Some Stereochemical and Synthetic Studies in Serrulatane Diterpenoid Chemistry

A Thesis
Submitted Towards the Degree of Doctor of Philosophy

by

Linda Marie Cowin
B. Sc. (Hons.)

Organic Chemistry Department
The University of Adelaide
March 1992
CONTENTS

ACKNOWLEDGEMENTS i
STATEMENT iii
ABSTRACT iv

INTRODUCTION 1

RESULTS AND DISCUSSION 11

CHAPTER 1 - Derivatives of serrulatenol (1) 11
1.1 Palladium hydrogenolysis for allylic carbon-oxygen bond cleavage 14
1.2 Metal/ammonia reduction for allylic carbon-oxygen bond cleavage 16
1.3 Conversion of the diol (22a) to the dihydro deoxy derivative (8) 18

CHAPTER 2 - Derivatives of the triol (2a) 24

CHAPTER 3 - Derivatives of the tetraol (2c) 30

CHAPTER 4 - Synthetic Studies 40
Methods for establishing 1,4 trans stereochemistry
4.1 Review of the recent literature methods with emphasis on control of the stereochemistry at the benzylic positions 42
4.2 An approach involving equilibration and kinetic resolution as key steps in the synthetic strategy 46
4.3 An approach which relies on kinetic resolution and hydrogenolysis of tertiary benzylic carbon-oxygen bonds 57
A method for establishing 1,4 cis stereochemistry

4.4 Via catalytic hydrogenation and metal/ammonia
   reduction of appropriate methylene precursors

CHAPTER 5 - A possible method for the conversion of the
tetraol (2c) into the aglycone of the seco-pseudopterosin (10)

EXPERIMENTAL

APPENDIX

REFERENCES
ACKNOWLEDGEMENTS

First and foremost, I would like to express my gratitude to my supervisor, Ralph Massy-Westropp, whose support, guidance, inspiration and friendship have made this thesis possible and, more importantly, have made the past few years an enjoyable and rewarding experience.

I would also like to thank my fiance, Joe, whose patience, love and understanding have been greatly appreciated, and my parents, who have always encouraged me to pursue my goals and have instilled in me the confidence and determination to fulfil them.

Further, I would like to thank all of the past and present members of the department, and in particular those from Lab 1, for their advice, humour and friendship and wish them all the best in their pursuits. My thanks also go to the technical staff, especially Phil Clements who was responsible for running my high field 'H n.m.r. spectra, and the departmental secretary, Marelle, for her help with the printing. To Jeff Holman, who patiently proof read this thesis, I extend my thanks and to my friend and typist, Gill Atkinson, who was kind enough to give up some of her holiday for me and did a wonderful job considering her limited chemical knowledge and the illegibility of my hand writing, I wish to express my most sincere gratitude.

Financial support in the form of an Australian Postgraduate Research Award is gratefully acknowledged.
The most beautiful experience we can have is the mysterious....
....the fundamental emotion which stands at the cradle of true art and true science.

Albert Einstein.

The quick harvest of applied science is the usable process, the medicine, the machine. The shy fruit of pure science is Understanding.

Lincoln Barnett.
STATEMENT

To the best of my knowledge, this thesis contains no material previously submitted for a degree or diploma and contains no material previously published, except where due reference is made. I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Linda Cowin (B. Sc. Hons.)
The leaves of *Eremophila duttonii* yielded two serrulatane diterpenes as the major constituents. One was the known triol (2a) and the other a new compound, the tetraol (2c). Both were isolated as their acetates to prevent oxidation.

Because of some discrepancies in the reported 'H n.m.r. and rotation data for the dimethoxy alcohol (7), several other derivatives including the dihydro deoxy compound (6b) were prepared for further comparisons of the data. Some ambiguity still existed, therefore, to exclude the possibility that the triol (2a) possessed the 5,8 dioxygenated pattern, the dihydro deoxy compound (8)
was also prepared from serrulatenol (1), isolated previously from *Eremophila rotundifolia*. This work is described in Chapter 1. In addition, this compound was required for structure correlation studies with new diterpenes of the 5,8 dioxygenated series, an area in which further work is planned. The aim of that project will be to obtain appropriate compounds for biological assay as discussed in Chapter 5.

The structure of the tetraol (2c) was established by correlation with the triol (2a). The two series were interconverted via the dihydro deoxy derivative (6b) which enabled the stereochemistry of the chiral centres C1, C4 and C11 to be assigned. The relative stereochemistry of the additional secondary hydroxyl group at C3 was determined by an analysis of the coupling constants in the 'H n.m.r. spectrum of the dimethoxy alcohol (43b). The stereochemical correlation of the tetraol (2c) with the triol (2a) is described in Chapters 2 and 3.
The reported isolation of some new biologically active marine natural products related to the serrulatane class, of which the seco-pseudopterosin (10) is an example, has prompted considerable interest in the synthesis of terpenes of this type in recent years. Chapter 4 focuses on some methods aimed at constructing the serrulatane skeleton with stereochemical control at the chiral centres C7, C4 and C11. Firstly, some interesting aspects of the recent literature methods are highlighted with the emphasis on control of the benzylic stereochemistry to obtain the 1,4 trans configuration. Next, two conceptually different approaches from those in the literature, which were explored as part of this study, are described. One involves the equilibration reactions of compounds with an exocyclic carbonyl group (i.e. with a carbonyl containing functional group attached to a benzylic carbon) and kinetic resolution via Sharpless epoxidation as the key steps for controlling the stereochemistry. The other relies on kinetic resolution and hydrogenolysis of tertiary benzylic carbon-oxygen bonds.
The final aspect of the synthetic work focuses on establishing the complementary 1,4 cis configuration by catalytic hydrogenation and metal/ammonia reduction of the appropriate methylene precursors. In addition to the triol (2a) and the tetraol (2c), which were suitable for the preparation of compounds for part of this study, some simple model compounds were also prepared. The hydrogenation reactions were found to be more stereoselective than the metal/ammonia reductions and particular steric interactions were found to favour high stereoselectivity. The results in Chapter 4 suggest particular features which would be incorporated in total syntheses of the 1,4 disubstituted tetrahydronaphthalene diterpenes.

Finally, Chapter 5 outlines a relatively short and efficient method which could be used to convert the tetraol (2c) into the aglycone of the seco-pseudopterosin (10). A considerable amount of the chemistry necessary for this conversion was already established by the correlation and synthetic studies. Further, the sequence would also provide access to stereoisomers of the aglycone of (10) which will be valuable for biological assay.
INTRODUCTION

As part of a continuing study of the chemistry of the *Eremophila* genus (family Myoporaceae) this thesis describes the results of some research in the area of serrulatane type diterpenes. *Eremophila* is an Australian genus of predominantly arid region shrubs of which there are over two hundred species. The species studied to date have yielded a great many structurally interesting sesquiterpenes and diterpenes\textsuperscript{1,2,3,4,5}. Few monoterpens have been reported\textsuperscript{6} and no triterpenes have been recorded. In earlier studies, the wood of *E. rotundifolia*, a species found in the Kingoonya area of northern South Australia, yielded eremophilane and serrulatane terpenooids, the major constituent being the diterpene serrulatenol (1). The absolute configuration of this compound was determined from the X-ray crystal structure of its p-bromobenzoate derivative\textsuperscript{7}.

![Diagram](image)

When this work began, it was known that *E. duttonii* leaves had yielded some diterpenoids, probably with the known serrulatane skeleton\textsuperscript{8} (see Fig. 1.1, Appendix) but nothing was known about their stereochemistry. The structures had been assigned only tentatively on the basis of limited spectroscopic data.
Further quantities of these diterpenoids were obtained by extraction of the leaves of E. duttonii. This extract was the waxy coating on the leaves obtained by allowing the leaves to stand in ether for a short period. The major components were isolated as their acetates. Acetylation facilitated isolation because oxidation to quinonoid products was a problem during chromatography.

One compound was a triol and the other a tetraol, with the structures (2a) and (2c) being compatible with the spectroscopic data. Based on the preliminary $^1$H n.m.r. studies, it was difficult to decide between the 5,8 and the 7,8 dioxygenated pattern in the aromatic ring. In addition to the 5,8 pattern present in serrulatenol (1) several examples of the 8 and 7,8 arrangements have been reported$^9$. These include the trihydroxy acid (3), isolated as its methyl ester from E. drummondii$^9$ and dihydroxy-serrulatic acid (4), whose structure was determined by X-ray crystallographic analysis$^8$. 
The triol (5) isolated from *E. linearis* Chinnock and several of its derivatives had 'H n.m.r. data similar to those for the triol (2a), and derivatives thereof, isolated from *E. duttonii*. The structure and stereochemistry of (5) was established by interrelation with the trihydroxy acid (3) via 7,8-dimethoxyserrulatane (6b). The structure of compound (3) was, in turn, established by interrelation with dihydroxy-serrulatic acid (4) of known absolute stereochemistry.
However, because of some wrong assignments of the resonances in the published 'H n.m.r. data of (5)\(^9\) and its derivatives, and differences in rotation data of the derivative (7) prepared in the present study, it was decided to prepare the compound (6b) for a further comparison of the data. It was considered probable that the triol (2a) and the tetraol (2c), because of their co-occurrence, would have skeletons of the same configuration. Therefore the derivative (6b) would be useful because it could be prepared from the tetraol (2c) and would thus provide a means of establishing if the triol (2a) and tetraol (2c) do indeed have the same configuration.

Because of the discrepancies in the data, it was decided also to prepare the corresponding isomer (8) with the 5,8 dioxygenated pattern from serrulatenol (1). The reason for choosing the dihydro compound (6b) as a target for comparison was because the preparation of (8) from serrulatenol would involve reduction or isomerisation of the double bond. The compound (8) would also be useful because most correlations of stereochemistry of various serrulatane derivatives will probably involve removal of the non-phenolic hydroxyls and comparisons of the basic skeletons in either the 5,8 or 7,8 or 8 oxygenated skeletons.
It is also necessary to consider that the diterpenes from *E. duttonii* may be diastereomeric with other *Eremophila* serrulatanes. Indeed, such compounds have been isolated from the Caribbean sea whip *Pseudopterogorgia elisabethae*\textsuperscript{10,11,12}. The pseudopterosin (9) and the seco-pseudopterosin (10) (configuration unknown) both exist as mixtures of monoacetates and both possess the 7,8 dioxygenated pattern. The oxidised compounds (11) and (12), corresponding to the seco-pseudopterosin and pseudopterosin skeletons, have also been reported recently\textsuperscript{13a}. 

![Chemical structures](image1)

(9) 

(10) 

(11) 

(12)
A very recent paper reported some further examples related to the pseudopterosin class which are of significance since they possess 1,4 cis stereochemistry as shown below\textsuperscript{13b}.

The structure and relative stereochemistry of the tricyclic diterpenoid glycoside (9) was determined by X-ray crystallographic analysis, which enabled it to be identified as a β-linked xylose\textsuperscript{10}. The absolute configuration followed from the isolation and characterisation of the sugar as D-xylose\textsuperscript{19}. The structure of the seco-pseudopterosin (10), related to compound (9) by bond cleavage at the C5-C13 position and therefore presumably a biogenetic precursor of pseudopterosin, was suggested on the basis of comprehensive spectral analysis and upon chemical modification\textsuperscript{12}. The sugar component was identified as L-arabinose, however the absolute configuration of neither the sugar nor the aglycone has been determined. Both classes of compound are highly biologically active, possessing potent anti-inflammatory and analgesic properties. In fact, their potency has been shown to be equivalent to, if not in excess of, that of the existing drug, indomethacin\textsuperscript{10,11}. Their mechanism of pharmacological action\textsuperscript{10,11} also appears to be unique which makes these compounds particularly fascinating from a biological point of view. The pseudopterosins also represent a new chemical class of cell division inhibitors\textsuperscript{14}.\n
The isolation of the diterpenes from the _Eremophila_ species and the appearance in the literature of the interesting new seco-pseudopterosin diterpenes of the serrulatane class, but possessing different stereochemistry, prompted an interest in the synthesis of compounds of this type. In addition to the diterpenes described, many interesting sesquiterpenes with the 1,4-disubstituted tetrahydronaphthalene skeleton have been reported. Recently, some new o-catechol derived sesquiterpenes with anti-infective properties were isolated from _Guardiola platyphylla_, an arid-adapted plant\textsuperscript{15}. The parent compound (13) and the dimer (14) exist as both cis and trans isomers although only the cis isomers are shown. Two further examples are the calamene based sesquiterpenes (15) and (16), isolated from marine\textsuperscript{16} and terrestrial\textsuperscript{17} sources respectively, which have oxygenation only at the 7 position in the aromatic ring. Clearly, any synthetic approach to the serrulatane type diterpenes would probably be suitable for these related sesquiterpenes.
The two main groups of diterpenes of the 1,4-disubstituted tetrahydronaphthalene class possess the 5,8 and 7,8 dioxygenated patterns. Our attention was therefore focussed towards general synthesis with stereochemical control at the C1, C4 and C11 positions for elaboration to any diterpene of this type. The different substitution patterns lead to different peri-interactions so it was considered necessary to investigate the synthesis with one or two peri-substituents to try to determine what effect, if any, this has on the selectivity. Since 1,4-disubstituted tetrahydronaphthalenes can possess either 1,4 cis or trans relative configuration, a successful synthesis relies on controlling the stereochemistry at the benzylic positions.

The early synthetic methods reported in the literature have been relatively unsuccessful in the stereoselective preparation of compounds of this type. Two approaches to the synthesis of the sesquiterpene hydrocarbon (+)-calamenene (17) from menthone resulted in the formation of mixtures of cis and trans isomers\textsuperscript{18,19} which were produced due to the epimerisation of carbonyl intermediates.

\[
\text{OH}
\]
\[
\text{CO}_2\text{Et}
\]

Similarly, approaches to the hydroxycalamenenes, of which compound (16) is an example, produced little stereocontrol because the cyclisations relied on electrophilic aromatic substitution\textsuperscript{20,21}. A more successful method which involved the catalytic hydrogenation of the endo-cyclic double bond in
compound (18) was reported to give exclusively the cis isomer in good yield\textsuperscript{22}. However, metal/ammonia reduction of the same compound or equilibration of the hydrogenation product each led to mixtures of isomers\textsuperscript{22}. Other methods of generating the skeleton either lacked selectivity or offered no generality\textsuperscript{23,24,25}. Clearly, there is a need for routes which give good stereoselective control at the three chiral centres C1, C4 and C11 during the construction of the serrulatane skeleton and also for an understanding of the factors which influence this selectivity. The triol (2a) and the tetraol (2c) isolated from \textit{E. duttonii} would be suitable compounds for these studies. The primary hydroxyl group in the triol and the additional secondary hydroxyl group in the tetraol allow manipulation of the chiral centres C1 and C4, and the 7,8 dioxygenation pattern in both series allows some information regarding peri-interactions to be obtained. In addition it was decided to prepare some synthetic model compounds as simple analogues which might suggest routes which would be suitable for total synthesis. These compounds were chosen with two peri-substituents as a model for the diterpenes possessing the 5,8 dioxygenation pattern, or with no peri-substituents for comparison with the 5,8 and 7,8 systems which were available with the terpene compounds. It was envisaged that investigation with synthetic models, coupled with the studies on the terpenes themselves, would enable valuable information to be obtained regarding synthetic approaches to terpenoids of this class.

The final aspect of the project involved the development of chemistry suitable for the conversion of the relatively accessible tetraol (2c) from \textit{E. duttonii} into the aglycone of seco-pseudopterosin (10) and its isomers. Essentially, this approach required the inversion of configuration of the chiral centres C1 and C4 in the tetraol and the removal of the primary and secondary hydroxyl groups to obtain the aglycone of (10). It is probable that a considerable amount of this chemistry will be encompassed by the stereoselective correlation work
and the synthetic studies described above. In addition to establishing the absolute stereochemistry of both the aglycone and the sugar of the seco-pseudopterosins, the chemistry should provide access to a number of stereoisomers of the seco-pseudopterosin aglycone. These would be important for biological assay, both as the aglycones and their arabinose glycosides. Towards the conclusion of this project, three papers appeared in the literature concerned with the synthesis of these new marine diterpenoid glycosides. The pseudopterosin class was the target of one synthesis\textsuperscript{26} and the two more recent papers described approaches to the aglycone of the seco-pseudopterosin group\textsuperscript{27,28}. Aspects of these synthetic methods will be discussed later in the thesis.
CHAPTER 1

Derivatives of serrulatenol (1)

When the triol (2a) was first isolated as the triacetate (2b) from the leaves of *E. duttonii*, it was difficult to decide between the 5,8 and the 7,8 dioxygenation pattern in the aromatic ring. The triacetate (2b) was reduced with lithium aluminium hydride to give the parent triol (2a) which had 'H n.m.r. data very similar to those reported for (5)^9, possessing the known serrulatane skeleton and stereochemistry^8. (See Fig. 1.1, Appendix). Methylation with sodium hydride and iodomethane in dimethyl sulphoxide gave the dimethoxy alcohol (7), again with 'H n.m.r. data similar to those reported for this compound, however, the assignments of the benzylic protons H1 and H4 appeared to be interchanged. Certainly, with our compound, irradiation of the benzylic proton at δ3·20 collapses the ABX signal for the hydroxymethyl group. Similarly, in the triacetate (2b), the $\text{H}_2\text{O} (\text{CH}_2\text{OAC})$ protons are coupled to the benzylic proton at δ3·15.

\[
\text{(5)}
\]

\[
\text{(6b)}
\]

The optical rotation, $[\alpha]_D +15·5$ (c, 1·4), measured on the dimethoxy alcohol (7) of high purity by 300MHz 'H n.m.r. spectroscopy, was significantly different from that reported, $[\alpha]_D +5·6$, at the same concentration in chloroform.
further derivative, the dihydro deoxy compound (6b) gave good agreement of
the 'H n.m.r. values with those reported, assuming the assignments of the six
proton methyl doublet, 15-(Me)₂, and the three proton methyl doublet, 1-Me,
are reversed, although again, the rotation values were not in agreement. It
should be noted that the chemical shift of the C11-methyl resonance at 80.93
excludes the possibility of the compound being epimeric at C11, where a
significant upfield shift is observed¹² (80.71) in a 7,8 dioxygenated compound
known to have 1,4 trans relative stereochemistry.

Because of the differences mentioned and the fact that compounds with a 5,8
dioxygenated pattern are known⁷ in the serrulatane class, it was decided to
prepare (8) from serrulatenol (1) for a comparison of the 'H n.m.r. data. The
route chosen to obtain compound (8) is outlined in Scheme 1.1.
Scheme 1.1

(1) \[ \text{OMe} \text{OMe} \]
\[ \begin{array}{c}
\text{OH} \\
\text{H}_2\text{O}
\end{array} \]

(19) \[ \text{OMe} \]
\[ \begin{array}{c}
\text{OH} \\
\text{H}_2\text{O}
\end{array} \]

(20) \[ \text{OMe} \]
\[ \begin{array}{c}
\text{OH} \\
\text{H}_2\text{O}
\end{array} \]

+ \[ \text{OMe} \]
\[ \begin{array}{c}
\text{OH} \\
\text{H}_2\text{O}
\end{array} \]

(23) \[ \text{OMe} \]
\[ \begin{array}{c}
\text{OH}
\end{array} \]

(21a) \[ \text{OMe} \]
\[ \begin{array}{c}
\text{OH}
\end{array} \]

(22a) \( R=\text{H} \)
(22c) \( R=\text{Ac} \)

(8) \[ \text{OMe} \]
\[ \begin{array}{c}
\text{OH}
\end{array} \]
1.1 Palladium hydrogenolysis for allylic carbon-oxygen bond cleavage

It is known that allylic carbon-oxygen bonds may be cleaved via catalytic hydrogenolysis or metal/ammonia reduction.30 Some information regarding the hydrogenolysis was available. Abell29 had reduced serrulatenol (1) in ethyl acetate with 10% palladium-on-carbon and had isolated the hydrogenation product (24) in 66% yield together with the hydrogenolysis product (25) which was isolated in 20% yield.

Only a limited amount of serrulatenol was available and because the dimethyl ether of the hydrogenolysis product would be required for subsequent reactions (see Scheme 1.1), several exploratory reductions were done on the methyl ether (19) in order to optimise the yield of the air stable mono ether (22a). The methylation of serrulatenol (1) with sodium hydride and methyl iodide in dimethyl sulfoxide proceeded in moderate yield to give the methyl ether (19).

In the reduction trials, varying amounts of acetic acid were added to the vessel to try to improve the percentage of hydrogenolysis product formed. Strong acids were not investigated because of the possibility of epimerisation at C11, adjacent to the hemiacetal. This would be expected from enolisation of the
aldehyde which would be present in equilibrium with the hemiacetal (21a). The conditions required to produce optimum formation of the hydrogenolysis product were found when ethyl acetate containing 10% acetic acid was used as solvent. This improved the proportion of hydrogenolysis product by 10% to give approximately 30% of the desired compound, as determined by $^1$H n.m.r. spectroscopy. Although on a small scale, catalytic reduction with palladium-on-carbon under the optimised conditions yielded a mixture of the hydrogenation product (20) and the hydrogenolysis product (21a) in the relative proportions of 70% and 30% respectively, as determined from the $^1$H n.m.r. spectrum, upon scaling the reaction up, the results were found to be non-reproducible, with the proportion of hydrogenolysis product varying. This led to an overall modest yield of the hemiacetal (21a).

The hemiacetal (21a) was found to be a mixture of epimers at C18, in the ratio of approximately 2:1, when analysed by high field $^1$H n.m.r. spectroscopy (300 MHz). The hemiacetal proton (H18) of the major epimer appeared at $\delta$5.23 as a doublet of doublets with coupling to both the vicinal proton, H11, of 8.9Hz, and the hydroxy proton. The analogous proton for the minor epimer, which showed coupling only to the hydroxyl proton, appeared downfield at $\delta$5.59.
Epimerisation at C18 was presumably due to the acid catalysed opening of the hemiacetal to give the phenolic aldehyde (26), with subsequent cyclisation back to the hemiacetal resulting in a mixture of isomers being formed. The possibility that enolisation of the aldehyde led to epimerisation at C11 was excluded when the mixture of hemiacetals (21a) and (21b) was reduced with lithium aluminium hydride to give the diol (22a), which was homogeneous by 300MHz 'H n.m.r. spectroscopy. The main evidence for the structure of the diol (22a) was the OH absorption at 3600 cm\(^{-1}\) in the infra-red spectrum and the pair of doublet of doublets at \(\delta3.38\) and \(\delta3.62\) corresponding to the AB part of the ABX system for the hydroxymethyl group.

1.2 Metal/ammonia reduction for allylic carbon-oxygen bond cleavage

Because of the moderate yields for the hydrogenolysis reaction and limited access to quantities of serrulatenol (1), without further collection of plant material and isolation, it was decided to explore the dissolving metal reduction as an alternative route to the diol (22a). Although base catalysed epimerisation of the intermediate aldehyde at C11 was expected, it was hoped that the rate of isomerisation would be low compared with that of reduction and could be minimised by control of the reaction conditions. When compound (19) was reduced with lithium in ammonia, a mixture of isomeric alkenes (27) and (28), which were epimeric at C11, was obtained. The mixture was hydrogenated to give the major diol (22a) and its C11 epimer (22b), for which several signals were distinct from those of (22a) in the \(^1\)H n.m.r. spectrum of the mixture. The diols (22a) and (22b) appeared as a single spot by t.l.c., however they were found to be separable by chromatography after conversion to their diacetates, (22c) and (22d).
Several factors were taken into consideration when choosing the conditions for the dissolving metal reduction which would minimise epimerisation at C11 and avoid reduction of the aromatic ring. Once the aldehyde (29), which is in equilibrium with the hemiacetal, is formed, there is competition between epimerisation of the aldehyde and reduction to the alcohol. If the rate of reduction is faster than the rate of equilibration then minimal epimerisation at C11 will occur.

The presence of ethanol as the proton source should be expected to exert a significant effect on the outcome of the reaction. When ethanol is used as the proton source, ethoxide ions are produced which are less likely to enolise the
aldehyde than the very basic amide ions. Although ethanol promotes the reduction of aromatic rings, it was expected that the reduction of the allylic acetal and the subsequent reduction of the aldehyde, would be much faster. The reaction time was kept relatively short to avoid reduction of the aromatic ring and little reduction of the ring was observed with a reaction time of less than fifteen minutes. Other factors which were found to be important were the order of addition of reagents and the presence or not of an added proton source. Under conditions favouring equilibration, e.g. when the reaction was done in the absence of ethanol and the compound was added to the lithium in ammonia, an approximately 1:1 mixture of epimers was obtained. However, when ethanol was present under the most suitable conditions, the dissolving metal reduction of (19), followed by catalytic hydrogenation, gave a 10:1 mixture of the diol (22a) and its C11 epimer (22b). Fortunately, conversion to the diacetates was unnecessary for separation because recrystallisation gave a pure sample of the desired compound (22a). Because identical isomers were obtained from both the catalytic hydrogenolysis route and from the metal/ammonia sequence (reduction favouring non-equilibration), it can be safely concluded that the configuration at C11 in the reduction products is the same as that in the natural product, serrulatenol (1).

1.3 Conversion of the diol (22a) to the dihydro deoxy derivative (8)
The final steps in the sequence involve the selective methylation of the phenolic hydroxyl group followed by deoxygenation of the primary alcohol to obtain 5,8-dimethoxyserrulatane (8). A possible alternative to this route would be preparation of the ditosylate then reduction with lithium aluminium hydride to give the deoxygenated product (30) followed by methylation to yield compound (8). In this way, the need for the selective methylation of the diol (22a) would be eliminated.
It was thought that lithium aluminium hydride reduction of the ditosylate would, in addition to deoxygenating the primary alcohol, reduce the phenolic tosylate back to the parent phenol since, in an earlier experiment, some serrulatenol (1) was recovered from its tosylate by reduction with lithium aluminium hydride. However, when the diol (22a) was treated with two equivalents of tosyl chloride in pyridine, the major product obtained was the relatively non-polar ether (31)

![Chemical structures](image)

The main evidence for the structure came from the mass spectrum, for which the correct molecular ion of 316 was obtained, and the infrared spectrum which showed ether and aromatic absorption bands and little else. The 'H n.m.r. spectrum also supported the proposed structure. The formation of this ether can be explained if tosylation of the primary hydroxyl group occurred relatively quickly and was followed by intramolecular displacement by the phenoxide ion. This route was therefore abandoned in favour of the original sequence.

The diol (22a) was successfully methylated selectively at the phenolic hydroxyl group, albeit in poor yield, to give the dimethoxy alcohol (23). The position of methylation was supported mainly by the chemical shifts of the methoxyl
groups at δ3·65 and δ3·78. In the case of aliphatic methyl ethers, there is generally a significant upfield shift observed in the chemical shift of the methoxyl group.

Deoxygenation of the primary hydroxyl group was then carried out by a standard method which involves conversion to a sulphonate derivative, in this case a mesylate, and reduction with a source of hydride ion such as lithium aluminium hydride. Mesylation of the dimethoxy alcohol (23) proceeded in high yield to give the methane sulphonate (32). Although this compound was not fully characterised, it was found to be of high purity by high field ¹H n.m.r. spectroscopy with the methyl group of the sulphonate resonating at δ2·81 and the AB part of the ABX system adjacent to the sulphonate being shifted downfield to δ3·94 and δ4·12 as expected.

Although there was no doubt that the mesylate (32) had been obtained, treatment of this compound with both lithium aluminium hydride and lithium triethylborohydride (super-hydride) failed to produce any of the reduction product (8). There appeared to be no rationale for the lack of reactivity of this compound toward the reducing agents. So, without further investigation, it was decided to explore an alternative method for the
deoxygenation which required conversion of the mesylate to the iodide (33) with subsequent reduction with tri-n-butylstannane to give the desired product (8). The radical induced deoxygenation of primary alcohols via alkyl halides is well known. Because of the limited amount of the mesylate (32) available, it was necessary to explore the chemistry using the dimethoxy alcohol (34), a derivative of the triol (2a) from \textit{E. duttonii}, as a model. The preparation of this compound is discussed in Chapter 2. The tosylation of the primary hydroxyl group in (34) proceeded well to give compound (35), as evidenced by the molecular ion at 502 in the mass spectrum.

The 'H n.m.r. spectrum also supported the formation of the tosylate with a resonance for the aromatic methyl group at δ2.44, the characteristic doublet of doublets for the four aromatic protons at δ7.32 and δ7.79 and the downfield shift of the non-equivalent methylene protons adjacent to the tosylate group to δ3.81 and δ4.21. An attempt to prepare the bromide directly from the alcohol with phosphorous tribromide was unsuccessful, however the iodide (36) was prepared readily from the tosylate (35) by treatment with sodium iodide in dry acetone. Reduction of the iodide (36) with tri-n-butylstannane then gave the dehalogenated product, 7,8-dimethoxyserrulatane (6b) in moderate yield. The success of the reaction was confirmed by characterisation of the product. In
particular, the appearance of a methyl doublet at 81.17 corresponding to the C1-methyl group was observed in the 'H n.m.r. spectrum.

Since this method of reduction to the methyl group was successful for the triol series, it was now applied to the mesylate (32), originally prepared from serrulatenol (1). Using the same reagents described above, the iodide (33) was prepared in high yield. The structure of the product was supported by the spectral data, in particular, the molecular ion at 458 in the mass spectrum. Subsequent treatment of the iodide (33) with tri-n-butylstannane gave the desired product (8) with the diagnostic feature being, once again, the appearance of a methyl doublet at 80.76 in the 'H n.m.r. spectrum corresponding to the C11-methyl group. Decoupling experiments provided further evidence for the correct assignment of the resonances. When the signal for H1 at 63.12 was irradiated, the methyl doublet at 61.12 corresponding to the C1-methyl collapsed. In the reverse experiment, irradiation of the signal at 61.12 caused the multiplet at 63.12 to collapse to a doublet, with a residual coupling of 5.7Hz.

A comparison of the 'H n.m.r. spectra of compound (8) from serrulatenol (1) with the corresponding dihydro deoxy compound (6b) prepared from the triol (2a) immediately revealed that the two compounds were different. Most noticeably, the chemical shift of the C11-methyl for (6b) was 60.93 compared with that for compound (8) at 60.76. The downfield shift for H4 from 62.52 in (6b) to 62.80 in (8), caused by the methoxyl at C5, together with the chemical shift differences for the aromatic protons (66.50 in (8) and 66.71 in (6b)) excludes the 5,8-dimethoxy pattern for compound (6b).

Further evidence to support the 7,8-dioxygenated pattern in the triol series was obtained by performing some Nuclear Overhauser Enhancement experiments
on the dimethoxy alcohol (7), also derived from the triol (2a). Irradiation of the aromatic proton at δ 6.76 resulted in the strong enhancement of both the benzylic methine proton H4 at δ 2.54 and the aromatic methyl group at δ 2.22. Several other signals were also enhanced, although not as significantly. In the reverse experiment, irradiation of the methine proton H4 at δ 2.54 resulted in the enhancement of the aromatic signal at δ 6.76.

![Structure of 7](image)

It is therefore concluded that the triol (2a) from *E. duttonii* has the same structure as compound (5) isolated from *E. linearis* Chinnock⁹.
Once the structure of the triol (2a) was established, it was necessary to determine the configuration of the tetraol (2c) by stereochemical correlation with (2a). It was expected that the stereochemistry of the skeleton of each of the two compounds would be the same since they are from the same plant species and thus, would probably have been generated via the same biosynthetic pathway. The dihydro deoxy compound (6b) was chosen as a suitable target for comparison of the basic skeletons in each series. Scheme 2.1 outlines the proposed route for the preparation of the derivative (6b) from the triacetate (2b).

The unsaturated triacetate (2b), obtained after acetylation and purification of the crude extract from the leaves of E. duttonii, had been partially characterised in an earlier study. (T. Webb, Honours Thesis, Adelaide University, 1986). Extraction of further quantities of (2b) for the present study enabled full characterisation of the compound. Catalytic hydrogenation of (2b) with platinum oxide gave the dihydro product (37) which was also characterised previously (T. Webb, Honours Thesis, Adelaide University, 1986). Lithium aluminium hydride reduction of the triacetate (37) gave the triol (38). Base hydrolysis was found to be less satisfactory than reduction with lithium aluminium hydride for removal of the acetate groups. Analysis of the crude product by 'H n.m.r. (60MHz) spectroscopy, in which the absence of acetate peaks was observed, and the t.l.c., which confirmed the consumption of starting material, indicated that the reduction was complete.
Therefore, due to the susceptibility of the triol to oxidation, the selective methylation was carried out immediately without purification. The triol (38) was treated with two equivalents of sodium hydride and an excess of iodomethane in dimethyl sulfoxide to yield to dimethoxy alcohol (34) in moderate yield. The structure of the dimethoxy alcohol (34) was supported by
the mass spectrum, with a molecular ion at 348 and the presence of the two methoxyl resonances at 83.80 and 83.87 in the 'H n.m.r. spectrum.

Since none of the compounds in this series so far had been solids, it was decided to try to obtain a solid derivative of the alcohol (34) which could be recrystallised to high purity. Viscous oils are difficult to completely purify as small amounts of impurity coinciding with the compound by t.l.c. remain after chromatography. More important than the purity aspect, if a suitable crystal could have been prepared, it would have enabled an X-ray crystal structure to be obtained. The problems associated with characterising the triol (2a) were outlined in Chapter 1 and arose from what appears to be errors in rotations and 'H n.m.r. assignments in the literature. The derivatives (34a) - (34e) were prepared and all were found to be oils except for the 2-anthraquinonecarboxylate (34e). It crystallised as a pale yellow solid, however, all attempts to produce a crystal suitable for X-ray crystal analysis were unsuccessful.
A β-glycoside of the alcohol (34) was also prepared as the tetrapivaloate ester (34f), in the hope that a solid would be obtained. The glycosylation reaction was based on methodology developed previously\textsuperscript{33,34a,b} whereby, under strictly anhydrous conditions, the dimethoxy alcohol (34) was treated with 1.2 equivalents of ortho ester in the presence of 4 equivalents of boron trifluoride-etherate for 15 minutes. Purification yielded the tetrapivaloyl-β-D-glucopyranoside (34f) in moderate yield.

Since it was found to be an oil, the product was not fully characterised, however, the structure and purity were confirmed by \textsuperscript{1}H n.m.r. spectroscopy. The resonances of the terpene unit were distinct from those of the sugar, enabling good data to be obtained. The tert-butyl groups of the pivaloate esters occurred at different chemical shifts of $\delta$1.12, 1.15, 1.18, and 1.21. The peaks
corresponding to each of the remaining sugar protons were readily assigned, with the anomeric proton H1' appearing at $\delta_{4.60}$ with coupling of $8.0\text{Hz}$ to H2'.

\[
\text{Piv} = \begin{array}{c}
\text{PivO} \\
\text{PivO} \\
\text{PivO}
\end{array}
\]

Despite the failure to prepare a useful solid, chromatography of the derivatives proved to be an effective method of removing trace impurities such that upon hydrolysis, the pure alcohol was recovered. The acetate (34g) was finally chosen as the derivative of preference as it could be further purified by distillation subsequent to chromatography. After the acetate (34g) was hydrolysed to yield the alcohol (34), esterification of (34) with tosyl chloride in pyridine gave the tosylate (35) for which the data has already been discussed (Chapter 1).

Lithium aluminium hydride reduction of the tosylate (35) resulted in the formation of the desired reduction product (6b). The specific rotation of this compound was found to be $-10.0$ (c, 0.2). The diagnostic feature of the 'H n.m.r. spectrum was the appearance of an upfield methyl doublet at $\delta_{1.17}$ corresponding to the C1-methyl group. Decoupling experiments once again confirmed the assignments of the benzylic protons H1 and H4. When the
signal for H1 at δ3·12 was irradiated, the doublet methyl at δ1·17 collapsed and the reverse experiment supported this result. Attempts to establish the coupling constants of the ring protons were unsuccessful as there were problems identifying the exact region to decouple in the complicated aliphatic region of the spectrum.

Now that the 7,8-dimethoxyserrulatane had been prepared from the triacetate (2b) and characterised, it remained to convert the tetraacetate (2d) into the corresponding derivative for comparison of the basic skeletons of the two compounds. A considerable amount of the chemistry described in this chapter will be useful for this interconversion, which is detailed in the following chapter.
CHAPTER 3
Derivatives of the tetraacetate (2d)

Support for the structure of the stable tetraacetate (2d) came from the spectral data (T. Webb, Honours Thesis, Adelaide University, 1986). H.R.M.S. established the molecular formula of the tetraacetate (2d) as C_{28}H_{38}O_{8}. The 'H n.m.r. spectrum showed acetate methyl resonances at δ2.06 (superimposed phenolic acetates), 2.28 and 2.36, which were confirmed by absorptions in the IR spectrum at ν_{max} 1760, 1730 cm\(^{-1}\). The 'H n.m.r. spectrum also showed resonances for a secondary methyl (δ0.61), two vinylic methyls (δ1.62 and 1.70) an aromatic methyl (δ2.15), an acetoxy methyl group (ABX system, δ3.76 and 4.52), a vinylic proton (δ5.12) and one aromatic proton (δ6.66). The benzylic protons appeared at δ3.28 and δ3.07, with the former being coupled to the protons of the hydroxy methyl group. The complex one proton multiplet at δ5.33 was assigned to a methine proton attached to a carbon bearing the additional acetate group. The position of this acetate group (C3) was confirmed by decoupling experiments performed on the dihydro product obtained by catalytic hydrogenation of the tetraacetate (2d). A successful stereochemical correlation of the tetraol (2c) with the triol (2a), both isolated from \textit{E. duttonii}, would enable the configuration of the skeleton of the former compound to be established. The proposed route to obtain the dihydro deoxy compound (6b), required for comparison with the corresponding derivative from the triol series, is outlined in Scheme 3.1. The unsaturated tetraacetate (2d) was isolated from the crude extract after acetylation and had been characterised in an earlier study (T. Webb, Honours Thesis, Adelaide University, 1986). As with the triol (2a), the position of the phenolic hydroxyl groups was not established and no information regarding the stereochemistry was available.
Scheme 3.1
A fraction rich in the tetraacetate (2d) but containing approximately 30% impurity was hydrogenated with platinum oxide in ethyl acetate to give the dihydro product (39). Chromatography of the crude product removed the impurities to give a pure sample of (39) which had been partially characterised previously. The diagnostic feature of the $^1$H n.m.r. spectrum was the appearance of a six proton doublet at $\delta$0.86 corresponding to the C15-methyl groups. Lithium aluminium hydride reduction of the tetraacetate (39) gave the tetraol (40). The mass spectrum of the crude product gave the expected molecular ion at 336 and the $^1$H n.m.r. spectrum (60MHz) showed the absence of peaks in the acetate region ($\delta$2.0 - 2.2) which, combined with t.l.c. analysis, confirmed that the starting material had reduced completely. Once again, the possibility of oxidation to quinonoid type products meant that direct methylation without further purification was desirable. The selective methylation of the phenolic hydroxyl groups was achieved by treatment of (40) with two equivalents of sodium hydride and an excess of iodomethane in dimethyl sulphoxide. The evidence to support the structure of the product (41) was provided by the mass spectrum with a molecular ion at 364, and the presence of two methoxy singlets at $\delta$3.80 and $\delta$3.85 in the $^1$H n.m.r. spectrum. Upon D$_2$O exchange, no change was observed in the spectrum, however the presence of hydroxyl functionality was confirmed by a strong OH stretching band in the infrared spectrum.

The selective tosylation of the primary hydroxyl group in the dimethoxy diol (41) was then carried out using one equivalent of tosyl chloride with pyridine in carbontetrachloride. The structure of (42) was supported, once again, by the mass and $^1$H n.m.r. spectra. The peaks for the aromatic methyl group at $\delta$2.44 and the aromatic protons at $\delta$7.32 and $\delta$7.77 confirmed the presence of the tosylate group, with each of the non-equivalent methylene protons at C20 appearing as a doublet of doublets at $\delta$3.84 and $\delta$4.31. However, when the
lithium triethylborohydride reduction of the mono tosylate (42) was carried out, a mixture of products was obtained. The major product corresponded to the parent alcohol (41) which suggested unexpected hydride attack predominantly at the sulphur of the tosylate group. A minor component with a molecular ion of 348, which is consistent with the desired reduction product, was also isolated. However because of the low yield and poor purity of this product, chemistry proceeding via the iodo compound which was used to obtain the dihydro deoxy compound (8) in the serrulatenol series (Chapter 1), was employed.

Treatment of the tosylate (42) with sodium iodide in acetone gave the iodo derivative (45). The expected molecular ion at 474 was observed in the mass spectrum, along with an upfield shift for the non-equivalent methylene protons in the 'H n.m.r. spectrum, which appeared at δ3.17 and δ3.64. Tri-n-butylstannane reduction of the iodide (45) produced the dehalogenated compound, the dimethoxy alcohol (43b), in good yield. This compound was found to be crystalline, however attempts to produce a crystal suitable for X-ray analysis were unsuccessful. The mass and infrared spectra both supported the structure, however the 'H n.m.r. spectrum was particularly useful with the most diagnostic feature being the three proton methyl doublet at δ1.26
corresponding to the C1-methyl group. D$_2$O exchange revealed the signal for the OH group at $\delta$1.57.

Extensive decoupling experiments enabled the correct assignment of chemical shift and, in addition, enabled the coupling data to be obtained for some, but not all, of the ring protons. Irradiation of the signal at $\delta$3.25 for H1 collapsed the methyl doublet at $\delta$1.26 and also affected a two proton multiplet at $\delta$2.08. The signal for H1 appears as a five line multiplet, which suggests an equivalent coupling of 7Hz to the C1 methyl group and one of the non-equivalent protons at C2 to give the five line pattern with a small (1Hz) coupling to the other proton. Irradiation of the methyl doublet at $\delta$1.26 collapsed the signal at $\delta$3.25, however the resolution of the residual pattern was poor and it was not possible to obtain the individual coupling constants of H1 to H2$\alpha$ and H2$\beta$. Irradiation of the other benzylic proton H4 at $\delta$2.79 resulted in the collapse of the signal at $\delta$4.31 to a doublet of doublets with residual couplings of 11.0Hz and 2.8Hz. Irradiation of the two proton multiplet at $\delta$2.08 affected H1 at $\delta$3.25 and H4 at $\delta$2.79 which was collapsed to a doublet with a residual coupling of 4.5Hz. This suggests that the multiplet at $\delta$2.08 comprises H11 and one of the H2 protons. Further to this, the proton at the chiral centre C3 is coupled to H4 with a coupling constant of 4.5Hz and to the protons at C2 with couplings of 2.8 and 11.0Hz. This information will be useful in deducing the relative stereochemistry at this chiral centre once the stereochemistry of the skeleton has been established.

The deoxygenation of the secondary hydroxyl group in (43b) must now be carried out to complete the sequence. The deoxygenation of secondary alcohols by reaction of the derived dithiocarbonate esters with tri-n-butylstannane has been shown to be a general reaction of value in the synthesis and modification
of natural products\textsuperscript{35a,b}. It was therefore decided to prepare the methyl xanthate ester (44) from the alcohol (43b). Initially, when carbon disulphide was used as solvent and the reaction was stirred for 24 hours, the yield of the xanthate ester (44) obtained was only 30%. This yield was improved by using tetrahydrofuran under reflux and by employing imidazole, a proton transfer catalyst. Sequential treatment of the alcohol (43b) with carbon disulphide and methyl iodide in the presence of sodium hydride and a catalytic amount of imidazole in refluxing tetrahydrofuran, then led smoothly to the formation of the methyl xanthate ester (44) in 56% yield. Although the product was not fully characterised due to lack of material, the spectral data confirmed the structure. The molecular ion was observed at 438 in the mass spectrum and the \textsuperscript{1}H n.m.r. spectrum showed the presence of the xanthate methyl singlet at \( \delta 2.76 \) together with the multiplet corresponding to H3, significantly downfield at \( \delta 6.14 \).

The xanthate ester (44) was reduced with tri-n-butylstannane to give a mixture of three products. The highest Rf product was identified as the desired deoxygenated product, 5,8-dimethoxyserrulatane (6b) and was isolated in 35% yield. The middle Rf product, which constituted approximately 30% of the mixture, was impure and the 300 MHz \textsuperscript{1}H n.m.r. spectrum indicated the presence of some starting material. The fraction was not investigated further. The low Rf product, isolated in 16% yield, was found to be the trimethoxy compound (46), which was produced in the reaction since it was absent from the dithiocarbonate precursor.
Confirmation of the proposed structure came from a molecular ion at 362 in the mass spectrum and a diagnostic 'H n.m.r. spectrum which showed three methoxyl singlets at 83.41, 83.79 and 83.85, with the upfield signal presumably corresponding to the aliphatic C3 methoxy group. The formation of this methoxy compound in the reaction is difficult to rationalise. In cases where the alkyl radical is relatively unstable, for example in the case of a primary alcohol, the alcohol may be regenerated in the reduction\textsuperscript{35a,35b}. This was explained by the "1,2" addition of tri-n-butylstannane (path B) competing with C-O fragmentation (path A) in Scheme 3.2.

When the substituent X is S-Me, the intermediate radical (47) is stabilised and fragmentation (path A) is favoured. However, with the dithiocarbonate of octadecan-1-ol, where the "1,2" addition probably occurred to give the intermediate (48), the alcohol was obtained on work-up. The formation of the ether in the present case could possibly arise from an intermediate like (48) by an unknown mechanism. We are unaware of a literature precedent for the formation of methyl ethers as by-products in the tri-n-butylstannane reduction of methyl xanthate esters. Therefore, it was decided to check the validity of this result by repeating the reaction. This required the repetition of many of
the steps in Scheme 3.1 and proved to be time consuming, but the experiment was eventually repeated and the results were found to be reproducible.

Scheme 3.2

\[
\begin{align*}
(A) & \quad \text{SnBu}_{3} + \text{R}^{\prime} + \text{O} & \xrightarrow{} & \text{SnBu}_{3} \\
\text{RO} - \text{C} - \text{X} & \quad (47) \\
(B) & \quad \text{SnBu}_{3} \\
\text{RO} - \text{C} - \text{X} & \rightarrow \text{ROH} \\
\text{H} & \quad (48)
\end{align*}
\]

The dihydro deoxy compound (6b) produced from the tetraacetate (2d) via Scheme 3.1 was compared with the corresponding derivative prepared from triacetate (2b) via Scheme 2.1. The two compounds were found to be almost identical in all respects. Although the specific rotation, \([\alpha]_{D}\), of (6b) produced via the tetraol series was -8.2 (c, 0.3) compared with -10.0 (c, 0.2) for the derivative (6b) from the triol series, the spectral data for the two compounds were in excellent agreement which was believed to be sufficient evidence for assigning the structure. The minor discrepancy in the rotation data was presumably due to the small samples available.
Thus, from the results of the stereochemical correlation of the tetraol (2c) with the triol (2a), both isolated from *E. duttonii*, it may be concluded that the tetraol (2c) has the same configuration of the chiral centres C1, C4 and C11 as the triol (2a). From an analysis of the coupling constants for the ring protons in the dimethoxy alcohol (43b) it is also possible to deduce the relative stereochemistry of the secondary hydroxyl group at C3 in the tetraol (2c). Because the relative stereochemistry of the 1,4 substituents in the tetraol (2c) is trans it is assumed that the favoured conformation is dipseudoaxial to minimise peri-interactions with the substituent at C8 in the aromatic ring. This infers that the benzylic proton H4 is in a pseudoequatorial position. The coupling constants for the proton H3 in compound (43) were found to be 4.5Hz to H4 and 2.8 and 11.0Hz to the two H2 protons. This is consistent with two small axial-equatorial interactions and one large axial-axial interaction for H3. This implies, assuming the ring is in a half-chair conformation, that H3 is an axial proton and therefore, that the hydroxyl substituent at C3 is equatorial. It can be concluded from this analysis that the relative stereochemistry of the 3,4 substituents is cis and that the absolute configuration of the tetraol (2c) from *E. duttonii* is as shown.
CHAPTER 4
Synthetic Studies

The lack of stereocontrol and generality of early synthetic approaches to sesquiterpenes of the 1,4 disubstituted tetrahydronaphthalene class and the isolation of many interesting diterpenes of the serrulatane class, from both marine and plant sources in recent years, prompted an interest in the synthesis of systems of this type by novel methods. This was particularly relevant in view of the fact that this research has been concerned with establishing the structures of the triol (2a) and the tetraol (2c), both of which possess the known serrulatane stereochemistry of the skeletons. The isolation of the highly biologically active seco-pseudopterosins, of which (10) is an example, has also generated considerable interest in the synthesis of this class of compound.

\[
\text{(2a) } R=H \\
\text{(2c) } R=OH
\]

The two main groups of diterpenes of the serrulatane class possess the 5,8 and 7,8 dioxygenated patterns, therefore the primary objective was general synthesis with stereochemical control at C1, C4 and C11 for elaboration to any
diterpene of this type. It was considered likely that the peri-interactions produced by the different substitution patterns would affect the selectivity so it was decided to investigate the synthesis with a variety of peri-substituents to explore this hypothesis. Gaining an understanding of the factors which influence the selectivity was considered to be a vital aspect of the study. In addition to the triol (2a) and the tetraol (2c), which were suitable compounds for part of the study, it was also necessary to prepare some synthetic analogues which would enable the range of peri-interactions to be encompassed and would suggest possible routes for total synthesis.

This chapter is structured in the following way. Firstly, a discussion of some aspects of the recently reported literature methods for the synthesis of dihydroxyserrulatic acid (4), the pseudopterinosin (9) and the seco-pseudopterinosin (10) classes of diterpenes and their limitations in establishing the 1,4 trans relative stereochemistry will be presented. Secondly, two approaches which are conceptually different from those described in the literature will be explored as possible methods for constructing the serrulatane skeleton with stereochemical control at C1, C4 and C11. One involved equilibration and kinetic resolution as the key steps for controlling the stereochemistry, and the other relies on kinetic resolution and hydrogenolysis. Since all of the emphasis thus far has been on establishing 1,4 trans stereochemistry, the final synthetic aspect of the project focuses on methods for obtaining the complementary 1,4 cis configuration. This aspect of the chemistry is potentially useful for the conversion of the tetraol (2c) into the aglycone of the seco-pseudopterinosin (10) and its isomers. Some interesting results were obtained by catalytic hydrogenation and metal/ammonia reduction of the methylene derivatives in each of the natural product and synthetic series.
Methods for establishing 1,4 trans stereochemistry

4.1 Review of the recent literature methods with emphasis on control of the stereochemistry at the benzylic positions

The first synthesis which appeared in the literature was concerned with the preparation of the tricyclic pseudopterosin skeleton\textsuperscript{26}, in which the sequence proceeded through a 1,4 disubstituted 1,2,3,4-tetrahydronaphthalene derivative. Starting from (S)-(−)-limonene (49), the key intermediate was produced, as a mixture of isomers, in approximately 15 steps. The important step in the synthesis involved the titanium tetrachloride catalysed reaction of (50) with compound (51), as shown in Scheme 4.1. A rationale for the mechanism was presented in the paper\textsuperscript{26}.

Scheme 4.1
'H n.m.r. evidence suggested that the intermediate condensation products had not undergone aromatisation under the influence of titanium tetrachloride and the mixture was therefore treated with sodium methoxide which gave the cis and trans phenols (52a) and (52b) in the ratio of 3:2. The synthesis was lengthy and not very efficient overall since the key reaction lacked stereochemical control and several steps were required to further elaborate the intermediates (52a) and (52b) to the pseudopterosin skeleton, including Friedel-Crafts alkylation and Baeyer-Villiger oxidation. One positive feature was the successful formation of the glycoside of the C8 phenolic hydroxyl group, with the β-glycoside being prepared in acceptable yield with good stereoselectivity.

Another very recent literature method provided an enantioselective approach to analogues of the pseudopterosin family of structures\textsuperscript{36}, starting from (S)-carvone. The intermediate (53), with trans stereochemistry established, was further modified to give compound (54) which underwent a Diels-Alder reaction with an appropriate dienophile to generate the aromatic ring, during which the 1,4 trans configuration was preserved. Although more efficient in terms of stereochemical control, the synthesis was still lengthy, requiring in excess of 25 steps.

\begin{align*}
\text{(53)} & \quad \text{(54)}
\end{align*}
The remaining two literature approaches to be reviewed are more relevant to this study since they are concerned specifically with the synthesis of the bicyclic seco-pseudopteratin skeleton rather than the pseudopteratin series. They are of particular importance because they represent novel methods for controlling the benzylic stereochemistry which are both interesting and efficient.

The first is an elegant tetralone-based route, the target of which was the aglycone of the seco-pseudopteratin class of compounds\textsuperscript{27}. The stereochemistry of the C4 and C11 positions (serrulatane numbering is used throughout this discussion) was established first, then the final stereocentre at C1 was generated by double bond reduction using "intramolecular ionic hydrogenation" as a new method for controlling benzylic stereochemistry. Treatment of the ditert-butylsilylether (55) with trifluoroacetic acid effected the reduction of the double bond with excellent stereochemical control to give the 1,4 trans configuration. Subsequent desilylation with tetrabutyl-ammonium fluoride gave the key intermediate (56). The mechanism of the intramolecular ionic hydrogenation is consistent with preferential hydride transfer to one face of the tertiary benzylic cation formed by protonation of the double bond, resulting in 1,4 trans stereochemistry as shown in Figure 4.1.
The second paper, which also appeared recently\textsuperscript{28}, was concerned with the synthesis of dihydroxyserrulatic acid (4), but the chemistry could probably be adapted for the synthesis of the seco-pseudopterins. The method utilises some characteristic properties of (arene) chromium complexes to control the stereochemistry of the products. The stereoselectivity of the reactions are dependent upon attack of the reagents from the side opposite the chromium which, with its ligands, effectively blocks one face of the molecule.

The key step for establishing the 1,4 relative stereochemistry relied on directed reduction, again employing "ionic hydrogenolysis", but in this case the reaction is intermolecular rather than intramolecular as described above. The endo-complex (57), which was formed as a 3:1 mixture of epimers at C11 favouring the isomer shown, was treated with methyl lithium. Reaction at the face opposite the chromium gave the alcohol (58) which was reduced with trimethylsilane and trifluoroacetic acid to effect the "ionic hydrogenolysis". This resulted in reduction of the tertiary benzylic hydroxyl group with
inversion of configuration to give the required 1,4 trans stereochemistry in (59), suitable for further elaboration to dihydroxyserrulatic acid (4).

4.2 An approach involving equilibration and kinetic resolution as key steps in the synthetic strategy

Two approaches aimed at controlling the 1,4 trans stereochemistry, which are conceptually different from the literature approaches discussed, were investigated as part of this study. The first approach, outlined in Scheme 4.2, involves equilibration and kinetic resolution as key steps for controlling the stereochemistry. Equilibration of the exocyclic ketone (60) should favour the thermodynamic trans product. It was also expected that the presence of peri-substituents in the ring would lead to enhanced selectivity. It was hoped to
avoid chromatography by having the selectivity high enough to enable recrystallisation of the product to high purity. It was proposed to convert the ketone (60) to the allylic alcohol (61) via the corresponding ester and to perform a Sharpless epoxidation with the aim of achieving a kinetic resolution. The high selectivity of the Sharpless epoxidation coupled with a successful kinetic resolution would produce a single enantiomer of the epoxide (62).

Scheme 4.2

Kinetic resolution via Sharpless epoxidation has certainly been successful for secondary allylic alcohols\(^\text{37}\), however it is not known whether it can be achieved in a compound possessing a chiral centre more remote from the
reaction site. It was hoped that the preferred conformation might favour
greater selectivity in the formation of the complex in the Sharpless reaction\textsuperscript{38a,38b}.

Assuming the kinetic resolution is successful, elaboration of the product to
give the appropriate side chain could be achieved by preferential reductive
opening of the epoxide at the more substituted carbon atom. A method for the
regioselective opening of epoxy alcohols at the more substituted carbon atom
using lithium borohydride in the presence of titanium tetraisopropoxide has
been reported\textsuperscript{39}. This reaction appears to involve complexation of the epoxy
alcohol with titanium which results in a weakening of the C-O bond more
distant from the hydroxyl group.

The success of this approach is therefore initially dependent upon good
selectivity in the equilibration step. In order to explore the equilibration, it was
decided to use the series of model compounds with methyl substituents in the
5,8 positions in the aromatic ring. This series was chosen as a model for the 5,8
dioxygenated diterpenes because it is more accessible than the methoxy series
and also possesses greater steric requirements, although polar effects were not
considered. Thus, if the chemistry is not highly selective in the dimethyl
series then it would presumably be even less selective for the dimethoxy series
assuming peri-effects influence the selectivity. Other substitution patterns, e.g.
7,8 dimethoxy, would also be expected to be less favourable. Scheme 4.3
outlines the sequence of reactions used to prepare the exocyclic ketones
necessary for this study.
The Friedel-Crafts reaction of γ-xylene (65) and γ-valerolactone (64) yielded the carboxylic acid (66) which was cyclised with polyphosphoric acid to the α-tetralone (67) as described in the literature \textsuperscript{42a,b}. The Wittig reaction of the α-tetralone (67) with ethyltriphenylphosphonium bromide and potassium tert-butoxide gave exclusively the (E)-isomer of the ethylidene compound (68) in moderate yield. The evidence for the formation of a single isomer,
homogeneous by t.l.c., came from the presence of a single one proton multiplet at $\delta 5.60$ in the $'H$ n.m.r. spectrum corresponding to the vinylic proton H1' (systematic numbering is used throughout this discussion). When the corresponding ethylidene compound was prepared in the series with no peri-substituents in the aromatic ring as a trial reaction, a mixture of (E) and (Z) isomers, (71) and (72) was produced, in the ratio of 5:2. The isomers were separable by chromatography and the signals for the vinylic protons H1' in the $'H$ n.m.r. spectrum were distinct, occurring at $\delta 5.52$ for the (Z)-isomer (72) and downfield at $\delta 6.07$ for the (E)-isomer (71), presumably due to the deshielding effect of the aromatic ring. The exclusive formation of the (E)-ethylidene derivative (68) can be attributed to the presence of a methyl substituent at the C8 position in the aromatic ring, which gives rise to significant steric interactions in the intermediate leading to the (Z)-isomer, preventing its formation in favour of the less hindered (E)-isomer.

![Diagram](image)

(71)  (72)

The alkene (68) was then hydroborated by treatment with borane-methyl sulphide complex followed by oxidative work-up to give a mixture of stereoisomeric alcohols (69). The complexity of the $'H$ n.m.r. spectrum and t.l.c. analysis after chromatography indicated the presence of isomers. The appearance of a one proton multiplet at $\delta 3.87$, corresponding to the methine proton H1, confirmed that the reaction had proceeded as expected. Therefore, without further characterisation, the mixture of alcohols was oxidised directly
with Jones reagent to yield the cis and trans methyl ketones (70a) and (70b). The major diagnostic feature in the 'H n.m.r. spectra of the products was the presence of a singlet methyl at δ2.08 in (70a) and δ2.22 in (70b), corresponding to the C1-methyl groups. The IR spectra also supported the structures, with absorptions at 1708 cm\(^{-1}\).

Both compounds were crystalline, but it was the cis isomer (70a) which gave crystals suitable for X-ray analysis, thereby allowing the unambiguous assignment of relative stereochemistry to each isomer. Despite the eludication of the coupling constants for the ring protons in (70a) and (70b), we were unable to assign the relative stereochemistry on the basis of this data alone. This fact once again emphasises the problems associated with attempting to assign the relative configuration of compounds of this type from 'H n.m.r. data. The X-ray crystal structure of the higher Rf cis isomer (70a) showed the preferred conformation\(^{40a,b}\) to be half-chair with the larger methyl substituent occupying a pseudo-axial position and the smaller acetyl group in a pseudo-equatorial position in order to minimise the peri-interactions with the methyl substituents on the aromatic ring.

The benzylic proton, H1' at δ3.89 is coupled to the two C2 ring protons with identical coupling constants of 9.0Hz and the other benzylic proton, H4' at δ3.13 is similarly coupled identically to (H3')\(_2\) with couplings of 4.3Hz, as calculated from the 'H n.m.r. spectrum. The values for these couplings, when determined from the X-ray crystal structure, were found to be in reasonable agreement with the 'H n.m.r. data, therefore, it was concluded that the preferred conformation of (70a) is probably similar in both the crystalline form and in solution. For the trans isomer, (70b), the benzylic proton H1' at δ3.91 has couplings of 7.6 and 0.7Hz to the vicinal protons at C2 and H4' at δ3.14 has couplings of 4.7 and 1.6Hz to the C3 protons.

* Unpublished data of Dr. E.R.T. Treikink
In addition to the two methyl ketones, (70a) and (70b), a further compound was isolated in significant quantity from the oxidation mixture with \( ^1H \) n.m.r. data consistent with compound (73). The mass spectrum gave a molecular ion at 216, suggesting the same molecular formula as the methyl ketones and the IR spectrum showed a strong carbonyl absorption. A methyl triplet at \( \delta 1.15 \) in the \( ^1H \) n.m.r. spectrum indicated the presence of an ethyl group but despite attempts to purify the compound, it remained inhomogeneous.

\[
\text{(73)}
\]

\[
\text{(74)}
\]

The proposal of structure (73) to account for the spectral data would require that the by-product arose from rearrangement of the ethylidene compound (68) during the hydroboration reaction to give some endocyclic alkene (74). Hydroboration of (74) would then give a mixture of alcohols which remained undetected until the oxidation reaction, whereupon the ketone (73) was isolated.

The cis and trans methyl ketones, (70a) and (70b), were independently equilibrated until no further change was observed by 60MHz \( ^1H \) n.m.r. spectroscopy. Each was equilibrated in fully deuterated methanol with a trace of sodium hydroxide at 60° under nitrogen. Initial heating at 35° overnight produced no change and it was therefore assumed that elevated temperatures were necessary to achieve equilibration. After the cis ketone (70a) had been heated for 2 hours, analysis by \( ^1H \) n.m.r. spectroscopy revealed the absence of
the signal for the benzylic proton H1' and the C1-methyl singlet, both α to the carbonyl group. At this point in time, approximately one fifth of the mixture corresponded to the trans isomer (70b).

The cis and trans isomers were readily distinguished due to their different polarities by t.l.c. and, more importantly, by the chemical shift of the methyl doublet for the C4'-Me which appeared at δ1.24 for the cis isomer (70a) and δ1.17 for the trans isomer (70b). Equilibrium was achieved after 48 hours when no further change was observed in the ratio of the products. The equilibrium ratio of trans isomer (70b) to cis isomer (70a) was approximately 5:2. This was confirmed by 300MHz ¹H n.m.r. spectroscopy. It is noteworthy that after heating for 2 hours, although almost complete deuterium exchange had taken place α to the carbonyl group, the compounds had only partially equilibrated and it was necessary to heat for a considerably longer period of time. This illustrates the extreme caution which needs to be exercised when analysing the results of equilibration experiments of this type.

The equilibrium ratio of 5:2 for the trans and cis isomers (70b) and (70a) was not favourable enough to make this an efficient approach. Ideally, the equilibration should proceed with good enough selectivity to allow the trans isomer to be obtained without chromatography. The need for chromatography makes the sequence less attractive overall from a synthetic point of view.

Although the equilibration was unsuccessful in this synthetic derivative, the possibility of exploring the equilibration using a derivative of the triol (2a) from E. duttonii existed. The different substitution pattern in the aromatic ring and the bulky substituent at the C4 position offered the potential for enhanced selectivity. If this equilibration was favourable then an approach to the synthesis of serrulatanes could involve establishing the stereochemistry at
C4 and C11 and finally equilibrating a substituent at C1 before deoxygenation of that substituent. The deoxygenation has already been discussed. The dimethoxy alcohol (34) was considered a suitable starting material which could be oxidised to an appropriate derivative for the equilibration study.

The oxidation of the alcohol (34) with Jones reagent yielded the aldehyde (75). The evidence to support the structure came from the IR spectrum, which showed a carbonyl stretch at 1718 cm\(^{-1}\), and the \(^1\)H n.m.r. spectrum in which an aldehydic proton resonance was observed at \(\delta 9.45\) with a coupling to H1 of 3.4Hz. However, upon equilibration of the aldehyde (75) with sodium
hydroxide, some decomposition occurred and the results were inconclusive. It was therefore decided to oxidise the alcohol to the carboxylic acid and use the more stable methyl ester for the equilibration. The ester is a suitable alternative to the aldehyde because studies have shown that the methoxycarbonyl and formyl groups have similar conformational preferences. The dimethoxy alcohol (34) was oxidised with sodium periodate and a catalytic amount of ruthenium trichloride to give a mixture of the carboxylic acid (76) and the aldehyde (75). The acid (76), which was separated from the aldehyde by chromatography, showed the characteristic broad hydroxyl stretch from 2500-3000 cm\(^{-1}\) and a carbonyl stretch at 1706 cm\(^{-1}\) in the IR spectrum. The 'H n.m.r. data also supported the structure. The carboxylic acid (76) was converted to the methyl ester (77) by treatment with diazomethane. The ester gave the expected molecular ion in the mass spectrum and a methoxyl singlet at \(\delta 3.70\) was present in the 'H n.m.r. spectrum.

\[
\begin{align*}
\text{(78)} & \quad \text{(79)}
\end{align*}
\]

The equilibration of the methyl ester (77) was carried out in methanol with a catalytic amount of sodium methoxide at 55°. The equilibration was found to be very slow and heating was continued for 5 days when t.l.c. revealed the presence of a higher and two lower \(R_f\) components. Isolation and
chromatography gave a mixture of trans and cis methyl esters (77) and (78) as two higher Rf products. Although isolated as a mixture, the products were separable by chromatography with the higher Rf spot corresponding to the minor isomer (78). The ratio of trans isomer (77) to cis isomer (78) was calculated from the methoxyl peaks in the 'H n.m.r. spectrum of the mixture which were distinct for each isomer and was found to be 3:1. The low Rf products were also isolated as a mixture and were found to correspond to the trans and cis carboxylic acids (76) and (79) in a similar ratio.

Clearly, hydrolysis had occurred and similar results were obtained in a further experiment. It was concluded that equilibration of the methyl ester (77) gave a mixture of trans and cis isomers in a ratio of approximately 3:1. Once again, the poor selectivity of the equilibration excludes this approach as an efficient method for controlling the benzylic stereochemistry.

The results obtained from the equilibration studies are in agreement with an example from the literature22. Catalytic hydrogenation of compound (18) gave exclusively the cis isomer, which, upon equilibration with potassium tert-butoxide yielded a mixture of the cis and trans esters, although the ratio was not reported. This supports the finding that equilibration of an exocyclic carbonyl group is not selective, leading to mixtures of isomers.
A further possibility for establishing the 1,4 trans configuration by this type of chemistry involves the equilibration of an endocyclic ketone, which is crucial for the conversion of the tetraol (2c) into the aglycone of seco-pseudopterosin (10) and will be discussed in more depth in Chapter 5. Because the equilibration reactions showed little promise of being selective, further reactions along the sequence outlined in Scheme 4.2 were not pursued.

4.3 An approach which relies on kinetic resolution and hydrogenolysis of tertiary benzylic carbon-oxygen bonds

The second approach considered to obtain 1,4 trans stereochemistry in this study involves the hydrogenolysis of tertiary benzylic carbon-oxygen bonds. There has been considerable interest within our research group in the enantioselective synthesis of the aryl propionic class of drugs, utilising the hydrogenolysis of tertiary benzylic epoxides as a key step in the synthetic strategy. It has been shown that the hydrogenolysis of an epoxide such as (80) proceeds with inversion of configuration when palladium-on-carbon is used as catalyst, to give the diol (81)\textsuperscript{43}.

Several other examples have given the same results (unpublished work). A further example of particular interest is the reported hydrogenolysis of the ether (82) of defined stereochemistry. The compound undergoes an inversion of configuration at each chiral centre, resulting in the exclusive formation of the cis product (83)\textsuperscript{44}.
Scheme 4.4 outlines the general synthetic strategy for this approach which involves a kinetic resolution and hydrogenolysis sequence and obviously requires isomerically pure precursors. It was hoped that the Sharpless epoxidation of the allylic alcohol (84) with the chiral centre remote from the allylic hydroxyl group, might still result in efficient kinetic resolution because of the highly ordered intermediate complex proposed to explain the selectivity observed in the Sharpless epoxidation\textsuperscript{38a,b}. Assuming the kinetic resolution is successful, there may still be problems associated with the stability of the resultant tertiary benzylic epoxides, particularly in the preparation of the terpenes in which electron donating methoxyl substituents are present in the aromatic ring. The attack of various nucleophiles at the less substituted carbon atom of an epoxide is well known\textsuperscript{45}, and occurs with inversion of configuration, thus, the preparation of (86) should be readily achieved.
If hydrogenolysis of the tertiary benzylic hydroxyl group in (86) proceeded with inversion of configuration, it would establish the 1,4 trans stereochemistry in the product. This would provide a reasonable method of controlling the stereochemistry in syntheses of diterpenes of the serrulatane class. The chemistry which has been carried out on the sequence outlined in Scheme 4.4 has only been exploratory due to time constraints. Therefore, although some promising results have been obtained, more work is required before definite conclusions concerning the success of this approach can be made. Scheme 4.5 outlines the preliminary work towards this approach which was carried out using the series of model compounds with no substituents in the aromatic ring. This series was used since it was the most accessible but would still provide information regarding the stability of the benzylic epoxides, which was a primary concern.
The α-tetralone (87) was produced in high yield by the Friedel-Crafts reaction of benzene with γ-valerolactone (64) in the presence of aluminium chloride as described in the literature\textsuperscript{46}. The reaction of the tetralone (87) with triethylphosphonoacetate, using potassium tert-butoxide or sodium hydride as bases, failed to give the expected (E) and (Z) alkenes (88) and (89), instead yielding only the equilibrated product, the endocyclic alkene (92). The evidence for the formation of this product, which was homogeneous by t.l.c.,
was the appearance of a singlet methylene peak corresponding to the protons $\alpha$ to the carbonyl group at $\delta 3.13$ and a one proton vinylic multiplet at $\delta 5.8$ in the $^1$H n.m.r. spectrum. Shortening the reaction time gave a mixture of (92) and the starting tetralone (87).

![Chemical Structure](image)

(92)

The problem was finally overcome by the use of the Peterson olefination reaction, in which the ketone was added to the anion formed from trimethylsilylacetae with lithium diisopropylamide as base at -78°C. The advantages of this reaction are the greater reactivity of the stabilised $\alpha$-silyl carbanions over the corresponding phosphorus ylids and the fact that the reactions are governed by kinetic control. The reaction proceeded smoothly to give a mixture of (E) and (Z) esters (88) and (89) in the ratio of 2:3. The signals in the $^1$H n.m.r. spectrum corresponding to the vinylic protons were distinct for each isomer. A singlet at $\delta 5.79$ appeared for the (Z)-isomer (89) and a triplet, due to small long range coupling of 1.8Hz, occurring downfield at $\delta 6.31$ for the (E)-isomer (88), presumably due to the deshielding effect of the aromatic ring. The mixture required extensive chromatography to separate the isomers which were close in Rf by t.l.c. The mass spectra of the purified esters gave the expected molecular ion at 230 and strong carbonyl absorptions at 1704 and 1708 cm$^{-1}$ were observed in the IR spectra. The presence of an ethoxy group was confirmed in the $^1$H n.m.r. spectra with a characteristic three proton triplet at $\delta 1.32$ and a two proton quartet at $\delta 4.20$ for the (E)-isomer.
A pure sample of the (E)-ester (88) was reduced with lithium aluminium hydride at 0° to give the (E)-allylic alcohol (90). A molecular ion of 188 coupled with an OH stretch at 3425 cm⁻¹ in the IR spectrum confirmed the structure of the product. The 'H n.m.r. spectrum with a vinylic triplet at δ6.14 and a two proton doublet at δ4.35 provided further evidence, with the hydroxyl proton at δ2.20 revealed by D₂O exchange. The (E)-allylic alcohol (90) was treated with m-chloroperoxybenzoic acid at 0° for 2 hours, buffered with sodium hydrogen carbonate to prevent acid catalysed opening or rearrangement of the epoxide during the reaction. Upon work-up, two distinct products were observed by t.l.c. but could only be isolated as a mixture after chromatography. The desired molecular ion of 204 was present in the mass spectrum which was consistent with the formation of the cis and trans epoxides (91a) and (91b). No vinylic signals were present in the 'H n.m.r. spectrum excluding the possibility that the epoxides had undergone elimination to give the unsaturated diol (93).
Despite the fact that the epoxidation appeared to be successful, it was difficult to assign the signals in the 'H n.m.r. spectrum. Clearly, the reaction mixture consisted of a 1:1 mixture of isomers, as the doublet methyl resonances for the C4'-methyl groups were distinct and of approximately equal integration, appearing at δ1.31 and δ1.40 for the two isomers. The only signals which could correspond to the epoxide protons, H2, occurred as similar doublets of doublets at δ4.35 and δ4.48, which is significantly far downfield relative to the characteristic chemical shift range for an epoxide proton of δ2-3 ppm. It is possible that, for these epoxides, the preferred conformation is such that the epoxide protons are significantly deshielded by the aromatic ring, leading to a dramatic downfield shift in the chemical shift of this proton. An effect of this type has been observed previously in this series in the case of (E) and (Z) isomers, for example the esters (88) and (89). For the (E)-isomer the vinylic proton, which is in close proximity to the aromatic ring, experiences a significant deshielding effect which causes it to resonate approximately 0.5ppm downfield from the vinylic proton in the (Z)-isomer (89).

In order to obtain more information about the epoxidation, the stability of the epoxides and the suitability of one over the other for analysis of products from a Sharpless epoxidation, it was decided to prepare the corresponding epoxide from the (Z)-allylic alcohol (94). Reduction of the (Z)-ester (89) with lithium aluminium hydride gave the allylic alcohol (94). The 'H n.m.r. spectrum (60MHz) of the purified product was in agreement with the expected structure, therefore, without further characterisation, the epoxidation was carried out. In this case, the epoxidation proceeded at a faster rate with no starting material present after 30 minutes and t.l.c. again indicated a mixture of epoxides. Purification by flash chromatography once again gave a mixture of two isomers, presumed to be cis and trans epoxides (95a) and (95b). Analysis by high field (300MHz) 'H n.m.r. spectroscopy showed one isomer to be in slight
excess over the other although, this time, the chemical shift difference in the signals for the C4'-methyl groups was much smaller with the resonances appearing at δ1.33 in the major isomer and δ1.32 in the minor isomer.

In fact, the differences in the spectra of the epoxides of the (E) and (Z) allylic alcohols were quite marked. Unlike the spectrum of the cis and trans epoxides (91a) and (91b), the resonances for the two isomers (95a) and (95b) were overlapping in all cases apart from those for the C4'-methyl group as already pointed out. Interestingly, the epoxide proton H2 occurred as a triplet at δ3.24 with a coupling of 6.1Hz in both isomers which is, at the minimum, approximately 1ppm upfield from the epoxide signals for (91a) and (91b). It is likely that the spectra correspond to the desired epoxidation products in both cases although obviously further data is required. Of the two, the (E)-allylic alcohol would be more suitable for Sharpless epoxidation because the outcome of the reaction could be readily monitored by observing the signals for the C4'-methyl groups of the cis and trans epoxides (91a) and (91b), since they have quite distinct chemical shifts.

The fact that the epoxidation of the (E) and (Z) allylic alcohols with m-chloroperoxybenzoic acid was not face selective giving essentially 1:1 mixtures of cis and trans epoxides in both cases was not considered to be of particular importance because the Sharpless reaction is highly face selective leaving only the question of kinetic resolution to be established. More important was the fact that these tertiary benzylic epoxides were shown to be relatively stable, which was a factor crucial to the success of this approach.

Although these epoxides were relatively stable, it was found that when electron donating methoxyl substituents are present in the aromatic ring, the epoxides are considerably more labile. For example, when the dimethoxy
alkene (96) from the triol series was treated with m-chloroperoxybenzoic acid under conditions similar to those described above, the epoxides were too labile to be isolated. It was assumed that the epoxides, once formed, underwent rearrangement to other products during the reaction. Although two components were isolated upon chromatography, neither corresponded to epoxide and their structures could not be further elucidated by spectral means.

\[
\text{OMe} \quad \text{OMe}
\]

\[
\text{H} \quad \text{H}
\]

Therefore, for this approach to be useful for terpene synthesis where methoxyl substituents are present in the aromatic ring, it would be necessary to introduce an electron withdrawing substituent into the ring. A bromo or iodo substituent would destabilise the incipient positive charge at the benzylic position. This substituent could be subsequently removed during the hydrogenolysis step. Alternatively, the aromatic methyl group which is present as a carboxyl or an hydroxy methyl group in some of the diterpenes could be carried through the synthesis as a methoxycarbonyl group. As mentioned earlier, the preliminary work towards this approach, although hopeful, is not sufficient to predict its success. Due to a lack of time, further studies focusing on the kinetic resolution and hydrogenolysis aspects could not be carried out, although it seems likely that the hydrogenolysis will be successful.
4.4 A method for establishing 1,4 cis stereochemistry via catalytic hydrogenation and metal/ammonia reduction of appropriate methylene precursors

All of the methods discussed so far have been concerned with establishing the 1,4 trans stereochemistry, which is present in all of the known serrulatane type diterpenes. However, it is also desirable to obtain access to derivatives with the 1,4 cis disubstituted 1,2,3,4-tetrahydroxynaphthalene configuration. The development of methods which will provide access to cis stereochemistry will be useful for the preparation of isomers of the naturally occurring 1,4 trans seco-pseudopterosins for biological assay and also for the synthesis of sesquiterpenes possessing cis stereochemistry, some examples of which were highlighted in the introduction. The recently reported isolation of some new diterpenes related to the pseudopterosin class but possessing cis stereochemistry\textsuperscript{13b} which were also mentioned in the introduction, provides an additional reason for pursuing this line of research.

The two methods which were explored for the construction of cis compounds were catalytic hydrogenation and metal/ammonia reduction of appropriate precursors. The synthetic methylene compounds required for these studies were prepared via Friedel-Crafts and Wittig chemistry, using compounds both without peri-substituents and with methyl substituents in the 5,8 positions in the aromatic ring, as outlined in Scheme 4.6.
The α-tetralone (87) was produced in a one-pot synthesis by the Friedel-Crafts reaction of benzene with γ-valerolactone\(^{46}\) (see Scheme 4.5). Treatment of the ketone (87) with potassium tert-butoxide and methyltriphenylphosphonium bromide yielded the methylene derivative (97). The moderate yield was probably due, in part, to the volatility of the product, despite appropriate care being taken in the isolation. The structure was confirmed by mass spectrometry, with a molecular ion at 158, accompanied by a peak at 160, corresponding to the addition of molecular hydrogen. The diagnostic feature of the 'H n.m.r. spectrum was the resonances for the methylene protons, one of which occurred at δ4.94 and the other downfield at δ5.45, both with small coupling of 1Hz.

The α-tetralone (67) was prepared in two steps. The first involved the Friedel-Crafts reaction of γ-valerolactone and p-xylene to yield an intermediate carboxylic acid which was cyclised with polyphosphoric acid to the tetralone (67)\(^{42a,b}\) (See Scheme 4.3). Once again, treatment of the ketone (67) with potassium tert-butoxide and methyltriphenylphosphonium bromide gave the methylene derivative (98). A molecular ion of 186 was observed in the mass spectrum of the product, along with a peak at 188 (+H\(_2\)). The signals for the
methylene protons were characteristically distinct, appearing as singlets as $\delta5.07$ and $\delta5.28$.

An alternative method for the preparation of methylene compounds of the type (97) was reported in the literature\textsuperscript{48}. Cyclisation of compounds with the general structure (99) with bromine led to intermediate bromides which underwent elimination with sodium amide to yield the methylene derivatives (100). It is not known if the method is applicable to compounds with substituents in the aromatic ring, but it could be useful in some cases.

![Diagram](image)

The appropriate methylene derivatives from the triol (2a) and the tetraol (2c) series were prepared via the route outlined in Scheme 4.7. In the triol series, the dimethoxy alcohol (34) was converted to the tosylate (35) (see Chapter 1) which was eliminated with sodium hydride to yield the alkene (96). As before, the diagnostic feature of the 'H n.m.r. spectrum was the signals for the methylene protons, which appeared as singlets at $\delta5.19$ and $\delta5.76$. Similar chemistry was used to prepare the corresponding methylene derivative in the tetraol series. The dimethoxy diol (41) was selectively tosylated at the primary hydroxyl group to give the mono-tosylate (42) (see Chapter 3). Subsequent base-catalysed elimination with potassium tert-butoxide yielded the methylene derivative (101), with the resonances for the vinylic protons occurring at $\delta5.28$ and $\delta6.01$ in the 'H n.m.r. spectrum. Varying the base appeared to have little
effect on the yield of product obtained, which was approximately 50% in each case.

Scheme 4.7

The chemistry described in this section is potentially important, firstly due to the accessibility of the methylene compounds as shown above, both in the synthetic derivatives and the two natural product series, and secondly, for the conversion of the tetraol (2c) into the aglycone of the seco-pseudopterosin (10) and its isomers. Table 4.1 summarises the results of the catalytic hydrogenation and metal/ammonia reductions of the methylene derivatives.
<table>
<thead>
<tr>
<th>Products</th>
<th>cis:trans ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cat. $H_2$</td>
</tr>
<tr>
<td>(102a) + (102b)</td>
<td>4:1</td>
</tr>
<tr>
<td>(103a) + (103b)</td>
<td>3:1</td>
</tr>
<tr>
<td>(6a) + (6b)</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>(43a) + (43b)</td>
<td>&gt;99:1</td>
</tr>
</tbody>
</table>
Focusing firstly on hydrogenation, in the series with no peri-substituents, the methylene compound (97) was hydrogenated with 5% palladium-on-carbon for 24 hours to yield an inseparable mixture of cis and trans 1,4-dimethyltetralins (102a) and (102b) in the ratio of 4:1 respectively. The isomers were distinguished by comparison of the 'H n.m.r. data with those reported in the literature\textsuperscript{49} and which had been assigned unambiguously to the particular isomers. The only signals in the spectrum which were distinct for each isomer were the six proton methyl doublets which occurred at δ1.27 in the cis isomer (102a) and at δ1.24 in the trans isomer (102b). There were also some characteristic differences in the \textsuperscript{13}C n.m.r. spectra of the two isomers for which the data were also available\textsuperscript{50} and in good agreement with those obtained. Once again, marked differences in the chemical shifts of the methyl group resonances were observed, occurring at δ22.6 in the cis isomer (102a) and at δ23.1 in the trans isomer (102b). Differences in most of the other resonances were also observed, although not to such an extent.

Diverging for a moment, the methylene derivative (97) was also treated with 9-borabicyclononane to determine whether any selectivity is obtained from hydroboration, since the borane should add preferentially to the less hindered face of the molecule, leading to predominantly cis products. Hydroboration of (97) produced poor selectivity, yielding an inseparable mixture of cis and trans alcohols (104a) and (104b) in the ratio of 3:2, as determined from the 'H n.m.r. spectrum. The structures were supported by an OH stretch at 3234 cm\textsuperscript{-1} in the IR spectrum, and the 'H n.m.r. spectrum which showed a two proton multiplet at δ3.60-3.80 corresponding to the methylene group carrying the hydroxyl group. The doublets for the C4'-methyl groups were distinct, occurring at δ1.29 in the cis isomer (104a) and δ1.25 in the trans isomer (104b). This allowed the ratio of the isomers to be calculated.
The cis and trans alcohols were identified by correlation with the hydrocarbons (102a) and (102b). Conversion of the mixture of alcohols to the tosylates (105a) and (105b), for which only the \(^1\)H n.m.r. data was obtained to confirm the structures, followed by lithium aluminium hydride reduction yielded a mixture of the cis and trans 1,4 dimethyltetralins (102a) an (102b) in the ratio of 3:2.

The result obtained for the hydroboration reaction was in agreement with an example in the literature\(^5\) in which the methylene compound (106) was hydroborated to yield a mixture of cis and trans alcohols in the ratio of 55:45 as calculated from the \(^1\)H n.m.r. spectrum.

Since hydroboration of the methylene derivative (97) with a bulky reagent was found to be less selective than catalytic hydrogenation, its usefulness as a potential means for generating cis stereochemistry was considered to be limited and further investigation in this direction was not undertaken.
A slight decrease in the selectivity was observed when the methylene derivative (98), with 5,8 methyl substituents, was catalytically hydrogenated. In this case, hydrogenation for 5 hours with platinum oxide as catalyst yielded an inseparable mixture of cis and trans products (103a) and (103b) in the ratio of 3:1. Although the 'H n.m.r. data for the isomers were not available in the literature, the resonances were assigned by analogy with the data for (102a) and (102b). The six proton methyl doublets corresponding to the chemically equivalent C1- and C4-methyl groups were distinct, with the signal at δ1.23 presumably corresponding to the major cis isomer (103a) and the signal at δ1.13 corresponding to the minor trans isomer (103b).

Hydrogenation of the methylene derivative (96) in the triol series for 72 hours with platinum oxide as catalyst led to the exclusive formation of the cis isomer (6a). No trace of the trans isomer (6b), for which the data was already available from the correlation work (Chapter 2), was detected by 'H n.m.r. spectroscopy. A three proton doublet at δ1.19 corresponding to the C1-methyl group confirmed the structure of the product. Many of the resonances in the 'H n.m.r. spectrum of the hydrogenation product (6a) were distinct from those of the trans isomer (6b) prepared earlier. In particular, the signal for the C11-methyl group at δ1.02, the benzylic proton H4 at δ2.68 and the aromatic proton H5, δ6.81, were different from those of (6b) which appeared at δ0.93, 2.52 and 6.71, respectively.

A similar result was obtained when the methylene derivative (101) from the tetraol series was catalytically hydrogenated. Under conditions identical with those described for (96), the cis isomer (43a) was produced exclusively. Once again, no trace of the 1,4 trans compound (43b), which was prepared for the correlation study (Chapter 3), could be detected by 300MHz 'H n.m.r.
spectroscopy. The resonance for the C1-methyl group appeared at δ1.34, confirming the structure of the product. Marked differences in the 'H n.m.r. spectra of the cis isomer (43a) and the trans isomer (43b) were again apparent, with the chemical shifts of most of the signals being distinct for each isomer. The most significant difference was the chemical shift of the proton H3, attached to the carbon bearing the hydroxyl group, which resonated at δ4.03 in the cis isomer (43a) and significantly further downfield at δ4.31 in the trans isomer (43b).

The results of the catalytic hydrogenation study are consistent with preferential addition of hydrogen from the less hindered face of the molecule, leading to predominantly 1,4 cis products as expected. The exclusive formation of the cis isomers in the two natural product series was an important result. At the outset of the synthetic studies, it was considered likely that the presence of a peri-substituent at C8 in the aromatic ring would lead to increased selectivity, since the groups in the 1,4 positions would be expected to adopt pseudo-axial conformations to relieve the peri-interaction, thus hindering the approach of reagents from one face of the molecule to a relatively greater extent. However, the trend which is apparent from the results obtained does not support this hypothesis. Instead, it can be concluded from the results that high stereoselectivity appears to be dependent upon the presence of a bulky substituent at the C4 position in the molecule. Thus, the selectivity in the synthetic compounds, which have methyl substituents at C4 (including a methyl peri-interaction), was relatively poor in both cases. In contrast, the selectivity in both the triol and tetraol series, which have bulky isopropyl-like substituents at C4 and hydrogen at C5, was excellent. The methyl-methyl peri-interaction did not have a significant influence on the sterochemical outcome of the reactions.
The results of the metal/ammonia reductions followed a similar trend, although the selectivity overall was not as great. The reduction of the methylene derivative (97), with no peri-substituents, with lithium in ammonia yielded a mixture of the cis and trans 1,4 dimethyltetralins (102a) and (102b) in the ratio of 3:1 respectively. Under similar conditions, the methylene compound (98) gave a 4:1 mixture of the corresponding cis and trans tetralins (103a) and (103b). The reduction of the alkene (96) from the triol series gave a mixture of epimers at C1, (6a) and (6b) in the ratio of 7:3 in favour of the cis isomer (6a). The metal/ammonia reduction of the methylene derivative (101) from the tetraol series was found to be the most selective, yielding a mixture of cis and trans isomers (43a) and (43b) in the ratio of 6:1.

The reaction times for all reductions were short, with a maximum time of 5 minutes, to prevent significant reduction of the aromatic ring. The reduction of compound (96) from the triol series was originally carried out with ethanol present as a proton source, however this was found to cause extensive reduction of the aromatic ring, as evidenced by the lack of methoxyl signals in the region from δ3.7-3.9 in the 'H n.m.r. spectrum of the crude product. Similarly, when one equivalent of tert-butanol was employed as the proton source, the yield of product was 23%, with the remaining material corresponding to over-reduction products. To overcome this problem, it was decided to reduce compound (101) from the tetraol series in the absence of a proton source. This was found to improve the yields of the desired product, with only slight over-reduction occurring. The reductions of the synthetic methylene compounds (97) and (98), which were both carried out in the absence of a proton source, gave yields of 57% and 74% respectively, with no indication of over reduction.
There is a literature precedent which supports the selective formation of cis products in systems of this type. With reference to Figure 4.2, the stereospecificity of the reaction is consistent with preferential axial attack during the final protonation, presumably allowing maximum orbital overlap with the adjacent aromatic ring and leading to the experimentally observed cis products.

![Figure 4.2](image)

The results of some research towards the synthesis of the hydroxycalamenenes which appeared in the literature was discussed briefly in the introduction and strongly supports some of the findings of this study. Hydrogenation of the endocyclic double bond in compound (18) gave exclusively the cis isomer (107a), which is consistent with the conclusion made previously that a bulky substituent at C1 or C4 is necessary to achieve good selectivity. Also, metal/ammonia reduction of (18) yielded a mixture of cis and trans alcohols (108a) and (108b) in the ratio of 3:1 respectively. The decrease in selectivity relative to catalytic hydrogenation as well as the formation of the cis isomer as the major product are also in agreement with the results obtained in this study.
In conclusion, although considerable progress was made towards the synthesis of the serrulatane class of diterpenes possessing the 1,4 trans stereochemistry, the most interesting and useful chemistry resulted from the preparation of compounds possessing the 1,4 cis configuration. Some applications of the results of this research will be discussed in the following chapter.
CHAPTER 5

This chapter describes a method which could be used for the conversion of the tetraol (2c) from *E. duttonii* into the aglycone of the biologically active seco-pseudopterosin (10). This method is potentially useful for a variety of reasons, including the accessibility of the tetraol compared with the marine species, which was isolated in small quantities, and the relatively few steps required to achieve the conversion to the aglycone (109), which has so far been prepared only via lengthy total syntheses. In addition to this, the absolute stereochemistry of neither the aglycone nor the sugar unit has been confirmed and further, the method provides access to stereoisomers which will also be useful for biological assay.

Essentially, what is required is the inversion of configuration of the chiral centres C1 and C4 and the deoxygenation of the primary and secondary hydroxyl groups in the tetraol (2c) to obtain the aglycone (109). The chemistry outlined in Scheme 5.1, most of which was encompassed by the earlier correlation and synthetic work, has already been established.
Scheme 5.1

(2d) \[\rightarrow\] (40)

(101) \[\rightarrow\] (41) \(R=H\)

(42) \(R=Ts\)

(43a) \[\rightarrow\] (110)
Catalytic hydrogenation of the double bond in the tetraacetate (2d) followed by lithium aluminium hydride reduction gave the tetraol (40). Selective methylation of the phenolic hydroxyl groups in (40) yielded the dimethoxy diol (41) which was converted to the mono-tosylate (42). This chemistry was discussed in detail as part of the stereochemical correlation (Chapter 3). The methylene derivative (101) was prepared as part of the synthetic study by base catalysed elimination of the tosylate (42) and subsequent catalytic hydrogenation gave exclusively the 1,4 cis reduction product (43a), with the required stereochemistry of the chiral centre C1 (Chapter 4). The only additional reaction in the sequence is the oxidation of the secondary hydroxyl group in (43a). Treatment with Jones reagent gave the ketone (110) in good yield, and although the reaction was investigated only on a small scale due to lack of material, the 300MHz 'H n.m.r. spectrum of the product strongly supported the proposed structure. The diagnostic features were the resonances for the benzylic proton H4 which appeared as a doublet at δ3.21 with a coupling of 5.8Hz to the vicinal proton H11, and the signals for the non-equivalent C2 methylene protons. One proton appeared as a doublet of doublets at δ2.43 with geminal coupling of 15.2Hz and coupling to H1 of 2.7Hz. The other also appeared as a doublet of doublets with identical geminal coupling and further coupling of 7.3Hz to H1.

Equilibration of the ketone (110) should give predominantly the 1,4 trans isomer, which would invert the configuration of C4 giving the required stereochemistry of the skeleton. This reaction was not performed due to lack of material and because the equilibration of an endocyclic ketone of this type in a sesquiterpene has been shown in the literature to proceed with good selectivity. It was found\textsuperscript{16} that when the ketone (111) was equilibrated, only the natural trans isomer shown was obtained. This provided convincing evidence that the trans isomer of (110) would be the thermodynamically more
stable epimer and would be expected to predominate under equilibrating conditions.

After equilibration to the 1,4 trans isomer, it would be necessary to deoxygenate at the C3 position. The most logical choice would be Wolff-Kishner reduction of the ketone, which may eliminate one step since equilibration and deoxygenation of (110) may both be achieved under the basic reduction conditions. Alternatively, hydride reduction to the alcohol and application of the radical induced deoxygenation chemistry via the xanthate ester may be suitable (Chapter 3).

The sequence outlined above is based mainly on chemistry which was already developed for other purposes, which will be useful for the preparation of the aglycone of seco-pseudopterosin (10). Obviously, for the synthesis of an authentic sample of the aglycone, several other factors need to be considered. Of these, the retention of the double bond in the sidechain is of primary importance. This may be achieved if the catalytic hydrogenation of the methylene derivative (101) is replaced by metal/ammonia reduction. Although not as favourable as catalytic hydrogenation, the dissolving metal reduction still produced good selectivity. It is also likely that the product will be crystalline since the alcohol (43a) was a solid, thereby enabling recrystallisation to yield the cis isomer of high purity. Another factor which needs to be addressed is the protection of the phenolic hydroxyl groups. Since
needs to be addressed is the protection of the phenolic hydroxyl groups. Since ultimately, it would be necessary to glycosylate at the C8 phenolic hydroxyl group, methods of demethylating the dimethoxy compound need to be explored. In addition to this, studies on the selective protection of the phenolic hydroxyl group at C7 to allow glycosylation at C8 are required.

Although no information is available regarding the preparation of α-glycosides in systems of this type, the formation of β-glycosides has been reported. As the final step in the total synthesis of the pseudopterosin (9)26, the β-xylose glycoside was prepared in reasonable yield with good stereoselectivity from a precursor in which the phenolic group at C7 was protected as a benzyl ether. It was however, necessary to employ eight equivalents of the bromo-sugar, which may reflect the greater degree of steric hindrance associated with glycosylation of the phenolic hydroxyl group at C8, relative to most successful literature reactions.

In conclusion, the conversion of the tetraol (2c) into the seco-pseudopterosin aglycone (109), using the chemistry developed in this work, should provide a relatively short and efficient means of obtaining not only the natural product itself but, by virtue of the synthetic route, isomers of the aglycone which will also be important for biological assay. Since the completion of this work, new plant material has been collected and extracted and the synthesis of the seco-pseudopterosins from the tetraol (2c) will be commenced by a new student.
EXPERIMENTAL

GENERAL

Melting points were determined using a Kofler hot-stage apparatus under a Reichert microscope and are uncorrected.

Elemental analyses were carried out by the Canadian Microanalytical Service Ltd., New Westminster, Canada.

Infrared spectra were recorded in solution using chloroform as solvent on a Jasco A-102 Spectrophotometer unless otherwise stated.

60MHz 'H n.m.r. spectra were recorded on a Varian T60 spectrometer. 300MHz 'H n.m.r. spectra were recorded on either a Bruker CXP-300 or a Bruker ACP-300 spectrometer. Unless otherwise stated, all spectra were recorded as (D) chloroform solutions and chemical shifts have been quoted in parts per million (p.p.m.) downfield from tetramethylsilane. Peak multiplicities have been abbreviated to s(singlet); d(doublet); t(triplet); q(quartet) and m(multiplet).

All thin layer chromatography was performed on Merck DC-Alufolien Kieselgel 60 F_{254} Art. 5554. T.L.C. plates were developed using a solution of 4% w/v phosphomolybdic acid in ethanol followed by heating. Flash chromatography\textsuperscript{53} was performed on Merck Kieselgel 60 (230-400 mesh ASTM). Dry column chromatography\textsuperscript{54} was performed on Merck Kieselgel 60 HF_{254} Art. 7739 (gradient increasing from the non-polar solvent to the polar solvent).
Electron impact mass spectra were recorded with an AEI MS-30 double focussing mass spectrometer operating at 70eV.

All solvents were distilled before use. Anhydrous diethyl ether, tetrahydrofuran and benzene were obtained by distillation from sodium benzophenone ketyl.

The optical rotations were determined using chloroform as solvent unless otherwise stated on a Perkin-Elmer 141 polarimeter.
DERIVATIVES OF SERRULATENOL (1)

Lithium aluminium hydride reduction of the tosylate of serrulatenol (1)

A two-necked flask was flame-dried and flushed with nitrogen. Lithium aluminium hydride (65mg; 1.71 mmol) was placed in the flask followed by the addition of the tosylate (200mg; 0.427 mmol) in dry ether (10ml). The reaction mixture was stirred at room temperature under nitrogen for 2 days. The reaction was terminated by the addition of water, then the mixture was acidified with dilute hydrochloric acid and extracted with dichloromethane. Drying and removal of solvent under reduced pressure, followed by purification by preparative t.l.c. (dichloromethane/light petroleum; 4:1), yielded the parent diterpene serrulatenol (1) (114mg; 85%) which had spectral data identical with those obtained previously.

Methylation of serrulatenol (1)

A two-necked flask was flame dried and flushed with nitrogen. Serrulatenol (1) (400mg; 1.27 mmol) was placed in the flask and sodium hydride (64mg; 2.68 mmol, approximately 50% in mineral oil) was added. Dimethyl sulphoxide (3.2ml) was injected and the mixture was stirred for 15 minutes. Iodomethane (0.47ml; 7.62 mmol; 6 molar equivs.) was then injected and the reaction mixture was left to stir at room temperature for 48h. Dilute hydrochloric acid (approx. 15ml) was added, followed by extraction with dichloromethane. Purification was achieved by removal of dimethyl sulphoxide under reduced pressure using an oil-pump followed by "dry column" flash chromatography (dichloromethane/light petroleum) to yield (13R,18R)-5,18:13,18-diepoxy-8-methoxyserrulat-14-ene (19) (300mg; 72%) m.p. 108-109° from methanol.
(twice). Found: C, 76.6; H, 8.4. C_{21}H_{22}O_{3} requires C, 76.8; H 8.6% v_{\text{max}}(\text{solution}) 2950, 2925, 2850, 1670, 1600, 1480, 1460, 1440, 1220, 1100, 1060, 970, 840 cm^{-1}. \text{H n.m.r. } \delta (300\text{MHz}) 1.21, 3H, d, J6.9Hz, (H20)_{3}; 1.53-2.37, m, methylene envelope; 1.76, 6H, s, (H16)_{3}, (H17)_{3}; 2.27, 3H, s, (H19)_{3}; 2.57, 1H, m, H4, 3-10, 1H, m, H1; 3.78, 3H, s, OMe; 5.12 - 5.25, 2H, m, H13, H14; 5.32, 1H, d, J5.7Hz, H18; 6.54, 1H, s, H7. m/z 328 (M), 205, 204, 190, 189, 175, 124, 91.

**Catalytic hydrogenolysis of the methyl ether (19)**

The methyl ether (19) (1.13g; 3.45 mmol) was hydrogenated portionwise in ethyl acetate containing 10% acetic acid in the presence of varying proportions of palladium-on-carbon (5-50%) for periods of 48h. The reaction mixtures were filtered through Celite and the filtrates evaporated under reduced pressure. The 60MHz \text{H n.m.r.} spectra of the resultant mixtures revealed formation of the higher Rf hydrogenation product, (13R, 18R)-5,18:13,18-diepoxy-8-methoxyserrulatane (20) and the lower Rf hydrogenolysis product, (18R)-5,18-epoxy-8-methoxyserrulatan-18-ol (21a) in relative proportions varying from 50-90% and 70-50% respectively.

The total mixture was separated by preparative t.l.c. (dichloromethane/light petroleum; 3:2) to yield the higher Rf hydrogenation product (20) (854mg; 75%) as a yellow oil. \text{H n.m.r. } \delta (60\text{MHz}) 0.98, 6H, d, J6Hz, (H16)_{3}, (H17)_{3}; 1.22, 3H, s, J6Hz, (H20)_{3}; 1.37-2.23, m, methylene envelope; 2.43-3.43, 2H, m, H1, H4; 3.80, 3H, s, OMe; 4.60, 7H, m, H13; 5.33, 1H, d, J5Hz, H18; 6.75, 1H, s, H7.

The lower Rf hydrogenolysis product (21a) (171mg; 15%) was subsequently recrystallised from light petroleum to yield (18R)-5,18-epoxy-8-methoxyserrulatan-18-ol (82mg; 7%) as colourless crystals, mp 115-116\degree. Accurate mass: 332.2364 (C_{21}H_{32}O_{3} requires 332.2351). v_{\text{max}} (\text{soln}) 3575, 2900,
2850, 1600, 1470, 1460, 1400, 1360, 1330, 1220, 1100, 1080, 1020 cm⁻¹. m/z 332 (M) 204, 189.

Analysis of the sharp melting solid by 'H n.m.r. spectroscopy (300MHz) revealed a mixture of (18R) and (18S)-5,18-epoxy-8-methoxyserrulatane-18-ol, (21a) and (21b), with one epimer present in approximately twice the proportion of the other.

'H n.m.r. δ (300MHz) (major component) 0.88, 6H, d, J6·6Hz, (H16)3, (H17)3; 1.23, 3H, d, J6·7Hz, (H20)3; 1.30-2.11, m, methylene envelope; 2·20, 3H, s, (H19)3; 2.39-3.27, 2H, m, H1, H4; 2.76, 1H, d, J6·6Hz, D2O exch, OH; 3.76, 3H, s, OMe; 5.23, 1H, dd, JH180H 6·6, JH18H11 8·9Hz, H18; 6.56, 1H, s, H7.

(minor component) 0.88, 6H, d, J6·6Hz, (H16)3, (H17)3; 1.23, 3H, d, J6·7Hz, (H20)3; 1.30-2.11, m, methylene envelope; 2·20, 3H, s, (H19)3; 2.39 - 3.27, 2H, m, H1, H4; 2·69, 1H, d, J3·7Hz, D2O exch., OH; 3.76, 3H, s, OMe; 5.59, 1H, d, JH180H 3.7Hz, H18; 6.58, 1H, s, H7.

The separation also yielded a mixed fraction (130mg) of (20), (21a) and (21b).

Lithium aluminium hydride reduction of the mixture of epimeric hemiacetals (21a) and (21b)

A two-necked flask was flame-dried and flushed with nitrogen. Lithium aluminium hydride (14mg; 0.361 mmol) was placed in the flask followed by dry tetrahydrofuran (5ml). After refluxing for 15 minutes, the solution was transferred to a flask containing the hemiacetals (21a) and (21b) (60mg; 0·181 mmol). The reaction mixture was gently refluxed for 3 days. Work-up and evaporation of the organic extracts gave the crude product. Purification was achieved by "dry column" flash chromatography (dichloromethane/light petroleum) followed by recrystallisation from light petroleum to yield 8-
methoxyserrulatane-5,18-diol (7) (50mg; 83%) m.p. 134-136°. Accurate mass 334.2513 (C₂₁H₃₅O₃ requires 334.2508). vₘₐₓ (soln) 3600, 3325, 2925, 2850, 1460, 1410, 1360, 1210, 1090 cm⁻¹. ¹H n.m.r. δ (300MHz) 0.88, 3H, d, J6.5Hz, 0.86, 3H, d, J6.7Hz, (H₁₆)₃, (H₁₇)₃, 1.12, 3H, d, J6.8Hz, (H₂₀)₃; 1.30-2.10, m, methylene envelope; 2.25, 3H, s, (H₁₉)₃; 3.02, 1H, m, H₄; 3.15, 1H, m, H₁; 3.38, 1H, dd, J₆.₁₂, J₁₈₉₂₂.₂Hz, 3.62, 1H, dd, J₆.₇Hz, (H₁₈)₂; 3.49, 1H, s, D₂O exch., OH; 3.77, 3H, s, OMe; 6.54, 1H, s, H₇. m/z 334 (M), 316, 205.

**Metal/ammonia reduction of the methyl ether (19) of serrulatenol**

To a flask containing liquid ammonia (the ammonia referred to in this and the following experiments was gas condensed into the reaction vessel directly from the cylinder) (20ml) was added the methyl ether (19) of serrulatenol, (30mg; 0.0915 mmol) in dry tetrahydrofuran (2ml), lithium (20mg; 2.9 mmol) and ethanol (0.3ml) in that order. This mixture was stirred for 5 minutes after which time the blue colour of the solution discharged. A further portion of lithium (20mg) was added and after 10 minutes isoprene (0.5ml) was added to remove the excess of metal. The ammonia was then allowed to evaporate and water was introduced. Extraction with dichloromethane, drying and removal of solvent gave the crude product which appeared to consist of two low Rf components, ΔRf <0.1. Without further purification, the mixture (27mg; 0.0813 mmol) was hydrogenated overnight with platinum oxide (10mg) in ethyl acetate (5ml). Filtration through Celite and evaporation of the filtrate under reduced pressure gave the crude produce. Purification by "dry column" flash chromatography (dichloromethane/hexane) yielded a mixture of epimeric diols (22mg; 71%) with identical Rf, in a ratio of 2:1. The major diol was identified as (11S)-8-methoxyserrulatane-5,18-diol (22a) which had spectral data identical with those obtained previously. The minor diol was found to be (11R)-8-methoxyserrulatane-5,18-diol (22b). ¹H n.m.r. δ (300MHz) 0.85 and 0.86
each 3H, d, J6·6, 6·9Hz, (H16)3, (H17)3; 1·12, 3H, d, J6·7Hz, (H20)3; 1·20 - 2·10, m,
methylene envelope; 2·23, 3H, s, (H19)3, 3·02, 1H, m, H4; 3·14, 1H, m, H1; 3·38,
1H, dd, Jgem10·9, JH18H112·0Hz, 3·62, 1H, dd, Jgem10·9, JH18H114·6Hz, (H18)2; 3·77,
3H, s, OMe; 6·51, 1H, s, H7.(OH not observed).

When this reaction was scaled up, three portions of methyl ether (19) (400mg; 1·22 mmol) were reduced and hydrogenated under conditions identical with those described above. For each run, the proportion of minor diol present was found to be less than 10%. The material was then combined and purified by flash chromatography (ethyl acetate/dichloromethane; 5:95) and subsequently recrystallised from hexane to give pure (11S)-8-methoxyserrulatane-5,18-diol (22a) (324mg; 27%) with melting point and spectral data identical with those obtained previously.

The residues from the purification (612mg; 50%) were also rich in the methoxy diol (22a) which could be recovered by further chromatography.

**Metal/ammonia reduction of the methyl ether (19) of serrulatenol with separation prior to hydrogenation**

The methyl ether (19) of serrulatenol (100mg; 0·304 mmol) was reduced as described previously to yield a mixture of epimeric alkene diols which appeared as two spots by t.l.c., ΔRF <0·1. Purification by "dry column" flash chromatography yielded high Rf material (30mg; 30%), low Rf material (19mg; 19%) and a mixed fraction (29mg; 29%). Hydrogenation of the high Rf material (13mg) in ethyl acetate (3ml) yielded a mixture of (11S)-8-methoxyserrulatane-5,18-diol (22a) and (11R)-8-methoxyserrulatane-5,18-diol (22b) in the relative proportions of 71% and 29% respectively.
**Variations of conditions on metal/ammonia reduction of methyl ether (19) of serrulatenol**

A. Short reaction time, cooling with external source, change in order of addition of reagents

To a solution of lithium (20mg; 2.86 mmol) in ammonia (20ml) was added the methyl ether (19) of serrulatenol, (50mg; 0.152 mmol) in dry tetrahydrofuran (2ml) and ethanol (0.3ml). After stirring for 3 minutes with a dry ice/acetone bath cooling the reaction flask, the reaction was worked up as described previously to yield the crude product mixture. A portion (16mg; 0.0482 mmol) was hydrogenated with platinum oxide (10mg) in ethyl acetate (3ml) for 2 h. Filtration through Celite and evaporation of the filtrate gave a mixture of the epimeric diols (13mg; 81%) (11S)-8-methoxyserrulatane-5,18-diol (22a) and (11R)-8-methoxyserrulatane-5,18-diol (22b) in the relative proportions of 55% and 45% respectively.

B. Short reaction time, cooling with external source, no added proton source.

To a flask containing ammonia (20ml) was added the methyl ether (19) of serrulatenol (50mg; 0.152 mmol) in dry tetrahydrofuran (2ml) and lithium (50mg; 7.14 mmol). After stirring for 4 minutes with a dry ice/acetone bath cooling the reaction flask, the reaction was quenched by the addition of isoprene and worked up as described to yield the crude mixture of products. A portion (18mg; 0.0542 mmol) was hydrogenated with platinum oxide (10mg) in ethyl acetate (3ml) for 2 h. Filtration through Celite and evaporation of the filtrate yielded a mixture of the epimeric diols (14mg; 78%) (11S) and (11R)-8-methoxyserrulatane-5,18-diol (22a) and (22b) each in the relative proportion of 50%.
Acetylation of the mixture of epimeric diols (22a) and (22b)

A mixture of the epimeric diols (22a) and (22b) (68mg; 0.204 mmol) in the relative proportion of 60% (11S)- and 40% (11R)- was acetylated with acetic anhydride (62mg; 0.608 mmol) and triethylamine (1ml) for 2 days. Dilute hydrochloric acid (5ml) was added and the mixture extracted with dichloromethane. The organic extracts were washed with water, dried and the solvent removed. The crude mixture (80mg; 94%) was purified by flash chromatography (dichloromethane) to yield a high Rf component (11S)-18-acetoxy-8-methoxyserrulatan-5-yl acetate (22c) (33mg; 39%) 'H n.m.r. δ (300MHz) 0.81, 6H, d, J 6-7Hz, (H16)₃, (H17)₃, 1-12, 3H, d, J6-9Hz, (H20)₃; 1.20 - 2.40, m, methylene envelope; 1.95, 3H, s, OAc; 2-10, 3H, s, (H19)₃; 2-32, 3H, s, 5-OAc; 3-16, 1H, m, H1; 3-80, 3H, s, OMe; 3-96, 2H, m, (H18)₂; 6-56, 1H, s, H7 and a low Rf component, (11R)-18-acetoxy-8-methoxyserrulatan-5-yl acetate (22d) (8mg; 9%) 'H n.m.r. δ (300MHz) 0.79 and 0.86, each 3H, d, J6-6, 6-5Hz, (H16)₃, (H17)₃; 1-14, 3H, d, J6-5Hz, (H20)₃; 1-10 - 2-70, m, methylene envelope; 1-89, 3H, s, OAC; 2-06, 3H, s, (H19)₃; 2-33, 3H, s, 5-OAc; 3-15, 1H, m, H1; 3-79, 3H, s, OMe; 5.17, 2H, m, (H18)₂; 6.54, 1H, s, H7.

A mixed fraction (28mg; 33%) was also obtained.

Lithium aluminium hydride reduction of the higher Rf diacetate (22c)

The higher Rf diacetate (22c) (111mg; .0263mmol) was treated with lithium aluminium hydride (40mg; 1.05 mmol) in dry tetrahydrofuran as described to afford (11S)-8-methoxyserrulatane-5,18-diol (22a) (8mg; 89%). The product had spectral data identical with those obtained previously.
**Attempted preparation of the bistosylate**

To the diol (22a) (24mg; 0.0704 mmol) was added p-toluenesulphonyl chloride (28mg; 0.150mmol) and dry pyridine (1ml). The mixture was left standing for two days then diluted with water (5ml) and extracted with dichloromethane (2x5ml). The organic extracts were dried and the solvent removed under reduced pressure to yield a mixture consisting of one major high Rf product plus several minor low Rf products which were not isolated. The major component was purified by preparative t.l.c. (dichloromethane/hexane; 3:7) and was identified as 5,18-epoxy-8-methoxyserrulatane (31) (10mg; 45%). Accurate mass 316.2392 (C₂₁H₃₂O₂ requires 316.2402). ν max (soln) 2952, 2875, 1466, 1260, 1102 cm⁻¹. H n.m.r. δ (300MHz) 0.88, 6H, d, J6.5Hz, (H16)₃, (H17)₃; 1.21, 3H, d, J6.6Hz, (H20)₃; 1.30 - 2.30, m, methylene envelope; 2.17, 3H, s, (H19)₃, 3.19, 1H, m, H1; 3.67, 1H, dd, Jgem 10.7, JH₁₈H₁₁ 10.7Hz, 4.33, 1H, dd, Jgem 10.7, JH₁₈H₁₁ 3.5Hz, (H18)₂; 3.76, 3H, s, OMe; 6.56, 1H, s, H7. m/z 316 (M), 301.

**Selective methylation of the diol (22a)**

A two-necked flask was flame-dried and flushed with nitrogen. The diol (22a) (205mg; 0.613 mmol) was placed in the flask and sodium hydride (21mg; 0.877 mmol, approx. 80% in mineral oil) was added. Dimethyl sulphoxide (7ml) was injected and the mixture was stirred for 15 min. Iodomethane (0.23ml; 3.74mmol) was then injected and the reaction mixture was stirred at room temperature for 2 days. Dilute hydrochloric acid was added followed by extraction with dichloromethane. Purification was achieved by removal of dimethyl sulphoxide under reduced pressure using an oil-pump followed by flash chromatography (ethyl acetate/dichloromethane; 1:99) to yield 5,8-dimethoxyserrulatan-18-ol (23) (102mg; 48%) as colourless crystals, m.p. 97-100°
from methanol/water. Found: C, 76·3; H, 10·3. C_{22}H_{36}O_{3} requires C, 75·8; H, 10·4% v_{\text{max}} (soln) 3460, 3016, 2948, 2869, 1604, 1466, 142, 1326, 1104 cm\(^{-1}\) 'H n.m.r. \(\delta\) (300Mz) 0·86, 6H, d, J=6·5Hz, (H16)\(_3\), (H17)\(_3\); 1·13, 3H, d, J=6·8Hz, (H20)\(_3\); 1·30 - 2·20, m, methylene envelope; 2·28, 3H, s, (H19)\(_3\); 2·86, 1H, m, H4; 3·11 and 3·38, each 1H, m, dd, J\text{gem}=1·3,H; 3·64 and 3·78, each 3H, s, 2xOMe; 6·52, 1H, s, H7. m/z 348 (M), 219.

**Mesylation of the dimethoxy alcohol (23)**

The dimethoxy alcohol (80mg; 0·230mmol) in dry pyridine (2ml) was cooled to 0\(^\circ\) and methanesulphonyl chloride (922mg; 8·05mmol) was added. The reaction mixture was then placed in the freezer overnight. Ice was added to the mixture which was then stirred for 30 min. Subsequent extraction with dichloromethane (2x10ml), followed by drying of the combined organic extracts and removal of the solvent, yielded the crude product. Purification by "dry column" flash chromatography gave **5,8-dimethoxy-serrulatan-18-yl mesylate** (32) (80mg; 82%) as an oil. 'H n.m.r. \(\delta\) (300 MHz) 0·84, 6H, d, J=6·6Hz, (H16)\(_3\), (H17)\(_3\) 1·13, 3H, d, J=6·9Hz, (H20)\(_3\); 1·20 - 2·20, m, methylene envelope; 2·26, 3H, s, (H19)\(_3\); 2·81, 3H, s, CH\(_3\)SO\(_2\); 3·04, 1H, m, H4; 3·14, 1H, m, H1; 3·64 and 3·78, each 3H, s, 2xOMe; 3·94, 1H, dd, J\text{gem}=9·7, J_{H18H119·7Hz}; 4·12, 1H, dd, J\text{gem}=9·7, J_{H18H116·3Hz}, (H18)\(_2\); 6·52, 1H, s, H7.
Attempted lithium aluminum hydride reduction of the dimethoxy mesylate (32)

The dimethoxy mesylate (13mg; 0.0305mmol) was treated with lithium aluminium hydride (12mg; 0.305mmol) in dry tetrahydrofuran (3ml) as described previously. The recovered material was found to be mainly starting material plus a low Rf component which had an Rf by t.l.c. corresponding to that of the dimethoxy alcohol (23). Further purification was not carried out.

Superhydride reduction of the dimethoxy mesylate (32)

A two-necked flask containing the dimethoxy mesylate (12mg; 0.0208mmol) was flame-dried and flushed with nitrogen. Dry tetrahydrofuran (3ml) was added followed by lithium triethylborohydride (0.1ml of 1M solution; 0.1mmol) and the reaction mixture refluxed for 24 hours. Ethyl acetate (0.2ml) was added to decompose the excess of hydride, followed by acidification with dilute hydrochloric acid (5ml) and extraction with dichloromethane. After drying and removal of solvent, it was found that the reaction had not proceeded to any significant extent, with mainly starting material plus some lower Rf material, presumably dimethoxy alcohol (23), being recovered. Further purification was considered unnecessary.

Preparation of the dimethoxy iodide (33)

The dimethoxy mesylate (32) (80mg; 0.188mmol) was refluxed with sodium iodide (85mg; 0.564mmol) in dry acetone (10ml) for 24 h. After the acetone was evaporated, water was added and the mixture was extracted with dichloromethane. Drying of the combined organic extracts and removal of the
solvent followed by flash chromatography yielded 18-iodo-5,8-dimethoxyserrulatane (33) (73mg; 85%) as an oil. νmax (soln) 2940, 1604, 1466, 1418, 1380, 1098 cm⁻¹. ¹H n.m.r. δ (300MHz) 0-82, 6H, d, J6-6Hz, (H16)₃, (H17)₃; 1-13, 3H, d, J6-9Hz, (H20)₃; 1-00-2-10, m, methylene envelope; 2-26, 3H, s, (H19); 2.98, 1H, dd, Jgem9-8, JH1₈αH1₇α9Hz, H1₈α; 3-33, 1H, dd, Jgem 9-8, JH1₈βH1₇β7-3Hz, H1₈β; 3-15, 2H, m, H1, H4; 3-66 and 3-79, each 3H, s, 2xOMe; 6-52, 1H, s, H7. m/z 458 (M), 219.

Tri-n-butylstannane reduction of the iodide (33)

A two-necked flask was flame-dried and flushed with nitrogen. The dimethoxy iodide (33) (73mg; 0.159mmol) in dry benzene (1.5ml) was added followed by AIBN (1mg). Tri-n-butylstannane (0.26ml; 0.956mmol) was injected and the mixture was gently refluxed overnight. After cooling, the solvent was evaporated under reduced pressure. The residue was then taken up in ether (5ml) and treated with dilute potassium fluoride solution after which the organic layer was collected, dried and concentrated. The tin byproducts were removed by flash chromatography by washing with hexane (400ml) and the product was subsequently eluted with dichloromethane/hexane (1:4). A further purification by flash chromatography to remove a trace of starting material yielded 5,8-dimethoxyserrulatane (8) (20mg; 38%) as a pale yellow oil. Accurate mass: 332.2721 (C₂₂H₃₆O₂ requires 332.271,5). [α]D -30.9 (c, 1.3). νmax (soln) 2928, 2864, 1466, 1402, 1260, 1226, 1102, 1008 cm⁻¹. ¹H n.m.r. δ (300MHz) 0-76, 3H, d, J6-9Hz, (H18)₃; 0-83, 6H, d, J6-7Hz, (H16)₃, (H17)₃; 1-12, 3H, d, J6-9Hz, (H20)₃; 1-20-2-10, m, methylene envelope; 2-27, 3H, s, (H19)₃; 2-80, 1H, m, H4; 3-12, 1H, m, H1; 3-63 and 3-78 , each 3H, s, 2xOMe; 6-50, 1H, s, H7. m/z 332 (M), 219.
DERIVATIVES OF THE TRIOL (2a)

Extraction of E. duttonii

Fresh leaves of *E. duttonii* (~1kg), collected on the plain east of Blinman, South Australia, were allowed to stand in ether (~3 litres) for a short period (~20 min.). Evaporation of the ether under reduced pressure yielded the crude extract (~100g) which was acetylated directly with acetic anhydride (120ml) and pyridine (120ml). After 48 h., ice/water was added and the mixture was extracted with ether, washed with 5% hydrochloric acid (150ml) then water (2x75ml) and the ether extracts dried, filtered and evaporated in vacuo. A portion of the crude, acetylated material (~15g) was purified by "dry column" flash chromatography (ethyl acetate/hexane) to yield a fraction rich in triacetate (~6g) and several other fractions presumably containing triacetate, tetraacetate and other components (~9g). The fraction rich in triacetate was further purified by "dry column" flash chromatography (ethyl acetate/hexane) to yield mainly two fractions, one containing high Rf material (3.9g) and the other relatively pure (1.0g). The most pure fraction (1.0g) was further purified by flash chromatography (ethyl acetate/hexane; 3:17) then distilled to yield 8,20-diacetoxyseirulat-14-en-7-yl acetate (2b) (410mg) b.p. 200-210°/0.04mm (block).

Found: C, 57.22%; H, 6.28%. C_{26}H_{36}O_{6} requires C, 57.13%; H, 6.41%. \nu_{\text{max}} \text{ (soln)} 2950, 2900, 1760, 1730, 1450, 1370, 1170, 910 cm^{-1}. \text{H n.m.r.} \delta (300MHz) 0.97, 3H, d, J5.8Hz, (H18)_{3}; 1.55, 1.65, each 3H, s, (H16)_{3}, (H17)_{3}, 2.05, 3H, s, 20'-OAc; 2.15, 3H, s, (H19)_{3}; 2.28, 2.37, each 3H, s, 2xOAc; 0.9-2.4, m, methylene envelope; 2.4, 1H, m, H4; 3.15, 1H, m, H1; 3.8, 1H, t, J8.1Hz, H20\alpha; 4.3, 1H, dd, J3.1, 3.6Hz, H20\beta; 4.97, 1H, t, J6.8Hz, H14; 6.95, 1H, s, H7. m/z 444 (M).
Lithium aluminium hydride reduction of the unsaturated triacetate (2b)

The unsaturated triacetate (2b) (410mg: 0.923mmol) in dry ether (10ml) was reduced with lithium aluminium hydride (88mg; 2.31mmol) in dry ether (10ml) for 2 h. After this time, water (5ml) was added and the mixture was acidified with concentrated hydrochloric acid to pH1. The ether phase was separated and the aqueous phase extracted with a further portion of ether (10ml). The organic extracts were combined, dried, filtered and evaporated in vacuo to yield serrulat-14-ene-7,8,20-triol (2a) (250mg: 85%). \( ^1H \) n.m.r. 8 (60MHz) 0.97, 3H, d, J7Hz, (H18)3; 1.56 and 1.67, 6H, s, (H16)3, (H17)3; 2.20, s, (H19)3; 1.20-4.0, m, methylene envelope; 4.97, 1H, t, J7Hz, H14; 6.45, brs, 2xOH; 6.53, 1H, s, H5.

Methylation of the unsaturated triol (2a)

Without further purification, the triol (2a) (250mg; 0.786mmol) was dissolved in dry dimethyl sulphoxide (5ml) and transferred via syringe to a flame-dried flask containing sodium hydride (48mg; 2.01mmol; 80% in mineral oil) under nitrogen. After stirring for 15 minutes, iodomethane (67mg; 0.29ml; 4.72mmol) was injected and the mixture stirred overnight. The dimethyl sulphoxide was then removed by heating under vacuum and 10% hydrochloric acid (10ml) was added. Extraction with dichloromethane (2x20ml) followed by drying of the combined organic extracts, filtration and removal of the solvent in vacuo yielded the crude product. Purification by flash chromatography (ethyl acetate/hexane; 1:4) gave 7,8-dimethoxyserrulat-14-en-20-ol (7) (84mg; 31%). \([\alpha]D^0 +15.50\) (c,1.4) lit.9\([\alpha]D^0 +5.60\) (c,1.4). \( \delta \) (300MHz) 0.98, 3H, d, J6-8Hz, (H18)3; 1.00-2.20, m, methylene envelope; 1.55 and 1.66, s, (H16)3, (H17)3; 2.22, 1H, s, (H19)3; 2.54, 1H, m, H4; 2.61, 1H, brs, OH; 3.20, m, H1; 3.55, 1H, dd, JH20αH1 7.5Hz, Jgem10-3Hz, H20α; 3.68, 1H, dd, JH20βH16-0Hz,
J$_{gem}$10.3 Hz, H$_{20}$β; 3.80 and 3.87, each 3H, s, 2xOMe; 5.00, 1H, t, J=6.6 Hz, H$_{14}$; 6.76, 1H, s, H$_{5}$.

lit. 9 H n.m.r. δ (90 MHz) 2.62, 1H, m, H$_{1}$; 3.23, 1H, m, H$_{4}$.

All other data were identical with those described in the literature$^9$.

NOEDS Experiments: Irradiation of the aromatic proton at δ6.76 resulted in the enhancement of several signals, the strongest being observed for the aromatic methyl at δ2.22 (4%) and the C4 methine proton at δ2.54 (3%). In the reverse experiment, irradiation of the methine proton (C4) at δ2.54 enhanced the aromatic signal at δ6.76 (4%).

**Catalytic reduction of the unsaturated triacetate (2b)**

The unsaturated triacetate (2b) (13-20g) was hydrogenated in ethyl acetate (200ml) in the presence of platinum oxide (400mg) for 48h. at room temperature. The reaction mixture was filtered through Celite and the filtrate was evaporated under reduced pressure to yield 8,20-diacetoxyserrulatan-7-yl acetate (37) (12.96g; 98%). The product had spectral data identical with those described previously (Honours Thesis, T. Webb, Adelaide University, 1986).

**Lithium aluminium hydride reduction of the triacetate (37) followed by selective methylation of the product triol (38)**

The triacetate (37) (12.96g; 29.06mmol) was reduced with lithium aluminium hydride (2.21g; 58.12mmol) in dry tetrahydrofuran (100ml) by the method described previously to yield serrulatane-7,8,20-triol (38) (8.64g; 93%). The 'H n.m.r. spectrum (60 MHz) confirmed that the reaction had proceeded to completion so, without further purification, the selective methylation was
carried out. The triol (8.64g; 27.0mmol) was stirred with sodium hydride (1.69g; 67.2mmol; approx. 80% in mineral oil) in dry dimethyl sulphoxide (50ml) at room temperature for 15 min. Iodomethane (101ml; 162mmol) was injected and the mixture was stirred for 3 days. After this time, the reaction was acidified with 10% hydrochloric acid (100ml) and extracted with dichloromethane (2x100ml). The organic extracts were dried and the solvent evaporated to give the crude product. Purification by "dry column" flash chromatography (ethyl acetate/light petroleum) yielded 7,8-dimethoxyserrulatan-20-ol (34) (5.05g; 54%) as an oil. Accurate mass 348.2674 (C22H35O1 requires 348.2664) νmax (soln) 3460, 2928, 1482, 1402, 1368, 1316, 126, 1104, 1070, 1012 cm⁻¹ 'H n.m.r. δ (300MHz) 0.82, 6H, d, J6-6Hz, (H16)₂, (H17)₂; 0.95, 3H, d, J6-8Hz, (H18)₃; 1.00-2.00, m, methylene envelope, 2.23, 3H, s, (H19)₃; 2.39, 1H, brs, -OH; 2.53, 1H, m, H4; 3.19, 1H, m, H1; 3.57 and 3.70, each 1H, dd, J₆₋⁶=10.2, JH₁H₂₀=7.5, 6.1Hz, (H20)₂; 3.80 and 3.87, each 3H, s, 2xOMe; 6.76, 1H, s, H5.

**Derivatisations of the alcohol (34)**

The following derivatives were prepared with the aim of obtaining a solid derivative for X-ray crystallographic analysis and also to facilitate purification of the alcohol (34). However, only the anthraquinone-2-carboxylate could be obtained crystalline, therefore the others were not fully characterised.

1. **Preparation of the p-nitrobenzoate (34a)**

To the dimethoxy alcohol (34) (690mg; 1.98mmol) was added p-nitrobenzoyl chloride (371mg; 1.98mmol) and triethylamine (0.33ml; 2.39mmol). The reaction mixture was stirred overnight after which saturated sodium bicarbonate solution (10ml) was added. Extraction with dichloromethane followed by washing of the organic extracts with dilute hydrochloric acid,
drying and removal of the solvent gave the crude product. Purification by preparative t.l.c. (dichloromethane; run twice) yielded 7,8-dimethoxyserrulatan-20-yl p-nitrobenzoate (34a) (167mg; 63%) as an oil. 'H n.m.r. δ (60MHz) 0.75-1.02, 9H, m, (H16)3, (H17)3, (H18)3; 1.10-2.17, m, methylene envelope; 2.28, 3H, s, (H19)3; 2.37-3.65, 2H, m, H1, H4; 3.83 and 3.97, each 3H, s, 2xOMe; 4.48, 2H, m, (H20)2; 6.83, 1H, s, H5; 8.33, 4H, s, arom.

2. Preparation of the 3,5-dinitrobenzoate (34b)

To the dimethoxy alcohol (34) (1.052g; 3.02mmol) was added 3,5-dinitrobenzoyl chloride (0.698g; 3.02mmol) and triethylamine (0.5ml; 3.59mol). The reaction mixture was stirred overnight and worked-up as described above to give the crude product. Purification by preparative t.l.c. (ethyl acetate/light petroleum; 3:7) yielded 7,8-dimethoxyserrulatan-20-yl 3,5-dinitrobenzoate (34b) (855mg; 52%) as an oil. 'H n.m.r. (60MHz) δCCl4 0.73 - 1.07, 9H, m, (H16)3, (H17)3, (H18)3; 1.07-2.10, m, methylene envelope; 2.23, 3H, s, (H19)3; 2.37-3.67, 2H, m, H1, H4; 3.77 and 3.93, each 3H, s, 2xOMe; 4.47, 2H, d, J5Hz, (H20)2; 6.73, 1H, s, H5; 9.18, 3H, m, arom.

**Hydrolysis of the 3,5-dinitrobenzoate (34b)**

The ester (34b) (664mg; 1.23mmol) was stirred for 2 days with sodium hydroxide (54mg; 1.35mmol) in methanol (10ml). Work-up yielded the alcohol (12) (385mg; 90%) with spectral data identical with those described previously.
3. Preparation of the p-phenylbenzoate (34c)

To the dimethoxy alcohol (12) (70mg; 0.201mmol) was added p-phenylbenzoyl chloride (44mg; 0.201mmol), triethylamine (0.033ml; 24mg; 0.241mmol) and dichloromethane (1ml). The reaction mixture was left standing for several days after which work-up was carried out as before. Purification was achieved by preparative t.l.c. (ethyl acetate/light petroleum; 2:8) to yield 7,8-dimethoxyserrulatar-20-yl p-phenylbenzoate (34c) (53mg; 50%) as an oil. 'H n.m.r. (60MHz) δCC14 0-70-1-07, 9H, m, (H16)3, (H17)3, (H18)3; 1-07-2.00, m, methylene envelope; 2.22, 3H, s, (H19)3; 2-37 - 3-70, 2H, m, H1, H4; 3-77 and 3-93, each 3H, s, 2xOMe; 4.27, 2H, m, (H20)2; 6-68, 1H, s, H5; 7-77, 9H, br m, arom.

4. Preparation of the p-bromobenzoate (34d)

To the dimethoxy alcohol (34) (1-01g; 2-92mmol), dimethylaminopyridine (18mg; 0.147mmol) and pyridine (6ml) in dichloromethane (5ml) was added p-bromobenzoyl chloride (636mg; 2.89mmol). The mixture was left standing at room temperature for 3 days. After this time, dilute hydrochloric acid (30ml) was added and the mixture extracted with dichloromethane (2x50ml). The organic extracts were dried, filtered and evaporated in vacuo to yield the crude ester. Purification by flash chromatography (ethyl acetate/hexane; 1:9) gave 7,8-dimethoxyserrulatan-20-yl p-bromobenzoate (34d) (547mg; 35%) as an oil. 'H n.m.r. δ (300MHz) 0-82, 6H, d, J6-6H, (H16)3, (H17)3, (H17)3; 0-96, 3H, d, J6-8Hz, (H18)3, 1-00-2-00, m, methylene envelope; 2-24, 3H, s, (H19)3; 2-58, 1H, m, H4; 3-50, 1H, m, H1; 3-78 and 3-52, each 3H, s, 2xOMe; 4-32, 1H, dd, Jgem10-4, JH1H20α10-4Hz, H20α; 4-47, 1H, d, Jgem10-4, JH1H20β 4-2Hz, H20β; 6-76, 1H, s, H5; 7-56, 7-92, A'AB'B system arom.
Some starting material, the dimethoxy alcohol (34) (313mg; 31%) was also recovered.

5. Preparation of the anthraquinone-2-carboxylate (34e)

To the dimethoxy alcohol (300mg; 0.860mmol) in dry pyridine (2ml) was added anthraquinone-2-carbonyl chloride (235mg; 0.867mmol) and dimethylaminopyridine (5mg; 0.0433mmol). After heating at 55° for 3 days, dilute hydrochloric acid (10ml) was added and the mixture extracted with dichloromethane (2x20ml). The combined organic extracts were dried, filtered and evaporated in vacuo to give the crude product. Purification by flash chromatography (ethyl acetate/hexane; 3:17) followed by recrystallisation from hexane yielded 7,8-dimethoxyserrulatan-2-yl anthraquinone-2-carboxylate (34e) (245mg; 49%) as a yellow solid, mp 61-63°. Accurate mass 582.3001 (C_{37}H_{42}O_{6} requires 582.2981) ¹H n.m.r. δ (300MHz) 0.83, 6H, d, J6.7Hz, (H16)₃, (H17)₃; 0.97, 3H d, J6.9Hz, (H18)₃; 1.00-2.00, m, methylene envelope; 2.24, 2H, s, (H19)₃; 2.60, 1H, m, H₄; 3.56, 1H, m, H₁; 3.79 and 3.93, each 3H, s, 2xOMe; 4.33 and 4.53, each 1H, t and dd, J_{gem}10.4Hz, J_{H2O,H1}10.4, J_{H2O,H1}4.3Hz (H2O)₂; 7.26, 1H, s, H₅; 7.8, 2H, m, H₆', H₇'; 8.3, 4H, br m, H₃', H₄', H₅', H₈'; 8.98, 1H, d, J1.6Hz, H₁'.

6. Glycosylation of the dimethoxy alcohol (34)

The following glycosylation procedure was based on a method developed previously.³⁴a, ³⁴b.

Under strictly anhydrous conditions and a nitrogen atmosphere, boron trifluoride etherate (0.087ml; 0.692mmol) was added to a solution of the alcohol (34) (50mg; 0.144mmol) and the ortho ester ³³ (109mg; 0.173mmol) in
dry dichloromethane (5ml) at 0°. The reaction was then warmed to room 
temperature and monitored by t.l.c. until it appeared to be proceeding no 
further. After 15 min., it was quenched by the addition of saturated sodium 
hydrogen carbonate until basic. The organic layer was separated and washed 
with water and brine, dried (MgSO4) and evaporated under reduced pressure to 
yield the crude product. Purification by flash chromatography (ethyl 
acetate/hexane; 1:9) gave the 5,8-dimethoxyserrulatan-20-yl tetra-O-pivaloyl-β-
D-glucopyranoside (34f) (50mg; 41%) as an oil. ¹H n.m.r. δ (300MHz) 0.81, 6H, d, 
J6.6Hz, (H16)₃, (H17)₃, 0.91, 3H, d, J6.8Hz, (H18)₃; 0.96-1.43, m, methylene 
envelope; 1.12, 1.15, 1.18 and 1.21, each 9H, s, 4xtert-butyl, 2.21, 3H, s, (H19)₃; 
2.47, 1H, m, H4; 3.15, 1H, m, H1; 3.61, 2H, d, J7.1Hz, (H20)₂; 3.70, 1H, m, H5', 3.77 
and 3.84, each 3H, s, 2xOMe; 4.04, 1H, dd, J12.2, 5.3Hz, H6β; 4.19, 1H, d, J12.1Hz, 
H6α; 4.60, 1H, d, J8.0Hz, H1'; 5.05, 1H, t, 8.9Hz, H2'; 5.13, 1H, t, J9.7Hz, H4'; 5.33, 
1H, t, J9.5Hz, H3'; 6.70, 1H, s, H5.

Some low Rf material (45mg) containing starting material and sugar residues 
was also isolated.

7. Preparation of the acetate (34g)

The dimethoxy alcohol (34) (1.56g; 4.48mmol) was stirred with acetic anhydride 
(0.42ml; 4.40mmol) and triethylamine (2ml; 27.72mmol) for 48h. After this 
period, dichloromethane (50ml) was added and the mixture washed with 
dilute hydrochloric acid (6x50ml) followed by water (3x50ml). The organic 
phase was then dried and evaporated under reduced pressure. Purification 
of the crude product by preparative t.l.c. (ethyl acetate/light petroleum; 2:8) 
followed by distillation yielded 7,8-dimethoxyserrulatan-20-yl acetate (34g) as a 
pale yellow oil (750mg; 43%) b.p. 198-201^oC/0.01mm (block). Found: C,73.58; H, 
9.85 C₂₄H₃₈O₄ requires C, 73.80; H, 9.81% νmax (soin) 2950, 1730, 1480, 1410, 1360,
1260, 1240, 1080, 1040 cm⁻¹ 'H n.m.r. δ (300MHz) 0.81, 6H, d, J6.6Hz, (H16)₃, (H17)₃, 0.94, 3H, d, J6.8Hz, (H18)₃; 1.06-2.00, m, methylene envelope; 2.07, 3H, s, OAc; 2.22, 3H, s, (H19)₃; 2.52, 1H, m, H4; 3.34, 1H, m, H1; 3.78 and 3.88, each 3H, s, 2xOMe; 4.00 and 4.17, each 1H, t and dd, J10.3Hz, J₉₂₀H₁₄.1Hz. (H20)₂; 6.72, 1H, s, H5. m/z 390 (M), 330, 217.

**Hydrolysis of the acetate (34g)**

The acetate (34g) (750ml; 1.92mmol) was stirred overnight with sodium hydroxide (84mg; 2.11mmol) in methanol (10ml). Work-up yielded the alcohol (12) (302mg; 45%) with all data identical with those described previously.

**Tosylation of the dimethoxy alcohol (34)**

The alcohol (34) (385mg; 1.11mmol) was dissolved in pyridine (1ml; 12.4mmol) and p-toluenesulphonyl chloride (212mg; 1.11mmol) was added. The mixture was stirred overnight. Subsequently, water (10ml) was added and the mixture extracted with dichloromethane. The organic extracts were washed with dilute hydrochloric acid (2x10ml), dried and concentrated. Purification by preparative t.l.c. (ethyl acetate/ light petroleum; 1:9) yielded 7,8-dimethoxyserrulatan-20-yl tosylate (35) (368mg; 66%) Accurate mass: 502.2774 (C₂₉H₄₂O₅S requires 502.2753) vₘₐₓ (soln) 2932, 1712, 1600, 1462, 1408, 1360, 1176, 1098, 1072, 948 cm⁻¹ 'H n.m.r. δ (300MHz) 0.81, 6H, d, J6.6Hz, (H16)₃, (H17)₃; 0.90, 3H, d, (H18)₃; 1.00-1.90, m, methylene envelope; 2.20, 3H, s, (H19)₃; 2.44, 3H, s, CH₃-Ar; 3.30, 1H, m, H1; 3.73 and 3.75 each 3H, s, 2xOMe; 3.81, 1H, dd, J₉₂₀H₁₀.5Hz, H₂₀α; 4.21, 1H, dd, J₉₂₀H₁₀.5Hz, H₂₀β; 6.69, 1H, s, H₅; 7.32, 7.79, AA¹BB¹ system arom. m/z 502 (M), 217.
Lithium aluminium hydride reduction of the tosylate (35) to give the dimethyl ether (6b)

The tosylate (35) (185mg; 0.370mmol) was reduced with lithium aluminium hydride (56mg; 1.47mmol) in dry tetrahydrofuran (5ml) under standard conditions to yield a mixture of products. Upon purification by preparative t.l.c. (ethyl acetate/light petroleum; 1:19) the major component was identified as 7,8-dimethoxyserrulatane (6b) (62mg; 50%) as a pale yellow oil. Accurate mass: 332.2709 (C_{22}H_{36}O_{2} requires 332.2715) [α]_{D} -10.0 (c, 0.2) lit.\[9\] [α]_{D} -18.3° (c, 1.7) \nu_{\text{max}} (soln) 2928, 2864, 1466, 1402, 1260, 1226, 1102, 1008 cm\(^{-1}\) \(\text{H n.m.r.} \ \delta\) (300MHz) 0.81, 6H, d, J6.5Hz, (H16)\(_{3}\), (H17)\(_{3}\); 0.93, 3H, d, J6.8Hz, (H18)\(_{3}\); 1.17, 3H, d, J7.0Hz, (H20)\(_{5}\); 1.19-1.89, m, methylene envelope; 2.22, 3H, s, (H19)\(_{3}\); 2.52, 1H, m, H4; 3.12, 1H, m, H1; 3.80 and 3.87, each 3H, s, 2xOMe; 6.71, 1H, s, H5. m/z 332 (M), 219. lit.\[9\] \(\text{H n.m.r.} \ \delta\) (90MHz) 0.82, 3H, d, J7Hz, (H18)\(_{3}\); 0.94, 6H, d, J7Hz, (H16)\(_{3}\), (H17)\(_{3}\). All other data were identical with those described above.

Attempted preparation of the dimethoxy bromide

The alcohol (34) (50mg; 0.144mmol) was stirred with phosphorus tribromide (19mg; 0.0718mmol) in dry tetrahydrofuran (1ml) for 24 h. The solvent was evaporated, saturated sodium bicarbonate solution (1ml) was added and the mixture extracted with dichloromethane (3x5ml). Drying of the organic extracts and removal of the solvent gave the crude product with was contaminated with a significant quantity of unknown material. Flash chromatography (ethyl acetate/dichloromethane; 1:9) failed to remove the impurity, as did prolonged warming under reduced pressure. As the outcome of the experiment was inconclusive, the reaction was abandoned.
**Preparation of the dimethoxy iodide (36)**

To the tosylate (35) (52mg; 0.104mmol) and sodium iodide (47mg; 0.311mmol) was added dry acetone (7ml) and the mixture brought to reflux. Refluxing was continued overnight, the mixture was then cooled and the solvent removed under reduced pressure. Water was introduced followed by extraction with dichloromethane. The organic extracts were washed with dilute sodium metabisulphite solution and then dried and evaporated. Purification by flash chromatography (dichloromethane/light petroleum; 3:17) yielded 20-iodo-7,8-dimethoxyserrulatane (36) (26mg; 55%) 'H n.m.r. δ (60MHz) 0.55, 3H, d, J7Hz, (H18)3; 0.88, 6H, d, J6Hz, (H16)3, (H17)3; 1.1-2.4, m, methylene envelope; 2.5-4.4, 4H, m, H1, H4, (H20)2; 3.80 and 3.92, each 3H, s, 2xOMe, 6.60, 1H, s, H5.

**Tri-n-butylstannane reduction of the dimethoxy iodide (36) to give the dimethyl ether (6b)**

All apparatus was flame-dried and flushed with nitrogen. To the iodide (36) (54mg; 0.118mmol) and AIBN (1mg) in dry benzene (1ml) was added tri-n-butylstannane (206mg; 0.19ml; 0.707mmol) slowly with stirring. The mixture was then refluxed overnight. After cooling, the solvent was removed and the residue taken up in ether (5ml). After washing with dilute potassium fluoride solution, the organic layer was dried and concentrated to give the crude product. This was placed on a flash column and washed with light petroleum (400ml) to remove tin byproducts. The product was then eluted (dichloromethane/light petroleum; 2:3) and was identified as 7,8-dimethoxyserrulatane (6b) (22mg; 56%) with all data identical with those obtained previously.
**Base catalysed elimination of the tosylate (36)**

To the tosylate (36) (163mg; 0.325mmol) in dry dimethyl sulphoxide (4ml) was added sodium hydride (49mg; 2.03mmol; approx. 80% in mineral oil) and the reaction mixture was stirred overnight. The dimethyl sulphoxide was removed by heating under vacuum and to the residue was added dilute hydrochloric acid. Extraction with dichloromethane followed by drying and removal of solvent gave the crude product. Purification by flash chromatography (dichloromethane/hexane; 3:7) yielded 7,8-dimethoxyserrulat-1(20)-ene (96) (61mg; 54%). Accurate mass: 330.2561 (C_{22}H_{34}O_{2} requires 330.2559) \( \nu_{\text{max}} \) (soln) 2925, 2875, 1600, 1470, 1300, 1230, 1080 cm\(^{-1} \) \(^{1}\)H n.m.r. \( \delta \) (300MHz) 0.83, 6H, d, J6.7Hz, (H16)\(_3\), (H17)\(_3\); 0.86, 3H, d, J7.3Hz, (H18)\(_3\); 0.96-2.70, m, methylene envelope, 2.23, 3H, s, (H19)\(_3\); 3.77 and 3.83, each 3\( \nu \), s, 2xOMe; 5.19 and 5.76, each 1\( \nu \), s, (M)\(_2\); 6.72, 1\( \nu \), s, H5. m/z 330 (M), 217.

**Catalytic reduction of the dimethoxy alkene (96) to give the epimer at C1, (6a)**

The dimethoxy alkene (96) (31mg; 0.939mmol) was hydrogenated in ethyl acetate (5ml) in the presence of platinum oxide (15mg) for 72h. at room temperature. The reaction mixture was filtered through Celite and the filtrate evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane/light petroleum; 2:3) to yield (1S)-7,8-dimethoxyserrulatane (6a) (23mg; 74%). Accurate mass: 332.2728 (C_{22}H_{36}O_{2} requires 332.2715). \( \nu_{\text{max}} \) (soln) 2928, 2864, 1466, 1402, 1260, 1226, 1102, 1008 cm\(^{-1} \). \(^{1}\)H n.m.r. \( \delta \) (300MHz) 0.81, 6H, d, J7.1Hz, (H16)\(_3\), (H17)\(_3\); 1.02, 3H, d, J6.8Hz, (H18)\(_3\); 1.19, 3H, d, J7.1Hz, (H20)\(_3\); 1.20-1.80, m, methylene envelope; 2.21, 3H, s, (H19)\(_3\); 2.68, 1\( \nu \), m, H4; 3.12, 1\( \nu \), m, H1; 3.80 and 3.88, each 3\( \nu \), s, 2xOMe, 6.81, 1\( \nu \), s, H5. m/z 332 (M), 219.
Metal ammonia reduction of the dimethoxy alkene (96) to give mainly the epimer at C1, (6a)

To a flask containing liquid ammonia (10ml) was added the dimethoxy alkene (96) (26mg; 0.0788mmol) in dry tetrahydrofuran (2ml), lithium (20mg; 2.9mmol) and tert-butanol (10mg; 0.135mmol) in dry tetrahydrofuran (0.5ml) in that order. The mixture was stirred for 3 min. after which time isoprene (0.5ml) was added to remove the excess of metal. The ammonia was then allowed to evaporate and water (10ml) was introduced. Extraction with dichloromethane (2x10ml), drying and removal of the solvent in vacuo yielded the crude product. Purification by flash chromatography (dichloromethane/hexane; 1:3) gave a mixture of epimers at C1, (1R)- and (1S)-7,8-dimethoxyserrulatane (6mg; 23%), (6b) and (6a), in the ratio 3:7 respectively. All spectral data were identical with those obtained previously.

The baseline material, which was presumed to correspond to over-reduced material, was not isolated.

Attempted epoxidation of the dimethoxy alkene (96)

To the dimethoxy alkene (36mg; 0.109mmol) and sodium bicarbonate (9mg; 0.109mmol) in dry dichloromethane (2ml) at 0° was added m-chloroperoxybenzoic acid (24mg; 0.136mmol, 80%) in dry dichloromethane (3ml). After 1h., t.l.c. analysis revealed the disappearance of the starting material accompanied by the formation of at least two low Rf compounds. The mixture was then treated with 10% sodium metabisulphite solution (5ml) and stirred until all remaining peracid was reduced. The organic layer was separated, washed with 10% potassium carbonate solution (5ml), dried, filtered
and evaporated in vacuo. Purification of the residue by flash chromatography (ethyl acetate/hexane; 3:7) yielded a higher Rf component (7mg) and a lower Rf component (13mg). Since neither appeared to correspond to epoxide and the structures could not be further elucidated, the experiment was abandoned.

**Jones oxidation of the dimethoxy alcohol(34)**

To the dimethoxy alcohol (100mg; 0.287mmol) in acetone at 0° was added Jones reagent dropwise with stirring until the orange colour just persisted. The solvent was then evaporated in vacuo, water (10ml) was added and the mixture extracted with dichloromethane (2x10ml). Purification of the crude product by flash chromatography (ethyl acetate/hexane; 1:9) yielded **7,8-dimethoxyserrulatan-20-al** (75) (46mg; 46%) as an oil. Accurate mass: 346.2518 (C22H34O3 requires 346.2508). νmax (soln) 2932, 2864, 1718, 1674, 1484, 1408, 1316, 1214, 1072, 1012 cm⁻¹. ¹H n.m.r. δ (300MHz) 0.82, 6H, d, J6.6Hz, (H16)3, (H17)3; 0.99, 3H, d, J6.8Hz, (H18)3; 1.00-2.00, m, methylene envelope, 2.26, 3H, s, (H19)3; 2.63, 1H, m, H4; 3.58, 1H, ddd, JH1H2α3.4, JH1H2β7.2, JH1H2β7.2Hz, H1; 3.78 and 3.80, each 3H, s, 2xOMe; 6.87, 1H, s, H5; 9.45, 1H, d, J3.4Hz, H20. m/z 346 (M), 317, 233.

**Attempted equilibration of the aldehyde (75)**

The dimethoxy aldehyde (75) (20mg; 0.578mmmol) was heated under nitrogen at 60° overnight with a trace of sodium hydroxide in D₄-methanol (0.5ml). Analysis by t.l.c. and n.m.r. (60MHz) revealed some decomposition and the results were inconclusive.

**Oxidation of the dimethoxy alcohol (34) to the carboxylic acid (76)**
To a solution of the dimethoxy alcohol (490mg; 1.41mmol) and sodium periodate (904mg; 4.22mmol) in carbon tetrachloride (6ml), acetonitrile (6ml) and water (9ml) was added ruthenium trichloride hydrate catalyst (6mg; 0.031mmol; 2.2%) and the reaction mixture was stirred vigorously for 2 h. Dichloromethane (50ml) was added and the layers were separated. The organic layer was evaporated in vacuo then the residue taken up in ether and filtered through celite. After removal of the solvent, the crude product mixture was purified by flash chromatography (ethyl acetate/hexane; 3:7) to yield a low Rf component, 7,8-dimethoxyserulatan-20-al (76) (116mg; 23%). Accurate mass: 362.2462 (C_{22}H_{34}O_{4} requires 362.2457). \( \nu_{\text{max}} \) (soln) 3100-2500, 2928, 1742, 1706, 1488, 1460, 1408, 1300, 1238, 1078, 1048, 1016 cm\(^{-1}\). 'H n.m.r. \( \delta \) (300MHz) 0.82, 6H, d, J6.7Hz, (H16)\(_3\), (H17)\(_3\); 0.99, 3H, d, J6.8Hz, (H18)\(_3\); 1.00-2.10, m, methylene envelope, 2.24, 3H, s, (H19)\(_3\); 2.64, 1H, m, H4; 3.75, 1H, M, H1, 3.75 and 3.83, each 3H, s, 2xOMe; 6.82, 1H, s, H5. m/z 362 (M), 317, 249, 203.

The high Rf component was identified as 7,8-dimethoxyserulatan-20-al (75) (167mg; 34%) with all spectral data identical with those obtained previously.

**Methylation of the carboxylic acid (76) with diazomethane**

The carboxylic acid (76) (106mg; 0.293mmol) in ether (5ml) was treated dropwise with an ether solution of diazomethane until no starting material remained by t.l.c. After 40 min., the solvent was evaporated in vacuo and the residue purified by flash chromatography (ethyl acetate/hexane; 1:9) to yield the desired product, methyl 7,8-dimethoxyserulatan-20-oate (77) (49mg; 45%) as an oil. Accurate mass: 376.2627 (C_{23}H_{36}O_{4} requires 376.2614) \( \nu_{\text{max}} \) (soln) 2932, 2864, 2252, 1730, 1486, 1462, 1382, 1168,1098, 1010 cm\(^{-1}\) 'H n.m.r. \( \delta \) (300MHz) 0.83, 6H, d, J6.5Hz, (H16)\(_3\), (H17)\(_3\); 0.99, 3H, d, J6.8Hz, (H18)\(_3\); 1.00-200, m, methylene
envelope, 2.23, 1H, s, (H19)3; 2.64, 1H, m, H4; 3.75, 1H, m, H1; 3.70, 3.76 and 3.79, each 3H, s, 3xOMe; 6.81, 1H, s, H5. m/z 376 (M).

**Equilibration of the methyl ester (77)**

The methyl ester (77) (19mg; 0.0505mmol) was heated at 55° with a catalytic amount of sodium methoxide in methanol (2ml) under nitrogen for 5 days. The solvent was evaporated in vacuo and to the residue was added 10% ammonium chloride solution (5ml). Extraction with dichloromethane (2x5ml) followed by drying, filtering and removal of the solvent in vacuo yielded the crude product mixture. Purification by flash chromatography (ethyl acetate/hexane; 1:4) yielded a mixture of epimeric methyl esters, (1R) - and (1S)-7,8-dimethoxyserrulatan-20-oate, (77) and (78) (4mg; 21%) in the ratio of 3:1 respectively. Although isolated as a mixture, the products were separable by chromatography with the higher Rf spot corresponding to the minor isomer.

Minor isomer (78) 'H n.m.r. δ (300MHz) 0.83, 6H, d, J6.5Hz, (H16)3, (H17)3; 0.99, 3H, d, J6.8Hz, (H18)3; 1.00-2.20, m, methylene envelope; 2.24, 3H, s, (H19)3; 2.64, 1H, m, H4; 3.75, 1H, m, H1; 3.69, 3.77 and 3.81, each 3H, s, 3xOMe; 6.81, 1H, s, H5. The 'H n.m.r. also contained peaks for the major isomer (77) identical with those described previously.

A low Rf fraction (2mg) consisting of two components was also isolated, presumably corresponding to the equilibrium mixture of the epimeric carboxylic acids, (76) and (79).

Prior to this, the equilibration was carried out for periods of both 12 h. and 24 h. at 55° under nitrogen however, during this time no change was observed by t.l.c. and the recovered methyl ester was found in both cases to be homogeneous by 'H n.m.r. spectroscopy (300MHz).
DERIVATIVES OF THE TETRAOL (2c)

Catalytic reduction of the unsaturated tetraacetate (2d)

The unsaturated tetraacetate (2d) (10.06g) comprising approximately 30% unknown impurities as detected by 'H n.m.r. spectroscopy (60MHz) was hydrogenated in ethyl acetate (150ml) in the presence of platinum oxide (150mg) for 48h. at room temperature. The reaction mixture was filtered through Celite and the filtrate evaporated under reduced pressure to give the crude product in quantitative yield. Subsequent purification by "dry column" flash chromatography (ethyl acetate/light petroleum) yielded (3R)-7,8,20-triacetoxy serrulatan-3-yl acetate (39) (5.31g; 53%). Accurate mass: 504.2738 (C_{28}H_{40}O_{8} requires 504.2723). All spectral data were identical with those described previously (T. Webb, Honous Thesis, Adelaide University, 1986).

Fractions rich in tetraacetate (39) but containing high Rf impurities (195mg; 2%) and low Rf impurities (3.15g; 31%) were also recovered from the purification.

Lithium aluminium hydride reduction of the tetraacetate (39) followed by selective methylation of the product tetraol (40)

The tetraacetate (39) (2.16g; 4.29mmol) was reduced with lithium aluminium hydride (652mg; 17.20mmol) in dry tetrahydrofuran (20ml) as described previously to yield (3R)-serrulatan-3,7,8,20-tetraol (40) (1.34g; 93%) m/z 336 (M). The 'H n.m.r. spectrum (60MHz) confirmed that the reaction had gone to completion so without further purification, the methylation was carried out. The tetraol (1.34g; 3.98mmol) was stirred with sodium hydride (251mg; 10.45mmol; approx. 80% in mineral oil) in dry dimethyl sulphoxide (20ml) at
room temperature for 15 min. Iodomethane (1.49ml; 23.9mmol) was injected and the mixture was stirred at room temperature for 3 days. After this time the mixture was acidified with dilute hydrochloric acid (20ml) and extracted with dichloromethane (2x50ml). The extracts were dried and the solvent evaporated to give the crude product. Purification by flash chromatography (ethyl acetate/light petroleum; 7:3) gave (3R)-7,8-dimethoxyserrulatane-3,20-diol (41) (474mg; 33%) as an oil. Accurate mass: 364.2610 (C_{22}H_{36}O_{4} requires 364.2613) \nu_{\text{max}} \text{(soln)} 3440, 3020, 2928, 1482, 1410, 1072 \text{ cm}^{-1} \text{ } ^{1}H \text{ n.m.r.} \delta (300MHz) 0.60, 3H d, J6.8Hz, (H18)_{3}; 0.89, 6H, d, J6.5Hz, (H16)_{3}, (H17)_{3}; 1.00-2.20, m, methylene envelope; 2.23, 3H, s, (H19)_{3}; 2.75, 1H, m, H4; 3.33, 1H, m, H1; 3.57 and 3.74, each 1H, m, (H20)_{2}; 3.80 and 3.85, each 3H, s, 2xOMe; 6.68, 1H, s, H5. m/z 364 (M), 233, 205.

A further fraction (188mg; 15%) rich in dimethoxy diol (41) was isolated.

A significant quantity of low Rf material, presumably rich in mono-methylated material, as suggested by the \(^1H \text{n.m.r. spectrum (60MHz)}, was also recovered (506mg; 36%).

**Tosylation of the dimethoxy diol (41)**

The dimethoxy diol (41) (290mg; 0.797mmol) was placed in a flask with p-toluenesulphonyl chloride (228mg; 1.20mmol) and dry pyridine (2ml). After cooling to 0\(^0\), carbon tetrachloride (2ml) was added and the reaction mixture was left standing at room temperature for 2 days. Subsequently, water (10ml) was added and after extraction with dichloromethane, the organic extracts were washed with dilute hydrochloric acid (2x10ml), dried and concentrated. Purification by flash chromatography (ethyl acetate/light petroleum; 1:3) yielded (3R)-hydroxy-7,8-dimethoxyserrulatan-20-yl tosylate (42) (234mg; 57%).
Accurate mass: 518.2667 (C_{29}H_{42}O_{8}S requires 518.27102) $\nu_{\text{max}}$ (soln) 3600, 2924, 2900, 1598, 1464, 1410, 1360, 1176, 960 cm$^{-1}$ $^1$H n.m.r. $\delta$ (300MHz) 0.52, 3H, d, J6.9Hz, (H18)$_3$; 0.87, 6H, d, J6.7Hz, (H16)$_3$, (H17)$_3$; 1.00-2.20, m, methylene envelope, 1.51, 1H, s, OH; 2.21, 3H, s, (H19)$_3$; 2.24, 3H, s, CH$_3$-Ar; 2.72, 1H, m, H4; 3.43, 1H, m, H1; 3.72 and 3.14, each 3H, s, 2xOMe; 3.84 and 4.31, each 1H, t and dd, $J_{\text{gem}}$10.2, $J_{1H_{1}H_{20}}$9.4, 3.7Hz, (H20)$_2$; 4.12, 1H, m, H3; 6.62, 1H, s, H5; 7.32, 7.77, AA$^1$BB$^1$ system arom. m/z 518 (M), 500.

**Attempted reduction of the hydroxy tosylate (42) with lithium triethylborohydride**

A two-necked flask was flame-dried and flushed with nitrogen. The hydroxy tosylate (42) (133mg; 0.257mmol) in dry tetrahydrofuran (5ml) was placed in the flask, followed by the addition of lithium triethylborohydride (1.29ml of 1M soln; 1.29mmol). The reaction mixture was refluxed for 24h. Ethyl acetate (1ml) was then added to decompose the excess of hydride, followed by acidification with dilute hydrochloric acid (5ml) and extraction with dichloromethane. Drying of the organic extracts and removal of solvent yielded a complex mixture of products not easily separable. Purification by flash chromatography (ethyl acetate/hexane; 1:9) gave a higher Rf component (23mg) which produced a molecular ion corresponding with that of the desired product, m/z 348 (M), however the high field $^1$H n.m.r. spectrum (3000MHz) was unsatisfactory and as such no conclusions could be made as to the structure of this compound. The major component, which was of lower Rf, was identified as (3R)-7,8-dimethoxyserrulatan-3,20-diol (41) (29mg; 31%) with spectral data identical with those described previously.

A complex mixture of minor components (27mg) was also recovered from the purification.
Preparation of the iodo alcohol (45)

To the tosylate (42) (84mg; 0.162mmol) in a flame-dried flask which had been flushed with nitrogen was added sodium iodide (146mg; 0.972mmol) and dry acetone (7ml). The mixture was refluxed for 48h. After this time, the solution was concentrated, water added and the mixture extracted with dichloromethane. After subsequent washing with dilute sodium thiosulphate solution, the organic extracts were dried and the solvent removed. Purification by flash chromatography (ethyl acetate/hexane; 1:9) yielded (3R)-20-iodo-7,8-dimethoxyxserrulatan-3-ol (45) (50mg; 65%). Accurate mass: 474.1613 (C_{22}H_{35}O_{3}I requires 474.1631). \nu_{\text{max}} (\text{soln}) 3604, 2952, 1480, 1408, 1180, 1076 cm^{-1}. 

{H} n.m.r. \delta (300MHz) 0.61, 3H, d, J6.9Hz, (H18)\_3; 0.88, 6H, d, J7.0Hz, (H16)\_3, (H17)\_3; 1.00-2.20, m, methylene envelope; 2.23, 3H, s, (H19)\_3; 2.73, 1H, m, H4; 3.17 and 3.64, each 1H, t and dd, J_{\text{gem}} 9.2, J_{H1H20} 9.8, 2.7Hz, (H20)\_2; 3.40, 1H, m, H1; 3.79 and 3.89, each 3H, s, 2xOMe; 4.25, 1H, m, H3; 6.66, 1H, s, H5. m/z 474 (M), 361.

Tri-n-butylstannane reduction of the iodo alcohol (45)

To the iodo alcohol (45) (36mg; 0.759mmol) and AIBN (2mg) in benzene (1ml) was added tri-n-butylstannane (132mg; 0.12ml; 0.456mmol) and the mixture refluxed overnight. After cooling to room temperature, the benzene was removed under vacuum and the residue taken up in ether (5ml). Washing with 10% potassium fluoride solution followed by drying of the organic layer and removal of solvent gave the crude product. The tin byproducts were removed by placing the crude material on a flash column and washing with light petroleum (400ml). The product was then eluted (ethyl acetate/hexane; 1:9) and identified as (3R)-7,8-dimethoxyxserrulatan-3-ol (43b) (17mg; 65%).
Accurate mass: 348.2674 (C_{22}H_{36}O_{3} requires 348.2664). v_{\text{max}} (soln) (345, 2924, 2864, 1602, 1466, 1408, 1380, 1328, 1204, 1068 cm^{-1}. \text{H n.m.r.} \delta (300MHz) 0.53, 3H d, J6.9Hz, (H18)_{2}; 0.88, 6H, d, J6.5Hz, (H16)_{3}, (H17)_{3}; 1.26, 3H, d, J7.0Hz, (H20)_{3}; 1.30-1.65, m, methylene envelope; 1.57, 1H, s, -OH, 2.08, 2H, m, H2α, H11; 2.23, 3H, s, (H19)_{3}; 2.79, 1H, dd, JH4H34.5, H4; 3.25, 1H, ddd, JH1H207.0Hz, H1; 3.79 and 3.85, each 3H, s, 2xOMe; 4.31, 1H, ddd, JH3H202.8, JH3H711.0, JH3H4 4.5Hz, H3; 6.62, 1H s. H5. m/z 348 (M), 235.

**Preparation of the xanthate ester (44) of the alcohol (43b)**

The dimethoxy alcohol (43b) (200mg; 6.0575mmol), sodium hydride (6mg; 0.246mmol; 80% in mineral oil) and imidazole (2mg; 0.0294mmol) were refluxed in dry tetrahydrofuran (2ml) for 4h. under nitrogen. Carbon disulphide (0.2ml; 3.34mmol) was added and refluxing was continued for a further 30 min., after which time iodomethane (0.049mg; 0.021ml; 0.345mmol) was introduced and reflux was again continued for 30 min. After cooling and removal of solvent under vacuum, dichloromethane was added. The organic phase was then washed with water, followed by saturated ammonium chloride solution then dried and concentrated. Purification by flash chromatography (dichloromethane/hexane; 1:1) yielded (3R)-O-7.8-dimethoxyserrulatan-3-yl S-methylidithiocarbonate (44) (14mg; 56%) as an oil. \text{H n.m.r.} \delta (300MHz) 0.55, 3H, d, J7.1Hz, (H18)_{3}; 0.87, 6H, d, J6.7Hz, (H16)_{3}, (H17)_{3}; 1.31, 3H, d, J7.0Hz, (H20)_{3}; 1.35-2.70,m, methylene envelope; 2.53, 3H, s, (H19)_{3}; 2.76, 3H, -SMe; 3.21, 1H, m, H4; 3.32, 1H, m, H1; 3.79 and 3.86, each 3H, s, 2xOMe; 6.14, 1H, m, H3; 6.59, 1H, s. H5. m/z 438 (M), 217.
Tri-n-butylstannane reduction of the xanthate ester (44) to give the dimethyl ether (6b)

The apparatus was flame-dried and flushed with nitrogen. The xanthate ester (22mg; 0.0502mmol) was added in dry benzene (2ml) to the flask containing AIBN (2mg) and the mixture was brought to reflux. Tri-n-butylstannane (0.1ml; 0.371mmol) was then added and refluxing was continued overnight. The solvent was evaporated in vacuo and water (5ml) was added. Extraction with dichloromethane (2x5ml) followed by drying and evaporation of the organic extracts in vacuo gave the crude products. The tin byproducts were removed by placing the crude material on a flash column and washing with light petroleum (400ml). Elution of the products (dichloromethane/hexane; 2:3) yielded a high Rf component which was identified as the desired product, 7,8-dimethoxyserrulatane (6b) (6mg; 35%). Accurate mass: 332.2728 (C_{22}H_{36}O_2 requires 332.2715) [α]_D -8.2 (c, 0.3) ν_max (soln) 2928, 2864, 1466, 1402, 1260, 1226, 1102, 1008 cm\(^{-1}\) \(\delta\) (300MHz) 0.82, 6H, d, J6.6Hz, (H16)_3, (H17)_3; 0.93, 3H, d, J6.8Hz, (H18)_3; 1.17, 3H, d, J6.9Hz, (H20)_3; 1.19-1.89, m; 2.22, 3H, s, (H19)_3; 2.52, 1H, m, H4; 3.12, 1H, m, H1; 3.80 and 3.87, each 3H, s, 2xOMe; 6.71, 1H, s, H5. m/z 332 (M), 219.

A low Rf component was also isolated and identified as (3R)-3,7,8-trimethoxyserrulatane (46) (3mg; 16%). Accurate mass: 362.2810 (C_{23}H_{38}O_3 requires 362.5358) \(\delta\) (300MHz) 0.41, 3H, d, J7.0Hz, (H18)_3; 0.89, 6H, d, J6.4Hz, (H16)_3, (H17)_3; 1.26, 3H, d, J6.9Hz, (H20)_3; 1.00-2.10, m, methylene envelope; 2.97, 1H, m, H4; 3.24, 1H, m, H1; 3.41, 3.79 and 3.85, each 3H, s, 2xOMe; 3.71, 1H, m, H3; 6.60, 1H, s, H5. m/z 362 (M), 249.
The middle Rf component (5mg) was not identified. The structure could not be elucidated from the 'H n.m.r. spectrum (300MHz) and mass spectral analysis failed to produce a molecular ion.

**Base catalysed elimination of the hydroxy tosylate (42)**

To the hydroxy tosylate (42) (653mg; 0.122mmol) in dry dimethyl sulphoxide (2ml) was added potassium tert-butoxide (30mg; 0.256mmol) and the reaction mixture was stirred overnight. The dimethyl sulphoxide was removed by heating under vacuum and to the residue was added dilute hydrochloric acid (10ml). Extraction with dichloromethane (2x10ml) followed by drying and removal of the solvent in vacuo gave the crude product. Purification by flash chromatography (ethyl acetate/hexane; 1:9) yielded (3R)-7,8-dimethoxyserrulat-1(20)-en-3-ol (101) (22mg; 52%). Recrystallisation (hexane) gave a crystalline solid, mp 70-72°. Accurate mass: 346.2497 (C22H34O3 requires 346.2507). \( \nu_{\text{max}} \) (soln) 3624, 2928, 2868, 1598, 1472, 1408, 1302, 1198, 1050 cm\(^{-1}\). 'H n.m.r. \( \delta \) (300MHz) 0.86, 6H, d, J6.5Hz, (H16)_3, (H17)_3; 0.90, 3H, d, J6.8Hz, (H18)_3; 1.00-2.20, m, methylene envelope; 1.56, 1H, s, -OH; 2.25, 3H, s, (H19)_3; 2.60, 1H, dd, Jgem14.6Hz, JH_2_1H_3 7.9Hz, H2β; 2.71, 2H, m, H2α, H4; 3.78 and 3.84, each , s, 2xOMe; 4.28, 1H, m, H3; 5.28 and 6.01, each 1H, s, (H2O)_2; 6.76, 1H, s, H5. m/z 346 (M), 233.

**Catalytic reduction of the dimethoxy alkenol (101) to give the epimer at Cl (43a)**

The dimethoxy alkenol (101) (20mg; 0.0578mmol) was hydrogenated in ethyl acetate (3ml) in the presence of platinum oxide (10mg) for 72h. The reaction mixture was filtered through Celite and the filtrate was evaporated under reduced pressure. Purification by flash chromatography (ethyl acetate/hexane;
1:9) yielded (1S, 3R)-7,8-dimethoxyserrulatan-3-ol (43a) (10mg; 50%) as an oil. Accurate mass: 348.26575 (C<sub>22</sub>H<sub>36</sub>O<sub>3</sub> requires 348.26644). v<sub>max</sub> (soln) 3450, 2924, 2864, 1602, 1466, 1408, 1380, 1328, 1204, 1068 cm<sup>-1</sup>. H n.m.r. δ (300MHz) 0.68, 3H, d, J7.0Hz, (H18)<sub>3</sub>; 0.89, 6H, d, J6.6Hz, (H16)<sub>3</sub>, (H17)<sub>3</sub>; 1.34, 3H, d, J6.8Hz, (H20)<sub>3</sub>; 1.37-2.05, m, methylene envelope; 1.52, 1H, s, -OH; 2.10, 1H, ddd, J<sub>H2αH1</sub> 8.6, J<sub>H2αH2β</sub> 12.5, J<sub>H2αH3</sub> 4.3Hz, H2α; 2.21, 3H, s, (H19)<sub>3</sub>; 2.71, 1H, dd, J<sub>H4H3</sub> 4.3, J<sub>H4H11</sub> 3.2Hz, H4; 3.17, 1H, ddd; J<sub>H1H2α</sub> 8.6, J<sub>H1H2β</sub> 8.6, J<sub>H1H20</sub> 6.8H, H1; 3.79 and 3.84, each 3H, s, 2xOMe; 4.03, 1H, ddd, J<sub>H3H2α</sub> 4.3, J<sub>H3H2β</sub> 12.1, J<sub>H3H4</sub> 4.3Hz, H3; 6.56, 1H, s, H5. m/z 348 (M), 235.

**Metal/ammonia reduction of the dimethoxy alkenol to give mainly the epimer at C1 (43a)**

A flask which had been flame-dried and flushed with nitrogen was charged with liquid ammonia (20ml). The alkenol (101) (29mg; 0.0838mmol) in dry tetrahydrofuran (2ml) was added followed by lithium (20mg; 2.86mmol) and the resulting blue solution was stirred for 3.5 min. The reaction was quenched by the addition of isoprene (0.5ml) and the ammonia was allowed to evaporate. Water (10ml) was then introduced, followed by extraction with ether (2x10ml). The organic extracts were dried, filtered and evaporated in vacuo to yield the crude product. Purification by flash chromatography ethyl acetate/hexane; 1:4) yielded a mixture of (1R,3R)- and (1S,3R)-7,8-dimethoxyserrulatan-3-ol, (43b) and (43a) (12mg; 41%) in the ratio of 1:6. All spectral data were identical with those obtained previously.

Some low Rf material (2mg) was also obtained, presumably over-reduction products.
Jones oxidation of the dimethoxy alcohol (43a)

The dimethoxy alcohol (43a) (18mg; 0.0517mmol) in acetone (2ml) was treated with Jones reagent dropwise at 0º until no starting material remained, as indicated by t.l.c. The solvent was evaporated in vacuo and saturated ammonium chloride solution (5ml) was added. Extraction with dichloromethane (2x5ml) followed by drying and removal of the solvent in vacuo gave the crude product. Purification by flash chromatography (ethyl acetate/hexane; 1:9) gave (1S)-7,8-dimethoxyserrulatan-3-one (110) (12mg; 67%) as an oil. 'H n.m.r. δ (300MHz) 0.86, 6H, d, J6.6Hz, (H16)3, (H17)3; 0.88, 3H, d, J6.9Hz, (H20)3; 1.00-1.60, m, methylene envelope; 2.24, 3H, s, (H19)3,2.43, 1H, dd, Jgem15.2, JH2αH12.7Hz, H2α; 2.70, 1H, dd, Jgem15.2, JH2βH1 7.3Hz, H2β; 3.21, 1H, d, J5.8Hz, H4; 3.58, 1H, ddd, JH1H207.3, JH1H2β7.3, JH1H2α2.7Hz, H1; 3.82 and 3.88, each 3H, s, 2xOMe; 6.68, 1H, s, H5.
SYNTHETIC COMPOUNDS

PART 1 - COMPOUNDS WITH HYDROGEN AT C5 AND C8

Preparation of 4-methyl-1,2,3,4-tetrahydronaphthalen-1-one (87)

The Friedel-Crafts reaction of γ-valerolactone (64) (60g; 0.60mol) with benzone (500ml; 5.60mol) in the presence of aluminium chloride (300g; 2.24mol) was carried out as described in the literature to yield 4-methyl-1,2,3,4-tetrahydronaphthalen-1-one (87) (83.2g; 87%) b.p. 79-82°/0.05mm (lit. 108-110°/1mm) \( \nu_{\text{max}} \) (soln) 3050, 2975, 1700, 1600, 1480, 1460, 1340, 1290, 1100, 770 cm\(^{-1}\) 'H n.m.r. \( \delta \) (300MHz) 1.40, 3H, d, J7.0Hz, C4-Me; 1.83-1.97, 2H, m, (H3)\(_2\); 2.52-2.89, 2H, m, 2H, (H2)\(_2\); 3.09, 1H, m, H4; 7.40, 3H, m, H5, H6, H7; 8.02, 1H, m, H8.

Preparation of (E)- and (Z)-4-ethylidene-1-methyl-1,2,3,4-tetrahydronaphthalenes, (71) and (72)

A two-necked flask was flame-dried and flushed with nitrogen. Potassium tert-butoxide (3.16g; 28.2mmol) was placed in the flask and dry ether (150ml) was added. Ethyltriphenylphosphonium iodide (11.79g; 28.2mmol) was added via Gooch glassware over 5 min. during which time a bright orange colouration of the solution was observed. After stirring for 1.5h., the tetralone (87) (3g; 18.8mmol) was added and the mixture was stirred overnight. Hexane (300ml) was then added and the solution was filtered to remove the precipitated solids. Removal of the solvent through a short column followed by distillation of the residue yielded a mixture of (E)- and (Z)-4-ethylidene-1-methyl-1,2,3,4-tetrahydronaphthalenes, (71) and (72), (1.74g; 54%) in the ratio of 5:2 respectively. b.p. 54-60°/ 0.01mm. Accurate mass: 172.1245 (C\(_{13}\)H\(_{16}\) requires
172.1252). $v_{\text{max}}$ (soln) 3064, 3024, 2964, 2865, 1602, 1482, 1450, 1378 cm$^{-1}$. 'H n.m.r. $\delta$ (300MHz) major product (71) 1.27, 3H, d, J7.0Hz, C1-Me; 1.47-1.65, 2H, m, (H2)$_2$; 1.72, 3H, d, J6.9Hz, C1'-Me; 2.30-2.60, 2H, m, (H3)$_2$; 2.86, 1H, m, H1; 6.07, 1H, m, H1'; 7.06-7.54, 4H, m, H5, H6, H7, H8.

Minor product (72) 1.29, 3H, d, J6.6Hz, C1-Me; 1.85-2.10, 2H, m, (H2)$_2$; 1.89, 3H, d, J7.2Hz, C1'-Me; 2.30-2.60, 2H, m, (H3)$_2$; 2.86. 1H, m, H1; 5.54, 1H, 9, J7.2Hz, H1'; 7.06-7.54, 4H, m, H5, H6, H7, H8.

**Attempted preparation of ethyl (E and Z)-4'-methyl-3',4'-dihydro-1'(2H)-naphthylidenacetates, (88) and (89)**

Triethyl phosphonoacetate (4.48ml; 31.3mmol) was added to sodium hydride (1.07g; 44.6mmol; 70% in mineral oil) in dry tetrahydrofuran (30ml) and stirred for 2h. The tetralone (87) (2g; 12.5mmol) was then added and the mixture was refluxed overnight. The reaction was quenched by the addition of water (50ml) then extracted with ether (2x50ml) and the organic layers were dried, filtered and evaporated in vacuo. The crude product, which was homogeneous by t.l.c., was not purified further as it was presumed to be ethyl 4'-methyl-3',4'-dihydro-1'-naphthalenyl acetate (92) 'H n.m.r. $\delta$ (CCl$_4$; 60MHz) 1.05-1.50, each 3H, t and d, J7Hz, (H2')$_3$, C4'-Me; 1.5-3.10, 3H, m, (H3')$_2$, H4; 3.3, 2H, s, (H2)$_2$; 4.1, 2H, q, J7Hz, (H1')$_2$; 5.8, 1H, m, H2'; 7.1, 4H, s, H5', H6', H7', H8'.

**Preparation of ethyl (E and Z)-4'-methyl-3',4'-dihydro-1'(2H)-naphthylidenacetates, (88) and (89)**

To a solution of lithium diisopropylamide (14.8ml; 19.6mmol; 2M solution) in dry tetrahydrofuran (60ml) at -78$^\circ$ was added ethyl (trimethylsilyl)acetate (5.42ml; 19.6mmol) dropwise. After 30 min., the tetralone (87) (4.73g; 29.6mmol) was added dropwise and the mixture was stirred at -78$^\circ$ for a further
2h. The reaction mixture was warmed to room temperature, quenched with saturated ammonium chloride solution (200ml) and extracted with ether (3x100ml). Purification of the crude material initially by "dry column" flash chromatography (ethyl acetate/hexane) followed by flash chromatography (ethyl acetate/hexane; 7:93) yielded a lower Rf component, ethyl (Z)-4'-methyl-3',4'-dihydro-1'(2H)-naphthyldienacetate (89) (1.89g; 28%). Accurate mass: 230.1318 (C₁₅H₁₈O₂ requires 230.1306) νmax (soln) 2956, 1708, 1628, 1464, 1380, 1172 cm⁻¹. 'H n.m.r. δ (300MHz) 1.23, 3H, t, J7.2Hz, (H2')₃; 1.32, 3H, d, J7.1Hz, C₄'-Me; 1.60 and 2.11, each 1H, m, (H₃')₂; 2.52, 2H, m, (H₂')₂; 2.94, 1H, m, H₄; 4.15, 2H, q, J7.2Hz, (H₁")₂; 5.79, 1H, s, H₂; 7.10-7.32, 3H, m, H₅', H₆', H₇'; 7.57, 1H, d, J7.7Hz, H₈'. m/z 230 (M), 185, 157.

The higher Rf component corresponded to ethyl (E)-4'-methyl-3',4'-dihydro-1'(2H)-naphthyldienacetate (88) (1.25g; 18%). Accurate mass: 230.1313 (C₁₅H₁₈O₂ requires 230.1306) νmax (soln) 2928, 1704, 1616, 1462, 1374, 1174 cm⁻¹. 'H n.m.r. δ (300MHz) 1.29, 3H, d, J6.9Hz, C₄'-Me; 1.32, 3H, t, J7.2Hz, (H₂')₃; 1.66 and 1.95, each 1H, m, (H₃')₂; 2.92, 1H, m, H₄¹; 3.24, 2H, m, (H₂')₂; 4.20, 2H, q, J7.2Hz, (H₁")₂; 6.31, 1H, t, J1.8Hz, H₂; 7.10-7.34, 3H, m, H₅', H₆', H₇'; 7.62, 1H, d, J7.8Hz, H₈'. m/z 230 (M), 185, 157.

A mixed fraction (424mg; 6%) was also recovered.

The remainder of the material isolated corresponded to the starting tetralone (87) (1.68g; 35%).

**Lithium aluminium hydride reduction of the (E)-ester (88)**

The (E)-ester (88) (590mg; 3.87mmol) was treated with lithium aluminium hydride (248mg; 6.52mmol) in dry ether (50ml) at 0° for 2h. as described
previously. Following isolation of the crude product, purification by flash chromatography (ethyl acetate/hexane; 3:7) and distillation yielded (E)-4'-methyl-3',4'-dihydro-1'(2H)-naphthylidenethanol (90) (280mg; 38%) b.p. 140-150°C/0.03mm (micro-analysis incorrect). Accurate mass: 188.1201 (C13H16O requires 188.1201). \( \nu_{\text{max}} \) (soln) 3425, 3020, 2940, 1590, 1490, 1465, 1380 cm\(^{-1}\). \( \delta(300\text{MHz}) \) 1.27, 3H, d, \( J = 7.7\text{Hz} \), C4'-Me; 1.58 and 1.91, each 1H, m, (H3')\(_2\); 2.20, 1H, br.s, -OH; 2.51, 2H, m, (H2')\(_2\); 2.89, 1H, m, H4'; 4.35, 2H, d, J6.5Hz, (H1)\(_2\); 6.14, 1H, t, J6.5Hz, H2; 7.18, 3H, m, H5', H6', H7'; 7.56, 1H, d, J7.4Hz, H8'. m/z 188 (M).

### Epoxidation of the (E)-allylic alcohol (90)

To a mixture of the (E)-allylic alcohol (90) (200mg; 1.06mmol) and sodium hydrogen carbonate (89mg; 1.06mmol) in dry dichloromethane (10ml) at 0°C was added to a solution of m-chloroperoxybenzoic acid (229mg; 1.33mmol; 80%) in dry dichloromethane (10ml). After stirring for 1h., t.l.c. analysis indicated some starting material remaining however, since the reaction did not appear to be proceeding further, the mixture was treated with 10% sodium metabisulphite solution (10ml) until the remaining peracid was reduced. The organic layer was then separated and washed with 10% potassium carbonate solution (10ml), dried, filtered and evaporated in vacuo. The residue was then purified by flash chromatography (ethyl acetate/hexane; 2:3) to yield a 1:1 mixture of isomeric epoxides which appeared as two spots by t.l.c., corresponding to cis and trans 2,1'-epoxy-2-(4'-methyl-1',2',3',4'-tetrahydro-1'-naphthalen)ethanol, (91a) and (91b), (80mg; 37%). \( \delta(300\text{MHz}) \) 1.31 and 1.40, each 3H, d, J7.0Hz, 2xC4'-Me; 1.50-2.20, 4H, m, 2x(H3')\(_2\); 2.22-2.70, 4H, m, 2x (H2')\(_2\); 2.80 and 3.06, each 1H, m, 2x H4'; 3.26 and 3.27, 3.49 and 3.50, each 2H, t, J13.6Hz, J8.8Hz, 2x(H1)\(_2\), 4.35 and 4.48, each 1H, dd, J8.8Hz, 2.8Hz, 2xH2, 7.06-8.10, 8H, m, 2x(H5', H6', H7', H8'). m/z 204 (M).
It was not possible to distinguish the peaks corresponding to each isomer therefore the data are quoted together.

**Lithium aluminium hydride reduction of the (Z)-ester (89)**

The (Z)-ester (89) (500mg; 2.17mmol) was reduced with lithium aluminium hydride as described previously to yield the crude alcohol (94). Purification by flash chromatography (ethyl acetate/hexane; 3:7) yielded (Z)-4'-methyl,3',4'-dihydro-1'(2H)-naphthylidenethanol (94) (163mg; 40%) \( ^1H \) n.m.r. \( \delta \) (CC14; 60MHz) 1.28, 3H, d, J\( 7Hz, C^4\)-Me; 1.40-3.20, 5H, m, (H\( 2'\))\( 2\), (H\( 3'\))\( 2\), H\( 4'\); 4.23, 2H, d, J7Hz, (H\( 1'\))\( 2\); 5.50, 1H, t, J6Hz, H\( 2'\); 7.07, 4H, m, H\( 5'\), H\( 6'\), H\( 7'\), H\( 8'\).

**Epoxidation of the (Z)-allylic alcohol (94)**

The (Z)-allylic alcohol (94) (163mg; 0.867mmol) was epoxidised with m-chloroperoxybenzoic acid (500mg; 2.89mmol, 80%) and sodium hydrogen carbonate (243mg; 2.89mmol) in a dry dichloromethane (20ml) at 0\( ^0\) for 30 min. After this time, t.l.c. analysis indicated that the starting material had been consumed therefore the mixture was worked-up as described above. Purification of the crude product by flash chromatography (ethyl acetate/hexane; 3:7) yielded a mixture of cis- and trans-2,1'-epoxy-2-(4'-methyl-1',2',3',4'-tetrahydro-1'-naphthalen)ethanol, (95a) and (95b), (77mg, 44%) with one isomer in slight excess over the other. Although separable by chromatography, the products were isolated as a mixture. \( ^1H \) n.m.r. \( \delta \) (300MHz) (major isomer) 1.33.3H, d, J6.8Hz, C\( 4'\)-Me; 1.50-1.80, 2H, m, (H\( 3'\))\( 2\); 1.97, 1H, brs, -OH; 2.10-2.30, 2H, m, (H\( 2'\))\( 2\); 3.03, 1H, m, H\( 4'\); 3.24, 1H, t, J6.1Hz, H\( 2'\); 3.64, 2H, m, (H\( 1'\))\( 2\); 7.13-7.39, 4H, m, H\( 5'\), H\( 6'\), H\( 7'\), H\( 8'\).
(minor isomer) δ 1.32, 3H, d, J7.0Hz, C4'-Me. All other peaks were superimposed with those of the major isomer above.

Preparation of 1-methyl-4-methylene-1,2,3,4-tetrahydronaphthalene (97)

A two-necked flask was flame-dried and flushed with nitrogen. Potassium tert-butoxide (4.21g; 37.6mmol) was placed in the flask and ether (100ml) was added. Methyltriphenylphosphonium bromide (13.42g; 39.6mmol) was added via Gooch glassware over a period of 5 min. during which time a bright yellow colouration of the solution was observed. After stirring for 15 min., the tetralone (87) (3.00g;18.8mmol) was added and the reaction mixture was stirred overnight. Hexane (200ml) was added and the mixture was filtered to remove inorganic salts and precipitated triphenylphosphine oxide. The solvent was then removed by distillation through a short column to yield the crude product. Purification by "dry column" flash chromatography (hexane) yielded 1-methyl-4-methylene-1,2,3,4-tetrahydronaphthalene (97) (844mg; 31%). Accurate mass: 160.1242 (C_{12}H_{14}+H_{2} requires 160.1252). ν max (soln) 3016, 2928, 1628, 1482, 1462, 1378, 1210, 888 cm⁻¹. ¹H n.m.r. δ (300MHz) 1.30, 3H, d, J6.9Hz, C1-Me; 1.66 and 2.00, each 1H, m, (H2)2; 2.47 and 2.65, each 1H, m, (H3)2; 2.98, 1H, m, H1; 4.94 and 5.45, each 1H, d, J1.0Hz, (H1')2; 7.20, 3H, m, H6, H7, H8; 7.62, 1H, d, J6.4Hz, H5. m/z 160 (+H_{2}), 158 (M), 145, 143. These data were in agreement with those described in the literature⁴⁸.
Preparation of cis- and trans-1,4-dimethyl-1,2,3,4-tetrahydronaphthalenes, (102a) and (102b)

A. Via lithium/ammonia reduction of the methylene derivative (97)

To a flask containing liquid ammonia (60ml) was added the alkene (97) (400mg; 2.53mmol) in dry ether (10ml) and lithium (177mg; 25.3mmol). The dark blue solution was stirred for 5 min. after which time isoprene (2ml) was added to remove the excess of metal. The ammonia was allowed to evaporate and water (20ml) was introduced. Extraction with dichloromethane (2x25ml) followed by drying and removal of the solvent in vacuo gave the crude product. Purification by "dry column" flash chromatography (hexane) yielded an inseparable mixture of cis and trans 1,4-dimethyl-1,2,3,4-tetrahydronaphthalenes (229mg; 57%), (102a) and (102b), respectively in the ratio of 3:1. Accurate mass: 160.1242 (C_{12}H_{16} requires 160.1252) ν_{max} (soln) 2924, 2860, 1488, 1464, 1378, 1022 cm\(^{-1}\) 'H n.m.r. (δCCl\(_4\); 300MHz) (102a) 1.27, 6H, d, J7Hz, 2xCH\(_3\); 1.4-2.1, 4H, m, (H2)\(_2\), (H3)\(_2\); 2.80, 2H, m, H1, H4; 6.9-7.1, 4H, m, H5, H6, H7, H8.

(102b) 1.24, 6H, d, J7Hz, 2xCH\(_3\); 1.4-2.1, 4H, m, (H2)\(_2\), (H3)\(_2\); 2.80, 2H, m, H1, H4; 6.9-7.1, 4H, m, H5, H6, H7, H8.

\(^{13}\)C n.m.r. δCCl\(_4\) (102a) 22.6, CH\(_3\); 28.7, C2; 32.8, C1; 125.6, C6; 127.8, C5; 141.8, C4a.

(102b) 23.1, CH\(_3\); 28.3, C2; 32.8, C1; 125.6, C6; 128.1, C5; 141.7, C4.

m/z 160 (M), 145.

These data are in agreement with those in the literature.\(^{49, 50}\)
B. Via catalytic hydrogenation of the methylene derivative (97)

The alkene (97) (100mg; 0.63mmol) was hydrogenated with palladium-on-carbon (30mg; 5%) in ethyl acetate (20ml) overnight. The mixture was filtered through Celite and the filtrate evaporated in vacuo to yield an inseparable mixture of cis and trans 1,4-dimethyl-1,2,3,4-tetrahydronaphthalenes (56mg; 55%), (102a) and (102b) respectively in the ratio 4:1. All data for the isomers were identical with those described above.

Hydroboration of the methylene derivative (97) with 9-borabicyclononane

9-Borabicyclononane (381mg; 1.56mmol) was added to a solution of the alkene (97) (456mg; 2.89mmol) in dry tetrahydrofuran (25ml) under nitrogen and stirred overnight. The reaction mixture was then oxidised by the addition of 3M sodium hydroxide (2ml) followed by 30% hydrogen peroxide (2ml) added dropwise and stirred for a further hour. The solvent was then evaporated under reduced pressure and 10% potassium carbonate solution (10ml) was added to the residue. Extraction with ether (2x10ml), drying and removal of solvent in vacuo gave the crude product. Purification by flash chromatography (ethyl acetate/hexane; 1:4) yielded an inseparable mixture of cis- and trans-1'-(4'-methyl-1',2',3',4'-tetrahydronaphthalenemethanol (234mg; 46%), (104a) and (104b) respectively, in the ratio 3:2. Accurate mass: 176.1206 (C_{12}H_{16}O requires 176.1201). \nu_{\text{max}} (soln) 3424, 2928, 1488, 1378, 1220, 1010, 910 cm^{-1}. H n.m.r. \delta (300MHz) (104a) 1.29, 3H, d, J7Hz, C4'-Me; 1.40-2.10, 4H, m, (H2')2, (H3')2; 2.20, 1H, brs, -OH; 2.80-3.00, 2H, m, H1', H4'; 3.60-3.80, 2H, m, (H1')2; 7.00-7.30, 4H, m, H5', H6', H7', H8'. (104b) 1.25, 3H, d, J7Hz, C4'-Me; 1.40-2.10, 4H, m, (H2')2, (H3')2; 2.20, 1H, brs, -OH; 2.80-3.00, 2H, m, H1', H4'; 3.60-3.80, 2H, m, (H1')2; 7.00-7.30, 4H, m, H5', H6', H7', H8'. m/z 176 (M), 145.
Preparation of mixture of cis and trans tosylates, (105a) and (105b)

To the mixture of alcohols, (104a) and (104b) (98mg; 0.598mmol) and p-toluenesulphonyl chloride (137mg; 0.717mmol) was added pyridine (1ml) and carbon tetrachloride (1ml). The mixture was allowed to stand at room temperature overnight. Water (5ml) was then added and the mixture was extracted with dichloromethane (2x5ml). The organic extracts were washed with 10% hydrochloric acid (5ml) then dried, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/hexane; 1:9) to yield a mixture of cis- and trans-(4'-methyl-1',2',3',4'-tetrahydro-1'-naphthalene)methyl tosylates (134mg; 68%), (105a), and (105b) ¹H n.m.r. δ (300MHz) (105a) 1.24, 3H, d, J7Hz, C4'-Me; 1.30-2.00, 4H, m, (H2')2, (H3')3; 2.44, 3H, s, CH3-Ar; 2.84, 1H, m, H4'; 3.11, 1H, m, H11; 3.97-4.22, 2H, m, (H1)2; 7.00-7.26, 4H, m, H5', H6', H7', H8'; 7.77, 7.93, AA'BB' system arom. (105b) 1.22, 3H, d, J7.6Hz, C4'-Me. The remainder of the spectrum was identical with that of (105a) above.

Lithium aluminium hydride reduction of the tosylates (105a) and (105b)

The mixture of tosylates (105a) and (105b) (107mg;0.336mmol) was reduced with lithium aluminium hydride (51mg; 1.35mmol) in dry tetrahydrofuran by the standard method described previously. The reaction mixture was refluxed overnight and after work-up in the usual manner, the crude product was obtained. Further purification was not considered necessary because the ¹H n.m.r. (60MHz) spectrum revealed the product to be a mixture of cis- and trans-1,4-dimethyl-1,2,3,4-tetrahydronaphthalenes (102a) and (102b) in the ratio of 3:2.
PART 2 - COMPOUNDS WITH METHYL SUBSTITUENTS AT C5 AND C8

Preparation of 4-(2',5'-dimethylphenyl)pentanoic acid (66)

The Friedel-Crafts reaction of p-xylene (65) (53g; 0.499 mol) and γ-valerolactone (64) (25g; 0.250mol) in the presence of aluminium chloride (34g; 0.250mol) was carried out as described in the literature\(^4^2\)\(^a\),\(^b\) to yield 4-(2',5'-dimethylphenyl)pentanoic acid (66) (31.97g; 62%) mp. 108-109° (lit\(^4^2\)\(^a\) 109-111°). All other data were identical with those described previously\(^4^2\)\(^a\).

Cyclisation of the acid (66) with PPA to yield the tetralone (67)

Phosphoric acid (60ml) and phosphorus pentoxide (60g) were heated to 100°. The acid (66) (31.97g; 155mmol) was added and the mixture was stirred for several minutes. The mixture was then poured onto ice and extracted with ether (2x250ml). The organic layers were dried, filtered and evaporated to give the crude product. Distillation yielded 4,5,8-trimethyl-3,4-dihydro-1(2H)-naphthalenone (67) (20.44g; 70%) bp 90°/0.05mm (lit\(^4^2\)\(^a\) 91-94°/0.16mm) \(^1\)H n.m.r. δ (300MHz) 1.24, 3H, d, J7.1Hz, C4-Me; 1.95 and 2.18, m, each 1H, (H3)\(_2\); 2.32, 3H, s, C5-Me; 2.57, 3H, s, C8-Me; 2.55 and 2.83, m, each 1H, (H2)\(_2\); 3.27, 1H, m, H4; 6.96 and 7.15, each 1H, d, J7.7Hz, H6, H7.

All other data were identical with those described in the literature\(^4^2\)\(^a\),\(^b\).

Preparation of (E)-4-ethyldiene-1,5,8-trimethyltetrahydronaphthalene (68)

A two-necked flask was flame-dried and flushed with nitrogen. Potassium tert-butoxide (14.9g; 133mmol) was placed in the flask and dry ether (600ml) was added. Ethyltriphenylphosphonium iodide (55.45g; 133mmol) was added
via Gooch glassware which resulted in a bright orange colouration of the solution. After stirring for 2.5h., the ketone (67) (12.47g; 663mmol) was added and the mixture was stirred for 2 days. Hexane (800ml) was added and the solution was filtered to remove insoluble salts. The solvent was removed by distillation through a short column and the residue purified by "dry column" flash chromatography (dichloromethane/hexane). Subsequent distillation yielded exclusively (E)-4-ethylidene-1,5,8-trimethyl-1,2,3,4-tetrahydronapthalene (68) (8.57g; 65%) bp 70-72°/0.07mm. Accurate mass: 200.1572 (C₁₅H₂₀ requires 200.1565) νmax (soln) 2928, 2864, 1464, 2864, 1464, 1382, 1202, 982 cm⁻¹ 'H n.m.r. δ (300MHz) 1.10, 3H, d, J7.1Hz, C₁-Me; 1.50-1.90, 2H, m, (H₂)₂; 1.78, 3H, d, J6.5Hz, (H₂)₃; 2.27 and 2.39, each 3H, s, C₅-and C₈-Me; 2.23 and 2.75, each 1H, m, (H₃)₂; 3.17, 1H, m, H₁; 5.60, 1H, m, H₁'; 6.90 and 7.02, each 1H, d, J7.7Hz, H₆, H₇. m/z 200 (M), 185.

**Hydroboration of the (E)-alkene (68) with borane-methyl sulphide complex**

A two-necked flask was flame-dried and flushed with nitrogen. The alkene (68) (2.38g; 11.9mmol) in dry tetrahydrofuran (100ml) was placed in the flask and borane-methyl sulphide (2.38ml; 23.8mmol; 10M solution in tetrahydrofuran) was added. After stirring for 48h., the mixture was oxidised by the dropwise addition of 10% sodium hydroxide solution (15ml) followed by 30% hydrogen peroxide (15ml). The solvent was evaporated in vacuo and to the residue was added 10% potassium carbonate solution (30ml). Extraction with ether (2x50ml) followed by drying, filtration and removal of the solvent in vacuo gave the crude product. Purification by "dry column" flash chromatography (ethyl acetate/hexane) yielded 1-(4',5',8'-trimethyl-1',2',3',4'-tetrahydro-1'-napthalen)ethanol (79) (1.85g; 71%) as a mixture of stereoisomers. 'H n.m.r. (δCDCl₃; 60MHz) 0.80-2.20, 4H, m, (H₂)₂, (H₃)₂; 1.20-1.60, 6H, m, C₁-
Me; C4'-Me; 2.27, 6H, s, C5'-Me, C8'-Me; 2.40-3.40, 2H, m, H1', H4'; 3.87, 1H, m, H1; 6.77, 2H, s, H6', H7'.

**Jones oxidation of the mixture of stereoisomeric alcohols (79)**

To a mixture of the alcohols (79) (2.37g; 10.9mmol) in acetone (5ml) at 0° was added Jones reagent dropwise until the orange colour just persisted. At this stage a green precipitate was also present. The solvent was then removed in vacuo, water (100ml) was added and the mixture extracted with dichloromethane (2x100ml). Purification by flash chromatography (ethyl acetate/hexane; 2:23) yielded a high Rf component, 1-ethyl-4,5,8-trimethyl-3,4-dihydro-2(1H)-naphthalenone (73) as an oil (459mg; 20%) bp 100°/0.05mm. Accurate mass 216.1520 (C15H20O requires 216.1514) \( \nu_{\text{max}} \) 2928, 2872, 1706, 1670, 1574, 1462, 1384, 1262 cm\(^{-1} \) 'H n.m.r. \( \delta \) (300MHz) 1.15, 3H, t, J7.4Hz, (H2)\(_3\); 1.26, 3H, d, C4-Me; 1.36-2.00, m, 2H, (H1)\(_2\); 2.35 and 2.57, each 3H, s, C5- and C8-Me; 2.86, 2H, m, (H3)\(_2\); 3.29, 1H, m, H4; 3.42, 1H, m, H1; 6.98 and 7.18, each 1H, d, J7.7Hz. m/z 216 (M). Although the sample appeared to be homogeneous by t.l.c., some spurious peaks were present in the 'H n.m.r. spectrum, suggesting significant impurity.

The middle Rf component was identified as cis-1-(4',5',8'-trimethyl-1',2',3',4'-tetrahydronaphthalen-1'-yl)ethanone (70a) (501mg; 21%). A portion was recrystallised from hexane, mp 62-64°. Found; C, 83.27; H, 9.19. C\(_{15}\)H\(_{20}\)O requires C, 83.28; H, 9.32%. \( \nu_{\text{max}} \) (soln) 2928, 2868, 1708, 1464, 1356, 1278, 1156, 908 cm\(^{-1} \) 'H n.m.r. \( \delta \) (300MHz) 1.24, 3H, d, J7.0Hz; C4'-Me; 1.70-1.80, 2H, m, (H3)\(_2\); 1.85-2.22, 2H, m, (H2)\(_2\); 2.06 and 2.32, each 3H, s, C5'-, C8'-Me; 2.08, 3H, s, C1-Me; 3.13, 1H, dq, J\(_{4'4'}\)C4'-Me 7.0, J\(_{4'4'}\)C4'-Me 7.0, J\(_{4'4'}\)H3'\(_{\alpha}\) 4.3, J\(_{4'4'}\)H3'\(_{\beta}\) 4.3Hz, H4'; 3.89, 1H, dd, J\(_{H1'H1'}\)H2'\(_{\alpha}\) 9.0, J\(_{H1'H1'}\)H2'\(_{\beta}\) 9.0Hz, H1'; 6.93 and 7.00, each 1H, d, J7.6Hz, H6', H7' m/z 216 (M), 173.
The low Rf component corresponded to trans-1-(4',5',8'-trimethyl-1',2',3',4'-tetrahydronaphthalen-1'-yl)ethanone (70b) (370mg; 16%). A portion was recrystallised from hexane, mp. 109-111°. Accurate mass: 216.1515 (C_{15}H_{20}O requires 216.1514) v_{max} (soln) 2944, 2864, 2732, 1708, 1464, 1382, 1358, 1224, 1156 cm\(^{-1}\) m/z 216 (M), 173 'H n.m.r. δ (300MHz) 1.17, 3H, d, J7.0Hz, C4'-Me; 1.62 and 1.81, each 1H, m, (H3')₂; 1.98 and 2.26, each 1H, m, (H2')₂; 2.06 and 2.32, each 3H, s, C5'-, C8'-Me; 2.22, 3H, s, C1-Me; 3.14, qdd, J_{H4'C4'-Me}7.0, J_{H4'H3'a}4.7, J_{H4'H3'β}1.6Hz, H4'; 3.91, 1H, dd, J_{H1'H2'α}7.6, J_{H1'H2'β}0.7Hz, H1':6.92 and 6.99, each 1H, d, J7.6Hz, H6', H7'. m/z 216 (M), 173.

Mixed fractions containing the high and middle Rf components (117mg; 5%) and the middle and low Rf compounds (141mg; 6%) were also obtained.

**Equilibration studies**

**A. Equilibration of the low Rf component, (70b)**

The trans methyl ketone (70b) (30mg; 0.139mmol) was equilibrated in fully deuterated methanol (0.5ml) with a trace of sodium hydroxide at 60° for 48h. under nitrogen. No further changes in the 'H n.m.r. spectrum were detected after this time. The solvent was evaporated in vacuo and to the residue was added saturated ammonium chloride solution (5ml). Extraction with dichloromethane (2x5ml) followed by drying, filtration and removal of the solvent gave the crude products, trans- and cis- 1-(4',5',8'-trimethyl-1',2',3',4'-tetrahydronaphthalen-1'-yl)ethanones, (70b) and (70a) in the ratio 5:2 respectively.
B. Equilibration of the middle Rf component, (70a)

The cis methyl ketone (70a) (30mg; 0.139mmol) was equilibrated under conditions identical with those described above. The 'H n.m.r. (60MHz) revealed that equilibration had taken place to give a similar mixture of trans and cis methyl ketones.

The crude equilibration products from parts A and B were therefore combined and purified by flash chromatography (ethyl acetate/hexane; 1:9) to yield a mixture of trans- and cis- 1-(4',5',8'-trimethyl-1',2,3',4'-tetrahydronaphthalen-1'-yl)ethanones (30mg; 50%), (70b) and (70a), in the ratio of 5:2 respectively, as detected by 'H n.m.r. spectroscopy (300MHz).

Preparation of 1,5,8-trimethyl-4-methylene-1,2,3,4-tetrahydronaphthalene (98)

A two-necked flask was flame-dried and flushed with nitrogen. Potassium tert-butoxide (1.07g; 9.57mmol) was added to the flask, followed by dry ether (25ml). Methyltriphenylphosphonium bromide (3.42g; 9.57mmol) was added via Gooch glassware over a period of 5 min. during which time a bright yellow colouration of the solution was observed. After stirring for 15 min., the ketone (67) (600mg; 3.19mmol) was added and the mixture was stirred for a further 3 days. Hexane (40ml) was added, the solution was filtered and the solvent removed by distillation through a short column. Purification of the residue by "dry column" flash chromatography (dichloromethane/hexane) followed by distillation yielded 1,5,8-trimethyl-5-methylene-1,2,3,4-tetrahydronaphthalene (98) (195mg; 35%) b.p. 48°/0.03mm. Accurate mass: 186.1409 (C14H18 requires 186.14163). v_max (soln) 2928, 2864, 1464, 1382, 1202, 982 cm⁻¹. 'H n.m.r. δ (300MHz) 1.16, 3H, d, J7.1Hz, C4-Me; 1.82, , m, (H3)2; 2.28, 3H, s, C5-Me; 2.42, 3H, s, C8-Me; 2.51 and 2.67, each 1H, m, (H2)2; 3.20, 1H, m, H4; 5.07 and 5.28, each
1H, s, (H1')$_2$; 6.94 and 6.99, each 1H, d, J7.8Hz, H6, H7. m/z 188 (+H$_2$), 186 (M), 173, 171.

Preparation of cis and trans 1,4,5,8-tetramethyl-1,2,3,4-tetrahydronaphthalenes, (103a) and (103b).

A. Via metal/ammonia reduction of the methylene derivative (98)

To a flask containing liquid ammonia (60ml) was added the alkene (98) (400mg; 2.15mmol) in dry ether (10ml) and lithium (151mg; 21.5mmol). The dark blue solution was stirred for 5 min. after which time isoprene (2ml) was added to remove the excess of metal. The ammonia was allowed to evaporate and water (20ml) was introduced. Extraction with dichloromethane (2x25ml) followed by drying, filtration and removal of the solvent in vacuo gave the crude reduction product. Distillation yielded an inseparable mixture of cis- and trans- 1,4,5,8-tetramethyl-1,2,3,4-tetrahydronaphthalene (297mg; 74%) b.p. 80°/0.055mm, (103a) and (103b) respectively in the approximate ratio of 4:1

Found: C, 88.68; H, 10.64. C$_{14}$H$_{20}$ requires C, 89.29; H10.71%. v$_{\text{max}}$ (soln) 2925, 2875, 1470, 1380, 1220 cm$^{-1}$. H n.m.r. δ (300MHz) (103a) 1.23, 6H, d, J7.1Hz, C1-, C4-Me; 1.70 and 1.84, each 2H, m, (H2)$_2$, (H3)$_2$; 2.28, 6H, s, C5- and C8-Me; 6.89, 2H, s, H6, H7. (103b) 1.13, 6H, d, J7.1Hz, C1- and C4-Me; 1.70 and 1.84, each 2H, m, (H2)$_2$, (H3)$_2$; 2.28, 6H, s, C5- and C8-Me; 6.88, 2H, s, H6, H7. m/z 188(M), 174.

B. Via catalytic reduction of the methylene derivative (98)

The alkene (98) (52mg; 0.280mmol) in ethyl acetate (10ml) was hydrogenated in the presence of platinum oxide (10mg) for 5 h. The mixture was filtered through celite and the filtrate evaporated in vacuo to yield a mixture of cis and
trans 4,5,8-tetramethyl-1,2,3,4-tetrahydronaphthalene (51mg; 96%), (103a) and (103b) in the ratio of 3:1 respectively.

All other data were identical with those described above.
APPENDIX

Figure 1.1

*Serrulatane skeleton and stereochemistry*
X-ray crystal structure of the cis methyl ketone (70a)
| C(1')  | --- O(1)  | 1.206(3) | H(1)  | --- C(1)  | 0.968(21) |
| C(1')  | --- C(1)  | 1.517(3) | C(2)  | --- C(1)  | 1.543(3)  |
| C(8a)  | --- C(1)  | 1.523(3) | C(2')  | --- C(1') | 1.502(4)  |
| H(2A)  | --- C(2)  | 1.037(27) | H(2B)  | --- C(2)  | 0.926(28) |
| C(3)   | --- C(2)  | 1.510(4) | H(2'A) | --- C(2') | 0.871(39) |
| H(2'B) | --- C(2') | 0.993(40)| H(2'C) | --- C(2') | 0.965(42) |
| H(3A)  | --- C(3)  | 1.055(25)| H(3B)  | --- C(3)  | 1.003(28) |
| C(4)   | --- C(3)  | 1.530(3) | C(4)   | --- C(4)  | 0.985(25) |
| C(4a)  | --- C(4)  | 1.512(3) | C(4')  | --- C(4)  | 1.522(4)  |
| C(5)   | --- C(4a) | 1.415(3) | C(8a)  | --- C(4a) | 1.399(3)  |
| H(4'A) | --- C(4') | 0.992(40)| H(4'B) | --- C(4') | 1.054(30) |
| H(4'C) | --- C(4') | 0.967(29)| C(5')  | --- C(5)  | 1.506(3)  |
| C(6)   | --- C(5)  | 1.379(3) | H(5'A) | --- C(5') | 0.892(40) |
| C(6)   | --- C(5)  | 1.379(3) | H(5'C) | --- C(5') | 0.964(48) |
| H(7)   | --- C(6)  | 0.948(26)| C(7)   | --- C(6)  | 1.368(3)  |
| H(8A)  | --- C(7)  | 0.923(26)| C(8)   | --- C(7)  | 1.387(3)  |
| H(8'C) | --- C(8)  | 1.406(3) | C(8')  | --- C(8)  | 1.501(3)  |
| H(8'B) | --- C(8') | 0.963(30)| H(8'B) | --- C(8') | 0.995(33) |
| H(8'C) | --- C(8') | 0.947(36)| | | |
REFERENCES


