Synthesis of Six Membered Heterocycles Containing Nitrogen or Oxygen

A thesis submitted to the

Board of the Faculty of Physical Sciences

in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

in the

University of Oxford

by

Peter G. Turner

Wolfson College

and

The Chemistry Research Laboratory

Michaelmas 2005

絕不放棄

For my family

Declaration

This thesis and the work of which it is a record has been carried out by myself. No portion of the work referred in this thesis has been submitted in support of an application for another or qualification of this or any other University or Institute of learning.

Peter Graham Turner

Michaelmas 2005

Abstract

Synthesis of 6-Membered Heterocycles Containing Nitrogen and Oxygen

Peter G. Turner *Chemical Research Laboratory* *Michaelmas 2005*

Six-membered heterocycles containing nitrogen and oxygen are prevalent in natural products and pharmaceutical drugs; hence efficient synthesis of these motifs is of great benefit. This thesis describes the successful rearrangements of 5-membered heterocycles containing nitrogen and oxygen through to the corresponding 6-membered compounds.

Chapter 1 – Project Conception
This section outlined the project conception and aims.

Chapter 2 – Radical Ring-Expansions
This section contains an introduction to the radical mediated ring-expansions, which firstly focused on carbocylic precedent, before an in depth discussion on work relating to the radical ring-expansion of heterocycles.

Chapter 3 – Synthesis of Piperidines and Pyrrolidines
An introduction to the rearrangement of nitrogen containing heterocycles was examined, with particular emphasis on the one carbon ring-expansion of pyrrolines, azetines and lactams.

Chapter 4 – Rearrangements of Nitrogen Heterocycles
This section detailed the one-carbon radical ring-expansion of the pyrrolines obtained from the Birch reduction of electron deficient pyrroles. The scope of the reaction was examined with respect to substitution around the pyrroline ring. A postulated mechanism was presented with experimental evidence in the form of the synthesis fused bicycles. Attempts at inducing either an ionic or cationic ring-expansion were examined and a novel pyrroline ring-opening reaction presented.

Chapter 5 – Synthesis of Tetrahydropyrans
The literature on the ring-expansion reactions to form tetrahydropyrans was discussed, with particular emphasis paid on the tetrahydrofuran to tetrahydropyran rearrangement, the ring-expansion of epoxides and the ring-expansion of thiiranium ions.

Chapter 6 – Rearrangements of Oxygen Heterocycles
The development of the ring-expansion of tetrahydrofurans to tetrahydropyrans was described, with focus centred on the stereochemical requirements for efficient ring-expansion. A hydride shift pathway to form open chain ketones was exploited in the enantiopure synthesis of spiroketals.

Acknowledgements

I would like to take this opportunity to thank all of those people whose help has contributed to the completion of my postgraduate studies. Professor Timothy Donohoe has supplied a constant source of advice, pragmatism and enthusiasm for the duration of my DPhil. Dr Rick Cousins, my industrial supervisor, helped with useful chemical suggestions, supplying both chemicals and chemical equipment and has given very helpful advice for the progression of my chemical career. In addition, Rick has also extensively proof read this thesis.

The technical staff and Donohoe group members at the University of Oxford for all their services: in particular Jo KirkPatrick, Robin Proctor and Neil Oldham for mass spec, and Andrew Cowley, Katherine Wheelhouse, Farrah Bhatti, David Klauber and Rhian Thomas for X-ray Crystal analysis.

I would like to thank Drs David House and David Carbery for help during the initial phases of my DPhil and Dr Richard Pye for continuing the support during my second and third years.

A special note of thanks must go to Katherine Wheelhouse and Dr Carole Bataille for the extensive proof reading of this thesis.

The last couple of years have been so enjoyable, mainly because of the lively atmosphere that has existed in the Donohoe group, so I would like to thank all the Donohoe group members from 2002-2005, in particular Greame Freestone, Sam Butterworth, Majid Chughtai, Allan Orr, Caroline Rigby, Richard Pye, Katherine Wheelhouse, Carole Bataille and Farrah Bhatti for laughs, banter, sarcasm, squash and an enjoyable social life.

The last three years have not only been highly enjoyable, but have brought with them many changes to my life, so I would like to take this opportunity to thank the people who have always been a friendly face and source of refuge away from it all: Neil Garrido, James Young, Chris Hennem and John Turner have been constant sources of laughs and support.

Finally I would like to thank all my family, in particular Helen Turner, who have always given me love and support, regardless of the situation or circumstance.

Abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	2,2'-azo*bisiso*butylonitrile
aq.	aqueous
Ar	aromatic group
BMEA	*bis*(methoxy)ethylamine
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
C	celsius
CAN	ceric ammonium nitrate
CI	chemical ionisation
conc.	concentrated
CSA	*RS*-camphor-10-sulfonic acid
DBB	di-*tert*-butylbiphenylide
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
d.e.	diastereomeric excess
d.r.	diastereomeric ratio
DEAD	diethyl azodicarboxylate
DHQD	dihydroquinidyl
DIAD	di-*iso*-propyl azodicarboxylate
DIBAL-H	di-*iso*-butylaluminium hydride
DMAP	4-(dimethyl)aminopyridine
DME	dimethoxyethane
DMF	*N*,*N*- dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6,-tetrahydro-2(1H)pyrimidinone
DMSO	dimethylsulfoxide
e.e.	enantiomeric excess
eq.	equivalents
Et	ethyl
FI	field ionisation
g	grams
hv	irradiation with light
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
Hz	hertz
i	*iso*
IR	infra-red
KHMDS	potassium hexamethyldisilazide
L	litre/ligand

LDA	lithium di-*iso*-propylamide
Me	methyl
mol	mole
mp	melting point
Mc	mono-choromethanesulfonyl
Ms	methanesulfonyl
MS	mass spectrometry
m/z	mass-to-charge ratio
NMR	nuclear magnetic resonance
PG	protecting group
Ph	phenyl
pH	$-\log_{10}[H_3O^+]$
PHAL	phthalazinyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
psi	pounds per square inch
PTC	phase transfer catalysis
Pyr	pyridine
R	generic alkyl group
R_f	retention fraction
t	tertiary
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBME	*tert*-butylmethyl ether
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
X	generic "leaving group"
[α]	specific rotation

Contents

Chapter 1

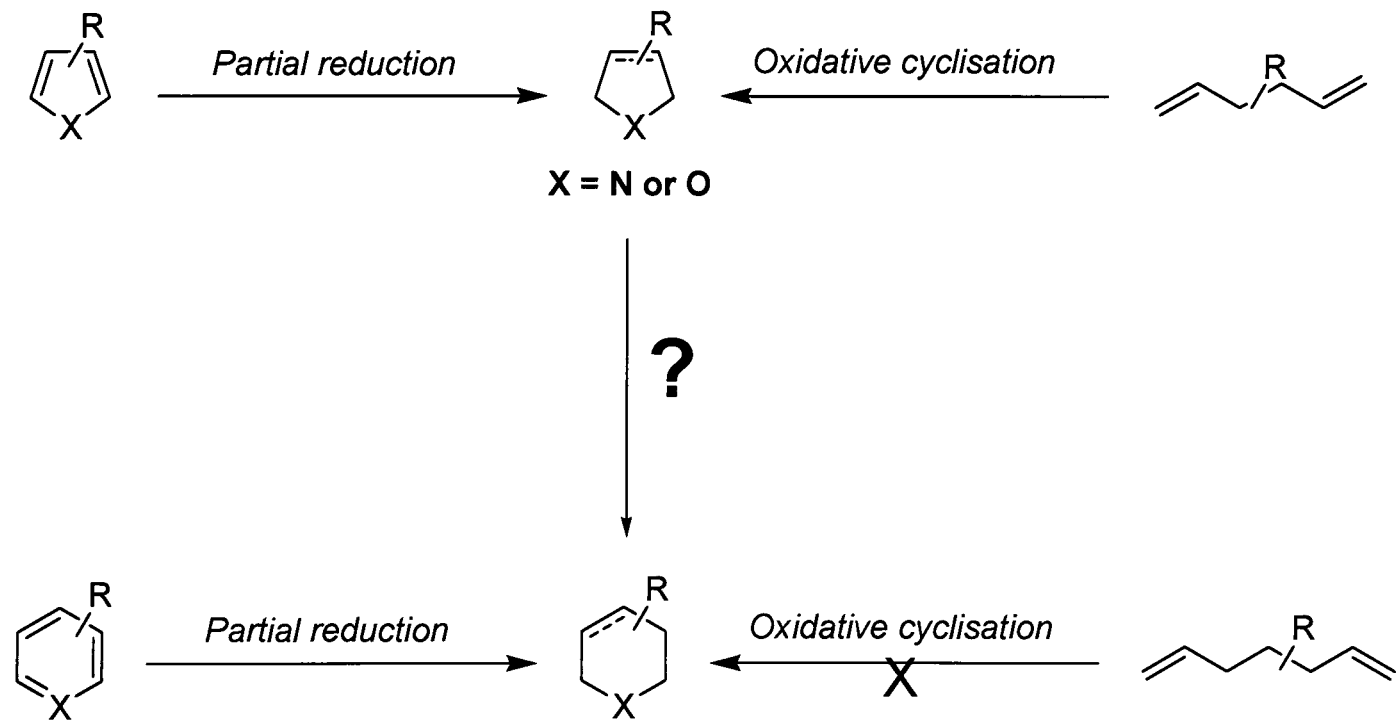
Project Conception

1.1 *Project conception.*

1.2 *Project aims and structure of thesis.*

1.1 *Project conception.*

One of the primary research areas within the Donohoe laboratories is the synthesis of heterocycles, specifically of five- and six-membered heterocycles containing nitrogen and oxygen atoms. Over the past decade, Donohoe and co-workers have developed two distinct approaches to the synthesis of these heterocycles: firstly, the partial reduction of aromatic compounds, and secondly, the oxidative cyclisation of 1,5-dienes (Scheme 1.1).



Scheme 1.1.

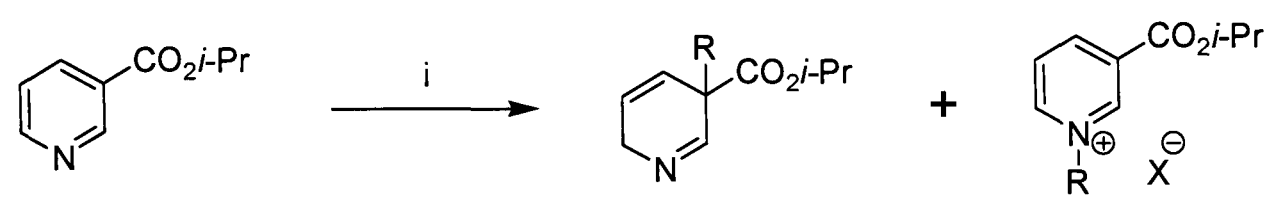
The high yielding partial reduction of electron deficient pyrroles[1-3] to furnish pyrrolines has been extended to a stereoselective variant, utilising chiral auxilaries.[4] The partial

reduction of an electron deficient pyrrole was exploited as the key step in the efficient synthesis of lactacystin's β-lactone.[5]

This methodology has also been applied to the partial reduction of electron deficient furans;[6] a stereoselective variant[7] allowed the synthesis of the natural product (+)-nemorensic acid[8] and the formal synthesis of (–)-secosyrin 1.[9]

The oxidative cyclisation of 1,5-dienes, using 5 mol% osmium tetroxide, to furnish 2,5-*syn*-tetrahydrofurans in high yields has been reported by Donohoe and co-workers.[10] The tetrahydrofuran products can be obtained in high enantiopurity by use of the appropriate enantiopure starting diol[11] and the methodology has been successively applied to the formal synthesis of (+)-*cis*-solamin. It should also be noted that prelimary results have shown that pyrrolidines can be prepared in an analogous manner using osmium tetroxide.*

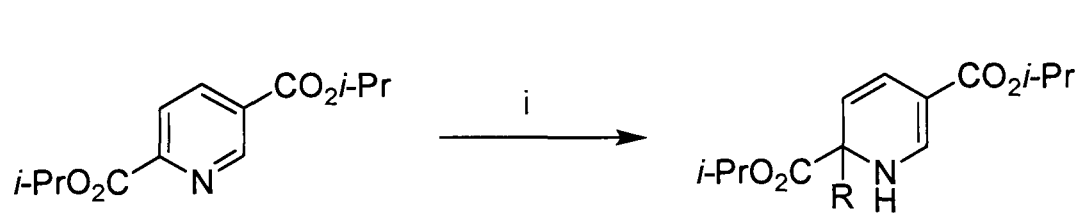
The partial reduction has been extended to pyridines; however when monoester **1** was reductively alkylated, unfortunately the desired dihydropyridines (**2a-c**) were obtained in low yields, the remainder of the mass was recovered as the pyridinium salts **3** (Scheme 1.2).[12, 13]



1 → **2a**, R=Me, 18%; **2b**, R=allyl, 40%; **2c**, R=propargyl, 34%. → **3**

Scheme 1.2. *Reagents and conditions*: i, Na, NH_3, THF, –78 °C; then RX; then NH_4Cl.

For efficient reduction, two electron-withdrawing moieties had to be present on the pyridine core. Diester **4** was successfully converted to the corresponding dihydropyridines (**5a-f**) in high yield (Scheme 1.3).[12, 13]



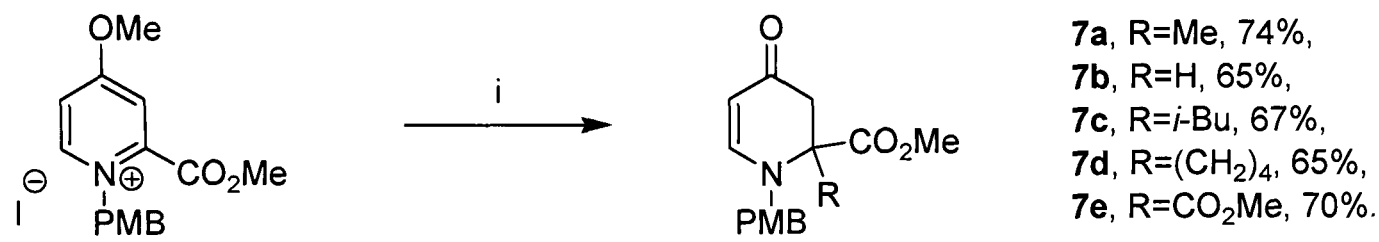
4

5a, R=Me, 99%,
5b, R=Et, 98%,
5c, R=*i*-Bu, 93%,
5d, R=allyl, 90%,
5e, R=$(CH_2)_3$, 96%,
5f, R=$(CH_2)_4$, 99%.

Scheme 1.3. *Reagents and conditions*: i, Na, NH_3, THF, –78 °C; then RX; then NH_4Cl.

* Pyrrolidines can be prepared from 1,2-amino alcohols. K. M. P Gosby and T. J Donohoe, *unpublished results*.

The use of pyridinium salt **6** as a partial reduction precursor allows the synthesis of a wide range of dihydropyridones (**7a-e**) in high yield (Scheme 1.4);[14] however, access to the biologically active tetrahydropyridine core[15-17] remains elusive.



6

Scheme 1.4. *Reagents and conditions*: i, Li, DBB, THF, –78 °C; then RX; then NH_4Cl.

1.2 *Project aims and structure of thesis.*

Owing to the limitations imposed by the partial reduction of pyridines and the fact that the osmium-catalysed oxidative cyclisation of 1,6-dienes has so far been unsuccessful (see Chapter 6), an alternative strategy was sought to access six-membered heterocycles containing nitrogen and oxygen.

This thesis describes the successful attempts to rearrange 5-membered heterocycles containing nitrogen and oxygen through to the corresponding six-membered heterocycles.

As the rearrangement of both pyrrolines and tetrahydrofurans are to be described, this thesis will be separated into two sections: the first section contains the introduction and results of the nitrogen series, utilising the partial reduction of electron deficient pyrroles to form the starting materials. The second section contains the introduction and results of the oxygen series, employing the oxidative cyclisation of 1,5-dienes to prepare the starting materials.

Chapter 2

Introduction – Radical Ring-Expansions

2.1 *Carbocyclic radical ring-expansion.*

2.2 *One carbon radical ring-expansions to form heterocycles.*

2.3 *Ring-expansion by attack onto an sp^2 centre other that a carbonyl moiety.*

2.4 *Methylidenecyclopropanes radical ring-expansions.*

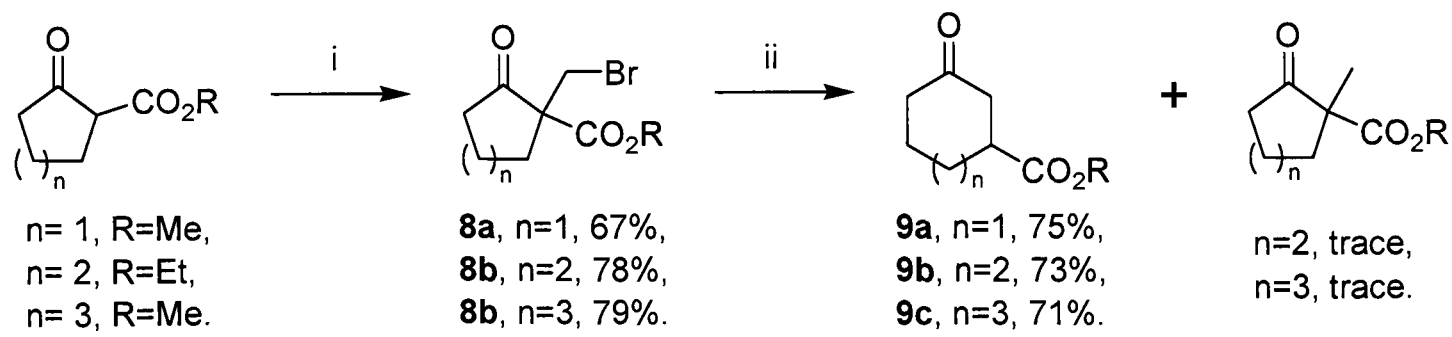
2.5 *Aziridine radical ring-expansions.*

2.6 *Epoxide radical ring-expansions.*

2.7 *Miscellaneous radical ring-expansion to form heterocycles.*

2.1 *Carbocyclic radical ring expansion.*

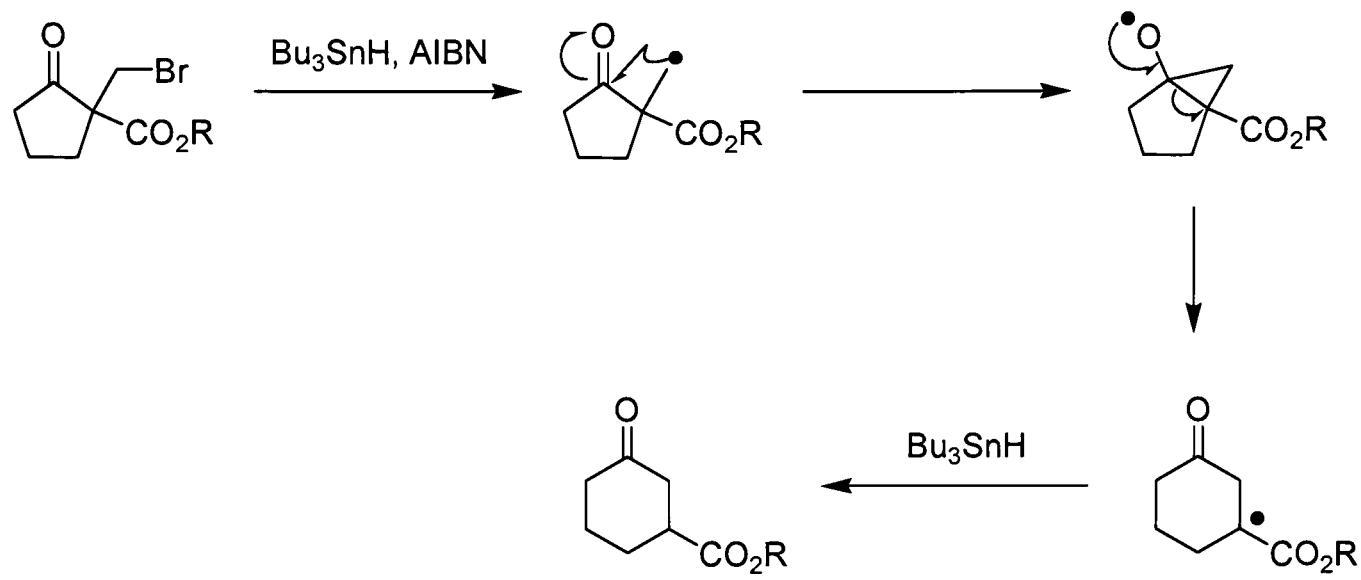
In 1987 Dowd published a pioneering one carbon ring-expansion of carbocyclic β-ketoesters (Scheme 2.1); the reaction has subsequently come to bear his name.[18] The cyclic β-ketoesters (prepared by the Dieckman condensation) starting materials were treated with sodium hydride and dibromomethane to yield the corresponding *exo*-cyclic bromomethyl compounds **8a-c** (Scheme 2.1), which upon treatment with tri-*n*-butyltin hydride and 2,2'-azo*bisiso*butylonitrile (AIBN) smoothly rearranged to the ring-expansion products **9a-c** in good yields.



Scheme 2.1. *Reagents and conditions*: i, NaH, CH_2Br_2, THF, Δ; ii, Bu_3SnH, AIBN, PhH, Δ.

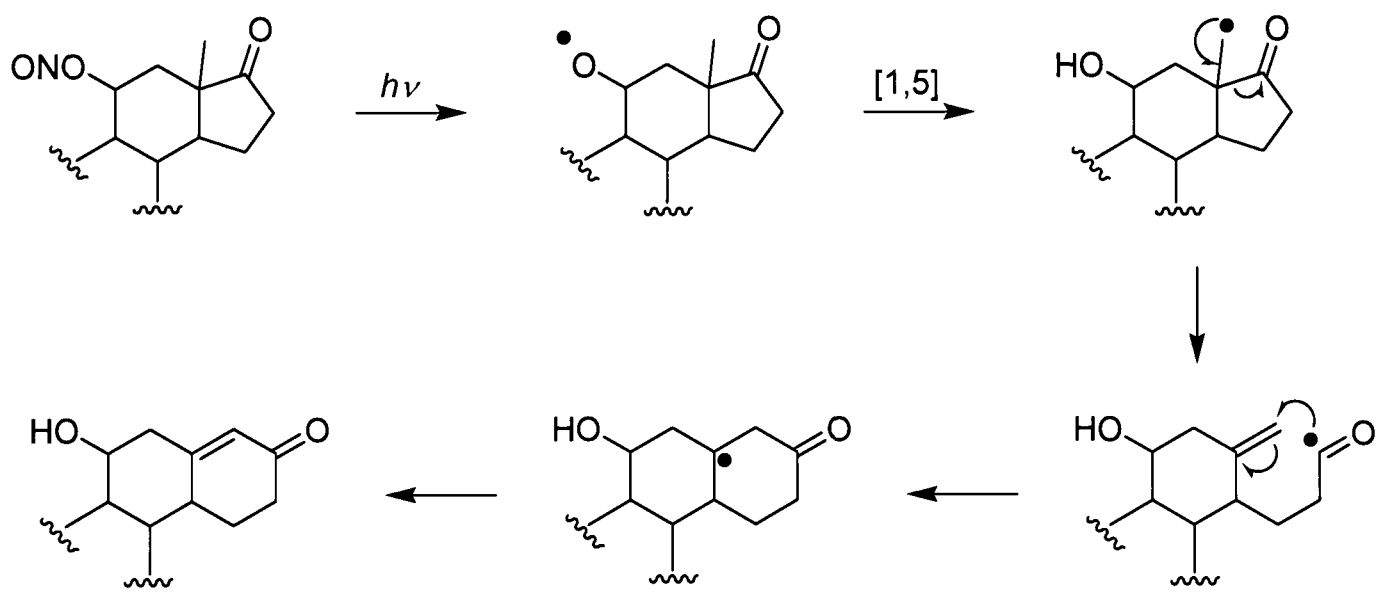
Beckwith extended the one carbon ring-expansion and found that rearrangement could be induced by using a β-ketoester bearing an *exo*-cyclic selenide-[19] or iodomethyl moiety.[20]

Dowd proposed that the primary radical formed attacks the neighbouring carbonyl group and the cyclopropyloxy radical undergoes ring cleavage to yield the stabilised radical adjacent to the ester (Scheme 2.2).[18]



Scheme 2.2. *Proposed mechanism for the Dowd ring-expansion.*

Radical attack onto a neighbouring carbonyl group had previously been reported in two early examples of radical ring-expansion reactions;[21, 22] however Barton proposed a ring-expansion *via* fragmentation to the open chain radical in his studies on the photolysis of steroid nitrate esters (Scheme 2.3).[22] It is difficult to differentiate between the two mechanisms; although general consensus inclines towards the cyclopropyloxy mechanism.[23-25]



Scheme 2.3. *Proposed mechanism for ring-expansion via a fragmentation pathway.*

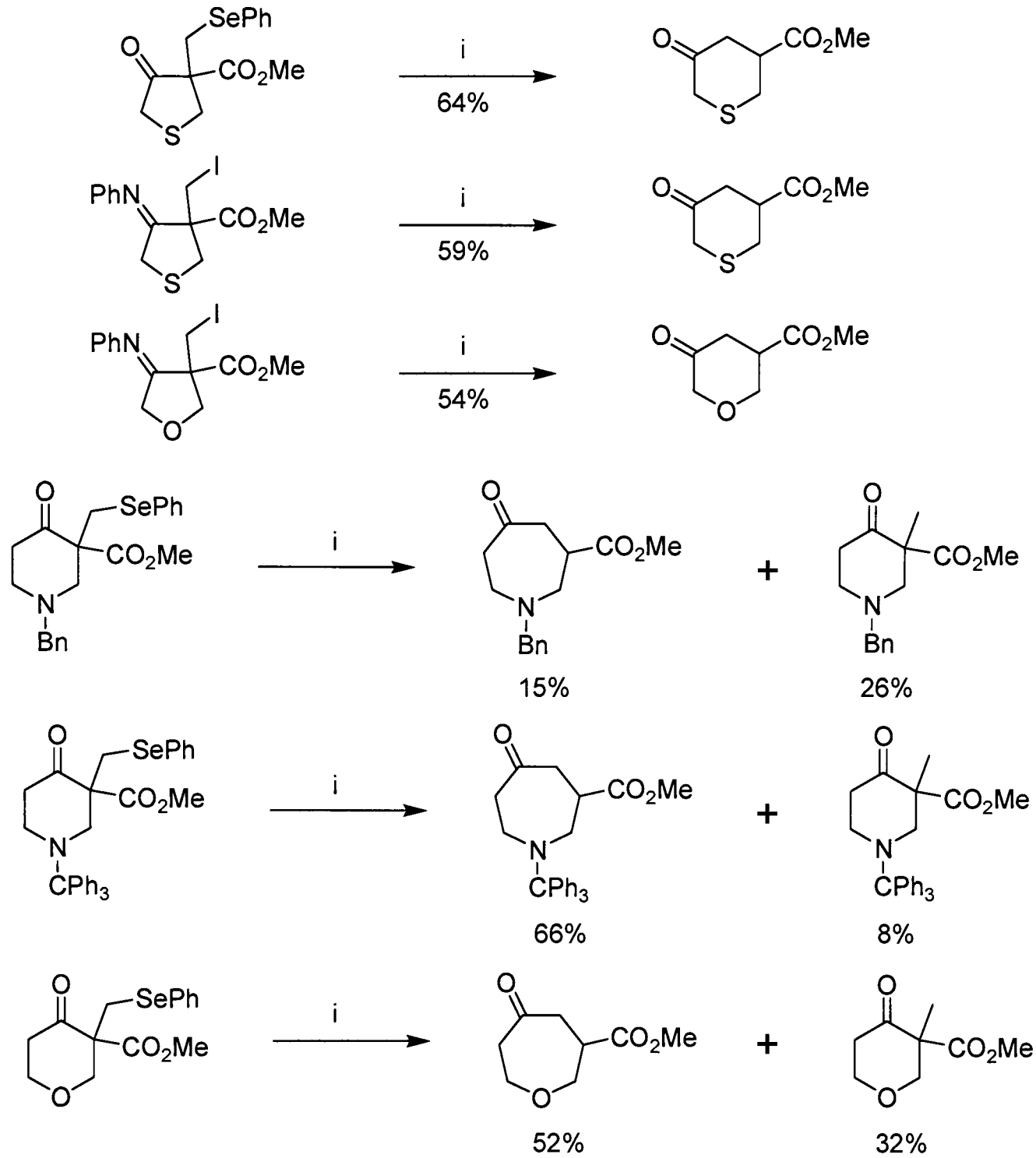
Dowd and co-workers have successfully completed the syntheses of larger carbocyclic rings by one carbon ring-expansions[26, 27] and ring-expansion by three or four carbon

increments.[28-32] Tri-*n*-butyltin hydride adducts have also been employed in a modification of the ring-expansion methodology leading to olefinic products[33-35] and in a reaction of penams to cephams.[36, 37]

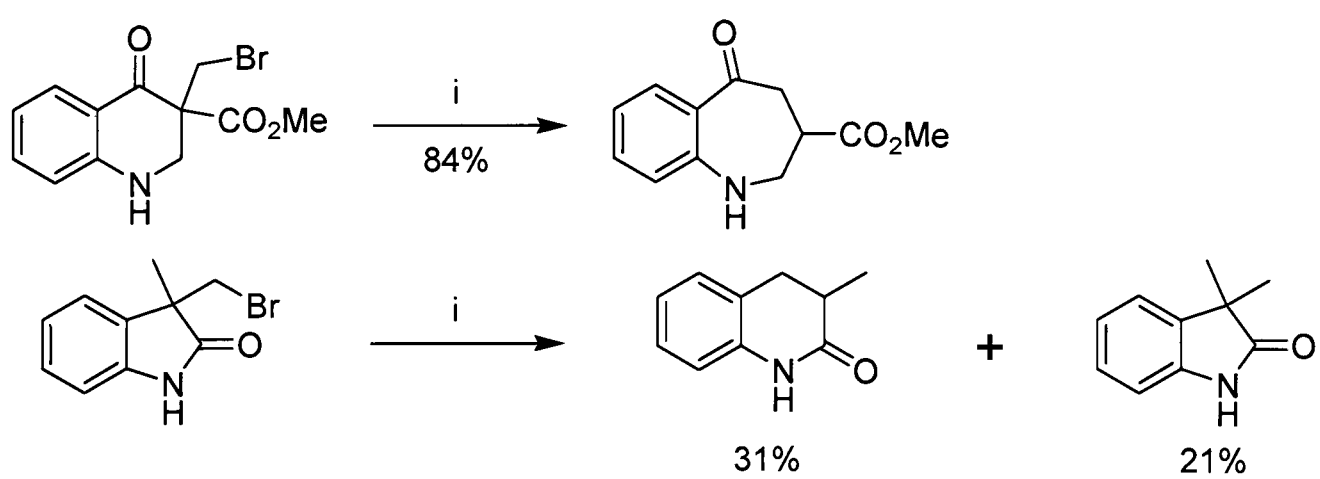
The area of carbocyclic radical ring-expansions and related annulations has been comprehensively reviewed;[23, 24] including free radicals in the synthesis of medium sized rings,[25] and the synthesis of heterocycles by radical cyclisation.[38, 39] As this thesis is concerned with the synthesis of heterocycles *via* rearrangement, the remainder of this chapter will focus on the synthesis of heterocycles containing nitrogen and oxygen by free radical ring-expansion processes.

2.2 *One carbon radical ring-expansions to form heterocycles.*

The carbon ring-expansion methodology has been extended to the synthesis of six- and seven-membered heterocycles.[40, 41] Ring-expansion of five-membered heterocycles from either a selenide or iodide radical precursor gave smooth rearrangement to the corresponding ring-expanded products in moderate yields (Scheme 2.4). Whereas in the five-membered series the sole product was the ring-expansion product, in the six-membered series, radical dehalogenation was a competing side reaction. A selenide radical precursor also had to be used, to prevent difficulty from internal alkylation (Scheme 2.4). The *exo*-cyclic bromomethyl precursor has been successfully employed in the benzazepine[23] and indole series[42] (Scheme 2.5).



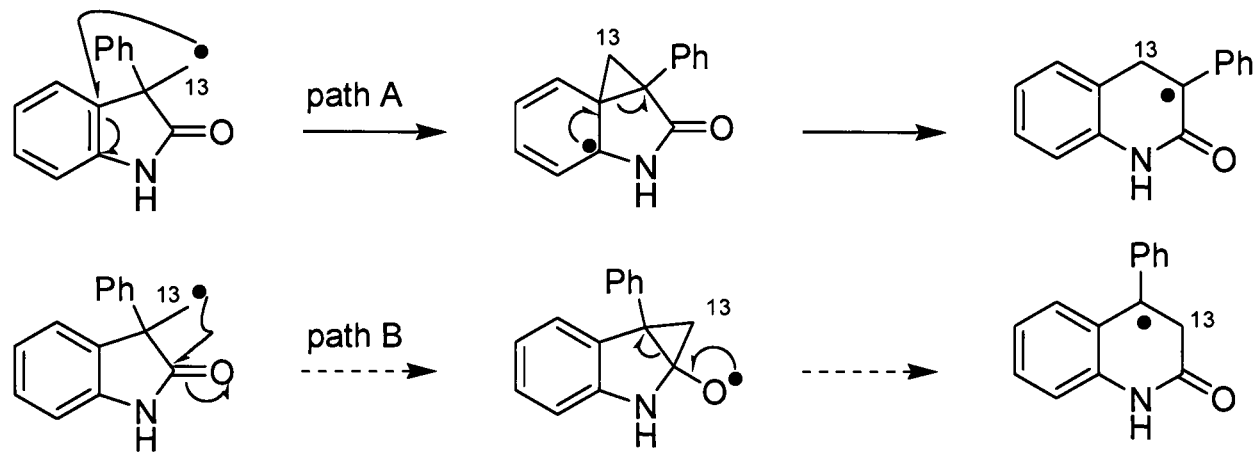
Scheme 2.4. *Reagents and conditions:* i, Bu_3SnH, AIBN, PhH, Δ.



Scheme 2.5. *Reagents and conditions:* i, Bu_3SnH, AIBN, PhH, Δ.

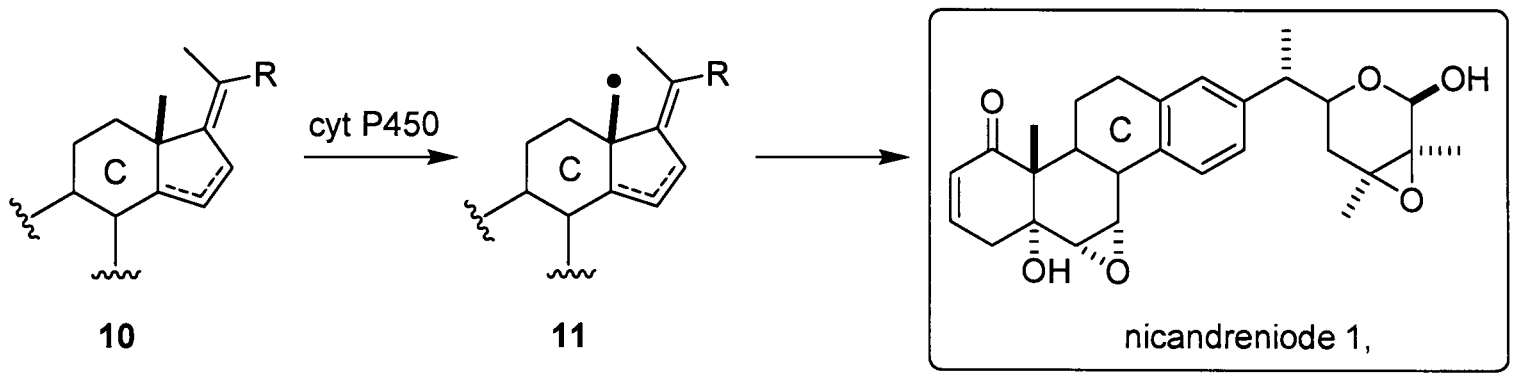
2.3 *Ring-expansion by attack onto an sp^2 centre other than a carbonyl moiety.*

Thus far all the rearrangements encountered had proceeded from a primary radical, which has cyclised onto a carbonyl moiety. However in the example of the indole ring-expansion (Scheme 2.5), there are two possible pathways. Carbon labelling experiments have given evidence that this ring-expansion occurs *via* attack onto the arene (a neophyl rearrangement, path A) as opposed to the carbonyl group as shown in path B (Scheme 2.6).[43]



Scheme 2.6. *Carbon labelling; evidence for a neophyl rearrangement.*

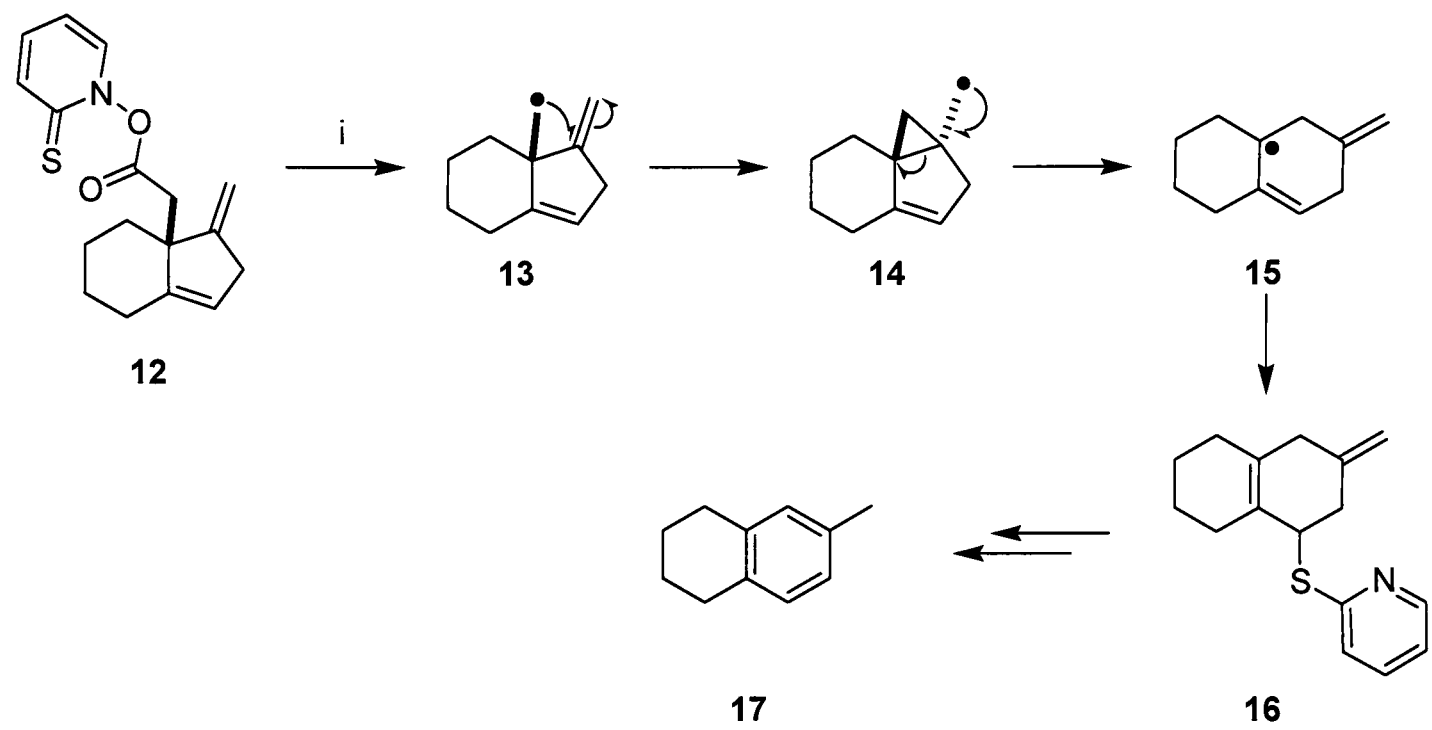
The majority of the examples from the literature of radical ring-expansion by one or more carbon atoms are promoted by initial attack onto a carbonyl moiety;[23-25] radical attacks onto an sp^2 centre other than a carbonyl moiety are rare, but there are a small number of rearrangements documented that initiate by radical attack onto an olefin, which will be discussed:



Scheme 2.7. *Proposed biogenesis of nicandrenoide 1.*

The nicandrenoides are a small sub-group from *Nicandra physaloides*, which contain the unique feature of an aromatic ring-D (Scheme 2.7). The biogenesis of nicandrenoide 1 (Scheme 2.7) had been postulated to occur *via* radical **11** which is formed by cytochrome P450 oxidation of a steroid derived from nicandrenoid 3 (**10**).

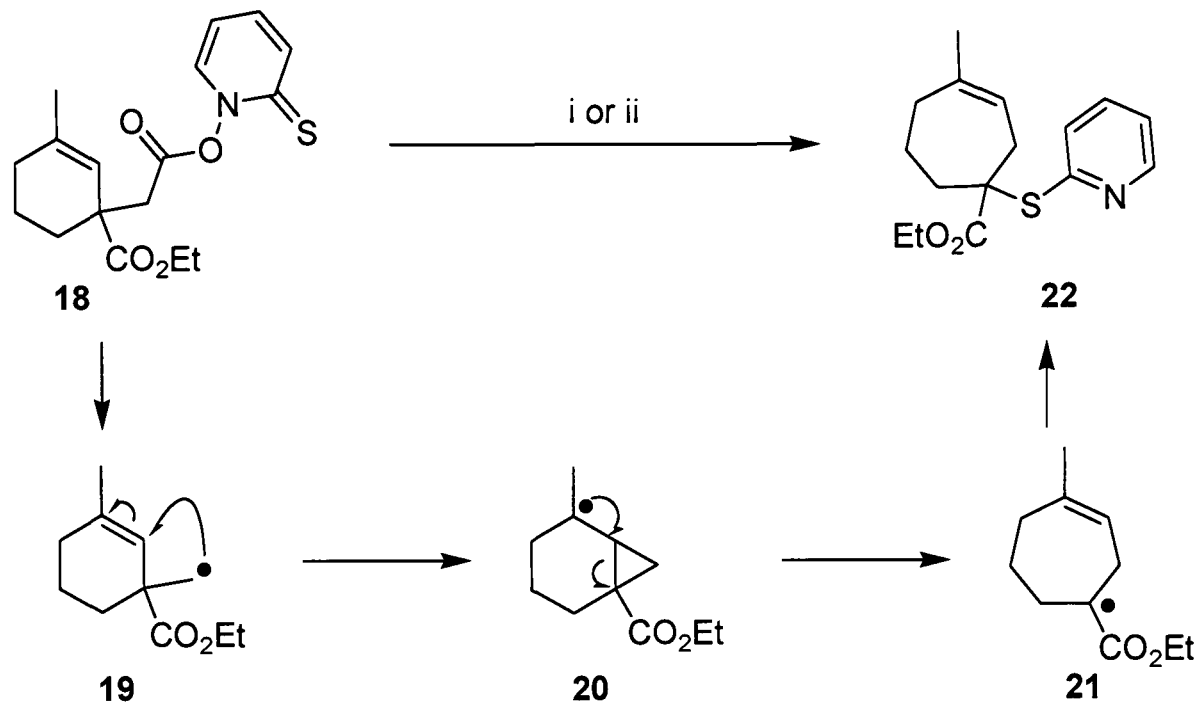
Whiting and Green undertook a study on the biomimetic radical ring-expansion and aromatisation of nicandrenoid 3.[44] When compound **12** was irradiated with a tungsten lamp for one hour, the ring-expanded aromatic compound **17** was obtained (Scheme 2.8), albeit in a very low yield of 2-5%. Whiting postulates that the initial radical **13** rearranges to the cyclopropyl species **14**. Strain driven cleavage produces intermediate **15** which is trapped as the 2-pyridinethiyl (**16**). Thermal elimination of 2-mercaptopyridine and prototropic shifts furnishes **17** (Scheme 2.8).[44]



Scheme 2.8. *Reagents and conditions*: i, *hv*.

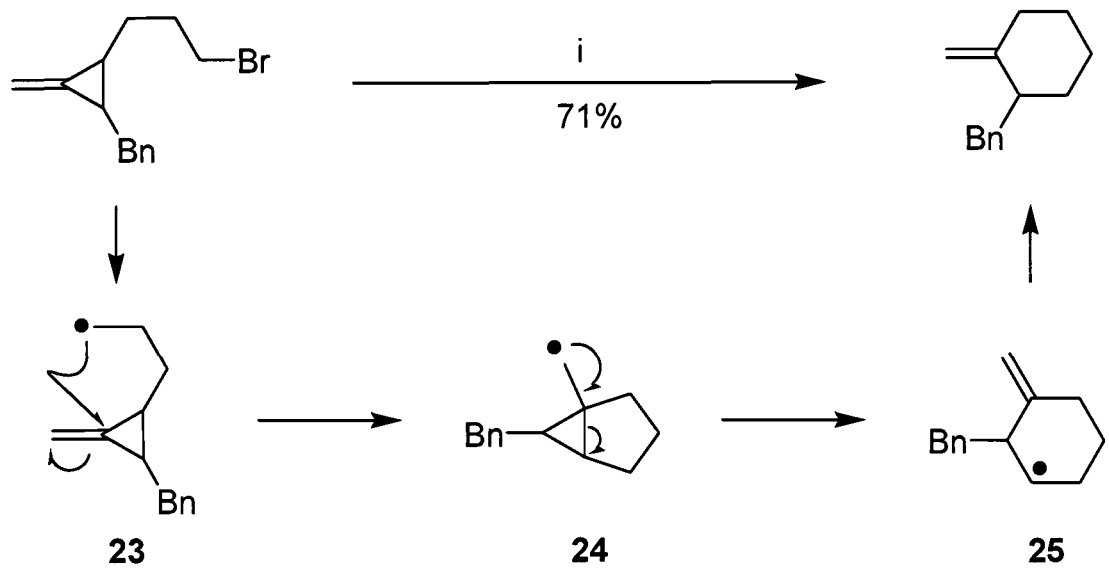
Zard and co-workers have also achieved a ring-expansion initiated by attack onto an olefin.[45,*] Attempting to synthesis a fused [5.6] spirocycle, *via* a 6-*endo*-trig cyclisation, Zard reported that the unexpected ring-expansion product **22** was obtained (Scheme 2.9).[45] Precursor **18** forms initial radical **19**, which undergoes a 3-*exo*-trig cyclisation to form cyclopropyl radical **20**. Zard postulates that a Thorpe-Ingold effect increases the rate of cyclopropyl formation, which can ring open to the stabilised cycloheptenyl radical **21**, this propagates the radical chain and is quenched to give the observed product **22**.

* This was a rather fortuitous result as it was not the intended product.



Scheme 2.9. *Reagents and conditions;* i, Phenylvinyl sulfone, CH_2Cl_2, room temperature, *hv*; ii, Cyclohexane, Δ, *hv*.

2.4 *Radical ring-expansions from methylidenecyclopropanes*

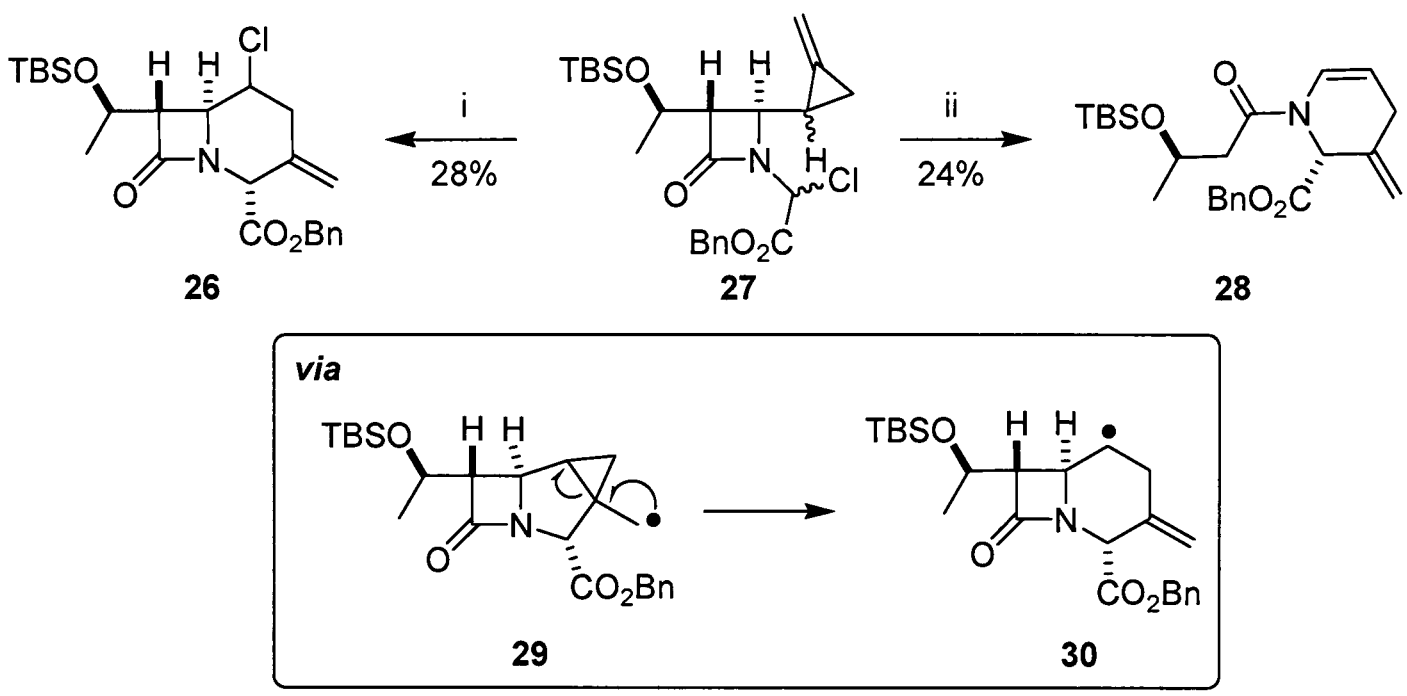


Scheme 2.10. *Reagents and conditions;* i, Bu_3SnH and AIBN, PhMe, syringe pump addition, Δ.

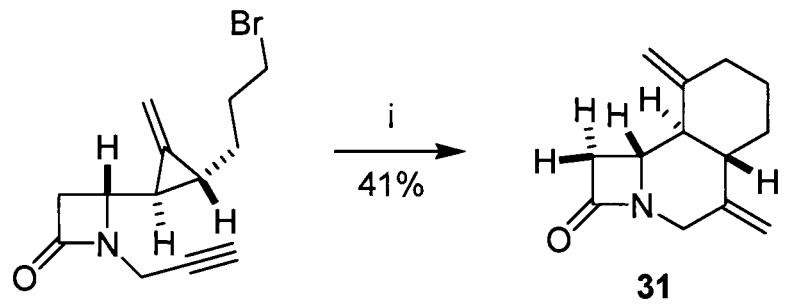
The cyclopropylcarbinyl to homoallyl radical rearrangement has been extensively scrutinised and this rearrangement becomes particularly powerful when combined with further radical reactions to allow the construction of various carbocyclic rings.[23, 46] Kilburn and Destabel reported a novel rearrangement of a 5-*exo*-trig cyclisation onto a

methylenecyclopropyl moiety (Scheme 2.10).[47] Radical **23** underwent a 5-*exo*-trig cyclisation, to form cyclopropyl radical **24**, which ring-opened to give the ring-expanded radical **25**.

Whereas (methylenecyclopropyl)propyl radicals underwent exclusive 5-*exo*-trig cyclisations, (methylenecyclopropyl)butyl radicals gave a mixture of the 6-*exo*-trig and 7-*endo*-trig cyclisation products.[48] This cyclisation has been extended to a radical cascade reaction which furnished *cis*-fused bicyclo-[3.4.0]-nonanes and bicycle-[4.4.0]-decanes.[49]



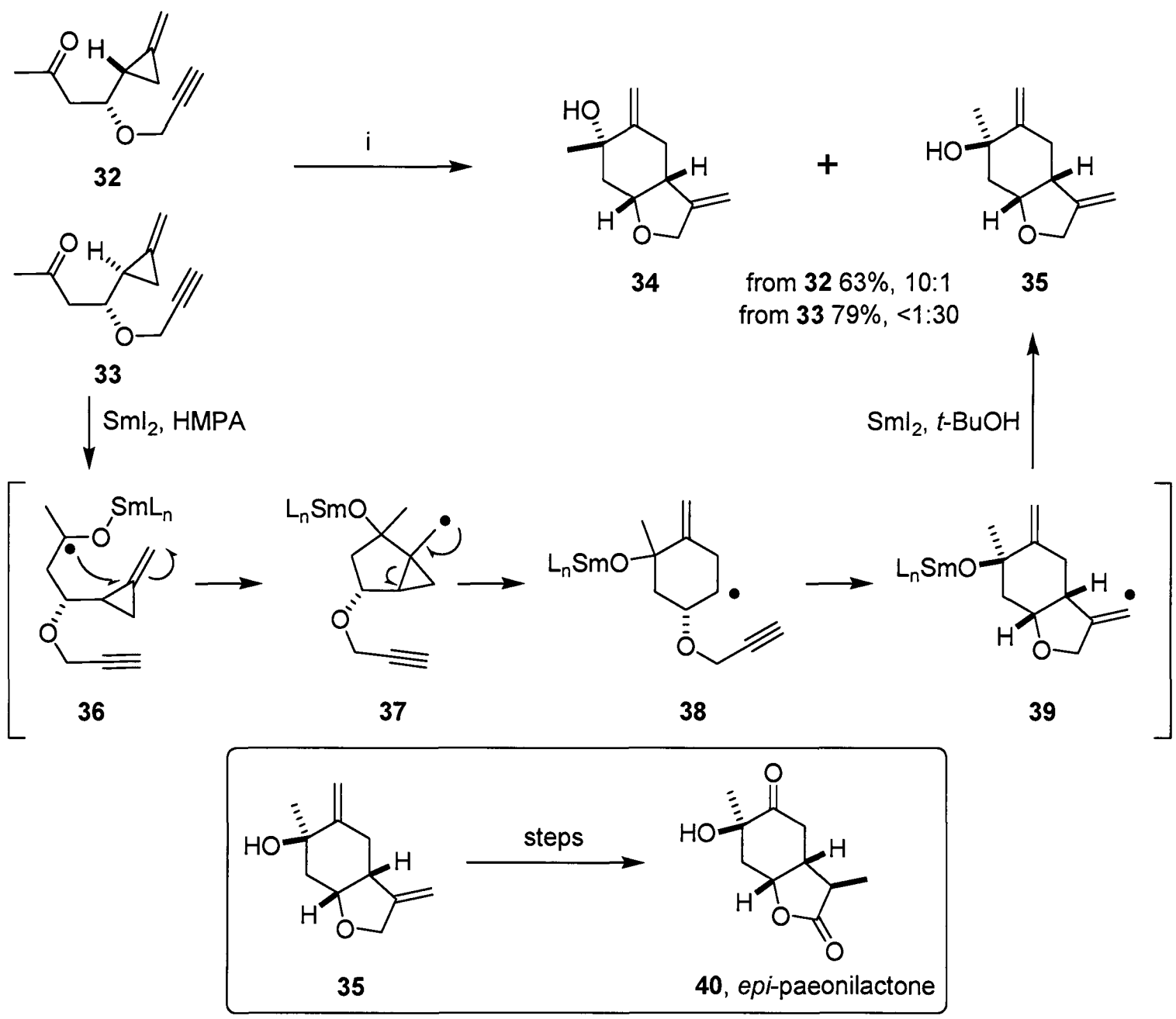
Scheme 2.11. *Reagents and conditions;* i, CuCl (30 mol%), bipyridine (30mol%), CH_2Cl_2, Δ; ii, Bu_3SnH and AIBN, PhMe, syringe pump addition, Δ.



Scheme 2.12. *Reagents and conditions;* i, Bu_3SnH and AIBN, PhMe, syringe pump addition, Δ.

Kilburn and co-workers have applied this methodology to the synthesis of fused β-lacatams (Scheme 2.11). Common precursor **27**, was reacted with either radical atom transfer conditions, which yielded β-lactam **26**; or to tri-*n*-butyltin hydride which furnished the amide **28** (Scheme 2.11), albeit low yields.[50] Both products arised from a 5-*exo*-trig cyclisation which yielded cyclopropyl intermediate **29**, before ring opening to furnish radical **30**. It was found the yields could be increased if the sequence was extended to a radical cascade reaction to form β-lactam **31** (Scheme 2.12).[50]

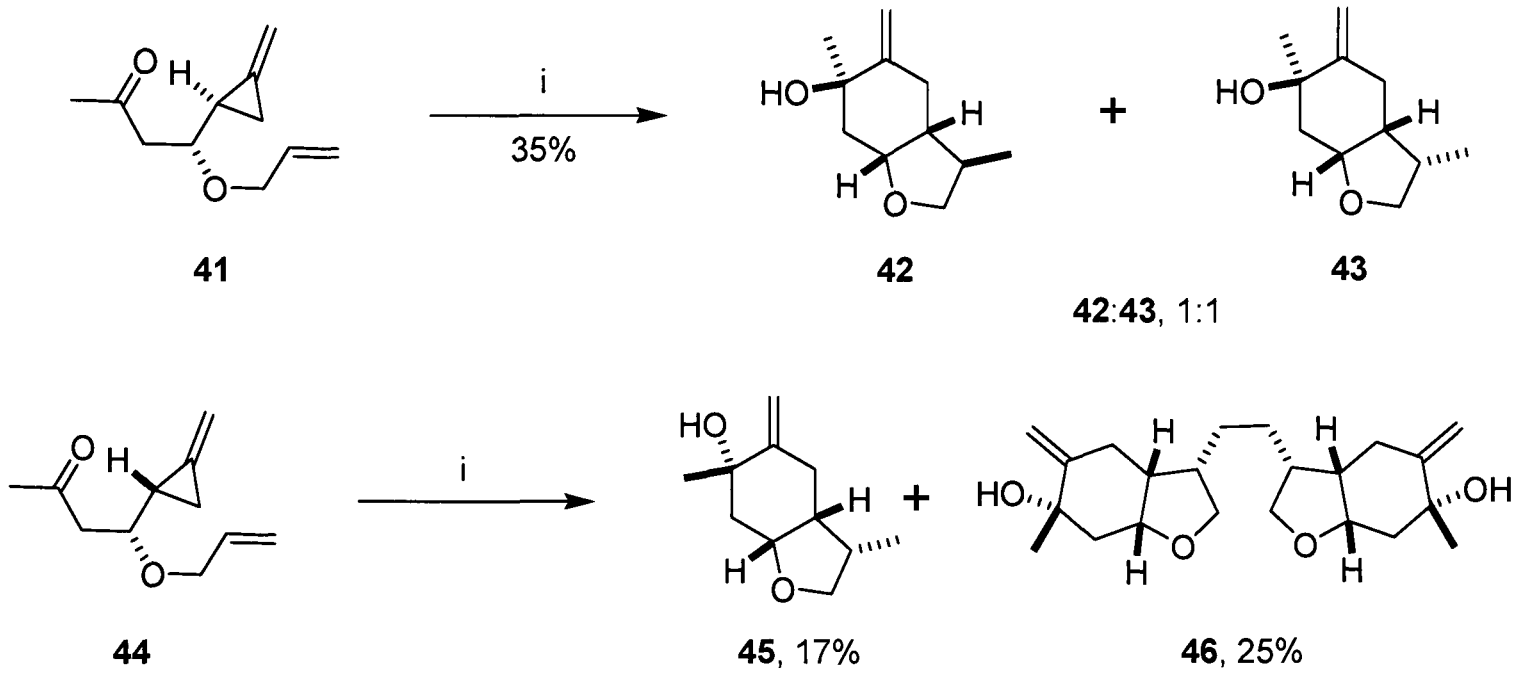
A samarium iodide promoted radical cascade of methylidenecyclopropanes **32** and **33** (Scheme 2.13) allowed the synthesis of monoterpenes (paeonilactone B and *epi*-paeonilactone, **40**).[51, 52]



Scheme 2.13. *Reagents and conditions;* i, SmI_2, HMPA, THF, *t*-BuOH, 0 °C.

In terms of the mechanism, the cascade works on the same principle as carbocyclic ring-expansion shown in Scheme 2.10. Ketyl radical **36** undergoes a 5-*exo*-trig cyclisation to form cyclopropylmethyl intermediate **37**, which rearranges to the homoallyl radical **38**. A 5-*exo*-dig cyclisation forms the fused bicycle **39** and abstracts a proton from 2-methylpropan-2-ol (Scheme 2.13). The different diastereoisomers **32** and **33** afforded a mixture of perhydrobenzofurans in good selectivities; **32** furnished **34** and **33** afforded **35** preferentially (Scheme 2.13). Kilburn postulated that this selectivity arose from the different conformational preferences of the two diastereoisomers in the transition state of the initial 5-*exo*-trig cyclisation.[51, 52]

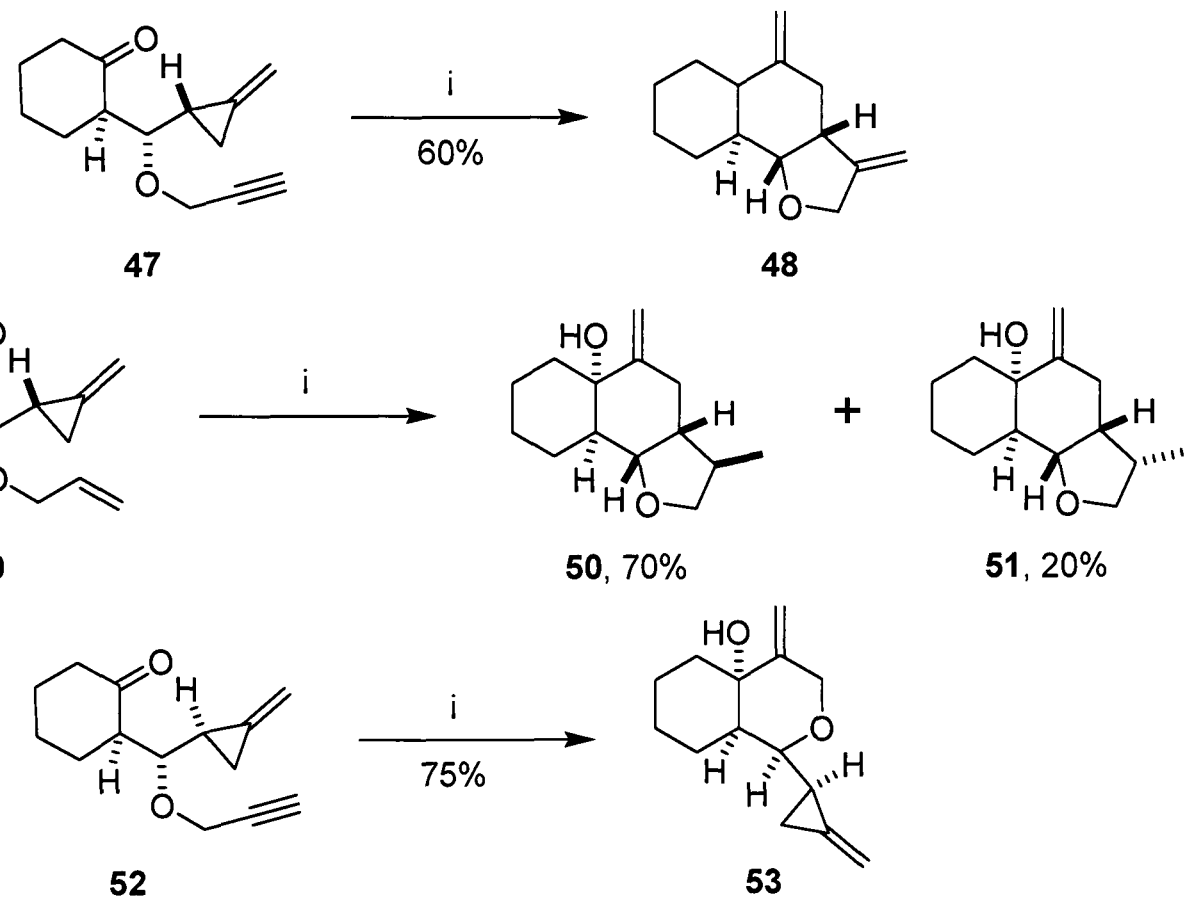
Kilburn and co-workers extended the study and investigated the construction of a fourth stereocentre (*i.e.* a homoallyl radical undergoing a 5-*exo*-trigcyclisation onto an olefin as opposed to an alkyne, Scheme 2.14), in the synthesis of a key intermediate of paeonilcatone A.[52, 53]



Scheme 2.14. *Reagents and conditions;* i, SmI_2, HMPA, THF, *t*-BuOH, 0 °C.

Diastereoisomers **41** and **44** gave the same high stereocontrol as their alkyne congeners (Scheme 2.13) in terms of the bridgehead and carbinol stereocentres; however divergent behaviour was observed with respect to the new stereocentre (Scheme 2.14). While diastereoisomer **41** furnished the two cyclic ethers **42** and **43** with no selectivity and low yield, diastereoisomer **44** gave cyclic ether **45**, together with the *meso*-dimer product **46**. All the stereogenic centres in both portions of the dimer are of the same relative configuration as **45**. It is of note that this was the only dimer product obtained, meaning dimerisation only occurs between two radicals that are opposite enantiomers.

Tricyclic products were obtained when the starting methylidenecyclpropane included a cyclic ketone to start the radical cascade (Scheme 2.15). Propargyl ether **47** cyclised to tricycle **48** in good yield, while allyl ether **49** cyclised to give a mixture of **50** and **51** (90% yield, 3.5:1 ratio of products respectively). If the solvent system is changed to tetrahydrofuran, 2-methyl-2-propanol and hexamethylphosphoric triamide, the selectivitites of **50**:**51** are reversed (10:1 respectively, although the yield is lower at 55%); Kilburn explained this observation by the comformation of the transition state for the final cyclisation - hexamethylphosphoric triamide favours a non-chelation model.[54]

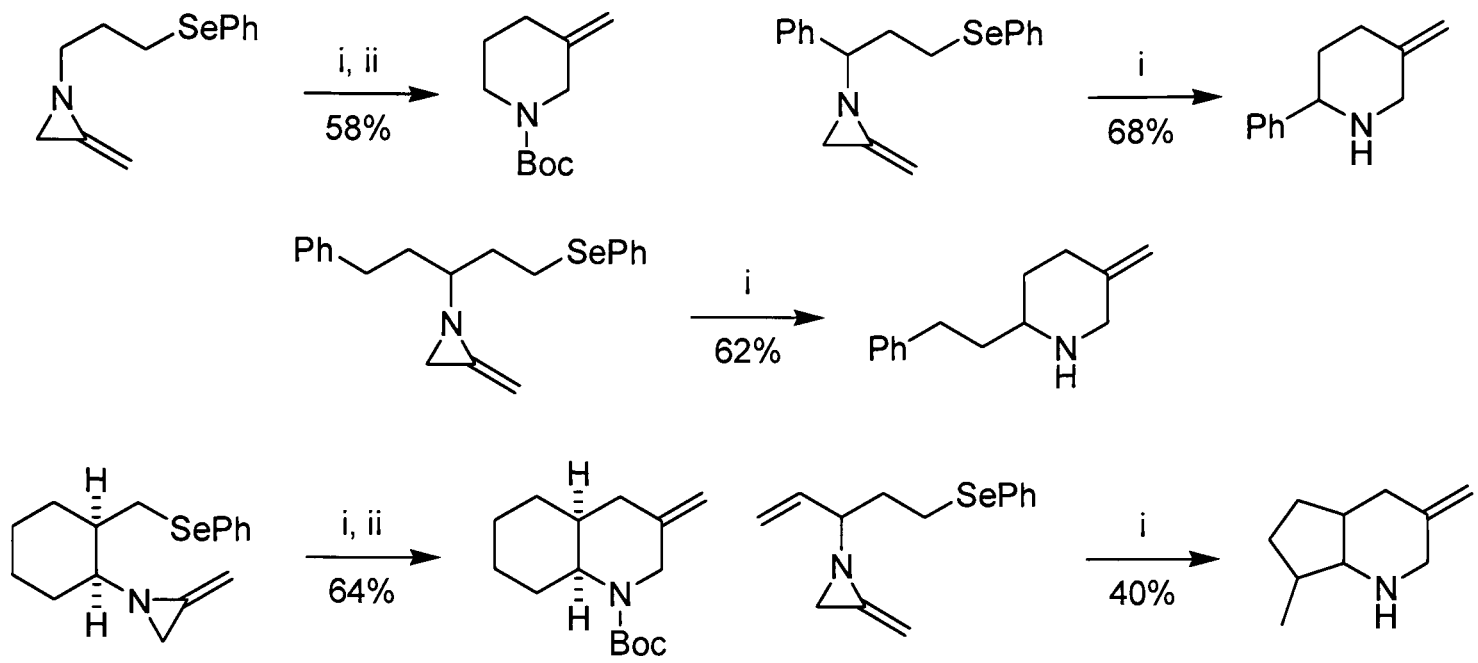


Scheme 2.15. *Reagents and conditions;* i, SmI_2, HMPA, THF:MeOH (4:1), *t*-BuOH, –78 °C.

When diastereosiomers **52** and **54** were cyclised, the 6-*exo* product from attack onto the alkyne or olefin was observed (fused bicycles **53** and **55** respectively). Presumably this is caused by the conformation of the initial radical, favouring attack onto the propargyl- or allyl-ether over the methylidenecyclopropane.

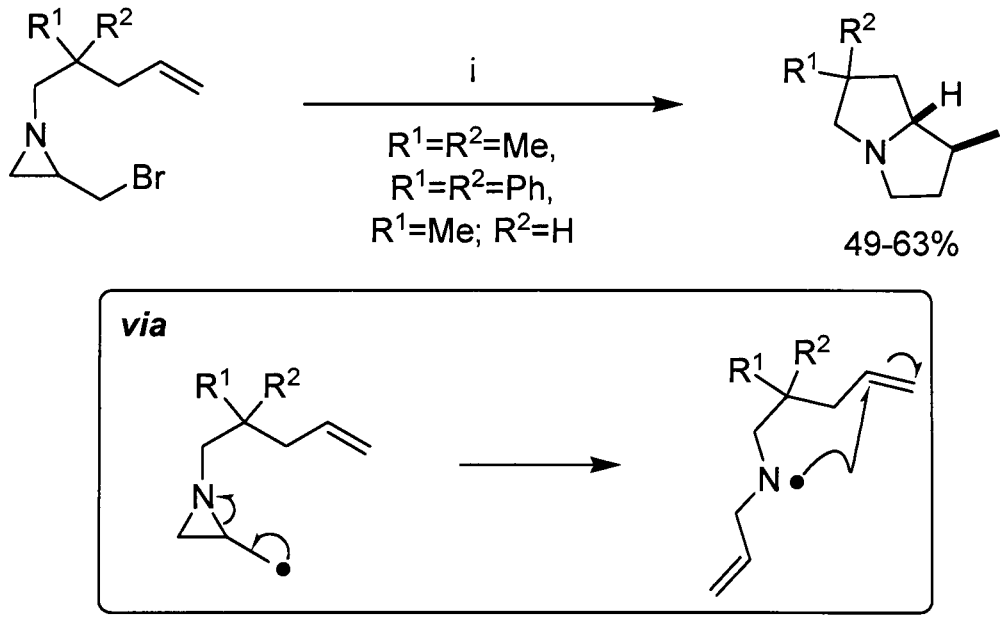
2.5 *Aziridine radical ring-expansions.*

Computational analysis has shown that the energy barrier for the cleavage of the C-C bond in aziridine is high (40.8 kJ mol^{-1}), while that for the C-N bond is much lower (15.4 kJ mol^{-1}). Hence the ring-opening by C-N bond cleavage is kinetically preferred even though the product is distinctly less stable.[55]



Scheme 2.16. *Reagents and conditions;* i, Bu_3SnH and AIBN, PhH, syringe pump addition, Δ; ii, Boc_2O, Et_3N.

Inspired by the work of Kilburn, Shipman and Prévost have published a radical rearrangement of 2-methyleneaziridines and applied it to the synthesis of substituted piperidines, dehydroquinolines and octahyroindolizines (Scheme 2.16).[56, 57] The mechanism follows the same pathway as that shown in Scheme 2.10; the ring-cleavage is now facilitated by the low energy barrier of C-N bond cleavage in aziridines.

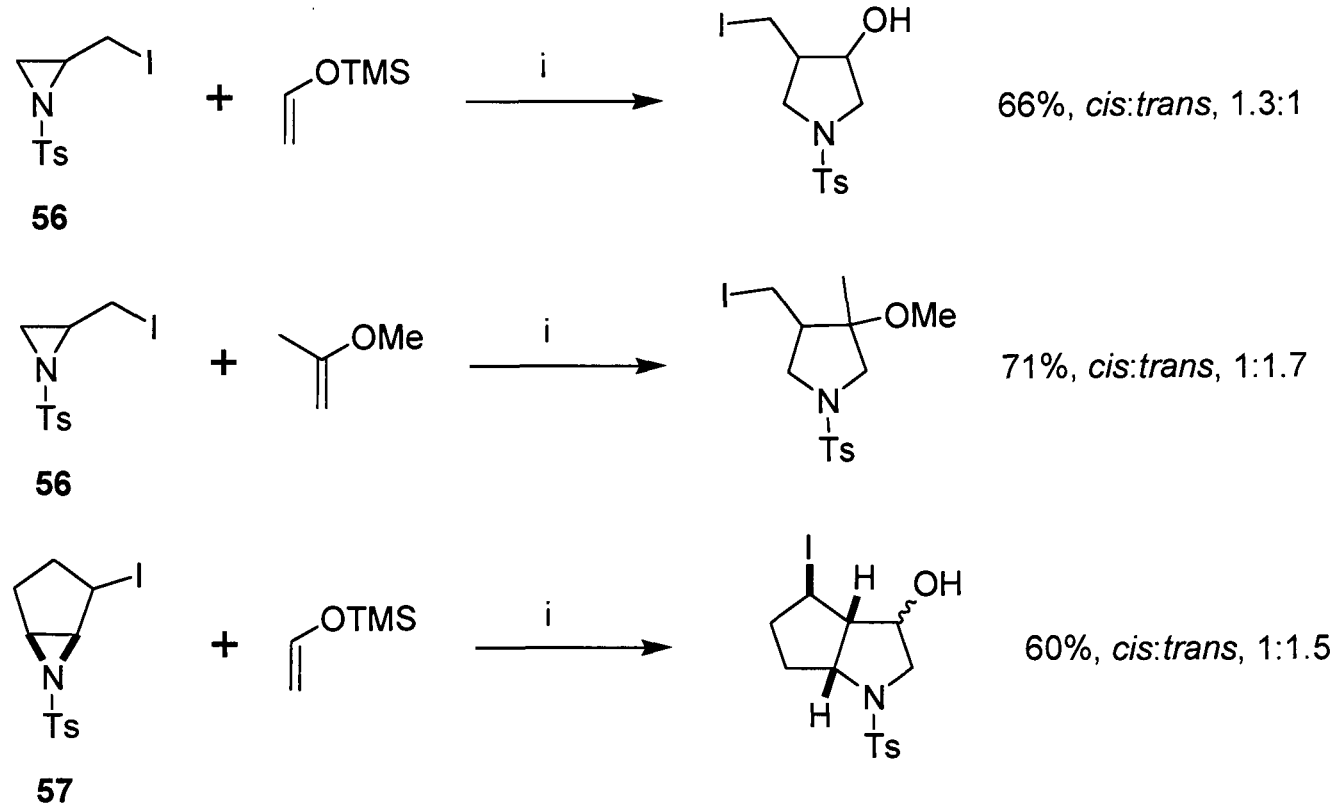


Scheme 2.17. *Reagents and conditions;* i, Bu_3SnH and AIBN, PhH, syringe pump addition, Δ.

[3+2] Cycloadditions of homoallyl radicals with an olefin is an attractive route to the cyclopenatanoid skeleton as it allows the synthesis of the aforementioned compounds in one step from a cyclopropylcarbinyl moiety.[58] De Kimpe has taken advantage of the analogous

aziridine to azahomoallyl rearrangement in the synthesis of a variety of fused pyrrolidines (Scheme 2.17).[59]

Taguchi and co-workers have recently extended this reaction to form pyrrolidines by the generation of an azahomoallyl radical.[60, 61] Taguchi postulated that use of electron deficient *N*-tosyl protected aziridines would produce a more electron deficient azahomoallyl radical which would therefore be more reactive towards electron rich olefins. Electron deficient aziridines **56** and **57** underwent cycloaddition to form pyrrolidines in good yields, although the *cis/trans* selectivities were poor (Scheme 2.18).

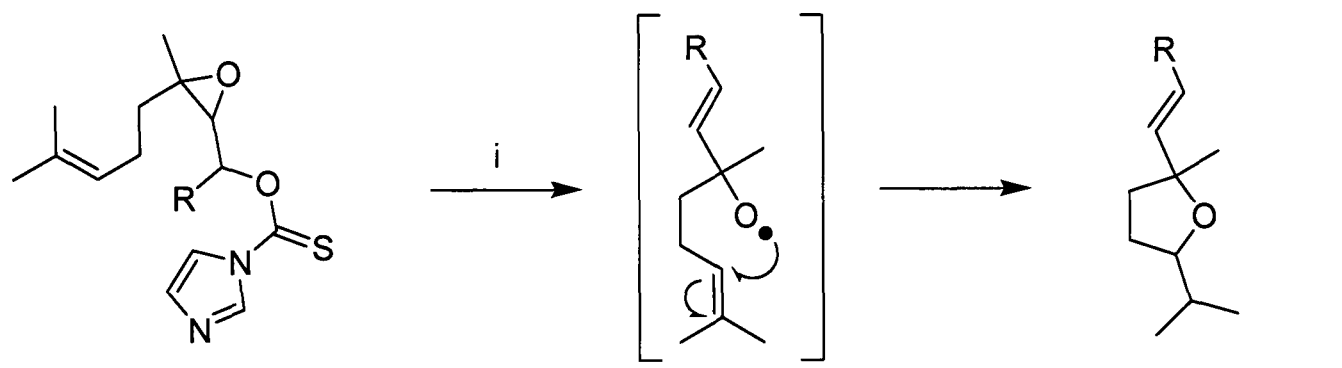


Scheme 2.18. *Reagents and conditions;* i, Et_3B, O_2, CH_2Cl_2; then $HCl_{(aq)}$.

2.6 *Epoxide radical ring-expansions.*

Alkoxide radicals have been known for some time but it was not until Murphy and Johns published the 5-*exo*- and 6-*exo*-trig alkoxide radical cyclisations (Scheme 2.19)[62] that alkoxide radicals had been used in anything other than simple reduction.[63, 64] Upon treatment with tri-*n*-butyltin hydride, radical precursors **58a-c** fragmented to give vinyl alkoxide radical **59**, which underwent a 5-*exo*-trig cyclisation to form tetrahydrofurans **60a-c** in low to moderate yields (Scheme 2.19). Epoxide **61** fragemented in an analogous manner and gave radical species **62** that cyclised to generate tetrahydropyran **63**. Walton and co-workers

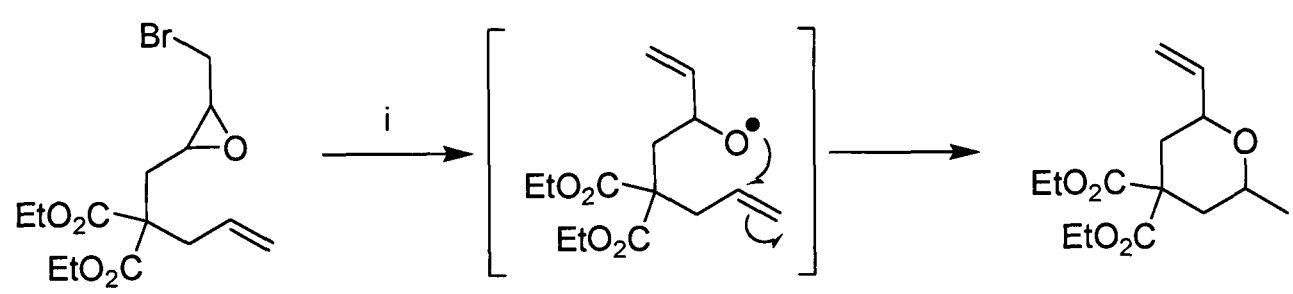
reported a very similar 5-*exo*-trig cyclisation to form tetrahydrofurans from an epoxide bearing an *exo*-cyclic methylbromide moiety.[65] Although the first cyclisation reactions, using the alkoxide radical generated from the fragmentation of an epoxide, were used to prepare oxygen containing heterocycles, the majority of the research into this area has focused on the use of alkoxide radicals in the preparation of various carbocycles.[66]



58a, R=H,
58b, R=Me,
58c, R=*n*-Bu.

59

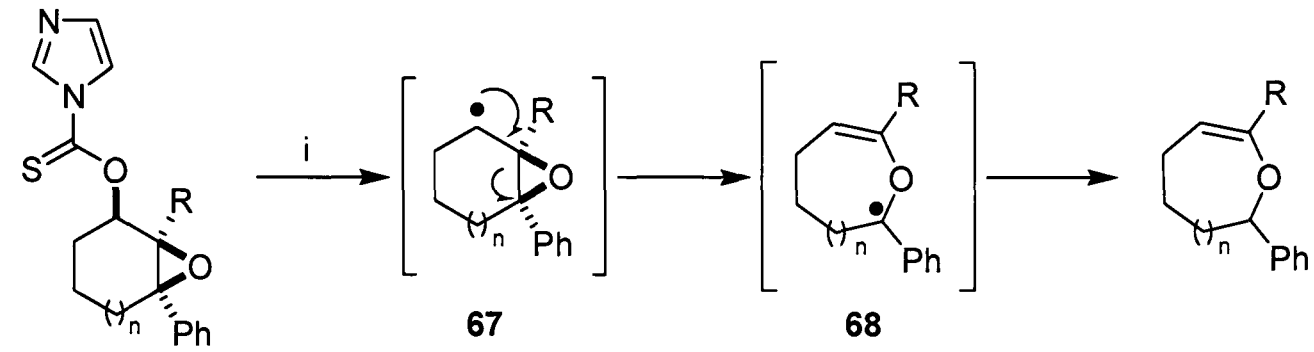
60a, R=H, 14%,
60b, R=Me, 53%,
60c, R=*n*-Bu, 63%.



61 **62** **63**, 27%

Scheme 2.19. *Reagents and conditions;* i, Bu_3SnH, AIBN, PhH, Δ.

Marples and co-workers utilised the radical fragmenation of epoxides to furnish ring-expanded enol ethers (Scheme 2.20).[67] Cyclic epoxides **64-66** were treated with tri-*n*-butyltin hydride and gave intermediate radical **67** that fragmented to the more stable benzylic radical **68**, before abstraction of a hydrogen atom furnished the cyclic enol ethers **69-71** in moderate to good yields (Scheme 2.20). In contrast to the analogous oxiranylcarbinyl system (Scheme 2.20), 3-arylaziridinylcarbinyl radicals have been shown to give only C-N bond cleavage products and not the expected ring-expanded enamines.[68]



64, R=H, n=1,
65, R=H, n=2,
66, R=Me, n=1.

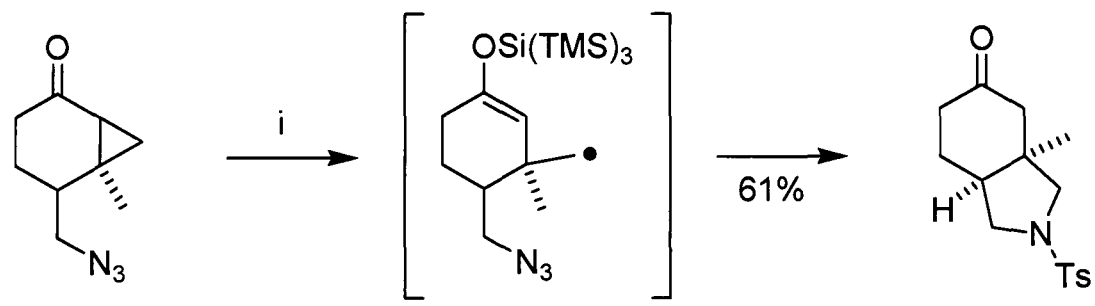
67 **68**

69, R=H, n=1, 72%,
70, R=H, n=2, 66%,
71, R=Me, n=1, 58%.

Scheme 2.20. *Reagents and conditions;* i, Bu_3SnH, AIBN, PhH, Δ.

2.7 *Miscellaneous radical ring-expansions.*

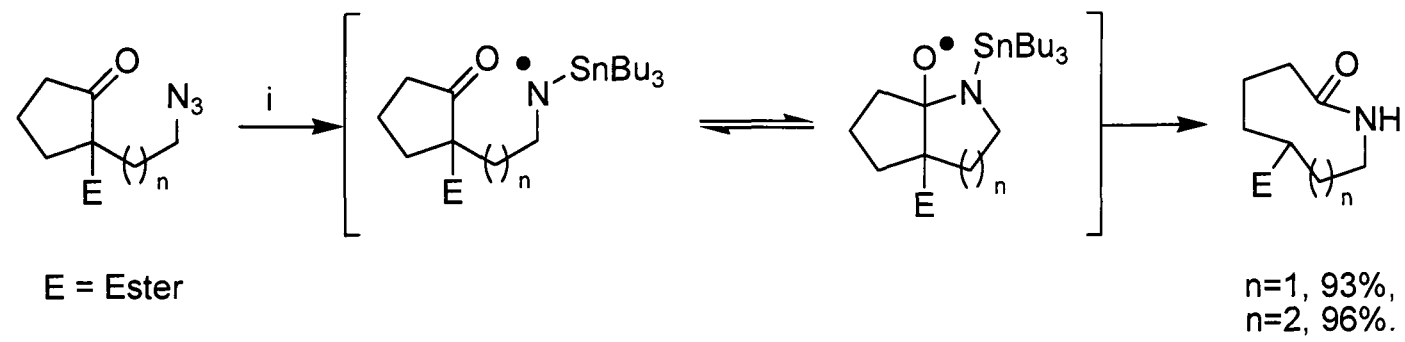
Kim and co-workers found that a keto group α to a cyclopropyl could be used as a radical initiator in the synthesis of fused pyrrolidines (Scheme 2.21).[69] Ketone **72** produced intermediate radical **73** *via* a β-fragmentation of the cyclopropyl ring, which cyclised onto the azide moiety *via* a 5-*exo*-trig process to furnish bicycle **74** (Scheme 2.21).



72 **73** **74**

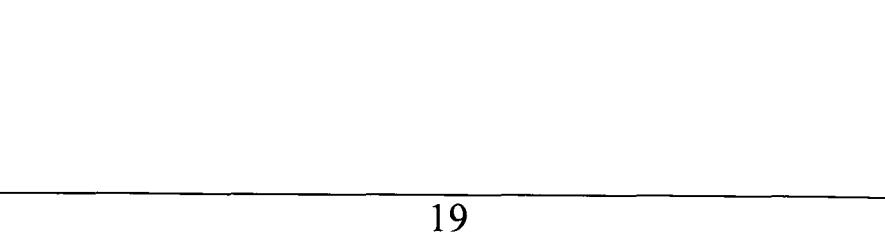
Scheme 2.21. *Reagents and conditions;* i, $(TMS)_3SiH$, AIBN, PhH, Δ; then TsCl, DMAP.

When an azide was used as precursor to an aminyl radical, addition onto a cyclic ketone furnished ring-expanded lactams high yields (Scheme 2.22).[70]



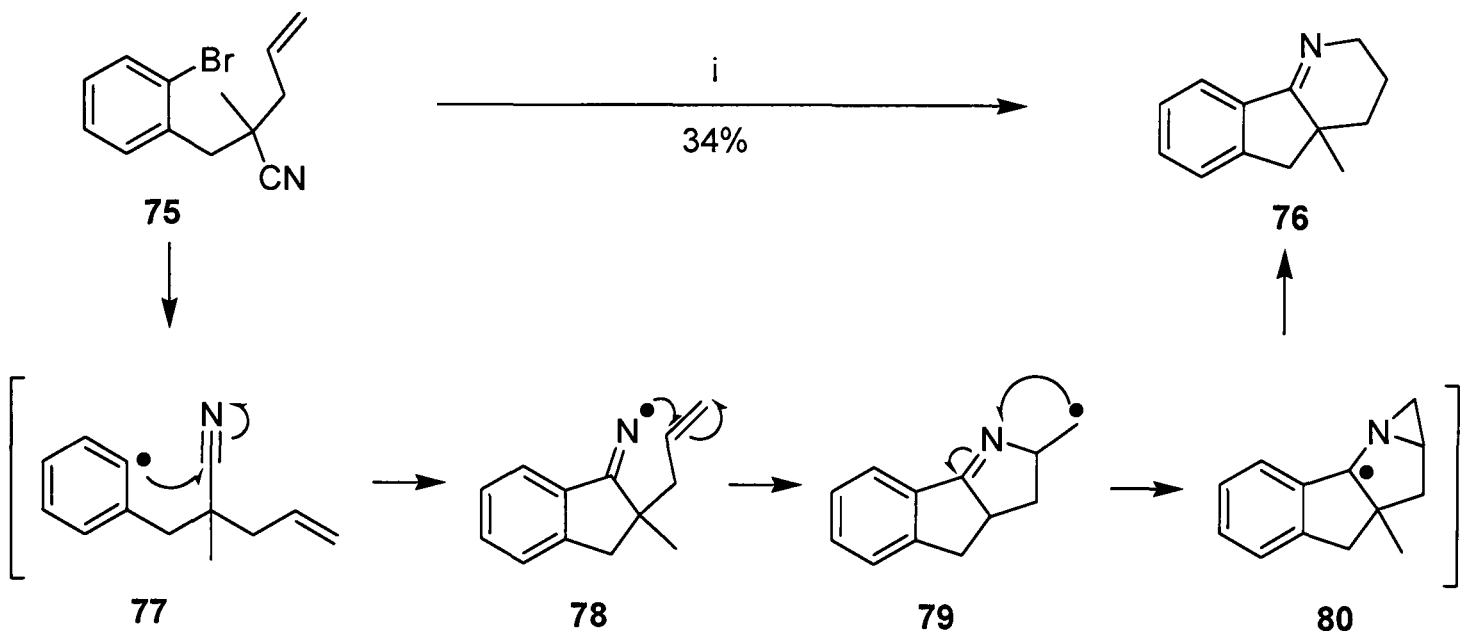
Scheme 2.22. *Reagents and conditions;* i, Bu_3SnH, AIBN, PhH, Δ.

Extending the ring-expansion of radicals through a methylidenecyclopropane, Kilburn and Santogostino formed an aza-spirocycle (Scheme 2.23) by ring-expansion followed by a 5-*exo* cyclisation onto the azide moiety.[71]



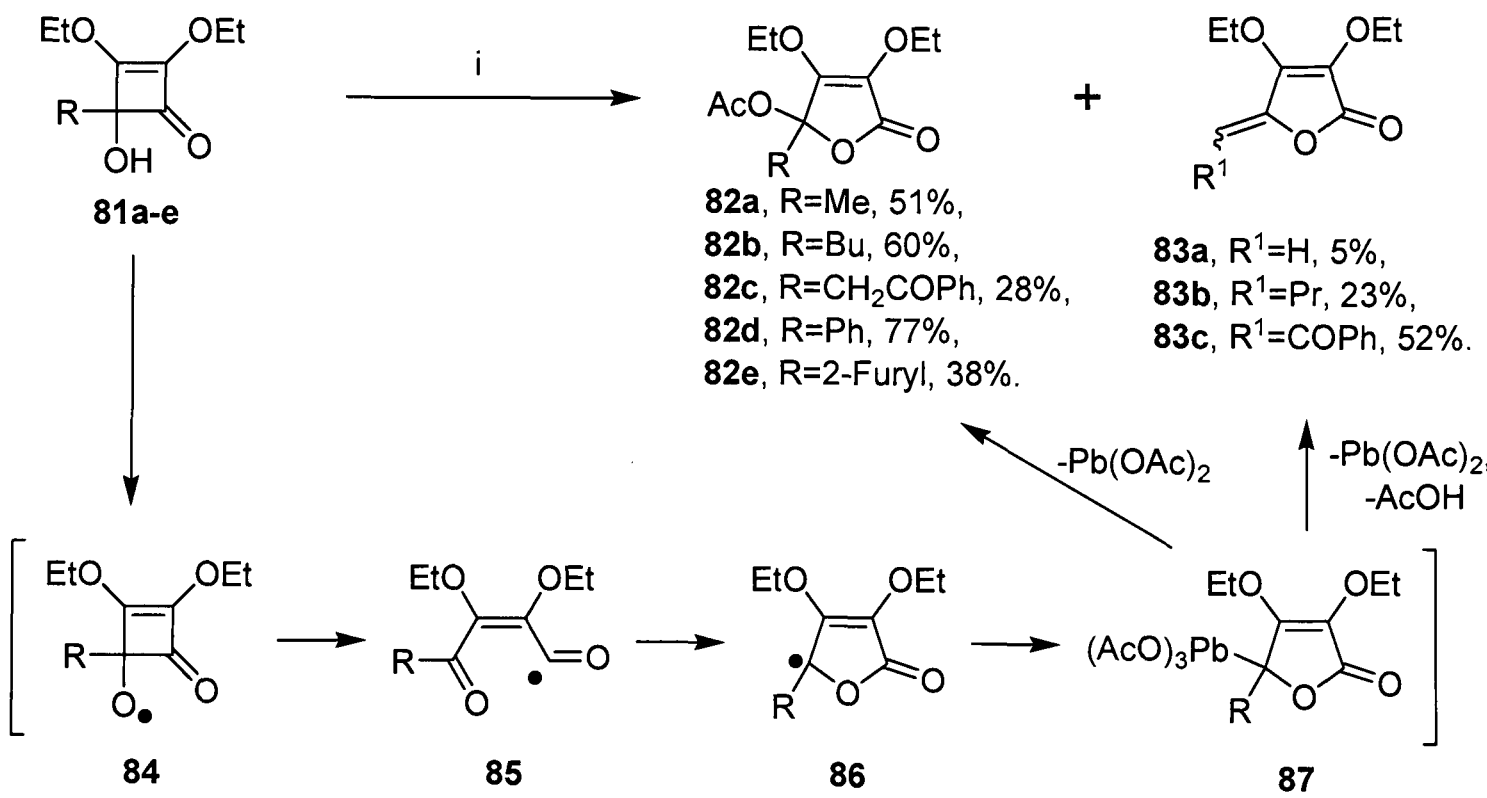
Scheme 2.23. *Reagents and conditions;* i, $(TMS)_3SiH$, AIBN, PhH, Δ; then TsCl, DMAP.

Bowman and co-workers found that nitrile **75** was smoothly converted to tricycle **76** by a tandem cyclisation and ring-expansion sequence (Scheme 2.24).[72] Radical **77** attacked the nitrile moiety in a 5-*exo*-dig cyclisation which gave species **78**. Iminyl radical **78** underwent a 5-*exo*-trig cyclisation and the carbon radical **79** rearranged to the doubly stabilised α-aminyl benzylic radical **80**. Bowman postulated that a 6-*endo* cyclisation did not occur (*i.e.* **78** to **76**) as this would not allow the formation of the thermodynamically stable benzylic aminyl radical **80** (Scheme 2.24).



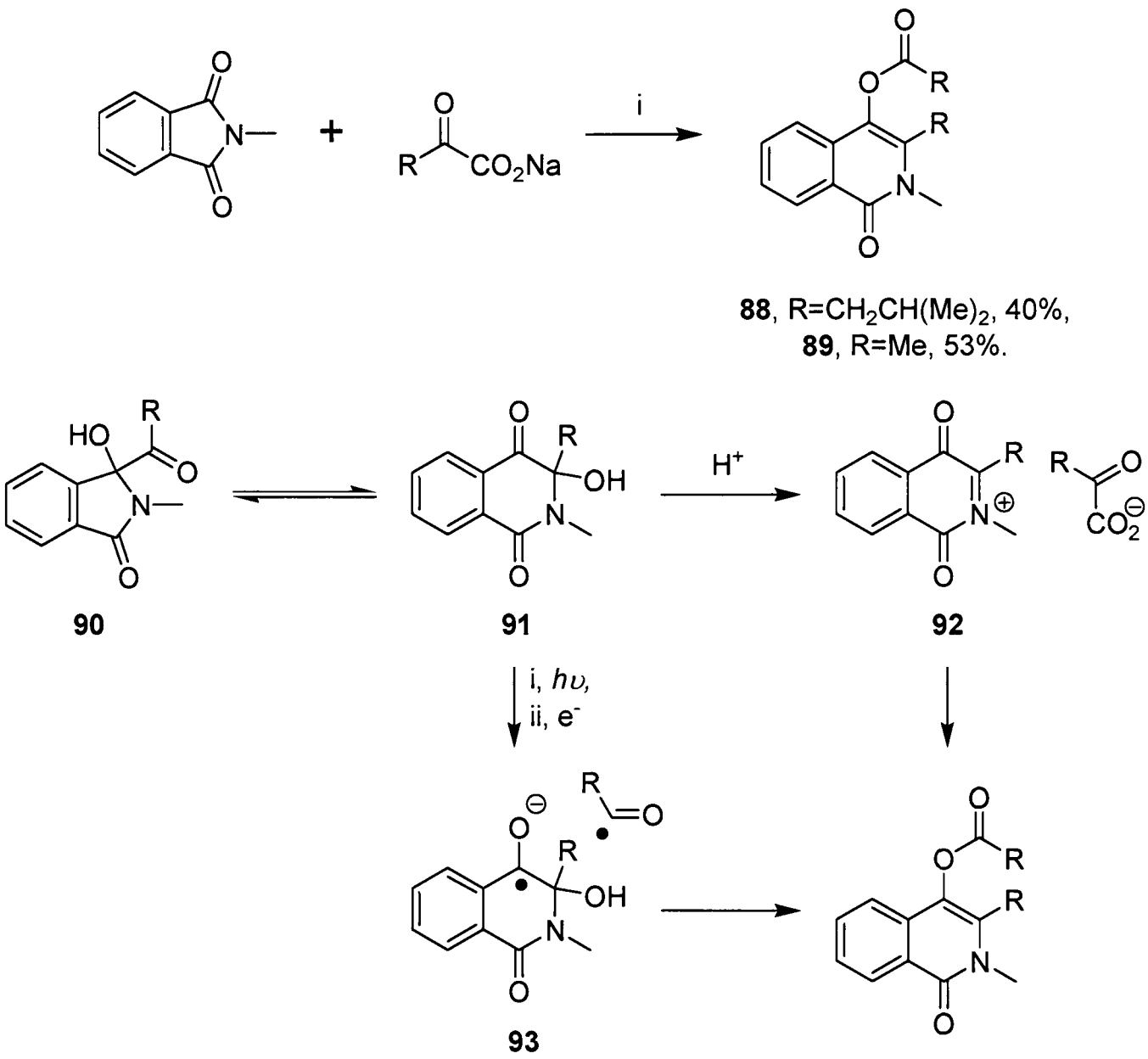
Scheme 2.24. *Reagents and conditions;* i, Bu_3SnH and AIBN, PhMe, 3 hour syringe pump addition, PhMe, Δ.

The radical mediated ring-expansion of cyclobutenones has been reported by Eguchi and co-workers.[73] Treatment of cyclobutenones **81a-e** with lead tetraacetate furnished furanones **82a-e** and **83a-c** (Scheme 2.25). Alkoxide radical **84** undergoes β-scission to produce acyl radical **85**. 5-*Endo* cyclisation onto the carbonyl oxygen gives radical furanone **86**, which can recombine with lead tetraacetate to produce intermediate **87**. Reductive elimination of lead$^{(II)}$ acetate furnishes furanones **82**, whilst loss of lead$^{(II)}$ acetate and acetic acid yields furanones **83a-c** (Scheme 2.25).



Scheme 2.25. *Reagents and conditions;* i, $Pb(OAc)_4$, PhMe, room temperature.

Finally Griesbeck and co-workers reported a ring-expansion of a phthalimide during their studies on photodecarboxylative additions of α-keto carboxylates to phthalimides (Scheme 2.26).[74] The exact mode of ring-expansion is not know, although it is believed that **90** ring-expands to intermediate species **91**. Griesbeck postulates that **91** can either undergo an acid catalysed elimination of water to form **92**, which can then tautomerise and acylate to form **88/89**; or **91** can accept an electron to form ketyl radical **93** which can combine with an acyl radical and extrude water to furnish **88/89** (Scheme 2.26).



Scheme 2.26. *Reagents and conditions;* i, *hv*, acetone, 20% H_2O, room temperature

Chapter 3

Introduction – Synthesis of Piperidines and Pyrrolidines

3.1 *General introduction.*

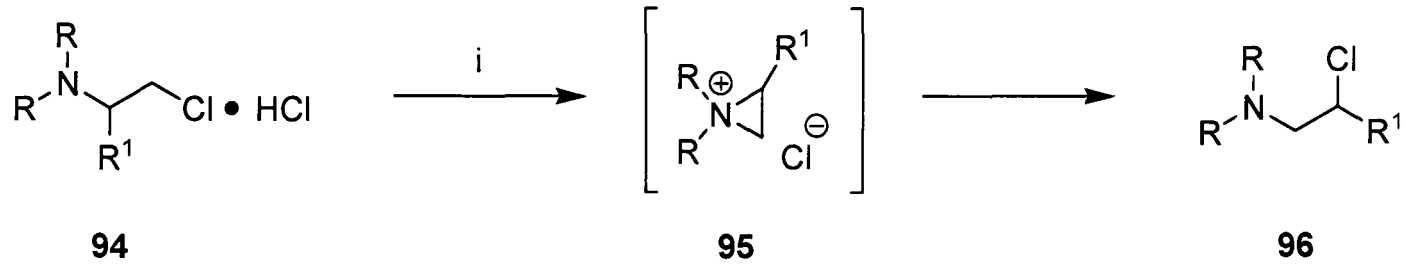
The functionalised piperidine motif is prevalent in natural products; such compounds are of great interest in the pharmaceutical industry due to their extensive range of biological activities. The synthesis of functionalised piperidines has been thoroughly scrutinised and many reviews have appeared.[15-17, 75-81] Much of the literature is focused on ring-forming reactions and over recent years attention has turned to the stereoselective synthesis of functionalised piperidines.[82, 83]

This thesis is concerned with the synthesis of heterocycles *via* rearrangements; hence the remainder of this chapter will focus on the synthesis of pyrrolidines and piperidines by ring-expansion processes.

3.2 *One carbon ring-expansions to form functionalised piperidines.*

The rearrangement of 1,2-aminochloroalkanes was first reported in 1947 (Scheme 3.1).[84-88] Various 1,2-aminochloroalkanes (Such as **94**) were treated with aqueous sodium

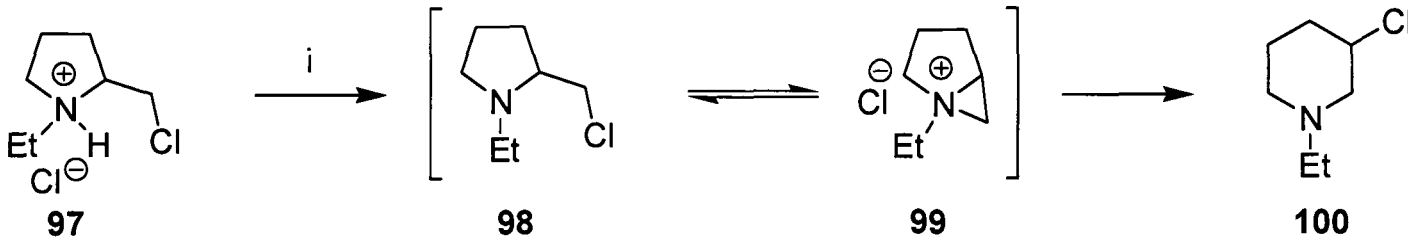
hydroxide to give intermidate an aziridinium ion (**95**), which ring-opened to furnish the corresponding isomerised aminochloroalkane (**96**).



94 **95** **96**

Scheme 3.1. *Reagents and conditions*: i, $NaOH_{(aq)}$, Δ.

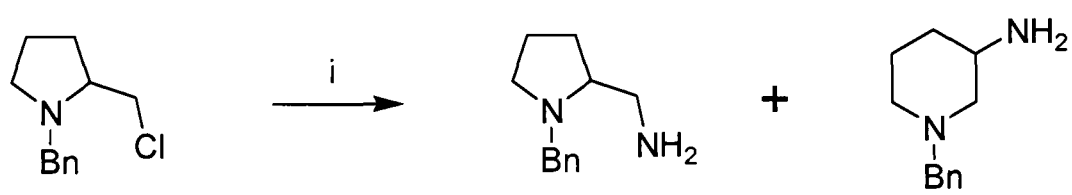
Zirkle and Fuson extended the rearrangement to encompass pyrrolidines (Scheme 3.2).[89] Treatment of hydrochloric salt **97** with aqueous sodium hydroxide liberated pyrrolidine **98** which rearranged to the aziridinium ion **99**; this then ring-opened to afford the more thermodynamically stable piperidine **100** (Scheme 3.2). Hammer and co-workers carried out synthetic, kinetic and stereochemical studies and discovered that the rearrangement was i) a two step process (*via* the aziridinium ion **99** postulated by Zirkle and Fuson);[90, 91] ii) completely stereoselective and iii) obeyed a simple first-order rate law.[92]



97 **98** **99** **100**

Scheme 3.2. *Reagents and conditions*: i, $NaOH_{(aq)}$, Δ.

Similarly the rearrangement of pyrrolidines to piperidines using the benzyl protected pyrrolidine **101** has also been reported (Scheme 3.3).[93] Treatment of either pyrrolidine **101** with sodium azide in aqueous alcohol, followed by reduction with lithium aluminium hydride gave an inseparable mix of pyrrolidine **102** and piperidine **103**.

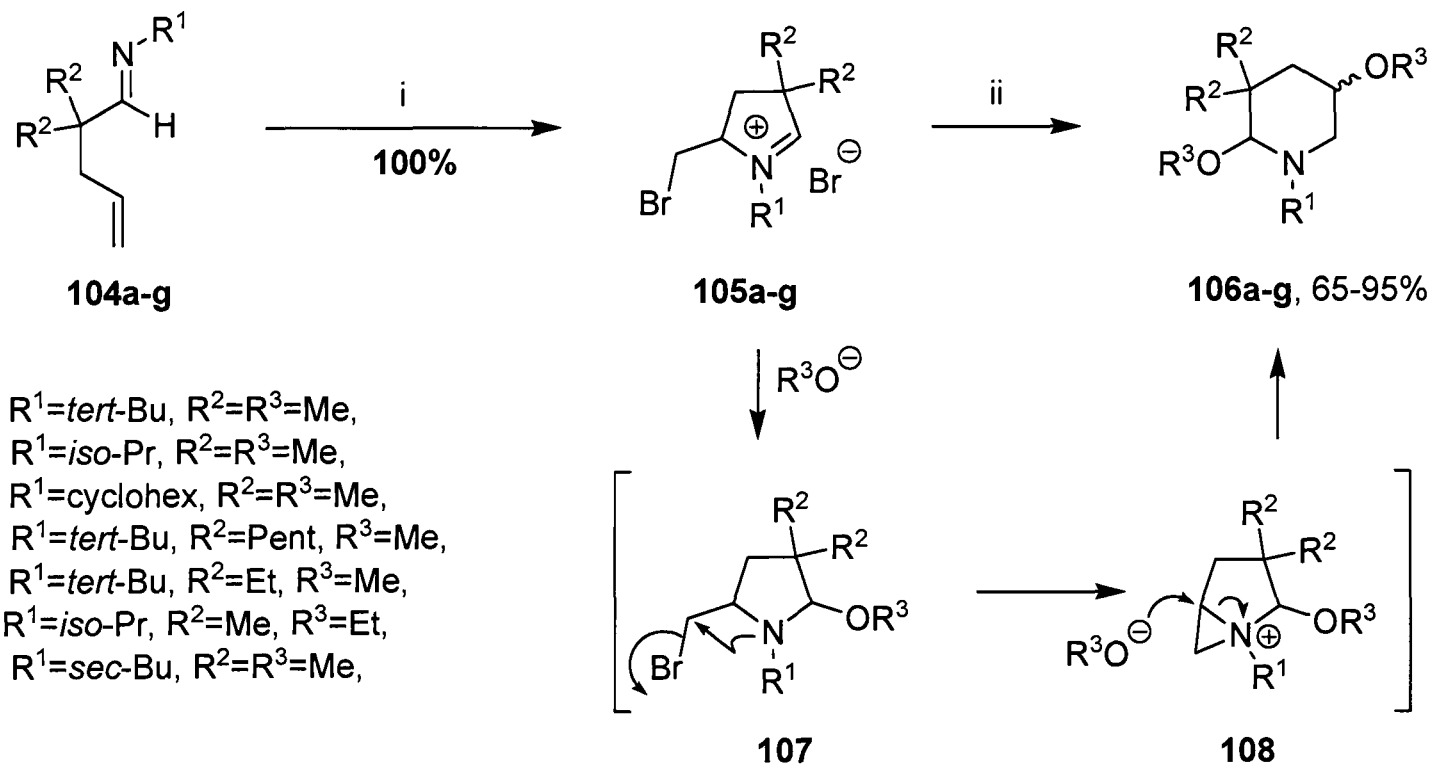


101 **102** **103**

Scheme 3.3. *Reagents and conditions*: i, NaN_3, aqueous alcohol, Δ; then $LiAlH_4$, ether, Δ.

Fasicularin and cylindricines A and B undergo interconversion between a fused pyrrolidine to a fused tetrahydropyridine motif *via* a putative azirdinium ion intermediate.[94] The ability of these natural products to damage DNA underlies their biological activities; Gates and co-workers have postulated this biological activity arises from their ability to form a DNA alkylating aziridinium ion intermediate.[95]

Syntheses of 5-(bromomethyl)-1-pyrrolium salts *via* intermediate aziridinium ions (**108**, Scheme 3.4) have been reported by De Kimpe and co-workers.[96, 97] Treatment of imines **104a-g** with bromine furnished pyrrolium salts **105a-g** in quantitative yield. Intermediate adduct **107** was formed on treatment of **105a-g** with basic aqueous alcohol and underwent an elimination to give aziridinium ion **108**, which then selectively ring-opened to yield the piperidines **106a-g** (>95:5, *trans*:*cis*) in moderate to high yields (Scheme 3.4).

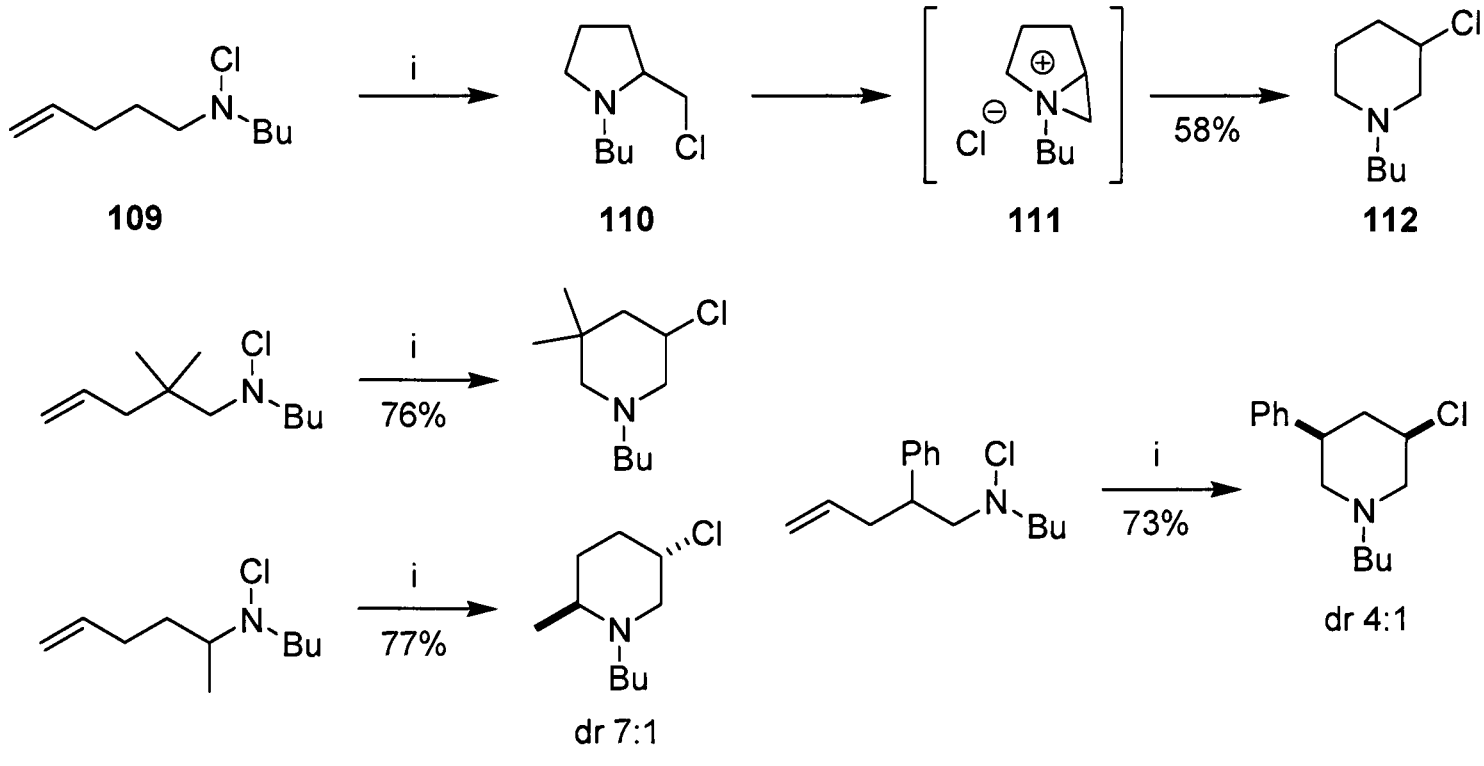


Scheme 3.4. *Reagents and conditions*: i, Br_2, CH_2Cl_2, 0 °C; ii, $NaOR^3$ (1.0-2.0 mol dm^{-3}), R^3OH, Δ.

Göttlich reported the cyclisation of *N*-chloroamines onto double bonds and *in situ* rearrangement of the resultant pyrrolidine to a piperidine (Scheme 3.5).[98] A radical cyclisation of *N*-chloroamine (**109**) in the presence of copper$^{(I)}$ chloride* furnished α-chloromethyl pyrrolidine **110**. Elimination of chlorine formed aziridinium **111,** which was ring-opened by chloride anion to afford piperidine **112**. This approached has allowed the high yielding syntheses of substituted piperidines in moderate stereoselectivities (Scheme 3.5). By

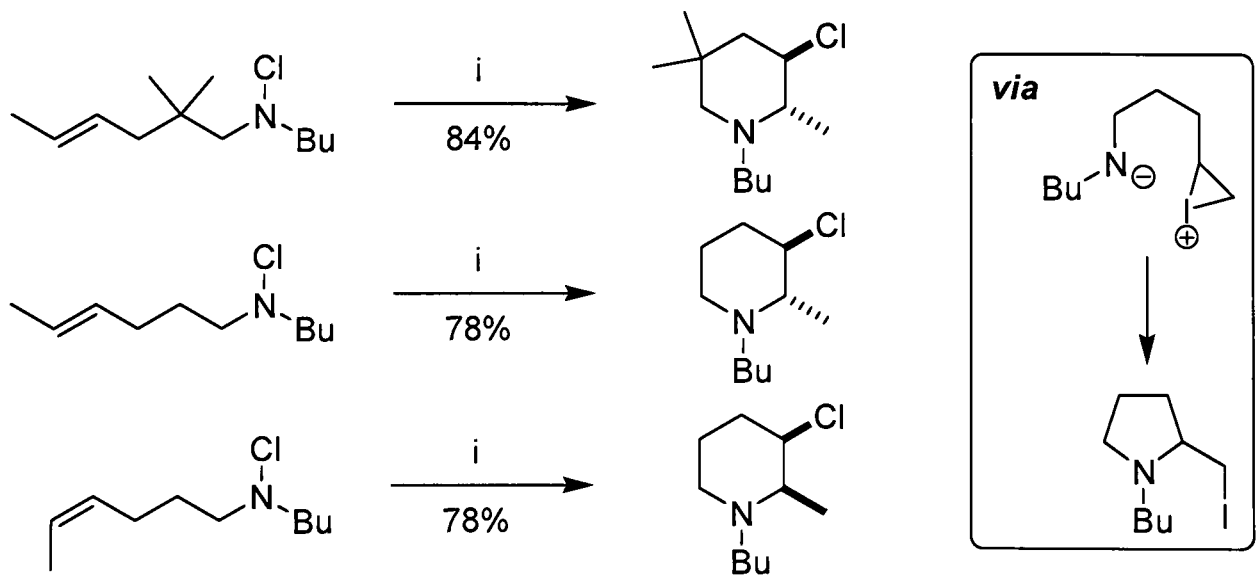
* The high levels of diastereoselectivity observed in this initial cyclisation step are due to the sterically demanding copper complex; the rearrangement of the pyrrolidine to piperidine is completely stereoselective.

changing the copper(I) counterion, the stereoselectivity of the reaction could be vastly improved; however this alteration was detrimental to the yield.[99]



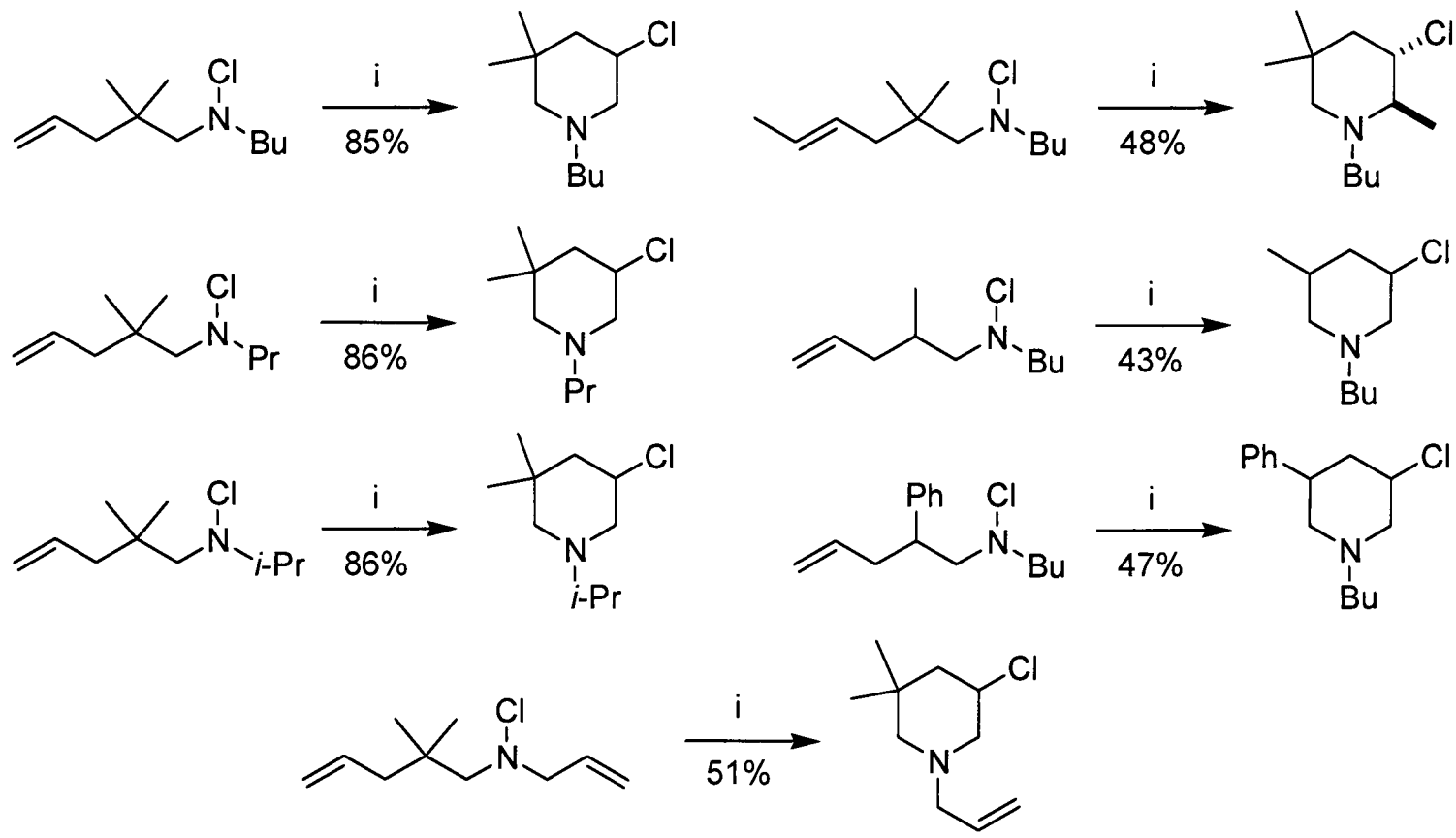
Scheme 3.5. *Reagents and conditions*: i, CuCl (10 mol%), THF, 50 °C.

Göttlich and co-workers extended the cyclisation of *N*-chloroamines and subsequent rearrangement to be induced by a range of catalysts. Samarium iodide has been successfully utilised in the cyclisations shown in Scheme 3.5 to obtain the desired products in comparable yields.[100] Tetra-*n*-butyl ammonium iodide initiated cyclisation *via* a 5-*exo*-trig process onto an iodonium ion which furnished substituted piperidines **113-115** in good yields (Scheme 3.6).[101]



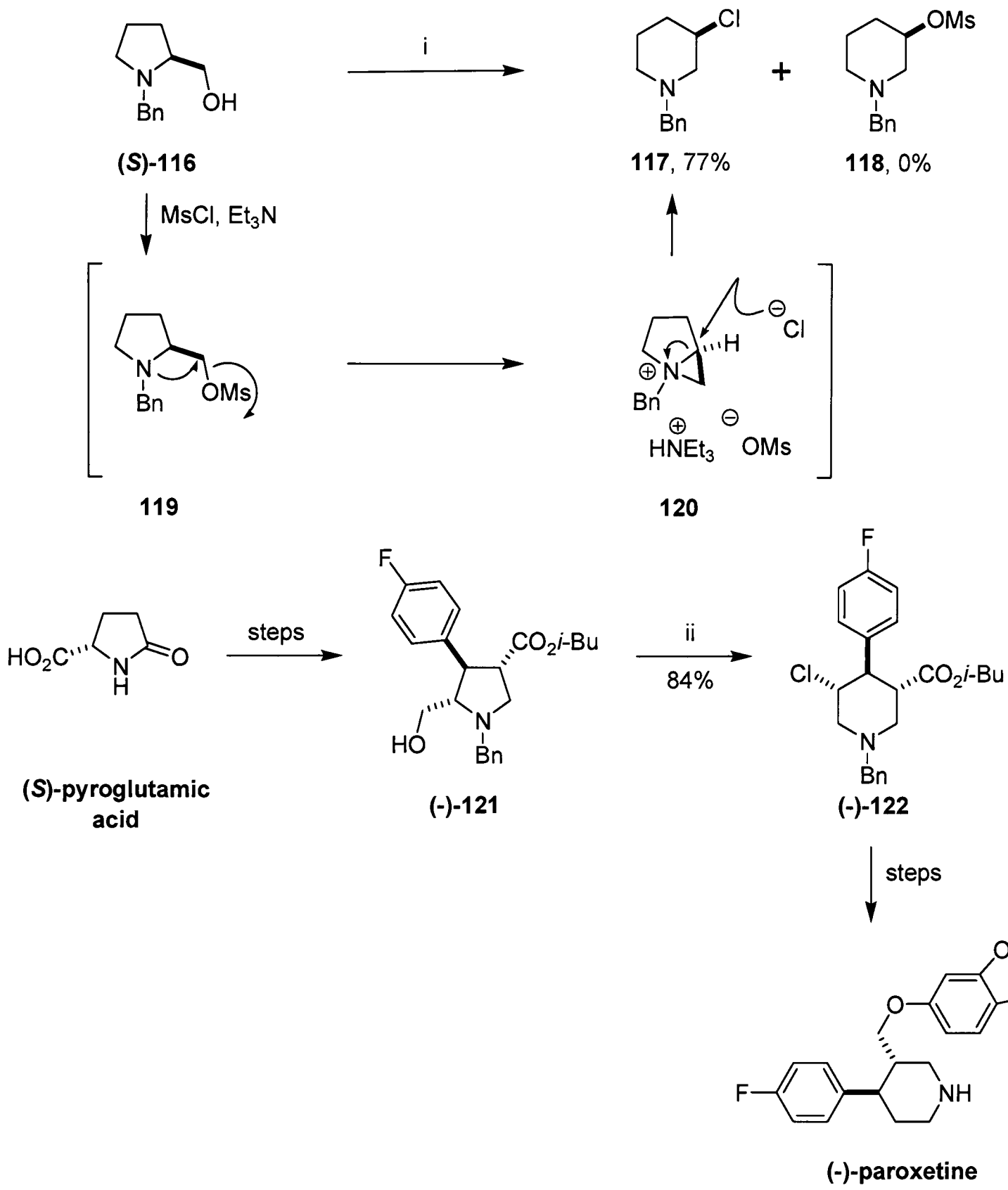
Scheme 3.6. *Reagents and conditions*: i, *n*-BuNI (10 mol%), $CHCl_3$, 50 °C.

Finally Göttlich and Helaja have also shown that palladium is an effective metal to induce cyclisation in a Heck-type reaction before rearrangement (Scheme 3.7).[102]



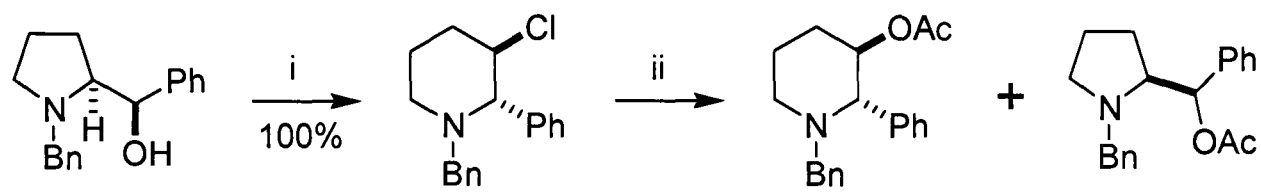
Scheme 3.7. *Reagents and conditions*: i, $Pd(Ph_3)_4$ (1 mol%), THF, room temperature.

Thus far all the rearrangements encountered have been initiated from a pyrrolidine bearing an *exo*-cyclic α-halomethyl moiety. Cossy and co-workers reported that the pyrrolidine to piperidine rearrangement could be initiated from a suitably activated alcohol (Scheme 3.8).[103] This is made particularly useful as the starting pyrrolidines are synthesised from proline derivatives and hence enantiopure piperidines can easily be obtained. When **116** was treated with mesyl chloride and triethylamine, piperidine **117** was obtained in good yield (Scheme 3.8). It was postulated that mesyl compound **119** eliminates the mesyloxy moiety to form aziridiunium ion **120** and the more nucleophilic chloride counter ion ring-opens the aziridinium to form piperidine **117** exclusively – no trace of **118** was observed (Scheme 3.8). This rearrangement has been employed as the key step in the total synthesis of (–)-paroxetine (Scheme 3.8);[104, 105] the ring-expansion precursor **121** was prepared from (*S*)-Pyroglutamic acid and was then converted to piperidine **122** in good yield and excellent selectivity (Scheme 3.8).



Scheme 3.8. *Reagents and conditions*: i, MsCl, Et_3N, THF, Δ; ii, MsCl, $ClCH_2CH_2Cl$, 0 °C → room temperature; then Et_3N, Δ.

Langlois and co-workers found that when pyrrolidine **123** was reacted with the ring-expansion conditions reported by Cossy, piperidine **124** was formed in quantitative yield (Scheme 3.9).[106] Treatment of piperidine **124** with acetic anhydride and sodium acetate gave an 8:2 mixture of piperidine **125** and pyrrolidine **126** (Scheme 3.9). Piperidine **125** was utilised in stereoselective syntheses of precursors to non-peptidic substance P antagonists.[107]

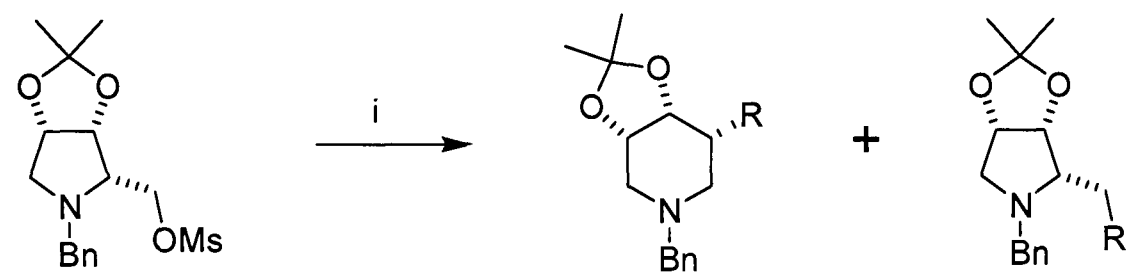


123 **124** **125** **126**

8:2 mixture

Scheme 3.9. *Reagents and conditions*: i, MsCl, Et_3N, THF, Δ; ii, Ac_2O, AcONa, Δ.

The opening of aziridinium ion intermediates with a range of nucleophiles (Scheme 3.10) was investigated by Kim and co-workers.[108] Pyrrolidine **127** was refluxed in *N*,*N*-dimethylformamide to promote elimination to the aziridinium ion in the presence of an external nucleophile; however all the nucleophiles tested gave a mixture of pyrrolidine **128** and piperidine **129** (Scheme 3.10). The best selectivity was obtained with the use of sodium azide as a nucleophile (**128**:**129**; 63:28%).

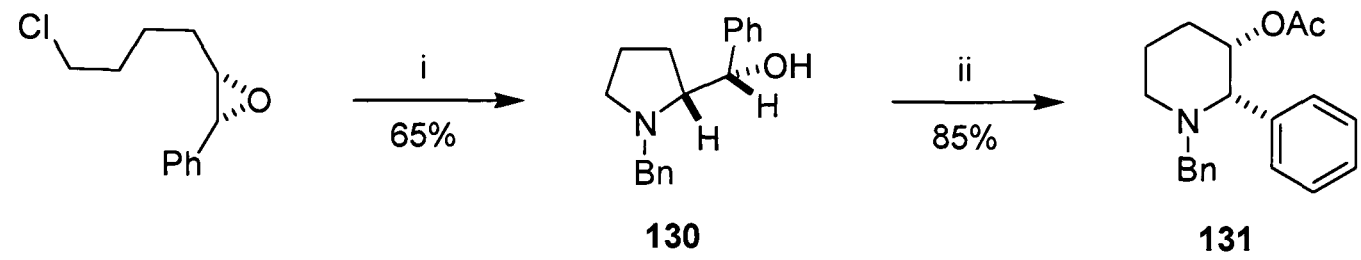


127 **128** **129**

Nu=NaN_3, R=N_3, **128:129**, 63:28%,
Nu=LiN_3, R=N_3, **128:129**, 61:29%,
Nu=AcONa, R=OAc, **128:129**, 55:40%,
Nu=DMF, R=OCHO, **128:129**, 38:50%.

Scheme 3.10. *Reagents and conditions*: i, Nucleophile (Nu), DMF, 100 °C.

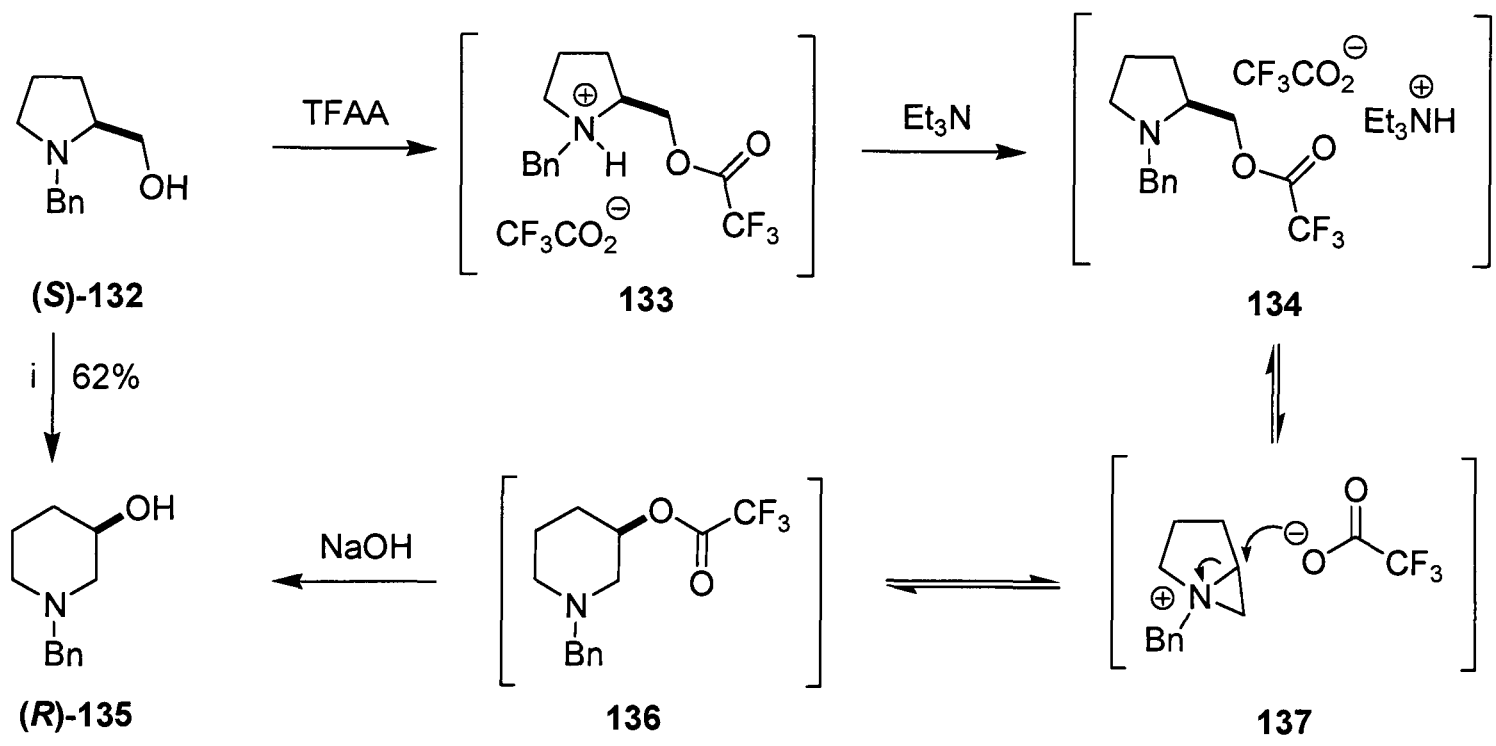
Lee and co-workers at Merck research laboratories, Rahway have extended the mesyl induced rearrangement; the aziridinium ion intermediate was opened with an oxygen nucleophile to furnish the piperidine product exclusively (Scheme 3.11).[109] Pyrrolidine **130** was initially treated with mesyl chloride to form the aziridinium ion intermediate, then tetra-*n*-butylammonium acetate was added to the mixture to afford piperidine **131** in high yield (Scheme 3.11).



130 **131**

Scheme 3.11. *Reagents and conditions*: i, $BnNH_2$, MeCN, Δ;
ii, MsCl, Et_3N, THF, -20 °C; then *n*-Bu_4NOAc, -20 °C → room temperature.

The pyrrolidine to piperidine rearrangement can be induced by the use of a trifluoroacetate activating group (Scheme 3.12)[110] as opposed to the mesyloxy moiety shown in Scheme 3.8. Pyrrolinol derivative **132** was esterified with trifluoroacetic anhydride to give the ammonium species **133**, addition of triethylamine liberates amine **134** which can undergo an elimination to form aziridinium ion **137**. The tight ion pair react to open the aziridine, giving trifluoroacetate **136** which upon saponification yields the 3-hydroxy piperidine **135** (Scheme 3.12).

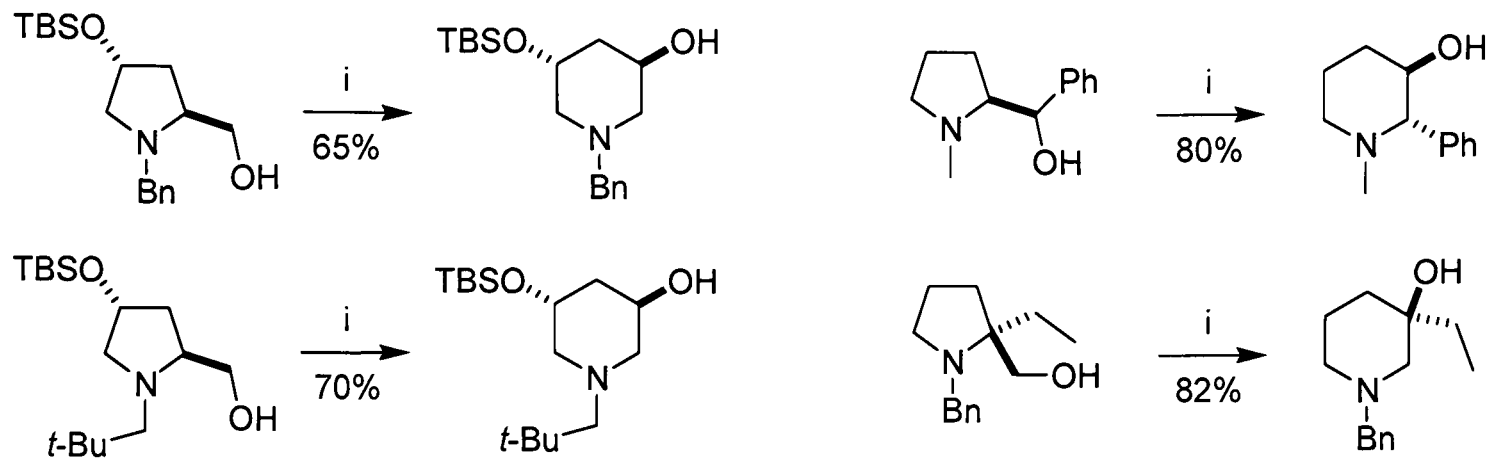


(*S*)-132 **133** **134**

(*R*)-135 **136** **137**

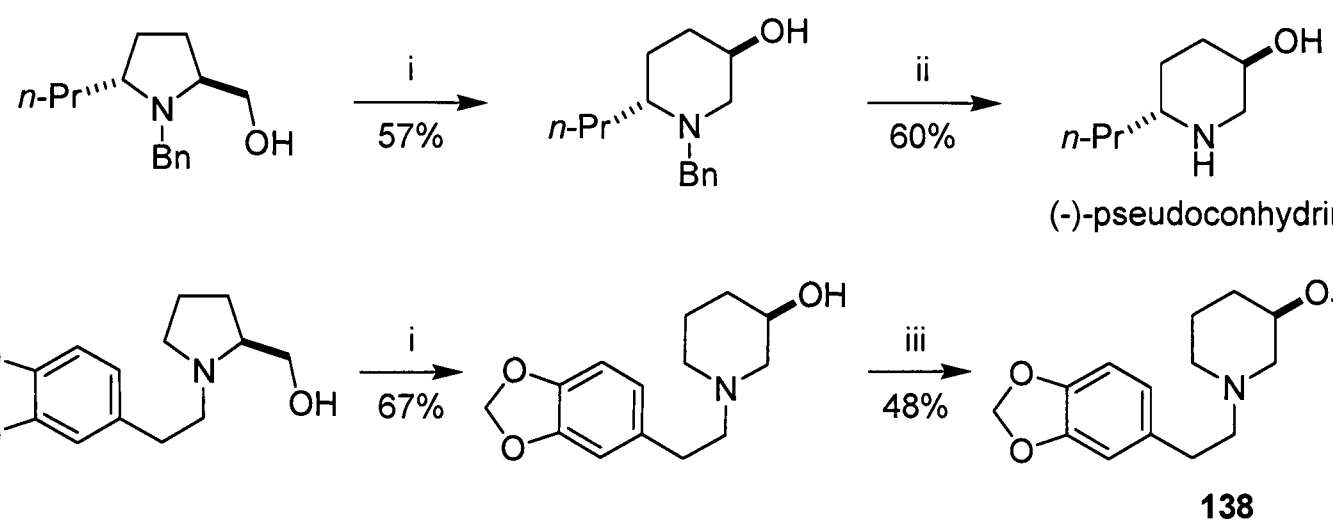
Scheme 3.12. *Reagents and conditions*: i, $(CF_3CO)_2$, THF, –78 °C;
then Et_3N, –78 °C → Δ; then NaOH (2.5 mol dm^{-3}), room temperature.

Cossy and co-workers have utilised this methodology in the syntheses of optically active 3-hydroxy piperidines (Scheme 3.13).[110]



Scheme 3.13. *Reagents and conditions*: i, $(CF_3CO)_2O$, THF, –78 °C; then Et_3N, –78 °C → Δ; then NaOH (2.5 mol dm^{-3}), room temperature.

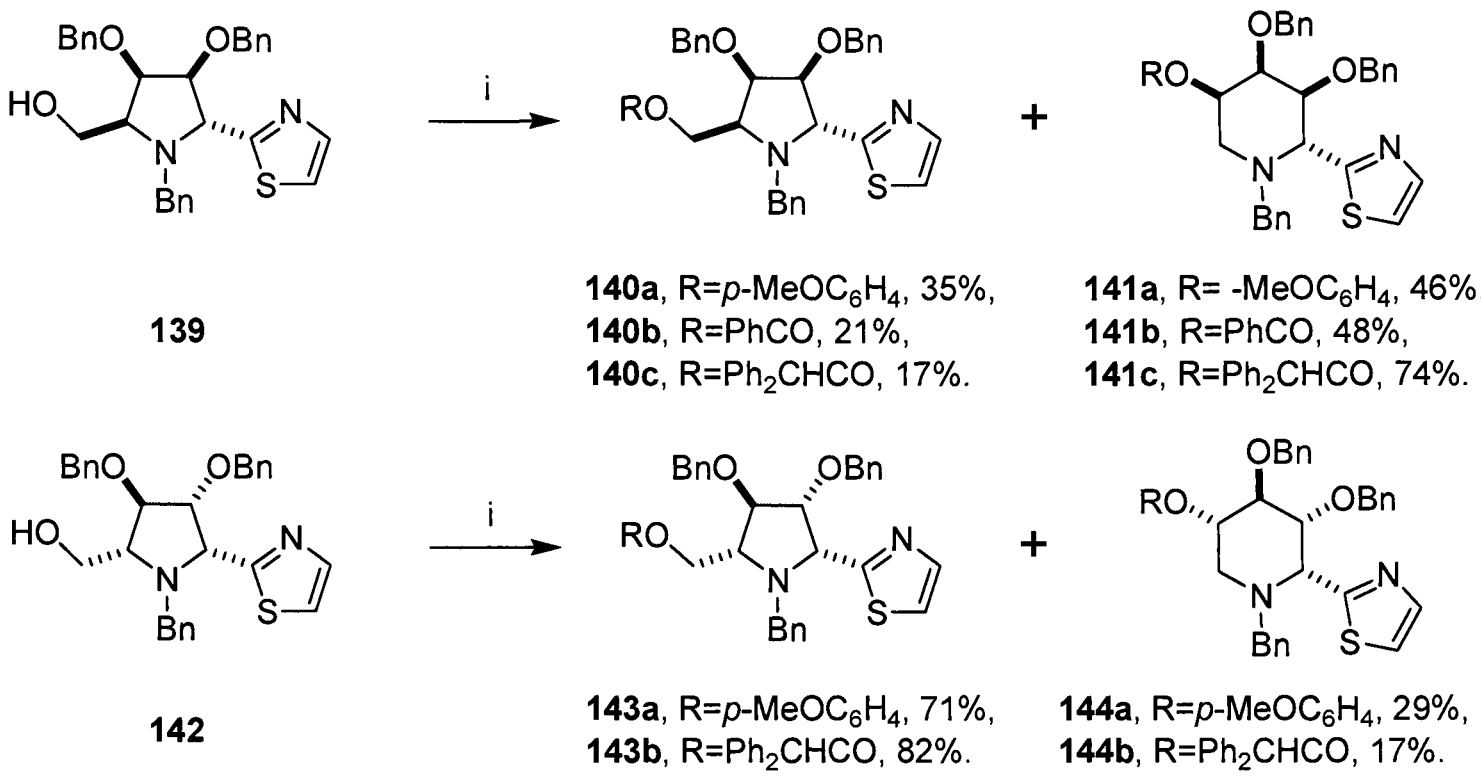
(3*S*,4*S*)-1-Benzyl-4-*N*-benzylamino-3-hydroxypiperidine;[111] the natural product (–)-pseudoconhydrine (**138**, Scheme 3.14);[112] the muscarinic M_3 receptor antagonist zamifenacin (**138**, Scheme 3.14)[113] and the piperidine core of velnanamine,[114] have all been synthesised using the trifluoroacetate rearrangement as the keystep.



Scheme 3.14. *Reagents and conditions*: i, $(CF_3CO)_2O$, THF, –78 °C; then Et_3N, –78 °C → Δ; then NaOH (2.5 mol dm^{-3}), room temperature; ii, H_2, $Pd(OH)_2$, MeOH, room temperature; iii, Ph_2CHCl, 100 °C.

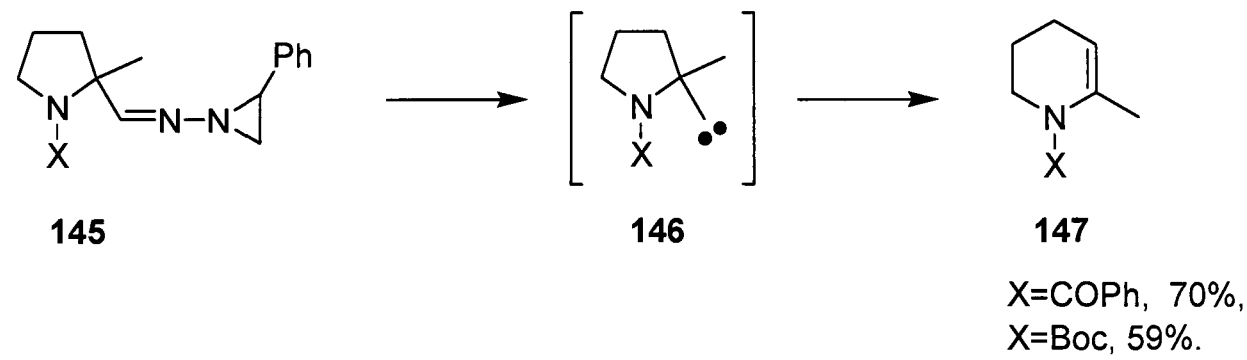
Dondoni and co-workers have published the ring-expansion of pyrrolidines under Mitsunobu-type conditions (Scheme 3.15).[115] Pyrrolidine **141** and piperidine **140** were obtained when pyrrolidine **139** was treated under Mitsunobu conditions using *para*-methoxyphenol as the nucleophile. It was found that diphenyl acetic acid was the most effective reagent to promote ring-expansion (74:17% in favour of **141**, Scheme 3.15). However, to the authors' surprise when the opposite pyrrolidine diastereoisomer (**142**) was

reacted with the Mitsunobu conditions, the trend was reversed: formation of pyrrolidine **143** was favoured over piperidine **144** (Scheme 3.15).



Scheme 3.15. *Reagents and conditions*: i, ROH, PPh$_3$, DIAD, THF, 80 °C.

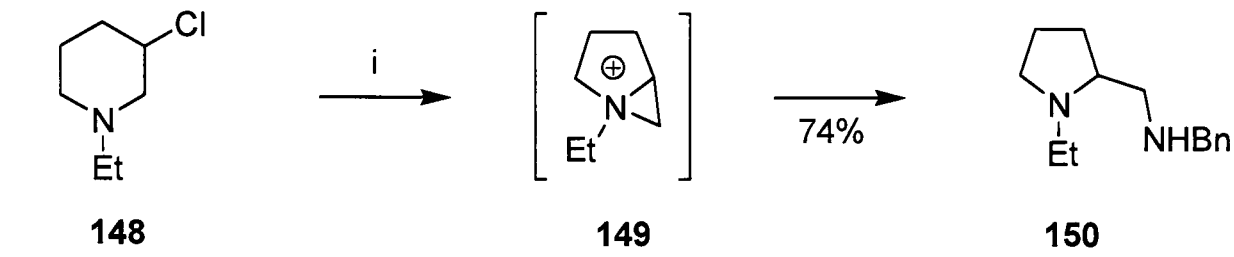
The one carbon ring-expansion of pyrrolidines can also be achieved *via* a carbene insertion (Scheme 3.16).[116] Kim and Yoon showed that carbene **146**, prepared by heating precursor **145**, rearranged to furnish the corresponding dihydropyridine **147** (Scheme 3.16), *via* direct insertion into a carbon-carbon bond.[117-119] This process can also be used to ring-expand six-membered lactams to the corresponding seven-membered compounds.[116]



Scheme 3.16. *Reagents and conditions*: i, PhMe, Δ.

Although the majority of the reports in the literature focus on the pyrrolidine to piperidine rearrangement, it should be noted that are examples of the piperidine to pyrrolidine rearrangement. Reitsema reported a rearrangement of a 3-chloro-piperidine ring (Scheme 3.17)[120] which essentially is the reverse of the rearrangement reported by Zircle and Fuson (Scheme 3.2). Heating **148** with benzylamine and water displaced the chlorine moiety and

furnished aziridium ion **149**, which was ring-opened with the nucleophilic benzylamine solvent furnishing pyrrolidine **150** (Scheme 3.17).



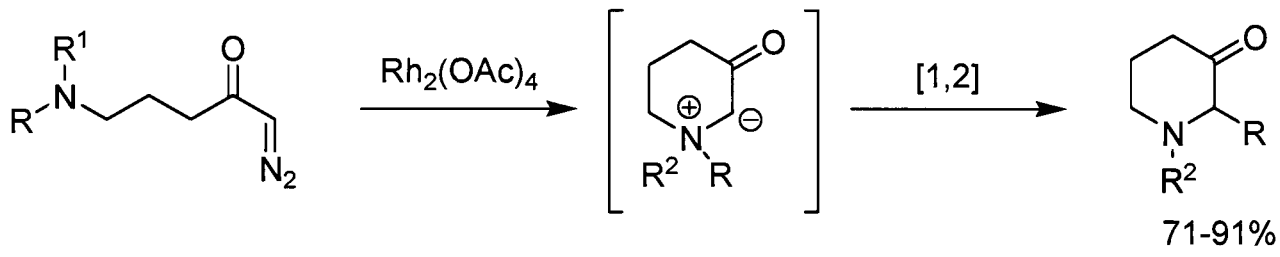
148 **149** **150**

Scheme 3.17. *Reagents and conditions*: i, $BnNH_2$, H_2O, Δ.

De Kimpe and co-worker have also reported ring-contractions of 3-oxygenated piperidines to 2-(bromomethyl)pyrrolidines, mediated by boron$^{(III)}$ bromide,[121] and the ring-contraction of a piperidine formed *in situ* from an amine cyclisation to a pyrrolidine ring.[122]

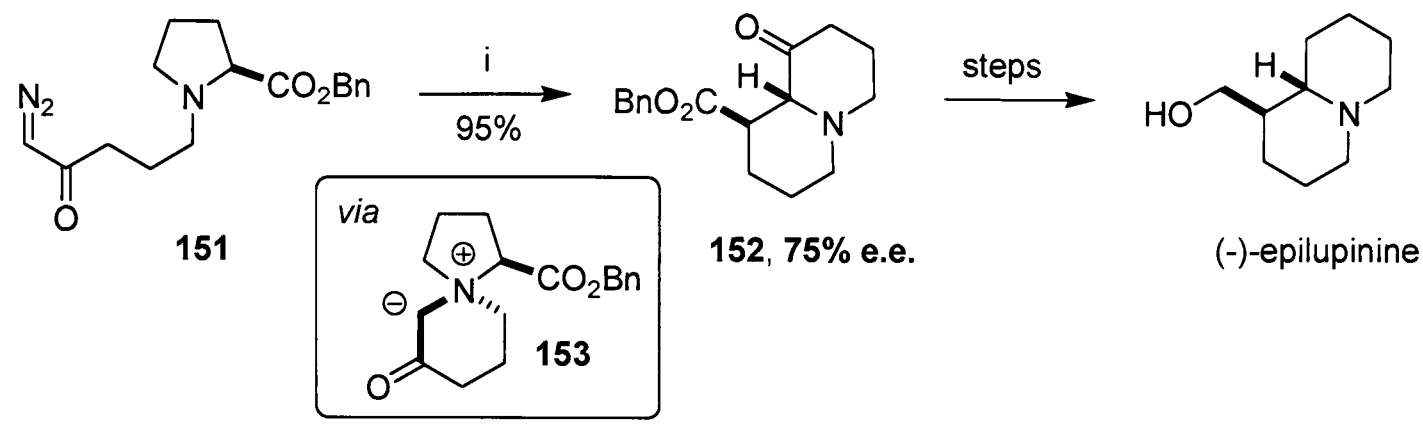
3.3 *One carbon ring-expansion to form fused piperidines and pyrrolidines.*

In 1993 West and Naidu published syntheses of substituted piperidines *via* the Stevens [1,2]-shift of ammonium ylides (Scheme 3.18)[123] and have extended the [1,2]-shift to the synthesis of morpholin-2-ones.[124]



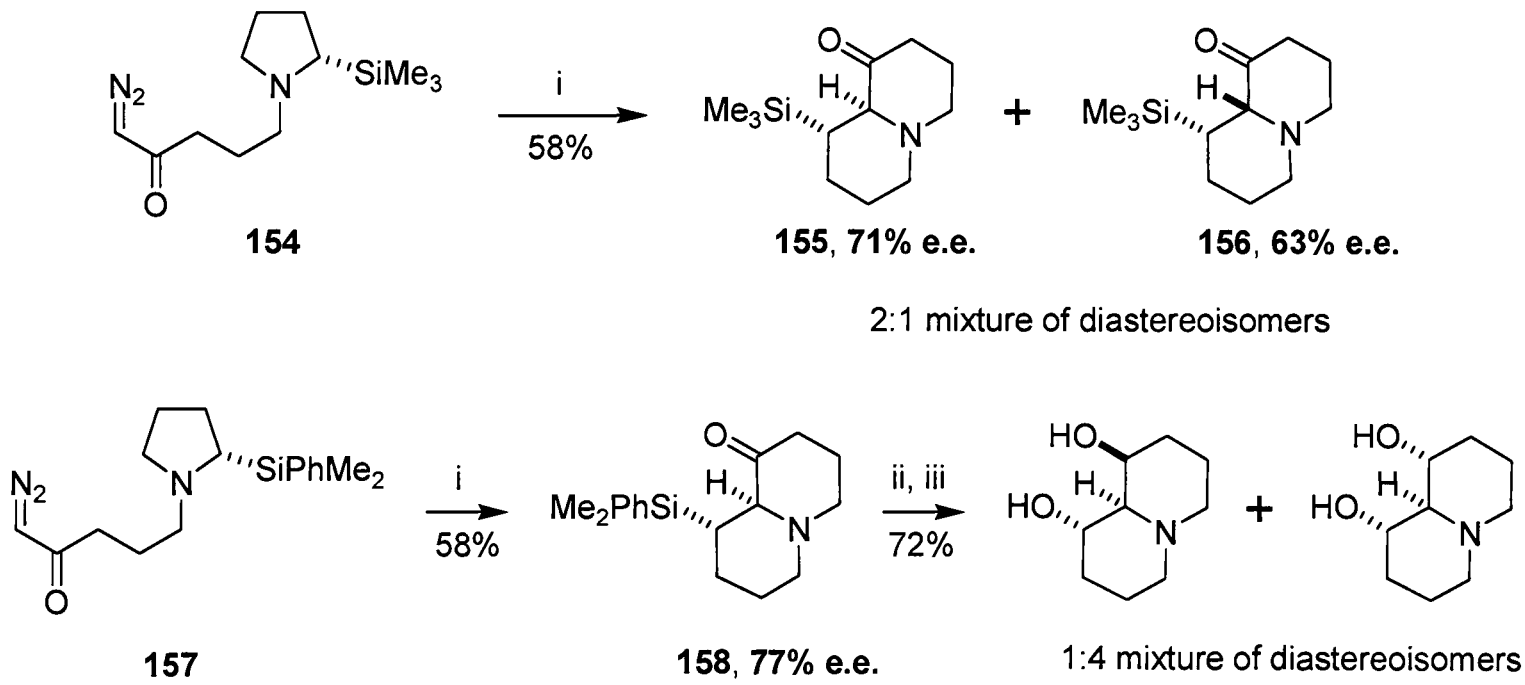
Scheme 3.18. *Synthesis of substituted piperidines via the Stevens [1,2] shift of ammonium ylides.*

Despite considerable mechanistic evidence in support of an intermediate radical, the Stevens [1,2]-shift has been shown to proceed with moderate to high retention of configuration when a chiral migrating group is employed.[125] West and Naidu utilised this phenomenon in the synthesis of fused piperidines *via* a one carbon ring-expansion of a pyrrolidine (Scheme 3.19) and applied it to a concise synthesis of (–)-epilupinine.[126, 127] Proline derivative **151** was treated with copper acetylacetonate to furnish piperidine **152** in high yield and good enantiomeric excess (Scheme 3.19); the good enantiomeric excess is due to the high levels of stereochemical retention in the Stevens rearrangement of ammonium ylide **153**.



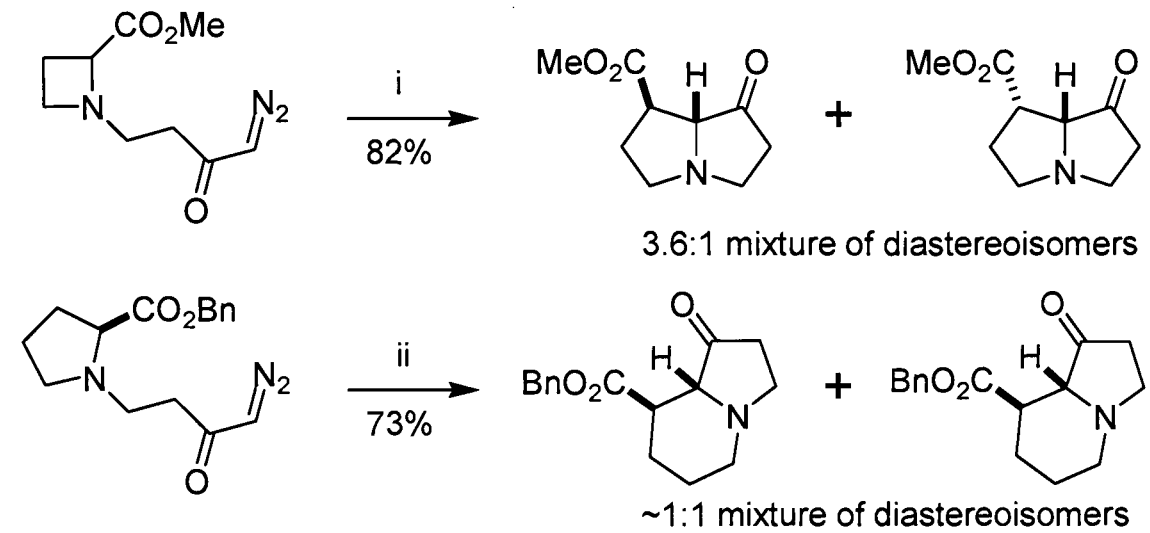
Scheme 3.19. *Reagents and conditions*: i, $Cu^{(II)}(acac)_2$ (5 mol%), PhMe, Δ.

One limitation encountered with the Stevens [1,2]-shift methodology had been the need of a conjugating group on the migrating carbon (typically a carbonyl or phenyl moiety),[123] presumably to stabilize the intermediate radical centre. West and Vanecko showed that the intermediate radical pair could also be stabilized by an α-silyl group (Scheme 3.20).[128] When pyrrolidine **154** was treated with copper acetylacetonate piperidines **155** and **156** were formed in a 2:1 mixture of diastereoisomers (Scheme 3.20), both with good levels of enantiomeric excess. However treatment of pyrrolidine **157** under the same conditions only afforded piperidine **158**. West postulated that the increased steric bulk of the phenyldimethylsilyl group gave the pyrrolidine higher conformational rigidity prior to carbenoid insertion; hydroxylated quinolizidine products were easily obtained from **158** (Scheme 3.20).



Scheme 3.20. *Reagents and conditions*: i, $Cu^{(II)}(acac)_2$ (5 mol%), PhMe, 85 °C; ii, $NaBH_4$, MeOH, 0 °C, 90%; iii, AcOH, TFA, $Hg(CO_2CF_3)$; AcOOH, room temperature, 80%.

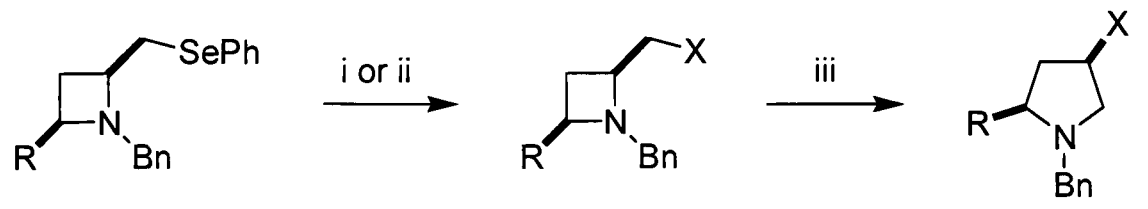
The Stevens [1,2]-shift has also been used in the synthesis of pyrrolizidine alkaloids *via* a ring-expansion of azetidinium ylides (Scheme 3.21).[129]



Scheme 3.21. *Reagents and conditions*: i, $Cu^{(II)}(acac)_2$ (10 mol%), PhMe, Δ; ii, $Rh_2(OAc)_4$ (5 mol%), PhH, Δ.

3.4 *One carbon ring-expansions to form pyrrolidines.*

The majority of ring-expansion reactions reported involve strained cyclic nitrogen intermediates, where strain-driven cleavage acts as a driving force. However reports on the ring-expansion of azetidine rings (in which ring-expansion should be favourable due to ring-strain) are scarce. Outurquin and co-workers recently published the thermal rearrangement of azetidines **159a-f** through to the corresponding 3-halo-pyrrolidines **160a-f** in moderate to good yields (Scheme 3.22).[130]

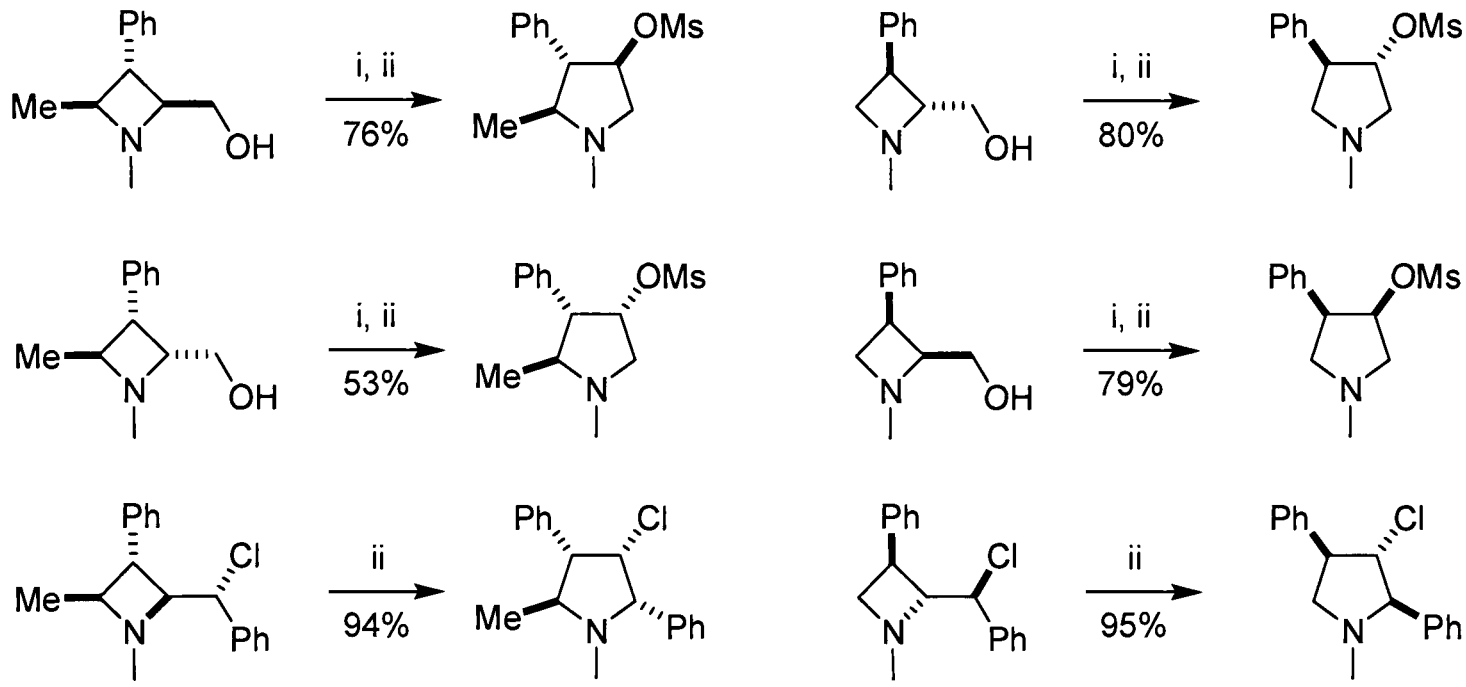


159a, X=Cl, R=Et, **160a**, 70%,
159b, X=Br, R=Et, **160b**, 58%,
159c, X=Cl, R=*i*-Pr, **160c**, 55%,
159d, X=Br, R=*i*-Pr, **160d**, 55%,
159e, X=Cl, R=*t*-Bu, **160e**, 68%,
159f, X=Br, R=*t*-Bu. **160f**, 60%.

Scheme 3.22. *Reagents and conditions*: i, $SOCl_2$, hexane; then CCl_4, Δ; ii, $SOCl_2$, hexane; then Br_2, Δ; iii, CH_3CN, Δ; yields shown are quoted over two steps.

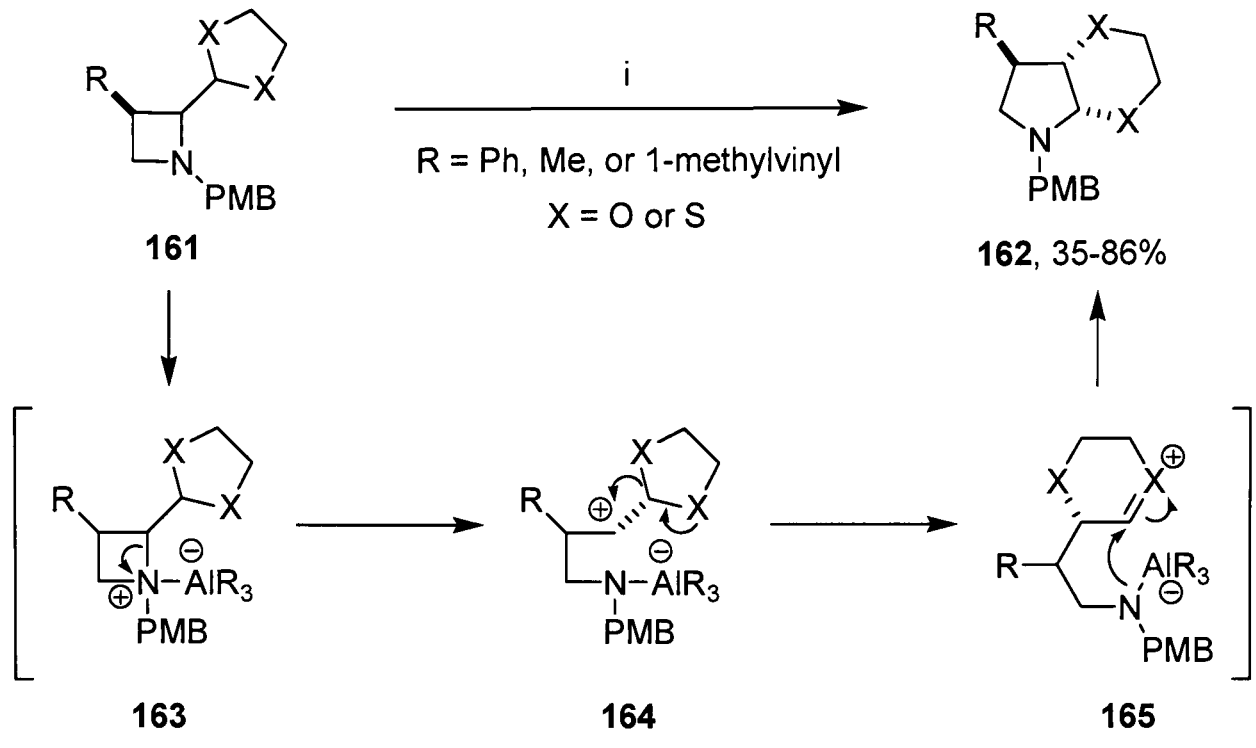
However the most comprehensive study of the azetidine to pyrrolidine rearrangement has come from the laboratories of Couty and co-workers (Scheme 3.23).[131]

In the analogous pyrrolidine to piperidine rearrangement (3.2), the reaction proceeds *via* an aziridinium ion intermediate; however Couty postulated that rearrangement *via* the analogous transient azetidinium ion does not occur. Instead it was postulated that the rearrangement proceeded in a concerted manner as the azetidinium ion was not detected by NMR studies upon treatment of the parent chloride with silver tetrafluoroborate in deuterated chloroform.



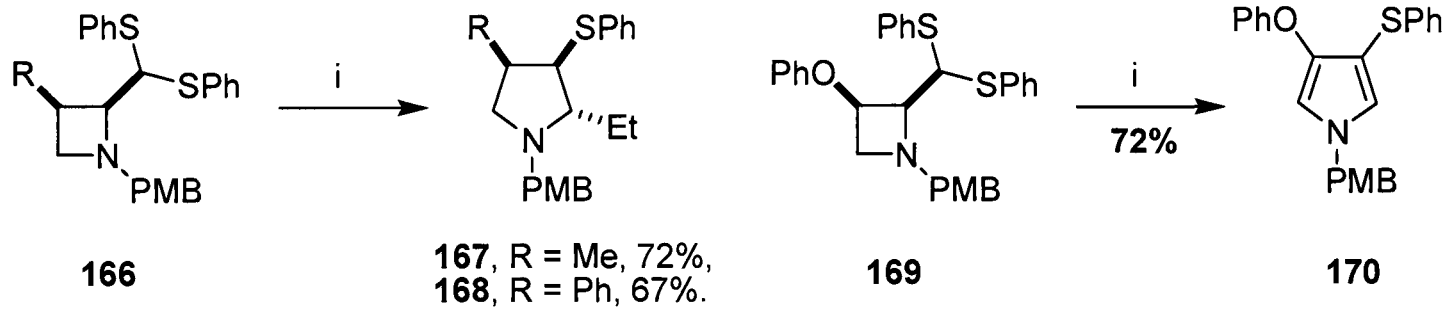
Scheme 3.23. *Reagents and conditions*: i, MsCl, Et_3N, THF; ii, CH_3Cl, Δ.

Alcaide and co-workers reported a diethylaluminium chloride mediated rearrangement of azetidines that allowed access to the corresponding pyrrolidines and pyrroles.[132] Azetonide **161** gave the fused pyrrolidines of type **162** in moderate to good yields (Scheme 3.24). The aluminium Lewis acid coordinates to the azetidine nitrogen (**163**) which ring-opens to give species **164**. The resulting species rearranges to the thermodynamically more stable cation **165**, which is hydrolysed upon work-up to furnish the fused pyrrolidines (**162**, Scheme 3.24).



Scheme 3.24. *Reagents and conditions*: i, $AlEt_2Cl$, CH_2Cl_2, room temperature or Δ.

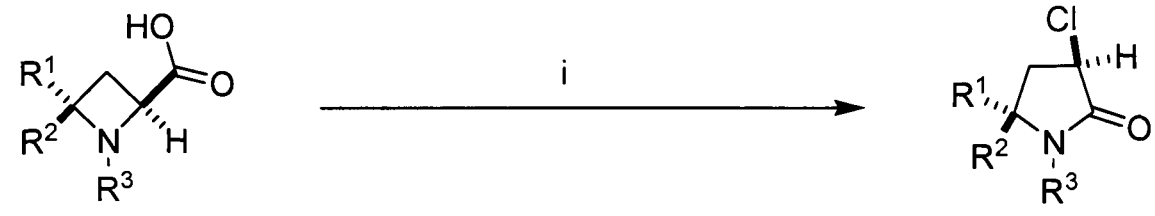
Simple pyrrolidines **166** and **168** and pyrrole **170** (Scheme 3.25) could also be prepared when the appropriate azetidines (**166** and **169** respectively) were treated with diethylaluminium chloride (Scheme 3.25).



Scheme 3.25. *Reagents and conditions*: i, $AlEt_2Cl$, CH_2Cl_2, room temperature.

3.5 *One carbon ring-expansions to form lactams.*

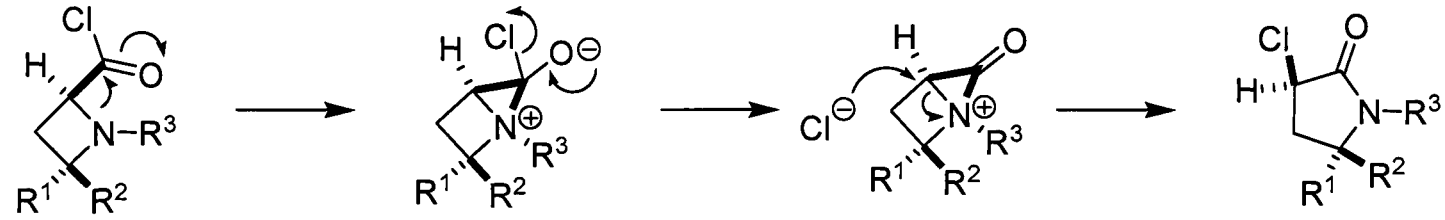
During their studies on the conversion of iminium salts to azetidinones,[133, 134] Wasserman and co-workers discovered that the 4-subsitituted system may react through another pathway depending on the nature and stereochemistry of the substituents in the 1- and 4-positions.[135] When azetidine carboxylic acids **171a-e** were reacted with oxalyl chloride, ring-expansions to the corresponding chloro-γ-lactams **172a-e** was observed in moderate to good yields (Scheme 3.26).[135]



171a, R^1=Me, R^2=H, R^3=*t*-Bu, **172a**, 69%,
171b, R^1=CO_2Me, R^2=H, R^3=Ph, **172b**, 46%,
171c, R^1=H, R^2=CO_2Me, R^3=Bn, **172c**, 68%,
171d, R^1=CO_2Me, R^2=H, R^3=cyclohexyl, **172d**, 58%,
171e, R^1=H, R^2=CO_2Me, R^3=cyclohexyl. **172e**, 59%.

Scheme 3.26. *Reagents and conditions*: i, $(COCl)_2$, CH_2Cl_2.

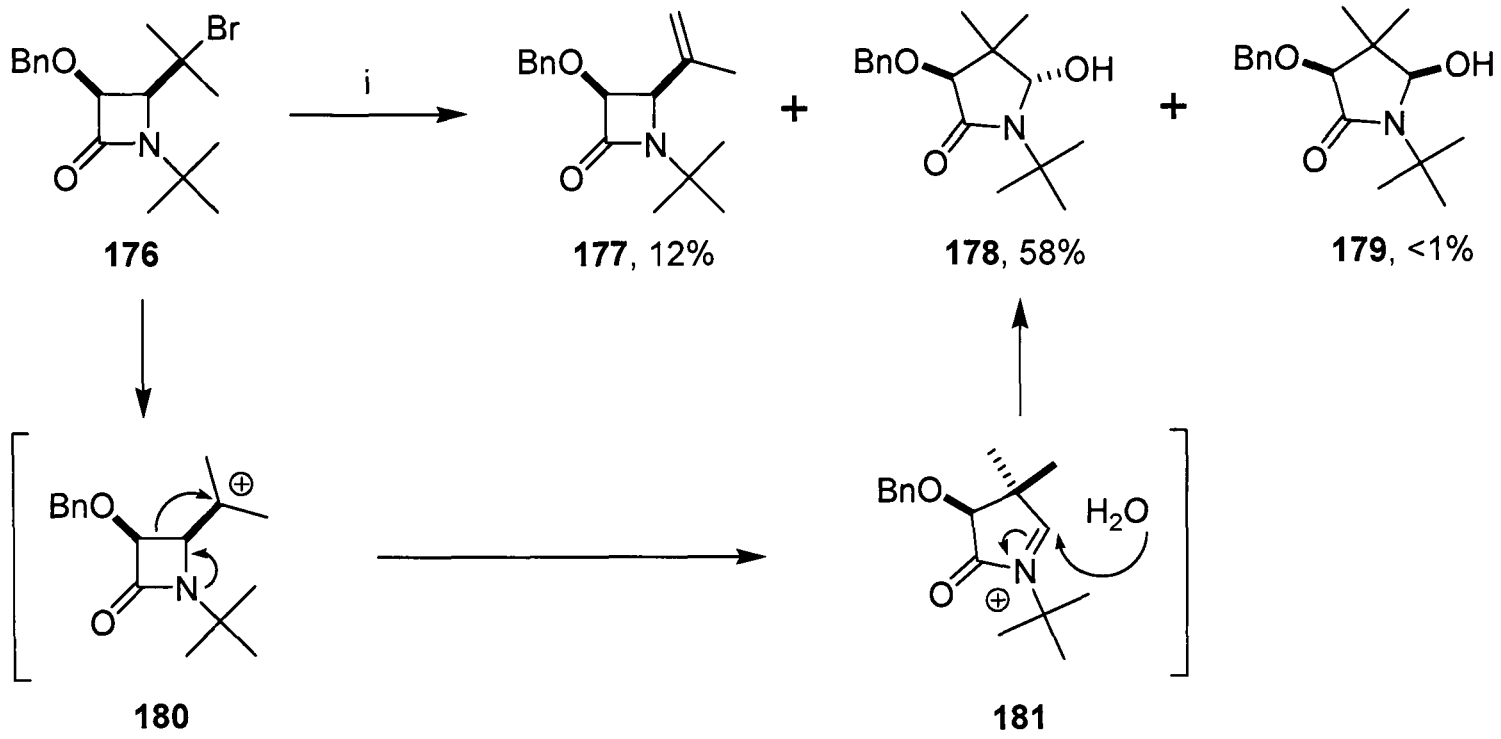
Wasserman postulated that after the initial formation of chloride **173**, the nitrogen lone pair electrons attack the carbonyl moiety to form the highly strained intermediate **174** that is opened by the chloride counter ion from the least hindered (top) face to give chloro-γ-lactam **175** (Scheme 3.27). If an alkyl group is in a *cis* relationship with the carboxylic acid no rearrangement occurs; both groups are held in an unfavourable 2,4-pseudoaxial interaction (intermediate **173**). Conversely when an ester is in the 2,4-pseudoaxial relationship, rearrangement takes place to alleviate unfavourable dipole-dipole interactions.*



Scheme 3.27. *Postulated mechanism for the β-lactam to chloro-γ-lactam rearrangement.*

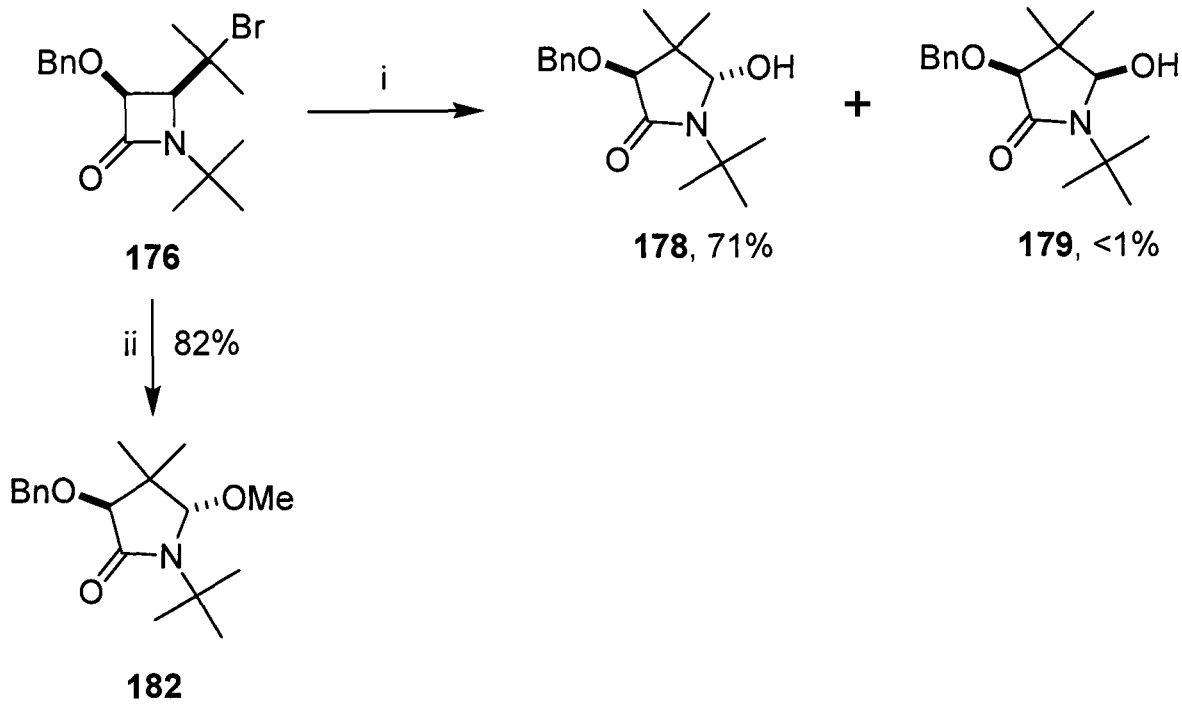
β-Lactams have been shown to rearrange through to γ-lactams *via* a cation-induced process (Scheme 3.28).[136] In a polar reaction medium (water and dimethylsulfoxide), β-lactam **176** rearranged to the corresponding γ-lactam **178** in moderate yield (Scheme 3.28); a small quantity of elimination product **177** and *cis* γ-lactam **179** were also observed. De Kimpe postulated that dissociation of the bromide gave tertiary cation **180**; this can be stabilised either by the loss of a proton (to give **177**) or by the ring-cleavage of the β-lactam to produce the more stable iminium cation **181**. The nucleophile attacks from the least hindered face to furnish the *trans* γ-lactam **178** as the favoured product (Scheme 3.28).

* Presumably this has the effect of flattering the puckered wing conformation of the β-lactam; hence reducing unfavourable 2,4-psudeoaxial interactions.



Scheme 3.28. *Reagents and conditions*: i, 20% H_2O in DMSO, room temperature.

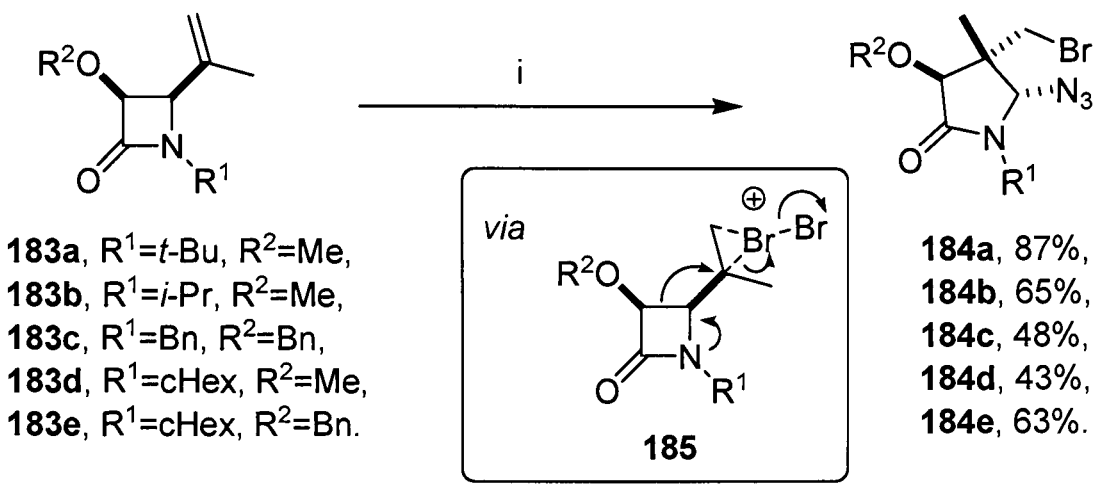
It was found that the competing elimination side reaction could be completely supressed by using basic condition (potassium *tert*-butoxide in tetrahydrofuran, Scheme 3.29); hence the yield of γ-lactam **178** was dramatically increased. If the reaction is quenched with methanol γ-lactam **182** is furnished in high yield (Scheme 3.29).



Scheme 3.29. *Reagents and conditions*: i, KO*t*-Bu, THF, Δ; then H_2O, Et_2O; ii, KO*t*-Bu, THF, Δ; then MeOH.

When the elimination products **183a-f** are treated with *N*-bromosuccinamide and trimethylsilyl azide the γ-lactams **184a-f** are obtained in moderate to high yields (Scheme

3.30);[137] the rearrangement is induced by a bromonium ion (**185**) as opposed to a tertiary cation (**180**, Scheme 3.28), hence no elimination product is observed.

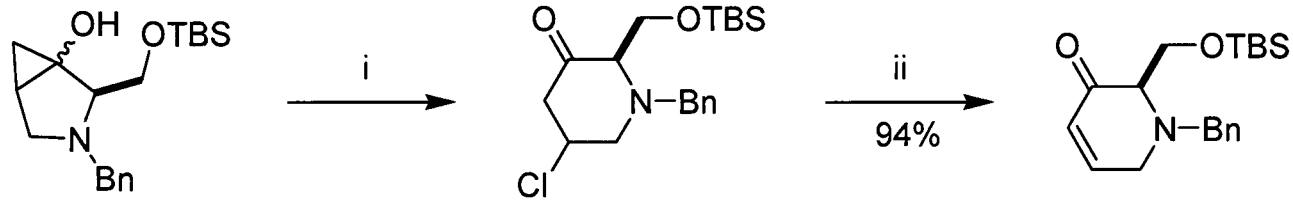


183a, R^1=*t*-Bu, R^2=Me,
183b, R^1=*i*-Pr, R^2=Me,
183c, R^1=Bn, R^2=Bn,
183d, R^1=cHex, R^2=Me,
183e, R^1=cHex, R^2=Bn.

184a, 87%,
184b, 65%,
184c, 48%,
184d, 43%,
184e, 63%.

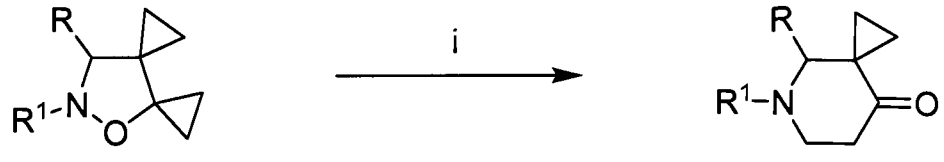
Scheme 3.30. *Reagents and conditions*: i, NBS (1.3 eq.), $TMSN_3$ (1.3 eq.), CH_2Cl_2/CH_3NO_2 (3:1), room temperature.

3.6 *Ring-expansion by the opening of cyclopropanes.*



Scheme 3.31. *Reagents and conditions*: i, $FeCl_3$, Et_2O; then ii, AcONa, MeOH, **94%** over two steps.

Although iron chloride mediated ring-expansions of bicyclic cyclopropanols to the corresponding 2-cycloalkenones have been widely employed within the carbocyclic framework,[138] there is only one reported application to the synthesis of *N*-heterocyclic systems (Scheme 3.31).[139]

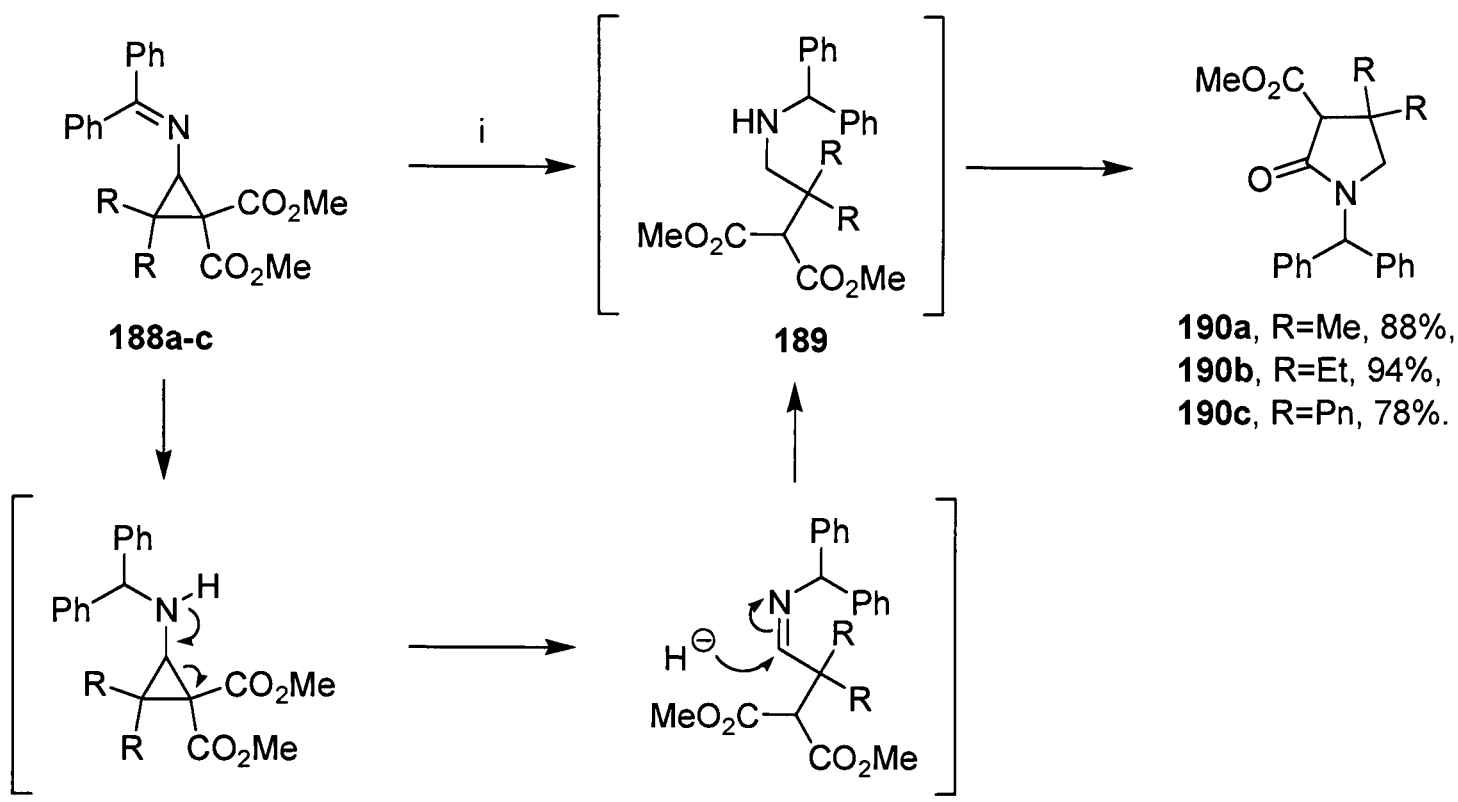


186a, R=Ph, R^1=Me,
186b, R=R^1=$CH_2CH_2CMe_2$,
186c, R=R^1=Bu.

187a, 63%,
187b, 76%,
187c, 68%.

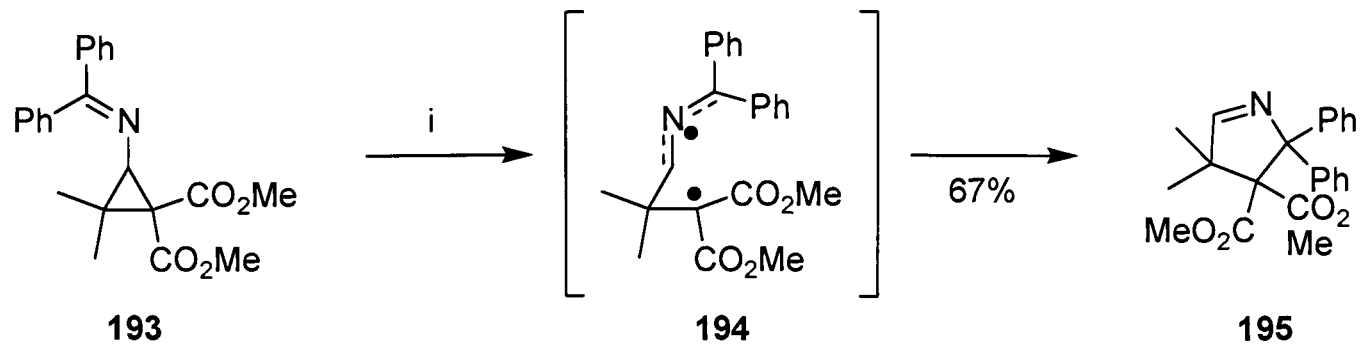
Scheme 3.32. *Reagents and conditions*: i, a, PhMe, Δ; b, PhH, Δ, c, Xylene, 120 °C.

When a 1.0 molar solution of isoxazolidines in benzene **186a-c** were heated clean rearrangement to the 3-spirocyclopropane pyridones **187a-c** was observed in good yields (Scheme 3.32).[140] The two cyclopropane rings at C-4 and C-5 behave differently upon heating; only the cyclopropane in the 5 position is cleaved during the rearrangement because it is adjacent to the labile N-O bond. Brandi and co-workers have utilised this rearrangement in the synthesis of heterocyclic ketones possessing DNA cleaving activity.[141]



Scheme 3.33. *Reagents and conditions*: i, $NaCNBH_3$, AcOH, MeOH, room temperature.

De Kimpe and Mangelinckx have reported that when cyclopropyl rings bearing *exo*-cyclic imines (**188a-c**, Scheme 3.33)[142] are treated under mild reduction conditions, the reduced cyclopropyl amine **191** ring-opened to iminium ion **192** which was subsequently reduced to intermediate amine **189**; this then self-cyclised to furnish pyrrolidinones **190a-c** in high yields (Scheme 3.33). When cyclopropyl imine **193** was treated with sodium chloride dissolved in dimethylsulfoxide and water, the cyclopropyl ring was cleaved to radical species **194** that cyclised and furnished **195** (Scheme 3.34).



193 **194** **195**

Scheme 3.34. *Reagents and conditions*: i, NaCl, DMSO, H_2O, Δ.

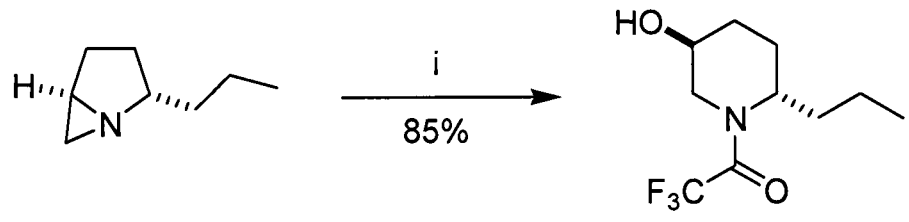
3.7 *Ring-expansion by the opening of aziridines.*

In 1965, Logothetis reported that bicyclic aziridines (**196a-b**) could be converted to piperidine salts (**197a-b**, Scheme 3.35).[143] Treatment with methyl iodide cleaved the C5-N bond of the bicyclic aziridine. Likewise Muchowski and Horning reported the interconversion of bicylo-aziridine **198** and piperidine **199** (Scheme 3.35).[144]

196 **197a**, R=H, **197b**, R=Me. **198** **199**

Scheme 3.35. *Reagents and conditions*: i, MeI; ii, HBr; iii, NaH.

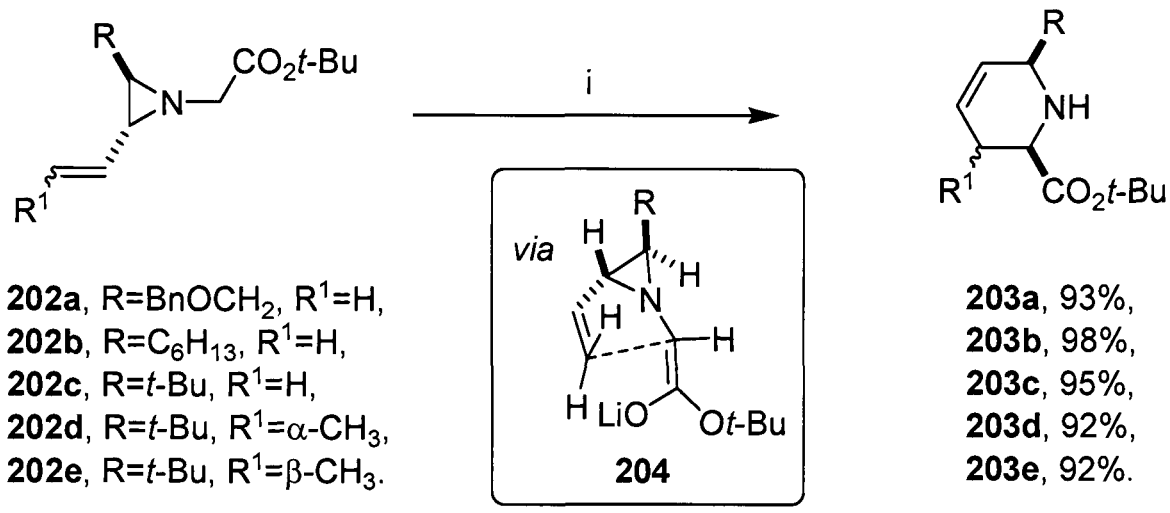
During their synthesis of (±)-pseudoconhydrine, Harding and Burks discovered that bicyclic aziridine **200** could be converted to piperidine **201** when treated with 1 equivalent of trifluroacetic acid in dichloromethane at low temperature (Scheme 3.36).[145]



200 **201**

Scheme 3.36. *Reagents and conditions*: i, CF_3CO_2H, CH_2Cl_2, –78 °C.

The aza-[2,3]-Wittig rearrangement of azirdines[146, 147] has been used to prepare tetrahydropyridines in high yields and diastereoselectivies (Scheme 3.37).[146] When *trans*-azirdines **202a-e** were treated with lithium di-*iso*-propylamine at low temperature swift rearrangement to the *cis*-tetrahydropyridines **203a-e** was observed (Scheme 3.37); all products were obtained as a single diastereoisomer. The high level of selectivity was attributed to the rearrangement occurring *via* intermediate enolate **204**.

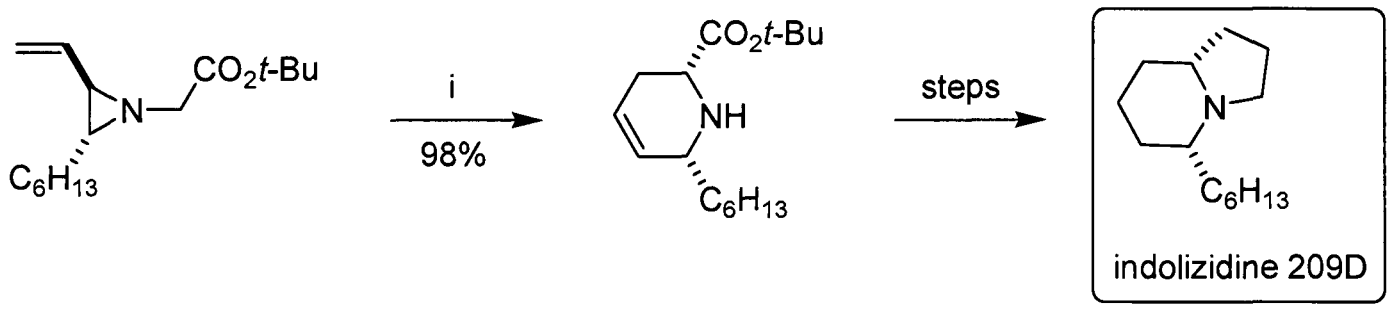


202a, R=$BnOCH_2$, R^1=H,
202b, R=C_6H_{13}, R^1=H,
202c, R=*t*-Bu, R^1=H,
202d, R=*t*-Bu, R^1=α-CH_3,
202e, R=*t*-Bu, R^1=β-CH_3.

203a, 93%,
203b, 98%,
203c, 95%,
203d, 92%,
203e, 92%.

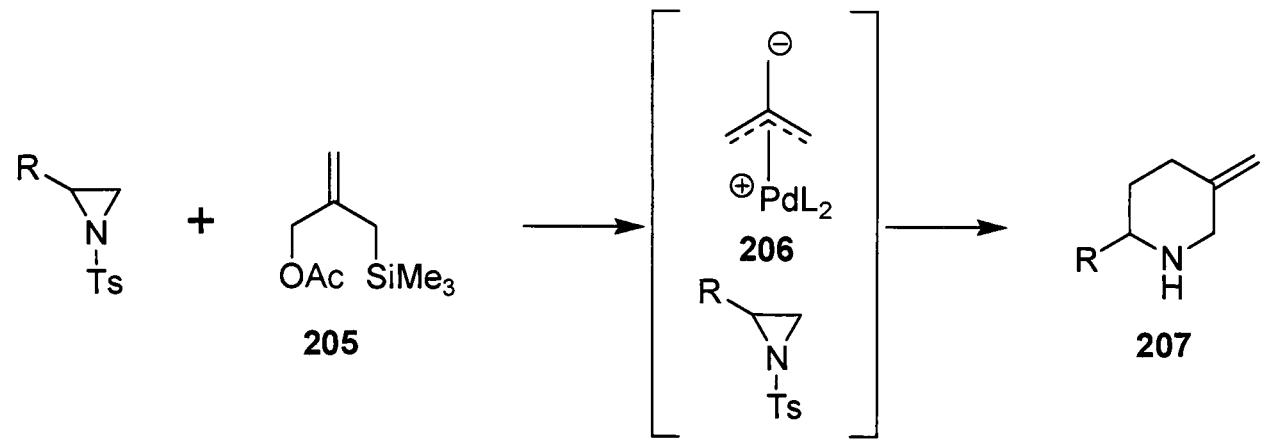
Scheme 3.37. *Reagents and conditions*: i, LDA, THF, –78 °C.

Somfai and Ahman have successfully applied the aza-[2,3]-Wittig rearrangement to the enantioselective total synthesis of indolizidine 209D (Scheme 3.38).[148]



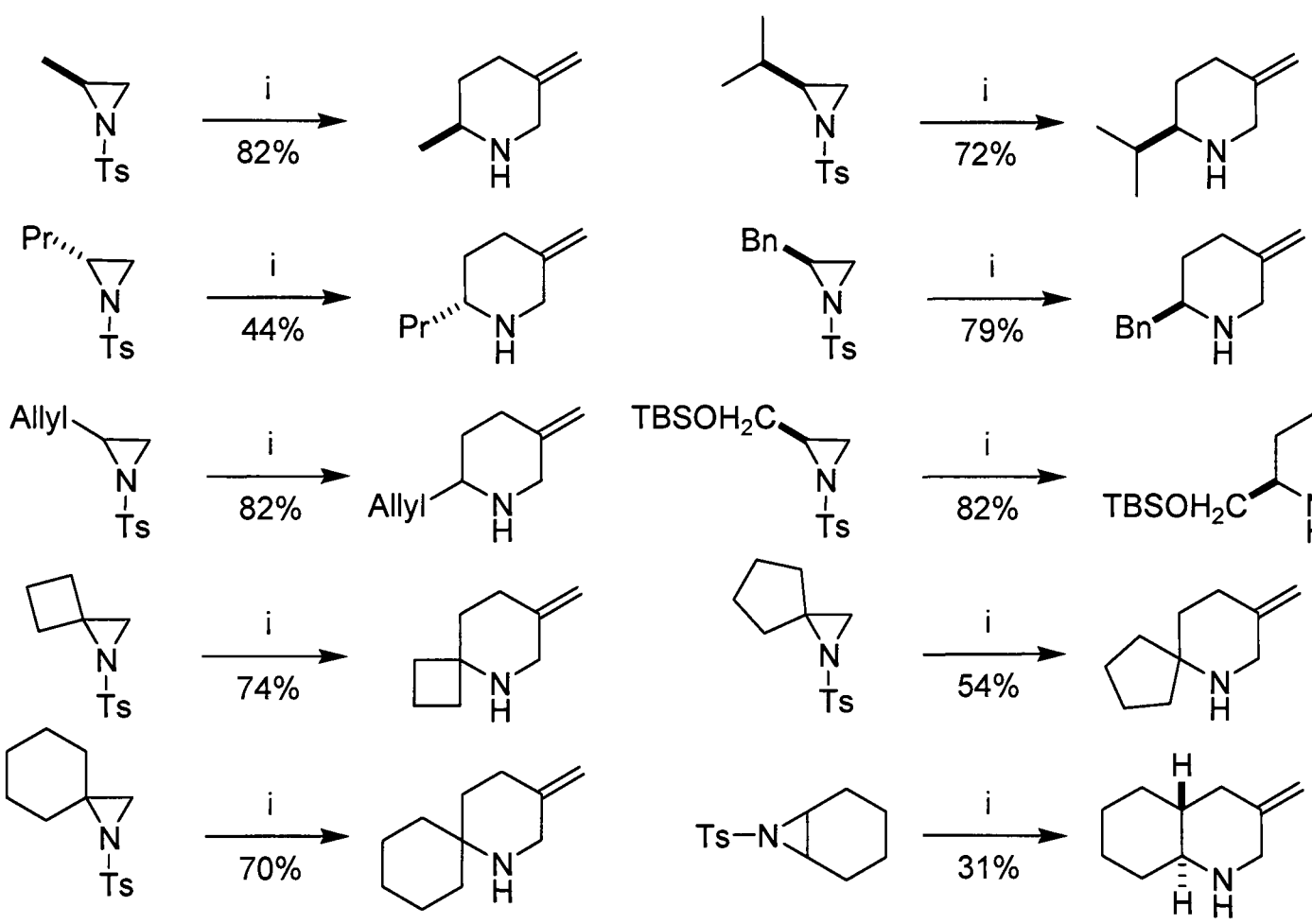
Scheme 3.38. *Reagents and conditions*: i, LDA, THF, –78 °C.

Aziridines have been utilised in the synthesis of functionalised piperidines *via* a [3+3] cycloaddition (Scheme 3.39).[149] In the presence of a palladium$^{(0)}$ source, olefin **205** forms the π-allyl complex **206** that undergoes a [3+3] cycloaddition with an aziridine to furnish functionalised tetrahydropyridines of type **207** (Scheme 3.39).



Scheme 3.39. *Reagents and conditions*: i, $Pd(OAc)_2$ (10 mol%), $P(i\text{-}OPr)_3$ (60%), *n*-BuLi (20 mol%), THF, 65 °C.

Harrity and co-workers have successfully applied this cycloaddition to the synthesis of various functionalised piperidines (Scheme 3.40).[150]



Scheme 3.40. *Reagents and conditions*: i, $Pd(OAc)_2$ (10 mol%), $P(i\text{-}OPr)_3$ (60%), *n*-BuLi (20 mol%), THF, 65 °C.

Aziridines also undergo carbon monoxide insertion to furnish β-lactams (Scheme 3.41).[151] The carbon monoxide inserts preferentially on the ring carbon that displays the most electrophilic behaviour.

R=CH_2OTBS, 96%,
R=CH_2OAc, 86%,
R=CH_2OH, 79%,
R=NH_2, 68%.

Scheme 3.41. *Reagents and conditions*: i, $Co_2(CO)_8$, CO (500 psi), DME, 100 °C.

3.8 *Miscellaneous ring-expansions.*

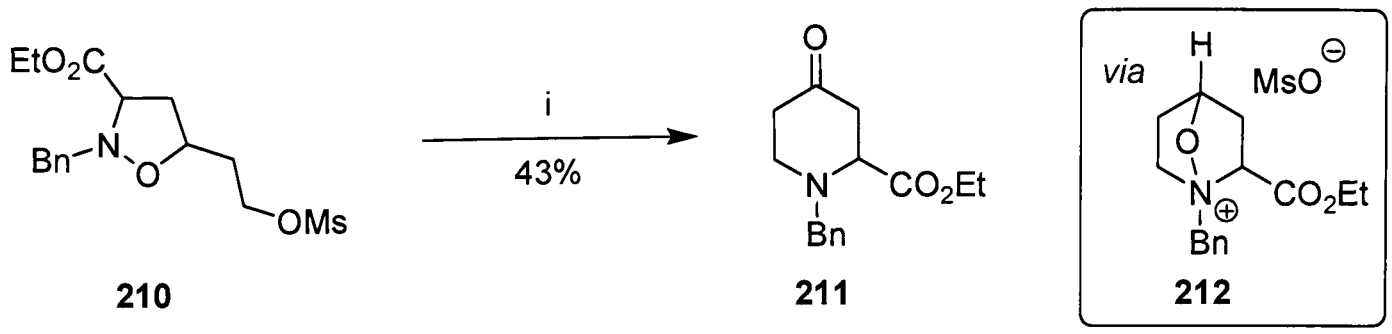
Vinyl oxazolidinones **208a-f** have been reported to undergo a palladium catalyzed decarboxylative carbonylation to furnish lactams **209a-f** in moderate to good yields (Scheme 3.42).[152]

208a, R^1=*i*-Pr, R^2=H,
208b, R^1=Bn, R^2=H,
208c, R^1=Ph, R^2=H,
208d, R^1=*i*-Pr, R^2=Me,
208e, R^1=Bn, R^2=Me,
208f, R^1=Ph, R^2=Me.

209a, 87%,
209b, 78%,
209c, 58%,
209d, 74%,
209e, 66%,
209f, 57%.

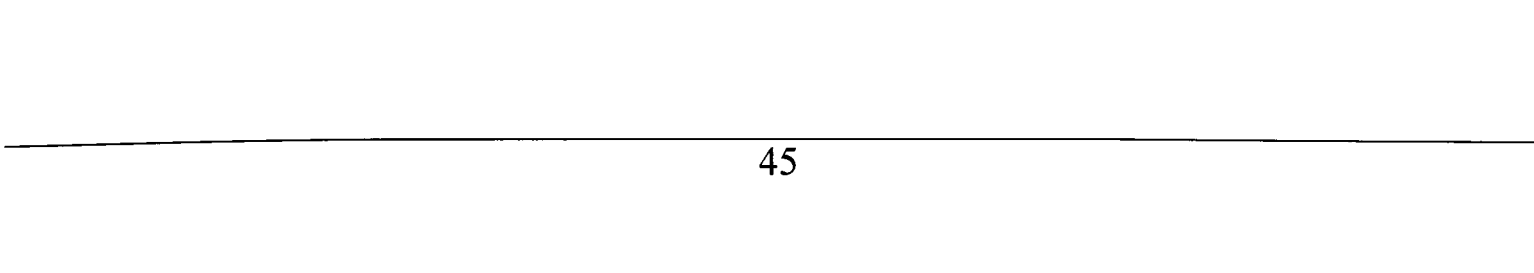
Scheme 3.42. *Reagents and conditions*: i, $Pd(Ph_3)_2(OAc)_2$ (5 mol%), EtOH, CO (65 atm.), 60-70 °C.

Machetti and co-workers have reported a synthesis of piperidones where heterocycle **210** underwent a base mediated rearrangement *via* salt **212** to yield piperidone **211** (Scheme 3.43).[153]



Scheme 3.43. *Reagents and conditions*: i, DABCO, MeCN, Δ.

Finally the furan nucleus is a latent 1,4-dicarbonyl equivalent; the aza-Achmatowicz reaction[154] exploits this reactivity in the oxidation of 2-furanyl amines to furnish tetrahydropyridines. Padwa and Harris have utilised this reaction to prepare trisubstituted piperidines in the synthesis of 6-*epi*-indolizidine 223A (Scheme 3.44).[155]



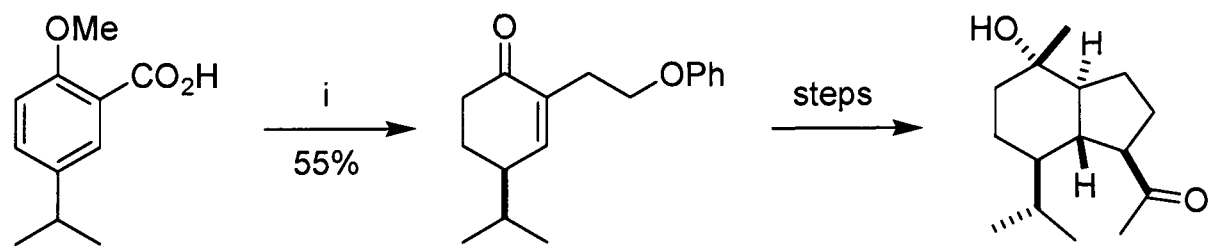
Scheme 3.44. *Reagents and conditions*: i, *m*-CPBA, CH_2Cl_2; ii, CH_2=$CHCH_2SiMe_3$, BF_3•OEt_2, CH_2Cl_2, 0 °C.

Chapter 4

Results and Discussion – Rearrangements of Nitrogen Heterocycles

4.1 *Rearrangement of α-halomethyl pyrrolines.*

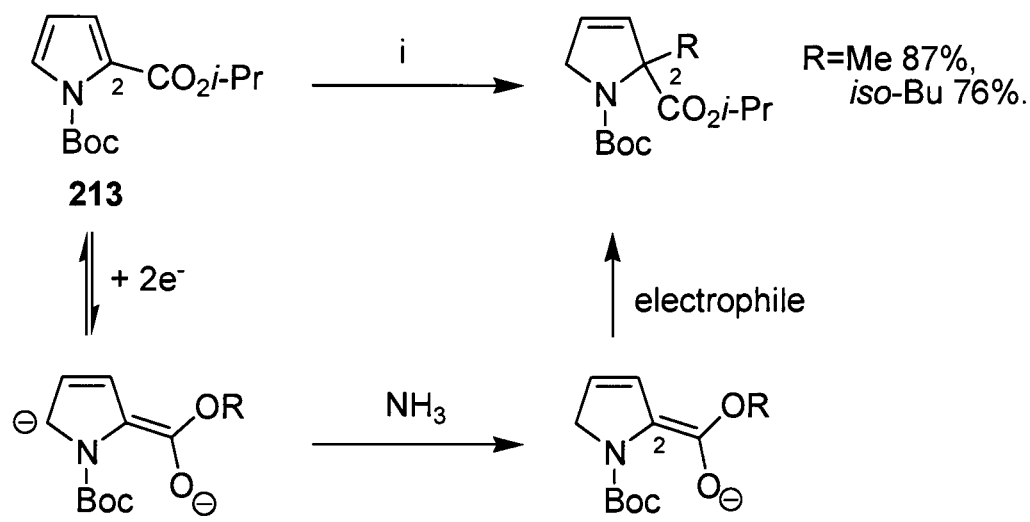
The use of alkali metals in liquid ammonia to reduce aromatic compounds represents an important method for the preparation of partially reduced six-membered rings. First discovered by Wooster and Godfrey,[156] the reaction has since come under intense scrutiny; the major developments resulted from the efforts of Birch[157] and the reaction has since come to bear his name. The reaction has been used as a key step in numerous natural product syntheses;[158] for example Taber and Korsmeyer employed the reduction of 2-methoxybenzoic acid in their short stereoselective synthesis of (±)-oplopanone (Scheme 4.1).[159]



Scheme 4.1. *Reagents and conditions*: i, Li, NH_3, THF, –78 °C;
then $PhOCH_2CH_2Br$ (1.1 eq.); then HCl (conc.).

The partial reduction using "Birch-type conditions*" has been comprehensively reviewed,[160] thus a detailed explanation of reaction conditions and mechanism will not be further explored in this thesis.

Although the Birch reduction has been extended beyond carbocyclic aromatics and onto many heteroaromatic systems,[161-163] the attempted Birch reduction of the pyrrole nucleus had until recently been met with failure. The LUMO energy for aromatic heterocycles can be ranked in the order pyridine<benzene<furan<pyrrole,[164] hence in general terms, the pyrrole nucleus is too electron-rich to accept electrons. In addition, the acidic proton on the pyrrole nitrogen (pK_a 17.5) would be deprotonated under Birch-type conditions, increasing the electron density in the pyrrole nucleus.



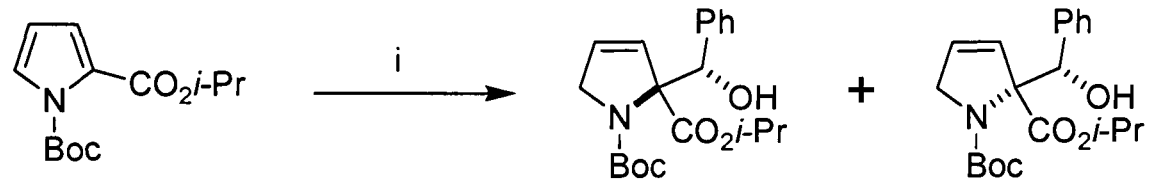
Scheme 4.2. *Reagents and conditions*: i, Na, NH_3, THF, –78 °C; then CH_3I (excess) or *i*-BuI (excess); then NH_4Cl.

Investigations within the Donohoe laboratories found that the electron affinity of the pyrrole nucleus could be increased by inclusion of an electron withdrawing group at the C-2 position on the pyrrole ring and an electron withdrawing nitrogen protecting group. Reductive alkylation of electron deficient pyrroles (such as **213**, Scheme 4.2) allowed access to the corresponding pyrrolines in high yields (Scheme 4.2).[1] Although only two representative electrophiles are shown in Scheme 4.2, a wide range of electrophiles can be tolerated under Birch-type conditions.[2]

One drawback to this methodology is that some electrophiles react with ammonia and cannot be used. Donohoe and co-workers found that by generation of the single electron reducing medium with preformed lithium di-*tert*-butylbiphenylide (LiDBB) reactive

* "Birch type conditions" refers to a single electron reducing medium generated by a group I or II metal dissolved in ammonia.

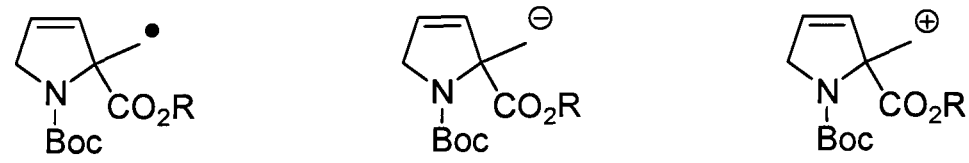
electrophiles that are incompatible under Birch-type conditions (for example chloroformates, acid chlorides and bromoacetates) could be used.[165] This reducing medium has successfully been applied to the reductive aldol reaction of electron deficient pyrroles (Scheme 4.3).[166, 167]



213 70%, 1:1 mix of diastereoisomers

Scheme 4.3. *Reagents and conditions*: i, LiDBB, THF, BMEA,* –78 °C; then PhCHO (excess); then NH_4Cl.

The first aim of the project was to rearrange the readily available pyrrolines through to the corresponding tetrahydropyridines, which are not themselves accessible *via* the partial reduction of pyridines.[12, 13] To allow rearrangement, the pyrrolines must possess a functional group that would allow further synthetic elaboration in the subsequent synthetic steps. It was thought that if a functional group could be installed that allowed access to synthons **214-216**, the desired rearrangement could potentially occur *via* a radical, anionic or cationic pathway (Figure 4.1).



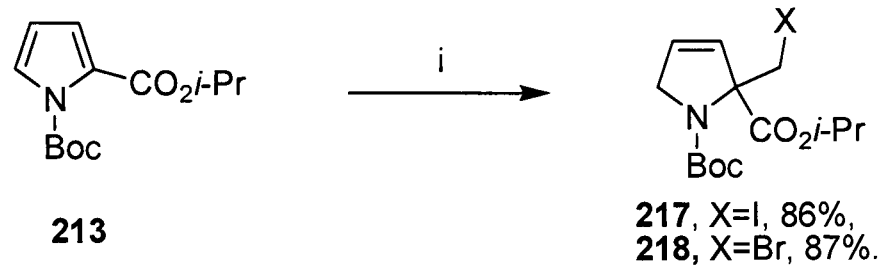
214 **215** **216**

Figure 4.1. *Pyrroline synthons*.

In Chapter 2, it was shown that the Dowd-Beckwith ring-expansion proceeds from a β-ketoester bearing an *exo*-cyclic α-methyl-iodide, –bromide or –selenide (Scheme 2.1). Synthons **214-216** could theoretically be prepared from a pyrroline bearing an *exo*-cyclic α-methylhalide. A pyrroline bearing this motif could be prepared from the partial reduction of an electron deficient pyrrole, quenching the enolate formed with a 1,1-dihaloalkane; a class of electrophile not previously utilised in the partial reduction of aromatic compounds.[†,160]

* BMEA – *bis*methyoxy(ethyl)amine, $pK_a \approx 34$, is used as the proton source to quench the dianion formed during the reaction mechanism.

† 1,2-dihaloalkanes have been widely used to quench excess electrons *before* the addition of the electrophile.

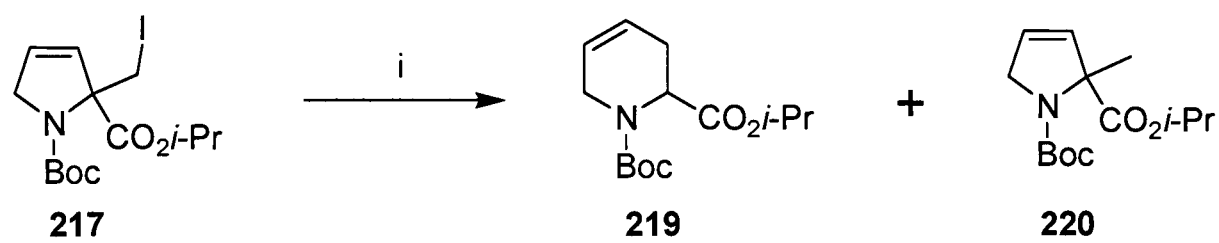


213

217, X=I, 86%,
218, X=Br, 87%.

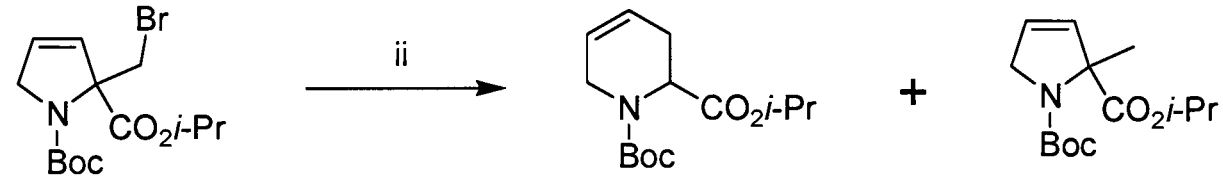
Scheme 4.4. *Reagents and conditions*: i, Na, NH_3, BMEA, THF, –78 °C; then isoprene;* then CH_2I_2 or CH_2Br_2; then NH_4Cl.

Previous preliminary investigations into this area by Donohoe and M^{c}Riner had found that electron deficient pyrrole **213** could be reductively alkylated using either diiodomethane or dibromomethane as the electrophile (Scheme 4.4).[168]



217 **219** **220**

88%, 5:1 mixture.



218 **219** **220**

97%, 10:1 mixture.

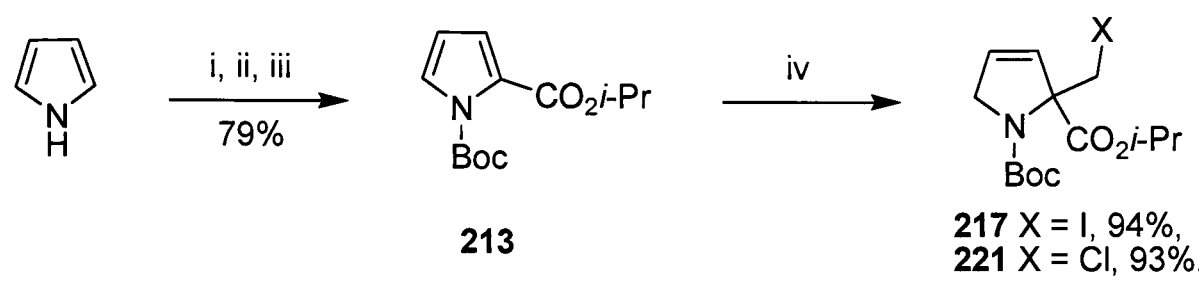
Scheme 4.5. *Reagents and conditions*: i, Bu_3SnH and AIBN, 4 hour syringe pump addition, PhH, Δ; ii. Bu_3SnH and AIBN, 12 hour syringe pump addition, PhH, Δ.

Exposure of pyrrolines **217** and **218** to tri-*n*-butyltin hydride furnished the desired radical ring-expansion product (tetrahydropyridine **219**) and the radical reduction product (pyrroline **220**, Scheme 4.5).[168] Despite the mixture of products obtained, the overall mass recovery was high.

Work for this thesis began by investigating the one carbon radical ring-expansion of pyrrolines in detail; the first goal was to obtain tetrahydropyridine **219** as the sole product of rearrangement.

* Isoprene is added to quench any excess electron in the reduction medium.

Electron deficient pyrrole **213** can easily be prepared in a three step sequence that can be carried out on a multi-gram scale (Scheme 4.6). The trichloroacetyl group, installed by electrophilic substitution of pyrrole with trichloroacetyl chloride, was displaced with the alkoxide of *iso*-propanol. The pyrrole nitrogen was protected as a carbamate with the sterically bulky and electron withdrawing *tert*-butyl carbonate (Boc) group to give electron deficient pyrrole **213** in high overall yield (Scheme 4.6).

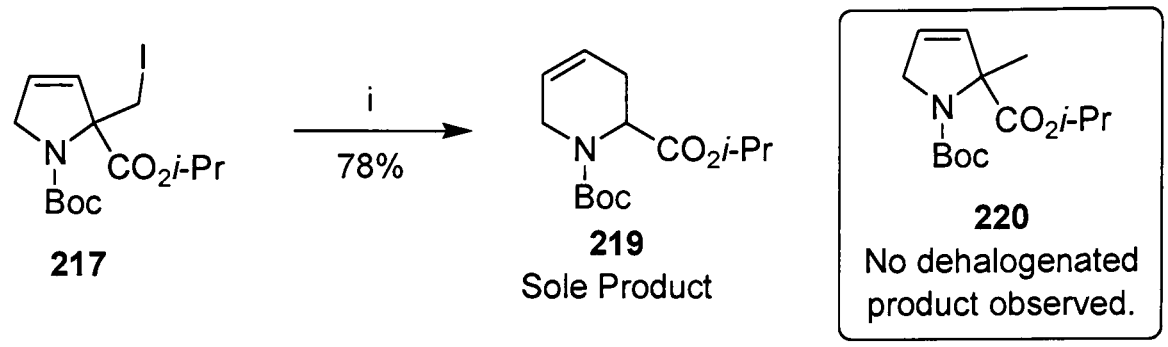


Scheme 4.6. *Reagents and conditions*: i, Trichloroacetyl chloride, Et_2O, 0 °C → room temperature, 95%; ii, NaH, *i*-PrOH, THF, room temperature, 87%; iii, Boc_2O, DMAP, CH_2Cl_2, room temperature, 96%; iv, Li, NH_3, BMEA, THF, –78 °C; then isoprene; then CH_2I_2 or $ClCH_2I$; then NH_4Cl.

When subjected to the partial reduction, using diiodomethane as the electrophile, pyrrole **213** was smoothly converted to pyrroline **217** in excellent yield. The rotamerically split proton NMR spectrum* showed the disappearance of the aromatic protons and the introduction of two olefin signals as doublets of triplets (6.12, 6.06 and 5.42, 5.39 ppm). The iodomethyl moiety was identified by the diastereotopic doublet (4.40, 4.12 and 3.80, 3.76 ppm) in the proton NMR and confirmed by its diagnostic upfield shift in the carbon-13 NMR (13.7 and 13.4 ppm).

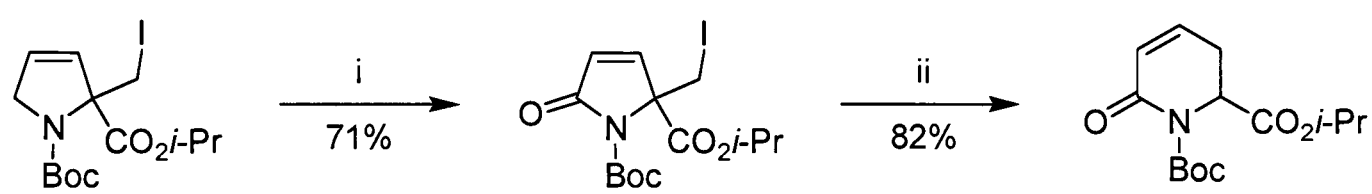
When chloroiodomethane was used as the electrophile, pyrroline **221** was obtained in high yield (Scheme 4.6). Evidence for the formation of **221** came from the proton NMR, which showed the disappearance of the aromatic protons, the introduction of two olefin signals as a doublet of triplets (6.10, 6.04 and 5.50, 5.47 ppm) and a diastereotopic doublet (4.51, 4.26 and 4.01, 3.97 ppm) due to the chloromethyl moiety. The 3:1 ratio of isotopes in the electrospray mass spectrum confirmed the introduction of chlorine into the molecule (MNa^+ 326 and 328).

* The presence of the Boc group on nitrogen often restricts free rotation of the molecule, caused by delocalistion of the nitrogen lone pair (the N-C bond of the Boc group has substantial sp^2 character), which is manifested in the proton and carbon NMR spectra by the doubling of peaks.



Scheme 4.7. *Reagents and conditions*: i, Bu_3SnH and AIBN in PhH (0.01 mol dm^{-3}), 12 hour syringe pump addition, PhH, Δ.

When pyrroline **217** was treated to a low concentration (0.01 mol dm^{-3}) of tri-*n*-butyltin hydride and AIBN, added over a 12 hour period *via* a syringe pump, tetrahydropyridine **219** was obtained as the sole product in high yield (Scheme 4.7), after removal of the tin residues as described by Curran.[169] Loss of the iodomethyl moiety and the introduction of the CH α to the nitrogen carbamate and ester was shown by proton NMR (5.04-4.94 and 4.79 ppm) and confirmed by carbon-13 NMR (52.5 and 51.2 ppm).



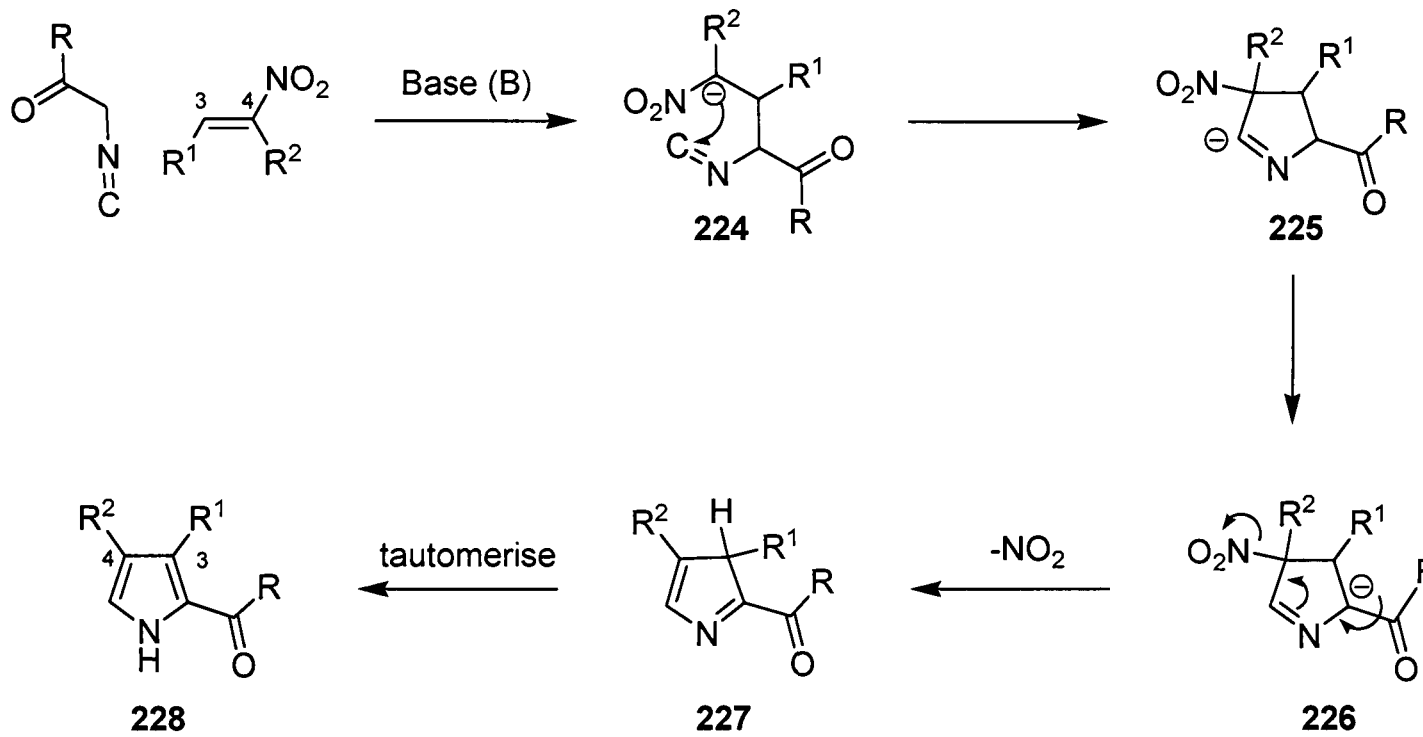
217 **222** **223**

Scheme 4.8. *Reagents and conditions*: i, CrO_3, H_2SO_4 (2.0 mol dm^{-3}), acetone, room temperature; ii, Bu_3SnH and AIBN in PhH (0.01 mol dm^{-3}), 12 hour syringe pump addition, PhH, Δ.

Focus centred on the general applicability of the ring-expansion methodology by examining substitution patterns around the pyrroline ring. Allylic oxidation[170] of pyrroline **217**, using Jones' reagent[171, 172] gave lactam **222** in good yield (Scheme 4.8). Presumably delocalisation of the nitrogen lone pair into the carbonyl group of the enone moiety permits the N-C bond of the Boc group more sp^3 character, allowing less hindered rotation; hence the NMR spectra ceased to be rotamerically split. Proton NMR showed the disappearance of the NCH_2 and the presence of the electron deficient olefin of the enone (doublets at 6.67 and 6.33 ppm). Carbon-13 NMR showed three carbonyl peaks (167.7, 164.9 and 148.4 ppm) and IR spectroscopy confirmed the introduction of the lactam by the presence of three carbonyl stretches (ν_{CO} 1788, 1754 and 1712 cm^{-1}).

Reaction of lactam **222** with tri-*n*-butyltin hydride furnished the ring expanded lactam **223** in high yield, after the removal of tin residues (Scheme 4.8). Although the work-up

procedure described by Curran was not successful, treatment of the reaction mixture with aqueous potassium fluoride, as described by Stille[173] and Leibner,[174] removed all tin residues. The disappearance of the iodomethyl group and appearance of the proton α to the carbamate as a multiplet (5.00-4.97 ppm) was shown by proton NMR. Carbon-13 NMR still showed the presence of all three carbonyl carbons (170.1, 162.5 and 152.2 ppm).



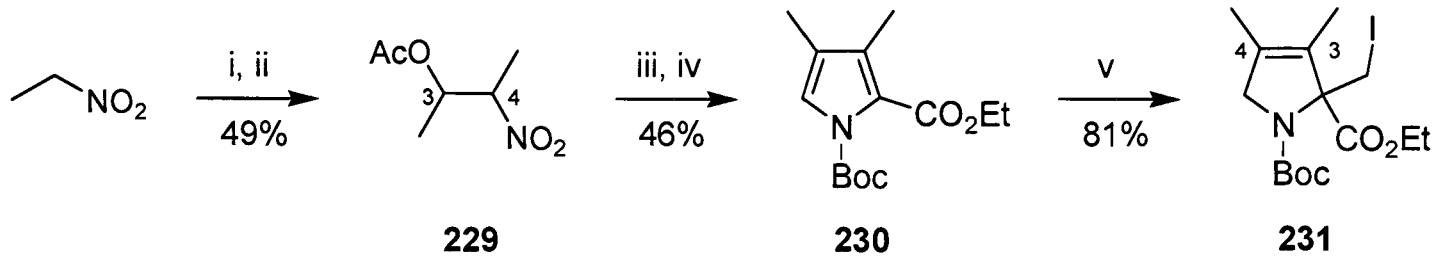
Scheme 4.9. *Mechanism of the Barton-Zard reaction.*

Use of the Barton-Zard reaction[175] allowed facile access to pyrroles bearing alkyl substituents at the C-3 and C-4 positions (Scheme 4.10). Essentially a condensation between a nitroolefin and an α-isocyano-ester, the Barton-Zard reaction takes advantage of the strong ability of a nitro group to activate an olefin towards Michael additions and propensity to act as a leaving group in situations where $E1_{CB}$ eliminations are favourable. Adduct **224** is formed from a Michael addition of the isocyanoester to the nitroolefin, which cyclises to species **225** through internal attack of the nitronate on the isocyano moiety. Proton exchange forms intermediate **226**, which eliminates the nitronate ion *via* an $E1_{CB}$ elimination to give **227**. A tautomerisation furnishes pyrrole **228** (Scheme 4.9).

Owing to their very reactive nature, nitroolefins are often formed *in situ* during the Barton-Zard procedure from nitro acetate precursors;[176,*] hence nitro acetate **229** was prepared as a 1:1 mixture of diastereoisomers by a nitroaldol condensation and protection of the free alcohol with acetic anhydride (Scheme 4.9). Proton NMR showed the methyl group of the

* This is an approach commonly used in large scale syntheses of pyrroles using the Barton-Zard reaction. See reference 176.

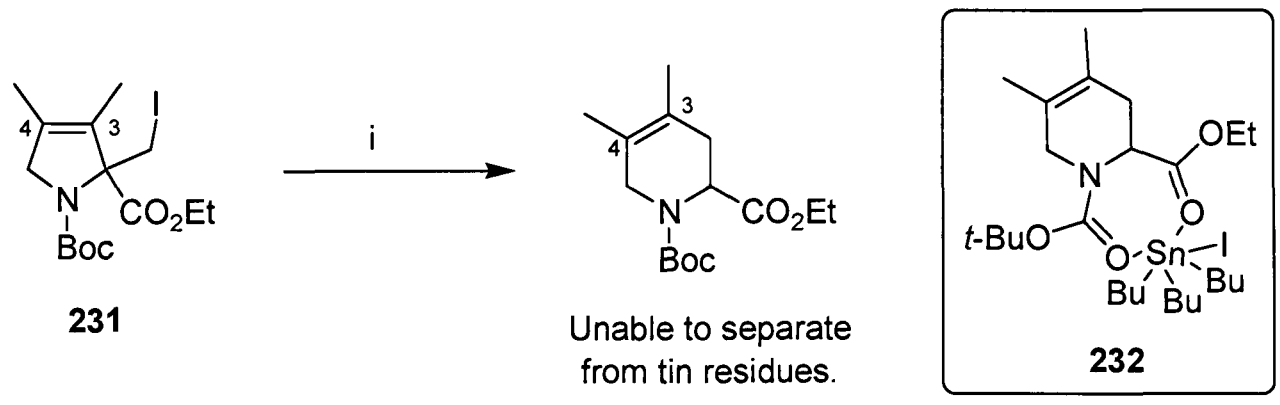
acetate moiety as two singlets* (2.1 and 1.9 ppm) and the proton α to the ester as a multiplet (5.34-5.23 ppm).



229 **230** **231**

Scheme 4.10. *Reagents and conditions*: i, Acetaldehyde, KF, *i*-PrOH, 0 °C → room temperature, 49%; ii, Ac_2O, DMAP, CH_2Cl_2, room temperature, 100%; iii, Ethyl isocyanoacetate, DBU, *i*-PrOH, THF, 0 °C → room temperature, 51%; iv, Boc_2O, DMAP, CH_2Cl_2, room temperature, 90%; v, Li, NH_3, BMEA, THF, –78 °C; then isoprene; then CH_2I_2; then NH_4Cl.

When ethyl isocyanoacetate† was used in the Barton-Zard reaction, the desired pyrrole bearing methyl groups at C-3 and C-4 was obtained (Scheme 4.10). The pyrrole nitrogen was protected with the Boc group in a moderate overall yield, but the sequence was amenable to large scale preparation of **230**. Partial reduction furnished pyrroline **231** in a good yield; the electron donating effect of the alkyl substituents on the pyrrole backbone causes the pyrrole to be less susceptible to reduction than pyrrole **213**. The diagnostic upfield shift in the carbon-13 NMR confirmed the successful inclusion of the iodomethyl moiety (12.9 and 12.7 ppm).



231

Unable to separate from tin residues.

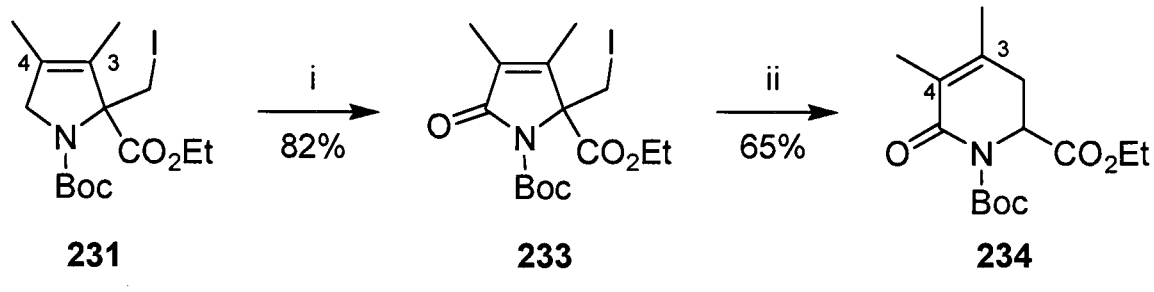
232

Scheme 4.11. *Reagents and conditions*: i, Bu_3SnH and AIBN in PhH (0.01 mol dm^{-3}), 12 hour syringe pump addition, PhH, Δ.

Although the radical ring-expansion of pyrroline **231** was successful, the tetrahydropyridine formed could never be fully separated from the tin residues (Scheme 4.11). A variety of published methods for the removal of tin residues were tried; borohydride,[177] trimethyl aluminium and aqueous sodium hydroxide,[178] cesium fluoride/cesium hydroxide

* One singlet for each diastereisomer; the lack of selectivity is not of concern as both diastereoisomers react to form the pyrrole in the Barton-Zard reaction in the following step.
† Isopropyl isocyanoacetate is not commercially available; hence ethyl isocyanoacetate was used, resulting in the pyrrole formed having an ethyl ester as opposed to an isopropyl ester.

absorbed onto silica gel,[179] thiophenol,[180] hexane/acetonitrile partitions,[181] 1,8-diazabicylco[5.4.0]undec-7-ene[169] and aqueous potassium fluoride[174] all proved to be unsuccessful. It was thought that, possibly, the Lewis acidic tri-*n*-butyltin iodide by-product was forming a chelate (**232**) between the Lewis basic carbonyl groups of the carbamate and the less sterically bulky ethyl ester (Scheme 4.11).



231 **233** **234**

Scheme 4.12. *Reagents and conditions*: i, CrO_3, H_2SO_4 (2.0 mol dm^{-3}), acetone, room temperature; ii, Bu_3SnH and AIBN in PhH (0.01 mol dm^{-3}), 12 hour syringe pump addition, PhH, Δ.

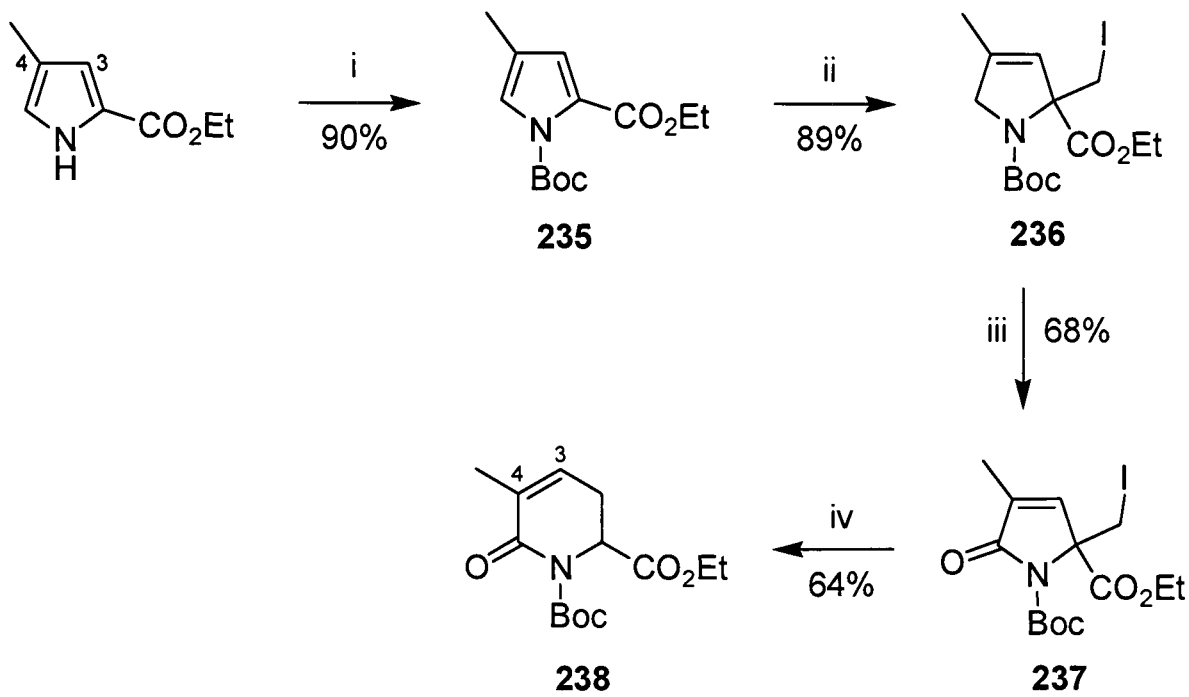
If one of the carbonyl groups was made less Lewis basic, the chelate to the tri-*n*-butyltin iodide would theoretically be weakened; hence lactam **233** was prepared in high yield by allylic oxidation (Scheme 4.12). Successful oxidation was verified by NMR, the spectra ceased to be rotamerically split and the proton NMR showed the disappearance of the NCH_2 moiety. Carbon-13 NMR showed the electron deficient olefin of the enone (148.8 and 132.4) and IR spectroscopy confirmed the formation of lactam **233** (three carbonyl stretches, ν_{CO} 1727, 1712 and 1707 cm^{-1}).

Reaction of lactam **233** with tri-*n*-butyltin hydride furnished the ring expanded lactam **234** in good yield (Scheme 4.12);* proton and carbon-13 NMR confirmed the loss of the iodomethyl moiety and the proton NMR showed the introduction of the proton α to the carbamate as a doublet of doublets at 4.93 ppm (Scheme 4.13).

Pyrroline **236**, bearing a methyl group at C-4, was prepared in an analogous sequence from pyrrole **235**.† Ensuing allylic oxidation, lactam **237** was successfully ring expanded to lactam **238** in good yield after the removal of the tin residues with aqueous potassium fluoride (Scheme 4.13). The successful reaction was first shown by the proton NMR, the electron deficient enone depicted as a multiplet (6.35-6.33 ppm) and the proton α to the carbamate also as a multiplet (4.97-4.95 ppm). Confirmation of the structure of lactam **238** came from the

* A hexane/acetonitrile partition was used to remove the tin residues.
† The starting pyrrole was prepared by Graeme Freestone within our Laboratories using the Barton-Zard method with 2-nitro-3-acetoxyl-propane and ethyl isocyanoacetate.

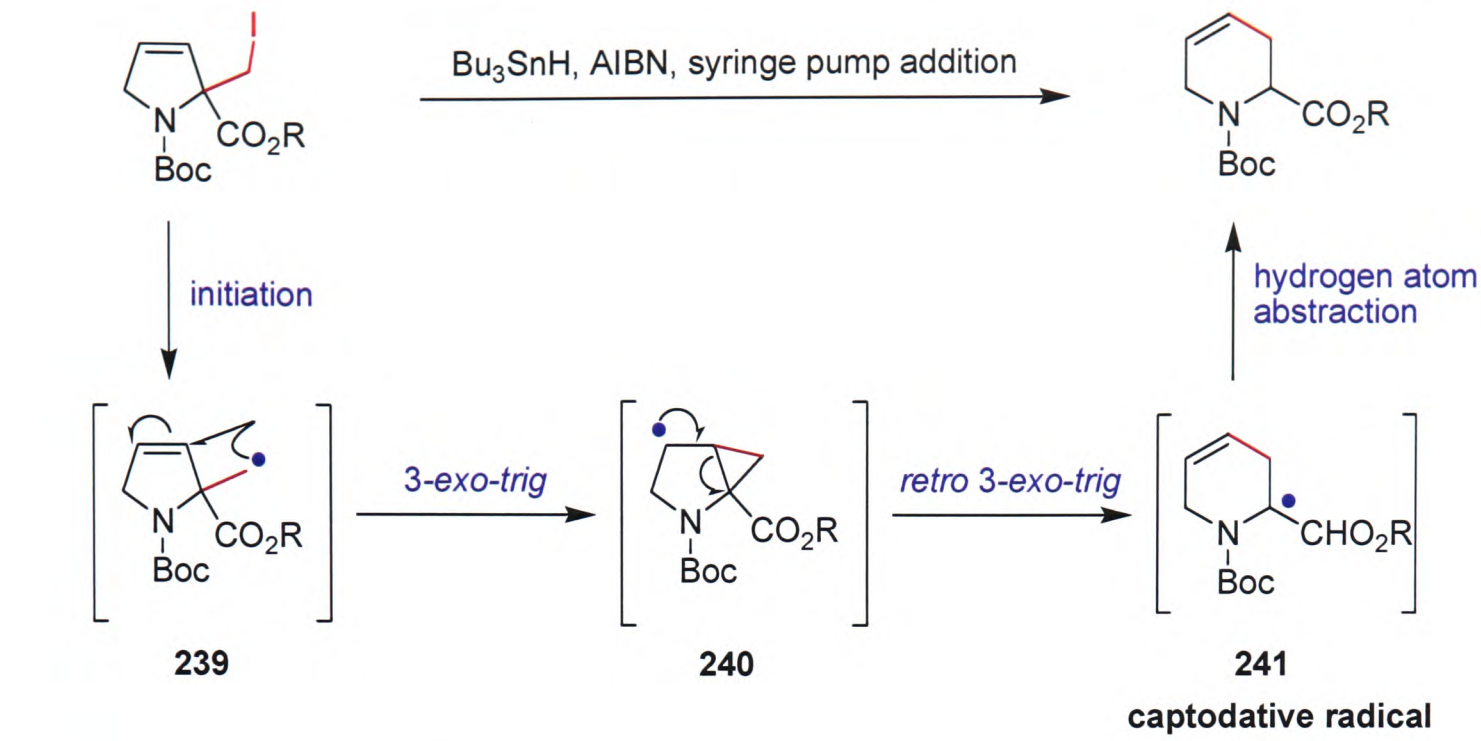
carbon-13 NMR and electrospray mass spectrum, which showed the enone olefin (134.0 and 133.0 ppm) and parent peak for MNa^+ (306) respectively.



Scheme 4.13. *Reagents and conditions*: i, Boc_2O, DMAP, CH_2Cl_2, room temperature; ii, Li, NH_3, BMEA, THF, –78 °C; then isoprene; then CH_2I_2; then NH_4Cl; iii, CrO_3, H_2SO_4 (2.0 mol dm^{-3}), acetone, room temperature; iv, Bu_3SnH and AIBN in PhH (0.01 mol dm^{-3}), 12 hour syringe pump addition, PhH, Δ.

4.2 *Mechanistic Studies.*

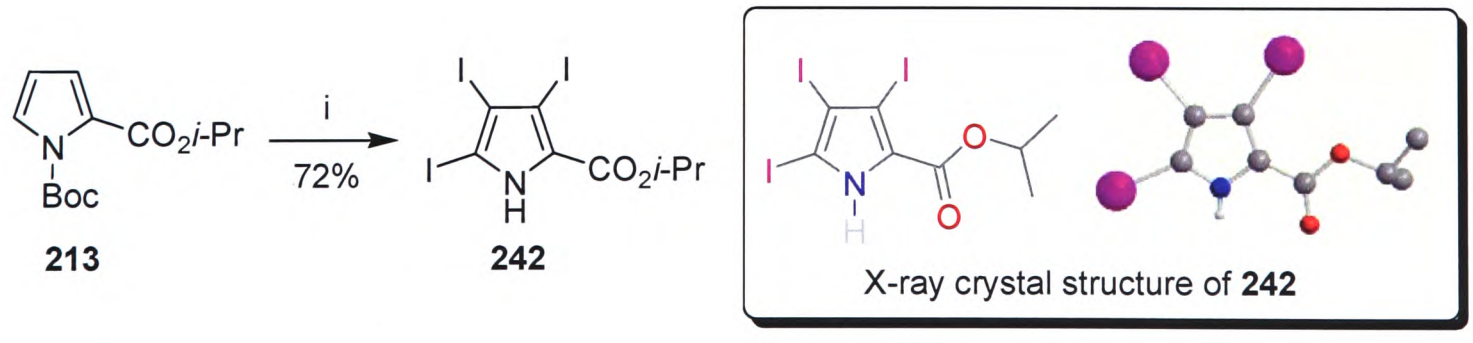
With regards to the mechanism of the one carbon ring-expansion (Scheme 4.14), we postulate that after initial formation of the SOMO (nucleophilic) radical **239**, a 3-*exo*-trig cyclisation onto the LUMO of the olefin forms intermediate **240**. A strain driven retro 3-*exo*-trig then opens the bicycle, to generate the thermodynamically more stable captodative and tertiary radical **241**. Abstraction of hydrogen atom from tri-*n*-butyltin hydride furnishes the tetrahydropyridine (Scheme 4.14).



Scheme 4.14. *Proposed mechanism for one carbon ring-expansion of pyrrolines.*

The mechanism proposed in this thesis is in accordance with that proposed by Dowd for the carbocyclic one carbon ring-expansion.[18] Although one carbon radical ring-expansions are well documented,[23-25] examples of initial attack of the radical onto an olefin to promote ring-expansion are extremely rare (see Chapter 2).

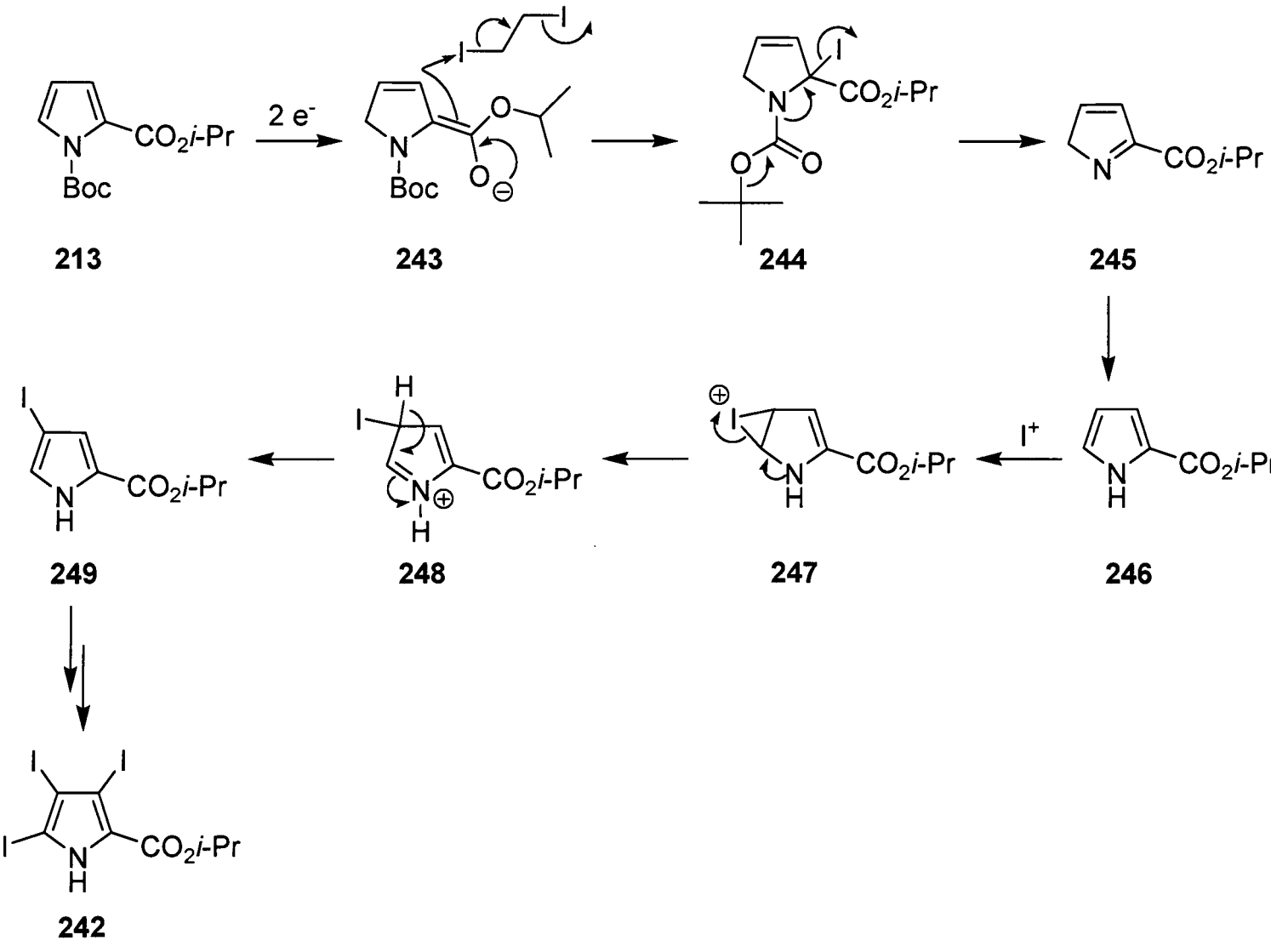
It has been shown that the one carbon radical ring-expansion is tolerant with respect to substitution patterns round the pyrroline ring; our next aim was to seek proof of the mechanism proposed in Scheme 4.14. The rearrangement of **240** is promoted by a strain induced retro 3-*exo*-trig cleavage. It was envisaged that formation of a more thermodynamically stable bicycle could prevent the ring-opening reaction. Hence, the cyclisation of pyrrolines with a longer alkyl tether before the halogen moiety was next investigated.



Scheme 4.15. *Reagents and conditions*: i, Li, NH_3, BMEA, THF, –78 °C; then isoprene; then ICH_2CH_2I; then NH_4Cl.

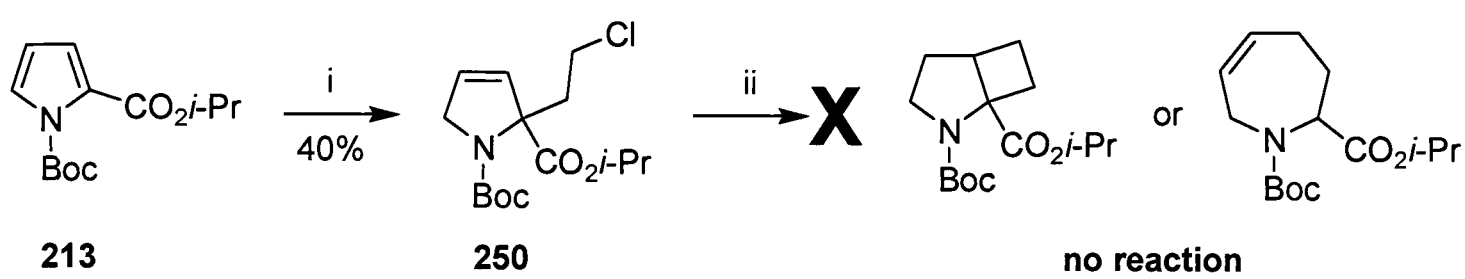
In an attempt to install a two carbon atom tether before the halogen moiety, pyrrole **213** was reductively alkylated with 1,2-dioodoethane which gave a crystalline product in good yield (Scheme 4.15). Although the proton NMR showed the disappearance of the aromatic protons, no new olefin signals were observed. Instead the proton NMR showed the presence of the *iso*-propyl ester (heptet at 5.06 ppm and a doublet at 1.29 ppm) and a miscellaneous singlet at 3.34 ppm. X-ray crystallography showed the structure to be the triiodo pyrrole **242** (Scheme 4.15).

With respect to a mechanism for the formation of pyrrole **242** (Scheme 4.16), we postulate that 1,2-diiodoethane acts as a source of electrophilic iodine (I^+); enolate **243** is iodinated to form iodide species **244**. The Boc group then collapses allowing an elimination of the iodide to furnish intermediate **245** that tautomerises to give pyrrole **246**. Iodination of the more electron rich olefin gives iodonium ion **247**, which is opened by the nitrogen lone pair to furnish species **248**. Loss of proton gives pyrrole **249** that can then under go the iodination elimination sequence until triiodo pyrrole **242** is formed.



Scheme 4.16. *Proposed mechanism for the formation of* ***242****.*

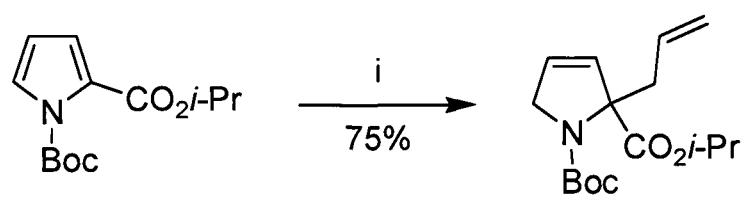
The desired two carbon tether could successfully be installed by a partial reduction of pyrrole **213** using 1,2-bromo-chloroethane as the electrophile, albeit in moderate yield (pyrroline **250**, Scheme 4.17). The success of the reaction was shown by the proton NMR, the aromatic protons had disappeared, and two new olefin signals as doublet of triplets (6.00, 5.93 and 5.54, 5.48 ppm) and the two protons α to the chlorine moiety as a multiplet (3.44-3.32 ppm) were present. The carbon-13 NMR showed the presence of a carbon α to chlorine (40.1 and 39.6 ppm) and the electrospray mass spectrum revealed the characteristic isotope splitting from the presence of a chlorine atom (342 and 340, MNa^+). However, when pyrroline **250** was reacted with the radical condition no reaction was observed, with only starting material returned (Scheme 4.17).



213 **250** **no reaction**

Scheme 4.17. *Reagents and conditions*: i, Li, NH_3, BMEA, THF, –78 °C; then isoprene; then $BrCH_2CH_2Cl$; then NH_4Cl; ii, Bu_3SnH and AIBN in PhH (0.01 mol dm^{-3}), 12 hour syringe pump addition, PhH, Δ.

Believing that this result was due to the combination of two facts: firstly, a primary radical is more difficult to initiate from a chloride than an iodide and secondly the chlorine atom is in a hindered position, pyrrole **213** was reductively alkylated using 1,3-diiodopropane in an attempt to introduce a three carbon tether before the iodide moiety (Scheme 4.18).



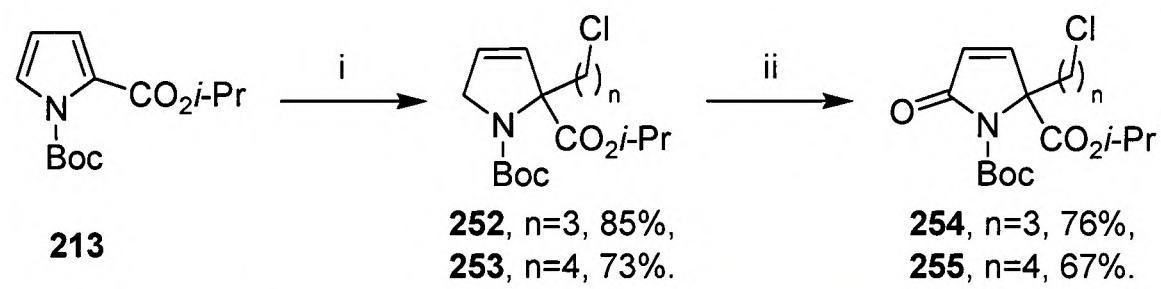
213 **251**

Scheme 4.18. *Reagents and conditions*: i, Li, NH_3, BMEA, THF, –78 °C; then isoprene; then $I(CH_2)_3I$; then NH_4Cl.

Although the proton NMR spectrum showed the disappearance of the aromatic protons, a signal corresponding to protons α to an iodide was not present. The structure was confirmed as the allyl pyrroline **251**; although the pyrrole was reductively alkylated, an E2 elimination (presumably under the basic reaction conditions) furnished the terminal olefin. Proton NMR showed an extra three protons in the olefin region; with the terminal olefin CH

as a multiplet at 5.66-5.53 ppm and the diagnostic upfield shift of the terminal olefin CH_2 (5.07-5.00 ppm). The electrospray mass spectrum also showed two mass peaks at 318 (MNa^+) and 296 (MH^+).

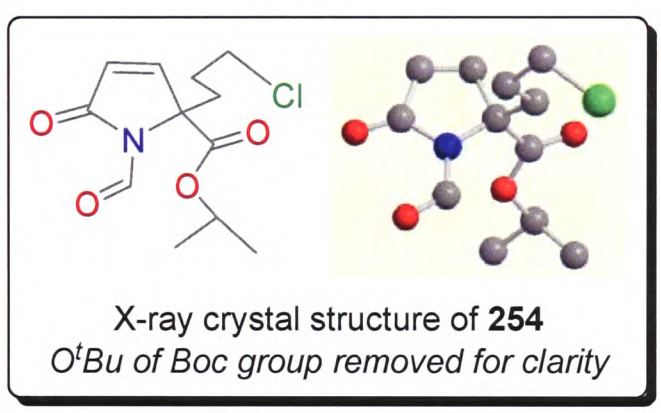
However, when pyrrole **213** was reductively alkylated using either 1,3-chloroiodopropane or 1,4-chloroiodobutane pyrrolines **252** and **253** were obtained in high yields (Scheme 4.19).



213

252, n=3, 85%,
253, n=4, 73%.

254, n=3, 76%,
255, n=4, 67%.



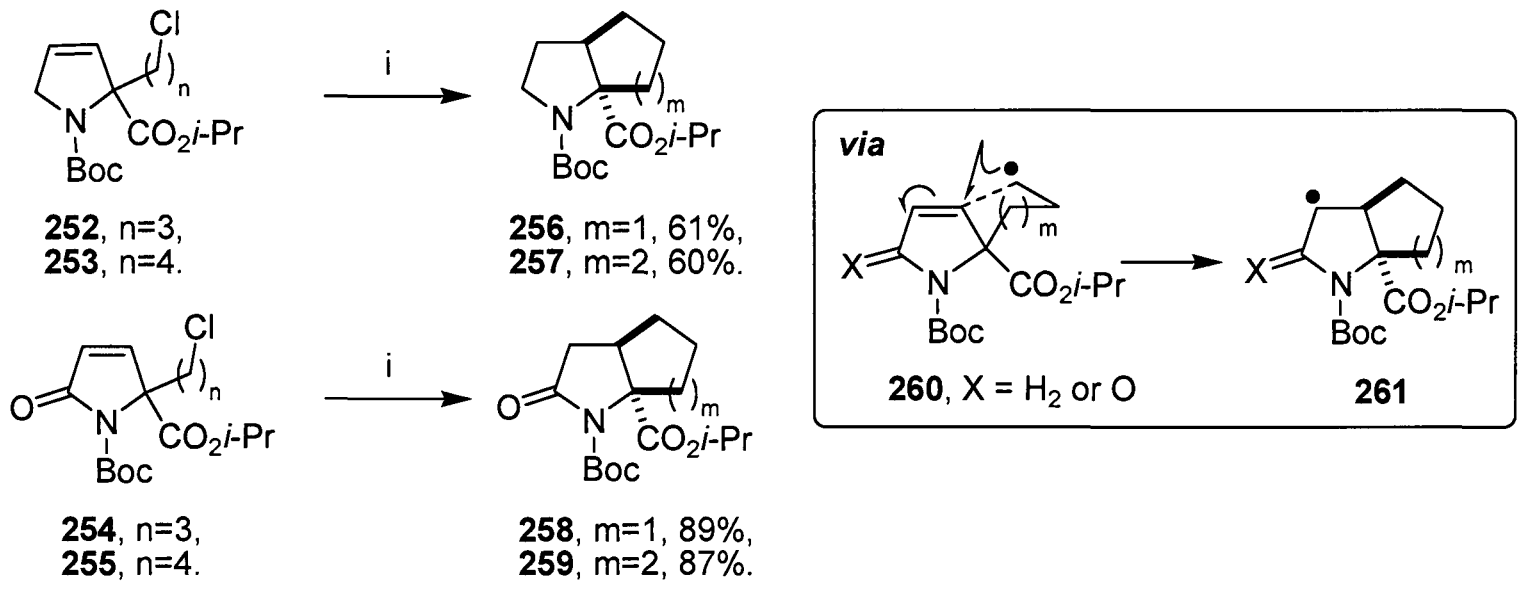
X-ray crystal structure of **254**
O^{t}Bu of Boc group removed for clarity

Scheme 4.19. *Reagents and conditions*: i, Li, NH_3, BMEA, THF, –78 °C; then isoprene; then $CI(CH_2)_3I$ or $CI(CH_2)_4I$; then NH_4Cl; ii, , CrO_3, H_2SO_4 (2.0 mol dm^{-3}), acetone, room temperature;

The electrospray mass spectra of both pyrroline **252** and **253** showed the diagnostic isotope splittings for the presence of a chlorine molecule (334 and 332, MH^+ for **252**; 370 and 368, MNa^+ for **253**) and the carbon-13 NMR revealed the carbon α to the chlorine moiety (45.0, 44.8 and 45.0, 44.7 ppm respectively). Allylic oxidation of pyrrolines **252** and **253** proceeded in good yields to give lactams **254** and **255** (Scheme 4.19). The NMR spectra ceased to be rotamerically split and the carbon-13 NMR showed the introduction of the carbonyl group for the enone (168.0 and 167.8 ppm respectively). Lactam **254** was a crystalline solid and X-ray crystallography was used to prove the structure; lactam **255** was assigned by analogy.

Pyrrolines **252-255** were treated with tri-*n*-butyltin hydride to give fused bicycles **256-259** (Scheme 4.20). After removal of the tin residues with the 1,8-diazabicylco[5.4.0]undec-7-ene work-up, bicycles **256** and **257** were obtained in good yields; however dehalogenated

side products were also observed (7:1 ratio in favour of the fused bicycles).* Both compounds' electrospray mass spectra showed the disappearance of the chlorine isotopes and the presence of parent ion peaks (298, MH^+ and 312, MH^+). Proton NMR revealed the disappearance of the olefin signals and the introduction of the CH moiety at the ring junction as multiplets (2.62-2.50 and 2.48-2.31 ppm respectively for bicycles **256** and **257**). The yields for the lactam cyclisation (**258** and **259**)† are significantly higher and no dehalogenated side product was observed. Presumably, this is due to the lower energy LUMO of the olefin in the enone moiety promoting addition onto the electrophilic olefin; the resultant radical is stabilised by the adjacent carbonyl moiety (intermediate **261**, Scheme 4.20). The electrospray mass spectra of the lactams revealed the loss of the chlorine moiety by the disappearance of the chlorine isotopes and the carbon-13 NMR showed the introduction of the CH carbon on the ring junction (41.1 and 35.4 ppm for **258** and **259** respectively).

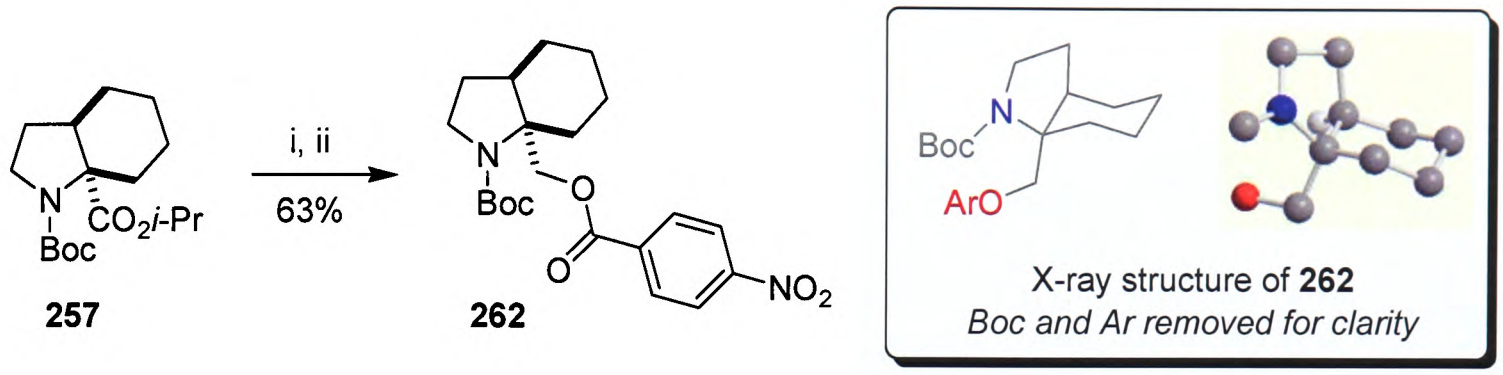


Scheme 4.20. *Reagents and conditions*: i, Bu_3SnH and AIBN in PhH (0.01 mol dm^{-3}), 12 hour syringe pump addition, PhH, Δ.

5-*Exo* and 6-*exo* radical cyclisations onto cyclic olefins to furnish the [3.3.0] and [3.4.0] fused ring systems have been well precedented to form the *cis* diastereoisomer at the ring junction;[182] for steric reasons the 5-*exo* and 6-*exo* annelation to cyclic olefins affords *cis* products. This *cis* cyclisation is interpreted in terms of favourable interactions between the methyl radical and the π-bond, which can occur very early in the transition state of radical additions to olefins (**260**, Scheme 4.20).[183] However to prove unambiguously the stereochemistry of the ring junction, bicycle **257** was converted to a crystalline derivative (Scheme 4.21). The ester was reduced with di-*iso*-butylaluminium hydride and the alcohol

* As determined by 400 MHz proton NMR of the crude reaction mixture.
† Potassium fluoride was used to remove the tin residues.

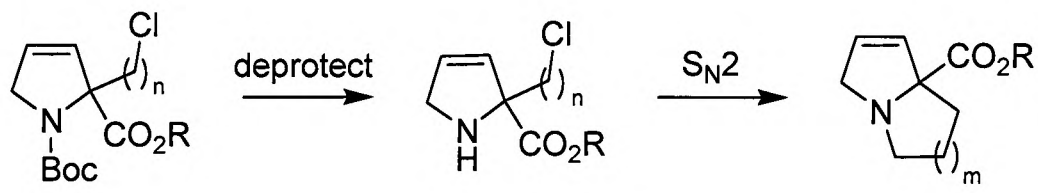
coupled with *para*-nitrobenzyol chloride in moderate overall yield. X-ray crystallography proved the structure of derivative **262** (Scheme 4.21); hence structures **256**, **258** and **259** were assigned by analogy.



Scheme 4.21. *Reagents and conditions*: i, DIBAL-H, CH_2Cl_2, –78 °C → room temperature; ii, *para*-nitrobenzyol chloride, Et_3N, DMAP, CH_2Cl_2, room temperature.

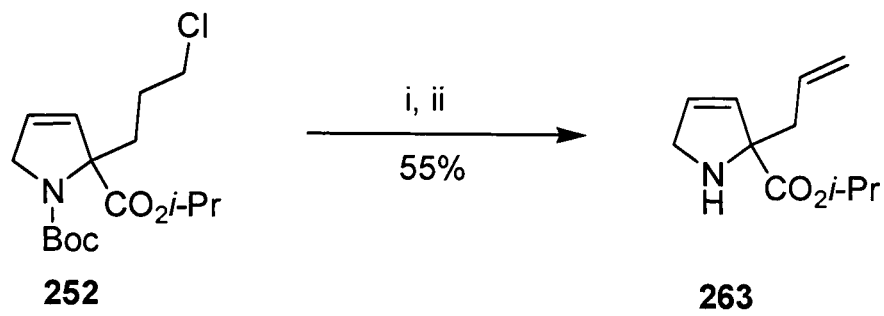
4.3 *Preparation of pyrrolizidines and indolizidines.*

The pyrrolizidine and indolizidine skeletons are found in a variety of natural products.[184-187] Pyrrolines **252** and **253** could provide easy access to these skeletons; deprotection of the nitrogen protecting group followed by S_N2 displacement should afford the pyrrolizidine or indolizidine core (Scheme 4.22).



Scheme 4.22. *Preparation of the pyrrolizidine and indolizidine skeleton.*

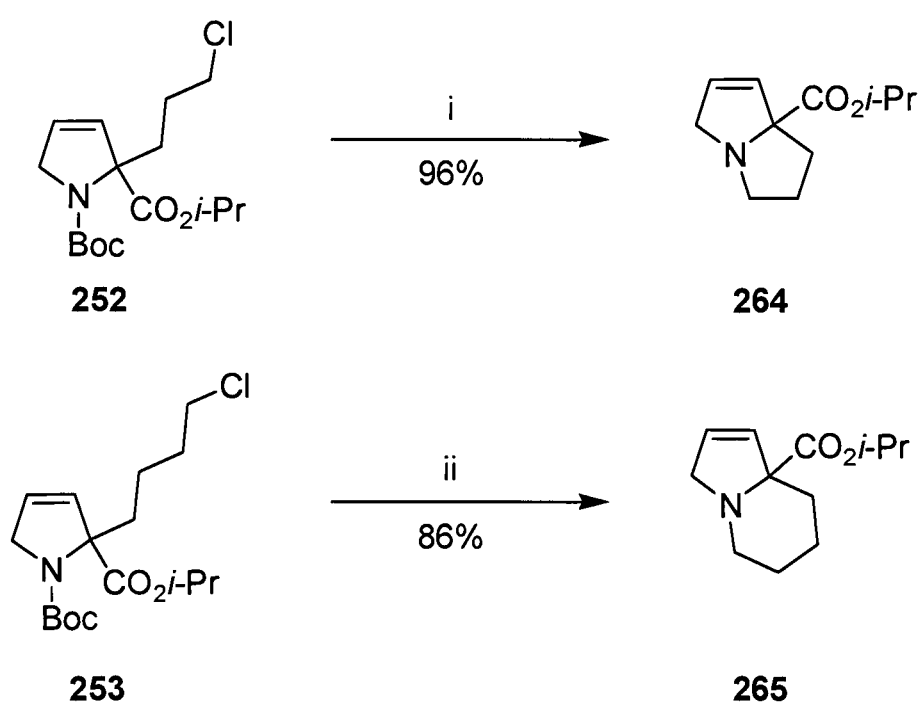
In an initial attempt to form the pyrrolizidine core, pyrroline **252** was reacted with sodium iodide to install a more potent leaving group and the crude product was reacted with acidic Boc deprotection conditions (Scheme 4.23). Although the loss of the Boc group was shown in the proton NMR, 3 extra olefin signals (*c.f.* allyl pyrroline **251**) were also revealed. The structure was identified as pyrroline **263** (Scheme 4.23); the carbon-13 NMR showed the presence of a terminal olefin carbon (118 ppm) and IR spectroscopy verified the presence of the free amine (ν_{NH} 2279 cm^{-1}).



252 **263**

Scheme 4.23. *Reagents and conditions*: i, NaI, acetone, Δ; ii, TFA; then $NaHCO_{3(aq)}$.

Owing to the fact that the elimination of HI appears to be quicker than the Boc deprotection, pyrroline **252** was reacted with the acidic deprotection conditions, utilising a weakly basic aqueous work-up (Scheme 4.24). Proton NMR showed the loss of the Boc group and the appearance of four protons α to nitrogen (3.99, 3.36, 3.28 and 2.62-2.56 ppm). The IR spectrum also did not show the amine stretch expected from deprotected pyrroline, but did show the presence of only one carbonyl (ν_{CO} 1725 cm^{-1}). The amine had spontaneously cyclised during the weakly basic work-up (aqueous sodium bicarbonate), which furnished dihydropyrrolizidine **264** in excellent yield (Scheme 4.24).



252 **264**

253 **265**

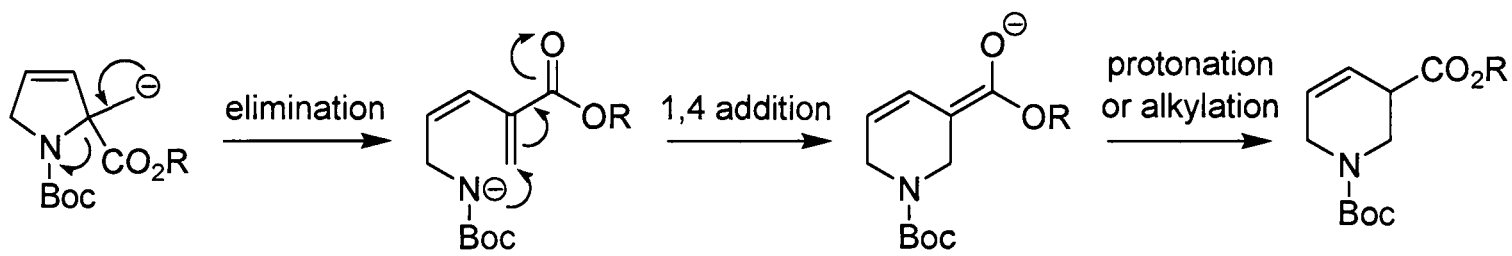
Scheme 4.24. *Reagents and conditions*: i, TFA; then $NaHCO_{3(aq)}$; ii, TFA, CH_2Cl_2; then Et_3N, PhMe, Δ.

Although pyrroline **253** did not self cyclise after nitrogen deprotection, indolizidine **265** was afforded in high yield after refluxing the intermediate trifluroacetic acid salt in toluene with excess triethylamine (Scheme 4.24). The IR spectrum showed the presence of only one carbonyl (ν_{CO} 1720 cm^{-1}) and the NMR spectra showed the introduction of four diastereotopic protons and three carbons α to nitrogen (3.79, 3.62, 3.24-3.17 and 2.92-2.88

ppm in the proton NMR spectrum; 72.2, 56.8 and 45.1 ppm in the carbon-13 NMR spectrum). The electrospray mass spectrum showed the parent ion peak of 210 (MH^+).

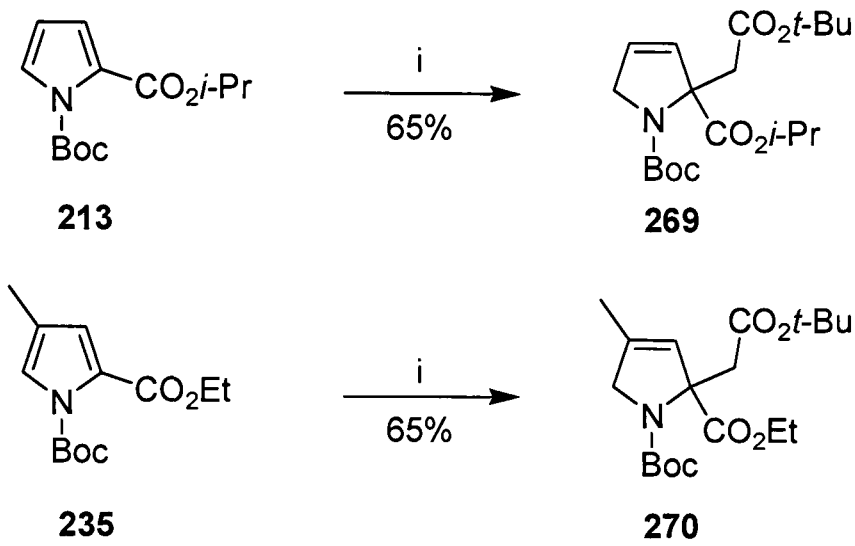
4.4 *Attempted anionic ring-expansions.*

In Chapter 4.1 it was shown that pyrrolines can undergo a ring-expansion rearrangement *via* the radical synthon **214** (Figure 4.1). A second approach to the partially reduced pyridine core using the anionic synthon **215** would allow access to tetrahydropyridines with the ester moiety at C-3 (Scheme 4.25) rather than C-2 (obtained from the radical ring-expansion). The underlying theory is shown in Scheme 4.25. β-Elimination of synthon **215** would give anion **266**, which could undergo a conjugate addition to form species **267**; protonation (or alkylation) of the enolate would then furnish tetrahydropyridine **268**.



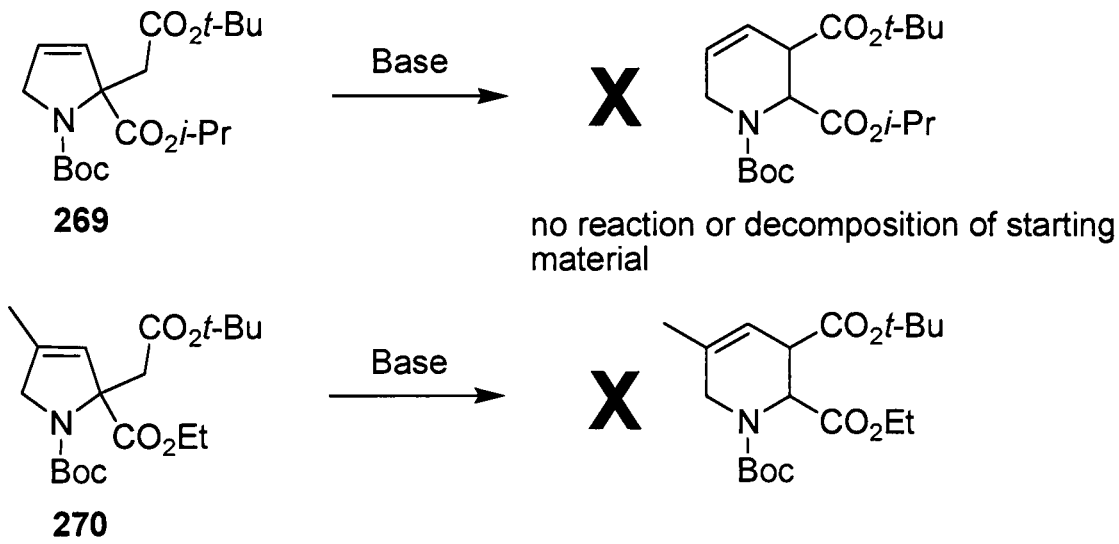
Scheme 4.25. *Preparation of tetrahydropyridines via anionic ring expansion.*

Preparation of synthon **215** by deprotonation was first attempted; Donohoe and House had previously shown that the pyrrole **213** can be reductively alkylated with *tert*-butyl bromoacetate under LiDBB conditions.[165] The electron-withdrawing ester group increases the acidity of the *exo*-cyclic methylene protons; hence pyrroline **269** and **270** were prepared in good yields (Scheme 4.26).



Scheme 4.26 *Reagents and conditions*: i, THF, BMEA, –78 °C; then $Br(CH_2)Br$; $BrCH_2CO_2t$-Bu (excess); then NH_4Cl.

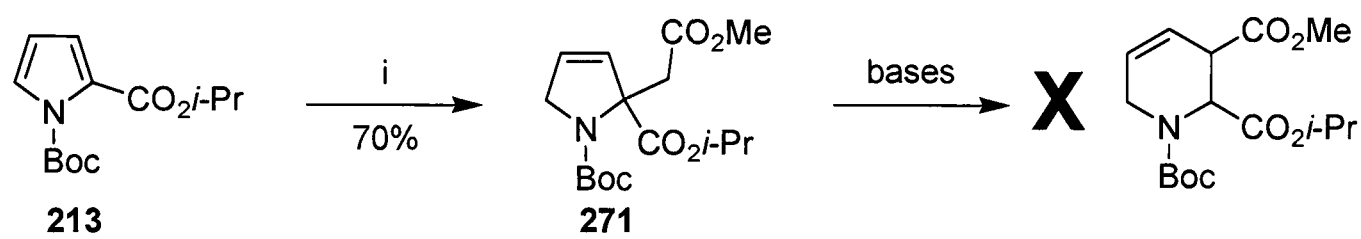
The proton NMR confirmed the conversion of the pyrroles **213** and **235** to pyrrolines **269** and **270** respectively. The aromatic protons disappeared and new signals corresponding to the olefin as doublets of triplets were introduced (5.96, 5.90 and 5.77, 5.68 ppm in the spectrum of **269**; 5.43, 5.38 ppm in the spectrum of **270**); the diastereotopic protons of the *exo*-cyclic methylene were also visible (3.22, 3.01 and 3.12, 2.91 in the spectrum of **269**; 4.28-3.97 ppm in the spectrum of **270**).



Scheme 4.27. *Treatment of pyrrolines with a range of bases to try and induce an anionic rearrangement, see text.*

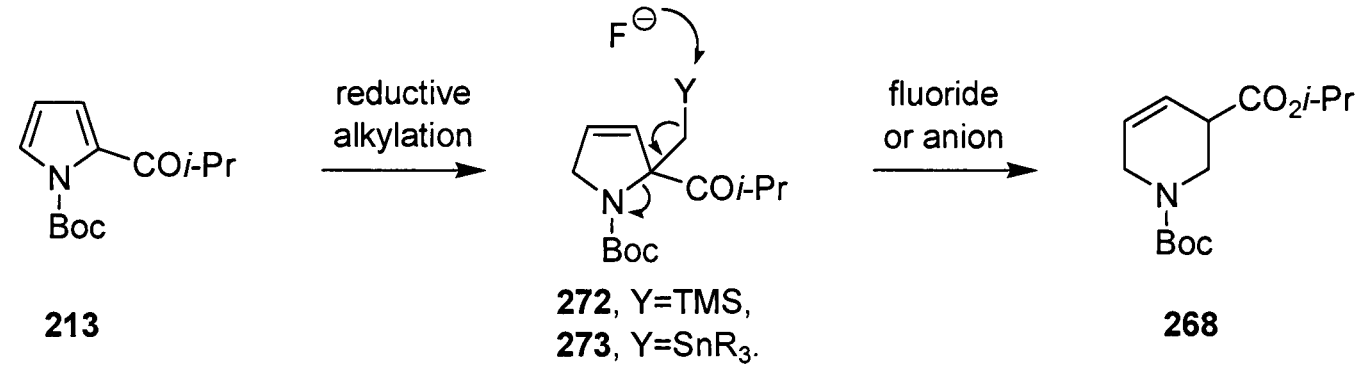
Pyrrolines **269** and **270** were treated with a range of bases to try to induce rearrangement (Scheme 4.27): proton sponge; lithium-, potassium- or sodium-hexamethyldisilazide; sodium hydride; 1,8-diazabicyclo[5.4.0]undec-7-ene; *sec*-butyl lithium and sodamide all failed to induce rearrangement, either returned starting material or decomposition products (as shown by TLC analysis and NMR on the reaction mixture).

It was thought that the sterically bulky *tert*-butyl esters may be preventing deprotonation; hence methyl ester pyrroline **271** was prepared (Scheme 4.28). Treatment with sodium hydride, proton sponge, 1,8-diazabicyclo[5.4.0]undec-7-ene (in dichloromethane and refluxing 1,2-dichloroethane), lithium di-*iso*-propylamine, *sec*-butyl lithium, *tert*-butyl lithium and sodamide all failed to induce rearrangement.



Scheme 4.28. *Reagents and conditions*: i, LiDBB, THF, BMEA, –78 °C; then $Br(CH_2)_2Br$; then $BrCH_2CO_2Me$ (excess); then NH_4Cl; ii, Range of bases see text.

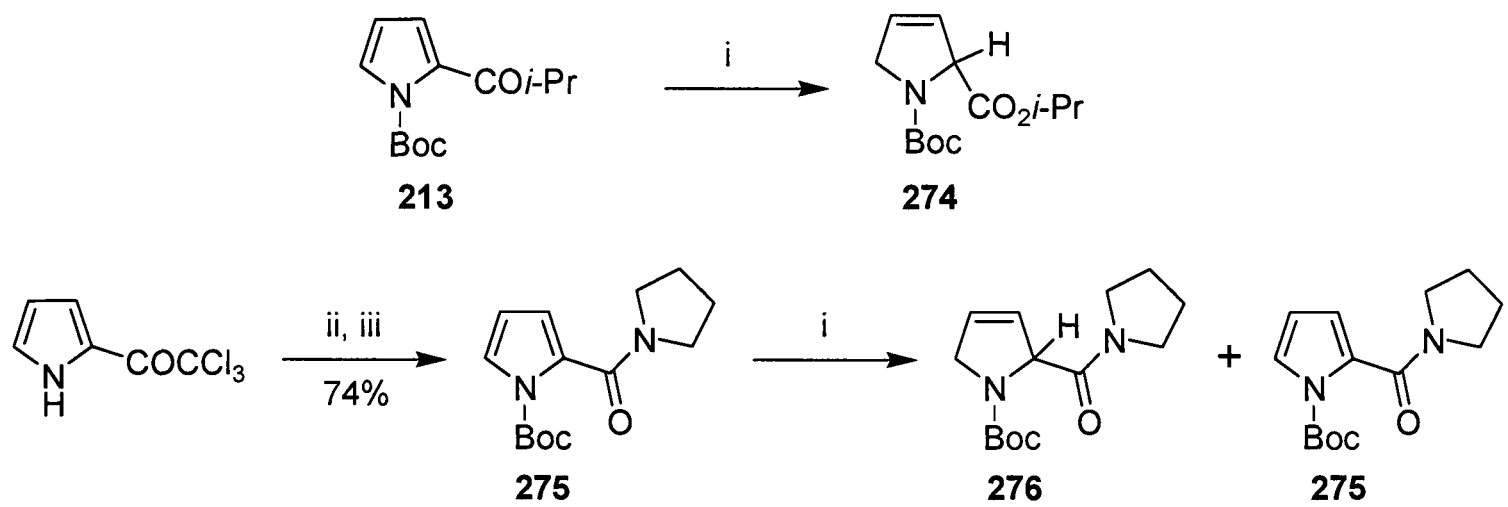
As preparation of synthon **215** (Figure 4.1) by deprotonation of a proton α to an ester was not a viable route, two alternative routes were next investigated. It was envisaged that pyrroline **272** and **272** (Scheme 4.29) could be obtained from the reductive alkylation of pyrrole **213**; treatment with a fluoride source could induce rearrangement to furnish tetrahydrodpyridine **268**.



Scheme 4.29. *Potential route to tetrahydropyridines via anionic ring-expansion.*

When pyrrole **213** was reductively alkylated using (iodomethyl)trimethylsilane as the electrophile (Scheme 4.30), the expected pyrroline was not obtained. Instead the proton NMR showed the presence of a doublet of doublets of doublets (4.94 and 4.87 ppm) which indicated the formation of known pyrroline **274**.[165] The electrophile was not reactive enough to alkylate the enolate at –78°C; the pyrroline ester enolate is not stable at temperatures above –78 °C, but the amide enolate is stable much higher temperature. Hence the known pyrrole amide **275** was prepared (Scheme 4.30); the proton NMR showed the introduction of the Boc moiety (singlet at 1.54 ppm) and the pyrrolidine "backbone" (multiplet at 1.95-1.85 ppm). (Iodomethyl)trimethylsilane was allowed to stir with the amide enolate at –78 °C, and then

warmed to –33 °C (the boiling temperature of ammonia); however the desired pyrroline was still not obtained. The crude proton NMR showed a mixture of the protonated compound **276** and pyrrole **275**.

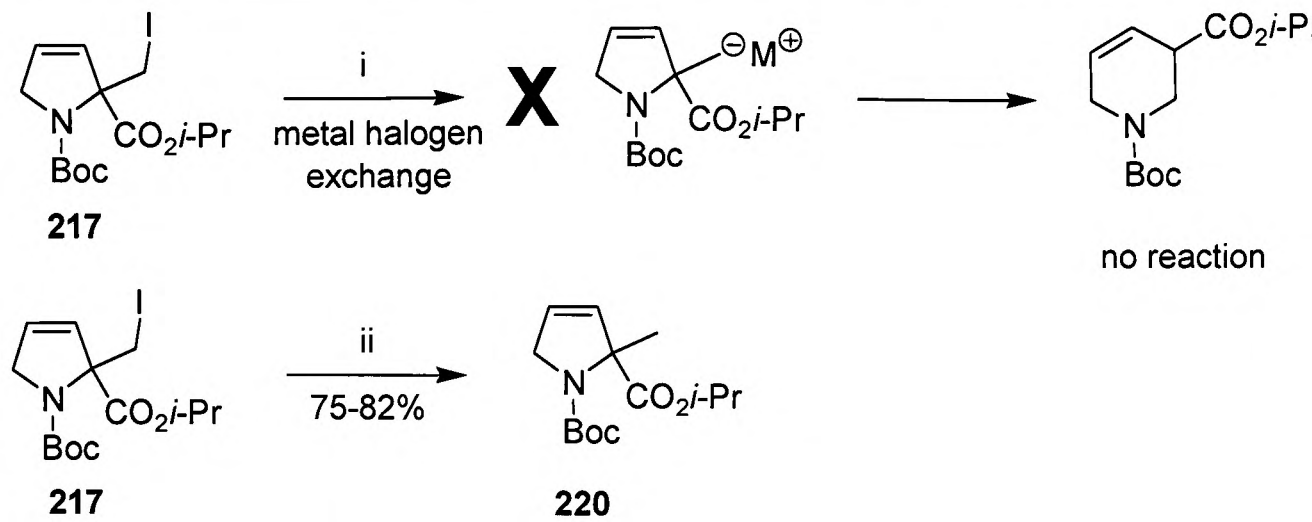


213 **274** **275** **276** **275**

Scheme 4.30. *Reagents and conditions*: i, Li, NH_3, BMEA, THF, –78 °C; then isoprene; then ICH_2TMS; then NH_4Cl; ii, Pyrrolidine, DMF, room temperature; iii, Boc_2O, DMAP, CH_2Cl_2, room temperature; iv, Na, NH_3, BMEA, THF, –78 °C; then isoprene; then ICH_2TMS, –78 °C → –33 °C; then NH_4Cl;

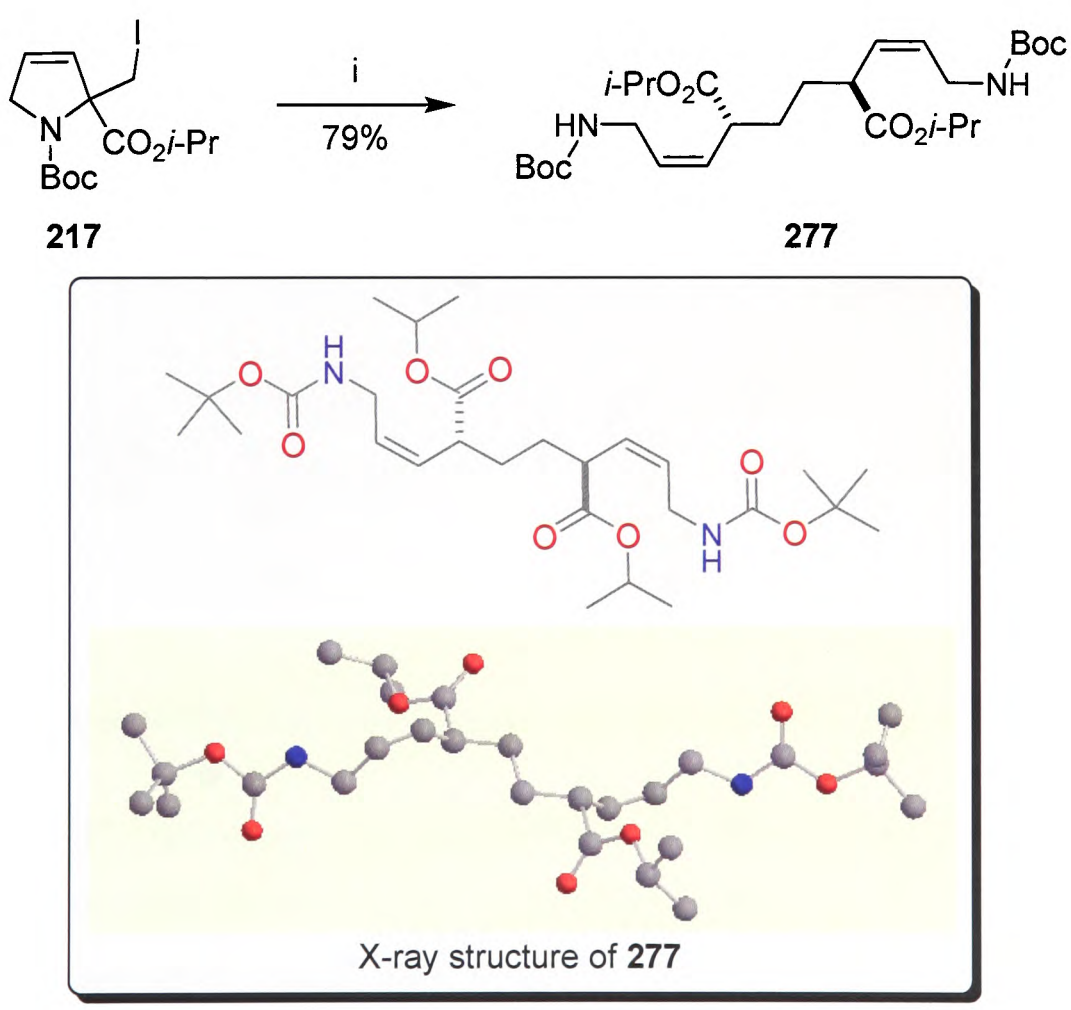
Owing to the problem associated with the reductive alkylation to form pyrroline **272**, attention focused on a halogen metal exchange approach to form the required anion synthon **215** from pyrroline **217** (Scheme 4.31). Initial attempts did not induce the intended rearrangement: *n*-butyl lithium, *n*-butyl lithium/tetramethylethylenediamine, *sec*-butyl lithium or *tert*-butyl lithium only returned starting material and attempts to transmetallate with magnesium (magnesium metal), nickel (nickel chloride), iron (iron$^{(III)}$ chloride) and palladium (palladium acetate) were all unsuccessful with only starting material returned.

Ring expansion of β-ketoesters with samarium iodide[188] and zinc[189] have both been reported, but when pyrroline **217** was treated with samarium iodide, no reaction took place and only starting material was recovered. When pyrroline **217** was treated with activated zinc metal under a variety of conditions, dehalogenated pyrroline **220** was obtained in good yields (Scheme 4.31).



Scheme 4.31. *Reagents and conditions*: i, See text;
ii, Zn, MeOH, AcOH, Δ, 82% or Zn, acetone, Δ, 80% or Zn, EtOH, H_2O, Δ, 75%.

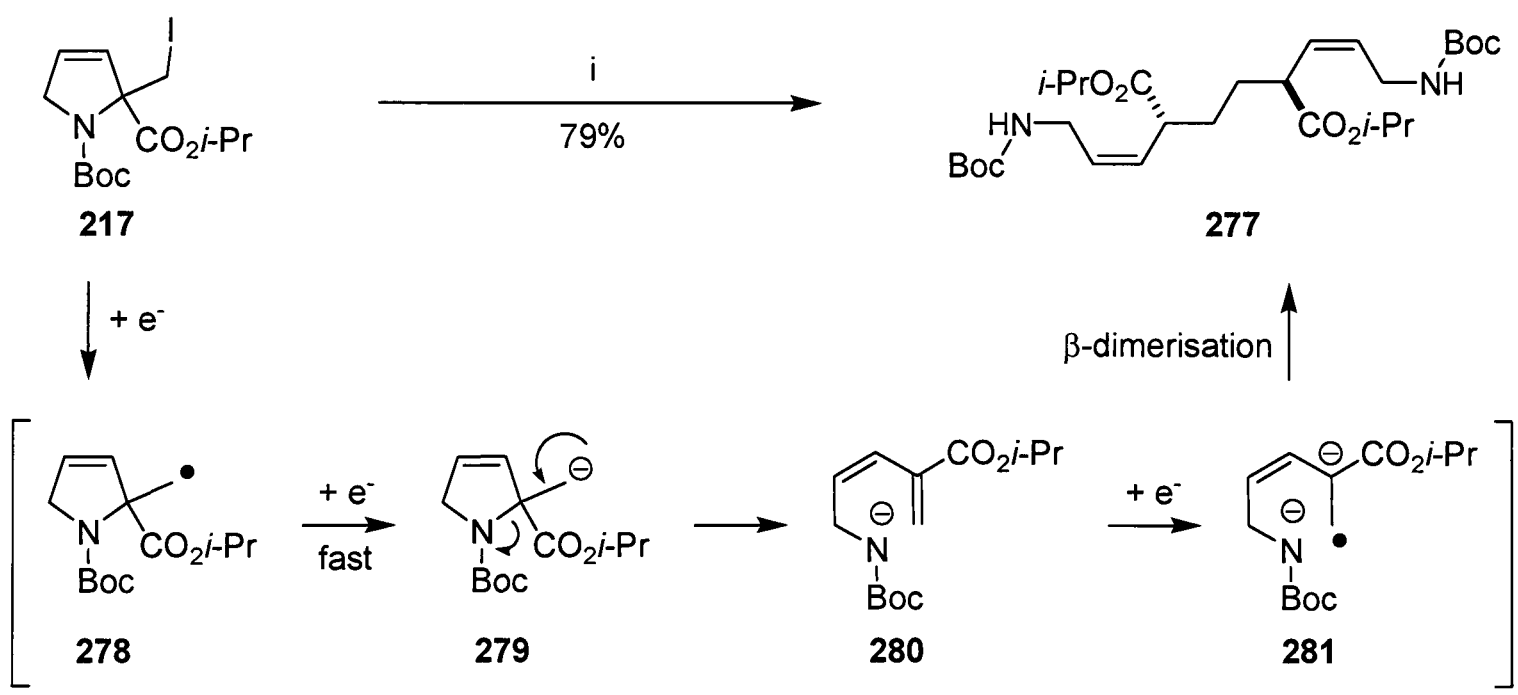
4.5 *Pyrroline ring openings.*



Scheme 4.32. *Reagents and conditions*: i, LiDBB, THF, –78 °C; then NH_4Cl.

With the steric demands of the neo-pentyl centre of the iodide moiety in pyrroline **217** and the success of the radical ring-expansion, formation of the anion (to form synthon **215**) *via* single electron transfer was explored. LiDBB has been widely reported to promote metal halogen exchange by single electron transfer,[190-194] hence pyrroline **217** was treated with LiDBB at –78 °C for two hours. A single crystalline product was obtained; however proton and carbon-13 NMR both ruled out the formation of the desired tetrahydropyridine **268**. Although the Boc group and ester were still present only one methylene group α to nitrogen was observed (3.84-3.69 ppm in the proton NMR and 37.7 in the carbon-13 NMR) and the IR spectrum indicated the presence of an amine (ν_{NH} 3370 cm^{-1}). The structure was solved by X-ray crystallography and assigned as dimer **277** (Scheme 4.32).

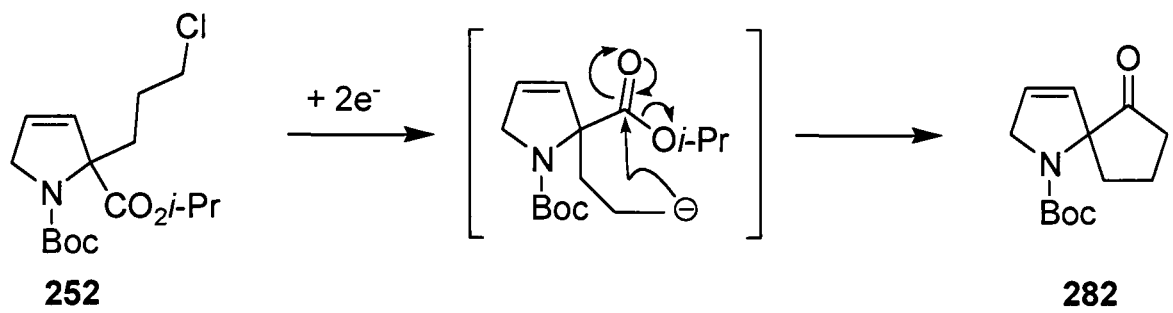
Donohoe and Compton have reported that the sequential addition of two electrons into a carbon-iodine bond is extremely rapid:[195] when the voltammetric response of pentyl iodide was recorded, only one reduction peak was observed, indicating that after the addition of one electron into the carbon-iodine bond, the radical species is immediately reduced to the anion.



Scheme 4.33. *Reagents and conditions*: i, LiDBB, THF, –78 °C; then NH_4Cl.

Pyrroline **217** can accept one electron to form radical **278**, which instantaneously accepts a second electron to be reduced to the anion **279** (Scheme 4.33). Anion **279** β-eliminates to the open chain species **280**, accepts a third electron to form radical anion **281** that dimerises through the β-position[196] and is protonated to give the *meso* dimer **277**. Presumably the stereoselective protonation takes place to give the *meso* compound due to steric constraints.

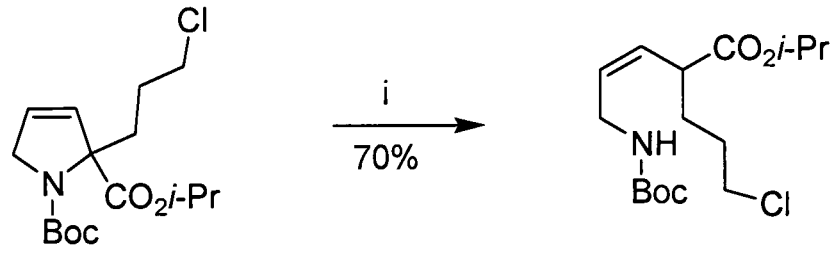
Although the desired tetrahydropyridine had not been obtained, it was envisaged that this methodology could be used to make spiro compound **282** which would complement the already described radical cyclisation and S_N2 cyclisations of pyrroline **252** (Scheme 4.34).



252 **282**

Scheme 4.34. *Proposed route to spiro-pyrrolines.*

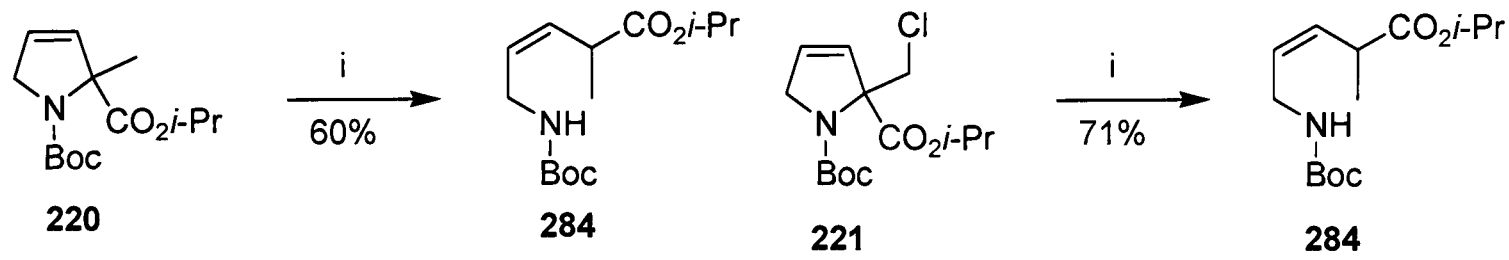
Reaction of pyrroline **252** with LiDBB for two hours yielded a clear oil. The proton NMR confirmed that spiro pyrroline **282** had not been formed; proton NMR showed the presence of an *iso*-propyl ester (heptet at 4.99 ppm) and indicated that an amine functionality may be present in the molecule (broad singlet at 4.62 ppm). Analysis of the mass spectrum showed the presence of chlorine isotopes and the carbon-13 NMR showed the chloromethyl moiety (44.5 ppm). The reaction had furnished the ring-opened compound **283** (Scheme 4.35).



252 **283**

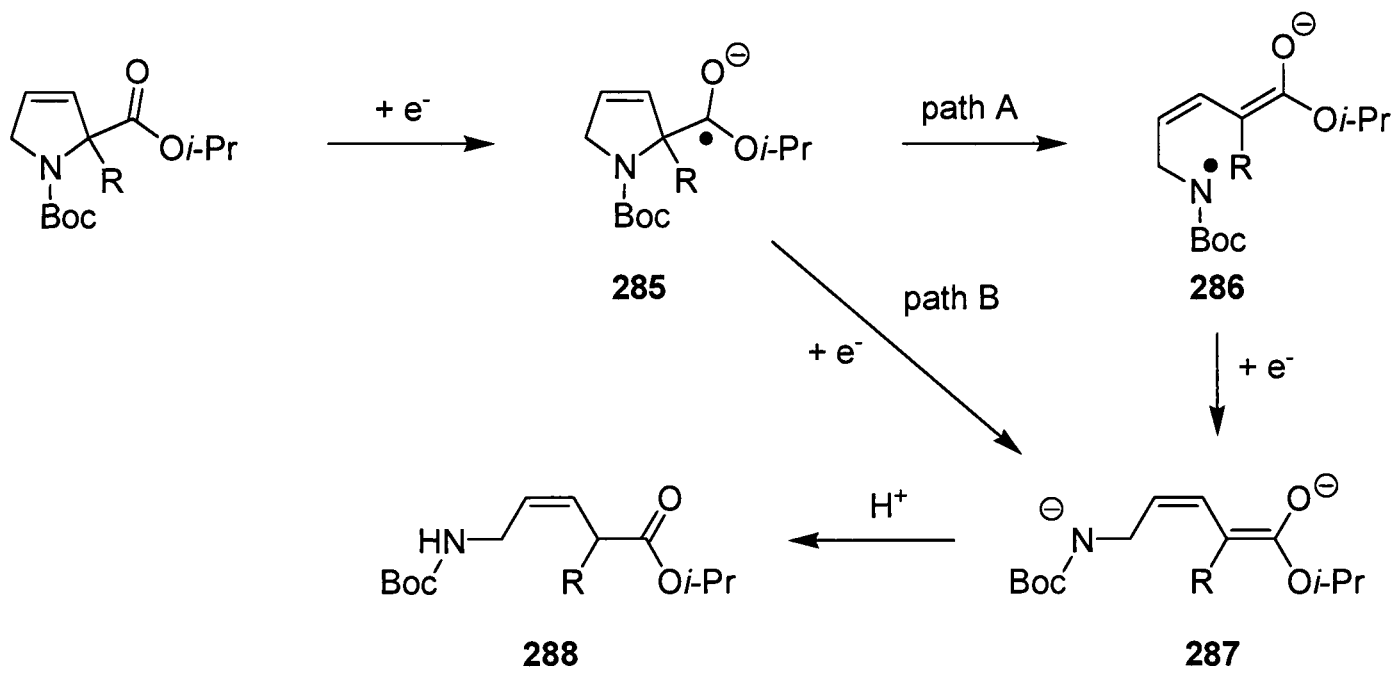
Scheme 4.35. *Reagents and conditions*: i, LiDBB, THF, –78 °C; then NH_4Cl.

The formation of **283** obviously cannot occur *via* the mechanism proposed in Scheme 4.33 for the formation of dimer **277** and as the chlorine moiety had been left in place during the reaction, the ring-opening must have proceeded through the ester moiety. Hence pyrroline **220** was treated with the LiDBB conditions (Scheme 4.36). The IR spectrum indicated the presence of the amine moiety (ν_{NH} 3386 cm^{-1}) and the proton NMR confirmed the presence of an amine by a broad singlet at 4.62 ppm. Carbon-13 NMR showed the downfield allylic methlene group α to the *iso*-propyl ester (38.4 ppm), hence the structure was assigned as ring-opened compound **284** (Scheme 4.36). When pyrroline **221** was reacted with LiDBB, an oil was obtained in good yield which was spectroscopically identical to **284** (Scheme 4.33).



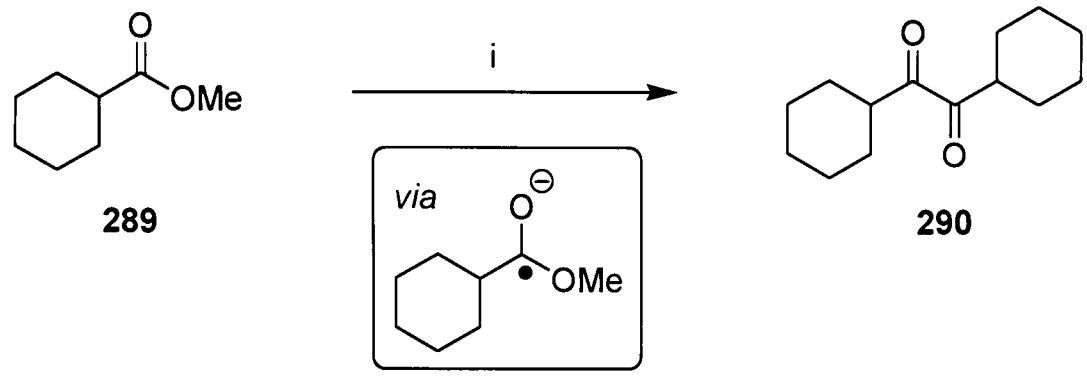
Scheme 4.36. *Reagents and conditions*: i, LiDBB, THF, –78 °C; then NH_4Cl.

The results in Schemes 4.35 and 4.36 put doubt in the mechanism proposed in Scheme 4.33, as neither compound possesses an iodomethyl moiety. Thus for pyrrolines **220**, **221** and **252** it was postulated that a ketyl radical **285** is formed *via* the single electron transfer conditions (Scheme 4.37). Ketyl radical **285** can either collapse to aminyl radical **286**, which accepts a second electron to form enolate **287** (path A), or accept a second electron before ring-opening and then ring-open to form enolate **287** (path B). Protonation furnishes the ring-opened product **288**.



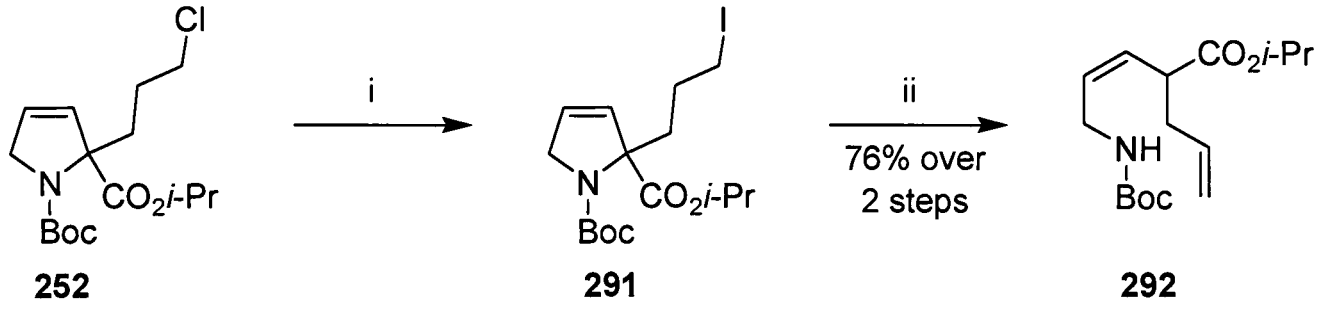
Scheme 4.37. *Postulated mechanism of pyrroline ring-opening for compounds 220, 221 and 252.*

Ketyl radicals generated from an ester have been reported under single electron reducing conditions. Shono and co-workers reported the acyloin-type reaction of ester **289** to give diketone **290** (Scheme 4.38).[197] This result was dependent on the use of magnesium electrodes; the magnesium deposited into the reaction mixture may be acting as a Lewis acid and provide electrophilic activation of the carbonyl group; it is not unreasonable to assume in the case of the pyrroline ring-openings already shown, the lithium within the reaction mixture is acting as a Lewis acid to activate the carbonyl moiety to electrophilic attack.



Scheme 4.38. *Reagents and conditions*: i, Mg electrodes, $LiClO_4$, THF.

A competition experiment was undertaken on a pyrroline (**291**) that had a long alkyl tether before the iodide moiety. The iodide moiety is now far enough removed from the ester group that induction does not activate it towards reduction. If the iodide moiety was transmetalled with lithium before the formation of a ketyl radical, spiro pyrroline **282** would be attained and if the ketyl radical was formed before transmetallation of the iodide moiety, a ring-opened product would be obtained. Thus pyrroline **252** was treated with sodium iodide in acetone and furnished iodide **291**. Treatment of **291** with the LiDBB conditions furnished the ring-opened compound **292** (Scheme 4.39).

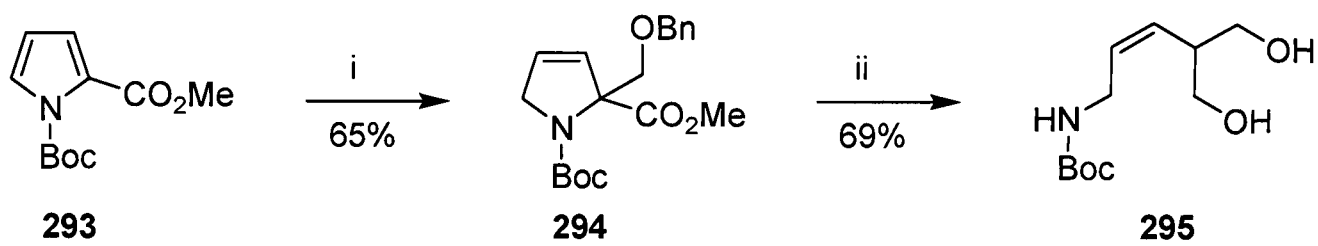


Scheme 4.39. *Reagents and conditions*: i, NaI, acetone, Δ; ii, LiDBB, THF, –78 °C; then NH_4Cl.

Proton NMR verified that spiro compound **282** had not been formed, as the *iso*-propyl ester was still present (heptet at 4.99 ppm) and the IR spectrum showed the presence of an amine moiety (ν_{NH} 3377 cm^{-1}). The proton and carbon-13 NMR spectra revealed the presence of the terminal olefin CH_2 (mulitplet at 5.09-4.94 ppm in the proton NMR and a peak at 128.8 ppm in the carbon-13 NMR spectrum) and the allylic methylene moiety α to the *iso*-propyl ester (doublet of doublets at 3.37 ppm in the proton NMR and 44.0 ppm in the carbon-13 NMR spectrum). Presumably the ring-opened compound underwent an elimination of HI during the work-up. Rather remarkably, the results of Scheme 4.39 showed that a ketyl radical species was formed in preference to the reduction of the carbon-iodine bond; hence it was postulated that the pyrroline ring opens *via* the mechanism shown in Scheme 4.37. In the

case of pyrroline **221**, no dimer product is observed as the leaving group ability of the chlorine atom is less than that of the iodine atom (pK_a HCl≈-7; pK_a HI≈-10); hence dehalogenation of the chlorine atom occurs to give carbamate **284** in preference to elimination to furnish enone intermediate **280** (which could then be reduced to radical **281**, Scheme 4.33) allowing formation of dimer **277**.

Thus far all the pyrroline ring-openings have been performed using LiDBB as the single electron medium. It was envisaged that the single electron medium of an alkali metal dissolved in ammonia could either furnish the ring-opened products and/or a Bouveault-Blanc reduction to transform the ester moiety into an alcohol.



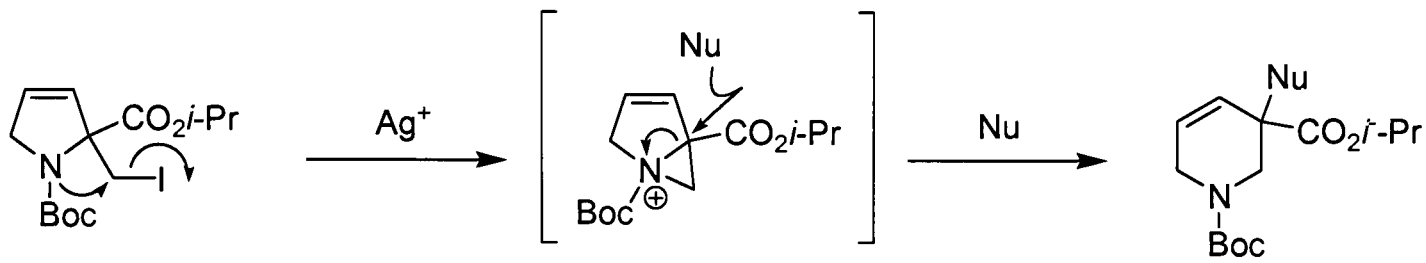
Scheme 4.40. *Reagents and conditions*: i, Li, NH_3, BMEA, THF, –78 °C; then isoprene; then BOMCl; then NH_4Cl; ii, Na, NH_3, THF, –78 °C; then NH_4Cl.

Pyrrole **293** was reductively alkylated using benzylchloromethyl ether in moderate yield (Scheme 4.40). The proton NMR revealed the loss of the aromatic pyrrole protons and introduction of the phenyl protons (multiplet at 7.34-7.24 ppm). Carbon-13 NMR showed the methylene α to the phenyl ring and the methylene α to the OBn moiety (70.2 and 69.4; 73.5 ppm respectively). Pyrroline **294** was treated with six equivalents of sodium dissolved in ammonia and the reaction furnished the amino diol **295**. In one step, the benzyl group had been removed, the pyrroline had undergone a ring-opening reaction and the methyl ester had been reduced to an alcohol (Scheme 4.40). The mass spectrum revealed the parent ion mass peaks (254, MNa^+ and 232, MH^+) and the proton NMR showed four protons α to oxygen as doublets of doublets (3.67 and 3.55 ppm) and two alcohol signals (broad singlet at 3.23 ppm). The IR spectrum confirmed the presence of the amine and alcohol moieties as a broad peak ($\nu_{NH/OH}$ 3352 cm^{-1}) and the carbon-13 NMR showed the presence of a single carbonyl moiety (156.3 ppm) and introduction of the allylic methylene α to the diol (42.8ppm).

Although a novel ring-opening reaction of pyrrolines had been discovered, attempts to prepare tetrahydropyridines *via* an anionic ring-expansion had not been successful; hence the rearrangement of pyrrolines *via* a cationic pathway was explored next (Synthon **216**, Figure 4.1).

4.6 *Attempted cationic ring-expansions.*

It was envisaged that if a pyrroline **217** was treated with a silver$^{(I)}$ salt, aziridinium ion (**296**) would be formed which could rearrange, initiated by attack of a nucleophile, through to the corresponding tetrahydropyridine (**297**, Scheme 4.41).



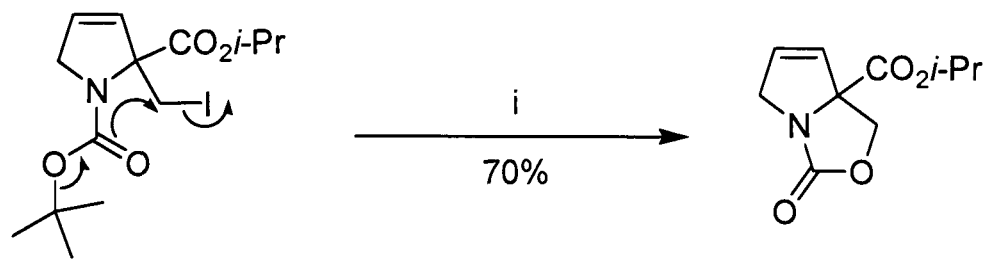
217 **296** **297**

Scheme 4.41. *Proposed route to form tetrahydropyridines via a cationic pathway.*

When pyrroline **217** was treated with silver$^{(I)}$ triflate for 17 hours in deoxygenated benzene, an oil was obtained (Scheme 4.42); the proton NMR showed it was not the desired tetrahydropyridine **297**. Although the spectrum showed the loss of the iodomethyl moiety, the *tert*-butyl group of the Boc goup had also disappeared and there were only two diastereotopic protons α to nitrogen (doublet of triplets at 4.45 and a doublet of multiplets at 4.05-4.04 and 4.01-4.00 ppm). The proton NMR also displayed two more diastereotopic protons α to a heteroatom as doublets (4.76 and 4.38 ppm). The large coupling constant of *J* 9.2 Hz implied that the methylene group was adjacent to two moieties, each bearing no protons.* The carbon-13 NMR showed only one quaternary carbon (76.7 ppm) but two carbonyl groups (169.9 and 161.8 ppm), thus the structure was assigned as pyrroline **298** (Scheme 4.42).

The nitrogen lone pair electrons are delocalised into the carbamate group and are not available to form an aziridinium ion; instead the Boc group collapses with the loss of the *tert*-butyl cation and cyclises to form the Boc cyclisation product **298**. Such cyclisations of the Boc group has been observed with very potent leaving group (such as triflates).[166]

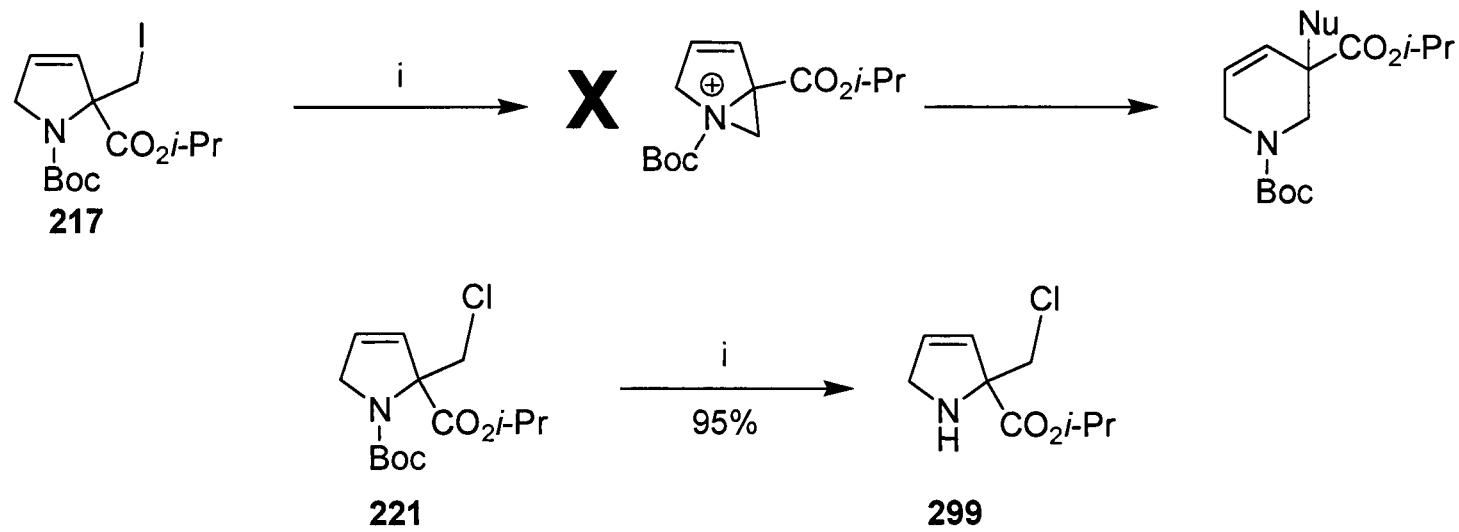
* *Vicinal* coupling as opposed to *geminal* coupling would be displayed in this scenario; hence the coupling constant would be expected to be greater than 7 Hz.



A04 **298**

Scheme 4.42. *Reagents and conditions*: i, $Ag^{(I)}OTf$, PhH, room temperature.

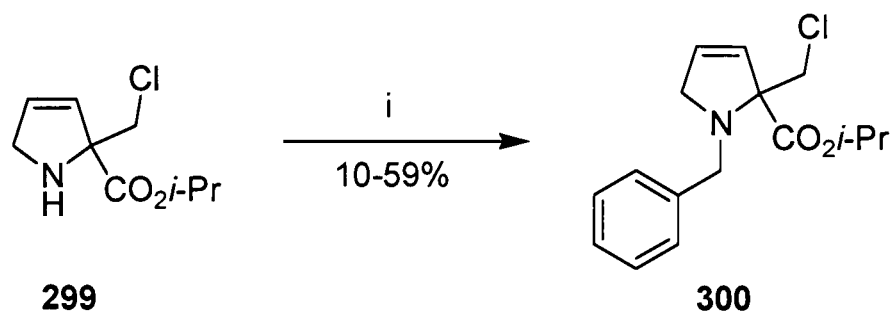
To circumvent the problem of Boc participation, it was decided to change protecting group. The Boc group is used as a nitrogen protecting group for pyrroles used in the reductive alkylation to facilitate the reduction, but an electron donating group is now required (to allow the nitrogen lone pair to form an aziridinium ion); thus the protecting group would have to be changed after the partial reduction. When pyrroline **217** was treated with trifluoroacetic acid no product could be isolated; however pyrroline **221** was successfully deprotected using trifluoroacetic acid to afford amine **299** in very high yield (Scheme 4.43). The proton and carbon-13 NMR revealed the loss of the Boc group and the IR spectrum showed the presence of an amine (ν_{NH} 3428 cm^{-1}).



217 **221** **299**

Scheme 4.43. *Reagents and conditions*: i, CF_3CO_2H, CH_2Cl_2, room temperature.

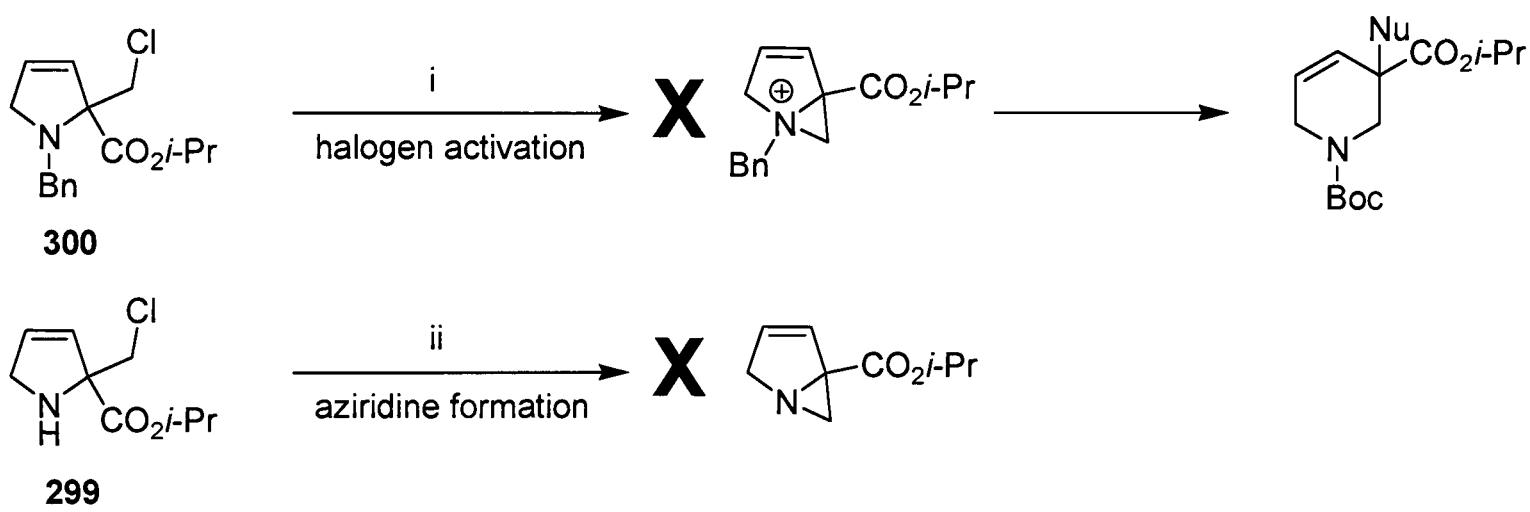
The benzyl protecting group was chosen for the amine (c.f. Cossy and co-workers' ring-expansion of pyrrolidines, Chapter 3). Numerous literature procedures for incorporating the benzyl group were tried with very limited success: reductive amination with benzaldehyde and sodium cyanoborohydride and alkylations with benzyl bromide using sodium hydride, potassium hydroxide, potassium *tert*-butoxide and s*ec*-butyl lithium were all unsuccessful.



299 **300**

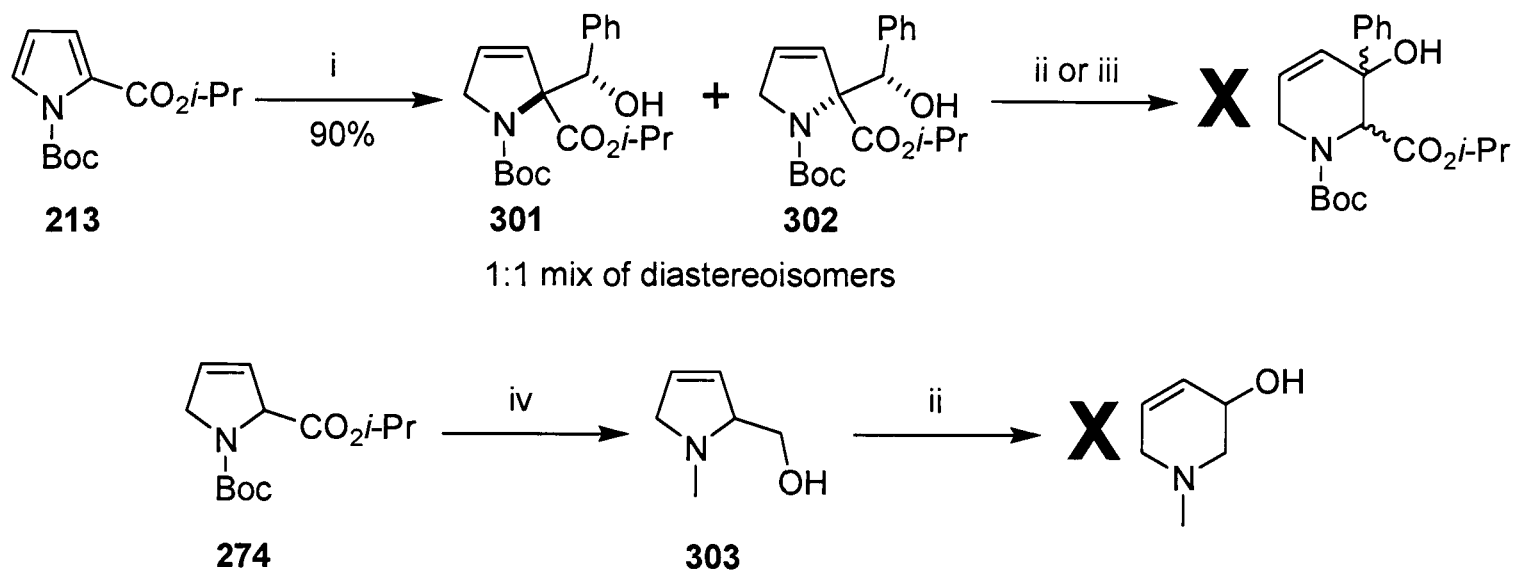
Scheme 4.44. *Reagents and conditions*: i, BnBr, K_2CO_3, CH_2Cl_2, H_2O, Δ.

The benzyl protecting group could be installed by refluxing pyrroline **299** in a water/dichloromethane solution with potassium carbonate and benzyl bromide to give pyrroline **300** (Scheme 4.44); however the yields for this reaction were never consistent and varied from 10-59%. The NMR spectra ceased to be rotamerically split and revealed the presence of a benzylic methylene group (doublets at 3.91 and 3.77 ppm in the proton NMR; 53.3 ppm in the carbon-13 NMR).



Scheme 4.45. *Reagents and conditions*: i, Range of conditions, see text; ii, Range of conditions, see text.

Pyrroline **300** was reacted with numerous conditions to try and induce rearrangement (Scheme 4.45); treatment with silver triflate or aluminium chloride only returned starting material; attempts at a thermally induced rearrangement were also unsuccessful, heating neat or as a solution in tetrahydrofuran, benzene, xylene all returned starting material, and diphenyl ether only decomposition of the pyrroline was observed. Thus efforts were made to form an aziridine from pyrroline **299** (Scheme 4.45); however all attempts were unsuccessful. Treatment with Lewis acids such as silver triflate and aluminium chloride or base (sodium hydride, *sec*-butyl lithium, *n*-butyl lithium, potassium hydroxide, potassium carbonate, triethylamine and sodium hydroxide) all returned starting material.



Scheme 4.46. *Reagents and conditions*: i Li, NH_3, BMEA, THF, –78 °C; then isoprene; then PhCHO; then NH_4Cl; ii, $(CF_3CO)_2O$, THF, Δ; then $NaOH_{(aq)}$, Δ; iii, CF_3CO_2H, CH_2Cl_2, room temperature; iv, Li, NH_3, BMEA, THF, –78 °C; then NH_4Cl.

Use of a halogen as a precursor for the cationic ring-expansion was abandoned due to problems with the synthesis of the starting materials required. A ring-expansion using Cossy and co-workers' precedent for the rearrangement of pyrrolidines was next investigated (Chapter 11).* Thus pyrrole **213** was subjected to a reductive aldol reaction using benzaldehyde (Scheme 4.46), furnishing the *syn* and *anti* diastereoisomers, which were separable by flash column chromatography, in excellent yield. The diastereoisomers were assigned by analogy with similar reported compounds.[165-167]

Reaction of either diastereoisomer (**301** or **302**) to the conditions described by Cossy and co-workers failed to promoted rearrangement and returned only starting material. It was thought that the electron withdrawing Boc group was preventing rearrangement but attempts at an acidic deprotection led only to decomposition of the starting material. A final attempt at ring-expansion was tried: pyrroline **274** was treated with lithium aluminium hydride to prepare the alcohol **303**, which could never be completely purified (Scheme 4.46) and the crude alcohol reacted with the conditions reported by Cossy and co-workers; however only starting material was returned. With this final result, attempts to try to induce a cationic ring-expansion of pyrrolines were abandoned and efforts focused in the rearrangement of tetrahydrofurans to tetrahydropyrans (Chapter 6).

* It should be noted that there have been no documented examples of pyrrolines being used in this type of ring-expansion.

4.7 *Chapter 4 summary.*

In section 4.1 it was shown that 1,1-dihaloalkanes were compatible with the partial reduction using Birch-type conditions. The resulting pyrrolines bearing an *exo*-cyclic iodomethyl moiety underwent a radically induced one carbon ring-expansion and furnished the corresponding tetrahydropyridine in high yields. This methodology can be applied to lactams and was tolerant to substitution at every position on the pyrroline ring. A mechanism was postulated in section 4.2, supported by evidence provided by the preparation of fused bicycles. The synthetic versatility of pyrrolines was shown by a one-pot, high yielding sequence to prepare pyrrolizidines and indolizines (section 4.3). The attempted anionic ring-expansion of pyrrolines was not successful; however a novel pyrroline ring-opening reaction was described in section 4.5. Finally, a cationic ring-expansion from pyrroline starting materials was briefly investigated but unsuccessful (section 4.6).

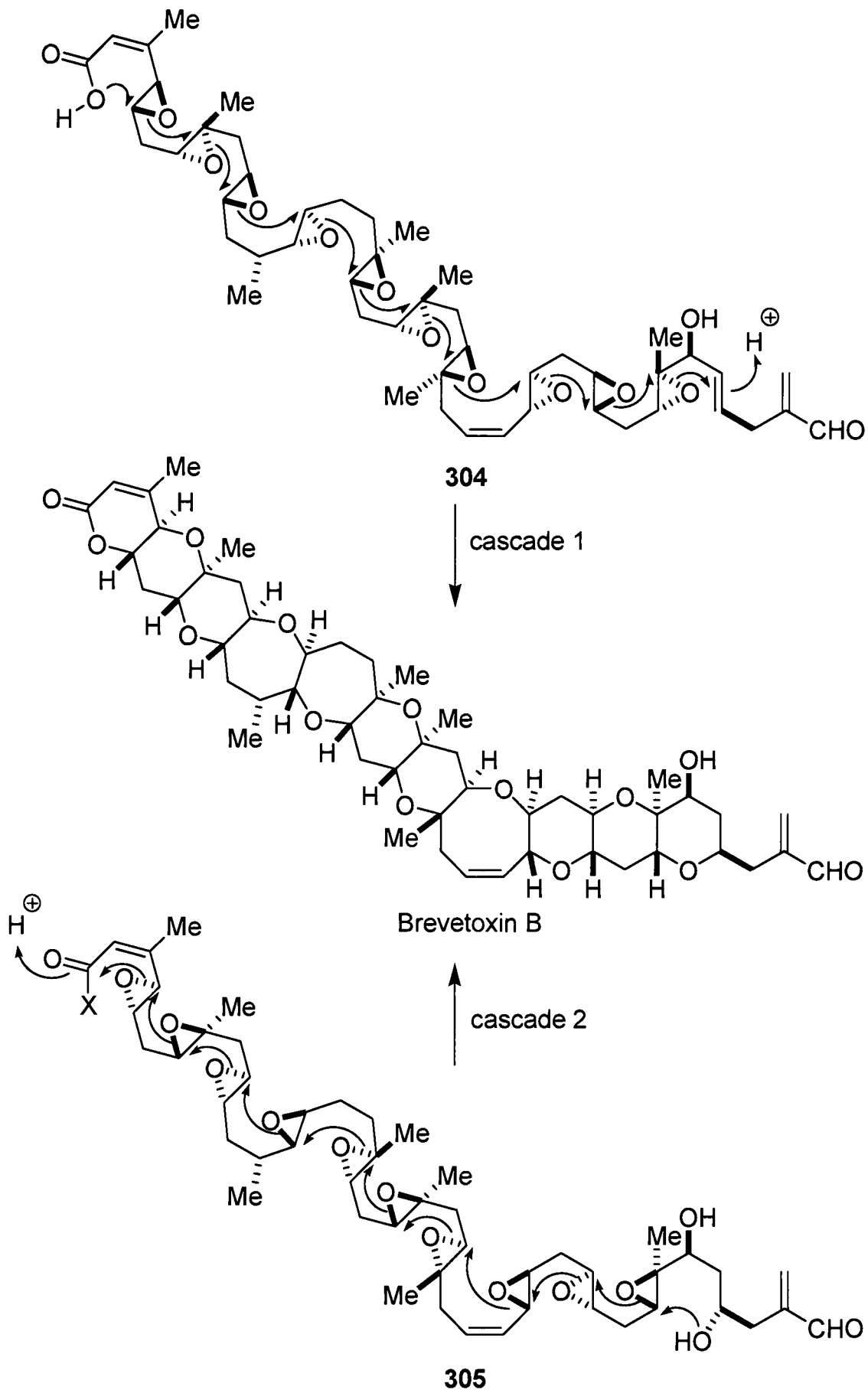
Chapter 5

Introduction – Synthesis of Tetrahydropyrans

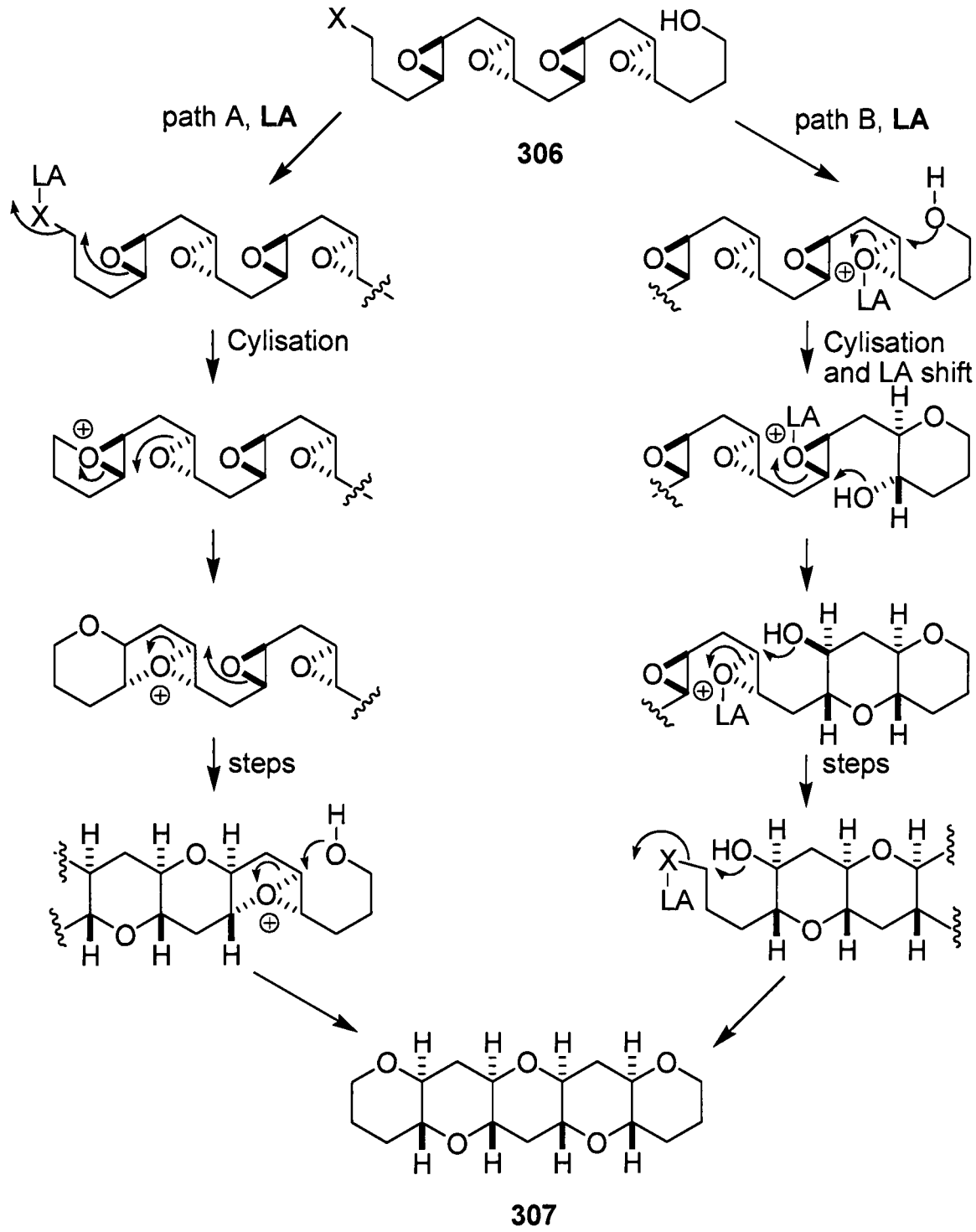
5.1 *General Introduction.*

The potent biological activities and complex structures of naturally occurring polycyclic ethers have attracted great attention from the scientific community.[198-204] Most polyethers are produced by marine dinoflagellates; brevetoxin B (Scheme 5.1) for example is a potent neurotoxin from the "red tide" dinoflagellate *gymnodinium breve*.[205]

The exact biosynthesis of the polyethers by dinoflagellates has still to be elucidated; however a domino cascade cyclisation of a polyepoxide precursor has been proposed as the key step – exemplified by the postulated biogenesis of brevetoxin B (Scheme 5.1).[206-208] An acid catalysed rearrangement of either polyepoxide precursor **304** or **305** with successive *endo* epoxide-opening reactions furnishes brevetoxin B. With precursor **304** the rearrangement is intiated by a carboxylic acid moiety and with precursor **305** by an alcohol functionality. Not only does the postulated mode of biosynthesis explain the observed *trans*-fused polycyclic cylization, it has also spurred a great deal of interest in the synthesis of poly-fused cyclic ethers from polyepoxide precursors.[209, 210]



Scheme 5.1. *Possible pathways for the biogenesis of Brevetoxin B.*



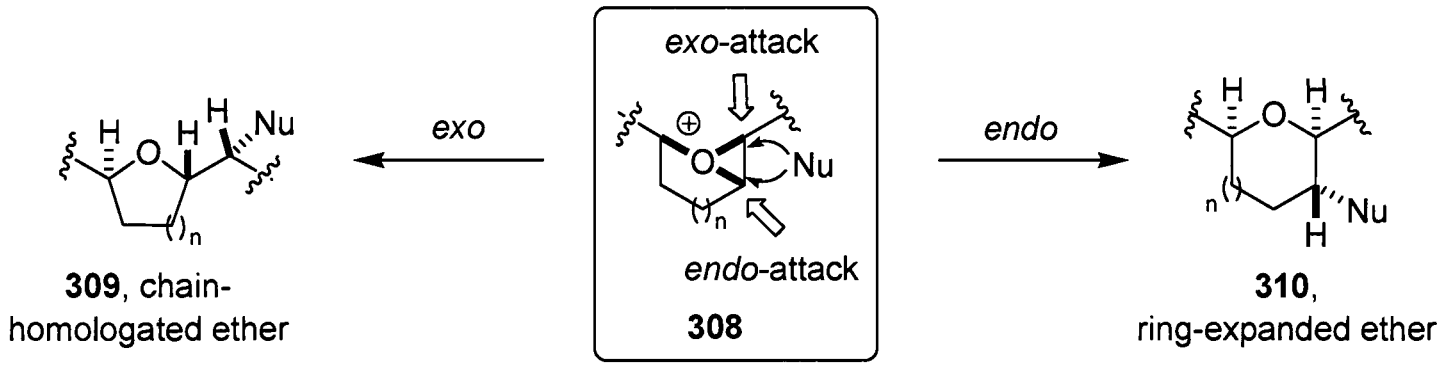
Scheme 5.2. *Interpretations of cascade epoxide-openings.*

The postulated cascade epoxide opening can be interpreted in two ways. For example in the hypothetical transformation of polyepoxide **306** into polyether **307** (Scheme 5.2), mediated by Lewis acidic (LA) activation, there are two pathways to explain the observed stereochemistry: In path A, leaving group X is activated by the Lewis acid, allowing the adjacent epoxide moiety to attack as a nucleophile forming a bicyclic oxonium ion. This oxonium ion is attacked by another epoxide to form a new bicyclic oxonium ion at the adjacent centre; this process continues until the terminal alcohol undergoes an *endo*-site attack on the bicyclic oxonium ion to furnish the polyether **307**. Hence in path A, the epoxide is acting as a nucleophile. Alternatively, in path B the epoxide adjacent to the terminal alcohol is activated by the Lewis acid to form a monocyclic oxonium ion. The alcohol acts as a

nucleophile and attacks the monocyclic oxonium ion at the *endo*-site to form a cyclic ether and the Lewis acid shifts to the next adjacent epoxide. The free alcohol attacks the new monocylic oxonium ion at the *endo*-site; this process continues until the Lewis acid activates the last available leaving group X to allow the free alcohol moiety to cyclise in an S_N2 manner to give **307** (Scheme 5.2); in path B the epoxide is acting as an electrophile.

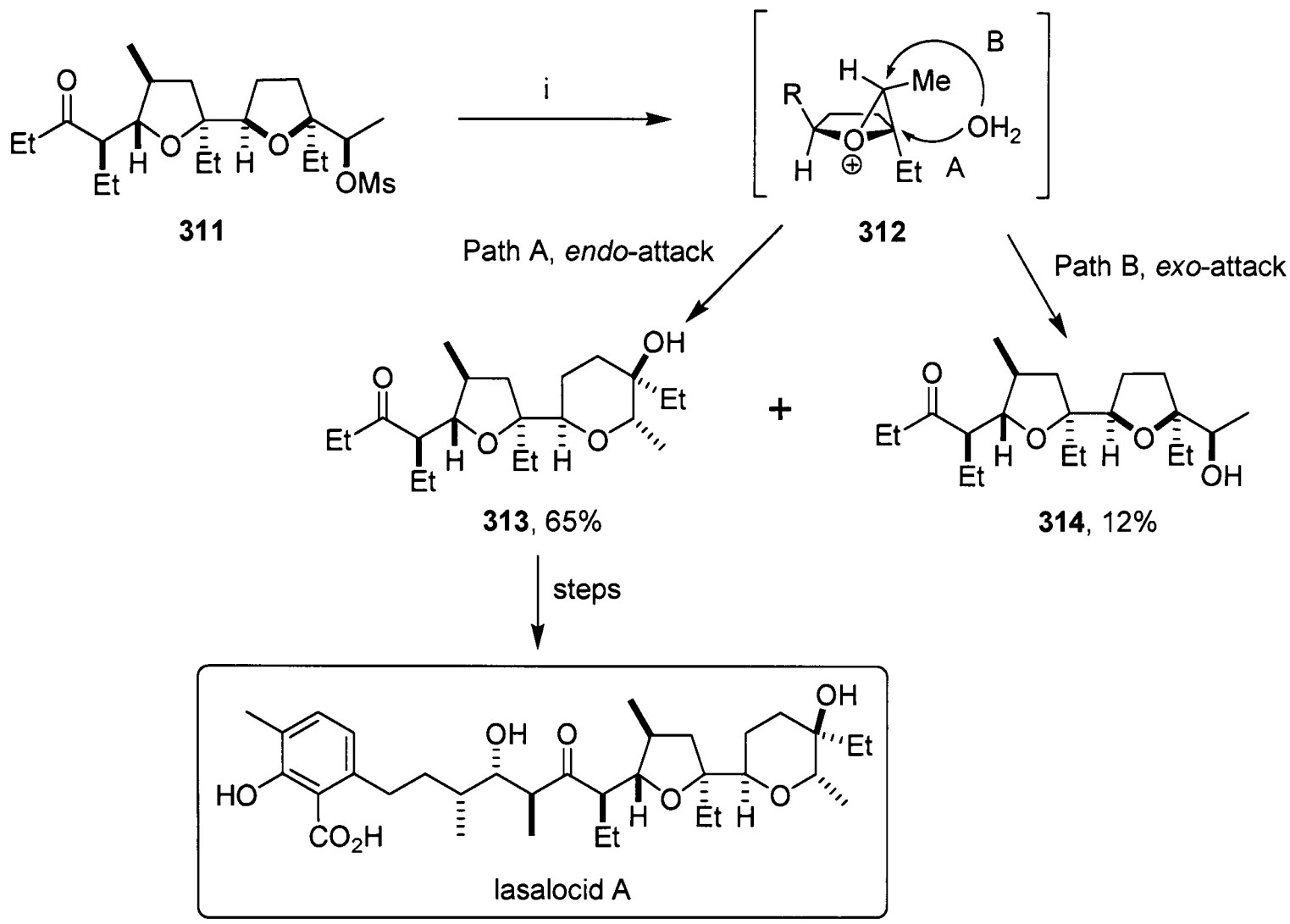
5.2 *One carbon ring-expansions of tetrahydrofurans.*

In Scheme 5.2 it was shown that bicyclic oxonium ion intermediates are opened to furnish the corresponding *trans*-fused poly ethers. If we consider oxonium ion **308** (Scheme 5.3), there are two potenitial sites for opening; firstly, a nucleophile could attack at the *exo*-site, furnishing cyclic ether **309**, where the *exo*-cyclic chain has been homologated or secondly, attack could occur at the *endo*-site to yield the ring-expanded cyclic ether **310**. This second approach has been widely employed in the ring-expansion of tetrahydrofurans to tetrahydropyrans.



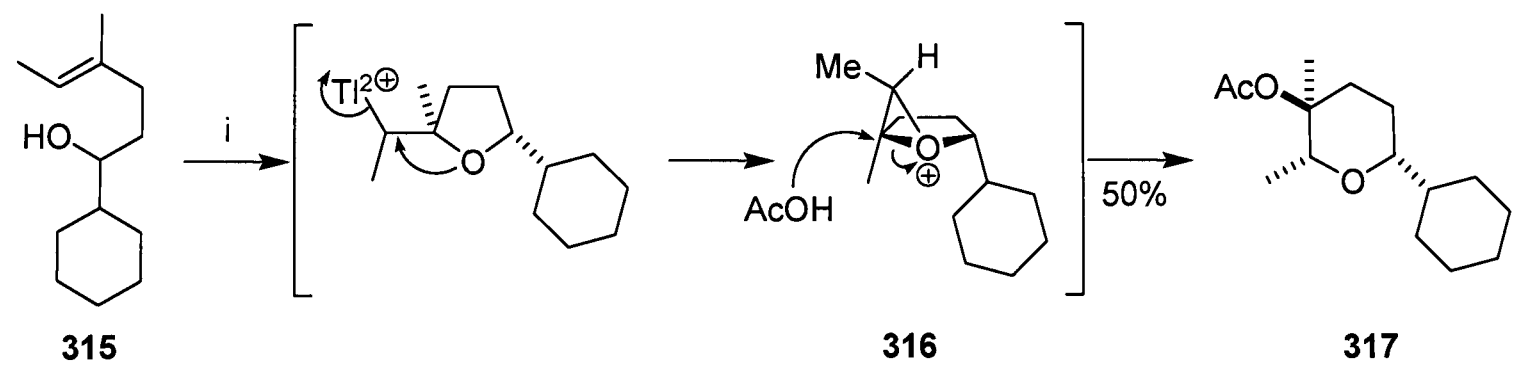
Scheme 5.3. *Bicyclic oxonium ion opening by exo- and endo-attack.*

In 1978 Kishi and co-workers reported the first total synthesis of lasalocid A, a polyether antibiotic, using a pioneering ether ring-expansion *via* a bicyclic oxonium ion (Scheme 5.4).[211] The tetrahydrofuran **311** eliminated the mesyloxy moiety under Lewis acidic conditions to form oxonium ion **312**, which was solvolysed to give ring-expanded cyclic ether **313** (path A, *endo*-attack) and alcohol **314** (path B, *exo*-attack).



Scheme 5.4. *Reagents and conditions*: i, $Ag(OAc)_2$, H_2O, acetone.

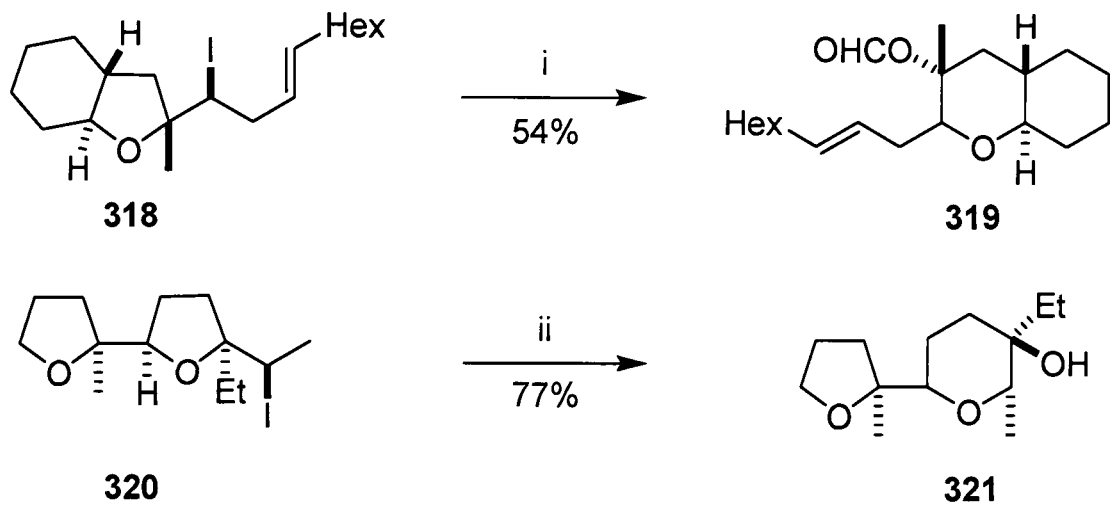
Bartlett and co-workers demonstrated that thallium$^{(III)}$ salts could be used to induce a cyclisation-ring-expansion sequence (Scheme 5.5).[212] For example treatment of alcohol **315** to thallium acetate sesquihydrate yielded tetrahydropyran **317**, presumably *via* the bicyclic oxonium ion **316**.



Scheme 5.5. *Reagents and conditions*: i, $Tl(OAc)_3$, AcOH, room temperature.

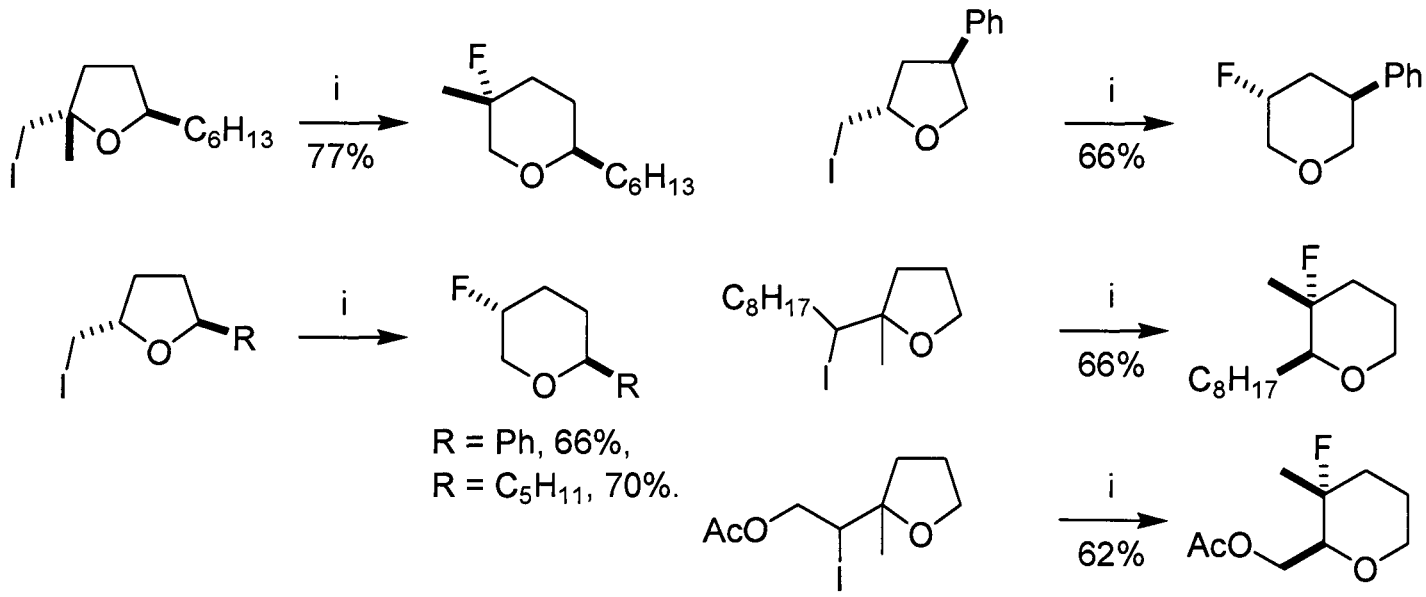
Similarly the groups of Bartlett and Brimble have reported ring-expansions of tetrahydrofurans bearing an *exo*-cyclic iodomethyl moiety to tetrahydropyrans (Scheme 5.6). Bartlett and co-workers subjected iodide **318** with silver tetrafluoroborate to furnish

tetrahydropyran **319**;[213] Brimble and co-workers used silver carbonate to convert iodide **320** to tetrahydropyran **321** (Scheme 5.6).[214, 215]



Scheme 5.6. *Reagents and conditions*: i, $AgBF_4$, DMF, 70 °C; ii, $Ag(OAc)_2$, H_2O, acetone, room temperature.

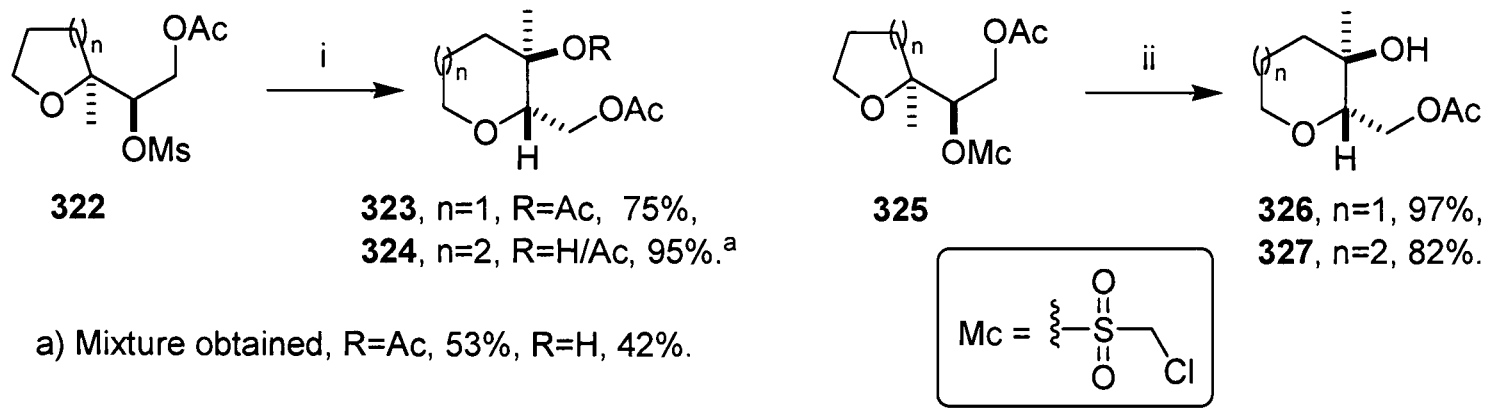
In a related ring-expansion of tetrahydrofurans, Hara and co-workers have reported the fluorinative ring-expansion of cyclic ethers using *para*-iodotoluene difluoride to furnish a range of fluorinated tetrahydropyrans (Scheme 5.7).[216] Fluorinated tetrahydrofurans were also prepared by the ring-expansion of oxetanes.[216]



Scheme 5.7. *Reagents and conditions*: i, *p*-Tol-IF_2, Et_3N-5HF, CH_2Cl_2, room temperature.

Other than Kocieński and co-workers who utilised the mesyloxy rearrangement in their synthesis of solinomycin,[217] the ring-expansion method pioneered by Kishi had received little attention until Nakata and co-workers developed the reaction into a more viable procedure. After screening a range of Lewis acids, they found that the yield of rearrangement could be increased to 75%; tetrahydrofuran **322** (Scheme 5.8) was treated with zinc acetate in aqueous acetic acid to furnish tetrahydropyran **323** (after acetylation with acetic anhydride).

However in the tetrahydropyran to oxepane rearrangement, oxepane **324** was obtained as a mixture of the acetylated and hydrolysis products.[218] By modifying the leaving group to the mono-chloromethansulfonate* (Mc), rearrangement could be induced without the need of an aqueous Brønsted acid as a co-solvent; hence no acetylated products were obtained from the rearrangement of tetrahydrofuran **325**, only alcohols **326** and **327** were afforded (Scheme 5.8).[219]



322

323, n=1, R=Ac, 75%,
324, n=2, R=H/Ac, 95%.[a]

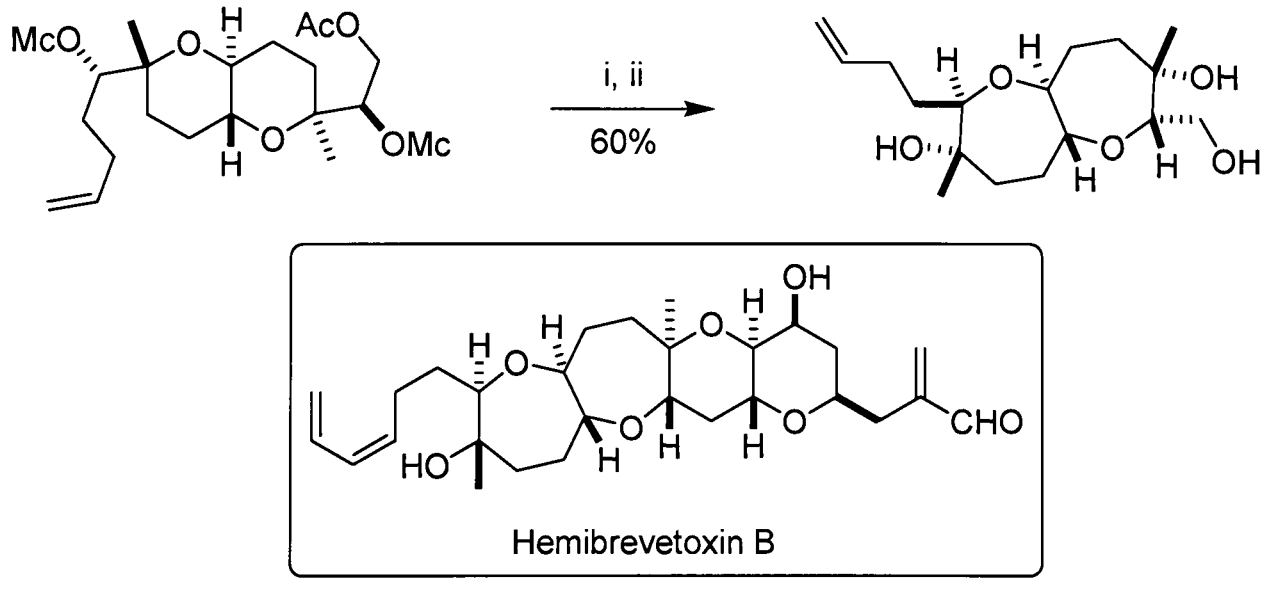
325

326, n=1, 97%,
327, n=2, 82%.

a) Mixture obtained, R=Ac, 53%, R=H, 42%.

Scheme 5.8. *Reagents and conditions*: i, $Zn(OAc)_2 \cdot 2H_2O$, AcOH, H_2O, Δ; then Ac_2O, pyridine, room temperature; ii, $Zn(OAc)_2 \cdot 2H_2O$, dioxane, H_2O, n=1 50 °C, n=2, 80 °C.

In Scheme 5.8, the mono-chloromethylsulfonate leaving group allowed rearrangement of the simple precursor **325** in high yield without the use of an aqueous protic acid; however when Nakata applied this methodology to more complex systems,[220-224] for example during his synthesis of hemibrevetoxin B (Scheme 5.9),[225] acetic acid was needed as a co-solvent to induce rearrangement. Hence this led to a mixture of acetylated and hydrolysis products.



Scheme 5.9. *Reagents and conditions*: i, $Zn(OAc)_2 \cdot 2H_2O$, AcOH, H_2O, 60-80 °C; ii, K_2CO_3, MeOH, room temperature.

* The inductive effect of the chlorine atom increases the leaving groups' reactivity.

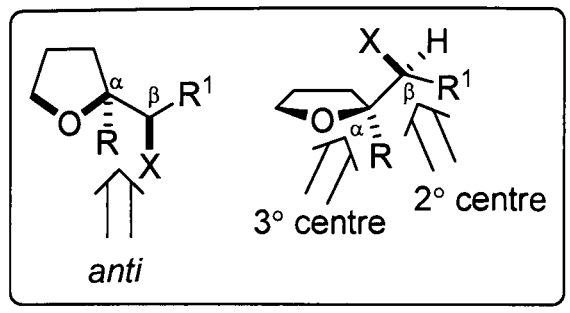
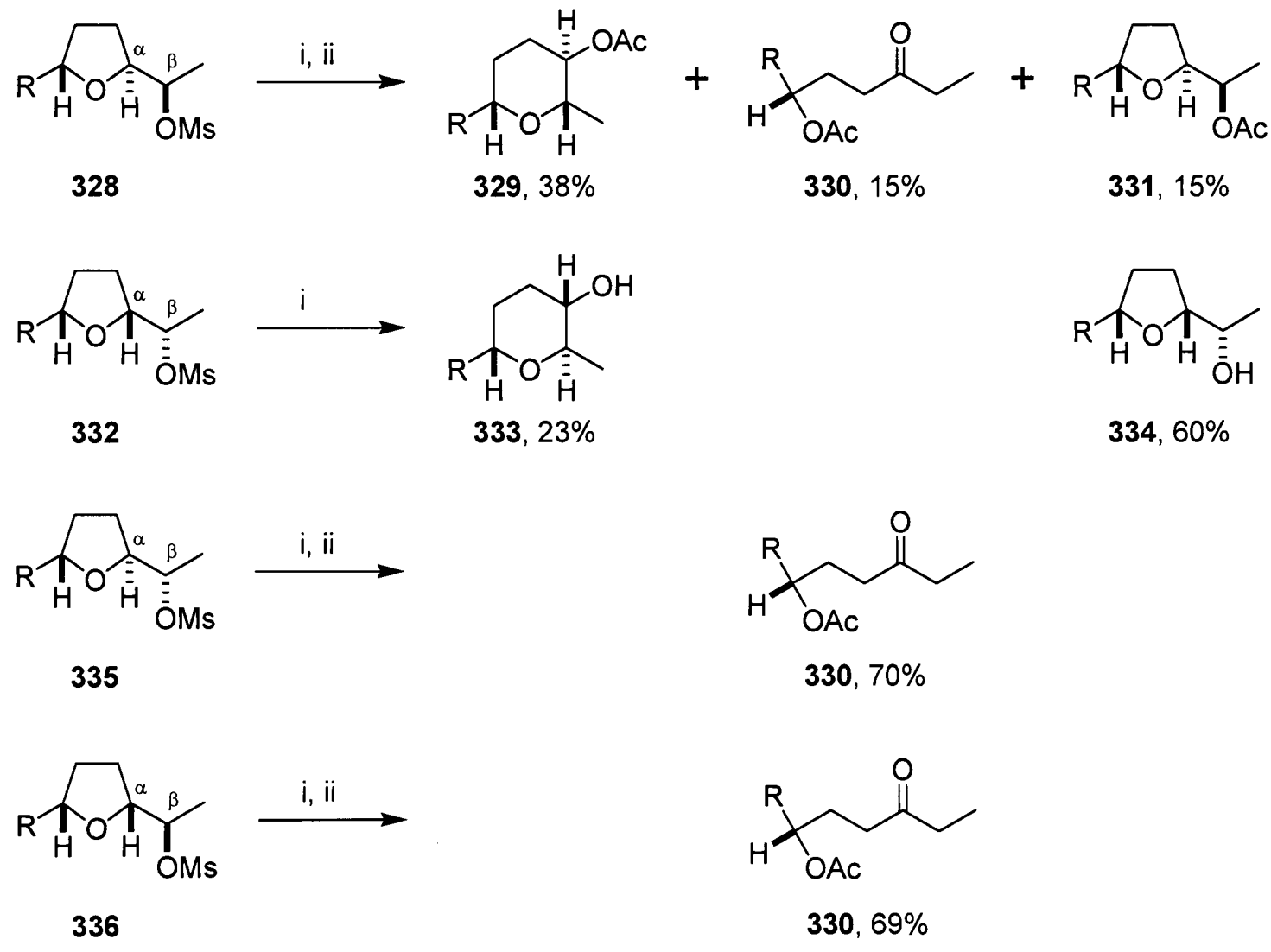


Figure 5.1. *Stereochemical relationship between the tetrahydrofuran and exo-cyclic leaving group required for rearrangement.*

Apart from the examples shown in Scheme 5.7, all the ring-expansion precursors have had the same *anti* relative stereochemistry with respect to the tetrahydrofuran and *exo*-cyclic leaving group. As exemplified by the generic tetrahydrofuran shown in Figure 5.1, all ring-expansion precursors possess a tertiary carbon at centre α and a secondary carbon at centre β with an *anti* relationship between the R group on carbon α and the leaving group (X) on carbon β.



328 → **329**, 38% + **330**, 15% + **331**, 15%

332 → **333**, 23% + **334**, 60%

335 → **330**, 70%

336 → **330**, 69%

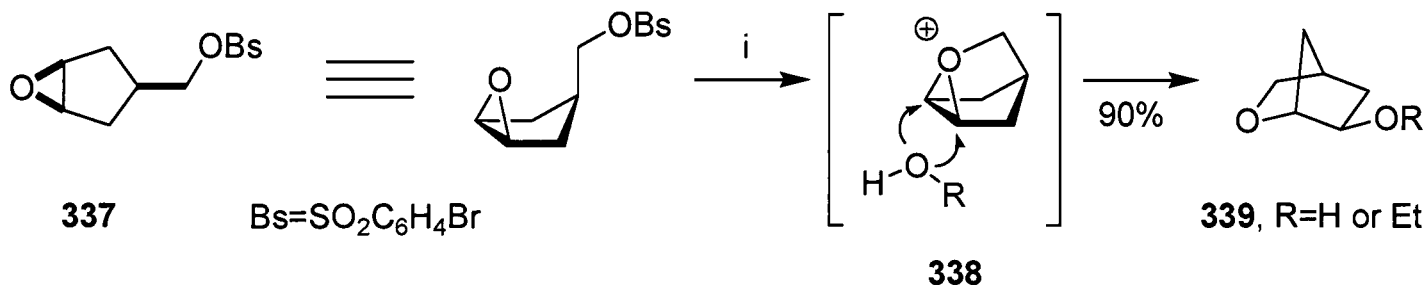
Scheme 5.10. *Reagents and conditions*: i, $Zn(OAc)_2 \cdot 2H_2O$, AcOH, H_2O, Δ; ii, Ac_2O, pyr, room temperature.

Nakata and co-workers have conducted limited investigations into the stereochemical requirements for ring-expansion (Scheme 5.10);[226] focusing on the effect of the relative stereochemistry between the secondary carbon α and secondary carbon β.

When tetrahydrofurans bearing an *anti* relationship between carbons α and β were investigated (**328** and **332**) a number of products isolated; *trans*-tetrahydrofuran **328** gave tetrahydropyran **329** (38%), ketone **330** (15%) and acetate **331** (15%), whereas *syn*-tetrahydrofuran **332** gave a small amount of tetrahydropyran **333** (23%) and the hydrolysis product **334** (60%). However when tetrahydrofurans bearing a *syn* relationship between carbons α and β (**335** and **336**) were investigated, the sole product was ketone **330** (70 and 69% respectively). During their synthesis of *bis*-2,5-linked tetrahydrofurans, Brimble and Edmonds reported a similar ketone product from a tetrahydrofuran bearing a primary *exo*-cyclic iodomethyl moiety, albeit in a low 24% yield (Scheme 5.10).[214]

Thus for an efficient ring-expansion reaction carbon α should be tertiary and the R group have an *anti* relationship to the secondary leaving group on carbon β. Similar observations were made when the analogous tetrahydropyran to oxepane rearrangement was investigated.[227]

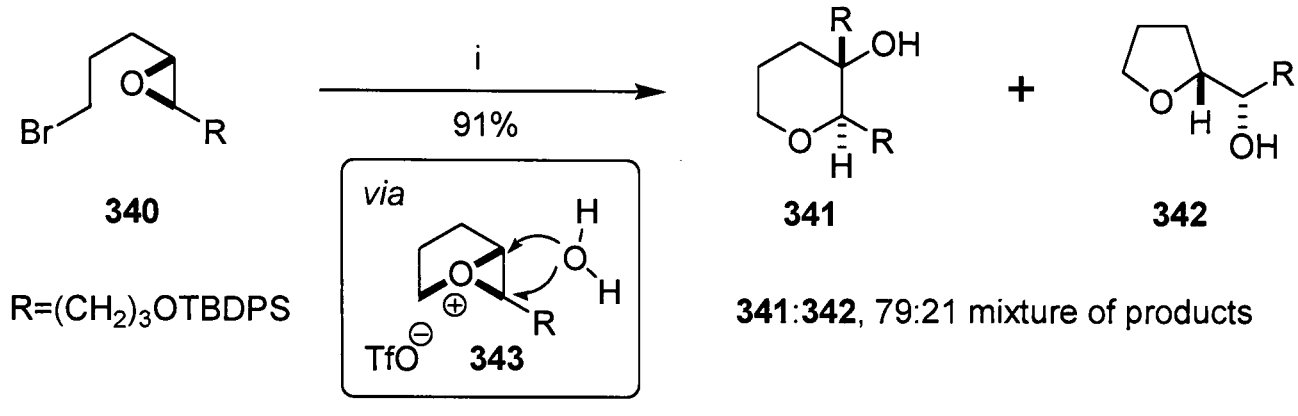
5.3 *Ring-expansion by the opening of epoxides to form tetrahydropyrans.*



Scheme 5.11. *Reagents and conditions*: i, EtOH, H_2O, $CaCO_3$, room temperature.

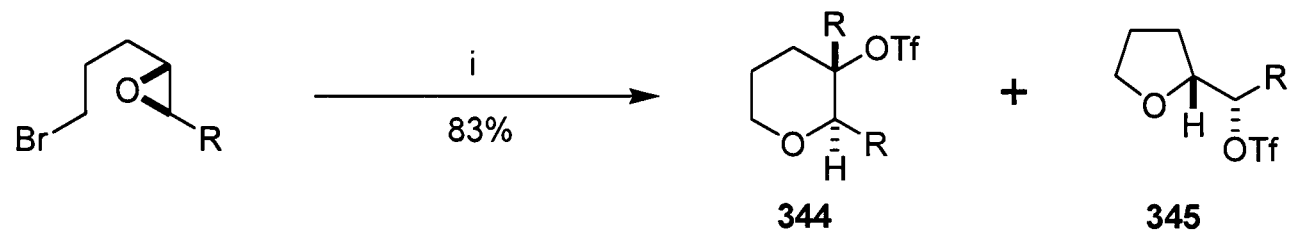
Generation of oxonium ions from epoxides has been known since 1969[228-230] and the ring-expansion of epoxides has subsequently become a useful method for the construction of cyclic ethers. For example, David reported the rearrangement of [3.1.0] fused epoxides to the corresponding [2.2.1] cyclic ethers (Scheme 5.11).[231] Epoxide **337** eliminated the sulfonate leaving group to form the strained oxonium ion **338**; solvolysis of the oxonium ion gave **339** in high yield (scheme 5.11).

The acyclic epoxide cascade has come under scrutiny in order to achieve a biomimetic construction of polyethers as proposed by Nakanishi and Shimizu (Scheme 5.1). Epoxide **340** was reacted with silver trifluoromethanesulfonate in the presence of water furnishing a 79:21 mixture of tetrahydropyran **341** and tetrahyrofuran **342** in high overall yield (Scheme 5.12).[210, 232-234] This result implies that tetrahydropyran **341** is the kinetic product; hence oxonium ion **343** is preferentially opened at the *endo*-site.



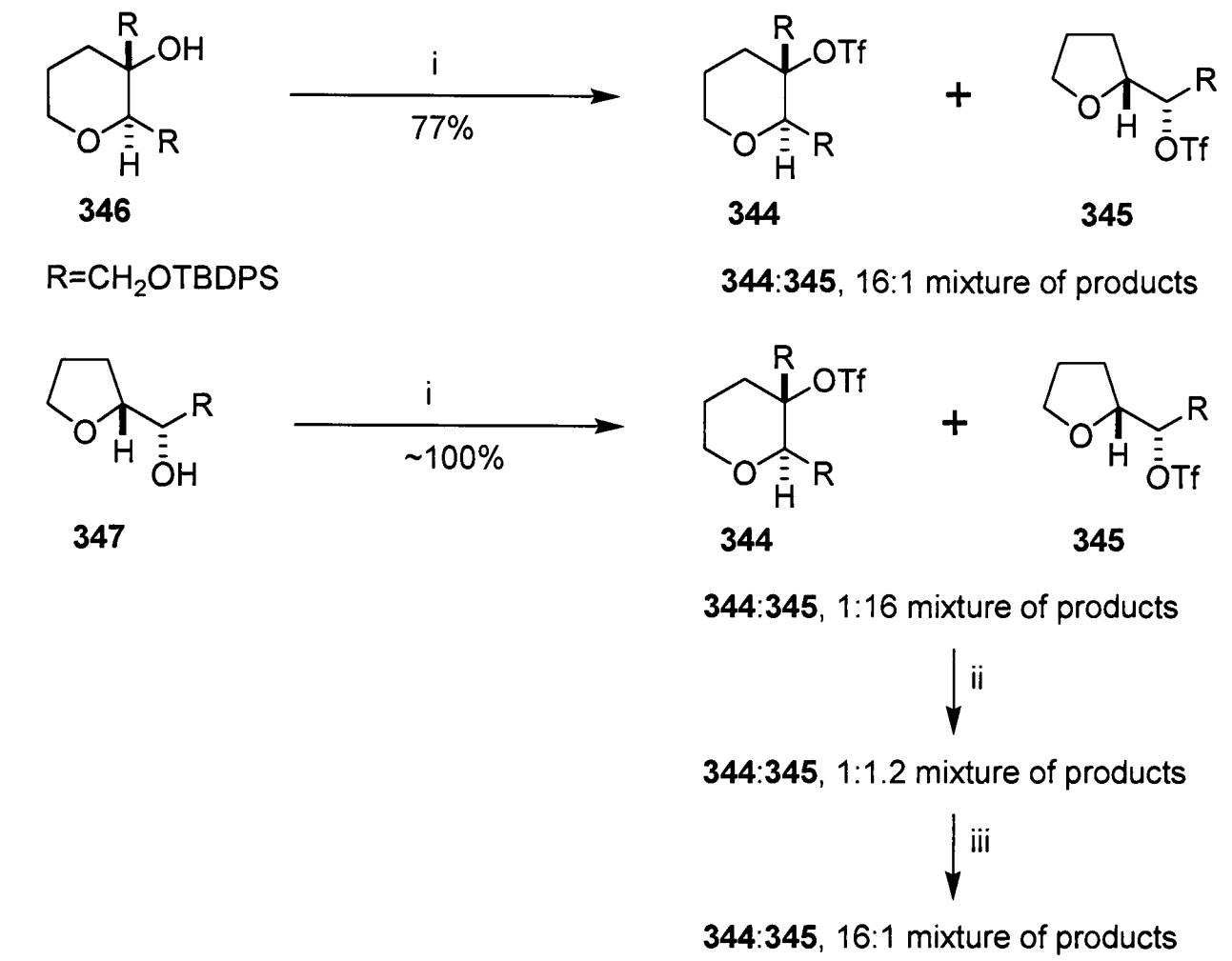
Scheme 5.12. *Reagents and conditions*: i, AgOTf, THF, H_2O, room temperature, 6 hours.

When the reaction was repeated under anhydrous conditions (Scheme 5.13), the weakly nucleophilic trifluoromesyloxy counterion opened the intermediate oxonium ion with a very high *endo*-site selectivity.[235]



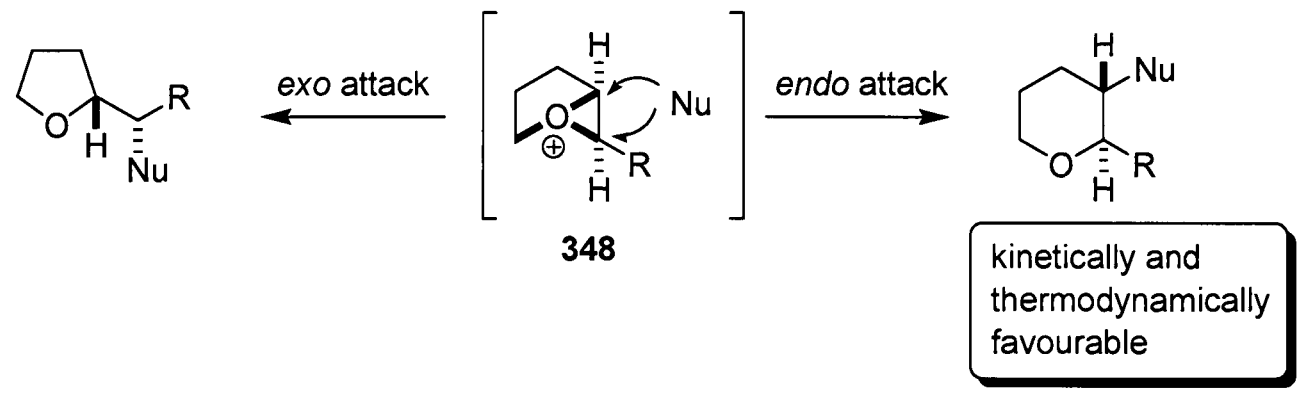
Scheme 5.13. *Reagents and conditions*: i, AgOTf, CH_2Cl_2, room temperature, 30 minutes.

Murai and co-workers found that an equilibrium existed between products **344** and **345** (Scheme I4.13).[210, 235] Tetrahydropyran **346** was treated with trifluoromethanesulfonic anhydride to give a 16:1 mixture of tetrahydropyran **344** and tetrahydrofuran **345**. When tetrahydrofuran **347** was treated with the same conditions, an initial 1:16 mixture of tetrahydropyran **344** and tetrahydrofuran **345** was observed; however this selectivity could be reversed with an increase of time and temperature to a 16:1 mixture of tetrahydropyran **344** and tetrahyrofuran **345** (after 5.5 hours at room temperature, Scheme 5.14).



Scheme 5.14. *Reagents and conditions*: i, Tf_2O, CH_2Cl_2, pyr, –15 °C, 30 minutes; ii, Tf_2O, CH_2Cl_2, pyr, room temperature, 30 minutes; iii, Tf_2O, CH_2Cl_2, pyr, room temperature, 5.5 hours.

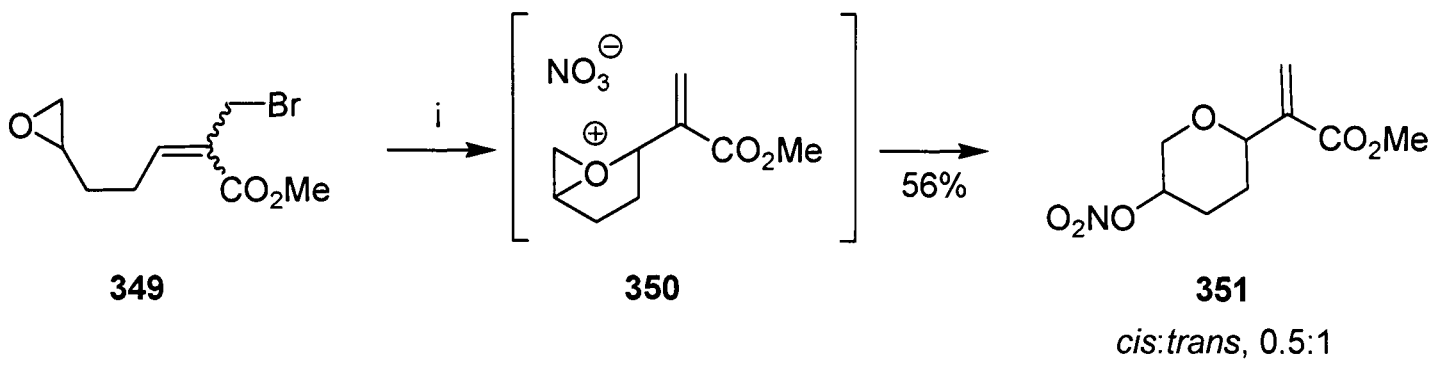
These results show that for a generic oxonium ion (for example **348**) as an example, *endo*-site ring-opening is kinetically and thermodynamically favoured (Scheme 5.15).



Scheme 5.15. *Ring-opening of bicyclic oxonium ions, kinetic and thermodynamic control.*

Although the tetrahydropyran product is favoured in the ring-opening of bicyclic oxonium ions, various methods have been published to try to induce exclusive ring-opening at the *endo*-site. Ohkata and co-workers have discovered that selective *endo*-site cleavage could be achieved for epoxide precursor **349**; the oxonium ion **350** was opened by a weakly

nucleophilic nitrate ion to give tetrahydropyran **351**, albeit in moderate yield and poor *cis*:*trans* selectivity (Scheme 5.16).[236]

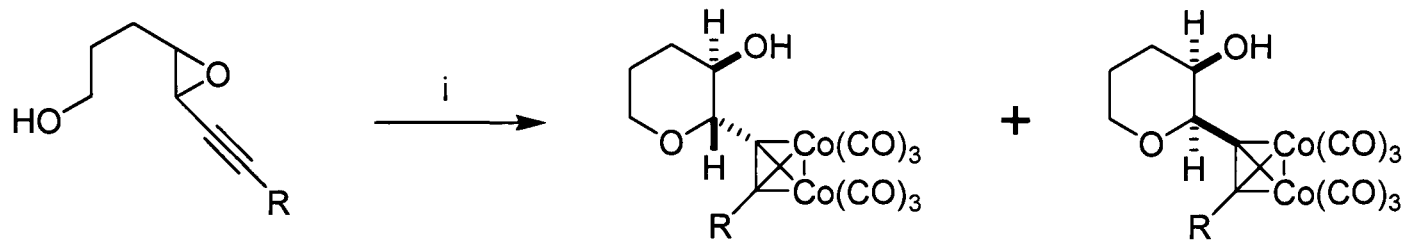


349 **350** **351**

cis:*trans*, 0.5:1

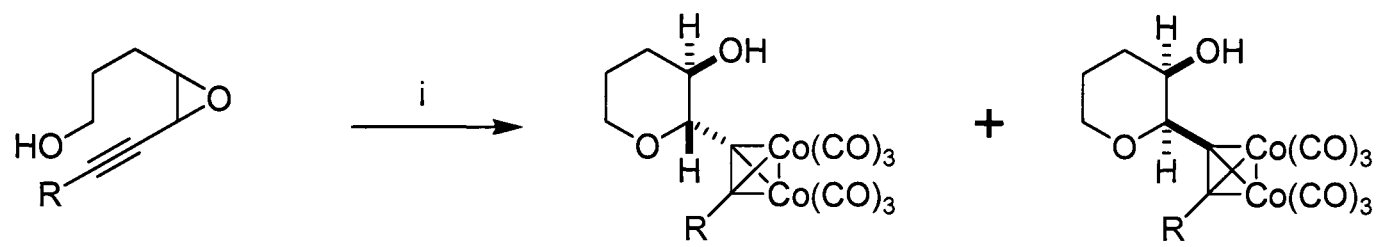
Scheme 5.16. *Reagents and conditions*: i, $AgNO_3/KPF_6$, CH_2Cl_2, room temperature.

The Nicholas reaction employs complexation of an alkyne to dicobalt hexacarbonyl and has been used to help stabilise carbocationic charge generated at the carbon α- to the alkyne moiety, prior to treatment with a nucleophile.[237, 238] This propynyl cation stabilising ability has been exploited by Mukai and co-workers for the regioselective *endo* ring-opening of epoxides (Scheme 5.17).[239, 240] The *endo*-site products (tetrahydropyran **353**) were formed exclusively regardless of the geometry of the starting expoxide (**352** and **354**) or the electronic effects of the R group.



352 *trans*-**353** *cis*-**353**

R	353 *cis*:*trans*	Yield (%)
H	96:4	65
TMS	91:9	86
n-Bu	97:3	97
Ph	99:1	96
Tol	98:2	98
C_6H_5CO	98:2	90



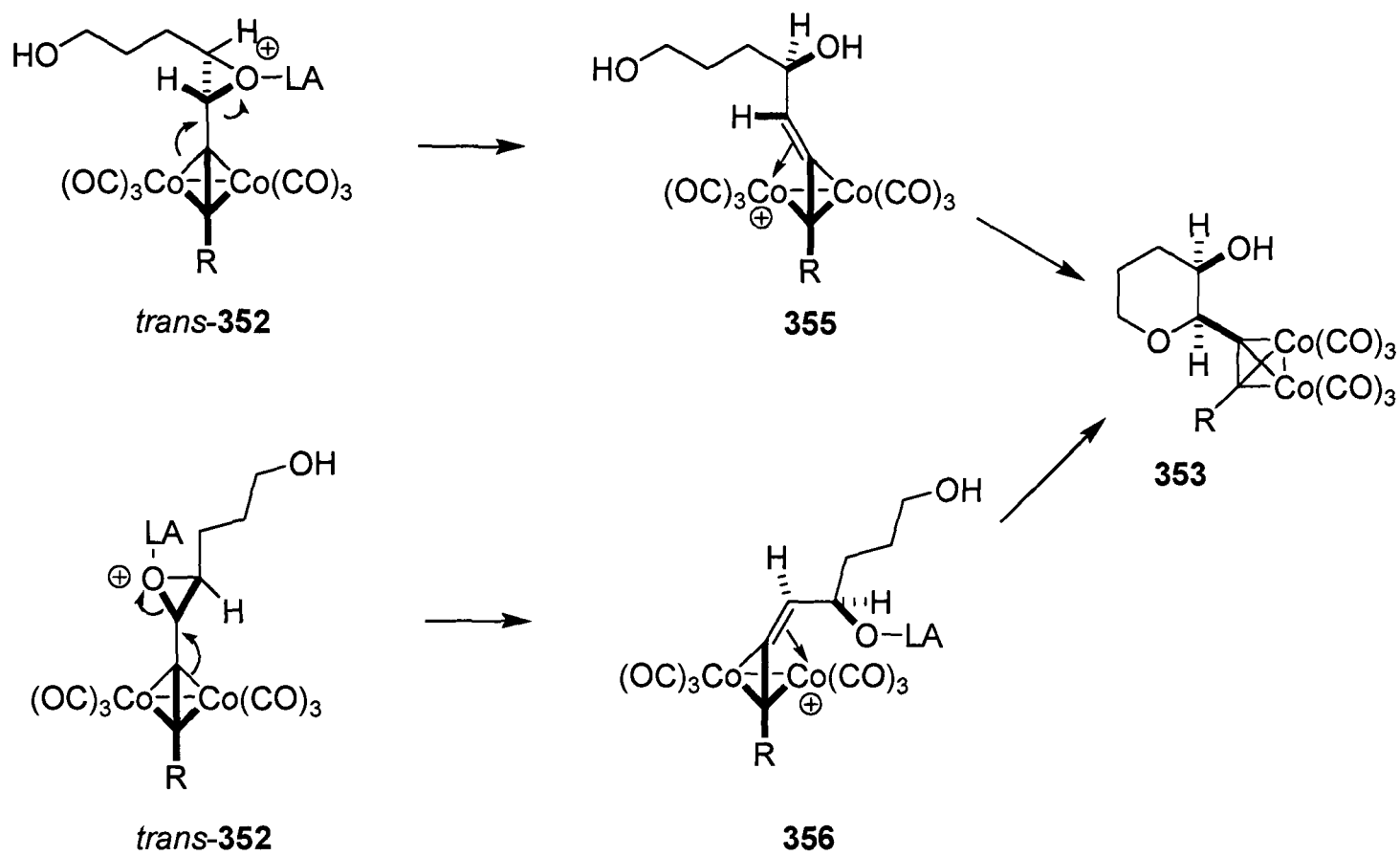
354 *trans*-**353** *cis*-**353**

R	353 *cis*:*trans*	Yield (%)
H	1:99	92
TMS	0:100	88
n-Bu	1:99	92
Ph	1:99	93
Tol	3:97	95
C_6H_5CO	3:97	89

Scheme 5.17. *Reagents and conditions*: i, $Co_2(CO)_8$, CH_2Cl_2, room temperature; then, $BF_3{\bullet}OEt_2$, CH_2Cl_2, –78 °C.

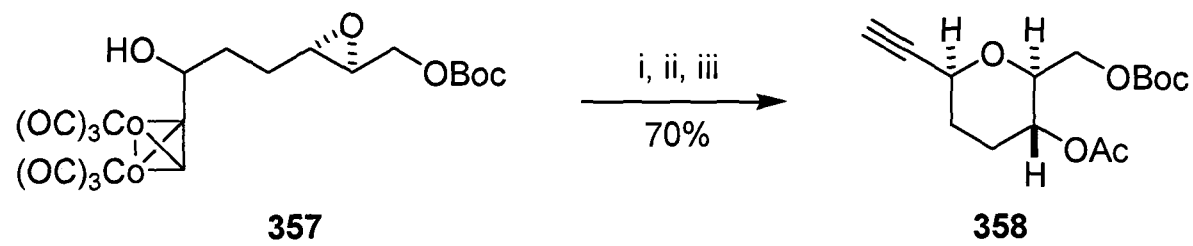
As shown in Scheme 5.17, ring-formation took place with retention of configuration at the propynyl position; hence *trans*-epoxide **352** gave predominantly *cis*-tetrahydrofuran **353** and *cis*-epoxide **354** furnished predominantly *trans*-tetrahydropyran **353**. If we consider the conversion of *trans*-epoxide **352** to *cis*-tetrahydropyran **353**, the carbon-oxygen cleavage of the epoxide by antiperiplanar anchimeric assistance of the cobalt atom inverts the propynyl stereogenic centre to give either cation **355** or **356** (Scheme 5.18). The terminal alcohol then acts as a nucleophile and attacks the cation, inverting the stereogenic centre (overall double inversion) to furnish *cis*-tetrahydropyran **353**. Similar methodologies utilising Nicholas

carbocations to afford tetrahydropyrans have been reported by the groups of Isobe[241, 242] and Martín.[243]



Scheme 5.18. *Mechanism for the conversion of trans-352 to cis-353.*

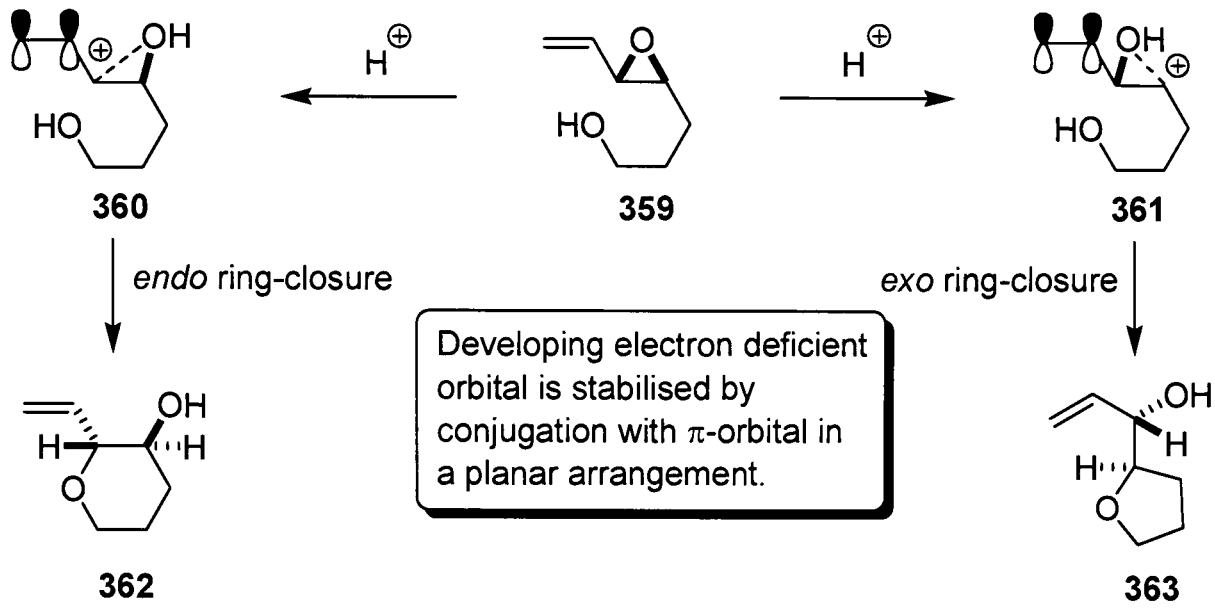
Martín and co-workers have reported the use of the Nicholas reaction in the formation of tetrahydropyrans with an epoxide moiety acting as the nucleophile (Scheme 5.19).[244] Epoxide **357** was successfully converted to tetrahydropyran **358** in high overall yield.



Scheme 5.19. *Reagents and conditions*: i, BF_3•OEt_2, CH_2Cl_2, room temperature; ii, Ac_2O, DMAP, room temperature; iii, CAN, acetone, 0 °C.

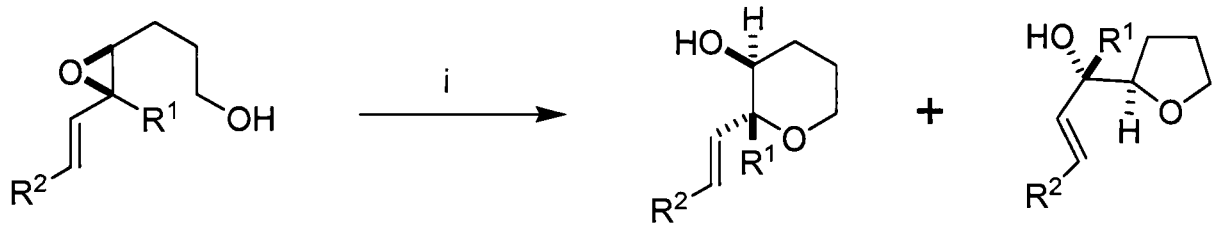
A practical method for *endo* selective openings of epoxides has been reported by Nicolaou and co-workers.[245] In the reaction of vinyl epoxide **359** under protic acid conditions (Scheme 5.20) there are two possibilities for ring-opening. Firstly, the epoxide could open at the *endo*-site (**360**), where the build up of positive charge is stabilised by π-electron donation from the adjacent olefin; hence the HOMO of the nucleophile (the alcohol) is essentially attacking the LUMO of an allyl cation, to furnish tetrahydropyran **362**. However, if the

epoxide is opened at the *exo*-site, the developing positive charge in **361** is not stabilised, and therefore formation of tetrahydrofuran **363** is not favoured (Scheme 5.20).



Scheme 5.20. *exo vs. endo Ring-opening of vinyl epoxides.*

When epoxide **364** was reacted with protic acid conditions, tetrahydropyran **365** was formed exclusively (R^2=H, Scheme 5.21). Not surprisingly, in the presence of an electron withdrawing group, the selectivity of the epoxide-opening was reduced, with formation of tetrahydrofuran **366** observed; presumably this was due to the reduced stability of the allyl cation like transition state. Nicolaou and co-workers used an iterative version of this method in the synthesis of the HIJ ring-system of brevetoxin A.[246] The Nicolaou methodology has been extended by Nakata and co-workers who found that styryl epoxides allowed exclusive *endo*-cyclisations in the synthesis of fused bicyclic systems that possess an angular methyl moiety.[247]

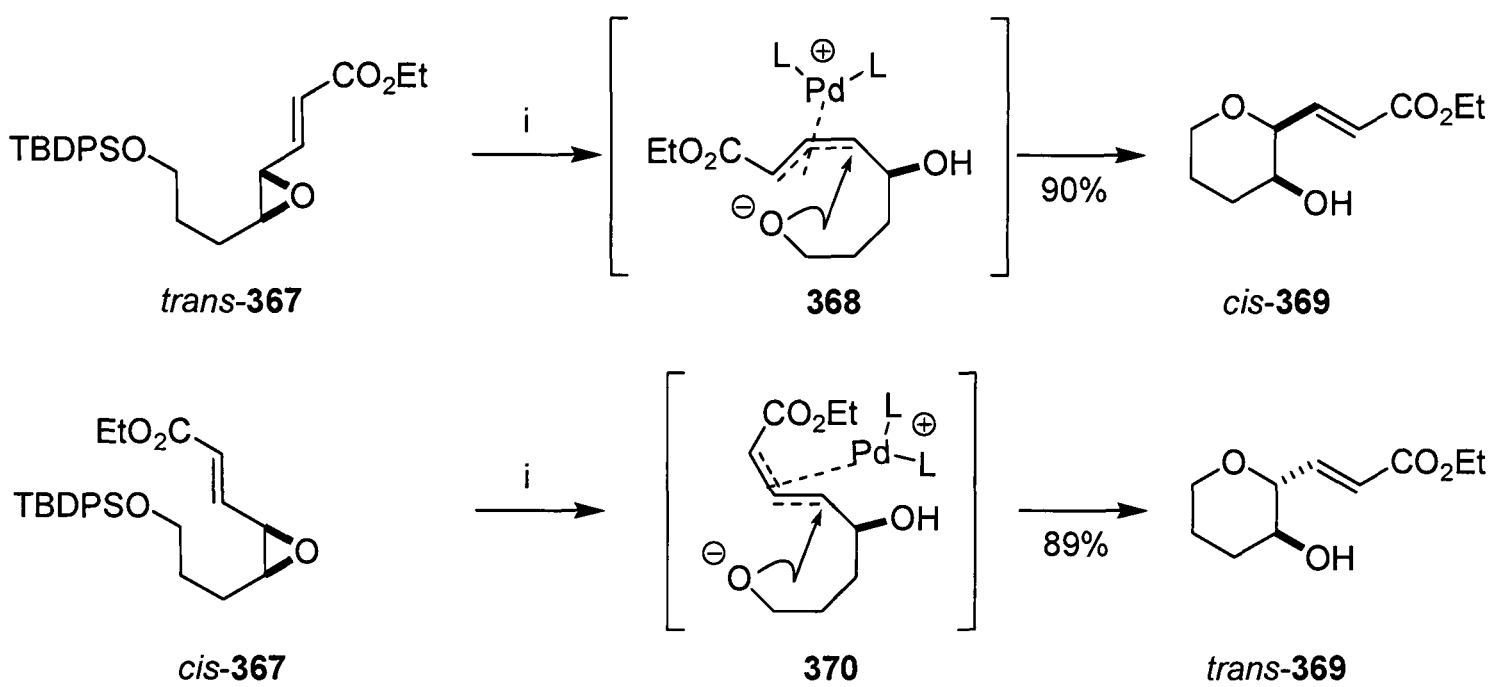


364 **365** **366**

R^1	R^2	365:366	Yield (%)
H	CO_2Me	60:40	96
H	H	100:0	95
Me	CO_2Me	66:34	92
Me	H	100:0	96

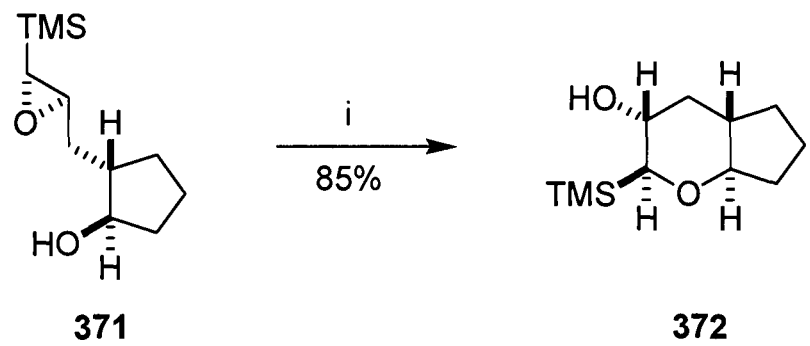
Scheme 5.21. *Reagents and conditions:* i, CSA (10 mol%), CH_2Cl_2, –40 °C → room temperature.

Hirama and co-workers reported the transformation of epoxide **367** into tetrahydropyran **369** *via* the palladium π-allyl intermediates **368** or **370** (Scheme 5.22).[248] The yields and selectivities were both high, with the reaction proceeding through a double inversion (*c.f.* Scheme 5.17 and 5.18); hence *trans*-epoxide **367** gave *cis*-tetrahydropyran **369** and *cis*-epoxide **367** furnished *trans*-tetrahydropyran **369** (Scheme 5.22).



Scheme 5.22. *Reagents and conditions*: i, TBAF, THF, room temperature; then, $Pd(PPh_3)_4$, PPh_3, CH_2Cl_2, room temperature.

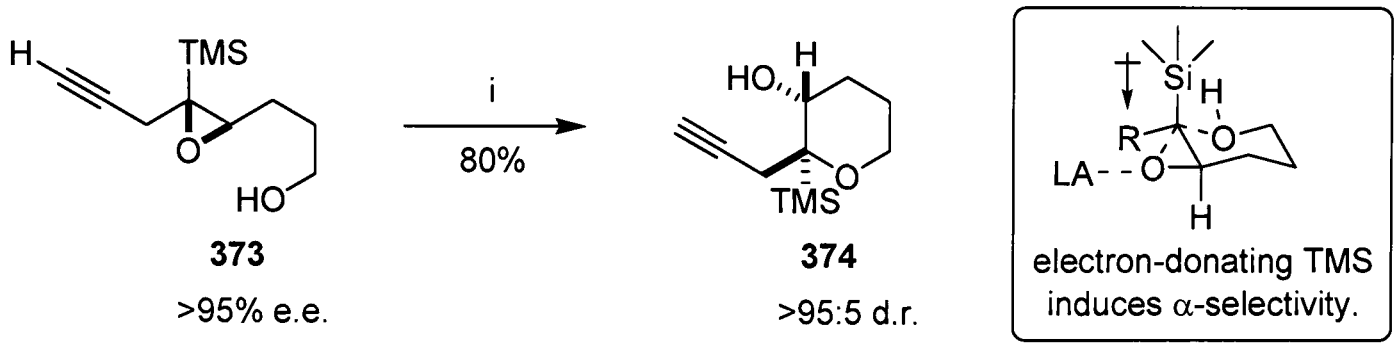
Trialkylsilyl groups have been shown to activate α,β-epoxy silanes towards nucleophilic opening at the α-site.[249] Schaumann and co-workers have applied this phenomenon to the 6-*endo*-cyclisation of hydroxy epoxides (Scheme 5.23); epoxide **371** was converted to tetrahydropyran **372** in high yield when treated with a protic acid.



Scheme 5.23. *Reagents and conditions*: i, PPTS or CSA, CH_2Cl_2.

Epoxysilanes can also undergo Lewis acid mediated 6-*endo*-cyclisation; chiral epoxide **373** was treated with boron trifluoride diethyl etherate to give tetrahydropyran **374** in a greater than 95:5 selectivity (Scheme 5.24).[250] The axial electron donating trimethylsilyl group helps promote *endo*-cyclisation by inducing α-selectivity. Jamison and Heffron have utilised this

method in an iterative homologation-epoxidation-cyclisation strategy for the synthesis of fused polytetrahydropyrans.[250]

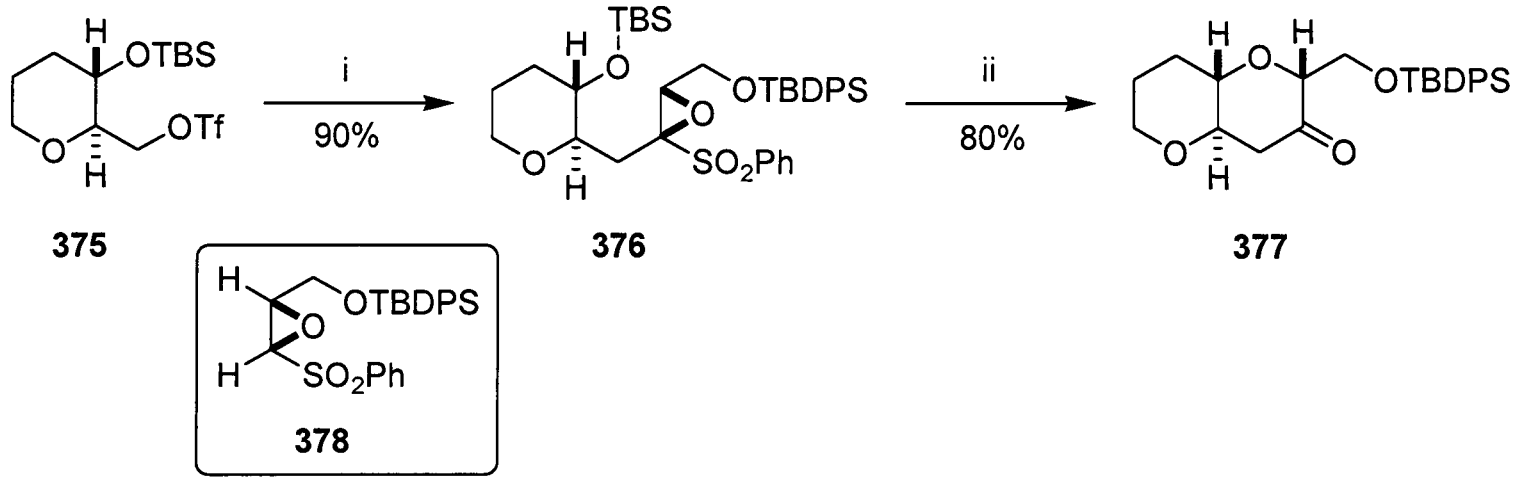


373
>95% e.e.

374
>95:5 d.r.

Scheme 5.24. *Reagents and conditions*: i, BF_3•OEt_2, CH_2Cl_2.

Thus far all the modes to induce *endo*-cyclisations have originated from activating the *endo*-site. Mori and co-workers showed that *endo*-selectivity could be induced successfully by deactivation of the *exo*-site.[251] Triflate **375** was displaced by the anion of epoxide **378** to form precursor **376** (Scheme 5.25). The sulfone deactivates the *exo*-site and upon treatment with a protic acid, exclusive *endo*-cyclisation yielded fused tetrahydropyran **377** in high yield. This methodology has successfully been applied to the total synthesis of hemibrevetoxin B.[252, 253]



375

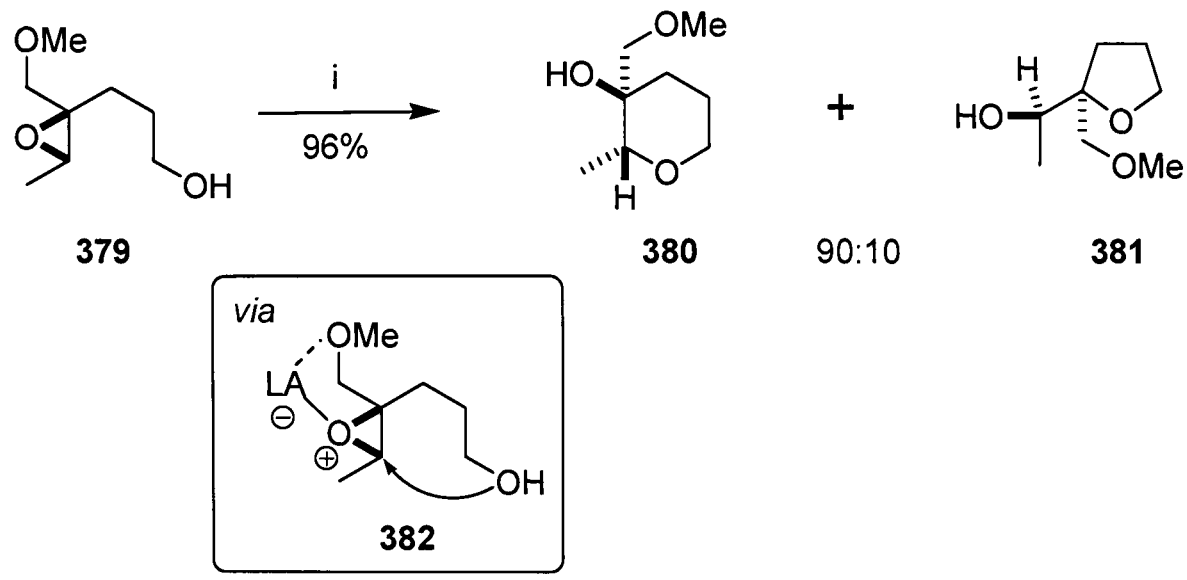
376

377

378

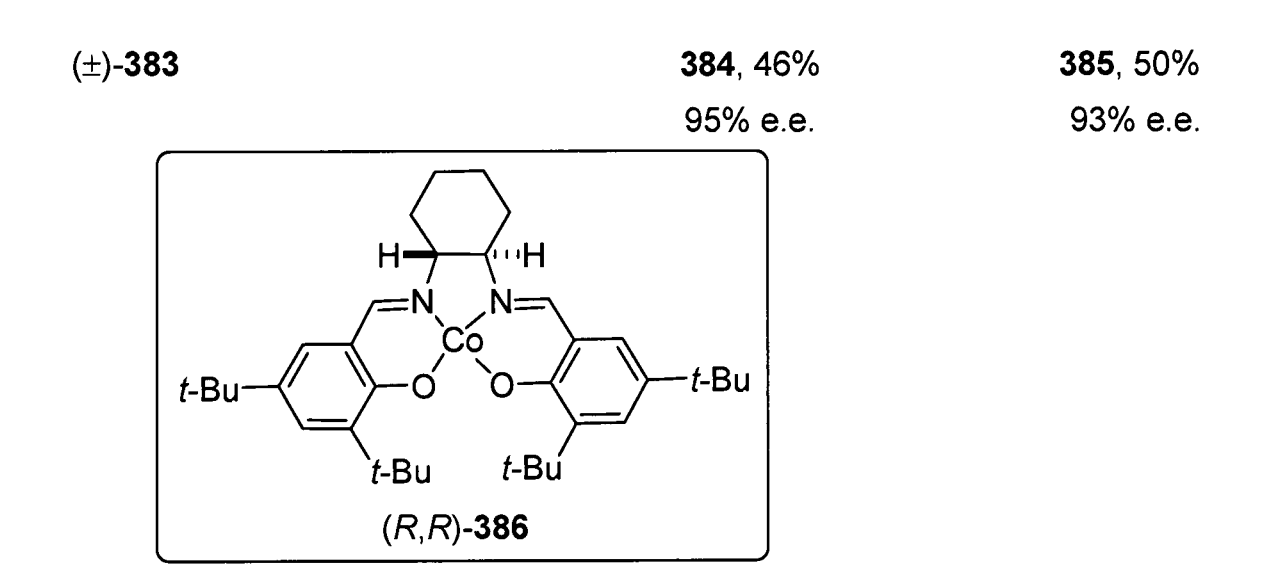
Scheme 5.25. *Reagents and conditions*: i, **378**, *n*-BuLi, THF, DMPU, –100 °C; ii, *p*-TsOH•H_2O, $CHCl_3$, 55 °C.

Murai and co-workers reported that when epoxide **379** was treated with hydrated lanthanum triflate, the corresponding tetrahydropyran **380** and tetrahydrofuran **381** were obtained in a 90:10 selectivity (Scheme 5.26).[254] The lanthanum coordinates between the epoxide and methoxy moieties to give intermediate species **382**.



Scheme 5.26. *Reagents and conditions*: i, $La(OTf)_3$ (1.1 eq.), H_2O (2.2 eq.), CH_2Cl_2.

During their studies on the regio- and enantioselective cyclisation of epoxy alcohols, Jacobsen and co-workers reported the transformation of epoxide **383** to the corresponding tetrahydropyran **384** and enantioenriched epoxide **385**, catalysed by the cobalt$^{(III)}$ salen complex **386** (Scheme 5.27).[255]

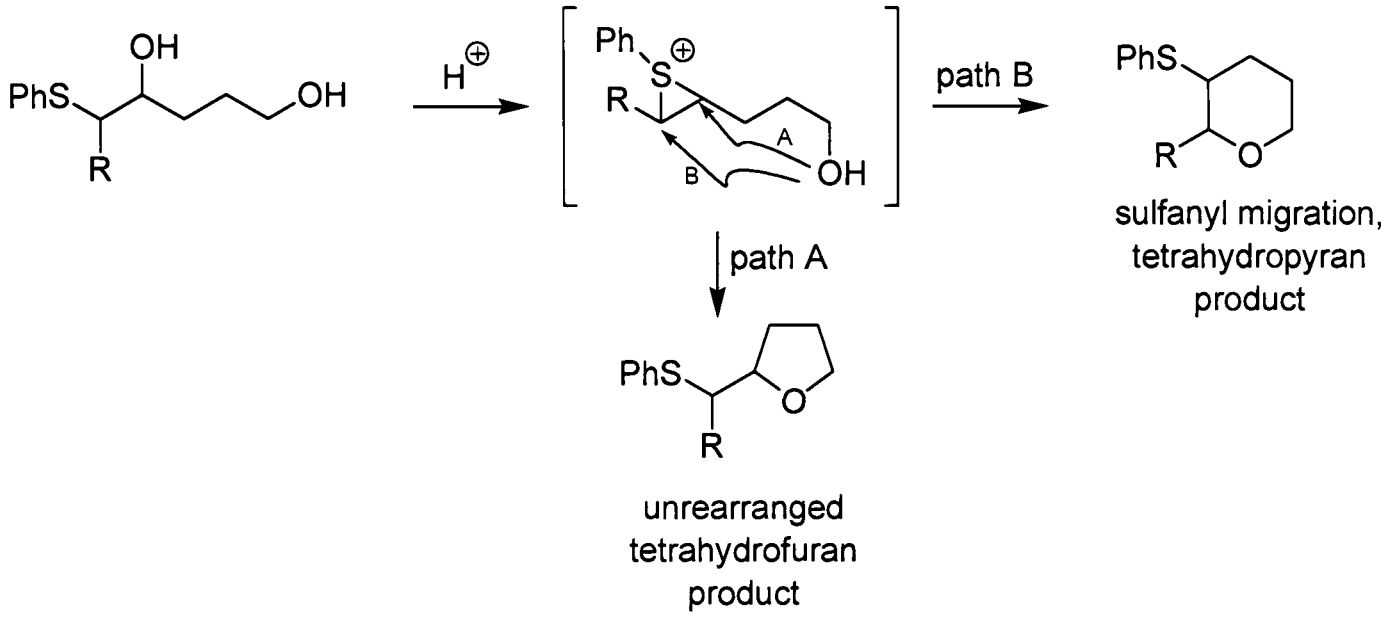


Scheme 5.27. *Reagents and conditions*: i, **386** (1-2 mol%), TBME, 0 °C.

5.4 *Ring-expansion by the opening of thiiranium ions to form tetrahydropyrans.*

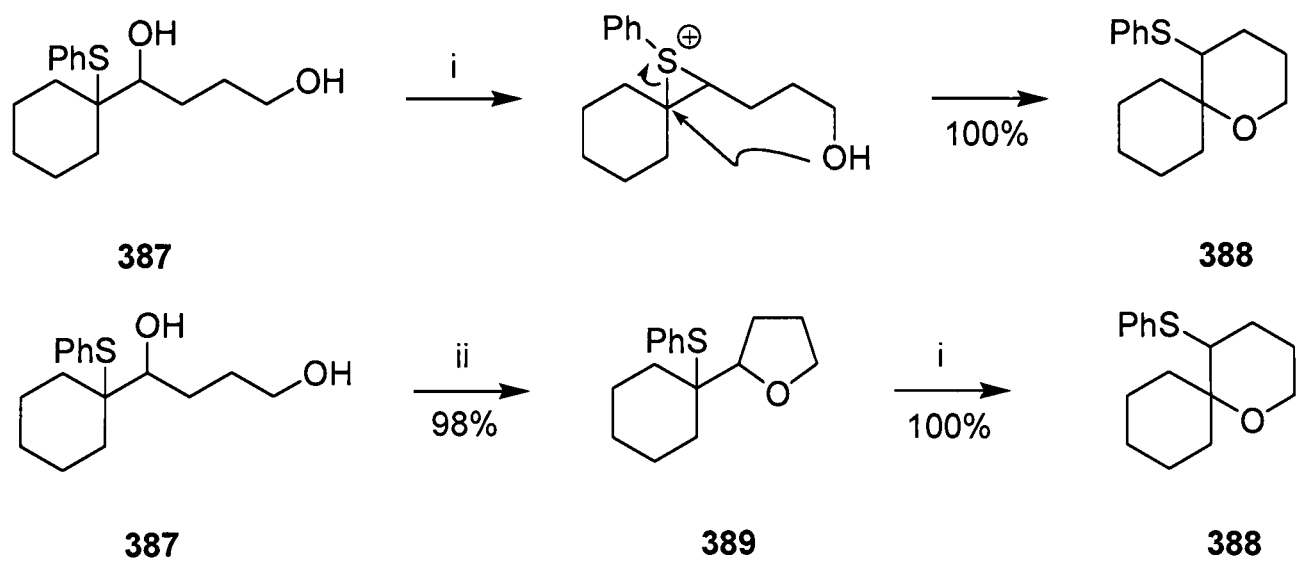
Warren and co-workers have demonstrated that intramolecular cyclisation of alcohols onto thiiranium ions form the corresponding saturated oxygen heterocycles in high yield.[256]

Since attack onto the thiiranium ion occurs *via* a "loose" S_N2-type transition state, stereochemical integrity is maintained. In the cyclisation of 1,4-diols there are two possible products (Scheme 5.28): either an unrearranged tetrahydrofuran (path A) or a tetrahydropyran in which a sulfanyl migration has occurred (path B).



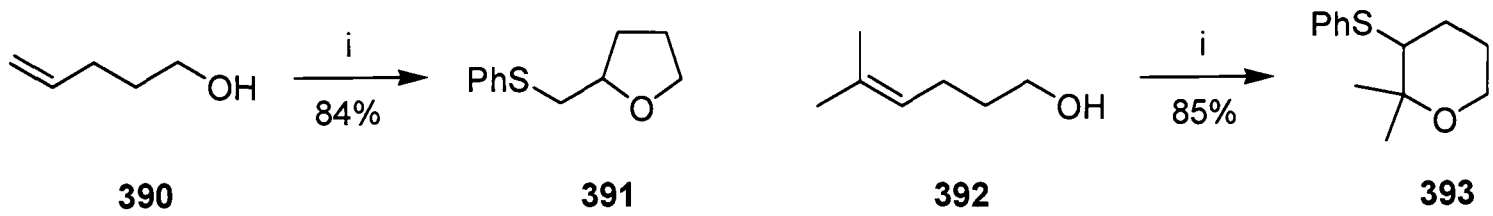
Scheme 5.28. *1,4-diol cyclisation onto a thiiranium ion.*

When alcohol **387** was treated with a protic acid, tetrahydropyran **388** was obtained as the sole product (Scheme 5.29). When tetrahydrofuran **389** was reacted with the protic acid conditions, rearrangement to tetrahydropyran **388** occurred, hence the tetrahydropyran (**388**) is the more stable product; the authors note that the position of the sulfanyl group is important: in the tetrahydropyran **388** the sulfur atom has moved "downhill" in energy to a secondary centre and the oxygen is now bonded to a tertiary centre.[257]



Scheme 5.29. *Reagents and conditions*: i, TsOH, CH_2Cl_2, 40 °C; ii, TsCl, pyridine, room temperature.

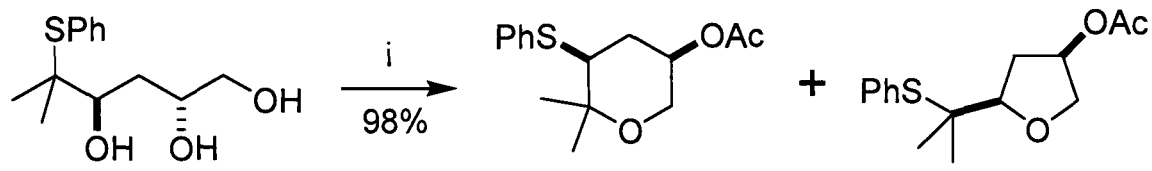
The importance of the positioning of the sulfur atom is shown in the cyclisation of olefins **390** and **392** (Scheme 5.30).[258] Treatment of olefin **390** with protic acid conditions furnished tetrahydrofuran **391** whereas trisubstituted olefin **392** gave tetrahydropyran **393**.



390 **391** **392** **393**

Scheme 5.30. *Reagents and conditions*: i, PhSCl, *i*-Pr_2NEt, MeCN, room temperature.

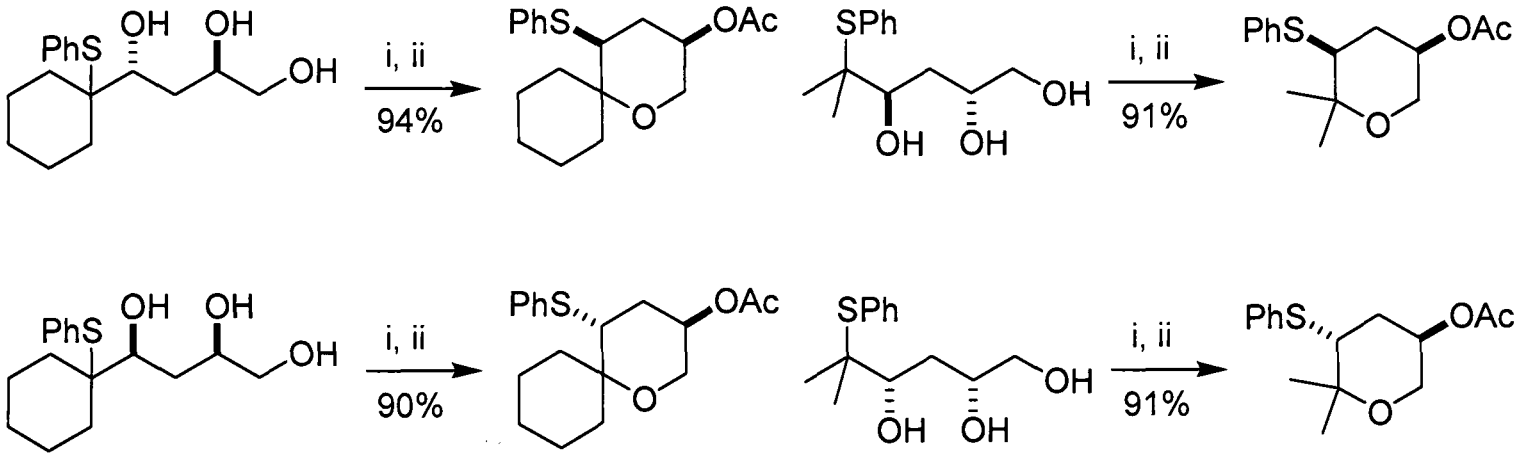
When triol **394** was reacted with trimethyl orthoacetate for 24 hours, tetrahydropyran **395** and tetrahydrofuran **396** were obtained as a 23:77 mixture of products in high yield (Scheme 5.31).[259]



394 **395** 23:77 **396**

Scheme 5.31. *Reagents and conditions*: i, $(MeO)_3CMe$, PPTS, CH_2Cl_2, room temperature, 24 hours.

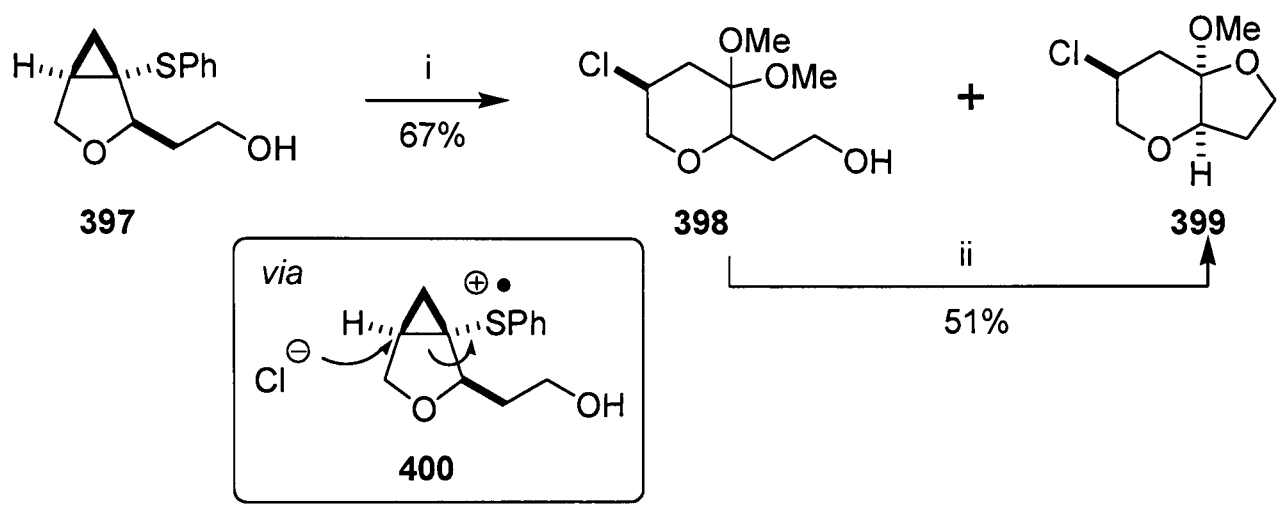
When the product mixture was treated *para*-toluenesulfonic acid, complete equilibration to the tetrahydropyran products was observed in high yield (Scheme 5.32); once again the authors' note that the products have moved "downhill" in energy as the sulfanyl group is now a secondary centre and the oxygen atom is bonded to a tertiary carbon.[259]



Scheme 5.32. *Reagents and conditions*: i, $(MeO)_3CMe$, PPTS, CH_2Cl_2, room temperature, 24 hours; ii, TsOH, CH_2Cl_2, room temperature.

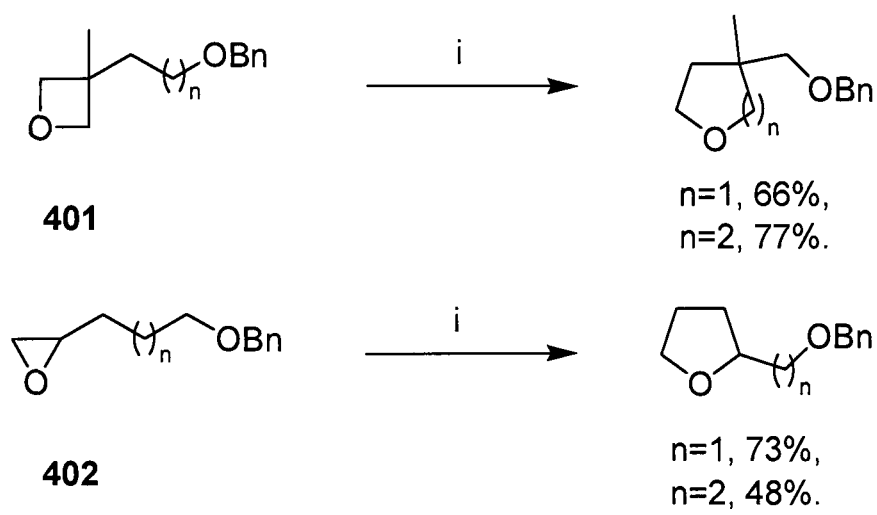
5.5 *Miscellaneous ring-expansion to form tetrahydropyrans.*

cis-Fused chlorinated bicylic ethers have been prepared from the oxidative ring-opening of cyclopropyl derivatives (Scheme 5.33).[260] When reacted with ceric ammonium nitrate, tetrahydrofuran **397** gave a mixture of monocylic tetrahydropyran **398** and the fused bicycle **399**; the single electron oxidation of the sulphur atom allowed the chloride nucleophile to ring-open cyclopropane **400**. Although a mixture of products was obtained, monocylic tetrahydropyran **398** could easily be converted to the bicyclic compound **399** with *para*-toluene sulfonic acid (Scheme 5.33).



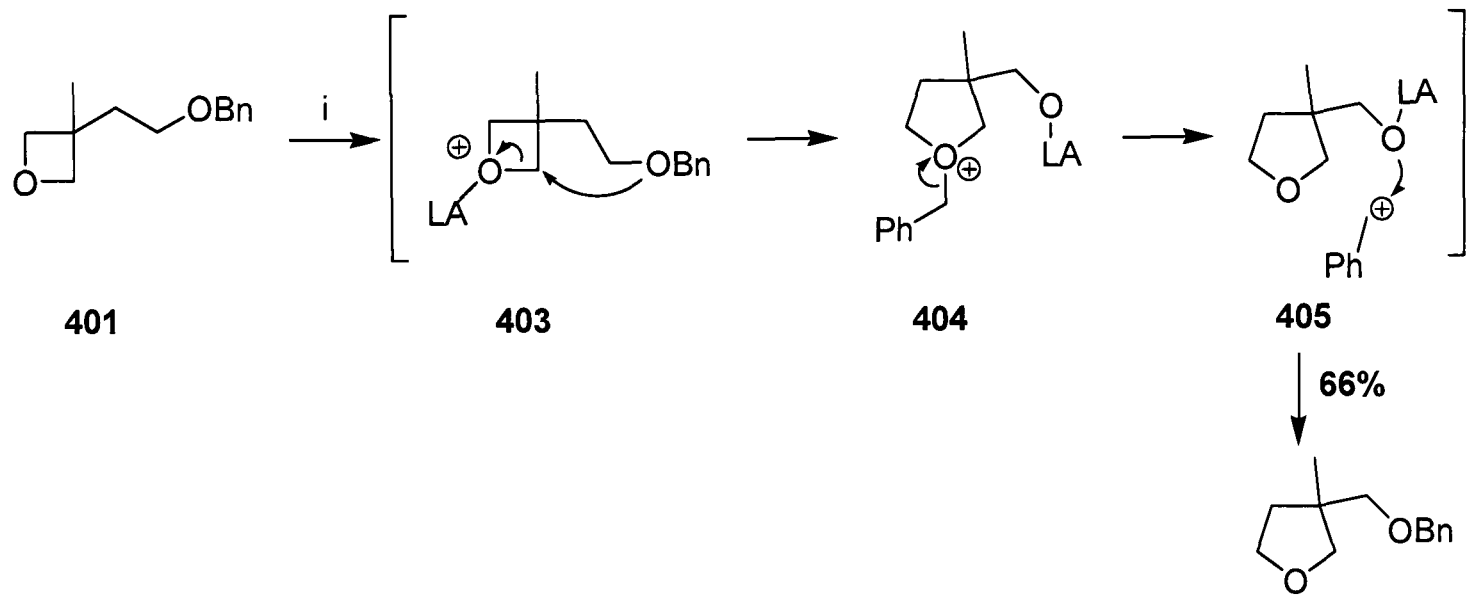
Scheme 5.33. *Reagents and conditions*: i, CAN, Me_4NCl, MeOH; ii, TsOH, PhH, room temperature.

Lewis acid mediated ring-expansion of oxetanes and epoxides (Scheme 5.34) has been reported by Masaki and co-workers.[261] Oxetanes **401** gave the corresponding tetrahydrofuran or tetrahydropyran in moderate to good yields, whereas the epoxides **402** gave the corresponding tetrahydrofuran products.



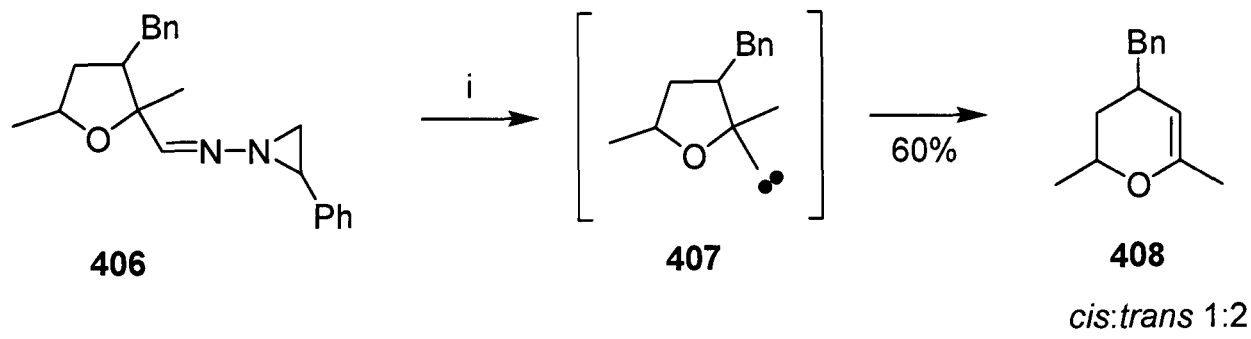
Scheme 5.34. *Reagents and conditions*: i, BF_3•OEt_2 (20 mol%), CH_2Cl_2, 0 °C.

Oxetane **401** coordinates to the Lewis acid to give activated species **403**, internal nucleophilic attack ring opens the oxetane to the tetrahydrofuran **404**, then loss of the benzyl group allows the free alcohol in intermediate **405** to capture the benylic cation furnishing the tetrahydrofuran product (Scheme 5.35).



Scheme 5.35. *Reagents and conditions*: i, BF_3•OEt_2 (20 mol%), CH_2Cl_2, 0 °C.

Finally, Kim and co-workers have reported the synthesis of a tetrahydropyran from a tetrahydrofuran precursor.[116, 262] When thermally initiated carbene precursor **406** ring opened to form carbene **407** (Scheme 5.36), which inserts directly into the carbon-carbon bond[117-119] to afford dihydropyran **408** in moderate yield, albeit in a poor *cis*:*trans* ratio (1:2).



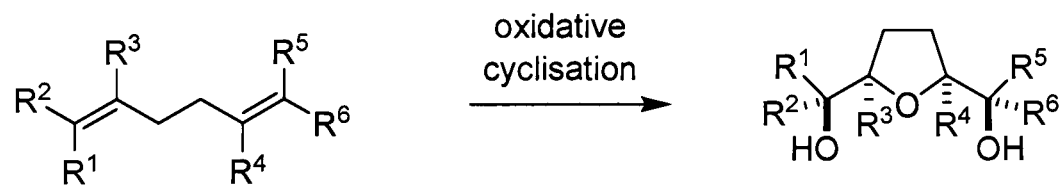
Scheme 5.36. *Reagents and conditions*: i, PhMe, 120 °C.

Chapter 6

Results and Discussion – Rearrangements of Oxygen Heterocycles

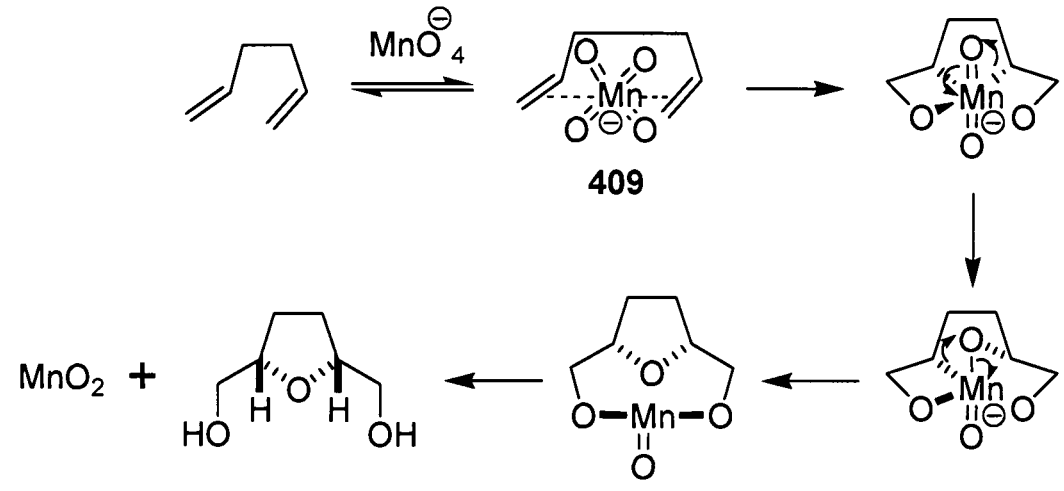
6.1 *Development of the tetrahydrofuran to tetrahydropyran ring-expansion.*

In 1965, Klein and Rojahn reported the first example of an oxidative cyclisation to furnish a tetrahydrofuran.[263] Treatment of 1,5-hexadiene with potassium permanganate afforded *cis*-2,5-*bis*(hydroxymethyl)-tetrahydrofuran. The reaction involves a stereospecific addition of two oxygen atoms across each of the olefins and a subsequent cyclisation to furnish *cis*-tetrahydrofurans; the four stereogenic centres are controlled by the geometry of the starting olefins (Scheme 6.1).



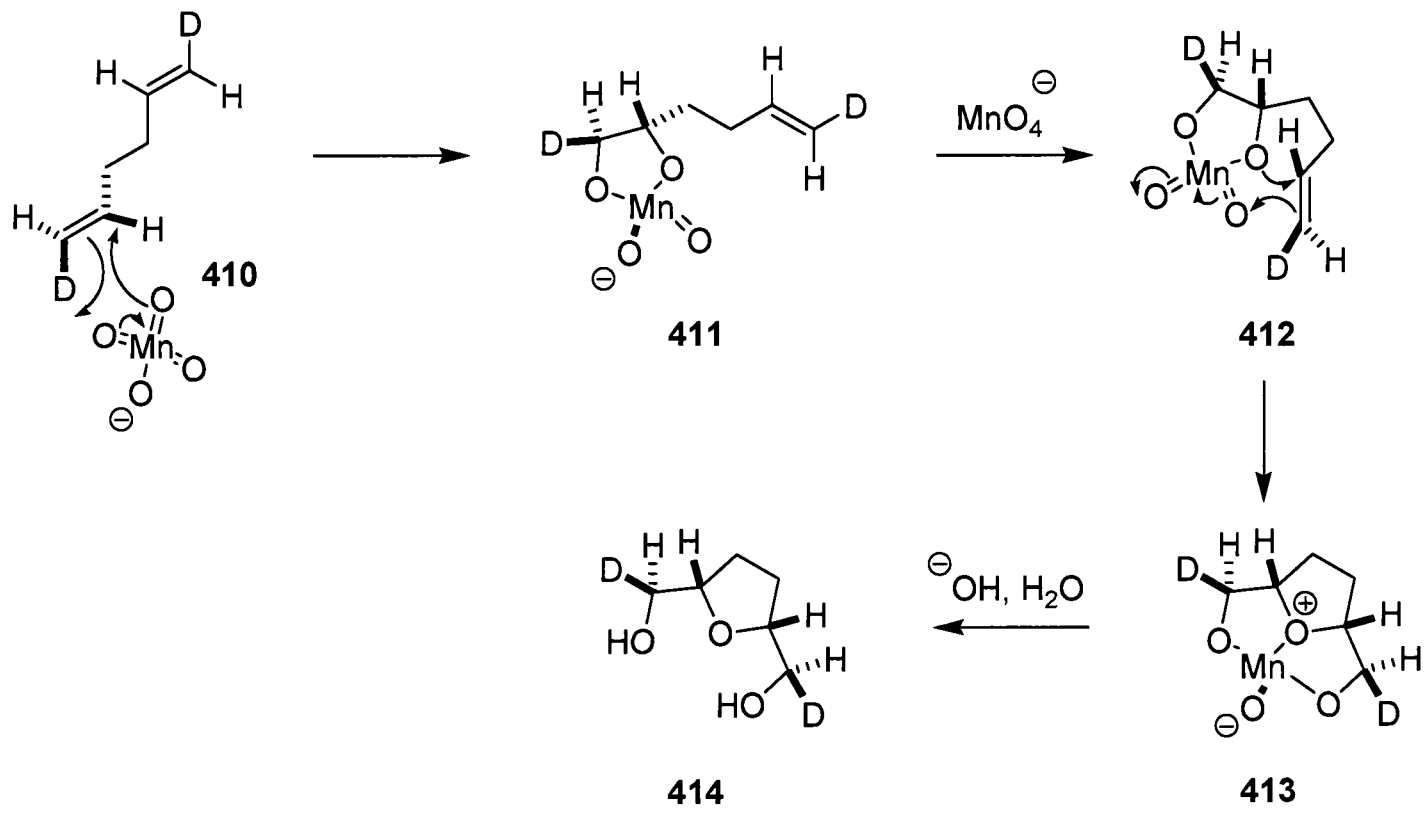
Scheme 6.1. *Stereospecific formation of cis-tetrahydrofurans.*

The mechanism had been the matter of some debate: Walba and co-workers had postulated that a *bis* π-metal complex (**409**) underwent consecutive [2+2] cycloadditions (Scheme 6.2).[264]



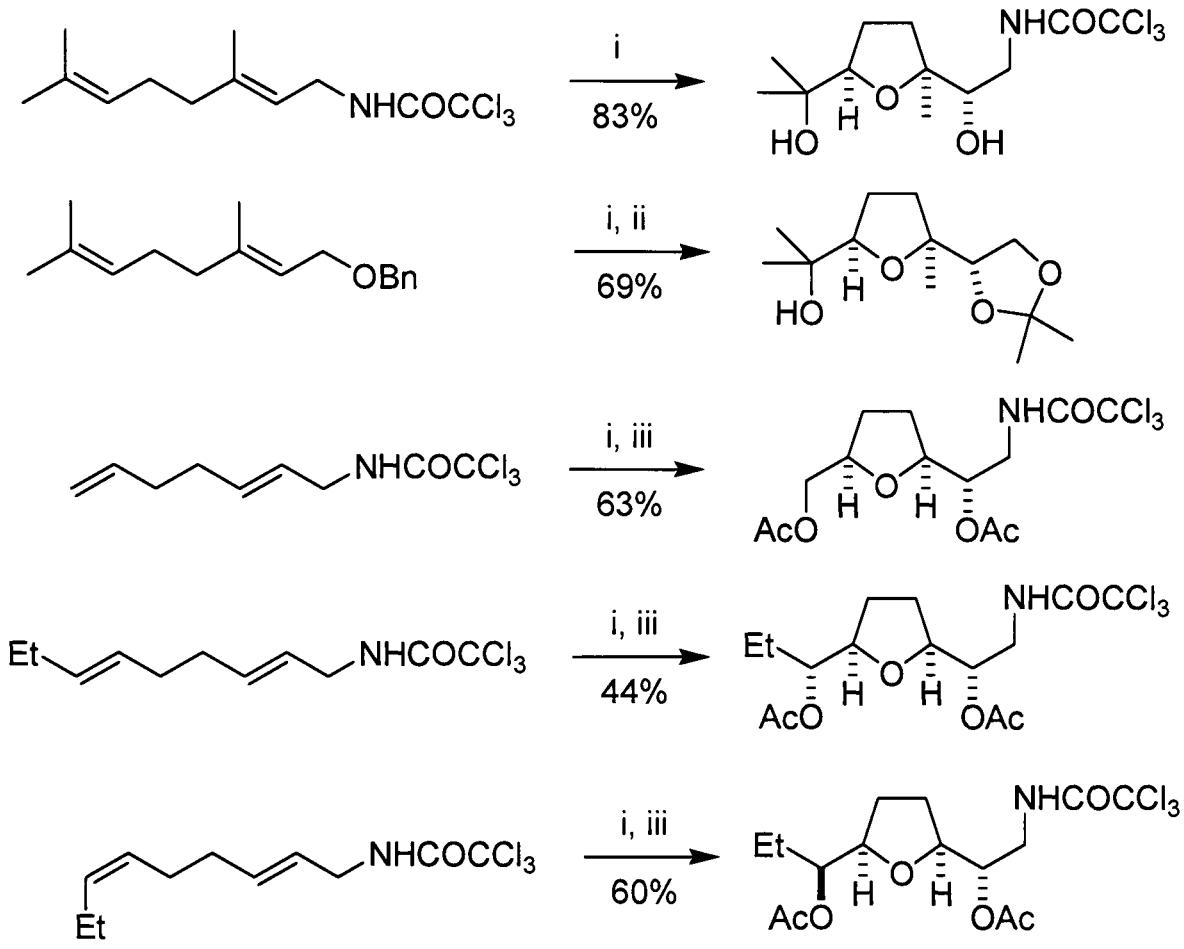
Scheme 6.2. *Stereospecific formation of cis-tetrahydrofurans.*

However, the modern day general consensus is that the mechanism follows a [3+2] cycloaddition pathway as proposed by Baldwin (Scheme 6.3).[265] Using labelled diolefin **410** Baldwin postulated that manganese ester **411** was oxidised to afford cyclisation precursor **412**. An intramolecular cycloaddition formed species **413** that upon hydrolysis furnished tetrahydrofuran **414**. Ingold and Wolfe repeated the reaction reported by Baldwin and co-workers in the presence of oxygen labelled water (92% $H_2{}^{18}O$); analysis of the mass spectrum proved the presence of one labelled oxygen atom in the tetrahydrofuran product; thus giving experimental evidence to the mechanism proposed by Baldwin.[266]



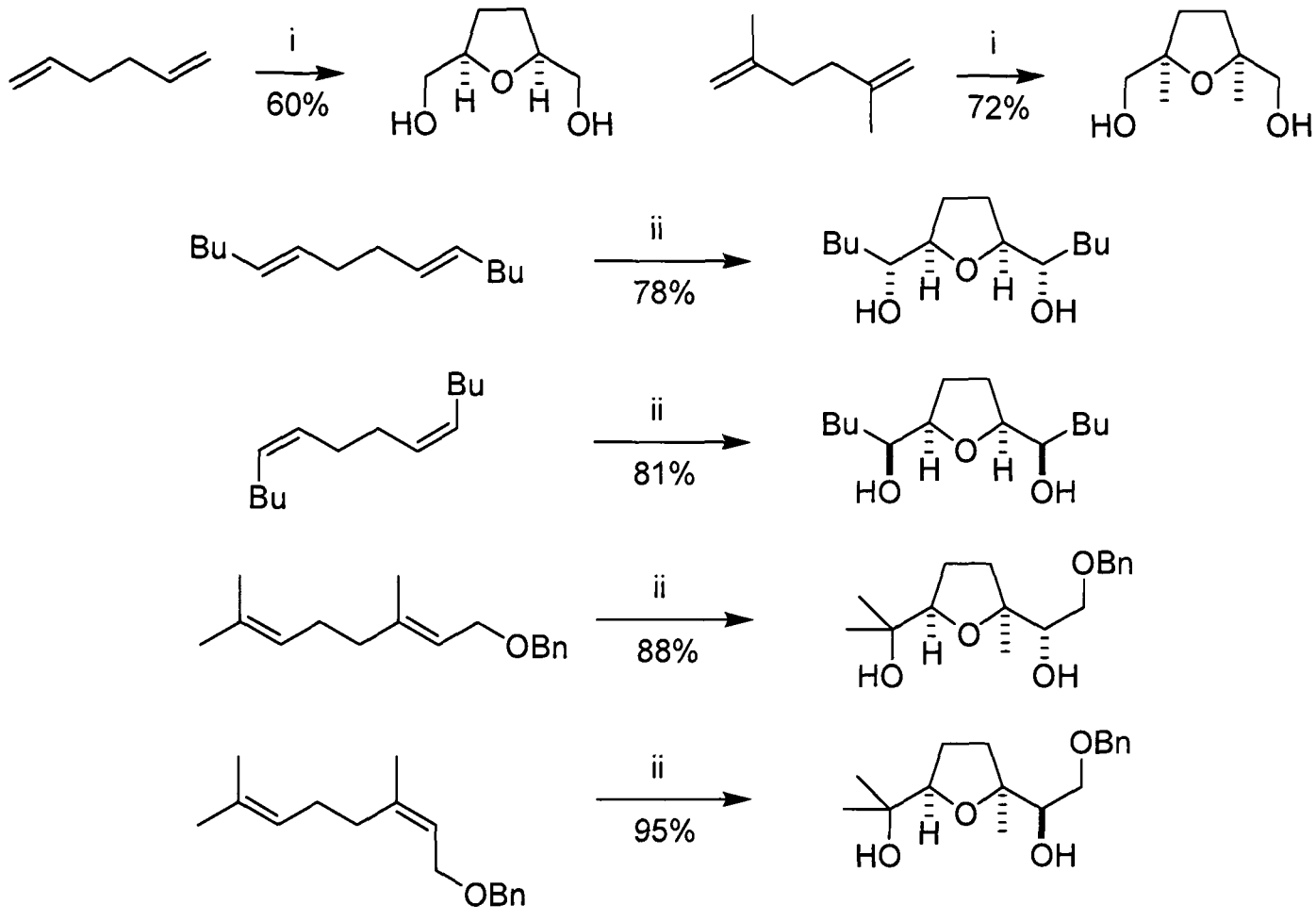
Scheme 6.3. *Proposed [3+2] cycloaddition mechanism for the oxidative cyclisation of 1,5-dienes.*

Since the original report, other strong oxidising reagents have been reported to promote cyclisation: procedures involving stoichiometric potassium permanganate[264, 265] and chromium trioxide[267] derivatives tend to suffer from low yields due to over-oxidation of the tetrahydrofuran products. Although catalytic systems using either osmium tetroxide[268] or ruthenium tetroxide[269-271] have been reported, they are not without limitations. Both methods use sodium periodate as the metal reoxidant; the osmium tetroxide procedure is neither high yielding nor general and the products obtained from the ruthenium tetroxide method are not completely stereoselective for the formation of *cis*-tetrahydrofurans.



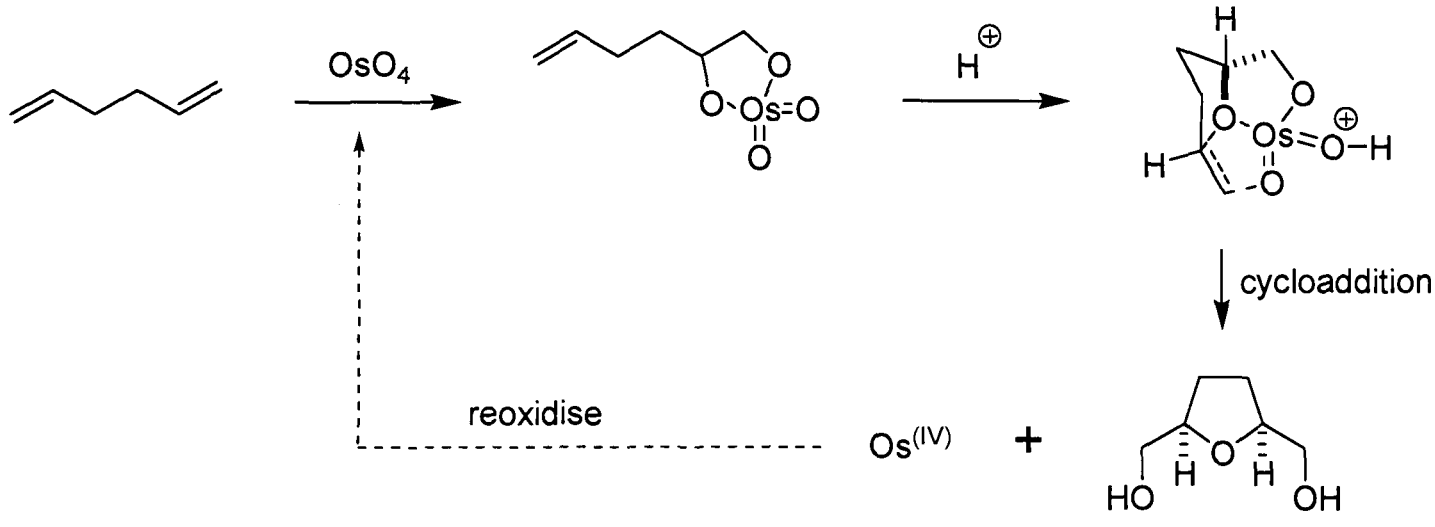
Scheme 6.4. *Reagents and conditions*: i, OsO_4 (1.0 eq.), TMEDA (1.0 eq.), CH_2Cl_2, –78 °C; then MeOH, HCl, room temperature; ii, $(MeO)_2CMe_2$, TFA, room temperature; iii, Ac_2O, Et_3N, CH_2Cl_2, room temperature.

Donohoe and co-workers reported that the use of osmium tetroxide and tetramethylethylenediamine could induce the oxidative cyclisation of a range of dienes under acidic conditions (Scheme 6.4).[272] The one drawback to this method was the use of stoichiometric osmium tetroxide (1.0 equivalent); however the reaction has been further developed by Donohoe and Butterworth into a variant that uses a sub-stoichiometric amount of osmium tetroxide, an amine-*N*-oxide metal reoxidant, and either camphorsulfonic acid or trifluoroacetic acid to lower the pH of the reaction mixture (Scheme 6.5).[10] The yields for the cyclisation of various 1,5-dienes were very high and no over oxidation side-products were observed.



Scheme 6.5. *Reagents and conditions*: i, OsO_4 (5 mol%), CSA, Me_3NO, CH_2Cl_2, room temperature; ii, $K_2OsO_4 \cdot 2H_2O$ (5 mol%), Me_3NO, TFA, acetone:H_2O (9:1), room temperature.

A similar [3+2] cycloaddition as proposed by Baldwin for the potassium permanganate oxidative cyclisation was evoked by Donohoe for the osmium catalysed oxidative cyclisation; the exact role of the acid is unkown, but Donohoe postulated that it protonates an oxo ligand on the osmium centre, making an electron deficient partner for the free olefin in the proceeding [3+2] cycloaddition (Scheme 6.6).[10]



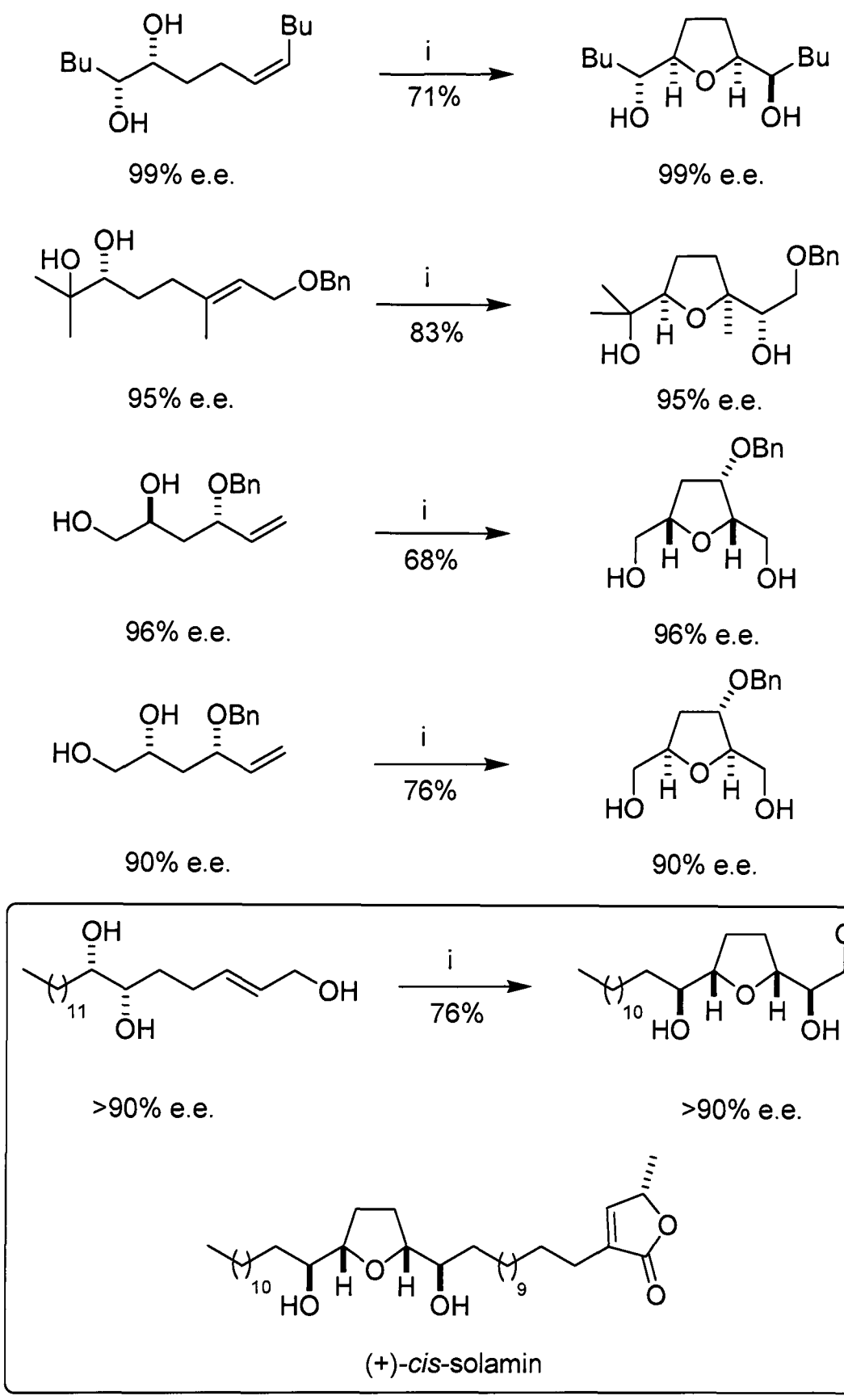
Scheme 6.6. *Proposed [3+2] cycloaddition mechanism for the oxidative cyclisation of 1,5-dienes catalysed by osmium.*

Theoretically an asymmetric version of the oxidative cyclisation should be possible as the mechanism proceeds *via* two stererospecific [3+2] cycloadditions (*c.f.* Sharpless asymmetric dihydroxylation).[273] Although several groups have published an enantioselective oxidative cyclisation, asymmetric induction has been introduced from either an acyl-derived chiral auxilary[217, 274-276] or chiral phase-transfer catalysts;[277] attempts at utilising the cinchona alkaloid ligands to induce asymmetric induction in the osmium catalysed oxidative cyclisation were not successful.[*,11] Donohoe and Butterworth have however reported the osmium catalysed oxidative cyclisation of pre-formed chiral diols (Scheme 6.7).[11] The process is high yielding, and the enantiomeric excess of the starting diol is completely retained in the tetrahydrofuran product. A sacrificial olefin is added to the reaction mixture and is thought to reduce osmium$^{(VIII)}$ to osmium$^{(VI)}$ which can undergo a *trans*-gylcolate exchange with the chiral diol forming a chiral osmate ester, an intramolecular cycloaddition furnishes the enantio-enriched tetrahydrofuran (*c.f.* Scheme 6.6). The oxidative cyclisation of a chiral diol was used as the key step in the formal synthesis of (+)–*cis*-solamin (Scheme 6.7).[11]

Although the osmium catalysed oxidative cyclisation of 1,5-dienes yields the corresponding tetrahydrofurans in excellent yields, the analogous process with 1,6-dienes has met with failure, with no desired tetrahydropyran products isolated.[278]

Thus the second major aim for this thesis is to investigate in detail the rearrangement of tetrahydrofurans through to the corresponding tetrahydropyrans to allow access to the motif not accessible by the oxidative cyclisation on 1,6-dienes. The use of the oxidative cyclisation of 1,5-dienes to prepare the tetrahydrofuran precursors allows facile access to highly stereochemically defined tetrahydrofurans, as the four stereogenic centres of the tetrahydrofuran are controlled by the geometry of the starting olefins (Scheme 6.1).

[*] The low pH of the reaction (measure at <1.0 pH) presumably means that the amine ligands are protonated and thus cannot coordinate to the osmium centre.

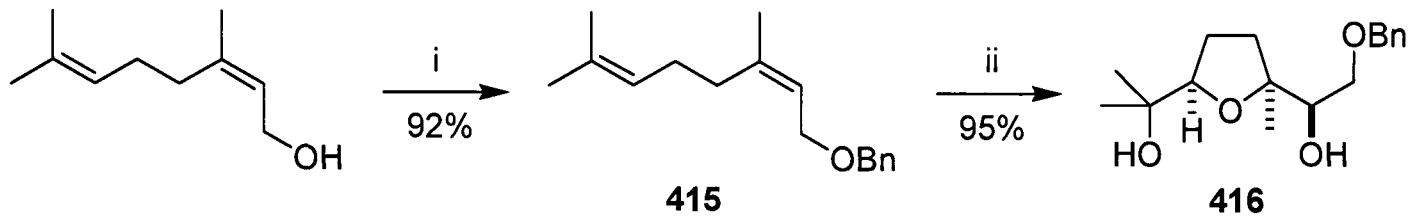


Scheme 6.7. *Reagents and conditions*: i, $K_2OsO_4 \cdot 2H_2O$ (5 mol%), Me_3NO, TFA, cyclohexene, acetone:H_2O (9:1), room temperature.

It was shown in Chapter 5 that tetrahydrofurans bearing an *exo*-cyclic α-halomethyl or activated alcohol functionality undergo rearrangement to the corresponding tetrahydropyrans (Chapter 5.2). To induce the tetrahydrofuran to tetrahydropyran rearrangement Kishi and co-workers reported the use of a mesyloxy leaving group[211] whereas Nakata and co-workers utilised a mono-chloromesyloxy leaving group.[219] Although the latter procedure was high

yielding for simple substrates, once structural complexity was introduced, protic acid co-solvents had to be utilised which led to isolation of a mixture of products from the reaction (Chapter 5.2).

The relative stereochemistry of the tetrahydrofuran precursor appears to be important, although no thorough stereochemical study has yet been reported (Figure 5.1); hence work to thoroughly investigate the tetrahydrofuran ring-expansion, including any stereochemical requirements, started with the synthesis of known tetrahydrofuran **416**,[10] which was prepared from benzyl ether **415** in high yield (Scheme 6.8).



Scheme 6.8. *Reagents and conditions*: i, NaH, BnBr, THF, room temperature; ii, $K_2OsO_4 \cdot 2H_2O$ (5 mol%), TFA, Me_3NO, acetone:H_2O (9:1), room temperature.

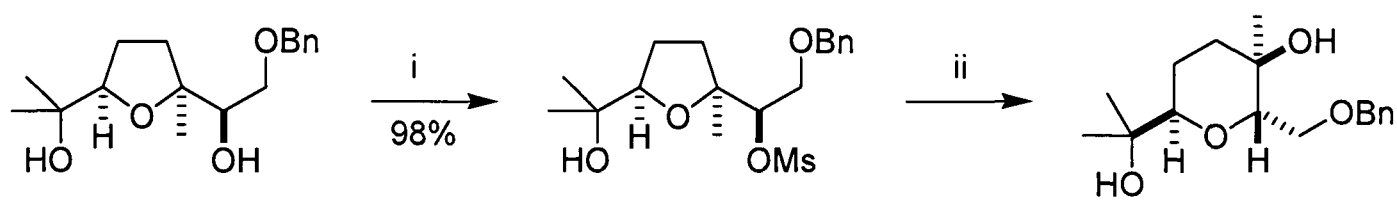
As the conditions reported by Nakata and co-workers were high yielding, but relied on the use of mono-chloromesyloxy leaving group.* Our studies focused on the readily accessible mesyloxy leaving group; however the yields using this leaving group are typically not as high, thus the first task was to develop a high yielding protocol for the rearrangement of tetrahydrofuran **416** through to the corresponding tetrahydropyran (**418**, Scheme 6.9). Tetrahydrofuran **416** was converted to the corresponding mesylate **417** in almost quantitative yield when treated with methanesulfonic anhydride (Scheme 6.9). The success of the reaction was verified by proton NMR: the methylene α to the mesyloxy moiety was revealed as a downfield doublet of doublets (4.79 ppm) and the methyl group of the mesyl moiety appeared as a diagnostic singlet at 3.03 ppm in the proton NMR spectrum and a peak at 38.9 ppm in the carbon-13 NMR spectrum.

The ring-expansion of mesylate **417** to tetrahydropyran **418** was investigated under a range of conditions (Scheme 6.9). Ring-expansion could not be promoted thermally (entries 1-2); either by heating a neat sample of mesylate **417** or a solution in tetrahydrofuran. Strong protic acids such as trifluoroacetic acid or *RS*-camphor-10-sulfonic acid failed to promote rearrangement (entries 3-5), as did strong Lewis acids (entries 6 and 7); boron trifluoride etherate returned starting material and tin tetrachloride led to decomposition products. When

* It should be noted the required mono-chloromethansufonic chloride starting material used to prepare mono-chloromesyloxy precursors is not readily available from commercial sources.

mesylate **417** was reacted with the conditions reported by Nakata and co-workers (zinc acetate dihydrate dissolved in a mixture of dioxane and water)*,[219] clean conversion to the tetrahydropyran **418** was observed. The proton and carbon-13 NMR spectra showed the loss of the mesyl moiety and the introduction of two methylene moieties α to the oxygen atom in tetrahydropyran ring (a doublet of doublets for the equatorial proton at 3.85 ppm and a multiplet at 3.42-3.37 ppm for the axial proton in the proton NMR; peaks at 80.9 and 76.0 ppm respectively for the methylene carbons in the carbon-13 NMR) and the electrospray mass spectrum also showed a parent ion peak at 317 (100%, MNa^+).

It was found that simple increase in the reaction temperature improved the isolated yield of tetrahydropyran **418** (entry 9, Scheme 6.9) and the use of zinc chloride allowed conversion in high yield (entry 10). The use of indium$^{(III)}$ chloride dissolved in *N*,*N*-dimethylformamide and water gave the tetrahydropyran **418** in excellent yield (entry 11); changing the Lewis acid to zinc acetate dihydrate and solvent to *N*,*N*-dimethylformamide and water allowed the ring-expansion to proceed in an excellent 94% yield (entry 12).



416 **417** **418**

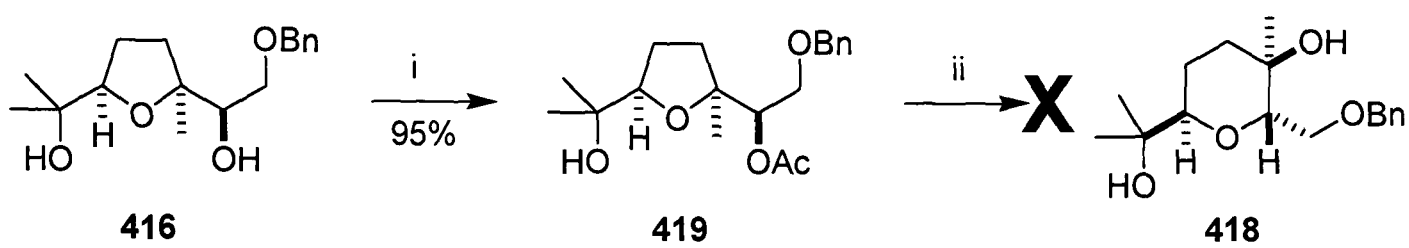
Entry	Conditions	Yield (%) 418
1	Neat, Δ	-
2	THF, Δ	-
3	TFA, H_2O, acetone, Δ	-
4	CSA, CH_2Cl_2, Δ	-
5	CSA, dioxane, H_2O, Δ	-
6	BF_3•OEt_2, CH_2Cl_2 or Et_2O, –78 °C	-
7	$SnCl_4$, CH_2Cl_2, –78 °C	-
8	*$Zn(OAc)_2$•$2H_2O$, dioxane, H_2O, 50 °C*	*70*
9	$Zn(OAc)_2$•$2H_2O$, dioxane, H_2O, Δ	79
10	$ZnCl_2$, DMF, H_2O, Δ	89
11	$InCl_3$, DMF, H_2O, Δ	93
12	$Zn(OAc)_2$•$2H_2O$, DMF, H_2O, Δ	94

Scheme 6.9. *Reagents and conditions*: i, Ms_2O, DMAP, CH_2Cl_2, room temperature; ii, Conditions; see table.

* It should be noted that these are the conditions Nakata and co-workers reported for the more activated mono-chloromesyloxy leaving group.

The yield of ring-expansion is comparable to those reported by Nakata and co-workers and is of special note as the mesyloxy precursor is used, not the more activated mono-chloromesyloxy precursor needed in their ring-expansion examples.[219]

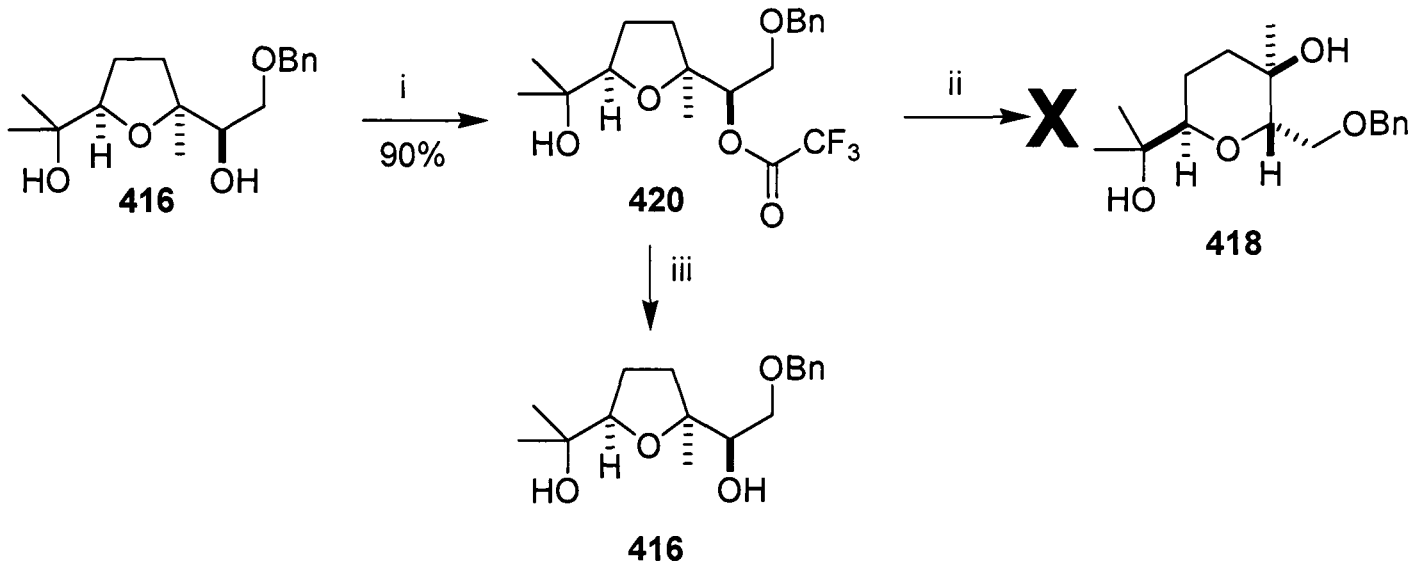
Although the mesyloxy group proved very successful in promoting ring-expansion, other initiating groups were also investigated. All the conditions shown in Scheme 6.9 were attempted on alcohol **416** to try to induce ring-expansion but in each case only starting material was recovered. Tetrahydrofuran **416** was acetylated to give acetyl compound **419** (Scheme 6.10); the proton NMR showed the introduction of acetyl methyl group (singlet at 2.08 ppm) and the carbon-13 NMR revealed the carbonyl moiety (170.5 ppm).



416 **419** **418**

Scheme 6.10. *Reagents and conditions*: i, Ac_2O, DMAP, CH_2Cl_2, room temperature; ii, Range of conditions, see text.

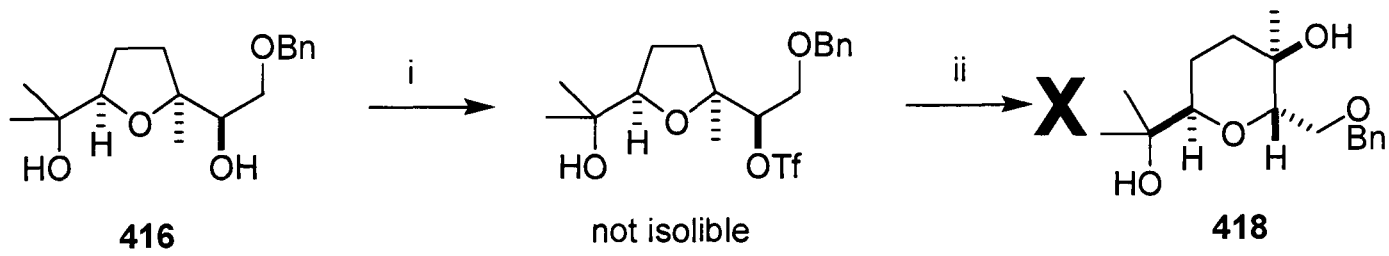
However treatment of acetate **416** under a range of conditions failed to induce ring-expansion to tetrahydropyran **418**: strong Lewis acids (boron trifluoride diethyl etherate, aluminium chloride or tin tetrachloride) either returned starting material or led to decomposition; protic acid (trifluoroacetic acid, *RS*-camphor-10-sulfonic acid and *para*-toluene sulfonic acid) all returned starting material as did zinc acetate dihydrate in refluxing *N*,*N*-dimethylformamide and water. Thus the more activated trifluoroacetate **420** was prepared (Scheme 6.11).



Scheme 6.11. *Reagents and conditions*: i, $(CF_3O)_2O$, DMAP, CH_2Cl_2, room temperature; ii, Range of conditions, see text; iii, $Zn(OAc)_2 \cdot 2H_2O$, DMF, H_2O, Δ.

The installation of the trifluoroacetate group was shown by the downfield doublet of doublets corresponding to the methylene α to the trifluoro acetate moiety in the proton NMR and a peak at 80.0 ppm in the carbon-13 NMR. Reaction of trifluoroacetate **419** to the range of conditions stated for acetate **419** either returned starting material or decomposition products; however when trifluoroacetate **420** was reacted with zinc acetate dihydrate, a hydrolysis reaction occurred and starting alcohol **416** was obtained.

Finally, as the more reactive trifluoroacetate leaving group was being hydrolysed under the ring-expansion conditions, a trifluoromesyloxy precursor was prepared (Scheme 6.12). However although the reaction went to completion (trifluoromethanesulfonic anhydride, triethylamine in dichloromethane at –78°C), attempts to purify the reaction led to decomposition. Thus the trifluoromesyloxy group was prepared *in situ* and then reacted with zinc acetate dihydrate; however this led to decomposition of the starting material, even at low temperature (–78 °C).



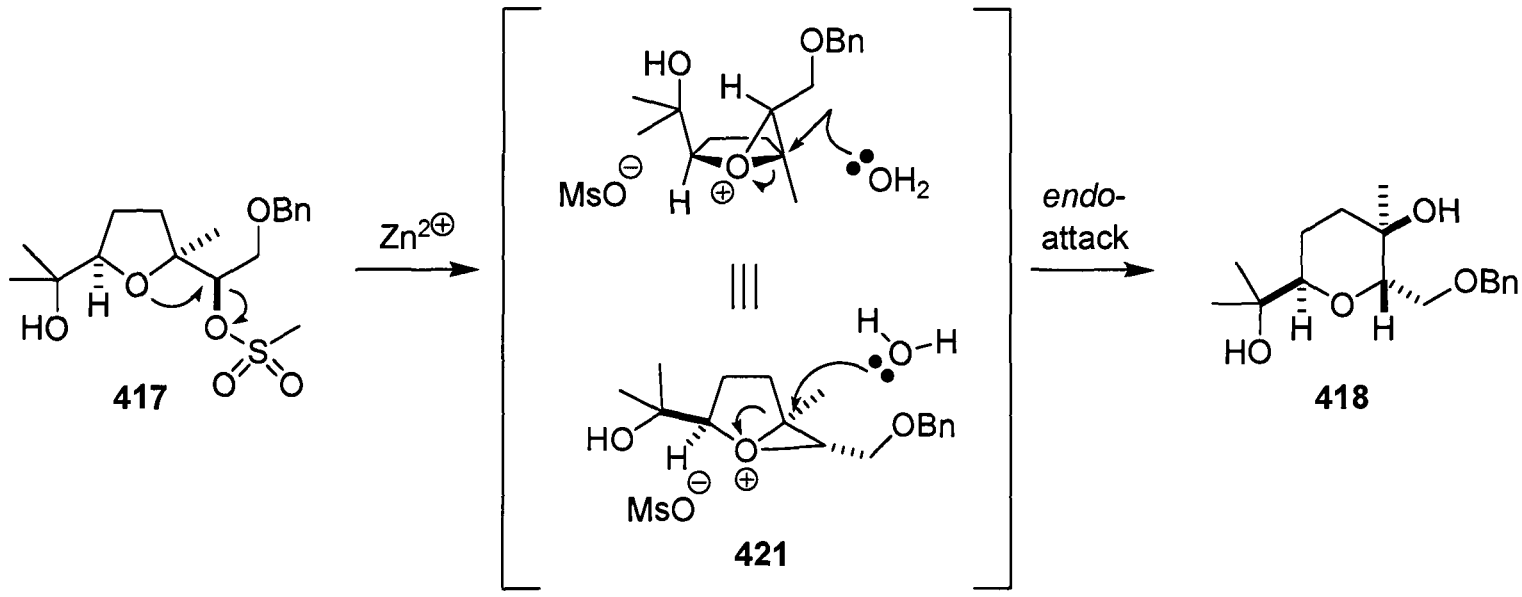
Scheme 6.12. *Reagents and conditions*: i, Tf_2O, Et_3N, CH_2Cl_2, –78 °C; iii, $Zn(OAc)_2 \cdot 2H_2O$, DMF, H_2O, range of temperatures, –78°C → Δ.

Although attempts to initiate ring-expansion using leaving groups other than a mesyloxy moiety were not successful, the ring-expansion of mesylate **417** had been developed

into a very high yielding process using zinc acetate dihydrate in a refluxing solution of *N*,*N*-dimethylformamide and water (Scheme 6.9); hence further investigations were conducted using these modified conditions.

6.2 *Ring-expansion mechanism and proof of stereochemistry.*

With regard to the mechanism of the one-carbon ring-expansion of mesylate **417** (Scheme 6.13), we postulate that the tetrahydrofuran oxygen lone pair electrons participate to form oxonium ion **421**, which is ring-opened by a molecule of water exclusively at the *endo*-site to furnish the tetrahydropyran **418** as the sole product. The exclusive *endo*-selectivity can be explained by simple analogy of the oxonium ion to a protonated epoxide; under acid catalysis, epoxides open at the most substituted centre for reason of cation stability, hence the oxonium ion **421** is opened at the most substituted carbon.

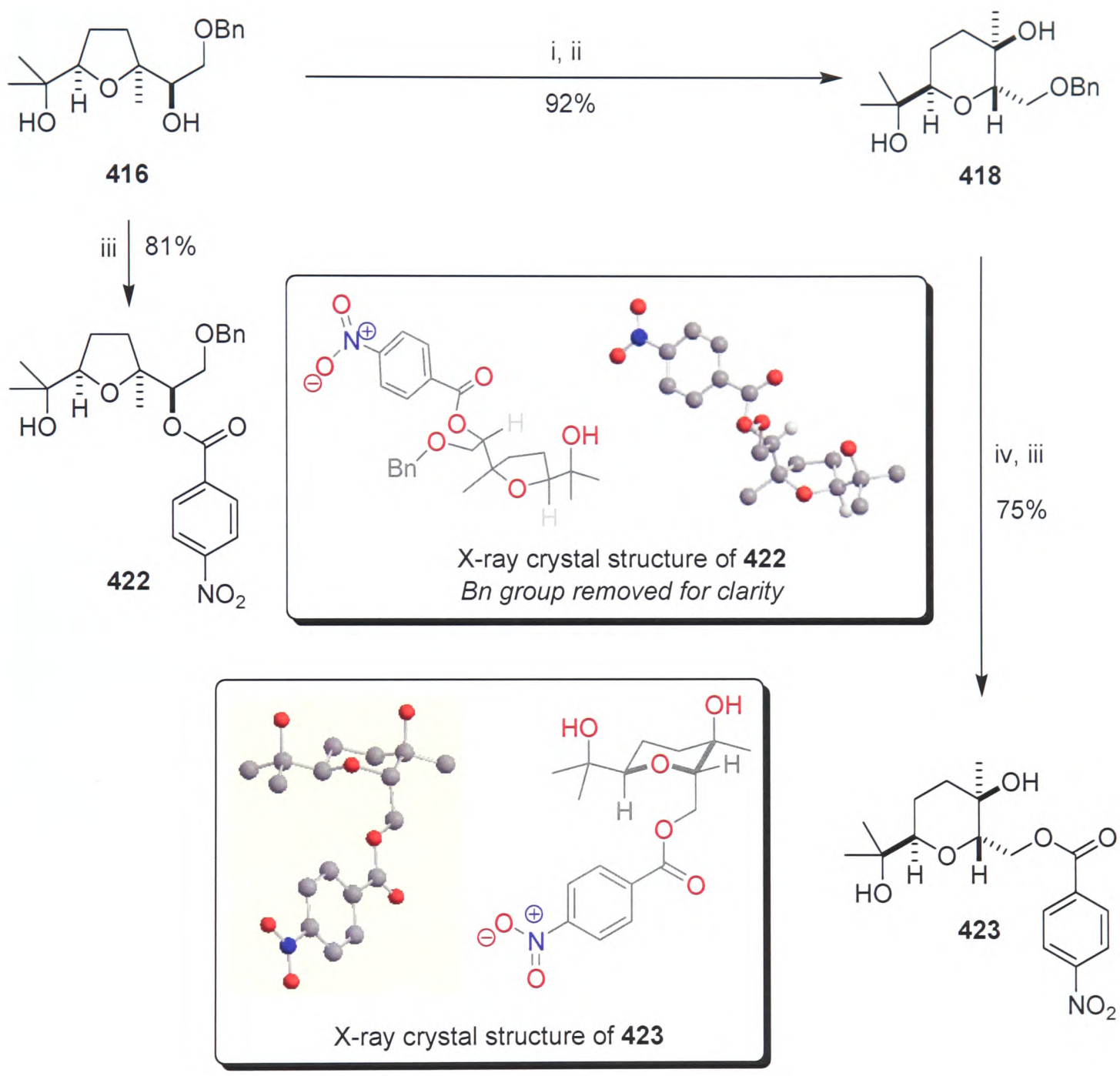


Scheme 6.13. *Prostulated mechanism for the tetrahydrofuran to tetrahydropyran ring-expansion.*

It was shown in Chapter 5.2 that the stereochemistry of the ring-expansion was important; the ring-expansion product, tetrahydropyran **418**, was shown to be a single diastereoisomer by proton and carbon-13 NMR. Crystalline derivatives were prepared to verify the relative stereochemistry of both the ring-expansion precursor and the ring-expansion product (Scheme 6.14); analysis by X-ray crystallography proved the structures of tetrahydrofuran **422** and tetrahydropyran **423** (Scheme 6.14).

Tetrahydrofuran **416** was treated with *para*-nitrobenzoyl chloride to form benzoate **422** while tetrahydropyran **418** was deprotected under hydrogenation conditions and then

coupled with *para*-nitrobenzoyl chloride to give benzoate **423**. X-ray crystallography verified the relative stereochemistry of the ring-expansion precursor and proved that the tetrahydropyran product was formed as a single diastereoisomer (Scheme 6.14), possessing the stereochemistry (inversion) as predicted by the mechanism shown in Scheme 6.13.



Scheme 6.14. *Reagents and conditions*: i, Ms_2O, DMAP, CH_2Cl_2, room temperature; ii, $Zn(OAc)_2 \cdot 2H_2O$, DMF, H_2O, Δ; iii, *p*-nitrobenzoyl chloride, DMAP, CH_2Cl_2, room temperature; iv, H_2, Pd/C, MeOH, room temperature.

6.3 *Role of stereochemistry in the ring-expansion of tetrahydrofurans.*

Focus next centred on the relative stereochemical requirements for the ring-expansion of α-mesyloxymethyl tetrahydrofurans (Figure 6.1). It was shown in Chapter 5.2 that Nakata and co-workers had conducted limited investigations into the stereochemical requirements for ring-expansion (Scheme 5.10);[226] only the relative stereochemistry between the secondary carbon α and secondary carbon β was investigated.

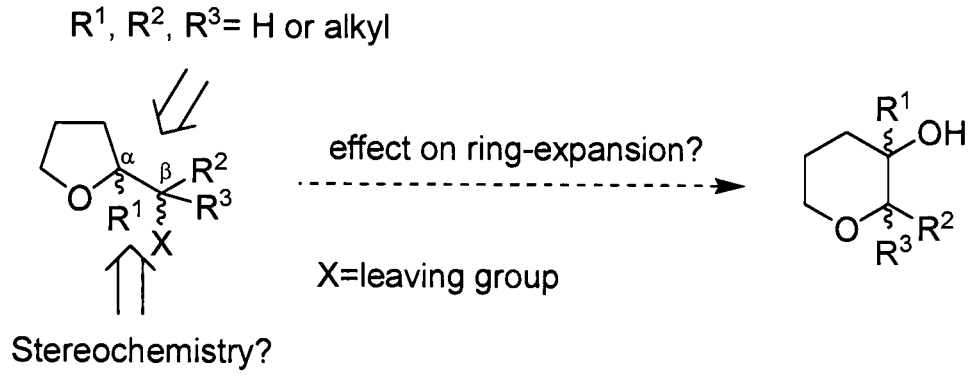
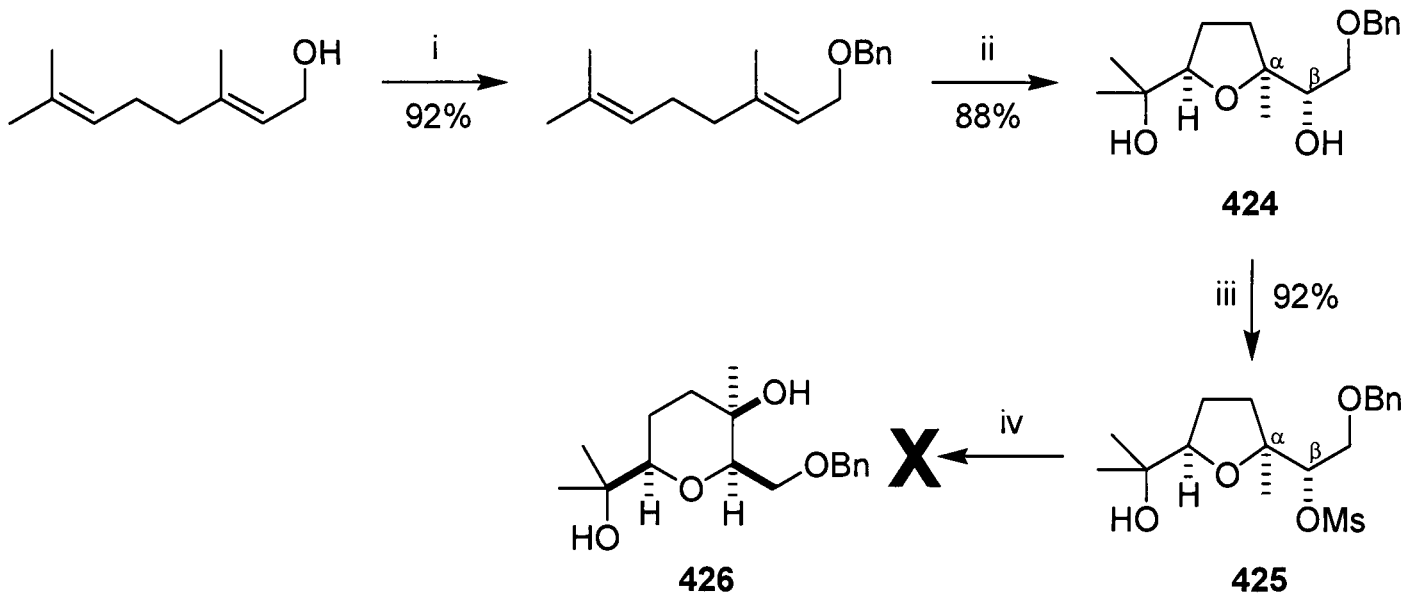


Figure 6.1. *Stereochemical requirement for ring-expansion.*

Thus a more thorough stereochemical study was undertaken examining the effect of substitution at carbons α and β (R^1, R^2 and R^3=H or alkyl) and the relative stereochemistry between these groups (effect of R^1 and X being in either a *syn*- or *anti*-relationship).



Scheme 6.15. *Reagents and conditions*: i, NaH, BnBr, THF, room temperature; ii, K_2OsO_4•$2H_2O$ (5 mol%), TFA, Me_3NO, acetone:H_2O (9:1), room temperature; iii, Ms_2O, DMAP, CH_2Cl_2, room temperature; iv, $Zn(OAc)_2$•$2H_2O$, DMF, H_2O, Δ.

The ring-expansion of mesylate **417** (Scheme 6.9) is an example of a ring-expansion of a tetrahydrofuran that possesses a tertiary centre at carbon α and a secondary centre at carbon β with an *anti*-relationship between R^1 and the X; thus the *syn*-diastereoisomer was

next investigated (Scheme 6.15). For this study known tetrahydrofuran **424**[10] was prepared in two high yielding steps from geraniol.

Treatment of tetrahydrofuran **424** with methanesulfonic anhydride yielded mesylate **425** in high yield; the NMR spectra showed the methyl group of the mesyl moiety (singlet at 3.05 ppm in the proton NMR; peak at 39.1 ppm in the carbon-13 NMR) and the electron deficient methylene moiety α to the mesyloxy group (triplet at 4.74 in the proton NMR; peak at 87.4 ppm in the carbon-13 NMR spectrum). However when mesylate **425** was reacted with the Lewis acid ring-expansion conditions, no rearrangement took place; only starting material was recovered from the reaction mixture. This result can be explained by considering the Newman projection of the ring-expansion precursor (Figure 6.2).

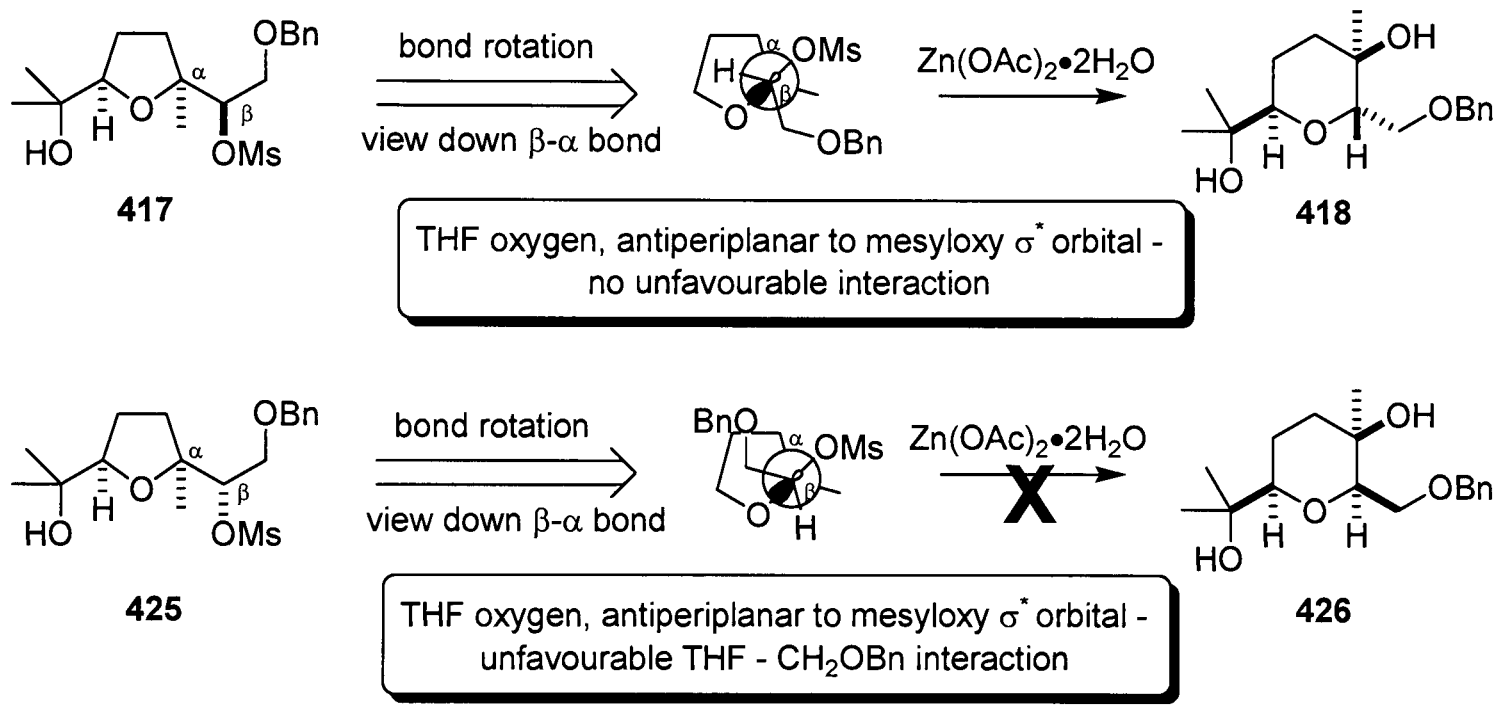


Figure 6.2. *Newman projection of ring-expansion precursors.*

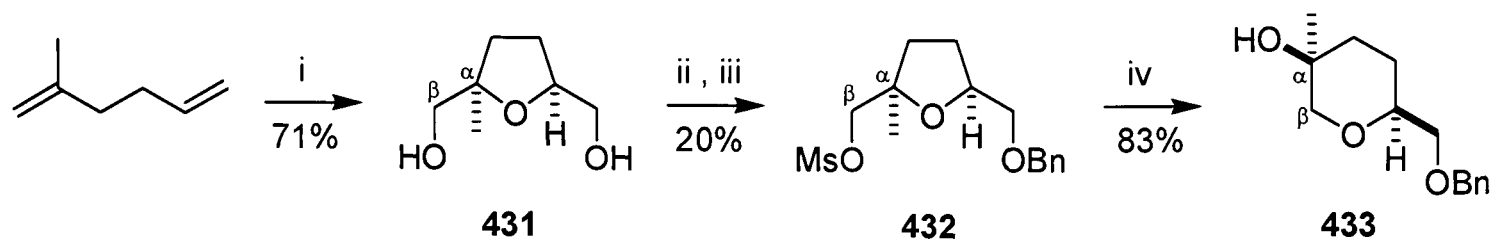
The tetrahydrofuran oxygen lone pair of electrons participates in the ring-expansion (Scheme 6.13), to form intermediate oxonium ion **421** from mesylate **417**. The oxygen lone pair is required to be in an antiperiplanar relationship to the mesyloxy moiety; this allows maximum overlap between the HOMO orbital of the tetrahydrofuran and the LUMO (σ* orbital) of the mesyloxy moiety (Figure 6.2). After a bond rotation around the carbon α-β bond (to allow this interaction) the hydrogen atom is positioned over the tetrahydrofuran and the benzyl ether moiety is placed in position where there are no unfavourable steric interactions. However, when mesylate **425** undergoes a bond rotation to allow maximum overlap between the HOMO of the tetrahydrofuran and LUMO of the mesyloxy leaving group, the benzyl ether is placed in a position over the tetrahydrofuran ring that causes an unfavourable steric interactions; thus formation of tetrahydyropyran **426** is disfavoured.

To investigate the effect of a primary leaving group (carbon β, R^2=R^3=H), known tetrahydrofuran **427**[10] was prepared (Scheme 6.16). The *meso*-tetrahydrofuran **427** was mono-benzylated by treatment with silver oxide and benzyl bromide, as reported by Bouzide and Sauve[279] and the resultant free alcohol activated with methanesulfonic anhydride which furnished mesylate **428**. The electrospray mass spectrum showed a parent ion peak at 387 (100%, $MMeCNNa^+$) and proton NMR showed the presence of the benzyl ether (5 aromatic protons as a multiplet 7.35-7.27 ppm, benzylic methylene moiety as a singlet at 4.54 ppm and the benzyl ether methylene group as diastereotopic doublets, *J* 9.5 Hz, at 3.36 and 3.30 ppm) and the mesyl methyl moiety (singlet at 2.91 ppm). When reacted with zinc acetate dihydrate, mesylate **428** was converted to the corresponding tetrahydropyran **429** *via* oxonium ion intermediate **430** in high yield. The NMR spectra revealed the loss of the mesyloxy moiety and introduction of the methylene ether (carbon β) in the tetrahydropyran ring (peak at 78.0 ppm in the carbon-13 NMR spectrum and a diastereotopic doublet, *J* 10.0 Hz at 3.56 and 3.40 ppm in the proton NMR spectrum).

Scheme 6.16. *Reagents and conditions*: i, OsO_4 (5 mol%), CSA, Me_3NO, CH_2Cl_2, room temperature; ii, Ag_2O, BnBr, DMF, room temperature, 76%; iii, Ms_2O, DMAP, CH_2Cl_2, room temperature, 100%; iv, $Zn(OAc)_2 \cdot 2H_2O$, DMF, H_2O, Δ.

Oxidative cyclisation of 2-methyl-1,5-hexadiene gave tetrahydrofuran **431** in good yield (Scheme 6.17); the success of the reaction was shown by the IR spectrum which revealed the presence of an alcohol (ν_{OH} 3384 cm^{-1}) and the proton NMR spectrum which revealed the tetrahydrofuran CH moiety (multiplet at 4.19-4.13 ppm). The carbon-13 NMR spectrum showed peaks correlating to the quaternary carbons and the methylene groups α to the hydroxyl moiety (84.2, 68.9 and 74.7 ppm respectively). Tetrahydrofuran **431** was mono-protected as the corresponding benzyl ether and the resultant alcohol activated with methanesulfonic anhydride (tetrahydrofuran **432**; proton NMR showed the methyl group of

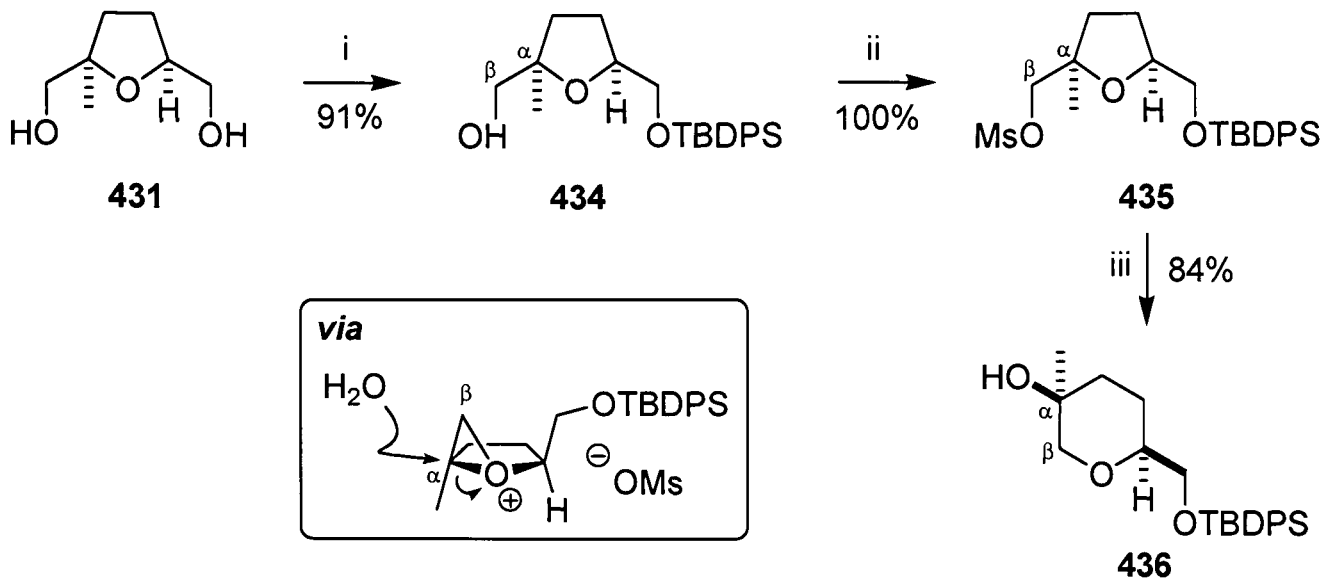
the mesylate at 2.96 ppm and 5 aromatic protons at 7.37-7.27 ppm in the proton NMR), albeit in low yield; although ring-expansion did occur in high yield (tetrahydropyran **433**, Scheme 6.17). The carbon-13 NMR spectrum revealed the presence of the new methylene ether (carbon β, peak at 73.1 ppm), the quaternary carbon (peak at 66.8 ppm) and OCH moiety (77.7 ppm).



431 **432** **433**

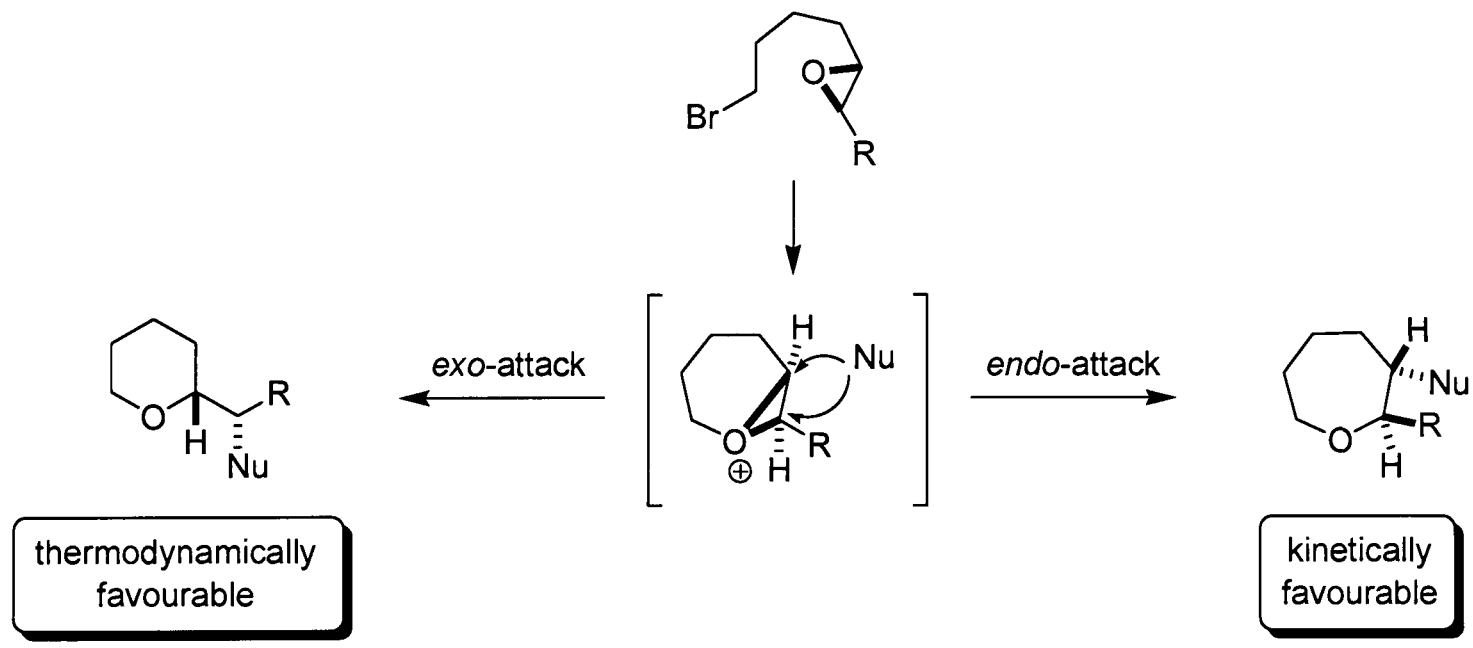
Scheme 6.17. *Reagents and conditions*: i, OsO_4 (5 mol%), CSA, Me_3NO, CH_2Cl_2, room temperature; ii, NaH, BnBr, THF, room temperature; iii, Ms_2O, DMAP, CH_2Cl_2, room temperature, 20% over two steps; iv, $Zn(OAc)_2 \cdot 2H_2O$, DMF, H_2O, Δ.

Even though the ring-expansion had been successful, the very low yield for the protection step was not acceptable. It was envisaged that a bulky protecting group would give more discrimination between the two alcohol moieties; hence tetrahydrofuran **431** was treated with *tert*-butyl(chloro)diphenylsilane which furnished silyl ether **434** in high yield (Scheme 6.18). The IR spectrum still showed the presence of an alcohol moiety (ν_{OH} 3441 cm^{-1}) and the proton NMR spectrum revealed the presence of the silyl ether by a singlet at 1.07 ppm corresponding to the *tert*-butyl group; the carbon-13 NMR showed the diagnostic upfield shift of the *tert*-butyl quaternary carbon bonded to silicon (19.2 ppm). Silyl ether **434** was converted to mesylate **435** (methylene α mesyloxy group shown as diastereotopic doublet, *J* 10.1, at 4.09 and 4.02 ppm in the proton NMR spectrum and a peak at 74.5 ppm in the carbon-13 NMR) and reacted with the ring-expansion conditions which furnished the tetrahydropyran **436** in high yield (Scheme 6.18). The IR spectrum showed the presence of an alcohol functionality (ν_{OH} 3340 cm^{-1}), the proton NMR spectrum revealed the OCH group in the tetrahydrofuran ring (a doublet of triplets, *J* 10.6 and 5.3, at 3.37 ppm) and the carbon-13 NMR spectrum verified the introduction of a new methylene ether moiety (carbon β; peak at 76.7 ppm) and the presence of the tertiary alcohol (peak at 66.9 ppm).



Scheme 6.18. *Reagents and conditions*: i, TBDPSCl, imidazole, DMF, room temperature; ii, Ms_2O, DMAP, CH_2Cl_2, room temperature; iii, $Zn(OAc)_2 \cdot 2H_2O$, DMF, H_2O, Δ.

During their synthesis of hemibrevetoxin B,[225] Nakata and co-workers reported the double ring-expansion of a tetrahydrofuran bearing two *exo*-cyclic mono-chloromesyloxy groups when treated with zinc acetate in refluxing aqueous acetic acid. The ring-expansion conditions developed in our laboratories use a less activated leaving group and the reaction is performed under milder conditions than those reported by Nakata.

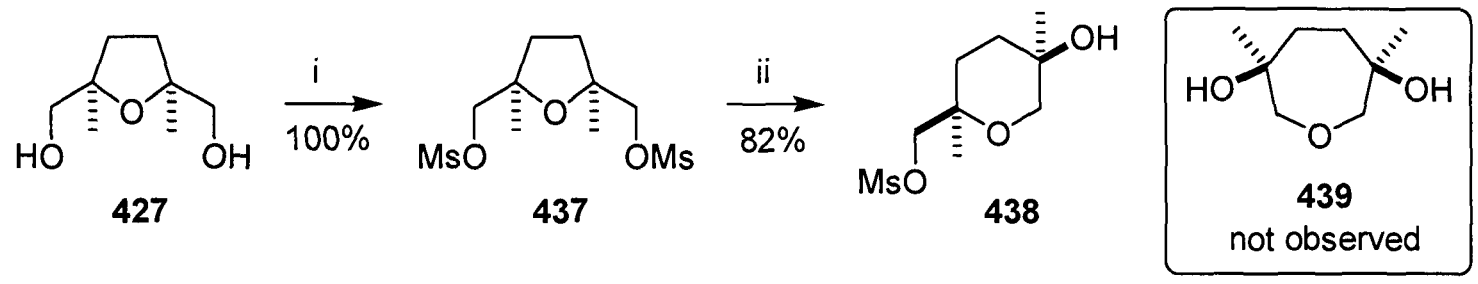


Scheme 6.19. *Ring-opening of bicyclic oxonium ions to form either tetrahydropyrans or oxepanes.*

It was envisaged that a tetrahydrofuran bearing two mesylates would undergo a single ring-expansion to afford a tetrahydropyran product; thus the mesylate group would act both as an activating group and a protecting group for the alcohol. This is not unreasonable as the conditions ustilised by Nakata and co-workers are more forcing and a more activated leaving group is employed. During their studies on the equilibrium in ring-expansion reaction of

bromo-epoxides,[235] Murai and co-workers reported that although the oxepane is the kinetic product, the tetrahydropyran is thermodynamically more stable (Scheme 6.19).

The *meso*-tetrahydrofuran **427** was converted to the corresponding *meso*-mesylate **437** in quantitative yield (Scheme 6.20); the proton NMR showed the methyl group of the mesyl moiety (6 protons, singlet at 3.07 ppm) and the methylene groups α to the mesyloxy moiety (4 protons, singlet at 4.05 ppm) and the electrospray mass spectrum revealed the parent ion at 339 (100%, MNa^+). When dimesylate **437** was reacted with the ring-expansion conditions; clean conversion to the corresponding tetrahydropyran **438** was achieved in high yield. The proton NMR revealed the loss of one mesyloxy group but also showed that the product still had one mesyloxy moiety (methylene α to the mesyloxy moiety as a diastereotopic doublet, *J* 10.6, at 4.13 and 4.06 ppm and a singlet corresponding to the methyl group at 3.07 ppm). The IR spectrum showed the introduction of the alcohol functionality (ν_{OH} 3425 cm^{-1}) and the electrospray mass spectrum showed only parent ion peaks corresponding to mono-mesylate compound **438** (peaks at 297, 100% corresponding to $MMeCNNa^+$ and at 256 corresponding to MNH_4^+).

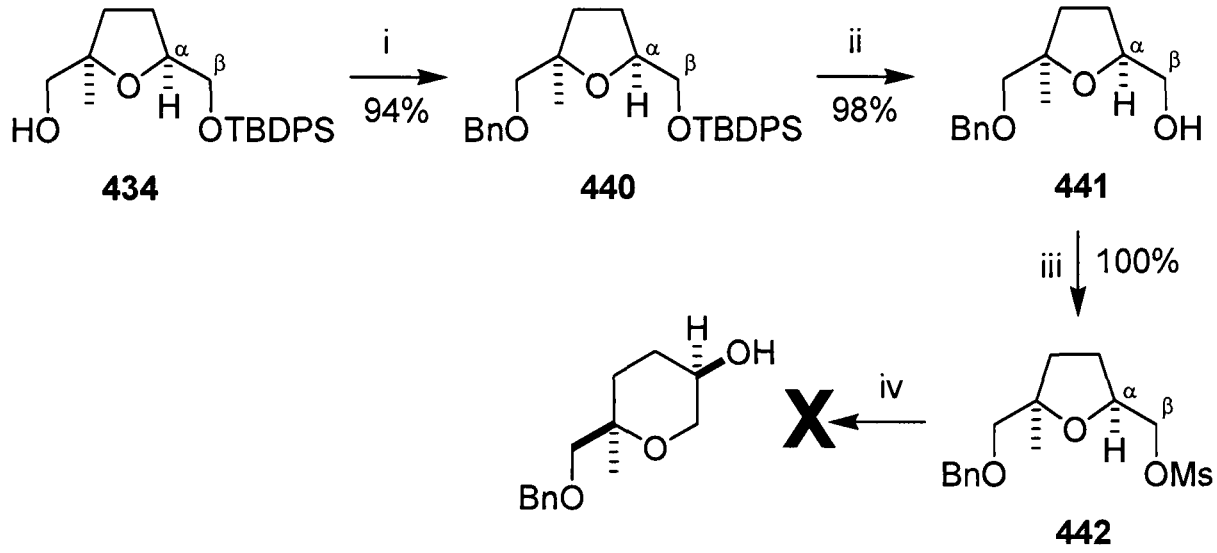


Scheme 6.20. *Reagents and conditions*: i, Ms_2O, DMAP, CH_2Cl_2, room temperature; ii, $Zn(OAc)_2 \cdot 2H_2O$, DMF, H_2O, Δ.

No formation of oxepane **439** was observed from the reaction; the exact reason why dimesylate **437** did not undergo a double ring-expansion is not fully understood. As mentioned earlier, the only examples of a double ring-expansion have been reported by Nakata and co-workers. The more activated mono-chloromesyloxy leaving group is employed, the reaction conditions were also harsher; a protic acid was used as a co-solvent. However, Murai and co-workers have shown that the tetrahydropyran product is thermodynamically favoured (Scheme 6.19); thus under the milder conditions employed in the reaction medium, the thermodynamic tetrahydropyran **438** was obtained rather than the kinetic oxepane product **439**.

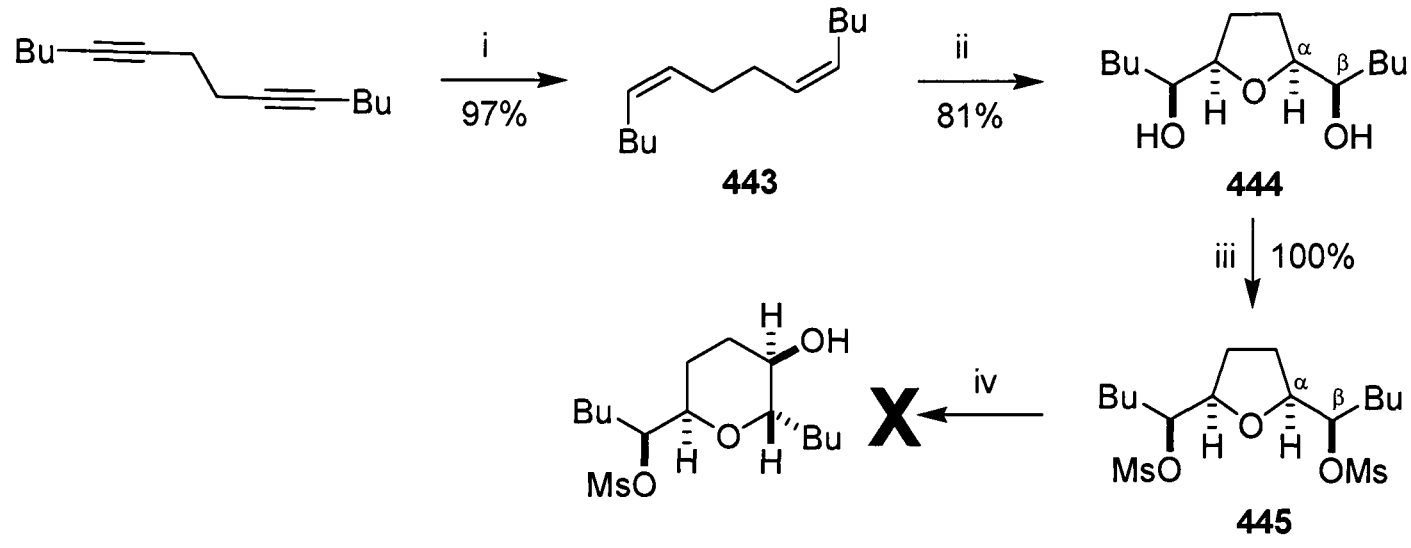
The ring-expansion has been shown to be successful when carbon α is a tertiary centre and carbon β possesses a primary leaving group (Figure 6.2), the effect of both carbons α and β possessing secondary centres was next examined.

Silyl ether **434** was treated with benzyl bromide and sodium hydride to furnish benzyl ether **440** (Scheme 6.21). The introduction of the benzyl group was confirmed by proton and carbon-13 NMR; a benzylic methylene as a multiplet at 4.58-4.49 pm and a methylene α to the benzyl ether as a diastereotopic doublet, *J* 9.4 Hz, at 3.37 and 3.32 ppm in the proton spectrum and peaks at 73.4 and 76.8 ppm respectively in the carbon-13 spectrum. The silyl ether was deprotected using tetra-*n*-butyl ammonium fluoride to furnish alcohol **441** in high yield, which was activated with methanesulfonic anhydride to yield the desired mesylate **442** in excellent yield (Scheme 6.21). The successful reaction was shown by the proton NMR spectrum, the introduction of the mesyl moiety revealed by signals for a methyl group at 3.02 ppm (singlet) and the methylene α to the mesyloxy group at 4.24 ppm (doublet of doublets, *J* 5.0 and 2.9 Hz); attempts to ring-expand mesylate **442** were unsuccessful and only starting material was obtained from the reactions.



Scheme 6.21. *Reagents and conditions*: i, BnBr, NaH, THF, room temperature; ii, TBAF, THF, room temperature; iii, Ms_2O, DMAP, CH_2Cl_2, room temperature; iv, $Zn(OAc)_2 \cdot 2H_2O$, DMF, H_2O, Δ.

The effect of carbons α and β both possessing a secondary centre (Figure 6.2) was next examined, starting with R^1 and X possessing an *anti*-relationship. 5,9-Tetradecadiyne was reduced to the *cis* diene **443** that was subsequently cyclised to the known *meso*-tetrahydrofuran **444**[10] (Scheme 6.22). However treatment with benzyl bromide and silver oxide did not give the desired mono-protected benzyl ether, with only starting material retrieved from the reaction.



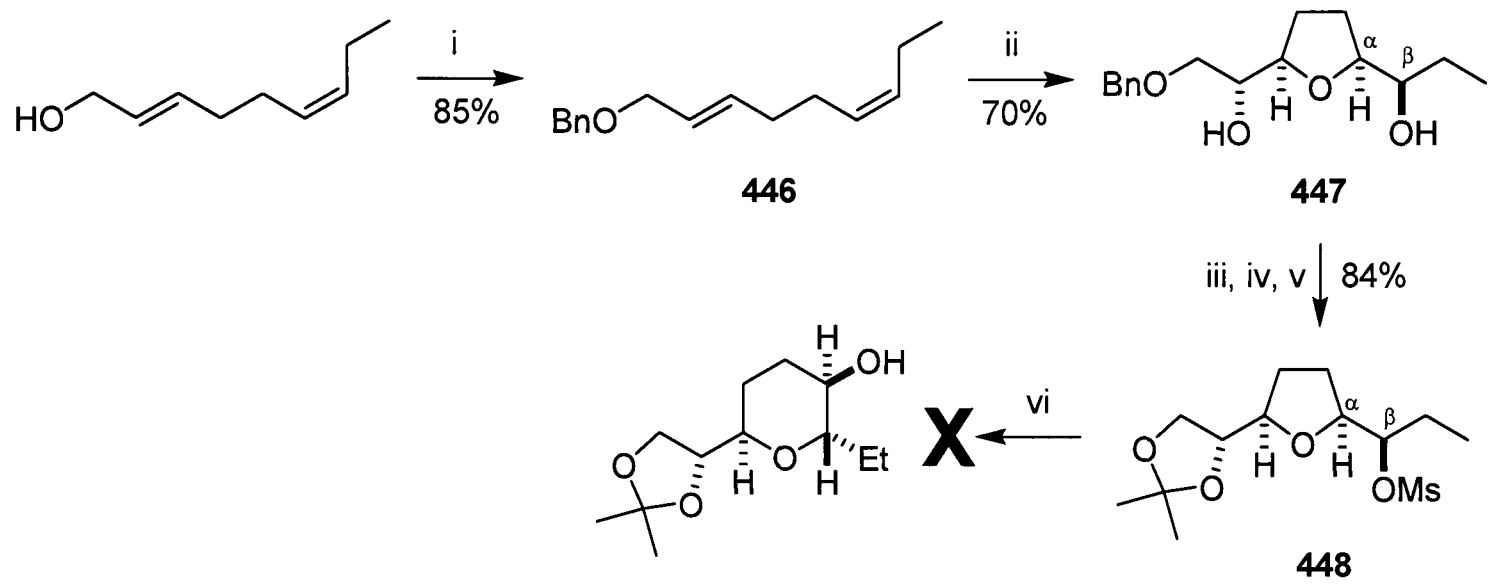
Scheme 6.22. *Reagents and conditions*: i, H_2, Lindlars catalyst, EtOH, room temperature; ii, OsO_4 (5 mol%), CSA, Me_3NO, CH_2Cl_2, room temperature; iii, Ms_2O, DMAP, CH_2Cl_2, room temperature; iv, $Zn(OAc)_2 \cdot 2H_2O$, DMF, H_2O, Δ.

Dimesylate **437** had previously been successfully converted to the corresponding tetrahydropyran **438** (Scheme 6.20); thus a similar strategy was employed to convert *meso*-tetrahydrofuran **444** to *meso*-dimesylate **445** (Scheme 6.22); the carbon-13 NMR spectrum showed the introduction of the mesyl moiety, with a peak for the methylene α to the mesyloxy group at 83.0 ppm and the methyl group of the mesyl moiety at 38.7 ppm. However only starting material was recovered when **445** was reacted with ring-expansion conditions.

It was not known, however, whether the ring-expansion failed because of the use of dimesylate strategy for protection and activation, or whether there was a fundamental bias within the relative stereochemical relationship of R^1 of tetrahydrofuran to the leaving group precluded ring-expansion; hence tetrahydrofuran **447** was synthesised where an alternative protecting group strategy could be employed (Scheme 6.23).

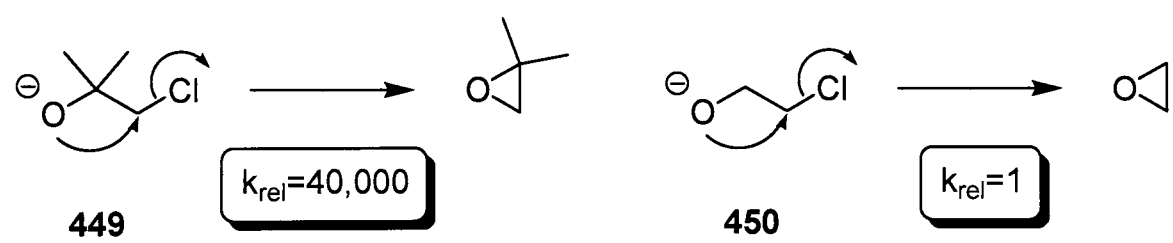
Benzyl ether **446** was prepared by treatment of (2-*cis*,6-*trans*)-nona-2,6-dienol with benzyl bromide and sodium hydride (Scheme 6.23). Oxidative cyclisation of benzyl ether **446** furnished tetrahydrofuran **447** in good yield. The IR spectrum showed the presence of an alcohol moiety (ν_{OH} 3396 cm^{-1}) and the NMR spectra revealed the OCH groups in the tetrahydrofuran ring (triplet of doublets, 4.00 and 3.94 ppm in the proton NMR spectrum and peaks at 82.9 and 78.9 ppm in the carbon-13 NMR spectrum) and the methylene moiety α to the alcohol functionality (multiplets, 3.79-3.74 and 3.73-3.70 ppm in the proton NMR spectrum and peaks at 74.0 and 72.7 ppm in the carbon-13 NMR spectrum). After deprotection, the 1,2-diol was protected as an acetonide and the resultant free alcohol was activated with methanesulfonic anhydride to furnish tetrahydrofuran **448** in high overall yield (Scheme 6.23). The successful inclusion of the mesylate moiety was shown by the proton

NMR spectrum: the methylene α to the mesyloxy group (carbon β) was present as a doublet of doublet of doublets (*J* 7.3, 5.6 and 3.7 Hz) at 4.69 ppm and the methyl group as singlet at 3.06 ppm. However when it was reacted with ring-expansion conditions only starting material was recovered from the reaction.



Scheme 6.23. *Reagents and conditions*: i, BnBr, NaH, THF, room temperature; ii, OsO_4 (5 mol%), CSA, Me_3NO, CH_2Cl_2, room temperature; iii, H_2, Pd/C, MeOH, room temperature; iv, 2-methoxypropene, CSA, DMF, room temperature; v, Ms_2O, DMAP, CH_2Cl_2, room temperature; vi, $Zn(OAc)_2 \cdot 2H_2O$, DMF, H_2O, Δ.

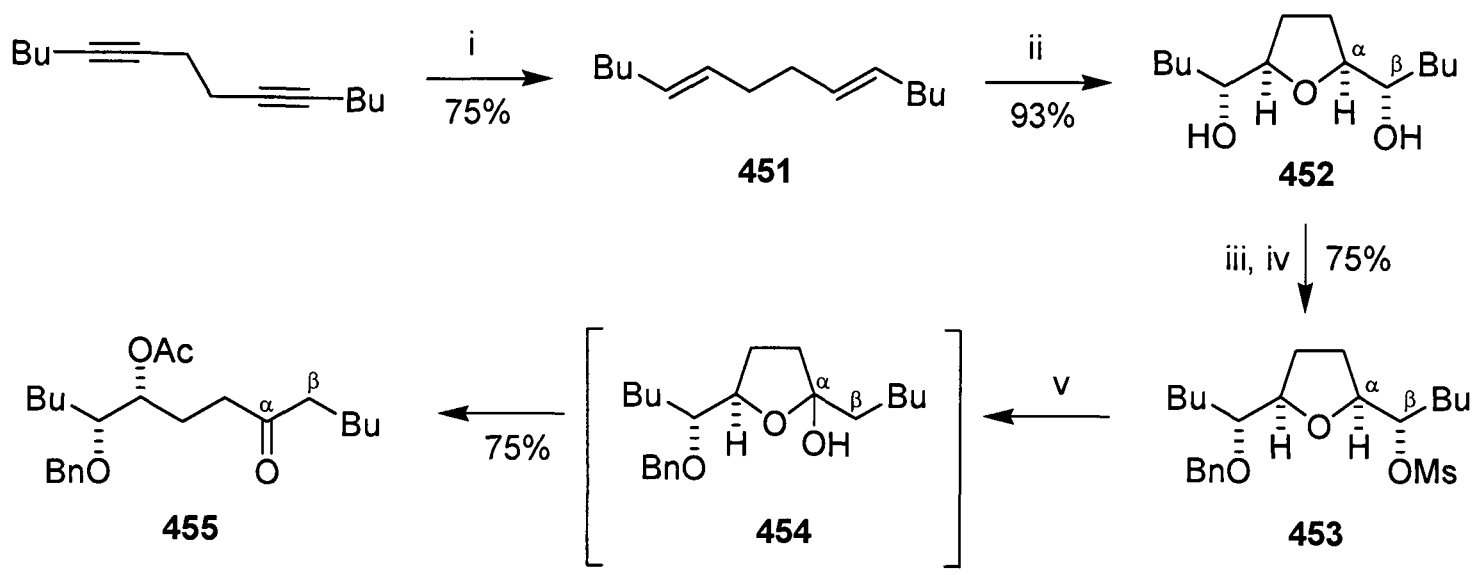
All attempts to induce ring-expansion with tetrahydrofuran precursors that possessed a secondary centre at carbon α (Figure 6.2) were unsuccessful. If we look at the mechanism of ring-expansion (Scheme 6.13), the first step is the formation of oxonium ion **421**, a ring-forming reaction. All the examples of ring-expansion shown in this section have had a methyl substituent at carbon α; hence we postulate that the Thorpe-Ingold effect is facilitating ring expansion. Essentially the formation of oxonium ion **421** is an epoxide formation; the relative rate for epoxide closure is 40,000 times faster for gem dimethyl alcohol **449** than for primary alcohol **450** (Scheme 6.24). This analogous kinetic acceleration allows ring-expansion of tetrahydrofurans that possess a tertiary carbon at position α.



Scheme 6.24. *Relative rates increase for epoxide formation due to the Thorpe-Ingold effect.*

It was shown in Chapter 5.2 that tetrahydrofurans bearing a *syn* relationship between the hydrogen atom on carbons α and the leaving group on carbon β underwent a ring-opening

reaction to form an open chain ketone (Scheme 5.10). It had already been demonstrated that our modified ring-expansion conditions allowed the rearrangement of various tetrahydrofurans into the corresponding tetrahydropyrans; it was then envisaged that these conditions could also promote the ring-opening reaction of tetrahydrofurans. Thus the known tetrahydrofuran **452**[10] was prepared in high overall yield from 5,9-tetradecadiyne; a single electron reduction medium furnished the desired *trans* diene **451** which subsequently underwent an oxidative cyclisation to form the desired tetrahydrofuran **452** (Scheme 6.25).



Scheme 6.25. *Reagents and conditions*: i, Na, NH_3, THF, –78 °C; ii, OsO_4 (5 mol%), CSA, Me_3NO, CH_2Cl_2, room temperature; iii, Ag_2O, BnBr, DMF, room temperature, 75%; iv, Ms_2O, DMAP, CH_2Cl_2, room temperature, 100%; v, $Zn(OAc)_2 \cdot 2H_2O$, DMF, H_2O, Δ; then Ac_2O, pyr, room temperature.

Tetrahydrofuran **452** was converted to the corresponding mono-benzyl ether by treatment with silver oxide and benzyl bromide and subsequently treated with methanesulfonic anhydride to furnish mesylate **453**. The NMR spectra showed the introduction of the benzyl protecting group (5 aromatic protons as a multiplet, 7.34-7.25 ppm in the proton spectrum; 6 aromatic carbon peaks at 138.9, 129.6, 128.5, 128.3, 127.6 and 127.4 ppm in the carbon-13 spectrum) and the mesyl moiety (methyl singlet at 3.03 ppm in the proton spectrum; peak at 38.8 ppm in the carbon-13 spectrum).

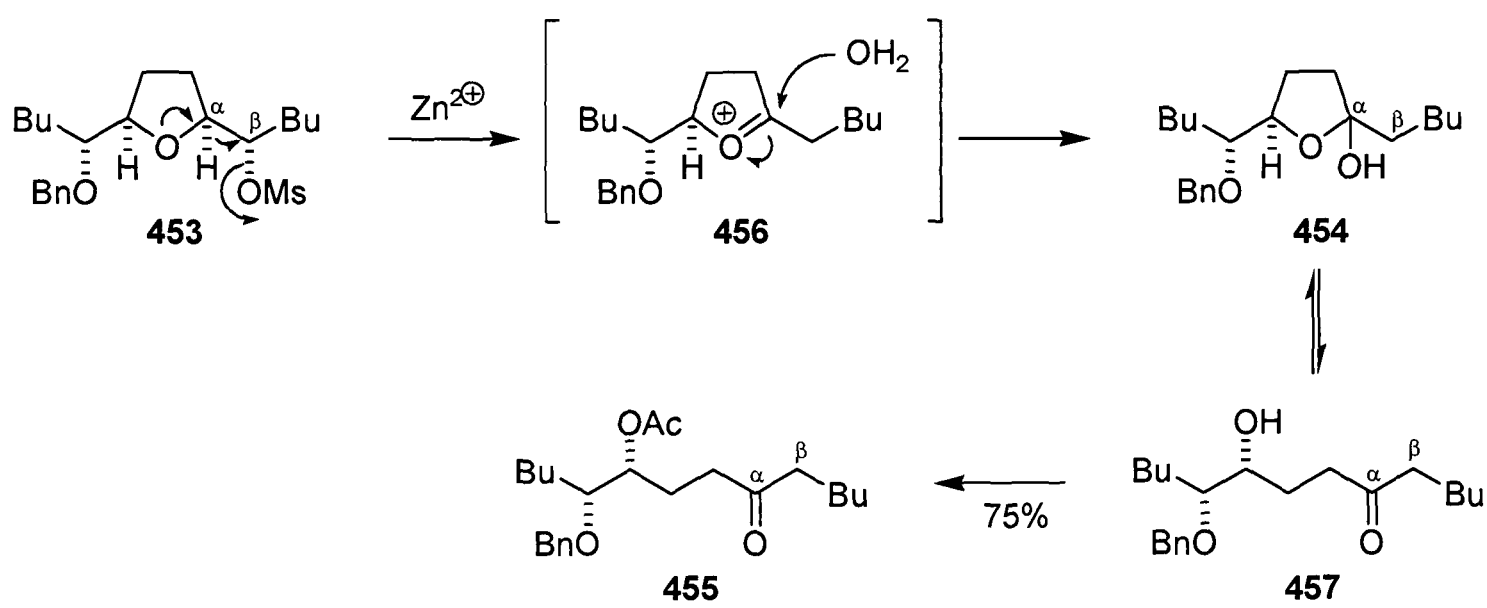
When treated with the ring-expansion conditions, tetrahydrofuran **453** was converted to lactol **454*** which was trapped out as the open chain ketone with acetic anhydride to yield ketone **455** (Scheme 6.25). The carbon-13 NMR spectrum showed the presence of a ketone (peak at 210.2 ppm) and the ester acetate carbonyl carbon (peak 170.8 ppm) and the proton NMR spectrum revealed the presence of two methylene groups α to a carbonyl (two doublets, *J* 8.2 Hz, at 2.38 and 2.34 ppm). The IR spectrum confirmed the presence of carbonyl

* The crude proton NMR spectrum showed that the lactol **454** was in equilibrium with the open chain ketone.

moieties (ν_{CO} 1735 cm^{-1}) and the electrospray mass spectrum showed the parent ion peak at 436 (100%, $MMeCNNa^{+}$).

6.4 *Hydride shift mechanism – application to the synthesis of spiroketals.*

With regard to the mechanism of the ring-opening of tetrahydofuran **453** to form ketone **455** we postulate that a hydride shift mechanism was in operation, although this has not been proven by labelling studies. The tetrahydrofuran oxygen lone pair of electrons can participate, inducing a hydride [1,2]-shift to form oxonium ion **456** (Scheme 6.26). Oxonium ion **456** undergoes a solvolysis reaction; water attacks to form lactol **454** that is in equilibrium with the open chain ketone **457**. The open chain ketone is trapped out with acetic anhydride to furnish acetate **455**.



Scheme 6.26. *Postulated mechanism for tetrahydrofuran ring-openings.*

We have evoked a hydride shift mechanism as only the *syn* diastereoisomer reacts to furnish the ketone. This result can be explained be considering the Newman projection of the ring-expansion precursor (Figure 6.3). For a hydride shift to occur, the hydrogen atom on carbon α is required to be in an antiperiplanar relationship to the mesyloxy moiety; this allows maximum overlap between the HOMO orbital of the hydrogen and LUMO (σ* orbital) of the mesyloxy moiety (Figure 6.3). As exemplified by generic tetrahydrofuran **458**, that bears a *syn* relationship between the hydrogen atom on carbon α and the mesyloxy leaving group on carbon β, after a bond rotation around the the α-β bond, the mesyloxy group is positioned over the tetrahydrofuran ring, antiperiplanar to the hydrogen on carbon σ. The bulky R group is

positioned away from the tetrahydrofuran ring, where there are a minimum of unfavoured steric interactions; hence a hydride shift can occur to form lactol **459**. However in the case of generic *anti* tetrahydrofuran **460**, after a bond rotation, the R group is placed in position where unfavourable steric interactions are enough to prevent a hydride shift occurring. If an E1 mechanism was in place, formation of lactol **459** should occur regardless of the relative stereochemistry between the hydrogen atom on carbon α and the mesyloxy group on carbon β; hence the tetrahydrofuran precursor bearing a *anti* relationship between the hydrogen atom on carbon α and the leaving group on carbon β (such as **448**) would also undergo rearrangement.

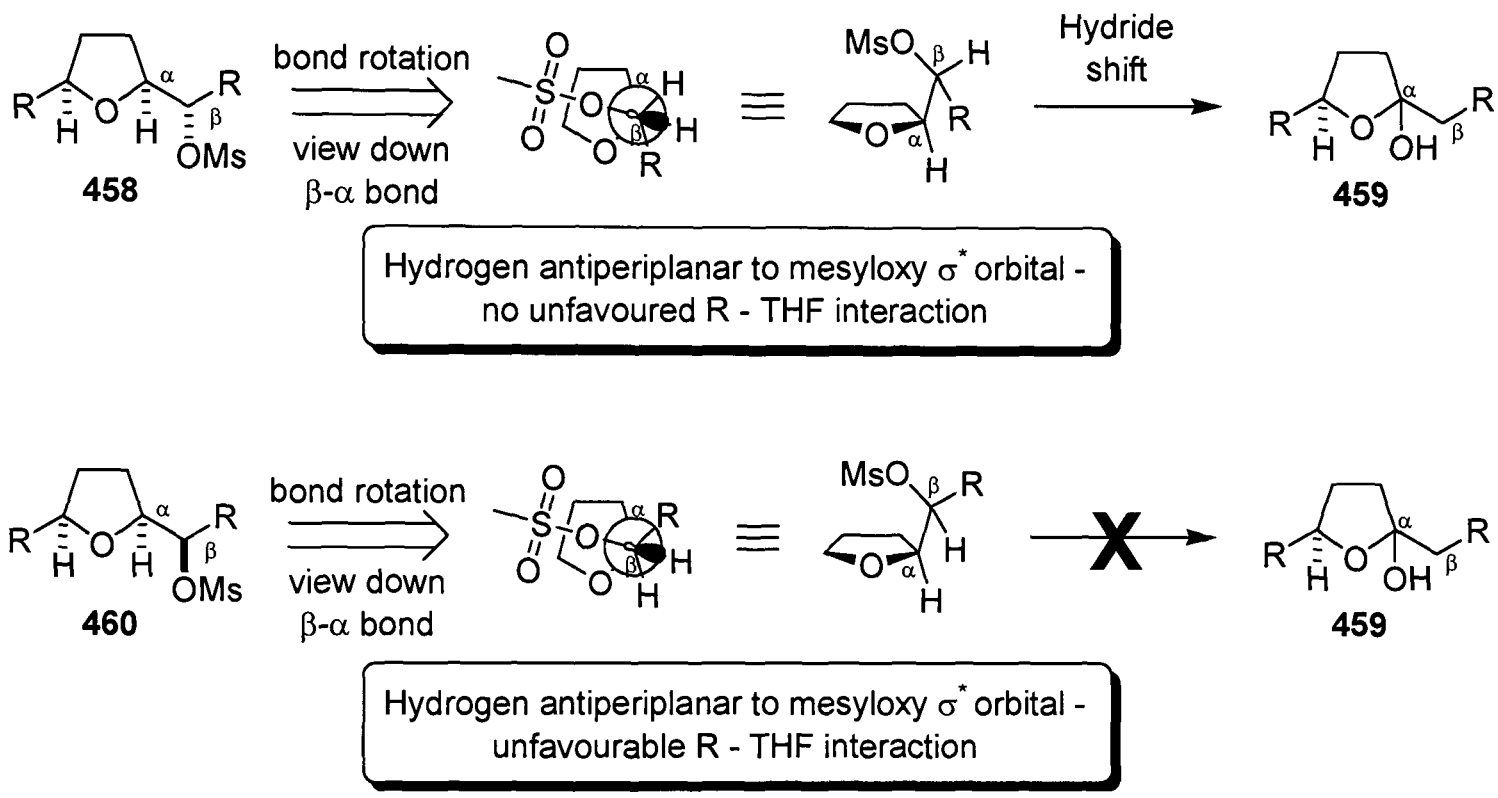
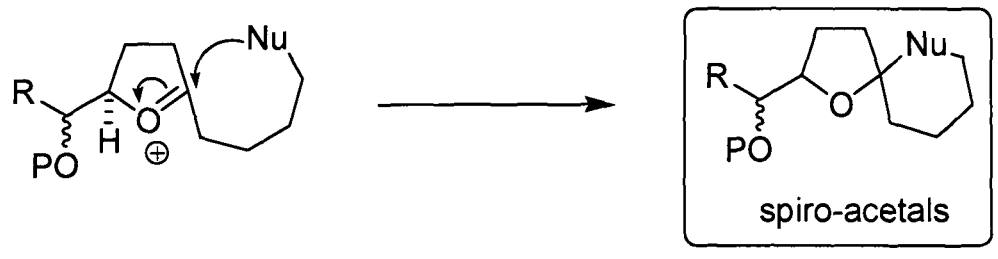


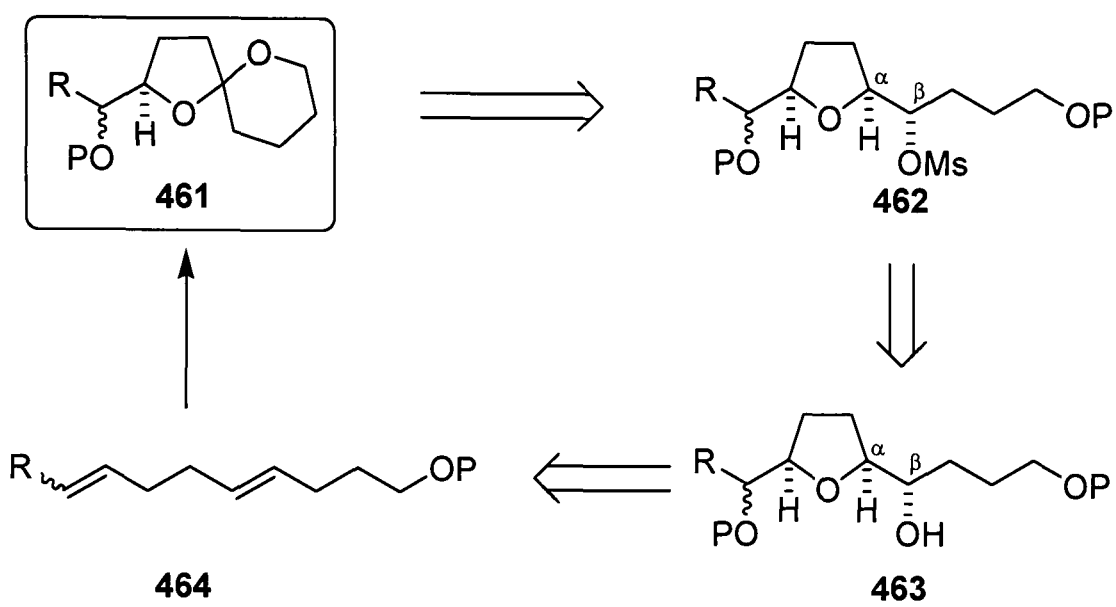
Figure 6.3. *Newman projection of hydride shift precursors.*

Although the groups of Nakata and Brimble have reported the ketone products, their use in synthesis has not been exploited. It was envisaged that the intermediate oxonium ion **456** could be trapped with a nucleophile other than water; for example if an internal tethered nucleophile was present, the sprio-acetal motif could be prepared (Scheme 6.27).



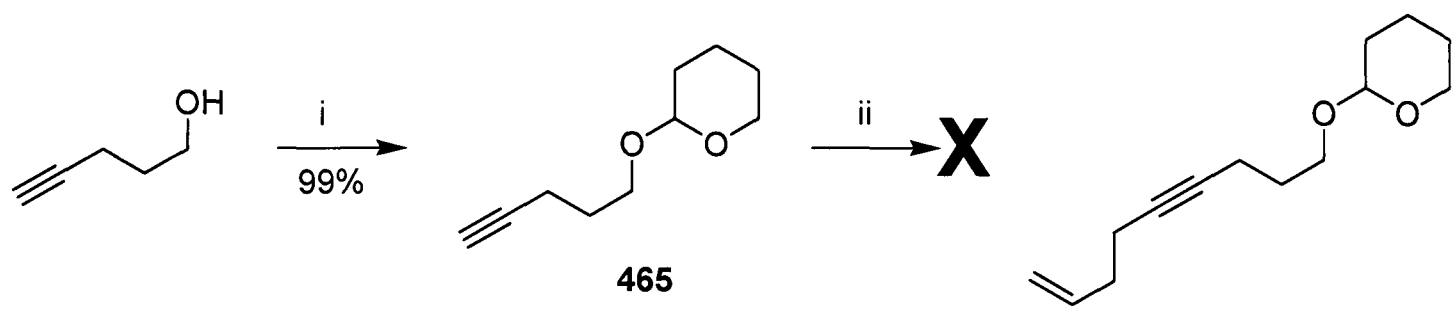
Scheme 6.27. *Potential formation of spiro-acetals*

In this way, it was envisaged that a novel route to the synthesis of the naturally abundant [4.5]-spiroketal motif[280, 281] could be employed. The retrosynthetic analysis is shown in Scheme 6.28; spiroketal **461** would come from the tetrahydrofuran **462** bearing a *syn* relationship between the hydrogen atom on carbon α and the leaving group on carbon β. The mesylate would be obtained from the parent tetrahydrofuran **463** that would be formed from the appropriate *trans* diene **464**. Thus structural complexity could be built up very quickly to afford spiroketals from a simple diene precursor.



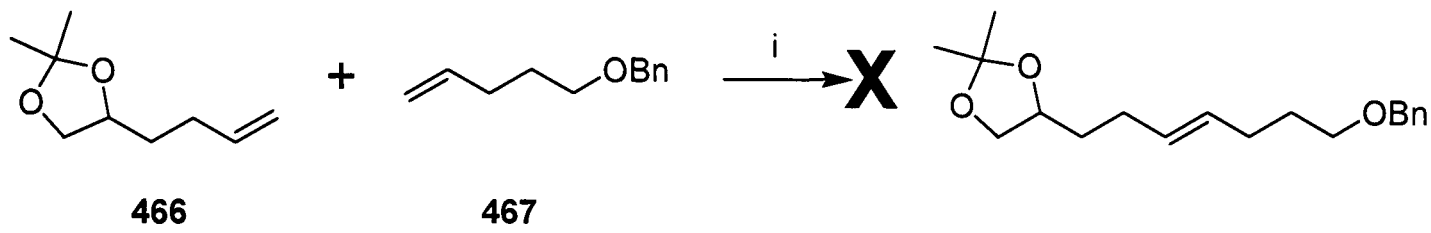
Scheme 6.28. *Potential formation of spiro-acetals*

Thus the first task was to complete the synthesis of the required *trans* diene that would allow formation of a tetrahydrofuran with the correct relative stereochemistry between carbons α and β requisite for a hydride shift pathway. Chong and Buck have published a convenient alkylation of 1-alkynes using *n*-butyl lithium;[282] however attempts to repeat a published example using the known alkyne **465**[283] with homoallyl bromide were not successful in our laboratories (Scheme 6.29).



Scheme 6.29. *Reagents and conditions*: i, 2,3-dihydropyran, CSA, CH_2Cl_2, room temperature; ii, *n*-BuLi, THF, –78 °C; then $Br(CH_2)_2CH{=}CH_2$, Δ.

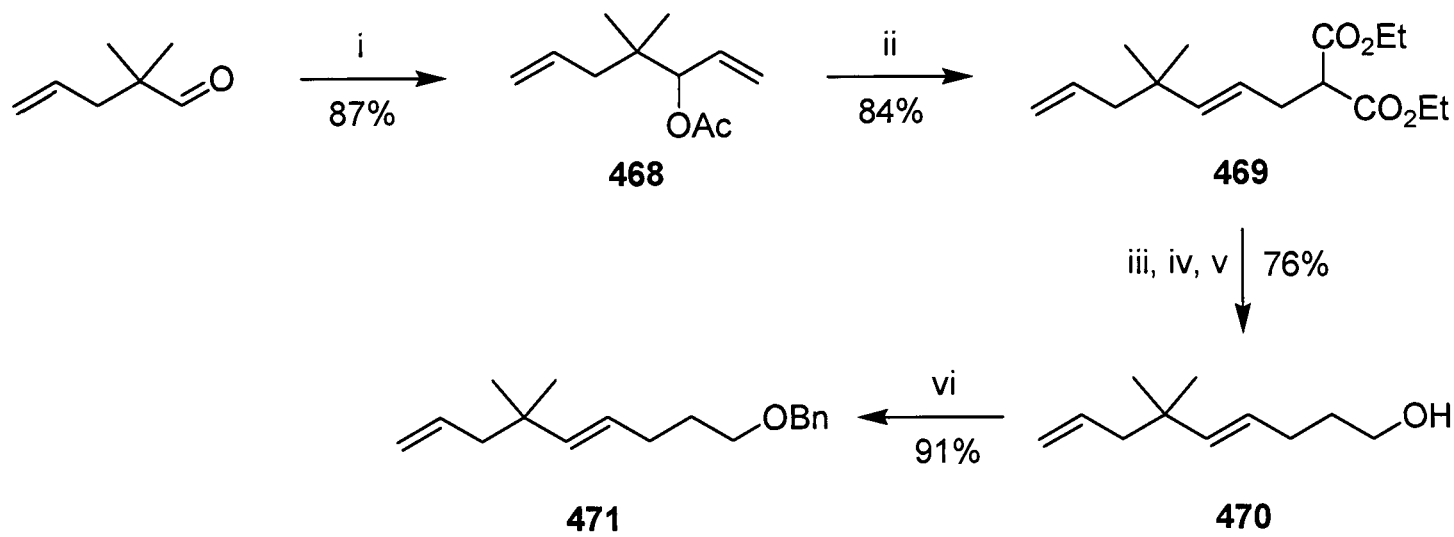
Grubbs and co-workers published a seminal paper on the cross metathesis reaction in 2003;[284] this method was attempted in the cross metathesis of known acetonide **466**[285] with olefin **467**, using the benzyl ether as solvent (Scheme 6.30); however this was not successful. The reaction gave complex mixtures of products; predominantly from the dimerisation of the benzyl ether **467**.



466 **467**

Scheme 6.30. *Reagents and conditions*: i, Grubbs' catalyst, second generation (5 mol%), room temperature.

Attention turned to the use of a palladium π-allyl system to install the required diene. Trost and Li have demonstrated that malonate nucleophiles can successfully add to such π-allyl systems;[286] thus known allylic alcohol **468**[286] was prepared by a vinyl Grignard addition to 2,2-dimethyl-4-pentenal (Scheme 6.31). The allyl acetate **468** was treated with allylchloride palladium dimer and the alkoxide of diethyl malonate as a nucleophile to furnish malonate **469**; the *gem*-dimethyl moiety directs attack of the malonate, thus the only product obtained arose from displacement at the terminal position of the olefin. Malonate **469** was hydrolysed to the diacid, decarboxylated and reduced to the primary alcohol **470** in good overall yield, before being protected as the benzyl ether **471**.



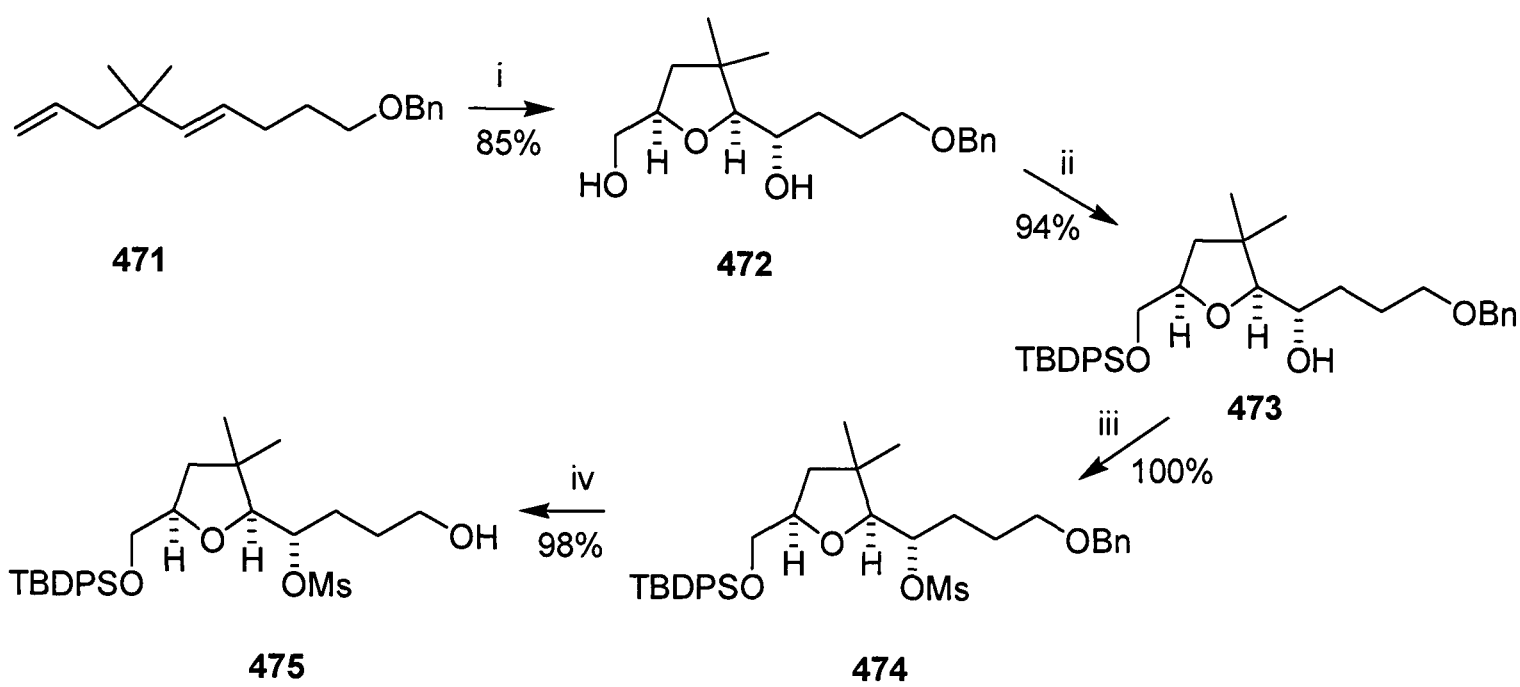
468 **469** **470** **471**

Scheme 6.31. *Reagents and conditions*: i, Vinylmagnesium bromide, THF, 0 °C → room temperature; then Ac_2O, room temperature; ii, $CH_2(CO_2Et)_2$, NaH, (η^3-$C_3H_5PdCl)_2$ (26 mol%), PPh_3 (20 mol%), THF, room temperature → Δ; iii, KOH, H_2O, EtOH, Δ, 91%; iv, 165 °C, neat; v, $LiAlH_4$, Et_2O, Δ, 83% over two steps; vi, BnBr, NaH, THF, room temperature.

The successful synthesis was shown by the NMR spectra; the proton NMR spectrum showed the introduction of 5 aromatic protons as multiplet at 7.38-7.28 ppm, the benzylic

methlene as a singlet at 4.51 ppm and the methylene α oxygen as a triplet at 3.48 ppm. The carbon-13 NMR spectrum revealed the four olefin carbons (140.4, 135.9, 125.4 and 116.5 ppm) and the quaternary carbon (35.6 ppm).

It should be noted that attempts were made to induce an Ireland-Claisen rearrangement on acetate **468**, but unfortunately were unsuccessful; hence the route shown in Scheme 6.31 was followed.



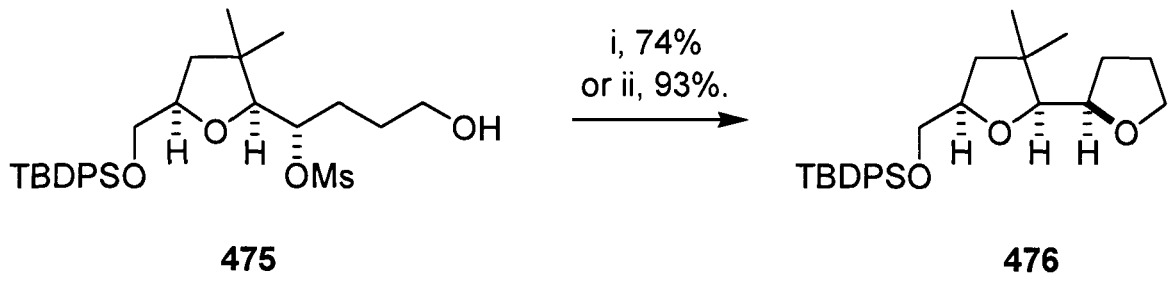
471 **472** **473** **474** **475**

Scheme 6.32. *Reagents and conditions*: i, OsO_4 (5 mol%), CSA, Me_3NO, CH_2Cl_2, room temperature; ii, TBDPSCl, imidazole, DMF, room temperature; iii, Ms_2O, DMAP, CH_2Cl_2, room temperature; iv, H_2, Pd/C, THF, 45 °C.

Oxidative cyclisation of diene **471** furnished tetrahydrofuran **472** in high yield (Scheme 6.32). The oxidative cyclisation of *trans*-olefins has been shown to furnish tetrahydrofurans with a *syn* relationship between the hydrogen atom on carbon α and the hydroxyl on carbon β;[10] however a crystalline derivative was later prepared (alcohol **487**, Scheme 6.38); hence all assignments of tetrahydrofuran stereochemistry were made by mechanistic analogy. The IR spectrum showed the introduction of the alcohol functionality (ν_{OH} 3356 cm^{-1}) and the proton NMR spectrum showed the methylene group on the tetrahydrofuran "backbone" as diastereotopic peaks (a multiplet 3.38-3.37 ppm and an apparent triplet, *J* 11.4 at 2.09 ppm). Carbon-13 NMR spectroscopy revealed the presence of four carbons α to oxygen (89.5, 78.3, 71.7 and 65.6 ppm) and carbons α to the benzyl ether oxygen atom (73.0 and 70.5 ppm). Tetrahydrofuran **472** was protected as the silyl ether **473** by treatment with *tert*-butyl(chloro)diphenylsilane; the proton NMR spectrum showed the introduction of the *tert*-butyl group (singlet at 1.08 ppm) and the carbon-13 NMR spectrum revealed the diagnostic upfield shift of the quaternary carbon bonded to silicon (19.1 ppm).

Mesylate **474** was afforded by treatment of silyl ether **473** with methanesulfonic anhydride; the IR spectrum also showed the loss of the alcohol functionality, with the methyl group of the mesyl moiety was present in the proton NMR sprectrum as a singlet at 3.04 ppm and as a peak at 39.2 carbon-13 NMR spectrum. Mesylate **474** was deprotected to furnish the primary alcohol **475**, whereupon the IR spectrum showed a stretch corresponding to the alcohol, ν_{OH} 3460 cm^{-1}.

In previous ring-expansion and hydride shift reactions, solvolysis of the intermediate oxonium ion occurs; however to allow formation of the spiroketal the internal alcohol functionality must act as the nucleophile. Thus to prevent competing nucleophilic attack on the intermediate oxonium ion formed, the reaction was carried out in the absence of water (Scheme 6.33). When alcohol **475** was reacted with these conditions an oil was obtained in good yield; however the proton NMR spectrum showed the presence of seven protons α to an oxygen atom as opposed to the five expected. The carbon-13 DEPT spectrum did show the presence of three OCH moieties α to oxygen (88.8, 78.6 and 77.8 ppm) and the IR spectrum showed the loss of the alcohol group. On this evidence the structure was assigned as the *bis*-tetrahydrofuran **476**; to verify this was correct assignment alcohol **475** was treated with sodium hydride. All the spectroscopic data were identical indicating formation of **476**.



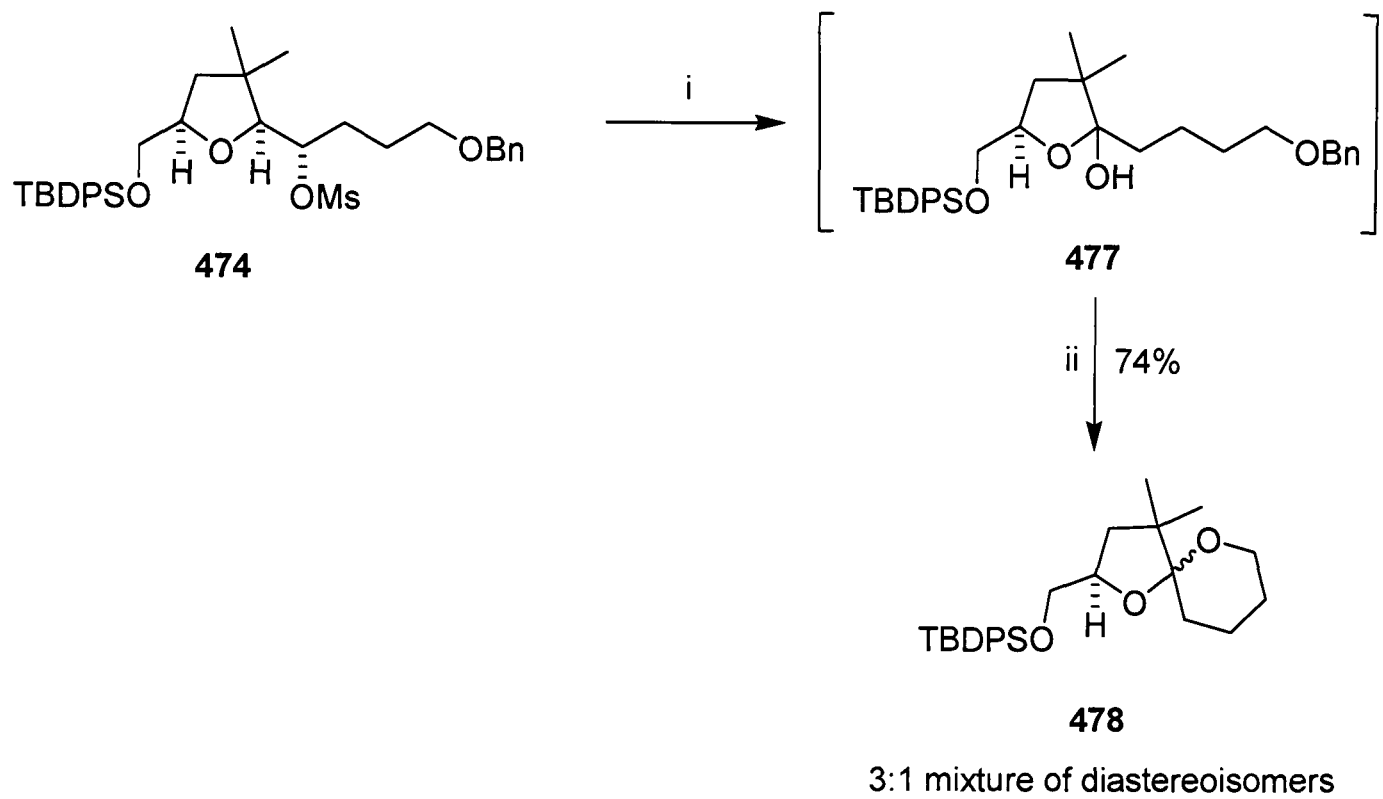
475 **476**

Scheme 6.33. *Reagents and conditions*: $Zn(OAc)_2 \cdot 2H_2O$, DMF, Δ; ii, NaH, THF, Δ.

It was shown in Scheme 6.33 that S_N2 displacement of the mesylate by the alcohol is faster than the hydride shift pathway. It was envisaged that the hydride shift could be performed to form the intermediate lactol, before the deprotection of the primary alcohol. Hence mesylate **474** was reacted with the hydride shift conditions to form intermediate lactol **477** (Scheme 6.34). The crude mixture was then treated with palladium on carbon (10%) in methanol under an atmosphere of hydrogen (1 atmosphere) to furnish spiroketal **478** as a 3:1* mixture of diastereoisomers (Scheme 6.34). The carbon-13 NMR revealed the diagnostic downfield shift of the spiro-quaternary carbon (107.3 and 107.1 ppm), the CH_2O moiety in the

* As determined from the 400 MHz NMR of the purified sample; hence there is a doubling of signals.

six-membered ring (60.9 and 60.8 ppm) and the CHO group of the tetrahydrofuran ring (77.5 and 77.2 ppm); the electrospray mass spectrum showed the parent ion peak at 439 (100%, MH^+).

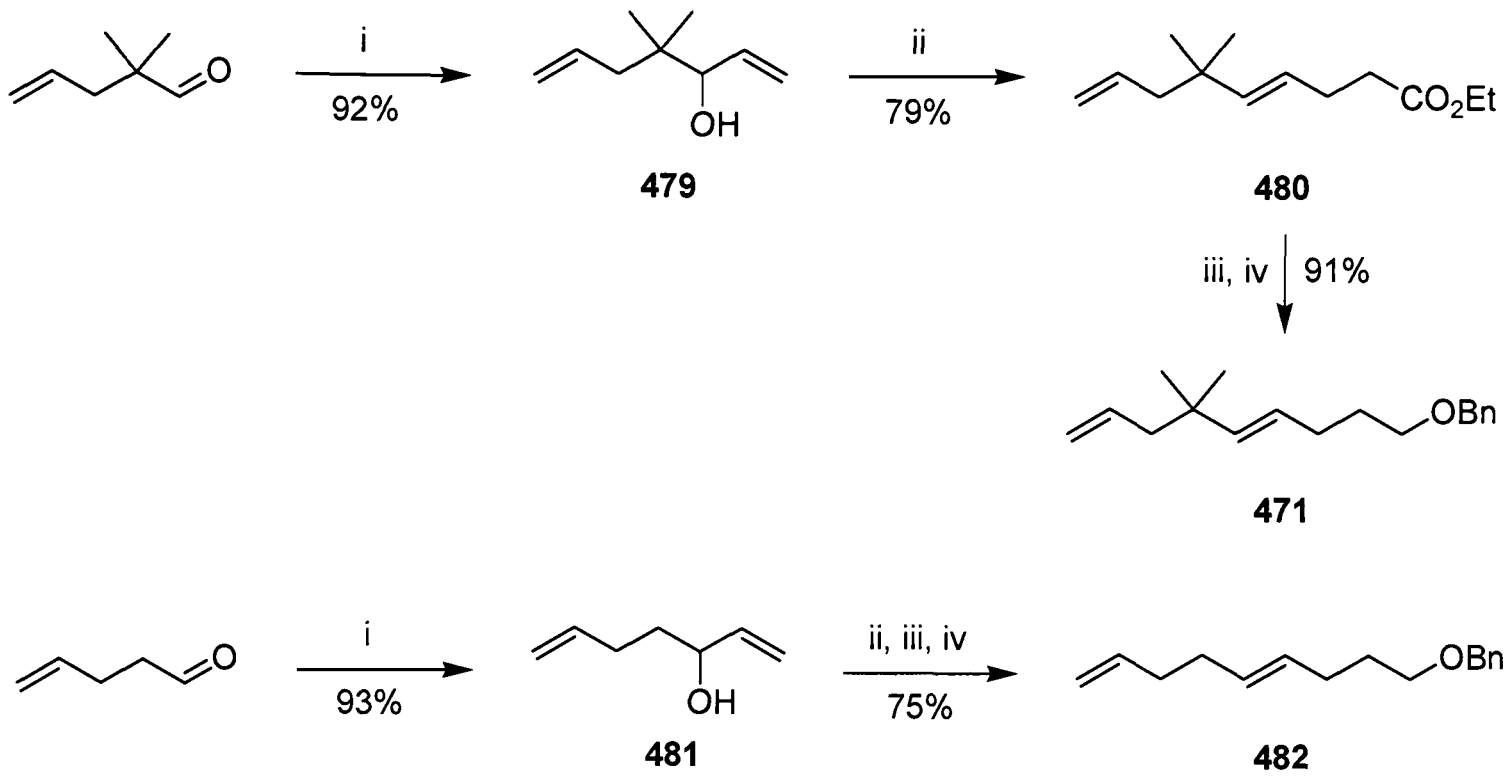


Scheme 6.34. *Reagents and conditions*: i, $Zn(OAc)_2 \cdot 2H_2O$, DMF, H_2O, Δ; then ii, H_2, Pd/C, MeOH, room temperature.

Starting diene **471** could also be synthesised by a shorter route using a Johnson-orthoester rearrangement (Scheme 6.35). 2,2-Dimethyl-4-pentenal was treated with vinylmagnesium bromide to furnish allylic alcohol **479**, which was reacted with triethyl orthoacetate in refluxing toluene to afford the ester **480**. Reduction with di-*iso*-butylaluminium hydride and benzylation of the resultant alcohol furnished the benzyl ether **471**; all spectroscopic data were consistent with those for the diene prepared *via* the palladium π-allyl route (Scheme 6.31).

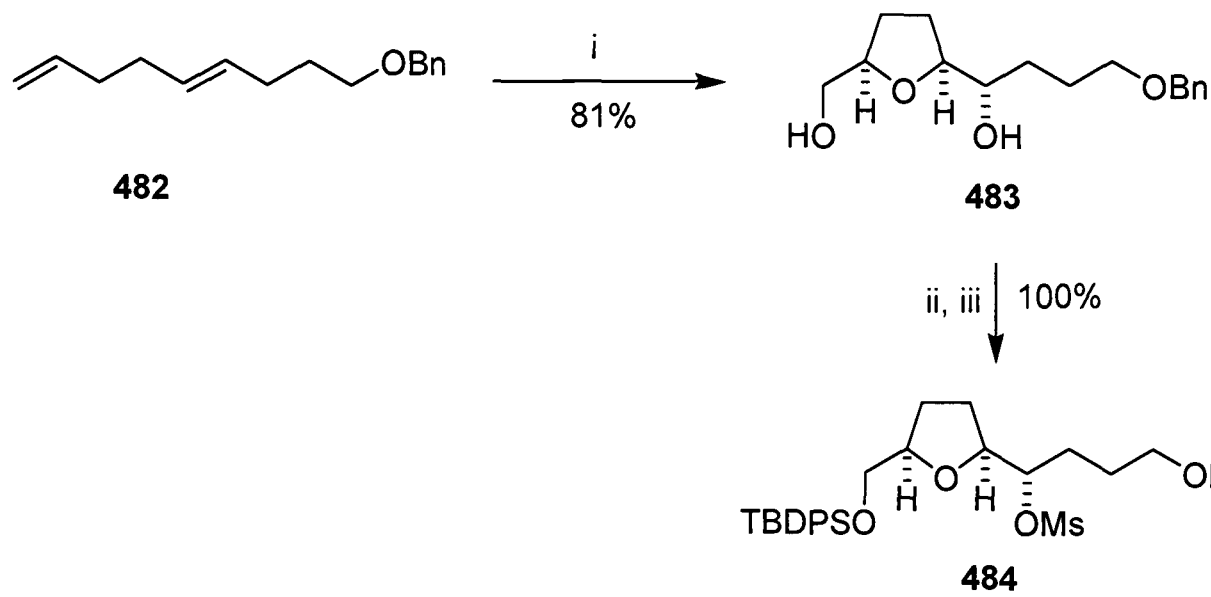
In order to demonstrate that our methodology for spiroketal formation was not just unique for the gem-dialkyl derivative shown in Scheme 6.34, diene **482** was prepared in an analogous manner to diene **471**, from alcohol **481** (Scheme 6.35). The proton NMR showed the presence of benzyl group (5 aromatic protons as a multiplet at 7.38-7.28 ppm; benzylic methylene as a singlet at 4.51 ppm), and the carbon-13 NMR verified the presence of four olefin carbons (138.5, 130.0* and 114.5 ppm).

* Two carbon signals were present at 130.0 ppm; as shown by the HMQC spectrum.



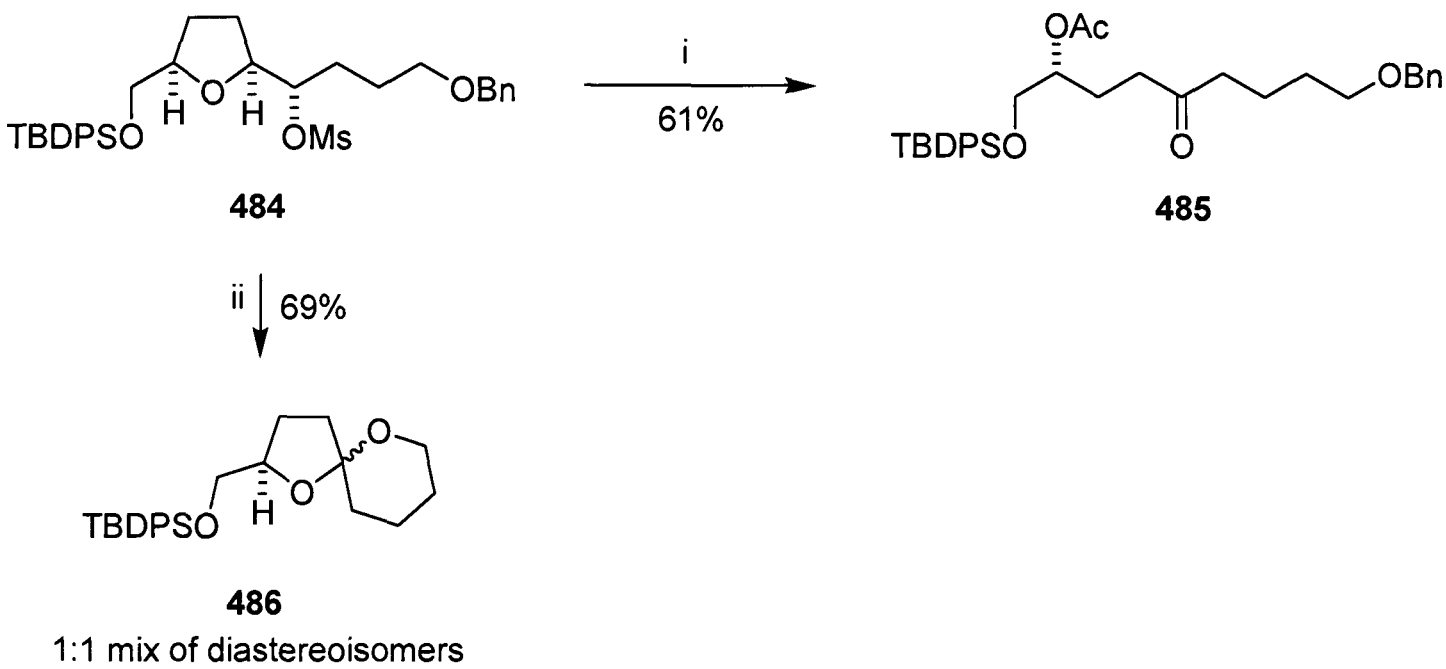
Scheme 6.35. *Reagents and conditions*: i, Vinylmagnesium bromide, THF, 0 °C → room temperature; ii, $(EtO)_3CMe$, propionic acid, PhMe, Δ; iii, DIBAL-H, CH_2Cl_2, 0 °C; iv, BnBr, NaH, THF, room temperature.

Oxidative cyclisation of diene **482** furnished the tetrahydrofuran **483** in high yield (Scheme 6.36); the IR spectrum revealed the introduction of alcohol moieties (ν_{OH} 3395 cm^{-1}). The proton NMR spectrum showed ten protons α to an oxygen atom (signals at 4.50, 3.85-3.80, 3.73, 3.52-3.46 and 3.21 ppm) and the carbon-13 NMR showed the two methylene ether carbons in the tetrahydrofuran ring (83.1 and 80.0 ppm). Tetrahydrofuran **483** was protected as the silyl ether and treated with methanesulfonic anhydride to furnish mesylate **484** in quantitative yield (the carbon-13 NMR spectrum showed the quaternary carbon bonded to silicon at 19.2 ppm and the proton NMR spectrum showed the methyl moiety of the mesylate group as a singlet at 3.07 ppm).



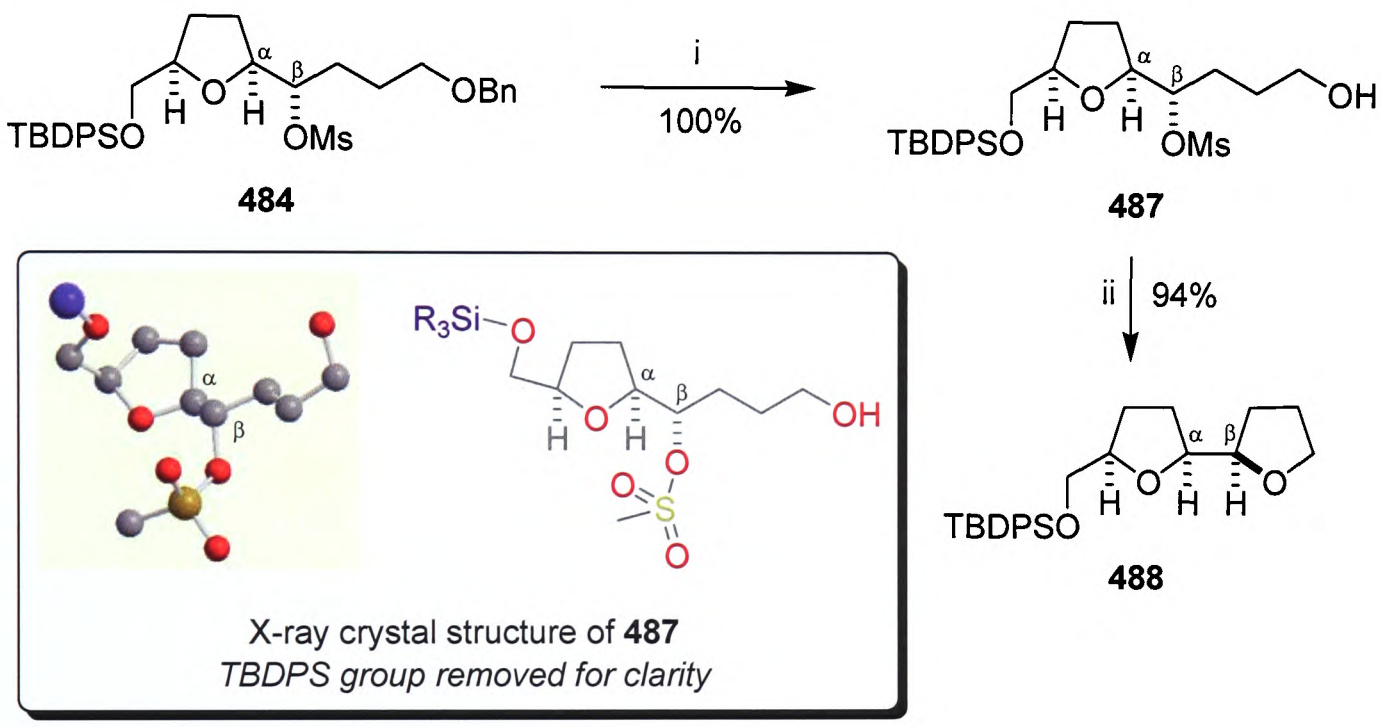
Scheme 6.36. *Reagents and conditions*: i, OsO_4 (5 mol%), CSA, Me_3NO, CH_2Cl_2, room temperature; ii, TBDPSCl, imidazole, DMF, room temperature; iii, Ms_2O, DMAP, CH_2Cl_2, room temperature.

Ketone **485** was obtained by subjecting mesylate **484** to the ring-expansion conditions and then acetic anhydride to push the lactol – ketone equilibrium to the side of the open-chain ketone **485** (Scheme 6.37). The IR spectrum showed a stretch corresponding to a carbonyl moiety (ν_{CO} 1738 cm^{-1}) and carbon-13 NMR spectroscopy showed two peaks corresponding to the carbonyl carbons at 209.7 and 170.7 ppm. Proton NMR revealed the methine α to the acetoxyl moiety as a quartet of triplets at 4.97 ppm (*J* 9.3 and 4.8 Hz) and the methylene groups α to the ketone as a triplet at 2.40 (*J* 7.2 ppm).



Scheme 6.37. *Reagents and conditions*: i, $Zn(OAc)_2 \cdot 2H_2O$, DMF, H_2O, Δ; then Ac_2O, pyr, room temperature; ii, $Zn(OAc)_2 \cdot 2H_2O$, DMF, H_2O, Δ; then H_2, Pd/C, MeOH, room temperature.

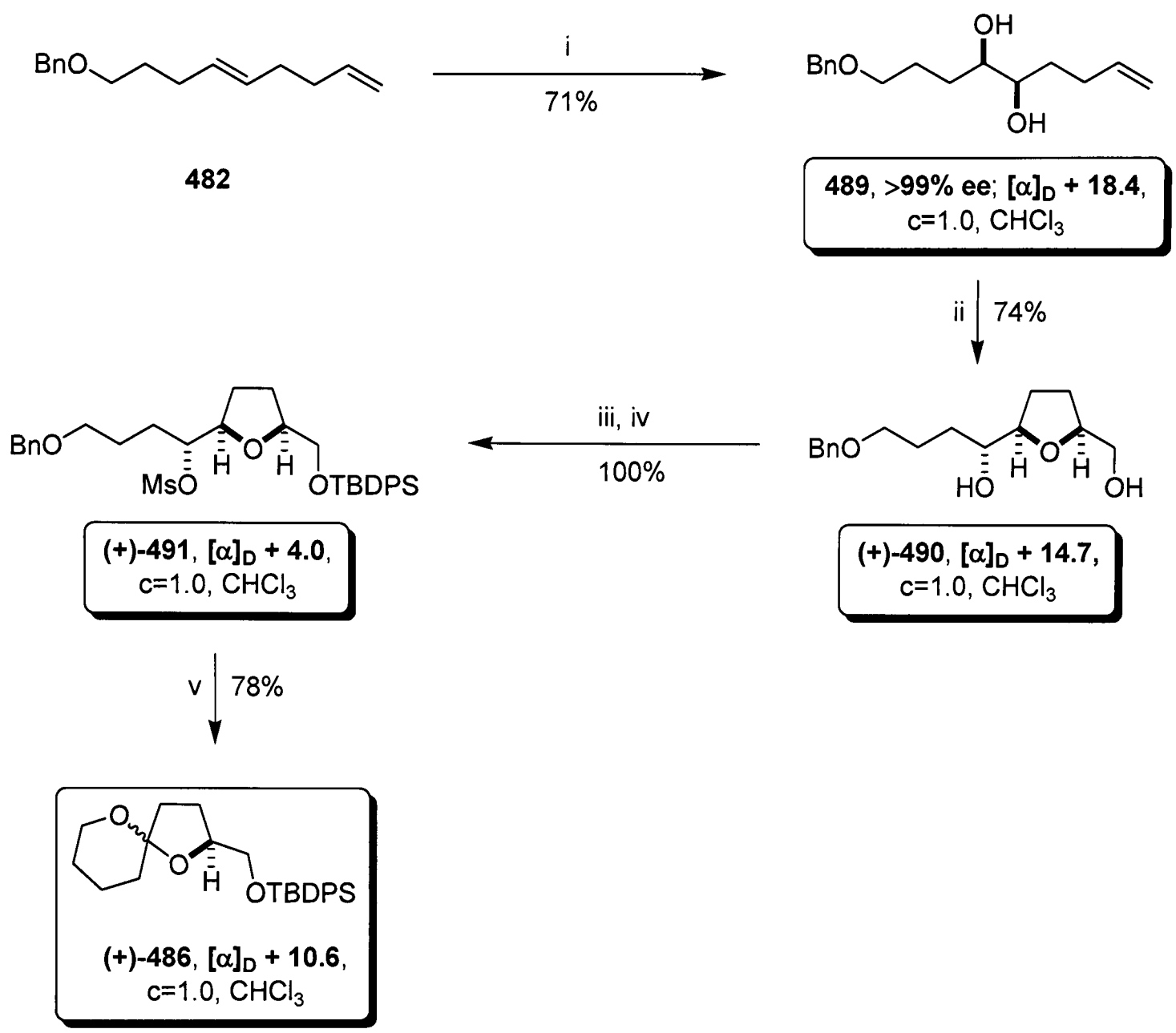
When mesylate was **484** was treated with the ring-expansion conditions followed by *in situ* deprotection of the benzyl group, spiro-ketal **486** was furnished in good yield as a 1:1 mixture of diastereoisomers (Scheme 6.37). The successful reaction was shown by the carbon-13 NMR spectrum which revealed the presence of the quaternary spiro carbon (106.2 and 105.8 ppm), the methylene α to oxygen in the tetrahydropyran ring (61.6 and 61.4 ppm) and the methylene α to oxygen in the tetrahydrofuran ring (80.8 and 78.7 ppm); the electrospray mass spectrum showed the parent ion peak at 433 (100%, MNa^+).



Scheme 6.38. *Reagents and conditions*: i, H_2, Pd/C, THF, 45 °C; ii, NaH, THF, Δ.

bis-Tetrahydrofuran **488** was prepared by deprotection of benzyl ether **484** and subsequent treatment of alcohol **487** with sodium hydride in refluxing tetrahydrofuran (Scheme 6.38). The proton NMR spectrum revealed seven protons α to an oxygen atom (4.09-4.04, 3.88-3.82, 3.79-3.78 and 3.67 ppm) and the carbon-13 NMR DEPT spectrum showed the OCH_2 group α to oxygen in the second tetrahydrofuran ring (68.4 ppm) and the OCH moieties present in both tetrahydrofuran rings (81.7 and 81.2 ppm).

Alcohol **487** was a crystalline solid and hence the structure was proven by X-ray crystallography (Scheme 6.38). The crystal structure revealed the *syn*-relationship between the hydrogen on carbon α and the mesyloxy group on carbon β (as required for the hydride shift pathway). It should be noted that the stereochemistry of all other tetrahydrofuran structures in Chapter 6.4 were assigned by analogy to alcohol **487**.



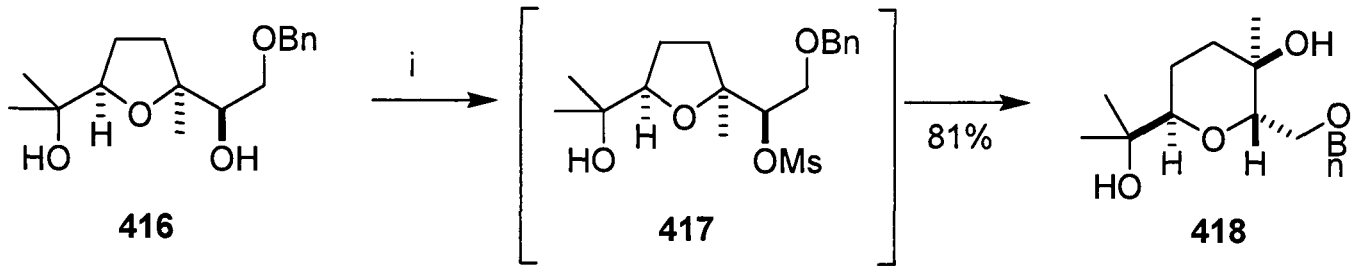
Scheme 6.39. *Reagents and conditions*: i, $K_2OsO_4 \cdot 2H_2O$ (2 mol%), K_2CO_3, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C → room temperature; ii, $K_2OsO_4 \cdot 2H_2O$ (5 mol%), TFA, Me_3NO, acetone:H_2O (9:1), room temperature; iii, TBDPSCl, imidazole, DMF, room temperature, **100%**; iv, Ms_2O, DMAP, CH_2Cl_2, room temperature, **100%**; v, $Zn(OAc)_2 \cdot 2H_2O$, DMF, H_2O, Δ; then H_2, Pd/C, MeOH, room temperature.

It was shown in Chapter 6.1 that the tetrahydrofuran products from the oxidative cyclisation can be made enantiopure by the use of the appriopiate starting diol (Scheme 6.7); hence it was envisaged that this method could be employed in the synthesis of enantioenriched spiroketals. Diene **482** was dihydroxylated selectively on the more reactive *trans* olefin,[269] using hydroquinindine-1,4-phthalainediyl diester as the ligand, to furnish diol **489** (Scheme 6.39) in good yield and excellent enantiomeric excess, as determined using a Daicel Chiralpak OD column (see Appendix 1 for HPLC trace); the IR spectrum showed the introduction of the alcohol moieties (ν_{OH} 3406 cm^{-1}) and the NMR spectra showed the methylene moieties α to the hydroxyl groups (multiplet at 3.44-3.38 ppm in the proton NMR spectrum; peaks at 74.1 and 73.9 ppm in the carbon-13 NMR spectrum). Reaction of diol **489** to osmium tetroxide furnished (+)-**490** (α_D=+14.7) in high yield. Tetrahydrofuran **(+)-490**

was converted to hydride shift precursor (+)-**491** (α_D=+4.0) in excellent yield and was reacted with zinc acetate to afforded the enantioenriched spiroketal (+)-**486** (α_D=+10.6) in an improved yield of 78% (Scheme 6.39); all spectroscopic data were identical to those for the racemic material previously synthesised.

6.5 *One-pot ring-expansion of tetrahydrofurans.*

Finally, a one-pot ring-expansion procedure was developed: tetrahydrofuran **416** could be converted to tetraydropyran **418** in high yield; treatment with methanesulfonic anhydride and 4-(dimethylamino)-pyridine in *N*,*N*-dimethylformamide formed the mesylate **417** *in situ* before the addition of zinc acetate dihydrate and water to induce rearrangement (Scheme 6.40).



416 **417** **418**

Scheme 6.40. *Reagents and conditions*: i Ms_2O, DMAP, DMF, room temperature; then $Zn(OAc)_2 \cdot 2H_2O$, H_2O.

6.6 *Chapter 6 summary.*

In Chapter 6.1 the ring-expansion of tetrahydrofurans to the corresponding tetrahydropyrans was developed to a two-step high yielding sequence from readily available starting materials; a mechanism and the stereochemistry of the starting materials and products was proved in section 6.2. A detailed study of the role of stereochemistry with respect to ring-expansion was undertaken in section 6.3 and section 6.4 detailed the mechanism for the ring-opening of tetrahydrofurans and its application to the enantiopure synthesis of spiroketal. Finally, it has been demonstrated that the ring-expansion sequence detailed in section 6.1 can be performed as a one-pot method.

Chapter 7

Conclusions

7.1 *Chapter 4 conclusions.*

7.2 *Chapter 6 conclusions.*

This thesis has described successful attempts to synthesise six-membered heterocycles containing nitrogen and oxygen that are not accessible by other means.

7.1 *Chapter 4 conclusions.*

It was shown in Chapter 4 that 1,1-dihaloalkanes can be successfully used as electrophiles in the reductive alkylation of electron-deficient pyrroles, to furnish the corresopnding α-halomethyl pyrrolines in high yields. When treated with tri-*n*-butyltin hydride, these pyrrolines undergo a rearrangement to furnish the corresponding tetrahydropyridines in high yields; the rearrangement has been demonstrated to be tolerant of subsititution around the pyrroline ring. A mechanism for the rearrangement has been proposed, supported by the synthesis of fused *cis*-bicyclic compounds from either a 5-*exo*-trig or 6-*exo*-trig cyclisation.

Although attempts at an anionic ring-expansion of α-halomethyl pyrrolines were unsuccessful, a novel pyrroline ring opening mediated by lithium di-*tert*-butylbiphenylide was instead discovered. A mechanism for the reaction has been postulated, with supporting evidence from a competition experiment.

Unfortunately the attempted cationic ring-expansion of pyrroline derivatives obtained from the partial reduction was not successful; the *tert*-butyl carbamate nitrogen protecting group underwent a cyclisation and the required benzyl protecting group could only be installed in low yield.

7.2 *Chapter 6 conclusions.*

It was shown in Chapter 6 that tetrahydrofurans obtained from the oxidative cyclisation could be converted to the corresponding tetrahydropyran products. The original reported ring-expansions conditions were modified to allow two step high yielding ring-expanion, starting from the parent alcohol. A thorough investigation into the required relative stereochemistry between the tetrahydrofuran ring and the leaving group was undertaken; it was shown, that substrates where a Thorpe-Ingold effect was possible underwent high yielding ring-expansion.

When no Thorpe-Ingold effect was present and the α-hydrogen and leaving group were in a *syn* relationship, the tetrahydrofuran instead underwent a hydride shift mechanism to form the open chain ketone. The intermediate oxonium ion has been trapped out by an internal nucleophile to allow the synthesis of spiroketals in high yield; use of a pre-formed chiral diol in the oxidative cyclisation allowed this sequence to prepare enantioenriched products.

Chapter 8

Experimental

8.1 *General experimental techniques.*

8.2 *General experimental procedures.*

8.3 *Chapter 4 experimental.*

8.4 *Chapter 6 experimental.*

8.1 *General experimental techniques.*

Tetrahydrofuran, dichloromethane, toluene and ether were dried prior to use by alumina column.[287-289] Triethylamine and *bis*(methoxyethyl)amine were dried by stirring over and distilling from calcium hydride and was stored over calcium hydride granules. Reagents obtained from Acros, Aldrich, Avocado, Fluka and Lancaster fine chemicals suppliers were used directly as supplied or following purification according to procedures described by Perrin and Armarego.[290] All non-aqueous reactions were carried out under an atmosphere of argon using oven- or flame- dried glassware.

Flash column chromatography was carried out according to the method of Still[291] using silica gel 60 (0.040-0.063 mm) (Merck) using head pressure by means of head bellows. Thin layer chromatography was performed on commercially available pre-coated glass-backed plates (Merck silica Kieselgel $60F_{254}$). Spots were made visible either by the quenching of UV fluorescence or by staining with a potassium permanganate, vanillin or anisaldehyde solution.

Proton and Carbon-13 NMR spectra were recorded on Bruker DPX 400 Fourier transform spectrometers using an internal deuterium lock. Chemical shifts are quoted in parts per million (ppm) downfield of tetramethylsilane and coupling constants *J* are quoted in Hz. Carbon spectra were recorded with broad band proton decoupling and Attached Proton Test. The symbols + and – after the carbon NMR shifts indicate odd and even numbers of attached protons respectively, where a carbon DEPT or carbon APT spectrum has been obtained. All

NMR spectra were recorded at 25 °C and NMR spectra that possess rotameric splitting, causing doubling of peaks, have both the split peaks listed then the description.

Infra-red spectra were recorded on a Bruker Tensor 27 Ft-IR spectrometer. Spectra were analysed either as thin films between NaCl plates or as KBr disks. All peaks are quoted and are not rationalised. Absorption maxima (ν_{max}) are recorded in wavenumbers (cm^{-1}) and refer to stretching vibrations unless otherwise stated.

Mass spectra (*m/z*) under the conditions of electrospray ionisation (ESI) were recorded on a Fisons Platform II. Accurate mass (HRMS) data were recorded under conditions of ESI on a Micromass LCT (resolution = 5000 FWHM) using a lock-spray source. The lock-mass used for calibration was tetraoctylammonium bromide in positive ion and sodium dodecyl sulfate in negative ion. *m/z* and HRMS data were recorded under conditions of field ionisation (FI) on a Micromass LCT (resolution = 5000 FWHM) using a temperature-programmed solid probe inlet. The lock-mass used for calibration was chloropentafluorobenzene. *m/z* and HRMS data were recorded under conditions of chemical ionisation (CI) on a Fisons Autospec-oaTof (resolution = 10000 FWHM) in CI^+ mode using NH_3 as the CI gas. *m/z* and HRMS data were also recorded under conditions of chemical ionisation (CI) and electron impact (EI) on a Micromass GCT. A split injection (split ratio 20-40) was used to introduce 0.3 μL of a 1 mg/ mL sample in CH_2Cl_2 onto a fused silica capillary column installed in an HP 6890 GC coupled to a Micromass GCT mass spectrometer. The column was a 12 m x 0.25 mm i.d. BPX5 column (SGE) and the injection port temperature was 240 °C. GC oven conditions were: 2 min at 80 °C then raised to 280 °C at 20 °C min^{-1} and kept at 280 °C for 10 min. The helium carrier gas flow was 1 mL min^{-1}.

Mass spectra were recorded in electron impact (EI^+) mode at an ionisation voltage of 70 eV and a source temperature of 150 °C using heptacosa as the lock-mass. A scan range of *m/z* 50-650 with a scan time of 0.45 s was employed. Mass spectra were recorded in chemical ionisation (CI^+) mode at an ionisation voltage of 60 eV and a source temperature of 150 °C using amyl acetate as the lock-mass and NH_3 as CI gas. A scan range of *m/z* 50-650 with a scan time of 0.90 s was employed. The data were controlled and stored by the Micromass Masslynx 3.5 software. Values are reported as ratio of mass to charge in Daltons. Assignable peaks observed are quoted and the parent ion peak (100%) shown.

Melting points were obtained using a Leica VMTG heated-stage microscope and are uncorrected.

Optical rotations ($[\alpha]_D$) were recorded on a Perkin-Elmer 241 polarimeter (using the sodium D line, 589 nm) and $[\alpha]_D$ are given in units of 10^{-1} deg dm^2 g^{-1}.
Analytical HPLC was used for the determination of enantiomeric excess, e.e., using a Waters 600E System Controller, a Waters 991 Photodiode Array detector and a Daicel Chiralpak OD column.

X-ray diffraction data were measured using an Enraf-Nonius Kappa CCD diffractometer (graphite-monochromated Mo Kα radiation, λ=0.71073 Å). Intensity data were processed using the DENZO-SMN package and further processing was carried out using the Crystals, Cameron and Mercury software.

8.2 *General experimental procedures.*

Method A. *N-Boc protection of pyrroles:* Di-*tert*-butyl dicarbonate (5.68 g, 26.0 mmol, 1.20 eq.) dissolved in dichloromethane (20 cm^3) was added to a solution of the pyrrole (21.7 mmol) and 4-(dimethylamino)pyridine (530 mg, 4.34 mmol, 0.20 eq.) dissolved in dichloromethane (30 cm^3) under an atmosphere of argon at ambient temperature. The resulting solution stirred until the reaction was judged complete by TLC (typically 24 – 36 hours). The mixture was poured into aqueous hydrochloric acid (1.0 mol dm^{-3}, 75 cm^3), separated and the aqueous layer extracted with ether (3 × 125 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure to give the crude product.

Method B. *Radical rearrangement of pyrrolines:* The pyrroline (923 μmol) dissolved in deoxygenated benzene (50 cm^3) was heated to initiate reflux under an atmosphere of argon; heating continued for 1 hour. Tri-*n*-butyltin hydride (0.328 cm^3, 1.20 mmol, 1.30 eq.) and AIBN (39.4 mg, 240 μmol, 0.20 eq.) dissolved in deoxygenated benzene (10 cm^3) were added over a 12 hour period *via* syringe pump to the refluxing solution and once the addition was complete, heating continued for a further 12 hours. The mixture was allowed to cool and evaporated under reduced pressure to give the crude product.

Method C. *Allylic oxidation of pyrrolines:* A solution of chromium$^{(VI)}$ trioxide (500 mg, 5.00 mmol, 5.00 eq.) dissolved in aqueous sulfuric acid (2.0 mol dm^{-3}, 2.0 cm^3) was added to the pyrroline (1.00 mmol) dissolved in acetone (5.0 cm^3) at ambient temperature and the resulting orange solution stirred until the reaction was judged complete by TLC (typically 7 days). Aqueous saturated sodium bicarbonate (5 cm^3) was added to the solution, the resulting mixture was evaporated under reduced pressure, dissolved in ether (10 cm^3), poured into aqueous saturated sodium bicarbonate (10 cm^3) and the layers separated. The aqueous layer was extracted with ethyl acetate (3 × 15 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure to give the crude product.

Method D. *Dihydropyrrole ring opening:* Freshly cut lithium wire (21 mg, 3.00 mmol, 3.00 eq.) was hammered out into a foil, cut into several small strips, and placed in a Schlenk tube containing 4,4-di-*tert*-butylbiphenyl (798 mg, 3.00 mmol, 3.00 eq.) and glass "antibumping" granules (2 spatula tips). The tube was evacuated and purged with argon several times. The contents of the Schlenk tube were then stirred with maximum vigour until the lithium foil had been completely reduced to a powder (typically 0.5 – 2 hours) under an atmosphere of argon. The Schlenk tube was cooled to –78 °C under an atmosphere of argon and tetrahydrofuran (25 cm^3) added, immediately resulting in a dark turquoise solution. The pyrroline (1.00 mmol) dissolved in tetrahydrofuran (30 cm^3) was added dropwise over a period of 2-5 min. The turquoise colour persisted throughout the course of the substrate addition. The reaction mixture was stirred at −78 °C for a further 2 hours and aqueous saturated ammonium chloride (5 cm^3) was added. The reaction mixture was poured into aqueous hydrochloric acid (1.0 mol dm^{-3}, 25 cm^3), separated and the aqueous layer extracted with ethyl acetate (3 × 15 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, light petroleum (bp 40-60 °C)] to remove excess 4,4-di-*tert*-butylbiphenyl and the solvent polarity then increased to isolate the desired material.

Method E. *Lithium 4,4-di-tert-butylbiphenyl partial reduction:* Freshly cut lithium wire (28.0 mg, 4.00 mmol, 4.00 eq.) was hammered out into a foil, cut into several small strips, and placed in a Schlenk tube containing 4,4-di-*tert*-butylbiphenyl (1.06 g, 4.00 mmol, 4.00 eq.) and glass "antibumping" granules (2 spatula tips). The tube was evacuated and purged with

argon several times. The contents of the Schlenk tube were then stirred with maximum vigour until the lithium foil had been completely reduced to a powder (typically 0.5-2 h) under an atmosphere of argon. The Schlenk tube was cooled to –78 °C under an atmosphere of argon and tetrahydrofuran (25 cm^3) added, immediately resulting in a dark turquoise solution. The pyrroline (1.00 mmol) and *bis*(methoxyethyl)amine (0.169 cm^3, 1.20 mmol, 1.20 eq.) dissolved in tetrahydrofuran (30 cm^3) was added dropwise over a period of 2 – 5 min. The turquoise colour persisted throughout the course of the substrate addition. The reaction mixture was stirred at –78 °C for a further 2 hours and 1,2-dibromoethane (typically 0.5 cm^3) was added dropwise until the turquoise disappeared, after which the electrophile (3.00 mmol) was added dropwise. Stirring continued for a further 20 minutes and aqueous saturated ammonium chloride (5 cm^3) was added. The reaction mixture was poured into aqueous hydrochloric acid (1.0 mol dm^{-3}, 25 cm^3), separated and the aqueous layer extracted with ethyl acetate (3 × 15 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, light petroleum (bp 40-60 °C)] to remove excess 4,4-di-*tert*-butylbiphenyl and the solvent polarity then increased to isolate the desired material.

Method F. *Benzylation of alcohols:* Sodium hydride (60% dispersion in mineral oil, 800 mg, 20.0 mmol, 2.00 eq.) was added portionwise to the alcohol (10.0 mmol) dissolved in tetrahydroduran (100 cm^3) under an atmosphere of argon at 0 °C. Benzyl bromide (1.44 cm^3, 12.0 mmol, 1.20 eq.) was added and the resulting mixture stirred until the reaction was judged complete by TLC (typically 24 – 48 hours). The mixture was poured into aqueous hydrochloric acid (1.0 mol dm^{-3}, 50 cm^3), separated and the aqueous layer extracted with ether (3 × 125 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure to give the crude product.

Method G. *Oxidative cyclisation of dienes using trifluoroacetic acid:* Trifluoroacetic acid (40 cm^3) was added cautiously to a stirring solution of diene (4.00 mmol) dissolved in a mixture of acetone (72 cm^3) and water (8 cm^3) at 0 °C; stirring continued for 5 minutes. Potassium osmate$^{(VI)}$ dihyrate (74 mg, 0.20 mmol, 0.05 eq.) was added and the reaction allowed to warm to ambient temperature. After 45 minutes, trimethylamine-*N*-oxide (2.22 g, 20.0 mmol, 5.00 eq.) was added and the reaction stirred until judged complete by TLC (typically 24 – 36 hours). Sodium sulfite (50 mg, 400 μmol, 0.10 eq.) was added and the

mixture stirred for 1 hour before being cooled to 0 °C. Aqueous sodium hydroxide (40% by weight) saturated with sodium chloride was added cautiously to basify the mixture to pH 8. The mixture was poured into ether (150 cm^3), separated and the aqueous layer extracted with ether (3 × 200 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate) and evaporated under reduced pressure to give the crude product.

Method H. *Mesylation of alcohols:* Methanesulfonic anhydride (348 mg, 2.00 mmol, 2.00 eq.) was added to a solution of alcohol (1.00 mmol) and 4-(dimethyl)aminopyridine (489 mg, 4.00 mmol, 4.00 eq.) dissolved in dichloromethane (50 cm^3) under an atmosphere of argon at ambient temperature and stirred for 12 hours. The mixture was poured into aqueous hydrochloric acid (3.0 mol dm^{-3}, 20 cm^3), separated and the aqueous layer extracted with ether (2 × 30 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate) and evaporated under reduced pressure to give the product, which was used without further purification.

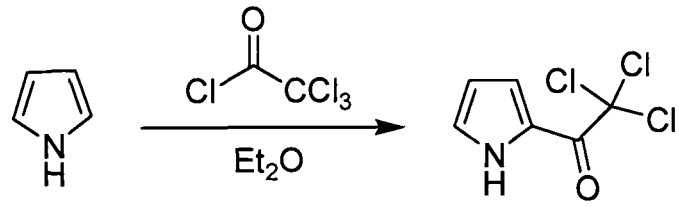
Method I. *Cationic ring-expansion of tetrahydrofurans:* Zinc acetate dihydrate (549 mg, 2.50 mmol, 5.00 eq.) was added to a stirring solution of the mesylate (0.50 mmol) dissolved in *N,N*-dimethylformamide (5 cm^3). Water was added dropwise until the solution just remained opaque (~ 3 cm^3) and heated to initiate reflux; heating continued until the reaction was judged complete by TLC (typically 18 hours). The mixture was diluted with ether (5 cm^3) and aqueous saturated sodium chloride (5 cm^3), separated and the aqueous layer extracted with ether (3 × 10 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate) and evaporated under reduced pressure to give the crude product.

Method J. *tert-Butyldiphenylsilyl protection of alcohols: tert*-Butyl(chloro)diphenylsilane (0.26 cm^3, 1.20 mmol, 1.20 eq.) was added to a solution of alcohol (1.00 mmol) and imidazole (136 mg, 2.00 mmol, 2.00 eq.) dissolved in *N,N*-dimethylformamide (3 cm^3) under an atmosphere of argon at ambient temperature. The reaction was stirred until judged complete by TLC (typically 2-4 hours). Water (15 cm^3) was added and the mixture stirred vigorously for 30 minutes before being poured into ether (15 cm^3). The layers were separated and the aqueous layer extracted with ether (3 × 15 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate) and evaporated under reduced pressure to give the crude product.

Method K. *Oxidative cyclisation of dienes using (RS)-camphor-10-sulfonic acid:* Osmium$^{(VIII)}$ tetroxide (51 mg, 0.20 mmol, 0.05 eq.) was added to the diene (4.00 mmol) and (*RS*)-camphor-10-sulfonic acid (5.58 g, 24.0 mmol, 6.00 eq.) dissolved in dichloromethane (200 cm^3) at ambient temperature and stirred for 30 minutes. Trimethylamine-*N*-oxide (1.78 g, 16.0 mmol, 4.00 eq.) was added to the stirring solution and the reaction stirred until judged complete by TLC (typically 36 hours). Sodium sulfite (50 mg, 400 μmol, 0.10 eq.) was added and the mixture stirred for 1 hour before being poured into aqueous sodium hydroxide (2.0 mol dm^{-3}, 150 cm^3) and separated. The aqueous layer was extracted with ether (3 × 200 cm^3), the combined organic extracts dried (anhydrous sodium sulfate) and evaporated under reduced pressure to give the crude product.

8.3 *Chapter 4 experimental.*

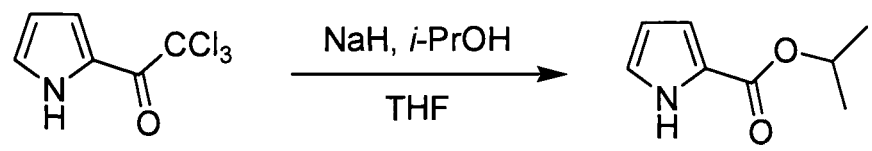
2-(Trichloroacetyl)pyrrole[292]



A solution of freshly distilled pyrrole (35.4 cm^3, 510 mmol) in ether (200 cm^3) was added dropwise over a period of 1 hour to a stirred solution of trichloroacetyl chloride (68.1 cm^3, 612 mmol, 1.20 eq.) in ether (150 cm^3) under an argon atmosphere at 0 °C. After the addition was complete, the reaction mixture was allowed to warm to ambient temperature and stirred for a further 2 hours. The reaction was cooled to 0 °C and aqueous potassium carbonate solution (50% by weight, 200 cm^3) was added slowly. The mixture was poured into ether (150 cm^3), the layers separated and the violet organic layer was washed with water (4 × 200 cm^3), aqueous saturated sodium chloride (2 × 200 cm^3) and dried (anhydrous magnesium sulfate). Evaporation under reduced pressure gave 2-(trichloroacetyl)pyrrole (103 g, 95%) as light purple needles, mp 73-75 °C (from dichloromethane-hexane)(lit.,[293] 73-75 °C); **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 9.65 (1 H, s, br, NH), 7.41-7.34 (1 H, m, ArH), 7.19-7.17 (1 H, m, ArH) and 6.40-6.34 (1 H, m, ArH); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 173.2$^-$ (CO), 127.3$^+$

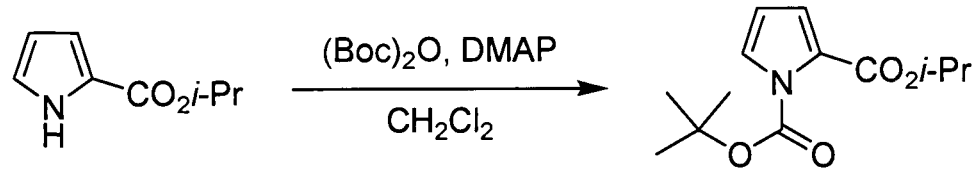
(ArC), 122.9$^-$ (ArC), 121.3$^+$ (ArC), 111.9$^+$ (ArC) and 94.9$^-$ (CCl_3). All spectroscopic data agreed with those previously published.[292]

Iso-propyl pyrrole-2-carboxylate[294]



Sodium hydride (60% dispersion in mineral oil, 1.96 g, 48.9 mmol, 1.30 eq.) was added portion-wise to a stirred solution of 2-(trichloroacetyl)pyrrole (8.00 g, 37.6 mmol) dissolved in tetrahydrofuran (200 cm^3) and *iso*-propanol (300 cm^3) under an atmosphere of argon at 0 °C. After the addition was complete the reaction was allowed to warm to ambient temperature and stirred for 4 hours. The mixture was evaporated under reduced pressure, poured into aqueous hydrochloric acid (0.1 mol dm^{-3}, 75 cm^3), separated and the aqueous layer extracted with ether (3 × 150 cm^3). The combined organic extracts were washed with aqueous saturated sodium chloride solution (50 cm^3), dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 10:90] to give *iso*-propyl pyrrole-2-carboxylate (5.01 g, 87%) as an oil; R_f [ether-light petroleum (bp 40-60 °C), 10:90] 0.17; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 9.58 (1 H, s, br, NH), 6.95-6.94 (1 H, m, ArH), 6.93-6.91 (1 H, m, ArH), 6.27-6.24 (1H, m, ArH), 5.22 (1 H, hp, *J* 6.3, OCH) and 1.34 (6 H, d, *J* 6.3, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 161.0$^-$ (CO), 123.3$^-$ (ArC), 122.7$^+$ (ArC), 115.0$^+$ (ArC), 110.2$^+$ (ArC), 67.7$^+$ (OCH) and 22.0$^+$ ($CHMe_2$). All spectroscopic data agreed with those previously published.[294]

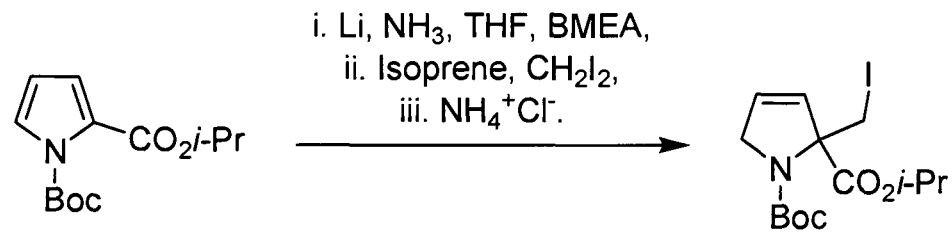
Iso-propyl 1-(_tert_-butoxycarbonyl)pyrrole-2-carboxylate[2] **213**



By method A, di-*tert*-butyl dicarbonate (5.68 g, 26.0 mmol, 1.20 eq.) dissolved in dichloromethane (20 cm^3) was added dropwise to a solution of *iso*-propyl pyrrole-2-carboxylate (3.32 g, 21.7 mmol) and 4-(dimethylamino)pyridine (530 mg, 4.34 mmol, 0.20

eq.) dissolved in dichloromethane (30 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 3:97] to give the protected pyrrole ester **213** (5.33 g, 96%) as an oil; R_f [ether-light petroleum (bp 40-60 °C), 10:90] 0.6; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.28 (1 H, dd, *J* 3.0 and 1.7, ArH), 6.79 (1 H, dd, *J* 3.5 and 1.8, ArH), 6.14 (1 H, t, *J* 3.5, ArH), 5.15 (1 H, hp, *J* 6.3, OCH), 1.57 (9 H, s, CMe_3) and 1.32 (6 H, d, *J* 6.1, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 160.3 (CO), 148.4 (NCO), 126.4 (ArC), 126.0 (ArC), 120.4 (ArC), 109.9 (ArC), 84.6 (CMe_3), 68.2 (OCH), 27.6 (CMe_3) and 21.9 ($CHMe_2$). All spectroscopic data agreed with those previously published.[2]

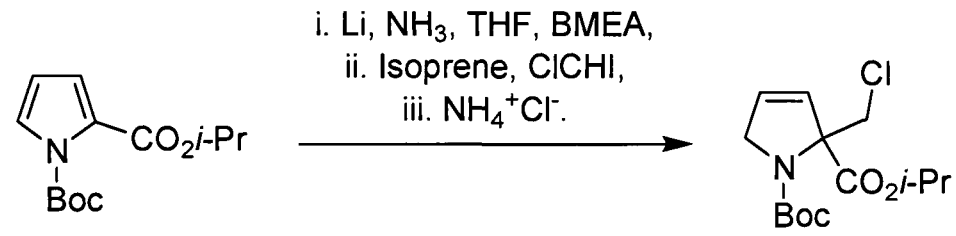
(*2RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-iodomethyl-2,5-dihydropyrrole-2-carboxylate 217



Ammonia (250 cm^3) was freshly distilled onto cut lithium wire (111 mg, 16.0 mmol, 4.00 eq.) under an atmosphere of argon at –78 °C. The resulting dark blue solution was stirred for 1 hour before the addition of *bis*(methoxyethyl)amine (5.90 cm^3, 40.0 mmol, 10.0 eq.) and tetrahydrofuran (20 cm^3). After 5 minutes *N*-Boc pyrrole **213** (1.01 g, 4.00 mmol) dissolved in tetrahydrofuran (30 cm^3) was added dropwise over 5 minutes and stirred for a further 55 minutes, the dark blue colour persisting throughout. Isoprene (~ 0.25 cm^3) was added until the dark blue colour disappeared. On addition of diiodomethane (2.26 cm^3, 28.0 mmol, 7.00 eq.) the rapidly stirring solution turned dark brown and was allowed to stir for 15 minutes before the addition of aqueous saturated ammonium chloride (5 cm^3). The reaction was allowed to warm to ambient temperature and ammonia evaporated. Aqueous citric acid (1.0 mol dm^{-3}, 125 cm^3) was added and the solution stirred for 5 minutes before being separated. The aqueous layer was extracted with ether (4 × 150 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 5:95] to give the *pyrroline* **217** (1.49 g, 94%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C), 5:95] 0.11; **IR** ν_{max} (thin film)/cm^{-1} 2978, 2933, 2866, 1727, 1704, 1391, 1258, 1217, 1177, and 1109; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 6.12, 6.06 (1H, dt, *J* 6.1 and 2.0, CH=C*H*-C), 5.42,

5.39 (1 H, dt, *J* 6.1 and 2.0, CH_2CH=CH), 4.99 (1 H, hp, *J* 6.3, OCH), 4.40, 4.12 (1 H, d, *J* 10.6, CH_AH_BI), 4.31-4.12 (2 H, m, NCH_2), 3.80, 3.76 (1 H, d, *J* 10.6, CH_AH_BI), 1.47, 1.45 (9 H, s, CMe_3) and 1.25-1.19 (6 H, m, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 168.0$^-$, 167.8$^-$ (CO), 153.1$^-$, 152.7$^-$ (NCO), 130.4$^+$, 130.2$^+$ (CH=*C*H), 129.4$^+$, 129.1$^+$ (*C*H=CH), 80.9$^-$, 80.1$^-$ (CMe_3), 75.1$^-$, 74.4$^-$ (NC), 69.9$^+$, 69.6$^+$ (OCH), 55.4$^-$, 55.2$^-$ (NCH_2), 28.4$^+$ (CMe_3), 21.7$^+$, 21.6$^+$ ($CHMe_2$) and 13.7$^-$, 13.4$^-$ (CH_2I); **MS** *m/z* (+ESI) 418 (MNa^+) and 396 (MH^+); **HRMS (ESI)** (Found MNa^+, 418.0482. $C_{14}H_{22}NO_4INa$ requires *MNa*, 418.0491).

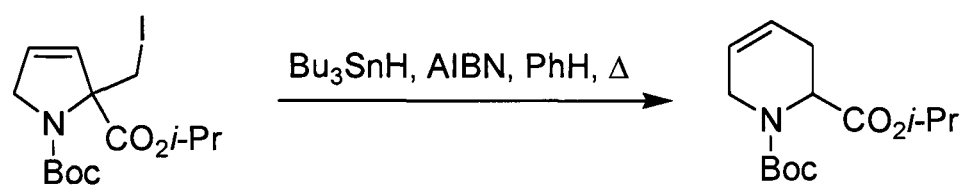
(*2RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-chloromethyl-2,5-dihydropyrrole-2-carboxylate 221



Ammonia (250 cm^3) was freshly distilled onto cut lithium wire (111 mg, 16.0 mmol, 4.00 eq.) under an atmosphere of argon at –78 °C. The resulting dark blue solution was stirred for 1 hour before the addition of *bis*(methoxyethyl)amine (5.90 cm^3, 40.0 mmol, 10.0 eq.) and tetrahydrofuran (20 cm^3). After 5 minutes *N*-Boc pyrrole **213** (1.01 g, 4.00 mmol) dissolved in tetrahydrofuran (30 cm^3) was added dropwise over 5 minutes and stirred for a further 55 minutes, the dark blue colour persisting throughout. Isoprene (~ 0.25 cm^3) was added until the dark blue colour disappeared. On addition of 1,1-chloro-iodo-methane (2.04 cm^3, 28.0 mmol, 7.00 eq.) the rapidly stirring solution turned light green and was allowed to stir for 10 minutes before the addition of aqueous saturated ammonium chloride (5 cm^3). The reaction was allowed to warm to ambient temperature and ammonia evaporated. Aqueous citric acid (1.0 mol dm^{-3}, 125 cm^3) was added and the solution stirred for 5 minutes before being separated. The aqueous layer was extracted with ether (4 × 150 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 5:95] to give the *pyrroline* **221** (1.13 g, 93%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C), 5:95] 0.25; **IR** ν_{max} (thin film)/cm^{-1} 2980, 1731, 1703, 1394, 1321, 1283, 1262, 1228, 1178, 1152, 1118. 1043, 995, 910, 774 and 717; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 6.10, 6.04 (1H, dt, *J* 6.2 and 1.9, CH=C*H*-C), 5.50, 5.47 (1 H, dt, *J* 6.2 and 2.2, CH_2CH=CH), 5.00 (1 H, hp, *J*

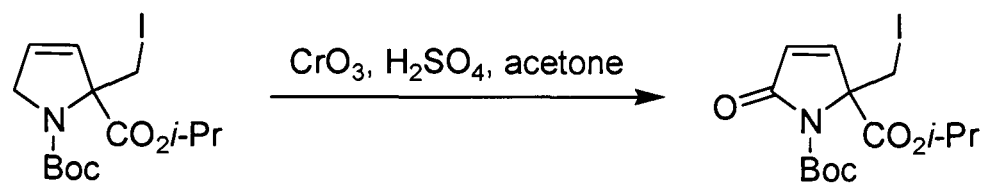
6.2, OCH), 4.51, 4.26 (1 H, d, *J* 11.6, CH_AH_BCl), 4.36-4.13 (2 H, m, NCH_2), 4.01, 3.97 (1 H, d, *J* 11.6, CH_AH_BCl), 1.46, 1.44 (9 H, s, CMe_3) and 1.25-1.19 (6 H, m, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 169.6$^-$, 169.4$^-$ (CO), 153.2$^-$, 152.7$^-$ (NCO), 130.5$^+$, 130.4$^+$ (CH=*C*H), 127.3$^+$ (*C*H=CH), 80.9$^-$, 80.1$^-$ (CMe_3), 75.8$^-$, 75.0$^-$ (NC), 69.6$^+$, 69.3$^+$ (OCH), 55.4$^-$, 55.2$^-$ (NCH_2), 46.8$^-$, 46.0$^-$ (CH_2Cl), 28.4$^+$, 28.3$^+$ (CMe_3) and 21.7$^+$, 21.6$^+$ ($CHMe_2$); **MS** *m/z* (+ESI) 326, 328 (100% MNa^+); **HRMS (ESI)** (Found MNa^+, 326.1137. $C_{14}H_{22}NO_4{}^{35}ClNa$ requires *MNa*, 326.1135).

(*2RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-3,6-dihydropyridine-2-carboxylate 219



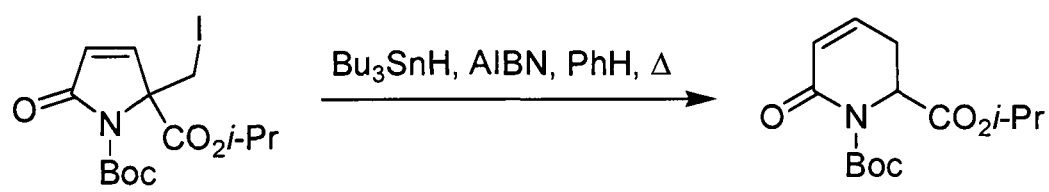
By method B, tri-*n*-butyltin hydride (0.318 cm^3, 1.20 mmol, 1.30 eq.) and AIBN (39 mg, 240 μmol, 0.20 eq.) dissolved in deoxygenated benzene (10 cm^3) were added over a 12 hour period *via* syringe pump to a refluxing solution of pyrroline **217** (365 mg, 923 μmol) dissolved in deoxygenated benzene (50 cm^3); heating continued for a further 12 hours to give a crude product. The residue was dissolved in ether (5 cm^3) and addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (0.448 cm^3, 3.00 mmol, 3.30 eq.) gave a white precipitate. This mixture was titrated with an ethereal iodine solution (0.1 mol dm^{-3}) until the colour just persisted, filtered through a short pad of silica eluting with ether and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60°C), 5:95] to give the *tetrahydropyridine* **219** (194 mg, 78%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C) 5:95] 0.15; **IR** ν_{max} (thin film)/cm^{-1} 2977, 2931, 1736, 1703, 1402, 1366, 1174, 1107, 1056 and 1018; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.74-5.59 (2 H, m, CH=CH), 5.04-4.94 (1.5 H, m, NCH and OCH), 4.79 (0.5 H, apparent d, *J* 6.6, OCH), 4.08-3.99 (1 H, m, NCH_AH_B), 3.81-3.68 (1 H, m, NCH_AH_B), 2.66-2.60 (1 H, m, CH=CHCH_AH_B), 2.49-2.42 (1 H, m, CH=CHCH_AH_B), 1.47, 1.44 (9 H, s, CMe_3) and 1.20, 1.18 (6 H, d, *J* 6.1, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 171.3, 171.1 (CO), 155.9, 155.2 (NCO), 124.2, 124.0 (*C*H=CH), 122.3, 121.9 (CH=*C*H), 80.0 (CMe_3), 68.6 (OCH), 52.5, 51.2 (NCH), 42.3, 41.6 (NCH_2), 28.3 (CMe_3), 26.6 (NCH*C*H$_2$), 21.7 ($CHMe_2$); **MS** *m/z* (+ESI) 292 (100%, MNa^+) and 170 (M - CO_2CMe_3); **HRMS (ESI)** (Found MNa^+, 292.1526. $C_{14}H_{23}NO_4Na$ requires *MNa*, 292.1525).

(*2RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-iodomethyl-5-oxo-2,5-dihydropyrrole-2-carboxylate 222



By method C, chromium$^{(VI)}$ trioxide (500 mg, 5.00 mmol, 5.00 eq.) dissolved in aqueous sulfuric acid (2.0 mol dm^{-3}, 2.0 cm^3) was added to a solution of pyrroline **217** (395 mg, 1.00 mmol) dissolved in acetone (5 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60°C), 10:90] to give the *lactam* **222** (290 mg, 71%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C) 20:80] 0.61; **IR** ν_{max} (thin film)/cm^{-1} 2982, 1788, 1754, 1712, 1370, 1323, 1252, 1161, 1105, 1066, 974, 842 and 825; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 6.67 (1 H, d, *J* 5.9, NCCH), 6.33 (1 H, d, *J* 6.0, NCOCH), 5.04 (1 H, hp, *J* 6.3, OCH), 4.25 (1 H, d, *J* 11.0, C*H*$_A$H$_B$I), 3.86 (1 H, d, *J* 11.0, CH$_A$*H*$_B$I), 1.54 (9 H, s, CMe_3) 1.23 (3 H, d, *J* 6.3, CH*Me*$_A$Me$_B$) and 1.20 (3 H, d, *J* 6.3, CHMe$_A$*Me*$_B$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 167.7$^-$ (CO), 164.9$^-$ (CO), 148.4$^-$ (NCO), 147.3$^+$ (CH=*C*H), 129.6$^+$ (*C*H=CH), 84.1$^-$ (CMe_3), 71.6$^-$ (NC), 71.3$^+$ (OCH), 28.0$^+$ (CMe_3), 21.5$^+$ ($CHMe_2$) and 7.17$^-$ (CH_2I); **MS** *m/z* (+ESI) 432 (100%, MNa^+), 410 (MH^+) and 310 (M - CO_2CMe_3); **HRMS (ESI)** (Found MH^+, 410.0460. $C_{14}H_{21}NO_5I$ requires *MH*, 410.0465); **Elemental analysis** (Found C, 40.98; H, 4.81; N, 3.32. $C_{14}H_{20}INO_5$ requires C, 41.09; H, 4.93; N, 3.42%).

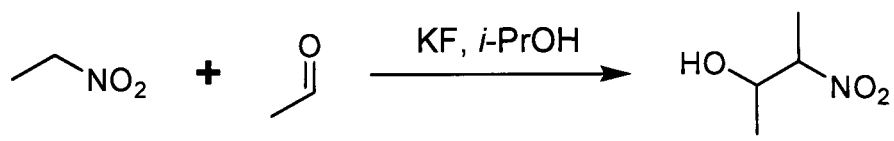
(*2RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-6-oxo-3,6-dihydropyridine-2-carboxylate 223



By method B, tri-*n*-butyltin hydride (60% solution, 0.140 cm^3, 316 μmol, 1.20 eq.) and AIBN (9.0 mg, 54 μmol, 0.20 eq.) dissolved in deoxygenated benzene (10 cm^3) were added over a 12 hour period *via* syringe pump to a refluxing solution of lactam **222** (107 mg, 270 μmol) dissolved in deoxygenated benzene (50 cm^3); heating continued for a further 12 hours to give a crude product. The residue was dissolved in aqueous sodium hydroxide (1.0 mol dm^{-3} 10

cm^3), stirred for 30 minutes, poured into ether (30 cm^3), separated and the aqueous layer extracted with ether (2 × 30 cm^3). The combined organic extracts were washed with aqueous potassium fluoride solution (10% by weight, 4 × 40 cm^3), dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, light petroleum (bp 40-60 °C), followed by ethyl acetate-light petroleum (bp 40-60 °C), 20:80] to give the *lactam* **223** (63 mg, 82%) as an off white solid, mp 37-39 °C [from light petroleum (bp 40-60 °C)]; R_f [ethyl acetate-light petroleum (bp 40-60 °C), 20:80] 0.5; **IR** ν_{max} (solution cell)/cm^{-1} 2982, 2936, 1773, 1721 br, 1457, 1388, 1369, 1297, 1240, 1160, 1107, 1045, 1001, 929 and 817; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 6.59 (1 H, ddd, *J* 6.1, 2.3 and 1.0, CCH=C*H*), 5.95 (1 H, dd, *J* 9.9 and 2.5, CC*H*=CH), 5.03 (1 H, hp, *J* 6.3, OCH), 5.00-4.97 (1 H, m, NCH), 2.87 (1 H, ddd, *J* 18.5, 6.0 and 1.5, CH_AH_B), 2.76 (1 H, ddt, *J* 18.5, 6.6 and 2.6, CH_AH_B), 1.53 (9 H, s, CMe_3) 1.20 (3 H, d, *J* 6.3, CHMe$_A$*Me*$_B$) and 1.20 (3 H, d, *J* 6.3, CHMe$_A$*Me*$_B$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 170.1 (CO), 162.5 (NCO), 152.2 (NCO), 139.6 (CH=*C*H), 126.7 (*C*H=CH), 83.5 (CMe_3), 69.8 (OCH), 55.8 (NCH), 28.0 (CMe_3), 27.2 (CH_2) and 21.6 ($CHMe_2$); **MS** *m/z* (+ESI) 589 ($2MNa^+$), 347 (100%, $MNaMeCN^+$) and 247 ($MNaMeCN^+$ - CO_2CMe_3); **HRMS (ESI)** (Found MNa^+, 306.1316. $C_{14}H_{21}NO_5Na$ requires *MNa*, 306.1317); **Elemental analysis** (Found C, 59.07; H, 7.55; N, 4.81. $C_{14}H_{20}INO_5$ requires C, 59.35; H, 7.47; N, 4.94%).

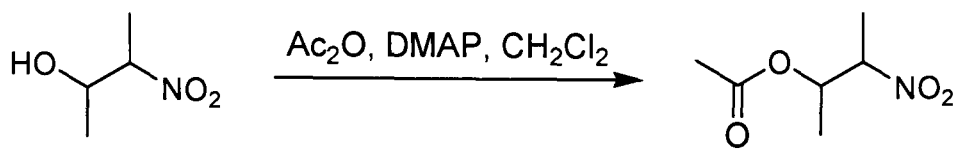
(*RS*)-(*SR*)-3-Nitro-2-butanol[176]



1-Nitroethane (6.03 cm^3, 84.0 mmol) was added dropwise to a solution of acetaldehyde (2.77 cm^3, 84.0 mmol) and potassium fluoride (244 mg, 4.20 mmol, 0.05 eq.) dissolved in *iso*-propanol (30 cm^3) under an atmosphere of argon at 0 °C and stirred for 45 minutes. The reaction was allowed to warm to ambient temperature and stirred for 18 hours. The mixture was filtered, the white filtrate evaporated under reduced pressure and poured into water (200 cm^3). After separation, the aqueous layer was extracted with ether (3 × 120 cm^3), the combined organics were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 20:80] to give 3-nitro-2-butanol (4.88 g, 49%) as a 1:1 mixture of diastereoisomers as a

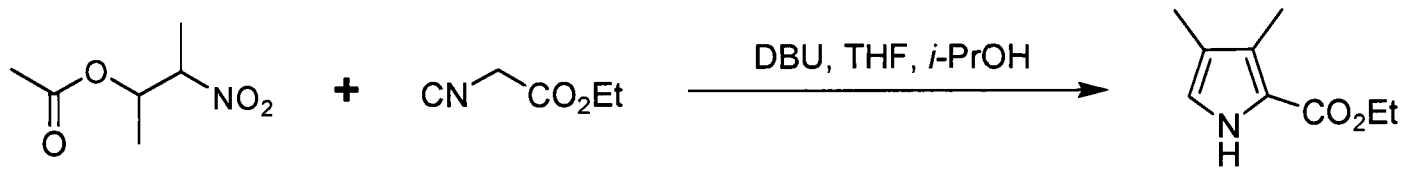
liquid; R_f [Ethyl acetate-light petroleum (bp 40-60 °C), 20:80] 0.6; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 4.50-4.40 (1 H, m, $CHNO_2$), 4.33-4.27 (0.5 H, m, CHOH), 4.13-4.06 (0.5 H, m, CHOH), 2.84 (1 H, s, br, OH), 1.51, 1.48 (3 H, d, *J* 6.8, $CHNO_2Me$) and 1.22, 1.20 (3 H, d, *J* 6.5, CHOHMe); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 88.9$^+$, 87.1$^+$ ($CHNO_2$), 69.2$^+$, 68.3$^+$ (CHOH), 19.2$^+$, 18.8$^+$ (CHOHMe) and 16.0$^+$, 12.6$^+$ ($CHNO_2Me$). All spectroscopic data agreed with those previously published.[176]

(*RS*)-(*SR*)-3-Nitro-2-acetoxyl-butane[176] 229



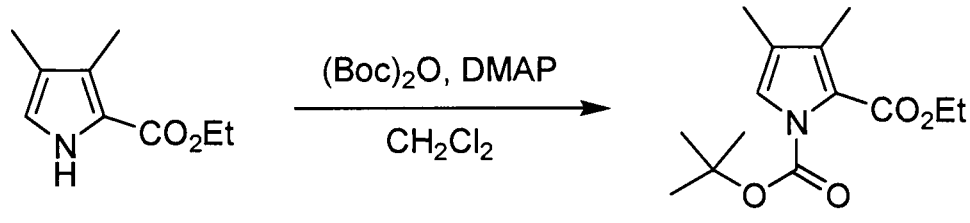
(*RS*)-(*SR*)-3-Nitro-2-butanol (25.0 g, 210 mmol) was added dropwise to solution of acetic anhydride (29.7 cm^3, 315 mmol, 1.50 eq.) and 4-(dimethylamino)pyridine (333 mg, 2.73 mmol, 0.01 eq.) dissolved in dichloromethane (30 cm^3) under an atmosphere of argon at ambient temperature and stirred for 18 hours. Methanol (90 cm^3) was added and the reaction stirred for 1 hour. The mixture was poured into aqueous sodium bicarbonate solution (10% by weight, 100 cm^3), the layers separated and the aqueous layer extracted with dichloromethane (3 × 70 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate), filtered through a short pad of silica eluting with ether and evaporated under reduced pressure to give the protected nitro alcohol **229** (33.7 g, 100%) in a 1:1 mixture of diastereoisomers as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.34-5.23 (1 H, m, CHOAc), 4.66-4.59 (1 H, m, $CHNO_2$), 2.1, 1.9 (3 H, s, $COCH_3$), 1.58-1.49 (3 H, m, CHOAc*Me*) and 1.37-1.33 (3 H, m, $CHNO_2$*Me*); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 169.9$^-$, 169.7$^-$ (CO), 85.5$^+$, 84.5$^+$ ($CHNO_2$), 70.6$^+$, 69.9$^+$ (CHOAc), 20.8$^+$, 20.6$^+$ ($COCH_3$), 16.1$^+$, 15.6$^+$ (CHOAcMe) and 13.6$^+$ ($CHNO_2Me$). All spectroscopic data agreed with those previously published.[176]

Ethyl 3,4-dimethyl pyrrole-2-carboxylate[176]



1,8-Diazabicyclo[5.4.0]undec-7-ene (30.4 cm^3, 203 mmol, 2.30 eq.) was added dropwise to a solution of acetylated nitroalcohol **229** (18.5 g, 115 mmol, 1.30 eq.) and ethyl isocyanoacetate (9.66 cm^3, 88.4 mmol) dissolved in tetrahydrofuran (80 cm^3) under an atmosphere of argon at 0 °C. The mixture stirred for 10 minutes, then *iso*-propanol (50 cm^3) was added and the solution was allowed to warm to ambient temperature before being stirred for 26 hours. The mixture was evaporated under reduced pressure, the residue dissolved in dichloromethane (250 cm^3) and washed successively with water (3 × 200 cm^3), aqueous hydrochloric acid (2.0 mol dm^{-3}, 3 × 200 cm^3), water (2 × 200 cm^3), aqueous saturated sodium bicarbonate (200 cm^3) and aqueous aqueous saturated sodium chloride (200 cm^3). The organic layer was dried (anhydrous magnesium sulfate) and evaporated under reduced pressure to give ethyl 3,4-dimethyl pyrrole-2-carboxylate (6.86 g, 51%) as prisms, mp 92-94 °C (from dichloromethane-hexane)(lit.,[295] 94-95 °C); R_f [ethyl acetate-light petroleum (bp 40-60 °C), 10:90] 0.4; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 8.80 (1 H, s, br, NH), 6.66 (1 H, d, *J* 2.8, NCH), 4.31 (2 H, q, *J* 7.1, OCH_2), 2.27 (3 H, s, NCCMe), 2.01 (3 H, d, *J* 0.8, NCHCMe) and 1.35 (3 H, t, *J* 7.1, CH_2CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 161.8$^-$ (CO), 126.5$^-$ (ArC), 120.5$^-$ (ArC), 120.2$^+$ (ArC), 119.2$^-$ (ArC), 59.8$^-$ (OCH_2), 14.5$^+$ (CH_2CH_3), 10.2$^+$ (CMe) and 9.9$^+$ (CMe). All spectroscopic data agreed with those previously published.[176]

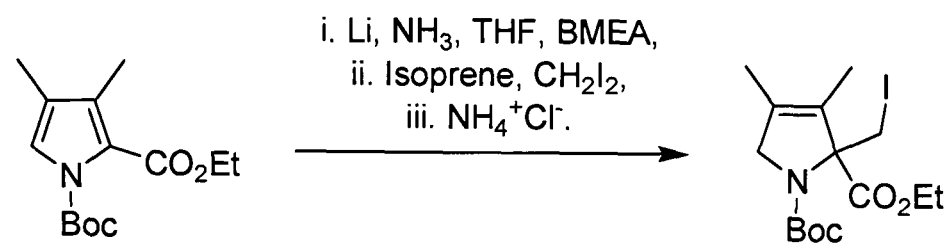
Ethyl 1-(*tert*-butoxycarbonyl)-3,4-dimethyl pyrrole-2-carboxylate 230



By method A, di-*tert*-butyl dicarbonate (2.06 g, 9.44 mmol, 1.20 eq.) dissolved in dichloromethane (10 cm^3) was added dropwise to a solution of ethyl 3,4-dimethyl pyrrole-2-carboxylate (1.32 g, 7.87 mmol) and 4-(dimethylamino)pyridine (192 mg, 1.57 mmol, 0.20 eq.) dissolved in dichloromethane (15 cm^3) to give a crude product. The residue was

chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 10:90] to give the *protected pyrrole ester* **230** (1.89 g, 90%) as a viscous oil; R_f [ether-light petroleum (bp 40-60 °C), 10:90] 0.3; **IR** ν_{max} (thin film)/cm^{-1} 2981, 1742, 1718, 1415, 1392, 1370, 1342, 1248, 1159 and 1075; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 6.98 (1 H, s, NCH), 4.30 (2 H, q, *J* 7.1, OCH_2), 2.09 (3 H, s, NCCMe), 1.94 (3 H, d, *J* 1.3, NCHCMe), 1.53 (9H, s, CMe_3) and 1.34 (3 H, t, *J* 7.1, CH_2CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 162.1$^-$ (CO), 148.5$^-$ (NCO), 130.4$^-$ (ArC), 122.2$^+$ (ArC), 122.1$^-$ (ArC), 121.3$^-$ (ArC), 83.7$^-$ (CMe_3), 60.6$^-$ (OCH_2), 27.7$^+$ (CMe_3), 14.2$^+$ (CH_2CH_3), 9.9$^+$ (CMe) and 9.8$^+$ (CMe); **MS** *m/z* (+ESI) 306 (100%, MK^+); **HRMS (ESI)** (Found MK^+, 306.1103. $C_{14}H_{21}NO_4K$ requires *MK*, 306.1108).

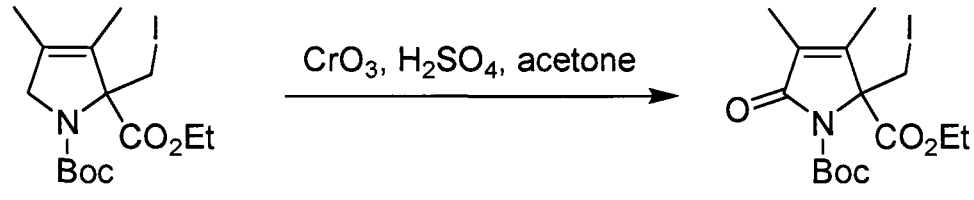
(*2RS*)-Ethyl 1-(*tert*-butoxycarbonyl)-2-iodomethyl-3,4-dimethyl-2,5-dihydropyrrole-2-carboxylate 231



Ammonia (100 cm^3) was freshly distilled onto cut lithium wire (55.5 mg, 8.00 mmol, 4.00 eq.) under an atmosphere of argon at –78 °C. The resulting dark blue solution was stirred for 1 hour before the addition of *bis*(methoxyethyl)amine (8.50 cm^3, 60.0 mmol, 30.0 eq.) and tetrahydrofuran (10 cm^3). After 5 minutes *N*-Boc pyrrole **230** (535 mg, 2.00 mmol) dissolved in tetrahydrofuran (25 cm^3) was added dropwise over 5 minutes and stirred for a further 2.5 hours, the dark blue colour persisting throughout. Isoprene (~ 0.25 cm^3) was added until the dark blue colour disappeared. On addition of diiodomethane (1.13 cm^3, 14.0 mmol, 7.00 eq.) the rapidly stirring solution turned dark brown and was allowed to stir for 45 minutes before the addition of aqueous saturated ammonium chloride (5 cm^3). The reaction was allowed to warm to ambient temperature and ammonia evaporated. Aqueous citric acid (1.0 mol dm^{-3}, 125 cm^3) was added and the solution stirred for 5 minutes before being separated. The aqueous layer was extracted with ether (4 × 150 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 5:95] to give the *pyrroline* **231** (666 mg, 81%) as an oil; R_f [ether-light petroleum (bp 40-60 °C), 10:90] 0.17; **IR** ν_{max} (thin film)/cm^{-1} 2977, 2935, 2858, 1730, 1708, 1394, 1231, 1173, 1126, 1096, 1072

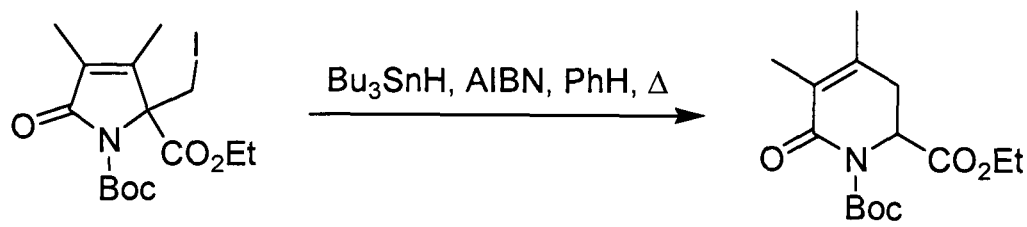
and 1026; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 4.39, 4.10 (1 H, d, *J* 10.8, CH_AH$_B$I), 4.25, 4.23 (2 H, q, *J* 7.1, OCH_2), 4.10-3.90 (2 H, m, NCH_2), 3.80, 3.78 (1 H, d, *J* 10.1, CH_AH_BI), 1.73, 1.71 (3 H, d, *J* 1.0, NCCMe), 1.50, 1.48 (3 H, d, *J* 1.0, NCH_2CMe), 1.46, 1.43 (9 H, s, CMe_3) and 1.24, 1.21 (3 H, t, *J* 7.1, CH_2CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 168.8$^-$ (CO), 153.1$^-$, 152.5$^-$ (NCO), 132.6$^-$, 132.4$^-$ (*C*=C), 127.7$^-$, 127.3$^-$ (C=*C*), 80.6$^-$, 80.0$^-$ (CMe_3), 79.9$^-$, 76.7$^-$ (NC), 61.7$^-$ (OCH_2), 58.0$^-$ (NCH_2), 28.4$^+$ (CMe_3), 14.2$^+$, 14.1$^+$ (CH_2CH_3), 12.9$^-$, 12.7$^-$ (CH_2I), 11.6$^+$ (CMe) and 8.8$^+$, 8.7$^+$ (CMe); **MS** *m/z* (+ESI) 473 (100%, $MMeCNNa^+$); **HRMS (ESI)** (Found $MMeCNNa^+$, 473.0920. $C_{17}H_{27}N_2O_4NaI$ requires *MMeCNNa*, 473.0913).

(*2RS*)-Ethyl 1-(*tert*-butoxycarbonyl)-2-iodomethyl-3,4-dimethyl-5-oxo-2,5-dihydropyrrole-2-carboxylate 233



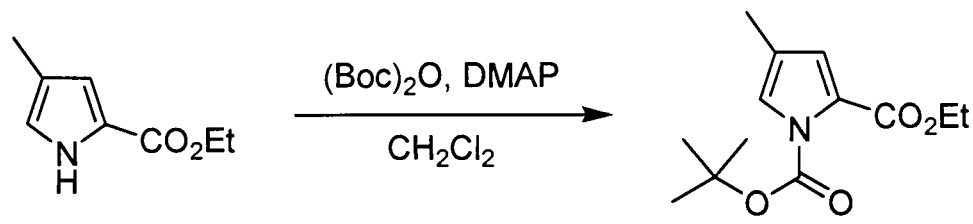
By method C, chromium$^{(VI)}$ trioxide (700 mg, 7.00 mmol, 7.00 eq.) dissolved in aqueous sulfuric acid (2.0 mol dm^{-3}, 3.0 cm^3) was added to a solution of pyrroline **231** (409 mg, 1.00 mmol) dissolved in acetone (5 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60°C), 10:90] to give the *lactam* **233** (351 mg, 82%) as a viscous oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C) 10:90] 0.19; **IR** ν_{max} (thin film)/cm^{-1} 2980, 1727, 1712, 1707, 1680, and 1237; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 4.26 (1 H, d, *J* 11.2, CH_AH$_B$I), 4.25, 4.24 (1 H, dq, *J* 10.6 and 7.1, OCH_AH$_B$), 4.12, 4.11 (1 H, dq, *J* 10.6 and 7.1, OCH_AH_B), 3.83 (1 H, d, *J* 11.2, CH_AH_BI), 1.86 (3 H, s, NCCMe), 1.82 (3 H, s, NCCCMe), 1.53 (9 H, s, CMe_3) and 1.22 (3 H, t, *J* 7.1, CH_2CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 168.8$^-$ (CO), 165.9$^-$ (NCO), 148.9$^-$ (NCO), 148.8$^-$ (*C*=C), 132.4$^-$ (C=*C*), 83.7$^-$ (CMe_3), 71.8$^-$ (NC), 62.8$^-$ (OCH_2), 28.0$^+$ (CMe_3), 14.0$^+$ (OCH_2CH_3), 10.1$^+$ (CMe), 8.8$^+$ (CMe) and 7.5$^-$ (CH_2I); **MS** *m/z* (+ESI) 885 (100%, $2MK^+$) and 462 (MK^+); **HRMS (ESI)** (Found MH^+, 424.0632. $C_{15}H_{23}NO_5I$ requires *MH*, 424.0621).

(2*RS*)-Ethyl 1-(*tert*-butoxycarbonyl)-6-oxo-4,5-dimethyl-3,6-dihydropyridine-2-carboxylate 234



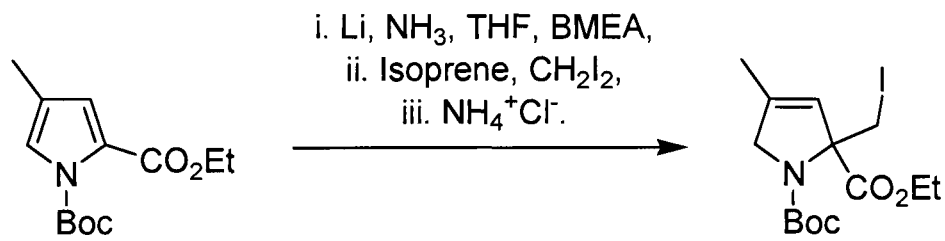
By method B, tri-*n*-butyltin hydride (0.053 cm^3, 199 μmol, 1.20 eq.) and AIBN (5 mg, 33.0 μmol, 0.20 eq.) dissolved in deoxygenated benzene (10 cm^3) were added over a 12 hour period *via* syringe pump to a refluxing solution of lactam **233** (70 mg, 165 μmol) dissolved in deoxygenated benzene (20 cm^3); heating continued for a further 12 hours. On cooling tetra-*n*-butylammonium fluoride (1.0 mol dm^{-3} solution in tetrahydrofuran, 0.2 cm^3, 200 μmol), was added and the mixture heated to reflux for 4 hours before being allowed to cool to ambient temperature. The mixture was evaporated under reduced pressure, the residue dissolved in ether (10 cm^3), poured into water (5 cm^3) and the layers separated. The aqueous layer was extracted with ether (2 × 5 cm^3), the combined organics were dried (anhydrous magnesium sulfated) and evaporated under reduced pressure. The residue was dissolved in acetonitrile (5 cm^3) and partitioned with hexane (4 × 5 cm^3) and the acetonitrile layer was evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 20:80] to give the *lactam* **234** (32 mg, 65%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C), 20:80] 0.19; **IR** ν_{max} (thin film)/cm^{-1} 2980, 1727 br, 1714, 1368, 1298 and 1156; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 4.93 (1 H, dd, *J* 6.4 and 2.1, NCH), 4.17 (2 H, q, *J* 7.1, OCH_2), 2.84-2.78 (1 H, dm, $CHCH_AH_B$), 2.68 (1 H, d, *J* 17.6, $CHCH_AH_B$), 1.88 (3 H, s, NCCCMe), 1.84 (3 H, s, NCCMe), 1.54 (9 H, s, CMe_3) and 1.21 (3 H, t, *J* 7.1, OCH_2CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 170.9$^-$ (CO), 163.8$^-$ (NCO), 152.9$^-$ (NCO), 143.8$^-$ (C=*C*), 126.8$^-$ (*C*=C), 83.2$^-$ (CMe_3), 61.7$^-$ (OCH_2), 55.0$^+$ (NCH), 33.0$^-$ ($NCHCH_2$), 28.0$^+$ (CMe_3), 20.4$^+$ (CMe), 14.1$^+$ (CH_2CH_3) and 12.3$^+$ (CMe); **MS** *m/z* (+ESI) 336 (100%, MK^+) and 320 (MNa^+); **HRMS (ESI)** (Found MK^+, 336.1216. $C_{15}H_{23}NO_5K$ requires *MK*, 336.1213).

Ethyl 1-(*tert*-butoxycarbonyl)-4-methyl pyrrole-2-carboxylate 235



By method A, di-*tert*-butyl dicarbonate (5.06 g, 23.2 mmol, 1.20 eq.) dissolved in dichloromethane (20 cm^3) was added dropwise to a solution of ethyl 4-methyl pyrrole-2-carboxylate* (2.96 g, 19.3 mmol) and 4-(dimethylamino)pyridine (470 mg, 3.87 mmol, 0.20 eq.) dissolved in dichloromethane (20 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 7:93] to give the *protected pyrrole ester* **235** (4.40 g, 90%) as an oil; R_f [ether-light petroleum (bp 40-60 °C), 5:95] 0.27; **IR** ν_{max} (thin film)/cm^{-1} 2977,1750, 1721, 1370, 1326, 1256, 1157, 1070, 849 and 774; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.06-7.05 (1 H, m, ArH), 6.65 (1 H, d, *J* 1.8, ArH), 4.27 (2 H, q, *J* 7.1, OCH_2), 2.02 (3 H, d, *J* 1.0, CCH_3), 1.55 (9 H, s, CMe_3) and 1.32 (3 H, t, *J* 7.1, CH_2CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 160.9 (CO), 148.3 (NCO), 125.3 (ArC), 124.0 (ArC), 122.4 (ArC), 120.5 (ArC), 84.2 (CMe_3), 60.7 (OCH_2), 27.7 (CMe_3), 14.2 (CH_2CH_3) and 11.4 (ArCMe); **MS** *m/z* (+ESI) 529 ($2MNa^+$), 317 (100%, $MMeCNNa^+$) and 276 (MNa^+); **HRMS (ESI)** (Found MNa^+, 276.1214. $C_{13}H_{19}NO_4Na$ requires *MNa*, 276.1212).

(*2RS*)-Ethyl 1-(*tert*-butoxycarbonyl)-2-iodomethyl-4-methyl-2,5-dihydropyrrole-2-carboxylate 236

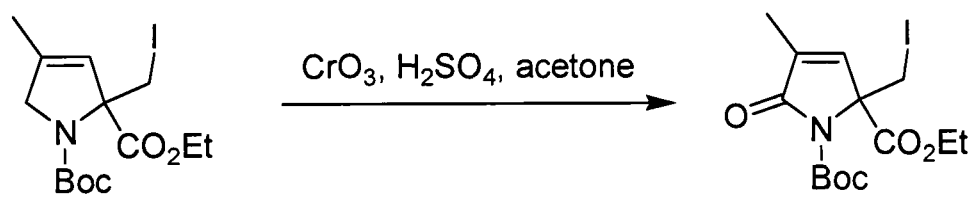


Ammonia (200 cm^3) was freshly distilled onto cut lithium wire (111 mg, 16.0 mmol, 4.00 eq.) under an atmosphere of argon at –78 °C. The resulting dark blue solution was stirred for 1 hour before the addition of *bis*(methoxyethyl)amine (17.7 cm^3, 120 mmol, 30.0 eq.) and tetrahydrofuran (20 cm^3). After 5 minutes *N*-Boc pyrrole **235** (1.01 g, 4.00 mmol) dissolved

* Prepared by Graeme Freestone within our Laboratories using the Barton-Zard method with 2-Nitro-3-acetoxyl-propane and ethyl isocyanoacetate.

in tetrahydrofuran (25 cm^3) was added dropwise over 5 minutes and stirred for a further 2 hours, the dark blue colour persisting throughout. Isoprene (~ 0.25 cm^3) was added until the dark blue colour disappeared. On addition of diiodomethane (4.51 cm^3, 28.0 mmol, 7.00 eq.) the rapidly stirring solution turned dark brown and was allowed to stir for 40 minutes before the addition of aqueous saturated ammonium chloride (5 cm^3). The reaction was allowed to warm to ambient temperature and ammonia evaporated. Aqueous citric acid (1.0 mol dm^{-3}, 125 cm^3) was added and the solution stirred for 5 minutes before being separated. The aqueous layer was extracted with ether (4 × 150 cm^3), the combined organic extracted were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 7:93] to give the *pyrroline* **236** (1.40 g, 89%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C), 10:90] 0.35; **IR** ν_{max} (thin film)/cm^{-1} 2936, 2930, 2836, 1733, 1707, 1448, 1393, 1367, 1273, 1233, 1168, 1116, 1073 and 962; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.08, 5.03 (1 H, dd, *J* 3.3 and 1.6, C=CH), 4.38, 4.08 (1 H, d, *J* 10.6, CH_AH$_B$I), 4.27-4.01 (4 H, m, NCH_2 and OCH_2), 3.79, 3.75 (1 H, d, *J* 10.6, CH_AH_BI), 1.83, 1.81 (3 H, d, *J* 1.3, CCH_3), 1.47, 1.43 (9 H, s, CMe_3) and 1.25, 1.23 (3 H, t, *J* 7.1, CH_2CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 169.0$^-$ (CO), 153.0$^-$, 152.5$^-$ (NCO), 140.8$^-$, 140.5$^-$ (*C*=CH), 123.5$^+$, 123.1$^+$ (C=*C*H), 80.7$^-$, 80.1$^-$ (CMe_3), 75.2$^-$, 74.6$^-$ (NC), 61.9$^-$, 61.8$^-$ (OCH_2), 58.2$^-$ (NCH_2), 28.4$^+$, 28.3$^+$ (CMe_3), 14.6$^-$, 14.2$^-$ (CH_2I), 14.1$^+$ (CCH_3) and 14.1$^+$ (CH_2CH_3); **MS** *m/z* (+ESI) 459 (100%, MMeCNNa$^+$), 396 (MH^+), 340 (MH^+ - CMe_3) and 296 (MH^+ - CO_2CMe_3); **HRMS (ESI)** (Found MMeCNNa$^+$, 459.0753. $C_{16}H_{25}N_2O_4NaI$ requires *MMeCNNa*, 459.0757).

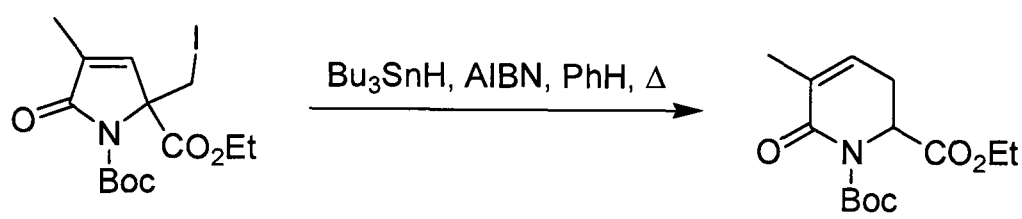
(*2RS*)-Ethyl 1-(*tert*-butoxycarbonyl)-2-iodomethyl-4-methyl-5-oxo-2,5-dihydropyrrole-2-carboxylate 237



By method C, chromium$^{(VI)}$ trioxide (1.05 g, 10.5 mmol, 7.00 eq.) dissolved in aqueous sulfuric acid (2.0 mol dm^{-3}, 2.0 cm^3) was added to a solution of pyrroline **236** (455 mg, 1.50 mmol) dissolved in acetone (5 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60°C), 10:90] to give the *lactam* **237** (306 mg, 68%) as a viscous oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C) 10:90]

0.25; **IR** ν_{max} (thin film)/cm^{-1} 2982, 1785, 1739, 1714, 1369, 1332, 1235, 1158, 1058 and 1020; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 6.40 (1 H, d, *J* 1.8, CH), 4.24, 4.23 (1 H, dq, *J* 10.6 and 7.1, OCH_AH_B), 4.23 (1 H, d, *J* 10.9, CH_AH_BI), 4.13, 4.12 (1 H, dq, *J* 10.6 and 7.1, OCH$_A H_B$), 3.86 (1 H, d, *J* 10.9, CH$_A H_B$I), 1.94 (3 H, d, *J* 1.3, CCH_3), 1.53 (9 H, s, CMe_3) and 1.23 (3 H, t, *J* 7.1, CH_2CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 168.5$^-$ (CO), 166.1$^-$ (NCO), 148.6$^-$ (NCO), 140.4$^+$ (CH), 138.1$^-$ (*C*=C), 83.9$^-$ (CMe_3), 69.3$^-$ (NC), 62.9$^-$ (OCH_2), 28.0$^+$ (CMe_3), 14.0$^+$ (CH_2CH_3), 10.9$^+$ (CCH_3) and 8.3$^-$ (CH_2I); **MS** *m/z* (+ESI) 841 (100%, 2MNa$^+$) and 432 (MNa$^+$); **HRMS (ESI)** (Found MMeCNNa$^+$, 473.0562. $C_{16}H_{23}N_2O_5NaI$ requires *MMeCNNa*, 473.0549).

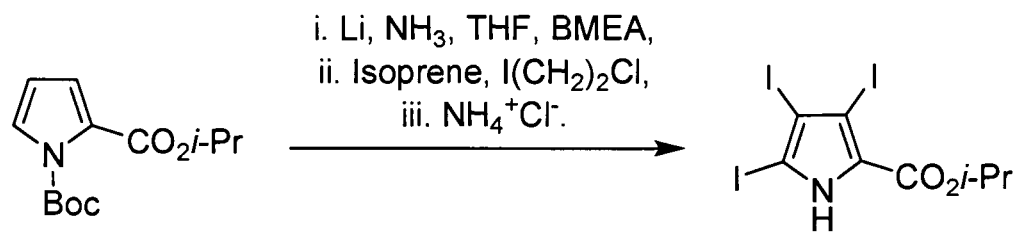
(2*RS*)-Ethyl 1-(*tert*-butoxycarbonyl)-6-oxo-5-methyl-3,6-dihydropyridine-2-carboxylate 238



By method B, tri-*n*-butyltin hydride (0.096 cm^3, 362 μmol, 1.30 eq.) and AIBN (9.0 mg, 56.0 μmol, 0.20 eq.) dissolved in deoxygenated benzene (10 cm^3) were added over a 12 hour period *via* syringe pump to a refluxing solution of lactam **237** (70 mg, 165 μmol) dissolved in deoxygenated benzene (20 cm^3); heating continued for a further 12 hours to give a crude product. The residue dissolved in ether (10 cm^3), titrated with an ethereal iodine solution (0.1 mol dm^{-3}) until the colour just persisted and stirred vigorously with aqueous potassium fluoride solution (10% by weight, 20 cm^3) for 20 minutes. The mixture was filtered through celite, separated and the organic layer washed with aqueous potassium fluoride solution (10% by weight, 3 × 10 cm^3), dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, light petroleum (bp 40-60 °C) then ethyl acetate-light petroleum (bp 40-60 °C), 20:80] to give the *lactam* **238** (51 mg, 64%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C), 10:90] 0.32; **IR** ν_{max} (thin film)/cm^{-1} 2982, 1770, 1748, 1716, 1369, 1295, 1258, 1211, 1027 and 851; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 6.35-6.33 (1 H, m, C=CH), 4.97-4.95 (1 H, m, NCH), 4.17, 4.17 (2 H, q, *J* 7.1, OCH_2), 2.76-2.73 (2 H, m, $CHCH_2$), 1.86 (3 H, d, *J* 1.8, CCH_3), 1.53 (9 H, s, CMe_3) and 1.22 (3 H, t, *J* 7.1, CH_2CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 170.9$^-$ (CO), 163.8$^-$ (NCO), 152.8$^-$ (NCO), 134.0$^+$ (C=*C*H), 133.0$^-$ (*C*=CH), 83.5$^-$ (CMe_3), 61.8$^-$ (OCH_2), 56.1$^+$ (NCH), 28.0$^+$ (CMe_3),

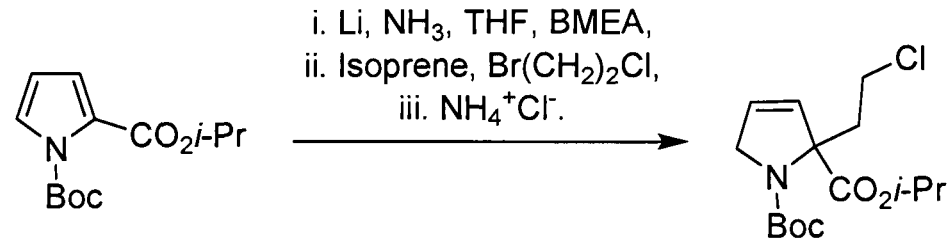
26.9^{-} ($CHCH_2$), 17.0^{+} (CCH_3) and 14.1^{+} (CH_2CH_3); **MS** *m/z* (+ESI) 589 (100%, $2MNa^{+}$), 347 ($MMeCNNa^{+}$) and 306 (MNa^{+}); **HRMS (ESI)** (Found MNa^{+}, 306.1323. $C_{14}H_{21}NO_5Na$ requires *MNa*, 306.1317).

Iso-propyl 3,4,5-triiodopyrrole-2-carboxylate 242



Ammonia (250 cm^3) was freshly distilled onto cut lithium wire (111 mg, 16.0 mmol, 4.00 eq.) under an atmosphere of argon at –78 °C. The resulting dark blue solution was stirred for 1 hour before the addition of *bis*(methoxyethyl)amine (5.90 cm^3, 40.0 mmol, 10.0 eq.) and tetrahydrofuran (20 cm^3). After 5 minutes *N*-Boc pyrrole **213** (1.01 g, 4.00 mmol) dissolved in tetrahydrofuran (30 cm^3) was added dropwise over 5 minutes and stirred for a further 55 minutes, the dark blue colour persisting throughout. Isoprene (~ 0.25 cm^3) was added until the dark blue colour disappeared. On addition of 1,2-diiodoethane (7.89 g, 28.0 mmol, 7.00 eq.) the rapidly stirring solution turned dark brown and was allowed to stir for 15 minutes before the addition of aqueous saturated ammonium chloride (5 cm^3). The reaction was allowed to warm to ambient temperature and ammonia evaporated. Aqueous citric acid (1.0 mol dm^{-3}, 125 cm^3) was added and the solution stirred for 5 minutes before being separated. The aqueous layer was extracted with ether (4 × 150 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 10:90] to give the *triiodopyrrole* **242** (1.53 g, 72%) as prisms; 137-140 °C [from EtOAc-pentane]; R_f [ethyl acetate-light petroleum (bp 40-60 °C), 10:90] 0.24; **IR** ν_{max} (thin film)/cm^{-1} 3226, 1669, 1379, 1225 and 1103; **^{1}H NMR** δ_H (400 MHz; DMSO) 5.06 (1 H, hp, *J* 6.2, OCH), 3.34 (1 H, s, NH) and 1.29 (6 H, d, *J* 6.2, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; DMSO) 156.7 (CO), 129.0 (NC), 93.3 (ArC), 86.7 (ArC), 82.2 (ArC), 67.9 (OCH) and 21.7 ($CHMe_2$); **MS** *m/z* (+ESI) 531 (MH^{+}); **HRMS (CI)** (Found M^{+}, 530.7704. $C_8H_8NO_2I_3$ requires *M*, 530.7689).

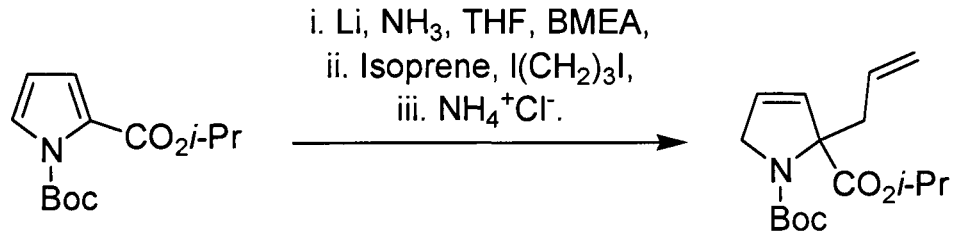
(*2RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-(2-chloroethyl)-2,5-dihydropyrrole-2-carboxylate 250



Ammonia (200 cm^3) was freshly distilled onto cut lithium wire (111 mg, 16.0 mmol, 4.00 eq.) under an atmosphere of argon at –78 °C. The resulting dark blue solution was stirred for 1 hour before the addition of *bis*(methoxyethyl)amine (2.93 cm^3, 20.0 mmol, 5.00 eq.) and tetrahydrofuran (20 cm^3). After 5 minutes *N*-Boc pyrrole **213** (1.01 g, 4.00 mmol) dissolved in tetrahydrofuran (30 cm^3) was added dropwise over 5 minutes and stirred for a further 55 minutes, the dark blue colour persisting throughout. Isoprene (~ 0.25 cm^3) was added until the dark blue colour disappeared. On addition of 1-bromo-2-chloroethane (2.33 cm^3, 28.0 mmol, 7.00 eq.) the rapidly stirring solution turned light green and then to a cream colour and was allowed to stir for 30 seconds before the addition of aqueous saturated ammonium chloride (10 cm^3). The reaction was allowed to warm to ambient temperature and ammonia evaporated. Aqueous citric acid (1.0 mol dm^{-3}, 125 cm^3) was added and the solution stirred for 5 minutes before being separated. The aqueous layer was extracted with ether (4 × 150 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 10:90] to give the *pyrroline* **250** (508 mg, 40%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C), 10:90] 0.17; **IR** ν_{max} (thin film)/cm^{-1} 2980, 1735, 1701, 1391, 1263, 1244, 1177, 1117, 1074, 1031, 1008, 993, 839 and 703; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 6.00, 5.93 (1 H, dt, *J* 6.3 and 1.7, CH=C*H*), 5.54, 5.48 (1 H, dt, *J* 6.2 and 2.1, C*H*=CH), 4.96, 4.94 (1 H, hp, *J* 6.3, OCH), 4.33, 4.26 (1 H, dt, *J* 15.8 and 2.1, NCH_AH_B), 4.16, 4.11 (1 H, dt, *J* 15.8 and 2.1, NCH_AH_B), 3.44-3.32 (2 H, m, CH_2Cl), 2.95-2.87, 2.77-2.70 (1 H, m, $CH_AH_BCH_2Cl$), 2.50-2.43 (1 H, m, $CH_AH_BCH_2Cl$), 1.45, 1.43 (9 H, s, CMe_3) and 1.24-1.17 (6 H, m, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 170.8$^-$, 170.7$^-$ (CO), 153.4$^-$, 153.3$^-$ (NCO), 129.2$^+$, 129.1$^+$ (CH=*C*H), 129.0$^+$, 128.8$^+$ (*C*H=CH), 80.8$^-$, 80.0$^-$ (CMe_3), 74.6$^-$, 74.1$^-$ (NC), 69.3$^+$, 68.9$^+$ (OCH), 55.1$^-$, 55.0$^-$ (NCH_2), 40.1$^-$, 39.6$^-$ (CH_2Cl), 36.4$^-$, 35.6$^-$ ($NCCH_2$), 28.4$^+$, 28.3$^+$ (CMe_3) and 21.7$^+$, 21.6$^+$ ($CHMe_2$); **MS** *m/z* (+ESI) 340,

342 (100%, MNa^+) and 318, 320 (MH^+); **HRMS (ESI)** (Found MNa^+, 340.1293. $C_{15}H_{24}{}^{35}ClNO_4Na$ requires *MNa*, 340.1292).

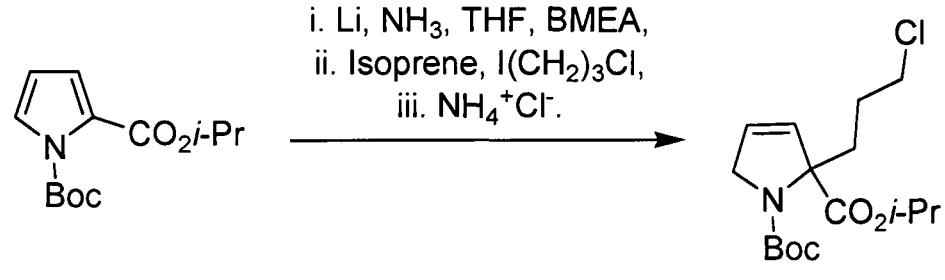
(*2RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-allyl-2,5-dihydropyrrole-2-carboxylate 251



Ammonia (250 cm^3) was freshly distilled onto cut lithium wire (111 mg, 16.0 mmol, 4.00 eq.) under an atmosphere of argon at –78 °C. The resulting dark blue solution was stirred for 1 hour before the addition of *bis*(methoxyethyl)amine (5.90 cm^3, 40.0 mmol, 10.0 eq.) and tetrahydrofuran (20 cm^3). After 5 minutes *N*-Boc pyrrole **213** (1.01 g, 4.00 mmol) dissolved in tetrahydrofuran (30 cm^3) was added dropwise over 5 minutes and stirred for a further 55 minutes, the dark blue colour persisting throughout. Isoprene (~ 0.25 cm^3) was added until the dark blue colour disappeared. On addition of 1,3-diiodo-propane (3.22 cm^3, 28.0 mmol, 7.00 eq.) the rapidly stirring solution turned brown and was allowed to stir for 20 minutes before the addition of aqueous saturated ammonium chloride (5 cm^3). The reaction was allowed to warm to ambient temperature and ammonia evaporated. Aqueous citric acid (1.0 mol dm^{-3}, 125 cm^3) was added and the solution stirred for 5 minutes before being separated. The aqueous layer was extracted with ether (4 × 150 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 5:95] to give the *pyrroline* **251** (886 mg, 75%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C), 5:95] 0.25; **IR** ν_{max} (thin film)/cm^{-1} 2979, 2943, 2866, 1721, 1704, 1642, 1456, 1393, 1321, 1250, 1180, 1110, 1047, 1007, 916, 870, 838, 794, 771 and 714; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$); 5.94, 5.88 (1 H, d, *J* 6.2, CH=C*H*), 5.66-5.53 (1 H, m, $CH{=}CH_2$), 5.50, 5.47 (1 H, d, *J* 6.2, C*H*=CH), 5.07-5.00 (2 H, m, $CH{=}CH_2$), 4.96 (1 H, hp, *J* 6.2, OCH), 4.29, 4.22 (1 H, d, *J* 15.6, NCH_AH_B), 4.08, 4.02 (1 H, d, *J* 15.6, NCH_AH_B), 3.16, 2.98 (1 H, dd, *J* 14.3 and 8.0, $CH_AH_BCH{=}CH_2$), 2.70 (1 H, dd, *J* 14.3 and 6.5, $CH_AH_BCH{=}CH_2$), 1.44, 141 (9 H, s, br, CMe_3) and 1.24-1.18 (6 H, dm, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 171.3$^-$, 171.2$^-$ (CO), 153.3$^-$, 153.1$^-$ (NCO), 133.3$^+$, 133.0$^+$ (CH=*C*H), 129.7$^+$, 129.6$^+$ (*C*H=CH), 128.2$^+$, 128.1$^+$ (*C*H=CH_2), 118.6$^-$, 118.5$^-$ (CH=*C*H_2), 80.3$^-$, 79.5$^-$ (CMe_3), 75.1$^-$, 74.5$^-$ (NC), 68.9$^+$,

68.6^{+} (OCH), 55.2^{-}, 55.1^{-} (NCH_2), 38.1^{-}, 37.0^{-} ($CH_2CH{=}CH_2$), 28.4^{+}, 27.9^{+} (CMe_3) and 21.8^{+}, 21.6^{+} ($CHMe_2$); **MS** *m/z* (+ESI) 613 (100% $2MNa^{+}$), 318 (MNa^{+}) and 296 (MH^{+}); **HRMS (ESI)** (Found MH^{+}, 296.1862 $C_{16}H_{26}NO_4$ requires *MH*, 296.1862).

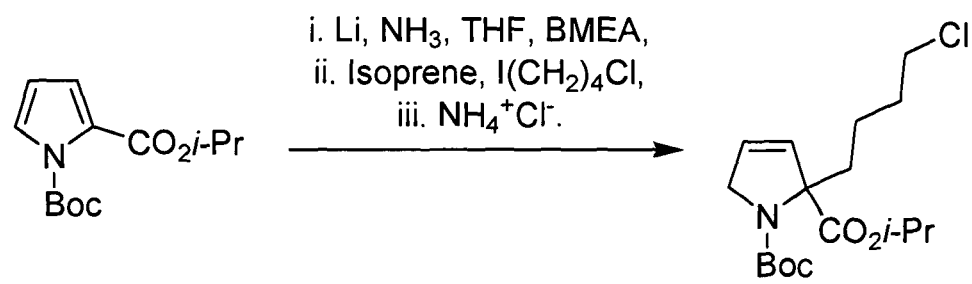
(*2RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-(3-chloropropyl)-2,5-dihydropyrrole-2-carboxylate 252



Ammonia (250 cm^3) was freshly distilled onto cut lithium wire (111 mg, 16.0 mmol, 4.00 eq.) under an atmosphere of argon at –78 °C. The resulting dark blue solution was stirred for 1 hour before the addition of *bis*(methoxyethyl)amine (2.93 cm^3, 20.0 mmol, 5.00 eq.) and tetrahydrofuran (20 cm^3). After 5 minutes *N*-Boc pyrrole **213** (1.01 g, 4.00 mmol) dissolved in tetrahydrofuran (30 cm^3) was added dropwise over 5 minutes and stirred for a further 55 minutes, the dark blue colour persisting throughout. Isoprene (~ 0.25 cm^3) was added until the dark blue colour disappeared. On addition of 1-chloro-3-iodopropane (3.01 cm^3, 28.0 mmol, 7.00 eq.) the rapidly stirring solution turned light green and then to a cream colour and was allowed to stir for 30 seconds before the addition of aqueous saturated ammonium chloride (10 cm^3). The reaction was allowed to warm to ambient temperature and ammonia evaporated. Aqueous citric acid (1.0 mol dm^{-3}, 125 cm^3) was added and the solution stirred for 5 minutes before being separated. The aqueous layer was extracted with ether (4 × 150 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 10:90] to give the *pyrroline* **252** (1.13 g, 85%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C), 10:90] 0.18; **IR** ν_{max} (thin film)/cm^{-1} 2979, 1736, 1703, 1627, 1451, 1452, 1393, 1323, 1258, 1221, 1179, 1146, 1118, 1076, 1008, 968, 838 and 702; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.93, 5.87 (1 H, dt, *J* 6.2 and 1.9, CH=C*H*C), 5.43, 5.40 (1 H, dt, *J* 6.2 and 1.9, $CH_2CH{=}CH$), 4.92 (1 H, hp, *J* 6.3, OCH), 4.28, 4.21 (1 H, dt, *J* 15.7 and 2.1, NCH_AH_B), 4.09, 4.04 (1 H, dt, *J* 15.7 and 2.1, NCH_ACH_B), 3.54-3.39 (2 H, m, CH_2Cl), 2.48-2.37 (1 H, m, CCH_AH_B), 2.10-1.95 (1 H, m, CCH_AH_B), 1.65-1.48 (2 H, m, CH_2CH_2Cl), 1.40, 1.39 (9 H, s, CMe_3) and 1.19-1.12 (6 H, m, $CHMe_2$); **^{13}C NMR** δ_C (100.6

MHz; $CDCl_3$) 171.4$^-$, 171.2$^-$ (CO), 153.3$^-$, (NCO), 129.8$^+$, 129.6$^+$ (*C*H=CH), 128.4$^+$, 128.1$^+$ (CH=*C*H), 80.4$^-$, 80.2$^-$ (CMe_3), 75.1$^-$, 74.6$^-$ (NC), 68.9$^+$, 68.6$^+$ (OCH), 55.2$^-$, 55.1$^-$ (NCH_2), 45.0$^-$, 44.8$^-$ (CH_2Cl), 30.9$^-$, 30.0$^-$ ($NCCH_2$), 28.4$^+$, 28.3$^+$ (CMe_3), 27.3$^-$, 26.7$^-$ (CH_2CH_2Cl) and 21.7$^-$, 21.6$^-$ ($CHMe_2$); **MS** *m/z* (+ESI) 332, 334 (100%, MH^+), 370, 372 (MK^+) and 276, 278 (MH^+ - CMe_3); **HRMS (ESI)** (Found MH^+, 332.1627. $C_{16}H_{27}{}^{35}ClNO_4$ requires *MH*, 332.1629).

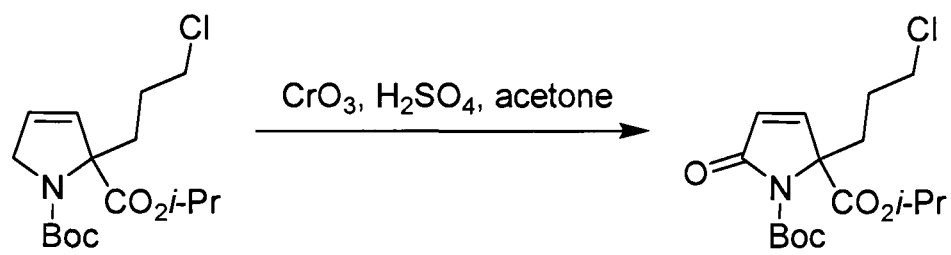
(*2RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-(4-chlorobutyl)-2,5-dihydropyrrole-2-carboxylate 253



Ammonia (200 cm^3) was freshly distilled onto cut lithium wire (111 mg, 16.0 mmol, 4.00 eq.) under an atmosphere of argon at –78 °C. The resulting dark blue solution was stirred for 1 hour before the addition of *bis*(methoxyethyl)amine (2.93 cm^3, 20.0 mmol, 5.00 eq.) and tetrahydrofuran (20 cm^3). After 5 minutes *N*-Boc pyrrole **213** (1.01 g, 4.00 mmol) dissolved in tetrahydrofuran (30 cm^3) was added dropwise over 5 minutes and stirred for a further 55 minutes, the dark blue colour persisting throughout. Isoprene (~ 0.25 cm^3) was added until the dark blue colour disappeared. On addition of 1-chloro-4-iodobutane (3.43 cm^3, 28.0 mmol, 7.00 eq.) the rapidly stirring solution turned light green and then to cream colour and was allowed to stir for 30 seconds before the addition of aqueous saturated ammonium chloride (10 cm^3). The reaction was allowed to warm to ambient temperature and ammonia evaporated. Aqueous citric acid (1.0 mol dm^{-3}, 125 cm^3) was added and the solution stirred for 5 minutes before being separated. The aqueous layer was extracted with ether (4 × 150 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 10:90] to give the *pyrroline* **253** (1.01 g, 73%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C), 10:90] 0.23; **IR** ν_{max} (thin film)/cm^{-1} 2978, 2867, 1735, 1703, 1393, 1252, 1178, 1110, 1005, 969 and 839; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.95, 5.89 (1 H, dt, *J* 6.2 and 1.9, CH=C*H*), 5.46, 5.42 (1 H, dt, *J* 6.2 and 1.9, CH_2CH=CH), 4.98, 4.94 (1 H, hp, *J* 6.3, OCH), 4.32, 4.25 (1 H, dt, *J* 15.7 and 2.1, NCH_AH_B), 4.15, 4.09 (1

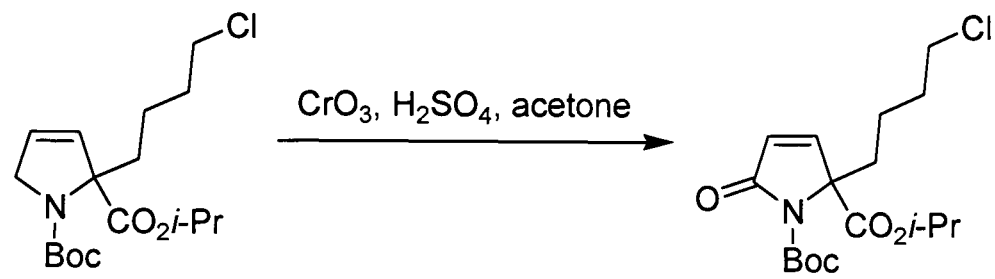
H, dt, *J* 15.6 and 2.1, NCH_ACH_B), 3.51, 3.50 (2 H, t, *J* 6.6, CH_2Cl), 2.43, 2.28 (1 H, ddd, *J* 14.0 11.8 and 5.3, $NCCH_AH_B$), 1.99-1.88 (1 H, m, $NCCH_ACH_B$), 1.82-1.69 (2 H, m, CH_2CH_2Cl), 1.44, 1.42 (9 H, s, CMe_3), 1.35-1.24 (2 H, m, $CH_2CH_2CH_2Cl$) and 1.24-1.18 (6 H, m, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 171.1, 171.5 (CO), 153.4, 153.3 (NCO), 129.9$^+$ (*C*H=CH), 128.2$^+$, 128.1$^+$ (CH=*C*H), 80.2, 79.6 (CMe_3), 75.4, 74.9 (NC), 68.8$^+$, 68.5$^+$ (OCH), 55.2, 55.1 (NCH_2), 45.0, 44.7 (CH_2Cl), 32.6, 32.5 (*C*H_2CH_2Cl), 32.4, 31.5 ($NCCH_2$), 28.4$^+$ (CMe_3), 21.8$^+$, 21.6$^+$ ($CHMe_2$) and 20.8, 20.5 (CH_2); **MS** *m/z* (+ESI) 370, 368 (100%, MNa^+), 290, 292 (MH^+ - CMe_3) and 246, 248 (MH^+ - CO_2CMe_3); **HRMS (ESI)** (Found MNa^+, 368.1603. $C_{17}H_{28}NO_4{}^{35}ClNa$ requires *MNa*, 368.1605).

(*2RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-(3-chloropropyl)-5-oxo-2,5-dihydropyrrole-2-carboxylate 254



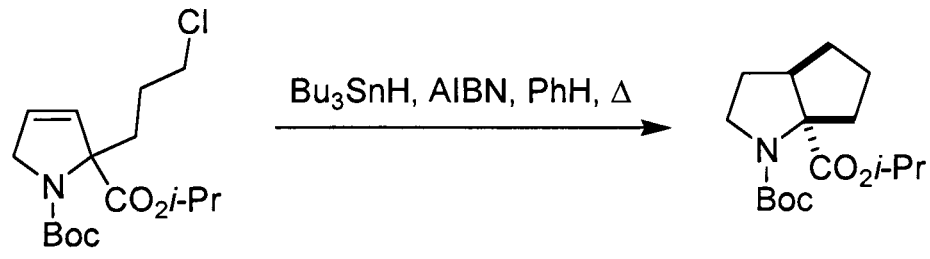
By method C, chromium$^{(VI)}$ trioxide (600 mg, 6.00 mmol, 6.00 eq.) dissolved in aqueous sulfuric acid (2.0 mol dm^{-3}, 2.0 cm^3) was added to a solution of pyrroline **252** (331 mg, 1.00 mmol) dissolved in acetone (5 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60°C), 10:90] to give the *lactam* **254** (263 mg, 76%) as a solid, mp 65-68 °C [from chloroform-light petroleum (bp 40-60 °C)]; R_f [ethyl acetate-light petroleum (bp 40-60 °C) 20:80] 0.16; **IR** ν_{max} (thin film)/cm^{-1} 2982, 2937, 1783, 1739, 1455, 1307, 1254, 1161, 1106, 1050, 842 and 827; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 6.88 (1 H, d, *J* 6.0, CH=C*H*), 6.21 (1 H, d, *J* 6.0, C*H*=CH), 5.00 (1 H, hp, *J* 6.3, OCH), 3.50 (2 H, t, *J* 6.3, CH_2Cl), 2.64 (1 H, ddd, *J* 14.4, 9.2 and 7.8, $CH_AH_BCH_2$), 2.31 (1 H, ddd, *J* 14.4, 9.2 and 7.8, $CH_AH_BCH_2$), 1.54-1.47 (2 H, m, CH_2), 1.51 (9 H, s, CMe_3) 1.21 (3 H, d, *J* 6.3, $CHMe_AMe_B$) and 1.18 (3 H, d, *J* 6.3, $CHMe_AMe_B$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 168.9 (CO), 167.8 (NCO), 148.5 (NCO), 148.5$^+$ (CH=*C*H), 128.1$^+$ (*C*H=CH), 83.9 (CMe_3), 72.9 (NC), 70.4$^+$ (OCH), 44.3 (CH_2Cl), 29.4 (CH_AH_B), 28.0$^+$ (CMe_3), 25.8 (CH_2) 21.6$^+$ ($CHMe_AMe_B$) and 21.5$^+$ ($CHMe_AMe_B$); **MS** *m/z* (+ESI) 732, 731, 730, 729 (100%, $2MK^+$) and 386, 384 (MK^+); **HRMS (ESI)** (Found MH^+, 346.1415. $C_{16}H_{25}{}^{35}ClNO_5$ requires *MH*, 346.1421).

(*2RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-(4-chlorobutyl)-5-oxo-2,5-dihydropyrrole-2-carboxylate 255



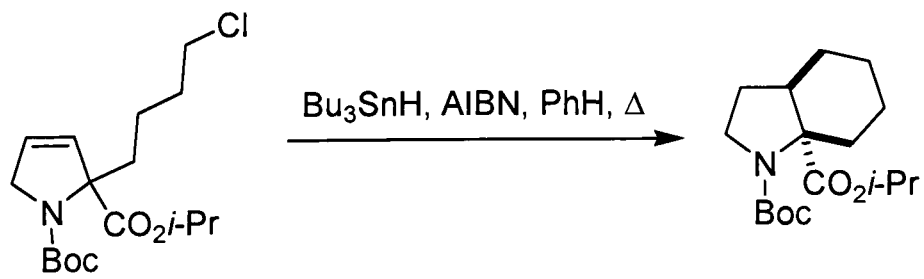
By method C, chromium$^{(VI)}$ trioxide (500 mg, 5.00 mmol, 5.00 eq.) dissolved in aqueous sulfuric acid (2.0 mol dm^{-3}, 2.0 cm^3) was added to a solution of pyrroline **253** (346 mg, 1.00 mmol) dissolved in acetone (5 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60°C), 10:90] to give the *lactam* **255** (241 mg, 67%) as a solid, mp 72-74 °C [from chloroform-light petroleum (bp 40-60 °C)]; R_f [ethyl acetate-light petroleum (bp 40-60 °C) 20:80] 0.34; **IR** ν_{max} (solution cell)/cm^{-1} 2980, 2980, 1783, 1738, 1370, 1328, 1254, 1161, 1106 and 842; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 6.87 (1 H, d, *J* 6.0, CH=C*H*), 6.20 (1 H, d, *J* 6.0, C*H*=CH), 5.00 (1 H, hp, *J* 6.3, OCH), 3.48 (2 H, td, *J* 6.6 and 1.8, CH_2Cl), 2.50-2.42 (1 H, m, CCH_AH_B), 2.21-2.13 (1 H, m, CCH_AH_B), 1.75 (2 H, apparent dt, *J* 13.6 and 6.6, CH_2CH_2Cl), 1.52 (9 H, s, CMe_3), 1.23-1.19 (2 H, m, $NCCH_2CH_2$), 1.21 (3 H, d, *J* 6.3, CH*Me*$_A$Me$_B$) and 1.17 (3 H, d, *J* 6.3, CHMe$_A$*Me*$_B$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 168.9$^-$ (CO), 168.0$^-$ (NCO), 148.7$^-$ (NCO), 148.6$^+$ (CH=*C*H), 128.0$^+$ (*C*H=CH), 83.6$^-$ (CMe_3), 73.2$^-$ (NC), 70.2$^+$ (OCH), 44.2$^-$ (CH_2Cl), 32.1$^-$ (*C*H_2CH_2Cl), 31.1$^-$ (NC*C*H_2), 28.0$^+$ (CMe_3), 21.5$^+$ (CH*Me*$_2$) and 19.7$^-$ ($NCCH_2CH_2$); **MS** *m/z* (+ESI) 741, 742, 743, 744 (100%, 2MNa$^+$) and 382, 384 (MNa$^+$); **HRMS (ESI)** (Found MNa$^+$, 382.1399. $C_{17}H_{26}NO_5{}^{35}ClNa$ requires *MNa*, 382.1397).

(*6RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)hexahydrocyclopenta pyrrole-6-carboxylate 256



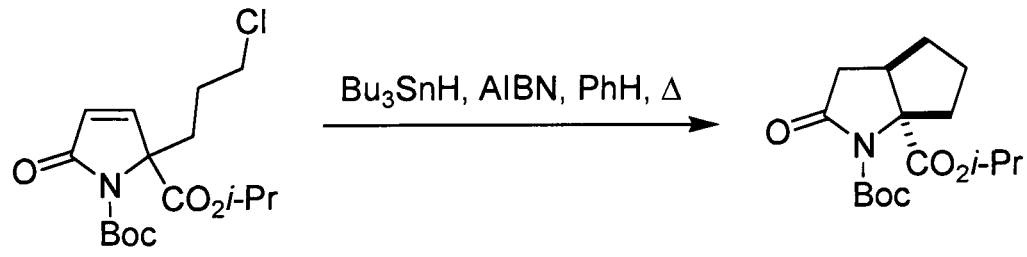
By method B, tri-*n*-butyltin hydride (0.159 cm^3, 600 μmol, 1.20 eq.) and AIBN (16 mg, 100 μmol, 0.20 eq.) dissolved in deoxygenated benzene (10 cm^3) were added over a 12 hour period *via* syringe pump to a refluxing solution of pyrroline **252** (166 mg, 500 μmol) dissolved in deoxygenated benzene (20 cm^3); heating continued for a further 12 hours to give the crude product. The residue was dissolved in ether (5 cm^3) and addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (0.224 cm^3, 1.50 mmol, 2.50 eq.) gave a white precipitate. This mixture was titrated with an ethereal iodine solution (0.1 mol dm^{-3}) until the colour just persisted, filtered through a short pad of silica eluting with ether and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 20:80] then [SiO_2, dichloromethane-ether 98:2] to give the *fused bicycle* **256** (90 mg, 61%) as an oil; R_f [dichloromethane-ether 98:2] 0.18; **IR** ν_{max} (thin film)/cm^{-1} 2978, 2873, 1733, 1700, 1391, 1260, 1171, 1106, 1030, 914, 773 and 732; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.03-4.93 (1 H, m, OCH), 3.63 (1 H, ddd, *J* 10.7, 8.1 and 5.2, NCH_AH_B), 3.56-3.43 (1 H, m, NCH_AH_B), 2.62-2.50 (2 H, m, CH and CH_AH_B), 2.02 (1 H, dq, *J* 12.5 and 7.8 $NCH_2CH_AH_B$), 1.89-1.80, 1.74-1.66 (5 H, m, CH_2 and CH_AH_B), 1.64-1.56 (1 H, m, $NCH_2CH_AH_B$), 1.44, 1.40 (9 H, s, CMe_3) and 1.24-1.18 (6 H, m, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 174.1, 174.0 (CO), 153.6 (NCO), 79.7, 79.3 (CMe_3), 75.6, 75.2 (NC), 68.3, 68.0 (OCH), 52.5, 51.0 (CH), 47.7, 47.3 (NCH_2), 36.8, 35.5 (CH_2), 32.2 (CH_2), 29.7, 28.8 (CH_2), 28.5, 28.4 (CMe_3), 26.0, 25.6 (CH_2) and 21.8, 21.7 ($CHMe_2$); **MS** *m/z* (+ESI) 320 (MNa^+), 298 (100%, MH^+), 242 (MH^+ - CMe_3) and 198 (MH^+ - CO_2CMe_3); **HRMS (ESI)** (Found MNa^+, 320.1835. $C_{16}H_{27}NO_4Na$ requires *MNa*, 320.1838).

(*6RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)hexahydroindole-6-carboxylate 257



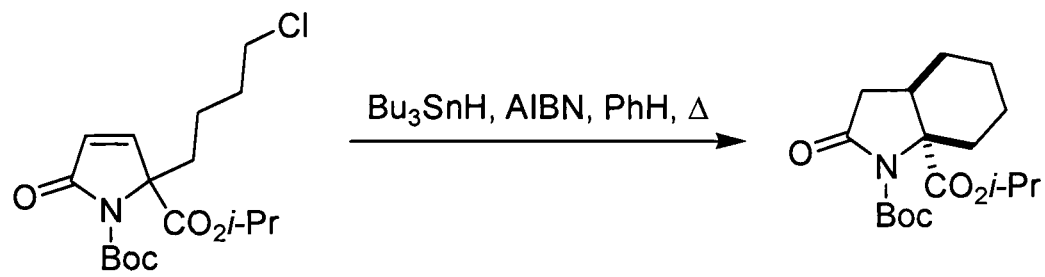
By method B, tri-*n*-butyltin hydride (0.164 cm^3, 600 μmol, 1.40 eq.) and AIBN (14 mg, 86.0 μmol, 0.20 eq.) dissolved in deoxygenated benzene (10 cm^3) were added over a 12 hour period *via* syringe pump to a refluxing solution of pyrroline **253** (149 mg, 430 μmol) dissolved in deoxygenated benzene (20 cm^3); heating continued for a further 12 hours to give a crude product. The resisdue was dissolved in ether (5 cm^3) and addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (0.224 cm^3, 1.50 mmol, 3.50 eq.) gave a white precipitate. This mixture was titrated with an ethedral iodine solution (0.1 mol dm^{-3}) until the colour just persisted, filtered through a short pad of silica eluting with ether and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 20:80] then [SiO_2, dichloromethane-ether 98:2] to give the *saturated indole* **257** (80 mg, 60%) as an oil; R_f [dichloromethane-ether 98:2] 0.32; **IR** ν_{max} (thin film)/cm^{-1} 2978, 2873, 1733, 1700, 1392, 1259, 1171, 1106, 1030, 993, 965, 935, 914, 866, 834, 774 and 732; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.03, 4.98 (1 H, hp, *J* 6.1, OCH), 3.64-3.58 (1 H, m, NCH_AH_B), 3.51-3.45 (1 H, m, NCH_AH_B), 2.48-2.31 (1 H, m, CH), 2.34-2.32, 2.03-1.45 (10 H, m, CH_2), 1.43, 1.40 (9 H, s, CMe_3) and 1.26-1.18 (6 H, m, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 173.8, 173.7 (CO), 154.1, 154.0 (NCO), 79.8, 79.0 (CMe_3), 68.1, 68.0 (OCH), 67.2, 66.3 (NC), 46.4, 46.3 (NCH_2), 43.8, 42.4 (CH), 30.0, 29.0 (NCH_2CH_2), 28.5, 28.4 (CMe_3), 27.5, 26.7 (CH_2), 26.5, 25.9 (CH_2), 22.4, 22.3 (CH_2), 21.9, 21.8 ($CHMe_2$) and 21.8, 21.7 (CH_2); **MS** *m/z* (+ESI) 645 ($2MNa^+$), 334 (MNa^+), 312 (100%, MH^+), 256 (MH^+ - CMe_3) and 212 (MH^+ - CO_2CMe_3); **HRMS (ESI)** (Found MH^+, 312.2174. $C_{17}H_{30}NO_4$ requires *MH*, 312.2175).

(*6RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-oxo-hexahydrocyclopenta pyrrole-6-carboxylate 258



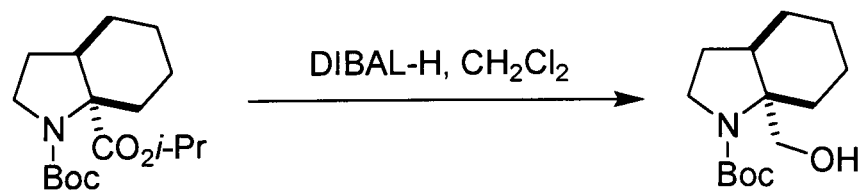
By method B, tri-*n*-butyltin hydride (0.115 cm^3, 434 μmol, 1.20 eq.) and AIBN (14 mg, 87.0 μmol, 0.20 eq.) dissolved in deoxygenated benzene (10 cm^3) were added over a 12 hour period *via* syringe pump to a refluxing solution of pyrroline **254** (125 mg, 361 μmol) dissolved in deoxygenated benzene (33 cm^3); heating continued for a further 12 hours to give a crude product. The residue was dissolved in ether (10 cm^3), titrated with an ethedral iodine solution (0.1 mol dm^{-3}) until the colour just persisted and stirred vigorously with aqueous potassium fluoride solution (10% by weight, 20 cm^3) for 20 minutes. This mixture was filtered through celite ®, separated and the organic layer washed with aqueous potassium fluoride solution (10% by weight, 3 × 10 cm^3), dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, light petroleum then acetone-light petroleum (bp 40-60 °C), 10:90] to give the *lactam* **258** (100 mg, 89%) as an oil; R_f [acetone-ether-light petroleum (bp 40-60 °C) 30:70] 0.61; **IR** ν_{max} (thin film)/cm^{-1} 2980, 1790, 1738, 1370, 1301, 1158, 1106 and 845; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.02 (1 H, hp, *J* 6.3, OCH), 2.80 (1 H, dd, *J* 18.0 and 10.0, NC(O)CH_AH_B), 2.78-2.71 (1 H, m, NCCH_AH_B), 2.43 (1 H, dtd, *J* 10.3, 7.9 and 2.6, CH), 2.30 (1 H, dd, *J* 18.0 and 2.6, NC(O)CH_AH_B), 2.09-2.01 (1 H, m, CHCH_AH_B), 1.87-1.63 (3 H, m, CH_2 and NCCH_AH_B), 1.47 (9 H, s, $CCMe_3$), 1.45-1.36 (1 H, m, CHCH_AH_B) and 1.22 (6 H, d, *J* 6.3, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 174.1$^-$ (CO), 172.3$^-$ (NCO), 149.1$^-$ (NCO), 83.4$^-$ (CMe_3), 75.3$^-$ (NC), 69.2$^+$ (OCH), 41.1$^+$ (CH), 37.6$^-$ (*C*H_2CH), 37.3$^-$ (CH_2), 34.4$^-$ (CH_2), 27.9$^+$ (CMe_3), 25.8$^-$ (CH_2) and 21.7$^+$ ($CHMe_2$); **MS** *m/z* (+ESI) 645 (100%, $2MNa^+$), 334 (MNa^+) and 312 (MH^+); **HRMS (ESI)** (Found MNa^+, 334.1626. $C_{16}H_{25}NO_5Na$ requires *MNa*, 334.1630).

(*6RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-oxo-hexahydroindole-6-carboxylate 259



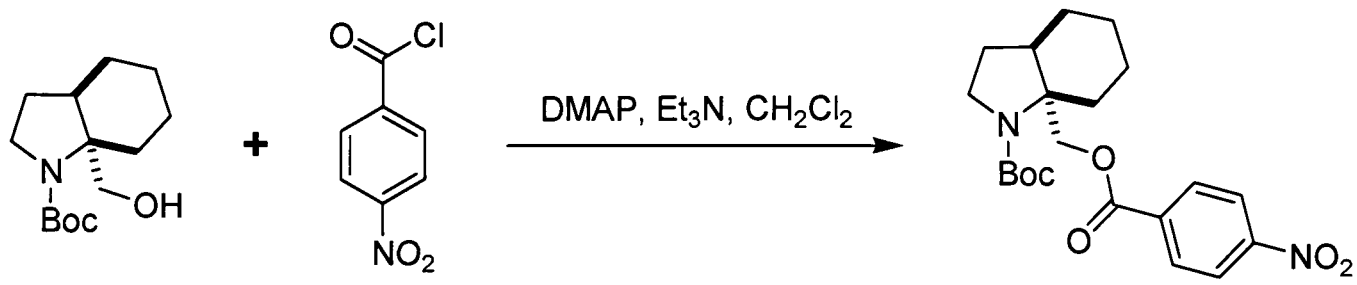
By method B, tri-*n*-butyltin hydride (0.114 cm^3, 416 μmol, 1.20 eq.) and AIBN (14 mg, 83.0 μmol, 0.20 eq.) dissolved in deoxygenated benzene (10 cm^3) were added over a 12 hour period *via* syringe pump to a refluxing solution of pyrroline **255** (125 mg, 347 μmol) dissolved in deoxygenated benzene (41 cm^3); heating continued for a further 12 hours to give a crude product. The residue was dissolved in ether (10 cm^3), titrated with an ethedral iodine solution (0.1 mol dm^{-3}) until the colour just persisted and stirred vigorously with aqueous potassium fluoride solution (10% by weight, 20 cm^3) for 20 minutes. This mixture was filtered through celite, separated and the organic layer washed with aqueous potassium fluoride solution (10% by weight, 3 × 10 cm^3), dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, light petroleum then ethyl acetate-light petroleum (bp 40-60 °C), 20:80] to give the *lactam* **259** (98 mg, 87%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C) 20:80] 0.38; **IR** ν_{max} (thin film)/cm^{-1} 2980, 2934, 1790, 1737, 1719, 1370, 1307, 1261, 1162, 1145, 1106, 1079, 979 and 848; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.03 (1 H, hp, *J* 6.2, OCH), 2.58-2.36 (4 H, dm, CH, CH_AH_B and CH_2), 1.74-1.50 (5 H, m, CH_AH_B and CH_2) 1.47 (9H, s, CMe_3), 1.23 (3 H, d, *J* 6.2, $CHMe_AMe_B$) and 1.22 (3 H, d, *J* 6.2, $CHMe_AMe_B$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 173.5$^-$ (CO), 171.5$^-$ (NCO), 149.5$^-$ (NCO), 83.4$^-$ (CMe_3), 69.0$^+$ (OCH), 67.4$^-$ (NC), 36.2$^-$ (CH_2), 35.4$^+$ (CH), 29.6$^-$ (CH_2CH), 28.0$^+$ (CMe_3), 25.6$^-$ (CH_2), 21.7$^+$ ($CHMe_2$), 21.3$^-$ (CH_2) and 20.1$^-$ (CH_2); **MS** *m/z* (+ESI) 673 (100%, $2MNa^+$) and 347 (MNa^+); **HRMS (ESI)** (Found MNa^+, 348.1787 $C_{17}H_{27}NO_5Na$ requires *MNa*, 348.1787).

(*6RS*)-7-Hydroxymethyl-1-(*tert*-butoxycarbonyl)octahydroindole



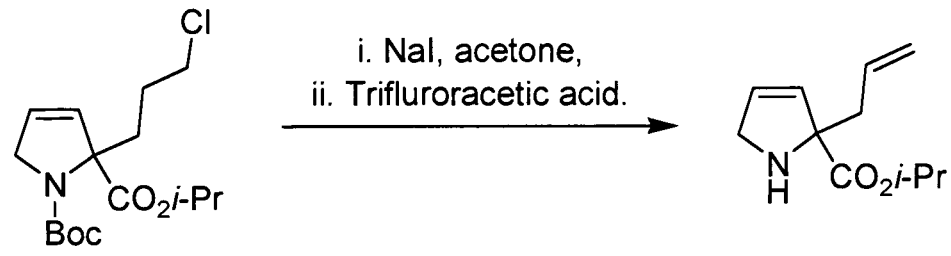
Di-*iso*-butylaluminium hydride (1.5 mol dm^{-3} solution in toluene, 1.63 cm^3, 2.44 mmol, 4.00 eq.) was added dropwise to ester **257** (190 mg, 609 μmol) dissolved in dichloromethane (10 cm^3) under an atmosphere of argon at –78°C. The resulting solution was stirred for 4 hours at –78°C and allowed to warm to ambient temperature before being stirred for a further 6 hours. Aqueous saturated ammonium chloride was added at 0 °C until no further gelatinous precipitate formed. Aqueous hydrochloric acid (3.0 mol dm^{-3}) was added until the precipitate dissolved and the solution separated, the aqueous layer was extracted with ethyl acetate (3 × 15 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate), and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 20:80] to give *7-hydroxymethyl-1-(tert-butoxycarbonyl)-octahydroindole* (135 mg, 87%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C), 20:80] 0.39; **IR** ν_{max} (thin film)/cm^{-1} 3392, 2930, 1668, 1461, 1399, 1366, 1274, 1257, 1177, 1158, 1073, 1042, 983 and 772; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 3.85 (1 H, d, *J* 12.2, CH_AH_BOH), 3.57 (1 H, d, *J* 12.2, CH_AH_BOH), 3.47 (1 H, t, *J* 10.0, NCH_AH_B), 3.25 (1 H, dt, *J* 10.7 and 7.4 NCH_AH_B), 2.46 (1 H, s br, OH), 2.00-1.89 (1 H, m, $NCH_ACH_AH_B$), 1.77-1.43 (10 H, m, $NCH_ACH_AH_B$, CH and CH_2) and 1.44 (9 H, s, CMe_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 79.9 (CMe_3), 66.3 (NC), 65.2 (CH_2OH), 46.1 (NCH_2), 40.2 (CH), 29.7 (CH_2), 28.5 (CMe_3), 25.8 (CH_2), 25.2 (CH_2), 22.1 (CH_2) and 20.7 (CH_2); **MS** *m/z* (+ESI) 273 (MNa^+) and 200 (100%, MH^+ - CMe_3); **HRMS (ESI)** (Found MNa^+, 278.1732. $C_{14}H_{25}NO_3Na$ requires *MNa*, 278.1732).

(*6RS*)-7-(4-Nitro-benzoyloxymethyl)-1-(*tert*-butoxycarbonyl)octahydroindole 262



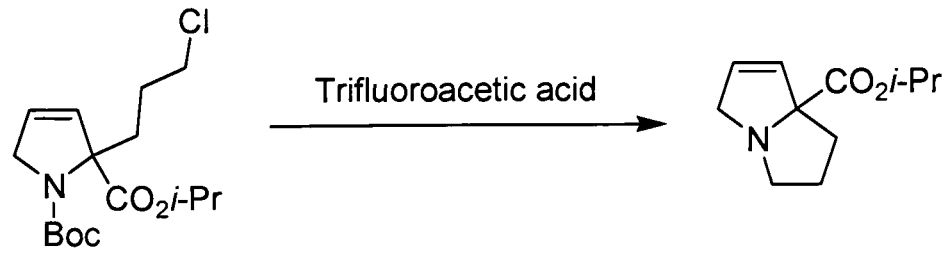
Triethylamine (0.221 cm^3, 1.58 mmol, 3.00 eq.) was added to a solution of 7-hydroxymethyl-1-(*tert*-butoxycarbonyl)-octahydroindole (135 mg, 528 μmol) and 4-(dimethylamino)pyridine (13 mg, 106 μmol, 0.20 eq.) dissolved in dichloromethane (7 cm^3) under an atmosphere of argon at ambient temperature. After 10 minutes *para*-nitrobenzoyl chloride (145 mg, 791 μmol, 1.50 eq.) was added in one portion; the resulting solution was stirred for 4 hours. Aqueous hydrochloric acid (1.0 mol dm^{-3}, 25 cm^{-3}) was added, the resulting mixture separated and the aqueous layer was extracted with ethyl acetate (3 × 25 cm^{-3}). The combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 20:80] to give the *para-nitrobenzoyl ester* **262** (160 mg, 75%) as needles, mp 96-98 °C [from chloroform-ethyl acetate]; **IR** ν_{max} (solution cell)/cm^{-1} 2930, 1728, 1689, 1529, 1392, 1275, 1177, 1119, 1102, 1061, 1014, 873 and 720; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 8.29-8.27 (2 H, dm, ArH), 8.17 (2 H, t, *J* 9.0, ArH), 4.80-4.28 (2 H, m, CH_2O), 3.71-3.53 (1 H, dm, NCH_AH_B), 3.46-3.30 (1 H, m, NCH_AH_B), 2.38-1.25 (11 H, m, CH and CH_2) and 1.42 (9 H, s, CMe_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 164.5 (CO), 154.2 (NCO), 150.5, 135.4, 130.7, 123.7, 123.5 (6 × ArC), 79.9 (CMe_3), 66.3 (CH_2O), 63.0 (NC), 46.8 (NCH_2), 40.1 (CH), 30.8 (CH_2), 28.5 (CMe_3), 26.5 (CH_2), 25.8 (CH_2), 22.4 (CH_2) and 21.3 (CH_2); **MS** *m/z* (+ESI) 405 (100%, MH^+); **HRMS (ESI)** (Found MH^+, 405.2025. $C_{21}H_{29}N_2O_6$ requires *MH*, 405.2026).

(*2RS*)-*Iso*-propyl-2-(2-allyl)-2,5-dihydropyrrole-2-carboxylate 263



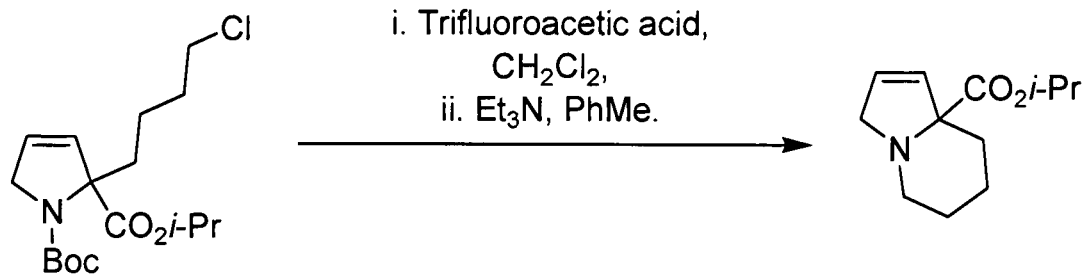
Sodium iodide (531 mg, 3.54 mmol, 10.0 eq.) was added to a solution of pyrroline **252** (114 mg, 354 μmol) dissolved in acetone (10 cm^3) and heated to initiate reflux; heating continued for 35 hours. On cooling, the mixture was evaporated under reduced pressure and the residue dissolved in ether (10 cm^3) and poured into aqueous saturated sodium thiosulfate (10 cm^3). The layers were separated and the organic layer dried (anhydrous magnesium sulfate) and evaporated under reduce pressure. Trifluoroacetic acid (1.20 cm^3) was added to the residue under an atmosphere of argon at ambient temperature and stirred for 30 minutes. The reaction was evaporated under reduced pressure, the residue dissolved in ethyl acetate (5 cm^3), poured into aqueous saturated sodium bicarbonate (5 cm^3) and stirred vigorously for 15 minutes. Ethyl acetate (25 cm^3) was added to the mixture, the layers were separated and the organic layer washed with aqueous saturated sodium bicarbonate (2 × 20 cm^3). The organic layer was dried (anhydrous magnesium sulfate) and evaporated under reduced. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60°C), 20:80] to give the *allyl pyrroline* **263** (38 mg, 55%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3379, 2980, 1732, 1704, 1371, 1251, 1108 and 916; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.89 (1 H, dt, *J* 5.7 and 1.9, CH=C*H*), 5.81-5.76 (1 H, m, CH=C*H*), 5.75-5.70 (1 H, m, CH=C*H*), 5.11-5.05 (2 H, dm, $CH=CH_2$), 5.00 (1 H, hp, *J* 6.3, OCH), 3.89 (1 H, dt, *J* 15.0 and 2.1, NCH_AH_B), 3.49 (1H, dt, *J* 15.0 and 2.0, NCH_AH_B), 2.58 (1 H, dd, *J* 13.6 and 7.8, CH_ACH_B), 2.34 (1 H, ddt, *J* 13.6, 6.5 and 1.2, CH_AH_B) and 1.23 (6 H, dd, *J* 6.3 and 3.7, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 174.1$^-$ (CO), 133.3$^+$ (CH=*C*H), 130.6$^+$ (*C*H=CH), 130.3$^+$ (*C*H=CH), 118.0$^-$ ($CH=CH_2$), 68.7$^-$ (OCH), 53.9$^-$ (NCH_2), 43.8$^-$ (*C*CH=CH_2), 21.8$^+$ ($CHMe_2$); **MS** *m/z* (+CI) 196 (MH^+); **HRMS (CI)** (Found MH^+, 196.1346. $C_{11}H_{18}NO_2$ requires *MH*, 196.1338).

(*7RS*)-*Iso*-propyl 5,6,7,7a-tetrahydro-3H-pyrrolizine-7a-carboxylate 264



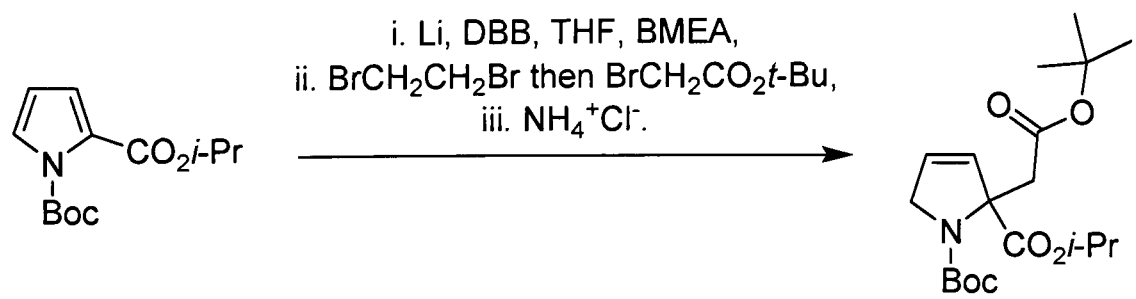
Trifluoroacetic acid (1.20 cm^3) was added to pyrroline **252** (140 mg, 420 μmol) under an atmosphere of argon at ambient temperature and stirred for 30 minutes. The reaction was evaporated under reduced pressure, the residue dissolved in ethyl acetate (5 cm^3), poured into aqueous saturated sodium bicarbonate (5 cm^3) and stirred vigorously for 15 minutes. Ethyl acetate (25 cm^3) was added to the mixture, the layers were separated and the organic layer washed with aqueous saturated sodium bicarbonate (2 × 20 cm^3). The organic layer was dried (anhydrous magnesium sulfate) and evaporated under reduced pressure to give the *dihydropyrrolizine* **264** (79 mg, 96%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 2978, 2872, 1725, 1467, 1455, 1374, 1273, 1180, 1146, 1102, 1096, 1000, 979, 913, 832 and 714; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.78-5.74 (2 H, m, C*H*=C*H*), 4.98 (1 H, hp, *J* 6.3, OCH), 3.99 (1 H, d, *J* 16.0, NCH_AH_BCH), 3.36 (1 H, d, *J* 15.9, NCH$_A$CH_BCH), 3.28 (1 H, apparent qui, *J* 5.1, NCH_AH_BCH$_2$), 2.62-2.56 (1 H, m, NCH$_A$$H_BCH_2$), 2.25-2.17 (1 H, m, CC$H_AH_B$), 1.85-1.76 (2 H, m, CCH$_A$$H_B$ and NCH$_2$CH_AH_B), 1.73-1.64 (1 H, m, NCH$_2$CH$_A$CH_B) and 1.21 (6 H, d, *J* 6.3, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 174.2$^-$ (CO), 130.5$^+$ (*C*H=CH), 128.0$^+$ (CH=*C*H), 83.7$^-$ (NC), 68.2$^+$ (OCH), 62.7$^-$ (N*C*H$_2$CH), 57.7$^-$ (N*C*H$_2$CH$_2$), 35.6$^-$ (CCH_2), 24.8$^-$ (NCH_2CH_2) and 21.7$^+$ ($CHMe_2$); **MS** *m/z* (+CI) 196 (100%, MH^+), 169 (MH^+ - CMe), and 108 (MH^+ - CO_2CHMe_2); **HRMS (CI)** (Found MH^+, 196.1339. $C_{11}H_{18}NO_2$ requires *MH*, 196.1338).

(*8RS*)-*Iso*-propyl 3,5,6,7,8,8a-hexahydroindolizine-8a-carboxylate 265



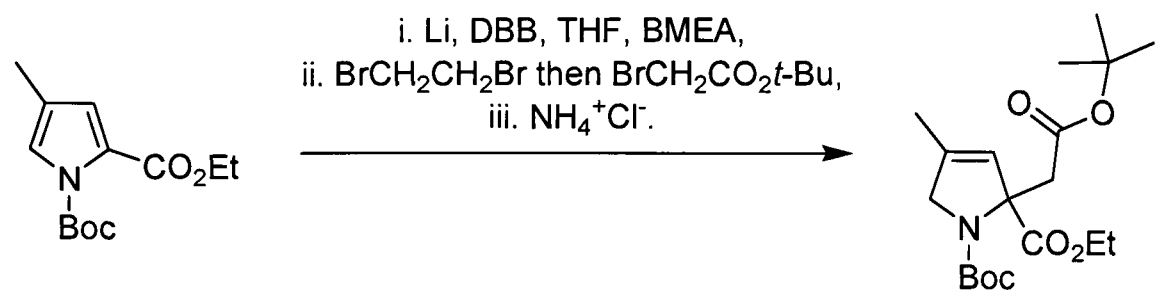
Trifluoroacetic acid (2.00 cm^3) was added dropwise to pyrroline **253** (346 mg, 1.00 mmol) dissolved in dichloromethane (3 cm^3) at ambient temperature, the mixture stirred for 1 hour and was evaporated under reduced pressure. Triethyl amine (0.697 cm^3, 5.00 mmol, 5.00 eq.) dissolved in toluene (5 cm^3) was added to the residue and the solution heated to initiate reflux under an atmosphere or argon; heating continued for 12 hours. On cooling, the mixture was filtered through a short pad of silica, eluting with ethyl acetate and evaporated under reduced pressure. The residue was chromatographed [SiO_2, dichloromethane-ether, 90:10] to give the *indolizine* **265** (180 mg, 86%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C), 20:80] 0.36; **IR** ν_{max} (thin film)/cm^{-1} 3076, 2934, 2857, 2786, 1720, 1560, 1451, 1332, 1287, 1225, 1176, 1159, 1103, 998, 974, 920, 880, 836, 770, 732 and 702; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.85 (2 H, dd, *J* 14.6 and 6.1 HC=C*H*), 5.02 (1 H, hp, *J* 6.3, OCH), 3.79 (1 H, dt, *J* 13.7 and 1.7, NC$H_A$$H_B$CH), 3.62 (1 H, dt, *J* 13.7 and 1.7, NCH$_A$$H_B$CH), 3.24-3.17 (1 H, m, NC$H_A$$H_B$$CH_2$), 2.92-2.88 (1 H, dm, NCH$_A$$H_B$$CH_2$), 2.12-2.09 (1 H, dm, CC$H_A$$H_B$), 1.63-1.59 (1 H, m, CCH_2C$H_A$$H_B$), 1.54-1.41 (1 H, m, NCH_2C$H_A$$H_B$), 1.39-1.25 (3 H, m, $NCH_2CH_A$$H_B$, $CCH_2CH_A$$H_B$ and $CCH_A$$H_B$) and 1.22 (6 H, d, *J* 6.3, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 173.2$^-$ (CO), 134.2$^+$ (HC=*C*H), 128.8$^+$ (H*C*=CH), 72.2$^-$ (NC), 67.9$^+$ (OCH), 56.8$^-$ (N*C*H_2CH), 45.1$^-$ (N*C*$H_2$$CH_2$), 31.7$^-$ (C*C*H_2), 21.8$^+$ ($CHMe_2$), 21.3$^-$ (CH_2) and 20.5$^-$ (CH_2); **MS** *m/z* (+ESI) 210 (100%, MH^+); **HRMS (ESI)** (Found MH^+, 210.1488. $C_{12}H_{19}NO_2$ requires *MH*, 210.1494).

(*2RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-*tert*-butoxylcarbonylmethyl-2,5-dihydropyrrole-2-carboxylate[165] 269



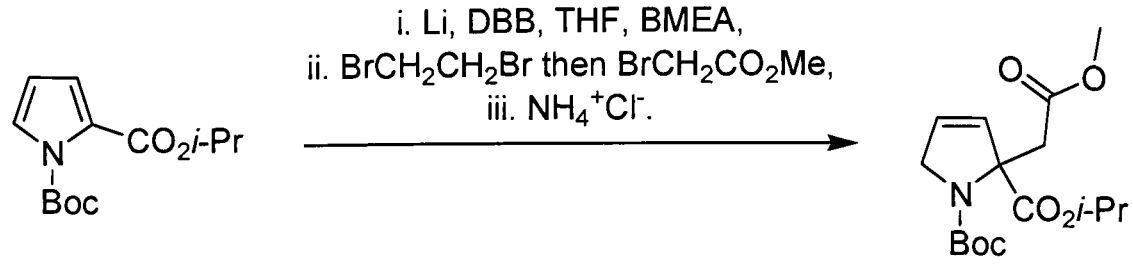
By method E, pyrrole **213** (253 mg, 1.00 mol), dissolved in tetrahydrofuran (20 cm^3) and *bis*(methoxy)ethylamine (0.180 cm^3, 1.20 mmol, 1.20 eq.) was added to a solution of lithium (28 mg, 4.00 mmol, 4.00 eq.), and 4,4-di-*tert*-butylbiphenyl (1.06 g, 4.00 mmol, 4.00 eq.) dissolved in tetrahydrofuran (20 cm^3). After addition of 1,2-dibromoethane *tert*-butyl bromoacetate (369 μcm^3, 2.50 mmol, 2.50 eq.) was added to give the crude product. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60°C), 10:90] to give the pyrroline **269** (240 mg, 65%) as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.96, 5.90 (1 H, dt, *J* 6.2 and 1.9, CH=C*H*), 5.77, 5.68 (1 H, dt, *J* 6.2 and 2.2, C*H*=CH), 4.99, 4.94 (1 H, hp, *J* 6.3, OCH), 4.30, 4.23 (1 H, dt, *J* 15.6 and 2.1, NCH_AH_B), 4.14, 4.09 (1 H, dt, *J* 15.6 and 2.1, NCH_AH_B), 3.22, 3.01 (1 H, d, *J* 14.2, $CH_AH_BCO_2$), 3.12, 2.91 (1 H, d, *J* 13.9, $CH_AH_BCO_2$), 1.45 (9 H, s, CMe_3), 1.38 (9 H, s, CMe_3) and 1.23, 1.18 (6 H, d, *J* 6.3, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 170.5^-, 170.3^- (CO), 169.7^-, 169.2^- (CO), 153.1^-, 152.9^- (NCO), 129.6^+, 129.4^+ (*C*=CH), 128.1^+, 128.0^+ (*C*=CH), 80.6^-, 80.4^- (CMe_3), 80.0^-, 79.7^- (CMe_3), 73.4^-, 73.0^- (NC), 69.3^+, 69.0^+ (OCH), 54.9^-, 54.7^- (NCH_2), 40.6^-, 39.5^- (CH_2CO_2), 28.4^+, 28.3^+ (CMe_3), 27.9^+ (CMe_3) and 21.7^+, 21.6^+ ($CHMe_2$). All spectroscopic data agreed with those previously published.[165]

(2*RS*)-Ethyl 1-(*tert*-butoxycarbonyl)-2-*tert*-butoxylcarbonylmethyl-4-methyl-2,5-dihydropyrrole-2-carboxylate 270



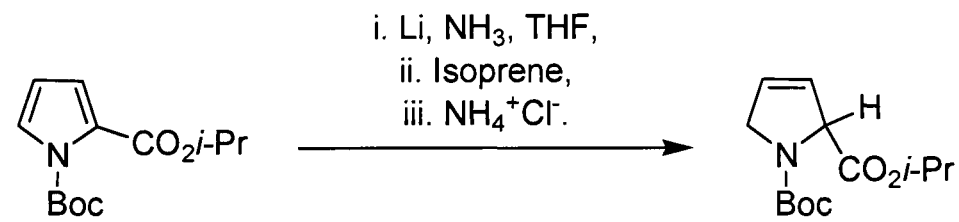
By method E, pyrrole **235** (253 mg, 1.00 mol), dissolved in tetrahydrofuran (20 cm^3) and *bis*(methoxy)ethylamine (0.18 cm^3, 1.20 mmol, 1.20 eq.) was added to a solution of lithium (28 mg, 4.00 mmol, 4.00 eq.), and 4,4-di-*tert*-butylbiphenyl (1.06 g, 4.00 mmol, 4.00 eq.) dissolved in tetrahydrofuran (20 cm^3). After addition of 1,2-dibromoethane *tert*-butyl bromoacetate (369 μcm^3, 2.50 mmol, 2.50 eq.) was added to give the crude product. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60°C), 10:90] to give the *pyrroline* **270** (240 mg, 65%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 2978, 1735, 1707, 1393, 1367, 1348, 1257, 1235, 1165, 1122, 1059, 1025, 947, 841 and 773; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.43, 5.38 (1 H, d, *J* 1.6, C=CH), 4.28-3.97 (4 H, m, NCH_2 and OCH_2), 3.20, 3.01 (1 H, d, *J* 14.1, NCH_AH_B), 3.07, 2.90 (1 H, d, *J* 13.8, NCH_AH_B), 1.79, 1.76 (3 H, s, Me), 1.46, 1.44 (9 H, s, CMe_3), 1.39 (9 H, s, CMe_3) and 1.25, 1.22 (3 H, t, *J* 7.1, CH_2CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 171.6, 171.3 (CO), 169.8, 169.4 (CO), 152.9, 152.8 (NCO), 138.3, 138.2 (*C*=CH), 123.3, 123.2 (*C*=CH), 80.4, 80.2 (CMe_3), 79.8, 79.7 (CMe_3), 73.6, 73.2 (NC), 61.6, 61.4 (OCH_2), 57.7 (NCH_2), 41.0, 39.7 (CH_2CO_2), 28.4, 28.2 (CMe_3), 27.9 (CMe_3) and 14.2 (CMe), 14.1 (OCH_2CH_3); **MS** *m/z* (+ESI) 392 (100%, MNa^+) and 370 (MH^+); **HRMS (ESI)** (Found MNa^+, 392.2047. $C_{19}H_{31}NO_6Na$ requires *MNa*, 392.2049).

(*2RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-methoxycarbonylmethyl-2,5-dihydropyrrole-2-carboxylate 271



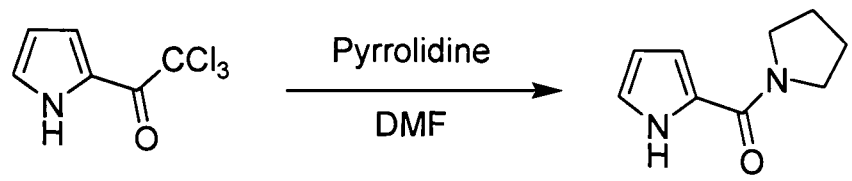
By method E, pyrrole **213** (507 mg, 2.00 mol), dissolved in tetrahydrofuran (20 cm^3) and *bis*(methoxy)ethylamine (0.551 cm^3, 2.40 mmol, 1.20 eq.) was added to a solution of lithium (56 mg, 8.00 mmol, 4.00 eq.), and 4,4-di-*tert*-butylbiphenyl (2.12 g, 8.00 mmol, 4.00 eq.) dissolved in tetrahydrofuran (20 cm^3). After addition of 1,2-dibromoethane methyl bromoacetate (0.462 μcm^3, 5.00 mmol, 2.5 eq.) was added to give the crude product. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60°C), 10:90] to give the *pyrroline* **271** (458 mg, 70%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 2980, 1740, 1701, 1392, 1258, 1215, 1177, 1145, 1106, 1108, 839, 772 and 704; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.98, 5.92 (1 H, dt, *J* 6.2 and 1.9, CH=C*H*), 5.80, 5.75 (1 H, dt, *J* 6.2 and 2.2, C*H*=CH), 4.99, 4.96 (1 H, hp, *J* 6.3, OCH), 4.29, 4.22 (1 H, dt, *J* 15.5 and 2.1, NCH_AH_B), 4.13, 4.09 (1 H, dt, *J* 1.5 and 2.1, NCH_AH_B), 3.61 (3 H, s, OMe), 3.21, 3.10 (2 H, s, CH_2CO_2Me), 1.45, 1.44 (9 H, s, CMe_3) and 1.23-1.17 (6 H, m, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 170.9^-, 170.4^- (CO), 170.4^-, 170.2^- (CO), 153.2^-, 152.9^- (NCO), 129.3^+, 129.0^+ (*C*H=CH), 128.6^+, 128.5^+ (CH=*C*H), 80.8^-, 79.9^- (CMe_3), 73.2^-, 72.6^- (NC), 69.5^+, 69.1^+ (OCH), 54.7^-, 54.6^- (NCH_2), 51.6^+, 51.4^+ (OMe), 39.4^-, 38.1^- (CH_2CO_2Me), 28.4^+, 28.2^+ (CMe_3) and 21.7^+, 21.6^+ ($CHMe_2$); **MS** *m/z* (+ESI) 350 (100%, MNa^+); **HRMS (ESI)** (Found MNa^+, 350.1578. $C_{16}H_{25}NO_6Na$ requires *MNa*, 350.1580).

(*2RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-*H*-2,5-dihydropyrrole-2-carboxylate[165] 274



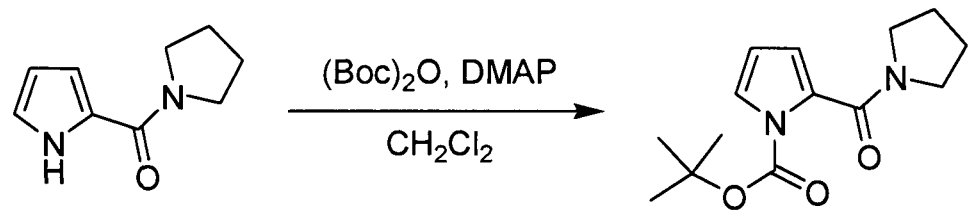
Ammonia (250 cm^3) was freshly distilled onto cut lithium wire (222 mg, 32.0 mmol, 4.00 eq.) under an atmosphere of argon at –78 °C. The resulting dark blue solution was stirred for 1 hour before the dropwise addition of *N*-Boc pyrrole **213** (2.02 g, 8.00 mmol) dissolved in tetrahydrofuran (50 cm^3); stirring continued for a further 10 minutes, the dark blue colour persisting throughout. Isoprene (~ 0.25 cm^3) was added until the dark blue colour disappeared. Aqueous saturated ammonium chloride (25 cm^3) was added, the mixture allowed to warm to ambient temperature and ammonia evaporated. Aqueous hydrochloric acid (1.0 mol dm^{-3}, 125 cm^3) was added and the solution stirred for 5 minutes before being separated. The aqueous layer was extracted with ether (3 × 150 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure to give the *pyrroline* **274** (2.00 g, 98%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 2979, 1751, 1708, 1621, 1467, 1456, 1400, 1368, 1329, 1311, 1256, 1197, 1107, 1010, 961, 911, 895, 868, 818, 794, 713 and 685; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.94, 5.89 (1 H, dq, *J* 6.1 and 2.0, CH=C*H*), 5.71, 5.67 (1 H, dq, *J* 6.3 and 2.2, C*H*=CH), 5.01, 4.99 (1 H, hp, *J* 6.3, OCH), 4.94, 4.87 (1 H, ddd, *J* 5.3, 5.3 and 2.3, NCH), 4.27-4.06 (2 H, m, NCH_2), 1.45, 1.41 (9 H, s, CMe_3) and 1.22, 1.18 (6 H, d, *J* 6.3, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 170.0^-, 169.7^- (CO), 153.7^-, 153.4^- (NCO), 129.1^+, 129.1^+ (CH=*C*H), 124.9^+, 124.9^+ (*C*H=CH), 80.0^-, 79.8^- (CMe_3), 68.6^+, 68.6^+ (OCH), 66.7^+, 66.5^+ (NCH), 53.5^-, 53.3^- (NCH_2), 28.4^+, 28.3^+ (CMe_3), 21.8^+, 21.7^+ ($CHMe_AMe_B$) and 21.7^+, 21.6^+ ($CHMe_AMe_B$); **MS** *m/z* (+ESI) 533 ($2MNa^+$) and 277 (100%, MNa^+); **HRMS (ESI)** (Found MNa^+, 278.1360. $C_{13}H_{21}NO_4Na$ requires *MNa*, 278.1368).

Pyrrolidine pyrrole-2-methanone[2]



Pyrrolidine (4.40 cm^3, 52.0 mmol, 2.20 eq) was added dropwise to a solution of 2-(trichloroacetyl)pyrrole (5.00 g, 23.6 mmol) dissolved in *N*-*N*-dimethylformamide (15 cm^3) under an atmosphere of argon at ambient temperature and the mixture stirred for 18 hours. The solution was poured into a mixture of water (40 cm^3) and aqueous hydrochloric acid (0.2 mol dm^{-3}, 20 cm^3) and separated. The aqueous layer was extracted with ethyl acetate (3 × 50 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was triturated with light petroleum (bp 40-60 °C) to give pyrrolidine pyrrole-2-methanone (3.18 g, 82%) as a solid; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 10.41 (1 H, s, br, NH), 6.93 (1 H, td, *J* 2.6 and 1.2, ArH), 6.59 (1 H, m, ArH), 6.24 (1 H, dd, *J* 6.2 and 2.6, ArH), 3.71 (4 H, s, br, 2 × NCH_2) and 1.99 (2 H, s, br, CH_AH_B and CH_AH_B) and 1.91 (2 H, s, br, CH_AH_B and CH_AH_B); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 160.5$^-$ (CO), 126.0$^-$ (ArC), 121.1$^+$ (ArC), 112.0$^+$ (ArC), 109.6$^+$ (ArC), 47.8$^-$ (NCH_2), 47.1$^-$ (NCH_2) and 23.9 (2 × CH_2). All spectroscopic data agreed with those previously published.[2]

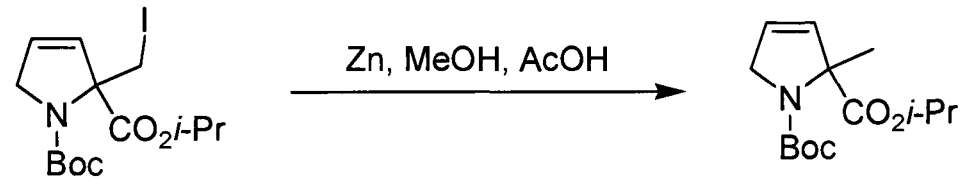
Pyrrolidine 1-(*tert*-butoxycarbonyl)pyrrole-2-methanone[2] **275**



By method A, di-*tert*-butyl dicarbonate (5.04 g, 23.7 mmol, 1.20 eq.) dissolved in dichloromethane (25 cm^3) was added dropwise to a solution of pyrrolidine pyrrole-2-methanone (3.16 g, 19.2 mmol) and 4-(dimethylamino)pyridine (470 mg, 3.85 mmol, 0.20 eq.) dissolved in dichloromethane (30 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 2:1] to give the protected pyrrole amide **275** (4.57 g, 90%) as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.22-7.21 (1 H, m, ArH), 6.29-6.27 (1 H, m, ArH), 6.14 (1 H, apparent t, *J* 3.3, ArH), 3.58 (2 H, t, *J* 6.5, NCH_2), 3.27 (2 H, t, *J* 6.2, NCH_2), 1.95-1.85 (4 H, m, 2 × CH_2) and 1.54 (9 H, s,

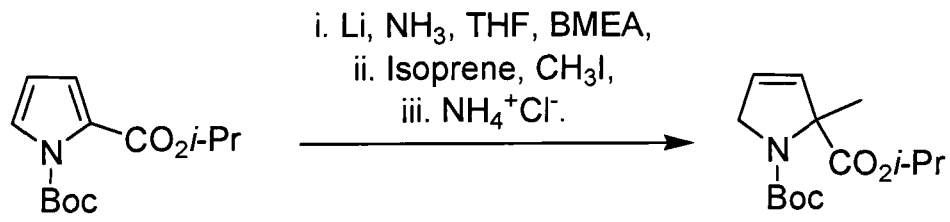
CMe_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 162.8$^-$ (CO), 148.3$^-$ (CO), 129.0$^-$ (ArC), 121.6$^+$ (ArC), 113.0$^+$ (ArC), 110.6$^+$ (ArC), 84.3$^-$ (CMe_3), 48.3$^-$ (NCH_2), 45.5$^-$ (NCH_2), 27.8$^+$ (Me_3), 25.8$^-$ (CH_2) and 24.6$^-$ (CH_2). All spectroscopic data agreed with those previously published.[2]

(*2RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-methyl-2,5-dihydropyrrole-2-carboxylate[2] 220



Acetic acid (4 drops) was added to a mixture of pyrroline **217** (198 mg, 500 μmol) and activated zince (163 mg, 2.50 mmol) dissolved in methanol (7 cm^{-3}) and the mixture heated to initiate reflux; heating continued for 3 hours. The mixture was evaporated under reduced pressure and the residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 5:95] to give the pyrroline **220** (135 mg, 82%) as an oil.

Alternatively:

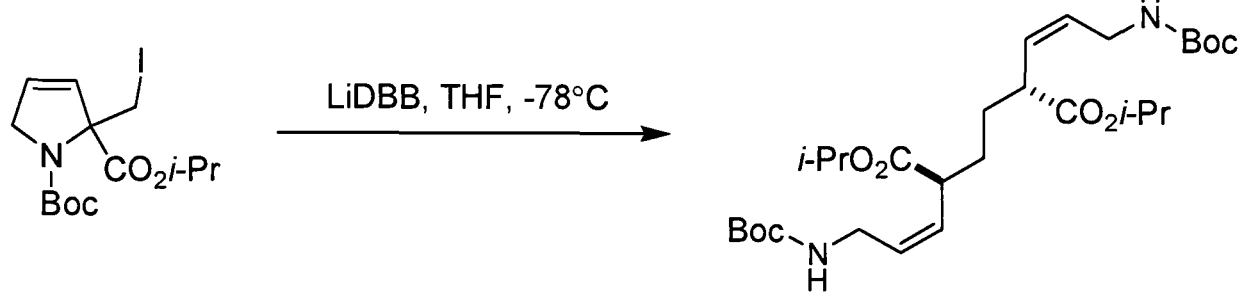


Ammonia (250 cm^3) was freshly distilled onto cut lithium wire (111 mg, 16.0 mmol, 4.00 eq.) under an atmosphere of argon at –78 °C. The resulting dark blue solution was stirred for 1 hour before the addition of *bis*(methoxyethyl)amine (5.90 cm^3, 40.0 mmol, 10.0 eq.) and tetrahydrofuran (20 cm^3). After 5 minutes *N*-Boc pyrrole **213** (1.01 g, 4.00 mmol) dissolved in tetrahydrofuran (30 cm^3) was added dropwise over 5 minutes and stirred for a further 55 minutes, the dark blue colour persisting throughout. Isoprene (~ 0.25 cm^3) was added until the dark blue colour disappeared. On addition of iodomethane (1.74 cm^3, 28.0 mmol, 7.00 eq.) the rapidly stirring solution turned dark brown and was allowed to stir for 15 minutes before the addition of aqueous saturated ammonium chloride (5 cm^3). The reaction was allowed to warm to ambient temperature and ammonia evaporated. Aqueous citric acid (1.0 mol dm^{-3}, 125 cm^3) was added and the solution stirred for 5 minutes before being separated.

The aqueous layer was extracted with ether (4 × 150 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 5:95] to give the pyrroline **220** (863 mg, 80%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C) 10:90] 0.27; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.87, 5.81 (1 H, dt, *J* 6.2 and 2.0, CH=C*H*), 5.57, 5.53 (1 H, dt, *J* 6.2 and 2.0, C*H*=CH), 4.97, 4.93 (1 H, hp, *J* 6.3, OCH), 4.30, 4.23 (1 H, dt, *J* 15.6 and 2.1, NCH_AH_B), 4.18, 4.12 (1 H, dt, *J* 15.6 and 2.1, NCH_AH_B), 1.62, 1.58 (3 H, s, CMe), 1.45, 1.43 (9 H, s, CMe_3) and 1.23-1.16 (6 H, m, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 171.8$^-$, 171.7$^-$ (CO), 153.5$^-$, 153.4$^-$ (NCO), 131.8$^+$, 131.7$^+$ (H*C*=CH), 126.8$^+$ (HC=C*H*), 80.1$^-$, 79.4$^-$ (CMe_3), 72.1$^-$, 71.7$^-$ (NC), 68.7$^+$, 68.4$^+$ (OCH), 54.5$^-$ (NCH_2), 28.4$^+$, 28.3$^+$ (CMe_3), 22.5$^+$ (CMe) and 21.7$^+$, 21.6$^+$ ($CHMe_2$). All spectroscopic data agreed with those previously published.[2]

(*Meso*)-Di-*iso*-propyl 2,5-*bis*-(3-*tert*-butoxycarbonylamino-propenyl)-hex-*cis*-enedioic-1-carboxylate 277

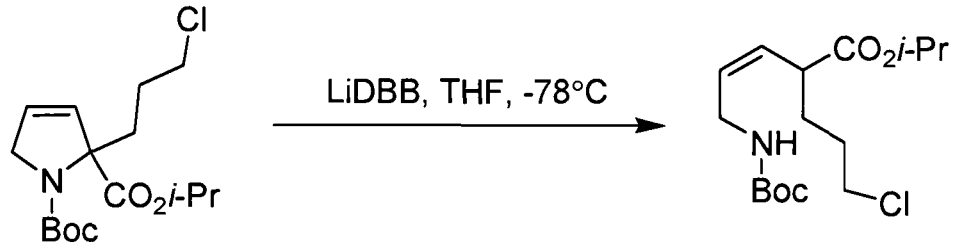
H



By method D, pyrroline **217** (366 mg, 926 μmol), dissolved in tetrahydrofuran (20 cm^3) was added to a solution of lithium (21 mg, 3.00 mmol, 3.00 eq.), and 4,4-di-*tert*-butylbiphenyl (798 mg, 3.00 mmol, 3.00 eq.) dissolved in tetrahydrofuran (20 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60°C), 10:90] to give the *meso carbamate* **277** (198 mg, 79%) as needles, mp 87-90 °C [(from dichloromethane-light petroleum (bp 40-60 °C)]; R_f [ethyl acetate-light petroleum (bp 40-60 °C) 20:80] 0.50; **IR** ν_{max} (solution cell)/cm^{-1} 3370, 2978, 2936, 1713, 1457, 1441, 1420, 1250, 1043 and 1021; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.63-5.57 (2 H, m, NCH_2CH=CH), 5.43 (2 H, t, *J* 10.3 NCH_2CH=C*H*), 4.97 (2 H, hp, *J* 6.3, OCH), 4.73-4.69 (2 H, br m, NH), 3.84-3.69 (4 H, dm, NCH_2), 3.27 (2 H, s, C*H*CO_2), 1.78-1.66 (2 H, m, CHCH_AH_B), 1.43 (20 H, apparent s, CMe_3 and CHCH_AH_B) and 1.22-1.19 (12 H, apparent t, *J* 6.3, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 172.7$^-$ (2 × CO), 155.7$^-$ (2 × NCO), 130.1$^+$ (2 × CH=*C*H), 129.2$^+$ (2 ×

*C*H=CH), 79.4$^-$ (2 × CMe_3), 68.2$^+$ (2 × OCH), 44.0$^+$ (2 × $CHCO_2$), 37.7$^-$ (2 × NCH_2), 29.6$^-$ (2 × $CHCH_2$), 28.4$^+$ (2 × CMe_3) and 21.6$^+$ (2 × $CHMe_2$); **^{1}H NMR** δ_H (400 MHz; C_6D_6) 5.47-5.36 (4 H, m, C*H*=C*H*), 4.96 (1 H, hp, *J* 6.3, OCH_A), 4.95 (1 H, hp, *J* 6.3, OCH_B), 4.55 (1 H, s, NH_A), 4.45 (1 H, s, NH_B), 3.91-3.81 (2 H, NCH_AH_B), 3.66-3.60 (2 H, m, NCH_ACH_B), 3.33 (2 H, s, $CHCO_2$), 1.84-1.77 (2 H, m, $CHCH_AH_B$), 1.58-1.47 (2 H, m, $CHCH_AH_B$), 1.44 (9 H, s, CMe_3), 1.43 (9 H, s, CMe_3) and 1.02 (6 H, d, *J* 6.3, CH_AMe_2), 1.00 (6 H, d, *J* 6.3, CH_BMe_2); **^{13}C NMR** δ_C (100.6 MHz; C_6D_6) 172.8 (2 × CO), 155.9 (2 × NCO), 130.5 (2 × CH=*C*H), 130.1 (2 × CH=*C*H), 78.9 (2 × CMe_3), 68.1 (2 × OCH), 44.4 (2 × $CHCO_2$), 38.3 (2 × NCH_2), 30.3 (2 × $CHCH_2$), 28.7 (2 × CMe_3) and 21.9 (2 × $CHMe_2$); **MS** *m/z* (+ESI) 563 (100%, MNa^+), 542 (MH^+) and 442 (MH^+ - CO_2CMe_3); **HRMS (ESI)** (Found MH^+, 541.3488. $C_{28}H_{49}N_2O_8$ requires *MH*, 541.3489).

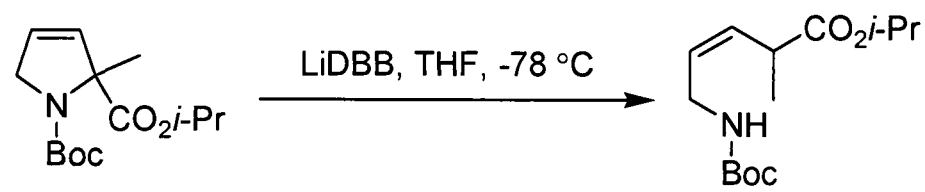
(*RS*)-*Iso*-propyl 5-(-*tert*-butoxycarbonylamino)-2-(3-chloropropyl)-pent-3-*cis*-enoic carboxylate 283



By method D, pyrroline **252** (250 mg, 750 μmol), dissolved in tetrahydrofuran (20 cm^3) was added to a solution of lithium (21 mg, 3.01 mmol, 4.00 eq.), and 4,4-di-*tert*-butylbiphenyl (802 mg, 3.01 mmol, 4.00 eq.) dissolved in tetrahydrofuran (20 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60°C), 10:90] to give the *carbamate* **283** (175 mg, 70%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C) 10:90] 0.23; **IR** ν_{max} (thin film)/cm^{-1} 3380, 2987, 1730, 1689, 1470, 1434, 1240, 1028, 1010 and 702; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.62 (1 H, dt, *J* 10.7 and 7.0 C*H*=CH), 5.47 (1 H, apparent t, *J* 10.7, CH=C*H*), 4.99 (1 H, hp, *J* 6.3, OCH), 4.62 (1 H, s, br, NH), 3.89-3.85 (1 H, m, NCH_AH_B), 3.74-3.68 (1 H, m, NCH_ACH_B), 3.52 (2 H, t, *J* 6.3, CH_2Cl), 3.31 (1 H, dd, *J* 16.3 and 7.2 $CHCO_2$), 1.94-1.86, 1.79-1.62 (4 H, m, CH_2), 1.44 (9 H, s, CMe_3) and 1.22 (6 H, d, *J* 6.2, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 172.7 (CO), 155.7 (NCO), 130.2 (CH=*C*H), 129.2 (*C*H=CH), 77.2 (CMe_3), 68.2 (OCH), 44.5 (CH_2Cl), 43.6 ($CHCO_2$), 37.7 (NCH_2), 30.0, (CH_2), 29.7 (CH_2), 28.4 (CMe_3) and 21.8 ($CHMe_2$); **MS** *m/z* (+ESI) 356, 358

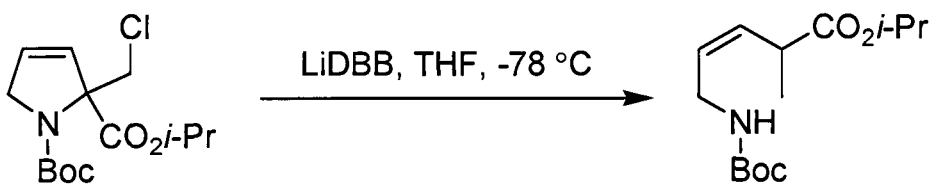
(100%, MNa^+) and 234, 236 (MH^+ - CO_2CMe_3); **HRMS (ESI)** (Found MNa^+, 356.1595. $C_{16}H_{28}NO_4{}^{35}ClNa$ requires *MNa*, 356.1605).

(*RS*)-*Iso*-propyl 5-(-*tert*-butoxycarbonylamino)-2-methyl-pent-3-*cis*-enoic carboxylate 284



By method D, pyrroline **220** (269 mg, 1.00 mmol), dissolved in tetrahydrofuran (20 cm^3) was added to a solution of lithium (28 mg, 4.00 mmol, 4.00 eq.) and 4,4-di-*tert*-butylbiphenyl (1.06 g, 4.00 mmol, 4.00 eq.) dissolved in tetrahydrofuran (20 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60°C), 10:90] to give the *carbamate* **284** (163 mg, 60%) as an oil;

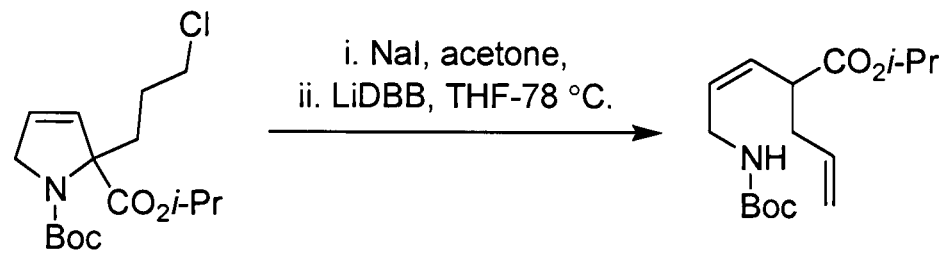
Alternatively:



By method D, pyrroline **221** (304 mg, 1.00 mmol), dissolved in tetrahydrofuran (20 cm^3) was added to a solution of lithium (27.8 mg, 4.00 mmol, 4.00 eq.) and 4,4-di-*tert*-butylbiphenyl (1.06 g, 4.00 mmol, 4.00 eq.) dissolved in tetrahydrofuran (20 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60°C), 10:90] to give the *carbamate* **284** (193 mg, 71%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3386, 1720, 1507, 1457, 1367, 1318, 1251, 1175 and 1108; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.56-5.46 (2 H, m, CH=CH), 4.99 (1 H, hp, *J* 6.3, OCH), 4.62 (1 H, br s, NH), 3.86-3.81 (1 H, m, NCH_AH_B), 3.73-3.68 (1 H, m, NCH_AH_B), 3.41-3.34 (1 H, m, $CHCO_2$), 1.42 (9 H, s, CMe_3), 1.24-1.21 (3 H, m, CHMe) 1.22 (3 H, d, *J* 6.1, $CHMe_AMe_B$) and 1.21 (3 H, d, *J* 6.1, $CHMe_AMe_B$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 173.7 (CO), 155.7 (NCO), 132.0 (CH=*C*H), 127.8 (*C*H=CH), 79.3 (CMe_3), 68.0 (OCH), 38.4 ($CHCO_2$) 37.6 (NCH_2), 28.4 (CMe_3), 21.7 ($CHMe_2$) and 17.6

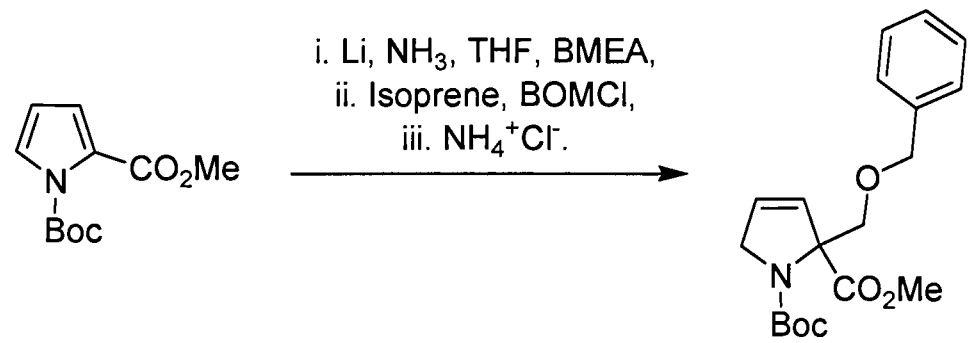
(CHMe); **MS** *m/z* (+ESI) 294 (100%, MNa^+) and 272 (MH^+); **HRMS (ESI)** (Found MNa^+, 294.1679. $C_{14}H_{25}NO_4Na$ requires *MNa*, 294.1681).

(*RS*)-*Iso*-propyl 5-(-*tert*-butoxycarbonylamino)-2-allyl-pent-3-*cis*-enoic carboxylate 292



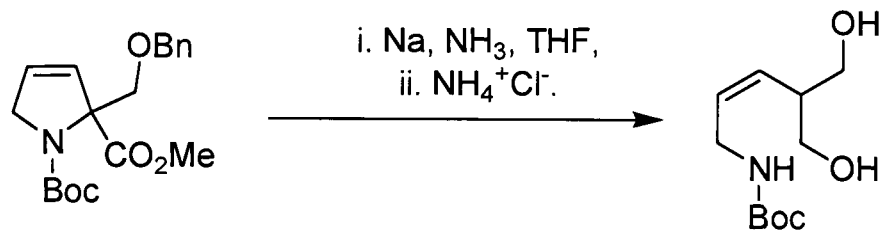
Sodium iodide (199 mg, 1.33 mmol, 10.0 eq.) was added to a solution of pyrroline **252** (44 mg, 133 μmol) dissolved in acetone (2 cm^3) and heated to initiate reflux; heating continued for 35 hours. On cooling, the mixture was evaporated under reduced pressure and the residue dissolved in ether (10 cm^3) and poured into aqueous saturated sodium thiosulfate (10 cm^3). The layers were separated and the organic layer dried (anhydrous magnesium sulfate) and evaporated under reduce pressure. By method D, the residue (56 mg, 133 μmol), dissolved in tetrahydrofuran (20 cm^3) was added to a solution of lithium (4 mg, 532 μmol, 4.00 eq.), and 4,4-di-*tert*-butylbiphenyl (142 mg, 532 μmmol, 4.00 eq.) dissolved in tetrahydrofuran (12 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60°C), 10:90] to give the *allyl carbamate* **292** (30 mg, 76%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C) 10:90] 0.35; **IR** ν_{max} (thin film)/cm^{-1} 3377, 2980, 1715, 1514, 1367, 1251, 1174, 1108 and 916; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.76-5.65 (1 H, m, C*H*=CH_2), 5.64-5.58 (1 H, m, C*H*=CH), 5.49 (1 H, apparent t, *J* 10.2, CH=C*H*), 5.09-4.94 (2 H, m, CH=CH_2), 4.99 (1 H, hp, *J* 6.3, OCH), 4.60 (1 H, br s, NH), 3.86-3.81 (1 H, m, NCH_AH_B), 3.76-3.69 (1 H, m, NCH_AH_B), 3.37 (1 H, dd, *J* 16.5 and 7.4 $CHCO_2$), 2.50 (1 H, dt, *J* 14.1 and 7.0, CH_AH_BCH), 2.26 (1 H, dt, *J* 14.2 and 7.2, CH_AH_BCH), 1.44 (9 H, s, CMe_3), 1.23 (3 H, d, *J* 6.1, CH*Me*$_A$Me$_B$) and 1.22 (3 H, d, *J* 6.1, CHMe$_A$*Me*$_B$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 172.6 (CO), 155.7 (NCO), 134.7 (*C*H=CH_2), 130.0 (CH=*C*H), 128.8 (CH=*C*H_2), 117.2 (CH=*C*H), 77.2 (CMe_3), 68.2 (OCH), 44.0 ($CHCO_2$), 37.7 (NCH_2), 36.5 (*C*H_2CH=CH_2), 28.4 (CMe_3) and 21.8 ($CHMe_2$); **MS** *m/z* (+ESI) 320 (100%, MNa^+); **HRMS (ESI)** (Found MNa^+, 320.1833. $C_{16}H_{27}NO_4Na$ requires *MNa*, 320.1838).

(*2RS*)-Methyl 1-(*tert*-butoxycarbonyl)-2-(benzyloxymethyl)-2,5-dihydropyrrole-2-carboxylate 294



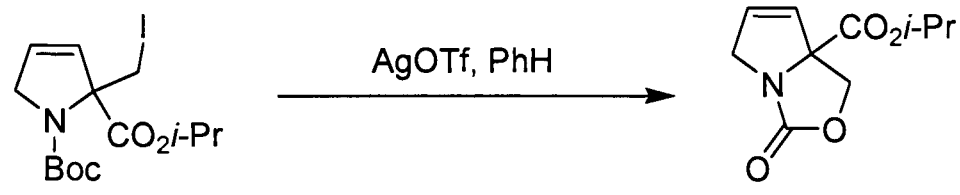
Ammonia (250 cm^3) was freshly distilled onto cut lithium wire (111 mg, 16.0 mmol, 4.00 eq.) under an atmosphere of argon at –78 °C. The resulting dark blue solution was stirred for 1 hour before the addition of *bis*(methoxyethyl)amine (5.90 cm^3, 40.0 mmol, 10.0 eq.) and tetrahydrofuran (20 cm^3). After 5 minutes *N*-Boc pyrrole **293** (901 mg, 4.00 mmol) dissolved in tetrahydrofuran (30 cm^3) was added dropwise over 5 minutes and stirred for a further 55 minutes, the dark blue colour persisting throughout. Isoprene (~ 0.25 cm^3) was added until the dark blue colour disappeared. On addition of benzyl chloromethyl ether (1.66 cm^3, 12.0 mmol, 3.00 eq.) the rapidly stirring solution turned white and was allowed to stir for 5 hours before the addition of aqueous saturated ammonium chloride (5 cm^3). The reaction was allowed to warm to ambient temperature and ammonia evaporated. Aqueous hydrochloric acid (1.0 mol dm^{-3}, 125 cm^3) was added and the solution stirred for 5 minutes before being separated. The aqueous layer was extracted with ether (4 × 150 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 2:98] to give the *pyrroline* **294** (903 mg, 65%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 2976, 2867, 1739, 1703, 1455, 1396, 1319, 1258, 1219, 1166, 1109, 1066, 971, 791, 771 and 743; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.34-7.24 (5 H, m, 5 × ArH), 6.05, 5.99 (1 H, d, *J* 6.2, CH=C*H*), 5.64-5.60 (1 H, m, C*H*=CH), 4.60-4.51 (2 H, m, OCH_2Ph), 4.38, 4.31 (1 H, dt, *J* 15.5 and 1.8, NCH_AH_B), 4.26-4.17 (1 H, dm, NCH_AH_B), 3.98 (2 H, s, CH_2O), 3.70 (3 H, s, CH_3) and 1.47, 1.39 (9 H, s, CMe_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 171.3$^-$, 171.0$^-$ (CO), 153.5$^-$, 153.0$^-$ (NCO), 138.5$^-$, 138.2$^-$ (ArC), 129.1$^+$, 129.0$^+$ (CH=*C*H), 128.4$^+$, 128.3$^+$ (*C*H=CH), 128.3$^+$ (ArC), 128.2$^+$ (ArC), 128.2$^+$ (ArC), 127.6$^+$ (ArC), 127.4$^+$ (ArC), 80.4$^-$, 80.0$^-$ (CMe_3), 75.6$^-$, 75.0$^-$ (NC), 73.5$^+$, 73.5$^+$ (CH_2O), 70.2$^+$, 69.4$^+$ (OCH_2Ph), 54.9$^-$, 53.3$^-$ (NCH_2), 52.3$^+$, 52.2$^+$ (OCH_3), and 28.4$^+$, 28.3$^+$ (CMe_3); **MS** *m/z* (+ESI) 370 (MNa^+) and 348 (MH^+); **HRMS (ESI)** (Found MH^+, 348.1810. $C_{19}H_{26}NO_5$ requires *MH*, 348.1811).

(RS)-*tert*-Butyl 5-hydroxy-4-(hydroxymethyl)pent-2-*cis*-enylcarbamate 295



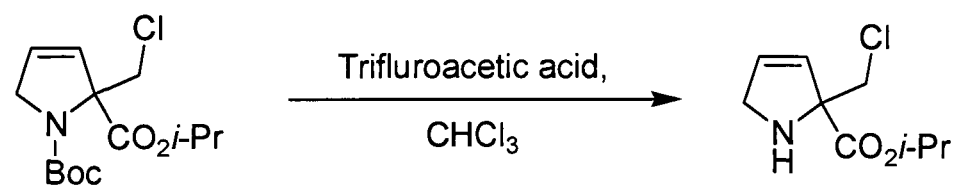
Ammonia (250 cm^3) was freshly distilled onto cut sodium (191 mg, 8.29 mmol, 6.00 eq.) under an atmosphere of argon at –78 °C. The resulting dark blue solution was stirred for 1 hour before the addition of pyrroline **294** (480 mg, 1.38 mmol) dissolved in tetrahydrofuran (30 cm^3), dropwise over 5 minutes and stirred for a further 10 minutes, the dark blue colour persisting throughout. Isoprene (~ 0.25 cm^3) was added until the dark blue colour disappeared. Aqueous saturated ammonium chloride (25 cm^3) was added and the mixture turned white. The reaction was allowed to warm to ambient temperature and ammonia evaporated. Aqueous hydrochloric acid (1.0 mol dm^{-3}, 125 cm^3) was added and the solution separated, the aqueous layer was extracted with ethyl acetate (3 × 150 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 2:98] to give the *carbamate* **295** (220 mg, 69%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3352 br, 2978, 1689, 1524, 1367, 1252, 1171, 1029, 932 and 863; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.60 (1 H, dt, *J* 10.7 and 7.1, C*H*=CH), 5.34 (1 H, apparent t, *J* 10.7, CH=C*H*), 5.01 (1 H, t, *J* 5.5, NH), 3.75 (2 H, t, *J* 3.8, NCH_2), 3.67 (2 H, dd, *J* 10.6 and 6.5, CH_2OH), 3.55 (2 H, dd, *J* 10.6 and 6.5, CH_2OH), 3.23 (2 H, s, br, 2 × OH), 2.92-2.91 (1 H, m, C*H*($CH_2OH)_2$) and 1.41 (9 H, s, CMe_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 156.3^-(NCO), 130.41^+ (*C*H=CH), 129.8^+ (CH=*C*H), 79.8^- (CMe_3), 64.2^+ (2 × CH_2OH), 42.8^+ (C*H*($CH_2OH)_2$), 38.9^- (NCH_2) and 28.4^+; **MS** *m/z* (+ESI) 254 (100%, MNa^+) and 232 (MH^+); **HRMS (ESI)** (Found MNa^+, 254.1364. $C_{11}H_{21}NO_4Na$ requires *MNa*, 254.1368).

(*2RS*)-*Iso*-propyl 1-(3-oxo-oxazole)-2,5-dihydropyrrole-2-carboxylate 298



Silver[(I)] trifluoromethanesulfonate (71 mg, 275 μmol, 1.10 eq) was added to pyrroline **217** (99 mg, 250 μmol) dissolved in deoxygenated benzene (5 cm^3) under an atmosphere of argon at ambient temperature. The mixture stirred for 17 hours, filtered through celite, poured into aqueous saturated sodium hydrogen carbonate (5 cm^3), separated and the aqueous layer extracted with ethyl acetate (3 × 10 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 20:80] to give the *pyrroline* **298** (37 mg, 70%) as an oil; R_f [ethyl acetate-light petroleum (bp 40-60 °C), 40:60] 0.47; **IR** ν_{max} (thin film)/cm^{-1} 2983, 1767 br, 1465, 1378, 1321, 1272, 1209, 1165, 1097, 1067, 1032, 1009, 948, 930, 842, 828, 788 and 699; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 6.17 (1 H, dt, *J* 5.8 and 1.6, CH=C*H*), 5.93 (1 H, dt, *J* 5.8 and 2.2, C*H*=CH), 5.04 (1 H, hp, *J* 6.3, OCH), 4.76 (1 H, d, *J* 9.2, OCH_AH_B), 4.45 (1 H, dt, *J* 15.7 and 2.9, NCH_AH_B), 4.38 (1 H, d, *J* 9.2, OCH_AH_B), 4.05-4.04, 4.01-4.00 (1 H, dm, NCH_AH_B), 1.25 (3 H, d, *J* 6.3, $CHMe_AMe_B$) and 1.24 (3 H, d, *J* 6.3, $CHMe_AMe_B$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 169.9 (CO), 161.8 (NCO), 133.0 (CH=*C*H), 128.7 (*C*H=CH), 76.7 (NC) 70.8 (OCH_2), 70.1 (OCH), 55.4 (NCH_2), 21.6 ($CHMe_AMe_B$), 21.5 ($CHMe_AMe_B$); **MS** *m/z* (+ESI) 212 (100%, MH^+); **HRMS (ESI)** (Found MH^+, 212.0922. $C_{10}H_{14}NO_4$ requires *MH*, 212.0923).

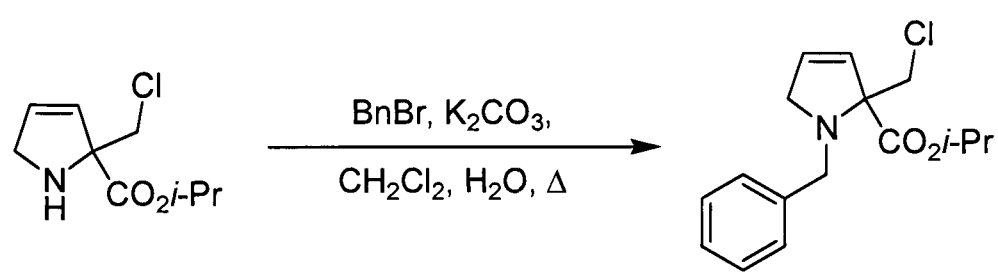
(*2RS*)-*Iso*-propyl-2-chloromethyl-2,5-dihydropyrrole-2-carboxylate 299



Trifluoroacetic acid (5 cm^3) was added dropwise to a solution of pyrroline **221** (750 mg, 2.47 mmol) dissolved in chloroform (5 cm^3) at ambient temperature, the resulting solution was stirred for 45 minutes and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (10 cm^3) and stirred vigorously with aqueous saturated sodium hydrogen

carbonate (15 cm^3) for 15 minutes. The layers were separated and the aqueous layer extracted with ethyl acetate (3 × 10 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure to give *pyrroline* **299** (478 mg, 95%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3428 br, 1728, 1644, 1467, 1420, 1375, 1284, 1262, 1194, 1106, 1065 and 994; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 6.03-6.01 (1 H, m, CH=C*H*), 5.64-5.61 (1 H, m, C*H*=CH), 5.35 (1 H, hpd, *J* 6.2 and 2.2, OCH), 3.96 (1 H, dd, *J* 15.4 and 2.1, NCH_AH_B), 3.88 (1 H, dd, *J* 10.5 and 2.0, CH_AH_BCl), 3.75 (1 H, dd, *J* 15.4 and 2.1, NCH_AH_B), 3.45 (1 H, dd, *J* 10.5 and 2.0, CH_AH_BCl), 3.00 (1 H, s, br, NH) and 1.27-1.22 (6 H, m, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 171.7$^-$ (CO), 133.3$^+$ (CH=*C*H), 127.4$^+$ (*C*H=CH), 77.7$^-$ (NC), 69.7$^+$ (OCH), 54.0$^-$ (NCH_2), 50.5$^-$ (CH_2Cl) and 21.7 ($CHMe_2$); **MS** *m/z* (+ESI) 304, 206 (100%, MH^+); **HRMS (ESI)** (Found MH^+, 204.0800. $C_9H_{15}NO_2{}^{35}Cl$ requires *MH*, 204.0791).

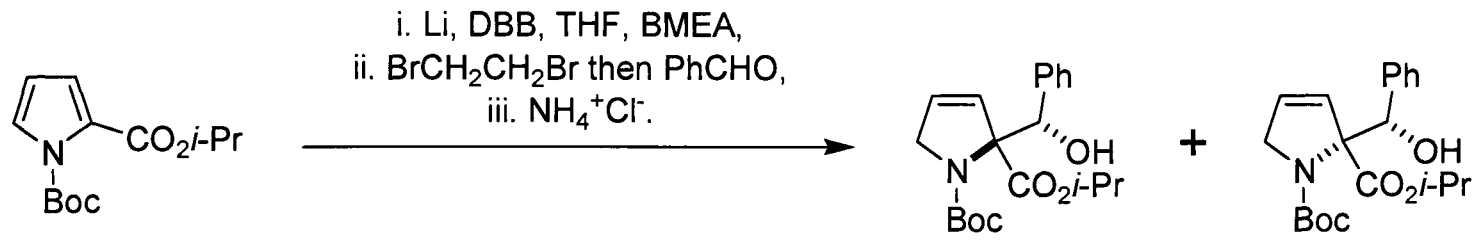
(*2RS*)-*Iso*-propyl 1-(benzyl)-2-iodomethyl-2,5-dihydropyrrole-2-carboxylate 300



Benzyl bromide (1.17 cm^3, 9.87 mmol, 3.00 eq.) was added to a mixture of pyrroline **299** (2.01 g, 3.29 mmol), potassium carbonate (2.73 g, 19.75 mmol, 3.00 eq.), dichloromethane (14 cm^3) and water (7 cm^3) and heated to intiate reflux; heating continued for a further 24 hours. The mixture was separated and the aqueous layer extracted with ethyl acetate (3 × 20 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 10:90] to give the *benzylated pyrroline* **300** (570 mg, 59%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 2981, 2801, 1724, 1495, 1454, 1374, 1248, 1180, 1106, 1073, 1059, 1015, 986, 912, 835, 739 and 700; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.38 (2 H, d, *J* 7.5, ArH), 7.32 (2 H, apparent t, *J* 7.4, ArH), 7.26-7.23 (1 H, m, ArH), 6.08 (1 H, dt, *J* 6.1 and 1.7, CH=C*H*), 5.79 (1 H, dt, *J* 6.1 and 2.1, C*H*=CH), 5.12 (1 H, hp, *J* 6.3, OCH), 4.06 (1 H, d, *J* 13.6, NCH_AH_BBn), 3.99 (1 H, d, *J* 11.2, CH_AH_BCl), 3.91 (1 H, d, *J* 13.6, NCH_AH_BBn), 3.77 (1 H, d, *J* 11.2, CH_AH_BCl), 3.65 (1 H, dt, *J* 13.8 and 2.0, NCH_AH_B), 3.50 (1 H, dt, *J* 13.8 and 2.0, NCH_AH_B), 1.32 (3 H, d, *J* 6.3, $CHMe_AMe_B$) and 1.29 (3 H, d, *J* 6.3, $CHMe_AMe_B$); **^{13}C**

NMR δ_C (100.6 MHz; $CDCl_3$) 170.7$^-$ (CO), 139.6$^-$ (ArC), 131.8$^+$ (ArC), 129.0$^+$ (ArC), 128.3$^+$ (ArC), 128.2$^+$ (ArC), 127.0$^+$ (ArC), 77.7$^-$ (NC), 69.0$^+$ (OCH), 59.5$^-$ (NCH_2), 53.3$^-$ (NCH_2Bn), 47.3$^-$ (CH_2Cl), 22.0$^+$ ($CHMe_AMe_B$) and 21.8$^+$ ($CHMe_AMe_B$); **MS** *m/z* (+ESI) 296, 294 (100%, MH^+); **HRMS (ESI)** (Found MH^+, 294.1255. $C_{16}H_{21}NO_2{}^{35}Cl$ requires *MH*, 294.1261).

(*1RS, 2RS*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-hydroxy(phenyl)methyl-2,5-dihydropyrrole-2-carboxylate *anti* 301 and (*1RS, 2SR*)-*Iso*-propyl 1-(*tert*-butoxycarbonyl)-2-hydroxy(phenyl)methyl-2,5-dihydropyrrole-2-carboxylate *syn* 302

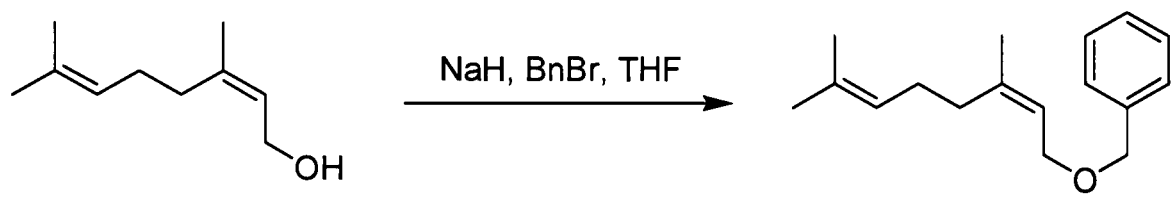


By method E, pyrrole **213** (253 mg, 1.00 mol), dissolved in tetrahydrofuran (20 cm^3) and *bis*(methoxy)ethylamine (0.180 cm^3, 1.20 mmol, 1.20 eq.) was added to a solution of lithium (27.8 mg, 4.00 mmol, 4.00 eq.), and 4,4-di-*tert*-butylbiphenyl (1.06 g, 4.00 mmol, 4.00 eq.) dissolved in tetrahydrofuran (20 cm^3). After addition of 1,2-dibromoethane, benzaldehyde (0.304 μcm^3, 3.00 mmol, 3.00 eq.) was added to give the crude product. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40-60 °C), 10:90] to give the *pyrrolines* **301** (163 mg, 45%) and **302** (163 mg, 45%) as oils; data for *anti* **301**; **IR** ν_{max} (thin film)/cm^{-1} 3521 br, 2980, 2935, 2935, 2867, 1699 br, 1626, 1455, 1396, 1329, 1163, 1104, 1035, 1008, 973, 913, 834, 774, 722, 703 and 606; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.29-7.21 (5 H, m, 5 × ArH), 5.92, 5.89 (1 H, dt, *J* 6.3 and 2.1, CH=C*H*), 5.79, 5.77 (1 H, dt, *J* 6.3 and 2.1, C*H*=CH), 5.75, 5.61 (1 H, s, C*H*(OH)Ph), 5.12, 5.04 (1 H, hp, *J* 6.3, $OCHMe_2$), 4.37 (1 H, s, br, OH), 4.05, 3.96 (1 H, dt, *J* 15.4 and 2.0, NCH_AH_B), 3.19, 3.11 (1 H, dt, *J* 15.4 and 2.0, NCH_AH_B), 1.56, 1.47 (9 H, s, CMe_3) and 1.30-1.21 (6 H, dm, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 173.4$^-$, 173.2$^-$ (CO), 153.5$^-$, 152.5$^-$ (NCO), 138.4$^-$, 138.1$^-$ (ArC), 130.4$^+$, 130.3$^+$ (CH=CH), 129.2$^+$, 127.7$^+$, 127.6$^+$, 127.4$^+$, 127.3$^+$, 127.1$^+$ (5 × ArC), 126.0$^+$, 125.9$^+$ (CH=CH), 124.9$^+$ (ArC), 81.2$^-$, 80.0$^-$ (CMe_3), 78.2$^-$, 77.8$^-$ (NC), 74.2$^+$, 74.1$^+$ (CHOH), 70.0$^+$, 69.4$^+$ (OCH), 54.8$^-$, 54.5$^-$ (NCH_2), 28.6$^+$, 28.4$^+$ (CMe_3), 21.8$^+$, 21.6$^+$ ($CHMe_AMe_B$) and 21.6$^+$, 21.5$^+$ ($CHMe_AMe_B$); **MS** *m/z* (+ESI) 746 (100% $2MNa^+$), 384 (MNa^+) and 362 (MH^+); **HRMS (ESI)** (Found MH^+, 362.1966 $C_{20}H_{28}NO_5$ requires *MH*, 362.1967). Data for *syn* **302**; **IR** ν_{max} (thin film)/cm^{-1} 3306 br, 2980, 2935, 1745, 1676, 1454, 1402, 1321, 1249, 1208,

1164, 1106, 1057, 1035, 993, 835, 793, 770, 733 and 701; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.35-7.20 (5 H, m, 5 × ArC), 7.11 (1 H, d, *J* 10.2, OH), 5.75-5.72 (1 H, m, CH=C*H*), 5.64-5.61 (1 H, m, C*H*=CH) 5.31 (1 H, d, *J* 10.1, CHOH), 5.17 (1 H, hp, *J* 6.2, OCH), 4.04 (1 H, d, *J* 15.6, NCH_AH_B), 3.34 (1 H, d, *J* 15.6, NCH_AH_B), 1.50 (9 H, s, CMe_3) and 1.32, 1.29 (6 H, d, *J* 6.2, $CHMe_2$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 168.8$^-$ (CO), 156.5$^-$ (NCO), 139.9$^-$ (ArC), 128.7$^+$ (CH=CH), 128.1$^+$ (CH=CH), 127.2$^+$, 127.6$^+$, 127.4$^+$, 127.3$^+$, 127.2$^+$ (5 × ArC), 81.9$^-$ (CMe_3), 81.2$^-$ (NC) , 77.3$^+$ (CHOH) 69.5$^+$ (OCH), 55.6$^-$ (NCH_2), 28.4$^+$ (CMe_3) and 21.8$^+$ ($CHMe_2$); **MS** *m/z* (+ESI) 746 ($2MNa^+$), 384 (MNa^+) and 362 (MH^+); **HRMS (ESI)** (Found MH^+, 362.1962 $C_{20}H_{28}NO_5$ requires *MH*, 362.1967).

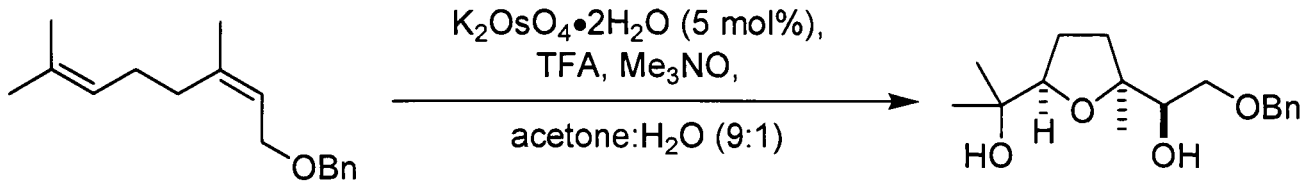
8.4 *Chapter 6 experimental.*

(2-*cis*)-1-Benzyloxy-3,7-dimethyl-octa-2,6-diene[296] 415



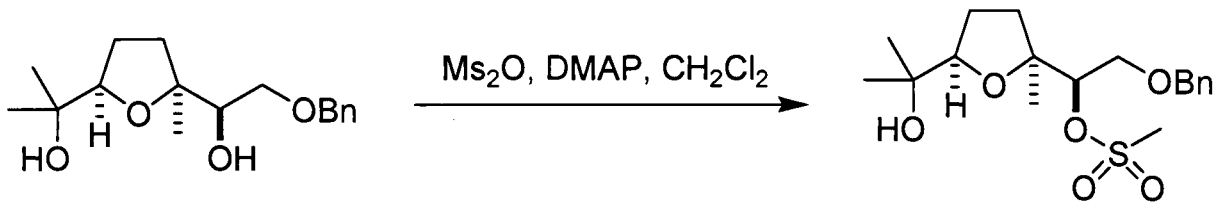
By method F, benzyl bromide (9.24 cm^3, 77.8 mmol, 1.20 eq.) was added dropwise to a mixture of nerol (11.4 cm^3, 64.8 mmol) and sodium hydride (60% dispersion in mineral oil, 5.18 g, 130 mmol, 2.00 eq.) dissolved in tetrahydrofuran (450 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 3:97] to give the benzyl ether **415** (14.6 g, 92%) as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.39-2.27 (5 H, m, 5 × ArC), 5.45 (1 H, td, *J* 6.7 and 1.2, C*H*CH_2OBn), 5.11 (1 H, s, br, $(Me)_2$C=CH), 4.53 (2 H, s, OCH_2Ph), 4.04 (2 H, dd, *J* 6.7 and 0.8, CH_2OBn), 2.09-2.08 (4 H, m, 2 × CH_2), 1.79 (3 H, s, CH_3), 1.70 (3 H, s, CH_3) and 1.61 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 140.6$^-$ (C), 138.6$^-$ (C), 131.9$^-$ (C), 128.8$^+$ (ArC), 128.5$^+$ (ArC), 128.4$^+$ (ArC), 127.8$^+$ (ArC), 127.5$^+$ (ArC), 123.9$^+$ ($(Me)_2$C=*C*H), 121.9$^+$ (C=*C*HCH_2OBn), 72.1$^-$ (OCH_2Ph), 66.4$^-$ (CH_2OBn), 32.3$^-$ (CH_2), 26.7$^-$ (CH_2) , 25.7$^+$ (CH_3), 23.5$^+$ (CH_3) and 17.7$^+$ (CH_3). All spectroscopic data agreed with those previously published.[296]

(*RS*)-2-((2*R*,5*S*)-5-((*R*)-2-(Benzyloxy)-1-hydroxyethyl)-5-methyl-tetrahydrofuran-2-yl)propan-2-ol[10] 416



By method G, trimethylamine-*N*-oxide dihydrate (2.22 g, 20.0 mmol, 5.00 eq.) was added to a solution of diene **415** (977 mg, 4.00 mmol) and potassium osmate$^{(VI)}$ dihydrate (74 mg, 0.20 mmol, 0.05 eq.) dissolved in acetone (72 cm^3), water (8 cm^3) and trifluroacetic acid (40 cm^3) to give a crude product. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 5:95] to give the tetrahydrofuran **416** (1.12 g, 95%) as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.37-7.28 (5 H, m, 5 × ArC), 4.55 (2 H, s, OCH_2Ph), 3.84 (1 H, dd, *J* 7.7 and 3.3, C*H*OH), 3.81 (1 H, t, *J* 7.5, OCH), 3.61 (1 H, dd, *J* 9.8 and 3.2, CH_AH_BOBn), 3.41 (1 H, dd, *J* 9.8 and 7.5, CH_AH_BOBn), 3.21 (1 H, s, br, OH), 2.19 (1 H, ddd, *J* 12.4, 8.4 and 6.9, THF CH_AH_BC(Me)O), 2.02-1.85 (2 H, m, THF CH_2-CHO), 1.52 (1 H, ddd, *J* 12.4, 8.4 and 6.9, THF CH_AH_BCOCH), 1.24 (3 H, s, CH_3), 1.15 (3 H, s, CH_3) and 1.09 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 137.8$^-$ (ArC), 128.4$^+$ (ArC), 127.8$^+$ (ArC), 127.7$^+$ (ArC), 127.6$^+$ (ArC), 127.4$^+$ (ArC), 84.9$^+$ (THF OCH), 83.9$^-$ (THF (Me)CO), 75.4$^+$ (CHOH), 73.4$^-$ (OCH_2PH), 71.7$^-$ (CH_2OBn), 71.2$^-$ ($(Me)_2COH$), 32.7$^-$ (THF *C*H_2COCH), 27.7$^+$ (CH_3), 26.5$^-$ (THF *C*H_2-CHO), 25.1$^+$ (CH_3) and 23.5$^+$ (CH_3). All spectroscopic data agreed with those previously published.[10]

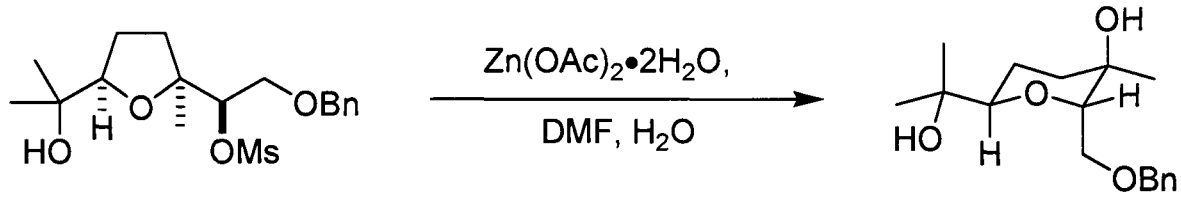
(*RS*)-(*R*)-2-(Benzyloxy)-1-((2*S*,5*R*)-5-(2-hydroxypropan-2-yl)-2-methyl-tetrahydrofuran-2-yl)ethyl methanesulfonate 417



By method H, methanesulfonic anhydride (348 mg, 2.00 mmol, 2.00 eq.) was added to a solution of alcohol **416** (194 mg, 1.00 mmol) and 4-(dimethyl)aminopyridine (489 mg, 4.00 mmol, 4.00 eq.) dissolved in dichloromethane (50 cm^3) to give the *mesylate* **417** (730 mg,

98%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3526 br. 3031, 2976, 2876, 1712, 1497, 1455, 1357 br, 1173, 1076, 919, 806, 748 and 701; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.40-7.28 (5 H, m, 5 × ArH), 4.79 (1 H, dd, *J* 7.9 and 2.3, CHOMs), 4.58 (1 H, d, *J* 11.8, OCH_AH_BPh), 4.52 (1 H, d, *J* 11.8, OCH_AH_BPh), 3.84-3.78 (1 H, m, CH_AH_BOBn)), 3.79 (1 H, t, *J* 7.5, OCH), 3.67-3.62 (1 H, m, CH_AH_BOBn), 3.03 (3 H, s, SO_2CH_3), 2.44 (1 H, s, br, OH), 2.17 (1 H, ddd, *J* 12.2, 9.1 and 5.2, THF CH_AH_BC(Me)O), 2.06-1.82 (2 H, m, THF CH_2-CHO), 1.60 (1 H, dt, *J* 12.6 and 8.0, THF CH_AH_BC(Me)O), 1.22 (3 H, s, CH_3), 1.19 (3 H, s, CH_3) and 1.09 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 137.8$^-$ (ArC), 128.6$^+$ (ArC), 128.4$^+$ (ArC), 128.0$^+$ (ArC), 127.9$^+$ (ArC), 127.8$^+$ (ArC), 85.3$^+$ (THF (Me)CO)), 84.5$^+$ (CHOMs), 82.3$^-$ (THF (Me)*C*O), 73.4$^-$ (OCH_2PH), 70.8$^-$ (COH) 69.2$^-$ (CH_2OBn), 38.9$^+$ (SO_2CH_3) 33.9$^-$ (THF *C*H_2COCH), 27.4$^+$ (CH_3), 25.6$^-$ (THF *C*H_2-CHO), 24.8$^+$ (CH_3) and 22.3$^+$ (CH_3); **MS** *m/z* (+ESI) 431 (100%, MMeCNNa$^+$); **HRMS (ESI)** (Found MMeCNNa$^+$, 390.1945. $C_{18}H_{32}O_6SNa$ requires *MNH*$_4$, 390.1950).

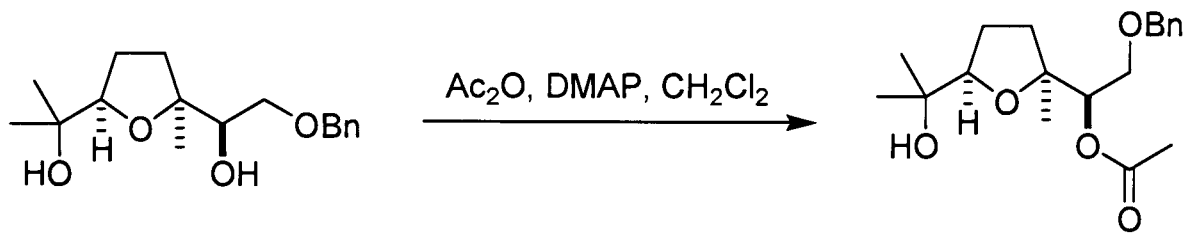
(*RS*)-2-(Benzyloxymethyl)-6-(2-hydroxypropan-2-yl)-3-methyl-tetrahydro-2H-pyran-3-ol 418



By method I, water (~3 cm^3) was added to a solution of zinc acetate dihydrate (549 mg, 2.50 mmol, 5.00 eq.) and mesylate **417** (186 mg, 0.50 mmol) dissolved in *N*,*N*-dimethylformamide (5 cm^3). The mixture was heated to initiate reflux to give a crude product. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 10:90] to give the *tetrahydropyran* **418** (138 mg, 94%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3418 br, 2971, 1454, 1366, 1173, 1092, 1014, 916, 737 and 698; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.37-7.28 (5 H, m, 5 × ArC), 4.58 (1 H, d, *J* 11.9, CH_AH_BPh), 4.51 (1 H, d, *J* 11.9, CH_AH_BPh), 3.85 (1 H, dd, *J* 10.4 and 7.7, OC$H_{equatorial}$), 3.77 (1 H, dd, *J* 7.6 and 4.2, CH_AH_BOBn), 3.54 (1 H, dd, *J* 10.4 and 4.2, CH_AH_BOBn), 3.42-3.37 (1 H, m, CH_{axial}O), 2.35 (2 H, s, br, 2 × OH), 1.71-1.62 (3 H, m, $CH_{axial}CH_2CH_AH_B$), 1.51-1.47 (1 H, m, $CH_{axial}CH_2CH_AH_B$), 1.19 (3 H, s, CH_3), 1.16 (3 H, s, CH_3) and 1.11 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 137.8$^-$, 128.4$^+$, 127.8$^+$, 127.7$^+$ (6 ×ArC), 80.9$^+$ ($OCH_{equatorial}$), 76.0$^+$ ($CH_{axial}O$), 73.3$^-$ (CH_2Ph), 71.8$^-$ (COH), 68.4$^-$ (COH), 67.6$^-$ (CH_2OBn), 32.7$^-$ ($CH_{axial}CH_2CH_2$), 26.2$^+$ (CH_3), 24.6$^+$ (CH_3), 23.7$^+$ (CH_3), and

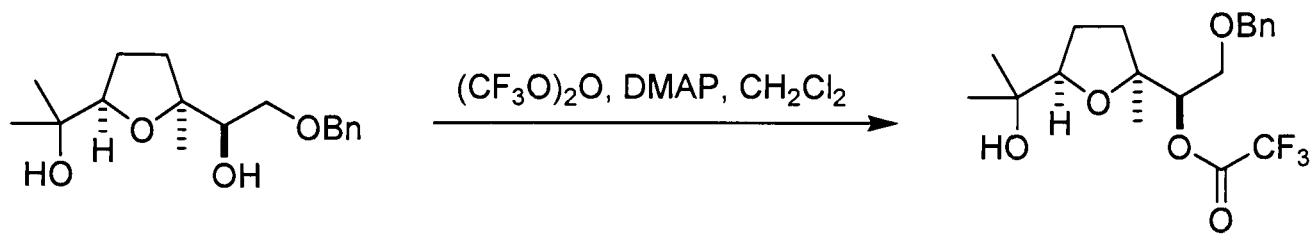
21.1^{-} ($CH_{axial}CH_2CH_2$); **MS** *m/z* (+ESI) 317 (100%, MNa^+); **HRMS (ESI)** (Found MNa^+, 317.1722. $C_{17}H_{26}O_4Na$ requires *MNa*, 317.1729).

(*RS*)-(*R*)-2-(Benzyloxy)-1-((2*S*,5*R*)-5-(2-hydroxypropan-2-yl)-2-methyl-tetrahydrofuran-2-yl)ethyl acetate 419



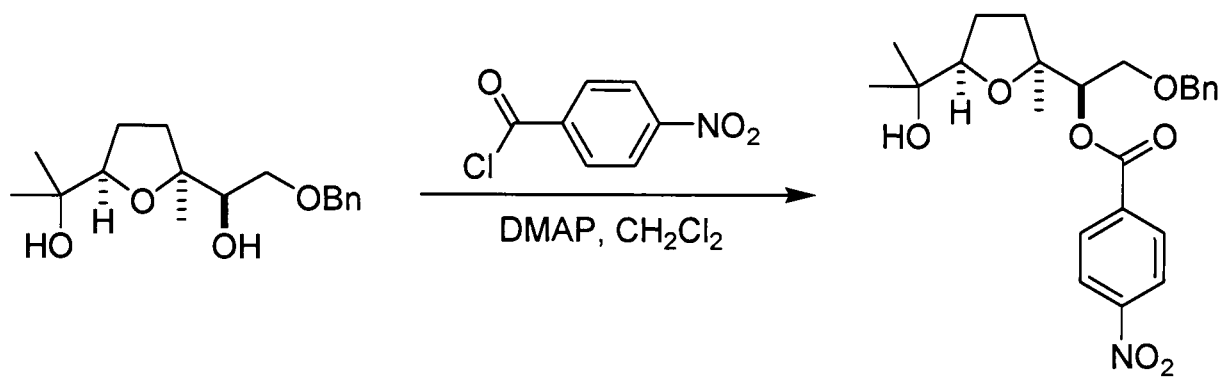
Acetic anhydride (0.057 cm^3, 600 μmol, 1.20 eq.) was added to a solution of tetrahydrofuran **416** (147 mg, 500 μmol) and 4-(dimethylamino)-pyridine (183 mg, 1.50 mmol, 3.00 eq.) dissolved in dichloromethane (2 cm^3) under an atmosphere of argon at ambient temperature and stirred for 18 hours. The solution was poured into aqueous hydrochloric acid (1.0 mol dm^{-3}, 5 cm^3), the layers separated and the aqueous layer extracted with ether (2 × 10 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 10:90] to give the *acetate* **419** (160 mg, 95%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3461 br, 2975, 2874, 1740, 1454, 1373, 1238, 1059, 954, 739 and 699; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.36-7.27 (5 H, m, 5 × ArH), 5.13-5.11 (1 H, m, CHOAc), 4.57 (1 H, d, *J* 12.2, CH_AH_BPh), 4.49 (1 H, d, *J* 12.2, CH_AH_BPh), 3.78-3.71 (2 H, m, THF OCH and CH_AH_BOBn), 3.53 (1 H, dd, *J* 10.9 and 6.0, CH_AH_BOBn), 2.11-1.97 (1 H, m, THF $OC(Me)CH_AH_B$), 2.08 (3 H, s, $COCH_3$), 1.94-1.78 (2 H, m, THF $C(Me)CH_AH_BCH_2$), 1.66-1.58 (1 H, m, $OC(Me)CH_AH_B$), 1.21 (3 H, s, CH_3), 1.19 (3 H, s, CH_3) and 1.09 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 170.5$^-$ (CO), 137.8$^-$, 128.4$^+$, 127.7$^+$, 127.6$^+$ (6 × ArC), 85.2$^+$ (THF OCH), 83.1$^-$ (THF OC), 75.6$^-$ (CHOAc), 73.0$^-$ (CH_2Ph), 70.8$^-$ (CMe_2OH) 69.1$^-$ CH_2OBn), 35.0$^-$ (THF $OCHCH_2$), 27.5$^+$ (CH_3), 26.3$^-$ (THF $OC(Me)CH_2$), 24.4$^+$ (CH_3), 22.9$^+$ (CH_3) and 21.2$^+$ (CH_3); **MS** *m/z* (+ESI) 395 (100%, $MMeCNNH_4^+$) and 359 (MNa^+); **HRMS (ESI)** (Found MNa^+, 359.1835. $C_{19}H_{28}O_5Na$ requires *MNa*, 359.1834).

(*RS*)-(*R*)-2-(Benzyloxy)-1-((2*S*,5*R*)-5-(2-hydroxypropan-2-yl)-2-methyl-tetrahydrofuran-2-yl)ethyl 2,2,2-trifluoroacetate 420



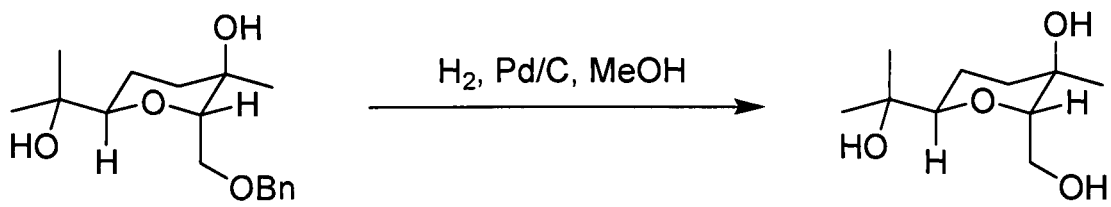
Trifluoroacetic anhydride (0.071 cm^3, 510 μmol, 1.50 eq.) was added to a solution of tetrahydrofuran **416** (100 mg, 340 μmol) and pyridine (0.110 cm^3, 1.36 mmol, 4.00 eq.) dissolved in dichloromethane (3 cm^3) under an atmosphere of argon at ambient temperature and stirred for 18 hours. The mixture evaporated under reduced pressure and the residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 5:95] to give the *triflurоracetate* **420** (126 mg, 90%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3547 br, 2984, 1789, 1671, 1610, 1498, 1455, 1374, 1221, 931, 862, 817, 776, 734 and 699; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.40-7.27 (5 H, m, 5 × ArH), 5.28 (1 H, dd, *J* 8.0 and 2.4 $CHOCOCF_3$), 4.57-4.46 (2 H, m, CH_2Ph), 4.06-4.03 (1 H, m, THF OCH), 3.78 (1 H, dd, *J* 11.1 and 2.4, CH_AH_BOBn), 3.66 (1 H, dd, *J* 11.1 and 8.0, CH_AH_BOBn), 2.06-1.96 (2 H, m, THF $CH_AH_BCH_AH_B$), 1.94-1.84 (1 H, m, $OC(H)CH_AH_B$), 1.75-1.68 (1 H, m, $OC(Me)CH_AH_B$), 1.54 (3 H, s, CH_3), 1.52 (3 H, s, CH_3) and 1.22 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 137.6^-, 128.4^+, 127.7^+, 127.4^+ (6 × ArC), 88.4^- (THF OC), 83.1^- (THF OCH), 82.8^- (CO), 80.0^+ (CHOCOCF$_3$), 73.1^- (CH_2Ph), 67.9^- CH_2OBn), 34.6^- (THF OC(H)CH_2), 26.3^- (THF OC(Me)CH_2), 22.1^+ (CH_3), 22.0^+ (CH_3) and 21.4^+ (CH_3); **MS** *m/z* (+ESI) 413 (100%, MNa^+); **HRMS (ESI)** (Found MNa^+, 413.1546. $C_{19}H_{25}O_5F_3Na$ requires *MNa*, 413.1552).

(*RS*)-(*R*)-2-(Benzyloxy)-1-((2*S*,5*R*)-5-(2-hydroxypropan-2-yl)-2-methyl-tetrahydrofuran-2-yl)ethyl 4-nitrobenzoate 422



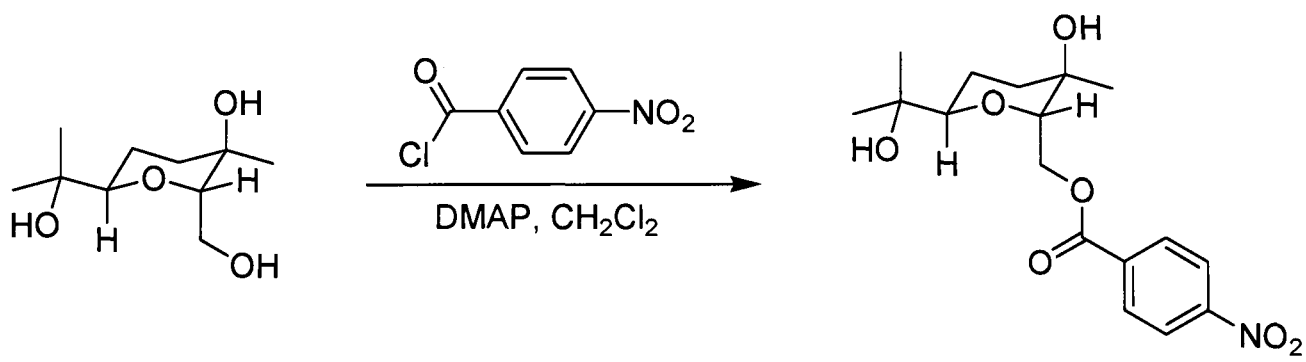
para-Nitrobenzoyl chloride (222 mg, 1.20 mmol, 1.20 eq.) was added to a solution of alcohol **416** (294 mg, 1.00 mmol) and 4-(dimethylamino)pyridine (366 mg, 3.00 mmol, 3.00 eq.) dissolved in dichloromethane (10 cm^3) under an atmosphere of argon at ambient temperature. The solution was stirred for 16 hours. Aqueous hydrochloric acid (1.0 mol dm^{-3}, 20 cm^{-3}) was added, the resulting mixture separated and the aqueous layer was extracted with ether (3 × 25 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 10:90] to give the *para-nitrobenzoyl ester* **422** (359 mg, 81%) as prisms, mp 70-72 °C [from chloroform-ethyl acetate-methanol]; **IR** ν_{max} (thin film)/cm^{-1} 3451 br. 2975, 2873, 1727, 1607, 1528, 1454, 1345, 1274, 1103, 1015, 953, 873, 841, 784, 719 and 699; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 8.30 (2 H, d, *J* 8.5, 2 × ArH), 8.21 (2 H, d, *J* 8.5, 2 × ArH), 7.30-7.27 (5 H, m, 5 × ArH), 5.42 (1 H, dd, *J* 6.2 and 3.4, CHOAr), 4.60 (1 H, d, *J* 12.3, CH_AH$_B$Ph), 4.52 (1 H, d, *J* 12.3, CH$_A$$H_B$Ph), 3.88 (1 H, dd, *J* 10.9 and 4.0, CH_AH$_B$OBn), 3.80 (1 H, dd, *J* 8.7 and 6.6, THF CHO), 3.69 (1 H, dd, *J* 10.9 and 6.3, CH$_A$$H_B$OBn), 2.17 (1 H, ddd, *J* 12.5, 8.1 and 4.2, THF CH_AH$_B$C(Me)O), 1.96-1.84 (2 H, m, (2 H, m, THF CH_2-CHO), 1.71 (1 H, ddd, *J* 12.5, 8.1 and 4.2, THF CH$_A$$H_B$COCH), 1.32 (3 H, s, CH_3), 1.18 (3 H, s, CH_3) and 1.06 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 164.1$^-$ (CO), 150.6$^-$, 137.6$^-$, 135.6$^-$, 131.0$^+$, 130.8$^+$, 128.4$^+$, 127.8$^+$, 127.6$^+$, 123.6$^+$ (12 × ArC), 85.4$^+$ (THF OCH), 83.1$^-$ (THF (Me)*C*O), 77.2$^+$ (CHOAr), 73.1$^-$ (CH_2Ph), 70.8$^-$ (COH), 68.9$^-$ CH_2OBn), 35.2$^-$ (THF *C*H$_2$C(Me)OCH), 27.5$^+$ (CH_3), 26.3$^-$ (THF *C*H$_2$-CHO), 24.4$^+$ (CH_3) and 23.0$^+$ (CH_3); **MS** *m/z* (+ESI) 466 (100%, MNa^+) and 444 (MH^+); **HRMS (ESI)** (Found MNa^+, 466.1844. $C_{24}H_{29}NO_7Na$ requires *MNa*, 466.1842).

(*RS*)-2-(Hydroxymethyl)-6-(2-hydroxypropan-2-yl)-3-methyl-tetrahydro-2H-pyran-3-ol



Palladium (10% on carbon, micro spatula tip) was added to benzyl ether **418** (294 mg, 1.00 mmol) dissolved in methanol (50 cm^3) and the flask evacuated and purged with argon three times before being evacuated and purged with hydrogen five times. The mixture stirred vigorously for 3 hours under an atmosphere of hydrogen (1 atm) and filtered through Celite®, eluting with dichloromethane (100 cm^3). The combined organic extracts were evaportated under reduced pressure to give *2-(hydroxymethyl)-6-(2-hydroxypropan-2-yl)-3-methyl-tetrahydro-2H-pyran-3-ol* (204 mg, 100%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3383 br, 2970, 1380, 1196, 1094, 915 and 757; **^{1}H NMR** δ_H (400 MHz; CD_3CN) 3.82 (1 H, t, *J* 10.5, CH_AH_BOH), 3.62 (1 H, dd, *J* 9.6 and 4.0, $OCH_{equatorial}$), 3.52 (1 H, d, *J* 11.1, CH_AH_B), 3.35 (1 H, d, *J* 10.9, $CH_{axial}O$), 3.20 (2 H, s, br, 2 × OH), 2.93 (1 H, s, br, OH), 1.74-1.58 (3 H, m, $CH_{axial}CH_2CH_AH_BC$), 1.49-1.45 (1 H, m, $CH_{axial}CH_2CH_AH_BC$), 1.14 (6 H, s, 2 × CH_3 and 1.02 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; CD_3CN) 82.9^+ ($OCH_{equatorial}$), 75.7^+ ($CH_{axial}O$), 71.9^- (COH), 67.9^- (COH), 58.6^- (CH_2OH), 33.1^- ($CH_{axial}CH_2CH_2$), 26.0^+ (CH_3), 25.2^+ (CH_3), 21.2^+ (CH_3), and 21.2^- ($CH_{axial}CH_2CH_2$); **MS** *m/z* (+ESI) 227 (100%, MNa^+); **HRMS (ESI)** (Found MNa^+, 227.1259. $C_{10}H_{20}O_4Na$ requires *MNa*, 227.1259).

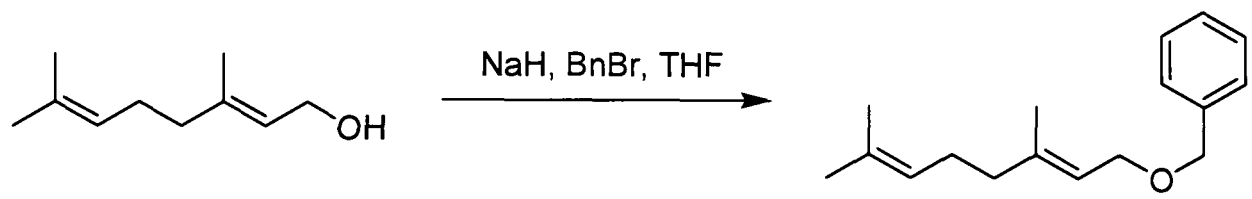
(*RS*)-(3-Hydroxy-6-(2-hydroxypropan-2-yl)-3-methyl-tetrahydro-2H-pyran-2-yl)methyl 4-nitrobenzoate 423



para-Nitrobenzoyl chloride (71 mg, 382 μmol, 1.30 eq.) was added to a solution 2-(hydroxymethyl)-6-(2-hydroxypropan-2-yl)-3-methyl-tetrahydro-2H-pyran-3-ol (60 mg, 294 μmol) and 4-(dimethylamino)pyridine (107 mg, 882 μmol, 3.00 eq.) dissolved in

dichloromethane (3 cm^3) under an atmosphere of argon at ambient temperature. The solution was stirred for 24 hours. Aqueous hydrochloric acid (1.0 mol dm^{-3}, 5 cm^{-3}) was added, the resulting mixture separated and the aqueous layer was extracted with ethyl acetate (3 × 10 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 40:60] to give the *para-nitrobenzoyl ester* **423** (78 mg, 75%) as needles, mp 84-85 °C [from chloroform-ethyl acetate-methanol-petroleum (bp 60-80 °C)]; **IR** ν_{max} (solution cell)/cm^{-1} 3432 br, 2973, 1726, 1608, 1529, 1455, 1349, 1277, 1175, 1097, 1015, 916, 874 and 720; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 8.29 (2 H, d, *J* 8.9, 2 × ArH), 8.22 (2 H, d, *J* 8.9, 2 × ArH), 4.81 (1 H, dd, *J* 11.9 and 10.3, OC$H_A$$H_B$Ar), 4.37 (1 H, dd, *J* 11.9 and 4.1, OC$H_A$$H_B$Ar), 4.07 (1 H, dd, *J* 10.1 and 3.9, $OCH_{equatorial}$), 3.44 (1 H, dd, *J* 11.2 and 2.2, OCH_{axial}), 2.50 (2 H, s, br, 2 × OH), 1.84-1.57 (4 H, m, 2 × CH_2), 1.21 (3 H, s, CH_3), 1.15 (3 H, s, CH_3) and 1.14 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 164.5$^-$ (CO), 150.7$^-$, 130.8$^+$, 123.7$^+$ (6 × ArC), 79.9$^+$ ($OCH_{equatorial}$), 75.2$^+$ ($CH_{axial}O$), 71.7$^-$ (COH), 67.8$^-$ (COH), 61.3$^-$ (CH_2OAr), 32.4$^-$ ($CH_{axial}CH_2CH_2$), 26.3$^+$ (CH_3), 24.9$^+$ (CH_3), 24.2$^+$ (CH_3), and 20.6$^-$ ($CH_{axial}CH_2CH_2$); **MS** *m/z* (+ESI) 376 (100%, MNa^+); **HRMS (ESI)** (Found MNa^+, 376.1366. $C_{17}H_{23}NO_7Na$ requires *MNa*, 376.1372).

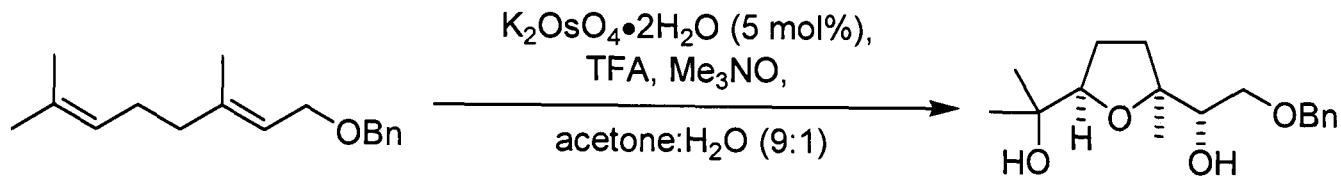
(2-*trans*)-1-Benzyloxy-3,7-dimethyl-octa-2,6-diene[297]



By method F, benzyl bromide (9.24 cm^3, 77.8 mmol, 1.20 eq.) was added dropwise to a mixture of geraniol (11.2 cm^3, 64.8 mmol) and sodium hydride (60% dispersion in mineral oil, 5.18 g, 130 mmol, 2.00 eq.) dissolved in tetrahydrofuran (450 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 3:97] to give (2-*trans*)-1-benzyloxy-3,7-dimethyl-octa-2,6-diene (14.6 g, 92%) as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.39-2.28 (5 H, m, 5 × ArC), 5.44 (1 H, td, *J* 6.8 and 1.2, C*H*CH_2OBn), 5.15-5.12 (1 H, m, $(Me)_2C$=CH), 4.53 (2 H, s, OCH_2Ph), 4.06 (2 H, d, *J* 6.8, CH_2OBn), 2.18-2.06 (4 H, m, 2 × CH_2), 1.71 (3 H, s, CH_3), 1.68 (3 H, s, CH_3) and 1.64 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 140.4$^-$ (C), 138.6$^-$ (C), 131.6$^-$ (C), 128.4$^+$, 127.9$^+$, 127.5$^+$ (5 × ArC), 124.0$^+$ ($(Me)_2C$=*C*H), 120.9$^+$ (C=*C*HCH_2OBn), 72.0$^-$ (OCH_2Ph), 66.6$^-$ (CH_2OBn), 39.6$^-$

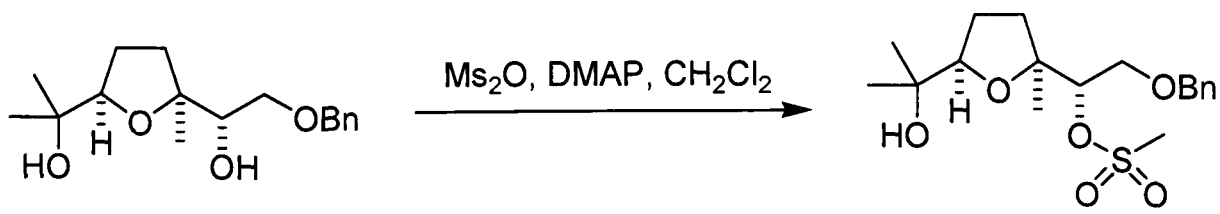
(CH_2), 26.4$^-$ (CH_2), 25.7$^+$ (CH_3), 17.7$^+$ (CH_3) and 16.5$^+$ (CH_3). All spectroscopic data agreed with those previously published.[297]

(*RS*)-2-((2*R*,5*S*)-5-((*S*)-2-(Benzyloxy)-1-hydroxyethyl)-5-methyl-tetrahydrofuran-2-yl)propan-2-ol[10] 424



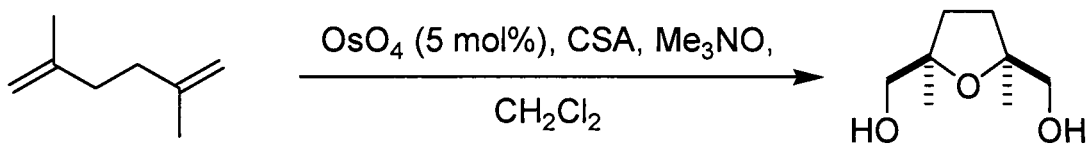
By method G, trimethylamine-*N*-oxide dihydrate (2.22 g, 20.0 mmol, 5.00 eq.) was added to a solution (2-*trans*)-1-benzyloxy-3,7-dimethyl-octa-2,6-diene (977 mg, 4.00 mmol) and potassium osmate$^{(VI)}$ dihydrate (74 mg, 0.20 mmol, 0.05 eq.) dissolved in acetone (72 cm^3), water (8 cm^3) and trifluroacetic acid (40 cm^3) to give a crude product. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 5:95] to give the tetrahydrofuran **424** (1.03 g, 88%) as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.36-7.27 (5 H, m, 5 × ArH), 4.57 (1 H, d, *J* 11.9, OC*H*$_A$H$_B$Ph), 4.53 (1 H, d, *J* 11.9, OCH$_A$*H*$_B$Ph), 3.83 (1 H, t, *J* 7.1, OCH), 3.72 (1 H, dd, *J* 8.3 and 3.2, C*H*OH), 3.65 (1 H, dd, *J* 9.6 and 3.4, C*H*$_A$H$_B$OBn), 3.55 (1 H, dd, *J* 9.6 and 8.4, CH$_A$*H*$_B$OBn), 3.30 (2 H, s, br, 2 × OH), 2.21 (1 H, ddd, *J* 12.3, 9.0 and 6.3, THF C*H*$_A$H$_B$C(Me)O), 2.02-1.84 (2 H, m, THF C*H*$_2$-CHO), 1.58 (1 H, ddd, *J* 12.3, 9.0 and 6.3, CH$_A$*H*$_B$C(Me)O), 1.21 (3 H, s, CH_3), 1.14 (3 H, s, CH_3) and 1.07 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 137.9$^-$, 128.4$^+$, 127.8$^+$, 127.7$^+$, 126.9$^+$ (6 × ArC), 85.7$^+$ (THF OCH), 83.9$^-$ (THF (Me)CO), 75.4$^+$ (CHOH), 73.4$^-$ (OCH_2PH), 72.1$^-$ (CH_2OBn), 71.3$^-$ ($(Me)_2COH$), 35.8$^-$ (THF *C*H$_2$COCH), 27.7$^+$ (CH_3), 26.5$^-$ (THF *C*H$_2$-CHO), 25.0$^+$ (CH_3) and 23.2$^+$ (CH_3). All spectroscopic data agreed with those previously published.[10]

(*RS*)-(*S*)-2-(Benzyloxy)-1-((2*S*,5*R*)-5-(2-hydroxypropan-2-yl)-2-methyl-tetrahydrofuran-2-yl)ethyl methanesulfonate 425



By method H, methanesulfonic anhydride (348 mg, 2.00 mmol, 2.00 eq.) was added to a solution of alcohol **424** (194 mg, 1.00 mmol) and 4-(dimethyl)aminopyridine (489 mg, 4.00 mmol, 4.00 eq.) dissolved in dichloromethane (50 cm^3) to give the *mesylate* **425** (685 mg, 92%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3518 br, 2975, 2876, 1497, 1454, 1342, 1173, 1075, 931, 803, 747 and 700; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.37-7.28 (5 H, m, 5 × ArH), 4.74 (1 H, t, *J* 5.4, CHOMs), 4.55 (2 H, s, CH_2Ph), 3.82 (1 H, dd, *J* 8.3 and 6.3, OCH), 3.66 (2 H, d, *J* 5.5, CH_2OBn), 3.05 (3 H, s, SO_2CH_3), 2.06-1.96 (2 H, m, $CH_AH_BCH_AH_B$), 1.92-1.83 (1 H, m, $CH_AH_BC(H)O$), 1.74-1.66 (1 H, m, $CH_AH_BC(Me)O$), 1.25 (3 H, s, CH_3), 1.22 (3 H, s, CH_3) and 1.09 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 137.2^-, 128.6^+, 128.0^+, 127.8^+ (6 × ArC), 87.4^+ (CHOMs), 85.9^+ (THF OCH), 82.3^- (THF OCMe), 73.4^- (CH_2Ph), 70.6^- (COH), 69.4^- (CH_2OBn), 39.1^+ (SO_2CH_3), 35.7^- (THF $CH_2C(Me)O$), 27.7^+ (CH_3), 26.3^- (THF $CH_2C(H)O$), 24.8^+ (CH_3) and 22.6^+ (CH_3); **MS** *m/z* (+ESI) 431 (100%, $MMeCNNH_4^+$) and 395 (MNa^+); **HRMS (ESI)** (Found MNa^+, 395.1505. $C_{18}H_{28}O_6SNa$ requires *MNa*, 395.1499).

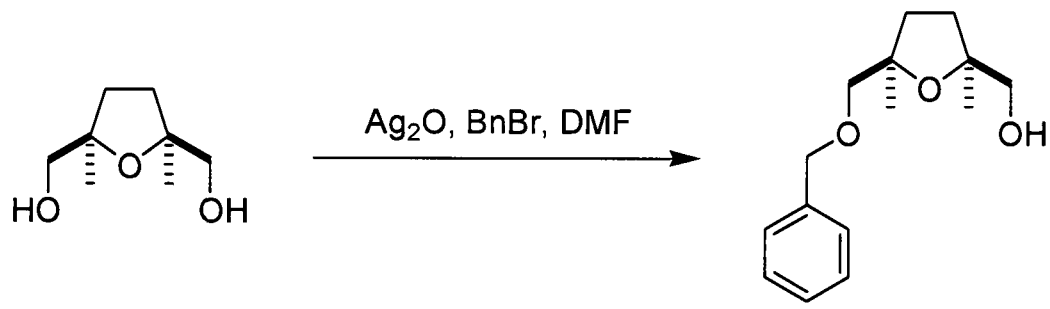
(*meso*)-((2*R*,5*S*)-2,5-Dimethyl-tetrahydrofuran-2,5-diyl)dimethanol[298] 427



Osmium$^{(VIII)}$ tetroxide (51 mg, 0.20 mmol, 0.10 eq.) was added to 2,5-dimethyl-1,5-hexadiene (0.297 cm^3, 2.00 mmol) and (*RS*)-camphor-10-sulfonic acid (2.79 g, 12.0 mmol, 6.00 eq.) dissolved in dichloromethane (100 cm^3) at ambient temperature and stirred for 30 minutes. Trimethylamine-*N*-oxide dihydrate (890 mg, 8.00 mmol, 4.00 eq.) was added to the stirring solution and the reaction stirred for 48 hours. Sodium sulfite (13 mg, 0.10 mmol, 0.10 eq.) was added and the mixture stirred for 1 hour before being evaporated under reduced pressure. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 20:80] to give the tetrahydrofuran **427** (237 mg, 74%) as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 3.86 (2

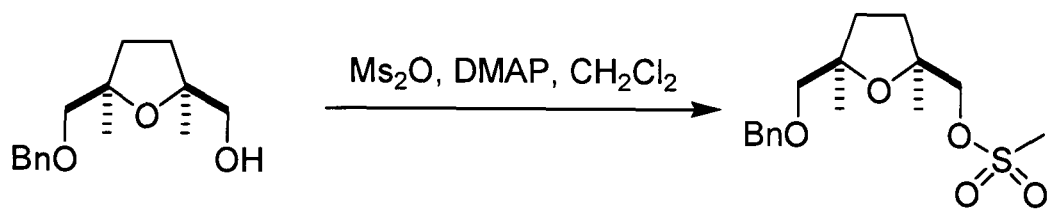
H, s, br, 2 × OH), 3.51 (2 H, d, *J* 11.3, 2 × C*H*$_A$H$_B$OH), 3.37 (2 H, d, *J* 11.3, 2 × CH$_A$*H*$_B$OH), 2.22-2.15 (2 H, m, 2 × C*H*$_A$H$_B$), 1.75-1.70 (2 H, m, CH$_A$*H*$_B$) and 1.17 (6 H, s, 2 × CH$_3$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 84.3$^-$ (2 × OC), 69.1$^-$ (2 × CH_2OH), 34.0$^-$ (2 × CH_2) and 25.4$^-$ (2 × CH_3). All spectroscopic data agreed with those previously published.[298]

(*RS*)-((2*S*,5*R*)-5-(Benzyloxymethyl)-2,5-dimethyl-tetrahydrofuran-2-yl)methanol



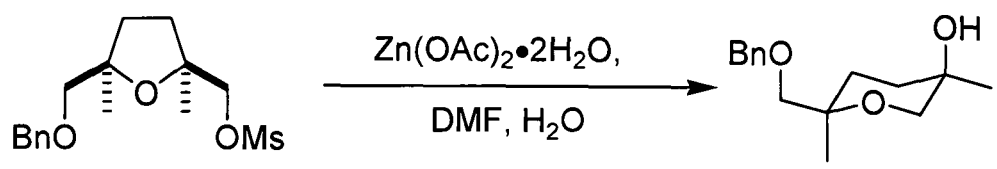
Silver$^{(I)}$ oxide (301 mg, 1.30 mmol, 1.60 eq.) was added to diol **427** (130 mg, 0.811 mmol) dissolved in *N*,*N*-dimethylformamide (2 cm^3) and stirred under an atmosphere of argon at ambient temperature in the dark for 45 minutes. Benzyl bromide (0.106 cm^3, 0.893 mmol, 1.10 eq.) was added and the mixture stirred for a further 48 hours. Water (10 cm^3) was added and the mixture stirred vigorously for 45 minutes before being poured into water (5 cm^3) and ether (15 cm^3). The layers were separated, the aqueous layer extracted with ether (3 × 10 cm^3), the combined organic extracts were washed with aqueous saturated sodium chloride (25 cm^3), dried (anhydrous sodium sufate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 40:60] to give *(RS)-((2S,5R)-5-(benzyloxymethyl)-2,5-dimethyl-tetrahydrofuran-2-yl)methanol* (154 mg, 76%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3450 br, 3031, 2968, 2868, 1497, 1454, 1372, 1317, 1254, 1201, 1100, 884, 851, 738 and 699; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.37-7.27 (5 H, m, 5 × ArH), 4.62 (1 H, d, *J* 12.1, C*H*$_A$H$_B$Ph), 4.52 (1 H, d, *J* 12.1, CH$_A$*H*$_B$Ph), 3.53 (1 H, d, *J* 11.3, C*H*$_A$H$_B$OH), 3.48 (1 H, d, *J* 9.5, C*H*$_A$H$_B$OBn), 3.33 (1 H, d, *J* 11.3, CH$_A$*H*$_B$OH), 3.30 (1 H, d, *J* 9.5, CH$_A$*H*$_B$OBn), 2.33 (1 H, dt, *J* 12.1 and 8.4, C*H*$_A$CH$_B$CH$_2$), 2.25-2.19 (1 H, m, CH_2C*H*$_A$H$_B$), 1.80 (1 H, dt, *J* 12.1 and 8.4, CH$_A$*H*$_B$CH$_2$), 1.72-1.66 (1 H, m, CH_2CH$_A$*H*$_B$) and 1.20 (3 H, s, CH_3) and 1.19 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 137.6$^-$, 128.5$^+$, 127.8$^+$, 127.8$^+$ (6 × ArC), 84.7$^-$ (CO), 83.2$^-$ (OC), 76.0$^-$ (CH_2OBn), 73.4$^-$ (CH_2Ph), 70.2$^-$ (CH_2OH), 34.5$^-$ (CH_2), 34.3$^-$ (CH_2), 25.9$^+$ (CH_3) and 25.7$^+$ (CH_3); **MS** *m/z* (+ESI) 273 (100%, MNa$^+$); **HRMS (ESI)** (Found MH$^+$, 251.1644. $C_{15}H_{23}O_3$ requires *MH*, 251.1647).

(*RS*)-((2*S*,5*R*)-5-(Benzyloxymethyl)-2,5-dimethyl-tetrahydrofuran-2-yl)methyl methanesulfonate 428



By method H, methanesulfonic anhydride (52 mg, 300 μmol, 3.00 eq.) was added to a solution of (RS)-((2S,5R)-5-(benzyloxymethyl)-2,5-dimethyl-tetrahydrofuran-2-yl)methanol (25 mg, 99.9 μmol) and 4-(dimethyl)aminopyridine (73 mg, 599 μmol, 6.00 eq.) dissolved in dichloromethane (10 cm^3) to give the *mesylate* **428** (33 mg, 100%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3030, 2972, 1721, 1497, 1455, 1356, 1176, 1104, 962, 836, 742 and 700; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.35-7.27 (5 H, m, 5 × ArH), 4.54 (2 H, s, CH_2Ph), 4.05 (1 H , d, *J* 9.8, CH_AH_BOMs), 4.01 (1 H, d, *J* 9.9, CH_AH_BOMs), 3.36 (1 H, d, *J* 9.5, CH_AH_BOBn), 3.30 (1 H, d, *J* 9.5, CH_AH_BOBn), 2.91 (3 H, s, SO_2CH_3), 2.17-2.00 (2 H, m, $CH_AH_BCH_AH_B$), 1.85-1.73 (2 H, m, $CH_AH_BCH_AH_B$) 1.32 (3 H, s, CH_3) and 1.26 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.3$^-$, 128.4$^+$, 127.6$^+$, 127.6$^+$ (6 × ArC), 84.2$^-$ (CO), 81.7$^-$ (OC), 76.4$^-$ (CH_2OBn), 74.7$^-$ (CH_2OMs), 73.4$^-$ (CH_2Ph), 37.1$^+$ (SO_2CH_3), 34.2$^-$ (CH_2), 33.8$^-$ (CH_2), 25.5$^+$ (CH_3) and 25.1$^+$ (CH_3); **MS** *m/z* (+ESI) 387 (100%, $MMeCNNa^+$) and 351 (MNa^+); **HRMS (ESI)** (Found MH^+, 329.1437. $C_{16}H_{25}O_5S$ requires *MH*, 329.1423).

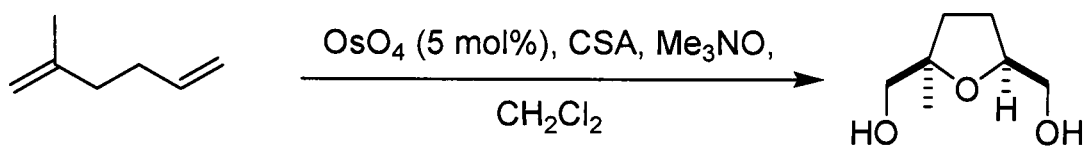
(*RS*)-6-(Benzyloxymethyl)-3,6-dimethyl-tetrahydro-2H-pyran-3-ol 429



By method I, water (~1 cm^3) was added to a solution of zinc acetate dihydrate (76 mg, 345 μmol, 5.00 eq.) and mesylate **428** (23 mg, 68.0 μmol) dissolved in *N*,*N*-dimethylformamide (2 cm^3). The mixture was heated to initiate reflux to give a crude product. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 40:60] to give the *tetrahydropyran* **429** (15 mg, 85%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3425 br, 2934, 1454, 1372, 1200, 1077, 737 and 698; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.35-7.28 (5 H, m, 5 × ArH), 4.62 (1 H, d, *J* 12.3 CH_AH_BPh), 4.57 (1 H, d, *J* 12.3 CH_AH_BPh), 3.56 (1 H, d, *J* 12.0,

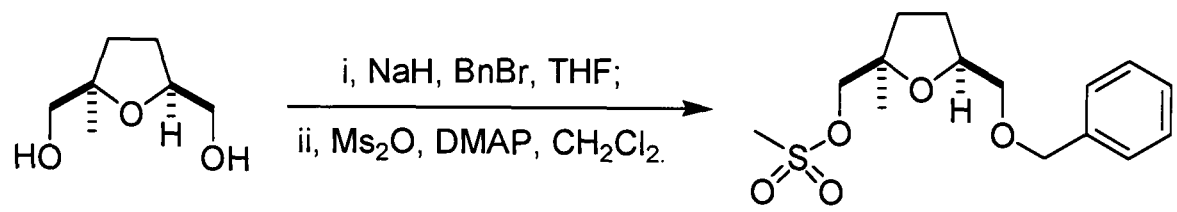
CH_AH_BOBn), 3.40 (1 H, d, *J* 12.0, CH_AH_BOBn), 3.37 (1 H, d, *J* 10.0, OCH_AH_B), 3.33 (1 H, d, *J* 10.0, OCH_AH_B), 2.24 (1 H, s, br, OH), 1.89 (1 H, dt, *J* 13.7 and 9.0, $CH_AH_BCH_2$), 1.66 (2 H, dd, *J* 9.9 and 3.9, $CH_AH_BCH_2$), 1.33 (1 H, dt, *J* 13.7 and 3.9, $CH_AH_BCH_2$), 1.23 (3 H, s, CH_3) and 1.13 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.4$^-$, 128.3$^+$, 127.5$^+$, 127.5$^+$ (6 × ArC), 78.0$^-$ (OCH_2), 73.5$^-$ (CH_2Ph), 73.3$^-$ (C), 70.3$^-$ (CH_2OBn), 66.7$^-$ (C), 31.9$^-$ (CH_2), 27.4$^-$ (CH_2), 24.7$^+$ (CH_3) and 17.4$^+$ (CH_3); **MS** *m/z* (+ESI) 273 (100%, MNa^+); **HRMS (ESI)** (Found MH^+, 215.1654. $C_{15}H_{23}O_3$ requires *MH*, 215.1647).

(*RS*)-((2*R*,5*S*)-2-Methyl-tetrahydrofuran-2,5-diyl)dimethanol 431



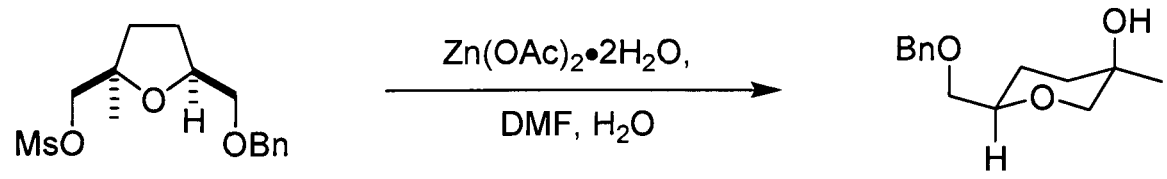
Osmium$^{(VIII)}$ tetroxide (51 mg, 0.20 mmol, 0.10 eq.) was added to 2-methyl-1,5-hexadiene (0.270 cm^3, 2.00 mmol) and (*RS*)-camphor-10-sulfonic acid (2.79 g, 12.0 mmol, 6.00 eq.) dissolved in dichloromethane (100 cm^3) at ambient temperature and stirred for 30 minutes. Trimethylamine-*N*-oxide dihydrate (890 mg, 8.00 mmol, 4.0 eq.) was added to the stirring solution and the reaction stirred for 48 hours. Sodium sulfite (13 mg, 0.1mmol, 0.1 eq.) was added and the mixture stirred for 1 hour before being evaporated under reduced pressure. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 30:70] to give the *tetrahydrofuran* **431** (208 mg, 71%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3384 br, 2967, 1652, 1457, 1238, 1065, 993 and 882; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 4.18-4.13 (1 H, m, OCH), 3.74 (1 H, dd, *J* 11.7 and 2.6, $OCHCH_AH_BOH$), 3.53 (1 H, d, *J* 11.5, CCH_AH_BOH), 3.50 (2 H, s, br, 2 × OH), 3.48 (1 H, dd, *J* 11.7 and 4.6, $OCHCH_AH_B$), 3.41 (1 H, d, *J* 11.5, CCH_AH_BOH), 2.08-2.01 (1 H, m, $CCH_AH_BCH_2$), 1.99-1.83 (2 H, m, $CCH_AH_BCH_2$), 1.63 (1 H, dt, *J* 10.8 and 7.7, $CCH_AH_BCH_2$) and 1.16 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 84.2$^-$ (C), 79.5$^+$ (OCH), 68.9$^-$ (CCH_2OH), 64.7$^-$ ($CHCH_2OH$), 33.6$^-$ (CH_2), 27.6$^-$ (CH_2) and 23.6$^+$ (CH_3); **MS** *m/z* (+CI) 164 (100 %, MNH_4^+) and 147 (MH^+); **HRMS (CI)** (Found MNH_4^+, 164.1288. $C_7H_{18}O_3$ requires *MNH*$_4$, 164.1287).

(*RS*)-((2*R*,5*S*)-5-(Benzyloxymethyl)-2-methyl-tetrahydrofuran-2-yl)methyl methanesulfonate 432



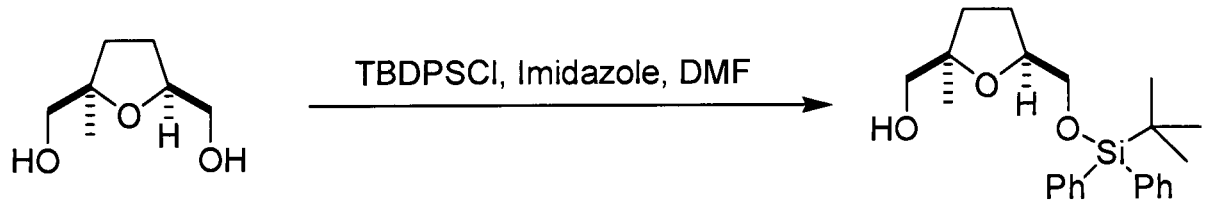
Sodium hydride (60% dispersion in mineral oil, 80 mg, 2.00 mmol, 2.00 eq.) was added portionwise to alcohol **431** (146 mg, 1.00 mmol) dissolved in tetrahydroduran (5 cm^3) under an atmosphere of argon at 0 °C. Benzyl bromide (0.143 cm^3, 1.20 mmol, 1.20 eq.) was added and the resulting mixture stirred for 24 hours. The mixture was poured into aqueous hydrochloric acid (1.0 mol dm^{-3}, 10 cm^3), separated and the aqueous layer extracted with ether (3 × 10 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure to give the crude product, which was dissolved in dichloromethane (10 cm^3) and purged with argon. 4-(Dimethyl)-aminopyridine (488 mg, 4.00 mmol, 4.00 eq.) was added and the resulting solution stirred for 10 minutes under an atmosphere of argon at ambient temperature. Methanesulfonic anhydride (348 mg, 2.00 mmol, 2.00 eq.) was added and the mixture stirred for 5 hours, before being poured into aqueous hydrochloric acid (1.0 mol dm^{-3}, 20 cm^3). The layers were separated, the aqueous layer extracted with ether (2 × 15 cm^3), the combined organic extracts were dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 10:90] to give the *mesylate* **432** (63 mg, 20%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 2933, 1454, 1356, 1176, 1101, 959, 816, 741 and 700; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.37-7.27 (5 H, m, 5 × ArH), 4.57 (1 H, d, J_{abq} 12.1, CH_AH$_B$OMs), 4.53 (1 H, d, J_{ab} 12.1, CH$_A$$H_B$OMs), 4.29-4.23 (1 H, m, OCH), 4.08 (1 H, d, J 10.2, CH_AH$_B$Ph), 4.04 (1 H, d, J 10.2, CH$_A$$H_B$Ph), 3.50 (1 H, dd, J 10.0 and 4.0, CH_AH$_B$OBn), 3.49 (1 H, dd, J 10.0 and 5.7, CH$_A$$H_B$OBn), 2.96 (3 H, s, SO_2CH_3), 2.07-1.99 (2 H, m, CH_AH$_B$CH_AH$_B$), 1.85-1.69 (2 H, m, CH$_A$$H_BCH_A$$H_B$) and 1.30 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.1$^-$, 128.4$^+$, 127.8$^+$, 127.7$^+$ (6 × ArC), 81.6$^-$ (C), 78.6$^+$ (OCH), 74.6$^-$ (CH_2Ph), 73.4$^-$ (CH_2OMs), 72.7$^-$ (CH_2OBn), 37.3$^+$ (SO_2CH_3), 34.1$^-$ (*C*H_2C(Me)O), 28.3$^-$ (*C*H_2C(H)O) and 23.8$^+$ (CH_3); **MS** *m/z* (+ESI) 373 (100 %, MMeCNNH_4^+) and 337 (MNa^+); **HRMS (ESI)** (Found MNa^+, 337.1069. $C_{15}H_{22}O_5SNa$ requires *MNa*, 337.1080).

(*RS*)-6-(Benzyloxymethyl)-3-methyl-tetrahydro-2H-pyran-3-ol 433



By method I, water (~1 cm^3) was added to a solution of zinc acetate dihydrate (105 mg, 477 μmol, 5.00 eq.) and mesylate **432** (30 mg, 95.4 μmol) dissolved in *N*,*N*-dimethylformamide (1.5 cm^3). The mixture was heated to initiate reflux to give a crude product. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 10:90] to give the *tetrahydropyran* **433** (19 mg, 83%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3341 br, 2931, 1720, 1497, 1453, 1365, 1280, 1205, 1097, 1028, 918, 855, 744 and 699; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.35-7.27 (5 H, m, 5 × ArH), 4.62 (1 H, d, *J* 12.2, CH_AH$_B$Ph), 4.54 (1 H, d, *J* 12.2, CH_AH$_B$Ph), 3.66 (1 H, dd, *J* 11.6 and 2.9, CH_AH$_B$OBn), 3.55-3.49 (2 H, m, OCH_AH$_B$ and OC*H*), 3.46-3.43 (1 H, m, OCH$_A$$H_B$), 3.36 (1 H, d, *J* 11.6, CH$_A$$H_B$OBn), 2.14 (1 H, s, br, OH), 1.81-1.77 (1 H, m, CH_AH$_B$CH$_2$), 1.64-1.49 (2 H, m, CH_2), 1.33-1.24 (1 H, m, CH$_A$$H_BCH_2$) and 1.20 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.0, 128.4, 127.8, 127.7 (6 × ArC), 77.4 (OCH), 76.7 (CH_2OBn), 73.5 (CH_2Ph), 73.1 (OCH_2), 66.8 (C), 35.3 (CH_2), 24.6 (CH_3) and 24.0 (CH_2); **MS** *m/z* (+ESI) 259 (100%, MNa^+); **HRMS (ESI)** (Found MNa^+, 259.1309. $C_{14}H_{20}O_3Na$ requires *MNa*, 259.1310).

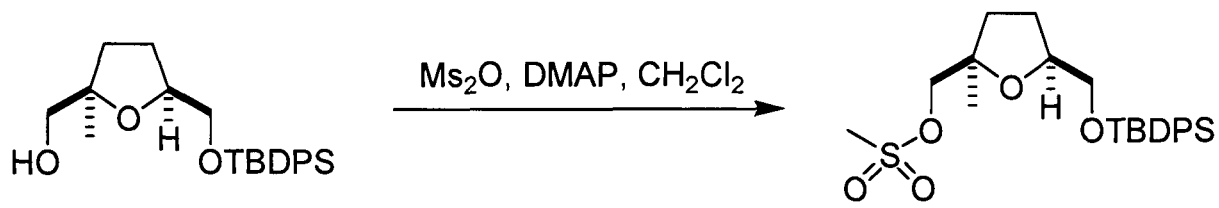
(*RS*)-((2*R*,5*S*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)-2-methyl-tetrahydrofuran-2-yl)methanol 434



By method J, *tert*-butyl(chloro)diphenylsilane (0.468 cm^3, 1.80 mmol, 1.20 eq.) was added to a solution of diol **431** (219 mg, 1.50 mmol) and imidazole (204 mg, 3.00 mmol, 2.00 eq.) dissolved in *N*,*N*-dimethylformamide (2 cm^3) to give a crude product. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 10:90] to give the *silyl ether* **434** (525 mg, 91%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3441 br, 3071, 3050, 2931, 2858, 1590, 1472, 1428, 1391, 1362, 1304, 1187, 1113, 998, 941, 853, 823, 741, 703 and 608; **^{1}H NMR**

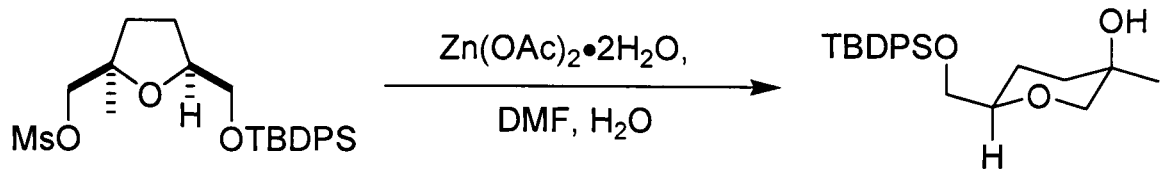
δ_H (400 MHz; $CDCl_3$) 7.71-7.67 (4 H, m, 4 × ArH), 7.45-7.37 (6 H, m, 6 × ArH), 4.17-4.12 (1 H, m, OCH), 3.83 (1 H, dd, *J* 10.9 and 3.7, $OCH_AH_BOTBDPS$), 3.60-3.55 (2 H, m, $CH_AH_BOTBDPS$ and CH_AH_BOH), 3.42 (1 H, d, *J* 11.2, OCH_AH_BOH), 2.47 (1 H, s, br, OH), 2.20-2.10 (2 H, m, $CH_AH_BCH_AH_B$), 1.99-1.90 (1 H, m, $CH_AH_BCH_AH_B$), 1.75-1.65 (1 H, m, $CH_AH_BCH_AH_B$), 1.21 (3 H, s, CH_3) and 1.07 (9 H, s, CMe_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 135.7^+, 135.6^+, 133.1^-, 129.8^+, 129.7^+, 127.7^+ (12 × ArC), 83.8^- (C), 79.3^+ (OCH), 69.8^- (CH_2OH), 65.6^- ($CH_2OTBDPS$), 34.2^- (CH_2), 28.1^- (CH_2), 26.8^+ (CMe_3), 23.9^+ (CH_3) and 19.2^- (SiC); **MS** *m/z* (+ESI) 407 (100%, MNa^+); **HRMS (ESI)** (Found MNa^+, 407.2008. $C_{23}H_{32}O_3SiNa$ requires *MNa*, 407.2018).

(*RS*)-((2*R*,5*S*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)-2-methyl-tetrahydrofuran-2-yl)methyl methanesulfonate 435



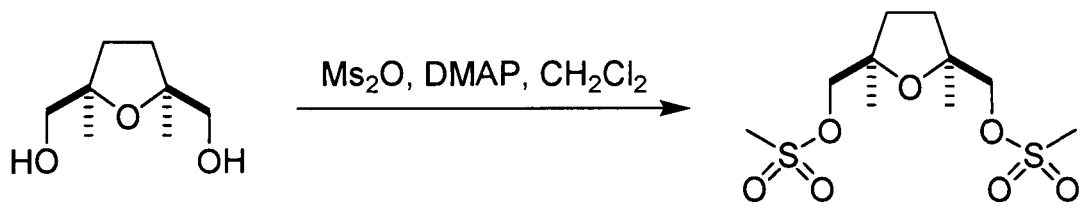
By method H, methanesulfonic anhydride (190 mg, 1.09 mmol, 3.00 eq.) was added to a solution of alcohol **434** (140 mg, 364 μmol) and 4-(dimethyl)aminopyridine (266 mg, 2.18 mmol, 6.00 eq.) dissolved in dichloromethane (50 cm^3) to give the *mesylate* **435** (168 mg, 100%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3072, 2933, 2859, 1589, 1472, 1428, 1358, 1177, 1113, 995, 824, 743, 705 and 612; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.68-7.66 (4 H, m, 4 × ArH), 7.50-7.37 (6 H, m, 6 × ArH), 4.20-4.15 (1 H, m, OCH), 4.09 (1 H, d, *J* 10.1, CH_AH_BOMs), 4.02 (1 H, d, *J* 10.1, CH_AH_BOMs), 3.66 (2 H, d, *J* 4.6, $CH_2OTBDPS$), 2.91 (3 H, s, SO_2CH_3), 2.07-1.90 (3 H, m, $CH_2CH_AH_B$), 1.76-1.69 (1 H, m, $CH_2CH_AI_B$), 1.30 (3 H, s, CH_3) and 1.06 (9 H, s, CMe_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 135.6^+, 135.6^+, 133.4^-, 133.3^-, 129.7^+, 129.7^+ (12 × ArC), 81.4^- (C), 80.0^+ (OCH), 74.5^- (CH_2OMs), 65.9^- ($CH_2OTBDPS$), 37.3^+ (SO_2CH_3), 34.1^- (CH_2), 27.7^- (CH_2), 26.9^+ (CMe_3), 23.6^- (CH_3) and 19.3^- (SiC); **MS** *m/z* (+ESI) 521 (100%, $MMeCNNa^+$) and 485 (MNa^+); **HRMS (ESI)** (Found MNa^+, 485.1793. $C_{24}H_{34}O_5SiSNa$ requires *MNa*, 485.1794).

(*RS*)-6-((*tert*-Butyldiphenylsilyloxy)methyl)-3-methyl-tetrahydro-2H-pyran-3-ol 436



By method I, water (~2 cm^3) was added to a solution of zinc acetate dihydrate (164 mg, 748 μmol, 5.00 eq.) and mesylate **435** (69 mg, 150 μmol) dissolved in *N*,*N*-dimethylformamide (3 cm^3). The mixture was heated to initiate reflux to give a crude product. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 5:95] to give the *tetrahydropyran* **436** (48 mg, 84%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3340 br, 2931, 2857, 1428, 1112, 824, 741 and 703; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.68-7.66 (4 H, m, 4 × ArH), 7.44-7.38 (6 H, m, 6 × ArH), 3.73 (1 H, dd, *J* 10.6 and 5.3, CH_AH$_B$OTBDPS), 3.63-3.59 (2 H, m, CH$_A$$H_B$OTBDPS and OC$H_AH_B$), 3.37 (1 H, dt, *J* 13.7 and 5.3, OCH), 3.31 (1 H, d, *J* 11.4, OCH$_A$$H_B$), 2.55 (1 H, s, br, OH), 1.79 (1 H, ddd, *J* 13.0, 6.1 and 3.0, OCHCH_AH$_B$), 1.65-1.60 (2 H, m, OCHCH$_A$$H_BCH_AH_B$), 1.54-1.45 (1 H, m, OCHCH$_A$H$_B$CH$_A$$H_B$), 1.11 (3 H, s, CH_3) and 1.06 (9 H, s, CMe_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 135.6$^+$, 133.5$^-$, 129.7$^+$, 129.7$^+$, 127.7$^+$, 127.6$^+$ (12 × ArC), 77.9$^+$ (OCH) 76.7$^-$ (OCH_2), 66.9$^-$ (C), 66.8$^-$ (CH_2OTBDPS), 35.3$^-$ (CH_2), 26.8$^+$ (CMe_3), 24.5$^+$ (CH_3), 24.0$^-$ (CH_2) and 19.3$^-$ (SiC); **MS** *m/z* (+ESI) 407 (100%, MNa^+); **HRMS (ESI)** (Found MNa^+, 407.2018. $C_{23}H_{32}O_3SiNa$ requires *MNa*, 407.2018).

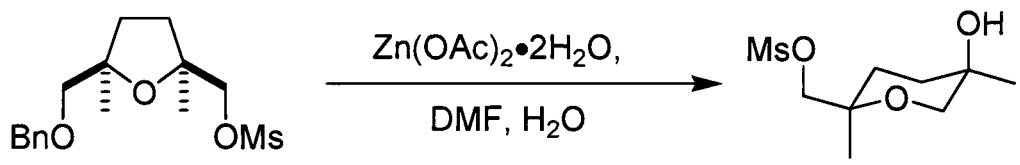
(*meso*)-((2*R*,5*S*)-2,5-Dimethyl-tetrahydrofuran-2,5-diyl)*bis*(methylene) dimethanesulfonate 437



By method H, methanesulfonic anhydride (490 mg, 2.81 mmol, 2.50 eq.) was added to a solution of diol **427** (180 mg, 1.12 mmol) and 4-(dimethyl)aminopyridine (824 mg, 6.74 mmol, 6.00 eq.) dissolved in dichloromethane (20 cm^3) to give the *bis-mesylate* **437** (354 mg, 100%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 2978, 1462, 1352, 1175, 1138, 967, 841 and 753; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 4.05 (4 H, s, 2 × CH_2OMs), 3.07 (6 H, s, 2 × SO_2CH_3), 2.17-2.04 (2 H, m, CH_AH$_B$CH_AH$_B$), 1.93-1.83 (2 H, m, CH$_A$$H_BCH_A$$H_B$) and 1.32 (6 H, s, 2 × CH_3); **^{13}C**

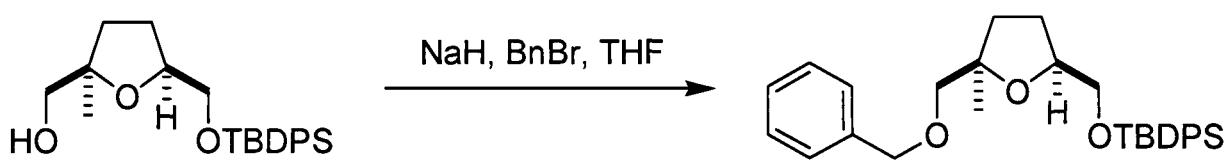
NMR δ_C (100.6 MHz; $CDCl_3$) 82.5$^-$ (2 × OC), 74.0$^-$ (2 × OCH_2OMs), 37.4$^+$ (2 × SO_2CH_3), 33.8$^-$ (2 × CH_2) and 25.0$^+$ (2 × CH_3); **MS** *m/z* (+ESI) 339 (100%, MNa^+); **HRMS (ESI)** (Found MNH_4^+, 334.0997. $C_{10}H_{24}NO_7S_2$ requires *MNH*$_4$, 334.0994).

(*RS*)-(5-Hydroxy-2,5-dimethyl-tetrahydro-2H-pyran-2-yl)methyl methanesulfonate 438



By method I, water (~2 cm^3) was added to a solution of zinc acetate dihydrate (188 mg, 857 μmol, 5.00 eq.) and mesylate **437** (54 mg, 171 μmol) dissolved in *N*,*N*-dimethylformamide (3 cm^3). The mixture was heated to initiate reflux to give a crude product. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 10:90] to give the *tetrahydropyran* **438** (33 mg, 82%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3425 br, 2940, 1643, 1456, 1350, 1297, 1174, 1081, 1174, 1081, 968, 917, 839 and 750; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 4.13 (1 H, d, *J* 10.6, C*H*$_A$H$_B$OMs), 4.07 (1 H, d, *J* 10.6, CH$_A$*H*$_B$OMs), 3.53 (1 H, d, *J* 12.1, OC*H*$_A$H$_B$), 3.42 (1 H, d, *J* 12.1, OCH$_A$*H*$_B$), 3.07 (3 H, s, SO_2CH_3), 2.54 (1 H, s, br, OH), 1.98-1.87 (1 H, C*H*$_A$H$_B$CH$_2$), 1.71-1.67 (2 H, m, CH$_A$H$_B$C*H*$_2$), 1.33 (1 H, dt, *J* 13.6 and 3.9, CH$_A$*H*$_B$CH$_2$), 1.25 (3 H, s, CH_3) and 1.14 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 76.0 (CH_2OMs), 72.0 (CO), 70.4 (OCH_2), 66.4 (CO), 37.8 (SO_2CH_3), 31.5 (CH_2), 26.4 (CH_2), 24.9 (CH_3) and 16.9 (CH_3); **MS** *m/z* (+ESI) 297 (100%, $MMeCNNa^+$) and 256 (MNH_4^+); **HRMS (ESI)** (Found MNH_4^+, 256.1224. $C_9H_{22}NO_5S$ requires *MNH*$_4$, 256.1219).

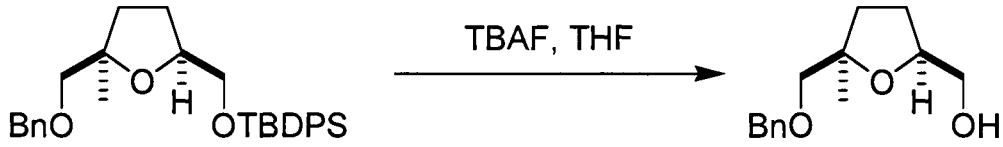
(*RS*)-(((2*S*,5*R*)-5-(Benzyloxymethyl)-5-methyl-tetrahydrofuran-2-yl)methoxy)(*tert*-butyl)diphenylsilane 440



By method F, benzyl bromide (0.460 cm^3, 385 μmol, 1.20 eq.) was added dropwise to a mixture of alcohol **434** (124 mg, 321 μmol) and sodium hydride (60% dispersion in mineral oil, 26 mg, 642 μmol, 2.00 eq.) dissolved in tetrahydrofuran (3 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 2:98] to give

the *benzyl ether* **440** (143 mg, 94%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3070, 2930, 2857, 1589, 1472, 1428, 1390, 1362, 1261, 1112, 999, 939, 823, 740, 702 and 608; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.74-7.67 (4 H, m, 4 × ArH from Si_2Ph), 7.44-7.35 (6 H, m, 6 × ArH from $SiPh_2$), 7.37-7.27 (5 H, m, 5 × ArH), 4.58-4.49 (2 H, m, CH_2Ph), 4.19-4.14 (1 H, m, OCH), 3.69 (1 H, dd, *J* 10.4 and 4.2, CH_AH$_B$OTBDPS), 3.62 (1 H, dd, *J* 10.4 and 5.8, CH$_A$$H_B$OTBDPS), 3.37 (1 H, d, *J* 9.4, OCH_AH$_B$OBn), 3.32 (1 H, d, *J* 9.4, OCH$_A$$H_B$OBn), 2.07-1.90 (3 H, m, CH_AH$_B$C$H_A$$H_B$), 1.69-1.62 (1 H, m, CH$_A$$H_BCH_AH_B$), 1.27 (3 H, s, CH_3), 1.09 (3 H, s, CMe) and 1.06 (6 H, s, CMe_2); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.7$^-$ [ArC from OBn], 135.7$^+$, 135.2$^+$, 134.8$^+$, 133.7$^-$ [ArC from $SiPh_2$], 129.7$^+$, 129.6$^+$, 128.4$^+$, 128.3$^+$, 127.8$^+$, 127.7$^+$, 127.6$^+$, 127.5$^+$, 127.4$^+$ (18 × ArC), 83.0$^-$ (O*C*Me), 79.4$^+$ (OCH), 76.8$^-$ (CH_2OBn), 73.4$^-$ (CH_2Ph), 66.3$^-$ (CH_2OTBDPS), 34.4$^-$ (*C*H$_2$C(H)O), 28.1$^-$ (*C*H$_2$C(Me)O), 26.9$^+$, 26.6$^+$ (CMe_3), 24.2$^+$ (CH_3) and 19.3$^-$, 19.0$^-$ (SiC); **MS** *m/z* (+ESI) 533 (100%, MMeCNNH$_4^+$); **HRMS (ESI)** (Found MNa$^+$, 497.2481. $C_{30}H_{38}O_3SiNa$ requires *MNa*, 497.2482).

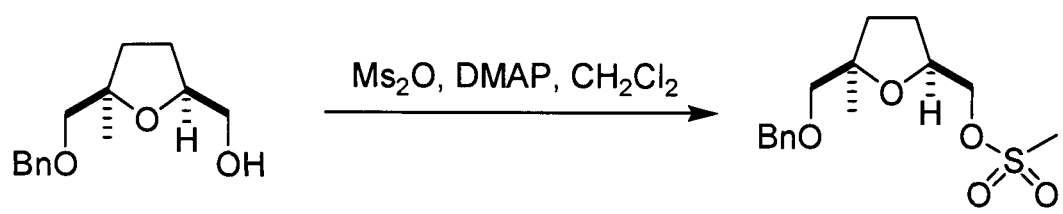
(*RS*)-((2*S*,5*R*)-5-(Benzyloxymethyl)-5-methyl-tetrahydrofuran-2-yl)methanol 441



Tetra-*n*-butylammonium fluoride solution (1.0 mol dm^{-3} solution in tetrahydrofuran containing 5% water, 2.50 cm^3, 2.50 mmol, 5.00 eq.) was added to a solution of silyl ether **440** (237 mg, 500 μmmol) dissolved in tetrahydrofuran (10 cm^3) at ambient temperature and stirred for 18 hours. Aqueous saturated sodium chloride (10 cm^3) was added, the layers separated and the aqueous layer extracted with ether (3 × 10 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 10:90] to give the *alcohol* **441** (116 mg, 98%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3441 br, 2869, 1454, 1371, 1099, 737 and 698; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.37-7.27 (5 H, m, 5 × ArH), 4.61 (1 H, d, *J* 12.2, CH_AH$_B$Ph), 4.54 (1 H, d, *J* 12.2, CH$_A$$H_B$Ph), 4.22-4.17 (1 H, m, OCH), 3.77 (1 H, dd, *J* 11.6 and 2.7, CH_AH$_B$OH), 3.48 (1 H, d, *J* 9.5, CH_AH$_B$OBn), 3.47-3.43 (1 H, m, CH$_A$$H_B$OH), 3.34 (1 H, d, *J* 9.5, CH$_A$$H_B$OBn), 2.96 (1 H, s, br, OH), 2.19 (1 H, ddd, *J* 12.2, 8.8 and 7.2, CH_AH$_B$C(Me)O), 2.07-1.94 (2 H, m, CH_2C(H)O), 1.63 (1 H, ddd, *J* 12.2, 8.2 and 6.2, CH$_A$$H_B$C(Me)O) and 1.19 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.8$^-$,

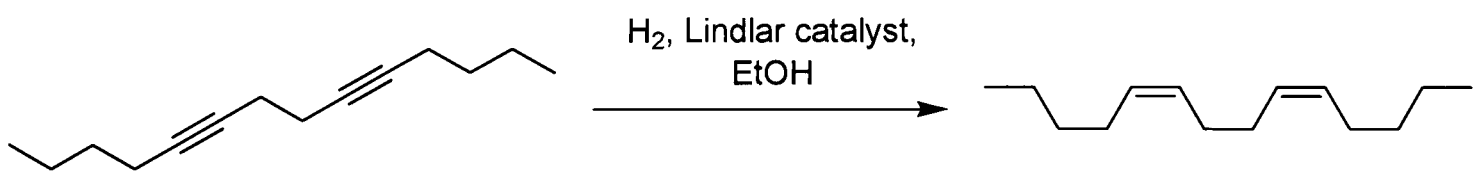
128.4^{+}, 127.8^{+}, 127.7^{+} (6 × ArC), 83.1^{-} (O*C*Me), 79.7^{+} (OCH), 76.3^{-} (CH_2OBn), 73.4^{-} (CH_2Ph), 65.6^{-} (CH_2OH), 34.3^{-} ($CH_2C(Me)O$), 27.7^{-} ($CH_2C(H)O$) and 24.5^{+} (CH_3); **MS** *m/z* (+CI) 238 (100%, MH^+) and 254 (MNH_4^+); **HRMS (CI)** (Found MH^+, 237.1485. $C_{14}H_{21}O_3$ requires *MH*, 237.1491).

(*RS*)-((2*S*,5*R*)-5-(Benzyloxymethyl)-5-methyl-tetrahydrofuran-2-yl)methyl methanesulfonate 442



By method H, methanesulfonic anhydride (147 mg, 846 μmol, 2.00 eq.) was added to a solution of alcohol **441** (100 mg, 423 μmol) and 4-(dimethyl)aminopyridine (207 mg, 1.69 mmol, 4.00 eq.) dissolved in dichloromethane (7 cm^3) to give the *mesylate* **442** (133 mg, 100%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 2933, 1454, 1356, 1176, 1101, 960, 816, 741 and 700; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.42-7.32 (5 H, m, 5 × ArH), 4.61 (2 H, s, CH_2Ph), 4.39-4.33 (1 H, m, OCH), 4.24 (2 H, dd, *J* 5.0 and 2.9, CH_2OMs), 3.43 (1 H, d, *J* 9.5, CH_AH_BOBn), 3.34 (1 H, d, *J* 9.5, CH_AH_BOBn), 3.02 (3 H, s, SO_2CH_3), 2.16-2.17 (2 H, m, $CH_AH_BCH_AH_B$), 1.93-1.83 (1 H, m, $CH_AH_BC(H)O$), 1.78-1.79 (1 H, m, $CH_AH_BC(Me)O$) and 1.30 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.5^{-}, 128.6^{+}, 127.8^{+}, 127.8^{+} (6 × ArC), 84.3^{-} (O*C*Me), 76.6^{+} (OCH), 76.6^{-} (CH_2OBn), 73.7^{-} (CH_2OMs), 72.1^{-} (CH_2OPh), 37.7^{+} (SO_2CH_3), 34.2^{-} ($CH_2C(Me)O$), 28.3^{-} ($CH_2C(H)O$) and 24.4^{+} (CH_3); **MS** *m/z* (+ESI) 373 (100%, $MMeCNNH_4^+$) and 337 (MNa^+); **HRMS (ESI)** (Found MH^+, 337.1077. $C_{15}H_{22}O_5SNa$ requires *MNa*, 337.1080).

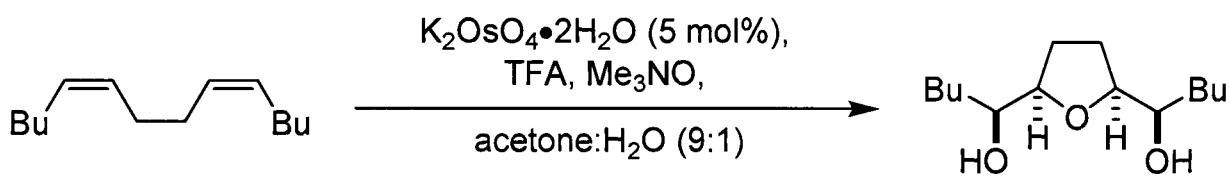
(5-*cis*,9-*cis*)-Tetradeca-5,9-diene[299] 443



Palladium (10% on calcium carbonate, poisoned with lead, micro spatula tip) was added to 5,9-tetradecadiyne (1.00 g, 525 mmol) dissolved in ethanol (250 cm^3). The flask evacuated

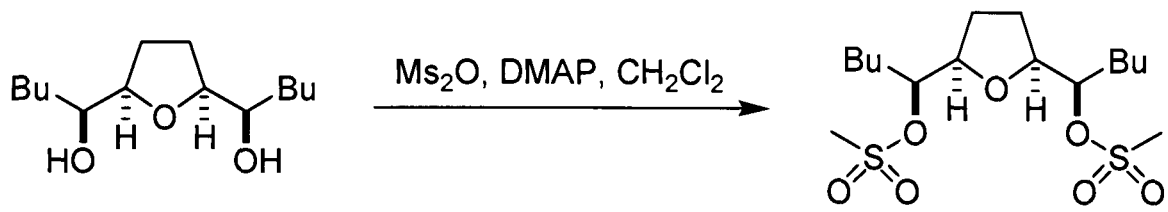
and purged with argon three times before being evacuated and purged with hydrogen five times. The mixture stirred vigorously for 4 hours under an atmosphere of hydrogen (1 atm) and filtered through Celite®, eluting with dichloromethane (100 cm^3), the combined organic extracts were evaporated under reduced pressure. The residue was chromatographed [SiO_2, light petroleum (bp 40-60 °C)] to give the diene **443** (990 mg, 97%) as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.42-5.40 (4 H, m, CH=CH and CH=CH), 2.10-2.08 (4 H, m, CH=CHCH_2CH_2CH=CH), 2.07-2.02 (4 H, m, 2 × CH_2CH=CH), 1.36-1.28 (8 H, m, 4 × CH_2) and 0.92-0.87 (6 H, m, 2 × CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 130.3$^+$ (2 × *C*H=CH), 129.1$^+$ (2 × CH=*C*H), 31.9$^-$ (CH*C*H_2*C*H_2CH), 27.4$^-$ (2 × CH_2CH=CH), 26.9$^-$ (2 × CH_2), 22.3$^-$ (2 × CH_2) and 14.1$^+$ (2 × CH_3). All spectroscopic data agreed with those previously published.[299]

(*meso*)-(1*R*,1'*S*)-1,1'-((2*R*,5*S*)-Tetrahydrofuran-2,5-diyl)dipentan-1-ol[10] 444



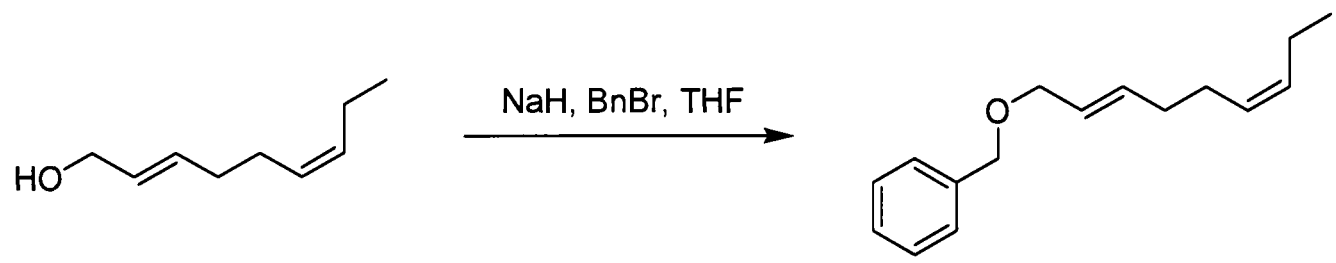
By method G, trimethylamine-*N*-oxide dihydrate (2.22 g, 20.0 mmol, 5.00 eq.) was added to a solution of diene **443** (777 mg, 4.00 mmol) and potassium osmate(VI) dihydrate (74 mg, 0.20 mmol, 0.05 eq.) dissolved in acetone (72 cm^3), water (8 cm^3) and trifluroacetic acid (40 cm^3) to give a crude product. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 10:90] to give the tetrahydrofuran **444** (792 mg, 81%) as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 3.91-3.88 (2 H, m, 2 × OCH), 3.85-3.82 (2 H, m, 2 × C*H*OH), 2.88 (2 H, s, br, 2 × OH), 1.99-1.89 (2 H, m, THF CH_AH$_B$CH_AH$_B$), 1.82-1.73 (2 H, m, THF CH$_A$$H_BCH_A$$H_B$), 1.50-1.24 (12 H, m, 6 × CH_2) and 0.89 (6 H, t, *J* 7.1, 2 × CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 82.4$^+$ (2 × OCH), 72.6$^+$ (2 × CHOH), 32.9$^-$ (2 × CH_2), 28.1$^-$ (2 × CH_2), 24.4$^-$ (THF 2 × CH_2), 22.7$^-$ (2 × CH_2) and 14.0$^+$ (2 × CH_3). All spectroscopic data agreed with those previously published.[10]

(*meso*)-(1*R*,1'*S*)-1,1'-((2*R*,5*S*)-Tetrahydrofuran-2,5-diyl)*bis*(pentane-1,1-diyl) dimethanesulfonate 445



By method H, methanesulfonic anhydride (177 mg, 1.02 mmol, 4.00 eq.) was added to a solution of alcohol **444** (63 mg, 255 μmol) and 4-(dimethyl)aminopyridine (187 mg, 1.53 mmol, 6.00 eq.) dissolved in dichloromethane (20 cm^3) to give the *bis-mesylate* **445** (102 mg, 100%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3030, 2958, 1782, 1718, 1467, 1415, 1351, 1175, 1077, 913, 835 and 783; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 4.73 (2 H, dt, *J* 7.2 and 5.0, 2 × CHOMs), 4.03-3.94 (2 H, m, 2 × OCH), 3.05 (6 H, s, 2 × SO_2CH_3), 2.02-1.95 (2 H, m, THF $CH_AH_BCH_AH_B$), 1.92-1.85 (2 H, m, THF $CH_AH_BCH_AH_B$), 1.80-1.63 (4 H, m, 2 × $CH(OMs)CH_2$), 1.47-1.29 (8 H, m, 4 × CH_2) and 0.91 (6 H, t, *J* 7.1, 2 × CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 83.0 (2 × CHOMs), 79.9 (2 × OCH), 38.7 (2 × SO_2CH_3), 31.6 (2 × CH_2), 27.1 (2 × CH_2), 26.3 (2 × CH_2), 22.5 (2 × CH_2) and 13.9 (2 × CH_3); **MS** *m/z* (+ESI) 459 (100%, $MMeCNNH_4^+$), 423 (MNa^+) and 418 (NH_4^+); **HRMS (ESI)** (Found MNH_4^+, 418.1931. $C_{16}H_{36}NO_7S_2$ requires *MNH_4*, 418.1933).

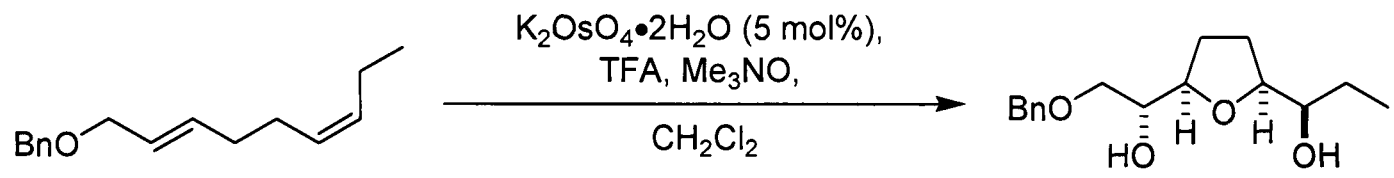
(((2-*trans*,6-*cis*)-Nona-2,6-dienyloxy)methyl)benzene 446



By method F, benzyl bromide (1.86 cm^3, 15.7 mmol, 1.10 eq.) was added dropwise to a mixture of (2*E*,6*Z*)-nona-2,6-dienol (2.00 g, 14.3 mmol) and sodium hydride (60% dispersion in mineral oil, 856 mg, 21.4 mmol, 1.50 eq.) dissolved in tetrahydrofuran (70 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 5:95] to give the *benzyl ether* **446** (2.80 g, 85%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3064, 3006, 2963, 2851, 1669, 1604, 1496, 1454, 1361, 1304, 1252, 1204, 1109, 1067, 1028, 970, 735 and 697; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.40-7.29 (5 H, m, 5 × ArH), 5.79-5.74 (1 H, m,

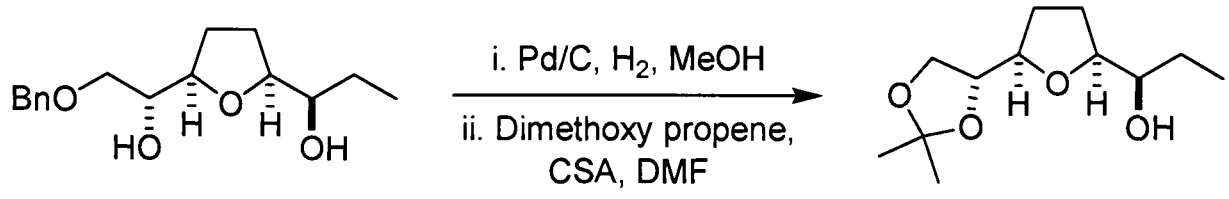
OCH_2CH=CH), 5.68-5.61 (1 H, m, OCH_2CH=C*H*), 5.45-5.33 (2 H, m, C*H*=C*H*CH_2CH_3), 4.53 (2 H, s, CH_2Ph), 4.00 (2 H, d, *J* 6.0, CH_2OBn), 2.15 (4 H, s, CH=CHCH_2CH_2CH=CH), 2.08-2.03 (2 H, m, CH_2CH_3) and 0.98 (3 H, t, *J* 7.5, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.5$^-$ (ArC), 134.3$^+$ (CH), 132.2$^+$ (CH), 128.4$^+$ (ArC and CH), 128.2$^+$ (ArC), 127.8$^+$ (ArC), 127.6$^+$ (ArC), 127.5$^+$ (ArC), 126.5$^+$ (CH), 71.8$^-$ (CH_2Ph), 70.9$^-$ (CH_2OBn), 32.4$^-$ (CH_2), 26.7$^-$ (CH_2), 20.6$^-$ (*C*H_2CH_3) and 14.3$^+$ (CH_3); **MS** *m/z* (+CI) 248 (100%, MNH_4^+); **HRMS (CI)** (Found MNH_4^+, 248.2014. $C_{16}H_{26}NO$ requires *MNH*$_4$, 248.2014).

(*RS*)-(*R*)-1-((2*S*,5*R*)-5-((*R*)-2-(Benzyloxy)-1-hydroxyethyl)-tetrahydrofuran-2-yl)propan-1-ol 447



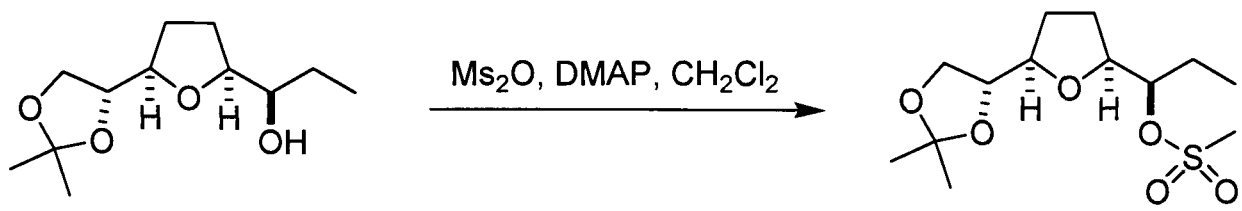
By method G, trimethylamine-*N*-oxide dihydrate (2.22 mg, 20.0 mmol, 5.00 eq.) was added to a solution of diene **446** (777 mg, 4.00 mmol) and potassium osmate$^{(VI)}$ dihydrate (74 mg, 0.20 mmol, 0.05 eq.) dissolved in acetone (72 cm^3), water (8 cm^3) and trifluroacetic acid (40 cm^3) to give a crude product. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 10:90] to give the *tetrahydrofuran* **447** (785 mg, 70%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3396 br, 3031, 2875, 1497, 1455, 1367, 1200, 1077, 966, 910, 737 and 699; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.34-7.27 (5 H, m, 5 × ArH), 4.54 (2 H, s, CH_2Ph), 4.00 (1 H, td, *J* 6.8 and 3.2, OC*H*(CH(OH)CH_2CH_3)), 3.94 (1 H, td, *J* 7.0 and 2.6, OC*H*(CHOH)CH_2OBn), 3.79-3.74 (1 H, m, C*H*(OH)CH_2CH_3), 3.73-3.70 (1 H, m, C*H*(OH)CH_2OBn), 3.60 (2 H, d, *J* 6.3, CH_2OBn), 3.25 (2 H, s, br, 2 × OH), 2.04-1.91 (3 H, m, THF C$H_AH_BCH_2$), 1.79-1.71 (1 H, m, THF CH_AH_BCH_2), 1.42-1.34 (2 H, m, CH_2CH_3) and 0.96 (3 H, t, *J* 7.5, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 137.9$^-$, 128.4$^+$, 127.8$^+$, 127.7$^+$, 127.6$^+$ (6 × ArC), 82.8$^+$ (THF O*C*H(CH(OCH)CH_2OBn), 78.9$^+$ (THF O*C*H(CH(OH)CH_2CH_3), 74.0$^+$ (*C*H(OH)CH_2CH_3), 73.4$^-$ (CH_2Ph), 72.7$^+$ (*C*H(OH)CH_2OBn), 72.7$^-$ (CH_2OBn), 28.4$^-$ (THF CH_2), 26.4$^-$ (CH_2), 23.9$^-$ (THF CH_2) and 10.5$^+$ (CH_3); **MS** *m/z* (+ESI) 303 (100%, MNa^+); **HRMS (ESI)** (Found MH^+, 281.1749. $C_{16}H_{25}O_4$ requires *MH*, 281.1753).

(*RS*)-(*R*)-1-((2*S*,5*R*)-5-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-tetrahydrofuran-2-yl)propan-1-ol



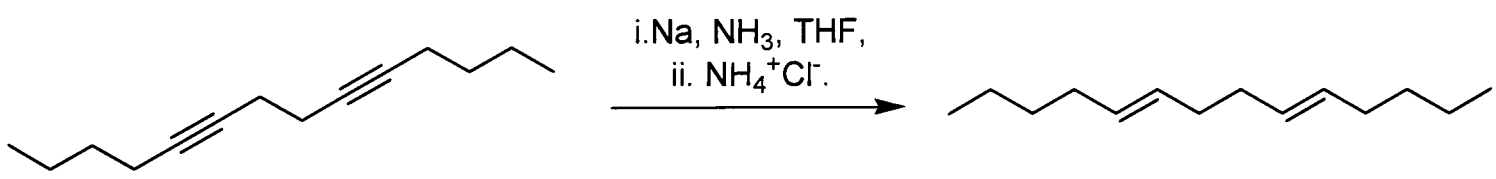
Palladium (10% on carbon, micro spatula tip) was added to benzyl ether **447** (561 mg, 2.00 mmol) dissolved in methanol (100 cm^3) and the flask evacuated and purged with argon three times before being evacuated and purged with hydrogen five times. The mixture stirred vigorously for 3 hours under an atmosphere of hydrogen (1 atm) and filtered through Celite®, eluting with dichloromethane (200 cm^3). The combined organics were evaporated under reduced pressure and the residue dissolved in *N*,*N*-dimethylformamide (6 cm^3). The flask was purged with argon before (*RS*)-camphor-10-sulfonic acid (47 mg, 200 μmol, 0.10 eq.) and 2-methoxypropene (0.345 cm^3. 3.60 mmol, 1.8 eq.) were added. After 2 hours of stirring at ambient temperature under an atmosphere of argon, the mixture was poured into aqueous saturated sodium bicarbonate solution (10 cm^3), aqueous saturated sodium chloride solution (10 cm^3) and ether (15 cm^3). The phases were separated, the aqueous layer extracted with ether (3 × 20 cm^3), the combined organic extracts washed with aqueous saturated sodium chloride solution (20 cm^3), dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 5:95] to give *(RS)-(R)-1-((2S,5R)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-tetrahydrofuran-2-yl)propan-1-ol* (387 mg, 84%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3426 br, 2879, 1462, 1372, 1214, 1157, 1061, 971 and 854; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 4.07 (1 H, ddd, *J* 7.7, 6.5 and 5.0, THF OC*H*(CHO)), 3.99 (1 H, dd, *J* 7.9 and 6.5, CH_AH$_B$O), 3.95-3.89 (2 H, m, THF OC*H*(CHOH) and OCH(C*H*O)), 3.77-3.71 (2 H, m, CH$_A$$H_B$O and OCH(C*H*OH)), 2.70 (1 H, s, br, OH), 1.99-1.90 (2 H, m, THF CH_AH$_B$CH_AH$_B$), 1.81-1.68 (2 H, m, THF CH$_A$$H_BCH_A$$H_B$), 1.43 (3 H, s, CCH_3), 1.41-1.37 (2 H, m, CH_2), 1.35 (3 H, s, CCH_3) and 0.95 (3 H, t, *J* 7.5, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 109.6$^-$ (CMe_2), 82.8$^+$ (THF O*C*H(CHOH), 79.0$^+$ (CHO), 78.0$^+$ (THF O*C*H(CHO)), 73.6$^+$ (CHOH), 66.2$^-$ (CH_2O), 28.3$^-$ (THF CH_2), 26.5$^+$ (CCH_3), 26.4$^-$ (CH_2), 25.5$^+$ (CCH_3), 23.9$^-$ (THF CH_2) and 10.5$^+$ (CH_3); **MS** *m/z* (+ESI) 253 (100%, MNa^+); **HRMS (ESI)** (Found MNa^+, 253.1425. $C_{12}H_{22}O_4Na$ requires *MNa*, 253.1416).

(*RS*)-(*R*)-1-((2*S*,5*R*)-5-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-tetrahydrofuran-2-yl)propyl methanesulfonate 448



By method H, methanesulfonic anhydride (348 mg, 2.00 mmol, 2.00 eq.) was added to a solution (*RS*)-(*R*)-1-((2*S*,5*R*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-tetrahydrofuran-2-yl)propan-1-ol (230 mg, 1.00 mmol) and 4-(dimethyl)aminopyridine (489 mg, 4.00 mmol, 4.00 eq.) dissolved in dichloromethane (20 cm^3) to give the *mesylate* **448** (308 mg, 100%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 2981, 2884, 1463, 1347, 1260, 1212, 1174, 1061, 934, 852, 779 and 735; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 4.69 (1 H, ddd, *J* 7.3, 5.6 and 3.7, CHOMs), 4.04-3.96 (4 H, m, C*H*$_A$H$_B$O, THF OC*H*(CHOMs), THF OC*H*(CHO) and OCH(C*H*O)), 3.62-3.56 (1 H, m, CH$_A$*H*$_B$O), 3.06 (3 H, s, SO_2CH_3), 1.95-1.87 (3 H, m, THF C*H*$_A$H$_B$C*H*$_2$), 1.79-1.65 (2 H, m, CH_2), 1.62-1.52 (1 H, m, THF CH$_A$*H*$_B$CH$_2$), 1.40 (3 H, s, CCH_3), 1.32 (3 H, s, CCH_3) and 0.99 (3 H, t, *J* 7.5, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 109.8$^-$ (CMe_2), 84.3$^+$ (CHOMs), 80.6$^+$ (THF O*C*H(CHO)), 79.7$^+$ (THF O*C*H(CHOMs)), 78.2$^+$ (CHO), 66.0$^-$ (CH_2O), 38.5$^+$ (SO_2CH_3), 27.2$^-$ (THF CH_2), 26.6$^+$ (C*C*H$_3$), 25.4$^-$ (THF CH_2 and CH_2) and 9.7$^+$ (CH_3); **MS** *m/z* (+ESI) 367 (100%, MMeCNNH$_4^+$) and 331 (MNa$^+$); **HRMS (ESI)** (Found MH$^+$, 309.1364. $C_{13}H_{25}O_6S$ requires *MH*, 309.1372).

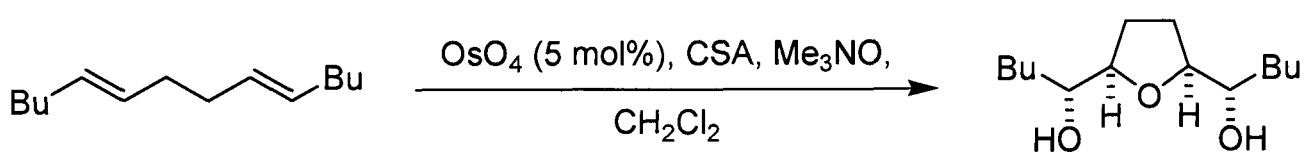
(5-*trans*,9-*trans*)-Tetradeca-5,9-diene[299] 451



Ammonia (200 cm^3) was freshly distilled onto cut sodium (2.42 g, 105 mmol, 7.00 eq.) under an atmosphere of argon at –78 °C. The resulting dark blue solution was stirred for 1 hour before the addition of 5,9-tetradecadiyne (2.86 g, 15.0 mmol) dissolved in tetrahydrofuran (10 cm^3); stirring continued for 10 minutes before the addition of aqueous saturated ammonium chloride (5 cm^3). The reaction was allowed to warm to ambient temperature and the ammonia evaporated. Light petroleum (bp 40-60 °C) (20 cm^3) was added and the layers were

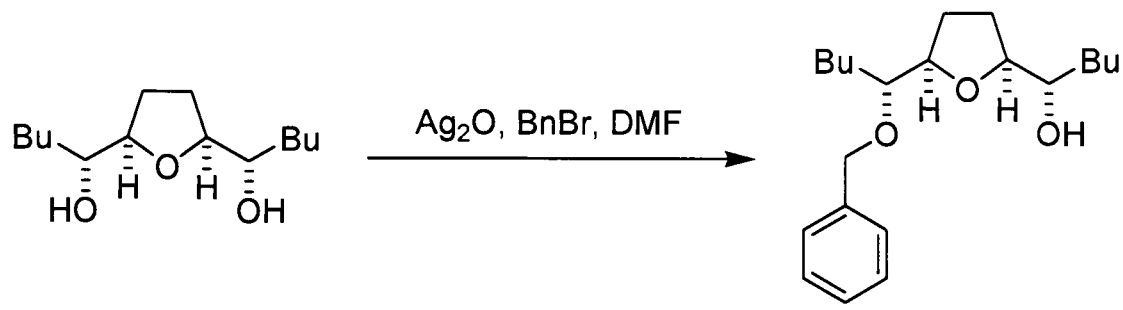
separated. The aqueous layer was extracted with light petroleum (bp 40-60 °C) (3 × 20 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, light petroleum (bp 40-60 °C)] to give the diene **451** (2.19 g, 75%) as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.42-5.38 (4 H, m, CH=CH and CH=CH), 2.04 (4 H, s, br, CH=CHCH_2CH_2CH=CH), 1.99-1.96 (4 H, m, 2 × CH_2CH=CH), 1.34 (8 H, m, 4 × CH_2) and 0.90 (6 H, t, *J* 7.1, 2 × CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 130.6$^+$ (2 × *C*H=CH), 129.7$^+$ (2 × CH=*C*H), 32.7$^-$ (CH*C*H_2*C*H_2CH), 32.3$^-$ (2 × CH_2CH=CH), 31.8$^-$ (2 × CH_2), 22.2$^-$ (2 × CH_2) and 13.9$^+$ (2 × CH_3). All spectroscopic data agreed with those previously published.[299]

(*meso*)-(1*S*,1'*R*)-1,1'-((2*R*,5*S*)-Tetrahydrofuran-2,5-diyl)dipentan-1-ol[10] 452



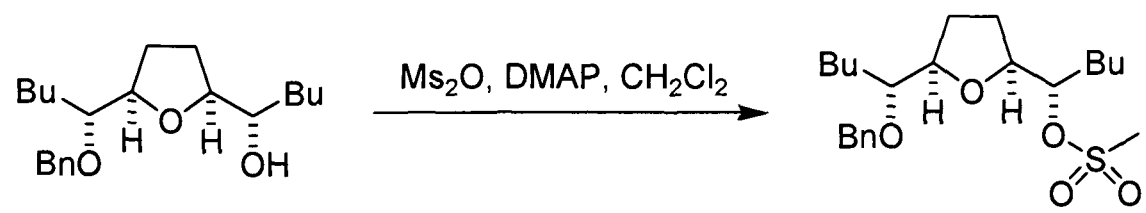
By method K, trimethylamine-*N*-oxide dihydrate (1.79 g, 16.0 mmol, 4.00 eq.) was added to a solution of diene **451** (777 mg, 4.00 mmol), (*RS*)-camphor-10-sulfonic acid (5.58 g, 24.0 mmol, 6.00 eq.) and osmium$^{(VIII)}$ tetroxide (51 mg, 0.20 mmol, 0.05 eq.) dissolved in dichloromethane (200 cm^3) to give a crude product. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 10:90] to give the tetrahydrofuran **452** (909 mg, 93%) as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 3.78 (2 H, dd, *J* 10.3 and 4.9, 2 × OCH), 3.37 (2 H, dd, *J* 11.0 and 5.5, 2 × C*H*OH), 3.17 (2 H, s, br, 2 × OH), 1.92-1.86 (2 H, THF CH_AH$_B$CH_AH$_B$), 1.73-1.67 (2 H, THF CH$_A$$H_BCH_A$$H_B$), 1.47-1.40 (4 H, m, 2 × CH(OH)CH_2), 1.33-1.26 (8 H, m, 4 × CH_2) and 0.86 (6 H, t, *J* 7.1, 2 × CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 82.8$^+$ (2 × OCH), 74.2$^+$ (2 × CHOH), 33.7$^-$ (2 × CH_2), 28.0$^-$ (2 × CH_2), 27.8$^-$ (2 × THF CH_2), 22.7$^-$ (2 ×CH_2) and 14.0$^+$ (2 × CH_3). All spectroscopic data agreed with those previously published.[10]

(*RS*)-(*S*)-1-((2*S*,5*R*)-5-((*R*)-1-(Benzyloxy)pentyl)-tetrahydrofuran-2-yl)pentan-1-ol



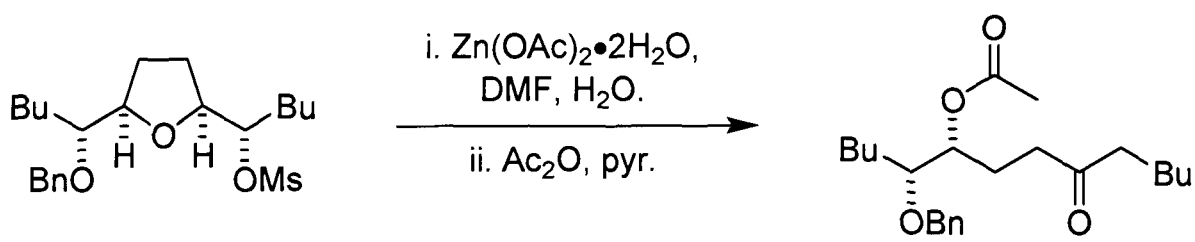
Silver[(I)] oxide (695 mg, 3.00 mmol, 1.50 eq.) was added to diol **452** (489 mg, 2.00 mmol) dissolved in *N*,*N*-dimethylformamide (5 cm^3) and stirred under an atmosphere of argon at ambient temperature in the dark for 45 minutes. Benzyl bromide (0.261 cm^3, 2.20 mmol, 1.10 eq.) was added and the mixture stirred for a further 48 hours. Water (10 cm^3) was added and the mixture stirred vigorously for 45 minutes before being poured into water (5 cm^3) and ether (15 cm^3). The layers were separated, the aqueous layer extracted with ethyl acetate (3 × 10 cm^3), the combined organic extracts were washed with aqueous saturated sodium chloride (25 cm^3), dried (anhydrous sodium sufate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 20:80] to give *(RS)-(S)-1-((2S,5R)-5-((R)-1-(benzyloxy)pentyl)-tetrahydrofuran-2-yl)pentan-1-ol* (909 mg, 75%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3462 br, 3031, 2956, 1497, 1456, 1379, 1264, 1205, 1068, 734 and 698; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.36-7.28 (5 H, m, 5 × ArH), 4.66 (1 H, d, *J* 11.6, CH_AH$_B$Ph), 4.61 (1 H, d, *J* 11.6, CH$_A$$H_B$Ph), 4.03 (1 H, td, *J* 6.9 and 4.6, THF C*H*OCHBn), 3.87-3.83 (1 H, m, THF OC*H*CHOH), 3.39-3.35 (1 H, m, C*H*OH), 3.32 (1 H, td, *J* 6.2 and 4.7, CHOBn), 2.58 (1 H, s, br, OH), 1.96-1.85 (2 H, m, THF CH_AH$_B$CH_AH$_B$), 1.84-1.72 (2 H, m, THF CH$_A$$H_BCH_A$$H_B$), 1.63-1.57 (2 H, m, CH_2), 1.48-1.30 (10 H, m, 5 × CH_2), 0.91 (3 H, t, *J* 7.1, CH_3) and 0.91 (3 H, t, *J* 7.1, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.6$^-$, 128.3$^+$, 128.2$^+$, 128.0$^+$, 127.6$^+$ (6 × ArC), 82.3$^+$ (THF CH), 81.4$^+$ (THF CH), 81.2$^+$ (CHOBn), 74.2$^+$ (CHOH), 72.5$^-$ (CH_2Ph), 34.1$^-$, 30.9$^-$, 28.1$^-$, 28.0$^-$, 27.8$^-$, 22.8$^-$ (8 × CH_2), and 14.1$^+$ (2 × CH_3); **MS** *m/z* (+ESI) 394 (100%, MMeCNNH$_4^+$); **HRMS (ESI)** (Found MH$^+$, 335.2583. $C_{21}H_{35}O_3$ requires *MH*, 335.2586).

(*RS*)-(*S*)-1-((2*S*,5*R*)-5-((*R*)-1-(Benzyloxy)pentyl)-tetrahydrofuran-2-yl)pentyl methanesulfonate 453



By method H, methanesulfonic anhydride (200 mg, 1.15 mmol, 3.00 eq.) was added to a solution of (*RS*)-(*S*)-1-((2*S*,5*R*)-5-((*R*)-1-(benzyloxy)pentyl)-tetrahydrofuran-2-yl)pentan-1-ol (128 mg, 383 μmol) and 4-(dimethyl)aminopyridine (281 mg, 2.30 mmol, 6.00 eq.) dissolved in dichloromethane (20 cm^3) to give the *mesylate* **453** (158 mg, 100%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3031, 2957, 2871, 1719, 1497, 1455, 1352, 1174, 1068, 914, 832, 783, 737 and 699; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.34-7.25 (5 H, m, 5 × ArH), 4.63 (2 H, s, CH_2Ph), 4.63-4.58 (1 H, m, CHOMs), 4.04-3.96 (2 H, m, 2 × THF OCH), 3.36 (1 H, dd, *J* 11.4 and 6.4, CHOBn), 3.03 (3 H, s, SO_2CH_3), 1.97-1.85 (2 H, m, THF CH_2), 1.73-1.61 (4 H, m, THF CH_2 and CH(OMs)CH_2), 1.56-1.25 (10 H, m, 5 × CH_2), 0.91 (3 H, t, *J* 7.0, CH_3) and 0.90 (3 H, t, *J* 7.0, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.9^-, 129.6^+, 128.5^+, 128.3^+, 127.6^+, 127.4^+ (6 × ArC), 86.4^+ (CHOMs), 81.7^+ (THF OCH), 81.3^+ (CHOBn), 80.2^+ (THF OCH), 72.2^- (CH_2Ph), 38.8^+ (SO_2CH_3), 31.4^- (CH_2), 30.5^- (CH_2), 28.1^- (CH_2), 27.8^- (CH_2), 27.5^- (CH_2), 27.0^- (CH_2), 22.9^- (CH_2), 22.5^- (CH_2), 14.0^+ (CH_3) and 13.9^+ (CH_3); **MS** *m/z* (+ESI) 471 (100%, $MMeCNNH_4^+$); **HRMS (ESI)** (Found MH^+, 413.2366. $C_{22}H_{37}O_5S$ requires *MH*, 413.2362).

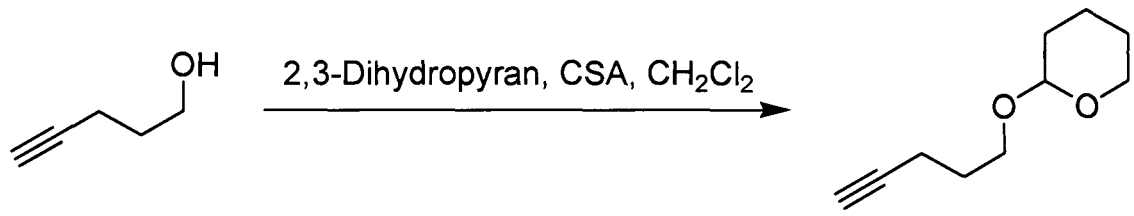
(*RS*)-(5*R*,6*R*)-5-(Benzyloxy)-9-oxotetradecan-6-yl acetate 455



By method I, water (~1 cm^3) was added to a solution of zinc acetate dihydrate (80 mg, 364 μmol, 5.00 eq.) and mesylate **453** (30 mg, 72.7 μmol) dissolved in *N*,*N*-dimethylformamide (1.1 cm^3). The mixture was heated to initiate reflux to give a crude product. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 20:80] to give the *lactol* and

ketone in equilibrium. The residue was dissolve in pyridine (2.0 cm^3) and the flask was purged with argon for 5 minutes. Acetic anhydride (1.0 cm^3) was added and the reaction stirred for 48 hours. Methanol (1.0 cm^3) was added to quench any excess acetic anhydride and the mixture stirred for 15 minutes before being evaporated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 10:90] to give the *ketone* **455** (21 mg, 75%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3031, 2956, 1735, 1497, 1455, 1373, 1240, 1029, 736, 699 and 604; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.34-7.28 (5 H, m, 5 × ArH), 5.01 (1 H, dt, *J* 9.5 and 3.9, CHOAc), 4.59 (2 H, s, CH_2Ph), 3.40 (1 H, dt, *J* 7.8 and 4.6, CHOBn), 2.38 (2 H, d, *J* 8.2, CH_2CO), 2.34 (2 H, d, *J* 8.2, $COCH_2$), 2.05 (3 H, s, $COCH_3$), 2.00-1.91 (1 H, m, C(OAc)CH_AH$_B$), 1.82 (1 H, ddt, *J* 14.4, 9.5 and 7.1, C(OAc)CH$_A$$H_B$), 1.58-1.48 (2 H, m, $COCH_2CH_2$), 1.46-1.20 (10 H, m, CH_2) and 0.90-0.85 (6 H, m, 2 × CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 210.2$^-$ (CO), 170.8$^-$ (CO), 138.4$^-$, 128.3$^+$, 127.9$^+$, 127.6$^+$ (6 × ArC), 79.3$^+$ (CHOBn), 75.5$^+$ (CHOAc), 72.4$^-$ (CH_2Ph), 42.8$^-$ (CH_2CO), 38.7$^-$ (CH_2CO), 31.4$^-$ (CH(OAc)CH_2CH$_2$CO), 29.5$^-$ (CH_2), 27.7$^-$ (CH_2), 23.8$^-$ (CH_2), 23.5$^-$ (CH_2), 22.7$^-$ (CH_2), 22.4$^-$ (CH_2), 21.1$^+$ ($COCH_3$), 14.0$^+$ (CH_3) and 13.9$^+$ (CH_3); **MS** *m/z* (+ESI) 436 (100%, MMeCNNH$_4^+$); **HRMS (ESI)** (Found MNH$_4^+$, 394.2956. $C_{23}H_{40}NO_4$ requires *MNH$_4$*, 394.2957).

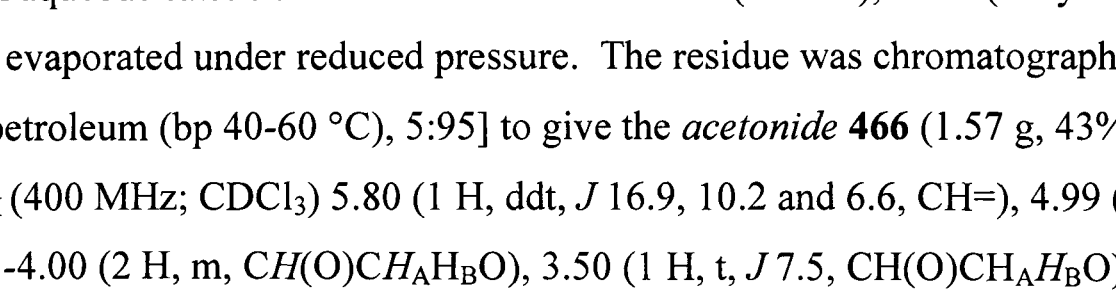
(*RS*)-2-(Pent-4-ynyloxy)-tetrahydro-2H-pyran[283] 465



4-Pentynol (1.11 cm^3, 11.9 mmol) was added dropwise to a solution of 2,3-dihydro-2H-pyran (1.63 cm^3, 17.8 mmol, 1.50 eq.) and pyridinium-*para*-toluenesulfonate (299 mg, 1.19 mmol, 0.10 eq.) dissolved in dichloromethane (85 cm^3) under an atmosphere of argon at ambient temperature and stirred for 20 hours. Aqueous saturated sodium chloride solution (100 cm^3) was added to the solution, the layers separated and the aqueous layer extracted with ether (100 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 4:96] to give the acetal **465** (1.98 g, 99%) as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 4.60-4.58 (1 H, m, OCHO), 3.89-3.79 (2 H, m, CH_AH$_B$OCHO and THP OCH_{axial}H$_{equatorial}$), 3.52-3.45 (2 H, m, CH$_A$$H_B$OCHO and THP OCH$_{axial}$$H_{equatorial}$), 2.32-2.28 (2

H, m, HC≡CCH_2), 1.94 (1 H, t, J 2.7, HC≡C), 1.84-1.78 (4 H, m, CH_2CH_2O and THP CH_2) and 1.60-1.49 (4 H, m, THP 2 × CH_2); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 98.8$^+$ (OCHO), 84.0$^-$ (HC≡*C*), 68.4$^-$ (HC≡), 65.8$^-$ (OCH_2), 62.2$^-$ (OCH_2), 30.6$^-$ (CH_2), 28.7$^-$ (CH_2), 25.5$^-$ (CH_2), 19.5$^-$ (CH_2) and 15.3$^-$ (HC≡C*C*H_2). All spectroscopic data agreed with those previously published.[283]

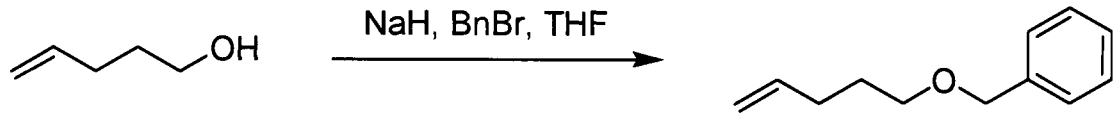
(*RS*)-4-(But-3-enyl)-2,2-dimethyl-1,3-dioxolane[285] 466



Potassium osmate$^{(VI)}$ dihyrate (179 mg, 487 μmol, 0.02 eq.) was added to 1,5-hexadiene (2.88 cm^3, 23.4 mmol), potassium carbonate (6.73 g, 48.7 mmol, 2.00 eq.), potassium ferricyanide (16.0 g, 48.7 mmol, 2.00 eq.), methanesulfonamide (2.32 g, 23.5 mmol, 1.00 eq.) and quinuclidine (104 mg, 936 mmol, 0.04 eq.) dissolved in a mixture of water (160 cm^3) and 2-methyl-2-propanol (160 cm^3) at ambient. The resulting mixture was stirred vigoursly for 48 hours. Sodium sulfite (306 mg, 2.34 mmol, 0.10 eq.) and ethyl acetate (120 cm^3) were added to the mixture and stirred vigoursly for 1 hour. The layers were separated, the aqueous layer extracted with ethyl acetate (3 × 150 cm^3), the combined organic extracts dried (anhydrous sodium sulfate), evaporated under reduced pressure and the residue dissolved in *N*,*N*-dimethylformamide (10 cm^3). The flask was purged with argon before (*RS*)-camphor-10-sulfonic acid (543 mg, 2.34 mmol, 0.10 eq.) and 2-methoxypropene (4.03 cm^3. 42.1 mmol, 1.8 eq.) were added. After 2 hours of stirring at ambient temperature under an atmosphere of argon, the mixture was poured into aqueous saturated sodium bicarbonate solution (50 cm^3), aqueous saturated sodium chloride solution (50 cm^3) and ether (65 cm^3). The mixture was separated, the aqueous layer extracted with ether (3 × 40 cm^3), the combined organic extracts washed with aqueous saturated sodium chloride solution (20 cm^3), dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 5:95] to give the *acetonide* **466** (1.57 g, 43%) as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.80 (1 H, ddt, J 16.9, 10.2 and 6.6, CH=), 4.99 (2 H, m, CH_2=), 4.11-4.00 (2 H, m, C*H*(O)CH_AH$_B$O), 3.50 (1 H, t, J 7.5, CH(O)CH$_A$$H_B$O), 2.21-2.03 (2 H, m, CH_2=CHCH_2), 1.78-1.69 (1 H, m, CH_2CH_AH$_B$CHO), 1.62-1.53 (1 H, m,

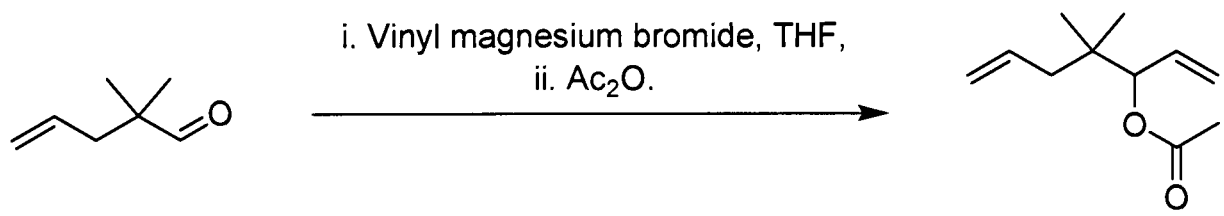
$CH_2CH_AH_BCHO$), 1.39 (3 H, s, CH_3) and 1.34 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 137.8$^+$ (CH=), 115.0$^-$ (CH_2=), 108.6$^-$ (C), 75.5$^+$ (CHO), 69.4$^-$ (CH_2O), 32.7$^-$ (CH_2CHO), 29.9$^-$ (CH_2=$CHCH_2$), 26.9$^+$ (CH_3) and 25.7$^+$ (CH_3). All spectroscopic data agreed with those previously published.[285]

((Pent-4-enyloxy)methyl)benzene 467



By method F, benzyl bromide (7.95 cm^3, 66.8 mmol, 1.20 eq.) was added dropwise to a mixture of 4-pentenol (4.00 g, 55.7 mmol) and sodium hydride (60% dispersion in mineral oil, 4.45 g, 111 mmol, 2.00 eq.) dissolved in tetrahydrofuran (125 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ether-light petroleum (bp 30-40 °C), 1:99] to give the *benzyl ether* **467** (7.95 g, 81%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 2938, 2856, 1641, 1496, 1454, 1364, 1206, 1103, 1028, 994, 912 and 736; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.39-7.30 (5 H, m, 5 × ArH), 5.91-5.80 (1 H, m, CH_2=C*H*), 5.09-4.99 (2 H, m, CH_2=CH), 4.54 (2 H, CH_2Ph), 3.52 (2 H, t, *J* 6.5, CH_2OBn), 2.22-2.17 (2 H, m, CH_2=$CHCH_2$) and 1.80-1.73 (2 H, m, CH_2CH_2OBn); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.7$^-$ (CH_2=CH), 138.3$^-$, 128.4$^+$, 127.8$^+$, 127.7$^+$, 127.5$^+$ (6 × ArC), 114.8$^-$ (CH_2=CH), 72.9$^-$ (CH_2Ph), 69.8$^-$ (CH_2OBn), 30.4$^-$ (CH_2=$CHCH_2$) and 29.0$^-$ (CH_2CH_2OBn); **MS** *m/z* (+CI) 194 (100%, MNH_4^+); **HRMS (CI)** (Found MNH_4^+, 194.1546. $C_{12}H_{20}NO$ requires *MNH*$_4$, 194.1545).

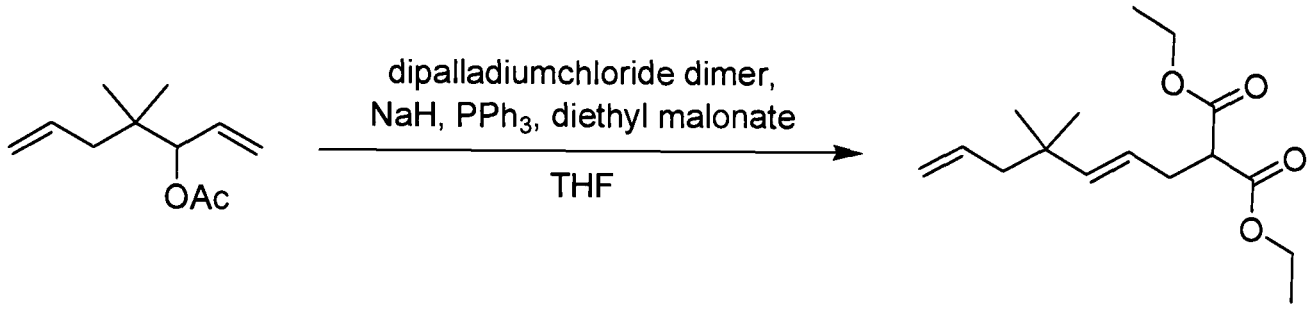
(*RS*)-4,4-Dimethylhepta-1,6-dien-3-yl acetate[286] 468



A vinylmagnesium bromide solution (1.0 mol dm^{-3} solution in tetrahydrofuran, 38.4 mmol, 1.20 eq.) was added to 2,2-dimethyl-4-pentenal (4.35 cm^3, 32.0 mmol) dissolved in tetrahydrofuran (40 cm^3) at 0 °C under an atmosphere of argon and stirred for 15 minutes before being allowed to warm to ambient temperature; stirring continued for a further 1.5 hours. The reaction was cooled to 0 °C before acetic anhydride (9.07 cm^3, 96.0 mmol, 3.00

eq.) was added, the mixture was allowed to warm to ambient temperature and stirred for a further 12 hours. Water (100 cm^3) was added and the mixture poured into ether (150 cm^3). The layers were separated, the aqueous layer extracted with ether (150 cm^3), and the combined organic extracts washed successively with aqueous saturated sodium bicarbonate solution (150 cm^3) and water (3 × 100 cm^3). The organic layer was dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 5:95] to give the vinyl acetate **468** (5.07 g, 87%) as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.84-5.74 (2 H, m, CH_2=C*H* and CH(OAc)C*H*=CH_2), 5.23-5.19 (2 H, m, CH_2=CH), 5.06-4.97 (3 H, m, CH_2=CH and CH(OAc), 2.09-1.94 (2 H, m, $CH_2C(Me)_2$), 2.06 (3 H, s, $COCH_3$), 0.90 (3 H, s, CH_3) and 0.87 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 170.1$^-$ (CO), 134.4$^+$ (CH_2=*C*H), 133.3$^+$ (CH_2=*C*H), 118.3$^-$ (*C*H_2=CH), 117.6$^-$ (*C*H_2=CH), 80.6$^+$ (CH(OAc), 43.3$^-$ (CH_2), 36.9$^-$ (C), 23.0$^+$ (CH_3), 22.8$^+$ (CH_3) and 21.1$^+$ (CH_3). All spectroscopic data agreed with those previously published.[286]

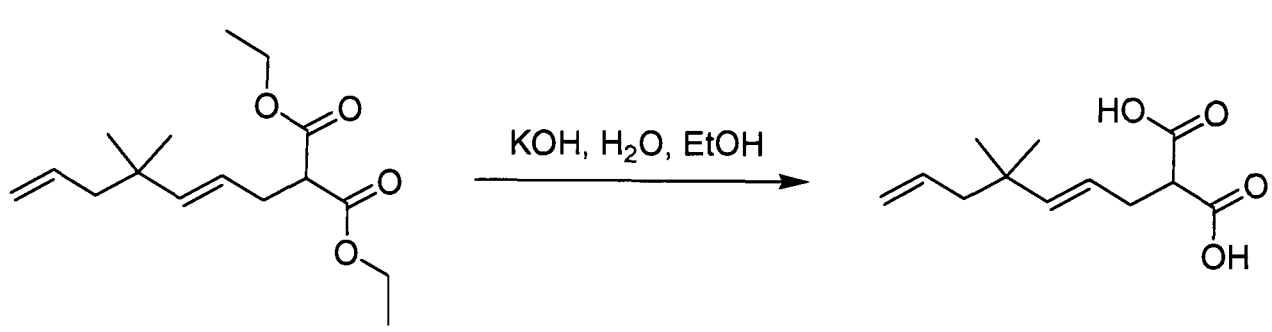
(*RS*)-(*trans*)-Diethyl 2-(4,4-dimethylhepta-2,6-dienyl)malonate 469



Sodium hydride (60% dispersion in mineral oil, 141 mg, 3.52 mmol, 1.85 eq.) was added to diethyl malonate (654 mg, 3.80 mmol, 2.00 eq.) dissolved in tetrahydrofuran (10 cm^3) under an atmosphere of argon at ambient temperature and the mixture stirred for 20 minutes. To this mixture, allypalladium chloride dimer (18 mg, 490 μmol, 0.26 eq.) and triphenylphosphine (100 mg, 380 μmol, 0.20 eq.) dissolved in tetrahydrofuran (3 cm^3) were added dropwise. After 10 minutes, vinyl acetate **468** (347 mg, 1.90 mmol) dissolved in tetrahydrofuran (3 cm^3) was added and the mixture heated to initiate reflux; heating continued for a further 16 hours. The mixture was allowed to cool, poured into water (25 cm^3) and ether (25 cm^3), the layers separated and the aqueous layer extracted with ether (2 × 50 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60

°C), 3:97] to give the *malonate* **469** (453 mg, 84%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3076, 2963, 1735, 1640, 1466, 1369, 1228, 1097, 1036, 977, 915 and 860; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.68 (1 H, ddt, *J* 17.6, 10.4 and 7.4, CH_2=CH), 5.50 (1 H, d, *J* 15.6, C(Me)$_2$C*H*=CH), 5.25 (1 H, dt, *J* 15.6 and 6.9, C(Me)$_2$CH=C*H*), 4.92-4.80 (2 H, m, CH_2=CH), 4.17 (4 H, dq, *J* 7.1 and 1.1, 2 × OCH_2), 3.35 (1 H, t, *J* 7.6, CH(CO_2Et)$_2$), 2.59-2.55 (2 H, m, CHC*H*$_2$CH(CO_2Et)$_2$), 1.97 (2 H, d, *J* 7.4, CHC*H*$_2$C(Me)$_2$), 1.25 (6 H, t, *J* 7.1, 2 × OCH_2CH_3) and 0.92 (6 H, s, 2 × CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 169.0$^-$ (2 × CO), 143.2$^+$ (CH_2=CH), 135.5$^+$ (C(Me)$_2$)*C*H=CH), 121.4$^+$ (C(Me)$_2$)CH=*C*H), 116.7$^-$ (CH_2=CH) 61.4$^-$ (OCH_2), 61.3$^-$ (OCH_2), 52.2$^+$ (CH_2*C*H(CO_2Et)$_2$), 47.2$^-$ (*C*H$_2$C(Me)$_2$), 35.8$^-$ (C), 32.0$^-$ (*C*H$_2$CH(CO_2Et)$_2$), 26.9$^+$ (2 × CH_3) and 14.0$^+$ (2 × OCH_2CH_3); **MS** *m/z* (+ESI) 305 (100%, MNa^+) and 283 (MH^+); **HRMS (ESI)** (Found MH^+, 283.1908. $C_{16}H_{27}O_4$ requires *MH*, 283.1909).

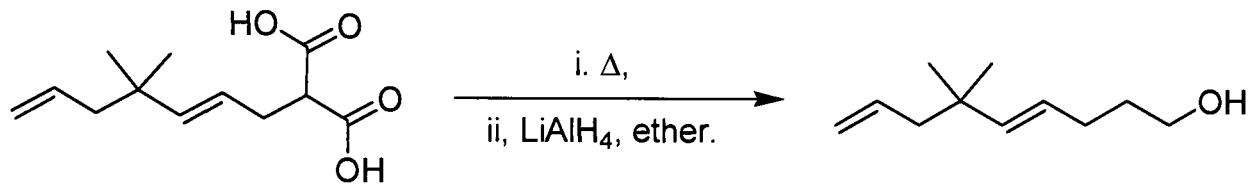
(*RS*)-(*trans*)-2-(4,4-Dimethylhepta-2,6-dienyl)malonic acid



Potassium hydroxide (2.44 g, 43.5 mmol, 4.1 eq.) dissolved in water (40 cm^3) was added dropwise to malonate **469** (3.00 g, 10.6 mmol) dissolved in ethanol (22 cm^3) and heated to intiate reflux; heating continued for a further 5 hours. The solution was allowed to cool, poured into dichloromethane (20 cm^3) and the layers separated. The aqueous layer was acidified with aqueous concentrated hydrochloric acid to pH ~ 1, extracted with ether (3 × 50 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure to give *(RS)-(trans)-2-(4,4-dimethylhepta-2,6-dienyl)malonic acid* (2.19 g, 91%) as a viscous oil; **IR** ν_{max} (thin film)/cm^{-1} 2962 br, 1715, 1416, 1253, 976, 915, 772 and 666; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 10.30 (2 H, s, br, 2 × OH), 5.73-5.63 (1 H, m, CH_2=CH), 5.55 (1 H, d, *J* 15.6, C(Me)$_2$C*H*=CH), 5.32-5.24 (1 H, m, C(Me)$_2$CH=C*H*), 4.99-4.93 (2 H, m, CH_2=CH), 3.48 (1 H, t, *J* 7.3, CH(CO_2H)$_2$), 2.62 (2 H, t, *J* 7.2, CHC*H*$_2$CH(CO_2H)$_2$), 1.98 (2 H, d, *J* 7.3, CHC*H*$_2$C(Me)$_2$) and 0.94 (6 H, s, 2 ×CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 174.2$^-$ (2 × CO), 144.2$^+$ (CH_2=CH), 135.3$^+$

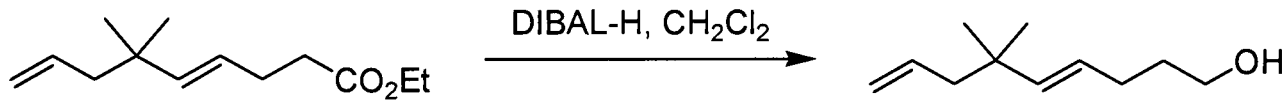
$(C(Me)_2CH=CH)$, 120.4$^+$ $(C(Me)_2CH=CH)$, 116.9$^-$ $(CH_2=CH)$, 52.1$^+$ $(CH_2CH(CO_2H)_2)$, 47.1$^-$ $(CH_2C(Me)_2)$, 31.9$^-$ $(CH_2CH(CO_2H)_2)$, and 28.9$^+$ (2 × CH_3); **MS** *m/z* (-ESI) 225 (100%, M-H); **HRMS (ESI)** (Found M-H, 225.1130. $C_{12}H_{17}O_4$ requires *M-H*, 225.1121).

(*trans*)-6,6-Dimethylnona-4,8-dien-1-ol



(*RS*)-(*trans*)-2-(4,4-dimethylhepta-2,6-dienyl)malonic acid (2.00 g, 8.84 mmol) was heated neat at 165 °C for 5 hours. The residue was added to aqueous sodium hydroxide (2.0 mol dm^{-3}, 20 cm^3) and stirred for 5 minutes before the addition of dichloromethane (10 cm^3). After the layers were separated, the aqueous layer was acidified with aqueous concentrated hydrochloric acid to pH ~1 and poured into ether (30 cm^3). The layers were separated, the aqueous layer was extracted with ether (2 × 50 cm^3), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. Lithium aluminium hydride powder (1.34 g, 35.4 mmol, 4.00 eq.) was dissolved in ether (50 cm^3) and the residue dissolved in tetrahydrofuran (100 cm^3) added at a rate to induce reflux; heating continued for 5 hours. After the mixture was allowed to cool to ambient temperature, aqueous saturated sodium sulfate solution was added until no further white precipitate was formed. The mixture was filtered through Celite®, eluting with dichloromethane (200 cm^3) and the combined organic extracts evaporated under reduced pressure. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 10:90] to give *(trans)-6,6-dimethylnona-4,8-dien-1-ol* (1.23 g, 83%) as an oil.

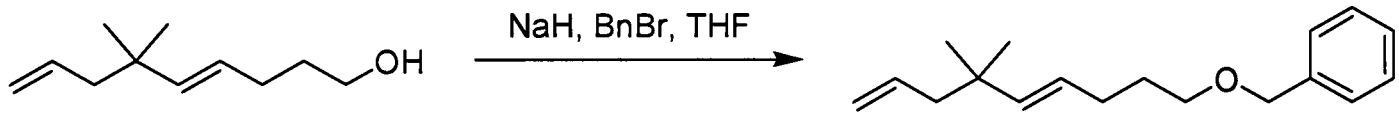
Alternatively:



Di-*iso*-butylaluminium hydride (1.0 mol dm^{-3} solution in dichloromethane, 79.8 cm^3, 79.8 mmol, 4.00 eq.) was added dropwise to ester **480** (4.19 g, 20.0 mmol) dissolved in dichloromethane (100 cm^3) under an atmosphere of argon at 0 °C and stirred for 10 minutes.

Saturated aqueous ammonium chloride was added at 0 °C until no further gelatinous precipitate formed. Aqueous hydrochloric acid (3.0 mol dm^{-3}) was added until the precipitate dissolved and the solution separated; the aqueous layer was extracted with ether (2 × 100 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate), and evaporated under reduced pressure to give *(trans)-6,6-dimethylnona-4,8-dien-1-ol* (3.37 g, 100%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3332 br, 3076, 2959, 1640, 1468, 1383, 1363, 1186, 1060, 996, 973 and 913; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.78-5.68 (1 H, m, CH_2=CH), 5.43 (1 H, dt, *J* 15.6 and 1.2, C(Me)$_2$C*H*=CH), 5.30 (1 H, dt, *J* 15.6 and 6.6, C(Me)$_2$CH=C*H*), 5.00-4.94 (2 H, m, CH_2=CH), 3.63 (2 H, t, *J* 6.5, CH_2OH), 2.11-2.05 (2 H, m, CH=CHCH_2), 2.00 (2 H, dt, *J* 7.3 and 1.1, CH_2=CHCH_2), 1.66-1.59 (2 H, m, CH_2CH_2OH), 1.52 (1 H, s, br, OH) and 0.95 (6 H, s, 2 × CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 140.6$^+$ (C(Me)$_2$*C*H=CH), 135.7$^+$ (CH_2=CH), 125.4$^+$ (C(Me)$_2$CH=*C*H), 116.6$^-$ (CH_2=CH), 62.5$^-$ (CH_2OH), 47.5$^-$ (CH_2=CH*C*H), 35.7$^-$ (C), 32.5$^-$ (CH=CH*C*H$_2$), 29.0$^-$ (*C*H$_2$CH$_2$OH) and 27.1$^+$ (2 × CH_3); **MS** *m/z* (+FI) 168 (100%, M); **HRMS (FI)** (Found M, 168.1506. $C_{11}H_{20}O$ requires *M*, 168.1514).

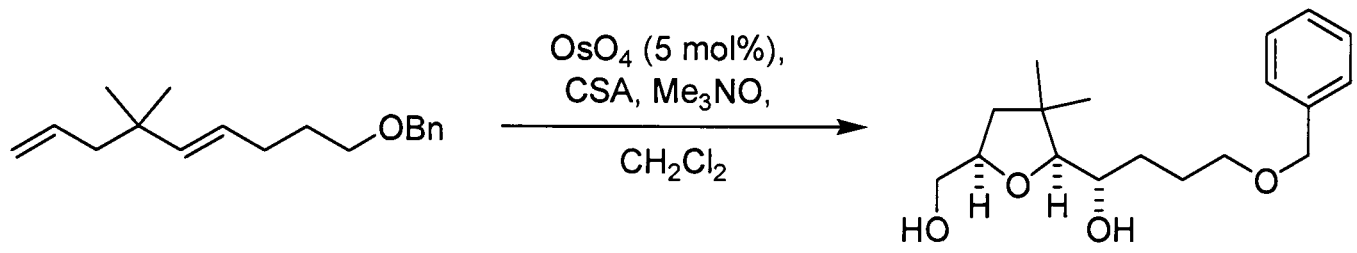
(*trans*)-((6,6-Dimethylnona-4,8-dienyloxy)methyl)benzene 471



By method F, benzyl bromide (2.44 cm^3, 20.5 mmol, 1.20 eq.) was added dropwise to a mixture of (*trans*)-6,6-dimethylnona-4,8-dien-1-ol (2.77 g, 17.1 mmol) and sodium hydride (60% dispersion in mineral oil, 1.37 g, 34.3 mmol, 2.00 eq.) dissolved in tetrahydrofuran (150 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 3:97] to give the *benzyl ether* **471** (4.02 g, 91%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3072, 3030, 2958, 1639, 1496, 1454, 1383, 1363, 1203, 1103, 1024, 974, 912, 735 and 697; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.38-7.28 (5 H, m, 5 × ArH), 5.74 (1 H, ddt, *J* 17.6, 10.5 and 7.3, CH_2=CH), 5.41 (1 H, d, *J* 15.6, C(Me)$_2$C*H*=CH), 5.30 (1 H, dt, *J* 15.6 and 6.5, C(Me)$_2$CH=C*H*), 5.00-4.95 (2 H, m, CH_2=CH), 4.51 (2 H, s, CH_2Ph), 3.48 (2 H, t, *J* 6.5, CH_2OBn), 2.10 (2 H, dt, *J* 7.4 and 7.1, CH=CHCH_2), 2.01 (2 H, d, *J* 7.3, CH_2=CHCH_2C(Me)$_2$), 1.73-1.66 (2 H, m, CH_2CH_2OBn) and 0.96 (6 H, s, 2 × CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 140.4$^+$ (C(Me)$_2$*C*H=CH), 138.7$^-$ (ArC), 135.9$^+$ (CH_2=*C*H), 128.4$^+$ (ArC), 127.8$^+$ (ArC), 127.6$^+$ (ArC), 127.5$^+$ (ArC), 125.4$^+$ (CH=*C*H), 116.5$^-$ (*C*H$_2$=CH), 72.9$^-$ (CH_2Ph), 69.7$^-$ (CH_2OBn), 47.5$^-$ (CH_2=CH*C*H$_2$C(Me)$_2$), 35.6$^-$ (C), 29.7$^-$ (*C*H$_2$CH$_2$OBn),

29.2$^-$ (CH=CH*C*H$_2$) and 27.2$^+$ (2 × CH$_3$); **MS** *m/z* (+CI) 276 (100%, MNH$_4^+$) and 259 (MH$^+$); **HRMS (CI)** (Found MNH$_4^+$, 276.2338. $C_{18}H_{30}NO$ requires *MNH*$_4$, 276.2327).

(*RS*)-(*S*)-4-(Benzyloxy)-1-((2*S*,5*R*)-5-(hydroxymethyl)-3,3-dimethyl-tetrahydrofuran-2-yl)butan-1-ol 472

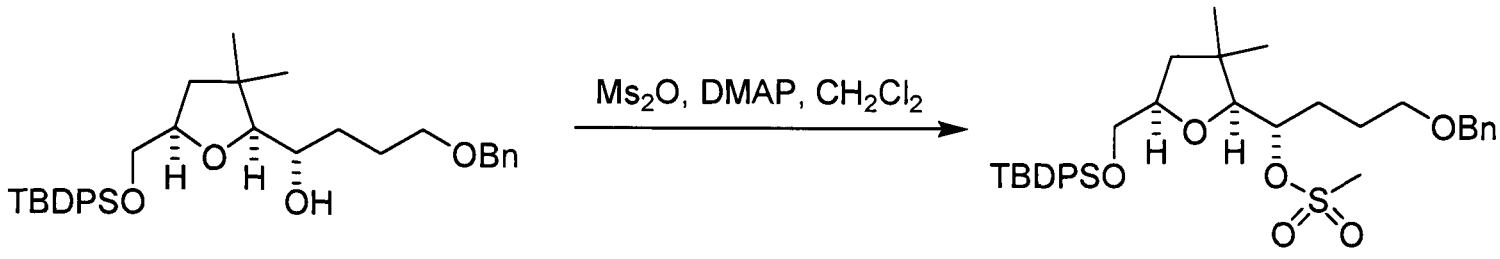


By method K, trimethylamine-*N*-oxide dihydrate (1.79 g, 16.0 mmol, 4.00 eq.) was added to a solution of diene **471** (1.03 g, 4.00 mmol), (*RS*)-camphor-10-sulfonic acid (5.58 g, 24.0 mmol, 6.00 eq.) and osmium$^{(VIII)}$ tetroxide (51 mg, 0.20 mmol, 0.05 eq.) dissolved in dichloromethane (200 cm^3) to give a crude product. The residue was chromatographed [SiO$_2$, acetone-light petroleum (bp 40-60 °C), 10:90] to give the *tetrahydrofuran* **472** (1.04 g, 85%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3356 br, 2871, 1953, 1718, 1602, 1585, 1099 and 818; **^{1}H NMR** δ_H (400 MHz; CDCl$_3$) 7.36-7.25 (5 H, m, 5 × ArH), 4.50 (2 H, s, CH$_2$Ph), 4.20-4.16 (1 H, m, THF OC*H*CH$_2$), 4.02 (2 H, s, br, 2 × OH), 3.93 (1 H, d, *J* 11.7, C*H*$_A$H$_B$OH), 3.55-3.49 (4 H, m, CH$_A$*H*$_B$OH, C*H*OH and C*H*$_2$OBn), 3.38-3.37 (1 H, m, THF OC*H*C(Me)$_2$), 2.09 (1 H, apparent t, *J* 11.4, THF C*H*$_A$H$_B$), 1.82-1.56 (4 H, m, 2 × CH$_2$), 1.49 (1 H, dd, *J* 12.0 and 6.4, THF CH$_A$*H*$_B$), 1.15 (3 H, s, CH$_3$) and 1.11 (3 H, s, CH$_3$); **^{13}C NMR** δ_C (100.6 MHz; CDCl$_3$) 138.2$^-$, 128.4$^+$, 127.8$^+$, 127.6$^+$ (6 × ArC), 89.5$^+$ (THF O*C*HC(Me)$_2$), 78.3$^+$ (THF O*C*HCH$_2$), 73.0$^-$ (CH$_2$Ph), 71.7$^+$ (CHOH), 70.5$^-$ (CH$_2$OBn), 63.6$^-$ (CH$_2$OH), 41.8$^-$ (THF C), 40.3$^-$ (THF CH$_2$), 32.5$^-$ (CH$_2$), 29.5$^+$ (CH$_3$), 26.4$^-$ (CH$_2$) and 22.9$^+$ (CH$_3$); **MS** *m/z* (+CI) 309 (MH$^+$); **HRMS (CI)** (Found MH$^+$, 309.2058. $C_{18}H_{29}O_4$ requires *MH*, 309.2066).

(*RS*)-(*S*)-4-(Benzyloxy)-1-((2*S*,5*R*)-5-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-dimethyl-tetrahydrofuran-2-yl)butan-1-ol 473

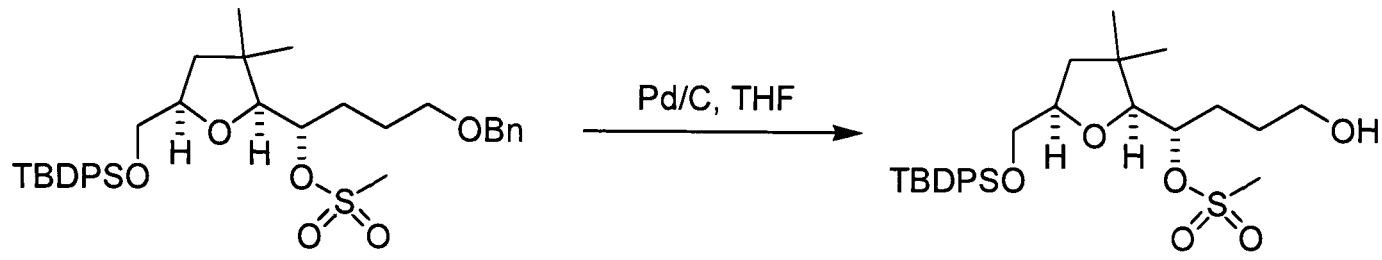
By method J, *tert*-butyl(chloro)diphenylsilane (0.735 cm^3, 2.83 mmol, 1.20 eq.) was added to a solution of tetrahydrofuran **472** (728 mg, 2.36 mmol) and imidazole (322 mg, 4.72 mmol, 2.00 eq.) dissolved in *N*,*N*-dimethylformamide (5 cm^3) to give a crude product. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 10:90] to give the *silyl ether* **473** (1.45 g, 94%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3460 br, 3071, 2932, 2859, 1472, 1428, 1391, 1364, 1163, 1112, 1005, 933, 823, 804, 741, 702 and 597; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.73-7.67 (4 H, m, 4 × ArH from $SiPh_2$), 7.45-7.37 (6 H, m, 6 × ArH from $SiPh_2$), 7.36-7.28 (5 H, m, 5 × ArH), 4.51 (2 H, s, CH_2Ph), 4.16-4.11 (1 H, m, THF $OCHCH_2$), 3.97 (1 H, dd, *J* 11.2 and 2.9, $CH_AH_BOTBDPS$), 3.56-3.46 (4 H, m, $CH_AH_BOTBDPS$, $CHOH$ and CH_2OBn), 3.45 (1 H, d, *J* 1.7, THF $OCH_AH_BC(Me)_2$), 3.32 (1 H, d, *J* 10.0, OH), 2.25 (1 H, t, *J* 11.2, THF $CH_AH_BC(Me)_2$), 1.90-1.91 (1 H, m, $CH_AH_BCH_2$), 1.76-1.60 (3 H, m, $CH_AH_BCH_2$), 1.52 (1 H, dd, *J* 11.9 and 6.1, THF $OCH_AH_BC(Me)_2$), 1.21 (3 H, s, CH_3), 1.11 (3 H, s, CH_3) and 1.08 (9 H, s, CMe_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.7^- [ArC from Obn], 135.7^+, 135.6^+, 134.8^+, 132.8^- [ArC from $SiPh_2$], 129.8^+, 129.6^+, 128.3^+, 127.8^+, 127.7^+, 127.6^+, 127.4^+ (18 × ArC), 89.6^+ (THF $OCHC(Me)_2$), 78.0^+ (THF $OCHCH_2$), 72.8^- (CH_2Ph), 71.5^+ (CHOH), 70.4^- (CH_2OBn), 65.3^- ($CH_2OTBDPS$), 41.5^- (THF C), 41.0^- (THF CH_2), 32.4^- (CH_2), 29.4^+ (CH_3), 26.7^+ (CMe_3), 26.6^- (CH_2), 23.1^+ (CH_3) and 19.1^- (SiC); **MS** *m/z* (+ESI) 605 (100%, $MMeCNNH_4^+$) and 569 (MNa^+); **HRMS (ESI)** (Found MH^+, 547.3234. $C_{34}H_{47}O_4Si$ requires *MH*, 547.3244).

(*RS*)-(*S*)-4-(Benzyloxy)-1-((2*S*,5*R*)-5-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-dimethyl-tetrahydrofuran-2-yl)butyl methanesulfonate 474



By method H, methanesulfonic anhydride (1.23 g, 7.08 mmol, 3.00 eq.) was added to a solution of alcohol **473** (1.29 g, 2.36 mmol) and 4-(dimethyl)aminopyridine (1.73 g, 14.2 mmol, 6.00 eq.) dissolved in dichloromethane (60 cm^3) to give the *mesylate* **474** (1.47 g, 100%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 2932, 2858, 1472, 1428, 1349, 1172, 1113, 926, 823, 741 and 703; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.74-7.67 (4 H, m, 4 × ArH from $SiPh_2$), 7.46-7.39 (6 H, m, 6 × ArH from $SiPh_2$), 7.33-7.27 (5 H, m, 5 × ArH), 4.73 (1 H, td, *J* 8.5 and 2.7, CHOMs), 4.50 (2 H, s, CH_2Ph), 4.11-4.05 (1 H, m, THF OC*H*CH_2), 3.71 (1 H, dd, *J* 10.8 and 6.6, CH_AH$_B$OTBDPS), 3.62 (1 H, dd, *J* 10.8 and 4.1, CH$_A$$H_B$OTBDPS), 3.58-3.50 (3 H, m, THF OCHC$(Me)_2$ and CH_2OBn), 3.04 (3 H, s, SO_2CH_3), 1.95-1.77 (4 H, m, THF CH_AH$_B$ and C(OMs)CH_2CH_AH$_B$), 1.71-1.63 (1 H, m, C(OMs)CH$_2$CH$_A$$H_B$), 1.58 (1 H, dd, *J* 12.7 and 7.0, THF CH$_A$$H_B$), 1.14 (3 H, s, CH_3), 1.11 (3 H, s, CH_3), 1.05 (6 H, s, $SiCMe_2$) and 1.00 (3 H, s, SiCMe); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.5$^-$ [ArC from OBn], 135.9$^+$, 135.6$^+$, 134.8$^+$, 133.4$^-$ [ArC from $SiPh_2$], 133.3$^-$ [ArC from $SiPh_2$], 129.8$^+$, 129.7$^+$, 129.6$^+$, 128.3$^+$, 127.8$^+$, 127.7$^+$, 127.6$^+$, 127.5$^+$ (18 × ArC), 87.4$^+$ (THF O*C*HC$(Me)_2$), 84.6$^+$ (CHOMs), 77.4$^+$ (THF O*C*HCH$_2$), 72.8$^-$ (CH_2Ph), 69.2$^-$ (CH_2OBn), 66.8$^-$ ($CH_2OTBDPS$), 45.0$^-$ (THF C), 41.0$^-$ (THF CH_2), 39.2$^+$ (SO_2CH_3), 28.1$^-$ (CH_2), 27.3$^+$ (CH_3), 26.8$^+$ ($SiCMe_2$), 26.6$^+$ (SiCMe), 25.2$^-$ (CH_2), 23.1$^+$ (CH_3) and 19.2$^-$ (SiC); **MS** *m/z* (+ESI) 683 (100%, MMeCNNH$_4^+$); **HRMS (ESI)** (Found MNH$_4^+$, 642.3302. $C_{35}H_{52}NO_6SiS$ requires *MNH$_4$*, 642.3285).

(*RS*)-(*S*)-1-((2*S*,5*R*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)-3,3-dimethyl-tetrahydrofuran-2-yl)-4-hydroxybutyl methanesulfonate 475

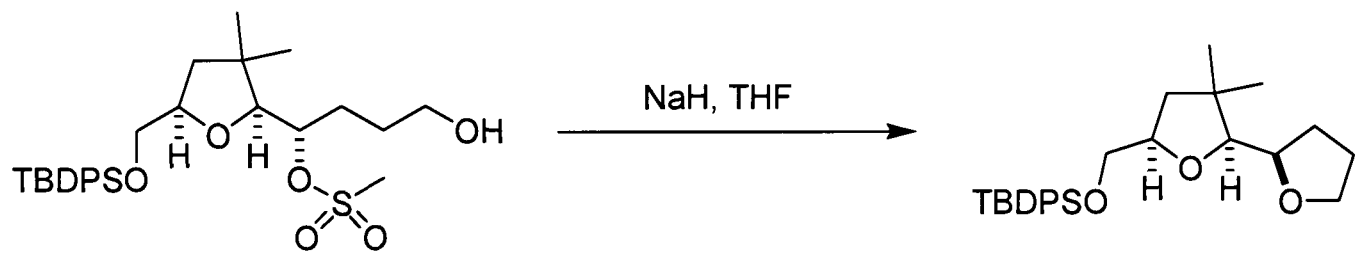


Palladium (10% on carbon, 294 mg) was added to benzyl ether **474** (294 mg, 1.00 mmol) dissolved in tetrahydrofuran (50 cm^3) and the flask evacuated and purged with argon three times before being evacuated and purged with hydrogen five times. The mixture stirred vigorously for 5 hours under an atmosphere of hydrogen (1 atm) at 45 °C and filtered through Celite®, eluting with dichloromethane (100 cm^3). The combined organics were evaporated under reduced pressure. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 30:70] to give the *alcohol* **475** (524 mg, 98%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3460 br, 2933, 1428, 1347, 1172, 1113, 926, 824, 742 and 704; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.68-7.65 (4 H, m, 4 × ArH), 7.46-7.38 (6 H, m, 6 × ArH), 4.74 (1 H, td, *J* 8.3 and 2.7, CHOMs), 4.11-4.04 (1 H, m, THF OC*H*CH_2), 3.74-3.67 (3 H, m, C$H_A$$H_B$OTBDPS and C$H_2$OH), 3.60 (1 H, dd, *J* 10.8 and 4.0, CH_AH_BOTBDPS), 3.52 (1 H, d, *J* 8.2, THF OCHC$(Me)_2$), 3.04 (3 H, s, SO_2CH_3), 1.88-1.64 (5 H, m, THF C$H_A$$H_B$ and CH(OMs)CH_2CH_2), 1.57 (1 H, dd, *J* 12.7 and 7.0, THF CH_AH_B), 1.17 (3 H, s, CH_3), 1.04 (9 H, s, CMe_3) and 1.01 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 135.6$^+$, 133.3$^-$, 130.0$^+$, 129.8$^+$, 127.9$^+$, 127.8$^+$, 127.6$^+$, 127.3$^+$, 127.2$^+$ (12 × ArC), 87.4$^+$ (CHOMs), 84.8$^+$ (THF OCHC$(Me)_2$), 77.4$^+$ (THF OCHCH_2), 66.7$^-$ (CH_2OTBDPS), 62.1$^-$ (CH_2OH), 44.9$^-$ (THF CH_2), 41.5$^-$ (THF C), 39.1$^+$ (SO_2CH_3), 27.9$^-$ (CH_2), 27.8$^-$ (CH_2), 27.3$^+$ (CH_3), 26.8$^+$ (CMe_3), 23.2$^+$ (CH_3) and 19.2$^-$ (SiC); **MS** *m/z* (+ESI) 593 (100%, MMeCNNH_4^+); **HRMS (ESI)** (Found MNH_4^+, 552.2818. $C_{28}H_{46}NO_6SiS$ requires *MNH_4*, 552.2815).

(*RS*)-*tert*-Butyl(((2*S*,2'*R*,5*R*)-3,3-dimethyl-octahydro-2,2'-bifuran-5-yl)methoxy)diphenylsilane 476

Zinc acetate dihydrate (549 mg, 2.50 mmol, 10.0 eq.) was added to alcohol **465** (134 mg, 250 μmol) dissolved in *N*,*N*-dimethylforamide (2 cm^3) and the mixture heated to intiate reflux; heating continued for a further 5 hours. After the solution was allowed to cool to ambient temperature, water (10 cm^3) was added, the mixture stirred vigorously for 30 minutes before being poured into ether (10 cm^3). The layers were separated, the aqueous layer extracted with ether (3 × 10 cm^3) and the combined organic extracts washed with aqueous saturated sodium chloride (10 cm^3). The organic layer was dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 3:97] to give the *bis-tetrahydrofuran* **J51** (81 mg, 74%) as an oil.

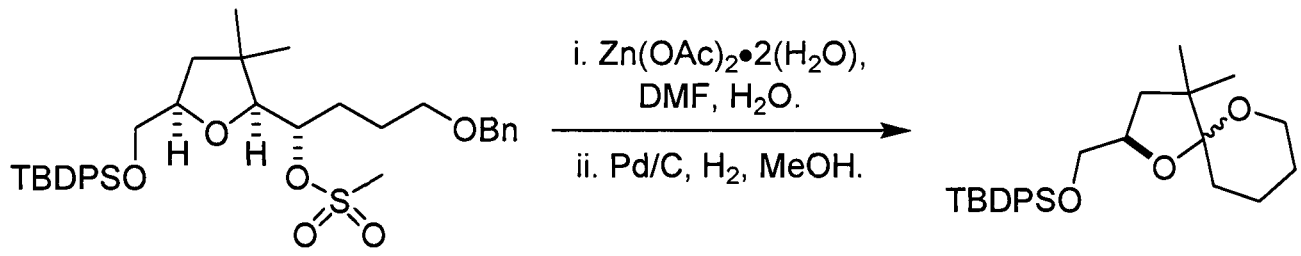
Alternatively:



Sodium hydride (60% dispersion in mineral oil, 43 mg, 1.07 mmol, 4.00 eq.) was added to alcohol **475** (134 mg, 250 μmol) dissolved in tetrahydrofuran (2 cm^3) under an atmosphere of argon and the mixture heated to initiate reflux; heating continued for 8 hours. The mixture was allowed to cool to ambient temperature, was poured into aqueous hydrochloric acid (1.0 mol dm^{-3}, 10 cm^3), the layers separated and the aqueous layer extracted with ether (3 × 10 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 30:70] to give the *bis-tetrahydrofuran* **476** (102 mg, 93%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 2931, 1472, 1428, 1363, 1113, 823, 740 and 702; **^{1}H NMR** δ_H (400 MHz;

$CDCl_3$) 7.72-7.69 (4 H, m, 4 × ArH), 7.45-7.37 (6 H, m, 6 × ArH), 4.07 (1 H, tt, *J* 7.8 and 5.0, OC*H*(CH_2OTBDPS)), 3.87-3.79 (2 H, m, OCH(CMe_2)C*H*OCH_AH_B), 3.75-3.65 (1 H, m, OCH(CMe_2)CHOCH_AH_B), 3.68 (2 H, d, *J* 5.0, CH_2OTBDPS), 3.34 (1 H, d, *J* 7.5, OC*H*C$(Me)_2$), 2.04-1.95 (1 H, m, OCH(CMe_2)CHOC$H_AH_BCH_2$), 1.94-1.81 (3 H, m, OCH(CMe_2)CH(O)C$H_AH_BCH_2$), 1.77 (1 H, dd, *J* 12.6 and 7.8, CH_AH_BC$(Me)_2$), 1.68 (1 H, dd, *J* 12.6 and 7.8, CH_AH_BC$(Me)_2$), 1.16 (3 H, s, CH_3), 1.07 (9 H, s, CMe_3) and 1.05 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 135.7$^+$, 135.6$^+$, 133.8$^-$, 133.6$^-$, 129.6$^+$, 127.7$^+$, 127.6$^+$ (12 × ArC), 88.8$^+$ (O*C*HC$(Me)_2$), 78.6$^+$ OCH(CMe_2)*C*HO), 77.8$^+$ (O*C*H(CH_2OTBDPS)), 68.1$^-$ (OCH(CMe_2)CHO*C*H_AH_B), 66.5$^-$ (CH_2OTBDPS), 43.5$^-$ (*C*H_2C$(Me)_2$)), 40.7$^-$ (C), 29.5$^-$ (OCHC(CMe_2)C(OCH_2)*C*H_2), 27.9$^+$ (CH_3), 26.8$^+$ (CMe_3), 25.7$^-$ (OCHC(CMe_2)C(OCH_2)CH_2*C*H_2), 24.0$^+$ (CH_3) and 19.3$^-$ (SiC); **MS** *m/z* (+ESI) 498 (100%, MMeCNNH_4^+); **HRMS (ESI)** (Found MNH_4^+, 456.2932. $C_{27}H_{42}NO_3Si$ requires *M*NH_4, 456.2934).

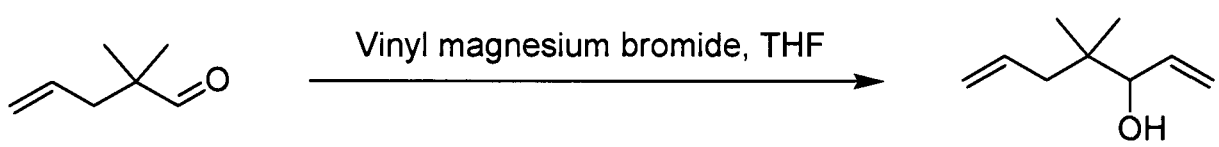
(*RS*)-*tert*-Butyl[(4,4-dimethyl-1,6-dioxaspiro[4.5]dec-2-yl)methoxy]diphenylsilane[(4,4-dimethyl-1,6-dioxaspiro[4.5]dec-2-yl)methoxy](1,1-dimethylethyl)diphenylsilane 478



By method I, water (~2 cm^3) was added to a solution of zinc acetate dihydrate (256 mg, 1.17 mmol, 5.00 eq.) and mesylate **474** (146 mg, 234 μmol) dissolved in *N*,*N*-dimethylformamide (3 cm^3). The mixture was heated to initiate reflux to give a crude product. Palladium (10% on carbon, micro spatula tip) was added to the residue dissolved in methanol (25 cm^3) and the flask evacuated and purged with argon three times before being evacuated and purged with hydrogen five times. The mixture stirred vigorously for 4 hours under an atmosphere of hydrogen (1 atm) and filtered through Celite®, eluting with dichloromethane (50 cm^3). The combined organics were evaporatated under reduce pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 2:98] to give the *spiro-ketal* **478** (76 mg, 74%) as a 0.75:0.25 mixture of diastereoisomers as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3072, 3050, 2959, 1640, 1590, 1472, 1428, 1389, 1362, 1306, 1189, 1111, 998, 973, 939, 913,

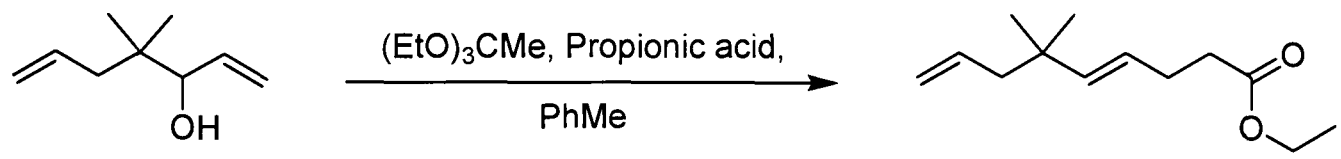
823, 739, 703 and 613; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.74-7.67 (4 H, m, 4 × ArH), 7.44-7.36 (6 H, m, 6 × ArH), 4.31-4.22 (0.75 H, m, OCH_α), 4.09 (0.25 H, td, *J* 10.2 and 5.2, OCH_β), 3.84-3.54 (3.25 H, m, $OCH_{A\alpha}H_{B\alpha}O$, $OCH_{A\beta}H_{B\beta}O$ and CH_2OTDPS), 3.41-3.37 (0.75 H, m, $OCH_{A\alpha}H_{B\alpha}$), 2.03 (0.25 H, dd, *J* 12.2 and 9.5, $OCHCH_{A\beta}H_B$), 1.82-1.36 (7.75 H, m, $OCHCH_{A\alpha}H_{B\alpha\beta}$ and 3 × CH_2), 1.07, 1.05 (9 H, s, CH_3), 1.01, 1.00 (3 H, s, CH_3) and 0.93 (2.25 H, s, $CH_{3\alpha}$), 0.82 (0.75 H, s, $CH_{3\beta}$); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 135.8^+, 135.7^+, 135.6^+, 135.5^+, 134.0^+, 133.9^-, 133.8^-, 129.6^+, 129.5^+, 128.3^+, 127.7^+, 127.6^+, 127.5^+ (12 × ArC), 107.3^-, 107.1^- (C), 77.5^+, 77.2^+ (OCH), 68.6^-, 67.0^- ($CH_2OTBDPS$), 60.9^-, 60.8^- (OCH_2), 45.3^-, 44.2^- (THF C), 41.9^-, 41.2^- (THF CH_2), 27.7^-, 27.3^- (CH_2), 26.8^+, 26.8^+ (CMe_3), 25.4^- (CH_2), 24.2^+ (CH_3), 22.4^+, 21.6^+ (CH_3), 20.0^- (CH_2) and 19.3^- (SiC); **MS** *m/z* (+ESI) 497 ($MMeCNNH_4^+$), 461 (MNa^+) and 439 (100%, MH^+); **HRMS (ESI)** (Found MNa^+, 461.2486. $C_{27}H_{38}O_3SiNa$ requires *MNa*, 461.2482).

(*RS*)-4,4-Dimethylhepta-1,6-dien-3-ol 479



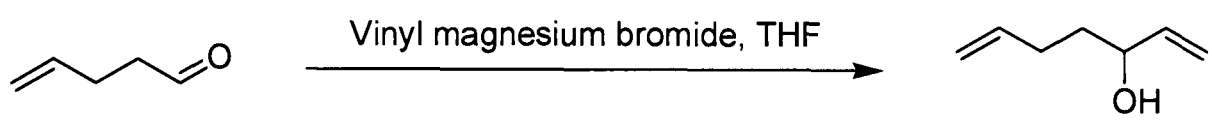
A vinylmagnesium bromide solution (1.0 mol dm^{-3} solution in tetrahydrofuran, 66.9 mmol, 1.50 eq.) was added to 2,2-dimethyl-4-pentenal (5.00 g, 44.6 mmol) dissolved in tetrahydrofuran (80 cm^3) at 0 °C under an atmosphere of argon and stirred for 15 minutes before being allowed to warm to ambient temperature; stirring continued for a further 4 hours. Aqueous saturated ammounium chloride (~10 cm^3) was added to quench the reaction prior to being poured into aqueous hydrochloric acid (1.0 mol dm^{-3}, 100 cm^3). The layers were separated, the aqueous layer extracted with ether (3 × 100 cm^3), the combined organic extracts dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 30-40 °C), 10:90] to give the *allylic alcohol* **479** (5.75 g, 92%) as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.97-5.81 (2 H, m, 2 × CH_2=C*H*), 5.26-5.17 (2 H, m, CH_2=CH), 5.07-5.02 (2 H, m, CH_2=CH), 3.82 (1 H, dt, *J* 6.7 and 1.1, C*H*OH), 2.13 (1 H, dd, *J* 13.6 and 7.6, CH_AH_B), 1.99 (1 H, dd, *J* 13.6 and 7.4, CH_AH_B), 1.60 (1 H, s, br, OH), 0.89 (3 H, s, CH_3) and 0.87 (3 H, s, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 137.8^+ (CH_2=*C*H), 135.3^+ (CH_2=*C*H), 117.3^- (*C*H_2=CH), 116.6^- (*C*H_2=CH), 79.7^+ (CHOH), 43.4^- (CH_2), 37.6^- (C), 23.0^+ (CH_3) and 22.5^+ (CH_3); **MS** *No satisfactory mass spectrometry data could be obtained.*

(*trans*)-Ethyl-6,6-dimethylnona-4,8-dienoate 480



Propionic acid (0.377 cm^3, 5.05 mmol, 0.20 eq.) was added to a solution of allylic alcohol **479** (3.54 g, 25.2 mmol) and triethyl orthoacetate (14.2 cm^3, 75.7 mmol, 3.00 eq.) dissolved in toluene (125 cm^3) under an atmosphere of argon. The mixture was heated to intiate reflux; heating continued for 12 hours. Ether (250 cm^3) was added to the solution at ambient temperature and the mixture was washed with aqueous saturated sodium carbonate (20 cm^3). The organic layer was dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 30-40 °C), 5:95] to give the *ester* **480** (4.19 g, 79%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3076, 2961, 1738, 1640, 1467, 1446, 1372, 1177, 1097, 1040, 997, 975 and 913; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.76-5.66 (1 H, m, CH_2=CH), 5.44 (1 H, d *J* 15.6, $C(Me)_2CH$=CH), 5.29 (1 H, dt, *J* 15.6 and 6.1, $C(Me)_2CH$=C*H*), 4.99-4.93 (2 H, m, CH_2=CH), 4.11 (2 H, q, *J* 7.1, OCH_2), 2.37-2.29 (4 H, m, CH=$CHCH_2CH_2CO_2Et$), 1.99 (2 H, d, *J* 7.4, CH_2=$CHCH_2C(Me)_2$), 1.25 (3 H, t, *J* 7.1, OCH_2CH_3) and 0.94 (6 H, s, 2 × CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 173.2$^-$ (CO), 141.1$^+$ (CH_2=CH), 135.6$^+$ ($C(Me)_2CH$=CH), 124.0$^+$ ($C(Me)_2CH$=CH), 116.6$^-$ (CH_2=CH), 60.2$^-$ (OCH_2), 47.3$^-$ (CH_2=$CHCH_2C(Me)_2$), 35.6$^-$ (C), 34.6$^-$ (CH_2), 28.1$^-$ (CH_2), 27.0$^+$ (2 × CH_3) and 14.3$^+$ (CH_3); **MS** *m/z* (+CI) 228 (MNH_4^+) and 211 (100%, MH^+); **HRMS (CI)** (Found MNH_4^+, 228.1962. $C_{13}H_{26}NO_2$ requires *MH*, 228.1964).

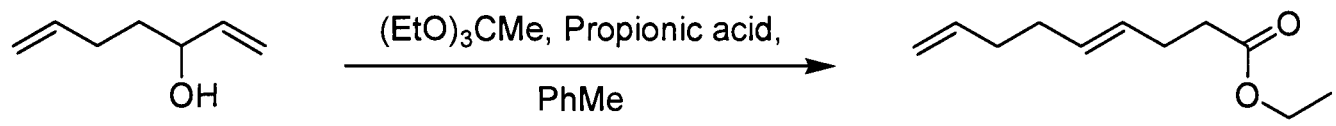
(*RS*)-Hepta-1,6-dien-3-ol[300] 481



A vinylmagnesium bromide solution (1.0 mol dm^{-3} solution in tetrahydrofuran, 89.0 mmol, 1.50 eq.) was added to 4-pentenal (5.00 g, 59.4 mmol) dissolved in ether (60 cm^3) at 0 °C under an atmosphere of argon and stirred for 15 minutes before being allowed to warm to ambient temperature; stirring continued for a further 4 hours. Aqueous saturated ammonium chloride (~10 cm^3) was added to quench the reaction prior to pouring the mixture into aqueous hydrochloric acid (1.0 mol dm^{-3}, 100 cm^3). The layers were separated, the aqueous

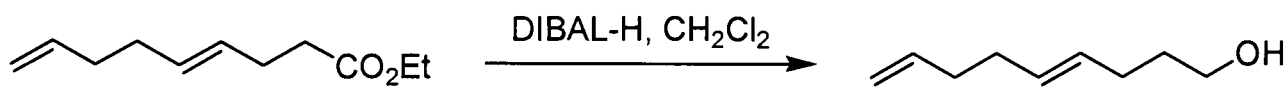
layer extracted with ether (3 × 100 cm^3), the combined organic extracts dried (anhydrous magnesium sulfate) and evaporated under reduce pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 30-40 °C), 10:90] to give the allylic alcohol **481** (6.20 g, 93%) as an oil; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.90-5.77 (2 H, m, 2 × CH_2=C*H*), 5.24-4.95 (4 H, m, 2 × C*H*$_2$=CH), 4.12 (1 H, br, C*H*OH), 2.17-2.09 (2 H, m, CH_2=CHC*H*$_2$), 1.81 (1 H, s, br, OH) and 1.65-1.59 (2 H, m, C*H*$_2$CHOH); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 141.0$^+$ (CH), 138.3$^+$ (CH), 114.9$^-$ (*C*H_2=CH), 114.8$^-$ (*C*H_2=CH), 72.6$^+$ (CHOH), 36.0$^-$ (*C*H_2CHOH) and 29.6$^-$ (CH_2=CH*C*H_2). All spectroscopic data agreed with those previously published.[300]

(*trans*)-Ethyl nona-4,8-dienoate



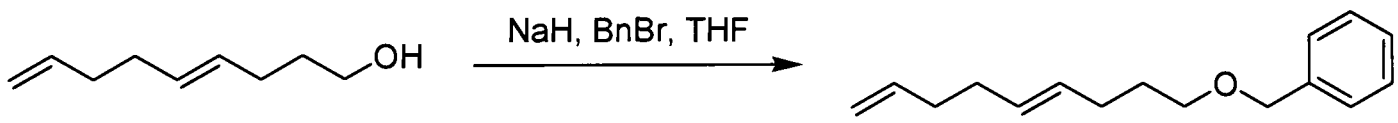
Propionic acid (0.379 cm^3, 5.08 mmol, 0.20 eq.) was added to a solution of allylic alcohol **481** (2.85 g, 25.4 mmol) and triethyl orthoacetate (14.3 cm^3, 76.3 mmol, 3.00 eq.) dissolved in toluene (125 cm^3) under an atmosphere of argon. The mixture was heated to intiate reflux; heating continued for 12 hours. Ether (250 cm^3) was added to the solution at ambient temperature and the mixture was washed with aqueous saturated sodium carbonate (20 cm^3). The organic layer was dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 30-40 °C), 2:98] to give *(trans)-ethyl nona-4,8-dienoate* (3.75 g, 81%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3078, 2981, 2925, 2847, 1738, 1641, 1446, 1372, 1345, 1163, 1039, 971, 912 and 859; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.83-5.74 (1 H, m, CH_2=CH), 5.55-5.38 (2 H, m, C*H*=C*H*), 5.01-4.93 (2 H, m, CH_2=CH), 4.11 (2 H, q, *J* 7.1, OCH_2), 2.37-2.30 (4 H, m, C*H*$_2$CH=CHC*H*$_2$), 2.08 (4 H, s, br CH_2=CHC*H*$_2$ and C*H*$_2$$CO_2$Et) and 1.24 (3 H, t, *J* 7.1, CH_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 173.2$^-$ (CO), 138.3$^+$ (CH_2=CH), 130.8$^+$ (CH), 128.5$^+$ (CH), 114.6$^-$ (CH_2=CH), 60.2$^-$ (OCH_2), 34.6$^-$ (CH_2), 33.6$^-$ (CH_2), 31.9$^-$ (CH_2), 27.9$^-$ (CH_2) and 14.2$^+$ (CH_3); **MS** *m/z* (+CI) 183 (100%, MH^+); **HRMS (CI)** (Found MH^+, 183.1390. $C_{11}H_{19}O_2$ requires *MH*, 183.1385).

(*trans*)-Nona-4,8-dien-1-ol



Di-*iso*-butylaluminium hydride (1.0 mol dm^{-3} solution in dichloromethane, 59.0 cm^3, 59.0 mmol, 4.00 eq.) was added dropwise to (*trans*)-ethyl nona-4,8-dienoate (2.69 g, 14.8 mmol) dissolved in dichloromethane (100 cm^3) under an atmosphere of argon at 0 °C and stirred for 10 minutes. Saturated aqueous ammonium chloride was added at 0 °C until no further gelatinous precipitate formed. Aqueous hydrochloric acid (3.0 mol dm^{-3}) was added until the precipitate dissolved and the solution separated, the aqueous layer extracted with ether (2 × 100 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate), and evaporated under reduced pressure to give *(trans)-nona-4,8-dien-1-ol* (2.07 g, 100%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3335 br, 3078, 2930, 1641, 1439, 1059. 969 and 911; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 5.85-5.75 (1 H, m, CH_2=CH), 5.44 (2 H, s, br, CH=CH), 5.03-4.94 (2 H, m, CH_2=CH), 3.64 (2 H, t, *J* 6.5, CH_2O), 2.09 (6 H, s, br, $CHCH_2CH_2CH$=$CHCH_2$) and 1.66-1.52 (3 H, m, CH_2 and OH); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.4^+ (CH_2=CH), 130.2^+ (*C*H=CH), 130.0^+ (CH=*C*H), 114.6^- (CH_2=CH), 62.5^- (CH_2OH), 33.7^- (CH_2), 32.4^- (CH_2), 31.9^- (CH_2) and 28.9^- (CH_2); **MS** *m/z No satifactory mass spectrometry data could be obtained.*

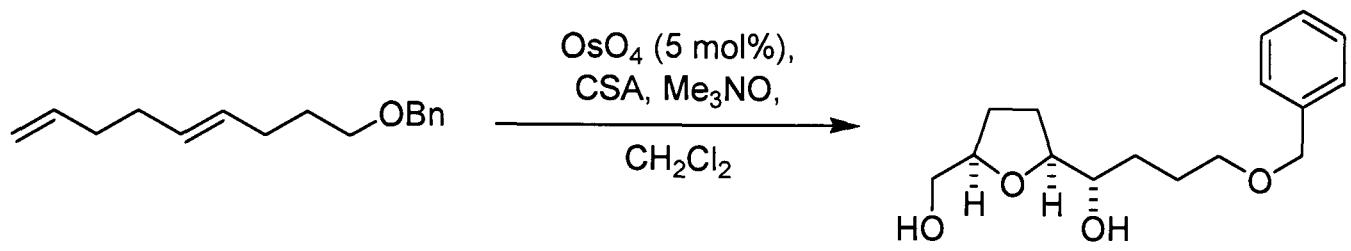
(*trans*)-((Nona-4,8-dienyloxy)methyl)benzene 482



By method F, benzyl bromide (0.785 cm^3, 6.00 mmol, 1.20 eq.) was added dropwise to a mixture of (*trans*)-nona-4,8-dien-1-ol (770 mg, 5.50 mmol) and sodium hydride (60% dispersion in mineral oil, 440 mg, 11.0 mmol, 2.00 eq.) dissolved in tetrahydrofuran (50 cm^3) to give a crude product. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 2:98] to give the *benzyl ether* **482** (14.6 g, 92%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3035, 3030, 2926, 2849, 1640, 1496, 1453, 1364, 1308, 1204, 1104, 1028, 970, 911, 735, 697 and 609; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.38-7.28 (5 H, m, 5 × ArH), 5.86-5.76 (1 H, m, CH_2=CH), 5.43 (2 H, s, C*H*=C*H*), 5.04-4.95 (2 H, m, CH_2=CH), 4.51 (2 H, s, CH_2Ph), 3.48 (2 H, t, *J* 6.6, CH_2OBn), 2.09 (6 H, s, 3 × C=CHCH_2) and 1.72-1.65 (2 H, m, CH_2CH_2OBn); **^{13}C**

NMR δ_C (100.6 MHz; $CDCl_3$) 138.7$^-$ (ArC), 138.5$^+$ (CH_2=*C*H), 130.0$^+$ (*C*H=*C*H) , 128.8$^+$ (ArC), 128.4$^+$ (ArC), 128.3$^+$ (ArC), 127.6$^+$ (ArC), 127.5$^+$ (ArC), 114.5$^-$ (*C*H_2=CH), 72.9$^-$ (CH_2Ph), 69.8$^-$ (CH_2OBn), 33.5$^-$ (C=CH*C*H_2), 32.0$^-$ (C=CH*C*H_2), 29.6$^-$ (C=CH*C*H_2) and 29.1$^-$ (*C*H_2CH_2OBn); **MS** *m/z* (+CI) 231 (100%, MH^+); **HRMS (CI)** (Found MH^+, 231.1759. $C_{16}H_{23}O$ requires *MH*, 231.1749).

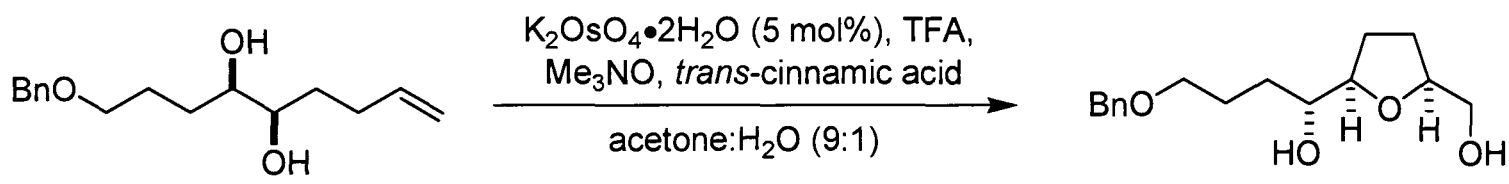
(*RS*)-(*S*)-4-(Benzyloxy)-1-((2*S*,5*R*)-5-(hydroxymethyl)-tetrahydrofuran-2-yl)butan-1-ol 483



By method K, trimethylamine-*N*-oxide dihydrate (1.79 g, 16.0 mmol, 4.00 eq.) was added to a solution of diene **482** (921 mg, 4.00 mmol), (*RS*)-camphor-10-sulfonic acid (5.58 g, 24.0 mmol, 6.00 eq.) and osmium$^{(VIII)}$ tetroxide (51 mg, 0.20 mmol, 0.05 eq.) dissolved in dichloromethane (200 cm^3) to give a crude product. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 10:90] to give the *tetrahydrofuran* **483** (908 mg, 81%) as an oil.

Alternatively:

(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-(hydroxymethyl)-tetrahydrofuran-2-yl)butan-1-ol 490



Trifluoroacetic acid (40 cm^3) was added cautiously to a stirring solution of diol **489** (1.06 g, 4.00 mmol) dissolved in acetone (72 cm^3) and water (8 cm^3) at 0 °C; stirring continued for 5 minutes. Potassium osmate$^{(VI)}$ dihyrate (74 mg, 0.20 mmol, 0.05 eq.) was added and the reaction allowed to warm to ambient temperature. After 45 minutes of stirring, trimethylamine-*N*-oxide dihydrate (2.22 g, 20.0 mmol, 5.00 eq.) and *trans*-cinnamic acid (593 mg, 4.00 mmol, 4.00 eq.) were added and the reaction stirred for 36 hours. Sodium sulfite (13 mg, 0.10 mmol, 0.10 eq.) was added and the mixture stirred for 1 hour before being cooled to

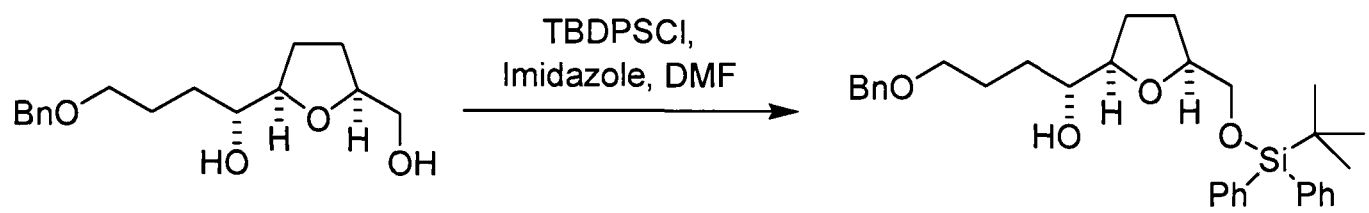
0 °C. Aqueous sodium hydroxide (40% by weight) saturated with sodium chloride was added cautiously to basify the mixture to pH 8. The mixture was poured into ether (150 cm^3), separated and the aqueous layer extracted with ether (3 × 200 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 30:70] to give the *tetrahydrofuran* **490** (830 mg, 74%) as an oil; **α_D** $[\alpha]_D^{23}$ +14.7; **IR** ν_{max} (thin film)/cm^{-1} 3395 br, 2869, 1650, 1496, 1454, 1363, 1204, 1099, 739 and 699; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.35-7.25 (5 H, m, 5 × ArH), 4.50 (2 H, s, CH_2Ph), 4.07 (1 H, s, br, THF OC*H*(CH_2OH)), 3.85-3.80 (1 H, m, THF OC*H*(CHOH)), 3.73 (1 H, d, *J* 11.4, CH_AH_BOH), 3.52-3.46 (5 H, m, CH_AH_BOH, C*H*OH, CH_2OBn and OH), 3.21 (1 H, s, br, OH), 1.95-1.87 (2 H, m, THF $CH_AH_BCH_AH_B$), 1.86-1.68 (4 H, m, THF $CH_AH_BCH_AH_B$ and CH_2) and 1.65-1.50 (2 H, m, CH_2); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.3$^-$, 128.4$^+$, 127.7$^+$, 127.6$^+$ (6 × ArC), 83.1$^+$ (THF O*C*H(CHOH)), 80.0$^+$ (THF O*C*H(CH_2OH)), 74.0$^+$ (CHOH), 73.0$^-$ (CH_2Ph), 70.3$^-$ (CH_2OBn), 65.1$^-$ (CH_2OH), 31.2$^-$ (CH_2), 28.3$^-$ (CH_2), 27.2$^-$ (CH_2) and 26.1$^-$ (CH_2); **MS** *m/z* (+ESI) 339 (100%, $MMeCNNH_4^+$) and 303 (MNa^+); **HRMS (ESI)** (Found MH^+, 281.1747. $C_{16}H_{25}O_4$ requires *MH*, 281.1753).

(*RS*)-(*S*)-4-(Benzyloxy)-1-((2*S*,5*R*)-5-((*tert*-butyldiphenylsilyloxy)methyl)-tetrahydrofuran-2-yl)butan-1-ol

By method J, *tert*-butyl(chloro)diphenylsilane (0.457 cm^3, 1.76 mmol, 1.10 eq.) was added to a solution of tetrahydrofuran **484** (448 mg, 1.60 mmol) and imidazole (218 mg, 3.20 mmol, 2.00 eq.) dissolved in *N*,*N*-dimethylformamide (4 cm^3) to give a crude product. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 10:90] to give *(RS)-(S)-4-(benzyloxy)-1-((2S,5R)-5-((tert-butyldiphenylsilyloxy)methyl)-tetrahydrofuran-2-yl)butan-1-ol* (830 mg, 100%) as an oil.

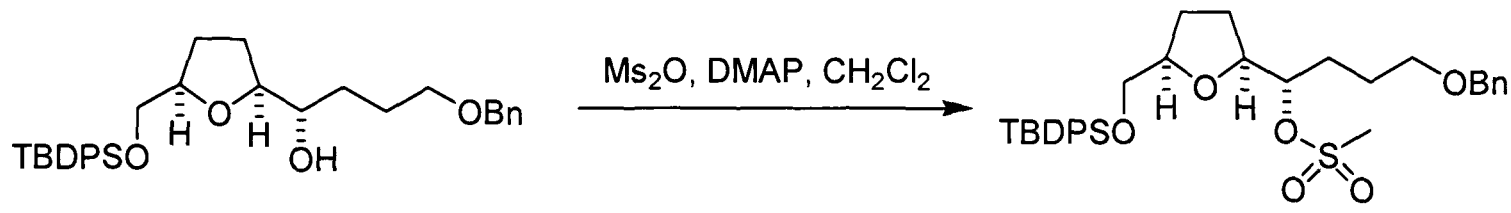
Alternatively:

(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-((*tert*-butyldiphenylsilyloxy)methyl)-tetrahydrofuran-2-yl)butan-1-ol



By method J, *tert*-butyl(chloro)diphenylsilane (0.457 cm^3, 1.76 mmol, 1.10 eq.) was added to a solution of tetrahydrofuran **490** (448 mg, 1.60 mmol) and imidazole (218 mg, 3.20 mmol, 2.00 eq.) dissolved in *N*,*N*-dimethylformamide (4 cm^3) to give a crude product. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 10:90] to give *(R)-4-(benzyloxy)-1-((2R,5S)-5-((tert-butyldiphenylsilyloxy)methyl)-tetrahydrofuran-2-yl)butan-1-ol* (830 mg, 100%) as an oil; **α_D** $[\alpha]_D^{23}$ +7.6; **IR** ν_{max} (thin film)/cm^{-1} 3468 br, 3070, 2931, 2858, 1589, 1472, 1428, 1390, 1362, 1264, 1191, 1113, 864, 824, 740, 702 and 611; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.70 (4 H, apparent t, *J* 6.5, 4 × ArH from $SiPh_2$), 7.45-7.38 (6 H, m, ArH from $SiPh_2$), 7.35-7.28 (5 H, m, ArH), 4.52 (2 H, s, CH_2Ph), 4.11-4.06 (1 H, m, THF OC*H*(CH_2OTBDPS)), 3.84 (1 H, q, *J* 6.0, THF OC*H*(CHOH)), 3.76 (1 H, dd, *J* 10.8 and 4.2, CH_AH$_B$OTBDPS), 3.62 (1 H, dd, *J* 10.8 and 3.9, CH$_A$$H_B$OTBDPS), 3.57-3.47 (2 H, m, CH_2OBn), 3.44-3.39 (1 H, m, C*H*OH), 2.53 (1 H, s, br, OH), 2.02-1.69 (6 H, m, THF CH_2CH_2 and CH_2), 1.65-1.48 (2 H, m, CH_2) and 1.08 (9 H, s, CMe_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.6$^-$ [ArC from OBn], 135.7$^+$, 135.6$^+$, 134.8$^+$, 133. 3$^-$ [ArC from $SiPh_2$], 129.7$^+$, 129.6$^+$, 128.4$^+$, 127.7$^+$ 127.5$^+$ (18 × ArC), 82.7$^+$ (THF O*C*H(CHOH)), 79.8$^+$ (THF O*C*H(CH_2OTBDPS)), 74.2$^+$ (CHOH), 72.9$^-$ (CH_2Ph), 70.3 (CH_2OBn), 65.9$^-$ (CH_2OTBDPS), 30.9$^-$ (CH_2), 28.2$^-$ (CH_2), 27.5$^-$ (CH_2), 26.8$^+$ (CMe_3), 26.1$^-$ (CH_2) and 19.2$^-$ (SiC); **MS** *m/z* (+ESI) 557 (100%, MMeCNNH$_4^+$); **HRMS (ESI)** (Found MH^+, 519.2928. $C_{32}H_{43}O_4Si$ requires *MH*, 519.2931).

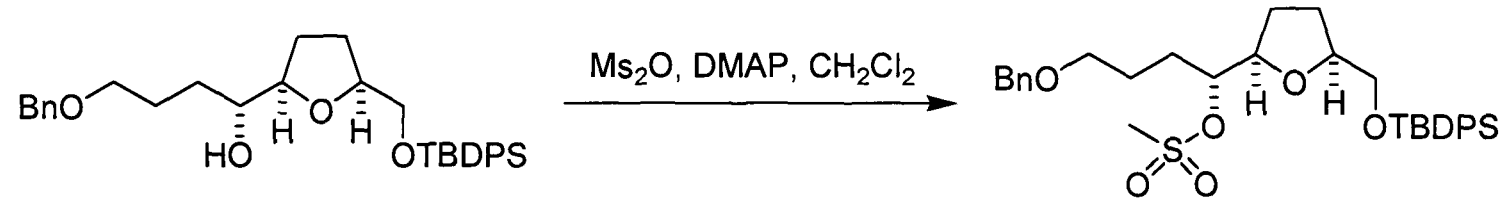
(*RS*)-(*S*)-4-(Benzyloxy)-1-((2*S*,5*R*)-5-((*tert*-butyldiphenylsilyloxy)methyl)-tetrahydrofuran-2-yl)butyl methanesulfonate 484



By method H, methanesulfonic anhydride (1.31 g, 7.50 mmol, 3.00 eq.) was added to a solution of (*RS*)-(*S*)-4-(benzyloxy)-1-((2*S*,5*R*)-5-((*tert*-butyldiphenylsilyloxy)methyl)-tetrahydrofuran-2-yl)butan-1-ol (1.30 g, 2.50 mmol) and 4-(dimethyl)aminopyridine (1.83 g, 15.0 mmol, 6.00 eq.) dissolved in dichloromethane (75 cm^3) to give the *mesylate* **484** (1.49 g, 100%) as an oil.

Alternatively:

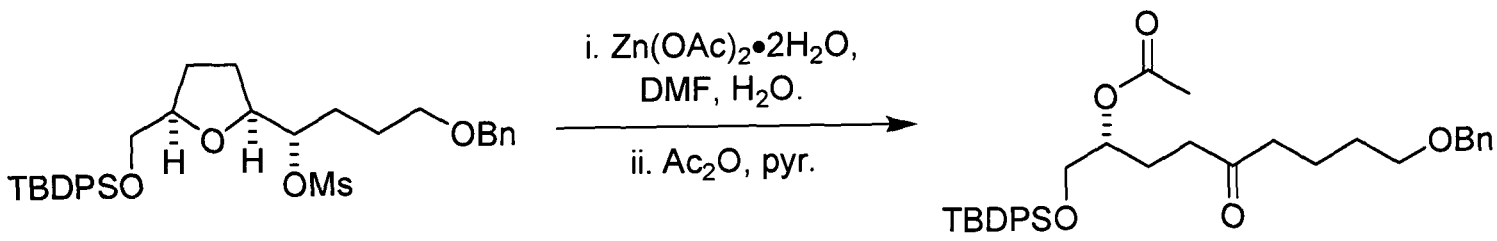
(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-((tert-butyldiphenylsilyloxy)methyl)-tetrahydrofuran-2-yl)butyl methanesulfonate 491



By method H, methanesulfonic anhydride (746 g, 4.29 mmol, 3.00 eq.) was added to a solution of (*R*)-4-(benzyloxy)-1-((2*R*,5*S*)-5-((*tert*-butyldiphenylsilyloxy)methyl)-tetrahydrofuran-2-yl)butan-1-ol (742 mg, 1.43 mmol) and 4-(dimethyl)aminopyridine (1.05 g, 4.29 mmol, 6.00 eq.) dissolved in dichloromethane (55 cm^3) to give a crude product. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 30:70] to give the *mesylate* **491** (853 mg, 100%) as an oil; **α_D** $[\alpha]_D^{23}$ +4.0; **IR** ν_{max} (thin film)/cm^{-1} 2931, 2858, 1717, 1472, 1428, 1353, 1173, 1112, 979, 929, 824, 742, 703 and 612; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.69-7.67 (4 H, m, 4 × ArH from $SiPh_2$), 7.46-7.38 (6 H, m, 6 × ArH from $SiPh_2$), 7.34-7.27 (5 H, m, 5 × ArH), 4.58 (1 H, td, *J* 8.5 and 2.6, CHOMs), 4.49 (2 H, s, CH_2Ph), 4.12-4.06 (1 H, m, THF OC*H*(CH_2OTBDPS)), 4.01-3.96 (1 H, m, OC*H*(CHOMs)), 3.67-3.59 (2 H, m, CH_2OTBDPS), 3.56-3.46 (2 H, m, CH_2OBn), 3.07 (3 H, s, SO_2CH_3), 2.00-1.89 (2 H, m, THF $CH_AH_BCH_AH_B$), 1.84-1.76 (4 H, m, THF $CH_AH_BCH_AH_B$ and $CH_AH_BCH_2$), 1.72-1.66 (1 H, m, $CH_AH_BCH_2$), 1.64-1.56 (1 H, m, THF $CH_AH_BCH_AH_B$) and 1.05 (9 H, s,

CMe_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.5$^-$ [ArC from OBn], 135.6$^+$, 134.8$^+$, 133.3$^-$ [ArC from $SiPh_2$], 129.8$^+$, 129.7$^+$, 128.4$^+$, 127.7$^+$, 127.7$^+$, 127.6$^+$ (18 × ArC), 86.7$^+$ (CHOMs), 80.9$^+$ (THF O*C*H(CHOMs)), 80.0$^+$ (THF OCH(CH_2OTBDPS)), 72.8$^-$ (CH_2Ph), 69.4 (CH_2OBn), 66.4$^-$ (CH_2OTBDPS), 38.9$^+$ (SO_2CH_3), 28.6$^-$ (CH_2), 28.1$^-$ (CH_2), 27.6$^-$ (CH_2), 26.8$^+$ (CMe_3), 25.2$^-$ (CH_2) and 19.2$^-$ (SiC); **MS** *m/z* (+ESI) 655 (100%, $MMeCNNH_4^+$); **HRMS (ESI)** (Found MH^+, 614.2964. $C_{33}H_{48}NO_6SiS$ requires *MH*, 614.2972).

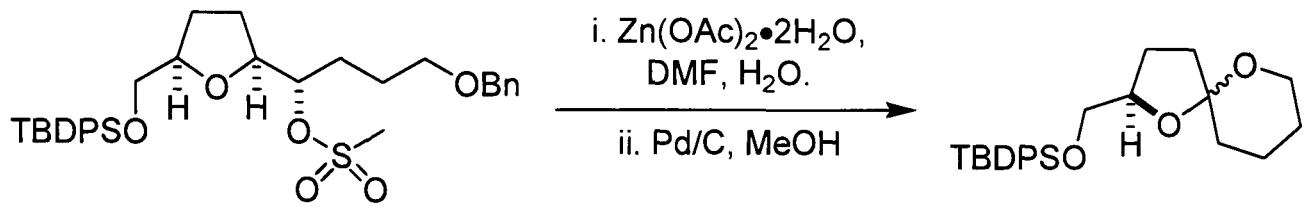
(*RS*)-(*R*)-8-(Benzyloxy)-1-(*tert*-butyldiphenylsilyloxy)-5-oxooctan-2-yl acetate 485



By method I, water (~2 cm^3) was added to a solution of zinc acetate dihydrate (202 mg, 992 μmol, 5.00 eq.) and mesylate **484** (110 mg, 183 μmol) dissolved in *N*,*N*-dimethylformamide (3 cm^3). The mixture was heated to initiate reflux to give a crude product. Acetic anhydride (1.0 cm^3) was added to a solution of the residue dissolved in pyridine (1 cm^3) under an atmosphere of argon and stirred for 18 hours. Methanol (~0.5 cm^3) was added to the solution to quench excess acetic anhydride, the solution stirred for 15 minutes and was evaporated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 2:98] to give the *ketone* **485** (61 mg, 61%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 2932, 2858, 1738, 1428, 1372, 1240, 1113, 824, 741 and 703; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.66-7.64 (4 H, m, 4 × ArH from $SiPh_2$), 7.45-7.26 (11 H, m, 6 × ArH from $SiPh_2$ and 5 × ArH), 4.97 (1 H, qt, *J* 9.3 and 4.8, CHOAc), 4.49 (2 H, s, CH_2Ph), 3.71-3.60 (2 H, m, CH_2OTBDPS), 3.47 (2 H, t, *J* 6.0, CH_2OBn), 2.40 (4 H, t, *J* 7.2, CH_2COCH_2), 2.01 (3 H, s, CH_3), 1.97-1.90 (1 H, m, CH(OAc)CH_AH$_B$CH_2CO), 1.87-1.77 (1 H, m, CH(OAc)CH_AH$_B$CH_2CO), 1.70-1.55 (2 H, m, 2 × CH_2) and 1.04 (9 H, s, CMe_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 209.7$^-$ (CO), 170.7$^-$ (O*C*OMe), 138.5$^-$ (ArC), 135.6$^+$ (ArC), 135.5$^-$ (ArC), 133. 3$^-$ (ArC), 129.9$^+$ (ArC), 129.8$^+$ (ArC), 129.7$^+$ (ArC), 128.4$^+$ (ArC), 127.9$^+$ (ArC), 127.7$^+$ (ArC), 127.6$^+$ (ArC), 73.6$^+$ (CHOAc), 72.9$^-$ (CH_2Ph), 70.0$^-$ (CH_2OBn), 65.0$^-$ (CH_2OTBDPS), 42.4$^-$ (CH(OAc)CH_2CH_2CO), 38.3$^-$ (CH(OAc)CH_2CH_2COCH_2), 29.2$^-$ (CH(OAc)*C*H_2), 26.7$^+$ (CMe_3), 24.5$^-$ (CH_2), 21.1$^+$ (CH_3), 20.5$^-$ (CH_2) and 19.2$^-$ (SiC); **MS** *m/z*

(+ESI) 619 (100%, $MMeCNNH_4^+$); **HRMS (ESI)** (Found MNH_4^+, 578.3305. $C_{34}H_{48}NO_5Si$ requires MNH_4, 578.3302).

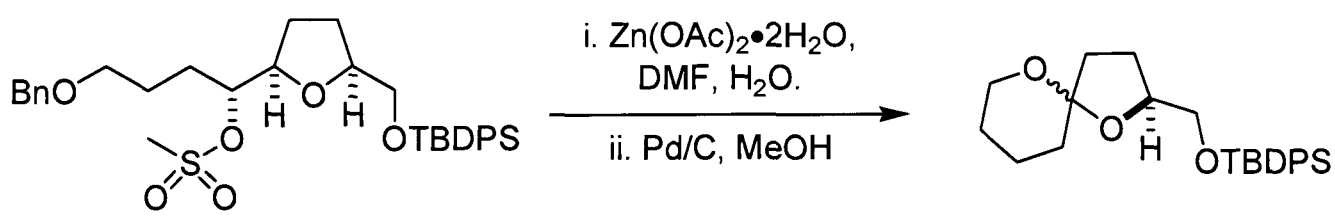
(*RS*)-*tert*-butyl(1,6-dioxaspiro[4.5]dec-2-ylmethoxy)diphenyllsilane-(1,1-dimethylethyl)(1,6-dioxaspiro[4.5]dec-2-ylmethoxy)diphenylsilane 486



By method I, water (~2 cm^3) was added to a solution of zinc acetate dihydrate (382 mg, 1.74 mmol, 5.00 eq.) and mesylate **484** (208 mg, 348 μmol) dissolved in *N*,*N*-dimethylformamide (3 cm^3). The mixture was heated to initiate reflux to give a crude product. Palladium (10% on carbon, micro spatula tip) was added to the residue dissolved in methanol (25 cm^3). The flask evacuated and purged with argon three times before being evacuated and purged with hydrogen five times. The mixture stirred vigorously for 4 hours under an atmosphere of hydrogen (1 atm) and filtered through Celite®, eluting with dichloromethane (100 cm^3). The combined organics were evaporated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 2:98] to give the *spiro-ketal* **486** (99 mg, 69%) as a 1:1 mixture of diastereoisomers as an oil.

Alternatively:

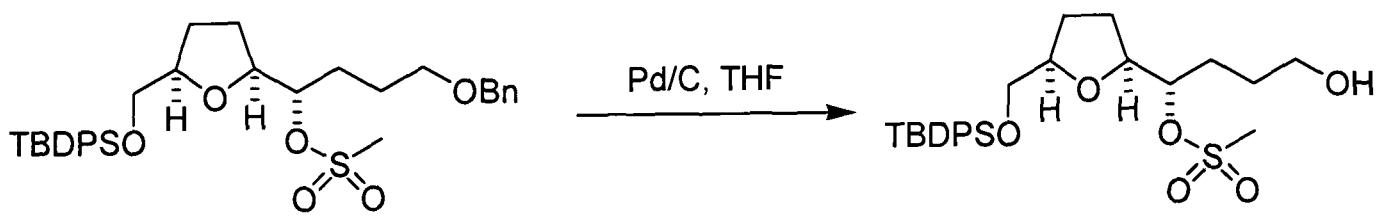
(*R*)-*tert*-butyl(1,6-dioxaspiro[4.5]dec-2-ylmethoxy)diphenyllsilane-(1,1-dimethylethyl)(1,6-dioxaspiro[4.5]dec-2-ylmethoxy)diphenylsilane (+)-486



By method I, water (~4 cm^3) was added to a solution of zinc acetate dihydrate (735 mg, 3.35 mmol, 5.00 eq.) and mesylate **491** (200 mg, 335 μmol) dissolved in *N*,*N*-dimethylformamide (5 cm^3). The mixture was heated to initiate reflux to give a crude product. Palladium (10% on carbon, micro spatula tip) was added to the residue dissolved in methanol (50 cm^3) and the flask evacuated and purged with argon three times before being evacuated and purged with

hydrogen five times. The mixture stirred vigorously for 4 hours under an atmosphere of hydrogen (1 atm) and filtered through Celite®, eluting with dichloromethane (200 cm^3). The combined organics were evaportated under reduce pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40-60 °C), 2:98] to give the *spiro-ketal* **492** (102 mg, 78%) as a 1:1 mixture of diastereoisomers as an oil; **α_D** $[\alpha]_D^{23}$ +10.6; **IR** ν_{max} (thin film)/cm^{-1} 3071, 3050, 2938, 1727, 1590, 1472, 1428, 1362, 1313, 1265, 1221, 1113, 974, 944, 905, 874, 823, 740, 703 and 612; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.75-7.69 (4 H, m, 4 ×ArH), 7.44-7.36 (6 H, m, 6 × ArH), 4.30-4.21 (1 H, m, OC*H*(CH_2OTBDPS), 3.89 (0.5 H, td, *J* 11.4 and 3.0, ½ OC$H_A$$H_B$), 3.80-3.59 (3 H, m, C$H_2$OTBDPS and ½ OC$H_A$$H_B$, ½ OC$H_A$$H_B$), 3.46-3.42 (0.5 H, m, ½ OC$H_A$$H_B$), 2.18-2.08, 2.03-1.46 (10 H, m, CH_2) and 1.07, 1.06 (9 H, s, CMe_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 135.7$^+$, 135.6$^+$, 133.9$^-$, 133.8$^-$, 133.7$^-$, 129.6$^+$, 129.5$^+$, 127.6$^+$ (18 × ArC), 106.2$^-$, 105.8$^-$ (C), 80.8$^+$, 78.7$^+$ (OCH), 68.0$^-$, 66.2$^-$ (CH_2OTBDPS), 61.6$^-$, 61.4$^-$ (OCH_2), 38.3$^-$, 37.5$^-$ (THF OCHCH_2), 33.8$^-$, 33.7$^-$ (CH_2), 27.0$^-$ (CH_2), 26.9$^+$, 26.8$^+$ (CMe_3), 25.4$^-$, 25.3$^-$ (CH_2), 20.3$^-$, 20.2$^-$ (CH_2) and 19.3$^-$ (SiC); **MS** *m/z* (+ESI) 433 (100%, MNa^+); **HRMS (ESI)** (Found MNa^+, 433.2178. $C_{25}H_{34}O_3SiNa$ requires *MNa*, 433.2175).

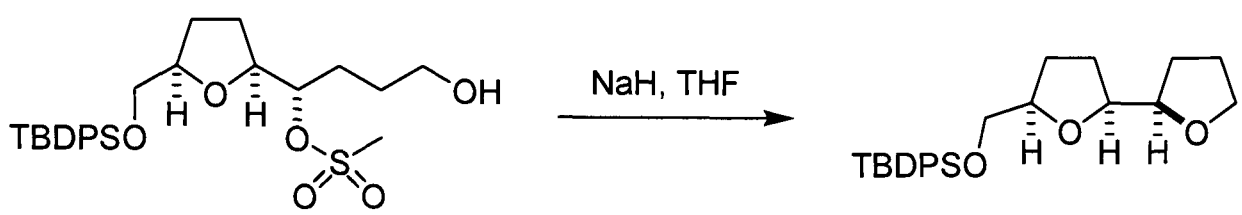
(*RS*)-(*S*)-1-((2*S*,5*R*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)-tetrahydrofuran-2-yl)-4-hydroxybutyl methanesulfonate 487



Palladium (10% on carbon, 597 mg) was added to benzyl ether **484** (597 mg, 1.00 mmol) dissolved in tetrahydrofuran (50 cm^3). The flask evacuated and purged with argon three times before being evacuated and purged with hydrogen five times. The mixture stirred vigorously for 5 hours under an atmosphere of hydrogen (1 atm) at 45 °C and filtered through Celite®, eluting with dichloromethane (100 cm^3). The combined organics were evaporated under reduced pressure. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 30:70] to give the *alcohol* **487** (507 mg, 100%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3375 br, 3071, 3049, 2858, 1960, 1898, 1589, 1472, 1428, 1390, 1361, 1262, 1189, 1112, 922, 867, 823, 741 and 608; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.68-7.64 (4 H, m, 4 × ArH), 7.44-7.38 (6 H, m, 6 × ArH), 4.63-4.59 (1 H, m, CHOMs), 4.12-4.06 (1 H, m, THF OC*H*(CH_2OTBDPS),

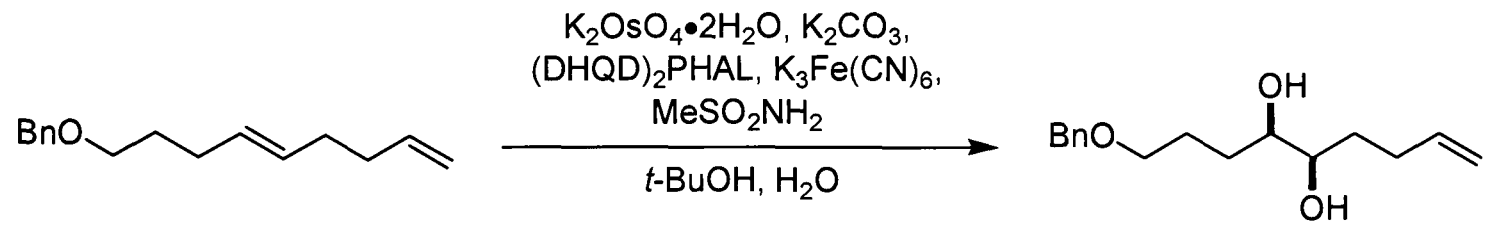
4.02-3.96 (1 H, m, THF OC*H*(CHOMs), 3.60-3.66 (2 H, m, CH_2OH), 3.63 (2 H, t, *J* 4.5, CH_2O), 3.07 (3 H, s, SO_2CH_3), 1.99-1.90 (2 H, m, THF $CH_AH_BCH_AH_B$), 1.84-1.63 (6 H, m, THF $CH_AH_BCH_AH_B$ and $CH_2CH_2CH_2OH$), 1.58 (1 H, s, br, OH), and 1.05 (9 H, s, CMe_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 135.6$^+$, 133.3$^-$, 129.8$^+$, 127.8$^+$ (12 × ArC), 86.7$^+$ (CHOMs), 80.9$^+$ (THF O*C*H(CHOMs)), 80.1$^+$ (THF O*C*H(CH_2OTBDPS)), 66.4$^-$ (CH_2OTBDPS), 62.2$^-$ (CH_2OH), 38.9$^+$ (SO_2CH_3), 28.2$^-$ (CH_2), 28.1$^-$ (CH_2), 28.0$^-$ (CH_2), 27.6$^-$ (CH_2), 26.8$^+$ (CMe_3) and 19.2$^-$ (SiC); **MS** *m/z* (+ESI) 1035 (100%, 2MNa$^+$) and 529 (100%, MNa$^+$); **HRMS (ESI)** (Found MNa$^+$, 529.2051. $C_{26}H_{38}O_6SiSNa$ requires *MNa*, 529.2056).

(*RS*)-*tert*-Butyl(((2*S*,2'*R*,5*R*)-octahydro-2,2'-bifuran-5-yl)methoxy)diphenylsilane 488



Sodium hydride (60% dispersion in mineral oil, 43 mg, 1.07 mmol, 4.00 eq.) was added to alcohol **487** (136 mg, 269 μmol) dissolved in tetrahydrofuran (2 cm^3) under an atmosphere of argon and the mixture heated to initiate reflux; heating continued for 8 hours. The mixture was allowed to cool to ambient temperature, was poured into aqueous hydrochloric acid (1.0 mol dm^{-3}, 10 cm^3), the layers separated and the aqueous layer extracted with ether (3 × 10 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 30:70] to give the *bis-tetrahydrofuran* **488** (104 mg, 94%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3071, 2931, 2858, 1589, 1472, 1428, 1390, 1361, 1113, 937, 824, 741, 703 and 608; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.73-7.68 (4 H, m, 4 × ArH), 7.45-7.36 (6 H, m, 6 × ArH), 4.09-4.04 (1 H, m, OC*H*(CH_2OTBDPS), 3.88-3.82 (2 H, m, CH_AH_BO and OCH), 3.79-3.79 (2 H, m, CH_AH_BO and OCH), 3.67 (2 H, d, *J* 4.7, CH_2OTBDPS), 2.04-1.75 (8 H, m, 4 × CH_2) and 1.06 (9 H, s, CMe_3); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 135.6$^+$, 134.8$^+$, 133.7$^-$, 133.6$^-$, 129.6$^+$, 127.7$^+$, 127.6$^+$ (12 × ArC), 81.7$^+$ (OCH), 81.2$^+$ (OCH), 79.9$^+$ (O*C*H(CH_2OTBDPS), 68.4 (OCH_2), 66.0$^-$ (CH_2OTBDPS), 28.5$^-$ (CH_2), 28.2$^-$ (CH_2), 27.4$^-$ (CH_2), 26.8$^+$ (CH_3), 25.8$^-$ (CH_2), and 19.3$^-$ (SiC); **MS** *m/z* (+ESI) 469 (MMeCNNH$_4^+$), 433 (MNa$^+$) and 428 (100%, MNH$_4^+$); **HRMS (ESI)** (Found MNa$^+$, 433.2166. $C_{25}H_{34}O_3SiNa$ requires *MNa*, 433.2175).

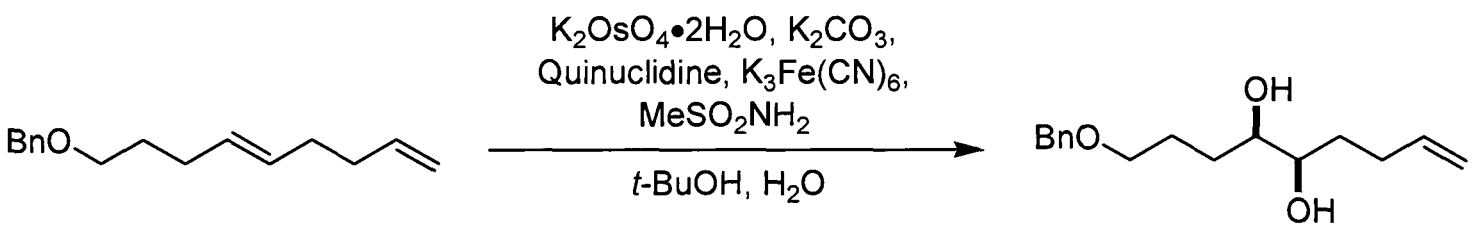
(4*R*,5*R*)-1-(Benzyloxy)non-8-ene-4,5-diol 489



Potassium osmate$^{(VI)}$ dihyrate (136 mg, 370 μmol, 0.02 eq.) was added to diene **482** (4.26 g, 18.5 mmol), potassium carbonate (5.11 g, 37.0 mmol, 2.5 eq.), potassium ferricyanide (12.1 g, 37.0 mmol, 2.5 eq.), methanesulfonamide (1.76 g, 18.5 mmol, 1.00 eq.) and hydroquinidine-1,4-phthalazinediyl diester (576 mg, 740 mmol, 0.04 eq.) dissolved in a mixture of water (120 cm^3) and 2-methyl-2-propanol (120 cm^3) at 0 °C. The resulting mixture was stirred vigoursly for 12 hours at ambient temperature. Sodium sulfite (233 mg, 1.85 mmol, 0.10 eq.) and ethyl acetate (120 cm^3) were added to the mixture and stirred vigoursly for 1 hour. The layers were separated, the aqueous layer extracted with ethyl acetate (3 × 150 cm^3), the combined organic extracts dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 20:80] to give the *diol* **489** (3.47 g, 71%) as an oil; **α_D** $[\alpha]_D^{23}$ +18.4; **HPLC** 100% e.e. Retention time 11.29, racemic standard retention time 11.35 (see Appendix 1).

Alternatively:

(4*RS*,5*RS*)-1-(Benzyloxy)non-8-ene-4,5-diol

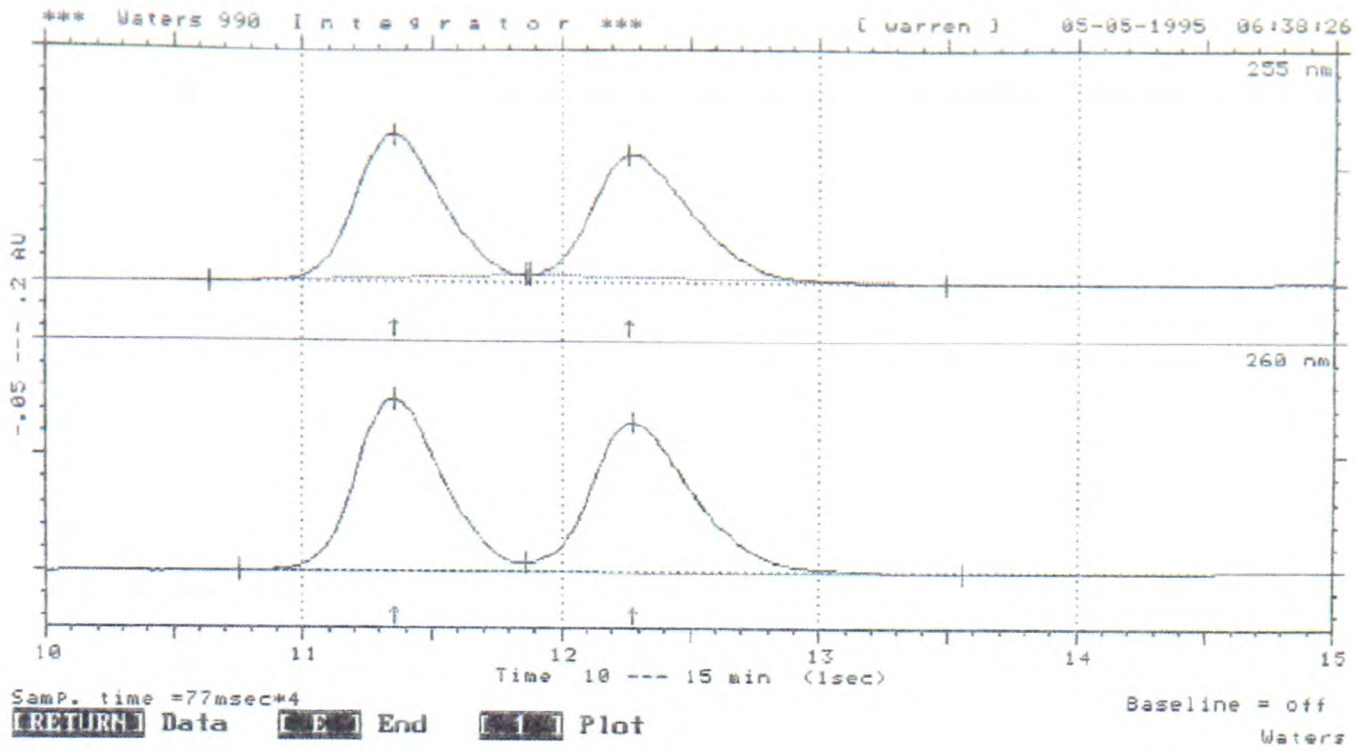


Potassium osmate$^{(VI)}$ dihyrate (15 mg, 40.0 μmol, 0.02 eq.) was added to diene **482** (460 mg, 2.00 mmol), potassium carbonate (636 mg, 4.6 mmol, 2.30 eq.), potassium ferricyanide (1.51 g, 4.6 mmol, 2.50 eq.), methanesulfonamide (190 mg, 2.00 mmol, 1.00 eq.) and quinuclidine (82 mg, 740 mmol, 0.04 eq.) dissolved in a mixture of water (15 cm^3) and 2-methyl-2-propanol (15 cm^3) at ambient temperature. The resulting mixture was stirred vigourously for 12 hours at ambient temperature. Sodium sulfite (25 mg, 200 μmol, 0.10 eq.) and ethyl acetate (20 cm^3) were added to the mixture and stirred vigoursly for 1 hour. The layers were separated, the aqueous layer extracted with ethyl acetate (3 × 20 cm^3), the combined organic extracts dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The

residue was chromatographed [SiO_2, acetone-light petroleum (bp 40-60 °C), 20:80] to give *(4RS,5RS)-1-(benzyloxy)non-8-ene-4,5-diol* (275 mg, 52%) as an oil; **IR** ν_{max} (thin film)/cm^{-1} 3406 br, 3066, 3031, 2940, 1640, 1496, 1454, 1362, 1274, 1205, 1098, 912, 737 and 698; **^{1}H NMR** δ_H (400 MHz; $CDCl_3$) 7.37-7.29 (5 H, m, 5 × ArH), 5.83 (1 H, ddt, *J* 16.9, 10.2 and 6.6, CH=), 5.07-4.96 (2 H, m, CH_2=CH), 4.52 (2 H, s, CH_2Ph), 3.52 (2 H, t, *J* 5.9, CH_2OBn), 3.44-3.38 (2 H, m, C*H*(OH)C*H*(OH)), 3.27 (1 H, d, *J* 4.3, OH), 2.64 (1 H, d, *J* 4.4, OH), 2.30-2.21 (1 H, m, CH_2=CHCH_AH_B), 2.19-2.09 (1 H, m, CH_2=CHCH_AH_B), 1.80-1.63 (4 H, m, CH_2CH_2CH_2OBn) and 1.59-1.47 (2 H, m, CH_2CH(OH)); **^{13}C NMR** δ_C (100.6 MHz; $CDCl_3$) 138.5$^+$ (CH_2=CH), 138.0$^-$ (ArC), 127.5$^+$, 127.8$^+$ (5 × ArC), 114.9$^-$ (CH_2=CH), 74.1$^+$ (CHOH), 73.9$^+$ (CHOH), 73.1$^-$ (CH_2Ph), 70.4$^-$ (CH_2OBn), 32.7$^-$ (CH(OH)CH_2), 31.0$^-$ (CH_2=CHCH_2), 30.0$^-$ (CH_2) and 26.1$^-$ (CH_2); **MS** *m/z* (+ESI) 287 (100%, MNa^+); **HRMS (ESI)** (Found MNa^+, 287.1611. $C_{16}H_{24}O_3Na$ requires *MNa*, 287.1623).

Appendix 1

HPLC Trace

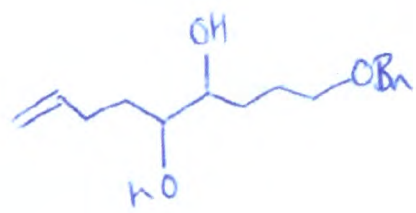


[255 nm]

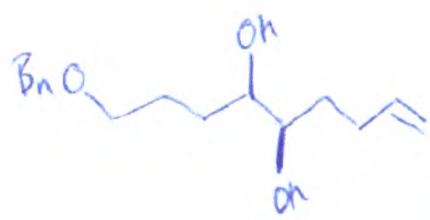
No.	Retention time	Height [AU]	Left time	Right time	Area [AU*min]	Area [%]	Mark
1	11.35	0.1240	10.64	11.88	0.046369	50.037	I
2	12.25	0.1046	11.87	13.49	0.046300	49.963	I

[260 nm]

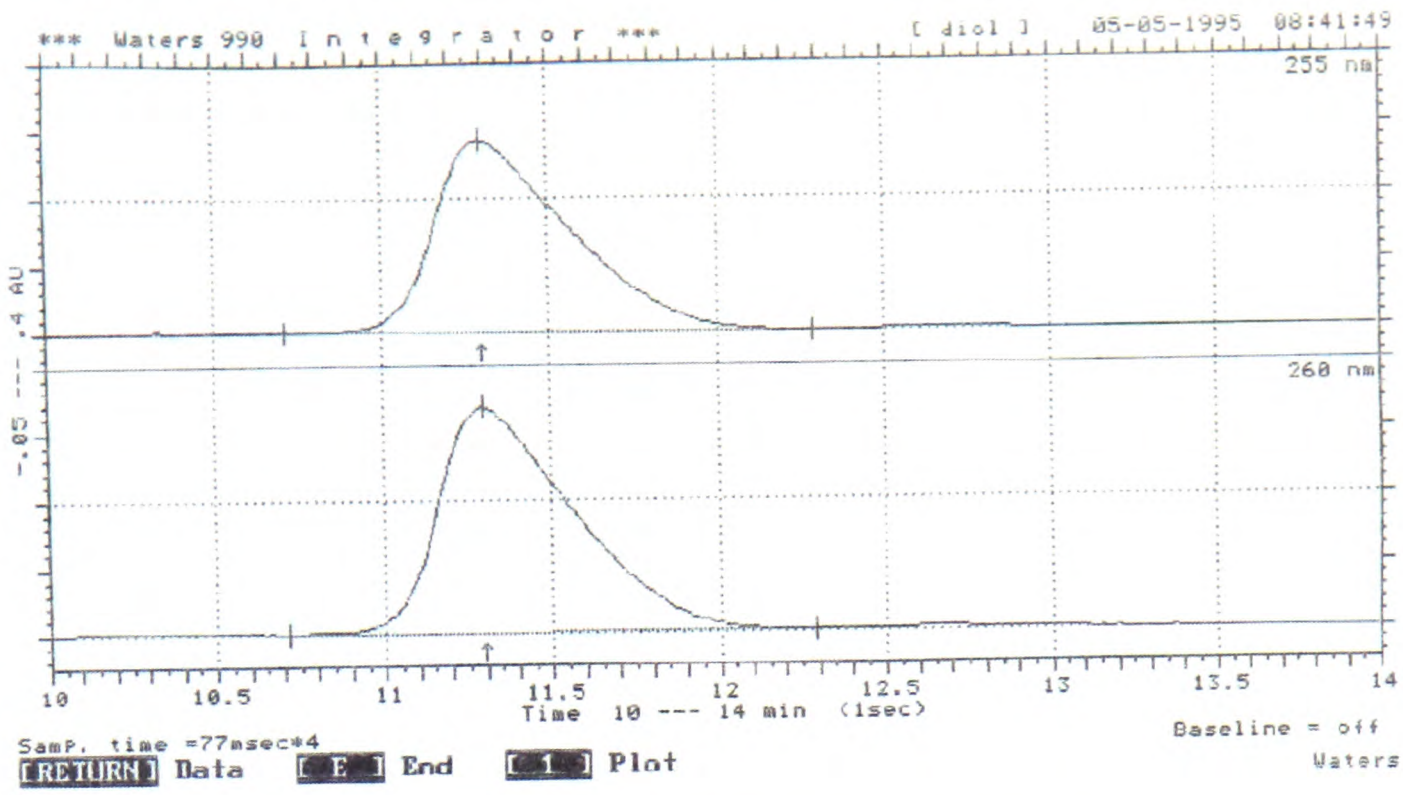
No.	Retention time	Height [AU]	Left time	Right time	Area [AU*min]	Area [%]	Mark
1	11.35	0.1505	10.75	11.87	0.059388	49.269	
2	12.28	0.1294	11.87	13.56	0.061151	50.731	V



OD Column.

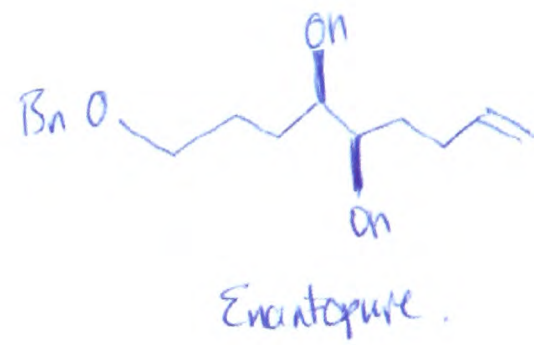


RAC standard.



[255 nm]

No.	Retention time	Height [AU]	Left time	Right time	Area [AU*min]	Area [%]	Mark
1	11.29	0.2858	10.71	12.29	0.134216	100.000	I



Enantiopure.

Next ---> push any key

[260 nm]

No.	Retention time	Height [AU]	Left time	Right time	Area [AU*min]	Area [%]	Mark
1	11.29	0.3355	10.71	12.29	0.158007	100.000	I

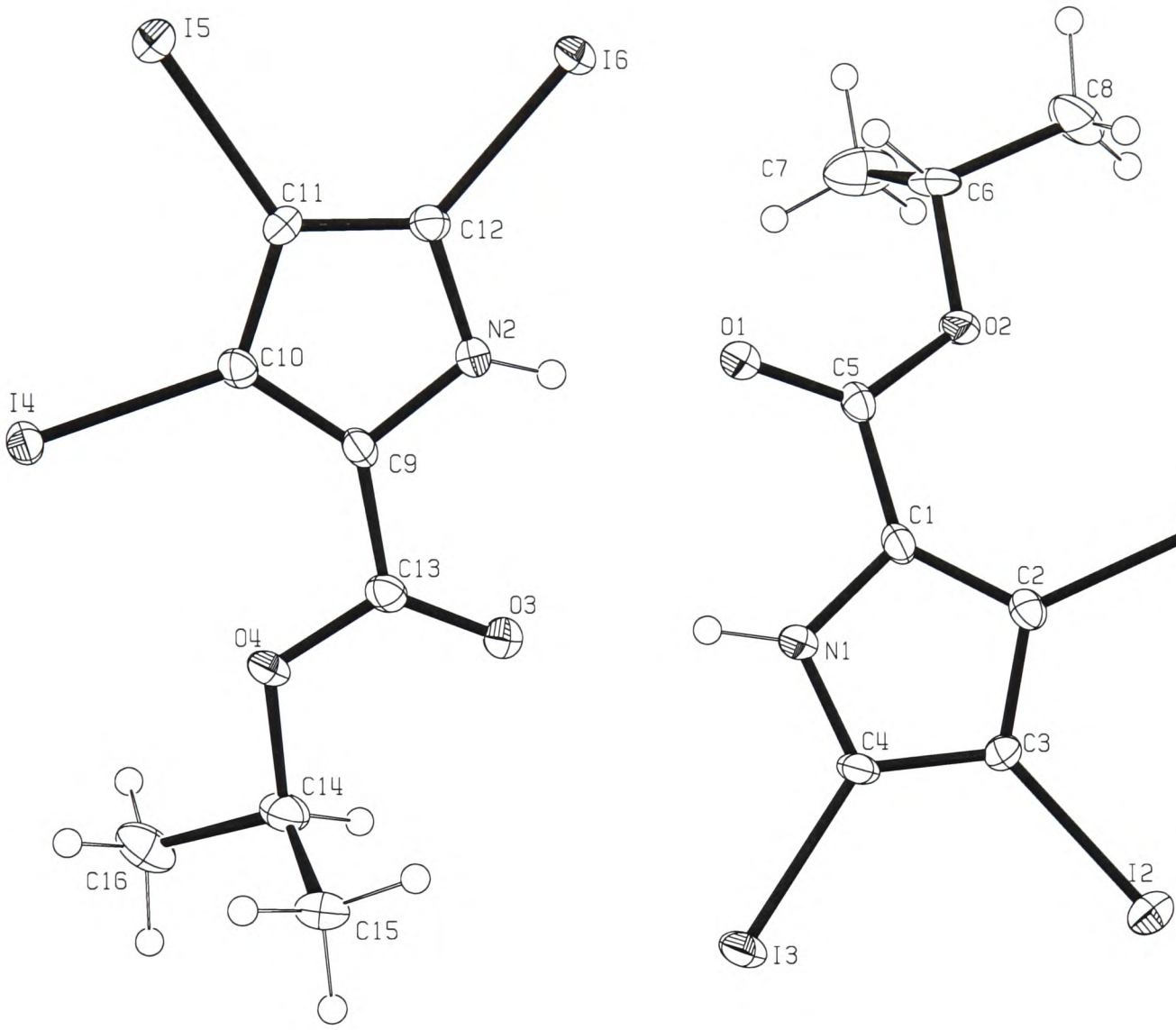
Appendix 2

Crystal Data

Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for $C_8H_8I_3NO_2$(ARC686)

Andrew R. Cowley
E-mail: a_r_cowley@hotmail.com
Tel. (2)70827



View of the asymmetric unit

Crystals of **ARC686** were grown by Peter Turner. A single crystal having dimensions approximately 0.06 x 0.08 x 0.10 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K in a stream of cold N_2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package[1].

Examination of the systematic absences of the intensity data showed the space group to be *P b c a*. The structure was solved using the direct-methods program SIR92[2], which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite[3]. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The NH hydrogen atoms were located in a difference Fourier map and their

coordinates and isotropic thermal parameters refined. Other hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give R = 0.0204, wR = 0.0225.

Attached is a thermal ellipsoid plot (ORTEP-3[4]) at 40% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning geometrically-positioned H atoms.

Comment:

The asymmetric unit contains two crystallographically-distinct molecules. These are linked by hydrogen bonds between each NH group and the carbonyl O of the other molecule to form a dimer (N(1)···O(3) 2.859(4), N(2)···O(1) 2.793(4) Å)..

References:

1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.

2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi ,M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.

3 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, CRYSTALS issue 11, Chemical Crystallography Laboratory, Oxford, UK, 2001.

4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC686
Chemical formula	$C_8H_8I_3NO_2$
Formula weight	530.87
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	*P b c a*
a (Å)	13.4945(2)
b (Å)	16.8482(2)
c (Å)	22.7998(3)
α (°)	90
β (°)	90
γ (°)	90
Cell volume (Å^3)	5183.72(12)
Z	16
Calculated density (Mg/m^3)	2.721
Absorption coefficient (mm^{-1})	7.214
F_{000}	3774.556
Crystal size (mm)	0.06 x 0.08 x 0.10
Description of crystal	Colourless block
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.49, 0.65
θ range for data collection (°)	$5.0 \leq \theta \leq 27.5$
Index ranges	$0 \leq h \leq 17$, $0 \leq k \leq 21$, $0 \leq l \leq 29$
Reflections measured	95859
Unique reflections	5904
R_{int}	0.055
Observed reflections ($I > 3\sigma(I)$)	4533
Refinement method	Full-matrix least-squares on *F*
Parameters refined	261
Weighting scheme	Chebychev 3-term polynomial
Goodness of fit	0.9829
R	0.0204
wR	0.0225
Residual electron density (min,max) (eÅ^{-3})	-0.99, 0.59

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($Å^2$) of non-hydrogen atoms

Atom	x	y	z	U_{equiv}
N(1)	0.3169(2)	0.59346(18)	0.27094(13)	0.0204
C(1)	0.2599(3)	0.5496(2)	0.30866(15)	0.0201
C(2)	0.1773(3)	0.5229(2)	0.27744(15)	0.0192
C(3)	0.1872(2)	0.5505(2)	0.21954(14)	0.0178
C(4)	0.2744(3)	0.5943(2)	0.21724(15)	0.0197
C(5)	0.2926(3)	0.5394(2)	0.36880(15)	0.0184
O(1)	0.3587(2)	0.57897(16)	0.39082(11)	0.0261
O(2)	0.2456(2)	0.48074(15)	0.3960(1)	0.0240
C(6)	0.2680(3)	0.4666(2)	0.45849(15)	0.0257
C(7)	0.3637(4)	0.4212(3)	0.4642(2)	0.0480
C(8)	0.1778(4)	0.4216(3)	0.4805(2)	0.0444
I(1)	0.053746(19)	0.465247(17)	0.310272(11)	0.0306
I(2)	0.093723(18)	0.528359(15)	0.14976(1)	0.0249
I(3)	0.33427(2)	0.656321(16)	0.14780(1)	0.0291
N(2)	0.4697(2)	0.71775(19)	0.40415(13)	0.0192
C(9)	0.5355(2)	0.7601(2)	0.37069(15)	0.0182
C(10)	0.5856(3)	0.8112(2)	0.40823(15)	0.0186
C(11)	0.5487(3)	0.7978(2)	0.46481(15)	0.0194
C(12)	0.4773(3)	0.7398(2)	0.46085(15)	0.0186
C(13)	0.5398(3)	0.7429(2)	0.30791(15)	0.0198
O(3)	0.4836(2)	0.69664(16)	0.28397(11)	0.0261
O(4)	0.6115(2)	0.78251(16)	0.28037(11)	0.0241
C(14)	0.6230(3)	0.7685(2)	0.21698(16)	0.0270
C(15)	0.5478(3)	0.8175(3)	0.18413(17)	0.0320
C(16)	0.7287(3)	0.7926(3)	0.2033(2)	0.0376
I(4)	0.690751(17)	0.895777(14)	0.38574(1)	0.0224
I(5)	0.58704(2)	0.854989(17)	0.542202(11)	0.0311
I(6)	0.386188(17)	0.691098(14)	0.52435(1)	0.0213

Table 3: Atomic coordinates and isotropic thermal parameters ($Å^2$) of hydrogen atoms

Atom	x	y	z	U_{iso}
H(1)	0.372(5)	0.620(3)	0.279(3)	0.052(16)
H(61)	0.2788	0.5159	0.4821	0.0308
H(71)	0.3784	0.4118	0.5066	0.0575
H(72)	0.4188	0.4525	0.4462	0.0575
H(73)	0.3574	0.3690	0.4436	0.0575
H(81)	0.1863	0.4092	0.5231	0.0532
H(82)	0.1172	0.4549	0.4750	0.0532
H(83)	0.1705	0.3710	0.4580	0.0532
H(2)	0.433(4)	0.685(3)	0.394(2)	0.032(13)
H(141)	0.6112	0.7122	0.2051	0.0324
H(151)	0.5554	0.8082	0.1411	0.0383
H(152)	0.5586	0.8750	0.1929	0.0383
H(153)	0.4796	0.8018	0.1967	0.0383
H(161)	0.7419	0.7846	0.1605	0.0451
H(162)	0.7384	0.8498	0.2135	0.0451
H(163)	0.7754	0.7592	0.2267	0.0451

Table 4: Anisotropic thermal parameters ($Å^2$)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N(1)	0.0236(15)	0.0223(15)	0.0154(14)	0.0020(11)	0.0012(12)	-0.0043(12)
C(1)	0.0173(16)	0.0207(17)	0.0222(16)	0.0039(14)	0.0019(13)	-0.0047(13)
C(2)	0.0173(15)	0.0199(16)	0.0205(16)	-0.0011(13)	0.0042(13)	-0.0006(13)
C(3)	0.0187(16)	0.0197(16)	0.0149(15)	-0.0028(13)	-0.0011(12)	-0.0019(13)
C(4)	0.0253(18)	0.0213(17)	0.0124(15)	0.0029(13)	0.0025(13)	-0.0022(14)
C(5)	0.0188(16)	0.0152(16)	0.0212(16)	-0.0015(13)	0.0043(13)	-0.0029(13)
O(1)	0.0288(14)	0.0309(14)	0.0185(12)	0.0009(11)	0.0014(11)	-0.0100(12)
O(2)	0.0323(14)	0.0240(13)	0.0156(11)	0.005(1)	-0.0017(11)	-0.0103(11)
C(6)	0.040(2)	0.0264(19)	0.0108(15)	0.0036(14)	0.0006(14)	0.0013(16)
C(7)	0.052(3)	0.059(3)	0.032(2)	0.006(2)	-0.006(2)	0.026(3)
C(8)	0.055(3)	0.043(3)	0.035(2)	0.014(2)	0.010(2)	-0.018(2)
I(1)	0.02219(12)	0.04140(15)	0.02816(13)	0.00434(11)	0.00242(9)	-0.01279(11)
I(2)	0.02397(12)	0.02869(13)	0.02190(12)	-0.00199(9)	-0.00604(9)	0.00185(9)
I(3)	0.03869(14)	0.03303(14)	0.01549(11)	0.00298(9)	0.0042(1)	-0.01126(11)
N(2)	0.0164(14)	0.0224(15)	0.0188(14)	0.0007(12)	0.0007(11)	-0.0043(12)
C(9)	0.0149(15)	0.0198(17)	0.0199(16)	0.0048(13)	0.0019(13)	-0.0023(13)
C(10)	0.0188(16)	0.0177(16)	0.0194(16)	0.0055(13)	-0.0016(13)	-0.0003(13)
C(11)	0.0208(16)	0.0207(16)	0.0165(16)	-0.0024(13)	-0.0030(13)	-0.0029(14)
C(12)	0.0161(16)	0.0243(17)	0.0155(15)	0.0014(13)	-0.0001(12)	0.0005(13)
C(13)	0.0216(17)	0.0188(16)	0.0190(16)	0.0052(13)	-0.0004(13)	0.0006(13)
O(3)	0.0308(14)	0.0272(13)	0.0205(12)	-0.0006(11)	-0.0003(11)	-0.0110(11)
O(4)	0.0298(13)	0.0267(13)	0.0158(12)	0.003(1)	0.004(1)	-0.0075(11)
C(14)	0.034(2)	0.028(2)	0.0184(17)	0.0008(15)	0.0060(15)	-0.0015(16)
C(15)	0.038(2)	0.040(2)	0.0176(18)	0.0055(17)	0.0008(16)	-0.0041(19)
C(16)	0.034(2)	0.044(3)	0.034(2)	0.0086(19)	0.0161(18)	0.0028(19)
I(4)	0.02054(11)	0.02397(11)	0.02266(11)	0.00653(9)	-0.00386(9)	-0.00730(9)
I(5)	0.03051(14)	0.04231(15)	0.02035(12)	-0.0065(1)	0.00027(9)	-0.01488(11)
I(6)	0.02188(11)	0.02468(12)	0.01738(11)	-0.00011(8)	0.00507(8)	-0.00396(9)

Table 5: Bond lengths (Å)

N(1) - C(1)	1.370(4)	N(2) - C(9)	1.371(4)
N(1) - C(4)	1.352(5)	N(2) - C(12)	1.349(5)
N(1) - H(1)	0.89(6)	N(2) - H(2)	0.78(5)
C(1) - C(2)	1.397(5)	C(9) - C(10)	1.389(5)
C(1) - C(5)	1.451(5)	C(9) - C(13)	1.461(5)
C(2) - C(3)	1.406(5)	C(10) - C(11)	1.401(5)
C(2) - I(1)	2.070(3)	C(10) - I(4)	2.075(3)
C(3) - C(4)	1.389(5)	C(11) - C(12)	1.376(5)
C(3) - I(2)	2.064(3)	C(11) - I(5)	2.076(3)
C(4) - I(3)	2.062(3)	C(12) - I(6)	2.069(3)
C(5) - O(1)	1.222(4)	C(13) - O(3)	1.217(4)
C(5) - O(2)	1.328(4)	C(13) - O(4)	1.332(4)
O(2) - C(6)	1.476(4)	O(4) - C(14)	1.472(4)
C(6) - C(7)	1.507(6)	C(14) - C(15)	1.507(6)
C(6) - C(8)	1.520(6)	C(14) - C(16)	1.515(6)

Note – geometrically-positioned H atoms have been excluded

Table 6: Bond angles (°)

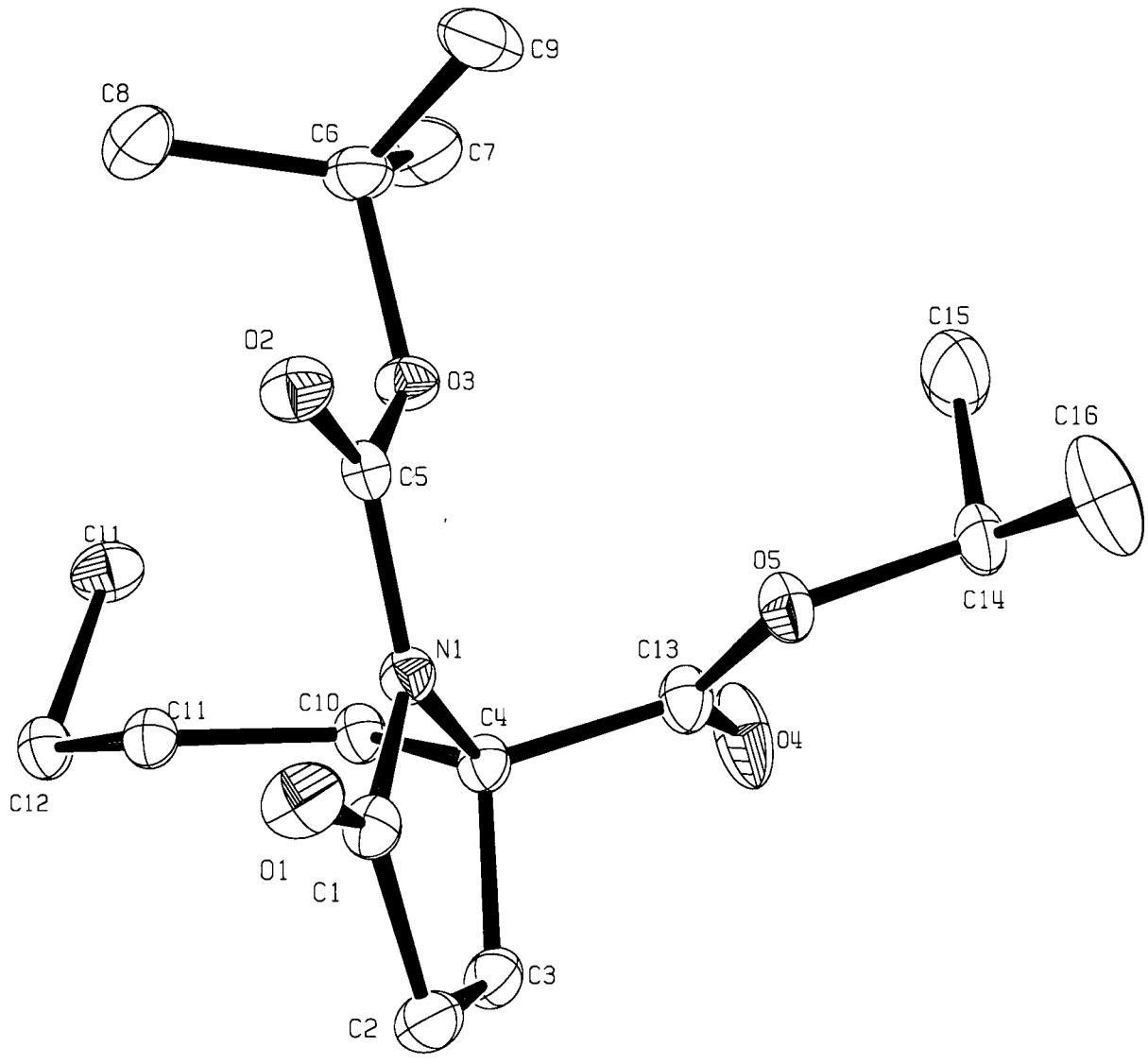
C(1) - N(1) - C(4)	109.6(3)	C(9) - N(2) - C(12)	109.9(3)
C(1) - N(1) - H(1)	128.(4)	C(9) - N(2) - H(2)	128.(4)
C(4) - N(1) - H(1)	123.(4)	C(12) - N(2) - H(2)	122.(4)
N(1) - C(1) - C(2)	107.6(3)	N(2) - C(9) - C(10)	107.1(3)
N(1) - C(1) - C(5)	119.1(3)	N(2) - C(9) - C(13)	117.8(3)
C(2) - C(1) - C(5)	133.4(3)	C(10) - C(9) - C(13)	135.0(3)
C(1) - C(2) - C(3)	107.2(3)	C(9) - C(10) - C(11)	107.1(3)
C(1) - C(2) - I(1)	127.6(3)	C(9) - C(10) - I(4)	127.3(3)
C(3) - C(2) - I(1)	124.8(3)	C(11) - C(10) - I(4)	125.5(3)
C(2) - C(3) - C(4)	107.0(3)	C(10) - C(11) - C(12)	107.6(3)
C(2) - C(3) - I(2)	127.3(2)	C(10) - C(11) - I(5)	128.3(3)
C(4) - C(3) - I(2)	125.7(3)	C(12) - C(11) - I(5)	124.1(3)
N(1) - C(4) - C(3)	108.6(3)	N(2) - C(12) - C(11)	108.1(3)
N(1) - C(4) - I(3)	122.3(3)	N(2) - C(12) - I(6)	121.1(3)
C(3) - C(4) - I(3)	129.1(3)	C(11) - C(12) - I(6)	130.7(3)
C(1) - C(5) - O(1)	123.1(3)	C(9) - C(13) - O(3)	122.8(3)
C(1) - C(5) - O(2)	112.5(3)	C(9) - C(13) - O(4)	113.0(3)
O(1) - C(5) - O(2)	124.3(3)	O(3) - C(13) - O(4)	124.2(3)
C(5) - O(2) - C(6)	118.2(3)	C(13) - O(4) - C(14)	117.3(3)
O(2) - C(6) - C(7)	109.9(3)	O(4) - C(14) - C(15)	109.2(3)
O(2) - C(6) - C(8)	103.6(3)	O(4) - C(14) - C(16)	105.0(3)
C(7) - C(6) - C(8)	113.8(4)	C(15) - C(14) - C(16)	112.6(3)

Note – geometrically-positioned H atoms have been excluded

Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for $C_{16}H_{24}ClNO_5$ (ARC690)

Andrew R. Cowley
E-mail: a_r_cowley@hotmail.com
Tel. (2)70827



H atoms not shown

Crystals of **ARC690** were grown by Peter Turner. A single crystal having dimensions approximately 0.05 x 0.28 x 0.42 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K in a stream of cold N_2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package[1].

Examination of the systematic absences of the intensity data showed the space group to be *P* $2_1/c$. The structure was solved using the direct-methods program SIR92[2], which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite[3]. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. Hydrogen atoms were positioned geometrically after each cycle of

refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give R = 0.0353, wR = 0.0416.

Attached is a thermal ellipsoid plot (ORTEP-3[4]) at 40% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References:

1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.

2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi ,M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.

3 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, CRYSTALS issue 11, Chemical Crystallography Laboratory, Oxford, UK, 2001.

4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC690
Chemical formula	$C_{16}H_{24}ClNO_5$
Formula weight	345.82
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P\,2_1/c$
a (Å)	10.8399(2)
b (Å)	8.6975(2)
c (Å)	18.8995(4)
α (°)	90
β (°)	99.3927(10)
γ (°)	90
Cell volume (Å^3)	1757.95(6)
Z	4
Calculated density (Mg/m^3)	1.307
Absorption coefficient (mm^{-1})	0.241
F_{000}	736.745
Crystal size (mm)	0.05 x 0.28 x 0.42
Description of crystal	Colourless plate
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.90, 0.99
θ range for data collection (°)	$5.0 \leq \theta \leq 27.5$
Index ranges	$-14 \leq h \leq 13$, $0 \leq k \leq 11$, $0 \leq l \leq 24$
Reflections measured	16417
Unique reflections	4254
R_{int}	0.034
Observed reflections ($I > 3\sigma(I)$)	2892
Refinement method	Full-matrix least-squares on F
Parameters refined	208
Weighting scheme	Chebychev 3-term polynomial
Goodness of fit	1.0559
R	0.0353
wR	0.0416
Residual electron density (min,max) (eÅ^{-3})	-0.24, 0.38

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($Å^2$) of non-hydrogen atoms

Atom	x	y	z	U_{equiv}
N(1)	0.34603(11)	0.35462(14)	0.39945(6)	0.0188
C(1)	0.40880(14)	0.22341(17)	0.43159(8)	0.0219
O(1)	0.5184(1)	0.19310(13)	0.43473(7)	0.0293
C(2)	0.31275(15)	0.13307(18)	0.46032(8)	0.0265
C(3)	0.20311(14)	0.20203(18)	0.44433(8)	0.0251
C(4)	0.21242(13)	0.35160(17)	0.40470(8)	0.0200
C(5)	0.40608(13)	0.47228(16)	0.36791(7)	0.0183
O(2)	0.51582(9)	0.47083(12)	0.36444(6)	0.0246
O(3)	0.32434(9)	0.58250(12)	0.34445(5)	0.0218
C(6)	0.37070(15)	0.72642(18)	0.31482(9)	0.0268
C(7)	0.25175(18)	0.8209(2)	0.29801(12)	0.0430
C(8)	0.46357(16)	0.80514(19)	0.3725(1)	0.0334
C(9)	0.42422(19)	0.6896(2)	0.2475(1)	0.0403
C(10)	0.16549(13)	0.48834(18)	0.44619(8)	0.0216
C(11)	0.26038(13)	0.54272(17)	0.50932(8)	0.0223
C(12)	0.20689(14)	0.65325(18)	0.55837(8)	0.0252
Cl(1)	0.13384(4)	0.81836(5)	0.50971(2)	0.0331
C(13)	0.12630(14)	0.33910(18)	0.33174(8)	0.0249
O(4)	0.01515(11)	0.35710(19)	0.32719(7)	0.0456
O(5)	0.18491(9)	0.30175(13)	0.27802(5)	0.0244
C(14)	0.10660(15)	0.29189(19)	0.20632(8)	0.0269
C(15)	0.0731(2)	0.4496(3)	0.17840(11)	0.0519
C(16)	0.1810(2)	0.1996(3)	0.1612(1)	0.0527

Table 3: Atomic coordinates and isotropic thermal parameters ($Å^2$) of hydrogen atoms

Atom	x	y	z	U_{iso}
H(21)	0.3283	0.0347	0.4877	0.0320
H(31)	0.1235	0.1603	0.4569	0.0304
H(71)	0.2711	0.9222	0.2774	0.0505
H(72)	0.2164	0.8382	0.3431	0.0505
H(73)	0.1893	0.7645	0.2625	0.0505
H(81)	0.4947	0.9016	0.3526	0.0395
H(82)	0.4215	0.8309	0.4143	0.0395
H(83)	0.5356	0.7346	0.3884	0.0395
H(91)	0.4552	0.7863	0.2277	0.0488
H(92)	0.4951	0.6155	0.2593	0.0488
H(93)	0.3577	0.6428	0.2110	0.0488
H(101)	0.0881	0.4553	0.4645	0.0259
H(102)	0.1452	0.5763	0.4122	0.0259
H(111)	0.2938	0.4508	0.5380	0.0269
H(112)	0.3302	0.5954	0.4903	0.0269
H(121)	0.2760	0.6899	0.5962	0.0302
H(122)	0.1429	0.5981	0.5814	0.0302
H(141)	0.0244	0.2399	0.2067	0.0316
H(151)	0.0202	0.4420	0.1300	0.0593
H(152)	0.0255	0.5042	0.2119	0.0593
H(153)	0.1512	0.5081	0.1746	0.0593
H(161)	0.1325	0.1888	0.1117	0.0626

H(162)	0.2619	0.2529	0.1589	0.0626
H(163)	0.1981	0.0953	0.1830	0.0626

Table 4: Anisotropic thermal parameters ($Å^2$)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N(1)	0.0158(5)	0.0214(6)	0.0193(5)	-0.0005(5)	0.0029(4)	-0.0012(4)
C(1)	0.0243(7)	0.0203(7)	0.0208(7)	-0.0021(5)	0.0024(5)	-0.0012(6)
O(1)	0.0226(5)	0.0254(6)	0.0393(6)	0.0034(5)	0.0033(5)	0.0028(4)
C(2)	0.0310(8)	0.0210(7)	0.0280(8)	0.0000(6)	0.0067(6)	-0.0039(6)
C(3)	0.0262(8)	0.0261(8)	0.0236(7)	-0.0027(6)	0.0063(6)	-0.0073(6)
C(4)	0.0161(6)	0.0241(7)	0.0200(6)	-0.0016(5)	0.0031(5)	-0.0018(5)
C(5)	0.0193(6)	0.0203(7)	0.0146(6)	-0.0022(5)	0.0010(5)	-0.0000(5)
O(2)	0.0178(5)	0.0268(6)	0.0301(5)	0.0020(4)	0.0063(4)	-0.0003(4)
O(3)	0.0183(5)	0.0224(5)	0.0250(5)	0.0047(4)	0.0040(4)	0.0001(4)
C(6)	0.0251(7)	0.0249(8)	0.0299(8)	0.0092(6)	0.0028(6)	-0.0018(6)
C(7)	0.0317(9)	0.0341(9)	0.0604(12)	0.0206(9)	-0.0007(8)	0.0046(8)
C(8)	0.0313(9)	0.0256(8)	0.0418(9)	-0.0011(7)	0.0015(7)	-0.0037(7)
C(9)	0.044(1)	0.0498(11)	0.0279(8)	0.0129(8)	0.0088(7)	-0.0065(9)
C(10)	0.0174(6)	0.0267(7)	0.0207(6)	-0.0021(6)	0.0029(5)	-0.0004(5)
C(11)	0.0197(7)	0.0257(7)	0.0218(7)	-0.0025(6)	0.0043(5)	-0.0013(6)
C(12)	0.0239(7)	0.0297(8)	0.0221(7)	-0.0032(6)	0.0037(5)	-0.0003(6)
Cl(1)	0.0357(2)	0.02442(19)	0.0409(2)	0.00139(16)	0.01134(17)	0.00228(16)
C(13)	0.0191(7)	0.0325(8)	0.0229(7)	-0.0052(6)	0.0029(5)	-0.0027(6)
O(4)	0.0198(6)	0.0866(11)	0.0290(6)	-0.0188(7)	0.0000(5)	0.0024(6)
O(5)	0.0200(5)	0.0337(6)	0.0190(5)	-0.0037(4)	0.0014(4)	-0.0000(4)
C(14)	0.0252(7)	0.0353(9)	0.0185(7)	-0.0050(6)	-0.0013(6)	-0.0024(6)
C(15)	0.0745(15)	0.0403(11)	0.034(1)	0.0024(8)	-0.0133(9)	-0.002(1)
C(16)	0.0505(12)	0.0795(16)	0.0266(9)	-0.015(1)	0.0017(8)	0.0202(11)

Table 5: Bond lengths (Å)

N(1) - C(1)	1.4139(19)	C(6) - C(7)	1.518(2)
N(1) - C(4)	1.4681(17)	C(6) - C(8)	1.520(2)
N(1) - C(5)	1.3975(18)	C(6) - C(9)	1.517(2)
C(1) - O(1)	1.2093(18)	C(10) - C(11)	1.518(2)
C(1) - C(2)	1.477(2)	C(11) - C(12)	1.515(2)
C(2) - C(3)	1.321(2)	C(12) - Cl(1)	1.8158(16)
C(3) - C(4)	1.513(2)	C(13) - O(4)	1.2041(19)
C(4) - C(10)	1.555(2)	C(13) - O(5)	1.3230(18)
C(4) - C(13)	1.538(2)	O(5) - C(14)	1.4794(17)
C(5) - O(2)	1.2021(17)	C(14) - C(15)	1.493(3)
C(5) - O(3)	1.3314(17)	C(14) - C(16)	1.498(3)
O(3) - C(6)	1.4916(18)		

Note – H atoms have been excluded

Table 6: Bond angles (°)

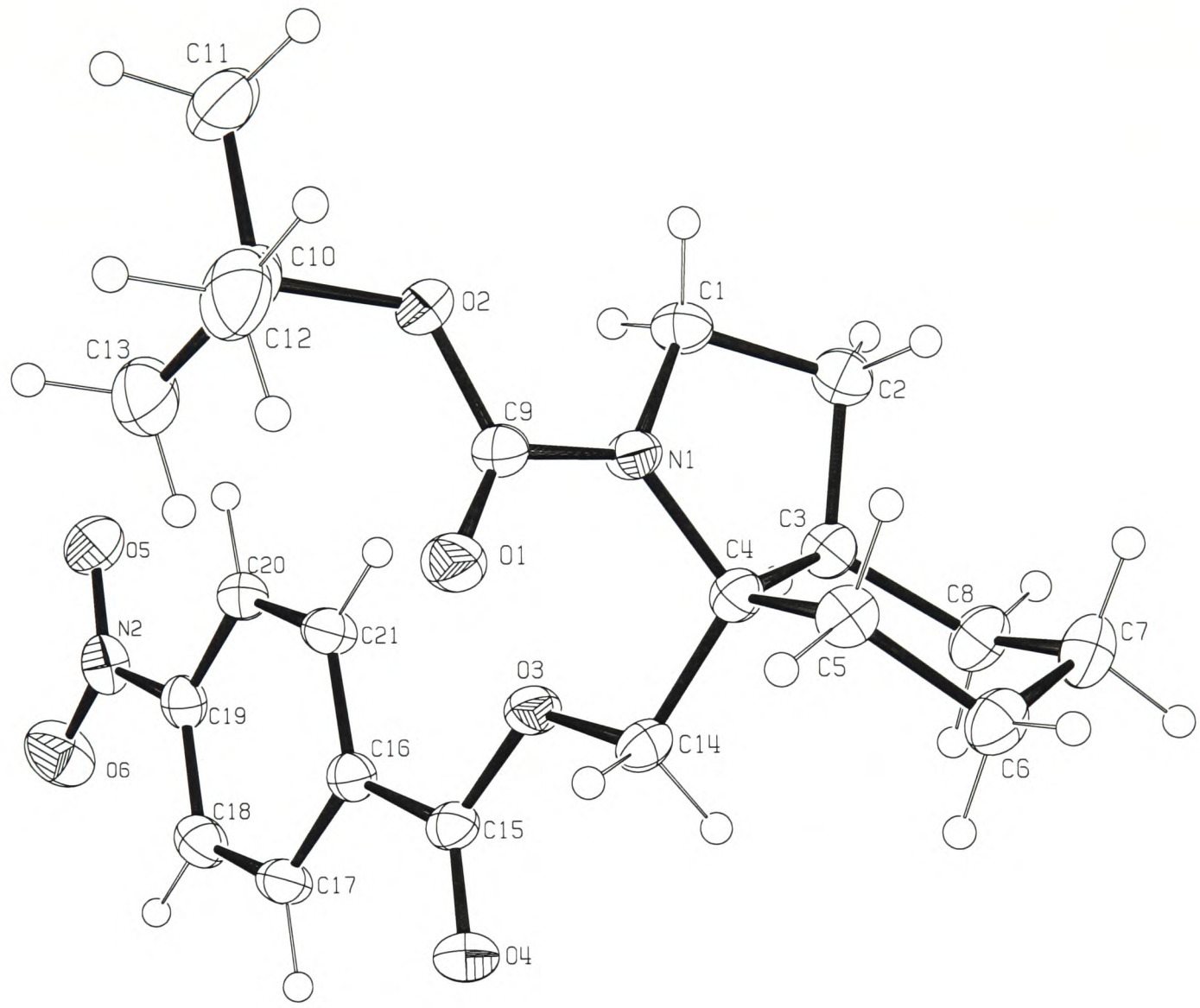
C(1) - N(1) - C(4)	111.56(11)	C(5) - O(3) - C(6)	118.86(11)
C(1) - N(1) - C(5)	123.32(12)	O(3) - C(6) - C(7)	101.89(12)
C(4) - N(1) - C(5)	125.12(12)	O(3) - C(6) - C(8)	109.46(13)
N(1) - C(1) - O(1)	126.67(14)	C(7) - C(6) - C(8)	110.28(15)
N(1) - C(1) - C(2)	105.58(12)	O(3) - C(6) - C(9)	109.65(13)
O(1) - C(1) - C(2)	127.75(14)	C(7) - C(6) - C(9)	111.52(15)
C(1) - C(2) - C(3)	109.65(14)	C(8) - C(6) - C(9)	113.41(14)
C(2) - C(3) - C(4)	111.92(13)	C(4) - C(10) - C(11)	113.52(12)
N(1) - C(4) - C(3)	101.25(11)	C(10) - C(11) - C(12)	113.62(12)
N(1) - C(4) - C(10)	115.34(11)	C(11) - C(12) - Cl(1)	111.76(11)
C(3) - C(4) - C(10)	110.75(12)	C(4) - C(13) - O(4)	120.58(13)
N(1) - C(4) - C(13)	113.70(11)	C(4) - C(13) - O(5)	114.09(12)
C(3) - C(4) - C(13)	107.67(12)	O(4) - C(13) - O(5)	125.27(14)
C(10) - C(4) - C(13)	107.79(12)	C(13) - O(5) - C(14)	116.20(11)
N(1) - C(5) - O(2)	123.34(13)	O(5) - C(14) - C(15)	109.91(13)
N(1) - C(5) - O(3)	109.77(11)	O(5) - C(14) - C(16)	105.69(13)
O(2) - C(5) - O(3)	126.88(13)	C(15) - C(14) - C(16)	114.43(17)

Note – H atoms have been excluded

Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for $C_{21}H_{28}N_2O_6$ (ARC979)

Andrew R. Cowley
E-mail: a_r_cowley@hotmail.com
Tel. (2)85018



Crystals of **ARC979** were grown by Peter Turner. A single crystal having dimensions approximately 0.18 x 0.36 x 0.40 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K in a stream of cold N_2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package[1].

Examination of the systematic absences of the intensity data showed the space group to be *P* $2_1/c$. The structure was solved using the direct-methods program SIR92[2], which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite[3]. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. Hydrogen atoms were positioned geometrically after each cycle of

refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give R = 0.0399, wR = 0.0452.

Attached is a thermal ellipsoid plot (ORTEP-3[4]) at 40% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References:

1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.

2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi ,M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.

3 CRYSTALS Issue 12, P. W. Betteridge, J. R. Cooper, R. I. Cooper, K. Prout and D. J. Watkin, *J. Appl. Cryst.*, 2003, **36**, 1487

4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC979
Chemical formula	$C_{21}H_{28}N_2O_6$
Formula weight	404.46
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P\,2_1/c$
a (Å)	6.5938(2)
b (Å)	16.4825(6)
c (Å)	19.2350(7)
α (°)	90
β (°)	93.4825(16)
γ (°)	90
Cell volume (Å^3)	2086.68(12)
Z	4
Calculated density (Mg/m^3)	1.287
Absorption coefficient (mm^{-1})	0.095
F_{000}	864
Crystal size (mm)	0.18 x 0.36 x 0.40
Description of crystal	Pale-yellow tablet
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.96, 0.98
θ range for data collection (°)	$5.0 \leq \theta \leq 27.5$
Index ranges	$-8 \leq h \leq 8$, $0 \leq k \leq 21$, $0 \leq l \leq 24$
Reflections measured	17619
Unique reflections	4906
R_{int}	0.061
Observed reflections ($I > 3\sigma(I)$)	2386
Refinement method	Full-matrix least-squares on F
Parameters refined	262
Weighting scheme	Chebychev 3-term polynomial
Goodness of fit	1.1003
R	0.0399
wR	0.0452
Residual electron density (min,max) (eÅ^{-3})	-0.18, 0.21

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($Å^2$) of non-hydrogen atoms

Atom	x	y	z	U_{equiv}
N(1)	0.7386(2)	0.50582(10)	0.22607(8)	0.0278
C(1)	0.5684(3)	0.55888(13)	0.24242(10)	0.0315
C(2)	0.5537(3)	0.61665(13)	0.18072(11)	0.0335
C(3)	0.6119(3)	0.56281(13)	0.12085(10)	0.0300
C(4)	0.7927(3)	0.51263(12)	0.15281(10)	0.0280
C(5)	0.9967(3)	0.55769(14)	0.14918(11)	0.0320
C(6)	1.0308(3)	0.59282(14)	0.07772(11)	0.0371
C(7)	0.8593(4)	0.65004(15)	0.05450(12)	0.0434
C(8)	0.6545(3)	0.60584(15)	0.05242(11)	0.0396
C(9)	0.8301(3)	0.45307(13)	0.27162(10)	0.0298
O(1)	0.9712(2)	0.40855(9)	0.25851(7)	0.0384
O(2)	0.7450(2)	0.45768(9)	0.33363(7)	0.0364
C(10)	0.7931(4)	0.39634(14)	0.38801(11)	0.0435
C(11)	0.6693(5)	0.42641(18)	0.44708(13)	0.0598
C(12)	1.0168(5)	0.39543(17)	0.40998(13)	0.0572
C(13)	0.7170(5)	0.31392(17)	0.36230(14)	0.0605
C(14)	0.8068(3)	0.43042(13)	0.11701(10)	0.0302
O(3)	0.6276(2)	0.38390(9)	0.13203(7)	0.0321
C(15)	0.6062(3)	0.31171(13)	0.10061(10)	0.0286
O(4)	0.7248(2)	0.28499(9)	0.06065(7)	0.0368
C(16)	0.4182(3)	0.26908(12)	0.11985(10)	0.0281
C(17)	0.3593(3)	0.19923(13)	0.08341(11)	0.0336
C(18)	0.1829(4)	0.15901(13)	0.09815(11)	0.0356
C(19)	0.0692(3)	0.18939(13)	0.14999(11)	0.0300
C(20)	0.1256(3)	0.25743(13)	0.18818(11)	0.0325
C(21)	0.3015(3)	0.29788(13)	0.17261(11)	0.0322
N(2)	-0.1233(3)	0.14895(11)	0.16446(10)	0.0371
O(5)	-0.2237(2)	0.17762(10)	0.21018(9)	0.0450
O(6)	-0.1754(3)	0.08962(11)	0.12949(11)	0.0581

Table 3: Atomic coordinates and isotropic thermal parameters ($Å^2$) of hydrogen atoms

Atom	x	y	z	U_{iso}
H(11)	0.5989	0.5888	0.2870	0.0378
H(12)	0.4401	0.5271	0.2456	0.0378
H(21)	0.6506	0.6630	0.1879	0.0401
H(22)	0.4124	0.6381	0.1724	0.0401
H(31)	0.4942	0.5285	0.1037	0.0359
H(51)	1.0001	0.6031	0.1837	0.0383
H(52)	1.1091	0.5187	0.1618	0.0383
H(61)	1.1622	0.6233	0.0799	0.0446
H(62)	1.0369	0.5475	0.0433	0.0446
H(71)	0.8563	0.6964	0.0879	0.0521
H(72)	0.8832	0.6711	0.0069	0.0521
H(81)	0.5443	0.6465	0.0418	0.0474
H(82)	0.6527	0.5643	0.0145	0.0474
H(111)	0.6896	0.3891	0.4879	0.0725
H(112)	0.7149	0.4823	0.4610	0.0725
H(113)	0.5221	0.4276	0.4312	0.0725
H(121)	1.0437	0.3533	0.4468	0.0678
H(122)	1.0582	0.4499	0.4289	0.0678
H(123)	1.0967	0.3825	0.3688	0.0678
H(131)	0.7493	0.2722	0.3990	0.0726
H(132)	0.7849	0.2991	0.3190	0.0726
H(133)	0.5666	0.3163	0.3520	0.0726
H(141)	0.9319	0.4013	0.1353	0.0365
H(142)	0.8118	0.4381	0.0656	0.0365
H(171)	0.4450	0.1780	0.0463	0.0404
H(181)	0.1390	0.1091	0.0718	0.0425
H(201)	0.0414	0.2772	0.2263	0.0393
H(211)	0.3446	0.3477	0.1992	0.0388

Table 4: Anisotropic thermal parameters ($Å^2$)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N(1)	0.0291(9)	0.0312(9)	0.0235(8)	-0.0006(7)	0.0038(7)	0.0040(7)
C(1)	0.0290(10)	0.0355(11)	0.0300(11)	-0.0039(9)	0.0019(9)	0.0054(9)
C(2)	0.0285(11)	0.0341(11)	0.0377(12)	-0.0014(9)	0.0007(9)	0.0052(9)
C(3)	0.0279(10)	0.0341(11)	0.0277(10)	0.0014(9)	-0.0016(8)	-0.0001(9)
C(4)	0.0262(10)	0.0307(11)	0.0272(10)	0.0015(9)	0.0029(8)	0.0005(8)
C(5)	0.0264(10)	0.0371(12)	0.0321(11)	-0.0005(9)	-0.0010(8)	-0.0020(9)
C(6)	0.0336(11)	0.0438(13)	0.0341(12)	0.0003(10)	0.0032(9)	-0.0103(10)
C(7)	0.0484(14)	0.0452(14)	0.0367(12)	0.0122(11)	0.0026(10)	-0.0055(11)
C(8)	0.0382(12)	0.0497(14)	0.0305(11)	0.0086(10)	-0.0002(9)	-0.0001(11)
C(9)	0.0344(11)	0.0293(11)	0.0258(10)	-0.0026(9)	0.0030(9)	-0.0013(9)
O(1)	0.0453(9)	0.0376(8)	0.0323(8)	0.0005(7)	0.0028(7)	0.0131(7)
O(2)	0.0498(9)	0.0363(9)	0.0236(7)	0.0025(6)	0.0066(6)	0.0030(7)
C(10)	0.0664(17)	0.0351(13)	0.0287(12)	0.0073(10)	0.0006(11)	-0.0080(12)
C(11)	0.086(2)	0.0593(17)	0.0355(13)	0.0028(12)	0.0180(13)	-0.0176(15)
C(12)	0.0728(19)	0.0568(17)	0.0399(13)	0.0126(13)	-0.0129(12)	-0.0039(14)
C(13)	0.091(2)	0.0403(15)	0.0503(16)	0.0011(12)	0.0040(14)	-0.0163(15)
C(14)	0.0272(10)	0.0365(12)	0.0275(10)	0.0005(9)	0.0078(8)	-0.0035(9)
O(3)	0.0328(8)	0.0317(8)	0.0330(8)	-0.0046(6)	0.0109(6)	-0.0039(6)
C(15)	0.0313(11)	0.0327(11)	0.0216(9)	0.0005(9)	0.0001(8)	0.0055(9)
O(4)	0.0349(8)	0.0411(9)	0.0352(8)	-0.0065(7)	0.0086(6)	0.0047(7)
C(16)	0.0283(10)	0.0287(11)	0.0271(10)	0.0013(9)	0.0000(8)	0.0052(9)
C(17)	0.0368(12)	0.0316(11)	0.0326(11)	-0.0056(9)	0.0045(9)	0.0067(10)
C(18)	0.0410(12)	0.0289(11)	0.0362(12)	-0.0039(10)	-0.0027(10)	0.0012(10)
C(19)	0.0260(10)	0.0286(10)	0.0350(11)	0.0050(9)	-0.0010(8)	0.0028(9)
C(20)	0.0348(11)	0.0304(11)	0.0331(11)	-0.0003(9)	0.0084(9)	0.0029(9)
C(21)	0.0337(11)	0.0298(11)	0.0335(11)	-0.0061(9)	0.0052(9)	0.0008(9)
N(2)	0.0337(10)	0.0318(10)	0.0451(11)	0.0064(9)	-0.0020(8)	-0.0005(8)
O(5)	0.0378(9)	0.0529(10)	0.0455(9)	0.0033(8)	0.0115(7)	-0.0053(8)
O(6)	0.0507(11)	0.0423(10)	0.0816(14)	-0.0128(10)	0.0067(9)	-0.0139(9)

Table 5: Bond lengths (Å)

N(1) - C(1)	1.471(3)	C(10) - C(12)	1.510(4)
N(1) - C(4)	1.479(2)	C(10) - C(13)	1.521(4)
N(1) - C(9)	1.351(3)	C(14) - O(3)	1.452(2)
C(1) - C(2)	1.520(3)	O(3) - C(15)	1.338(2)
C(2) - C(3)	1.521(3)	C(15) - O(4)	1.212(2)
C(3) - C(4)	1.547(3)	C(15) - C(16)	1.491(3)
C(3) - C(8)	1.536(3)	C(16) - C(17)	1.391(3)
C(4) - C(5)	1.542(3)	C(16) - C(21)	1.394(3)
C(4) - C(14)	1.525(3)	C(17) - C(18)	1.383(3)
C(5) - C(6)	1.521(3)	C(18) - C(19)	1.377(3)
C(6) - C(7)	1.519(3)	C(19) - C(20)	1.379(3)
C(7) - C(8)	1.533(3)	C(19) - N(2)	1.475(3)
C(9) - O(1)	1.223(2)	C(20) - C(21)	1.386(3)
C(9) - O(2)	1.351(2)	N(2) - O(5)	1.227(2)
O(2) - C(10)	1.475(3)	N(2) - O(6)	1.224(2)
C(10) - C(11)	1.521(4)		

Note – H atoms have been excluded

Table 6: Bond angles (°)

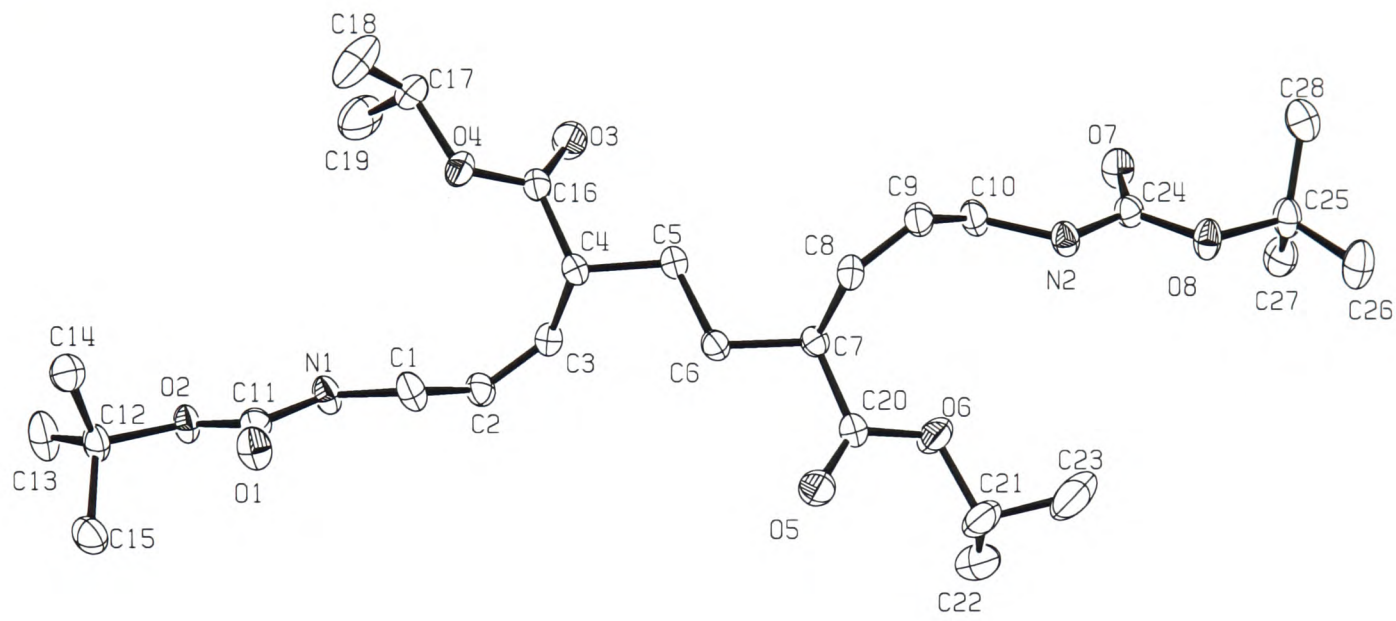
C(1) - N(1) - C(4)	112.92(16)	O(2) - C(10) - C(12)	111.70(19)
C(1) - N(1) - C(9)	124.10(16)	C(11) - C(10) - C(12)	110.7(2)
C(4) - N(1) - C(9)	122.89(16)	O(2) - C(10) - C(13)	109.21(19)
N(1) - C(1) - C(2)	102.65(15)	C(11) - C(10) - C(13)	110.6(2)
C(1) - C(2) - C(3)	102.61(17)	C(12) - C(10) - C(13)	112.3(2)
C(2) - C(3) - C(4)	103.58(16)	C(4) - C(14) - O(3)	107.85(15)
C(2) - C(3) - C(8)	116.54(18)	C(14) - O(3) - C(15)	116.40(15)
C(4) - C(3) - C(8)	114.26(17)	O(3) - C(15) - O(4)	123.68(19)
N(1) - C(4) - C(3)	101.23(15)	O(3) - C(15) - C(16)	111.95(16)
N(1) - C(4) - C(5)	109.94(16)	O(4) - C(15) - C(16)	124.36(19)
C(3) - C(4) - C(5)	112.20(17)	C(15) - C(16) - C(17)	118.44(18)
N(1) - C(4) - C(14)	112.81(16)	C(15) - C(16) - C(21)	121.62(18)
C(3) - C(4) - C(14)	111.24(17)	C(17) - C(16) - C(21)	119.95(19)
C(5) - C(4) - C(14)	109.28(16)	C(16) - C(17) - C(18)	120.41(19)
C(4) - C(5) - C(6)	113.67(17)	C(17) - C(18) - C(19)	118.39(19)
C(5) - C(6) - C(7)	110.73(18)	C(18) - C(19) - C(20)	122.68(19)
C(6) - C(7) - C(8)	110.59(19)	C(18) - C(19) - N(2)	118.99(19)
C(3) - C(8) - C(7)	113.79(18)	C(20) - C(19) - N(2)	118.31(19)
N(1) - C(9) - O(1)	124.62(18)	C(19) - C(20) - C(21)	118.57(19)
N(1) - C(9) - O(2)	110.08(17)	C(16) - C(21) - C(20)	119.97(19)
O(1) - C(9) - O(2)	125.29(19)	C(19) - N(2) - O(5)	117.97(18)
C(9) - O(2) - C(10)	120.30(16)	C(19) - N(2) - O(6)	118.24(19)
O(2) - C(10) - C(11)	101.8(2)	O(5) - N(2) - O(6)	123.77(19)

Note – H atoms have been excluded

Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for $C_{28}H_{48}N_2O_8$ (ARC623)

Andrew R. Cowley
E-mail: a_r_cowley@hotmail.com
Tel. (2)70827



H atoms not shown

Crystals of **ARC623** were grown by Peter Turner. A single crystal having dimensions approximately 0.07 x 0.07 x 0.28 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K in a stream of cold N_2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package[1].

Examination of the systematic absences of the intensity data showed the space group to be *P* $2_1/c$. The structure was solved using the direct-methods program SIR92[2], which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite[3]. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The NH hydrogen atoms were located in a difference Fourier map and their coordinates and isotropic thermal parameters subsequently refined. Other hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give R = 0.0441, wR = 0.0531.

Attached is a thermal ellipsoid plot (ORTEP-3[4]) at 40% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning geometrically-positioned H atoms.

Comments:

The molecule has no crystallographic symmetry but has an approximate local centre of inversion. This is located in the unit cell in such a way that if it were a true symmetry operator the *a* axis would be halved. The deviations from this approximate symmetry are largely due to the isopropyl and *t*-butoxycarbonyl groups.

Both NH groups participate in hydrogen bonding, each interacting with the carbonyl O atom of a *t*-butoxycarbonyl group of one of the neighbouring molecules (N(1)···O(7)' 2.950(2) Å, symmetry operator -*x*, 1-*y*, 1-*z*, N(2)···O(1)" 3.039(2) Å, symmetry operator 1-*x*, 1-*y*, 1-*z*). These bonds link the molecules to form chains running prallel to the crystallographic *a* axis.

References:

1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.

2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi ,M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.

3 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, CRYSTALS issue 11, Chemical Crystallography Laboratory, Oxford, UK, 2001.

4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC623
Chemical formula	$C_{28}H_{48}N_2O_8$
Formula weight	540.70
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P\,2_1/c$
a (Å)	10.1710(2)
b (Å)	14.2506(3)
c (Å)	21.5644(6)
α (°)	90
β (°)	92.5897(8)
γ (°)	90
Cell volume (Å^3)	3122.41(13)
Z	4
Calculated density (Mg/m^3)	1.150
Absorption coefficient (mm^{-1})	0.083
F_{000}	1176
Crystal size (mm)	0.07 x 0.07 x 0.28
Description of crystal	Colourless prism
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.98, 0.99
θ range for data collection (°)	$5.0 \leq \theta \leq 27.5$
Index ranges	$-13 \leq h \leq 13$, $0 \leq k \leq 18$, $0 \leq l \leq 27$
Reflections measured	29116
Unique reflections	7318
R_{int}	0.069
Observed reflections ($I > 3\sigma(I)$)	3262
Refinement method	Full-matrix least-squares on F
Parameters refined	351
Weighting scheme	Chebychev 3-term polynomial
Goodness of fit	1.0568
R	0.0441
wR	0.0531
Residual electron density (min,max) (eÅ^{-3})	-0.19, 0.21

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($Å^2$) of non-hydrogen atoms

Atom	x	y	z	U_{equiv}
N(1)	0.31337(19)	0.41372(15)	0.23575(9)	0.0345
C(1)	0.3460(2)	0.43937(19)	0.2999(1)	0.0372
C(2)	0.2339(2)	0.49189(16)	0.3260(1)	0.0334
C(3)	0.1841(2)	0.47927(16)	0.3813(1)	0.0301
C(4)	0.2265(2)	0.40845(15)	0.4303(1)	0.0275
C(5)	0.2105(2)	0.44720(16)	0.4958(1)	0.0297
C(6)	0.3003(2)	0.53118(15)	0.5093(1)	0.0286
C(7)	0.2796(2)	0.57447(15)	0.5729(1)	0.0271
C(8)	0.3229(2)	0.50777(16)	0.6244(1)	0.0296
C(9)	0.2673(2)	0.49470(16)	0.6779(1)	0.0317
C(10)	0.1483(2)	0.54375(17)	0.6998(1)	0.0347
N(2)	0.18100(19)	0.59687(14)	0.75642(8)	0.0323
C(11)	0.4088(2)	0.39259(16)	0.1970(1)	0.0301
O(1)	0.52535(15)	0.39240(13)	0.21141(7)	0.0411
O(2)	0.35556(14)	0.37443(11)	0.13956(7)	0.0334
C(12)	0.4384(2)	0.33817(17)	0.09028(11)	0.0346
C(13)	0.3404(3)	0.3285(2)	0.03523(12)	0.0523
C(14)	0.4943(3)	0.24386(19)	0.10992(13)	0.0473
C(15)	0.5436(2)	0.40841(19)	0.07516(12)	0.0430
C(16)	0.1427(2)	0.32123(16)	0.4202(1)	0.0319
O(3)	0.03526(18)	0.30981(13)	0.44020(9)	0.0505
O(4)	0.20263(16)	0.26004(11)	0.38429(8)	0.0387
C(17)	0.1326(3)	0.17328(18)	0.36692(12)	0.0453
C(18)	0.2387(4)	0.1013(2)	0.35935(19)	0.0754
C(19)	0.0491(3)	0.1911(2)	0.30893(15)	0.0669
C(20)	0.3568(2)	0.66528(16)	0.5804(1)	0.0311
O(5)	0.44933(19)	0.68679(14)	0.55126(9)	0.0540
O(6)	0.30990(19)	0.71727(13)	0.6254(1)	0.0582
C(21)	0.3691(3)	0.8104(2)	0.63710(16)	0.0615
C(22)	0.2766(5)	0.8818(2)	0.60815(18)	0.0819
C(23)	0.3857(4)	0.8193(2)	0.70642(18)	0.0795
C(24)	0.0888(2)	0.61715(16)	0.7966(1)	0.0296
O(7)	-0.02629(14)	0.59347(12)	0.79038(7)	0.0391
O(8)	0.14106(14)	0.66765(12)	0.84454(7)	0.0361
C(25)	0.0590(2)	0.69942(18)	0.89514(11)	0.0361
C(26)	0.1577(3)	0.7542(2)	0.93600(13)	0.0502
C(27)	-0.0475(2)	0.76517(19)	0.86983(12)	0.0436
C(28)	0.0056(3)	0.6158(2)	0.92903(12)	0.0479

Table 3: Atomic coordinates and isotropic thermal parameters (Å^2) of hydrogen atoms

Atom	x	y	z	U_{iso}
H(1)	0.235(3)	0.411(2)	0.2235(13)	0.049(8)
H(2)	0.258(3)	0.6135(17)	0.7635(12)	0.033(7)
H(11)	0.4263	0.4799	0.3017	0.0446
H(12)	0.3635	0.3812	0.3249	0.0446
H(21)	0.1921	0.5417	0.2990	0.0399
H(31)	0.1100	0.5217	0.3917	0.0361
H(41)	0.3219	0.3935	0.4265	0.0331
H(51)	0.2326	0.3966	0.5266	0.0357
H(52)	0.1170	0.4672	0.4998	0.0357
H(61)	0.3939	0.5101	0.5078	0.0344
H(62)	0.2820	0.5800	0.4767	0.0344
H(71)	0.1835	0.5876	0.5756	0.0326
H(81)	0.4028	0.4691	0.6171	0.0355
H(91)	0.3091	0.4472	0.7067	0.0380
H(101)	0.0791	0.4963	0.7084	0.0417
H(102)	0.1141	0.5878	0.6667	0.0417
H(131)	0.3866	0.3041	-0.0014	0.0630
H(132)	0.3012	0.3913	0.0249	0.0630
H(133)	0.2691	0.2839	0.0460	0.0630
H(141)	0.5504	0.2190	0.0767	0.0574
H(142)	0.5488	0.2511	0.1494	0.0574
H(143)	0.4206	0.1990	0.1166	0.0574
H(151)	0.5984	0.3825	0.0418	0.0521
H(152)	0.6009	0.4210	0.1132	0.0521
H(153)	0.5012	0.4682	0.0605	0.0521
H(171)	0.0708	0.1504	0.3983	0.0543
H(181)	0.1977	0.0398	0.3474	0.0897
H(182)	0.2911	0.0942	0.3994	0.0897
H(183)	0.2979	0.1222	0.3262	0.0897
H(191)	0.0008	0.1324	0.2966	0.0794
H(192)	-0.0156	0.2421	0.3168	0.0794
H(193)	0.1065	0.2107	0.2748	0.0794
H(211)	0.4567	0.8199	0.6188	0.0747
H(221)	0.3136	0.9461	0.6152	0.0982
H(222)	0.1893	0.8771	0.6274	0.0982
H(223)	0.2654	0.8696	0.5625	0.0982
H(231)	0.4257	0.8815	0.7172	0.0944
H(232)	0.2978	0.8141	0.7252	0.0944
H(233)	0.4446	0.7680	0.7230	0.0944
H(261)	0.1129	0.7798	0.9727	0.0604
H(262)	0.2310	0.7116	0.9505	0.0604
H(263)	0.1942	0.8071	0.9116	0.0604
H(271)	-0.1027	0.7863	0.9044	0.0526
H(272)	-0.0060	0.8209	0.8505	0.0526
H(273)	-0.1042	0.7316	0.8379	0.0526
H(281)	-0.0498	0.6380	0.9632	0.0578
H(282)	0.0805	0.5775	0.9469	0.0578
H(283)	-0.0490	0.5765	0.8993	0.0578

Table 4: Anisotropic thermal parameters ($Å^2$)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N(1)	0.024(1)	0.0546(13)	0.0247(9)	-0.0055(9)	0.0027(8)	-0.0029(9)
C(1)	0.0279(12)	0.0591(16)	0.0247(11)	-0.0036(11)	0.0026(9)	-0.0041(11)
C(2)	0.0371(13)	0.0387(13)	0.0240(11)	-0.000(1)	-0.0015(9)	-0.002(1)
C(3)	0.0302(11)	0.0327(12)	0.0273(11)	-0.0048(9)	0.0005(9)	0.0015(9)
C(4)	0.0278(11)	0.0323(12)	0.023(1)	-0.0007(9)	0.0049(8)	0.0016(9)
C(5)	0.0324(12)	0.0332(12)	0.024(1)	-0.0020(9)	0.0034(9)	0.0008(9)
C(6)	0.0285(11)	0.0328(12)	0.0248(11)	0.0002(9)	0.0040(8)	-0.0012(9)
C(7)	0.0254(11)	0.0300(11)	0.0261(11)	0.0001(9)	0.0035(8)	0.0019(8)
C(8)	0.0320(11)	0.0318(12)	0.0250(11)	-0.0051(9)	0.0001(9)	0.0054(9)
C(9)	0.0357(12)	0.0338(12)	0.0255(11)	-0.002(1)	0.0012(9)	0.001(1)
C(10)	0.0336(12)	0.0475(14)	0.0231(11)	-0.004(1)	0.0022(9)	-0.0056(11)
N(2)	0.026(1)	0.0450(12)	0.026(1)	-0.0055(9)	0.0041(8)	-0.0061(9)
C(11)	0.0265(11)	0.0345(12)	0.0292(11)	-0.0005(9)	0.0012(9)	-0.0030(9)
O(1)	0.0254(8)	0.0606(11)	0.0374(9)	-0.0067(8)	0.0009(7)	0.0002(8)
O(2)	0.0252(7)	0.048(1)	0.0274(8)	-0.0106(7)	0.0054(6)	0.0002(7)
C(12)	0.0286(11)	0.0458(14)	0.0301(12)	-0.009(1)	0.0093(9)	0.000(1)
C(13)	0.0371(14)	0.084(2)	0.0365(14)	-0.0190(14)	0.0068(11)	0.0002(14)
C(14)	0.0506(15)	0.0415(15)	0.0515(16)	-0.0060(13)	0.0196(12)	-0.0005(12)
C(15)	0.0393(14)	0.0492(15)	0.0417(14)	0.0010(12)	0.0133(11)	0.0015(11)
C(16)	0.0363(13)	0.0346(12)	0.0249(11)	-0.003(1)	0.0031(9)	-0.003(1)
O(3)	0.0446(11)	0.0518(11)	0.0569(11)	-0.0154(9)	0.0216(9)	-0.0162(9)
O(4)	0.045(1)	0.0322(9)	0.0389(9)	-0.0108(7)	0.0077(7)	-0.0026(7)
C(17)	0.0613(17)	0.0335(14)	0.0408(14)	-0.0081(11)	0.0014(12)	-0.0096(12)
C(18)	0.087(2)	0.0428(17)	0.095(3)	-0.0271(18)	-0.017(2)	0.0110(17)
C(19)	0.083(2)	0.0560(19)	0.059(2)	-0.0071(15)	-0.0218(17)	-0.0103(17)
C(20)	0.0328(12)	0.0351(13)	0.0256(11)	-0.002(1)	0.0039(9)	0.001(1)
O(5)	0.0524(11)	0.0537(12)	0.0583(12)	-0.016(1)	0.0290(9)	-0.0227(9)
O(6)	0.0653(13)	0.0430(11)	0.0693(14)	-0.0269(9)	0.036(1)	-0.0224(9)
C(21)	0.0651(19)	0.0451(17)	0.076(2)	-0.0272(16)	0.0278(16)	-0.0261(15)
C(22)	0.129(3)	0.052(2)	0.064(2)	0.0026(16)	0.003(2)	-0.032(2)
C(23)	0.112(3)	0.0409(18)	0.083(3)	-0.0182(17)	-0.024(2)	-0.0073(18)
C(24)	0.0274(11)	0.0349(12)	0.0265(11)	-0.0008(9)	0.0005(9)	-0.001(1)
O(7)	0.0233(8)	0.0557(11)	0.0383(9)	-0.0091(8)	0.0027(7)	-0.0045(7)
O(8)	0.0241(8)	0.052(1)	0.0323(9)	-0.0148(8)	0.0053(6)	-0.0011(7)
C(25)	0.0282(11)	0.0495(15)	0.0310(12)	-0.0109(11)	0.0073(9)	0.002(1)
C(26)	0.0393(14)	0.0672(18)	0.0444(15)	-0.0231(14)	0.0046(11)	0.0012(13)
C(27)	0.0396(13)	0.0465(15)	0.0453(14)	-0.0094(12)	0.0087(11)	0.0063(11)
C(28)	0.0477(15)	0.0597(18)	0.0371(14)	-0.0024(12)	0.0107(11)	0.0040(13)

Table 5: Bond lengths (Å)

N(1) - C(1)	1.455(3)	C(10) - N(2)	1.463(3)
N(1) - C(11)	1.343(3)	N(2) - C(24)	1.337(3)
N(1) - H(1)	0.83(3)	N(2) - H(2)	0.83(3)
C(1) - C(2)	1.494(3)	C(9) - C(10)	1.492(3)
C(2) - C(3)	1.330(3)	C(8) - C(9)	1.321(3)
C(3) - C(4)	1.509(3)	C(6) - C(7)	1.527(3)
C(4) - C(5)	1.532(3)	C(7) - C(8)	1.512(3)
C(4) - C(16)	1.517(3)	C(7) - C(20)	1.519(3)
C(5) - C(6)	1.526(3)		
C(11) - O(1)	1.212(2)	C(24) - O(7)	1.220(3)
C(11) - O(2)	1.354(3)	C(24) - O(8)	1.349(3)
O(2) - C(12)	1.479(3)	O(8) - C(25)	1.475(3)
C(12) - C(13)	1.521(3)	C(25) - C(26)	1.521(3)
C(12) - C(14)	1.512(4)	C(25) - C(27)	1.515(4)
C(12) - C(15)	1.511(3)	C(25) - C(28)	1.512(4)
C(16) - O(3)	1.204(3)	C(20) - O(5)	1.195(3)
C(16) - O(4)	1.332(3)	C(20) - O(6)	1.325(3)
O(4) - C(17)	1.467(3)	O(6) - C(21)	1.475(3)
C(17) - C(18)	1.503(4)	C(21) - C(22)	1.502(5)
C(17) - C(19)	1.501(4)	C(21) - C(23)	1.502(5)

Note – geometrically-positioned H atoms have been excluded

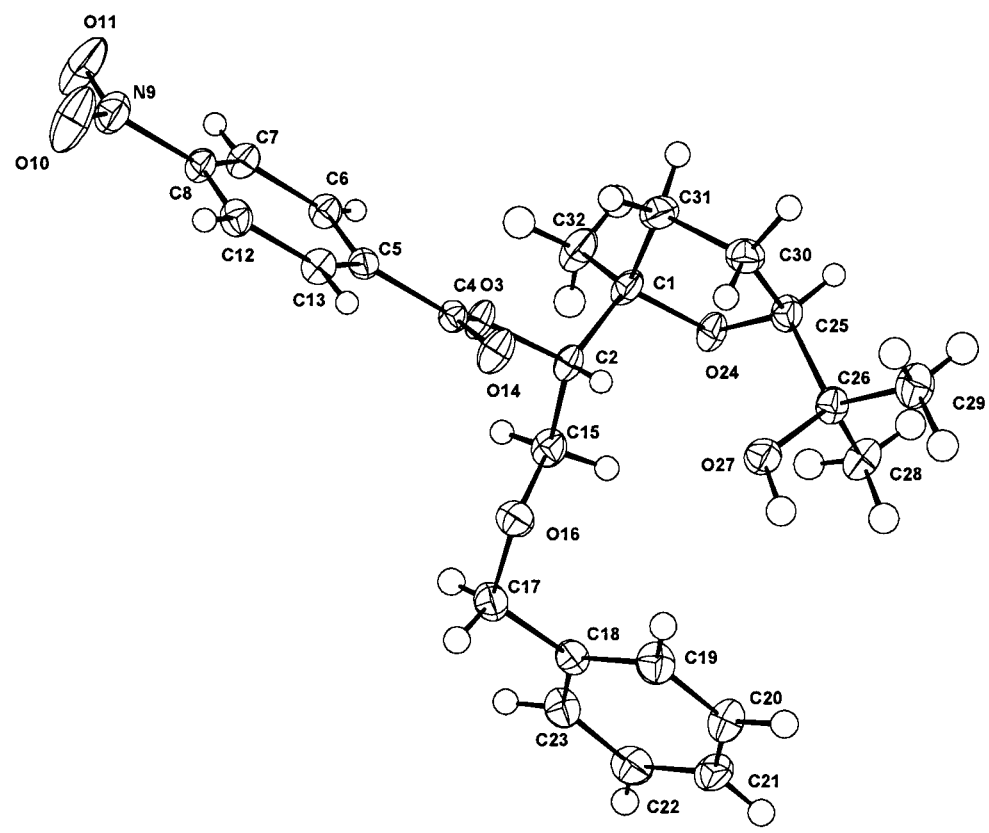
Table 6: Bond angles (°)

C(1) - N(1) - C(11)	120.53(19)	C(10) - N(2) - C(24)	120.89(19)
C(1) - N(1) - H(1)	119.5(20)	C(10) - N(2) - H(2)	118.8(17)
C(11) - N(1) - H(1)	120.0(20)	C(24) - N(2) - H(2)	120.3(17)
N(1) - C(1) - C(2)	109.78(18)	C(9) - C(10) - N(2)	110.39(18)
C(1) - C(2) - C(3)	126.7(2)	C(8) - C(9) - C(10)	126.5(2)
C(2) - C(3) - C(4)	127.6(2)	C(7) - C(8) - C(9)	127.5(2)
C(3) - C(4) - C(5)	111.42(18)	C(6) - C(7) - C(8)	111.00(17)
C(3) - C(4) - C(16)	107.91(18)	C(8) - C(7) - C(20)	108.98(17)
C(5) - C(4) - C(16)	110.14(17)	C(6) - C(7) - C(20)	110.41(17)
C(4) - C(5) - C(6)	111.80(17)	C(5) - C(6) - C(7)	112.52(17)
N(1) - C(11) - O(1)	124.5(2)	N(2) - C(24) - O(7)	124.5(2)
N(1) - C(11) - O(2)	109.99(18)	N(2) - C(24) - O(8)	110.38(18)
O(1) - C(11) - O(2)	125.5(2)	O(7) - C(24) - O(8)	125.1(2)
C(11) - O(2) - C(12)	120.45(16)	C(24) - O(8) - C(25)	120.94(17)
O(2) - C(12) - C(13)	102.57(18)	O(8) - C(25) - C(26)	101.83(17)
O(2) - C(12) - C(14)	109.18(19)	O(8) - C(25) - C(27)	110.04(19)
C(13) - C(12) - C(14)	111.3(2)	C(26) - C(25) - C(27)	109.5(2)
O(2) - C(12) - C(15)	110.83(19)	O(8) - C(25) - C(28)	110.1(2)
C(13) - C(12) - C(15)	109.7(2)	C(26) - C(25) - C(28)	111.5(2)
C(14) - C(12) - C(15)	112.8(2)	C(27) - C(25) - C(28)	113.3(2)
C(4) - C(16) - O(3)	125.0(2)	C(7) - C(20) - O(5)	125.3(2)
C(4) - C(16) - O(4)	110.52(18)	C(7) - C(20) - O(6)	110.66(18)
O(3) - C(16) - O(4)	124.5(2)	O(5) - C(20) - O(6)	124.0(2)
C(16) - O(4) - C(17)	118.09(18)	C(20) - O(6) - C(21)	118.09(19)
O(4) - C(17) - C(18)	105.1(2)	O(6) - C(21) - C(22)	107.2(3)
O(4) - C(17) - C(19)	108.7(2)	O(6) - C(21) - C(23)	105.8(3)
C(18) - C(17) - C(19)	114.0(3)	C(22) - C(21) - C(23)	113.4(3)

Note – geometrically-positioned H atoms have been excluded

Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for $C_{24}H_{29}NO_7$ (TJD002).



Crystals of **TJD002** were grown by Peter Turner. A single crystal having dimensions approximately 0.3 x 0.3 x 1.0 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N_2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package[1]. Examination of the systematic absences of the intensity data showed the space group to be P n 2_1 a. The structure was solved in this space group using the direct-methods program SIR92[2], which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F using the CRYSTALS program suite[3]. Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give R = 0.0450, wR = 0.0723.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

Comment:

The OH group forms a hydrogen bond to the carbonyl O atom of a neighbouring molecule (O(27)···O(14)' 2.8889 Å) and the carbonyl O atom forms a hydrogen bond to the OH group of a second neighbouring molecule (O(14)···O(27)" 2.8889 Å). The molecules are packed as interlocking ribbons along the c axis. The oscillating motion of the nitro group results in a large Ueq(max)/Ueq(min) ratio.

References:

1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.

2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi ,M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.

3 CRYSTALS Issue 12, P. W. Betteridge, J. R. Cooper, R. I. Cooper, K. Prout and D. J. Watkin, *J. Appl. Cryst.*, 2003, **36**, 1487

Table 1: Crystal data and refinement details

Crystal identification	TJD002
Chemical formula	$C_{24}H_{29}NO_7$
Formula weight	443.50
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	P n 2_1 a
a (Å)	11.5139(2)
b (Å)	13.4043(3)
c (Å)	14.6078(3)
□ (°)	90
□ (°)	90
□ (°)	90
Cell volume (Å^3)	2254.51(8)
Z	4
Calculated density (Mg/m^3)	1.307
Absorption coefficient (mm^{-1})	0.096
F_{000}	944
Crystal size (mm)	0.3 x 0.3 x 1.0
Description of crystal	Colourless fragment
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.36, 0.97
□ range for data collection (°)	5.0 ≤ □ ≤ 27.5
Index ranges	$0 \leq h \leq 14$, $0 \leq k \leq 17$, $0 \leq l \leq 18$
Reflections measured	14629
Unique reflections	2665
R_{int}	0.041
Observed reflections (I > -3□(I))	2665
Refinement method	Full-matrix least-squares on *F*
Parameters refined	289
Weighting scheme	Modified statistical
Goodness of fit	0.9168
R	0.0450
wR	0.0723
Residual electron density (min,max) (eÅ^{-3})	-0.26, 0.22

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($Å^2$) of non-hydrogen atoms

Atom	x	y	z	U_{equiv}
C(1)	0.64098(17)	0.25232(17)	0.50154(13)	0.0264
C(2)	0.59505(17)	0.35077(15)	0.45911(13)	0.0236
O(3)	0.48283(11)	0.37048(11)	0.50197(9)	0.0245
C(4)	0.38855(16)	0.37911(14)	0.44991(12)	0.0197
C(5)	0.28064(16)	0.39237(14)	0.50535(13)	0.0203
C(6)	0.28226(17)	0.37860(15)	0.60017(13)	0.0227
C(7)	0.18014(17)	0.38881(15)	0.64969(14)	0.0254
C(8)	0.07982(17)	0.41436(15)	0.60354(14)	0.0251
N(9)	-0.02754(16)	0.42653(14)	0.65708(13)	0.0349
O(10)	-0.11473(14)	0.45253(17)	0.61768(11)	0.0593
O(11)	-0.02360(16)	0.41063(17)	0.73867(12)	0.0618
C(12)	0.07639(17)	0.42997(14)	0.51025(13)	0.0256
C(13)	0.17801(17)	0.41777(14)	0.46121(13)	0.0245
O(14)	0.38881(12)	0.37535(12)	0.36698(8)	0.0322
C(15)	0.67258(18)	0.43951(16)	0.47553(14)	0.0281
O(16)	0.63515(12)	0.51737(11)	0.41565(10)	0.0294
C(17)	0.70024(18)	0.60688(16)	0.42827(17)	0.0330
C(18)	0.82348(18)	0.60327(15)	0.39278(14)	0.0276
C(19)	0.8536(2)	0.54996(17)	0.31458(15)	0.0335
C(20)	0.9659(2)	0.55474(18)	0.27975(15)	0.0360
C(21)	1.04871(19)	0.61258(17)	0.32324(16)	0.0347
C(22)	1.02088(19)	0.66424(17)	0.40210(16)	0.0339
C(23)	0.90909(18)	0.65866(16)	0.43689(14)	0.0303
O(24)	0.75577(11)	0.23644(11)	0.46485(9)	0.0262
C(25)	0.75295(18)	0.16705(16)	0.38928(13)	0.0263
C(26)	0.81491(19)	0.21253(16)	0.30665(13)	0.0265
O(27)	0.74743(13)	0.29758(11)	0.27999(10)	0.0324
C(28)	0.93695(19)	0.24459(18)	0.33284(14)	0.0348
C(29)	0.8180(2)	0.13719(18)	0.22802(14)	0.0379
C(30)	0.62533(18)	0.14030(16)	0.37472(15)	0.0310
C(31)	0.57159(18)	0.16345(16)	0.46796(14)	0.0315
C(32)	0.65297(19)	0.25885(19)	0.60522(13)	0.0366

Table 3: Atomic coordinates and isotropic thermal parameters ($Å^2$) of hydrogen atoms

Atom	x	y	z	U_{iso}
H(21)	0.58348(17)	0.34082(15)	0.39198(13)	0.0311
H(61)	0.35270(17)	0.36262(15)	0.63047(13)	0.0282
H(71)	0.17841(17)	0.38025(15)	0.71446(14)	0.0313
H(121)	0.00631(17)	0.44852(14)	0.48124(13)	0.0324
H(131)	0.17877(17)	0.42651(14)	0.39550(13)	0.0305
H(151)	0.66589(18)	0.46057(16)	0.54051(14)	0.0339
H(152)	0.75373(18)	0.42084(16)	0.46225(14)	0.0345
H(171)	0.70236(18)	0.62007(16)	0.49595(17)	0.0421
H(172)	0.65840(18)	0.65854(16)	0.39490(17)	0.0419
H(191)	0.7960(2)	0.50940(17)	0.28644(15)	0.0416
H(201)	0.9864(2)	0.51690(18)	0.22552(15)	0.0446
H(211)	1.12488(19)	0.61723(17)	0.29914(16)	0.0442
H(221)	1.07938(19)	0.70313(17)	0.43142(16)	0.0431
H(231)	0.88835(18)	0.69338(16)	0.49116(14)	0.0384
H(251)	0.79623(18)	0.10621(16)	0.40775(13)	0.0319
H(281)	0.97161(19)	0.27900(18)	0.28370(14)	0.0527
H(282)	0.93054(19)	0.28657(18)	0.38618(14)	0.0531
H(283)	0.98133(19)	0.18566(18)	0.34802(14)	0.0531
H(291)	0.8577(2)	0.16827(18)	0.17550(14)	0.0580
H(292)	0.8618(2)	0.07723(18)	0.24646(14)	0.0582
H(293)	0.7382(2)	0.11900(18)	0.20946(14)	0.0580
H(301)	0.61525(18)	0.06962(16)	0.35738(15)	0.0374
H(302)	0.59145(18)	0.18394(16)	0.32785(15)	0.0374
H(311)	0.58221(18)	0.10513(16)	0.50874(14)	0.0387
H(312)	0.48881(18)	0.17983(16)	0.46216(14)	0.0382
H(321)	0.68048(19)	0.19490(19)	0.62918(13)	0.0560
H(322)	0.70967(19)	0.31142(19)	0.62054(13)	0.0562
H(323)	0.57797(19)	0.27361(19)	0.63202(13)	0.0561
H(11)	0.77822(13)	0.33066(11)	0.23538(10)	0.0511

Table 4: Anisotropic thermal parameters ($Å^2$)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	0.0180(10)	0.0357(11)	0.0255(9)	0.0072(9)	0.0059(8)	0.0051(9)
C(2)	0.0158(10)	0.0309(10)	0.0241(10)	-0.0008(8)	0.0030(8)	0.0026(8)
O(3)	0.0135(7)	0.0373(8)	0.0229(6)	-0.0012(6)	0.0021(5)	0.0038(6)
C(4)	0.0150(10)	0.0205(9)	0.0237(9)	-0.0014(8)	-0.0009(8)	0.0008(7)
C(5)	0.0187(10)	0.0194(9)	0.0228(9)	-0.0012(8)	-0.0003(8)	-0.0007(7)
C(6)	0.0186(10)	0.0256(10)	0.0240(9)	0.0006(9)	-0.0020(8)	0.0014(8)
C(7)	0.0245(11)	0.0300(11)	0.0219(9)	0.0002(8)	0.0027(8)	0.0002(9)
C(8)	0.0197(10)	0.0260(10)	0.0294(10)	-0.0022(8)	0.0059(9)	-0.0007(8)
N(9)	0.0260(10)	0.0406(10)	0.0381(11)	-0.0048(9)	0.0079(9)	-0.0007(9)
O(10)	0.0201(9)	0.1093(17)	0.0485(10)	-0.0064(11)	0.0024(8)	0.0138(10)
O(11)	0.0412(11)	0.1043(17)	0.0401(10)	0.0159(10)	0.0205(9)	0.0166(11)
C(12)	0.0193(10)	0.0267(11)	0.0309(10)	-0.0026(9)	-0.0019(8)	0.0020(8)
C(13)	0.0225(11)	0.0291(11)	0.0220(10)	0.0006(8)	-0.0028(8)	0.0004(8)
O(14)	0.0236(8)	0.0523(9)	0.0206(7)	-0.0020(7)	0.0000(6)	0.0025(7)
C(15)	0.0200(11)	0.0331(11)	0.0312(11)	0.0013(9)	-0.0014(9)	0.0028(9)
O(16)	0.0227(8)	0.0272(7)	0.0385(8)	0.0020(6)	-0.0028(6)	-0.0008(6)
C(17)	0.0264(12)	0.0259(11)	0.0465(13)	-0.0048(10)	0.0036(10)	0.0008(9)
C(18)	0.0276(11)	0.0233(10)	0.0320(11)	-0.0007(8)	0.0012(9)	0.0012(9)
C(19)	0.0322(14)	0.0342(11)	0.0343(12)	-0.0070(10)	-0.0033(10)	-0.0021(10)
C(20)	0.0347(14)	0.0420(12)	0.0313(12)	-0.0033(10)	0.0055(10)	0.0023(11)
C(21)	0.0235(12)	0.0377(12)	0.0430(13)	0.0066(10)	0.0049(10)	0.0009(10)
C(22)	0.0232(11)	0.0318(11)	0.0466(12)	0.0016(10)	-0.0065(10)	-0.0026(9)
C(23)	0.0283(12)	0.0289(11)	0.0338(11)	-0.0040(9)	-0.0031(9)	0.0020(9)
O(24)	0.0184(7)	0.0347(7)	0.0254(7)	0.0001(6)	0.0022(6)	0.0057(6)
C(25)	0.0232(10)	0.0279(10)	0.0280(10)	0.0013(9)	0.0022(9)	0.0055(8)
C(26)	0.0254(11)	0.0293(10)	0.0248(10)	-0.0001(9)	0.0006(9)	0.0041(8)
O(27)	0.0321(9)	0.0328(8)	0.0322(7)	0.0093(6)	0.0048(7)	0.0064(6)
C(28)	0.0297(12)	0.0446(13)	0.0301(11)	-0.0018(10)	0.0060(9)	-0.0011(10)
C(29)	0.0409(14)	0.0421(13)	0.0308(12)	-0.0064(10)	0.0027(10)	0.0015(11)
C(30)	0.0271(12)	0.0269(10)	0.0391(11)	0.0035(9)	0.0000(10)	-0.0022(9)
C(31)	0.0251(11)	0.0317(11)	0.0376(12)	0.0091(10)	0.0051(9)	-0.0002(9)
C(32)	0.0293(12)	0.0518(14)	0.0287(11)	0.0116(11)	0.0079(9)	0.0111(11)

Table 5: Bond lengths (Å)

C(1) - C(2)	1.551(3)	C(12) - C(13)	1.382(3)
C(1) - O(24)	1.442(2)	C(15) - O(16)	1.428(3)
C(1) - C(31)	1.516(3)	O(16) - C(17)	1.427(2)
C(1) - C(32)	1.523(3)	C(17) - C(18)	1.511(3)
C(2) - O(3)	1.460(2)	C(18) - C(19)	1.391(3)
C(2) - C(15)	1.506(3)	C(18) - C(23)	1.392(3)
O(3) - C(4)	1.330(2)	C(19) - C(20)	1.391(3)
C(4) - C(5)	1.494(3)	C(20) - C(21)	1.383(3)
C(4) - O(14)	1.212(2)	C(21) - C(22)	1.382(3)
C(5) - C(6)	1.398(3)	C(22) - C(23)	1.386(3)
C(5) - C(13)	1.389(3)	O(24) - C(25)	1.444(2)
C(6) - C(7)	1.387(3)	C(25) - C(26)	1.529(3)
C(7) - C(8)	1.381(3)	C(25) - C(30)	1.527(3)
C(8) - N(9)	1.472(3)	C(26) - O(27)	1.434(2)
C(8) - C(12)	1.379(3)	C(26) - C(28)	1.518(3)
N(9) - O(10)	1.209(2)	C(26) - C(29)	1.530(3)
N(9) - O(11)	1.212(2)	C(30) - C(31)	1.528(3)

Note – H atoms have been excluded

Table 6: Bond angles (°)

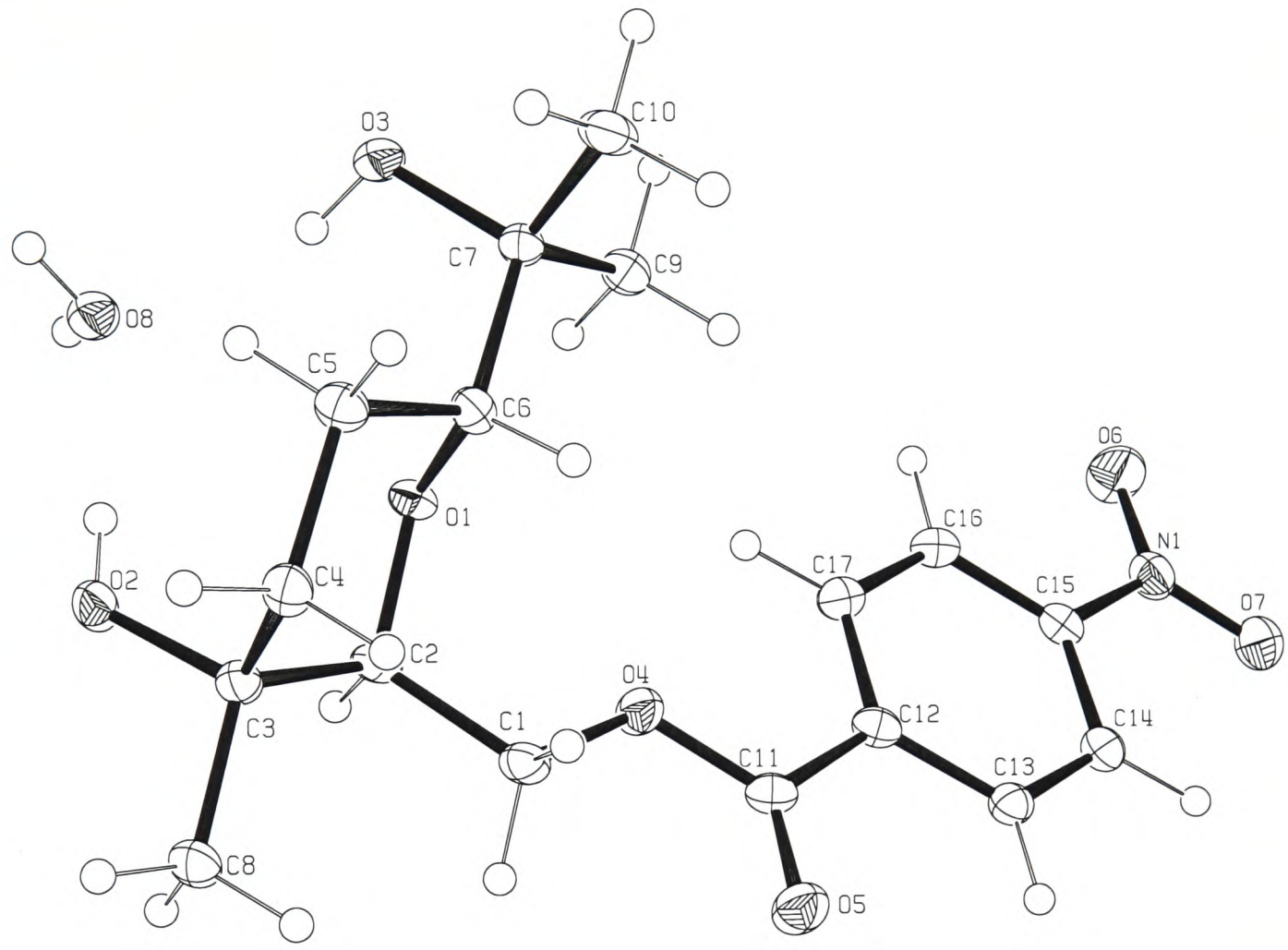
C(2) - C(1) - O(24)	106.84(15)	C(5) - C(13) - C(12)	120.60(18)
C(2) - C(1) - C(31)	111.08(15)	C(2) - C(15) - O(16)	107.50(15)
O(24) - C(1) - C(31)	104.29(17)	C(15) - O(16) - C(17)	112.14(15)
C(2) - C(1) - C(32)	112.29(18)	O(16) - C(17) - C(18)	114.96(17)
O(24) - C(1) - C(32)	107.15(16)	C(17) - C(18) - C(19)	122.14(19)
C(31) - C(1) - C(32)	114.49(18)	C(17) - C(18) - C(23)	119.26(18)
C(1) - C(2) - O(3)	106.52(15)	C(19) - C(18) - C(23)	118.53(19)
C(1) - C(2) - C(15)	113.96(16)	C(18) - C(19) - C(20)	120.5(2)
O(3) - C(2) - C(15)	108.26(16)	C(19) - C(20) - C(21)	119.9(2)
C(2) - O(3) - C(4)	119.52(14)	C(20) - C(21) - C(22)	120.3(2)
O(3) - C(4) - C(5)	112.28(14)	C(21) - C(22) - C(23)	119.6(2)
O(3) - C(4) - O(14)	124.44(17)	C(18) - C(23) - C(22)	121.1(2)
C(5) - C(4) - O(14)	123.28(17)	C(1) - O(24) - C(25)	111.02(15)
C(4) - C(5) - C(6)	120.70(17)	O(24) - C(25) - C(26)	109.64(16)
C(4) - C(5) - C(13)	119.03(17)	O(24) - C(25) - C(30)	106.22(16)
C(6) - C(5) - C(13)	120.26(18)	C(26) - C(25) - C(30)	115.63(17)
C(5) - C(6) - C(7)	119.50(18)	C(25) - C(26) - O(27)	106.19(16)
C(6) - C(7) - C(8)	118.62(18)	C(25) - C(26) - C(28)	110.23(16)
C(7) - C(8) - N(9)	118.08(17)	O(27) - C(26) - C(28)	110.18(18)
C(7) - C(8) - C(12)	122.96(18)	C(25) - C(26) - C(29)	109.89(18)
N(9) - C(8) - C(12)	118.95(18)	O(27) - C(26) - C(29)	109.47(16)
C(8) - N(9) - O(10)	118.46(18)	C(28) - C(26) - C(29)	110.78(18)
C(8) - N(9) - O(11)	118.15(19)	C(25) - C(30) - C(31)	102.58(17)
O(10) - N(9) - O(11)	123.39(19)	C(1) - C(31) - C(30)	103.57(16)
C(8) - C(12) - C(13)	118.03(19)		

Note – H atoms have been excluded

Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for $C_{17}H_{23}NO_7 \cdot H_2O$ (ARC998)

Andrew R. Cowley
E-mail: a_r_cowley@hotmail.com
Tel. (2)85018



One orientation of the disordered hydroxyl groups is shown

Crystals of **ARC998** were grown by Peter Turner. A single crystal having dimensions approximately 0.08 x 0.20 x 0.28 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K in a stream of cold N_2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package[1]. Examination of the diffraction pattern clearly showed the crystal to be composed of multiple diffracting components. It was indexed as being due to a twin containing two components related by a 180° rotation about the reciprocal *c* axis. The intensity data were processed using the orientation matrix corresponding to the predominant component, but the contributions of both components to overlapping reflections were taken into account during the refinement.

The structure was solved in the space group $P\bar{1}$ using the direct-methods program SIR92[2], which located all non-hydrogen atoms. Subsequent full-matrix least-

squares refinement was carried out using the CRYSTALS program suite[3]. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The OH hydrogen atoms were located in a difference Fourier map, which clearly showd them to be disordered. Two of the hydrogen atoms (H(2), H(8)) formed hydrogen bonds across crystallographic centres of inversion and consequently their occupancies were fixed at 0.5 as were those of H(1) and H(5) as required in order to give a reasonable assembly of hydrogen bonds. The OH hydrogen atom coordinates, site occupancies (where not fixed) and a common isotropic thermal parameter were subsequently refined, subject to restraint of the O-H bond lengths to 0.85(5) Å. Other hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give R = 0.0486, wR = 0.0592.

An attempt was made to solve and refine the structure in the lower-symmetry space group *P* 1. Refinement of the structure in this space group failed to converge and the disorder of the hydroxyl groups wasd still evident, suggesting the original assignment of symmetry to be correct.

Attached is a thermal ellipsoid plot (ORTEP-3[4]) at 40% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning geometrically-positioned H atoms.

Comments:

All of the hydroxyl groups participate in hydrogen bonding as summarised below. This forms infinite two-dimensional bilayers running parallel to the crystallographic *ab* plane. The ether, ester and nitro oxygen atoms do not participate in formation of hydrogen bonds.

Donor	H atom	Acceptor	Symmetry operator generating acceptor	O···O distance (Å)
O(2)	H(1)	O(8)		2.804(2)
O(2)	H(2)	O(2)	2-*x*, 1-*y*, 2-*z*	2.822(3)*
O(3)	H(3)	O(8)		2.853(2)
O(3)	H(4)	O(8)	1-*x*, -*y*, 2-*z*	2.813(2)
O(8)	H(5)	O(2)		2.804(2)
O(8)	H(6)	O(3)		2.853(2)
O(8)	H(7)	O(3)	1-*x*, -*y*, 2-*z*	2.813(2)
O(8)	H(8)	O(8)	2-*x*, -*y*, 2-*z*	2.840(4)*

*hydrogen bond lies across crystallographic centre of inversion

An attempt was made to study the variation of the unit-cell parameters with changing temperature, to invsetigate the possibility of the crystal becoming ordered at low temperature. As a result of the twinned nature of the crystal this failed to give useful results.

References:

1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.

2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi ,M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.
3 CRYSTALS Issue 12, P. W. Betteridge, J. R. Cooper, R. I. Cooper, K. Prout and D. J. Watkin, *J. Appl. Cryst.*, 2003, **36**, 1487
4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC998
Chemical formula	$C_{17}H_{25}NO_8$
Formula weight	371.39
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	$P\ \bar{1}$
a (Å)	6.5550(2)
b (Å)	7.8413(3)
c (Å)	17.7603(7)
α (°)	102.3525(14)
β (°)	93.7401(15)
γ (°)	91.0004(17)
Cell volume (Å^3)	889.38(6)
Z	2
Calculated density (Mg/m^3)	1.387
Absorption coefficient (mm^{-1})	0.110
F_{000}	396
Crystal size (mm)	0.08 x 0.20 x 0.28
Description of crystal	Pale-yellow plate
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.97, 0.99
θ range for data collection (°)	$5.0 \leq \theta \leq 27.5$
Index ranges	$-8 \leq h \leq 8, -10 \leq k \leq 10, 0 \leq l \leq 22$
Reflections measured	9457
Unique reflections	3969
R_{int}	0.044
Observed reflections ($I > 3\sigma(I)$)	2644
Refinement method	Full-matrix least-squares on *F*
Parameters refined	262
Weighting scheme	Chebychev 3-term polynomial
Goodness of fit	1.0693
R	0.0486
wR	0.0592
Residual electron density (min,max) (eÅ^{-3})	-0.36, 0.51

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($Å^2$) of non-hydrogen atoms

Atom	x	y	z	U_{equiv}
C(1)	0.7521(3)	0.3533(3)	0.74171(13)	0.0226
C(2)	0.7960(3)	0.3025(3)	0.81888(13)	0.0200
C(3)	0.7530(3)	0.4468(3)	0.88842(13)	0.0201
C(4)	0.5212(3)	0.4628(3)	0.89284(13)	0.0217
C(5)	0.4152(3)	0.2861(3)	0.89107(13)	0.0217
C(6)	0.4735(3)	0.1508(3)	0.82180(12)	0.0195
C(7)	0.3948(3)	-0.0370(3)	0.81762(12)	0.0199
O(1)	0.6933(2)	0.14238(18)	0.82294(9)	0.0191
O(2)	0.8376(3)	0.3952(2)	0.95671(10)	0.0264
O(3)	0.4560(3)	-0.0900(2)	0.88854(9)	0.0237
C(8)	0.8582(4)	0.6191(3)	0.88536(14)	0.0251
C(9)	0.4861(4)	-0.1622(3)	0.75111(13)	0.0254
C(10)	0.1625(4)	-0.0501(3)	0.80835(15)	0.0278
O(4)	0.7685(3)	0.1945(2)	0.68236(9)	0.0247
C(11)	0.7509(3)	0.2166(3)	0.60946(13)	0.0222
O(5)	0.7321(3)	0.3562(2)	0.59246(10)	0.0310
C(12)	0.7552(3)	0.0455(3)	0.55217(13)	0.0212
C(13)	0.7465(3)	0.0523(3)	0.47409(13)	0.0213
C(14)	0.7522(3)	-0.1030(3)	0.41859(13)	0.0233
C(15)	0.7634(3)	-0.2590(3)	0.44330(13)	0.0230
C(16)	0.7696(3)	-0.2684(3)	0.52080(13)	0.0246
C(17)	0.7668(3)	-0.1136(3)	0.57530(13)	0.0244
N(1)	0.7735(3)	-0.4219(3)	0.38447(12)	0.0288
O(6)	0.7878(4)	-0.5597(2)	0.40579(12)	0.0473
O(7)	0.7695(3)	-0.4110(2)	0.31625(10)	0.0338
O(8)	0.8002(3)	0.0614(2)	0.98862(10)	0.0254

Table 3: Atomic coordinates, isotropic thermal parameters (Å^2) and site occupnacies of hydrogen atoms

Atom	x	y	z	U_{iso}	Occupancy
H(1)	0.826(8)	0.294(5)	0.964(3)	0.023(5)	0.5
H(2)	0.920(7)	0.465(7)	0.983(3)	0.023(5)	0.5
H(3)	0.572(6)	-0.043(6)	0.906(3)	0.023(5)	0.60(3)
H(4)	0.348(8)	-0.061(9)	0.912(4)	0.023(5)	0.40(3)
H(11)	0.8544	0.4443	0.7352	0.0268	
H(12)	0.6113	0.3994	0.7384	0.0268	
H(21)	0.9466	0.2838	0.8219	0.0242	
H(41)	0.4936	0.5458	0.9420	0.0257	
H(42)	0.4645	0.5092	0.8478	0.0257	
H(51)	0.4579	0.2464	0.9395	0.0258	
H(52)	0.2636	0.2993	0.8877	0.0258	
H(61)	0.4085	0.1912	0.7764	0.0231	
H(81)	0.8267	0.7100	0.9315	0.0298	
H(82)	1.0094	0.6042	0.8853	0.0298	
H(83)	0.8076	0.6565	0.8372	0.0298	
H(91)	0.4340	-0.2839	0.7489	0.0299	
H(92)	0.6387	-0.1569	0.7596	0.0299	
H(93)	0.4455	-0.1278	0.7013	0.0299	
H(101)	0.1155	-0.1733	0.8058	0.0341	
H(102)	0.1053	0.0286	0.8535	0.0341	
H(103)	0.1139	-0.0141	0.7597	0.0341	
H(131)	0.7365	0.1669	0.4581	0.0258	
H(141)	0.7483	-0.1018	0.3623	0.0279	
H(161)	0.7760	-0.3834	0.5365	0.0300	
H(171)	0.7731	-0.1156	0.6315	0.0296	
H(5)	0.795(8)	0.161(6)	0.977(3)	0.023(5)	0.5
H(6)	0.706(9)	0.007(8)	0.958(3)	0.023(5)	0.40(3)
H(7)	0.734(7)	0.071(6)	1.030(2)	0.023(5)	0.60(3)
H(8)	0.918(6)	0.014(7)	0.993(3)	0.023(5)	0.5

Table 4: Anisotropic thermal parameters ($Å^2$)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	0.0291(11)	0.0150(9)	0.0230(11)	0.0020(8)	0.0048(9)	-0.0031(8)
C(2)	0.0189(9)	0.0143(9)	0.0274(11)	0.0063(8)	0.0001(8)	-0.0025(7)
C(3)	0.0225(10)	0.0171(9)	0.0211(10)	0.0064(8)	-0.0023(8)	-0.0017(8)
C(4)	0.0280(11)	0.0147(9)	0.0215(10)	0.0023(8)	0.0003(8)	0.0030(8)
C(5)	0.0211(10)	0.0186(10)	0.0249(11)	0.0031(8)	0.0033(8)	0.0006(8)
C(6)	0.0194(10)	0.0173(9)	0.0210(10)	0.0035(8)	-0.0012(8)	-0.0002(7)
C(7)	0.0251(11)	0.0145(9)	0.0204(10)	0.0054(8)	-0.0015(8)	-0.0030(8)
O(1)	0.0184(7)	0.0145(7)	0.0246(8)	0.0045(6)	0.0008(6)	-0.0018(5)
O(2)	0.0349(9)	0.0197(8)	0.0241(8)	0.0081(6)	-0.0111(7)	-0.0050(7)
O(3)	0.0264(8)	0.0223(8)	0.0247(8)	0.0111(6)	0.0001(7)	-0.0034(7)
C(8)	0.0325(12)	0.0150(10)	0.0270(11)	0.0047(8)	-0.0029(9)	-0.0028(8)
C(9)	0.0338(12)	0.0159(10)	0.0250(11)	0.0022(8)	0.0003(9)	-0.0053(8)
C(10)	0.0239(11)	0.0248(11)	0.0365(13)	0.0129(10)	-0.0028(10)	-0.0078(9)
O(4)	0.0348(9)	0.0200(7)	0.0193(8)	0.0035(6)	0.0034(6)	-0.0004(6)
C(11)	0.0197(10)	0.0221(10)	0.0263(11)	0.0073(9)	0.0053(8)	-0.0018(8)
O(5)	0.0439(11)	0.0232(8)	0.0274(9)	0.0084(7)	0.0029(8)	0.0012(7)
C(12)	0.0170(10)	0.0203(10)	0.0267(11)	0.0053(8)	0.0035(8)	-0.0009(8)
C(13)	0.0184(10)	0.0224(10)	0.0238(11)	0.0072(9)	0.0004(8)	-0.0008(8)
C(14)	0.0200(10)	0.0251(11)	0.0246(11)	0.0057(9)	-0.0006(8)	-0.0018(8)
C(15)	0.0207(10)	0.0208(10)	0.0262(11)	0.0030(9)	-0.0001(9)	-0.0036(8)
C(16)	0.0258(11)	0.0214(10)	0.0279(12)	0.0079(9)	0.0032(9)	-0.0024(8)
C(17)	0.0260(11)	0.0239(11)	0.0242(11)	0.0070(9)	0.0030(9)	-0.0016(9)
N(1)	0.0307(10)	0.0248(10)	0.0287(11)	0.0028(8)	-0.0030(8)	-0.0035(8)
O(6)	0.0806(16)	0.0203(9)	0.0396(11)	0.0063(8)	-0.0031(10)	-0.0042(9)
O(7)	0.0412(10)	0.0310(9)	0.0262(9)	0.0004(7)	0.0004(8)	-0.0027(8)
O(8)	0.0262(9)	0.0249(8)	0.0263(9)	0.0089(7)	-0.0009(7)	-0.0015(7)

Table 5: Bond lengths (Å)

C(1) - C(2)	1.519(3)	O(2) - H(2)	0.81(4)
C(1) - O(4)	1.460(3)	O(3) - H(3)	0.85(4)
C(2) - C(3)	1.531(3)	O(3) - H(4)	0.85(4)
C(2) - O(1)	1.432(2)	O(4) - C(11)	1.341(3)
C(3) - C(4)	1.532(3)	C(11) - O(5)	1.202(3)
C(3) - O(2)	1.440(3)	C(11) - C(12)	1.502(3)
C(3) - C(8)	1.519(3)	C(12) - C(13)	1.397(3)
C(4) - C(5)	1.533(3)	C(12) - C(17)	1.397(3)
C(5) - C(6)	1.517(3)	C(13) - C(14)	1.396(3)
C(6) - C(7)	1.537(3)	C(14) - C(15)	1.386(3)
C(6) - O(1)	1.442(3)	C(15) - C(16)	1.392(3)
C(7) - O(3)	1.444(3)	C(15) - N(1)	1.473(3)
C(7) - C(9)	1.528(3)	C(16) - C(17)	1.382(3)
C(7) - C(10)	1.520(3)	N(1) - O(6)	1.222(3)
O(2) - H(1)	0.83(4)	N(1) - O(7)	1.231(3)
O(8) - H(5)	0.85(4)	O(8) - H(7)	0.87(4)
O(8) - H(6)	0.84(4)	O(8) - H(8)	0.87(4)

Note – geometrically-positioned H atoms have been excluded

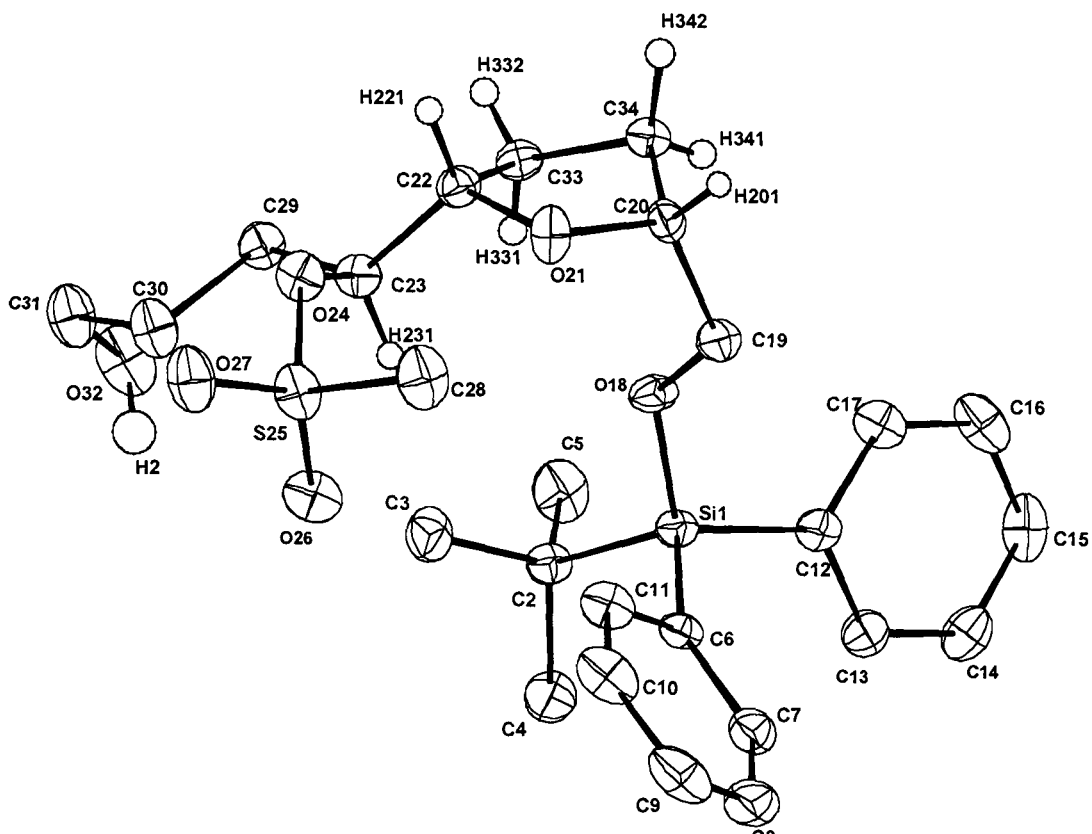
Table 6: Bond angles (°)

C(2) - C(1) - O(4)	106.37(17)	C(3) - O(2) - H(1)	123(4)
C(1) - C(2) - C(3)	113.53(17)	C(3) - O(2) - H(2)	114(4)
C(1) - C(2) - O(1)	112.75(17)	C(7) - O(3) - H(3)	109(3)
C(3) - C(2) - O(1)	110.42(17)	C(7) - O(3) - H(4)	98(5)
C(2) - C(3) - C(4)	109.16(17)	C(1) - O(4) - C(11)	115.07(17)
C(2) - C(3) - O(2)	107.48(17)	O(4) - C(11) - O(5)	123.9(2)
C(4) - C(3) - O(2)	109.02(18)	O(4) - C(11) - C(12)	111.55(18)
C(2) - C(3) - C(8)	111.70(18)	O(5) - C(11) - C(12)	124.5(2)
C(4) - C(3) - C(8)	112.14(18)	C(11) - C(12) - C(13)	116.89(19)
O(2) - C(3) - C(8)	107.18(17)	C(11) - C(12) - C(17)	122.0(2)
C(3) - C(4) - C(5)	111.70(17)	C(13) - C(12) - C(17)	121.1(2)
C(4) - C(5) - C(6)	110.44(17)	C(12) - C(13) - C(14)	119.1(2)
C(5) - C(6) - C(7)	115.73(17)	C(13) - C(14) - C(15)	118.5(2)
C(5) - C(6) - O(1)	109.36(16)	C(14) - C(15) - C(16)	123.2(2)
C(7) - C(6) - O(1)	105.63(16)	C(14) - C(15) - N(1)	118.1(2)
C(6) - C(7) - O(3)	109.84(16)	C(16) - C(15) - N(1)	118.6(2)
C(6) - C(7) - C(9)	110.11(17)	C(15) - C(16) - C(17)	117.8(2)
O(3) - C(7) - C(9)	108.15(17)	C(12) - C(17) - C(16)	120.3(2)
C(6) - C(7) - C(10)	111.14(17)	C(15) - N(1) - O(6)	118.6(2)
O(3) - C(7) - C(10)	107.04(18)	C(15) - N(1) - O(7)	117.8(2)
C(9) - C(7) - C(10)	110.48(19)	O(6) - N(1) - O(7)	123.6(2)
C(2) - O(1) - C(6)	114.42(15)		
H(5) - O(8) - H(6)	100(6)	H(5) - O(8) - H(8)	119(5)
H(5) - O(8) - H(7)	105(5)	H(6) - O(8) - H(8)	120(6)
H(6) - O(8) - H(7)	96(6)	H(7) - O(8) - H(8)	113(5)

Note – geometrically-positioned H atoms have been excluded

Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for $C_{26}H_{38}O_6SSi$ (TJD004).



Crystals of **TJD004** were grown by Peter Turner. A single crystal having dimensions approximately 0.2 x 0.2 x 0.1 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N_2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package[1].
Examination of the systematic absences of the intensity data showed the space group to be *P -1*. The structure was solved in this space group using the direct-methods program SIR92[2], which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F^2 using the CRYSTALS program suite[3]. Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give R = 0.0433, wR = 0.0799.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

Comment

The OH group forms a hydrogen bond to the sulfone O atom of a neighbouring molecule (O(32)···O(26)' 3.4745 Å). The molecules exist as hydrogen bonded dimers.

References:

1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.

2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi ,M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.

3 CRYSTALS Issue 12, P. W. Betteridge, J. R. Cooper, R. I. Cooper, K. Prout and D. J. Watkin, *J. Appl. Cryst.*, 2003, **36**, 1487

Table 1: Crystal data and refinement details

Crystal identification	TJD004
Chemical formula	$C_{26}H_{38}O_6Ssi$
Formula weight	506.74
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	***P –1***
a (Å)	9.9645(3)
b (Å)	10.2631(4)
c (Å)	13.4555(4)
α (°)	76.6842(19)
β (°)	83.159(2)
γ (°)	78.8620(12)
Cell volume (Å^3)	1309.81(8)
Z	2
Calculated density (Mg/m^3)	1.285
Absorption coefficient (mm^{-1})	0.208
F_{000}	544
Crystal size (mm)	0.1 x 0.2 x 0.2
Description of crystal	Colourless fragment
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.67, 0.98
θ range for data collection (°)	$5.0 \leq \theta \leq 27.5$
Index ranges	$-12 \leq h \leq 12$, $-12 \leq k \leq 13$, $0 \leq l \leq 17$
Reflections measured	21673
Unique reflections	5874
R_{int}	0.066
Observed reflections ($I > -3\sigma(I)$)	21673
Refinement method	Full-matrix least-squares on *Fsqd*
Parameters refined	307
Weighting scheme	Auto-statistical
Goodness of fit	0.9485
R	0.0433
wR	0.0799
Residual electron density (min,max) (eÅ^{-3})	-0.40, 0.26

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($Å^2$) of non-hydrogen atoms

Atom	x	y	z	U_{equiv}
Si(1)	0.62046(6)	0.22678(6)	0.12698(4)	0.0213
C(2)	0.6643(2)	0.0475(2)	0.20348(16)	0.0238
C(3)	0.5693(2)	0.0235(2)	0.30162(17)	0.0354
C(4)	0.8126(2)	0.0216(3)	0.23368(18)	0.0359
C(5)	0.6504(3)	-0.0537(2)	0.13917(18)	0.0418
C(6)	0.6612(2)	0.3545(2)	0.19313(15)	0.0220
C(7)	0.7801(2)	0.4116(2)	0.17259(17)	0.0296
C(8)	0.8034(3)	0.5062(3)	0.22472(19)	0.0394
C(9)	0.7068(3)	0.5485(3)	0.29749(19)	0.0428
C(10)	0.5869(3)	0.4942(3)	0.32033(18)	0.0390
C(11)	0.5655(3)	0.3983(2)	0.26936(17)	0.0320
C(12)	0.7090(2)	0.2372(2)	-0.00498(16)	0.0225
C(13)	0.8520(2)	0.2215(2)	-0.02352(17)	0.0286
C(14)	0.9173(3)	0.2231(2)	-0.12004(18)	0.0339
C(15)	0.8411(3)	0.2384(2)	-0.20203(18)	0.0367
C(16)	0.7001(3)	0.2524(2)	-0.18717(17)	0.0364
C(17)	0.6353(3)	0.2513(2)	-0.08992(16)	0.0287
O(18)	0.45319(14)	0.25746(14)	0.11875(10)	0.0251
C(19)	0.3750(2)	0.3893(2)	0.08179(17)	0.0247
C(20)	0.2245(2)	0.3833(2)	0.09448(15)	0.0230
O(21)	0.17538(16)	0.35808(15)	0.20128(10)	0.0299
C(22)	0.1360(2)	0.2264(2)	0.23339(16)	0.0249
C(23)	0.1954(2)	0.1568(2)	0.33387(15)	0.0244
O(24)	0.12080(15)	0.23115(15)	0.41211(10)	0.0279
S(25)	0.19602(7)	0.30600(6)	0.47273(4)	0.0308
O(26)	0.33953(16)	0.24972(17)	0.47224(11)	0.0370
O(27)	0.11660(18)	0.30176(17)	0.56891(11)	0.0399
C(28)	0.1766(3)	0.4735(2)	0.40187(18)	0.0387
C(29)	0.1781(2)	0.0096(2)	0.37053(16)	0.0275
C(30)	0.2244(3)	-0.0548(2)	0.47720(16)	0.0335
C(31)	0.2371(3)	-0.2072(2)	0.50408(18)	0.0373
O(32)	0.34968(19)	-0.27215(17)	0.44564(12)	0.0464
C(33)	0.1862(2)	0.1535(2)	0.14558(15)	0.0263
C(34)	0.1867(2)	0.2714(2)	0.05234(16)	0.0267

Table 3: Atomic coordinates and isotropic thermal parameters ($Å^2$) of hydrogen atoms

Atom	x	y	z	U_{iso}
H(31)	0.5979(2)	-0.0663(2)	0.34531(17)	0.0498
H(32)	0.5677(2)	0.0934(2)	0.33939(17)	0.0492
H(33)	0.4762(2)	0.0279(2)	0.28294(17)	0.0503
H(41)	0.8347(2)	-0.0703(3)	0.27141(18)	0.0500
H(42)	0.8242(2)	0.0846(3)	0.27605(18)	0.0503
H(43)	0.8770(2)	0.0326(3)	0.17241(18)	0.0507
H(51)	0.6683(3)	-0.1467(2)	0.17902(18)	0.0630
H(52)	0.7163(3)	-0.0448(2)	0.07695(18)	0.0638
H(53)	0.5579(3)	-0.0347(2)	0.11650(18)	0.0637
H(71)	0.8466(2)	0.3850(2)	0.12321(17)	0.0356
H(81)	0.8833(3)	0.5403(3)	0.21003(19)	0.0491
H(91)	0.7209(3)	0.6124(3)	0.33094(19)	0.0536
H(101)	0.5229(3)	0.5213(3)	0.37023(18)	0.0472
H(111)	0.4869(3)	0.3582(2)	0.28688(17)	0.0389
H(131)	0.9070(2)	0.2096(2)	0.03217(17)	0.0350
H(141)	1.0139(3)	0.2117(2)	-0.13045(18)	0.0405
H(151)	0.8835(3)	0.2398(2)	-0.26632(18)	0.0431
H(161)	0.6472(3)	0.2612(2)	-0.24328(17)	0.0425
H(171)	0.5385(3)	0.2586(2)	-0.08050(16)	0.0336
H(191)	0.3930(2)	0.4545(2)	0.11960(17)	0.0287
H(192)	0.4004(2)	0.4224(2)	0.00890(17)	0.0281
H(201)	0.1758(2)	0.4736(2)	0.06171(15)	0.0253
H(221)	0.0352(2)	0.2384(2)	0.24319(16)	0.0290
H(231)	0.2919(2)	0.1656(2)	0.32989(15)	0.0285
H(291)	0.0836(2)	0.0026(2)	0.36901(16)	0.0328
H(292)	0.2326(2)	-0.0408(2)	0.32325(16)	0.0331
H(301)	0.3138(3)	-0.0324(2)	0.48108(16)	0.0399
H(302)	0.1621(3)	-0.0200(2)	0.52617(16)	0.0406
H(311)	0.2483(3)	-0.2420(2)	0.57804(18)	0.0431
H(312)	0.1542(3)	-0.2319(2)	0.48785(18)	0.0441
H(331)	0.2784(2)	0.1016(2)	0.15617(15)	0.0319
H(332)	0.1273(2)	0.0933(2)	0.13949(15)	0.0322
H(341)	0.2512(2)	0.2484(2)	-0.00132(16)	0.0321
H(342)	0.0959(2)	0.3011(2)	0.02536(16)	0.0332
H(1)	0.2258(3)	0.5210(2)	0.43418(18)	0.0572
H(2)	0.42029(19)	-0.25883(17)	0.46337(12)	0.0693
H(4)	0.2155(3)	0.4706(2)	0.33249(18)	0.0574
H(281)	0.0793(3)	0.5090(2)	0.40340(18)	0.0573

Table 4: Anisotropic thermal parameters ($Å^2$)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Si(1)	0.0202(4)	0.0196(4)	0.0249(3)	-0.0051(3)	-0.0044(3)	-0.0032(3)
C(2)	0.0225(14)	0.0200(13)	0.0288(12)	-0.0058(10)	-0.0043(10)	-0.0012(10)
C(3)	0.0336(15)	0.0282(15)	0.0373(14)	0.0026(11)	-0.0018(11)	-0.0006(12)
C(4)	0.0276(15)	0.0316(15)	0.0423(15)	-0.0006(12)	-0.0037(11)	0.0020(12)
C(5)	0.0597(19)	0.0239(15)	0.0439(15)	-0.0086(12)	-0.0072(13)	-0.0088(13)
C(6)	0.0217(13)	0.0206(13)	0.0242(12)	-0.0038(10)	-0.0083(10)	-0.0019(10)
C(7)	0.0333(15)	0.0263(14)	0.0296(13)	-0.0030(11)	-0.0084(11)	-0.0060(12)
C(8)	0.0471(18)	0.0316(16)	0.0450(16)	-0.0022(13)	-0.0178(14)	-0.0188(13)
C(9)	0.070(2)	0.0230(15)	0.0411(16)	-0.0096(12)	-0.0286(15)	-0.0048(15)
C(10)	0.0497(19)	0.0322(16)	0.0358(14)	-0.0161(12)	-0.0125(13)	0.0074(14)
C(11)	0.0325(15)	0.0298(15)	0.0346(14)	-0.0105(11)	-0.0073(11)	-0.0004(12)
C(12)	0.0268(14)	0.0141(12)	0.0289(12)	-0.0073(10)	-0.0050(10)	-0.0043(10)
C(13)	0.0311(15)	0.0258(14)	0.0306(13)	-0.0069(10)	-0.0029(11)	-0.0076(11)
C(14)	0.0342(15)	0.0290(15)	0.0399(15)	-0.0114(12)	0.0053(12)	-0.0091(12)
C(15)	0.0549(19)	0.0220(14)	0.0305(14)	-0.0076(11)	0.0084(13)	-0.0049(13)
C(16)	0.057(2)	0.0243(14)	0.0290(14)	-0.0102(11)	-0.0133(13)	0.0013(13)
C(17)	0.0341(15)	0.0206(13)	0.0332(14)	-0.0098(10)	-0.0077(11)	-0.0007(11)
O(18)	0.0179(9)	0.0191(9)	0.0374(9)	-0.0030(7)	-0.0079(7)	-0.0010(7)
C(19)	0.0238(14)	0.0165(13)	0.0321(13)	-0.0006(10)	-0.0064(10)	-0.0019(10)
C(20)	0.0243(14)	0.0232(13)	0.0194(11)	-0.0006(9)	-0.0030(9)	-0.0027(10)
O(21)	0.0412(11)	0.0231(9)	0.0238(8)	-0.0046(7)	0.0046(7)	-0.0067(8)
C(22)	0.0215(13)	0.0243(14)	0.0286(12)	-0.0042(10)	-0.0023(10)	-0.0043(11)
C(23)	0.0228(13)	0.0261(14)	0.0251(12)	-0.0093(10)	-0.0009(10)	-0.0021(11)
O(24)	0.0305(10)	0.0265(9)	0.0280(8)	-0.0117(7)	0.0008(7)	-0.0027(7)
S(25)	0.0430(4)	0.0226(4)	0.0271(3)	-0.0080(3)	-0.0020(3)	-0.0033(3)
O(26)	0.0376(11)	0.0338(10)	0.0409(10)	-0.0124(8)	-0.0085(8)	-0.0002(8)
O(27)	0.0586(12)	0.0367(11)	0.0243(9)	-0.0114(8)	0.0045(8)	-0.0067(9)
C(28)	0.0570(18)	0.0222(15)	0.0372(14)	-0.0083(11)	-0.0020(13)	-0.0062(13)
C(29)	0.0314(14)	0.0237(14)	0.0287(12)	-0.0069(11)	-0.0028(10)	-0.0061(11)
C(30)	0.0468(17)	0.0264(15)	0.0263(13)	-0.0073(11)	-0.0010(11)	-0.0028(12)
C(31)	0.0520(18)	0.0278(15)	0.0299(13)	-0.0053(11)	-0.0010(12)	-0.0035(13)
O(32)	0.0642(13)	0.0354(11)	0.0375(10)	-0.0134(8)	-0.0045(9)	0.0040(10)
C(33)	0.0274(14)	0.0277(14)	0.0280(12)	-0.0074(10)	-0.0054(10)	-0.0113(11)
C(34)	0.0239(14)	0.0324(15)	0.0250(12)	-0.0049(11)	-0.0051(10)	-0.0070(11)

Table 5: Bond lengths (Å)

Si(1) - C(2)	1.887(2)	C(16) - C(17)	1.387(3)
Si(1) - C(6)	1.872(2)	O(18) - C(19)	1.435(2)
Si(1) - C(12)	1.876(2)	C(19) - C(20)	1.501(3)
Si(1) - O(18)	1.6476(15)	C(20) - O(21)	1.443(2)
C(2) - C(3)	1.530(3)	C(20) - C(34)	1.516(3)
C(2) - C(4)	1.537(3)	O(21) - C(22)	1.437(3)
C(2) - C(5)	1.531(3)	C(22) - C(23)	1.507(3)
C(6) - C(7)	1.392(3)	C(22) - C(33)	1.525(3)
C(6) - C(11)	1.406(3)	C(23) - O(24)	1.486(2)
C(7) - C(8)	1.388(3)	C(23) - C(29)	1.514(3)
C(8) - C(9)	1.373(3)	O(24) - S(25)	1.5728(17)
C(9) - C(10)	1.386(4)	S(25) - O(26)	1.4350(17)
C(10) - C(11)	1.383(3)	S(25) - O(27)	1.4305(15)
C(12) - C(13)	1.401(3)	S(25) - C(28)	1.750(2)
C(12) - C(17)	1.396(3)	C(29) - C(30)	1.521(3)
C(13) - C(14)	1.380(3)	C(30) - C(31)	1.506(3)
C(14) - C(15)	1.375(3)	C(31) - O(32)	1.436(3)
C(15) - C(16)	1.379(3)	C(33) - C(34)	1.529(3)

Note – H atoms have been excluded

Table 6: Bond angles (°)

C(2) - Si(1) - C(6)	112.00(10)	C(15) - C(16) - C(17)	120.2(2)
C(2) - Si(1) - C(12)	108.96(10)	C(12) - C(17) - C(16)	121.7(2)
C(6) - Si(1) - C(12)	112.72(10)	Si(1) - O(18) - C(19)	124.36(13)
C(2) - Si(1) - O(18)	106.64(9)	O(18) - C(19) - C(20)	110.40(17)
C(6) - Si(1) - O(18)	107.18(9)	C(19) - C(20) - O(21)	111.07(17)
C(12) - Si(1) - O(18)	109.10(9)	C(19) - C(20) - C(34)	114.15(19)
Si(1) - C(2) - C(3)	111.30(15)	O(21) - C(20) - C(34)	105.48(17)
Si(1) - C(2) - C(4)	109.58(16)	C(20) - O(21) - C(22)	111.06(17)
C(3) - C(2) - C(4)	108.22(17)	O(21) - C(22) - C(23)	108.62(19)
Si(1) - C(2) - C(5)	109.83(15)	O(21) - C(22) - C(33)	106.00(17)
C(3) - C(2) - C(5)	108.7(2)	C(23) - C(22) - C(33)	114.77(18)
C(4) - C(2) - C(5)	109.14(19)	C(22) - C(23) - O(24)	106.78(17)
Si(1) - C(6) - C(7)	125.08(18)	C(22) - C(23) - C(29)	114.60(19)
Si(1) - C(6) - C(11)	118.54(18)	O(24) - C(23) - C(29)	107.02(17)
C(7) - C(6) - C(11)	116.4(2)	C(23) - O(24) - S(25)	122.01(14)
C(6) - C(7) - C(8)	121.9(2)	O(24) - S(25) - O(26)	110.22(9)
C(7) - C(8) - C(9)	120.3(3)	O(24) - S(25) - O(27)	104.54(10)
C(8) - C(9) - C(10)	119.7(3)	O(26) - S(25) - O(27)	118.82(10)
C(9) - C(10) - C(11)	119.7(2)	O(24) - S(25) - C(28)	104.06(10)
C(6) - C(11) - C(10)	122.0(2)	O(26) - S(25) - C(28)	108.70(12)
Si(1) - C(12) - C(13)	122.62(16)	O(27) - S(25) - C(28)	109.48(11)
Si(1) - C(12) - C(17)	121.13(17)	C(23) - C(29) - C(30)	114.0(2)
C(13) - C(12) - C(17)	116.1(2)	C(29) - C(30) - C(31)	113.8(2)
C(12) - C(13) - C(14)	122.5(2)	C(30) - C(31) - O(32)	111.96(19)
C(13) - C(14) - C(15)	119.7(2)	C(22) - C(33) - C(34)	102.58(18)
C(14) - C(15) - C(16)	119.8(2)	C(20) - C(34) - C(33)	103.45(17)

Note – H atoms have been excluded

Appendix 3

References

1 T. J. Donohoe and P. M. Guyo, *J. Org. Chem.*, 1996, **61**, 7664.

2 T. J. Donohoe, P. M. Guyo, R. L. Beddoes, and M. Helliwell, *J. Chem. Soc., Perkin Trans. 1,* 1998, 667.

3 T. J. Donohoe, R. R. Harji, and R. P. C. Cousins, *Chem. Commun.*, 1999, 141.

4 T. J. Donohoe, P. M. Guyo, and M. Helliwell, *Tetrahedron Lett.*, 1999, **40**, 435.

5 T. J. Donohoe, H. Sintim, L. Sisangia, and J. D. Harling, *Angew. Chem., Int. Edit.,* 2004, **43**, 2293.

6 T. J. Donohoe, A. A. Calabrese, C. A. Stevenson, and T. Ladduwahetty, *J. Chem. Soc., Perkin Trans. 1,* 2000, 3724.

7 T. J. Donohoe, J. B. Guillermin, A. A. Calabrese, and D. S. Walter, *Tetrahedron Lett.*, 2001, **42**, 5841.

8 T. J. Donohoe, J. B. Guillermin, C. Frampton, and D. S. Walter, *Chem. Commun.*, 2000, 465.

9 T. J. Donohoe, J. W. Fisher, and P. J. Edwards, *Org. Lett.*, 2004, **6**, 465.

10 T. J. Donohoe and S. Butterworth, *Angew. Chem., Int. Edit.,* 2003, **42**, 948.

11 T. J. Donohoe and S. Butterworth, *Angew. Chem., Int. Edit.,* 2005, **44**, 4766.

12 T. J. Donohoe, A. J. McRiner, and P. Sheldrake, *Org. Lett.*, 2000, **2**, 3861.

13 T. J. Donohoe, A. J. McRiner, M. Helliwell, and P. Sheldrake, *J. Chem. Soc., Perkin Trans. 1,* 2001, 1435.

14 T. J. Donohoe, D. J. Johnson, L. H. Mace, M. J. Bamford, and O. Ichihara, *Org. Lett.*, 2005, **7**, 435.

15 A. R. Pinder, *Nat. Prod. Rep.*, 1990, **7**, 447.

16 A. R. Pinder, *Nat. Prod. Rep.*, 1992, **9**, 491.

17 A. R. Pinder, *Nat. Prod. Rep.*, 1992, **9**, 17.

18 P. Dowd and S. C. Choi, *J. Am. Chem. Soc.*, 1987, **109**, 3493.

19 A. L. J. Beckwith, D. M. Oshea, S. Gerba, and S. W. Westwood, *Chem. Commun.*, 1987, 666.

20 A. L. J. Beckwith, D. M. Oshea, and S. W. Westwood, *J. Am. Chem. Soc.*, 1988, **110**, 2565.

21 W. Reusch, C. K. Johnson, and J. A. Manner, *J. Am. Chem. Soc.*, 1966, **88**, 2803.

22 H. Riemann, A. S. Capomaggi, T. Strauss, E. P. Oliverto, and D. H. R. Barton, *J. Am. Chem. Soc.*, 1961, **83**, 4481.

23 P. Dowd and W. Zhang, *Chem. Rev.*, 1993, **93**, 2091.

24 A. J. McCarroll and J. C. Walton, *Angew. Chem., Int. Edit.,* 2001, **40**, 2225.

25 L. Yet, *Tetrahedron*, 1999, **55**, 9349.

26 P. Dowd and S. C. Choi, *Tetrahedron Lett.*, 1991, **32**, 565.

27 P. Dowd and S. C. Choi, *Tetrahedron*, 1992, **48**, 4773.

28 P. Dowd and S. C. Choi, *J. Am. Chem. Soc.*, 1987, **109**, 6548.

29 P. Dowd, W. Zhang, and K. Mahmood, *Tetrahedron*, 1995, **51**, 39.

30 P. Dowd and S. C. Choi, *Tetrahedron*, 1989, **45**, 77.

31 W. Zhang, Y. Hua, S. J. Geib, G. Hoge, and P. Dowd, *Tetrahedron*, 1994, **50**, 12579.
32 W. Zhang, M. R. Collins, K. Mahmood, and P. Dowd, *Tetrahedron Lett.*, 1995, **36**, 2729.
33 J. E. Baldwin, R. M. Adlington, and J. Robertson, *Chem. Commun.,* 1988, 1404.
34 J. E. Baldwin, R. M. Adlington, and J. Robertson, *Tetrahedron*, 1989, **45**, 909.
35 J. E. Baldwin, R. M. Adlington, and R. Singh, *Tetrahedron*, 1992, **48**, 3385.
36 J. E. Baldwin, R. M. Adlington, T. W. Kang, E. Lee, and C. J. Schofield, *Chem. Commun.,* 1987, 104.
37 J. E. Baldwin, R. M. Adlington, T. W. Kang, E. Lee, and C. J. Schofield, *Tetrahedron*, 1988, **44**, 5953.
38 W. R. Bowman, A. J. Fletcher, and G. B. S. Potts, *J. Chem. Soc., Perkin Trans. 1,* 2002, 2747.
39 W. Zhang, *Curr. Org. Chem.,*, 2004, **8**, 757.
40 P. Dowd and S. C. Choi, *Tetrahedron Lett.*, 1989, **30**, 6129.
41 P. Dowd and S. C. Choi, *Tetrahedron*, 1991, **47**, 4847.
42 W. R. Bowman and P. J. Westlake, *Tetrahedron*, 1992, **48**, 4027.
43 H. McNab, *Chem. Commun.,* 1990, 543.
44 S. P. Green and D. A. Whiting, *Chem. Commun.,* 1992, 1754.
45 E. Bacque, F. Pautrat, and S. Z. Zard, *Org. Lett.,*, 2003, **5**, 325.
46 D. C. Nonhebel, *Chem. Soc. Rev.*, 1993, **22**, 347.
47 C. Destabel and J. D. Kilburn, *Chem. Commun.,* 1992, 596.
48 C. Destabel, J. D. Kilburn, and J. Knight, *Tetrahedron Lett.*, 1993, **34**, 3151.
49 K. G. Pike, C. Destabel, M. Anson, and J. D. Kilburn, *Tetrahedron Lett.*, 1998, **39**, 5877.
50 D. J. Penfold, K. Pike, A. Genge, M. Anson, J. Kitteringham, and J. D. Kilburn, *Tetrahedron Lett.*, 2000, **41**, 10347.
51 R. J. Boffey, M. Santagostino, W. G. Whittingham, and J. D. Kilburn, *Chem. Commun.*, 1998, 1875.
52 R. J. Boffey, W. G. Whittingham, and J. D. Kilburn, *J. Chem. Soc., Perkin Trans. 1,* 2001, 487.
53 R. J. Boffey, W. G. Whittingham, and J. D. Kilburn, *Tetrahedron Lett.*, 1999, **40**, 5625.
54 F. C. Watson and J. D. Kilburn, *Tetrahedron Lett.*, 2000, **41**, 10341.
55 D. M. Smith, A. Nicolaides, B. T. Golding, and L. Radom, *J. Am. Chem. Soc.*, 1998, **120**, 10223.
56 N. Prevost and M. Shipman, *Org. Lett.,*, 2001, **3**, 2383.
57 N. Prevost and M. Shipman, *Tetrahedron*, 2002, **58**, 7165.
58 T. R. Rheault and M. P. Sibi, *Synthesis*, 2003, 803.
59 D. De Smaele, P. Bogaert, and N. De Kimpe, *Tetrahedron Lett.*, 1998, **39**, 9797.
60 O. Kitagawa, S. Miyaji, Y. Yamada, H. Fujiwara, and T. Taguchi, *J. Org. Chem.*, 2003, **68**, 3184.
61 O. Kitagawa, S. Miyaji, C. Sakuma, and T. Taguchi, *J. Org. Chem.*, 2004, **69**, 2607.
62 A. Johns and J. A. Murphy, *Tetrahedron Lett.*, 1988, **29**, 837.
63 E. C. Sabatino and R. J. Gritter, *J. Org. Chem.*, 1963, **28**, 3437.
64 D. H. R. Barton, R. S. H. Motherwell, and W. B. Motherwell, *J. Chem. Soc., Perkin Trans. 1,* 1981, 2363.
65 R. C. Gash, F. Maccorquodale, and J. C. Walton, *Tetrahedron*, 1989, **45**, 5531.
66 A. Gansauer, T. Lauterbach, and S. Narayan, *Angew. Chem., Int. Edit.,* 2003, **42**, 5556.
67 D. A. Corser, B. A. Marples, and R. K. Dart, *Synlett*, 1992, 987.

68 B. A. Marples and R. C. Toon, *Tetrahedron Lett.*, 1999, **40**, 4873.
69 S. Kim, G. H. Joe, and J. Y. Do, *J. Am. Chem. Soc.*, 1994, **116**, 5521.
70 S. Kim, G. H. Joe, and J. Y. Do, *J. Am. Chem. Soc.*, 1993, **115**, 3328.
71 M. Santagostino and J. D. Kilburn, *Tetrahedron Lett.*, 1995, **36**, 1365.
72 W. R. Bowman, C. F. Bridge, and P. Brookes, *Tetrahedron Lett.*, 2000, **41**, 8989.
73 Y. Yamamoto, M. Ohno, and S. Eguchi, *J. Am. Chem. Soc.*, 1995, **117**, 9653.
74 A. G. Griesbeck, M. Oelgemoller, and J. Lex, *Synlett*, 2000, 1455.
75 D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435.
76 P. M. Weintraub, J. S. Sabol, J. A. Kane, and D. R. Borcherding, *Tetrahedron*, 2003, **59**, 2953.
77 M. G. P. Buffat, *Tetrahedron*, 2004, **60**, 1701.
78 R. W. Bates and K. Sa-Ei, *Tetrahedron*, 2002, **58**, 5957.
79 J. Cossy, *Chem. Rec.*, 2005, **5**, 70.
80 A. R. Pinder, *Nat. Prod. Rep.*, 1987, **4**, 527.
81 A. R. Pinder, *Nat. Prod. Rep.*, 1989, **6**, 515.
82 P. D. Bailey, P. A. Millwood, and P. D. Smith, *Chem. Commun.*, 1998, 633.
83 S. Laschat and T. Dickner, *Synthesis*, 2000, 1781.
84 J. F. Kerwin, G. E. Ullyot, R. C. Fuson, and C. L. Zirkle, *J. Am. Chem. Soc.,* 1947, **69**, 2961.
85 S. D. Ross, *J. Am. Chem. Soc.,* 1947, **69**, 2982.
86 E. M. Schultz, C. M. Robb, and J. M. Sprague, *J. Am. Chem. Soc.,* 1947, **69**, 188.
87 E. M. Schultz and J. M. Sprague, *J. Am. Chem. Soc.,* 1948, **70**, 48.
88 N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, 1965, **30**, 821.
89 R. C. Fuson and C. L. Zirkle, *J. Am. Chem. Soc.,* 1948, **70**, 2760.
90 C. F. Hammer, M. M. Ali, and J. D. Weber, *Tetrahedron*, 1973, **29**, 1767.
91 C. F. Hammer, S. R. Heller, and J. H. Craig, *Tetrahedron*, 1972, **28**, 239.
92 C. F. Hammer and J. D. Weber, *Tetrahedron*, 1981, **37**, 2173.
93 J. Moragues, J. Prieto, R. G. W. Spickett, and A. Vega, *J. Chem. Soc., Perkin Trans. 1,* 1976, 938.
94 A. J. Blackman, C. P. Li, D. C. R. Hockless, B. W. Skelton, and A. H. White, *Tetrahedron*, 1993, **49**, 8645.
95 S. Dutta, H. Abe, S. Aoyagi, C. Kibayashi, and K. S. Gates, *J. Am. Chem. Soc.,* 2005, **127**, 15004.
96 N. DeKimpe, M. Boelens, and J. Contreras, *Tetrahedron Lett.*, 1996, **37**, 3171.
97 N. Dekimpe, M. Boelens, J. Piqueur, and J. Baele, *Tetrahedron Lett.*, 1994, **35**, 1925.
98 R. Gottlich, *Synthesis*, 2000, 1561.
99 G. Heuger, S. Kalsow, and R. Gottlich, *Eur. J. Org. Chem.*, 2002, 1848.
100 R. Gottlich and M. Noack, *Tetrahedron Lett.*, 2001, **42**, 7771.
101 M. Noack and R. Gottlich, *Eur. J. Org. Chem.*, 2002, 3171.
102 J. Helaja and R. Gottlich, *Chem. Commun.*, 2002, 720.
103 J. Cossy, C. Dumas, and D. G. Pardo, *Eur. J. Org. Chem.*, 1999, 1693.
104 J. Cossy, O. Mirguet, D. G. Pardo, and J. R. Desmurs, *Tetrahedron Lett.*, 2001, **42**, 5705.
105 J. Cossy, O. Mirguet, D. G. Pardo, and J. R. Desmurs, *Eur. J. Org. Chem.*, 2002, 3543.
106 O. Calvez, A. Chiaroni, and N. Langlois, *Tetrahedron Lett.*, 1998, **39**, 9447.
107 O. Calvez and N. Langlois, *Tetrahedron Lett.*, 1999, **40**, 7099.
108 D. K. Kim, G. H. Kim, and Y. W. Kim, *J. Chem. Soc., Perkin Trans. 1,* 1996, 803.
109 J. Lee, T. Hoang, S. Lewis, S. A. Weissman, D. Askin, R. P. Volante, and P. J. Reider, *Tetrahedron Lett.*, 2001, **42**, 6223.
110 J. Cossy, C. Dumas, P. Michel, and D. G. Pardo, *Tetrahedron Lett.*, 1995, **36**, 549.

111 N. Langlois and O. Calvez, *Synth. Commun.*, 1998, **28**, 4471.
112 J. Cossy, C. Dumas, and D. G. Pardo, *Synlett*, 1997, 905.
113 J. Cossy, C. Dumas, and D. G. Pardo, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1343.
114 J. Cossy, O. Mirguet, and D. G. Pardo, *Synlett*, 2001, 1575.
115 A. Dondoni, B. Richichi, A. Marra, and D. Perrone, *Synlett*, 2004, 1711.
116 S. Kim and J. Y. Yoon, *Synthesis*, 2000, 1622.
117 P. Yates and S. Danishefski, *J. Am. Chem. Soc.*, 1962, **84**, 879.
118 J. M. Wilt, J. F. Zawadski, and D. G. Schultenover, *J. Org. Chem.*, 1966, **31**, 876.
119 J. W. Wilt, J. M. Kosturik, and R. C. Orlowski, *J. Org. Chem.*, 1965, **30**, 1052.
120 R. H. Reitsema, *J. Am. Chem. Soc.*, 1949, **71**, 2041.
121 K. A. Tehrani, K. Van Syngel, M. Boelens, J. Contreras, N. De Kimpe, and D. W. Knight, *Tetrahedron Lett.*, 2000, **41**, 2507.
122 N. DeKimpe, C. Stevens, and M. Virag, *Tetrahedron*, 1996, **52**, 3303.
123 F. G. West and B. N. Naidu, *J. Am. Chem. Soc.*, 1993, **115**, 1177.
124 F. G. West and B. N. Naidu, *J. Org. Chem.*, 1994, **59**, 6051.
125 W. D. Ollis, M. Rey, and I. O. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1009.
126 F. G. West and B. N. Naidu, *J. Am. Chem. Soc.*, 1994, **116**, 8420.
127 B. N. Naidu and F. G. West, *Tetrahedron*, 1997, **53**, 16565.
128 J. A. Vanecko and F. G. West, *Org. Lett.*, 2002, **4**, 2813.
129 J. A. Vanecko and F. G. West, *Org. Lett.*, 2005, **7**, 2949.
130 F. Outurquin, X. Pannecoucke, B. Berthe, and C. Paulmier, *Eur. J. Org. Chem.*, 2002, 1007.
131 F. Couty, F. Durrat, and D. Prim, *Tetrahedron Lett.*, 2003, **44**, 5209.
132 B. Alcaide, P. Almendros, C. Aragoncillo, and N. R. Salgado, *J. Org. Chem.*, 1999, **64**, 9596.
133 H. H. Wasserman and A. W. Tremper, *Tetrahedron Lett.*, 1977, 1449.
134 H. H. Wasserman, A. W. Tremper, and J. S. Wu, *Tetrahedron Lett.*, 1979, 1089.
135 H. H. Wasserman, W. T. Han, J. M. Schaus, and J. W. Faller, *Tetrahedron Lett.*, 1984, **25**, 3111.
136 W. Van Brabandt and N. De Kimpe, *J. Org. Chem.*, 2005, **70**, 3369.
137 W. Van Brabandt and N. De Kimpe, *J. Org. Chem.*, 2005, **70**, 8717.
138 Y. Ito, S. Fujii, M. Nakatsuka, F. Kawamoto, and T. Saegusa, *Organic Syntheses*, 1988, **6**, 327.
139 M. Shirai, S. Okamoto, and F. Sato, *Tetrahedron Lett.*, 1999, **40**, 5331.
140 A. Brandi, A. Goti, S. Kozhushkov, and A. Demeijere, *Chem. Commun.*, 1994, 2185.
141 A. Goti, B. Anichini, A. Brandi, A. Demeijere, L. Citti, and S. Nevischi, *Tetrahedron Lett.*, 1995, **36**, 5811.
142 S. Mangelinckx and N. De Kimpe, *Synlett*, 2005, 1521.
143 A. L. Logothetis, *J. Am. Chem. Soc.*, 1965, **87**, 749.
144 D. E. Horning and Muchowsk.Jm, *Can. J. Chem., Rev. Can. Chim.*, 1974, **52**, 1321.
145 K. E. Harding and S. R. Burks, *J. Org. Chem.*, 1984, **49**, 40.
146 J. Ahman and P. Somfai, *J. Am. Chem. Soc.*, 1994, **116**, 9781.
147 I. Coldham, A. J. Collis, R. J. Mould, and R. E. Rathmell, *Tetrahedron Lett.*, 1995, **36**, 3557.
148 J. Ahman and P. Somfai, *Tetrahedron Lett.*, 1995, **36**, 303.
149 S. J. Hedley, W. J. Moran, A. Prenzel, D. A. Price, and J. P. A. Harrity, *Synlett*, 2001, 1596.
150 S. J. Hedley, W. J. Moran, D. A. Price, and J. P. A. Harrity, *J. Org. Chem.*, 2003, **68**, 4286.
151 P. Davoli, A. Forni, I. Moretti, F. Prati, and G. Torre, *Tetrahedron*, 2001, **57**, 1801.

152 J. G. Knight, S. W. Ainge, A. M. Harm, S. J. Harwood, H. I. Maughan, D. R. Armour, D. M. Hollinshead, and A. A. Jaxa-Chamiec, *J. Am. Chem. Soc.,* 2000, **122**, 2944.
153 F. Machetti, F. M. Cordero, F. De Sarlo, and A. Brandi, *Tetrahedron*, 2001, **57**, 4995.
154 M. A. Ciufolini, C. Y. W. Hermann, Q. Dong, T. Shimizu, S. Swaminathan, and N. Xi, *Synlett*, 1998, 105.
155 J. M. Harris and A. Padwa, *J. Org. Chem.*, 2003, **68**, 4371.
156 C. B. Wooster and K. L. Godfrey, *J. Am. Chem. Soc.,* 1937, **59**, 596.
157 A. J. Birch, *J. Chem. Soc.,* 1944, 430.
158 J. M. Hook and L. N. Mander, *Nat. Prod. Rep.,* 1986, **3**, 35.
159 D. F. Taber and R. W. Korsmeyer, *J. Org. Chem.,* 1978, **43**, 4925.
160 P. W. Rabideau and Z. Marcinow, *Organic Reactions*, 1992, **42**, 1.
161 S. Siegel, 'Comprehensive Organic Synthesis', ed. B. M. Trost and I. Fleming, Peragmon, 1991.
162 G. W. Gribble, 'Comprehensive Organic Synthesis', ed. B. M. Trost and I. Fleming, Pergamon, 1991.
163 T. J. Donohoe, R. Garg, and C. A. Stevenson, *Tetrahedron. Asymm.*, 1996, **7**, 317.
164 A. J. Birch and J. Slobbe, *Heterocycles*, 1976, **5**, 905.
165 T. J. Donohoe and D. House, *J. Org. Chem.,* 2002, **67**, 5015.
166 T. J. Donohoe and D. House, *Tetrahedron Lett.*, 2003, **44**, 1095.
167 T. J. Donohoe, D. House, and K. W. Ace, *Org. Biomol. Chem.*, 2003, **1**, 3749.
168 A. J. M^{c}Riner, 'Studies Towards the Synthesis of Stable Dihydro- and Tetrahydro-Pyridines', University of Manchester, Manchester, 2000.
169 D. P. Curran and C. T. Chang, *J. Org. Chem.,* 1989, **54**, 3140.
170 K. E. Harding, L. M. May, and K. F. Dick, *J. Org. Chem.,* 1975, **40**, 1664.
171 K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.,* 1946, 39.
172 C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.,* 1956, **21**, 1547.
173 D. Milstein and J. K. Stille, *J. Am. Chem. Soc.,* 1978, **100**, 3636.
174 J. E. Leibner and J. Jacobus, *J. Org. Chem.,* 1979, **44**, 449.
175 D. H. R. Barton, J. Kervagoret, and S. Z. Zard, *Tetrahedron*, 1990, **46**, 7587.
176 Q. Q. Chen, T. Y. Wang, Y. Zhang, Q. A. Wang, and J. S. Ma, *Synth. Commun.*, 2002, **32**, 1031.
177 D. Crich and S. X. Sun, *J. Org. Chem.,* 1996, **61**, 7200.
178 P. Renaud, E. Lacote, and L. Quaranta, *Tetrahedron Lett.,* 1998, **39**, 2123.
179 B. S. Edelson, B. M. Stoltz, and E. J. Corey, *Tetrahedron Lett.,* 1999, **40**, 6729.
180 J. Robertson, M. A. Peplow, and J. Pillai, *Tetrahedron Lett.,* 1996, **37**, 5825.
181 J. M. Berge and S. M. Roberts, *Synthesis,* 1979, 471.
182 W. P. Neumann, *Synthesis,* 1987, 665.
183 B. Giese, *Angew. Chem., Int. Edit.* 1985, **24**, 553.
184 J. R. Liddell, *Nat. Prod. Rep.,* 2001, **18**, 441.
185 J. P. Michael, *Nat. Prod. Rep.,* 2002, **19**, 719.
186 J. P. Michael, *Nat. Prod. Rep.,* 2003, **20**, 458.
187 J. P. Michael, *Nat. Prod. Rep.,* 2004, **21**, 625.
188 S. H. Chung, M. S. Cho, J. Y. Choi, D. W. Kwon, and Y. H. Kim, *Synlett*, 2001, 1266.
189 M. Sugi, D. Sakuma, and H. Togo, *J. Org. Chem.*, 2003, **68**, 7629.
190 P. K. Freeman and L. L. Hutchinson, *J. Org. Chem.,* 1980, **45**, 1924.
191 J. Stapersma and G. W. Klumpp, *Tetrahedron*, 1981, **37**, 187.
192 N. Hommes, F. Bickelhaupt, and G. W. Klumpp, *Tetrahedron Lett.,* 1988, **29**, 5237.
193 C. P. Vlaar and G. W. Klumpp, *Tetrahedron Lett.,* 1991, **32**, 2951.
194 D. J. Rawson and A. I. Meyers, *Tetrahedron Lett.,* 1991, **32**, 2095.

195 C. E. Banks, R. G. Evans, J. Rodrigues, P. G. Turner, T. J. Donohoe, and R. G. Compton, *Tetrahedron*, 2005, **61**, 2365.
196 I. Fleming, 'Frontier Orbitals and Organic Reactions', John Wiley and Sons, 1976.
197 S. Kashimura, Y. Murai, M. Ishifune, H. Masuda, H. Murase, and T. Shono, *Tetrahedron Lett.,* 1995, **36**, 4805.
198 Y. Shimizu, *Chem. Rev.*, 1993, **93**, 1685.
199 T. Yasumoto and M. Murata, *Chem. Rev.*, 1993, **93**, 1897.
200 P. J. Scheuer, *Tetrahedron*, 1994, **50**, 3.
201 M. Murata and T. Yasumoto, *Nat. Prod. Rep.*, 2000, **17**, 293.
202 Y. Shimizu, *Curr. Opin. Microbiol.*, 2003, **6**, 236.
203 A. Abiko, J. F. Liu, and S. Masamune, *J. Org. Chem.*, 1996, **61**, 2590.
204 T. Yasumoto, *Chem. Rec.*, 2001, **1**, 228.
205 Y. Y. Lin, M. Risk, S. M. Ray, D. Vanengen, J. Clardy, J. Golik, J. C. James, and K. Nakanishi, *J. Am. Chem. Soc.*, 1981, **103**, 6773.
206 M. S. Lee, D. J. Repeta, K. Nakanishi, and M. G. Zagorski, *J. Am. Chem. Soc.*, 1986, **108**, 7855.
207 M. S. Lee, G. W. Qin, K. Nakanishi, and M. G. Zagorski, *J. Am. Chem. Soc.*, 1989, **111**, 6234.
208 H. N. Chou and Y. Shimizu, *J. Am. Chem. Soc.*, 1987, **109**, 2184.
209 K. Fujiwara and A. Murai, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 2129.
210 N. Hayashi, K. Fujiwara, and A. Murai, *Tetrahedron*, 1997, **53**, 12425.
211 T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smithpalmer, and Y. Kishi, *J. Am. Chem. Soc.*, 1978, **100**, 2933.
212 J. P. Michael, P. C. Ting, and P. A. Bartlett, *J. Org. Chem.*, 1985, **50**, 2416.
213 P. A. Bartlett and P. C. Ting, *J. Org. Chem.*, 1986, **51**, 2230.
214 M. A. Brimble and M. K. Edmonds, *Tetrahedron*, 1995, **51**, 9995.
215 M. A. Brimble and H. Prabaharan, *J. Chem. Soc., Perkin Trans. 1,* 1999, 2795.
216 T. Inagaki, Y. Nakamura, M. Sawaguchi, N. Yoneda, S. Ayuba, and S. Hara, *Tetrahedron Lett.*, 2003, **44**, 4117.
217 P. J. Kocienski, R. C. D. Brown, A. Pommier, M. Procter, and B. Schmidt, *J. Chem. Soc., Perkin Trans. 1,* 1998, 9.
218 T. Nakata, S. Nomura, and H. Matsukura, *Tetrahedron Lett.*, 1996, **37**, 213.
219 N. Hori, K. Nagasawa, T. Shimizu, and T. Nakata, *Tetrahedron Lett.*, 1999, **40**, 2145.
220 T. Nakata, S. Nomura, and H. Matsukura, *Chem. Pharm. Bull.*, 1996, **44**, 627.
221 K. Nagasawa, N. Hori, R. Shiba, and T. Nakata, *Heterocycles*, 1997, **44**, 105.
222 G. Matsuo, N. Hori, H. Matsukura, and T. Nakata, *Tetrahedron Lett.*, 2000, **41**, 7677.
223 T. Nakata, S. Nomura, H. Matsukura, and M. Morimoto, *Tetrahedron Lett.*, 1996, **37**, 217.
224 S. Takahashi, K. Fujisawa, N. Sakairi, and T. Nakata, *Heterocycles*, 2000, **53**, 1361.
225 M. Morimoto, H. Matsukura, and T. Nakata, *Tetrahedron Lett.*, 1996, **37**, 6365.
226 K. Nagasawa, N. Hori, H. Koshino, and T. Nakata, *Heterocycles*, 1999, **50**, 919.
227 Y. Sakamoto, M. Koshizuka, H. Koshino, and T. Nakata, *Heterocycles*, 2002, **56**, 113.
228 A. Padwa, N. C. Das, and D. Eastman, *J. Am. Chem. Soc.,* 1969, **91**, 5178.
229 H. Morita and S. Oae, *Tetrahedron Lett.*, 1969, **10**, 1347.
230 H. G. Richey and D. V. Kinsman, *Tetrahedron Lett.*, 1969, **10**, 2505.
231 F. David, *J. Org. Chem.*, 1981, **46**, 3512.
232 N. Hayashi, H. Noguchi, and S. Tsuboi, *Tetrahedron*, 2000, **56**, 7123.
233 N. Hayashi, K. Fujiwara, and A. Murai, *Chem. Lett.*, 1996, 341.
234 N. Hayashi, K. Fujiwara, and A. Murai, *Tetrahedron Lett.*, 1996, **37**, 6173.
235 N. Hayashi, K. Fujiwara, and A. Murai, *Synlett*, 1997, 793.

236 M. Tokumasu, A. Sasaoka, R. Takagi, Y. Hiraga, and K. Ohkata, *Chem. Commun.*, 1997, 875.
237 K. M. Nicholas, *Accounts Chem. Res.*, 1987, **20**, 207.
238 B. J. Teobald, *Tetrahedron*, 2002, **58**, 4133.
239 C. Mukai, Y. Ikeda, Y. Sugimoto, and M. Hanaoka, *Tetrahedron Lett.*, 1994, **35**, 2179.
240 C. Mukai, Y. Sugimoto, Y. Ikeda, and M. Hanaoka, *Tetrahedron*, 1998, **54**, 823.
241 M. Isobe, R. Nishizawa, S. Hosokawa, and T. Nishikawa, *Chem. Commun.*, 1998, 2665.
242 S. Takai, N. Sawada, and M. Isobe, *J. Org. Chem.*, 2003, **68**, 3225.
243 J. M. Betancort, T. Martin, J. M. Palazon, and V. S. Martin, *J. Org. Chem.*, 2003, **68**, 3216.
244 F. R. P. Crisostomo, T. Martin, and V. S. Martin, *Org. Lett.*, 2004, **6**, 565.
245 K. C. Nicolaou, C. V. C. Prasad, P. K. Somers, and C. K. Hwang, *J. Am. Chem. Soc.*, 1989, **111**, 5330.
246 K. C. Nicolaou, G. Q. Shi, J. L. Gunzner, P. Gartner, P. A. Wallace, M. A. Ouellette, S. H. Shi, M. E. Bunnage, K. A. Agrios, C. A. Veale, C. K. Hwang, J. Hutchinson, C. V. C. Prasad, W. W. Ogilvie, and Z. Yang, *Chem.-Eur. J.*, 1999, **5**, 628.
247 H. Matsukura, M. Morimoto, and T. Nakata, *Chem. Lett.*, 1996, 487.
248 T. Suzuki, O. Sato, and M. Hirama, *Tetrahedron Lett.*, 1990, **31**, 4747.
249 P. F. Hudrlik, A. M. Hudrlik, R. J. Rona, R. N. Misra, and G. P. Withers, *J. Am. Chem. Soc.*, 1977, **99**, 1993.
250 T. P. Heffron and T. F. Jamison, *Org. Lett.*, 2003, **5**, 2339.
251 Y. Mori, K. Yaegashi, and H. Furukawa, *J. Am. Chem. Soc.*, 1996, **118**, 8158.
252 Y. Mori, K. Yaegashi, and H. Furukawa, *J. Am. Chem. Soc.*, 1997, **119**, 4557.
253 Y. Mori, K. Yaegashi, and H. Furukawa, *J. Org. Chem.*, 1998, **63**, 6200.
254 K. Fujiwara, T. Tokiwano, and A. Murai, *Tetrahedron Lett.*, 1995, **36**, 8063.
255 M. H. Wu, K. B. Hansen, and E. N. Jacobsen, *Angew. Chem., Int. Edit.*, 1999, **38**, 2012.
256 D. J. Fox, D. House, and S. Warren, *Angew. Chem., Int. Edit.*, 2002, **41**, 2462.
257 L. Djakovitch, J. Eames, R. V. H. Jones, S. McIntyre, and S. Warren, *Tetrahedron Lett.*, 1995, **36**, 1723.
258 P. Bird, J. Eames, A. G. Fallis, R. V. H. Jones, M. Roddis, C. F. Sturino, S. Osullivan, S. Warren, M. S. Westwell, and J. Worrall, *Tetrahedron Lett.*, 1995, **36**, 1909.
259 D. House, F. Kerr, and S. Warren, *Chem. Commun.*, 2000, 1779.
260 Y. Takemoto, T. Ibuka, H. Hayase, A. Iwanaga, S. Yamagata, C. Iwata, and T. Tanaka, *Tetrahedron Lett.*, 1998, **39**, 7545.
261 A. Itoh, Y. Hirose, H. Kashiwagi, and Y. Masaki, *Heterocycles*, 1994, **38**, 2165.
262 S. G. Kim, J. Y. Yoon, and C. M. Cho, *Chem. Commun.*, 1996, 909.
263 E. Klein and W. Rojahn, *Tetrahedron*, 1965, **21**, 2353.
264 D. M. Walba, M. D. Wand, and M. C. Wilkes, *J. Am. Chem. Soc.*, 1979, **101**, 4396.
265 J. E. Baldwin, M. J. Crossley, and E. M. M. Lehtonen, *Chem. Commun.*, 1979, 918.
266 S. Wolfe and C. F. Ingold, *J. Am. Chem. Soc.*, 1981, **103**, 940.
267 D. M. Walba and G. S. Stoudt, *Tetrahedron Lett.*, 1982, **23**, 727.
268 M. de Champdore, M. Lasalvia, and V. Piccialli, *Tetrahedron Lett.*, 1998, **39**, 9781.
269 P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3936.
270 V. Piccialli and N. Cavallo, *Tetrahedron Lett.*, 2001, **42**, 4695.
271 V. Piccialli and T. Caserta, *Tetrahedron Lett.*, 2004, **45**, 303.
272 T. J. Donohoe, J. J. G. Winter, M. Helliwell, and G. Stemp, *Tetrahedron Lett.*, 2001, **42**, 971.

273 H. C. Kolb, M. S. Vannieuwenhze, and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
274 D. M. Walba, C. A. Przybyla, and C. B. Walker, *J. Am. Chem. Soc.*, 1990, **112**, 5624.
275 A. R. L. Cecil and R. C. D. Brown, *Org. Lett.*, 2002, **4**, 3715.
276 R. C. D. Brown, C. J. Bataille, R. M. Hughes, A. Kenney, and T. J. Luker, *J. Org. Chem.*, 2002, **67**, 8079.
277 R. C. D. Brown and J. F. Keily, *Angew. Chem., Int. Edit.*, 2001, **40**, 4496.
278 S. Butterworth, University of Oxford, Oxford, 2004.
279 A. Bouzide and G. Sauve, *Tetrahedron Lett.*, 1997, **38**, 5945.
280 F. Perron and K. F. Albizati, *Chem. Rev.*, 1989, **89**, 1617.
281 B. E. Evans, K. E. Rittle, M. G. Bock, R. M. Dipardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer, and J. Hirshfield, *J. Med. Chem.*, 1988, **31**, 2235.
282 M. Buck and J. M. Chong, *Tetrahedron Lett.*, 2001, **42**, 5825.
283 M. F. Buffet, D. J. Dixon, S. V. Ley, D. J. Reynolds, and R. I. Storer, *Org. Biomol. Chem.*, 2004, **2**, 1145.
284 A. K. Chatterjee, T. L. Choi, D. P. Sanders, and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360.
285 J. R. Vyvyan, J. A. Meyer, and K. D. Meyer, *J. Org. Chem.*, 2003, **68**, 9144.
286 B. M. Trost and Y. Li, *J. Am. Chem. Soc.*, 1996, **118**, 6625.
287 A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, and F. J. Timmers, *Organometallics*, 1996, **15**, 1518.
288 P. J. Alaimo, D. W. Peters, J. Arnold, and R. G. Bergman, *J. Chem. Educ.*, 2001, **78**, 64.
289 D. J. Spielvogel, W. M. Davis, and S. L. Buchwald, *Organometallics*, 2002, **21**, 3833.
290 D. D. Perrin and W. L. F. Armarego, 'Purification of Laboratory Chemicals', Pergamon Press, 1988.
291 W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
292 D. M. Wallace, S. H. Leung, M. O. Senge, and K. M. Smith, *J. Org. Chem.*, 1993, **58**, 7245.
293 D. M. Bailey, R. E. Johnson, and N. F. Albertson, *Org. Synth*, 1988, **50-9**, 618.
294 J. W. Harbuck and H. Rapoport, *J. Org. Chem.*, 1972, **37**, 3618.
295 G. G. Kleinspehn, *J. Am. Chem. Soc.*, 1955, **77**, 1546.
296 E. Alonso, D. J. Ramon, and M. Yus, *Tetrahedron*, 1997, **53**, 14355.
297 H. Sajiki and K. Hirota, *Tetrahedron*, 1998, **54**, 13981.
298 L. Albarella, D. Musumeci, and D. Sica, *Eur. J. Org. Chem.*, 2001, 997.
299 W. Boland, P. Ney, and L. Jaenicke, *Synthesis*, 1980, 1015.
300 R. G. Salomon, D. J. Coughlin, S. Ghosh, and M. G. Zagorski, *J. Am. Chem. Soc.*, 1982, **104**, 998.