Desymmetrisation Reactions of Cyclohexa-1,4-dienes

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Abstract

This thesis describes the development of diastereotopic group selective processes allowing the desymmetrisation of 1,4-cyclohexadiene derivatives and their application to target synthesis.

Chapter 1 discusses some of the benefits that may be derived by the use of desymmetrisation, and demonstrates some of the ways in which it has recently been applied in compounds based on 1,4-cyclohexadiene.

Chapter 2 describes a novel use of the Prins reaction to desymmetrise cyclohexadiene derivatives with high diastereoselectivity, and the optimisation of this resulting in an effective, practical and straightforward procedure.

Chapter 3 details the investigation into desymmetrisation through diastereoselective iodocyclisation reactions, much higher stereoselectivity is observed than found previously in cyclohexadiene based substrates and an explanation is suggested by examination of structural differences.

Chapter 4 reviews some of the previous synthetic approaches to members of the fawcettimine group of Lycopodium alkaloids. This is followed by the results of our first approach to the core tetracyclic ring system of lycoposerramine A, based on the discovery of a novel base induced diastereotoselective cyclisation reaction.

Chapter 5 describes our revised approach, leading to the construction of a closely related tetracycle, although not permitting the construction of the target.

Chapter 6 discusses the synthesis of the core tricyclic system of lycoposerramine S by a different strategy. NMR spectra obtained from the final product are found to closely match those obtained from the natural product.

Acknowledgements

I would like to thank my parents, firstly, for their consistent love and support, which is very much appreciated. And thank you to all the family, especially Jennifer for all of the delicious cake, and for continuing to give me pocket money!

Thank you Mark for providing an excellent project and much helpful advice and discussion, and being a great boss. It's been a pleasure working for you!

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Thank you to all the staff, in particular Rob and Robin for their help with MS and NMR, Gaz, Jamie and Dave for bringing lots of solvents and mirth, and Mal for keeping the Dewar full, even when the vacuum was broken!

Thanks also to Stephen Baldwin and Mike Butters at Astra Zeneca for generously obtaining many of the MS data used.

Dedication

I dedicate this work to my parents.

Table of Contents

Detailed Table of Contents

Abbreviations

Ac	Acetyl
AIBN	2,2`-Azobisisobutyronitrile
APCI	Atmospheric Pressure Chemical Ionisation
Bn	Benzyl
Boc	*t*-Butyloxycarbonyl
n-Bu	*n*-Butyl
i-Bu	*i*-Butyl
t-Bu	*t*-Butyl
CI	Chemical ionisation
m-CPBA	*m*-Chloroperoxybenzoic acid
DBU	Diaza-1,3-bicyclo[5.4.0]undecane
d.e.	Diastereomeric excess
DIPEA	*N,N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethyoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DPA	*N,N*-Diisopropylamine
e.e.	Enantiomeric excess

EI	Electron impact
Equiv.	Equivalents
ES+	Positive Ionisation Electrospray
Fmoc	9-Fluorenylmethyloxycarbonyl
HMPA	Hexamethylphosphoramide
IR	Infra-red
LDA	Lithium diisopropylamide
Me	Methyl
MOM	Methoxymethyl
NBS	*N*-Bromosuccinimide
NMNO	4-Methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Enhancement Spectroscopy
Ns	4-Nitrobenzenesulfonyl
Nu	Nucleophile
Ph	Phenyl
PMP	*p*-Methoxyphenyl
PPTS	Pyridinium *p*-toluenesulfonate
i-Pr	Isopropyl

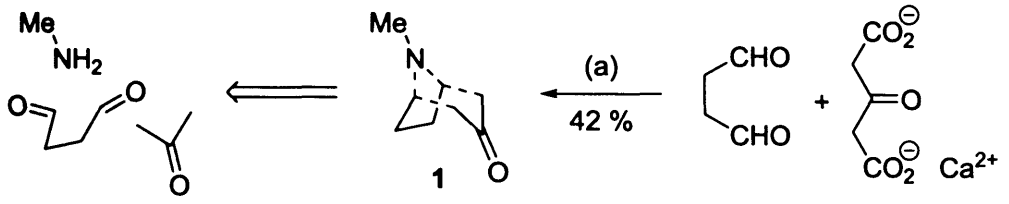
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
tlc	Thin layer chromatography
Ts	4-Toluenesulfonyl

Chapter 1

Introduction

1.1 Symmetry in Synthetic Chemistry

The potential for many organic compounds to be assembled simply and efficiently by consideration of their symmetry was recognised, and applied to remarkable effect, by Robinson over 90 years ago. Disconnecting tropinone **1** at the bonds indicated, and appropriately functionalising both termini of the four carbon fragment, he suggested its synthesis by simply combining the three symmetrical synthons shown in Scheme **1**.[1]



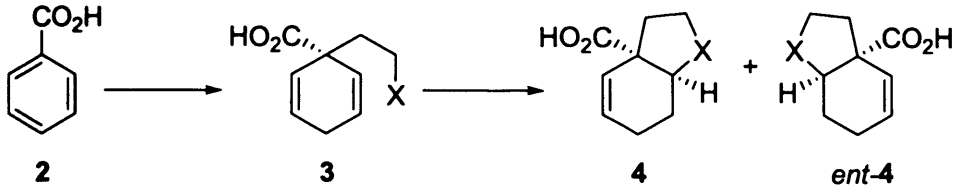
Scheme 1. *Reagents and Conditions*: (a) i) $MeNH_2$, H_2O, 72 h; ii) H^+.

This was, indeed, found to be the case, and by use of a more readily enolised acetone surrogate the cascade of reactions was found to be so effective under such mild conditions that he proposed that it may also be the mechanism of its biosynthesis.[2]

This example illustrates some of the benefits that may be derived by maintaining an element of symmetry through a sequence; firstly, the starting materials are relatively simple, and also, therefore, generally cheap and easy to obtain. Also, there are fewer selectivity issues, due to the equivalence of the two pairs of functional groups. This allows the simultaneous homologation of both in a single step, and can be an extremely effective means of constructing long, acyclic, chains.[3]

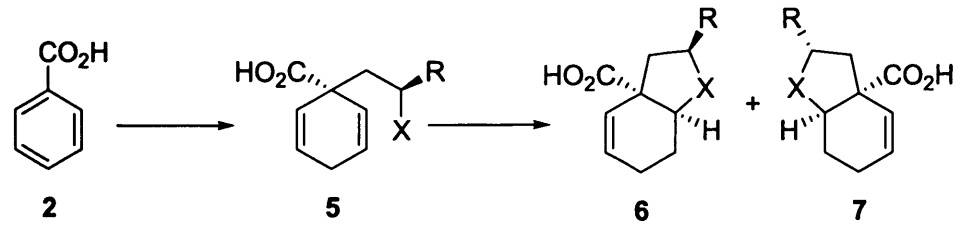
Although there are a great number of symmetrical target molecules there are, by necessity, many more that are asymmetrical.[4] These generally have at least some symmetry, however, and their synthesis can be facilitated by the same benefits described above if selected symmetry elements can be broken at a later stage. The various methods through which this can be achieved have received extensive reviews.[3-7] This process of desymmetrisation alone can offer certain advantages, illustrated by the example in Scheme **2**. The Birch reduction / alkylation sequence readily affords 1,1-disubstituted 2,5-cyclohexadienes such as **3**, containing a

prochiral quaternary centre. Transformation of one of the enantiotopic double bonds, often in a cyclisation reaction, results in a loss of symmetry, thus determining the configuration of the quaternary centre in a process separate from its bond formation. This may, in many cases, provide higher selectivity than the more conventional direct approach, and can be even more effective when applied to a substrate containing several prochiral centres.



Scheme 2. Desymmetrisation of a 1,1-disubstituted-2,5-cyclohexadiene.

Such an enantioselective transformation, of course requires the use of a chiral catalyst or reagent. It is also relatively difficult to determine the success, or otherwise, of the reaction. By incorporating a stereogenic centre prior to desymmetrisation, as in compound **5**, Scheme **3**, for instance, the substrate is able to control which of the, now diastereotopic, groups is involved in the reaction. Since the products of the reaction are diastereoisomers, they are easily differentiated, and often separable simply by flash column chromatography. The success of the transformation is, therefore, straightforward to determine with a racemic substrate, while still allowing for asymmetric synthesis by use of a chiral alkylating reagent following the Birch reduction.



Scheme 3. Desymmetrisation by diastereotopic group selectivity.

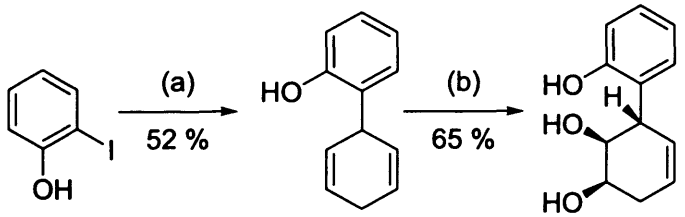
1.2 Desymmetrisation of Achiral Cyclohexadienes

While enantiotopic group selectivity requires the use of a chiral reagent or catalyst, desymmetrisation can still be achieved by the same processes used on chiral substrates, although resulting in racemic products.

1.2.1 Non-Group Selective Desymmetrisation

A novel alternative to the more common entry into these substrates, the Birch reduction, was reported recently by Crich to allow the preparation of 1-aryl-2,5-cyclohexadienes. The addition of aryl radicals to benzene was shown to occur when benzeneselenol or diphenyl diselenide was added as a catalyst. Over a series of publications, a wide range of aryl iodides were shown to undergo this addition, and the products were then desymmetrised by a variety of reactions.[8]

Dihydroxylation of **9**, for example, with strictly 1 equiv. of NMNO in aqueous acetone, gave diol **10**. This could be further oxidised, allowing access to various cyclitols.[9] The preference observed for dihydroxylation *anti* to the substituent was also found by Landais in similar cases.[10]

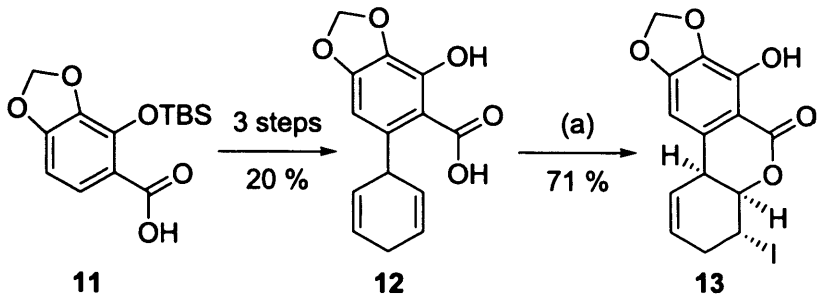


8 **9** **10**

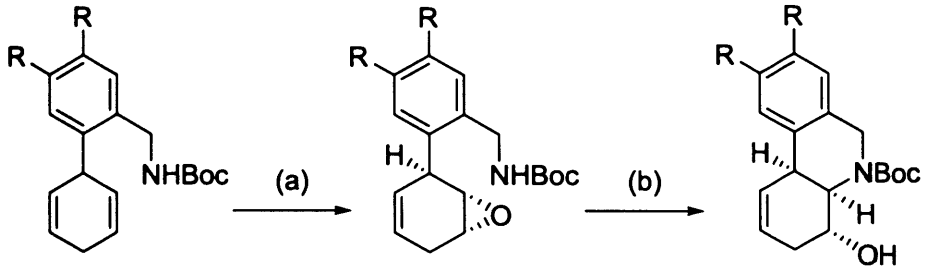
Scheme 4. *Reagents and Conditions:* (a) Bu_3SnH, AIBN, $(PhSe)_2$, PhH, reflux; (b) OsO_4, NMNO (1 equiv.), acetone, water, 2:1.

The preparation of benzoic acid derivative **12** in this manner allowed the preparation of Danishefsky's pancratistatin precursor **13**, shown in Scheme **5**. This route required 3 fewer steps than the original procedure and provided a slight increase in overall yield.[11]

An interesting epoxycyclisation was also reported, effected by treatment of epoxides **15a** and **15b**, shown in Scheme **6**, with $BF_3.OEt_2$.

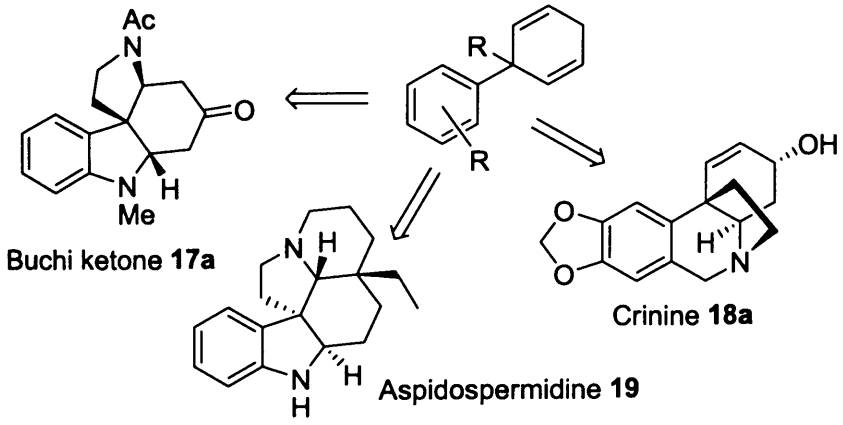


Scheme 5. *Reagents and Conditions:* (a) I_2, $NaHCO_3$, THF.



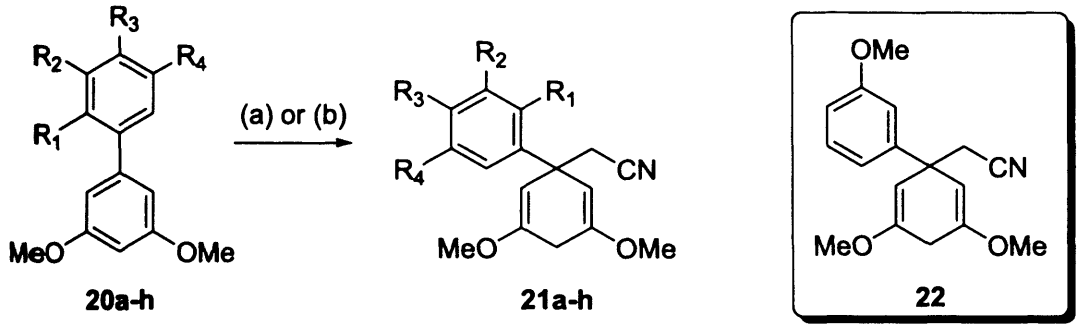
Scheme 6. *Reagents and Conditions:* (a) *m*CPBA, CH_2Cl_2, 0 °C; (b) $BF_3.Et_2O$, 0 °C.

A major disadvantage of this approach is that it cannot easily be applied to the preparation of 1,1-disubstituted cyclohexadienes. Landais realised that many targets, those shown in Scheme **7** for example, may be accessible by the desymmetrisation of such substrates, and initiated a study into their synthesis by the Birch reduction / alkylation of biaryl compounds.[12]



Scheme 7. Targets potentially accessible through Birch reduction of biaryls.

The rate of reduction of each ring was found to be influenced by the substituents in the same order found in simple mono-aryl systems, where ArOMe > ArH > ArOH. In many cases, this allowed the highly regioselective reduction of a series of substrates **20a-h**, shown in Table **1**, affording the corresponding 2-aryl-2-(3,5-dimethoxy-2,5-cyclohexadienyl)acetonitriles **21a-h** in high yield.

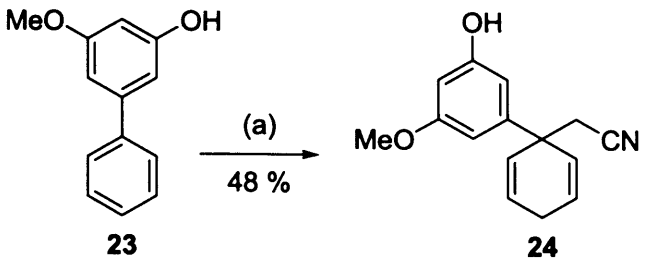


20a-h **21a-h** **22**

Entry	*Substrate*	R_1	R_2	R_3	R_4	*Conditions*	*Yield **21** (%)*
1	**20a**	H	H	H	H	(a)	88 %
2	**20b**	OH	H	H	H	(b)	82 %
3	**20c**	H	OH	H	H	(b)	75 %
4	**20d**	OH	OMe	H	H	(b)	82 %
5	**20e**	H	OMe	OH	H	(b)	86 %
6	**20f**	H	OMe	OMe	H	(a)	0 %[a]
7	**20g**	H	OMe	H	OMe	(a)	91 %
8	**20h**	NHBoc	H	H	H	(b)	50 %

Table 1. *Reagents and Conditions:* (a) i) Li, NH_3, THF, -78 °C; ii) $ClCH_2CN$; (b) i) n-BuLi; ii) Li, NH_3, THF, -78 °C; iii) $ClCH_2CN$. [a] A mixture of **22** and **20f** (approx. 1:1) was obtained in 78 % yield.

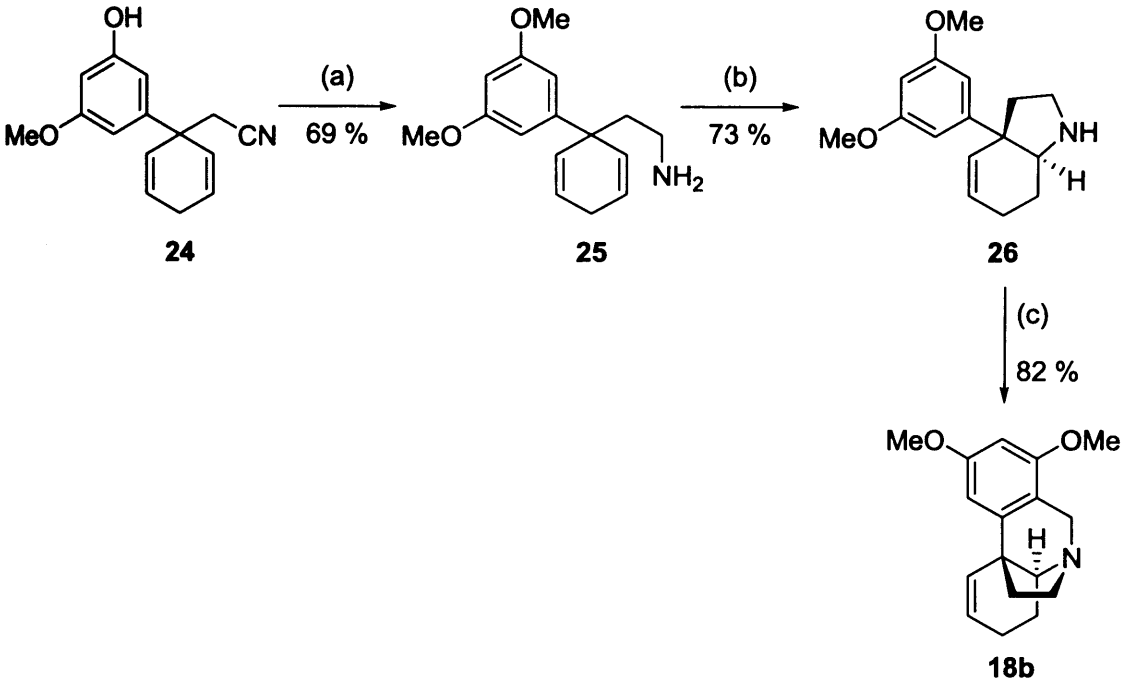
The unsubstituted aryl group of compound **23**, shown in Scheme **8**, was found to be reduced preferentially, allowing the preparation of simple 1,1-disubstituted cyclohexa-2,5-dienes by this method.



23 24

Scheme 8. *Reagents and Conditions:* (a) i) *n*-BuLi; ii) Li, NH_3, THF; iii) $ClCH_2CN$, -33 °C.

The product **24** was used in an very concise synthesis of crinine analog **18b**, shown in Scheme **9**. Alkylation of phenol **24**, followed by reduction of the nitrile, gave compound **25**. This was desymmetrised in an LDA catalysed hydroamination reaction, allowing formation of the remaining ring by a Pictet-Spengler reaction.

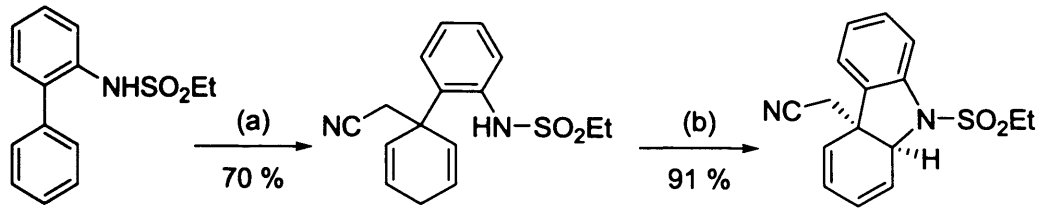


24 25 26 18b

Scheme 9. *Reagents and Conditions:* (a) i) Me_2SO_4, K_2CO_3, acetone, reflux, 20 h; ii) $LiAlH_4$, $AlCl_3$, Et_2O, room temp., 4 h.; (b) LDA (0.4 equiv.), THF, 20 °C, 4 h; (c) $CH_2{=}NH_2I^+I^-$, THF, 40 °C, 60 h.

Prior deprotonation of the sulfonamide group by treatment with *n*-BuLi also allowed the selective reduction of the unsubstituted aryl group of compound **27**. The alkylated product **28** was then desymmetrised in an oxidative amination reaction, catalysed by Pd(II), as shown in Scheme **10**. The optimum conditions were found to

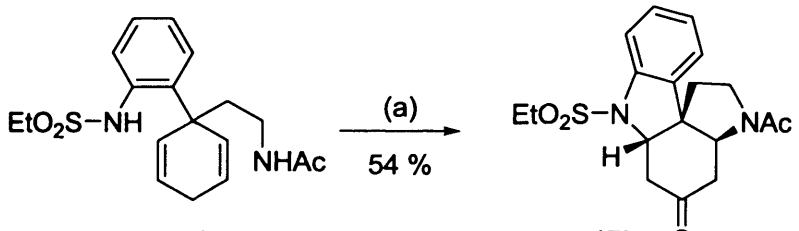
use NaOAc as the base and activated carbon as a support to facilitate the re-oxidation of precipitated Pd(0).[13]



27 **28** **29**

Scheme 10. *Reagents and Conditions:* (a) i) *n*-BuLi ii) Li, NH_3, THF, -78 °C; ii) $ClCH_2CN$; (b) $Pd(OAc)_2$ (10 mol %), Carbon, NaOAc (2 equiv.), O_2, DMSO, 55 °C, 24 h.

Reduction of the nitrile group of **28**, followed by protection of the resulting amine, allowed the synthesis of the protected Büchi ketone **17b** in a cascade-type sequence, as shown in Scheme **11**. This was proposed to occur by oxidation of **30** at the allylic position, followed by conjugate addition of both the amide and sulfonamide.



30 **17b**

Scheme 11. *Reagents and Conditions:* (a) i) Pd(0), t-BuOOH, CH_2Cl_2; ii) DBU, CH_2Cl_2, reflux.

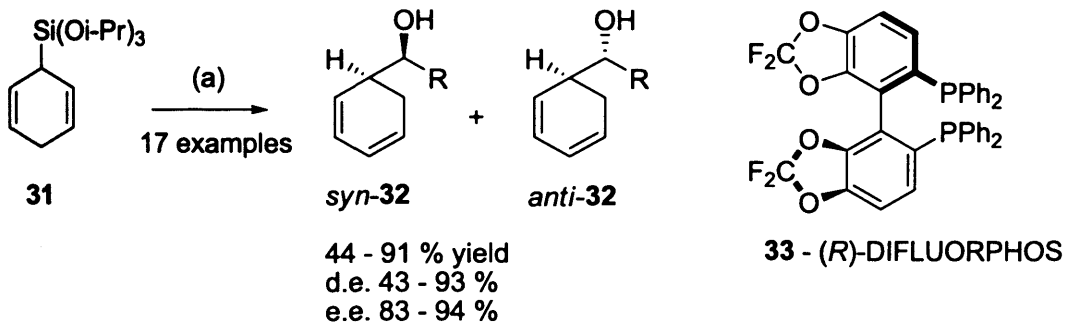
1.2.2 Enantioselective Desymmetrisation of Cyclohexadienes

There are also several examples of the enantiotopic group selective desymmetrisation of cyclohexadienes. Landais has conducted extensive investigation into the dihydroxylation and aminohydroxylation of silylated cyclohexadienes, for example,[10] and also recently reviewed the area.[7]

Studer recently reported the development of a catalytic system capable of mediating the selective addition of a cyclohexadienyl species, generated *in situ* from treatment of silane **31** with TBAF, to a range of aldehydes.[14] Out of the range of metal sources

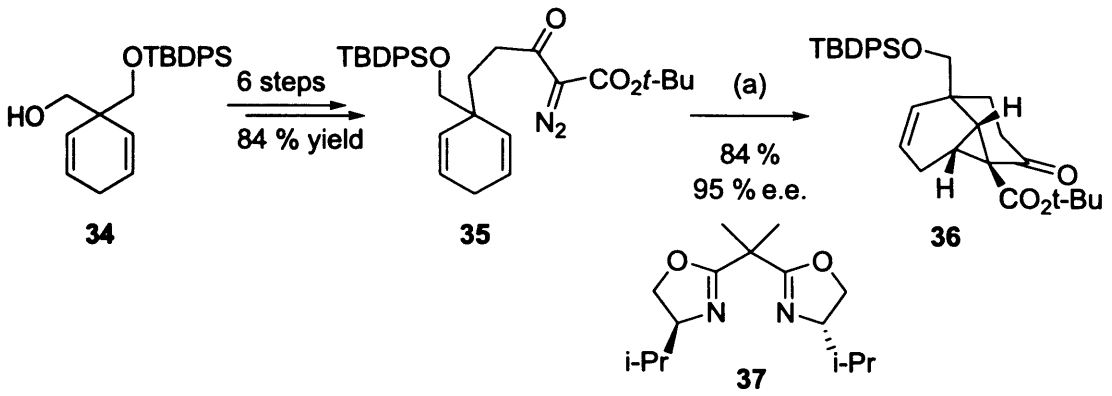
and ligands screened, a combination of copper(I) or (II) triflate and the DIFLUORPHOS ligand **33** provided the highest diastereo- and enantioselectivity, although in less than 40 % yield.

The conditions shown in Scheme **12** were found to be optimal, the addition of 3 equivalents of CF_3CH_2OH resulted in a substantial increase in yield without any loss of selectivity. Application of these conditions to a range of aromatic and heteroaromatic aldehydes provided compounds **32** in good yield and with comparable enantioselectivity to that previously reported to be obtained from the use of a stoichiometric amount of a chiral titanium complex.[15] Diastereoselectivity, favouring the formation of *syn*-**32**, was also good, although lower, in many cases, than that found in the corresponding reactions with the titanium complex.



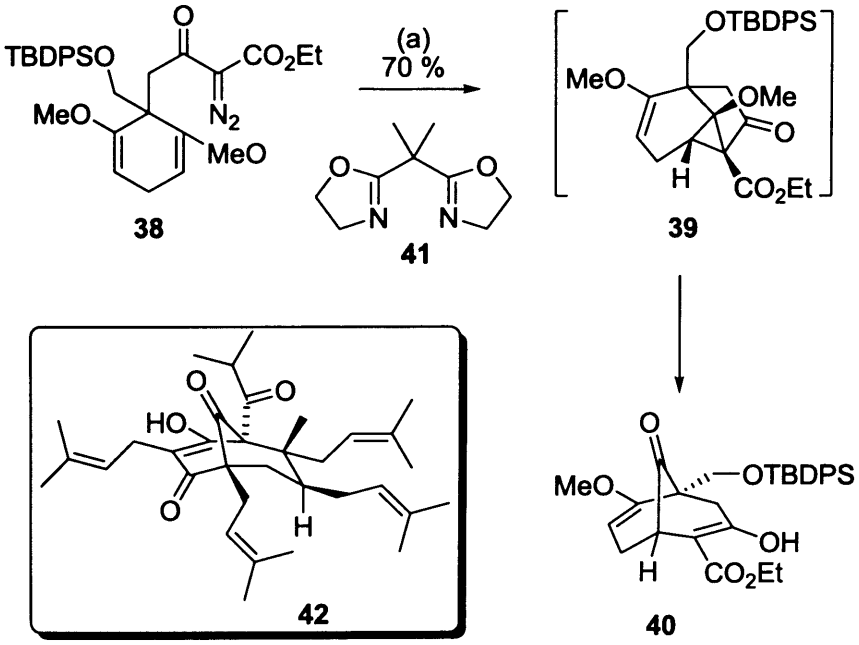
Scheme 12. *Reagents and Conditions:* **31** (3 equiv.), $Cu(OTf)_2$ (10 mol %), **33** (10 mol %), CF_3CH_2OH (3 equiv.), TBAF (1 equiv.), ArCHO (1 equiv.), THF, -25 °C, 20 h.

Nakada recently reported a catalytic asymmetric intramolecular cyclopropanation of a cyclohexadiene derived α-diazo-β-ketosulfone,[16] later also applying the procedure to the analagous β-ketoesters. Diazo compound **35**, prepared by a rather lengthy, although straightforward and efficient sequence, was cyclised in excellent yield and enantioselectivity with a catalyst based on chiral bisoxazoline **37**, as shown in Scheme **13**.[17]



Scheme 13. *Reagents and Conditions:* (a) $Cu(OTf)_2$ (10 mol %), **37** (15 mol %), toluene, room temp., 4 h.

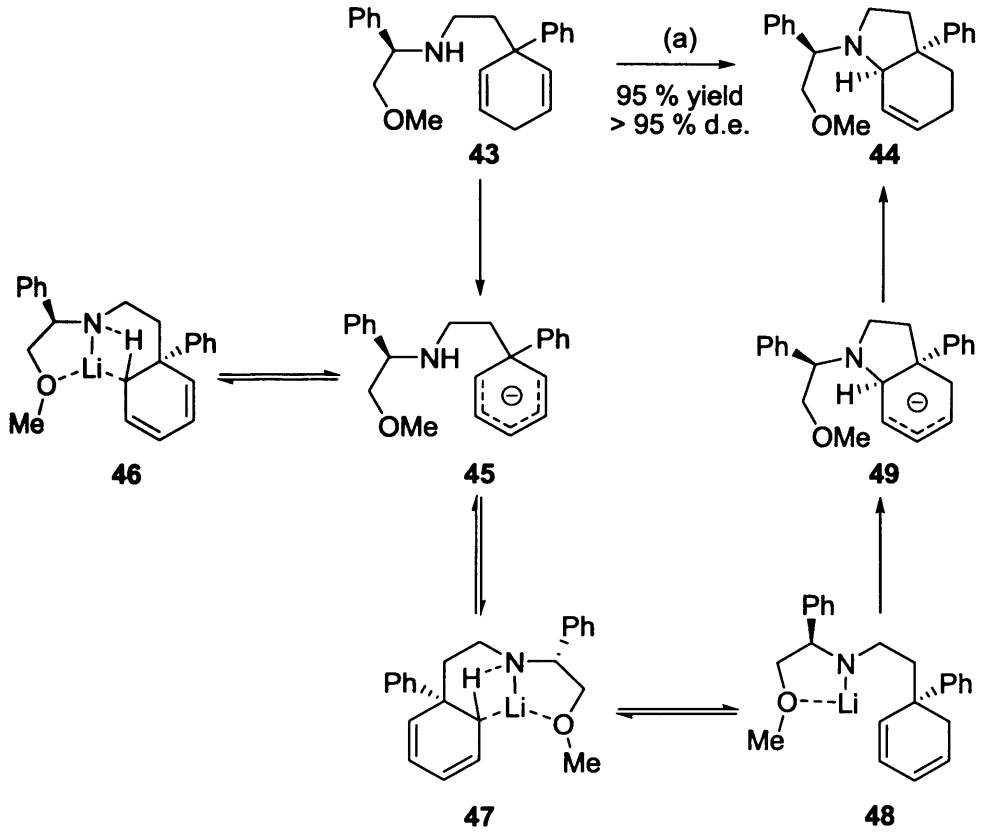
The potential application of this approach to the natural product hyperforin **42**, shown in Scheme **14**, was then demonstrated, although with an achiral bisoxazoline ligand. Diazo compound **38**, derived *via* the Birch reduction of 2,6-dimethoxybenzoic acid, was cyclised to intermediate **39**.[18] Treatment with $ZnCl_2$ then allowed fragmentation to the bicyclo[3.3.1]nonane ring system found in **42**.



Scheme 14. *Reagents and Conditions:* (a) i) $Cu(OTf)_2.C_6H_6$ (5 mol %), **41** (15 mol %), toluene, 80 °C, 1.5 h; ii) $ZnCl_2$ (1.5 equiv.), room temp., 3.5 h.

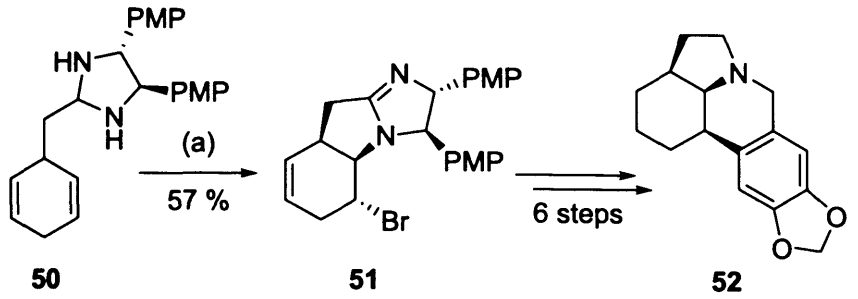
1.3 Diastereoselective Desymmetrisation of Cyclohexadienes

A novel diastereoselective desymmetrisation was reported recently by Landais.[19] Attempted base catalysed hydroamination of amine **43**, shown in Scheme **15**, generated a cyclised product in high yield and diastereoselectivity. On closer inspection of the data, however, the product was determined to be the allylic amine **44**, which is unlikely to result from the expected process. The mechanism proposed to explain this finding involves an initial diastereoselective protonation of cyclohexadienyl anion **45**, favouring the formation of intermediate **48**. Addition of the amide anion to this diene, followed by protonation of the allylic anion **49** at the less hindered position, yields the product **44**.



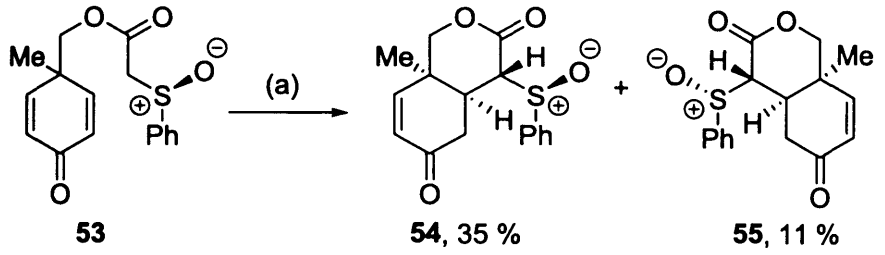
Scheme 15. *Reagents and Conditions:* (a) BuLi (20 mol %), THF, 20 °C, 4 h.

Fujioka and Kita reported the diastereoselective desymmetrisation of aminal **50** in a bromocyclisation reaction. Further oxidation of the initial product resulted in the isolation of dihydroimidazole **51** in good yield, as shown in Scheme **16**.[20] This allowed an efficient synthesis of (-)-γ-lycorane **52**.



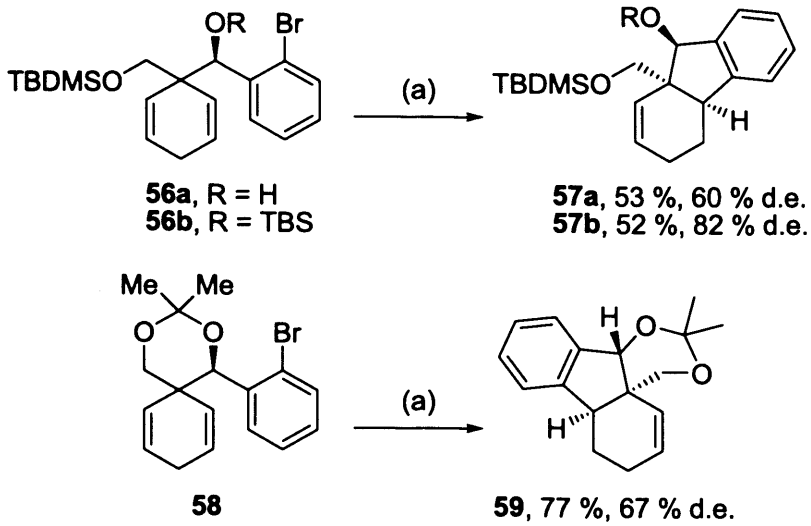
Scheme 16. *Reagents and Conditions:* (a) NBS (2.1 equiv.), CH_2Cl_2. PMP = 4-MeO-C_6H_4.

Recent examples from our group include the conjugate addition reaction shown in Scheme **17**, the chiral sulfoxide exerting moderate diastereocontrol over the cyclisation of compound **53**.[21]



Scheme 17. *Reagents and Conditions:* (a) *t*-BuOK, THF, room temp.

The radical cyclisation reactions shown in Scheme **18** were more successful. The chiral secondary alcohol of compound **56a** directing addition of the generated aryl radical with good diastereocontrol. This was further improved by the addition of the bulky silyl ether of **56b**, while protection as an acetonide in **58** resulted in formation of the other diastereoisomer, also with fairly good stereocontrol.[22]



56a, R = H
56b, R = TBS

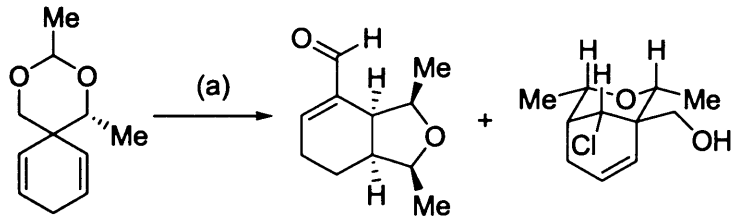
57a, 53 %, 60 % d.e.
57b, 52 %, 82 % d.e.

58

59, 77 %, 67 % d.e.

Scheme 18. *Reagents and Conditions:* (a) Bu_3SnH, AIBN, PhH, reflux.

Also, the first reported group selective Prins reaction, as shown in Scheme **19**, finally demonstrated excellent diastereoselectivity, with no minor diastereoisomers of either aldehyde **61a** or tetrahydropyran **62a** apparent by NMR analysis.[23] The yields were poor, however, and the optimisation of this reaction is discussed in the following chapter.



60a

61a, 14 %

62a, 3 %

Scheme 19. *Reagents and Conditions:* (a) $TiCl_4$, CH_2Cl_2, -78 °C, 2 h.

1.4 Objectives

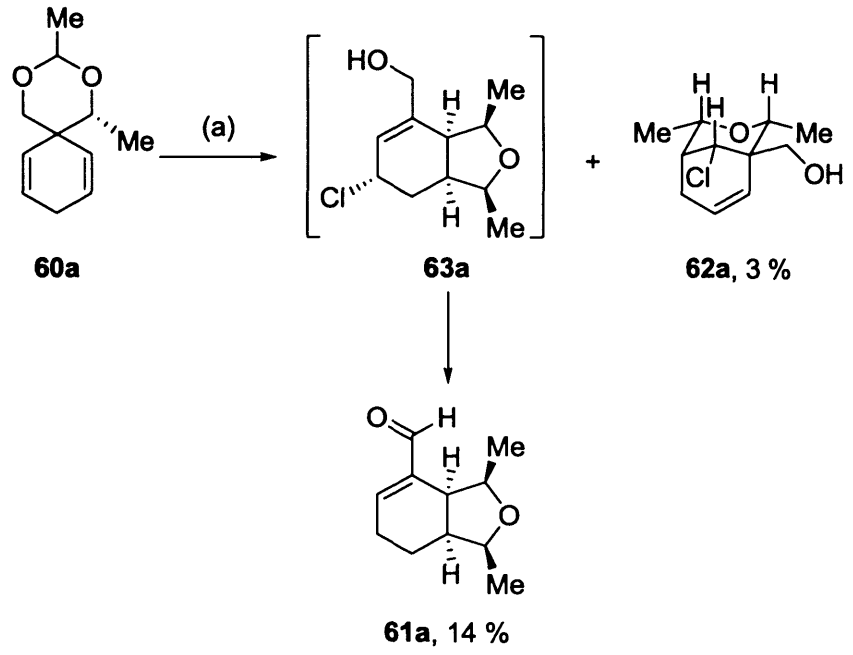
The aim of the project was to investigate possible alternative and / or improved methods of desymmetrising cyclohexadiene based compounds, and also to demonstrate the value of such methods by their application to synthesis of appropriate targets.

Chapter 2

Prins Cyclisation Reactions of 1,4-Cyclohexadienes

2.1 Introduction

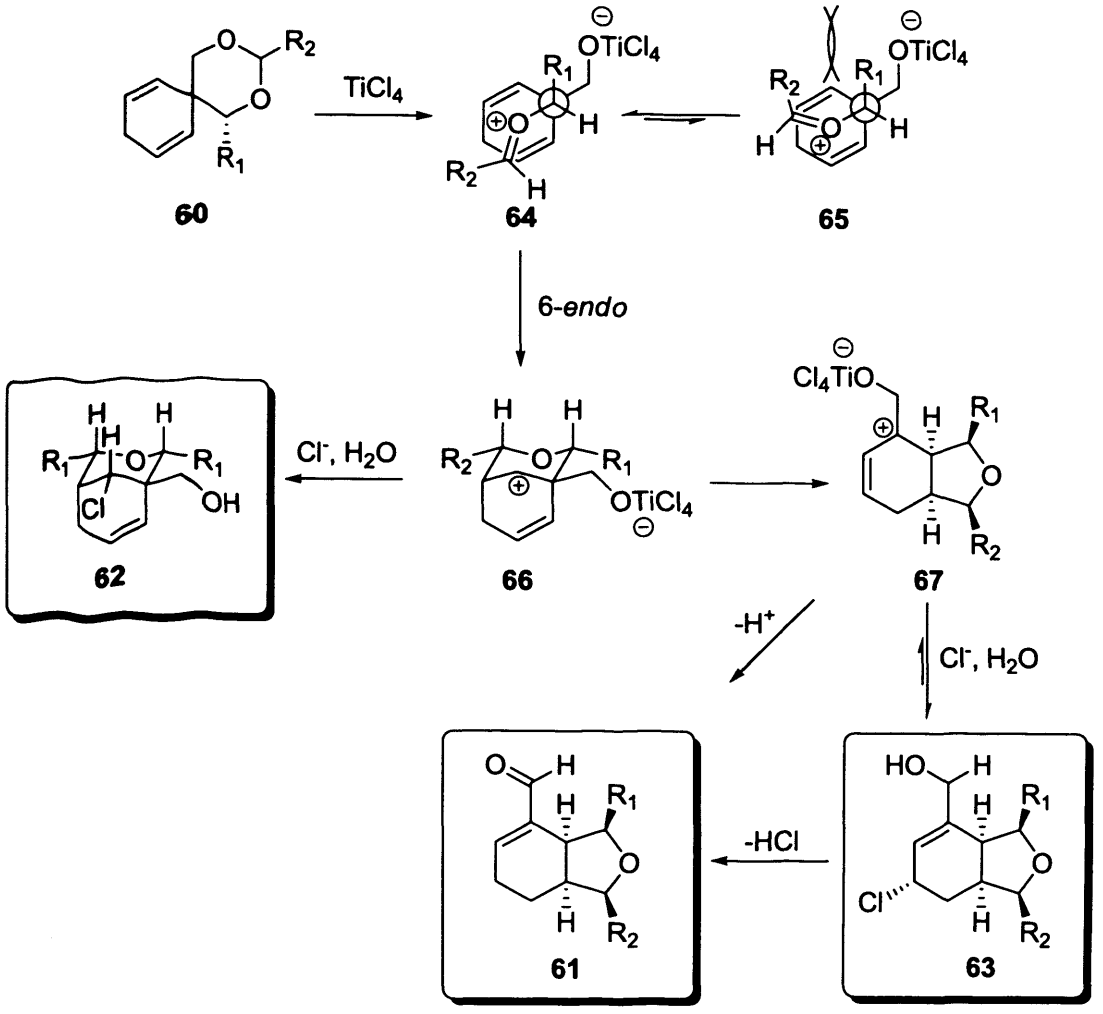
The Prins reaction of cyclic acetal derivatives permits an extremely versatile entry into highly functionalised tetrahydropyrans,[24] and has been widely used in total synthesis.[25] Previous work within the Elliott group had established that the Prins reaction could be used to effect a novel and highly diastereoselective desymmetrisation of chiral cyclohexa-1,4-diene derived acetals.[26] For example, treatment of acetal **60a** with $TiCl_4$ resulted in the formation of three compounds, **61a**, **62a** and **63a**, shown in Scheme **20**.



Scheme 20. *Reagents and Conditions:* (a) $TiCl_4$, CH_2Cl_2, -78 °C, 2 h.

The ^1H NMR spectrum obtained from the crude reaction mixture showed it to consist predominantly of alcohol **63a.** This product was found to be relatively unstable, however, and only pyran **62a** and aldehyde **61a** were isolated by chromatography.

The mechanism shown in Scheme **21** was proposed by El Sayed to explain this result. The stereochemistry of the products is determined by the Prins cyclisation of the oxocarbenium ion generated from acetal **60**. Of the two chair conformers, **64** and **65**, from which a transition state is accessible, **64** is the least destabilised by $A^{1,3}$ strain generated between the R_1 and R_2 groups. Cyclisation therefore favours the formation of carbocation **66** with the stereochemistry indicated.

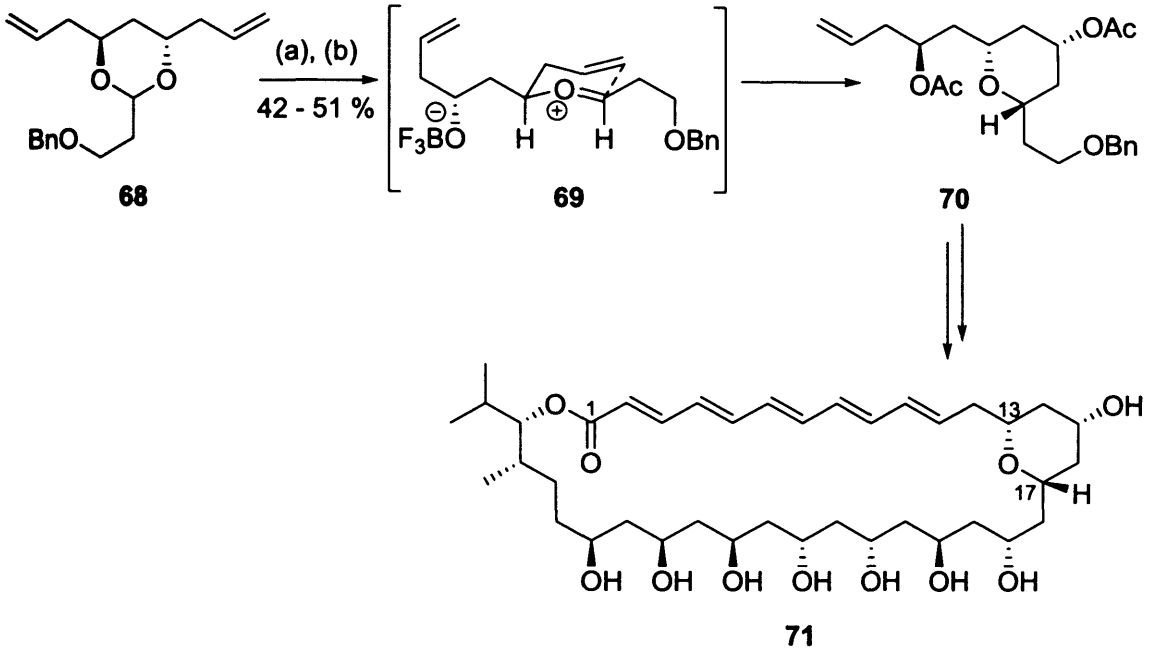


Scheme 21. Mechanism of the Prins cyclisation and subsequent reactions.

The final products suggest that two pathways of similar importance are available to this intermediate. Addition of a chloride ion affords the stable tetrahydropyran **62**. This depends, however, on the availability of a chloride ion, if there are none in the vicinity a lesser degree of stabilisation can be attained by an intramolecular carbocation rearrangement, for which the Prins reaction is well known. A Wagner-Meerwein shift results in the formation of tetrahydrofuran **67**, where the cation now occupies a position where it is both tertiary and allylic. This is far less unstable, and, although it will still readily trap a chloride ion, it will also release it again more easily, thereby allowing equilibration to the thermodynamically favoured enal **61**.

Suprisingly, there was only one report that could be found in the literature at the time where the Prins reaction had been employed in a desymmetrisation. Rychnovsky, during his synthesis of 17-deoxyroflamycoin **71**, reported the

preparation of tetrahydropyran intermediate **70** by a diastereoselective Prins cyclisation of diene **68**, shown in Scheme **22**.[27] While this is a desymmetrisation, it is simply a result of monofunctionalisation, the possibility of group selectivity between the enantiotopic double bonds was not investigated.

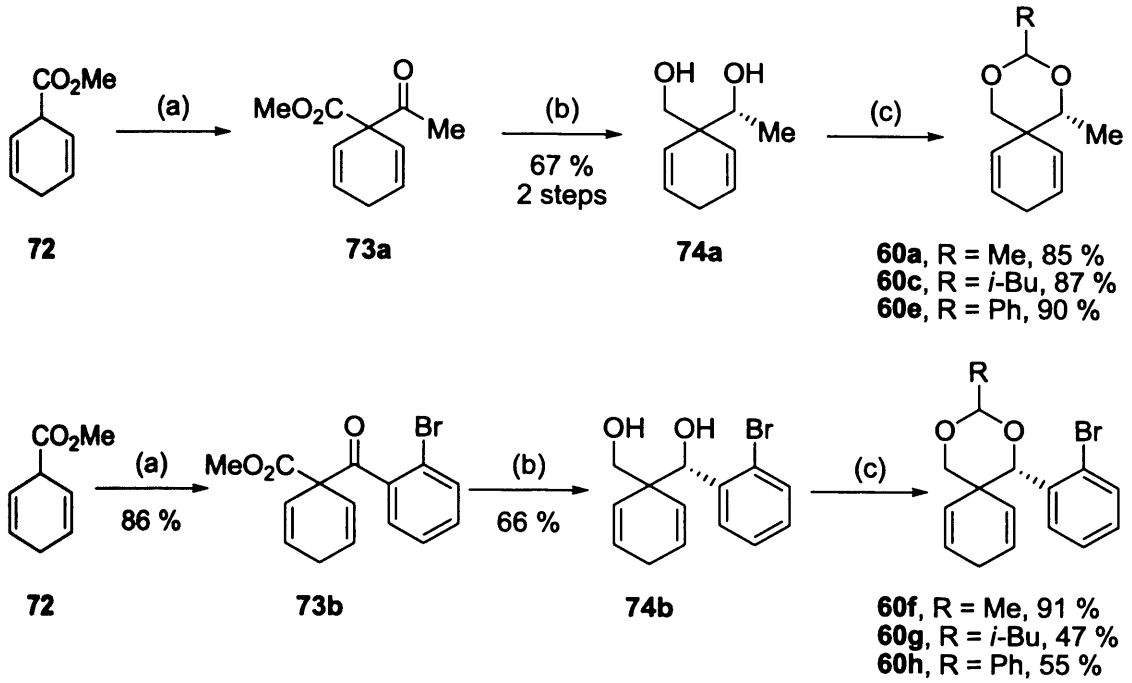


Scheme 22. *Reagents and Conditions:* (a) $BF_3.OEt_2$, HOAc, cyclohexane; (b) Ac_2O, Et_3N, DMAP.

The novel results found by El Sayed were thus felt to potentially be very useful, however, significant optimisation would be required. As this work was begun towards the end of her project there was insufficient time for this to be investigated. I took over the project with this aim, beginning by attempting to optimise the reaction conditions and purification procedure.

2.2 Results and Discussion

A range of substrates were prepared by the procedure reported by El Sayed,[26] as shown in Scheme **23**. These were obtained as single diastereoisomers, presumably the *syn* isomers which allow both substituents to occupy equatorial positions. As the acetal stereocentre is lost on oxocarbenium ion formation, this aspect was not investigated further. The 2-bromophenyl substituent of diol **74b** was maintained for consistency with the results and data obtained by El Sayed.[21]



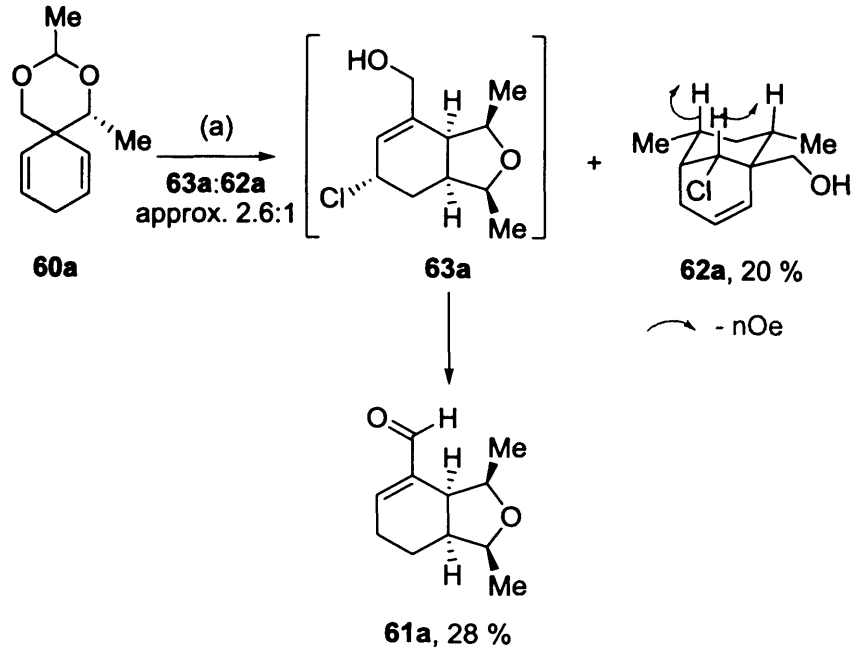
Scheme 23. *Reagents and Conditions:* (a) i) LDA, THF, -78 °C; ii) CH_3COCl or 2-BrC_6H_4COCl, -78 °C to r.t.; (b) $LiAlH_4$, THF; (c) RCHO, PPTS, CH_2Cl_2 or RCHO, H_2SO_4, DMF.

2.2.1 $TiCl_4$ Mediated Prins Reactions

Before looking into the use of other catalysts the reactions were first repeated by the originally reported procedure. As the ^1H NMR spectra of the crude product mixtures previously obtained appeared to be relatively clean it was suspected that reasonable yields could be achieved simply by careful repetition of the reactions and chromatography. Frequent monitoring by tlc, for example, showed that much less time was sometimes required for complete consumption of the substrate.

The simplest of the substrates, acetal **60a**, was chosen for the first attempt. Analysis by tlc showed the complete consumption of the starting acetal after only one hour and the reaction was promptly quenched. Only two compounds were observed in the ^1H NMR spectrum of the crude product, allylic alcohol **63a**, and pyran **62a**, in an approximate ratio of 2.6:1, as shown in Scheme **24**. The formation of aldehyde **61a**, noted to be present in the crude material obtained by El Sayed, would appear avoidable by allowing the reaction to proceed only for the minimum time required.

The crude product was chromatographed immediately and the time spent in contact with the silica gel stationary phase kept as brief as possible in an attempt to minimise the decomposition of aldehyde **63a**. The two fractions that were eleuted were, nonetheless, found to contain the same products isolated by El Sayed, although the yield was greatly improved, approaching 50 % in total.



60a **63a** **62a**, 20 %

61a, 28 %

Scheme 24. *Reagents and Conditions:* (a) $TiCl_4$ (2 equiv.), CH_2Cl_2, -78 °C, 1 h.

The stereochemistry of these products was unable to be assigned by El Sayed, only pyran **62a** showing a useful nOe between one, or both, of the protons indicated, lending tentative support to the structure as shown.

Although the combined isolated yield was reasonable, the isolated yields of individual compounds were still poor, limiting the utility of the reaction. The estimated yield of alcohol **63a** that could be expected, were it stable enough to be isolated, was a much more acceptable 52 %. This value is unlikely to be particularly accurate, though the discrepancy between this and the yield of aldehyde **61a** isolated is large enough to suggest that a significant improvement may be realised by prevention of this transformation.

The silica gel used for chromatography was thought to be the most likely culprit, and the reaction repeated and chromatographed on silica neutralised by washing with triethylamine in petroleum ether. This was unsuccessful, as were attempts with

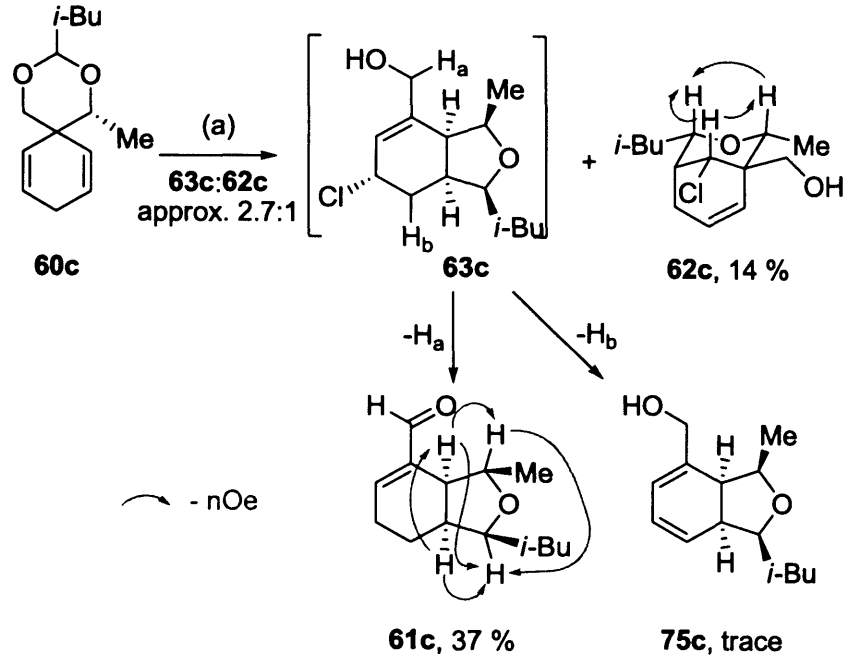
alumina, in both neutral and basic forms; the same two products being found in each case.

We next considered the possibility that derivatisation of alcohol **63a** may increase its stability. Treatment of the crude reaction mixture with AcCl, Et_3N and DMAP, however, resulted only in decomposition to aldehyde **61a**, as did attempted silyl ether formation with TBDMSCl and imidazole. Although derivatisation may be possible under acidic conditions, we did not invesitgate this matter any further.

Isobutyl acetal **60c** was then cyclised, as shown in Scheme **25**. This required a slightly longer reaction time, possibly due to the more crowded acetal ring. The ^1H NMR spectrum of the crude material showed it to consist of alcohol **63c** and pyran **62c**, in approximately the same ratio found in the previous example. In this case, however, aldehyde **61c** was isolated in a yield more in line with that expected from this ratio.

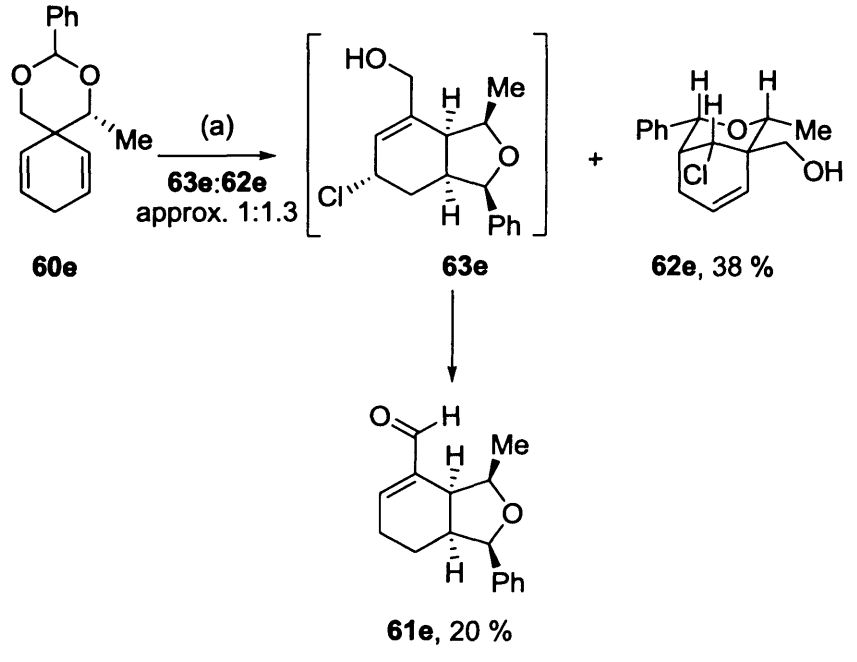
A small amount of a third compound, proposed as being diene **75c**, was also isolated. Although this could not be fully characterised, the ^1H NMR spectrum obtained from this material corresponded closely to the spectra given by related compounds of this structure. This is presumably formed by the elimination of H_b from alcohol **63c**.

The stereochemistry of aldehyde **61c** and pyran **62c** was assigned by El Sayed based on the results of nOe experiments. Aldehyde **61c** showed nOe's between all four protons of the tetrahydrofuran ring, these must, therefore, all lie on the same side of this ring. In compound **62c**, it was determined that the three protons shown were in close proximity, and therefore all axial on the tetrahydropyran ring.



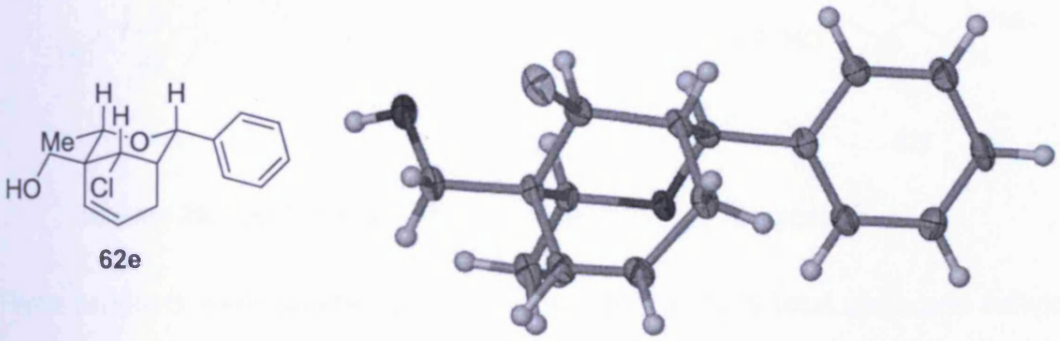
Scheme 25. *Reagents and Conditions:* (a) $TiCl_4$ (2 equiv.), CH_2Cl_2, -78 °C, 2 h.

Cyclisation of acetal **60e** also required 2 hours for completion, yielding a crude material composed of alcohol **63e** and pyran **62e**, as shown in Scheme **26**. In this case, however, the pyran **62e** was found to be the major product, suggesting that rearrangement following the Prins cyclisation is less favourable. A similar preference was also observed on cyclisation of benzaldehyde derived acetal **60h**, shown in Scheme **30**, Page 24, although the reason for this is not clear.



Scheme 26. *Reagents and Conditions:* (a) $TiCl_4$ (2 equiv.), CH_2Cl_2, -78 °C, 2 h.

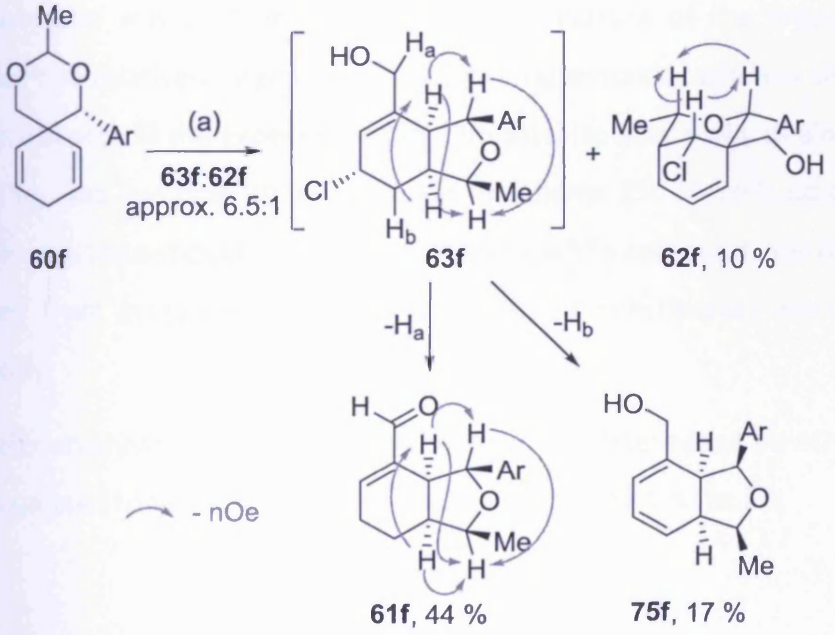
Although no diagnostic nOe's were observed by El Sayed in the spectra obtained from these products, the tetrahydropyran **62e** was crystalline and its structure determined by X-ray crystallography to be as shown in Fig. **1**, consistent with previous results and predictions.



62e

Fig. 1. ORTEP plot of the crystal structure of compound **62e**. Thermal ellipsoids drawn at the 50 % probability level.[26]

The first of the 2-bromophenyl substituted series, acetal **60f**, required even longer to reach completion. The ratio of the two products was determined from the ^{1}H NMR spectrum of the crude material to lie significantly in favour of the tetrahydrofuran **63f**, as shown in Scheme **27**.

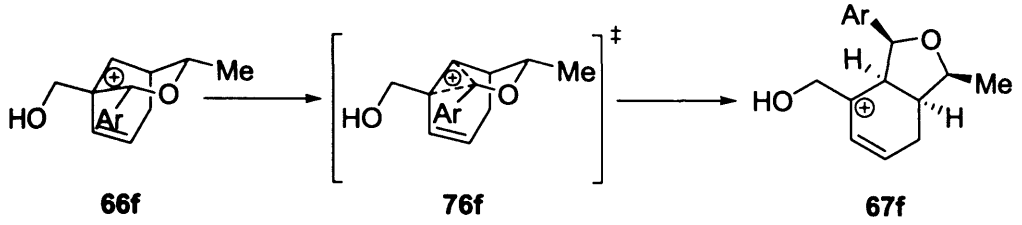


60f **63f** **62f**, 10 %

61f, 44 % **75f**, 17 %

Scheme 27. *Reagents and Conditions:* (a) $TiCl_4$ (2 equiv.), CH_2Cl_2, -78 °C, 4 h. Ar = 2-Br-C_6H_4.

This may be due to stabilisation of transition state **76f**, shown in Scheme **28**, by delocalisation of the positive charge around the aromatic ring, thereby increasing the contribution from the rearrangement pathway.



66f **76f** **67f**

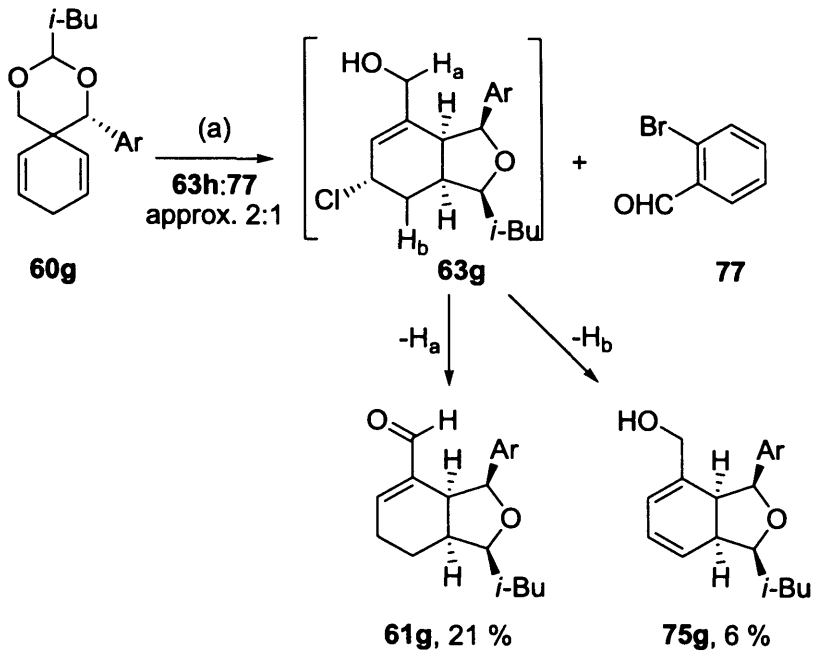
Scheme 28. Possible stabilisation of cation during rearrangement.

Three products were isolated by chromatography in 71 % total yield, and individual yields were in close agreement with the ratio observed in the crude material. The formation of diene **75f** was again observed, this time in a significant amount. A possible explanation is the increased steric hindrance of proton H_a caused by the bulky aryl substituent, increasing the proportion of elimination by loss of H_b.

With the exception of diene **75f**, the stereochemistry of the products was determined by El Sayed based on the observation of the indicated nOe's.

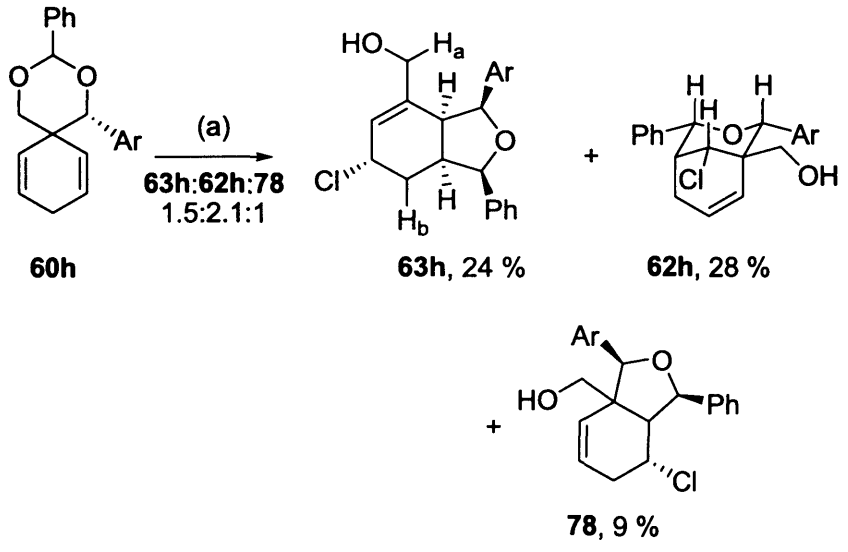
Cyclisation of acetal **60g** appeared to be complete after 2 hours, although significant decomposition was evident in the ^{1}H NMR spectrum of the crude product. The presence of a relatively large amount of 2-bromobenzaldehyde was also apparent, as was the absence of the expected pyran. The total isolated yield, of aldehyde **61g** and diene **75g**, was less than 30 %, as shown in Scheme **29**. There is no obvious reason why this substrate should give such a low yield, while comparatively high yields were obtained from acetals **60c** and **60f** where these substituents were each present separately.

The stereochemistry of the products could not be determined by nOe experiments, but is expected to be as indicated by analogy with previous results.



Scheme 29. *Reagents and Conditions:* (a) $TiCl_4$ (2 equiv.), CH_2Cl_2, -78 °C, 2 h. Ar = 2-Br-C_6H_4.

Cyclisation of the final substrate, acetal **60h**, as shown in Scheme **30**, gave several unique results. Firstly, the reaction was complete within only 15 minutes, in contrast to the relatively slow cyclisation of the mono-aryl substituted acetals **60e** and **60f**.

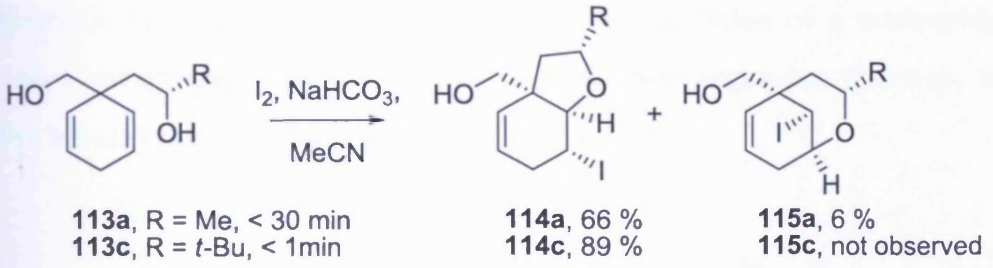


Scheme 30. *Reagents and Conditions:* (a) $TiCl_4$ (2 equiv.), CH_2Cl_2, -78 °C, 15 min. Ar = 2-Br-C_6H_4.

Secondly, the allylic alcohol **63h** was, in this case, sufficiently stable for isolation by chromatography. The reason for this is not clear, although access to both positions required for elimination does appear to be somewhat hindered.

Finally, compound **78**, the product of Prins cyclisation *via* a 5-*endo* pathway, was also isolated. A similar trend where increasing substituent bulk leads to preferential formation of the smaller ring size was later observed in iodocyclisation reactions, as shown in Scheme **31**. Although the reason for this is not clear, it may be partly due to a gem-dimethyl type effect on bond angles.

The stereochemistry of allylic alcohol **63h** and the 5-*endo* cyclisation product **78** could not be determined by nOe experiments, the tetrahydropyran **62h**, however, was a crystalline solid and the X-ray crystal structure shown in Fig. **2** was obtained by El Sayed.

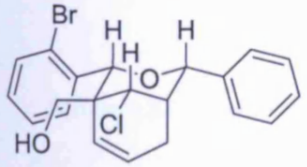


113a, R = Me, < 30 min
113c, R = *t*-Bu, < 1min

114a, 66 %
114c, 89 %

115a, 6 %
115c, not observed

Scheme 31. Effect of steric bulk on regioisomer ratios.



62h

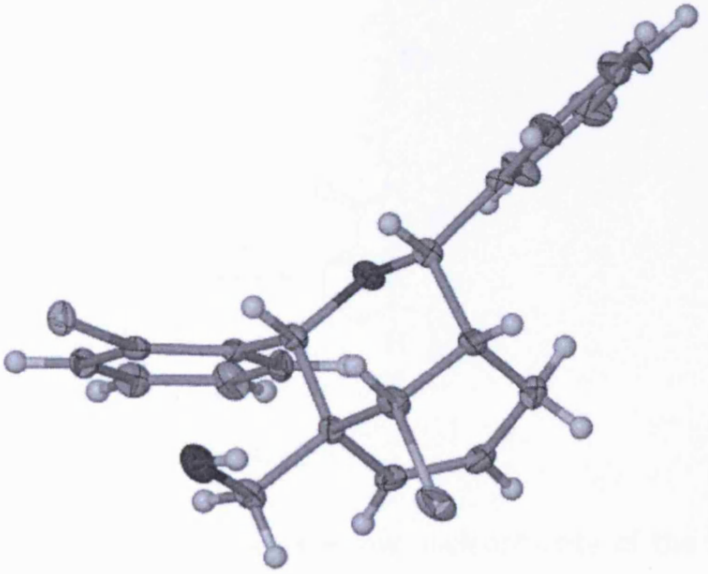
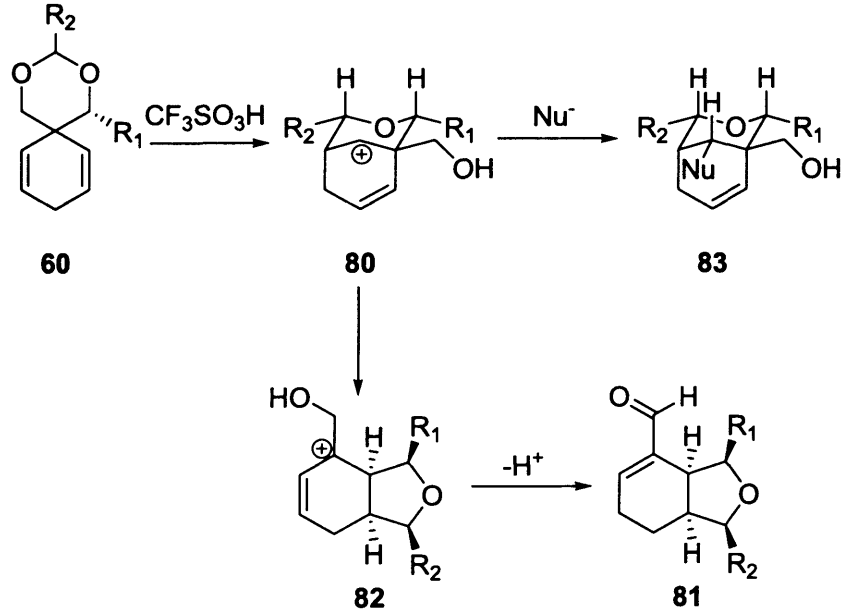


Fig. 2. ORTEP plot of the crystal structure of compound **62h**. Thermal ellipsoids drawn at the 50 % probability level.[26]

In summary, the Prins reaction was applied as a means of desymmetrising cyclohexadienes with high diastereoselectivity. The stereochemistry of the products appears to correspond to cyclisation through the more stable of the two possible transition states. Total yields were improved significantly over those found initially, mostly by the minimisation of reaction times and prompt purification following work-up. Low selectivity between several possible reaction pathways remained a problem, however, and no single compound could be obtained in greater than 50 % yield.[28]

2.2.2 Triflic Acid Mediated Prins Reactions

A possible solution to the selectivity problem may be to employ an acid catalyst with a less nucleophilic counter-ion. The cationic Prins cyclisation product **80**, shown in Scheme **32**, would then be forced to undergo rearrangement, ultimately leading to the tetrahydrofuran derivative **81**. Alternatively, the addition of a nucleophile to serve as a cation trap may, by suppressing the rearrangement pathway, allow selective access to tetrahydropyran derivatives **83**.

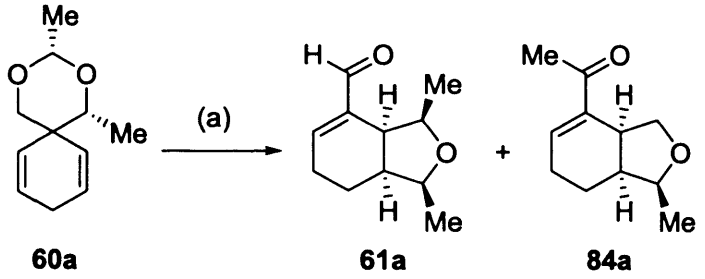


Scheme 32. Possible Prins Reactions with Triflic Acid.

Triflic acid seemed ideally suited to this task, given the low nucleophilicity of the triflate anion. An ice-cold solution of acetal **60a** in CH_2Cl_2 was, therefore, treated with 1.5 equivalents of triflic acid, as shown in Scheme **33**. Examination of the ^1H

NMR spectrum of the crude product confirmed this hypothesis, showing aldehyde **61a** to be the dominant product and no evidence of the presence of pyran **62a**.

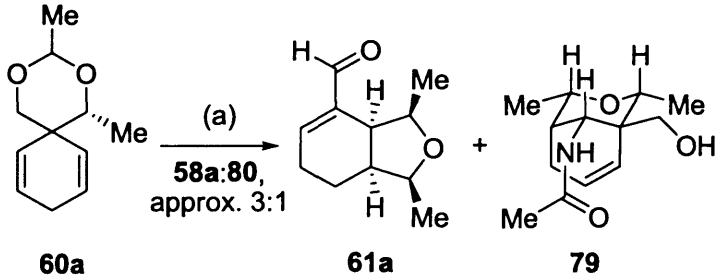
Aldehyde **61a** was obtained in good yield following chromatography, as well as a small amount of ketone **84a**, presumably due to the reduced regioselectivity of acetal opening. As this constituted less than 10 % of the total product, the selectivity was deemed more than adequate, and the yield of **61a** was more than double that obtained from the use of $TiCl_4$.



60a **61a** **84a**

Scheme 33. *Reagents and Conditions:* (a) TfOH (1.6 equiv.), CH_2Cl_2, 0 °C, 15 min.

The possibility of favouring tetrahydropyran formation was tested by performing the reaction in a solution of acetonitrile, as shown in Scheme **34**. This proved ineffective at suppressing rearrangement, as the major product evident in the ^1H NMR spectrum obtained from the crude material was still aldehyde **61a**. A minor product was apparent, however, in a ratio of 1:3 to aldehyde **61a**, that appeared to fit the structure of pyran **79**, although this was not isolated and characterised further due to the poor selectivity.

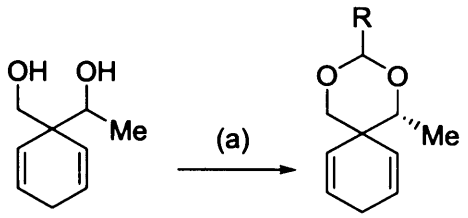


60a **61a** **79**

Scheme 34. *Reagents and Conditions:* (a) TfOH (2 equiv.), MeCN, 0 °C.

Pleased with the outcome of the first example, we synthesised two series of substrates in order to investigate further. Two additional acetals were added to the

series derived from methyl substituted diol **74a**, shown in Scheme **35**, in order to obtain a more complete picture of the scope and limitations of the reaction.

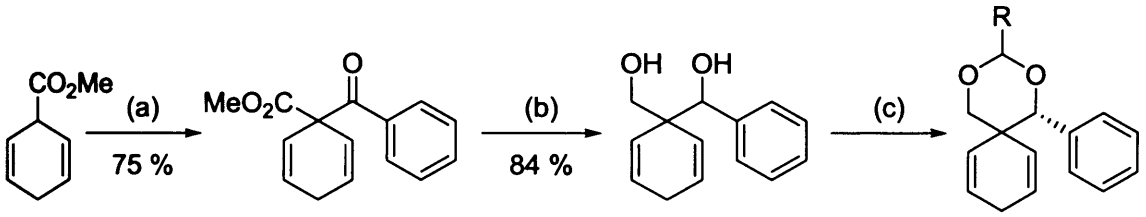


74a

60b, R = *n*-Bu, 88 %
60d, R = *t*-Bu, 75 %

Scheme 35. *Reagents and Conditions:* (a) RCHO, PPTS, CH_2Cl_2.

Rather than prepare a series of aryl substituted acetals from diol **74b**, we chose to use diol **74c** instead for simplicity. Acetal formation with the same five aldehydes provided all but the *t*-Bu substituted member of series **85a-e**, shown in Scheme **36.**

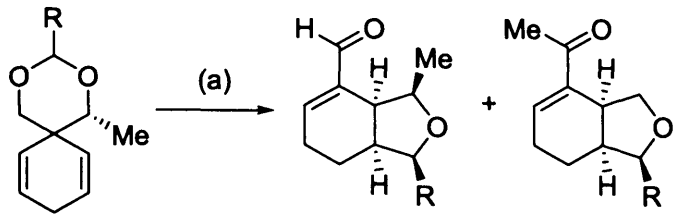


72 **73c** **74c**

85a, R = Me, 71 %
85b, R = *n*-Bu, 66 %
85c, R = *i*-Bu, 66 %
85d, R = *t*-Bu, 0 %
85e, R = Ph, 42 %

Scheme 36. *Reagents and Conditions:* (a) i) LDA, THF, PhCOCl, -78 °C to r.t.; (b) $LiAlH_4$, THF; (c) RCHO, PTSA, CH_2Cl_2/DMF (approx 10:1).

The remaining methyl substituted acetals, **60b-e**, cyclised similarly to **60a**, giving the results summarised in Table **2**. Yields were reasonably good in most cases, with the exception of Entries **4** and **5**. Acetal **60d** was simply very slow to cyclise, this could likely be overcome by the use of a larger excess of triflic acid, which can be seen in Entries **1-3** to result in a large increase in rate. The aryl substituted acetal, **60e**, on the other hand, cyclised extremely rapidly, the comparatively low yield apparently a result of product decomposition.

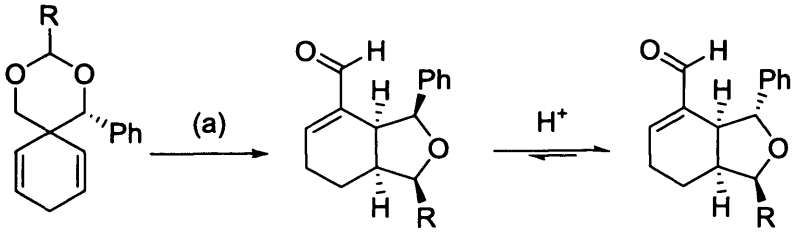


60a-e **61a-e** **84a-e**

Entry	*Acetal*	*R =*	*TfOH (equiv.)*	*Time (min)*	*Yield **61** (%)*	*Yield **84** (%)*
1	**60a**	Me	1.6	15	66	6
2	**60b**	*n*-Bu	1.2	90	60	8
3	**60c**	*i*-Bu	1.1	90	53	7
4	**60d**	*t*-Bu	1.1	240	11[a]	5
5	**60e**	Ph	1.5	5	42	trace

Table 2. *Reagents and Conditions:* (a) TfOH, CH_2Cl_2, 0 °C to r.t. [a]25 % of starting material was recovered.

Cyclisation of the phenyl substituted acetals was also quite successful, the results are summarised in Table **3**. Although the formation of minor by-products was observed in this series also, these were found to be the epimeric aldehydes **87**. Regioselectivity of the initial acetal opening appears to be higher in this series, as none of the ketones found in the previous series were detected. This is perhaps due to increased steric hindrance from the larger phenyl substituent.



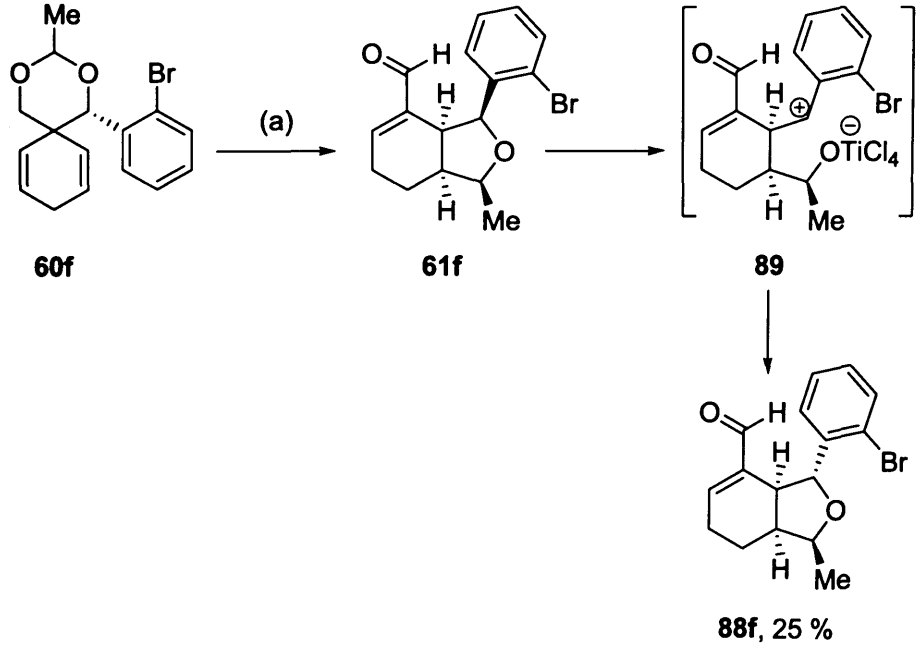
85a-e **86a-e** **87a-e**

Entry	*Acetal*	*R =*	*TfOH (equiv.)*	*Time (min)*	*Yield **86** (%)*	*Yield **87** (%)*
1	**85a**	Me	5	15	64	0
2	**85a**	Me	1.1	60	50	8
3	**85a**	Me	1.5	90	0	61
4	**85b**	*n*-Bu	1.1	60	51	4
5	**85c**	*i*-Bu	5	15	58	0
6	**85e**	Ph	5	15	61	0

Table 3. *Reagents and Conditions:* TfOH, CH_2Cl_2, 0 °C to r.t.

Epimerisation was also noted to occur by El Sayed when Prins cyclisations of aryl substituted substrates with $TiCl_4$ were allowed to warm to room temperature for extended periods of time. Isomerisation of aldehyde **61f** to **88f**, shown in Scheme **37**, for example, presumably occurs *via* ring opening of the heterocycle to give the stabilised benzylic carbocation **89**.[26] This was easily avoided in cyclisations catalysed by triflic acid by employing a fairly large excess of acid. Cyclisation then proceeded extremely rapidly allowing isolation of the kinetic products in good yield, as in Entries **1**, **5** and **6**, for example.

Alternatively, the extended reaction time of Entry **3** allowed complete epimerisation of aldehyde **86a**, affording aldehyde **87a** in good yield. This would presumably also be successful with the other alkyl substituted substrates, though this was not investigated. Acetal **85e** was best cyclised under the conditions of Entry **6**, longer reaction times allowing decomposition of the product to occur.



60f **61f** **89** **88f**, 25 %

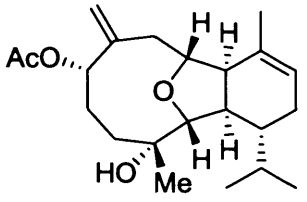
Scheme 37. *Reagents and Conditions:* (a) $TiCl_4$, CH_2Cl_2, -78 °C to r.t., 24 h.

2.3 Conclusion

The Prins desymmetrisation of chiral 2,5-cyclohexadiene based acetals with $TiCl_4$ was shown to allow access to several complex products with essentially complete diastereocontrol. Though such compounds may be valuable synthetic intermediates,

the lack of control over reactivity resulted to low yields, limiting the utility of the method.

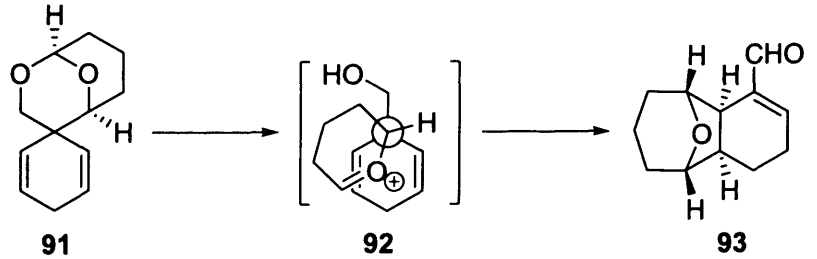
The cause of the low selectivity was determined to be due to competing rearrangement and quenching of the carbenium ion produced by the Prins cyclisation. By employing triflic acid instead, the carbenium ion is forced to undergo rearrangement resulting in the selective formation of tetrahydrofuran derivatives. The procedure developed was shown to be applicable to a range of substrates and is likely to be of use in the synthesis of complex molecules. Investigations into the synthesis of the cladiellin diterpene 7-deacetoxyalcyonin acetate **90**, for example, have since been undertaken by our group.[29]



90

Fig. 3. 7-deacetoxyalcyonin acetate.

Although this requires that the two pairs of ring junction protons be *anti*, in contrast to the *syn* relationship obtained thus far, it was thought that this be achieved by incorportation of a tethering chain, such as in acetal **91**, shown in Scheme **38**. The resulting oxocarbenium ion would favour the near-attack conformation **92** over the alternative eclipsed conformation, thus generating the desired stereochemistry.

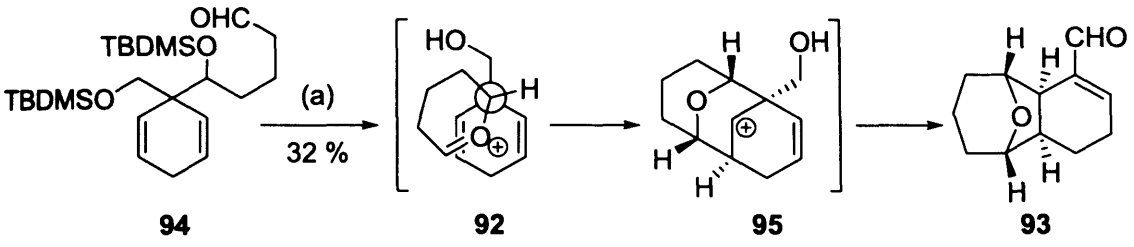


91 **92** **93**

Scheme 38.

This was recently shown by a colleague to be the case, simply treating *bis*-silyl protected aldehyde **94** with triflic acid effected concomitant deprotection,

oxocarbenium ion formation and Prins cyclisation, followed by rearrangement to aldehyde **93**, as shown in Scheme **39**.



94 **92** **95** **93**

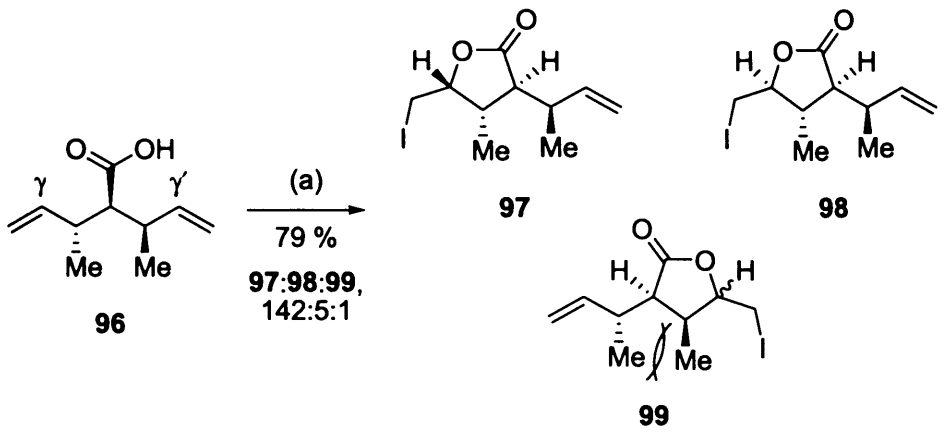
Scheme 39. *Reagents and Conditions:* (a) TfOH (1 equiv.), CH_2Cl_2, 0 °C to room temp.

Chapter 3

Iodocyclisation Reactions of 1,4-Cyclohexadienes

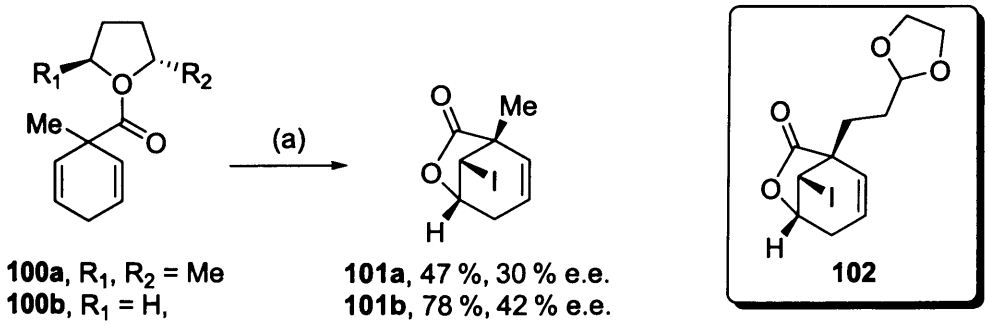
3.1 Introduction

The selective desymmetrisation of a diene in an iodocyclisation reaction was first reported by Kurth over 20 years ago. Cyclisation onto the γ-position of substrate **96** was found to be favoured by a factor of almost 150:1 over cyclisation onto the γ'-position, as shown in Scheme **40**. This group selectivity presumably results from repulsion between the methyl and *iso*-butene substituents in the transition state leading to compound **99**.[30]

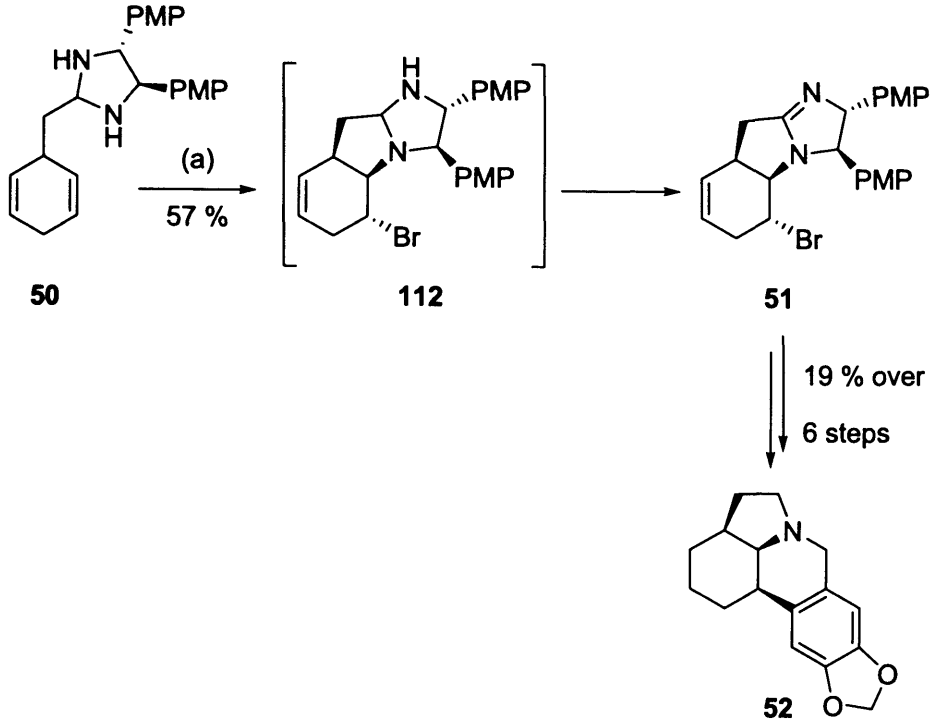


Scheme 40. *Reagents and Conditions:* (a) I_2, CH_2Cl_2, sat. aq. $NaHCO_3$, 20 min.

Hart attempted a similar desymmetrisation of a cyclohexa-2,5-diene, as shown in Scheme **41**, in an effort to prepare intermediate **102** enantioselectively, thereby achieving an asymmetric synthesis of pleurotin.[31] The model substrates, **100a** and **100b**, were found to cyclise with insufficient selectivity, however, and this aspect of the work was abandoned.



Scheme 41. *Reagents and Conditions:* (a) I_2, THF, H_2O.



Scheme 46. *Reagents and Conditions:* (a) NBS (2.1 equiv.), CH_2Cl_2. PMP = 4-MeO-C_6H_4.

The acyclic diene **96** is the only substrate reported where the stereodirecting element is actually within the ring formed by cyclisation, as shown in Fig. **4**. This clearly exerts far greater stereocontrol and suggests that iodocyclisation of cyclohexadienes such as **74**, **116**, and **121**, shown in Scheme **47**, may also occur with very high group selectivity.

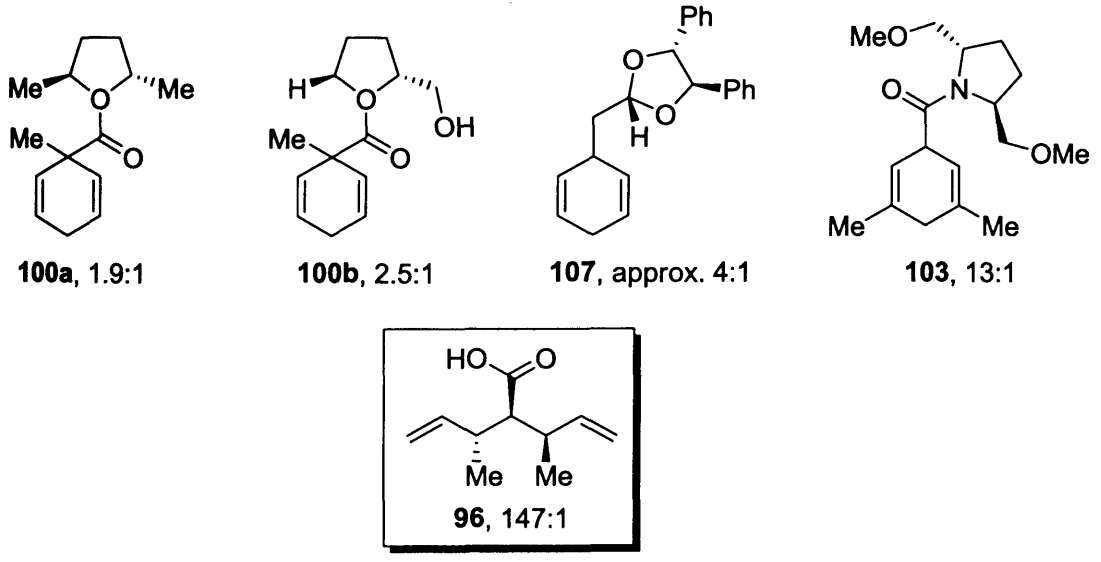
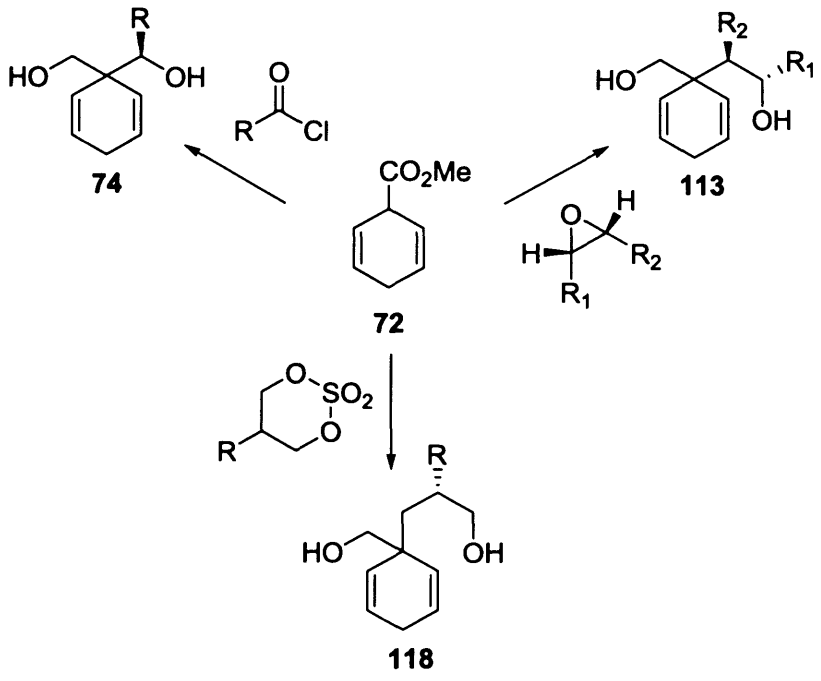


Fig. 4. Features of iodocyclisation substrates.

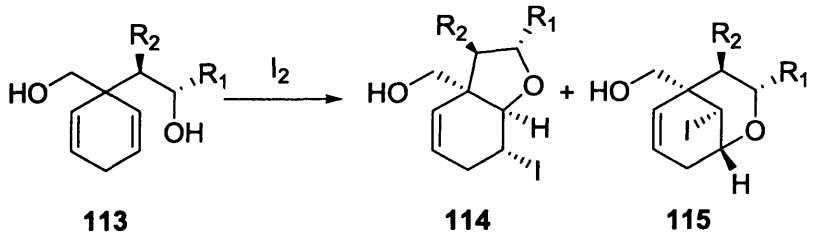
Such substrates would be readily accessible by alkylation of ester **72** with acyl chlorides, epoxides or epoxide equivalents, allowing a detailed investigation into several modes of cyclisation.



Scheme 47. Examples of substrates accessible from ester **72**.

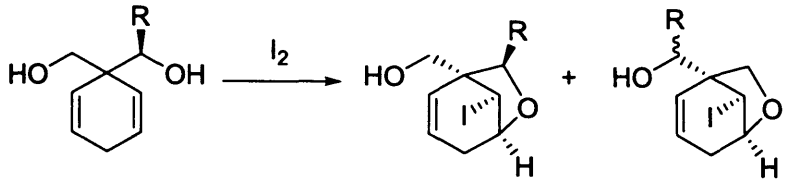
3.2 Results and Discussion

Substrates **113** were studied in most detail, the products expected by competing 5-*exo* and 6-*endo* processes are shown in Scheme **48**.



Scheme 48. 5-*exo* / 6-*endo* iodocyclisations.

Diols **74** were available from the work on the Prins reactions discussed in Chapter 2, and would allow investigation into 5-*endo* cyclisations, as shown in Scheme **49**.



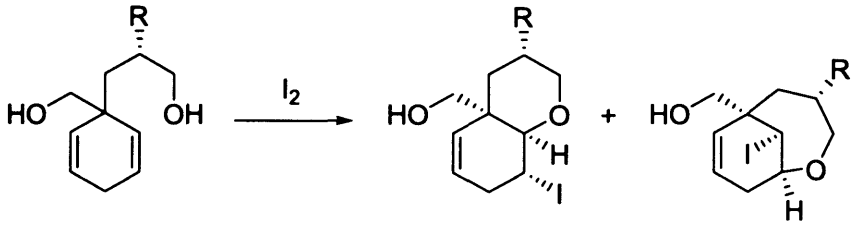
74a, R = Me
74b, R = 2-Br-C_6H_4

116a
116b

117a
117b

Scheme 49. 5-*endo* iodocyclisations.

Another possibility is the alkylation of ester **72** with a cyclic sulfate, allowing cyclisation by 6-*exo* and 7-*endo* pathways to be investigated, as shown in Scheme **50**.

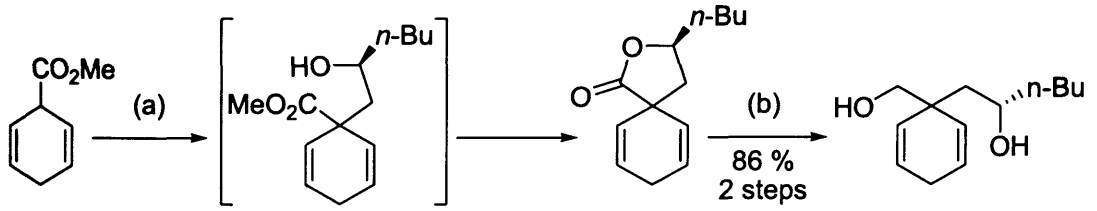


118 **119** **120**

Scheme 50. 6-*exo* / 7-*endo* cyclisations

3.2.1 5-*exo* / 6-*endo* Cyclisation Reactions

In order to test our hypothesis a suitable substrate was required, the *n*-Bu substituted diol **113b** was chosen as a starting point. Alkylation of methyl 2,5-cyclohexadiene carboxylate with hexene oxide gave lactone **121b**, as was reported to result from a similar alkylation by Kraus.[38] This was easily reduced to the required substrate with $LiAlH_4$, as shown in Scheme **51**.

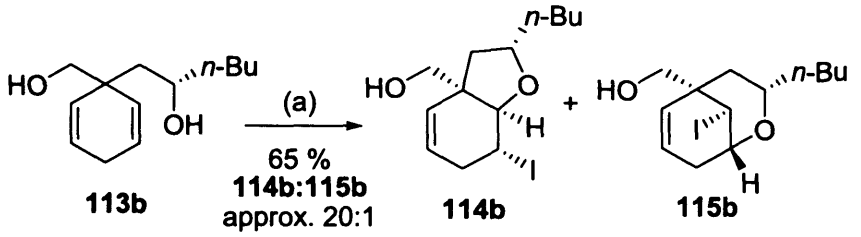


72 **121b** **113b**

Scheme 51. *Reagents and Conditions:* (a) i) LDA, THF, -78 °C; ii) hexene oxide, -78 °C to room temp.; (b) $LiAlH_4$, THF.

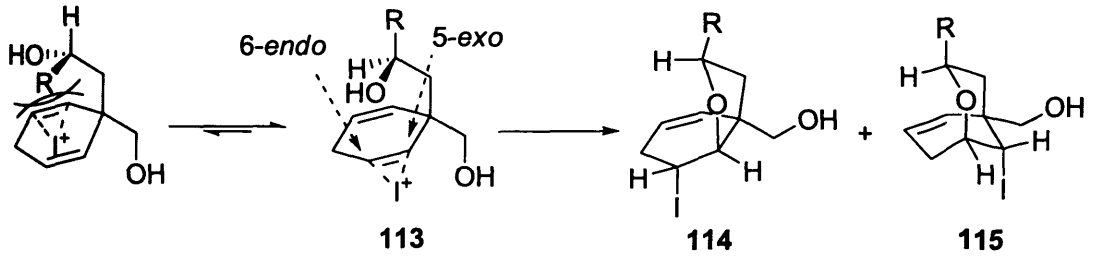
Reaction of **113b** with iodine and $NaHCO_3$ in acetonitrile for 1 h gave a crude material composed primarily of one compound. The purity of this was sufficient to

allow the structure to be determined as that of **114b**, shown in Scheme **52**, by ^{1}H - ^{1}H and ^{1}H - ^{13}C correlation NMR spectroscopy. The stereochemistry of this product could not be determined from the NMR data generated, however, it was expected to be as shown based on examination of models of diol **113b**. The minor product was not isolated due to the small quantity present, the structure and stereochemistry were assigned as that of **115b** by analogy with later results.



Scheme 52. *Reagents and Conditions:* (a) I_2, $NaHCO_3$, MeCN, 1 h.

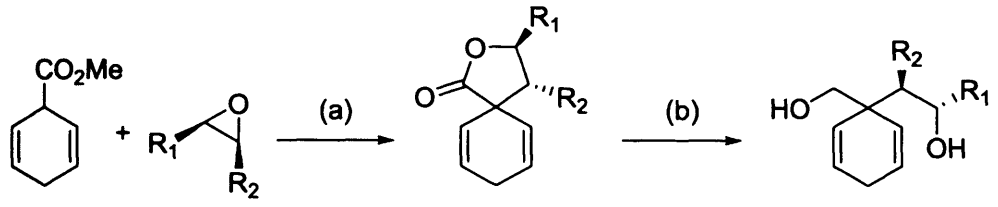
This regioselectivity can be explained by the model shown in Scheme **53**; as suggested by Baldwin, the angle of attack required of the alcohol nucleophile for a 5-*exo* ring closure would appear to require a much less strained geometry than the competing 6-*endo* ring closure.[39] The basis for the predicted stereochemistry can also be seen, as cyclisation onto one of the double bonds results in a destabilising interaction between the substituent and the cyclohexadiene ring. This is avoided by cyclisation onto the other double bond, which allows the substituent to occupy a *pseudo*-equatorial position in the new ring.



Scheme 53. Origin of stereo- and regioselectivity.

As high diastereoselectivity is obviously possible by this method, with no minor diastereoisomers being observed, a series of related substrates were prepared in order to determine the scope and limitations of the reaction. Most of these additional substrates were prepared in the same manner, simply by varying the epoxide used in the alkylation step, as shown in Table **4**.

Alkylation of ester **72** with just 0.5 equivalents of unprotected glycidol gave a reasonable yield of lactone **121e** (Entry **3**), which was then reduced to triol **113e**. Alkylation with vinylcyclohexane oxide and cyclohexene oxide (Entries **4** and **6**) provided acceptable yields of diols **113f** and **113i**, respectively. The lactone isolated following alkylation with styrene oxide (Entry **5**) was **121h**, the product of epoxide opening at the benzylic position. Reduction to diol **113h** therefore allowed the possibility of stereocontrol by a more distant stereogenic centre to be studied.

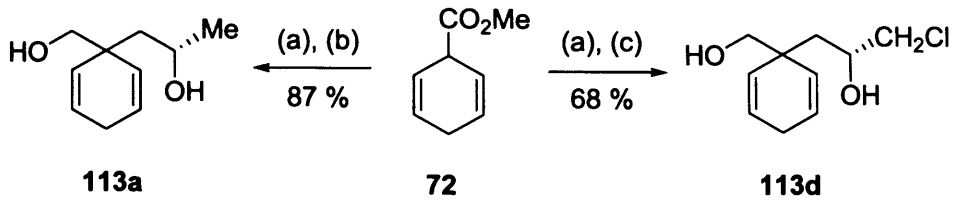


72 **121a-i** **113a-i**

Entry	*Diol*	R_1 =	R_2 =	*Yield **121** (%)*	*Yield **113** (%)*
1	**113a**	Me	H	-	87[a]
2	**113b**	*n*-Bu	H	-	86[a]
3	**113e**	CH_2OH	H	23	56
4	**113f**	*c*-C_6H_{11}	H	55	91
5	**113h**	H	Ph	40	84
6	**113i**	-$(CH_2)_4$-		34	92

Table 4. *Reagents and Conditions:* (a) LDA, THF, -78 °C to room temp.; (b) $LiAlH_4$, THF. [a] Yield over 2 steps.

Diol **113a** (Entry **1**) was the unexpected product of reduction of lactone **121d** with $LiAlH_4$, as shown in Scheme **54**. Prevention of dehalogenation by the use of the minimum required amount of hydride and ice cooling was only moderately successful, and chromatographic separation of the products was fairly tedious. A method based on that reported by Chaveriat, with $NaBH_4$ as the reductant, was eventually found to be much simpler.[40]

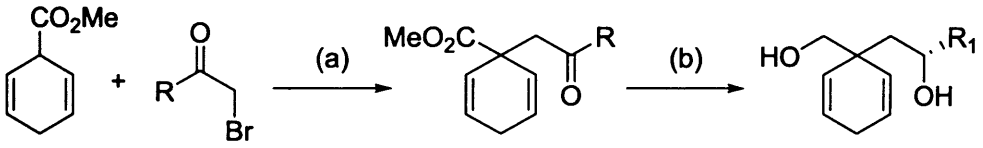


113a **72** **113d**

Scheme 54. *Reagents and Conditions:* (a) LDA, epichlorohydrin, THF, -78 °C to room temp.; (b) $LiAlH_4$, THF; (c) $NaBH_4$, EtOH.

Substrates **113c** and **113g**, shown in Scheme **55**, were felt likely to be useful additions to the series, but were found to be difficult to obtain in the same manner. Alkylation with styrene oxide formed mostly lactone **121h** rather than **121g**, while the epoxide required to prepare lactone **121c** was not commercially available and its synthesis was difficult due to its volatility.

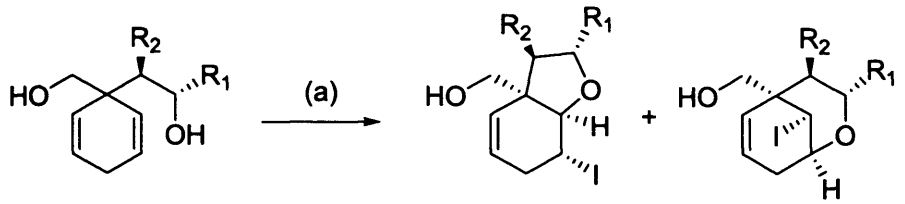
Both diols were found to be very conveniently prepared by alkylation of ester **72** with α-bromoketones, followed by reduction of keto-esters **122c** and **122g** as shown in Scheme **55**. The apparent low yield obtained by reduction of keto-ester **122g** was at least partly due to a spillage during its isolation.



72 **122c**, R = *t*-Bu, 90 % **122g**, R = Ph, 87 % **113c**, 57 % **113g**, 35 %

Scheme 55. *Reagents and Conditions:* (a) LDA, THF, -78 °C to room temp.; (b) $LiAlH_4$, THF.

With a selection of substrates now in hand, we were pleased to find that all cyclised readily, with results similar to that obtained with diol **113b**, as shown in Table **5**. Isolated yields of the 5-*exo* cyclisation products were good to excellent; except in the case of Entry **3**, the only significant byproducts observed in the ^1H NMR spectra of the crude material were the corresponding 6-*endo* cyclisation products. Diastereoselectivity is, therefore, at least greater than the regioselectivity shown.



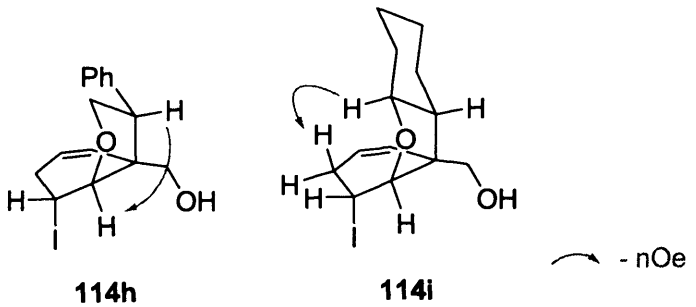
113a-i **114a-i** **115a-i**

Entry	*Diol*	R_1 =	R_2 =	*Base*	*Time (min)*	*Ratio **114:115***	*Yield **114** (%)*	*Yield **115** (%)*
1	**113a**	Me	H	$NaHCO_3$	30	11:1	66	6
2	**113b**	*n*-Bu	H	Na_2CO_3	60	20:1	65	-
3	**113c**	*t*-Bu	H	$NaHCO_3$	1	>99:1	89	-
4	**113d**	CH_2Cl	H	Na_2CO_3	30	17:1	87	-
5	**113e**	CH_2OH	H	$NaHCO_3$	1	19:1	91	-
6	**113f**	*c*-C_6H_{11}	H	Na_2CO_3	30	30:1	44	-
7	**113g**	Ph	H	Na_2CO_3	30	10:1	59	4
8	**113h**	H	Ph	Na_2CO_3	30	19:1	79	3
9	**113i**	-$(CH_2)_4$-		Na_2CO_3	30	10:1	62	-

Table 5. *Reagents and Conditions:* (a) I_2, Base (see table), MeCN.

It should be noted that while the base used was mostly Na_2CO_3, $NaHCO_3$ was used in some cases to similar effect. Also, the reaction times given are not necessarily the minimum required, two cases (Entries **3** and **5**) were analysed by tlc after just one minute and found to already be complete.

As was found initially in the cyclisation of diol **113b** (Entry **2**), the stereochemistry of these additional 5-*exo* products was often also difficult to determine by NMR spectroscopy. Diagnostic cross-peaks were observed in the NOESY spectra of only two compounds, **114i** and **114h**, shown in Fig. **5**, and a further two compounds, **114c** and **114g**, were crystalline solids suitable for stereochemical determination by X-ray diffraction, the results of which are shown in Fig. **6**.



114h **114i**

Fig. 5. Stereochemical determination of 5-*exo* products.

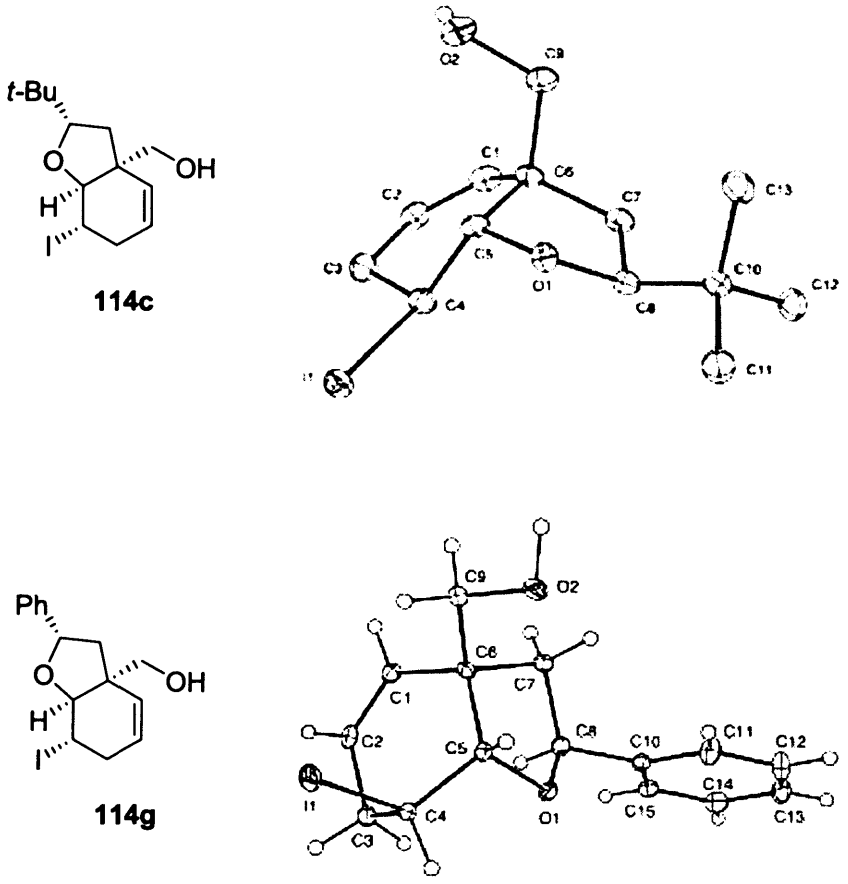


Fig. 6. ORTEP plots of the crystal structures of compounds **114c** and **114g**. Thermal ellipsoids are drawn at the 50 % probability level.

All four compounds have the stereochemistry predicted by the model shown previously in Scheme **53**; cyclisation occurs onto the alkene which allows the least hindered approach and results in the substituents occupying the *pseudo*-equatorial positions on the tetrahydrofuran ring. Since these four compounds cover the range of substitution patterns found in the remaining examples it is likely that these will also be of this stereochemistry.

It was a great relief to find that the stereochemistry of the minor products was comparatively straightforward to ascertain by NMR. Compound **115a**, shown in Fig. **7**, showed a large *trans*-diaxial coupling from the proton indicated, therefore the methyl substituent must be equatorial. Compounds **115g**, **115h** and **115i** gave diagnostic nOe's as indicated, all in support of the stereochemistry predicted.

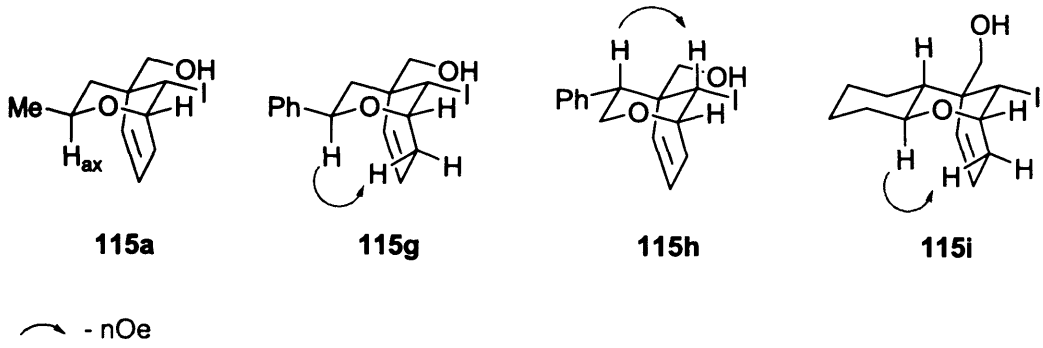


Fig. 7. Stereochemical determination of 6-*endo* products.

The regioselectivity of the cyclisations shown in Table **5** appears to correlate with the steric bulk of the substituents. Entries **1-3**, for example, where R_1 ranges from Me, through *n*-Bu to *t*-Bu, show the selectivity for 5-*exo* cyclisation to increase from 10:1 to 20:1 to greater than 99:1. A possible explanation for this may be that by increasing the R-CHOH-C bond angle, strain between the substituent and the adjacent CH_2 group can be reduced, as shown in Fig. **8**. This would simultaneously place the alcohol in closer proximity to the nearer end of the double bond, increasing both the relative probability and rate of the 5-*exo* cyclisation. Semi-empirical geometry optimisation at the MNDO level of theory gave the bond angles shown, supporting this theory, however, more definitive proof was not obtained.

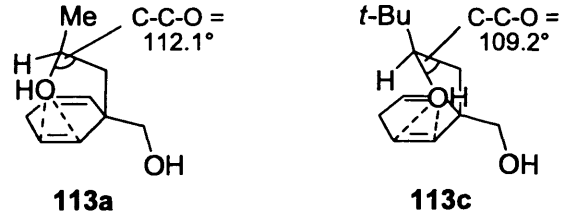
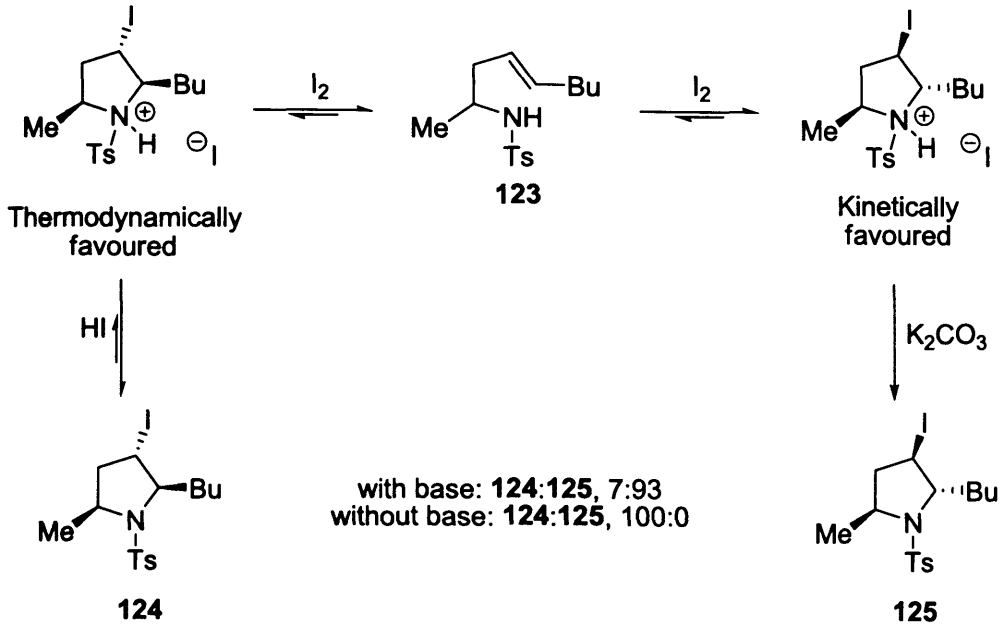


Fig. 8. Effect of substituent size on computed bond angles.

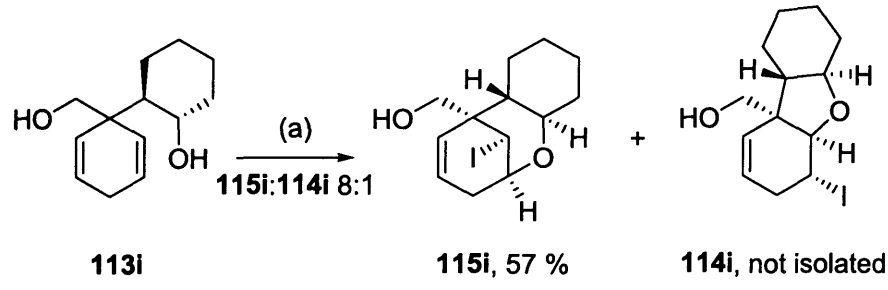
The addition of a weak base prevents equilibration to the thermodynamic product, shown by Knight to occur *via* protonation of the ring heteroatom, as shown in Scheme **56**.[41]



Scheme 56.

We thought that, in our case, omission of the base and extenstion of the reaction time may affect the regiochemical outcome of the reaction. With most substrates a small shift in the product distribution was, indeed, observed, although this was often not to a useful extent. Cyclisation of diol **113a** (R_1 = Me, R_2 = H) in this manner, for example, gave the two products **114a** and **115a** in a ratio of approximately 5:1 after 20 hours.

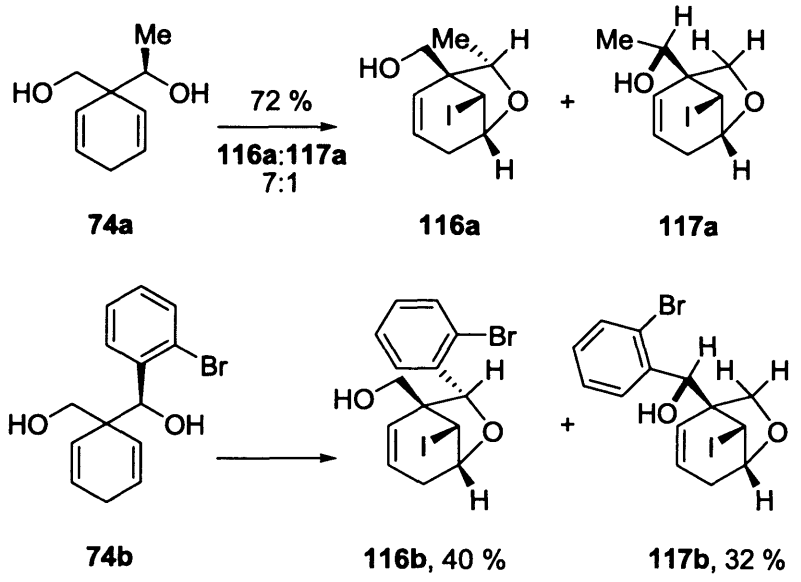
Diol **113i**, however, did show selectivity for formation of the 6-*endo* product under these conditions, the ratio after 24 hours being approximately 8:1 in favour of **115i**, as shown in Scheme **57**. In this case, presumably, significant stabilisation can result from isomerisation to the *trans*-decalin system.



Scheme 57. *Reagents and Conditions:* (a) I_2, MeCN, room temp., 24 h.

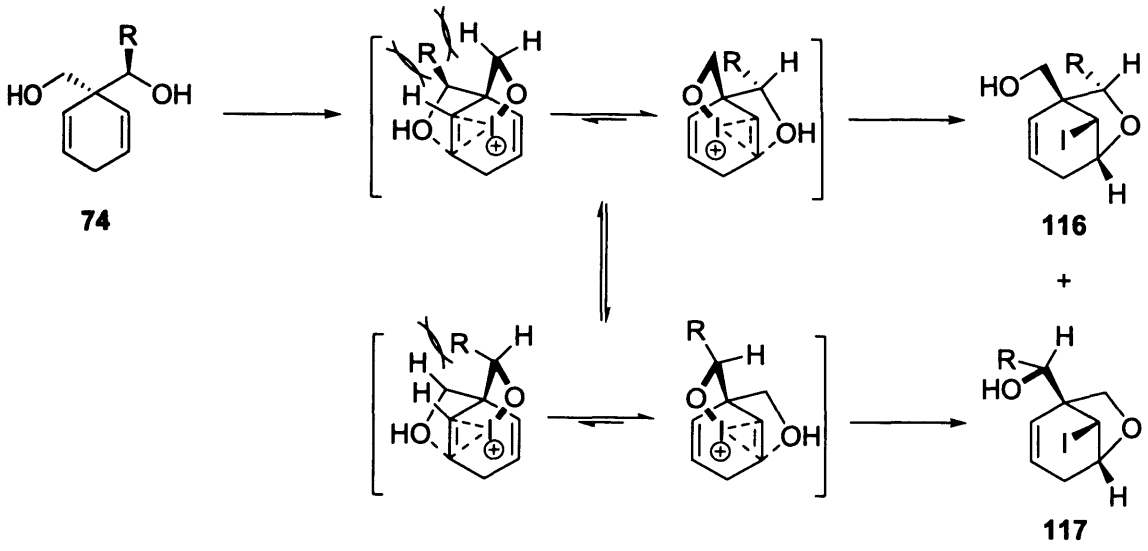
3.2.2 5-*endo* Cyclisation Reactions

Cyclisation of alcohols **74a** and **74b** also yielded mixtures of two compounds, these were identified as the products of 5-*endo* cyclisation of both the primary and secondary alcohols, as shown in Scheme **58**. While this was not unexpected, we were suprised to find that both products were formed as essentially single diastereoisomers.



Scheme 58. *Reagents and Conditions:* I_2, $NaHCO_3$, MeCN, room temp, 1 h.

The mechanism responsible for stereocontrol in the cyclisation of the primary alcohol is not clear, it seems highly unlikely to be due to direct interaction with the distant stereogenic centre. An indirect mechanism of transmission may be possible, for example, by group selective intramolecular iodonium ion formation followed by cyclisation of the primary alcohol, as shown in Scheme **59**. A similar mechanism involving the intramolecular delivery of 'I^{+}' from an acyl hypoiodite was proposed by Bartlett[42] to explain the unusual selectivity for formation of the 3,4-*cis* isomer on iodocyclisation of some 3-substituted 4-pentenoic acids under kinetic conditions, a phenomena also noted by Kurth in the opening example of the chapter.[30]



Scheme 59. Plausible mechanism of stereocontrol in 5-*endo* cyclisations.

The stereochemistry of compounds **116a** and **116b** was confirmed to be as predicted in Scheme **59** by the observation of the nOe's shown in Fig. **9**. The ^{1}H NMR spectrum obtained from compound **116b** also showed a relatively low chemical shift (δ 4.63 ppm) for one of the alkene protons, suggesting its close proximity to the aromatic ring. Assignment of the predicted stereochemistry of compounds **117a** and **117b** was not possible by NMR experiments due to the free rotation of the chiral side-chain.

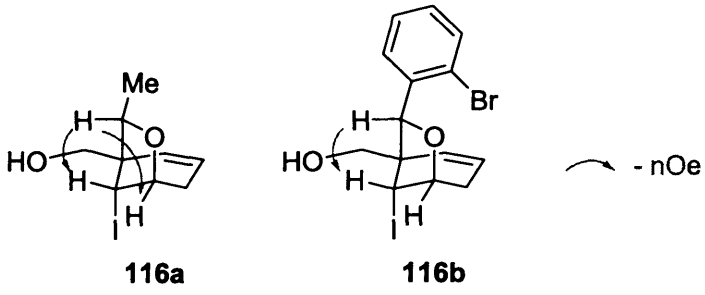
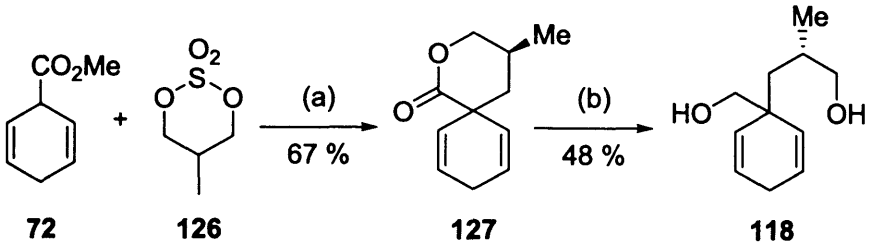


Fig. 9. Determination of stereochemistry of **116a** and **116b**.

Regioselectivity in these examples appears to support the hypothesis proposed in the previous section, as the bulky aryl substituents reduced the extent of cyclisation through the secondary alcohol. Rather than cyclise in a 4-*exo* manner, however, 5-*endo* cyclisation of the primary alcohol appears to be preferable.

3.2.3 6-*endo* / 7-*exo* Cyclisation Reactions

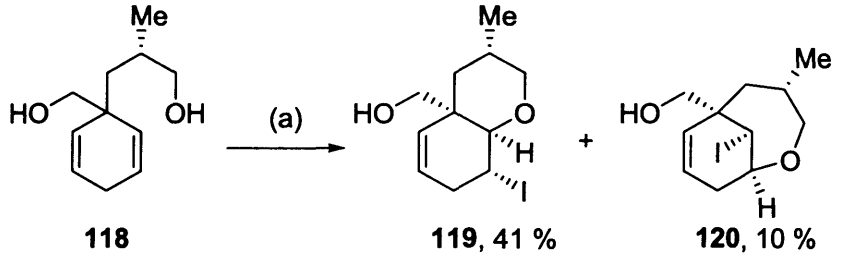
Ester **72** was also alkylated with the cyclic sulfate ester **126**, as shown in Scheme **60**, allowing 6-*exo* / 7-*endo* cyclisations to be investigated.



72 **126** **127** **118**

Scheme 60. *Reagents and Conditions:* (a) LDA, THF, -78 °C to room temp.; (b) $LiAlH_4$, THF.

Cyclisation of diol **118** under the same conditions gave the 6-*exo* and 7-*endo* products, **119** and **120**, both as single diastereoisomers as shown in Scheme **61**. The selectivity between the two pathways was lower than in the 5-*exo* / 6-*endo* examples, as might be expected.



118 **119**, 41 % **120**, 10 %

Scheme 61. *Reagents and Conditions:* I_2, $NaHCO_3$, MeCN, room temp.

The stereochemistry of the tetrahydropyran **119** can be understood as arising from cyclisation onto the double bond that allows the methyl substituent to lie equatorial in the transition state. This was confirmed by observation of an n.O.e. between the CH next to iodine and one of the CH's next to oxygen on the tetrahydropyran ring. As this gave a large axial coupling to the CH with the attached methyl group, the methyl group must be equatorial. The stereochemistry of the 7-*endo* isomer **120** could not be proven but is presumably the same as the 6-*exo* isomer.

3.3 Conclusion

Iodocyclisation reactions of cyclohexadienes containing one or more stereogenic centres in the tethering chain have been found to proceed with excellent diastereotopic group selectivity in all cyclisation modes investigated. The synthesis of these substrates is highly versatile and this reaction should, therefore, be useful in synthesis.[43]

Chapter 4

Synthesis of Lycoposerramine Alkaloids

4.1 Introduction

The Lycopodium genus has revealed an abundance of alkaloids of wide functional variety yet based principally on one of the 16 carbon scaffolds shown in Fig. **10**.[44]

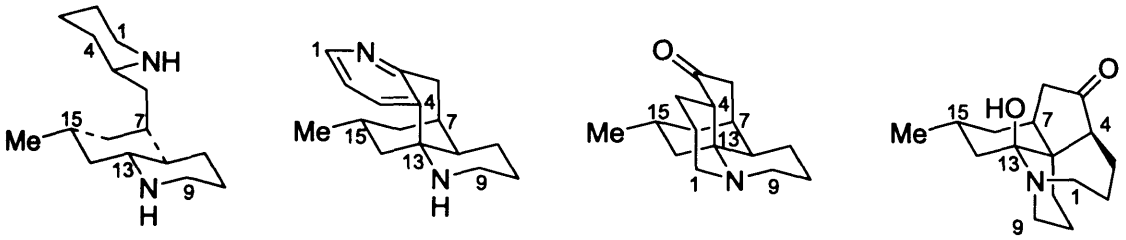


Fig. 10. Sub-groups of the Lycopodium alkaloids.

Lycopodine **130** was the first of the Lycopodium alkaloids to be isolated and identified. The class which takes its name is the most populous, containing just over a third of the currently known alkaloids.

The Lycodine class contains just over ten percent of Lycopodium alkaloids, some of which are active as acetylcholinesterase inhibitors. This is the only class currently known to contain such inhibitors.[45]

Fawcettimine **131** is the prototype of the second most abundant class, possibly derived from the Lycopodine class by migration of C_4 from C_{13} to C_{12}. It has been proposed that all of these alkaloids could be derived from phlegmarine **128**, which could in turn be the product of coupling two 2-propylpiperidine moieties, indicated by the dashed lines in Fig. **10**.

4.2 Synthesis of Fawcettimine Class Compounds

We were most interested in synthesis of fawcettimine derivatives such as those shown in Fig. **11**, as these compounds should be accessible through a Birch reduction, alkylation, desymmetrisation (BRAD) strategy.

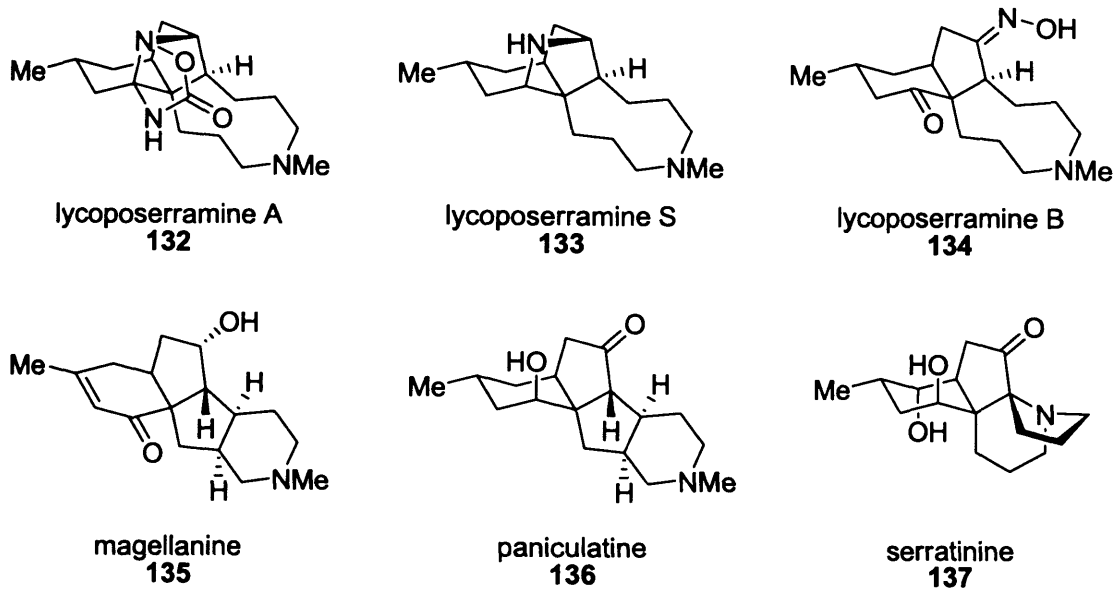


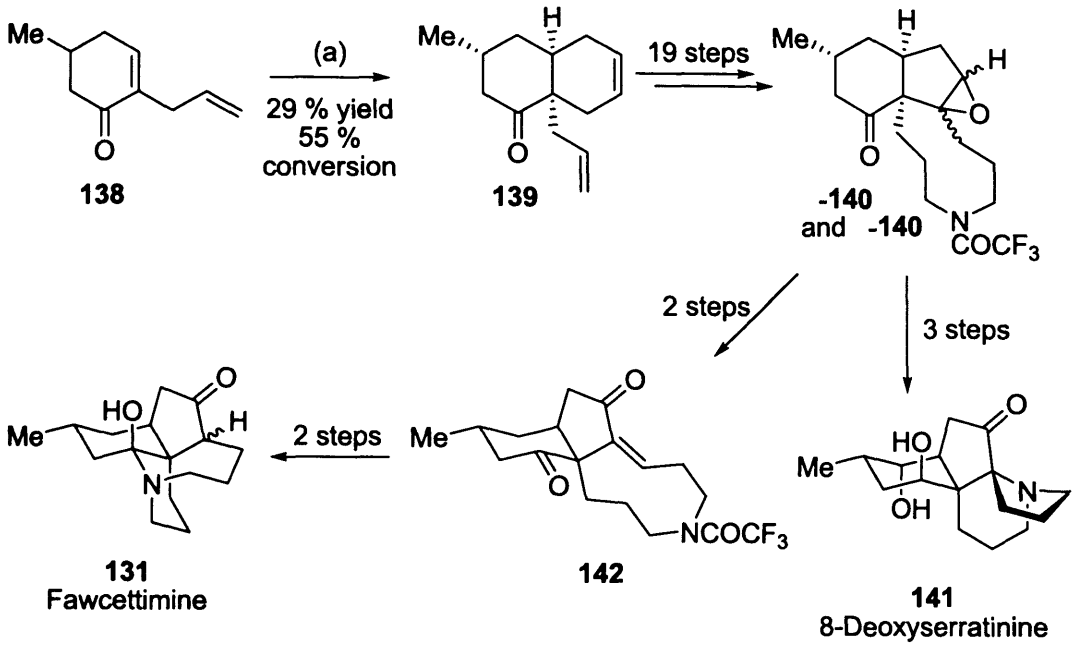
Fig. 11. Examples of fawcettimine type alkaloids.

4.2.1 Fawcettimine

Fawcettimine and 8-deoxyserratinine were the first of the class to be synthesised, by Inubushi and coworkers, in 1980.[46] The key step was a Diels-Alder reaction between the racemic cyclohexenone **138** and 1,3-butadiene, giving the [6,6]-bicyclic intermediate **139** with the correct stereochemistry, as shown in Scheme **62**. A further 19 steps were required in order to transform this into a mixture of epoxide diastereoisomers α-**140** and β-**140**.

Epoxide α-**140** was rearranged to the allylic alcohol and oxidised to enone **142**. Hydrogenation and hydrolysis of the trifluoroacetamide group gave racemic fawcettimine in a total of 24 steps with 0.26 % overall yield. This was found to be identical to a authentic sample, proving the structure, although the stereochemistry at C_4 remained uncertain since it is not clear which face of the enone would be preferred for hydrogenation.

Amide hydrolysis of β-**140** allowed cyclisation of the free amine onto the epoxide. Oxidation to the diketone and selective reduction of the six membered ring ketone gave 8-deoxyserratinine **141** in a total of 23 steps with 0.28 % overall yield.

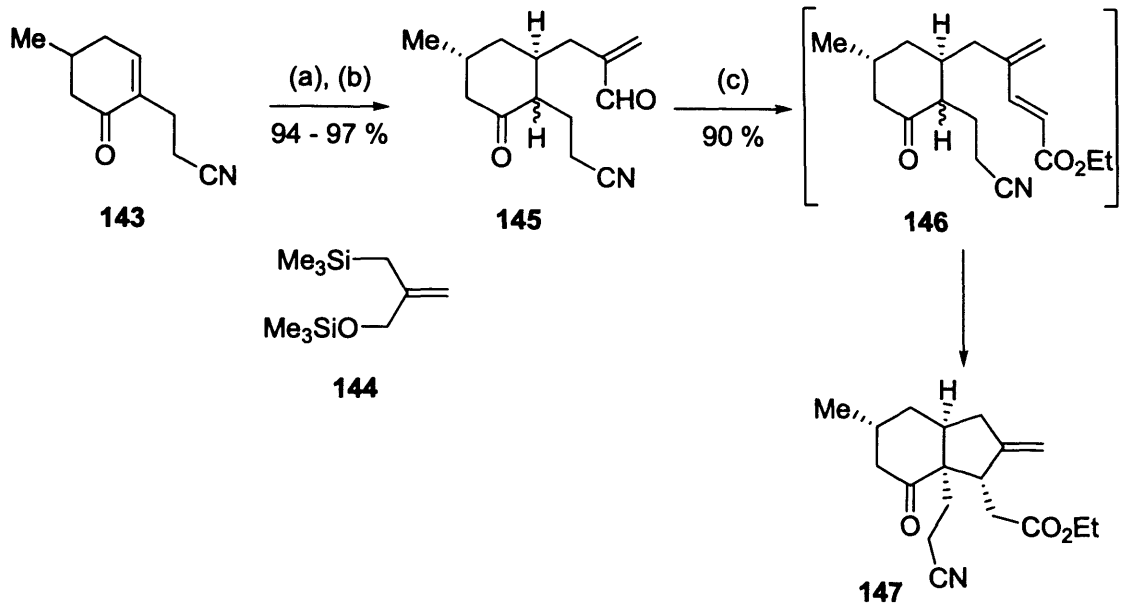


Scheme 62. *Reagents and Conditions*: (a) **140**, butadiene, $BF_3.OEt_2$.

In 1986 Heathcock and coworkers reported a much more practical and elegant synthesis from a similar 2-alkyl-5-methylcyclohexeneone precursor, again allowing the methyl substituent to control the stereochemistry of the subsequent transformations.[47] Fawcettimine was obtained in 10 steps and 9 % overall yield from enone **143**. This was later optimised further, the sequence described below giving 17 % overall yield though also in 10 steps.

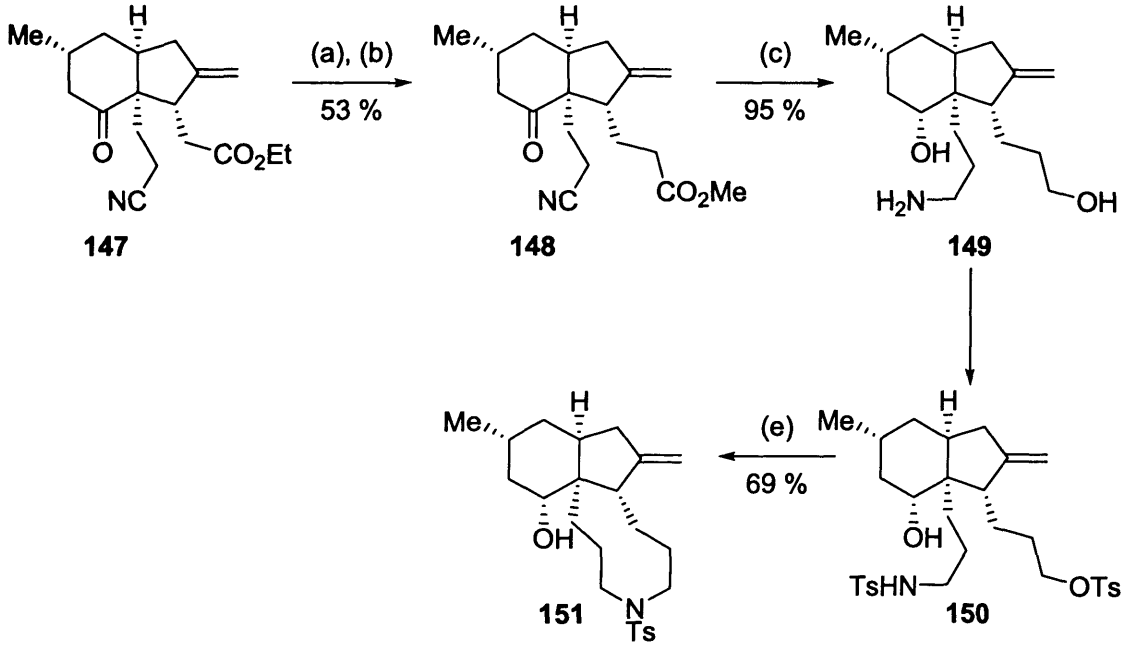
The methyl substituent of enone **143** allowed a stereoselective Sakurai reaction with allylsilane **144**, as shown in Scheme **63**, oxidation of the product providing aldehyde **145** in near-quantitative yield. A Horner-Wadsworth-Emmons reaction then allowed formation of the bicyclic hydrindanone core by an intramolecular Michael reaction. The 1,4-addition product **147** is favoured under Baldwin's rules, being a 5-*exo-trig* cyclisation. The alternative 1,6-addition would be a 5-*endo-trig* cyclisation.

Saponification of ester **147** followed by Arndt-Eistert homologation of the resulting acid provided the remaining carbon atom of the nine-membered ring. Reduction with $LiAlH_4$ in ether at -110 °C gave amino-diol **149** as the major diastereoisomer of a 9:1 mixture of alcohol isomers. Selective tosylation of both the amine and primary alcohol then allowed cyclisation of *bis*-tosylate **150**, forming the nine-membered ring in good yield, as shown in Scheme **64**.



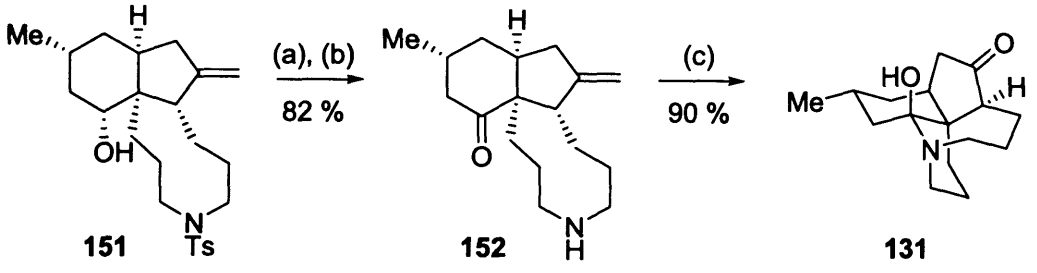
Scheme 63. *Reagents and Conditions*: (a) **144**, $TiCl_4$, CH_2Cl_2; (b) CrO_3, pyridine; (c) ethyl trimethylphosphonoacetate, NaOEt, EtOH, DMF.

Sodium naphthalenide effected deprotection of sulfonamide **151** without reduction of the double bond, as shown in Scheme **65**. Oxidation of the secondary alcohol with chromium trioxide in 80 % aqueous acetic acid gave compound **152**, which was found to exist almost entirely in the keto-amine form.



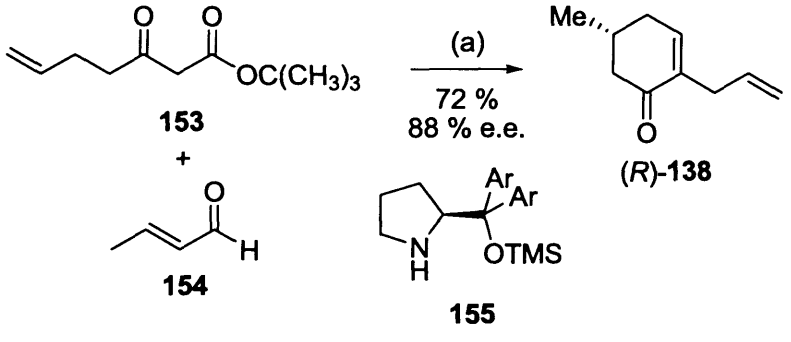
Scheme 64. *Reagents and Conditions*: (a) NaOH, EtOH, H_2O; (b) i) $(COCl)_2$, benzene; ii) CH_2N_2; iii) $PhCO_2Ag$, Et_3N, MeOH; (c) $LiAlH_4$, ether; (d) Ts_2O, DMAP, CH_2Cl_2; (e) Bu_4NOH, benzene.

Fawcettimine exists mostly in the hemi-aminal form, suggesting this intermediate to be the C_4 epimer of fawcettimine. Ozonolysis of the perchlorate salt of **152** allowed spontaneous isomerisation at the C_4 position, and the synthetic fawcettimine thus obtained was found to be identical to the natural material. Further confiramtion of the C_4-stereochemistry was provided by x-ray crystallography.



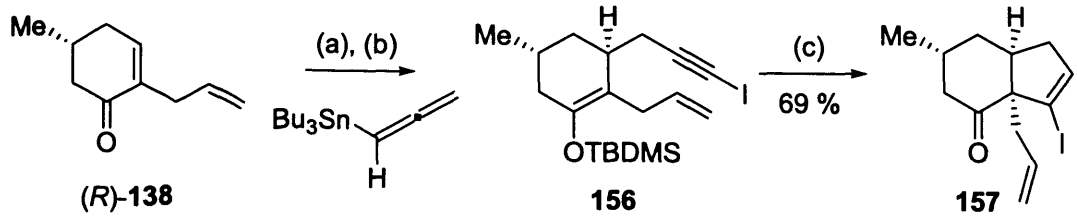
Scheme 65. *Reagents and Conditions:* (a) Na, naphthalene, DME; (b) CrO_3, HOAc; (c) i) $HClO_4$; ii) O_3; iii) $NaHCO_3$.

The first asymmetric synthesis was recently published by Toste, starting from the same enone precursor **138** used by Inubushi. This was prepared as a single enantiomer by a Robinson annulation catalysed by the chiral proline derived base **155**, as shown in Scheme **66**.[48]



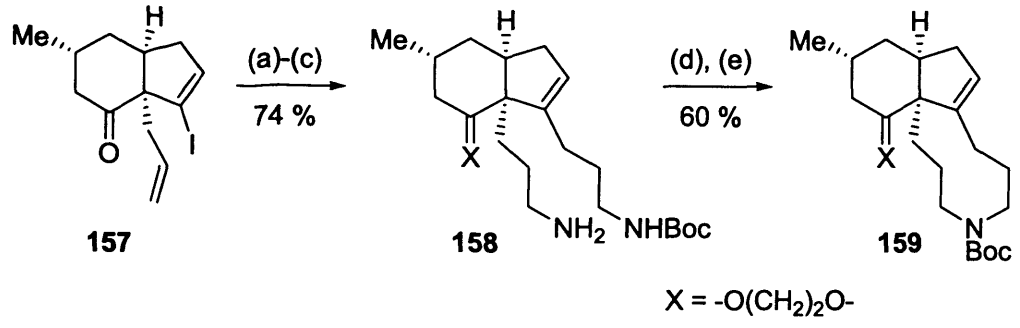
Scheme 66. *Reagents and Conditions*: (a) i) 10 mol % **155**, neat, 60 h, 0 °C; ii) TsOH, toluene, reflux. Ar = 3,5-$(CF_3)_2C_6H_3$.

Conjugate addition of allenyltributylstannane gave the *trans*-silyl enol ether **156** with high selectivity (> 95:5 d.r.). Iodination of the alkyne then set the stage for the key gold(I) catalysed 5-*endo-dig* cyclisation of the silyl enol ether onto the alkyne, completing the [6,5]-bicyclic core, as shown in Scheme **67**.



Scheme 67. *Reagents and Conditions*: (a) allenyltributylstannane, TBDMSOTf, CH_2Cl_2; (b) NIS, $AgNO_3$, DMF; (c) 10 mol % $(PPh_3)AuCl$, $AgBF_4$, CH_2Cl_2 / MeOH.

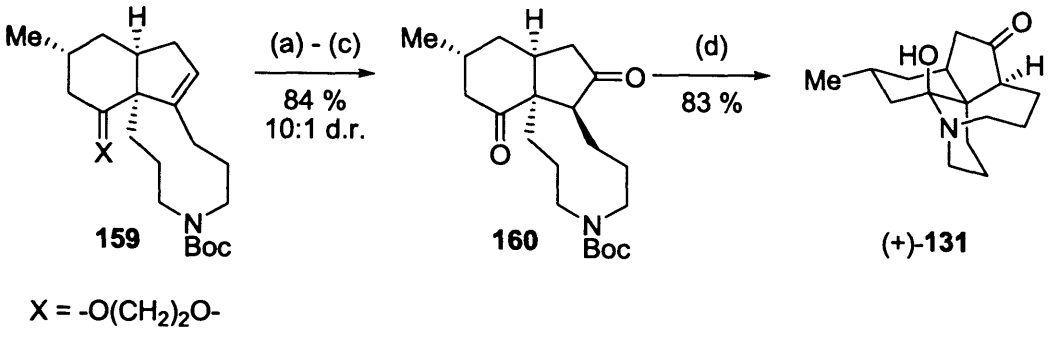
Following protection of the ketone, the remaining three carbon atoms and nitrogen atom of the nine-membered ring were introduced by a palladium catalysed cross-coupling of **157** with the product of hydroboration of N-Boc allylamine. Hydroboration / oxidation of the terminal alkene then gave alcohol **158**, which was converted to the iodide allowing closure of the nine-membered ring with potassium *tert*-butoxide, shown in Scheme **68**.



Scheme 68. *Reagents and Conditions*: (a) $(CH_2OH)_2$, TsOH, benzene, reflux; (b) i) $CH_2=CHCH_2NHBoc$, 9-BBN; ii) $[PdCl_2(dppf)]$, $AsPh_3$, Cs_2CO_3, DMF; (c) BH_3; (d) PPh_3, I_2, imidazole, CH_2Cl_2; (e) *t*-BuOK, THF.

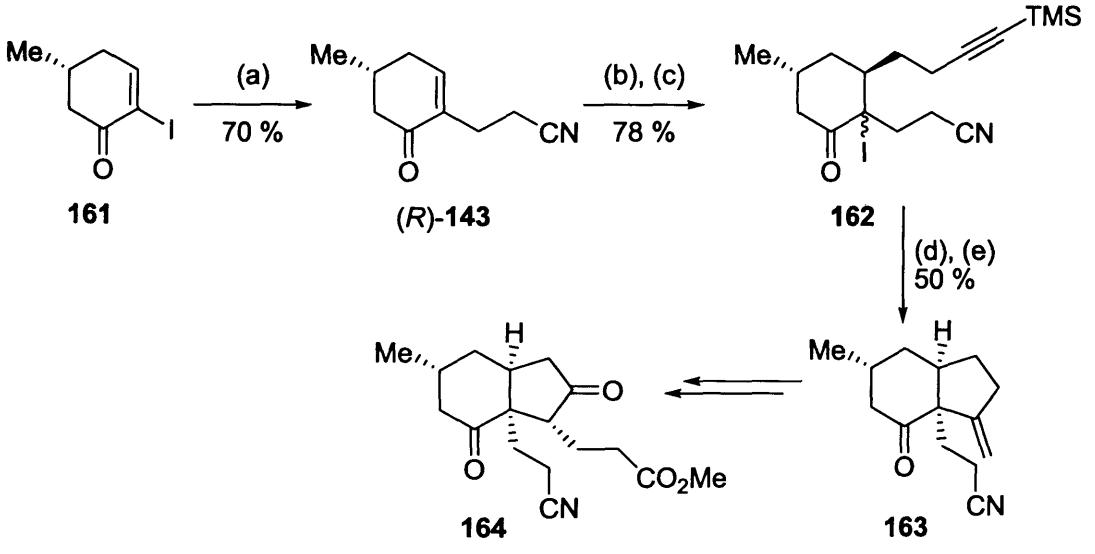
To complete the synthesis, the ketal protecting group of **159** was removed and the remaining ketone introduced by hydroboration and a two step oxidation. Removal of the Boc protecting group then gave (+)-fawcettimine ((+)-**131**).

A formal asymmetric synthesis was published shortly after by Liu and Chau.[49] They synthesised (*R*)-2-iodo-5-methylcyclohexenone **161** as a single enantiomer from (*R*)-pulegone, as shown in Scheme **70**. This was converted into Heathcock's cyano-enone **143** by an intermolecular radical conjugate addition to acrylonitrile.



Scheme 69. *Reagents and Conditions*: (a) PPTS, acetone / water; (b) i) BH_3.THF, THF; ii) NaOH, H_2O_2; (c) Dess-Martin periodinane, DCM; (d) TFA, CH_2Cl_2.

Conjugate addition of a protected acetylenic Grignard reagent to **143** followed by enolate iodination gave compound **162**, allowing formation of the five-membered ring by an intramolecular 5-*exo-dig* radical cyclisation onto the alkyne. Removal of the silyl group and a two step allylic oxidation of **163** enabled the conjugate addition of the silyl enol ether of methyl acetate to give **164**. Presumably this could be converted into (+)-fawcettimine in a similar manner to Heathcock's intermediate.

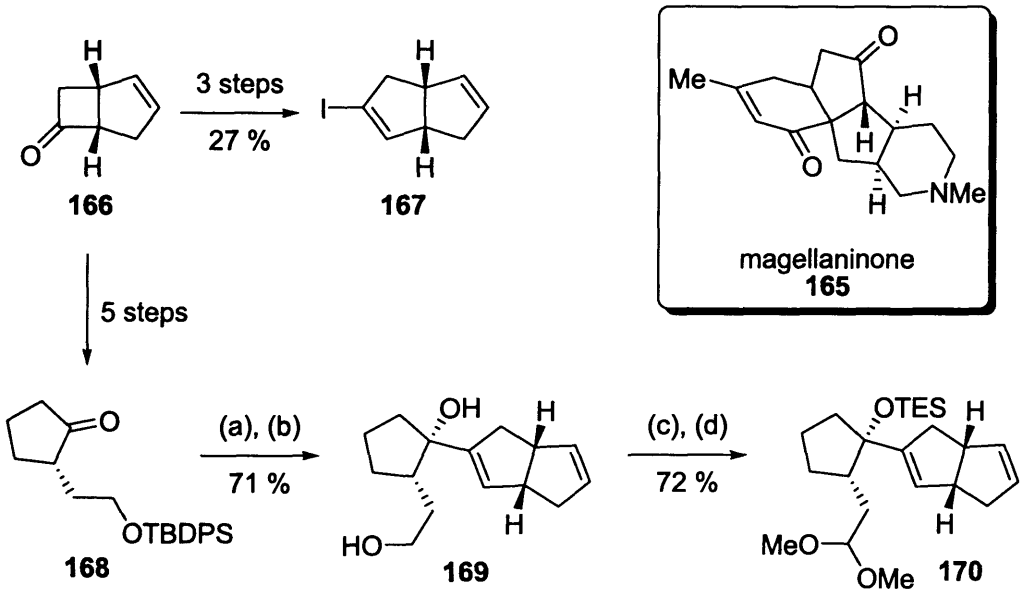


Scheme 70. *Reagents and Conditions*: (a) acrylonitrile, Bu_3SnH, AIBN, PhH; (b) 4-trimethylsilylbut-3-ynyl chloride, Mg, CuI, TMSCl, HMPA, THF; (c) NaI, *m*CPBA, THF; (d) Bu_3SnH, AIBN, PhH, slow addition; (e) TFA, CH_2Cl_2.

4.2.2 Magellanine

Magellanine **135** is probably the only other alkaloid in this class to have received so much synthetic attention. The first total synthesis by Overman yielded magellanine and magellaninone **165** in 25 and 26 steps, respectively, from the single enantiomer cyclobutanone **166** shown in Scheme **71**.[50]

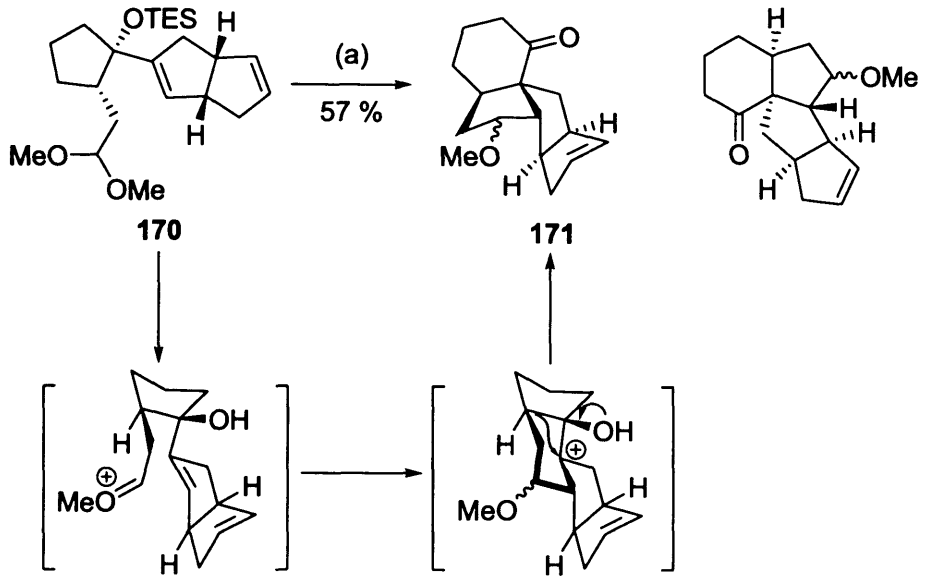
Protected keto-alcohol **168** was prepared from **166** by a five step sequence involving a Baeyer-Villiger reaction to open the four membered ring. Iodide **167** was prepared from the same precursor in 27 % yield over three rather lengthy steps. Addition of the vinyllithium generated from **167** to ketone **168**, followed by deprotection gave diol **169**. This was protected as the *bis*-silyl ether, the primary protected alcohol oxidised by a Swern reaction and the resulting aldehyde converted into the dimethyl acetal **170** in preparation for the key Prins-Pinacol sequence.



Scheme 71. *Reagents and Conditions*: (a) i) **167**, *t*-BuLi, Et_2O, -110 °C; ii) **168**; (b) TBAF, THF; (c) Et_3SiCl, DMAP, imidazole, CH_2Cl_2; (d) i) Swern oxidation; ii) $(MeO)_3CH$, PPTS, CH_2Cl_2.

Prins cyclisation of acetal **170** by treatment with $TiCl_4$ in CH_2Cl_2 gave compound **171**, with the stereochemistry predicted to result from attack on the oxonium ion by the outer face of the bicyclic alkene, as shown in Scheme **72**. The product was, however,

found to consist of a 2:1 mixture of epimers of the adjacent ether. This mixture was taken through a further 12 steps to give magellanine **135** at which point the minor epimer was separated and oxidised to magellaninone **165**.

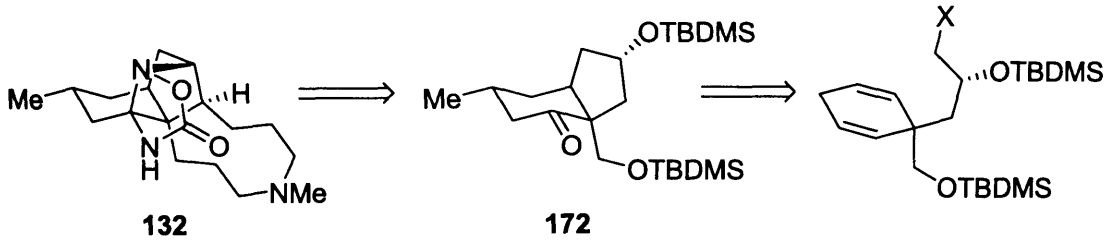


Scheme 72. *Reagents and Conditions*: (a) $TiCl_4$, CH_2Cl_2, -78 °C to -20 °C.

There have since been a number of other synthetic approaches to magellanine and the structurally-related natural product paniculatine.[51]

4.2.3 Lycoposerramine A

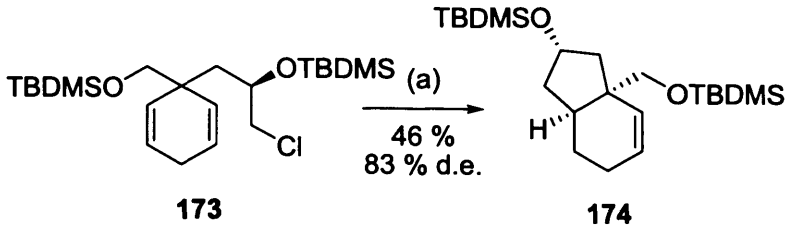
Synthetic studies on Lycoposerramine A **132** have so far not been reported. This compound contains a novel oxadiazolidinone ring system and is so far the only natural product found to contain this motif. We decided to first concentrate on this ring system, choosing compound **172**, shown in Scheme **73**, as an initial target. The quaternary stereocenter and 6,5-bicyclic system make a desymmetrisation an ideal strategy for its synthesis.



Scheme 73. Retrosynthesis of Lycoposerramine A.

4.3 Initial Approach to Key Fragment 172

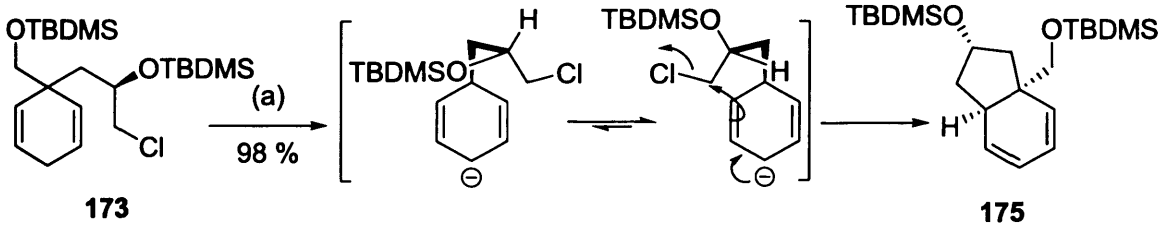
We had planned to construct the the hydrindanone core of **172** by a radical cyclisation of chloride **173**, reported by El Sayed to afford compound **174** in moderate yield and with good diastereocontrol.[26]



173 **174**

Scheme 74. *Reagents and Conditions*: (a) Bu_3SnH, AIBN, PhH, reflux, 30 h.

While attempting to optimise this reaction, however, we discovered that **173** could also be cyclised under strongly basic conditions. Treatment with *n*-BuLi, as shown in Scheme **75**, afforded 1,3-diene **175** as a single diastereoisomer in almost quantitative yield. This was proposed to occur by cyclisation of an intermediate cyclohexadienyl anion onto the alkyl chloride, comparable to the initial diastereoselective protonation step of Landais' protonation-hydroamination sequence described in Chapter 1, Page 11. We were unable to determine the configuration of the secondary silyl ether, although it was expected to be as indicated, based on modelling of the transition state.

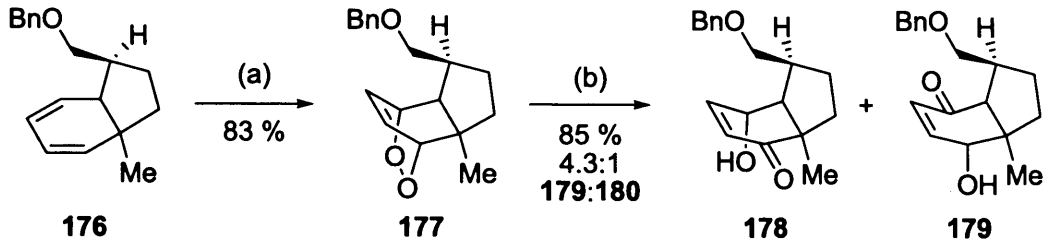


173 **175**

Scheme 75. *Reagents and Conditions*: (a) n-BuLi (1.1 equiv.), THF, -78 °C to room temp., 1 h.

Given the many advantages of this method over the radical cyclisation, we began to consider possible routes to target **172** through this intermediate instead. While the additional double-bond was expected to complicate matters, a sequence involving cycloaddition onto a similar 1,3-diene, reported by Shibasaki, suggested it may, in fact, prove beneficial.

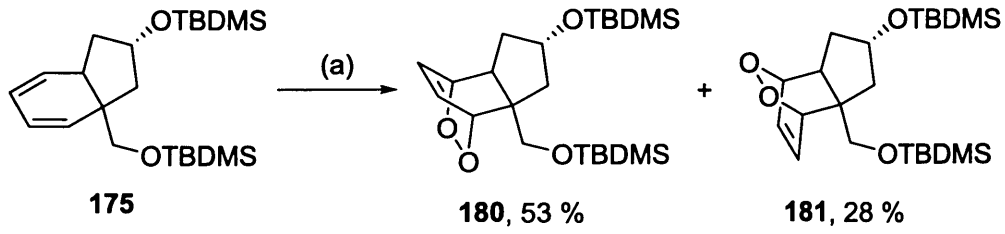
Reaction of diene **176**, shown in Scheme **76**, with photochemically-generated singlet oxygen, provided endoperoxide **177** as a single diastereoisomer. Treatment with base initiated rearrangement to two regioisomeric γ-hydroxyenones, **178** and **179**, the former being favoured by a factor of 4.3:1.[52]



Scheme 76. *Reagents and Conditions*: (a) O_2, hν, Rose Bengal, *i*-PrOH; (b) Et_3N, CH_2Cl_2.

A similar outcome from application of this sequence to diene **175** would also, therefore, allow rapid access to the cores of the serratinine type alkaloids, while alcohol deoxygenation and conjugate addition would furnish our initial target, ketone **172**.

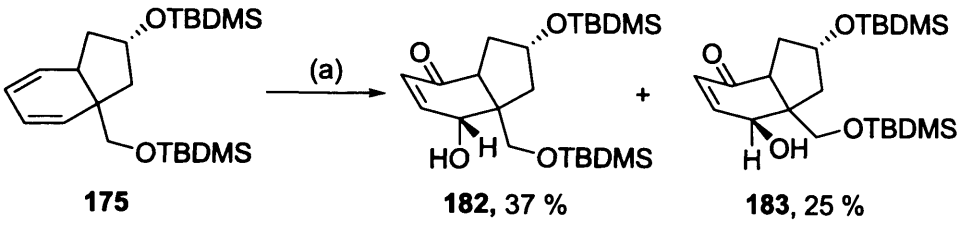
Irradiation of a solution of **175** and a catalytic amount of Rose Bengal in isopropanol, bubbled with a stream of dry oxygen, afforded a 2:1 mixture of endoperoxide diastereoisomers in high yield. The major isomer **180** was presumed to result from cycloaddition to the outer face of the bicyclic system, although the stereochemistry was not proven.



Scheme 77. *Reagents and Conditions:* (a) O_2, Rose Bengal, hν, *i*-PrOH.

While the selectivity of cycloaddition with **175** was lower than in Shibasaki's example, Kornblum-DeLaMare rearrangement of the crude endoperoxide mixture showed no evidence of minor regioisomers. Unfortunately, however, the products were found to be the undesired isomers **182** and **183**, shown in Scheme **78**. It seems that the large,

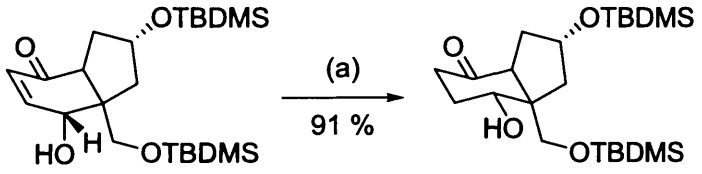
though more distant, CH_2OBn group of endoperoxide **177** is more effective in obstructing the approach of the base than the quaternary center.



175 **182**, 37 % **183**, 25 %

Scheme 78. *Reagents and Conditions:* (a) i) O_2, Rose Bengal, hv, *i*-PrOH; ii) Et_3N, *i*-PrOH, room temp., 48 h.

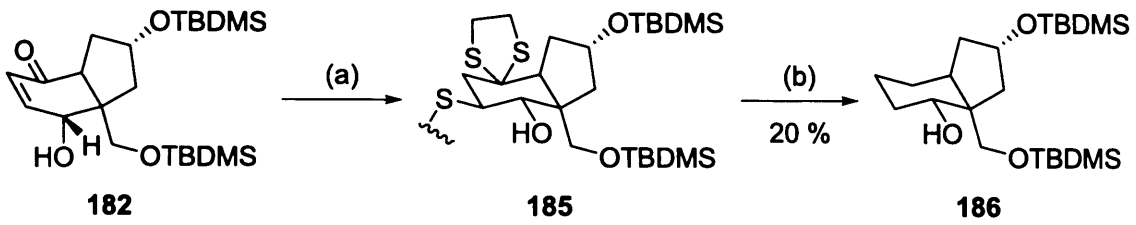
As we now required the complete reduction of the ketone, we began investigating the various methods known to achieve this. The Huang-Minlon modification of the Wolff-Kishner reaction failed to yield any product, as did the milder tosylhydrazone reduction with both $NaBH_4$ and $LiAlH_4$.[53] Many attempted thioketal formations with various acid catalysts and dithiol derivatives, such as *bis*-trimethylsilylethanedithiol,[54] also failed, presumably due to the acid sensitivity of the silyl protecting groups. Many of these attempts were also performed with the saturated ketone **184**, obtained by the hydrogenation of enone **182** as shown in Scheme **79**, although also without success.



182 **184**

Scheme 79. *Reagents and Conditions*: (a) NH_4CO_2H, Pd/C, EtOH, reflux, 1 h.

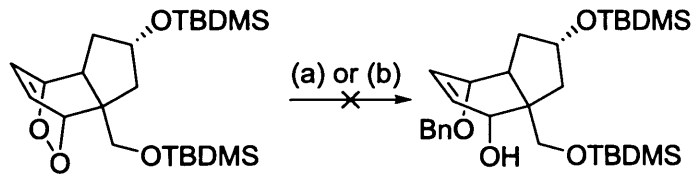
It was finally found that reaction of enone **182** and ethanedithiol with Me_2AlCl, at 0 °C, with frequent monitoring by tlc, gave a material that appeared to be a thioacetal of some form. The complicated NMR spectrum obtained may be due to the formation of a mixture of monomeric and dimeric conjugate addition products, although this was not investigated and the material simply treated with freshly prepared Raney nickel in EtOH and heated to reflux overnight. Chromatography of the crude product resulted in the isolation of a substance tentatively assigned as **186**, shown in Scheme **80**, based the limited data obtained. As this result could not be reproduced, however, we chose to abandon this approach.



182 **185** **186**

Scheme 80. *Reagents and Conditions*: (a) $HS(CH_2)_2SH$, Me_2AlCl, CH_2Cl_2, 0 °C, 1 h; (b) Raney Ni, EtOH, reflux, 18 h.

Another option would be to oxidise to the dienone and then attempt the selective reduction of the less hindered carbonyl group, although this was not investigated. We turned our attention instead to alternative reactions of the endoperoxides. Reaction with a good nucleophile, for instance, is reported to occur by attack on the weak O-O bond, and should, therefore, result in alkylation of the less hindered oxygen atom, leaving the other free for oxidation to the enone.[55] Reaction of peroxide **180** with BnLi or simply *n*-BuLi, as shown in Scheme **81**, however, was extremely slow and no identifiable products could be observed.



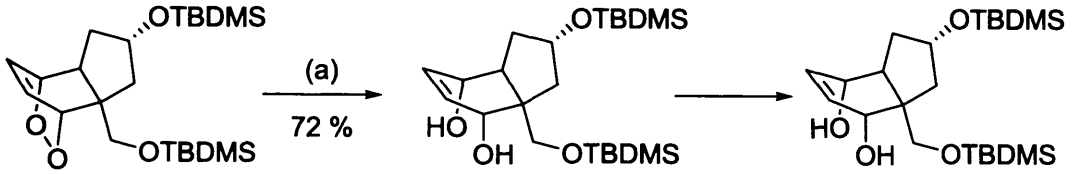
180 **187**

Scheme 81. *Reagents and Conditions*: (a) i) BnBr, BuLi, THF, -78 °C, 30 min; ii) **180**, THF, -78 °C to r.t., 24 h; (b) BuLi, THF, -78 °C to room temp., 24 h.

Attack on the peroxide by $LiAlH_4$, on the other hand, was extremely rapid, as shown in Scheme **82**, and the prospects for selective formation of a tosylate or xanthate from the expected product, diol **188**, seemed reasonable. This plan was scuppered when the product was found to be the triol **189** resulting from deprotection of the primary silyl ether. This was not considered a useful intermediate due to the number of additional steps expected to be required.

Attempts to circumvent this side-reaction by the use of milder reducing agents were unsuccessful; sodium borohydride was unreactive towards endoperoxide **180**, while the use of lithium triethylborohydride resulted in its complete destruction. The use of

a bulkier/more robust protecting group for the primary alcohol would provide a likely solution, and may also aid in discrimination between the two alcohols.



180 **188** **189**

Scheme 82. *Reagents and Conditions:* (a) $LiAlH_4$, THF, room temp., 1 h 30.

4.4 Conclusion

The *Lycopodium* group of alkaloids is comprised of many widely varied, complex structures, with high potential medicinal value yet limited natural availability. As such, they present important and challenging targets for total synthesis.

Following a review of the synthesis of the fawcettimine group of alkaloids, we outline our strategy for accessing a key bicyclic intermediate to the tetracyclic core of lycoposerramine A by a desymmetrising radical cyclisation.

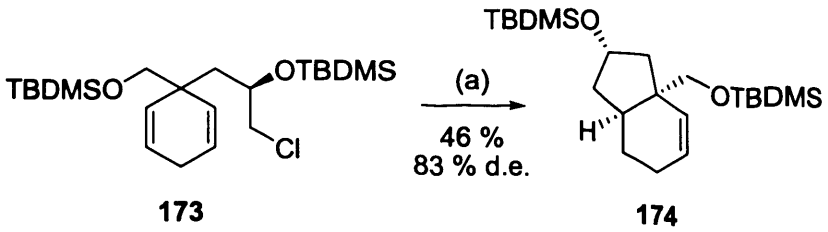
A novel alternative cyclisation was discovered, however, allowing access to a similar intermediate, though with far greater efficiency and simplicity. Many unsuccessful attempts were made to employ this intermediate, and we eventually chose to abandon this approach and return to the original plan, the results of which are discussed in the following chapter.

Chapter 5

Revised Approach to the Synthesis of Lycoposerramine A

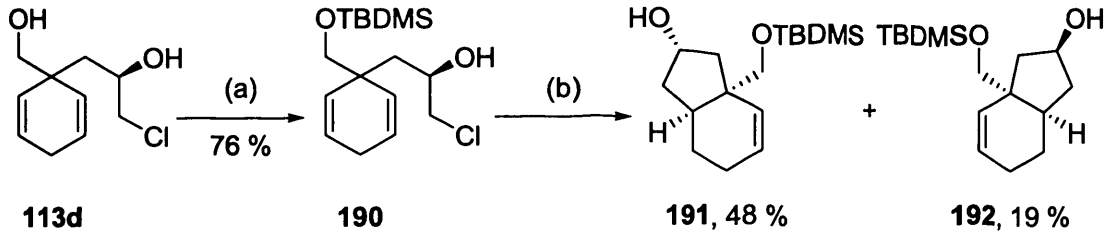
5.1 Radical Cyclisation Approach

Finding ourselves unable to derive any of the benefits from the anionic cyclisation we chose to return to the radical cyclisation, expecting the product to be more amenable to appropriate functionalisation. Compound **174**, shown in Scheme **83**, was obtained by El Sayed in reasonable yield and with good d.e., presumably favouring the diastereoisomer indicated, although this was not proven.[26]



Scheme 83. *Reagents and Conditions*: (a) Bu_3SnH, AIBN, PhH, reflux, 30 h.

After establishing conditions for completion of the sequence from **174** to the key intermediate **172**, we determined that protection of the secondary alcohol should be unnecessary, as this removes the need for differential protection and a deprotection step, mono-silyl ether **190** was prepared and cyclised as shown in Scheme **84**. While the diastereoselectivity was slightly reduced in the absence of the bulky protecting group, the two isomers were now separable by chromatography, and the major isomer **191** was obtained in good yield.

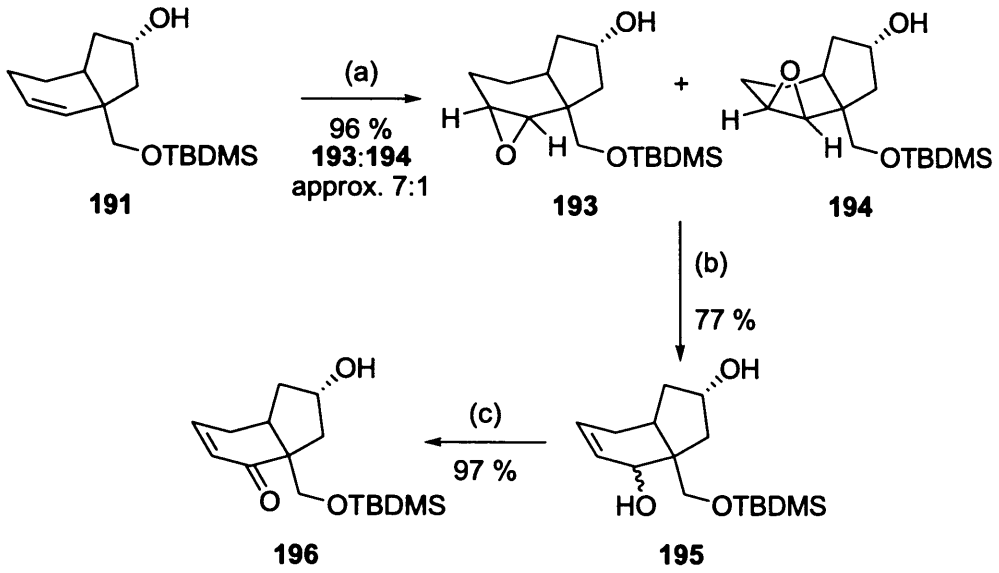


Scheme 84. *Reagents and Conditions*: (a) TBDMSCl, imidazole, DCM; (b) Bu_3SnH, AIBN, PhH, 16 h.

5.2 Functionalisation of the Cyclohexene Ring

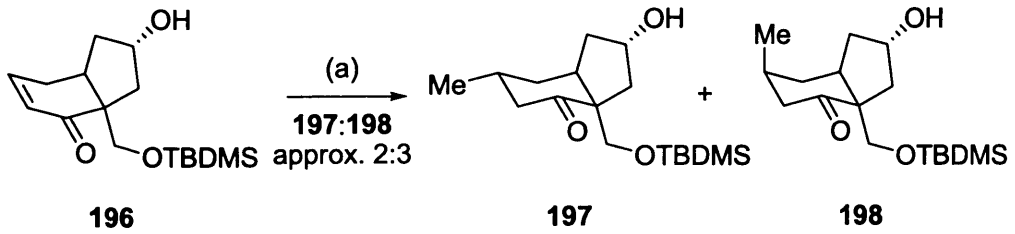
Conversion of **191** into the required enone was now straightforward by the three step sequence shown in Scheme **85**. Reaction with mCPBA provided a mixture of epoxide diastereoisomers **193** and **194**, in an approximate ratio of 7:1. As these stereocentres

are lost in the following steps, separation of these isomers was not attempted.[56] Epoxide opening with the phenylselenyl anion, followed by selenoxide elimination gave allylic alcohol **195** in good yield.[57] Finally, selective oxidation of the allylic alcohol with MnO_2 afforded enone **196**.[58]



Scheme 85. *Reagents and Conditions:* (a) *m*CPBA, $NaHCO_3$, CH_2Cl_2, (b) i) PhSeNa EtOH, ii) H_2O_2, THF, (c) MnO_2, CH_2Cl_2.

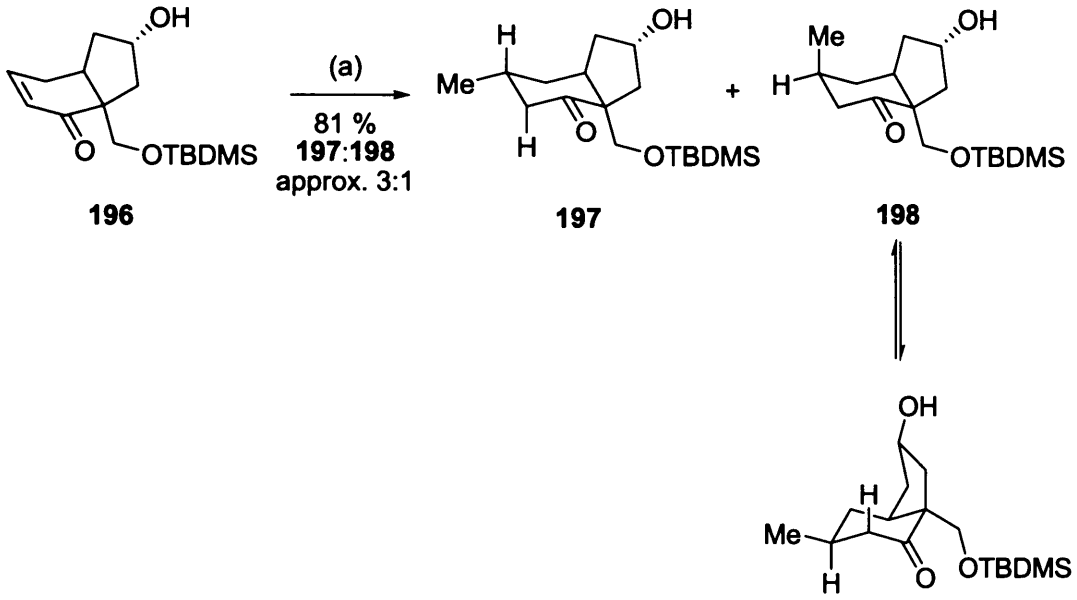
Introduction of the methyl substituent by conjugate addition to enone **196** was attempted firstly with MeLi/CuCN at -78 °C, as shown in Scheme **86**. As no reaction was observed even on warming to room temperature, the mixture was re-cooled to 0 °C and treated with $BF_3.OEt_2$.[59] The ^1H NMR spectrum of the resulting crude material showed it to consist of a mixture of diastereoisomeric addition products, later proven to be **197** and **198**, in an approximate ratio of 2:3.



Scheme 86. *Reagents and Conditions:* (a) i) MeLi (2.4 equiv.), CuCN (1.2 equiv.), THF, -78 °C, 5 min; ii) **196**, -78 °C to room temp., 1 h; iii) $BF_3.OEt_2$, 0 °C, 30 min.

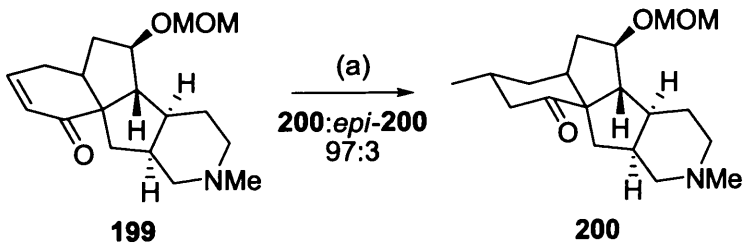
Use of $Me_3Al/Cu(OTf)_2$ in toluene, however, favoured the formation of compound **197** over **198** by a factor of approximately 3:1, as shown in Scheme **87**. While the major

product of this reaction was thought to be the desired diastereoisomer, due to the large axial coupling observed between the CHMe and one of the $CH_2C{=}O$ protons indicated, this was later realised to be inconclusive as the minor isomer could also adopt a conformation that would show a similar coupling. Only by proceeding with this mixture of isomers could the stereochemical assignments of **197** and **198** be confirmed to be as indicated.



Scheme 87. *Reagents and Conditions:* (a) Me_3Al (3 equiv.), $Cu(OTf)_2$ (0.1 equiv.), toluene, 0 °C to room temp., 8 h.

Although we did not attempt further optimisation of this result, a similar system has recently been reported by Mukai to undergo a highly diastereoselective conjugate addition reaction, as shown in Scheme **88**.[60]



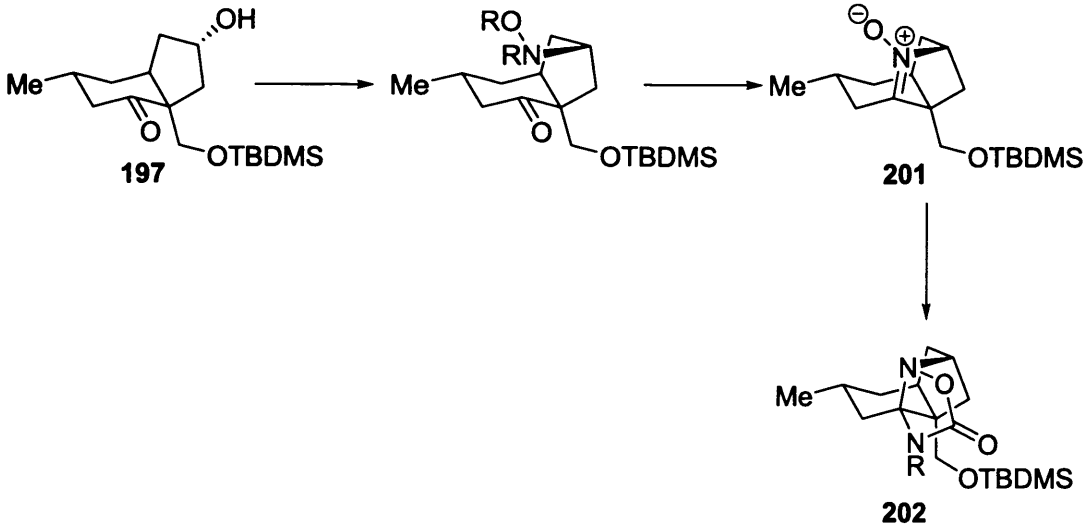
Scheme 88. *Reagents and Conditions:* (a) i) MeLi, CuCN, Et_2O, 0 °C, 15 min; ii) **199**, TMEDA, -40 °C, 12 h.

The formation of compound **200**, an intermediate in the synthesis of magellanine and paniculatine, was found to be favoured by a factor of 97:3 over its C_{15}-epimer under

these conditions. The addition of TMEDA presumably serves to activate the mixed cuprate, a strategy which may also prove more successful in our case, as the use of $BF_3.OEt_2$ or Me_3SiCl can affect the stereoselectivity of the reaction.

5.3 Attempted Construction of the Oxadiazolidinone Ring

With key intermediate **197** now in hand we turned our attention to construction of the oxadiazolidinone ring system. It was initially envisaged that a Mitsunobu reaction with a suitably protected hydroxylamine derivative, followed by deprotection, would allow cyclisation onto the ketone to give nitrone **201**, as shown in Scheme **89**. 1,3-Dipolar cycloaddition of a suitable isocyanate would then allow access to a derivative of the target compound **202**.

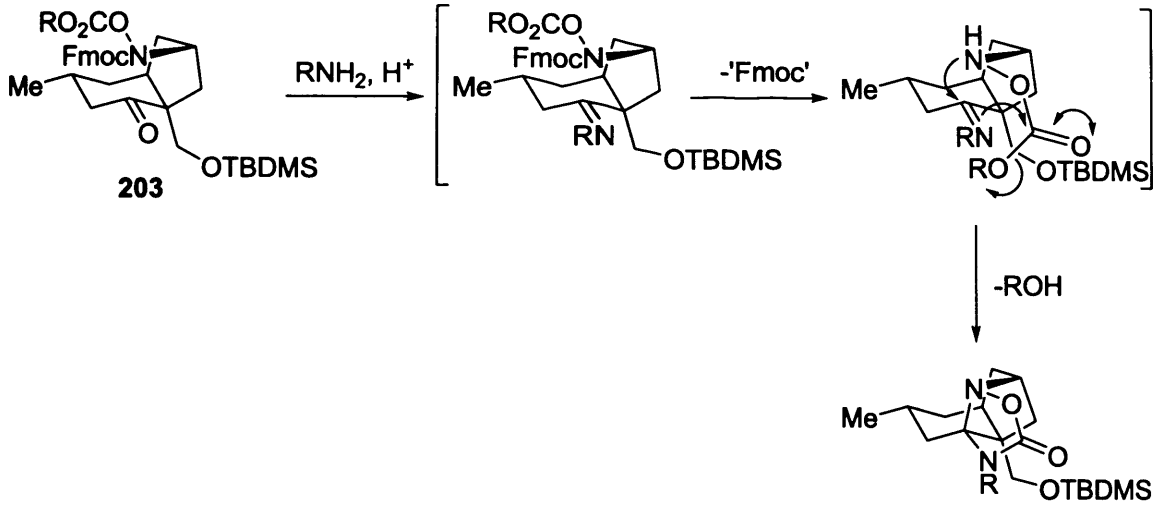


Scheme 89. Proposed route to oxadiazolidinone ring.

Construction of a model, however, suggested that nitrone **201** would experience significant strain as a result of the bridgehead alkene, and that it was, therefore, unlikely to be a suitable intermediate. As the cycloaddition of an isocyanate to a nitrone is the only reported means of accessing this heterocyclic system, we faced quite a challenge in devising an alternative.

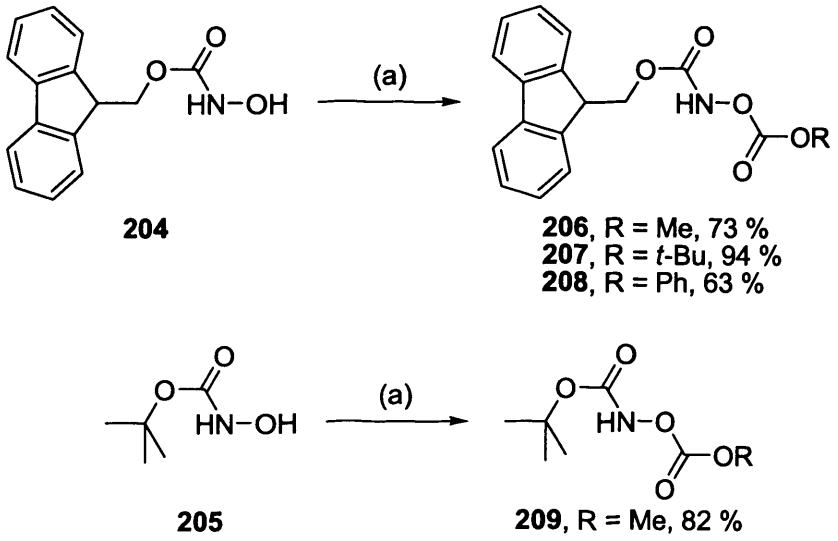
Nevertheless, we conceived of a plausible solution involving a hydroxylamine with orthogonal carbamate and carbonate protecting groups. Following formation of an imine from ketone **203** for instance, deprotection of the base-labile carbamate would allow cyclisation of the free hydroxylamine nitrogen onto the imine, which could, in

turn, cyclise onto the carbonate protecting group with loss of an alcohol, as shown in Scheme **90**.



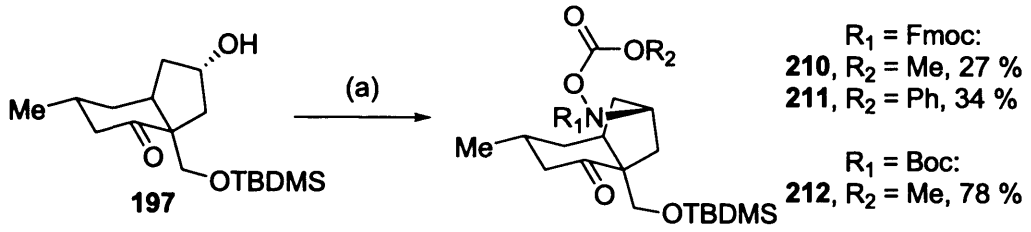
Scheme 90. Proposed alternative cyclisation mechanism.

A range of suitably protected hydroxylamines were prepared in order to test this hypothesis.[61] Schotten-Baumen reaction of *N*-Fmoc hydroxylamine **204**[62] with methyl chloroformate, Boc anhydride and phenylchloroformate, as shown in Scheme **91**, furnished hydroxylamines **206**, **207** and **208** in good yields. Also prepared was the Boc carbamate **209**, by reaction of *N*-Boc hydroxylamine **205** with Boc anhydride.



Scheme 91. *Reagents and Conditions:* (a) ROCOCl (1.0 equiv.), 1:1 THF / EtOAc : saturated aqueous $NaHCO_3$, 0 °C to room temp., 16 h.

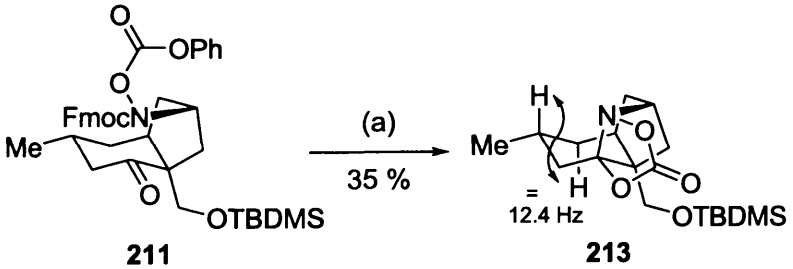
Mitsunobu reaction of **197** with just 1.1 equivalents each of hydroxylamine **206**, DIAD and PPh_3 gave the deired product **210**, although in only low yield and with 26 % recovered starting material. By use of 1.7 equivalents each of **208**, DIAD and PPh_3 the yield of **211** was marginally improved, while the Boc carbamate **212** was obtained in high yield by reaction with 2.0 equivalents of **209** and 1.5 equivalents each of DIAD and PPh_3. The low yields of Fmoc carbamates may be due to the slightly basic nature of the reaction mixture.



Scheme 92. *Reagents and Conditions:* (a) **206**, **208** or **209**, DIAD, PPh_3, DCM, 30 - 60 min.

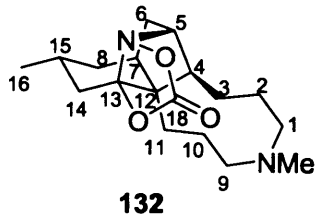
The NMR spectra obtained from these compounds showed very broad signals, presumably due to restricted carbamate bond rotation, and could not be assigned; as such, the spectra are included with the experimental details.

We were delighted to find the product obtained by treatment of **211** with DBU, as shown in Scheme **93**, to be the tetracyclic dioxazolidinone **213**. Since the conformation of the cyclohexane ring is locked in this compound, we were also now able to confirm the methyl group stereochemistry by observation of a large *trans*-diaxial coupling between the methine proton indicated and an adjcaent methylene proton.

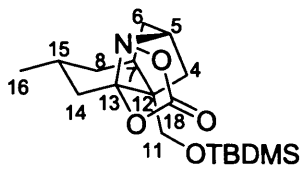


Scheme 93. *Reagents and Conditions:* (a) DBU (2.8 equiv.), THF, room temp., 1 h.

The spectral data obtained from compound **213** were in close agreement with those obtained from the natural product, and are summarised in Table **6**.



132

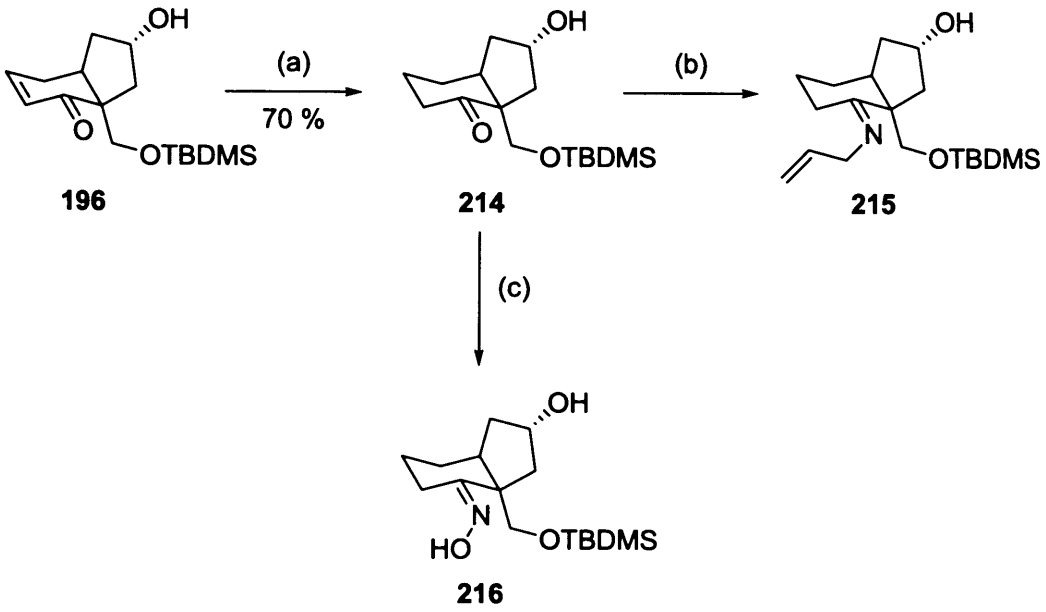


213

	Lycoposerramine A **132**		Compound **213**	
Position	δ_H	δ_C	δ_H	δ_C
4	1.61 (br. s)	52.1	1.64 (d, 11.8) 2.04-1.96 (m)	37.8 or 37.1
5	3.66 (d, 4.3)	69.4	3.73-3.70 (m)	65.4
6	1.84 (m) 1.28 (dd, 13.1, 4.6)	30.4	1.94 (ddd, 13.6, 11.8, 4.1) 1.40 (dt, 13.6, 3.8)	30.8
7	2.06 (m)	35.1	2.37 (dq, 11.5, 3.8)	34.3
8	1.02 (ddd, 13.1, 3.4) 1.42 (m)	31.8	1.24 (ddd, 14.1, 12.4, 3.8) 1.48 (br. d, 14.1)	32.3
12		53.1		54.1
13		88.6		106.6
14	1.20 (dd, 12.7, 12.7) 1.84 (m)	40.5	1.54 (t, 13.5) 2.04-1.96 (m)	37.8 or 37.1
15	1.93 (m)	22.6	2.04-1.96 (m)	23.6
16	0.91 (d, 6.4)	21.4	0.98 (d, 6.4)	21.3
18		157.0		154.1

Table 6. ^{1}H and ^{13}C NMR data of lycoposerramine A **132** and compound **213** in $CDCl_3$.

Given this result, we were optimistic that the target oxadiazolidinone ring system would be accessible by imine formation from the ketone of **211**. Unfortunately, however, we were unable to achieve this, despite many attempts under various conditions. The reason for this is not clear, as the formation of imine **215** from the simplified model compound **214**, shown in Scheme **94**, appeared to be successful, as was the formation of oxime **215** under the conditions reported by Takayama.[63]



Scheme 94. *Reagents and Conditions:* (a) H_2, Pd/C, EtOH / EtOAc (1:2), 4 h; (b) allylamine (3 equiv.), Me_3Al, CH_2Cl_2, 16 h; (c) $NH_2OH.HCl$ (1.2 equiv.), NaOAc (2 equiv.), EtOH, reflux, 16 h.

5.4 Conclusion

The desymmetrising free radical cyclisation of **190** enabled access to an analog of our initial target **172**. Mitsunobu reactions of **197** with protected hydroxylamine derivates then allowed the formation of the dioxazolidinone analog **213** of the core of lycoposerramine A in a novel cascade cyclisation.

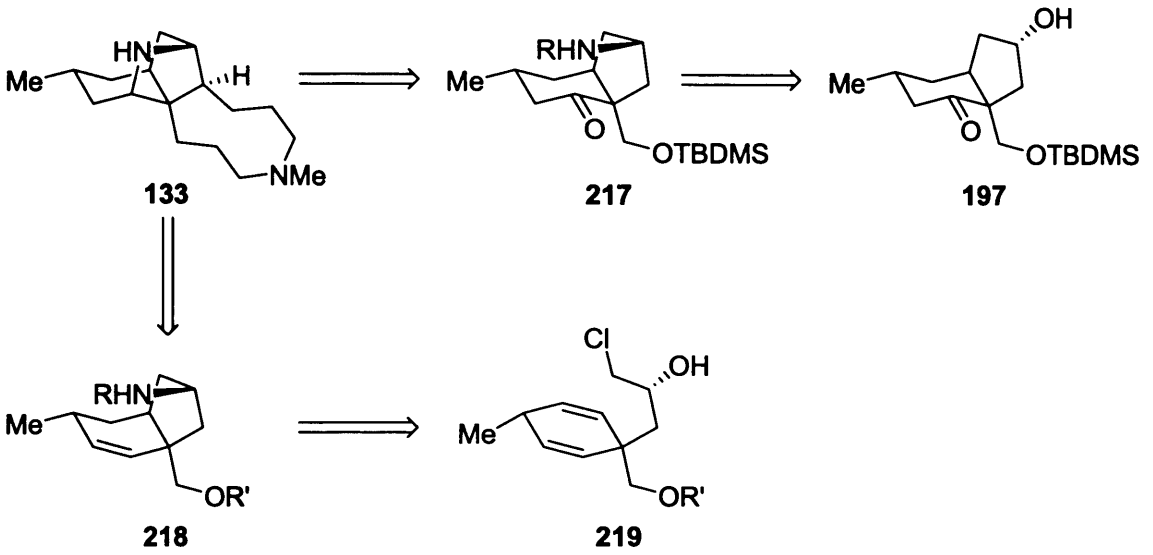
Although imine formation would potentially allow oxadiazolidinone derivatives **202** to be prepared by this method, we were unable to achieve this with hydroxylamines **210-212**. It may be possible to introduce the protected hydroxylamine subsequent to imine formation, however this was not investigated.

Chapter 6

Studies Towards the Synthesis of Lycoposerramine S

6.1 Introduction

We began to consider the possibility of accessing the tricyclic pyrrolidine core of lycoposerramine S **133**[64] by a similar strategy, shown in Scheme **95**. Although amine **217** should be easily prepared from alcohol **197**, cyclisation by an intramolecular reductive amination was not expected to be successful due to the requirement for the formation of a bridgehead imine.

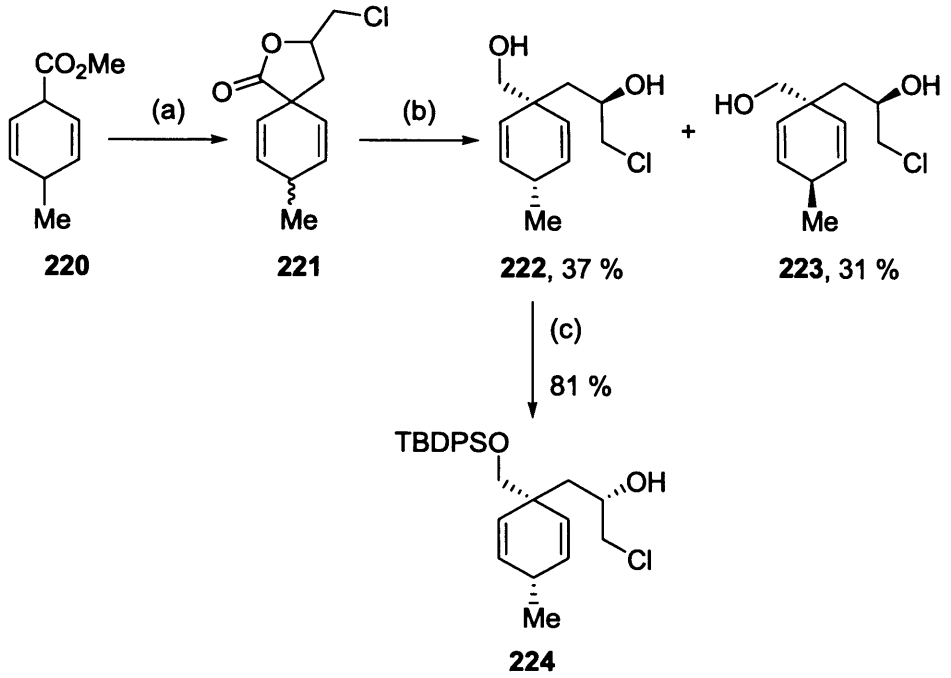


Scheme 95. Retrosynthesis of lycoposerramine S.

Cyclisation onto an alkene such as **218** would more likely be effective, but provides no simple opportunity to introduce the methyl group. We chose, therefore, to begin with the Birch reduction of *p*-toluic acid and accept the poor selectivity expected to result from alkylation of ester **220**.[38]

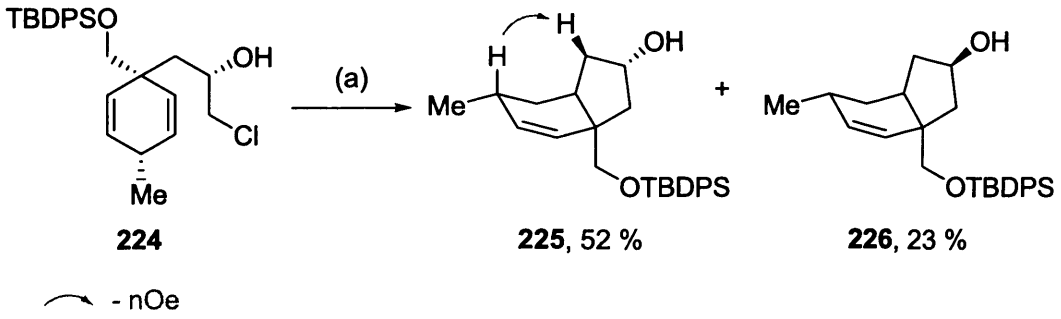
6.2 Results and Discussion

Lactone **221** was, indeed, obtained as nearly a 1:1 mixture of diastereoisomers by alkylation of **220** with epichlorohydrin, as shown in Scheme **96**. As these were inseparable by tlc, the crude mixture was reduced with $NaBH_4$, allowing diols **222** and **223** to be separated by careful chromatography. As we were unable to determine which was which, the first, slightly larger, fraction was chosen and protected as the TBDPS ether **224**. Radical cyclisation, as shown in Scheme **97**, resulted in a mixture of diastereoisomers **225** and **226**, readily separable by chromatography.



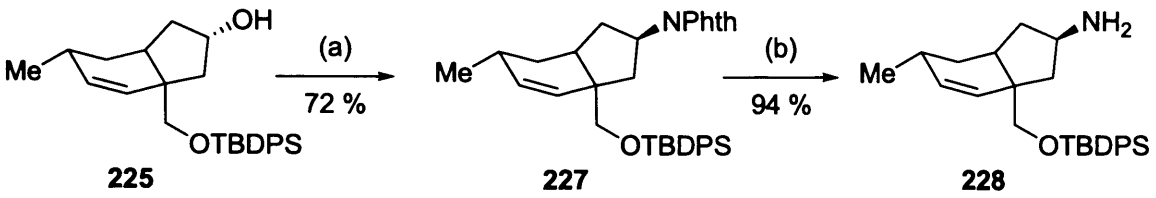
Scheme 96. *Reagents and Conditions:* (a) i) LDA, THF, -78 °C; ii) epichlorohydrin, -78 °C to room temp.; (b) i) $NaBH_4$, EtOH, ii) chromatography; (c) TBDPSCl, imidazole, DCM.

The major isomer **225** showed an nOe between the protons indicated, confirming the methyl group stereochemistry to be as required. The stereochemistry of the secondary alcohol was assumed to be as indicated and was, again, not possible to determine by nOe experiments.



Scheme 97. *Reagents and Conditions:* (a) Bu_3SnH, AIBN, PhH, reflux, 16 h.

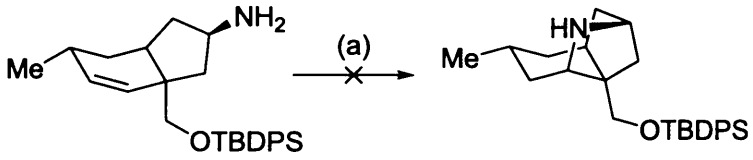
Introduction of the secondary amine was achieved by a Mitsunobu reaction of alcohol **225** with phthalimide, followed by deprotection with hydrazine giving the free amine **228**, as shown in Scheme **98**.



225 227 228

Scheme 98. *Reagents and Conditions:* (a) Phthalimide, PPh_3, DIAD, DCM, (b) $N_2H_2.H_2O$, EtOH, reflux.

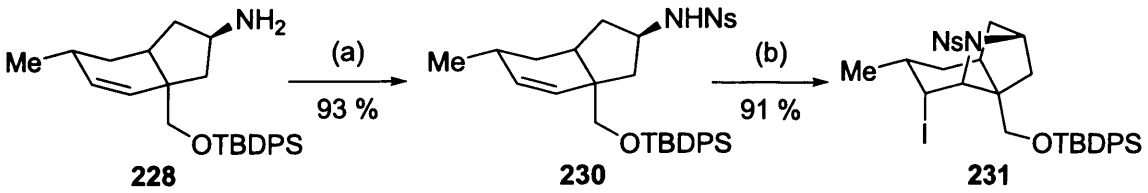
Although direct cyclisation of **228** in a hydroamination reaction would complete the tricyclic core in a single step, the silyl protecting group would be incompatible with the strong acids generally required. The use of a strong base or a transition metal catalyst is a possibility, but this was not investigated. An attempt was made at cyclisation by an aminomercuration reaction, as shown in Scheme **99**, without success.



228 **229**

Scheme 99. *Reagents and Conditions:* (a) i) $Hg(OAc)_2$, $NaHCO_3$, THF/H_2O, 16 h; ii) $NaBH_4$.

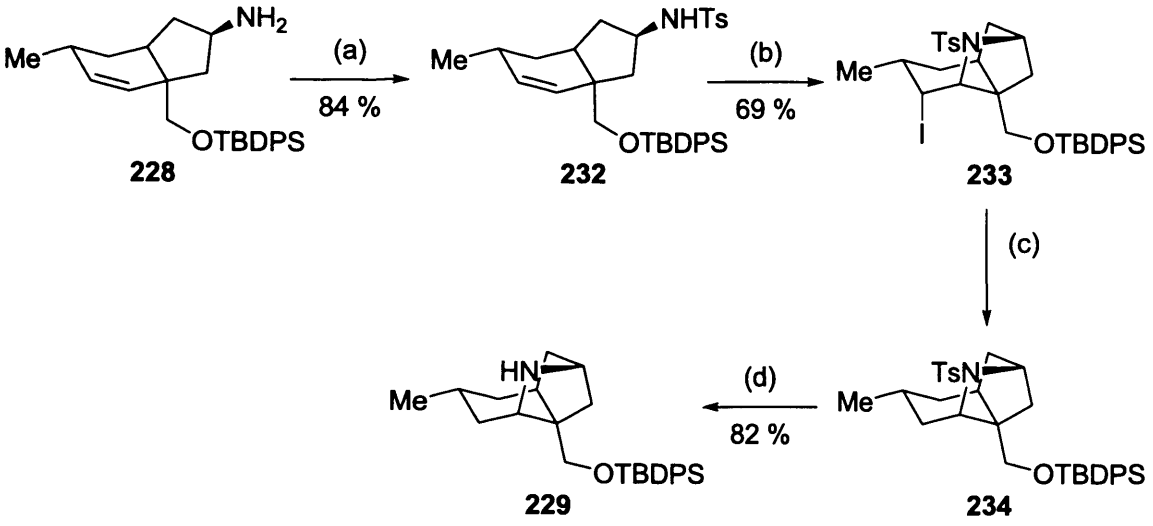
Amine **228** was, therefore, protected as the 4-nitrobenzenesulfonamide **230**, shown in Scheme **100**, which underwent successful iodocyclisation to afford compound **231** in excellent yield. We were unable to remove dehalogenate this compound, however, and attempted deprotection of the nosyl group also failed.



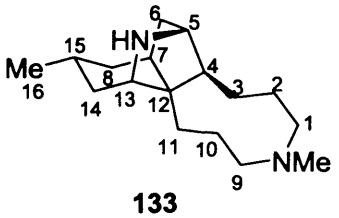
228 **230** **231**

Scheme 100. *Reagents and Conditions:* (a) 4-$NO_2C_6H_4SO_2Cl$, Et_3N, CH_2Cl_2; (b) I_2, $NaHCO_3$, MeCN.

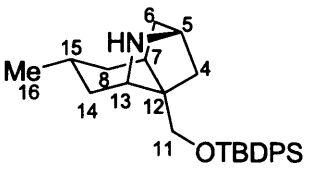
Protection of amine **228** as the tosylate, followed by iodocyclisation, as shown in Scheme **101**, finally allowed both dehalogenation and deprotection of **233**, furnishing the target compound **229**.



Scheme 101. *Reagents and Conditions:* (a) TsCl, Et_3N, CH_2Cl_2; (b) I_2, $NaHCO_3$, MeCN; (c) Bu_3SnH, AIBN, PhH, reflux; (d) Na, naphthalene, THF, -78 °C.



133



229

	Lycoposerramine S **133**		Compound **229**	
Position	δ_H	δ_C	δ_H	δ_C
4	1.57 (m)	50.5	1.55 (d, 9.3) 1.71 (dt, 9.3, 2.2)	44.9
5	3.00 (br. s)	60.2	3.29 (br. s)	56.0
6	1.34 (m) 1.75 (m)	35.6	1.35 (dt, 12.3, 3.4) 1.85 (td, 12.3, 2.8)	38.2
7	1.94 (m)	35.0	2.11-2.05 (m)	34.1
8	1.05 (td, 13.0, 3.2) 1.43 (m)	33.0	0.98-0.88 (m) 1.45 (br. d, 13.7)	33.3
12		49.5		49.8
13	2.97 (br. s)	59.0	3.22 (br. s)	55.2
14	1.69 (m) 1.00 (td, 12.2, 2.7)	33.7	1.62 (br. d, 14.3) 0.98-0.88 (m)	34.6
15	1.87 (m)	20.7	1.86-1.75 (m)	19.7
16	0.88 (d, 6.4)	22.1	0.85 (dd, 6.5)	21.9

Table 7. ^1H and ^{13}C NMR data of lycoposerramine S (**133**) and compound **229** in $CDCl_3$.

The NMR data obtained from compound **229** show many similarities with those of the natural product, as shown in Table **7** and Figures **12** and **13**.[65]

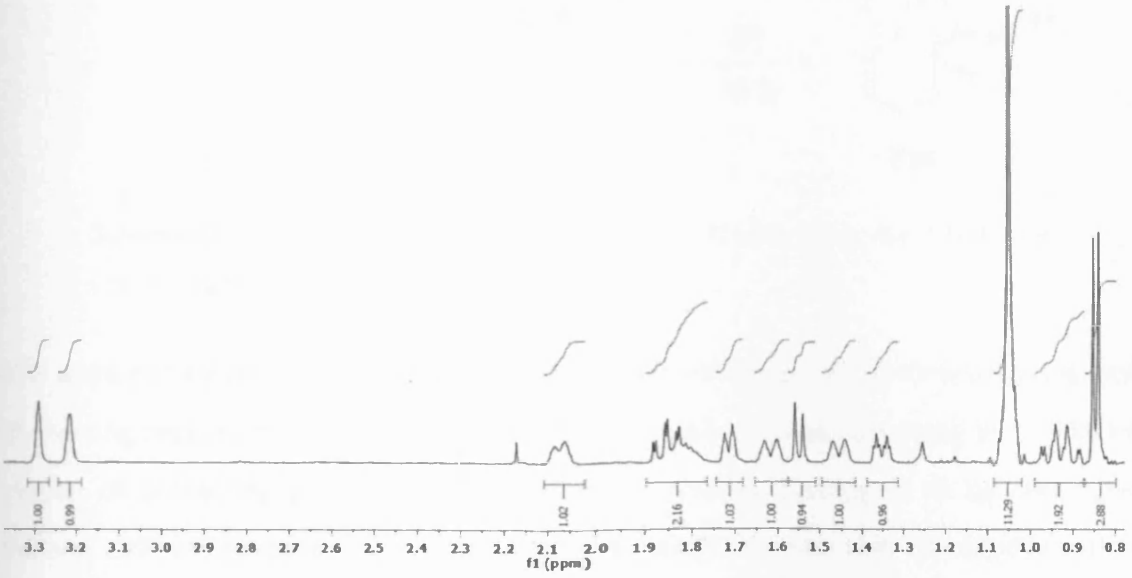


Fig. 12. ^{1}H NMR Spectrum of Compound **229** in $CDCl_3$.

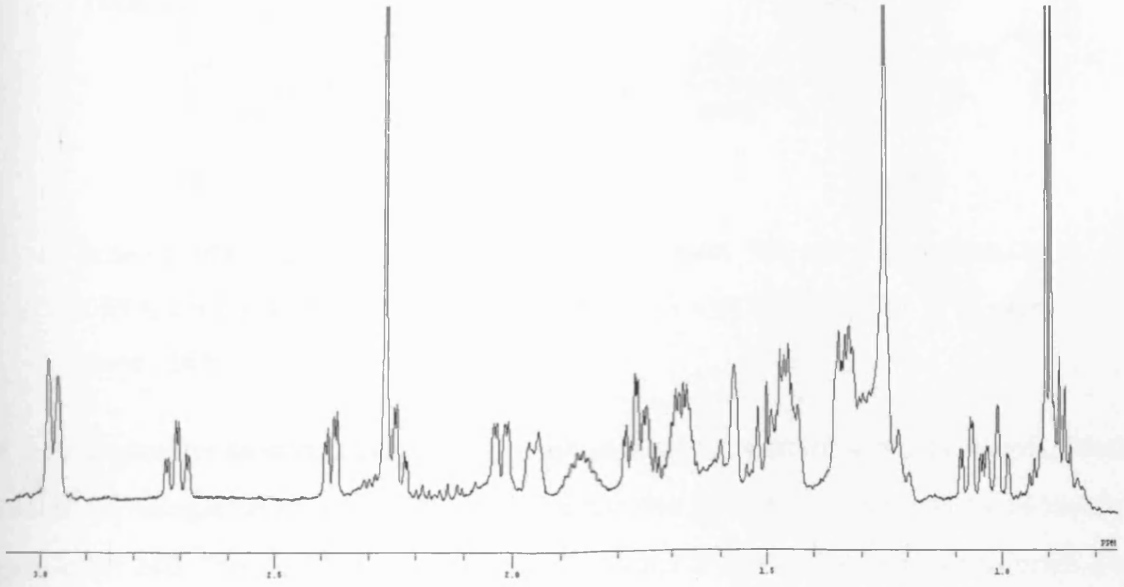
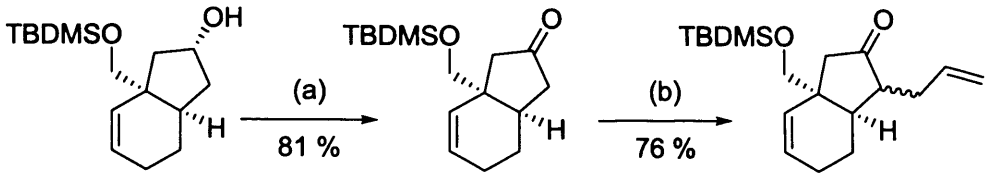


Fig. 13. ^{1}H NMR Spectrum of lycoposerramine S (**133**) in $CDCl_3$.

6.3 The Azonane Ring

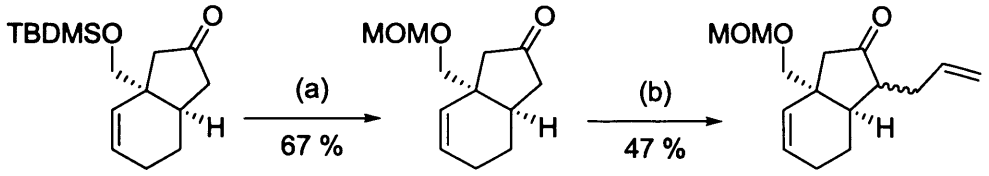
Completing the synthesis of these alkaloids *via* this strategy requires a means by which to form the remaining 9-membered ring. We decided to investigate the possibility of achieving this by alkylation of ketone **235**, obtained by oxidation of alcohol **191**, as shown in Scheme **102**.



191 **235** **236**

Scheme 102. *Reagents and Conditions:* (a) PDC, CH_2Cl_2, 16 h; (b) i) LDA, THF, -78 °C; ii) allyl iodide, -78 °C to room temp., 16 h.

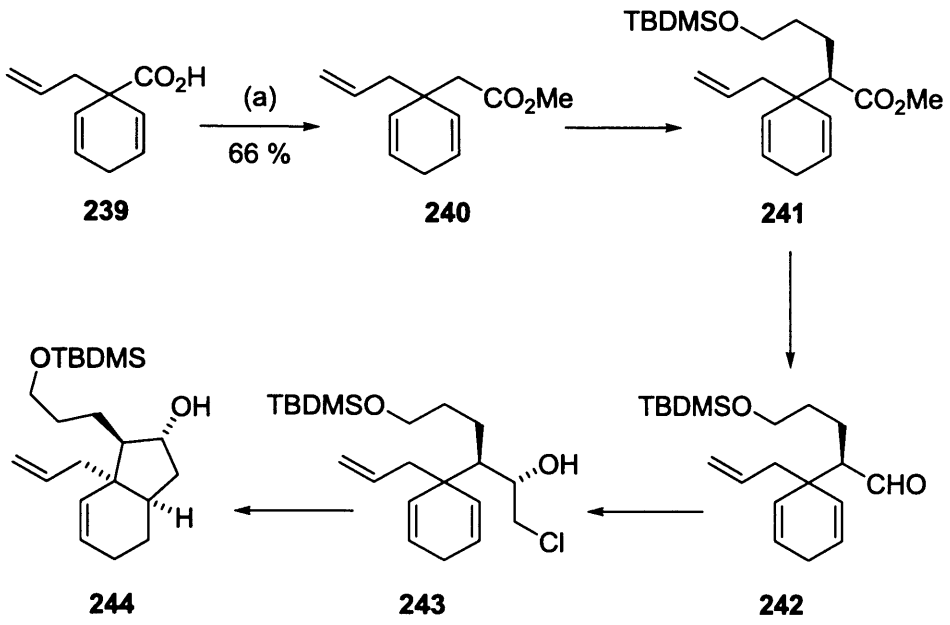
We were not surprised to find that alkylation of this compound with allyl iodide gave the wrong regioisomer **236**, and thought this problem may be overcome by a different choice of protecting group, hopefully allowing enolate formation to be controlled. Ketone **237** was prepared, as shown in Scheme **103**, however this did not change the regioselectivity of alkylation, which gave compound **238**.



191 **237** **238**

Scheme 103. *Reagents and Conditions:* (a) i) TBAF, THF, 30 min; ii) MOM-Cl, DIPEA, CH_2Cl_2, 16 h; (b) i) LDA, THF, -78 °C; ii) allyl bromide, -78 °C to room temp., 16 h.

It may be simpler to introduce this fragment at an earlier point in the synthesis, Arndt-Eistert homologation of acid **239**, prepared by the procedure reported by El-Sayed,[26] gave ester **240**. This could presumably be alkylated and transformed into chloride **243**, where the additional 3-carbon chain would be expected to reinforce the directing effect of the alcohol, allowing radical cyclisation to proceed with higher selectivity. There was insufficient time for this to be investigated, however.



Scheme 104. *Reagents and Conditions:* (a) i) MeO_2CCl, Et_3N, THF, 30 min; ii) CH_2N_2; iii) $AgO_2CC_6H_5$, MeOH, reflux.

6.4 Conclusion

The tricyclic core of lycoposerramine S was synthesized *via* a route involving a desymmetrising free radical cyclisation. Completion of the synthesis requires a means for forming the 9-membered azonane ring. An enolate alkylation strategy was investigated briefly, without success, and an alternative strategy proposed which we were unable to investigate.

Chapter 7

Experimental Details

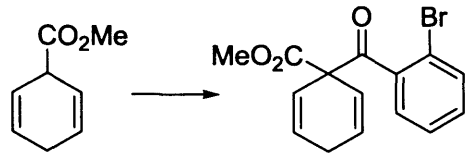
7.1 General Experimental Points

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, or relative to residual $CHCl_3$. Coupling constants (*J*) are reported in Hz. Multiplicity in ^{1}H-NMR 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 was obtained using the DEPT pulse sequence. All NMR spectra were obtained in $CDCl_3$, unless otherwise noted. Flash chromatography was performed using Matrex silica 60 35-70 micron.

Solvents for moisture sensitive reactions were dried by distillation; THF, benzene and toluene from sodium benzophenone ketal and CH_2Cl_2 from CaH_2. Such reactions were conducted under an atmosphere of dry nitrogen.

7.2 Experimental Data for Chapter 2

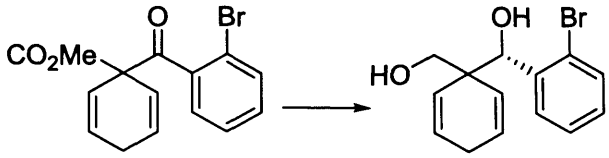
Methyl 1-(2-Bromobenzoyl)cyclohexa-2,5-dienecarboxylate (73b)



72 **73b**

2.5 M *n*-BuLi (4.4 mL, 11 mmol, 1.1 equiv.) was added to DPA (1.5 mL, 10.7 mmol, 1.0 equiv.) at 0 °C. After stirring for 30 min, the resulting gel was dissolved in THF (10 mL) and cooled to -78 °C. A solution of methyl cyclohexa-2,5-diene-1-carboxylate **72** (1.5 g, 10.8 mmol) in THF (5 mL) was added and the stirring was continued for another 30 min. 2-Bromobenzoyl chloride (2.38 g, 10.8 mmol, 1.0 equiv.) was then added as a solution in THF (5 mL) and the reaction mixture was stirred for 1 h at -78 °C, then at room temperature for 18 h. 2 M aqueous HCl (50 mL) was added, the organic layer separated and the aqueous phase extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (14 % EtOAc in hexane) to afford the *title compound* (2.98 g, 86 %) as a yellow solid, m.p. 43 - 45 °C; ν_{max} (neat) 3051, 2952, 2882, 1741, 1705, 1433, 1286, 1231, 1052, 922, 737 cm^{-1}; δ_H (400 MHz) 7.49 (1 H, d, *J* 7.4, aromatic CH), 7.24 - 7.14 (3 H, m, 3 x aromatic CH), 6.03 (2 H, br. d, *J* 10.2, 2 x alkene CH), 5.93 (2 H, br. d, *J* 10.2, 2 x alkene CH), 3.78 (3 H, s, CH_3O), 2.63 (1 H, br. d, *J* 23.5, one of ring CH_2) and 2.45 (1 H, br. d, *J* 23.5, one of ring CH_2); δ_C (100 MHz) 200.4 (C), 170.4 (C), 170.4 (C), 140.7 (C), 133.0 (CH), 130.7 (CH), 128.6 (2 x CH), 127.2 (CH), 126.5 (CH), 122.6 (2 x CH), 118.7 (C), 62.7 (C), 53.0 (CH_3) and 26.1 (CH_2).

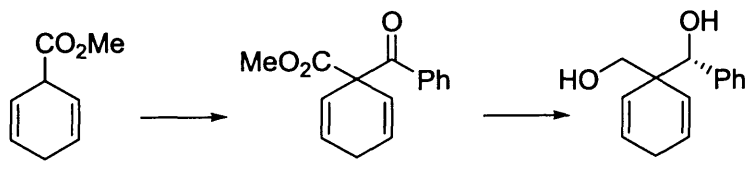
1-(2-Bromophenyl)-(1-(hydroxymethyl)cyclohexa-2,5-dienyl)methanol (74b)



73b **74b**

A solution of methyl 1-(2-bromobenzoyl)cyclohexa-2,5-dienecarboxylate **73b** (2.98 g, 9.8 mmol) in THF (10 mL) was added to a stirred suspension of $LiAlH_4$ (1.1 g, 28.9 mmol, 3.0 equiv.) in THF (20 mL). After stirring for 1 h the reaction was quenched with 2 M aqueous NaOH, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica (33 % EtOAc in hexane) to give the *title compound* (1.90 g, 66 %) as a colourless viscous oil; ν_{max} (neat) 3374, 3025, 2878, 2814, 1469, 1435, 1020 and 749 cm^{-1}; δ_H (400 MHz) 7.44 (1 H, dd, *J* 7.9, 1.8, aromatic CH), 7.41 (1 H, dd, *J* 8.0, 1.1, aromatic CH), 7.24 - 7.18 (1 H, m, aromatic CH), 7.03 (1 H, app. td, *J* 7.6, 1.7, aromatic CH), 6.00 (1 H, app. dtd, *J* 10.3, 3.3, 1.6, one of alkene CH), 5.83 (1 H, app. dq, *J* 10.3, 2.0, one of alkene CH), 5.77 (1 H, app. dtd, *J* 10.3, 3.3, 1.5, one of alkene CH), 5.56 (1 H, app. dq, *J* 10.3, 2.0, one of alkene CH), 5.21 (1 H, s, C*H*OH), 3.79 (1 H, d, *J* 10.5, one of CH_2OH), 3.49 (1 H, d, *J* 10.5, one of CH_2OH), 2.49 (1 H, app. dtt, *J* 23.1, 3.6, 1.8, one of CH_2) and 2.25 (1 H, app. double quintet, *J* 23.1, 2.7, one of CH_2). δ_C (100 MHz) 139.9 (C), 132.3 (CH), 130.2 (CH), 129.6 (CH), 129.0 (CH), 128.5 (CH), 126.9 (CH), 125.8 (CH), 125.4 (CH), 123.9 (C), 76.3 (CH), 69.2 (CH_2), 48.8 (C) and 26.7 (CH_2).

(1-(Hydroxymethyl)cyclohexa-2,5-dienyl)phenylmethanol (74c)



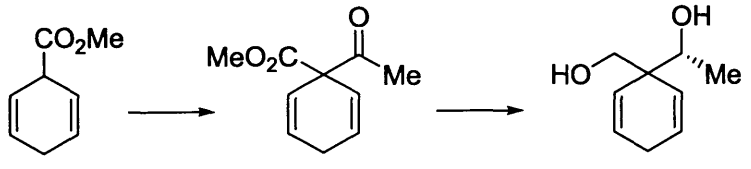
72 **73c** **74c**

2.5 M *n*-BuLi was added to a cooled (-78 °C) solution of DPA (6.1 mL, 43.5 mmol, 1.0 equiv.) in THF (20 mL). This was allowed to warm to room temperature and recooled to -78 °C. A solution of ester **72** (6.0 g, 43.5 mmol) in THF (4 mL) was added slowly and stirring continued for 30 min. A solution of benzoyl chloride (5.1 mL, 43.5 mmol, 1.0

equiv.) in THF (5 mL) was added slowly and the reaction allowed to warm to room temperature. Saturated aqueous NH_4Cl (30 mL) was added, the organic layer separated and the aqueous phase extracted with Et_2O (2 x 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by Kugelrohr distillation (oven temp. 200 °C at 0.5 mm Hg) to give the keto-ester **73c** (7.9 g, 75 %) as a pale yellow oil.

This was added as a solution in THF (20 mL) to a suspension of $LiAlH_4$ (2.5 g, 65 mmol, 2 equiv.) in THF (60 mL). After stirring for 30 min the reaction was quenched with 2 M aqueous NaOH, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (30 - 50 % EtOAc in petroleum ether) giving the *title compound* (5.89 g, 84 %) as a viscous, pale yellow oil. ν_{max} (CH_2Cl_2) 3362, 3027, 2876, 1453, 1022 and 700 cm^{-1}; δ_H (500MHz) 7.30 - 7.15 (5 H, m, 5 x aromatic CH), 5.93 (1 H, dtd, *J* 10.2, 3.3, 1.6, one of alkene CH), 5.81 (1 H, dtd, *J* 10.2, 3.3, 1.6, one of alkene CH), 5.67 (1 H, dq, *J* 10.2, 2.0, one of alkene CH), 5.41 (1 H, dq, *J* 10.2, 2.0, one of alkene CH), 4.59 (1 H, s, PhCH), 3.51 (1 H, d, *J* 10.5, one of CH_2OH), 3.41 (1 H, d, *J* 10.5, one of CH_2OH), 2.80 - 2.60 (1 H, br. s, OH), 2.50 (1 H, dtt, *J* 23.0, 3.5, 1.8, one of CH_2), 2.34 (1 H, dtt, *J* 23.0, 3.0, 2.4, one of CH_2) and 2.25 - 2.00 (1 H, br. s, OH); δ_C (125 MHz) 140.4 (C), 128.9 (CH), 128.3 (CH), 127.6 (2 x CH), 127.5 (2 x CH), 127.5 (CH), 126.5 (CH), 126.1 (CH), 78.9 (CH), 68.6 (CH_2), 47.5 (C) and 26.8 (CH_2).

1-(1-(Hydroxymethyl)cyclohexa-2,5-dienyl)ethanol (74a)



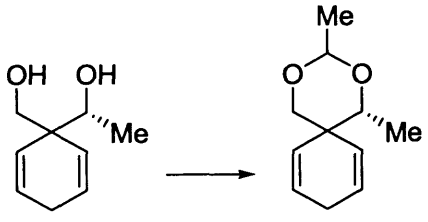
72 **73a** **74a**

To a solution of DPA (2.0 mL, 14.3 mmol, 1.0 equiv.) in THF (50 mL) at -78 °C was added 2.5 M *n*-BuLi (5.7 mL, 14.3 mmol, 1.0 equiv.). After stirring for 30 min a solution of methyl cyclohexa-2,5-diene-1-carboxylate **72** (2.0 g, 14.5 mmol) in THF (10 mL) was added and stirring was continued for another 30 min. Acetyl chloride (1.1 mL, 15.5 mmol, 1.1 equiv.) was added and the reaction mixture was stirred for 1 h at -78 °C,

then at room temperature for 18 h. Saturated NH_4Cl solution (50 mL) was added, the organic layer separated and the aqueous phase extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give the crude keto-ester **73a** (3.3 g) as an orange oil.

This was dissolved in THF (10 mL) and added to a stirred suspension of $LiAlH_4$ (1.5 g, 39.5 mmol, 2.7 equiv.) in THF (30 mL). After stirring for 1 h, the reaction was quenched with 2 M NaOH, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue chromatographed on silica (33 % EtOAc in hexane) to give the *title compound* (1.50 g, 67 %) as a colourless solid, m.p. 50 - 52 °C; ν_{max} (CH_2Cl_2) 3394, 3022, 2973, 2879, 1635, 1421, 1372, 1130, 1025, 904 cm^{-1}; δ_H (400 MHz) 5.99 (1 H, m, one of alkene CH), 5.88 (1 H, m, one of alkene CH), 5.68 (1 H, app. dd, *J* 10.3, 2.0, one of alkene CH), 5.36 (1 H, app. dd, *J* 10.3, 2.0, one of alkene CH), 3.75 (1 H, q, *J* 6.4, C*H*OH), 3.58 (1 H, d, *J* 10.5, one of CH_2OH), 3.50 (1 H, d, *J* 10.5, one of CH_2OH), 2.70 - 2.56 (2 H, m, CH_2), 2.52 (2 H, br. s, 2 x OH) and 1.04 (3 H, d, *J* 6.4 Hz, CH_3); δ_C (100 MHz) 128.4 (CH), 127.9 (CH), 127.0 (CH), 125.5 (CH), 72.9 (CH), 69.6 (CH_2), 46.7 (C), 27.2 (CH_2) and 19.1 (CH_3).

1,3-Dimethyl-2,4-dioxaspiro(5.5)undeca-7,10-diene (60a)

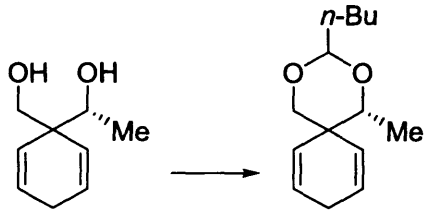


74a **60a**

To a solution of 1-(1-(hydroxymethyl)cyclohexa-2,5-dienyl)ethanol **74a** (440 mg, 2.9 mmol) and acetaldehyde (3.2 mL , 57.1 mmol, 20 equiv.) in CH_2Cl_2 (20 mL) was added PPTS (500 mg, 2.0 mmol, 0.43 equiv.). After stirring for 18 h the reaction was quenched with water (20 mL), the organic layer separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (5 % Et_2O in petroleum ether) to give the *title compound* (444 mg, 85 %) as a colourless oil; ν_{max}

(neat) 2981, 2844, 1454, 1410, 1378, 1320, 1234, 1147, 956, 868 and 703 cm^{-1}; δ_H (400 MHz) 6.04 - 5.96 (1 H, m, one of alkene CH), 5.89 - 5.77 (2 H, m, 2 x alkene CH), 5.09 - 5.01 (1 H, m, one of alkene CH), 4.70 (1 H, q, *J* 5.0, CHO_2), 3.65 (1 H, d, *J* 11.0, one of CH_2O), 3.52 (1 H, q, *J* 6.3, CH_3CHO), 3.45 (1 H, d, *J* 11.0, one of CH_2O), 2.64 - 2.57 (2 H, m, ring CH_2), 1.30 (3 H, d, *J* 5.0, CH_3) and 1.00 (3 H, d, *J* 6.3, CH_3); δ_C (100 MHz) 128.7 (CH), 126.6 (CH), 126.2 (CH), 125.3 (CH), 99.3 (CH), 79.2 (CH), 76.1 (CH_2), 39.7 (C), 27.4 (CH_2), 21.1 (CH_3) and 16.9 (CH_3).

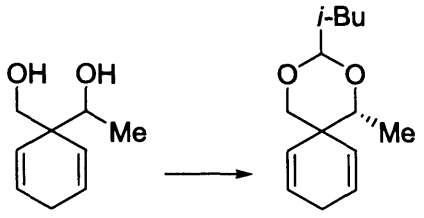
3-Butyl-1-methyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (60b)



74a **60b**

To a solution of 1-(1-(hydroxymethyl)cyclohexa-2,5-dienyl)-ethanol **74a** (385 mg, 2.5 mmol) and valeraldehyde (1.3 mL, 12.5 mmol, 5 equiv.) in CH_2Cl_2 (20 mL) was added PPTS (126 mg, 0.5 mmol, 0.2 equiv.). After stirring for 18 h the reaction was quenched with water (20 mL) and the organic layer separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic extracts dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (5 % Et_2O in petroleum ether) to give the *title compound* (488 mg, 88 %) as a colourless oil. ν_{max} (neat) 2956, 2860, 1455, 1410, 1376, 1146, 1022, 748 and 704 cm^{-1}; δ_H (400 MHz) 6.06 (1 H, app. dq, *J* 10.3, 1.9, one of alkene CH), 5.90 (2 H, m, 2 x alkene CH), 5.12 (1 H, app. dq, *J* 11.0, 2.0, one of alkene CH), 4.60 (1 H, t, *J* 5.1, CHO_2), 3.73 (1 H, d, *J* 11.0, one of CH_2O), 3.57 (1 H, q, *J* 6.4, CHO), 3.51 (1 H, d, *J* 11.0, one of CH_2O), 2.70-2.65 (2 H, m, ring CH_2), 1.69 - 1.63 (2 H, m, CH_2CHO_2), 1.45 - 1.30 (4 H, m, alkyl CH_2), 1.06 (3 H, d, *J* 6.4, $CHOCH_3$) and 0.90 (3 H, t, *J* 7.2, CH_2CH_3); δ_C (125 MHz) 128.6 (CH), 126.7 (CH), 126.4 (CH), 125.1 (CH), 102.5 (CH), 79.2 (CH), 76.2 (CH_2), 39.9 (C), 34.7 (CH_2), 27.4 (CH_2), 26.1 (CH_2), 22.6 (CH_2), 16.9 (CH_3) and 14.0 (CH_3).

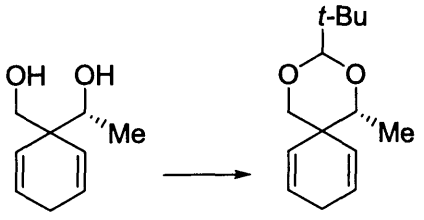
3-Isobutyl-1-methyl-2,4-dioxaspiro(5.5)undeca-7,10-diene (60c)



74a **60c**

To a solution of 1-(1-(hydroxymethyl)cyclohexa-2,5-dienyl)-ethanol **74a** (413 mg, 2.7 mmol) and isovaleraldehyde (1.4 mL, 13.4 mmol, 5 equiv.) in CH_2Cl_2 (20 mL) was added PPTS (135 mg, 0.54 mmol, 0.2 equiv.). After stirring for 18 h the reaction was quenched with water (20 mL) and the organic layer separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic extracts dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (5 % Et_2O in petroleum ether) to give the *title compound* (518 mg, 87 %) as a colourless oil; ν_{max} (neat) 3017, 2954, 2869, 1454, 1410, 1375, 1261, 1099, 800 cm^{-1}; δ_H (400 MHz) 5.99 (1 H, app. dd, *J* 10.4, 1.7, one of alkene CH), 5.87 - 5.78 (2 H, m, 2 x alkene CH), 5.05 (1 H, app. dd, *J* 10.4, 1.8, one of alkene CH), 4.58 (1 H, t, *J* 5.4, CHO_2), 3.66 (1 H, d, *J* 11.0, one of CH_2O), 3.50 (1 H, q, *J* 6.4, CH_3CHO), 3.45 (1 H, d, *J* 11.0, one of CH_2O), 2.70 - 2.53 (2 H, m, ring CH_2), 1.76 (1 H, app. nonet, *J* 6.8, $CH(CH_3)_2$), 1.55 - 1.39 (2 H, m, $CH_2CH(CH_3)_2$), 0.99 (3 H, d, *J* 6.4, CH_3) and 0.85 (6 H, app. d, *J* 6.6, 2 x CH_3); δ_C (100 MHz) 128.6 (CH), 126.7 (CH), 126.3 (CH), 125.2 (CH), 101.5 (CH), 79.3 (CH), 76.2 (CH_2), 43.7 (CH_2), 39.9 (C), 27.4 (CH_2), 23.9 (CH), 23.0 (CH_3), 22.7 (CH_3) and 16.9 (CH_3).

3-*tert*-Butyl-1-methyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (60d)

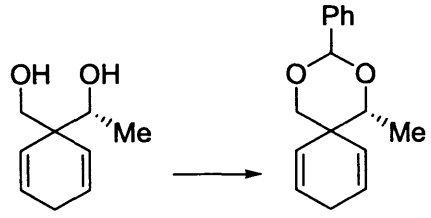


74a **60d**

To a solution of 1-(1-(hydroxymethyl)cyclohexa-2,5-dienyl)-ethanol **74a** (268 mg, 1.7 mmol) and pivalaldehyde (0.95 mL, 8.7 mmol, 5 equiv.) in CH_2Cl_2 (20 mL) was added

PPTS (87 mg, 0.35 mmol, 0.2 equiv.). After stirring for 18 h the reaction was quenched with water (20 mL) and the organic layer separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic extracts dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (5 - 100 % Et_2O in petroleum ether) to give the *title compound* (269 mg, 71 %) as a colourless oil; ν_{max} (neat) 2958, 2839, 1484, 1454, 1404, 1382, 1361, 1214, 1163, 1135, 1098, 1045, 1022, 990, 942, 746 and 704 cm^{-1}; δ_H (400 MHz) 6.01 (1 H, app. dq, *J* 10.3, 2.0, one of alkene CH), 5.87 (2 H, m, 2 x alkene CH), 5.11 (1 H, app. dq, *J* 10.3, 2.0, one of alkene CH), 4.18 (1 H, s, CHO_2), 3.73 (1 H, d, *J* 10.8, one of CH_2O), 3.52 (1 H, q, *J* 6.5, CHO), 3.48 (1 H, d, *J* 10.8, one of CH_2O), 2.70 - 2.64 (2 H, m, ring CH_2), 1.02 (3 H, d, *J* 6.5, CH_3) and 0.93 (9 H, s, $C(CH_3)_3$); δ_C (125 MHz) 128.3 (CH), 127.0 (CH), 126.6 (CH), 124.8 (CH), 107.6 (CH), 79.0 (CH), 76.2 (CH_2), 40.0 (C), 34.9 (C), 27.4 (CH_2), 24.7 (CH_3) and 16.9 (CH_3).

(1*RS*,3*SR*)-1-Methyl-3-phenyl-2,4-dioxaspiro(5.5)undeca-7,10-diene (60e)

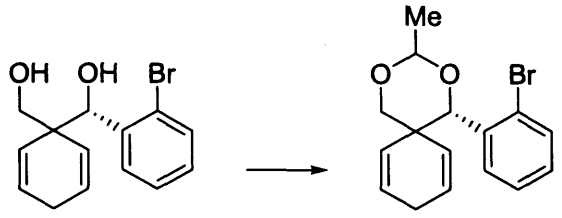


74a **60e**

To a solution of 1-(1-(hydroxymethyl)cyclohexa-2,5-dienyl)ethanol **74a** (408 mg, 2.6 mmol) and benzaldehyde (1.35 mL, 13.2 mmol, 5 equiv.) in CH_2Cl_2 (20 mL) was added PPTS (132 mg, 0.53 mmol, 0.2 equiv.). After stirring for 18 h the reaction mixture was quenched with water (20 mL) and the organic layer separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic extracts dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (5 % Et_2O in petroleum ether) to give the *title compound* (575 mg, 90 %) as a colourless oil; ν_{max} (neat) 3033, 2978, 2840, 1452, 1400, 1373, 1161, 1132, 1087, 1021, 970, 746 cm^{-1}; δ_H (400 MHz) 7.47 - 7.43 (2 H, m, 2 x aromatic CH), 7.33 - 7.23 (3 H, m, 3 x aromatic CH), 6.14 (1 H, app. dq, *J* 10.4, 2.0, one of alkene CH), 5.91 - 5.83 (2 H, m, 2 x alkene CH), 5.50 (1 H, s, ArCHO), 5.12 (1 H, app. dq, *J* 10.4, 2.0, one of alkene CH), 3.83 (1 H, d,

J 11.0, one of CH_2O), 3.74 (1 H, q, *J* 6.4, CH_3CHO), 3.66 (1 H, d, *J* 11.0, one of CH_2O), 2.72 - 2.56 (2 H, m, ring CH_2) and 1.07 (3 H, d, *J* 6.4, CH_3); δ_C (100 MHz) 138.6 (C), 129.0 (CH), 128.9 (CH), 128.4 (2 x CH), 126.6 (CH), 126.3 (2 x CH), 126.2 (CH), 125.4 (CH), 102.0 (CH), 80.0 (CH), 76.6 (CH_2), 39.9 (C), 27.5 (CH_2) and 17.0 (CH_3).

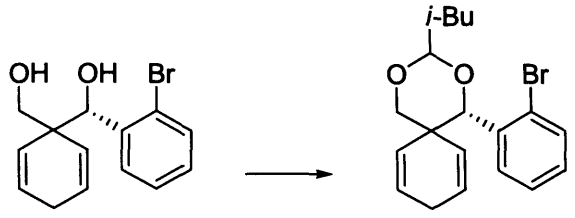
(1*SR*,3*SR*)-1-(2-Bromophenyl)-3-methyl-2,4-dioxaspiro(5.5)undeca-7,10-diene (60f)



74b **60f**

To a solution of 1-(2-bromophenyl)-(1-(hydroxymethyl)-cyclohexa-2,5-dienyl)methanol **74b** (808 mg, 2.73 mmol) and acetaldehyde (5.0 mL, 89.4 mmol, 33 equiv.) in CH_2Cl_2 (20 mL) was added PPTS (0.5 g, 2.0 mmol, 0.7 equiv.). After stirring for 48 h the reaction was quenched with water (20 mL) and the organic layer separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL), the combined organic extracts dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (5 % Et_2O in petroleum ether) to afford the *title compound* (667 mg, 76 %) as an off-white solid, m.p. 52 - 54 °C; ν_{max} (CH_2Cl_2) 3025, 2991, 2858, 2360, 1698, 1474, 1410, 1162, 1117, 1032, 911 cm^{-1}; δ_H (400 MHz) 7.37 (2 H, m, 2 x aromatic CH), 7.20 - 7.14 (1 H, m, aromatic CH), 7.01 (1 H, app. td, *J* 7.6, 1.8, aromatic CH), 6.21 (1 H, app. dq, *J* 10.3, 2.0 Hz, one of alkene CH), 5.74 - 5.68 (1 H, m, one of alkene CH), 5.65 - 5.59 (1 H, m, one of alkene CH), 5.48 (1 H, app. dq, *J* 10.1, 2.0, one of alkene CH), 5.08 (1 H, s, CHAr), 4.94 (1 H, q, *J* 5.0, CH_3CHO), 3.81 (1 H, d, *J* 11.0, one of CH_2O), 3.76 (1 H, d, *J* 11.0, one of CH_2O), 2.34 (1 H, app. dtt, *J* 22.8, 3.7, 1.8, one of ring CH_2), 1.90 (1 H, app. double quintet, *J* 22.8, 2.6, one of ring CH_2) and 1.38 (3 H, d, *J* 5.0, CH_3CHO); δ_C (100 MHz) 137.3 (C), 131.9 (CH), 130.9 (CH), 128.9 (CH), 128.5 (CH), 126.4 (CH), 126.4 (CH), 126.3 (CH), 125.3 (CH), 123.6 (C), 100.2 (CH), 83.7 (CH), 76.5 (CH_2), 42.1 (C), 26.8 (CH_2) and 21.1 (CH_3) ppm.

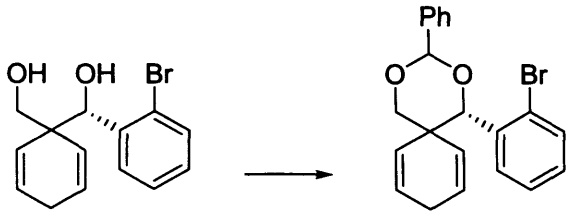
(1*SR*,3*SR*)-1-(2-Bromophenyl)-3-isobutyl-2,4-dioxaspiro(5.5)undeca-7,10-diene (60g)



74b **60g**

A solution of 1-(2-bromophenyl)-(1-(hydroxymethyl)cyclohexa-2,5-dienyl)methanol **74b** (758 mg, 2.6 mmol) isovaleraldehyde (2.7 mL, 25.7 mmol, 10 equiv.) and PPTS (0.5 g, 2.0 mmol, 0.8 equiv.) in CH_2Cl_2 (20 mL) was stirred for 48 h. The reaction was quenched with water (20 mL), the organic layer separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL) The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica (5 % Et_2O in petroleum ether) to give the *title compound* (644 mg, 69 %) as a colourless oil; ν_{max} (neat) 3026, 2956, 2923, 2854, 1467, 1439, 1362, 1260, 1128, 1017 and 804 cm^{-1}; δ_H (400 MHz) 7.38 (1 H, dd, *J* 8.0, 1.1 Hz, aromatic CH), 7.36 (1 H, dd, *J* 7.8, 1.8, aromatic CH), 7.19 - 7.14 (1 H, m, aromatic CH), 7.00 (1 H, app. td, *J* 7.6, 1.8 Hz, aromatic CH), 6.19 (1 H, app. dq, *J* 10.4, 1.9, one of alkene CH), 5.72 - 5.67 (1 H, m, one of alkene CH), 5.65 - 5.59 (1 H, m, one of alkene CH), 5.49 (1 H, app. dq, *J* 10.2, 1.9, one of alkene CH), 5.05 (1 H, s, ArCH), 4.82 (1 H, t, *J* 5.4, CHO), 3.81 (1 H, d, *J* 11.0, one of CH_2O), 3.74 (1 H, d, *J* 11.0, one of CH_2O), 2.35 (1 H, app. dtt, *J* 22.9, 3.7, 1.9, one of ring CH_2), 1.89 (1 H, app. doubled quintet, *J* 22.9, 2.7, one of ring CH_2), 1.80 (1 H, app. nonet, *J* 6.7, $CH(CH_3)_2$), 1.64 - 1.48 (2 H, m, $CH_2CH(CH_3)_2$), 0.88 (3 H, d, *J* 6.7, CH_3) and 0.86 (3 H, d, *J* 6.7, CH_3); δ_C (100 MHz) 137.5 (C), 131.9 (CH), 131.0 (CH), 128.9 (CH), 128.4 (CH), 126.4 (CH), 126.3 (CH), 126.3 (CH), 125.4 (CH), 123.5 (C), 102.2 (CH), 83.8 (CH), 76.5 (CH_2), 43.7 (CH_2), 42.1 (C), 26.8 (CH_2), 23.8 (CH), 23.2 (CH_3) and 22.8 (CH_3).

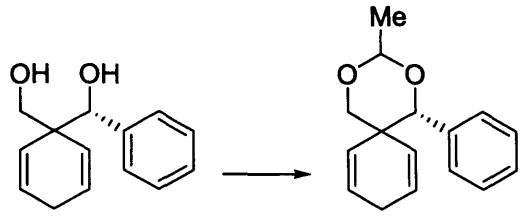
(1*SR*,3*SR*)-1-(2-Bromophenyl)-3-phenyl-2,4-dioxaspiro(5.5)undeca-7,10-diene (60h)



74b **60h**

To a solution of 1-(2-bromophenyl)-(1-(hydroxymethyl)cyclohexa-2,5-dienyl)methanol **74b** (1.0 g, 3.4 mmol) and benzaldehyde (3.5 mL, 34 mmol, 10 equiv.) in CH_2Cl_2 (20 mL) was added PPTS (0.5 g, 2.0 mmol, 0.6 equiv.). The resulting mixture was stirred at room temperature for 6 d. The reaction mixture was quenched with saturated $NaHCO_3$ and the organic layer separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic extracts dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (5 % Et_2O in petroleum ether) to give the *title compound* (716 mg, 55 %) as a colourless solid, m.p. 104 - 105 °C; ν_{max} (CH_2Cl_2) 3022, 2886, 2852, 1449, 1401, 1322, 1223, 1112, 1023 and 753 cm^{-1}; δ_H (400 MHz) 7.82 (2 H, d, *J* 7.8, 2 x aromatic CH), 7.75 (1 H, dd, *J* 7.8, 1.6 Hz, aromatic CH), 7.70 (1 H, dd, *J* 8.0, 0.9 Hz, aromatic CH), 7.67 - 7.58 (3 H, m, 3 x aromatic CH), 7.48 (1 H, app. t, *J* 7.9, aromatic CH), 7.32 (1 H, app. td, *J* 7.7, 1.7, aromatic CH), 6.65 (1 H, app. dq, *J* 10.3, 1.6 Hz, one of alkene CH), 6.11 - 6.02 (2 H, m, one of alkene CH and PhCHO), 5.98 (1 H, br. d, *J* 10.1, one of alkene CH), 5.88 (1 H, app. dq, *J* 10.2, 1.7, one of alkene CH), 5.62 (1 H, s, ArCH), 4.30 (2 H, app. singlet, CH_2O), 2.75 - 2.63 (1 H, m, one of ring CH_2) and 2.29 - 2.18 (1 H, m, one of ring CH_2); δ_C (100 MHz) 138.3 (C), 137.2 (C), 131.9 (CH), 131.1 (CH), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.3 (2 x CH), 126.6 (CH), 126.4 (CH), 126.3 (2 x CH), 126.1 (CH), 125.2 (CH), 123.6 (C), 102.5 (CH), 84.2 (CH), 76.9 (CH_2), 42.3 (C) and 26.8 (CH_2).

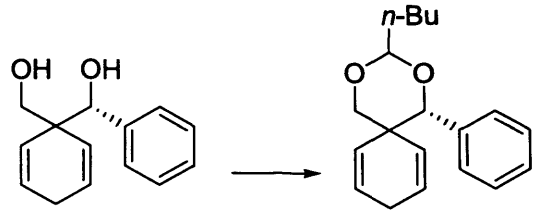
3-Methyl-1-phenyl-2,4-dioxaspiro(5.5)undeca-7,10-diene (85a)



74c **85a**

To a solution of (1-(hydroxymethyl)cyclohexa-2,5-dienyl)phenylmethanol **74c** (494 mg, 2.3 mmol) in CH_2Cl_2 (20 mL) was added acetaldehyde (2.6 mL, 45.8 mmol, 20 equiv.), PTSA (approx. 20 mg) and DMF (1 mL). After stirring for 24 h the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL), the organic layer separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (5 % Et_2O in petroleum ether) to give the *title compound* (392 mg, 71 %) as a colourless oil. ν_{max} (neat) 3031, 2961, 2845, 1496, 1454, 1410, 1354, 1119, 1024 and 712 cm^{-1}; δ_H (500 MHz) 7.20 - 7.11 (5 H, m, 5 x aromatic CH), 6.11 (1 H, app. dq, *J* 10.2, 2.0, one of alkene CH), 5.69 (1 H, app. dtd, *J* 10.2, 3.4, 1.5, one of alkene CH), 5.58 (1 H, app. dtd, *J* 10.2, 3.4, 1.5, one of alkene CH), 5.26 (1 H, app. dq, *J* 10.2, 2.0, one of alkene CH), 4.89 (1 H, q, *J* 5.0, CH_3CHO), 4.48 (1 H, s, ArCH), 3.79 (1 H, d, *J* 11.0, one of CH_2O), 3.67 (1 H, d, *J* 11.0, one of CH_2O), 2.33 (1 H, app. dtt, *J* 22.8, 3.4, 2.0, one of ring CH_2), 1.92 (1 H, app. dtt, *J* 22.8, one of ring CH_2) and 1.41 (3 H, d, *J* 5.0, CH_3); δ_H (100 MHz) 138.2 (C), 129.2 (CH), 127.5 (CH), 127.2 (CH), 127.0 (CH), 126.4 (CH), 125.7 (CH), 125.4 (CH), 99.8 (CH), 85.6 (CH), 76.4 (CH_2), 41.1 (C), 26.9 (CH_2) and 21.1 (CH_3).

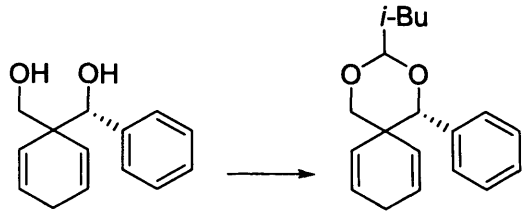
3-Butyl-1-phenyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (85b)



74c **85b**

To a solution of (1-(hydroxymethyl)cyclohexa-2,5-dienyl)phenylmethanol **74c** (452 mg, 2.1 mmol) in CH_2Cl_2 (20 mL) was added valeraldehyde (1.1 mL, 10.5 mmol, 5 equiv.), PTSA (approx. 20 mg) and DMF (1 mL). After stirring for 24 h the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL), the organic layer separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (5 % Et_2O in petroleum ether) to give the *title compound* (394 mg, 66 %) as a colourless oil. ν_{max} (neat) 3031, 2956, 2860, 1452, 1410, 1360, 1142, 1025 and 713 cm^{-1}; δ_H (500 MHz) 7.19 - 7.11 (5 H, m, 5 x aromatic CH), 6.08 (1 H, app. dq, *J* 10.3, 2.0, one of alkene CH), 5.69 (1 H, app. dtd, *J* 10.3, 3.4, 1.5, one of alkene CH), 5.57 (1 H, app. dtd, *J* 10.3, 3.4, 1.5, one of alkene CH), 5.27 (1 H, app dq, *J* 10.3, 2.0, one of alkene CH), 4.73 (1 H, t, *J* 4.9, CHO), 4.47 (1 H, s, ArCH), 3.80 (1 H, d, *J* 11.0, one of CH_2O), 3.65 (1 H, d, *J* 11.0, one of CH_2O), 2.33 (1 H, app. dtt, *J* 22.8, 3.4, 2.0, one of ring CH_2), 1.92 (1 H, app. dtt, *J* 22.8, 3.4, 2.0, one of ring CH_2), 1.73 - 1.68 (2 H, m), 1.45 - 1.37 (2 H, m), 1.29 (2 H, app. sextet, *J* 7.3, CH_2CH_3) and 0.85 (3 H, t, *J* 7.3, CH_3); δ_C (125 MHz) 138.5 (C), 129.1 (CH), 127.4 (CH), 127.1 (CH), 127.0 (CH), 126.5 (CH), 125.8 (CH), 125.3 (CH), 102.7 (CH), 85.4 (CH), 76.4 (CH_2), 41.3 (C), 34.7 (CH_2), 26.9 (CH_2), 25.9 (CH_2), 22.7 (CH_2) and 14.0 (CH_3).

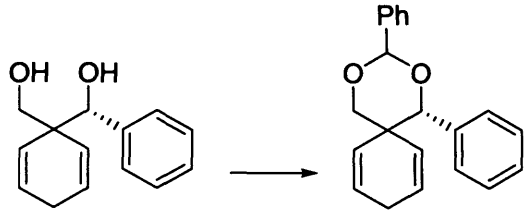
3-Isobutyl-1-phenyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (85c)



74c **85c**

To a solution of (1-(hydroxymethyl)cyclohexa-2,5-dienyl)phenylmethanol **74c** (474 mg, 2.2 mmol) in CH_2Cl_2 (20 mL) was added isovaleraldehyde (1.2 mL, 11.0 mmol, 5 equiv.), PTSA (approx. 20 mg) and DMF (1 mL). After stirring for 24 h the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL), the organic layer separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (5 % Et_2O in petroleum ether) to give the *title compound* (410 mg, 66 %) as a colourless oil. ν_{max} (neat) 3033, 2957, 2867, 1450, 1411, 1361, 1122, 1022 and 706 cm^{-1}; δ_H (400 MHz) 7.25 - 7.19 (5 H, m, 5 x aromatic CH), 6.15 (1 H, app. dq, *J* 10.1, 2.0, one of alkene CH), 5.77 (1 H, app. dtd, *J* 10.1, 3.3, 1.5, one of alkene CH), 5.63 (1 H, app. dtd, *J* 10.1, 3.3, 1.5, one of alkene CH), 5.34 (1 H, app. dq, *J* 10.1, 2.0, one of alkene CH), 4.84 (1 H, t, *J* 5.3, CHO), 4.55 (1 H, s, ArCHO), 3.86, (1 H, d, *J* 11.0, one of CH_2O), 3.73 (1 H, d, *J* 11.0, one of CH_2O), 2.40 (1 H, app. dtt, *J* 23.0, 3.3, 2.0, one of ring CH_2), 1.99 (1 H, app. dtt, *J* 23.0, 3.3, 2.0, one of ring CH_2), 1.95 - 1.84 (1 H, m, $CH(CH_3)_2$), 1.70 - 1.65 (2 H, m, CH_2CHO) and 0.95 (6 H, d, *J* 6.7, CH_3); δ_C (125 MHz) 138.5 (C), 129.1 (CH), 127.4 (CH), 127.0 (CH), 127.0 (CH), 126.6 (CH), 125.9 (CH), 125.2 (CH), 101.9 (CH), 85.5 (CH), 76.5 (CH_2), 43.1 (CH_2), 41.4 (C), 26.9 (CH_2), 23.8 (CH), 23.1 (CH_3) and 22.9 (CH_3).

1,3-Diphenyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (85e)

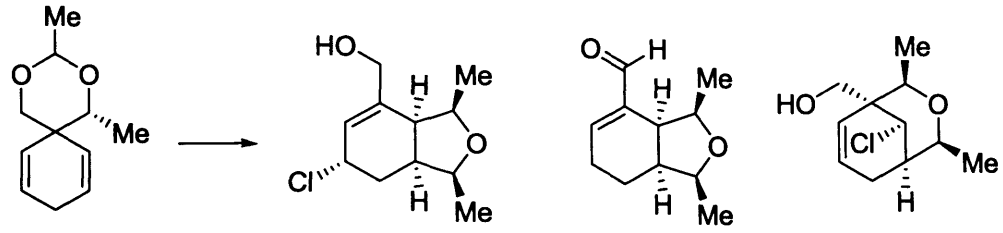


74c **85e**

To a solution of (1-(hydroxymethyl)cyclohexa-2,5-dienyl)phenylmethanol **74c** (474 mg, 2.2 mmol) in CH_2Cl_2 (20 mL) was added benzaldehyde dimethyl acetal (1.7 mL, 11.0 mmol, 5 equiv.), PTSA (approx. 20 mg) and DMF (1 mL). After stirring for 24 h the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL), the organic layer separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (5 % Et_2O in petroleum ether) to give the *title compound* (280 mg, 42 %) as a colourless solid. ν_{max} (CH_2Cl_2) 3032, 2956, 2842, 1497, 1452, 1399, 1360, 1123, 1027 and 698 cm^{-1}; δ_H (500 MHz) 7.56 - 7.52 (2 H, m, 2 x aromatic CH), 7.36 - 7.27 (3 H, m, 3 x aromatic CH), 7.25 - 7.21 (2 H, m, 2 x aromatic CH), 7.19 - 7.12 (3 H, m, 2 x aromatic CH), 6.23 (1 H, app. dq, *J* 10.2, 2.0, one of alkene CH), 5.75 (1 H, app. dtd, *J* 10.2, 3.4, 1.5, one of alkene CH), 5.70 (1 H, s, Ar*C*HO_2), 5.61 (1 H, app. dtd, *J* 10.2, 3.4, 1.5, one of alkene CH), 5.35 (1 H, app. dq, *J* 10.2, 2.0, one of alkene CH), 4.72 (1 H, s, Ar*C*HO), 3.97 (1 H, d, *J* 11.0, one of CH_2O), 3.90 (1 H, d, *J* 11.0, one of CH_2O), 2.36 (1 H, app. dtt, *J* 22.8, 3.6, 1.8, one of ring CH_2) and 1.94 (1 H, app. dtt, *J* 22.8, 3.0, 2.4, one of ring CH_2); δ_C (125 MHz) 138.5 (C), 138.2 (C), 129.5 (CH), 128.9 (CH), 128.3 (CH), 127.5 (CH), 127.2 (CH), 127.0 (CH), 126.3 (CH), 126.3 (CH), 125.6 (CH), 125.6 (CH), 102.1 (CH), 86.0 (CH), 76.8 (CH_2), 41.4 (C) and 26.9 (CH_2).

7.2.1 Prins Reactions with $TiCl_4$

Prins Cyclisation of Acetaldehyde Acetal 60a



60a **63a** **61a** **62a**

Titanium tetrachloride (0.32 mL, 2.9 mmol, 2 equiv.) was added to a cooled (-78 °C) solution of acetaldehyde acetal **60a** (260 mg, 1.44 mmol) in CH_2Cl_2 (10 mL). After stirring for 1 h the reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (14 % EtOAc in petroleum ether) to give compound **61a** as a yellow oil (73 mg, 28 %) and compound **62a** as a pale yellow oil (61 mg, 20 %), respectively. While compound **63a** was not isolated its existence was evident from the data obtained from the crude reaction mixture.

((1*RS*,2*RS*,4*SR*,5*RS*,9*RS*)-9-Chloro-2,4-dimethyl-3-oxabicyclo-(3.3.1)non-7-en-1-yl)methanol (62a)

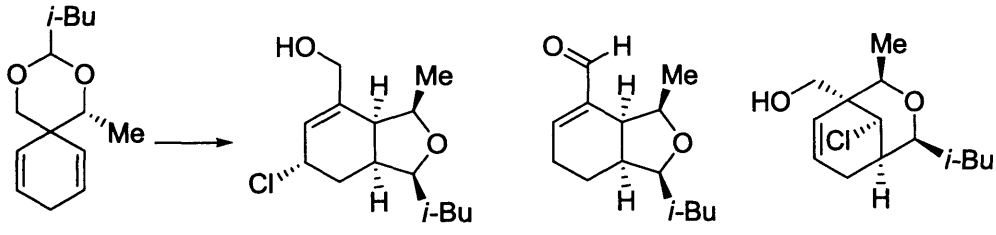
62a (61 mg, 20 %): (Found: MNH_4^+ 234.1256. $C_{11}H_{21}{}^{35}ClNO_2$ requires M, 234.1255); ν_{max} (CH_2Cl_2) 3418, 2978, 1684, 1376, 1075, 722 cm^{-1}; δ_H (400 MHz) 5.92 (1 H, app. dt, *J* 10.0, 3.4, CCH=C*H*), 5.02 (1 H, app. dq, *J* 10.0, 1.8, C*CH*=CH), 4.45 (1 H, app. dd, *J* 3.3, 1.2, CHCl), 3.91 (1 H, d, *J* 11.2, one of C*H*$_2$OH), 3.72 (1 H, q, *J* 6.3, CC*H*CH$_3$), 3.70 (1 H, app. dq, *J* 1.7, 6.4, CHC*H*CH$_3$), 3.57 (1 H, d, *J* 11.2, one of C*H*$_2$OH), 2.33 (1 H, app. ddt, *J* 19.3, 5.9, 2.9, one of C*H*$_2$CH=CH), 2.28 - 2.20 (1 H, m, one of C*H*$_2$CH=CH), 2.00 - 1.95 (1 H, m, C*H*CHCH$_3$), 1.17 (3 H, d, *J* 6.4, CHCHC*H*$_3$) and 1.09 (3 H, d, *J* 6.3, CCHC*H*$_3$); δ_C (100 MHz) 130.8 (CH), 121.8 (CH), 76.5 (CH), 76.3 (CH), 63.5 (CH_2), 63.3 (CH), 45.6 (C), 41.2

(CH), 22.7 (CH_2), 19.0 (CH_3) and 16.3 (CH_3). *m/z* (CI) 234 ($M+NH_4^+$, 100 %), 198 (79), 181 (48), 137 (27), 121 (27).

(1*SR*,3*RS*,3a*SR*,7a*SR*)-1,3,3a,6,7,7a-Hexahydro-1,3-dimethylisobenzofuran-4-carbaldehyde (61a)

61a (73 mg, 28 %): (Found: M^+ 180.1161. $C_{11}H_{16}O_2$ requires M, 180.1150); ν_{max} (CH_2Cl_2) 2924, 1686, 1458, 1375, 1259, 1165 cm^{-1}; δ_H (400 MHz) 9.40 (1 H, s, CHO), 6.95 (1 H, br. singlet, C=CH), 4.39 - 4.30 (1 H, m, CCHC*H*O), 4.02 - 3.94 (1 H, m, CH_2CHC*H*O), 3.18 (1 H, app. t, *J* 8.0, CC*H*CHO), 2.54 - 2.42 (1 H, m, one of C*H*$_2$CH=C), 2.28 - 2.15 (1 H, m, one of C*H*$_2$CH=C), 2.00 - 1.86 (1 H, m, CH_2C*H*CHO), 1.76 - 1.67 (1 H, m, one of C*H*$_2$CHCHO), 1.41 - 1.27 (1 H, m, one of C*H*$_2$CHCHO), 1.18 (3 H, d, *J* 6.4, CH_2CHCHC*H*$_3$) and 0.87 (3 H, d, *J* 6.4, CCHCHC*H*$_3$); δ_C (100 MHz) 194.5 (CH), 152.8 (CH), 140.9 (C), 76.2 (CH), 74.8 (CH), 40.2 (CH), 39.4 (CH), 25.7 (CH_2), 19.8 (CH_3), 19.2 (CH_2) and 15.1 (CH_3). *m/z* (EI) 180 (M^+, 12 %), 178 (37), 136 (100), 107 (98), 79 (98).

Prins Cyclisation of Isobutyl Acetal 60c



60c **63c** **61c** **62c**

Titanium tetrachloride (0.18 mL, 1.6 mmol) was added to a cooled (-78 °C) solution of isobutyl acetal **60c** (188 mg, 0.85 mmol) in CH_2Cl_2 (10 mL). After stirring for 2 h the reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (14 % EtOAc in petroleum ether) to give compound **61c** as a yellow oil (70 mg, 37%), and compound **62c** as a pale yellow solid (31 mg, 14%), respectively. While compound **63c** was not isolated its existence was evident from the data obtained from the crude reaction mixture.

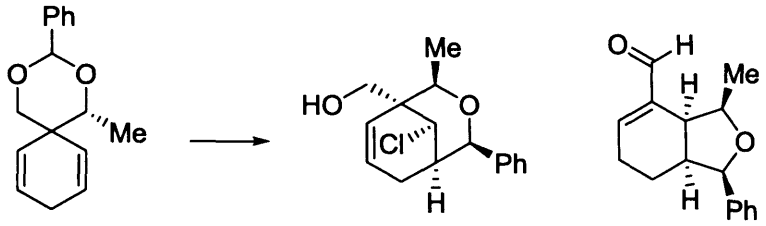
((1*RS*,2*RS*,4*SR*,5*RS*,9*RS*)-9-Chloro-4-isobutyl-2-methyl-3-oxabicyclo(3.3.1)non-7-en-1-yl)methanol (62c)

62c (31 mg, 14 %): m.p. 70 - 72 °C; (Found: MNH_4^+ 276.1723. $C_{14}H_{27}{}^{35}ClNO_2$ requires M, 276.1725); ν_{max} (neat) 3442, 3024, 2955, 1467, 1369, 1107 and 1042 cm^{-1}; δ_H (400 MHz) 5.92 (1 H, app. dt, *J* 10.0, 3.5, CCH=C*H*), 5.02 (1 H, app. dq, *J* 10.0, 1.9, CC*H*=CH), 4.48 (1 H, app. dd, *J* 3.2, 1.3, CHCl), 3.91 (1 H, d, *J* 11.4, one of C*H*$_2$OH), 3.69 (1 H, q, *J* 6.4, CCHO), 3.57 (1 H, d, *J* 11.4, one of C*H*$_2$OH), 3.56 - 3.51 (1 H, m, CHC*H*O), 2.32 (1 H, app. ddt, *J* 19.3, 6.0, 2.7, one of C*H*$_2$CH=CH), 2.24 - 2.16 (1 H, m, one of C*H*$_2$CH=CH), 2.01 - 1.96 (1 H, m, C*H*CHO), 1.67 (1 H, app. nonet, *J* 6.6, isobutyl CH), 1.53 (1 H, app. ddd, *J* 13.9, 8.4, 6.4, one of isobutyl CH_2), 1.16 - 1.10 (1 H, m, 1 H, one of isobutyl CH_2), 1.08 (3 H, d, *J* 6.4, CCHC*H*$_3$), 0.84 (3 H, d, *J* 6.4, C*H*$_3$) and 0.83 (3 H, d, *J* 6.4, C*H*$_3$); δ_C (100 MHz) 130.9 (CH), 121.9 (CH), 79.1 (CH), 76.4 (CH), 63.5 (CH and CH_2), 45.9 (C), 42.0 (CH_2), 40.2 (CH), 24.6 (CH), 23.2 (CH_2), 23.0 (CH_3), 22.5 (CH_3) and 16.2 (CH_3) ppm. *m/z* (CI) 276 ($M + NH_4^+$, 100 %), 240 (50), 223 (22), 179 (23).

(1*SR*,3*SR*,3a*SR*,7a*SR*)-1-Isobutyl-1,3,3a,6,7,7a-hexahydro-3-methylisobenzofuran-4-carbaldehyde (61c)

61c (70 mg, 37%): (Found: M^+ 222.1623. $C_{14}H_{22}O_2$ requires M, 222.1611); ν_{max} (neat) 2954, 1684, 1642, 1466, 1371, 1093 cm^{-1}; δ_H (400 MHz) 9.39 (1 H, s, CH=O), 6.94 (1 H, app. d, *J* 5.1, HC=C), 4.31 (1 H, app. dq, *J* 9.9, 6.4, CCHC*H*O), 3.86 (1 H, ddd, *J* 7.3, 6.1, 4.0, CH_2CHC*H*O), 3.16 (1 H, app. t, *J* 8.1, CC*H*CHO), 2.45 (1 H, app. dtd, *J* 20.0, 4.2, 1.1, one of C*H*$_2$CH=C), 2.26 - 2.12 (1 H, m, one of C*H*$_2$CH=C), 1.90 (1 H, app. ddt, *J* 13.1, 6.9, 4.0, CH_2C*H*CHO), 1.72 - 1.59 (2 H, m, one of C*H*$_2$CHCHO and isobutyl CH), 1.47 (1 H, app. dt, *J* 13.6, 7.2, one of isobutyl CH_2), 1.41 - 1.27 (2 H, m, one of isobutyl CH_2 and one of C*H*$_2$CHCHO) and 0.91 - 0.84 (9 H, m, 3 x CH_3); δ_C (100 MHz) 194.5 (CH), 152.7 (CH), 141.0 (C), 78.7 (CH), 74.5 (CH), 39.4 (CH), 39.2 (CH), 38.8 (CH_2), 25.7 (CH_2), 25.5 (CH), 23.3 (CH_3), 22.8 (CH_3), 19.8 (CH_3) and 19.3 (CH_2). *m/z* (CI) 222 (M^+, 1 %), 178 (26), 136 (59), 107 (81), 91 (100).

Prins Cyclisation of Benzaldehyde Acetal 60e



60e **62e** **61e**

Titanium tetrachloride (0.17 mL, 1.5 mmol, 2 equiv.) was added to a cooled (-78 °C) solution of benzaldehyde acetal **60e** (183 mg, 0.76 mmol) in CH_2Cl_2 (10 mL). After stirring for 15 min the reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (10 % EtOAc in petroleum ether) to give the aldehyde **61e** as a colourless solid (36 mg, 20 %) and alcohol **62e** as a colourless solid (80 mg, 38 %), respectively.

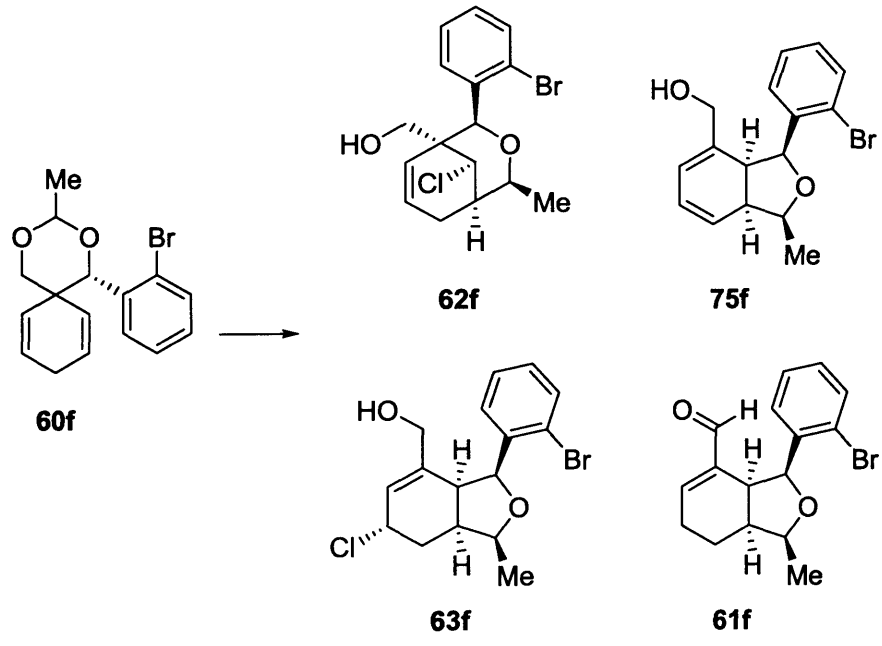
((1*RS*,2*RS*,4*SR*,5*RS*,9*RS*)-9-Chloro-2-methyl-4-phenyl-3-oxabicyclo(3.3.1)non-7-en-1-yl)methanol (62e)

62e (80 mg, 38%): m.p. 144 - 145 °C; (Found: $[M - OC_2H_4]^+$ 234.0829. $C_{14}H_{15}{}^{35}ClO$ requires M, 234.0811); ν_{max} (CH_2Cl_2) 3429, 3030, 2924, 1653, 1451, 1387, 1368, 1310, 1250, 1119, 1058, 1031, 724 cm^{-1}; δ_H (400 MHz) 7.31 - 7.16 (5 H, m, 5 x aromatic CH), 5.87 (1 H, app. dt, *J* 10.0, 3.4, CCH=C*H*), 5.06 (1 H, app. dq, *J* 10.0, 1.9, CC*H*=CH), 4.70 (2 H, m, C*H*CHO and CHCl), 3.96 (1 H, d, *J* 11.2, one of CH_2OH), 3.90 (1 H, q, *J* 6.2, CCHO), 3.64 (1 H, d, *J* 11.2, one of CH_2OH), 2.42 - 2.36 (1 H, m, C*H*CHO), 2.09 (1 H, app. ddt, *J* 19.3, 6.7, 2.7, one of CH_2CH=CH), 1.87 - 1.78 (1 H, m, one of CH_2CH=CH) and 1.20 (3 H, d, *J* 6.2, CH_3); δ_C (100 MHz) 140.2 (C), 130.9 (CH), 128.2 (2 x CH), 127.2 (CH), 125.6 (2 x CH), 121.5 (CH), 81.7 (C), 77.1 (CH), 63.6 (CH_2), 63.1 (CH), 46.6 (C), 41.9 (CH), 23.2 (CH_2) and 16.3 (CH_3). *m/z* (EI) 234 ($[M - OC_2H_4]^+$, 8 %), 198 (12), 181 (15), 107 (25), 91 (100).

(1*RS*,3*RS*,3a*SR*,7a*SR*)-1,3,3a,6,7,7a-Hexahydro-3-methyl-1-phenylisobenzofuran-4-carbaldehyde (61e)

61e (36 mg, 20%): m.p. 94 - 96 °C; (Found: MNa^+ 265.1200. $C_{16}H_{18}NaO_2$ requires M, 265.1199); ν_{max} (CH_2Cl_2) 2966, 2925, 2885, 2805, 1671, 1637, 1449, 1172, 1092 and 1027 cm^{-1}; δ_H (400 MHz) 9.40 (1 H, s, HC=O), 7.27 (3 H, m, 3 x aromatic CH), 7.22 - 7.15 (2 H, m, 2 x aromatic CH), 6.94 (1 H, app. d, *J* 4.8, HC=C), 5.04 (1 H, d, *J* 4.4, CH_2CHCHO), 4.57 (1 H, dq, *J* 10.0, 6.4, CCHCHO), 3.39 (1 H, app. t, *J* 8.2, CCHCHO), 2.35 (1 H, app. dtd, *J* 20.0, 5.3, 1.3, one of CH_2CH=C), 2.21 (1 H, app. ddt, *J* 13.1, 6.8, 4.6, CH_2CHCHO), 2.14 - 2.02 (1 H, m, one of CH_2CH=C), 1.18 (1 H, app. dq, *J* 13.3, 5.3, one of CH_2CHCHO), 1.09 - 1.01 (1 H, m, one of CH_2CHCHO) and 0.99 (3 H, d, *J* 6.4, CH_3); δ_C (100 MHz) 194.3 (CH), 152.9 (CH), 140.8 (C), 138.9 (C), 128.1 (2 x CH), 127.0 (CH), 125.9 (2 x CH), 82.1 (CH), 75.1 (CH), 41.6 (CH), 39.6 (CH), 25.7 (CH_2), 20.2 (CH_2) and 20.0 (CH_3). *m/z* (APCI) 260 ($M + NH_4^+$, 100), 257 (54), 198 (13).

Prins Cyclisation of Acetaldehyde Acetal 60f



Titanium tetrachloride (0.18 mL, 1.64 mmol, 2.2 equiv.) was added to a cooled (-78 °C) solution of acetaldehyde acetal **60f** (235 mg, 0.73 mmol) in CH_2Cl_2 (10 mL). After stirring for 30 min the reaction was quenched with saturated $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL).

The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (17 % EtOAc in hexane) to give compound **75f** as a colourless oil (40 mg, 17 %), compound **62f** as a pale yellow oil (26 mg, 10 %) and compound **61f** as a colourless oil (104 mg, 44 %), respectively. While compound **63f** was not isolated, its existence was evident from the data obtained from the crude reaction mixture.

((1*SR*,3*SR*,3a*SR*,7a*SR*)-3-(2-Bromophenyl)-6-chloro-1,3,3a,6,7,7a-hexahydro-1-methylisobenzofuran-4-yl)methanol (63f)

This compound was not isolated pure. These data are obtained from the crude reaction mixture under the above conditions. δ_H (400 MHz) 7.44 (1 H, d, *J* 8.2, aromatic CH), 7.22 - 7.17 (1 H, m, aromatic CH), 7.10 - 7.02 (2 H, m, 2 x aromatic CH), 5.84 (1 H, d, *J* 5.0, HC=C), 5.41 (1 H, d, *J* 9.9, ArCHO), 4.72 - 4.64 (1 H, m, ClC*H*CH=C), 4.10 (1 H, dq *J* 6.3, 4.8, MeC*H*O), 3.48 (1 H, d, *J* 14.4, one of CH_2OH), 3.35 - 3.28 (2 H, m, C*H*CHAr and one of CH_2OH), 2.70 - 2.61 (1 H, m, C*H*CHMe), 2.15 - 2.20 (2 H, m, CH_2CHCl) and 1.30 (3 H, d, *J* 6.3, CH3); δ_C (100 MHz) 140.9 (C), 138.0 (C), 132.5 (CH), 129.8 (CH), 129.4 (CH), 127.6 (CH), 125.0 (CH), 124.0 (C), 81.1 (CH), 76.9 (CH), 64.6 (CH_2), 53.9 (CH), 43.3 (CH), 36.9 (CH), 29.9 (CH_2) and 14.8 (CH_3).

((1*RS*,2*SR*,4*SR*,5*RS*,9*RS*)-2-(2-Bromophenyl)-9-chloro-4-methyl-3-oxabicyclo(3.3.1)non-7-en-1-yl)methanol (62f)

62f (26 mg, 10 %): (Found: MH^+ 356.0167. $C_{16}H_{18}O_2{}^{79}Br^{35}Cl$ requires M 356.0173); ν_{max} (CH_2Cl_2) 3578, 3024, 2925, 1725, 1694, 1470, 1440, 1386, 1204, 1084 cm^{-1}; δ_H (400 MHz) 7.46 (1 H, dd, *J* 8.0, 1.2, aromatic CH), 7.40 (1 H, dd, *J* 7.8, 1.7, aromatic CH), 7.23 - 7.17 (1 H, m, aromatic CH), 7.08 (1 H, app. dt, *J* 7.6, 1.7, aromatic CH), 6.01 (1 H, app. dt, *J* 9.9, 3.4, one of alkene CH), 4.97 (1 H, s, ArCHO), 4.81 (1 H, app. dq, *J* 9.9, 1.9, one of alkene CH), 4.68 (1 H, dd, *J* 3.3, 1.5 Hz, CHCl), 3.89 (1 H, dq, *J* 1.7, 6.3, MeCHO), 3.60 (1 H, d, *J* 12.3, one of CH_2OH), 3.22 (1 H, d, *J* 12.3, one of CH_2OH), 2.47 - 2.30 (2 H, m, CH_2CH=CH), 2.12 - 2.06 (1 H, m, C*H*CHCl) and 1.22 (3 H, d, *J* 6.3, CH_3); δ_C (100 MHz) 137.5 (C), 132.3 (CH), 131.5 (CH), 130.3 (CH), 129.7 (CH), 127.3 (CH), 123.5 (C), 121.8

(CH), 80.7 (CH), 77.3 (CH), 63.2 (CH_2), 63.1 (CH), 46.5 (C), 41.1 (CH), 22.8 (CH_2) and 18.9 (CH_3). *m/z* (APCI) 361 (MH^+ ($^{81}Br^{37}Cl$), 13 %), 359 (MH^+ ($^{79}Br^{37}Cl$), 48), 257 (44), 187 (65), 185 (75), 157 (25), 155 (65), 149 (29), 137 (100).

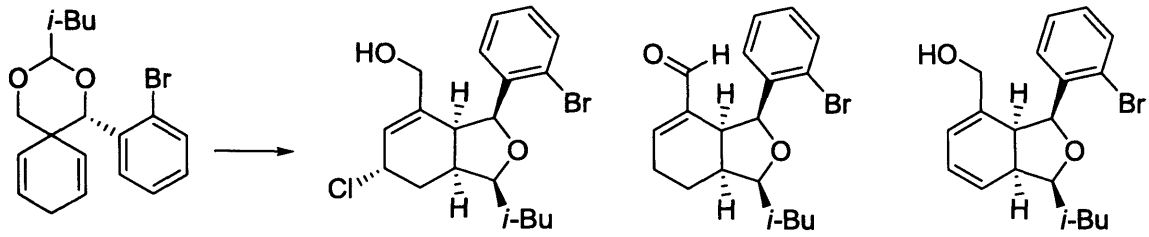
(1*SR*,3*SR*,3a*SR*,7a*SR*)-3-(2-Bromophenyl)-1,3,3a,6,7,7a-hexahydro-1-methylisobenzofuran-4-carbaldehyde (61f)

61f (104 mg, 44%): (Found: MH^+ 321.0480. $C_{16}H_{18}{}^{79}BrO_2$ requires M, 321.0490); ν_{max} (CH_2Cl_2) 2935, 1685, 1641, 1472, 1441, 1392, 1212, 1162, 1089 and 1018 cm^{-1}; δ_H (400 MHz) 8.79 (s, 1 H, CHO), 7.38 (1 H, app. dd, *J* 8.7, 1.1, aromatic CH), 7.11 - 7.04 (2 H, m, 2 x aromatic CH), 6.97 - 6.91 (1 H, app. ddd, *J* 8.1, 6.5, 2.5, aromatic CH), 6.75 (1 H, app. ddd, *J* 5.0, 3.3, 1.0, one of alkene CH), 5.54 (1 H, d, *J* 9.4, ArCH), 4.07 (1 H, dq, *J* 6.5, 5.1, MeCH), 3.56 (1 H, m, C*H*CHAr), 2.45 (1 H, app. dq, *J* 19.1, 4.8, one of CH_2CH=C), 2.32 - 2.24 (1 H, m, C*H*CHMe), 2.24 - 2.13 (1 H, m), 1.80 - 1.63 (2 H, m, C=CHCH_2CH_2) and 1.31 (3 H, d, *J* 6.5, CH_3); δ_H (100 MHz) 192.2 (CH), 151.0 (CH), 141.0 (C), 137.6 (C), 132.6 (CH), 130.3 (CH), 128.8 (CH), 126.5 (CH), 125.1 (C), 81.4 (CH), 77.1 (CH), 39.9 (CH), 39.5 (CH), 24.7 (CH_2), 20.2 (CH_2) and 14.8 (CH_3). *m/z* (APCI) 323 (MH^+ (^{81}Br), 89 %), 321 (MH^+ (^{79}Br), 100), 305 (24), 303 (27), 279 (40), 277 (27), 243 (16), 229 (11), 185 (18).

((1*SR*,3*SR*,3a*SR*,7a*SR*)-3-(2-bromophenyl)-1-methyl-1,3,3a,7a-tetrahydroisobenzofuran-4-yl)methanol (75f)

75f (40 mg, 17%): δ_H (400 MHz) 7.40 - 7.30 (2 H, m, 2 x aromatic CH), 7.12 (1 H, app. td, *J* 7.8, 1.0, aromatic CH), 7.00 (1 H, app. td, *J* 7.6, 1.7, aromatic CH), 5.85 (1 H, ddd, *J* 9.9, 5.5, 2.6, C=CHC*H*=CH), 5.74 (1 H, dd, *J* 9.9, 2.6, C=CHCH=C*H*), 5.69 (1 H, d, *J* 5.5, C=C*H*CH=CH), 5.49 (1 H, d, *J* 9.8, ArCH), 4.24 (1 H, app. quintet, *J* 6.1, CH_3C*H*), 3.69 (1 H, d, *J* 11.5, one of CH_2OH), 3.59 (1 H, dd, *J* 11.4, 9.8 Hz, CC*H*CHAr) 3.51 (1 H, d, *J* 11.5, one of CH_2OH), 3.17 (1 H, app. ddt, *J* 11.4, 5.0, 2.6, C*H*CHCH$_3$), 1.51 (1 H, br. s, OH), 1.43 (3 H, d, *J* 6.3, CH_3); Hydrogen connectivity fully supported by 1H-1H COSY NMR spectroscopy.

Prins Cyclisation of 3-Methylbutyraldehyde Acetal 60g



60g **63g** **61g** **75g**

Titanium tetrachloride (0.18 mL, 1.64 mmol, 2.7 equiv.) was added to a cooled (-78 °C) solution of 3-methylbutyraldehyde acetal **60g** (217 mg, 0.6 mmol) in CH_2Cl_2 (10 mL). After stirring for 2 h the reaction was quenched with saturated $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (14 % EtOAc in petroleum ether) to give compound **75g** as a colourless oil (12 mg, 6 %) and compound **61g** as a colourless oil (46 mg, 21 %). While compound **63g** was not isolated, its existence was evident from the data obtained from the crude reaction mixture.

((1*SR*,3*SR*,3a*SR*,7a*SR*)-3-(2-Bromophenyl)-6-chloro-1,3,3a,6,7,7a-hexahydro-1-isobutylisobenzofuran-4-yl)methanol (63g)

This compound was not isolated pure. These data are obtained from the crude reaction mixture under the above conditions. δ_H (400 MHz) 7.44 (1 H, d, *J* 7.9, aromatic CH), 7.21 - 7.16 (1 H, m, aromatic CH), 7.10 - 7.01 (2 H, m, aromatic CH), 5.86 (1 H, dd, *J* 5.0, 1.0, C=CH), 5.40 (1 H, d, *J* 9.9, ArCHO), 4.71 - 4.62 (1 H, m, CHCl), 4.00 (1 H, app. dt, *J* 7.8, 4.9, *i*-BuC*H*O), 3.51 (1 H, d, *J* 14.3, one of CH_2OH), 3.32 (1 H, d, *J* 14.3, one of CH_2OH), 3.30 (1 H, app. t, *J* 8.7, HC=CC*H*O), 2.72 - 2.62 (1 H, m, *i*-BuCHC*H*), 2.14 - 2.03 (2 H, m, CH_2CHCl), 1.78 - 1.40 (4 H, m, isobutyl CH2, isobutyl CH and OH) and 0.91 (6 H, app. d, *J* 5.0, 2 x CH_3); δ_C (100 MHz) 141.0 (C), 138.2 (C), 132.5 (CH), 129.9 (CH), 129.4 (CH), 127.6 (CH), 124.8 (CH), 124.1 (C), 81.0 (CH), 76.4 (CH), 64.7 (CH_2), 54.1 (CH), 43.3 (CH), 38.3 (CH), 36.2 (CH), 29.9 (CH_2), 25.6 (CH), 23.3 (CH_3) and 22.8 (CH_3).

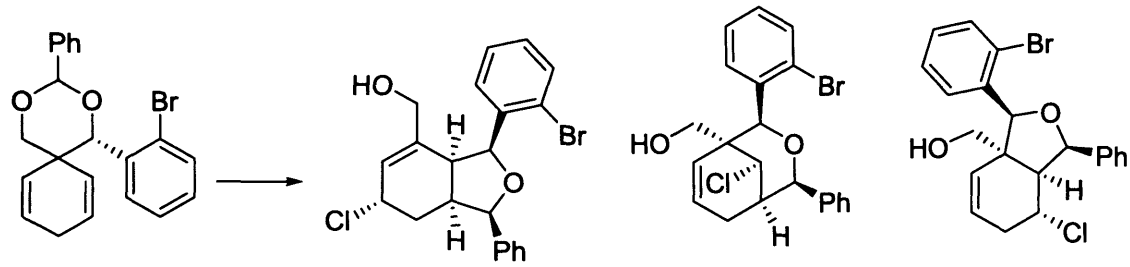
(1*SR*,3*SR*,3a*SR*,7a*SR*)-3-(2-Bromophenyl)-1,3,3a,6,7,7a-hexahydro-1-isobutylisobenzofuran-4-carbaldehyde (61g)

61g (46 mg, 21%): (Found: MH^+ 363.0946. $C_{19}H_{24}{}^{79}BrO_2$ requires M, 363.0960); ν_{max} (CH_2Cl_2) 2952, 1687, 1641, 1469, 1367, 1208, 1160, 1026, 751 cm^{-1}; δ_H (400 MHz) 8.79 (s, 1 H, CHO), 7.37 (1 H, d, *J* 7.6, aromatic CH), 7.11 - 7.05 (2 H, m, aromatic CH), 6.94 (1 H, app. ddd, 8.1, 6.0, 2.9, aromatic CH), 6.72 (1 H, br. app. t, *J* 3.6, one of alkene CH), 5.51 (1 H, d, *J* 9.5, ArCHO), 3.95 (1 H, app. dt, *J* 7.9, 5.1, *i*BuCHO), 3.54 (1 H, app. t, *J* 8.6, C*H*CHAr), 2.45 (1 H, app. dq, *J* 19.4, 4.7, one of CH_2CH=C), 2.30 - 2.22 (1 H, m, *i*BuCHC*H*), 2.22 - 2.11 (1 H, m, one of CH_2CH=C), 1.80 - 1.40 (5 H, m, ring CH_2, *i*Bu CH_2 and isobutyl CH) and 0.91 (6 H, app. d, *J* 6.6, 2 x CH_3); δ_H (100 MHz) 192.2 (CH), 150.8 (CH), 141.1 (C), 137.8 (C), 132.6 (CH), 130.5 (CH), 128.7 (CH), 126.4 (CH), 125.1 (C), 81.2 (CH), 79.7 (CH), 39.8 (CH), 38.9 (CH), 38.4 (CH_2), 25.7 (CH), 24.7 (CH_2), 23.4 (CH_3), 22.8 (CH_3) and 20.2 (CH_2). *m/z* (ES+) 365 (MH^+ (^{81}Br), 100 %), 363 (MH^+ (^{79}Br), 95), 347 (18), 345 (17), 279 (25), 277 (23), 207 (54), 179 (19).

((1*SR*,3*SR*,3a*SR*,7a*SR*)-3-(2-Bromophenyl)-6-chloro-1,3,3a,7a-tetrahydro-1-isobutylisobenzofuran-4-yl)methanol (75g)

75g (12 mg, 6 %): δ_H (400 MHz) 7.42 - 7.33 (2 H, m, aromatic CH), 7.12 (1 H, app. dt, *J* 7.6, 1.0, aromatic CH), 7.04 - 6.95 (1 H, m, aromatic CH), 5.83 (1 H, ddd, *J* 9.9, 5.5, 2.6, C=CHC*H*=CH), 5.72 (1 H, dd, *J* 9.9, 2.6, C=CHCH=C*H*), 5.67 (1 H, d, *J* 5.5, C=C*H*CH=CH), 5.46 (1 H, d, *J* 9.8, ArCH), 5.14 (1 H, app. dt, *J* 7.9, 5.0, *i*BuCH), 3.74 (1 H, d, *J* 11.4, one of CH_2OH), 3.56 (1 H, dd, *J* 11.1, 9.8, CC*H*CHAr), 3.52 (1 H, d, *J* 11.4, one of CH_2OH), 3.19 (1 H, app. ddt, *J* 11.1, 4.7, 2.3, C*H*CH*i*Bu), 1.80 (1 H, br. s, OH), 1.76 - 1.54 (3 H, m, isobutyl CH_2 and CH), 0.94 (3 H, d, *J* 6.4, CH_3) and 0.93 (3 H, d, *J* 6.5, CH_3).

Prins Cyclisation of Benzaldehyde Acetal 60h



60h **63h** **62h** **78**

Titanium tetrachloride (0.16 mL, 1.5 mmol, 2 equiv.) was added to a cooled (-78 °C) solution of benzaldehyde acetal **60h** (280 mg, 0.73 mmol) in CH_2Cl_2 (10 mL). After stirring for 15 min the reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (10 % EtOAc in petroleum ether) to give compound **62h** as a colourless solid (85 mg, 28 %), compound **78** as a pale yellow oil (30 mg, 9 %) and compound **63h** as a pale yellow solid (74 mg, 24 %), respectively.

((1*RS*,3*SR*,3a*SR*,7a*SR*)-3-(2-Bromophenyl)-6-chloro-1,3,3a,6,7,7a-hexahydro-1-phenylisobenzofuran-4-yl)methanol (63h)

63h (74 mg, 24 %): m.p. 50 - 52 °C; (Found: MNH_4^+ 400.0909. $C_{21}H_{23}{}^{79}BrNO_2$ requires M, 400.0912); ν_{max} (CH_2Cl_2) 3426, 3061, 3021, 2929, 1732, 1567, 1470, 1367, 1267, 1206, 1121, 916 cm^{-1}; δ_H (400 MHz) 7.82 (2 H, d, *J* 7.8, 2 x aromatic CH), 7.14 (3 H, m, 3 x aromatic CH), 7.10 - 7.05 (2 H, m, 2 x aromatic CH), 7.05 - 6.99 (2 H, m, 2 x aromatic CH), 6.14 (1 H, d, *J* 7.4, C=CH), 5.36 (1 H, d, *J* 5.0, CCHC*H*O), 5.25 (1 H, d, *J* 9.2, CH_2CHC*H*O), 3.53 (1 H, app. t, *J* 5.7, CC*H*CHO), 3.40 - 3.32 (1 H, m, CH_2C*H*CHO), 3.32 - 3.26 (1 H, m, CHCl), 2.93 (1 H, d, *J* 13.5, one of CH_2OH), 2.84 (1 H, d, *J* 13.5, one of CH_2OH) and 2.01 - 1.89 (2 H, m, CH_2CHCHO); δ_C (100 MHz) 139.0 (C), 136.4 (C), 135.9 (C), 132.6 (CH), 132.2 (CH), 130.9 (CH), 130.8 (CH), 129.1 (CH), 128.6 (CH), 127.6 (CH), 127.6 (CH), 127.0 (CH), 126.7 (CH), 121.3 (C), 83.6 (CH), 77.6 (CH), 64.7 (CH2), 44.1 (CH), 37.7 (CH), 35.1 (CH) and 29.6 (CH_2). *m/z* (ES+) 402 (MNH_4^+ - HCl, (^{81}Br), 86 %), 400 (89), 367 (84), 365 (100).

((1*RS*,2*SR*,4*SR*,5*RS*,9*RS*)-2-(2-Bromophenyl)-9-chloro-4-phenyl-3-oxabicyclo(3.3.1)non-7-en-1-yl)methanol (62h)

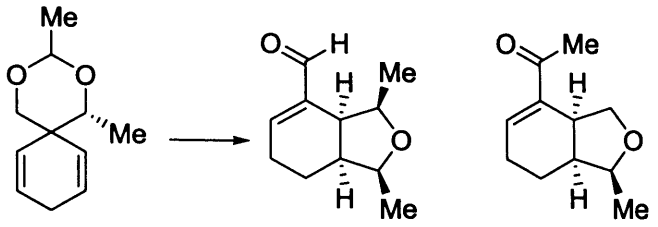
62h (85 mg, 28 %): m.p. 70 - 72 °C. ν_{max} (CH_2Cl_2) 3466, 3061, 3027, 2924, 1472, 1266, 1122, 1071, 1030, 751 cm^{-1}; δ_H (400 MHz) 7.59 (1 H, dd, *J* 7.9, 1.6, aromatic CH), 7.49 (1 H, dd, *J* 8.0, 0.9, aromatic CH), 7.32 - 7.24 (5 H, m, 5 x aromatic CH), 7.23 - 7.17 (1 H, m, aromatic CH), 7.12 (1 H, app. td, *J* 7.7, 1.7, aromatic CH), 5.99 (1 H, app. dt, *J* 9.9, 3.4, CCH=C*H*), 5.16 (1 H, s, CCHO), 4.92 (2 H, m, CHCl and CHC*H*O), 4.87 (1 H, app. dd, *J* 9.9, 1.6, CC*H*=CH), 3.66 (1 H, dd, *J* 12.3, 7.6 Hz, one of CH_2OH), 3.31 (1 H, dd, *J* 12.3, 4.8, one of CH_2OH), 2.52 - 2.47 (1 H, m, C*H*CHO), 2.19 (1 H, app. ddt, *J* 19.4, 6.7, 2.6, one of CH_2CH=CH), 2.14 - 2.09 (1 H, m, OH) and 2.01 - 1.91 (1 H, m, one of CH_2CH=CH); δ_C (100 MHz) 139.6 (C), 137.5 (C), 132.3 (CH), 131.6 (CH), 130.6 (CH), 129.8 (CH), 128.3 (2 x CH), 127.4 (CH), 127.3 (CH), 125.6 (2 x CH), 123.5 (C), 121.7 (CH), 82.4 (CH), 80.9 (CH), 63.2 (CH_2), 62.7 (CH), 46.6 (C), 41.1 (CH) and 23.2 (CH_2) ppm.

((1*RS*,3*SR*,3a*RS*,7*RS*,7a*SR*)-3-(2-Bromophenyl)-7-chloro-1,6,7,7a-tetrahydro-1-phenylisobenzofuran-3a-yl)methanol (78)

78 (30 mg, 9 %): ν_{max} (neat) 3450, 3065, 3032, 2931, 1470, 1439, 1374, 1269, 1206, 1067, 1020, 909, 733 cm^{-1}; δ_H (400 MHz) 7.54 (1 H, dd, *J* 7.9, 1.6, aromatic CH), 7.49 (1 H, dd, *J* 8.0, 0.9, aromatic CH), 7.42 (2 H, d, *J* 7.4, 2 x aromatic CH), 7.35 - 7.22 (4 H, m, 4 x aromatic CH), 7.12 (1 H, app. td, *J* 7.6, 1.6, aromatic CH), 5.66 (1 H, app. dt, *J* 10.2, 4.1, CCH=C*H*), 5.25 (1 H, d, *J* 7.5, CHCHC*H*O), 5.23 (1 H, s, CCHO), 4.81 (1 H, app. dt, *J* 10.2, 1.7, CC*H*=CH), 4.04 - 4.01 (1 H, m, CHCl), 3.89 (1 H, d, *J* 11.3, one of CH_2OH), 3.83 (1 H, *J* 11.3, one of CH_2OH), 3.23 (1 H, app. t, *J* 7.0, CHC*H*CHO) and 2.20 - 2.06 (2 H, m, CH_2CH=CH); δ_C (100 MHz) 137.6 (C), 137.2 (C), 132.6 (CH), 130.9 (CH), 129.4 (CH), 128.3 (2 x CH), 127.7 (CH), 127.7 (CH), 127.2 (CH), 127.0 (CH), 126.5 (2 x CH), 122.6 (C), 82.4 (CH), 81.3 (CH), 66.3 (CH2), 55.4 (CH), 55.0 (C), 51.3 (CH) and 32.5 (CH_2).

7.2.2 Prins Reactions with Triflic Acid

Prins Cyclisation of Acetaldehyde Acetal 60a



60a **61a** **84a**

Reaction of acetal **60a** (183 mg, 1.02 mmol) with TfOH (0.15 mL, 1.6 mmol, 1.6 equiv.) in CH_2Cl_2 (10 mL) at 0 °C for 10 min gave **61a** (120 mg, 66 %) as a yellow solid followed by **84a** (10 mg, 6 %) as a yellow oil.

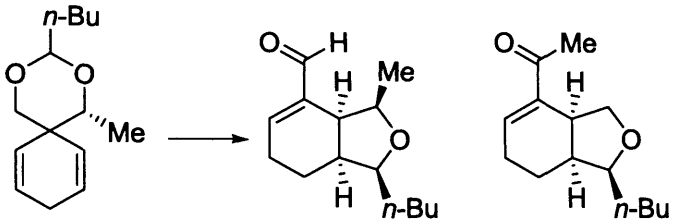
(1*SR*,3*RS*,3a*SR*,7a*SR*)-1,3-dimethyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-carbaldehyde (61a)

61a (120 mg, 66 %): See data in Section **7.2.1**.

1-((1*SR*,3a*SR*,7a*SR*)-1-Methyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-yl)ethanone (84a)

84a (10 mg, 6 %): ν_{max} (CH_2Cl_2) 2966, 2925, 2885, 2805, 1671, 1637, 1449, 1172, 1092 and 1027 cm^{-1}; δ_H (400 MHz) 6.97 (1 H, br. d, *J* 5.7, CH_2CH=C), 4.26 (1 H, dd, *J* 8.4, 9.6, one of $CHCH_2O$), 4.09 (1 H, dq, *J* 6.4, 4.4, MeCHO), 3.37 (1 H, app. t, *J* 8.4, one of $CHCH_2O$), 3.18 (1 H, app. br. q, *J* 8.2, C=CC*H*), 2.42 (1 H, dtd, *J* 19.4, 5.7, 1.9, one of CH_2CH=C), 2.28 (3 H, s, CH_3), 2.27 - 2.15 (1 H, m, one of CH_2CH=C), 1.96 (1 H, ddt, *J* 13.1, 6.6, 4.2, one of C=CHCH$_2$CH_2), 1.73 - 1.65 (1 H, m, C*H*CHMe), 1.34 - 1.19 (1 H, m, one of C=CHCH$_2$CH_2) and 1.22 (3 H, d, *J* 6.4, CH_3); δ_C (100 MHz) 199.1 (C), 141.4 (CH), 140.8 (C), 77.4 (CH), 72.2 (CH_2), 40.2 (CH), 38.1 (CH), 25.5 (CH_2), 25.2 (CH_3), 18.0 (CH_2) and 15.1 (CH_3).

Prins Cyclisation of Valeraldehyde Acetal 60b



60b **61b** **84b**

Reaction of acetal **60b** (200 mg, 0.90 mmol) with TfOH solution (1.51 mL, 1.1 mmol, 1.2 equiv.) in CH_2Cl_2 (10 mL) at 0 °C to r.t. for 1 h 30 min gave **61b** (120 mg, 60 %) as a yellow oil followed by **84b** (15 mg, 8 %) as a yellow oil.

(1*SR*,3*RS*,3a*SR*,7a*SR*)-1-Butyl-3-methyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-carbaldehyde (61b)

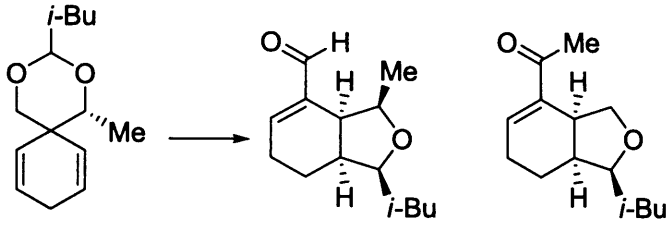
61b (120 mg, 60 %): ν_{max} (CH_2Cl_2) 2934, 2870, 1683, 1458, 1376, 1458, 1375, 1223, 1163, 1093, 960, 735 and 684 cm^{-1}; δ_H (400 MHz) 9.43 (1 H, s, CHO), 7.00 (1 H, br. d, *J* 4.5, C*H*=CC=O), 4.39 (1 H, app. dq, *J* 9.8, 6.4, MeCHO), 3.82 (1 H, td, *J* 6.8, 4.0, BuCHO), 3.21 (1 H, app. br. t, *J* 8.2, C*H*CHMe), 2.52 (1 H, dtd, *J* 20.2, 5.4, 1.5, one of CH_2CH=C), 2.32 - 2.20 (1 H, m, one of CH_2CH=C), 1.97 (1 H, ddt, *J* 13.1, 6.8, 4.1, C*H*CHBu), 1.74 (1 H, br. dt, *J* 13.4, 4.4), 1.64 - 1.59 (1 H, m, one of CHOCH_2CH$_2$), 1.59 - 1.49 (1 H, m, one of CHOCH_2CH$_2$), 1.59 - 1.27 (5 H, m) and 0.95 - 0.89 (6 H, m, 2 x CH_3); δ_C (100 MHz) 194.4 (C), 152.7 (CH), 140.9 (C), 80.8 (CH), 74.5 (CH), 39.1 (CH), 39.0 (CH), 29.5 (CH_2), 28.7 (CH_2), 25.7 (CH_2), 22.9 (CH_2), 19.8 (CH_3), 19.1 (CH_2) and 14.0 (CH_2).

1-((1*SR*,3a*SR*,7a*SR*)-1-Butyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-yl)ethanone (84b)

84b (15 mg, 8 %): ν_{max} (CH_2Cl_2) 2933, 2870, 1667, 1467, 1383, 1356, 1250, 1061 and 783cm^{-1}; δ_H (400 MHz) 6.97 (1 H, br. d, *J* 5.1, C*H*=CC=O), 4.25 (1 H, dd, *J* 9.6, 8.3, one of CH_2O), 3.88 (1 H, td, *J* 6.7, 4.3, BuCHO), 3.36 (1 H, app. t, *J* 8.5, one of CH_2O), 3.16 (1 H, app. br. q, *J* 8.6, C*H*CH_2O), 2.40 (1 H, dtd, *J* 19.4, 5.6, 1.7, one of CH_2CH=C), 2.28 (3 H, s, CH_3), 2.27 - 2.15 (1 H, m, one of CH_2CH=C), 1.99 (1 H, ddt, *J* 13.1, 6.3, 4.2, C*H*CHO), 1.70 - 1.63 (1 H, m, one of CHCH_2CH$_2$), 1.63 - 1.46 (2 H, m, CHOCH_2CH2), 1.46 - 1.22 (5

H, m) and 0.90 (3 H, t, *J* 7.0, CH_3); δ_C (100 MHz) 199.1 (C), 141.4 (CH), 140.8 (C), 82.1 (CH), 72.0 (CH_2), 39.2 (CH), 37.9 (CH), 29.8 (CH_2), 28.9 (CH_2), 25.5 (CH_2), 25.2 (CH_3), 22.9 (CH_2), 18.0 (CH_2) and 14.0 (CH_3).

Prins Cyclisation of Isovaleraldehyde Acetal 60c



60c **61c** **84c**

Reaction of acetal **60c** (218 mg, 0.98 mmol) with TfOH solution (1.54 mL, 1.1 mmol, 1.1 equiv.) in CH_2Cl_2 (10 mL) at 0 °C for 1 h 30 min gave **61c** (116 mg, 53 %) as a yellow oil followed by **84c** (15 mg, 7 %) as an orange oil.

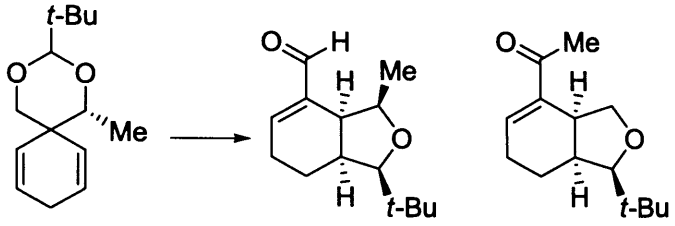
(1*SR*,3*RS*,3a*SR*,7a*SR*)-1-Isobutyl-3-methyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-carbaldehyde (61c)

61c (116 mg, 53 %): See data in Section **7.2.1**.

1-((1*SR*,3a*SR*,7a*SR*)-1-Isobutyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-yl)ethanone (84c)

84c: (15 mg, 7 %): ν_{max} (CH_2Cl_2) 2952, 2869, 1667, 1467, 1426, 1384, 1248 and 1063 cm^{-1}; δ_H (400 MHz) 6.97 (1 H, br. d, *J* 5.0, CHC=CC=O), 4.25 (1 H, dd, *J* 9.7, 8.3, one of C*H*$_2$O), 4.01 - 3.95 (1 H, m, CHO), 3.36 (1 H, app. t, *J* 8.3, one of C*H*$_2$O), 3.17 (1 H, app. br. q, *J* 8.3, C*H*CH_2O), 2.40 (1 H, dtd, *J* 19.4, 5.8, 2.1, one of C*H*$_2$CH=C), 2.27 (3 H, s, CH_3), 2.26 - 2.15 (1 H, m, one of C*H*$_2$CH=C), 1.98 (1 H, ddt, *J* 13.1, 6.4, 4.1, C*H*CHO), 1.77 - 1.60 (2 H, m, C*H*$(CH_3)_2$ and one of C*H*$_2$CH$_2$CH=C), 1.51 (1 H, ddd, *J* 14.2, 8.1, 6.5, one of C*H*$_2$CHO), 1.40 - 1.18 (2 H, m, one of C*H*$_2$O and one of C*H*$_2$CHO), 0.94 (3 H, d, *J* 6.6, CH_3) and 0.93 (3 H, d, *J* 6.6, CH_3); δ_C (100 MHz) 199.1 (C), 141.3 (CH), 140.9 (C), 80.0 (CH), 72.0 (CH_2), 39.6 (CH), 39.0 (CH_2), 37.9 (CH), 25.6 (CH), 25.6 (CH_2), 25.2 (CH_3), 23.3 (CH_3), 22.7 (CH_3) and 18.2 (CH_2).

Prins Cyclisation of Pivalaldehyde Acetal 60d



60d **61d** **84d**

Reaction of acetal **60d** (219 mg, 0.99 mmol) with TfOH solution (1.55 mL, 1.1 mmol, 1.1 equiv.) in CH_2Cl_2 (10 mL) at 0 °C to r.t. for 4 h gave unreacted acetal **60d** (55 mg, 25 %), followed by **61d** (24 mg, 11 %) as a yellow oil, and finally **84d** (11 mg, 5 %) as a yellow oil.

(1*RS*,3*RS*,3a*SR*,7a*SR*)-1-tert-Butyl-3-methyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-carbaldehyde (61d)

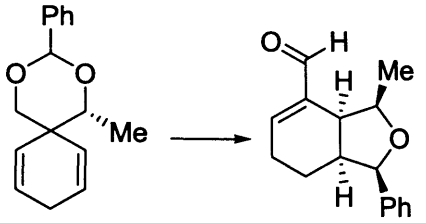
61d (24 mg, 11 %): ν_{max} (CH_2Cl_2) 2958, 1683, 1461, 1367, 1161, 1094, 1033, 939, 800 and 678 cm^{-1}; δ_H (400 MHz) 9.45 (1 H, s, CHO), 6.97 (1 H, br. d, *J* 5.4, CH=CC=O), 4.41 (1 H, dq, *J* 9.9, 6.4, CH_3CHO), 3.48 (1 H, d, *J* 3.7, $C(CH_3)_3CHO$), 3.15 (1 H, br. t, *J* 8.0, $CHCHCH_3$), 2.50 (1 H, dtd, *J* 20.1, 5.5, 1.1, one of CH_2CH=C), 2.28 - 2.16 (1 H, m, one of CH_2CH=C), 2.02 (1 H, ddt, *J* 13.3, 6.6, 4.0, $CHCHC(CH_3)_3$), 1.90 (1 H, br. dt, *J* 13.1, 4.8, one of CH_2CH_2CH=C), 1.51 (1 H, qd, *J* 13.1, 5.2, one of CH_2CH_2CH=C), 1.01 (9 H, s, $C(CH_3)_3$) and 0.91 (3 H, d, *J* 6.4, CH_3); δ_C (100 MHz) 194.4 (CH), 152.2 (CH), 141.0 (C), 88.2 (CH), 73.9 (CH), 39.3 (CH), 39.3 (CH), 33.1 (C), 27.5 (CH_3), 26.1 (CH_2), 21.0 (CH_2) and 20.0 (CH_3).

1-((1*RS*,3a*SR*,7a*SR*)-1-tert-Butyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-yl)ethanone (84d)

84d (11 mg, 5 %): ν_{max} (CH_2Cl_2) 2961, 1671, 1365, 1259, 1056, 800, 733 and 700 cm^{-1}; δ_H (400 MHz) 6.96 (1 H, br. d, *J* 5.9, CH=CC=O), 4.29 (1 H, dd, *J* 8.1, 9.6, one of CH_2O), 3.55 (1 H, d, *J* 3.8, CHO), 3.38 (1 H, dd, *J* 8.1, 9.2, one of CH_2O), 3.13 (1 H, br. q, *J* 8.6, $CHCH_2O$), 2.39 (1 H, dtd, *J* 19.3, 5.9, 1.5, one of CH_2CH=C), 2.27 (3 H, s, CH_3) and 2.24 - 2.15 (1 H, m, one of CH_2CH=C), δ_C (100 MHz) 199.1 (C), 141.1 (CH), 140.7 (C),

89.7 (CH), 71.6 (CH_2), 39.6 (CH), 38.0 (CH), 33.5 (C), 27.5 (CH_3), 26.1 (CH_2), 25.2 (CH_3) and 19.9 (CH_2).

Prins Cyclisation of Benzaldehyde Acetal 60e



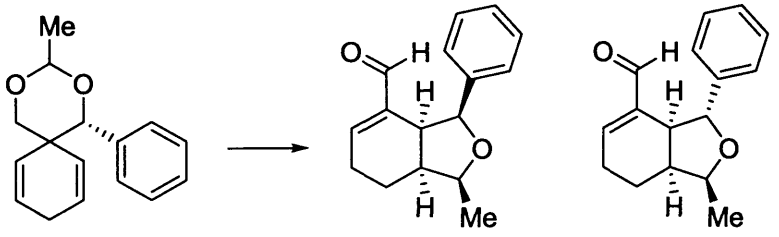
60e **61e**

Reaction of acetal **60e** (237 mg, 0.98 mmol) with TfOH solution (2.10 mL, 1.5 mmol, 1.5 equiv.) in CH_2Cl_2 (10 mL) at 0 °C for 5 min and chromatography on silica (6 % to 10 % EtOAc in petroleum ether) gave **61e** (100 mg, 42 %) as a yellow oil.

(1*RS*,3*RS*,3a*SR*,7a*SR*)-3-Methyl-1-phenyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-carbaldehyde (61e)

61e (100 mg, 42 %): See data in Section **7.2.1**.

Prins Cyclisation of Acetaldehyde Acetal 85a



85a **86a** **87a**

Reaction of acetal **85a** (0.6 mmol) with TfOH at 0 °C, as specified in Table **3**, followed by chromatography on silica (10 % to 15 % EtOAc in petroleum ether) gave **86a** (see Table **3**) as a yellow solid, followed by **87a** (see Table **3**) as a yellow solid.

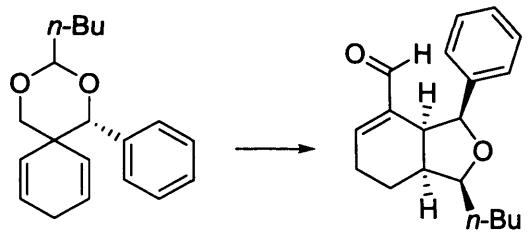
(1*RS*,3*RS*,3a*SR*,7a*SR*)-3-Methyl-1-phenyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-carbaldehyde (86a)

86a: ν_{max} (CH_2Cl_2) 3033, 2977, 2933, 2867, 1683, 1450, 1273, 1175, 1092, 1020, 734 and 701 cm^{-1}; δ_H (400 MHz) 9.04 (1 H, s, CHO), 7.20 - 7.16 (4 H, m, 4 x aromatic CH), 7.16 - 7.19 (1 H, m, ArCH), 6.68 (1 H, br. d, *J* 3.9, HC=C), 5.33 (1 H, d, *J* 10.2, ArCHO), 4.25 (1 H, qd, *J* 6.3, 4.4, CH_3CHO), 3.60 (1 H, br. t, *J* 8.4, CC*H*CHO), 2.43 (1 H, dtd, *J* 20.0, 5.3, 1.7, one of C*H*$_2$CH=C), 2.25 - 2.13 (1 H, m, one of C*H*$_2$CH=C), 2.09 (1 H, ddt, *J* 13.0, 6.9, 4.5, one of C*H*$_2$CHCHO), 1.86 - 1.78 (1 H, m, CH_2C*H*CHO), 1.68 (1 H, qd, *J* 13.0, 5.5, one of C*H*$_2$CHCHO) and 1.40 (3 H, d, *J* 6.4, CH_3); δ_C (100 MHz) 193.7 (C), 151.6 (CH), 141.0 (C), 140.0 (C), 127.9 (2 x CH), 127.4 (2 x CH), 127.0 (CH), 82.1 (CH), 77.0 (CH), 41.1 (CH), 39.9 (CH), 25.2 (CH_2), 19.0 (CH_2) and 14.9 (CH_3).

(1*SR*,3*RS*,3a*SR*,7a*SR*)-3-Methyl-1-phenyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-carbaldehyde (87a)

87a: ν_{max} (CH_2Cl_2) 3033, 2978, 2933, 2867, 1689, 1450, 1383, 1217, 1167, 1083, 1011, 756 and 700 cm^{-1}; δ_H (400 MHz) 9.23 (1 H, s, CHO), 7.30 - 7.21 (5 H, m, 5 x aromatic CH), 6.86 (1 H, dd, *J* 5.1, 2.5, CH=C), 4.56 (1 H, qd, *J* 6.4, 4.9, CCHC*H*O), 4.53 (1 H, d, *J* 8.9, PhCHO), 3.29 (1 H, br. t, *J* 7.4, CC*H*CHO), 2.57 (1 H, dtd, *J* 20.2, 5.4, 1.7, one of C*H*$_2$CH=C), 2.36 - 2.24 (1 H, m, one of C*H*$_2$CH=C), 2.16 (1 H, br. dq, *J* 12.8, 4.9, CH_2C*H*CHMe), 1.80 (1 H, br. dt, *J* 13.3, 4.5, one of C*H*$_2$CHCHMe), 1.63 (1 H, qd, *J* 13.3, 5.6, one of C*H*$_2$CHCHMe) and 1.25 (3 H, d, *J* 6.4, CH_3); δ_C (100 MHz) 192.5 (C), 151.2 (CH), 142.8 (C), 140.7 (C), 128.1 (2 x CH), 127.6 (CH), 126.7 (2 x CH), 85.7 (CH), 78.0 (CH), 45.2 (CH), 41.2 (CH), 25.9 (CH_2), 18.8 (CH_2) and 15.8 (CH_3).

Prins Cyclisation of Valeraldehyde Acetal 85b



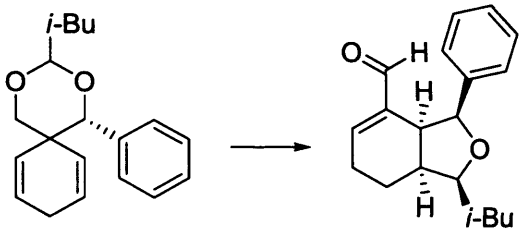
85b **86b**

Reaction of acetal **85b** (0.6 mmol) with TfOH at 0 °C, as specified in Table **3**, followed by chromatography on silica (10 % to 15 % EtOAc in petroleum ether) gave **86b** (see Table **3**) as a yellow oil.

(1*RS*,3*RS*,3a*SR*,7a*SR*)-3-Butyl-1-phenyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-carbaldehyde (86b)

86b: ν_{max} (CH_2Cl_2) 3056, 2956, 2870, 1689, 1451, 1273, 1110, 736 and 713 cm^{-1}; δ_H (400 MHz) 9.04 (1 H, s, CHO), 7.19 - 7.09 (5 H, m, ArH), 6.67 (1 H, br. d, *J* 3.3, CH=C), 5.31 (1 H, d, *J* 10.2, PhCHO), 4.03 (1 H, td, *J* 6.8, 4.2, BuCHO), 3.57 (1 H, br. t, *J* 8.3, CC*H*CHO), 2.41 (1 H, dtd, *J* 20.2, 5.3, 1.4, one of CH_2CH=C), 2.24 - 2.06 (2 H, m, one of CH_2CH=C), 1.87 - 1.75 (2 H, m), 1.75 - 1.63 (2 H, m), 1.57 - 1.47 (1 H, m), 1.45 - 1.30 (3 H, m), 0.94 (2 H, t, *J* 7.1, CH_3); δ_C (100 MHz) 192.4 (C), 151.2 (CH), 143.1 (C), 140.9 (C), 128.1 (2 x CH), 127.5 (CH), 126.6 (2 x CH), 85.4 (CH), 82.7 (CH), 45.1 (CH), 40.2 (CH), 30.2 (CH2), 28.7 (CH2), 25.9 (CH2), 22.9 (CH_2), 18.7 (CH_2) and 14.0 (CH_3).

Prins Cyclisation of Isobutyraldehyde Acetal 85c



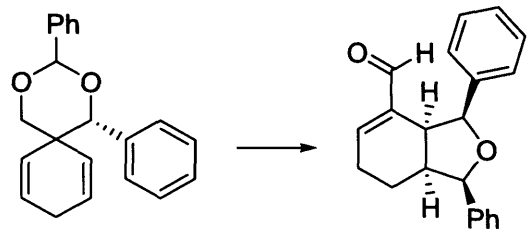
85c **86c**

Reaction of acetal **85c** (0.6 mmol) with TfOH at 0 °C, as specified in Table **3**, followed by chromatography on silica (10 % to 15 % EtOAc in petroleum ether) gave **86c** (see Table **3**) as a yellow oil.

(1*SR*,3*SR*,3a*SR*,7a*SR*)-1-Isobutyl-3-phenyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-carbaldehyde (86c)

86c: ν_{max} (CH_2Cl_2) 2955, 2869, 1685, 1451, 1271, 1174, 1109, 735 and 701 cm^{-1}; δ_H (400 MHz) 9.04 (1 H, s, CHO), 7.19 - 7.08 (5 H, m, 5 x aromatic CH), 6.66 (1 H, br. d, *J* 4.0, CH=C), 5.30 (1 H, d, *J* 10.2, ArCH), 4.13 (1 H, ddd, *J* 7.7, 5.5, 4.5, *i*BuCHO), 3.61 - 3.53 (1 H, m, CC*H*CHAr), 2.40 (1 H, dtd, *J* 20.1, 5.3, 1.5, one of C=CHCH_2), 2.24 - 2.04 (2 H, m, two of butyl CH_2), 1.87 - 1.62 (4 H, m, four of butyl CH_2), 1.53 (1 H, ddd, *J* 13.0, 7.0, 5.7, one of CCH_2CH_2), 1.00 (3 H, app. d, *J* 6.5, CH_3) and 0.99 (3 H, app. d, *J* 6.5, CH_3); δ_C (100 MHz) 193.7 (CH), 151.5 (CH), 141.0 (C), 140.2 (C), 127.8 (2 x CH), 127.3 (2 x CH), 126.8 (CH), 81.7 (CH), 79.5 (CH), 40.9 (CH), 39.1 (CH), 38.5 (CH_2), 25.6 (CH), 25.2 (CH_2), 23.3 (CH), 22.8 (CH) and 19.0 (CH_2).

Prins Cyclisation of Benzaldehyde Acetal 85e



85e **86e**

Reaction of acetal **85e** (0.6 mmol) with TfOH at 0 °C, as specified in Table **3**, followed by chromatography on silica (10 % to 15 % EtOAc in petroleum ether), gave **86e** (see Table **3**) as a yellow oil.

(1*RS*,3*SR*,3a*SR*,7a*SR*)-1,3-Diphenyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-carbaldehyde (86e)

86e: ν_{max} (CH_2Cl_2) 3030, 2926, 2856, 1702, 1599, 1495, 1451, 1268, 1025, 734 and 700 cm^{-1}; δ_H (400 MHz) 8.98 (1 H, s, CHO), 7.40 (2 H, app. d, *J* 8.3, ArH), 7.32 (2 H, app. t, *J* 7.5, ArH), 7.25 - 7.19 (2 H, m, ArH), 7.19 - 7.13 (2 H, m, ArH), 7.13 - 7.09 (2 H, m, ArH), 6.59 (1 H, br. d, *J* 3.4, HC=C), 5.45 (1 H, d, *J* 10.3, CCHC*H*OCH), 5.20 (1 H, d, *J* 4.4, CH_2CHCHO), 3.72 (1 H, br. t, *J* 8.4, C=CC*H*CHO), 2.35 (1 H, ddt, *J* 13.2, 6.8, 4.6, one of CH_2CHCHO), 2.21 (1 H, dtd, *J* 20.2, 5.4, 1.4, one of CH_2CH=C), 1.99 (1 H, dddt, *J* 20.2, 11.7, 6.0, 2.5, one of CH_2CH=C), 1.43 (1 H, br. qd, *J* 13.2, 5.6, one of CH_2CHCHO) and 1.19 - 1.10 (1 H, m, CH_2CHCHO); δ_C (100 MHz) 193.6 (C), 151.8 (CH), 140.7 (C), 139.9 (C), 138.5 (C), 128.1 (2 x CH), 128.0 (2 x CH), 127.5 (2 x CH), 127.1 (CH), 127.0 (CH), 125.5 (2 x CH), 82.3 (CH), 82.1 (CH), 41.0 (CH), 41.0 (CH), 25.1 (CH_2) and 19.8 (CH_2).

7.3 Experimental Data for Chapter 3

General Procedure 1 **- Formation of Lactones (121 and 127) and Ketoesters (122)**

Methyl cyclohexa-2,5-diene-1-carboxylate **72** (1.38 g, 10 mmol) in THF (3 ml) was added dropwise to a cooled (-78 °C) solution of LDA (11 mmol, 1.1 equiv.) in THF (30 ml). The resulting suspension was stirred for 30 min before addition of the epoxide or α-bromoketone (11 mmol, 1.1 equiv.). The reaction was allowed to warm slowly to room temperature and monitored by TLC. On completion (typically 4 h) the reaction was quenched with saturated aqueous NH_4Cl (30 ml). The phases were separated and the aqueous phase extracted with ether (2 x 25 ml). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel.

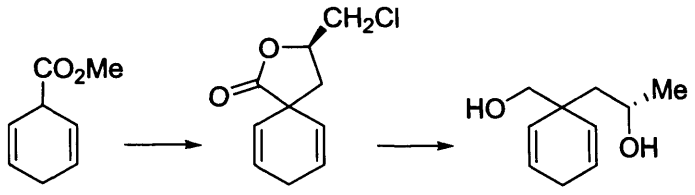
General Procedure 2 **- Reduction of Lactones (121 and 127) and Ketoesters (122)**

The lactone **121** or **127**, or ketoester **122** (5 mmol) in THF (5 ml) was added to a suspension of $LiAlH_4$ (380 mg, 10 mmol, 2 equiv.) in THF (20 ml). After stirring for 15 min, the reaction was quenched with 2M aqueous NaOH (2 ml), dried over Na_2SO_4 and filtered. Concentration of the filtrate followed by chromatography on silica gave the diol.

General Procedure 3 **- Iodocyclisation Reactions**

Iodine (762 mg, 3 mmol) and $NaHCO_3$ (252 mg, 3 mmol) were added to a solution of diol (1 mmol) in acetonitrile (10 ml). Stirring was continued for the time shown in Table **5**, Scheme **58**, or Scheme **61**, before addition of saturated aqueous sodium thiosulfate (15 ml). The organic phase was separated and the aqueous phase extracted with ether (2 x 10 ml). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* and the residue purified by chromatography on silica gel.

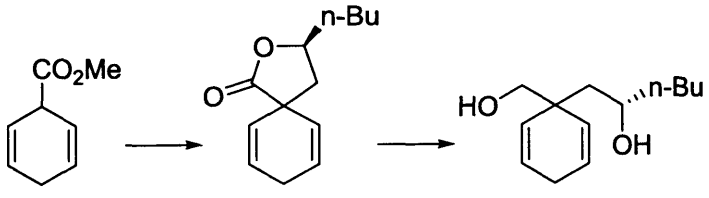
1-(1-(Hydroxymethyl)cyclohexa-2,5-dienyl)propan-2-ol (113a)



72 **121d** **113a**

Lactone **121d** was prepared from epichlorohydrin according to *general procedure 1*. Reduction according to *general procedure 2* followed by Kugelrohr distillation (200 °C, 0.5 mmHg) gave the *title compound* (741 mg, 87 %, 2 steps) as a colourless solid, m.p. 70 - 72 °C (Found: M^+-H_2O, 150.1040. $C_{10}H_{14}O$ requires M, 150.1045); ν_{max} (Nujol) 3244, 1060, 1021, 739 and 713 cm^{-1}; δ_H (400 MHz) 6.07 - 5.97 (2 H, m, 2 x alkene CH), 5.68 (1 H, app. dq, *J* 10.1, 2.0, one of alkene CH), 5.43 (1 H, app. dq, *J* 10.1, 2.0, one of alkene CH), 4.04 - 3.95 (1 H, m, C*H*OH), 3.35 (2 H, app. s, C*H*$_2$OH), 2.79-2.63 (2 H, m, C*H*$_2$CH=CH), 2.24 (1 H, br. s, OH), 1.79 (1 H, br. s, OH), 1.53 (1 H, dd, *J* 14.2, 9.2, one of CH_2), 1.41 (1 H, dd, *J* 14.2, 2.2, one of CH_2) and 1.14 (3 H, d, *J* 6.3, CH_3); δ_C (100 MHz) 130.5 (CH), 129.5 (CH), 128.1 (CH), 127.4 (CH), 70.4 (CH_2), 65.5 (CH), 46.4 (CH_2), 42.3 (C), 26.5 (CH_2) and 24.0 (CH_3); *m/z* (TOF ES+) 150 (M-H_2O, 1%), 119 (14), 92 (18) and 91 (100).

1-(1-(Hydroxymethyl)cyclohexa-2,5-dienyl)-hexan-2-ol (113b)

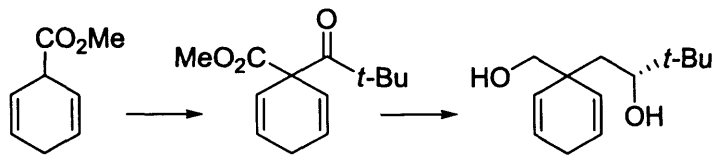


72 **121b** **113b**

Lactone **121b** was prepared according to *general procedure 1*. Reduction according to *general procedure 2* followed by Kugelrohr distillation (220 °C, 0.5 mmHg) gave the *title compound* (1.97 g, 86 %, 2 steps) as a colourless oil (Found: MH^+, 211.1696. $C_{13}H_{23}O_2$ requires M, 211.1698); ν_{max} (neat) 3417, 2950, 1652, 1463, 1204, 1141, 1048, 887, 776, 730 and 667 cm^{-1}; δ_H (400 MHz) 6.05 - 5.97 (2 H, m, 2 x alkene CH), 5.69 (1 H, app. dq, *J* 10.3, 2.1, one of alkene CH), 5.43 (1 H, app. dq, *J* 10.3, 2.1, one of alkene CH),

3.82 - 3.76 (1 H, m, C*H*OH), 3.35 (2 H, app. s, CH_2OH), 2.79 - 2.64 (2 H, m, CH_2CH=CH), 2.10 (2 H, br. s, 2 x OH), 1.49 (1 H, dd, *J* 14.2, 9.0, one of CH_2), 1.43 (1 H, dd, *J* 14.2, 2.4, one of CH_2), 1.40 - 1.24 (6 H, m, 3 x CH_2) and 0.88 (3 H, t, *J* 7.0, CH_3); δ_C (100 MHz) 130.6 (CH), 129.6 (CH), 127.9 (CH), 127.3 (CH), 70.4 (CH_2), 69.2 (CH), 44.8 (CH_2), 42.2 (C), 37.6 (CH_2), 27.7 (CH_2), 26.5 (CH_2), 22.7 (CH_2) and 14.1 (CH_3); *m/z* (TOF ES+) 252 ($MH^+.CH_3CN$, 100%), 211 (MH^+, 12), 193 (14) and 175 (3).

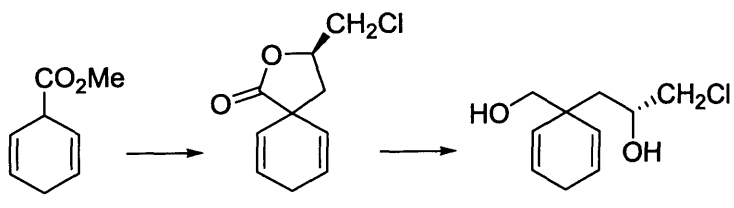
1-(1-(Hydroxymethyl)cyclohexa-2,5-dienyl)-3,3-dimethylbutan-2-ol (113c)



72 **122c** **113c**

Ketoester **122c** (2.37 g, 90 %) was prepared according to *General Procedure 1*. Reduction according to *General Procedure 2* followed by crystallisation from Et_2O/petroleum ether gave the *title compound* (1.2 g, 57 %) as a colourless solid, m.p. 81 - 84 °C (Found: $M^+ - H_2O$, 193.1585. $C_{13}H_{20}O$ requires M, 193.1592); ν_{max} (Nujol) 3280, 1063, 1010 and 714 cm^{-1}; δ_H (400 MHz) 6.05 - 5.97 (2 H, m, 2 x alkene CH), 5.67 (1 H, app. dq, *J* 10.0, 2.0, one of alkene CH), 5.42 (1 H, app. dq, *J* 10.3, 2.2, one of alkene CH), 3.45 - 3.36 (3 H, m, CH_2OH and C*H*OH), 2.81 - 2.65 (2 H, m, CH_2CH=CH), 2.05 (1 H, br. s, OH), 1.77 (1 H, br. s, OH), 1.53 (1 H, dd, *J* 14.3, 0.8, one of CH_2CHO), 1.38 (1 H, dd, *J* 14.3, 9.5, one of CH_2CHO) and 0.87 (9 H, s, $C(CH_3)_3$); δ_C (100 MHz) 130.5 (CH), 129.8 (CH), 127.9 (CH), 127.4 (CH), 76.5 (CH), 70.4 (CH_2), 42.2 (C), 39.5 (CH_2), 34.8 (C), 26.5 (CH_2) and 25.7 (CH_3); *m/z* (TOF AP^+) 193 (M - H_2O, 48%) and 175 (100).

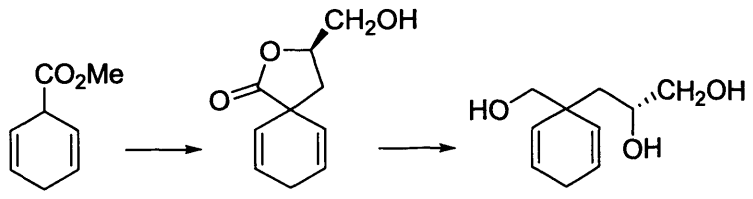
1-Chloro-3-(1-(hydroxymethyl)cyclohexa-2,5-dienyl)propan-2-ol (113d)



72 **121d** **113d**

Lactone **121d** (5.47 g, 97 %) was prepared according to *General Procedure 1*. Sodium borohydride (1.9 g, 50.4 mmol, 2 equiv.) was added in one portion to a solution of the crude lactone (5.0 g, 25.2 mmol) in ethanol (200 ml). The reaction was stirred for 2 h until complete consumption of starting material was evident (TLC). Glacial acetic acid was carefully added until hydrogen evolution ceased and the ethanol removed under reduced pressure. Water (200 ml) and diethyl ether (100 ml) were added to dissolve the residue and the organic layer separated. The aqueous phase was further extracted with diethyl ether (2 x 50 ml) and the combined organic extracts washed with water (2 x 100 ml). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. Chromatography of the residue on silica (33 % EtOAc in petroleum ether) gave the *title compound* (3.5 g, 70 %) as a colourless oil (Found: M^+ - H, 201.0683. $C_{10}H_{14}ClO_2$ requires M, 201.0682); ν_{max} (neat) 3372, 2920, 1422, 1328, 1047, 947, 877 and 720 cm^{-1}; δ_H (400 MHz) 6.09 - 6.01 (2 H, m, 2 x alkene CH), 5.67 (1 H, app. dq, *J* 10.2, 2.1, one of alkene CH), 5.48 (1 H, app. dq, *J* 10.6, 2.1, one of alkene CH), 4.04 - 3.97 (1 H, m, C*H*OH), 3.58 (1 H, dd, *J* 11.1, 4.0, one of CH_2Cl), 3.49 (1 H, dd, *J* 11.1, 6.6, one of CH_2Cl), 3.41 (2 H, app. s, CH_2OH), 2.76 - 2.71 (2 H, m, CH_2CH=CH), 2.56 (1 H, br. s, OH), 1.77 (1 H, br. s, OH), 1.67 (1 H, dd, *J* 14.3, 8.1, one of CCH_2CHOH) and 1.58 (1 H, dd, *J* 14.3, 3.4, one of CCH_2CHOH); δ_C (100 MHz) 129.5 (CH), 129.4 (CH), 128.0 (CH), 127.7 (CH), 70.3 (CH_2), 69.0 (CH), 50.3 (CH_2), 41.9 (C), 41.8 (CH_2) and 26.5 (CH_2); *m/z* (TOF ES+) 203 (M^+ - H (^{37}Cl), 12%), 201 (37), 95 (46) and 91 (100).

3-(1-(Hydroxymethyl)cyclohexa-2,5-dienyl)propane-1,2-diol (113e)

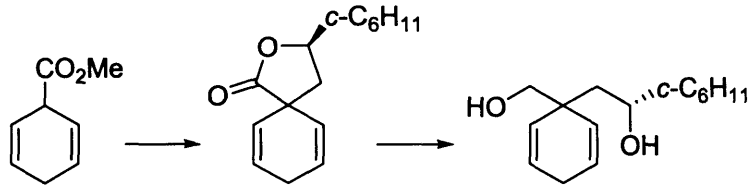


72 **121e** **113e**

Lactone **121e** (330 mg, 23 %) was prepared according to *General Procedure 1*. Reduction according to *General Procedure 2* followed by chromatography on silica (EtOAc) gave the *title compound* (179 mg, 56 %) as a colourless solid, m.p. 78 - 80 °C; ν_{max} (Nujol) 3272, 1234, 1036 and 715 cm^{-1}; δ_H (400 MHz) 6.00 - 5.93 (2 H, m, 2 x

alkene CH), 5.62 (1 H, app. dq, *J* 10.2, 2.1, one of alkene CH), 5.37 (1 H, app. dq, *J* 10.1, 2.1, one of alkene CH), 3.85 (1 H, dddd, *J* 8.9, 7.5, 3.2, 2.5, C*H*OH), 3.50 (1 H, dd, *J* 11.0, 3.2, one of CH_2OH), 3.36 (1 H, dd, *J* 11.0, 7.5, one of CH_2OH), 3.32 (2 H, app. s, CH_2OH), 2.68 - 2.64 (2 H, m, CH_2CH=CH), 2.46 (1 H, br. s, OH), 1.94 (1 H, br. s, OH), 1.70 (1 H, br. s, OH), 1.50 (1 H, dd, *J* 14.3, 8.9, one of CCH_2CHOH) and 1.33 (1 H, dd, *J* 14.3, 2.5, one of CCH_2CHOH); δ_C (100 MHz) 130.0 (CH), 129.5 (CH), 127.9 (CH), 127.4 (CH), 70.4 (CH_2), 69.6 (CH), 67.1 (CH_2), 41.9 (C), 40.9 (CH_2) and 26.5 (CH_2).

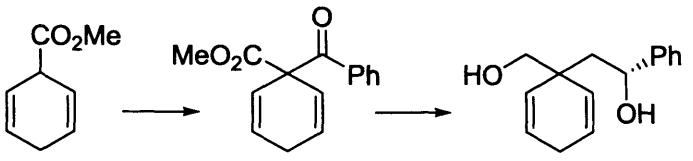
1-Cyclohexyl-2-(1-(hydroxymethyl)cyclohexa-2,5-dienyl)ethanol (113f)



72 **121f** **113f**

Lactone **121f** (1.39 g, 55 %) was prepared according to *General Procedure 1*. Reduction according to *General Procedure 2* gave the *title compound* (0.65 g, 91 %) as a colourless oil (Found: M^+ - OH, 219.1760. $C_{15}H_{23}O$ requires M, 219.1749); ν_{max} (neat) 3364, 2910, 2855, 1451, 1422, 1035 and 711 cm^{-1}; δ_H (400 MHz) 6.05 - 5.96 (2 H, m, 2 x alkene CH), 5.68 (1 H, app. dq, *J* 10.4, 2.1, one of alkene CH), 5.41 (1 H, app. dq, *J* 10.4, 2.1, one of alkene CH), 3.59 (1 H, app. dt, *J* 8.5, 4.4, C*H*OH), 3.37 (2 H, app. s, CH_2OH), 2.79 - 2.64 (2 H, m, CH_2CH=CH), 2.01 (1 H, br. s, OH), 1.78 - 1.59 (7 H, m), 1.49 - 1.42 (2 H, m, CH_2) and 1.32 - 0.93 (5 H, m); δ_C (100 MHz) 130.6 (CH), 129.7 (CH), 127.9 (CH), 127.4 (CH), 73.0 (CH), 70.4 (CH_2), 44.2 (CH), 42.3 (C), 41.9 (CH_2), 29.0 (CH_2), 27.7 (CH_2), 26.5 (CH_2), 26.5 (CH_2), 26.3 (CH_2) and 26.2 (CH_2); *m/z* (TOF ES+) 219 (M - OH, 89%), 201 (100) and 155 (62).

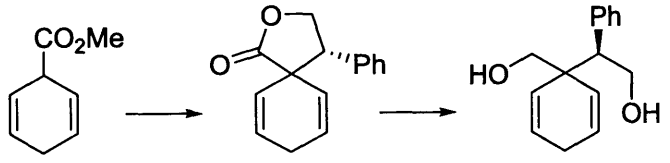
2-(1-(Hydroxymethyl)cyclohexa-2,5-dienyl)-1-phenylethanol (113g)



72 **122g** **113g**

Ketoester **122g** (3.2 g, 87 %) was prepared according to *General Procedure 1*. Reduction according to *General Procedure 2*, followed by crystallisation (CH_2Cl_2/hexane) gave the title compound (1.0 g, 35 %) as a colourless solid, m.p. 77 - 80 °C (Found: MH^+, 231.1378. $C_{15}H_{19}O_2$ requires M, 231.1385); ν_{max} (Nujol) 3281, 1048, 1021, 712 and 699 cm^{-1}; δ_H (400 MHz) 7.36 - 7.33 (3 H, m, aromatic CH), 7.31 - 7.24 (2 H, m, aromatic CH), 6.13 (1 H, app. dtd, J 10.2, 3.2, 1.6, one of alkene CH), 6.05 (1 H, app. dtd, J 10.2, 3.2, 1.6, one of alkene CH), 5.82 (1 H, app. dq, J 10.2, 2.0, one of alkene CH), 5.50 (1 H, app. dq, J 10.2, 2.0, one of alkene CH), 4.92 (1 H, app. br. d, J 9.7, C*H*OH), 3.44 (1 H, d, J 11.1, one of CH_2OH), 3.40 (1 H, d, J 11.1, one of CH_2OH), 2.86 - 2.71 (2 H, m, CH_2CH=CH), 2.54 (1 H, br. s, OH), 1.89 (1 H, dd, J 14.4, 9.7, one of CH_2), 1.79 (1 H, br. s, OH) and 1.67 (1 H, dd, J 14.4, 2.3, one of CH_2); δ_C (100 MHz) 144.8 (C), 130.3 (CH), 129.4 (CH), 128.4 (CH), 128.3 (CH), 127.6 (CH), 127.4 (CH), 125.7 (CH), 71.9 (CH), 70.4 (CH2), 47.5 (CH_2), 42.6 (C) and 26.6 (CH_2); *m/z* (TOF ES+) 231 (MH^+, 41%), 230 (M^+, 63), 213 (16), 195 (19), 132 (25) and 105 (100).

2-(1-(Hydroxymethyl)cyclohexa-2,5-dienyl)-2-phenylethanol (113h)

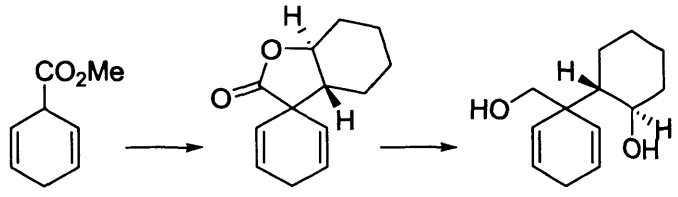


72 **121h** **113h**

Lactone **121h** (1.29 g, 40 %) was prepared from styrene oxide according to *General Procedure 1*. Reduction according to *General Procedure 2* followed by chromatography on silica (33 % EtOAc in petroleum ether) gave the *title compound* (1.1 g, 84 %) as a colourless solid, m.p. 83 - 86 °C (Found: MH^+, 231.1397. $C_{15}H_{19}O_2$ requires M, 231.1385); ν_{max} (Nujol) 3265, 1377, 1032, 1000, 724 and 698 cm^{-1}; δ_H (400 MHz)

7.28 - 7.13 (5 H, m, aromatic CH), 5.99 (1 H, app. dtd, *J* 10.2, 3.3, 1.7, one of alkene CH), 5.89 (1 H, app. dtd, *J* 10.3, 3.3, 1.7, one of alkene CH), 5.60 (1 H, app. dq, *J* 10.2, 2.1, one of alkene CH), 5.43 (1 H, app. dq, *J* 10.3, 2.1, one of alkene CH), 3.92 (1 H, dd, *J* 11.3, 5.4, one of C*H*$_2$OH), 3.82 (1 H, dd, *J* 11.3, 9.1, one of C*H*$_2$OH), 3.27 (1 H, d, *J* 10.6, one of C*H*$_2$OH), 3.07 (1 H, d, *J* 10.6, one of C*H*$_2$OH), 2.86 (1 H, dd, *J* 9.1, 5.4, CHAr), 2.60 (1 H, app. dtt, *J* 23.2, 3.5, 1.9, one of C*H*$_2$CH=CH) and 2.53 (1 H, app. dtt, *J* 23.2, 3.1, 2.2, one of C*H*$_2$CH=CH); δ_C (100 MHz) 138.2 (C), 129.6 (CH), 129.6 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.1 (CH), 126.6 (CH), 69.0 (CH_2), 63.7 (CH_2), 54.2 (CH), 44.5 (C) and 26.6 (CH_2); *m/z* (TOF ES+) 272 (MH^+.CH_3CN, 43 %), 231 (MH^+, 12), 213 (100) and 195 (58).

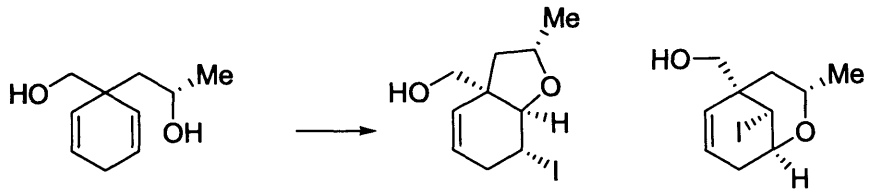
(1*SR*,2*RS*)-2-(1-(Hydroxymethyl)cyclohexa-2,5-dienyl)cyclohexanol (113i)



72 **121i** **113i**

Lactone **121i** (1.19 g, 34 %) was prepared according to *General Procedure 1*. Reduction according to *General Procedure 2* followed by chromatography on silica (33 % EtOAc in petroleum ether) gave the *title compound* (1.1 g, 92 %) as a colourless solid, m.p. 67 - 70 °C (Found: MH^+, 209.1540. $C_{13}H_{21}O_2$ requires M, 209.1542); ν_{max} (CH_2Cl_2) 3296, 2926, 2855, 1450, 1422, 1352, 1058, 980 and 713 cm^{-1}; δ_H (400 MHz) 5.95 (1 H, app. dtd, *J* 10.2, 3.3, 1.7, one of alkene CH), 5.87 (1 H, app. dtd, *J* 10.2, 3.3, 1.6, one of alkene CH), 5.72 (1 H, app. dq, *J* 10.3, 2.0, one of alkene CH), 5.53 (1 H, app. dq, *J* 10.3, 2.0, one of alkene CH), 3.61 (1 H, app. dt, *J* 10.1, 4.3, C*H*OH), 3.58 (1 H, d, *J* 10.8, one of C*H*$_2$OH), 3.49 (1 H, d, *J* 10.8, one of C*H*$_2$OH), 2.99 (2 H, br. s, OH), 2.71 - 2.58 (2 H, m, C*H*$_2$CH=CH), 1.99 - 1.92 (1 H, m), 1.76 - 1.59 (3 H, m), 1.43 (1 H, ddd, *J* 12.5, 10.1, 3.7, C*H*CHOH), 1.33 - 1.04 (3 H, m) and 0.96 (1 H, app. dq, *J* 12.8, 3.3, one of CH_2); δ_C (100 MHz) 130.0 (CH), 129.4 (CH), 127.0 (CH), 125.4 (CH), 71.3 (CH), 69.8 (CH_2), 50.0 (CH), 44.8 (C), 36.4 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 25.7 (CH_2) and 24.7 (CH_2); *m/z* (TOF ES+) 250 (MH^+.CH_3CN, 100 %), 209 (MH^+, 38), 191 (12) and 173 (11).

((2*SR*,3a*RS*,7*RS*,7a*RS*)-7-Iodo-2-methyl-2,3,3a,6,7,7a-hexahydrobenzofuran-3a-yl)methanol (114a) and ((1*RS*,3*RS*,5*SR*,9*RS*)-9-Iodo-3-methyl-2-oxabicyclo(3.3.1)non-6-en-5-yl)methanol (115a)



113a **114a** **115a**

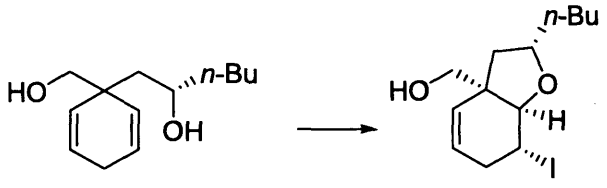
Iodocyclisation of diol **113a** (178 mg, 1.06 mmol) according to *General Procedure 3* followed by chromatography on silica (10 % EtOAc in petroleum ether) gave the *title compounds* as colourless oils (**115a**: 17 mg, 5.5 %; **114a**: 204 mg, 65.5 %).

Data for compound **114a**: Found: MH^+, 295.0202. $C_{10}H_{16}IO_2$ requires M, 295.0195; ν_{max} (neat) 3444, 2966, 1456, 1384, 1205, 1060, 834, 724 and 668 cm^{-1}; δ_H (400 MHz) 5.74 (1 H, app. dt, *J* 10.0, 3.9, CH_2CH=CH), 5.68 (1 H, app. dt, *J* 10.0, 1.5, CH_2CH=C*H*), 4.38 - 4.36 (2 H, m, CHIC*H*O and C*H*ICHO), 4.11 (1 H, app. doubled quintet, *J* 8.7, 6.1, CH_3CHO), 3.69 (1 H, d, *J* 10.7, one of CH_2OH), 3.60 (1 H, d, *J* 10.7, one of CH_2OH), 2.81 - 2.74 (1 H, m, one of CH_2CH=CH), 2.62 (1 H, dddd, *J* 17.8, 7.7, 3.6, 1.9, one of CH_2CH=CH), 1.95 (1 H, dd, *J* 12.5, 6.4, one of CH_2CHO), 1.73 (1 H, br. s, OH), 1.59 (1 H, dd, *J* 12.5, 8.7, one of CH_2CHO) and 1.26 (3 H, d, *J* 6.0, CH_3); δ_C (100 MHz) 130.4 (CH), 127.3 (CH), 83.3 (CH), 73.3 (CH), 68.6 (CH_2), 50.8 (C), 43.5 (CH_2), 33.8 (CH_2), 27.0 (CH) and 21.0 (CH_3). *m/z* (TOF ES+) 295 (MH^+, 56%), 277 (100), 132 (37) and 119 (40).

Data for compound **115a**: Found: MH^+, 295.0179. $C_{10}H_{16}IO_2$ requires M, 295.0195; ν_{max} (CH_2Cl_2) 3396, 2933, 1457, 1417, 1380, 1344, 1209, 1153, 1046, 789, 720 and 688 cm^{-1}; δ_H (400 MHz) 6.01 (1 H, app. dt, *J* 10.0, 3.4, CH_2CH=CH), 5.29 (1 H, app. dq, *J* 10.0, 2.0, CH_2CH=C*H*), 4.50 - 4.48 (1 H, m, C*H*ICHO), 4.29 (1 H, app. br. t, *J* 4.5, CHIC*H*O), 3.97 (1 H, app. dqd, *J* 12.2, 6.1, 2.8, CH_3CHO), 3.63 (1 H, dd, *J* 10.9, 4.8, one of CH_2OH), 3.50 (1 H, dd, *J* 10.9, 5.4, one of CH_2OH), 2.83 (1 H, app. ddt, *J* 19.9, 5.4, 2.5, one of CH_2CH=CH), 2.34 (1 H, app. br. d, *J* 19.9, one of CH_2CH=CH), 1.80 (1 H, dd, *J* 13.0, 11.3, one of CH_2CHO), 1.67 (1 H, br. t, *J* 5.6, OH), 1.57 (1 H, dd, *J* 13.0, 2.8, one of CH_2CHO) and 1.14 (3 H, d, *J* 6.1, CH_3); δ_C (100 MHz) 128.4 (CH), 127.2 (CH), 72.7 (CH), 71.4 (CH_2),

65.0 (CH), 41.2 (CH_2), 40.2 (C), 36.2 (CH), 30.1 (CH_2) and 21.2 (CH_3); *m/z* (TOF ES+) 295 (10 %), 277 (18), 208 (100) and 146 (14).

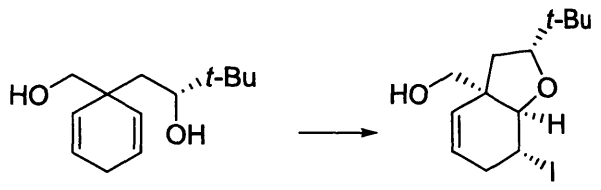
((2*SR*,3a*RS*,7*RS*,7a*RS*)-2-Butyl-7-iodo-2,3,3a,6,7,7a-hexahydrobenzofuran-3a-yl)methanol (114b)



113b **114b**

Iodocyclisation of diol **113b** (480 mg, 2.29 mmol) according to *General Procedure 3* followed by chromatography on silica (14 % EtOAc in petroleum ether) gave the *title compound* (153 mg, 65 %) as a pale yellow oil (Found: MH^+, 337.0667. $C_{13}H_{22}IO_2$ requires M, 337.0665); ν_{max} (neat) 3419, 2928, 2863, 1456, 1046 and 728 cm^{-1}; δ_H (400 MHz) 5.75 (1 H, app. dt, *J* 9.9, 3.8, CH_2CH=CH), 5.68 (1 H, app. br. d, *J* 9.9, CH_2CH=C*H*), 4.37 (1 H, app. dt, *J* 4.5, 7.2, C*H*ICHO), 4.34 (1 H, d, *J* 7.3, CHIC*H*O), 3.92 (1 H, app. dq, *J* 9.0, 6.3, BuC*H*O), 3.69 (1 H, d, *J* 10.7, one of CH_2OH), 3.60 (1 H, d, *J* 10.7, one of CH_2OH), 2.77 (1 H, app. dtd, *J* 17.9, 4.5, 1.3, one of CH_2CH=CH), 2.62 (1 H, dddd, *J* 17.9, 7.2, 3.5, 1.8, one of CH_2CH=CH), 1.91 (1 H, dd, *J* 12.5, 6.3, one of CH_2CHO), 1.71 (1 H, br. s, OH), 1.70 - 1.62 (1 H, m, one of CH_2), 1.61 (1 H, dd, *J* 12.5, 9.0, one of CH_2CHO), 1.50 - 1.39 (1 H, m, one of CH_2), 1.35 - 1.24 (4 H, m, 2 x CH_2) and 0.89 (3 H, t, *J* 7.0, CH_3); δ_C (100 MHz) 130.4 (CH), 127.3 (CH), 82.8 (CH), 77.4 (CH), 68.6 (CH_2), 50.3 (C), 41.7 (CH_2), 35.3 (CH_2), 33.7 (CH_2), 28.2 (CH_2), 26.7 (CH), 22.7 (CH_2) and 14.0 (CH_3); *m/z* (TOF ES+) 337 (MH^+, 81 %), 319 (71), 268 (100), 250 (87), 209 (48), 191 (46), 173 (34), 161 (49) and 132 (38).

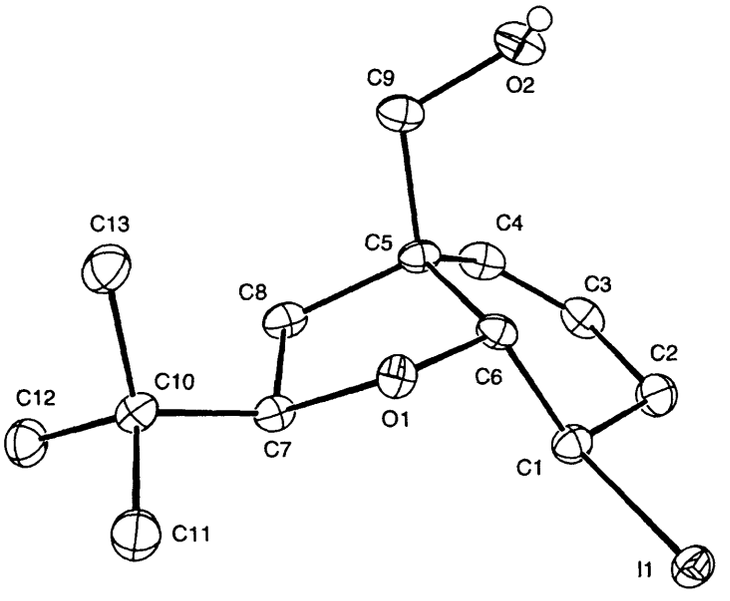
((2*RS*,3a*RS*,7*RS*,7a*RS*)-2-*tert*-Butyl-7-iodo-2,3,3a,6,7,7a-hexahydrobenzofuran-3a-yl)methanol (114c)



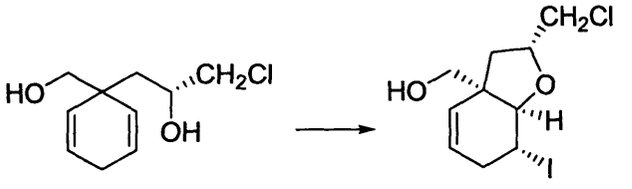
113c **114c**

Iodocyclisation of diol **113c** (186 mg, 0.89 mmol) according to *General Procedure 3* followed by chromatography on silica (14 % EtOAc in petroleum ether) gave the *title compound* (265 mg, 89 %) as a colourless solid, m.p. 84 - 86 °C (Found: MH^+, 337.0675. $C_{13}H_{22}IO_2$ requires M, 337.0665); ν_{max} (CH_2Cl_2) 3389, 2954, 2858, 1464, 1396, 1362, 1205, 1044, 973, 780 and 727 cm^{-1}; δ_H (400 MHz) 5.71 (1 H, app. dt, *J* 10.0, 3.9, CH_2CH=CH), 5.62 (1 H, app. dt, *J* 10.0, 1.5, CH_2CH=C*H*), 4.36 (1 H, app. td, *J* 7.0, 4.8, C*H*ICHO), 4.23 (1 H, d, *J* 7.0, CHIC*H*O), 3.65 (1 H, dd, *J* 10.4, 4.5, one of CH_2OH), 3.58 - 3.52 (2 H, m, one of CH_2OH and *t*BuCHO), 2.73 (1 H, app. dtd, *J* 17.9, 4.6, 1.6, one of CH_2CH=CH), 2.52 (1 H, dddd, *J* 17.9, 6.9, 3.8, 1.7, one of CH_2CH=CH), 1.67 (1 H, dd, *J* 12.5, 9.9, one of CH_2CHO), 1.61 (1 H, dd, *J* 12.5, 6.5, one of CH_2CHO), 1.56 (1 H, br. s, OH) and 0.82 (9 H, s, $C(CH_3)_3$); δ_C (100 MHz) 130.4 (CH), 127.2 (CH), 85.0 (CH), 82.3 (CH), 68.3 (CH_2), 49.9 (C), 36.8 (CH_2), 33.2 (CH_2), 33.1 (C), 26.6 (CH) and 25.7 (3 x CH_3); *m/z* (TOF ES+) 337 (MH^+, 28 %) and 319 (100).

Single crystal X-ray diffraction data for this compound has been deposited with the CCDC, number 646880, and can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif. The Ortep plot (50% probability thermal ellipsoids) is shown below:



((2*RS*,3a*RS*,7*RS*,7a*RS*)-2-(Chloromethyl)-7-iodo-2,3,3a,6,7,7a-hexahydrobenzofuran-3a-yl)methanol (114d)

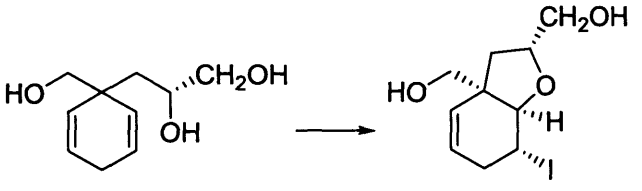


113d **114d**

Iodocyclisation of diol **113** (81 mg, 0.40 mmol) according to *General Procedure 3* followed by chromatography on silica (14 % EtOAc in petroleum ether) gave the *title compound* (115 mg, 87 %) as a colourless oil; (Found: M^+ - I, 201.0681. $C_{10}H_{14}{}^{35}ClO_2$ requires M, 201.0682); ν_{max} (neat) 3418, 2936, 2874, 1424, 1371, 1315, 1204, 1140, 1047, 971 and 729 cm^{-1}; δ_H (400 MHz) 5.77 (1 H, app. dt, *J* 10.0, 3.9, CH_2CH=CH), 5.68 (1 H, app. dt, *J* 10.0, 1.7, CH_2CH=C*H*), 4.43 (1 H, d, *J* 7.0, CHIC*H*O), 4.37 (1 H, app. td, *J* 6.8, 4.8, *CH*ICHO), 4.24 - 4.17 (1 H, m, CH_2CHO), 3.77 (1 H, d, *J* 10.8, one of CH_2OH), 3.70 (1 H, d, *J* 10.8, one of CH_2OH), 3.62 (1 H, dd, *J* 11.2, 4.9, one of CH_2Cl), 3.57 (1 H, dd, *J* 11.2, 5.6, one of CH_2Cl), 2.82 (1 H, app. dtd, *J* 18.1, 4.3, 1.7, one of CH_2CH=CH), 2.61 (1 H, dddd, *J* 18.1, 6.4, 3.9, 1.7, one of CH_2CH=CH) and 1.98 (2 H, app. d, *J* 7.7, CH_2CHO); δ_C (100 MHz) 130.3 (CH), 127.4 (CH), 83.3 (CH), 78.7 (CH), 68.5 (CH_2), 50.2

(C), 43.4 (CH_2), 33.9 (CH_2), 27.1 (CH) and 21.1 (CH_3); *m/z* (TOF ES+) 203 $((M\text{-}I)^+$ (^{37}Cl), 11 %), 201 $((M\text{-}I)^+$ (^{35}Cl), 32), 105 (28) and 91 (100).

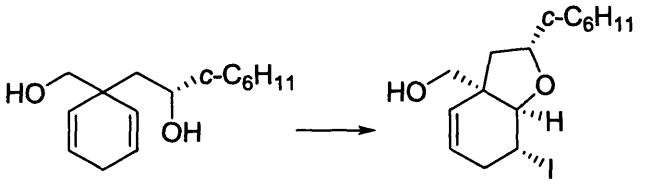
((2*RS*,3a*RS*,7*RS*,7a*RS*)-2-Hydroxymethyl-7-iodo-2,3,3a,6,7,7a-hexahydrobenzofuran-3a-yl)methanol (114e)



113e **114e**

Iodocyclisation of triol **113e** (45 mg, 0.25 mmol) according to *General Procedure 3* followed by chromatography on silica (67 % EtOAc in petroleum ether) gave the *title compound* (69 mg, 91 %) as a colourless solid, m.p. 87 - 88 °C (Found: $MH^+.CH_3CN$, 352.0407. $C_{12}H_{19}INO_3$ requires M, 352.0410); ν_{max} (Nujol) 3215, 1144, 1042, 1029 and 726 cm^{-1}; δ_H (400 MHz) 5.69 - 5.60 (2 H, m, 2 x alkene CH), 4.34 (1 H, d, *J* 8.2, CHIC*H*O), 4.28 (1 H, app. td, *J* 8.1, 4.8, C*H*ICHO), 4.11 - 4.02 (1 H, m, CH_2CHO), 3.76 (1 H, dd, *J* 12.0, 2.4, one of CH_2OH), 3.64 (1 H, d, *J* 10.8, one of CH_2OH), 3.54 (1 H, d, *J* 10.8, one of CH_2OH), 3.48 (1 H, dd, *J* 12.0, 4.1, one of CH_2OH), 2.74 (1 H, app. dtd, *J* 17.9, 4.6, 1.1, one of CH_2CH=CH), 2.62 - 2.54 (1 H, dddd, *J* 17.9, 7.8, 2.9, 1.9, one of CH_2CH=CH), 2.38 (1 H, br. s, OH), 2.23 (1 H, br. s, OH), 1.88 (1 H, dd, *J* 12.7, 8.4, one of CH_2CHO) and 1.79 (1 H, dd, *J* 12.7, 7.4, one of CH_2CHO); δ_C (100 MHz) 130.3 (CH), 127.3 (CH), 83.7 (CH), 77.4 (CH), 68.2 (CH_2), 63.9 (CH_2), 50.5 (C), 36.5 (CH_2), 34.3 (CH_2) and 26.6 (CH_2); *m/z* (TOF ES+) 352 ($MH^+.CH_3CN$, 32 %), 328 (25), 293 (100) and 165 (42).

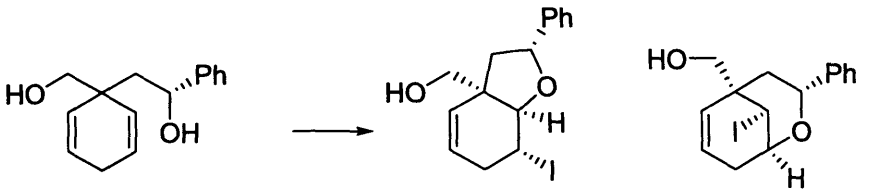
((2*RS*,3a*RS*,7*RS*,7a*RS*)-2-Cyclohexyl-7-iodo-2,3,3a,6,7,7a-hexahydrobenzofuran-3a-yl)methanol (114f)



113f **114f**

Iodocyclisation of diol **113** (277 mg, 1.17 mmol) according to *General Procedure 3* followed by chromatography on silica (14 % EtOAc in petroleum ether) gave the *title compound* (188 mg, 44 %) as a pale yellow oil (Found: MH^+, 363.0828. $C_{15}H_{24}IO_2$ requires M, 363.0821); ν_{max} (neat) 3403, 2914, 1446, 1385, 1356, 1266, 1204, 1048, 975, 777 and 668 cm^{-1}; δ_H (400 MHz) 5.75 (1 H, app. dt, *J* 9.9, 3.9, CH_2CH=CH), 5.68 (1 H, app. br. d, *J* 9.9, CH_2CH=C*H*), 4.38 (1 H, app. td, *J* 7.2, 4.7, C*H*ICHO), 4.31 (1 H, d, *J* 7.4, CHIC*H*O), 3.71 - 3.61 (2 H, m, one of C*H*$_2$OH and CH_2C*H*O), 3.59 (1 H, d, *J* 10.4, one of C*H*$_2$OH), 2.77 (1 H, app. dtd, *J* 17.8, 4.5, 1.3, one of C*H*$_2$CH=CH), 2.60 (1 H, dddd, *J* 17.8, 7.2, 3.6, 1.8, one of C*H*$_2$CH=CH), 1.95 - 1.87 (1 H, br. resonance, OH), 1.81 (1 H, dd, *J* 12.5, 6.3, one of C*H*$_2$CHO), 1.76 - 1.54 (5 H, m), 1.44 - 1.35 (1 H, m), 1.30 - 1.10 (3 H, m) and 0.99 - 0.83 (3 H, m); δ_C (100 MHz) 130.4 (CH), 127.3 (CH), 82.5 (CH), 81.6 (CH), 68.5 (CH_2), 50.0 (C), 42.7 (CH), 39.3 (CH_2), 33.5 (CH_2), 30.0 (CH_2), 28.6 (CH_2), 26.9 (CH), 26.5 (CH_2), 25.9 (CH_2) and 25.8 (CH_2); *m/z* (TOF ES+) 363 (MH^+, 100 %), 294 (61), 276 (73) and 199 (58).

((2*RS*,3a*RS*,7*RS*,7a*RS*)-7-Iodo-2-phenyl-2,3,3a,6,7,7a-hexahydrobenzofuran-3a-yl)methanol (114g) and ((1*RS*,3*SR*,5*SR*,9*RS*)-9-Iodo-3-phenyl-2-oxabicyclo(3.3.1)non-6-en-5-yl)methanol (115g)

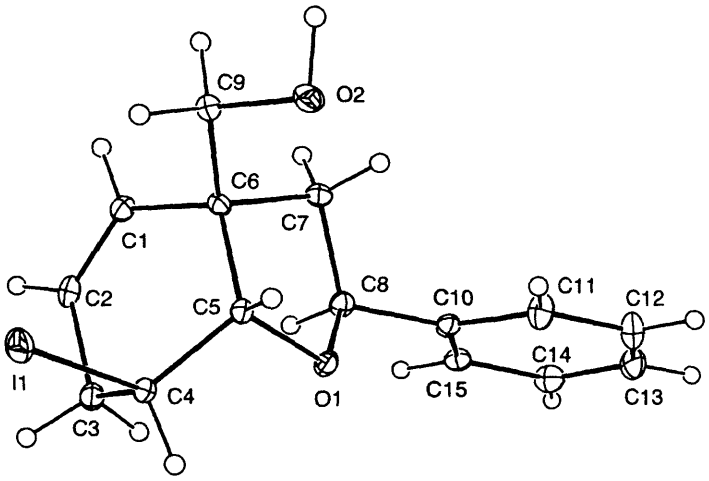


113g **114g** **115g**

Iodocyclisation of diol **113g** (198 mg, 0.86 mmol) according to *General Procedure 3* followed by chromatography on silica (14 % EtOAc in petroleum ether) gave compound **114g** (181 mg, 59 %) as a colourless solid and compound **115g** (12 mg, 4 %) as a pale yellow waxy solid.

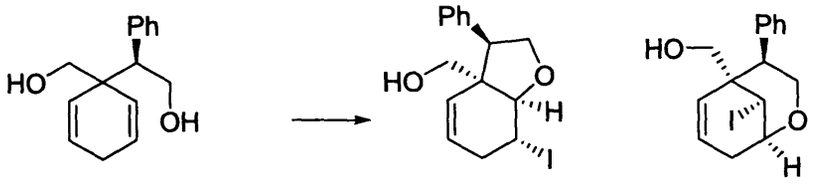
Data for compound **114g**: Found: MH^+, 357.0363. $C_{15}H_{18}IO_2$ requires M, 357.0352; ν_{max} (Nujol) 3442, 1199, 1014, 721 and 700 cm^{-1}; δ_H (400 MHz) 7.29 - 7.18 (5 H, m, 5 x aromatic CH), 5.80 (1 H, app. dt, *J* 10.2, 4.0, CH_2CH=CH), 5.68 (1 H, app. br. d, *J* 10.2, CH_2CH=C*H*), 4.89 (1 H, dd, *J* 9.6, 6.2, C*H*Ar), 4.56 (1 H, d, *J* 6.2, CHIC*H*O), 4.46 (1 H, app. q, *J* 5.6, C*H*ICHO), 3.76 (1 H, dd, *J* 10.7, 6.9, one of CH_2OH), 3.67 (1 H, dd, *J* 10.7, 50.0, one of CH_2OH), 2.83 (1 H, app. br. d, *J* 18.3, one of CH_2CH=CH), 2.57 (1 H, app. br. dt, *J* 18.3, 4.9, one of CH_2CH=CH), 2.15 (1 H, dd, *J* 12.6, 6.2, one of CH_2CHAr), 1.99 (1 H, dd, *J* 12.6, 9.6, one of CH_2CHAr) and 1.62 (1 H, dd, *J* 6.9, 5.0, OH); δ_C (100 MHz) 141.7 (C), 129.7 (CH), 128.5 (CH), 127.7 (CH), 127.3 (CH), 125.8 (CH), 82.6 (CH), 79.3 (CH), 68.2 (CH_2), 50.3 (C), 45.1 (CH_2), 32.8 (CH_2) and 25.9 (CH); *m/z* (TOF ES+) 374 ($MH^+.NH_4$, 43 %), 357 (MH^+, 52), 339 (43), 311 (30), 270 (25), 194 (38) and 183 (100).

Single crystal X-ray diffraction data for this compound has been deposited with the CCDC, number 646881, and can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif. The Ortep plot (50% probability thermal ellipsoids) is shown below:



Data for compound **115g**: Found: MH^+, 357.0314. $C_{15}H_{18}IO_2$ requires M, 357.0352; ν_{max} (CH_2Cl_2) 3427, 2920, 2852, 1494, 1453, 1415, 1344, 1264, 1151, 1026, 979, 937, 745 and 689 cm^{-1}; δ_H (400 MHz) 7.28 - 7.18 (5 H, m, 5 x aromatic CH), 6.07 (1 H, app. dt, *J* 10.1, 3.3, CH_2CH=CH), 5.33 (1 H, app. dq, *J* 10.1, 1.7, CH_2CH=C*H*), 4.83 (1 H, dd, *J* 11.5, 2.8, C*H*Ar), 4.60 - 4.58 (1 H, br. s, CHIC*H*O), 4.42 (1 H, app. t, *J* 4.4, C*H*ICHO), 3.61 (1 H, br. d, *J* 10.8, one of CH_2OH), 3.47 (1 H, dd, *J* 10.8, 3.0, one of CH_2OH), 2.86 (1 H, app. ddt, *J* 20.0, 5.2, 2.6, one of CH_2CH=CH), 2.40 (1 H, br. app. d, *J* 20.0, one of CH_2CH=CH), 2.06 (1 H, dd, *J* 13.4, 11.5, one of CH_2CHAr), 1.73 (1 H, dd, *J* 13.4, 2.8, one of CH_2CHAr) and 1.51 (1 H, br. s, OH); δ_C (100 MHz) 141.7 (C), 128.9 (CH), 128.4 (CH), 127.6 (CH), 127.1 (CH), 126.0 (CH), 73.0 (CH), 71.5 (CH), 71.3 (CH_2), 41.7 (CH_2), 40.5 (C), 35.6 (CH) and 30.1 (CH_2); *m/z* (TOF ES+) 357 (MH^+, 12 %), 270 (100), 211 (49), 193 (41) and 183 (35).

((3*RS*,3a*SR*,7*RS*,7a*RS*)-7-Iodo-3-phenyl-2,3,3a,6,7,7a-hexahydrobenzofuran-3a-yl)methanol (114h) and ((1*RS*,4*SR*,5*RS*,9*RS*)-9-Iodo-4-phenyl-2-oxabicyclo(3.3.1)non-6-en-5-yl)methanol (115h)



113h **114h** **115h**

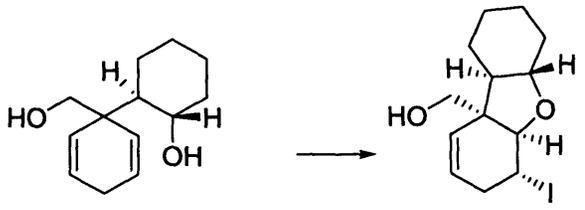
Iodocyclisation of diol **113h** (200 mg, 0.87 mmol) according to *General Procedure 3* followed by chromatography on silica (14 % EtOAc in petroleum ether) gave compound **114h** (243 mg, 79 %) as a colourless solid, m.p. 89 - 91 °C and compound **115h** (10 mg, 3 %) as a pale yellow waxy solid.

Data for compound **114h**: Found: $M^+.NH_3$, 374.0599. $C_{15}H_{21}NO_2I$ requires M, 374.0617; ν_{max} (Nujol) 3313, 1044, 1011, 726 and 704 cm^{-1}; δ_H (400 MHz) 7.28 - 7.18 (3 m, m, 3 x aromatic CH), 7.12 - 7.09 (2 H, m, 2 x aromatic CH), 5.75 (1 H, app. dt, *J* 10.2, 4.1, CH_2CH=CH), 4.94 (1 H, app. br. d, *J* 10.2, CH_2CH=C*H*), 4.54 (1 H, d, *J* 6.0, CHIC*H*O), 4.39 (1 H, app. q, *J* 5.8, C*H*ICHO), 4.09 (1 H, dd, *J* 8.6, 7.2, one of CH_2O), 3.93 (1 H, dd, *J* 9.6, 8.6, one of CH_2O), 3.78 (1 H, d, *J* 11.0, one of CH_2OH), 3.54 (1 H, dd, *J* 9.6, 7.2, C*H*Ar), 3.50 (1 H, d, *J* 11.0, one of CH_2OH), 2.76 (1 H, app. dtd, *J* 18.0, 4.5, 2.1, one of CH_2CH=CH), 2.56 - 2.48 (1 H, m, one of CH_2CH=CH) and 1.52 (1 H, br. s, OH); δ_C (100 MHz) 136.6 (C), 129.3 (2 x CH), 128.2 (2 x CH), 128.1 (CH), 127.3 (CH), 127.1 (CH), 82.4 (CH), 71.6 (CH_2), 66.2 (CH_2), 52.2 (C), 50.8 (CH), 32.4 (CH_2) and 26.1 (CH); *m/z* (TOF ES+) 398 ($MH^+.CH_3CN$, 100 %), 374 (59), 357 (59) and 270 (30).

Data for compound **115h**: Found: MH^+, 357.0364. $C_{15}H_{18}IO_2$ requires M, 357.0352; ν_{max} (CH_2Cl_2) 3436, 2924, 1494, 1462, 1416, 1352, 1266, 1151, 1062, 970, 910, 868, 796, 721, 734 and 702 cm^{-1}; δ_H (400 MHz) 7.24 - 7.16 (3 H, m, aromatic CH), 7.12 (2 H, app. br. d, *J* 6.5, aromatic CH), 6.13 (1 H, app. dt, *J* 10.0, 3.2, CH_2CH=CH), 4.99 (1 H, app. dq, *J* 10.0, 1.6, CH_2CH=C*H*), 4.76 - 4.73 (1 H, m, C*H*ICHO), 4.33 (1 H, app. br. t, *J* 4.3, CHIC*H*O), 3.98 (1 H, app. t, *J* 11.7, one of CH_2O), 3.75 (1 H, dd, *J* 11.7, 4.6, one of CH_2O), 3.47 (1 H, dd, *J* 11.9, 4.6, C*H*Ar), 3.41 (1 H, d, *J* 11.1, one of CH_2OH), 3.20 (1 H, d, *J* 11.1, one of CH_2OH), 2.89 (1 H, app. dtt, *J* 20.1, 5.3, 2.6, one of CH_2CH=CH), 2.42 (1 H, app.

br. d, *J* 20.1, one of C*H*$_2$CH=CH) and 1.45 (1 H, br. s, OH); δ_C (100 MHz) 137.8 (C), 129.2 (CH), 128.3 (4 x CH), 127.5 (CH), 125.1 (CH), 72.6 (CH), 67.7 (CH_2), 64.0 (CH_2), 47.6 (CH), 43.8 (C), 37.0 (CH) and 30.3 (CH_2); *m/z* (TOF ES+) 374 ($MH^+.NH_4$, 63 %), 357 (MH^+,29), 310 (50), 280 (30) and 229 (100).

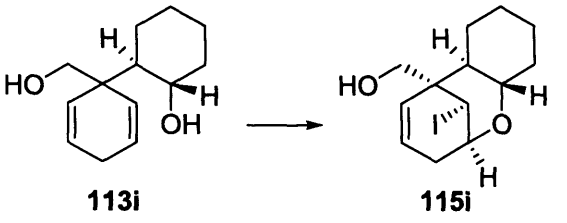
((4a*SR*,5a*RS*,6*RS*,9a*SR*,9b*RS*)-6-Iodo-1,2,3,4,4a,5a,6,7,9a,9b-decahydrodibenzo(b,d)furan-9a-yl)methanol (114i)



113i **114i**

Iodocyclisation of diol **113i** (223 mg, 1.07 mmol) according to *General Procedure 3* followed by chromatography on silica (14 % EtOAc in petroleum ether) gave the *title compound* (222 mg, 62 %) as a colourless oil (Found: $MH^+.CH_3CN$, 376.0770. $C_{15}H_{23}INO_2$ requires M, 376.0774); ν_{max} (neat) 3418, 2929, 2858, 1454, 1427, 1336, 1197, 1125, 1088, 1052, 959, 878, 836 and 726 cm^{-1}; δ_H (400 MHz) 5.95 - 5.90 (1 H, m, CH_2CH=CH), 5.59 (1 H, app. br. dd, *J* 10.4, 2.6, CH_2CH=C*H*), 4.52 (1 H, app. q, *J* 3.5, C*H*ICHO), 4.48 (1 H, d, *J* 3.5, CHIC*H*O), 3.90 (1 H, d, *J* 11.0, one of CH_2OH), 3.80 (1 H, d, *J* 11.0, one of CH_2OH), 3.12 (1 H, app. dt, *J* 10.7, 4.0, CHC*H*O), 2.75 (1 H, app. ddt, *J* 18.5, 4.7, 2.5, one of CH_2CH=CH), 2.56 - 2.49 (1 H, m, one of CH_2CH=CH), 2.09 - 2.04 (1 H, m), 1.90 - 1.65 (5 H, m) and 1.31 - 1.00 (4 H, m); δ_C (100 MHz) 127.3 (CH), 126.9 (CH), 81.5 (CH), 81.1 (CH), 66.8 (CH_2), 51.8 (CH), 49.0 (C), 31.6 (CH_2), 30.9 (CH_2), 26.6 (CH), 25.4 (CH_2), 25.1 (CH_2) and 24.0 (CH_2); *m/z* (TOF AP^+) 376 ($MH^+.CH_3CN$, 100 %) and 173 (10).

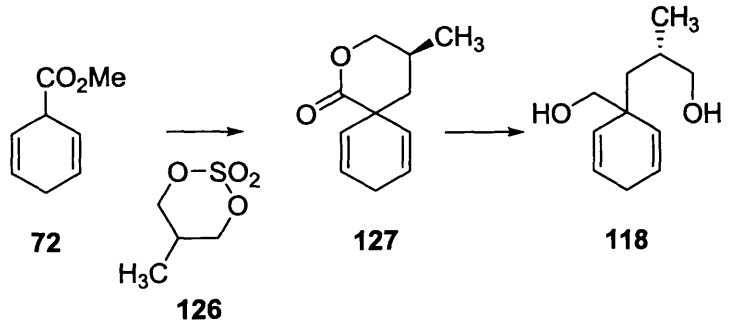
((1*SR*,2*RS*,6*RS*,8*RS*,13*RS*)-13-Iodo-7-oxotricyclo(6.4.1^{2,6}.0)tridec-3-en-2-yl)methanol (115i)



113i **115i**

Iodocyclisation of compound **113i** (113 mg, 0.54 mmol) according to *General Procedure 3, with the omission of $NaHCO_3$*, followed by chromatography on silica (14 % EtOAc in petroleum ether) gave the *title compound* (103 mg, 57 %) as a colourless oil (Found: $MH^+.CH_3CN$, 376.0770. $C_{15}H_{23}INO_2$ requires M, 376.0774); ν_{max} (CH_2Cl_2) 3425, 2927, 2857, 1448, 1416, 1365, 1264, 1150, 1067, 962, 923, 904, 868, 805, 737 and 700 cm^{-1}; δ_H (400 MHz) 5.98 (1 H, app. dt, *J* 10.1, 3.1, CH_2CH=CH), 5.03 (1 H, app. dq, *J* 10.1, 2.0, CH_2CH=C*H*), 4.67 - 4.65 (1 H, m, C*H*ICHO), 4.29 - 4.25 (1 H, m, CHIC*H*O), 3.75 (1 H, d, *J* 11.5, one of C*H*$_2$OH), 3.53 (1 H, d, *J* 11.5, one of C*H*$_2$OH), 3.33 (1 H, app. td, *J* 10.5, 3.9, CHC*H*O), 2.81 (1 H, app. ddt, *J* 20.0, 5.6, 2.8, one of C*H*$_2$CH=CH), 2.31 (1 H, app. br. dt, *J* 20.0, 2.5, one of C*H*$_2$CH=CH), 1.87 - 1.50 (6 H, m, cyclohexane CH and OH), 1.31 - 1.09 (3 H, m, cyclohexane CH) and 0.77 (1 H, app. qd, *J* 12.4, 3.6, cyclohexane CH); δ_C (100 MHz) 129.5 (CH), 125.6 (CH), 72.5 (CH), 72.2 (CH), 66.7 (CH_2), 46.6 (CH), 42.7 (C), 38.9 (CH), 32.3 (CH_2), 30.5 (CH_2), 26.3 (CH_2), 25.7 (CH_2) and 24.5 (CH_2); *m/z* (TOF AP^+) 376 ($MH^+.CH_3CN$, 100 %) and 173 (9).

3-(1-(Hydroxymethyl)cyclohexa-2,5-dienyl)-2-methylpropan-1-ol (118)

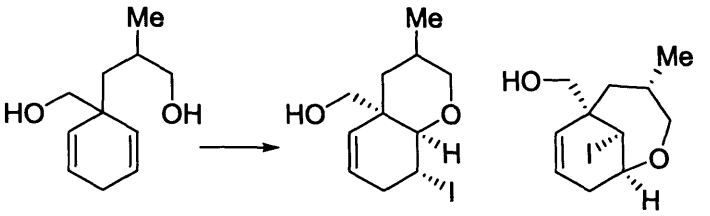


72 **126** **127** **118**

A solution of methyl cyclohexa-2,5-diene-1-carboxylate **72** (1.50 g, 10.9 mmol) in THF (3 ml) was added dropwise to a cooled (-78 °C) solution of LDA (12 mmol, 1.1 equiv.) in

THF (30 ml). The resulting suspension was stirred for 30 min before addition of 5-methyl-2,2-dioxo-1,3,2-dioxathiane **126**[66] (1.82 g, 12 mmol) as a solution in THF (5 mL). After stirring at -78 °C for 1 h the reaction was allowed to warm to room temperature and stirred overnight. 2M aqueous HCl (50 ml) was added, the organic layer separated and the aqueous phase extracted with diethyl ether (2 x 25 ml). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo*. Chromatography of the residue on silica (14 % EtOAc in petroleum ether) gave the lactone, **127** (1.29 g, 67 %), as a pale yellow oil. A solution of lactone **127** (1.20 g, 6.7 mmol) in THF (4 ml) was added to a suspension of $LiAlH_4$ (0.46 g, 13.5 mmol, 2 equiv.) in THF (20 ml). After stirring for 15 min the reaction was quenched with sufficient 2M aqueous NaOH to turn the aluminium salts into a granular consistency. The mixture was dried over sodium sulfate, filtered and concentrated to give a residue that was purified by chromatography on silica (33 % EtOAc in petroleum ether) to give the *title compound* (0.59 g, 48 %) as a colourless oil (Found: MH^+, 183.1370. $C_{11}H_{19}O_2$ requires M, 183.1385); ν_{max} ($CDCl_3$) 3358, 2922, 1456, 1423, 1378, 1034, 947 and 711 cm^{-1}; δ_H (400 MHz) 5.96 - 5.87 (2 H, m, 2 x alkene CH), 5.40 (1 H, app. dq, *J* 10.1, 2.1, one of alkene CH), 5.35 (1 H, app. dq, *J* 10.1, 2.1, one of alkene CH), 3.37 (1 H, dd, *J* 10.4, 6.0, one of CH_2OH), 3.33 (1 H, dd, *J* 10.4, 6.3, one of CH_2OH), 3.25 (1 H, d, *J* 10.5, one of CH_2OH), 3.23 (1 H, d, *J* 10.5, one of CH_2OH), 2.68 - 2.56 (2 H, m, $CH_2CH{=}CH$), 1.69 - 1.61 (1 H, m, $CHCH_3$), 1 54, (2 H, br. s, OH), 1.38 (1 H, dd, *J* 13.9, 4.7, one of CH_2CHCH_3), 1.03 (1 H, dd, *J* 13.9, 6.6, one of CH_2CHCH_3) and 0.86 (3 H, d, *J* 6.8, CH_3); δ_C (100 MHz) 130.4 (CH), 130.0 (CH), 127.7 (CH), 127.1 (CH), 70.7 (CH_2), 68.7 (CH_2), 43.3 (C), 40.2 (CH_2), 32.4 (CH), 26.6 (CH_2) and 18.9 (CH_3); *m/z* (TOF ES+) 224 ($MH^+.CH_3CN$, 100 %), 183 (MH^+, 11) and 165 (53).

((3*SR*,4a*RS*,8*RS*,8a*RS*)-8-Iodo-3-methyl-3,4,4a,7,8,8a-hexahydro-2*H*-chromen-4a-yl)methanol (119) and ((1*SR*,4*SR*,6*RS*,10*SR*)-10-iodo-4-methyl-2-oxabicyclo(4.3.1)dec-7-en-6-yl)methanol (120)



118 **119** **120**

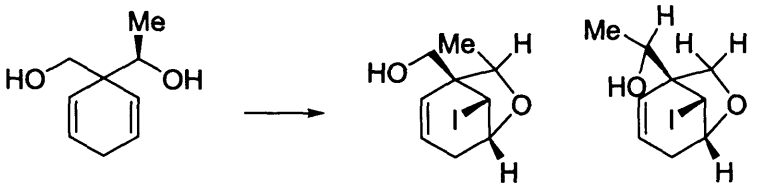
Iodocyclisation of diol **118** (60 mg, 0.33 mmol) according to *General Procedure 3* followed by chromatography on silica (14 % EtOAc in petroleum ether) gave compound **119** (42 mg, 41 %) as a colourless oil and compound **120** (10 mg, 10 %) as a colourless oil.

119 (42 mg, 41 %): Found: MH^+, 309.0372. $C_{10}H_{14}O$ requires M, 309.0352; ν_{max} (neat) 3406, 2923, 2874, 1456, 1383, 1213, 1090, 1053, 923 and 717 cm^{-1}; δ_H (400 MHz) 5.66 (1 H, app. dt, *J* 10.1, 3.8, CH_2CH=CH), 5.37 (1 H, app. br. d, *J* 10.1, CH_2CH=C*H*), 4.49 (1 H, app. q, *J* 6.0, *CH*ICHO), 3.99 (1 H, d, *J* 6.2, CHIC*H*O), 3.96 (1 H, dd, *J* 11.3, 4.9, one of CH_2OH), 3.78 (1 H, ddd, *J* 11.2, 4.6, 0.9, one of CH_2O), 3.54 (1 H, dd, *J* 11.3, 8.3, one of CH_2OH), 3.11 (1 H, dd, *J* 11.2, 8.5, one of CH_2O), 3.04 (1 H, dddd, *J* 18.9, 6.2, 4.2, 1.8, one of CH_2CH=CH), 2.72 (1 H, dddd, *J* 18.9, 5.5, 3.5, 2.4, one of CH_2CH=CH), 1.80 - 1.72 (1 H, m, $CHCH_3$), 1.64 (1 H, dd, *J* 8.3, 4.9, OH), 1.56 - 1.53 (2 H, m, CH_2CHCH_3) and 0.89 (3 H, d, *J* 6.8, CH_3); δ_C (100 MHz) 131.2 (CH), 126.4 (CH), 76.4 (CH), 70.2 (CH_2), 69.4 (CH_2), 41.7 (C), 39.0 (CH_2), 34.9 (CH_2), 27.1 (CH), 22.2 (CH) and 18.1 (CH_3); *m/z* (TOF ES+) 350 ($MH^+.CH_3CN$, 11 %), 309 (MH^+, 12), 291 (100), 181 (20), 164 (47) and 145 (27).

120 (10 mg, 10 %): Found: MH^+, 309.0367. $C_{10}H_{14}O$ requires M, 309.0352; ν_{max} ($CDCl_3$) 3432, 2922, 1460, 1421, 1273, 1106, 1055, 872, 806 and 690 cm^{-1}; δ_H (400 MHz) 5.79 - 5.73 (1 H, m, one of alkene CH), 5.22 (1 H, app. ddt, *J* 10.4, 2.9, 1.6, one of alkene CH), 4.76 (1 H, app. dt, *J* 3.5, 1.6, *CH*ICHO), 4.53 - 4.50 (1 H, m, CHIC*H*O), 3.64 - 3.56 (2 H, m, CH_2OH), 3.49 (1 H, app. dt, *J* 12.9, 2.2, one of CH_2O), 3.35 (1 H, dd, *J* 12.9, 9.8, one of CH_2O), 2.90 (1 H, app. dq, *J* 18.5, 2.9, one of CH_2CH=CH), 2.31 (1 H, app. ddq, *J* 18.5, 5.2, 1.7, one of CH_2CH=CH), 1.88 (1 H, app. br. t, *J* 7.0, OH), 1.86 - 1.79 (1 H, m, $CHCH_3$), 1.70 (1 H, ddd, *J* 14.0, 4.6, 1.7, one of CH_2CHCH_3), 1.54 (1 H, dd, *J* 14.0, 12.4,

one of CH_2CHCH_3) and 0.83 (3 H, d, *J* 6.9, CH_3); δ_C (100 MHz) 126.0 (CH), 125.4 (CH), 77.3 (CH_2), 74.7 (CH), 69.5 (CH_2), 42.6 (C), 42.2 (CH_2), 37.1 (CH), 33.1 (CH), 32.0 (CH_2) and 17.9 (CH_3); *m/z* (TOF AP^+) 309 (MH^+, 100 %) and 291 (23).

((1*RS*,5*SR*,7*RS*,8*SR*)-8-Iodo-7-methyl-6-oxabicyclo(3.2.1)oct-2-en-1-yl)methanol (116a) and 1-((1*SR*,5*SR*,8*SR*)-8-iodo-6-oxabicyclo(3.2.1)oct-2-en-1-yl)ethanol (117a)



74a **116a** **117a**

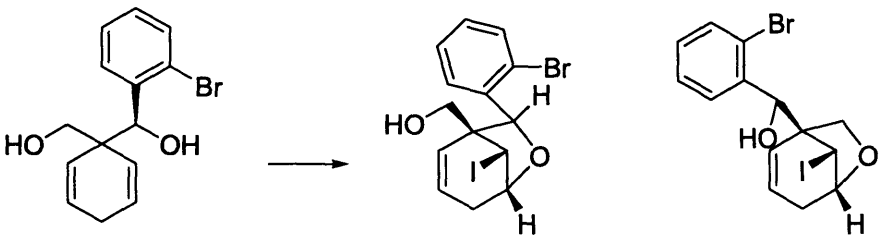
Iodocyclisation of diol **74a** (90 mg, 0.58 mmol) according to *General Procedure 3* followed by chromatography on silica (14 % EtOAc in petroleum ether) gave a mixture of the *title compounds* (118 mg, 72 %) as a colourless oil. Further chromatography on silica gel (10 % EtOAc in petroleum ether) provided analytical samples of the individual compounds.

Data for compound **116a**: Found: $M^+.CH_3CN$, 322.0327. $C_{11}H_{17}INO_2$ requires M, 322.0304; ν_{max} (CH_2Cl_2) 3419, 2927, 1417, 1379, 1318, 1235, 1202, 1172, 1124, 1056, 1004, 918, 876, 848, 815, 737 and 638 cm^{-1}; δ_H (400 MHz) 5.74 (1 H, app. dtd, *J* 9.8, 3.1, 1.5, CH_2CH=CH), 5.14 (1 H, app. dq, *J* 9.8, 1.7, CH_2CH=C*H*), 4.47 (1 H, dd, *J* 5.4, 1.2, C*H*ICHO), 4.27 (1 H, app. br. dd, *J* 5.0, 1.9, CHIC*H*O), 4.21 (1 H, q, *J* 6.2, C*H*CH_3), 3.63 (1 H, dd, *J* 11.4, 5.4, one of C*H*$_2$OH), 3.59 (1 H, dd, *J* 11.4, 5.1, one of C*H*$_2$OH), 2.59 (1 H, br. app. dq, *J* 18.7, 1.7, one of C*H*$_2$CH=CH), 2.26 (1 H, app. dq, *J* 18.7, 2.6, one of C*H*$_2$CH=CH), 1.61 (1 H, app. t, *J* 5.3, OH) and 1.18 (3 H, d, *J* 6.2, CH_3); δ_C (100 MHz) 127.0 (CH), 126.9 (CH), 80.2 (CH), 75.5 (CH), 62.1 (CH_2), 49.7 (C), 35.4 (CH_2), 27.5 (CH) and 16.8 (CH_3); *m/z* (TOF ES+) 322 ($MH^+.CH_3CN$, 6 %), 280 (9), 262 (49), 218 (100) and 132 (60).

Data for compound **117a**: Found: $MH^+.CH_3CN$, 322.0300. $C_{11}H_{17}INO_2$ requires M, 322.0304; ν_{max} (CH_2Cl_2) 3435, 2930, 1458, 1418, 1376, 1250, 1169, 1073, 1013, 919, 872, 824 and 725 cm^{-1}; δ_H (400 MHz) 5.66 (1 H, app. dtd, *J* 9.8, 3.2, 1.5, CH_2CH=CH), 5.51 (1 H, app. dq, *J* 9.8, 1.8, CH_2CH=C*H*), 4.46 (1 H, dd, *J* 5.5, 1.5, C*H*ICHO), 4.36 - 4.33

(1 H, m, CHIC*H*O), 3.93 (1 H, d, *J* 6.8, one of CH_2O), 3.86 (1 H, q, *J* 6.5, C*H*CH_3), 3.80 (1 H, d, *J* 6.8, one of CH_2O), 2.61 (1 H, app. doubled quintet, *J* 18.8, 2.2, one of C*H*$_2$CH=CH), 2.34 - 2.28 (1 H, m, one of C*H*$_2$CH=CH), 1.60 (1 H, br. s, OH) and 1.20 (3 H, d, *J* 6.5, CH_3); δ_C (100 MHz) 130.3 (CH), 126.2 (CH), 77.2 (CH), 73.7 (CH_2), 66.5 (CH), 50.4 (C), 34.8 (CH_2), 26.9 (CH) and 18.6 (CH_3); *m/z* (TOF ES+) 322 (MH^+.CH_3CN, 28%) and 263 (100).

((1*RS*,5*SR*,7*RS*,8*SR*)-7-(2-Bromophenyl)-8-iodo-6-oxabicyclo(3.2.1)oct-2-en-1-yl)methanol (116b) and (2-bromophenyl)-((1*SR*,5*SR*,8*SR*)-8-iodo-6-oxabicyclo(3.2.1)oct-2-en-1-yl)methanol (117b)



74b **116b** **117b**

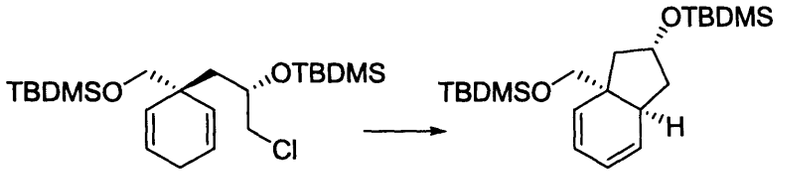
Iodocyclisation of diol **74b** (191 mg, 0.65 mmol) according to *General Procedure 3* followed by chromatography on silica (14 % EtOAc in petroleum ether) gave compound **116b** (109 mg, 40 %) as a colourless solid and compound **117b** (88 mg, 32 %) as a colourless oil.

116b (109 mg, 40 %): m.p. 130 - 132 °C; ν_{max} (CH_2Cl_2) 3454, 2906, 1470, 1418, 1267, 1203, 1171, 1105, 1036, 1011, 916, 750, 732 and 637 cm^{-1}; δ_H (400 MHz) 7.43 (1 H, dd, *J* 8.0, 1.2, aromatic CH), 7.35 (1 H, dd, *J* 7.9, 1.7, aromatic CH), 7.22 (1 H, app. td, *J* 7.9, 0.8, aromatic CH), 7.09 (1 H, app. td, *J* 7.6, 1.8, aromatic CH), 5.79 (1 H, app. dtd, *J* 9.8, 3.1, 1.6, CH_2CH=CH), 5.48 (1 H, s, CHAr), 4.83 (1 H, dd, *J* 5.5, 1.3, C*H*ICHO), 4.63 (1 H, app. dq, *J* 9.8, 1.9, CH_2CH=C*H*), 4.50 (1 H, br. app. dd, *J* 5.1, 2.0, CHIC*H*O), 3.70 (1 H, dd, *J* 12.5, 5.9, one of C*H*$_2$OH), 3.58 (1 H, dd, *J* 12.5, 7.9, one of C*H*$_2$OH), 2.78 (1 H, br. app. d, *J* 19.0, one of C*H*$_2$CH=CH), 2.55 (1 H, app. dq, *J* 19.0, 2.5, one of C*H*$_2$CH=CH) and 2.02 (1 H, dd, *J* 7.9, 5.9, OH); δ_C (100 MHz) 136.4 (C), 132.3 (CH), 130.9 (CH), 129.5 (CH), 127.2 (CH), 126.9 (CH), 126.4 (CH), 122.6 (C), 82.6 (CH), 76.1 (CH), 60.6 (CH_2), 52.5 (C), 35.3 (CH_2) and 27.5 (CH).

117b (88 mg, 32 %): ν_{max} (CH_2Cl_2) 3396, 2892, 1469, 1436, 1418, 1262, 1194, 1167, 1029, 972, 918, 877, 825, 736 and 623 cm^{-1}; δ_H (400 MHz) 7.50 (1 H, dd, *J* 8.1, 1.2, aromatic CH), 7.36 (1 H, dd, *J* 7.9, 1.8, aromatic CH), 7.28 (1 H, app. td, *J* 7.9, 1.2, aromatic CH), 7.12 (1 H, ddd, *J* 8.0, 7.3, 1.8, aromatic CH), 5.61 - 5.55 (1 H, m, one of alkene CH), 5.44 (1 H, app. dq, *J* 9.9, 1.9, one of alkene CH), 5.40 (1 H, d, *J* 3.9, CHAr), 4.65 (1 H, dd, *J* 5.6, 1.6, C*H*ICHO), 4.37 - 4.34 (1 H, m, CHIC*H*O), 4.29 (1 H, d, *J* 6.5, one of CH_2O), 3.70 (1 H, d, *J* 6.5, one of CH_2O), 2.66 (1 H, app. doubled quintet, *J* 18.8, 2.2, one of C*H*$_2$CH=CH), 2.26 (1 H, app. dq, *J* 18.8, 2.3, one of C*H*$_2$CH=CH) and 2.22 (1 H, br. s, OH); δ_C (100 MHz) 139.8 (C), 132.9 (CH), 129.7 (CH), 129.7 (CH), 128.8 (CH), 128.0 (CH), 125.7 (CH), 124.2 (C), 76.6 (CH), 73.8 (CH_2), 71.2 (CH), 51.3 (C), 34.5 (CH_2) and 27.7 (CH).

7.4 Experimental Data for Chapter 4

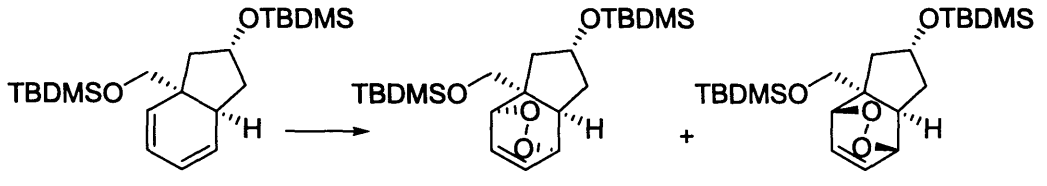
tert-Butyl(((2*RS*,3a*SR*,7a*SR*)-2-(*tert*-butyldimethylsilyloxy)-2,3,3a,7a-tetrahydro-1*H*-inden-3a-yl)methoxy)dimethylsilane (175)



173 **175**

1.6 M BuLi (12.1 mL, 19.4 mmol, 1.1 equiv.) was slowly added to a solution of chloride **173** (7.6 g, 17.7 mmol) in THF (50 mL) at -78 °C. The cooling bath was removed and the reaction allowed to warm to room temperature. After stirring for 1 h at this temperature, 2 M HCl (50 mL) was added, the organic layer was separated and the aqueous phase extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give the *title compound* as a pale yellow oil (6.75 g, 97 %); (Found: MO_2H^+, 427.2729. $C_{22}H_{43}O_4Si_2$ requires M, 427.2700); ν_{max} (CH_2Cl_2) 2942, 2855, 1472, 1255, 1098, 836 and 774 cm^{-1}; δ_H (500 MHz) 5.78 - 5.74 (1 H, m, one of alkene CH), 5.74 - 5.71 (2 H, m, 2 x alkene CH), 5.43 (1 H, d, *J* 9.5, one of alkene CH), 4.12 (1 H, app. tt, *J* 5.5, 3.8, CHOTBDMS), 3.46 (1 H, d, *J* 9.2, one of CH_2O), 3.34 (1 H, d, *J* 9.2, one of CH_2O), 2.66 - 2.60 (1 H, m, ring junction CH), 1.97 - 1.90 (2 H, m, one of CCH_2CHO and one of $CHCH_2CHO$), 1.67 (1 H, dd, *J* 13.6, 5.6, one of CCH_2CHO), 1.59 (1 H, ddd, *J* 12.4, 10.2, 5.5, one of $CHCH_2CHO$), 0.87 (18 H, s, 2 x $SiC(CH_3)_3$), 0.04 (6 H, s, 2 x $SiCH_3$), 0.01 (3 H, s, $SiCH_3$) and 0.01 (3 H, s, $SiCH_3$); δ_C (125 MHz) 132.4 (CH), 129.9 (CH), 120.8 (CH), 120.3 (CH), 70.4 (CH), 69.6 (CH_2), 46.3 (CH_2), 46.0 (C), 44.3 (CH_2), 37.8 (CH), 25.9 (CH_3), 25.9 (CH_3), 18.3 (C), 18.1 (C), -4.7 (CH_3), -4.8 (CH_3) and -5.4 (CH_3); *m/z* (TOF ES+) 428 (10) and 427 (MH^+, 100 %).

Endoperoxides 180 and 181



175 **180** **181**

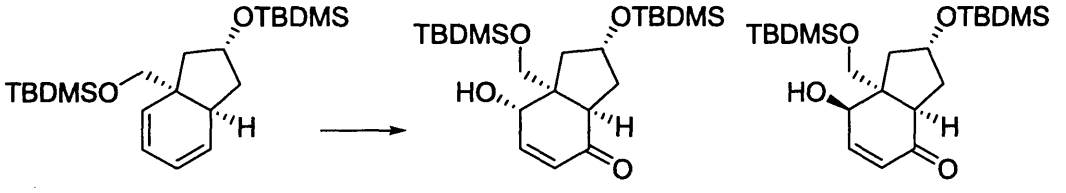
A solution of diene **175** (2.67 g, 6.7 mmol) and Rose bengal (cat., approx 100 mg) in IPA (50 mL) was cooled to approximately 15 °C by an external flow of tap-water. While passing a steady stream of dry O_2, the solution was irradiated by a 500 W halogen lamp from a distance of approximately 10 cm for 18 h. The solvent was removed *in vacuo*, with the minimum heat possible, and the residue purified by chromatography on silica (1 - 2 % Et_2O in petroleum ether) giving the major isomer **180** (1.53 g, 53 %) and minor isomer **181** (0.81 g, 28 %), both pale yellow oils.

180 (1.53 g, 53 %): Found: MH^+ 427.2719, $C_{22}H_{43}O_4Si_2$ requires 427.2700; ν_{max} (CH_2Cl_2) 2955, 2856, 1636, 1472, 1361, 1254, 1071, 836 and 774 cm^{-1}; δ_H (400 MHz) 6.65 (1 H, ddd, *J* 7.9, 6.1, 1.5, one of alkene CH), 6.52 (1 H, ddd, *J* 7.9, 6.1, 1.5, one of alkene CH), 4.73 (1 H, app. dt, *J* 6.1, 1.5, CCHO), 4.61 (1 H, app. ddt, *J* 6.1, 4.4, 1.5, CHC*H*O), 4.20 (1 H, app. tt, *J* 4.4, 1.8, CHOTBDMS), 3.88 (1 H, dd, *J* 8.9, 1.3, one of CH_2OTBDMS), 3.81 (1 H, d, *J* 8.9, one of CH_2OTBDMS), 2.18 (1 H, app. td, *J* 8.4, 4.4, ring junction CH), 2.03 (1 H, app. dt, *J* 13.8, 1.8, one of CCH_2CHO), 1.82 (1 H, ddt, *J* 13.3, 8.4, 1.8, one of CHCH_2CHO), 1.19 (1 H, ddd, *J* 13.3, 8.4, 4.4, one of CHCH_2CHO), 1.14 (1 H, dd, *J* 13.8, 4.4, one of CCH_2CHO), 0.89 (9 H, s, $SiC(CH_3)_3$), 0.87 (9 H, s, $SiC(CH_3)_3$), 0.05 (6 H, s, 2 x $SiCH_3$), 0.02 (3 H, s, $SiCH_3$) and 0.02 (3 H, s, $SiCH_3$); δ_C (125 MHz) 133.1 (CH), 131.3 (CH), 74.3 (CH), 74.0 (CH), 73.6 (CH), 66.7 (CH_2), 49.1 (C), 41.9 (CH), 41.1 (CH_2), 39.9 (CH_2), 25.9 (CH_3), 25.9 (CH_3), 18.3 (C), 18.0 (C), -4.8 (CH_3), -4.9 (CH_3), -5.3 (CH_3) and -5.4 (CH_3); *m/z* (TOF ES+) 427 (MH^+, 100 %) and 295 (10).

181 (0.81 g, 28 %): Found: MH^+ 427.2730, $C_{22}H_{43}O_4Si_2$ requires 427.2700; ν_{max} (CH_2Cl_2) 2942, 2856, 1466, 1361, 1255, 1094, 836 and 775 cm^{-1}; δ_H (400 MHz) 6.63 - 6.60 (2 H, m, 2 x alkene CH), 4.64 - 4.58 (1 H, m, CHOTBDMS), 4.54 - 4.49 (1 H, m, one of HC=CHC*H*O), 4.35 - 4.31 (1 H, m, one of HC=CHC*H*O), 3.64 (1 H, d, *J* 9.3, one of CH_2OTBDMS), 3.23 (1 H, d, *J* 9.3, one of CH_2OTBDMS), 2.19 (1 H, dd, *J* 13.3, 4.8, one of

CCH_2CHO), 2.12 (1 H, ddd, *J* 13.1, 7.1, 4.8, one of CHCH_2CHO), 1.86 (1 H, ddd, *J* 13.3, 3.0, 2.0, one of CCH_2CHO), 1.77 (1 H, dddd, *J* 13.1, 8.6, 3.0, 2.0, one of CHCH_2CHO), 1.61 (1 H, ddd, *J* 8.6, 7.1, 2.0, ring junction CH), 0.88 (9 H, s, SiC$(CH_3)_3$), 0.87 (9 H, s, SiC$(CH_3)_3$), 0.06 (6 H, s, 2 x $SiCH_3$), 0.01 (3 H, s, $SiCH_3$) and 0.00 (3 H, s, $SiCH_3$); δ_C (125 MHz) 132.1 (CH), 131.3 (CH), 76.4 (CH), 76.2 (CH), 74.6 (CH), 70.2 (CH_2), 48.1 (C), 39.2 (CH), 38.9 (CH_2), 37.0 (CH_2), 25.9 (CH_3), 25.8 (CH_3), 18.1 (C), 18.1 (C), -4.7 (CH_3), -4.8 (CH_3), -5.4 (CH_3) and -5.6 (CH_3); *m/z* (TOF ES+) 427 (MH^+, 100 %) and 295 (10).

(2*RS*,3a*RS*,7*SR*,7a*SR*)-2-(*tert*-Butyldimethylsilyloxy)-7a-((*tert*-butyldimethylsilyloxy)methyl)-7-hydroxy-3,3a,7,7a-tetrahydro-1*H*-inden-4(2*H*)-one (182) and (2*RS*,3a*RS*,7*RS*,7a*SR*)-2-(*tert*-butyldimethylsilyloxy)-7a-((*tert*-butyldimethylsilyloxy)methyl)-7-hydroxy-3,3a,7,7a-tetrahydro-1*H*-inden-4(2*H*)-one (183)



175 **182** **183**

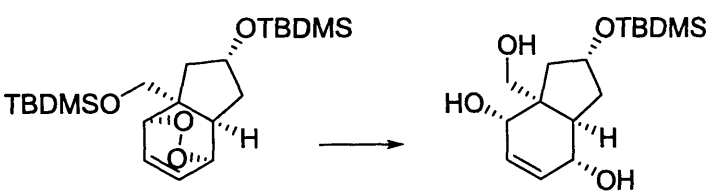
Oxidation of diene **175** (3.80 g, 9.6 mmol) was conducted as described above, after 18 h irradiation the lamp and oxygen supply were removed and Et_3N (10 mL) added. After stirring for a further 48 h the solvent was removed *in vacuo* and the residue chromatographed on silica (5 - 10 % EtOAc in petroleum ether) to give the *title compounds* **182** (1.51 g, 37 %) as a light yellow oil, followed by **183** (1.03 g, 25 %) as a yellow oil.

182 (1.51 g, 37 %): Found: MH^+ 427.2701, $C_{22}H_{43}O_4Si_2$ requires M, 427.2700; ν_{max} (CH_2Cl_2) 3448, 2943, 2857, 1666, 1472, 1256, 1083, 837 and 776 cm^{-1}; δ_H (400 MHz) 6.95 (1 H, dd, *J* 10.2, 2.2, *HC*=CHC=O), 5.95 (1 H, dd, *J* 10.2, 1.9, CH=C*H*C=O), 4.67 (1 H, d, *J* 7.4, OH), 4.33 - 4.38 (1 H, app. tt, *J* 5.7, 2.3, CHOTBDMS), 4.37 - 4.33 (1 H, app. tt, *J* 7.4, 2.2, *CH*OH), 4.09 (1 H, d, *J* 10.0, one of CH_2OTBDMS), 3.61 (1 H, d, *J* 10.0, one of CH_2OTBDMS), 2.66 (1 H, dd, *J* 11.3, 8.1, ring junction CH), 2.38 (1 H, dd, *J* 14.4, 6.2, one of CCH_2CHO), 2.08 - 1.94 (2 H, m, CHCH_2CHO), 1.72 (1 H, br. d, *J* 14.4, one of CCH_2CHO),

0.89 (9 H, s, $SiC(CH_3)_3$), 0.87 (9 H, s, $SiC(CH_3)_3$), 0.09 (3 H, s, $SiCH_3$), 0.07 (3 H, s, $SiCH_3$) and 0.04 (6 H, s, 2 x $SiCH_3$); δ_C (125 MHz) 153.0 (CH), 127.2 (CH), 72.7 (CH), 71.8 (CH), 69.6 (CH_2), 51.8 (C), 51.0 (CH), 45.0 (CH_2), 38.7 (CH_2), 25.8 (CH_3), 25.7 (CH_3), 18.0 (C), -4.8 (CH_3), -4.8 (CH_3) and -5.7 (CH_3); *m/z* (TOF ES+) 427 (MH^+, 10 %), 336 (77), 295 (62), 277 (100) and 163 (11).

183 (1.03 g, 25 %): Found: MH^+ 427.2729, $C_{22}H_{43}O_4Si_2$ requires M, 427.2700; ν_{max} (CH_2Cl_2) 3449, 2943, 2857, 1675, 1471, 1362, 1256 and 1085 cm^{-1}; δ_H (400 MHz) 6.74 (1 H, dd, *J* 10.3, 1.9, C*H*=CHC=O), 5.95 (1 H, dd, *J* 10.3, 2.4, CH=C*H*C=O), 4.81 (1 H, app. q, *J* 2.2, C*H*OH), 4.28 - 4.22 (1 H, m, CHOTBDMS), 3.93 (1 H, d, *J* 9.4, one of CH_2OTBDMS), 3.74 (1 H, d, *J* 9.4, one of CH_2OTBDMS), 3.43 (1 H, d, *J* 3.0, OH), 2.62 (1 H, ddd, *J* 13.8, 7.1, 2.3, one of CHCH_2CHO), 2.45 (1 H, br. d, *J* 8.4, ring junction CH), 2.02 (1 H, dd, *J* 14.5, 8.1, one of CCH_2CHO), 1.88 (1 H, ddd, *J* 13.8, 8.4, 5.7, one of CHCH_2CHO), 1.75 (1 H, br. d, *J* 14.5, one of CCH_2CHO), 0.92 (9 H, s, $SiC(CH_3)_3$), 0.86 (9 H, s, $SiC(CH_3)_3$), 0.11 (6 H, s, 2 x $SiCH_3$) and 0.01 (6 H, s, 2 x $SiCH_3$); δ_C (125 MHz) 199.6 (C), 151.3 (CH), 127.2 (CH), 71.5 (CH), 70.8 (CH), 70.2 (CH_2), 52.6 (C), 49.9 (CH), 39.9 (CH_2), 38.0 (CH_2), 25.9 (CH_3), -4.7 (CH_3) and -5.5 (CH_3); *m/z* (TOF ES+) 428 (9), 427 (MH^+, 100 %) and 295 (11).

(2*RS*,3a*SR*,4*SR*,7*RS*,7a*RS*)-2-(*tert*-Butyldimethylsilyloxy)-3a-(hydroxymethyl)-2,3,3a,4,7,7a-hexahydro-1*H*-indene-4,7-diol (189)

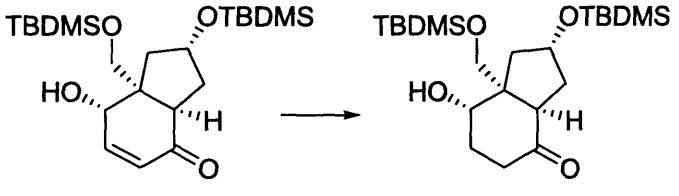


180 **189**

To a solution of peroxide **180** (379 mg, 0.89 mmol) in THF (10 mL) was added a 1 M solution of $LiAlH_4$ in THF (2.0 mL, 2.0 mmol, 2.2 equiv.). After stirring for 90 min the reaction was quenched with 2 M NaOH, dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* and the residue crystallised from Et_2O and petroleum ether to give the *title compound* (191 mg, 72 %) as a colourless solid, m.p. 84 - 87 °C; (Found: MH^+ 315.1996, $C_{16}H_{31}O_4Si$ requires M, 315.1992); ν_{max} (CH_2Cl_2) 3406, 2924, 2856, 1458, 1260, 1089, 1022, 800 and 750 cm^{-1}; δ_H (500 MHz) 6.07 (1 H, dd, *J* 9.8, 3.7, one of

alkene CH), 6.00 (1 H, br. dd, *J* 9.8, 4.9, one of alkene CH), 4.29 - 4.23 (1 H, m, CHOTBDMS), 4.08 (1 H, br. s, one of HC=CHC*H*OH), 4.00 - 3.92 (2 H, m, one of HC=CHC*H*OH and one of CH_2OH), 3.69 (1 H, br. d, *J* 10.9, one of CH_2OH), 3.09 (1 H, br. s, OH), 3.01 (1 H, br. d, *J* 5.3, OH), 2.85 (1 H, d, *J* 8.2, OH), 2.41 (1 H, ddd, *J* 11.8, 7.9, 2.0, ring junction CH), 1.89 (1 H, app. ddt, *J* 13.4, 7.9, 1.5, one of CHCH_2CHO), 1.86 (1 H, dd, *J* 13.8, 5.9, one of CCH_2CHO), 1.58 - 1.49 (2 H, m, one of CHCH_2CHO and one of CCH_2CHO), 0.87 (9 H, s, SiC(CH_3)$_3$) and 0.04 (6 H, s, 2 x SiCH_3); δ_C (125 MHz) 134.2 (CH), 130.5 (CH), 71.3 (CH), 70.5 (CH), 69.1 (CH_2), 66.2 (CH), 48.7 (C), 47.9 (CH), 45.5 (CH_2), 41.0 (CH_2), 25.8 (CH_3), 18.0 (C), -4.8 (CH_3) and -4.8 (CH_3); *m/z* (TOF ES+) 315 (MH^+, 29 %), 183 (4) and 165 (100).

(2*SR*,3a*RS*,7*SR*,7a*SR*)-2-(*tert*-Butyldimethylsilyloxy)-3a-((*tert*-butyldimethylsilyloxy)methyl)-7-hydroxyhexahydro-1*H*-inden-4(2*H*)-one (184)



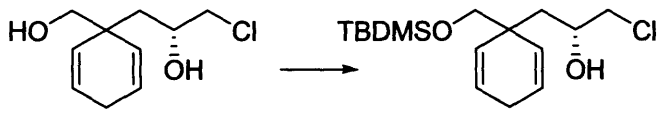
182 **184**

10 % Pd/C (100 mg) and ammonium formate (560 mg, 8.9 mmol) were added to a solution of enone **182** (377 mg, 0.88 mmol) in EtOH (10 mL). This was heated to reflux for 2 h, allowed to cool and filtered through a pad of silica, washing with Et_2O. The filtrate was concentrated *in vacuo* and the residue partitioned between Et_2O (20 mL) and brine (20 mL). The organic layer was separated and the aqueous phase extracted with Et_2O (2 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to yield the *title compound* (341 mg, 91 %) as a pale yellow oil (Found: MH^+, 429.2870. $C_{22}H_{45}O_4Si_2$ requires M, 429.2856); ν_{max} (CH_2Cl_2) 3446, 2942, 2857, 1706, 1472, 1362, 1255, 1075, 837 and 776 cm^{-1}; δ_H (400 MHz) 4.53 (1 H, br. s, OH), 4.35 - 4.29 (1 H, m, CHOTBDMS), 4.00 (1 H, d, *J* 10.1, one of CH_2O), 3.91 - 3.85 (1 H, m, C*H*OH), 3.77 (1 H, d, *J* 10.1, one of CH_2O), 2.77 (1 H, app. t, *J* 7.7, ring junction CH), 2.67 (1 H, ddd, *J* 16.5, 10.1, 7.2, one of CH_2C=O), 2.29 (1 H, ddd, *J* 16.5, 6.3, 4.1, one of CH_2C=O), 2.23 (1 H, ddd, *J* 13.2, 7.7, 5.4, one of CHCH_2CHO), 2.13 - 1.92 (2 H, m,

CH_2CH_2CHOH), 1.83 - 1.75 (1 H, m, one of $CHCH_2CHO$), 1.75 (1 H, dd, *J* 14.3, 6.0, one of CCH_2CHO), 1.51 (1 H, br. d, *J* 14.3, one of CCH_2CHO), 0.90 (9 H, s, $SiC(CH_3)_3$), 0.86 (9 H, s, $SiC(CH_3)_3$), 0.10 (3 H, s, $SiCH_3$), 0.10 (3 H, s, $SiCH_3$), 0.03 (3 H, s, $SiCH_3$) and 0.03 (3 H, s, $SiCH_3$); δ_C (100 MHz) 213.3 (C), 72.8 (CH), 72.0 (CH), 69.6 (CH_2), 52.8 (C), 51.8 (CH), 43.4 (CH_2), 38.1 (CH_2), 34.0 (CH_2), 27.5 (CH_2), 25.8 (CH_3), 25.7 (CH_3), 18.0 (C), 17.9 (C), -4.8 (CH_3), -5.0 (CH_3) and -5.7 (CH_3).

7.5 Experimental Data for Chapter 5

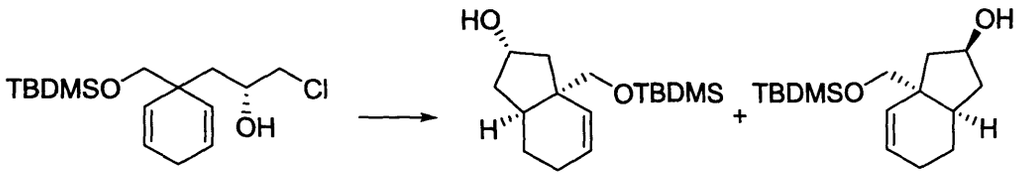
(*RS*)-1-(1-((*tert*-Butyldimethylsilyloxy)methyl)cyclohexa-2,5-dienyl)-3-chloropropan-2-ol (190)



113d **190**

Imidazole (2.53 g, 40 mmol, 2.2 equiv.) and TBDMSCl (2.72 g, 18 mmol, 1.0 equiv.) were added to a solution of diol **113d** (3.65 g, 18 mmol) in CH_2Cl_2 (30 mL). After stirring for 1 h saturated aqueous NH_4Cl (30 mL) was added and the organic phase separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL), the combined organic phases were dried over Na_2SO_4 and the residue purified by chromatography on silica (10 % Et_2O in petroleum ether) to give the *title compound* (4.35 g, 76 %) as a colourless oil; (Found: MH^+ 317.1710, $C_{16}H_{30}O_2SiCl$ requires M, 317.1724); ν_{max} (neat) 3426, 2942, 2855, 1471, 1409, 1361, 1255, 1107, 940, 837, 776, 723 and 698 cm^{-1}; δ_H (500 MHz) 5.91 - 5.82 (2 H, m, 2 x alkene CH), 5.70 (1 H, app. dq, *J* 10.2, 2.0, one of alkene CH), 5.48 (1 H, app. dq, *J* 10.2, 2.0, one of alkene CH), 3.98 - 3.92 (1 H, m, C*H*OH), 3.53 (1 H, dd, *J* 11.0, 4.4, one of CH_2Cl), 3.48 (1 H, dd, *J* 11.0, 4.4, one of CH_2Cl), 3.41 (1 H, d, *J* 9.5, one of CH_2O), 3.40 (1 H, d, *J* 9.5, one of CH_2O), 2.99 (1 H, d, *J* 2.9, OH), 2.69 - 2.66 (2 H, m, CH=CH-C*H*$_2$), 1.76 - 1.69 (2 H, m, C*H*$_2$CHOH), 0.89 (9 H, s, $SiC(CH_3)_3$) and 0.03 (6 H, s, 2 x $SiCH_3$); δ_C (125 MHz) 130.1 (CH), 130.0 (CH), 126.2 (CH), 125.6 (CH), 71.3 (CH_2), 69.2 (CH), 50.2 (CH_2), 42.5 (CH_2), 40.9 (C), 26.7 (CH_2), 25.9 (CH_3), 18.3 (C) and -5.4 (CH_3); *m/z* (TOF ES+) 319 (5), 317 (MH^+, 21 %), 187 (9) and 185 (100).

(2*RS*,3a*RS*,7a*RS*)-7a-((*tert*-Butyldimethylsilyloxy)methyl)-2,3,3a,4,5,7a-hexahydro-1*H*-inden-2-ol (191) and (2*SR*,3a*RS*,7a*RS*)-7a-((*tert*-butyldimethylsilyloxy)methyl)-2,3,3a,4,5,7a-hexahydro-1*H*-inden-2-ol (192)



190 **191** **192**

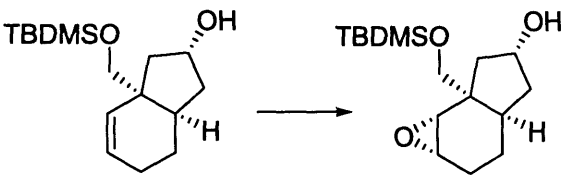
Chloride **190** (2.265 g, 7.16 mmol) was dissolved in benzene (30 mL) and the solution heated to reflux. Solutions of AIBN (235 mg, 1.43 mmol, 0.2 equiv.) and Bu_3SnH (2.3 mL, 8.59 mmol, 1.2 equiv.), each in 5 mL benzene, were added over 10 h by syringe pump. After a further 6 h at reflux the solvent was removed *in vacuo* and the residue chromatographed on silica containing approximately 10 % w/w NaF (7 - 10 % EtOAc in petroleum ether).

191 (960 mg, 48 %): Found: MH^+ 283.2091, $C_{16}H_{31}O_2Si$ requires M, 283.2093; ν_{max} (neat) 3369, 2930, 2851, 1652, 1470, 1253, 1096, 838, 756, 709 and 677 cm^{-1}; δ_H (500 MHz) 5.70 (1 H, ddd, *J* 10.0, 5.4, 2.4, CH_2CH=CH), 5.36 (1 H, br. d, *J* 10.0, CH_2CH=C*H*), 4.14 - 4.09 (1 H, m, C*H*OH), 3.39 (1 H, d, *J* 9.5, one of CH_2O), 3.38 (1 H, d, *J* 9.5, one of CH_2O), 3.14 (1 H, d, *J* 9.0, OH), 2.41 (1 H, app. ddt, *J* 11.4, 7.5, 4,1, one of CH_2CH=CH), 2.02 - 1.93 (1 H, m, one of CH_2CH=CH), 1.88 (1 H, app. dqd, *J* 17.6, 4.7, 1.2, one of CH_2CH=CH), 1.84 (1 H, dt, *J* 14.1, 1.7), 1.75 - 1.56 (5 H, m), 0.92 (9 H, s, $SiC(CH_3)_3$) and 0.09 (6 H, s, 2 x $SiCH_3$); δ_C (125 MHz) 132.3 (CH), 126.6 (CH), 71.1 (CH), 68.4 (CH_2), 45.7 (CH_2), 45.7 (C), 39.7 (CH), 26.0 (CH_3), 22.1 (CH_2), 20.5 (CH_2), 18.4 (C), -5.5 (CH_3) and -5.5 (CH_3); *m/z* (TOF ES+) 283 (MH^+, 92 %), 189 (17) and 133 (100).

192 (385 mg, 19 %): ν_{max} (neat) 3336, 2927, 2856, 1652, 1472, 1255, 1093, 837, 774, 705 and 668 cm^{-1}; δ_H (500 MHz) 5.76 (1 H, ddd, *J* 10.0, 5.0, 2.5, CH_2CH=CH), 5.52 (1 H, app. ddt, *J* 10.0, 2.6, 1.4, CH_2CH=C*H*), 4.21 (1 H, app. tdd, *J* 7.0, 5.4, 4.2, C*H*OH), 3.34 (1 H, d, *J* 9.7, one of CH_2O), 3.32 (1 H, d, *J* 9.7, one of CH_2O), 2.20 - 2.03 (4 H, m, $CHCH_2CHOH$, one of CCH_2CHOH and one of $HC{=}CHCH_2$), 1.95 (1 H, app. dtdd, *J* 18.1, 5.0, 3.0, 1.4, one of $HC{=}CHCH_2$), 1.68 - 1.50 (3 H, m, $HC{=}CHCH_2CH_2$ and ring junction CH), 1.45 (1 H, dd, *J* 13.4, 4.2, one of CCH_2CHO), 0.88 (9 H, s, $SiC(CH_3)_3$), 0.02 (3 H, s,

$SiCH_3$) and 0.02 (3 H, s, $SiCH_3$); δ_C (125 MHz) 133.5 (CH), 127.4 (CH), 72.4 (CH), 68.2 (CH_2), 46.6 (C), 44.4 (CH_2), 39.7 (CH_2), 36.4 (CH), 25.9 (CH_3), 22.2 (CH_2), 20.7 (CH_2), 18.3 (C), -5.5 (CH_3) and -5.5 (CH_3).

(1a*SR*,3a*RS*,5*RS*,6a*SR*,6b*RS*)-6a-((*tert*-Butyldimethylsilyloxy)methyl)octahydro-1a*H*-indeno(4,5-b)oxiren-5-ol (193)

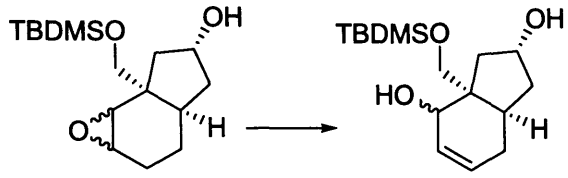


191 **193**

$NaHCO_3$ (0.84 g, 10 mmol, 1.5 equiv.) and *m*CPBA (77 %, 2.24 g, 10 mmol, 1.5 equiv.) were added to a solution of alkene **191** (1.88 g, 6.67 mmol) in CH_2Cl_2 (40 mL). The resulting suspension was stirred for 3 h at room temperature before quenching with saturated aqueous $Na_2S_2O_3$ (30 mL) and saturated aqueous $NaHCO_3$ (10 mL). After stirring vigorously for 10 min the organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was filtered through a column of silica, washing with Et_2O, to give the *title compound* as the major component of an approx. 7:1 mixture of diastereoisomers (1.90 g, 96 %) as a colourless oil; (Found: MH^+, 299.2043. $C_{16}H_{31}O_3Si$ requires M, 299.2042); ν_{max} (CH_2Cl_2) 3438, 2932, 2856, 1471, 1256, 1083, 1063, 838 and 779 cm^{-1}; δ_H (500 MHz) 4.13 (1 H, app. br. t, *J* 3.8, C*H*OH), 3.66 (1 H, d, *J* 9.5, one of CH_2O), 3.61 (1 H, d, *J* 9.5, one of CH_2O), 3.17 (1 H, app. br. t, *J* 3.3, CH_2CH(O)CH), 2.75 (1 H, dd, *J* 4.1, 0.7, $CH_2CH(O)CH$), 2.19 (1 H, app. tdd, *J* 13.1, 6.7, 4.6, ring junction CH), 1.94 (1 H, app. ddt, *J* 13.1, 4.6, 2.3, one of $CCHCH_2CH_2$), 1.85 (1 H, dd, *J* 14.4, 2.7, one of CCH_2CHOH), 1.84 (1 H, app. tdd, *J* 13.1, 4.6, 0.7, one of $CCHCH_2CH_2$), 1.78 (1 H, dd, *J* 14.4, 4.6, one of CCH_2CHOH), 1.74 (1 H, app. tt, *J* 13.1, 4.6, one of $CCHCH_2CH_2$), 1.62 (1 H, ddd, *J* 12.9, 6.7, 2.2, one of $CHCH_2CHOH$), 1.52 (1 H, td, *J* 12.9, 3.5, one of $CHCH_2CHOH$) 1.27 (1 H, app. ddt, *J* 13.1, 4.6, 2.3, one of $CCHCH_2CH_2$), 0.92 (9 H, s, $SiC(CH_3)_3$), 0.14 (3 H, s, $SiCH_3$) and 0.13 (3 H, s, $SiCH_3$); δ_C (125 MHz) 71.8 (CH), 67.3 (CH_2), 56.0 (CH), 51.3 (CH), 44.1 (CH_2), 43.1 (C), 40.1 (CH_2), 32.3 (CH), 25.9

(CH_3), 19.2 (CH_2), 18.4 (C), 16.9 (CH_2) -5.6 (CH_3) and -5.6 (CH_3); *m/z* (TOF ES+) 299 (MH^+, 100 %), 281 (19), 167 (47) and 149 (21).

(2*RS*,3a*SR*,4*SR*,7a*RS*)-3a-((*tert*-Butyldimethylsilyloxy)methyl)-2,3,3a,4,7,7a-hexahydro-1*H*-indene-2,4-diol (195)

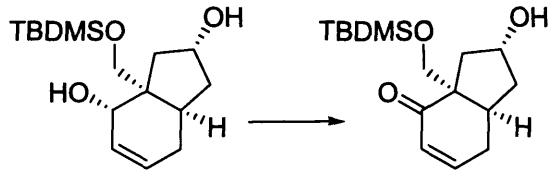


193 + 194 **195**

$NaBH_4$ (291 mg, 7.66 mmol, 1.2 equiv.) was added in small portions to a suspension of $(PhSe)_2$ (1.20 g, 3.83 mmol, 0.6 equiv.) in EtOH (30 mL). After hydrogen evolution had subsided, a mixture of epoxide diastereoisomers **193** and **194** (1.90 g, 6.38 mmol) were added as a solution in EtOH (10 mL). The solution was heated to reflux overnight, the solvent removed *in vacuo* and the residue re-dissolved in THF (30 mL). H_2O_2 (5 mL, 49 mmol, 30 % aqueous solution) was added and the mixture was carefully warmed in an oil bath until a vigorous exothermic reaction began. The oil bath was removed until the reaction began to subside, and then replaced in order to maintain reflux for a total of 1 h, resulting in a clear homogeneous solution. This was washed with brine (30 mL) and the aqueous phase extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with $Na_2S_2O_3$ (30 mL) then dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (25 - 50 % EtOAc in petroleum ether) to give the *title compound* (1.46 g, 77 %) as a colourless waxy solid, m.p. 87 - 94 °C (Found: MH^+, 299.2047. $C_{16}H_{31}O_3Si$ requires M, 299.2042); ν_{max} (CH_2Cl_2) 3394, 2934, 1648, 1435 and 1049 cm^{-1}; δ_H (400 MHz) 5.89 - 5.79 (1 H, br. d, *J* 9.9, one of alkene CH), 5.75 - 5.68 (1 H, app. dtd, *J* 9.9, 4.6, 2.0, one of alkene CH), 4.41 (1 H, app. tdd, *J* 6.2, 2.8, 1.7, CH_2CHOH), 3.96 (1 H, br. s, CH=CHCHOH), 3.93 (1 H, d, *J* 9.7, one of CH_2O), 3.48 (1 H, d, *J* 9.7, one of CH_2O), 2.38 (1 H, dd, *J* 14.2, 6.2, one of CCH_2CHOH), 2.27 (1 H, ddd, *J* 17.1, 7.4, 4.6, one of $CH_2CH=CH$), 2.05 (1 H, app. dtd, *J* 11.7, 7.4, 4.2, ring junction CH), 1.84 (1 H, app. ddt, *J* 13.5, 7.4, 1.4, one of $CHCH_2CHOH$), 1.79 (1 H, ddd, *J* 17.1, 4.2, 2.0, one of $CH_2CH=CH$), 1.68 (1 H, ddd, *J* 14.2, 2.8, 1.4, one of CCH_2CHOH),

1.63 (1 H, ddd, *J* 13.5, 11.7, 6.2, one of CHC*H*$_2$CHOH), 0.90 (9 H, s, SiC(CH$_3$)$_3$), 0.09 (3 H, s, SiCH$_3$) and 0.08 (3 H, s, SiCH$_3$); δ_C (100 MHz) 132.2 (CH), 125.9 (CH), 73.1 (CH), 71.5 (CH), 69.2 (CH_2), 49.3 (C), 44.5 (CH_2), 43.0 (CH_2), 37.4 (CH), 26.8 (CH_2), 25.8 (CH_3), 18.1 (C) and -5.7 (CH_3); *m/z* (TOF ES+) 300 (8), 299 (MH^+, 100 %).

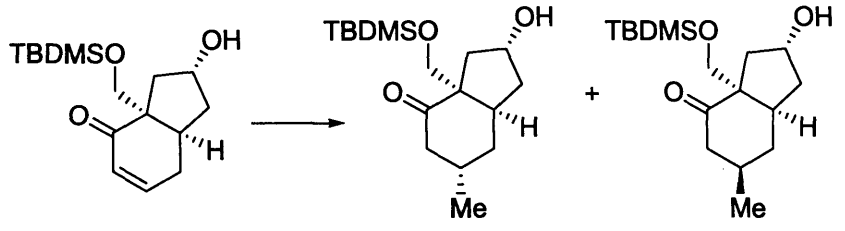
(2*RS*,3a*SR*,7a*RS*)-3a-((*tert*-Butyldimethylsilyloxy)methyl)-2-hydroxy-3,3a,7,7a-tetrahydro-1*H*-inden-4(2*H*)-one (196)



195 **196**

MnO_2 (4.25 g, 49 mmol, 10 equiv.) was added to a solution of allylic alcohol **195** (1.46 g, 4.9 mmol) in CH_2Cl_2 (40 mL), and the resulting suspension stirred for 24 h. The mixture was filitered through a pad of silica, washing well with EtOAc, and the solvent removed *in vacuo* giving the *title compound* (1.40 g, 97 %) as a pale yellow oil (Found: MH^+ 297.1880, $C_{16}H_{29}O_3Si$ requires 297.1886); ν_{max} (CH_2Cl_2) 3410, 2929, 2856, 1657, 1471, 1393, 1253, 1089, 839 and 777 cm^{-1}; δ_H (400 MHz) 6.84 (1 H, dddd, *J* 10.1, 5.7, 2.4, 1.3, C*H*=CHC=O), 6.04 (1 H, ddd, *J* 10.1, 2.8, 1.2, CH=C*H*C=O), 4.23 - 4.18 (1 H, m, CHO), 3.82 (1 H, d, *J* 9.3, one of CH_2O), 3.60 (1 H, d, *J* 9.3, one of CH_2O), 2.85 (1 H, app. dt, *J* 12.3, 7.0, ring junction CH), 2.78 (1 H, app. ddt, *J* 19.1, 7.0, 2.8, one of CH=CHC*H*$_2$), 2.47 (1 H, dd, *J* 14.7, 6.3, one of CC*H*$_2$CHOH), 2.33 (1 H, br. dd, *J* 19.1, 5.7, one of CHCHC*H*$_2$), 1.83 (1 H, app. ddt, *J* 13.3, 7.0, 1.7, one of CHC*H*$_2$CHOH), 1.75 (1 H, ddd, *J* 13.3, 12.3, 5.2, one of CHC*H*$_2$CHOH), 1.62 (1 H, dt, *J* 14.7, 2.1, one of CCH$_2$CHOH), 0.85 (9 H, s, SiC(CH$_3$)$_3$), 0.03 (3 H, s, SiCH$_3$) and 0.00 (3 H, s, SiCH$_3$); δ_C (100 MHz) 202.5 (C), 148.3 (CH), 129.3 (CH), 70.7 (CH), 68.8 (CH_2), 56.9 (C), 43.6 (CH_2), 42.3 (CH_2), 37.4 (CH), 26.9 (CH_2), 25.8 (CH_3), 18.2 (C), -5.7 (CH_3) and -5.7 (CH_3); *m/z* (TOF ES+) 297 (MH^+, 100 %).

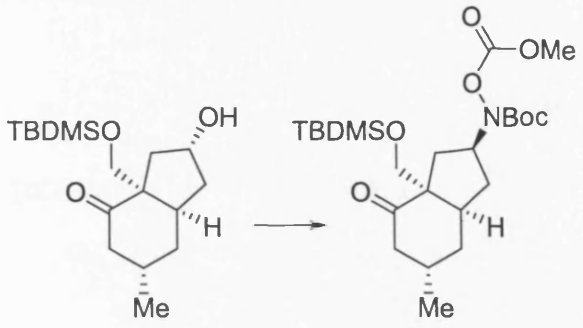
(2*RS*,3a*SR*,6*SR*,7a*RS*)-3a-((*tert*-Butyldimethylsilyloxy)methyl)-2-hydroxy-6-methylhexahydro-1*H*-inden-4(2*H*)-one (197) and (2*RS*,3a*SR*,6*RS*,7a*RS*)-3a-((*tert*-butyldimethylsilyloxy)methyl)-2-hydroxy-6-methylhexahydro-1*H*-inden-4(2*H*)-one (198)



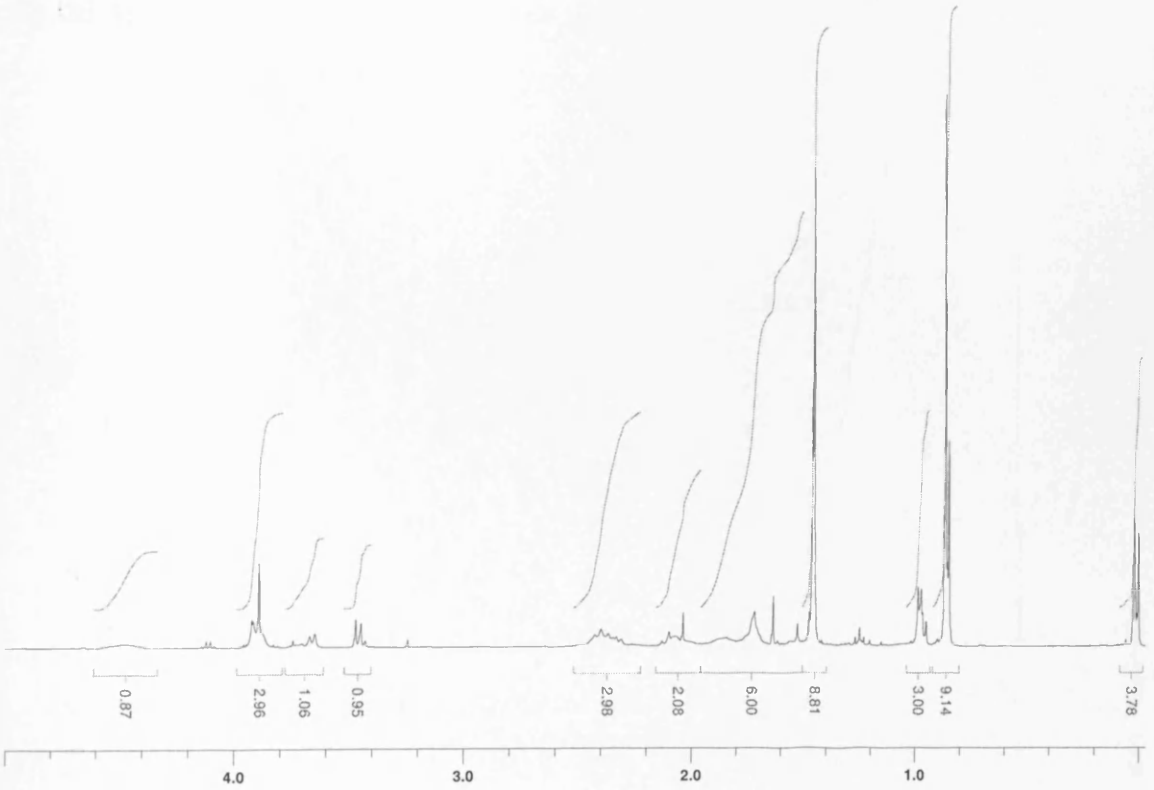
196 **197** **198**

$Cu(OTf)_2$ (29 mg, 0.08 mmol, 0.1 equiv.) was added to a solution of enone **196** (235 mg, 0.79 mmol) in toluene (10 mL) and the resulting suspension cooled to 0 °C. A 2 M solution of Me_3Al in hexanes (1.2 mL, 2.37 mmol, 3 equiv.) was added dropwise, the cooling bath was removed and the reaction stirred for 8 h before quenching carefully with saturated aqueous $NaHCO_3$ (20 mL). This was all filtered through a pad of silica, washing with Et_2O, and the organic layer separated. The aqueous phase was extracted with Et_2O (2 x 20 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (20 - 25 % EtOAc in hexane) to give the *title compounds*, **197** and **198**, approx. 3:1, as a pale yellow oil (200 mg, 81 %); ν_{max} (CH_2Cl_2) 3388, 2952, 1694, 1455, 1344 and 1041 cm^{-1}; δ_H (400 MHz) 4.21 - 4.16 (1 H, m, *CH*OH), 3.68 (1 H, d, *J* 9.2, one of CH_2O), 3.62 (1 H, d, *J* 9.2, one of CH_2O), 2.79 - 2.75 (1 H, m, ring junction CH), 2.55 (1 H, dd, *J* 14.8, 5.8, one of CCH_2CHOH), 2.38 (1 H, app. ddd, *J* 14.6, 3.5, 1.9, one of $CH_2C{=}O$), 2.10 (1 H, dd, *J* 14.6, 12.6, one of $CH_2C{=}O$), 2.05 - 1.90 (1 H, m, MeCH), 1.79 - 1.66 (3 H, m, one of $CHCH_2CHOH$ and $MeCHCH_2CH$), 1.60 (1 H, app. td, *J* 13.2, 4.8, one of $CHCH_2CHOH$), 1.51 (1 H, app. dt, *J* 14.8, 2.1, one of CCH_2CHOH), 1.00 (3 H, d, *J* 6.4, Me), 0.89 (9 H, s, $SiC(CH_3)_3$), 0.06 (3 H, s, $Si(CH_3)_2$), 0.04 (3 H, s, $Si(CH_3)_2$).

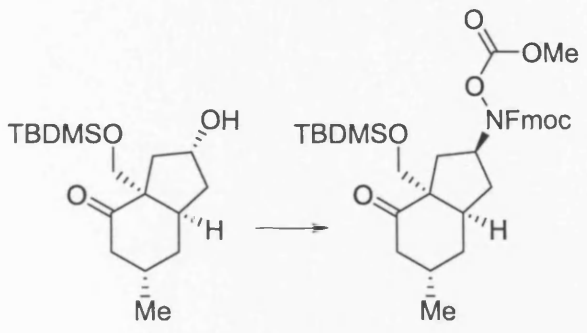
tert-Butyl (2_SR_,3a_SR_,6_SR_,7a_RS_)-3a-((_tert_-butyldimethylsilyloxy)methyl)-6-methyl-4-oxooctahydro-1_H_-inden-2-yl(methoxycarbonyloxy)carbamate (212)



To a solution of alcohol **197** (220 mg, 0.74 mmol) in CH_2Cl_2 (10 mL) was added PPh_3 (291 mg, 1.1 mmol, 1.5 equiv.) and $BocNHOCO_2Me$ (283 mg, 1.5 mmol, 2.0 equiv.). DIAD (0.22 mL, 1.1 mmol, 1.5 equiv.) was added dropwise and stirring continued for 15 min. The solvent was removed *in vacuo* and the residue purified by chromatography on silica (10 % EtOAc in petroleum ether) to give the *title compound* (280 mg, 78 %) as a viscous colourless oil. ν_{max} (neat) 2953, 1794, 1713, 1455, 1393, 1371, 1337, 1259, 1156, 1102, 937, 839 and 772 cm^{-1}.

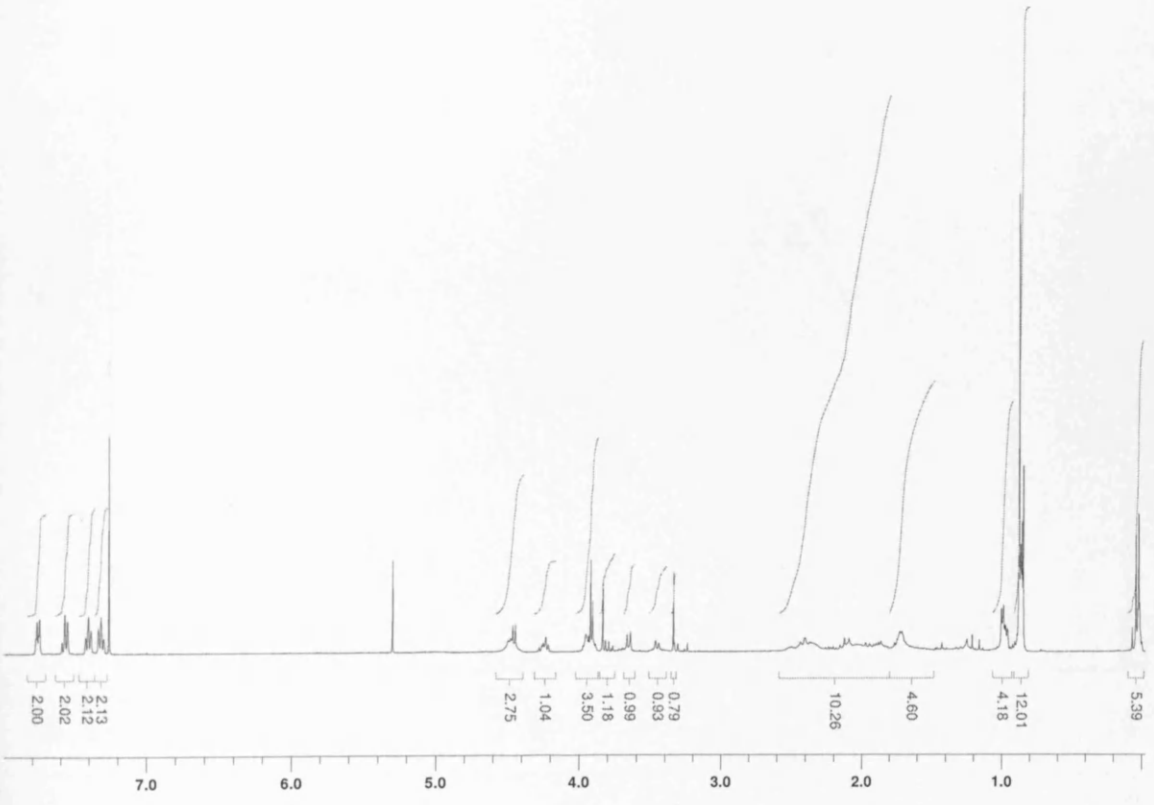


(9*H*-Fluoren-9-yl)methyl-(2*SR*,3a*SR*,6*SR*,7a*RS*)-3a-((*tert*-butyldimethylsilyloxy)methyl)-6-methyl-4-oxooctahydro-1*H*-inden-2-yl(methoxycarbonyloxy)carbamate (210)

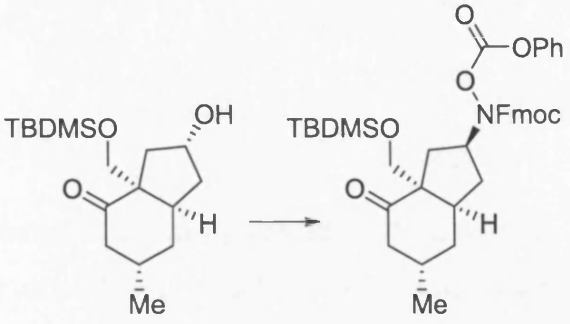


197 **210**

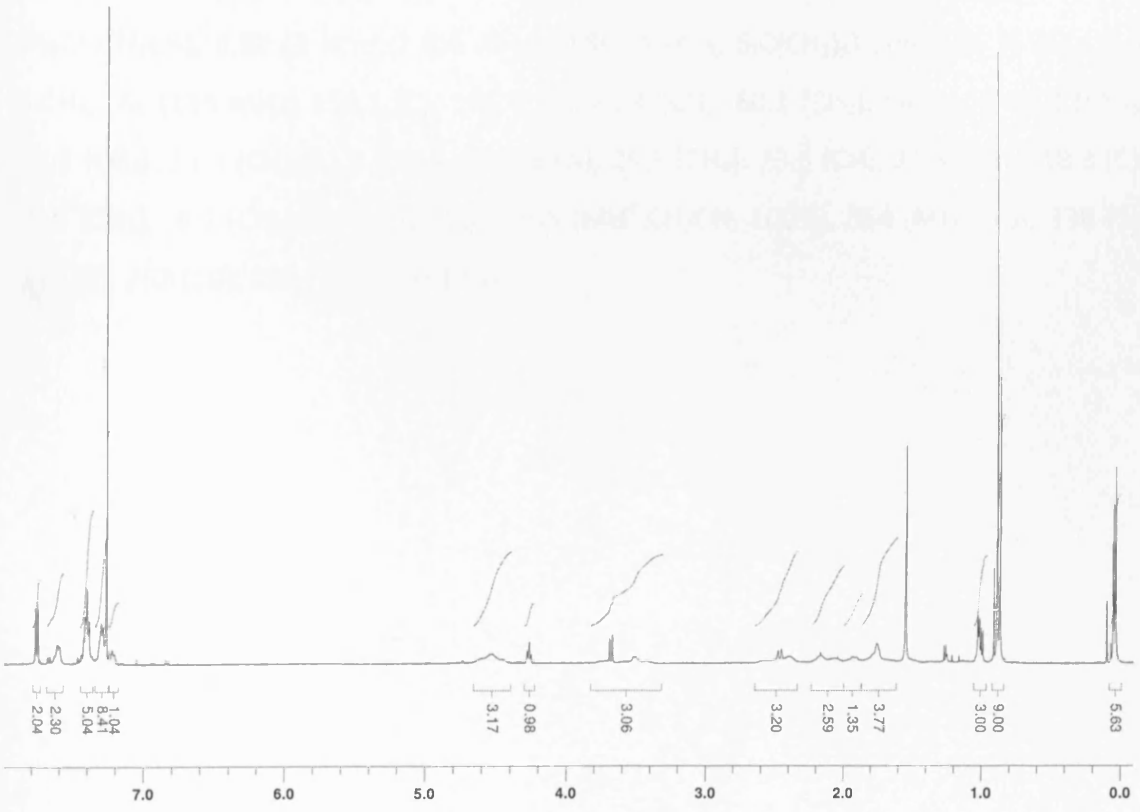
PPh_3 (387 mg, 1.47 mmol, 1.2 equiv.) and $FmocNHOCO_2Me$ (420 mg, 1.34 mmol, 1.1 equiv.) were added to a stirred solution of alcohol **197** (390 mg, 1.25 mmol) in CH_2Cl_2 (10 mL). DIAD (0.29 mL, 1.47 mmol, 1.2 equiv.) was added dropwise and stirring continued for 1 h. The solvent was removed *in vacuo* and the residue purified by chromatography on silica (10 - 25 % EtOAc in petroleum ether), giving the *title compound* (200 mg, 27 %) as a colourless oil, followed by unreacted alcohol **197** (100 mg, 26 %).



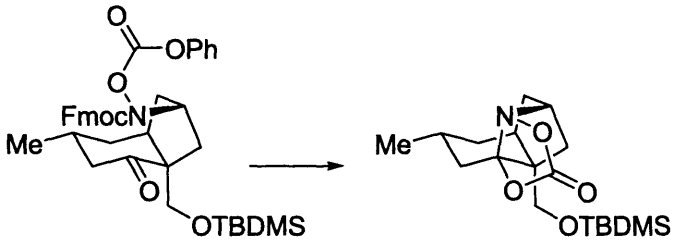
(9*H*-Fluoren-9-yl)methyl (2*SR*,3a*SR*,6*SR*,7a*RS*)-3a-((*tert*-butyldimethylsilyloxy)methyl)-6-methyl-4-oxooctahydro-1*H*-inden-2-yl(phenoxycarbonyloxy)carbamate (211)



To a solution of alcohol **197** (177 mg, 0.60 mmol) in CH_2Cl_2 (10 mL) was added PPh_3 (255 mg, 0.97 mmol, 1.6 equiv.) and $FmocNHOCO_2Ph$ (365 mg, 0.97 mmol, 1.6 equiv.). DIAD (0.19 mL, 0.97 mmol, 1.6 equiv.) was added dropwise and stirring continued for 15 min. The solvent was removed *in vacuo* and the residue purified by chromatography on silica (10 % EtOAc in petroleum ether) to give the *title compound* (130 mg, 36 %) as a viscous colourless oil. ν_{max} (CH_2Cl_2) 3060, 2955, 2857, 1808, 1731, 1714, 1593, 1454, 1394, 1318, 1209, 1104, 840 and 742 cm^{-1}.



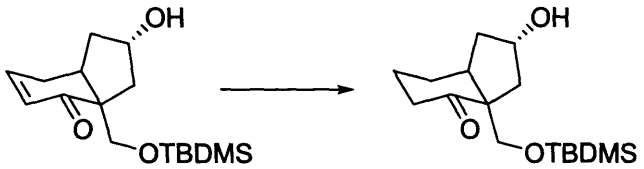
Carbonate 213



211 **213**

DBU (0.02 mL, 0.13 mmol, 2.8 equiv.) was added to a solution of ketone **211** (32 mg, 0.05 mmol) in THF (2 mL). After stirring for 1 hr the solvent was concentrated *in vacuo* and the residue chromatographed on silica (5 - 10 % EtOAc in petroleum ether) giving the *title compound* (6 mg, 35 %) as a colourless oil (Found: MH^+, 354.2125. $C_{18}H_{32}NO_4Si$ requires M, 354.2101); ν_{max} (CH_2Cl_2) 2928, 2855, 1808, 1704, 1471, 1257, 1097, 838 and 777 cm^{-1}; δ_H (400 MHz) 3.86 (1 H, d, *J* 10.5, one of CH_2O), 3.78 (1 H, d, *J* 10.5, one of CH_2O), 3.73 - 3.70 (1 H, m, CHN), 2.37 (1 H, app. dq, *J* 11.5, 3.8, ring junction CH), 2.04 - 1.96 (3 H, m, MeCH, one of CCH_2CHN and one of $MeCHCH_2C$), 1.94 (1 H, ddd, *J* 13.6, 11.8, 4.1, one of $CHCH_2CHN$), 1.64 (1 H, d, *J* 11.8, one of CCH_2CHN), 1.54 (1 H, app. t, *J* 13.5, one of $MeCHCH_2C$), 1.48 (1 H, br. d, *J* 14.1, one of $MeCHCH_2CH$), 1.40 (1 H, app. dt, *J* 13.6, 3.8, one of $CHCH_2CHN$), 1.24 (1 H, ddd, *J* 14.1, 12.4, 3.8, one of $MeCHCH_2CH$), 0.98 (3 H, d, *J* 6.4, CH_3), 0.89 (9 H, s, $SiC(CH_3)_3$) and 0.06 (6 H, s, 2 x $SiCH_3$); δ_C (125 MHz) 154.1 (C), 106.6 (C), 65.4 (CH), 60.1 (CH_2), 54.1 (C), 37.8 (CH_2), 37.1 (CH_2), 34.3 (CH), 32.3 (CH_2), 30.8 (CH_2), 25.9 (CH_3), 23.6 (CH), 21.3 (CH_3), 18.3 (C), -5.5 (CH_3), -5.5 (CH_3); *m/z* (TOF ES+) 395 ($MH^+.CH_3CN$, 100%), 354 (MH^+, 15), 338 (5), 310 (9), 262 (10), 234 (7) and 191 (3).

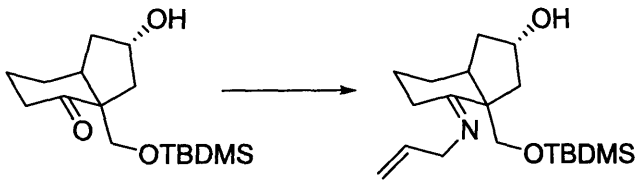
(2*SR*,3a*RS*,7a*SR*)-3a-((*tert*-Butyldimethylsilyloxy)methyl)-2-hydroxyhexahydro-1*H*-inden-4(2*H*)-one (214)



196 **214**

Pd / C (100 mg, 10 % w/w) was added to a solution of enone **196** (0.5 g, 1.7 mmol) in EtOAc / EtOH (10 mL, 2:1) and the reaction placed under an atmosphere of H_2. After stirring for 4 h, the mixture was filtered through a short pad of silica, washing well with EtOAc. The filtrate was concentrated under reduced pressure to afford the *title compound* (0.36 g, 71 %) as a pale yellow oil; δ_H (400 MHz) 4.20 (1 H, app. tt, *J* 5.3, 1.8, C*H*OH), 3.72 (1 H, d, *J* 9.2, one of CH_2OTBDMS), 3.64 (1 H, d, *J* 9.2, one of CH_2OTBDMS), 2.71 (1 H, app. dq, *J* 12.1, 5.8, ring junction CH), 2.48 (1 H, dd, *J* 14.7, 5.8, one of CHC*H*$_2$CHOH), 2.41 - 2.35 (2 H, m), 2.07 - 1.76 (4 H, m), 1.65 - 1.48 (3 H, m), 0.91 (9 H, s, $SiC(CH_3)_3$) and 0.09 (6 H, s, 2 x $SiCH_3$).

(2*SR*,3a*SR*,7a*SR*)-4-(Allylimino)-3a-((*tert*-butyldimethylsilyloxy)methyl)octahydro-1*H*-inden-2-ol (215)

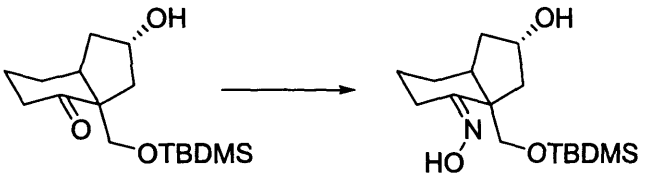


214 **215**

2 M Me_3Al (2 mL, 4 mmol, 9 equiv.) was added to a solution of ketone **214** (140 mg, 0.47 mmol) and allylamine (0.25 mL, 3.3 mmol, 7 equiv.) in DCM (10 mL). After stirring overnight, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL). The organic layer was separated, the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic layers dried over Na_2SO_4. The solvent was removed under reduced pressure to give the *title compound* (approx 140 mg) as a pale yellow oil; δ_H (400 MHz) 5.97 (1 H, app. ddt, *J* 17.2, 10.4, 5.2, CH_2=C*H*CH_2), 5.12 (1 H, app. dq, *J* 17.2, 1.9, one of C*H*$_2$=$CHCH_2$), 5.08 (1 H, app. dq, *J* 10.4, 1.9, one of C*H*$_2$=$CHCH_2$), 4.12 (1 H,

br. t, *J* 4.8, C*H*OH), 4.05 - 3.99 (1 H, m, one of CH_2=CHCH_2), 3.97 - 3.91 (1 H, m, one of CH_2=CHCH_2), 3.64 (1 H, d, *J* 9.1, one of CH_2OTBDMS), 3.51 (1 H, d, *J* 9.1, one of CH_2OTBDMS), 2.69 (1 H, dd, *J* 14.7, 5.4, one of CCH_2CHOH), 2.56 (1 H, app. dq, *J* 11.9, 7.0, ring junction CH), 2.49 - 2.41 (1 H, m), 2.14 - 2.06 (1 H, m), 1.99 - 1.86 (2 H, m), 1.76 (1 H, br. d, *J* 14.7, one of CCH_2CHOH), 1.73 - 1.62 (1 H, m), 1.47 (1 H, ddd, *J* 12.6, 12.0, 4.5, one of CHCH_2CHOH), 1.26 - 1.17 (1 H, m), 0.91 (9 H, s, $SiC(CH_3)_3$) and 0.09 (6 H, s, 2 x $SiCH_3$).

(2*SR*,3a*SR*,7a*SR*)-3a-((*tert*-butyldimethylsilyloxy)methyl)-2-hydroxyhexahydro-1*H*-inden-4(2*H*)-one oxime (216)

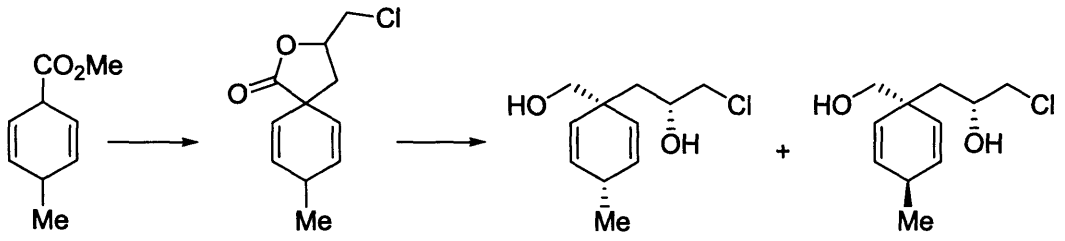


214 **216**

A solution of ketone **214** (16 mg, 0.05 mmol), $NH_4OH.HCl$ (4.5 mg, 0.6 mmol, 1.2 equiv.) and NaOAc (14.6 mg, 0.11 mmol, 2.0 equiv.) was refluxed for 16 h. The solvent was removed under reduced pressure and the residue partitioned between water (10 mL) and Et_2O (10 mL). The organic layer was separated, the aqueous phase extracted with Et_2O (10 mL) and the combined organic layers dried over Na_2SO_4. Concentration under reduced pressure gave the *title compound* (approx 15 mg) as a colourless oil; δ_H (500 MHz) 4.13 (1 H, m, C*H*OH), 3.57 (1 H, d, *J* 9.3, one of CH_2OTBDMS), 3.48 (1 H, d, *J* 9.3, one of CH_2OTBDMS), 2.84 (1 H, ddd, *J* 18.0, 8.6, 6.9), 2.53 - 2.45 (2 H, m), 2.19 (1 H, app. dt, *J* 18.0, 5.8), 1.95 - 1.87 (2 H, m), 1.79 (1 H, br. d, *J* 14.5, one of CCH_2CHOH), 1.74 - 1.66 (1 H, m), 1.57 - 1.45 (2 H, m), 1.20 - 1.12 (1 H, m), 0.91 (9 H, s, $SiC(CH_3)_3$), 0.10 (3 H, s, $SiCH_3$) and 0.09 (3 H, s, $SiCH_3$); δ_c (125 MHz) 163.0 (C), 71.4 (CH), 70.8 (CH_2), 51.9 (C), 44.4 (CH_2), 43.3 (CH_2), 38.0 (CH), 28.1 (CH_2), 25.9 (CH_3), 23.1 (CH_2), 19.7 (CH_2), 18.4 (C), -5.5 (CH_3) and -5.6 (CH_3).

7.6 Experimental Data for Chapter 6

1,4-*cis*-1-(3-Chloro-2-hydroxypropyl)-1-hydroxymethyl-4-methylcyclohexa-2,5-diene (222) and 1,4-*trans*-1-(3-chloro-2-hydroxypropyl)-1-hydroxymethyl-4-methylcyclohexa-2,5-diene (223)



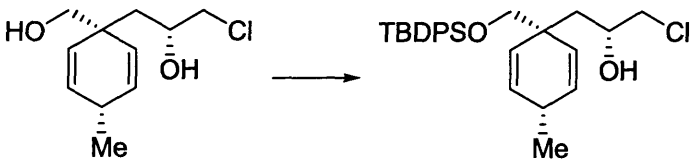
To a solution of DPA (5.0 mL, 35.5 mmol, 1.1 equiv.) in THF (30 mL) at -78 °C was added *n*-BuLi (22.2 mL, 1.6 M, 1.1 equiv.) and the resulting solution allowed to warm to room temperature. After re-cooling to -78 °C ester **220** (4.91 g, 32.3 mmol) was added dropwise. Stirring was continued for 30 min before the addition of epichlorohydrin (3.3 mL, 42 mmol, 1.3 equiv.), the reaction was then allowed to warm to 5 °C over approx. 3 h. Saturated aqueous NH_4Cl (75 mL) was added and after stirring for a few minutes the organic layer was separated and the aqueous layer extracted with Et_2O (2 x 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude intermediate lactone **221** (7.72 g) as an orange oil. This lactone was dissolved in ethanol (200 mL) and $NaBH_4$ (2.45 g, 64.6 mmol, 2 equiv.) added in one portion. The exothermic reaction was allowed to subside and stirring continued for 1 h before quenching with glacial AcOH (approx. 3 mL). The solvent was removed *in vacuo* and the residue partitioned between saturated aqueous $NaHCO_3$ (200 mL) and EtOAc (100 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 75 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (50 % Et_2O in petroleum ether) to give **222** (2.57 g, 37 %) and **223** (2.15, 31 %), both as a colourless oils.

Major diastereoisomer **222**: Found: MH^+ - CH_3OH, 184.0667. $C_{11}H_{13}ClO$ requires M, 184.0655; ν_{max} (neat) 3364, 2958, 2869, 1516, 1429, 1047, 803 and 743 cm^{-1}; δ_H (400

MHz) 5.89 (1 H, ddd, *J* 10.2, 3.1, 1.9, one of alkene CH), 5.87 (1 H, ddd, *J* 10.2, 3.1, 1.9, one of alkene CH), 5.58 (1 H, app. dt, *J* 10.2, 2.1, one of alkene CH), 5.39 (1 H, app. dt, *J* 10.2, 2.1, one of alkene CH), 3.94 (1 H, app. ddt, *J* 10.4, 7.0, 3.4, C*H*OH), 3.53 (1 H, dd, *J* 11.1, 4.1, one of CH_2Cl), 3.45 (1 H, dd, *J* 11.1, 6.5, one of CH_2Cl), 3.36 (1 H, d, *J* 11.4, one of CH_2OH), 3.34 (1 H, d, *J* 11.4, one of CH_2OH), 2.83 (1 H, d, *J* 3.1, OH), 2.81 - 2.73 (1 H, m, MeCH), 1.64 (1 H, dd, *J* 14.3, 8.1, one of CH_2CHOH), 1.55 (1 H, dd, *J* 14.3, 3.4, one of CH_2CHOH) and 1.08 (3 H, d, *J* 7.3, CH_3); δ_C (100 MHz) 134.3 (CH), 134.0 (CH), 128.3 (CH), 128.1 (CH), 69.9 (CH_2), 69.0 (CH), 50.2 (CH_2), 42.2 (C), 41.8 (CH_2), 30.9 (CH) and 22.3 (CH_3); *m/z* (TOF ES+) 184 (M - CH_3OH, 17 %) and 167 (100).

Minor diastereoisomer **223:** Found: MH^+ - CH_3OH, 184.0655. $C_{11}H_{13}ClO$ requires M, 184.0655; ν_{max} (neat) 3412, 2957, 1516, 1454, 1048, 805 and 748 cm^{-1}; δ_H (400MHz) 5.94 -5.86 (2 H, m, two of alkene CH), 5.61 - 5.55 (1 H, m, one of alkene CH), 5.42 - 5.37 (1 H, m, one of alkene CH), 3.94 (1 H, app. ddt, *J* 8.0, 6.4, 3.8, C*H*OH), 3.55 (1 H, dd, *J* 11.1, 4.1, one of CH_2Cl), 3.45 (1 H, dd, *J* 11.1, 6.4, one of CH_2Cl), 3.37 (2 H, app. s, CH_2OH), 2.83 - 2.73 (1 H, m, MeCH), 2.70 (1 H, broad s, OH), 2.01 (1 H, broad s, OH), 1.64 (1 H, dd, *J* 14.3, 8.0, one of CH_2CHOH), 1.54 (1 H, dd, *J* 14.3, 3.5, one of CH_2CHOH) and 1.09 (3 H, d, *J* 7.3, CH_3); δ_c (100 MHz) 134.4 (CH), 134.0 (CH), 128.2 (CH), 128.1 (CH), 70.2 (CH_2), 69.0 (CH), 50.2 (CH_2), 42.2 (CH_2), 41.6 (C), 30.8 (CH) and 21.9 (CH_3); *m/z* (TOF ES+) 184 (M - CH_3OH, 21 %) and 167 (100).

1-((1*SR*,4*SR*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-4-methylcyclohexa-2,5-dienyl)-3-chloropropan-2-ol (224)

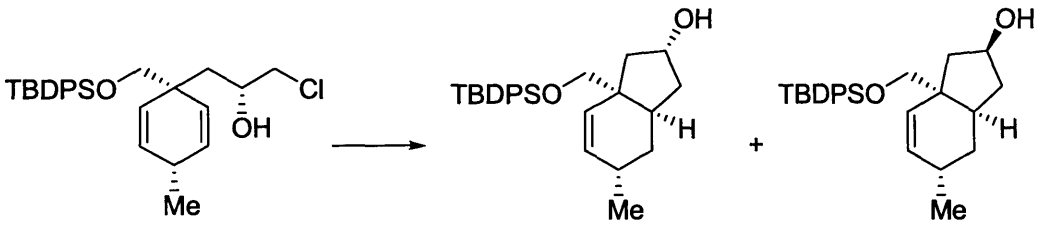


222 **224**

To a solution of diol **222** (2.57 g, 11.9 mmol) in CH_2Cl_2 (20 mL) was added imidazole (1.68 g, 26.2 mmol, 2.2 equiv) followed by TBDPSCl (3.4 mL, 13.1 mmol, 1.1 equiv.). After stirring overnight the reaction was quenched with saturated aqueous NH_4Cl (30 mL) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL) and the combined organic extracts dried over Na_2SO_4 and concentrated *in*

vacuo. The residue was purified by chromatography on silica (10 % Et_2O in petroleum ether) to give the *title compound* (4.35 g, 81 %) as a colourless viscous oil (Found: MH^+, 455.2190. $C_{27}H_{36}ClO_2Si$ requires M, 455.2173); ν_{max} (neat) 3420, 3072, 2931, 2858, 1590, 1516, 1470, 1428, 1390, 1362, 1303, 1261 and 1111 cm^{-1}; δ_H (400 MHz) 7.66 - 7.63 (4 H, m, 4 x aromatic CH), 7.45 - 7.35 (6 H, m, 6 x aromatic CH), 5.83 - 5.77 (2 H, m, 2 x alkene CH), 5.69 (1 H, app. dt, *J* 10.0, 1.9, one of alkene CH), 5.49 (1 H, app. dt, *J* 10.0, 1.9, one of alkene CH), 3.97 - 3.91 (1 H, m, C*H*OH),3.55 (1 H, dd, *J* 11.0, 4.2, one of CH_2Cl), 3.48 (1 H, dd, *J* 11.0, 6.3, one of CH_2Cl), 3.44 (1 H, d, *J* 10.3, one of CH_2O), 3.42 (1 H, d, *J* 10.3, one of CH_2O), 2.80 - 2.73 (1 H, m, MeCH), 2.60 - 2.50 (1 H, br. s, OH), 1.80 - 1.72 (2 H, m, CH_2CHOH), 1.06 (9 H, s, $SiC(CH_3)_3$) and 1.02 (3 H, d, *J* 7.3, CH_3); δ_C (125 MHz) 135.7 (3 x CH), 134.8 (CH), 133.3 (C), 132.7 (2 x CH), 132.4 (2 x CH), 129.7 (2 x CH), 129.4 (CH), 128.6 (CH), 127.7 (C), 127.6 (3 x CH), 72.5 (CH_2), 69.6 (CH), 53.4 (C), 50.2 (CH_2), 42.0 (CH_2), 41.7 (C), 31.1 (CH), 26.9 (CH_3), 22.0 (CH_3) and 19.4 (C); *m/z* (TOF ES+) 457 (26 %), 455 (MH^+, 100), 280 (12) and 199 (10).

(2*RS*,3a*RS*,5*SR*,7a*RS*)-7a-((*tert*-Butyldiphenylsilyloxy)methyl)-5-methyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-2-ol (225) and (2*SR*,3a*RS*,5*SR*,7a*RS*)-7a-((*tert*-butyldiphenylsilyloxy)methyl)-5-methyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-2-ol (226)

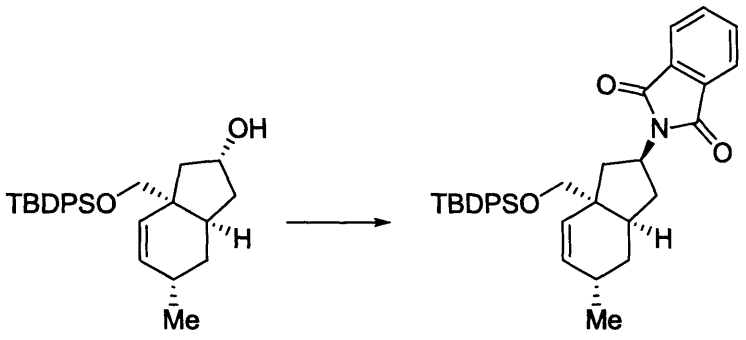


A solution of chloride **224** (2.43 g, 5.35 mmol) in benzene (40 mL) was heated to reflux and solutions of AIBN (88 mg, 0.54 mmol, 0.1 equiv.) and Bu_3SnH (1.7 mL, 6.42 mmol, 1.2 equiv.), each in 5 mL benzene, were added over 10 h by syringe pump. After a total of 18 h reflux the solution was concentrated and purified by silica gel chromatography (5 - 10 % EtOAc in petroleum ether) to give compound **225** (1.16 g, 52 %) followed by compound **226** (0.51 g, 23 %), both as colourless oils.

Major diastereoisomer **225**: Found: MH^+, 421.2605. $C_{27}H_{37}O_2Si$ requires M, 421.2563; ν_{max} (neat) 3361, 3071, 2952, 1657, 1464, 1428, 1391, 1110, 822, 743 and 703 cm^{-1}; δ_H (400 MHz) 7.70 - 7.65 (4 H, m, 4 x aromatic CH), 7.47 - 7.36 (6 H, m, 6 x aromatic CH), 5.45 (1 H, br. d, *J* 10.1, CHCH=C*H*), 5.26 (1 H, br. dd, *J* 10.1, 2.4, CHC*H*=CH), 4.19 (1 H, app. tt, *J* 4.6, 2.2, C*H*OH), 3.40 (2 H, app. s, CH_2O), 2.59 (1 H, app. tt, *J* 7.2, 3.5, ring junction CH), 2.16 - 2.08 (1 H, m, MeCH), 1.95 (1 H, app. dt, *J* 14.0, 2.1, one of CH_2CHOH), 1.81 - 1.64 (4 H, m, one of MeCHCH_2 and three of CH_2CHOH), 1.18 (1 H, ddd, *J* 13.3, 11.1, 4.6, one of MeCHCH_2), 1.08 (9 H, s, $SiC(CH_3)_3$) and 0.93 (3 H, d, *J* 7.0, CH_3); δ_C (100 MHz) 135.7 (2 x CH), 135.7 (2 x CH), 133.0 (C), 132.9 (C), 132.9 (CH), 131.5 (CH), 129.8 (2 x CH), 127.7 (4 x CH), 71.4 (CH), 69.0 (CH_2), 45.8 (C), 45.7 (CH_2), 39.7 (CH_2), 35.4 (CH), 31.2 (CH_2), 26.9 (CH_3), 25.3 (CH), 21.5 (CH_3) and 19.2 (C); *m/z* (TOF ES+) 422 (18) and 421 (MH^+, 100 %).

Minor diastereoisomer **226:** Found: MH^+, 421.2570. $C_{27}H_{37}O_2Si$ requires M, 421.2563; ν_{max} (neat) 3360, 3030, 2943, 1649, 1590, 1461, 1425, 1390, 1108, 820, 744 and 697 cm^{-1}; δ_H (400 MHz) 7.67 - 7.62 (4 H, m, 4 x aromatic CH), 7.45 - 7.35 (6 H, m, 6 x aromatic CH), 5.57 (1 H, br. d, *J* 10.1, CHCH=C*H*), 5.49 (1 H, dd, *J* 10.1, 1.8, CHC*H*=CH), 4.22 (1 H, app. tt, *J* 6.8, 4.5, C*H*OH), 3.41 (1 H, d, *J* 9.8, one of CH_2O), 3.38 (1 H, d, *J* 9.8, one of CH_2O), 2.26 - 2.13 (4 H, m, MeCH, ring junction CH and two of CH_2CHOH), 1.70 - 1.55 (2 H, m, one of MeCHCH_2 and one of CH_2CHOH), 1.51 (1 H, dd, *J* 13.4, 4.5, one of CH_2CHOH), 1.25 - 1.14 (1 H, m, one of MeCHCH_2), 1.06 (9 H, s, $SiC(CH_3)_3$) and 0.97 (3 H, d, *J* 7.0, CH_3); δ_C (100 MHz) 135.7 (2 x CH), 135.6 (2 x CH), 133.7 (CH), 133.6 (C), 133.6 (C), 132.8 (CH), 129.6 (CH), 129.6 (CH), 127.6 (4 x CH), 72.4 (CH), 69.0 (CH_2), 46.6 (C), 44.6 (CH_2), 40.0 (CH_2), 36.8 (CH), 31.2 (CH_2), 26.9 (CH_3), 25.5 (CH), 21.3 (CH_3) and 19.4 (C).

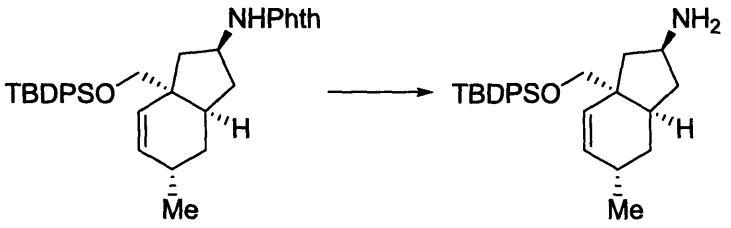
2-((2*SR*,3a*RS*,5*SR*,7a*RS*)-7a-((*tert*-Butyldiphenylsilyloxy)methyl)-5-methyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-2-yl)isoindoline-1,3-dione (227)



225 **227**

To a solution of alcohol **225** (705 mg, 1.68 mmol) in CH_2Cl_2 (15 mL) was added PPh_3 (660 mg, 2.52 mmol, 1.5 equiv.) and phthalimide (370 mg, 2.52 mmol, 1.5 equiv.). After the phosphine had dissolved DIAD (0.49 mL, 2.52 mmol, 1.5 equiv.) was added dropwise. The resulting yellow orange solution was stirred for 20 min, concentrated *in vacuo* and chromatographed on silica (10 % Et_2O in petroleum ether) to give the *title compound* (665 mg, 72 %) as a colourless oil; (Found: MH^+, 550.2775. $C_{35}H_{40}NO_3Si$ requires M, 550.2777); ν_{max} (neat) 3071, 3011, 2954, 2855, 1770, 1713, 1614, 1590, 1468, 1372, 1105, 910, 820, 703, 648 and 609 cm^{-1}; δ_H (400 MHz) 7.81 (1 H, d, *J* 5.4, aromatic CH), 7.79 (1 H, d, *J* 5.4, aromatic CH), 7.71 - 7.66 (6 H, m, 6 x aromatic CH), 7.46 - 7.37 (6 H, m, 6 x aromatic CH), 5.60 (1 H, br. d, *J* 10.1, CHCH=C*H*), 5.48 (1 H, dd, *J* 10.1, 1.8, CHC*H*=CH), 4.71 - 4.60 (1 H, m, CHN), 3.45 (2 H, app. s, CH_2O), 2.53 (1 H, app. q, *J* 11.9, one of CHCH_2CHN), 2.32 - 2.19 (3 H, m, MeCH, ring junction CH and one of CCH_2CHN), 2.10 (1 H, dd, *J* 12.6, 10.3, one of CCH_2CHN), 1.79 (1 H, app. dt, *J* 11.9, 6.2, one of CHCH_2CHN), 1.71 (1 H, app. dt, *J* 13.4, 3.5, one of MeCHCH_2), 1.27 - 1.22 (1 H, m, one of MeCHCH_2), 1.10 (9 H, s, $SiC(CH_3)_3$) and 0.98 (3 H, d, *J* 7.0, CH_3); δ_C (100 MHz) 168.4 (2 x C), 135.7 (2 x CH), 135.7 (2 x CH), 133.7 (2 x CH), 133.6 (2 x C), 132.1 (2 x C), 132.0 (CH), 131.9 (CH), 129.6 (2 x CH), 127.6 (2 x CH), 127.6 (2 x CH), 122.9 (2 x CH), 69.4 (CH_2), 48.8 (CH), 45.6 (C), 37.5 (CH_2), 37.4 (CH), 33.1 (CH_2), 31.4 (CH_2), 26.9 (CH_3), 25.8 (CH), 21.4 (CH_3) and 19.4 (C); *m/z* (TOF ES+) 551 (20%), 550 (MH^+, 100) and 294 (14).

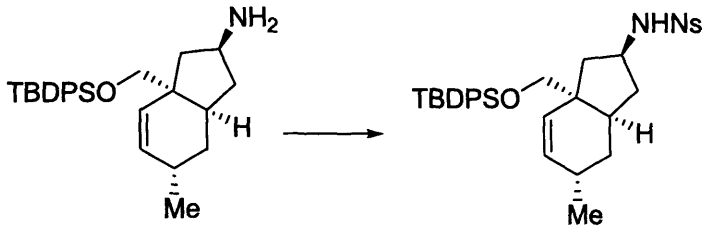
(2*SR*,3a*RS*,5*SR*,7a*RS*)-7a-((*tert*-Butyldiphenylsilyloxy)methyl)-5-methyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-2-amine (228)



227 **228**

To a solution of phthalimide **227** (1.05 g, 1.91 mmol) in EtOH (15 mL) was added hydrazine hydrate (0.42 mL, 8.60 mmol, 4.5 equiv.) and the mixture bought up to reflux. After 20 min the suspension of hydrazide was cooled and diluted with Et_2O (30 mL) with good stirring. The precipitate was removed by filtration and the filter cake washed well with Et_2O. The filtrate was concentrated *in vacuo* to give the *title compound* (0.75 g, 94 %) as an essentially-pure colourless oil (Found: MH^+, 420.2733. $C_{27}H_{38}NOSi$ requires M, 420.2723); ν_{max} ($CDCl_3$) 3364, 3070, 3002, 2930, 2856, 1643, 1589, 1459, 1428, 1390, 1110, 822, 741 and 703 cm^{-1}; δ_H (400 MHz) 7.68 - 7.63 (4 H, m, 4 x aromatic CH), 7.45 - 7.35 (6 H, m, 6 x aromatic CH), 5.47 (1 H, br. d, *J* 10.1, CHCH=C*H*), 5.41 (1 H, dd, *J* 10.1, 1.5, CHC*H*=CH), 3.39 (1 H, d, *J* 9.7, one of CH_2O), 3.37 (1 H, d, *J* 9.7, one of CH_2O), 3.31 - 3.22 (1 H, m, CHN), 2.26 (1 H, dd, *J* 13.1, 8.1, one of CCH_2CHN), 2.22 - 2.09 (2 H, m, MeCH and ring junction CH), 1.94 (1 H, app. dt, *J* 12.2, 6.5, one of CHCH_2CHN), 1.64 - 1.57 (1 H, m, one of MeCHCH_2), 1.37 (1 H, app. td, *J* 12.2, 9.5, one of CHCH_2CHN), 1.28 - 1.11 (2 H, m, one of MeCHCH_2 and one of CCH_2CHN), 1.05 (9 H, s, SiC$(CH_3)_3$) and 0.95 (3 H, d, *J* 7.0, CH_3); δ_C (100 MHz) 135.7 (2 x CH), 135.7 (2 x CH), 133.7 (C), 133.7 (C), 132.8 (CH), 132.0 (CH), 129.5 (2 x CH), 127.6 (4 x CH), 69.5 (CH_2), 51.0 (CH), 46.2 (CH_2), 45.8 (C), 40.9 (CH_2), 37.9 (CH), 31.4 (CH_2), 26.9 (CH_3), 25.6 (CH), 21.5 (CH_3) and 19.4 (C); *m/z* (TOF ES+) 461 ($MH^+.CH_3CN$, 36 %) and 420 (MH^+, 100).

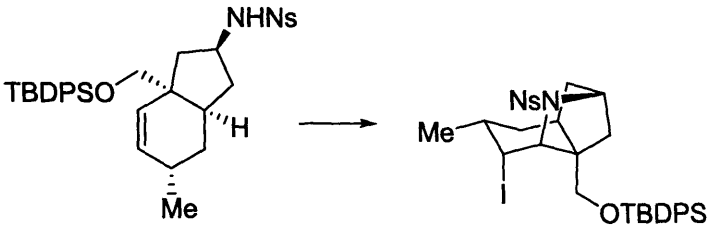
***N*-((2*SR*,3a*RS*,5*SR*,7a*RS*)-7a-((*tert*-Butyldiphenylsilyloxy)methyl)-5-methyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-2-yl)-4-nitrobenzenesulfonamide (230)**



228 **230**

To a solution of amine **228** (0.75 g, 1.79 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.37 mL, 2.69 mmol, 1.5 equiv.) followed by 4-nitrobenzenesulfonyl chloride (0.52 g, 2.33 mmol, 1.3 equiv.). The resulting solution was stirred overnight, concentrated *in vacuo* and chromatographed on silica (10 - 20 % EtOAc in petroleum ether) to give the *title compound* (1.01 g, 93 %) as a pale yellow oil (Found MH^+, 605.2538. $C_{33}H_{41}N_2O_5SSi$ requires M, 605.2505); ν_{max} (CH_2Cl_2) 3282, 3071, 2956, 2857, 1707, 1607, 1531, 1427, 1349, 1310, 1265, 1165, 1093, 924, 855, 822, 738, 704 and 614 cm^{-1}; δ_H (400 MHz) 8.32 (2 H, d, *J* 8.8, 2 x aromatic CH), 8.02 (2 H, d, *J* 8.8, 2 x aromatic CH), 7.61 - 7.55 (4 H, m, 4 x aromatic CH), 7.47 - 7.33 (6 H, m, 6 x aromatic CH), 5.51 (1 H, br. d, *J* 10.0, CHCH=C*H*), 5.29 (1 H, dd, *J* 10.0, 1.6, CHC*H*=CH), 4.81 (1 H, d, *J* 8.9, NH), 3.80 - 3.69 (1 H, m, CHN), 3.32 (1 H, d, *J* 9.9, one of CH_2O), 3.31 (1 H, d, *J* 9.9, one of CH_2O), 2.15 (2 H, m, ring junction CH and one of CH_2CHN), 2.10 - 1.98 (2 H, m, MeCH and one of CH_2CHN), 1.56 (1 H, app. dt, *J* 13.6, 3.6, one of MeCHCH_2), 1.40 (1 H, app. dt, *J* 11.8, 8.4, one of CHCH_2CHN), 1.19 (1 H, dd, *J* 13.3, 6.2, one of CCH_2CHN), 1.13 - 1.05 (1 H, m, one of MeCHCH_2), 1.02 (9 H, s, $SiC(CH_3)_3$) and 0.93 (3 H, d, *J* 7.1, CH_3); δ_C (100 MHz) 149.9 (C), 146.9 (C), 135.6 (2 x CH), 135.5 (2 x CH), 133.8 (CH), 133.3 (C), 133.2 (C), 131.6 (CH), 129.7 (2 x CH), 128.2 (2 x CH), 127.7 (4 x CH), 124.3 (2 x CH), 68.4 (CH_2), 52.9 (CH), 46.1 (C), 42.5 (CH_2), 37.8 (CH_2), 36.7 (CH), 30.4 (CH_2), 26.8 (CH_3), 25.4 (CH), 21.2 (CH_3), 19.3 (C); *m/z* (TOF ES+) 606 (33%), 605 (MH^+, 100), 418 (29) and 280 (63).

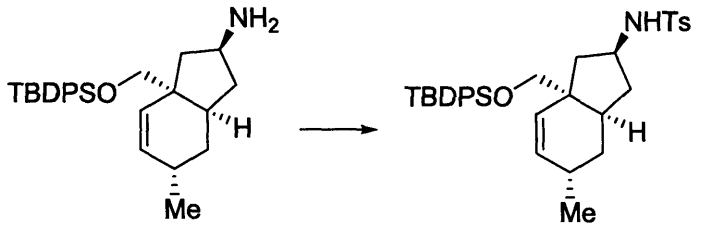
(2*RS*,3*aSR*,4*RS*,6*RS*,7*RS*,7*aRS*)-3*a*-(*tert*-Butyldimethylsilyloxymethyl)-7-iodo-6-methyl-1-(4-nitrobenzenesulfonyl)-2,4-methanooctahydroindole (231)



230 **231**

To a solution of sulfonamide **230** (400 mg, 0.66 mmol) in MeCN (10 mL) was added $NaHCO_3$ (167 mg, 1.98 mmol, 3 equiv.) and I_2 (505 mg, 1.98 mmol, 3 equiv.). The reaction was stirred overnight before quenching with saturated aqueous Na_2SO_3 (10 mL). The organic layer was separated and the aqueous phase extracted with Et_2O (2 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica (10 % EtOAc in petroleum ether) to give the *title compound* (437 mg, 91 %) as a colourless oil that crystallised on standing, m.p. 173 - 175 °C (Found MH^+, 731.1436. $C_{33}H_{40}IN_2O_5SSi$ requires M, 731.1472); ν_{max} (CH_2Cl_2) 3071, 2959, 2857, 1605, 1533, 1470, 1428, 1351, 1312, 1263, 1155, 1109, 959, 926, 856, 800, 740, 704, 632 and 601 cm^{-1}; δ_H (400 MHz) 8.18 (2 H, d, *J* 8.8, 2 x aromatic CH), 7.96 (2 H, d, *J* 8.8, 2 x aromatic CH), 7.52 - 7.47 (4 H, m, 4 x aromatic CH), 7.45 - 7.27 (6 H, m, 6 x aromatic CH), 4.92 (1 H, br. s, CHI), 4.19 (1 H, d, *J* 10.7, one of CH_2O), 3.99 (1 H, br. d, *J* 2.2, CHIC*H*N), 3.92 (1 H, br. s, CH_2CHN), 3.71 (1 H, d, *J* 10.7, one of CH_2O), 1.91 - 1.85 (2 H, m, ring junction CH and one of CH_2CHN), 1.80 - 1.71 (1 H, m, one of CH_2CHN), 1.61 - 1.50 (1 H, m, MeCH), 1.29 - 1.10 (2 H, m, $MeCHCH_2$), 0.99 - 0.94 (13 H, m, CH_3, $SiC(CH_3)_3$ and one of CH_2CHN) and 0.74 (1 H, br. d, *J* 10.3, one of CH_2CHN); δ_C (100 MHz) 150.0 (C), 143.2 (C), 135.8 (2 x CH), 135.6 (2 x CH), 133.3 (C), 132.9 (C), 129.8 (CH), 129.8 (CH), 128.8 (2 x CH), 127.6 (2 x CH), 127.5 (2 x CH), 124.5 (2 x CH), 64.5 (CH_2), 64.2 (CH), 59.6 (CH), 52.5 (C), 43.1 (CH_2), 40.7 (CH), 37.0 (CH_2), 34.1 (CH), 29.3 (CH_2), 26.9 (CH_3), 24.1 (CH and CH_3) and 19.3 (C).

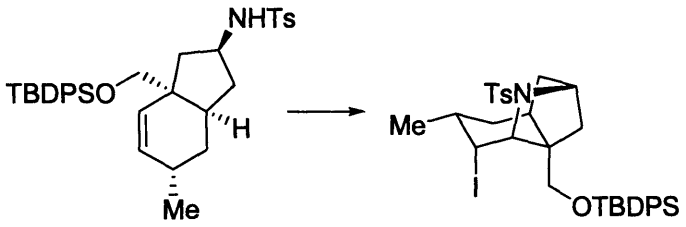
***N*-((2*SR*,3a*RS*,5*SR*,7a*RS*)-7a-((*tert*-Butyldiphenylsilyloxy)methyl)-5-methyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-2-yl)-toleuenesulfonamide (232)**



228 **232**

To a solution of amine **228** (230 mg, 0.55 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.11 mL, 0.83 mmol, 1.5 equiv.) and TsCl (126 mg, 0.66 mmol, 1.2 equiv.). After stirring overnight the solution was concentrated and chromatographed on silica (20 % EtOAc in petroleum ether) to give the *title compound* as a colourless oil (265 mg, 84 %). (Found: MNH_4^+, 591.3063. $C_{34}H_{47}N_2O_3SSi$ requires M, 591.3077); ν_{max} ($CDCl_3$) 3271, 3071, 2955, 2857, 1598, 1428, 1325, 1160, 1094, 910, 815, 735, 704, 665 cm^{-1}; δ_H (400 MHz) 7.66 (2 H, d, *J* 8.3, aromatic CH), 7.53 - 7.49 (4 H, m, aromatic CH), 7.38 - 7.27 (6 H, m, aromatic CH), 7.19 (2 H, d, *J* 8.3, aromatic CH), 5.40 (1 H, br. d, *J* 10.1, CHCH=C*H*), 5.22 (1 H, dd, *J* 10.1, 1.7, CHC*H*=CH), 4.62 (1 H, d, *J* 8.7, NH), 3.57 (1 H, m, CHN), 3.23 (1 H, d, *J* 9.8, one of CH_2O), 3.20 (1 H, d, *J* 9.8, one of CH_2O), 2.33 (3 H, s, $ArCH_3$), 2.05 1.94 (2 H, m, ring junction CH and MeCH), 2.03 (1 H, dd, *J* 13.3, 8.2, one of CCH_2CHN), 1.92 (1 H, app. dt, *J* 12.3, 7.3, one of $CHCH_2CHN$), 1.46 (1H, app. dt, *J* 13.5, 3.7, one of $MeCHCH_2$), 1.37–1.27 (1 H, ddd, *J* 12.3, 11.5, 8.3, one of $CHCH_2CHN$), 1.11 (1 H, dd, *J* 13.3, 6.3, one of CCH_2CHN), 1.00 (1 H, ddd, *J* 13.5, 10.8, 4.1, one of $MeCHCH_2$), 0.93 (9 H, s, $SiC(CH_3)_3$) and 0.84 (3 H, d, *J* 7.0, CH_3CH); δ_C (125 MHz) 143.1 (C), 138.0 (C), 135.6 (2 × CH), 135.6 (2 × CH), 133.5 (C), 133.4 (C), 133.3 (CH), 131.9 (CH), 129.6 (2 × CH), 127.6 (4 × CH), 127.1 (2 × CH), 68.8 (CH_2), 52.6 (CH), 46.0 (C), 42.5 (CH_2), 37.8 (CH_2), 36.8 (CH), 30.7 (CH_2), 26.9 (CH_3), 25.4 (CH), 21.5 (CH_3), 21.2 (CH_3) and 19.3 (C); *m/z* (TOF ES+) 593 (19%), 592 (53) and 591 ($M.NH_4^+$, 100).

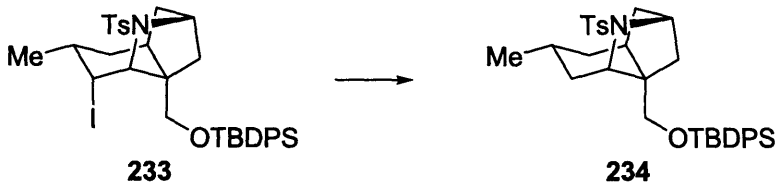
(2*RS*,3*aSR*,4*RS*,6*RS*,7*RS*,7*aRS*)-3*a*-(*tert*-Butyldimethylsilyloxymethyl)-7-iodo-6-methyl-1-(4-toluenesulfonyl)-2,4methanooctahydroindole (233)



232 **233**

To a solution of sulfonamide **232** (250 mg, 0.44 mmol) in MeCN (5 mL) was added $NaHCO_3$ (110 mg, 1.31 mmol, 3 equiv.) and I_2 (332 mg, 1.31 mmol, 3 equiv.). After stirring overnight the reaction was quenched by the addition of saturated aqueous Na_2SO_3 (10 mL), the organic layer separated and the aqueous phase extracted with Et_2O (2 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica (10 % EtOAc in petroleum ether) to give the *title compound* (210 mg, 69 %) as a colourless oil that crystallised on standing, m.p. 150–152 °C (Found: MH^+, 700.1765. $C_{34}H_{43}INO_3SSi$ requires M, 700.1778); ν_{max} (CH_2Cl_2) 3070, 2958, 2857, 1597, 1469, 1428, 1346, 1260, 1153, 1110, 958, 926, 802, 740, 704 and 665 cm^{-1}; δ_H (500 MHz) 7.68 (2 H, d, *J* 8.3, 2 x aromatic CH), 7.54 - 7.51 (4 H, m, 4 x aromatic CH), 7.45 - 7.29 (6 H, m, 6 x aromatic CH), 7.14 (2 H, d, *J* 8.3, 2 x aromatic CH), 4.94 (1 H, br. t, *J* 3.1, CHI), 4.15 (1 H, d, *J* 10.6, one of CH_2O), 4.01 (1 H, br. d, *J* 2.3, CHIC*H*N), 3.88 (1 H, br. s, CH_2CHN), 3.69 (1 H, d, *J* 10.6, one of CH_2O), 2.36 (3 H, s, $ArCH_3$), 1.87 - 1.80 (2 H, m, ring junction CH and one of CH_2CHN), 1.76 - 1.70 (1 H, m, one of CH_2CHN), 1.65 - 1.50 (1H, m, MeCH), 1.28 - 1.11 (2 H, m, $MeCHCH_2$), 0.99 (9 H, s, $SiC(CH_3)_3$), 0.95 (3 H, d, *J* 6.4, CH_3CH), 0.95 - 0.91 (1 H, m, one of CH_2CHN) and 0.85 (1 H, app. dt, *J* 10.1, 2.2, one of $CHCH_2CHN$); δ_C 143.5 (C), 135.9 (2 × CH), 135.7 (2 × CH), 133.7 (C), 133.3 (C), 129.9 (2 × CH), 129.7 (CH), 129.6 (CH), 127.7 (2 × CH), 127.5 (2 × CH),127.4 (2 × CH), 64.7 (CH2), 64.0 (CH), 59.3 (CH), 52.3 (C), 42.9 (CH_2), 42.1 (CH), 37.1 (CH_2), 34.2 (CH), 29.5 (CH_2), 27.0 (CH_3), 24.2 (CH_3), 24.1 (CH), 21.5 (CH_3) and 19.3 (C); *m/z* (TOF ES+) 701 (25%), 700 (MH^+, 100) and 572 (14).

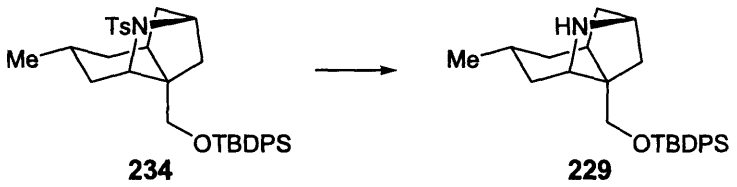
(2*RS*,3*aSR*,4*RS*,6*RS*,7*RS*,7*aRS*)-3*a*-(*tert*-Butyldimethylsilyloxymethyl)-6-methyl-1-(4-toluenesulfonyl)-2,4-methanooctahydroindole (234)



233 **234**

To a solution of iodide **233** (40 mg, 0.06 mmol) in benzene (10 mL) was added Bu_3SnH (0.15 mL, 0.57 mmol, 10 equiv.) and AIBN (25 mg, 0.15 mmol, 2.7 equiv.). The solution was heated to reflux overnight, concentrated and chromatographed on silica containing approx. 10 % w/w NaF (10 % EtOAc in petroleum ether) to give the *title compound* (33 mg, 100 %) as a yellow oil (Found: MH^+, 574.2834. $C_{34}H_{44}NO_3SSi$ requires M, 574.2811); ν_{max} (CH_2Cl_2) 3071, 2956, 2855, 1599, 1457, 1428, 1341, 1156, 1111, 957, 934, 898, 802, 739 and 705 cm^{-1}; δ_H (500 MHz) 7.71 (2 H, d, *J* 8.3, 2 x aromatic CH), 7.56 - 7.50 (4 H, m, 4 x aromatic CH), 7.45 - 7.33 (6 H, m, 6 x aromatic CH), 7.24 (2 H, d, *J* 8.3, 2 x aromatic CH), 4.04 (1 H, br. s, CCH_2CHN), 3.62 - 3.58 (2 H, m, $MeCH_2CHN$ and one of CH_2O), 3.49 (1 H, d, *J* 10.6, one of CH_2O), 2.39 (3 H, s, $ArCH_3$), 2.12 (1 H, br. d, *J* 13.9, one of $MeCHCH_2CHN$), 2.07 - 1.95 (1 H, m, MeCH), 1.88 - 1.78 (2 H, m, ring junction CH and one of $CCHCH_2CHN$), 1.72 - 1.62 (1 H, m, one of $CCHCH_2CHN$), 1.44 (1 H, br. d, *J* 13.8, one of $MeCHCH_2CH$), 1.02 (1 H, app. d, *J* 9.8, one of CCH_2CHN), 0.98 - 0.89 (11 H, m, one of CCH_2CHN, one of $MeCHCH_2CHN$ and $SiC(CH_3)_3$), 0.88 - 0.83 (1 H, m, one of $MeCHCH_2CH$) and 0.86 (3 H, d, *J* 6.6, CH_3); δ_C (125 MHz) 142.9 (C), 135.6 (2 × CH), 135.5 (2 × CH_2), 133.1 (C), 133.1 (C), 129.8 (CH), 129.8 (CH), 129.7 (2 × CH), 127.7 (2 × CH), 127.7 (2 × CH), 127.6 (2 × CH), 62.8 (CH_2), 59.8 (CH), 59.7 (CH), 51.3 (C), 41.2 (CH2), 37.2 (CH2), 34.9 (CH), 33.7 (CH_2), 33.5 (CH_2), 26.8 (CH_3), 21.6 (CH_3), 21.5 (CH_3), 20.2 (CH) and 19.2 (C); *m/z* (TOF ES+) 575 (22%) and 574 (MH^+, 100).

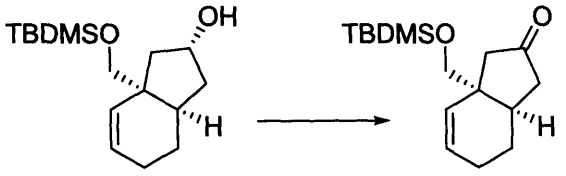
(2*RS*,3*aSR*,4*RS*,6*RS*,7*RS*,7*aRS*)-3*a*-(*tert*-Butyldimethylsilyloxymethyl)-6-methyl-2,4-methanooctahydroindole (229).



To a solution of naphthalene (125 mg, 0.98 mmol) in THF (2 mL) was added sodium (22 mg, 0.96 mmol) and the metal crushed with a spatula. After stirring for 30 min a 1 mL aliquot of the resulting green solution was added dropwise to a -78 °C solution of tosylate **234** (25 mg, 0.04 mmol) in THF (3 mL), giving a permanent green colour. After stirring for 15 min the reaction was quenched by addition of 2 M NaOH (10 mL) and allowed to warm to room temperature. The organic layer was separated and the aqueous phase extracted with Et_2O (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica (10 % EtOAc in petroleum ether followed by 1 % Et_3N in MeOH) to give a yellow oil which proved to be a salt by ^1H NMR. This was dissolved in CH_2Cl_2 (10 mL) and washed with 2 M NaOH (10 mL). The aqueous phase was extracted with CH_2Cl_2 (10 mL) and the combined organic phases dried over NaOH and concentrated *in vacuo* to give the *title compound* (15 mg, 82 %) as a yellow oil (Found MH^+, 420.2731. $C_{27}H_{38}NOSi$ requires M, 420.2723); ν_{max} (neat) 3398, 3072, 2929, 2861, 1587, 1428, 1111, 1097, 823, 737 and 703 cm^{-1}; δ_H (500 MHz) 7.66 (4 H, app. br. d, *J* 7.1, 4 x aromatic CH), 7.45 - 7.36 (6 H, m, 6 x aromatic CH), 3.70 (1 H, d, *J* 10.5, one of CH_2O), 3.69 (1 H, d, *J* 10.5, one of CH_2O), 3.29 (1 H, br. s, CCH_2CHN), 3.22 (1 H, br. s, CCHN), 2.07 (1 H, m, ring junction CH), 1.85 (1 H, app. td, *J* 12.3, 2.8, one of $CHCH_2CHN$), 1.86 - 1.75 (1 H, m, MeCH), 1.71 (1 H, app. dt, *J* 9.3, 2.2, one of CCH_2CHN), 1.62 (1 H, br. d, *J* 14.3, one of $MeCHCH_2CHN$), 1.55 (1 H, d, *J* 9.3, one of CCH_2CHN), 1.45 (1 H, br. d, *J* 13.7, one of $MeCHCH_2CH$), 1.35 (1 H, app. dt, *J* 12.3, 3.4, one of $CCHCH_2CHN$), 1.05 (9 H, s, $SiC(CH_3)_3$), 0.98 - 0.88 (2 H, m, one of $MeCHCH_2CH$ and one of $MeCHCH_2CHN$) and 0.85 (3 H, d, *J* 6.5, CH_3); δ_C (125 MHz) 135.7 (4 x CH), 133.8 (2 x C), 129.6 (2 x CH), 127.6 (4 x CH), 63.8 (CH_2), 56.0 (CH), 55.2 (CH), 49.8 (C), 44.9 (CH_2), 38.2 (CH_2), 34.6 (CH_2), 34.2

(CH), 33.6 (CH_2), 26.9 (CH_3), 21.9 (CH_3), 19.7 (CH) and 19.4 (C); *m/z* (TOF ES+) 422 (10%), 421 (35) and 420 (MH^+, 100).

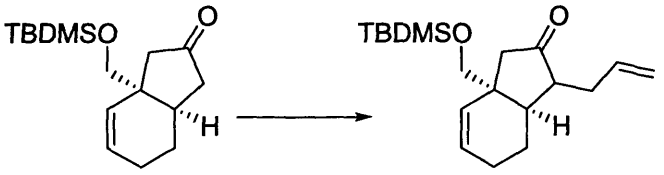
(3a*RS*,7a*RS*)-3a-((*tert*-Butyldimethylsilyloxy)methyl)-3,3a,7,7a-tetrahydro-1*H*-inden-2(6*H*)-one (235)



191 **235**

PDC (500 mg, 1.3 mmol, 1.5 equiv.) was added to a solution of alcohol **191** (250 mg, 0.89 mmol) in CH_2Cl_2. After stirring for 16 h, the mixture was filtered through a short column of silica gel, washing well with CH_2Cl_2. Removal of the solvent *in vacuo* afforded the *title compound* (200 mg, 81 %) as a pale yellow oil. δ_H (500 MHz) 5.81 (1 H, app. dt, *J* 10.1, 3.8, one of alkene CH), 5.38 (1 H, app. dt, *J* 10.1, 1.9, one of alkene CH), 3.50 (1 H, d, *J* 9.9, one of CH_2OTBS), 3.43 (1 H, d, *J* 9.9, one of CH_2OTBS), 2.52 (1 H, d, *J* 18.2, one of C*C*H_2C=O), 2.47 - 2.39 (2 H, m), 2.12 - 2.02 (3 H, m), 2.05 (1 H, d, *J* 18.2, one of C*C*H_2C=O), 1.77 (1 H, dddd, *J* 13.8, 7.7, 6.2, 3.5), 1.55 (1 H, app. dq, *J* 13.7, 5.9), 0.89 (9 H, s, SiC(CH_3)$_3$) and 0.04 (6 H, s, 2 x $SiCH_3$).

(3a*SR*,7a*RS*)-1-Allyl-3a-((*tert*-butyldimethylsilyloxy)methyl)-3,3a,7,7a-tetrahydro-1*H*-inden-2(6*H*)-one (236)

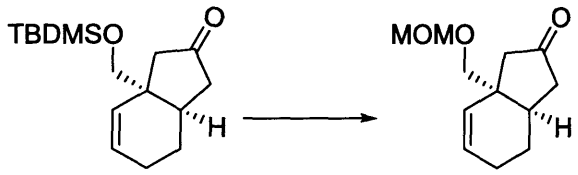


235 **236**

A solution of ketone **235** (0.5 g, 1.8 mmol) in THF (2 mL) was added to a solution of 2M LDA (1.1 mL, 2.2 mmol, 1.2 equiv.) in THF (10 mL) at -78 °C. After stirring for 30 min, allyl iodide (0.21 mL, 2.3 mmol, 1.3 equiv.) was added dropwise and the reaction allowed to warm to room temperature while stirring overnight. Saturated aqueous

NH_4Cl (20 mL) was added, the organic layer separated and the aqueous phase extracted with Et_2O (2 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (2 % Et_2O in petroleum ether) giving the *title compound* (300 mg, 76 %) as a yellow oil. δ_H (500 MHz) 5.85 - 5.69 (2 H, m, 2 x alkene CH), 5.40 - 5.28 (1 H, m, alkene CH), 5.11 - 4.97 (2 H, m, 2 x alkene CH), 3.50 (1 H, d, *J* 10.1, one of CH_2OTBS), 3.39 (1 H, d, *J* 10.1, one of CH_2OTBS), 2.57 (1 H, d, *J* 18.3, one of $CCH_2C{=}O$), 2.38 - 2.27 (2 H, m), 2.18 (1 H, app. dtd, *J* 11.3, 5.8, 1.5), 2.10 - 1.99 (3 H, m), 1.82 - 1.67 (2 H, m), 1.55 (1 H, app. dq, *J* 13.7, 5.6), 0.88 (9 H, s, $SiC(CH_3)_3$) and 0.03 (6 H, s, 2 x $SiCH_3$); δ_C (100 MHz) 135.3 (CH), 130.5 (CH), 129.0 (CH), 116.6 (CH_2), 65.0 (CH_2), 48.6 (CH), 45.7 (CH_2), 43.0 (C), 37.7 (CH), 32.8 (CH_2), 25.6 (CH_3), 19.9 (CH_2), 18.7 (CH_2), 17.9 (C), -5.8 (C) and -5.8 (C).

(3a*RS*,7a*RS*)-3a-((Methoxymethoxy)methyl)-3,3a,7,7a-tetrahydro-1*H*-inden-2(6*H*)-one (237)

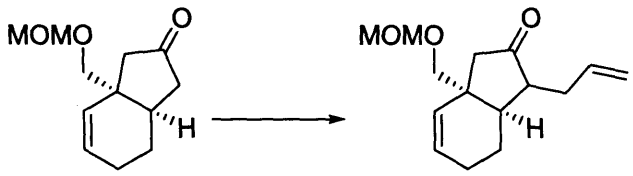


235 **237**

A 1 M THF solution of TBAF (3 mL, 3 mmol, 1.5 equiv.) was added to a solution of ketone **235** (0.6 g, 2.1 mmol) in THF (10 mL). After stirring for 30 min, the reaction was quenched with water (20 mL), the organic layer separated and the aqueous phase extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL) then dried over Na_2SO_4. The solvent was removed *in vacuo* and the residual orange oil (364 mg) dissolved in DCM (20 mL). DIPEA (1.74 mL, 5 mmol, 2.5 equiv.) was added, followed by an approximately 1 M solution of MOM-Cl in CH_2Cl_2. After stirring for 16 h, the reaction was quenched with 2 M HCl (20 mL), the organic layer separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced

pressure, and the resulting residue purified by chromatography on silica (15 % EtOAc in petroleum ether) to yield the *title compound* (0.29 g, 67 %) as a colourless oil.

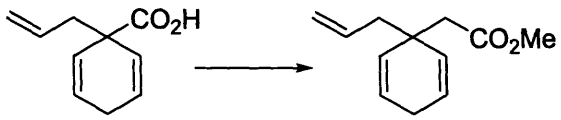
(3a*SR*,7a*RS*)-1-Allyl-3a-((methoxymethoxy)methyl)-3,3a,7,7a-tetrahydro-1*H*-inden-2(6*H*)-one (238)



237 **238**

A solution of ketone **237** (0.29 g, 1.4 mmol) in THF (2 mL) was added to a solution of 2M LDA (0.84 mL, 1.7 mmol, 1.2 equiv.) in THF (10 mL) at -78 °C. After stirring for 30 min, allyl bromide (0.24 mL, 2.8 mmol, 2.0 equiv.) was added dropwise and the reaction allowed to warm to room temperature while stirring overnight. Saturated aqueous NH_4Cl (20 mL) was added, the organic layer separated and the aqueous phase extracted with Et_2O (2 x 10 mL). The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure, and the residue purified by chromatography on silica gel (8 % EtOAc in petroleum ether) giving the *title compound* (165 mg, 47 %) as a yellow oil; δ_H (500 MHz) 5.88 - 5.66 (2 H, m, 2 x alkene CH), 5.40 - 5.35 (1 H, m, one of alkene CH), 5.13 - 4.98 (2 H, m, 2 x alkene CH), 4.62 (3 H, s, OCH_3), 3.47 (1 H, d, *J* 9.6, one of CH_2OMOM), 3.42 (1 H, d, *J* 9.6, one of CH_2OMOM), 3.49 (2 H, s, OCH_2O), 2.48 (1 H, d, *J* 18.4, one of $CCH_2C{=}O$), 2.46 - 2.38 (1 H, m, one of $C{=}CHCH_2$), 2.33 - 2.19 (3 H, m), 2.16 (1 H, d, *J* 18.4, one of $CCH_2C{=}O$), 2.06 - 1.99 (2 H, m), 1.83 (1 H, dddd, *J* 13.8, 10.2, 6.8, 3.5) and 1.75 (1 H, app. ddt, *J* 14.1, 5.8, 2.7).

Methyl 2-(1-allylcyclohexa-2,5-dienyl)acetate (240)



239 **240**

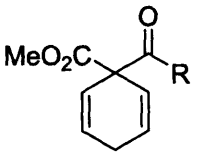
Methyl chloroformate (1.32 mL, 16.7 mmol, 1.1 equiv.) was added dropwise to an ice-cold solution of acid **239** (2.5 g, 15.2 mmol) and Et_3N (2.32 mL, 16.7 mmol, 1.1 equiv.) in Et_2O (50 mL). The resulting suspension was stirred for 30 min, while a suspension of Diazald (4.9 g, 22.8 mmol, 1.5 equiv.) in EtOH (10 mL) was prepared and warmed to approx. 50 °C in a separate flask. A solution of KOH (5 g) in H_2O (8 mL) was added dropwise to the well stirred Diazald suspension and the gas generated was passed into the flask containing the mixed anhydride.

Stirring was continued for 30 min before the crude diazoketone solution was filtered through a short column of silica, washing well with Et_2O. Removal of the solvent under reduced pressure gave a residue which was redissolved in MeOH (50 mL) and treated with a solution of freshly prepared silver (I) benzoate (100 mg) in Et_3N (10 mL). This was heated cautiously to reflux, resulting in vigorous gas evolution. After 4 h at reflux, the mixture was again filtered through a short column of silica, washing with Et_2O, and the filtrate concentrated under reduced pressure. The residue was purified by chromatography on silica (2 - 10 % EtOAc in petroleum ether) to afford the *title compound* (1.24 g, 42 %) as a colourless oil; δ_H (500 MHz) 5.82 - 5.78 (2 H, m, 2 x alkene CH), 5.71 (1 H, app. ddt, *J* 17.6, 10.4, 7.2, alkene CH), 5.56 - 5.52 (2 H, m, 2 x alkene CH), 5.07 - 4.98 (2 H, m, 2 x alkene CH), 3.62 (3 H, s, OMe), 2.56 (2 H, app. tdd, *J* 5.4, 3.3, 2.1, $CHCH_2CH$), 2.36 (2 H, s, CH_2CO_2Me) and 2.20 (2 H, br. d, *J* 7.2, $CH_2=CHCH_2$).

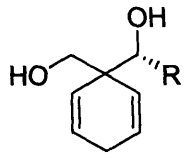
Appendix A

Compound Lists

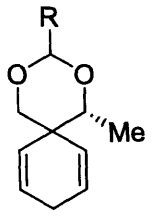
Appendix A-1. Compound List for Chapter 2



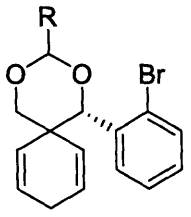
73a, R = Me
73b, R = 2-BrC_6H_4
73c, R = Ph



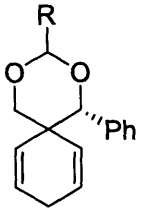
74a, R = Me
74b, R = 2-BrC_6H_4
74c, R = Ph



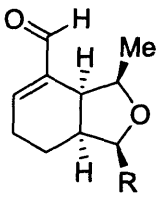
60a, R = Me
60b, R = *n*-Bu
60c, R = *i*-Bu
60d, R = *t*-Bu
60e, R = Ph



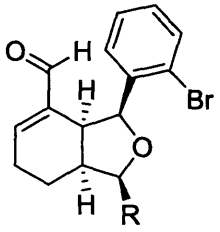
60f, R = Me
60g, R = *i*-Bu
60h, R = Ph



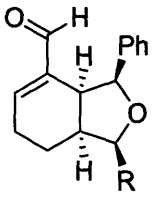
85a, R = Me
85b, R = *n*-Bu
85c, R = *i*-Bu
85e, R = Ph



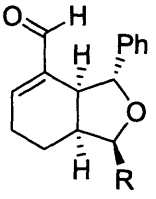
61a, R = Me
61b, R = *n*-Bu
61c, R = *i*-Bu
61d, R = *t*-Bu
61e, R = Ph



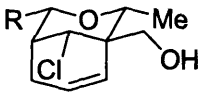
61f, R = Me
61g, R = *i*-Bu
61h, R = Ph



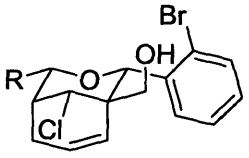
86a, R = Me
86b, R = *n*-Bu
86c, R = *i*-Bu
86e, R = Ph



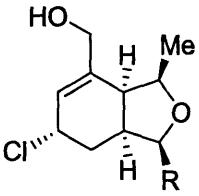
87a, R = Me
87b, R = *n*-Bu



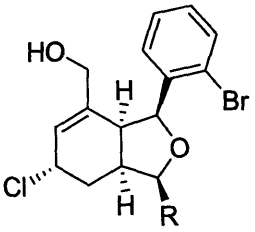
62a, R = Me
62c, R = *i*-Bu
62e, R = Ph



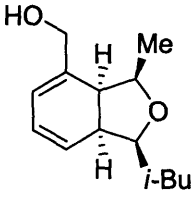
62f, R = Me
62g, R = *i*-Bu
62h, R = Ph



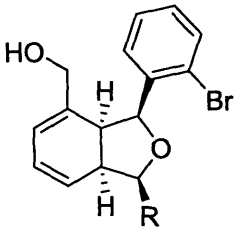
63a, R = Me
63c, R = *i*-Bu
63e, R = Ph



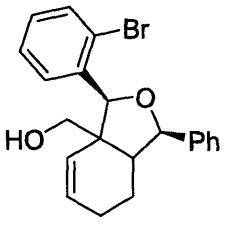
63f, R = Me
63g, R = *i*-Bu
63h, R = Ph



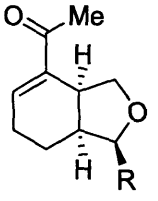
75c



75f, R = Me
75g, R = *i*-Bu

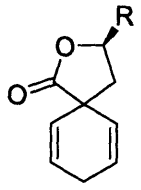


78

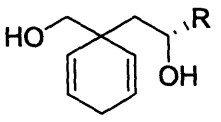


84a, R = Me
84b, R = *n*-Bu
84c, R = *i*-Bu
84e, R = Ph

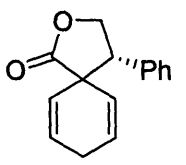
Appendix A-2. Compound List for Chapter 3



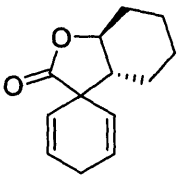
121a, R = Me
121b, R = *n*-Bu
121c, R = *t*-Bu
121d, R = CH_2Cl
121e, R = CH_2OH
121f, R = *c*-C_6H_{11}
121g, R = Ph



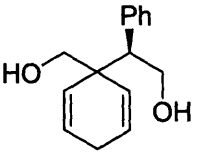
113a, R = Me
113b, R = *n*-Bu
113c, R = *t*-Bu
113d, R = CH_2Cl
113e, R = CH_2OH
113f, R = *c*-C_6H_{11}
113g, R = Ph



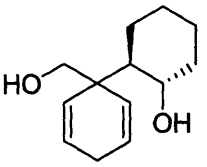
121h



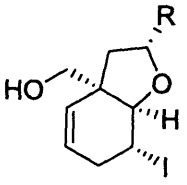
121i



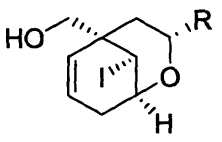
113h



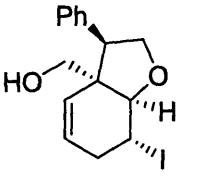
113i



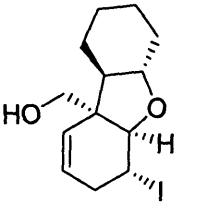
114a, R = Me
114b, R = *n*-Bu
114c, R = *t*-Bu
114d, R = CH_2Cl
114e, R = CH_2OH
114f, R = *c*-C_6H_{11}
114g, R = Ph



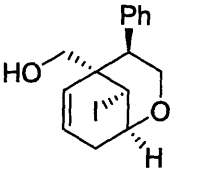
115a, R = Me
115b, R = *n*-Bu
115g, R = Ph



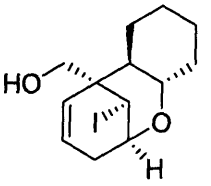
114h



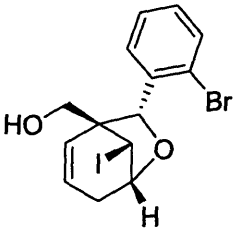
114i



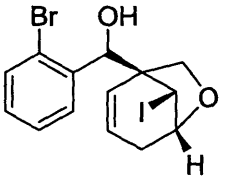
115h



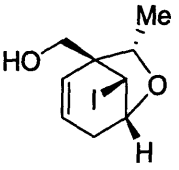
115i



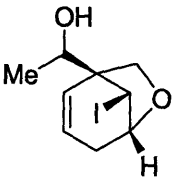
116b



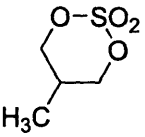
117b



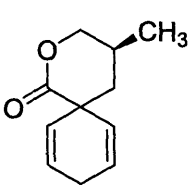
116a



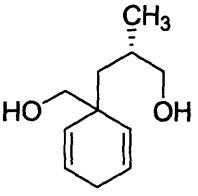
117a



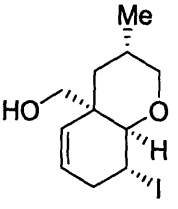
126



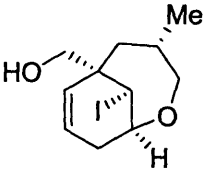
127



118

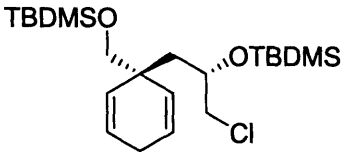


119

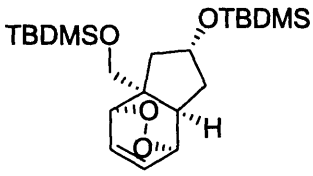


120

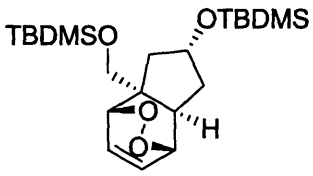
Appendix A-3. Compound List for Chapter 4



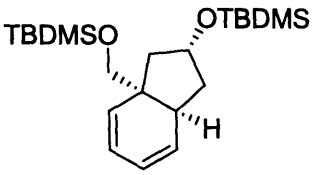
174



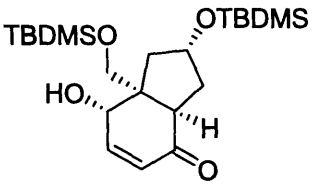
180



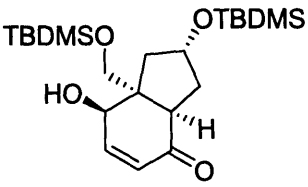
181



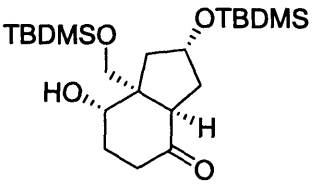
175



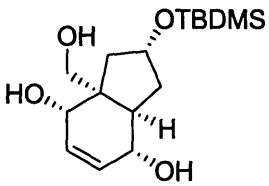
182



183

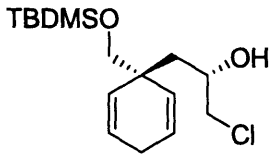


189

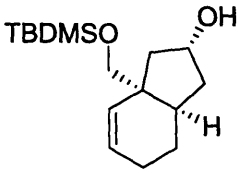


189

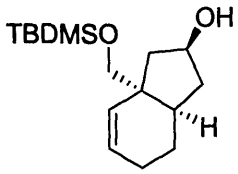
Appendix A-4. Compound List for Chapter 5



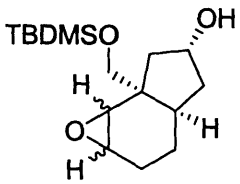
190



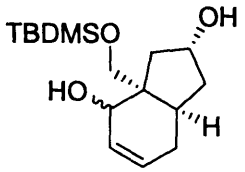
191



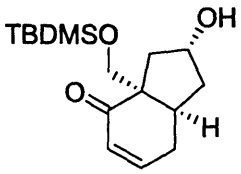
192



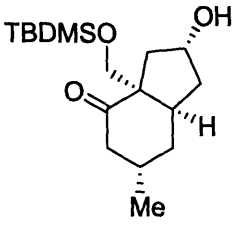
193 and
194



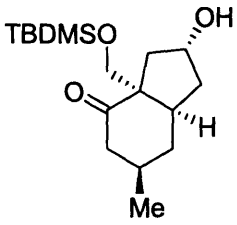
195



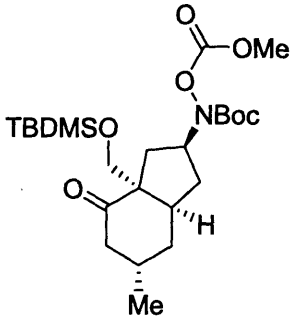
196



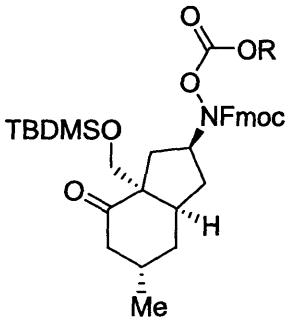
197



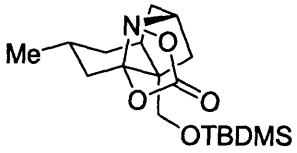
198



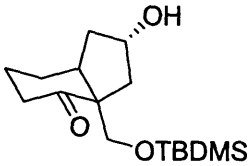
212



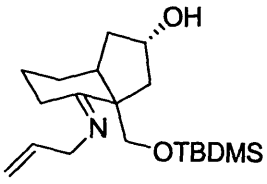
210, R = Me
211, R = Ph



213



214



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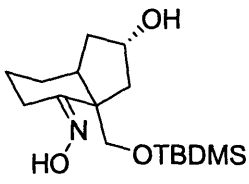
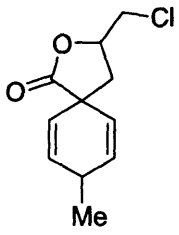


216

Appendix A-5. Compound List for Chapter 6



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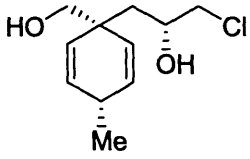

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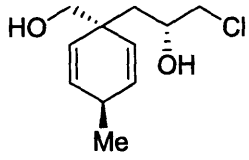

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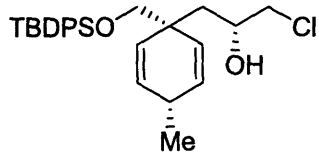

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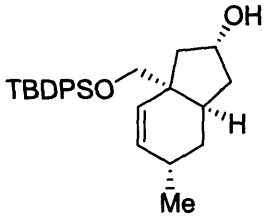

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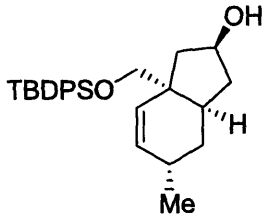

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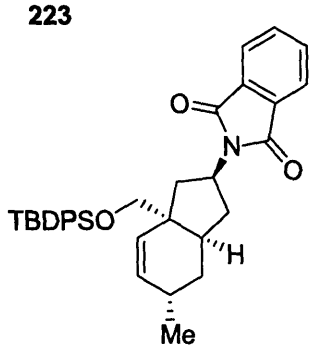

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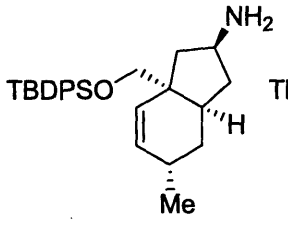

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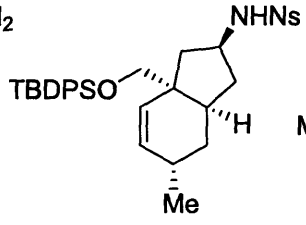

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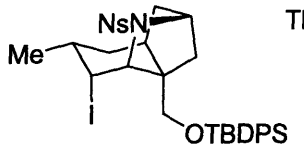

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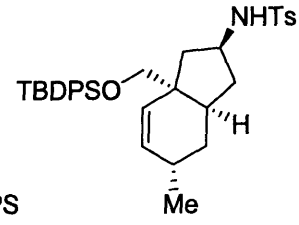

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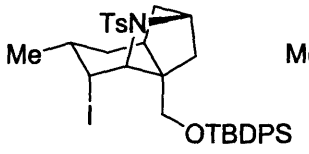

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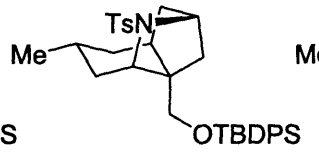

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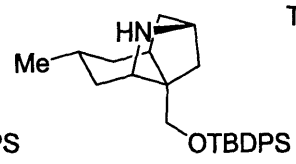

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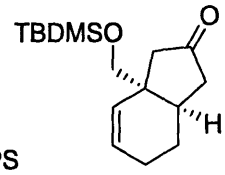

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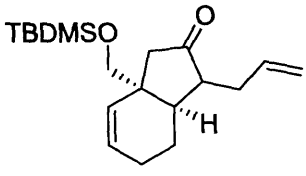

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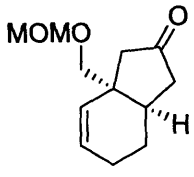

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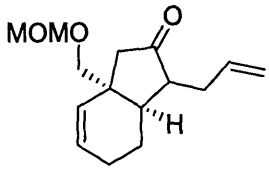

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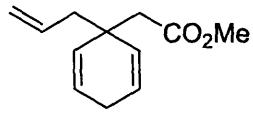

240

Appendix B

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