, *J* 6.5 Hz, C(6)**H**$_3$ M), 1.40 (9H, s, C(C**H**$_3$)$_3$ M), 1.43 (3H, C(7)**H**$_3$ M), 1.46 (9H, s, C(C**H**$_3$)$_3$ m), 1.48 (3H, s, C(7)**H**$_3$ m), 1.59-1.77 (4H, m, C(3)**H**H′ and C(4)**H**H′ M and m), 2.10-2.45 (4H, m, C(3)H**H′** and C(4)H**H′** M and m), 3.74 (3H, s, OC**H**$_3$ m), 3.80 (3H, s, OC**H**$_3$ M), 4.01 (1H, app. quin., *J* 7.0 Hz, C(5)**H** m), 4.18 (1H, app. quin., *J* 7.0 Hz, C(5)**H** m), 6.07 (1H , d, *J* 12.0 Hz, C**H**=CH m), 6.25 (1H, d, *J* 12.0 Hz, C**H**=CH M), 6.78 (1H, d, *J* 12.0 Hz, CH=C**H** M), 6.86 (1H, d, *J* 12.0 Hz, CH=C**H** m); δ_C (125 MHz, $CDCl_3$) 19.6 (**C**(6)H_3 m), 20.1 (**C**(6)H_3 M), 20.2 (**C**(7)H_3 M), 20.6 (**C**(7)H_3 m), 28.2 (C(**C**H_3)$_3$ M), 28.5 (C(**C**H_3)$_3$ m), 29.8 (**C**(4)H_2 M), 30.2 (**C**(4)H_2 m), 34.7 (**C**(3)H_2 m), 35.0 (**C**(3)H_2 M), 51.9 (O**C**H_3 m), 52.0 (O**C**H_3 M), 54.4 (**C**(5)H m), 54.6 (**C**(5)H M), 70.4 (**C**(2) M and m), 80.0 (**C**$(CH_3)_3$ m), 81.1 (**C**$(CH_3)_3$ M), 126.2 (**C**H=CH m), 130.8 (**C**H=CH M), 131.7 (CH=**C**H M), 140.4 (CH=**C**H m), 152.8 (**C**O*t*-Bu M), 153.6 (**C**O*t*-Bu m), 166.1 (**C**O_2Me m), 167.0 (**C**O_2Me M), 199.8 (**C**(1) M), 203.1 (**C**(1) m); *m/z* (ESI^+) 212 ($[M-Boc]H^+$, 36%), 334 (MNa^+, 74), 366 ($[M+MeOH+Na]^+$, 68), 645 (M_2Na^+, 99), 677 ($[M_2+MeOH+Na]^+$, 100); HRMS (ESI^+) found 334.1624; $C_{16}H_{25}NNaO_5$ (MNa^+) requires 334.1625.

4-[(2*SR*,5*SR*)-1-(*tert*-Butoxycarbonyl)-2,5-dimethylpyrrolidin-2-yl]-4-hydroxybut-2-ynoic acid (1.175)

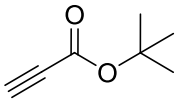


Propiolic acid (15 mg, 0.22 mmol) was dissolved in THF (0.4 mL) and HMPA (0.2 mL) and cooled to −40 °C. *n*-Butyllithium (1.6 M in hexanes, 276 μL, 0.44 mmol) and further HMPA (0.2 mL) were added and the solution was warmed to 0 °C. A solution of aldehyde **1.120** (50 mg, 0.22 mmol) in THF (0.4 mL) was added *via* cannula and the reaction was stirred at 0 °C for 1 h 30 mins before being quenched with ammonium chloride solution (sat. aq., 10 mL) and extracted with ethyl acetate (2 ×

10 mL). The organic phase was acidified with citric acid (5% aq., 10 mL) and extracted again with ethyl acetate (15 mL). The combined organic phases were washed with brine (sat. aq., 10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 9:1, ethyl acetate/methanol) gave *acid* **1.175** as a colourless oil (50 mg, 77%).

R_f 0.09 (9:1, ethyl acetate/methanol); δ_H (500 MHz, $CDCl_3$) 1.21 (3H, m, C(6′)**H₃**), 1.36 (3H, s, C(7′)**H₃**), 1.45-1.55 (10H, m, C(4′)**H**H′ and C(C**H₃**)₃), 1.65-1.68 (1H, m, C(3′)**H**H′), 2.04-2.19 (2H, m, C(3′)H**H′** and C(4′)H**H′**), 4.01 (1H, app. quin., *J* 6.5 Hz, C(5′)**H**), 4.45 (1H, s, C(4)**H**), 7.00-7.45 (2H, br m, 2 × O**H**); δ_C (125 MHz, $CDCl_3$) 19.2 (**C**(7′)H_3), 19.5 (**C**(6′)H_3), 27.4 (C(**C**H_3)₃), 27.6 (**C**(4′)H_2), 34.1 (**C**(3′)H_2), 54.7 (**C**(5′)H), 64.4 (**C**(4)H), 68.1 (**C**(2)), 87.5 (**C**(3)), 103.3 (**C**(CH_3)₃), 154.3 (**C**(1)), 155.1 (**C**O*t*-Bu); *m/z* (ESI^+) 250 (54%), 320 (MNa^+, 100), 366 (44), 477 (47), 617 (M_2Na^+, 87), 937 (41); HRMS (ESI+) found 320.1463; $C_{15}H_{23}NNaO_5$ (MNa^+) requires 320.1468.

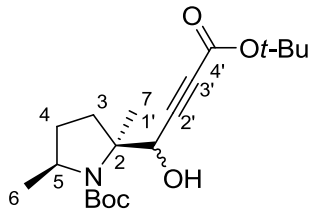
***tert*-Butyl propiolate**



A suspension of phosphorous pentoxide (4.00 g, 28.6 mmol) in DCM (40 mL) was stirred at RT for 15 mins before propiolic acid (880 μL, 14.3 mmol) was added dropwise. The reaction mixture was stirred for 60 h whereupon it was poured onto iced water (100 mL), extracted with ether (3 × 50 mL) and the combined organic extracts were dried ($MgSO_4$). Purification by flash chromatography (SiO_2, 20:1, petrol/ether) gave *tert*-butyl propiolate as a colourless oil (1.3 g, 72%).

R_f 0.51 (10:1, petrol/ether); δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, C(C**H₃**)₃), 2.76 (1H, s, ≡C**H**); δ_C (100 MHz, $CDCl_3$) 27.9 (C(**C**H_3)₃), 72.1 (C≡C**H**), 76.0 (**C**≡CH), 84.1 (**C**(CH_3)₃), 151.7 (**C**=O). Data as reported.[17]

(2*SR*,5*SR*)-*tert*-Butyl 2-(4-tert-butoxy-1-hydroxy-4-oxobut-2-ynyl)-2,5-dimethylpyrrolidine-1-carboxylate (1.149)

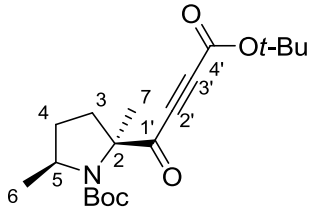


LHMDS (1M in THF, 1.41 mL, 1.41 mmol) was added dropwise to a solution of *tert*-butyl propiolate (178 mg, 1.41 mmol) in THF (4 mL) stirring at −40 °C. . The resultant solution was stirred for 20 mins before being quickly warmed to 0 °C whereupon aldehyde **1.120** (160 mg, 0.70 mmol) in THF (1.0 mL) was added *via* cannula. After 2 h the reaction was quenched with water (5 mL) and diluted with ether (10 mL). The layers were separated, the aqueous layer extracted with ether (20 mL) and the combined organic layers washed with brine (sat. aq., 3 × 10 mL) and dried ($MgSO_4$). Purification by flash chromatography (SiO_2, 5:1, petrol/ether) gave *alcohol* **1.149** as a brown oil in a separable mixture of the two diastereomers in a 8:1 ratio (as determined by ^{1}H NMR analysis) (combined yield 170 mg, 90%).

Major: R_f 0.31 (5:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 3321br, 2976br, 1709s, 1662s, 1457br, 1399s, 1257s, 1160br, 1099w, 1035w; δ_H (500 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.5 Hz, C(6)**H$_3$**), 1.35 (6H, s, C(7)**H$_3$**), 1.46 (9H, s, C(C**H$_3$**)$_3$), 1.48 (9H, s, C(C**H$_3$**)$_3$), 1.61-1.68 (2H, m, C(3)**H**H′ and C(4)**H**H′), 2.03-2.18 (2H, m, C(3)H**H′** and C(4)H**H′**), 6.62 (1H, app quin., *J* 6.5 Hz, C(5)**H**), 4.34 (1H, d, *J* 11.0 Hz, C(1′)**H**), 6.76 (1H, d, *J* 11.0 Hz, O**H**); δ_C (125 MHz, $CDCl_3$) 20.2 and 20.4 (**C**(6)H$_3$ and **C**(7)H$_3$), 27.9 and 28.4 (2 × C(**C**H$_3$)$_3$), 28.7 (**C**(4)H$_2$), 35.2 (**C**(3)H$_2$), 55.6 (**C**(5)H), 68.4, 69.2, 77.7, 80.6, 83.0 and 84.6 (**C**(1′)H, **C**(2), **C**≡**C**, and 2 × **C**(CH$_3$)$_3$), 156.0 and 152.4 (2 × **C**O$_2$C(CH$_3$)$_3$); *m*/*z* (ESI$^+$) 376 (MNa$^+$, 74%), 603 (100), 729 (M$_2$Na$^+$, 98), 785 (99); HRMS (ESI$^+$) found 376.2094; $C_{19}H_{31}NNaO_5$ (MNa$^+$) requires 376.2094.

Minor: R_f 0.18 (5:1, petrol/ether); HRMS (ESI$^+$) found 376.2093; $C_{19}H_{31}NNaO_5$ (MNa$^+$) requires 376.2094. The minor isomer was not isolated cleanly enough in sufficient quantity to obtain accurate NMR data.

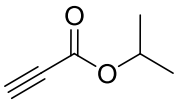
(2*SR*,5*SR*)-*tert*-Butyl 2-(4-tert-butoxy-4-oxobut-2-ynoyl)-2,5-dimethylpyrrolidine-1-carboxylate (1.150)



Alcohol **1.149** (32 mg, 0.09 mmol) was dissolved in DCM (1.15 mL) and cooled to 0 °C. DMP (40 mg, 0.10 mmol) was added and the resultant mixture stirred at 0 °C for 30 mins before being warmed to RT and stirred for 16 h before a second portion of DMP (40 mg, 0.10 mmol) was added. After a further 3 h the reaction was diluted with ether (5 mL) and quenched by stirring with sodium hydroxide (1.3 M aq., 5 mL) for 15 mins. The layers were separated, the aqueous layer extracted with ether (10 mL) and the combined organic layers washed with sodium hydroxide (1.3 M aq., 2 × 10 mL) and brine (10 mL) and dried ($MgSO_4$). Purification by flash chromatography (SiO_2, 4:1 petrol/ether) gave *acetylenic ketone* **1.150** as a colourless oil, in a 1.7:1 ratio of rotamers (as determined by ^{1}H NMR analysis) (29 mg, 100%).

R_f 0.16 (7:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2978br, 1698br, 1369br, 1273br, 1156br, 1108m, 751w; δ_H (500 MHz, $CDCl_3$) **Major (M) and minor (m) rotamers**: 1.32 (3H, d, *J* 6.5 Hz, C(6)**H$_3$** M), 1.33 (3H, d, *J* 6.5 Hz, C(6)**H$_3$** m), 1.42-1.48 (42H, m, C(7)**H$_3$** and 2 × C(C**H$_3$**)$_3$ M and m), 1.58-1.72 (4H, m, C(3)**H**H′ and C(4)**H**H′ M and m), 2.12-2.38 (4H, m, C(3)H**H′** and C(4)H**H′** M and m), 4.04 (1H, dq, *J* 7.0 and 6.5 Hz, C(5)**H** M), 4.17 (1H, app. quin., *J* 6.5 Hz, C(5)**H** m); δ_C (125 MHz, $CDCl_3$) 18.5 (**C**(7)H$_3$ m), 19.4 (**C**(7)H$_3$ M), 19.7 (**C**(6)H$_3$ M), 20.2 (**C**(6)H$_3$ m), 27.8, 27.9, 28.1 and 28.5 (2 × C(**C**H$_3$)$_3$ M and m), 30.0 (**C**(4)H$_2$ M), 31.1 (**C**(4)H$_2$ m), 33.8 (**C**(3)H$_2$ m), 35.1 (**C**(3)H$_2$ M), 54.4 (**C**(5)H m), 54.8 (**C**(5)H M), 63.7 and 65.8 (**C**(2) M and m), 71.3, 71.5, 77.3, 77.8, 80.4, 81.3, 84.7 and 85.1 (2 × **C**(CH$_3$)$_3$, C(2′) and C(3′) M and m), 150.8 and 152.4 (N**C**O$_2$C(CH$_3$)$_3$ and C(4′) M), 151.1 and 153.6 (N**C**O$_2$C(CH$_3$)$_3$ and C(4′) m), 187.7 (**C**(1′) m), 188.0 (**C**(1′) M); *m/z* (ESI$^+$) 374 (MNa$^+$, 71%), 437 (73), 502 (84), 603 (76), 725 (M$_2$Na$^+$, 100), 781 (94); HRMS (ESI$^+$) found 374.1931; $C_{19}H_{29}NNaO_5$ (MNa$^+$) requires 374.1938.

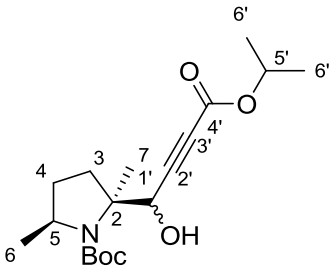
Isopropyl propiolate



A solution of propiolic acid (1.00 g, 14.3 mmol) and boron trifluoride diethyl etherate (3.63 mL, 29.4 mmol) in isopropyl alcohol (7.7 mL) was stirred at reflux for 1 h 40 mins and then at RT for 1 h 30 mins before being quenched with water (5 mL) and extracted with DCM (3 × 10 mL). The organic layers were washed with brine (sat. aq., 20 mL), dried ($MgSO_4$) and carefully evaporated *in vacuo* to give isopropyl propiolate as a colourless liquid (1.3 g, 45%).

δ_H (400 MHz, $CDCl_3$) 1.32 (6H, d, *J* 6.0 Hz, 2 × C**H**$_3$), 2.86 (1H, s, C≡C**H**), 5.13 (1H, sept, *J* 6.0 Hz, C**H**); δ_C (100 MHx, $CDCl_3$) 21.6 (2 × **C**H_3), 65.8 (C≡**C**H), 70.5 (**C**H), 75.1 (**C**≡CH), 152.3 (**C**=O). Data as reported.[18]

(2*SR*,5*SR*)-*tert*-Butyl 2-(1-hydroxy-4-isopropoxy-4-oxobut-2-ynyl)-2,5-dimethylpyrrolidine-1-carboxylate (1.176)



LHMDS (1 M in THF, 1.1 mL, 1.1 mmol) was added dropwise to a solution of isopropyl propiolate (123 mg, 1.10 mmol) in THF (2.0 mL) stirring at –40 °C. The resultant solution was stirred for 20 mins before being quickly warmed to 0 °C whereupon aldehyde **1.120** (100 mg, 0.44 mmol) in THF (0.5 mL) was added *via* cannula. After 2 h 30 the reaction was quenched with water (5 mL) and diluted with ether (5 mL). The layers were separated, the aqueous layer extracted with ether (10 mL) and the combined organic layers washed with brine (sat. aq., 3 × 5 mL) and dried ($MgSO_4$) to give a

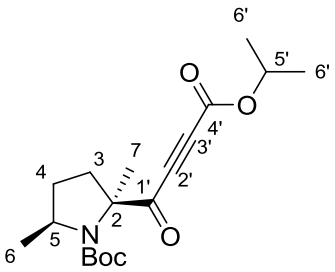
mixture of major and minor diastereomers (7:1) of *alcohol* **1.176** as a brown oil (150 mg). This material was found to be of sufficient purity to be taken crude through to the next step.

A sample of this material was purified by flash chromatography (SiO_2, 5:1, petrol/ether) to give two separable, diastereomeric products. The relative stereochemistry of the two products is unknown.

Major isomer: R_f 0.23 (5:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 3406br, 2978m, 2936m, 2360m, 2340m, 2236w, 1711s, 1661s, 1455br, 1400s, 1252s, 1169br, 1103m, 1041m; δ_H (500 MHz, $CDCl_3$) 1.23 and 1.24 (6H, 2 × d, *J* 6.5 Hz, 2 × C(6′)**H$_3$**), 1.25 (3H, d, *J* 6.5 Hz, C(6′)**H$_3$**), 1.36 (3H, s, C(7)**H$_3$**), 1.48 (9H, s, C(C**H$_3$**)$_3$), 1.43-1.51 (1H, m, C(4)**H**H′), 1.60-1.68 (1H, m, C(3)**H**H′), 2.06-2.16 (2H, m, C(3)H**H′** and C(4)H**H′**), 4.01 (1H, app. quin, *J* 5.0 Hz, C(5)**H**), 4.37 (1H, d, *J* 10.5 Hz, C(1′)**H**), 5.07 (1H, sept, *J* 6.5 Hz, C(5′)**H**), 6.78 (1H, d, *J* 11.0 Hz, O**H**); δ_C (125 MHz, $CDCl_3$) 20.2 and 20.4 (**C**(6)H_3 and **C**(7)H_3), 21.6 (2 × **C**(6′)H_3), 28.4 (C(**C**H_3)$_3$), 28.6 (**C**(4)H_2), 35.2 (**C**(3)H_2), 55.6 (**C**(5)H), 68.4 (**C**(2)), 69.2 (**C**(5′)H), 69.6 (**C**(1′)HOH), 80.6 (**C**$(CH_3)_3$), 76.9 and 86.6 (**C**≡**C**), 152.9 (**C**$O_2C(CH_3)_3$), 156.0 (**C**(4′)); *m/z* (ESI^+) 362 (MNa^+, 53%), 474 (39), 589 (59), 701 (100), 929 (41); HRMS found 362.1936; $C_{18}H_{29}NNaO_5$ (MNa^+) requires 362.1938.

Minor isomer: R_f 0.12 (5:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 3406br, 2979m, 2935br, 2879w, 2850w, 2238w, 1711s, 1691s, 1666m, 1455m, 1389br, 1308w, 1253s, 1221w, 1169m, 1129m, 1105m, 1035m; δ_H (500 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.5 Hz, C(6)**H$_3$**), 1.27 (6H, d, *J* 6.5 Hz, 2 × C(6′)**H$_3$**), 1.41-1.48 (13H, m, C(4)**H**H′, C(C**H$_3$**)$_3$ and C(7)**H$_3$**), 1.82-1.88 (1H, m, C(3)**H**H′), 1.98-2.13 (2H, C(3)H**H′** and C(4)H**H′**), 4.02-4.09 (1H, m, C(5)**H**), 4.66 (1H, br s, C(1′)**H**), 5.08 (1H, sept, *J* 6.5 Hz, C(5′)**H**), 6.55 (1H, br s, O**H**); δ_C (125 MHz, $CDCl_3$) 17.9 (**C**(7)H_3), 18.5 (**C**(6)H_3), 21.7 (2 × **C**(6′)H_3), 28.4 (C(**C**H_3)$_3$), 29.7 (**C**(4)H_2), 35.9 (**C**(3)H_2), 56.3 (**C**(5)H), 68.3 (**C**(5′)H), 72.7 (**C**(1′)HOH), 65.9 (**C**(2)), 76.5 and 85.7 (**C**≡**C**), 80.9 (**C**$(CH_3)_3$), 153.0 (**C**$O_2C(CH_3)_3$), 156.1 (**C**(4′)); *m/z* (ESI^+) 362 (MNa^+, 53%), 474 (39), 589 (59), 701 (100), 929 (41); HRMS found 362.1937; $C_{18}H_{29}NNaO_5$ (MNa^+) requires 362.1938.

(2*SR*,5*SR*)-*tert*-Butyl 2-(4-isopropoxy-4-oxobut-2-ynoyl)-2,5-dimethylpyrrolidine-1-carboxylate (1.151)

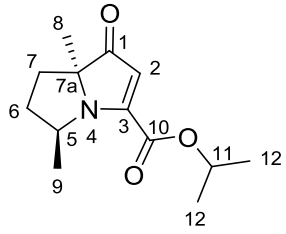


Alcohol **1.176** (0.44 mmol) was dissolved in DCM (6 mL) and cooled to 0 °C. DMP (373 mg, 0.88 mmol) was added and the resultant mixture stirred at 0 °C for 30 mins before being warmed to RT and stirred for 1 hr 30 mins. The reaction was diluted with ether (10 mL) and quenched by stirring with sodium hydroxide (1.3 M aq., 10 mL) for 15 mins. The layers were separated, the aqueous layer extracted with ether (10 mL) and the combined organic layers washed with sodium hydroxide (1.3 M aq., 2 × 10 mL) and brine (10 mL) and dried ($MgSO_4$). Purification by flash chromatography (SiO_2, 4:1, petrol/ether) gave *acetylenic ketone* **1.151** as a colourless oil, in a 1.6:1 ratio of rotamers (as determined by ^{1}H NMR analysis) (130 mg, 88% over two steps).

R_f 0.39 (5:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2980m, 2936m, 2880w, 1716s, 1699s, 1462m, 1389s, 1367s, 1304w, 1262s, 1246s, 1170m, 1128w, 1104s, 1072m, 1037w; δ_H (500 MHz, $CDCl_3$) **Major (M) and minor (m) rotamers**: 1.27 (6H, d, *J* 6.5 Hz, 2 × C(6′)**H$_3$** M) 1.28 (6H m, d, *J* 6.5 Hz, 2 × C(6′)**H$_3$** m), 1.33 (3H, d, *J* 6.5 Hz, C(6)**H$_3$** M and m), 1.42 (3H, s, C(7)**H$_3$** M), 1.43 (9H, s, C(C**H$_3$**)$_3$ M), 1.46 (3H, s, C(7)**H$_3$** m), 1.48 (9H, s, C(C**H$_3$**)$_3$ m), 1.64-1.73 (2H, m, C(3)**H**H′ and C(4)**H**H′ M and m), 2.13-2.29 (3H, m, C(4)H**H′** M and m and C(3)H**H′** m), 2.35 (1H, dt, *J* 12.5, 6.5 Hz, C(3)H**H′** M), 4.04 (1H, quin, *J* 6.5 Hz, C(5)**H** m), 4.17 (1H, quin, *J* 6.5 Hz, C(5)**H** M), 5.11 (1H, sept, *J* 6.5 Hz, C(5′)**H** m), 5.12 (1H, sept, *J* 6.5 Hz, C(5′)**H** M); δ_C (500 MHz, $CDCl_3$) 18.5 (**C**(7)H$_3$ m), 19.5 (**C**(7)H$_3$ M), 19.7 (**C**(6)H$_3$ M), 20.3 (**C**(6)H$_3$ m), 21.5 (2 × **C**(6′)H$_3$ M and m), 28.1 (C(**C**H$_3$)$_3$ M), 28.4 (C(**C**H$_3$)$_3$ m), 30.0 (**C**(4)H$_2$ M), 31.1 (**C**(4)H$_2$ m), 33.7 (**C**(3)H$_2$ m), 35.1 (**C**(3)H$_2$ M), 54.3 (**C**(5)H m), 54.8 (**C**(5)H M), 70.8, 71.0, 71.3 and 71.5 (**C**(5′)H and **C**(2) M and m), 79.3, 79.4, 79.6, 80.4 and 81.3 (**C**(CH$_3$)$_3$, **C**(3′) and **C**(2′) M and m), 151.5 (**C**(4′) M), 151.7 (**C**(4′) m), 152.4 (**C**O$_2$C(CH$_3$)$_3$ M), 153.6

(**C**O_2C$(CH_3)_3$ m), 187.5 (**C**(1′) m), 187.8 (**C**(1′) M); *m/z* (ESI$^+$) 355 (MNH_4^+, 10%), 360 (MNa^+, 25), 396 ([M+MeCN+NH_4]$^+$, 24), 474 (34), 589 (45), 697 (M_2Na^+, 100), 926 (56); HRMS found 360.1780; $C_{18}H_{27}NNaO_5$ (MNa^+) requires 360.1781.

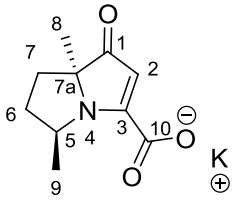
(5*SR*,7a*SR*)-Isopropyl 5,7a-dimethyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizine-3-carboxylate (1.152)



Ester **1.151** (50 mg, 0.15 mmol) was dissolved in DCM (1.25 mL) and the solution cooled to −30 °C before trimethylsilyl trifluoromethanesulfonate (40 µL, 0.22 mmol) was added and the reaction mixture allowed to warm to 0 °C over 2 h. $NaHCO_3$ (sat. aq., 5 mL) was added and the reaction extracted with DCM (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 3:2, petrol/ether) gave *ester* **1.152** as a bright yellow oil (70 mg, 63%).

R_f 0.32 (1:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 3357br, 2977s, 1730s, 1687s, 1539s, 1377br, 1243s, 1105m, 1080s, 1001w, 925m, 900m, 833w, 785m; δ_H (500 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.5 Hz, C(9)**H$_3$**), 1.29 (3H, s, C(8)**H$_3$**), 1.31 and 1.32 (6H, 2 × d, *J* 6.0 Hz, 2 × C(12)**H$_3$**), 1.65-1.83 (3H, m, C(6)**H**H′ and C(7)**H$_2$**), 2.36-2.48 (1H, m, C(6)H**H′**), 4.03-4.12 (1H, m, C(5)**H**), 5.16 (1H, sept, *J* 6.0 Hz, C(11)**H**), 5.77 (1H, s, C(2)**H**); δ_C (125 MHz, $CDCl_3$) 15.3 (**C**(9)H_3), 21.6 (2 × **C**(12)H_3), 24.2 (**C**(8)H_3), 27.6 (**C**(7)H_2), 35.3 (**C**(6)H_2), 55.0 (**C**(5)H), 70.2 (**C**(11)H), 77.8 (**C**(7a)), 111.5 (**C**(2)H), 162.0 (**C**(3)), 165.6 (**C**(10)), 208.8 (**C**(1)); *m/z* (ESI$^+$) 238 (MH^+, 16%), 260 (MNa^+, 66), 292 ([M+MeOH+Na]$^+$, 38), 497 (M_2Na^+, 100); HRMS found 260.1257; $C_{13}H_{19}NO_3Na$ (MNa^+) requires 260.1257.

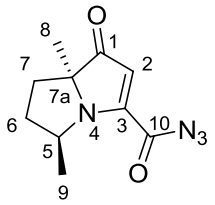
Potassium (5*SR*,7a*SR*)-5,7a-dimethyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizine-3-carboxylate (1.177)



KOH (6.8 mg, 0.12 mmol) was added to a solution of ester **1.152** (25 mg, 0.11 mmol) in acetonitrile (0.75 mL) and water (0.75 mL) and the resultant solution stirred for 1 h before being evaporated *in vacuo* to give *potassium salt* **1.177** as a pale yellow oil (26 mg, 100%).

δ_H (500 MHz, D_2O) 1.13 (3H, d, *J* 6.5 Hz, C(9)**H$_3$**), 1.26 (3H, s, C(8)**H$_3$**), 1.64-1.74 (2H, m, C(7)**H$_2$**), 1.81 (1H, app. tt, *J* 10.0, 3.0 Hz, C(6)**H**H′), 2.52 (1H, ddt, *J* 13.0, 10.5, 7.5 Hz, C(6)H**H′**), 4.00 (1H, dqd, *J* 7.5, 6.5, 3.0 Hz, C(5)**H**), 5.27 (1H, s, C(2)**H**); δ_C (125 MHz, D_2O) 19.0 (**C**(9)H_3), 21.8 (**C**(8)H_3), 27.2 (**C**(7)H_2), 35.9 (**C**(6)H_2), 54.0 (**C**(5)H), 78.4 (**C**(7a)), 101.9 (**C**(2)H), 169.0 (**C**(3)), 175.8 (**C**(10)), 210.8 (**C**(1)).

(5*SR*,7a*SR*)-5,7a-Dimethyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizine-3-carbonyl (1.153)

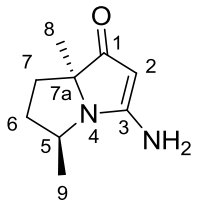


Isopropyl ester **1.152** (10 mg, 0.042 mmol) was dissolved in acetonitrile (0.3 mL) and water (0.3 mL). KOH (2.6 mg, 0.046 mmol) was added and the reaction mixture stirred for 1 h before being evaporated *in vacuo*. The crude residue was redissolved in DMF (0.12 mL), cooled to 0 °C and DPPA (9.1 µL, 0.042 mmol) was added. The reaction was stirred for 2 h 30 mins before being quenched with $NaHCO_3$ (sat. aq., 1 mL) and extracted with ether (2 × 2 mL). The combined organic layers were washed with $NaHCO_3$ (sat. aq., 2 × 3 mL) and brine (3 mL), dried ($MgSO_4$) and evaporated *in vacuo*.

Purification by flash chromatography (SiO_2, 2:1, petrol/ether) gave *acyl azide* **1.153** as a bright yellow oil (8.8 mg, 95%).

R_f 0.38 (1:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2974w, 2153m, 1692s, 1537m, 1421w, 1381w, 1208br, 1128m, 1069w; δ_H (500 MHz, $CDCl_3$) 1.06 (3H, d, *J* 6.5 Hz, C(9)**H$_3$**), 1.33 (3H, s, C(8)**H$_3$**), 1.74-1.88 (3H, m, C(6)**H**H′ and C(7)**H$_2$**), 2.44-2.52 (1H, m, C(6)H**H′**), 4.17 (1H, quin. d, *J* 6.5, 1.5 Hz, C(5)**H**), 5.94 (1H, s, C(2)**H**); δ_C (125 MHz, $CDCl_3$) 20.0 (**C**(9)H_3), 24.4 (**C**(8)H_3), 27.5 (**C**(7)H_2), 35.3 (**C**(6)H_2), 55.2 (**C**(5)H), 78.5 (**C**(7a)), 113.2 (**C**(2)H), 164.4 (**C**(3)), 168.7 (**C**(10)), 209.0 (**C**(1)); HRMS data unobtainable.

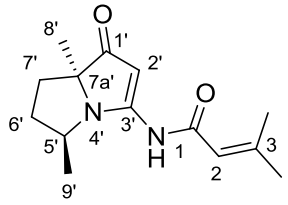
(5*SR*,7a*SR*)-3-Amino-5,7a-dimethyl-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-1-one (1.154)



Acyl azide **1.153** (8.8 mg, 0.04 mmol) was dissolved in acetic acid (95% aq., 376 µL) and heated at 120 °C for 1 h before being cooled and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 9:1, ethyl acetate/methanol) gave *amine* **1.154** as a white solid (6 mg, 90%).

R_f 0.07 (9:1, ethyl acetate/methanol); m.p. 158 °C; ν_{max} (KBr disc)/cm^{-1} 3334br, 2987w, 1660m, 1600s, 1539s, 1455s, 1380w, 1261w, 1214w, 1157w; δ_H (400 MHz, $CDCl_3$ + 1 drop CD_3OD) 1.32 (3H, d, *J* 6.5 Hz, C(9)**H$_3$**), 1.36 (3H, s, C(8)**H$_3$**), 1.69 (1H, ddd, *J* 12.5, 6.5, 3.5 Hz, C(7)**H**H′), 1.80 (1H, ddt, *J* 13.0, 7.0, 3.5 Hz, C(6)**H**H′), 1.94 (1H, ddd, *J* 12.5, 11.0, 7.0 Hz, C(7)H**H′**), 2.33-2.42 (1H, m, C(6)H**H′**), 3.84 (1H, quin. d, *J* 6.5, 3.5 Hz, C(5)**H**), 4.68 (1H, br s, C(2)**H**), 5.26 (2H, br s, N**H$_2$**); δ_C (100 MHz, $CDCl_3$ + 1 drop CD_3OD) 16.5 (**C**(9)H_3), 24.4 (**C**(8)H_3), 28.8 (**C**(6)H_2), 35.9 (**C**(7)H_2), 53.3 (**C**(5)H), 76.5 (**C**(7a)), 153.3 (**C**(2)H), 172.4 (**C**(3)), 200.6 (**C**(1)); *m/z* (ESI^+) 167 (MH^+, 54%), 189 (MNa^+, 73), 355 (M_2Na^+, 100); HRMS (ESI^+) found 189.0999; $C_9H_{14}N_2NaO$ (MNa^+) requires 189.0998.

***N*-[(5*SR*,7a*SR*)-5,7a-Dimethyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-3-yl]-3-methylbut-2-enamide [(±)-NP-25302] (1.43)**

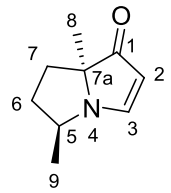


NaH (10.1 mg, 0.25 mmol) was added to a solution of amine **1.154** (31 mg, 0.19 mmol) in THF (5.5 mL) stirring at RT and the resultant slurry was stirred for 10 mins before 3-methyl-2-butenoyl chloride (21 μL, 0.19 mmol) was added. The reaction was stirred for a further 1 h 30 mins before being quenched with water (10 mL) and extracted with DCM (3 × 10 mL). The organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, ethyl acetate) gave (±)-NP25302 (**1.43**) as a pale yellow solid (35 mg, 76%).

R_f 0.16 (ethyl acetate); mp 154 ˚C; ν_{max} (thin film)/cm^{-1} 2973br, 1712w, 1635m, 1566m, 1493br, 1379m, 1361m, 1309w, 1228m, 1122br, 1064w, 1041w, 749br; δ_H (500 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.5 Hz, C(9′)**H$_3$**), 1.33 (3H, s, C(8′)**H$_3$**), 1.73-1.92 (3H, m, C(6′)**H**H′ and C(7′)**H$_2$**), 1.93 and 2.23 (6H, 2 × d, *J* 1.0 Hz, 2 × C(3)C**H$_3$**), 2.42 (1H, app. sept., *J* 6.5 Hz, C(6′)H**H′**), 3.98 (1H, qd, *J* 6.5, 1.5 Hz, C(5′)**H**), 5.68 (1H, s, C(2′)**H**), 5.84 (1H, app. br sept., *J* 1.0 Hz, C(2)**H**), 8.65 (1H, br s, N**H**); δ_C (125 MHz, $CDCl_3$) 17.3 (**C**(9′)H_3), 20.5 (C(3)**C**H_3), 24.7 (**C**(8′)H_3), 27.8 (C(3)**C**H_3), 28.4 (**C**(7′)H_2), 35.3 (**C**(6′)H_2), 55.0 (**C**(5′)H), 74.8 (**C**(7a′)), 94.1(**C**(2′)H), 117.2 (**C**(2)H), 158.7 (**C**(3)), 163.6 (**C**(1)), 166.7 (**C**(3′)), 205.7 (**C**(1′)); *m/z* (ESI^+) 247 ($[M–H]^-$, 100%), 283 (83), 310 (34); HRMS (ESI^+) found 271.1417; $C_{14}H_{20}N_2NaO_2$ (MNa^+)requires 271.1417. Data as reported.[13]

Crystal structure obtained (see **Appendix G**).

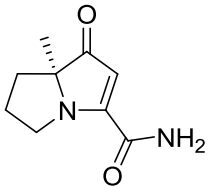
(5*SR*,7a*SR*)-5,7a-Dimethyl-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-1-one (1.157)



Ketone **1.146** (75 mg, 0.30 mmol) was dissolved in DCM (2.5 mL) and the solution cooled to −30 °C before trimethylsilyl trifluoromethanesulfonate (81.0 μL, 0.45 mmol) was added and the reaction mixture allowed to warm to 0 °C over 1 h 30 mins. $NaHCO_3$ (sat. aq., 10 mL) was added and the reaction extracted with DCM (3 × 10 mL) and ethyl acetate (10 mL). The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo* to give *pyrrolizidine* **1.157** as a bright yellow oil (35 mg, 77%).

R_f 0.23 (ether); m.p. 114 °C; $[\alpha]_D^{25}$ +281.2 (c 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.33-1.35 (6H, m, C(8)**H$_3$** and C(9)**H$_3$**), 1.47-1.52 (1H, m, C(6)**H**H′), 1.72 (dt, *J* 13.0, 7.5 Hz, C(7)**H**H′), 1.99 (ddd, *J* 13.0, 9.0, 4.5 Hz, C(7)H**H′**), 2.13 (1H, dddd, *J* 12.5, 7.5, 6.0, 4.5 Hz, C(6)H**H′**), 3.69 (1H, ddd, *J* 9.0, 6.5 Hz, C(5)**H**), 5.22 (1H, d, *J* 3.5 Hz, C(2)**H**), 7.83 (1H, d, *J* 3.5 Hz, C(3)**H**); δ_C (100 MHz, $CDCl_3$) 17.0 (**C**(9)H_3), 22.6 (**C**(8)H_3), 31.6 (**C**(6)H_2), 35.2 (**C**(7)H_2), 54.5 (**C**(5)H), 73.9 (**C**(7a)), 106.8 (**C**(2)H), 164.5 (**C**(3)H), 209.0 (**C**(1)); *m*/*z* (ESI^+) 152 (MH^+,46%), 174 (MNa^+, 100), 206 ($[M+MeOH+Na]^+$, 100), 285 (64), 303 (M_2H^+, 98); HRMS (ESI^+) found 174.0890; $C_9H_{13}NNaO$ (MNa^+) requires 174.0889.

(*S*)-7a-Methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizine-3-carboxamide (1.159)



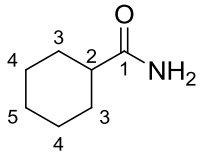
Pre-cooled NH_3 (conc. aq., 90 μL) was added to methyl ester **1.56** (150 mg, 0.78 mmol) at 0 °C. After 20 mins the reaction was diluted in ethyl acetate (10 mL) and brine (sat. aq., 10 mL), the layers were

separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to give *amide* **1.159** a**s** a pale yellow solid (110 mg, 78%).

R_f 0.05 (ether); m.p. 114 °C; $[\alpha]_D^{25}$ +281.2 (c 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3430br, 1693br; δ_H (400 MHz, $CDCl_3$) 1.36 (3H, s, C(8)**H$_3$**), 1.74-1.84 (1H, m, C(7)**H**H′), 1.86 (1H, dd, *J* 13.0, 7.5 Hz, C(7)H**H′**), 2.01 (1H, dtt, *J* 13.0, 7.5, 6.5 Hz, C(6)**H**H′), 2.06-2.18 (1H, m, C(6)H**H′**), 3.41 (1H, ddd, *J* 14.0, 11.5, 7.0 Hz, C(5)**H**H′), 3.51 (1H, ddd, *J* 11.5, 7.0, 6.5 Hz, C(5)H**H′**), 5.63 (1H, s, C(2)**H**), 6.14 (1H, br s, N**H**H′), 6.35 (1H, br s, NH**H′**); δ_C (100 MHz, $CDCl_3$) 22.1 (**C**(8)H_3), 27.0 (**C**(6)H_2), 32.2 (**C**(7)H_2), 48.6 (**C**(5)H_2), 76.3 (**C**(7a)), 106.3 (**C**(2)H), 163.1 and 170.7 (**C**(3) and **C**(O)NH_2), 208.0 (**C**(1)); *m*/*z* (ESI^+) 203 (MNa^+, 83%), 383 (M_2Na^+, 100); HRMS (ESI^+) found 203.0795; $C_9H_{12}N_2NaO_2$ (MNa^+) requires 203.0791

Crystal structure obtained (see **Appendix F**).

Cyclohexanecarboxamide (1.160)

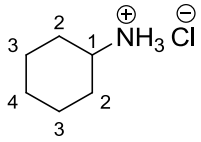


Thionyl chloride (427 μL, 5.85 mmol) was added dropwise to cyclohexanecarboxylic acid (500 mg, 3.90 mmol) and the resulting mixture stirred for 3 mins before being heated to 50 °C. After 1 h the reaction was cooled to 10 °C and NH_3 (088 M aq., 2.60 mL) was added carefully. The resulting slurry was stirred for 30 mins before being filtered and the precipitate washed with $NaHCO_3$ (10% aq., 5 mL) and water (5 mL). The precipitate was dried *in vacuo* to give amide **1.160** as a white solid (380 mg, 40%).

δ_H (400 MHz, $CDCl_3$) 1.15-1.35 (3H, m, C(5)**H**H′ and 2 × C(4)**H**H′), 1.43 (2H, qd, *J* 12.0, 3.0 Hz, 2 × C(3)**H**H′), 1.62-1.84 (3H, m, 2 × C(4)H**H′** and C(5)H**H′**), 1.86-1.92 (2H, m, 2 × C(3)H**H′**), 2.15 (1H,

tt, *J* 12.0, 3.5 Hz, C(2)**H**), 5.32-5.70 (2H, m, N**H**$_2$); δ_C (100 MHz, $CDCl_3$) 25.66 and 25.70 (2 × **C**(4)H_2 and **C**(5)H_2), 29.7 (2 × **C**(3)H_2), 44.8 (**C**(2)H), 178.7 (**C**(1)). Data as reported.[19]

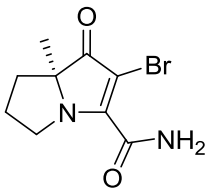
Cyclohexylammonium chloride (1.178)



PIFA (340 mg, 0.79 mmol) was added to a solution of amide **1.160** (100 mg, 0.79 mmol) in acetonitrile (1.2 mL) and water (1.2 mL) and the reaction stirred for 16 h before being quenched by addition of water (15 mL) and HCl (conc., 1.6 mL). The aqueous layer was washed with ether (20 mL) and evaporated *in vacuo* to give amine **1.178** as a white solid (61 mg, 93%).

δ_H (400 MHz, DMSO-d_6) 0.99-1.13 (1H, m, C(4)**H**H′), 1.15-1.33 (4H, m, 2 × C(2)**H**H′ and 2 × C(3)**H**H′), 1.51-1.58 (1H, m, C(4)H**H′**), 1.64-1.72 (2H, m, 2 × C(3)H**H′**), 1.86-1.93 (1H, m, 2 × C(2)H**H′**), 2.84-2.95 (1H, m, C(1)**H**), 8.11 (3H, br s, N**H**$_3$); δ_C (100 MHz, DMSO-d_6) 23.9 (2 × **C**(3)H_2), 24.7 (**C**(4)H_2), 30.4 (2 × **C**(2)H_2), 49.5 (**C**(1)H). Data as reported.[20]

(*S*)-2-Bromo-7a-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizine-3-carboxamide (1.161)



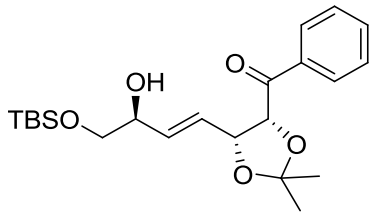
Amide **1.159** (15 mg, 0.08 mmol) was added to a solution of NaOH (16.7 mg, 0.42 mmol) and Br_2 (5.0 μL, 0.10 mmol) in water (0.76 mL) stirring at 0 °C. The reaction was allowed to warm to RT and stirred for 5 mins before being heated to 70 °C for 1 h. The reaction was cooled to RT, diluted with water (5 mL) and extracted with DCM (5 mL). The aqueous layer was neutralised with 1M HCl and extracted with DCM (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and

evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 4:1, ethyl acetate/methanol) gave *brominated amide* **1.161** as a pale orange oil (18 mg, 87%).

R_f 0.27 (4:1, ethyl acetate/methanol); δ_H (500 MHz, CD_3OD) 1.52 (3H, s, C(8)**H$_3$**), 1.90-1.99 (1H, m, C(7)**H**H′), 2.04-2.24 (3H, m, C(7)H**H′** and C(6)**H$_2$**), 3.65-3.72 (1H, m, C(5)**H**H′), 3.91-3.94 (1H, m, C(5)H**H′**); δ_C (100 MHz, $CDCl_3$) 19.0 (**C**(8)H_3), 27.4 (**C**(6)H_3), 35.7 (**C**(7)H_2), 45.8 (**C**(5)H_2), 71.5 (**C**(7a)), 99.8 (**C**(2)), 162.5 (**C**(3)), 171.7 (**C**(O)NH_2), 192.5 (**C**(1)); *m*/*z* (ESI$^-$) 258 ($[M-H]^-$, 100%); HRMS not found.

EXPERIMENTAL FOR CHAPTER 2

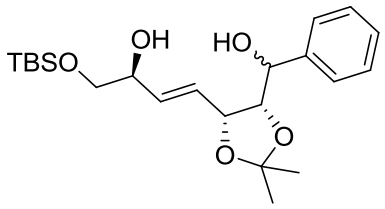
{(4*R*,5*R*)-5-[(*S*,*E*)-4-(*tert*-Butyldimethylsilyloxy)-3-hydroxybut-1-enyl]-2,2-dimethyl-1,3-dioxolan-4-yl}(phenyl)methanone (2.21)



A solution of Hoveyda-Grubbs II (10.7 mg, 17 μmol) in extensively degassed DCM (1.37 mL) was added *via* cannula to a neat mixture of protected diol **2.20** (130 mg, 0.35 mmol) and acetonide **2.5** (40 mg, 0.17 mmol) in a vacuum dried flask. The resultant mixture was stirred at 50 °C for 3 h before being evaporated to dryness *in vacuo*. Purification by flash chromatography of the residue (SiO_2, 3:1 toluene/ether) gave *allylic alcohol* **2.21** as a colourless oil (70 mg, 97%).

R_f 0.35 (3:1, toluene/ether); $[\alpha]_D^{25}$ +26.4 (c 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3502br, 2930s, 2858s, 1696s, 1598w, 1449m, 1381m, 1253s, 1216s, 1163m, 1104br, 936w, 881m, 837s, 777m, 690m; δ_H (500 MHz, $CDCl_3$) 0.00 (6H, s, 2 × SiC**H**$_3$), 0.85 (9H, s, SiC(C**H**$_3$)$_3$), 1.48 (3H, s, C**H**$_3$), 1.69 (1H, br s, O**H**), 1.71 (3H, s, C**H**$_3$), 3.03 (1H, dd, *J* 10.0, 8.5 Hz, C**H**H′OTBS), 3.29 (1H, dd, *J* 10.0, 4.0 Hz, CH**H′**OTBS), 3.88-3.93 (1H, m, C**H**OH), 4.99-5.02 (1H, m, C=CHC**H**CH), 5.50 (1H, ddd, *J* 15.5, 7.5, 1.0 Hz, C=C**H**CHCH), 5.59-5.65 (2H, m, C(OH)C**H**=CH and C=CHCHC**H**), 7.46 (2H, t, *J* 7.5 Hz, **Ar**), 7.53-7.59 (1H, m, **Ar**), 7.88 (2H, d, *J* 7.5 Hz, **Ar**); δ_C (125 MHz, $CDCl_3$) −5.4 and −5.6 (2 × Si**C**H$_3$), 18.2 (Si**C**(CH$_3$)$_3$), 25.4 (**C**H$_3$), 25.8 (SiC(**C**H$_3$)$_3$), 27.1 (**C**H$_3$), 66.5 (**C**H$_2$OTBS), 71.5 (**C**HOH), 78.4 (C=CH**C**HCH), 80.5 (C=CHCH**C**H), 110.7 (**C**(CH$_3$)$_2$), 126.8 (**C**=C), 128.4, 128.6, 128.9 and 133.4 (**Ar**), 133.7 (C=**C**), 136.0 (quat. **Ar**), 195.1 (**C**=O); *m/z* (ESI^+) 424 (MNH_4^+, 14%), 429 (MNa^+, 78), 819 (100), 837 (96); HRMS (ESI+) found 429.2063; $C_{22}H_{34}O_5NaSi$ (MNa^+) requires 429.2068.

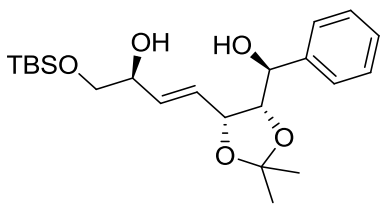
(*S*,*E*)-1-(*tert*-Butyldimethylsilyloxy)-4-{(4*R*,5*S*)-5-[(*S*)-hydroxy(phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}but-3-en-2-ol (2.22) and **(*S*,E)-1-(*tert*-Butyldimethylsilyloxy)-4-{(4*R*,5*S*)-5-[(*R*)-hydroxy(phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}but-3-en-2-ol (2.23)**



L-selectride (149 µL, 1 M in THF, 0.15 mmol) was added to a solution of ketone **2.21** (40 mg, 0.10 mmol) in THF (2.1 mL) at −78 °C and stirred for 1 h before being warmed to 0 °C and quenched with ammonium chloride solution (sat. aq., 1.5 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL) and the combined organic phases washed with sodium bicarbonate (sat. aq., 10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 1:1, petrol/ether) gave *diols* **2.22** and **2.23** (40 mg, 99%) in an inseparable mixture of diastereomers as a colourless oil (7.2:1 ratio from ^{1}H NMR analysis).

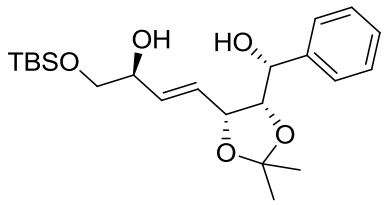
Mixture of isomers: R_f 0.26 (1:1, petrol/ether); $[\alpha]_D^{25}$ −10.1 (c 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3418br, 2930br, 1712w, 1462m, 1380s, 1255s, 1217s, 1110br, 1062br, 838s, 779m, 699m; *m/z* (ESI$^+$) 413 (59%), 431 (MNa^+, 23), 799 (72), 803 (98), 821 (100); HRMS (ESI+) found 431.2209; $C_{22}H_{36}O_5NaSi$ (MNa^+) requires 431.2224.

(*S*,*E*)-1-(*tert*-Butyldimethylsilyloxy)-4-{(4*R*,5*S*)-5-[(*S*)-hydroxy(phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}but-3-en-2-ol (2.22)



δ_H (500 MHz, $CDCl_3$) 0.07-0.09 (6H, m, 2 × SiC**H**$_3$), 0.91 (9H, s, SiC(C**H**$_3$)$_3$), 1.30 (3H, s, C**H**$_3$), 1.47 (3H, s, C**H**$_3$), 2.20-2.92 (2H, br m, 2 × O**H**), 3.49-3.51 (1H, m, TBSOC**H**H′), 3.70 (1H, dd, *J* 10.0, 4.0 Hz, TBSOCH**H′**), 4.22-4.27 (1H, m, TBSOCH_2C**H**(OH)), 4.28 (1H, dd, *J* 9.0, 6.5 Hz, C**H**CHPh), 4.62-4.66 (1H, m, C**H**Ph), 4.76 (1H, app. t, *J* 7.0 Hz, C**H**CHCHPh), 5.84 (1H, dd, *J* 15.5, 6.0 Hz, CH(OH)C**H**=CH), 6.08 (1H, ddd, *J* 15.5, 7.0, 1.5 Hz, CH=C**H**CHCH), 7.24-7.42 (5H, m, **Ar**); δ_C (125 MHz, $CDCl_3$) −5.4 and −5.3 (2 × Si**C**H_3), 18.3 (Si**C**(CH_3)$_3$), 25.2 (**C**H_3), 25.8 (SiC(**C**H_3)$_3$), 27.8 (**C**H_3), 66.9 (**C**H_2OTBS), 71.9 (**C**HPh), 72.0 (**C**HOH), 78.1 (**C**HCHCHPh), 81.0 (**C**HCHPh), 108.9 (**C**(CH_3)$_2$), 127.0, 127.8 and 128.2 (**Ar**), 128.4 (CH=**C**HCHCH), 132.1 (CH(OH)**C**H=CH), 141.6 (quat. **Ar**).

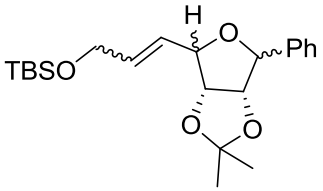
(*S*,*E*)-1-(*tert*-Butyldimethylsilyloxy)-4-{(4*R*,5*S*)-5-[(*R*)-hydroxy(phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}but-3-en-2-ol (2.23)



δ_H (500 MHz, $CDCl_3$) 0.07-0.09 (6H, m, 2 ×SiC**H**$_3$), 0.91 (9H, s, SiC(C**H**$_3$)$_3$), 1.41 (3H, s, C**H**$_3$), 1.59 (3H, s, C**H**$_3$), 2.20-2.92 (2H, br m, 2 × O**H**), 3.38 (1H, dd, *J* 10.0, 8.0 Hz, TBSOC**H**H′), 3.61 (1H, dd, *J* 10.0, 4.0 Hz, TBSOCH**H′**), 4.14-4.21 (2H, m, C**H**(OH)CH_2OTBS and C**H**CHPh), 4.41 (1H, app t, *J* 6.0 Hz, C**H**Ph), 4.56 (1H, app t, *J* 7.5 Hz, C**H**CHCHPh), 5.66 (1H, dd, *J* 15.5, 5.5 Hz, CH(OH)C**H**=CH), 5.89 (1H, ddd, *J* 15.5, 7.5, 1.5 Hz, CH=C**H**CHCH), 7.24-7.42 (5H, m, **Ar**); δ_C (125 MHz, $CDCl_3$) −5.4 and −5.3 (2 × Si**C**H_3), 18.3 (Si**C**(CH_3)$_3$), 25.1 (**C**H_3), 25.9 (SiC(**C**H_3)$_3$), 27.5 (**C**H_3), 65.8 (**C**H_2OTBS), 71.9 (**C**HPh), 72.3 (**C**HOH), 78.0 (**C**HCHCHPh), 81.5 (**C**HCHPh), 108.9 (**C**(CH_3)$_2$), 127.0, 127.8 and 128.2 (**Ar**), 128.5 (CH=**C**HCHCH), 133.5 (CH(OH)**C**H=CH), 140.4 (quat. **Ar**).

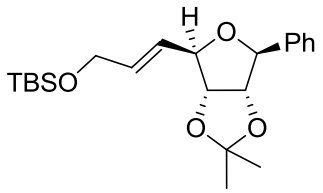
t*ert*-Butyl{(E)-3-[(3a*R*,4*R*,6*S*,6a*S*)-2,2-dimethyl-6-phenyltetrahydrofuro(3,4-d)(1,3)dioxol-4-yl]allyloxy}dimethylsilane (2.24), *tert*-Butyl{(Z)-3-[(3a*R*,4*S*,6*S*,6a*S*)-2,2-dimethyl-6-phenyltetrahydrofuro(3,4-d)(1,3)dioxol-4-yl]allyloxy}dimethylsilane (2.25)

and **t*ert*-Butyl{(E)-3-[(3a*R*,4*R*,6*R*,6a*S*)-2,2-dimethyl-6-phenyltetrahydrofuro(3,4-d)(1,3)dioxol-4-yl]allyloxy}dimethylsilane (2.26)**



DCM (1.0 mL) was added to a foil-covered flask containing chloro(triphenylphosphine)gold(I) (7.9 mg, 16 µmmol), silver triflate (4.1 mg, 16 µmol) and 4 Å molecular sieves under argon. The mixture was left to stir for 2 mins at RT before a solution of diols **2.22** and **2.23** (65 mg, 0.16 mmol) in DCM (1.0 mL) was added *via* cannula. The reaction mixture was stirred at RT for 2 h before being filtered through celite and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 25:1, petrol/ether) gave *dioxolanes* **2.24** (12 mg, 19%), **2.25** (26 mg, 42%) and **2.26** (8 mg, 13%) as colourless oils.

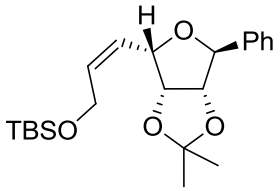
***tert*-Butyl{(*E*)-3-[(3a*R*,4*R*,6*S*,6a*S*)-2,2-dimethyl-6-phenyltetrahydrofuro(3,4-d)(1,3)dioxol-4-yl]allyloxy}dimethylsilane (2.24)**



R_f 0.25 (25:1, petrol/ether); $[\alpha]_D^{25}$ +3.9 (c 0.7 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2931s, 2857s, 1462w, 1373w, 1255m, 1212m, 1080s, 837s, 777m, 699m; δ_H (500 MHz, $CDCl_3$) 0.09 (6H, s, 2 × SiC**H**$_3$), 0.93 (9H, s, SiC(C**H**$_3$)$_3$), 1.36 (3H, s, C**H**$_3$), 1.64 (3H, s, C**H**$_3$), 4.24 (2H, d, *J* 4.0 Hz, C**H**$_2$OTBS), 4.49 (1H, app t, *J* 6.5 Hz, C=CHC**H**O), 4.53 (1H, dd, *J* 7.0, 5.0 Hz, C**H**CHCHPh), 4.57 (1H, dd, *J* 7.0,

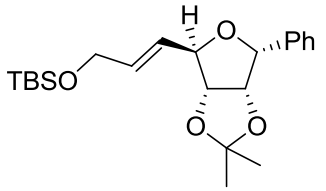
5.0 Hz, C**H**CHPh), 4.90 (1H, d, *J* 5.0 Hz, C**H**Ph), 5.89 (1H, dd, *J* 15.5, 6.5 Hz, TBSOCH$_2$CH=C**H**), 6.00 (1H, dd, *J* 15.5, 4.0 Hz, TBSOCH$_2$C**H**=CH), 7.28-7.42 (5H, m, **Ar**); δ_C (125 MHz, $CDCl_3$) −5.3 and −5.0 (2 × Si**C**H$_3$), 18.4 (Si**C**(CH$_3$)$_3$), 25.6 (**C**H$_3$), 25.9 (SiC(**C**H$_3$)$_3$), 27.5 (**C**H$_3$), 62.9 (**C**H$_2$OTBS), 84.4 (C=CH**C**HO), 85.2 and 85.3 (**C**HCH**C**HPh), 87.1 (**C**HCHPh), 115.3 (**C**(CH$_3$)$_2$), 125.8 (**Ar**), 126.5 (TBSOCH$_2$CH=**C**H), 127.8 and 128.4 (**Ar**), 132.8 (TBSOCH$_2$**C**H=CH), 139.6 (quat. **Ar**); *m/z* (ESI$^+$) 408 (MNH$_4^+$, 92%), 413 (MNa$^+$, 100), 803 (M$_2$Na$^+$, 100); HRMS (ESI$^+$) found 413.2121; $C_{22}H_{34}O_4NaSi$ (MNa$^+$) requires 413.2119.

***tert*-Butyl{(*Z*)-3-[(3a*R*,4*S*,6*S*,6a*S*)-2,2-dimethyl-6-phenyltetrahydrofuro(3,4-d)(1,3)dioxol-4-yl]allyloxy}dimethylsilane (2.25)**



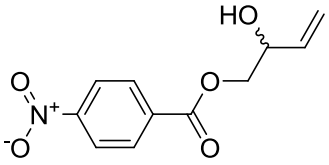
R_f 0.20 (25:1, petrol/ether); $[\alpha]_D^{25}$ +27.0 (c 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2931s, 2857s, 1495w, 1463m, 1381m, 1255s, 1210s, 1163m, 1090br, 978m, 838s, 777s, 741m, 701m; δ_H (500 MHz, $CDCl_3$) 0.06 and 0.07 (6H, 2 × s, 2 × Si**CH$_3$**), 0.89 (9H, s, SiC(C**H$_3$**)$_3$), 1.38 (3H, s, C**H$_3$**), 1.60 (3H, s, C**H$_3$**), 4.28 (1H, ddd, *J* 13.5, 5.5, 1.5 Hz, TBSOC**H**H′), 4.34 (1H, ddd, *J* 13.5, 5.5, 1.5 Hz, TBSOCH**H′**), 4.63 (1H, dd, *J* 5.5, 4.0 Hz, C**H**CHCHPh), 4.65-4.69 (1H, m, C=CHC**H**O), 5.00 (1H, d, *J* 5.5 Hz, C**H**CHPh), 5.23 (1H, s, C**H**Ph), 5.79 (1H, ddt, *J* 11.5, 7.5, 1.5 Hz, TBSOCH$_2$CH=C**H**), 5.87 (1H, dt, *J* 11.5, 5.5 Hz, TBSOCH$_2$C**H**=CH), 7.27-7.39 (5H, m, Ar); δ_C (125 MHz, $CDCl_3$) −5.3 and −5.2 (2 × Si**C**H$_3$), 18.4 (Si**C**(CH$_3$)$_3$), 25.5 (**C**H$_3$), 25.9 (SiC(**C**H$_3$)$_3$), 26.3 (**C**H$_3$), 60.0 (TBSO**C**H$_2$), 76.4 (**C**HCHCHPh), 83.0 (C=CH**C**HO), 84.5 (C**H**Ph), 87.6 (**C**HCHPh), 112.8 (**C**(CH$_3$)$_2$), 124.6 (TBSOCH$_2$CH=**C**H), 125.6, 127.4 and 128.6 (**Ar**), 134.1 (TBSOCH$_2$**C**H=CH), 138.6 (quat. **Ar**); *m/z* (ESI$^+$) 391 (MH$^+$, 30%), 413 (MNa$^+$, 98%), 803 (M$_2$Na$^+$, 100); HRMS (ESI$^+$) found 413.2118; $C_{22}H_{34}O_4NaSi$ (MNa$^+$) requires 413.2119.

***tert*-Butyl{(*E*)-3-[(3a*R*,4*R*,6*R*,6a*S*)-2,2-dimethyl-6-phenyltetrahydrofuro(3,4-d)(1,3)dioxol-4-yl]allyloxy}dimethylsilane (2.26)**



R_f 0.13 (25:1, petrol/ether); $[\alpha]_D^{25}$ −15.4 (c 0.5 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2934s, 2855m, 1492s, 1218m, 1087s; δ_H (500 MHz, C_6D_6) 0.14 (6H, s, 2 × SiC**H**$_3$), 1.07 (9H, s, SiC(C**H**$_3$)$_3$), 1.22 (3H, s, C**H**$_3$), 1.52 (3H, s, C**H**$_3$), 4.10-4.13 (2H, m, C**H**$_2$OTBS), 4.44 (1H, dd, *J* 5.5, 4.0 Hz, C**H**CHPh), 4.59 (1H, dd, *J* 5.5 Hz, C**H**CHCHPh), 4.93 (1H, d, *J* 4.0 Hz, C**H**Ph), 5.02-5.05 (1H, m, CH=CHC**H**O), 5.76-5.82 (1H, m, CH=C**H**CHO), 5.87-5.94 (1H, m, TBSOCH$_2$C**H**=CH), 7.21-7.62 (obscured by solvent, 5H, m, **Ar**); δ_C (125 MHz, C_6D_6) −5.1 (2 × Si**C**H$_3$), 18.5 (Si**C**(CH$_3$)$_3$), 25.1 (**C**H$_3$), 26.1 (SiC(**C**H$_3$)$_3$), 26.5 (**C**H$_3$), 63.1 (TBSO**C**H$_2$), 82.5 (**C**HPh), 82.9 (**C**HCHPh), 83.7 (C=CH**C**HO), 86.1 (**C**HCHCHPh), 112.4 (**C**(CH$_3$)$_2$), 126.5 (TBSOCH$_2$CH=**C**H), aromatic CH peaks obscured by solvent, 131.3 (TBSOCH$_2$**C**H=CH), 137.3 (quat. **Ar**); *m/z* (ESI^+) 413 (MNa^+, 100%), 803 (M_2Na^+, 65); HRMS (ESI^+) found 413.2116; $C_{22}H_{34}O_4NaSi$ (MNa^+) requires 413.2119.

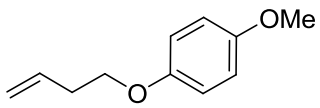
2-Hydroxybut-3-enyl 4-nitrobenzoate (2.30)



Pyridine (96 μL, 1.19 mmol) was added to a solution of 3-butene-1,2-diol (100 mg, 1.13 mmol) and 4-nitrobenzoyl chloride (221 mg, 1.19 mmol) in DCM (1.0 mL) and the resulting solution stirred for 16 h before being quenched with water and extracted with ethyl acetate (3 ×10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 2:1, petrol/ether) gave *monoprotected diol* **X** as a white solid (230 mg, 86%).

R_f 0.23 (2:1, petrol/ether); m.p. 55 °C; ν_{max} (KBr disc)/cm^{-1} 3267br, 1721s, 1606m, 1524s, 1410w, 1347s, 1284br, 1153m, 1106s, 1015s, 982m, 944m, 903m, 903w, 876m, 856m, 824w, 785w, 719s, 666w; δ_H (400 MHz, $CDCl_3$) 2.49-2.63 (1H, br m, O**H**), 4.35 (1H, ddd, *J* 11.5, 7.0, 1.5 Hz, C**H**H′O), 4.41-4.46 (1H, m, CH**H′**O), 4.55 (1H, br s, C**H**OH), 5.28 (1H, dd, *J* 10.5, 1.0 Hz, CH=C**H**H′), 5.44 (1H, app d, *J* 17.0 Hz, =CH**H′**), 5.93 (1H, dddd, *J* 17.0, 10.5, 5.6, 1.0 Hz, CH_2=C**H**), 8.18-8.28 (4H, m, **Ar**); δ_C (100 MHz, $CDCl_3$) 68.8 (**C**H_2O), 70.9 (**C**HOH), 117.5 (CH=**C**H_2), 123.6 and 130.8 (**Ar**), 135.2 (quat **Ar**), 136.0 (**C**H=CH_2), 150.6 (quat **Ar**), 164.8 (**C**=O); *m/z* (ESI^+) 260 (MNa^+, 97%), 292 ($[M+MeOH+Na]^+$, 56), 409 (100), 591 (21), 620 (21); HRMS (ESI^+) found 260.0530; $C_{11}H_{11}NNaO_5$ (MNa^+) requires 260.0529.

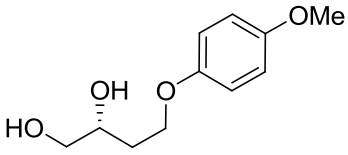
1-(But-3-enyloxy)-4-methoxybenzene (2.41)



Triphenylphosphine (2.35 g, 8.97 mmol) and 4-methoxyphenol (2.58 g, 20.8 mmol) were added to a solution of 3-buten-1-ol (500 mg, 6.90 mmol) in THF (5.0 mL). Diethyl azodicarboxylate (1.41 mL, 8.97 mmol) was added and the reaction mixture heated at reflux for 3 h before being concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 3:1, petrol/ether) gave alkene **2.41** as a colourless oil (1.1 g, 90%).

R_f 0.60 (1:1, petrol/ether); δ_H (500 MHz, $CDCl_3$) 2.51-2.25 (2H, m, OCH_2C**H$_2$**), 3.78 (3H, s, OC**H$_3$**), 3.97 (2H, t, *J* 7.0 Hz, OC**H$_2$**), 5.15 (1H, dm, *J* 10.0 Hz, CH=C**H**H′), 5.17 (1H, dd, *J* 17.0, 1.5 Hz, CH=CH**H′**), 5.91 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C**H**=CHH′), 6.82-6.87 (4H, m, **Ar**); δ_C (125 MHz, $CDCl_3$) 33.4 (OCH_2**C**H_2), 55.7 (O**C**H_3), 68.0 (O**C**H_2), 114.6 and 115.6 (**Ar**), 116.9 (CH=**C**H_2), 134.6 (**C**H=CH_2), 153.0 and 153.8 (quat. **Ar**). Data as reported.[1]

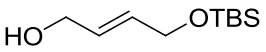
(*R*)-4-(4-Methoxyphenoxy)butane-1,2-diol (2.31)



AD-mix β (3.90 g) was added to a solution of alkene **2.41** (500 mg, 2.81 mmol) in *tert*-butanol (14 mL) and water (14 mL) stirring at 0 °C and the mixture stirred at 0 °C for 4 h. The reaction was quenched by addition of Na_2SO_3 (4.22 g) and the resulting slurry stirred for 30 mins before being extracted with ethyl acetate (3 × 50 mL) and the combined organic layers dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, ether) gave diol **2.31** as a colourless oil (590 mg, 99%).

R_f 0.19 (ether); $[\alpha]_D^{25}$ +3.1 (c 1.9 in $CHCl_3$) [lit reported +5.4 (c 1.9 in $CHCl_3$)];[1] δ_H (400 MHz, $CDCl_3$) 1.88-2.00 (2H, m, C**H**$_2$CH(OH)CH$_2$OH), 2.07 (1H, t, *J* 5.5 Hz, CH$_2$O**H**), 2.68 (1H, d, *J* 4.0 Hz, CHO**H**), 3.50-3.60 (1H, m, C**H**H′OH), 3.73 (1H, ddd, *J* 11.5, 5.5, 3.5 Hz, CH**H′**OH), 3.78 (3H, s, OC**H**$_3$), 3.94-4.06 (1H, m, C**H**OH), 4.07-4.17 (2H, m, C**H**$_2$OAr), 6.82-6.88 (4H, m, **Ar**); δ_C (100 MHz, $CDCl_3$) 32.6 (**C**H$_2$CH(OH)CH$_2$OH), 55.7 (O**C**H$_3$), 66.1 (**C**H$_2$OAr), 66.7 (**C**H$_2$OH), 70.4 (**C**HOH), 114.7 and 115.5 (**Ar**), 152.6 and 154.1 (quat. **Ar**). Data as reported.[1]

(*E*)-4-(*tert*-Butyldimethylsilyloxy)but-2-en-1-ol (2.33)

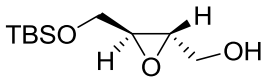


NaH (908 mg, 60% dispersion in mineral oil, 2.27 mmol) was added portionwise to a solution of 2-buten-1,4-diol (2.00 g, 2.27 mmol) in THF (79 mL) stirring at RT. *tert*-Butyldimethylsilyl chloride (3.42 g, 2.27 mmol) was added to the reaction and the mixture stirred for 2 h 45 mins before being quenched with water (40 mL). The phases were separated and the aqueous phase extracted with ether (3 × 40 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and

evaporated *in vacuo*. Flash chromatography (SiO_2, 3:1 petrol/ether) gave silyl ether **2.33** as a colourless oil (4.38 g, 95%).

R_f 0.30 (3:1, petrol/ether); δ_H (400 MHz, $CDCl_3$) 0.07-0.09 (6H, m, 2 × SiC**H₃**), 0.90 (9H, s, SiC(C**H₃**)₃), 2.80 (1H, br s, O**H**), 4.16-4.19 and 4.23-4.27 (4H, 2 × m, C**H₂**OH and C**H₂**OTBS), 5.60-5.75 (2H, m, C**H**=C**H**); δ_C (100 MHz, $CDCl_3$) −5.3 and −5.2 (2 × Si**C**H₃), 18.3 (Si**C**(CH₃)₃), 25.9 (SiC(**C**H₃)₃), 58.6 and 59.5 (**C**H₂OH **C**H₂OTBS), 130.0 and 131.1 (**C**H=**C**H). Data as reported.[2]

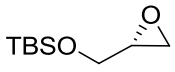
{(2*SR*,3*SR*)-3-[(*tert*-Butyldimethylsilyloxy)methyl]oxiran-2-yl}methanol (2.32)



Mono-silyl ether **2.33** (200 mg, 0.99 mmol) was dissolved in DCM (4.51 mL) and *tert*-butylhydrogenperoxide (258 µL, 5-6 M in decane, 1.29 mmol) was added, followed by vanadyl acetylacetonate (13.1 mg, 0.05 mmol). The mixture was then heated at reflux for 3 h before being quenched with sodium sulfite solution (sat. aq., 5 mL), diluted in ether (5 mL), the layers separated and the aqueous layer extracted with ether (2 × 10 mL). The combined organic layers were washed with brine (sat. aq., 2 × 10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 2:1 petrol/ether) gave epoxide **2.32** (140 mg, 65%) as a colourless oil.

δ_H (500 MHz, $CDCl_3$) 0.11 and 0.12 (6H, 2 × s, 2 × SiC**H₃**), 0.92 (9H, SiC(C**H₃**)₃), 2.07 (1H, t, *J* 5.5 Hz, O**H**), 3.20-3.27 (2H, m, 2 × C**H**O), 3.73-3.85 (3H, m, C**H₂**OH and C**H**H′OTBS), 3.95 (1H, dd, *J* 11.5, 5.5 Hz, CH**H′**OTBS); δ_C (125 MHz, $CDCl_3$) −5.4 and −5.3 (2 × Si**C**H₃), 18.3 (Si**C**(CH₃)₃), 25.9 (SiC(**C**H₃)₃), 55.9 and 56.3 (2 × **C**HO), 60.9 (**C**H₂OH), 61.7 (**C**H₂OTBS). Data as reported.[3]

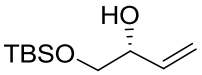
(*R*)-*tert*-Butyldimethyl(oxiran-2-ylmethoxy)silane (2.42)



(*S*)-Glycidol (300 mg, 4.05 mmol) was added dropwise to a solution of imidazole (441 mg, 6.48 mmol) and *tert*-butyldimethylsilyl chloride (793 mg, 5.26 mmol) in anhydrous dimethylformamide (2.40 mL) stirring at 0 °C. The reaction was stirred at 0 °C for 30 mins before being warmed to RT and stirred for a further 1 h 30 mins. The reaction was quenched with brine (sat. aq., 6 mL) and the resultant mixture stirred for 20 mins before the layers were separated, the aqueous layer extracted with ether (2 × 15 mL) and the combined organic layers washed with water (10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (neutral Al_2O_3, 49:1, petrol/ethyl acetate) gave silyl ether **2.42** as a colourless oil (726 mg, 95%).

R_f 0.15 (49:1, petrol/ethyl acetate); $[\alpha]_D^{25}$ −2.1 (c 1.0 in $CHCl_3$) [Lit. reported −4.7 (c 1.0 in $CHCl_3$)];[4] δ_H (500 MHz, $CDCl_3$) 0.07-0.10 (6H, m, 2 × SiC**H**$_3$), 0.91 (9H, s, SiC(C**H**$_3$)$_3$), 2.65 (1H, dd, *J* 5.0, 2.5 Hz, C**H**H′(O)CH), 2.78 (1H, dd, *J* 5.0, 4.5 Hz, CH**H′**(O)CH), 3.10 (1H, app quin, *J* 3.5 Hz, C**H**), 3.67 (1H, dd, *J* 12.0, 5.0 Hz, C**H**H′OTBS), 3.86 (1H, dd, *J* 12.0, 3.0 Hz, CH**H′**OTBS); δ_C (125 MHz, $CDCl_3$) −5.4 and −5.3 (2 × Si**C**H$_3$), 18.4 (Si**C**(CH$_3$)$_3$), 25.9 (SiC(**C**H$_3$)$_3$), 44.5 (**C**H$_2$(O)CH), 52.4 (CH$_2$(O)**C**H), 63.7 (**C**H$_2$OTBS). Data as reported.[4]

(*R*)-1-(*tert*-Butyldimethylsilyloxy)but-3-en-2-ol (2.35)

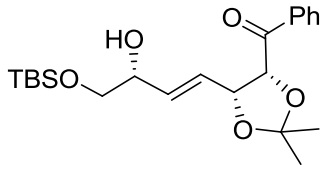


n-Butyllithium (3.96 mL, 1.6 M in hexanes, 6.34 mmol) was added to a suspension of trimethylsilyl iodide (1.34 g, 6.56 mmol) in THF (20.4 mL) stirring at −10 °C. After 30 mins epoxide **2.42** (400 mg, 2.19 mmol) was added and the resultant milky suspension warmed to 0 °C over 30 mins and then stirred at RT for 2 h before being quenched with water (10 mL). The layers were separated and the aqueous layer extracted with ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and

evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 49:1, petrol/ethyl acetate) furnished alcohol **2.35** as a colourless liquid (310 mg, 72%).

R_f 0.09 (49:1, petrol/ethyl acetate); $[\alpha]_D^{25}$ −3.7 (c 1.0 in $CHCl_3$) [Lit. reported $[\alpha]_D^{25}$ 4.6 (c 1.0 in $CHCl_3$)];[5] δ_H (500 MHz, $CDCl_3$) 0.09 (6H, s, 2 × SiC**H₃**), 0.92 (9H, s, SiC(C**H₃**)₃), 2.57 (1H, d, *J* 3.5 Hz, O**H**), 3.46 (1H, dd, *J* 10.0, 8.0 Hz, C**H**H′OTBS), 3.67 (1H, dd, *J* 10.0, 4.0 Hz, CH**H′**OTBS), 4.15-2.21 (1H, m, C**H**OH), 5.20 (1H, d, *J* 10.5 Hz, C**H**H′=CH), 5.35 (1H, d, *J* 17.0 Hz, CH**H′**=CH), 5.82 (1H, ddd, *J* 17.0, 10.5, 6.0 Hz, CH_2=C**H**); δ_C (125 MHz, $CDCl_3$) −5.4 (2 × Si**C**H_3), 18.3 (Si**C**$(CH_3)_3$), 25.9 (SiC(**C**H_3)₃), 66.9 (**C**H_2OTBS), 73.0 (**C**HOH), 116.5 (**C**H_2=CH), 136.6 (CH_2=**C**H). Data as reported.[5]

{(4*R*,5*R*)-5-[(*R*,*E*)-4-(*tert*-Butyldimethylsilyloxy)-3-hydroxybut-1-enyl]-2,2-dimethyl-1,3-dioxolan-4-yl}(phenyl)methanone (2.37)

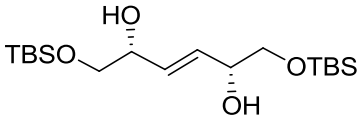


A solution of Hoveyda-Grubbs II (26.9 mg, 43 μmol) in extensively degassed DCM (0.55 mL) was added *via* cannula to a neat mixture of alcohol **2.35** (174 mg, 0.86 mmol) and acetonide **2.5** (100 mg, 0.43 mmol) in a vacuum dried flask. The resultant mixture was stirred at 50 °C for 1.5 h before being evaporated to dryness *in vacuo*. Purification by flash chromatography of the residue (SiO_2, 3:1 toluene/ether) gave *allylic alcohol* **2.37** as a colourless oil (139 mg, 79%).

R_f 0.23 (2:1, petrol/ether); $[\alpha]_D^{25}$ +18.8 (c 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3450br, 2931s, 2858s, 1698s, 1598w, 1449m, 1381m, 1254s, 1217s, 1163m, 1105br, 1039m, 838s; δ_H (500 MHz, $CDCl_3$) −0.01 (6H, 2 × s, 2 × SiC**H₃**), 0.85 (9H, s, SiC(C**H₃**)₃), 1.49 (3H, s, C**H₃**), 1.71 (3H, s, C**H₃**), 2.30 (1H, br s, O**H**), 2.86 (1H, dd, *J* 10.0, 8.5 Hz, TBSOC**H**H′), 3.06 (1H, dd, *J* 10.0, 3.5 Hz, TBSOCH**H′**), 3.87-3.91 (1H, m, C**H**OH), 5.00 (1H, t, *J* 7.5 Hz, =CHC**H**CH), 5.46 (1H, ddd, *J* 15.5, 7.5, 1.0 Hz, CH=C**H**CHCH), 5.55 (1H, dd, *J* 15.5, 6.5, CH(OH)C**H**=CH), 5.62 (1H, d, *J* 7.5 Hz, =CHCHC**H**),

7.46 (2H, td, *J* 7.5, 1.5 Hz, **Ar**), 7.58 (1H, tt, *J* 7.5, 1.5 Hz, **Ar**), 7.87-7.89 (2H, m, **Ar**); δ_C (125 MHz, $CDCl_3$) −5.5 and −5.4 (2 × Si**C**H_3), 18.2 (Si**C**$(CH_3)_3$), 25.3 (**C**H_3), 25.8 (SiC(**C**$H_3)_3$), 27.1 (**C**H_3), 66.4 (TBSO**C**H_2), 71.7 (**C**HOH), 78.6 (=CH**C**HCH), 80.4 (=CHCH**C**H), 110.7 (**C**$(CH_3)_2$), 127.3 (CH=**C**HCHCH), 128.4, 128.5 and 133.5 (**Ar**), 133.8 (CH(OH)**C**H=CH), 135.9 (quat **Ar**), 194.8 (**C**=O); *m/z* (ESI^+) 424 (MNH_4^+, 53%), 429 (MNa^+, 75), 459 (98), 465 ([M+MeCN+NH_4^+], 58), 835 (M_2Na^+, 100), 865 (98); HRMS (ESI^+) found 429.2069; $C_{22}H_{34}O_5NaSi$ (MNa^+) requires 429.2068.

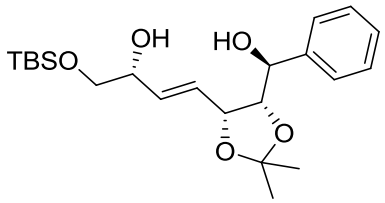
(6*R*,9*R*,*E*)-2,2,3,3,12,12,13,13-Octamethyl-4,11-dioxa-3,12-disilatetradec-7-ene-6,9-diol (2.43)



Diol **2.43** isolated as a white crystalline side-product in the above reaction (80 mg from 174 mg monomer **2.35**, 50%).

R_f 0.19 (2:1, petrol/ether); m.p. 59 °C; $[\alpha]_D^{19}$ −2.3 (c 5.0 in $CHCl_3$); ν_{max} (KBr disc)/cm^{-1} 3284br, 2928s, 1471m, 1338w, 1256m, 1117s, 1027m, 972w, 939w, 837s, 774s; δ_H (500 MHz, $CDCl_3$) 0.09 (12H, s, 4 × SiC**H**$_3$), 0.91 (18H, s, 2 × SiC(C**H**$_3)_3$), 2.56 (2H, br s, 2 × O**H**), 3.44 (2H, dd, *J* 10.0, 8.0 Hz, 2 × C**H**H′OTBS), 3.66 (2H, dd, *J* 10.0, 3.5 Hz, 2 × CH**H′**OTBS), 4.20 (2H, app dt, *J* 8.0, 3.5 Hz, 2 × C**H**OH), 5.78 (2H, dd, *J* 3.0, 1.5 Hz, C**H**=C**H**); δ_C (125 MHz, $CDCl_3$) −5.4 (4 × Si(**C**$H_3)_2$), 18.3 (2 × Si**C**$(CH_3)_3$), 25.8 (2 × SiC(**C**$H_3)_3$), 67.1 (2 × **C**H_2OTBS), 72.1 (2 × **C**HOH), 130.4 (**C**H=**C**H); *m/z* (ESI^+) 400 (MNa^+, 99%), 415 (MK^+, 82), 429 (100), 509 (61), 539 (49), 587 (95), 775 (M_2Na^+, 50), 835 (86); HRMS (ESI^+) found 399.2358; $C_{18}H_{40}O_4$ Na Si_2 (MNa^+) requires 399.2357.

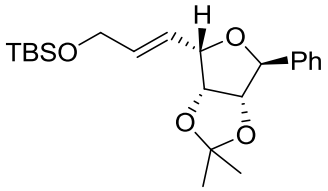
(*R*,*E*)-1-(*tert*-Butyldimethylsilyloxy)-4-{(4*R*,5*S*)-5-[(*S*)-hydroxy(phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}but-3-en-2-ol (2.36)



L-selectride (443 μL, 1 M in THF, 0.44 mmol) was added to a solution of ketone **2.37** (120 mg, 0.30 mmol) in THF (6.3 mL) at −78 °C and stirred for 1 h before being warmed to 0 °C and quenched with ammonium chloride solution (sat. aq., 4.5 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic phases were washed with sodium bicarbonate (sat. aq., 20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (basic Al_2O_3, 1:1, petrol/ether) gave *diol* **2.36** (73 mg, 60%) as a colourless oil.

R_f 0.19 (1:1, petrol/ether); $[\alpha]_D^{25}$ −6.2 (c 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3418br, 2930br, 2858s, 1724w, 1462m, 1380m, 1257s, 1217m, 1166w, 1108br, 1062br, 838s, 779m, 699m; δ_H (500 MHz, $CDCl_3$) 0.08 (6H, 2 × s, 2 × Si(C**H**$_3$)$_2$), 0.91 (9H, s, SiC(C**H**$_3$)$_3$), 1.31 (3H, s, C**H**$_3$), 1.48 (3H, s, C**H**$_3$), 2.41 (1H, br s, O**H**), 2.57 (1H, br s, O**H**), 3.50 (1H, dd, *J* 10.0, 7.5 Hz, TBSOC**H**H′), 3.66 (1H, dd, *J* 10.0, 4.0 Hz, TBSOCH**H′**), 4.22-4.27 (1H, m, TBSOCH$_2$C**H**(OH)), 4.29 (1H, dd, *J* 8.5, 6.5 Hz, C**H**CHPh), 4.66 (1H, d, *J* 8.5 Hz, C**H**Ph), 4.78 (1H, t, *J* 6.5 Hz, C**H**CHCHPh), 5.86 (1H, ddd, *J* 15.5, 5.5, 1.0 Hz, CH(OH)C**H**=CH), 6.10 (1H, ddd, *J* 15.5, 6.5, 1.5 Hz, CH=C**H**CHCH), 7.27-7.41 (5H, m, **Ar**); δ_C (125 MHz, $CDCl_3$) −5.4 (Si(**C**H$_3$)$_2$), 18.3 (Si**C**(CH$_3$)$_3$), 25.2 (**C**H$_3$), 25.9 (SiC(**C**H$_3$)$_3$), 27.8 (**C**H$_3$), 66.9 (**C**H$_2$OTBS), 72.0 (TBSOCH$_2$**C**H(OH)), 72.1 (**C**HCHPh), 77.8 (**C**HPh), 81.0 (**C**HCHCHPh), 108.8 (**C**(CH$_3$)$_2$), 127.0 and 127.8 (**Ar**), 128.2 (**Ar** and CH=**C**HCHCH), 131.9 (CH(OH)**C**H=CH), 141.3 (quat. **Ar**); *m/z* (ESI^+) 429 (85%), 431 (MNa^+, 100), 447 (53), 541 (75), 839 (M_2Na^+, 99), 897 (62), 943 (85); HRMS (ESI+) found 431.2225; $C_{22}H_{36}O_5NaSi$ (MNa^+) requires 431.2224.

***tert*-Butyl{(*E*)-3-[(3a*R*,4*S*,6*S*,6a*S*)-2,2-dimethyl-6-phenyltetrahydrofuro(3,4-d)(1,3)dioxol-4-yl]allyloxy}dimethylsilane (2.37)**

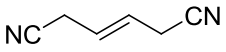


DCM (0.30 mL) was added to a foil-covered flask containing chloro(triphenylphosphine)gold(I) (2.4 mg, 5 μmmol), silver triflate (1.3 mg, 5 μmol) and 4 Å molecular sieves under argon. The mixture was left to stir for 2 mins at RT before a solution of diol **2.36** (20 mg, 0.05 mmol) in DCM (0.30 mL) was added *via* cannula. The reaction mixture was stirred at RT for 1 h before being filtered through celite and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 25:1, petrol/ether) gave *dioxolane* **2.37** (13 mg, 67%) as a colourless oil.

R_f 0.18 (25:1, petrol/ether); $[\alpha]_D^{25}$ +9.4 (c 0.5 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2930s, 2856s, 1462w, 1381m, 1258m, 1210s, 1096br, 977m, 837s, 778s, 701w; δ_H (500 MHz, $CDCl_3$) 0.09 (6H, s, 2 × SiC**H**$_3$), 0.93 (9H, s, SiC(C**H**$_3$)$_3$), 1.37 (3H, s, C**H**$_3$), 1.59 (3H, s, C**H**$_3$), 4.24-4.26 (2H, m, TBSOC**H**$_2$), 4.38 (1H, dd, *J* 6.0, 4.0 Hz, C=CHC**H**O), 4.66 (1H, dd, *J* 6.0, 4.0 Hz, C**H**CHCHPh), 4.98 (1H, dd, *J* 6.0, 1.5 Hz, C**H**CHPh), 5.21 (1H, s, C**H**Ph), 5.93 (1H, dd, *J* 15.5, 4.0 Hz, TBSOCH$_2$C**H**=CH), 5.98 (1H, ddd, *J* 15.5, 6.0, 1.0 Hz, TBSOCH$_2$CH=C**H**), 7.37-7.39 (5H, m, Ar); δ_C (125 MHz, $CDCl_3$) − 5.3 (Si(**C**H$_3$)$_2$), 18.4 (Si**C**(CH$_3$)$_3$), 25.2 (**C**H$_3$), 25.9 (SiC(**C**H$_3$)$_3$), 26.3 (**C**H$_3$), 60.2 (TBSO**C**H$_2$), 81.4 (C=CH**C**HO), 83.0 (**C**HCHCHPh), 84.5 (**C**HPh), 87.6 (**C**HCHPh), 112.8 (O$_2$**C**(CH$_3$)$_2$), 124.4 (CH=**C**H), 125.6, 127.4 and 128.6 (**Ar**), 134.5 (**C**H=CH), 138.8 (quat. **Ar**); *m/z* (ESI^+) 408 (MNH_4^+, 81%), 413 (MNa^+, 100%), 429 (MK^+, 55), 523 (86), 803 (M_2Na^+, 73); HRMS (ESI^+) found 413.2116; $C_{22}H_{34}O_4NaSi$ (MNa^+) requires 413.2119.

EXPERIMENTAL FOR CHAPTER 3

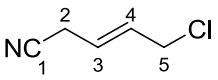
(*E*)-Hex-3-enedinitrile (3.29)



1,4-Dibromo-2-butene (50 mg, 0.23 mmol) was added to a refluxing suspension of sodium cyanide (28 mg, 0.58 mmol) and copper chloride (3.5 mg, 0.04 mmol) in acetonitrile (48 µL). The resultant slurry was stirred at reflux for 20 h before being filtered and washed with hot acetonitrile (5 mL) and the filtrate concentrated *in vacuo* to give dicyanide **3.29** as a pale brown oil (40 mg, 100%).

m.p. 62 °C (lit. reported 76–76.5 °C);[1] δ_H (400 MHz, $CDCl_3$) 3.17-3.19 (4H, m, 2 × C**H**$_2$), 5.82-5.85 (2H, m, 2 × C**H**); δ_C (100 MHz, $CDCl_3$) 20.1 (2 × **C**H_2), 118.3 (2 × **C**≡N), 123.1 (2 × **C**H). Data as reported.[1]

(*E*)-5-Chloropent-3-enenitrile (3.32)

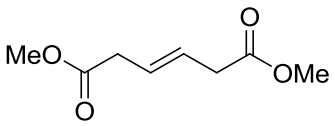


1,4-Dichloro-2-butene (100 mg, 0.80 mmol) was added to a reluxing suspension of sodium cyanide (98 mg, 2.0 mmol) and copper chloride (12 mg, 0.12 mmol) in acetonitrile (167 µL). The resultant slurry was stirred at reflux for 24 h before being filtered and washed with hot acetonitrile (5 mL) and the filtrate concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 6:1, petrol/ether) gave *chloride* **3.32** as a colourless oil (40 mg, 43%).

R_f 0.17 (6:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2964w, 1738s, 1366m, 1217br, 1093br, 1023br, 798br; δ_H (400 MHz, $CDCl_3$) 3.17 (2H, dd, *J* 5.5, 1.5 Hz, C(2)**H**$_2$), 4.08 (2H, dd, *J* 7.0, 1.0 Hz, C(5)**H**$_2$), 5.73 (1H, dt, *J* 15.5, 5.5, 1.0 Hz, C(3)**H**), 6.04 (1H, dtt, *J* 15.5, 7.0, 1.5 Hz, C(4)**H**); δ_C (100 MHz, $CDCl_3$)

20.1 (**C**(2)H_2), 43.3 (**C**(5)H_2), 116.7 (**C**(1)), 122.0 (**C**(3)H), 131.0 (**C**(4)H); *m/z* (ESI^+) 289 ($[M_2+MeCN+NH_4]^+$, 53%), 413 (100); HRMS found 138.0086; $C_5H_6ClNNa^+$ requires 138.0081.

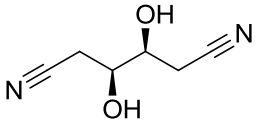
(*E*)-Dimethyl hex-3-enedioate (3.30)



H_2SO_4 (1 drop) was added to a solution of *trans*-β-hydromuconic acid (200 mg, 1.39 mmol) in methanol (5 mL) and the resulting solution heated at 90 °C for 16 h. The reaction was cooled, partitioned between DCM (15 mL) and water (25 mL) and the layers separated. The aqueous layer was extracted with DCM (2 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated *in vacuo* to give diester **3.30** as a colourless oil (236 mg, 99%).

δ_H (400 MHz, $CDCl_3$) 3.10 (4H, d, *J* 5.5 Hz, 2 × C**H**$_2$), 3.69 (6H, s, 2 × OC**H**$_3$), 5.70 (2H, t, *J* 5.5 Hz, C**H**=C**H**); δ_C (100 MHz, $CDCl_3$) 37.6 (2 × **C**H_2), 51.8 (2 × O**C**H_3), 125.9 (**C**H=**C**H), 171.9 (2 × **C**=O). Data as reported.[2]

(3*SR*,4*SR*)-3,4-Dihydroxyhexanedinitrile (3.34)

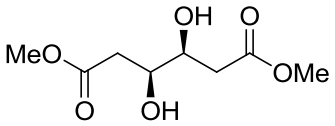


Sodium metaperiodate (151 mg, 0.70 mmol) was added to sulphuric acid (2 M, 94 µL, 0.094 mmol) and water (0.35 mL) and the mixture stirred until all the solids were completely dissolved. The solution was cooled to 0 °C and ruthenium chloride (0.1 M aq., 23 µL, 35 µmoL) was added. The solution was stirred until a bright yellow colour had developed before ethyl acetate (1.4 mL) and acetonitrile (1.4 mL) were added and after 5 mins dicyanide **3.29** (50 mg, 0.47 mmol) was added. After 5 mins the reaction mixture was poured onto sodium thiosulphate (sat. aq., 6 mL) and sodium

bicarbonate (sat. aq., 4 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 2:1, ethyl acetate/petrol) gave diol **3.34** as a pale brown oil (40 mg, 62%).

R_f 0.19 (2:1, ethyl acetate/petrol); δ_H (400 MHz, $(CD_3)CO$) 2.70 (2H, dd, *J* 16.5, 7.5 Hz, 2 × C**H**H′), 2.77 (2H, dd, *J* 16.5, 5.0 Hz, 2 × CH**H′**), 3.97-4.02 (2H, m, 2 × C**H**), 4.75 (2H, d, *J* 7.0 Hz, 2 × O**H**); δ_C (100 MHz, $(CD_3)CO$) 21.9 (2 × **C**H_2), 69.5 (2 × **C**H), 118.4 (2 × **C**≡N); Data as reported.[3]

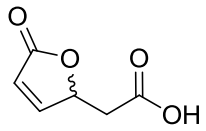
(3*SR*,4*SR*)-Dimethyl 3,4-dihydroxyhexanedioate (3.35)



Diester **3.30** (500 mg, 2.91 mmol) and citric acid (419 mg, 2.18 mmol) were dissolved in *tert*-butanol (3.1 mL) and water (3.1 mL). Potassium osmate(VI) dihydrate (1.07 mg, 2.91 μmol) and 4-methylmorpholine *N*-oxide (50% wt aq., 750 mg, 3.20 mmol) were added and the reaction stirred at RT for 16 h. The solvents were removed *in vacuo* and the residue redissolved in water (20 mL) and ethyl acetate (30 mL). The mixture was acidified with HCl (1N, 20 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2 × 20 mL) and the combined organics were dried ($MgSO_4$) and evaporated *in vacuo* to give *diol* **3.35** as a fine white powder (520 mg, 88%).

R_f 0.08 (1:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 3437br, 2917br, 1731s, 1438m, 1263m, 1162br, 1059br; δ_H (500 MHz, $CDCl_3$) 2.55-2.60 (4H, m, C$\mathbf{H_2}$), 3.67 (6H, s, OC$\mathbf{H_3}$), 3.85-4.00 (4H, m, C**H** and O**H**); δ_C (125 MHz, $CDCl_3$) 37.9 (2 × **C**H_2), 51.9 (2 × O**C**H_3), 69.9 (2 × **C**H), 172.9 (2 × **C**=O); *m*/*z* (ESI^+) 229 (MNa^+); HRMS found 229.0682; $C_8H_{14}NaO_6^+$ (MNa^+) requires 229.0683.

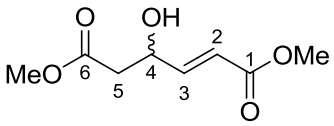
(*S*)-2-(5-Oxo-2,5-dihydrofuran-2-yl)acetic acid (3.36)



In attempts to cyclise dinitrile **3.42**, varying amounts of lactone **3.36** were isolated as a white powder. Peaks belonging to this compound were also observed in attempts to form or cyclise dinitrile diol **3.34** and diester diol **3.35**. Despite in the first case being obtained from chiral starting materials, the sample had no observable optical rotation [lit. reported +39.1 (c 0.66 in ethanol)].[4]

δ_H (400 MHz, $(CD_3)CO$) 2.69 (1H, dd, *J* 16.5, 8.0 Hz, C(2)**H**H′), 3.43 (1H, ddd, *J* 16.5, 5.5 Hz, C(2)H**H′**), 5.45 (1H, dddd, *J* 8.0, 5.5, 2.0, 1.5 Hz, C(2′)**H**), 6.17 (1H, dd, *J* 6.0, 2.0 Hz, C(4′)**H**), 7.80 (1H, dd, *J* 6.0, 1.5 Hz, C(3′)**H**); δ_C (100 MHz, $(CD_3)CO$) 37.5 (**C**(2)H_2), 79.8 (**C**(2′)H), 121.5 (**C**(4′)H), 157.1 (**C**(3′)H, 170.5 (**C**(1′)), 172.6 (**C**(1)). Data as reported.[5]

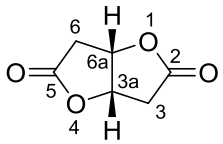
(*S*,*E*)-Dimethyl 4-hydroxyhex-2-enedioate (3.37)



In attempts to obtain dilactone **3.8** varying amounts of lactone **3.37** were isolated as a white powder.

δ_H (400 MHz, $CDCl_3$) 2.54 (1H, dd, *J* 16.5, 9.0 Hz, C(5)**H**H′), 2.66 (1H, ddd, *J* 16.5, 4.0 Hz, C(5)**H**H′), 3.74 (3H, s, OC**H**$_3$), 3.75 (3H, s, OC**H**$_3$), 4.69-4.77 (1H, br s, O**H**), 6.15 (1H, dd, *J* 15.5, 2.0 Hz, C(2)**H**), 6.91 (1H, dd, *J* 15.5, 4.0 Hz, C(3)**H**); δ_C (100 MHz, $CDCl_3$) 40.1 (**C**(5)H_2), 51.7 and 52.1 (2 × OC**H**$_3$), 67.1 (**C**(4)H), 120.9 (**C**(2)H), 147.5 (**C**(3)H), 166.7 and 172.2 (**C**(1) and **C**(6)). Data as reported.[6]

Tetrahydrofuro[3,2-b]furan-2,5-dione ((±)-3.8)

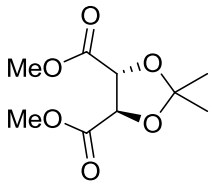


HCl (6 M aq., 0.26 mL) was added to a solution of diol **3.34** (20 mg, 0.14 mmol) in THF (0.26 mL) and the reaction heated at RT for 4 h. The solvent was evaporated *in vacuo* and the residue redissolved in DCM (5 mL). The solution was neutralized with sodium bicarbonate (sat. aq., 2 mL) and the aqueous layer extracted with DCM (3 × 2 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 3:1, ethyl acetate/petrol) gave dilactone (±)-**3.8** as a white powder (15 mg, 77%).

R_f 0.24 (3:1, ethyl acetate/petrol); m.p. 105 °C (lit. reported 132 °C);[7] δ_H (400 MHz, $(CD_3)CO$) 2.79 (2H, d, *J* 18.5 Hz, C(3)**H**H′ and C(6)**H**H′), 3.09-3.17 (2H, m, C(3)H**H′** and C(6)H**H′**), 5.37-5.40 (2H, m, C(3a)**H** and C(6a)**H**); δ_C (100 MHz, $(CD_3)CO$) 35.2 (**C**(3)H_2 and **C**(6)H_2), 79.4 (**C**(3a)H and **C**(6a)H), 174.0 (**C**(5) and **C**(2)). Data as reported.[7]

Crystal structure obtained (see **Appendix H**).

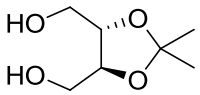
(4*R*,5*R*)-Dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (3.121)



PTSA monohydrate (125 mg, 0.66 mL) was added to a solution of dimethyl (L)-tartrate (10.0 g, 56.1 mmol) in 2,2-dimethoxypropane (44 mL) and the reaction heated at reflux for 16 h before being cooled and diluted in ether (150 mL). The organic layer was washed with sodium bicarbonate (2 × 100 mL), dried (MgSO4) and carefully evaporated in vacuo to give acetonide protected diester **3.121** as a colourless liquid (12.2 g, 100%).

R_f 0.57 (1:1, petrol/ether); $[\alpha]_D^{20}$ – 63.0 (c 1.38 in methanol) [lit. reported –58 (c 0.86 in methanol)];[8] δ_H (400 MHz, $CDCl_3$) 1.50 (6H, s, 2 × C**H**$_3$), 3.83 (6H, s, 2 × OC**H**$_3$), 4.81 (2H, s, 2 × C**H**); δ_C (100 MHz, $CDCl_3$) 26.3 (2 × **C**H_3), 52.8 (2 × O**C**H_3), 77.0 (2 × **C**H), 113.9 (**C**$(CH_3)_2$), 170.1 (2 × **C**=O). Data as reported.[8]

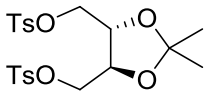
[(4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]dimethanol (3.39)



A solution of diester **3.121** (12.2 g, 56 mmol) in ether (117 mL) was added dropwise to a suspension of lithium aluminium hydride (4.7 g, 123 mmol) in ether (187 mL) stirring at RT. After 3 h the reaction was carefully quenched with water (6.9 mL), sodium hydroxide (1.3 M aq., 22.2 mL) and water (16.6 mL) and left to stir for 1 h before filtration and evaporation of the filtrate *in vacuo*. Purification by flash chromatography (SiO_2, 1:1, petrol/ether → ether) gave diol **3.39** as a colourless oil (6.9 g, 76%)

R_f 0.15 (ether); $[\alpha]_D^{20}$ + 3.2 (c 5.0 in chloroform) [lit. reported + 3.9 (c 5.0 in chloroform)][9]; δ_H (400 MHz, $CDCl_3$) 1.45 (6H, s, 2 × C**H**$_3$), 2.06 (2H, br s, 2 × O**H**), 3.71 (2H, dm, *J* 11.5 Hz, 2 × C**H**H′), 3.83 (2H, app. ddd, *J* 11.5, 2.5, 1.0 Hz, 2 × CH**H′**), 4.03 (2H, app. tt, *J* 2.5, 1.5 Hz, 2 × C**H**); δ_C (100 MHz, $CDCl_3$) 27.0 (2 × **C**H_3), 61.9 (2 × C**H**$_2$OH), 77.8 (2 × C**H**), 109.2 (**C**$(CH_3)_2$). Data as reported.[9]

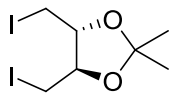
[(4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]bis(methylene) bis(4-methylbenzenesulfonate) (3.40)



DMAP (30.5 mg, 0.25 mmol), *p*-toluenesulfonyl chloride (515 mg, 2.70 mmol) and triethylamine (376 µL, 2.70 mmol) were added to a stirred solution of diol **3.39** (200 mg, 1.23 mmol) in DCM (9.26 mL). After 1 h the reaction was quenched by the addition of water (10 mL) and extracted with DCM (3 × 15 mL). The combined organics were washed with brine (25 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 2:1, petrol/ethyl acetate) gave bistosylate **3.40** as white, needle-like crystals (530 mg, 93%).

R_f 0.21 (2:1, petrol/ethyl acetate); m.p. 52 °C (lit reported 80-81 °C);[10] $[\alpha]_D^{20}$ – 13.0 (c 5.0 in chloroform) [lit. reported – 12.9 (c 9.4 in chloroform)];[10] δ_H (400 MHz, $CDCl_3$) 1.31 (6H, s, 2 × C**H**$_3$), 2.47 (6H, s, 2 × ArC**H**$_3$), 4.01-4.03 (2H, m, 2 × C**H**), 4.10 (4H, app. dd, *J* 4.5, 2.0 Hz, 2 × C**H**$_2$), 7.37 (4H, dm, *J* 8.5 Hz, Ar C**H**), 7.80 (4H, app. dt, *J* 8.5, 2.0 Hz, Ar C**H**); δ_C (100 MHz, $CDCl_3$) 21.7 (2 × Ar**C**H_3), 26.7 (2 × **C**H_3), 68.4 (2 × **C**H_2), 75.0 (2 × **C**H), 110.8 (**C**$(CH_3)_2$), 128.0 and 130.0 (Ar **C**H), 132.4 and 145.2 (quat. **Ar**). Data as reported.[9]

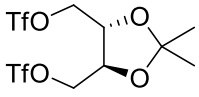
(4*R*,5*R*)-4,5-bis(Iodomethyl)-2,2-dimethyl-1,3-dioxolane (3.41)



Sodium iodide (35 mg, 0.23 mmol) was added to a solution of bistosylate **3.40** (50 mg, 0.11 mmol) in acetone (1.0 mL). The solution was heated to reflux in a sealed tube for 2 h before being cooled, filtered and the filtrate evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 10:1, petrol/ethyl acetate) gave diiodide **3.41** as a colourless oil (42 mg, 99%).

R_f 0.60 (10:1, petrol/ethyl acetate); $[\alpha]_D^{25}$ +3.1 (c 1.0 in chloroform); δ_H (400 MHz, $CDCl_3$) 1.47 (6H, s, 2 × C**H**$_3$), 3.34-3.42 (4H, m, 2 × C**H**$_2$I), 3.83-3.88 (2H, m, 2 × C**H**); δ_C (100 MHz, $CDCl_3$) 6.3 (2 × **C**H_2I), 27.7 (2 × **C**H_3), 80.2 (2 × **C**H), 110.1 (**C**$(CH_3)_2$). Data as reported.[11]

[(4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]bis(methylene) bis(trifluoromethanesulfonate) (3.122)

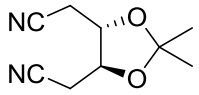


Pyridine (1.9 mL, 23.8 mmol) was added slowly to a solution of diol **3.39** (500 mg, 3.1 mmol) in DCM (25 mL) stirring at –40 °C. Triflic anhydride (1.45 mL, 8.64 mmol) was added dropwise and the reaction stirred for 5 mins before being quenched with HCl (1 M aq., 15 mL) and diluted in DCM (20 mL). The layers were separated and the organic layer washed with water (15 mL) and brine (15 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the product immediately dissolved in DMF for reaction in the next step.

A sample was taken for characterisation and purified by flash chromatography (SiO_2, 19:1, petrol/ether) to give *triflate* **1.122** as a colourless oil which rapidly decomposed upon standing.

R_f 0.31 (19:1, petrol/ether); δ_H (400 MHz, $CDCl_3$) 1.47 (6H, s, 2 × C**H**$_3$), 4.25 (2H, app ddd *J* 4.0, 2.5, 1.5 Hz, 2 × C**H**), 4.58 (2H, dd, *J* 11.0, 3.5 Hz, 2 × C**H**H′), 4.68 (2H, dd, *J* 11.0, 3.5 Hz, 2 × CH**H′**); δ_C (100 MHz, $CDCl_3$) 26.7 (2 × **C**H_3), 73.1 (2 × **C**H_2), 74.2 (2 × **C**H), 117.2 (2 × **C**F_3), 119.8 (**C**$(CH_3)_2$).

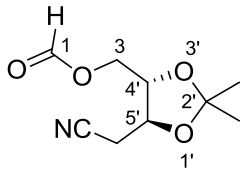
2,2′-[(4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]diacetonitrile (3.42)



Sodium cyanide (333 mg, 6.8 mmol) was added to a solution of triflate **3.122** (3.1 mmol theoretical) in DMF (34 mL) stirring at 0 °C. The reaction was warmed to RT and stirred for 2 h before being quenched with water (50 mL) and extracted with ether (2 × 20 mL). The combined organic layers were washed with water (3 × 25 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give *dinitrile* **3.42** as a colourless oil (200 mg, 36% over two steps).

R_f 0.08 (1:1, petrol/ether); $[\alpha]_D^{17}$ + 4.4 (c 1.0 in chloroform); ν_{max} (thin film)/cm^{-1} 835w, 912w, 979w, 1083br, 1164s, 1227br, 1377s, 1417m, 1725w, 2254m, 2991br, 3508br; δ_H (400 MHz, $CDCl_3$) 1.49 (6H, s, 2 × C**H**$_3$), 2.77 (1H, app. ddd, *J* 17.0, 3.0, 1.5 Hz, 2 × C**H**H′), 2.84 (1H, app. ddd, *J* 17.0, 3.5, 2.0 Hz, 2 × CH**H′**), 4.07-4.13 (2H, m, 2 × C**H**); δ_C (100 MHz, $CDCl_3$) 21.2 (2 × **C**H_2), 26.9 (2 × **C**H_3), 74.7 (2 × **C**H), 111.0 (**C**$(CH_3)_2$), 115.6 (2 × **C**N); *m*/*z* (ESI^+) 203 (MNa^+, 55%), 265 (100), 275 (68); HRMS found 203.0791; $C_9H_{12}N_2NaO_2$ (MNa^+) requires 203.0791.

[(4*S*,5*S*)-5-(Cyanomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl formate (3.43)

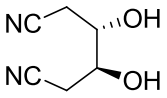


In attempts to obtain dinitrile **3.42**, varying amounts of *formate* **3.43** were also obtained as a brown oil (9~15%).

R_f 0.20 (1:1, petrol/ether); $[\alpha]_D^{17}$ – 8.4 (c 1.0 in chloroform); ν_{max} (thin film)/cm^{-1} 2990br, 1723s, 1374m, 1221br, 1162br, 1087br; δ_H (400 MHz, $CDCl_3$) 1.44 (3H, s, C**H**$_3$), 1.49 (3H, s, C**H**$_3$), 2.70 (1H, dd, *J* 17.0, 4.5 Hz, C**H**H′), 2.82 (1H, dd, *J* 17.0, 5.0 Hz, CH**H′**), 4.05-4.14 (2H, m, C(4′)**H** and C(5′)**H**), 4.33 (1H, dd, *J* 12.0, 4.5 Hz, C(3)**H**H′), 4.38 (1H, dd, *J* 12.0, 4.5 Hz, C(3)H**H′**), 8.11-8.12

(1H, m, C(1)**H**); δ_C (100 MHz, $CDCl_3$) 21.6 (**C**H_2), 26.9 (2 × **C**H_3), 62.5 (**C**(3)H_2), 73.1 (**C**(5′)H), 77.4 (**C**(4′)H), 110.8 (**C**$(CH_3)_2$), 116.0 (**C**N), 160.3 (**C**(1)H); *m*/*z* (ESI^+) 173 (100%), 222 (MNa^+, 29), 236 (84), 353 (89), 481 (78), 533 (30); HRMS found 222.0738; $C_9H_{13}NNaO_4$ (MNa^+) requires 222.0737.

(3*S*,4*S*)-3,4-Dihydroxyhexanedinitrile (3.44)

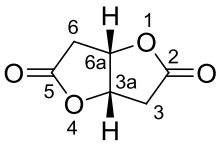


HCl (6 M aq., 0.84 mL) was added to a solution of acetonide **3.42** (80 mg, 0.44 mmol) in methanol (0.84 mL) and the reaction heated at reflux for 14 h. The solvent was evaporated *in vacuo* and the residue purified by flash chromatography (SiO_2, 3:1, ethyl acetate/petrol) to give diol **3.44** as a pale brown oil (50 mg, 81%).

$[\alpha]_D^{21}$ + 1.4 (c 1.0 in chloroform)

Other data as for achiral material (**3.34**).

(3a*S*,6a*S*)-Tetrahydrofuro[3,2-b]furan-2,5-dione (3.8)

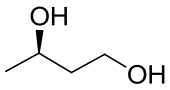


HCl (6 M aq., 0.21 mL) was added to a solution of dicyanide **3.42** (20 mg, 0.11 mmol) in THF (0.21 mL) and the reaction heated at reflux for 14 h. The solvent was evaporated *in vacuo* and the residue purified by flash chromatography (SiO_2, 3:1, ethyl acetate/petrol) to give dilactone **3.8** as a white powder (9 mg, 58%).

m.p. 92 °C (lit. reported 122 °C);[12] $[\alpha]_D^{25}$ −157.7 (c 1.0 in water) [lit. reported −145 (c 1.0 in water)].[12]

Other data as for achiral material.

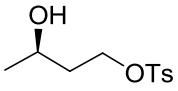
(*R*)-Butane-1,3-diol (3.45)



PHB (3.0 g, 34.9 mmol of monomer) was added in 5 portions to a suspension of lithium aluminium hydride (1.0 g, 26.4 mmol) in THF (46 mL) stirred at RT. After 2 h the reaction was heated to reflux for 5 h before being cooled to RT and stirred for 15 h. The reaction was then quenched with water (1.0 mL), sodium hydroxide (1.3 M, 1.0 mL) and water (3.0 mL) and stirred for 5 mins before being filtered. The precipitate was washed with ethyl acetate (100 mL) and then stirred with boiling ether (75 mL) for 30 mins before filtering again. This process was repeated with another portion of boiling ether (75 mL). The combined filtrates were evaporated *in vacuo* to give diol **3.45** as a colourless oil (3.1 g, 100%).

$[\alpha]_D^{25}$ −30.7 (c 1.2 in methanol) [lit. reported −31 (c 1.20 in methanol)];[13] δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.5 Hz, C**H**$_3$), 1.65-1.70 (2H, m, C**H**$_2$CH_2OH) 3.24 (2H, br s, 2 × O**H**), 3.75-3.90 (2H, m, C**H**$_2$OH), 4.00-4.10 (1H, m, C**H**OH); δ_C (100 MHz, $CDCl_3$) 23.7 (**C**H_3), 40.0 (**C**H_2CH_2OH), 61.4 (**C**H_2OH), 68.0 (**C**HOH). Data as reported.[14]

[(*R*)-3-Hydroxybutyl] 4-methylbenzenesulfonate (3.123)

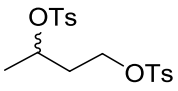


1,3-Butanediol (300 mg, 3.33 mmol) was dissolved in pyridine (0.98 mL) and the solution stirred at −25 °C. Toluenesulfonyl chloride (691 mg, 3.62 mmol) in pyridine (1.47 mL) was added dropwise and the resultant mixture stirred at −25 °C for 3.5 h before being quenched with water (10 mL) and the

reaction stirred at 0 °C for 20 min. The mixture was then diluted in ethyl acetate (20 mL), the layers separated and the organic layer washed with sulphuric acid (2 M aq., 25 mL), Na_2CO_3 (sat. aq., 25 mL) and brine (sat. aq., 25 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 3:2, ether/petrol) gave tosyl alcohol **3.123** as a colourless oil (560 mg, 69%), along with some of the bistosylated product **3.124**, also as a colourless oil (55 mg, 4%).

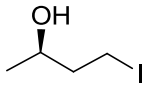
R_f 0.21 (3:2, ether/petrol); $[\alpha]_D^{23}$ – 14.8 (c 1.0 in DCM) [lit. reported – 14.9(c 1.0 in DCM)];[14] δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.5 Hz, C(4′)**H$_3$**), 1.62-1.75 (2H, m, C(2′)**H**H′ and O**H**), 1.78-1.88 (1H, m, C(2′)H**H′**), 2.46 (3H, s, ArC**H$_3$**), 3.91-3.99 (1H, m, C(3′)**H**OH), 4.12 (1H, dd, *J* 5.5, 1.0 Hz, C(1′)**H**H′), 4.22-4.28 (1H, m, C(1′)H**H′**), 7.36 (2H, d, *J* 8.0 Hz, **Ar**), 7.80 (2H, d, *J* 8.0 Hz, **Ar**); δ_C (100 MHz, $CDCl_3$) 15.3 (Ar**C**H_3), 23.6 (**C**(4′)H_3), 37.9 (**C**(2′)H_2), 64.1 (**C**(3′)H), 67.8 (**C**(1′)H_2), 127.8 and 129.9 (**Ar**), 133.0 and 144.8 (**Ar** quat.). Data as reported.[15]

Butane-1,3-diyl bis(4-methylbenzenesulfonate) (3.124)



R_f 0.42 (3:2, ether/petrol); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6.5 Hz, C(4)**H$_3$**), 1.84-1.99 (2H, m, C(2)**H$_2$**), 2.45 and 2.46 (6H, 2 × s, 2 × ArC**H$_3$**), 3.93 (1H, ddd, *J* 10.5, 7.5, 5.8 Hz, C(1)**H**H′), 4.02 (1H, dt, *J* 10.5, 6.1 Hz, C(1)H**H′**), 4.70 (1H, qdd, *J* 6.5, 6.1, 5.8 Hz, C(3)**H**), 7.35 (4H, d, *J* 7.5 Hz, **Ar**), 7.75 (4H, d, *J* 7.5 Hz, **Ar**); δ_C (100 MHz, $CDCl_3$) 20.8 (**C**H_3), 21.6 (Ar**C**H_3), 35.8 (**C**$H_2$$CH_2$OTs), 66.0 (**C**$H_2$OTs), 76.1 (**C**HOTs), 127.7, 127.9 and 129.9 (Ar **C**H), 132.7, 133.9, 144.9, 145.0 (Ar **C**). Data as reported.[16]

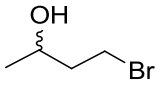
(*R*)-4-Iodobutan-2-ol (3.47)



NaI (230 mg, 1.54 mmol) was added to a solution of tosylate **3.123** (300 mg, 1.23 mmol) in acetone (1.93 mL) and the resulting solution stirred in the dark at RT for 48 h before being filtered, the residue washed with chloroform and the filtrate evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 2:1, petrol/ether) gave iodoalcohol **3.47** as a pale yellow oil (250 mg, 100%).

R_f 0.24 (2:1, petrol/ether); $[\alpha]_D^{25}$ −16.9 (c 1.0 in DCM); δ_H (500 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6.5 Hz, C**H**$_3$), 1.53 (1H, br s, O**H**), 1.91-1.99 (2H, m, C**H**$_2$CH_2I), 3.26-3.30 (2H, m, C**H**$_2$I), 3.94 (1H, dqd, *J* 8.0, 6.5, 4.5 Hz, C**H**OH); δ_C (125 MHz, $CDCl_3$) 2.7 (**C**H_2I), 23.3 (**C**H_3), 42.3 (**C**H_2CH_2I), 67.9 (**C**HOH). Data as reported.[17]

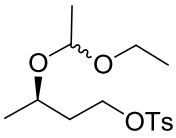
4-Bromobutan-2-ol (3.125)



LiBr (52.1 mg, 0.60 mmol) was added to a solution of tosylate (±)-**3.123** (50 mg, 0.20 mmol) in acetone (0.87 mL) and the reaction heated at reflux for 2 h 30 mins. The reaction was cooled, poured onto $NaHCO_3$ (sat. aq., 10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with water (20 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 1:1, petrol/ether) gave bromide **3.125** as a colourless oil (14 mg, 46%).

R_f 0.44 (1:1, petrol/ether); δ_H (500 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.5 Hz, C**H**$_3$), 1.60 (1H, br s, O**H**), 1.96-2.00 (2H, m, C**H**$_2$CH_2Br), 3.47-3.59 (2H, m, C**H**$_2$Br), 4.04 (1H, dqd, *J* 7.5, 6.5, 5.0 Hz, C**H**); δ_C (125 MHz, $CDCl_3$) 23.5 (**C**H_3), 30.3 (**C**H_2CH_2Br), 41.5 (**C**H_2Br), 66.1 (**C**H). Data as reported.[18]

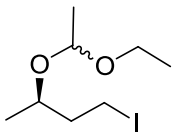
(*R*)-3-(1-Ethoxyethoxy)butyl 4-methylbenzenesulfonate (3.126)



Ethyl vinyl ether (58 µL, 0.61 mmol) was added dropwise to a solution of alcohol **3.123** (50 mg, 0.20 mmol) and PPTS (5 mg, 0.02 mmol) in DCM (0.15 mL) stirring at 0 °C. After 1 h the reaction was warmed to RT and stirred for 2 h before being quenched with $NaHCO_3$ (sat. aq., 5 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organics were washed with brine (sat. aq., 10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 4:1, petrol/ether) gave *ether* **3.126** as a colourless oil (65 mg, 100%).

R_f 0.15 (4:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2970br, 1354m, 1175s, 947br, 892br, 816m, 664m; δ_H (400 MHz, $CDCl_3$) (both diastereomers) 1.09-1.28 (18 H, m, 6 × C**H$_3$**), 1.72-1.94 (4H, m, 2 × C(2)**H$_2$**), 2.46 (6H, s, 2 × ArC**H$_3$**), 3.30-3.89 (6H, m, 2 × C(3)**H** and 2 × OC**H$_2$**CH_3), 4.05-4.25 (4H, m, 2 × C(1)**H$_2$**), 4.56 and 4.69 (2H, 2 × q, *J* 5.5 Hz, 2 × OC**H**(CH_3)O), 7.32-7.38 (4H, m, **Ar**), 7.78-7.82 (4H, m, **Ar**); δ_C (100 MHz, $CDCl_3$) 15.2 and 15.3 (2 × OCH_2**C**H_3), 20.2, 20.3, 20.7 and 21.2 (4 × **C**H_3), 21.6 (2 × Ar**C**H_3), 36.3 and 36.6 (2 × **C**(2)H_2), 60.3 and 60.4 (2 × O**C**H_2CH_3), 67.4 and 69.3 (2 × **C**(3)H), 67.5 and 67.7 (2 × **C**(1)H_2), 97.9 and 99.9 (2 × O**C**H(CH_3)O), 127.88, 127.91, 129.80 and 129.84 (Ar **C**H), 133.0, 133.2, 144.7 and 144.8 (Ar **C**); *m*/*z* (ESI^+) 267 (80%), 339 (MNa^+, 38), 511 (100); HRMS found 339.1225; $C_{15}H_{24}NaO_5S$ (MNa^+) requires 339.1237.

(*R*)-3-(1-Ethoxyethoxy)-1-iodobutane (3.48)

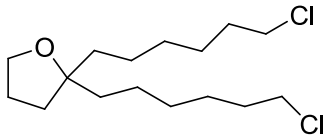


PPTS (63 mg, 0.25 mmol) was added to a solution of alcohol **3.47** (500 mg, 2.5 mmol) in DCM (10 mL) stirring at 0 °C. Ethyl vinyl ether (718 µL, 7.5 mmol) was added dropwise and the reaction

allowed to warm to RT over 2 h before being quenched with $NaHCO_3$ (sat. aq., 25 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organics were washed with brine (sat. aq., 50 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 9:1, petrol/ether) gave *iodide* **3.48** as a colourless oil (526 mg, 77%).

R_f 0.28 (9:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 3331br, 2966s, 2928br, 1419br, 1375m, 1236s, 1176s, 1147m, 1118m, 1076s, 1047s, 928br; δ_H (400 MHz, $CDCl_3$) 1.15-1.35 (18 H, m, 6 × C**H**$_3$), 1.87-2.14 (2H, m, 2 × C(2)**H**$_2$), 3.22-3.33 (4H, m, 2 × C(1)**H**$_2$), 3.45-3.92 (6H, m, 2 × C(3)**H** and 2 × OC**H**$_2$$CH_3$), 4.67-4.80 (2H, m, 2 × OC**H**(CH_3)O); δ_C (100 MHz, $CDCl_3$) 2.8 and 2.9 (2 × **C**(1)H_2), 15.3 and 15.4 (2 × OCH_2**C**H_3), 19.8, 20.67, 20.75 and 20.84 (2 × **C**H_3), 40.9 and 41.5 (2 × **C**(2)H_2), 60.3 and 60.4 (2 × O**C**H_2CH_3), 71.1 and 72.8 (2 × **C**HOEE), 97.8 and 99.9 (2 × O**C**H(CH_3)O); *m*/*z* (ESI^+) 295 (MNa^+, 100%), 413 (87); HRMS found 295.0166; $C_8H_{17}INaO_2$ requires 295.1065.

2,2-bis(6-Chlorohexyl)tetrahydrofuran (3.50)

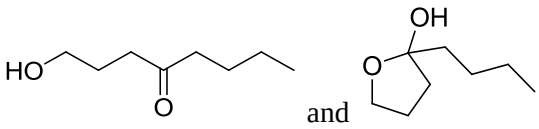


tert-Butyllithium (1.7 M in pentane, 1.25 mL, 2.1 mmol) was added dropwise to a solution of 1-iodo-6-hexane (250 mg, 1.01 mmol) in ether (4.0 mL) stirring at −78 °C. After 15 mins, γ-butyrolactone (105 μL, 1.01 mmol) was added and the reaction stirred for 1 h before being quenched with NH_4Cl (sat. aq., 20 mL) and warmed to RT. The mixture was extracted with ether (3 × 30 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 2:1, petrol/ether) gave *THF* **3.50** as a colourless oil (82 mg, 25%).

R_f 0.09 (2:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 3345m, 2934s, 2859s, 1461br, 1287br, 1056br, 725s, 649s; δ_H (400 MHz, $CDCl_3$) 1.28-1.38 (8H, m, 2 × C(2′)**H**$_2$ and 2 × C(4′)**H**$_2$), 1.42-1.51 (8H, m, 2 × C(1′)H_2 and 2 × C(3′)**H**$_2$), 1.52-1.67 (4H, m, C(3)**H**$_2$ and C(4)**H**$_2$), 1.79 (4H, ddt, *J* 7.5, 7.0, 6.5 Hz, 2 × C(5′)**H**$_2$), 3.55 (4H, t, *J* 6.5 Hz, 2 × C(6′)**H**$_2$), 3.68 (2H, t, *J* 6.0 Hz, C(5)**H**$_2$); δ_C (100 MHz, $CDCl_3$)

23.4 and 29.5 (2 × **C**(2′)H_2 and 2 × **C**(4′)H_2), 26.7 (**C**(4)H_2), 26.8 (2 × **C**(3′)H_2), 32.6 (2 × **C**(5′)H_2), 36.0 (**C**(3)H_2), 39.1 (2 × **C**(1′)H_2), 45.1 (2 × **C**(6′)H_2), 63.4 (**C**(5)H_2), 74.1 (**C**(2)); *m*/*z* (ESI$^+$) 315 (73%), 349 (82), 401 (47), 675 ([M_2+MeCN+NH_4]$^+$, 100); HRMS not found.

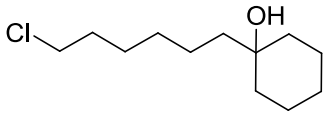
1-Hydroxyoctan-4-one (3.52) and **2-Butyltetrahydrofuran-2-ol**



n-Butyllithium (1.6 M in hexanes, 2.45 mL, 3.92 mmol) was added dropwise to a solution of γ-butyrolactone (268 μL, 3.5 mmol) in ether (7.0 mL) stirring at **–**90 °C. After stirring for 1 h at this temperature, the reaction mixture was allowed to warm to RT over 6 h before being quenched with NH_4Cl (sat. aq., 7 mL) and extracted with ether (2 × 20 mL). The combined organics were washed with NaOH (10% aq., 20 mL) and brine (sat. aq., 20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 5:3, petrol/ether) gave ketone **3.52** as a colourless oil, in a 9:2 ratio (as determined by ^{1}H NMR analysis) of the inseparable open/cyclised forms (400 mg, 79%).

R_f 0.21 (1:1 petrol/ether); δ_H (400 MHz, $CDCl_3$) Data reported for open chain isomer: 0.88 (3H, t, *J* 7.3 Hz, C(8)**H$_3$**), 1.28 (2H, tq, *J* 7.6, 7.3 Hz, C(7)**H$_2$**), 1.53 (2H, quin, *J* 7.6 Hz, C(6)**H$_2$**), 1.80 (2H, tt, *J* 7.0, 6.5 Hz, C(2)**H$_2$**), 2.41 (2H, t, *J* 7.6 Hz, C(5)**H$_2$**), 2.53 (2H, t, *J* 7.0 Hz, C(3)**H$_2$**), 3.61 (2H, t, *J* 6.5 Hz, C(1)**H$_2$**); δ_C (100 MHz, $CDCl_3$) 13.8 (**C**(8)H_3), 22.3 (**C**(7)H_2), 25.9 (**C**(6)H_2), 26.5 (**C**(2)H_2), 39.4 (**C**(3)H_2), 42.6 (**C**(5)H_2), 62.1 (**C**(1)H_2), 212.1 (**C**(4)). Data as reported.[19]

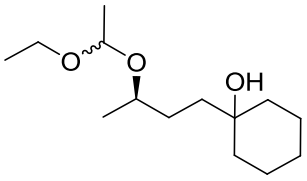
1-(6-Chlorohexyl)cyclohexanol (3.53)



tert-Butyllithium (1.7 M in pentane, 1.25 mL, 2.1 mmol) was added dropwise to a solution of 1-iodo-6-chlorohexane (154 μL, 1.01 mmol) in ether (3.82 mL) stirring at −78 °C. After 15 mins, cyclohexanone (105 μL, 1.01 mmol) was added and the reaction stirred for 1 h before being quenched with NH_4Cl (sat. aq., 20 mL) and warmed to RT. The mixture was extracted with ethyl acetate (3 × 30 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 9:1, petrol/ether) gave *alcohol* **3.53** as a colourless oil (156 mg, 65%).

R_f 0.08 (9:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 3426br, 2933br, 2858s, 1697w, 1448m, 966w; δ_H (400 MHz, $CDCl_3$) 1.13-1.79 (20 H, m, 10 × C**H**$_2$), 3.46-3.51 (2H, m, C(6′)**H**$_2$); δ_C (100 MHz, $CDCl_3$) 22.6 (**C**(3)H_2 and **C**(5)H_2), 23.1, 26.2, 27.3, 29.9 and 33.0 (**C**(2′)H_2, **C**(4)H_2, **C**(4′)H_2, **C**(3′)H_2 and **C**(5′)H_2), 37.8 (**C**(1′)H_2, **C**(2)H_2 and **C**(6)H_2), 45.5 (**C**(6′)H_2Cl), 71.7 (**C**(1)); *m*/*z* (ESI^+) 219 (MNa^+, 100%), 304 (68), 415 (62); HRMS found 241.1330; $C_{12}H_{23}ClNaO$ (MNa^+) requires 241.1330.

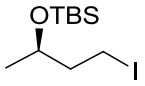
(*R*)-1-(3-(1-Ethoxyethoxy)butyl)cyclohexanol (3.54)



tert-Butyllithium (1.7 M in pentane, 454 μL, 0.77 mmol) was added dropwise to a solution of iodide **3.48** (100 mg, 0.37 mmol) in ether (1.39 mL) stirring at −78 °C. After 20 mins, cyclohexanone (38 μL, 0.37 mmol) was added and the reaction stirred for 2 h before being quenched with NH_4Cl (sat. aq., 10 mL) and warmed to RT. The mixture was extracted with ether (3 × 10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 6:1 → 2:1, petrol/ether) gave *alcohol* **3.54** as a colourless oil (80 mg, 89%).

R_f 0.26 (2:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 3455br, 2933br, 1448m, 1376s, 1334s, 1261m, 1125br, 980s; δ_H (400 MHz, $CDCl_3$) Both diastereomers: 1.11-1.68 (46 H, m, 14 × C**H**$_2$ and 6 × C**H**$_3$), 3.43-3.75 (6H, m, 2 × C**H**OEE and 2 × OC**H**$_2$$CH_3$), 4.72 and 4.75 (2H, 2 × q, *J* 5.5 Hz, 2 × OC**H**(CH_3)O); δ_C (100 MHz, $CDCl_3$) Both diastereomers 15.28 and 15.31 (2 × OCH_2**C**H_3), 20.0, 20.6, 20.8 and 21.0 (4 × **C**H_3), 22.2 (2 × **C**(3)H_2 and 2 × **C**(5)H_2), 25.8 and 25.9 (2 × **C**(4)H_2), 29.9 and 30.6 (2 × **C**(2′)H_2), 37.37, 37.45, 37.53 and 37.68 (2 × **C**(2)H_2, 2 × **C**(6)H_2 and 2 × **C**(1′)H_2), 59.85 and 59.94 (2 × O**C**$H_2$$CH_3$), 70.97 and 71.01 (2 × **C**(1)), 71.9 and 73.2 (2 × **C**HOEE), 97.7 and 99.1 (2 × O**C**H(CH_3)O); *m*/*z* (ESI^+) 267 (MNa^+, 100%), 511 (M_2Na^+, 57); HRMS found 267.1923; $C_{14}H_{28}NaO_3$ (MNa^+) requires 267.1931.

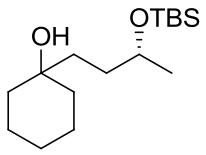
(*R*)-*tert*-Butyl(4-iodobutan-2-yloxy)dimethylsilane (3.59)



DIPEA (139 μL, 0.80 mmol) was added to a flask containing *tert*-butyldimethylsilyl chloride (150.7 mg, 0.65 mmol) and NaI (105 mg, 0.70 mmol). Acetonitrile (0.6 mL) was added and the fuming mixture was stirred for 15 mins before iodoalcohol **3.47** (100 mg, 0.50 mmol) was added and the reaction heated to 60 °C for 3 h before being cooled and diluted in petrol (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with 1:1 petrol/ether (30 mL). The combined organic layers were washed with $NaHSO_3$ (sat. aq., 20 mL) and water (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, petrol) gave iodide **3.59** as a colourless liquid (144 mg, 91%).

R_f 0.25 (petrol); $[\alpha]_D^{25}$ −46.3 (c 0.41 in chloroform) [lit. reported −46.3 (c 0.41 in chloroform)];[20] δ_H (400 MHz, $CDCl_3$) 0.09 and 0.10 (6H, 2 × s, 2 × SiC**H**$_3$), 0.89 (9H, s, SiC(C**H**$_3$)$_3$), 1.16 (3H, d, *J* 6.0 Hz, C**H**$_3$), 1.85-1.89 (2H, m, C**H**$_2$$CH_2$I), 3.17-3.26 (2H, m, C**H**$_2$I), 3.89 (1H, dqd, *J* 7.5, 6.0, 4.5 Hz, C**H**OTBS); δ_C (100 MHz, $CDCl_3$) –4.6 and –4.2 (2 × Si**C**H_3), 3.6 (**C**H_2I), 18.0 (Si**C**(CH_3)$_3$), 23.5 (**C**H_3), 25.9 (SiC(**C**H_3)$_3$), 43.3 (**C**$H_2$$CH_2$I), 68.3 (**C**HOTBS). Data as reported.[20]

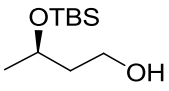
(*R*)-1-[3-(*tert*-Butyldimethylsilyloxy)butyl]cyclohexanol (3.55)



tert-Butyllithium (1.7 M in pentane, 656 μL, 1.05 mmol) was added dropwise to a solution of iodide **3.59** (158 mg, 0.50 mmol) in ether (1.91 mL) stirring at –78 °C. After 15 mins, cyclohexanone (52 μL, 0.50 mmol) was added and the reaction stirred for 1 h 30 mins before being quenched with NH_4Cl (sat. aq., 20 mL) and warmed to RT. The mixture was extracted with ethyl acetate (2 × 30 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 5:1, petrol/ether) gave *alcohol* **3.55** as a colourless oil (113 mg, 79%).

R_f 0.38 (5:1, petrol/ether); δ_H (400 MHz, $CDCl_3$) 0.07 (6H, s, 2 × SiC**H**$_3$), 0.90 (9H, s, SiC(C**H**$_3$)$_3$), 1.16 (3H, d, *J* 6.0 Hz, C**H**$_3$), 1.36-1.65 (14H, m, 7 × C**H**$_2$), 3.80-3.87 (1H, m, C**H**OTBS); δ_C (100 MHz, $CDCl_3$) −4.7 and −4.5 (2 × Si**C**H$_3$), 18.1 (Si**C**(CH$_3$)$_3$), 22.26 and 22.34 (2 × **C**H$_2$), 23.4 (**C**H$_3$), 25.9 (SiC(**C**H$_3$)$_3$), 32.6 (**C**H$_2$), 37.2 (2 × **C**H$_2$), 37.9 (2 × **C**H$_2$), 69.0 (**C**HOTBS), 70.9 (C).

(*R*)-3-(*tert*-Butyldimethylsilyloxy)butan-1-ol (3.127)



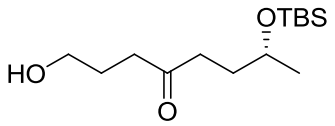
Alcohol **3.127** was obtained on a number of occasions during attempts at lithiation and alkylation using iodide **3.59**. An example of such an experiment is given below is given:

t-BuLi (1.7 M in pentane, 196 μL, 0.33 mmol) was added dropwise to a solution of iodide **3.59** (50 mg, 0.16 mmol) in ether (0.20 mL) stirring at –78 °C. After 10 mins, the solution was added *via* cannula to a solution of aldehyde **3.72** (41 mg, 0.16 mmol) in ether (0.12 mmol) stirring at –90 °C. After 45 mins the reaction was quenched with water (5 mL) and warmed to RT. The mixture was extracted with ethyl acetate (3 × 10 mL), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by

flash chromatography (SiO_2, 1:1, petrol/ether) gave *addition product* **3.73** (6.5 mg, 10%) and alcohol **X** (23 mg, 70%).

R_f 0.24 (1:1, petrol/ether); $[\alpha]_D^{23}$ −14.1 (c 0.41 in chloroform) [lit. reported −17.8 (c 0.41 in chloroform)][20]; δ_H (400 MHz, $CDCl_3$) 0.10 (6H, 2 × s, 2 × SiC**H**$_3$), 0.90 (9H, s, SiC(C**H**$_3$)$_3$), 1.21 (3H, d, *J* 6.5 Hz, C**H**$_3$), 1.60-1.68 (2H, m, C**H**H′CH_2OH), 1.76-1.84 (1H, m, CH**H′**CH_2OH), 2.54 (1H, app t, *J* 4.0 Hz, O**H**), 3.70-3.77 (1H, m, C**H**H′OH), 3.85 (1H, ddt, *J* 11.5, 8.0, 4.0 Hz, CH**H′**OH), 4.12 (1H, dtd, *J* 12.5, 6.5, 4.0 Hz, C**H**OTBS); δ_C (100 MHz, $CDCl_3$) –5.0 and –4.4 (2 × Si**C**H_3), 17.9 (Si**C**$(CH_3)_3$), 23.4 (**C**H_3), 25.8 (SiC(**C**H_3)$_3$), 40.4 (**C**H_2CH_2OH), 60.5 (**C**H_2OH), 68.4 (**C**HOTBS). Data as reported.[20]

(*R*)-7-(*tert*-Butyldimethylsilyloxy)-1-hydroxyoctan-4-one (3.57)

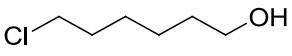


n-BuLi (1.6 M in hexanes, 725 µL, 1.16 mmol) was added dropwise to a solution of iodide **3.59** (365 mg, 1.16 mmol) in ether (1.33 mL) stirring at –78 °C. After 10 mins, the solution was added *via* cannula to a solution of γ-butyrolactone (90 µL, 1.16 mmol) in ether (1.0 mL) stirring at –90 °C. After 1 h 15 mins the reaction was quenched with NH_4Cl (sat. aq., 5 mL) and extracted with ether (2 × 20 mL). The combined organics were washed with NaOH (10% aq., 20 mL) and brine (sat. aq., 20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 1:1, petrol/ether) gave ketone **3.57** as a colourless oil (146 mg, 46%) and *ketone* **3.52**, arising from *n*-butyllithium addition, also as a colourless oil (40 mg, 24%). Only trace amounts of the cyclised form of **3.57** could be observed by ^{1}H NMR spectroscopy.

R_f 0.29 (1:1 petrol/ether); $[\alpha]_D^{25}$ –11.4 (c 1.0 in chloroform); ν_{max}(thin film)/cm^{-1} 3400br, 2930br, 1636s, 1375m, 1253s, 1056br, 834s, 774s; δ_H (400 MHz, $CDCl_3$) 0.03 and 0.05 (6H, 2 × s, 2 × SiC**H**$_3$), 0.88 (9H, s, SiC(C**H**$_3$)$_3$), 1.13 (3H, d, *J* 6.0 Hz, C(8)**H**$_3$), 1.58-1.79 (2H, m, C(6)**H**$_2$), 1.80-1.94 (2H, m, C(2)**H**$_2$), 2.41-2.54 (2H, m, C(3)**H**$_2$), 2.57 (2H, t, *J* 7.0 Hz, C(5)**H**$_2$), 3.62-3.72 (2H, m, C(1)**H**$_2$), 3.83

(1H, dqd, 7.5, 6.0, 4.5 Hz, C(7)**H**); δ_C (100 MHz, $CDCl_3$) –4.8 and –4.4 (2 × Si**C**H_3), 18.1 (Si**C**$(CH_3)_3$), 23.7 (**C**(8)H_3), 25.8 (SiC(**C**$H_3)_3$), 26.5 (**C**(2)H_2), 33.1 (**C**(6)H_2), 38.8 (**C**(3)H_2), 39.5 (**C**(5)H_2), 62.3 (**C**(1)H_2), 67.5 (**C**(7)H), 211.63 (**C**(4)); *m*/*z* (ESI^+) 102 (100%), 297 (MNa^+, 40), 571 (M_2Na^+, 30); HRMS found 297.1850; $C_{14}H_{30}NaO_3Si$ (MNa^+) requires 297.1856.

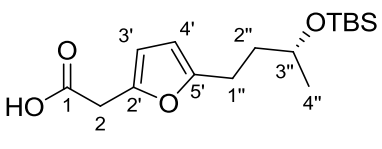
6-Chlorohexan-1-ol (3.58)



t-BuLi (1.7 M in pentane, 185 µL, 0.32 mmol) was added dropwise to a solution of 6-chloro-1-iodohexane (36 mg, 0.15 mmol) in ether (0.55 mL) stirring at –78 °C. After 10 mins, a solution of dilactone **3.8** (21 mg, 0.15 mmol) in THF (0.4 mL) was added *via* cannula. After 1 h 30 mins the reaction was quenched with NH_4Cl (sat. aq., 5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organics were washed with brine (sat. aq., 10 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give *alcohol* **3.58** as a colourless oil (14 mg, 68%).

δ_H (500 MHz, $(CD_3)CO$) 1.37-1.57 (6H, m, 4 × C**H**$_2$), 1.75-1.83 (2H, m, C**H**$_2$), 3.42 (1H, t, *J* 5.0 Hz, O**H**), 3.55 (2H, dt, *J* 6.5, 5.0 Hz, C**H**$_2$OH), 3.62 (2H, t, *J* 6.5 Hz, C**H**$_2$Cl); δ_C (125 MHz, $(CD_3)CO$) 26.0, 29.2, 33.5 and 33.6 (4 × **C**H_2), 45.7 (**C**H_2Cl), 62.3 (**C**H_2OH). Data as reported.[21]

(*R*)-2-(5-[3-(*tert*-Butyldimethylsilyloxy)butyl]furan-2-yl)acetic acid (3.60)

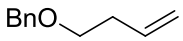


t-BuLi (1.7 M in pentane, 618 µL, 1.05 mmol) was added dropwise to a solution of iodide **3.59** (156 mg, 0.50 mmol) in ether (0.56 mL) stirring at –78 °C. After 10 mins, the solution was added *via* cannula to a solution of dilactone **3.8** (70 mg, 0.50 mmol) in ether (1.0 mL) stirring at –90 °C. After 40 mins the reaction was quenched with NH_4Cl (sat. aq., 5 mL) and extracted with ethyl acetate (2 ×

20 mL). The combined organics were washed with brine (sat. aq., 20 mL), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, ether) gave *furan* **3.60** as a colourless oil (35 mg, 23%).

R_f 0.25 (ether); ν_{max} (thin film)/cm^{-1} 3413br, 2918br, 1738br; δ_H (500 MHz, $CDCl_3$) 0.05 (6H, s, 2 × SiC**H$_3$**), 0.90 (9H, s, SiC(C**H$_3$**)$_3$, 1.16 (3H, d, *J* 6.5 Hz, C(4′′)**H$_3$**), 1.71-1.78 (2H, m, C(2′′)**H$_2$**), 2.60 (1H, ddd, *J* 16.0, 10.0, 7.5 Hz, C(1′′)**H**H′), 2.69 (1H, ddd, *J* 16.0, 9.5, 6.5 Hz, C(1′′)H**H′**), 3.69 (2H, s, C(2)**H$_2$**), 3.84 (1H, app. sext, *J* 6.0 Hz, C(3′′)**H**), 5.93 (1H, d, *J* 3.0 Hz) and 6.14 (1H, d, *J* 3.0 Hz) (C(3′)**H** and C(4′)**H**); δ_C (125 MHz, $CDCl_3$) –4.8 and –4.4 (2 × Si**C**H_3), 18.1 (Si**C**$(CH_3)_3$), 23.7 (**C**(4′′)H_3), 24.3 (**C**(1′′)H_2), 25.9 (SiC(**C**H_3)$_3$), 30.3 (**C**(2)H_2), 37.6 (**C**(2′′)H_2), 67.8 (**C**(3′′)H), 105.5 and 108.9 (**C**(3′)H and **C**(4′)H), 144.9 and 156.2 (**C**(2′) and **C**(5′)), 198.5 (**C**(1)H); *m/z* (ESI^+) 335 (MNa^+, 64%), 353 (100), 523 (41), 683 ($[M_2+MeCN+NH_4]^+$, 39); HRMS found 335.1643; $C_{16}H_{28}NaO_4Si$ (MNa^+) requires 335.1649.

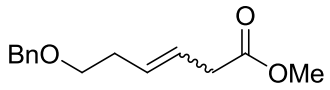
[(But-3-enyloxy)methyl]benzene (3.66)



NaH (60% dispersion in mineral oil, 723 mg, 18.1 mmol) was added in three portions to a solution of buten-1-ol (1.20 mL, 13.9 mmol) in THF (20 mL) stirring at 0 °C. After 10 mins, benzyl bromide (1.82 mL, 15.3 mmol) was added dropwise and the reaction mixture was allowed to warm to RT over 16 h before being quenched with brine (sat. aq., 85 mL) and extracted with ether (2 × 150 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 19:1, petrol/ether) gave benzyl ether **3.66** as a colourless liquid (2.30 g, 100%).

R_f 0.14 (19:1, petrol/ether); δ_H (400 MHz) 2.40 (2H, qdd, *J* 7.0, 2.0, 1.5 Hz, C**H$_2$**CH_2OBn), 3.55 (2H, t, *J* 7.0 Hz, C**H$_2$**OBn), 4.54 (2H, s, C**H$_2$**Ph), 5.07 (1H, ddt, *J* 10.0, 2.0, 1.5 Hz, CH=C**H**H′), 5.13 (1H, dq, *J* 17.0, 1.5 Hz, CH=CH**H′**), 5.87 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C**H**=CHH′), 7.27-7.37 (5H, m, **Ar**); δ_C (100 MHz) 34.2 (**C**$H_2$$CH_2$OBn), 69.6 (**C**$H_2$OBn), 72.9 (**C**$H_2$Ph), 116.4 (CH=**C**$H_2$), 127.5, 127.6 and 128.4 (Ar C**H**), 135.3 (**C**H=CH_2), 138.5 (**Ar** quat.). Data as reported.[22]

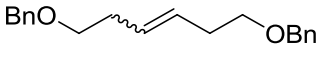
(*E*)-Methyl 6-(benzyloxy)hex-3-enoate and **(*Z*)-methyl 6-(benzyloxy)hex-3-enoate (3.65)**



Hoveyda-Grubbs' II (50 mg, 0.08 mmol) was dissolved in DCM (14 mL) and extensively degassed. This solution was added *via* cannula to a flask containing benzyl ether **3.66** (376 mg, 2.32 mmol) and diester **3.30** (275 mg, 1.60 mmol) which had also been degassed. The resulting solution was stirred at RT for 3 h before being filtered through a short frit of silica and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 10:1, petrol/ether) gave alkene **3.65** as a colourless oil, in a 4.5:1 *E*-/*Z*- ratio (as determined by ^{1}H NMR analysis) (300 mg, 80%, 100% brsm diester **3.30**) along with a small amount of *benzyl dimer* **3.128** as a colourless oil, in a 2.5:1 *E*-/*Z*- ratio (as determined by ^{1}H NMR analysis) (60 mg, 6% wrt benzyl ether **3.66**).

R_f 0.21 (10:1, petrol/ether); δ_H (400 MHz) 2.35-2.42 (2H *E*- and *Z*-, qt, *J* 7.0, 1.5 Hz, C**H$_2$**CH$_2$OBn), 3.07 (2H *E*-, dt, *J* 5.5, 1.0 Hz, C**H$_2$**CO$_2$Me), 3.14 (2H *Z*-, d, *J* 5.5 Hz, C**H$_2$**CO$_2$Me), 3.51 (2H *Z*-, t, *J* 7.0 Hz, C**H$_2$**OBn), 3.52 (2H *E*-, t, *J* 7.0 Hz, C**H$_2$**OBn), 3.68 (3H *Z*-, s, CO$_2$**Me**), 3.69 (3H *E*-, s, CO$_2$**Me**), 4.52 (2H *E*- and *Z*-, s, C**H$_2$**Ph), 5.61-5.69 (2H *E*- and *Z*-, m, C**H**=C**H**), 7.27-7.38 (5H *E*- and *Z*-, m, **Ar**); δ_C (100 MHz) Data given for *E*- isomer: 32.9 (**C**H$_2$CH$_2$OBn), 37.9 (**C**H$_2$CO$_2$Me), 51.8 (CO$_2$**Me**), 69.7 (**C**H$_2$OBn), 72.9 (O**C**H$_2$Ph), 122.8 (**C**H=CH), 127.55, 127.64 and 128.4 (Ar **C**H), 131.0 (CH=**C**H), 138.4 (Ar **C**), 172.4 (**C**O$_2$Me). Data as reported.[23]

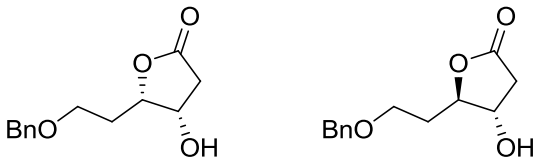
(*E*)-1,6-Bis(benzyloxy)hex-3-ene and **(*Z*)-1,6-Bis(benzyloxy)hex-3-ene (3.128)**



R_f 0.28 (15:1 petrol/ether); ν_{max} (thin film)/cm^{-1} 2927br, 1701s, 1273s, 1098br, 1070s, 1026s; δ_H (500 MHz, $CDCl_3$) ***E*-**: 2.32-2.36 (4H, m, C(2)**H$_2$** and C(5)**H$_2$**), 3.50 (4H, t, *J* 7.0 Hz, C(1)**H$_2$** and C(6)**H$_2$**), 4.52 (4H, s, 2 × C**H$_2$**Ph), 5.51-5.56 (2H, m, C(3)**H** and C(4)**H**), 7.27-7.37 (5H, m, **Ar**); ***Z*-**: 2.40 (2H, d, *J* 12.5 Hz, C(2)**H**H′ and C(5)**H**H′), 2.42 (2H, d, *J* 12.5 Hz, C(2)H**H′** and C(5)H**H′**), 3.49 (4H, t, *J*

7.0 Hz, C(1)$\mathbf{H_2}$ and C(6)$\mathbf{H_2}$), 4.52 (4H, s, 2 × C$\mathbf{H_2}$Ph), 5.51-5.56 (2H, m, C(3)**H** and C(4)**H**), 7.27-7.37 (5H, m, **Ar**); δ_C (125 MHz, $CDCl_3$) 28.1 (**C**H_2CH_2OBn, *Z*-), 33.2 (**C**H_2CH_2OBn, *E*-), 69.9 (**C**H_2OBn, *Z*-), 70.1 (**C**H_2CH_2OBn, *E*-), 72.9 (O**C**H_2Ph, *E*- and *Z*-), 127.6, 127.67, 127.70, 127.74 128.4, 128.6 (Ar **C**H and **C**H=**C**H, *E*- and *Z*-), 138.6 (Ar **C**, *E*- and *Z*-); *m*/*z* (ESI$^+$) 319 (MNa^+, 91%), 349 (100), 367 (97), 381 (94); HRMS found 319.1662; $C_{20}H_{24}NaO_2$ (MNa^+) requires 319.1669.

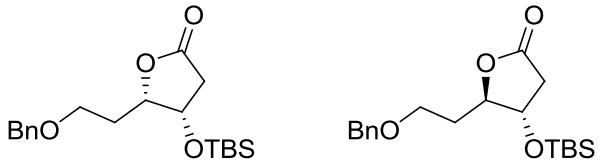
(4*S*,5*S*)-5-[2-(Benzyloxy)ethyl]-4-hydroxydihydrofuran-2(3*H*)-one (3.68) and **(4*S*,5*R*)-5-[2-(Benzyloxy)ethyl]-4-hydroxydihydrofuran-2(3*H*)-one (3.69)**



AD-mix α (3.60 g) was added to a solution of alkene **3.65** (600 mg, 2.56 mmol) in *tert*-butanol (12.9 mL) and water (12.9 mL) and the resulting solution stirred at RT for 60 h. The reaction was quenched by saturation of the aqueous layer with solid Na_2SO_3 and the resultant mixture stirred for 5 mins. The mixture was extracted with ethyl acetate (3 × 30 mL) and the combined organics were dried (Na_2SO_4) and evaporated *in vacuo* to give lactones **3.68** and **3.69** as a colourless oil in an inseperable mixture of diastereomers (550 mg, 91%).

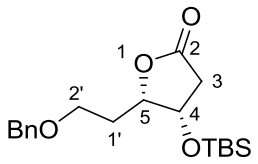
R_f 0.21 (15:1, ether); δ_H (400 MHz) Data reported for major (*S*,*S*)- diastereomer **3.68**: 0.06 (3H, s, Si(C$\mathbf{H_3}$)$_2$), 0.07 (3H, s, Si(C$\mathbf{H_3}$)$_2$), 0.88 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 1.92 (1H, dtd, *J* 14.5, 7.5, 4.0 Hz, C(1′)**H**H′), 2.11 (1H, ddt, *J* 14.5, 9.0, 5.0 Hz, C(1′)H**H′**), 2.44 (1H, dd, *J* 17.0, 1.0 Hz, C(3)**H**H′), 2.73 (1H, dd, *J* 17.0, 5.0 Hz, C(3)H**H′**), 3.66 (2H, dd, *J* 7.5, 5.0 Hz, C(2′)$\mathbf{H_2}$), 4.40 (1H, ddd, *J* 5.0, 4.0, 1.0 Hz, C(4)**H**), 4.50 (1H, d, *J* 11.5 Hz, C**H**H′Ph), 4.56 (1H, d, *J* 11.5 Hz, CH**H′**Ph), 4.64 (1H, dt, *J* 9.0, 4.0 Hz, C(5)**H**); δ_C (100 MHz) Data reported for major *S*,*S* diastereomer: −5.1 and −4.7 (2 × Si**C**H_3), 18.0 (Si**C**$(CH_3)_3$), 25.6 (SiC(**C**$H_3)_3$), 29.6 (**C**(1′)H_2), 39.9 (**C**(3)H_2), 66.4 (**C**(2′)H_2), 69.8 (**C**(4)H), 73.3 (**C**H_2Ph), 82.0 (**C**(5)H), 127.7, 127.8 and 128.4 (**Ar C**H), 138.1 (**Ar** quat.), 175.4 (R**C**O_2R′). Data as reported.[23]

(4*S*,5*S*)-5-[2-(Benzyloxy)ethyl]-4-(*tert*-butyldimethylsilyloxy)dihydrofuran-2(3*H*)-one (3.70) and **(4*S*,5*R*)-5-[2-(Benzyloxy)ethyl]-4-hydroxydihydrofuran-2(3*H*)-one (3.71)**



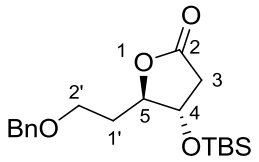
tert-Butyldimethylsilyl triflate (62 μL, 0.27 mmol) was added to a solution of alcohols **3.68** and **3.69** (43 mg, 0.18 mmol) and di-*tert*-butylpyridine (82 μL, 0.36 mmol) in DCM (1.15 mL) stirring at 0 °C. The reaction was stirred for 10 mins before being quenched with methanol (2 mL) and water (5 mL) and extracted with ether (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 4:1, petrol/ether) gave protected lactone **3.70** (47 mg, 75%) and its diastereomer, *lactone* **3.71** (8 mg, 13%), both as colourless oils.

(4*S*,5*S*)-5-[2-(Benzyloxy)ethyl]-4-(*tert*-butyldimethylsilyloxy)dihydrofuran-2(3*H*)-one (3.70)



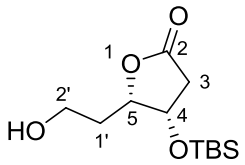
R_f 0.48 (1:1, petrol/ether); $[\alpha]_D^{25}$ –36.7 (c 1.3 in $CHCl_3$) [lit. reported $[\alpha]_D^{20}$ –35.5 (c 1.3 in $CHCl_3$)];[23] δ_H (400 MHz) 0.06 and 0.07 (6H, 2 × s, 2 × Si(C**H**$_3$)$_2$), 0.88 (9H, s, SiC(C**H**$_3$)$_3$), 1.92 (1H, dtd, *J* 14.5, 7.5, 4.0 Hz, C(1′)**H**H′), 2.11 (1H, ddt, *J* 14.5, 9.0, 5.0 Hz, C(1′)H**H′**), 2.44 (1H, dd, *J* 17.0, 1.0 Hz, C(3)**H**H′), 2.73 (1H, dd, *J* 17.0, 5.0 Hz, C(3)H**H′**), 3.66 (2H, dd, *J* 7.5, 5.0 Hz, C(2′)**H**$_2$), 4.40 (1H, ddd, *J* 5.0, 4.0, 1.0 Hz, C(4)**H**), 4.50 (1H, d, *J* 11.5 Hz, C**H**H′Ph), 4.56 (1H, d, *J* 11.5 Hz, CH**H′**Ph), 4.64 (1H, dt, *J* 9.0, 4.0 Hz, C(5)**H**), 7.29-7.39 (5H, m, **Ar**); δ_C (100 MHz) −5.1 and −4.7 (2 × Si**C**H$_3$), 18.0 (Si**C**(CH$_3$)$_3$), 25.6 (SiC(**C**H$_3$)$_3$), 29.6 (**C**(1′)H$_2$), 39.9 (**C**(3)H$_2$), 66.4 (**C**(2′)H$_2$), 69.8 (**C**(4)H), 73.3 (**C**H$_2$Ph), 82.0 (**C**(5)H), 127.7, 127.8 and 128.4 (**Ar C**H), 138.1 (**Ar** quat.), 175.4 (R**C**O$_2$R′). Data as reported.[23]

(4*S*,5*R*)-5-[2-(Benzyloxy)ethyl]-4-hydroxydihydrofuran-2(3*H*)-one (3.71)



R_f 0.54 (1:1, petrol/ether); $[\alpha]_D^{25}$ –17.2 (c 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2929br, 2857m, 1781s, 1363m, 1254w, 1203w, 1166m, 1079s, 1005w, 938w, 834s, 778s, 736s, 697s, 667m;δ_H (400 MHz) 0.07 (6H, s, 2 × Si(C**H**$_3$)$_2$), 0.89 (9H, s, SiC(C**H**$_3$)$_3$), 1.83 (1H, ddt, *J* 14.5, 8.5, 5.5 Hz, C(1′)**H**H′), 2.01 (1H, dddd, *J* 14.5, 7.5, 6.3, 5.0 Hz, C(1′)H**H′**), 2.44 (1H, dd, *J* 17.5, 4.5 Hz, C(3)**H**H′), 2.75 (1H, dd, *J* 17.5, 6.5 Hz, C(3)H**H′**), 3.60-3.66 (2H, m, C(2′)**H**$_2$), 4.30 (1H, ddd, *J* 6.5, 4.5, 3.5 Hz, C(4)**H**), 4.43-4.49 (1H, m, C(5)**H**), 4.55 (1H, s, C**H**H′Ph), 4.56 (1H, s, CH**H′**Ph), 7.28-7.38 (5H, m, **Ar**); δ_C (100 MHz) −4.9 and −4.8 (2 × Si**C**H$_3$), 17.9 (Si**C**(CH$_3$)$_3$), 25.6 (SiC(**C**H$_3$)$_3$), 33.1 (**C**(1′)H$_2$), 38.0 (**C**(3)H$_2$), 66.0 (**C**(2′)H$_2$), 72.4 (**C**(4)H), 73.3 (**C**H$_2$Ph), 85.3 (**C**(5)H), 127.66, 127.72 and 128.4 (**Ar C**H), 138.0 (**Ar** quat.), 175.0 (R**C**O$_2$R′); *m*/*z* (ESI^+) 373 (MNa^+, 86%), 405 ($[M+Na+MeOH]^+$, 66), 443 (72), 468 (91), 723 (M_2Na^+, 100); HRMS found 373.1803; $C_{19}H_{30}NaO_4Si$ (MNa^+) requires 373.1806.

(4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(2-hydroxyethyl)dihydrofuran-2(3H)-one (3.129)

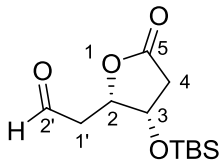


Benzyl ether **3.70** (200 mg, 0.57 mmol) was dissolved in ethanol (4.0 mL) and palladium on carbon (10%, 8 mg, 7.5 μmol) was added. The flask was purged several times with argon, then evacuated and filled with hydrogen. The reaction was stirred under an atmosphere of hydrogen for 1 h 45 mins before being filtered through a celite pad with ether and the filtrate evaporated *in vacuo* to furnish alcohol **3.129** as a white, waxy solid (130 mg, 88%).

R_f 0.38 (ether); m.p. 37 °C; $[\alpha]_D^{25}$ –31.6 (c 2.0 in chloroform) [lit. reported –35.4 (c 2.0 in chloroform)];[23] δ_H (400 MHz, $CDCl_3$) 0.07 (6H, s, Si(C**H**$_3$)$_2$), 0.88 (9H, s, SiC(C**H**$_3$)$_3$, 1.79-1.87 (1H,

m, C(1′)**H**H′), 2.06 (1H, app. tq, *J* 10.0, 5.0 Hz, C(1′)H**H′**), 2.15 (1H, br s, O**H**), 2.43 (1H, dd, *J* 17.0, 1.5 Hz, C(3)**H**H′), 2.75 (1H, dd, *J* 17.0, 5.0 Hz, C(3)H**H′**), 3.82 (2H, dd, *J* 7.0, 5.0 Hz, C(2′)**H₂**), 4.45 (1H, ddd, *J* 5.5, 4.0, 1.5 Hz, C(4)**H**), 4.88 (1H, dt, 9.5, 4.0 Hz, C(5)**H**); δ_C (100 MHz, $CDCl_3$) – 5.1 and – 4.7 (2 × Si**C**H_3), 18.0 (Si**C**$(CH_3)_3$), 25.6 (SiC(**C**$H_3)_3$), 31.9 (**C**(1′)H_2), 39.7 (**C**(3)H_2), 59.1 (**C**(2′)H_2), 69.9 (**C**(4)H), 82.3 (**C**(5)H), 175.6 (**C**(2)). Data as reported.[23]

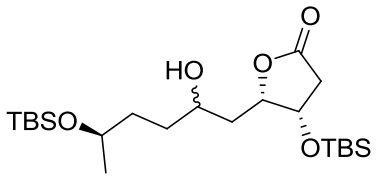
2-[(2*S*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-oxotetrahydrofuran-2-yl]acetaldehyde (372)



DMP (225 mg, 0.53 mmol) was added to a solution of alcohol **3.129** (80 mg, 0.31 mmol) in DCM (5.9 mL) stirring at 0 °C. After 30 mins the reaction was warmed to RT and stirred for a further 4 h before being quenched with NaOH (1.3 M aq., 5 mL) and diluted with DCM (10 mL). This mixture was stirred for 15 mins before the layers were separated and the aqueous layer was extracted with DCM (10 mL). The combined organic layers were washed with NaOH (1.3 M aq., 2 × 10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give *aldehyde* **3.72** as a pale yellow oil (78 mg, 98%).

R_f 0.58 (ether); $[\alpha]_D^{25}$ + 7.3 (c 1.0 in chloroform); ν_{max} (thin film)/cm^{-1} 2931br, 2858m, 1784s, 1726m, 1258m, 1157m, 1092m, 937w, 839m, 778m; δ_H (500 MHz, $CDCl_3$) 0.04 (3H, s, SiC**H₃**), 0.09 (3H, s, SiC**H₃**), 0.88 (9H, s, SiC(C**H₃**)$_3$), 2.47 (1H, dd, *J* 17.5, 1.0 Hz, C(4)**H**H′), 2.78 (1H, dd, *J* 17.5, 5.5 Hz, C(4)H**H′**), 3.02 (2H, d, *J* 6.5 Hz, C(1′)**H₂**), 4.61 (1H, ddd, *J* 5.5, 4.0, 1.0 Hz, C(3)**H**),4.88 (1H, td, 6.5, 4.0 Hz, C(2)**H**), 9.82 (1H, s, C(2′)**H**); δ_C (125 MHz, $CDCl_3$) – 5.2 and –4.7 (2 × Si**C**H_3), 17.9 (Si**C**$(CH_3)_3$), 25.6 (SiC(**C**$H_3)_3$), 39.1 (**C**(4)H_2), 42.7 (**C**(1′)H_2), 69.1 (**C**(3)H), 79.4 (**C**(2)H), 174.6 (**C**(5)), 198.5 (**C**(2′)H); *m*/*z* (ESI⁻) 257 ([M–H]⁻, 97%), 325 (100), 547 (53); HRMS found 281.1180; $C_{12}H_{22}NaO_4Si$ (MNa^+) requires 281.1180.

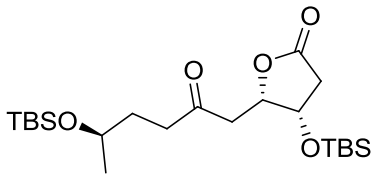
(4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-[(*R*)-5-(*tert*-butyldimethylsilyloxy)-2-hydroxyhexyl]dihydrofuran-2(3*H*)-one (3.73)



t-BuLi (1.7 M in pentane, 196 µL, 0.33 mmol) was added dropwise to a solution of iodide **3.59** (50 mg, 0.16 mmol) in ether (0.20 mL) stirring at –78 °C. After 10 mins, the solution was added *via* cannula to a solution of aldehyde **3.72** (41 mg, 0.16 mmol) in ether (0.12 mL) stirring at –90 °C. After 45 mins the reaction was quenched with water (5 mL) and warmed to RT. The mixture was extracted with ethyl acetate (3 × 10 mL), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 1:1, petrol/ether) gave *alcohol* **3.73** as a mixture of two diastereomers, in a 0.81:1 ratio A to B (as determined by ^{1}H NMR analysis) (6.5 mg, 10%).

R_f 0.52 and 0.41 (ether, two diastereomers); δ_H (500 MHz, $CDCl_3$) 0.06-0.11 (12H A and B, m, 4 × SiC**H$_3$**), 0.89-0.91 (18H A and B, m, 2 × SiC(C**H$_3$**)$_3$), 1.16 (3H A and B, d, *J* 6.0 Hz) and 1.18 (3H A and B, d, *J* 6.0 Hz, C(11)**H$_3$**), 1.53-1.66 (5H A and B, m, C(8)**H$_2$**, C(9)**H$_2$** and C(6)**H**H′), 1.86-2.02 (1H A and B, C(6)H**H′**), 2.41-2.48 (1H A and B, m, C(3)**H**H′), 2.72 (1H B, dd, *J* 12.5, 5.0 Hz, C(3)H**H′**), 2.75 (1H A, dd, *J* 12.5, 5.5 Hz, C(3)H**H′**), 3.20 (1H A and B, br s, O**H**), 3.75-4.00 (2H A and B, m, C(7)**H** and C(10)**H**), 4.42 (1H A, ddd, *J* 4.5, 4.0, 1.0 Hz, C(4)**H**), 4.49 (1H B, ddd, *J* 4.5, 4.0, 0.5 Hz, C(4)**H**), 4.63 (1H B, app td, *J* 7.0, 3.5 Hz, C(5)**H**), 4.73 (1H A, ddd, *J* 10.5, 3.5, 3.0 Hz, C(5)**H**); δ_C (125 MHz, $CDCl_3$) –5.1, –4.7, –4.6 and –4.5 (4× Si**C**H$_3$ A and B), 18.0 and 18.1 (2 × Si**C**(CH$_3$)$_3$ A and B), 22.7 and 23.3 (**C**(11)H$_3$ A and B), 25.6 and 25.9 (2 × SiC(**C**H$_3$)$_3$ A and B), 33.0, 33.8, 34.7 and 35.75 (**C**(8)H$_2$, and **C**(9)H$_2$ A and B), 35.80 (**C**(6)H$_2$ B), 37.2 (**C**(6)H$_2$ A), 39.6 (**C**(3)H$_2$ A), 40.0 (**C**(3)H$_2$ B), 68.4, 68.5, 68.6 and 68.7 (**C**(7)H and **C**(10)H A and B), 69.4 (**C**(4)H B), 70.3 (**C**(4)H A), 82.4 (**C**(5)H A), 83.1 (**C**(5)H B), 175.2 (**C**(2) B), 175.6 (**C**(2) A).

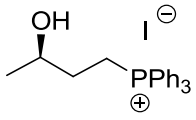
(4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-[(*R*)-5-(*tert*-butyldimethylsilyloxy)-2-oxohexyl]dihydrofuran-2(3*H*)-one (3.74)



A mixture of diastereomeric alcohol **3.73** (6.5 mg, 15 μmol) was dissolved in DCM (0.25 mL) and cooled to 0 °C. DMP (9.3 mg, 0.022 mmol) was added and the reaction stirred for 30 mins before being warmed to RT and stirred at this temperature for 30 mins before a further portion of DMP (3.2 mg, 0.0075 mmol) was added. After a further 1 h 30 the reaction was quenched with NaOH (1.3 M aq., 0.5 mL), diluted with ether (3 mL) and stirred for 10 mins. The layers were separated and the aqueous layer was extracted with ether (2 × 3 mL). The combined organic layers were washed with NaOH (1.3 M aq., 5 mL), water (5 mL) and brine (2 × 5 mL), dried ($MgSO_4$) and evaporated *in vacuo*, Purification by flash chromatography (SiO_2, 3:1, petrol/ether) gave *ketone* **3.74** as a colourless oil (5.2 mg, 78%).

R_f 0.07 (3:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2956s, 2930s, 2858m, 1785s, 1715m, 1472w, 1380br, 1255m, 1207w, 1152br, 1094m, 1031br, 837s, 808w, 776s; δ_H (500 MHz, $CDCl_3$) 0.01, 0.05, 0.06 and 0.08 (12H, 4 × s, 4 × SiC**H**$_3$), 0.88 and 0.89 (18H, 2 × s, 2 × SiC(C**H**$_3$)$_3$), 1.14 (3H, d, *J* 6.0 Hz, C(11)**H**$_3$), 1.64-1.76 (2H, m, C(9)**H**$_2$), 2.43 (1H, d, *J* 17.5 Hz, C(3)**H**H′), 2.46 (1H, ddd, *J* 17.5, 9.5, 6.5 Hz, C(8)**H**H′), 2.60 (1H, ddd, *J* 17.5, 9.5, 6.0 Hz, C(8)H**H′**), 2.78 (1H, dd, *J* 17.5, 5.0 Hz, C(3)H**H′**), 2.95 (1H, dd, *J* 18.0, 7.5 Hz, C(6)**H**H′), 3.01 (1H, dd, *J* 18.0, 6.0 Hz, C(6)H**H′**), 3.85 (1H, dq, *J* 11.0, 6.0 Hz, C(10)H), 4.59 (1H, ddd, *J* 5.0, 4.0, 1.0 Hz, C(4)**H**), 4.84 (1H, ddd, *J* 7.5, 6.0, 4.0 Hz, C(5)**H**); δ_C (125 MHz, $CDCl_3$) – 5.3, **–**4.8, **–**4.7 and – 4.4 (4 × Si**C**H$_3$), 17.9 and 18.1 (2 × Si**C**(CH$_3$)$_3$), 23.5 (**C**(11)H$_3$), 25.6 and 25.8 (2 × SiC(**C**H$_3$)$_3$), 32.9 (**C**(9)H$_2$), 39.2 and 39.3 (**C**(3)H$_2$ and **C**(8)H$_2$), 41.1 (**C**(6)H$_2$), 67.4 (**C**(10)H), 69.2 (**C**(4)H), 80.5 (**C**(5)H), 174.9 (**C**(2)), 207.6 (**C**(7)); *m*/*z* (ESI$^+$) 467 (MNa^+, 43%), 912 (M_2Na^+, 100); HRMS found 467.2619; $C_{22}H_{44}O_5Si_2Na^+$ (MNa^+) requires 467.2619.

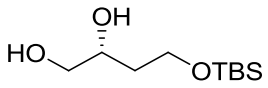
(*R*)-(3-Hydroxybutyl)triphenylphosphonium iodide (3.7)



PPh_3 (656 mg, 2.50 mmol) was added to a solution of iodide **3.47** (100 mg, 0.50 mmol) in benzene (5.0 mL). The resulting solution was heated at 80 °C for 16 h before being cooled and filtered and the precipitate washed with benzene (10 mL) and dried *in vacuo* to give phosphonium salt **3.7** as a white powder (135 mg, 60%).

m.p. 188 °C decomposition; $[\alpha]_D^{21}$ −12.5 (c 1.6 in methanol) [lit. reported −3.1 (c 1.6 in methanol)];[24] δ_H (400 MHz, CD_3OD) 1.22 (3H, d, *J* 6.5 Hz, C**H$_3$**), 1.65-1.88 (2H, m, C**H$_2$**CH_2PPh_3), 3.44-3.63 (2H, m, C**H$_2$**PPh_3), 3.95 (1H, dqd, *J* 7.5, 6.5, 4.0 Hz, C**H**OH), 7.75-7.95 (15H, m, **Ar**); δ_C (100 MHz, CD_3OD) 18.8 (d, *J* 53.5 Hz, **C**H_2PPh_3), 22.3 (**C**H_3), 31.4 (**C**$H_2CH_2PPh_3$), 66.9 (**C**HOH), 118.9 (d, *J* 85.5 Hz, P**C**(Ar)), 130.7, 133.9 and 135.3 (Ar **C**H); δ_P (162 MHz, CD_3OD) 24.5 (**P**Ph_3). Data as reported.[24]

(*R*)-4-(*tert*-Butyldimethylsilyloxy)butane-1,2-diol (3.76)

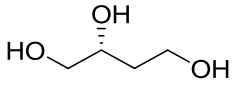


AD-mix β (1.51 g) was added to a solution of alkene **3.77** (200 mg, 1.08 mmol) in *tert*-butanol (5.4 mL) and water (5.4 mL) stirring at 0 °C. After 15 mins the reaction was allowed to warm to RT and stirred for a further 20 h before being quenched by the addition of solid Na_2SO_3 (1.63 g). The reaction was extracted with ethyl acetate (3 × 25 mL) and the combined organic layers dried ($MgSO_4$) and evaporated *in vacuo* to give diol **3.76** as a colourless oil (195 mg, 82%).

R_f 0.13 (1:1, petrol/ether); $[\alpha]_D^{25}$ −7.9 (c 1.0 in chloroform); δ_H (400 MHz, $CDCl_3$) 0.07 and 0.08 (6H, 2 × s, 2 × SiC**H$_3$**), 0.89-0.90 (9H, m, SiC(C**H$_3$**)$_3$), 1.60-1.67 (1H, m, C(3)**H**H′), 1.69-1.78 (1H, m, C(3)H**H′**), 2.71 (2H, br s, O**H**), 3.50 (1H, ddd, *J* 11.0, 6.0, 1.5 Hz, C(4)**H**H′), 3.61 (1H, ddd, *J* 11.0,

3.5, 2.0 Hz, C(4)H**H′**), 3.81 (1H, ddd, *J* 10.0, 4.0, 2.0 Hz, C(1)**H**H′), 3.86 (1H, ddd, *J* 10.0, 5.5, 2.0 Hz, C(1)H**H′**), 3.88-3.95 (1H, m, C**H**OH); δ_C (100 MHz, $CDCl_3$) −5.55 and −5.58 (2 × Si**C**H_3), 18.0 (Si**C**$(CH_3)_3$), 25.8 (SiC(**C**$H_3)_3$), 34.9 (**C**H_2), 61.7 (**C**H_2), 66.6 (**C**H_2), 71.8 (**C**HOH).[25]

(*R*)-Butane-1,2,4-triol (3.78)



Method A: Acetic acid (215 mL) was added to a solution of silyl ether **3.76** (5.86 g, 26.6 mmol) in water (145 mL) and the solution stirred at RT for 2 h before being evaporated *in vacuo* to give triol **3.78** as a colourless gel, clean enough to be taken through to the next reaction without purification.

$[\alpha]_D^{25}$ +13.5 (c 1.0 in methanol) [lit. reported +26.7 (c 1.0 in methanol)].[26]

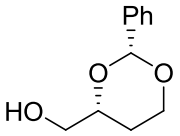
Method B: Trimethyl borate (12.2 mL, 110 mmol) was added dropwise to $BH_3.SMe_3$ (60 mL, 2.0 M in THF, 119 mmol) stirring at 0 °C. After 15 mins, (*R*)-malic acid (5.0 g, 37.3 mmol) was added carefully, in 10 portions. The reactions was allowed to warm to RT over 24 h before being cooled to 0 °C, quenched with methanol (30 mL) and evaporated to dryness to give triol **3.78** as a colourless gel, clean enough to be taken through to the next reaction without purification.

$[\alpha]_D^{21}$ +22.9 (c 1.0 in methanol) [lit. reported +26.7 (c 1.0 in methanol)].[26]

δ_H (400 MHz, $(CD_3)CO$) 1.59 (1H, ddtd, *J* 14.0, 8.0, 6.0, 1.0 Hz, C(3)**H**H′), 1.66-1.74 (1H, m, C(3)H**H′**), 3.43 (1H, ddd, *J* 1.0, 6.5, 1.0 Hz, C(1)**H**H′), 3.49 (1H, ddd, *J* 11.0, 4.5, 0.5 Hz, C(1)H**H′**), 3.72 (2H, t, *J* 6.0 Hz, C(4)**H₂**), 3.76-3.82 (1H, m, C(2)**H₂**), 4.88 (3H, br s, O**H**); δ_C (100 MHz, $(CD_3)CO$) 36.6 (**C**(3)H_2), 59.7 (**C**(4)H_2), 66.9 (**C**(1)H), 70.8 (**C**(2)H. Data as reported.[26]

The (*S*)- enantiomer was prepared as for the (*R*)- enantiomer, using **Method B**.

[(2*R*,4*R*)-2-Phenyl-1,3-dioxan-4-yl]methanol (3.79)



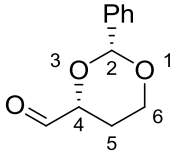
Camphorsulfonic acid (131 mg, 0.56 mmol) was added to a solution of triol **3.78** (1.19 g, 11.2 mmol) and benzaldehyde dimethyl acetal (1.79 mL, 12.0 mmol) in DCM (38 mL). The reaction was stirred at RT for 24 h before being quenched with triethylamine (165 μL, 1.18 mmol) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 2:1, petrol/ethyl acetate) gave alcohol **3.79** as a colourless oil (2.1 g, 97%).

R_f 0.25 (2:1, petrol/ethyl acetate); $[\alpha]_D^{25}$ −10.3 (c 0.59 in chloroform) [lit. reported −10.6 (c 0.59 in chloroform)];[27] δ_H (400 MHz, $CDCl_3$) 1.47 (1H, dsept, *J* 13.0, 1.0 Hz, C(5′)**H**H′), 1.95 (1H, qdd, *J* 13.0, 5.0, 1.5 Hz, C(5′)H**H′**), 2.10 (1H, br s, O**H**), 3.64 (2H, m, C(1)**H₂**), 3.96-4.07 (2H, m, C(4′)**H** and C(6′)**H**H′), 4.32 (1H, dd, *J* 11.5, 5.0 Hz, C(6′)H**H′**), 5.56 (1H, s, C(2′)**H**), 7.34-7.42 (3H, m, **Ar**), 7.48-7.53 (2H, m, **Ar**); δ_C (100 MHz, $CDCl_3$) 26.8 (**C**(5′)H_2), 65.7 (**C**(1)H_2), 66.6 (**C**(6′)H_2), 77.5 (**C**(4′)H), 101.3 (**C**(2′)H), 126.1, 128.3 and 129.0 (Ar **C**H), 138.4 (Ar **C**). Data as reported.[28]

The (*S*,*S*)- enantiomer **3.86** was prepared by the same method as the (*R*,*R*)-.

$[\alpha]_D^{21}$ +8.1 (c 0.59 in chloroform) [lit. reported +10.6 (c 0.59 in chloroform)];[27] other data as reported for (*R*,*R*)- enantiomer.

(2*R*,4*R*)-2-Phenyl-1,3-dioxane-4-carbaldehyde (3.80)



A solution of SO_3.pyridine complex (248 mg, 1.56 mmol) in DMSO (0.5 mL) was added dropwise to a solution of alcohol **3.79** (100 mg, 0.52 mmol) and triethylamine (360 μL, 2.58 mmol) in DCM (0.5

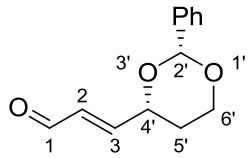
mL) stirring at 0 °C. The reaction was stirred for 2 h before being quenched with ammonium chloride (sat. aq., 20 mL) and diluted in DCM (50 mL). The organic layer was wahed with water (2 × 50 mL), $CuSO_4$ (sat. aq., 2 × 50 mL) and brine (30 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give aldehyde **3.80** as a colourless oil. Key NMR peaks were identified from the crude material.

R_f 0.13 (1:1, petrol/ether); δ_H (400 MHz, $CDCl_3$) 1.75-2.10 (2H, m, C(5)**H$_2$**), 3.63-4.43 (3H, m, C(4)**H** and C(6)**H$_2$**), 5.62 (1H, s, C(2)**H**), 7.30-7.63 (5H, m, **Ar**), 9.73 (1H, s, C**H**O); δ_C (100 MHz, $CDCl_3$) 26.4 (**C**(5)H_2), 67.0 (**C**(6)H_2), 80.8 (**C**(4)H), 101.7 (**C**(2)H), 126.6, 128.6 and 129.7 (Ar **C**H), 138.1 (Ar **C**), 201.0 (**C**=O).

The (*S*,*S*)- enantiomer **3.87** was prepared by the same method as the (*R*,*R*)-.

All data as reported for (*R*,*R*)- enantiomer

(*E*)-3-[(2*R*,4*R*)-2-Phenyl-1,3-dioxan-4-yl]acrylaldehyde (3.81)

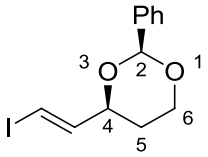


(Triphenylphosphoranylidene)acetaldehyde (158 mg, 0.52 mmol) was added to a solution of aldehyde **3.80** (0.52 mmol theoretical) in acetonitrile (2.08 mL) and the resulting solution stirred at reflux for 2 h before being cooled and evaporated *in vacuo*. Purification by flash chromatography gave α,β-unsaturated aldehyde **3.81** as a colourless oil (45 mg, 40%).

R_f 0.22 (2:1, petrol/ether); δ_H (400 MHz, $CDCl_3$) 1.73-1.76 (1H, m, C(5′)**H**H′), 1.95-2.04 (1H, m, C(5′)H**H′**), 4.07 (1H, td, *J* 12.0, 2.5 Hz, C(6′)**H**H′), 4.36 (1H, ddd, *J* 12.0, 5.0, 1.5 Hz, C(6′)H**H′**), 4.70 (1H, app. ddt, *J* 11.5, 4.0, 2.0 Hz, C(4′)**H**), 5.63 (1H, s, C(2′)**H**), 6.40 (1H, ddd, *J* 16.0, 8.0, 2.0 Hz, C(2)**H**), 6.84 (1H, dd, *J* 16.0, 4.0 Hz, C(3)**H**), 7.34-7.43 (3H, m, **Ar**), 7.48-7.54 (2H, m, **Ar**), 9.61 (1H, d, *J* 8.0 Hz, C(1)**H**); δ_C (100 MHz, $CDCl_3$) 30.4 (**C**(5′)H_2), 66.7 (**C**(6′)H_2), 75.3 (**C**(4′)H), 101.2

(**C**(2′)H), 126.0, 128.3 and 129.1 (Ar **C**H), 131.1 (**C**(2)H), 137.9 (Ar **C**), 154.2 (**C**(3)H), 193.3 (**C**(1)H). Data as reported.[29]

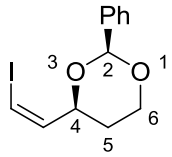
(2*S*,4*S*)-4-[(*E*)-2-Iodovinyl]-2-phenyl-1,3-dioxane (3.88)



Aldehyde **3.87** (100 mg, 0.52 mmol) and iodoform (615 mg, 1.56 mmol) in THF (1.72 mmol) were added to a slurry of chromium(II) chloride (384 mg, 3.13 mmol) in THF (1.72 mL) stirring at 0 °C in the dark. After 30 mins the reaction was warmed to RT and stirred for 16 h before being quenched with water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organics were washed with sodium thiosulphate solution (sat. aq., 15 mL) and brine (sat. aq., 15 mL), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 19:1, petrol/ether) gave a separable mixture of *vinyl iodide* **3.88** as a yellow oil (50 mg, 30% yield over two steps) and *vinyl iodide* **3.130** (this isomer could not be isolated cleanly enough to give an accurate yield), in a 3.6:1 *E*-/*Z*- ratio (as determined by ^{1}H NMR analysis).

R_f 0.16 (19:1, petrol/ether); $[\alpha]_D^{25}$ **–**17.1 (c 1.0 in chloroform); ν_{max} (thin film)/cm^{-1} 2957br, 2852br, 1454w, 1396m, 1360m, 1308m, 1242m, 1215w, 1178m, 1128s, 1100s, 1063w, 1024s; δ_H (400 MHz, $CDCl_3$) 1.61-1.66 (1H, m, C(5)**H**H′), 1.92-2.00 (1H, m, C(5)H**H′**), 4.00 (1H, app. td, *J* 12.0, 2.5 Hz, C(6)**H**H′), 4.29 (1H, ddd, *J* 12.0, 5.0, 1.5 Hz, C(6)H**H′**), 4.35-4.40 (1H, m, C(4)**H**), 5.56 (1H, s, C(2)**H**), 6.50 (1H, ddd, *J* 14.5, 1.5, 0.5 Hz, CH=C**H**I), 6.65 (1H, dd, *J* 14.5, 5.5 Hz, C**H**=CHI), 7.34-7.40 (3H, m, **Ar**), 7.49-7.52 (2H, m, **Ar**); δ_C (100 MHz, $CDCl_3$) 30.8 (**C**(5)H_2), 66.6 (**C**(6)H_2), 78.6 (CH=**C**HI), 78.7 (**C**(4)H), 101.2 (**C**(2)H), 126.1, 128.3 and 129.0 (Ar **C**H), 138.2 (Ar **C**), 144.8 (**C**H=CHI); *m*/*z*: 334 (40%), 338 (MNa^+, 41), 354 (43), 393 (50), 413 (100), 429 (78), 443 (69), 450 (58); HRMS found 338.9847; $C_{12}H_{13}INaO_2$ (MNa^+) requires 338.9852.

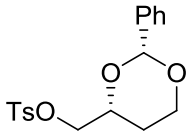
(2*S*,4*S*)-4-[(*Z*)-2-Iodovinyl]-2-phenyl-1,3-dioxane (3.130)



Samples of this isomer could not be isolated cleanly enough to give any data more than key NMR peaks.

R_f 0.23 (19:1, petrol/ether); δ_H (400 MHz, $CDCl_3$) 1.72 (1H, dddd, *J* 13.0, 3.0, 2.5, 1.5 Hz C(5)**H**H′), 1.95 (1H, dddd, *J* 13.0, 12.5, 11.5, 5.0 Hz, C(5)H**H′**), 4.08 (1H, ddd, *J* 12.5, 11.5, 2.5 Hz, C(6)**H**H′), 4.32 (1H, ddd, *J* 11.5, 5.0, 1.5 Hz, C(6)H**H′**), 4.69 (1H, ddd, *J* 11.5, 6.5, 3.0 Hz, C(4)**H**), 5.63 (1H, s, C(2)**H**), 6.39 (1H, dd, *J* 8.0, 0.5 Hz, CH=C**H**I), 6.43 (1H, dd, *J* 8.0, 6.5 Hz, C**H**=CHI), 7.32-7.40 (3H, m, **Ar**), 7.49-7.57 (2H, m, **Ar**); δ_C (100 MHz, $CDCl_3$) 29.2 (**C**(5)H_2), 66.6 (**C**(6)H_2), 80.2 (**C**(4)H), 82.2 (CH=**C**HI), 100.9 (**C**(2)H), 126.0, 128.4 and 128.9 (Ar **C**H), 138.2 (Ar **C**), 140.0 (**C**H=CHI).

((2*R*,4*R*)-2-Phenyl-1,3-dioxan-4-yl)methyl 4-methylbenzenesulfonate (3.89)

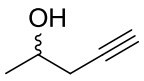


A solution of *p*-toluenesulfonyl chloride (99 mg, 0.52 mmol) in DCM (0.52 mL) was added dropwise to a solution of alcohol **3.79** (50 mg, 0.26 mmol) and triethylamine (43 μL, 0.31 mmol) in DCM (0.26 mL) stirring at 0 °C. The reaction was stirred at this temperature for 3 h before being evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 2:1, petrol/ether) gave tosyl ether **3.89** as a colourless oil (90 mg, 99%).

R_f 0.21 (2:1, petrol/ether); $[\alpha]_D^{23}$ +4.6 (c 1.4 in chloroform) [lit. reported +2.1 (c 1.4 in chloroform)];[28] δ_H (400 MHz, $CDCl_3$) 1.54 (1H, dm, *J* 13.0 Hz, C(5′)**H**H′), 1.75-1.87 (1H, m, C(5′)H**H′**), 2.42 (3H, s, C**H**$_3$), 3.94 (1H, app. ddd, *J* 12.5, 11.5, 2.5 Hz, C(6′)**H**H′), 4.04-4.18 (3H, m, C(4′)**H** and C**H**$_2$OTs), 4.27 (1H, ddd, *J* 11.5, 5.0, 1.5 Hz, C(6′)H**H′**), 5.46 (1H, s, C(2′)**H**), 7.27-7.44 (7H, m, **Ar**), 7.80 (2H,

dt, *J* 8.5, 2.0 Hz, **Ar**); δ_C (100 MHz, $CDCl_3$) 21.7 (**C**H_3), 27.2 (**C**(5′)H_2), 66.3 (**C**(6′)H_2), 71.6 (**C**H_2OTs), 74.1 (**C**(4′)H), 101.0 (**C**(2′)H), 126.1, 128.0, 128.2, 128.9 and 129.8 (Ar **C**H), 132.7, 138.0 and 144.9 (Ar **C**). Data as reported.[28]

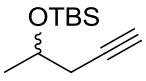
Pent-4-yn-2-ol (3.131)



Propylene oxide (2.5 mL, 35.7 mmol) was added to a solution of lithium acetylide EDA complex (3.78 g, 41.1 mmol) in DMSO (63 mL) stirring at 0 °C. After 30 mins the reaction was warmed to RT and stirred for 24 h before being poured onto ice-cold water (100 mL). The aqueous layer was extracted with ether (2 × 100 mL) and the combined organics were washed with brine (2 × 100 mL) and water (100 mL), dried ($MgSO_4$) and carefully evaporated *in vacuo* to give alcohol **3.131** as a colourless liquid which was used without purification in the next step.

R_f 0.30 (1:1, petrol/ether); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.5 Hz, C**H**$_3$), 2.00 (1H, br s, O**H**), 2.07 (1H, dd, *J* 3.0, 2.5 Hz, C≡C**H**), 2.33 (1H, ddd, *J* 16.5, 6.5, 2.5 Hz, C**H**H′), 2.41 (1H, ddd, *J* 16.5, 5.0, 3.0 Hz, CH**H′**), 3.98 (1H, app. sext, *J* 6.0 Hz, C**H**OH); δ_C (100 MHz, $CDCl_3$) 22.3 (**C**H_3), 28.9 (**C**H_2), 66.2 (**C**HOH), 70.8 (C≡**C**H), 80.8 (**C**≡CH). Data as reported.[30]

***tert*-Butyldimethyl(pent-4-yn-2-yloxy)silane (3.91)**

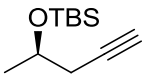


tert-Butyldimethylsilyl chloride (6.19 g, 41.1 mmol) and imidazole (3.65 g, 53.6 mmol) were added to a solution of alcohol **3.131** (3.00 g, 35.7 mmol) in DCM (12 mL) and MeCN (12 mL). The reaction was stirred for 60 h before it was quenched with water (50 mL) and diluted in DCM (150 mL). The organic layer was washed with brine (100 mL), dried ($MgSO_4$) and carefully evaporated *in vacuo*.

Purification by flash chromatography (SiO_2, petrol) gave silyl ether **3.91** as a colourless liquid (3.70 g, 52% over two steps).

R_f 0.26 (petrol); δ_H (400 MHz, $CDCl_3$) 0.08 (6H, 2 × s, 2 × SiC**H**$_3$), 0.90 (9H, s, SiC(C**H**$_3$)$_3$), 1.24 (3H, d, *J* 6.0 Hz, C**H**$_3$), 1.97 (1H, t, *J* 3.0 Hz, C≡C**H**), 2.24 (1H, ddd, *J* 16.5, 7.0, 3.0 Hz, C**H**H′), 2.36 (1H, ddd, *J* 16.5, 5.5, 3.0 Hz, CH**H′**), 3.98 (1H, dqd, *J* 7.0, 6.0, 5.5 Hz, C**H**OTBS); δ_C (100 MHz, $CDCl_3$) **–** 4.8 and **–**4.7 (2 × Si**C**H$_3$), 18.1 (Si**C**(CH$_3$)$_3$), 23.2 (**C**H$_3$), 25.8 (SiC(**C**H$_3$)$_3$), 29.4 (**C**H$_2$), 67.5 (**C**HOTBS), 69.7 (C≡**C**H), 81.9 (**C**≡CH). Data as reported.[30]

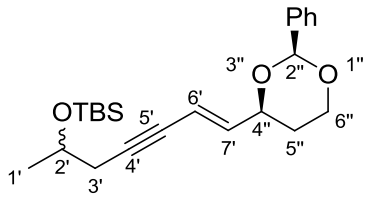
(*R*)-*tert*-Butyldimethyl(pent-4-yn-2-yloxy)silane (3.94)



$[\alpha]_D^{21}$ +0.80 (c 10.7 in chloroform) [lit. reported +0.67 (c 10.7 in chloroform)][30]

Other data as reported for achiral.

***tert*-Butyldimethyl{(*E*)-7-[(2*S*,4*S*)-2-phenyl-1,3-dioxan-4-yl]hept-6-en-4-yn-2-yloxy}silane (3.93)**

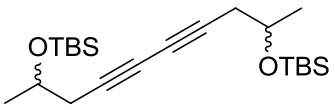


CuI (13.6 mg, 0.07 mmol) and bis(triphenylphosphine)palladium(II) dichloride (10 mg, 14 μmol) were added to a solution of vinyl iodide **3.88** (45 mg, 0.14 mmol) and alkyne **3.91** (28 mg, 0.14 mmol) in acetonitrile (6.5 mL) stirring at −20 °C. After 5 mins triethylamine (118 μL, 0.85 mmol) was added, the reaction allowed to warm to RT over 15 mins and stirred at this temperature for a further 45 mins during which time a colour change from orange to yellow and back to orange again was observed. The reaction was quenched with phosphate buffer (pH 6.5, 5 mL), extracted with ethyl acetate (3 × 5 mL)

and the combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, petrol → 9:1, petrol/ether) gave *enyne* **3.93** as a colourless oil (53 mg, 97%) and trace quantities of *Glaser coupling product* **3.94**.

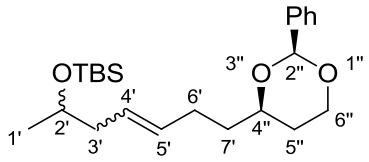
R_f 0.26 (19:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2928br, 2855br, 1462w, 1361br, 1255m, 1129br, 1097br, 997br, 834s, 807m, 776s, 752m, 698s; δ_H (400 MHz, $CDCl_3$) 0.08 and 0.09 (6H, 2 × s, 2 × Si**C**H_3), 0.90 (9H, s, SiC(C**H₃**)$_3$), 1.23 (3H, d, *J* 6.0 Hz, C(1′)**H₃**), 1.58-1.64 (1H, m, C(5″)**H**H′), 1.87-1.99 (1H, m, C(5″)H**H′**), 2.36 (1H, ddd, *J* 16.5, 7.0, 2.5 Hz, C(3′)**H**H′), 2.48 (1H, ddd, *J* 16.5, 6.0, 2.5 Hz, C(3′)H**H′**), 3.92-4.05 (2H, m, C(2′)**H** and C(6″)**H**H′), 4.30 (1H, ddd, *J* 11.5, 5.0, 1.0 Hz, C(6″)H**H′**), 4.42 (1H, ddt, *J* 11.0, 5.5, 2.0 Hz, C(4″)**H**), 55.7 (1H, s, C(2″)H), 5.80 (1H, app. ddd, *J* 16.0, 3.5, 2.0 Hz, C(6′)**H**), 6.11 (1H, dd, *J* 16.0, 5.5 Hz, C(7′)**H**), 7.32-7.41 (3H, m, **Ar**), 7.49-7.54 (2H, m, **Ar**); δ_C (100 MHz, $CDCl_3$) −4.8 and −4.7 (2 × Si**C**H_3), 18.1 (Si**C**$(CH_3)_3$), 23.4 (**C**H_3), 25.8 (SiC(**C**$H_3)_3$), 30.4 (**C**(3′)H_2), 31.2 (**C**(5″)H_2), 66.8 (**C**(6″)H_2), 67.8 (**C**(2′)H), 76.6 (**C**(4″)H), 79.7 and 89.1 (**C≡C**), 101.1 (**C**(2″)H), 111.1 (**C**(6′)H), 126.1, 128.2 and 128.8 (Ar **C**H), 138.4 (Ar **C**), 140.6 (**C**(7′)H); *m*/*z*/ (ESI^+) 409 (MNa^+, 100%); HRMS found 409.2168; $C_{23}H_{34}NaO_3Si$ (MNa^+) requires 409.2169.

2,2,3,3,5,12,14,14,15,15-Decamethyl-4,13-dioxa-3,14-disilahexadeca-7,9-diyne (3.94)



ν_{max} (thin film)/cm^{-1} 2929br, 2857br, 1255m, 1124s, 1098br, 998s, 835br, 774s; δ_H (400 MHz, $CDCl_3$) 0.07 and 0.08 (12H, 2 × s, 4 × SiC**H₃**), 0.89 (18H, s, 2 × SiC(C**H₃**)$_3$), 1.23 (6H, d, *J* 6.0 Hz, 2 × C**H₃**), 2.30 (2H, ddd, *J* 16.5, 6.5, 1.0 Hz, 2 × C**H**H′C≡C), 2.42 (2H, dd, *J* 16.5, 6.0 Hz, 2 × CH**H′**C≡C), 3.96 (2H, dquin, *J* 6.5, 6.0 Hz, 2 × C**H**OTBS); δ_C (100 MHz, $CDCl_3$) −4.82 and −4.76 (4 × Si**C**H_3), 18.1 (2 × Si**C**$(CH_3)_3$), 23.4 (2 × **C**H_3), 25.8 (2 × SiC(**C**$H_3)_3$), 30.1 (2 × **C**H_2), 66.7 (2 × CH_2C≡**C**), 67.5 (2 × **C**HOTBS), 74.9 (2 × CH_2**C**≡C); *m*/*z* (ESI^+) 395 (MH^+, 87%), 417 (MNa^+, 100); HRMS found 417.2607; $C_{22}H_{42}NaO_2Si_2$ (MNa^+) requires 417.2616.

***tert*-Butyldimethyl{7-[(2*S*,4*R*)-2-phenyl-1,3-dioxan-4-yl]hept-4-en-2-yloxy}silane (3.98)**



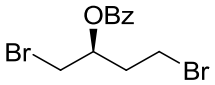
Pyridine (187 μL, 2.31 mmol) and Lindlar catalyst ($Pd/CaCO_3$ reduced, 5%, 37.5 mg) were added to a solution of enyne **3.93** (10 mg, 26 μmol) in ethyl acetate (1.5 mL). The flask was purged several times with argon, then evacuated and filled with hydrogen. The reaction was stirred under an atmosphere of hydrogen for 45 mins before being filtered and the filtrate washed with HCl (0.5 M aq., 10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 19:1, petrol/ether) gave *alkene* **3.98** as a colourless oil (8 mg, 79%).

R_f 0.26 (19:1, petrol/ether); δ_H (400 MHz, $CDCl_3$) 0.09 and 0.10 (6H, 2 × s, 2 × SiC**H$_3$**), 0.90 (9H, s, SiC(C**H$_3$**)$_3$), 1.12 (3H, d, *J* 6.0 Hz, C(1′)**H$_3$**), 1.21-2.45 (8H, m, C(3′)**H$_2$**, C(6′)**H$_2$**, C(7′)**H$_2$** and C(5″)**H$_2$**), 3.76-3.87 (2H, m, C(6″)**H$_2$**), 3.92-4.04 (1H, m, C(2′)**H**), 4.28 (1H, dd, *J* 11.5, 4.5 Hz, C(4″)**H**), 5.45-5.60 (3H, m, C(2″)**H** and C(4′)**H** and C(5′)**H**), 7.31-7.40 (3H, m, **Ar**), 7.48-7.54 (2H, m, **Ar**); HRMS found 413.2491; $C_{23}H_{38}NaO_3Si$ (MNa^+) requires 413.2482.

Hanessian reaction of benzylidene acetal 3.86

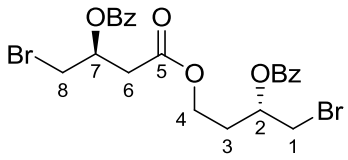
$BaCO_3$ (44 mg, 0.22 mmol) and *N*-bromosuccinimide (106 mg, 0.60 mmol) were added to a solution of alcohol **3.86** (100 mg, 0.52 mmol) in carbon tetrachloride (5.5 mL) and the resulting solution heated at reflux for 1 h, over which time an orange colour developed and then disappeared. The reaction was filtered, washing the residue with hot carbon tetrachloride (25 mL) and the filtrate was evaporated *in vacuo*. The residue was dissolved in ether (30 mL), washed with water (2 × 15 mL), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 3:1 → 2:1, petrol/ether) gave *dibromoalkane* **3.132** (6 mg, 3%), *ester* **3.95** (65 mg, 23%), *bromoalcohol* **3.133** (15 mg, 11%), and *bromoalcohol* **3.134** (15 mg, 11%), all as colourless oils.

(*S*)-1,4-Dibromobutan-2-yl benzoate (3.132)



R_f 0.77 (3:1, petrol/ether); $[\alpha]_D^{21}$ −11.0 (c 0.6 in chloroform); ν_{max} (thin film)/cm^{-1} 2962w, 1721s, 1437w, 1270br, 1176w, 1109br, 1026w, 799w, 712m; δ_H (400 MHz, $CDCl_3$) 2.37 (1H, dddd, *J* 15.0, 8.0, 7.0, 4.0 Hz, C**H**H′CH_2Br), 2.52 (1H, ddt, *J* 15.0, 8.5, 6.0 Hz, CH**H′**CH_2Br), 3.48 (1H, ddd, *J* 10.5, 8.0, 6.0 Hz, CH_2C**H**H′Br), 3.51 (1H, ddd, *J* 10.5, 7.0, 6.0 Hz, CH_2CH**H′**Br), 3.62 (1H, dd, *J* 11.0, 4.0 Hz, C**H**H′Br), 3.72 (1H, dd, *J* 11.0, 5.0 Hz, CH**H′**Br), 5.44 (1H, ddt, *J* 8.5, 5.0, 4.0 Hz, C**H**OBz), 7.45-7.71 (3H, m, **Ar**), 8.06-8.08 (2H, m, **Ar**); δ_C (100 MHz, $CDCl_3$) 28.0 (CH_2**C**H_2Br), 33.4 (**C**H_2Br), 35.7 (**C**H_2CH_2Br), 70.9 (**C**HOBz), 128.4, 129.8 and 133.4 (Ar **C**H), 129.5 (Ar **C**), 165.7 (O**C**(O)Ph); *m*/*z* (ESI$^+$) 301 (97%), 333 (MH^+, 91), 363 (MNa^+, 87), 580 (100), 591 (55), 691 (M_2Na^+, 35), 857 (100); HRMS found 356.9086, 358.9068 and 360.9042; $C_{11}H_{12}{}^{79}Br_2NaO_2$ (MNa^+) requires 356.9096, $C_{11}H_{12}{}^{79}Br^{81}BrNaO_2$ (MNa^+) requires 358.9076 and $C_{11}H_{12}{}^{81}Br_2NaO_2$ (MNa^+) requires 360.9055.

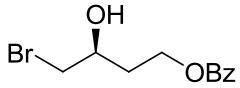
(*S*)-4-[(*S*)-3-(Benzoyloxy)-4-bromobutanoyloxy]-1-bromobutan-2-yl benzoate (3.95)



R_f 0.26 (3:1, petrol/ether); $[\alpha]_D^{21}$ −2.4 (c 1.0 in chloroform); ν_{max} (thin film)/cm^{-1} 1720s, 1270s, 1176br, 1109s, 1070w, 1026w, 710s; δ_H (400 MHz, $CDCl_3$) 2.10-2.26 (2H, m, C(3)**H₂**), 2.90 (2H, d, *J* 6.5 Hz, C(6)**H₂**), 3.57 (1H, dd, *J* 11.0, 4.5 Hz, C(1)**H**H′), 3.66 (1H, dd, *J* 11.0, 4.5 Hz, C(1)H**H′**), 3.69 (1H, dd, *J* 11.0, 4.5 Hz, C(8)**H**H′), 3.74 (1H, dd, *J* 11.0, 4.5 Hz, C(8)H**H′**), 4.17-4.30 (2H, m, C(4)**H₂**), 5.38 (1H, app tt, *J* 8.5, 4.5 Hz, C(2)**H**), 5.60 (1H, app tt, *J* 6.5, 4.5 Hz, C(7)**H**), 7.42-7.49 (4H, m, **Ar**), 7.55-7.61 (2H, m, **Ar**), 8.02-8.08 (4H, m, **Ar**); δ_C (100 MHz, $CDCl_3$) 31.8 (**C**(3)H_2), 33.5 (C(8)H_2), 34.0 (**C**(1)H_2), 37.5 (**C**(6)H_2), 60.9 (**C**(4)H_2), 69.1 (**C**(7)H), 69.7 (**C**(2)H), 128.5, 129.76, 129.80 and 133.4 (Ar **C**H), 129.5 and 129.6 (Ar **C**), 165.3 and 165.6 (O**C**(O)Ph), 169.4 (**C**(5)); *m*/*z* (ESI$^+$) 294

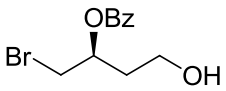
(53%), 563.0 (M_2Na^+, 78), 565.0 (M_2Na^+, 100) and 566.0 (M_2Na^+, 72); HRMS found 562.9668, 564.9653 and 566.9644; $C_{22}H_{22}{}^{79}Br_2NaO_6$ (MNa^+) requires 562.9675, $C_{22}H_{22}{}^{79}Br^{81}BrNaO_6$ (MNa^+) requires 564.966 and $C_{22}H_{22}{}^{81}Br_2NaO_6$ (MNa^+) requires 566.9636.

(*S*)-4-Bromo-3-hydroxybutyl benzoate (3.133)



R_f 0.17 (3:1, petrol/ether); $[\alpha]_D^{21}$ −6.7 (c 0.5 in chloroform); ν_{max} (thin film)/cm^{-1} 3464br, 1717s, 1276br, 1116m, 712s; δ_H (500 MHz, $CDCl_3$) 1.98 (1H, ddt, *J* 14.5, 9.0, 5.0 Hz, C**H**H′CH_2OBz), 2.09 (1H, dddd, *J* 14.5, 9.0, 5.5, 4.0 Hz, CH**H′**CH_2OBz), 2.54 (1H, br s, O**H**), 3.48 (1H, dd, *J* 10.5, 6.5 Hz, C**H**H′Br), 3.60 (1H, dd, *J* 10.5, 4.0 Hz, CH**H′**Br), 3.99-4.05 (1H, m, C**H**OH), 4.43 (1H, ddd, *J* 11.0, 5.5, 5.0 Hz, C**H**H′OBz), 4.57 (1H, ddd, *J* 11.0, 9.0, 5.0 Hz, CH**H′**OBz), 7.44-7.48 (2H, m, **Ar**), 7.57-7.60 (1H, m, **Ar**), 8.03-8.06 (2H, m, **Ar**); δ_C (125 MHz, $CDCl_3$) 34.2 (**C**H_2CH_2OBz), 39.8 (**C**H_2Br), 61.5 (**C**H_2OBz), 68.0 (**C**HOH), 128.5, 129.6 and 133.1 (Ar **C**H), 129.9 (Ar **C**), 166.7 (O**C**(O)Ph); *m*/*z* (ESI^+) 295 (MNa^+, 94%), 297 (MNa^+, 100), 413 (44), 565 (58), 651 (47); HRMS found 294.9938 and 296.9918; $C_{11}H_{13}{}^{79}BrNaO_3$ (MNa^+) requires 29.9940 and $C_{11}H_{13}{}^{81}BrNaO_3$ (MNa^+) requires 296.9920.

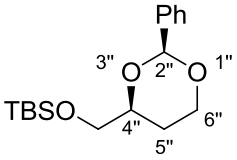
(*S*)-1-Bromo-4-hydroxybutan-2-yl benzoate (3.134)



R_f 0.11 (3:1, petrol/ether); $[\alpha]_D^{21}$ −16.0 (c 1.0 in chloroform); ν_{max} (thin film)/cm^{-1} 3436br, 2920br, 1719s, 1452w, 1316w, 1275s, 1177w, 1114br, 1070m, 1027w, 712s; δ_H (500 MHz, $CDCl_3$) 1.80 (1H, br s, O**H**), 2.02 (1H, dt, *J* 14.5, 4.5 Hz, C**H**H′CH_2OH), 2.08 (1H, ddt, *J* 14.5, 8.5, 5.0 Hz, CH**H′**CH_2OH), 3.65 (1H, dd, *J* 11.0, 5.5 Hz, C**H**H′Br), 3.71 (1H, dd, *J* 11.0, 4.0 Hz, CH**H′**Br), 3.68-3.71 (1H, m, C**H**H′OH), 3.77 (1H, ddd, *J* 11.5, 5.0, 4.5 Hz, CH**H′**OH), 5.48 (1H, dddd, *J* 8.5, 5.5, 4.5,

4.0 Hz, C**H**OBz), 7.44-7.50 (2H, m, **Ar**), 7.61 (1H, tt, *J* 7.5, 1.5 Hz, **Ar**), 8.06-8.11 (2H, m, **Ar**); δ_C (100 MHz, $CDCl_3$) 34.6 (**C**H_2Br), 36.0 (**C**$H_2$$CH_2$OH), 58.3 (**C**$H_2$OH), 70.5 (**C**HOBz), 128.5, 133.5 and 135.7 (Ar **C**H), 133.3 (Ar **C**), 166.7 (O**C**(O)Ph); *m*/*z* (ESI^+) 233 (73%), 295 (MNa^+, 95), 297 (MNa^+, 100), 569 (M_2Na^+, 88); HRMS found 294.9949 and 296.9931; $C_{11}H_{13}{}^{79}BrNaO_3$ requires 294.9940 and $C_{11}H_{13}{}^{81}BrNaO_3$ requires 296.9920.

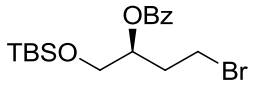
***tert*-Butyldimethyl{[(2S,4S)-2-phenyl-1,3-dioxan-4-yl]methoxy}silane (3.96)**



DMAP (605 mg, 4.95 mmol) was added to a solution of alcohol **3.79** (2.40 g, 12.4 mmol), *tert*-butyldimethylsilyl chloride (2.24 g, 14.9 mmol) and triethylamine (1.90 mL, 13.6 mmol) in DMF (60 mL). The reaction was stirred for 60 h before being diluted in water (100 mL), extracted with ether (3 × 100 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 19:1, petrol/ether) gave *silyl ether* **3.96** (2.76 g, 67%).

R_f 0.42 (19:1, petrol/ether); $[\alpha]_D{}^{21}$ −1.3 (c 1.0 in chloroform); ν_{max} (thin film)/cm^{-1} 2890br, 1254w, 1108br, 906s, 837m, 727br; δ_H (400 MHz, $CDCl_3$) 0.08 and 0.09 (6H, 2 × s, 2 × SiC**H**$_3$), 0.92 (9H, s, SiC(C**H**$_3$)$_3$), 1.65 (1H, dtd, *J* 13.5, 2.5, 1.5 Hz, C(5′′)**H**H′), 1.78-1.90 (1H, m, C(5′′)H**H′**), 3.64 (1H, dd, *J* 10.5, 6.0 Hz, C**H**H′OTBS), 3.83 (1H, dd, *J* 10.5, 5.5 Hz, CH**H′**OTBS), 3.93-4.04 (2H, m, C(4′′)**H** and C(6′′)**H**H′), 4.32 (1H, ddd, *J* 11.5, 5.0, 1.5 Hz, C(6′′)H**H′**), 5.54 (1H, s, C(2′′)**H**), 7.30-7.41 (3H, m, **Ar**), 7.47-7.53 (2H, m, **Ar**); δ_C (100 MHz, $CDCl_3$) −5.4 and −5.3 (2 × Si**C**H_3), 18.3 (Si**C**$(CH_3)_3$), 25.9 (SiC(**C**H_3)$_3$), 28.3 (**C**(5′′)H_2), 66.2 (**C**H_2OTBS), 67.0 (**C**(6′′)H_2), 77.6 (**C**(4′′)H), 101.2 (**C**(2′′)H), 126.1, 128.2 and 128.7 (Ar **C**H), 138.6 (Ar **C**); *m*/*z* (ESI^+) 331 (MNa^+, 100%), 639 (M_2Na^+, 98); HRMS found 331.1703; $C_{17}H_{28}NaO_3Si$ (MNa^+) requires 331.1700.

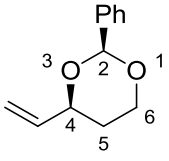
(*S*)-4-Bromo-1-(*tert*-butyldimethylsilyloxy)butan-2-yl benzoate (3.97)



$BaCO_3$ (4.1 mg, 20 μmol) and *N*-bromosuccinimide (10 mg, 60 μmol) were added to a solution of alcohol **3.96** (15 mg, 50 μmol) in carbon tetrachloride (1.0 mL) and the resulting solution heated at reflux for 4 h. The reaction was filtered, washing the residue with hot carbon tetrachloride (10 mL) and the filtrate was evaporated *in vacuo*. The residue was dissolved in ether (20 mL), washed with water (2 × 5 mL), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 30:1, petrol/ether) gave *bromoalkane* **3.97** as a colourless oil (14 mg, 72%).

R_f 0.30 (30:1, petrol/ether); $[\alpha]_D^{21}$ −16.8 (c 1.0 in chloroform); ν_{max} (thin film)/cm^{-1} 2955br, 2929br, 2857w, 1722s, 1272s, 1109br, 837m, 778m, 711m; δ_H (500 MHz, $CDCl_3$) 0.04 (6H, m, 2 × SiC**H$_3$**), 0.88 (9H, s, SiC(C**H$_3$**)$_3$), 2.28-2.43 (2H, m, C**H$_2$**CH_2Br), 3.45-3.55 (2H, m, C**H$_2$**Br), 3.82 (2H, d, *J* 4.5 Hz, C(4)**H$_2$**), 5.28 (1H, app sext, *J* 4.5 Hz, C**H**OBz), 7.44-7.48 (2H, m, **Ar**), 7.56-7.60 (1H, m, **Ar**), 8.04-8.08 (2H, m, **Ar**); δ_C (125 MHz, $CDCl_3$) −5.5 (2 × Si**C**H_3), 18.2 (Si**C**$(CH_3)_3$), 25.8 (SiC(**C**H_3)$_3$), 28.9 (**C**H_2Br), 34.1 (**C**H_2CH_2Br), 63.8 (**C**H_2OTBS), 73.3 (**C**HOBz), 128.4, 129.6 and 133.1 (Ar **C**H), 130.0 (Ar **C**), 166.0 (O**C**(O)Ph); *m*/*z* (ESI^+) 409 (MNa^+, 75%), 411 (MNa^+, 81), 795 (M_2Na^+, 100); HRMS found 409.0807 and 411.0787; $C_{17}H_{27}{}^{79}BrNaO_3Si$ (MNa^+) requires 409.0805 and $C_{17}H_{27}{}^{81}BrNaO_3Si$ (MNa^+) requires 411.0785.

(2*S*,4*S*)-2-Phenyl-4-vinyl-1,3-dioxane (3.100)

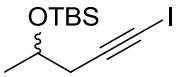


n-Butyllithium (1.57 M in THF, 554 μL, 0.87 mmol) was added to a suspension of methyltriphenylphosphonium bromide (389 mg, 1.09 mmol) in THF (4.6 mL) stirring at 0 °C. The bright orange solution was stirred for 30 mins before a solution of aldehyde **3.87** (100 mg, 0.52 mmol)

in THF (1.2 mL) was added *via* cannula. After 10 mins the reaction was warmed to RT and stirred at this temperature for 16 h, by which time the orange colour had disappeared. The reaction was quenched with water (5 mL) and extracted with ether (3 × 10 mL). The combined organic layers were washed with brine (sat. aq., 10 mL), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 19:1, petrol/ether) gave *alkene* **3.100** as a colourless oil (90 mg, 91%).

$[\alpha]_D^{21}$ +13.5 (c 1.0 in chloroform); ν_{max} (thin film)/cm^{-1} 2852br, 1393w, 1307w, 1242w, 1215w, 1146w, 1097s, 1024s, 988s, 922m; δ_H (400 MHz, $CDCl_3$) 1.63 (1H, dtd, *J* 13.5, 2.5, 1.5 Hz, C(5)**H**H′), 1.96 (1H, dddd, *J* 13.5, 12.5, 11.5, 5.0 Hz, C(5)H**H′**), 4.03 (1H, ddd, *J* 12.5, 11.5, 2.5 Hz, C(6)**H**H′), 4.31 (1H, ddd, *J* 11.5, 5.0, 1.5 Hz, C(6)H**H′**), 4.37-4.43 (1H, m, C(4)**H**), 5.37 (1H, dt, *J* 10.5, 1.5 Hz, C**H**H′=CH), 5.37 (1H, dt, *J* 17.5, 1.5 Hz, CH**H′**=CH), 5.60 (1H, s, C(2)**H**), 5.98 (1H, ddd, *J* 17.5, 10.5, 5.5 Hz, CH_2=C**H**), 7.32-7.42 (3H, m, **Ar**), 7.53-7.57 (2H, m, **Ar**); δ_C (100 MHz, $CDCl_3$) 31.2 (**C**(5)H_2), 66.9 (**C**(6)H_2), 77.6 (**C**(4)H), 101.2 (**C**(2)H), 115.6 (**C**H_2=CH), 126.1, 128.2 and 128.8 (Ar **C**H), 137.9 (CH_2=**C**H), 138.6 (Ar **C**); *m/z* (ESI^+) 213 (MNa^+, 18%), 413 (31%), 548 (100); HRMS found 213.0886; $C_{12}H_{14}NaO_2$ requires 213.0886.

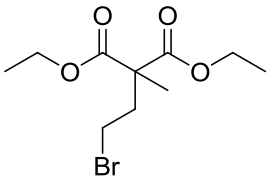
tert-Butyl(5-iodopent-4-yn-2-yloxy)dimethylsilane (3.101)



n-BuLi (1.57 M in THF, 177 µL, 0.28 mmol) was added dropwise to a solution of alkyne **3.91** (50 mg, 0.25 mmol) in ether (0.82 mL) at −78 °C. After 15 mins, a solution of iodine (71 mg, 0.28 mmol) in THF (0.57 mL) was added *via* cannula. The reaction was stirred in the dark for 30 mins and then allowed to warm to RT slowly. After 1 h 30 mins the reaction was quenched with water (5 mL) and diluted in ether (10 mL). The organic layer was washed with water (5 mL) and sodium thiosulphate solution (sat. aq., 2 × 5 mL), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, petrol) gave *alkynyl iodide* **3.101** as a colourless oil (75 mg, 93%).

R_f 0.40 (petrol); ν_{max} (thin film)/cm^{-1} 2956br, 2929br, 2857br, 1472w, 1377w, 1254m, 1128s, 1100s, 998br, 835s, 775s; δ_H (400 MHz, $CDCl_3$) 0.08 (6H, 2 × s, 2 × SiC**H$_3$**), 0.90 (9H, s, SiC(C**H$_3$**)$_3$), 1.22 (3H, d, *J* 6.0 Hz, C**H$_3$**), 2.41 (1H, dd, *J* 16.5, 6.6 Hz, C**H**H′), 2.52 (1H, dd, *J* 6.5, 6.3 Hz, CH**H′**), 3.96 (1H, ddq, *J* 6.6, 6.3, 6.0 Hz, C**H**OTBS); δ_C (100 MHz, $CDCl_3$) −5.5 (C≡**C**I), −4.8 and −4.7 (2 × Si**C**H$_3$), 18.1 (Si**C**(CH$_3$)$_3$), 23.5 (**C**H$_3$), 25.8 (SiC(**C**H$_3$)$_3$), 31.6 (**C**H$_2$), 67.6 (**C**HOTBS), 92.2 (**C**≡CI); *m*/*z* (ESI$^+$) 301 (56%), 347 (MNa$^+$, 82), 379 (53), 413 (80), 461 (100); HRMS found 347.0313; $C_{11}H_{21}INaOSi$ requires 347.0299.

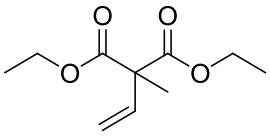
Diethyl 2-(2-bromoethyl)-2-methylmalonate (3.106)



A solution of diethylmethylmalonate (500 mg, 2.87 mmol) in DMF (1.50 mL) was added dropwise to a stirring suspension of NaH (117 mg, 60% dispersion in mineral oil, 2.92 mmol) in DMF (0.75 mL). After 15 mins the reaction was cooled to 0 °C, dibromoethane (260 μL, 3.02 mmol) was added and the reation was warmed slowly over 5 h. The reaction was quenched with ammonium chloride (sat. aq., 5 mL), extracted with ether (3 × 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 49:1, petrol/ether) gave bromoalkane **3.106** as a colourless oil (350 mg, 43%).

R_f 0.23 (49:1, petrol/ether); δ_H (400 MHz, $CDCl_3$) 1.26 (6H, t, *J* 7.0 Hz, 2 × CO_2CH_2C**H$_3$**), 1.45 (3H, s, C**H$_3$**), 2.42-2.47 (2H, m, C**H$_2$**CH_2Br), 3.37-3.41 (2H, m, C**H$_2$**Br), 4.20 (4H, q, *J* 7.0 Hz, 2 × CO_2C**H$_2$**CH_3); δ_C (100 MHz, $CDCl_3$) 14.0 (2 × CO_2CH_2**C**H_3), 20.1 (**C**H$_3$), 27.2 (**C**H$_2$Br), 39.1 (**C**H$_2$CH$_2$Br), 53.8 (**C**CH$_3$), 61.6 (2 × CO_2**C**H_2CH_3), 171.2 (2 × **C**O$_2$Et). Data as reported.[31]

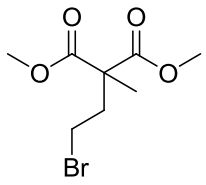
Diethyl 2-methyl-2-vinylmalonate (3.108)



DBU (100 μL, 0.67 mmol) was added to bromoalkane **3.106** (150 mg, 0.53 mmol) and the mixture heated at 75 °C for 1 h 15 mins before being cooled to RT, diluted in ether (10 mL) and quenched with ammonium chloride (sat. aq., 10 mL). The layers were separated and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic layers were washed with HCl (0.5 M aq., 5 mL), $NaHCO_3$ (sat. aq., 5 mL) and brine (sat. aq., 5 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give vinyl malonate **3.108** as a colourless oil (35 mg, 33%).

R_f 0.48 (9:1, petrol/ether); δ_H (400 MHz, $CDCl_3$) 1.25 (6H, t, *J* 7.0 Hz, 2 × $CO_2CH_2C\mathbf{H_3}$), 1.55 (3H, s, $C\mathbf{H_3}$), 4.20 (4H, q, *J* 7.0 Hz, 2 × $CO_2C\mathbf{H_2}CH_3$), 5.20 (1H, d, *J* 17.5 Hz, CH=C**H**H′), 5.26 (1H, d, *J* 10.5 Hz, CH=CH**H′**), 6.30 (1H, dd, *J* 17.5, 10.5 Hz, C**H**=CH_2); δ_C (100 MHz, $CDCl_3$) 14.0 (2 × $CO_2CH_2\mathbf{C}H_3$), 19.6 (**C**H_3), 56.2 (**C**CH_3), 61.5 (2 × $CO_2\mathbf{C}H_2CH_3$), 115.9 (CH=**C**H_2), 136.1 (**C**H=CH_2), 171.0 (2 × **C**O_2Et). Data as reported.[31]

Dimethyl 2-(2-bromoethyl)-2-methylmalonate (3.107)

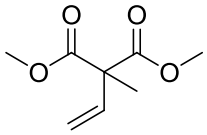


A solution of dimethylmethylmalonate (500 mg, 3.42 mmol) in DMF (1.80 mL) was added dropwise to a stirring suspension of NaH (205 mg, 60% dispersion in mineral oil, 5.13 mmol) in DMF (0.90 mL). After 15 mins the reaction was cooled to 0 °C, dibromoethane (309 μL, 3.59 mmol) was added and the reation was warmed slowly over 5 h 30 mins. The reaction was quenched with ammonium chloride (sat. aq., 5 mL), extracted with ether (3 × 10 mL) and the combined organics dried ($MgSO_4$)

and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 49:1, petrol/ether) gave *bromoalkane* **3.107** as a colourless oil (770 mg, 89%).

R_f 0.18 (49:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2954br, 1729s, 1435br, 1264br, 1219m, 1161s, 1113s; δ_H (400 MHz, $CDCl_3$) 1.43 (3H, s, C**H$_3$**), 2.38-2.45 (2H, m, C**H$_2$**), 3.31-3.38 (2H, m, C**H$_2$**Br), 3.72 (3H, s, 2 × CO_2C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 20.2 (**C**H_3), 27.1 (**C**H_2Br), 39.1 (**C**H_2), 52.7 (2 × CO_2**C**H_3) 53.7 (**C**CH_3), 171.6 (2 × **C**O_2Me); *m*/*z* (ESI^+) 275 (MNa^+, 100%); HRMS found 274.9892 and 276.9872; $C_8H_{13}{}^{79}BrNaO_4$ (MNa^+) requires 274.9889 and $C_8H_{13}{}^{81}BrNaO_4$ (MNa^+) requires 276.9869.

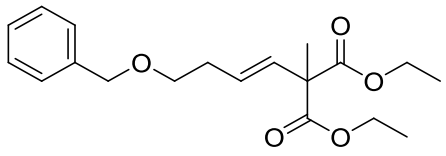
Dimethyl 2-methyl-2-vinylmalonate (3.103)



DBU (148 μL, 1.0 mmol) was added to bromoalkane **3.107** (200 mg, 0.79 mmol) and the mixture heated at 60 °C for 1 h 20 mins before being cooled to RT, diluted in ether (10 mL) and quenched with ammonium chloride (sat. aq., 10 mL). The layers were separated and the aqueous layer extracted with ether (2 × 10 mL). The combined organic layers were washed with HCl (0.5 M aq., 5 mL), $NaHCO_3$ (sat. aq., 5 mL) and brine (sat. aq., 5 mL), dried ($MgSO_4$) and carefully evaporated *in vacuo* to give *vinyl malonate* **3.103** as a colourless oil (135 mg, 100%).

R_f 0.63 (9:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2917br, 1733s, 1435m, 1261s, 1113br, 752br; δ_H (400 MHz, $CDCl_3$) 1.57 (3H, s, C**H$_3$**), 3.75 (6H, s, 2 × CO_2C**H$_3$**), 5.20 (1H, d, *J* 7.5 Hz, CH=C**H**H′), 5.28 (1H, d, *J* 10.5 Hz, CH=CH**H′**), 6.29 (1H, dd, *J* 17.5, 10.5 Hz, C**H**=CH_2); δ_C (100 MHz, $CDCl_3$) 19.7 (**C**H_3), 52.8 (2 × CO_2**C**H_3), 56.2 (**C**CH_3), 116.1 (CH=**C**H_2), 135.8 (**C**H=CH_2), 171.4 (2 × **C**O_2Me); *m*/*z* (ESI^+) 195 (MNa^+, 23%), 409 (52), 581 (100); HRMS found 195.0627; $C_8H_{12}NaO_4$ (MNa^+) requires 195.0628.

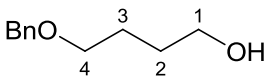
(*E*)-Diethyl 2-[4-(benzyloxy)but-1-enyl]-2-methylmalonate (3.109)



Grubbs' II (7.4 mg, 8.75 μmol) was dissolved in DCM (2.0 mL) and extensively degassed. This solution was added *via* cannula to a flask containing benzyl ether **3.66** (56.7 mg, 0.35 mmol) and diester **3.108** (35 mg, 0.18 mmol). The resulting solution was stirred at reflux for 2 h before being evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 9:1, petrol/ether) gave *alkene* **3.109** as a colourless oil (12 mg, 10%).

R_f 0.24 (9:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2932br, 1731s, 1454w, 1365w, 1258s, 1100br, 1019s, 862w, 799s; δ_H (500 MHz, $CDCl_3$) 1.24 (6H, t, *J* 7.0 Hz, 2 × $CO_2CH_2C\mathbf{H_3}$), 1.54 (3H, s, $C\mathbf{H_3}$), 2.42 (2H, qd, *J* 7.0, 1.5 Hz, $C\mathbf{H_2}CH{=}CH$), 3.52 (2H, t, *J* 7.0 Hz, $BnOC\mathbf{H_2}$), 4.19 (4H, q, *J* 7.0 Hz, 2 × $CO_2C\mathbf{H_2}CH_3$), 4.51 (2H, $C\mathbf{H_2}Ph$), 5.64 (1H, dt, *J* 16.0, 7.0 Hz, $CH_2C\mathbf{H}{=}CH$), 6.01 (1H, dt, *J* 16.0, 1.5 Hz, $CH_2CH{=}C\mathbf{H}$), 7.27-7.38 (5H, m, **Ar**); δ_C (125 MHz, $CDCl_3$) 14.0 (2 × $CO_2CH_2\mathbf{C}H_3$), 20.2 ($\mathbf{C}H_3$), 33.1 ($\mathbf{C}H_2CH{=}CH$), 55.5 ($CH{=}CH\mathbf{C}Me$), 61.4 (2 × $CO_2\mathbf{C}H_2CH_3$), 69.6 ($\mathbf{C}H_2OBn$), 72.9 ($O\mathbf{C}H_2Ph$), 127.5, 127.6 and 128.3 (Ar **C**H), 128.4 and 129.7 (**C**H=**C**H), 138.4 (Ar **C**), 171.3 (2 × $\mathbf{C}O_2Et$); *m*/*z* (ESI^+) 357 (MNa^+, 23%); HRMS found 357.1670; $C_{19}H_{26}NaO_5$ (MNa^+) requires 357.1672.

4-(Benzyloxy)butan-1-ol (3.135)

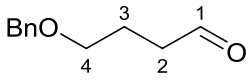


1,4-butanediol (4.40 g, 50.0 mmol) was added over 15 mins to a suspension of NaH (4.00 g, 60% dispersion in mineral oil, 100 mmol) in THF (150 mL) stirring at 0 °C. The mixture was stirred at RT for 2 h before being cooled to 0 °C for the dropwise addition of benzyl bromide (5.90 mL, 50.0 mmol) and tetrabutylammonium iodide (525 mg, 5.00 mmol). The reaction was stirred for 12 h then quenched with ice water (50 mL) and the organic solvents removed *in vacuo*. The aqueous layer was extracted with ethyl acetate (2 × 30 mL) and the combined organic layers washed with brine (sat. aq., 30 mL),

dried (Na_2SO_4) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 3:1, petrol/ether) gave monoprotected diol **3.135** as a colourless oil (4.90 g, 54%).

R_f 0.30 (3:1, petrol/ether); δ_H (400 MHz, $CDCl_3$) 1.61-1.75 (4H, m, C(2)**H₂** and C(3)**H₂**), 2.95 (1H, br s, O**H**), 3.53 (2H, t, *J* 6.0 Hz, C(4)**H₂**), 3.60 (2H, t, *J* 6.0 Hz, C(1)**H₂**), 4.52 (2H, C**H₂**Ph), 7.25-7.38 (5H, m, **Ar**); δ_C (100 MHz, $CDCl_3$) 26.5 (**C**(2)H_2), 29.9 (**C**(3)H_2), 62.4 (**C**(1)H_2), 70.3 (**C**(4)H_2), 73.0 (**C**H_2Ph), 127.6, 127.7 and 128.4 (Ar **C**H), 138.2 (Ar **C**). Data as reported.[32]

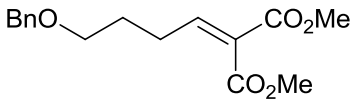
4-(Benzyloxy)butanal (3.112)



DMSO (1.55 mL, 20.0 mmol) was added dropwise to a solution of oxalyl chloride (1.45 mL, 16.9 mmol) in DCM (26 mL) stirring at −78 °C. After 15 mins a solution of alcohol **3.135** (2.00 g, 11.1 mmol) in DCM (4.5 mL) was added *via* cannula and the reaction stirred for 30 mins before triethylamine (9.30 mL, 66.7 mmol) was added dropwise. The mixture was warmed to RT and stirred for 30 mins before being quenched with water (30 mL) and extracted with DCM (2 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 9:1, petrol/ether) gave aldehyde **3.112** (1.50 g, 76%).

R_f 0.36 (9:1, petrol/ether); δ_H (400 MHz, $CDCl_3$) 1.95 (2H, tt, *J* 7.0, 6.0 Hz, C(3)**H₂**), 2.55 (2H, td, *J* 7.0, 1.5 Hz, C(2)**H₂**CHO), 3.51 (2H, t, *J* 6.0 Hz, C(4)**H₂**OBn), 4.49 (2H, s, C**H₂**Ph), 7.26-7.38 (5H, m, **Ar**), 9.78 (1H, t, *J* 1.5 Hz, C(1)**H**); δ_C (100 MHz, $CDCl_3$) 22.6 (**C**(3)H_2), 40.9 (**C**(2)H_2), 69.1 (**C**(4)H_2), 72.9 (**C**H_2Ph), 127.56, 127.61 and 128.4 (Ar **C**H), 138.3 (Ar **C**), 202.3 (**C**(1)H). Data as reported.[32]

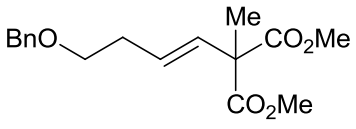
Dimethyl 2-[4-(benzyloxy)butylidene]malonate (3.111)



L-Proline (42.6 mg, 0.37 mmol) was added to a solution of aldehyde **3.112** (500 mg, 2.81 mmol) in DMSO (1.3 mL) and the reaction stirred for 15 mins before dimethylmalonate (642 μL, 5.62 mmol) was added. The resulting solution was stirred for 16 h before being diluted with ethyl acetate (15 mL), washed with water (4 × 10 mL) and brine (10 mL), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 4:1, petrol/ether) gave *alkylidene malonate* **3.111** as a colourless oil (545 mg, 66%).

R_f 0.19 (4:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2952br, 1721s, 1645w, 1436m, 1365m, 1225br, 1102br, 1059s, 737s, 698s; δ_H (400 MHz, $CDCl_3$) 1.80 (2H, tt, *J* 7.5, 6.0 Hz, $BnOCH_2C\mathbf{H_2}$), 2.43 (2H, q, *J* 7.5 Hz, $C\mathbf{H_2}CH{=}C$), 3.49 (2H, t, *J* 6.0 Hz, $BnOC\mathbf{H_2}$), 3.76 and 3.79 (6H, 2 × s, 2 × $CO_2C\mathbf{H_3}$), 4.48 (2H, s, $C\mathbf{H_2}Ph$), 7.06 (1H, t, *J* 7.5 Hz, C**H**=C), 7.24-7.37 (5H, m, **Ar**); δ_C (100 MHz, $CDCl_3$) 26.8 ($\mathbf{C}H_2CH{=}C$), 28.4 ($BnOCH_2\mathbf{C}H_2$), 52.2 and 52.3 (2 × $CO_2\mathbf{C}H_3$), 69.2 ($BnO\mathbf{C}H_2$), 72.8 ($\mathbf{C}H_2Ph$), 127.5, 127.6 and 128.3 (Ar **C**H), 128.2 (CH=**C**), 138.4 (Ar **C**), 149.9 (**C**H=C), 164.3 and 165.8 (2 × $\mathbf{C}O_2CH_3$); *m/z* (ESI^+) 315 (MNa^+, 97), 447 (100), 607 (M_2Na^+, 100); HRMS found 315.1201; $C_{16}H_{20}NaO_5$ (MNa^+) requires 315.1203.

(*E*)-Dimethyl 2-[4-(benzyloxy)but-1-enyl]-2-methylmalonate (3.102)

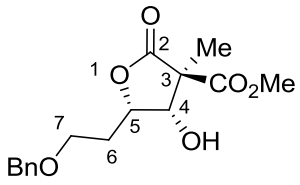


LDA (246 μL, 1.8 M in THF, 0.44 mmol) was added to a solution of alkylidene malonate **3.111** (100 mg, 0.34 mmol) and DMPU (183 μL, 1.51 mmol) in THF (0.40 mL) stirring at −78 °C and the resulting solution stirred for 45 mins before methyl iodide (41 μL, 0.65 mmol) was added. The reaction was allowed to warm to RT over 2 h before being heated at reflux for 30 mins. After cooling,

the reaction was quenched with HCl (0.5 M, 2 mL), extracted with ether (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 9:1, petrol/ether) gave *methylated alkene* **3.102** as a colourless oil (60 mg, 58%).

R_f 0.21 (9:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 2953br, 1732s, 1454m, 1375w, 1253br, 1106br, 971m, 737m, 698m; δ_H (500 MHz, $CDCl_3$) 1.58 (3H, s, C**H**$_3$), 2.42 (2H, dtd, *J* 7.0, 6.5, 1.5 Hz, C**H**$_2$CH=CH), 3.52 (2H, t, *J* 6.5 Hz, BnOC**H**$_2$), 3.73 (6H, s, 2 × CO_2C**H**$_3$), 4.51 (2H, s, C**H**$_2$Ph), 5.64 (1H, dt, *J* 16.0, 7.0 Hz, CH_2C**H**=CH), 6.00 (1H, dt, *J* 16.0, 1.5 Hz, CH_2CH=C**H**), 7.27-7.37 (5H, m, **Ar**); δ_C (125 MHz, $CDCl_3$) 20.3 (**C**H_3), 33.0 (**C**H_2CH=CH), 55.7 (2 × CO_2**C**H_3), 55.5 (CH=CH**C**), 69.5 (BnO**C**H_2), 72.8 (**C**H_2Ph), 127.5, 128.4 and 128.6 (Ar **C**H and CH_2**C**H=CH_2), 129.5 (CH_2CH=**C**H), 138.4 (Ar **C**), 171.7 (2 × **C**O_2CH_3); *m*/*z* (ESI^+) 307 (MH^+, 37%), 329 (MNa^+, 100); HRMS found 329.1353; $C_{17}H_{22}NaO_5$ (MNa^+) requires 329.1359.

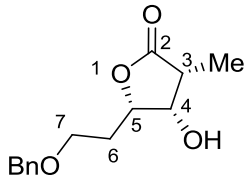
(4*S*,5*S*)-Methyl 5-[2-(benzyloxy)ethyl]-4-hydroxy-3-methyl-2-oxotetrahydrofuran-3-carboxylate (3.113)



AD-mix α (253 mg) was added to a solution of alkene **3.102** (55 mg, 0.18 mmol) in *tert*-butanol (0.89 mL) and water (0.89 mL). The resulting mixture was stirred at RT for 48 h before being quenched with Na_2SO_3 (800 mg), extracted with ethyl acetate (3 × 10 mL) and the combined organic layers dried (Na_2SO_4) and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, 1:1, petrol/ether) gave *lactone* **3.113** (20 mg, 36%) and *decarboxylation product* **3.114** (8 mg, 18%) as colourless oils.

R_f 0.18 (1:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 3445br, 2954br, 1778s, 1737s, 1454m, 1255br, 1196m, 1114br; δ_H (500 MHz, $CDCl_3$) 1.50 (3H, s, C**H$_3$**), 2.16 (1H, dddd, *J* 15.0, 5.0, 4.5, 2.0 Hz, C(6)**H**H′), 2.26 (1H, dtd, *J* 15.0, 10.5, 3.5 Hz, C(6)H**H′**), 3.56 (1H, ddd, *J* 10.5, 10.0, 2.0 Hz, C(7)**H**H′), 3.60 (1H, d, *J* 3.5 Hz, O**H**), 3.74 (1H, ddd, *J* 10.0, 4.5, 3.5 Hz, C(7)H**H′**), 3.78 (3H, s, CO_2C**H$_3$**), 4.46 (1H, t, *J* 3.5 Hz, C(4)**H**), 4.49 (1H, s, OC**H**H′Ph), 4.51 (1H, s, OCH**H′**Ph), 4.61 (1H, ddd, *J* 10.5, 5.0, 3.5 Hz,C(5)**H**), 7.28-7.41 (5H, m, **Ar**); δ_C (125 MHz, $CDCl_3$) 14.2 (**C**H_3), 28.4 (**C**(6)H_2), 53.2 (CO_2**C**H_3), 57.2 (**C**(3)), 69.9 (**C**(7)H_2), 73.6 (**C**(4)H), 73.9 (**C**H_2Ph), 81.7 (**C**(5)H), 127.9, 128.3 and 128.7 (Ar **C**H), 136.7 (Ar **C**), 170.1 (**C**O_2CH_3), 174.1 (**C**(2)); *m*/*z* (ESI^+) 309 (MH^+, 18%), 331 (MNa^+, 100), 639 (52); HRMS found 331.1148; $C_{16}H_{20}NaO_6$ (MNa^+) requires 331.1152.

(4*S*,5*S*)-5-[2-(Benzyloxy)ethyl]-4-hydroxy-3-methyldihydrofuran-2(3*H*)-one (3.114)



R_f 0.09 (1:1, petrol/ether); ν_{max} (thin film)/cm^{-1} 3453br, 2939br, 1769s, 1183br, 1097br, 992br; δ_H (500 MHz, $CDCl_3$) 1.28 (3H, d, *J* 7.5 Hz, C**H$_3$**), 2.16 (1H, dddd, *J* 15.0, 5.5, 4.5, 2.5 Hz, C(6)**H**H′), 2.24 (1H, dddd, *J* 15.0, 10.5, 9.5, 3.5 Hz, C(6)H**H′**), 2,72 (1H, qdd, *J* 7.5, 5.5, 1.0 Hz, C(3)**H**), 3.25 (1H, app. dd, *J* 3.0, 1.0 Hz, O**H**), 3.56 (1H, ddd, *J* 10.5, 10.0, 2.5 Hz, C(7)**H**H′), 3.72 (1H, ddd, *J* 10.0, 4.5, 3.5 Hz, C(7)H**H′**), 4.31 (1H, dt, *J* 5.5, 3.0 Hz, C(4)**H**), 4.37 (1H, ddd, *J* 9.5, 5.5, 3.0 Hz, C(5)**H**), 4.53 (1H, d, *J* 12.0 Hz, OC**H**H′Ph), 4.57 (1H, d, *J* 12.0 Hz, OCH**H′**Ph), 7.28-7.41 (5H, m, **Ar**); δ_C (125 MHz, $CDCl_3$) 8.1 (**C**H_3), 28.6 (**C**(6)H_2), 41.2 (**C**(3)H), 65.9 (**C**(7)H_2), 71.2 (**C**(4)H), 73.8 (**C**H_2Ph), 81.7 (**C**(5)H), 127.9, 128.2 and 128.7 (Ar **C**H), 137.0 (Ar **C**), 178.4 (**C**(2)); *m*/*z* (ESI^+) 273 (MNa^+, 100%), 409 (48), 523 (M_2Na^+, 61), 581 (47); HRMS found 273.1102; $C_{14}H_{18}NaO_4$ (MNa^+) requires 273.1097.

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APPENDICES

Appendices A−F: Single crystal X-ray crystallography

Single crystal X-ray analysis was performed by the author at the University of Oxford Chemical Crystallography Laboratory. Crystals were mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation = 0.71073 Å). Intensity data were processed using the DENZO-SMN package.

Structures were solved using the direct-methods program SIR92[9] which located all nonhydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite.[10] Coordinates and anisotropic thermal parameters of all nonhydrogen atoms were refined. Figures were prepared using the molecular graphics program CAMERON[11] or Mercury.

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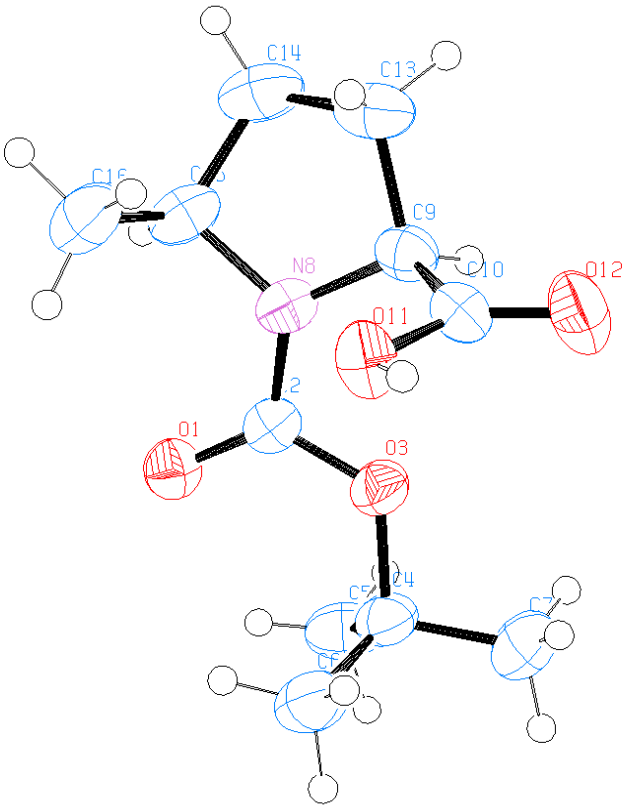
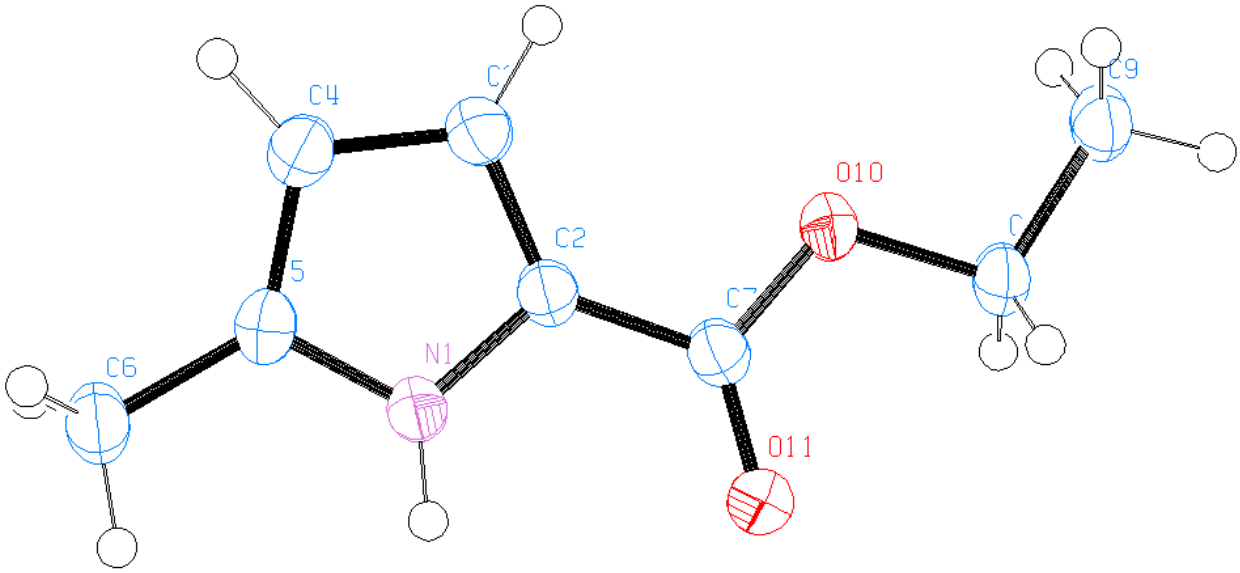
Appendix A: Single Crystal X-ray Diffraction report for 1.110



Chemical Formula	$C_{11}H_{19}NO_4$
Space Group (Herman-Mauguin)	P 2_1 2_1 2_1
a (Å)	6.3458 (2)
b (Å)	9.7433 (3)
c (Å)	21.3968 (5)
α (°)	90
β (°)	90
γ (°)	90
Cell Volume (Å^3)	1322.94 (7)
R (I > 2σ(I))	0.0359
wR (I > 2σ(I))	0.0842

Full data can be found in the cif file located on the attached CD

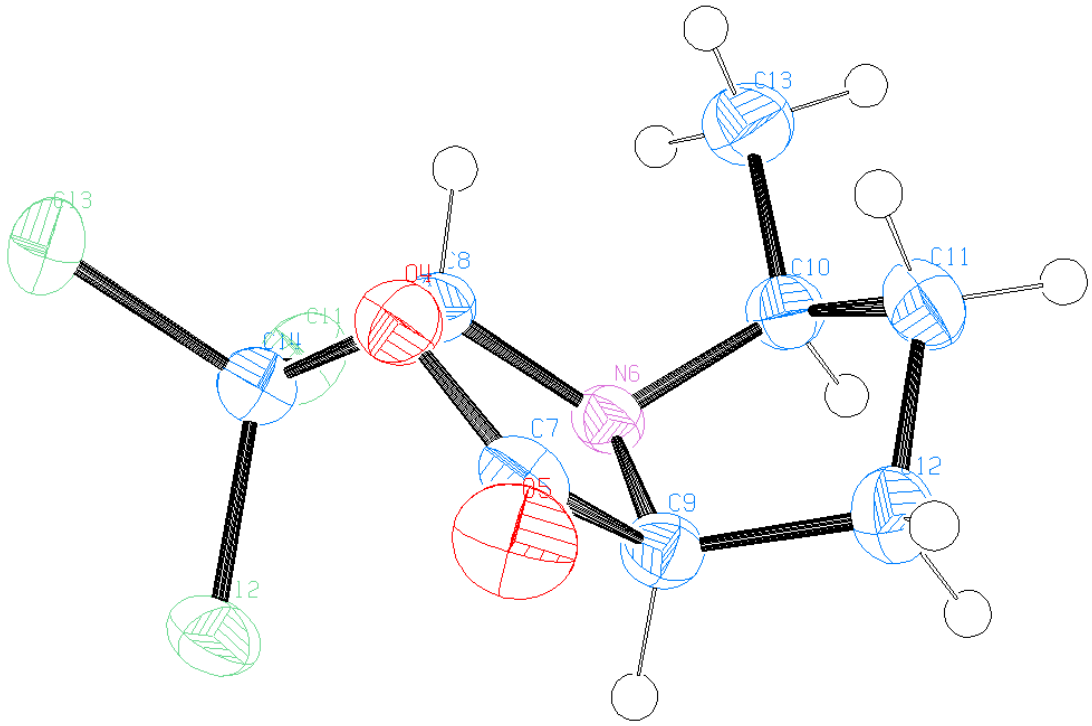
Appendix B: Single Crystal X-ray Diffraction report for 1.111



Chemical Formula	$C_8H_{11}N_1O_2$
Space Group (Herman-Mauguin)	P 1 2_1/a 1
a (Å)	6.3624 (2)
b (Å)	18.2268 (6)
c (Å)	7.1046 (3)
α (°)	90
β (°)	103.390 (2)
γ (°)	90
Cell Volume (Å^3)	801.50 (5)
R (I > 2σ(I))	0.0367
wR (I > 2σ(I))	0.0880

Full data can be found in the cif file located on the attached CD

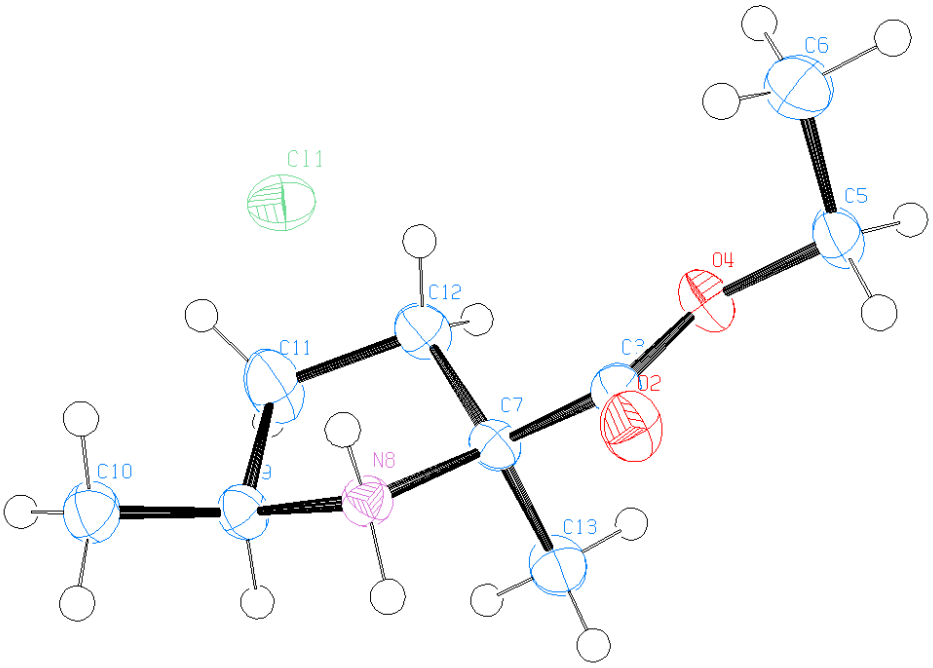
Appendix C: Single Crystal X-ray Diffraction report for 1.113



Chemical Formula	$C_8H_{10}Cl_3NO_2$
Space Group (Herman-Mauguin)	P 2_1 2_1 2_1
a (Å)	8.8313 (3)
b (Å)	9.3109 (3)
c (Å)	13.0854 (5)
α (°)	90
β (°)	90
γ (°)	90
Cell Volume (Å^3)	1075.98 (7)
R (I > 2σ(I))	0.0341
wR (I > 2σ(I))	0.0679

Full data can be found in the cif file located on the attached CD

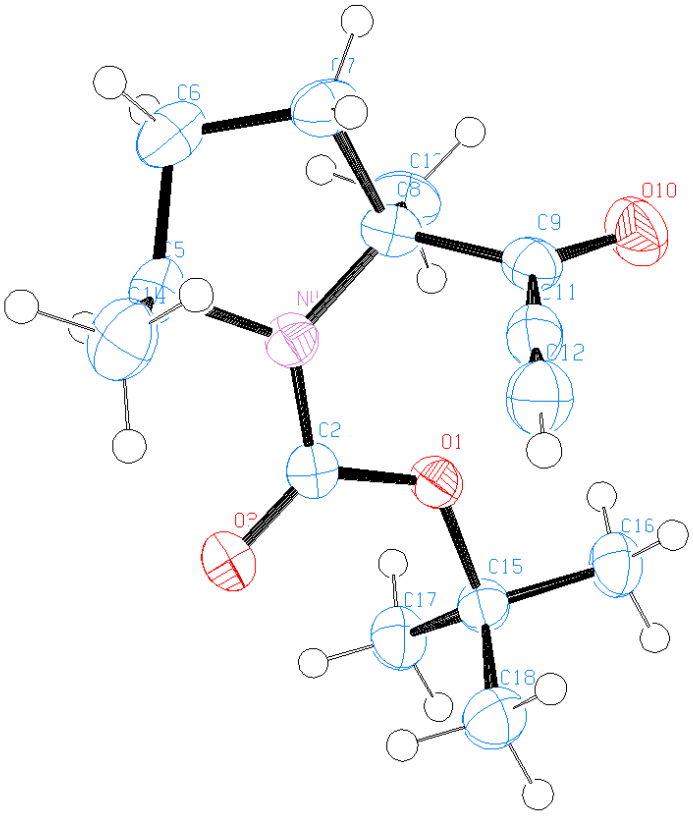
Appendix D: Single Crystal X-ray Diffraction report for the HCl salt of 1.117



Chemical Formula	$C_9H_{18}ClNO_2$
Space Group (Herman-Mauguin)	P b c a
a (Å)	7.87500 (10)
b (Å)	16.2180 (3)
c (Å)	17.3099 (3)
α (°)	90
β (°)	90
γ (°)	90
Cell Volume ($Å^3$)	2210.76 (6)
R ($I > 2\sigma(I)$)	0.0342
wR ($I > 2\sigma(I)$)	0.0785

Full data can be found in the cif file located on the attached CD

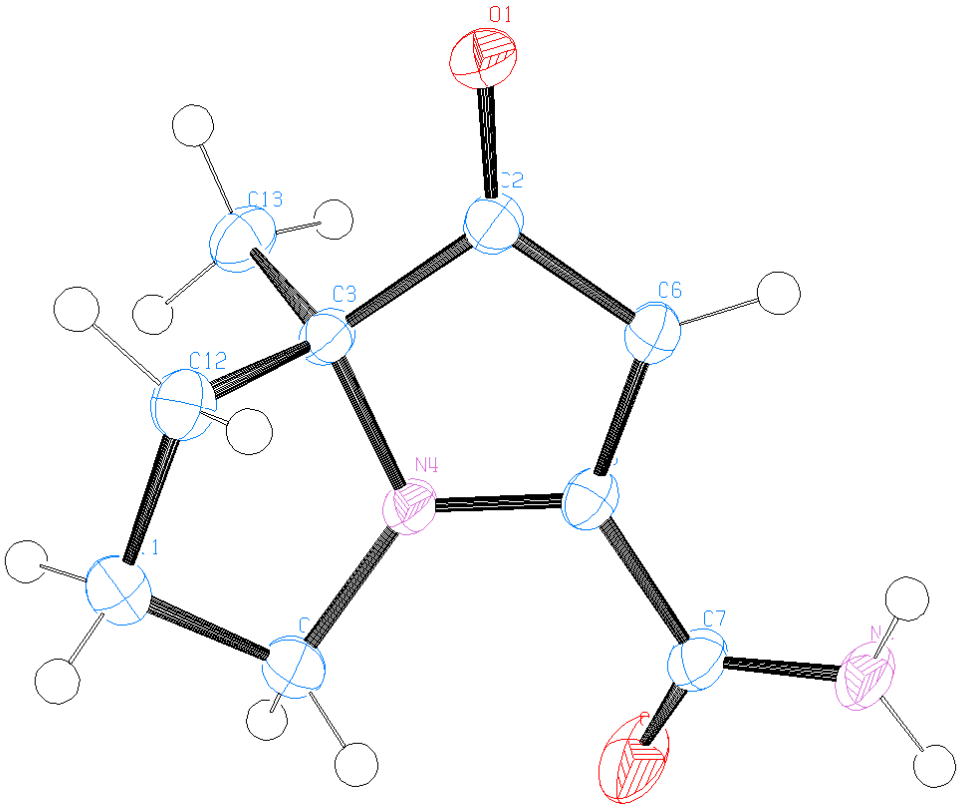
Appendix E: Single Crystal X-ray Diffraction report for 1.146



Chemical Formula	$C_{14}H_{21}NO_3$
Space Group (Herman-Mauguin)	P 1 2_1/n 1
a (Å)	8.3843 (2)
b (Å)	16.9036 (5)
c (Å)	10.3263 (3)
α (°)	90
β (°)	99.8691 (11)
γ (°)	90
Cell Volume (Å^3)	1441.84 (7)
R (I > 2σ(I))	0.0437
wR (I > 2σ(I))	0.0888

Full data can be found in the cif file located on the attached CD

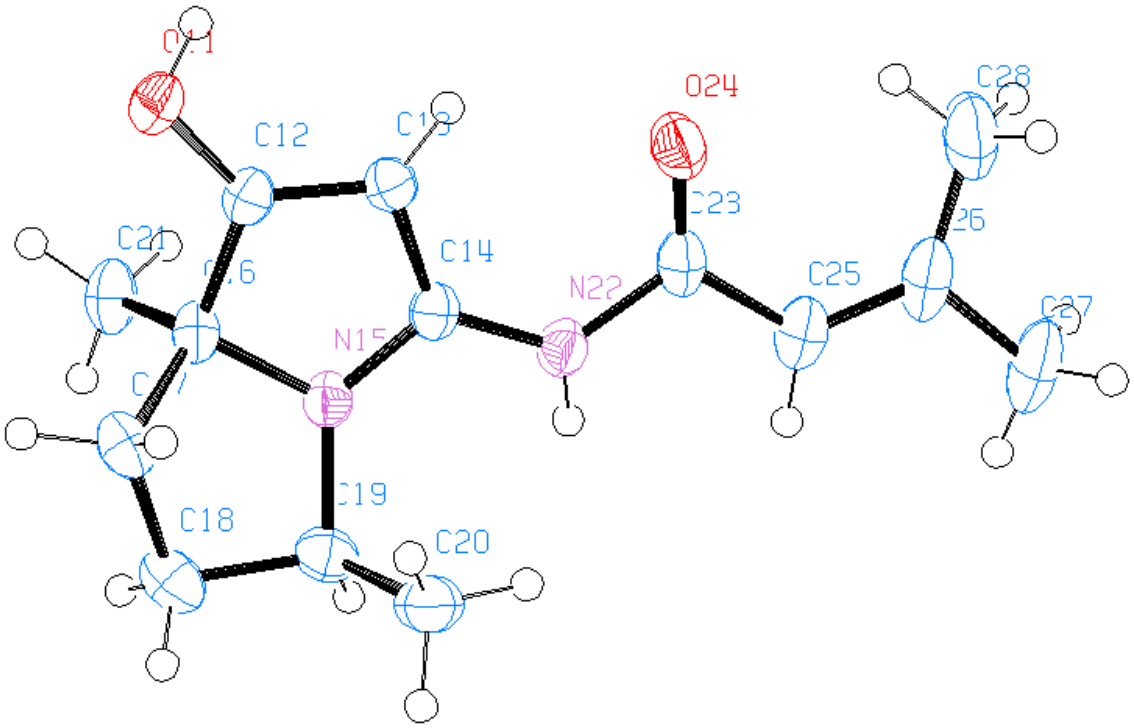
Appendix F: Single Crystal X-ray Diffraction report for 1.159



Chemical Formula	$C_9H_{12}N_2O_2$
Space Group (Herman-Mauguin)	P 2_1 2_1 2_1
a (Å)	8.2577 (2)
b (Å)	9.7622 (3)
c (Å)	11.2194 (3)
α (°)	90
β (°)	90
γ (°)	90
Cell Volume (Å^3)	904.43 (4)
R (I > 2σ(I))	0.0288
wR (I > 2σ(I))	0.0680

Full data can be found in the cif file located on the attached CD

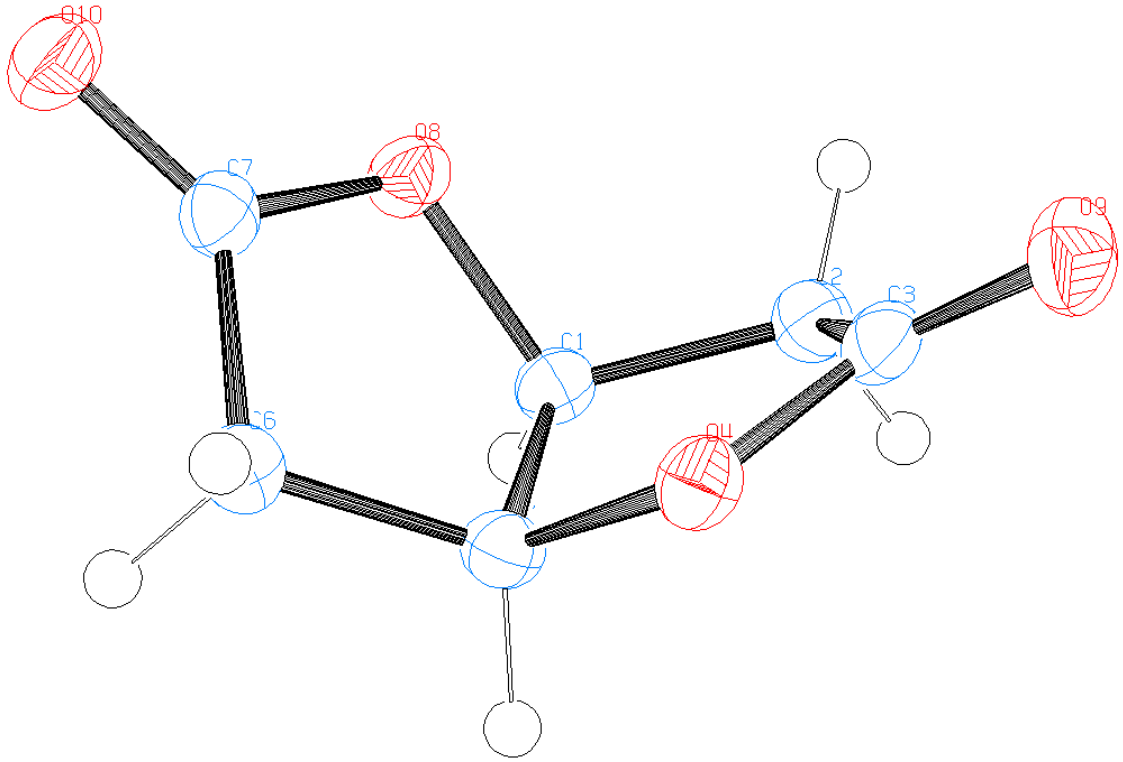
Appendix G: Single Crystal X-ray Diffraction report for 1.43 (with TFA removed for clarity)



Chemical Formula	$C_{18}H_{28}F_3N_4O_2$
Space Group (Herman-Mauguin)	P 1 2_1/c 1
a (Å)	15.1572 (4)
b (Å)	12.8333 (3)
c (Å)	9.6065 (3)
α (°)	90
β (°)	106.574 (3)
γ (°)	90
Cell Volume (Å^3)	1790.99 (9)
R (I > 2σ(I))	0.0611
wR (I > 2σ(I))	0.1468

Full data can be found in the cif file located on the attached CD

Appendix H: Single Crystal X-ray Diffraction report for 3.8



Chemical Formula	$C_{12}O_8$
Space Group (Herman-Mauguin)	P 2_1/n
a (Å)	9.9658 (3)
b (Å)	6.1656 (2)
c (Å)	10.4017 (4)
α (°)	90
β (°)	113.5569 (18)
γ (°)	90
Cell Volume (Å^3)	585.87 (4)
R (I > 2σ(I))	0.0426
wR (I > 2σ(I))	0.0926

Full data can be found in the cif file located on the attached CD.