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Synthesis of the E Ring of Salinomycin

A thesis presented in partial fulfilment of the requirements for the degree of
Doctor of Philosophy
at Massey University

Michael Kevin Edmonds

January 1995
To Mum, Dad, Leo and Julie
Thanks for all the support.
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Abstract

The synthesis of (2R*, 5R*, 2'S*) and (2S*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofurans 331a, 331b in a 5:1 ratio by the iodoetherification of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol 330a is described. Subsequent iodoetherification of ether derivatives 385 - 389 of hydroxyalkene 330a was then effected to produce predominantly the cis iodide 331b. (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-1-(2", 6"-dichlorobenzylx)oxy)-4-pentene 387 proved most successful in this respect affording iodides 331a, 331b in a 1:10 ratio.

Attempted silver catalysed ring expansion of iodide 331a proved ineffective affording only (5R*, 2'S*)-5-(2'-methyltetrahydro-2'-yl)-5-hydroxypentan-2-one 344.

The synthesis of (E)-1-bromo-3-ethyl-3-pentene 146 is described, the key step in its formation being the diastereoselective reaction of 2-ethyl-1-butene 364 with butyl glyoxylate 367, in the presence of a titanium catalyst formed in situ from diisopropoxytitanium(VI) dichloride 362 and (+)-1,1'-bi-2-naphthol 363, to afford butyl (E)-4-ethyl-2-hydroxy-4-hexenoate 370.

The synthesis of (2S*, 3R*, 6R*, 2'S*)-3-ethyl-3-hydroxy-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran 323 from 2-methyl-2-tetrahydrofuraldehyde 322 is described, thereby modelling the synthesis of the E ring of salinomycin. The synthesis began with the coupling of the organolithium derivative of (E)-1-bromo-3-ethyl-3-pentene 146 to 2-methyl-2-tetrahydrofuraldehyde 322 to afford (4E, 1R*, 2'S*)- and (4E, 1S*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol 348a, 348b in a 3:1 ratio. Following separation of the alcohols 348a, 348b via formation of their acetate derivatives 383a, 383b, iodoetherification of (4E, 1R*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol 348a afforded (2R*, 5R*, 1'S*, 2"S*)- and (2S*, 5'R*, 1'R*, 2"S*)-2-ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofurans 347a and 347b in a 3:1 ratio. Subsequent ring expansion of iodide 347b resulted in formation of the target pyran 323 in 77% yield.

Iodoetherification of the trimethylsilyl derivative 392 of (4E, 1R*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol 348a produced the iodides 347a and 347b in a 1:1 ratio, while the 2,6-dichlorobenzyl 390 and 4-bromobenzyl 391 derivatives were too sterically hindered for iodoetherification to occur.
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Chapter 1

Introduction

1.1 Polyether Antibiotics.

The polyether antibiotics are a group of structurally related natural products which selectively complex group I or II metal cations. Primarily of bacterial origin, they are produced by micro-organisms of the *Streptomyces* genus, although a small number have been recently isolated from marine sources.

Also known as the monocarboxylic acid ionophores, the polyether antibiotics display potent biological activity. By binding to, and encapsulating, a metal cation they provide a hydrophobic sheath which allows transport of the metal cation across the lipophilic interior of the cell wall. The resulting increased permeability of the cell to the cation effectively uncouples oxidative phosphorylation and ultimately leads to cell death.

While most of the polyether antibiotics exhibit relatively nonspecific cytotoxicity several such as salinomycin, narasin and monensin display enough selectivity to be of commercial use as both anticoccidial agents in poultry and growth promotants in ruminants.

In order to compare the structure and stereochemistry of the polyether antibiotics Westley *et al* divided them into four main classes based on cation selectivity and chemical structure: 1) The monovalent polyethers. This includes all the non-spiroketal, spiroketal and *bis*-spiroketal antibiotics which complex monovalent metal cations (e.g. salinomycin and monensin); 2) The divalent polyethers (e.g. lasalocid A); 3) The pyrrole containing ethers (e.g. A23187); and 4) The acyltetronic acids (e.g. ICI139603), so named due to the acyltetronic acid subunits they possess. In addition to these four classes, a fifth class containing the recently discovered marine polyether antibiotics (e.g. okadaic acid and norhalichondrin A) is probably justified due to the unique structures of these compounds. Representative members of the various classes are illustrated (Figures 1 and 2).

The ion selectivity of the polyether ionophores is a combined function of the ion's desolvation energy and the ligating energy obtained on complexation which, due to the highly constrained backbone, generally has a maximum value for an ion of a specific radius.

In 1967, the first X-ray structure of a polyether antibiotic, monensin, was solved. Since then, over 80 different polyether antibiotics have been isolated and their
Figure 1

Salinomycin (1; R=H) (class 1)
Narasin (2; R=Me) (class 1)

Monensin 3 (class 1)

Lasalocid A 4 (class 2)

Antibiotic A23187 5 (class 3)

ICI139603 6 (class 4)
Each member of this family of natural products consists of a linear backbone which incorporates rigidifying substructures of oxygen heterocycles such as 2,5-disubstituted tetrahydrofurans, substituted tetrahydropyrans and spiroketal systems. These cyclic ethers, in combination with an array of chiral centres, assist in the destabilisation of undesired rotomers and help to position the ligating atoms in order
that the metal cation may be bound effectively. Most polyether antibiotics also contain a terminal carboxylate group which serves to secure the molecule about the central cation via intramolecular, head to tail, bonding.

While X-ray crystallography determines the absolute stereochemical structure of the polyether ionophores, it provides no direct information regarding their biologically active conformations. However, recent work by Mronga et al. with sodium complexed salinomycin has shown that the combined use of 2D NMR techniques and molecular dynamics calculations can deliver detailed insight into the solution state structure of the polyether antibiotics. In the case of the salinomycin complex (Figure 3), the ligating oxygens (O2, O4, O5, O10, O11 and O9) were found to form a distorted pentagonal pyramid around the sodium ion and the complex was stabilised with O8H→O2 and O8H→O4 hydrogen bonding in addition to the usual head to tail hydrogen bonding (O11H→O1C).

Almost all polyether antibiotics contain one or more tetrahydrofuran rings connected, at the 2 and 5 positions, into the molecule's backbone. Often the tetrahydrofuran ring is part of a ring assembly involving at least one other tetrahydrofuran ring or a tetrahydropyran ring (e.g. salinomycin 1, monensin 3 and nigericin 9).

A common feature of the commercially used coccidiostats, salinomycin 1, narasin 2, monensin 3 and lasalocid A 4, is the presence of a tetrahydrofuran-tetrahydropyran bis-ether at the opposite end of the molecule to the carboxylate group. It would appear that this substructure is highly effective in ligating reversibly to the central metal cation. For example, in the case of sodium complexed salinomycin this
**bis-ether** supplies three of the six ligating oxygen atoms (Figure 3) as well as containing the hydroxyl 'tail' which hydrogen bonds to the carboxylate.

Another feature common to all but one of the polyether antibiotics is the presence of a β-hydroxyketone moiety, although in some cases it is hidden (see antibiotic X-206, Scheme 50). This unit is of great synthetic value with its construction by a stereoselective crossed aldol reaction affording a highly convergent step for synthesis. This reaction is so efficient that it has been utilised in every synthesis of polyether antibiotics to date.

### 1.2 Total Syntheses of Salinomycin and/or Narasin

#### 1.2.1 Kishi et al

In 1981, Kishi et al reported total syntheses of the polyether antibiotics salinomycin 1 and narasin 2.

The first step in their retrosynthetic pathway was the disconnection of the C9-C10 bond (Scheme 1), equivalent to a stereoselective crossed aldol condensation in the synthetic direction. Precedent for the use of this reaction in the synthesis of polyether antibiotics is well documented. The two fragments afforded by this disconnection, tetrahydropyran 10 (or 11 in the case of narasin) and bis-spiroketal 12, are conventionally termed the left and right hand fragments, respectively.

**Synthesis of the left hand fragments**

It was proposed that the tetrahydropyran fragments 10, 11 would be prepared by the base catalysed cyclisation of the highly functionalised acyclic mesylates 13, 14. Synthesis of the mesylates was carried out (Schemes 2 and 3) by chain extension of small chiral molecules using epoxidations to set up the required stereocentres, a method favoured by the authors.

L-(+)-citronellol 15 was selected to form the central core around which the salinomycin series mesylate 13 was formed (Scheme 2). After truncation of the molecule via ozonolysis, the resulting six carbon alcohol 16 was extended by way of the selenide 17-12,13 to form allylic alcohol 18. Subsequent application of stereoselective epoxidation and cuprate methodology added two new chiral centres, in the form of diol 19. Protection of the 1,3-diol 19 as the acetonide followed by removal of the silyl protecting group gave alcohol 20, thereby setting up the left hand end of the molecule for extension using Seyferth's methodology (Scheme 3). Hydrolysis and selective reprotaction of the resulting dichloroalkene 21 followed by lithium-halogen exchange and acylation afforded propargylic ester 22, which was then reduced to the...
allylic alcohol 23. A second application of the epoxide/organometallic methodology produced the remaining chiral centres as diol 24. Reduction of the vinyl group followed by a sequence of selective protections and mesylation afforded the target mesylate 13.

Synthesis of mesylate 14 (required for narasin) began with extension of alcohol 25 (Scheme 4) via the Wittig reaction, followed by incorporation of two new chiral
Scheme 1

Reagents and conditions: (i) a: C₆H₅CH₂Br, KH, 0°C to RT; b: O₃, MeOH, -78°C; c: NaBH₄, MeOH; 
(ii) a: 'BuPh₂SiCl, DMF, imidazole; b: H₂, Pd/C, MeOH; c: o-NCSe(C₆H₄)NO₂, Bu₃P, THF, 0°C; 
(iii) a: O₃, NaOAc, MeOH, CH₂Cl₂, -78°C then O₃, Me₂S, RT; b: Et₂OCH=PH₃, ClCH₂CH₂Cl, 
 Δ; c: Dibal, CH₂Cl₂, -40°C; (iv) a: Ti(OBu₄)₄, D(-)-diethyl tartrate, 'BuOOH, CH₂Cl₂, -23°C; b: 
Me₃CuCNLi₂, THF, -20°C to RT; (v) a: Me₂C(O(Me)₂), CSA, acetone, RT; b: 'Bu₄NF, THF.

Scheme 3

Reagents and conditions: (i) a: DMSO, (COCl)₂, CH₂Cl₂, -60°C then Et₃N; b: CBr₄, Ph₃P, CH₂Cl₂, 
0°C; (ii) a: 'BuLi, THF, -78°C then CICO₂Me; (iii) a: H₂, Lindlar catalyst, quinoline, hexane; b: 
Dibal, CH₂Cl₂, -78°C; (iv) MCPBA, CH₂Cl₂, -10°C; (v) CH₂=CHMgBr, CuI, Et₂O, -24°C; (vi) 
a: MeC(O(Me)₂), acetone, CSA; b: H₂, Lindlar catalyst, hexanes; c: Li, NH₃, TIIF, -33°C; (vii) a: 
DMSO, (COCl)₂, CH₂Cl₂, -60°C then Et₃N; b: PhHgCl₂Br, Ph₃P, benzene, Δ; c: 'BuLi, THF, 
-78°C then CICO₂Me; d: H₂, Lindlar catalyst, hexanes; e: Dibal, CH₂Cl₂, -40°C; (viii) a: MCPBA, 
CH₂Cl₂, 0°C; b: Me₂CuLi, Et₂O, -25°C.
Scheme 3

Reagents and conditions: (i) a: DMSO, (COCl)$_2$, CH$_2$Cl$_2$, -60°C then Et$_3$N; b: PhHgCCl$_2$Br, Ph$_3$P, benzene, Δ; (ii) a: AcOH, H$_2$O, RT; b: NaH, MeOCH$_2$Br, THF, -12°C; c: KH, C$_6$H$_5$CH$_2$Br, THF/DMF, 0°C; (iii) $^3$BuLi, THF, -78°C then ClCO$_2$Me; (iv) a: H$_2$, Lindlar catalyst, quinoline, hexane; b: DIBAL, CH$_2$Cl$_2$, -40°C; (v) a: Ti($^3$PrO)$_4$, D-(-)-diethyl tartrate, $^4$BuOOH, CH$_2$Cl$_2$, -23°C; b: CH$_2$=CHMgBr, CuI, Et$_2$O, -24°C to RT; (vi) H$_2$, Lindlar catalyst, Et$_2$O; b: Me$_3$CC(OC)Cl, pyridine; (vii) a: Ms$_2$O, DMAP, pyridine, CH$_2$Cl$_2$, 0°C to RT; b: H$_2$, Pd/C, MeOH.
centres using the epoxidation/organometallic methodology mentioned previously. Repetition of this sequence, this time using Seyferth's reagent\textsuperscript{14, 15}, afforded a further two chiral centres in the form of alcohol 26. After the removal of the C5 hydroxyl group by formation and subsequent reduction of the thionocarbonate 27 (Scheme 5), the molecule was again extended using Wittig/epoxidation methodology to give diol 28. The diol 28 was then converted to the required mesylate 14 by a sequence of selective protections and mesylation.

\textbf{Scheme 5}

![Scheme 5](image)

\textit{Reagents and conditions:} (i) \(\text{Cl}_2\text{CS}, \text{DMAP, CH}_2\text{Cl}_2\); (ii) a: \(\text{Bu}_3\text{SnH, AIBN, toluene}\); b: \(\text{CSA, Me}_2\text{C(OMe)_2}\); c: \(\text{NaOH, H}_2\text{O, RT}\); (iii) a: \(\text{DMSO, (COCl)_2, CH}_2\text{Cl}_2, -60^\circ\text{C to RT}\); b: \(\text{EtO}_2\text{CCCH=PPPh}_3, \text{ClICH}_2\text{CH}_2\text{Cl}\); \(\Delta\); (iv) a: \(\text{DIBAL, CH}_2\text{Cl}_2, -40^\circ\text{C}\); b: \(\text{Ti(OC}^\text{Pr})_4, \text{D-(-)-diethyl tartrate, BuOOH, CH}_2\text{Cl}_2, -23^\circ\text{C to RT}\); c: \(\text{Me}_3\text{CuCNLi}_2, \text{THF, -20}^\circ\text{C to RT}\); d: \(\text{Me}_3\text{CCOCl, pyridine}\); e: \(\text{Ms}_2\text{O, DMAP, pyridine, CH}_2\text{Cl}_2, 0^\circ\text{C to RT}\); f: \(\text{H}_2, \text{Pd-C, MeOH}\).

With the mesylates 13, 14 in hand, cyclisation to the tetrahydropyrans 10, 11 was pursued (Scheme 6). In the salinomycin case, treatment of mesylate 13 with excess potassium hydride in ether (\(0^\circ\text{C} \rightarrow \text{RT}\)) afforded the desired tetrahydropyran structure 29 in 59% yield. Synthesis of the narasin tetrahydropyran 30 from mesylate 14, however, proved to be more problematic. After intensive study\textsuperscript{11}, the best cyclisation conditions found were to dissolve the mesylate 14 in hexane/toluene and to add excess
potassium hydride to the mixture at 0°C. In this way the cyclic pyran 30 was obtained, albeit in 14% yield.

At this point all that remained was to adjust the oxidation levels of the two sidechains. Thus, the cyclic pyrans 29, 30 were converted to the target tetrahydropyrans 10, 11 via the same selective deprotection and oxidation sequence outlined.

The disappointing yield in the cyclisation of the narasin series mesylate 14 was attributed to the extensive steric crowding which occurs during formation of the pyran product. Consequently, a more efficient synthesis of the narasin aldehyde 11 was pursued, this time involving the stereocontrolled addition of an alkyl group to a preformed tetrahydropyran nucleus 31 (Scheme 7). Based on previous observations\textsuperscript{17}, it was anticipated that the stereoelectronically preferred axial attack by the nucleophile on oxonium ion 32\textsubscript{a} leading to the tetrahydrofuran 33 would predominate as it lacks the unfavourable steric interactions R' ↔ Nu that are present with the addition of the nucleophile to oxonium ion 32\textsubscript{b}.

The acetates 34\textsubscript{a}, 35\textsubscript{a} required for this investigation were produced (Scheme 8) from aldehyde 36\textsubscript{a}, a readily available degradation product of natural narasin. Conversion of the aldehyde 36\textsubscript{a} to olefin 37\textsubscript{a}, followed by ozonolysis afforded ketone 38\textsubscript{a} which underwent Baeyer-Villiger oxidation to give the axial acetate 34\textsubscript{a}. Facile hydrolysis of the axial acetate, followed by reacetylation yielded almost exclusively the equatorial acetate 35\textsubscript{a}. An analogous series of reactions was used to produce the salinomycin series of acetates 34\textsubscript{b}, 35\textsubscript{b}.

Reagents and conditions: (i) KH; (ii) a: LiAlH\textsubscript{4}, Et\textsubscript{2}O, RT; b: Jones reagent, acetone, 0°C to RT; (iii) a: Dowex-50, dioxane, H\textsubscript{2}O, Δ; b: PCC, CH\textsubscript{2}Cl\textsubscript{2}.
Reagents and conditions: (i) a: NaBH₄, MeOH, 0°C; b: o-NO₂C₆H₄SeCN, Bu₃P, THF followed by H₂O₂ treatment, 0°C to RT; c: LiAlH₄, Et₂O, 0°C; d: C₆H₅CH₂Br, KH, THF/DMF (4:1), 0°C to RT; (ii) O₃, MeOH, -78°C, followed by Me₂S work-up; (iii) MCPBA, Na₂HPO₄, CH₂Cl₂; (iv) NaOMe, MeOH; (v) Ac₂O, pyridine.
Separate treatment of each of the acetates 34a and 35a with the enol silyl ethers 39 followed by sodium borohydride reduction afforded alcohols 40a and 41a in an approximately 4:1 ratio (Scheme 9). Both diastereomers were then converted to a single tetrahydropyran 42a, analysis of which confirmed that, as anticipated, only axial nucleophilic attack had taken place affording the desired configuration for the A ring of narasin. Parallel results were observed for the salinomycin series 34b, 35b with an approximately 3:1 ratio of the alcohols 40b and 41b.

Scheme 9

Reagents and conditions: (i) a: (E) and (Z) MeCH=CHOTMS 39 (ca. 4.5 eq), ZnCl₂ (excess), CH₂Cl₂, 0°C; b: NaBH₄, MeOH, 0°C; (ii) a: MeOCH₂Br, (Pr)₂EtN, CH₂Cl₂; b: H₂, Pd-C, MeOH; (iii) a: o-NO₂C₆H₄SeCN, {Bu}₂P, THF; b: H₂O₂, 0°C to RT; (iv) a: hexylborane, THF, 0°C; b: H₂O₂, OH⁻; c: MeOCH₂Br, (Pr)₂EtN, CH₂Cl₂; d: H₂, Pd-C, MeOH.

An alternative synthetic route to lactol 43a (Scheme 8), which had been derived directly from natural narasin for this study, was not detailed but an assertion was made that it could be derived from an intermediate occurring in their previous synthesis of narasin (probably alcohol 26, Scheme 4).

Synthesis of the right hand fragments.

The right hand fragment 12 of salinomycin 1 and narasin 9 was designated as being synthetically equivalent to the open chain diketone 44, which was further disconnected into the three fragments 45, 46, 47 (Scheme 1).

Methodology developed for the synthesis of the left hand section of narasin 9 proved invaluable in preparing the pyran lactone 45. Beginning with the previously prepared alcohol 48 (Scheme 4), the molecule was extended (Scheme 10) via the Wittig reaction to give the allylic alcohol 49 which subsequently underwent selective
epoxidation and organometallic addition to produce the two new chiral centres of diol 50. Removal of the secondary alcohol was then carried out by formation and reduction of the thionocarbonate 51\textsuperscript{19} to afford the alcohol 52. Ruthenium catalysed oxidation\textsuperscript{20} of the alcohol 52 followed by treatment with acetic acid resulted in formation of the lactone 53, which, upon protection with tert-butylchlorodiphenylsilane afforded the desired pyran synthon 45.

\textbf{Scheme 10}

\includegraphics{Scheme_10}

\textit{Reagents and conditions:} (i) a: DMSO, (COCl)\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, -60°C, then Et\textsubscript{3}N; b: EtO\textsubscript{2}CCH=PPh\textsubscript{3}, CICH\textsubscript{2}CH\textsubscript{2}Cl, Δ; (ii) a: DIBAL, CH\textsubscript{2}Cl\textsubscript{2}, -40°C; b: Ti(\textsuperscript{O}Pr\textsubscript{4}), D-(-)-diethyl tartrate, \textsuperscript{1}BuOOH, CH\textsubscript{2}Cl\textsubscript{2}, -23°C; (iii) Me\textsubscript{2}CuCNLi\textsubscript{2}, THF, -24°C to RT; (iv) (imidhCS, xylene, Δ; (v) a: Bu\textsubscript{3}SnH, AIBN, toluene; b: CSA, Me\textsubscript{2}C(O)Me\textsubscript{2}; c: NaOH, H\textsubscript{2}O, RT; (vi) RuO\textsubscript{2}-NaIO\textsubscript{4} (cat.), NaHCO\textsubscript{3}, acetone/H\textsubscript{2}O; (vii) AcOH; (viii) \textsuperscript{1}BuPh\textsubscript{2}SiCl, imidazole, DMF.

Structural similarities between lactone 47 and intermediates in the synthesis of the right hand side of lasalocid A\textsuperscript{39} suggested methodology for construction of this fragment (Scheme 11). Beginning with tetrahydrofuran 54\textsuperscript{9}, the benzylated tetrahydrofuran underwent oxidative cleavage by treatment with osmium tetroxide/sodium periodate\textsuperscript{21} followed by selective Grignard addition to afford the alcohol 55. Swern oxidation\textsuperscript{22,23} and subsequent chelation controlled Grignard addition served to establish the desired erythro alcohol 56. Conversion of the alcohol 56 to the
lactone 57 was effected by oxidative olefin cleavage followed by pyridinium chlorochromate oxidation\textsuperscript{24}. After deprotection and mesylation of the tertiary alcohol moiety, solvolysis of the resulting mesylate 58 in the presence of strontium carbonate afforded the desired lactone 47 in a 4:1 ratio with the furan lactone 59.

**Scheme 11**

\[
\text{Reagents and conditions: (i) a: KH, BzBr, THF, DMF, 0°C to RT; b: OsO}_4\text{-NaIO}_4, \text{dioxane, H}_2\text{O; c: CH}_2\text{=CHCH}_2\text{CH}_2\text{MgBr, Et}_2\text{O, -10°C; (ii) a: DMSO, (COCl)}_2, \text{CH}_2\text{Cl}_2, -60°C, \text{then Et}_3\text{N, -60°C to RT; c: MeMgBr, Et}_2\text{O, -10°C; (iii) a: OsO}_4\text{-NaIO}_4, \text{dioxane, H}_2\text{O; b: PCC, CH}_2\text{Cl}_2; (iv) a: H}_2, \text{Pd-C, MeOH; (v) MsCl, pyridine, 0°C; (vi) SrCO}_3, \text{dioxane, H}_2\text{O, 100°C.}}
\]

In order for the lactone 47 to be incorporated into the diketone 44 it was necessary to convert it to the dithianediol synthon 60 (Scheme 12). This was accomplished by reduction to the corresponding lactol followed by thioacetalisation to give dithiane 61 which then underwent THP protection to yield the desired synthon 60.

**Scheme 12**

\[
\text{Reagents and conditions: (i) a: DIBAL, CH}_2\text{Cl}_2, -78°C; b: HS(CH}_2)_3\text{SH, BF}_3\text{-Et}_2\text{O, CH}_2\text{Cl}_2, -10°C to RT; (ii) PPTS, DHP, CH}_2\text{Cl}_2.}
\]
With the synthetic routes to the lactone 45 and pyran 60 subunits established, work began on the assembly of the bis-spiroketal unit 12 (Scheme 13). Reaction of the lithium acetylide derivative of propargyl alcohol, protected as the tetrahydropyranyl ether 46, with lactone 45, afforded a mixture of hemiketals which was immediately treated with p-toluenesulphonic acid in methanol, removing the THP groups and forming the α and β methyl ketals 62 in a 1:3 ratio. Stereocontrol of this reaction is not important as the ketal carbon eventually becomes a spirocentre, the configuration of which is determined by anomeric, steric and hydrogen bonding effects.

**Scheme 13**

Reagents and conditions: (i) Li-C≡CCH₂OTHP 46, THF, -78°C; b: MeOH, TSA; (ii) CrO₃-2Py, CH₂Cl₂, celite; (iii) nBuLi, THF, -20°C; (iv) TSA, MeOH.

**Scheme 14**

Reagents and conditions: (i) MnO₂, CH₂Cl₂; (ii) NaBH₄, MeOH, -12°C;
Oxidation of the alcohol 62 with Collins reagent\textsuperscript{25} gave aldehyde 63 which, following reaction with the lithium anion of dithiane 60 and removal of the THP group, afforded alcohols 64 and 65. Additional amounts of the desired alcohol 64 were produced by oxidation/reduction of alcohol 65 (Scheme 14).

The next step involved removal of the dithiane functionality using \( \text{N-} \)chlorosuccinimide in methanol, followed by acid induced cyclisation and acetylation to give the acetate 66 (Scheme 15). Reduction of the acetylene to the \textit{cis} olefin and subsequent acid catalysed intramolecular ketalisation afforded the \textit{bis}-spiroketal structure 67. Extension of the left sidechain and reprotction of the allylic hydroxyl group was then carried out to give ketone 68 in preparation for the crossed aldol reaction that was to follow.

**Coupling of the Left and Right Hand Fragments**

With methodology established for synthesis of tetrahydropyrans 10 and 11 (Scheme 6), and \textit{bis}-spiroketal 68 (Scheme 15), the crossed aldol condensation was investigated (Scheme 16). It was found that the optimum conditions\textsuperscript{11}, using dicyclohexylamidomagnesium to generate the enolate, afforded, after desilylation, a single isomer of the aldol products 69 and 70 in 58\% yield, the properties of which were identical to those of naturally occurring \textit{epi}-salinomycin and \textit{epi}-narasin, respectively.

Thermodynamic isomerisation of the \textit{epi}-isomers 69 and 70 under acidic conditions (trifluoroacetic acid in dichloromethane) afforded at least a 7:1 ratio of salinomycin 1: \textit{epi}-salinomycin 69 and narasin 2: \textit{epi}-narasin 70 respectively, demonstrating a significant thermodynamic preference for the natural products over that of the C17 epimers.

Acetylation of the C20 hydroxyl group of salinomycin and narasin followed by treatment with trifluoroacetic acid in dichloromethane affords exclusively \textit{epi}-narasin acetate 71 or \textit{epi}-salinomycin acetate 72 (Figure 4). This observation, coupled with the
Scheme 15

Reagents and conditions: (i) a: NCS, MeOH; b: TSA; c: Ac₂O, pyridine; (ii) a: H₂, Lindlar catalyst, MeOH; b: 80% aq. AcOH; (iii) a: "Bu₄NF, THF; b: CrO₃, 2Py, CH₂Cl₂; (iv) a: EtMgCl, Et₂O, -40°C to RT; b: CrO₃, 2Py, CH₂Cl₂; c: K₂CO₃, MeOH; d: "BuMe₂SiCl, DMAP, DMF, 80°C.
**Scheme 16**

Reagents and conditions: (i) a: \((\text{C}_6\text{H}_{12})_2\text{NMgBr, THF, -50°C then 10 or 11, -50°C, 20 min; b: } \text{Bu}_4\text{NF, THF; (ii) TFA, 4A molecular sieves, CH}_2\text{Cl}_2\).
fact that upon treatment with acid (TFA, CH₂Cl₂) the epimeric bis-spiroketalts 73 and 74 were favoured over the conformations of bis-spiroketalts 75 and 76 (Scheme 17), suggests that the allylic hydroxyl group serves to stabilise the observed conformations of the natural products through the formation of long distance intramolecular hydrogen bonding, a theory corroborated by the recently published solution structure of sodium complexed salinomycin⁶.

1.2.2 Yonemitsu et al²⁶-²⁹

Synthesis of the Right Hand Fragment

In 1987, a second formal synthesis of salinomycin 1 was detailed by Yonemitsu et al²⁶, in a paper describing methodology for the synthesis and coupling of the middle (C10-C17) 77 and right (C18-C30) 78 segments of salinomycin (Scheme 18).
Synthesis of the aldehyde 77 was carried out using glucose derivative 79\textsuperscript{30} (Scheme 19). Displacement of the tosylate 79 with lithium dimethylcuprate and subsequent protecting group manipulation afforded benzyl ether 80. Hydrolysis of the isopropylidene group then allowed oxidative cleavage of the resulting diol to the aldehyde 81. Using the Wittig-Horner reaction the molecule was extended to give \( \alpha, \beta \)-unsaturated ester 82 which was immediately cyclised to afford lactone 83. Reduction to the lactol and formation of an isopropyl acetal was followed by reduction using Raney Nickel then Rh-Al\textsubscript{2}O\textsubscript{3} to give the alcohol 84 with excellent stereoselectivity. Swern oxidation\textsuperscript{22,23} of the alcohol 84 followed by Grignard addition of ethylmagnesium bromide yielded only the Cram product 85 in high yield. After hydrolysis of the isopropyl acetal the resultant lactol was reduced to give triol 86. Subsequent protection of the 1,3-diol as an acetonide followed by oxidation of the remaining free hydroxyl group afforded the desired middle section synthons 77.

Scheme 19

\begin{align*}
\text{Reagents and conditions:} & \quad \text{(i) a: CuI, MeLi, Et}_2\text{O, -25°C; b: 1M HCl, MeOH; c: C}_6\text{H}_5\text{CH}_2\text{Cl, DMSO/THF, NaH; (ii) a: 4M HCl, THF, 45°C; b: NaIO}_4, \text{THF/MeOH; (iii) (MeO)}_2\text{P(O)CHMeCO}_2\text{Me, NaH, THF, -78 to -15°C; (iv) K}_2\text{CO}_3, \text{MeOH; (v) a: DIBAL, toluene, -80°C; b: CSA, }^1\text{PrOH; c: Raney Ni(W-2), EtOH; d: Rh-Al}_2\text{O}_3, \text{EtOH; (vi) a: DMSO, (COCl)}_2, \text{CH}_2\text{Cl}_2, -78°C \text{ then Et}_3\text{N; b: EtMgBr, Et}_2\text{O, -50°C; (vii) a: 1M HCl, THF, 50°C; b: LiAlH}_4, \text{THF; (viii) a: CSA, Me}_2\text{C(OMe)}_2; \text{ b: DMSO, (COCl)}_2, \text{CH}_2\text{Cl}_2, -78°C \text{ then Et}_3\text{N.}}
\end{align*}
The right segment (C18-C30) 78 was further divided into two subunits, aldehyde 87 and phosphonate 88 (Scheme 18). Aldehyde 87 was synthesised starting from diacetone glucose 89 (Scheme 20). Key steps in the synthesis included selective acetonide hydrolysis followed by oxidative cleavage and conversion to the benzyl derivative 90. Hydrolysis of the remaining acetonide followed again by oxidative cleavage provided a 1,3-diol system which was protected as the acetonide, affording compound 91. Finally, removal of the benzyl group allowed oxidation to the desired aldehyde 87.

**Scheme 20**

Reagents and conditions: (i) a: p-MeOC₆H₄CH₂Cl, NaH, DMSO/THF; b: 2% H₂SO₄, MeOH; c: NaO₄, MeOH/H₂O; d: NaBH₄; e: BzCl, NaH, THF/DMSO; (ii) a: 4M HCl, THF, 55°C; b: NaO₄, THF, MeOH/H₂O; c: LiAlH₄, THF, 0°C; d: (MeO)₂C(Me)₂, CSA, acetone; (iii) a: Raney Ni (W-2), EtOH; b: DMSO, (COCl)₂, CH₂Cl₂, -78°C then Et₃N.

Synthesis of phosphonate 88 (Scheme 21) began with the Wittig-Horner coupling of L-glyceraldehyde derivative 92 and β-ketophosphonate 93, derived from L-lactate, to afford an enone which underwent hydrogenation to give ketone 94. Chelation controlled addition of ethyl magnesium bromide followed by selective manipulation of the protecting groups and tosylation produced diol 95 which upon treatment with sodium hydride cyclised to form tetrahydropyran 96. Finally, extension of the left side of the molecule afforded the required phosphonate 88.

The phosphonate 88 and aldehyde 87 were then coupled (Scheme 22), and the resulting enone reduced, to give ketone 97. Following treatment of the ketone 97 with methyllithium, selective protection/deprotection was carried out to afford the triol 98. Protection of the primary alcohol with a TBDMS group, followed by Swern oxidation of the secondary alcohol gave ketone 99 which underwent cyclisation.
Scheme 21

\[ \text{Reagents and conditions: (i) a: NaH, DMSO/THF, 0°C then 92; b: H}_2 \text{, Pd-C, EtOAc; (ii) a: EtMgBr, THF, -93°C; b: BzBr, NaH, DMF; c: 4M HCl, THF, 50°C; d: TsCl, pyridine; (iii) NaH, DMSO, THF; (iv) a: CrO}_3 \text{, H}_2\text{SO}_4 \text{, acetone, 0°C; b: CH}_2\text{N}_2 \text{; c: (MeO)}_2\text{P(O)Me, }{^\text{t}}\text{BuLi, THF, -93°C.} ]

Scheme 22

\[ \text{Reagents and conditions: (i) a: NaH, DMSO/THF, 0°C then 87; b: H}_2 \text{, Pd-C, EtOAc; (ii) a: MeLi, Et}_2\text{O, -93°C; b: 1M HCl, THF; (iii) a: }{^\text{t}}\text{BuMe}_2\text{SiCl, imidazole, CH}_2\text{Cl}_2 \text{; b: DMSO, (COCl)}_2 \text{, CH}_2\text{Cl}_2 \text{, -78°C then Et}_3\text{N; (iv) a: CSA, MeOH; b: DMSO, (COCl)}_2 \text{, CH}_2\text{Cl}_2 \text{, -78°C then Et}_3\text{N; (v) a: PhHgCCl}_2\text{Br, Ph}_3\text{P, benzene, 80°C; b: }{^\text{t}}\text{BuLi, THF, -78°C.} ]

and methylation to give the acetal 100. Subsequently acetal 100 was converted to the
desired acetylene synthon 78, via a dichloroolesfin14,15.

Coupling of the aldehyde 77 and acetylene 78 in the presence of n-butyllithium
afforded a propargylic alcohol which was readily oxidised to the ynone 101 (Scheme
23). Treatment of the ynone 101 with camphorsulphonic acid effected hydrolysis of the
acetonide producing a mixture of diastereoisomeric methoxy acetals 102. Partial
hydrogenation of the acetylene 102 over Lindlar catalyst afforded the cis olefins 103
which underwent bis-spiroketalisation, followed by selective deprotection and
oxidation, to give bis-spiroketals 104. Removal of the remaining protecting groups and
acetylation of the allylic hydroxyl group gave a mixture of diastereomers which were
isomerised under acidic conditions to give the acetate derivative 74 of the target
compound 12, solely in the epimeric form. Since acetate 74 was converted by Kishi et
al7 to salinomycin 1 after condensation with the left hand (C1-C9) 10 segment, a formal
synthesis of salinomycin 1 was claimed.

In 1988, methodology for synthesis and coupling of the C1-C9 10 fragment to
aldehyde 1228 was accompanied by an improved method for the synthesis of aldehyde
12 (Scheme 24). In this amended procedure, postponement of intramolecular
ketalisation until after the coupling of aldehyde 77 and alkyne 105 resulted in both
improved yields and a simpler diastereomeric mixture.

Beginning with tetrahydropyran 98, an intermediate in an earlier pathway (see
Scheme 22), application of selective protection/deprotection followed by Seyferth's
methodology14,15 afforded acetylene 105. Coupling of the acetylene 105 to aldehyde 77
and subsequent assembly of the bis-spiroketal, under similar conditions to the previous
pathway (see Scheme 23), afforded an isomeric mixture of bis-spiroketals 106 and 107
or 108 and 109, the ratios of which depend on the protecting group involved.

Synthesis of the Left Hand Fragment

The left hand fragment 10 (see Scheme 1) was synthesised (Scheme 25) from
the aldehyde 110. Precise details for the synthesis of this precursor have not been
reported, but its construction from D-glucose has been alluded to in previous work by
Oikawa et al32.

Chain extension by conversion of aldehyde 110 to the aldehyde 111 followed by
coupling with the β-ketophosphonate 112, the preparation of which has, again, yet to be
detailed, afforded the ketone 113 which was stereoselectively converted to the epoxide
114. This allowed generation of the tetrahydropyran 115 under acid catalysed
conditions, which was subsequently converted to the desired intermediate 10.
Scheme 23

Reagents and conditions: (i) a: "BuLi, THF, -78°C then 77; b: MnO₂, CH₂Cl₂; (ii) a: CSA, MeOH; b: Ac₂O, Et₃N, DMAP, CH₂Cl₂; (iii) H₂, Lindlar catalyst, MeOH/AcOH; (iv) a: 80% AcOH; b: KOH, aq. MeOH, 60°C; c: PCC, CH₂Cl₂; (v) a: DDQ, H₂O/CH₂Cl₂ (1:10); b: Ac₂O, Et₃N, DMAP, CH₂Cl₂; c: CSA, CH₂Cl₂.
Reagents and conditions: (i) C₆H₅CH₂Cl, pyridine, CH₂Cl₂, 0°C; b: BuMe₂SiOTf, Et₃N, CH₂Cl₂, 0°C; c: KOH, MeOH, 55°C; (ii) a: H₂, Raney Nickel, EtOH, 60°C; b: Me₂C(OMe)₂, CSA, benzene; c: MeOC₆H₄CH₂Cl, NaH, DMF; d: CSA, MeOH; (iii) DMSO, (COCl)₂, CH₂Cl₂, -78°C then Et₃N; (iv) P₂ = Bz a: PhHgCCl₂Br, Ph₃P, benzene, 80°C; b: BuLi, THF, -78°C; (iv) P₂ = MPM a: CBr₄, Ph₃P, CH₂Cl₂, -78°C; b: LDA, THF, -30°C; (v) a: BuLi, THF, -78°C then 77; b: CSA, MeOH; c: Bu₄NF, THF/dioxane, 65°C; (vi) Lindlar catalyst, H₂, MeOH; (vii) DMSO, (COCl)₂, CH₂Cl₂, -78°C then Et₃N; b: CSA, CH₂Cl₂.
**Coupling of the Left and Right Hand Fragments**

Having obtained the two fragments 10 and 106-109, which constitute the left and right hand portions of salinomycin, they were combined (Scheme 26) in a crossed aldol reaction in the precise same manner that Kishi carried out this step. Deprotection of the aldol product 116, followed by equilibration in acid, afforded a single isomer of the natural product, salinomycin 1.
The recent synthesis of salinomycin 1 by Brown and Kocienski\textsuperscript{33,34} centres on the use of an oxidative rearrangement of 2-acyl furan 117 to form the complex bis-spiroketal moiety of the ketone subunit 118 (Scheme 27).

Retrosynthetic analysis of salinomycin 1 was carried out as detailed in Scheme 27. Following the standard retro-aldol disconnection to give the aldehyde 10 and ketone 118 the ketone subunit was further disconnected, via the acyl furan 117, to give the furan 119 and the lactone 120.

The starting material selected for synthesis of the furan fragment 119 (Scheme 28) was the homochiral acid 121, readily prepared by the methanolyis, and subsequent resolution of meso-2,4-dimethylglutaric anhydride\textsuperscript{35,36} using (-)-\textalpha-\textalpha-methylbenzylamine\textsuperscript{37-39}. Selective reduction of the carboxylic acid 121 with borane-methyl sulphide and protection of the resulting alcohol afforded the benzylxoxymethyl ether 122. Reduction of the ester 122 followed by Swern oxidation to the aldehyde 123.
then provided the necessary functionality for a highly diastereoselective Sn(II)
catalysed aldol reaction with (S)-N-butanoyl-4-isopropylazolidine-2-thione\textsuperscript{40} to give
the oxazolidinethione \textsuperscript{124}. Facile reductive cleavage of the oxazolidinethione \textsuperscript{124}\textsuperscript{41}
with sodium borohydride afforded a 1,3-diol which was subsequently protected as the
di-\textit{tert}-butylsilane derivative \textsuperscript{125}\textsuperscript{42,43}. Following removal of the benzyloxymethyl
protecting group and Swern oxidation\textsuperscript{22,23} of the hydroxyl group to the aldehyde 126, addition of 3,3-diethoxypropynyllithium gave the hydroxyalkyne 127 which underwent partial hydrogenation and acid catalysed cyclisation to produce the required furan 119.

Synthesis of the lactone fragment 120 began (Scheme 29) with the alkylation of the readily available allylic chloride 128\textsuperscript{33} using propynyldilithium\textsuperscript{44} to afford a terminal alkyne which was further extended by metallation and subsequent methoxycarbonylation to give the ynoate ester 129. Stereoselective carbometallation of the ynoate ester 129 was then effected using diethyllithium cuprate to produce the (Z)-enoate ester 130. Attachment of Oppolzer’s (2S)-bomane-10,2-sultam\textsuperscript{45} chiral auxiliary followed by treatment with potassium permanganate resulted in asymmetric oxidation\textsuperscript{46} of compound 131 to afford the tetrahydrofuran 132 in a 6:1 ratio with the corresponding diastereomer.

Oxidation of the acetal moiety of alcohol 132 followed by acid catalysed cyclisation produced the lactone 133. Reduction of the N-acyl sultam\textsuperscript{47} and removal of
the primary hydroxyl of the resulting diol by reduction of the corresponding iodide\textsuperscript{48,49}, afforded alcohol 134. Expansion of the tetrahydrofuran ring of the alcohol 134 to the required tetrahydropyran ring 120 was then effected using methodology first reported by Kishi\textsuperscript{8}. Thus, the mesylate derived from alcohol 134 was displaced with participation of the neighbouring oxygen to give an oxirionium ion whose capture by water produced the desired tetrahydropyran structure. A simple triethylsilylation then completed the synthesis to give lactone 120.

Coupling of the two subunits was accomplished (Scheme 30) by metallation of the furan 119 followed by addition of the lactone 120 to afford the 2-acyl furan 117 which was subsequently deprotected with pyridine-hydrogen fluoride to produce the triol 135. Oxidative rearrangement of the triol 135 with \( \text{N-bromosuccinimide} \text{\textsuperscript{50}} \) in
Reagents and conditions: (i) 'BuLi, THF, -80 to 0°C then 120 -80°C to RT; (ii) Py-HF, pyridine/THF; (iii) a: NBS, THF/H2O (3:1); b: 5% HF, MeCN/H2O; (iv) a: TESOTf, 2,6-lutidine; b: NaBH₄, CeCl₃·7H₂O, MeOH; (v) a: Ac₂O, pyridine, DMAP, CH₂Cl₂; b: Py-HF, pyridine/THF; (vi) a: Dess-Martin oxidation; b: EtMgCl, THF; c: Dess-Martin oxidation; (vii) K₂CO₃, MeOH; (viii) a: ArCOOH, Ph₃P, DEAD, benzene; b: K₂CO₃, MeOH.
tetrahydrofuran/water (3:1) was followed immediately by treatment with 5% hydrogen fluoride in acetonitrile/water to give a separable mixture of bis-spiroketal 136 and the corresponding C21 epimer. At this point it is worth noting that the stereochemistry of bis-spiroketal 136 differs from the salinomycin bis-spiroketal at C17 and C21.

Following protection of the hydroxyl groups of bis-spiroketal 136 the allylic ketone was stereoselectively reduced\(^{51}\) to afford a 7:1 mixture of the allylic alcohols 137 and 138, respectively. After protection of the allylic hydroxyl group and selective deprotection of the primary triethylsilyl ether, the left hand side of the molecules 137, 138 were elaborated to give the desired ketone sidechains 139, 140. Hydrolysis of the acetate 139, followed by Mitsunobu inversion\(^{52}\) afforded bis-spiroketal 141, which possesses the correct stereochemistry at C20.

### Scheme 31

\[
\begin{align*}
\text{Reagents and conditions: (i) a: CSA, CH}_2\text{Cl}_2; \text{ b: TESOTf, 2,6-lutidine}; \text{ c: K}_2\text{CO}_3, \text{ MeOH}; \text{ d: TESCl, Et}_3\text{N, DMAP.}
\end{align*}
\]

Treatment of bis-spiroketal 140 with camphorsulphonic acid (Scheme 31) effected isomerisation at C21 to give bis-spiroketal 142, analogous to the bis-spiroketal 68 prepared by Kishi et al\(^{7}\) in the first synthesis of salinomycin (Scheme 16). Consequently, conversion of bis-spiroketal 124 to salinomycin 1 was effected using the methodology established earlier by Kishi et al\(^{7}\) (see Scheme 16) whereby, the magnesium enolate of bis-spiroketal 142 was coupled to aldehyde 10, and following the removal of the triethylsilyl groups, the resulting epi-salinomycin was isomerised by treatment with trifluoroacetic acid to afford the target natural product, salinomycin 1.

### 1.2.4 Synthesis of the Bis-spiroketal Moiety of Epi-17-deoxy-(O-8)-salinomycin

The synthetic strategies employed by Kishi et al\(^{7}\), Yonemitsu et al\(^{26-28}\) in the construction of the bis-spiroketal moiety of salinomycin share several common elements. In both strategies the terminal tetrahydropyran ring is incorporated into the molecule prior to the assembly of the central bis-spiroketal moiety and the bis-spiroketal unit is assembled in a stepwise manner using acid catalysed intramolecular
ketalisation reactions to form both spirocentres. The synthetic strategy employed by Brown and Kocienski\textsuperscript{33,34} also involves incorporation of the terminal tetrahydropyran ring prior to assembly of the central \textit{bis}-spiroketal moiety, although in this case the spiroketal unit is assembled by the oxidative arrangement of a 2-acyl furan.

In 1992, however, an alternative approach to the synthesis of the \textit{bis}-spiroketal section of \textit{epi}-17-deoxy-(O-8)-salinomycin 143 was reported by Brimble and Williams\textsuperscript{53} (Scheme 32). Following a standard aldol disconnection to afford aldehyde 10 and ketone 144, the terminal tetrahydropyran ring of ketone 144 was disconnected to give the central \textit{bis}-spiroketal 145 and the trisubstituted bromoalkene 146. The key step for construction of the \textit{bis}-spiroketal 145 then involved oxidative cyclisation of the bicyclic hydroxyspiroketal 147 which was disconnected further to the lactone 45 and the acetylene 148.

Synthesis of the acetylene 148 (Scheme 33) began with the conversion of levulinic acid 149 to the racemic lactonic acid 150 using the procedure of Iwami and Kawai\textsuperscript{54}. Resolution of the acid was then carried out using Mori's method\textsuperscript{55}, whereby formation of the highly crystalline cinchonine salt of the desired (-)-acid allowed it to be separated from the non-crystalline salt of the (+)-acid. Subsequent acid hydrolysis of the resolved (-)-salt afforded the desired (S)-(S)-acid S-150 in pure form. Reduction of the (S)-(S)-acid S-150 with lithium aluminium hydride produced the (S)-triol 151 which, following acetonide protection of the 1,2-diol moiety, was oxidised to the

**Scheme 33**

\[ \text{Reagents and conditions: (i) NaCN, NaOAc, H}_2\text{O then HCl conc. } \Delta; \text{ (ii) cinchonine, EtOH, crystallisation then HCl; (iii) LiAlH}_4, \text{Et}_2\text{O; (iv) a: acetone, TsOH; b: DMSO, TFAA, CH}_2\text{Cl}_2, -65^\circ\text{C, Et}_3\text{N; (v) HCl=CCH}_2\text{MgBr, Et}_2\text{O; (vi) a: } ^3\text{BuPh}_2\text{SiCl, imidazole, CH}_2\text{Cl}_2; \text{ b: MeOH, Amberlite IR 120 resin; c: TsCl, pyridine.} \]
Scheme 32

epi-17-Deoxy-(O-8)-salinomycin 143

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aldehyde 152. Grignard addition of propargylmagnesium bromide to the aldehyde 152 afforded the (S)-acetylene 15356 which, following protection of the homopropargylic hydroxyl group and hydrolysis of the acetonide, was converted to the target tosylate 148.

A synthesis of the lactone 45 was detailed previously since it was an intermediate in the synthesis of salinomycin by Kishi et al7 (see Scheme 10). However, recent work by Brimble57 has provided an alternative route to the lactone 45 (Scheme 34) based on a synthesis of a Prelog-Djerassi acid58 reported by Evans et al59. Starting with butanoyloxazolidinone 154, prepared by the reaction of lithiated oxazolidinone 155 with butanoic chloride, formation of the Z-boron enolate 15660,61 followed by addition of aldehyde 157 afforded the desired 2',3'-erythro-3',4'-threo aldol product 158 in a 6:1 ratio with the 2',3'-threo-3',4'-threo diastereomer. After protection of the secondary hydroxyl group as the silyl ether 159, hydroboration of the olefin functionality afforded a separable mixture of the 6' R-160 and 6' S-161 alcohols in a ratio of 3.7:1. Protection of the 6' R alcohol 160 as the tert-butyldimethylsilyl ether and subsequent removal of the oxazolidinone chiral auxiliary with lithium borohydride62 gave alcohol 162 which, after selective manipulation of the protecting groups, yielded diol 163. Finally, diol 163 was oxidised, using tris(triphenylphosphine)ruthenium (II) chloride and 4-methylmorpholine-N-oxide, to the lactone 45.

The aldehyde 157 used in the preparation of lactone 45 was synthesised using a modification of the literature procedure57 (Scheme 35). Acylation of oxazolidinone 155

![Scheme 35](image)

Reagents and conditions: (i) BuLi, THF, -78°C, CH3CH2COCl; (ii) LDA, -78°C, then CH2=C(CH3)CH2I; (iii) LiAlH4, Et2O, 0°C; (iv) tetrapropylammonium perruthenate (cat.), NMO, CH2Cl2, 4A molecular sieves (powder).
Scheme 34

Reagents and conditions: (i) BuLi, CH₃CH₂CH₂COCl; (ii) R₂BOSO₂CF₃ (R₂B = 9-borabicyclo-[3.3.1]non-9-yl), Et₃N, CH₂Cl₂, 0°C, then -78°C, 15; (iii) 1-(Me₅Si)imidazole, CH₂Cl₂; (iv) BH₃, (CH₃)₂C=CH(CH₃)₂, 0°C then 17, -40°C; (v) a: BuMe₂SiOTf, 2,6-lutidine, CH₂Cl₂, 0°C; b: LiBH₄, THF; (vi) a: BuPh₂SiCl, imidazole, Et₃N, CH₂Cl₂; b: PPTS (cat.), EtOH; (vii) NMO, Ru(Ph₃P)₃Cl₂, 4Å molecular sieves (powder), acetone.
with propanoyl chloride afforded propanoyloxazolidinone 164 which was subsequently treated with lithium diisopropylamide and methallyl iodide to give the desired (2'S)-product 165. Reductive removal of the oxazolidinone moiety using lithium borohydride afforded alcohol 166 which was oxidised to the target aldehyde 157 using tetrapropylammonium per ruthenate catalyst and 4-methylmorpholine-N-oxide.

With the lactone 45 and tosylate 148 in hand assembly of the bis-spiroket al target 145 was pursued (Scheme 36). However before coupling of these subunits was attempted, the tert-butyldiphenylsilyl ether functionality of tosylate 148 was removed and replaced with the more labile trimethylsilyl ether so that it could be distinguished from the tert-butyldiphenylsilyl ether group of lactone 45. Treatment of acetylene 167 with n-butyllithium at -78°C afforded the lithium acetylide derivative which was reacted with lactone 45 to afford the hemiketal 168. Treatment of the hemiketal 168 with Amberlite IR 120 resin in methanol afforded the corresponding methoxyacetal 169 with concomitant removal of the trimethylsilyl protecting group. Partial hydrogenation of the diol 169 afforded the cis olefin 170 which was treated with pyridinium-p-toluenesulphonate to give a 1:1 mixture of tosylates 171 and 172 (Scheme 37).
Scheme 37

Reagents and conditions: (i) PPTS, CH₂Cl₂; (ii) NaH, THF; (iii) LiI, THF, BF₃·Et₂O, -50°C; (iv) iodine, iodobenzenediacetate, 18°C, hv.
Following separation of the tosylates using column chromatography the individual tosylates were converted to the corresponding epoxides and then opened with lithium iodide to form the iodohydrins.

The critical oxidative cyclisation was then achieved upon irradiation of either iodohydrin or iodohydrin in a solution of cyclohexane, containing iodine and iodobenzenediacetate affording the trans-bis-spiroketal and the cis-bis-spiroketal in a ratio of 1.7:1. This outcome may be explained by the proposed mechanism (Scheme 38) whereby both diastereomeric precursors and form the same radical or carbocation intermediate which is subsequently trapped predominantly from the least hindered face to give the trans-bis-spiroketal as the major product.

Having synthesised the desired bis-spiroketal moiety of epo-17-deoxy-(O-8)-salinomycin in the form of the trans-bis-spiroketal all that remained was to convert the iodide group to the alcohol (Scheme 39). Extensive work by Williams concluded that treatment of the iodide with potassium superoxide and 18-crown-6 in dimethylsulphoxide was the most effective way of forming the alcohol although this was accompanied by the undesirable removal of the terminal tert-butyldiphenylsilyl group. However, it was proposed that this difficulty could be avoided by replacing the silyl group at an earlier stage of the synthesis with a protecting group (possibly a benzyl ether) which will remain unaffected by the potassium superoxide reaction conditions.

Scheme 39

Reagents and conditions: (i) KO₂, 18-crown-6, DMSO.

Thus, to date a synthesis of bis-spiroketal has been completed. This advanced intermediate for the synthesis of epo-17-deoxy-(O-8)-salinomycin contains functionality at both the left hand and right hand ends of the molecule which will enable the synthesis of epo-17-deoxy-(O-8)-salinomycin to be extended.
Scheme 38

\[\text{175} \rightarrow \text{hν} \rightarrow \text{[1,5]H} \rightarrow \text{178a} \rightarrow \text{I}_2 \rightarrow \text{178b} \rightarrow \alpha, \beta \rightarrow \text{177} \]

\[\text{176} \rightarrow \text{hν} \rightarrow \text{[1,5]H} \rightarrow \text{178a} \rightarrow \text{I}_2 \rightarrow \text{178b} \rightarrow \alpha, \beta \rightarrow \text{177} \]
1.3 Synthesis of Polyether Antibiotics Containing Terminal Tetrahydrofuran-Tetrahydropyran Units

Of the polyether antibiotics which have been successfully synthesised to date a large percentage of them contain terminal substructures strongly reminiscent of the tetrahydrofuran-tetrahydropyran moiety in salinomycin 1 (i.e. rings D and E). Thus, a study of the methodology employed to construct these related subunits should provide valuable information regarding construction of the tetrahydrofuran-tetrahydropyran (D,E-ring) moiety of salinomycin. Polyether antibiotics which contain structural units similar to the D and E rings of salinomycin (or tetrahydrofuran-tetrahydrofuran precursors thereof) include lasalocid A 469, antibiotic X-206 18070, ferensimycin B 18171 and lysocellin 18272 (Figure 5).

1.3.1 Lasalocid A

The polyether antibiotic lasalocid A 4 (Figure 5) contains a terminal bis-ether unit almost identical to the one present in salinomycin. In terms of overall structure, however, lasalocid A is a much simpler molecule. Consequently, much of the early work developing methodology for construction of tetrahydrofuran-tetrahydropyran bis-ethers centred on the total synthesis of lasalocid A 8-10,73-78.

1.3.1.1 Nakata and Kishi8-10

The total synthesis of lasalocid A 4 was first achieved in 1978 by Nakata et al8. The final step in their synthesis consists of a stereoselective crossed aldol condensation
Figure 5

Salinomycin 1

Lasalocid A 4

Antibiotic X-206 180

Ferensimycin B 181

Lysocellin 182
of aldehyde 183 with ketone 184 (Scheme 40). This type of reaction is so efficient that it is a common feature for all lasalocid A syntheses as well as those of other polyether antibiotics including salinomycin 1, narasin 2, and monensin 3.

Synthesis of the right hand section 184 of lasalocid A began with the conversion of ethyl (4E, 8E)-2-methyl-4,8-dieethyldecadienoate 185 (readily synthesised by adapting Johnsons method79) to ketone 186 (Scheme 41). Stereoselective reduction of ketone 186 was then carried out using lithium aluminium hydride and dl-2-(o-toluidinomethyl)pyrrolidine to afford alcohol 187 in greater than 10:1 ratio with its diastereomer. Epoxidation of the alcohol 187, followed by an acetic acid workup gave the tetrahydropyran 188 along with a small amount of its stereoisomer (8:1 ratio). Repetition of the epoxidation under the same conditions, followed by acetylation allowed isolation of the epoxide 189. After inversion of the epoxide 189, an acetic acid workup and subsequent protection afforded the bis-ether 190. Birch reduction80 of the p-methoxyphenyl group followed by epoxidation and oxidative cleavage afforded ester 191 which was subsequently converted to the ketone 192. Equilibration of the ketone 192 resulted in a 1:1 mixture of the ketones 192 and 193, which were easily separated by column chromatography. Ketone 192 was recycled while mesylation of the isolasalocid series ketone 193 and subsequent solvolysis in the presence of silver carbonate afforded a mixture of the desired lasalocid ketone 184 and ketone 193, which was recycled.

In 1978, a second route by Nakata and Kishi was reported9,10, this time using only acyclic precursors in a short, efficient and stereospecific synthesis of the isolasalocid ketone 193.

Beginning with the readily available unsaturated ketone 1949 (Scheme 42), stereoselective epoxidation and reduction afforded the intermediate epoxyalcohol 195 which upon acetic acid workup cyclised to give the tetrahydrofuran 54. Protection of the hydroxyl group followed by ozonolysis afforded the aldehyde 196, ready for Grignard addition of 2-methyl-3-butenylmagnesium bromide to yield the alcohol 197. After oxidation of the alcohol 197, a second chelation controlled Grignard addition of ethyl magnesium bromide afforded the tertiary alcohol 198. Ozonolysis of the alkene moiety followed by dimethyl sulphide work up gave lactol 199 which was extended by addition of the magnesium enolate to afford ketone 200. Subsequent treatment of ketone 200 with p-toluenesulphonic acid and deprotection yielded epi-isolasalocid A ketone 192 and isolasalocid A ketone 193 as a 1:1 mixture after equilibration. Following separation by column chromatography, epi-ketone 192 was recycled while the isolasalocid A ketone 193 was readily converted to the lasalocid A ketone 184 using established methodology8 (see Scheme 41).
Scheme 41

Reagents and conditions: (i) a: LiAlH₄, Et₂O; b: PCC, CH₂Cl₂; c: Et₂O, p-MeOC₆H₄MgBr; d: Jones oxidation; (ii) LiAlH₄, d,l-2-(o-toluidinomethyl)pyrroldidine, Et₂O, -78°C; (iii) BuOOH, VO(acac)₂, NaOAc, benzene then AcOH; (iv) a: BuOOH, VO(acac)₂, NaOAc, benzene; b: AcOH, pyridine; (v) a: 0.1 M H₂SO₄/acetone/H₂O; b: TsCl, pyridine; c: K₂CO₃, MeOH; d: AcOH (vi) MeOCH₂Br, KH, THF; (vii) a: Li, liq. NH₃, EtOH; b: MCPBA, aq. NaHCO₃, CH₂Cl₂; c: HIO₄, aq. dioxane; (viii) a: LiAlH₄, THF, reflux; b: TsCl, pyridine, 0°C; c: LiAlH₄, Et₂O, RT; d: B₂H₆, THF; e: Jones oxidation; f: TrBF₄, CH₂Cl₂; (ix) NaOH, aq. dioxane; (x) a: MsCl, pyridine; b: Ag₂CO₃, aq. acetone.
Scheme 42

Reagents and conditions: (i) tBuOOH, VO(acac)₂, benzene; (ii) a: LiAlH₄, d,l-2-(o-toluidinomethyl)pyrrolidine, Et₂O, 0°C; b: AcOH; (iii) a: BzBr, KH, THF; b: O₃, MeOH, -78°C; (iv) (R)-2-methyl-3-butenylmagnesium bromide, Et₂O; (v) a: Jones oxidation; b: EtMgBr, Et₂O; (vi) O₃, MeOH, -78°C then DMS work-up; (vii) 4-bromo-3-hexanone, Mg; (viii) a: TSA, benzene, reflux; b: H₂, Pd-C, MeOH; (ix) NaOH, aq. dioxane.
1.3.1.2 Ireland et al.\textsuperscript{72,73}

The synthesis of lasalocid A by Ireland et al.\textsuperscript{73} in 1980 utilised carbohydrate precursors in a highly convergent "building block" approach (Scheme 43). Following the standard aldol disconnection to give aldehyde 183 and ketone 184, the ketone was disconnected further to give the three subunits 201\textsuperscript{*}, 202\textsuperscript{*}, 203\textsuperscript{*}.

![Scheme 43]

Synthesis of the pyranoid subunit 201\textsuperscript{*} began with the selective protection of 6-deoxy-L-glucose 204\textsuperscript{81} to give the pyran 205 (Scheme 44). Removal of the benzyl group afforded lactol 206 which after treatment with hexamethylphosphorus triamide...
and carbon tetrachloride, followed by excess lithium in ammonia afforded the pyran synthon 201.

![Scheme 44](image)

Reagents and conditions: (i) a: CH₃COCH₃, H⁺; b: BzOH, HCl; c: CH₃OCH₂Cl, KH; (ii) H₂, Pd-C, EtOAc; (iii) HMPT, CCl₄, Li, NH₃.

The starting point for the synthesis of the furanoid subunit 203* (Scheme 45) was "α"-D-glucosaccharino-1,4-lactone 207, readily available by the treatment of invert sugar with aqueous calcium hydroxide. After appropriate blocking, lactone 207 was reduced to lactol 208 which upon treatment with hexamethylphosphoramide and carbon tetrachloride, followed by excess lithium in ammonia afforded the glycal 209. The left hand side chain was then formed by the addition of butyryl chloride and subsequent ester enolate Claisen rearrangement. The resulting carboxylic acid 210 was converted to the corresponding methyl ester and reduced to an alcohol which was protected as the benzyl ether. The alkene moiety was then stereoselectively reduced to give the tetrahydrofuran 211 and finally conversion of tetrahydrofuran 211 to the furanoid synthon 203 required only selective manipulation of the oxidation states of the terminal carbons.

Following the conversion of the carboxylic acid 203 to the corresponding acid chloride, the furanoid 203 and pyranoid 201 subunits were coupled through the application of the enolate Claisen rearrangement (Scheme 46). Treatment with diazomethane then afforded the esters 212 and 213 (1:3 ratio) which were separated by column chromatography. The desired syn isomer 213 was hydrogenated and the ester group was reduced to give the aldehyde 214, which was converted, via the Wittig reaction, to the required ethyl group 215. Removal of the MOM protecting group followed by Swern oxidation of the resulting alcohol afforded ketone 216.
Conversion of the ketone 216 to the alkene via the Wittig reaction followed by epoxidation afforded the epoxide 217 which underwent dimethyl cuprate cleavage to give the desired pyran moiety 218. Finally, elaboration of the left hand end of alcohol 218 yielded the desired ketone 184.

1.3.1.3 Horita/Yonemitsu

The synthesis of the lasalocid A series ketone 184 by Horita et al.75-78 (Scheme 47) involves the coupling of the highly substituted acyclic chain 219 to the preformed tetrahydropyran unit 220 followed by stereoselective cyclisation to afford the tetrahydrofuran ring.

The starting material for the synthesis of the tetrahydropyran synthon 220 was aldehyde 221 (Scheme 48), readily synthesised from S-(−)-ethyl lactate84. The aldehyde 221 was converted to the alcohol 222 by the Grignard addition of 3-butenylmagnesium bromide. Swern oxidation22,23 of the alcohol 222 followed by the chelation controlled
Reagents and conditions: (i) (COCl)$_2$, benzene; (ii) n-BuLi, THF, LDA, TMSCI, RT, H$_2$O, OH$^-$, CH$_2$N$_2$; (iii) a: H$_2$, Raney Ni, EtOAc; b: DIBAL, Et$_2$O; (iv) a: (C$_6$H$_5$)$_3$P=CH$_2$, THF; b: 10% HCl, THF; c: H$_2$, Raney Ni, EtOAc; d: H$_2$, Pd–C, EtOAc; (v) DMSO, (COCl)$_2$, Et$_3$N; (vi) a: (C$_6$H$_5$)$_3$P=CH$_2$, THF; b: MCPBA, CH$_2$Cl$_2$; (vii) a: (CH$_3$)$_2$CuLi, pentane; b: Li, NH$_3$; (viii) a: PCC, CH$_2$Cl$_2$; b: EtMgBr, THF; c: PCC, CH$_2$Cl$_2$. 
Reagents and conditions: (i) "BuLi, Et₂O/hexane (1:1), 220; (ii) a: DMSO, (COCl)₂, CH₂Cl₂, -78°C; b: Al-Hg, THF; (iii) a: MeOC₆H₄C≡CLi, Et₂O, -78°C to 30°C; b: LiAlH₄, THF; (iv) ZnBr₂, CH₂Cl₂, 40°C; (v) a: TBDMSCl, imidazole, CH₂Cl₂; b: OsO₄, NMO, acetone/H₂O (5:2); c: Pb(OAc)₄, benzene; (vi) Ph₃P=CH₂, THF; (vii) a: "Bu₄NF, THF; b: H₂, Pd(OH)₂, EtOAc; (viii) PCC, 3A MS, CH₂Cl₂; (ix) a: EtMgBr, THF, 0°C; b: PCC, 3A MS, CH₂Cl₂.
Grignard addition of ethylmagnesium bromide afforded alcohol 223. Subsequent manipulation of the protecting groups followed by oxidative cleavage of the double bond produced the aldehyde 224 which was extended, via the Wittig reaction, to give the MP-allyl alcohol 225. Treatment of the alcohol 225 with zinc bromide at -20°C for 1.5 hours afforded the pyran 226 in a 14:1 ratio with the corresponding diastereomer. Finally, oxidative cleavage of the double bond moiety of pyran 226 afforded the desired aldehyde 220.

**Scheme 48**

![Scheme 48](image)

*Reagents and conditions: (i) CH₂=CHCH₂CH₂MgBr, THF, 0°C; (ii) a: DMSO, (COCl)₂, CH₂Cl₂, -78°C then Et₃N; b: EtMgBr, THF, 0°C; (iii) a: BzBr, NaH, DMF; b: 4M HCl/THF (1:2) 40-60°C; c: TBDMSCI, imidazole, DMF, 80°C; d: OsO₄, NMO, acetone/THF (4:1); e: NaIO₄, MeOH; (iv) a: (MeO)₂P(O)CH₂COC₆H₄OMe, NaH, THF, 0°C; b: NaBH₄, CeCl₃, MeOH, 0°C; (v) a: ZnBr₂, CH₂Cl₂, -20°C; (vi) a: OsO₄, NMO, acetone/H₂O (10:1); b: NaIO₄.*

Synthesis of the sulphone precursor 219 of the tetrahydrofuran ring (Scheme 49) began with the aldehyde 227, readily derived from D-glucose. Reduction of the aldehyde 227 and selective protection of the resulting primary hydroxyl group afforded alcohol 228 which was hydrogenated over palladium charcoal and the resulting diol was converted to the acetonide 229. Removal of the pivaloyl protecting group enabled formation of the tosylate which was readily converted to the desired sulphone 219.

Coupling of the two subunits was carried out by the reaction of the aldehyde 220 with the anion of sulphone 219 to afford a mixture four diastereoisomeric β-hydroxysulphones 230 (Scheme 47). Swern oxidation of the sulphones 230 followed by desulphonization with aluminium amalgam gave the ketone 231 which was treated
Reagents and conditions: (i) a: LiAlH₄, Et₂O, 0°C to RT; b: PvP, pyridine, 0°C to RT; (ii) a: H₂, Pd-C, EtOAc; b: CSA, Me₂C(OMe)₂, benzene; (iii) a: LiAlH₄, Et₂O, 0°C to RT; b: TsCl, pyridine, 0°C to RT; (iv) a: NaI, acetone, Δ; PhSO₂Na, DMF, 60°C.

with p-methoxyphenylethynyllithium at -78°C to give, after partial reduction with lithium aluminium hydride, the alcohol 232 as the only product. Treatment of the alcohol 232 with zinc bromide afforded the necessary tetrahydrofuran ring structure 233 in a 3:1 ratio with the other diastereomer.

Elaboration of the bis-ether system 233 was then effected. Following protection of the primary hydroxyl group oxidative cleavage of the double bond produced the aldehyde 234 which was converted to the olefin 235 via the Wittig reaction. Deprotection of the primary alcohol followed by reduction of the ethylene moiety afforded alcohol 236 which, after oxidation to the corresponding aldehyde 237, underwent Grignard addition and a second oxidation to afford the target lasalocid A series ketone 184.

1.3.2 Antibiotic X-206

In 1988, the first total synthesis of the polyether antibiotic X-206 180 was reported by Evans et al. This antibiotic, while lacking the bis-spiroketal unit present in salinomycin, contains an almost identical terminal tetrahydrofuran-tetrahydropyran unit.

The retrosynthetic analysis of antibiotic X-206 180 (Scheme 50) began with the aldol disconnection of the C16-C17 bond of its β-hydroxyketone tautomer 238 to afford the aldehyde 239 and ketone 240. The aldehyde 239, which contains the tetrahydrofuran-tetrahydropyran unit of interest, was further disconnected into segments; alkene 241, hydrazone 242 and epoxide 243.
Synthesis of the alkene 241 began (Scheme 51) with the alkylation of the lithium enolate of imide 244 with 2,3-dibromopropene\(^8\) to afford a 98:2 mixture of diastereomers which were separated by chromatography to give the major imide 245 in pure crystalline form. Reduction of the imide 245 to the alcohol followed by Swern oxidation\(^22,23\) afforded the desired aldehyde 241. Finally, treatment with isopropylidenediphenylphosphorane masked the aldehyde 241 as the dialkene 246.

**Scheme 51**

Reagents and conditions: (i) a: LDA, CH\(_2\)=C(Br)CH\(_2\)Br, THF, -35°C; (ii) LiAlH\(_4\), THF, -78 to 0°C; (iii) a: DMSO, (COCl\(_2\), CH\(_2\)Cl\(_2\), -65°C then Et\(_3\)N, -70 to -10°C; b: Ph\(_3\)P+=Pr\(^+\), \(^\text{Bu}\)Li, THF, -78 to 25°C.

Synthesis of the epoxide 243 on the other hand was effected by a twofold application of the asymmetric epoxidation reaction (Scheme 52).

Beginning with racemic 2-methyl-1-penten-3-ol 247, Sharpless asymmetric epoxidation with \textit{tert}-butyl hydroperoxide followed by protection of the hydroxyl group as the \textit{p}-methoxybenzyl (PMB) ether afforded epoxide 248. Regiospecific opening of the epoxide 248 with allylmagnesium chloride afforded a tertiary alcohol which was subsequently benzylated to give the alkene 249. Ozonolysis of the alkene 249 and extension of the resulting aldehyde, \textit{via} the Wittig reaction, afforded the \(\alpha,\beta\)-unsaturated ester predominantly as the (E)-isomer 250 (E:Z 94:6) which was easily separated by column chromatography. Oxidative cleavage of the PMB ether 250\(^8\), followed by reduction of the ester group with diisobutylaluminium hydride produced the diol 251. Application of the second asymmetric epoxidation, using (+)-diethyl tartrate as the chiral ligand, afforded an intermediate epoxide which underwent intramolecular attack by the C35 hydroxyl group to form the tetrahydropyran 252. Selective tosylation of the primary hydroxyl group followed by treatment with potassium carbonate in methanol effected ring closure to provide a 40:1 diastereomeric
Scheme 52

**Reagents and conditions:**

(i) a: BuOOH, Ti(OiPr)$_4$, (+)-diisopropyl tartrate, CH$_2$Cl$_2$; b: p-MeOC$_6$H$_4$CH$_2$Cl, NaH, DMF, 0°C; (ii) a: CH$_2=CHCH_2MgCl$, THF; b: BzBr, KH, THF; (iii) a: O$_3$, -78°C, MeOH then Ph$_3$P, CH$_2$Cl$_2$; b: Ph$_3$P=C(Me)CO$_2$Et, CH$_2$Cl$_2$; (iv) a: DDQ, CH$_2$Cl$_2$/H$_2$O; b: DIBAL, CH$_2$Cl$_2$, -78 to 0°C; (v) BuOOH, Ti(OiPr)$_4$, (+)-diethyl tartrate, CH$_2$Cl$_2$, -78 to 0°C; (vi) a: TsCl, pyridine; b: K$_2$CO$_3$, MeOH, 0°C.

mixture of the epoxides. Removal of the small amount of unwanted epoxide by column chromatography afforded pure epoxide 243 as a crystalline solid.

The synthesis of the D-ring tetrahydrofuran synthon 242 (Scheme 53) began with the stereoselective aldol reaction of imide 253 with (E)-4-methyl-4-heptanal 254 to give the alcohol 255. Epoxidation of the γ,δ-unsaturated alcohol 255 followed by in situ cyclisation afforded a 95:5 mixture of diastereomeric products which were separated by column chromatography affording the major diastereomer 256 in 89% yield. Transamination of the oxazolidinone 256 with the aluminium amide reagent prepared from N,O-dimethylhydroxylamine hydrochloride and trimethyl aluminium yielded the amide 257 which was readily oxidised to the ketone 258. Following removal of the benzyl group and reprotection as a more labile methoxyisopropyl (MOP) ether, the right hand carbonyl group was converted to the hydrazone 242 thereby affording the appropriate synthon for coupling to the epoxide. While ketone enolates have proven to be quite unreactive towards epoxides the Schiff base formed by the hydrazone should not only afford a highly reactive enolate equivalent, but its greatly
Reagents and conditions: (i) Bu₂BOTf, Et₃N, CH₂Cl₂ then 254; (ii) BuOOH, VO(acac)₂ (cat.), CH₂Cl₂; (iii) AlMe₃, MeONHMe-HCl, CH₂Cl₂, 0°C; (iv) aq. H₂CrO₄, Et₂O; (v) a: H₂, Pd-C, HClO₄ (cat.), EtOH; b: CH₂=C(Me)OMe, PPTS, 0°C; c: Me₂NNH₂, Me₃SiCl, 0°C.

decreased electrophilicity should also prevent reaction with the C27 carbonyl during the coupling of the tetrahydrofuran 242 and epoxide 243 synthons.

The assembly of the right half of antibiotic X-206 began with the reaction of the organolithium derivative of bromoalkene 246 with the hydrazone 242, to give the stable tetrahedral intermediate 259 (Scheme 54). Metallation of this intermediate 259 with lithium disopropylamide followed by addition of the epoxide 243 produced the desired tricyclic system 260. After removal of the hydrazinolactol and methoxyisopropyl groups by treatment with aqueous acid, hydrogenation with Wilkinson's catalyst afforded hydroxyalkene 261 in a 93:7 ratio with its diastereomer. Following chromatographic purification, the E-ring of hydroxyalkene 261 was converted to methoxy ketal 262 under non-epimerising conditions. Protection of the secondary hydroxyl group and subsequent ozonolysis of the alkene moiety produced the desired aldehyde target 239.
Scheme 54

Reagents and conditions: (i) 2 equiv. 'BuLi, 242, Et₂O, -78 to 0°C; (ii) LDA, 0°C, 243, 0°C; (iii) a: 1M NaHSO₄, 25% CH₂Cl₂/pentane; b: H₂, (Ph₃P)₃RhCl, PhMe; (iv) a: PPTS, (MeO)₃CH, MeOH, 0°C; b: BzOCH₂Br, H⁺ sponge, MeCN, 25 to 45°C; (v) O₃, MeOH/CH₂Cl₂, -78°C.
1.3.3 Ferensimycin B

In 1991, Evans et al.\textsuperscript{92} reported the first total synthesis of ferensimycin B 181 (Scheme 55), a member of the lysocellin family of polyether antibiotics. Ferensimycin B contains a terminal tetrahydrofuran-tetrahydrofuran ring assembly which has been reported to undergo ring chain equilibration (Figure 6) to give a tetrahydrofuran-tetrahydropyran moiety which closely resembles the terminal ring assembly of salinomycin.

As expected the first disconnection in the retrosynthetic analysis of ferensimycin B 181 is an aldol transform affording the aldehyde 263 and ketone 264. The synthesis of bis-tetrahydrofuran 264 is of particular relevance to the present study. Ketone 264 was further disconnected to give the hydrazone 265 and epoxide 266.

![Scheme 55](image)

![Figure 6](image)
Synthesis of the ring B synthon 265 (Scheme 56) began with the Johnson ortho-ester Claisen rearrangement of 2-methyl-1-penten-3-ol to give ester 267 which was saponified to afford the corresponding acid 268. Acylation of the lithium salt of oxazolidinone 269 with the mixed pivaloyl anhydride derived from acid 268 afforded the imide 270. Treatment of the imide 270 with sodium hexamethyldisilazide followed by addition of methyl iodide furnished the desired α-methylcarboximide 271 in a 91:9 ratio with the corresponding diastereomer. Following purification by preparative HPLC, reductive removal of the chiral auxiliary and subsequent Swern oxidation22,23 afforded the aldehyde 272. Using the boron aldol addition89, aldehyde 272 was coupled to imide 273 providing adduct 274 in greater than 99% diastereomeric purity.

Epoxidation of the bis-homoallylic alcohol 274 and subsequent acid catalysed ring opening of the intermediate epoxide provided the diastereomeric tetrahydrofurans 275 and 276 in a 96:4 ratio from which the major isomer 276 was obtained by chromatographic methods.

Swern oxidation22,23 of the tetrahydrofuran 276 afforded aldehyde 277, which was subsequently transformed to the hydroxamic acid derivative 278. Treatment of the ketone 278 with excess N,N-dimethylhydrazine in the presence of trimethylsilyl chloride afforded the hydrazone synthon 279 as a single diastereomer. It is interesting to note that introduction of the hydroxamic acid moiety prior to epoxidation affords significantly lower stereoselectivity. It was speculated92 that compound 280, with its more basic carbonyl oxygen might be acting as a bidentate chelate during epoxidation which, for unanticipated reasons, is deleterious to the stereoselectivity of the vanadate directed oxidation.

The second synthon, epoxide 266, was obtained via a Sharpless epoxidation94 of racemic 2-ethyl-1-penten-3-ol 281 and purified by preparative HPLC (Scheme 57).

**Scheme 57**

```
Reagents and conditions: (i) a: tBuOOH, Ti(O\text{O}Pr)\text{4}, (+)-diisopropyl tartrate;  
b: p-MeOCH\text{2}H\text{2}Br, NaH, THF/DMF, 0°C.
```

Coupling of the two synthons, 279 and 266, was effected (Scheme 58) by application of methodology developed in Evans et al's earlier synthesis of antibiotic X-20686 (see Scheme 41) whereby hydrazone 279 was first treated with ethyllithium to
Reagents and conditions: (i) aq. 2.0 M KOH, MeOH; (ii) Me3CCOCl, Et3N, Li-269; (iii) NaHMDS, MeI, -78°C; (iv) a: LiAlH4, THF, 0°C; b: DMSO, (COCl)2, CH2Cl2, -78°C then Et3N; (v) Bu2BOTf, Et3N, 273; (vi) MeONHMe-HCl, Me3Al, THF; (vii) a: ′BuOOH, VO(acac)2, benzene; b: AcOH; (viii) DMSO, (COCl)2, CH2Cl2, -78°C then Et3N; (ix) a: LiOH, H2O2, THF/H2O 0°C to RT; b: MeONHMe-HCl, CH2Cl2, DMAP, Me2CHN=C=NCHMe2; (x) Me2NNH2, TMSCI.
Reagents and conditions: (i) EtLi, Et₂O, -78°C; (ii) Et₂NLi, THF, -78°C then Mg-266; (iii) NaHSO₄, H₂O.

protect the carbonyl moiety as the stable tetrahedral intermediate. Lithiation of the hydrazone functionality then afforded the reagent 282 which reacted with the magnesium alkoxide derivative of the epoxide 266 to form the desired hydrazinyltetrahydrofuran 283.

Treatment of the crude hydrazinyltetrahydrofurans with a biphasic solution of aqueous sodium bisulphate and pentane/dichloromethane (3:1 v/v) afforded the stable lactol isomers 284, 264 in a 1:9 ratio in 48% combined yield.

With the lactol 264 in hand, reaction of the corresponding zinc enolate with the aldehyde 265 (Scheme 55) was effected to afford the target natural product, ferensimycin B 181.
1.3.4 Lysocellin

The total synthesis of the polyether antibiotic lysocellin \(182\) was reported in 1992 by Yonemitsu et al\(^5,96\). Lysocellin is almost identical in structure to ferensimycin B, differing only in the lack of a methyl substituent at \(C2\).

Following the standard aldol disconnection of lysocellin \(182\) to form the aldehyde \(285\) and ketone \(264\), the ketone \(264\) was further disconnected into the two acyclic subunits, iodide \(286\) and aldehyde \(287\) (Scheme 59).

Preparation of the iodide \(286\) (Scheme 60) was reportedly carried out by using the alcohol precursor to the pivaloyl derivative \(229\), previously prepared in the synthesis of lasalocid \(A75-78\) (see Scheme 49). Although no details were given for this conversion, formation of the tosylate followed by reaction with sodium iodide should provide an effective route to the iodide \(286\).
Synthesis of the aldehyde section 287 began with the Wittig Horner coupling of the chiral phosphonate 288, derived from 3,4-O-isopropylidene-D-mannitol, and the D-glyceraldehyde derivative 92 to afford the $\alpha,\beta$-unsaturated ketone 289 (Scheme 61). Treatment of the ketone 289 with dimethyl lithium cuprate, proceeding via Michael addition, followed by Swern oxidation$^{22,23}$ produced ketone 290 in a 6.3:1 ratio with the corresponding diastereomer. The chelation controlled addition$^{97,98}$ of ethylmagnesium bromide to ketone 290 proceeded stereoselectively, affording the desired alcohol 291 in quantitative yield.

**Scheme 61**

**Reagents and conditions:** (i) NaH, DMSO/THF, 0°C; (ii) Me$_2$CuLi, Et$_2$O/THF, -78 to -20°C; (iii) EtMgBr, THF, -78°C; (iv) a: TBDMSOTf, Et$_3$N, 0°C to RT; b: 1M H$_2$SO$_4$/THF/MeOH (2:4:1); c: 4-MeOC$_6$H$_4$CH(OMe)$_2$, PPTS, CH$_2$Cl$_2$; (v) a: LiAlH$_4$-AlCl$_3$ (1:3), Et$_2$O, -50°C; b: DMSO, (COCl)$_2$, CH$_2$Cl$_2$, -78°C then Et$_3$N.
After protection of the alcohol 291 as a silyl ether, the isopropylidene group was replaced with a 4-methoxybenzylidene protecting group to afford silyl ether 292. This then underwent regioselective reduction of the aryl acetal functionality followed by Swern oxidation\textsuperscript{22,23} of the freed hydroxyl group to afford the desired aldehyde subunit 287.

With the required subunits in hand, assembly of the ketone 264 began (Scheme 62) with the coupling of the lithium anion\textsuperscript{99} of the iodide 286 and aldehyde 287 to give the alcohol 293. Swern oxidation of the alcohol 293 followed by chelation controlled addition\textsuperscript{97,98} of methylmagnesium iodide afforded only the desired alcohol 294. After removal of the MPM protecting group by DDQ oxidation\textsuperscript{100} and subsequent reduction of the resulting 4-methoxybenzoate the freed secondary hydroxyl group was selectively mesylated to give alcohol 295, which was readily converted to tetrahydrofuran 296 via formation and acid catalysed cyclisation of the epoxyalcohol 297.

Selective acetylation of the C17 hydroxyl group via three conventional reactions afforded acetate 298 which underwent Swern oxidation\textsuperscript{22,23} followed by the Grignard addition of ethylmagnesium bromide to give alcohol 299. Following removal of the TBDMS and acetate protecting groups by treatment with tetrabutylammonium fluoride, oxidation of the resulting triol with pyridinium chlorochromate\textsuperscript{24} in the presence of 3A molecular sieves produced a mixture of the lactols 300, 301. Equilibration of the lactols 300 and 301 in an acidic medium afforded the more thermodynamically stable \(\alpha\)-lactol 301 which, following the removal of the benzyl protecting group, afforded the required ketone 264. Finally, the synthesis of lysocellin was completed in that ketone 264 was coupled to the left hand portion of the molecule 284 (see Scheme 59) using an aldol condensation similar to that used in the synthesis of ferensimycin B\textsuperscript{92}.

1.4 Electrophilic Cyclisation as a Method to Construct Polyethers

At present there is a great deal of interest in the stereocontrolled synthesis of substituted tetrahydrofuran\textsuperscript{101} and tetrahydropyran rings due to their presence in a number of important natural products such as the polyether antibiotics\textsuperscript{3} (\textit{vide supra}), acetogenins\textsuperscript{102} and C-glycosides\textsuperscript{103}. One useful approach to the synthesis of these heterocyclic structures is the electrophile mediated intramolecular cyclisation of an hydroxyl (or alkoxyl) group with an appropriately positioned double bond\textsuperscript{104,105}. This electrophile mediated cyclisation strategy plays an important role in the present work as a method to incorporate the E ring of salinomycin, hence a discussion of this reaction is described herein.
Reagents and conditions: (i) t-BuLi, Et₂O, -78°C, 287; (ii) a: DMSO, (COCl)₂, CH₂Cl₂, -78°C then Et₃N; b: MeMgI, Et₂O, -78 to -20°C; (iii) a: DDQ, CH₂Cl₂/H₂O (20:1); b: LiAlH₄, Et₂O, 0°C; c: MsCl, pyridine, 0°C; (iv) a: 1M H₂SO₄/THF (2:5); b: K₂CO₃, MeOH; (v) CSA, CH₂Cl₂, 0°C; (vi) a: TBDMSI, imidazole, CH₂Cl₂, 0°C to RT; b: Ac₂O, Et₃N, DMAP, CH₂Cl₂; c: 1M HCl/THF (2:5); (vii) a: DMSO, (COCl)₂, CH₂Cl₂, -78°C then Et₃N; b: EtMgBr, THF, -78 to -20°C; (viii) a: n-Bu₄NF, DME; b: PCC, 3Å MS, CH₂Cl₂; (ix) 1M H₂SO₄/THF (1:3), 0°C to RT; (x) H₂, Raney Ni (W-2), EtOH.
Cyclisation of γ,δ-unsaturated alcohols has, in theory, the potential to afford either a tetrahydrofuran or tetrahydropyran ring, depending on the mode of ring closure involved (Scheme 63). In practise, however, the tetrahydrofuran ring frequently predominates unless significant orientational effects, such as ring strain or Markovnikov's rule are present to override the normally stereoelectronically favoured 5-exo mode of closure. As well as controlling the regioselective outcome of the cyclisation reaction there are a number of factors which, if successfully utilised, can produce desired stereoselectivity.

Scheme 63

\[
\begin{align*}
\text{R} & \quad \text{5-exo} \quad \text{E} \\
\text{R} & \quad \text{6-endo} \quad \text{E}
\end{align*}
\]

It is generally accepted that the electrophilic cyclisation of secondary γ,δ-unsaturated alcohols under thermodynamic conditions produces \textit{trans} 2,5-disubstituted tetrahydrofurans. However, in 1981, Bartlett \textit{et al}\textsuperscript{106} demonstrated that formation and subsequent cyclisation of ether analogues produced predominantly the corresponding \textit{cis} isomer (Table 1). These results are rationalised by the mechanism depicted (Scheme 64). Where R=H, the \textit{trans} intermediates 302a, 302b are thermodynamically more stable than the \textit{cis} intermediate 303 therefore the \textit{trans} isomer is favoured. However, if R is a large bulky ether group the resulting steric hindrance \((R \leftrightarrow R' \text{ or } R \leftrightarrow E)\)

Scheme 64
Table 1
Stereocontrolled Iodoetherification of γ,δ-Unsaturated Alkoxyalkenes

Reagents and conditions: I₂, CH₃CN, 0°C, (NaHCO₃ added when R¹=H).

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Ratio cis/trans</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>1:2</td>
<td>66</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>1:2</td>
<td>15</td>
</tr>
<tr>
<td>CH₂Ph</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>2:1</td>
<td>60</td>
</tr>
<tr>
<td>Si²BuPh₂</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>3:1</td>
<td>43</td>
</tr>
<tr>
<td>Si²BuPh₂</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>8:1</td>
<td>30</td>
</tr>
<tr>
<td>BB</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>3.7:1</td>
<td>74</td>
</tr>
<tr>
<td>DCB</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>21:1</td>
<td>63</td>
</tr>
<tr>
<td>H</td>
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<td>H</td>
<td>H</td>
<td>1:4</td>
<td>88</td>
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<tr>
<td>DCB</td>
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<td>H</td>
<td>20:1</td>
<td>95</td>
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<tr>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>1:2</td>
<td>99</td>
</tr>
<tr>
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<td>Me</td>
<td>H</td>
<td>25:1</td>
<td>75</td>
</tr>
<tr>
<td>H</td>
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<td>DCB</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>12:1</td>
<td>47</td>
</tr>
<tr>
<td>CH₂Ph</td>
<td>Me</td>
<td>CO₂Me</td>
<td>H</td>
<td>6:1</td>
<td>55</td>
</tr>
<tr>
<td>DCB</td>
<td>Me</td>
<td>CO₂Me</td>
<td>H</td>
<td>50:1</td>
<td>60</td>
</tr>
<tr>
<td>BB</td>
<td>Me</td>
<td>CO₂Me</td>
<td>Me</td>
<td>10:1</td>
<td>44</td>
</tr>
<tr>
<td>tBu</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>28:1</td>
<td>91</td>
</tr>
</tbody>
</table>

destabilises the trans intermediates and the cis isomer predominates. The choice of R is important, with benzyl derivatives¹⁰⁶ and tert-butoxy ethers¹⁰⁷ affording the best results due to their electrofugal capabilities. The cleavage of the C-O bond must take place on a reasonable time scale to allow equilibration of the intermediates to take place.

The presence of an allylic hydroxyl group in γ,δ-unsaturated alcohols has a pronounced effect on the stereochemical outcome of cyclisations under kinetic conditions¹⁰⁸ (Scheme 65). Generally if there is no (Z) substituent on the double bond the 2,3-cis product is favoured, while the presence of a (Z) substituent favours the trans product. These observations may be rationalised using the model proposed by
Chamberlain et al.\textsuperscript{109} (Scheme 66) in which preferential attack of the electrophile on the OH in plane conformer \textsuperscript{304} occurs from the face of the double bond \textit{syn} to the allylic hydrogen. Thus, when \( R^1 = H \) the 2,3-\textit{cis} isomer is formed as the major product. However, when there is a (\textit{Z}) substituent on the double bond the resulting steric hindrance destabilises the OH in plane conformer making the hydrogen in-plane conformer \textsuperscript{305} energetically more accessible. Hence, the 2,3-\textit{trans} isomer becomes favoured. Examples of such stereoselectivity are shown in Scheme 65 (reactions 1, 2 and 3). Furthermore, the 1,3 \textit{syn} or \textit{anti} relationship of the allylic and C6 hydroxyl...
Scheme 66

\[
\begin{align*}
\text{Scheme 66} & \\
\text{E}^+ & \uparrow \\
\text{H} & \text{OH} \\
\text{304} & \\
\text{OR} & \\
\text{R}^1 & \\
\text{H} & \text{OR} \\
\text{H} & \text{OH} \\
\text{E}^+ & \downarrow \\
\text{H} & \text{OH} \\
\text{305} & \\
\text{OR} & \\
\text{R}^1 & \neq \text{H} \\
\end{align*}
\]

Scheme 67

\[
\begin{align*}
\text{Scheme 67} & \\
\text{Ph} & \text{R}^1 & \text{R}^2 \\
\text{syn} & \rightarrow & \text{Ph} & \text{OH} \\
\text{OH} & \text{OH} & \text{A} & \text{R}^1 \\
\text{H} & \text{R}^2 & \text{I} & \rightarrow & \text{3,5 trans} & \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \text{R}^1 & \text{R}^2 \\
\text{anti} & \rightarrow & \text{Ph} & \text{OH} \\
\text{OH} & \text{OH} & \text{B} & \text{R}^1 \\
\text{H} & \text{R}^2 & \text{I} & \rightarrow & \text{3,5 cis} & \text{disfavoured} \\
\text{3,5 trans} & \rightarrow & \text{favoured} \\
\end{align*}
\]
groups has a strong influence on the regioselectivity of the reaction. Thus, while electrophilic cyclisation of the syn diols result in formation of the expected tetrahydrofuran products, cyclisation of the anti diols often form predominantly the tetrahydropyran product (Scheme 65, reactions 4 and 6). An explanation of this regioselectivity, based on steric interactions in the transition states, is presented (Scheme 67).

The transition state B arising from the anti isomer has more severe steric hindrance than the transition state of the syn isomer A. Thus, while good stereoselectivity is observed with conversion of syn compounds to 2,3-trans tetrahydrofurans, there is a drop in the stereoselectivity, regioselectivity and reactivity with the iodoetherification of the anti dihydroxyalkene.

The electronic character of homoallylic substituents has also been reported to affect the stereochemical outcome (Table 2), with electron withdrawing groups favouring a 1,3-trans product and electron donating groups favouring the corresponding cis isomer. The electrophilic attack is proposed to take place via a chair-like conformation, with electron withdrawing substituents assuming an axial position (Figure 7). The same diastereofacial selectivity has also been reported by Bravo et al.112,113 in the cyclisation of the monofluorinated alcohols (Scheme 68).

<table>
<thead>
<tr>
<th>X</th>
<th>cis : trans ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>1 : 4</td>
</tr>
<tr>
<td>OMe</td>
<td>1 : 4.6</td>
</tr>
<tr>
<td>F</td>
<td>1 : 6.3</td>
</tr>
<tr>
<td>Me</td>
<td>3.6 : 1</td>
</tr>
</tbody>
</table>

Figure 7

![Figure 7](image_url)
An interesting method for the stereoselective synthesis of trans 2,5-disubstituted tetrahydrofurans has been reported by Bartlett and Ting. Noting that 1,3 relative asymmetric induction is attained more readily in six membered rings than in five membered rings, methodology was developed for the formation of trans 2,5-disubstituted tetrahydrofurans by Ag$^+$ catalysed ring contraction of tetrahydropyrans (Scheme 69). Thus alcohol 306, when treated with 2,4,4,6-tetabromo-2,5-cyclohexadienone affords a 3:1 mixture of the tetrahydropyran 307 and tetrahydrofuran 308. Subsequent treatment of the tetrahydropyran 307 with silver tetrafluoroborate afforded solely the trans tetrahydrofuran 309.

Cyclisation of the trans enol ether 310 (Scheme 70) affords the tetrahydropyrans 311 and 312 which undergo ring contraction to the tetrahydrofurans 313, 314, respectively. The unexpected formation of tetrahydrofuran 314 from tetrahydropyran 312 is attributed to severe steric interactions in the transition state and therefore the reaction must proceed via an intermediate cation in a non-concerted manner. In contrast, the cis enol ether 315 gives tetrahydropyran 316 with bromine in the axial position which is not suitable for ring contraction.

Better results have been obtained by using Tl(III) as the electrophile. Due to its ability to act as a nucleofuge Tl(III) allows formation of an intermediate tetrahydropyran which, by means of a bridged oxonium ion, is converted to the corresponding trans 2,5-disubstituted tetrahydrofuran in a one step process (Scheme 71).
71). Reaction can also occur in the reverse direction, with the formation of tetrahydropyran rings from suitably substituted tetrahydrofuran rings. This methodology has been investigated (Scheme 72) for use in the synthesis of the trans, syn, trans fused structures present in the brevetoxins, which are potent neuro and cardiotoxins\textsuperscript{116}.
C-glycosides are useful synthons and potent metabolic inhibitors\textsuperscript{118}. Methodology for the synthesis of the C-glycosides using electrophile-mediated cyclisations of hydroxyalkenes was developed by Russo and Nicotra\textsuperscript{119} (Scheme 73). Following the reaction of commercially available D-pentoses with divinylzinc, mercury cyclisation was used to afford the desired pyran structure (Table 3). Generally there is preferential formation of the diastereomer possessing a \textit{cis} relationship between the hydroxyl group at C-2 of the starting sugar and the newly formed stereogenic centre. An exception to this is D-mannitol, 317, which affords the \textit{trans} product 318.
Scheme 73

Reagents: (i) divinylzinc; (ii) a: Hg(OAc)$_2$; b: KCl.

Table 3
Synthesis of C-Glycosides via Mercury Cyclisation

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image 1" /></td>
<td><img src="image2" alt="Image 2" /></td>
<td>20</td>
</tr>
<tr>
<td><img src="image3" alt="Image 3" /></td>
<td><img src="image4" alt="Image 4" /></td>
<td>71</td>
</tr>
<tr>
<td><img src="image5" alt="Image 5" /></td>
<td><img src="image6" alt="Image 6" /></td>
<td>73</td>
</tr>
<tr>
<td><img src="image7" alt="Image 7" /></td>
<td><img src="image8" alt="Image 8" /></td>
<td>73</td>
</tr>
<tr>
<td><img src="image9" alt="Image 9" /></td>
<td><img src="image10" alt="Image 10" /></td>
<td><img src="image11" alt="Image 11" /></td>
</tr>
</tbody>
</table>
A preferred 1,3 *cis* relationship between the C4 hydroxyl group and the newly formed stereogenic centre has been observed in the formation of 2,3,4-trisubstituted tetrahydrofurans from 1,2-diols, using either iodine or phenylselenyl chloride\(^\text{120}\) (Scheme 74). However, the opposite facial selectivity is reported in the cyclisation of diol 319, where minimisation of unfavourable steric repulsions between the C2 and C3 substituents and the $Z$ configuration of the double bond leads to the exclusive formation of the 1,3-*trans* compound 320.

Scheme 74

Reagents: (i): I\(_2\), MeCN; (ii): PhSeCl.
The electrophilic cyclisation of ethyl (E)-5,6-dihydroxyhex-2-enoate has shown that the choice of solvent can affect the stereochemical outcome, with less polar solvents improving the selectivity (Table 4). Slower rates are observed with these solvents due to the lower iodine concentrations involved.

Table 4

The Effect of Solvent on the Stereoselective Cyclisation of 5,6-Dihydroxyhex-2-enoate

<table>
<thead>
<tr>
<th>solvent</th>
<th>trans : cis ratio</th>
<th>ϵ</th>
<th>I₂ (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>4.5 : 1</td>
<td>7.58</td>
<td>4.87</td>
</tr>
<tr>
<td>DME</td>
<td>5.2 : 1</td>
<td>7.20</td>
<td>2.05</td>
</tr>
<tr>
<td>tert-butyl methyl ether</td>
<td>7 : 1</td>
<td>-</td>
<td>1.15</td>
</tr>
<tr>
<td>diethyl ether</td>
<td>8.6 : 1</td>
<td>4.34</td>
<td>0.88</td>
</tr>
<tr>
<td>diisopropyl ether</td>
<td>12 : 1</td>
<td>3.88</td>
<td>0.27</td>
</tr>
</tbody>
</table>

As with the γ,δ-unsaturated alcohols, the β,γ-unsaturated alcohols can lead to 2,5-disubstituted tetrahydrofurans when treated with an electrophile. Lipshutz has shown that the choice of electrophile can influence the stereoselectivity of the reaction to give exclusive formation of either the cis or the trans product (Scheme 75).
In summary, the synthesis of highly functionalised tetrahydrofuran and tetrahydropyran units has been accomplished via the use of electrophile mediated cyclisations of hydroxy- or alkoxyalkenes. This work described herein is concerned with the use of an electrophile mediated cyclisation reaction as a key step for the conversion of bis-spiroketal moiety 179 of salinomycin to the tetracyclic ether 321 (Scheme 76).
Chapter 2

Discussion

2.1 Preliminary investigations

The recent work by Brimble and Williams\textsuperscript{53} in establishing methodology for the synthesis of the central \textit{bis}-spiroketal moiety of \textit{epi-17-deoxy-(O-8)}-salinomycin \textsuperscript{143} culminated in the synthesis of iodide \textsuperscript{177} and proposed methodology for the preparation of the corresponding alcohol \textsuperscript{179}. In order to complete a total synthesis of \textit{epi-17-deoxy-(O-8)}-salinomycin \textsuperscript{143} methodology is now required for elaboration of the right hand of the molecule to include the \textit{E} ring (Scheme \textsuperscript{77}). Beginning with alcohol \textsuperscript{179}, it was proposed that oxidation to the corresponding aldehyde \textsuperscript{145} would provide an effective "handle" from which construction of the \textit{E} ring could be developed.

\begin{center}
\textbf{Scheme 77}
\end{center}

In order to develop methodology for construction of the \textit{E} ring of \textit{epi-17-deoxy-(O-8)}-salinomycin \textsuperscript{143} a suitable model system was required. Thus, due to its strong
resemblance to the D ring of salinomycin and the presence of an apparently facile procedure for its preparation in the literature, 2-methyltetrahydrofur-2-aldehyde 322 was selected as a model for bis-spiroketal 145. Consequently, methodology for conversion of tetrahydrofuran 322 to bis-ether 323 (Scheme 78) was required which could be applied to the conversion of bis-spiroketal 145 to the tetracyclic ether 321 (Scheme 77).

Scheme 78

The model aldehyde 322 was prepared according to the method of Amouroux et al (Scheme 79). 2-Acetyl-γ-butyrolactone 324, was converted to 5-bromo-2-pentanone 325 using 48% hydrobromic acid. This was an adaptation of the original procedure to prepare 5-chloro-2-pentanone 123, albeit in much lower yield. 5-Bromo-2-pentanone 325 was then heated under reflux with copper cyanide 124 to produce 2-cyano-2-methyltetrahydrofuran 326 in 65% yield.

Scheme 79

Reagents and conditions: (i) 48% hydrobromic acid, Δ, 31%; (ii) Cu(C₆H₅)₂, toluene, Δ, 65%; (iii) a: LiAlH₄, Et₂O; b: 3M HCl, 68%.

The literature preparation 122 of 2-methyltetrahydrofur-2-aldehyde 322 by the partial reduction and hydrolysis of the nitrile 326 proved difficult to reproduce with the reaction often producing significant amounts of imine byproduct. Attempts to improve the purity of the product by varying the reaction conditions and using alternative
reducing agents, i.e. diisobutylaluminium hydride or triethoxyalumino hydride were unsuccessful. It was found, however, that the aldehyde 322 could be successfully purified by distillation under reduced pressure.

Treatment of the purified aldehyde 322 with lithium aluminium hydride in diethyl ether afforded the corresponding alcohol 327 in good yield (Scheme 80). Thus, at this point it was deemed advantageous to develop methodology for the oxidation of the alcohol 179 to the aldehyde 145 (Scheme 77) using the alcohol 327 as a model.

**Scheme 80**

\[
\begin{array}{cccc}
\text{CHO} & \rightarrow & \text{CH}_{2}\text{OH} \\
\text{Me} & 322 & \rightarrow & 327 \\
\end{array}
\]

*Reagents and conditions:* (i) LiAlH₄, Et₂O, 64%.

Conversion of the alcohol 327 to the aldehyde 322 was first attempted using the chromium oxidising agents pyridinium chlorochromate²⁴ and pyridinium dichromate¹²⁵,¹²⁶, however no aldehyde 322 was detected by NMR or IR in the filtered crude product. Use of the Swern oxidation²²,²³ also proved unsuitable affording a complex mixture of compounds. Finally, treatment of the alcohol 327 with the Dess-Martin periodinane¹²⁷,¹²⁸ (Scheme 81) afforded an acceptable yield (57%) of the desired aldehyde 322.

**Scheme 81**

\[
\begin{array}{cccc}
\text{CH}_{2}\text{OH} & \rightarrow & \text{CHO} \\
\text{Me} & 327 & \rightarrow & 322 \\
\end{array}
\]

*Reagents and conditions:* (i) Dess-Martin periodinane, CH₂Cl₂, 58%.

With the aldehyde 322 in hand, work was initiated on the development of methodology for E ring construction. The first proposed pathway to the target bis-ether 323 (Scheme 82) centred on the formation of the pyran ring 328 via iodoetherification and ring expansion followed by elaboration of the pyran skeleton to afford the required stereocentre at C3.
Beginning with the aldehyde 322, chelation controlled addition of the Grignard derived from 4-bromo-1-butene 329 (Diagram 1) according to the method of Amouroux et al. affords predominantly the erythro[129] hydroxyalkene 330a which subsequently undergoes iodoetherification to produce the iodide 331. Conversion of the iodide 331 to the aldehyde 332 followed by the addition of methylmagnesium bromide then affords alcohol 333. After conversion of the alcohol 333 to the mesylate 334 it was anticipated that treatment with silver carbonate in acetone/H2O, as previously used by Kishi et al.
Chelation controlled Grignard addition of 4-bromo-1-butene 329 to aldehyde 322 affords predominantly the erythro product 330a in the synthesis of lasalocid A (see Scheme 41), would effect ring expansion to the desired pyran skeleton 328. Elaboration of the C3 position would then be effected by oxidation of alcohol 328 to ketone 335, followed by conversion to the epoxide 336 which when treated with dimethyllithium cuprate undergoes ring opening to afford the target bis-ether 323. Direct addition of organometallic reagents to ketone 335 (Scheme 83) produces a mixture of tertiary alcohols in which the undesired alcohol 337 predominates due to attack from the β-face of the molecule in order to avoid the steric hindrance of the adjacent axial methyl group.

The proposed synthesis of the bis-ether 323 began as anticipated (Scheme 84) with the Grignard addition of 3-butenylmagnesium bromide to the aldehyde 322 affording predominantly the erythro alcohol 330a with an overall yield (64%) and erythro/threo ratio (4:1; determined by 1H NMR) comparable to that observed by Amouroux et al (69%; 82% erythro, 18% threo - as determined by vapour phase chromatography). Separation of the two isomers by flash chromatography proved difficult at this stage due to their similar polarity. However, treatment with acetic
Reagents and conditions: (i) Mg, THF then 2-methyl-2-tetrahydrofuraldehyde 322, 68%; (ii) Ac₂O, Et₃N, DMAP, CH₂Cl₂, 86%; (iii) K₂CO₃, 95% MeOH, 80%; (iv) I₂, Na₂CO₃, MeCN, 93%.

Anhydride and triethylamine in the presence of a catalytic quantity of DMAP afforded the corresponding acetates 338a, 338b in 88% yield which were readily separated by column chromatography. Hydrolysis of the erythro acetate 338a was then effected using potassium carbonate in 95% methanol to give the erythro alcohol 330a in 80% yield for which the spectral data were consistent with that reported in the literature.¹²²

The most significant feature in the NMR spectra of the alcohols 330a and 330b (Tables 5 and 6) centred on the 2 chiral centres at C₂' and C₁. The ¹H NMR chemical shift of the 1-H proton of the erythro alcohol 330a (δ 3.53) was further downfield than that of the threo alcohol 330b (δ 3.40). A similar pattern was observed in the ¹³C NMR spectra with the chemical shift of the 2'-Me carbon of erythro alcohol 330a (δ 22.9) appearing downfield from that of the 2'-Me carbon of the threo alcohol 330b (δ 19.9).

Iodoetherification of the erythro hydroxyalkene 330a produced a 5:1 ratio of the erythro trans and erythro cis iodoethers 331a, 331b (Scheme 84) in an overall yield of 93% which were separated by flash column chromatography. Similarly, iodoetherification of the threo hydroxyalkene 330b, formed by the hydrolysis of threo acetate 338b, produced a 5:1 ratio of the threo trans and threo cis iodoethers 339a,
**Table 5**

$^1$H NMR Chemical Shifts for (1R*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-4-penten-1-ol 330a and (1S*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-4-penten-1-ol 330b

<table>
<thead>
<tr>
<th>Compound</th>
<th>CH$_3$</th>
<th>4 × CH$_2$</th>
<th>OH</th>
<th>CHOH</th>
<th>CH$_2$O</th>
<th>5-H$_A$</th>
<th>5-H$_B$</th>
<th>4-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>330a erythro</td>
<td>1.12</td>
<td>1.31 - 2.44</td>
<td>2.73</td>
<td>3.53</td>
<td>3.85</td>
<td>4.97</td>
<td>5.05</td>
<td>5.85</td>
</tr>
<tr>
<td>330b threo</td>
<td>1.14</td>
<td>1.39 - 2.41</td>
<td>2.73</td>
<td>3.40</td>
<td>3.83</td>
<td>4.97</td>
<td>5.05</td>
<td>5.84</td>
</tr>
</tbody>
</table>

**Table 6**

$^{13}$C NMR Chemical Shifts for (1R*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-4-penten-1-ol 330a and (1S*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-4-penten-1-ol 330b

<table>
<thead>
<tr>
<th>Compound</th>
<th>CH$_3$</th>
<th>CH$_2$</th>
<th>CH$_2$</th>
<th>CH$_2$</th>
<th>C-5'</th>
<th>C-1</th>
<th>C-2'</th>
<th>C-5</th>
<th>C-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>330a erythro</td>
<td>22.9</td>
<td>26.2</td>
<td>30.7</td>
<td>30.9</td>
<td>67.7</td>
<td>75.6</td>
<td>85.6</td>
<td>114.5</td>
<td>138.4</td>
</tr>
<tr>
<td>330b threo</td>
<td>19.9</td>
<td>26.3</td>
<td>30.7</td>
<td>31.0</td>
<td>67.3</td>
<td>75.8</td>
<td>85.2</td>
<td>114.6</td>
<td>138.4</td>
</tr>
</tbody>
</table>
339b in an overall yield of 85% (Scheme 85).

Scheme 85

Reagents and conditions: (i) K₂CO₃, 95% MeOH, 85%; (ii) NaH, 2,6-Cl₂C₆H₃CH₂Br, THF, 0°C, 74%; (iii) R=H: I₂, Na₂CO₃, MeCN, 85%; (iii) R=DCB: I₂, MeCN, 65%.

Determination of the *threo* *trans*: *threo* *cis* ratio was made by ¹H NMR, as the two iodides were inseparable by column chromatography. Although the *threo* *trans* 339a and *threo* *cis* 339b isomers were inseparable by column chromatography, accurate assignment of their individual spectra was relatively facile as iodoetherification of the corresponding dichlorobenzyl derivative 340 afforded predominantly the *threo* *cis* iodide 339b. A detailed discussion of the reversal in iodoetherification product ratio through the use of dichlorobenzyl ethers will be presented in a later section.

In each case, the assignment of the major and minor iodoetherification products as the *trans* and *cis* iodides, respectively, was made on the basis of their ¹H NMR spectra, although previous work by Bartlett and Rychnovsky¹⁰⁶ did indeed suggest that the *trans* isomer should predominate. The most significant feature in the ¹H NMR spectra was the difference in the chemical shift of the proton at the C5 and C2 positions (Table 7). In the ¹H NMR spectra of the *trans* isomers both the 5-H and 2-H protons have chemical shifts further downfield than the corresponding chemical shifts in the *cis* isomer. Work by Cassady *et al.*¹³⁰ has indicated that a *trans* relationship between the C2 and C5 positions of 2,5-disubstituted tetrahydrofuran rings will result in a chemical shift (δ) of between 4.00 - 4.11 for the 5-H proton, whilst a *cis* relationship will exhibit a 5-H chemical shift between 3.89 - 3.93.
Table 7

\(^1\text{H NMR Chemical Shift Values for 2-(Iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofurans 331a, 331b, 339a and 339b}\)

<table>
<thead>
<tr>
<th>Assignment</th>
<th>331a (\text{erythro trans})</th>
<th>331b (\text{erythro cis})</th>
<th>339a (\text{threo trans})</th>
<th>339b (\text{threo cis})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CH}_3)</td>
<td>1.15</td>
<td>1.17</td>
<td>1.12</td>
<td>1.15</td>
</tr>
<tr>
<td>(4 \times \text{CH}_2)</td>
<td>1.56 - 2.28</td>
<td>1.57 - 2.07</td>
<td>1.57 - 2.28</td>
<td>1.61 - 2.06</td>
</tr>
<tr>
<td>(\text{CH}_3\text{I})</td>
<td>3.15</td>
<td>3.24 - 3.28</td>
<td>3.18</td>
<td>3.18</td>
</tr>
<tr>
<td>(\text{CH}_3\text{B})</td>
<td>3.31</td>
<td>3.24 - 3.28</td>
<td>3.28</td>
<td>3.25</td>
</tr>
<tr>
<td>(\text{CH}_2\text{O})</td>
<td>3.85</td>
<td>3.86</td>
<td>3.77 - 3.91</td>
<td>3.83 - 3.92</td>
</tr>
<tr>
<td>5-H</td>
<td>4.07</td>
<td>3.93</td>
<td>4.03</td>
<td>3.83 - 3.92</td>
</tr>
<tr>
<td>2-H</td>
<td>4.05 - 4.16</td>
<td>3.89 - 3.99</td>
<td>4.00 - 4.10</td>
<td>4.02 - 4.13</td>
</tr>
</tbody>
</table>

Table 8

\(^{13}\text{C NMR Chemical Shift Values for 2-(Iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofurans 331a, 331b, 339a and 339b}\)

<table>
<thead>
<tr>
<th>Assignments</th>
<th>331a (\text{erythro trans})</th>
<th>331b (\text{erythro cis})</th>
<th>339a (\text{threo trans})</th>
<th>339b (\text{threo cis})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CH}_2\text{I})</td>
<td>10.7</td>
<td>10.7</td>
<td>10.7</td>
<td>10.2</td>
</tr>
<tr>
<td>2'-\text{Me}</td>
<td>22.7</td>
<td>23.3</td>
<td>22.9</td>
<td>23.2</td>
</tr>
<tr>
<td>(\text{CH}_2)</td>
<td>26.1</td>
<td>26.3</td>
<td>26.3</td>
<td>26.2</td>
</tr>
<tr>
<td>(\text{CH}_2)</td>
<td>28.0</td>
<td>27.0</td>
<td>27.4</td>
<td>26.3</td>
</tr>
<tr>
<td>(\text{CH}_2)</td>
<td>32.9</td>
<td>31.4</td>
<td>33.0</td>
<td>31.4</td>
</tr>
<tr>
<td>(\text{CH}_2)</td>
<td>33.4</td>
<td>33.2</td>
<td>34.6</td>
<td>34.8</td>
</tr>
<tr>
<td>(\text{CH}_2\text{O})</td>
<td>68.1</td>
<td>68.2</td>
<td>68.4</td>
<td>68.6</td>
</tr>
<tr>
<td>C-2</td>
<td>79.1</td>
<td>78.2</td>
<td>79.0</td>
<td>79.0</td>
</tr>
<tr>
<td>C-2'</td>
<td>84.3</td>
<td>83.9</td>
<td>84.1</td>
<td>83.1</td>
</tr>
<tr>
<td>C-5</td>
<td>85.4</td>
<td>85.9</td>
<td>85.6</td>
<td>86.2</td>
</tr>
</tbody>
</table>
Another notable difference between the cis and trans iodides is the diastereotopicity exhibited by the \( \text{CH}_2\text{I} \) protons. With both the erythro and threo iodides, the difference in the chemical shifts of the \( \text{CH}_2\text{I} \) protons of the trans isomers is greater than that of the cis isomers, although this difference is particularly noticeable with erythro iodides. While the individual diastereotopic \( \text{CH}_2\text{I} \) protons of the erythro trans iodide 331a exhibit a significant difference in chemical shift (\( \Delta \delta = 0.16 \)) the resonances for these same protons in the erythro cis iodide 331b have merged into a complex multiplet (\( \Delta \delta < 0.02 \)). This difference is probably due to the fact that the \( \text{CH}_2\text{I} \) group of the erythro cis isomer 331b experiences greater steric interaction with the tetrahydrofuran ring at the C5 position thereby creating a similar environment for the two \( \text{CH}_2\text{I} \) protons.

One further difference in the \( ^1\text{H} \) NMR spectra of the two trans isomers 331a, 339a compared to the cis isomers 331b, 339b is that the trans isomers 331a, 339a have a multiplet equivalent to 1 proton (1/2 \( \times \text{CH}_2 \)) at \(-2.25 \) ppm, while the chemical shifts of the \( \text{CH}_2 \) protons of the corresponding cis isomers 331b, 339b are all below \(-2.07 \) ppm.

Similarities in the \( ^{13}\text{C} \) NMR spectra of the cis and the trans iodides proved less obvious (Table 8). However, general patterns were observed in the chemical shifts of the C5, C2' and 2'-Me carbon atoms with the C5 and 2'-Me carbon atoms of the cis iodides exhibiting larger chemical shifts than those of the corresponding trans iodides, while the C2' carbon atoms of the trans iodides possess larger chemical shifts than those of the corresponding cis iodides.

It is interesting to note that the mercuric acetate induced cyclisation of the erythro alcohol 330a followed by reduction with sodium borohydride as carried out by Amouroux et al\(^{122} \) (Scheme 86) afforded the methyl ethers 341a and 341b in a 7:1 ratio which is comparable to that observed in the iodoetherification (5:1).

**Scheme 86**

\[
\begin{align*}
330a & \quad \xrightarrow{i} \quad 341a, 341b  \\
& \quad \xrightarrow{\text{ii}} \quad 341 7:1 \text{trans:cis}
\end{align*}
\]

*Reagents and conditions:* (i) \( \text{Hg(OAc)}_2, \text{THF/H}_2\text{O} \); (ii) \( \text{NaBH}_4, \text{OH}^- \)
Attempts to corroborate the cis and trans assignments of the iodides 331a, 331b using NOESY NMR techniques were unsuccessful as no useful interactions were observed. Subsequent reduction of the iodides using tributyltin hydride and AIBN provided the corresponding methyl compounds 341a, 341b (Scheme 87) in the hope that they might provide confirmation of stereochemistry using NOE experiments. Unfortunately, this approach also met with little success. However, analysis of the chemical shifts of the 5-H protons of these compounds indicated that they too conform to the general pattern described by Cassady et al.\textsuperscript{130} (Table 9) wherein H-2 and H-5 of the trans isomer resonate downfield of the same protons in the cis isomer. The results were also in agreement with the $^1$H NMR data reported by Gagnaire and Monzeglio\textsuperscript{131} for the cis and trans 2,5-dimethyltetrahydrofuran 342a and 342b (Table 10).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Compound & CH$_3$ & CH$_3$ & 4 x CH$_2$ & CH$_2$O & 5'-H & 2'-H \\
\hline
341a trans & 1.15 & 1.23 & 1.42 - 2.05 & 3.86 & 3.99 & 4.10 \\
341b cis & 1.15 & 1.23 & 1.31 - 2.01 & 3.79 - 3.87 & 3.79 - 3.87 & 4.00 \\
\hline
\end{tabular}
\caption{$^1$H NMR Chemical Shift Values for (2S*, 5R*, 2'S*)-2-Methyl-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 341a and (2R*, 5R*, 2'S*)-2-Methyl-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 341b.}
\end{table}
Table 10

<table>
<thead>
<tr>
<th>Compound</th>
<th>2-H, 5-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>342a (trans)</td>
<td>4.02</td>
</tr>
<tr>
<td>342b (cis)</td>
<td>3.86</td>
</tr>
</tbody>
</table>

The next step to be investigated was the conversion of the iodide 331a to the aldehyde 332a (see Scheme 82). The first literature method applied was treatment of the iodide with trimethylamine N-oxide in DMSO, a method shown by Godfrey and Ganem\textsuperscript{132} to be effective in the conversion of bromides to aldehydes. However, although thin layer chromatography suggested the formation of a small amount of aldehyde 332a the predominant product appeared to be a much more polar compound, probably the hydrate. A second procedure reported by Griffith et al.\textsuperscript{133} involved the use of the ruthenium catalyst Ph$_4$P[Ru$_2$(OAc)$_2$] and N-methylmorpholine-N-oxide. Unfortunately, however, the iodide 331a proved unreactive under these conditions.

Consequently, it was decided to take a less direct approach and convert the iodide 331a to the aldehyde 332a via the alcohol 343a (Scheme 88). Treatment of the iodide 331a with potassium superoxide and 18-crown-6 afforded the desired alcohol 343a but the yield was so low (23%) that the subsequent oxidation was abandoned.

\textit{Reagents and conditions:} (i) KO$_2$, 18-crown-6, THF/DMSO 25:1, 23%.
At this point, it was proposed that the ability of iodine to act as a good leaving group might allow ring expansion to occur by directly treating the iodide \( \text{331a} \) with silver carbonate in acetone\(^8\). However, when this reaction was carried out only the ketoalcohol \( \text{344} \) was produced, suggesting the mechanism detailed in Scheme 89. Thus, treatment of the iodide \( \text{331a} \) with silver carbonate in wet acetone afforded the carbocation \( \text{345} \) which, instead of the anticipated movement of the adjacent C-O bond (arrow b), underwent hydride migration (arrow a) to give the more stable carbocation \( \text{346} \) which following addition of H\(_2\)O afforded ketoalcohol \( \text{344} \).

From this result, it became clear that in order for successful ring expansion to occur, a tetrasubstituted C2 carbon is required, to eliminate the possibility of hydride shift occurring upon formation of the intermediate carbocation.

Consequently, it was proposed (Scheme 90) that the target bis-ether \( \text{323} \) be synthesised by ring expansion of the C2 tetrasubstituted iodide \( \text{347a} \) which would in turn be prepared by iodoetherification of the erythro hydroxyalkene \( \text{348a} \) produced by
the addition of the Grignard reagent from trisubstituted bromide 146 to the model aldehyde 322.

Scheme 90

In order to pursue the proposed pathway for formation of the C2 tetrasubstituted iodoether 347a, it was first necessary to develop methodology for the stereoselective synthesis of the (E)-trisubstituted bromoalkene 146.

2.2 Synthesis of (E)-1-Bromo-3-ethyl-3-pentene [146]

The most obvious method to prepare alkene 146 involved the use of the Wittig reaction on a hydroxyl protected derivative of 1-hydroxy-3-pentanone 349 (Scheme 91). Consequently, 1-hydroxy-3-pentanone 349 was synthesised (Scheme 92) using the methodology reported by Albizati et al.134,135 via protection of ethyl propionylacetate 350 as the dioxolane derivative 351 followed by reduction to the corresponding alcohol 352. Treatment of alcohol 352 with 10% oxalic acid and silica gel then afforded the desired 1-hydroxy-3-pentanone 349.

Scheme 91

Reagents and conditions: (i) 'BuPh2SiCl, imidazole, CH2Cl2.
Reagents and conditions: (i) HOCH₂CH₂OH, TSA, benzene, 94%; (ii) LiAlH₄, Et₂O, 0°C, 98%; (iii) 100-200M silica gel, 10% oxalic acid, CH₂Cl₂, 84%.

Formation of the desired (E)-alkene requires that an α-stabilised ylide be used under salt-free conditions. Thus, the first Wittig reaction was attempted using methyl (triphenylphosphoranylidene)acetate 353 and sodium hydride with both the hydroxypentanone 349 and the silyl protected analogue 354 (Scheme 91), however, no reaction occurred even when heated under reflux in benzene. Preparation of the silyl derivative 354 was effected in the usual manner from 1-hydroxy-3-pentanone 349. The Wittig reactions were then repeated this time using triethylphosphonoacetate 355 as the Wittig reagent, however none of the desired alkene was produced.

While the literature contains a wide variety of Wittig reagents, which might have been applied at his point, a new approach was investigated using organochromium chemistry to produce trisubstituted alkenes. In 1987, a paper by Takai et al. reported the use of gem-dichromium reagents, formed in situ by the reduction of gem-diiodoalkenes with chromium(II) chloride, to form (E)-alkenes upon reaction with aldehydes. The reaction mechanism is detailed in Scheme 93, whereby formation of the geminal dichromium reagent 356 is followed by addition of the carbonyl compound to afford a β-oxyxmetal substituted organometallic compound 357 which then eliminates to give the olefin 358. Although most of this work concentrated on the preparation of 1,2-disubstituted (E)-alkenes using aldehydes (Table 11), reaction of gem-dichromioethane with several ketones to form the corresponding trisubstituted alkenes (shaded area, Table 11) suggested that this reaction could readily be applied to the synthesis of the target trisubstituted alkene moiety. While the fact that the only nonsymmetrical
ketone, 1-tetralone, afforded predominantly the (Z)-isomer was of some concern it was felt that the organochromium methodology could not be discounted on the results of one reaction. It is worth noting that reactions of ketones with gem-dichromium reagents other than dichromioethane were low yielding.

Consequently, the organochromium methodology was applied to the synthesis of alkene 359 (Scheme 94) whereby gem-dichromioethane, prepared in situ from chromium(II) chloride and 1,1-diiodoethane, was reacted with 1-(tert-butylidiphenylsilyloxy)-3-pentanone 354 to afford an unsatisfactory 2:3 mixture of the
Reagents and conditions: (i) CrCl₂, THF, DMF then MeCH₂ and 354, 23%.

(E) and (Z)-alkenes 359 with an overall yield of 23%. From these results it would appear that while the application of gem dichromium reagents to the synthesis of (E)-1,2-disubstituted alkenes produces good results, extension of this work to the formation of (E)-trisubstituted alkenes from unsymmetric ketones may result in predominance of the (Z)-alkene.

In 1989, Mikami et al. first described the use of an asymmetric glyoxylate-ene reaction for the formation of α-hydroxyesters in high enantio- and diastereoselective yield (Table 12). Included in this work was the synthesis of methyl (E)-4-ethyl-2-hydroxy-4-hexenoate 360 (Scheme 95) which contains the desired (E)-alkene moiety. With the presence of the hydroxy and ester functionalities suggesting several potential methods for conversion of the α-hydroxyester 360 to the target bromide 146 work began developing a new approach for synthesis of the bromide 146 based on this reaction product.

Reagents and conditions: (i) 361, 4A M.S., CH₂Cl₂ then 364 and 365, -70 → -30°C, 8h, 89%.

The literature preparation of methyl (E)-4-ethyl-2-hydroxy-4-hexenoate 360 began with the in situ formation of the required chiral titanium catalyst (R)-361 by the reaction of (iPrO)₂TiCl₂ 362 with (R)-(−)-1,1'-bi-2-naphthol (R)-363 in the presence of 4A molecular sieves (Scheme 96). The reaction mixture was then cooled to -70°C and 2-ethyl-1-butene 364 and methyl glyoxylate 365 were added (Scheme 95). The reaction was allowed to warm to -30°C and stirred for 8 hours before quenching with saturated sodium bicarbonate. After filtration through celite, the reaction mixture underwent standard workup conditions and purification by column chromatography to afford
Table 12
Enantio- and Diastereoselective Syntheses using the Asymmetric Glyoxylate-Ene Reaction\textsuperscript{138,139}

<table>
<thead>
<tr>
<th>Alkene</th>
<th>((\text{PrO})_2\text{TiX}_2) (X)</th>
<th>Product</th>
<th>Yield %</th>
<th>% enantiomeric excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{PhCH} = \text{CH}_2)</td>
<td>Cl</td>
<td>(\text{PhCH} = \text{CH} - \text{OH})</td>
<td>97</td>
<td>95 (R)</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>(\text{PhCH} = \text{CH} - \text{OH})</td>
<td>98</td>
<td>95 (R)</td>
</tr>
<tr>
<td>(\text{C}_2\text{H}_4)</td>
<td>Cl</td>
<td>(\text{C}_2\text{H}_4 - \text{OH})</td>
<td>89</td>
<td>94 (R)\textsuperscript{b}</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>(\text{C}_2\text{H}_4 - \text{OH})</td>
<td>91</td>
<td>98 (R)\textsuperscript{b}</td>
</tr>
<tr>
<td>(\text{C}<em>6\text{H}</em>{11})</td>
<td>Cl</td>
<td>(\text{C}<em>6\text{H}</em>{11} - \text{OH})</td>
<td>82</td>
<td>97 (R)</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>(\text{C}<em>6\text{H}</em>{11} - \text{OH})</td>
<td>89</td>
<td>98 (R)</td>
</tr>
<tr>
<td>(\text{C}<em>5\text{H}</em>{9})</td>
<td>Cl</td>
<td>(\text{C}<em>5\text{H}</em>{9} - \text{OH})</td>
<td>87</td>
<td>48 (R)</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>(\text{C}<em>5\text{H}</em>{9} - \text{OH})</td>
<td>92</td>
<td>89 (R)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} (S)-Binaphthol was used instead of the (R) counterpart. \textsuperscript{b} E/Z ratio = 10 : 1.

Scheme 96

\(\text{(R)-363} + \text{Ti(PrO)}_2\text{Cl}_2 \rightarrow \text{(R)-361}\)

Reagents and conditions: (i) \((\text{R})-(\text{+})-363, 362, 4\text{A MS, hexane, 6h, RT, 20\%}.\)
methyl (E)-4-ethyl-2-hydroxy-4-hexenoate 360 in 68% yield with an enantiomeric excess of 75% and in a 10:1 ratio with the corresponding (Z)-isomer. Parallel work using Ti(iPrO)2Br2 derived catalyst 366 (Figure 8) afforded the (E)-hexenoate 360 in 73% yield with an enantiomeric excess of 98% and E:Z ratio of 10:1.

When initial attempts to duplicate the literature procedure were low yielding (10 - 15%) due to difficulties with the preparation and purification of the methyl glyoxylate 365, butyl glyoxylate 367 was used instead. Methyl glyoxylate 365 was prepared from dimethyl tartrate 368 (Scheme 97) using one of three available literature preparations140-142. Mikami et al138,139 did not report which procedure they used for its synthesis. All three literature methods were attempted and all proved problematic in providing suitable material for the glyoxylate ene reaction. Schuda et al140 stated that their product was a mixture of hydrated and nonhydrated forms of methyl glyoxylate which, if purified, afforded only low yields of pure methyl glyoxylate 365, whilst Schmidt et al141 noted that their product contained 5% water. The third procedure described by Thompson et al142 did not include a purification method as the methyl glyoxylate was used in its crude form.

Following the formation of methyl glyoxylate 365 by the aforementioned procedures, distillation from phosphorus pentoxide afforded the "pure" methyl glyoxylate 365 in low yield (10 - 15%). The viscous nature of the product suggested the
possibility of reversible polymerisation, an idea which has been suggested by Schmidt et al.\textsuperscript{141}. Attempts to use the crude methyl glyoxylates in the glyoxylate-ene reaction also proved ineffective.

Butyl glyoxylate 367 was prepared\textsuperscript{143} by the oxidative cleavage of dibutyl tartrate\textsuperscript{144} 369 with sodium periodate in water (Scheme 98). Following standard workup procedures the crude glyoxylate was distilled under vacuum from phosphorus pentoxide to afford butyl glyoxylate 367, the purity of which was confirmed by the disappearance of the broad 3456 cm\textsuperscript{-1} OH peak present in the I.R. spectra of the crude butyl glyoxylate. The oxidative cleavage of dibutyl tartrate 369 by periodic acid in diethyl ether was also investigated as a means of preparing butyl glyoxylate 367, however, as no significant improvement in the yield or purity of the butyl glyoxylate produced was observed the periodate method was retained.

\textbf{Scheme 98}

\[
\begin{align*}
\text{BuO}_2\text{C} & \quad \text{H} \\
\text{H} & \quad \text{OH} \\
\text{H} & \quad \text{CO}_2\text{Bu} \\
\end{align*}
\]

\textit{Reagents and conditions:} (i) NaIO\textsubscript{4}, H\textsubscript{2}O, 50%.

With butyl glyoxylate 367 in hand, the asymmetric glyoxylate-ene reaction was carried out (Scheme 99) affording butyl (E)-4-ethyl-2-hydroxy-4-hexenoate\textsuperscript{(R)}\textsuperscript{370} in 54% yield. The reaction conditions were altered so that following the addition of the 2-ethyl-1-butene 364 and the butyl glyoxylate 367 the reaction was allowed to warm to room temperature and stir for 24 hours. If the butyl glyoxylate-ene reaction was carried out under the conditions detailed for the methyl glyoxylate-ene reaction (8 hours at -30°C) the resulting yield of butyl (E)-4-ethyl-2-hydroxy-4-hexenoate (R)-370 was low (<20%) suggesting perhaps that the increased size of butyl glyoxylate results in lower reactivity due to the greater steric hindrance between the butyl glyoxylate 367 and the

\textbf{Scheme 99}

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{364} & \quad + \\
\text{H} & \quad \text{CO}_2\text{Bu} \\
\text{367} & \quad \rightarrow \\
\end{align*}
\]

\textit{Reagents and conditions:} (i) (R)-363, 362, 4A MS, CH\textsubscript{2}Cl\textsubscript{2}, 1h then 364 and 367, -70°C to RT, 24h, 57%.
titanium catalyst 361.

At this point it was decided to study the effect a racemic titanium catalyst would have on the outcome of the reaction. By replacing the $R$-$(+)$-1,1'-bi-2-naphthol (R)-363 with its racemic counterpart 363 in the synthesis of the titanium catalyst (Scheme 96), it was found that if the resulting racemic complex 361 was used to catalyse the butyl glyoxylate-ene reaction the E/Z ratio and overall yield remained the same while the enantioselectivity at C2 disappeared (Scheme 100). As it was anticipated that the C1-C2 bond would be cleaved in order to prepare the trisubstituted bromide 146, chirality at C2 was deemed unnecessary and the less expensive racemic catalyst was retained for all subsequent syntheses.

Having established an acceptable procedure for the formation of butyl (E)-4-ethyl-2-hydroxy-4-hexenoate 370 methodology was then developed for its conversion to the target bromide 146.

The first proposed route to the bromide (Scheme 101) envisaged that hydrolysis of the ester 370 to the corresponding $\alpha$-hydroxyacid 371 followed by periodate cleavage would afford the aldehyde 372 which after reduction to the alcohol 373 could be converted to the bromide 146 by one of the many alcohol to bromide conversions present in the literature.\(^{145}\)
Pursuing the aforementioned route it was found that although the hydrolysis of the ester 370 occurred in high yield (93%) the subsequent sodium periodate cleavage was low yielding (10-18%). The cleavage was then carried out using tetrabutylammonium periodate, purported to be a selective oxidant of α-hydroxycarboxylic acids. However, the reaction showed little improvement with yields no greater than 20%.

At this point it was decided that reduction of the α-hydroxyester 370 to the diol 374 prior to periodate cleavage (Scheme 102) might prove to be a more effective means of producing the alcohol 373. Thus, reaction of ester 370 with lithium aluminium hydride afforded diol 374 in 94% yield, however, cleavage with the periodate reagent still proved to be low yielding. With the failure of the periodate reagent to provide aldehyde 372 in good yield a complementary reagent, namely lead tetraacetate, was used instead to produce aldehyde 372 which was subsequently reduced with lithium aluminium hydride to afford the alcohol 373 in 63% yield over the two steps.

**Scheme 102**

![Scheme 102](image)

Reagents and conditions: (i) LiAlH₄, Et₂O, 94%; (ii) a: NaIO₄, MeOH; b: LiAlH₄, Et₂O, 23%; (iii) a: Pb(OAc)₄, Na₂CO₃, CH₂Cl₂, 16h; b: LiAlH₄, Et₂O, 63%.

Having successfully synthesised the alcohol 373 all that remained was conversion to the corresponding bromide 146. The first method investigated for the formation of the bromide 146 involved treatment of the alcohol 373 with carbon tetrabromide and triphenylphosphine in the presence of 2,6-lutidine (Scheme 103), the reaction proceeding via the formation of an intermediate phosphonium salt 375 (Scheme 104). However, although this reaction proved successful in that significant

**Scheme 103**

![Scheme 103](image)

Reagents and conditions: (i) CBr₄, Ph₃P, 2,6-lutidine, 75%.
quantities of the bromide 146 were produced, it proved difficult to remove the bromoform by-product 376 by column chromatography or distillation. Consequently, an alternative method for the synthesis of the bromide 146 was pursued.

Scheme 104

\[
\text{Ph}_3\text{P} + \text{CBr}_4 + \text{ROH} \rightarrow \text{Ph}_3\text{POR}, \text{Br} + \text{CHBr}_3
\]

Following several unsuccessful attempts to perform a one pot synthesis of the bromide using chlorotrimethylsilane and LiBr\textsuperscript{148}, a clean and efficient conversion of the alcohol 373 to the bromide 146 was achieved using a two step process whereby formation and subsequent displacement of the corresponding mesylate with lithium bromide afforded the desired bromide 146 in 71% yield (Scheme 105).

Scheme 105

\[
\text{Me} \quad \text{Et} \quad \text{OH} \quad \text{i} \quad \text{Me} \quad \text{Et} \quad \text{Br}
\]

Reagents and conditions: (i) a: MsCl, Et\textsubscript{3}N, CH\textsubscript{2}O\textsubscript{2}; b: LiBr, acetone, Δ, 71%.

2.3 Synthesis of (2S*, 3R*, 6R*, 2'S*)-3-Ethyl-3-hydroxy-2-methyl-6-(2'-methyltetrahydrofur-2'-yI)tetracyclopentane [323]

With the bromide in hand attention then focussed on the reaction pathway described in Scheme 90. It was anticipated that the trisubstituted hydroxyalkene 348a would be synthesised via the addition of the Grignard reagent to the aldehyde 322 in a procedure analogous to that used in the synthesis of the monosubstituted hydroxyalkene 330a (Scheme 84). This reaction, however, proved to be low yielding due to the formation of the dimeric by-product 377 (Scheme 106). At this point it became obvious
that in order to find the best method for synthesising the trisubstituted hydroxyalkene 348a intensive investigation would be necessary requiring significant amounts of the trisubstituted bromide 146. In order to have access to larger quantities of bromide 146 it was decided that preliminary work would be carried out using an E/Z mixture of the trisubstituted bromide 146 prepared from an (E/Z)-mixture of alcohol 373, which in turn was produced in 55% yield by the tin(IV) tetrachloride catalysed ene reaction of 2-ethyl-1-butene 364 with formaldehyde (Scheme 107). Thus, the (E/Z)-mixture trisubstituted bromoalkene 146 was produced in two easy steps compared to the four more time consuming steps required to prepare the corresponding (E)-bromoalkene 146.

In earlier work by Henrick et al.\textsuperscript{149} using the trisubstituted bromides 378, 379 (Figure 9) it was observed that "the major synthetic problem encountered ..... is the preparation of the homoallylic Grignard reagent itself." However, methodology was eventually developed whereby slow addition of the homoallylic bromides 378, 379 to magnesium afforded the corresponding Grignard reagents in good (70%) yield.
Attempts to apply the same "slow addition" technique to (E/Z)-bromide 146 proved unsuccessful, however, with yields remaining at around 25%.

The chloride 380 and iodide 381 analogues of bromide 146 were then prepared (Scheme 108), anticipating that a more successful Grignard reaction might be effected. However, the chloride 380 proved unreactive and the iodide 381 produced only low yields of alcohol 348 (< 15%) when used in place of the bromide 146.

**Scheme 108**

Reagents and conditions: (i) a: MsCl, Et3N, CH2Cl2; b: LiCl, DMF, Δ, 62%; (ii) a: MsCl, Et3N, CH2Cl2; b: NaI, acetone, Δ, 71%.

When further attempts to improve the yield in the Grignard reaction through the use of chemically activated magnesium150 or entrainment techniques151 proved unsuccessful, it was decided to take a new approach using tert-butyllithium to produce the organolithium analogue of the Grignard reagent. Initial attempts to use the organolithium reagent were carried out using benzaldehyde (Scheme 109) in place of...
the model aldehyde 322, and proved no more successful than the Grignard reagent until inverse addition techniques were adopted. Thus, \((E/Z)\)-bromide 146 was added to a -80°C solution of tert-butyllithium in tetrahydrofuran, to afford a 66% yield of alcohol 382. This compares well to the 24% yield of alcohol 382 produced by the corresponding Grignard reaction (Scheme 109).

Once the inverse addition technique had been perfected using benzaldehyde, formation of the organolithium reagent and subsequent addition of the model aldehyde 322 resulted in formation of the hydroxyalkene 348 (Scheme 110) as a 3:1 mixture of the erythro and threo isomers (348a, 348b, respectively) in 54% yield. As with the monosubstituted hydroxyalkenes 330 (Scheme 84), separation of the erythro and threo isomers 348a, 348b was effected by formation of the acetates 383a, 383b which allowed facile separation by column chromatography. Subsequent hydrolysis of the erythro acetate 383a was then effected to provide the erythro hydroxyalkene 348a in pure form.

Assignment of the alcohols 348a and 348b as erythro and threo, respectively, was made by comparison of their \(^1\)H and \(^13\)C NMR spectra with those of the monosubstituted hydroxyalkenes 330a, 330b (Table 13). Although a number of

<table>
<thead>
<tr>
<th>Compound</th>
<th>(^1)H NMR chemical shift</th>
<th>(^13)C NMR chemical shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>(348a) (erythro)</td>
<td>2'-Me 1.12 1-H 3.52</td>
<td>2'-Me 23.8 C-1 76.2</td>
</tr>
<tr>
<td>(348b) (threo)</td>
<td>2'-Me 1.14 1-H 3.38</td>
<td>2'-Me 20.2 C-1 76.5</td>
</tr>
<tr>
<td>(330a) (erythro)</td>
<td>2'-Me 1.12 1-H 3.53</td>
<td>2'-Me 22.9 C-1 75.6</td>
</tr>
<tr>
<td>(330b) (threo)</td>
<td>2'-Me 1.14 1-H 3.40</td>
<td>2'-Me 19.9 C-1 75.8</td>
</tr>
</tbody>
</table>

Table 13
Comparison of the \(^1\)H and \(^13\)C NMR Spectra of the Erythro and Threo Isomers of Hydroxyalkenes 348 and 330.
correlations were observed between the two erythro alcohols 330a, 348a and the two threo alcohols 330b, 348b the most significant correlations were observed with the 1-H and 2'-Me groups. The $^1$H NMR spectra of these alcohols shows that the erythro alcohols 330a, 348a exhibit 1-H chemical shifts significantly upfield from those of the 1-H proton in the corresponding threo alcohols 330b, 348b. Similarly in the $^{13}$C NMR spectra the 2'-Me carbon atoms of the erythro alcohols 330a, 348a exhibit chemical
shifts significantly downfield of the corresponding 2'-Me chemical shifts in the *threo* alcohols 330b, 348b.

Iodoetherification of *erythro* hydroxyalkene 348a afforded two iodides 347a, 347b each with a molecular formula of C$_{13}$H$_{23}$O$_2$I (established by FAB accurate mass spectrometry) in a ratio of 3:1, with an overall yield of 79%. Following separation by column chromatography, treatment of each iodide with silver carbonate in wet acetone afforded in each case a single, but different, ring expanded product with a molecular formula of C$_{13}$H$_{24}$O$_3$ (established by FAB accurate mass spectrometry). Assignment of relative configurations of the iodides 347a, 347b and the ring expanded products 384, 323 was made on the basis of their $^1$H and $^{13}$C NMR spectra.

Iodoetherification of the *erythro* hydroxyalkene 348a takes place by *anti* addition of the hydroxyl functionality to intermediate iodonium ions and can form two possible iodides 347a and 347b (Scheme 111). The $^1$H NMR spectra of iodide 347a possessed a 5-H chemical shift of $\delta$ 4.02 compared with $\delta$ 3.94 for the 5-H chemical shift of iodide 347b (Table 14). Tentative assignment of the major iodide 347a as the *trans* isomer and the minor iodide 347b as the *cis* isomer was made on the basis of the chemical shifts of the 5-H protons, using work by Cassady *et al*\textsuperscript{130} which established

**Scheme 111**
that the chemical shift for the 5-H proton of the trans isomer should be in the range δ 4.00 - 4.11 while that of the cis isomer should be at δ 3.89 - 3.93. The 13C NMR spectra of iodides 347a and 347b (Table 15) reflected the difference in configuration at the C2 and Cl' atoms with the chemical shifts of the C-1' of iodide 347a (δ 40.2) exhibiting a chemical shift significantly downfield of the corresponding C-1' atom of iodide 347b (δ 35.6). The chemical shifts of the carbon atoms at 2'-Me, C-2 and C-2" of the two iodides 347a and 347b also differed, albeit to a lesser extent. NOESY spectra of the two iodides were recorded so that data supporting this assignment might be produced, however, no useful NOE interactions were observed.

Table 14

1H NMR Chemical Shifts for (2R*, 5R*, 1'S*, 2"S*)-2-Ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofuran 347a and (2S*, 5R*, 1'R*, 2"S*)-2-Ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofuran 347b.

<table>
<thead>
<tr>
<th>Compound</th>
<th>CH3 (Et)</th>
<th>2&quot;-CH3</th>
<th>1'-CH3</th>
<th>4 x CH2</th>
<th>CH2O</th>
<th>5-H</th>
<th>1'-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>347a trans</td>
<td>0.92</td>
<td>1.16</td>
<td>1.84</td>
<td>1.59 - 2.07</td>
<td>3.84</td>
<td>4.02</td>
<td>4.52</td>
</tr>
<tr>
<td>347b cis</td>
<td>0.90</td>
<td>1.14</td>
<td>1.89</td>
<td>1.58 - 2.10</td>
<td>3.84</td>
<td>3.94</td>
<td>4.41</td>
</tr>
</tbody>
</table>

Table 15

13C NMR Chemical Shifts for (2R*, 5R*, 1'S*, 2"S*)-2-Ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofuran 347a and (2S*, 5R*, 1'R*, 2"S*)-2-Ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofuran 347b

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-2&quot;</th>
<th>2'-Me</th>
<th>C-2'</th>
<th>C-1'</th>
<th>C-2, C-2&quot;</th>
<th>C-5'</th>
<th>C-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>347a trans</td>
<td>7.8</td>
<td>22.5</td>
<td>23.9</td>
<td>40.2</td>
<td>83.5, 86.6</td>
<td>68.2</td>
<td>85.0</td>
</tr>
<tr>
<td>347b cis</td>
<td>7.5</td>
<td>22.6</td>
<td>22.9</td>
<td>35.6</td>
<td>83.9, 85.6</td>
<td>68.1</td>
<td>86.6</td>
</tr>
</tbody>
</table>
Separate treatment of each iodide 347a, 347b with silver carbonate in wet acetone afforded in each case a single, but different, ring expanded product (347a → 384, 68%; 347b → 323, 77%). The ring expanded products 384, 323 were readily purified by column chromatography.

The stereospecificity of the silver catalysed ring expansions indicates that the reaction is occurring via intermediate oxiranium ions (Scheme 112) to produce the pyran structure 384 or 323. Assignment of relative configurations of the ring expanded products 384, 323 was made on the basis of their 1H and 13C NMR spectra. Analysis of the 1H NMR spectra of pyrans 384 and 323 (Table 16) showed that the chemical shift of the 2-Me of pyran 323 (δ 1.24) was significantly downfield from that observed for the 2-Me of pyran 384 (δ 1.11). The 2-H and 6-H protons of pyran 323 (δ 3.75 - 3.89 and 3.46, respectively) also possessed chemical shifts downfield of the corresponding 2-H (δ 3.35) and 6-H (δ 3.25) protons of pyran 384. Similarly the 13C spectra of pyrans 384 and 323 (Table 17) exhibited differences in the chemical shifts of the C2 and C6
carbons with those of pyran 323 (δ 74.0 and 74.8) being significantly upfield of the C2 and C6 carbons of pyran 384 (δ 80.8 and 82.9). NOE analysis of the pyrans 384, 323 proved fruitful with an interaction observed between the 2-Me and 6-H of the pyran 323 confirming the relative configuration of the C2 and C6 atoms (Figure 10).

Figure 10

Having established that pyran 323 contains the same stereochemistry as that present in the E-ring of salinomycin 1, a comparison of the 1H and 13C NMR spectra of the pyrans 384 and 323 with a number of literature compounds containing this substructure or similar structures was carried out. Thus, a comparison of the chemical shifts exhibited by the 2-H, 6-H and 2-Me protons in the 1H NMR spectra and the chemical shifts of the C2 and C6 atoms in the 13C NMR spectra of the pyrans 384 and 323 with the literature compounds 1, 4, 47 and 61 (Table 18) demonstrated a far greater correlation between pyran 323 and the literature compounds than between pyran 384 and the literature compounds, thereby confirming that pyran 323 exhibits the correct stereochemistry for the E ring of salinomycin 1.

Thus, it has been shown that the Ag+ catalysed ring expansion of iodoether 347a forms exclusively pyran 384, while Ag+ catalysed ring expansion of iodoether 347b forms exclusively the target bis-ether 323. As the target bis-ether 323 is derived from the minor product of the iodoetherification reaction 347b, an investigation of the stereocontrol involved in this iodoetherification was carried out in the hope that the iodide 347b might be made to predominate.

Initial studies were carried out using the monosubstituted hydroxyalkene 330a, which in its free hydroxyl form produces the iodides 331a (trans) and 331b (cis) in a ratio of 4:1 trans:cis. However, previous work by Bartlett and Rychnovsky106 has shown (Table 19) that conversion of the alcohol to an ether derivative prior to iodoetherification can result in selective formation of the cis isomer. This stereocontrol is rationalised by the mechanism depicted (Scheme 113).
### Table 16

**1H NMR Chemical Shifts for (2R*, 3S*, 6R*, 2'S*)-3-Ethyl-3-hydroxyl-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran 384 and (2S*, 3R*, 6R*, 2'S*)-3-Ethyl-3-hydroxyl-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran 323**

<table>
<thead>
<tr>
<th>Compound</th>
<th>CH₃ (Et)</th>
<th>2-Me</th>
<th>2'-Me</th>
<th>4 × CH₂</th>
<th>6-H</th>
<th>2-H</th>
<th>CH₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>384</td>
<td>0.90</td>
<td>1.11</td>
<td>1.14</td>
<td>1.16 - 2.10</td>
<td>3.25</td>
<td>3.35</td>
<td>3.82</td>
</tr>
<tr>
<td>323</td>
<td>0.92</td>
<td>1.24</td>
<td>1.16</td>
<td>1.16 - 1.92</td>
<td>3.46</td>
<td>3.84</td>
<td>3.75 - 3.89</td>
</tr>
</tbody>
</table>

### Table 17

**13C NMR Chemical Shifts for (2R*, 3S*, 6R*, 2'S*)-3-Ethyl-3-hydroxyl-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran 384 and (2S*, 3R*, 6R*, 2'S*)-3-Ethyl-3-hydroxyl-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran 323**

<table>
<thead>
<tr>
<th>Compound</th>
<th>CH₃(Et)</th>
<th>2-Me</th>
<th>2'-Me</th>
<th>CH₂</th>
<th>CH₂</th>
<th>CH₂</th>
<th>CH₂</th>
<th>CH₂O</th>
<th>C-3</th>
<th>C-2, C-6</th>
<th>C-2'</th>
</tr>
</thead>
<tbody>
<tr>
<td>384</td>
<td>6.7</td>
<td>14.0</td>
<td>22.3</td>
<td>22.5</td>
<td>24.6</td>
<td>26.2</td>
<td>33.9</td>
<td>68.3</td>
<td>71.3</td>
<td>80.9, 82.9</td>
<td>83.7</td>
</tr>
<tr>
<td>323</td>
<td>7.0</td>
<td>13.0</td>
<td>21.0</td>
<td>22.1</td>
<td>22.8</td>
<td>25.8</td>
<td>29.1</td>
<td>35.5</td>
<td>68.2</td>
<td>71.1</td>
<td>74.0, 74.8</td>
</tr>
</tbody>
</table>

![Chemical structures](image)
Table 18

Comparison of $^1$H and $^{13}$C NMR Chemical Shifts of (2R*, 3S*, 6R*, 2'S*)-3-Ethyl-3-hydroxyl-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran 384 and (2S*, 3R*, 6R*, 2'S*)-3-Ethyl-3-hydroxyl-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran 323 with known literature compounds.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$^1$H NMR</th>
<th>$^{13}$C NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-H</td>
<td>6-H</td>
</tr>
<tr>
<td>384</td>
<td>3.35</td>
<td>3.25</td>
</tr>
<tr>
<td>323</td>
<td>3.84</td>
<td>3.46</td>
</tr>
<tr>
<td>salinomycin 1</td>
<td>3.83</td>
<td>3.93</td>
</tr>
<tr>
<td>lasalocid A 4</td>
<td>3.76</td>
<td>3.57</td>
</tr>
<tr>
<td>47</td>
<td>3.77</td>
<td>3.65</td>
</tr>
<tr>
<td>61</td>
<td>3.79</td>
<td>3.42</td>
</tr>
</tbody>
</table>

Salinomycin 1

Lasalocid A 4

47

61
Table 19
Stereocontrolled Iodoetherification of $\gamma,\delta$-Unsaturated Alkoxyalkenes

Reagents and conditions: I$_2$, CH$_3$CN, 0°C, (NaHCO$_3$ added when R$^1$=H);

<table>
<thead>
<tr>
<th>R$^1$</th>
<th>R$^2$</th>
<th>R$^3$</th>
<th>R$^4$</th>
<th>Ratio cis/trans</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>1 : 2</td>
<td>66</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>1 : 2</td>
<td>15</td>
</tr>
<tr>
<td>CH$_2$Ph</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>2 : 1</td>
<td>60</td>
</tr>
<tr>
<td>Si$^t$BuPh$_2$</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>3 : 1</td>
<td>43</td>
</tr>
<tr>
<td>Si$^t$BuPh$_2$</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>8 : 1</td>
<td>30</td>
</tr>
<tr>
<td>BB</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>3.7 : 1</td>
<td>74</td>
</tr>
<tr>
<td>DCB</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>21 : 1</td>
<td>63</td>
</tr>
<tr>
<td>H</td>
<td>Me$_2$CH</td>
<td>H</td>
<td>H</td>
<td>1 : 4</td>
<td>88</td>
</tr>
<tr>
<td>DCB</td>
<td>Me$_2$CH</td>
<td>H</td>
<td>H</td>
<td>20 : 1</td>
<td>95</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>1 : 2</td>
<td>99</td>
</tr>
<tr>
<td>DCB</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>25 : 1</td>
<td>75</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>2 : 5</td>
<td>81</td>
</tr>
<tr>
<td>DCB</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>12 : 1</td>
<td>47</td>
</tr>
<tr>
<td>CH$_2$Ph</td>
<td>Me</td>
<td>CO$_2$Me</td>
<td>H</td>
<td>6 : 1</td>
<td>55</td>
</tr>
<tr>
<td>DCB</td>
<td>Me</td>
<td>CO$_2$Me</td>
<td>H</td>
<td>50 : 1</td>
<td>60</td>
</tr>
<tr>
<td>BB</td>
<td>Me</td>
<td>CO$_2$Me</td>
<td>Me</td>
<td>10 : 1</td>
<td>44</td>
</tr>
<tr>
<td>$t$Bu</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>28 : 1</td>
<td>91</td>
</tr>
</tbody>
</table>
Where \( R = H \), the \textit{trans} intermediates 302a and 302b are more stable than the \textit{cis} intermediate 303 therefore the \textit{trans} isomer is favoured. However, if \( R \) is a large bulky ether group the resulting steric hindrance (\( R \leftrightarrow R' \) or \( R \leftrightarrow E \)) destabilises the \textit{trans} intermediates and the \textit{cis} isomer predominates.

Thus, a variety of ether derivatives, 338a, 385-389, of alcohol 330a were synthesised and the ratio of the iodides 331a and 331b, produced by iodoetherification of the ethers 338a, 385-389, was determined by \( ^1H \) NMR. The benzyl derivatives were prepared by treatment of alcohol 330a with sodium hydride followed by addition of the appropriate benzyl bromide (Scheme 114). The trimethylsilyl derivative 388 was prepared by the treatment of alcohol 330a with 1-(trimethylsilyl)imidazole and the \textit{tert}-butyldimethylsilyl derivative 389 was prepared using \textit{tert}-butyldimethylsilyl trifluoromethanesulphonate (Scheme 115).

The results of this study (Table 20) indicate that, as with Bartlett's work, the benzyl ethers (esp. the dichlorobenzyl ether) provide the best stereoselective formation of the \textit{cis} isomer with a 10:1 ratio of the \textit{cis} and \textit{trans} iodides in the case of the 2,6-dichlorobenzyl ether 387. The inability of the silyl derivatives to effect any \textit{cis} stereocontrol suggests that the silyl groups are too labile and are displaced before the steric interactions necessary for stereocontrol can occur. It is notable that the ethers 385-389 show a much lower preference for the \textit{cis} iodide 331b while the alcohol 330a shows a greater preference for the \textit{trans} iodide 331a when compared with the stereoselectivities observed by Bartlett and Rychnovsky\textsuperscript{106} (Table 19). This can be explained in terms of the increased steric hindrance produced in the intermediate oxonium ions by the presence of the large
tetrahydrofuran moiety at the C5 position on the newly formed tetrahydrofuran ring (Scheme 116).

Scheme 114

Scheme 115
Table 20

Stereocontrolled Iodoetherification of γ,δ-Unsaturated Alkoxyalkenes derived from Hydroxyalkene 330a

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Yield %</th>
<th>331a:331b</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>330a</td>
<td>H</td>
<td>93</td>
<td>5:1</td>
<td>I₂, Na₂CO₃, MeCN, 0°C</td>
</tr>
<tr>
<td>338a</td>
<td>Ac</td>
<td>no reaction</td>
<td>-</td>
<td>I₂, MeCN, 0°C</td>
</tr>
<tr>
<td>385</td>
<td>Bz</td>
<td>67</td>
<td>5:4</td>
<td>I₂, MeCN, 0°C</td>
</tr>
<tr>
<td>386</td>
<td>BB</td>
<td>46</td>
<td>2:3</td>
<td>I₂, MeCN, 0°C</td>
</tr>
<tr>
<td>387</td>
<td>DCB</td>
<td>63</td>
<td>1:10</td>
<td>I₂, MeCN, 0°C</td>
</tr>
<tr>
<td>388</td>
<td>SiMe₃</td>
<td>68</td>
<td>5:1</td>
<td>I₂, MeCN, 0°C</td>
</tr>
<tr>
<td>389</td>
<td>Si²BuMe₂</td>
<td>57</td>
<td>5:1</td>
<td>I₂, MeCN, 0°C</td>
</tr>
</tbody>
</table>

Scheme 116

![Scheme 116](image-url)
Having established that the dichlorobenzyl ether 387 provides the most effective method for cis stereocontrol in the iodoetherification of the monosubstituted hydroxyalkene, this work was extended to the trisubstituted hydroxyalkene system.

Following preparation of the dichlorobenzyl ether 390 in 67% yield by the reaction of alcohol 348a with sodium hydride and 2,6-dichlorobenzyl bromide, the iodoetherification was carried out (Scheme 117), but the resulting reaction mixture contained neither of the predicted iodides 347a, 347b. Anticipating that the reaction had failed due to excessive steric interaction between the ethyl and methyl substituents on the alkene and the bulky dichlorobenzyl ether, the reaction was repeated using the smaller 4-bromobenzyl ether 391 but again the iodides 347a, 347b were not detected in this product mixture.

Scheme 117

Reagents and conditions: (i) I₂, MeCN, 0°C.

Concluding that the benzyl group itself was too bulky to allow iodoetherification of the trisubstituted hydroxyalkene it was anticipated that the trimethylsilyl ether 392 might provide enough steric hindrance to allow selective formation of the cis iodide, but not so much that cyclisation would be prevented. Following its formation by the reaction of alcohol 348a with 1-(trimethylsilyl)imidazole, trimethylsilyl ether 392 was treated
with iodine in acetonitrile affording a 1:1 mixture of the cis and trans iodides 347a, 347b in 75% total yield (Scheme 118). Repetition of this reaction using bulkier silyl derivatives 393 - 395 of alcohol 330a was then carried out (Table 21), however, there was no noticeable improvement in the ratio of 347b:347a, while the yield appeared to decrease significantly.

**Scheme 116**

Reagents and conditions: (i) I$_2$, MeCN, -5°C, 75%.

**Table 21**

Stereocontrolled Iodoetherification of Silyl Derivatives of Trisubstituted Hydroxyalkene

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Prepared from 348a and:</th>
<th>yield</th>
<th>Iodoetherification conditions</th>
<th>yield</th>
<th>347a/347b</th>
</tr>
</thead>
<tbody>
<tr>
<td>392</td>
<td>SiMe$_3$</td>
<td>(TMS)imid.</td>
<td>96%</td>
<td>I$_2$, CH$_3$CN, -5°C</td>
<td>75%</td>
<td>1:1</td>
</tr>
<tr>
<td>393</td>
<td>SiEt$_3$</td>
<td>(TES)Tf</td>
<td>94%</td>
<td>I$_2$, CH$_3$CN, 0°C</td>
<td>46%</td>
<td>1:1</td>
</tr>
<tr>
<td>394</td>
<td>Si’Pr$_3$</td>
<td>(TIPS)Tf</td>
<td>93%</td>
<td>I$_2$, CH$_3$CN, 0°C</td>
<td>47%</td>
<td>1:1</td>
</tr>
<tr>
<td>395</td>
<td>Si’BuMe$_2$</td>
<td>(TBDMS)Tf</td>
<td>90%</td>
<td>I$_2$, CH$_3$CN, 0°C</td>
<td>27%</td>
<td>1:1</td>
</tr>
</tbody>
</table>
These results can be rationalised using the mechanism depicted in Scheme 119. When R = H, it is assumed that the 1,2-syn interaction between R and the adjacent Et or CHMe groups of the oxonium ions 396a, 396b and 397 is negligible. Consequently, formation of iodide 347a is more favourable since the substituted THF ring is 1,3-syn to an ethyl group rather than the bulkier CHMe group as in intermediate 397.

In converting alcohol 348a into the ether derivatives 390-395 it was anticipated that by increasing the size of the R group, the 1,2-syn interactions between R and the bulkier CHMe group in intermediate 396b would become more significant and the reaction occurring via oxonium ion 397 would become more competitive. However, while this did indeed prove to be the case with the silyl ethers 392 - 395 with the formation of the iodides 347a and 347b in a 1:1 ratio, it would appear that with the benzyl derivatives 390 and 391, their bulk is enough to create sufficient steric hindrance between themselves and the substituents on the double bond to prevent iodoetherification from occurring.

An investigation of the iodoetherification reaction conditions was then undertaken (Table 22), using kinetic (Na₂CO₃, low temperature) and thermodynamic (No Na₂CO₃) conditions in the hope that one set of conditions might improve the 347b:347a (cis:trans) ratio. However, it was demonstrated that the trans isomer was favoured under both kinetic or thermodynamic conditions.

Thus at this point in time, the formation and subsequent iodoetherification of the silyl ether 392 affords the most effective method of producing iodide 347b, required to
Stereocontrolled iodoetherification of (4E, 1R*, 2'S*)-4-Ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol 348a and (4E, 1R*, 2'S*)-4-Ethyl-1-(trimethylsilyloxy)-1-(2'-methyltetrahydrofur-2'-yl)-4-hexene 392: Kinetic vs Thermodynamic conditions.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>347a:347b</th>
<th>Yield</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>348a</td>
<td>H</td>
<td>2 : 1</td>
<td>70%</td>
<td>I$_2$, Na$_2$CO$_3$, MeCN, 0°C, 50 min.</td>
</tr>
<tr>
<td>348a</td>
<td>H</td>
<td>3.2 : 1</td>
<td>78%</td>
<td>I$_2$, Na$_2$CO$_3$, MeCN, -43°C, 15 min.</td>
</tr>
<tr>
<td>348a</td>
<td>H</td>
<td>1.8 : 1</td>
<td>19%</td>
<td>I$_2$, MeCN, 60°C, 20 min.</td>
</tr>
<tr>
<td>348a</td>
<td>H</td>
<td>2.5 : 1</td>
<td>88%</td>
<td>I$_2$, MeCN, -32°C, 10 min.</td>
</tr>
<tr>
<td>392</td>
<td>SiMe$_3$</td>
<td>3 : 4</td>
<td>50%</td>
<td>I$_2$, MeCN, 0°C, 15 min.</td>
</tr>
<tr>
<td>392</td>
<td>SiMe$_3$</td>
<td>1 : 1</td>
<td>75%</td>
<td>I$_2$, MeCN, -5°C, 5 min.</td>
</tr>
</tbody>
</table>

form the target bis-ether 323. Iodoetherification of derivative 392 affords iodide 347b in 38% yield. Separation of iodide 347b from the other major product of the reaction, iodide 347a (37%), is readily achieved by column chromatography.

Finally, a different approach for the conversion of iodide 347a to pyran 384 was investigated using mercuric acetate (Scheme 120). Following the conversion of iodide 347a to alkene 398 by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene, alkene 398 was treated with mercuric acetate followed by sodium borohydride in 0.5NaOH
solution, anticipating that formation of the carbocation 399 would be followed by ring expansion to afford the desired pyran system. However, only alcohol 400 was produced, in 39% yield, indicating that ring expansion had not occurred.

2.4 Summary

Methodology for construction of the E ring of salinomycin, as evidenced by the conversion of aldehyde 322 to bis-ether 323, has now been developed. This should allow, in combination with previous work on the bis-spiroketal moiety of epi-17-deoxy-(O-8)-salinomycin, a total synthesis of epi-17-deoxy-(O-8)-salinomycin 143. The presence of E ring like structures in a number of other polyether antibiotics (e.g. lasalocid A 4, antibiotic X-206 180) means that the aforementioned methodology could also lend itself to the development of new syntheses of these compounds.

In a broader perspective, this work has provided methodology for the addition of terminal tetrahydrofuran and tetrahydropyran rings to suitably functionalised molecules. This could prove to be of great use in the synthesis of other polyether derived compounds such as the acetogenins and tetrahydrofuran podands (see Future Work section).

The use of the asymmetric glyoxylate-ene reaction to synthesise the bromide 146 has laid the foundations for a new pathway for the stereoselective synthesis of (E)-homoallylic bromides. It is anticipated that this procedure could be adapted to produce a number of analogous bromides by varying the olefin used in the glyoxylate-ene reaction.

In developing the iodoetherification reaction for use in forming the tetrahydrofuran precursor to bis-ether 323 new information regarding the stereocontrol of this reaction has been obtained. It has been demonstrated that the dichlorobenzyl group, while effective for the cis-selective iodoetherification of monosubstituted γ,δ-alkoxyalkenes, is too sterically hindered to afford the iodoether product when applied to trisubstituted γ,δ-alkoxyalkenes. Conversely the silyl ethers which proved ineffective in providing any cis selectivity in forming the tetrahydrofuran 331, proved to be the most effective of all the ethers investigated in increasing the cis:trans ratio of the iodoetherification products produced by iodoetherification of the trisubstituted hydroxyalkene 348a.
2.5 Future Work

Acetogenins and Podands

The application of the methodology developed for E ring construction could easily be applied to the synthesis of acetogenins and tetrahydrofuran podands.

The acetogenin family of compounds has attracted much interest recently due to their wide range of biological activities and unique structures. These tetrahydrofuranic compounds (Figure 11) can be classified into four groups according to the number and arrangement of the tetrahydrofuran rings they contain: 1) the mono-tetrahydrofurans (e.g. solamin 401); 2) the adjacent bis-tetrahydrofurans (e.g. asimicicin 402, rolliniastatin 403); 3) the non-adjacent bis-tetrahydrofurans (e.g. squamostatin-D 404); and 4) the tritetrahydrofurans (e.g. goniocin 405).

Synthesis of the central tetrahydrofuran moieties of the adjacent bis-tetrahydrofurans, using the methodology developed for E ring construction is envisioned as follows. Beginning with a suitably structured aldehyde (Scheme 121), Grignard addition of 4-bromo-1-butene affords the hydroxyalkene 407.

Scheme 121

![Scheme 121 Diagram](image-url)
Iodoetherification of hydroxyalkene 407 could then be carried out stereoselectively to afford either predominantly the trans iodide 408, which is found in most of the naturally occurring acetogenins, or the cis iodide 409, which is found in only a few of the acetogenins such as rolliniastatin 403. Conversion of the iodides 408, 409 to the corresponding alcohols 410, 411 would then provide a useful synthetic "handle" which could be used to complete the acetogenin synthesis.
In contrast to the many organic syntheses of natural polyether ionophores (e.g. lasalocid A and salinomycin) which have been reported over the past 15 years, it is only very recently that the construction of "artificial" polyether antibiotics, or podands, has been investigated. One such podand which has recently been presented in the literature is the oligo-THF molecule. It is anticipated that the methodology developed for E-ring construction could afford a new and versatile method of synthesising such molecules. Thus, following the formation of iodides such as iodide (Scheme 121), conversion to the corresponding aldehyde (Scheme 122) would then allow the E ring methodology to be applied a second time to form a third tetrahydrofuran ring. This iodide → aldehyde/Grignard reaction/iodoetherification sequence could then be repeated until the desired number of tetrahydrofuran rings has been produced. This pathway is also quite versatile in that by altering the structure.
of the 4-bromo-1-butene used and/or using dichlorobenzyl groups to form cis tetrahydrofuran rings, a wide variety of interesting oligo-THF podands could be produced. One such pathway is described in Scheme 123. This versatility could also be applied to the synthesis of interesting acetogenin analogues, including those of the tri-tetrahydrofurans.

Scheme 123
Application of the Asymmetric Dihydroxylation Reaction to E ring Construction

An alternative route to the E ring of salinomycin has now been proposed (Scheme 124) using the asymmetric dihydroxylation procedure recently developed by Sharpless\textsuperscript{159}. Beginning with hydroxyalkene 348a treatment with AD-mix β to afford the triol 416 would be followed by conversion to the epoxide 417 which when treated with acetic acid would afford the bis-tetrahydrofuran 418. Formation of the mesylate and subsequent ring expansion by treatment with Ag\textsuperscript{+}, as previously carried out by Kishi et al\textsuperscript{8}, would then afford the desired E ring 323.
Chapter 3

Experimental

General Details

Melting points were determined using Kofler hot stage apparatus and are uncorrected.

Infra-red spectra were recorded using a BIO-RAD FTS-7 spectrometer as thin films or nujol mulls between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm\(^{-1}\)) with the following abbreviations: s = strong, m = medium, w = weak and br = broad.

\(^1\)H nuclear magnetic resonance spectra were obtained at 270 MHz using a JEOL GX270 spectrometer. \(^1\)H nuclear magnetic resonance data are expressed in parts per million downfield shift from tetramethylsilane as an internal reference and are reported as position (\(\delta_H\)), relative integral, multiplicity (s = singlet, d = doublet, dd = double doublet, ddt = double double triplet, t = triplet, q = quartet and m = multiplet), coupling constant (J Hz) and assignment.

\(^13\)C nuclear magnetic resonance spectra were obtained at 67.8 MHz using a JEOL GX270 spectrometer. \(^13\)C nuclear magnetic resonance data are expressed in parts per million downfield shift from tetramethylsilane as an internal reference and are reported as position (\(\delta_C\)) and assignment.

Mass spectra were recorded using a Varian VG70-250S double focusing magnetic sector mass spectrometer with an ionisation potential of 70 eV. Major fragmentations are given as percentages relative to the base peak intensity.

Flash chromatography was performed according to the procedure of Still et al\(^65\) using Merck Kieselgel 60 (230-400 mesh) with the indicated solvents.

Thin layer chromatography was performed using precoated silica gel plates (Merck Kieselgel 60F\(_{254}\)) and compounds were visualised by ultra-violet fluorescence or by staining with vanillin in methanolic sulphuric acid or phosphomolybdic acid.

Solvents were dried and purified according to the methods of Perrin, Perrin and Amarego\(^{160}\).
5-Bromo-2-pentanone 325

To a solution of hydrobromic acid (48%, 200 ml, 1.77 mol) and distilled water (130 ml) in a distilling flask was added 2-acetylbutyrolactone 324 (131.2 g, 1.02 mol). Carbon dioxide was evolved and the solution began to change colour. Once a red colour was observed the reaction was heated and steam distillation commenced. Additional hot water (200 ml) was added as required until approximately 250 ml of distillate had been collected. The green layer in the distillate was separated and the aqueous layer was extracted with diethyl ether (3 × 60 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure. The resulting dark green residue was distilled under reduced pressure to afford 5-bromo-2-pentanone 325 as a colourless liquid (51.6 g, 31%), b.p. 79.0-79.5°C/18 mm Hg (lit.161, 73-75°C/12 mm Hg).

2-Cyano-2-methyltetrahydrofuran 326124

Copper cyanide (18.0 g, 201 mmol) was added to a solution of 5-bromo-2-pentanone 325 (30.2 g, 184 mmol) in toluene (60 ml) and the resulting suspension was heated under reflux for 8 h. The solid was removed by filtration and washed with diethyl ether (80 ml). The combined organic solvent was dried over magnesium sulphate and the diethyl ether and toluene were removed by distillation at atmospheric pressure. The residue was distilled under reduced pressure to give 2-cyano-2-methyl-tetrahydrofuran 326 as a colourless liquid (13.3 g, 65%), b.p. 67°C/18 mm Hg (lit.124, 63°C/16 mm Hg).
Potassium bromate (18.7 g, 112 mmol) was added over a 90 min. period to a vigorously stirred mixture of 2-iodobenzoic acid (21.0, 84.7 mmol) and 0.73 M sulphuric acid (171 ml). During addition the temperature was maintained below 55°C. The mixture was then warmed to 65°C and stirred for 4 h. Bromine gas was given off and removed by passing a flow of argon gas passing into a saturated aqueous solution of sodium bisulphite. The reaction mixture was then cooled to 0°C and the resulting white precipitate was removed by filtration and washed with distilled water (100 ml) and ethanol (4 x 10 ml). The solid was dried under vacuum for 10 min. to afford 1-hydroxy-1,2-benziodoxol-3(1H)-one (22.0, 93%) as a white crystalline solid.

The 1-hydroxy-1,2-benziodoxol-3(1H)-one (22.0 g, 78.6 mmol) was added to a solution of p-toluenesulphonic acid monohydrate (109 mg, 0.573 mmol) in acetic anhydride (88 ml). The reaction was heated to 80-90°C and stirred for 2 h. under a drying tube. The reaction mixture was then cooled to 0°C and the resulting precipitate was filtered off and washed with dry diethyl ether (4 x 15 ml) to afford the Dess-Martin periodinane (30.1 g, 90%) as a white crystalline solid which was quickly transferred to an argon flushed amber-glass bottle and stored in a freezer: m.p. 133-134°C (lit.128 m.p. 134°C).

2-Methyl-2-tetrahydrofuraldehyde 322122

Procedure A
To a suspension of lithium aluminium hydride (225 mg, 5.93 mmol) in dry diethyl ether at -10°C under nitrogen was added 2-cyano-2-methyltetrahydrofuran (1.50 g, 13.5 mmol). The reaction was stirred at this temperature for 1.75 h. with additional lithium aluminium hydride (200 mg) being added after 1 h. The reaction was quenched by slow addition of 3M hydrochloric acid (30 ml) followed by vigorous stirring for 80 min. The organic layer was then decanted off and the aqueous layer was extracted with diethyl ether (3 x 40 ml) and dichloromethane (2 x 30 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed at reduced pressure to afford 2-methyl-2-tetrahydrofuraldehyde as a pungent pale yellow oil (1.04 g, 67%), which was purified by distillation at atmospheric pressure, b.p. 142-143°C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 1732 (s, C=O); \( \delta_{\text{H}} \) (270 MHz; CDCl\(_3\)) 1.31 (3H, s, CH\(_3\)), 1.64-1.75 (1H, m, 3-H\(_1\)), 1.86-2.02 (2H, m, 4-H, 4-H\(_1\)), 2.14-2.24 (1H, m, 3-H), 3.84-3.92 (1H, m, 5-H), 4.01-4.07 (1H, m, 5-H) and 9.57 (1H, s, CHO); \( \delta_{\text{C}} \) (67.8 MHz; CDCl\(_3\)) 20.7 (CH\(_3\)), 25.8 (CH\(_2\)), 32.9 (CH\(_2\)), 69.0 (CH\(_2\)O), 86.2 (quat., C-2) and 203.0 (C=O).

IR and \(^1\text{H} \text{NMR}\) data were in agreement with that reported in the literature\(^{122}\).

**Procedure B**

![Chemical structure](image)

To a solution of 2-methyl-2-tetrahydrofurfuryl alcohol (20 mg, 0.17 mmol) in dry dichloromethane (1.5 ml) was added Dess Martin reagent (\textit{vide supra}) (88 mg, 0.21 mmol). After stirring for 1.5 h the solvent was removed under reduced pressure and the residue was purified by flash chromatography, using pentane/diethyl ether as eluant (1:1), to afford 2-methyl-2-tetrahydrofuraldehyde (11.2 mg, 58%) for which the IR and \(^1\text{H} \text{NMR}\) data were in agreement with the literature\(^{122}\) and that reported for the product using the procedure described above.
To a solution of 2-methyl-2-tetrahydrofuraldehyde 322 (81 mg, 0.71 mmol) in dry diethyl ether (7 ml) was added lithium aluminium hydride (15 mg, 0.40 mmol). The reaction mixture was stirred for 30 min. then carefully quenched with 3M hydrochloric acid (2 ml). The aqueous layer was extracted with diethyl ether (3 x 10 ml) and the combined organic layers were dried over magnesium sulphate. The solvent was removed at reduced pressure to afford a yellow residue which was purified by flash chromatography, using pentane/diethyl ether (1:1) as eluant, to afford 2-methyl-2-tetrahydrofuranyl alcohol 327 as a colourless oil (53 mg, 64%) (Found: (Cl, NH₃) M + H, 117.0917. C₆H₁₃O₂ requires M + H, 117.0916.); υmax/cm⁻¹ (film) 3387 (s, br, OH), 2961, 2923, 2865 (s, C-H), 1454 (s, C-H), 1113 (s, C-O-C) and 1049 (s, C-OH); δH (270 MHz; CDCl₃) 1.20 (3H, s, CH₃), 1.64 (1H, s, OH), 1.88-2.00 (4H, m, CH₂), 3.43-3.48 (2H, m, CH₂OH) and 3.82-3.90 (2H, m, CH₂O); δC (67.8 MHz; CDCl₃) 23.3 (CH₃), 26.5 (CH₂), 33.5 (CH₂), 68.0 (CH₂, C-5), 68.6 (CH₂, C-1') and 82.9 (quat., C-2); m/z 117 (M + H, 100%), 99 (M - OH, 39) and 85 (C₅H₉O, 77).

Ethyl 2-(2'-ethyl-1',3'-dioxolan-2'-yl)acetate 351

A mixture of ethyl propionylacetate 350 (5.15 g, 35.7 mmol), ethylene glycol (2.00 ml, 35.8 mmol) and a catalytic quantity of p-toluenesulphonic acid (~20 mg) in benzene (180 ml) was heated under reflux for 6 h. using Dean-Stark apparatus. The reaction mixture was then dried over magnesium sulphate and the solvent was removed under reduced pressure. The residue was purified by column chromatography, using hexane/ethyl acetate (9:1) as eluant, to afford ethyl 2-(2'-ethyl-1',3'-dioxolan-2'-yl)acetate 351 as a pale yellow oil (6.29 g, 94%); υmax/cm⁻¹ (film) 2973, 2885 (vs, C-
H), 1739 (vs, C=O), 1462 (s, C-H), 1351 (s, C-H), 1236 (s, C-O-C), 1122 (s, C-O-C) and 1060 (s, C-O); δH (270 MHz; CDCl₃) 0.94 (3H, t, J2",1" 7.3, CH₃), 1.26 (3H, t, J2",1" 7.1, OCH₂CH₃), 1.83 (2H, q, J1",2" 7.3, CH₂CH₃), 2.64 (2H, s, CH₂CO), 3.96-4.01 (4H, m, OCH₂CH₂O) and 4.15 (2H, q, J1",2" 7.1, OCH₂CH₃); δC (67.8 MHz; CDCl₃) 7.6 (CH₃, C-2"), 14.0 (CH₃, C-2"'), 30.4 (CH₂, C-1"), 42.1 (CH₂, C-2), 60.3 (CH₂, C-1"'), 65.0 (CH₂, C-4', C-5'), 109.5 (quat., C-2') and 169.4 (quat., C=O).

IR, ¹H and ¹³C NMR were consistent with that reported in the literature¹³⁵.

2-(2'-Ethyl-1',3'-dioxolan-2'-yl)ethanol ³⁵²

To a suspension of lithium aluminium hydride (700 mg, 18.4 mmol) in dry diethyl ether (100 ml) at 0°C was added slowly ethyl 2-(2'-ethyl-1',3'-dioxolan-2'-yl)acetate ³⁵¹ (3.31 g, 17.6 mmol). The reaction was stirred at 0°C for 1.5 h. then ethyl acetate (15 ml) was added slowly. Distilled water was added until a solid white precipitate formed. The reaction mixture was filtered through a plug of glass wool and washed with diethyl ether (2 x 20 ml) and ethyl acetate (2 x 20 ml). The combined organic layers were then dried over magnesium sulphate and the solvent was removed under reduced pressure. Purification of the residue by column chromatography, using hexane/ethyl acetate (1:1) as eluant, afforded 2-(2'-ethyl-1',3'-dioxolan-2'-yl)ethanol ³⁵² as a pale yellow oil (2.52 g, 98%); ʋmax/cm⁻¹ (film) 3420 (vs, br, OH), 2963, 2880 (vs, C-H), 1461 (s, C-H), 1351 (s, C-H), 1199 (s, C-O-C), 1151 (vs, C-O-C) and 1068 (s, C-O); δH (270 MHz; CDCl₃) 0.92 (3H, t, J2",1" 7.3, CH₃), 1.67 (2H, q, J1",2" 7.3, CH₂CH₃), 1.93 (2H, t, J2,1 5.5, CH₂CH₂OH), 3.00-3.04 (1H, br, OH), 3.74 (2H, q, J1,2 5.5, CH₂OH) and 3.98-4.03 (4H, m, OCH₂CH₂O); δC (67.8 MHz; CDCl₃) 8.1 (CH₃, C-2"), 29.9 (CH₂, C-1"), 37.9 (CH₂, C-2), 58.8 (CH₂, C-1), 64.9 (CH₂, C-4', C-5') and 112.3 (quat., C-2').

IR, ¹H and ¹³C NMR were in agreement with that reported in the literature¹³⁵.
I-Hydroxy-3-pentanone 349\textsuperscript{134,135}

![Chemical structure of 1-Hydroxy-3-pentanone](image)

To a stirred slurry of 100-200 M silica gel (6 g) in dichloromethane (8 ml) was added slowly a 10\% aqueous oxalic acid solution (0.9 ml). After stirring vigorously for 5 min. 2-(2'-ethyl-1',3'-dioxolan-2'-yl)ethanol 352 (1.81 g, 12.4 mmol) was added and the reaction was stirred for 24 h. at room temperature. Sodium bicarbonate (0.6 g, 7.14 mmol) was added and after stirring for 5 min. the silica was filtered off and washed with dichloromethane (2 x 25 ml) and diethyl ether (2 x 25 ml). The solvent was removed from the combined organic layers and the residue was purified by column chromatography, using hexane/ethyl acetate (1:1) as eluant, to afford 1-hydroxy-3-pentanone 349 as a colourless oil (1.06 g, 84\%); \nu_{\text{max}}/\text{cm}^{-1} (\text{film}) 3430 (s, s, OH), 2967, 2889 (s, C-H), 1708 (s, C=O), 1457 (s, C-H) and 1042 (s, C-O); \delta_{\text{H}} (270 MHz; CDCl\textsubscript{3}) 1.05 (3H, t, J=5.47.3, CH\textsubscript{3}), 2.50 (2H, q, J=4.57.3, CH\textsubscript{2}CH\textsubscript{3}), 2.68 (2H, t, J=2.16.2, CH\textsubscript{2}OH), 3.35 (1H, br, OH) and 3.84 (2H, m, CH\textsubscript{2}OH); \delta_{\text{C}} (67.8 MHz; CDCl\textsubscript{3}) 7.1 (CH\textsubscript{3}, C-5), 36.1 (CH\textsubscript{2}, C-4), 44.0 (CH\textsubscript{2}, C-2), 57.1 (CH\textsubscript{2}, C-1) and 211.7 (C=O).

IR, \textsuperscript{1}H and \textsuperscript{13}C NMR were in agreement with that reported in the literature\textsuperscript{135}.

\textbf{1-(}tert\text{-Butyldiphenylsilyloxy)-3-pentanone 354}

![Chemical structure of 1-(tert-Butyldiphenylsilyloxy)-3-pentanone](image)

To a solution of 1-hydroxy-3-pentanone 349 (1.03 g, 10.1 mmol) in dry dichloromethane (50 ml) were added imidazole (1.37 g, 20.1 mmol) and tert-butylichlorodiphenylsilane (2.90 ml, 11.2 mmol). After stirring for 1 h. at room temperature distilled water (20 ml) was added and the reaction mixture was extracted with dichloromethane (4 x 40 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure. The residue was purified
by column chromatography, using hexane/ethyl acetate (4:1) as eluant, to afford 1-(tert-
butyldiphenylsilyloxy)-3-pentanone \(354\) as a colourless oil (3.2 g, 93%) (Found: (CI,
NH\(_3\)) \(M + H, 341.1925.\) \(C_{21}H_{29}O_{2}Si\) requires \(M + H, 341.1937.\); \(\nu_{\text{max}}/\text{cm}^{-1}\) (film)
2947, 2931, 2876 (s, CH\(_3\)), 1735 (vs, C=O), 1466, 1424 (s, C-H), 822 (s, Si-CH\(_3\)),
735 (s, Si-C), 705 (s, monosub. benzene); \(\delta_H\) (270 MHz; CDCl\(_3\)) 1.03 (9H, s, Si-
(C(H\(_3\))\(_3\)), 1.05 (3H, t, \(J_{5,4} 7.3,\) CH\(_3\)), 2.49 (2H, q, \(J_{4,5} 7.3,\) CH\(_2\)CH\(_3\)), 2.62 (2H, t,
\(J_{2,1} 6.2,\) CH\(_2\)CH\(_2\)OSi), 3.94 (2H, t, \(J_{1,2} 6.2,\) CH\(_2\)OSi), 7.36-7.43 (6H, m, Ar-H) and
7.64-7.67 (4H, m, Ar-H); \(\delta_C\) (67.8 MHz; CDCl\(_3\)) 7.6 (CH\(_3\), C-5), 19.1 (quat., \(^1\)Bu),
26.7 (CH\(_3\), \(^1\)Bu), 36.9 (CH\(_2\), C-4), 45.0 (CH\(_2\), C-2), 59.8 (CH\(_2\), C-1), 127.7, 129.7,
135.5 (CH, Ar), 133.4 (quat., Ar) and 210.4 (C=O); \(m/z\) 341 (M + H, 0.5%), 283 (M -
\(^1\)Bu, 100), 253 (38), 199 (34), 139 (12) and 45 (28).

1,1-Diiodoethane\(^{162}\)

\[
\text{CH}_3\text{CHCl}_2 + 2 \text{CH}_3\text{CH}_2\text{I} \xrightarrow{\text{AlCl}_3} \text{CH}_3\text{CH}_2\text{I} + 2 \text{CH}_3\text{CH}_2\text{Cl}
\]

A mixture of 1,1-dichloroethane (3.37 ml, 40 mmol) and iodoethane (9.59 ml,
120 mmol) was heated with aluminium chloride (0.2 g, 1.5 mmol) on a water bath for 2
h. The mixture was then washed with distilled water (20 ml), followed by 12% sodium
bisulphite solution (70 ml). The organic layer was dried over magnesium sulphate
and distilled under reduced pressure to afford 1,1-diiodoethane as a yellow liquid (5.11 g,
47%). b.p. 66°C/18 mmHg (lit.\(^{162}\), b.p. 75-76°C/25 mmHg).

(E)- and (Z)-1-(tert-Butyldiphenylsilyloxy)-3-ethyl-3-pentene

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Procedure A
To a stirred suspension of chromium(II) chloride (361 mg, 2.94 mmol) in dry tetrahydrofuran (8 ml) was added dimethylformamide (0.23 ml, 2.97 mmol). The reaction mixture was stirred at room temperature for 30 min. then a solution of diiodoethane (207 mg, 0.734 mmol) and 1-(tert-butyldiphenylsilyloxy)-3-pentanone 354 (125 mg, 0.368 mmol) in dry tetrahydrofuran (4 ml) was added. After stirring for a further 4 h. at room temperature distilled water (5 ml) was added and the reaction mixture was extracted with ethyl acetate (3 × 50 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure. Purification of the residue by column chromatography, using hexane/ethyl acetate (20:1) as eluant, afforded a (2:3) ratio of the (E)- and (Z)-1-(tert-butyldiphenylsilyloxy)-3-ethyl-3-pentene 359 as a pale yellow oil (30 mg, 23%); \( \nu_{\text{max}}/\text{cm}^{-1} \) (film) 3069 (m, =C-H), 2951, 2924, 2857 (vs, C-H), 1465 (m, C-H), 1424 (m, C-H), 822 (s, =C-H), 735 (s, Si-C) and 702 (vs, Si-C); \( \delta_{\text{H}} \) (270 MHz; CDCl₃) E-isomer 0.87 (3H, t, J₂',₁' 7.3, CH₂CH₃), 1.03 (9H, s, Si-C(CH₃)₃), 1.54 (3H, d, J₅,₄ 6.6, CH₃C=), 1.95 (2H, q, J₁',₂' 7.3, CH₂CH₃), 2.21 (2H, t, J₁,₂ 7.3, CH₂CH₂OSi), 3.69 (2H, t, J₁,₂ 7.3, CH₂O), 5.15 (1H, q, J₄,₅ 6.6, =CH), 7.33-7.43 (6H, m, Ar-H) and 7.66-7.69 (4H, m, Ar-H); Z-isomer 0.90 (3H, t, J₂',₁' 7.3, CH₂CH₃), 1.04 (9H, s, Si-C(CH₃)₃), 1.48 (3H, d, J₅,₄ 6.6, CH₃C=), 1.89 (2H, q, J₁',₂' 7.3, CH₂CH₃), 2.32 (2H, t, J₁,₂ 7.3, CH₂CH₂OSi), 3.64 (2H, t, J₁,₂ 7.3 CH₂O), 5.22 (1H, q, J₄,₅ 6.6, =CH), 7.34-7.45 (6H, m, Ar-H) and 7.65-7.70 (4H, m, Ar-H); \( \delta_{\text{C}} \) (67.8 MHz; CDCl₃) E-isomer 12.8 (CH₃, C-2'), 13.0 (CH₃, C-5), 19.1 (quat., tBu), 22.9 (CH₂, C-1'), 26.8 (CH₃, tBu), 39.7 (CH₂, C-2), 63.4 (CH₂OSi), 120.0 (CH, C-4), 127.6, 129.5, 135.6 (CH, Ar), 134.1 (quat., Ar) and 138.5 (quat., C-3); Z-isomer 12.8 (CH₃, C-2'), 13.2 (CH₃, C-5), 19.1 (quat., tBu), 30.1 (CH₂, C-1'), 33.4 (CH₃, tBu), 39.7 (CH₂, C-2), 62.5 (CH₂OSi), 119.1 (CH, C-4), 127.6, 129.5, 135.6 (CH, Ar), 134.1 (quat., Ar) and 138.6 (quat., C-3).

**Procedure B**

![Chemical Structure](image)

To a solution of (E)-3-ethyl-3-penten-1-ol 373 (50 mg, 0.438 mmol) in dry dichloromethane (2 ml) were added imidazole (59.5 mg, 0.874 mmol) and tert-butyldichlorodiphenylsilane (120 mg, 0.437 mmol). After stirring for 1 h. at room
temperature distilled water (2 ml) was added and the reaction mixture was extracted with dichloromethane (4 × 5 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure. The residue was purified by column chromatography using hexane/ethyl acetate (9:1) as eluant, to afford (E)-1-tert-butyldiphenylsilyloxy)-3-ethyl-3-pentene 359 (111 mg, 72%) as a colourless oil.

1H and 13C NMR data for this product were identical to the data listed for the E-isomer in procedure A.

(1R*, 2'S*) and (1S*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-4-penten-1-ol [erythro and threo] 330a, 330b

To a suspension of magnesium filings (230 mg, 9.46 mmol) in freshly distilled tetrahydrofuran (3 ml) was added 4-bromo-1-butene 329 (214 mg, 1.59 mmol) and the reaction was initiated by scratching the surface of the magnesium with a glass rod. A solution of 4-bromo-1-butene (856 mg, 6.31 mmol) in tetrahydrofuran (5 ml) was then added slowly over 20 min. The reaction was stirred for 30 min. then freshly prepared 2-methyl-2-tetrahydrofuraldehyde 322 (900 mg, 7.89 mmol) was added. After stirring for a further 20 min, the reaction was quenched with saturated aqueous ammonium chloride (10 ml) and left to stir for 16 h. The reaction mixture was extracted with diethyl ether (3 × 40 ml) and the combined organic layers were dried over magnesium sulphate. Removal of the solvent at reduced pressure and purification of the residue by flash chromatography, using hexane/ethyl acetate (4:1) as eluant, afforded the title compound 330 as an inseparable (4:1, 1H NMR) mixture of the erythro and threo products as a colourless oil (917 mg, 68%).

Separation of the isomers was effected by formation of the acetates, which are separable by flash chromatography, followed by deprotection to afford pure samples of the erythro and threo isomers (vide infra).
(1R*, 2'S*) and (1S*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-1-pent-4-enyl acetate [erythro and threo] 338a, 338b

To a solution of (1R*, 2'S*) and (1S*, 2'S*)-1-(2-methyltetrahydrofur-2-yl)-4-penten-1-ol (4:1, 330a:330b) (1.50 g, 8.81 mmol) in dry dichloromethane (110 ml) under nitrogen were added triethylamine (1.62 ml, 11.6 mmol), acetic anhydride (0.91 ml, 9.64 mmol) and a catalytic quantity of 4-dimethylaminopyridine (~5 mg). After stirring for 24 h, the solvent was removed under reduced pressure to afford a cloudy yellow residue which was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant to afford:

(1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-1-pent-4-enyl acetate 338a [erythro] (1.29 g, 69%) (Found: (Cl, NH3) M + H, 213.1503. C12H21O3 requires M + H, 213.1491); \( \nu_{\text{max}} \text{cm}^{-1} \) (film) 3068 (m, =C-H), 2967, 2863 (s, C-H), 1738 (vs, C=O), 1637 (m, C=C), 1442, 1370 (s, C-H), 1235 (vs, C-O-C) and 911 (vs, =CH2); \( \delta_{\text{H}} \) (270 MHz; CDCl3) 1.10 (3H, s, CH3), 1.55-1.67 (2H, m, CH2), 1.68-1.80 (1H, m, CH2), 1.86-1.92 (3H, m, CH2), 1.95-2.03 (2H, m, CH2), 2.08 (3H, s, CH3CO), 3.80-3.86 (2H, m, CH2O), 4.83-4.91 (2H, m, CHOAc, 5A-H), 4.94 (1H, d, J5B,4 17.2, 5B-H) and 5.81 (1H, ddt, J4,5B 17.2 J4,5A 10.3 J4,3 6.6, 4-H); \( \delta_{\text{C}} \) (67.8 MHz; CDCl3) 21.1 (CH3, CH3CO), 22.4 (CH3, 2'-Me), 25.9 (CH2), 29.0 (CH2), 30.3 (CH2), 34.5 (CH2), 68.3 (CH2O), 77.0 (CHOAc), 83.5 (quat, C-2'), 114.8 (=CH2), 137.8 (=CH) and 170.7 (C=O); \( m/z \) 213 (M + H, 2%), 153 (M - CH3COO, 6), 111 (2), 98 (4), 85 (C5H9O, 100) and 55(2).

(1S*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-1-pent-4-enyl acetate 338b [threo] (319 mg, 17%) (Found: (Cl, NH3) M + H, 213.1503. C12H21O3 requires M + H, 213.1491); \( \nu_{\text{max}} \text{cm}^{-1} \) (film) 3066 (m, =C-H), 2966, 2862 (s, C-H), 1739 (vs, C=O), 1637 (m,
C=C), 1445, 1370 (s, C-H), 1237 (vs, C-O-C) and 915 (vs, =CH2); δH (270 MHz; CDCl3) 1.19 (3H, s, CH3), 1.59-1.69 (3H, m, CH2), 1.75-1.80 (1H, m, CH2), 1.85-1.96 (2H, m, CH2), 1.98-2.09 (2H, m, CH2), 2.10 (3H, s, CH3CO), 3.79-3.89 (2H, m, CH2O), 4.91-4.99 (2H, m, CHOAc, 5a-H), 5.02 (1H, d, J5b,4 17.2, 5b-H) and 5.80 (1H, ddt, J4,5b 17.2 J4,5a 10.3 J4,3 6.6, 4-H); δC (67.8 MHz; CDCl3) 21.1 (CH3, Ac), 22.4 (CH3), 26.2 (CH2), 29.5 (CH2), 30.4 (CH2), 34.6 (CH2), 67.7 (CH2O), 77.1 (CHOAc), 83.6 (quat., C-2'), 115.0 (=CH2), 137.8 (=CH) and 170.9 (C=O); m/z 213 (M + H, 2%), 153 (M - CH3COO, 6), 111 (2), 98 (4), 85 (C5H9O, 100) and 55(2).

(1R*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-4-penten-1-ol [erythro] 330a

To a solution of (1R*, 2'S*)-1-(2-methyltetrahydrofur-2'-yl)-1-pent-4-enyl acetate 338a (454 mg, 2.14 mmol) in 95% aqueous methanol (40 ml) was added potassium carbonate (1.18 g, 8.54 mmol). After stirring for 16 h. the reaction mixture was filtered and the solvent was removed under reduced pressure. Saturated aqueous sodium chloride solution (5 ml) was added and the mixture was extracted with dichloromethane (6 x 30 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure. The residue was purified by flash chromatography, using hexane/ethyl acetate (9:1) as eluent, to afford (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol 330a as a colourless oil (291 mg, 80%); νmax/cm⁻¹ (film) 3451 (br, vs, OH), 3075 (m, =CH), 2973, 2869 (s, C-H), 1077 (s, C-O-C), 1044 (vs, C-O), 1000 (m, =CH) and 910 (s, =CH2); δH (270 MHz; CDCl3) 1.12 (3H, s, CH3), 1.31-1.81 (4H, m, CH2), 1.87-2.05 (2H, m, CH2), 2.07-2.12 (1H, m, CH2), 2.30-2.44 (1H, m, CH2), 2.73 (1H, s, OH), 3.53 (1H, dd, J1,2a 10.3, J1,2b 4.0, CHOH), 3.85 (2H, m, CH2O), 4.97 (1H, d, J5a,4 10.1, 5a-H), 5.05 (1H, d, J5b,4 17.2, 5b-H) and 5.85 (1H, ddt, J4,5b 17.2 J4,5a 10.1 J4,3 6.6, 4-H); δC (67.8 MHz; CDCl3) 22.9 (CH3), 26.2 (CH2), 30.7 (CH2), 30.9 (CH2), 34.3 (CH2), 67.7 (CH2O), 75.6 (CHOH), 85.6 (quat., C-2'), 114.5 (=CH2) and 138.4 (=CH); m/z 171 (M + H, 4%), 153 (M - OH, 15), 111 (35), 85 (C5H9O, 75) and 43 (100).
To a solution of (1S*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-1-pent-4-enyl acetate 338b (400 mg, 1.88 mmol) in 95% aqueous methanol (30 ml) was added potassium carbonate (1.04 g, 7.53 mmol). After stirring for 18 h, the reaction mixture was filtered and the solvent was removed under reduced pressure. Saturated aqueous sodium chloride solution (20 ml) was added and the mixture was extracted with dichloromethane (6 × 30 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure. The residue was purified by flash chromatography, using hexane/ethyl acetate (20:1) as eluant, to afford (1S*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol 330b as a colourless oil (272 mg, 85%); νmax/cm⁻¹ (film) 3450 (br, vs, OH), 3074 (m, =CH), 2973, 2869 (s, C-H), 1075 (s, C-O-C), 1045 (vs, C-O), 1000 (m, =CH) and 911 (s, =CH₂); δH (270 MHz; CDCl₃) 1.14 (3H, s, CH₃), 1.39-1.52 (2H, m, CH₂), 1.57-1.79 (2H, m, CH₂), 1.87-2.05 (2H, m, CH₂), 2.07-2.15 (1H, m, CH₂), 2.32-2.41 (1H, m, CH₂), 2.73 (1H, s, OH), 3.40 (1H, dd, J₁,₂A 8.4 J₁,₂B 4.0, CHOH), 3.83 (2H, m, CH₂O), 4.97 (1H, d, J₅A₄ 10.1, 5A-H), 5.05 (1H, d, J₅B₄ 17.0, 5B-H) and 5.84 (1H, ddt, J₄₅B 17.2, J₄₅ₐ 10.1, J₄₃ 6.6, 4-H); δC (67.8 MHz; CDCl₃) 19.9 (CH₃), 26.3 (CH₂), 30.7 (CH₂), 31.0 (CH₂), 34.4 (CH₂), 67.3 (CH₂O), 75.8 (CHOH), 85.2 (quat., C-2'), 114.6 (=CH₂) and 138.4 (=CH); m/z 171 (M + H, 4%), 153 (M - OH, 15), 111 (35), 85 (C₅H₉O, 75) and 43 (100).
To a solution of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol 330a (270 mg, 1.59 mmol) in dry tetrahydrofuran (5 ml) at 0°C under nitrogen was added sodium hydride (58 mg, 80% oil dispersion, 1.94 mmol). After stirring for 10 min. 2,6-dichlorobenzyl bromide (400 mg, 1.67 mmol) was added and the reaction was stirred for 24 h. The reaction mixture was filtered and washed with dry diethyl ether (60 ml). The solvent was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford the title compound 387 as a colourless oil (409 mg, 78%) (Found: M + H, 329.1061. C\textsubscript{17}H\textsubscript{23}O\textsubscript{2}Cl\textsubscript{2} requires M + H, 329.1075.); \(\nu_{\text{max}}/\text{cm}^{-1}\) (film) 3073 (m, =C-H), 2972, 2868 (s, C-H), 1581 (m, Ar-H), 1099 (vs, C-O-C), 993 (s, =CH), 111 (s, =CH\textsubscript{2}), 777 and 765 (vs, Ar); \(\delta_{\text{H}}\) (270 MHz; CDCl\textsubscript{3}) 1.15 (3H, s, CH\textsubscript{3}), 1.40-1.70 (3H, m, CH\textsubscript{2}), 1.85-2.00 (2H, m, CH\textsubscript{2}), 2.03-2.18 (2H, m, CH\textsubscript{2}), 2.22-2.38 (1H, m, CH\textsubscript{2}), 3.43 (1H, dd, \(J_{1,2A}\) 9.5 \(J_{1,2B}\) 2.9, CHO), 3.87 (2H, t, \(J_{5',4'}\) 6.4, CH\textsubscript{2}O), 4.85 (1H, d, \(J_{HA,HB}\) 10.6, CH\textsubscript{A}H\textsubscript{B}Ar), 4.88-5.03 (2H, m, =CH\textsubscript{2}), 5.05 (1H, d, \(J_{HB,HA}\) 10.6, CH\textsubscript{A}H\textsubscript{B}Ar), 5.81 (1H, ddt, \(J_{4,5B}\) 16.9 \(J_{4,5A}\) 10.3 \(J_{4,3}\) 6.6, 4-H), 7.13-7.19 (1H, m, Ar-H) and 7.27-7.33 (2H, m, Ar-H); \(\delta_{\text{C}}\) (67.8 MHz; CDCl\textsubscript{3}) 23.3 (CH\textsubscript{3}), 26.2 (CH\textsubscript{2}), 30.6 (CH\textsubscript{2}), 31.2 (CH\textsubscript{2}), 33.2 (CH\textsubscript{2}), 67.4 (CH\textsubscript{2}O), 68.8 (CH\textsubscript{2}Ar), 84.7 (CHO), 86.0 (quat., C-2'), 114.4 (=CH\textsubscript{2}), 128.4, 129.6 (Ar-H), 134.4, 136.8 (Ar-CH\textsubscript{2}, Ar-Cl) and 138.9 (=CH); mA 329 (M + H, 1%), 161 (20), 159 (C\textsubscript{7}H\textsubscript{5}Cl\textsubscript{2}, 31), 85 (C\textsubscript{3}H\textsubscript{9}O, 100) and 43 (48).
(1S*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-1-(2",6"-dichlorobenzyl oxy)-4-pentene 340

To a solution of (1S*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol 330a (30 mg, 0.18 mmol) in dry tetrahydrofuran (0.5 ml) at 0°C under nitrogen was added sodium hydride (6 mg, 80% oil dispersion, 0.20 mmol). After stirring for 15 min. 2,6-dichlorobenzyl bromide (46 mg, 0.19 mmol) was added and the reaction was stirred for 24 h. The reaction mixture was filtered and washed with dry diethyl ether (5 ml). The solvent was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford the title compound 340 as a colourless oil (44 mg, 74%) (Found: M + H, 329.1065. C_{17}H_{23}O_{2}Cl_{2} requires M + H, 329.1075); \( \nu_{\text{max}} / \text{cm}^{-1} \) (film) 3073 (m, =C-H), 2971, 2867 (s, C-H), 1579 (m, Ar-H), 1098 (vs, C-O-C), 991 (s, =CH), 908 (s, =CH\(2\)), 777 and 764 (vs, Ar); \( \delta_{H} \) (270 MHz; CDCl\(3\)) 1.23 (3H, s, CH\(3\)), 1.43-1.76 (4H, m, CH\(2\)), 1.85-2.02 (2H, m, CH\(2\)), 2.02-2.11 (1H, m, CH\(2\)), 2.21-2.40 (1H, m, CH\(2\)), 3.34 (1H, dd, \( J_{1,2A} = 9.2 \), \( J_{1,2B} = 2.9 \), CHO), 3.76-3.99 (2H, m, CH\(2\)), 4.81 (1H, d, \( J_{HA,HB} = 10.6 \), CH\(A\)), 4.86-5.03 (2H, m, =CH\(2\)), 5.21 (1H, d, \( J_{HB,HA} = 10.6 \), CH\(A\)), 5.76 (1H, ddt, \( J_{4,5A} = 16.9 \), \( J_{4,5A} = 10.3 \), \( J_{4,3} = 6.6 \), 4-H), 7.13-7.19 (1H, m, Ar-H) and 7.26-7.32 (2H, m, Ar-H); \( \delta_{C} \) (67.8 MHz; CDCl\(3\)) 21.0 (CH\(3\)), 25.7 (CH\(2\)), 30.7 (CH\(2\)), 31.4 (CH\(2\)), 35.4 (CH\(2\)), 67.6 (CH\(2\)), 68.4 (CH\(2\)), 85.1 (CHO), 86.5 (quat., C-2'), 114.6 (=CH\(2\)), 128.3, 129.6 (Ar-H), 134.5, 136.9 (Ar-CH\(2\), Ar-Cl) and 138.9 (=CH); \( m/z \) 329 (M + H, 1%), 161 (20), 159 (C\(7\)H\(5\)Cl\(2\), 32), 85 (C\(5\)H\(9\)O, 100) and 43 (49).
(1R*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-1-(4''-bromobenzyl)oxy)-4-pentene 386

To a stirred solution of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol 330a (400 mg, 2.35 mmol) in dry tetrahydrofuran (4ml) at 0°C under nitrogen was added sodium hydride (85 mg, 80% oil dispersion, 2.83 mmol). After stirring for 10 min. 4-bromobenzyl bromide (586 mg, 2.34 mmol) and tetrabutylammonium iodide (87 mg, 0.236 mmol) were added and the reaction was stirred for 24 h. The reaction mixture was filtered and washed with dry diethyl ether (50 ml). The solvent was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (20:1) as eluant, to afford the title compound 386 as a colourless oil (409 mg, 51%) (Found: M + H, 338.0867, 340.0861. C17H24O279Br, C17H24O281Br require M + H, 338.0881, 340.0861); νmax/cm⁻¹ (film) 3074 (m, =C-H), 2971, 2866 (s, C-H), 1485 (s, Ar), 1447 (C-H), 1113 (vs, C-O-C), 914 (s, =CH2) and 802 (vs, Ar); δH (270 MHz; CDCl3) 1.15 (3H, s, CH3), 1.45-1.64 (3H, m, CH2), 1.85-1.95 (2H, m, CH2), 2.02-2.13 (2H, m, CH2), 2.24-2.30 (1H, m, CH2), 3.36 (1H, dd, J1,2A 9.5 J1,2B 2.9, CHO), 3.73-3.91 (2H, m, CH2O), 4.55 (1H, d, JHA,HB 11.7, CHAHBAr), 4.73 (1H, d, JHB,HA 11.7, CHAHBAr), 4.95-5.04 (2H, m, =CH2) 5.81 (1H, ddt, J4,5B 16.9 J4,5A 10.3 J4,3 6.6, 4-H), 7.21-7.24 (2H, m, Ar-H) and 7.44-7.47 (2H, m, Ar-H); δC (67.8 MHz; CDC13) 23.9 (CH3), 26.4 (CH2), 30.7 (CH2), 31.1 (CH2), 32.7 (CH2), 67.7 (CH2O, C-5'), 73.8 (CH2Ar), 84.5 (CHO), 86.1 (quat., C-2'), 114.7 (=CH2), 121.0 (quat., Ar-Br) 129.2, 131.2 (Ar-H) 138.3 (quat., Ar-CH2) and 138.5 (=CH); m/z 340 (M + H, 1%), 338 (M + H, 1), 171 (C7H681Br, 34), 169 (C7H679Br, 36), 85 (C5H9O, 100) and 43 (69).
(1R*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-1-benzylxyo-4-pentene 385

To a solution of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol 330a (508 mg, 2.98 mmol) in dry tetrahydrofuran (6 ml) at 0°C under nitrogen was added sodium hydride (107 mg, 80% oil dispersion, 3.57 mmol). After stirring for 20 min. benzyl bromide (0.354 ml, 2.98 mmol) and tetrabutylammonium iodide (102 mg, 0.276 mmol) were added and the reaction was stirred for 24 h. The reaction mixture was filtered and washed with dry diethyl ether (60 ml). The solvent was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (20:1) as eluant, to afford the title compound 385 as a colourless oil (340 mg, 44%) (Found: M+ 260.1770. C17H24O2 require M, 260.1776; \nu_{\text{max/cm}^{-1}} (\text{film}) 3064 (m, =C-H), 2971, 2865 (s, C-H), 1450 (C-H), 1107 (vs, C-O-C), 910 (s, =CH2), 735 and 697 (s, C-H); \delta_H (270 MHz; CDCl3) 1.16 (3H, s, CH3), 1.43-1.67 (3H, m, CH2), 1.86-1.96 (2H, m, CH2), 2.04-2.16 (2H, m, CH2), 2.26-2.31 (1H, m, CH2), 3.37 (1H, dd, J_{1,2A} 9.5 J_{1,2B} 2.9, CHO), 3.70-3.93 (2H, t, m, CH2O), 4.59 (1H, d, J_{HA,HB} 11.0, CHAHBAr), 4.79 (1H, d, J_{HB,HA} 11.0, CHAHBAr), 4.95-5.04 (2H, m, =CH2) 5.80 (1H, ddt, J_{4,5B} 16.9 J_{4,4A} 10.3 J_{4,3} 7.0, 4-H) and 7.26-7.40 (5H, m, Ar-H); \delta_C (67.8 MHz; CDCl3) 23.9 (CH3), 26.5 (CH2), 30.8 (CH2), 31.2 (CH2), 33.0 (CH2), 67.8 (CH2O, C-5'), 74.7 (CH2Ar), 84.4 (CHO), 86.2 (quat., C-2'), 114.6 (=CH2), 127.3, 127.7, 128.3 (C-H, Ar), 138.8 (=CH) and 139.3 (quat., Ar); \text{m/z} 260 (M+, 0.5%), 91 (33), 85 (C5H9O, 100) and 43 (24).
(1R*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-1-(trimethylsilyloxy)-4-pentene 388

To a solution of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol 330a (170 mg, 1.00 mmol) in dry dichloromethane (1 ml) was added 1-(trimethylsilyl)-imidazole (0.29 ml, 2.0 mmol). After 15 min. the reaction was quenched with water (2 drops), the solvent was removed under reduced pressure, and the residue was purified by flash chromatography, using hexane/ethyl acetate (20:1) as eluant, to afford the title compound 388 as a colourless oil (225 mg, 93%) (Found: (Cl, NH₃) M + H, 243.1786. C₁₃H₂₇O₂Si requires M + H, 243.1780.); v_max/cm⁻¹ (film) 3069 (m, =C-H), 2962, 2864 (vs, C-H), 1637 (s, C=C), 1447 (s, C-H), 1371 (s, C-H), 1248 (s, Si-CH₃), 1106 (vs, C-O-C), 908 (s, =CH₂) and 838 (vs, Si-CH₃); δ_H (270 MHz, CDCl₃) 0.01 (9H, s, CH₃Si), 0.98 (3H, s, CH₃), 1.21-1.55 (4H, m, CH₂), 1.69-1.93 (3H, m, CH₂), 2.07-2.13 (1H, m, CH₂), 3.42 (1H, dd, J₁,₂A 9.9 J₁,₂B 2.6, CHO), 3.67 (2H, t, J₅',₄' 6.6, CH₂O), 4.84 (1H, d, J₅₆₄₅ 10.3, 5₆-H), 4.91 (1H, d, J₅₆₄₅ 17.2, 5₆-H) and 5.71 (1H, ddt, J₅₆₄₅ 17.2 J₅₆₄₅ 10.3 J₅₆₄₅ 6.6, 4-H); δ_C (67.8 MHz; CDCl₃) 0.80 (CH₃, SiMe₂), 22.8 (CH₃), 26.2 (CH₂), 30.9 (CH₂), 32.4 (CH₂), 32.9 (CH₂), 67.5 (CH₂O), 77.5 (CHO), 85.4 (quat., C-2'), 114.4 (=CH₂) and 138.8 (=CH); m/z 243 (M + H, 25%), 207 (29), 171 (32), 153 (M - OSiMe₃, 51), 95 (26), 85 (C₅H₉O, 100), 74 (Me₃SiH, 73).

(1R*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-1-(tert-butyl-dimethylsilyloxy)-4-pentene 389
To a stirred solution of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol 330a (170 mg, 1.00 mmol) in dry dichloromethane (1 ml) were added 2,6-lutidine (0.23 ml, 2.0 mmol) and tert-butyldimethylsilyl trifluoromethanesulphonate (397 mg, 1.50 mmol). The reaction was stirred at room temperature for 2 h. after which time water (1 ml) was added. The aqueous layer was extracted with diethyl ether (3 x 5 ml) and the combined organic layers were dried over magnesium sulphate. After removal of the solvent under reduced pressure the residue was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford the title compound 389 as a colourless oil (191 mg, 67%) (Found: (Cl, NH3) M + H, 285.2259. C_{16}H_{32}O_2Si requires M + H, 285.2250.); $\nu_{max}$/cm$^{-1}$ (film) 3069 (m, =C-H), 2926, 2853 (vs, C-H), 1636 (m, C=C), 1465 (s, C-H), 1102 (vs, C-O-C), 908 (vs, =CH$_2$) and 835 (vs, Si-CH$_3$); $\delta_H$ (270 MHz; CDCl$_3$) 0.05 (3H, s, SiMe), 0.06 (3H, s, SiMe), 0.88 (9H, s, tBu), 1.09 (3H, s, 2'-Me), 1.35-1.72 (4H, m, CH$_2$), 1.80-2.09 (4H, m, CH$_2$), 2.17-2.22 (1H, m, CH$_2$), 3.52 (1H, dd, $J_{1,2B}$ 8.1 $J_{1,2A}$ 3.3, CHOSi), 3.74-3.83 (2H, m, CH$_2$0), 4.93 (1H, d, $J_{5A,4}$ 10.3, 5A-H), 5.00 (1H, dd, $J_{5B,4}$ 17.2 $J_{5B,5A}$ 1.8, 5B-H) and 5.80 (1H, ddt, $J_{4,5B}$ 17.2 $J_{4,5A}$ 10.3 $J_{4,3}$ 6.6, 4-H); $\delta_C$ (67.8 MHz; CDCl$_3$) -4.1 (CH$_3$, SiMe), 18.2 (quat., tBu), 22.3 (CH$_3$, 2'-Me), 67.2 (CH$_2$O), 77.0 (CHO), 85.5 (quat., C-2'), 114.1 (=CH$_2$) and 139.0 (=CH); m/z 285 (M + H, 100%), 269 (M - CH$_3$, 10), 227 (M - tBu, 27), 153 (M - OSi'tBuMe$_2$, 81) and 85 (C$_5$H$_9$O).

(2R*, 5R*, 2'S*) and (2S*, 5R*, 2'S*)-2-(Iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran [trans and cis] 331a, 331b

**Procedure A**
To a solution of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol 330a (200 mg, 1.17 mmol) in dry acetonitrile (12 ml) were added sodium carbonate (1.24 g, 1.17 mmol) and iodine (1.49 g, 5.87 mmol). After 1 h, the reaction was extracted with diethyl ether (50 ml) and washed with 10% aqueous sodium sulphite (20 ml), followed by saturated aqueous sodium chloride solution (20 ml). The organic layer was dried over magnesium sulphate and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, afforded:

(2R*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 331a

[trans] as a colourless oil (265 mg, 77%) (Found: M + H, 297.0356. C_{10}H_{18}O_{2}I requires M + H, 297.0352.); \nu_{\text{max}}/\text{cm}^{-1} (\text{film}) 2971, 2867 (s, C-H), 1459 (m, C-H), 1095 (s, C-O-C), 1051 (vs, C-O-C) and 491 (s, C-I); \delta_{H} (270 MHz; CDCl_{3}) 1.15 (3H, s, CH_{3}), 1.56-1.80 (3H, m, CH_{2}), 1.86-2.08 (4H, m, CH_{2}), 2.18-2.28 (1H, m, CH_{2}), 3.15 (1H, dd, J_{HA,HB} 9.7 J_{HA,HB} 8.0, CH_{AHBI}), 3.31 (1H, dd, J_{HB,HA} 9.7 J_{HB,2.4.4}, CH_{AB}), 3.85 (2H, t, J_{5',4'} 6.4, CH_{2}O), 4.07 (1H, dd, J_{5,4A} 8.6 J_{5,4B} 6.4, 5-H) and 4.05-4.16 (1H, m, 2-H); \delta_{C} (67.8 MHz; CDCl_{3}) 10.7 (CH_{2}I), 22.7 (CH_{3}), 26.1 (CH_{2}), 28.0 (CH_{2}), 32.9 (CH_{2}), 33.4 (CH_{2}), 68.1 (CH_{2}O), 79.1 (CHO, C-2), 84.3 (quat., C-2') and 85.4 (CHO, C-5); m/z 297 (M + H, 5%), 279 (M - OH, 2), 211 (5), 111 (2), 85 (C_{5}H_{9}O, 100), 55 (13) and 43 (54).

(2'S*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 331b

[cis] as a colourless oil (54 mg, 16%) (Found: M + H, 297.0344. C_{10}H_{18}O_{2}I requires M + H 297.0352.); \nu_{\text{max}}/\text{cm}^{-1} (\text{film}) 2963, 2863 (s, C-H), 1455 (m, C-H), 1092 (s, C-O-C), 1057 (vs, C-O-C) and 504 (s, C-I); \delta_{H} (270 MHz; CDCl_{3}) 1.17 (3H, s, CH_{3}), 1.57-1.78 (3H, m, CH_{2}), 1.84-2.07 (5H, m, CH_{2}), 3.24-3.28 (2H, m, CH_{2}I), 3.86 (2H, t, J_{5',4'} 6.6, CH_{2}O), 3.93 (1H, dd, J_{5,4A} 8.4 J_{5,4B} 6.6, 5-H) and 3.89-3.99 (1H, m, 2-H); \delta_{C} (67.8 MHz; CDCl_{3}) 10.7 (CH_{2}I), 23.3 (CH_{3}), 26.3 (CH_{2}), 27.0 (CH_{2}), 31.4 (CH_{2}), 33.2 (CH_{2}), 68.2 (CH_{2}O), 78.2 (CHO, C-2), 83.9 (quat., C-2') and 85.9 (CHO, C-5); m/z 297 (M + H, 1%), 211 (2), 85 (C_{5}H_{9}O, 100), 55 (12) and 43 (64).
To a solution of each of the protected hydroxyalkenes 385 - 389 (1.0 mmol) in dry acetonitrile (9 ml) at 0°C was added iodine (5.0 mmol). After 10 min. the reaction was extracted with diethyl ether (20 ml) and washed with 10% aqueous sodium sulphite (20 ml). The aqueous layer was extracted with diethyl ether (4 × 25 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, afforded (2R*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 331a [trans] and (2S*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 331b [cis].

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<td>385</td>
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<td>acetate</td>
<td>no reaction</td>
<td>-</td>
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(2S*, 5S*, 2'S*) and (2R*, 5S*, 2'S*)-2-(Iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran [trans and cis] 339a, 339b

**Procedure A**

To a solution of (1S*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol 330b (100 mg, 0.58 mmol) in dry acetonitrile (6 ml) were added sodium carbonate (0.63 g, 0.59 mmol) and iodine (0.75 g, 2.96 mmol). After 1 h. the reaction was extracted with diethyl ether (30 ml) and washed with 10% aqueous sodium sulphite (10 ml), followed by saturated aqueous sodium chloride solution (10 ml). The organic layer was dried over magnesium sulphate and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, afforded an inseparable mixture of:

(2S*, 5S*, 2'S*)-2-(Iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 339a [trans] as a colourless oil (126 mg, 73%) (Found: M + H, 297.0341. C10H18O2I requires M + H, 297.0352.; υmax/cm⁻¹ (film) 2970, 2869 (s, C-H), 1459 (m, C-H), 1095 (s, C-O-C), 1051 (vs, C-O-C) and 491 (s, C-I); δH (270 MHz; CDC13) 1.12 (3H, s, CH3), 1.57-1.67 (2H, m, CH2), 1.84-2.04 (5H, m, CH2), 2.17-2.28 (1H, m, CH2), 3.18 (1H, dd, JHA,HB 9.9 JHA,2 7.3, CHAHB1), 3.28 (1H, dd, JHB,HA 9.9 JHB,2 4.8, CHA HB1), 3.77-3.91 (2H, m, CH2O) and 4.00-4.10 (2H, m, 5-H, 2-H); δC (67.8 MHz; CDC13) 10.7 (CH2I), 22.9 (CH3), 26.3 (CH2), 27.4 (CH2), 33.0 (CH2), 34.6 (CH2), 68.4 (CH2O), 79.0 (CHO, C-2), 84.1 (quat., C-2') and 85.6 (CHO, C-5); m/z 297 (M + H, 1%), 211 (3), 111 (1), 85 (C5H9O, 100), 55 (9) and 43 (39).

(2R*, 5S*, 2'S*)-2-(Iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 339b [cis] as a colourless oil (22 mg, 13%) (Found: M + H, 297.0358. C10H18O2I requires M
Procedure B

To a solution of (1S*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-1-(2", 6"-dichlorobenzoyloxy)-4-pentene (40 mg, 0.12 mmol) in dry acetonitrile (1 ml) at 0°C was added iodine (154 mg, 0.61 mmol). After 10 min. the reaction was extracted with diethyl ether (5 ml) and washed with 10% aqueous sodium sulphite (4 ml). The aqueous layer was extracted with diethyl ether (4×5 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, afforded an inseparable mixture of (2R*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 339a (2 mg, 6%) and (2S*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran (21 mg, 59%) 339b.
(2S*, 5R*, 2'S*)-2-Methyl-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 341a

To a solution of (2R*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 331a (677 mg, 2.29 mmol) in dry toluene (70 ml) under nitrogen were added tributyltin hydride (0.615 ml, 2.29 mmol) and a catalytic quantity (~10 mg) of azobisisobutyronitrile. After stirring for 2 h, the toluene was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (20:1) as eluant to afford (2S*, 5R*, 2'S*)-2-methyl-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 341a as a colourless oil (330 mg, 85%) (Found: (Cl, NH₃) M+H, 171.13±0.90. ClOH₁₉O₂ requires M+H, 171.13±85.); \( \nu_{\text{max}}/\text{cm}^{-1} \) (f Ilm) 2965, 2864 (vs, C-H), 1454 (s, C-H), 1373 (s, C-H), 1194 (m, C-O-C) and 1086 (vs, C-O-C); \( \delta_H \) (270 MHz; CDCl₃) 1.15 (3H, s, 2'-Me), 1.23 (3H, d, \( J_{2-Me;1} 5.9 \), 2-Me), 1.42-1.73 (3H, m, CH₂), 1.86-2.05 (5H, m, CH₂), 3.86 (2H, t, \( J_{5',4'} 6.4 \), CH₂O), 3.99 (1H, dd, \( J_{5;4} 8.8 \), \( J_{5,4A} 6.2 \), 5-H) and 4.10 (1H, qt, \( J_{2,2-Me} 5.9 \), \( J_{2,3} 8.8 \), 2-H); \( \delta_C \) (67.8 MHz; CDCl₃) 21.1 (CH₃, 2-Me), 22.6 (CH₃, 2'-Me), 26.0 (CH₂), 28.1 (CH₂), 33.3 (CH₂), 34.2 (CH₂), 67.9 (CH₂O), 75.9 (CHO, C-2), 83.8 (CHO, C-5) and 84.5 (quat., C-2'); m/z 171 (M + H, 1%), 155 (M - CH₃, 18), 131 (9), 111(7), 105 (7), 91 (4), 85 (CsH₉O, 100), 66 (4) and 55 (3).

(2R*, 5R*, 2'S*)-2-Methyl-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 341b

To a solution of (2S*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 334b (55 mg, 0.19 mmol) in dry toluene (10 ml) under nitrogen were added tributyltin hydride (50 \( \mu \)l, 0.19 mmol) and a catalytic quantity (~3 mg) of
azoisobutyronitrile. After stirring for 2 h, the toluene was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (20:1) as eluant, to afford (2S*, 5R*, 2'S*)-2-(methyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 341b as a colourless oil (26.6 mg, 82%) (Found: M + H, 171.1385. C₁₀H₁₉O₂ requires M + H, 171.1385); νₘₐₓ/cm⁻¹ (film) 2967, 2865 (s, C-H), 1454 (s, C-H), 1371(s, CH₃), 1194 (m, C-O-C) and 1086 (vs, C-O-C); δₜₜ (270 MHz; CDCl₃) 1.15 (3H, s, 2'-Me), 1.23 (3H, d, J₂-Me 6.2, 2-Me), 1.31-1.73 (4H, m, CH₂), 1.87-2.01 (4H, m, CH₂), 3.85 (2H, t, J₃',₄' 6.4, CH₂O), 3.80-3.85 (IH , m, 5-H) and 4.10 (1H, qd, J₂₂-Me 6.2 J₂₃₅ 1.5, 2-H); δC (67.8 MHz; CDCl₃) 21.0 (CH₃, 2-Me), 22.7 (CH₃, 2'-Me), 26.3 (CH₂), 27.4 (CH₂), 33.1 (CH₂), 33.5 (CH₂), 68.1 (CH₂O), 75.5 (CH, C-2), 84.0 (quat., C-2') and 84.5 (CH, C-5); m/z 171 (M + H, 9%), 85 (C₅H₉O, 100), 66 (26) and 43 (16).

(5R*, 2'S*)-5-(2'-Methyltetrahydrofur-2'-yl)-5-hydroxypentan-2-one 344

![Chemical structure](image)

To a solution of (2R*, 5R*, 2'S*)-2-iodomethyl-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 331a (118 mg, 0.398 mmol) in acetone (2 ml) and distilled water (2 drops) was added silver carbonate (110 mg, 0.399 mmol). The reaction was heated under reflux for 8 h., during which time additional amounts of silver carbonate (2 × 50 mg) were added. The reaction mixture was filtered, washed with ethyl acetate (10 ml), and dried over magnesium sulphate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (1:1) as eluant, to afford:

the title compound 344 as a colourless oil (18 mg, 24%) (Found: (acetate derivative) M + H 229.1431. C₁₂H₂₁O₄ requires M + H, 229.1440.; νₘₐₓ/cm⁻¹ (film) 3402 (br, s, OH), 2971, 2872 (s, C-H), 1713 (s, C=O), 1453 (m, C-H) and 1044 (C-O); δH (270 MHz; CDCl₃) 1.14 (3H, s, 2'-Me), 1.48-2.04 (6H, m, CH₂), 2.17 (3H, s, CH₃CO), 2.52-2.82 (2H, m, CH₂CO), 2.66 (1H, s, OH), 3.48 (1H, dd, J₅₄₆ 11.0 J₅₄₆ 2.0, CHOH) and 3.78-3.97 (2H, m, CH₂O); δC (67.8 MHz; CDCl₃) 22.9 (CH₃, 2'-Me), 25.5 (CH₂), 26.2 (CH₂), 30.1 (CH₃, C-1), 30.7 (CH₂), 40.9 (CH₂C=O), 67.9
(CH₂O), 75.9 (CHOH), 85.3 (quat., C-2') and 209.4 (C=O); m/z 187 (M + H, 3%), 169 (M - OH, 100), 136 (11), 111 (32) and 85 (C₅H₉O) and recovered (2R*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 331a (42 mg, 36%)

(5R*, 2'S*)-5-(2'-Methyltetrahydrofur-2'-yl)-5-acetoxypentan-2-one

To a solution of (5R*, 2'S*)-5-(2'-methyltetrahydrofur-2'-yl)-5-hydroxypentan-2-one 344 (20 mg, 0.11 mmol) in dry dichloromethane (2 ml) under nitrogen were added triethylamine (20 µl, 0.14 mmol), acetic anhydride (11 µl, 0.12 mmol) and a catalytic quantity of 4-dimethylaminopyridine (~0.5 mg). After stirring for 24 h. the solvent was removed under reduced pressure and purified by flash chromatography, using hexane/ethyl acetate as eluant (9:1), to afford the title compound as a colourless oil (22.7%, 91%) (Found: M + H, 229.1431. C₁₂H₂₁O₄ requires M + H, 229.1440); v_max/cm⁻¹ (film) 2972, 2868 (s, C-H), 1749 (s, C=O), 1720 (s, C=O), 1454 (m, C-H), 1380 (s, C-H) and 1248 (s, C-O-C); δH (270 MHz; CDCl₃) 1.18 (3H, s, 2'-Me), 1.58-2.10 (6H, m, CH₂), 2.08 (3H, s, CH₃COO), 2.13 (3H, s, CH₃CO), 2.43-2.48 (2H, m, CH₂CO), 3.75-3.90 (2H, m, CH₂O) and 4.86 (1H, dd, J₅₄A 10.4 J₅₄B 2.8, CHOAc); δC (67.8 MHz; CDCl₃) 21.1 (CH₃, Ac), 22.6 (CH₃, C-2'), 23.8 (CH₂, C-4), 25.9 (CH₂), 30.0 (CH₃, C-1), 34.4 (CH₂), 40.1 (CH₂C=O), 68.4 (CH₂O), 77.1 (CHOAc), 83.5 (quat., C-2'), 171.0 (C=O, Ac) and 208.0 (C=O, C-2); m/z 229 (M + H, 8%), 169 (M - OCOCH₃), 111 (27), 85 (C₅H₉O, 100) and 43 (90).
(2R*, 5R*, 2'S*)-2-(Hydroxymethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 343a

To a stirred solution of (2R*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 331a (414 mg, 1.40 mmol) in dry tetrahydrofuran (25 ml) and dimethyl sulphoxide (1 ml) were added 18-crown-6 (370 mg, 1.40 mmol) and potassium superoxide (497 mg, 6.99 mmol). After 2.5 h. the reaction was quenched with distilled water (7 ml) and extracted with diethyl ether (4 x 60 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography, using a hexane/ethyl acetate eluant (2:1), afforded:

(2R*, 5R*, 2'S*)-2-(hydroxymethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 343a as a white crystalline solid (60.4 mg, 23%) m.p. 109-110°C (ethyl acetate) (Found: M + H, 187.1336. C_{10}H_{19}O_{3} requires M + H, 187.1334.);  \nu_{\text{max}}/\text{cm}^{-1} \text{ (film)} 3434 (s, OH), 2971, 2871 (s, C-H), 1451 (m, C-H) and 1047 (s, C-O);  \delta_{\text{H}} (270 MHz; \text{CDCl}_3) 1.15 (3H, s, CH₃), 1.57-2.05 (8H, m, CH₂), 2.13 (1H, s, OH), 3.50 (1H, dd, \text{J}_{\text{HA,HB}} 11.7, \text{J}_{\text{HA,2}} 5.9, \text{CHAHBOH}), 3.69 (1H, dd, \text{J}_{\text{HB,HA}} 11.7, \text{J}_{\text{HB,2}} 2.9, \text{CHAHBOH}), 3.86 (2H, t, J₅',₄' 6.6, CH₂O), 3.98 (1H, dd, J₅,₄A 8.8 J₅,₄B 6.2, 5-H) and 4.07-4.16 (1H, m, 2-H); \delta_{\text{C}} (67.8 MHz; \text{CDCl}_3) 23.0 (CH₃), 26.2 (CH₂), 27.7 (CH₂), 28.3 (CH₂), 33.0 (CH₂), 64.8 (CH₂O), 68.1 (CH₂O), 80.3 (CHO, C-2) and 84.7 (CHO and quat., C-5 and C-2'); \text{m/z} 187 (M + H, 2%), 169 (M - OH, 18), 155 (M - CH₂O, 2), 111 (11), 85 (C₅H₉O, 100) and 43 (49); and (5R*, 2'S*)-5-(2'-methyltetrahydrofur-2'-yl)-5-hydroxypentan-2-one 344 as a colourless oil (118 mg, 45%).
Dibutyl (+)-tartrate 369\textsuperscript{144}

\[
\begin{align*}
\text{OH} & \quad \text{OH} \quad \text{CO}_2\text{H} \\
\text{Ho}_2\text{C} & \quad \text{H} \\
\text{H} & \quad \text{1-butanol} \quad \text{Zerolit 225/H}^+ \\
\text{OH} & \quad \text{OH} \quad \text{CO}_2\text{Bu} \\
\text{BuO}_2\text{C} & \quad \text{H}
\end{align*}
\]

A mixture of (+)-tartaric acid (75 g, 0.50 mol), Zerolit 225/H\textsuperscript{+} resin (15 g) and 1-butanol (135 ml, 1.48 mol) in AR benzene (150 ml) was heated under reflux for 8 h, in a 500 ml flask equipped with an overhead stirrer and Dean and Stark apparatus. The organic layer was decanted off and the resin was washed with hot benzene (2 \times 30 ml). The combined organic layer was then washed with saturated aqueous sodium bicarbonate (3 \times 70 ml) and distilled water (70 ml) then dried over magnesium sulphate. The benzene was then removed under reduced pressure and the residual oil was distilled under reduced pressure to afford dibutyl tartrate 369 as a colourless solid (89 g, 68\%), b.p. 135\textdegree C/0.3 mm Hg (lit.\textsuperscript{144}, b.p. 150\textdegree C/1.5 mm Hg).

Butyl glyoxylate 367\textsuperscript{143}

\[
\begin{align*}
\text{OH} & \quad \text{OH} \quad \text{CO}_2\text{Bu} \\
\text{BuO}_2\text{C} & \quad \text{H} \\
\text{H} & \quad \text{NaIO}_4 \quad \text{H}_2\text{O} \\
\text{O} & \quad 2 \text{BuO}_2\text{CC}-\text{H}
\end{align*}
\]

Dibutyl (+)-tartrate 369 (4.33 g, 16.5 mmol) was stirred vigorously with a 0.486 mol/L sodium periodate solution (34 ml, 16.5 mmol) for 40 h. After filtration to remove the white precipitate which had formed, the filtrate was extracted with diethyl ether (3 \times 30 ml) and the combined organic layers were dried over magnesium sulphate. The solvent was removed under reduced pressure to afford a pale pink liquid which was distilled under reduced pressure from phosphorus pentoxide to afford butyl glyoxylate 367 as a colourless oil (2.18 g, 50.4\%), b.p. 68-69\textdegree C/5 mm Hg (lit.\textsuperscript{144}, b.p. 66-69\textdegree C/5 mm Hg).
Diisoproxytitanium(IV) dichloride 362

\[
\text{TiCl}_4 + \text{Ti(PrO)}_4 \rightarrow 2\text{Ti(PrO)}_2\text{Cl}_2
\]

To a solution of titanium(IV) isopropoxide (2.98 mL, 10 mmol) in hexane (10 mL) was added titanium(IV) chloride (1.10 mL, 10 mmol) slowly at room temperature. After stirring for 10 min. the reaction was allowed to stand for 6 h. at room temperature. The precipitate was then collected, washed with hexane (2 x 5 mL) and dried under high vacuum for 12 h. to give diisoproxytitanium(IV) dichloride 362 as a white solid (958 mg, 20%).

Butyl (E)-4-ethyl-2-hydroxy-4-hexenoate 370

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 + \text{CO}_2\text{Bu} + \text{Ti(PrO)}_2\text{Cl}_2 + \text{binaphthol} \rightarrow \text{C}_12\text{H}_{22}\text{O}_3
\]

To a suspension of activated powdered 4A molecular sieves (6.0 g) in dry dichloromethane (60 mL) were added diisoproxytitanium(IV) dichloride 362 (264 mg, 1.11 mmol) and (±)-1,1'-bi-2-naphthol 363 (318 mg, 1.11 mmol) at room temperature under a nitrogen atmosphere. After stirring for 1 h. at room temperature the mixture was cooled to -70°C. To the mixture was added 2-ethyl-1-butene 364 (2.96 g, 35.2 mmol) followed by freshly distilled butyl glyoxylate 367 (2.29 g, 17.6 mmol). The reaction mixture was then allowed to warm to room temperature and stirred for 24 h. The molecular sieves were removed by filtering the reaction mixture through a plug of celite and the resulting deep red solution was poured into a saturated aqueous solution of sodium bicarbonate (120 mL), stirred for 5 min., then extracted with ethyl acetate (3 x 60 mL). The combined organic layer was dried over magnesium sulphate then reduced to an orange oil. Purification of the oil by flash chromatography, using hexane/ethyl acetate (9:1) as eluant, afforded butyl (E)-4-ethyl-2-hydroxy-4-hexenoate 370 as an oil and as a 5:1 mixture of E/Z isomers (2.16 g, 57%) (Found: M+, 214.1570. C12H22O3 requires M, 214.1569.); \(\nu_{\text{max}}/\text{cm}^{-1}\) (film) 3485 (br, s, OH) 2878, 2937, 2969 (s, C-H) and 1739 (s, C=O); \(\delta_H\) (270 MHz; CDCl3) 0.92-1.02 (6H, m, 2 x CH3), 1.35-1.44 (2H, m, CH2), 1.59-1.67 (2H, m, CH2), 1.62 (3H, d, \(J_{6,5} 6.7\), CH3C=), 2.04-2.11 (2H, m,
CH₂, 2.28 (1H, dd, J₃A,3B 14.2 and J₃A,2 8.4, CH₃H₂BCHOH), 2.53 (1H, dd, J₃B,3A 14.2 and J₃B,2 4.5, CH₃H₂BCHOH), 2.84 (1H, m, OH), 4.17 (2H, t, J₁⁻,₂⁻ 6.7, CO₂CH₂), 4.25 (1H, m, CH₃OH) and 5.31 (1H, q, J₅,₆ 6.7, =CH); δC (67.8 MHz; CDCl₃) 12.7 (CH₃, C-2'), 13.2 (CH₃, C-6), 13.7 (CH₃, C-4'), 19.1 (CH₂, C-3''), 22.6 (CH₂, C-1'), 30.6 (CH₂, C-2''), 41.7 (CH₂, C-3), 65.3 (CH₂, C-1''), 69.4 (CHO), 122.5 (=CH), 136.9 (quat., C-4) and 175.0 (C=O, C-1); m/z 214 (M⁺, 3%), 196 (M - H₂O, 33), 140 (M - C₆H₉O, 59), 95 (C₆H₁₁, 64), 83 (C₆H₁₁, 63) and 55 (100).

The Z isomer gave an additional ¹H NMR resonance at δ 5.43 (1/5H, q, J₅,₆ 6.7, =CH).

(E)-4-Penten-1,2-diol 374

To a solution of butyl (E)-4-ethyl-2-hydroxy-4-hexenoate 370 (1.68 g, 7.84 mmol) in dry diethyl ether (80 ml) was added lithium aluminium hydride (167 mg, 4.40 mmol). After stirring for 1 h. the reaction was quenched carefully with 3M hydrochloric acid until residual lithium/aluminium salts formed solid clumps. These were then washed with diethyl ether (3 × 20 ml) and the ether was decanted off. Additional 3M hydrochloric acid (20 ml) was added to the solid and the resulting aqueous solution was extracted with diethyl ether (3 × 30 ml). The combined organic layers were dried over magnesium sulphate. The solvent was removed under reduced pressure and the resultant oil was purified by flash chromatography, using hexane/ethyl acetate (1:1) as eluant, to afford (E)-4-penten-1,2-diol 374 (1.06 g, 94%) as a colourless oil; (Found: M⁺, 114.1151. C₈H₁₆O₂ requires M⁺, 144.1150.); νmax/cm⁻¹ (film) 3384 (br, vs, OH), 2965, 2934, 2875 (m, CH₂), 1031 (s, C-O primary) and 1067 (s, C-O secondary); δH (270 MHz; CDCl₃) 0.98 (3H, t, J₂',₁' 7.5, CH₂CH₃), 1.63 (3H, d, J₆,₅ 6.6, CH₃C=), 1.95-2.24 (4H, m, CH₂), 2.37 (1H, s, OH), 2.52 (1H, s, OH), 3.46 (1H, dd, J₁A,₁B 11.0, J₁A,₂ 6.8, CH₃H₂BBOH), 3.67 (1H, dd, J₁B,₁A 11.0, J₁B,₂ 2.9, CH₃H₂BBOH), 3.75-3.83 (1H, m, CH₃OH) and 5.30 (1H, q, J₅,₆ 6.6, =CH); δC (67.8 MHz; CDCl₃) 12.6 (CH₃, C-2'), 13.0 (CH₃, C-6), 22.6 (CH₂, C-1'), 40.4 (CH₂, C-3), 66.4 (CH₂O), 69.9 (CHO), 121.8 (=CH) and 137.7 (quat., C-4); m/z 144 (M⁺, 3%), 126 (M - H₂O, 10), 113 (M - H₂O, 10).
To a solution of (E)-4-penten-1,2-diol 374 (1.06 g, 7.35 mmol) in dry dichloromethane (70 ml) at 0°C under argon was added sodium carbonate (1.63 g, 15.4 mmol) followed by lead tetraacetate (3.91 g, 8.82 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. then filtered and washed with additional dry dichloromethane (3 × 30 ml). The solvent was removed under reduced pressure to afford a pungent pale yellow oil. This oil was dissolved in dry diethyl ether (75 ml) and lithium aluminium hydride (78 mg, 2.06 mmol) was carefully added with stirring. After stirring for 1 h. the reaction was quenched by the slow addition of 3M hydrochloric acid (5 ml) until residual lithium/aluminium salts formed solid clumps. These were then washed with diethyl ether (2 × 30 ml) and the ether was decanted off. Additional 3M hydrochloric acid (15 ml) was added to the solid and the resulting aqueous solution was extracted with diethyl ether (2 × 30 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to give a yellow oil which was purified by flash chromatography, using hexane/ethyl acetate (4:1) as eluant, to afford (E)-3-ethyl-3-penten-1-ol 373 as a yellow oil (530 mg, 63%) (Found: M⁺, 114.1043. C₇H₁₄O requires M, 114.1045; νmax/cm⁻¹ (film) 3342, 3325 (br, s, OH), 3017 (m, =CH), 2955, 2924, 2867 (s, C-H), 1041 (s, CH₂-OH) and 824 (m, =C-H); δH (270 MHz; CDCl₃) 0.98 (3H, t, J2',1' 7.7, CH₃), 1.62 (3H, d, J5,4 6.6, CH₃C=), 2.05 (2H, q, J1',2' 7.7, CH₂CH₃), 2.26 (2H, t, J2,1 6.2, 2-CH₂), 3.65 (2H, t, J1,2 6.2, CH₂OH) and 5.29 (1H, q, J4,5 6.6, =CH); δC (67.8 MHz; CDCl₃) 12.5 (CH₃, C-2'), 12.8 (CH₃, C-5), 22.4 (CH₂, C-1'), 39.4 (CH₂, C-2), 60.4 (CH₂O), 120.6 (=CH, C-4) and 137.9 (quat., C-3); m/z 114 (M⁺, 29%), 96 (M - H₂O, 15), 81 (M - CH₅O, 53), 67 (45), 55 (100), 41 (45) and 29 (C₂H₅, 14).
(E)-1-Bromo-3-ethyl-3-pentene 146

To a stirred solution of (E)-3-ethyl-3-penten-1-ol 373 (200 mg, 1.75 mmol) in dry dichloromethane (10 ml) under argon was added triethylamine (0.37 ml, 2.65 mmol). The reaction mixture was then cooled to -25°C and methanesulphonyl chloride (0.15 ml, 1.94 mmol) was added. After stirring for 30 min. the reaction mixture was quenched with distilled water (5 ml). The aqueous layer was then extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to afford a yellow oil. The oil was dissolved in dry acetone (5 ml) and heated under reflux with lithium bromide (456 mg, 5.25 mmol) for 5 h. Distilled water (2 ml) was added and the reaction mixture was extracted with dichloromethane (4 × 10 ml). The combined organic layers were dried over magnesium sulphate, the solvent evaporated under reduced pressure, and the resulting oil was purified by column chromatography, using hexane/ethyl acetate (20:1) as eluant, to afford (E)-1-bromo-3-ethyl-3-pentene 146 as a colourless oil (220 mg, 71%) (Found: M⁺, 176.0203, 178.0181. C₇H₁₅Br, C₇H₁₅Br require M, 176.0201, 178.0180.); v_max/cm⁻¹ (film) 2956, 2922, 2863 (s, C-H), 1736 (m, C=C), 1455 (m, C-H), 828 (m, =CH) and 567 (m, C-Br); δ_H (270 MHz; CDCl₃) 0.97 (3H, t, J₂',₁' 7.3, CH₃CH₂), 1.60 (3H, d, J₅,₄ 6.8, CH₃C=), 2.03 (2H, q, J₁',₂' 7.3 , CH₂CH₃), 2.54 (2H, t, J₂,₁ 7.7, CH₂), 3.41 (2H, t, J₁,₂ 7.7, CH₂Br) and 5.27 (1H, q, J₄,₅ 6.8); δ_C (67.8 MHz; CDCl₃) 12.8 (CH₃, C-2'), 13.0 (CH₃, C-5), 22.5 (CH₂, C-1'), 31.9 (CH₂, C-1), 40.2 (CH₂, C-2), 121.3 (CH, C-4) and 138.7 (quat., C-3); m/z 178 (M⁺, 20%), 176 (M⁺, 20), 97 (M - Br, 44), 69 (27), 55 (100) and 21 (32).

(E) and (Z)-3-ethyl-3-pentan-1-ol 373

(E)- and (Z)-3-ethyl-3-pentan-1-ol 373
A solution of 2-ethyl-1-butene 364 (8.0 g, 95.1 mmol) and paraformaldehyde (1.38 g, 46.0 mmol) in dry dichloromethane (70 ml) was stirred for 20 min. Tin(IV) tetrachloride (62 µl, 0.38 mmol) was added and the reaction mixture was stirred for 16 h. at room temperature. The reaction mixture was quenched with 2M aqueous sodium hydroxide solution (20 ml) and after stirring for 5 min. the aqueous layer was separated and extracted with diethyl ether (3 x 25 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure. Purification of the residual oil by flash chromatography, using hexane/ethyl acetate (20:1) as eluant, afforded a (4:3) mixture of (E)- and (Z)-3-ethyl-3-penten-1-ol 373 (2.87 g, 55%); $\nu_{\text{max}}$/cm$^{-1}$ (film) 3342, 3325 (s, OH), 3017 (m, =CH), 2955, 2924, 2867 (s, C-H), 1041 (s, CH$_2$-OH) and 824 (m, =C-H); $\delta_H$ (270 MHz, CDCl$_3$) (E)-isomer 0.99 (3H, t, $J_{2',1'}$ 7.5, CH$_3$), 1.61 (3H, d, $J_{5,4}$ 6.6, CH$_3$C=), 2.05 (2H, q, $J_{1',2'}$ 7.5, CH$_2$CH$_3$), 2.25 (2H, t, $J_{2,1}$ 6.6, CH$_2$CH$_2$OH), 3.63 (2H, t, $J_{1,2}$ 6.6, CH$_2$OH) and 5.26 (1H, q, $J_{4,5}$ 6.6, =CH) (Z)-isomer 0.97 (3H, t, $J_{2',1'}$ 7.5, CH$_3$), 1.63 (3H, d, $J_{5,4}$ 6.6, CH$_3$C=), 2.02 (2H, q, $J_{1',2'}$ 7.5, CH$_2$CH$_3$), 2.34 (2H, t, $J_{2,1}$ 7.1, CH$_2$CH$_2$OH), 3.61 (2H, t, $J_{1,2}$ 7.1, CH$_2$OH) and 5.35 (1H, q, $J_{4,5}$ 6.6, =CH); $\delta_C$ (67.8 MHz; CDCl$_3$) (E)-isomer 12.5 (CH$_3$, C-2'), 12.8 (CH$_3$, C-5), 22.4 (CH$_2$, C-1'), 39.4 (CH$_2$, C-2), 60.4 (CH$_2$O, C-1), 120.6 (=CH, C-4) and 137.9 (quat., C-3) (Z)-isomer 12.5 (CH$_3$, C-2'), 12.8 (CH$_3$, C-5), 29.6 (CH$_2$, C-1'), 33.1 (CH$_2$, C-2), 60.3 (CH$_2$O, C-1), 119.7 (=CH, C-4) and 137.5 (quat., C-3); $m/z$ 114 (M$^+$, 29%), 96 (M - H$_2$O, 15), 81 (M - CH$_2$O, 53), 67 (45), 55 (100), 41 (45) and 29 (C$_2$H$_5$, 14).

(E)- and (Z)-1-Bromo-3-ethyl-3-pentene 146

![Chemical structure](image)

Using the procedure described above for preparation of (E)-1-bromo-3-ethyl-3-pentene a (4:3) mixture of (E)- and (Z)-1-bromo-3-ethyl-3-pentene 146 (3.04 g, 76%) was prepared from a (4:3) mixture of (E)- and (Z)-3-ethyl-3-penten-1-ol 373; $\nu_{\text{max}}$/cm$^{-1}$ (film) 2956, 2922, 2863 (s, C-H), 1736 (m, C=C), 1455 (m, C-H), 828 (m, =CH) and 567 (m, C-Br); $\delta_H$ (270 MHz; CDCl$_3$) (Z)-isomer 1.00 (3H, t, $J_{2',1'}$ 7.3 , CH$_3$CH$_2$), 1.62 (3H, d, $J_{5,4}$ 6.8, CH$_3$C=), 2.06 (2H, q, $J_{1',2'}$ 7.3, CH$_2$CH$_3$), 2.62 (2H, t, $J_{2,1}$ 8.1, CH$_2$), 3.37 (2H, t, $J_{1,2}$ 8.1, CH$_2$Br) and 5.36 (1H, q, $J_{4,5}$ 6.8); $\delta_C$ (67.8 MHz;
CDCl₃ (Z)-isomer 12.8 (CH₃, C-2'), 13.3 (CH₃,C-5), 29.4 (CH₂, C-1'), 30.8 (CH₂, C-1), 33.9 (CH₂, C-2), 120.7 (CH, C-4) and 138.5 (quat., C-3); m/z 178 (M⁺, 20%), 176 (M⁺, 20), 97 (M - Br, 44), 69 (27), 55 (100) and 21 (32).

(E)- and (Z)-1-Chloro-3-ethyl-3-pentene 380

To a solution of a (4:3) mixture of (E)- and (Z)-ethyl-3-penten-1-ol 373 (1.64 g, 14.4 mmol) in dry dichloromethane (60 ml) under argon was added triethylamine (3.00 ml, 21.5 mmol). The reaction mixture was then cooled to -25°C and methanesulphonyl chloride (1.22 ml, 15.8 mmol) was added. After stirring for 45 min. the reaction mixture was quenched with distilled water (30 ml) and the aqueous layer was extracted with dichloromethane (3 × 40 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to afford a yellow oil. The oil was dissolved in dry N,N-dimethylformamide (10 ml) and heated at 80°C with lithium chloride (2.35 g, 55.4 mmol) for 1.5 h. Distilled water (10 ml) was added and the reaction mixture was extracted with diethyl ether (5 × 30 ml). The combined organic layers were dried over magnesium sulphate, the solvent evaporated and the resulting oil was purified by column chromatography, using hexane/ethyl acetate (20:1) as eluant, to afford a (4:3) mixture of (E)- and (Z)-1-chloro-3-ethyl-3-pentene 380 as a colourless oil (1.19 g, 62%) (Found: M⁺, 132.0706, 134.0673, C₇H₁₃Cl₃5, C₇H₁₃Cl₃7 require M, 132.0706, 134.0676.); νmax/cm⁻¹ (film) 2967, 2925, 2866 (s, C-H), 1457 (s, C-H), 831 (m, =CH) and 720 (s, C-Cl); δH (270 MHz; CDCl₃) (E)-isomer 0.97 (3H, t, J2',1' 7.5, CH₃CH₂), 1.60 (3H, d, J₅,₄ 6.8, CH₃C=), 2.04 (2H, q, J₁',₂' 7.5, CH₂CH₃), 2.44 (2H, t, J₂,₁ 7.7, CH₂), 3.55 (2H, t, J₁₂,₁ 7.7, CH₂Cl) and 5.27 (1H, q, J₄,₅ 6.8) (Z)-isomer 1.00 (3H, t, J₂',₁' 7.5, CH₃CH₂), 1.63 (3H, d, J₅,₄ 6.8, CH₃C=), 2.06 (2H, q, J₁',₂' 7.5, CH₂CH₃), 2.53 (2H, t, J₂,₁ 7.7, CH₂), 3.51 (2H, t, J₁₂,₁ 7.7, CH₂Cl) and 5.36 (1H, q, J₄,₅ 6.8); δC (67.8 MHz; CDCl₃) (E)-isomer 12.8 (CH₃, C-2'), 13.0 (CH₃, C-5), 22.6 (CH₂, C-1'), 39.9 (CH₂, C-2), 43.5 (CH₂, C-1), 121.3 (CH, C-4) and 137.9 (quat., C-3); (Z)-isomer 12.7 (CH₃, C-2'), 13.3 (CH₃,C-5), 29.6 (CH₂, C-1'), 33.6 (CH₂, C-2), 42.7 (CH₂, C-1), 120.8 (CH, C-4) and 137.6 (quat., C-3); m/z 134 (M⁺, 10%), 132 (M⁺, 30), 97 (M - Cl, 10), 69 (35), 55 (100) and 41 (42).
To a solution of a (4:3) mixture of (E)- and (Z)-ethyl-3-penten-1-ol 373 (435 mg, 3.81 mmol) in dry dichloromethane (20 ml) under argon was added triethylamine (0.81 ml, 5.8 mmol). The reaction mixture was then cooled to -25°C and methanesulphonyl chloride (0.32 ml, 4.1 mmol) was added. After stirring for 30 min. the reaction mixture was quenched with distilled water (10 ml) and the aqueous layer was extracted with dichloromethane (3 x 30 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to afford a yellow oil. The oil was dissolved in dry acetone (20 ml) and heated under reflux with sodium iodide (1.86 g, 12.4 mmol) for 5 h., over which time additional sodium iodide (2 x 200 mg) was added. The reaction mixture was filtered, and the solid was washed with hot acetone (20 ml). 10% Aqueous sodium thiosulphate (25 ml) was added to the filtrate and the resultant mixture was extracted with dichloromethane (4 x 30 ml). The combined organic layer was dried over magnesium sulphate and the solvent was removed under reduced pressure. The resulting oil was purified by column chromatography, using hexane/ethyl acetate (20:1) as eluant, to afford a (4:3) mixture of (E)- and (Z)-1-iodo-3-ethyl-3-pentene 381 as a colourless oil (605 mg, 71%) (Found: M⁺, 224.0058. C₇H₁₃I requires M⁺, 224.0062); \( \nu_{\text{max}}/\text{cm}^{-1} \) (film) 2956, 2921, 2864 (s, C-H), 1457 (s, C-H) and 827 (m, =CH); \( \delta_H \) (270 MHz; CDCl₃) (E)-isomer 0.96 (3H, t, J₂,₁ 7.7, CH₃CH₂), 1.59 (3H, d, J₅,₄ 6.8, CH₃C=), 2.02 (2H, q, J₁₂,₂ 7.7, CH₂CH₃), 2.55 (2H, t, J₂₁ 7.9, CH₂), 3.19 (2H, t, J₁₁,₂ 7.9, CH₂), and 5.25 (1H, q, J₄,₅ 6.8) (Z)-isomer 0.99 (3H, t, J₂,₁ 7.5, CH₃CH₂), 1.59 (3H, d, J₅,₄ 6.8, CH₃C=), 2.04 (2H, q, J₁₂,₂ 7.5, CH₂CH₃), 2.64 (2H, t, J₂₁ 8.2, CH₂), 3.14 (2H, t, J₁₁,₂ 8.2, CH₂), and 5.36 (1H, q, J₄,₅ 6.8); \( \delta_C \) (67.8 MHz; CDCl₃) (E)-isomer 5.0 (CH₂, C-1'), 12.8 (CH₃, C-2), 13.0 (CH₃, C-5), 22.2 (CH₂, C-1'), 41.2 (CH₂, C-2), 120.8 (CH, C-4) and 140.4 (quat., C-3); (Z)-isomer 3.2 (CH₂, C-1), 12.7 (CH₃, C-2'), 13.3 (CH₃, C-5), 29.0 (CH₂, C-1'), 34.8 (CH₂, C-2), 120.1 (CH, C-4) and 140.3 (quat., C-3); m/z 224 (M⁺, 15%), 97 (M - I, 100), 69 (7), 55 (41) and 41 (8).
(E)- and (Z)-1-Phenyl-4-ethyl-4-hexen-1-ol 382

To dry tetrahydrofuran (7.5 ml) cooled to -80°C under argon was added tert-butyllithium (2.0 ml of a 1.7 M solution in pentane, 3.4 mmol). After stirring for 5 min. 1-bromo-3-ethyl-3-pentene 146 (a 4:3 mixture of E:Z isomers) (300 mg, 1.70 mmol) was added followed by benzaldehyde (212 mg, 2.0 mmol) after a further 20 min. The reaction was then allowed to warm to -30°C over 40 min. Saturated aqueous ammonium chloride (5 ml) was added and after stirring for 5 min. the aqueous layer was extracted with diethyl ether (3 × 30 ml) and dichloromethane (2 × 30 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure. The residue was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford a (4:3) mixture of (E)- and (Z)-1-phenyl-4-ethyl-4-hexen-1-ol 382 (230 mg, 66%) (Found: M+, 204.15 12. C14 H20O requires M, 204.1514.).

$\nu_{\text{max}}$/cm$^{-1}$ (film) 3364 (br, s, OH), 3025 (m, =C-H), 2959, 2927, 2866 (s, C-H), 1451 (s, C-H) and 699 (vs, monosub. benzene, C-H); $\delta_{\text{H}}$ (270 MHz; CDCl$_3$) 0.90-0.98 (3H, m, CH$_2$CH$_3$), 1.53 (3/7 × 3H, d, J$_{6.5}$ 6.6, CH$_3$C=), 1.57 (4/7 × 3H, d, J$_{6.5}$ 6.6, CH$_3$C=), 1.72-2.15 (6H, m, 3 × CH$_2$), 2.26 (1H, br, s, OH), 4.59-4.64 (1H, m, CH$_2$OH), 5.15-5.24 (1H, m, 5-H) and 7.15-7.37 (5H, m, Ar-H); $\delta_{\text{C}}$ (67.8 MHz, CDCl$_3$) 12.7 (CH$_3$, C-2'), 12.9 (CH$_3$, C-6), 22.7 (CH$_2$), 26.1 (CH$_2$), 29.5 (CH$_2$), 32.8 (CH$_2$), 37.2 (CH$_2$), 37.3 (CH$_2$), 74.3, 74.5 (CH, C-1), 117.7, 118.3 (CH, C-5), 125.8, 127.4, 128.3 (CH, Ar), 141.1 and 144.7 (quat., C-4, Ar); $m/z$ 204 (M$^+$, 5%), 186 (M - H$_2$O, 12), 157 (48), 120 (100), 107 (53), 79 (40), 55 (22) and 41 (21).
(4E, 1R*, 2'S*)- and (4E, 1S*, 2'S*)-4-Ethyl-1-(2'-methyl-tetrahydrofur-2'-yl)-4-hexen-1-ol 348a, 348b

Procedure A

To magnesium filings (83 mg, 3.41 mol) covered with dry tetrahydrofuran (0.5 ml) under argon was added (E)-1-bromo-3-ethyl-3-pentene 146 (90 mg, 0.51 mmol). Heat was evolved and a solution of (E)-1-bromo-3-ethyl-3-pentene 146 (310 mg, 1.76 mmol) in tetrahydrofuran (5 ml) was added slowly over 5 min. After stirring for 20 min. a solution of 2-methyl-2-tetrahydrofuraldehyde 322 (258 mg, 2.26 mmol) in tetrahydrofuran (2 ml) was added slowly. After stirring for a further 20 min. the reaction was quenched with a saturated aqueous solution of ammonium chloride (5 ml) then extracted with diethyl ether (3 x 20 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to give an oily residue which was purified by column chromatography, using hexane/ethyl acetate (20:1) as eluant, to afford:

(4E, 1R*, 2'S*)- and (4E, 1S*, 2'S*)-4-Ethyl-1-(2'-methyltetrahydro-2'-furyl)-4-hexen-1-ol 348 as a colourless oil (54 mg, 12%) and (2E, 8E)-3,8-diethyl-2,8-pentadiene 377 as a colourless oil (51 mg, 23 %) (Found: (CI, NH3) M - H, 193.1957. C14H25 requires M - H, 193.1956.); \nu_{max}/cm^{-1} (film) 2957, 2923, 1862 (s, C-H), 1660 (m, C=C), 1458 (vs, C-H) and 822 (s, trisub. alkene); \delta_{H} (270 MHz; CDCl3) 0.94 (6H, t, J2',1' 7.3, CH3CH2), 1.27-1.40 (4H, m, 5-CH2, 6-CH2), 1.57 (6H, d, J1,2 7.0, CH3=), 1.94-2.06 (8H, m, 4-CH2, 7-CH2, 1'-CH2, 1''-CH2) and 5.16 (2H, q, J2,1 7.0, =CH); \delta_{C} (67.8 MHz, CDCl3) 12.8 (CH3, C-2', C-2''), 13.2 (CH3, C-1, C-10), 22.7
(CH₂, C-1', C-1''), 28.0 (CH₂, C-5, C-6), 36.6 (CH₂, C-4, C-7), 117.0 (CH₂, C-2, C-9) and 142.0 (quat., C-3, C-8); m/z 193 (M - H, 19%), 74 (100) and 58 (66).

**Procedure B**

To dry tetrahydrofuran (7 ml) at -90°C under argon was added tert-butyllithium (2.10 ml of a 1.7 M solution in pentane, 3.57 mmol). After stirring for 2 min. a solution of (E)-1-bromo-3-ethyl-3-pentene 146 (296 mg, 1.68 mmol) in dry tetrahydrofuran (0.2 ml) was added and the reaction mixture was stirred at -80°C for 10 min. Freshly prepared 2-methyl-2-tetrahydrofuraldehyde 322 (300 mg, 2.63 mmol) was then added and the reaction mixture was stirred for 2 h., allowing it to warm to -30°C. The reaction was quenched with saturated ammonium chloride (10 ml) and stirred for 16 h. Water (1 ml) was added and the reaction mixture was extracted with diethyl ether (3 × 20 ml) and dichloromethane (2 × 20 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to give a pale yellow residue which was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford an inseparable (3:1, ¹H NMR) mixture of the erythro and threo products as a colourless oil (189 mg, 53%).

Separation of the isomers was effected by formation of the acetates, which are separable by flash chromatography, followed by deprotection to afford pure erythro and threo products (*vide infra*).
(4E, 1R*, 2'S*)- and (4E, 1S*, 2'S*)-4-Ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-yl acetate 383a, 383b

To a solution of (4E, 1R*, 2'S*)- and (4E, 1S*, 2'S*)-4-ethyl-1-(2'-methyltetrahydro-2'-furyl)-4-hexen-1-ol 348 (117 mg, 0.551 mmol) in dry dichloromethane were added triethylamine (92 µl, 0.66 mmol), acetic anhydride (52 µl, 0.55 mmol) and a catalytic quantity of 4-dimethylaminopyridine (~5 mg). After 3 h, the solvent was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford:

(4E, 1R*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-yl acetate 383a [erythro] as a colourless oil (101 mg, 72%); \( \nu_{\text{max}}/\text{cm}^{-1} \) (film) 2961, 2865 (vs, C-H), 1739 (vs, C=O), 1452 (m, C-H), 1370 (s, C-H) and 1237 (vs, C-O-C); \( \delta_H \) (270 MHz; CDCl3) 0.94 (3H, t, J2",1" 7.7, CH2CH3), 1.17 (3H, s, 2'-Me), 1.57 (3H, d, J6,5 7.0, CH3-C=), 1.53-1.62 (2H, m, CH2), 1.69-1.75 (1H, m, CH2), 1.85-2.10 (7H, m, CH2), 2.07 (3H, s, CH3CO), 3.74-3.88 (2H, m, CH2O), 4.90 (1H, dd, J1,2A 10.4 J1,2B 2.4, CHOAc) and 5.18 (1H, q, J5,6 7.0, =CH); \( \delta_C \) (67.8 MHz; CDCl3) 12.7 (CH3, C-2"), 12.9 (CH3, C-6), 21.1 (CH3, Ac), 22.5 (CH3, 2'-Me), 25.9 (CH2), 28.3 (CH2), 29.4 (CH2), 33.0 (CH2), 34.4 (CH2), 68.3 (CH2O), 77.8 (CHOAc), 83.6 (quat., C-2"), 118.1 (=CH), 140.9 (quat., C-4) and 170.8 (C=O).

(4E, 1S*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-yl acetate 383b [threo] as a colourless oil (35.9 mg, 26%); \( \nu_{\text{max}}/\text{cm}^{-1} \) (film) 2961, 2865 (vs, C-H), 1739 (vs, C=O), 1451 (m, C-H), 1369 (s, C-H) and 1236 (vs, C-O-C); \( \delta_H \) (270 MHz; CDCl3) 0.94 (3H, t, J2",1" 7.7, CH2CH3), 1.19 (3H, s, 2'-Me), 1.57 (3H, d, J6,5 7.0, CH3-C=), 1.53-1.66 (2H, m, CH2), 1.71-2.21 (8H, m, CH2), 2.09 (3H, s, CH3CO), 3.75-3.90 (2H, m, CH2O), 4.88-4.93 (1H, m, CHOAc) and 5.19 (1H, q, J5,6 7.0,
\( (4E, 1R^*, 2'S^*) -4\text{-} \text{Ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-}
\text{hexen-1-ol [erythro]} 348a \)

[Diagram of the compound]

To a solution of \((4E, 1R^*, 2'S^*)-4\text{-} \text{ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-}
\text{hexen-1-yl acetate 383a (79.4 mg, 0.312 mmol)}\) in 95\% methanol (5 ml) was added
potassium carbonate (173 mg, 1.25 mmol). After stirring for 16 h., a saturated solution of
sodium chloride (5 ml) was added and extracted with dichloromethane \((4 \times 10 \text{ ml})\). The
combined organic layers were dried over magnesium sulphate and the solvent was
removed under reduced pressure to give a residue which was purified by flash
chromatography, using hexane/ethyl acetate \((30:1)\) as eluant, to afford the title compound
348a as a pale yellow oil \((55.2 \text{ mg, 83\%})\) (Found: \(M^+, 212.1776. \text{C}_{13}\text{H}_{24}\text{O}_2\) requires
\(M, 212.1776\).); \(\nu_{\text{max}}/\text{cm}^{-1} \) (film) 3451 (vs, OH), 2961, 2865 (vs, C-H), 1454 (s, C-H),
1372 (m, CH3), 1079 (s, C-O-C) and 459 (vs, C-O-C); \(\delta_C (67.8 \text{ MHz; CDCl}_3) 12.8 \text{ (CH}_3, \text{ C-2'\)}, \text{ 13.0 (CH}_3, \text{ C-6), 21.2 (CH}_3, \text{ Ac),}
22.3 (CH3, 2'-Me), 26.3 (CH2), 28.5 (CH2), 28.8 (CH2), 33.1 (CH2), 34.7 (CH2),
67.8 (CH2O), 77.6 (CHOAc), 83.7 (quat., C-2'), 118.3 (=CH), 140.9 (quat., C-4) and
170.9 (C=O).
(4E, 1S*, 2'S*)-4-Ethyl-1-(2'-methyltetrahydrofurfuryl)-4-hexen-1-ol [threo] 348b

![Chemical structure](image)

To a solution of (4E, 1S*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofurfuryl)-4-hexen-1-yl acetate 383b (118 mg 0.464 mmol) in 95% methanol (7 ml) was added potassium carbonate (257 mg, 1.86 mmol). After stirring for 16 h. a saturated solution of sodium chloride (5 ml) was added and extracted with dichloromethane (4 x 10 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to give a residue which was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford the title compound 348b as a pale yellow oil (80 mg, 82%) (Found: M+, 212.1776. C_{13}H_{24}O_{2} requires M, 212.1776.); ν_{max}/cm^{-1} (film) 3451 (vs, OH), 2961, 2865 (vs, C-H), 1454 (s, C-H), 1372 (m, CH_{3}), 1079 (s, C-O-C) and 459 (vs, C-O-C); δ_{H} (270 MHz; CDCl_{3}) 0.97 (3H, t, J_{2',1'} 7.5, CH_{2}CH_{3}), 1.14 (3H, s, 2'-Me), 1.38-1.47 (2H, m, CH_{2}), 1.59 (3H, d, J_{6,5} 6.6, CH_{3}-C=), 1.57-1.65 (1H, m, CH_{2}), 1.72-1.80 (1H, m, CH_{2}), 1.87-2.10 (5H, m, CH_{2}), 2.30-2.35 (1H, m, CH_{2}), 2.41 (1H, d, J_{1,OH} 2.6, OH), 3.35-3.41 (1H, m, CH_{2}OH), 3.79 (1H, t, J_{5'AH} 7.0, 5'-HA) 3.86-3.91 (1H, m, 5'-HB) and 5.24 (1H, q, J_{5,6} 6.6, =CH); δ_{C} (67.8 MHz; CDCl_{3}) 12.8 (CH_{3}, C-2'), 13.0 (CH_{3}, C-6), 20.2 (CH_{3}, 2'-Me), 22.8 (CH_{2}), 26.5 (CH_{2}), 30.5 (CH_{2}), 33.7 (CH_{2}), 34.6 (CH_{2}), 67.5 (CH_{2}O, C-5'), 76.5 (CHO, C-1), 85.4 (quat., C-2'), 118.0 (CH, C-5) and 141.6 (quat., C-4); m/z 212 (M^{+}, 4%), 85 (C_{5}H_{9}O, 100), 55 (9) and 43 (26).
(4E, 1R*, 2'S*)-4-Ethyl-1-(2"',6"'-dichlorobenzyl oxy)-1-(2'-methyltetrahydrofur-2'-yl)-4-hexene 390

To a solution of (4E,1R*, 2'S*)-4-ethyl-1-(2'-methyltetrahydro-2'-furyl)-4-hexen-1-ol 348a (12.8 mg, 60.3 μmol) in dry tetrahydrofuran (0.4 ml) at 0°C was added sodium hydride (2.5 mg, 80% oil dispersion, 83 μmol). After 10 min. 2,6-dichlorobenzyl bromide (15 mg, 63 μmol) was added and the reaction mixture was stirred for 16 h. then filtered, and the solid removed was washed with dry diethyl ether (15 ml). The solvent was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford the title compound 390 as a colourless oil (15 mg, 67%) (Found: M + H, 371.1537. C20H29O2Cl2 requires M + H, 371.1545.); νmax/cm⁻¹ (film) 2959, 2925, 2864 (vs, C-H), 1454 (vs, C-H), 1196 (s, C-O-C), 1098 (vs, C-O-C) and 774 (vs, trisub. benzene, C-H); δH (270 MHz; CDCl3) 0.93 (3H, t, J2",1" 7.5, 2"-CH3), 1.15 (3H, s, 2'-Me), 1.37-1.64 (3H, m, CH2), 1.56 (3H, d, J6,5 6.8, CH3C=C), 1.89-2.11 (6H, m, CH2), 2.28-2.30 (1H, m, CH2), 3.39 (1H, dd, Jt,2A 9.2 J1,2B 2.6, CHO), 3.86 (2H, t, J5',4' 6.8, CH2O), 4.87 (1H, d, JHA,HB 10.6, CHAHBAr), 5.03 (1H, d, JHB,HA 10.6, CHAHBAr), 5.15 (1H, q, J5,6 6.8, =CH), 7.13-7.19 (1H, m, Ar-H) and 7.26-7.33 (2H, m, Ar-H); δC (67.8 MHz; CDCl3) 12.8 (CH3, C-2"), 13.0 (CH3, C-6), 22.8 (CH3, 2'-Me), 23.4 (CH2), 26.3 (CH2), 30.7 (CH2), 33.2 (CH2), 33.5 (CH2), 67.5 (CH2O), 68.8 (OCH2Ar), 85.3 (CHO), 86.1 (quat., C-2'), 117.6 (=CH), 128.4, 129.6 (CH, Ar-H), 134.5 (quat, Ar), 136.9 (quat., Ar-Cl) and 142.0 (quat., C-4); m/z 371 (M + H, 8%), 195 (M - C7H5Cl2O, 15), 159 (C7H5Cl2, 24), 111 (16), 85 (C5H9O, 100) and 43 (16).
To a solution of (4E, 1R*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol 348a (55.2 mg, 0.26 mmol) at 0°C under nitrogen was added sodium hydride (10 mg, 80% oil dispersion, 0.42 mmol). After 20 min. 4-bromobenzyl bromide (66 mg, 0.26 mmol) and tetrabutylammonium iodide (9 mg, 24 μmol) were added and the reaction mixture was stirred for 15 h. Then filtered and the solid was washed with diethyl ether (50 ml). The solvent was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford the title compound 391 as a colourless oil (67.3 mg, 68%) (Found: M + H (FAB) 383.1404. C20H30O2Br requires M + H, 383.1409.); νmax/cm⁻¹ (film) 2958, 2924, 2861 (s, C-H), 1483 (m, C-H), 1454 (vs, C-H), 1100 (vs, C-O-C), 827 (m, =C-H) and 802 (s, disub. benzene, C-H); δH (270 MHz; CDCl3) 0.94 (3H, t, J2", 1" 7.5, 2"-CH3), 1.15 (3H, s, 2'-Me), 1.42-1.63 (3H, m, CH2), 1.57 (3H, d, J6,5 6.6, CH3), 1.85-2.08 (6H, m, CH2), 2.19-2.28 (1H, m, CH2), 3.32 (1H, dd, J1,2A 9.5 J1,2B 2.6, CHO), 3.71-3.87 (2H, m, CH2O), 4.53 (1H, d, JHA,HB 11.7, CHABAr), 4.74 (1H, d, JHB,HA 11.7, CHABAr), 5.15 (1H, q, Js,6 6.6, =CH), 7.22 (2H, d, J 8.4, Ar-H) and 7.45 (2H, d, J 8.4, Ar-H); δC (67.8 MHz; CDCl3) 12.8 (CH3, C-2'), 13.0 (CH3, C-6), 22.6 (CH2), 24.1 (CH3), 26.6 (CH2), 30.5 (CH2), 32.7 (CH2), 33.5 (CH2), 67.9 (CH2O, C-5'), 73.9 (CH2Ar), 85.1 (CH, C-1), 86.3 (quart., C-2'), 118.1 (CH, C-5), 129.7, 131.3 (CH, Ar-H), 121.1 (quart., Ar-Br), 138.5 (quart., Ar-CH2) and 141.5 (quart., C-4); m/z 383 (M + H, 8%), 381 (M + H, 10), 195 (M - C7H6OBr, 15), 171 (C7H6Br, 24), 169 (C7H6Br, 25) 111 (15), 85 (C3H9O, 100) and 43 (18).
(4E, 1R*, 2'S*)-4-Ethyl-1-(trimethylsilyloxy)-1-(2'-methyltetrahydrofur-2'-yl)-4-hexene 392

To a stirred solution of (4E, 1R*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol 348a (45 mg, 0.21 mmol) in dry dichloromethane (0.2 ml) was added 1-(trimethylsilyl)imidazole (63 µl, 0.43 mmol). After 15 min. distilled water (1 drop) was added and the solvent was removed under reduced pressure. The residue was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford the title compound 392 as a colourless oil (58.4 mg, 98%) (Found: M*, 284.2184. C16H32O2Si requires M, 284.2172.); \(\nu_{\text{max}}/\text{cm}^{-1}\) (film) 2957, 2864 (s, C-H), 1451 (m, C-H), 1369 (m, C-H), 1247 (s, Si-CH3), 1107 (vs, C-O-C), 863 (s, Si-C) and 838 (vs, Si-CH3); \(\delta_H\) (270 MHz; CDCl3) 0.12 (9H, s, SiMe3), 0.96 (3H, t, \(J_{2'\text{-Me}}\) 7.5, CH3), 1.10 (3H, s, 2'-Me), 1.26-1.62 (3H, m, CH2), 1.58 (3H, d, \(J_{6',5'\text{-Me}}\) 6.6, CH3=), 1.82-2.08 (6H, m, CH2), 2.17-2.25 (1H, m, CH2), 3.51 (1H, dd, \(J_{1',2'\text{Me}}\) 5.9 \(J_{1',2'\text{CH2}}\) 3.7, CHO(Si)), 3.78 (2H, t, \(J_{5',4'\text{CH2O}}\) and 5.21 (1H, q, \(J_{5',6'\text{CH3}}\) 6.6, =CH); \(\delta_C\) (67.8 MHz; CDCl3) 0.80 (CH3Si), 12.8 (CH3, C-2'), 13.0 (CH3, C-6), 22.9 (CH3, 2'-Me), 26.3 (CH2), 27.6 (CH2), 32.0 (CH2), 33.0 (CH2), 33.9 (CH2), 67.5 (CH2O, C-5'), 78.2 (CHO, C-1), 85.5 (quat., C-2'), 117.0 (CH, C-5) and 141.9 (quat., C-4); \(m/z\) 284 (M*, 0.5%), 199 (M - C5H9O, 9), 109 (17), 101 (4), 85 (C5H9O, 100), 73 (SiMe3, 18), 55 (11) and 43 (19).

Other Silyl Derivatives

(4E, 1R*, 2'S*)-4-Ethyl-1-(triethylsilyloxy)-1-(2'-methyltetrahydrofur-2'-yl)-4-hexene 393 was prepared in 94% yield by reaction of alcohol 348a (79 µmol) with triethylsilyl trifluoromethanesulphonate (119 µmol) and 2,6-lutidine (163 µmol) in dichloromethane (0.5 ml); \(\delta_H\) (270 MHz, CDCl3) 0.53 (6H, q, \(J_{7.9\text{SiCH2}}\), 0.93 (9H, t, \(J_{7.9\text{SiCH2CH3}}\)), 0.97 (3H, t, \(J_{2',1\text{CHOSi}}\) 7.5, CH3), 1.10 (3H, s, CH3), 1.20-1.64 (3H, m, CH2), 1.58 (3H, d, \(J_{6',5'\text{CH3}}\) 6.6, CH3=), 1.86-2.06 (6H, m, CH2), 2.16-2.28 (1H, m, CH2), 3.53 (1H, m, CHO(Si)), 3.79-3.84 (2H, m, CH2O) and 5.18 (1H, q, \(J_{5',6'\text{CH3}}\) 6.6, =CH); \(\delta_C\) (67.8 MHz; CDCl3) 6.8 (SiCH2), 7.1 (SiCH2CH3), 12.9 (CH3, C-2'), 13.0
(CH₃, C-6), 22.9 (CH₃, 2'-Me), 26.0 (CH₂), 27.5 (CH₂), 29.7 (CH₂), 32.5 (CH₂),
33.4 (CH₂), 67.4 (CH₂O, C-5'), 78.2 (CHO, C-1), 85.6 (quat., C-2'), 117.5 (CH, C-5)
and 142.2 (quat., C-4).

(4E, 1R*, 2'S*)-4-Ethyl-1-(triisopropylsilyloxy)-1-(2'-methyltetrahydrofur-2'-yl)-4-
hexene 394 was prepared in 93% yield by the reaction of alcohol 348a (68 µmol) with
triisopropyl trifluoromethanesulphonate (100 µmol) and 2,6-lutidine (138 µmol) in
dichloromethane (0.5 ml); δH 0.97 (3H, t, J₂⁻,₁ 7.3, CH₃), 1.09 (21H, m, SiC(CH₃),
SiCH) 1.20-2.09 (9H, m, CH₂), 1.58 (3H, d, J₆,₅ 6.6, CH₃-), 1.20-2.09 (9H, m,
CH₂), 2.15-2.30 (1H, m, CH₂), 3.70-3.83 (3H, m, CHOSi, CH₂O) and 5.17 (1H, q,
J₅,₆ 6.6, =CH); δC (67.8 MHz; CDCl₃) 12.9 (CH₃, C-2'), 13.0 (CH₃, C-6), 18.1
(quat., 'Bu), 18.2 (CH₃, 'Bu), 22.8 (CH₃, 2'-Me), 25.9 (CH₂), 27.2 (CH₂), 29.6
(CH₂), 33.3 (CH₂), 34.3 (CH₂), 67.2 (CH₂O, C-5'), 78.0 (CHO, C-1), 86.0 (quat., C-
2'), 117.5 (CH, C-5) and 142.3 (quat., C-4).

(4E, 1R*, 2'S*)-4-Ethyl-1-(tert-butyldimethylsilyloxy)-1-(2'-methyltetrahydrofur-2'-yl)-4-
hexene 395 was prepared in 90% yield by the reaction of alcohol 348a (51 µmol) with
tert-butyldimethylsilyl trifluoromethanesulphonate (91 µmol) and 2,6-lutidine (103
µmol) in dichloromethane (0.3 ml); δH (270 MHz, CDCl₃) 0.08 (3H, s, SiCH₃), 0.09
(3H, SiMe₃), 0.87 (9H, s, 'Bu), 0.96 (3H, t, J₂⁻,₁ 7.3, CH₃), 1.11 (3H, s, CH₃),
1.20-2.30 (10H, m, CH₂), 1.58 (3H, d, J₆,₅ 7.0, CH₃-), 3.51 (1H, dd, J₁,₂₈ 5.5
J₁,₂₉ 3.3, CHOSi), 3.75-3.82 (2H, m, CH₂O) and 5.18 (1H, q, J₅,₆ 7.0, =CH); δC
(67.8 MHz; CDCl₃) -3.0 (SiMe₃), -4.1 (SiMe₃), 12.8 (CH₃, C-2''), 13.0 (CH₃, C-6),
18.0 (quat., Si'Bu) 22.7 (CH₃, 2'-Me), 25.7 (CH₂), 26.0 (CH₃, 'Bu), 27.3 (CH₂),
29.7 (CH₂), 32.6 (CH₂), 33.6 (CH₂), 67.3 (CH₂O, C-5'), 77.6 (CHO, C-1), 85.6
(quat., C-2'), 117.4 (CH, C-5) and 142.2 (quat., C-4).
(2R*, 5R*, 1'S*, 2''S*)- and (2S*, 5R*, 1'R*, 2''S*)-2-Ethyl-2-(1'-iodoethyl)-5-(2''-methyltetrahydrofur-2''-yl)tetrahydrofuran [trans and cis] 347a, 347b

Procedure A

To a solution of (4E, 1'R*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol 348a (17.5 mg, 82.4 μmol) in dry acetonitrile (1 ml) at °43°C under nitrogen was added sodium carbonate (88 mg, 0.830 mmol), followed by iodine (105 mg, 0.414 mmol). After stirring for 15 min. diethyl ether (5 ml) was added and the resulting solution was washed with 10% aqueous sodium sulphite solution (5 ml). The aqueous layer was extracted with diethyl ether (3 x 10 ml) and the combined organic layers were then dried over magnesium sulphate. The solvent was evaporated at reduced pressure to afford a yellow oil which was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford:

(2R*, 5R*, 1'S*, 2''S*)-2-ethyl-2-(1'-iodoethyl)-5-(2''-methyltetrahydrofur-2''-yl)-tetrahydrofuran 347a [trans] (16.6 mg, 60%) as a colourless oil (Found: M+, 338.0743. C_{13}H_{23}O_{2}I requires M, 338.0743); νmax/cm⁻¹ (film) 2966, 2933, 2866 (s, C-H), 1050 (s, C-O), 1458 (m, C-H) and 1370 (m, GIC); δC (270 MHz; CDCl₃) 0.92 (3H, t, J 7.3, CH₂C₅H₃), 1.16 (3H, d, J 2',1' 7.3, C₅H₃CH₃), 1.84 (3H, 2'-Me), 1.84 (3H, d, J 2',1' 7.3, C₅H₃CH₃), 1.59-2.07 (10H, m, CH₂), 3.84 (2H, t, J₂'₄' 6.4, CH₂O), 4.02 (1H, dd, J₅,₄A 10.6, J₅,₄B 5.1, CHO) and 4.52 (1H, q, J₁',₂' 7.3, CHI); δC (67.8 MHz; CDCl₃) 7.8 (CH₃, C-2''), 22.5, (CH₃, 2'-Me), 23.9 (CH₃, C-2'), 26.2 (CH₂), 27.9 (CH₂), 28.2 (CH₂), 34.4 (CH₂), 35.2 (CH₂), 40.2 (CH, C-1''), 68.2 (CH₂O), 83.5, 86.6 (quat., C-2, C-2') and 85.0 (CHO); m/z 339 (M + H, 10%), 338 (M⁺, 1), 111 (9), 85 (C₅H₉O, 100) and 43 (28).
(2S* 5R*, 1'R*, 2"S*)-2-ethyl-2-(1'-idoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofuran 347b [cis] (5.2 mg, 19%) as a colourless oil (Found: (FAB) M + H, 339.0821. C_{13}H_{24}O_2I requires M + H, 339.0821); ν_{max}/cm^{-1} (film) 2966, 2933, 2866 (s, C-H), 1050 (s, C-O), 1458 (m, C-H), 1370 (m, CH₃); δ_{H} (270 MHz; CDCl₃) 0.90 (3H, t, J = 7.4, CH₂CH₃), 1.14 (3H, s, 2"-Me), 1.89 (3H, d, J₂,₁' = 6.9, CH₃CHI), 1.59-2.10 (10H, m, CH₂), 3.84 (2H, t, J₅",₄" = 6.5, CH₂O), 3.94 (1H, dd, J₅,₄A = 10.3, J₅,₄B = 5.3, CHO) and 4.41 (1H, q, J₁',₂' = 6.9, CHI); δ_{C} (67.8 MHz; CDCl₃) 7.5 (CH₃, C-2"'), 22.6 (CH₃, 2"-Me), 22.9 (CH₃, C-2'), 26.3 (CH₂), 28.5 (CH₂), 31.7 (CH₂), 32.9 (CH₂), 33.8 (CH₂), 35.6 (CH, C-1'), 68.1 (CH₂O), 83.9, 85.6 (quat., C-2, C-2') and 86.6 (CHO); m/z (FAB) 339 (M + H, 31%), 338 (M⁺, 7), 213 (25), 211 (17), 139 (22), 111 (18), 85 (C₅H₉O, 100) and 43 (28).

Procedure B

To a solution of each of the silyl protected hydroxylkenes 392 - 395 (50 μmol) in dry acetonitrile (0.5 ml) at 0°C under nitrogen was added iodine (250 μmol). After stirring for 15 min. diethyl ether (1 ml) was added and the resulting solution was washed with a 10% aqueous sodium sulphite solution (1 ml). The aqueous layer was extracted with diethyl ether (4 × 1 ml) and the combined organic layers were dried over magnesium sulphate. The solvent was evaporated at reduced pressure to afford a yellow oil which was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford (2R* 5R*, 1'S*, 2"S*)-2-ethyl-2-(1'-idoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofuran 347a and (2S* 5R*, 1'R*, 2"S*)-2-ethyl-2-(1'-idoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofuran 347b.
(2R*, 3S*, 6R*, 2'S*)-3-Ethyl-3-hydroxy-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran 384

To a solution of (2R*, 5R*, 1'S*, 2'S*)-2-ethyl-2-(1'-iodoethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 347a (6.0 mg, 18 μmol) in acetone (0.3 ml) were added silver carbonate (5.0 mg, 18 μmol) and distilled water (4 drops). After stirring for 2 h. the reaction mixture was filtered through glass wool, washing with ethyl acetate (30 ml). After drying over magnesium sulphate the solvent was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (1:1) as eluant, to afford the title compound 384 (2.8 mg, 68%) as a colourless oil (Found: M+, 228.1698. C13H24O3 requires M, 228.1725.); νmax/cm⁻¹ (film) 3438 (s, OH), 2962, 2863 (s, CH₃), 1100 (s, C-O) and 1452 (s, CH₃); δH (270 MHz; CDCl₃) 0.90 (3H, t, J₂₊,₁₇ 7.5, CH₂CH₃), 1.11 (3H, d, J₂-Me,₂ 6.6, 2-Me), 1.14 (3H, s, 2'-Me), 1.16-2.10 (10H, m, CH₂), 3.25 (1H, dd, J₆₅A 5.3, J₆₅B 11.0, CHO), 3.35 (1H, q, J₆₅-Me 6.6, CHO) and 3.75-3.88 (2H, m, CH₂O); δC (67.8 MHz; CDCl₃) 6.65 (CH₃, C-2"), 14.0 (CH₃, 2-Me), 22.3 (CH₃, 2'-Me), 22.5 (CH₂), 24.6 (CH₂), 26.2 (CH₂), 33.9 (CH₂), 34.6 (CH₂), 68.3 (CH₂O), 71.3 (quat., C-3), 80.9, 82.9 (C-2, C-6), 83.7 (quat., C-2"); m/z 228 (M⁺, 0.1%), 199 (1), 143 (6), 125 (5), 111 (4), 95 (6), 85 (C₅H₉O, 100) and 43 (16).
(2S*, 3R*, 6R*, 2'S*)-3-Ethyl-3-hydroxy-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran 323

To a solution of (2S*, 5R*, 1'R*, 2'S*)-2-ethyl-2-(1'-iodoethyl)-5-(2''-methyltetrahydrofur-2''-yl)tetrahydrofuran 347b (12.9 mg, 38 μmol) in acetone (0.3 ml) were added silver carbonate (12.7 mg, 46 μmol) and distilled water (5 drops). After stirring for 3 h, the reaction mixture was filtered through glass wool, washing with ethyl acetate (25 ml). After drying over magnesium sulphate the solvent was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (4:1) as eluant, to afford the title compound 323 (6.7 mg, 77%) as a colourless oil (Found: (FAB) M+H, 229.1796. C13H25O3 requires M+H, 229.1804); $\nu_{\text{max}}$/cm$^{-1}$ (film) 3432 (s, OH), 2966, 2867 (s, CH3), 1457 (m, C-H), 1371 (m, C-H), 1102 (s, C-O) and 1046 (s, C-OH); $\delta$H (270 MHz; CDCl3) 0.92 (3R, t, $J=7.5$, CH2I), 1.24 (3R, d, $J=6.7$, 2-Me), 1.16 (3H, s, 2'-Me), 1.42-1.95 (10H, m, CH2), 3.46 (1H, dd, $J=3.5$, $J=3.5$, CHO) and 3.75-3.89 (3H, m, CH2O, 2'-CHO); $\delta$C (67.8 MHz; CDCl3) 7.0 (CH3, C-2''), 13.0 (CH3, 2-Me), 21.0 (CH3, 2'-Me), 22.1 (CH2), 22.8 (CH2), 25.8 (CH2), 29.1 (CH2), 35.5 (CH2), 68.2 (CH2O), 71.1 (quat., C-3), 74.0, 74.8 (CH, C-2, C-6); m/z 229 (M + H, 63%), 211 (M - OH, 95), 183 (49), 111 (61), 85 (100) and 43 (47).

(2R*, 5R*, 1'S*, 2''S*)-2-Ethyl-2-ethenyl-5-(2''-methyltetrahydrofur-2''-yl)tetrahydrofuran 398
To a solution of (2R*, 5R*, 1'S*, 2''S*)-2-ethyl-2-(1'-iodoethyl)-5-(2''-methyltetrahydrofuran-2''-yl)tetrahydrofuran (12.7 mg, 37.5 µmol) in dry benzene (0.2 ml) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (6.0 µl, 40 µmol). The reaction mixture was heated under reflux for 4 h., cooled and 1M sulphuric acid (5 ml) was added. The reaction mixture was extracted with diethyl ether (4 × 10 ml), and after drying with magnesium sulphate, the solvent was removed under reduced pressure. The residue was purified by flash chromatography, using hexane/ethyl acetate (9:1) as eluant, to afford the title compound 398 as a colourless oil (7.0 mg, 88%) (Found: M + H, 211.1690). C_{13}H_{23}O_{2} requires M + H, 211.1698); ν_{max}/cm^{-1} (film) 2963, 2866 (s, C-H), 1129 (m, C-O-C), 1052 (s, =CH_{2}) and 919 (s, =CH_{2}); δ_{H} (270 MHz; CDCl_{3}) 0.88 (3H, t, J 7.3, CH_{2}CH_{3}), 1.16 (3H, s, 2''-Me), 1.56-1.74 (5H, m, CH_{2}), 1.83-2.00 (5H, m, CH_{2}), 3.83-3.91 (3H, m, CHO, CH_{2}O), 5.05 (1H, dd, J_{2'A,1'} 10.6 J_{2'A,2'B} 1.8, 2''-HA), 5.17 (1H, dd, J_{2'B,1'} 17.2 J_{2'B,2'A} 1.8, 2''-HB) and 5.78 (1H, dd, J_{1',2'A} 17.8 J_{1',2'B} 10.6, 1''-H); δ_{C} (67.8 MHz; CDCl_{3}) 8.7 (CH_{3}, C-2'''), 22.3 (CH_{3}, 2''-CH_{3}), 26.2 (CH_{2}), 26.9 (CH_{2}), 33.0 (CH_{2}), 34.2 (CH_{2}), 34.5 (CH_{2}), 68.1 (CH_{2}, C-5''), 83.4 (CH, C-5), 84.1, 86.0 (quat.,C-2, C-2''), 112.3 (CH_{2}, C-2') and 142.5 (CH, C-1'); m/z 211 (M + H, 10%), 162 (8), 149 (7), 113 (11) and 85 (C_{5}H_{9}O, 100).

(2R*, 5R*, 1'RS, 1''S*)-2-Ethyl-2-(1-hydroxyethyl)-5-(2''-methyltetrahydrofuran-2''-yl)tetrahydrofuran 400

To a solution of mercuric acetate (4.7 mg, 15 µmol) in distilled water (0.2 ml) was added (2R*, 5R*, 1'S*, 2''S*)-2-ethyl-2-(1'-ethenyl)-5-(2''-methyltetrahydrofuran-2''-yl)tetrahydrofuran 398 (3.1 mg, 15 µmol) in dry tetrahydrofuran (0.2 ml). After stirring for 0.5 h. 2M sodium hydroxide solution (1 ml) was added, followed by sodium borohydride (1 mg, 26 µmol). The reaction mixture was then filtered, washing with diethyl ether (4 × 2 ml). The combined organic layers were dried over magnesium sulphate and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography, using hexane/ethyl acetate (2:1) as eluant, to afford the title compound 400 as a colourless oil (1.3 mg, 39%) (Found: (Cl, NH_{3}) M + H, 229.1806. C_{13}H_{25}O_{3} requires M + H, 229.1804.; δ_{H} (270 MHz; CDCl_{3}) 0.91 (3H, t, J_{2'',1''} 7.3,
CH$_2$CH$_3$), 1.09 (3 × 3/7H, d, $J_{2',1'}$ 6.6, 1'-Me), 1.11 (3 × 4/7H, d, $J_{2',1'}$ 6.6, 1'-Me), 1.15 (4/7 × 3H, s, 2''-Me), 1.17 (3/7 × 3H, s, 2''-Me), 1.23-1.77 (6H, m, CH$_2$), 1.85-2.15 (4H, m, CH$_2$), 2.26 (1H, s, OH), 3.73 (1H, q, $J_{1',2'}$ 6.6, CHOH) 3.82-3.89 (2H, m, CH$_2$O) and 3.97 (1H, dd, $J_{5,4A}$ 10.6, $J_{5,4B}$ 5.1, CHO); $\delta$C (67.8 MHz; CDCl$_3$) 7.7 (CH$_3$, C-2''), 17.1 (CH$_3$, C-2'), 23.4 (CH$_3$, 2''-CH$_3$), 26.4 (CH$_2$), 28.2 (CH$_2$), 29.3 (CH$_2$), 30.0 (CH$_2$), 32.8 (CH$_2$), 68.1 (CH$_2$O, C-5''), 71.4 (CHO, C-1'), 84.1, 86.9 and 88.5 (quat., C-2, C-2''); m/z 229 (M + H, 19%), 212 (23), 183 (38), 111 (36) and 85 (C$_5$H$_9$O, 100).
### References


Erythro and threo designations in this work follow the definition suggested by Noyori et al (R. Noyori, I. Nishida and J. Sakata, J. Am. Chem. Soc., 1981, 103, 2106) whereby the ligands of the two adjacent carbon atoms are equated in terms of their relative sequence rule priority and paired accordingly. If all three pairs can then be positioned opposite each other across the C-C bond then the compound is assigned as erythro. Alternatively, if only one pair of ligands can be positioned in this way then the compound is assigned as threo.


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