Desymmetrisation reactions of cyclohexa-1,4-dienes and marine natural product synthesis

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Abstract

This thesis describes novel diastereoselective group selective processes for the desymmetrisation of cyclohexa-1,4-dienes, and their application to target synthesis of the cladiellin diterpenes. In addition, an enantioselective approach to batzelladine C methyl ester is described, permitting stereochemical assignment of batzelladine C.

Chapter 1 describes the use of diastereoselective iodocyclisation reactions for the desymmetrisation of cyclohexa-1,4-dienes, and also details a novel epoxidation-cyclisation transformation, enabling the formation of up to six contiguous stereogenic centres, selectively, in a single step.

Chapter 2 introduces the cladiellin diterpenes and describes the application of novel diastereoselective Prins chemistry for the synthesis of a model of the cladiellin core.

Chapter 3 describes our attempts at elaborating the cladiellin model to approach the cladiellin framework and discusses an unexpected but interesting Prins cyclisation/rearrangement process.

Chapter 4 describes an enantioselective synthesis of batzelladine C methyl ester, permitting assignment of the relative and absolute stereochemistry of batzelladine C.

Acknowledgements

Firstly, I would like to thank Mark for providing me with this excellent project to work on, for all the help and support over the past three years and for always letting me pick the music! It's been great working for you.

I'd also like to thank Mike Butters at AstraZeneca for his input into the project and for his help while I was on placement, as well as for all the lovely free lunches!

Thanks to all the past and present members of the group and labs 1.107 and 1.119 for all the interesting discussion and advice.

Thank you to all the staff, particularly Rob and Robin for general help with MS and NMR, for always bumping important MS samples up the queue for me and for helping me try to get *that* ^{13}C NMR spectrum!

Finally, a big thank you to my parents for their constant love and support, and to all my family and friends.

Dedication

In memory of Rob 'Mags' McGowan (1983-2008)

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Abbreviations

Ac	Acetyl
acac	Acetylacetonate
APCI	Atmospheric Pressure Chemical Ionisation
AIBN	2,2'-Azobisisobutyronitrile
Bn	Benzyl
Cbz	Benzyloxycarbonyl
9-BBN	9-Borabicyclo[3.3.1]nonane
n-Bu	*n*-Butyl
t-Bu	*t*-Butyl
BHT	Butylated hydroxytoluene
CDI	Carbonyldiimidazole
m-CPBA	*m*-Chloroperoxybenzoic acid
CD4	Cluster of Differentiation 4
COSY	Correlation Spectroscopy
cAMP	Cyclic adenosine monophosphate
d.r.	Diastereomeric ratio
4-DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
DMM	Di(propylene glycol) dimethyl ether
EI	Electron Impact
ES	Electrospray
e.e.	Enantiomeric excess

equiv.	Equivalents
Et	Ethyl
EDTA	Ethylenediaminetetraacetic Acid
gp120	Glycoprotein 120
HMBC	Heteronuclear Multiple Bond Correlation
HSQC	Heteronuclear Single Quantum Correlation
HIV	Human Immunodeficiency Virus
*i*Pr	Isopropyl
LHMDS	Lithium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
MS	Mass Spectrometry
Men	Menthyl
PMB	*p*-Methoxybenzyl
Me	Methyl
NMO	4-Methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Enhancement Spectroscopy
Ph	Phenyl
PDC	Pyridinium dichromate
PPTS	Pyridinium *p*-toluenesulfonate
Boc	*tert*-Butoxycarbonyl
TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TBAF	Tetrabutylammonium fluoride

THF	Tetrahydrofuran
TMEDA	N,N,N',N'-Tetramethylethylenediamine
TFA	Trifluoroacetic acid
Tf	Trifluoromethanesulfonyl
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl

Chapter 1

Iodocyclisation and Epoxidation-Cyclisation Reactions of Cyclohexa-1,4-dienes

1.1 Introduction

The desymmetrisation of cyclohexa-1,4-dienes provides a very efficient way of developing complex compounds from simple precursors in a single transformation. The ability to distinguish between the two double bonds permits the selective formation of at least two new stereogenic centres.

Enantioselective desymmetrisation of achiral cyclohexa-1,4-dienes can be effected by use of a chiral catalyst or reagent (**Figure 1**).

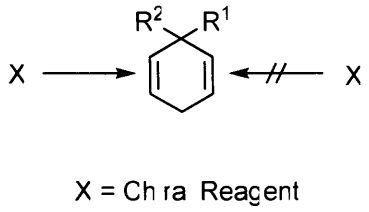
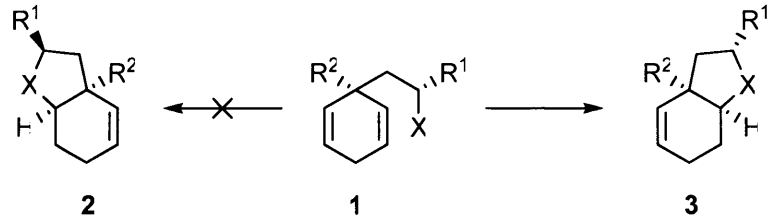


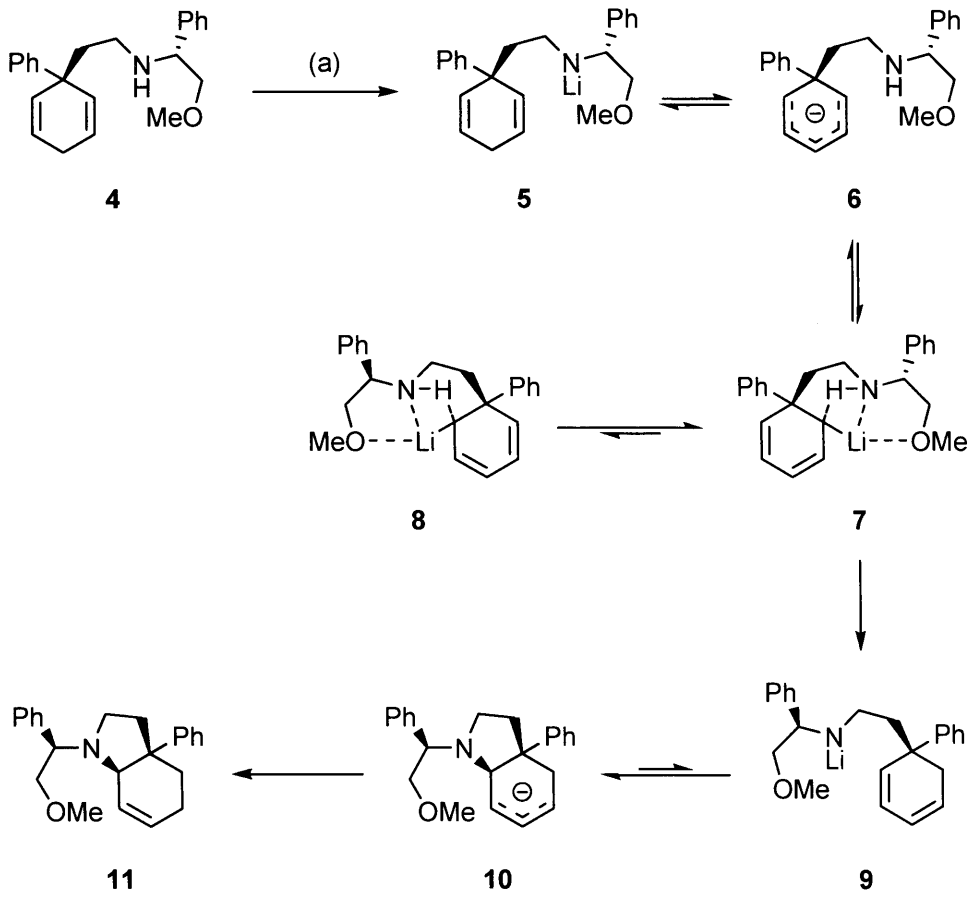
Figure 1. Enantioselective desymmetrisation of cyclohexa-1,4-dienes.

Alternatively, a pre-existing stereogenic centre within the cyclohexadiene system can be used to facilitate diastereotopic group selection (**Scheme 1**).



Scheme 1. Diastereotopic group selection for desymmetrisation.

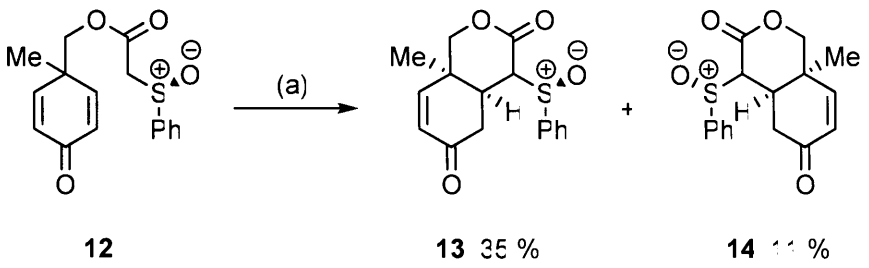
There is a wealth of methodology in this area and the desymmetrisation of cyclohexa-1,4-dienes has been the subject of a number of reviews.[1] More recent literature includes an intramolecular hydroamination desymmetrisation sequence pioneered by Landais and co-workers (**Scheme 2**).[2]



Scheme 2. *Reagents and Conditions*: (a) *n*-BuLi (20 mol %), THF, 20 °C, 4 h; 95 % yield, >95 % d.e.

Treatment of secondary amine **4** with catalytic *n*-butyllithium results in the formation of allylic amine **11** with very high levels of regio- and diastereocontrol. Formation of the allylic amine indicates that the reaction is not simply a direct hydroamination of one of the diastereotopic double bonds. In fact, Landais suggests that treatment of the amine **4** with strong base permits removal of both the amine and cyclohexadienyl protons, resulting in an equilibrium between the cyclohexadienyl anion **6** and the amide anion **5**. The cyclohexadienyl anion **6** can subsequently undergo diastereoselective protonation from the secondary amine and the resulting lithium amide **9** adds selectively to the 1,3-diene on the other side of the ring, as summarised in **Scheme 2**.

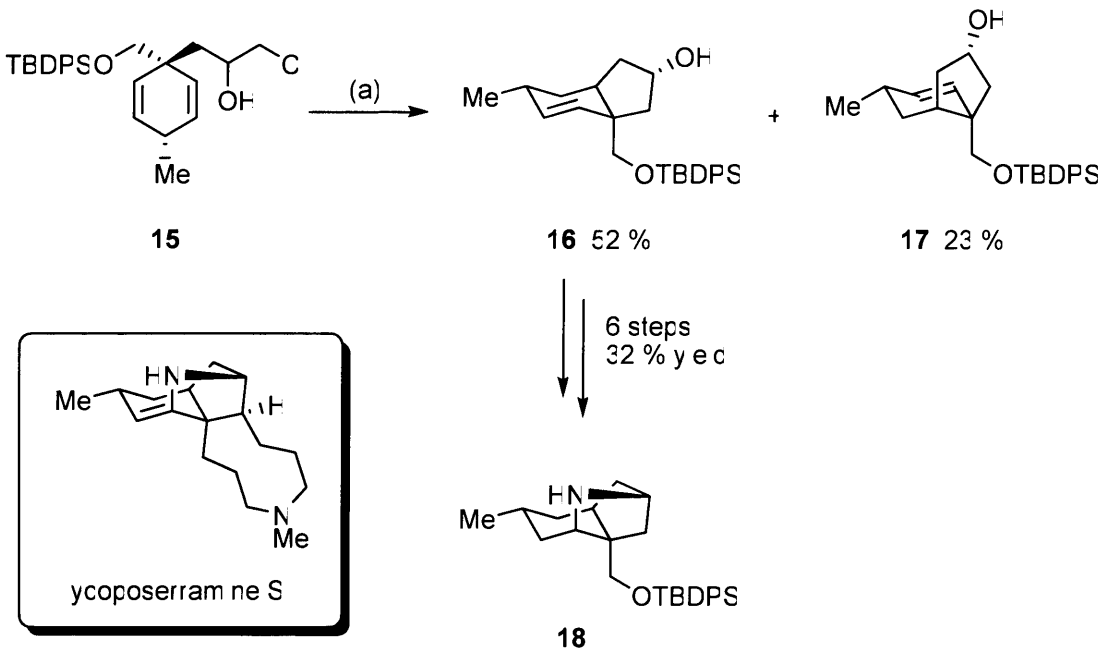
Work within our own group has yielded extensive methodology for the desymmetrisation of cyclohexa-1,4-dienes. Examples include chiral sulfoxide directed conjugate addition to a cyclohexadienone **12**, which proceeds with moderate diastereocontrol, as shown in **Scheme 3**.[3]



12 **13** 35 % **14** 11 %

Scheme 3. *Reagents and Conditions*: (a) *t*-BuOK, THF, room temperature.

A diastereoselective free-radical cyclisation reaction has also been developed,[4] which has recently been employed in the synthesis of the tricyclic core **18** of lycoposerramine S (**Scheme 4**).[5]



15 **16** 52 % **17** 23 %

18

Scheme 4. *Reagents and Conditions*: (a) Bu_3SnH, AIBN, benzene, reflux, 18 h.

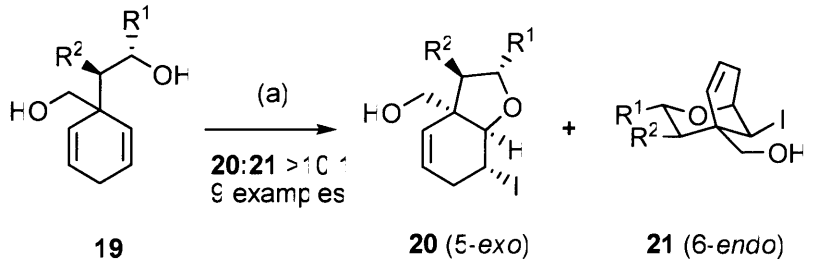
More recent examples include group selective iodocyclisation[6] and Prins chemistry,[7a,b] which will be discussed later in this chapter and subsequent chapters.

1.2 Iodocyclisations

1.2.1 Introduction

Iodocyclisation reactions have been shown to allow formation of a variety of heterocyclic ring sizes, often with excellent sterocontrol.[8] Previous work within the Elliott group has shown that chiral cyclohexa-1,4-diene derived substrates will undergo desymmetrisation by haloetherification reactions with essentially complete diastereocontrol.[6] A range of products of varying ring sizes, formed via both *exo* and *endo* cyclisation modes are permitted with the stereochemistry dictated by chirality present within the tethering chain.

For example, chiral diols **19**, with a range of substituents in the R^1 and R^2 positions, give predominantly 5-*exo* cyclisation products **20**, with some 6-*endo* products **21**, as single diastereoisomers, when submitted to standard reaction conditions (**Scheme 5**).



19 **20** (5-*exo*) **21** (6-*endo*)

Scheme 5. *Reagents and Conditions:* (a) I_2, base, CH_3CN; 60 – 90 % yields.

This preference for 5-*exo* cyclisation is of course expected, owing to Baldwin's rules.[9] In this case, the 5-*exo* cyclisation mode presents a much more

favourable transition state geometry than the 6-*endo* mode in which the bond angles of the transition state would be severely distorted in order to achieve the necessary trajectory of attack (**Figure 2**).

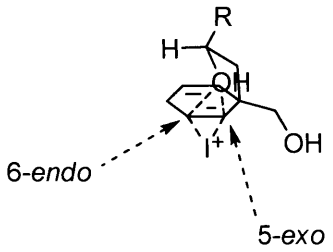


Figure 2. Regioselectivity of iodocyclisation.

The diastereoselectivity of these reactions can be explained by interaction of the substituent on the tethering chain with the cyclohexadiene ring. While cyclisation can proceed onto either double bond, one results in a large steric interaction between the substituent and the ring, drastically destabilising the transition state. Hence the favoured geometry of attack is that in which the substituent is furthest from the cyclohexadiene ring (**Figure 3**). As a result, cyclisation occurs onto only one of the diastereotopic double bonds, giving complete diastereocontrol.

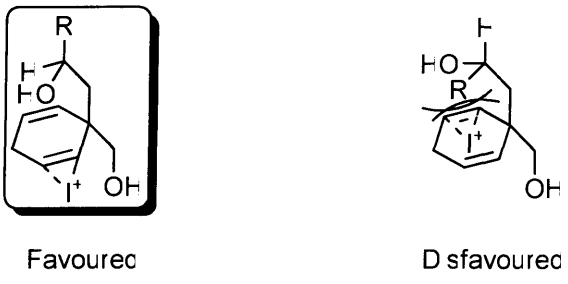
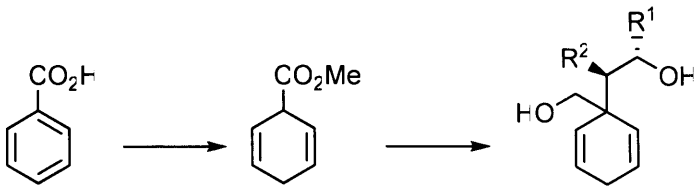


Figure 3. Diastereoselectivity of iodocyclisation.

The requisite substrates for these cyclisation reactions are yielded via a Birch reduction/ alkylation sequence[10] of benzoic acid (**Scheme 6**). As such, all contain a carbon quaternary centre, with a hydroxymethyl group in addition to the chiral tethering chain.



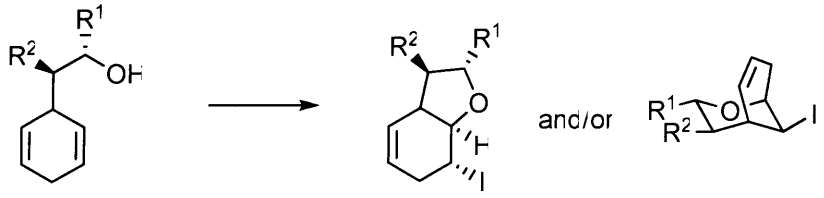
22 23 19

Scheme 6. Birch Reduction/ alkylation sequence of benzoic acid.

With our knowledge of the origin of the stereocontrol of these reactions, it was considered that omission of the hydroxymethyl group in the substrates would still permit diastereoselective iodocyclisation. My contribution to the project was to investigate this with a view to expanding this methodology further.

1.2.2 Results and Discussion

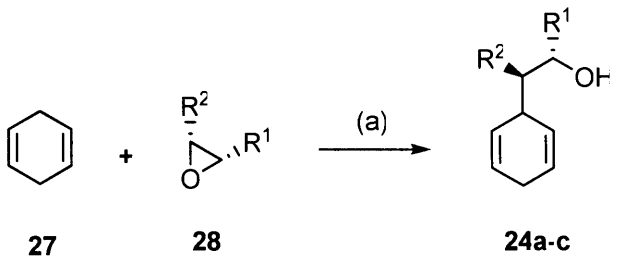
In this case only 5-*exo* and competing 6-*endo* cyclisation modes were investigated. The expected products are shown in **Scheme 7**.



24 25 26

Scheme 7. Anticipated outcome of iodocyclisations.

The substrates for cyclisation **24** were prepared by deprotonation of cyclohexa-1,4-diene **27**, using conditions devised by Woerpel[11] and employed by Landais,[12] followed by reaction with an epoxide **28** (**Scheme 8**). The reactions all proceeded smoothly and in moderate to good yield, providing a range of substrates for investigation, as shown in **Table 1**.



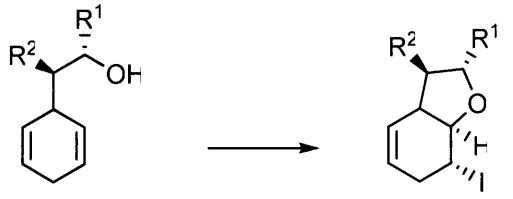
27 **28** **24a-c**

Scheme 8. *Reagents and Conditions*: (a) *n*-BuLi, TMEDA, THF, -78 °C to room temperature, 1 h.

Entry	Epoxide	R^1	R^2	Yield **24** (%)
1	**28a**	*n*-Bu	H	66
2	**28b**	Ph	H	27
3	**28c**		$-(CH_2)_4-$	44

Table 1.

Pleasingly all three compounds underwent successful cyclisation when treated with iodine and $NaHCO_3$ in acetonitrile for only 10 minutes. ^1H NMR spectra of the crude reaction mixtures showed, in all three cases, formation of a single diastereoisomer. Also, in this case, only single regioisomers were observed, with no 6-*endo* cyclisation products formed. Compounds **25** were easily isolated by column chromatography in high yield (**Table 2**) and determined to be of the structure shown in **Scheme 9** by analogy with the group's previous iodocyclisation work.



24a-c **25a-c**

Scheme 9. *Reagents and Conditions*: I_2, $NaHCO_3$, CH_3CN, 10 minutes.

Entry	Alcohol	R^1 =	R^2 =	Yield **25** (%)
1	**24a**	*n*-Bu	H	66
2	**24b**	Ph	H	63
3	**24c**		$-(CH_2)_4-$	60

Table 2.

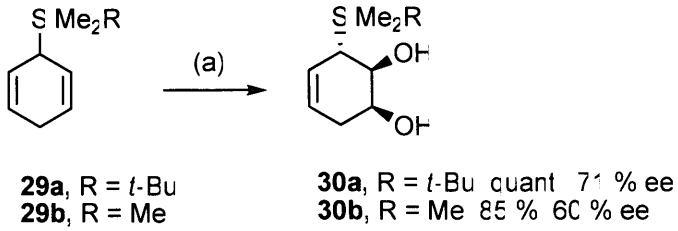
The stereochemical outcome of these reactions can be explained as before. The complete regiocontrol observed in these examples is presumably due to the lack of the hydroxymethyl group altering the geometry in such a way that the 6-*endo* transition state is even more strained, to the extent that this cyclisation process is not observed at all.

While, only 5-*exo* and competing 6-*endo* cyclisation modes were investigated in this case, owing to these results and the group's previous work, there seems to be no reason why the methodology cannot be extended to incorporate larger ring sizes.

1.3 Tandem Epoxidation-Cyclisation Reactions

1.3.1 Introduction

Selective oxidation of cyclohexa-1,4-dienes systems has been reported extensively by Landais.[12,13] The Sharpless asymmetric dihydroxylation was used to great effect in the desymmetrisation of cyclohexadienylsilanes **29** (**Scheme 10**). Landais *et al.* also employed further selective oxidation of these systems, by means of Sharpless asymmetric epoxidation, to achieve total syntheses of conduritol E and a number of deoxyinositols.

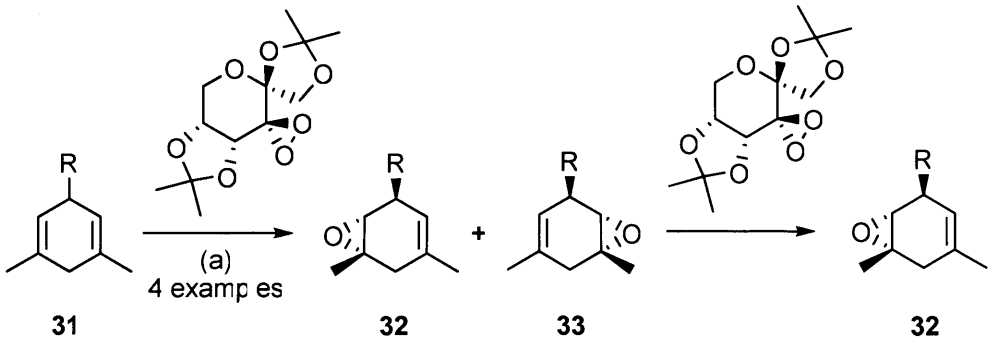


29a, R = *t*-Bu
29b, R = Me

30a, R = *t*-Bu quant 71 % ee
30b, R = Me 85 % 60 % ee

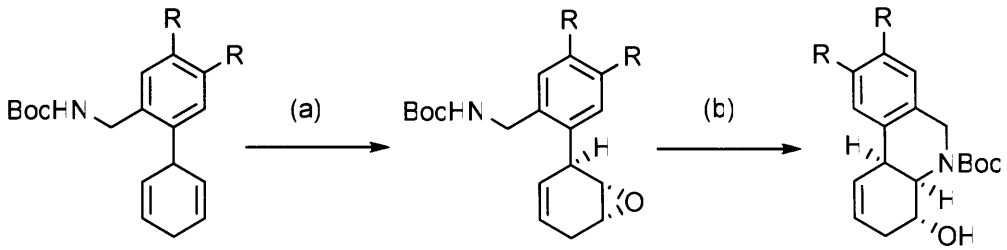
Scheme 10. *Reagents and Conditions*: (a) $K_2OsO_2(OH)_4$, K_2CO_3, $K_3Fe(CN)_6$, *t*-BuOH/H_2O (1:1), $MeSO_2NH_2$, $(DHQ)_2Pyr$, 0 °C, 12 h.

Use of epoxidation for the desymmetrisation of cyclohexa-1,4-dienes has also been reported by Shi.[14] A chiral dioxirane, generated from a fructose-derived ketone, and oxone are used to effect desymmetrisation and subsequent kinetic resolution, permitting highly selective mono-epoxidation of these systems (**Scheme 11**).



Scheme 11. *Reagents and Conditions*: (a) Oxone, K_2CO_3, CH_3CN/DMM/0.05 M $Na_2B_4O_7.10H_2O$ of aqueous EDTA, 0 °C. 53 – 87 % yields, 79 – 95 % ee.

Crich has previously reported epoxidation-cyclisation reactions of cyclohexadiene systems.[15] Treatment of substrates **34** with *m*-CPBA, followed by $BF_3.OEt_2$ to effect cyclisation, results in the formation of compounds **36** (**Scheme 12**). However, the cyclisation step is in fact non-group selective, since careful control of the amounts of *m*-CPBA used ensure only the mono-epoxide is formed.



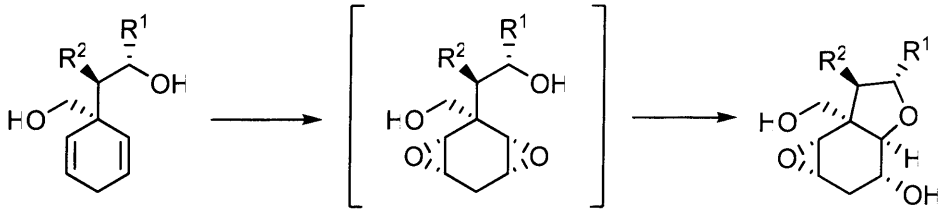
34a, R = H
34b, R = -OCH_2O-

35a, R = H 67 %
35b, R = -OCH_2O-
60 %

36a, R = H 86 %
36b, R = -OCH_2O-
68 %

Scheme 12. *Reagents and Conditions*: (a) *m*-CPBA, CH_2Cl_2, 0 °C; (b) $BF_3.OEt_2$, 0 °C.

The substrates **19** used for our group's initial iodocyclisation studies, derived from the Birch reduction/ alkylation sequence, contain two hydroxyl groups, one of which is homoallylic. We speculated that this homoallylic alcohol could be used to direct the facial selectivity of epoxidation of the cyclohexadiene ring, and that the chirality present in the tether could again be used to facilitate diastereotopic group selection (**Scheme 13**). The conformational bias provided by the chiral tether should ensure ring opening of only one epoxide, giving rise to highly functionalised tetrahydrofurans **38** as single diastereoisomers.



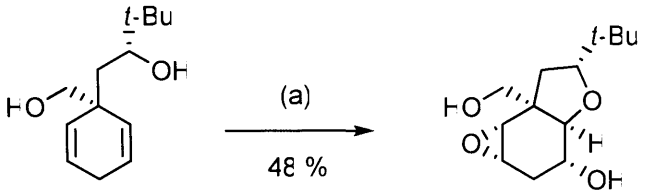
19 **37** **38**

Scheme 13. Anticipated outcome of epoxidation.

1.3.2 Results and Discussion

1.3.2.1 Diastereoselective Epoxidation-Cyclisation Reactions

With a range of substrates in hand from the iodocyclisation studies, the *t*-Bu substituted diol **19b** was chosen as a starting point for the investigation. The first method of epoxidation considered was simple *m*-CPBA oxidation. Diol **19b** was treated with 2.2 equivalents *m*-CPBA in dichloromethane with $NaHCO_3$ as base for 24 h.



19b **38b**

Scheme 14. *Reagents and Conditions*: (a) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to room temperature, 24 h.

^1H NMR spectroscopic data of the crude reaction mixture was promising. The starting material had been completely consumed and the crude material appeared to consist of one major compound with a few minor impurities. After purification by column chromatography, the major product was determined to be of structure **38b,** as shown in **Scheme 14**, from ^1H and ^{13}C NMR spectroscopic data. The stereochemistry was determined crystallographically (**Figure 4**) and is in line with the results obtained from the corresponding iodocyclisation reaction of compound **19b**.[6]

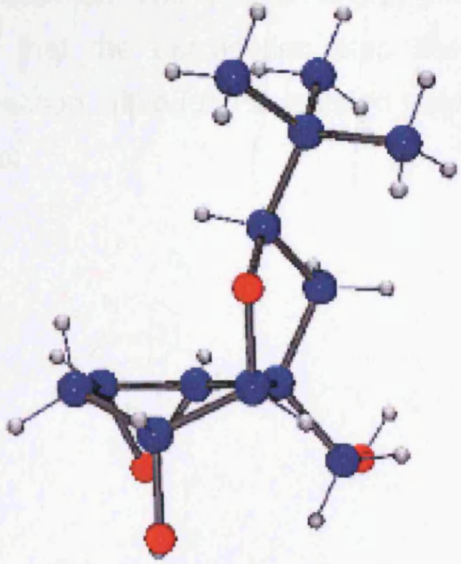
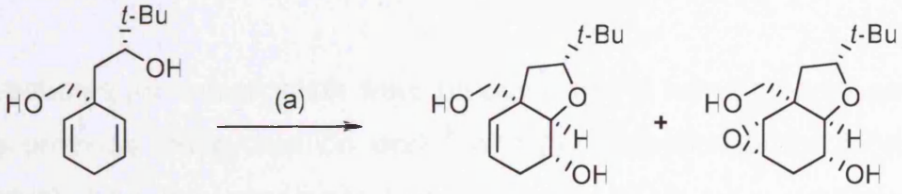


Figure 4. ORTEP plot of compound **38b**. Thermal ellipsoids are shown at the 50 % probability level.

With this result in hand, the next task was to try and optimise the reaction conditions in an attempt to improve upon the yield. Payne epoxidation conditions (H_2O_2/ $NaHCO_3$/ MeCN) were evaluated, but showed very slow epoxidation, such that no products were characterised. With vanadyl acetylacetonate and *t*-butyl hydroperoxide a mixture of compounds **39** and **38b** were obtained (**Scheme 15**).

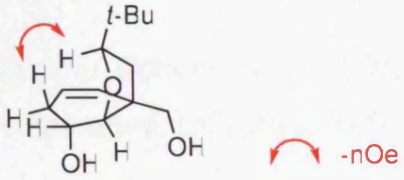


19b **39**, 15 % **38b**, 5 %

Scheme 15. *Reagents and Conditions*: (a) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, 0 °C to room temperature, 16 h.

The stereochemistry of compound **39** was determined by NOESY NMR spectroscopy (**Figure 5**) and arises from directed mono-epoxidation of the

substrate followed by cyclisation. The isolation of only this compound and small amounts of **38b** hints that the epoxidation step itself may exhibit some diastereotopic group selection, although the isolated yield of **39** is far too low to categorically confirm this.

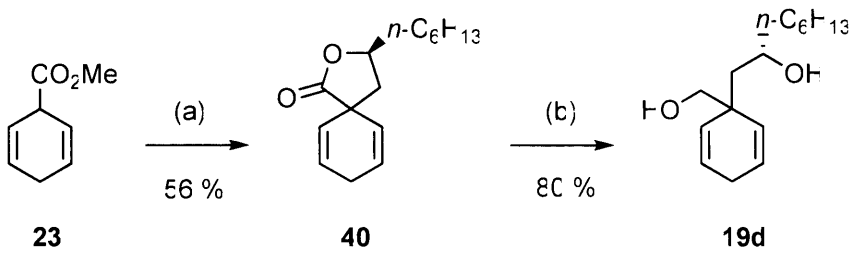


39

Figure 5. Stereochemical determination of **39**.

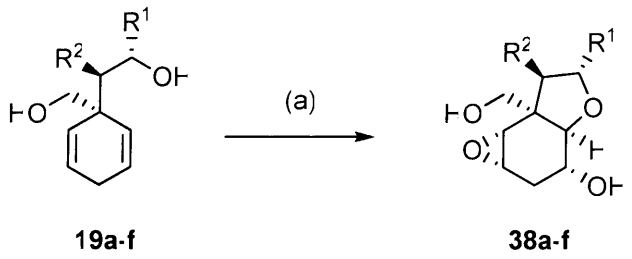
Owing to the limited success of these two different epoxidation methods, it was decided best to try and optimise the original *m*-CPBA epoxidation conditions. After testing a range of reaction times and reagent quantities, suitable conditions were determined, allowing the yield of **38b** isolated to be increased to 75 %. This involved adding an initial two equivalents of *m*-CPBA, again with $NaHCO_3$ as base and stirring for 24 h, followed by addition of 0.1 equivalents of *m*-CPBA for every subsequent hour until complete consumption of the starting material. Typically a total of 2.4 equivalents of *m*-CPBA were required. With the improved conditions we could now test the diversity of this methodology with a range of examples.

The substrates for investigation were prepared in the same manner as for the group's previous iodocyclisation work,[6] with the exception of the *n*-hexyl diol **19d**, which had not previously been prepared. This was synthesised by alkylation of ester **23** with *n*-hexyl oxirane to give lactone **40**, which was subsequently reduced to the diol **19d** by treatment with $LiAlH_4$ (**Scheme 16**).



Scheme 16. *Reagents and Conditions*: (a) LDA, *n*-hexyl oxirane, THF, -78 °C to room temperature; (b) $LiAlH_4$, THF.

Pleasingly, all but one of the diols investigated underwent successful reaction, with similar results to that obtained with diol **38b** as shown in **Scheme 17** and **Table 3**. The reaction yields are moderate to good and ^1H NMR spectra of crude reaction mixtures show the formation of no other diastereoisomers, in all cases. There appears to be no logical trend in the yields observed, in terms of the variation in substituent size and character. As such, the reason for the lower yields observed with entries 1 and 4 is not readily apparent, since no other compounds were isolated and the products **38a** and **38d** are stable to chromatography.



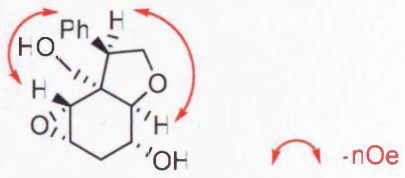
Scheme 17. *Reagents and Conditions*: (a) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to room temperature.

Entry	Diol	R^1	R^2	Yield **38** (%)
1	**19a**	*n*-Bu	H	40
2	**19b**	*t*-Bu	H	75
3	**19c**	$-(CH_2)_4-$		52
4	**19d**	n-C_6H_{13}	H	36
5	**19e**	Ph	H	0
6	**19f**	H	Ph	55

Table 3.

Entry 5, with a phenyl group in the R^1 position shows a key limitation to the methodology. The presence of a benzylic alcohol in the substrate led to no identifiable products. This limitation cannot be explained by consideration of steric factors, since the same substrate undergoes successful iodocyclisation. ^{1}H NMR spectroscopic data of the crude reaction mixture showed no starting material, just a complex mixture of products, suggesting that the substrate is decomposing under these conditions.

The stereochemistry of these compounds was assigned by analogy with compound **38b** and additionally, the stereochemistry of compound **38f** was determined by NOESY NMR spectroscopy (**Figure 6**). It should be noted that all reactions were also completely regioselective, with only 5-*exo* cyclisation modes observed.

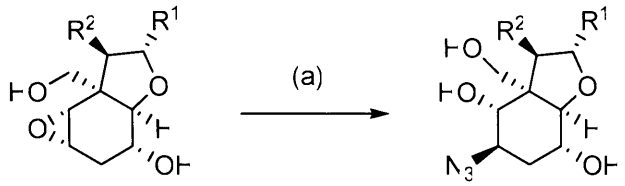


38f

Figure 6. Stereochemical determination of **38f**.

1.3.2.2 Regioselective Epoxide Opening

These compounds are ripe for further elaboration, for example, the other epoxide can be regioselectively opened with sodium azide, providing access to highly functionalised benzofuran derivatives and sugar analogues. Treatment of compounds **38** with sodium azide and NH_4Cl in $MeOH/H_2O$ (8:1) at 80 °C for 20 h[16] afforded azides **41** as single regioisomers in moderate to excellent yield, as shown in **Scheme 18** and **Table 4**.



38 **41**

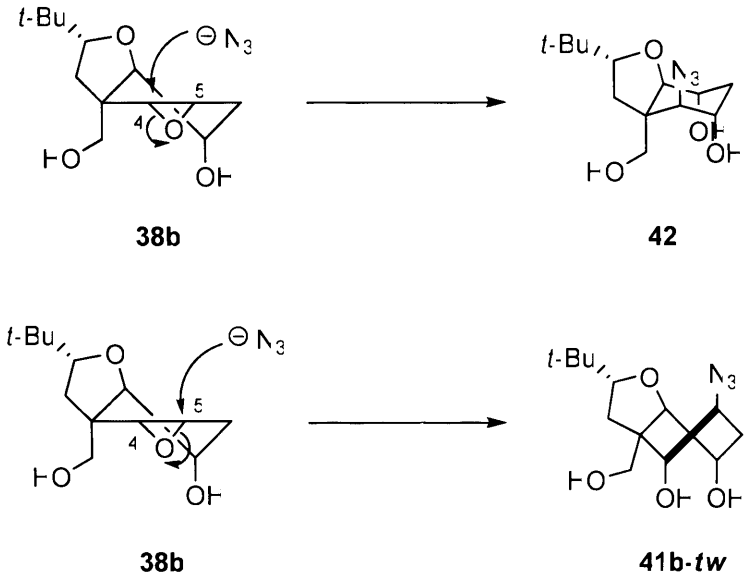
Scheme 18. *Reagents and Conditions*: (a) NaN_3, NH_4Cl, $MeOH/H_2O$ (8:1), 80 °C, 20 h.

Entry	Epoxide	R^1	R^2	Yield **41** (%)
1	**38a**	*n*-Bu	H	36
2	**38b**	*t*-Bu	H	67
3	**38c**	-$(CH_2)_4$-		46
4	**38d**	*n*-C_6H_{13}	H	96
5	**38f**	H	Ph	67

Table 4.

In each case, the regioselective epoxide opening occurs at the least hindered end, which actually contradicts the outcome predicted by the Fürst-Plattner rule.[17] The Fürst-Plattner rule states that ring-opening of cyclohexene oxide derivatives leads directly to *trans*-diaxial products. This can be used to predict the regioselectivity of such reactions. For example, in the case of compound **38b**, the kinetic product of attack at the more hindered C-4 position will be

compound **42**, as shown in **Scheme 19**. This is generally the more favoured mode of attack since the reaction proceeds via a chair-like transition state. Attack at the other end of the epoxide (C-5) will proceed via a diaxial twist-boat conformation **41b-*tw***, which is approximately 21 kJ mol^{-1} higher in energy than the chair conformation,[18] normally making attack at this end much less favourable.

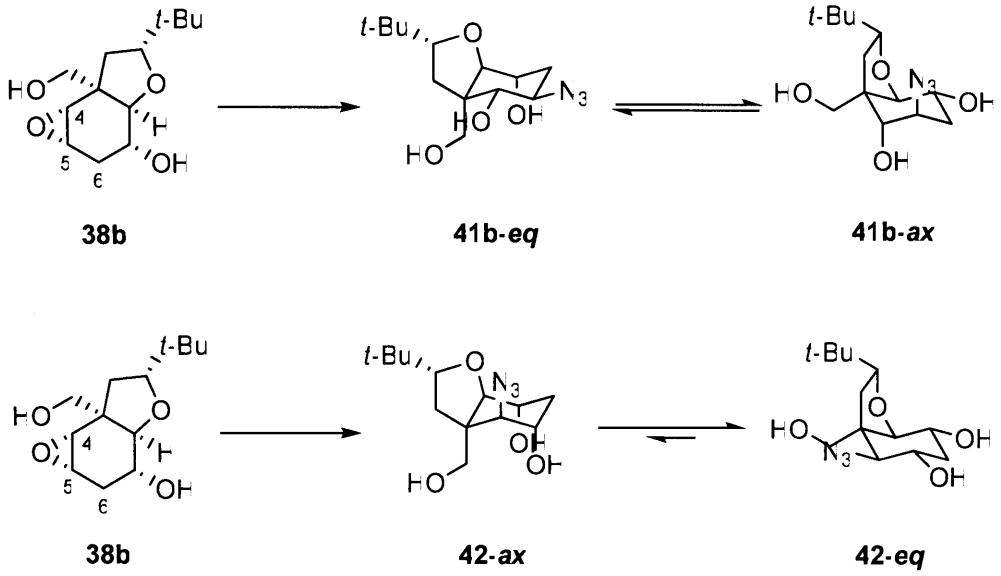


Scheme 19. Epoxide opening reaction pathways.

However, in the case of compounds **38**, attack at the more hindered C-4 position would result in significant steric interactions between the incoming nucleophile and the tetrahydrofuran ring, which outweighs the conformational energy barrier to attack at the other end. As such, the epoxides are opened at the least hindered C-5 position.

The regiochemistry of the epoxide-opening reactions was determined by analysis of coupling constants in the ^{1}H NMR spectra. Of the two possible outcomes of the epoxide-opening, each product can potentially exist in one (or both) of two chair conformations (**Scheme 20**). The two conformations **41b-*eq*** and **41b-*ax*** arising from attack at the least hindered end (C-5) will, most likely, be similar in terms of stability, and as such this compound would be expected to exist as both conformers. The more favoured conformer arising from

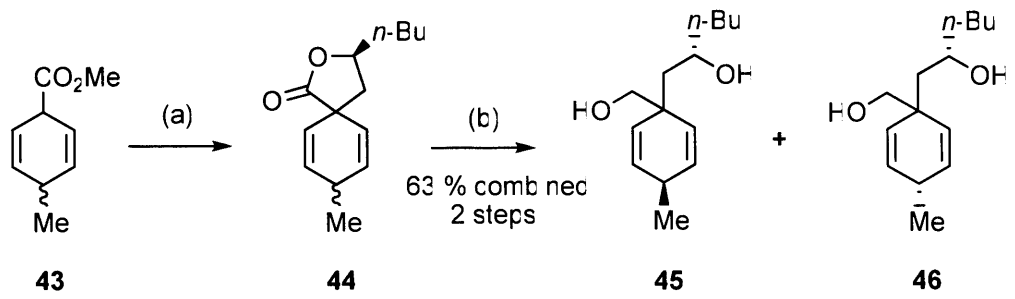
ring-opening at the other end (C-4) would presumably be **42-*eq***. The protons at C-6 are clearly visible in the ^{1}H NMR spectra of all of the compounds and in each case one shows a single *trans*-diaxial coupling. From ring-opening at the C-4 position, zero (conformer **42-*ax***) or two (conformer **42-*eq***) *trans*-diaxial couplings to this proton would be expected. For conformers **41b-*eq*** and **41b-*ax***, arising from attack at C-5, one *trans*-diaxial coupling would be expected in each case, as is observed. Hence it can be concluded that the epoxide opening is occurring at the C-5 position.



Scheme 20. Regiochemical determination of azides **41**.

1.3.2.3 Formation of Six Contiguous Stereogenic Centres

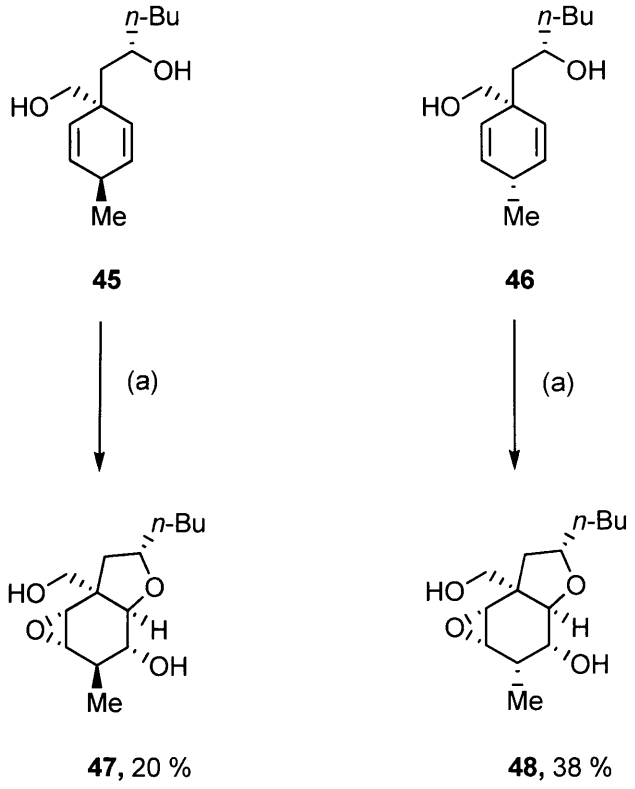
In order to really test the potential of the epoxidation-cyclisation methodology, we sought to try and incorporate yet more stereochemistry into these compounds. Ester **43** is easily prepared by Birch reduction and esterification of *p*-toluic acid.[19] Alkylation of this ester with *n*-butyl oxirane to give lactone **44** as a 1:1 mixture of diastereoisomers, followed by treatment with $LiAlH_4$, afforded a mixture of isomers **45** and **46** in overall good yield (**Scheme 21**). Samples of the individual isomers for investigation were obtained by extensive chromatography on silica gel, although complete separation was not possible.



43 **44** **45** **46**

Scheme 21. *Reagents and Conditions*: (a) LDA, *n*-butyl oxirane, THF, -78 °C to 5 °C, 3 h; (b) $LiAlH_4$, THF.

Diols **45** and **46** were submitted to our standard epoxidation conditions and pleasingly both underwent successful epoxidation-cyclisation to give, in each case, a single diastereoisomer of epoxides **47** and **48** (**Scheme 22**).



Scheme 22. *Reagents and Conditions*: (a) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to room temperature.

The stereochemistry of compound **48** was assigned by X-ray diffraction (**Figure 7**) and the stereochemistry of diols **45** and **46** assigned retrospectively. The yields are relatively low, but the complexity of the stereochemistry gained in some way justifies this; we are obtaining formation of six contiguous stereogenic centres, selectively, in a single step.

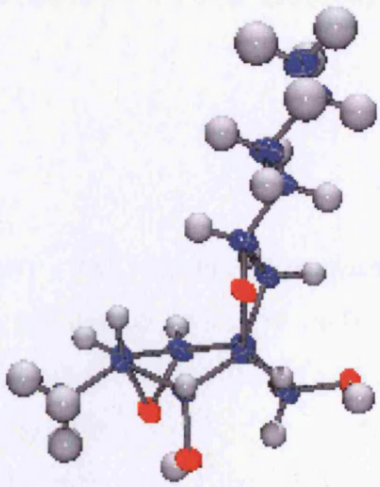


Figure 7. ORTEP plot of compound **48**. Thermal ellipsoids are shown at the 50 % probability level.

The higher yield of compound **48** compared to that of compound **47** is unexpected. For diol **46**, with the methyl group on the lower face of the cyclohexadiene ring, we predicted a significant steric interaction between this group and the incoming epoxidising agent (**Figure 8**), lowering the rate of epoxidation and hence the yield of compound **48**. This appears not to be the case, and in fact there appears to be a greater barrier to reaction of diol **45** under these conditions. This is presumably due to the presence of the methyl group on the top face of the ring hindering attack of the free hydroxyl group on the same face, as illustrated in **Figure 8**.

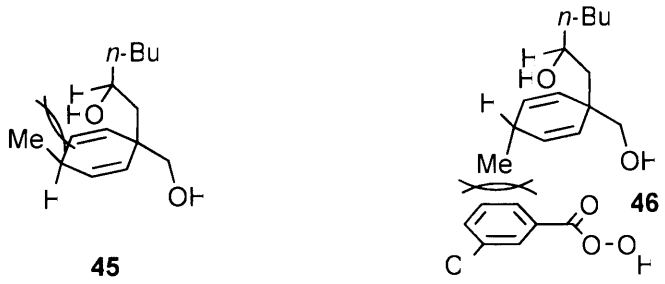


Figure 8. Steric barrier to reaction of compounds **45** and **46**.

1.4 Conclusion

In conclusion, iodocyclisation and epoxidation-cyclisation reactions of cyclohexadienes have been shown to proceed with complete regio- and diastereocontrol, providing access to highly functionalised tetrahydrofurans. Novel epoxidation methodology has enabled the selective formation of six contiguous stereogenic centres in a single step. Furthermore, the epoxides yielded can be elaborated further allowing facile access to complex sugar analogues. As such this methodology should be of great use in synthesis.

Chapter 2

The Cladiellin Diterpenes and Prins Cyclisation Reactions of Cyclohexa-1,4-dienes

2.1 Introduction

2.1.1 The Cladiellin Diterpenes

Over the past 40 years, a large number of cyclic diterpenoids containing one of the heterocyclic frameworks shown in **Figure 9** have been isolated from marine invertebrates.[20] These secondary marine metabolites, extracted from octocorals, have been classified into four categories: the cladiellins (also known as the eunicellins), the briarellins, the asbestinins and the sarcodictyins.

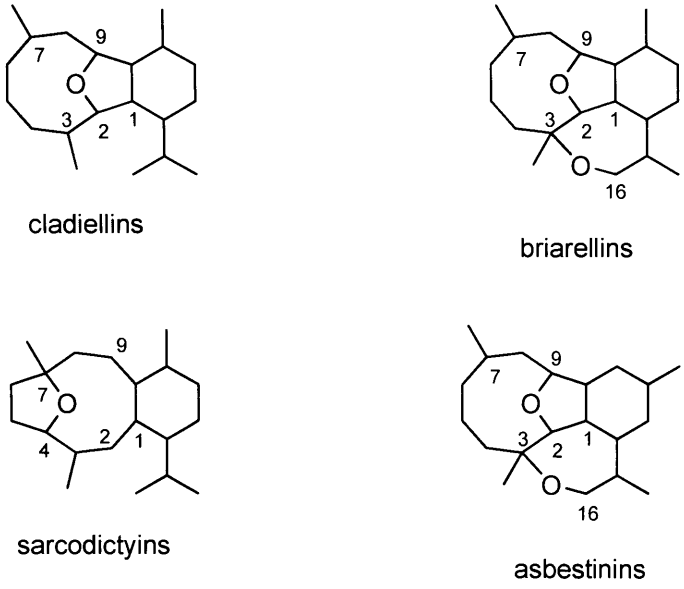


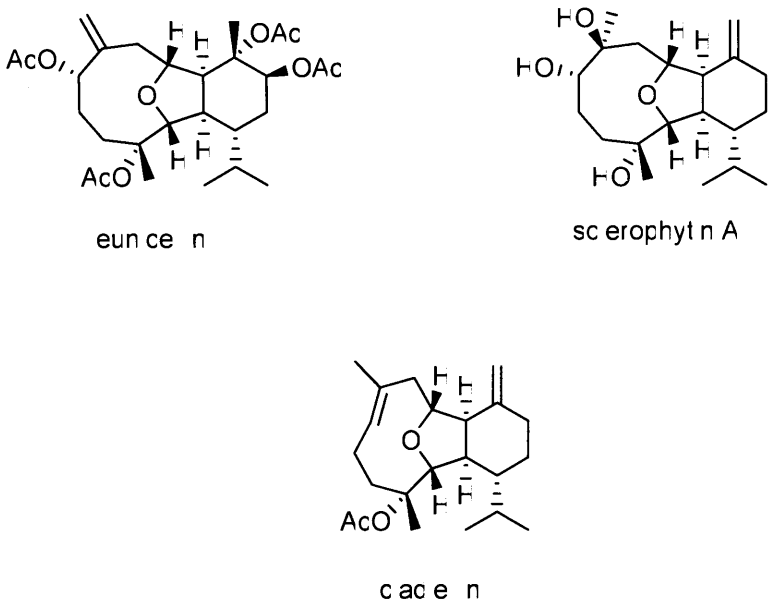
Figure 9. General framework of the cladiellins, briarellins, asbestinins and sarcodictyins.

The cladiellins, briarellins and asbestinins are all structurally similar, being comprised primarily of a rare oxatricyclic ring system, made up of octahydroisobenzofuran and oxacyclononane moieties. The briarellins and asbestinins also feature an additional 7-membered ether bridge between C-3 and C-16. The sarcodictyins contain a single ether bridge in a different position to the others; between C-4 and C-7.

The cladiellins represent the most abundant class of these fascinating natural products, and indeed the first of such cyclic diterpenoids isolated was a

member of the cladiellin family. Eunicellin (**Figure 10**) was isolated by Djerassi *et al* in 1968 after extraction of *Eunicella stricta*, a species of gorgonian coral collected off the coast of Banyuls-sur-Mer, France.[21] Since then more than 60 members of the cladiellin family have been isolated.[20]

The relative and absolute stereochemistries of a number of cladiellins have been determined by X-ray crystallographic analysis.[20] Additionally, stereochemical configurations have been established or confirmed by total synthesis. The relative stereochemistry of the core is characterised by an *anti* relationship between the two pairs of ring junction protons, as shown in the examples in **Figure 10**.



eun ce n sc erophyt n A

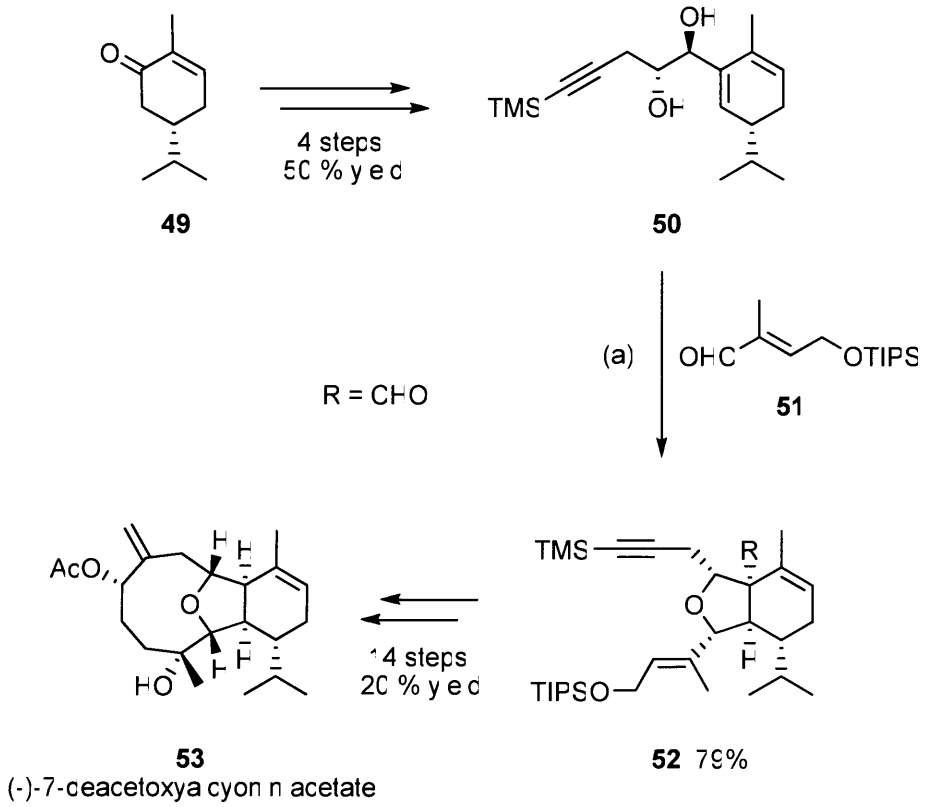
c ac e n

Figure 10. Examples of cladiellin diterpenes.

The cladiellin diterpenes exhibit an interesting array of biological activity. These secondary metabolites appear to naturally function as a defence mechanism of octocorals against predation, possessing, amongst other activities, mollusc and brine shrimp lethality.[22] This class of compounds also exhibit some interesting pharmacological potential, such as anti-inflammatory and anti-tumour activity. For example, sclerophytin A (**Figure 10**) shows very potent cytotoxic activity

against L1210 leukemia cells[23] and cladiellin (**Figure 10**) has been shown to be a cAMP phosphodiesterase inhibitor, providing anti-inflammatory activity.[20]

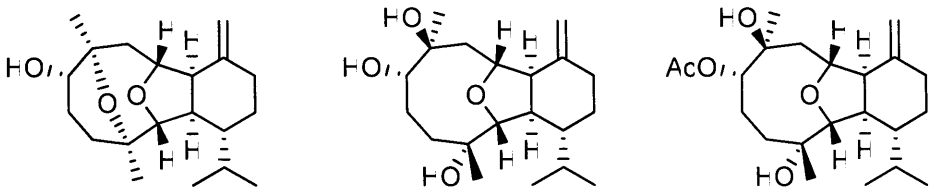
Owing to their intriguing structure and interesting pharmacological activity, the cladiellins have seen a great deal of interest from a number of synthetic research groups, especially the groups of Overman,[24] Paquette,[25] Molander,[26] Kim,[27] Crimmins[28] and Hoppe.[29] The Overman group was the first to report a total synthesis of a member of the cladiellin family in 1995.[24a] Overman *et al.* employed their key stereoselective Prins-pinacol condensation-rearrangement methodology to synthesise the isobenzofuran core **52**. The core was then further elaborated to achieve an enantioselective total synthesis of (-)-7-deacetoxyalcyonin acetate **53** (**Scheme 23**).



Scheme 23. *Reagents and Conditions*: (a) $BF_3.OEt_2$, CH_2Cl_2, -55 °C to -20 °C.

In 2001, two independent syntheses of sclerophytin A were reported by the groups of Overman and Paquette,[24c,25c] enabling revision of its structural

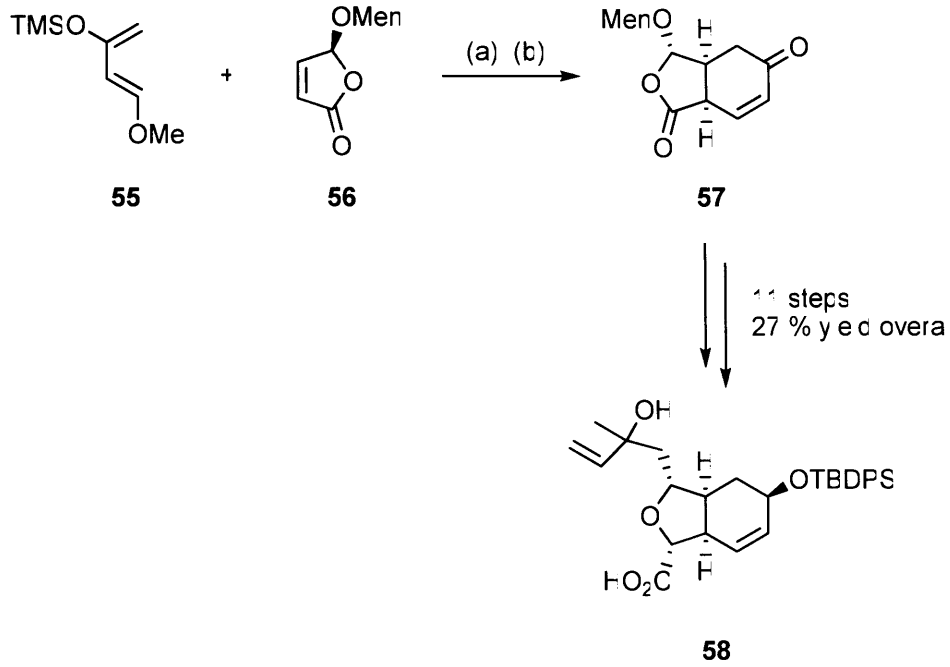
formulation. Previous targeted syntheses by both groups had shown the originally proposed structure **54** of sclerophytin A to be incorrect (see **Figure 11**).[24b,25a] Subsequent detailed spectroscopic re-evaluation of sclerophytin B (the monoacetate of sclerophytin A) by the Paquette group, suggested the absence of the second ether bridge in these natural products.[25b] As such, subsequent syntheses were approached accordingly.



54 sclerophytin A sclerophytin B

Figure 11. Structural revision of sclerophytin A and B.

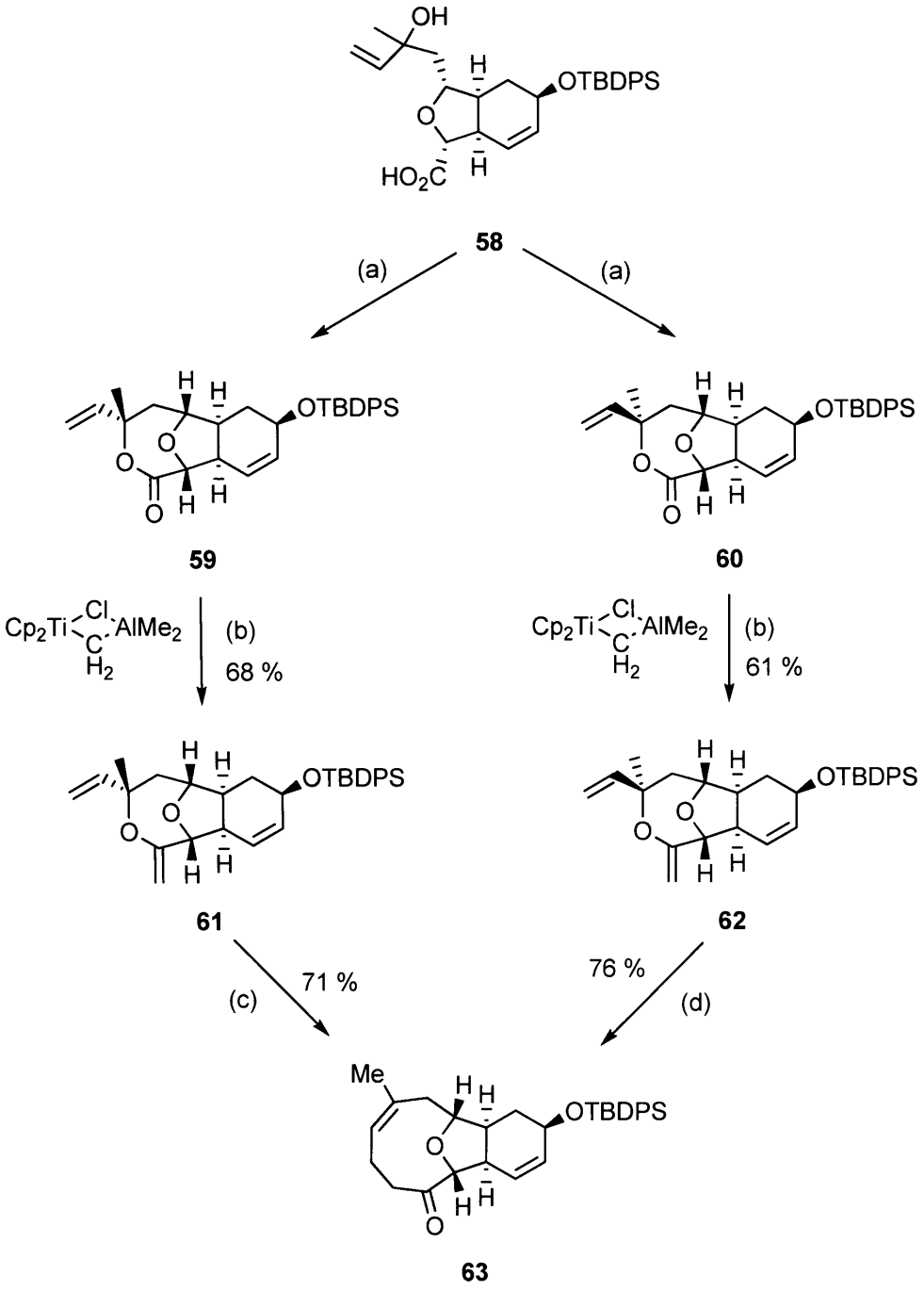
The Paquette group devised a synthesis involving a tandem Tebbe-Claisen ring expansion strategy for installing the nine-membered ring.[25c] Beginning with a Diels-Alder cycloaddition of diene **55** and furanone **56**, compound **58** was synthesised in 13 synthetic steps (**Scheme 24**).



55 56 57 58

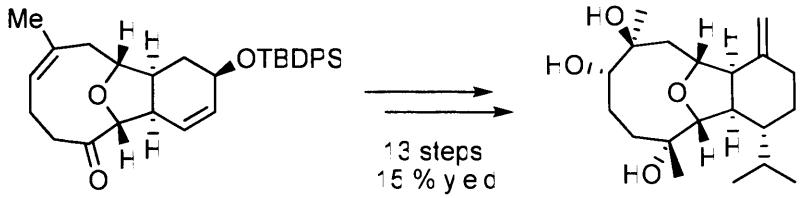
Scheme 24. *Reagents and Conditions*: (a) Toluene, reflux; (b) TMSOTf, pyridine, CH_2Cl_2, -78 °C.

Macrolactonisation of compound **58** gave a separable mixture of diastereoisomers **59** and **60**, which were then separately submitted to Tebbe olefination to give compounds **61** and **62** (**Scheme 25**). Claisen rearrangement of both compounds **61** and **62** gave compound **63**.



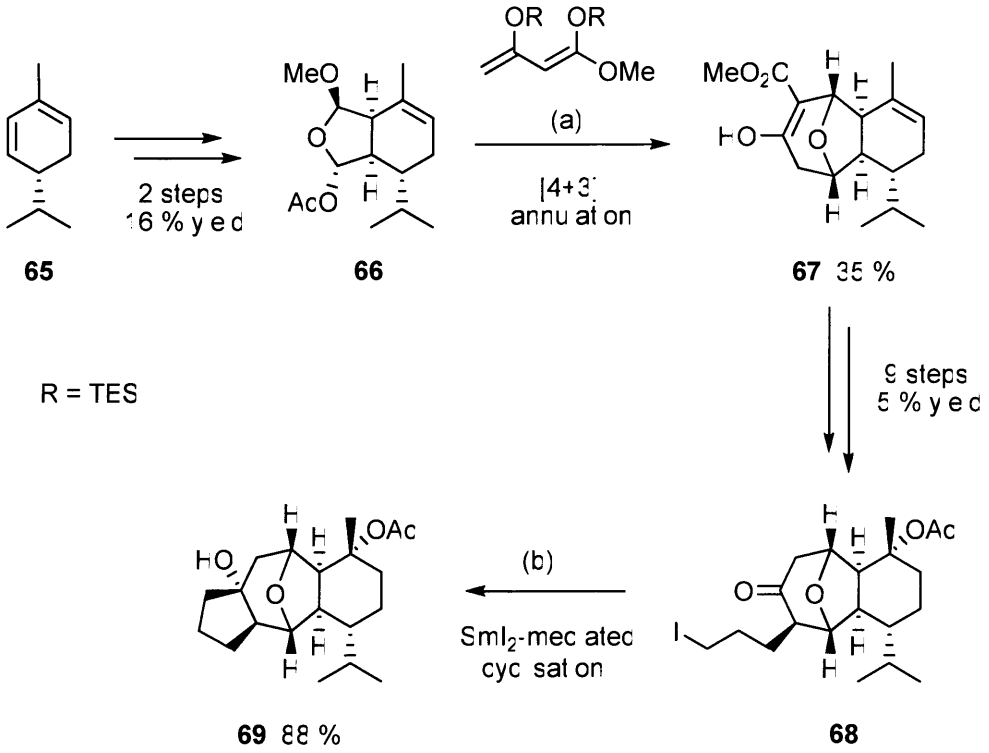
Scheme 25. *Reagents and Conditions*: (a) $Cl_3C_6H_2COCl$, Et_3N, 4-DMAP, toluene; (b) Pyridine, THF, -50 °C to 20 °C; (c) *p*-cymene, 140 °C, 3 h; (d) *p*-cymene, 130 °C, 1.5 h.

Compound **63** was subsequently converted into sclerophytin A (**64**) in a further 13 steps (**Scheme 26**). The spectroscopic data of synthetic **64** was identical to that of natural sclerophytin A, confirming the structural revision.



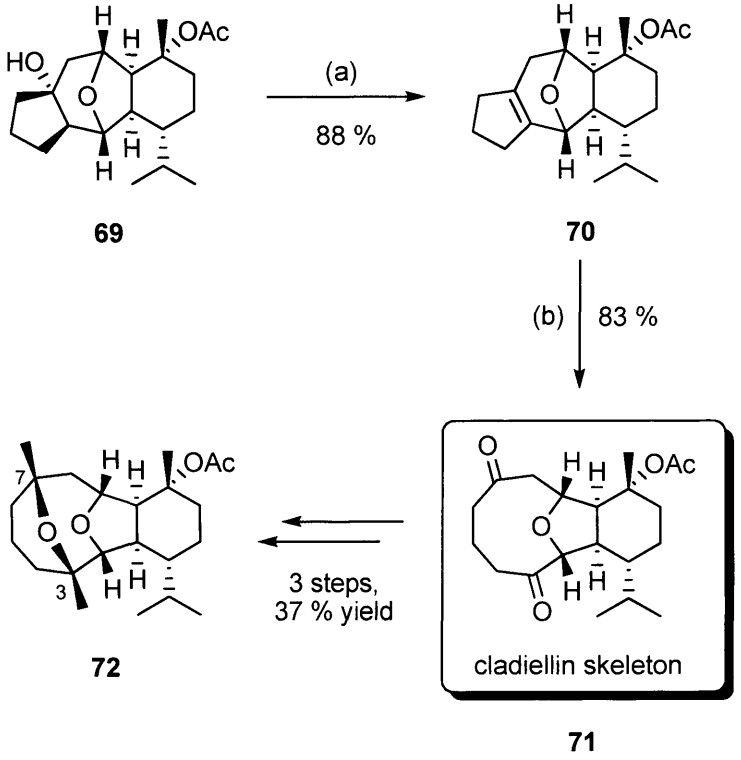
Scheme 26. Synthesis of sclerophytin A (**64**).

The Molander group have reported a concise approach to the cladiellin skeleton, employing a [4 + 3] annulation strategy to create the octahydroisobenzofuran moiety **67**, followed by an SmI_2-mediated cyclisation reaction to install the nine-membered ring.[26b] The precursor for the SmI_2-mediated cyclisation **68** was synthesised in 12 steps, including the [4 + 3] annulation, from R-(-)-α-phellandrene **65** (**Scheme 27**).



Scheme 27. *Reagents and Conditions*: (a) $TiCl_4$, CH_2Cl_2; (b) SmI_2, HMPA, THF.

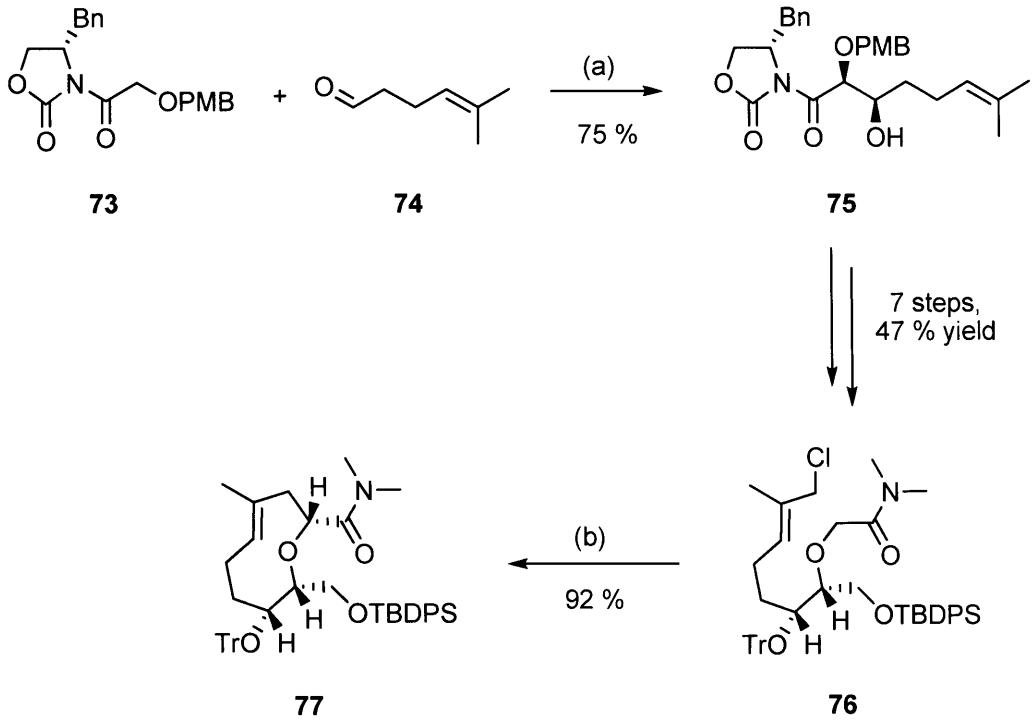
Elimination of the cyclisation product **69**, followed by oxidative cleavage of the resulting double bond enabled formation of the cladiellin skeleton **71** in a total of 15 steps (**Scheme 28**). Further elaboration of the skeleton resulted in the synthesis of of the 3,7-diastereoisomer of polyanthellin A (**72**).



69 **70** **72** **71**

Scheme 28. *Reagents and Conditions*: (a) Burgess reagent, DMF; (b) O_3, CH_2Cl_2 then Me_2S.

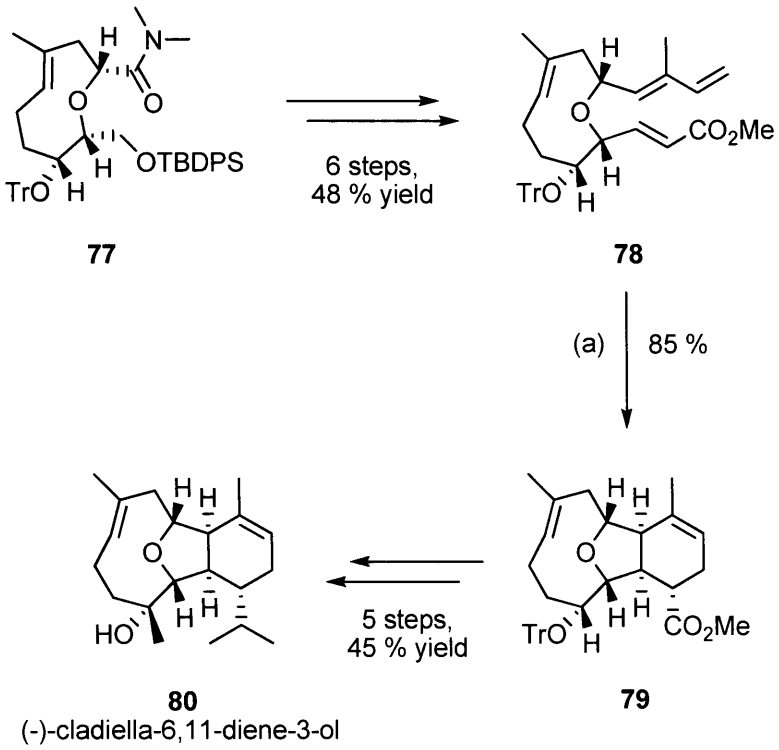
The group of Kim developed a neat strategy for the first synthesis of a (6E)-cladiellin, (-)-cladiella-6,11-diene-3-ol, in 2006.[27] Using a different approach to these compounds, the Kim group began with construction of the nine-membered ring sub-unit **77**, *via* a key intramolecular amide enolate alkylation reaction (**Scheme 29**). Treatment of amide **76** with LHMDS in THF resulted in the formation of the desired (E)-oxonene **77** as a single diastereoisomer, through control of the enolate geometry in the transition state.



73 74 75 76 77

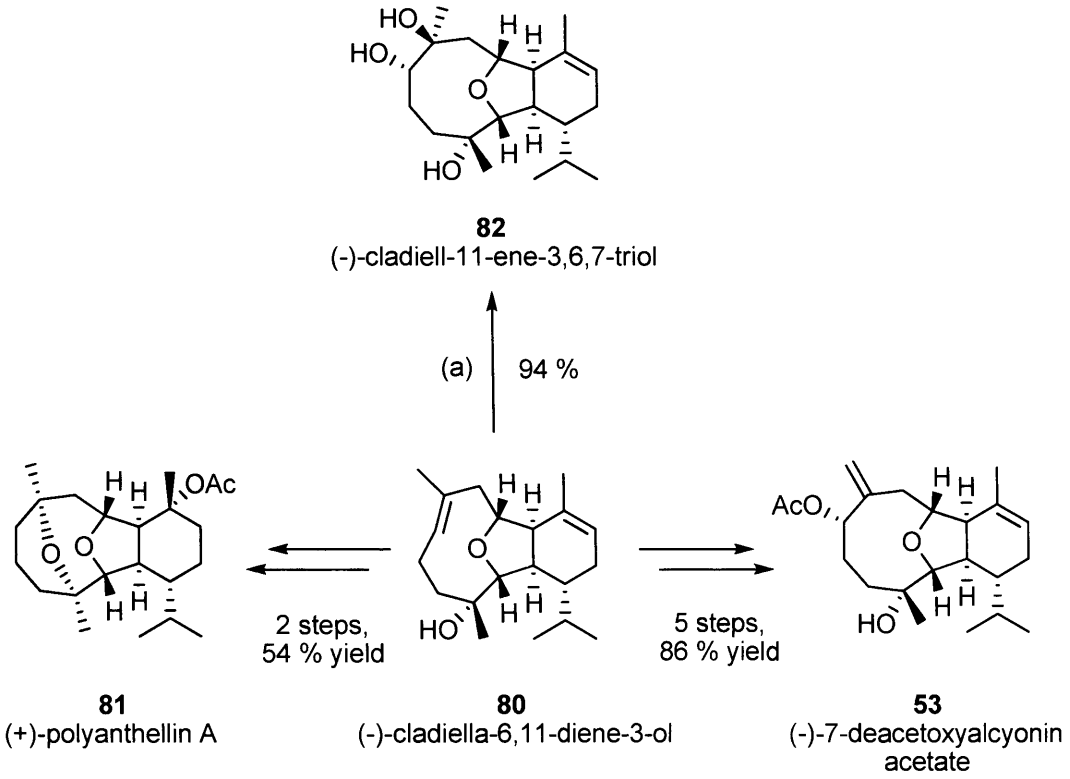
Scheme 29. *Reagents and Conditions*: (a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, -78 °C to 0 °C, 2 h; (b) LHMDS, THF, 45 °C, 1 h.

Further elaboration of the (E)-oxonene **77** yielded compound **78**, which was submitted to an intramolecular Diels-Alder strategy, previously reported by both Crimmins[28] and Holmes,[30] for construction the hydroisobenzofuran core (**Scheme 30**). A further five steps completed the synthesis of (-)-cladiella-6,11-diene-3-ol **80**.[27]



Scheme 30. *Reagents and Conditions*: (a) BHT, xylene, reflux, 1 h.

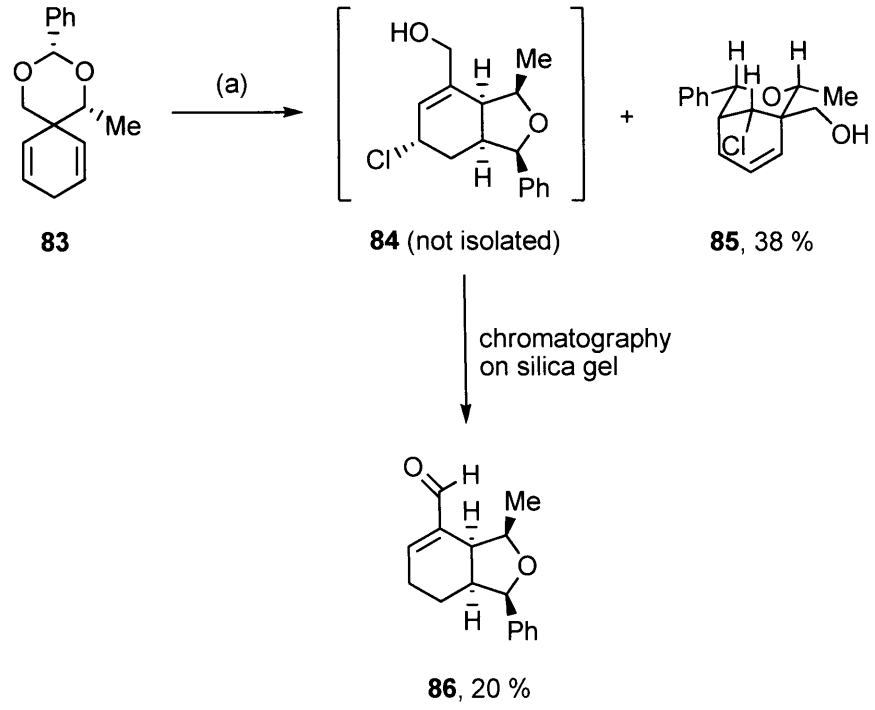
Kim *et al.* were then able to further elaborate (-)-cladiella-6,11-diene-3-ol **80** to achieve the total synthesis of three additional cladiellins in relatively few synthetic steps. (+)-polyanthellin A **81**, (-)-cladiell-11-ene-3,6,7-triol **82**, and (-)-7-deacetoxyalcyonin acetate **53** were synthesised using (-)-cladiella-6,11-diene-3-ol **80** as a common intermediate (**Scheme 31**).



Scheme 31. *Reagents and Conditions*: (a) OsO_4, NMO, THF/H_2O (3:1), 0 °C, 1 h.

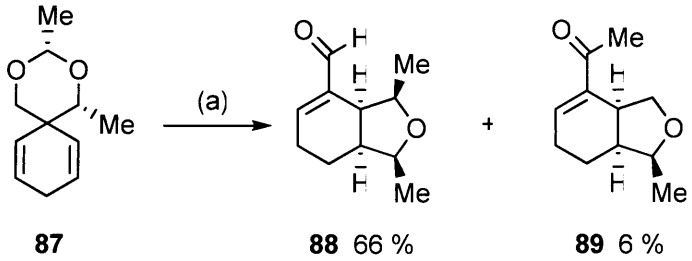
2.1.2 Diastereoselective Prins-Mediated Desymmetrisation of Cyclohexa-1,4-dienes

In recent years our group has established methodology for the desymmetrisation of cyclohexa-1,4-dienes via a diastereoselective Prins reaction.[7a,b] Chiral cyclohexa-1,4-diene derived acetals can be treated with a Lewis acid catalyst to effect cyclisation reactions with very high levels of diastereocontrol. For example, treatment of acetal **83** with $TiCl_4$ results in the formation of three cyclisation products, **84**, **85** and **86**, as shown in **Scheme 32**.[7a]



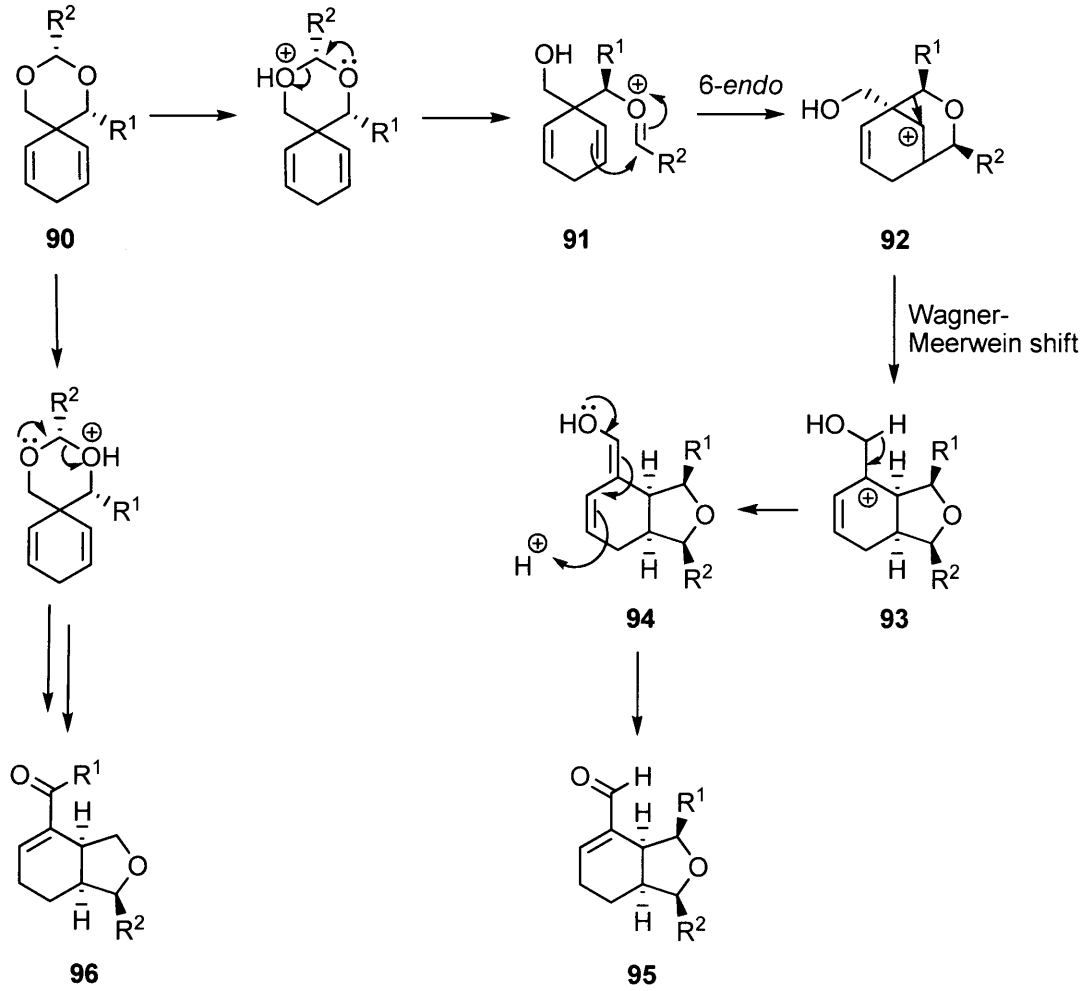
Scheme 32. *Reagents and Conditions*: (a) $TiCl_4$, CH_2Cl_2, -78 °C, 2 h.

This $TiCl_4$-mediated reaction is highly diastereoselective, however the low selectivity for any one compound posed a problem for any subsequent application of the methodology. More recent work within in the group has overcome this problem by employing the use of an acid catalyst with a non-nucleophilic counter-ion.[7b] For example, when treated with triflic acid, acetal **87** gives predominantly aldehyde **88** along with small amounts of ketone **89,** both as single diastereoisomers (**Scheme 33**).



Scheme 33. *Reagents and Conditions*: (a) TfOH (1.6 equiv.), CH_2Cl_2, room temperature, 15 min.

The formation of these products can be explained by the proposed mechanism shown in **Scheme 34**. Protonation of the least hindered oxygen atom of acetal **90**, followed by acetal opening gives oxocarbenium ion **91**. 6-*endo* cyclisation onto one of the diastereotopic double bonds then proceeds, followed by a Wagner-Meerwein shift, to give the more stable tertiary allylic cation **93**. Deprotonation to give the conjugated enol **94**, followed by a keto-enol tautomerism, gives the aldehyde **95.** The ketone product **96** arises from protonation of the more hindered oxygen atom of the acetal **90**, followed by a similar sequence.

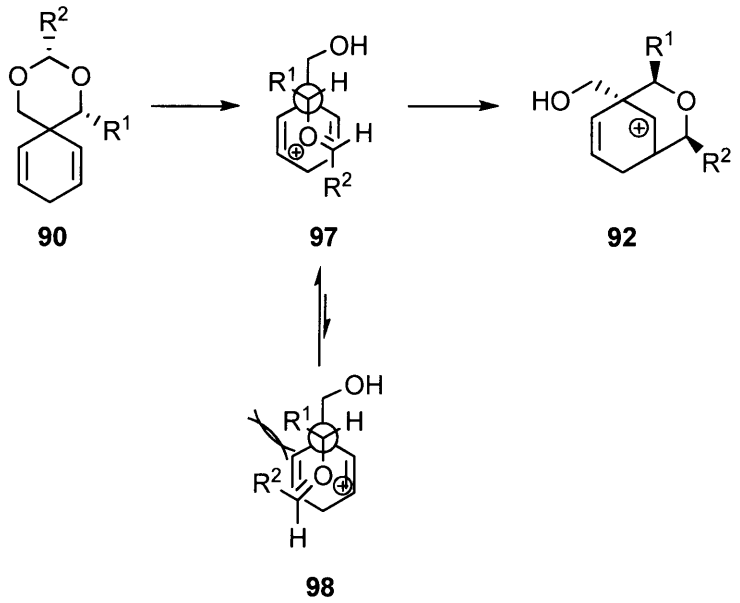


Scheme 34. Proposed mechanism of Prins cyclisation and rearrangement.

Clearly, reduction in the size of the acid cation, when moving from the use of $TiCl_4$ to triflic acid, reduces the regioselectivity of the acetal opening, which is why small amounts ketone are observed with the triflic acid-mediated reactions.

The major products **95** of these Prins cyclisation/rearrangement reactions are hydroisobenzofurans similar in structure to the core of the cladiellin diterpenes, with one major discrepancy- the relative stereochemistry. Instead of the *anti* relationship observed between the ring junction protons in the cladiellins, we are obtaining the opposite *syn* stereochemistry.

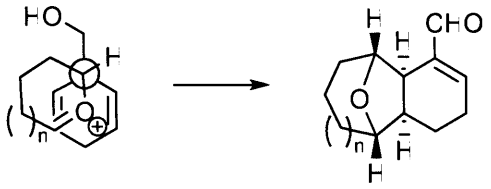
The stereochemistry of the formation of compounds **95** is determined by minimisation of $A^{1,3}$ strain in the transition state (**Scheme 35**). The transition state will preferentially adopt a conformation in which the R^1 and R^2 groups are furthest away from each other, as in conformer **97**, minimising steric interactions. This gives rise to the high levels of diastereocontrol observed.



Scheme 35. Origin of the stereochemistry of the Prins cyclisation/rearrangement.

Owing to this rationale, we proposed that the stereochemical outcome of the reaction could be reversed by tethering the R^1 and R^2 groups, as shown in

Scheme 36. The generated oxocarbenium ion would preferentially adopt the near-attack conformation **99** rather than the alternative eclipsed conformation, generating the desired cladiellin stereochemistry. The presence of the tethering chain would also have the additional benefit of introducing an extra ring into the product **100**.

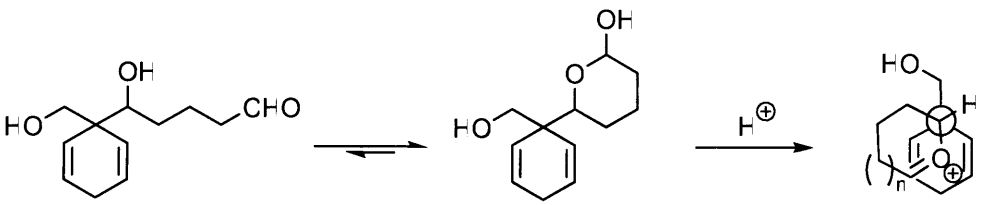


99 **100**

Scheme 36.

2.2 Results and Discussion

In order to test the theory, we first needed to devise a suitable substrate. We considered that a compound of structure **101**, which would presumably exist predominantly as the lactol **102**, should give the desired oxocarbenium ion **99**, when treated with an acid catalyst (**Scheme 37**).



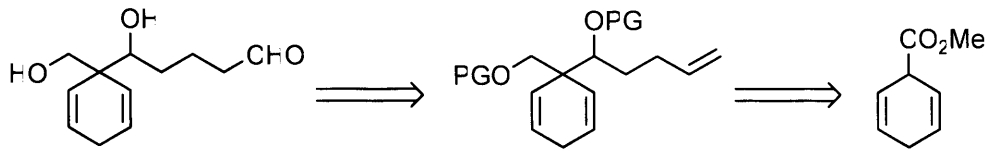
101 **102** **99**

(n = 1)

Scheme 37. Proposed Prins substrate.

2.2.1 First Generation Approach to the Cladiellin Core

To construct the substrate **101**, we envisaged installing the aldehyde functionality by hydroboration and subsequent oxidation of the corresponding terminal alkene **103**. Synthesis of the alkene **103** would be approached via alkylation of ester **23** (**Scheme 38**).

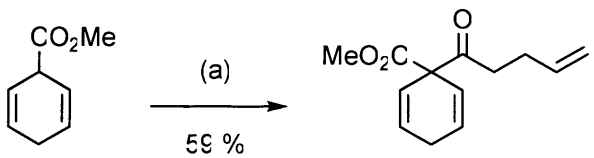


101 **103** **23**

(PG = protecting group)

Scheme 38. Retrosynthesis of compound **101**.

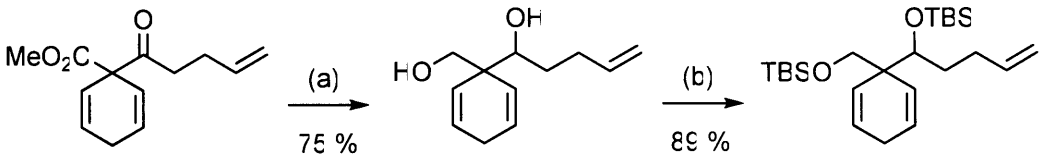
From previous work in the group, we knew that ester **23** could be acylated efficiently with acyl chlorides.[7a] As such we sought to install the alkenyl side-chain with 4-pentenoyl chloride, which was made by a known literature procedure from 4-pentenoic acid.[31] Ester **23** was deprotonated by treatment with LDA and, following reaction of the resulting enolate with 4-pentenoyl chloride, gave compound **104** in good yield (**Scheme 39**).



23 **104**

Scheme 39. *Reagents and Conditions*: (a) LDA, THF, -78 °C then 4-pentenoyl chloride.

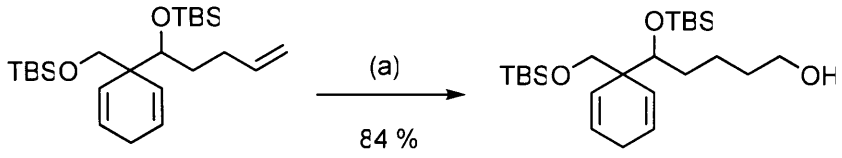
The β-keto-ester **104** was then globally reduced with $LiAlH_4$ and the resulting diol **105** was treated with TBSOTf to protect the free hydroxyl groups as silyl ethers (**Scheme 40**).



104 **105** **106**

Scheme 40. *Reagents and Conditions*: (a) $LiAlH_4$, THF; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to room temperature, 18 h.

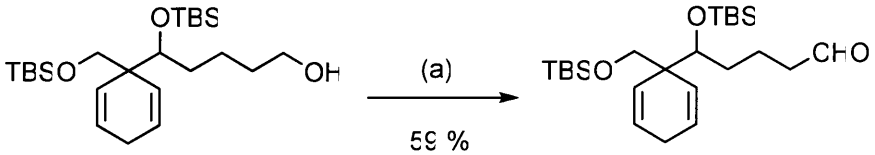
Hydroboration of compound **106** required the use of a significantly hindered organoborane, which would selectively attack the terminal alkene rather than the cyclohexadiene double bonds. For this purpose, 9-BBN was chosen. Treatment of compound **106** with 9-BBN in THF, followed by a hydrogen peroxide work-up gave the bis-protected triol **107** in excellent yield (**Scheme 41**).



106 **107**

Scheme 41. *Reagents and Conditions*: (a) 9-BBN, THF, 18 h then H_2O_2, NaOH.

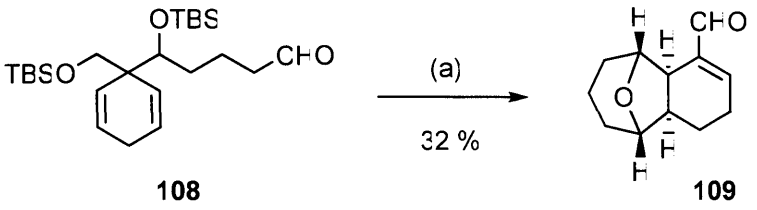
Compound **107** was subsequently oxidised to the aldehyde **108**, using PDC as the oxidising agent (**Scheme 42**).



107 **108**

Scheme 42. *Reagents and Conditions*: (a) PDC, CH_2Cl_2, 18 h.

With the aldehyde **108** in hand, we initially decided to treat this compound directly with triflic acid in an attempt to effect deprotection and subsequent Prins cyclisation/rearrangement in a one-pot reaction. Compound **108** was treated with 1 equivalent of triflic acid in dichloromethane for 20 minutes at room temperature. We were very pleased to find that this gave compound **109** as a single diastereoisomer, albeit in moderate yield (**Scheme 43**).



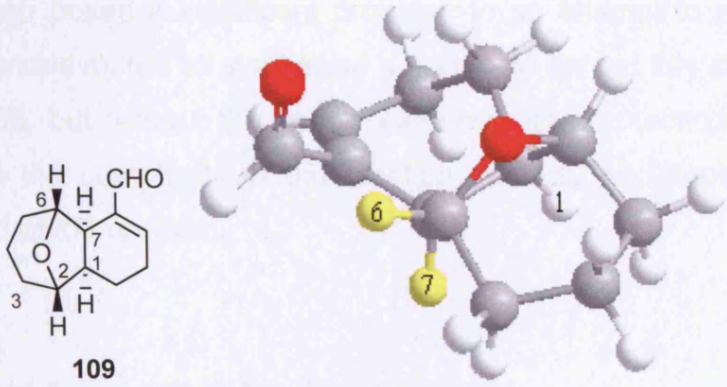
108 **109**

Scheme 43. *Reagents and Conditions*: (a) TfOH (1 equiv.), CH_2Cl_2, 0 °C to room temperature, 20 minutes.

The mass balance for the reaction was low, such that the crude reaction mixture consisted almost entirely of compound **109**. The relatively low yield observed can be attributed to the complexity of the chemistry involved in the sequence; deprotection of the primary and secondary alcohols followed by lactol formation, oxocarbenium ion generation and the Prins cyclisation/rearrangement. Attempts were made to improve the overall efficiency of the process by initial deprotection of compound **97**, but to no avail. Treatment of the aldehyde **108** with TBAF in THF resulted in a complex mixture of products.

Confirming the stereochemistry of compound **109** was not straightforward as there were no diagnostic cross-peaks in the NOESY NMR spectrum. However, based on molecular modelling of the two possible diastereoisomers, the observed ^{1}H NMR coupling constants are far more compatible with compound **109**. For example the signal for H-7 in the ^{1}H NMR spectrum appears as a doublet of *J* 8.6 Hz and H-1 shows an 8.6 Hz coupling, which is presumably to H-7. We would expect H-7 to show coupling to both H-1 and H-6. However molecular modelling of diastereoisomer **109** shows that the dihedral angle

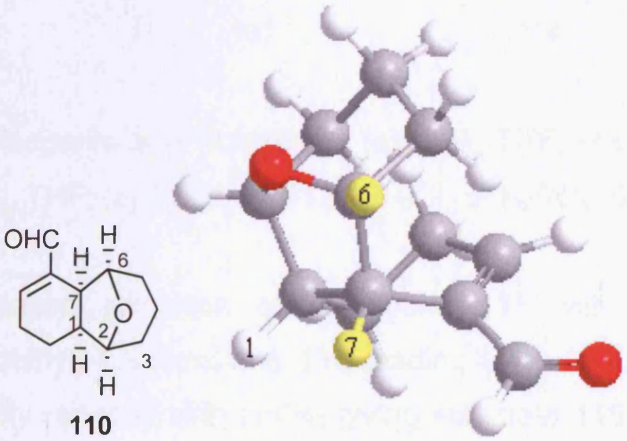
between H-6 and H-7 is approaching 90°, as illustrated in **Figure 12**. As such, a coupling constant of close to 0 Hz would be expected between these two protons, so it is very feasible that the signal of H-7 would appear as a doublet of *J* 8.6 Hz in the ^{1}H NMR spectrum of this diastereoisomer.



109

Figure 12. Chem3D representation of diastereoisomer **109**.

For the alternative diastereoisomer **110**, molecular modelling shows that the dihedral angle between H-6 and H-7 is approaching 0°, as illustrated in **Figure 13**. Hence for this diastereoisomer, a relatively large coupling constant would be expected between these two protons, so we would expect a more complex coupling pattern for H-7 than is observed.



110

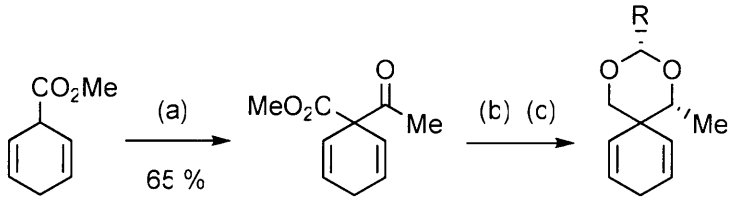
Figure 13. Chem3D representation of diastereoisomer **110**.

Owing to this evidence and our previous mechanistic reasoning, we are confident in the stereochemical assignment of compound **109**.

We were very pleased with this result; we had obtained the cladiellin core as a single diastereoisomer in relatively few synthetic steps. However, the low yield of our key step posed a significant problem. In an attempt to overcome this problem we endeavoured to synthesise a substrate for our key step, similar to compound **108**, but without the use of extensive silyl protecting groups. This would reduce the complexity of the reaction pathway and hopefully improve upon the yield of the reaction.

2.2.2 Improved Approach to the Cladiellin Core

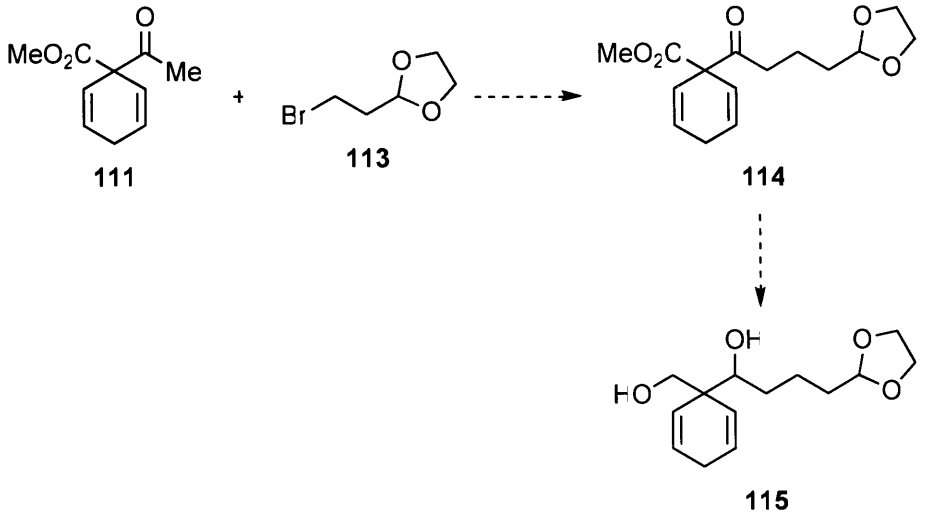
Previous work in the group had identified β-keto-ester **111** as an intermediate in the synthesis of a number of the chiral acetals **112** used in the initial Prins cyclisation/rearrangement studies (**Scheme 44**).[7a]



23 **111** **112**

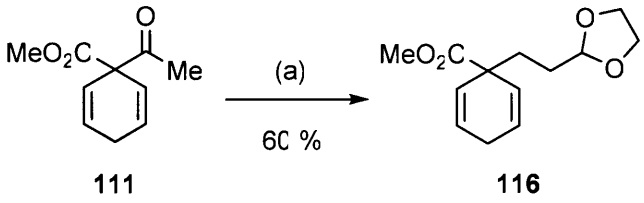
Scheme 44. *Reagents and Conditions*: (a) LDA, THF, -78 °C then AcCl; (b) $LiAlH_4$, THF; (c) RCHO, PPTS, CH_2Cl_2 or H_2SO_4, DMF.

We originally envisaged alkylation of compound **111** with commercially available 2-(2-bromoethyl)-1,3-dioxolane **113** leading to compound **114**. This could then be globally reduced with $LiAlH_4$ giving substrate **115** for the Prins reaction in very few steps (**Scheme 45**).



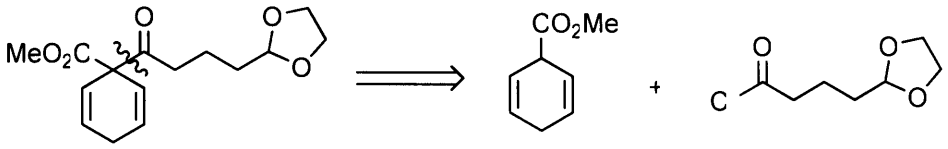
Scheme 45. Proposed synthesis of substrate **115**.

Unfortunately, treatment of compound **111** with LDA as base resulted in deacylation of the β-keto-ester **111** and the resulting anion went on to react with the 2-(2-bromoethyl)-1,3-dioxolane **113** to give compound **116**, as shown in **Scheme 46**.



Scheme 46. *Reagents and Conditions*: (a) LDA, THF, -78 °C then 2-(2-bromoethyl)-1,3-dioxolane **113**.

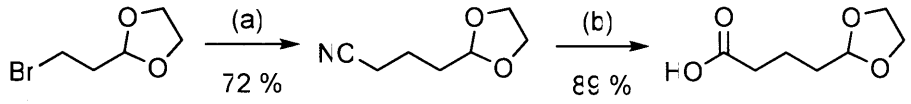
Owing to this result, we attempted a different approach (**Scheme 47**). Again, with the knowledge that ester **23** could be readily alkylated with acyl chlorides, we endeavoured to synthesise compound **117**. This would hopefully then allow access to compound **114** and subsequently substrate **115**.



114 23 117

Scheme 47. Retrosynthesis of compound **103**.

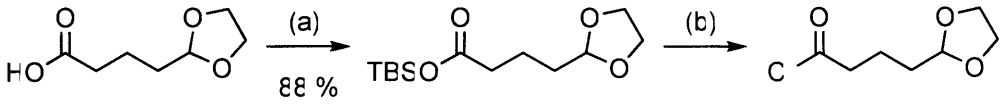
Starting with 2-(2-bromoethyl)-1,3-dioxolane **113**, a two carbon homologation was performed with acetonitrile, to give nitrile **118** in good yield. Hydrolysis of compound **118** with KOH in EtOH/H_2O (2:1) gave acid **119**, as shown in **Scheme 48**.



113 118 119

Scheme 48. *Reagents and Conditions*: (a) LDA, MeCN, THF, -78 °C to room temperature, 18 h; (b) KOH, EtOH/H_2O (2:1), reflux, 16 h.

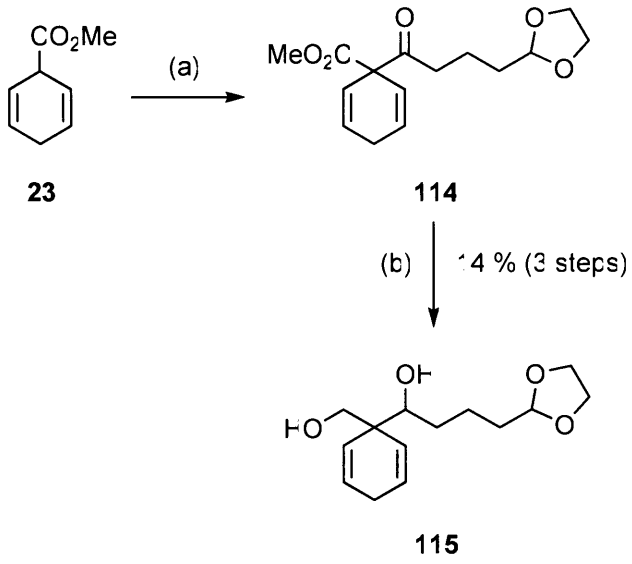
The group of Wissner reported a strategy for forming acyl chlorides from carboxylic acids containing additional acid-sensitive functionality.[32] The methodology involved converting the acid to the corresponding *tert*-butyldimethylsilyl ester, which was then treated with oxalyl chloride and catalytic DMF at room temperature to give the acyl chloride. This enabled the formation of acyl chlorides under much milder conditions than would usually be required. Applying these conditions to acid **119**, silyl ester **120** was obtained in excellent yield and was converted successfully into compound **117** (**Scheme 49**).



119 120 117

Scheme 49. *Reagents and Conditions*: (a) TBS-Cl, imidazole, 4-DMAP, CH_2Cl_2, 30 minutes; (b) $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C to room temperature, 2 h.

The acyl chloride **117** was relatively unstable, such that any attempts at purification resulted in its decomposition. As a result, it was used directly in subsequent reactions and an isolated yield was never recorded. Alkylation of ester **23** proceeded smoothly and the resulting keto-ester **114** was immediately reduced with $LiAlH_4$ to give compound **115** (**Scheme 50**).

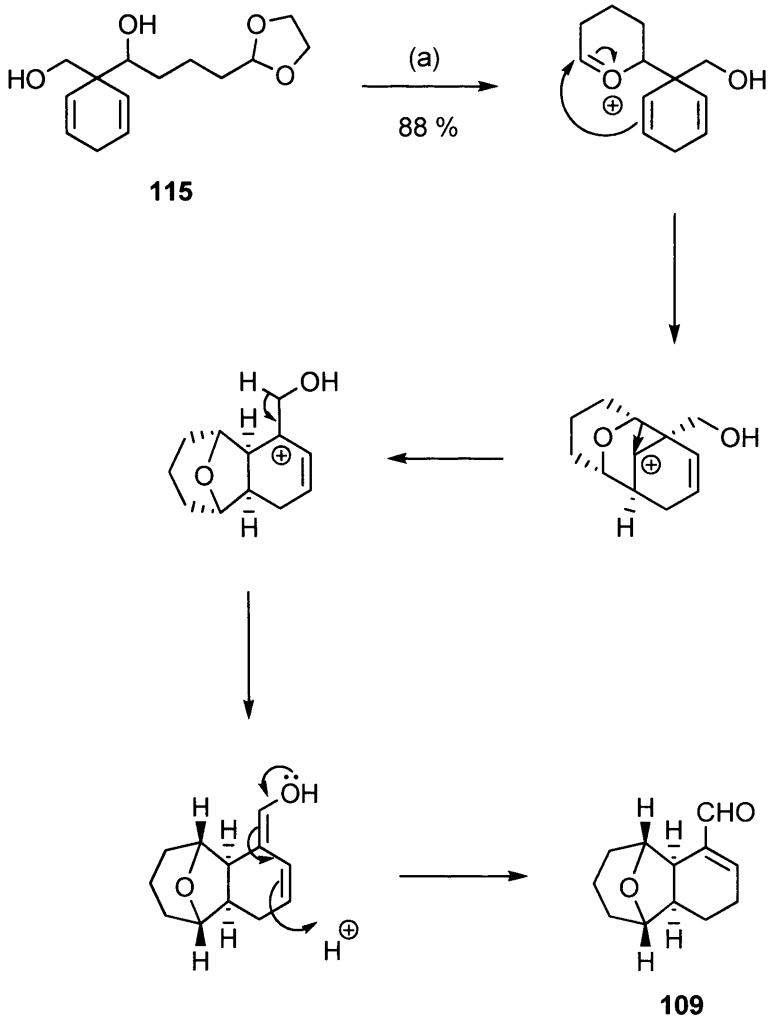


23 114 115

Scheme 50. *Reagents and Conditions*: (a) LDA, THF, -78 °C then **117**; (b) $LiAlH_4$, THF.

The stated yield of compound **115** is low, although it actually represents the yield over 3 steps from the silyl ester **120**. In any case, the sequence yielded enough of substrate **115** to test our key Prins cyclisation/rearrangement reaction. Gratifyingly, treatment of compound **115** with triflic acid under the

same conditions as before gave compound **109** as a single diastereoisomer in 88 % yield (**Scheme 51**).



Scheme 51. *Reagents and Conditions*: (a) TfOH (1 equiv.), CH_2Cl_2, 0 °C to room temperature, 20 minutes.

2.3 Conclusion

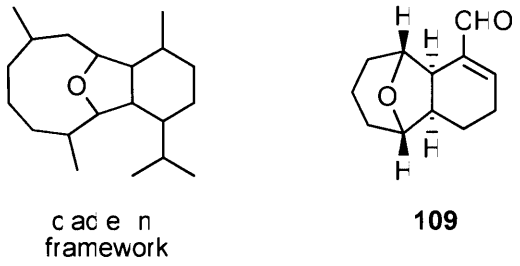
A model for the hydroisobenzofuran core (**109**) of the cladiellin diterpenes has been synthesised, as a single diastereoisomer, using Prins cyclisation/rearrangement methodology developed within the group. A revised approach enabled our key step to be optimised to an excellent 88 % yield. The results obtained now provided scope for access to the cladiellin diterpenes.

Chapter 3

Studies Towards the Synthesis of the Cladiellin Framework

3.1 Introduction

With our model of the cladiellin core in hand, we could now think about expanding the model to approach the cladiellin framework. In order to achieve this, we first needed to find a way of incorporating a larger ring size into the system. As previously stated, the cladiellins contain a nine-membered oxacyclic component in addition to the octahydroisobenzofuran moiety, whereas our model compound (**109**) only contains an additional six-membered ring (**Figure 14**).

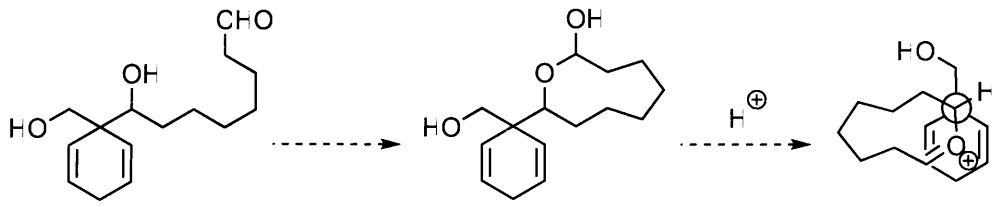


c ac e n framework

109

Figure 14.

We considered that attempting to install the nine-membered ring directly by formation of a nine-membered lactol **122** and generation of the corresponding oxocarbenium ion **123** (**Scheme 52**) would be a near-impossible task.

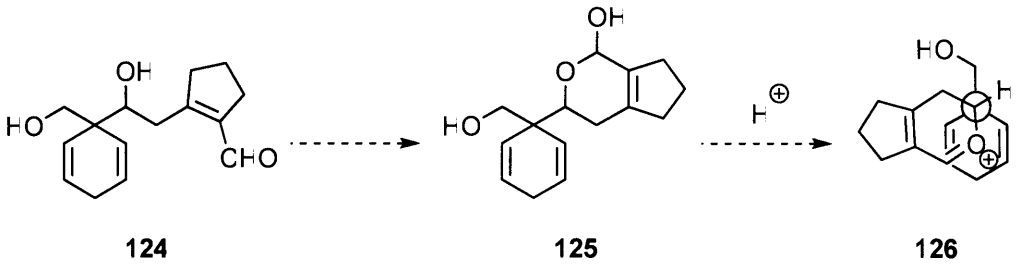


121 **122** **123**

Scheme 52.

Consequently, we proposed that a compound of structure **125** with an additional five-membered ring fused onto the six-membered lactol might be more easily obtained (**Scheme 53**). Subsequent generation of the

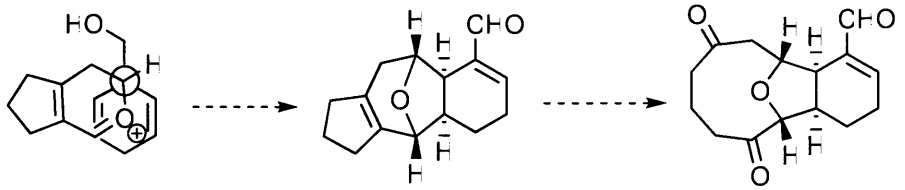
corresponding oxocarbenium ion **126** is also more plausible as we have already demonstrated the formation and successful Prins cyclisation of a six-membered cyclic oxocarbenium ion in the model studies.



124 **125** **126**

Scheme 53. Proposed Prins substrate.

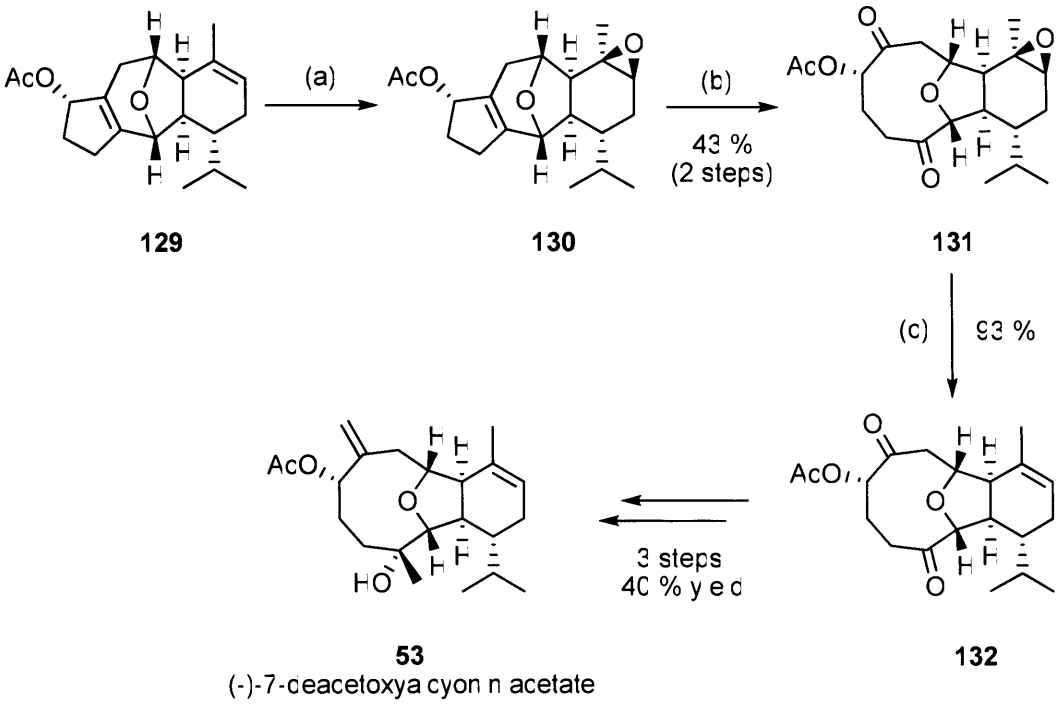
Successful Prins cyclisation/rearrangement of oxocarbenium ion **126** would theoretically give compound **127** (**Scheme 54**). From this point, we could consider converging with Molander's approach to the cladiellin skeleton.[26] We could envisage selective oxidative cleavage of the tetra-substituted double bond, to give the nine-membered ring directly,[33] as shown in **Scheme 54**.



126 **127** **128**

Scheme 54. Proposed selective oxidative cleavage of compound **127**.

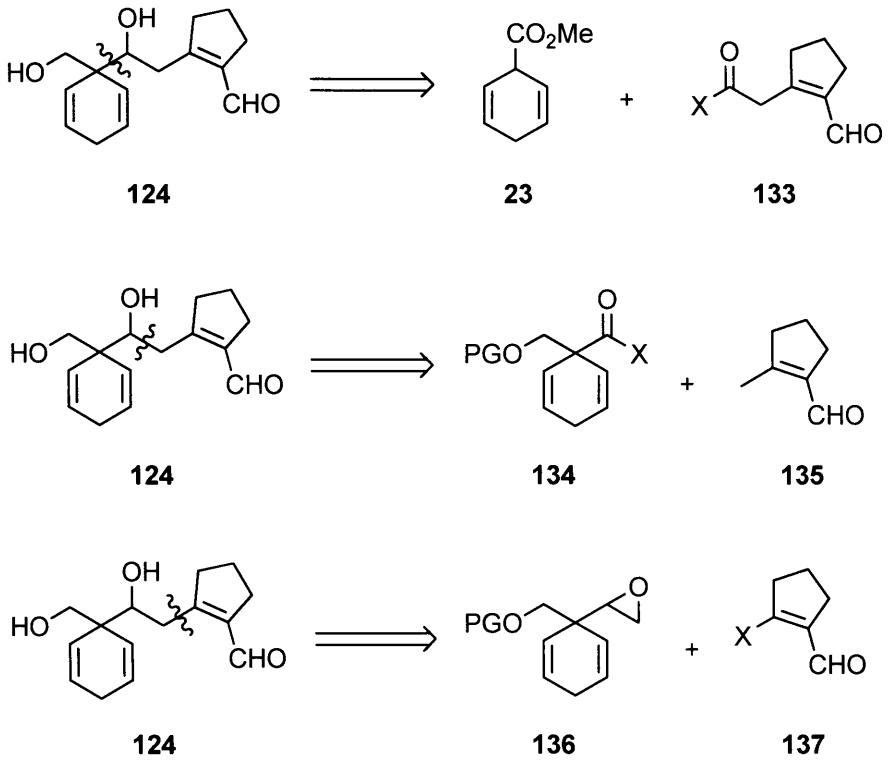
However, the Molander group were unable to achieve selective oxidative cleavage of the tetra-substituted double bond in a similar compound, during their synthesis of (-)-7-deacetoxyalcyonin acetate **53**.[26a] To overcome this problem, Molander *et al.* chemoselectively protected the tri-substituted double bond as the epoxide **130** before the oxidative cleavage step (**Scheme 55**). The epoxide **130** was subsequently reduced using Sharpless' reagent and a further three synthetic steps led to (-)-7-deacetoxyalcyonin acetate **53**.



Scheme 55. *Reagents and Conditions*: (a) *m*-CPBA, 0 °C, 1 h; (b) O_3, -78 °C, then DMS, room temperature, 3 h; (c) WCl_6, *n*-BuLi (2 equiv.).

Molander's work would suggest that selective oxidative cleavage of compound **127** could be difficult, although the presence of the more electron-deficient enal in compound **127** might facilitate more selective cleavage of the tetra-substituted double bond. If selective cleavage is not possible, the enal could potentially be protected as the epoxide first, to allow cleavage of the desired double bond.

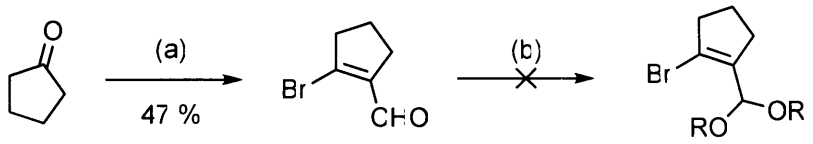
There are a number of possible retrosynthetic approaches to substrate **124**, a few of which are illustrated in **Scheme 56**. We chose the third approach as our starting point. We proposed that if we could synthesise compound **137**, where X is a halogen, we could generate the corresponding organolithium reagent *via* a lithium-halogen exchange. This could then be reacted with the epoxide **136** to give our desired substrate **124**.



Scheme 56. Retrosyntheses of substrate **124**.

3.2 Results and Discussion

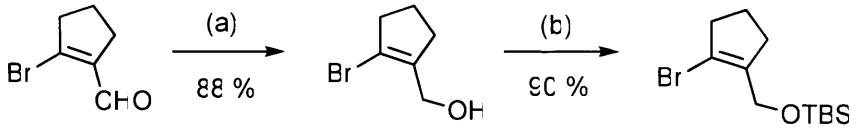
2-Bromocyclopent-1-enecarbaldehyde **139** was easily prepared from cyclopentanone **138** by a known literature procedure (**Scheme 57**).[34] Before any subsequent organolithium reactions however, the aldehyde **139** needed to be protected. We originally envisaged protecting the aldehyde functionality as an acetal **140**. Unfortunately any attempts at forming an acetal, under a variety of standard conditions, resulted in decomposition of the aldehyde **139**.



138 **139** **140**

Scheme 57. *Reagents and Conditions*: (a) PBr_3, DMF, CH_2Cl_2, 0 °C to room temperature, 18 h; (b) *Attempted Conditions*: (i) MeOH, NH_4Cl, reflux, 1 h; (ii) MeOH, NH_4Cl, room temperature, 18 h; (iii) MeOH, TMSCl, room temperature, 16 h.

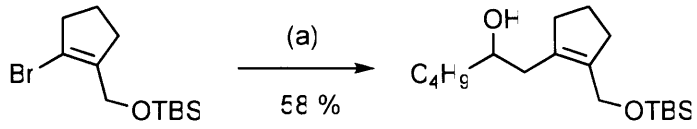
As a result, we decided to reduce the aldehyde **139** and protect the resulting alcohol **141**, in the hope that deprotection and subsequent oxidation could be achieved at a later stage. Treatment of aldehyde **139** with sodium borohydride, according to a known literature procedure,[35] gave compound **141,** which was subsequently protected as the silyl ether **142** (**Scheme 58**).



139 **141** **142**

Scheme 58. *Reagents and Conditions*: (a) $NaBH_4$, MeOH, 0 °C to room temperature, 1 h; (b) TBSCl, imidazole, 4-DMAP, CH_2Cl_2, 18 h.

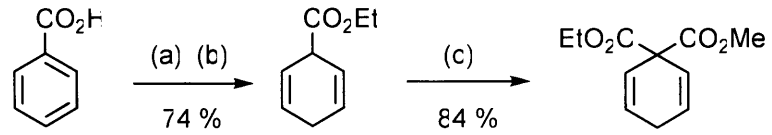
In order to test whether compound **142** could be effectively lithiated and reacted with an epoxide, a model study was conducted. Compound **142** was treated with *t*-butyllithium and the resulting organolithium reagent was reacted with *n*-butyloxirane. Pleasingly, this gave compound **143** in good yield (**Scheme 59**).



142 **143**

Scheme 59. *Reagents and Conditions*: (a) *t*-BuLi, THF, -78 °C, then *n*-butyloxirane, $BF_3.OEt_2$.

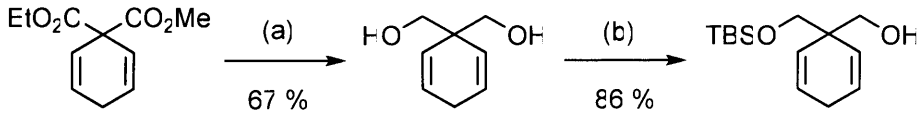
With this result in hand, we were confident in our approach and could now devise a synthesis of the desired epoxide **136**. Ester **144** was prepared by Birch reduction and subsequent esterification of benzoic acid **22**. Alkylation of ester **144** with methyl chloroformate afforded the diester **145** in excellent yield (**Scheme 60**).



22 **144** **145**

Scheme 60. *Reagents and Conditions*: (a) Na, NH_3-EtOH (4:1), -78 °C; (b) EtOH, H_2SO_4, 16 h; (c) LDA, THF, -78 °C, then methyl chloroformate.

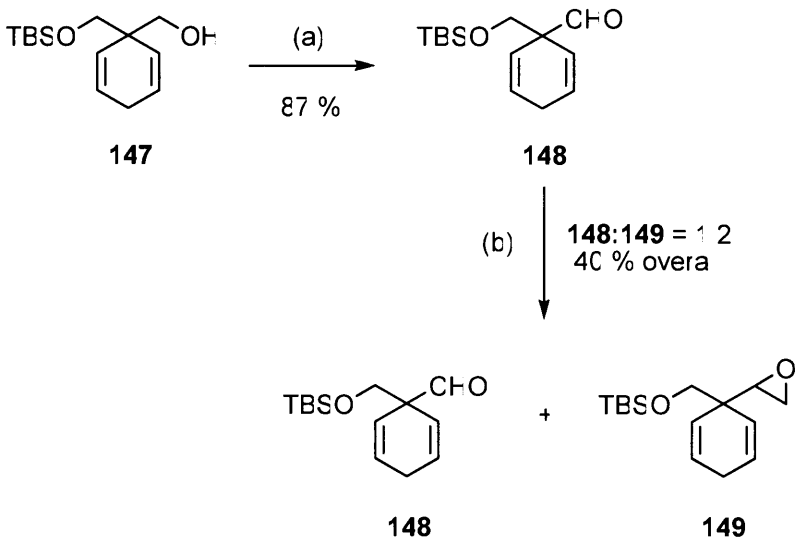
Compound **145** was then globally reduced by treatment with $LiAlH_4$ and the resulting diol **146** was mono-protected as the silyl ether **147** (**Scheme 61**).



145 **146** **147**

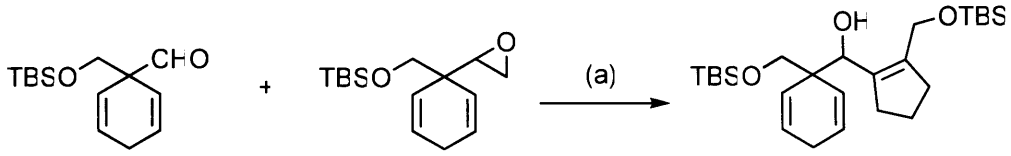
Scheme 61. *Reagents and Conditions*: (a) $LiAlH_4$, THF, 2 h; (b) *n*-BuLi, -78 °C to room temperature, then TBSCl, imidazole, 16 h.

Oxidation of compound **147** under Swern conditions proceeded smoothly, giving aldehyde **148** in excellent yield. To make the epoxide **149**, aldehyde **148** was treated with dibromomethane and *n*-butyllithium. An incomplete reaction gave a 1:2 mixture of starting material and product, which were inseparable by column chromatography (**Scheme 62**).



Scheme 62. *Reagents and Conditions*: (a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 °C to room temperature, 2 h; (b) *n*-BuLi, CH_2Br_2, THF, -78 °C to room temperature, 18 h.

From this point, we decided to react the inseparable mixture of compounds **148** and **149** with the organolithium reagent derived from compound **142**, in the hope that we might be able to separate the two possible coupling products. Compound **142** was treated sequentially with *t*-butyllithium and the mixture of compounds **148** and **149**. Unfortunately, the only species isolated from the reaction was compound **150**, arising from coupling of the bromide **142** and the aldehyde **148** (**Scheme 63**).

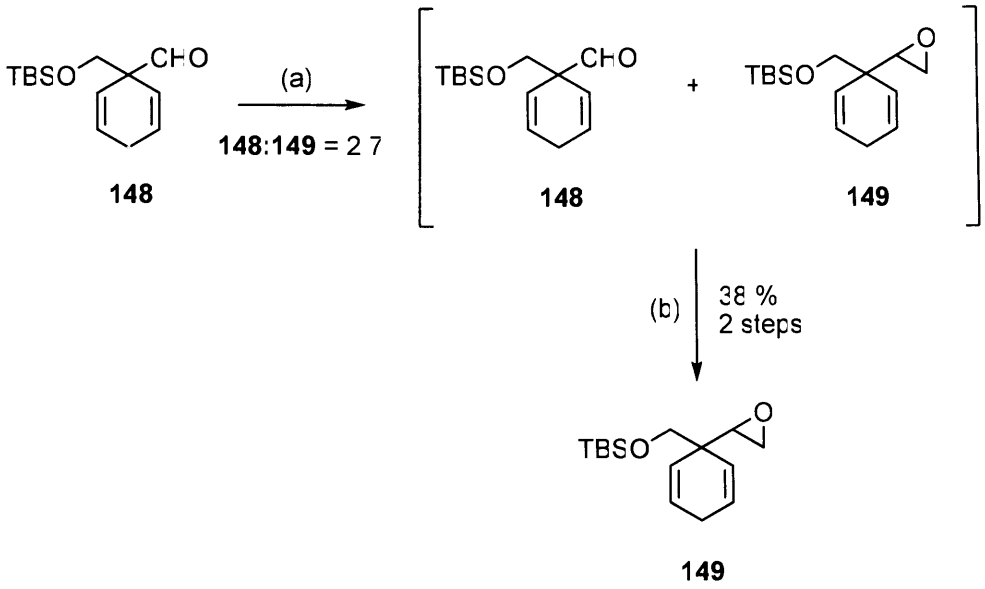


148 **149** **150** 65 %*

* *Yield based on the calculated amount of aldehyde **148** present in the 1:2 mixture of compounds **148** and **149**.*

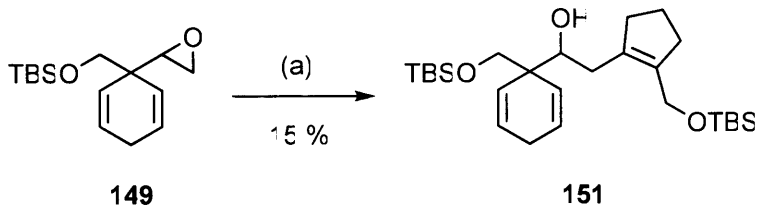
Scheme 63. *Reagents and Conditions*: (a) *t*-BuLi, **142**, $BF_3.OEt_2$, THF, -78 °C.

Compound **150** could theoretically be elaborated to give a substrate for our Prins cyclisation reaction, but it would give the wrong ring size for the cladiellin framework. Consequently, we decided it was necessary to find a way of either driving the epoxide formation to completion, or separating the aldehyde **148** and epoxide **149** after the reaction. In an effort to achieve this, the reaction time of the epoxide formation was increased from 18 h to 24 h. While this still gave incomplete conversion of the starting material, we did see an increase in the amount of epoxide **149** formed relative to recovered aldehyde **148** (**Scheme 64**). We were then able to treat the mixture of compounds **148** and **149** with sodium borohydride to reduce the remaining aldehyde **148** to the alcohol **147**, allowing facile isolation of the epoxide **149**.



Scheme 64. *Reagents and Conditions*: (a) *n*-BuLi, CH_2Br_2, THF, -78 °C to room temperature, 24 h; (b) $NaBH_4$, MeOH, 0 °C to room temperature, 1 h.

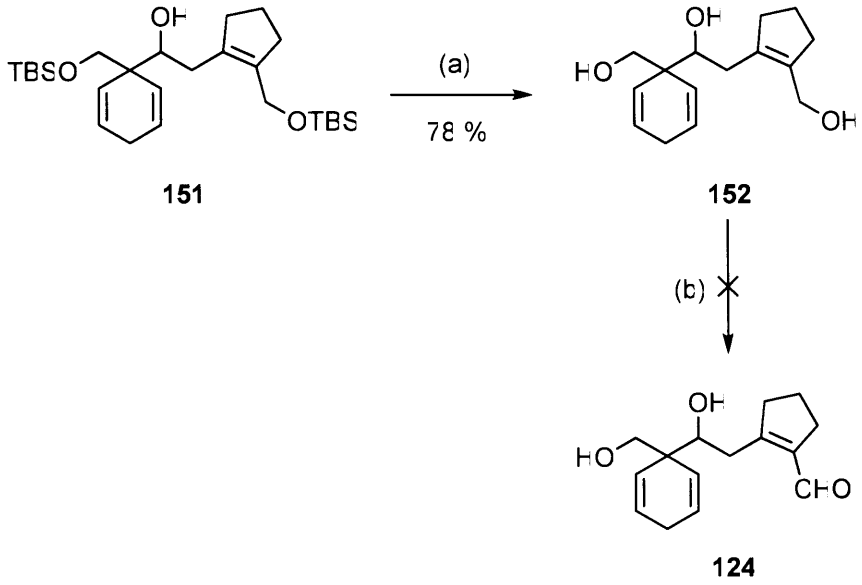
With the epoxide **149** in hand, we were now in a position to attempt coupling the two fragments. Compound **149** was treated with the organolithium reagent derived from compound **142** and gratifyingly this gave compound **151**, albeit in a relatively low yield (**Scheme 65**).



Scheme 65. *Reagents and Conditions*: (a) *t*-BuLi, **142**, $BF_3.OEt_2$, THF, -78 °C.

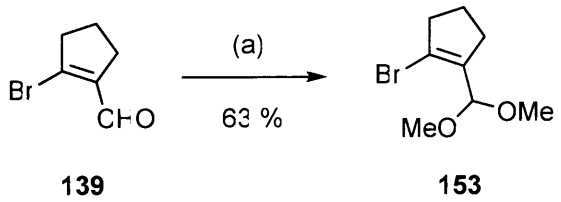
From this point, we envisaged global deprotection of compound **151** followed by selective oxidation of the allylic alcohol, to give the substrate **124** for our key Prins cyclisation/rearrangement step. Unfortunately, whilst effective deprotection of both primary alcohols was possible, attempted selective

oxidation of the allylic alcohol with manganese dioxide resulted in a complex mixture of products (**Scheme 66**).



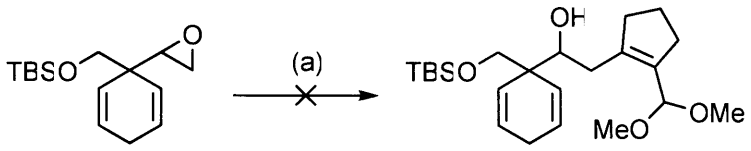
Scheme 66. *Reagents and Conditions*: (a) TBAF, THF, 18 h; (b) MnO_2, CH_2Cl_2, room temperature, 1 h.

Owing to the limited amount of compound **151** we were able to synthesise, rather than testing a range of different oxidising agents at this point, we devised a new plan. We decided it was necessary to develop a more orthogonal protecting group strategy, preferably working with the cyclopentene fragment at the desired aldehyde oxidation level. Pleasingly, searching the literature identified a procedure for protecting aldehyde **139** as the dimethyl acetal **153** (**Scheme 67**).[36]



Scheme 67. *Reagents and Conditions*: (a) $CH(OMe)_3$, MeOH, camphorsulfonic acid, 18 h.

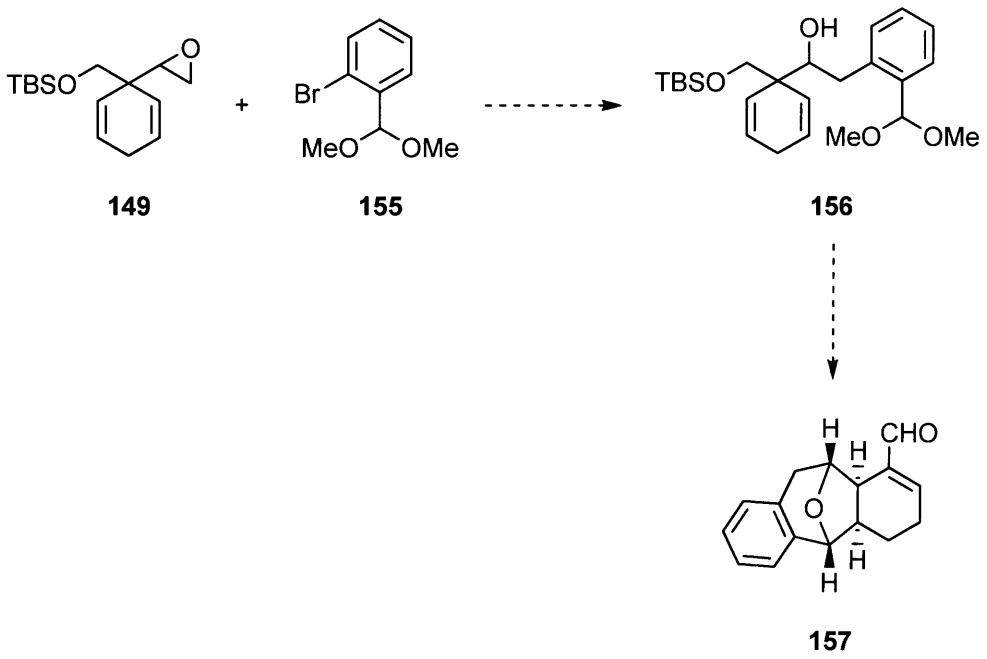
However, compound **153** proved to be relatively unstable and unfortunately any attempts at effecting lithiation and subsequent reaction with the epoxide **149** were unsuccessful (**Scheme 68**).



149 **154**

Scheme 68. *Reagents and Conditions*: (a) *t*-BuLi, **153**, $BF_3.OEt_2$, THF, -78 °C.

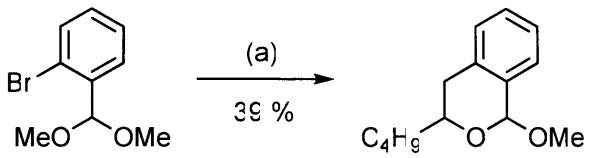
Owing to this result, we decided to carry out another model study. We considered that acetal **155**, with a benzene ring in place of the cyclopentene ring, might be more stable and more easily reacted with the epoxide **149** (**Scheme 69**). The presence of the benzene ring in substrate **156** should still allow it to undergo successful Prins cyclisation reaction, although obviously the product **157** could not be further elaborated to achieve the cladiellin framework. However, this study would provide proof of concept.



149 **155** **156** **157**

Scheme 69. Proposed model study.

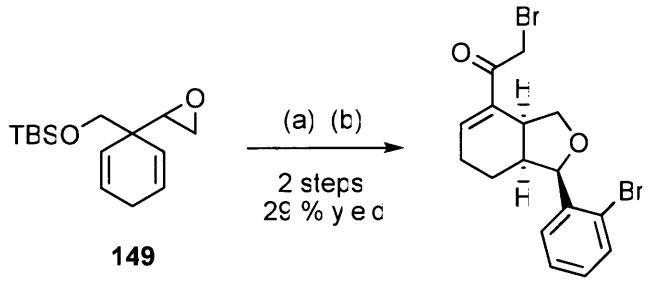
Acetal **155** was prepared according to a known literature procedure.[37] In order to assess the ability to lithiate compound **155** and react it with an epoxide, a test reaction was conducted. Compound **155** was treated with *t*-butyllithium, followed by *n*-butyloxirane and gratifyingly this gave compound **158**, albeit in moderate yield (**Scheme 70**).



155 **158**

Scheme 70. *Reagents and Conditions*: (a) *t*-BuLi, THF, -78 °C, then *n*-butyloxirane, $BF_3.OEt_2$.

With this result in hand, the reaction was repeated, this time with epoxide **149** instead of *n*-butyloxirane. After chromatography on silica gel, the reaction initially appeared to have given compound **156**, by analysis of ^1H and ^{13}C NMR spectroscopic data. However, submitting this reaction product to our Prins cyclisation conditions did not give the desired compound **157**. Instead, the major product of the reaction was compound **159**, as shown in **Scheme 71**.

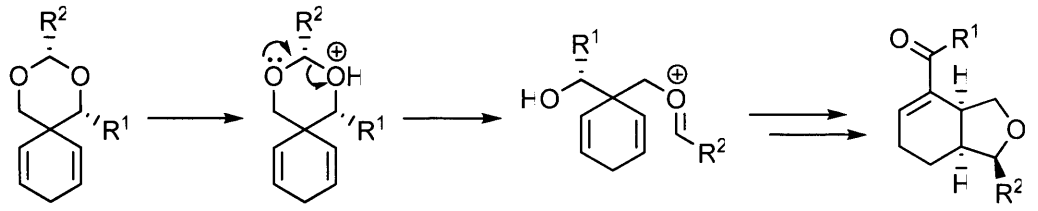


149 **159**

Scheme 71. Apparent outcome of reaction. *Reagents and Conditions*: (a) *t*-BuLi, **155**, $BF_3.OEt_2$, THF, -78 °C; (b) TfOH (2 equiv.), CH_2Cl_2, 0 °C to room temperature, 25 minutes.

The structural assignment of compound **159** was by no means straightforward. Extensive analysis of ^{1}H and ^{13}C NMR spectroscopic data, and $^{1}H - ^{1}H$ and $^{1}H - ^{13}C$ correlation data (COSY, HMBC and HSQC) enabled determination of the carbon-hydrogen framework connectivity. Mass spectrometric studies identified the presence of the two bromine atoms in the compound **159**.

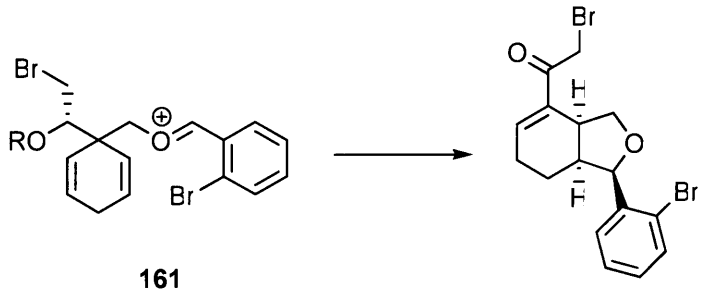
The unexpected formation of compound **159** clearly showed that the isolated species from the coupling reaction was not compound **156**. Ketone products, similar to compound **159**, were observed in our group's original Prins cyclisation studies.[7b] As previously stated (see *Chapter 2*), these products arise from protonation of the more hindered oxygen atom of the cyclic acetal **90**, and the reaction proceeds *via* an oxocarbenium ion **160**, as illustrated in **Scheme 72**.



90 **160** **96**

Scheme 72. Origin of ketone **96**.

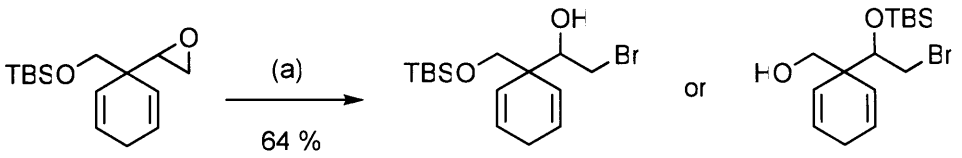
Owing to this, we can deduce that we must be generating a similar oxocarbenium ion (**161**) in the formation of compound **159**, as shown in **Scheme 73**.



161 **159**

Scheme 73. Formation of compound **159**.[38]

The coupling reaction between epoxide **149** and compound **155** was subsequently repeated under similar conditions (**Scheme 74**). This time, after extensive chromatography of the crude reaction mixture on silica gel, one of two possible regioisomers **162** and **163** was isolated. The regiochemistry, with regards to the position of the silyl group, could not be ascertained spectroscopically.

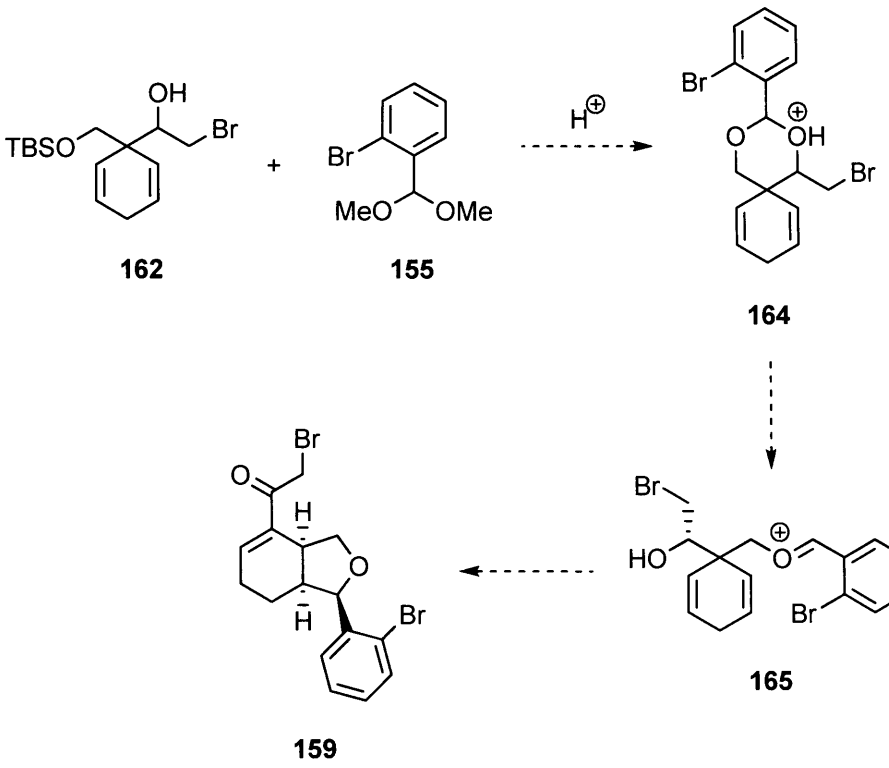


149 **162** **163**

Scheme 74. *Reagents and Conditions*: (a) *t*-BuLi, **155**, BF_3.THF, THF, -78 °C.

Subsequent re-evaluation of the ^1H and ^{13}C NMR spectroscopic data of the initial coupling reaction identified the presence of either compound **162** or compound **163**, along with one other major compound. This other compound was identified as acetal **155** by comparison of ^1H and ^{13}C NMR spectroscopic data, the recovery of which would suggest incomplete lithiation during the reaction.

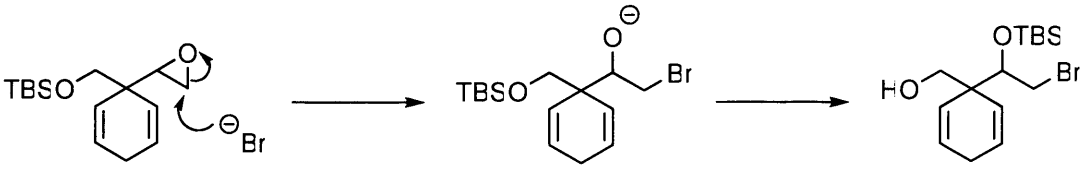
Owing to the fact that we must have generated oxocarbenium ion **161** to give the ketone product **159**, it seems far more likely that the silyl protecting group is on the secondary alcohol, as in compound **163**. For the alternative regioisomer **162**, silyl deprotection would need to occur before the Prins cyclisation/rearrangement sequence in order to generate the ketone product **159**. If this was the case, we might expect the reaction to proceed *via* a cyclic acetal intermediate **164** (**Scheme 75**). Formation of the necessary oxocarbenium ion **165** from this acetal **164** requires protonation of the more hindered oxygen atom, which would imply a directing effect from the bromine atom. Since this is highly unlikely, we can conclude with some confidence that the silyl group is on the secondary alcohol, as in compound **163**.



162 **155** **164** **165** **159**

Scheme 75.

Explaining this apparent silyl migration is not straightforward. Firstly, we might propose that the lithium bromide, generated from the lithium-halogen exchange of compound **155**, provides a source of bromide, which preferentially opens the epoxide **149**, instead of the organolithium reagent doing so (**Scheme 76**). From this point, a direct silyl migration from the primary to the secondary alcohol would give compound **163**.



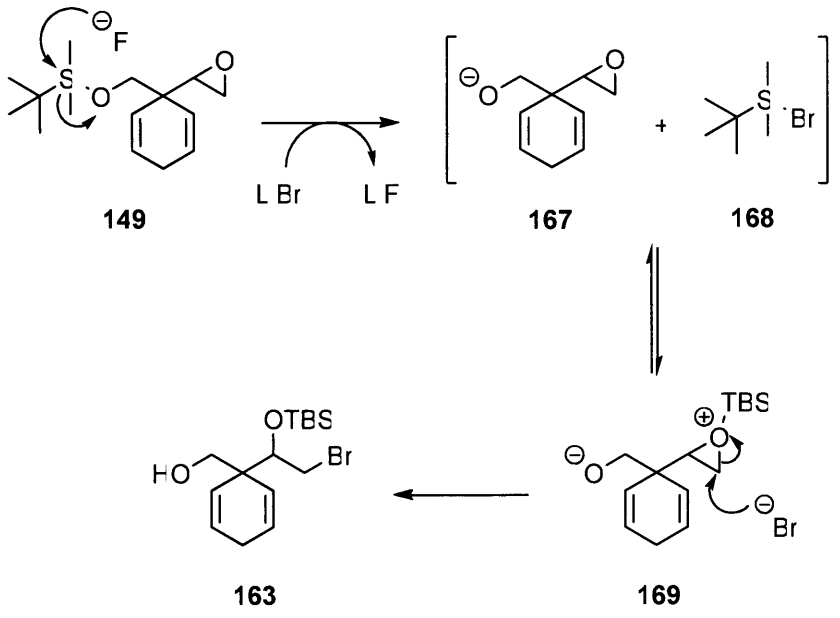
149 **166** **163**

Scheme 76. Direct silyl migration.

However, while there are many examples of silyl groups migrating from secondary to primary alcohols in the literature,[39] we could find no evidence of

primary to secondary migration, and we assume that such a process would be kinetically disfavoured.

Alternatively, we might consider that boron trifluoride present in the reaction mixture, instead of activating the epoxide **149**, provides a source of fluoride for removal of the TBS group from the primary alcohol. The lithium bromide generated then provides a source of bromide, which exchanges with the fluoride to give the silyl bromide **168**. The group of Detty have reported the reaction of silyl halides with oxiranes giving silylated halohydrins.[40] The reaction is initiated by electrophilic attack of silicon onto the oxygen atom of the epoxide to give an oxonium ion **169**. Ring-opening by the halide then proceeds to give the silylated halohydrin **163** (**Scheme 77**).



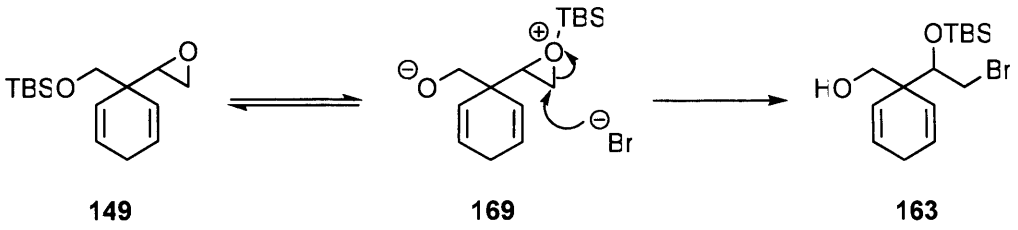
149 **167** **168** **163** **169**

Scheme 77. Reaction of silyl bromide **168** with epoxide **149**.

However, this pathway also seems unlikely. The displacement of fluoride with bromide would require breaking the comparatively strong silicon-fluorine bond, which would be energetically disfavoured under these reaction conditions.

Perhaps in fact, there is a combination of these two proposed pathways occurring, whereby the silyl group is removed and it coordinates directly to the

oxygen atom of the epoxide, giving oxonium ion **169**. Ring-opening by the bromide, derived from lithium bromide, then proceeds to give compound **163** (**Scheme 78**).

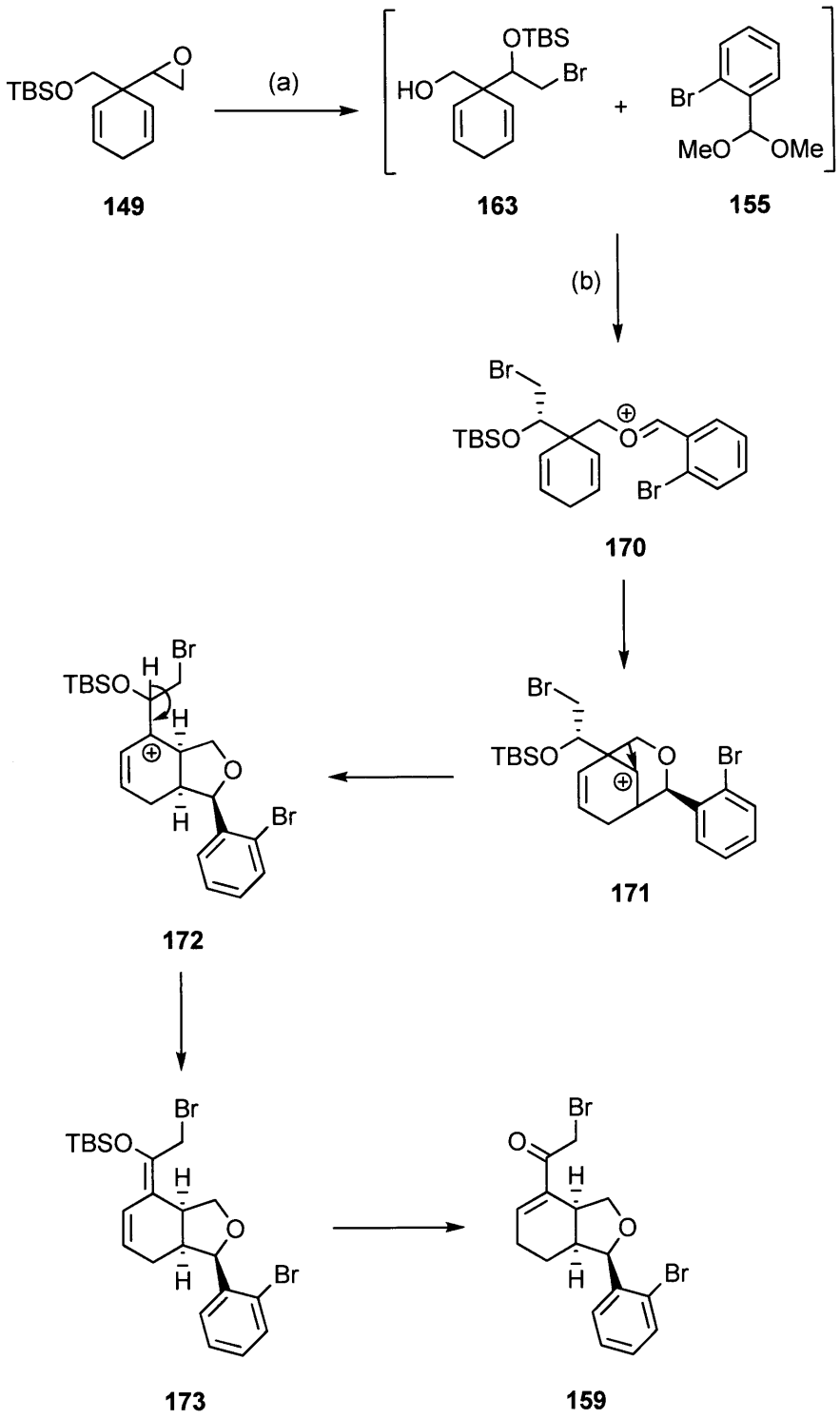


149 **169** **163**

Scheme 78. Proposed formation of compound **163**.

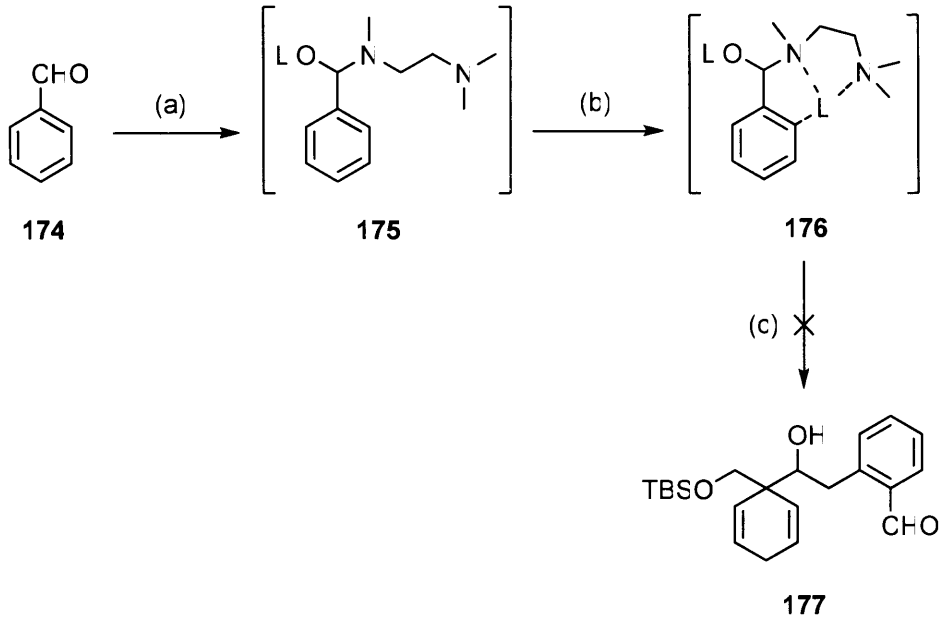
We subsequently reviewed ^{1}H NMR spectroscopic data of crude reaction mixtures from all of the previous attempts at coupling the various alkyl and aryl bromides with the epoxide **149**. In each case we were able to identify compound **163** as one of the major reaction products, showing that formation of this silylated bromohydrin is highly favoured under these conditions.

Having established the formation of regioisomer **163**, we could now propose a plausible mechanism for its subsequent reaction with compound **155** to give compound **159** (**Scheme 79**). Treatment of the mixture of compounds **155** and **163** with triflic acid results in them condensing to give oxocarbenium ion **170**. 6-*endo* cyclisation then proceeds onto one of the diastereotopic double bonds, followed by a Wagner-Meerwein shift to give cation **172**. Deprotonation gives the silyl enol ether **173**, and finally removal of the silyl protecting group and a keto-enol tautomerism gives compound **159**.



Scheme 79. Proposed pathway to compound **159**. *Reagents and Conditions*: (a) *t*-BuLi, **155**, $BF_3.OEt_2$, THF, -78 °C; (b) TfOH (2 equiv.), CH_2Cl_2, 0 °C to room temperature, 25 minutes.

Owing to the outcome of this sequence and the apparent role of the bromide in the attempted coupling reactions, in a final attempt to synthesise a substrate for our Prins cyclisation reaction, we considered that omission of the source of bromide in the reaction would remove the undesired reaction pathway. To achieve this we opted for a directed lithiation reaction, instead of the lithium-halogen exchange approach. Comins *et al.* have reported an effective strategy for directing ortho lithiation of benzaldehyde **174**.[41] This involves forming an α-amino alkoxide **175** with *N,N,N'*-trimethylethylenediamine, which has the effect of protecting the aldehyde functionality as well as directing lithiation (**Scheme 80**). Reaction of the lithiated species **176** with epoxide **149** was attempted, but unfortunately this gave a complex mixture of products.



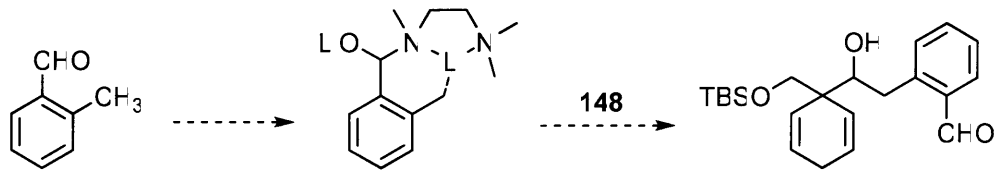
174 **175** **176** **177**

Scheme 80. *Reagents and Conditions*: (a) *N,N,N'*-trimethylethylenediamine, *n*-BuLi (1 equiv.), THF, -20 °C, 15 minutes; (b) *n*-BuLi (3 equiv.), 24 h; (c) **149**, BF_3.THF, -42 °C, 40 minutes.

3.3 Conclusion

From these studies it can be concluded that the described synthetic strategy is not ideal for approaching the cladiellin framework. The main weakness in the sequence appears to be the use of epoxide **149** as a synthetic intermediate. Formation of the silylated bromohydrin **163** appears to be the dominant process in each of the lithium-halogen exchange experiments with epoxide **149**. This process appears to be triggered by the removal of the silyl protecting group from the primary alcohol with boron trifluoride. Unfortunately, the use of boron trifluoride is necessary for activation of the epoxide, as no reaction is observed when this reagent is omitted. Whilst simply changing from a silyl protecting group might inhibit the undesired reaction process, the unreliable formation of the epoxide **149** from the aldehyde **148** still poses a significant problem.

However, the aldehyde **148** has been shown to react very effectively with the organolithium reagent derived from compound **142**. Owing to this, the next logical step would be to devise a strategy for using aldehyde **148** directly. Comins has also described a method for directed lateral lithiation of *o*-tolualdehyde **178**, again by forming an α-amino alkoxide with *N,N,N'*-trimethylethylenediamine.[41] Using these conditions, we could envisage coupling *o*-tolualdehyde **178** with aldehyde **148** directly, to give a model substrate **177** for the Prins cyclisation (**Scheme 81**).

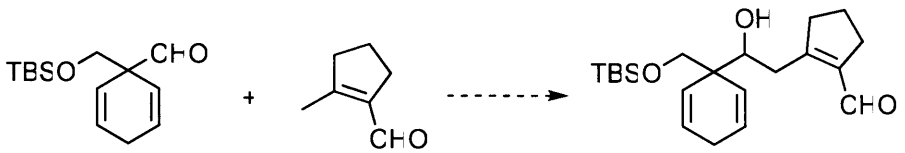


178 **179** **177**

Scheme 81. Proposed route to compound **177**.

If this approach proves successful, directed lateral lithiation of 2-methylcyclopent-1-enecarbaldehyde **180** and subsequent reaction with

aldehyde **148** is also plausible (**Scheme 82**). Successful Prins cyclisation of compound **181** would provide the desired ring system for installing the oxacyclononane moiety observed in the cladiellin diterpenes.



148 **180** **181**

Scheme 82.

Unfortunately, due to time constraints I was not able to pursue this proposed work, but hopefully it will provide a good starting point for future investigation.

Chapter 4

An Enantioselective Approach to Batzelladine C Methyl Ester

4.1 Introduction

4.1.1 The Batzelladine Alkaloids

The batzelladine alkaloids are a family of biologically and structurally intriguing natural products isolated from marine sources. Containing acyclic, bicyclic and tricyclic guanidine moieties, in some cases all within the same compound (**Figure 15**), the batzelladines present a significant synthetic challenge.

A total of 15 of these fascinating compounds have been isolated to date. The first, batzelladines A – E, were isolated from the Caribbean marine sponge *Batzella sp.* in 1995 by a group from SmithKline Beecham.[42] A further four compounds, batzelladines F – I, were isolated two years later.[43] Batzelladine J was isolated from the Caribbean marine sponge *Monanchora unguifera* in 2005,[44] and finally batzelladines K – N and dehydrobatzelladine C were isolated from the same sponge in 2007.[45]

The batzelladine alkaloids exhibit an interesting array of biological activity. Most significantly, a number of these natural products have been shown to exhibit anti-HIV functionality.[42,44,45] The HIV virus affects the human immune system by targeting vital cells, particularly CD4+ T-cells. When the number of CD4+ cells falls below a certain critical level, the immune system loses its ability to regenerate and combat other infections.[46] HIV binds to the CD4 receptor through the gp120 protein on the surface of the virus.[47] A number of the batzelladine alkaloids and batzelladine analogues have been shown to inhibit gp120-CD4 binding.[41,48]

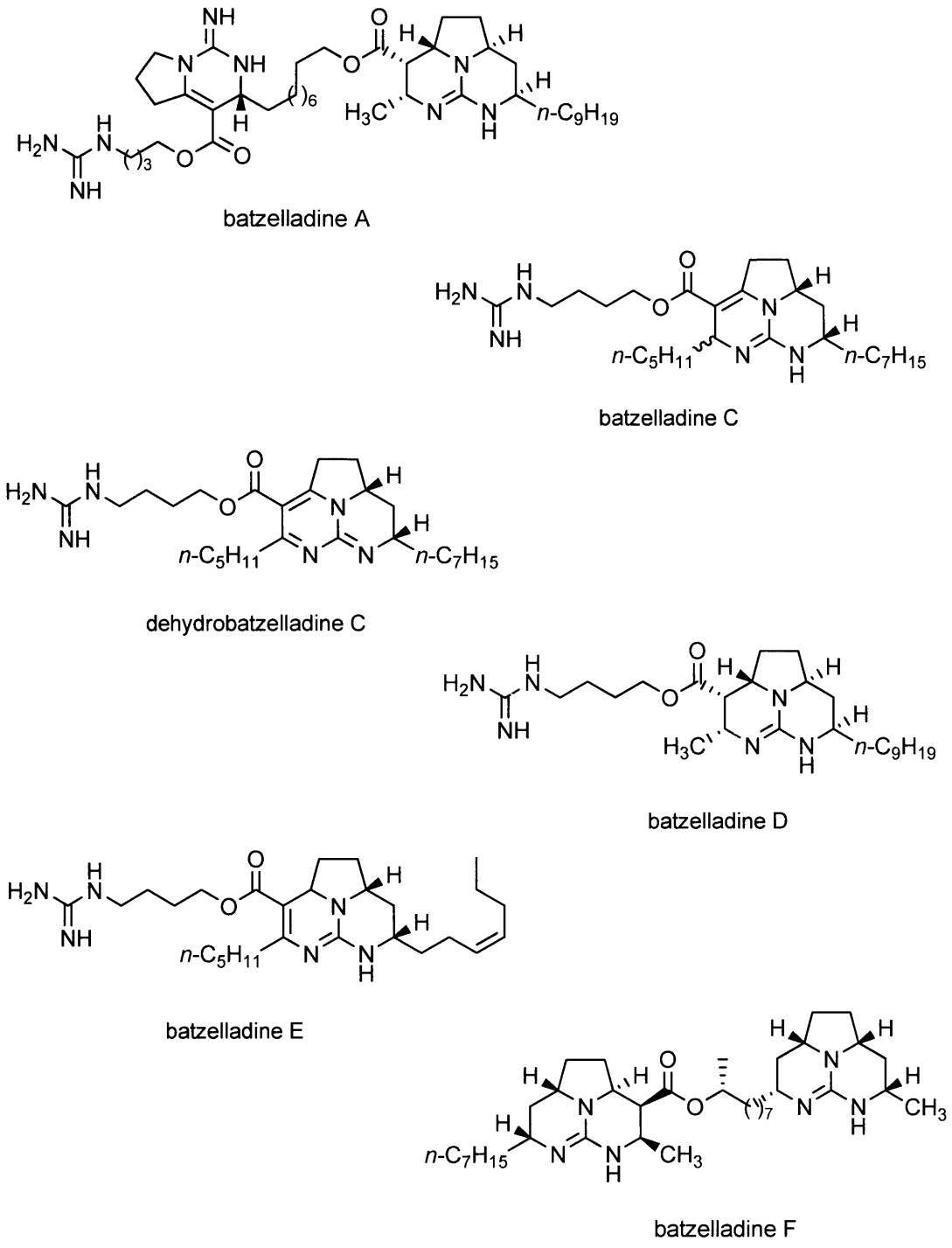
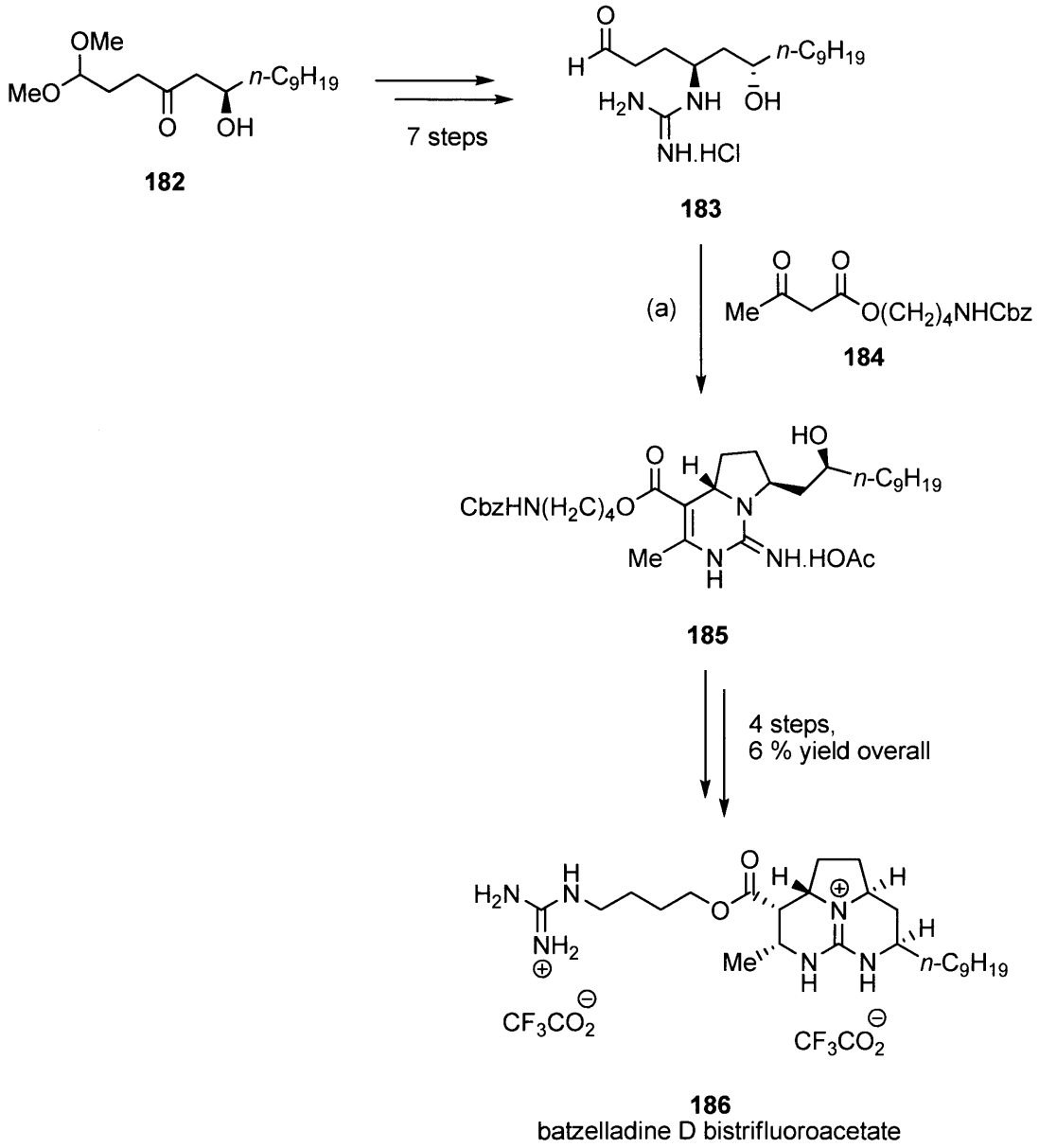


Figure 15. Representative examples of the batzelladine alkaloids.

Owing to their challenging structures and biological potential, the batzelladines have seen a great deal of interest from a number of research groups in recent years, particularly the groups of Overman,[49] Gin,[50] Nagasawa,[51] Snider,[52] Murphy[53] and Evans.[54] The Overman group reported the first enantioselective total synthesis of a batzelladine alkaloid, batzelladine D, in 1999.[49a] Overman

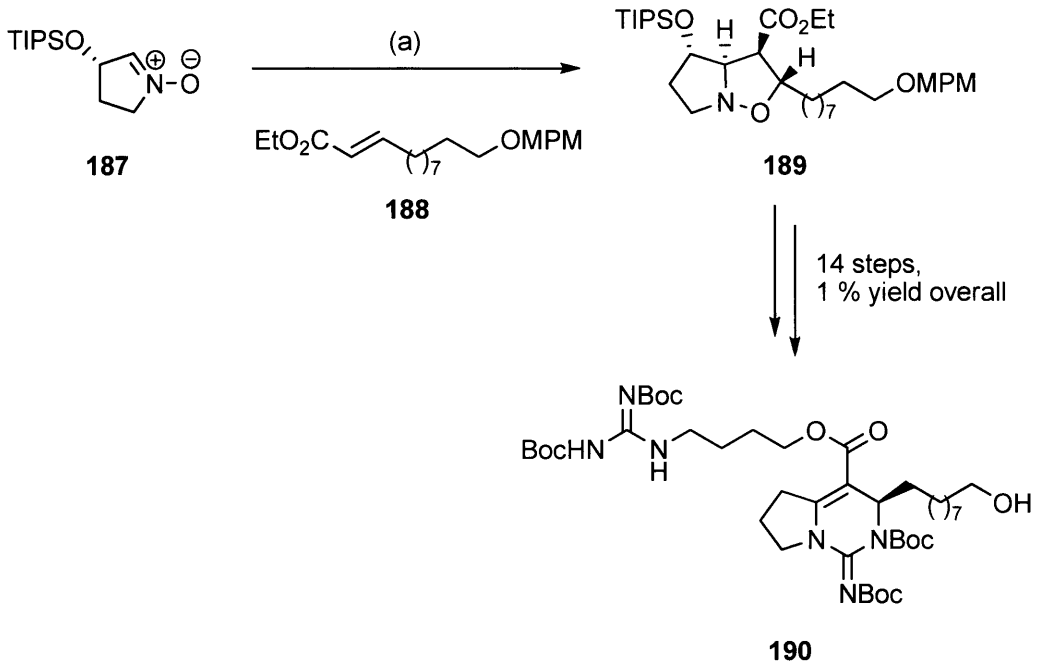
et al. employed their key tethered Biginelli condensation of a guanidine aldehyde **183** and an acetoacetic ester **184** to generate the bicyclic guanidine moiety **185** (**Scheme 83**). Further elaboration of compound **185** gave batzelladine D as the bistrifluoroacetate salt (**186**) in a total of 12 steps from compound **182**.



Scheme 83. *Reagents and Conditions*: (a) morpholinium acetate, Na_2SO_4, CF_3CH_2OH, 70 °C.

The Overman group also employed this Biginelli chemistry to achieve total syntheses of batzelladine F[49d] and dehydrobatzelladine C.[49g]

The group of Nagasawa reported an enantioselective approach to batzelladine A in 2004.[51d] Starting with an enantiopure nitrone **187**, a key 1,3-dipolar cycloaddition with an α,β-unsaturated ester **188** gave compound **189**, which was further elaborated to give the left-hand side of batzelladine A (**190**) (**Scheme 84**).

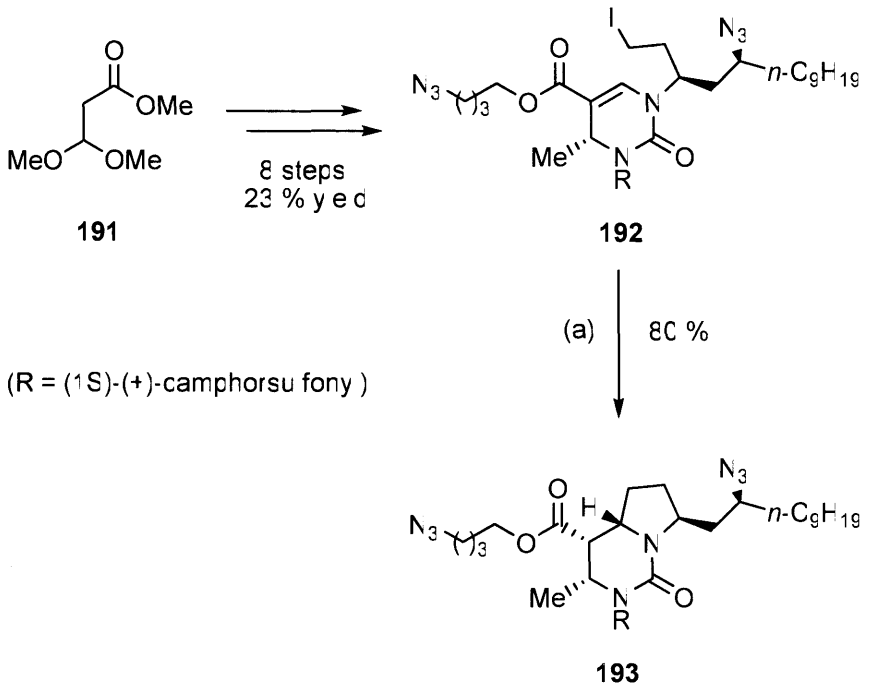


Scheme 84. *Reagents and Conditions*: (a) toluene, 90 °C.

The Nagasawa group synthesised the right-hand side of batzelladine A, again employing a key 1,3-dipolar cycloaddition, in a similar sequence to their synthesis of batzelladine D (the right-hand side of batzelladine A is identical to that of batzelladine D).[51c] Coupling of the two fragments and some further manipulation gave batzelladine A.

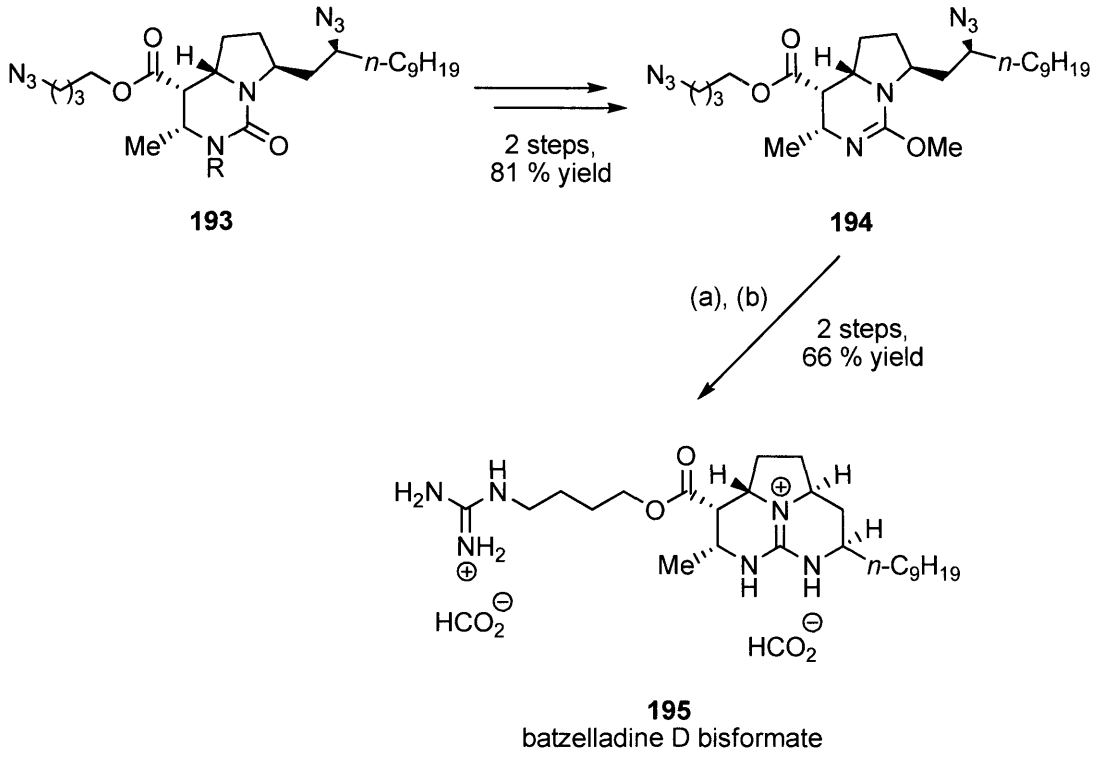
More recently, the Evans group have reported an enantioselective approach to batzelladine D.[54] Throughout the majority of the sequence, Evans employs the clever use of azides as latent amines, avoiding the use of extensive protecting

group chemistry. The key step was a stereoselective radical cyclisation of compound **192**, which was synthesised in 8 steps from compound **191** (**Scheme 85**).



Scheme 85. *Reagents and Conditions*: (a) Bu_3SnH, Et_3B, PhH, O_2, room temperature.

From compound **193**, a further two synthetic steps generated compound **194**. Hydrogenation of the diazide **194**, to promote reductive cyclisation, followed by installation of the acyclic guanidine, gave batzelladine D as the bisformate salt (**195**) (**Scheme 86**).



Scheme 86. *Reagents and Conditions*: (a) 10 % Pd/C, H_2, MeOH, room temperature; (b) 1H-pyrazole-1-carboxamidine hydrochloride, *i*Pr_2NEt, DMF, room temperature.

4.1.2 Batzelladine C

Batzelladine C is a tricyclic guanidine, which has not yet been synthesised. The stereochemistry at the C-4 position[55] is unknown, as is the absolute stereochemistry (**Figure 16**), an ambiguity which is shared by batzelladines J, M and N.

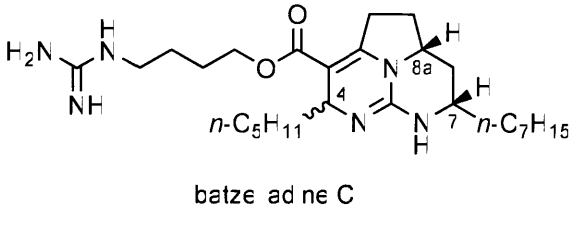
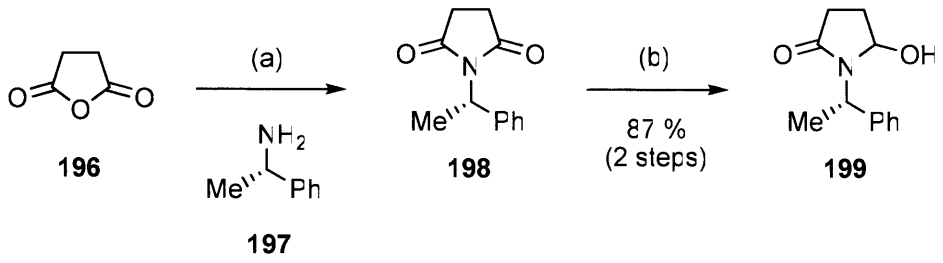


Figure 16. Batzelladine C.

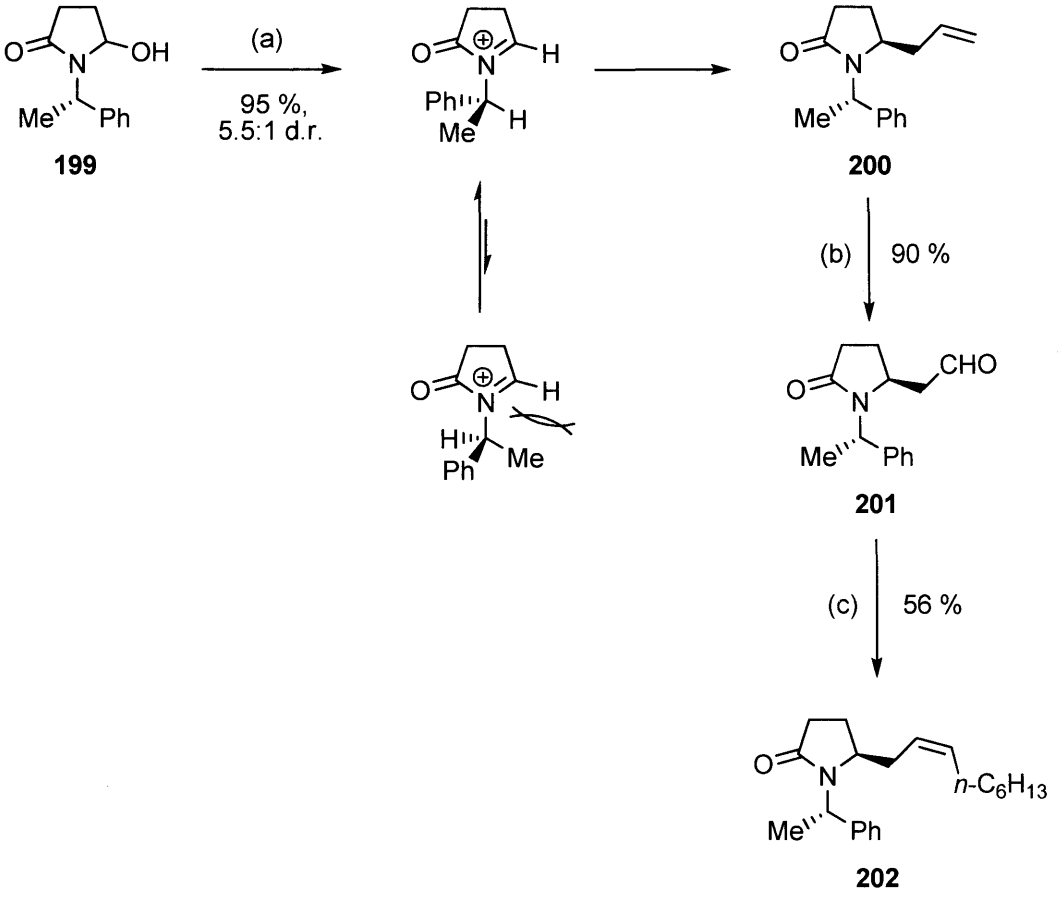
Recent work within our group has been focussed on an approach to batzelladine C and assignment of its relative and absolute stereochemistry. My predecessor developed a strategy for synthesising the tricyclic guanidine moiety,[56] beginning with commercially available succinic anhydride **196**. Condensation of succinic anhydride **196** with (S)-(-)-α-methylbenzylamine **197**, followed by chemoselective reduction of the resulting imide **198**, gave compound **199** (**Scheme 87**).



196 **197** **198** **199**

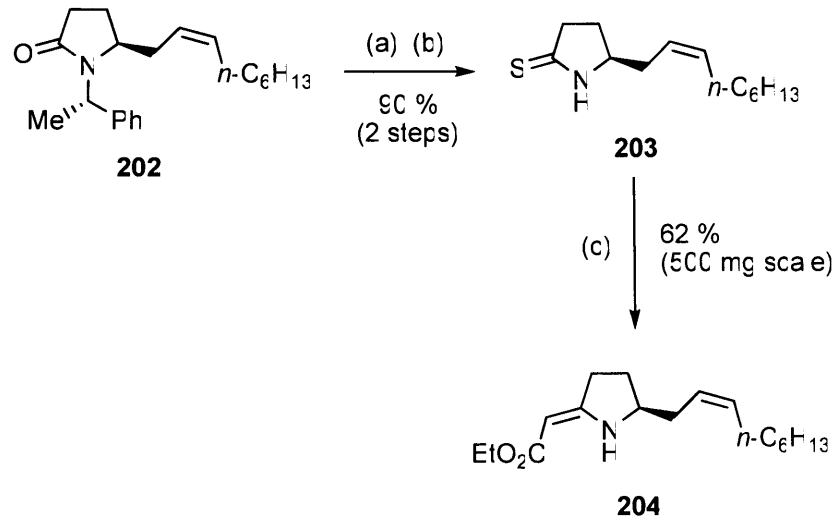
Scheme 87. *Reagents and Conditions*: (a) (i) toluene, reflux, (ii) CDI, THF, reflux; (b) $LiEt_3BH$, THF.

Introduction of an allyl side-chain, followed by an oxidative cleavage of the double bond, gave compound **201**. The aldehyde **201** was subsequently submitted to a *Z*-selective Wittig reaction, affording compound **202** (**Scheme 88**).



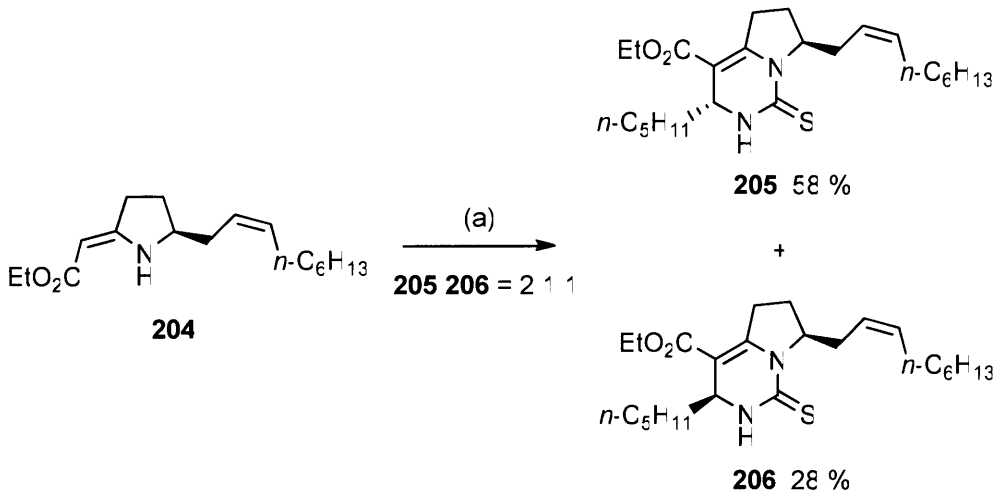
Scheme 88. *Reagents and Conditions*: (a) $BF_3.OEt_2$, allyltrimethylsilane, CH_2Cl_2, -78 °C; (b) $K_2OsO_4.2H_2O$, $NaIO_4$, 2,6-lutidine, dioxane-H_2O; (c) $C_7H_{15}PPh_3I$, *n*-BuLi, THF.

From this point, removal of the chiral auxiliary, followed by thionation with Lawesson's reagent gave compound **203**, which was submitted to an Eschenmoser sulfide contraction, giving compound **204** (**Scheme 89**).



Scheme 89. *Reagents and Conditions*: (a) Na, NH_3-EtOH-THF; (b) Lawesson's reagent, THF; (c) (i) $BrCH_2CO_2Et$, CH_2Cl_2, (ii) PPh_3, *t*BuOK, xylene, reflux.

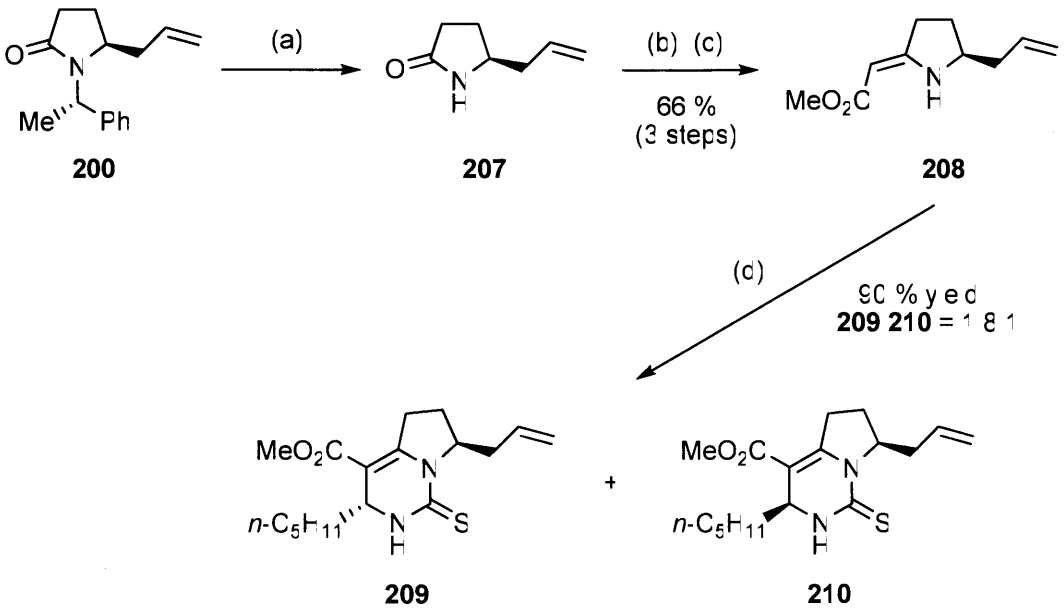
The alkylidenepyrrolidine **204** was submitted to a three-component coupling reaction, originally developed by Kishi,[57] to give a separable mixture of diastereoisomers **205** and **206** (**Scheme 90**).



Scheme 90. *Reagents and Conditions*: (a) TMS-NCS, hexanal, CH_2Cl_2, room temperature, 45 minutes.

The stereochemical outcome of the three-component coupling was determined with a model study. Compound **208** was synthesised in three steps from the

allyl lactam **200**, using methodology developed within the group.[58] Submitting the alkylidenepyrrolidine **208** to the three-component coupling reaction, gave a 1.8:1 mixture of separable diastereoisomers **209** and **210** (**Scheme 91**).[56]



Scheme 91. *Reagents and Conditions*: (a) Na, NH_3-EtOH-THF; (b) Boc_2O, NEt_3, 4-DMAP, CH_2Cl_2; (c) (i) MeOAc, LDA, THF, (ii) TFA; (d) TMS-NCS, hexanal, CH_2Cl_2, room temperature, 1 h.

The major diastereoisomer **209** provided suitable crystals for X-ray analysis, which confirmed the *trans* relationship between protons H^a and H^b. (**Figure 16**).

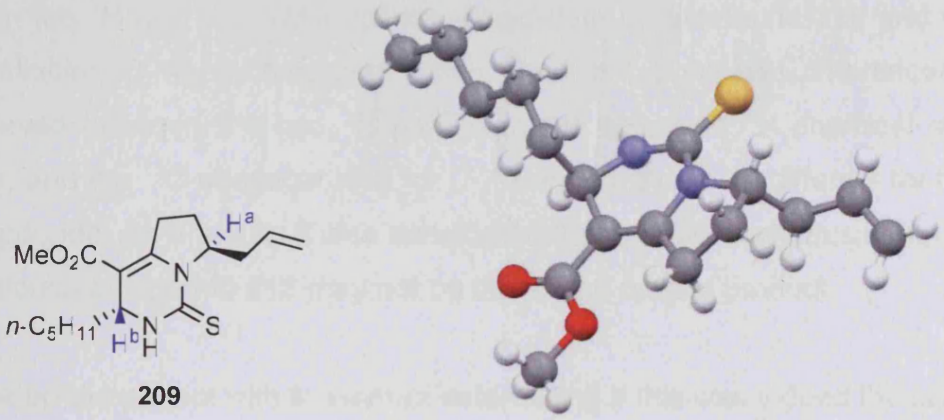
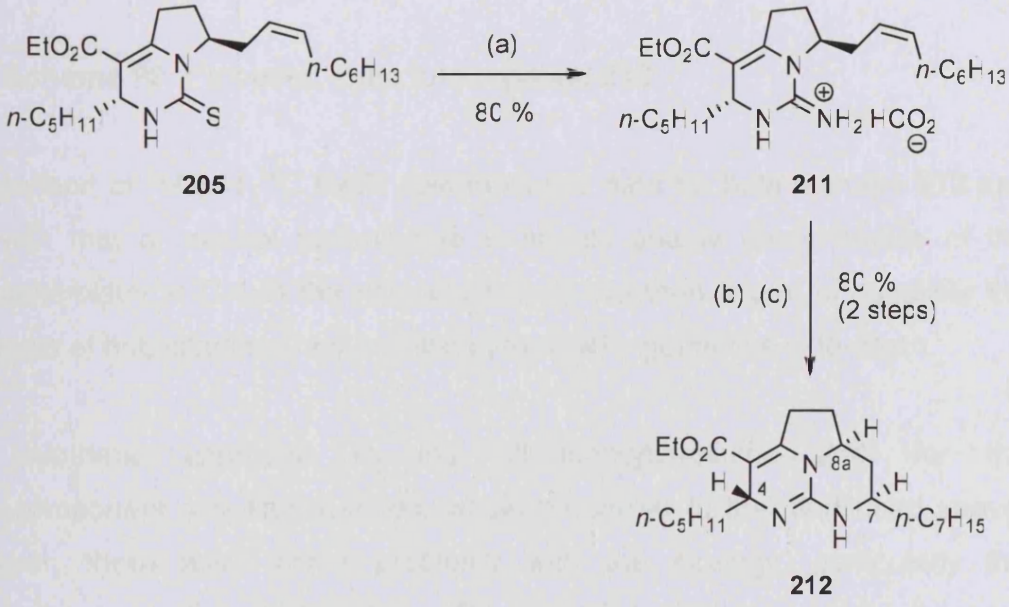


Figure 16. Structure of compound **209** from X-ray data.[59]

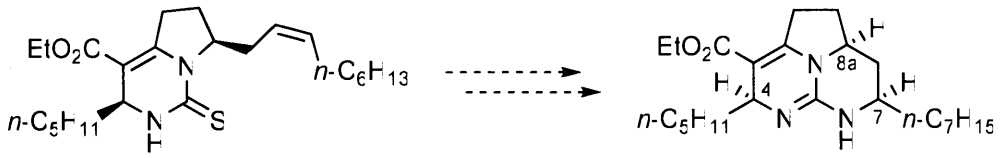
With the stereochemistry confirmed, compound **205** was subsequently converted into the guanidine **211**. Intramolecular iodoamination of compound **211**, followed by immediate hydrogenolysis to remove the iodine, afforded the tricyclic guanidine **212** (**Scheme 92**).



Scheme 92. *Reagents and Conditions*: (a) (i) MeI, MeOH, reflux, (ii) NH_3, NH_4OAc, MeOH, sealed tube, 80 °C, 60 h; (b) I_2, K_2CO_3, MeCN, room temperature; (c) H_2, Pd/C, NEt_3, EtOAc, room temperature.

When the ^{1}H and ^{13}C NMR spectroscopic data of compound **212** and natural batzelladine C were compared, some small but significant differences were observed between the two. In particular, the observed ^{1}H chemical shift for H-8a, and the ^{13}C chemical shift for C-7 were considerably different for the two compounds. As a result, it was considered that the stereochemistry at the C-4 position in compound **212** may not be that of the natural product.

I took up the project with the aim of determining if this was indeed the case. We hoped to achieve this by converting the minor diastereoisomer **206**, from the three-component coupling reaction, to the corresponding tricyclic guanidine **213** (**Scheme 93**).



206 **213**

Scheme 93. Proposed route to compound **213**.

Comparison of ^{1}H and ^{13}C NMR spectroscopic data for both epimers **212** and **213** with that of natural batzelladine C should enable determination of the stereochemistry at C-4 in the natural product. We then hoped to complete the synthesis of batzelladine C by installing the acyclic guanidine side-chain.

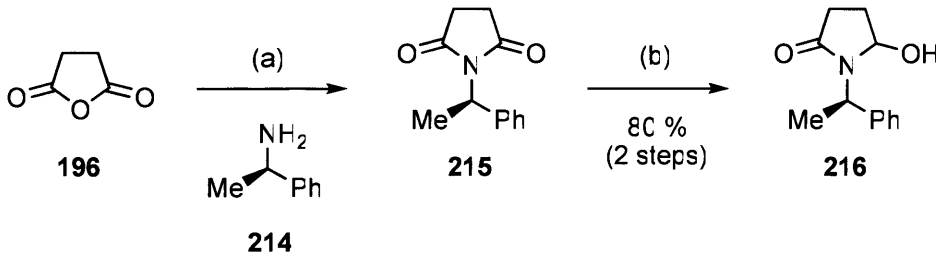
The synthetic approach to the alkylidenepyrrolidine **204**, for the three-component coupling reaction, would be similar to that described above. However, there were some problems with the strategy, particularly the Eschenmoser sulfide contraction. This reaction had proved to be very unreliable, especially on scales above 500 milligrams, which limited the amount of synthetic material that could be quickly brought through the sequence. As such we hoped to improve upon this reaction and rectify the problem.

There had also been similar problems with subsequent formation of guanidine **211** from the thiourea **205**. As well as proving unreliable, the 60 h reaction time made the reaction highly impractical. Again, we hoped to resolve this issue.

4.2 Results and Discussion

4.2.1 A Synthetic Approach to Batzelladine C Methyl Ester

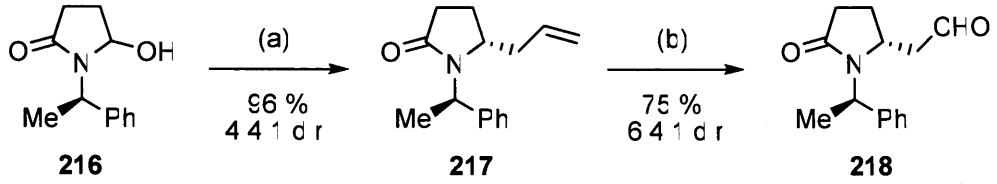
At this point, the absolute stereochemistry of batzelladine C was unknown, and since we had proposed that the relative stereochemistry of compound **212** was not that of the natural product, it was not clear which enantiomeric series would give the natural product stereochemistry. As a result, and due to the ready availability of (R)-(+)-α-methylbenzylamine **214** in our lab, we initiated the sequence with the opposite enantiomer to before. Condensation of succinic anhydride **196** and (R)-(+)-α-methylbenzylamine **214** proceeded smoothly, and following chemoselective reduction of the imide **215** with Super-Hydride®, gave compound **216** (**Scheme 94**).



Scheme 94. *Reagents and Conditions*: (a) (i) toluene, reflux, 18 h, (ii) acetic anhydride, reflux, 2 h; (b) (i) $LiEt_3BH$, THF, -78 °C, 40 minutes, (ii) 30 % H_2O_2.

From this point, the allyl side-chain was introduced by formation of an *N*-acyl iminium ion from compound **216** with boron trifluoride, followed by subsequent reaction with allyltrimethylsilane, according to conditions described by Polniaszek and co-workers.[60] The terminal alkene was then oxidatively cleaved

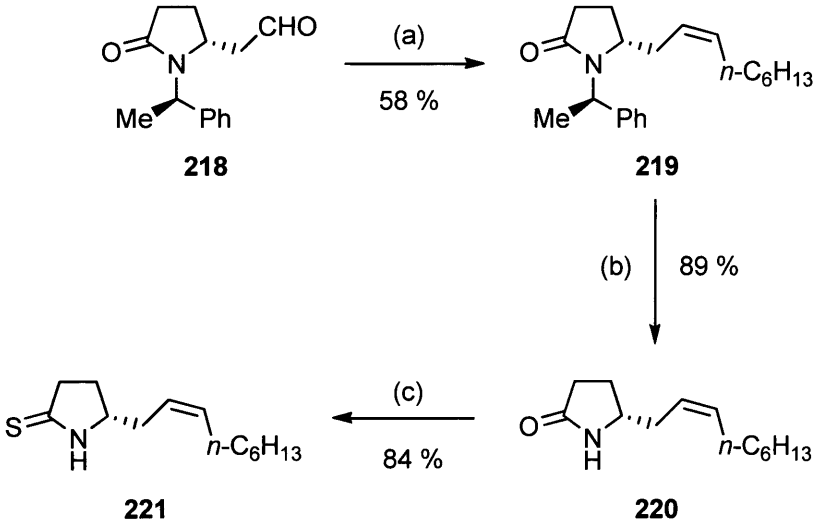
with potassium osmate dihydrate and sodium periodate, to give compound **218** as a 6.4:1 mixture of diastereoisomers (**Scheme 95**).



216 **217** **218**

Scheme 95. *Reagents and Conditions*: (a) $BF_3.OEt_2$, allyltrimethylsilane, CH_2Cl_2, -78 °C to room temperature, 16 h; (b) $K_2OsO_4.2H_2O$, $NaIO_4$, 2,6-lutidine, dioxane-H_2O, 18 h.

Aldehyde **218** was subsequently submitted to a *cis*-selective Wittig reaction to give compound **219**, by which time the diastereomeric ratio had been increased to 6.6:1. The chiral auxiliary was removed by treatment with sodium metal in liquid ammonia, giving compound **220**, which was then converted to the thiolactam **221** with Lawesson's reagent (**Scheme 96**).

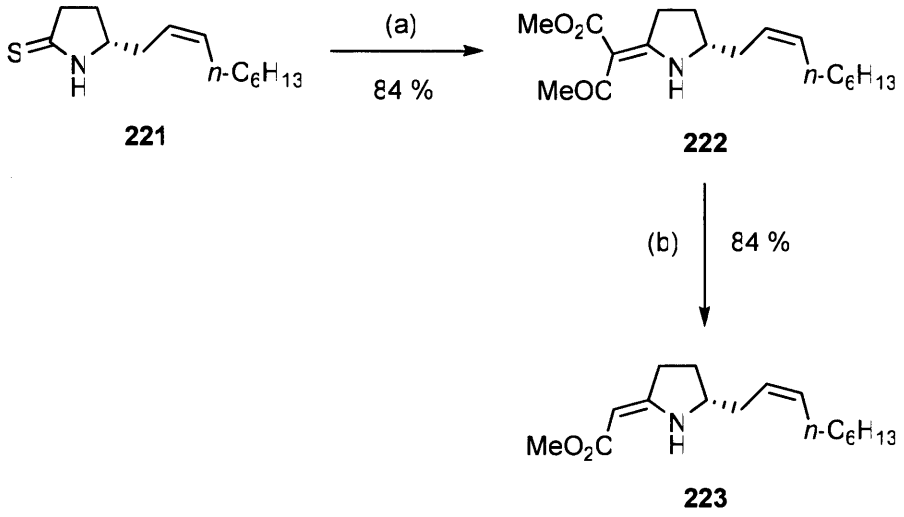


218 **219** **220** **221**

Scheme 96. *Reagents and Conditions*: (a) $C_7H_{15}PPh_3I$, *n*-BuLi, THF, -78 °C to room temperature, 16 h; (b) Na, NH_3-EtOH-THF (8:1:1), -78 °C; (c) Lawesson's reagent, THF, 2 h.

The *cis*-geometry of compound **219** could not be confirmed spectroscopically, however the selectivity of the Wittig reaction was proved later in the sequence by analysis of coupling constants in the ^{1}H NMR spectrum of compound **221**.

At this point, instead of employing the unreliable single-step sulfide contraction used initially, we opted for a different two-step sequence, which had previously been used within the group on a similar compound.[61] Compound **221** was treated with methyl 2-bromoacetoacetate and pleasingly this gave compound **222** in excellent yield (**Scheme 97**). A simple deacetylation of compound **222** with sodium methoxide, gave alkylidenepyrrolidine **223**, again in excellent yield.



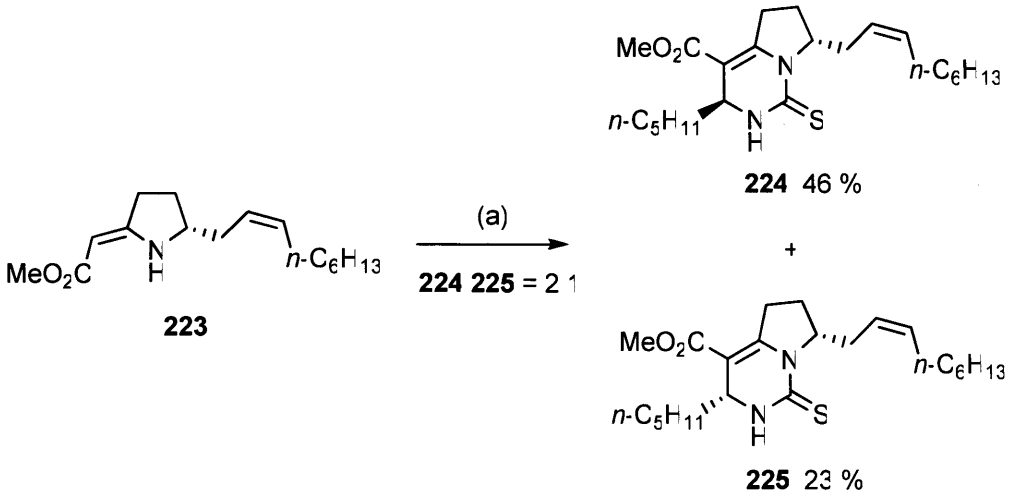
221 **222** **223**

Scheme 97. *Reagents and Conditions*: (a) methyl 2-bromoacetoacetate, $NaHCO_3$, CH_2Cl_2, reflux, 16 h; (b) NaOMe, MeOH, reflux, 2 h.

This two-step sequence proved to be much more reliable and scaleable, allowing fast access to multi-gram quantities of the alkylidenepyrrolidine **223**. The decision was made to install the methyl rather than the ethyl ester at this point, as this would eventually allow direct comparison with batzelladine C methyl ester, which the original isolation team prepared by methanolysis of natural batzelladine C.[42]

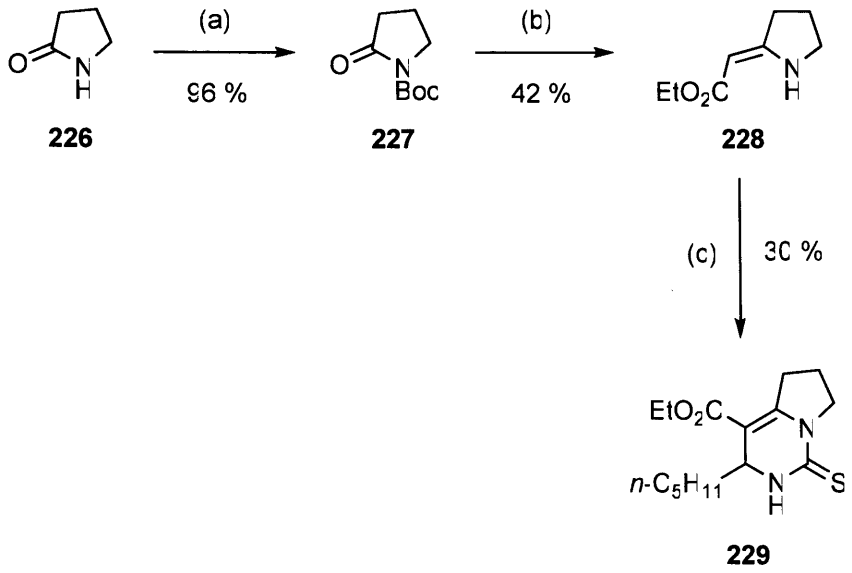
With compound **223** in hand, the three-component coupling reaction was carried out, giving a 2:1 mixture of separable diastereoisomers **224** and **225**

(**Scheme 98**). Stereochemical assignments were made by analogy with compounds **205** and **206**.[56]



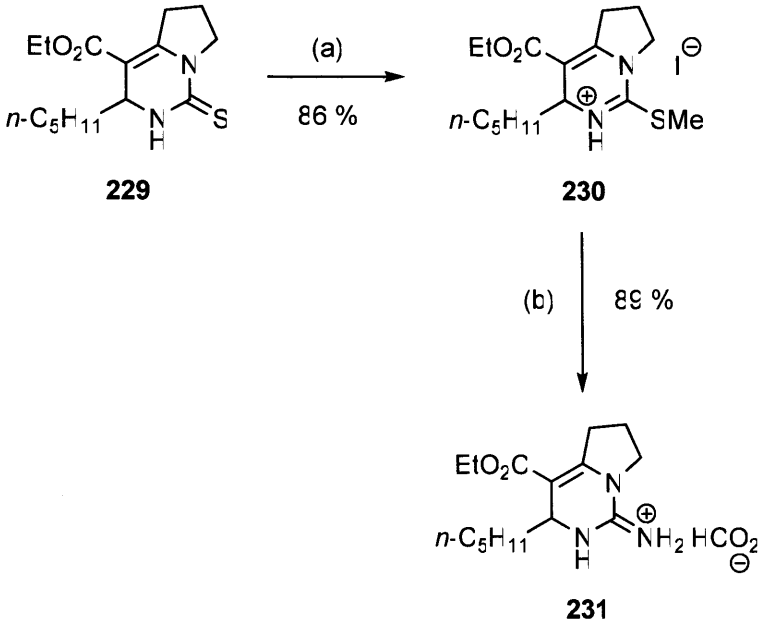
Scheme 98. *Reagents and Conditions*: (a) TMS-NCS, hexanal, CH_2Cl_2, room temperature, 75 minutes.

At this point, in an attempt to improve upon the current unreliable guanidine formation, a model study was carried out. Compound **228** was prepared in two steps from 2-pyrrolidinone **226**, using methodology developed within the group.[58] This alkylidenepyrrolidine **228** was then submitted to the three-component coupling reaction, to give compound **229** (**Scheme 99**).



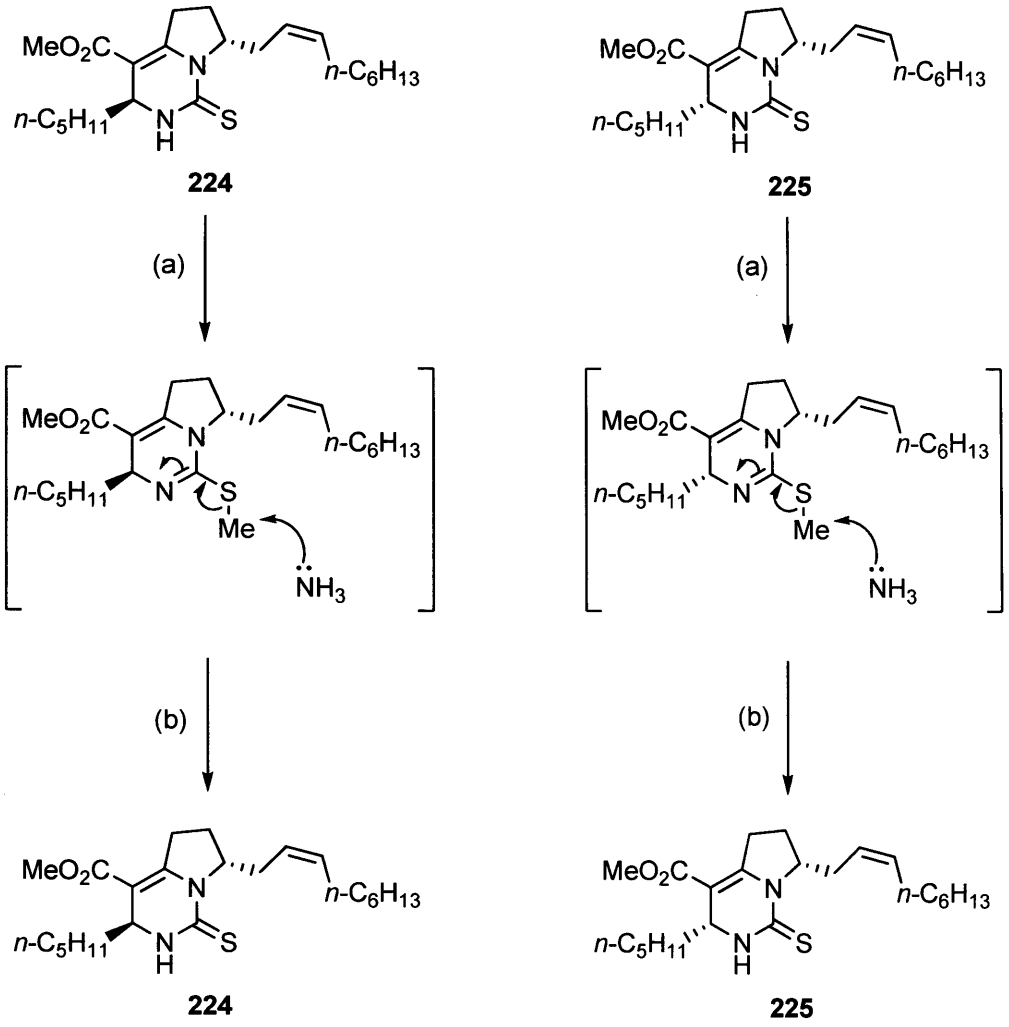
Scheme 99. *Reagents and Conditions*: (a) Boc_2O, NEt_3, 4-DMAP, CH_2Cl_2, 18 h; (b) (i) EtOAc, LDA, THF, -78 °C to room temperature, 18 h, (ii) TFA, 3 h; (c) TMS-NCS, hexanal, CH_2Cl_2, room temperature, 75 minutes.

Peters *et al.* have reported a strategy for forming guanidines from thioureas, which involves fully *S*-methylating the thiourea before heating in a microwave with ammonium hydroxide.[62] Using similar conditions, compound **229** was treated with methyl iodide to give the isothiourea **230**, which was subsequently heated in a microwave with ammonium hydroxide. Pleasingly this gave compound **231** in excellent yield (**Scheme 100**).



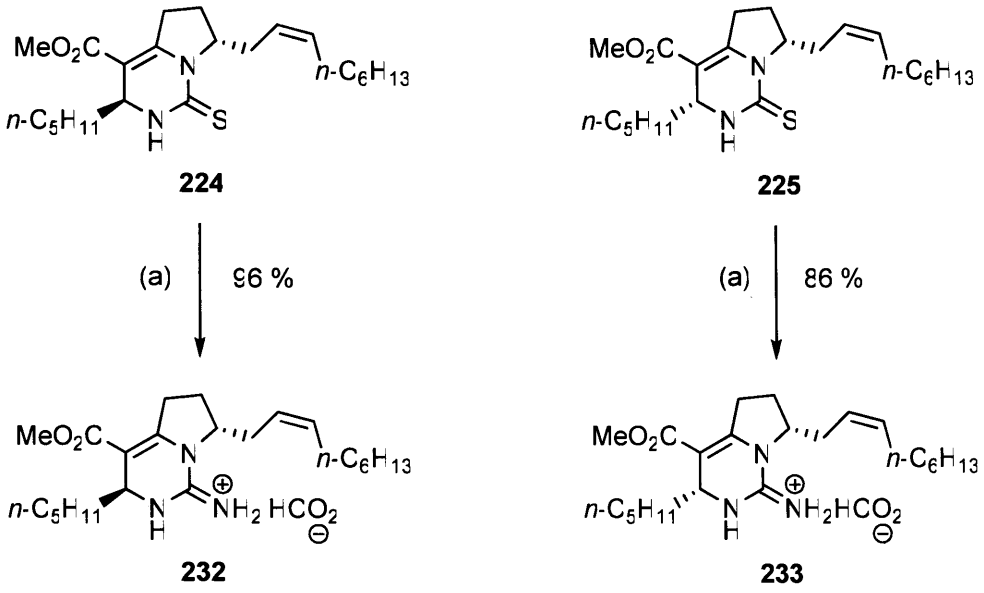
Scheme 100. *Reagents and Conditions*: (a) MeI, Me_2CO, 18 h; (b) NH_4OH, H_2O-MeCN (1:1), microwave, 130 °C, 15 minutes, then 165 °C, 30 minutes.

This methodology dramatically reduced the reaction time of the guanidine formation and the result was reproducible with the model system. Unfortunately however, when the same conditions were applied to compounds **224** and **225**, we simply observed regeneration of starting material (**Scheme 101**). Clearly, the added steric bulk of the alkenyl side-chain, in both cases, causes the ammonia nucleophile to attack at the wrong position, resulting in reformation of the thiourea.



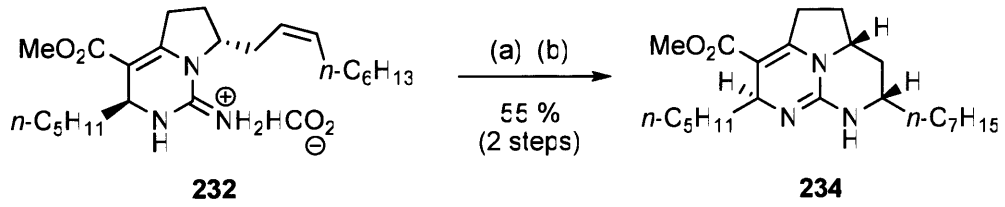
Scheme 101. *Reagents and Conditions*: (a) MeI, Me_2CO, 18 h; (b) NH_4OH, H_2O-MeCN (1:1), microwave, 130 °C, 15 minutes, then 165 °C, 30 minutes.

Owing to this, we decided to proceed with our original conditions for guanidine formation. While we were able to successfully synthesise both guanidines **232** and **233** (**Scheme 102**), the reactions did not work well on scales above 200 milligrams and were not always reproducible, which limited the amount of synthetic material obtained.



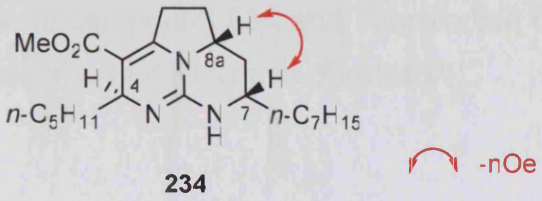
Scheme 102. *Reagents and Conditions*: (a) (i) MeI, MeOH, reflux, 1h, (ii) NH_4OAc, NH_3, MeOH, 80 °C, sealed tube, 48 h.

From this point, iodoamination of compound **232** proceeded smoothly under standard conditions, and following removal of the iodine by hydrogenolysis, gave compound **234** (**Scheme 103**).



Scheme 103. *Reagents and Conditions*: (a) I_2, K_2CO_3, MeCN, room temperature, 3 h; (b) H_2, Pd/C, NEt_3, EtOAc, room temperature, 16 h.

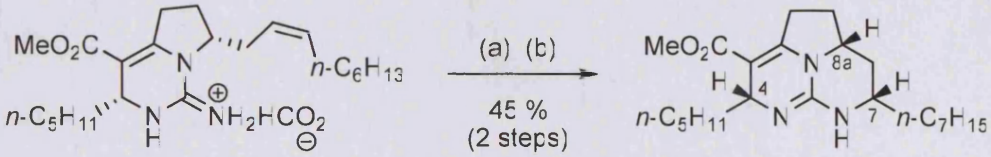
The relative stereochemistry of protons H-7 and H-8a was determined by NOESY NMR spectroscopy (**Figure 17**).



234

Figure 17. Determination of the relative stereochemistry of compound **234**.

Iodoamination of compound **233** proved slightly more troublesome, but was eventually effected using iodine monochloride and potassium carbonate in dichloromethane. Again, immediate hydrogenolysis to remove the iodine gave compound **235** (**Scheme 104**). The relative stereochemistry of protons H-7 and H-8a was assigned by analogy with compound **234**.



233 **235**

Scheme 104. *Reagents and Conditions*: (a) ICl, K_2CO_3, CH_2Cl_2, 0 °C to room temperature, 3 h; (b) H_2, Pd/C, NEt_3, EtOAc, room temperature, 16 h.

The reason for the more difficult iodoamination of compound **233** is not readily apparent. Calculations show that there is a significant conformational difference between the bicyclic portions of compounds **232** and **233**.[63] However, this does not seem to result in the side-chain double bond being further from the guanidine nitrogen in compound **233**.

4.2.2 Stereochemical Assignment of Batzelladine C

With both epimers **234** and **235** in hand, we could now compare NMR spectroscopic data of the two, with that of natural batzelladine C. When

comparing ^{1}H NMR spectra of compound **234** and batzelladine C,[64] we could immediately identify some significant differences (**Figure 18**).

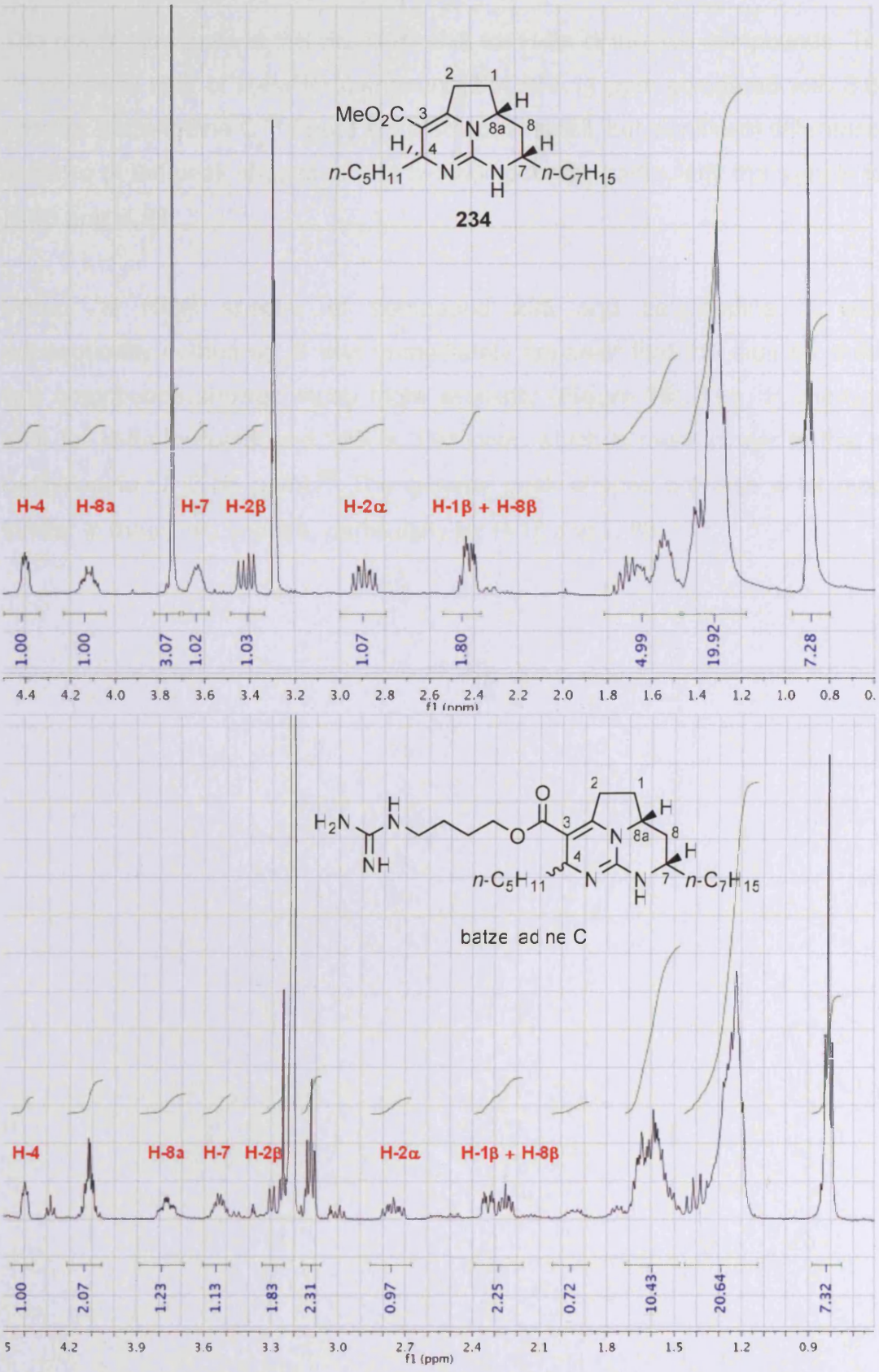


Figure 18. ^{1}H NMR spectra of compound **234** and batzelladine C (400 MHz; MeOD).

The major difference is the chemical shift for H-8a in the two compounds. The ^{1}H chemical shift of H-8a for compound **234** is 4.11 ppm compared with 3.86 ppm for batzelladine C.[42] There are also some small, but significant differences in some of the peak shapes for the two compounds, particularly the signals for H-1β and H-8β.

When ^{1}H NMR spectra of compound **235** and batzelladine C were subsequently compared, it was immediately apparent that the data for these two compounds showed much more similarity (**Figure 19**). The ^{1}H chemical shift for H-8a in compound **235** is 3.93 ppm, which is much closer to that of batzelladine C (3.86 ppm).[42] The general peak shapes are also a lot more similar in these two spectra, particularly for H-1β and H-8β.

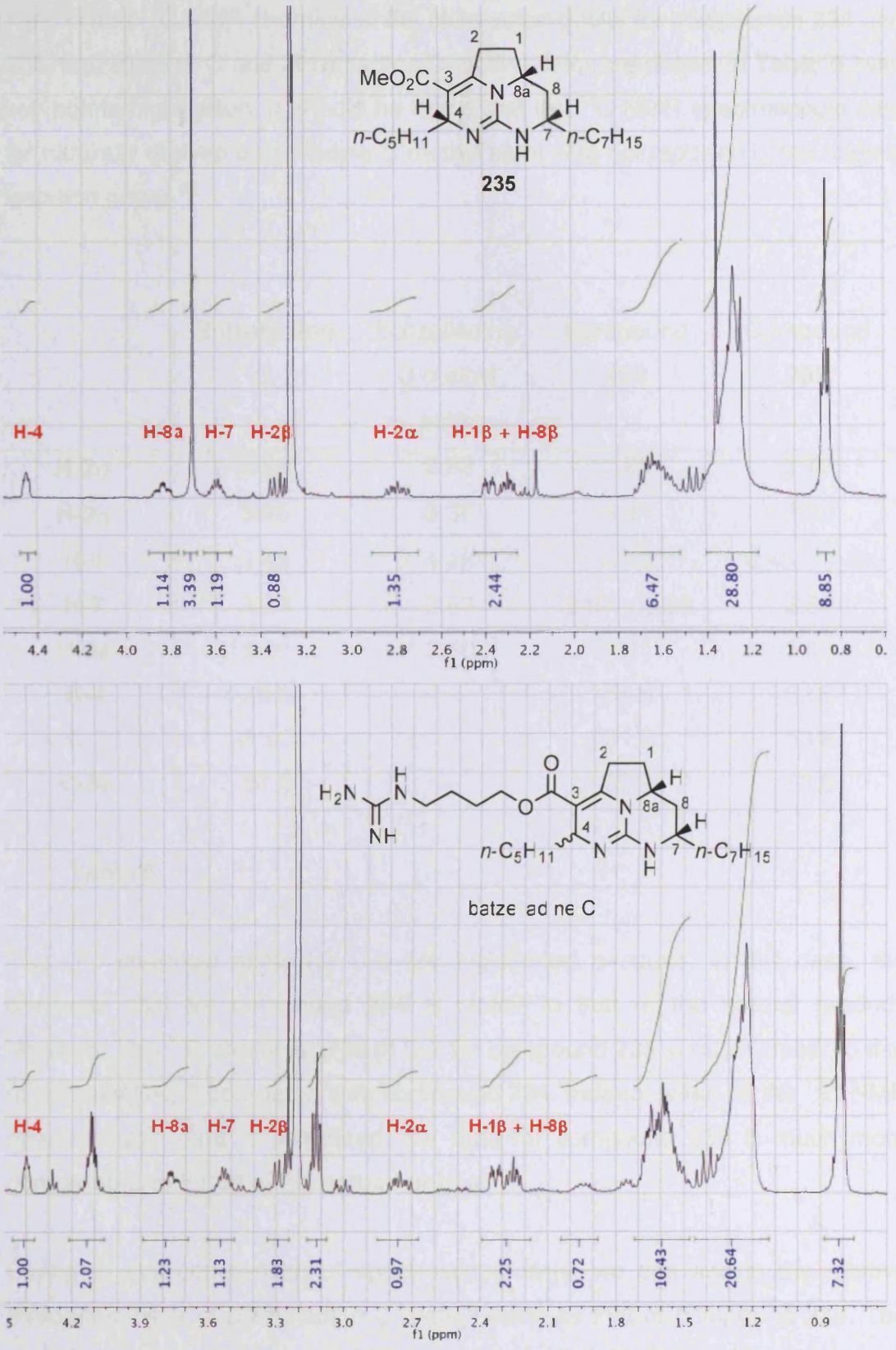


Figure 19. ^{1}H NMR spectra of compound **235** and batzelladine C (400 MHz; MeOD).

The ^{1}H and ^{13}C NMR chemical shifts of selected peaks for compounds **234** and **235**, batzelladine C and batzelladine C methyl ester are shown in **Table 5**, with key points highlighted. It should be noted that the ^{13}C NMR spectroscopic data for naturally derived batzelladine C methyl ester was not reported in the original isolation paper.[42]

	Batzelladine C	Batzelladine C methyl ester	Compound **234**	Compound **235**
H-2α	2.84	2.82	2.89	2.79
H-2β	3.35	3.37	3.41	3.32
H-4	4.45	4.48	4.40	4.46 – 4.44
H-7	3.61	3.62	3.67 – 3.60	3.60
H-8a	3.86	3.86	4.11	3.93
C-4	49.8	–	50.9	52.5
C-7	53.2	–	51.3	53.8
C-8a	57.3	–	57.4	58.9

Table 5.

The ^{13}C chemical shifts for C-4 are highlighted because, in this case, the chemical shift for compound **234** is closer to that of the natural product. However, the ^{13}C chemical shift of C-7 for compound **235** is much closer to that of batzelladine C compared with compound **234**. Indeed, when all the ^{13}C NMR spectroscopic data is compared, the data for compound **235** is much more comparable with that of the natural product.

Owing to this comparison of spectroscopic data, we can assign the relative stereochemistry of batzelladine C methyl ester as that of compound **235**. The specific rotation of compound **235** was – 2.4 (c. 0.5, MeOH) compared to – 4.2 (c. 0.93, MeOH) for the same compound formed by methanolysis of natural batzelladine C. As a result, we can also assign the absolute stereochemistry of

batzelladine C methyl ester as that of compound **235**. Hence, the relative and absolute stereochemistry of batzelladine C is readily deduced as shown in **Figure 20**.

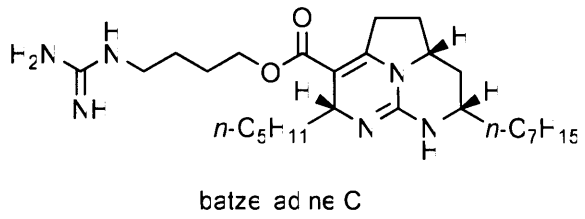
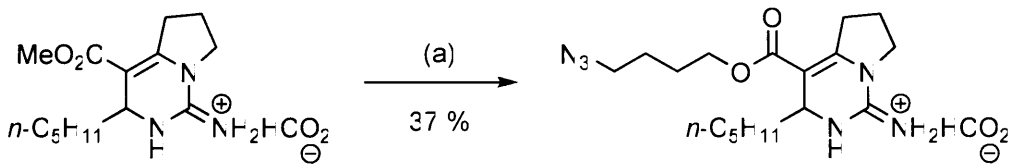


Figure 20. Stereochemistry of batzelladine C.

4.2.3 Further Manipulation of Batzelladine C Methyl Ester

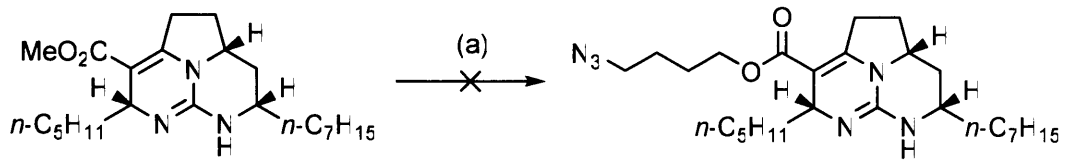
Having determined the stereochemistry of batzelladine C, we now aimed to complete the synthesis of the natural product. We envisaged using Evans' method for installing the acyclic guanidine side-chain by transesterification with 4-azidobutanol.[54] The azide could then be reduced and converted to the guanidine. Before attempting this with compound **235**, a model study was conducted. Compound **236** was refluxed with 4-azidobutanol and Otera's catalyst[65] in toluene, and pleasingly this gave compound **237**, albeit in moderate yield (**Scheme 105**).



236 **237**

Scheme 105. *Reagents and Conditions*: (a) $(ClBu_2Sn)_2O$, $N_3(CH_2)_4OH$, toluene, reflux, 24 h.

Unfortunately, applying the same conditions to compound **235** resulted in a complex mixture of products (**Scheme 106**).



235 **238**

Scheme 106. *Reagents and Conditions*: (a) $(ClBu_2Sn)_2O$, $N_3(CH_2)_4OH$, toluene, reflux, 24 h.

My predecessor had previously attempted a number of different methods for introducing the acyclic guanidine side-chain, but to no avail.[56] Owing to this and the failed transesterification of compound **235**, combined with the small amounts of synthetic material available, we decided not to pursue the synthesis further.

4.3 Conclusion

The two possible diastereoisomers of batzelladine C methyl ester **234** and **235** have been synthesised, each in 13 steps from commercially available succinic anhydride **196**, with 4.3 % and 1.6 % overall yields respectively. Comparison of spectroscopic data of the two compounds with that of the natural product has enabled assignment of the relative and absolute stereochemistry of batzelladine C.

Chapter 5

Experimental Details

5.1 General Experimental Points

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on a Fisons VG Platform II spectrometer and on a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C at 25 ◦C, or on a Bruker Avance 500 spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C at 25 ◦C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (*J*) are reported in Hz. Multiplicity in ^{1}H NMR spectroscopy is reported as singlet (s), doublet (d), double doublet (dd), double triplet (dt), double quartet (dq), triplet (t), and multiplet (m). Multiplicity in ^{13}C NMR spectroscopy was obtained using the DEPT pulse sequence. Optical rotations were recorded on an Optical Activity AA 100 polarimeter. Specific rotations are reported in units of deg dm^{-1} cm^{3} g^{-1}. Flash chromatography was performed using Matrex silica 60 35–70 micron.

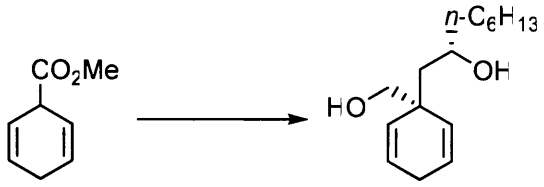
Solvents for moisture-sensitive reactions were dried by distillation; THF over sodium benzophenone ketal, CH_2Cl_2 and toluene over CaH_2, and MeOH over $Mg(OMe)_2$. Such reactions were carried out under an atmosphere of nitrogen.

Where mixtures of diastereoisomers were not separated, NMR data reported are for the major diastereoisomer.

Supporting mass spectrometric data for compounds **41c**, **115**, **145**, **146**, **148** and **158** could not be obtained.

5.2 Experimental Data for Chapter 1

1-(1-(Hydroxymethyl)cyclohexa-2,5-dienyl)octan-2-ol (19d)



23 **19d**

n-Butyllithium (8.79 ml of a 1.6 M solution in hexanes, 14.1 mmol) was added to a solution of diisopropylamine (1.97 ml, 14.1 mmol) in dry THF (20 ml) at 0 °C, and the resulting solution was allowed to stir at 0 °C for 15 minutes. The reaction mixture was then cooled to –78 °C and the ester **23** (1.74 g, 12.6 mmol) added dropwise. After stirring at –78 °C for 30 minutes, *n*-hexyloxirane (1.8 g, 14.1 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with diethyl ether, the combined extracts being dried over Na_2SO_4 before the solvent was removed *in vacuo.* Chromatography on silica gel (Et_2O/petroleum ether 1:19) afforded the intermediate lactone **40** (1.64 g, 56%) as a colourless oil. This lactone **40** (1.64 g, 7.01 mmol) was immediately re-dissolved in dry THF (10 ml) and added dropwise to a suspension of $LiAlH_4$ (266 mg, 7.01 mmol) in dry THF (20 ml). The resulting suspension was allowed to stir for 15 minutes before the reaction was quenched with 2 M NaOH. The solution was filtered and dried over Na_2SO_4 before the solvent was removed *in vacuo.* Chromatography on silica gel (eluent 2:1 hexane:ethyl acetate) afforded the *title compound* (1.33 g, 80%) as a colourless oil.

ν_{max} (Neat): 3354, 3017, 2930, 2882, 2856, 1615, 1516, 1458, 1377, 1244, 1040, 947, 877, 823 and 711 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 6.00–5.93 (2 H, m, alkene CH), 5.63 (1 H, app. dq, *J* 10.2, 2.0, alkene CH), 5.37 (1 H, app. dq, *J* 10.9, 2.1, alkene CH), 3.77–3.71 (1 H, m, C*H*OH), 3.30 (2 H, app. s, CH_2OH), 2.68–2.66 (2 H, m, ring CH_2), 1.67 (2

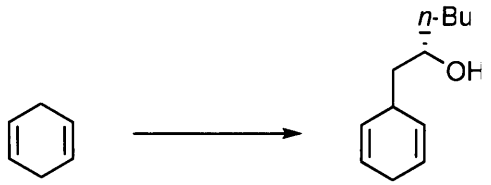
H, broad s, 2 x OH), 1.43 (1 H, dd, *J* 14.2, 9.0, one of C*H*$_2$CHOH), 1.36 (1 H, dd, *J* 14.2, 2.3, one of C*H*$_2$CHOH), 1.33–1.27 (2 H, m, CH_2), 1.26–1.16 (8 H, m, $(CH_2)_4$) and 0.81 (3 H, t, *J* 6.8, CH_3).

δ_C (100 MHz; $CDCl_3$): 130.6 (CH), 129.7 (CH), 128.0 (CH), 127.4 (CH), 70.4 (CH_2), 69.4 (CH), 44.9 (CH_2), 42.3 (C), 38.0 (CH_2), 31.9 (CH_2), 29.3 (CH_2), 26.6 CH_2), 25.6 (CH_2), 22.6 (CH_2) and 14.1 (CH_3).

MS-EI: *m/z* (%) = 220 (M^+ – H_2O, 13), 202 (98), 190 (90), 131 (93), 117 (97) and 104 (100).

HRMS-EI: *m/z* $[M - H_2O]^+$ calcd for $C_{15}H_{24}O$: 220.1827; found: 220.1837.

1-(Cyclohexa-2,5-dienyl)hexan-2-ol (24a)



27 **24a**

To a solution of 1,4-cyclohexadiene **27** (323 mg, 4.03 mmol) in dry THF (10 ml) at -78 °C were added n-butyllithium (2.5 M solution in hexanes, 1.77 ml, 4.43 mmol) and TMEDA (0.67 ml, 4.43 mmol). The yellow solution was warmed to -41 °C and after 2.5 h was treated with *n*-butyloxirane **28a** (0.58 ml, 4.84 mmol). After 10 minutes at -41 °C the solution was warmed to room temperature and left to stir for 1 h before being quenched with saturated ammonium chloride solution. The product was then extracted with ether, the ether extracts being washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the product purified by chromatography on silica gel (1:5 EtOAc:hexane), yielding the *title compound* (422 mg, 66%) as a colourless oil.

ν_{max} (Neat): 3354, 3022, 2930, 2857, 1466, 1033 and 699 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 5.72 – 5.60 (3 H, m, alkene CH), 5.51 – 5.45 (1 H, m, alkene CH), 3.73 – 3.66 (1 H, m, C*H*OH), 2.89 – 2.81 (1 H, m, CH), 2.58 – 2.51

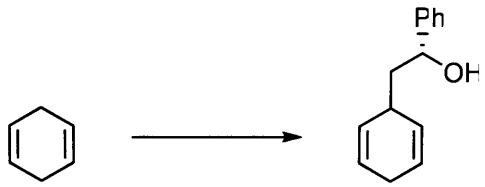
(2 H, m, CH_2), 1.51 – 1.38 (5 H, m, 2 x CH_2 and OH), 1.34 – 1.26 (2 H, m, CH_2), 1.25 – 1.15 (2 H, m, CH_2) and 0.77 (3 H, t, *J* 7.0, CH_3).

δ_C (100 MHz; $CDCl_3$): 129.3 (CH), 129.1 (CH), 124.9 (CH), 124.5 (CH), 69.5 (CH), 43.7 (CH_2), 37.7 (CH_2), 35.6 (CH), 27.8 (CH_2), 26.2 (CH_2), 22.8 (CH_2) and 14.1 (CH_3).

MS-EI: *m/z* (%) = 180 (M^+, 3), 162 (9), 131 (12), 117 (25), 92 (92) and 91 (100).

HRMS-EI: *m/z* $[M]^+$ calcd for $C_{12}H_{20}O$: 180.1514; found: 180.1514.

2-(Cyclohexa-2,5-dienyl)-1-phenylethanol (24b)



27 **24b**

To a solution of 1,4-cyclohexadiene **27** (397 mg, 4.95 mmol) in dry THF (10 ml) at -78 °C were added n-butyllithium (2.5 M solution in hexanes, 2.18 ml, 5.45 mmol) and TMEDA (0.82 ml, 5.45 mmol). The yellow solution was warmed to -41 °C and after 2.5 h was treated with styrene oxide **28b** (0.68 ml, 5.95 mmol). After 10 minutes at -41 °C the solution was warmed to room temperature and left to stir for 1 h before being quenched with saturated ammonium chloride solution. The product was then extracted with ether, the ether extracts being washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the product purified by chromatography on silica gel (9:1 Et_2O:petroleum ether), yielding the *title compound* (268 mg, 27%) as a colourless oil.

ν_{max} (Neat): 3384, 3026, 2926, 2818, 1603, 1493, 1453, 1054 and 700 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 7.24 – 7.12 (5 H, m, aromatic CH), 5.71 – 5.62 (3 H, m, alkene CH), 5.54 (1 H, app. ddt, *J* 12.2, 3.5, 1.6, alkene CH), 4.78 (1 H, ddd, *J* 9.1, 4.0, 2.8), 2.87 – 2.78 (1 H, m, CH), 2.58 – 2.52 (2 H, m, CH_2), 1.93 (1 H,

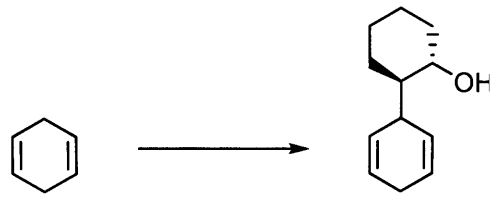
broad d, *J* 2.8, OH), 1.82 (1 H, ddd, *J* 14.2, 9.1, 5.4, one of CH_2) and 1.64 (1 H, ddd, *J* 14.2, 7.2, 4.0, one of CH_2).

δ_C (100 MHz; $CDCl_3$): 144.8 (C), 129.0 (CH), 128.8 (CH), 128.5 (CH), 127.5 (CH), 125.8 (CH), 125.0 (CH), 124.7 (CH), 72.2 (CH), 45.9 (CH_2), 32.7 (CH) and 26.2 (CH_2).

MS-ES: *m/z* (%) = 200 (M^+, 37), 182 (79) and 121 (100).

HRMS-ES: *m/z* $[M]^+$ calcd for $C_{14}H_{16}O$: 200.1201; found 200.1199.

(1SR,2RS)-2-(Cyclohexa-2,5-dienyl)cyclohexanol (24c)



27 **24c**

To a solution of 1,4-cyclohexadiene **27** (314 mg, 3.92 mmol) in dry THF (10 ml) at -78 °C were added n-butyllithium (2.5 M solution in hexanes, 1.72 ml, 4.31 mmol) and TMEDA (0.65 ml, 4.31 mmol). The yellow solution was warmed to -41 °C and after 2.5 h was treated with cyclohexene oxide **28c** (0.48 ml, 4.70 mmol). After 10 minutes at -41 °C the solution was warmed to room temperature and left to stir for 1h before being quenched with saturated ammonium chloride solution. The product was then extracted with ether, the ether extracts being washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the product purified by chromatography on silica gel (1:6 EtOAc:hexane), yielding the *title compound* (309 mg, 44%) as a colourless oil.

ν_{max} (Neat): 3385, 3023, 2927, 2855, 1448, 1261 and 698 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 5.77 – 5.65 (3 H, m, alkene CH), 5.52 – 5.46 (1 H, m, alkene CH), 3.44 (1 H, app. dt, *J* 4.3, 10.1, CHO), 3.15 – 3.07 (1 H, m, CH), 2.62 – 2.56 (2 H, m, CH_2), 2.06 (1 H, broad s, OH), 1.94 – 1.88 (1 H, m, CH),

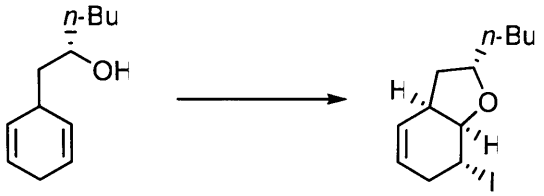
1.66 – 1.51 (3 H, m), 1.35 – 1.28 (1 H, app. ddt, *J* 12.0, 10.2, 3.1) and 1.23 – 0.96 (4 H, m).

δ_C (100 MHz; $CDCl_3$): 128.1 (CH), 127.4 (CH), 125.4 (CH), 125.4 (CH), 71.7 (CH), 49.8 (CH), 35.9 (CH), 35.8 (CH), 27.1 (CH_2), 26.5 (CH_2), 25.8 (CH_2) and 25.0 (CH_2).

MS-ES: *m/z* (%) = 178 (M^+, 3), 160 (100), 117 (76), 104 (40) and 92 (78).

HRMS-ES: *m/z* $[M]^+$ calcd for $C_{12}H_{18}O$: 178.1358; found 178.1361.

(2SR,3aRS,7RS,7aRS)-2-Butyl-2,3,3a,6,7,7a-hexahydro-7-iodobenzofuran (25a)



24a **25a**

To a solution of alcohol **24a** (224 mg, 1.24 mmol) in MeCN (20 ml) were added iodine (948 mg, 3.73 mmol) and sodium hydrogen carbonate (314 mg, 3.73 mmol). The reaction was monitored by TLC and on complete consumption of the starting material (10 min) the reaction was quenched with saturated sodium thiosulfate solution. The product was then extracted with ether, the ether extracts being washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the product purified by chromatography on silica gel (1:50 Et_2O :petroleum ether), yielding the *title compound* (252 mg, 66%) as a pale oil.

ν_{max} (Neat): 3026, 2927, 2858, 1653, 1456, 1085 and 686 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 5.36 – 5.54 (2 H, m, alkene CH), 4.40 – 4.33 (2 H, m, CHO and CHI), 3.90 (1 H, app. dq, *J* 9.4, 6.2, CHO), 3.00 – 2.93 (1 H, m, CH), 2.80 – 2.71 (1 H, m, one of CH_2), 2.43 – 2.35 (1 H, m, one of CH_2), 1.79 (1 H,

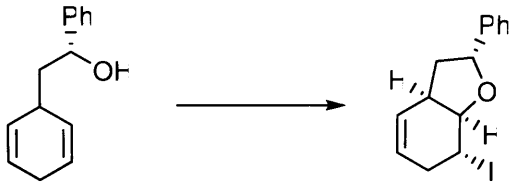
ddd, *J* 12.2, 5.4, 2.5, one of CH_2), 1.69 (1 H, ddd, *J* 12.2, 9.4, 7.5, one of CH_2), 1.57 – 1.48 (1 H, m), 1.38 – 1.12 (5 H, m) and 0.82 (3 H, t, *J* 7.0, CH_3).

δ_C (100 MHz; $CDCl_3$): 128.1 (CH), 124.8 (CH), 80.5 (CH), 80.3 (CH), 38.0 (CH_2), 37.9 (CH), 35.8 (CH_2), 30.3 (CH_2), 28.2 (CH_2), 27.5 (CH), 22.8 (CH_2) and 14.1 (CH_3).

MS-ES: *m/z* (%) = 348 ($MH^+.CH_3CN$, 100) and 224 (19).

HRMS-ES: *m/z* [M + H + CH_3CN]$^+$ calcd for $C_{14}H_{23}INO$: 348.0824; found 348.0838.

(2RS,3aRS,7RS,7aRS)-2,3,3a,6,7,7a-Hexahydro-7-iodo-2-phenylbenzofuran (25b)



24b **25b**

To a solution of alcohol **24b** (178 mg, 0.89 mmol) in MeCN (20 ml) were added iodine (680 mg, 2.67 mmol) and sodium hydrogen carbonate (220 mg, 2.67 mmol). The reaction was monitored by TLC and on complete consumption of the starting material (10 min) the reaction was quenched with saturated sodium thiosulfate solution. The product was then extracted with ether, the ether extracts being washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the product purified by chromatography on silica gel (1:20 EtOAc:hexane), yielding the *title compound* (182 mg, 63%) as a pale oil.

ν_{max} (Neat): 3026, 2930, 2870, 1493, 1450, 1082, 950 and 698 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 7.29 – 7.16 (5 H, m, aromatic CH), 5.73 – 5.68 (1 H, m, alkene CH), 5.64(1 H, app. dt, *J* 10.2, 2.6, alkene CH), 4.94 (1 H, dd, *J* 9.5, 5.7, CH-Ph), 4.66 (1 H, app. t, *J* 5.0, CHO), 4.44 (1 H, app. q, *J* 4.2, CHI), 3.15 – 3.07 (1 H, m, CH), 2.86 (1 H, app. ddq, *J* 18.7, 4.9, 2.5, one of CH_2), 2.48 –

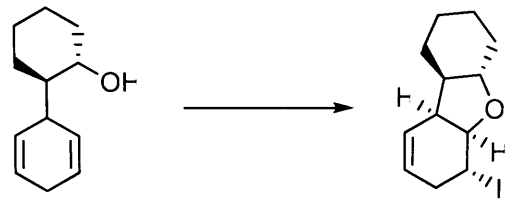
2.40 (1 H, m, one of CH_2), 2.12 (1 H, ddd, *J* 12.4, 5.7, 2.6, one of CH_2) and 2.03 (1 H, ddd, *J* 12.4, 9.5, 7.0, one of CH_2).

δ_C (100 MHz; $CDCl_3$): 142.8 (C), 128.5 (CH), 127.5 (CH), 127.4 (CH), 125.6 (CH), 125.4 (CH), 81.9 (CH), 81.6 (CH), 41.4 (CH_2), 38.3 (CH), 30.3 (CH_2) and 26.8 (CH).

MS-ES: *m/z* (%) = 326 (M^+, 2), 199 (100), 105 (81) and 91 (68).

HRMS-ES: *m/z* $[M]^+$ calcd for $C_{14}H_{15}IO$: 326.0168; found 326.0163.

(4aSR,5aRS,6RS,9aSR,9bRS)-6-Iodo 1,2,3,4,4a,5a,6,7,9a,9bdecahydrodibenzo[b,d]furan (25c)



24c **25c**

To a solution of alcohol **24c** (290 mg, 1.63 mmol) in MeCN (20 ml) were added iodine (1.24 g, 4.89 mmol) and sodium hydrogen carbonate (410 mg, 4.89 mmol). The reaction was monitored by TLC and on complete consumption of the starting material (10 min) the reaction was quenched with saturated sodium thiosulfate solution. The product was then extracted with ether, the ether extracts being washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the product purified by chromatography on silica gel (1:9 EtOAc:hexane), yielding the *title compound* (299 mg, 60%) as an orange/brown solid, m.p. 61 – 62 °C.

ν_{max} (Nujol): 2960, 1612, 1413, 1260, 1020, 797 and 688 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 5.74 (1 H, broad app. ddd, *J* 10.2, 6.0, 1.3, alkene CH), 5.62 (1 H, app. dt, *J* 10.2, 3.2, alkene CH), 4.49 – 4.42 (2 H, m, CHO and CHI), 3.22 (1 H, app. dt, *J* 4.0, 10.7, CHO), 2.95 – 2.89 (1 H, m, CH), 2.72 – 2.64 (1 H, m, one of CH_2), 2.36 (1 H, broad app. ddd, *J* 18.6, 6.0, 1.3, one of CH_2),

2.02 – 1.96 (1 H, m), 1.85 – 1.80 (1 H, m), 1.74 – 1.56 (3 H, m) and 1.26 – 1.05 (4 H, m).

δ_C (100 MHz; $CDCl_3$): 126.3 (CH), 125.3 (CH), 82.7 (CH), 80.6 (CH), 49.4 (CH), 39.4 (CH), 32.1(CH_2), 29.4 (CH_2), 27.8 (CH), 26.1 (CH_2), 25.6 (CH_2) and 24.0 (CH_2).

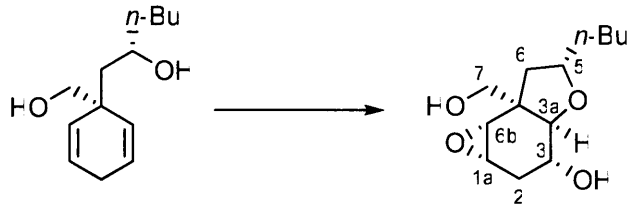
MS-ES: *m/z* (%) = 346 (MH^+.CH3CN, 60), 279 (74) and 177 (100).

HRMS-ES: *m/z* [M + H + CH_3CN]$^+$ calcd for $C_{14}H_{21}INO$: 346.0668; found 346.0667.

***General Procedure 1*- Epoxidation Reactions**

50% *m*-CPBA (1.04 g, 3.01 mmol) and solid $NaHCO_3$ (379 mg, 4.51 mmol) were added to a solution of diol **19a-f, 45, 46** (1.50 mmol) in CH_2Cl_2 (20 ml) at 0 °C. The solution was stirred for 24 hours, after which an additional 0.1 equivalents of *m*-CPBA was added every hour until complete consumption of the starting material (TLC; typically 2.4 equivalents of *m*-CPBA was required). The reaction was quenched with saturated aqueous sodium thiosulfate solution and extracted with CH_2Cl_2 (3 × 25 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (50 ml) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica gel to give the pure epoxide **38**.

(1*aSR*,3*RS*,3*aRS*,5*SR*,6*aRS*,6*bRS*)-5-Butyl-octahydro-6*a*-(hydroxymethyl)-7-oxa-bicyclo[4.1.0]hept-1(6)-eno[3,2-*b*]furan-3-ol (38a)



19a **38a**

Epoxide **38a** was prepared from diol **19a** (316 mg, 1.50 mmol) according to *general procedure 1*. Purification by flash column chromatography (eluent 1:1 ethyl acetate:hexane) afforded the *title compound* (144 mg, 40%) as a colourless oil.

ν_{max} **(Neat):** 3415, 2922, 2862, 1466, 1426, 1381, 1259, 1127, 1058 and 838 cm^{-1}.

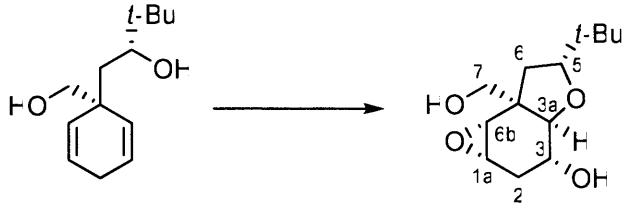
δ_H **(400 MHz; $CDCl_3$):** 3.88–3.81 (1 H, m, H-5), 3.82 (1 H, d, *J* 10.9, one of H-7), 3.79–3.74 (1 H, m, H-3), 3.74–3.72 (1 H, d, *J* 5.3, H-3a), 3.67 (1 H, d, *J* 10.9, one of H-7), 3.39–3.38 (1 H, m, H-1a), 3.30 (1 H, broad s, OH), 3.16 (1 H, app. dd, *J* 4.1, 1.2, H-6b), 2.60 (1 H, broad s, OH), 2.24–2.17 (1 H, m, one of H-2), 2.13 (1 H, ddd, *J* 15.8, 3.8, 1.3, one of H-2), 2.02 (1 H, dd, J 12.8, 5.3, one of H-6), 1.76 (1 H, dd, *J* 12.8, 9.9, one of H-6), 1.60–1.51 (1 H, m, one of $CH_2(CH_2)_2CH_3$), 1.43–1.35 (1 H, m, one of $CH_2(CH_2)_2CH_3$), 1.32–1.19 (4 H, m, $(CH_2)_2$) and 0.83 (3 H, t, *J* 7.0, CH_3).

δ_C **(100 MHz; $CDCl_3$):** 78.6 (CH), 78.1 (CH), 67.6 (CH_2), 67.0 (CH), 56.6 (CH), 53.5 (CH), 46.5 (C), 41.8 (CH_2), 35.3 (CH_2), 28.2 (CH_2), 25.7 (CH_2), 22.7 (CH_2) and 14.1 (CH_3).

MS-EI: *m/z* (%) = 242 (M^+, 1), 211 (100), 149 (80) and 95 (94).

HRMS-EI: *m/z* $[M]^+$ calcd for $C_{13}H_{22}O_4$: 242.1518; found: 242.1519.

(1*aSR*,3*RS*,3*aRS*,5*RS*,6*aRS*,6*bRS*)-5-*tert*-Butyl-octahydro-6*a*-(hydroxymethyl)-7-oxa-bicyclo[4.1.0]hept-1(6)-eno[3,2-*b*]furan-3-ol (38b)



19b **38b**

Epoxide **38b** was prepared from diol **19b** (161 mg, 0.77 mmol) according to *general procedure 1*. Purification by flash column chromatography (eluent 3:1 ethyl acetate:hexane) gave the *title compound* (139 mg, 75%) as a colourless solid, m.p. 86–87 °C.

ν_{max} **(Nujol):** 3388, 2923, 2853, 1259 and 1059 cm^{-1}.

δ_H **(400 MHz; $CDCl_3$):** 3.89 (1 H, d, *J* 10.9, one of H-7), 3.87–3.85 (1 H, m, H-3), 3.74–3.72 (1 H, m, H-3a), 3.72 (1 H, d, *J* 10.9, one of H-7), 3.60 (1 H, dd, *J* 10.8, 5.8, H-5), 3.46–3.43 (1 H, m, H-1a), 3.17 (1 H, app. dd, *J* 4.0, 1.2, H-6b), 2.75 (2 H, broad s, 2 x OH), 2.25 (1 H, app. dt, *J* 15.8, 2.4, one of H-2), 2.18 (1 H, ddd, *J* 15.8, 3.8, 1.3, one of H-2), 1.93 (1 H, dd, *J* 12.8, 10.8, one of H-6), 1.88 (1 H, dd, *J* 12.8, 5.8, one of H-6) and 0.86 (9 H, s, *t*-Bu).

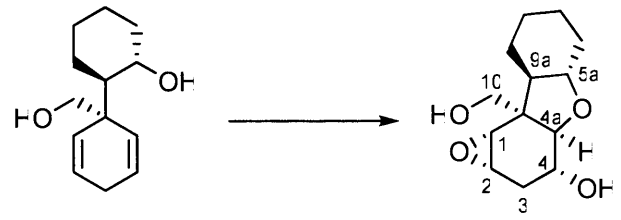
δ_C **(100 MHz; $CDCl_3$):** 85.8 (CH), 79.3 (CH), 67.9 (CH_2), 67.0 (CH), 56.7 (CH), 53.7 (CH), 46.4 (C), 37.2 (CH_2), 33.6 (C), 25.7 (CH_2) and 25.6 (3 x CH_3).

MS-EI: *m/z* (%) = 224 ($M^+ - H_2O$, 3), 185 (100), 149 (33), 121 (44) and 95 (39).

HRMS-EI: *m/z* $[M]^+$ calcd for $C_{13}H_{20}O_3$: 224.1412; found: 224.1413.

Crystallographic data for compound 38b. $C_{13}H_{22}O_4$, FW = 242.31, T = 150(2) K, λ= 0.71073 Å, monoclinic, $P2_1/a$, a = 11.8532(3) Å, b = 7.1565(2) Å, c = 16.0428(4), β= 102.4210(10), V = 1329.02(6) $Å^3$, Z = 4, ρ(calc) = 1.211 Mg/m^3, crystal size = 0.38 x 0.25 x 0.10 mm^3, reflections collected = 20521, independent reflections = 3023, R(int)= 0.109, parameters = 160, R1 [$I>2\sigma(I)$]= 0.075, wR2 [$I>2\sigma(I)$] = 0.19, R1 (all data) = 0.10, wR2 (all data) = 0.21, Flack parameter = 0.056(10).

(1*RS*,2*SR*,4*RS*,4*aRS*,5*aSR*,9*aRS*,9*bSR*)-9*b*-(Hydroxymethyl)-1,2-epoxydodecahydrodibenzo[*b*,*d*]furan-4-ol 38c



19c **38c**

Epoxide **38c** was prepared from diol **19c** (85 mg, 0.41 mmol) according to *general procedure 1*. Purification by flash column chromatography (eluent 1:1 ethyl acetate:hexane) afforded the *title compound* (51 mg, 52%) as a colourless solid, m.p. 153–154 °C.

ν_{max} **(Nujol):** 3417, 2927, 2854, 1064, 1046 and 722 cm^{-1}.

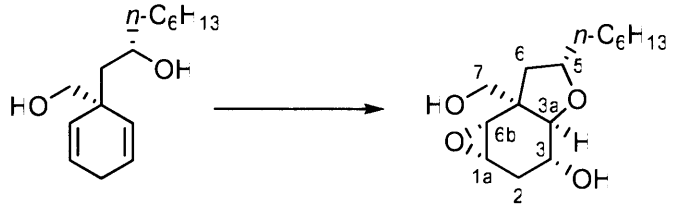
δ_H **(400 MHz; $CDCl_3$):** 3.92–3.86 (2 H, m, H-4 and H-4a), 3.91 (1 H, d, *J* 11.0, one of H-10), 3.87 (1 H, d, *J* 11.0, one of H-10), 3.47–3.44 (1 H, m, H-2), 3.36–3.29 (2 H, m, H-1 and H-5a), 2.35 (1 H, app. broad d, *J* 16.0, one of H-3), 2.20–2.01 (4 H, m, one of H-3, H-9a and 2 × OH), 1.85–1.77 (2 H, m, cyclohexyl CH_2), 1.74–1.66 (2 H, m, cyclohexyl CH_2) and 1.39–1.13 (4 H, m, 2 × cyclohexyl CH_2).

δ_C **(100 MHz; $CDCl_3$):** 81.1 (CH), 79.2 (CH), 67.7 (CH), 67.1 (CH_2), 53.8 (CH), 53.5 (CH), 52.3 (CH), 45.8 (C), 32.2 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 25.2 (CH_2) and 23.9 (CH_2).

MS-ES: *m/z* (%) = 222 ($M^+ - H_2O$, 1), 192 (86) and 79 (100).

HRMS-ES: *m/z* $[M - H_2O]^+$ calcd for $C_{13}H_{18}O_3$: 222.1256; found: 222.1253.

(1*aSR*,3*RS*,3*aRS*,5*SR*,6*aRS*,6*bRS*)-5-Hexyl-octahydro-6*a*-(hydroxymethyl)-7-oxa-bicyclo[4.1.0]hept-1(6)-eno[3,2-*b*]furan-3-ol (38d)



19d **38d**

Epoxide **38d** was prepared from diol **19d** (509 mg, 2.14 mmol) according to *general procedure 1*. Purification by flash column chromatography (eluent 2:1 hexane:ethyl acetate) afforded the *title compound* (209 mg, 36%) as a colourless solid, m.p. 72–73 °C.

ν_{max} **(Nujol):** 3406, 2922, 2854, 1249, 1130, 1075, 1057, 1021, 932, 840, 721 and 668 cm^{-1}.

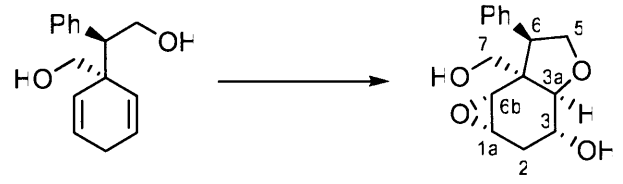
δ_H **(400 MHz; $CDCl_3$):** 3.89–3.84 (1 H, m, H-5), 3.85 (1 H, d, *J* 10.8, one of H-7), 3.82–3.77 (1 H, m, H-3), 3.75 (1 H, d, *J* 3.9, H-3a), 3.69 (1 H, d, *J* 10.8, one of H-7), 3.40–3.37 (1 H, m, H-1a), 3.26 (1 H, app. dd, *J* 4.0, 1.2, H-6b), 2.22 (1 H, app. dt, *J* 15.8, 2.5, one of H-2), 2.13 (1 H, ddd, *J* 15.8, 3.8, 1.4, one of H-2), 2.03 (1 H, dd, *J* 12.8, 5.3, one of H-6), 1.75 (1 H, dd, *J* 12.8, 9.9, one of H-6), 1.58–1.50 (2 H, m, $CH_2(CH_2)_4CH_3$), 1.43–1.14 (10 H, m, $(CH_2)_4$ and 2 × OH) and 0.81 (3 H, t, *J* 6.8, CH_3).

δ_C **(100 MHz; $CDCl_3$):** 78.8 (CH), 78.1 (CH), 68.0 (CH_2), 67.0 (CH), 56.6 (CH), 53.5 (CH), 46.5 (C), 41.9 (CH_2), 35.7 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 26.0 (CH_2), 25.8 (CH_2) 22.6 (CH_2) and 14.1 (CH_3).

MS-ES: *m/z* (%) = 252 ($M^+ - H_2O$, 40), 185 (100), 123 (98) and 95 (88).

HRMS-ES: *m/z* $[M - H_2O]^+$ calcd for $C_{15}H_{24}O_3$: 252.1725; found: 252.1725.

(1*aSR*,3*RS*,3*aRS*,6*RS*,6*aRS*,6*bRS*)-Octahydro-6*a*-(hydroxymethyl)-6-phenyl-7-oxa-bicyclo[4.1.0]hept-1(6)-eno[3,2-*b*]furan-3-ol (38f)



19f **38f**

Epoxide **38f** was prepared from diol **19f** (136 mg, 0.59 mmol) according to *general procedure 1*. Purification by flash column chromatography (eluent 3:2 hexane:ethyl acetate) afforded the *title compound* (85 mg, 55%) as a colourless solid, m.p. 89–90 °C.

ν_{max} **(Nujol):** 3488, 3335, 2923, 2851, 1076, 1059 and 1040 cm^{-1}.

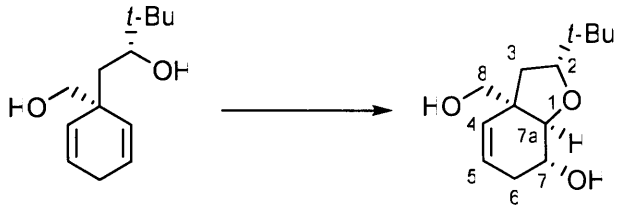
δ_H **(400 MHz; $CDCl_3$):** 7.39–7.25 (5 H, m, Ph), 4.20 (1 H, dd, *J* 9.1, 5.0, one of H-5), 4.10 (1 H, dd, *J* 9.1, 6.8, one of H-5), 4.03–3.98 (1 H, m, H-3), 3.92 (1 H, d, *J* 11.0, one of H-7), 3.90 (1 H, d, *J* 11.0, one of H-7), 3.86–3.83 (1 H, m, H-3a), 3.71 (1 H, dd, *J* 6.8, 5.0, H-6), 3.50 (1 H, broad s, OH), 3.15–3.11 (1 H, m, H-1a), 2.77 (1 H, app. dd, *J* 4.2, 1.5, H-6b), 2.34–2.23 (2 H, m, H-2) and 1.65 (1 H, broad s, OH).

δ_C **(100 MHz; $CDCl_3$):** 139.1 (C), 128.6 (2 × CH), 128.5 (2 × CH), 127.2 (CH), 80.6 (CH), 72.5 (CH_2), 66.7 (CH_2), 66.3 (CH), 55.4 (CH), 53.6 (CH), 51.5 (CH), 48.5 (C) and 25.7 (CH_2).

MS-ES: *m/z* (%) = 244 ($M^+ - H_2O$, 9), 214 (100), 171 (21) and 104 (85).

HRMS-ES: *m/z* $[M - H_2O]^+$ calcd for $C_{15}H_{16}O_3$: 244.1099; found: 244.1091.

(2*RS*,3*aRS*,7*RS*,7*aRS*)-2-*tert*-Butyl-3*a*-(hydroxymethyl)-2,3,3a,6,7,7a-hexahydro-benzo[*b*]furan-7-ol (39)



19b **39**

Vanadyl acetylacetonate (73 mg, 0.28 mmol) and *tert*-butyl hydroperoxide (1.22 ml of 5.0–6.0 M solution in decane, 6.08 mmol) were added to a solution of diol **19b** (580 mg, 2.76 mmol) in CH_2Cl_2 (10 ml) at 0 °C. The reaction mixture was allowed to warm slowly to room temperature and stirred for 16 h. The reaction was quenched with saturated aqueous Na_2SO_3 solution and extracted with CH_2Cl_2 (3 × 10 ml). The combined organic extracts were dried over Na_2SO_4 before the solvent was removed *in vacuo*. Chromatography on silica gel (eluent hexane:ethyl acetate 2:1) afforded the *title compound* (93 mg, 15%) as a colourless solid, m.p. 83–85 °C.

ν_{max} **(Nujol):** 3186, 2922, 2856, 1205, 1171, 1131, 1043, 964, 910, 836, 776 and 746 cm^{-1}.

δ_H **(400 MHz; $CDCl_3$):** 5.83–5.79 (1 H, m, H-5), 5.43 (1 H, d, *J* 10.2, H-4), 4.22 (2 H, broad s, 2 × OH), 4.05–4.01 (1 H, m, H-7), 3.88 (1 H, d, *J* 3.9, H-7a), 3.62 (1 H, d, *J* 10.4, one of H-8), 3.55 (1 H, dd, *J* 10.5, 5.6, H-2), 3.46 (1 H, d, *J* 10.4, one of H-8), 2.36–2.31 (1 H, m, one of H-6), 2.04 (1 H, app. dd, *J* 17.9, 4.7, one of H-6), 1.52 (1 H, dd, *J* 12.1, 10.5, one of H-3), 1.48 (1 H, dd, *J* 12.1, 5.6, one of H-3) and 0.82 (9 H, d, $C(CH_3)_3$).

δ_C **(100 MHz; $CDCl_3$):** 129.7 (CH), 126.5 (CH), 85.2 (CH), 83.5 (CH), 68.0 (CH_2), 64.7 (CH), 48.8 (C), 36.6 (CH_2), 33.5 (C), 28.2 (CH_2) and 25.7 (3 × CH_3).

MS-AP: *m/z* (%) = 209 ($MH^+ - H_2O$, 100).

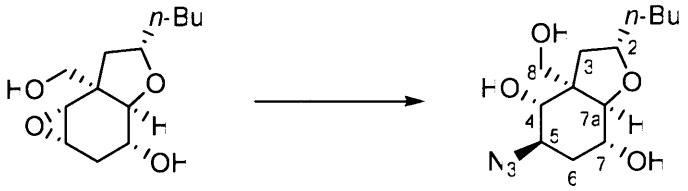
HRMS-AP: *m/z* $[MH - H_2O]^+$ calcd for $C_{13}H_{21}O_2$: 209.1542; found: 209.1532.

In addition, compound **38b** (34 mg, 5%) was obtained.

General Procedure 2- Azide Ring-Openings

Sodium azide (285 mg, 4.38 mmol) and ammonium chloride (117 mg, 2.19 mmol) were added portionwise to a solution of the epoxide **38a-d**, **38f** (0.44 mmol) in an 8:1 mixture of methanol/water (9 ml). The solution was stirred at 80 °C for 24 hours before being cooled to room temperature and quenched with water. The crude product was extracted into CH_2Cl_2 (3 × 10 ml). The combined organic extracts were dried over Na_2SO_4 and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel to give the pure azide **41**.

(2*SR*,3*aSR*,4*RS*,5*RS*,7*RS*,7*aRS*)-5-Azido-2-butyl-octahydro-3*a*-(hydroxymethyl)benzofuran-4,7-diol (41a)



38a **41a**

Azide **41a** was prepared from epoxide **38a** (106 mg, 0.44 mmol) according to *general procedure 2*. Purification by flash column chromatography (eluent 2:1 hexane:ethyl acetate) afforded the *title compound* (45 mg, 36%) as a colourless solid, m.p. 107–108 °C.

ν_{max} **(Nujol):** 3185, 2923, 2853, 2111, 1082, 721 and 668 cm^{-1}.

δ_H **(400 MHz; CD_3OD):** 4.02 (1 H, app. tt, *J* 12.9, 6.5, H-2), 3.91 (1 H, ddd, *J* 12.3, 10.3, 4.3, H-5 or H-7), 3.89–3.85 (2 H, m, one of H-8 and H-5 or H-7), 3.69 (1 H, app. broad s, H-4 or H-7a), 3.48 (1 H, d, *J* 11.0, one of H-8), 3.40 (1

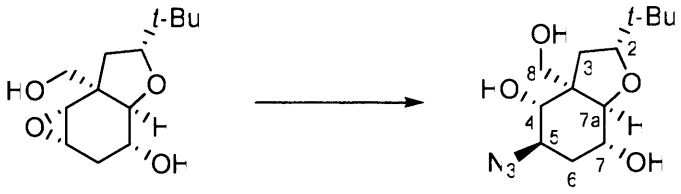
H, d, *J* 10.2, H-4 or H-7a), 2.18 (1 H, dd, *J* 12.7, 6.5, one of H-3), 1.88 (1 H, app. dt, *J* 13.8, 3.1, one of H-6), 1.65–1.49 (2 H, m, one of H-6 and butyl H), 1.44–1.18 (6 H, m, one of H-3 and butyl H) and 0.86 (3 H, t, *J* 6.8, CH_3).

δ_C (100 MHz; CD_3OD): 85.1 (CH), 78.3 (CH), 76.5 (CH), 66.9 (CH), 65.0 (CH_2), 60.9 (CH), 53.9 (C), 41.3 (CH_2), 37.5 (CH_2), 34.6 (CH_2), 29.3 (CH_2), 23.8 (CH_2) and 14.5 (CH_3).

MS-ES: *m/z* (%) = 267 ($M^+ - H_2O$, 26), 208 (100), 181 (58), 155 (64) and 72 (81).

HRMS-ES: *m/z* $[M - H_2O]^+$ calcd for $C_{13}H_{21}N_3O_3$: 267.1583; found: 267.1588.

(2*RS*,3*aSR*,4*RS*,5*RS*,7*RS*,7*aRS*)-2-*tert*-Butyl-5-azido-octahydro-3*a*-(hydroxymethyl)benzofuran-4,7-diol (41b)



38b **41b**

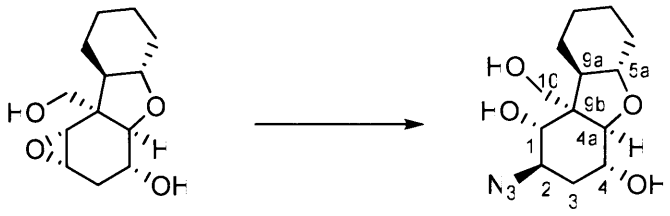
Azide **41b** was prepared from epoxide **38b** (101 mg, 0.42 mmol) according to *general procedure 2*. Purification by flash column chromatography (eluent 2:1 hexane:ethyl acetate) afforded the *title compound* (80 mg, 67%) as a colourless solid, m.p. 155–156 °C.

ν_{max} (Nujol): 3192, 2920, 2853, 2113, 1258 and 1070 cm^{-1}.

δ_H (400 MHz; CD_3OD): 4.03–3.92 (3 H, m, one of H-8, H-5 and H-7), 3.78 (1 H, dd, *J* 9.9, 6.6, H-2), 3.69 (1 H, app. broad s, H-4 or H-7a), 3.54 (1 H, d, *J* 11.0, one of H-8), 3.48 (1 H, d, *J* 10.3, H-4 or H-7a), 2.02 (1 H, app. dd, *J* 12.9, 6.6, one of H-3), 1.93 (1 H, app. broad d, *J* 13.4, one of H-6), 1.67 (1 H, ddd, *J* 13.4, 12.7, 3.0, one of H-6), 1.57 (1 H, app. dd, *J* 12.9, 9.9, one of H-3) and 0.88 (9 H, s, *t*-Bu).

δ_C (100 MHz; CD_3OD): 86.5 (CH), 86.1 (CH), 76.5 (CH), 67.0 (CH), 65.0 (CH_2), 60.8 (CH), 53.9 (C), 35.9 (CH_2), 35.6 (C), 34.5 (CH_2) and 25.9 (3 × CH_3).
MS-EI: *m/z* (%) = 267 (M^+ – H_2O, 34), 240 (17), 182 (100), 137 (38), 111 (33) and 81 (28).
HRMS-EI: *m/z* $[M - H_2O]^+$ calcd for $C_{13}H_{21}N_3O_3$: 267.1583; found: 267.1581.

(1*RS*,2*RS*,4*RS*,4a*RS*,5a*SR*,9a*RS*,9b*SR*)-2-Azido-9*b*-(hydroxymethyl)dodecahydrodibenzo[*b*,*d*]furan-1,4-diol (41c)

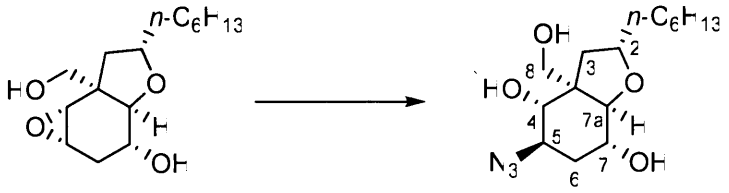


38c **41c**

Azide **41c** was prepared from epoxide **38c** (78 mg, 0.33 mmol) according to *general procedure 2*. Purification by flash column chromatography (eluent 1:1 hexane:ethyl acetate) afforded the *title compound* (42 mg, 46%) as a colourless solid, m.p. 156–157 °C.

ν_{max} (Nujol): 3418, 2922, 2103, 1303, 1064, 1036, 979, 826 and 722 cm^{-1}.
δ_H (400 MHz; CD_3OD): 3.75 (1 H, d, *J* 11.1, one of H-10), 3.72 (1 H, app. broad d, *J* 3.6, H-1 or H-4a), 3.70–3.65 (1 H, broad m, H-2 or H-4), 3.60 (1 H, d, *J* 11.1, one of H-10), 3.33–3.26 (2 H, m, H-5a and H-2 or H-4), 3.18 (1 H, app. d, *J* 3.1, H-1 or H-4a), 2.15 (1 H, app. broad d, *J* 16.0, one of H-3), 2.04 (1 H, app. ddd, *J* 16.0, 3.7, 1.0, one of H-3), 2.00–1.91 (2 H, broad m, H-9a and one of CH_2), 1.70–1.62 (3 H, broad m, one of CH_2 and CH_2) and 1.33–1.10 (4 H, m, 2 × CH_2).
δ_C (100 MHz; CD_3OD): 80.9 (CH), 78.9 (CH), 67.5 (CH), 65.0 (CH_2), 53.0 (CH), 52.8 (CH), 51.8 (CH), 45.5 (C), 32.1 (CH_2), 25.5 (CH_2), 25.4 (CH_2), 24.7 (CH_2) and 23.6 (CH_2).

(2*SR*,3*aSR*,4*RS*,5*RS*,7*RS*,7*aRS*)-5-Azido-2-hexyl-octahydro-3*a*-(hydroxymethyl)benzofuran-4,7-diol (41d)



38d **41d**

Azide **41d** was prepared from epoxide **38d** (67 mg, 0.25 mmol) according to *general procedure 2*. Purification by flash column chromatography (eluent 2:1 hexane:ethyl acetate) afforded the *title compound* (75 mg, 96%) as a colourless solid, m.p. 97–98 °C.

ν_{max} **(Nujol):** 3199, 2927, 2853, 2114, 1256, 1183, 1068, 1037, 1009, 961, 921 and 802 cm^{-1}.

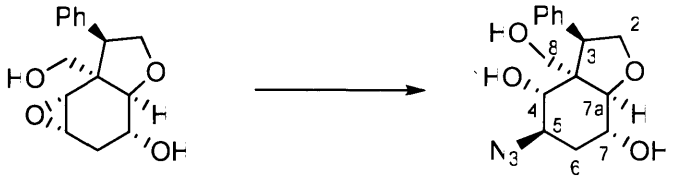
δ_H **(400 MHz; CD_3OD):** 4.13–4.03 (1 H, m, H-2), 3.97 (1 H, ddd, *J* 12.2, 10.2, 4.3, H-5 or H-7), 3.95–3.91 (2 H, m, one of H-8 and H-5 or H-7), 3.76–3.74 (1 H, m, H-4 or H-7a), 3.55 (1 H, d, *J* 11.0, one of H-8), 3.46 (1 H, d, *J* 10.2, H-4 or H-7a), 2.24 (1 H, dd, *J* 12.7, 6.5, one of H-3), 1.94 (1 H, app. broad d, *J* 13.7, one of H-6), 1.67 (1 H, ddd, *J* 13.7, 12.4, 3.0, one of H-6), 1.62–1.48 (1 H, m, hexyl H), 1.49–1.24 (9 H, m, hexyl H), 1.37 (1 H, dd, *J* 12.7, 9.0, one of H-3) and 0.91 (3 H, t, *J* 6.8, CH_3).

δ_C **(100 MHz; CD_3OD):** 85.1 (CH), 78.3 (CH), 76.5 (CH), 66.9 (CH), 65.0 (CH_2), 60.9 (CH), 53.9 (C), 41.3 (CH_2), 37.8 (CH_2), 34.6 (CH_2), 33.1 (CH_2), 30.5 (CH_2), 27.1 (CH_2), 23.7 (CH_2) and 14.5 (CH_3).

MS-ES: *m/z* (%) = 331 (M + NH_4^+, 67), 287 (22), 286 (100), 268 (7), 252 (2) and 222 (1).

HRMS-ES: *m/z* $[M + NH_4]^+$ calcd for $C_{15}H_{31}N_4O_4$: 331.2345; found: 331.2359.

(3*RS*,3*aSR*,4*RS*,5*RS*,7*RS*,7*aRS*)-5-Azido-octahydro-3*a*-(hydroxymethyl)-3-phenylbenzofuran-4,7-diol (41f)



38f **41f**

Azide **41f** was prepared from epoxide **38f** (45 mg, 0.17 mmol) according to *general procedure 2*. Purification by flash column chromatography (eluent 1:1 hexane:ethyl acetate) afforded the *title compound* (35 mg, 67%) as a colourless solid, m.p. 140–141 °C.

ν_{max} **(Nujol):** 3260, 2924, 2854, 2100, 1246, 1158, 1061 and 722 cm^{-1}.

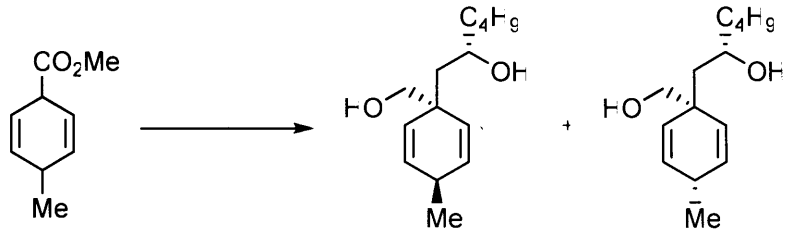
δ_H **(400 MHz; CD_3OD):** 7.24–7.12 (5 H, m, Ph), 4.21 (1 H, dd, *J* 9.9, 8.9, one of H-2), 4.03 (1 H, app. t, *J* 8.7, one of H-2), 3.99 (1 H, d, *J* 10.9, one of H-8), 3.90 (1 H, app. q, *J* 3.1, H-5 or H-7), 3.86 (1 H, app. d, *J* 2.8, H-4 or H-7a), 3.84–3.78 (1 H, m, H-5 or H-7), 3.68 (1 H, d, *J* 9.9, H-4 or H-7a), 3.53 (1 H, d, *J* 10.9, one of H-8), 3.40 (1 H, app. t, *J* 9.5, H-3), 1.87 (1 H, app. dt, *J* 13.5, 3.9, one of H-6) and 1.71–1.64 (1 H, m, one of H-6).

δ_C **(100 MHz; CD_3OD):** 136.7 (C), 128.4 (CH), 128.3 (CH), 128.2 (CH), 126.8 (CH), 126.6 (CH), 85.9 (CH), 71.1 (CH), 69.1 (CH_2), 65.8 (CH), 62.7 (CH_2), 60.8 (CH), 53.9 (C), 51.0 (CH) and 32.5 (CH_2).

MS-ES: *m/z* (%) = 323 ($M + NH_4^+$, 100), 278 (97), 260 (14) and 242 (1).

HRMS-ES: *m/z* $[M + NH_4]^+$ calcd for $C_{15}H_{23}N_4O_4$: 323.1719; found: 323.1734.

(±)-1-((1,4-*trans*)-1-(Hydroxymethyl)-4-methylcyclohexa-2,5-dienyl)hexan-2-ol (45) and (±)-1-((1,4-*cis*)-1-(hydroxymethyl)-4-methylcyclohexa-2,5-dienyl)hexan-2-ol (46)



23 **45** **46**

n-Butyllithium (10.1 ml of a 2.5 M solution in hexanes, 25.3 mmol) was added to a solution of diisopropylamine (3.55 ml, 25.3 mmol) in dry THF (30 ml) at –78 °C and the resulting solution was allowed to warm to room temperature. After re-cooling to –78 °C, the ester **23** (3.50 g, 23.0 mmol) was added dropwise. After stirring for 30 minutes at –78 °C, *n*-butyloxirane **28a** (3.61 ml, 29.9 mmol) was added and the reaction mixture allowed to warm to 5 °C over 3 h. The reaction was quenched with saturated aqueous ammonium chloride solution (50 ml) and extracted with diethyl ether (3 × 30 ml). The combined organic extracts were dried over Na_2SO_4 before the solvent was removed *in vacuo* affording the crude intermediate lactones **44** (5.44 g) as a yellow oil. These lactones (3.99 g, 18.1 mmol) were redissolved in dry THF (20 ml) and added dropwise to a suspension of $LiAlH_4$ (688 mg, 18.1 mmol) in dry THF (30 ml). The resulting suspension was allowed to stir for 15 minutes before the reaction was quenched slowly with 2 M NaOH. The solution was filtered and dried over Na_2SO_4 before the solvent was removed *in vacuo.* Chromatography on silica gel (eluent hexane:diethyl ether 2:1) afforded a 1:1 mixture of diols **45** and **46** (2.56 g, 63%) as a colourless oil. Further chromatography (eluent hexane:diethyl ether 4:1) provided pure samples of the individual diastereoisomers.

Data for compound 45

ν_{max} **(Neat):** 3384, 3011, 2957, 2928, 2871, 1636, 1456, 1378, 1278, 1122, 1037, 918, 804 and 746 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 5.97–5.88 (2 H, m, alkene CH), 5.65 (1 H, app. dt, *J* 10.3, 2.3, alkene CH), 5.38 (1 H, app. dt, *J* 10.8, 2.1, alkene CH), 3.82–3.74 (1 H, broad m, C*H*OH), 3.35 (2 H, s, CH_2OH), 2.85–2.77 (1 H, broad m, C*H*CH_3), 1.99 (2 H, broad s, 2 × OH), 1.50 (1 H, dd, *J* 14.2, 9.1, one of CCH_2), 1.42 (1 H, dd, *J* 14.2, 2.1, one of CCH_2), 1.38–1.22 (6 H, broad m, $(CH_2)_3$), 1.06 (3 H, d, *J* 7.3, CH_3) and 0.88 (3 H, t, *J* 6.8, CH_3).

δ_C (100 MHz; $CDCl_3$): 134.4 (CH), 133.7 (CH), 129.5 (CH), 128.4 (CH), 70.4 (CH_2), 69.2 (CH), 44.6 (CH_2), 42.7 (C), 37.6 (CH_2), 30.9 (CH), 27.8 (CH_2), 22.8 (CH_2), 22.1 (CH_3) and 14.1 (CH_3).

MS-EI: *m/z* (%) = 206 ($M^+ - H_2O$, 32), 188 (100), 176 (62), 159 (50), 145 (97) and 131 (99).

HRMS-EI: *m/z* $[M - H_2O]^+$ calcd for $C_{14}H_{22}O$: 206.1671; found: 206.1668.

Data for compound 46

ν_{max} (Neat): 3355, 3012, 2957, 2928, 2871, 1457, 1124, 1038, 945, 899, 802 and 746 cm^{-1}.

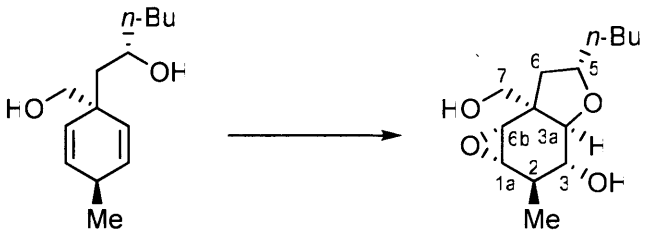
δ_H (400 MHz; $CDCl_3$): 5.96–5.89 (2 H, m, alkene CH), 5.64 (1 H, app. dt, *J* 10.1, 2.0, alkene CH), 5.38 (1 H, app. dt, *J* 10.6, 2.0, alkene CH), 3.82–3.75 (1 H, broad m, C*H*OH), 3.34 (2 H, s, CH_2OH), 2.86–2.77 (1 H, broad m, C*H*CH_3), 1.82 (2 H, broad s, 2 × OH), 1.51 (1 H, dd, *J* 14.2, 9.0, one of CCH_2), 1.44 (1 H, dd, *J* 14.2, 2.3, one of CCH_2), 1.41–1.22 (6 H, broad m, $(CH_2)_3$), 1.11 (3 H, d, *J* 7.3, CH_3) and 0.89 (3 H, t, *J* 6.7, CH_3).

δ_C (100 MHz; $CDCl_3$): 134.2 (CH), 133.7 (CH), 129.5 (CH), 128.5 (CH), 70.0 (CH_2), 69.3 (CH), 44.9 (CH_2), 42.7 (C), 37.7 (CH_2), 30.9 (CH), 27.8 (CH_2), 22.7 (CH_2), 22.4 (CH_3) and 14.1 (CH_3).

MS-AP: *m/z* (%) = 207 ($MH^+ - H_2O$, 30), 189 (100), 146 (3), 118 (3) and 91 (1).

HRMS-AP: *m/z* $[MH - H_2O]^+$ calcd for $C_{14}H_{23}O$: 207.1749; found: 207.1757.

(1*aSR*,2*RS*,3*RS*,3*aRS*,5*SR*,6*aRS*,6*bRS*)-5-Butyl-octahydro-6*a*-(hydroxymethyl)-2-methyl-7-oxa-bicyclo[4.1.0]hept-1(6)-eno[3,2-*b*]furan-3-ol (47)



45 **47**

Epoxide **47** was prepared from diol **45** (105 mg, 0.47 mmol) according to *general procedure 1*. Purification by flash column chromatography (eluent 2:1 diethyl ether:hexane) afforded the *title compound* (24 mg, 20%) as a colourless oil.

ν_{max} **(Solution in CH_2Cl_2):** 3410, 2931, 1645, 1456, 1379, 1034, 899 and 837 cm^{-1}.

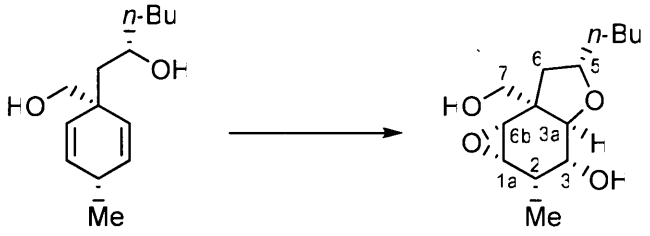
δ_H **(400 MHz; $CDCl_3$):** 3.95 (1 H, app. quintet, *J* 6.9, H-5), 3.76 (1 H, d, *J* 10.8, one of H-7), 3.69 (1 H, d, *J* 10.8, one of H-7), 3.65 (1 H, d, *J* 6.9, H-3a), 3.42 (1 H, app. dt, *J* 6.9, 4.8, H-3), 3.16 (1 H, d, *J* 3.8, H-1a), 3.00 (1 H, dd, *J* 3.8, 1.0, H-6b), 2.56 (2 H, broad s, 2 × OH), 2.09–2.02 (1 H, m, H-2), 1.97 (1 H, dd, *J* 13.1, 7.6, one of H-6), 1.71 (1 H, dd, *J* 13.1, 7.1, one of H-6), 1.61–1.52 (1 H, m, one of $CH_2(CH_2)_2CH_3$), 1.45–1.36 (1 H, m, one of $CH_2(CH_2)_2CH_3$), 1.30–1.22 (4 H, m, $(CH_2)_2$), 1.18 (3 H, d, *J* 7.5, CH_3) and 0.83 (3 H, t, *J* 7.0, CH_3).

δ_C **(100 MHz; $CDCl_3$):** 81.5 (CH), 77.0 (CH), 70.7 (CH), 67.9 (CH_2), 57.5 (CH), 56.9 (CH), 47.2 (C), 38.6 (CH_2), 36.2 (CH_2), 34.6 (CH), 28.4 (CH_2), 22.7 (CH_2), 15.9 (CH_3) and 14.1 (CH_3).

MS-EI: *m/z* (%) = 238 ($M^+ - H_2O$, 9), 190 (75), 147 (100), 121 (82) and 91 (71).

HRMS-EI: *m/z* $[M - H_2O]^+$ calcd for $C_{14}H_{22}O_3$: 238.1569; found: 238.1573.

(1*aSR*,2*SR*,3*RS*,3*aRS*,5*SR*,6*aRS*,6*bRS*)-5-Butyl-octahydro-6*a*-(hydroxymethyl)-2-methyl-7-oxa-bicyclo[4.1.0]hept-1(6)-eno[3,2-*b*]furan-3-ol (48)



46 **48**

Epoxide **48** was prepared from diol **46** (278 mg, 1.24 mmol) according to *general procedure 1*. Purification by flash column chromatography (eluent 2:1 diethyl ether:hexane) afforded the *title compound* (120 mg, 38%) as a colourless solid, m.p. 66–68 °C.

ν_{max} **(Nujol)**: 3394, 2926, 2853, 1644, 1152, 1053 and 834 cm^{-1}.

δ_H **(400 MHz; $CDCl_3$):** 3.86–3.77 (3 H, m, one of H-7, H-3a and H-5), 3.66 (1 H, d, *J* 10.9, one of H-7), 3.59 (1 H, app. broad s, H-3), 3.21 (1 H, d, *J* 4.2, H-1a), 3.17 (1 H, dd, *J* 4.2 1.5, H-6b), 2.94 (2 H, broad s, 2 × OH), 2.23 (1 H, app. qd, *J* 7.3, 3.3, H-2), 2.02 (1 H, dd, *J* 12.8, 5.1, one of H-6), 1.77 (1 H, dd, *J* 12.8, 10.2, one of H-6), 1.59–1.51 (1 H, m, one of $CH_2(CH_2)_2CH_3$), 1.42–1.34 (1 H, m, one of $CH_2(CH_2)_2CH_3$), 1.25 (3 H, d, *J* 7.3, CH_3) 1.25–1.20 (4 H, m, $(CH_2)_2$) and 0.83 (3 H, t, *J* 7.0, CH_3).

δ_C **(100 MHz; $CDCl_3$):** 79.9 (CH), 78.3 (CH), 71.4 (CH), 67.9 (CH_2), 58.9 (CH), 58.0 (CH), 46.7 (C), 42.1 (CH_2), 35.3 (CH_2), 28.2 (CH_2), 27.9 (CH), 22.8 (CH_2), 14.4 (CH_3) and 14.1 (CH_3).

MS-EI: *m/z* (%) = 238 ($M^+ - H_2O$, 12), 190 (69), 147 (100) and 121 (86).

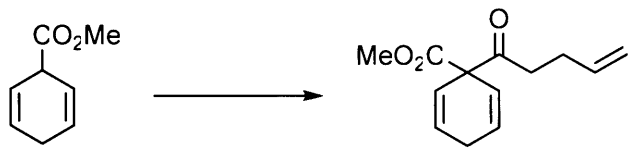
HRMS-EI: *m/z* $[M - H_2O]^+$ calcd for $C_{14}H_{22}O_3$: 238.1569; found: 238.1574.

Crystallographic data for compound 48. $C_{14}H_{24}O_4$, FW = 256.33, T = 150(2) K, λ = 0.71073 Å, triclinic, P-1, a = 6.3080(2) Å, b = 13.5420(5) Å, c = 17.5900(7) Å, α= 73.293(2)°, β= 81.756(2)°, γ= 79.108(2)°, V = 1406.88(9) $Å^3$, Z = 4, ρ(calc) = 1.210 Mg/m^3, crystal size = 0.50 × 0.18 × 0.08 mm^3, reflections

collected = 7267, independent reflections = 4761, R(int) = 0.079, parameters = 333, R1 [I>2σ(I)]= 0.14, wR2 [I>2σ(I)] = 0.34, R1 (all data) = 0.19, wR2 (all data) = 0.37. The asymmetric unit of compound **48** consists of two independent molecules. The higher R indices for **48** are due to the poor quality of the available sample and thus data were recorded using a twinned crystal.

5.3 Experimental Data for Chapter 2

Methyl 1-pent-4-enoylcyclohexa-2,5-dienecarboxylate (104)



23 **104**

n-Butyllthium (15.8 ml of a 2.5 M solution in hexanes, 39.6 mmol) was added to a solution of diisopropylamine (5.55 ml, 39.6 mmol) in THF (50 ml) at 0 °C. After stirring for 30 mins at 0°C, the reaction mixture was cooled to -78 °C before the ester **23** (4.97 g, 36.0 mmol) was added dropwise. The resulting red suspension was allowed to stir for 30 mins at -78 °C before 4-pentenoyl chloride (4.37 ml, 39.6 mmol) was added drop-wise. The yellow solution was allowed to stir for 20 minutes before being quenched at -78 °C with sat. aqueous NH_4Cl solution. The aqueous layer was extracted with diethyl ether, the combined organic extracts being dried over Na_2SO_4, before the solvent was removed *in vacuo*. Chromatography on silica gel (1:49 Et_2O:petroleum ether) afforded the *title compound* (4.67 g, 59 %) as a colourless oil.

ν_{max} (Neat): 3042, 2969, 2830, 1719, 1640, 1435, 1351, 1237, 1098, 1057, 991, 915, 795, 711 and 647 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 6.08 – 6.04 (2 H, m, ring alkene CH), 5.99 – 5.96 (2 H, m, ring alkene CH), 5.76 (1 H, ddt, *J* 17.1, 10.2, 6.5, alkene CH), 5.01 (1 H, app. ddd, *J* 17.1, 3.3, 1.5, one of terminal alkene CH_2), 4.96 (1 H, app. ddd, *J* 10.2,

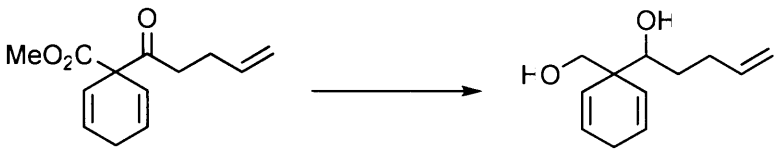
3.0, 1.5, one of terminal alkene CH_2), 3.75 (3 H, s, OCH_3), 2.79 – 2.76 (2 H, m, ring CH_2), 2.62 (2 H, t, *J* 7.3, $CH_2C{=}O$) and 2.31 – 2.25 (2 H, m, CH_2).

δ_C (100 MHz; $CDCl_3$): 205.2 (C), 170.9 (C), 136.9 (CH), 128.1 (2 x CH), 122.8 (2 x CH), 115.3 (CH_2), 62.7 (C), 52.7 (CH_3), 37.6 (CH_2), 27.6 (CH_2) and 26.1 (CH_2).

MS-ES: *m/z* (%) = 221 (MH^+, 32), 203 (5), 173 (11), 161 (14), 143 (12) and 116 (5).

HRMS-ES: *m/z* $[M + H]^+$ calcd for $C_{13}H_{17}O_3$: 221.1178; found: 221.1171.

1-(1-(Hydroxymethyl)cyclohexa-2,5-dienyl)pent-4-en-1-ol (105)



104 **105**

A solution of the keto-ester **104** (1.64 g, 7.01 mmol) in THF (5 ml) was added dropwise to a suspension of lithium aluminium hydride (266 mg, 7.01 mmol) in THF (15 ml). The suspension was allowed to stir for 20 mins before being quenched slowly with 2 M aqueous NaOH solution. The solution was filtered and dried over Na_2SO_4 before the solvent was removed *in vacuo*. Chromatography on silica gel (1:4 EtOAc:hexane) afforded the *title compound* (1.02 g, 75 %) as a colourless solid, m.p. 61 – 62 °C.

ν_{max} (Nujol): 3306, 1404, 1338, 1312, 1260, 1136, 1097, 720 and 650 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 5.96 – 5.92 (1 H, m, ring alkene CH), 5.88 (1 H, app. dtd, *J* 10.2, 3.4, 1.6, ring alkene CH), 5.77 (1 H, app. ddt, *J* 17.1, 10.2, 6.9, alkene CH), 5.70 (1 H, app. ddd, *J* 10.3, 3.9, 1.8, ring alkene CH), 5.37 (1 H, app. dq, *J* 10.2, 1.9, ring alkene CH), 5.00 (1 H, ddd, *J* 17.1, 3.3, 1.6, one of terminal alkene CH_2), 4.94 – 4.91 (1 H, m, one of terminal alkene CH_2), 3.59 – 3.53 (3 H, m, C*H*$_2$OH and C*H*OH), 3.18 (2 H, broad s, 2 x OH), 2.70 – 2.57 (2 H, m, ring CH_2), 2.28 – 2.19 (1 H, m, one of $CH_2C{=}C$), 2.09 – 1.99 (1 H, m, one of

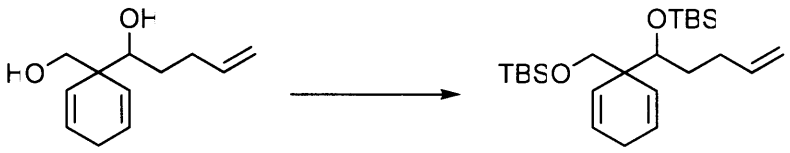
$CH_2C{=}C$), 1.51 (1 H, dddd, *J* 14.2, 9.2, 7.1, 2.0, one of CH_2) and 1.36 (1 H, dddd, *J* 14.2, 10.5, 8.9, 5.3, one of CH_2).

δ_C (100 MHz; $CDCl_3$): 138.7 (CH), 127.6 (CH), 127.5 (2 x CH), 125.6 (CH), 114.8 (CH_2), 76.0 (CH), 69.5 (CH_2), 46.4 (C), 32.3 (CH_2), 30.6 (CH_2) and 27.2 (CH_2).

MS-EI: *m/z* (%) = 176 ($M^+ - H_2O$, 10), 158 (50), 143 (67), 128 (85), 117 (91), 105 (63), 91 (100), 77 (87) and 65 (37).

HRMS-EI: *m/z* $[M - H_2O]^+$ calcd for $C_{12}H_{16}O$: 176.1201; found: 176.1202.

tert-Butyl(1-(1-((*tert*-butyldimethylsilyloxy)methyl)cyclohexa-2,5-dienyl)pent-4-enyloxy)dimethylsilane (106)



105 **106**

2,6-Lutidine (6.20 ml, 53.2 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (9.16 ml, 39.9 mmol) were added to a solution of diol **105** (2.58 g, 13.3 mmol) in CH_2Cl_2 (30 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 18 h, before being quenched with water. The crude product was extracted with CH_2Cl_2, the combined extracts being dried over Na_2SO_4. Chromatography on silica gel (hexane) afforded the *title compound* (5.01 g, 89 %) as a colourless oil.

ν_{max} (Neat): 3027, 2954, 2857, 2360, 1640, 1471, 1255, 1086, 835, 775, 720 and 667 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 5.85 – 5.80 (1 H, m, ring alkene CH), 5.79 – 5.71, (2 H, m, one of ring alkene CH and alkene CH) 5.63 (1 H, app. dq, *J* 10.3, 2.0, ring alkene CH), 5.52 (1 H, app. dq, *J* 10.3, 2.0, ring alkene CH), 4.96 (1 H, app. ddd, *J* 17.1, 3.6, 1.6, one of terminal alkene CH_2), 4.90 (1 H, ddt, *J* 10.2, 2.2, 1.2, one of terminal alkene CH_2), 3.83 (1 H, dd, *J* 6.6, 3.8, C*H*OTBS), 3.62 (1 H,

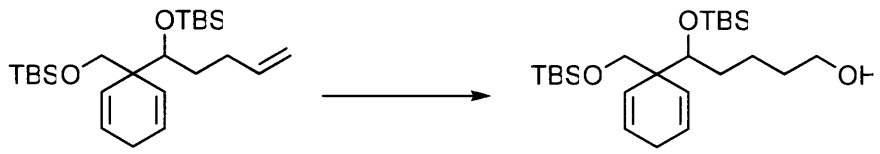
d, *J* 9.3, one of C*H*$_2$OTBS), 3.27 (1 H, d, *J* 9.3, one of C*H*$_2$OTBS), 2.65 – 2.62 (2 H, m, ring CH_2), 2.23 – 2.13 (1 H, m, one of $CH_2C{=}C$), 2.04 – 1.94 (1 H, m, one of $CH_2C{=}C$), 1.61 (1 H, dddd, *J* 14.6, 10.9, 5.6, 3.8, one of CH_2), 1.44 – 1.35 (1 H, m, one of CH_2), 0.91 (9 H, s, *t*-Bu), 0.89 (9 H, s, *t*-Bu), 0.09 (3 H, s, Me), 0.07 (3 H, s, Me) and 0.00 (6 H, s, 2 x Me).

δ_C (100 MHz; $CDCl_3$): 139.4 (CH), 129.9 (CH), 127.2 (CH), 126.1 (CH), 124.7 (CH), 113.9 (CH_2), 73.0 (CH), 67.9 (CH_2), 47.5 (C), 34.0 (CH_2), 31.0 (CH_2), 27.4 (CH_2), 26.1 (3 x CH_3), 26.0 (3 x CH_3), 18.4 (2 x C), -3.9 (CH_3), -4.2 (CH_3), -5.1 (CH_3) and -5.4 (CH_3).

MS-EI: *m/z* (%) = 422 (M^+, 12), 365 (49), 199 (100) and 147 (70).

HRMS-EI: *m/z* $[M]^+$ calcd for $C_{24}H_{46}O_2Si_2$: 422.3036; found: 422.3035.

5-(*tert*-Butyldimethylsilyloxy)-5-(1-((*tert*-butyldimethylsilyloxy)methyl)cyclohexa-2,5-dienyl)pentan-1-ol (107)



106 **107**

0.5 M 9-BBN (4.00 ml, 2.00 ml) was added to a solution of the bis-protected diol **106** (767 mg, 1.82 mmol) in THF (15 ml) and the resulting solution was allowed to stir for 18 h. Aqueous 0.5 M NaOH solution (7 ml, 3.5 mmol) and aqueous hydrogen peroxide solution (30 %, 8 ml) were then added slowly at 0 °C. The solution was allowed to warm to room temperature and stirred for 3 h, before being diluted with ethyl acetate, washed with brine and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and the solvent removed *in vacuo*. Chromatography on silica gel (1:9 Et_2O:petroleum ether) afforded the *title compound* (673 mg, 84 %) as a colourless oil.

ν_{max} (Neat): 3331, 3027, 2928, 2859, 2364, 1472, 1361, 1255, 1085, 939, 838, 775, 719 and 666 cm^{-1}.

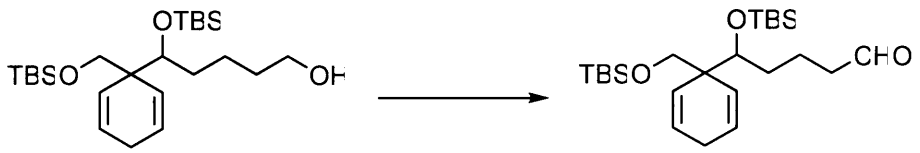
δ_H (400 MHz; $CDCl_3$): 5.82 (1 H, app. dtd, *J* 10.2, 3.2, 1.6, alkene CH), 5.75 (1 H, app. dtd, *J* 10.3, 3.3, 1.6, alkene CH), 5.63 (1 H, app. dq, *J* 10.3, 1.9, alkene CH), 5.51 (1 H, app. dq, *J* 10.3, 1.9, alkene CH), 3.79 (1 H, dd, *J* 5.8, 3.3, C*H*OTBS), 3.63 – 3.58 (3 H, m, CH_2OH and one of CH_2OTBS), 3.26 (1 H, d, *J* 9.3, one of CH_2OTBS), 2.65 – 2.62 (2 H, m, ring CH_2), 1.57 – 1.44 (4 H, broad m, alkyl), 1.38 – 1.27 (2 H, broad m, alkyl), 0.90 (9 H, s, *t*-Bu), 0.88 (9 H, s, *t*-Bu), 0.09 (3 H, s, CH_3), 0.06 (3 H, s, CH_3) and 0.00 (6 H, s, 2 x CH_3).

δ_C (100 MHz; $CDCl_3$): 130.0 (CH), 127.3 (CH), 126.1 (CH), 124.6 (CH), 73.5 (CH), 67.9 (CH_2), 63.0 (CH_2), 47.5 (C), 34.5 (CH_2), 33.3 (CH_2), 27.4 (CH_2), 26.1 (3 x CH_3), 26.0 (3 x CH_3), 22.9 (CH_2), 18.4 (2 x C), -3.9 (CH_3), -4.3 (CH_3), -5.1 (CH_3) and -5.4 (CH_3).

MS-ES: *m/z* (%) = 441 (MH^+, 24), 315 (53), 309 (100), 259 (65), 177 (79) and 159 (28).

HRMS-ES: *m/z* $[M + H]^+$ calcd for $C_{24}H_{49}O_3Si_2$: 441.3220; found: 441.3226.

5-(*tert*-Butyldimethylsilyloxy)-5-(1-((*tert*-butyldimethylsilyloxy)methyl)cyclohexa-2,5-dienyl)pentanal (108)



107 **108**

A solution of the bis-protected triol **107** (866 mg, 1.97 mmol) in DCM (10 ml) was added to a suspension of PDC (1.11 g, 2.95 mmol) in DCM (10 ml). The reaction mixture was allowed to stir for 18 h, before being filtered through silica and the solvent removed *in vacuo*. Chromatography on silica gel (1:99 Et_2O:petroleum ether) afforded the *title compound* (505 mg, 59 %) as a colourless oil.

ν_{max} **(Neat):** 3027, 2955, 2857, 2361, 1729, 1471, 1361, 1255, 1085, 1006, 938, 837, 775, 720 and 666 cm^{-1}.

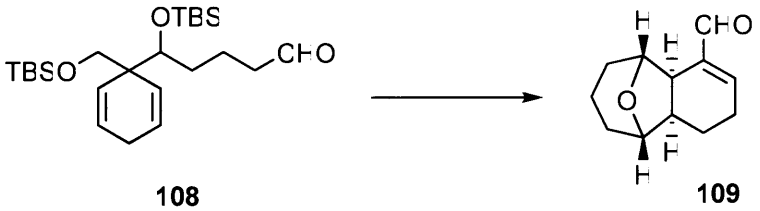
δ_H **(400 MHz; $CDCl_3$):** 9.71 (1 H, t, *J* 2.0, aldehyde CH), 5.83 (1 H, app. dtd, *J* 10.3, 3.1, 1.5, alkene CH), 5.76 (1 H, app. dtd, *J* 10.3, 3.3, 1.6, alkene CH), 5.62 (1 H, app. ddd, *J* 10.2, 4.0, 2.2, alkene CH), 5.53 – 5.49 (1 H, m, alkene CH), 3.84 – 3.80 (1 H, m, C*H*OTBS), 3.62 (1 H, d, *J* 9.3, one of CH_2OTBS), 3.25 (1 H, d, *J* 9.3, one of CH_2OTBS), 2.66 – 2.59 (2 H, broad m, ring CH_2), 2.33 (2 H, app. tt, *J* 7.4, 2.0, CH_2 next to aldehyde), 1.84 – 1.66 (1 H, broad m, alkyl), 1.64 – 1.48 (2 H, broad m, alkyl), 1.41 – 1.30 (1 H, broad m, alkyl), 0.90 (9 H, s, *t*-Bu), 0.88 (9 H, s, *t*-Bu), 0.10 (3 H, s, CH_3), 0.07 (3 H, s, CH_3) and 0.00 (6 H, s, 2 x CH_3).

δ_C **(100 MHz; $CDCl_3$):** 202.9 (aldehyde CH), 129.7 (CH), 127.1 (CH), 126.2 (CH), 124.8 (CH), 73.1 (CH), 67.8 (CH_2), 47.4 (C), 44.4 (CH_2), 34.4 (CH_2), 27.3 (CH_2), 26.1 (3 x CH_3), 26.0 (3 x CH_3), 19.5 (CH_2), 18.4 (2 x C), -3.9 (CH_3), -4.3 (CH_3), -5.1 (CH_3) and -5.4 (CH_3).

MS-ES: *m/z* (%) = 439 (MH^+, 8), 308 (26), 307 (100) and 175 (9).

HRMS-ES: *m/z* $[M + H]^+$ calcd for $C_{24}H_{47}O_3Si_2$: 439.3064; found: 439.3083.

Compound 109



108 **109**

Trifluoromethanesulfonic acid (0.02 ml, 0.18 mmol) was added dropwise to a solution of aldehyde **108** (78 mg, 0.18 mmol) in CH_2Cl_2 (2 ml) at 0 °C. The resulting brown solution was warmed to room temperature and stirred for 20 min before being quenched with saturated aqueous sodium hydrogen carbonate solution. The crude product was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 before the solvent was removed in

vacuo. Chromatography on silica gel (1:6 EtOAc/ petroleum ether) afforded compound **109** (11 mg, 32%) as a colourless oil.

ν_{max} (Neat): 2933, 2850, 1682, 1643, 1464, 1430, 1177, 1010, 872, 739 and 668 cm^{-1}.

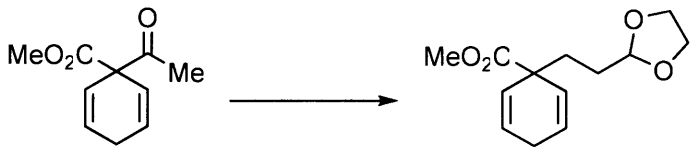
δ_H (400 MHz; $CDCl_3$): 9.37 (1 H, s, aldehyde), 6.97 (1 H, dd, *J* 5.1, 4.1, alkene CH), 3.96 (1 H, app. s, CH–O), 3.89 (1 H, app. br s, CH–O), 2.95 (1 H, d, *J* 8.6, ring junction CH), 2.41 (1 H, app. dt, *J* 8.6, 5.5, ring junction CH), 2.33 – 2.24 (1 H, m, one of CH_2C=C), 2.21 – 2.11 (1 H, m, one of CH_2C=C), 1.72 – 1.53 (7 H, m) and 1.44 – 1.38 (1 H, m)

δ_C (100 MHz; $CDCl_3$): 194.5 (CH), 153.3 (CH), 143.8 (C), 82.5 (CH), 82.3 (CH), 39.4 (CH), 38.9 (CH), 30.7 (CH_2), 30.6 (CH_2), 26.5 (CH_2), 23.0 (CH_2) and 16.5 (CH_2).

MS-EI: *m/z* (%) = 192 (M^+, 76), 145 (44) and 91 (100).

HRMS-EI: *m/z* $[M]^+$ calcd for $C_{12}H_{16}O_2$: 192.1150; found: 192.1141.

Methyl 1-(2-(1,3-dioxolan-2-yl)ethyl)cyclohexa-2,5-dienecarboxylate (116)



111 **116**

n-Butyllithium (9.20 ml of a 1.6 M solution in hexanes, 14.7 mmol) was added to a solution of diisopropylamine (2.06 ml, 14.7 mmol) in THF (30 ml) at 0 °C. After stirring for 30 minutes, the solution was cooled to -78 °C and the β-keto-ester **111** (2.41 g, 13.4 mmol) was added. The resulting solution was stirred at -78 °C for a further 40 minutes before 2-(2-bromoethyl)-1,3-dioxolane (**113**) (1.89 ml, 16.1 mmol) was added. The solution was warmed to room temperature and stirred for 2.5 h before being quenched with water. The reaction mixture was extracted with Et_2O, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica

gel (Et_2O: hexane 1:9) afforded the *title compound* (1.90 g, 60 %) as a colourless oil.

δ_H (400 MHz; $CDCl_3$): 5.93 – 5.88 (2 H, m, alkene CH), 5.73 – 5.71 (1 H, m, alkene CH), 5.70 – 5.69 (1 H, m, alkene CH), 4.84 (1 H, t, *J* 4.6, OCHO), 3.96 – 3.93 (2 H, m, OC*H*HC*H*HO), 3.85 – 3.81 (2 H, m, OCH*H*CH*H*O), 3.68 (3 H, s, OCH_3), 2.65 – 2.61 (2 H, m, ring CH_2), 1.82 – 1.78 (2 H, m, CH_2) and 1.61 – 1.55 (2 H, m, CH_2).
δ_C (100 MHz; $CDCl_3$): 175.1 (C), 126.7 (2 x CH), 126.2 (2 x CH), 104.3 (CH), 64.9 (2 x CH_2), 52.1 (CH_3), 47.3 (C), 33.2 (CH_2), 28.8 (CH_2) and 26.1 (CH_2).

4-(1,3-Dioxolan-2-yl)butanenitrile (118)

113 **118**

n-Butyllithium (22.1 ml of a 2.5 M solution in hexanes, 55.2 mmol) was added to a solution of diisopropylamine (7.74 ml, 55.2 mmol) in THF (50 ml) at 0°C. The resulting solution was stirred for 30 minutes before being cooled to -78°C. Acetonitrile (5.77 ml, 110 mmol) was added and the mixture allowed to stir at -78°C for 1 hour before 2-(2-bromoethyl)-1,3-dioxolane (**113**) (5.03 g, 27.8 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 18 hours. The reaction was quenched with water and the aqueous layer extracted with ether. The combined extracts were dried over Na_2SO_4 before the solvent was removed *in vacuo.* Chromatography on silica gel (EtOAc: hexane 1:3) afforded the *title compound* (2.84 g, 72 %) as a colourless oil.

ν_{max} (Neat): 2952, 2885, 2246, 1475, 1457, 1412, 1364, 1219, 1182, 1142, 1048, 942, 839, 814 and 710 cm^{-1}.

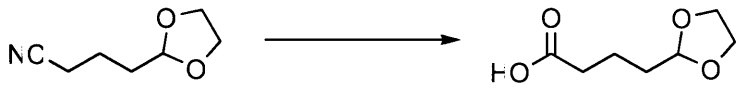
δ_H (400 MHz; $CDCl_3$): 4.90 – 4.88 (1 H, m, OCHO), 4.01 – 3.93 (2 H, m, OC*H*HC*H*HO), 3.90 – 3.82 (2 H, m, OCH*H*CH*H*O), 2.44 – 2.41 (2 H, m, CH_2CN) and 1.84 – 1.78 (4 H, m, 2 x CH_2).

δ_C (100 MHz; $CDCl_3$): 119.6 (C), 103.5 (CH), 65.0 (2 x CH_2), 32.3 (CH_2), 19.9 (CH_2) and 17.2 (CH_2).

MS-EI: *m/z* (%) = 140 ($M - H^+$, 56), 110 (15), 96 (23), 74 (100) and 71 (10).

HRMS-EI: *m/z* $[M - H]^+$ calcd for $C_7H_{10}NO_2$: 140.0712; found: 140.0707.

4-(1,3-Dioxolan-2-yl)butanoic acid (119)



118 119

Potassium hydroxide (13.6 g, 242 mmol) was added to a solution of nitrile **118** (2.84 g, 20.1 mmol) in a 2:1 mixture of ethanol and water (60 ml). The resulting solution was heated under reflux for 16 hours before being cooled to room temperature and acidified to ~pH 2 with 2 M HCl. The aqueous layer was extracted with ether and the combined extracts dried over Na_2SO_4. The solvent was removed *in vacuo* affording the *title compound* (2.86 g, 89 %) as a pure colourless oil.

ν_{max} (Neat): 3172, 2962, 2889, 1716, 1412, 1228, 1142, 1029, 943, 827 and 710 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 4.88 (1 H, t, *J* 4.3, OCHO), 4.01 – 3.93 (2 H, m, OC*H*HC*H*HO), 3.90 – 3.81 (2 H, m, OCH*H*CH*H*O), 2.43 (2 H, t, *J* 7.2, $CH_2C{=}O$) and 1.83 – 1.71 (4 H, broad m, 2 x CH_2).

δ_C (100 MHz; $CDCl_3$): 179.4 (C), 104.1 (CH), 64.9 (2 x CH_2), 33.7 (CH_2), 32.9 (CH_2) and 19.0 (CH_2).

MS-AP: *m/z* (%) = 161 (MH^+, 100), 143 (65), 99 (6) and 83 (3).

HRMS-AP: *m/z* $[M + H]^+$ calcd for $C_7H_{13}O_4$: 161.0814; found: 161.0817.

tert-Butyldimethylsilyl 4-(1,3-dioxolan-2-yl)butanoate (120)

119 120

tert-Butyldimethylsilyl chloride (1.33 g, 8.8 mmol), imidazole (1.20 g, 17.6 mmol) and 4-DMAP (cat.) were added to a solution of acid **119** (1.28 g, 8 mmol) in CH_2Cl_2 (10 ml). The resulting solution was allowed to stir for 30 minutes at room temperature before being quenched with water. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4 before the solvent was removed *in vacuo*. Dry flash chromatography (EtOAc: petroleum ether 1:1) afforded the *title compound* (1.93 g, 88 %) as a colourless oil.

ν_{max} **(Neat):** 2931, 2859, 1724, 1473, 1412, 1364, 1336, 1253, 1174, 1142, 1050, 940, 876, 781, 742 and 669 cm^{-1}.

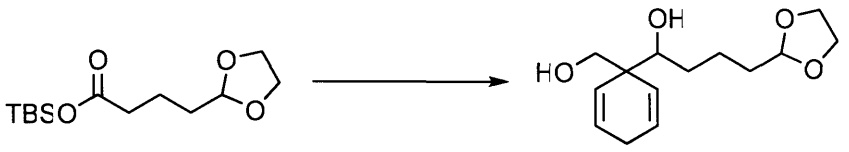
δ_H **(400 MHz; $CDCl_3$):** 4.87 (1 H, t, *J* 4.4, OCHO), 4.00 – 3.91 (2 H, m, OC*H*HC*H*HO), 3.89 – 3.80 (2 H, m, OCH*H*CH*H*O), 2.37 (2 H, t, *J* 7.2, $CH_2C{=}O$), 1.78 – 1.66 (4 H, broad m, 2 x CH_2), 0.92 (9 H, s, *t*-Bu) and 0.26 (6 H, s, 2 x CH_3).

δ_C **(100 MHz; $CDCl_3$):** 173.8 (C), 104.2 (CH), 64.9 (2 x CH_2), 35.7 (CH_2), 33.1 (CH_2), 25.6 (3 x CH_3), 19.6 (CH_2), 17.6 (C) and -4.8 (2 x CH_3).

MS-AP: *m/z* (%) = 275 (MH^+, 100), 273 (4), 231 (4) and 143 (5).

HRMS-AP: *m/z* $[M + H]^+$ calcd for $C_{13}H_{27}O_4Si$: 275.1679; found: 275.1672.

4-(1,3-Dioxolan-2-yl)-1-(1-(hydroxymethyl)cyclohexa-2,5-dienyl)butan-1-ol (115)



120 115

Oxalyl chloride (0.43 ml, 4.98 mmol) and a few drops of DMF were added to a solution of silyl ester **120** (1.24 g, 4.53 mmol) in CH_2Cl_2 (20 ml) at 0°C. The resulting solution was allowed to stir for 1.5 hours at 0°C and 0.5 hours at room temperature before the solvent was removed *in vacuo*. The acyl chloride **117** was immediately re-dissolved in THF (5 ml) and added to a solution of lithium cyclohexa-2,5-dienylidene(methoxy)methanolate (3.78 mmol) in THF (10 ml) at -78°C. The resulting solution was allowed to stir for 20 minutes at -78°C and 10 minutes at 0°C before being quenched with water. The aqueous layer was extracted with ether, the combined extracts being dried over Na_2SO_4 before the solvent was removed *in vacuo*.

The crude β-keto-ester **114** was then immediately re-dissolved in THF (10 ml) and added to a suspension of $LiAlH_4$ (143 mg, 3.78 mmol) in THF (20 ml). The reaction mixture was allowed to stir for 30 minutes at room temperature before being quenched slowly with 2 M NaOH. The mixture was diluted with ether, dried over Na_2SO_4 and filtered before the solvent was removed *in vacuo*. Chromatography on silica gel (EtOAc: petroleum ether 1:1) afforded the *title compound* (163 mg, 14 %) as a colourless oil.

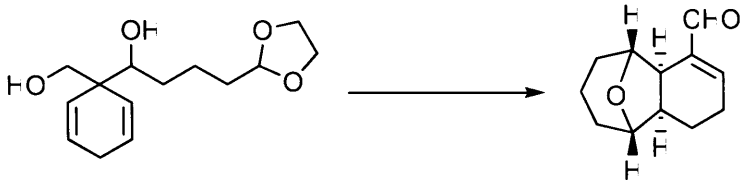
ν_{max} (Neat): 3410, 2938, 2874, 1616, 1456, 1411, 1371, 1315, 1212, 1139, 1027, 980, 946, 913 and 732 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 6.03 (1H, dtd, *J* 10.3, 3.3, 1.6, alkene CH), 5.96 (1H, dtd, *J* 10.2, 3.3, 1.6, alkene CH), 5.74 (1H, app. dq, *J* 10.3, 2.1, alkene CH), 5.40 (1H, app. dq, *J* 10.2, 2.1, alkene CH), 4.85 (1H, t, *J* 4.5, OCHO), 3.98 – 3.92 (2H, m, OC*H*HC*H*HO), 3.89 – 3.83 (2H, m, OCH*H*CH*H*O), 3.67 (1H, d, *J* 10.6, one of CH_2OH), 3.62 – 3.55 (2H, m, one of CH_2OH and C*H*OH), 2.71 – 2.68 (2H, broad m, CH_2 ring), 2.20 – 2.12 (1H, broad s, OH), 2.07 – 1.96 (1H, broad

s, OH), 1.79 – 1.70 (1H, m, one of CH_2), 1.69 – 1.66 (2H, m, CH_2), 1.65 – 1.63 (1H, m, one of CH_2) and 1.55 – 1.41 (2H, broad m, CH_2).

δ_C (100 MHz; $CDCl_3$): 128.0 (CH), 127.3 (CH), 125.9 (2 x CH), 104.5 (CH), 76.6 (CH), 69.6 (CH_2), 64.9 (2 x CH_2), 46.9 (C), 33.4 (CH_2), 32.7 (CH_2), 27.2 (CH_2) and 20.8 (CH_2).

Compound 109



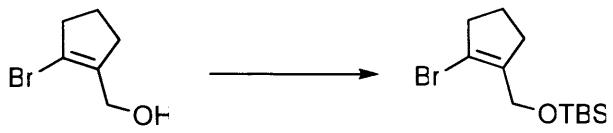
115 **109**

Trifluoromethanesulfonic acid (8 µl, 0.091 mmol) was added dropwise to a solution of diol **115** (23 mg, 0.091 mmol) in CH_2Cl_2 (1 ml) at 0 °C. The resulting brown solution was warmed to room temperature and stirred for 20 min before being quenched with saturated aqueous sodium hydrogen carbonate solution. The crude product was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 before the solvent was removed in vacuo. Chromatography on silica gel (1:6 EtOAc/ petroleum ether) afforded compound **109** (15 mg, 88 %) as a colourless oil.

Spectroscopic data as previously reported (see page 130).

5.4 Experimental Data for Chapter 3

((2-Bromocyclopent-1-enyl)methoxy)(*tert*-butyl)dimethylsilane (142)



141 **142**

tert-Butyldimethylsilyl chloride (2.17 g, 14.4 mmol), imidazole (1.96 g, 28.8 mmol) and 4-DMAP (cat.) were added to a solution of alcohol **141** (2.32 g, 13.1 mmol) in CH_2Cl_2 (30 ml). The resulting suspension was allowed to stir at room temperature for 18 h before being quenched with water. The mixture was extracted with CH_2Cl_2, the combined extracts being dried (Na_2SO_4), before the solvent was removed *in vacuo*. Chromatography on silica gel (petroleum ether) afforded the *title compound* (3.41 g, 90 %) as a colourless oil.

ν_{max} (Neat): 2955, 2929, 2896, 2856, 1657, 1471, 1463, 1370, 1255, 1104, 1071, 1007, 899 and 776 cm^{-1}.

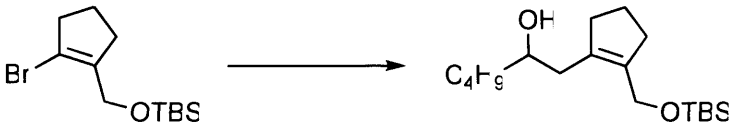
δ_H (400 MHz; $CDCl_3$): 4.27 – 4.26 (2 H, m, CH_2OTBS), 2.67 – 2.61 (2 H, m, CH_2), 2.45 – 2.40 (2 H, m, CH_2), 1.97 – 1.90 (2 H, m, CH_2), 0.90 (9 H, s, *t*-Bu) and 0.08 (6 H, s, 2 x CH_3).

δ_C (100 MHz; $CDCl_3$): 140.3 (C), 115.9 (C), 61.1 (CH_2), 40.2 (CH_2), 32.3 (CH_2), 25.9 (3 x CH_3), 21.5 (CH_2), 18.3 (C) and -5.3 (2 x CH_3).

MS-EI: *m/z* (%) = 289 ($M - H^+$, 32), 233 (100), 169 (100) and 97 (100).

HRMS-EI: *m/z* $[M - H]^+$ calcd for $C_{12}H_{22}OSi^{79}Br$: 289.0623; found: 289.0622.

1-(2-((*tert*-Butyldimethylsilyloxy)methyl)cyclopent-1-enyl)hexan-2-ol (143)



142 **143**

t-Butyllithium (1.30 ml of 1.7 M solution in pentane, 2.21 mmol) was added to a solution of bromide **142** (322 mg, 1.11 mmol) in THF (10 ml) at -78 °C. After stirring for 10 minutes *n*-butyloxirane (92 mg, 0.922 mmol) was added. The resulting solution was stirred for 30 minutes at -78 °C before $BF_3.OEt_2$ (0.11 ml, 0.922 mmol) was added. After stirring for an additional 30 minutes, the reaction was quenched at -78 °C with saturated aqueous NH_4Cl solution. The mixture was extracted with Et_2O, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: petroleum ether 1:9) afforded the *title compound* (168 mg, 58 %) as a colourless oil.

ν_{max} **(Neat):** 2954, 2929, 2857, 1464, 1255, 1074, 1006, 838 and 776 cm^{-1}.

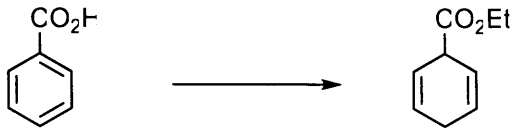
δ_H **(400 MHz; $CDCl_3$):** 4.21 (1 H, d, *J* 12.1, one of CH_2OTBS), 4.15 (1 H, d, *J* 12.1, one of CH_2OTBS), 3.66 – 3.60 (1 H, m, C*H*OH), 2.49 – 2.37 (3 H, broad m, CH_2 and one of CH_2), 2.35 – 2.24 (2 H, m, CH_2), 2.19 – 2.16 (1 H, m, one of CH_2), 1.81 (2 H, app. quintet, *J* 7.5, CH_2), 1.49 – 1.40 (3 H, broad m, alkyl), 1.38 – 1.29 (3 H, m, alkyl), 0.92 – 0.86 (12 H, m, *t*-Bu and CH_3 alkyl) and 0.07 (6 H, s, 2 x CH_3).

δ_C **(125 MHz; $CDCl_3$):** 138.2 (C), 135.6 (C), 69.4 (CH), 59.6 (CH_2), 37.2 (CH_2), 37.0 (CH_2), 36.8 (CH_2), 34.9 (CH_2), 28.0 (CH_2), 25.9 (3 x CH_3), 22.8 (CH_2), 21.7 (CH_2), 18.4 (C), 14.1 (CH_3) and -5.3 (2 x CH_3).

MS-AP: *m/z* (%) = 311 ($M - H^+$, 46), 237 (58), 195 (56), 179 (100), 161 (100), 135 (30), 121 (100) and 75 (100).

HRMS-AP: *m/z* $[M - H]^+$ calcd for $C_{18}H_{35}O_2Si$: 311.2406; found: 311.2409.

Ethyl cyclohexa-2,5-dienecarboxylate (144)[66]



22 **144**

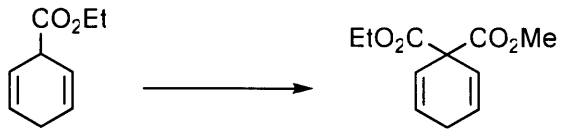
Sodium metal (6.22 g, 270 mmol) was added in portions to a solution of benzoic acid **22** (10.0g, 81.9 mmol) in liquid NH_3-EtOH (4:1, 500ml) at -78 °C. After the blue colour had subsided, solid NH_4Cl (17.5 g) was added and the ammonia allowed to evaporate. The mixture was acidified by addition of 2 M HCl and the aqueous layer extracted with Et_2O. The combined extracts were dried (Na_2SO_4) before the solvent was removed *in vacuo*. The residue was re-dissolved in EtOH (250 ml) and treated with conc. H_2SO_4 (~0.5 ml). The resulting solution was allowed to stir at room temperature for 16 h. The solvent was removed *in vacuo* and the reaction mixture neutralized by addition of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the combined extracts dried over Na_2SO_4. The solvent was removed *in vacuo* affording the *title compound* (9.23 g, 74 %) as a pure colourless oil.

ν_{max} **(Nujol):** 2981, 2873, 2821, 1735, 1366, 1179, 1034, 942, 898, 715 and 668 cm^{-1}.

δ_H **(400 MHz; $CDCl_3$):** 5.90 – 5.86 (2 H, m, alkene CH), 5.84 – 5.79 (2 H, m, alkene CH), 4.16 (2 H, q, *J* 7.1, CH_2O), 3.75 – 3.68 (1 H, broad m, CH), 2.71 – 2.66 (2 H, broad m, CH_2) and 1.27 (3 H, t, *J* 7.1, CH_3).

δ_C **(100 MHz; $CDCl_3$):** 172.6 (C=O), 126.3 (2 x CH), 122.2 (2 x CH), 60.9 (CH_2), 41.7 (CH), 25.8 (CH_2) and 14.2 (CH_3).

1-Ethyl 1-methyl cyclohexa-2,5-diene-1,1-dicarboxylate (145)



144 **145**

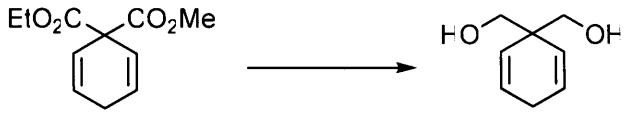
n-Butyllithium (13.2 ml of a 2.5 M solution in hexanes, 32.9 mmol) was added drop-wise to a solution of diisopropylamine (4.61 ml, 32.9 mmol) in THF (50 ml) at 0 °C. The mixture was allowed to stir for 30 minutes at the same temperature before being cooled to -78 °C. The ester **144** (5.01 g, 33.0 mmol) was added drop-wise and the reaction mixture allowed to stir for 30 minutes at -78 °C before methyl chloroformate (2.80 ml, 36.2 mmol) was added. The resulting solution was stirred for a further 15 minutes at -78 °C before the reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with Et_2O, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: petroleum ether 1: 19) afforded the *title compound* (5.84 g, 84 %) as a colourless oil.

ν_{max} **(Neat):** 2984, 2956, 1735, 1436, 1251, 1205, 1064, 1038, 860, 801, 778 and 704 cm^{-1}.

δ_H **(400 MHz; $CDCl_3$):** 6.07 – 6.02 (2 H, m, alkene CH), 5.98 (2 H, app. dt, *J* 10.4, 1.8, alkene CH), 4.20 (2 H, q, *J* 7.1, CH_2O), 3.75 (3 H, s, OCH_3), 2.72 – 2.70 (2 H, m, ring CH_2) and 1.26 (3 H, t, *J* 7.1, CH_3).

δ_C **(100 MHz; $CDCl_3$):** 170.3 (C), 169.6 (C), 127.8 (2 x CH), 122.2 (2 x CH), 61.9 (CH_2), 55.4 (C), 52.9 (CH_3), 25.9 (CH_2) and 14.0 (CH_3).

Cyclohexa-2,5-diene-1,1-diyldimethanol (146)



145 **146**

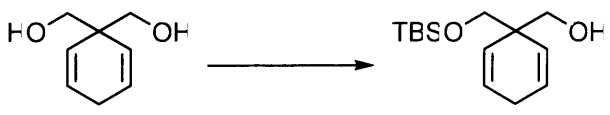
A solution of diester **145** (5.84 g, 27.8 mmol) in THF (20 ml) was added slowly to a suspension of $LiAlH_4$ (2.11 g, 55.6 mmol) in THF (60 ml). The mixture was allowed to stir at room temperature for 2 h before being quenched by slow addition of aqueous 2 M NaOH solution. The solution was dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. Chromatography on silica gel (EtOAc: petroleum ether 2: 1) afforded the *title compound* (2.59 g, 67 %) as a colourless solid, m.p. 82 – 84 °C.

ν_{max} **(Nujol):** 3399, 2923, 2855, 1633, 1252, 1100, 1023, 984, 940, 898 and 707 cm^{-1}.

δ_H **(400 MHz; $CDCl_3$):** 6.09 – 6.04 (2 H, m, alkene CH), 5.60 – 5.56 (2 H, m, alkene CH), 3.52 (4 H, s, 2 x CH_2O), 2.72 (2 H, app. tt, *J* 3.4, 2.1, ring CH_2) and 1.69 (2 H, broad s, 2 x OH).

δ_C **(100 MHz; $CDCl_3$):** 128.5 (2 x CH), 126.9 (2 x CH), 68.0 (2 x CH_2), 44.6 (C) and 26.9 (CH_2).

(1-((*tert*-Butyldimethylsilyloxy)methyl)cyclohexa-2,5-dienyl)methanol (147)



146 **147**

n-Butyllithium (2.40 ml of 2.5 M solution in hexanes, 6.01 mmol) was added to a solution of diol **146** (886 mg, 6.33 mmol) in THF (15 ml) at -78 °C. The resulting solution was allowed to warm to room temperature over 1 h before a

solution of *tert*-butyldimethylsilyl chloride (859 mg, 5.70 mmol) in THF (5 ml) was added. The reaction mixture was stirred for 30 minutes before imidazole (cat.) was added. The resulting mixture was stirred for 16 h at room temperature before the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with Et_2O, the combined extracts being dried (Na_2SO_4) before the solvent was removed in vacuo. Chromatography on silica gel (EtOAc: petroleum ether 1: 1) afforded the *title compound* (1.38 g, 86 %) as a colourless oil.

ν_{max} (Neat): 3419, 3028, 2954, 2929, 2885, 2857, 1635, 1471, 1464, 1255, 1084, 1046, 940, 838, 776 and 708 cm^{-1}.

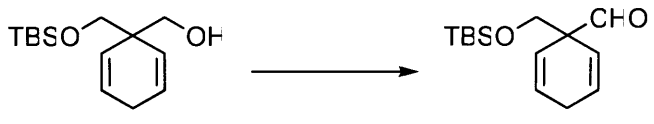
δ_H (500 MHz; $CDCl_3$): 5.94 – 5.91 (2 H, m, alkene CH), 5.62 (2 H, app. dt, *J* 10.5, 2.0, alkene CH), 3.59 (2 H, s, CH_2OH), 3.54 (2 H, s, CH_2OTBS), 2.70 – 2.68 (2 H, m, ring CH_2), 2.17 – 1.87 (1 H, broad s, OH), 0.89 (9 H, s, *t*-Bu) and 0.04 (6 H, s, 2 x CH_3).

δ_C (125 MHz; $CDCl_3$): 127.3 (2 x CH), 127.0 (2 x CH), 69.7 (CH_2), 69.1 (CH_2), 43.6 (C), 27.1 (CH_2), 25.8 (3 x CH_3), 18.2 (C) and -5.6 (2 x CH_3).

MS-AP: *m/z* (%) = 255 (MH^+, 100), 237 (21), 177 (17), 156 (7), 130 (6) and 105 (3).

HRMS-AP: *m/z* $[M + H]^+$ calcd for $C_{14}H_{27}O_2Si$: 255.1780; found: 255.1776.

1-((*tert*-Butyldimethylsilyloxy)methyl)cyclohexa-2,5-dienecarbaldehyde (148)[67]



147 **148**

Oxalyl chloride (0.59 ml, 6.89 mmol) was added drop-wise to a solution of DMSO (1.12 ml, 15.7 mmol) in CH_2Cl_2 (20 ml) at -78 °C. The solution was stirred for 10 minutes before the alcohol **147** (499 mg, 1.96 mmol) was added drop-wise. After stirring for a further 10 minutes at -78 °C, triethylamine (3.57

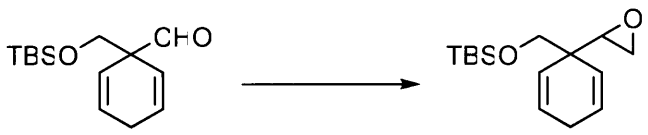
ml, 25.6 mmol) was added and the reaction mixture allowed to warm to room temperature over 2 h. The reaction was quenched by pouring into saturated aqueous $NaHCO_3$ solution. The crude product was extracted with CH_2Cl_2, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: petroleum ether 1: 49) afforded the *title compound* (429 mg, 87 %) as a colourless oil.

ν_{max} **(Neat):** 3032, 2955, 2929, 2886, 2857, 1729, 1651, 1634, 1471, 1420, 1256, 1111, 1083, 839, 778 and 704 cm^{-1}.

δ_H **(400 MHz; $CDCl_3$):** 9.51 (1 H, s, aldehyde CH), 6.04 – 6.00 (2 H, m, alkene CH), 5.71 (2 H, app. dt, *J* 10.5, 2.0, alkene CH), 3.76 (2 H, s, CH_2OTBS), 2.74 – 2.72 (2 H, m, ring CH_2), 0.86 (9 H, s, *t*-Bu) and 0.03 (6 H, s, 2 x CH_3).

δ_C **(100 MHz; $CDCl_3$):** 200.9 (aldehyde CH), 128.3 (2 x CH), 122.7 (2 x CH), 67.3 (CH_2), 55.3 (C), 27.0 (CH_2), 25.7 (3 x CH_3), 18.2 (C) and -5.6 (2 x CH_3).

tert-Butyldimethyl((1-(oxiran-2-yl)cyclohexa-2,5-dienyl)methoxy)silane (149)



148 **149**

n-Butyllithium (1.75 ml of a 2.5 M solution in hexanes, 4.37 mmol) was added to a solution of aldehyde **148** (1.00 g, 3.97 mmol) and dibromomethane (0.42 ml, 5.95 mmol) in THF (30 ml) at -78 °C. The reaction mixture was warmed to room temperature and stirred for 24 h, before being quenched with saturated aqueous NH_4Cl. The mixture was extracted with ether, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo* affording a crude mixture of aldehyde and epoxide (aldehyde: epoxide ~ 2:7, 1.09 g). The aldehyde and epoxide were inseparable by column chromatography, so the crude mixture was re-dissolved in MeOH (15 ml) and $NaBH_4$ (75 mg, 1.98 mmol) added to reduce the excess aldehyde. After stirring for 1 h at room

temperature, the reaction was quenched with water and the mixture extracted with ether, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: petroleum ether 1:49) afforded the *title compound* (400 mg, 38 %) as a colourless oil.

ν_{max} (Neat): 2955, 2929, 2886, 2857, 1471, 1464, 1254, 1106, 1080, 840, 777 and 719 cm^{-1}.

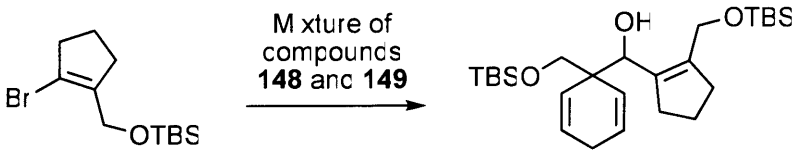
δ_H (400 MHz; $CDCl_3$): 5.91 – 5.83 (2 H, m, alkene CH), 5.67 (1 H, app. dq, *J* 10.1, 2.0, alkene CH), 5.37 (1 H, app. dq, *J* 10.3, 2.0, alkene CH), 3.63 (1 H, d, *J* 9.3, one of CH_2OTBS), 3.48 (1 H, d, *J* 9.3, one of CH_2OTBS), 3.13 (1 H, dd, *J* 4.0, 2.9, epoxide CH), 2.66 – 2.64 (3 H, m, one of epoxide CH_2 and ring CH_2), 2.60 (1 H, dd, *J* 5.1, 2.9, one of epoxide CH_2), 0.90 (9 H, s, *t*-Bu), 0.05 (3 H, s, CH_3) and 0.04 (3 H, s, CH_3).

δ_C (100 MHz; $CDCl_3$): 127.6 (CH), 126.2 (CH), 126.1 (CH), 124.9 (CH), 68.6 (CH_2), 55.2 (CH), 44.3 (CH_2), 41.8 (C), 27.0 (CH_2), 25.8 (3 x CH_3), 18.3 (C) and -5.5 (2 x CH_3).

MS-AP: *m/z* (%) = 267 (MH^+, 100), 249 (28), 176 (8), 156 (13), 132 (22) and 115 (3).

HRMS-AP: *m/z* $[M + H]^+$ calcd for $C_{15}H_{27}O_2Si$: 267.1780; found: 267.1771.

(1-((*tert*-Butyldimethylsilyloxy)methyl)cyclohexa-2,5-dienyl)(2-((tert-butyldimethylsilyloxy)methyl)cyclopent-1-enyl)methanol (150)



142 **150**

t-Butyllithium (1.68 ml of 1.7 M solution in pentane, 2.86 mmol) was added to a solution of bromide **142** (416 mg, 1.43 mmol) in THF (10 ml) at -78 °C. After stirring for 10 minutes, a mixture of aldehyde **148** and epoxide **149** (1:2, 317 mg) in THF (5 ml) was added. The resulting solution was stirred at -78 °C for

20 minutes before $BF_3.OEt_2$ (0.15 ml, 1.19 mmol) was added. After stirring for 1 h at -78 °C the reaction was quenched by addition of saturated aqueous NH_4Cl solution. The reaction mixture was extracted with Et_2O, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: petroleum ether 3:97) afforded the *title compound* (127 mg, 65 %*) as a colourless oil.

* *Yield based on the calculated amount of aldehyde **148** present in the 1:2 mixture of compounds **148** and **149**.*

ν_{max} **(Neat):** 3480, 3029, 2954, 2929, 2886, 2857, 1471, 1463, 1362, 1255, 1086, 1006, 838 and 776 cm^{-1}.

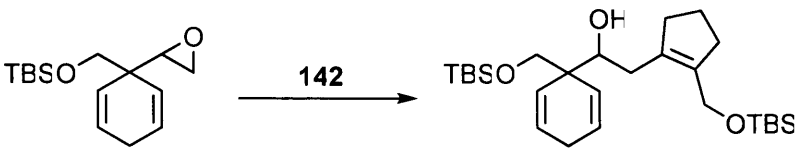
δ_H **(400 MHz; $CDCl_3$):** 5.88 – 5.82 (2 H, m, alkene CH), 5.78 – 5.73 (1 H, m, alkene CH), 5.44 (1 H, app. dt, *J* 10.3, 1.8, alkene CH), 4.68 (1 H, s, C*H*OH), 4.29 (1 H, d, *J* 12.5, one of allylic CH_2OTBS), 4.11 (1 H, d, *J* 12.5, one of allylic CH_2OTBS), 3.62 (1 H, d, *J* 9.4, one of CH_2OTBS), 3.51 (1 H, d, *J* 9.4, one of CH_2OTBS), 2.65 – 2.62 (2 H, broad m, 6-membered ring CH_2), 2.53 – 2.26 (4 H, broad m, 2 x CH_2-allyl), 1.70 (2 H, quintet, *J* 7.3, 5-membered ring CH_2), 1.64 – 1.55 (1 H, broad s, OH), 0.91 (9 H, app. s, *t*-Bu), 0.89 (9 H, app. s, *t*-Bu), 0.06 (9 H, s, 3 x CH_3) and 0.05 (3 H, s, CH_3).

δ_C **(100 MHz; $CDCl_3$):** 139.0 (C), 137.6 (C), 127.4 (2 x CH), 125.9 (CH), 125.5 (CH), 73.5 (CH), 71.2 (CH_2), 59.9 (CH_2), 45.6 (C), 34.4 (CH_2), 33.7 (CH_2), 27.1 (CH_2), 25.9 (3 x CH_3), 22.3 (CH_2), 18.3 (C), 18.2 (C), -5.2 (CH_3), -5.3 (CH_3) and -5.6 (2 x CH_3).

MS-AP: *m/z* (%) = 465 (MH^+, 6), 447 (7), 333 (7), 317 (10), 315 (100), 241 (12), 183 (56) and 156 (2).

HRMS-AP: *m/z* $[M + H]^+$ calcd for $C_{26}H_{49}O_3Si_2$: 465.3220; found: 465.3241.

1-(1-((*tert*-Butyldimethylsilyloxy)methyl)cyclohexa-2,5-dienyl)-2-(2-((tert-butyldimethylsilyloxy)methyl)cyclopent-1-enyl)ethanol (151)



149 **151**

t-Butyllithium (2.06 ml of 1.7 M solution in pentane, 3.51 mmol) was added to a solution of bromide **142** (511 mg, 1.75 mmol) in THF (10 ml) at -78 °C. After stirring for 10 minutes, epoxide **149** (389 mg, 1.46 mmol) was added. The resulting solution was stirred for 20 minutes at -78 °C before $BF_3.OEt_2$ (0.18 ml, 1.46 mmol) was added. After stirring for an additional 2 h, the reaction was quenched at -78 °C with saturated aqueous NH_4Cl solution. The mixture was extracted with Et_2O, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: petroleum ether 1:99) afforded the *title compound* (103 mg, 15 %) as a colourless oil.

ν_{max} **(Neat):** 3466, 2953, 2928, 2886, 2857, 1471, 1463, 1255, 1104, 1056, 837, 776 and 734 cm^{-1}.

δ_H **(400 MHz; $CDCl_3$):** 5.92 (1 H, app. dtd, *J* 10.3, 3.3, 1.6, alkene CH), 5.84 (1 H, app. dtd, *J* 10.3, 3.4, 1.5, alkene CH), 5.79 (1 H, app. dq, *J* 10.3, 1.9, alkene CH), 5.44 (1 H, app. dq, *J* 10.3, 2.0, alkene CH), 4.16 (2 H, s, allylic CH_2OTBS), 3.76 (1 H, dd, *J* 10.5, 2.5, C*H*OH), 3.67 (1 H, d, *J* 9.5, one of CH_2OTBS), 3.57 (1 H, d, *J* 9.5, one of CH_2OTBS), 2.68 – 2.65 (2 H, broad m, 6-membered ring CH_2), 2.50 – 2.37 (3 H, broad m, CH_2 and one of CH_2), 2.32 – 2.21 (2 H, m, one of CH_2 and one of CH_2), 2.13 – 2.09 (1 H, m, one of CH_2), 1.79 (2 H, quintet, *J* 6.9, 5-membered ring CH_2), 0.89 (9 H, s, *t*-Bu), 0.89 (9 H, s, *t*-Bu), 0.06 (3 H, s, CH_3), 0.06 (3 H, s, CH_3), 0.04 (3 H, s, CH_3) and 0.04 (3 H, s, CH_3).

δ_C **(100 MHz; $CDCl_3$):** 137.1 (C), 136.5 (C), 128.1 (CH), 126.4 (CH), 126.2 (2 x CH), 73.7 (CH), 70.2 (CH_2), 59.7 (CH_2), 45.7 (C), 36.7 (CH_2), 34.7 (CH_2), 32.5 (CH_2), 27.3 (CH_2), 26.0 (3 x CH_3), 25.9 (3 x CH_3), 21.6 (CH_2), 18.5 (C), 18.3 (C), -5.2 (CH_3), -5.3 (CH_3) and -5.5 (2 x CH_3).

MS-ES: *m/z* (%) = 479 (MH^+, 34), 347 (100), 329 (4), 215 (5) and 185 (6).
HRMS-ES: *m/z* $[M + H]^+$ calcd for $C_{27}H_{51}O_3Si_2$: 479.3377; found: 479.3387.

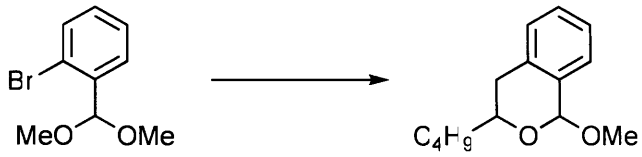
1-(1-(Hydroxymethyl)cyclohexa-2,5-dienyl)-2-(2-(hydroxymethyl)cyclopent-1-enyl)ethanol (152)

151 **152**

Tetrabutylammonium fluoride (0.55 ml of a 1 M solution in THF, 0.55 mmol) was added to a solution of compound **151** (88 mg, 0.18 mmol) in THF (5 ml) and the resulting solution was allowed to stir for 18 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and the crude product extracted with Et_2O. The combined extracts were dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (EtOAc: petroleum ether 3:1) afforded the *title compound* (36 mg, 78 %) as a colourless oil.

δ_H (400 MHz; MeOD): 5.92 (1 H, dtd, *J* 10.3, 3.3, 1.6, alkene CH), 5.84 (1 H, dtd, *J* 10.2, 3.3, 1.6, alkene CH), 5.63 (1 H, app. dq, *J* 10.3, 1.9, alkene CH), 5.45 (1 H, app. dq, *J* 10.2, 1.9, alkene CH), 4.07 – 3.95 (2 H, m, allyl C*H*$_2$OH), 3.61 (1 H, dd, *J* 10.5, 2.3, C*H*OH), 3.53 (1 H, d, *J* 10.6, one of C*H*$_2$OH), 3.46 (1 H, d, *J* 10.6, one of C*H*$_2$OH), 2.63 – 2.60 (2 H, broad m, 6-membered ring CH_2), 2.45 – 2.31 (3 H, broad m, CH_2 and one of CH_2), 2.28 – 2.19 (2 H, m, one of CH_2 and one of CH_2), 2.10 (1 H, app. d, *J* 14.4, one of CH_2) and 1.79 – 1.72 (2 H, m, CH_2).

3-Butyl-1-methoxyisochroman (158)



155 **158**

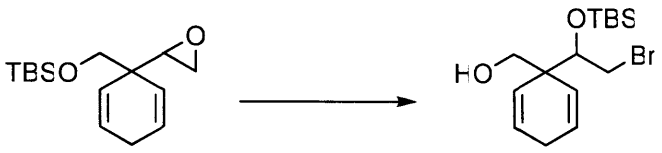
t-Butyllithium (2.35 ml of 1.7 M solution in pentane, 3.99 mmol) was added to a solution of bromide **155** (461 mg, 2.00 mmol) in THF (10 ml) at -78 °C. After stirring for 10 minutes *n*-butyloxirane (100 mg, 0.998 mmol) was added. The resulting solution was stirred for 15 minutes at -78 °C before BF_3.THF (0.11 ml, 0.998 mmol) was added. After stirring for an additional 30 minutes, the reaction was quenched at -78 °C with saturated aqueous NH_4Cl solution. The mixture was extracted with Et_2O, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: hexane 1:49) afforded the *title compound* (85 mg, 39 %) as a colourless oil.

ν_{max} **(Neat):** 2931, 2825, 1456, 1365, 1207, 1186, 1092, 1052, 1030, 747 and 668 cm^{-1}.

δ_H **(400 MHz; $CDCl_3$):** 7.18 – 7.12 (3 H, m, aromatic CH), 7.04 – 7.02 (1 H, m, aromatic CH), 5.43 (1 H, s, OCHO), 4.03 – 3.97 (1 H, m, CHO), 3.48 (3 H, s, OCH_3), 2.61 – 2.59 (2 H, m, benzylic CH_2), 1.67 – 1.46 (3 H, broad m, alkyl), 1.40 – 1.28 (3 H, broad m, alkyl) and 0.88 (3 H, t, *J* 7.2, CH_3).

δ_C **(100 MHz; $CDCl_3$):** 134.4 (C), 134.0 (C), 128.4 (CH), 128.1 (CH), 127.3 (CH), 126.3 (CH), 98.5 (CH), 66.9 (CH), 55.2 (CH_3), 35.3 (CH_2), 34.1 (CH_2), 27.8 (CH_2), 22.7 (CH_2) and 14.1 (CH_3).

(1-(2-Bromo-1-(tert-butyldimethylsilyloxy)ethyl)cyclohexa-2,5-dienyl)methanol (163)

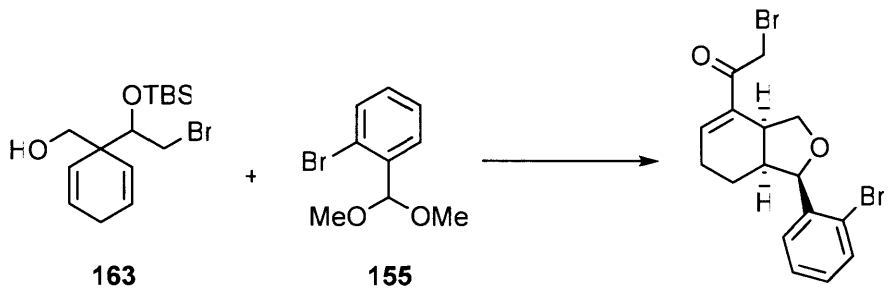


149 **163**

t-Butyllithium (1.00 ml of 1.7 M solution in pentane, 1.70 mmol) was added to a solution of bromide **155** (196 mg, 0.850 mmol) in THF (10 ml) at -78 °C. After stirring for 10 minutes epoxide **149** (113 mg, 0.425 mmol) was added. The resulting solution was stirred for 15 minutes at -78 °C before BF_3.THF (0.05 ml, 0.425 mmol) was added. After stirring for an additional 1 h, the reaction was quenched at -78 °C with saturated aqueous NH_4Cl solution. The mixture was extracted with Et_2O, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: hexane 1:99) afforded the *title compound* (94 mg, 64 %) as a colourless oil.

ν_{max} (Neat): 3478, 3029, 2928, 2857, 1472, 1253, 1106, 837, 777 and 655 cm^{-1}.
δ_H (400 MHz; $CDCl_3$): 5.95 – 5.86 (2 H, m, alkene CH), 5.81 (1 H, ddd, *J* 10.4, 4.0, 2.0, alkene CH), 5.43 (1 H, ddd, *J* 10.1, 4.1, 2.0, alkene CH), 4.01 (1 H, app. broad d, *J* 10.5, CHOTBS), 3.72 (1 H, s, OH), 3.67 (1 H, d, *J* 9.5, one of CH_2OH), 3.58 (1 H, d, *J* 9.5, one of CH_2OH), 3.51 (1 H, dd, *J* 10.5, 1.8, one of CH_2Br), 3.26 (1 H, app. t, *J* 10.5, one of CH_2Br), 2.68 – 2.64 (2 H, m, ring CH_2), 0.89 (9 H, s, *t*-Bu) and 0.05 (6 H, s, 2 x CH_3).
δ_C (100 MHz; $CDCl_3$): 127.4 (CH), 127.1 (CH), 126.6 (CH), 124.4 (CH), 76.5 (CH), 70.8 (CH_2), 45.2 (C), 37.9 (CH_2), 27.2 (CH_2), 25.8 (3 x CH_3), 18.2 (C) and -5.6 (2 x CH_3).
MS-AP: *m/z* (%) = 349 (MH^+, 100), 347 (MH^+, 94), 331 (27), 329 (24), 217 (53), 215 (50), 199 (34), 197 (35), 158 (6), 156 (13), 132 (18) and 117 (12).
HRMS-AP: *m/z* $[M + H]^+$ calcd for $C_{15}H_{28}O_2Si^{79}Br$: 347.1042; found: 347.1030.

2-Bromo-1-((1RS,3aSR,7aSR)-1-(2-bromophenyl)-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-yl)ethanone (159)



163 **155** **159**

Trifluoromethanesulfonic acid (0.01 ml, 0.12 mmol) was added to a mixture of compounds **163** and **155** (approx. 1:1, 51 mg) in CH_2Cl_2 (2 ml) at 0 °C. The resulting solution was warmed to room temperature and stirred for 15 minutes before a further portion of trifluoromethanesulfonic acid (0.01 ml, 0.12 mmol) was added. After stirring for an additional 10 minutes, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution. The crude mixture was extracted with CH_2Cl_2, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: hexane 1:9) afforded the *title compound* (22 mg, 29 %*) as a colourless oil.

** Yield calculated over 2 steps.*

δ_H (400 MHz; $CDCl_3$): 7.56 – 7.51 (2 H, m, aromatic CH), 7.30 (1 H, app. td, *J* 7.5, 1.0, aromatic CH), 7.13 (1 H, app. td, *J* 7.6, 1.6, aromatic CH), 7.07 (1 H, app. dd, *J* 5.3, 1.7, alkene CH), 5.31 (1 H, d, *J* 4.8, CHO), 4.50 (1 H, app. dd, *J* 9.1, 8.2, one of CH_2O), 4.19 (2 H, s, CH_2Br), 3.63 (1 H, app. dd, *J* 9.1, 8.3, one of CH_2O), 3.49 – 3.41 (1 H, m, ring junction CH), 2.80 (1 H, ddt, *J* 13.2, 6.6, 4.8, ring junction CH), 2.32 (1 H, dtd, *J* 19.7, 5.3, 2.0, one of $CH_2C{=}C$), 2.24 – 2.14 (1 H, broad m, one of $CH_2C{=}C$), 1.08 (1 H, app, qd, *J* 13.2, 5.3, one of CH_2) and 0.90 – 0.82 (1 H, m, one of CH_2).

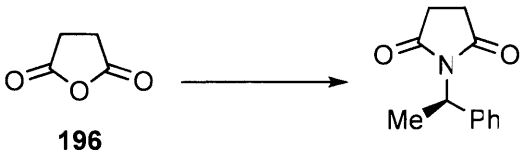
δ_C (100 MHz; $CDCl_3$): 192.1 (C=O), 143.6 (alkene CH), 138.7 (C), 137.3 (C), 132.3 (CH), 128.6 (CH), 128.2 (CH), 127.0 (CH), 121.3 (C), 82.8 (CH), 72.0 (CH_2), 38.4 (CH), 38.3 (CH), 29.7 (CH_2), 25.8 (CH_2) and 19.2 (CH_2).

MS-AP: *m/z* (%) = 403 (48), 401 (100), 399 ($M+H^+$, 52), 385 (33), 383 (65), 381 (34) and 219 (34).

HRMS-AP: *m/z* $[M + 1]^+$ calcd for $C_{16}H_{17}O_2{}^{79}Br_2$: 398.9595; found: 398.9585.

5.5 Experimental Data for Chapter 4

(R)-1-(1-Phenylethyl)pyrrolidine-2,5-dione (215)



196 **215**

(R)-(+)-α-Methyl benzylamine **214** (13.8 ml, 107 mmol) was added to a suspension of succinic anhydride **196** (10.7 g, 107 mmol) in toluene (250 ml) and the mixture was heated under ruflux for 18 h. The solvent was removed *in vacuo* and the residue re-dissolved in acetic anhydride (100 ml). The resulting solution was heated under reflux for 2 h, before being poured onto crushed ice with stirring. The mixture was extracted with CH_2Cl_2, the combined extracts being washed thoroughly with saturated aqueous $NaHCO_3$ solution and dried over Na_2SO_4. The solvent was removed *in vacuo* affording the *title compound* (21.7 g, 100 %) as a pure colourless oil.

ν_{max} (Neat): 2979, 2941, 1679, 1393, 1219, 1188, 1101, 1066, 1023, 953, 821 and 786 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 7.39 (2 H, d, *J* 8.0, aromatic CH), 7.28 – 7.19 (3 H, m, aromatic CH), 5.36 (1 H, q, *J* 7.3, CH-Me), 2.57 (4 H, s, 2 x CH_2) and 1.76 (3 H, d, *J* 7.3, Me).

δ_C (100 MHz; $CDCl_3$): 177.1 (2 x C=O), 139.7 (C), 128.5 (2 x CH), 127.9 (CH), 127.7 (2 x CH), 50.4 (CH), 28.2 (2 x CH_2) and 16.6 (CH_3).

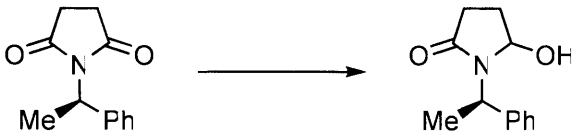
$[\alpha]_D$: +63 (c = 1, MeOH).

$[\alpha]_D$: +91 (c = 1, CH_2Cl_2), Lit.[ref] **$[\alpha]_D$:** +91.9 (c = 4, CH_2Cl_2)

MS-AP: *m/z* (%) = 204 (MH^+, 100), 141 (33) and 105 (6).

HRMS-AP: *m/z* $[M + H]^+$ calcd for $C_{12}H_{14}NO_2$: 204.1025; found: 204.1018.

5-Hydroxy-1-((R)-1-phenylethyl)pyrrolidin-2-one (216)



215 **216**

$LiEt_3BH$ (82.8 ml of 1.0 M solution in THF, 82.8 mmol) was added drop-wise to a solution of lactam **215** (12.0 g, 59.1 mmol) in THF (150 ml) at -78 °C. The mixture was allowed to stir for 40 mins before the THF was removed *in vacuo*. The residue was cooled to 0 °C and the reaction quenched by drop-wise addition of saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2, the combined extracts being treated with 30 % H_2O_2 solution (10 ml), washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* affording the *title compound* (9.7 g, 80 %) as a pure colourless solid (approx. 2:1 mixture of diastereoisomers), m.p. 82 – 84 °C.

ν_{max} (Nujol): 3226, 2922, 2853, 1644, 1426, 1329, 1284, 1248, 1211, 1178, 1059, 1025, 989, 914, 790, 700 and 671 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 7.37 – 7.26 (5 H, m, aromatic CH), 5.41 – 5.34 (1 H, m, C*H*-Me), 4.93 (1 H, t, *J* 6.0, C*H*OH), 2.69 – 2.58 (1 H, m, one of $CH_2C{=}O$), 2.34 – 2.27 (1 H, m, one of $CH_2C{=}O$), 2.24 – 2.07 (1 H, m, one of pyrrolidine CH_2), 1.90 – 1.79 (1 H, m, one of pyrrolidine CH_2) and 1.67 (3 H, d, *J* 7.2, Me).

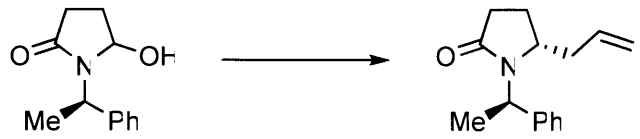
δ_C (100 MHz; $CDCl_3$): 174.8 (C), 140.0 (C), 128.9 (2 x CH), 127.9 (CH), 127.8 (2 x CH), 82.4 (CH), 50.4 (CH), 29.2 (CH_2), 29.1 (CH_2) and 19.0 (CH_3).

$[\alpha]_D$: +60 (c = 0.5, CH_2Cl_2).

MS-ES: *m/z* (%) = 247 (MH^+ + MeCN, 100), 206 (MH^+, 85), 205 (31), 188 (14), 164 (13) and 155 (2).

HRMS-ES: *m/z* $[M + H]^+$ calcd for $C_{12}H_{16}NO_2$: 206.1181; found: 206.1177.

(R)-5-Allyl-1-((R)-1-phenylethyl)pyrrolidin-2-one (217)



216 **217**

Boron trifluoride diethyl etherate (5.79 ml, 47.0 mmol) was added drop-wise to a solution of hydroxyl lactam **216** (6.43 g, 31.4 mmol) in CH_2Cl_2 at -78 °C. Allyl trimethylsilane (15.0 ml, 94.1 mmol) was then added drop-wise and the reaction mixture allowed to warm to room temperature over 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and the aqueous layer extracted with CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4 before the solvent was removed *in vacuo* affording the *title compound* (6.88 g, 96 %) as a pure orange oil (4.4:1 mixture of diastereoisomers).

ν_{max} **(Neat):** 3063, 2976, 2936, 1681, 1368, 1286, 1215, 1183, 1055, 1028, 998, 917 and 788 cm^{-1}.

δ_H **(400 MHz; $CDCl_3$):** 7.39 (2 H, d, *J* 7.5, aromatic CH), 7.33 – 7.29 (2 H, m, aromatic CH), 7.26 – 7.24 (1 H, m, aromatic CH), 5.51 – 5.39 (2 H, m, alkene CH and C*H*-Ph), 4.98 – 4.95 (1 H, m, one of alkene CH_2), 4.88 (1 H, app. dq, *J* 17.1, 1.4, one of alkene CH_2), 3.76 (1 H, app. ddd, *J* 11.9, 8.4, 3.5, CH-allyl), 2.53 – 2.44 (1 H, m, one of $CH_2C{=}O$), 2.32 (1 H, app. ddd, *J* 17.0, 9.9, 4.7, one of $CH_2C{=}O$), 2.06 (1 H, ddt, *J* 12.9, 9.8, 8.2, one of pyrrolidine CH_2), 1.92 – 1.86 (1 H, m, one of $CH_2C{=}C$), 1.78 – 1.67 (2 H, m, one of pyrrolidine CH_2 and one of $CH_2C{=}C$) and 1.65 (3 H, d, *J* 7.3, Me).

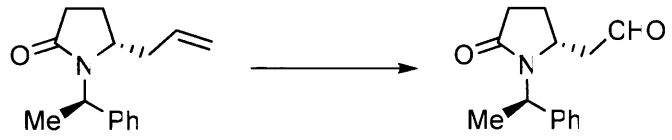
δ_C **(100 MHz; $CDCl_3$):** 175.6 (C=O), 142.0 (C), 133.5 (CH), 128.6 (2 x CH), 127.6 (CH), 127.4 (2 x CH), 118.4 (CH_2), 56.5 (CH), 49.7 (CH), 39.0 (CH_2), 30.5 (CH_2), 24.2 (CH_2) and 16.5 (CH_3).

$[\alpha]_D$ **:** +147 (c = 1, MeOH).

MS-ES: *m/z* (%) = 230 (MH^+, 100).

HRMS-ES: *m/z* $[M + H]^+$ calcd for $C_{15}H_{20}NO$: 230.1545; found: 230.1547.

2-((R)-5-Oxo-1-((R)-1-phenylethyl)pyrrolidin-2-yl)acetaldehyde (218)



217 **218**

Potassium osmate dihydrate (cat.), sodium periodate (24.1 g, 113 mmol) and 2,6-lutidine (6.56 ml, 56.3 mmol) were added to a solution of allyl lactam **217** (6.45 g, 28.2 mmol) in dioxane-H_2O (3:1, 520 ml) and the resulting suspension was allowed to stir at room temperature for 18 h. The reaction was quenched with water and the mixture extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 before the solvent was removed *in vacuo*. Flash chromatography on silica gel (EtOAc: Me_2CO 1:2) afforded the *title compound* (4.87 g, 75 %) as a colourless oil (6.4:1 mixture of diastereoisomers).

ν_{max} (Neat): 3061, 2975, 1720, 1670, 1417, 1373, 1286, 1215, 1182, 1026, 788 and 758 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 9.33 (1 H, s, aldehyde), 7.34 – 7.24 (5 H, m, aromatic CH), 5.52 (1 H, q, *J* 7.2, C*H*-Me), 4.20 (1 H, app. ddd, *J* 11.8, 7.9, 3.5, CHN), 2.54 – 2.45 (1 H, m, one of pyrrolidine CH_2C=O), 2.36 (1 H, ddd, *J* 16.7, 9.7, 4.2, one of pyrrollidine CH_2C=O), 2.26 (1 H, ddd, *J* 17.9, 12.7, 8.5, one of pyrrolidine CH_2), 2.15 (1 H, app. dd, *J* 18.0, 8.9, one of CH_2CHO), 2.06 (1 H, dd, *J* 18.1, 3.5, one of CH_2CHO), 1.65 – 1.61 (1 H, m, one of pyrrolidine CH_2) and 1.58 (3 H, d, *J* 7.3, Me).

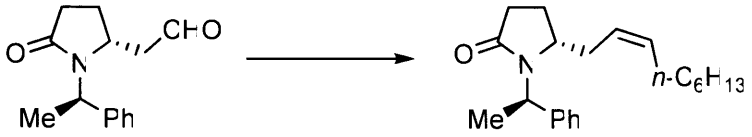
δ_C (100 MHz; $CDCl_3$): 199.8 (aldehyde CH), 175.2 (lactam C=O), 141.3 (C), 128.8 (2 x CH), 127.9 (CH), 127.4 (2 x CH), 50.8 (CH), 48.9 (CH), 48.6 (CH_2), 30.0 (CH_2), 25.9 (CH_2) and 16.0 (CH_3).

$[\alpha]_D$: +124 (c = 1, MeOH).

MS-ES: *m/z* (%) = 232 (MH^+, 100).

HRMS-ES: *m/z* $[M + H]^+$ calcd for $C_{14}H_{18}NO_2$: 232.1338; found: 232.1330.

(R)-5-((Z)-Non-2-enyl)-1-((R)-1-phenylethyl)pyrrolidin-2-one (219)



218 **219**

n-Butyllithium (15.3 ml of a 2.5 M solution in hexanes, 38.3 mmol) was added drop-wise to a solution of heptyl phosphonium iodide (18.7 g, 38.3 mmol) in THF (150 ml) at 0 °C. The solution was allowed to stir at 0 °C for 2 h before a solution of aldehyde **218** (4.42 g, 19.1 mmol) in THF (15 ml) was added at -78 °C. The resulting solution was allowed to warm to room temperature and stirred for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and the aqueous layer extracted with CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4 before the solvent was removed *in vacuo.* Chromatography on silica gel (EtOAc: hexane 1:2) afforded the *title compound* (3.45 g, 58 %) as a yellow oil (6.6:1 mixture of diastereoisomers).

ν_{max} (Neat): 2928, 2855, 1686, 1416, 1365, 1265, 1216, 1182, 1118 and 787 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 7.39 (2 H, d, *J* 7.4, aromatic CH), 7.31 (2 H, app. t, *J* 7.4, aromatic CH), 7.25 (1 H, d, *J* 7.0, aromatic CH), 5.49 – 5.36 (2 H, m, C*H*Me and alkene CH), 5.09 – 5.02 (1 H, m, alkene CH), 3.76 – 3.65 (1 H, m, CHN), 2.51 (1 H, app. dt, *J* 17.1, 8.8, one of CH_2C=O), 2.35 (1 H, ddd, *J* 17.1, 9.8, 4.9, one of CH_2C=O), 2.10 – 2.00 (2 H, m, CH_2C=C), 1.94 – 1.88 (1 H, m, one of pyrrolidine CH_2), 1.81 (2 H, app. q, *J* 6.5, CH_2C=C), 1.73 – 1.67 (1 H, m, one of pyrrolidine CH_2), 1.65 (3 H, d, *J* 7.2, Me), 1.30 – 1.22 (8 H, broad m, alkyl) and 0.88 (3 H, t, *J* 7.0, CH_3 alkyl).

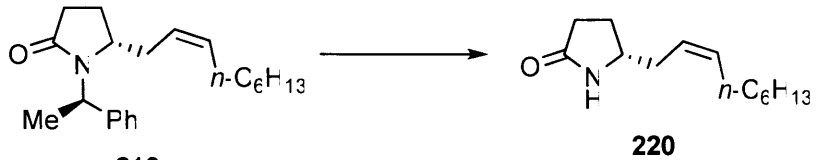
δ_C (100 MHz; $CDCl_3$): 175.6 (C=O), 142.1 (C), 133.4 (CH), 128.5 (2 x CH), 127.5 (CH), 127.3 (2 x CH), 124.0 (CH), 57.1 (CH), 49.7 (CH), 32.2 (CH_2), 31.9 (CH_2), 30.5 (CH_2), 29.6 (CH_2), 29.1 (CH_2), 27.6 (CH_2), 24.4 (CH_2), 22.8 (CH_2), 16.5 (CH_3) and 14.3 (CH_3).

$[\alpha]_D$: +110 (c = 1, MeOH).

MS-ES: *m/z* (%) = 314 (MH^+, 100).

HRMS-ES: *m/z* $[M + H]^+$ calcd for $C_{21}H_{32}NO$: 314.2484; found: 314.2499.

(R,Z)-5-(Non-2-enyl)pyrrolidin-2-one (220)



219 **220**

Sodium metal (1.19 g, 51.6 mmol) was added portion-wise to a solution of alkenyl lactam **219** (3.23 g, 10.3 mmol) in liquid NH_3-THF-EtOH (8:1:1, 240 ml) at -78 °C until the blue colour persisted for longer than 3 mins. After the solution had turned colourless, solid NH_4Cl was added and the ammonia allowed to evaporate. The reaction mixture was then washed with water and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 before the solvent was removed *in vacuo* affording the *title compound* (1.93 g, 89 %) as a pure yellow oil.

ν_{max} (Neat): 3225, 2920, 2860, 1694, 1462, 1379, 1346, 1292, 1262, 1204, 1083 and 734 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 6.00 – 5.73 (1 H, broad s, NH), 5.59 – 5.52 (1 H, m, alkene CH), 5.34 – 5.27 (1 H, m, alkene CH), 3.71 – 3.64 (1 H, m, C*H*NH), 2.38 – 2.32 (2 H, m, CH_2C=O), 2.30 – 2.17 (3 H, m, CH_2C=C and one of pyrrolidine CH_2), 2.03 (2 H, app. q, *J* 7.1, CH_2C=C), 1.80 – 1.71 (1 H, m, one of pyrrolidine CH_2), 1.35 – 1.22 (8 H, broad m, alkyl) and 0.88 (3 H, t, *J* 6.8, CH_3 alkyl).

δ_C (100 MHz; $CDCl_3$): 178.2 (C=O), 134.1 (CH), 124.1 (CH), 54.6 (CH), 34.5 (CH_2), 31.9 (CH_2), 30.4 (CH_2), 29.7 (CH_2), 29.2 (CH_2), 27.7 (CH_2), 27.0 (CH_2), 22.8 (CH_2) and 14.3 (CH_3).

$[\alpha]_D$: +15 (c = 1, MeOH).

MS-AP: *m/z* (%) = 251 (MH^+ + MeCN, 100), 210 (MH^+, 43), 124 (4) and 83 (3).

HRMS-AP: *m/z* $[M + H]^+$ calcd for $C_{13}H_{24}NO$: 210.1858; found: 210.1848.

(R,Z)-5-(Non-2-enyl)pyrrolidine-2-thione (221)

220 **221**

Lawesson's reagent (1.91 g, 4.71 mmol) was added to a solution of lactam **220** (1.79 g, 8.56 mmol) in THF (80 ml). The resulting solution was allowed to stir at room temperature for 2 h before the solvent was removed *in vacuo*. Chromatography on silica gel (EtOAc: petroleum ether 1:9) afforded the *title compound* (1.62 g, 84 %) as a yellow oil.

ν_{max} (Neat): 3162, 2925, 2854, 1530, 1456, 1377, 1294, 1119, 1068 and 726 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 7.87 – 7.63 (1 H, broad s, NH), 5.60 (1 H, dt, *J* 11.4, 7.5, alkene CH), 5.35 – 5.27 (1 H, m, alkene CH), 3.94 (1 H, app. quintet, *J* 7.0, C*H*NH), 2.98 (1 H, ddd, *J* 18.2, 9.4, 5.2, one of CH_2C=S), 2.93 – 2.84 (1 H, m, one of CH_2C=S), 2.39 – 2.24 (3 H, m, CH_2C=C and one of pyrrolidine CH_2), 2.06 – 2.00 (2 H, m, CH_2C=C), 1.90 – 1.81 (1 H, m, one of pyrrolidine CH_2), 1.39 – 1.27 (8 H, broad m, alkyl) and 0.88 (3 H, t, *J* 6.8, CH_3 alkyl).

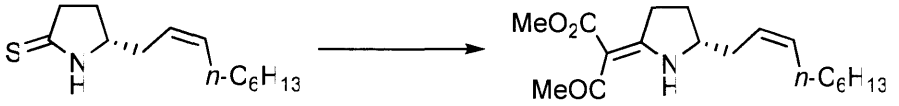
δ_C (100 MHz; $CDCl_3$): 205.6 (C=S), 134.7 (CH), 123.4 (CH), 62.5 (CH), 43.2 (CH_2), 33.3 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.2 (2 x CH_2), 27.7 (CH_2), 22.8 (CH_2) and 14.3 (CH_3).

$[\alpha]_D$: +37 (c = 1, MeOH).

MS-ES: *m/z* (%) = 226 (MH^+, 100).

HRMS-ES: *m/z* $[M + H]^+$ calcd for $C_{13}H_{24}NS$: 226.1629; found: 226.1621.

(E)-Methyl 2-((R)-5-((Z)-non-2-enyl)pyrrolidin-2-ylidene)-3-oxobutanoate (222)



221 **222**

To a solution of thiolactam **221** (1.51 g, 6.71 mmol) in CH_2Cl_2 (50 ml) were added solid $NaHCO_3$ (2.26 g, 26.8 mmol) and methyl 2-bromoacetoacetate (2.62 g, 13.4 mmol), and the mixture was heated under reflux for 16 h. The reaction mixture was then cooled before being filtered through silica and concentrated *in vacuo*. Chromatography on silica gel (Et_2O: petroleum ether 1:9) afforded the *title compound* (1.74 g, 84 %) as an orange oil.

ν_{max} (Neat): 3203, 2928, 2855, 1694, 1600, 1538, 1434, 1359, 1315, 1242, 1189, 1069, 1013, 914 and 784 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 5.61 – 5.54 (1 H, m, alkene CH), 5.36 – 5.29 (1 H, m, alkene CH), 3.93 (1 H, app. quintet, *J* 6.6, C*H*NH), 3.73 (3 H, s, OCH_3), 3.22 (1 H, ddd, *J* 18.6, 9.5, 5.4, one of pyrrolidine $CH_2C{=}C$), 3.07 (1 H, app. ddd, *J* 18.6, 9.4, 7.3, one of pyrrolidine $CH_2C{=}C$), 2.40 (3 H, s, CH_3), 2.38 – 2.22 (2 H, m, $CH_2C{=}C$), 2.18 – 2.09 (1 H, m, one of pyrrolidine CH_2), 2.01 (2 H, app. q, *J* 6.8, $CH_2C{=}C$), 1.70 – 1.61 (1 H, m, one of pyrrolidine CH_2), 1.37 – 1.21 (8 H, broad m, alkyl) and 0.87 (3 H, t, *J* 6.9, CH_3 alkyl).

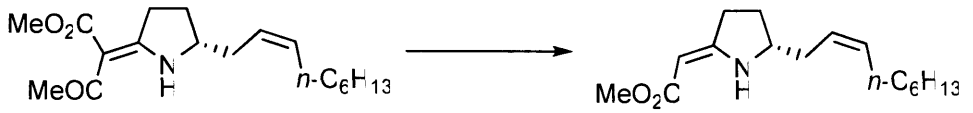
δ_C (100 MHz; $CDCl_3$): 197.9 (C=O), 173.8 (C), 169.4 (C), 134.3 (CH), 123.7 (CH), 98.6 (C), 60.9 (CH), 50.7 (CH_3), 35.1 (CH_2), 33.7 (CH_2), 31.9 (CH_2), 31.0 (CH_3), 29.7 (CH_2), 29.1 (CH_2), 27.6 (CH_2), 26.9 (CH_2), 22.8 (CH_2) and 14.3 (CH_3).

$[\alpha]_D$: +73 (c = 1, MeOH).

MS-AP: *m/z* (%) = 308 (MH^+, 100) and 276 (22).

HRMS-AP: *m/z* $[M + H]^+$ calcd for $C_{18}H_{30}NO_3$: 308.2226; found: 308.2221.

(Z)-Methyl 2-((R)-5-((Z)-non-2-enyl)pyrrolidin-2-ylidene)acetate (223)



222 **223**

Sodium metal (128 mg, 5.57 mmol) was dissolved in dry MeOH (15 ml) under nitrogen and allowed to stir for 30 mins. A solution of β- keto-ester **222** (1.71 g, 5.57 mmol) in dry MeOH (5 ml) was then added and the mixture heated at reflux for 2 h. The solvent was removed *in vacuo* and the resulting residue dissolved in chloroform, washed with saturated aqueous sodium carbonate solution and dried over sodium sulphate. The solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: petroleum ether 1:9) afforded the *title compound* (1.24 g, 84 %) as a yellow oil.

ν_{max} **(Neat):** 3362, 2925, 2855, 1667, 1606, 1469, 1430, 1376, 1294, 1237, 1147 and 1041, cm^{-1}.

δ_H **(400 MHz; $CDCl_3$):** 8.08 – 7.87 (1 H, broad s, NH), 5.57 – 5.50 (1 H, m, alkene CH), 5.38 – 5.30 (1 H, m, alkene CH), 4.48 (1 H, s, CHC=O), 3.79 (1 H, app. quintet, *J* 6.5, C*H*NH), 3.63 (3 H, s, OCH_3), 2.68 – 2.53 (2 H, m, pyrrolidine CH_2C=C), 2.30 (1 H, app. dt, *J* 14.3, 7.2, one of CH_2C=C), 2.24 – 2.17 (1 H, m, one of CH_2C=C), 2.13 – 2.06 (1 H, m, one of pyrrolidine CH_2), 2.02 (2 H, app. q, *J* 6.8, CH_2C=C), 1.65 – 1.56 (1 H, m, one of pyrrolidine CH_2), 1.35 – 1.20 (8 H, broad m, alkyl) and 0.87 (3 H, t, *J* 6.9, CH_3 alkyl).

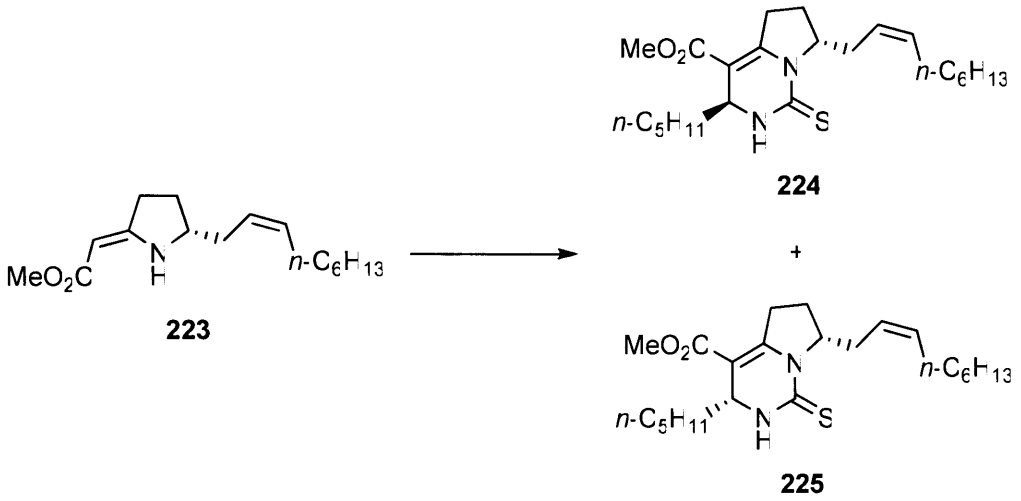
δ_C **(100 MHz; $CDCl_3$):** 171.1 (C), 166.0 (C), 133.7 (CH), 124.5 (CH), 76.3 (CH), 59.8 (CH), 50.3 (CH_3), 34.1 (CH_2), 32.1 (CH_2), 32.0 (CH_2), 29.7 (CH_2), 29.2 (CH_2), 28.0 (CH_2), 27.7 (CH_2), 22.8 (CH_2) and 14.3 (CH_3).

$[\alpha]_D$: +149 (c = 1, MeOH).

MS-ES: *m/z* (%) = 266 (MH^+, 100).

HRMS-ES: *m/z* $[M + H]^+$ calcd for $C_{16}H_{28}NO_2$: 266.2120; found: 266.2108.

(3S,7R)-Methyl 7-((Z)-non-2-enyl)-3-pentyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (224) and (3R,7R)-methyl 7-((Z)-non-2-enyl)-3-pentyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (225)



To a solution of trimethylsilyl isothiocyanate (1.27 ml, 8.98 mmol) in CH_2Cl_2 (40 ml) was added hexanal (1.10 ml, 8.98 mmol) and the solution was stirred at room temperature for 30 mins. A solution of alkylidine pyrrolidine **223** (1.19 g, 4.49 mmol) in CH_2Cl_2 (10 ml) was then added and the resulting solution allowed to stir for 45 mins. The reaction was quenched with ~0.1 M NaOH solution and the aqueous layer extracted with CH_2Cl_2. The combined extracts were dried over sodium sulphate before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: petroleum ether 1:9) afforded, in order of elution, compound **224** (833 mg, 46 %) and compound **225** (425 mg, 23 %), both as yellow oils.

Data for compound 224:

ν_{max} **(Neat):** 3198, 2914, 2860, 1699, 1660, 1432, 1386, 1222, 1162, 1098, 971, 933, 893, 827 and 776 cm^{-1}.

δ_H **(400 MHz; $CDCl_3$):** 6.72 (1 H, broad s, NH), 5.53 (1 H, dt, *J* 10.8, 7.4, alkene CH), 5.34 – 5.27 (1 H, m, alkene CH), 4.56 (1 H, app. ddt, *J* 8.5, 6.4, 3.2,

CHNC=S), 4.28 – 4.26 (1 H, m, CH-pentyl), 3.72 (3 H, s, OCH_3), 3.39 – 3.32 (1 H, m, one of pyrrolidine $CH_2C=C$), 3.06 (1 H, app. dd, *J* 13.4, 6.2, one of pyrrolidine $CH_2C=C$), 2.97 – 2.87 (1 H, m, one of $CH_2C=C$), 2.21 (1 H, dt, *J* 13.7, 9.3, one of $CH_2C=C$), 2.08 (2 H, app. broad q, *J* 7.3, $CH_2C=C$), 1.95 – 1.90 (2 H, m, pyrrolidine CH_2), 1.63 – 1.50 (2 H, broad m, alkyl), 1.43 – 1.21 (14 H, broad m, alkyl) and 0.89 – 0.86 (6 H, m, 2 x CH_3 alkyl).

δ_C (100 MHz; $CDCl_3$): 175.5 (C=S), 166.3 (C=O), 150.0 (C), 134.0 (CH), 124.4 (CH), 99.9 (C), 63.4 (CH), 52.3 (CH), 51.5 (CH_3), 38.0 (CH_2), 32.0 (CH_2), 31.6 (CH_2), 30.7 (CH_2), 29.9 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 27.9 (CH_2), 26.0 (CH_2), 23.7 (CH_2), 22.9 (CH_2), 22.8 (CH_2) and 14.3 (2 x CH_3).

$[\alpha]_D$: - 36 (c = 1, MeOH).

MS-ES: *m/z* (%) = 407 (MH^+, 100).

HRMS-ES: *m/z* $[M + H]^+$ calcd for $C_{23}H_{39}N_2O_2S$: 407.2732; found: 407.2728.

Data for compound 225:

ν_{max} (Neat): 3198, 2980, 1693, 1644, 1427, 1381, 1333, 1223, 1155, 1105, 976, 933, 889 and 778 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 6.98 (1 H, app. broad d, *J* 3.4, NH), 5.54 (1 H, dt, *J* 10.8, 7.3, alkene CH), 5.35 – 5.28 (1 H, m, alkene CH), 4.91 (1 H, tt, *J* 8.6, 2.9, CHNC=S), 4.28 (1 H, app. dt, *J* 7.5, 3.8, CH-pentyl), 3.73 (3 H, s, OCH_3), 3.29 (1 H, ddd, *J* 18.9, 9.9, 2.9, one of pyrrolidine $CH_2C=C$), 3.01 (1 H, app. dt, *J* 18.9, 9.4, one of pyrrolidine $CH_2C=C$), 2.69 – 2.63 (1 H, m, one of $CH_2C=C$), 2.43 – 2.35 (1 H, m, one of $CH_2C=C$), 2.13 – 1.95 (3 H, broad m, $CH_2C=C$ and one of pyrrolidine CH_2), 1.86 – 1.79 (1 H, m, one of pyrrolidine CH_2), 1.57 – 1.42 (2 H, broad m, alkyl), 1.39 – 1.20 (14 H, broad m, alkyl) and 0.89 – 0.85 (6 H, m, 2 x CH_3 alkyl).

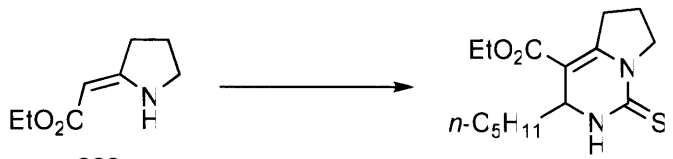
δ_C (100 MHz; $CDCl_3$): 176.0 (C=S), 166.2 (C=O), 150.7 (C), 134.2 (CH), 123.8 (CH), 100.5 (C), 63.1 (CH), 52.0 (CH), 51.6 (CH_3), 37.0 (CH_2), 32.0 (CH_2), 31.6 (CH_2), 31.2 (CH_2), 30.6 (CH_2), 29.8 (CH_2), 29.2 (CH_2), 27.8 (CH_2), 24.9 (CH_2), 23.9 (CH_2), 22.8 (2 x CH_2), 14.3 (CH_3) and 14.2 (CH_3).

$[\alpha]_D$: + 99 (c = 1, MeOH).

MS-ES: *m/z* (%) = 407 (MH^+, 100).

HRMS-ES: *m/z* $[M + H]^+$ calcd for $C_{23}H_{39}N_2O_2S$: 407.2732; found: 407.2734.

Ethyl 3-pentyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate (229)



228 **229**

A solution of trimethylsilyl isothiocyanate (1.84 ml, 13.0 mmol) and hexanal (1.60 ml, 13.0 mmol) in CH_2Cl_2 (20 ml) was stirred at room temperature for 30 minutes before a solution of (Z)-ethyl 2-(pyrrolidin-2-ylidene)acetate **228** (1.01 g, 6.52 mmol) in CH_2Cl_2 (5 ml) was added. The reaction mixture was allowed to stir for a further 45 minutes at room temperature before being quenched with ~0.1 M NaOH. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts dried over Na_2SO_4 before the solvent was removed *in vacuo.* Chromatography on silica gel (EtOAc: hexane, 1:9) afforded the *title compound* (585 mg, 30 %) as a yellow oil.

ν_{max} (Neat): 3197, 2928, 2857, 1694, 1650, 1537, 1379, 1305, 1250, 1219, 1162, 1102, 1073, 1037, 935, 905, 877, 776, 729 and 638 cm^{-1}.

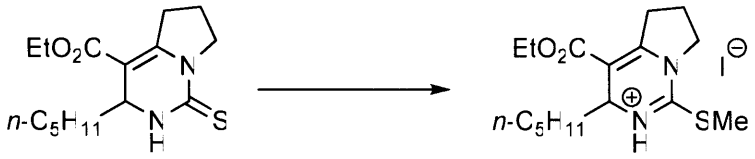
δ_H (400 MHz; $CDCl_3$): 6.94 (1 H, s, NH), 4.29 (1 H, app. dt, *J* 7.7, 3.7, CHN), 4.23 – 4.15 (2 H, m, CH_2O), 4.06 – 3.96 (2 H, m, CH_2N), 3.31 (1 H, ddd, *J* 18.2, 8.4, 3.7, one of CH_2C=C), 2.99 (1 H, app. dt, *J* 18.2, 9.0, one of CH_2C=C), 2.12 – 2.01 (1 H, broad m, one of pyrrolidine CH_2), 1.99 – 1.89 (1 H, m, one of pyrrolidine CH_2), 1.61 – 1.46 (2 H, broad m, alkyl), 1.45 – 1.35 (1 H, broad m, alkyl), 1.34 – 1.23 (8 H, m, CH_3CH_2O and alkyl) and 0.87 (3 H, t, *J* 6.9, CH_3 alkyl).

δ_C (100 MHz; $CDCl_3$): 176.3 (C), 165.5 (C), 150.2 (C), 100.7 (C), 60.3 (CH_2), 52.0 (CH), 36.9 (CH_2), 32.0 (CH_2), 31.4 (CH_2), 23.8 (CH_2), 22.6 (CH_2), 21.2 (CH_2), 14.4 (CH_3) and 14.1 (CH_3).

MS-EI: *m/z* (%) = 296 (M^+, 9), 251 (10), 225 (100), 197 (93), 179 (24), 165 (9), 151 (33), 120 (3), 92 (5) and 65 (4).

HRMS-EI: *m/z* $[M]^+$ calcd for $C_{15}H_{24}N_2O_2S$: 296.1559; found: 296.1558.

4-(Ethoxycarbonyl)-1-(methylthio)-3-pentyl-3,5,6,7-tetrahydropyrrolo[1,2-*c*]pyrimidin-2-ium iodide (230)



229 **230**

Iodomethane (0.35 ml, 5.64 mmol) was added to a solution of thiourea **229** (556 mg, 1.88 mmol) in acetone (5 ml) and the resulting solution was stirred at room temperature for 18 h. The volatiles were removed *in vacuo*, affording the *title compound* (705 mg, 86 %) as a pure orange oil.

ν_{max} (Neat): 3411, 2957, 2870, 1698, 1668, 1563, 1466, 1428, 1381, 1335, 1260, 1232, 1200, 1074, 734 and 700 cm^{-1}.

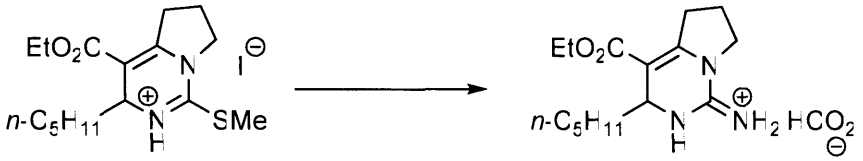
δ_H (400 MHz; $CDCl_3$): 5.09 – 5.02 (1 H, m, CHN), 4.30 – 4.14 (2 H, m, CH_2O), 3.92 – 3.87 (1 H, m, one of CH_2N), 3.73 – 3.67 (1 H, m, one of CH_2N), 3.40 (1 H, ddd, *J* 18.5, 8.3, 2.7, one of CH_2C=C), 3.16 (3 H, s, SCH_3), 3.04 – 2.94 (1 H, m, one of CH_2C=C), 2.36 – 2.25 (1 H, m, one of pyrrolidine CH_2), 2.20 – 2.08 (1 H, m, one of pyrrolidine CH_2)1.78 – 1.61 (2 H, broad m, CH_2 alkyl), 1.40 – 1.23 (9 H, broad m, CH_3CH_2O and alkyl) and 0.89 – 0.84 (3 H, m, CH_3 alkyl).

δ_C (100 MHz; $CDCl_3$): 164.6 (C), 164.0 (C), 148.9 (C), 104.3 (C), 61.2 (CH_2), 51.9 (CH), 50.1 (CH_2), 36.5 (CH_2), 31.4 (CH_2), 30.3 (CH_2), 23.4 (CH_2), 22.4 (2 x CH_2), 17.7 (CH_3), 14.3 (CH_3) and 14.0 (CH_3).

MS-CI: *m/z* (%) = 311 (MH^+, 61), 297 (44), 239 (100), 225 (42), 211 (25), 143 (77) and 117 (19).

HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{16}H_{27}N_2O_2S$: 311.1793; found: 311.1799.

4-(Ethoxycarbonyl)-3-pentyl-2,3,6,7-tetrahydropyrrolo[1,2-*c*]pyrimidin-1(5*H*)-iminium formate (231)



230 **231**

A solution of isothiourea **230** (100 mg, 0.228 mmol) in a mixture of 30 % aqueous ammonium hydroxide solution and acetonitrile (1:1, 3 ml) was heated in a microwave at 130 °C for 15 minutes and then at 165 °C for 30 minutes. The reaction mixture was extracted with CH_2Cl_2, the combined extracts being dried over Na_2SO_4 before the solvent was removed *in vacuo*. Chromatography on silica gel (CH_2Cl_2: MeOH: HCO_2H: H_2O 85:14:0.5:0.5) afforded the *title compound* (66 mg, 89 %) as an orange oil.

ν_{max} (Neat): 3346, 2959, 2953, 1682, 1651, 1456, 1397, 1332, 1310, 1250, 1220, 1187, 1104 and 732 cm^{-1}.

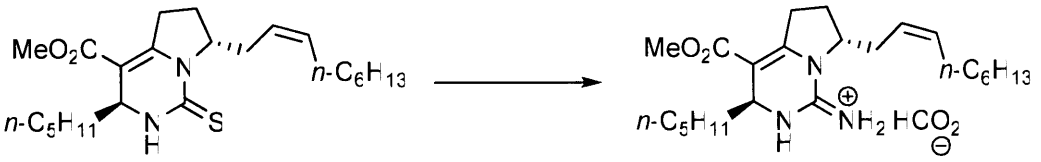
δ_H (400 MHz; $CDCl_3$): 5.80 (1 H, broad s, NH), 4.31 – 4.26 (1 H, m, CHN), 4.21 – 4.12 (2 H, m, CH_2O), 3.70 – 3.66 (2 H, m, CH_2N), 3.21 (1 H, ddd, *J* 18.2, 8.5, 4.5, one of CH_2C=C), 3.05 – 2.95 (1 H, m, one of CH_2C=C), 2.07 – 1.88 (2 H, m, pyrrolidine CH_2), 1.54 – 1.49 (2 H, m, alkyl), 1.44 – 1.31 (2 H, broad m, alkyl), 1.31 – 1.23 (7 H, broad m, CH_3CH_2O and alkyl) and 0.86 (3 H, t, *J* 6.9, CH_3 alkyl).

δ_C (100 MHz; $CDCl_3$): 165.8 (C), 165.4 (CH formate), 153.6 (2 x C), 98.8 (C), 59.9 (CH_2), 51.8 (CH), 46.6 (CH_2), 37.1 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 24.1 (CH_2), 22.6 (CH_2), 21.5 (CH_2), 14.4 (CH_3) and 14.0 (CH_3).

MS-ES: *m/z* (%) = 280 (MH^+, 100), 226 (2) and 197 (1).

HRMS-ES: *m/z* $[M + H]^+$ calcd for $C_{15}H_{26}N_3O_2$: 280.2025; found: 280.2038.

(3S,7R)-4-(Methoxycarbonyl)-7-((Z)-non-2-enyl)-3-pentyl-2,3,6,7-tetrahydropyrrolo[1,2-c]pyrimidin-1(5H)-iminium formate (232)



224 **232**

To a solution of bicyclic thiourea **224** (118 mg, 0.291 mmol) in dry MeOH (3 ml) was added iodomethane (0.02 ml, 0.291 mmol) and the mixture was heated at reflux for 1 h. The volatiles were removed *in vacuo* and the resulting residue re-dissolved in dry MeOH (3 ml). The solution was transferred to a mixture of NH_4OAc (112 mg, 1.45 mmol) in dry MeOH (2 ml) and liquid ammonia bubbled through the reaction for 10 mins. The resulting suspension was heated in a sealed tube at 80°C for 48 h. The solvent was removed *in vacuo* before chromatography on silica gel (CH_2Cl_2: MeOH: HCO_2H: H_2O 84:14:0.5:0.5) afforded the *title compound* (121 mg, 96%) as an orange oil.

ν_{max} (Solution in CH_2Cl_2): 3229, 3155, 2927, 2856, 1699, 1649, 1599, 1548, 1438, 1379, 1346, 1212, 1177, 1104, 912 and 646 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 8.18 (1 H, s, NH), 8.08 – 7.77 (2 H, broad s, NH_2), 5.57 (1 H, dt, *J* 11.0, 7.2, alkene CH), 5.52 – 5.43 (1 H, m, alkene CH), 4.73 – 4.69 (1 H, m, CHNC=N), 4.46 – 4.42 (1 H, m, CH-pentyl), 3.74 (3 H, s, OCH_3), 3.32 (1 H, dd, *J* 18.7, 7.9, one of pyrrolidine CH_2C=C), 2.93 – 2.83 (1 H, m, one of pyrrolidine CH_2C=C), 2.49 – 2.45 (1 H, m, one of CH_2C=C), 2.34 (1 H, dt, *J* 14.3, 9.1, one of CH_2C=C), 2.11 – 1.95 (4 H, broad m, CH_2C=C and pyrrolidine CH_2), 1.71 – 1.50 (3 H, broad m, alkyl), 1.43 – 1.24 (12 H, broad m, alkyl) and 0.89 – 0.85 (6 H, m, 2 x CH_3 alkyl).

δ_C (100 MHz; $CDCl_3$): 165.1 (C=O), 150.9 (C=N), 149.7 (C), 134.7 (CH), 123.0 (CH), 102.0 (C), 60.3 (CH), 51.9 (CH_3), 50.9 (CH), 37.5 (CH_2), 31.9 (CH_2), 31.4

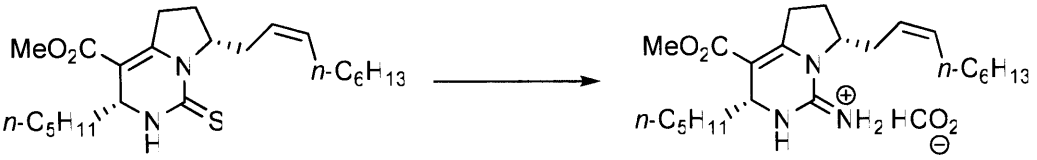
(CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 27.7 (CH_2), 26.6 (CH_2), 24.1 (CH_2), 22.8 (CH_2), 22.6 (CH_2) and 14.3 (2 x CH_3).

$[\alpha]_D$: + 7 (c = 1, MeOH).

MS-AP: *m/z* (%) = 390 (MH^+, 100).

HRMS-AP: *m/z* $[M + H]^+$ calcd for $C_{23}H_{40}N_3O_2$: 390.3121; found: 390.3134.

(3R,7R)-4-(Methoxycarbonyl)-7-((Z)-non-2-enyl)-3-pentyl-2,3,6,7-tetrahydropyrrolo[1,2-c]pyrimidin-1(5H)-iminium formate (233)



225 **233**

To a solution of bicyclic thiourea **225** (252 mg, 0.621 mmol) in dry MeOH (5 ml) was added iodomethane (0.04 ml, 0.621 mmol) and the mixture was heated at reflux for 1 h. The volatiles were removed *in vacuo* and the resulting residue re-dissolved in dry MeOH (5 ml). The solution was transferred to a mixture of NH_4OAc (239 mg, 3.10 mmol) in dry MeOH (3 ml) and liquid ammonia bubbled through the reaction for 10 mins. The resulting suspension was heated in a sealed tube at 80°C for 48 h. The solvent was removed *in vacuo* before chromatography on silica gel (CH_2Cl_2: MeOH: HCO_2H: H_2O 84:14:0.5:0.5) afforded the *title compound* (233 mg, 86%) as an orange oil.

ν_{max} (Solution in CH_2Cl_2): 3241, 3148, 2957, 2927, 2856, 1696, 1681, 1655, 1548, 1436, 1385, 1349, 1184 and 1106 cm^{-1}.

δ_H (400 MHz; $CDCl_3$): 8.99 – 8.65 (1 H, broad s, NH), 8.16 – 7.60 (2 H, broad s, NH_2), 5.58 (1 H, dt, *J* 10.6, 7.4, alkene CH), 5.39 – 5.32 (1 H, m, alkene), 4.96 – 4.88 (1 H, m, CHNC=N), 4.43 (1 H, app. dd, *J* 7.0, 3.8, CH-pentyl), 3.74 (3 H, s, OCH_3), 3.20 (1 H, ddd, *J* 19.0, 10.0, 3.8, one of pyrroldine CH_2C=C), 3.07 – 2.98 (1 H, m, one of pyrrolidine CH_2C=C), 2.52 – 2.36 (2 H, m, CH_2C=C), 2.21 (1 H, app. dq, *J* 12.7, 9.1, one of pyrrolidine CH_2), 2.00 (2 H, app. q, *J* 6.6,

CH_2C=C), 1.93 – 1.86 (1 H, m, one of pyrrolidine CH_2), 1.58 – 1.40 (3 H, m, alkyl), 1.36 – 1.24 (13 H, broad m, alkyl) and 0.87 (6 H, app. t, *J* 6.4, 2 x CH_3 alkyl).

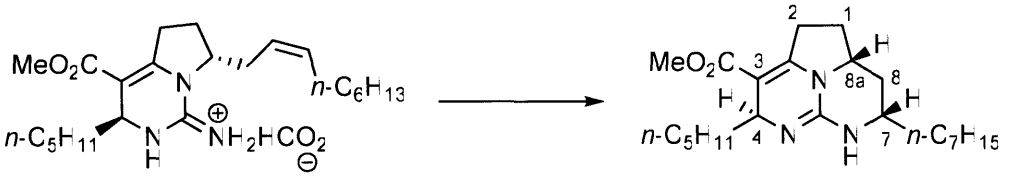
δ_C (100 MHz; $CDCl_3$): 165.2 (C=O), 151.4 (C=S), 150.6 (C), 135.1 (CH), 122.2 (CH), 102.8 (C), 60.1 (CH), 51.9 (CH_3), 50.3 (CH), 36.7 (CH_2), 31.9 (CH_2), 31.5 (CH_2), 30.9 (CH_3), 29.7 (CH_2), 29.2 (2 x CH_2), 27.8 (CH_2), 26.4 (CH_2), 24.1 (CH_2), 22.8 (CH_2), 22.7 (CH_2) 14.3 (CH_3) and 14.2 (CH_3).

$[\alpha]_D$: + 19 (c = 1, MeOH).

MS-AP: *m/z* (%) = 390 (MH^+, 100) and 376 (1).

HRMS-AP: *m/z* $[M + H]^+$ calcd for $C_{23}H_{40}N_3O_2$: 390.3121; found: 390.3113.

(4*S*,7*S*,8a*R*)-Methyl 7-heptyl-4-pentyl-1,2,4,5,7,8-hexahydro-11a*H*-2a^1,5,6-triaza-acenaphthylene-3-carboxylate (234)



232 **234**

To a solution of bicyclic guanidine **232** (100 mg, 0.230 mmol) in MeCN (3 ml) were added iodine (350 mg, 1.38 mmol) and potassium carbonate (95 mg, 0.690 mmol) and the resulting mixture was allowed to stir at room temperature for 3 h. The reaction mixture was filtered through silica and concentrated *in vacuo*. The crude tricyclic guanidine was immediately re-dissolved in EtOAc (6 ml), and triethylamine (0.16 ml, 1.15 mmol) and 10 % Pd/C (cat.) added. The black suspension was de-gassed and stirred under an atmosphere of H_2 for 16 h. The reaction mixture was filtered through celite and the solvent removed *in vacuo*. Chromatography on silica gel (EtOAc:CH_2Cl_2 1:2) afforded the *title compound* (49 mg, 55 %) as a yellow oil.

ν_{max} (Solution in CH_2Cl_2): 3180, 2931, 2856, 1704, 1679, 1644, 1573, 1493, 1437, 1373, 1335, 1227, 1195, 1115, 1080, 917 and 702 cm^{-1}.

δ_H (400 MHz; CD_3OD): 4.40 (1 H, app. dd, *J* 7.4, 4.2, H-4), 4.11 (1 H, app. tdd, *J* 10.3, 6.5, 3.8, H-8a), 3.74 (3 H, s, OCH_3), 3.67 – 3.60 (1 H, m, H-7), 3.41 (1 H, app. dd, *J* 18.7, 9.0, H-2β), 2.89 (1 H, ddd, *J* 18.7, 11.4, 8.9, H-2α), 2.46 – 2.39 (2 H, m, H-1β and H-8β), 1.77 – 1.62 (2 H, m, H-1α and H-8α), 1.60 – 1.48 (3 H, m, three of H-10/H-15), 1.41 – 1.27 (17 H, m, one of H-10/H-15 and alkyl) and 0.90 – 0.87 (6 H, m, 2 x CH_3).

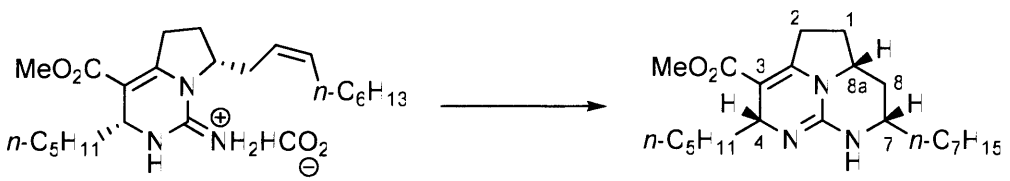
δ_C (100 MHz; $CDCl_3$): 165.0 (C), 149.1 (C), 148.5 (C), 103.3 (C), 57.4 (CH), 52.0 (CH_3), 51.3 (CH), 50.9 (CH), 37.1 (CH_2), 34.7 (CH_2), 33.9 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 30.0 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 25.5 (CH_2), 24.3 (CH_2), 22.8 (CH_2), 22.6 (CH_2) and 14.3 (2 x CH_3).

$[\alpha]_D$: - 13 (c = 0.5, MeOH).

MS-ES: *m/z* (%) = 390 (MH^+, 100), 146(2) and 130 (4).

HRMS-ES: *m/z* $[M + H]^+$ calcd for $C_{23}H_{40}N_3O_2$: 390.3121; found: 390.3111.

(4*R*,7*S*,8a*R*)-Methyl 7-heptyl-4-pentyl-1,2,4,5,7,8-hexahydro-11a*H*-2a^1,5,6-triaza-acenaphthylene-3-carboxylate (batzelladine C methyl ester) (235)



233 **235**

To a solution of bicyclic guanidine **233** (53 mg, 0.12 mmol) in dry CH_2Cl_2 (2 ml) at 0 °C was added potassium carbonate (51 mg, 0.37 mmol), followed by iodine monochloride (0.18 ml of a 1 M solution in CH_2Cl_2, 0.18 mmol) dropwise. The resulting suspension was allowed to warm to room temperature and stirred for ~3 h (TLC). The solvent was removed *in vacuo* before chromatography on silica gel (EtOAc: CH_2Cl_2 1:2) afforded the tricyclic guanidine (51 mg, 81 %) as a brown oil. The tricyclic guanidine (41 mg, 0.080 mmol) was immediately re-dissolved in EtOAc (3 ml), and triethylamine (0.05 ml, 0.40 mmol) and 10 % Pd/C (cat.) added. The black suspension was de-gassed and stirred under an atmosphere of H_2 for 16 h. The reaction mixture was filtered before

chromatography on silica gel (MeOH:EtOAc 1:19) afforded the *title compound* (17 mg, 55 %) as a yellow oil).

ν_{max} (Solution in CH_2Cl_2): 3177, 2926, 2856, 1682, 1644, 1574, 1435, 1372, 1336, 1199, 1097 and 736 cm^{-1}.

δ_H (400 MHz; CD_3OD): 4.46 – 4.44 (1 H, m, H-4), 3.93 (1 H, tdd, *J* 11.4, 5.4, 2.7, H-8a), 3.70 (3 H, s, Me ester), 3.60 (1 H, app. td, *J* 11.1, 6.4, H-7), 3.32 (1 H, dd, *J* 18.2, 7.8, H-2β), 2.79 (1 H, dddd, *J* 18.2, 12.0, 7.5, 1.4, H-2α), 2.38 (1 H, ddd, *J* 13.1, 3.9, 2.9, H-8β), 2.33 – 2.27 (1 H, m, H-1β), 1.72 – 1.52 (5 H, broad m, H-1α, H-10 and H-15), 1.35 – 1.24 (17 H, m, H-8α and alkyl) and 0.88 – 0.85 (6 H, m, 2 x CH_3 alkyl).

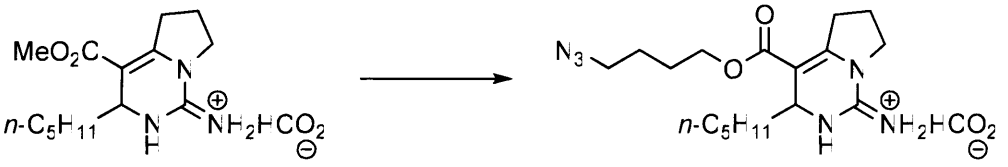
δ_C (125 MHz; CD_3OD): 58.9 (CH), 53.8 (CH), 52.5 (CH), 52.2 (CH_3), 38.2 (CH_2), 36.0 (CH_2), 33.3 (CH_2), 33.1 (CH_2), 32.7 (CH_2), 31.1 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 26.1 (CH_2), 24.5 (CH_2), 23.8 (CH_2), 23.7 (CH_2), 14.5 (CH_3) and 14.4 (CH_3).

$[\alpha]_D$: -2.4 (c = 0.5, MeOH), lit. **$[\alpha]_D$:** -4.2 (c = 0.93, MeOH)

MS-ES: *m/z* (%) = 390 (MH^+, 100), 361 (8) and 342 (1).

HRMS-ES: *m/z* $[M + H]^+$ calcd for $C_{23}H_{40}N_3O_2$: 390.3121; found: 390.3113.

4-((4-Azidobutoxy)carbonyl)-3-pentyl-2,3,6,7-tetrahydropyrrolo[1,2-*c*]pyrimidin-1(5*H*)-iminium formate (237)



236 **237**

4-Azidobutanol (214 mg, 1.86 mmol) and Otera's catalyst[65] (103 mg, 0.19 mmol) were added to a solution of guanidine **236** (58 mg, 0.19 mmol) in toluene (1 ml). The resulting mixture was heated under reflux for 24 h before the solvent was removed in vacuo. Chromatography on silica gel (MeOH: CH_2Cl_2 1:19) afforded the title compound (27 mg, 37 %) as a yellow oil.

ν_{max} **(Neat):** 3228, 3140, 2941, 2857, 2099, 1685, 1674, 1437, 1355, 1252, 1176, 1104 and 734 cm^{-1}.

δ_H **(400 MHz; $CDCl_3$):** 8.81 (1 H, s, NH), 8.19 – 7.92 (2 H, broad s, NH_2), 4.47 – 4.41 (1 H, broad m, C*H*NH), 4.19 (2 H, t, *J* 5.8, CH_2O), 3.98 (2 H, app. dd, *J* 8.5, 5.3, CH_2N), 3.35 – 3.27 (3 H, m, CH_2N_3 and one of $CH_2C{=}C$), 2.96 (1 H, app. dt, *J* 18.6, 9.5, one of $CH_2C{=}C$), 2.31 – 2.19 (1 H, broad m, one of pyrrolidine CH_2), 2.15 – 2.04 (1 H, broad m, one pyrrolidine CH_2), 1.82 – 1.73 (2 H, broad m, CH_2 alkyl), 1.70 – 1.46 (6 H, broad m, alkyl), 1.44 – 1.25 (4 H, broad m, alkyl) and 0.88 (3 H, t, *J* 6.7, CH_3 alkyl).

δ_C **(100 MHz; $CDCl_3$):** 164.4 (C), 151.9 (C), 150.3 (C), 102.6 (C), 64.0 (CH_2), 50.9 (CH_2), 50.4 (CH), 48.7 (CH_2), 36.8 (CH_2), 31.3 (CH_2), 30.8 (CH_2), 26.1 (CH_2), 25.6 (CH_2), 23.9 (CH_2), 22.5 (CH_2), 22.0 (CH_2) and 14.1 (CH_3).

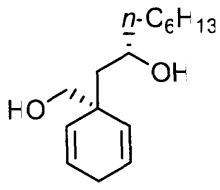
MS-ES: *m/z* (%) = 349 (MH^+, 100%) and 266 (3).

HRMS-ES: *m/z* $[M + H]^+$ calcd for $C_{17}H_{29}N_6O_2$: 349.2352; found: 349.2363.

Appendix A

Compound Lists

Appendix A-1. Compound List for Chapter 1



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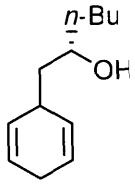

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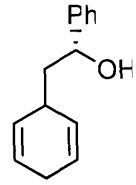

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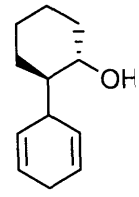

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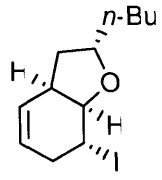

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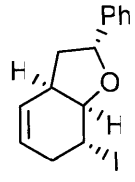

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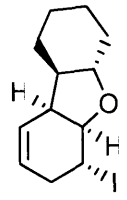

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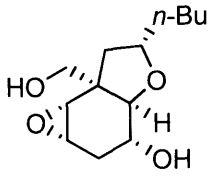

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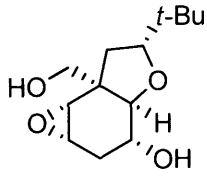

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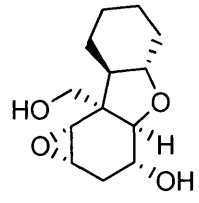

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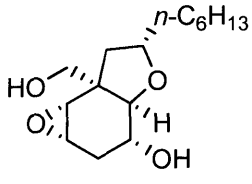

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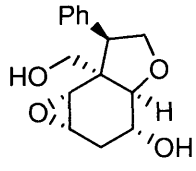

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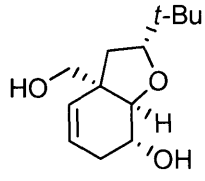

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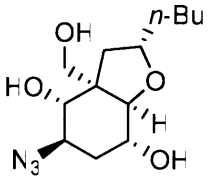

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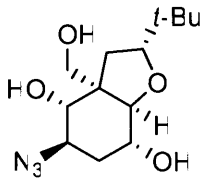

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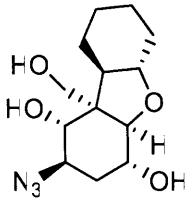

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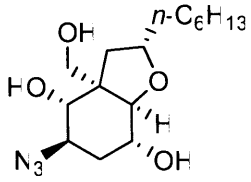

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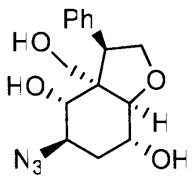

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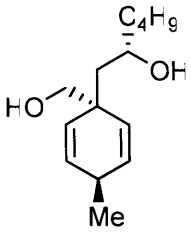

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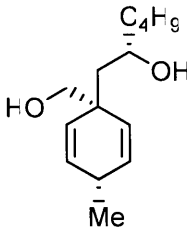

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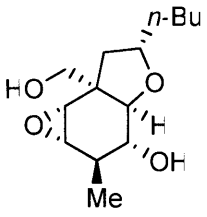

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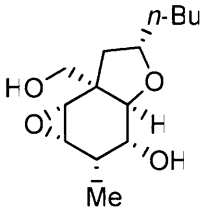
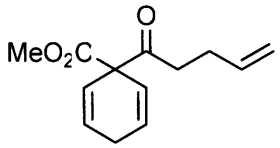


48

Appendix A-2. Compound List for Chapter 2



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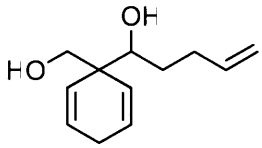

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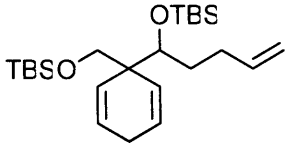

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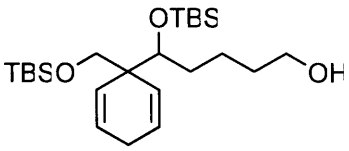

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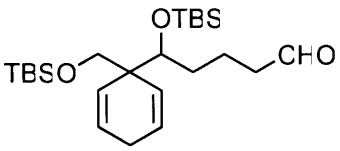

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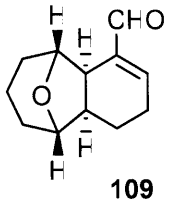

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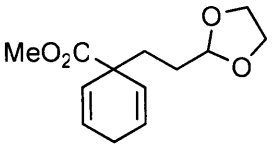

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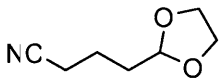

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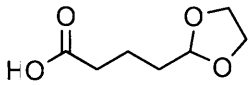

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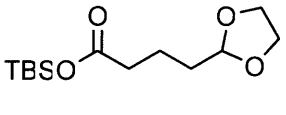

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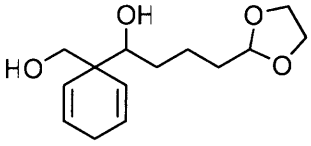

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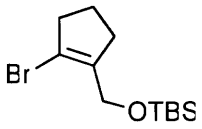
Appendix A-3. Compound List for Chapter 3



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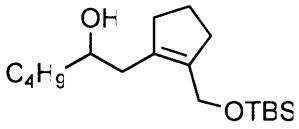

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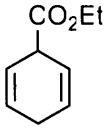

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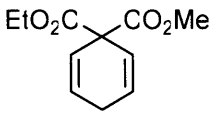

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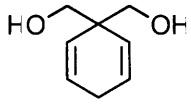

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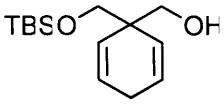

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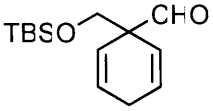

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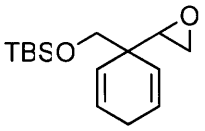

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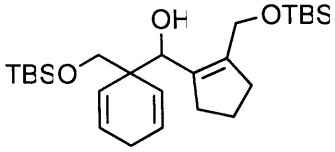

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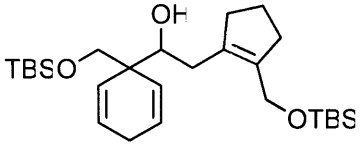

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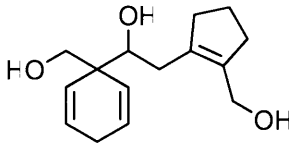

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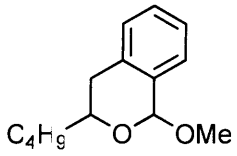

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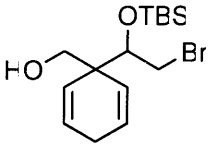

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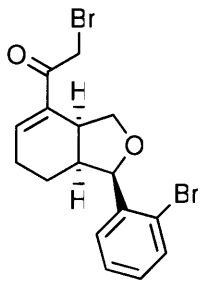

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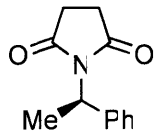
Appendix A-4. Compound List for Chapter 4



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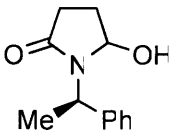

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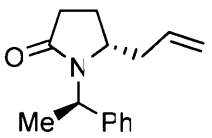

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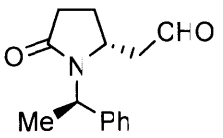

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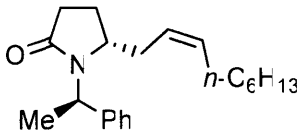

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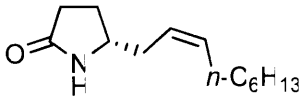

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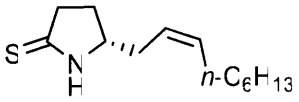

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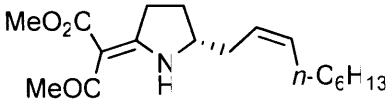

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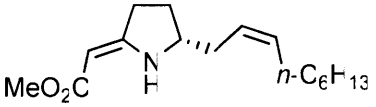

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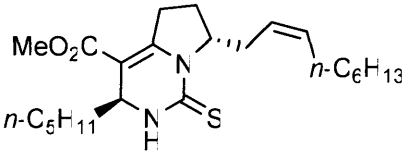

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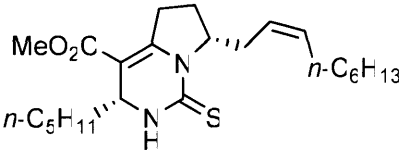

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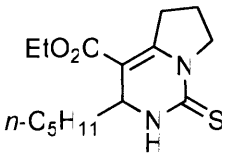

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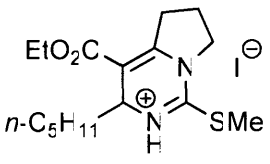

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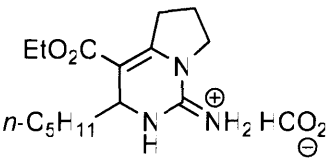

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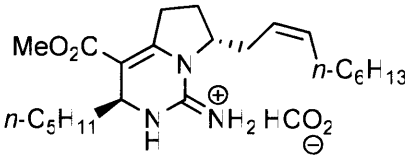

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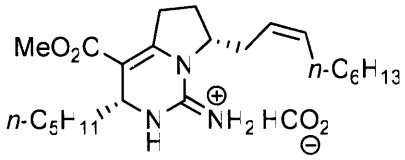

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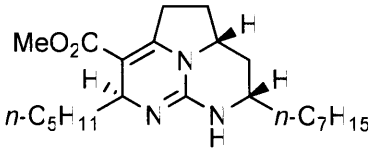

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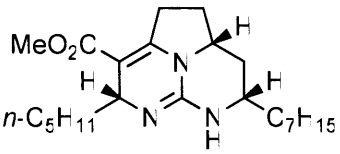

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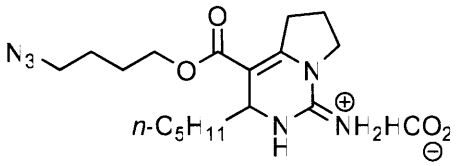

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Appendix B

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