Synthesis of the E Ring of Salinomycin

A thesis presented in partial fulfilment of the requirements for the degree of

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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"-dichlorobenzyloxy)-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*, 5R*, 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.

Contents

Abbreviations

Ac	=	acetyl
acac	=	2,4-pentanedione
AD	=	asymmetric dihydroxylation
AIBN	=	2,2'-azobisisobutyronitrile
aq.	=	aqueous
BB	=	4-bromobenzyl
BOM	=	benzyloxymethyl
Bz	=	benzyl
cat.	=	catalytic
CSA	=	camphorsulphonic acid
DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
DCB	=	2,6-dichlorobenzyl
DDQ	=	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	=	diethyl azodicarboxylate
DHP	=	dihydropyranyl
DIBAL	=	diisobutylaluminium hydride
DMAP	=	4-dimethylaminopyridine
DME	=	1,2-dimethoxyethane
DMF	=	*N,N*-dimethylformamide
DMS	=	dimethylsulphide
DMSO	=	dimethylsulphoxide
HMDS	=	1,1,1,3,3,3-hexamethyldisilazane
HMPA	=	hexamethylphosphoramide
HMPT	=	hexamethylphosphorus triamide
HPLC	=	high performance liquid chromatography
imid.	=	imidazole
IR	=	infra-red
LDA	=	lithium diisopropylamide
MCPBA	=	*meta*-chloroperoxybenzoic acid
MOM	=	methoxymethyl
MOP	=	methoxyisopropyl
MP	=	methoxyphenyl
MPM	=	*p*-methoxyphenylmethyl
MS	=	molecular sieves
Ms	=	methanesulphonyl

NCS	=	*N*-chlorosuccinimide
NIS	=	*N*-iodosuccinimide
NMO	=	4-methylmorpholine-*N*-oxide
NMR	=	nuclear magnetic resonance
NOESY	=	nuclear Overhauser and exchange spectroscopy
PCC	=	pyridinium chlorochromate
PDC	=	pyridinium dichromate
Ph	=	phenyl
PPTS	=	pyridinium *p*-toluenesulphonate
Pv	=	pivaloyl
Py	=	pyridine
RT	=	room temperature
TBCO	=	2,4,4,6-tetrabromo-2,5-cyclohexadienone
TBDMS	=	*tert*-butyldimethylsilyl
TES	=	triethylsilyl
Tf	=	trifluoromethanesulphonyl
TFA	=	trifluoroacetic acid
TFAA	=	trifluoroacetic anhydride
THF	=	tetrahydrofuran
THP	=	tetrahydropyranyl
TIPS	=	triisopropylsilyl
tlc	=	thin layer chromatography
TMS	=	trimethylsilyl
TSA	=	*para*-toluenesulphonic acid

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[1].

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.

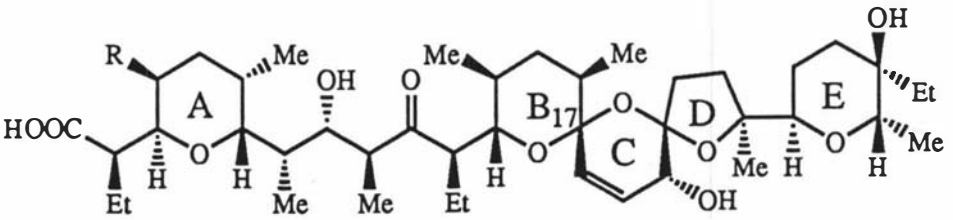
While most of the polyether antibiotics exhibit relatively nonspecific cytotoxicity several such as salinomycin **1**, narasin **2** and monensin **3** display enough selectivity to be of commercial use as both anticoccidial agents in poultry and growth promotants in ruminants[2].

In order to compare the structure and stereochemistry of the polyether antibiotics Westley *et al*[3] 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 **1** and monensin **3**); 2) The divalent polyethers (e.g. lasalocid A **4**) which bind divalent metal cations; 3) The pyrrole containing ethers (e.g. A23187 **5**); and 4) The acyltetronic acids (e.g. ICI139603 **6**), 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[1] (e.g. okadaic acid **7** and norhalichondrin A **8**) is probably justified due to the unique structures of these compounds. Representative members of the various classes are illustrated (Figures 1 and 2).

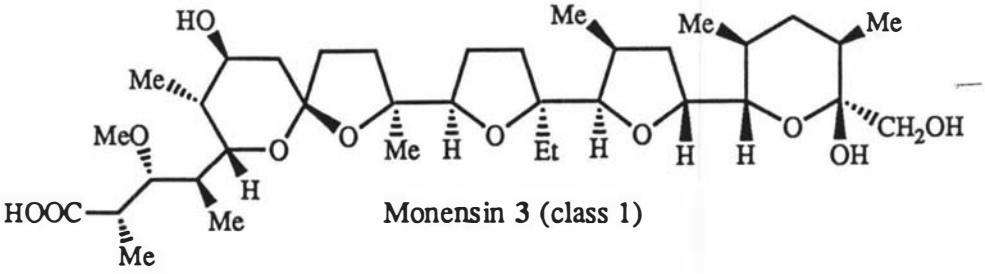
The ion selectivity of the polyether ionophores is a combined function of the ion's desolvation energy and the ligating energy obtained on complexation which, due to the highly constrained backbone, generally has a maximum value for an ion of a specific radius[4].

In 1967, the first X-ray structure of a polyether antibiotic, monensin **3**[5], was solved. Since then, over 80 different polyether antibiotics have been isolated and their

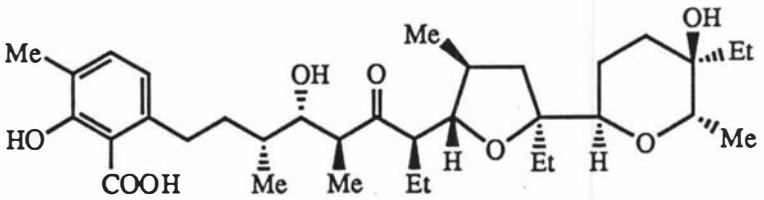
Figure 1



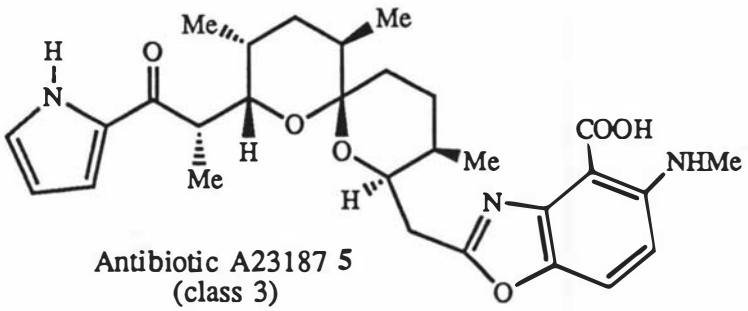
Salinomycin (**1**; R=H) (class 1)
Narasin (**2**; R=Me)



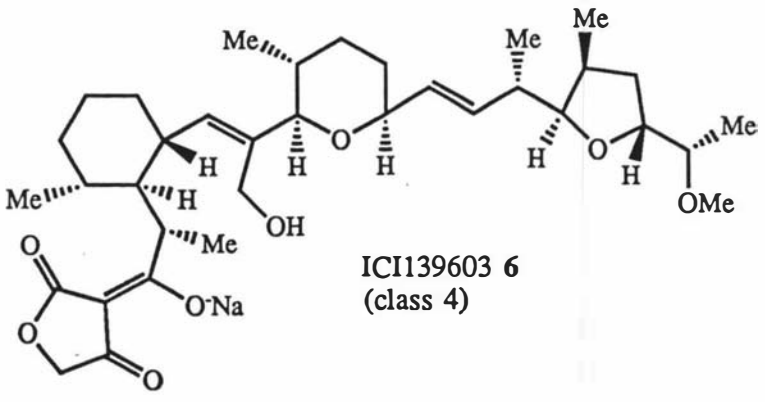
Monensin **3** (class 1)



Lasalocid A **4** (class 2)

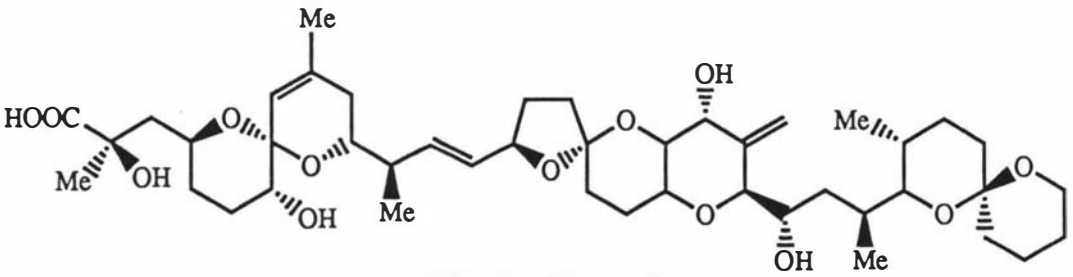


Antibiotic A23187 **5**
(class 3)

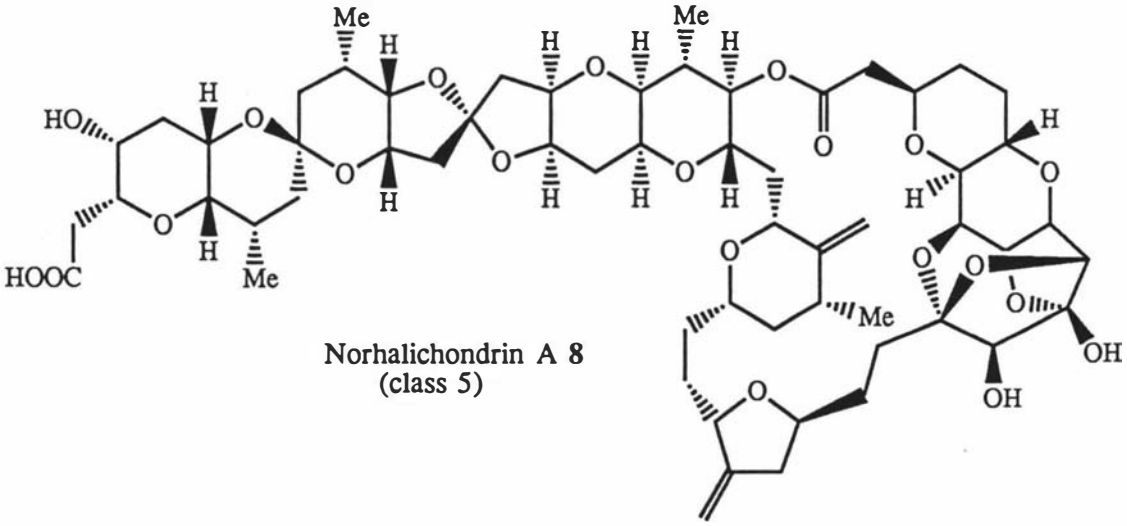


ICI139603 **6**
(class 4)

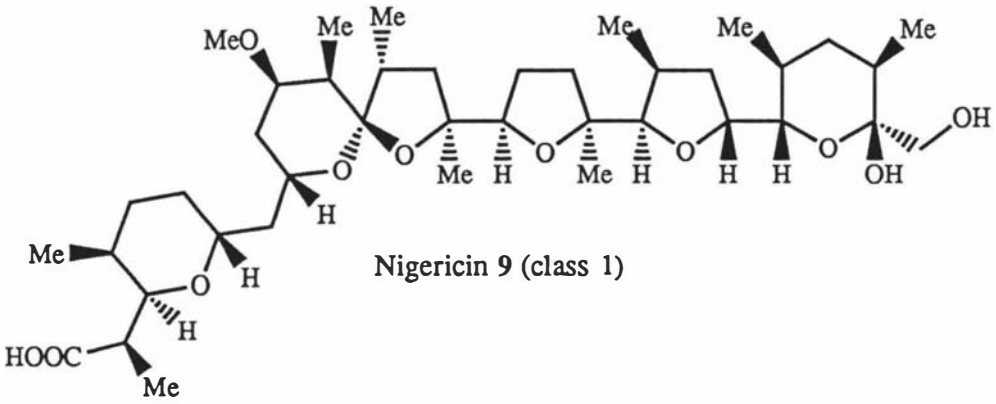
Figure 2



Okadaic acid **7** (class 5)



Norhalichondrin A **8**
(class 5)



Nigericin **9** (class 1)

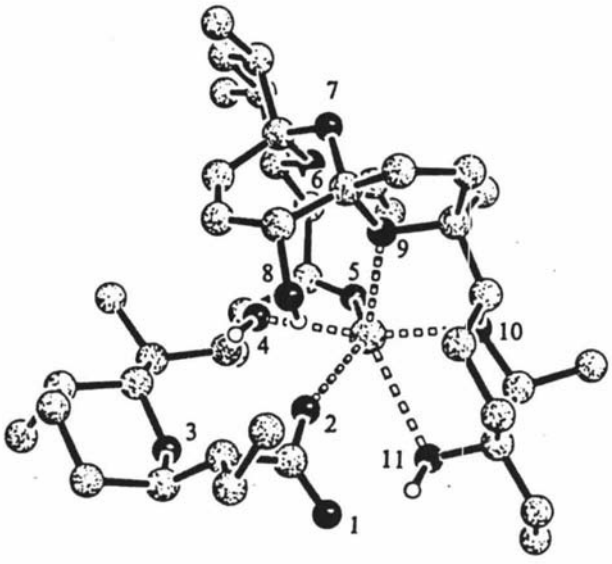
structures deduced by X-ray crystallography and partial synthesis.

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[4].

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*[6] 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).

Figure 3



Sodium complexed Salinomycin
dark atoms = Oxygen

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*[7]

In 1981, Kishi *et al*[7] reported total syntheses of the polyether antibiotics salinomycin **1** and narasin **2**.

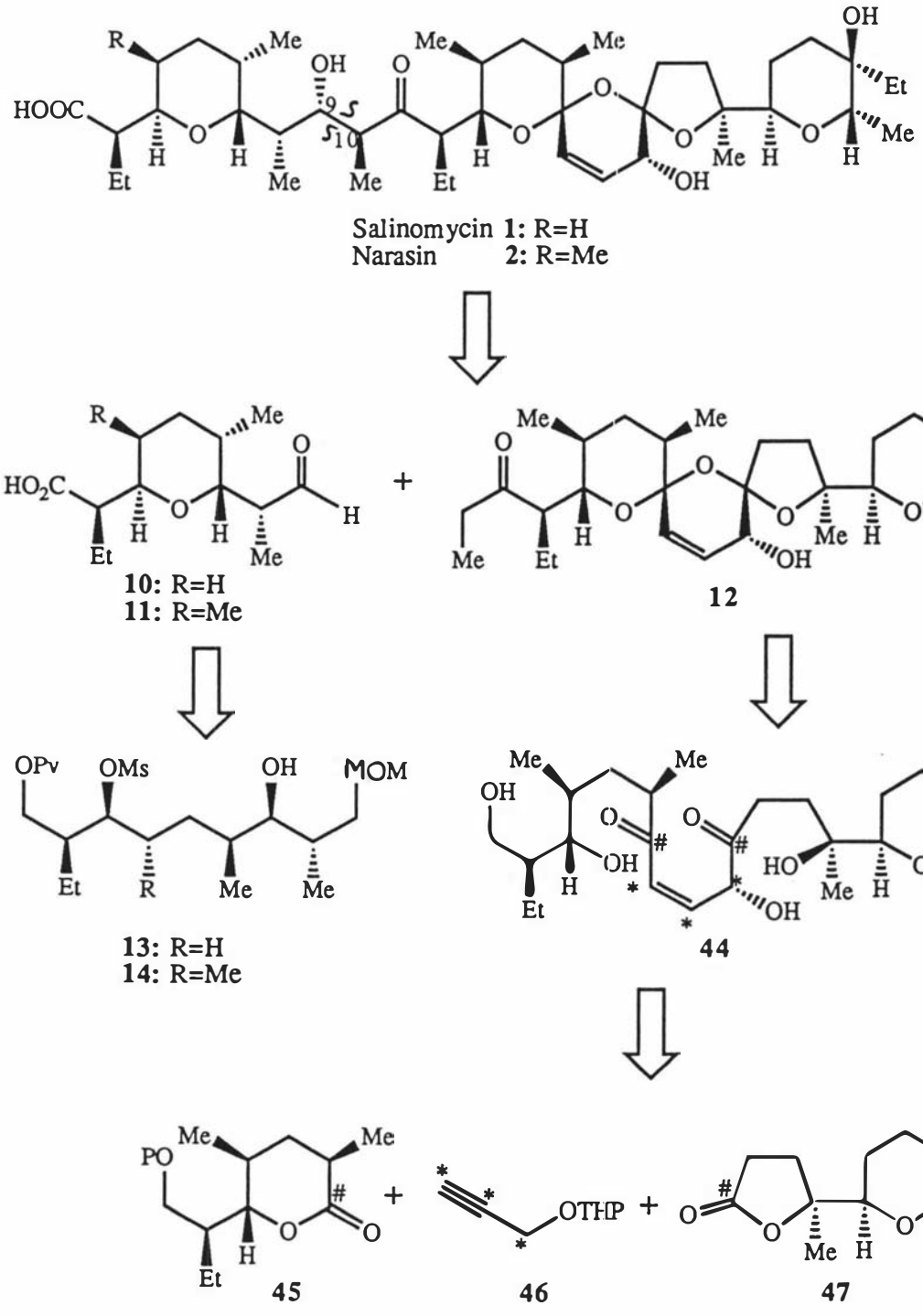
The first step in their retrosynthetic pathway was the disconnection of the C9-C10 bond (Scheme 1), equivalent to a stereoselective crossed aldol condensation in the synthetic direction. Precedent for the use of this reaction in the synthesis of polyether antibiotics is well documented[8-10]. The two 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[11] 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[14,15] (Scheme 3). Hydrolysis and selective reprotection of the resulting dichloroalkene **21** followed by lithium-halogen exchange and acylation afforded propargylic ester **22**, which was then reduced to the

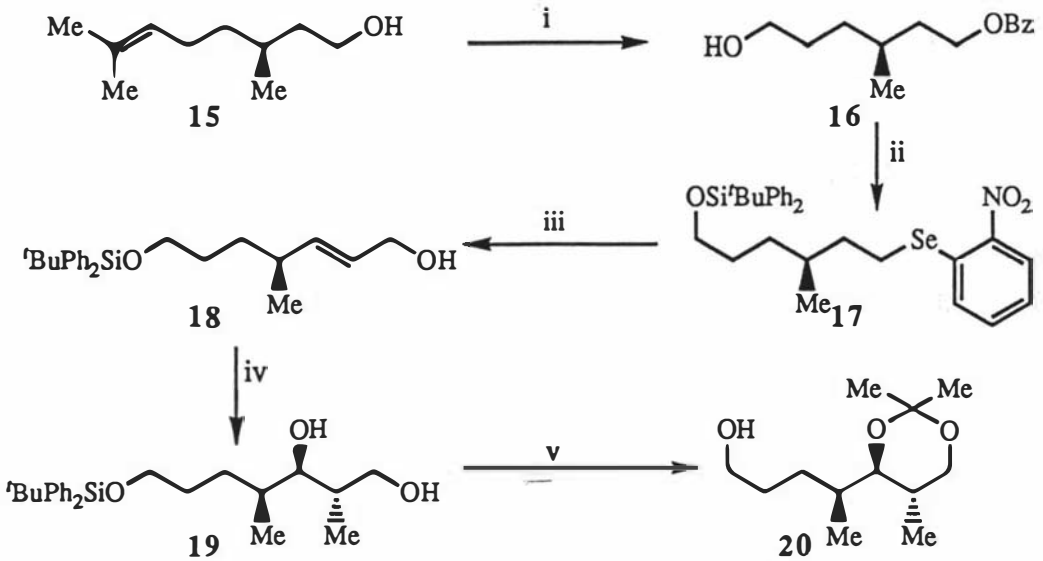
Scheme 1



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**.

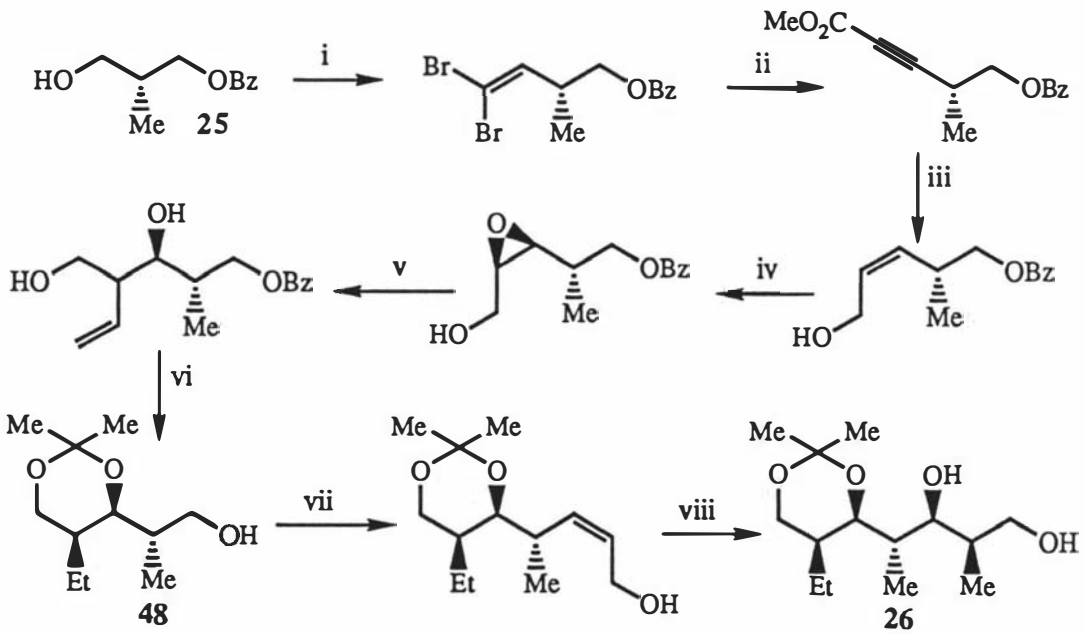
Synthesis of mesylate **14** (required for narasin) began with extension of alcohol **25** (Scheme 4) *via* the Wittig reaction, followed by incorporation of two new chiral

Scheme 2



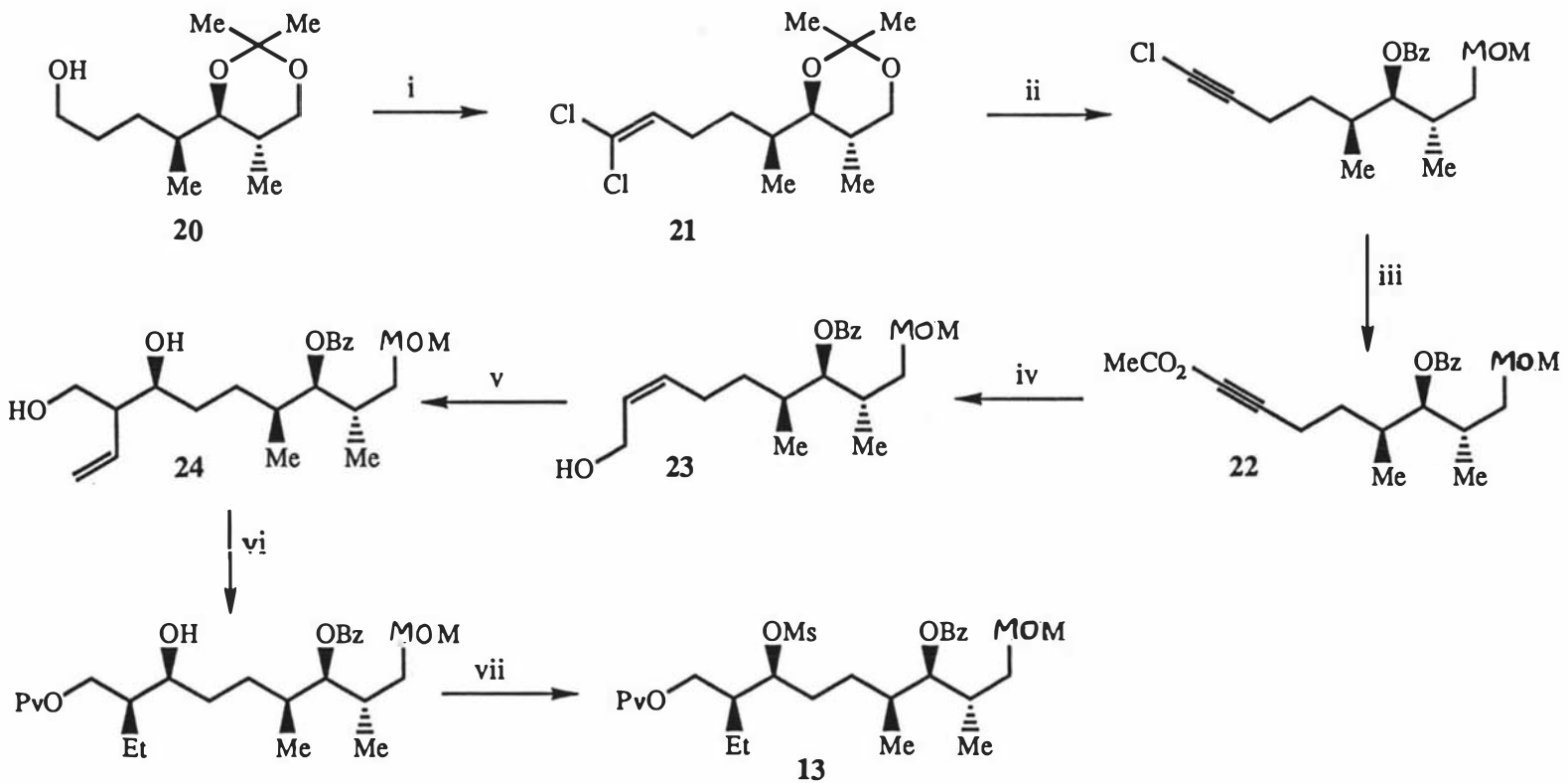
Reagents and conditions: (i) a: $C_6H_5CH_2Br$, KH, 0°C to RT; b: O_3, MeOH, -78°C; c: $NaBH_4$, MeOH; (ii) a: ^{t}BuPh$_2$SiCl, DMF, imidazole; b: H_2, Pd/C, MeOH; c: *o*-NCSe(C_6H_4)NO_2, Bu_3P, THF, 0°C; (iii) a: O_3, NaOAc, MeOH, CH_2Cl_2, -78°C then O_3, Me_2S, RT; b: $EtO_2CCH{=}PPh_3$, $ClCH_2CH_2Cl$, Δ; c: DIBAL, CH_2Cl_2, -40°C; (iv) a: Ti(O^{i}Pr$_4$), D-(-)-diethyl tartrate, ^{t}BuOOH, CH_2Cl_2, -23°C; b: $Me_3CuCNLi_2$, THF, -20°C to RT; (v) a: $Me_2C(OMe)_2$, CSA, acetone, RT; b: ^{n}Bu$_4$NF, THF.

Scheme 4



Reagents and conditions: (i) a: DMSO, $(COCl)_2$, CH_2Cl_2, -60°C then Et_3N; b: CBr_4, Ph_3P, CH_2Cl_2, 0°C; (ii) a: ^{n}BuLi, THF, -78°C then $ClCO_2Me$; (iii) a: H_2, Lindlar catalyst, quinoline, hexane; b: DIBAL, CH_2Cl_2, -78°C; (iv) MCPBA, CH_2Cl_2, -10°C; (v) $CH_2{=}CHMgBr$, CuI, Et_2O, -24°C; (vi) a: $MeC(OMe)_2$, acetone, CSA; b: H_2, Lindlar catalyst, hexanes; c: Li, NH_3, THF, -33°C; (vii) a: DMSO, $(COCl)_2$, CH_2Cl_2, -60°C then Et_3N; b: PhHgCCl_2Br, Ph_3P, benzene, Δ; c: ^{n}BuLi, THF, -78°C then $ClCO_2Me$; d: H_2, Lindlar catalyst, hexanes; e: DIBAL, CH_2Cl_2, -40°C; (viii) a: MCPBA, CH_2Cl_2, 0°C; b: Me_2CuLi, Et_2O, -25°C.

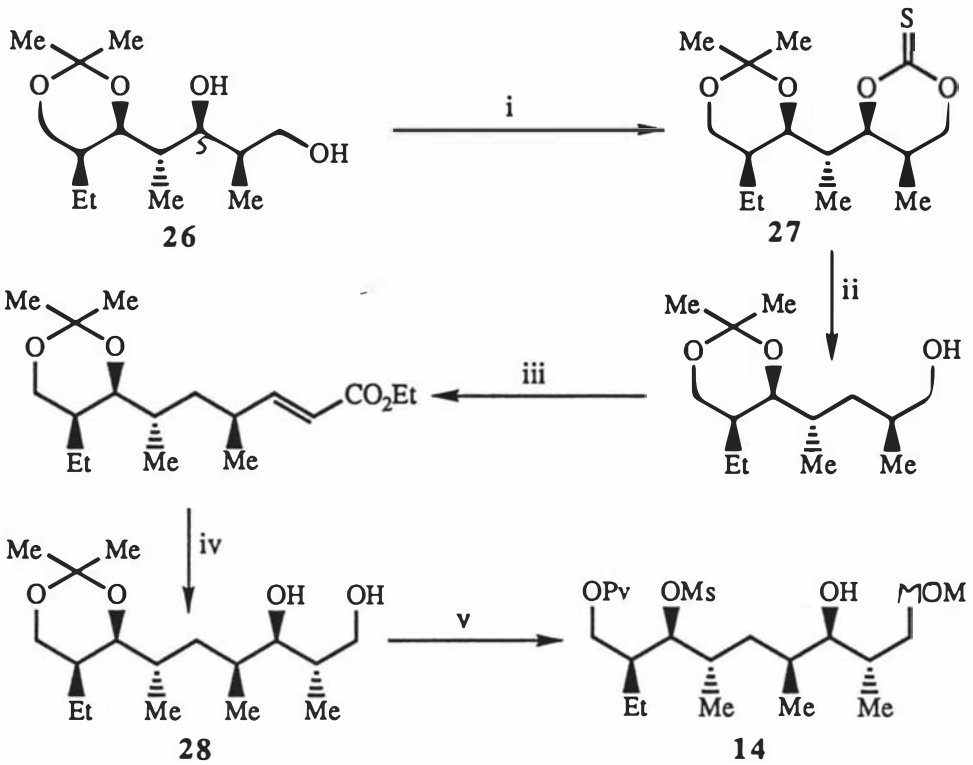
Scheme 3



Reagents and conditions: (i) a: DMSO, $(COCl)_2$, CH_2Cl_2, -60°C then Et_3N; b: $PhHgCCl_2Br$, Ph_3P, benzene, Δ; (ii) a: AcOH, H_2O, RT; b: NaH, $MeOCH_2Br$, THF, -12°C; c: KH, $C_6H_5CH_2Br$, THF/DMF, 0°C; (iii) ^nBuLi, THF, -78°C then $ClCO_2Me$; (iv) a: H_2, Lindlar catalyst, quinoline, hexane; b: DIBAL, CH_2Cl_2, -40°C; (v) a: $Ti(^iPrO)_4$, D-(-)-diethyl tartrate, ^tBuOOH, CH_2Cl_2, -23°C; b: CH_2=CHMgBr, CuI, Et_2O, -24°C to RT; (vi) H_2, Lindlar catalyst, Et_2O; b: $Me_3CC(O)Cl$, pyridine; (vii) a: Ms_2O, DMAP, pyridine, CH_2Cl_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[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.

Scheme 5

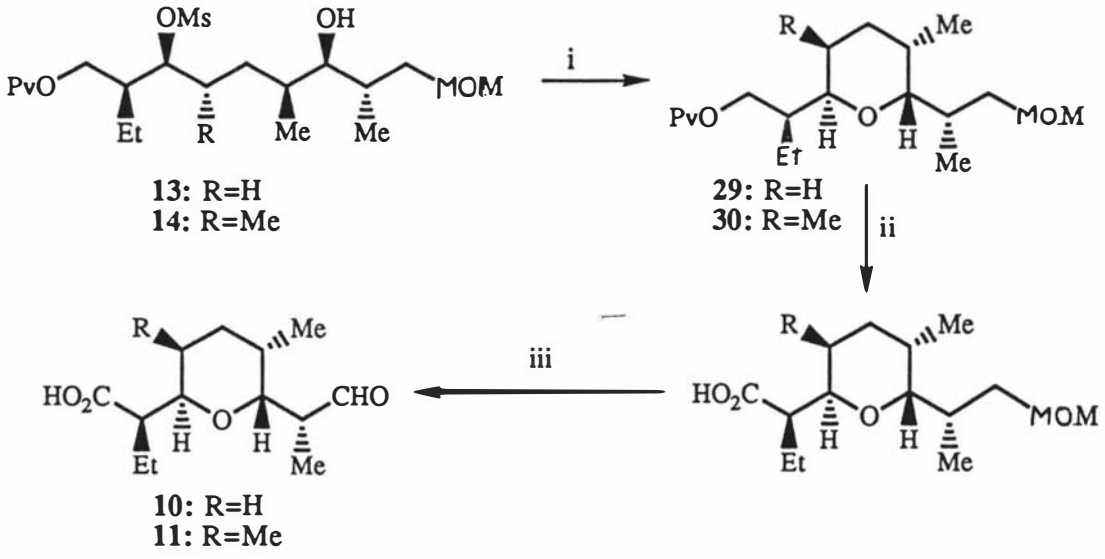


Reagents and conditions: (i) Cl_2CS, DMAP, CH_2Cl_2; (ii) a: Bu_3SnH, AIBN, toluene; b: CSA, $Me_2C(OMe)_2$; c: NaOH, H_2O, RT; (iii) a: DMSO, $(COCl)_2$, CH_2Cl_2, -60°C to RT; b: $EtO_2CCH{=}PPh_3$, $ClCH_2CH_2Cl$, Δ; (iv) a: DIBAL, CH_2Cl_2, -40°C; b: $Ti(O^iPr)_4$, D-(-)-diethyl tartrate, ^tBuOOH, CH_2Cl_2, -23°C; c: $Me_3CuCNLi_2$, THF, -20°C to RT; (v) a: $MeOCH_2Br$, NaH, THF,-12°C; b: BzBr, KH, THF, DMF, 0°C; c: AcOH, H_2O, RT; d: Me_3CCOCl, pyridine; e: Ms_2O, DMAP, pyridine, CH_2Cl_2, 0°C to RT; f: H_2, 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°C→ 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[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.

Scheme 6



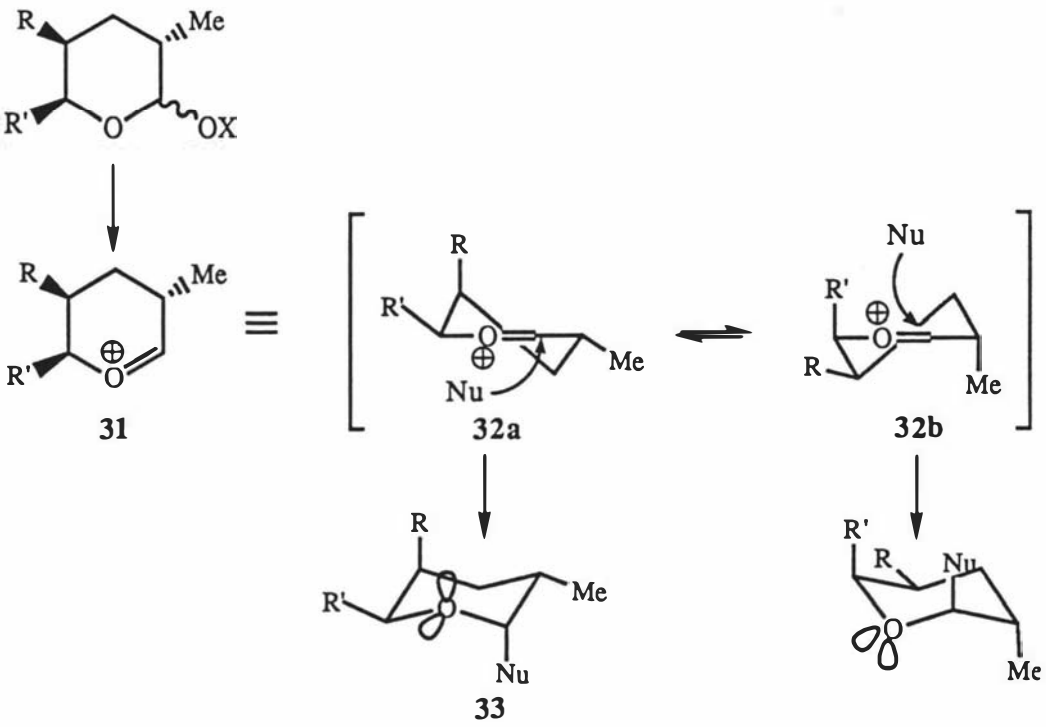
Reagents and conditions: (i) KH; (ii) a: $LiAlH_4$, Et_2O, RT; b: Jones reagent, acetone, 0°C to RT; (iii) a: Dowex-50, dioxane, H_2O, Δ; b: PCC, CH_2Cl_2.

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.

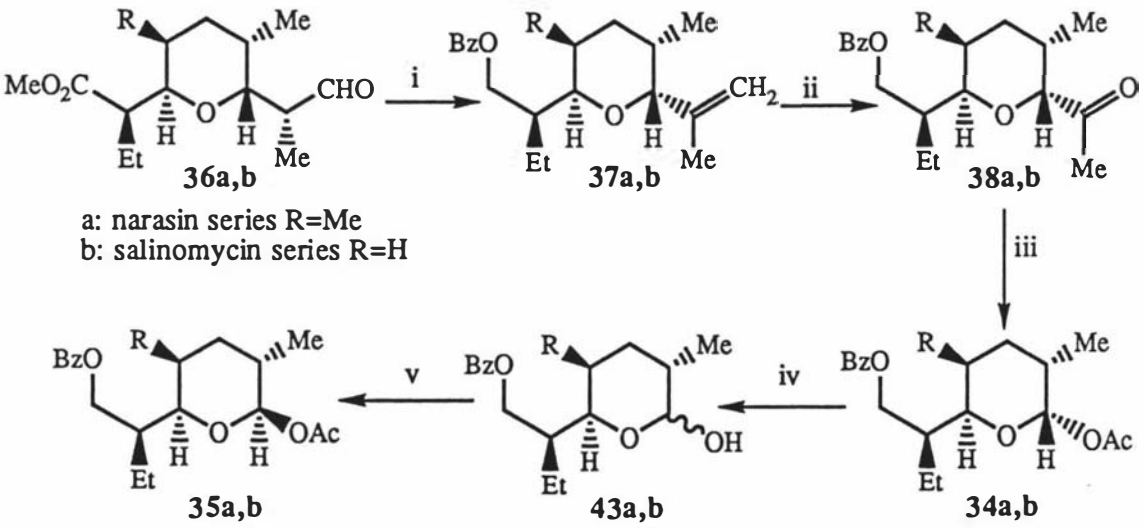
The disappointing yield in the cyclisation of the narasin series mesylate **14** was attributed to the extensive steric crowding which occurs during formation of the pyran product. Consequently, a more efficient synthesis of the narasin aldehyde **11** was pursued, this time involving the stereocontrolled addition of an alkyl group to a preformed tetrahydropyran nucleus **31**[16] (Scheme 7). Based on previous observations[17], it was anticipated that the stereoelectronically preferred axial attack by the nucleophile on oxonium ion **32a** 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 **32b**.

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

Scheme 7



Scheme 8

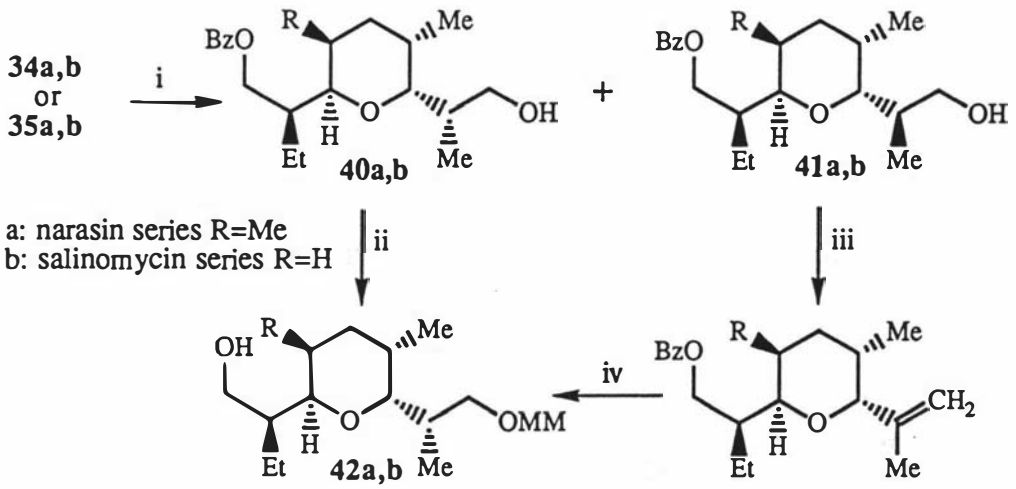


a: narasin series R=Me
b: salinomycin series R=H

Reagents and conditions: (i) a: $NaBH_4$, MeOH, 0°C; b: *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF followed by H_2O_2 treatment, 0°C to RT; c: $LiAlH_4$, Et_2O, 0°C; d: $C_6H_5CH_2Br$, KH, THF/DMF (4:1), 0°C to RT; (ii) O_3, MeOH, -78°C, followed by Me_2S work-up; (iii) MCPBA, Na_2HPO_4, CH_2Cl_2; (iv) NaOMe, MeOH; (v) Ac_2O, pyridine.

Separate treatment of each of the acetates **34a** and **35a** with the enol silyl ethers **39**[18] 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), $ZnCl_2$ (excess), CH_2Cl_2, 0°C; b: $NaBH_4$, MeOH, 0°C; (ii) a: $MeOCH_2Br$, $(^iPr)_2EtN$, CH_2Cl_2; b: H_2, Pd-C, MeOH; (iii) a: *o*-$NO_2C_6H_4SeCN$, $(^nBu)_3P$, THF; b: H_2O_2, 0°C to RT; (iv) a: thexylborane, THF, 0°C; b: H_2O_2, OH^-; c: $MeOCH_2Br$, $(^iPr)_2EtN$, CH_2Cl_2; d: H_2, 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[7] (probably alcohol **26**, Scheme 4).

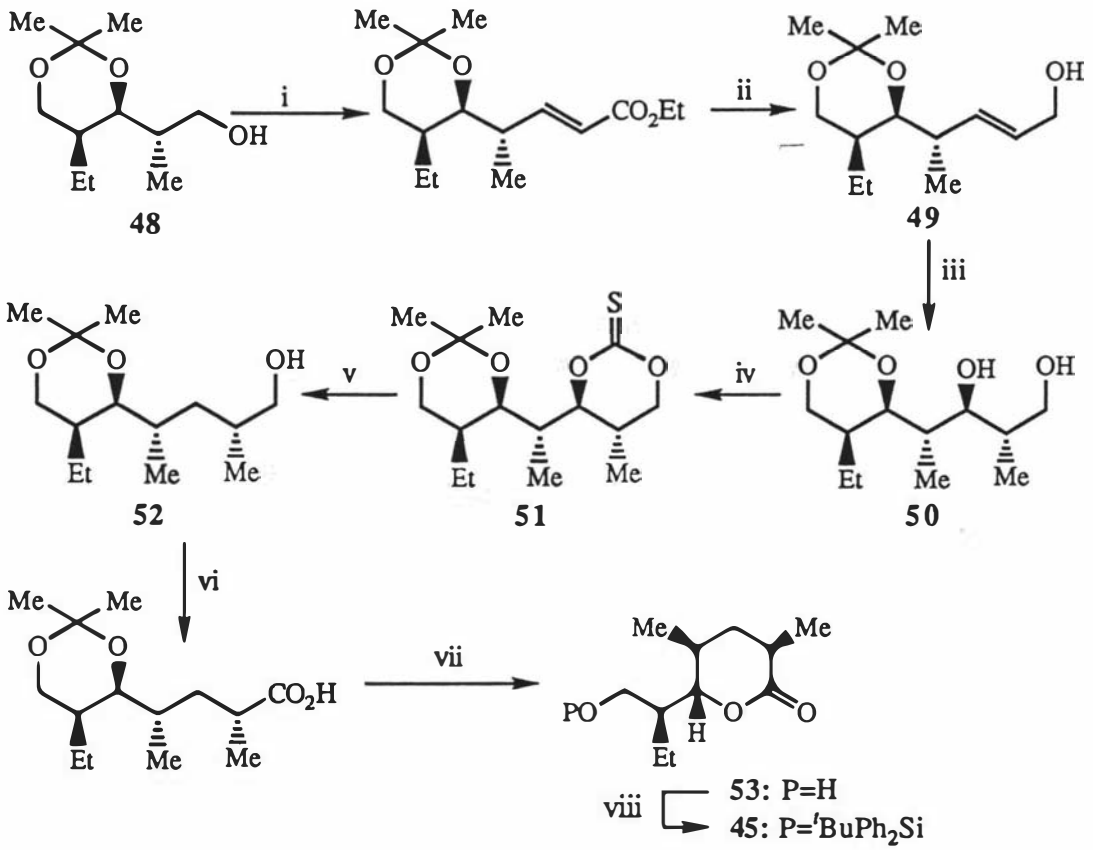
Synthesis of the right hand fragments.

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[11] **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**[19] to afford the alcohol **52**. Ruthenium catalysed oxidation[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**.

Scheme 10

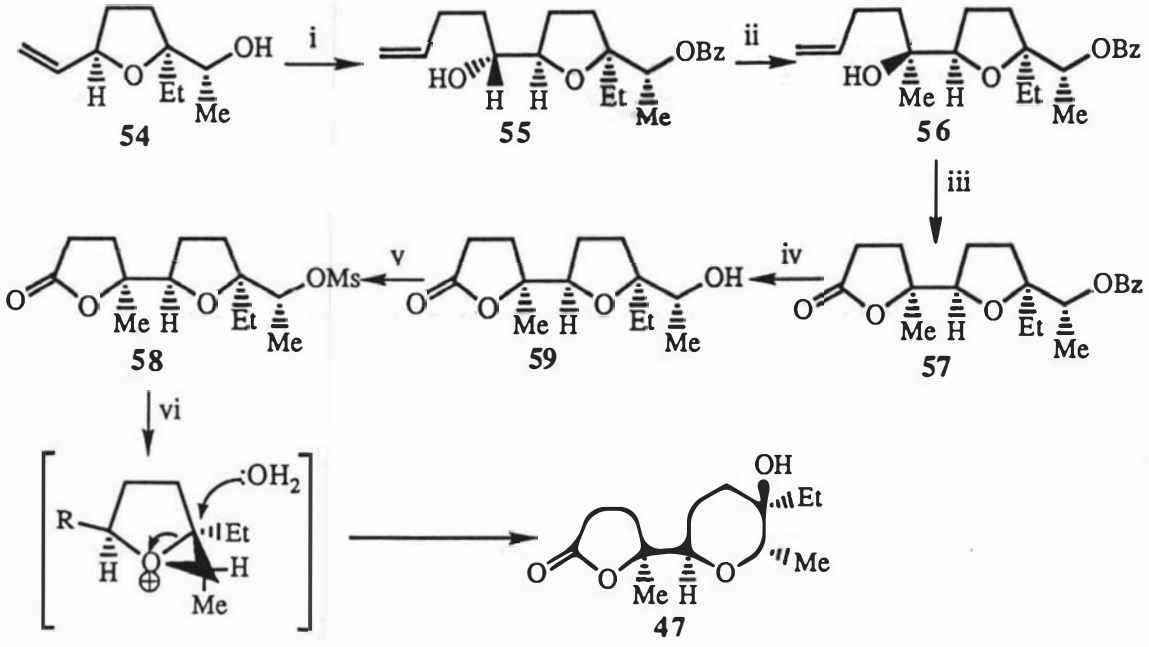


Reagents and conditions: (i) a: DMSO, $(COCl)_2$, CH_2Cl_2, -60°C, then Et_3N; b: $EtO_2CCH{=}PPh_3$, $ClCH_2CH_2Cl$, Δ; (ii) a: DIBAL, CH_2Cl_2, -40°C; b: $Ti(O^iPr)_4$, D-(-)-diethyl tartrate, ^tBuOOH, CH_2Cl_2, -23°C; (iii) $Me_3CuCNLi_2$, THF, -24°C to RT; (iv) $(imid)_2CS$, xylene, Δ; (v) a: Bu_3SnH, AIBN, toluene; b: CSA, $Me_2C(OMe)_2$; c: NaOH, H_2O, RT; (vi) RuO_2-$NaIO_4$ (cat.), $NaHCO_3$, acetone/H_2O; (vii) AcOH; (viii) $^tBuPh_2SiCl$, imidazole, DMF.

Structural similarities between lactone **47** and intermediates in the synthesis of the right hand side of lasalocid A **3**[9] suggested methodology for construction of this fragment (Scheme 11). Beginning with tetrahydrofuran **54**[9], the benzylated tetrahydrofuran underwent oxidative cleavage by treatment with osmium tetroxide/sodium periodate[21] followed by selective Grignard addition to afford the alcohol **55**. Swern oxidation[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[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**.

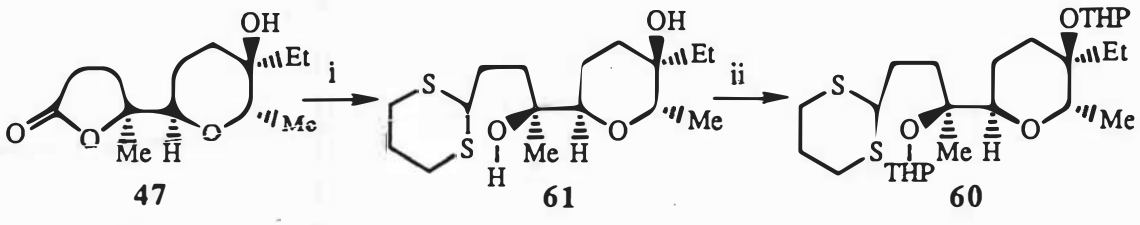
Scheme 11



Reagents and conditions: (i) a: KH, BzBr, THF, DMF, 0°C to RT; b: OsO_4-$NaIO_4$, dioxane, H_2O; c: CH_2=$CHCH_2CH_2MgBr$, Et_2O, -10°C; (ii) a: DMSO, $(COCl)_2$, CH_2Cl_2, -60°C, then Et_3N, -60°C to RT; c: MeMgBr, Et_2O, -10°C; (iii) a: OsO_4-$NaIO_4$, dioxane, H_2O; b: PCC, CH_2Cl_2; (iv) a: H_2, Pd-C, MeOH; (v) MsCl, pyridine, 0°C; (vi) $SrCO_3$, dioxane, H_2O, 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**.

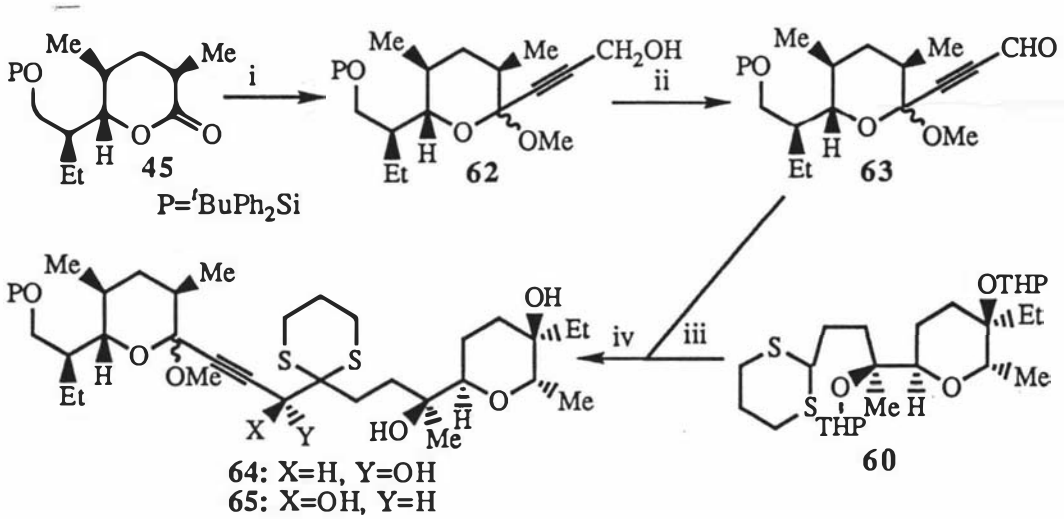
Scheme 12



Reagents and conditions: (i) a: DIBAL, CH_2Cl_2, -78°C; b: $HS(CH_2)_3SH$, BF_3-Et_2O, CH_2Cl_2, -10°C to RT; (ii) PPTS, DHP, CH_2Cl_2.

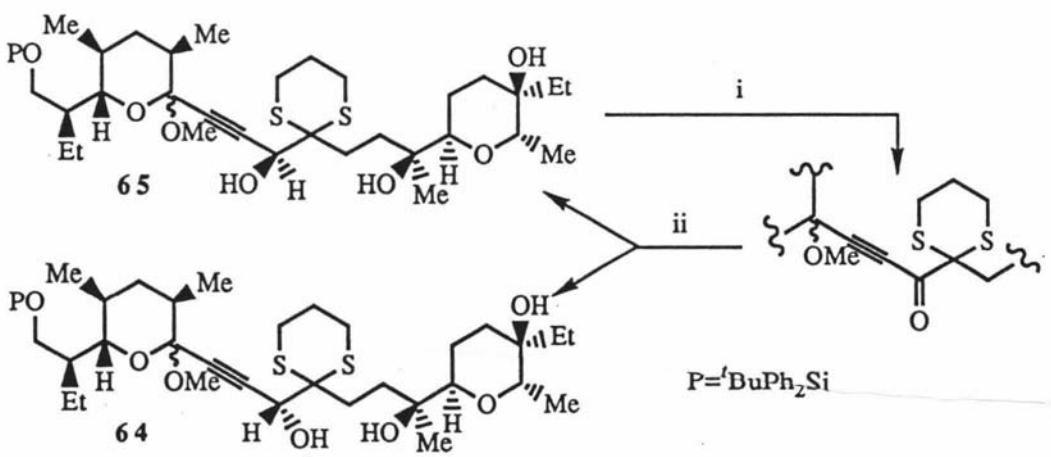
With the synthetic routes to the lactone **45** and pyran **60** subunits established, work began on the assembly of the *bis*-spiroketal unit **12** (Scheme 13). Reaction of the lithium acetylide derivative of propargyl alcohol, protected as the tetrahydropyranyl ether **46**, with lactone **45**, afforded 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) a: Li-C≡CCH$_2$OTHP **46**, THF, -78°C; b: MeOH, TSA; (ii) CrO_3-2Py, CH_2Cl_2, celite; (iii) ^{n}BuLi, THF, -20°C; (iv) TSA, MeOH.

Scheme 14



Reagents and conditions: (i) MnO_2, CH_2Cl_2; (ii) $NaBH_4$, MeOH, -12°C;

Oxidation of the alcohol **62** with Collins reagent[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 *N*-chlorosuccinimide in methanol, followed by acid induced cyclisation and acetylation to give the acetate **66** (Scheme 15). Reduction of the acetylene to the *cis* olefin and subsequent acid catalysed intramolecular ketalisation afforded the *bis*-spiroketal structure **67**. Extension of the left sidechain and reprotection of the allylic hydroxyl group was then carried out to give ketone **68** in preparation for the crossed aldol reaction that was to follow.

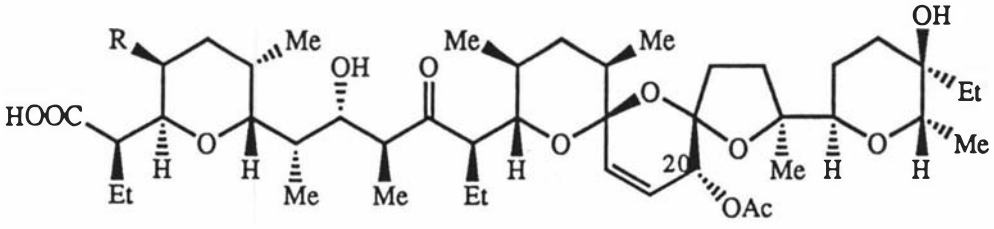
Coupling of the Left and Right Hand Fragments

With methodology established for synthesis of tetrahydropyrans **10** and **11** (Scheme 6), and *bis*-spiroketal **68** (Scheme 15), the crossed aldol condensation was investigated (Scheme 16). It was found that the optimum conditions[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 *epi*-salinomycin and *epi*-narasin, respectively.

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

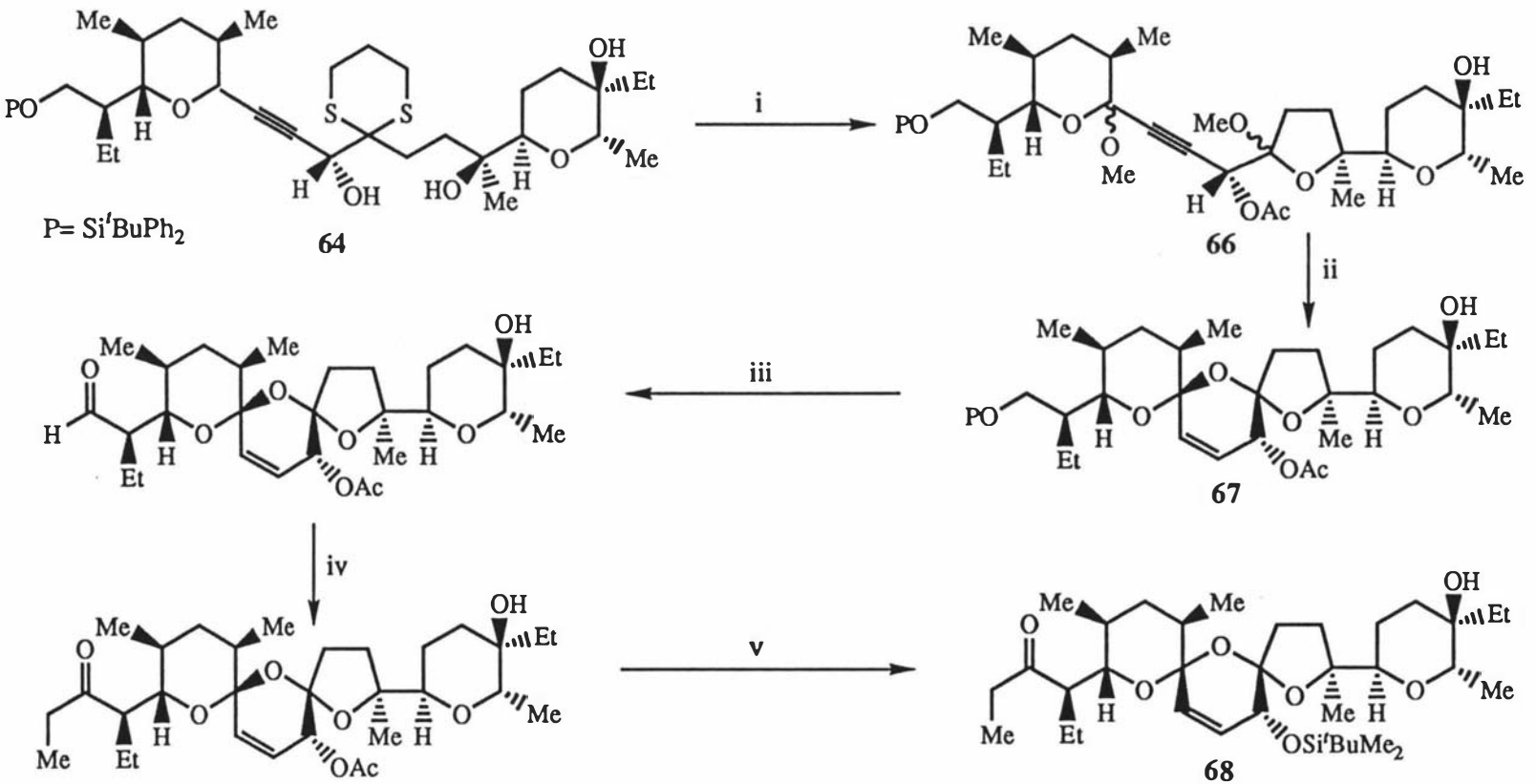
Acetylation of the C20 hydroxyl group of salinomycin and narasin followed by treatment with trifluoroacetic acid in dichloromethane affords exclusively *epi*-narasin acetate **71** or *epi*-salinomycin acetate **72** (Figure 4). This observation, coupled with the

Figure 4



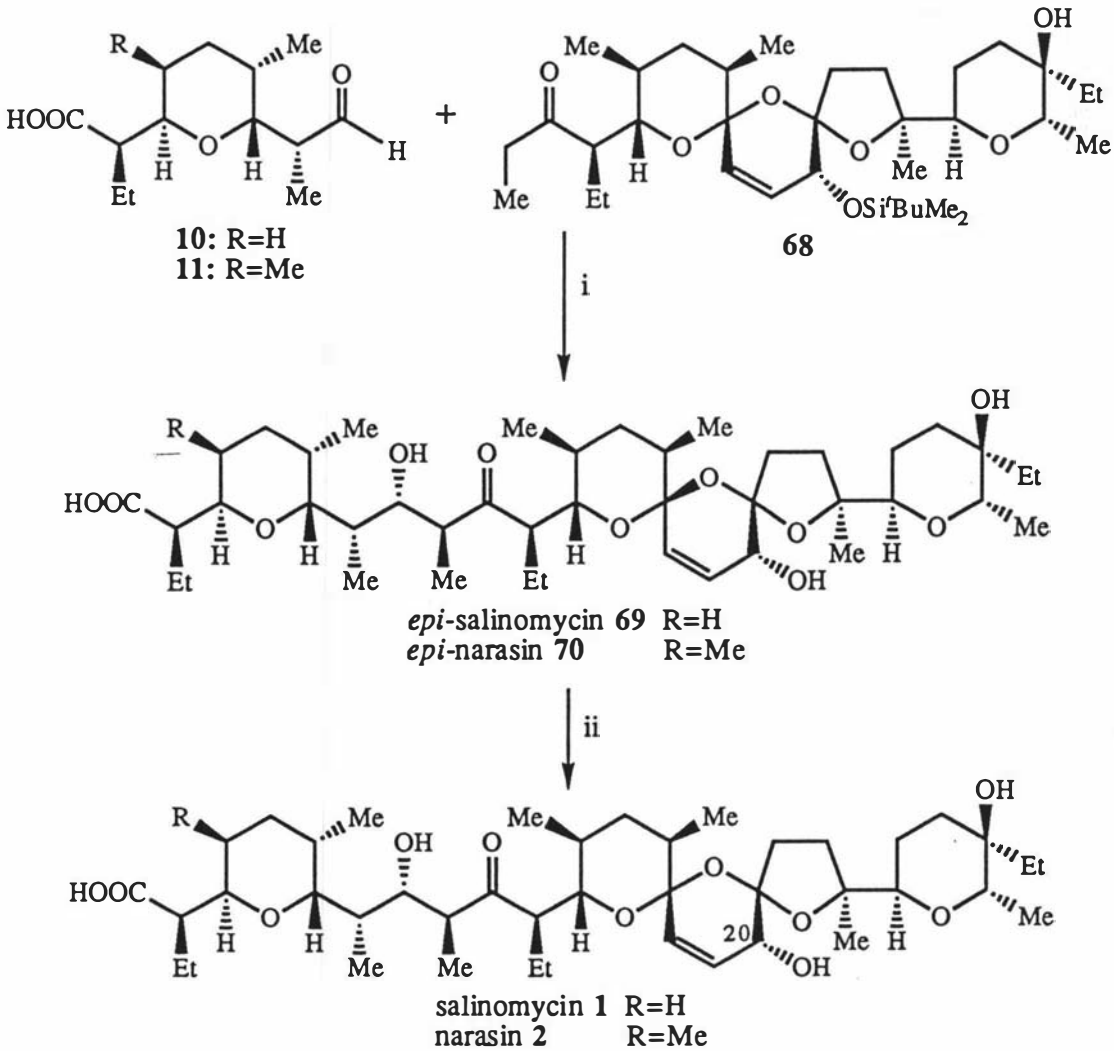
epi-narasin acetate **71** R=Me
epi-salinomycin acetate **72** R=H

Scheme 15



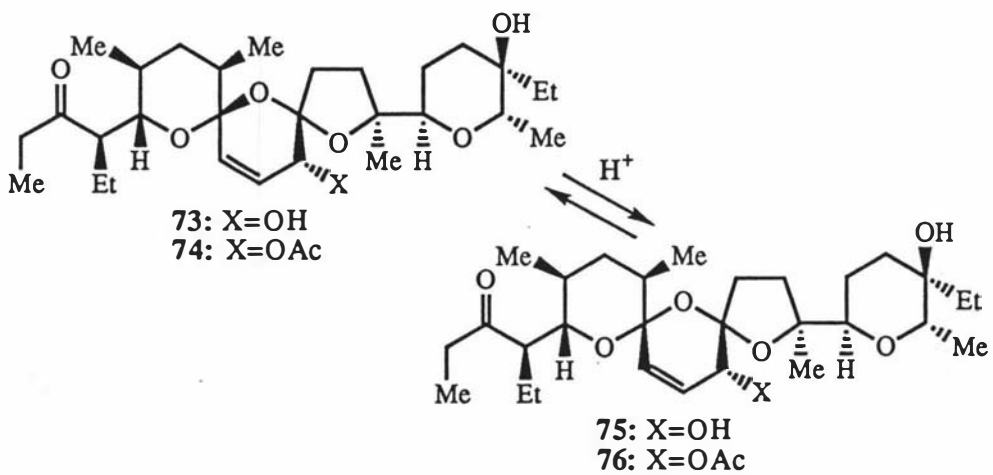
Reagents and conditions: (i) a: NCS, MeOH; b: TSA; c: Ac_2O, pyridine; (ii) a: H_2, Lindlar catalyst, MeOH; b: 80% aq. AcOH; (iii) a: $^nBu_4NF$, THF; b: CrO_3.2Py, CH_2Cl_2; (iv) a: EtMgCl, Et_2O, -40°C to RT; b: CrO_3-2Py, CH_2Cl_2; c: K_2CO_3, MeOH; d: $^tBuMe_2SiCl$, DMAP, DMF, 80°C.

Scheme 16



Reagents and conditions: (i) a: $(C_6H_{11})_2NMgBr$, THF, -50°C then **10** or **11**, -50°C, 20 min; b: $^nBu_4NF$, THF; (ii) TFA, 4A molecular sieves, CH_2Cl_2.

Scheme 17



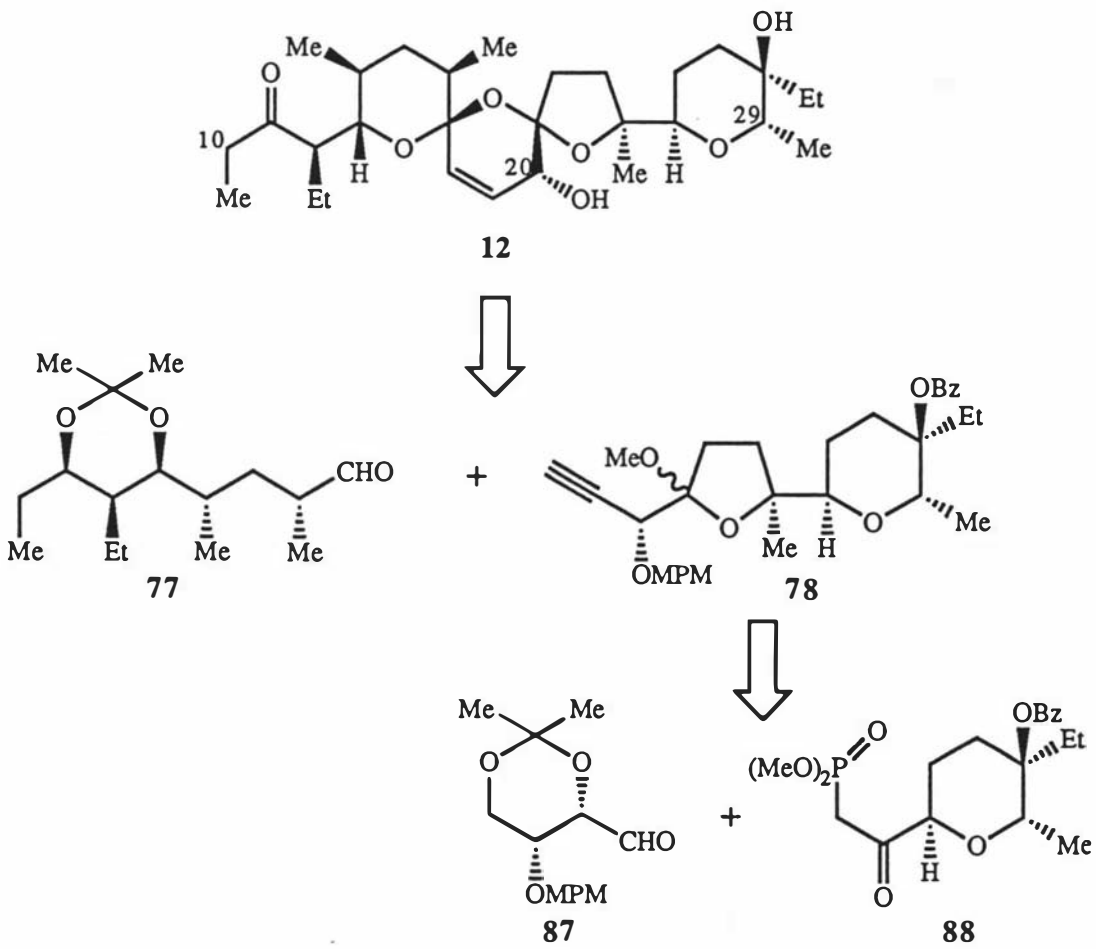
fact that upon treatment with acid (TFA, CH_2Cl_2) the epimeric *bis*-spiroketals **73** and **74** were favoured over the conformations of *bis*-spiroketals **75** and **76** (Scheme 17), suggests that the allylic hydroxyl group serves to stabilise the observed conformations of the natural products through the formation of long distance intramolecular hydrogen bonding, a theory corroborated by the recently published solution structure of sodium complexed salinomycin[6].

1.2.2 Yonemitsu *et al* [26-29]

Synthesis of the Right Hand Fragment

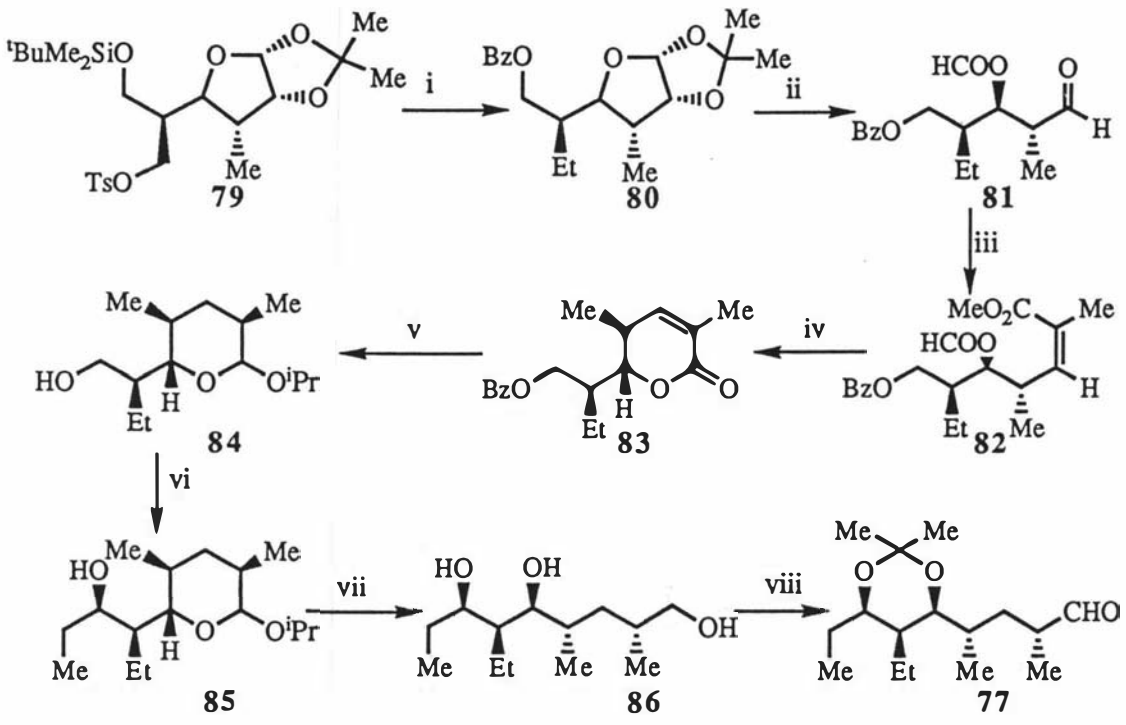
In 1987, a second formal synthesis of salinomycin **1** was detailed by Yonemitsu *et al*[26], in a paper describing methodology for the synthesis and coupling of the middle (C10-C17) **77** and right (C18-C30) **78** segments of salinomycin (Scheme 18).

Scheme 18



Synthesis of the aldehyde **77** was carried out using glucose derivative **79**[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 α, β-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_2O_3 to give the alcohol **84** with excellent stereoselectivity. Swern oxidation[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 synthon **77**.

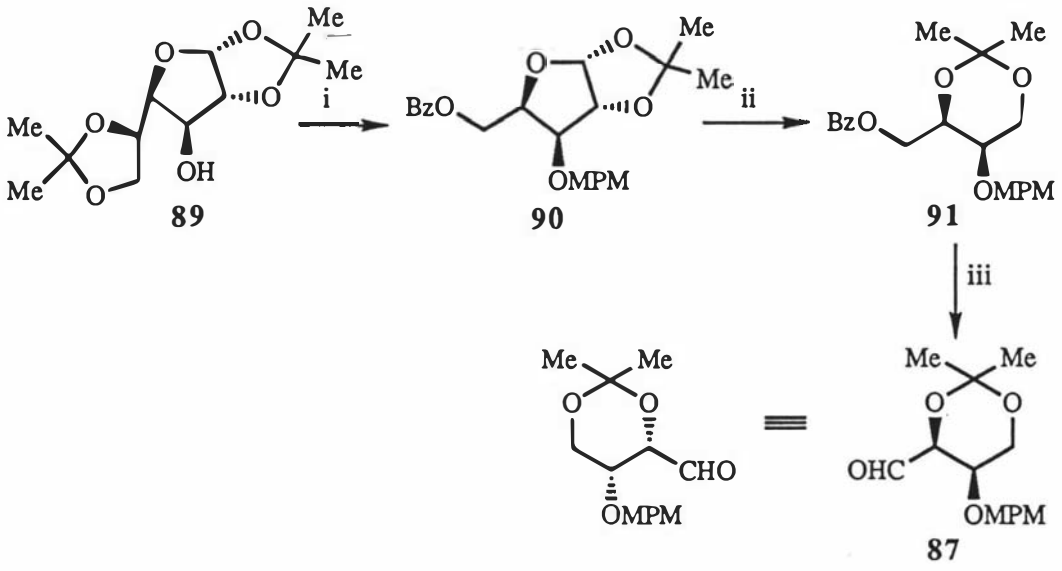
Scheme 19



Reagents and conditions: (i) a: CuI, MeLi, Et_2O, -25°C; b: 1M HCl, MeOH; c: $C_6H_5CH_2Cl$, DMSO/THF, NaH; (ii) a: 4M HCl, THF, 45°C; b: $NaIO_4$, THF/MeOH; (iii) $(MeO)_2P(O)CHMeCO_2Me$, NaH, THF, -78 to -15°C; (iv) K_2CO_3, MeOH; (v) a: DIBAL, toluene, -80°C; b: CSA, ^iPrOH; c: Raney Ni(W-2), EtOH; d: Rh-Al_2O_3, EtOH; (vi) a: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N; b: EtMgBr, Et_2O, -50°C; (vii) a: 1M HCl, THF, 50°C; b: $LiAlH_4$, THF; (viii) a: CSA, $Me_2C(OMe)_2$; b: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N.

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



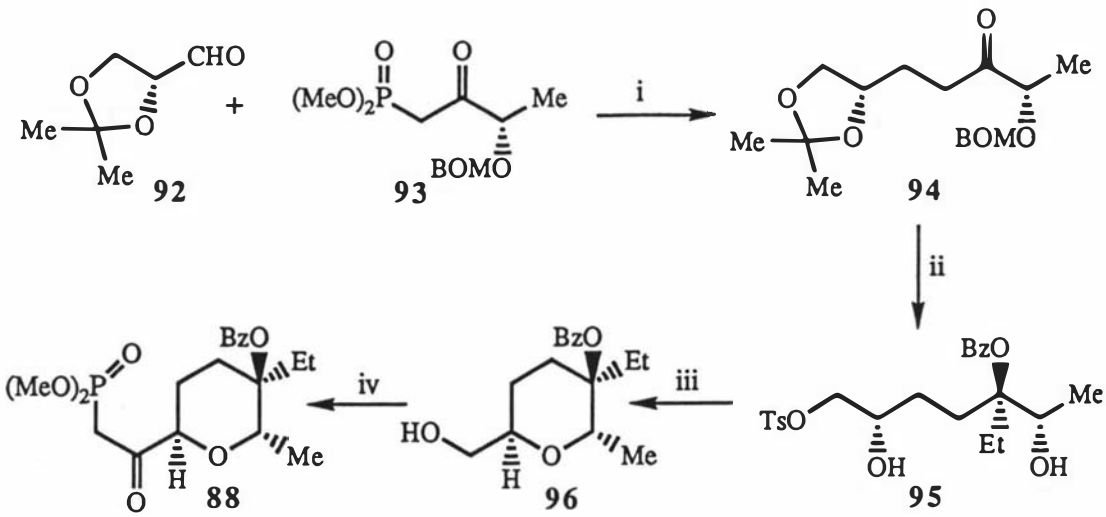
89 **90** **91** **87**

Reagents and conditions: (i) a: *p*-$MeOC_6H_4CH_2Cl$, NaH, DMSO/THF; b: 2% H_2SO_4, MeOH; c: $NaIO_4$, $MeOH/H_2O$; d: $NaBH_4$; e: BzCl, NaH, THF/DMSO; (ii) a: 4M HCl, THF, 55°C; b: $NaIO_4$, THF, $MeOH/H_2O$; c: $LiAlH_4$, THF, 0°C; d: $(MeO)_2C(Me)_2$, CSA, acetone; (iii) a: Raney Ni (W-2), EtOH; b: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N.

Synthesis of phosphonate **88** (Scheme 21) began with the Wittig-Horner coupling of L-glyceraldehyde derivative **92**[27] and β-ketophosphonate **93**, derived from L-lactate[31], 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**.

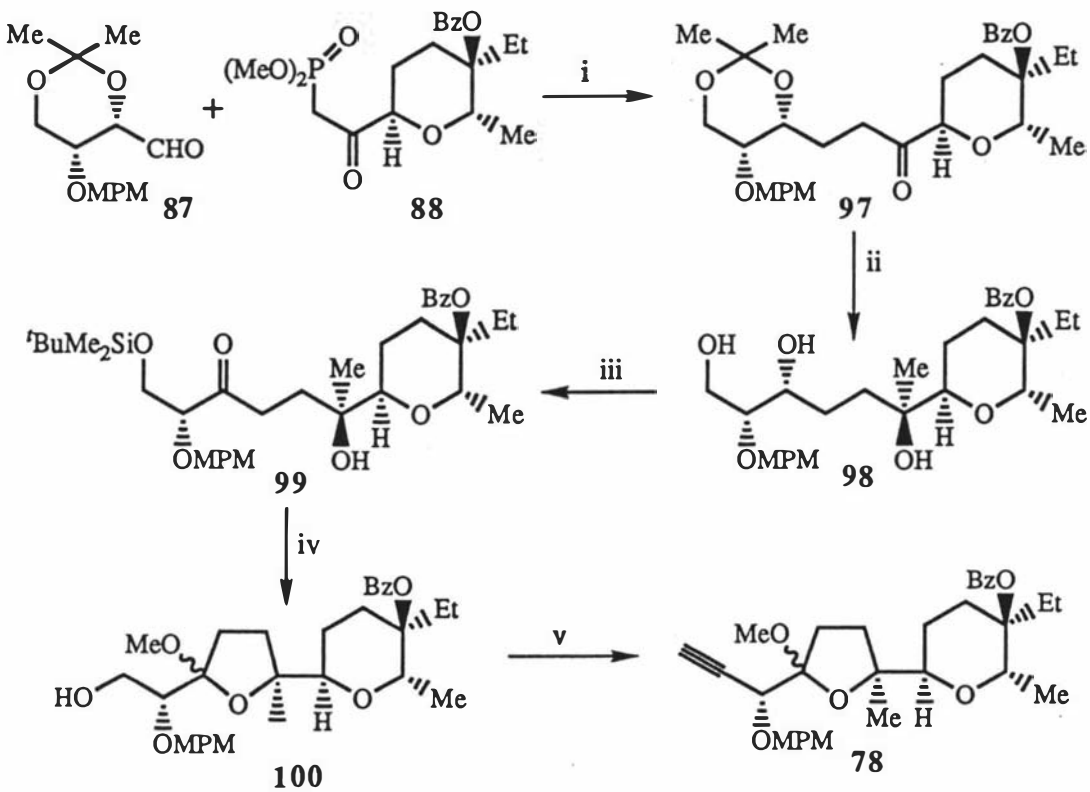
The phosphonate **88** and aldehyde **87** were then coupled (Scheme 22), and the resulting enone reduced, to give ketone **97**. Following treatment of the ketone **97** with methyllithium, selective protection/deprotection was carried out to afford the triol **98**. Protection of the primary alcohol with a TBDMS group, followed by Swern oxidation[22,23] of the secondary alcohol gave ketone **99** which underwent cyclisation

Scheme 21



Reagents and conditions: (i) a: NaH, DMSO/THF, 0°C then **92**; b: H_2, 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, H_2SO_4, acetone, 0°C; b: CH_2N_2; c: $(MeO)_2P(O)Me$, ^nBuLi, THF, -93°C.

Scheme 22



Reagents and conditions: (i) a: NaH, DMSO/THF, 0°C then **87**; b: H_2, Pd-C, EtOAc; (ii) a: MeLi, Et_2O, -93°C; b: 1M HCl, THF; (iii) a: $^tBuMe_2SiCl$, imidazole, CH_2Cl_2; b: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N; (iv) a: CSA, MeOH; b: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N; (v) a: $PhHgCCl_2Br$, Ph_3P, benzene, 80°C; b: ^nBuLi, THF, -78°C.

and methylation to give the acetal **100**. Subsequently acetal **100** was converted to the desired acetylene synthon **78**, *via* a dichloroolefin[14,15].

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 al*[7] 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 **12**[28] 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.

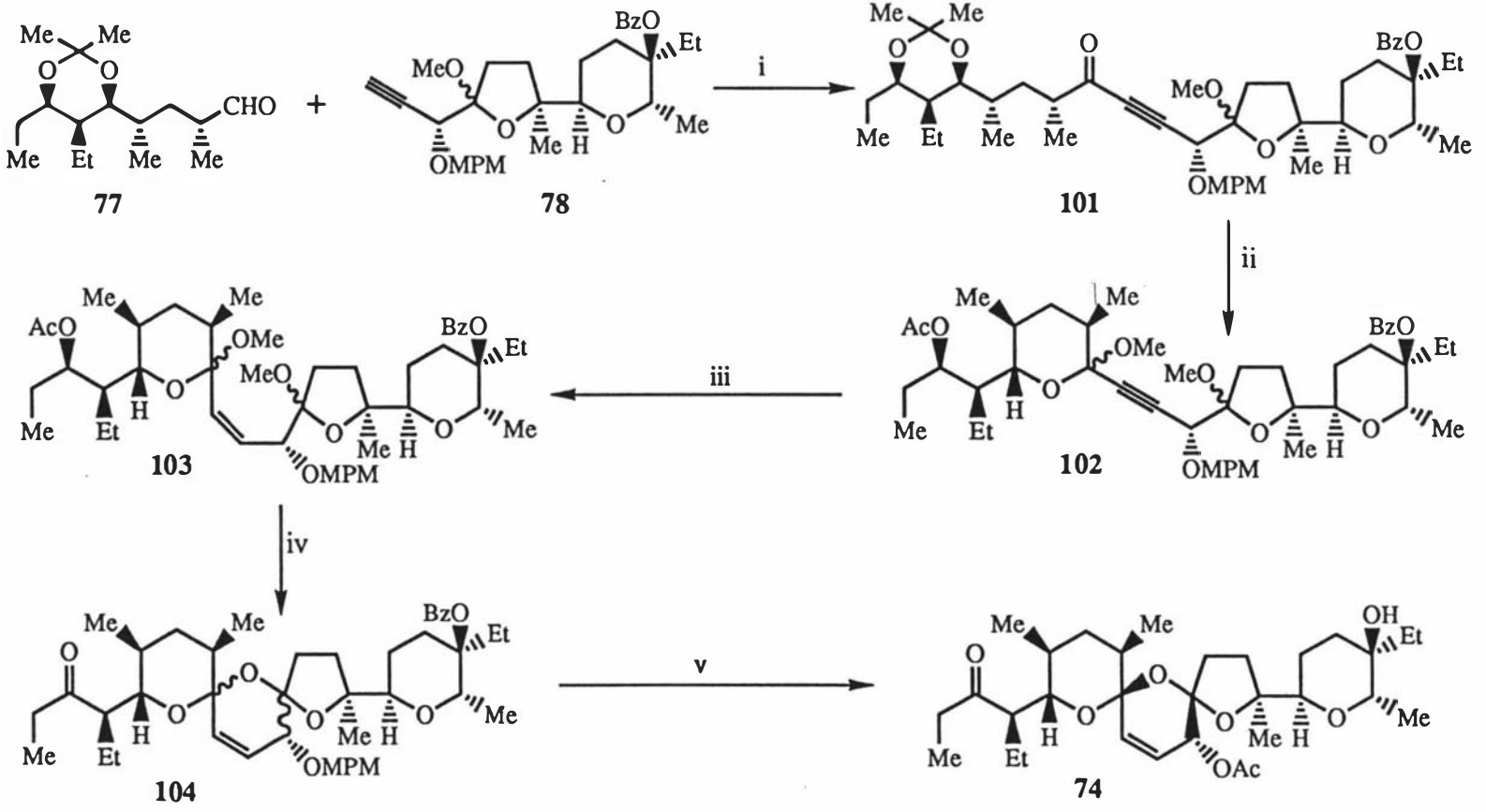
Beginning with tetrahydropyran **98**, an intermediate in an earlier pathway (see Scheme 22), application of selective protection/deprotection followed by Seyferth's methodology[14,15] afforded acetylene **105**. Coupling of the acetylene **105** to aldehyde **77** and subsequent assembly of the *bis*-spiroketal, 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 al*[32].

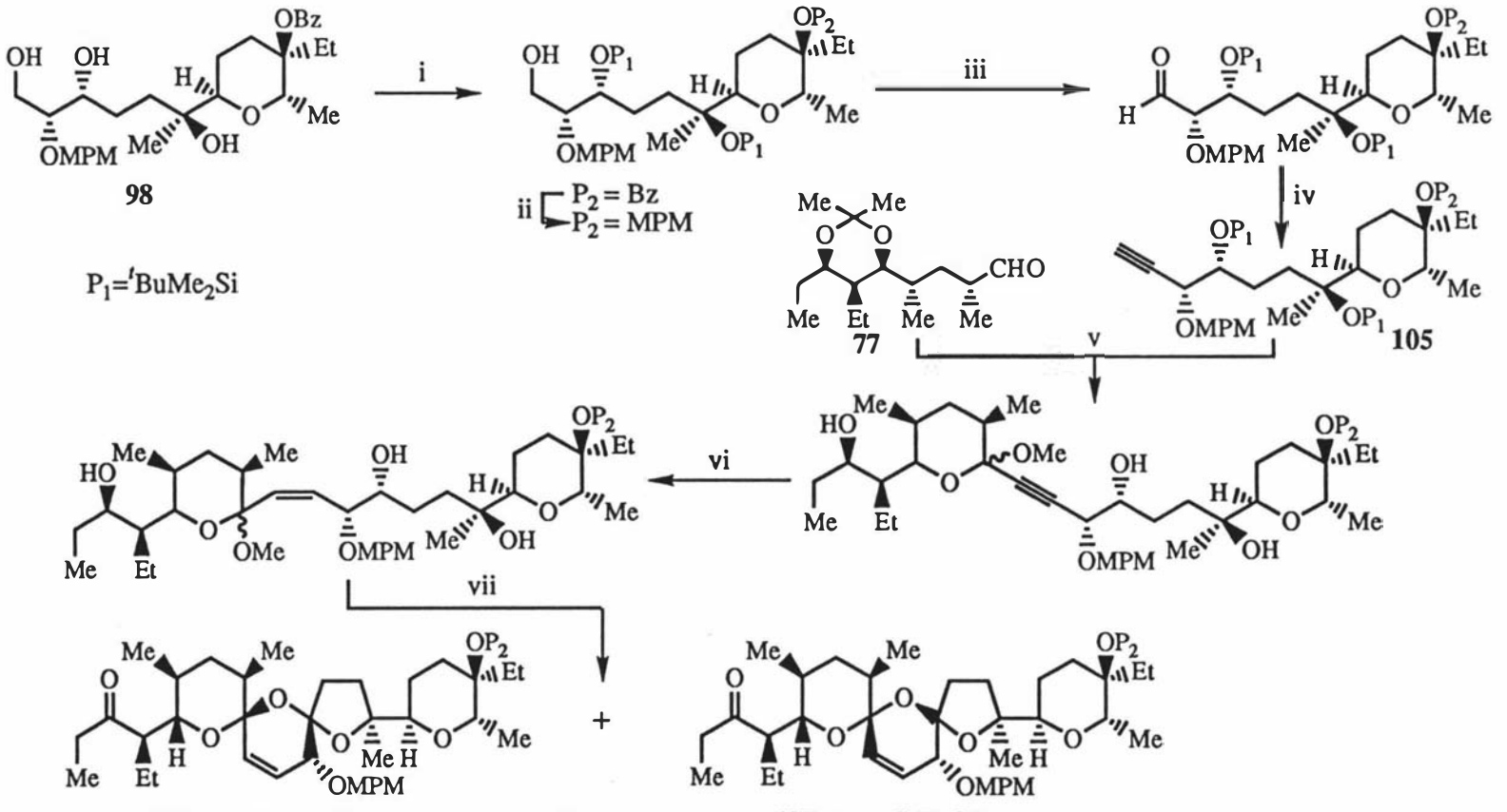
Chain extension by conversion of aldehyde **110** to the aldehyde **111** followed by coupling with the β-ketophosphonate **112**, the preparation of which has, again, yet to be detailed, afforded the ketone **113** which was stereoselectively converted to the epoxide **114**. This allowed generation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

Scheme 23



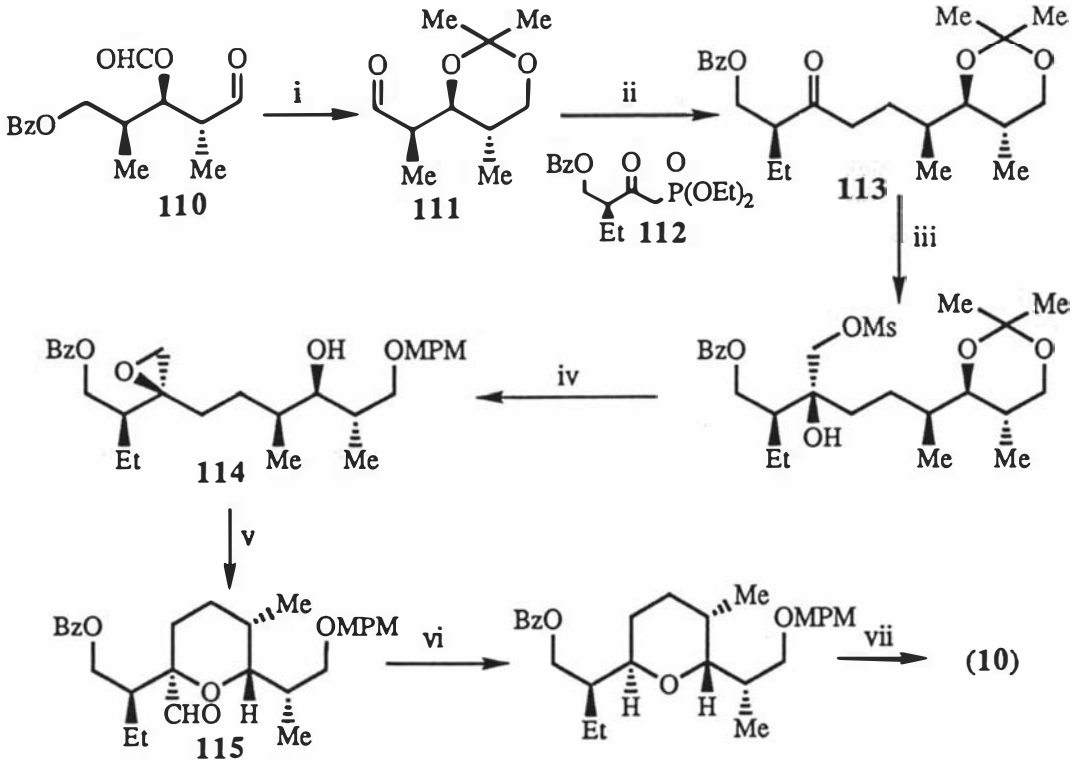
Reagents and conditions: (i) a: ^{n}BuLi, THF, -78°C then **77**; b: MnO_2, CH_2Cl_2; (ii) a: CSA, MeOH; b: Ac_2O, Et_3N, DMAP, CH_2Cl_2; (iii) H_2, Lindlar catalyst, MeOH/AcOH; (iv) a: 80% AcOH; b: KOH, aq. MeOH, 60°C; c: PCC, CH_2Cl_2; (v) a: DDQ, H_2O/CH_2Cl_2 (1:10); b: Ac_2O, Et_3N, DMAP, CH_2Cl_2; c: CSA, CH_2Cl_2.

Scheme 24



Reagents and conditions: (i) $C_6H_5CH_2Cl$, pyridine, CH_2Cl_2, 0°C; b: $^tBuMe_2SiOTf$, Et_3N, CH_2Cl_2, 0°C; c: KOH, MeOH, 55°C; (ii) a: H_2, Raney Nickel, EtOH, 60°C; b: $Me_2C(OMe)_2$, CSA, benzene; c: $MeOC_4H_6CH_2Cl$, NaH, DMF; d: CSA, MeOH; (iii) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N; (iv) P_2 = Bz a: $PhHgCCl_2Br$, Ph_3P, benzene, 80°C; b: ^nBuLi, THF, -78°C; (iv) P_2 = MPM a: CBr_4, Ph_3P, CH_2Cl_2, -78°C; b: LDA, THF, -30°C; (v) a: ^nBuLi, THF, -78°C then **77**; b: CSA, MeOH; c: $^nBu_4NF$, THF/dioxane, 65°C; (vi) Lindlar catalyst, H_2, MeOH; (vii) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N; b: CSA, CH_2Cl_2.

Scheme 25

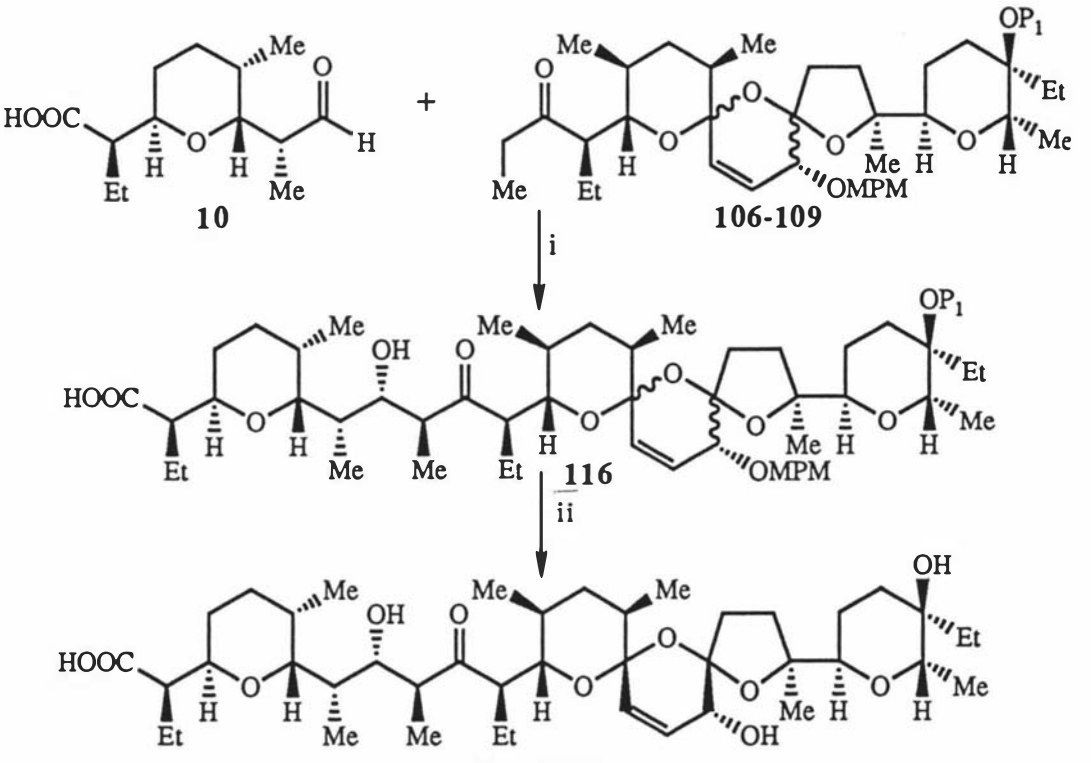


Reagents and conditions: (i) a: $LiAlH_4$, Et_2O, 0°C; b: $Me_2C(OMe)_2$, CSA; c: H_2, Pd-C, EtOH; d: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C, then Et_3N; (ii) a: NaH, DMF/THF, 0°C; b: H_2, Pd-C, EtOAc; (iii) a: CH_2=CHMgBr, THF, -78°C; b: O_3, CH_2Cl_2, -78°C, $NaBH_4$; c: MsCl, Et_3N, CH_2Cl_2, 0°C; (iv) a: 1M HCl, THF; b: K_2CO_3, MeOH; c: *p*-$MeOC_6H_4CH_2Cl$, NaH, THF; (v) a: CSA, CH_2Cl_2, 0°C; b: DMSO, $(COCl)_2$, CH_2Cl_2 then Et_3N; (vi) $(Ph_3P)_3RhCl$ (Wilkinsons's catalyst), MeCN, 160°C; (vii) a: DDQ, CH_2Cl_2/H_2O (20:1); b: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N; c: $(CH_2OH)_2$, TsOH, benzene; d: H_2, Pd-C, EtOAc; e: CrO_3, H_2SO_4, acetone; f: 2M HCl, THF.

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[7]. Deprotection of the aldol product **116**, followed by equilibration in acid, afforded a single isomer of the natural product, salinomycin **1**.

Scheme 26



Reagents and conditions: (i) $(C_6H_{11})_2NMgBr$, THF, -55°C; (ii) (For $P_1 = C_6H_5CH_2$) DDQ, CH_2Cl_2, buffer (pH 6.86), RT, 1.5 h., 15%; (ii) (For $P_1 = p$-$MeOC_6H_4CH_2$) a: DDQ, CH_2Cl_2/H_2O (10:1), RT, 10 min., 95%; b: TFA, CH_2Cl_2, 70%.

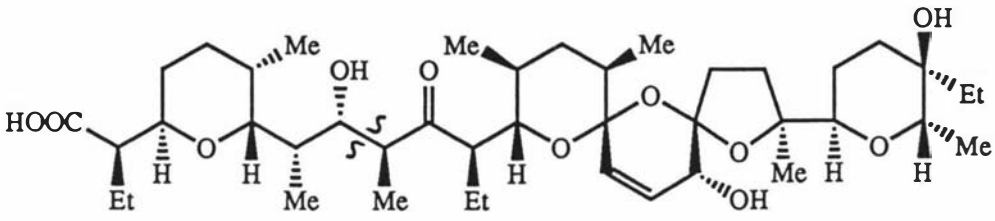
1.2.3 Brown and Kocienski[33,34]

The recent synthesis of salinomycin **1** by Brown and Kocienski[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).

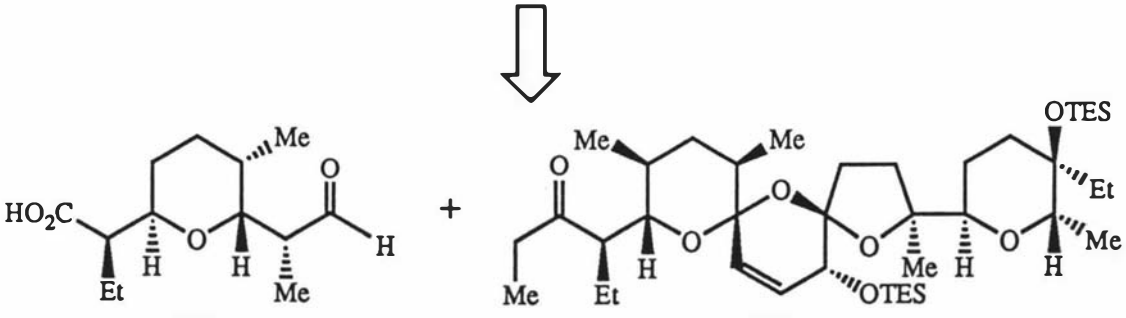
Retrosynthetic analysis of salinomycin **1** was carried out as detailed in Scheme 27. Following the standard retro-aldol disconnection to give the aldehyde **10** and ketone **118** the ketone subunit was further disconnected, *via* the acyl furan **117**, to give the furan **119** and the lactone **120**.

The starting material selected for synthesis of the furan fragment **119** (Scheme 28) was the homochiral acid **121**, readily prepared by the methanolysis, and subsequent resolution of *meso*-2,4-dimethylglutaric anhydride[35,36] using (-)-α-methylbenzyl-amine[37-39]. Selective reduction of the carboxylic acid **121** with borane-methyl sulphide and protection of the resulting alcohol afforded the benzyloxymethyl ether **122**. Reduction of the ester **122** followed by Swern oxidation to the aldehyde **123**

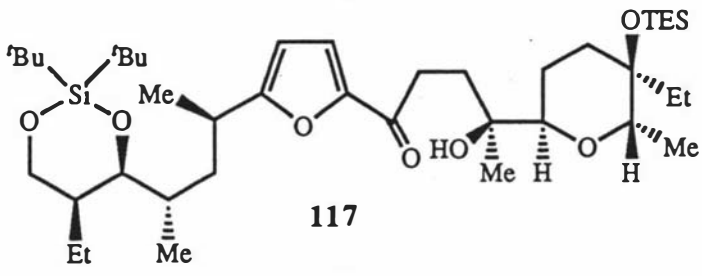
Scheme 27



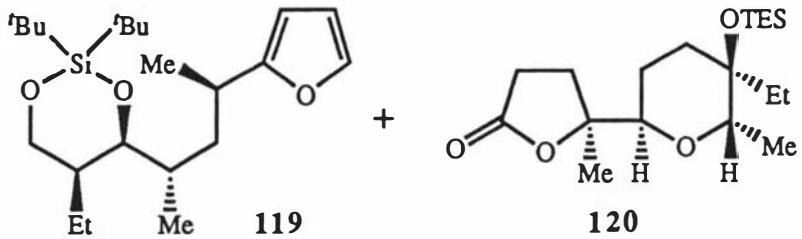
salinomycin **1**



10 **118**



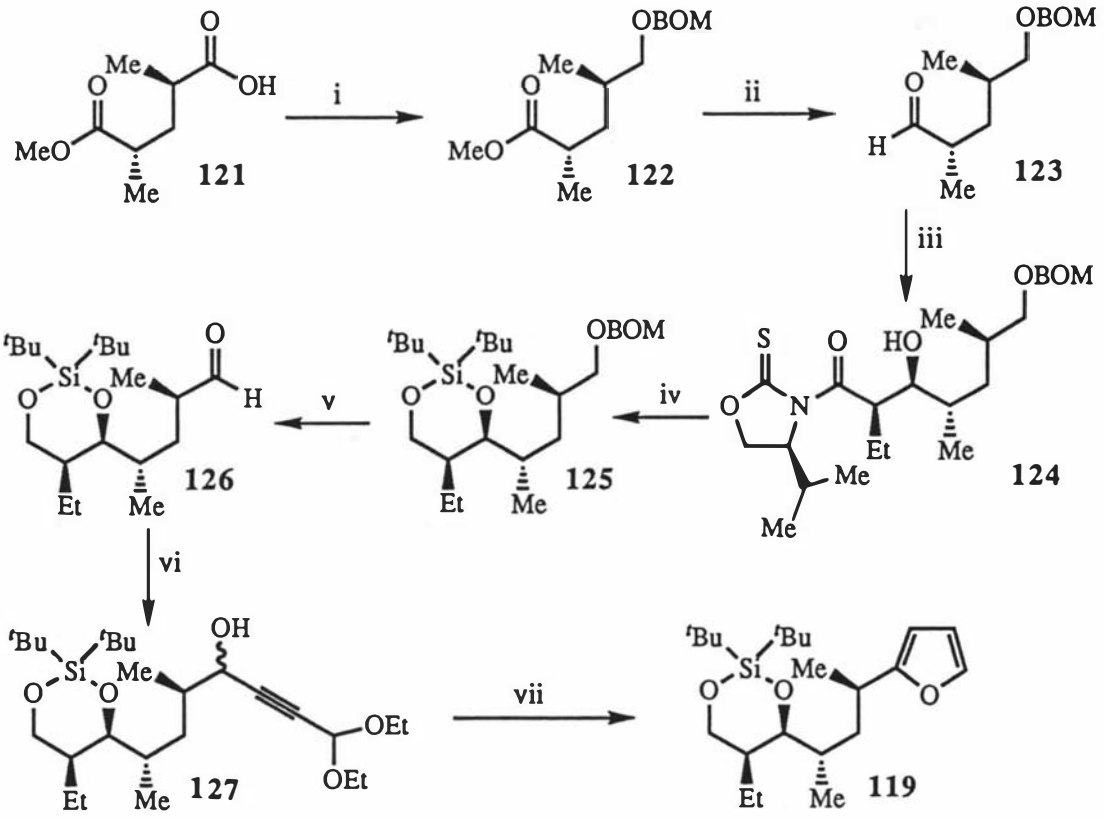
117



119 **120**

then provided the necessary functionality for a highly diastereoselective Sn(II) catalysed aldol reaction with (S)-*N*-butanoyl-4-isopropyloxazolidine-2-thione[40] to give the oxazolidinethione **124**. Facile reductive cleavage of the oxazolidinethione **124**[41] with sodium borohydride afforded a 1,3-diol which was subsequently protected as the di-*tert*-butylsilane derivative **125**[42,43]. Following removal of the benzyloxymethyl

Scheme 28



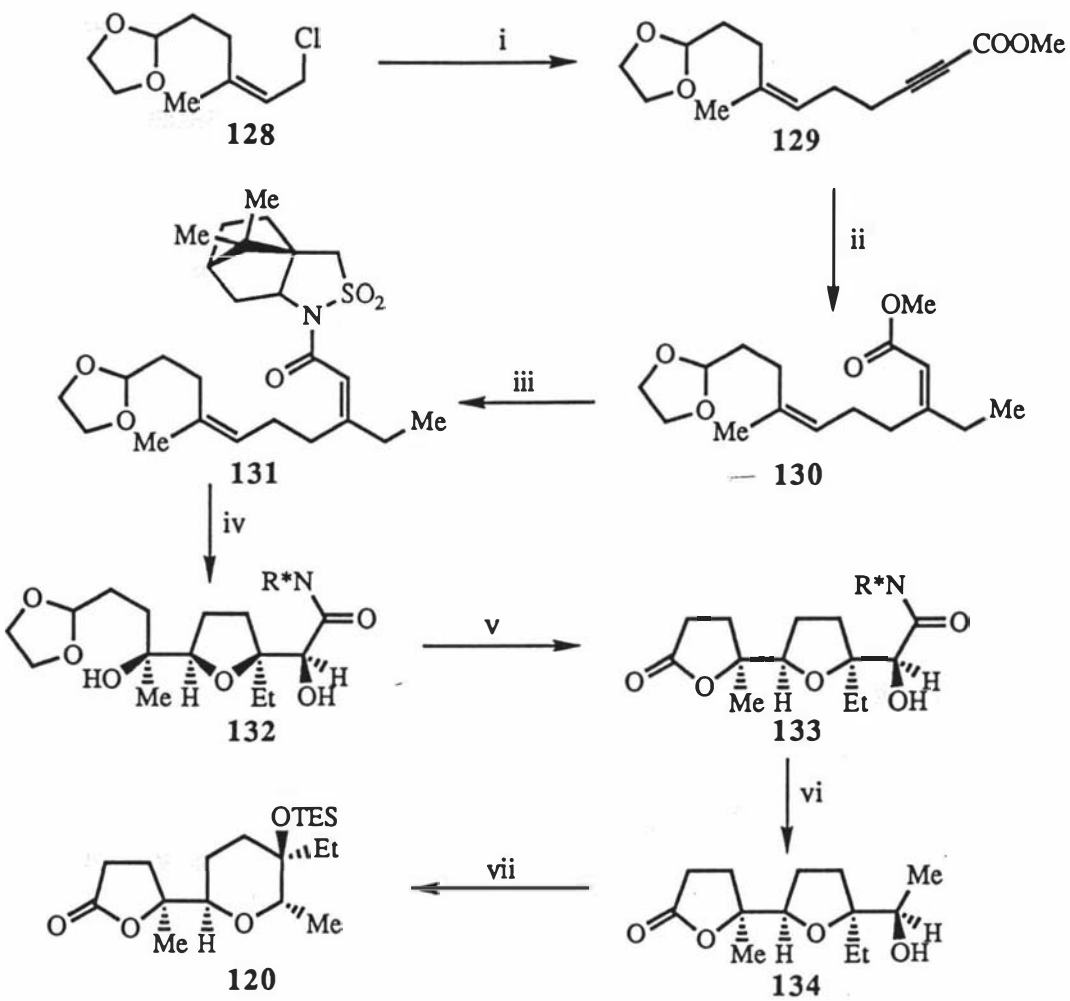
Reagents and conditions: (i) a: BH_3·SMe_2; b: BOMCl, Bu_4NI, $(^iPr)_2NEt$; (ii) a: $LiAlH_4$; b: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N; (iii) (S)-*N*-butanoyl-4-isopropyloxazolidine-2-thione, $Sn(OTf)_2$, N-ethylpiperidine, CH_2Cl_2, -80°C; (iv) a: $NaBH_4$, THF/H_2O; b: $^tBu_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2; (v) a: H_2, Raney Ni, EtOH; b: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N; (vi) $(EtO)_2CH$-C≡C-Li, THF, -78°C; (vii) a: H_2, Pd-$BaSO_4$, quinoline, MeOH; b: PPTS, CH_2Cl_2.

protecting group and Swern oxidation[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**[33] using propynyldilithium[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)-bornane-10,2-sultam[45] chiral auxiliary followed by treatment with potassium permanganate resulted in asymmetric oxidation[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[47] and removal of

Scheme 29

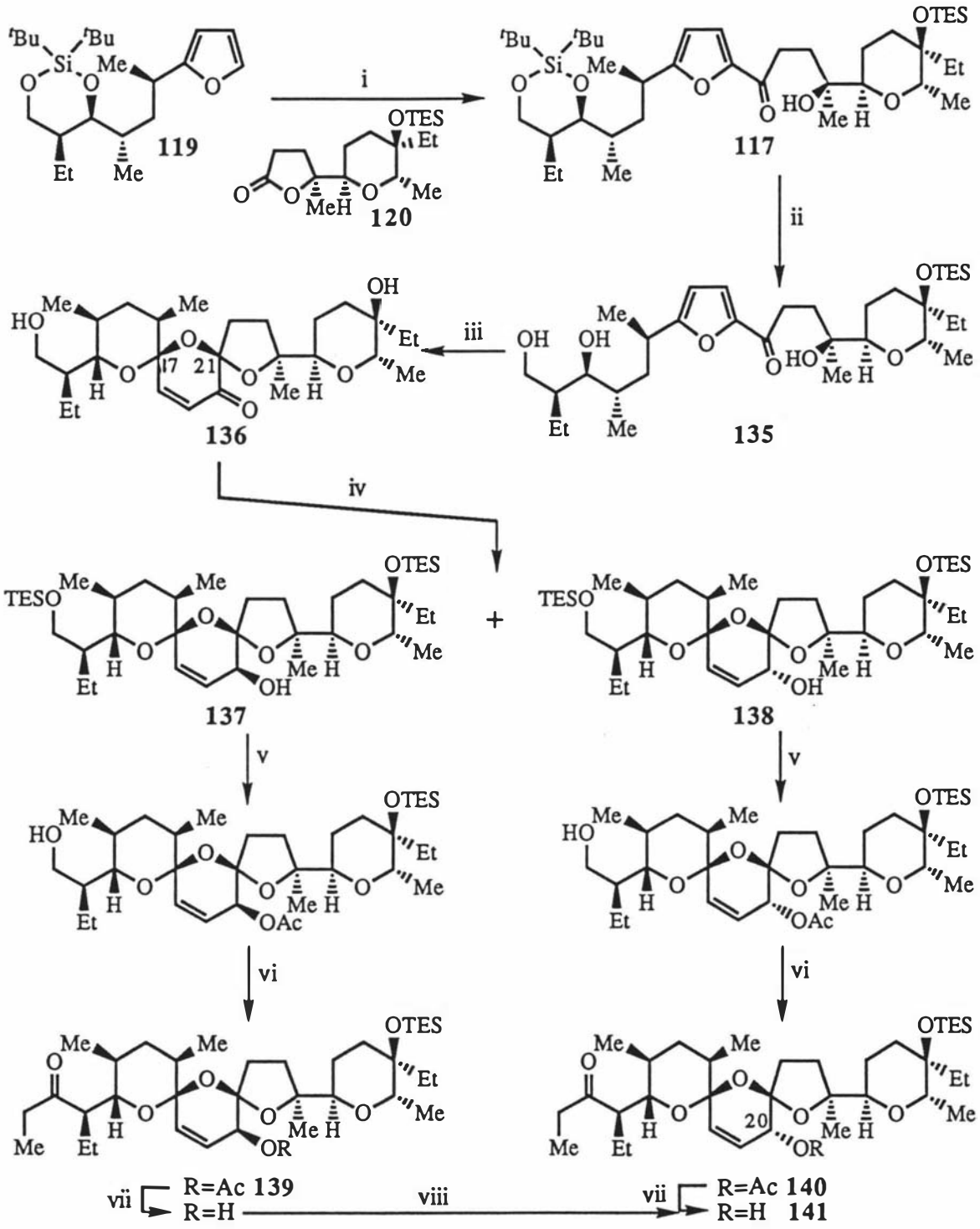


Reagents and conditions: (i) a: Li-C≡C-CH_2Li, Et_2O, -78° to RT; b: BuLi, THF; c: ClCOOMe, -80°C; (ii) Et_2CuLi; (iii) a: NaOH; b: BuLi; c: $(COCl)_2$; d: R*NLi; (iv) $KMnO_4$, AcOH, NaOAc, acetone/H_2O, -35°C; (v) a: O_3, EtOAc, -80°C; b: TSA, CH_2Cl_2; (vi) a: $NaBH_4$, BH_3·SMe_2, THF; b: TsCl, Et_3N, DMAP, CH_2Cl_2; c: Bu_3SnH, NaI, AIBN, DME, 80°C; (vii) a: MsCl, Et_3N, CH_2Cl_2, -10°C; b: Ag_2CO_3, acetone/H_2O, Δ; c: TESOTf, 2,6-lutidine, CH_2Cl_2.

the primary hydroxyl of the resulting diol by reduction of the corresponding iodide[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[8]. Thus, the mesylate derived from alcohol **134** was displaced with participation of the neighbouring oxygen to give an oxironium 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 *N*-bromosuccinimide[50] in

Scheme 30

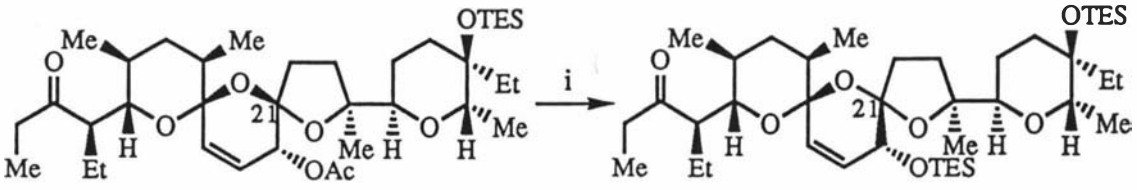


Reagents and conditions: (i) ^{t}BuLi, THF, -80 to 0°C then **120** -80°C to RT; (ii) Py·HF, pyridine/THF; (iii) a: NBS, THF/H_2O (3:1); b: 5% HF, MeCN/H_2O; (iv) a: TESOTf, 2,6-lutidine; b: $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH; (v) a: Ac_2O, pyridine, DMAP, CH_2Cl_2; b: Py·HF, pyridine/THF; (vi) a: Dess-Martin oxidation; b: EtMgCl, THF; c: Dess-Martin oxidation; (vii) K_2CO_3, MeOH; (viii) a: ArCOOH, Ph_3P, DEAD, benzene; b: K_2CO_3, 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



140 **142**

Reagents and condititions: (i) a: CSA, CH_2Cl_2; b: TESOTf, 2,6-lutidine; c: K_2CO_3, MeOH; d: TESCl, Et_3N, DMAP.

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

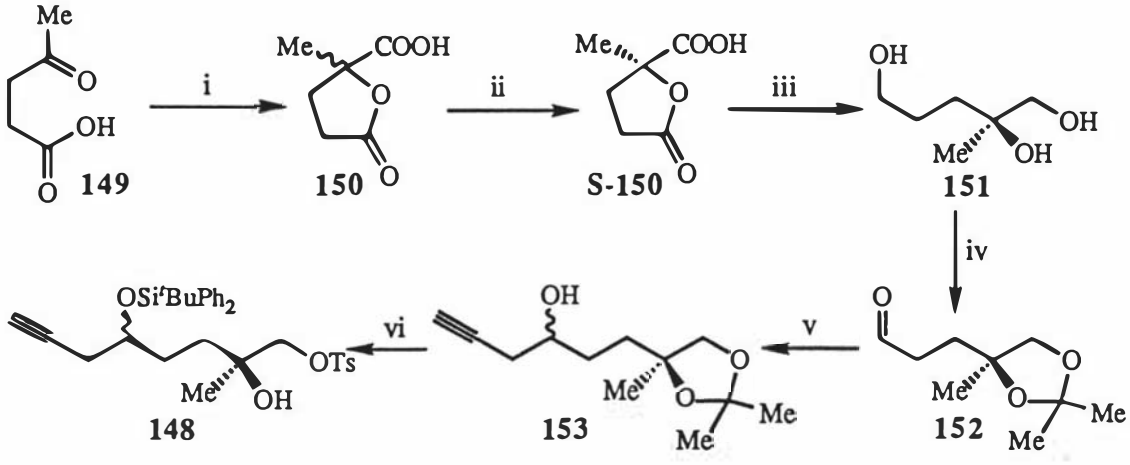
The synthetic strategies employed by Kishi *et al*[7], Yonemitsu *et al*[26-28] in the construction of the *bis*-spiroketal moiety of salinomycin share several common elements. In both strategies the terminal tetrahydropyran ring is incorporated into the molecule prior to the assembly of the central *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[33,34] also involves incorporation of the terminal tetrahydropyran ring prior to assembly of the central *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 *bis*-spiroketal section of *epi*-17-deoxy-(O-8)-salinomycin **143** was reported by Brimble and Williams[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 *bis*-spiroketal **145** and the trisubstituted bromoalkene **146**. The key step for construction of the *bis*-spiroketal **145** then involved oxidative cyclisation of the bicyclic hydroxyspiroketal **147** which was disconnected further to the lactone **45** and the acetylene **148**.

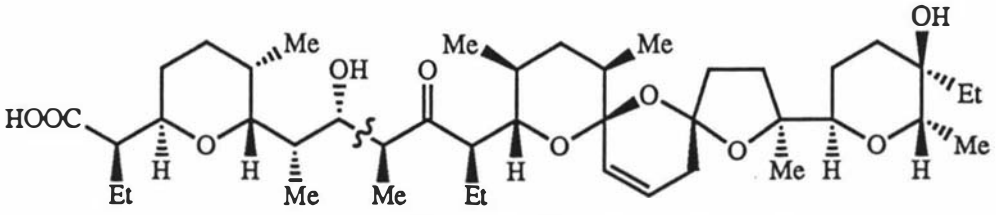
Synthesis of the acetylene **148** (Scheme 33) began with the conversion of levulinic acid **149** to the racemic lactonic acid **150** using the procedure of Iwami and Kawai[54]. Resolution of the acid was then carried out using Mori's method[55], whereby formation of the highly crystalline cinchonine 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)-(-)-acid **S-150** in pure form. Reduction of the (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

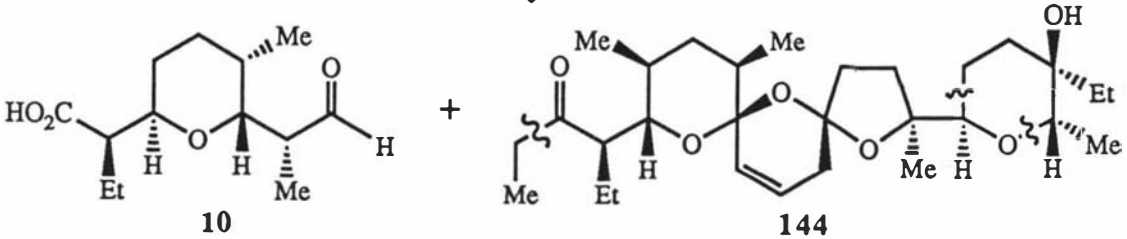


Reagents and conditions: (i) NaCN, NaOAc, H_2O then HCl conc. Δ; (ii) cinchonine, EtOH, crystallisation then HCl; (iii) $LiAlH_4$, Et_2O; (iv) a: acetone, TsOH; b: DMSO, TFAA, CH_2Cl_2, -65°C, Et_3N; (v) $HC{\equiv}CCH_2MgBr$, Et_2O; (vi) a: ^{t}BuPh$_2$SiCl, imidazole, CH_2Cl_2; b: MeOH, Amberlite IR 120 resin; c: TsCl, pyridine.

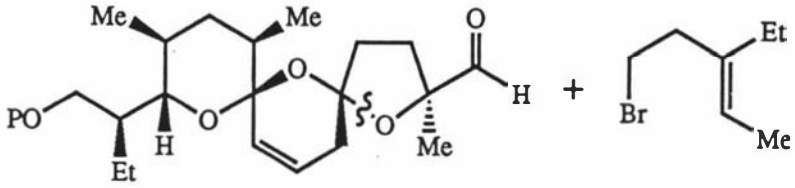
Scheme 32



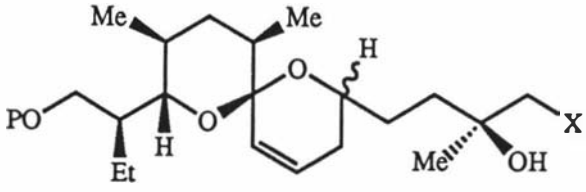
epi-17-Deoxy-(O-8)-salinomycin **143**



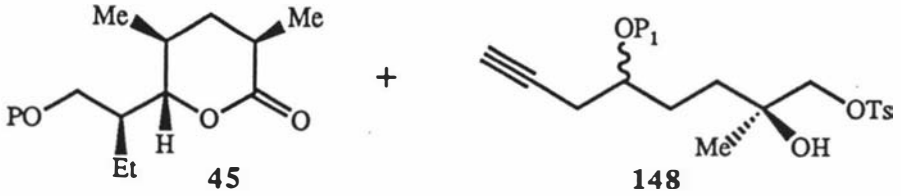
10 **144**



145 **146**



147



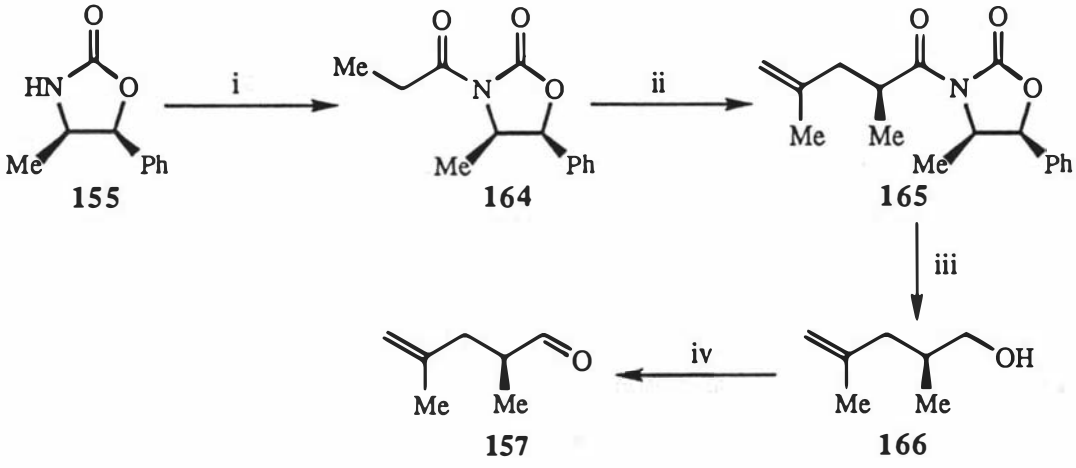
45 **148**

aldehyde **152**. Grignard addition of propargylmagnesium bromide to the aldehyde **152** afforded the (S)-acetylene **153**[56] 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 al*[7](see Scheme 10). However, recent work by Brimble[57] has provided an alternative route to the lactone **45** (Scheme 34) based on a synthesis of a Prelog-Djerassi acid[58] reported by Evans *et al*[59]. Starting with butanoyloxazolidinone **154**, prepared by the reaction of lithiated oxazolidinone **155** with butanoyl chloride, formation of the Z-boron enolate **156**[60,61] 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 borohydride[62] 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**.

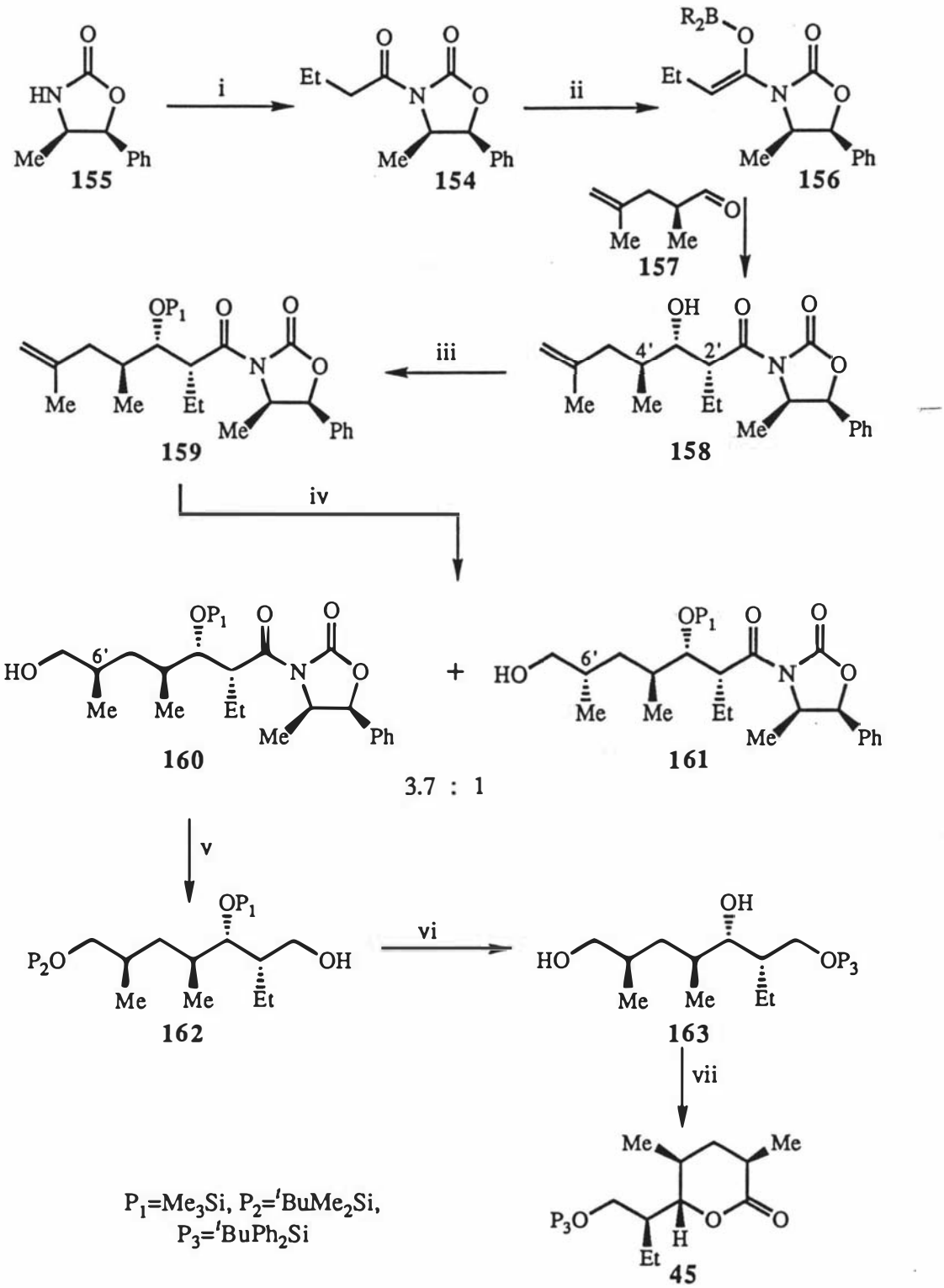
The aldehyde **157** used in the preparation of lactone **45** was synthesised using a modification of the literature procedure[57] (Scheme 35). Acylation of oxazolidinone **155**

Scheme 35



Reagents and conditions: (i) ^{n}BuLi, THF, -78°C, CH_3CH_2COCl; (ii) LDA, -78°C, then $CH_2=C(CH_3)CH_2I$, -50 to -20°C; (iii) $LiAlH_4$, Et_2O, 0°C; (iv) tetrapropylammonium perruthenate (cat.), NMO, CH_2Cl_2, 4A molecular sieves (powder).

Scheme 34

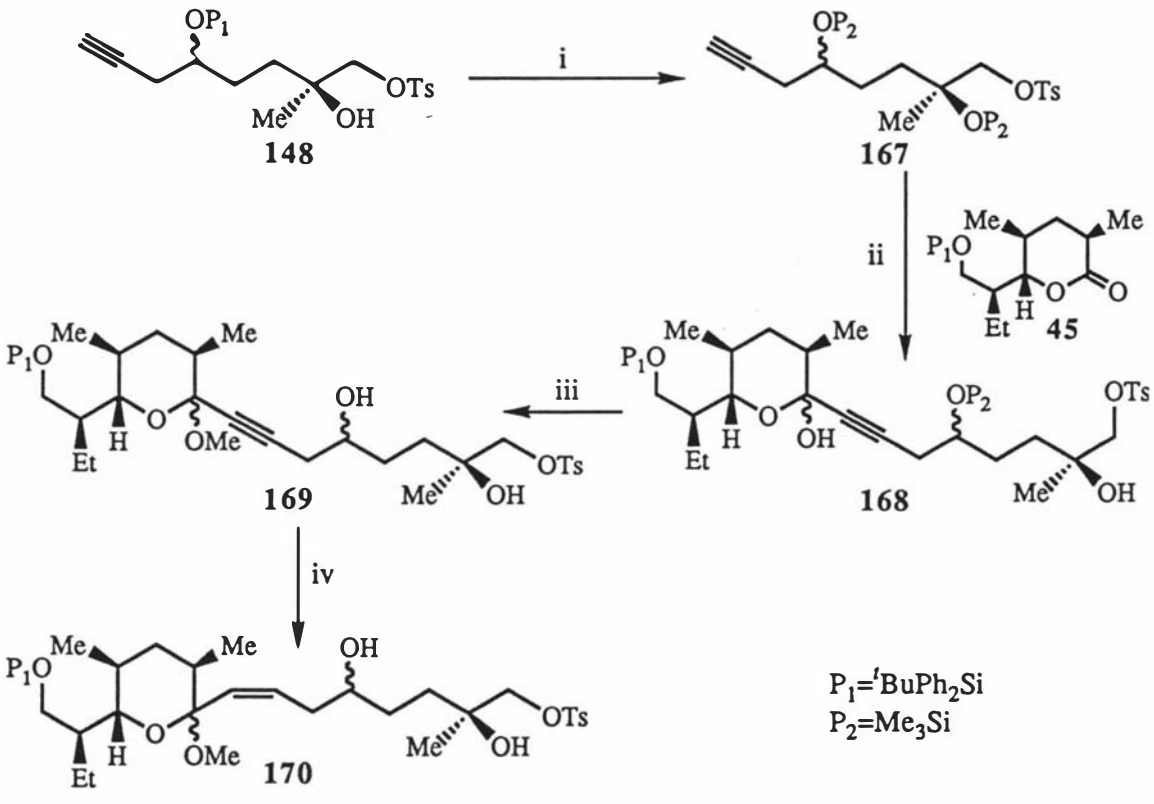


Reagents and conditions: (i) ^{n}BuLi, $CH_3CH_2CH_2COCl$; (ii) $R_2BOSO_2CF_3$ (R_2B= 9-borabicyclo-[3.3.1]non-9-yl), Et_3N, CH_2Cl_2, 0°C, then -78°C, **15**; (iii) 1-(Me_3Si)imidazole, CH_2Cl_2; (iv) BH_3, $(CH_3)_2C{=}C(CH_3)_2$, 0°C then **17**, -40°C; (v) a: $^{t}BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 0°C; b: $LiBH_4$, THF; (vi) a: $^{t}BuPh_2SiCl$, imidazole, Et_3N, CH_2Cl_2; b: PPTS (cat.), EtOH; (vii) NMO, $Ru(Ph_3P)_3Cl_2$, 4A 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 perruthenate catalyst and 4-methylmorpholine-*N*-oxide[63].

With the lactone **45** and tosylate **148** in hand assembly of the *bis*-spiroketal target **145** was pursued (Scheme 36). However before coupling of these subunits was attempted, the *tert*-butyldiphenylsilyl ether functionality of tosylate **148** was removed[64] 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**

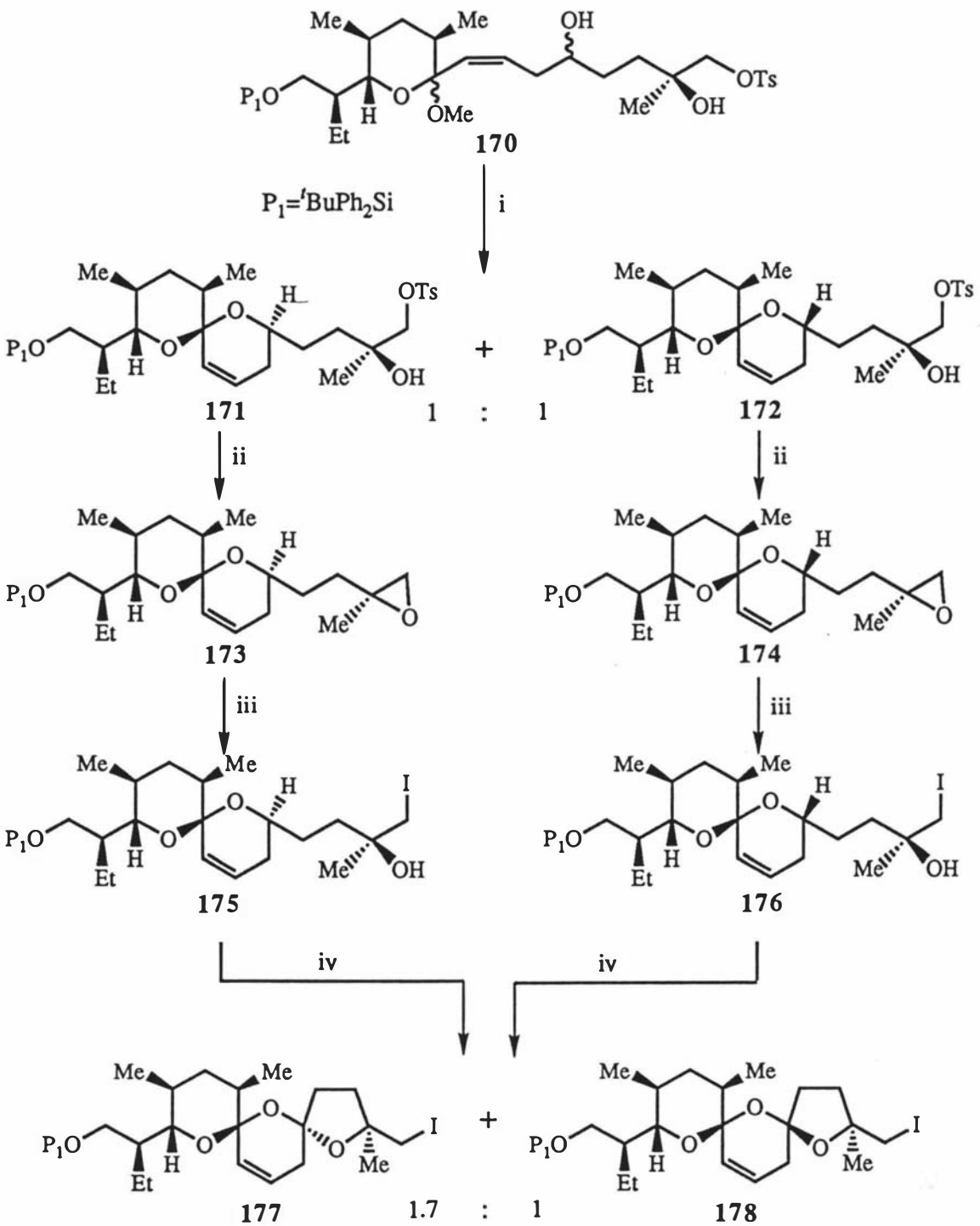
Scheme 36



Reagents and conditions: (i) a: 2% HF (excess), CH_3CN; b: 1-(Me_3Si)imidazole, CH_2Cl_2; (ii) ^{n}BuLi, THF, -78°C, then **45**; (iii) MeOH, Amberlite IR 120 resin; (iv) H_2, Lindlar catalyst, hexane/EtOAc.

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



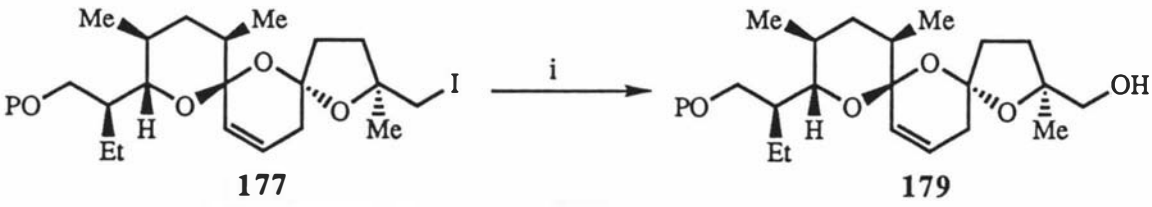
Reagents and conditions: (i) PPTS, CH_2Cl_2; (ii) NaH, THF; (iii) LiI, THF, $BF_3.Et_2O$, -50°C; (iv) iodine, iodobenzenediacetate, 18°C, hυ.

Following separation of the tosylates using column chromatography[65] the individual tosylates were converted to the corresponding epoxides **173, 174** and then opened with lithium iodide to form the iodohydrins **175, 176.**

The critical oxidative cyclisation was then achieved upon irradiation of either iodohydrin **175** or iodohydrin **176** in a solution of cyclohexane, containing iodine and iodobenzenediacetate affording the *trans-bis*-spiroketal **177** and the *cis-bis*-spiroketal **178** in a ratio of 1.7:1. This outcome may be explained by the proposed mechanism[66,67] (Scheme 38) whereby both diastereomeric precursors **175** and **176** form the same radical **178a** or carbocation intermediate **178b** which is subsequently trapped predominantly from the least hindered α-face to give the *trans*-bis-spiroketal **177** as the major product.

Having synthesised the desired *bis*-spiroketal moiety of *epi*-17-deoxy-(O-8)-salinomycin in the form of the *trans-bis*-spiroketal **177** all that remained was to convert the iodide group to the alcohol **179** (Scheme 39). Extensive work by Williams[68] concluded that treatment of the iodide with potassium superoxide and 18-crown-6 in dimethylsulphoxide was the most effective way of forming the alcohol **179** 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

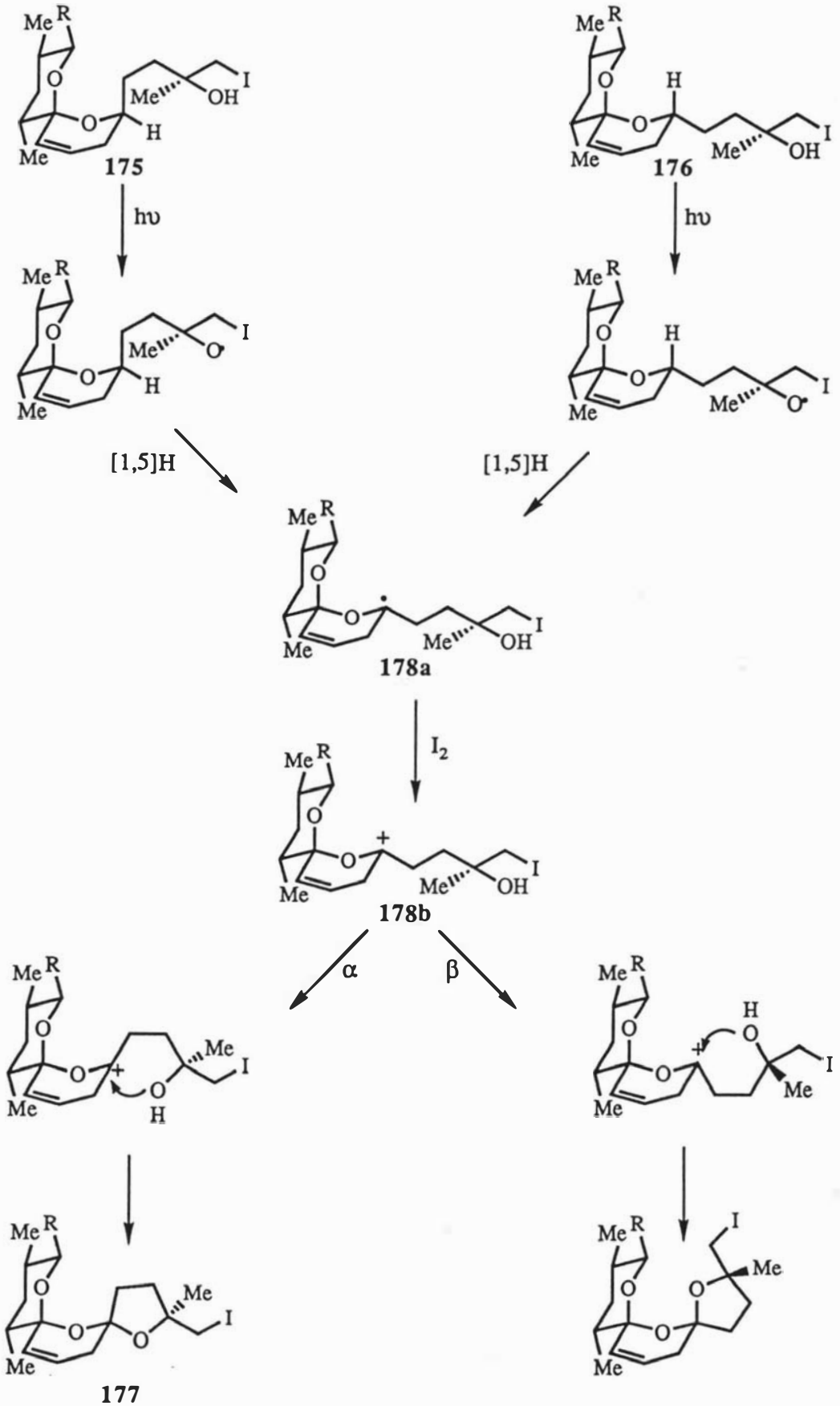


177 **179**

Reagents and conditions: (i) KO_2, 18-crown-6, DMSO.

Thus, to date a synthesis of *bis*-spiroketal **177** has been completed[68]. This advanced intermediate for the synthesis of *epi*-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 *epi*-17-deoxy-(O-8)-salinomycin to be extended.

Scheme 38



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 **4**[69], antibiotic X-206 **180**[70], ferensimycin B **181**[71] and lysocellin **182**[72] (Figure 5).

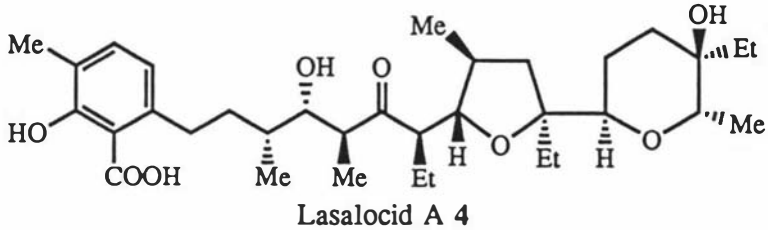
1.3.1 Lasalocid A

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].

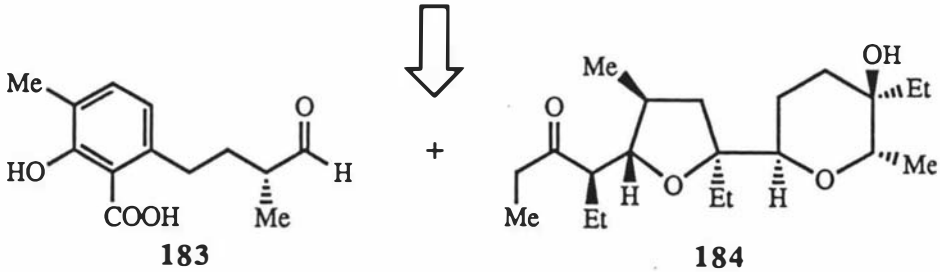
1.3.1.1 Nakata and Kishi[8-10]

The total synthesis of lasalocid A **4** was first achieved in 1978 by Nakata *et al*[8]. The final step in their synthesis consists of a stereoselective crossed aldol condensation

Scheme 40

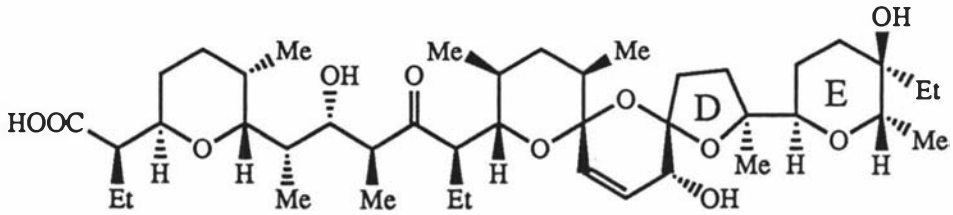


Lasalocid A **4**

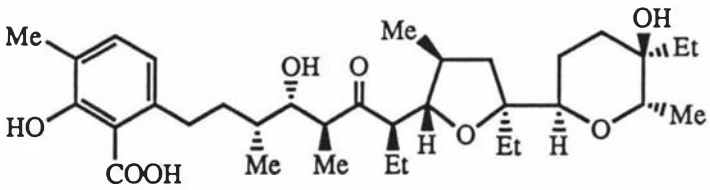


183 **184**

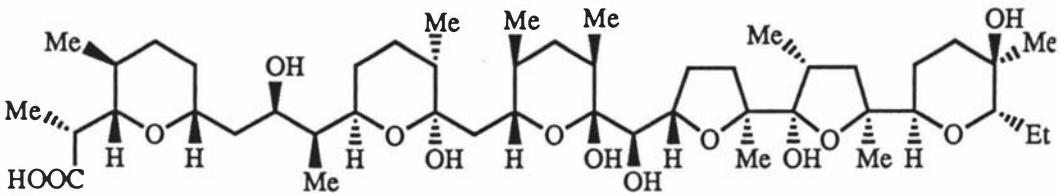
Figure 5



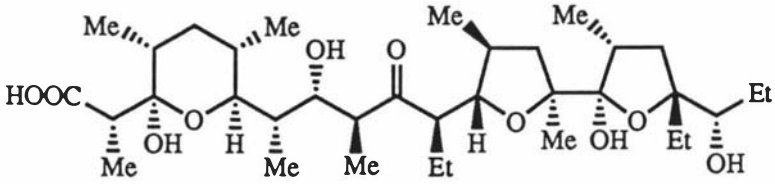
Salinomycin **1**



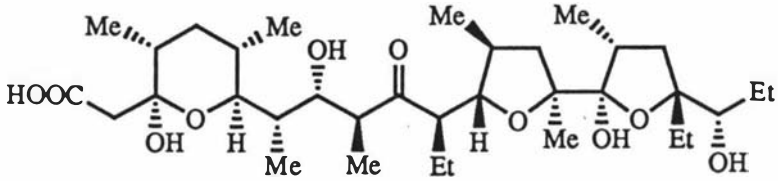
Lasalocid A **4**



Antibiotic X-206 **180**



Ferensimycin B **181**



Lysocellin **182**

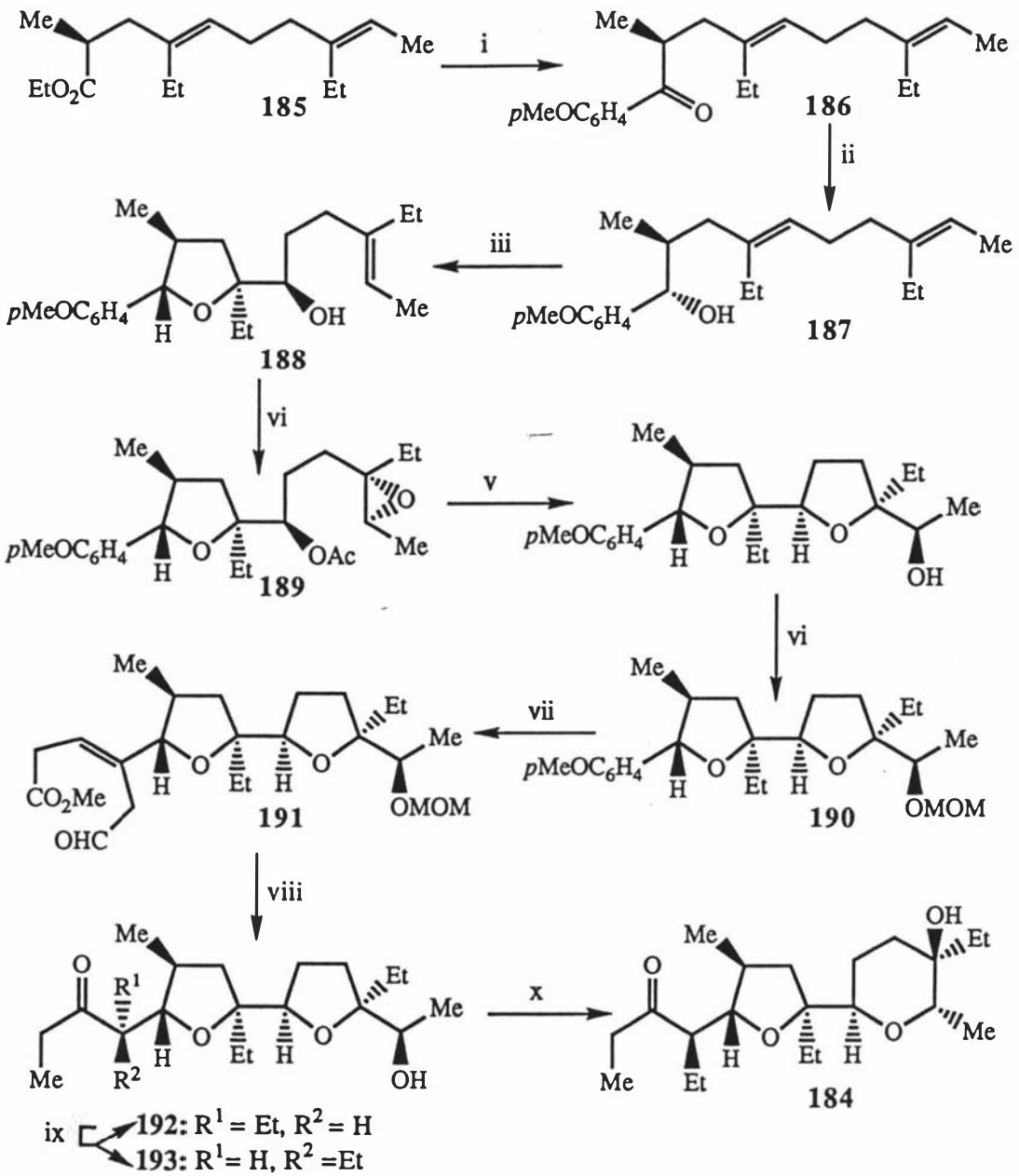
of aldehyde **183** with ketone **184** (Scheme 40). This type of reaction is so efficient that it is a common feature for all lasalocid A syntheses as well as those of other polyether antibiotics including salinomycin **1**, narasin **2**, and monensin **3**.

Synthesis of the right hand section **184** of lasalocid A began with the conversion of ethyl (4E, 8E)-2-methyl-4,8-diethyldecadienoate **185** (readily synthesised by adapting Johnsons method[79]) 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 reduction[80] 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 reported[9,10], this time using only acyclic precursors in a short, efficient and stereospecific synthesis of the isolasalocid ketone **193**.

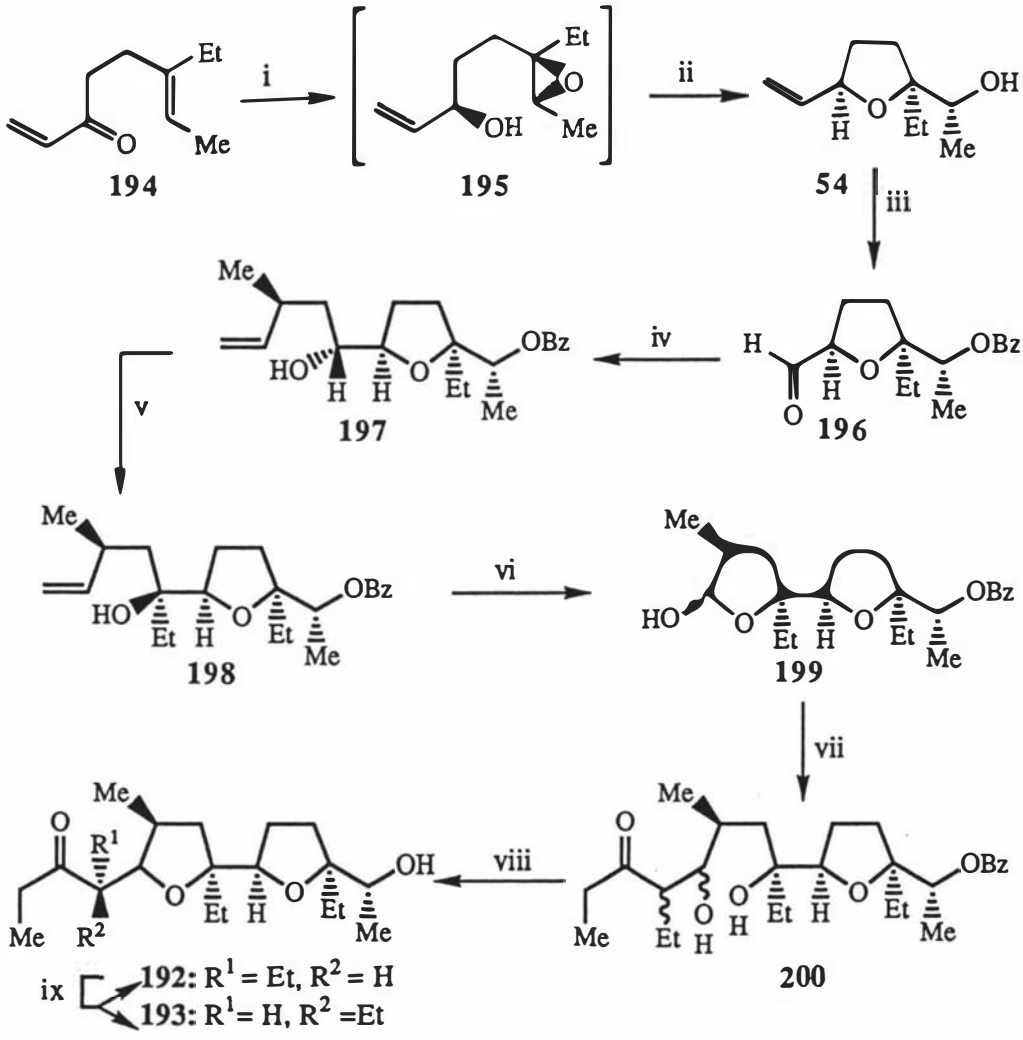
Beginning with the readily available unsaturated ketone **194**[9] (Scheme 42), stereoselective epoxidation and reduction afforded the intermediate epoxyalcohol **195** which upon acetic acid workup cyclised to give the tetrahydrofuran **54**. Protection of the hydroxyl group followed by ozonolysis afforded 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 methodology[8] (see Scheme 41).

Scheme 41



Reagents and conditions: (i) a: $LiAlH_4$, Et_2O; b: PCC, CH_2Cl_2; c: Et_2O, *p*-$MeOC_6H_4MgBr$; d: Jones oxidation; (ii) $LiAlH_4$, *d,l*-2-(*o*-2-toluidinomethyl)pyrrolidine, Et_2O, -78°C; (iii) ^tBuOOH, $VO(acac)_2$, NaOAc, benzene then AcOH; (iv) a: ^tBuOOH, $VO(acac)_2$, NaOAc, benzene; b: AcOH, pyridine; (v) a: 0.1 M H_2SO_4/acetone/H_2O; b: TsCl, pyridine; c: K_2CO_3, MeOH; d: AcOH (vi) $MeOCH_2Br$, KH, THF; (vii) a: Li, liq. NH_3, EtOH; b: MCPBA, aq. $NaHCO_3$, CH_2Cl_2; c: HIO_4, aq. dioxane; (viii) a: $LiAlH_4$, THF, reflux; b: TsCl, pyridine, 0°C; c: $LiAlH_4$, Et_2O, RT; d: B_2H_6, THF; e: Jones oxidation; f: $TrBF_4$, CH_2Cl_2; (ix) NaOH, aq. dioxane; (x) a: MsCl, pyridine; b: Ag_2CO_3, aq. acetone.

Scheme 42

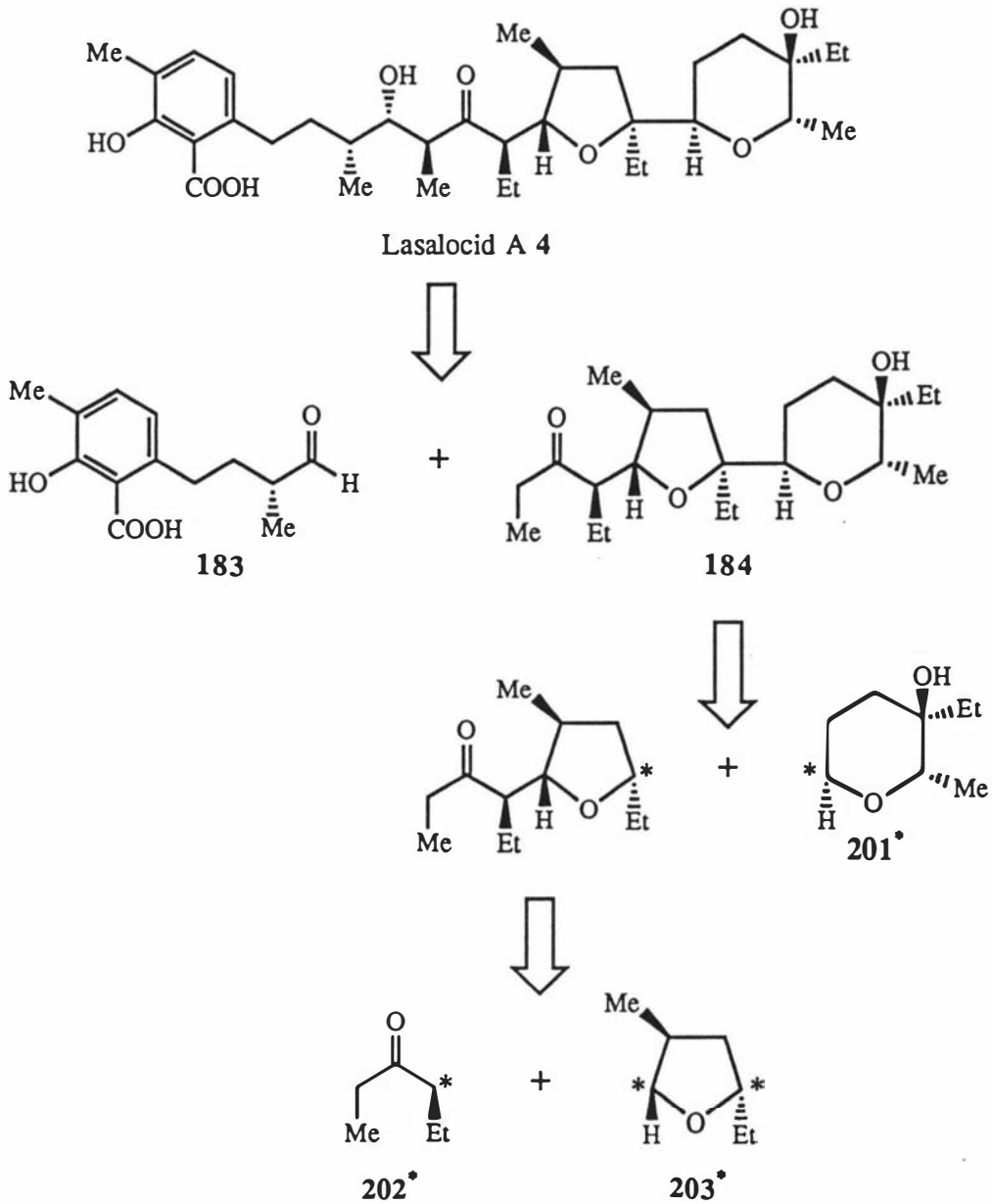


Reagents and conditions: (i) ^{t}BuOOH, $VO(acac)_2$, benzene; (ii) a: $LiAlH_4$, *d,l*-2-(*o*-toluidinomethyl)pyrrolidine, Et_2O, 0°C; b: AcOH; (iii) a: BzBr, KH, THF; b: O_3, MeOH, -78°C; (iv) (R)-2-methyl-3-butenylmagnesium bromide, Et_2O; (v) a: Jones oxidation; b: EtMgBr, Et_2O; (vi) O_3, MeOH, -78°C then DMS work-up; (vii) 4-bromo-3-hexanone, Mg; (viii) a: TSA, benzene, reflux; b: H_2, Pd-C, MeOH; (ix) NaOH, aq. dioxane.

1.3.1.2 Ireland *et al*[72,73]

The synthesis of lasalocid A by Ireland *et al*[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***, **202***, **203***.

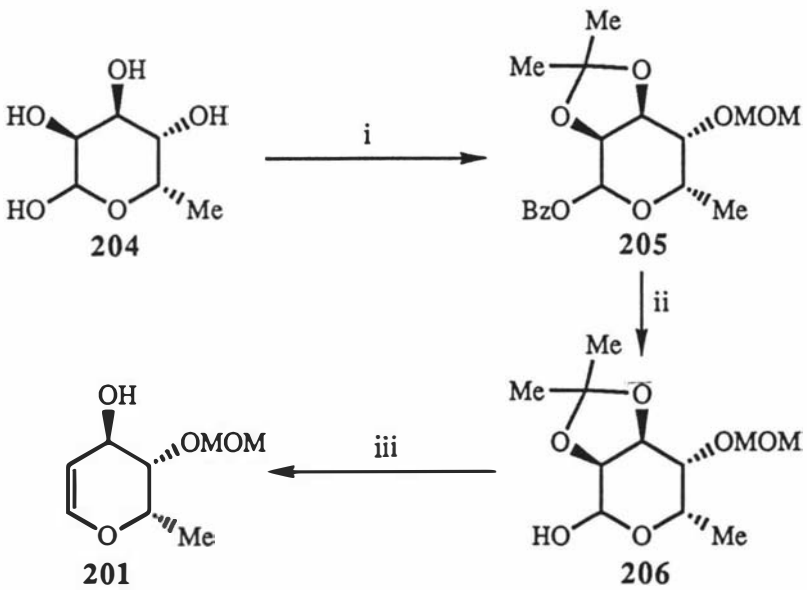
Scheme 43



Synthesis of the pyranoid subunit **201*** began with the selective protection of 6-deoxy-L-glucose **204**[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

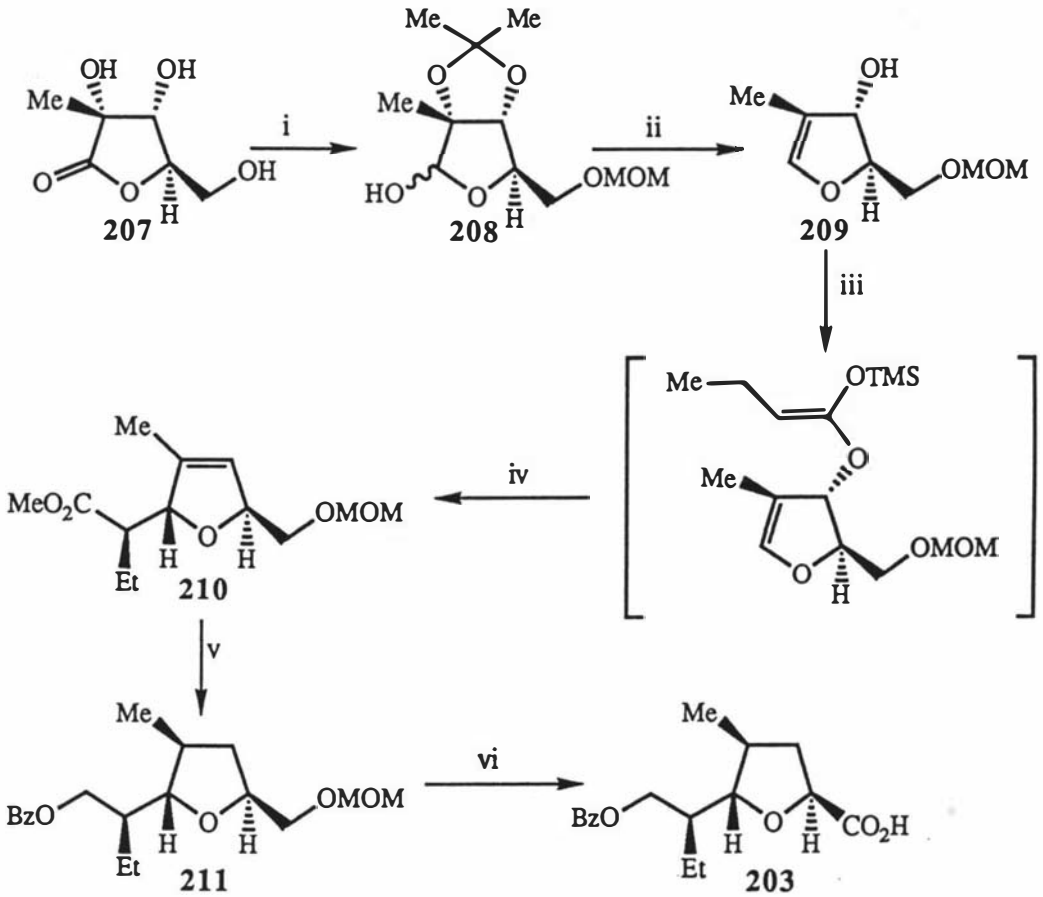


Reagents and conditions: (i) a: CH_3COCH_3, H^+; b: BzOH, HCl; c: CH_3OCH_2Cl, KH; (ii) H_2, Pd-C, EtOAc; (iii) HMPT, CCl_4, Li, NH_3.

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[82]. 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[83]. 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[83] (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[22,23] of the resulting alcohol afforded ketone **216**.

Scheme 45



Reagents and conditions: (i) a: CH_3COCH_3, H^+; b: CH_3OCH_2Cl, KH; c: DIBAL, Et_2O; (ii) $(Me_2N)_3P$, CCl_4, Li, NH_3; (iii) ^nBuLi, $CH_3(CH_2)_2COCl$, then LDA, 23% HMPA-THF, TMSCl, -78°C; (iv) RT, H_2O, OH^-, CH_2N_2; (v) a: $LiAlH_4$, Et_2O; b: BzBr, KH; c: H^+; (vi) a: H^+; b: O_2, Pt, aq. $NaHCO_3$.

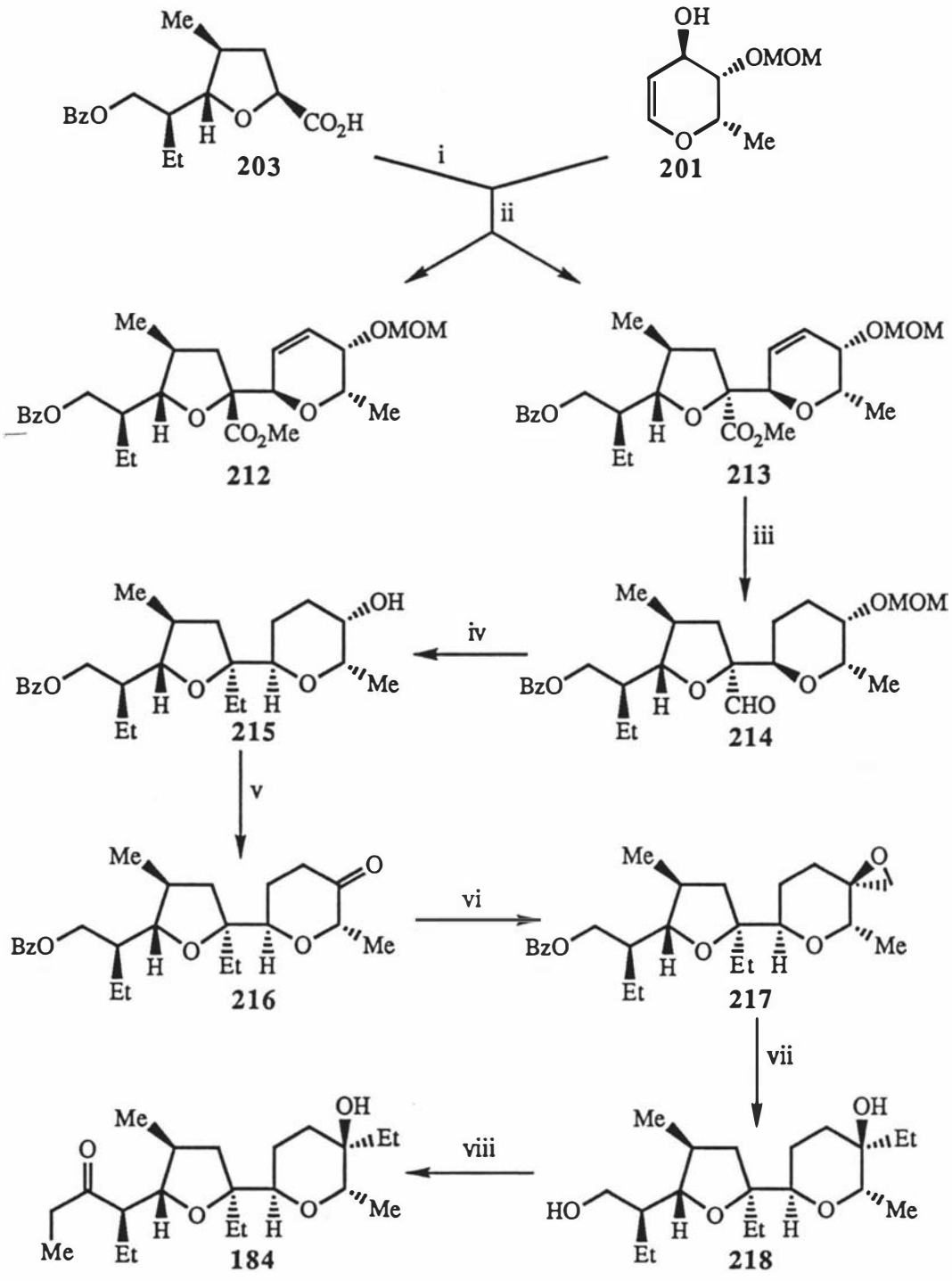
Conversion of the ketone **216** to the alkene *via* the Wittig reaction followed by epoxidation afforded the epoxide **217** which underwent dimethyl cuprate cleavage to give the desired pyran moiety **218**. Finally, elaboration of the left hand end of alcohol **218** yielded the desired ketone **184**.

1.3.1.3 Horita/Yonemitsu[75-78]

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.

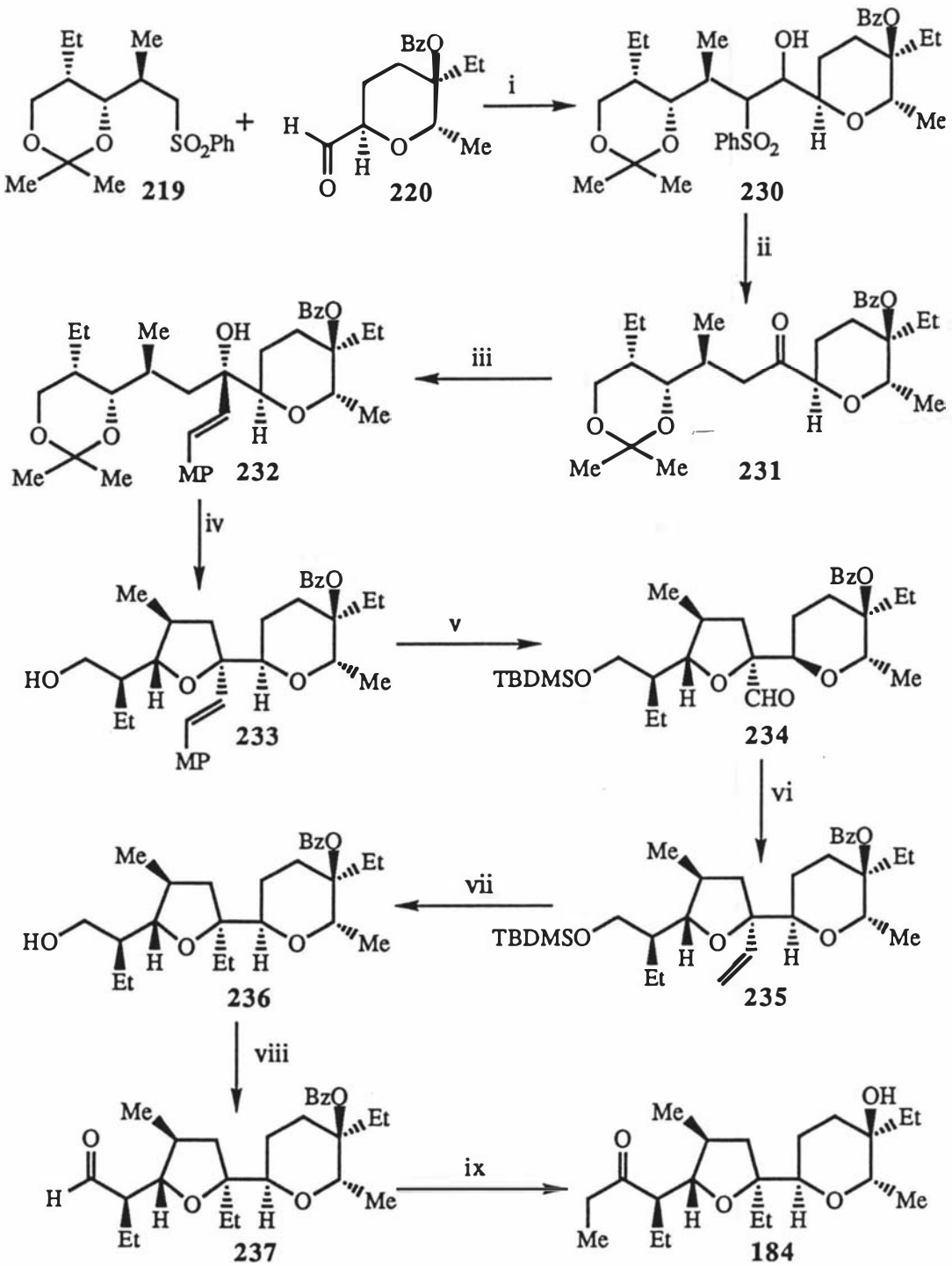
The starting material for the synthesis of the tetrahydropyran synthon **220** was aldehyde **221** (Scheme 48), readily synthesised from S-(-)-ethyl lactate[84]. The aldehyde **221** was converted to the alcohol **222** by the Grignard addition of 3-butenylmagnesium bromide. Swern oxidation[22,23] of the alcohol **222** followed by the chelation controlled

Scheme 46



Reagents and conditions: (i) $(COCl)_2$, benzene; (ii) ^{n}BuLi, THF, LDA, TMSCl, RT, H_2O, OH^-, CH_2N_2; (iii) a: H_2, Raney Ni, EtOAc; b: DIBAL, Et_2O; (iv) a: $(C_6H_5)_3P{=}CH_2$, THF; b: 10% HCl, THF; c: H_2, Raney Ni, EtOAc; c: H_2, Pd-C, EtOAc; (v) DMSO, $(COCl)_2$, Et_3N; (vi) a: $(C_6H_5)_3P{=}CH_2$, THF; b: MCPBA, CH_2Cl_2; (vii) a: $(CH_3)_2CuLi$, pentane; b: Li, NH_3; (viii) a: PCC, CH_2Cl_2; b: EtMgBr, THF; c: PCC, CH_2Cl_2.

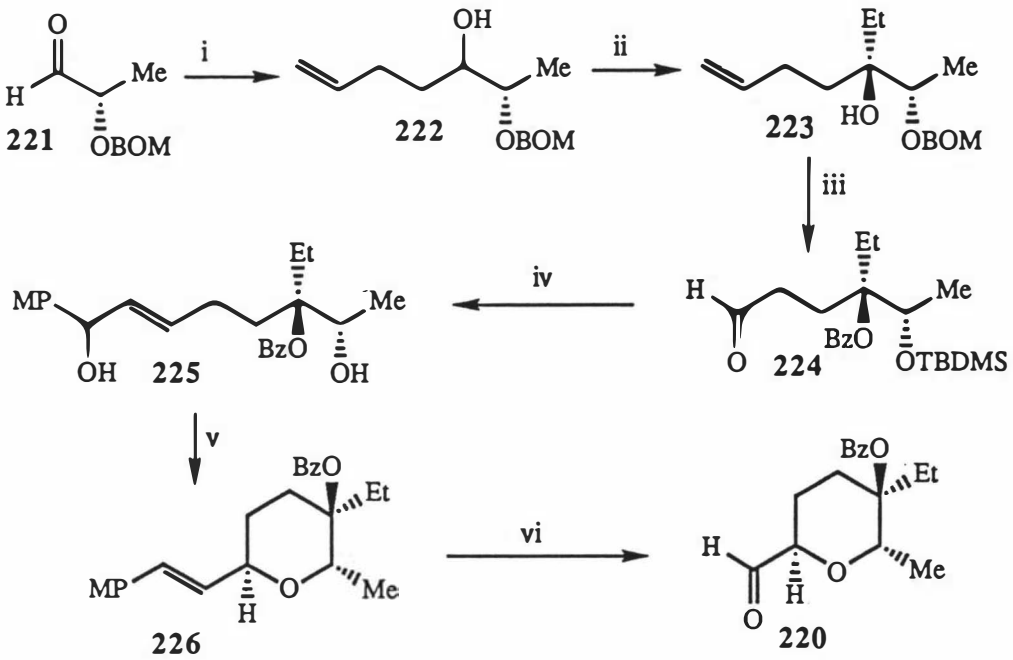
Scheme 47



Reagents and conditions: (i) ^{n}BuLi, Et_2O/hexane (1:1), 220; (ii) a: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C; b: Al-Hg, THF; (iii) a: $MeOC_6H_4C{\equiv}CLi$, Et_2O, -78° to 30°C; b: $LiAlH_4$, THF; (iv) $ZnBr_2$, CH_2Cl_2, 40°C; (v) a: TBDMSCl, imidazole, CH_2Cl_2; b: OsO_4, NMO, acetone/H_2O (5:2); c: $Pb(OAc)_4$, benzene; (vi) $Ph_3P{=}CH_2$, THF; (vii) a: $^{n}Bu_4NF$, THF; b: H_2, $Pd(OH)_2$, EtOAc; (viii) PCC, 3A MS, CH_2Cl_2; (ix) a: EtMgBr, THF, 0°C; b: PCC, 3A MS, CH_2Cl_2.

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

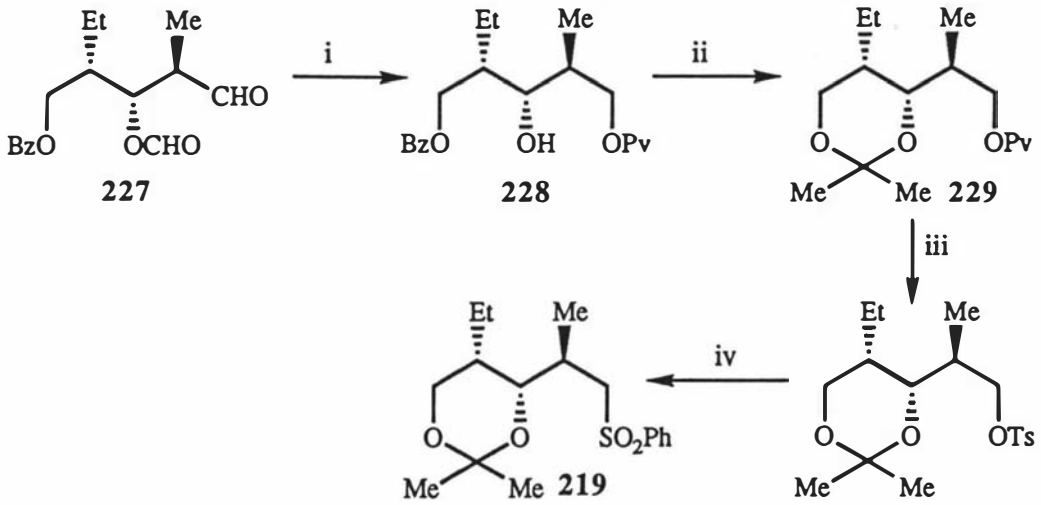


Reagents and conditions: (i) CH_2=$CHCH_2CH_2MgBr$, THF, 0°C; (ii) a: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N; b: EtMgBr, THF, 0°C; (iii) a: BzBr, NaH, DMF; b: 4M HCl/THF (1:2) 40-60°C; c: TBDMSCl, imidazole, DMF, 80°C; d: OsO_4, NMO, acetone/THF (4:1); e: $NaIO_4$, MeOH; (iv) a: $(MeO)_2P(O)CH_2COC_6H_4OMe$, NaH, THF, 0°C; b: $NaBH_4$, $CeCl_3$, MeOH, 0°C; (v) a: $ZnBr_2$, CH_2Cl_2, -20°C; (vi) a: OsO_4, NMO, acetone/H_2O (10:1); b: $NaIO_4$.

Synthesis of the sulphone precursor **219** of the tetrahydrofuran ring (Scheme 49) began with the aldehyde **227**[29], 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[85] gave the ketone **231** which was treated

Scheme 49



Reagents and conditions: (i) a: $LiAlH_4$, Et_2O, 0°C to RT; b: PvCl, pyridine, 0°C to RT; (ii) a: H_2, Pd-C, EtOAc; b: CSA, $Me_2C(OMe)_2$, benzene; (iii) a: $LiAlH_4$, Et_2O, 0°C to RT; b: TsCl, pyridine, 0°C to RT; (iv) a: NaI, acetone, Δ; $PhSO_2Na$, 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.

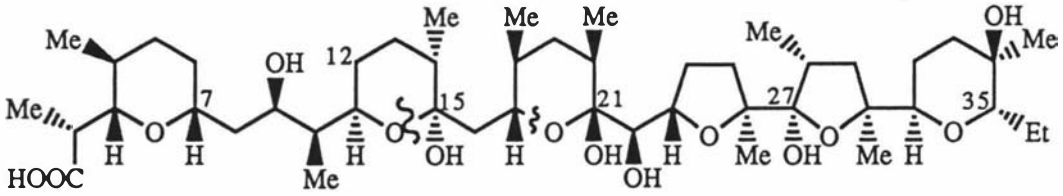
Elaboration of the *bis*-ether system **233** was then effected. Following protection of the primary hydroxyl group oxidative cleavage of the double bond produced the aldehyde **234** which was converted to the olefin **235** *via* the Wittig reaction. Deprotection of the primary alcohol followed by 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

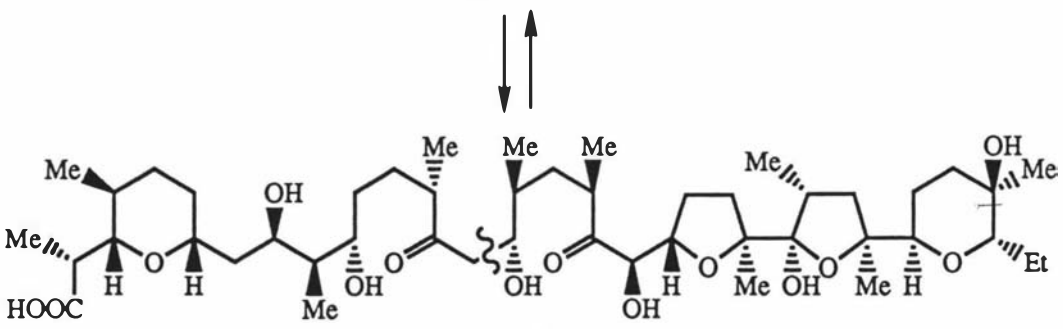
In 1988, the first total synthesis of the polyether antibiotic X-206 **180** was reported by Evans *et al*[86]. This antibiotic, while lacking the *bis*-spiroketal unit present in salinomycin, contains an almost identical terminal tetrahydrofuran-tetrahydropyran unit.

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**.

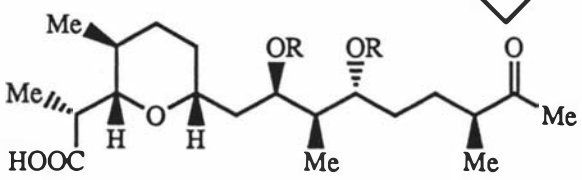
Scheme 50



180 antibiotic X-206

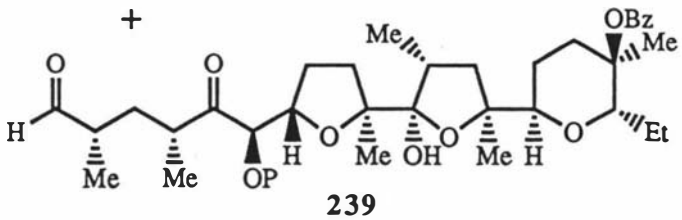


238

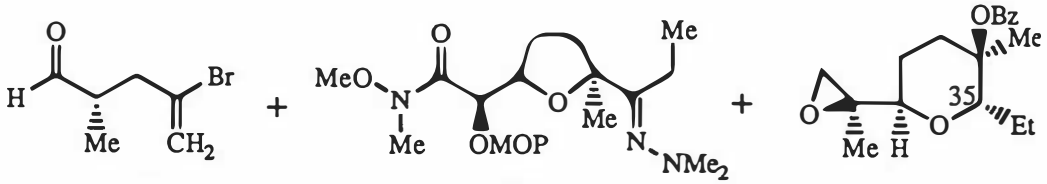


240

+



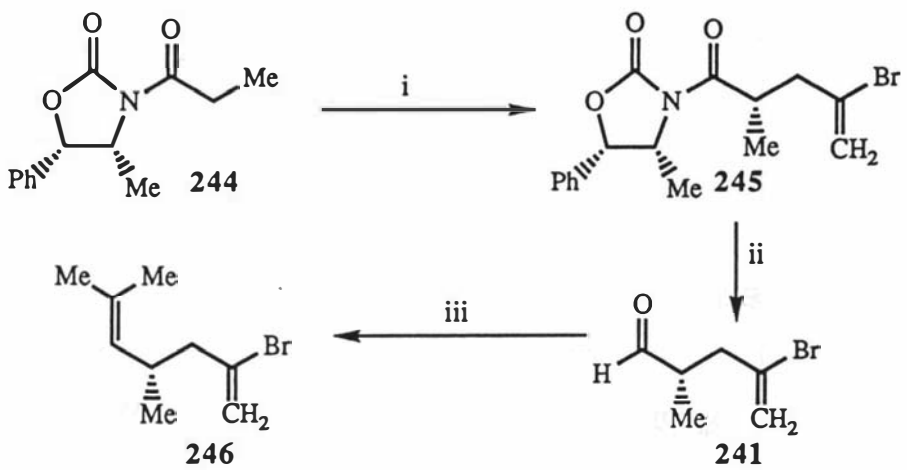
239



241 **242** **243**

Synthesis of the alkene **241** began (Scheme 51) with the alkylation of the lithium enolate of imide **244** with 2,3-dibromopropene[87] 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 isopropylidenetriphenylphosphorane masked the aldehyde **241** as the dialkene **246**.

Scheme 51

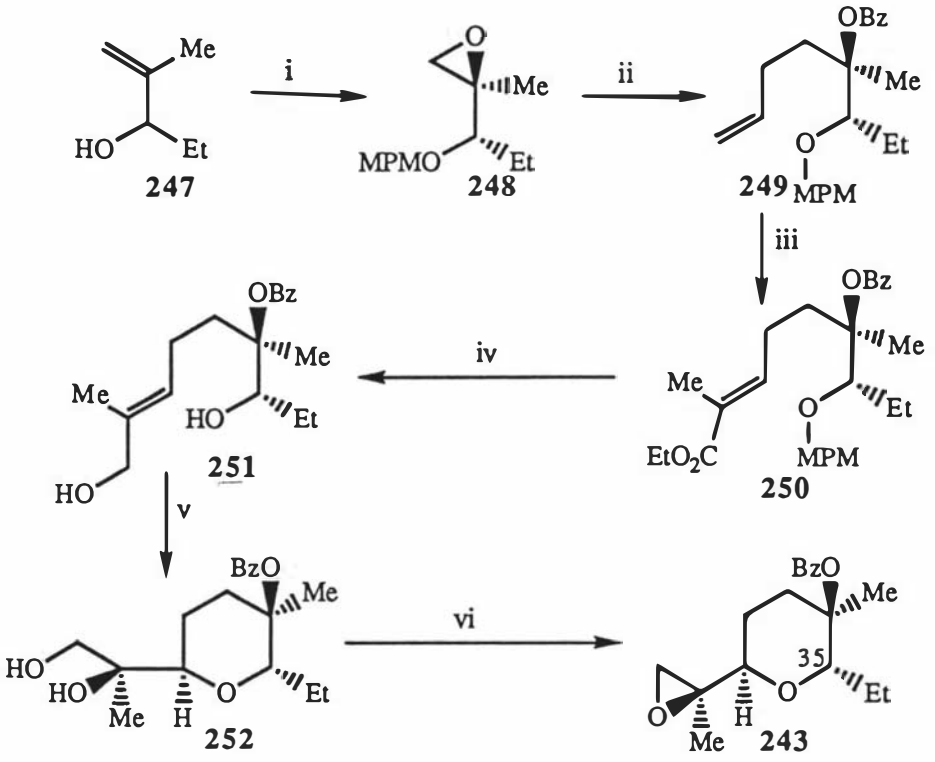


Reagents and conditions: (i) a: LDA, CH_2=C(Br)CH_2Br, THF,-35°C; (ii) $LiAlH_4$, THF, -78 to 0°C; (iii) a: DMSO, $(COCl)_2$, CH_2Cl_2, -65°C then Et_3N, -70 to -10°C; b: $Ph_3P^{+i}PrI^-$, ^nBuLi, THF, -78 to 25°C.

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 *tert*-butyl hydroperoxide followed by protection of the hydroxyl group as the *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, *via* the Wittig reaction, afforded the α,β-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**[88], 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

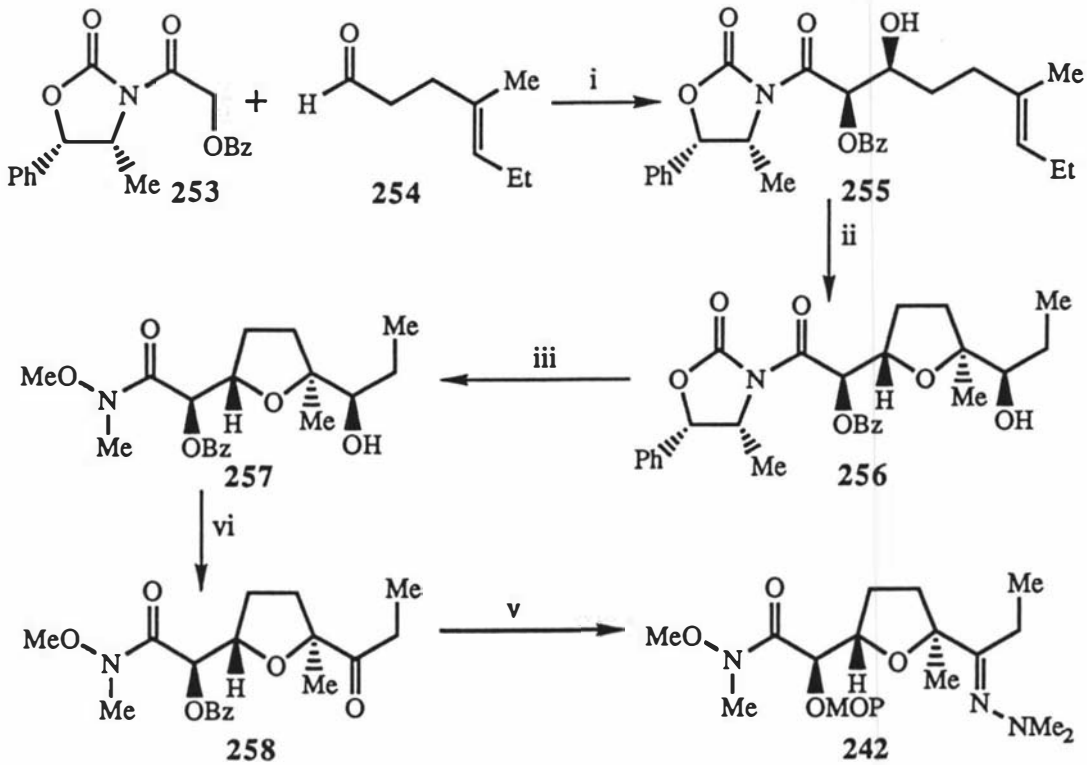


Reagents and conditions: (i) a: ^{t}BuOOH, Ti(O^{i}Pr)$_4$, (+)-diisopropyl tartrate, CH_2Cl_2; b: *p*-$MeOC_6H_4CH_2Cl$, NaH, DMF, 0°C; (ii) a: CH_2=$CHCH_2MgCl$, THF; b: BzBr, KH, THF; (iii) a: O_3, -78°C, MeOH then Ph_3P, CH_2Cl_2; b: Ph_3P=$C(Me)CO_2Et$, CH_2Cl_2; (iv) a: DDQ, CH_2Cl_2/H_2O; b: DIBAL, CH_2Cl_2, -78 to 0°C; (v) ^{t}BuOOH, Ti(O^{i}Pr)$_4$, (+)-diethyl tartrate, CH_2Cl_2, -78 to 0°C; (vi) a: TsCl, pyridine; b: K_2CO_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[89] 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**[90,91] 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[86] the Schiff base formed by the hydrazone should not only afford a highly reactive enolate equivalent, but its greatly

Scheme 53

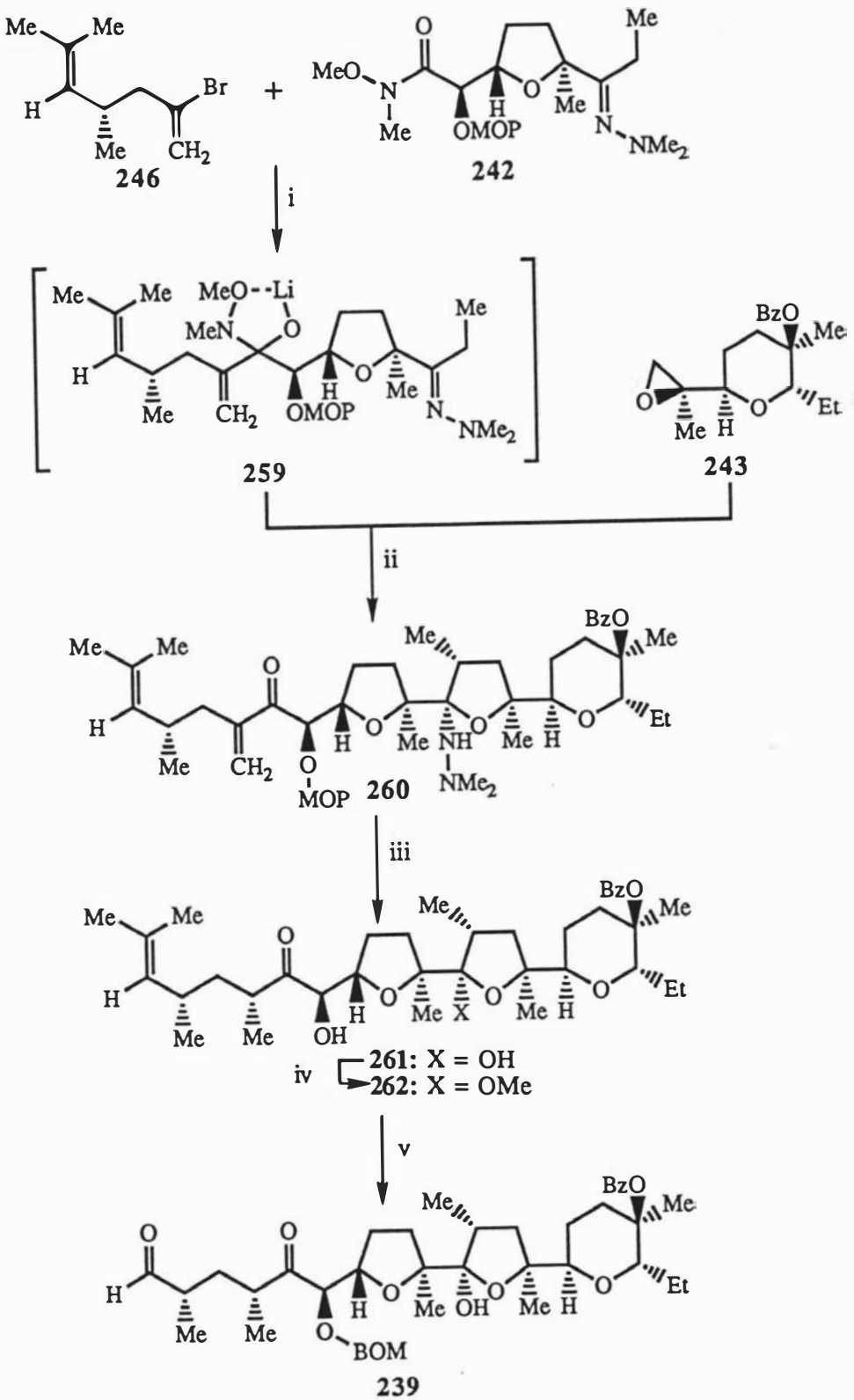


Reagents and conditions: (i) $^{n}Bu_2BOTf$, Et_3N, CH_2Cl_2 then **254**; (ii) $^{t}BuOOH$, $VO(acac)_2$ (cat.), CH_2Cl_2; (iii) $AlMe_3$, MeONHMe-HCl, CH_2Cl_2, 0°C; (iv) aq. H_2CrO_4, Et_2O; (v) a: H_2, Pd-C, $HClO_4$ (cat.), EtOH; b: CH_2=C(Me)OMe, PPTS, 0°C; c: Me_2NNH_2, Me_3SiCl, 0°C.

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 diisopropylamide 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

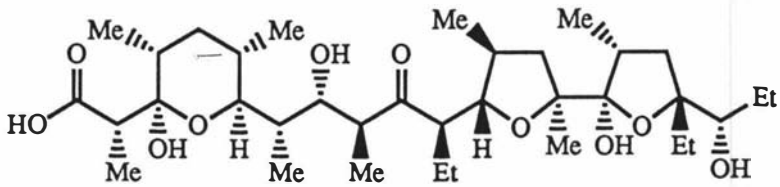


Reagents and conditions: (i) 2 equiv. ^{t}BuLi, **242**, Et_2O, -78 to 0°C; (ii) LDA ,0°C, **243**, 0°C; (iii) a: 1M $NaHSO_4$, 25% CH_2Cl_2/pentane; b: H_2, $(Ph_3P)_3RhCl$, PhMe; (iv) a: PPTS, $(MeO)_3CH$, MeOH, 0°C; b: $BzOCH_2Br$, H^+ sponge, MeCN, 25 to 45°C; (v) O_3, MeOH/CH_2Cl_2, -78°C.

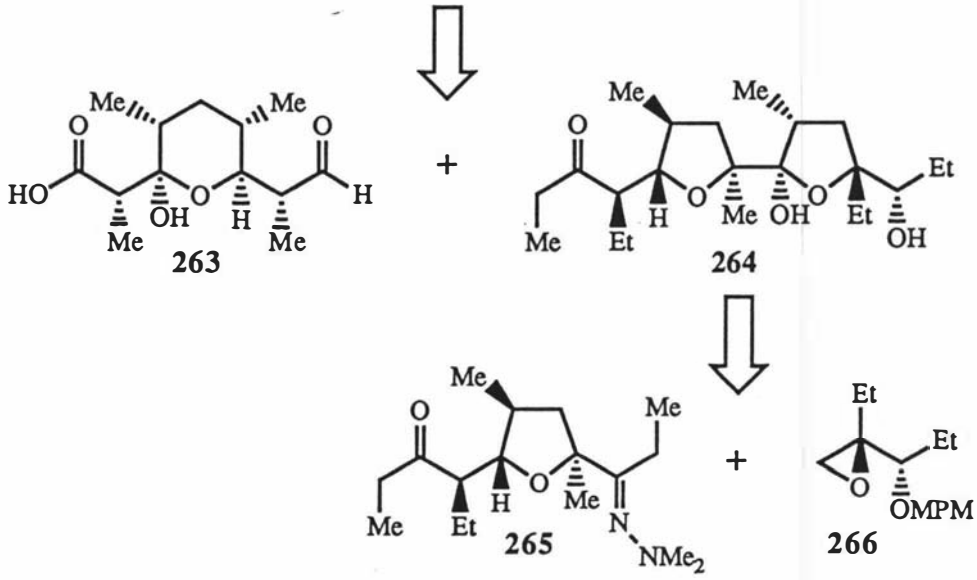
1.3.3 Ferensimycin B

In 1991, Evans *et al*[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.

Scheme 55



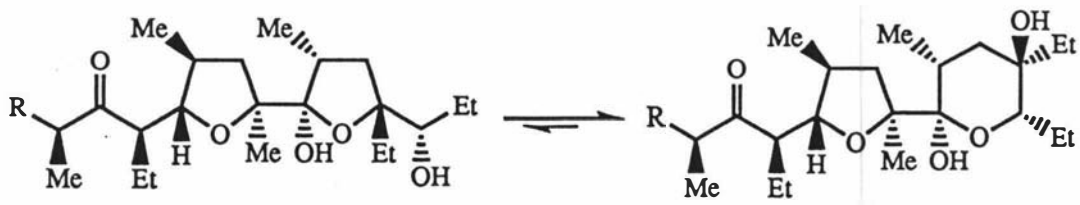
Ferensimycin B **181**



263 **264** **265** **266**

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**.

Figure 6



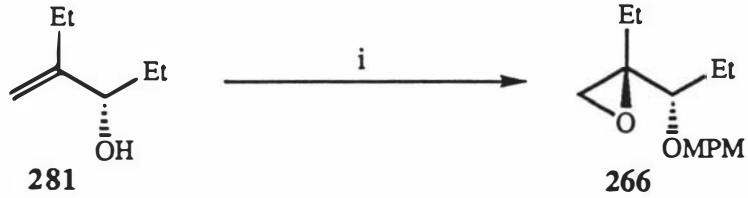
Synthesis of the ring B synthon **265** (Scheme 56) began with the Johnson[79] ortho-ester Claisen rearrangement of 2-methyl-1-penten-3-ol to give ester **267** which was saponified to afford the corresponding acid **268**. Acylation of the lithium salt of oxazolidinone **269**[93] with the mixed pivaloyl 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 oxidation[22,23] afforded the aldehyde **272**. Using the boron aldol addition[89], 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 oxidation[22,23] 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 speculated[92] 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 epoxidation[94] of racemic 2-ethyl-1-penten-3-ol **281** and purified by preparative HPLC (Scheme 57).

Scheme 57

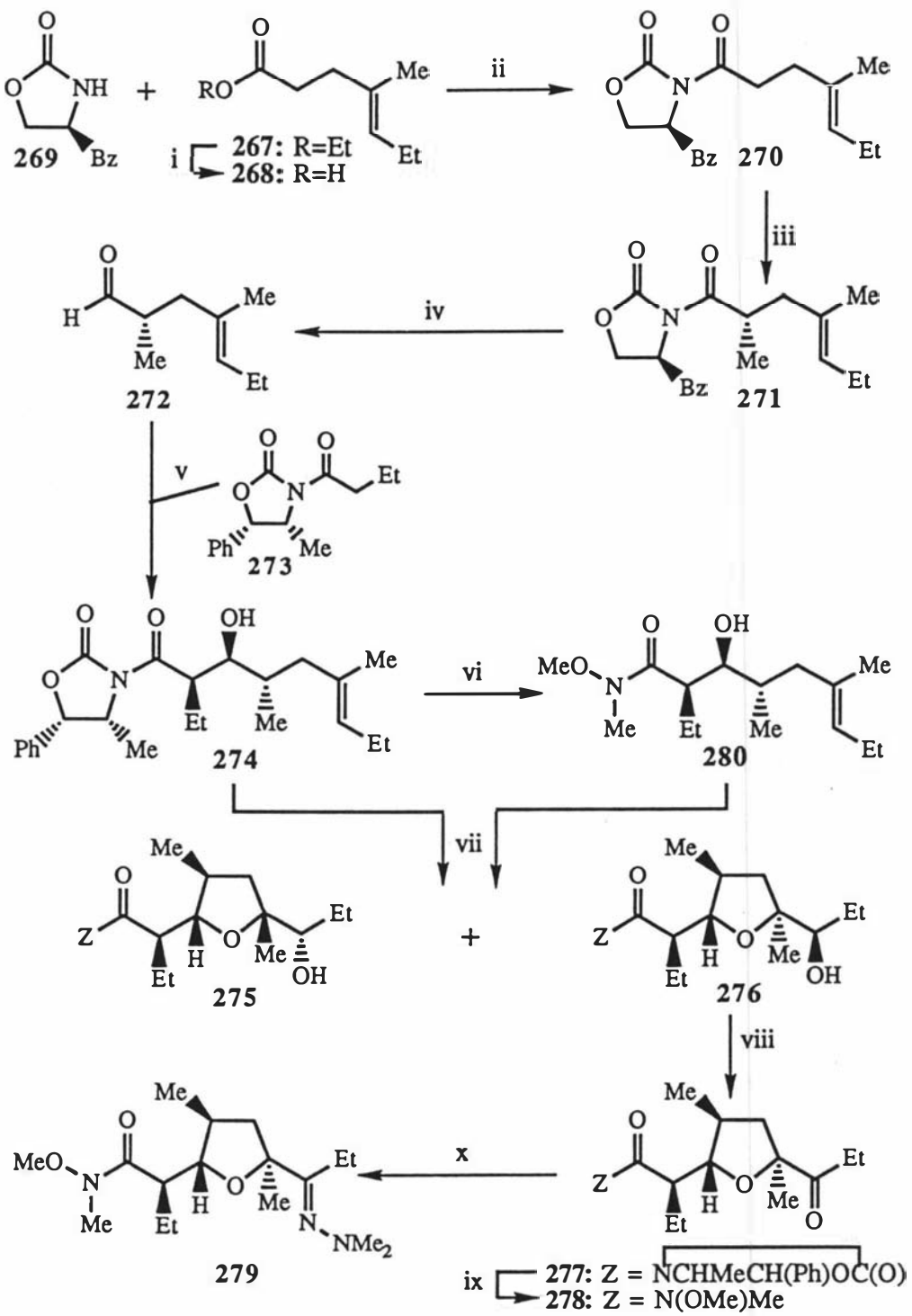


281 **266**

Reagents and conditions: (i) a: ^{t}BuOOH, Ti(O^{i}Pr)$_4$, (+)-diisopropyl tartrate; b: *p*-MeOC$_6$H$_4$CH$_2$Br, NaH, THF/DMF, 0°C.

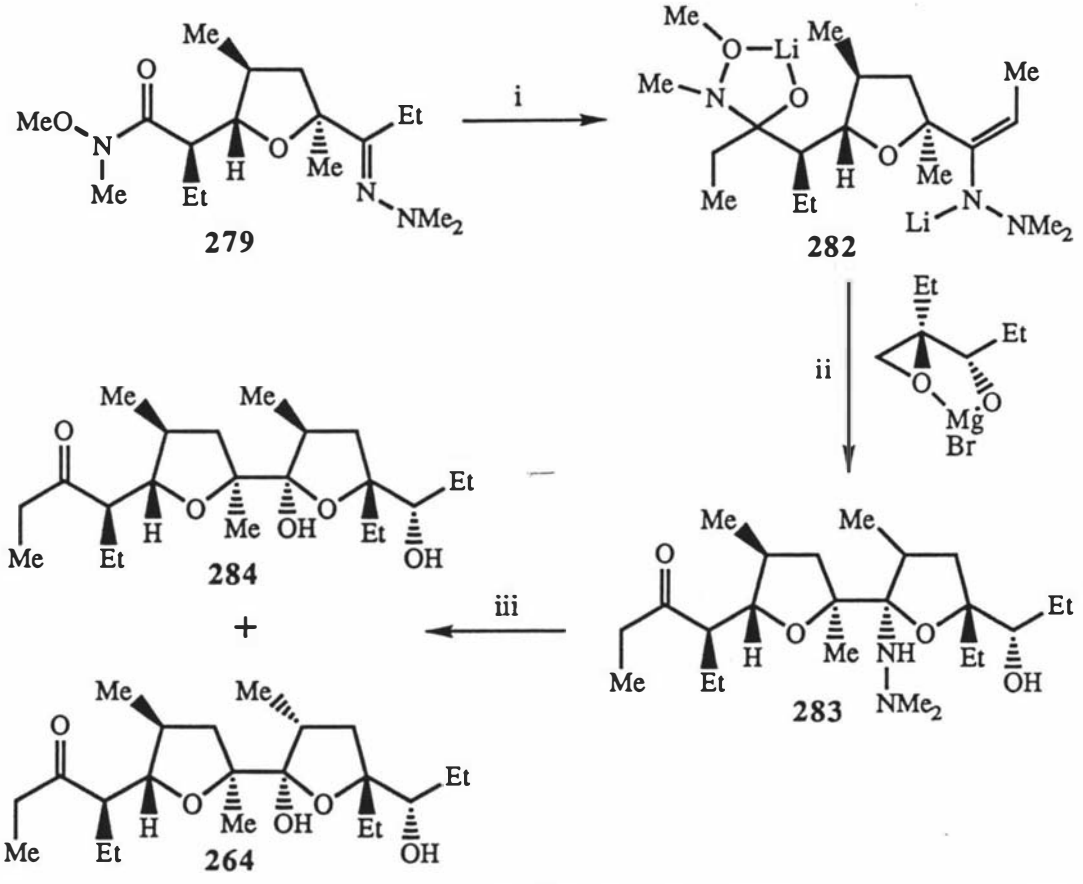
Coupling of the two synthons, **279** and **266**, was effected (Scheme 58) by application of methodology developed in Evans *et al*'s earlier synthesis of antibiotic X-206[86] (see Scheme 41) whereby hydrazone **279** was first treated with ethyllithium to

Scheme 56



Reagents and conditions:(i) aq. 2.0 M KOH, MeOH; (ii) Me_3CCOCl, Et_3N, Li-**269**; (iii) NaHMDS, MeI, -78°C; (iv) a: $LiAlH_4$, THF, 0°C; b: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N; (v) Bu_2BOTf, Et_3N, **273**; (vi) MeONHMe-HCl, Me_3Al, THF; (vii) a: ^tBuOOH, $VO(acac)_2$, benzene; b: AcOH; (viii) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N; (ix) a: LiOH, H_2O_2, THF/H_2O 0°C to RT; b: MeONHMe -HCl, CH_2Cl_2, DMAP, $Me_2CHN{=}C{=}NCHMe_2$; (x) Me_2NNH_2, TMSCl.

Scheme 58



Reagents and conditions: (i) EtLi, Et_2O, -78°C; (ii) Et_2NLi, THF, -78°C then Mg-**266**; (iii) $NaHSO_4$, H_2O.

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**.

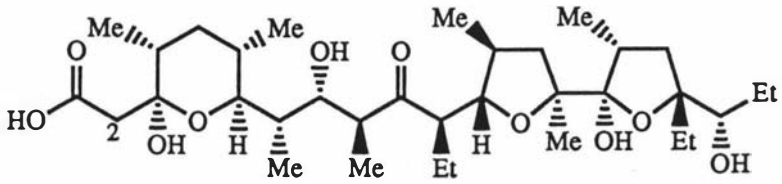
Treatment of the crude hydrazinyltetrahydrofurans with a biphasic solution of aqueous sodium bisulphate and pentane/dichloromethane (3:1 v/v) afforded the stable lactol isomers **284, 264** in a 1:9 ratio in 48% combined yield.

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**.

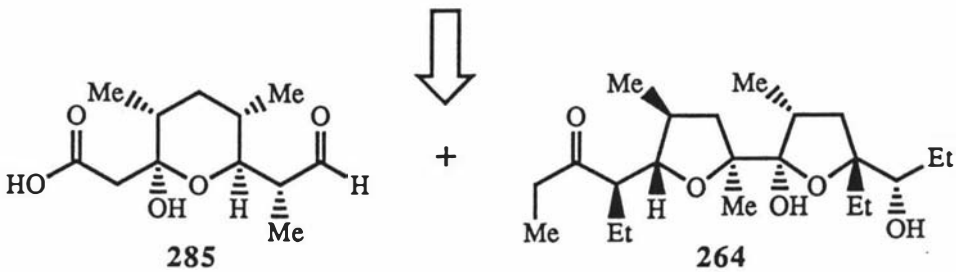
1.3.4. Lysocellin

The total synthesis of the polyether antibiotic lysocellin **182** was reported in 1992 by Yonemitsu *et al*[95,96]. Lysocellin is almost identical in structure to ferensimycin B, differing only in the lack of a methyl substituent at C2.

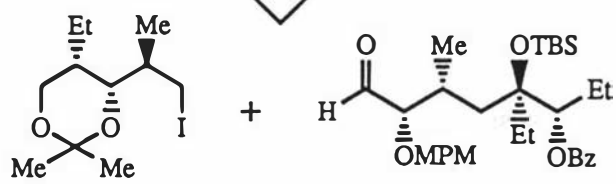
Scheme 59



Lysocellin **182**



285 **264**



286 **287**

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).

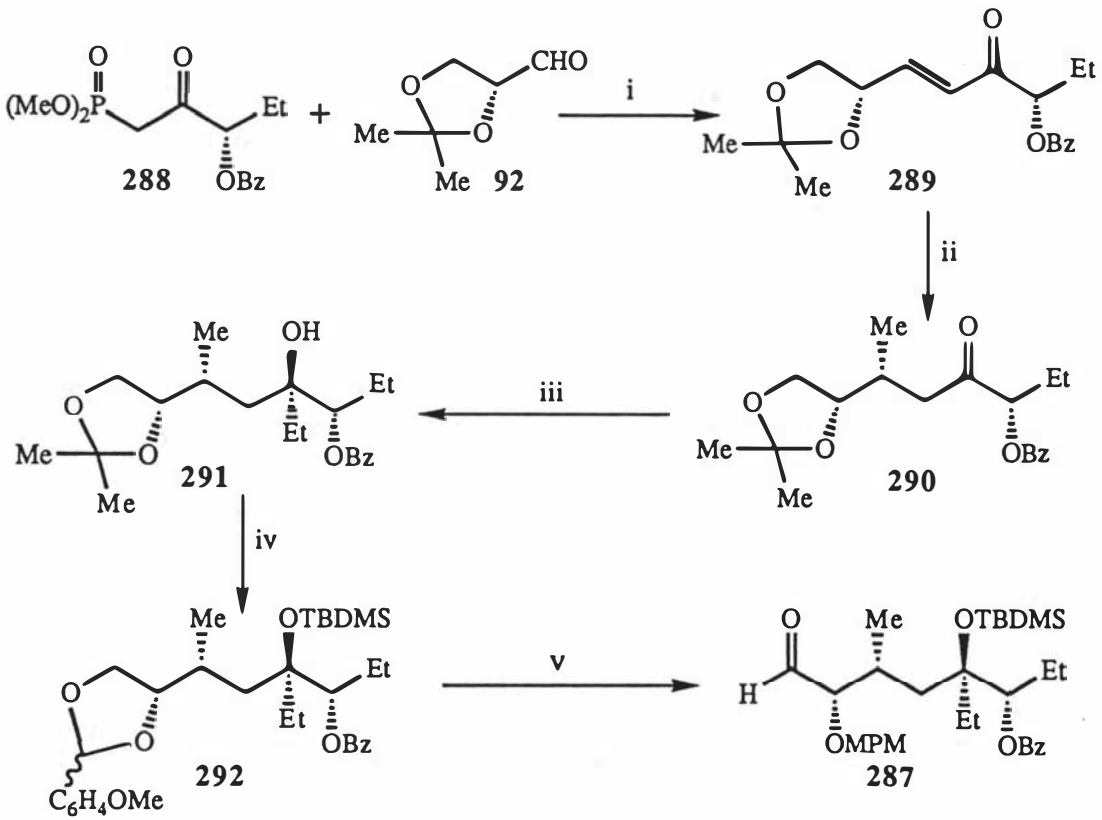
Preparation of the iodide **286** (Scheme 60) was reportedly carried out by using the alcohol precursor to the pivaloyl derivative **229**, previously prepared in the synthesis of lasalocid A[75-78] (see Scheme 49). Although no details were given for this conversion, formation of the tosylate followed by reaction with sodium iodide should provide an effective route to the iodide **286**.

Scheme 60

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 α,β-unsaturated ketone **289** (Scheme 61). Treatment of the ketone **289** with dimethyllithium 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_2CuLi, Et_2O/THF, -78 to -20°C; (iii) EtMgBr, THF, -78°C; (iv) a: TBDMSOTf, Et_3N, 0°C to RT; b: 1M H_2SO_4/THF/MeOH (2:4:1); c: 4-$MeOC_6H_4CH(OMe)_2$, PPTS, CH_2Cl_2; (v) a: $LiAlH_4$-$AlCl_3$ (1:3), Et_2O, -50°C; b: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N.

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[22,23] of the freed hydroxyl group to afford the desired aldehyde subunit **287**.

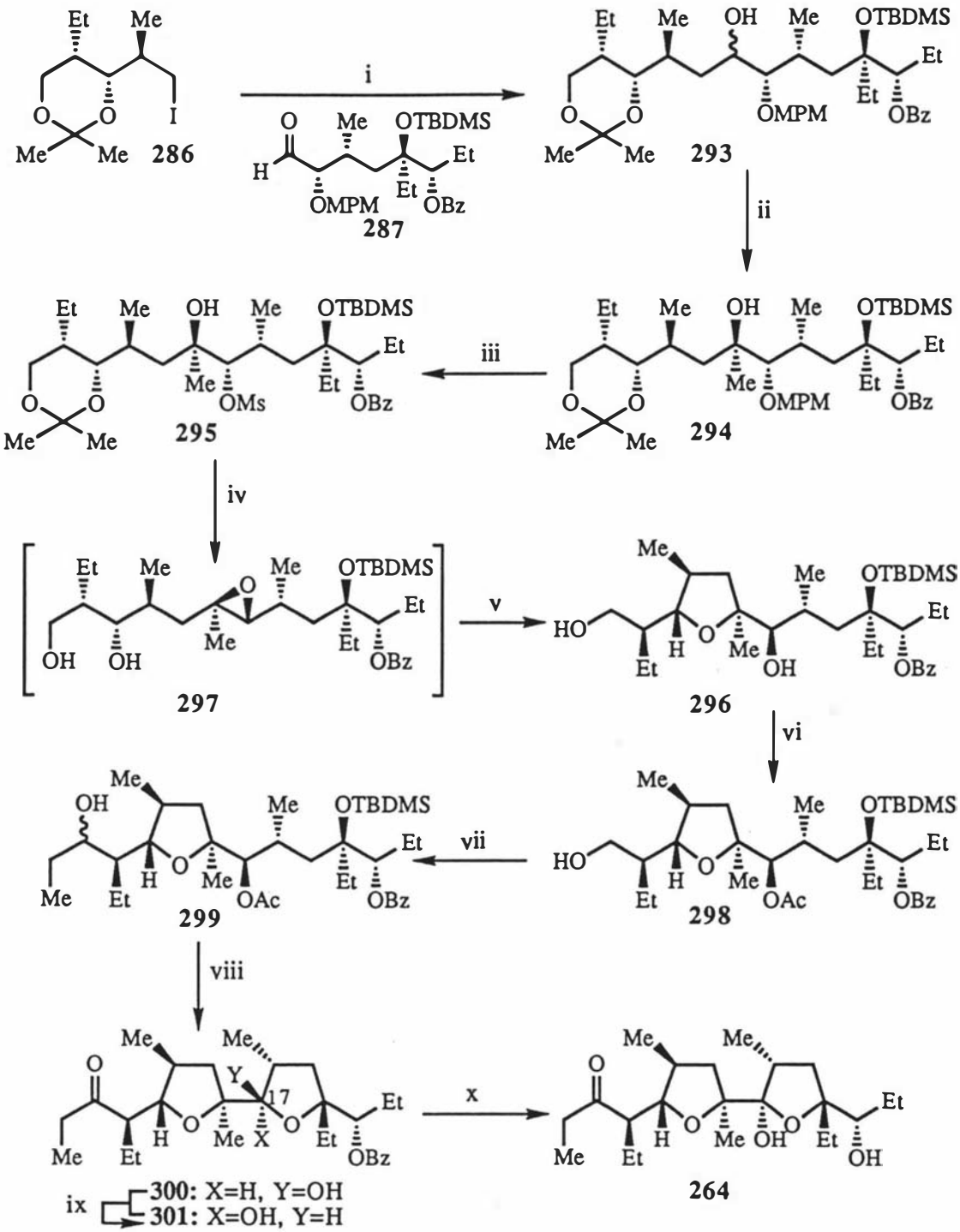
With the required subunits in hand, assembly of the ketone **264** began (Scheme 62) with the coupling of the lithium anion[99] of the iodide **286** and aldehyde **287** to give the alcohol **293**. Swern oxidation of the alcohol **293** followed by chelation controlled addition[97,98] of methylmagnesium iodide afforded only the desired alcohol **294**. After removal of the MPM protecting group by DDQ oxidation[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[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[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 α-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[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[101] and tetrahydropyran rings due to their presence in a number of important natural products such as the polyether antibiotics[3] (*vide supra*), acetogenins[102] and C-glycosides[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[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.

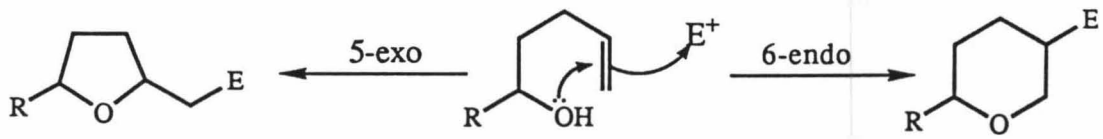
Scheme 62



Reagents and conditions: (i) ^{t}BuLi, Et_2O, -78°C, **287**; (ii) a: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N; b: MeMgI, Et_2O, -78 to -20°C; (iii) a: DDQ, CH_2Cl_2/H_2O (20:1); b: $LiAlH_4$, Et_2O, 0°C; c: MsCl, pyridine, 0°C; (iv) a: 1M H_2SO_4/THF (2:5); b: K_2CO_3, MeOH; (v) CSA, CH_2Cl_2, 0°C; (vi) a: TBDMSCl, imidazole, CH_2Cl_2, 0°C to RT; b: Ac_2O, Et_3N, DMAP, CH_2Cl_2; c: 1M HCl/ THF (2:5); (vii) a: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N; b: EtMgBr, THF, -78 to -20°C; (viii) a: $^{n}Bu_4NF$, DMF; b: PCC, 3A MS, CH_2Cl_2; (ix) 1M H_2SO_4/THF (1:3), 0°C to RT; (x) H_2, 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



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

Scheme 64

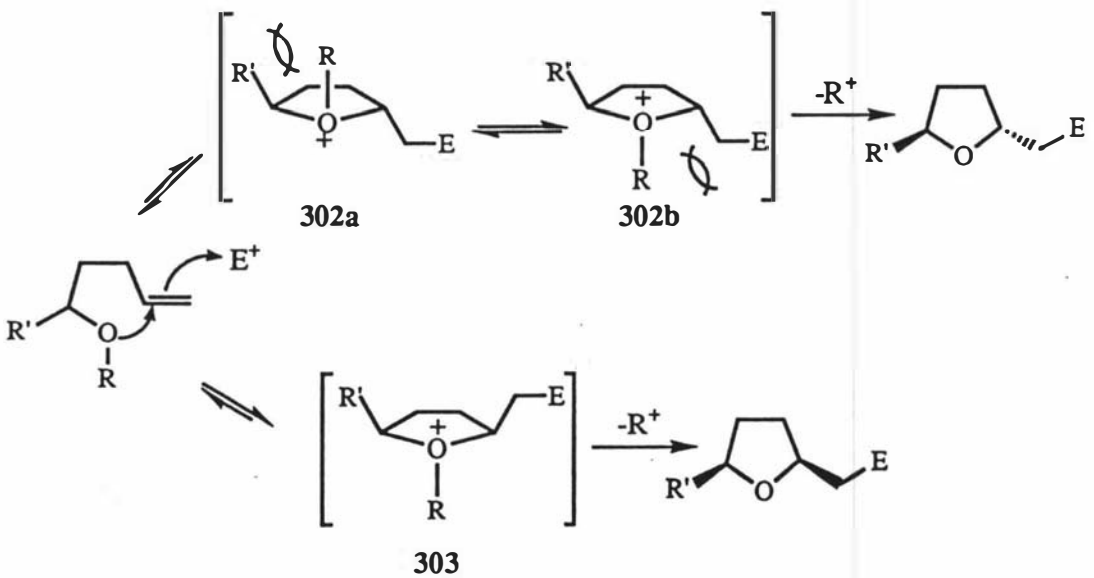
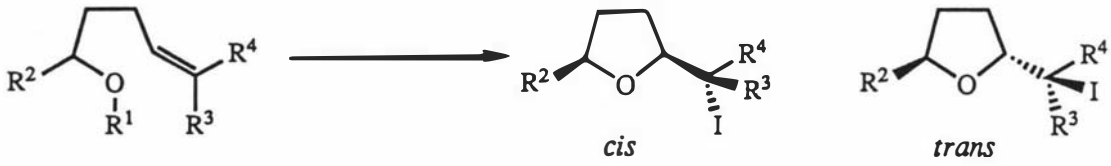


Table 1

Stereocontrolled Iodoetherification of γ,δ-Unsaturated Alkoxyalkenes



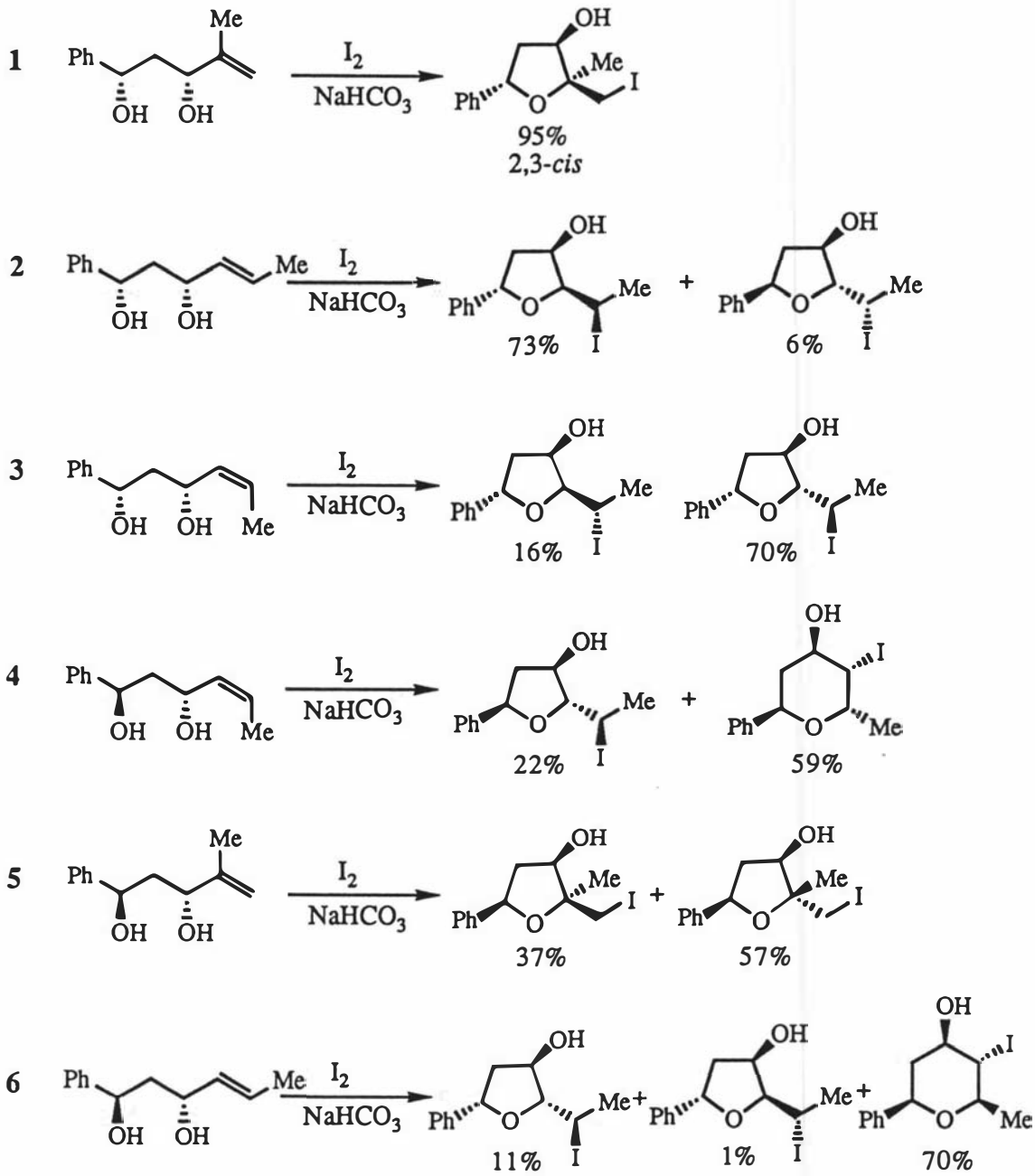
Reagents and conditions: I_2, CH_3CN, 0°C, ($NaHCO_3$ added when R^1=H).

R^1	R^2	R^3	R^4	Ratio *cis*/*trans*	Yield (%)
H	Me	H	H	1 : 2	66
Me	Me	H	H	1 : 2	15
CH_2Ph	Me	H	H	2 : 1	60
Si^tBuPh_2	Me	H	H	3 : 1	43
Si^tBuPh_2	Me	Me	H	8 : 1	30
BB	Me	H	H	3.7 : 1	74
DCB	Me	H	H	21 : 1	63
H	Me_2CH	H	H	1 : 4	88
DCB	Me_2CH	H	H	20 : 1	95
H	Me	Me	H	1 : 2	99
DCB	Me	Me	H	25 : 1	75
H	Me	H	Me	2 : 5	81
DCB	Me	H	Me	12 : 1	47
CH_2Ph	Me	CO_2Me	H	6 : 1	55
DCB	Me	CO_2Me	H	50 : 1	60
BB	Me	CO_2Me	Me	10 : 1	44
^{t}Bu	Me	H	H	28 : 1	91

destabilises the *trans* intermediates and the *cis* isomer predominates. The choice of R is important, with benzyl derivatives[106] and *tert*-butoxy ethers[107] 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.

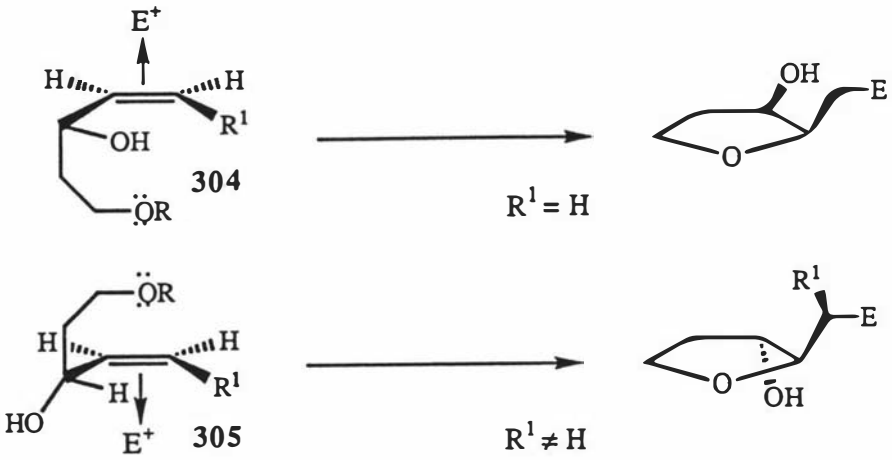
The presence of an allylic hydroxyl group in γ,δ-unsaturated alcohols has a pronounced effect on the stereochemical outcome of cyclisations under kinetic conditions[108] (Scheme 65). Generally if there is no (Z) substituent on the double bond the 2,3-*cis* product is favoured, while the presence of a (Z) substituent favours the *trans* product. These observations may be rationalised using the model proposed by

Scheme 65

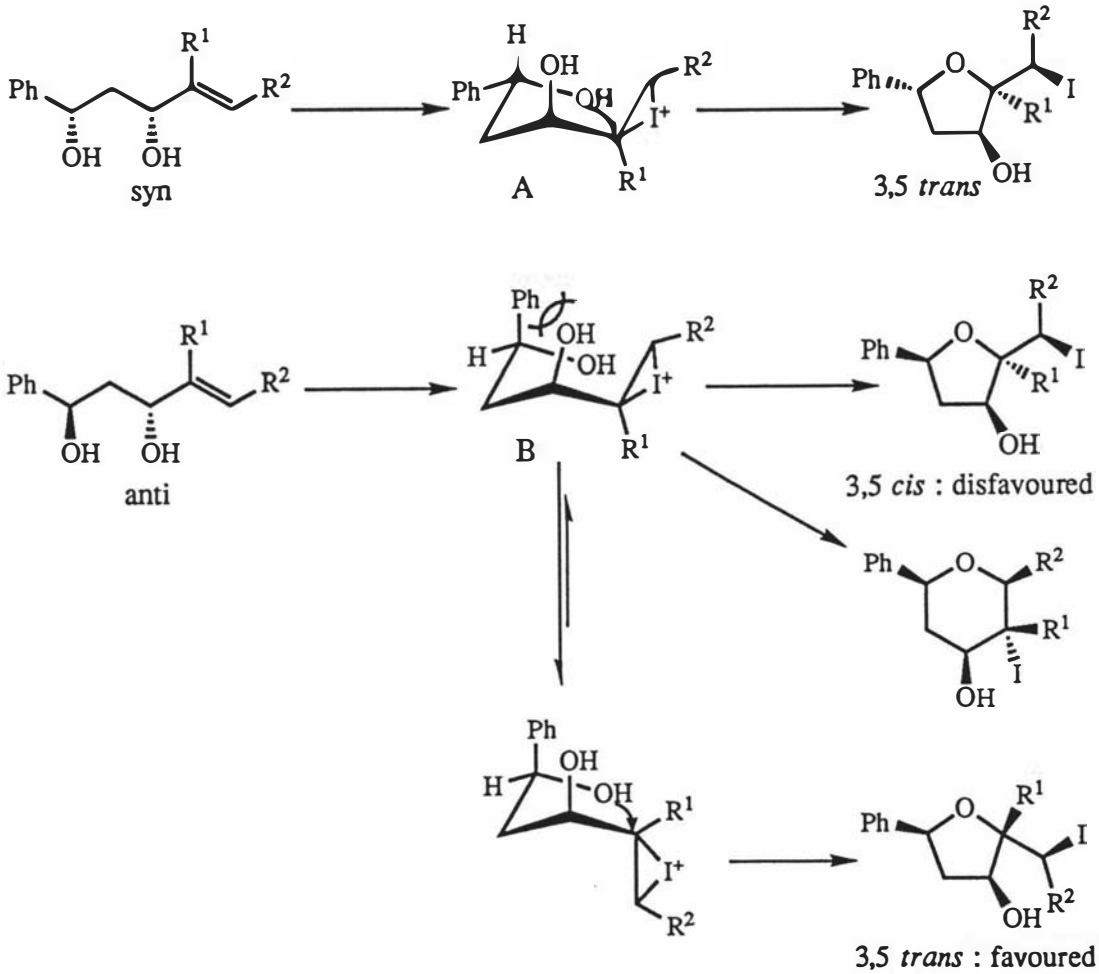


Chamberlain *et al*[109] (Scheme 66) in which preferential attack of the electrophile on the OH in plane conformer **304** occurs from the face of the double bond *syn* to the allylic hydrogen. Thus, when R^1=H the 2,3-*cis* isomer is formed as the major product. However, when there is a (Z) substituent on the double bond the resulting steric hindrance destabilises the OH in plane conformer making the hydrogen in-plane conformer **305** energetically more accessible. Hence, the 2,3-*trans* isomer becomes favoured. Examples of such stereoselectivity are shown in Scheme 65 (reactions 1, 2 and 3). Furthermore, the 1,3 *syn* or *anti* relationship of the allylic and C6 hydroxyl

Scheme 66



Scheme 67



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.

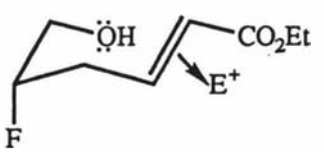
The electronic character of homoallylic substituents has also been reported to affect the stereochemical outcome (Table 2), with electron withdrawing groups favouring a 1,3-*trans* product and electron donating groups favouring the corresponding *cis* isomer. The electrophilic attack is proposed[111] 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 2

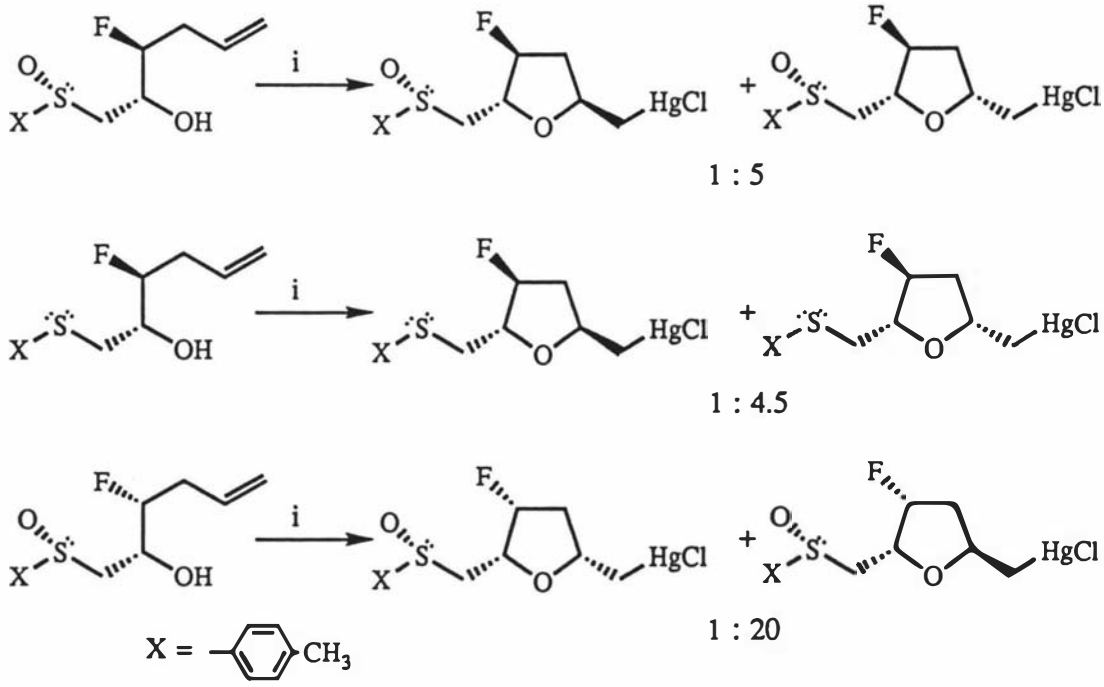
Effect of homoallylic substituents on stereoselective iodoetherification.

X	cis : trans ratio
OH	1 : 4
OMe	1 : 4.6
F	1 : 6.3
Me	3.6 : 1

Figure 7



Scheme 68



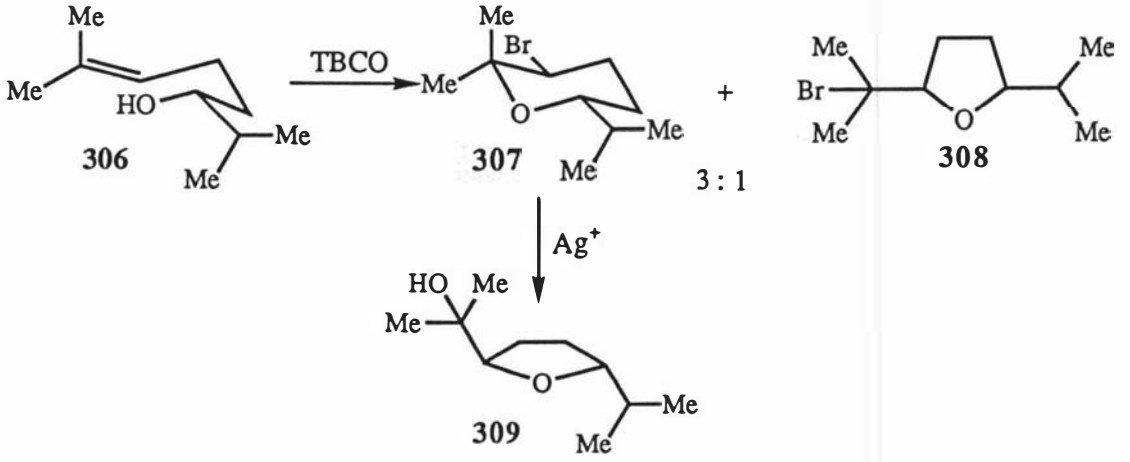
Reagents: (i) a: $Hg(OTFA)_2$,THF; b: KCl

An interesting method for the stereoselective synthesis of *trans* 2,5-disubstituted tetrahydrofurans has been reported by Bartlett and Ting[114]. 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[115] of tetrahydropyrans (Scheme 69). Thus alcohol **306**, when treated with 2,4,4,6-tetrabromo-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**.

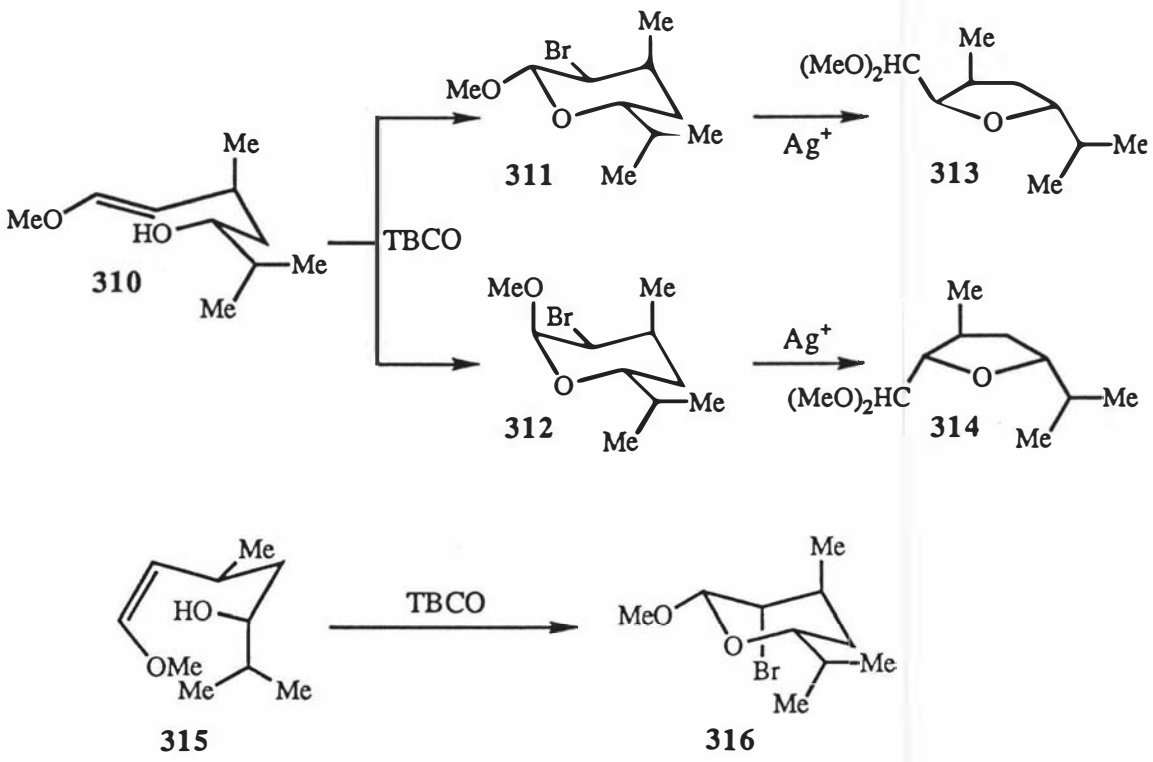
Cyclisation of the *trans* enol ether **310** (Scheme 70) affords the tetrahydropyrans **311** and **312** which undergo ring contraction to the tetrahydrofurans **313, 314**, respectively. The unexpected formation of tetrahydrofuran **314** from tetrahydropyran **312** is attributed to severe steric 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[116]. 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

Scheme 69

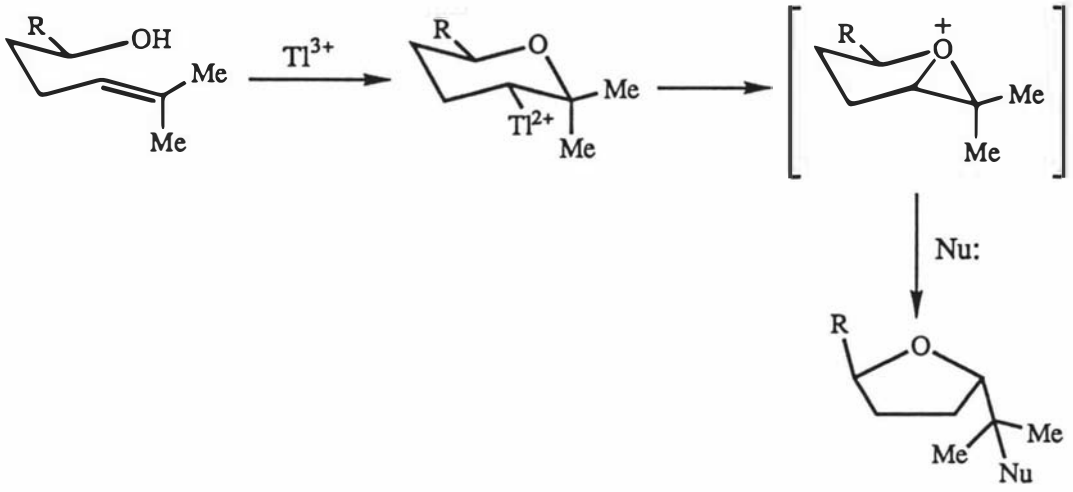


Scheme 70

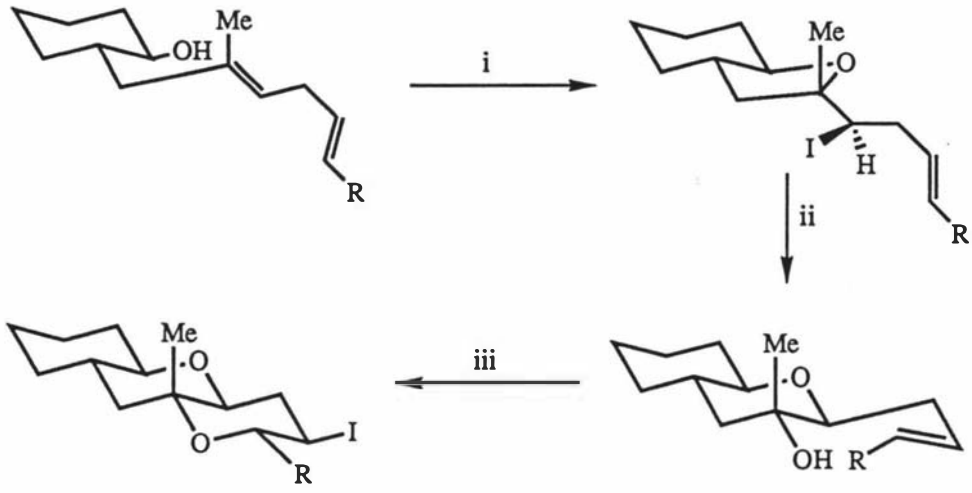


71). Reaction can also occur in the reverse direction, with the formation of tetrahydropyran rings from suitably substituted tetrahydrofuran rings. This methodology has been investigated (Scheme 72) for use in the synthesis of the *trans*, *syn*, *trans* fused structures present in the brevetoxins, which are potent neuro and cardiotoxins[116].

Scheme 71



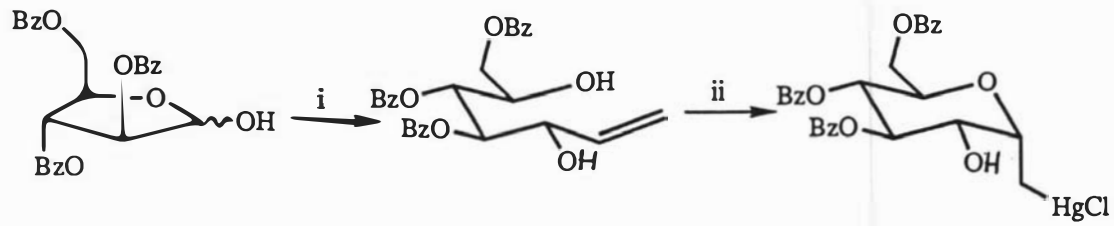
Scheme 72



Reagents: (i) NIS; (ii) Ag^{+}, DMF; (iii) I_2, MeCN.

C-glycosides are useful synthons and potent metabolic inhibitors[118]. Methodology for the synthesis of the C-glycosides using electrophile-mediated cyclisations of hydroxyalkenes was developed by Russo and Nicotra[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 *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 *trans* product **318**.

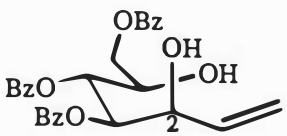
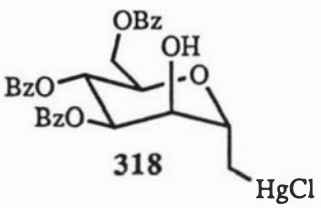
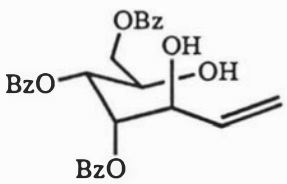
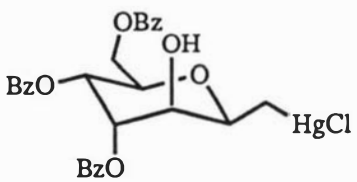
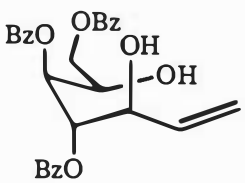
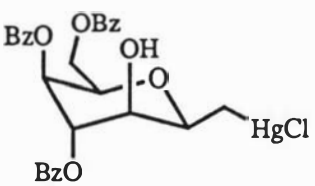
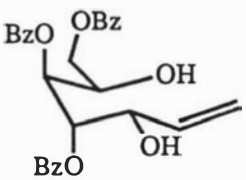
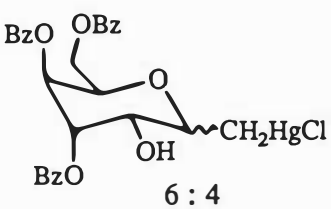
Scheme 73



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

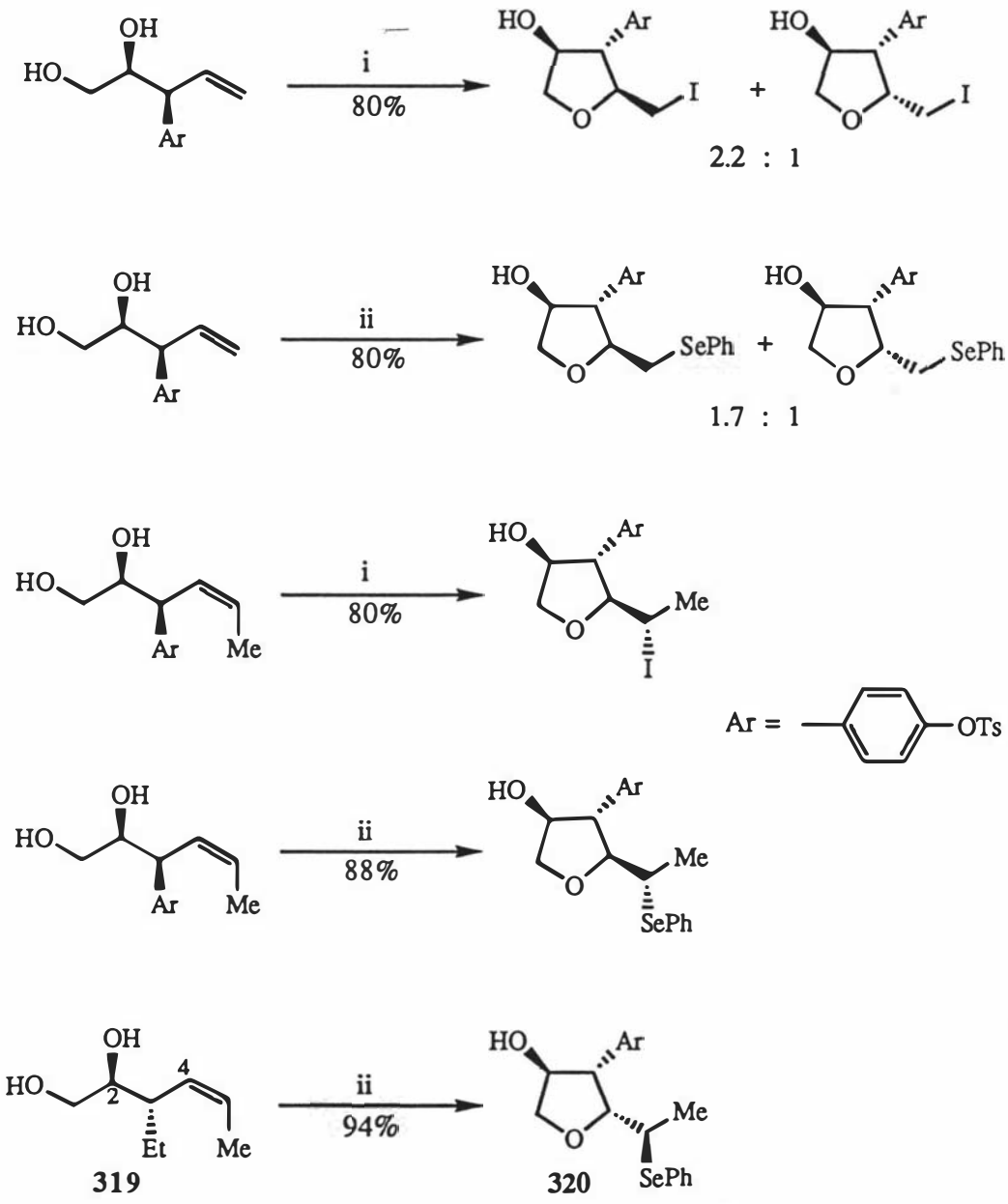
Table 3

Synthesis of C-Glycosides *via* Mercury Cyclisation

Substrate	Product	Yield %
 **317**	 **318**	20
		71
		73
	 6 : 4	73

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[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[111] (Table 4). Slower rates are observed with these solvents due to the lower iodine concentrations involved.

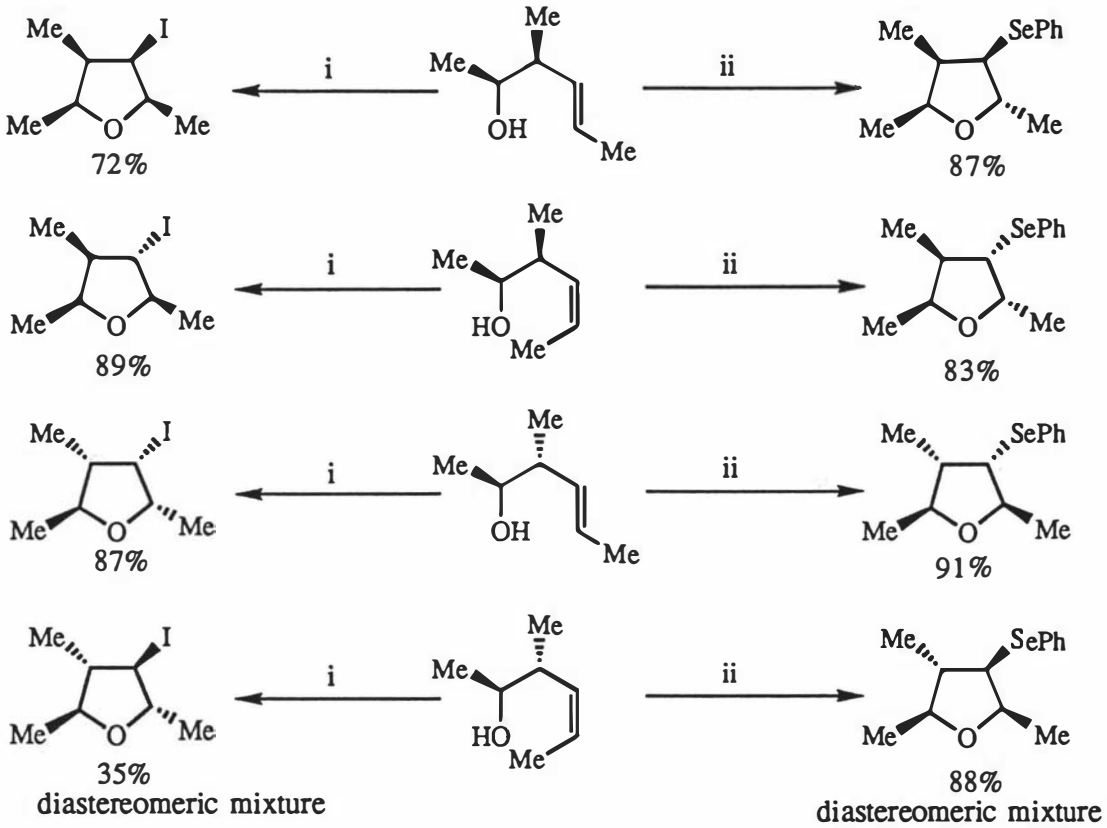
Table 4

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

solvent	trans : cis ratio	ε	I_2 (M)
THF	4.5 : 1	7.58	4.87
DME	5.2 : 1	7.20	2.05
^{t} butyl methyl ether	7 : 1	-	1.15
diethyl ether	8.6 : 1	4.34	0.88
diisopropyl ether	12 : 1	3.88	0.27

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[121] 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).

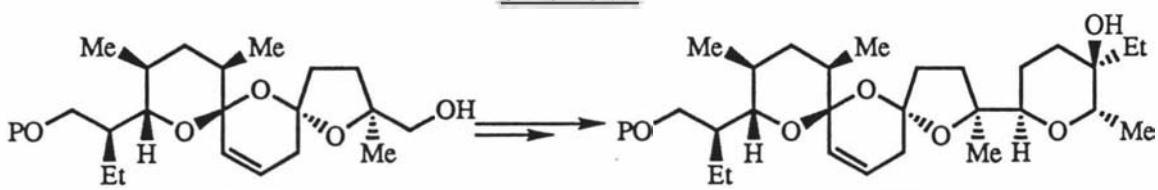
Scheme 75



Reagents: (i): I_2, F_3CCO_2Ag; (ii) PhSeCl.

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).

Scheme 76



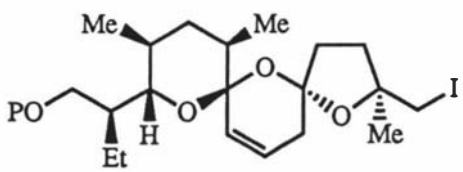
179 **321**

Chapter 2

Discussion

2.1 Preliminary investigations

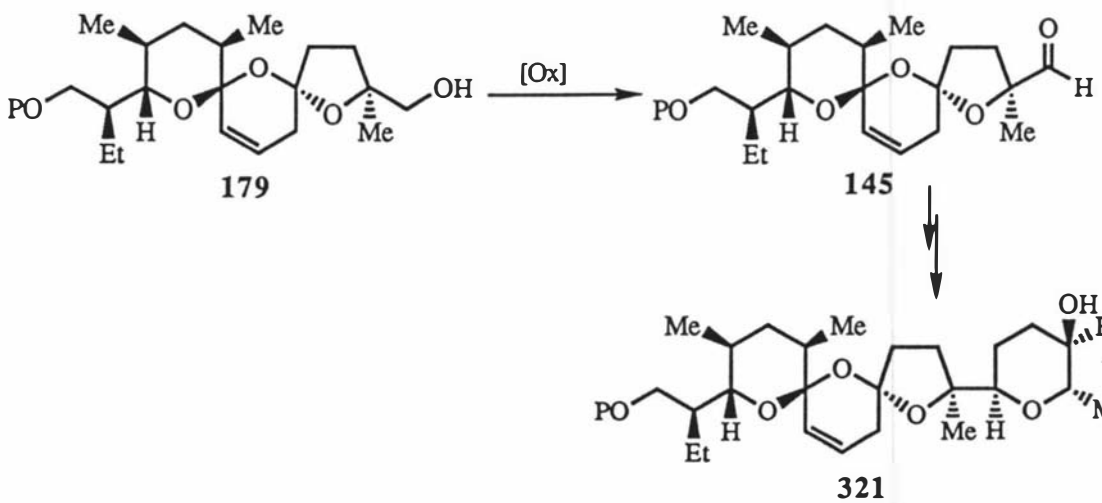
The recent work by Brimble and Williams[53] in establishing methodology for the synthesis of the central *bis*-spiroketal moiety of *epi*-17-deoxy-(*O*-8)-salinomycin **143** culminated in the synthesis of iodide **177** and proposed methodology for the preparation of the corresponding alcohol **179**. In order to complete a total synthesis



177

of *epi*-17-deoxy-(*O*-8)-salinomycin **143** methodology is now required for elaboration of the right hand of the molecule to include the E ring (Scheme 77). Beginning with alcohol **179**, it was proposed that oxidation to the corresponding aldehyde **145** would provide an effective "handle" from which construction of the E ring could be developed.

Scheme 77



179 **145** **321**

In order to develop methodology for construction of the E ring of *epi*-17-deoxy-(*O*-8)-salinomycin **143** a suitable model system was required. Thus, due to its strong

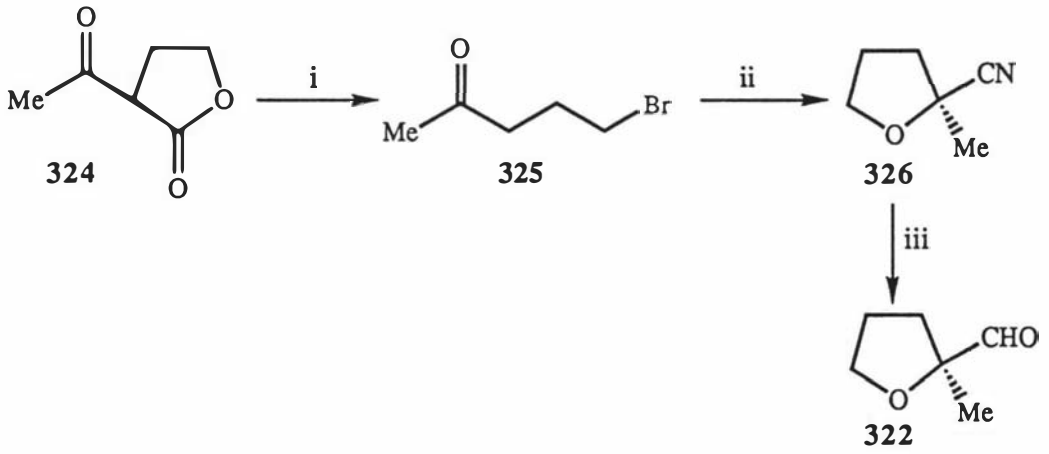
resemblance to the D ring of salinomycin and the presence of an apparently facile procedure for its preparation in the literature[122], 2-methyltetrahydrofur-2-aldehyde **322** was selected as a model for *bis*-spiroketal **145**. Consequently, methodology for conversion of tetrahydrofuran **322** to *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

322 **323**

The model aldehyde **322** was prepared according to the method of Amouroux *et al*[122] (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



324 **325** **326** **322**

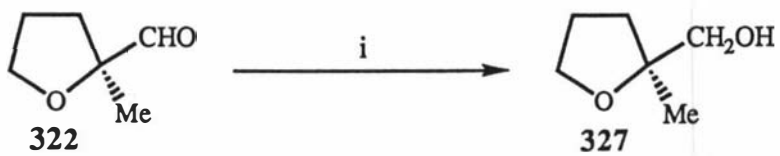
Reagents and conditions: (i) 48% hydrobromic acid, Δ, 31%; (ii) Cu(C)$_2$, toluene, Δ, 65%; (iii) a: $LiAlH_4$, Et_2O; b: 3M HCl, 68%.

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 triethoxyaluminohydride 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

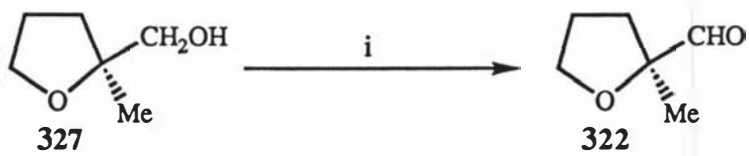


322 **327**

Reagents and conditions: (i) $LiAlH_4$, Et_2O, 64%.

Conversion of the alcohol **327** to the aldehyde **322** was first attempted using the chromium oxidising agents pyridinium chlorochromate[24] and pyridinium dichromate[125,126], however no aldehyde **322** was detected by NMR or IR in the filtered crude product. Use of the Swern oxidation[22,23] also proved unsuitable affording a complex mixture of compounds. Finally, treatment of the alcohol **327** with the Dess-Martin periodinane[127,128] (Scheme 81) afforded an acceptable yield (57%) of the desired aldehyde **322**.

Scheme 81

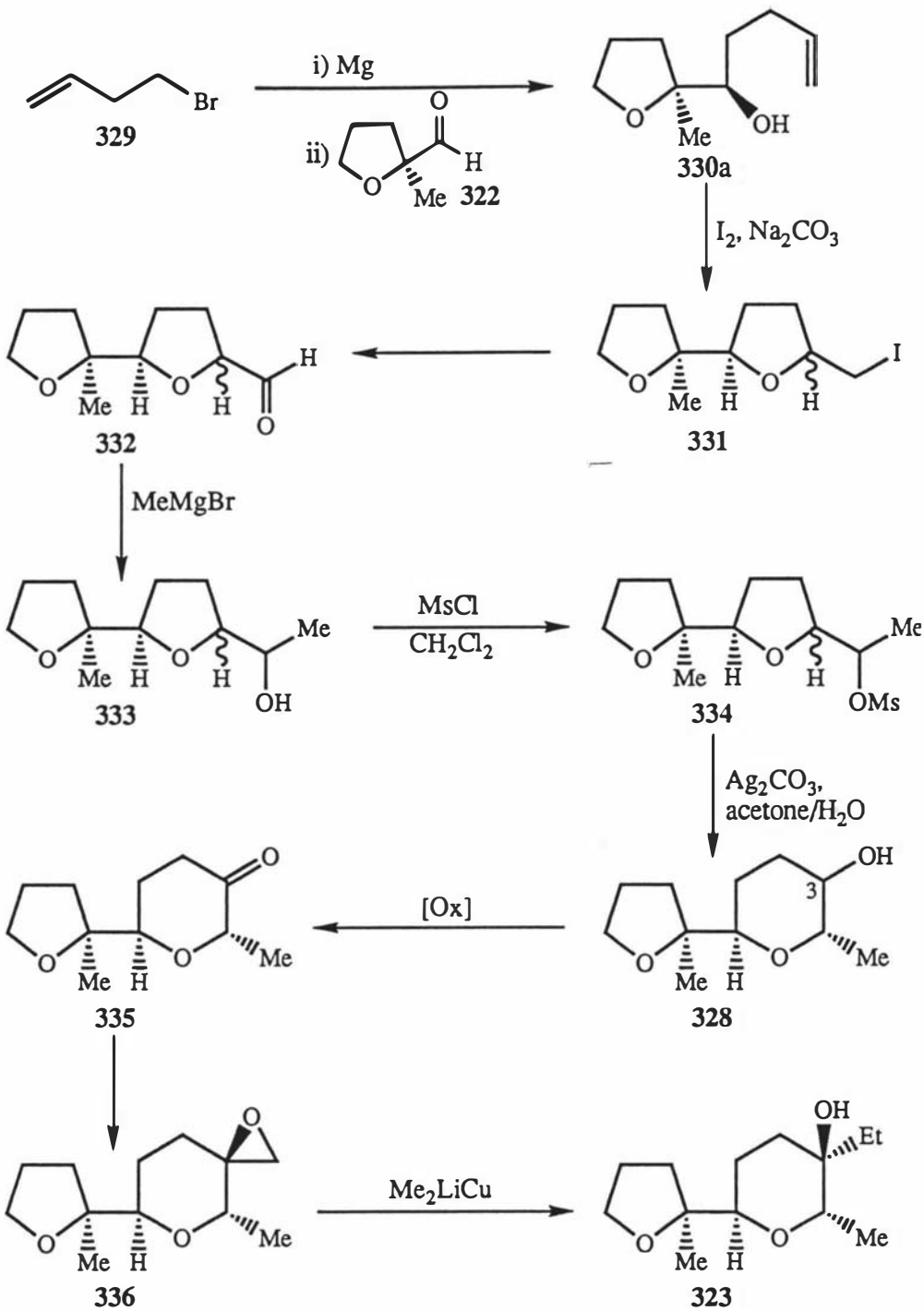


327 **322**

Reagents and conditions: (i) Dess-Martin periodinane, CH_2Cl_2, 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.

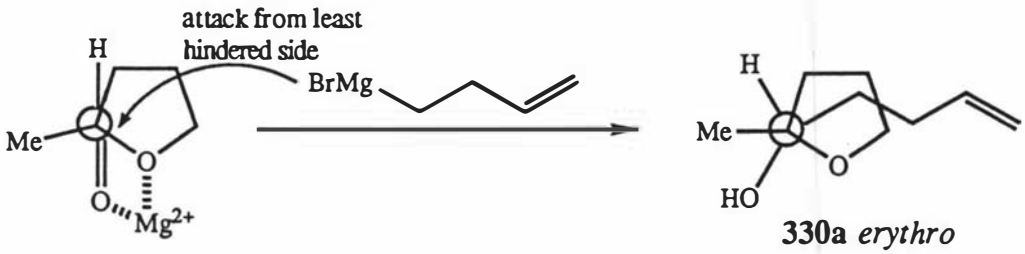
Scheme 82



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*[122] 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/H_2O, as previously used by Kishi *et al*[8]

Diagram 1

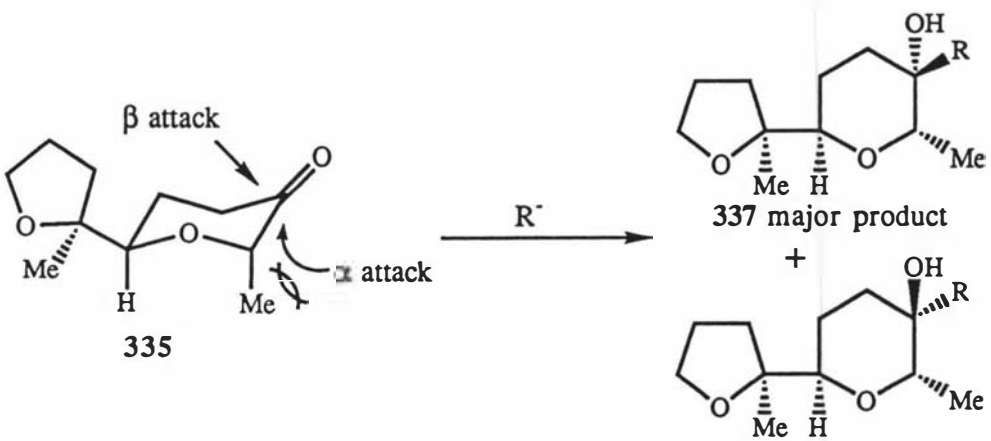
Chelation controlled Grignard addition of 4-bromo-1-butene **329** to aldehyde **322** affords predominantly the erythro product **330a**



330a *erythro*

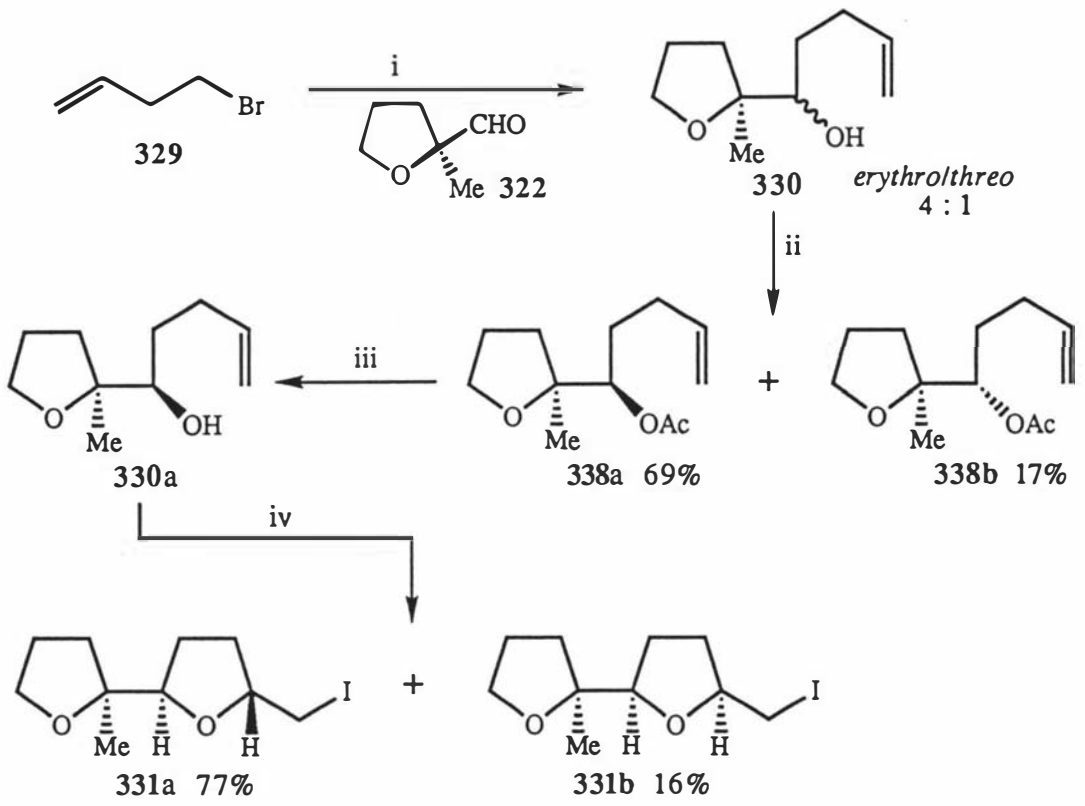
in the synthesis of lasalocid A (see Scheme 41), would effect ring expansion to the desired pyran skeleton **328**. Elaboration of the C3 position would then be effected by oxidation of alcohol **328** to ketone **335**, followed by conversion to the epoxide **336** which when treated with dimethyllithium cuprate undergoes ring opening to afford the target *bis*-ether **323**. Direct addition of organometallic reagents to ketone **335** (Scheme 83)[74] 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.

Scheme 83



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 ^{1}H NMR) comparable to that observed by Amouroux *et al*[122] (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

Scheme 84



Reagents and conditions: (i) Mg, THF then 2-methyl-2-tetrahydrofuraldehyde **322**, 68%; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 86%; (iii) K_2CO_3, 95% MeOH, 80%; (iv) I_2, Na_2CO_3, 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 ^{13}C 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

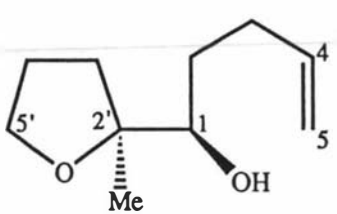
^{1}H NMR Chemical Shifts for (1R*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-4-penten-1-ol **330a** and (1S*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-4-penten-1-ol **330b**

Compound	CH_3	$4 \times CH_2$	OH	CHOH	CH_2O	5-H_A	5-H_B	4-H
330a *erythro*	1.12	1.31 - 2.44	2.73	3.53	3.85	4.97	5.05	5.85
330b *threo*	1.14	1.39 - 2.41	2.73	3.40	3.83	4.97	5.05	5.84

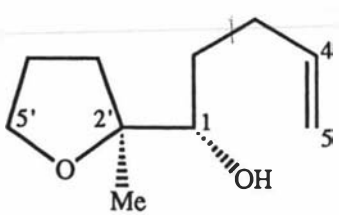
Table 6

^{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**

Compound	CH_3	CH_2	CH_2	CH_2	CH_2	C-5'	C-1	C-2'	C-5	C-4
330a *erythro*	22.9	26.2	30.7	30.9	34.3	67.7	75.6	85.6	114.5	138.4
330b *threo*	19.9	26.3	30.7	31.0	34.4	67.3	75.8	85.2	114.6	138.4



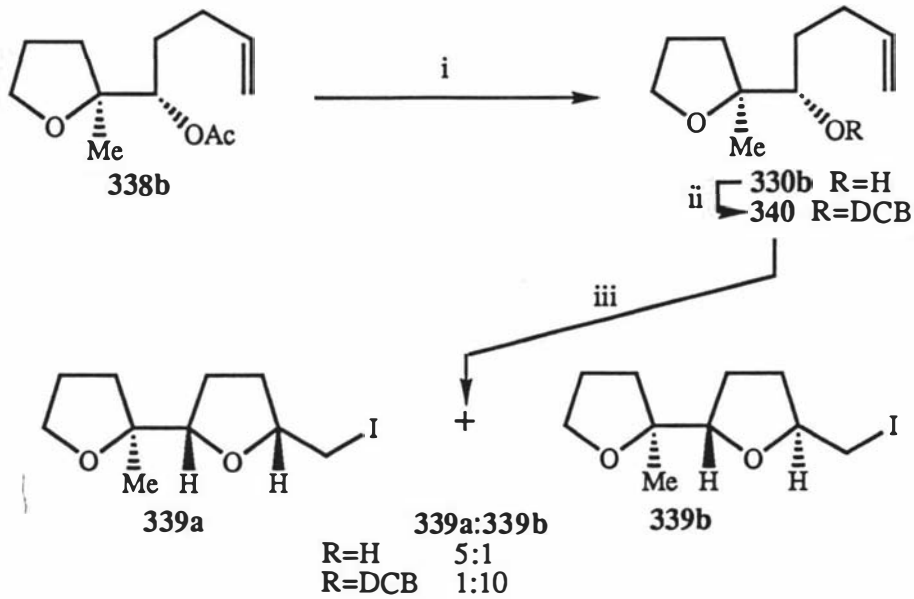
330a



330b

339b in an overall yield of 85% (Scheme 85).

Scheme 85



Reagents and conditions: (i) K_2CO_3, 95% MeOH, 85%; (ii) NaH, 2,6-$Cl_2C_6H_3CH_2Br$, THF, 0°C, 74%; (iii) R=H: I_2, Na_2CO_3, MeCN, 85%; (iii) R=DCB: I_2, MeCN, 65%.

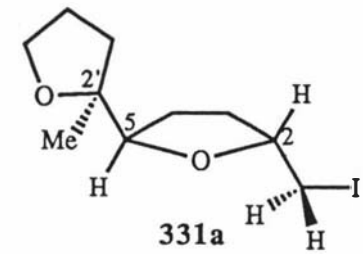
Determination of the *threo trans*:*threo cis* ratio was made by ^1H NMR, as the two iodides were inseparable by column chromatography. Although the *threo trans* **339a** and *threo cis* **339b** isomers were inseparable by column chromatography, accurate assignment of their individual spectra was relatively 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 Rychnovsky[106] 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.

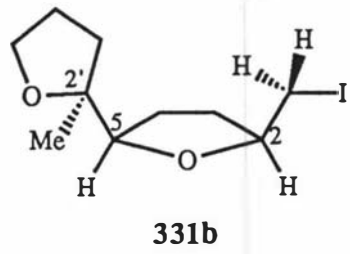
Table 7

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

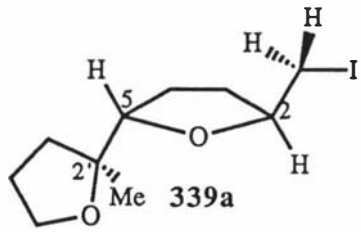
Assignment	**331a** *erythro trans*	**331b** *erythro cis*	**339a** *threo trans*	**339b** *threo cis*
CH_3	1.15	1.17	1.12	1.15
$4 \times CH_2$	1.56 - 2.28	1.57 - 2.07	1.57 - 2.28	1.61 - 2.06
CH_AI	3.15	3.24 - 3.28	3.18	3.18
CH_BI	3.31	3.24 - 3.28	3.28	3.25
CH_2O	3.85	3.86	3.77 - 3.91	3.83 - 3.92
5-H	4.07	3.93	4.03	3.83 - 3.92
2-H	4.05 - 4.16	3.89 - 3.99	4.00 - 4.10	4.02 - 4.13



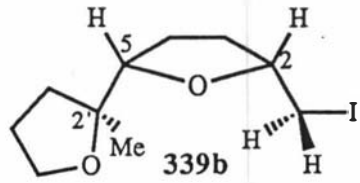
331a



331b



339a



339b

Table 8

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

assignments	**331a** *erythro trans*	**331b** *erythro cis*	**339a** *threo trans*	**339b** *threo cis*
CH_2I	10.7	10.7	10.7	10.2
2'-Me	22.7	23.3	22.9	23.2
CH_2	26.1	26.3	26.3	26.2
CH_2	28.0	27.0	27.4	26.3
CH_2	32.9	31.4	33.0	31.4
CH_2	33.4	33.2	34.6	34.8
CH_2O	68.1	68.2	68.4	68.6
C-2	79.1	78.2	79.0	79.0
C-2'	84.3	83.9	84.1	83.1
C-5	85.4	85.9	85.6	86.2

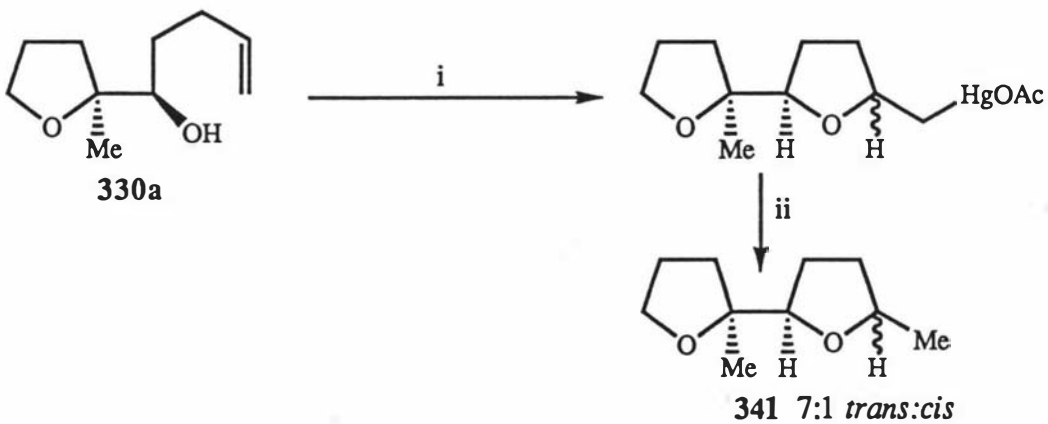
Another notable difference between the *cis* and *trans* iodides is the diastereotopicity exhibited by the CH_2I protons. With both the *erythro* and *threo* iodides, the difference in the chemical shifts of the CH_2I protons of the *trans* isomers is greater than that of the *cis* isomers, although this difference is particularly noticable with *erythro* iodides. While the individual diastereotopic CH_2I 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 CH_2I 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 CH_2I protons.

One further difference in the ^1H 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 ($1/2 \times CH_2$) at ~2.25 ppm, while the chemical shifts of the CH_2 protons of the corresponding *cis* isomers **331b, 339b** are all below 2.07 ppm.

Similarities in the ^{13}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



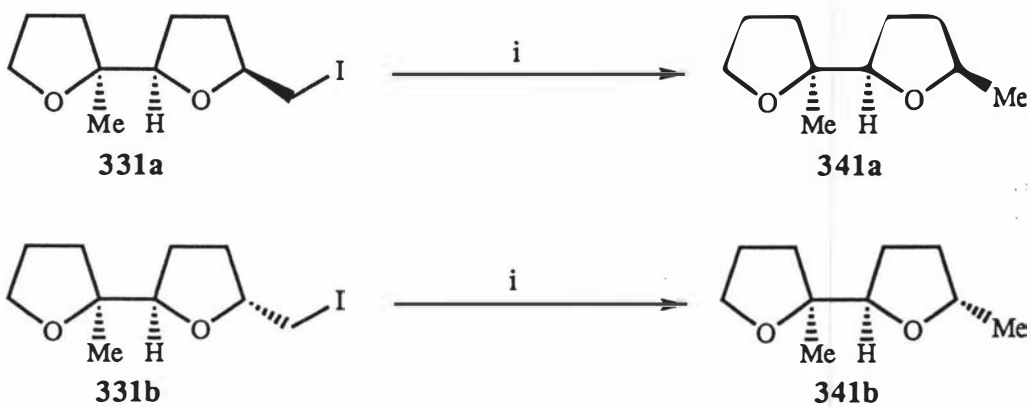
330a

341 7:1 *trans:cis*

Reagents and conditions: (i) $Hg(OAc)_2$, THF/H_2O; (ii) $NaBH_4$, 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*[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[131] for the *cis* and *trans* 2,5-dimethyltetrahydrofuran **342a** and **342b** (Table 10).

Scheme 87

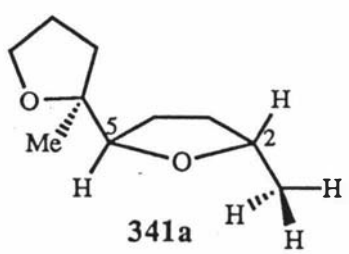


Reagents and conditions: (i) Bu_3SnH, AIBN, toluene, 84%.

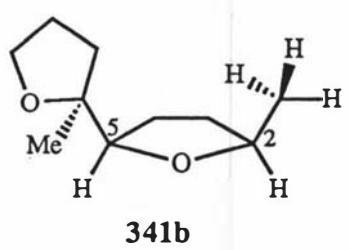
Table 9

^{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**.

Compound	CH_3	CH_3	$4 \times CH_2$	CH_2O	5'-H	2'-H
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



341a

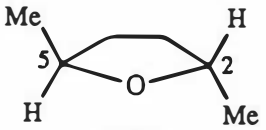


341b

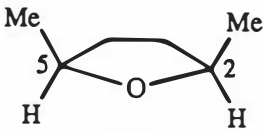
Table 10

^{1}H NMR chemical shift values for (2S, 5S)-2,5-dimethyltetrahydrofuran **342a** and (2S, 5R)-2,5-tetrahydrofuran **342b**

Compound	2-H, 5-H
342a (*trans*)	4.02
342b (*cis*)	3.86



342a

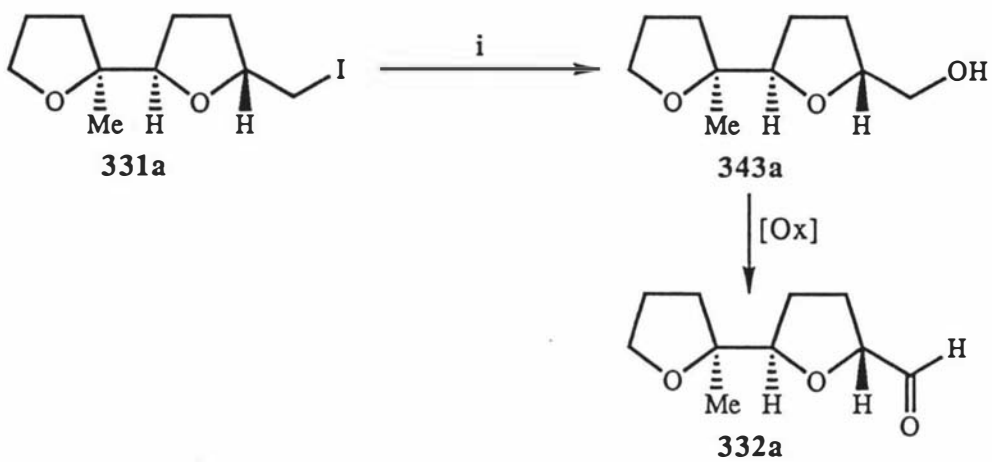


342b

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[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*[133] involved the use of the ruthenium catalyst $Ph_4P[RuO_2(OAc)Cl_2]$ 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.

Scheme 88

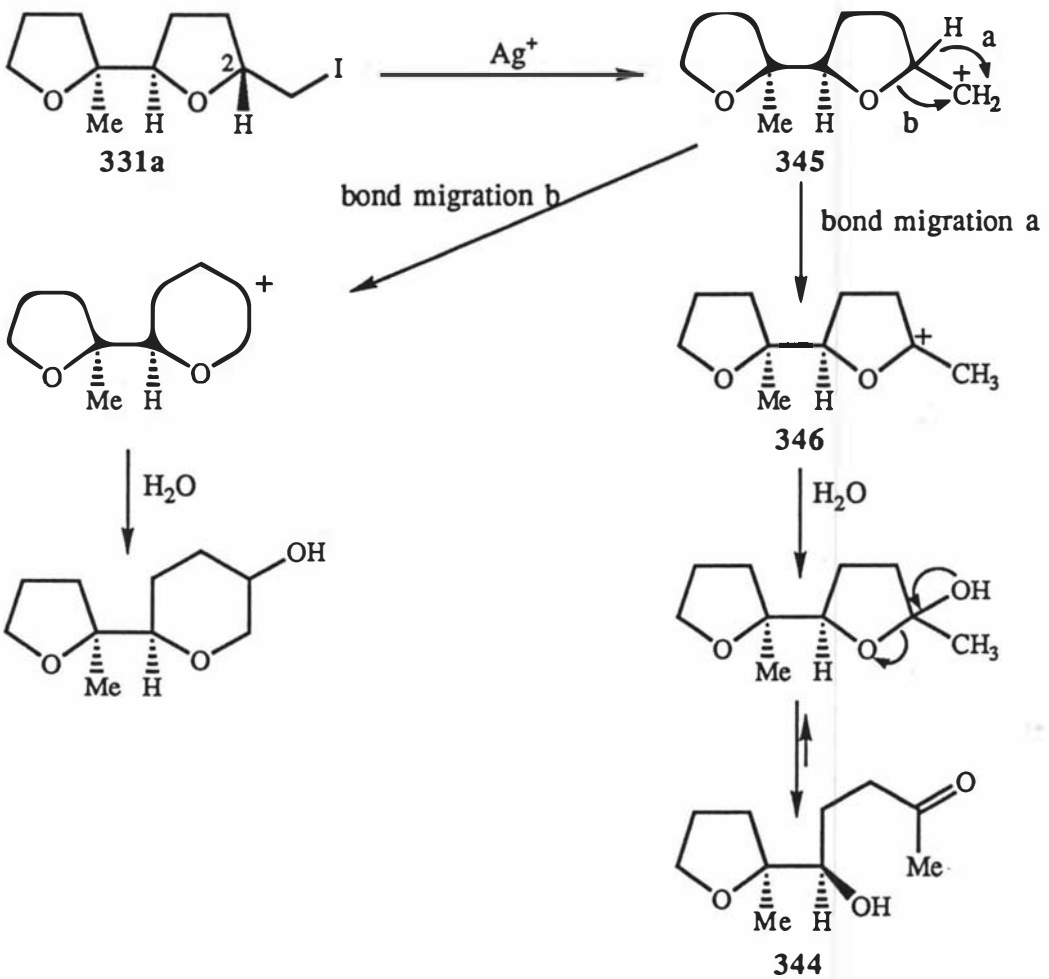


331a **343a** **332a**

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 **331a** with silver carbonate in acetone[8]. However, when this reaction was carried out only the ketoalcohol **344** was produced, suggesting the mechanism detailed in Scheme 89. Thus, treatment of the iodide **331a** with silver carbonate in wet acetone afforded the carbocation **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 **346** which following addition of H_2O afforded ketoalcohol **344**.

Scheme 89

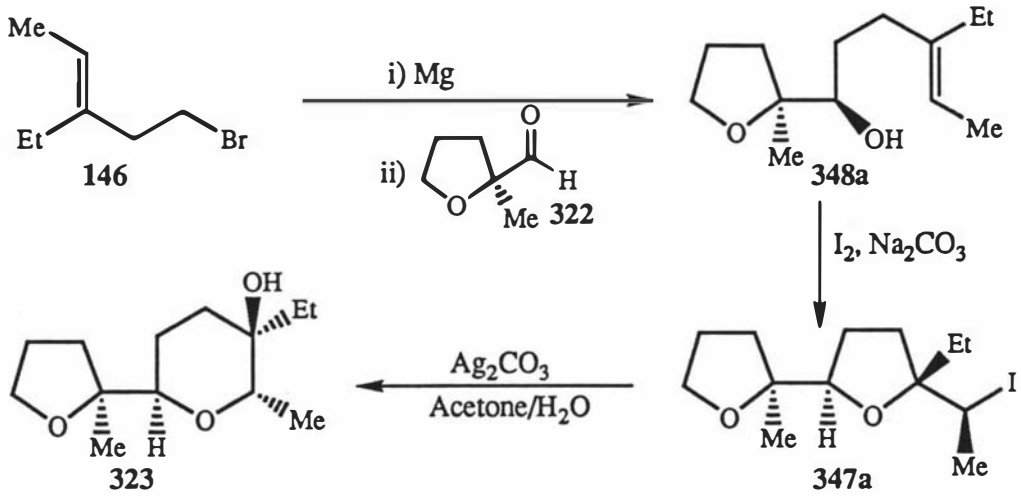


From this result, it became clear that in order for successful ring expansion to occur, a tetrasubstituted C2 carbon is required, to eliminate the possibility of hydride shift occurring upon formation of the intermediate carbocation.

Consequently, it was proposed (Scheme 90) that the target *bis*-ether **323** be synthesised by ring expansion of the C2 tetrasubstituted iodide **347a** which would in turn be prepared by iodoetherification of the *erythro* hydroxyalkene **348a** produced by

the addition of the Grignard reagent from trisubstituted bromide **146** to the model aldehyde **322**.

Scheme 90

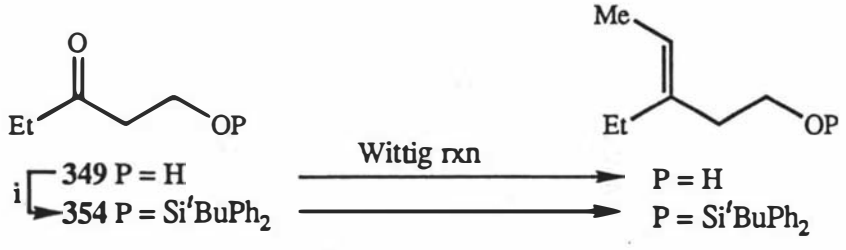


In order to pursue the proposed pathway for formation of the C2 tetrasubstituted iodoether **347a**, it was first necessary to develop methodology for the stereoselective synthesis of the (E)-trisubstituted bromoalkene **146**.

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

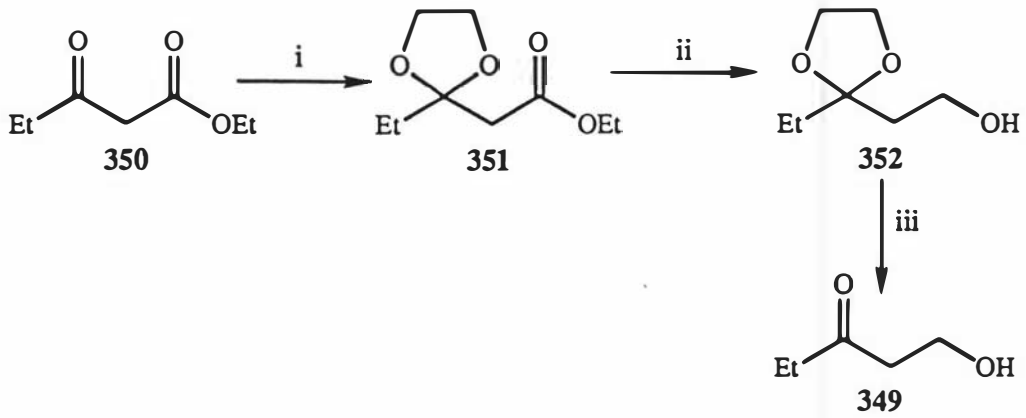
The most obvious method to prepare alkene **146** involved the use of the Wittig reaction on a hydroxyl protected derivative of 1-hydroxy-3-pentanone **349** (Scheme 91). Consequently, 1-hydroxy-3-pentanone **349** was synthesised (Scheme 92) using the methodology reported by Albizati *et al*[134,135] *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) $^{t}BuPh_2SiCl$, imidazole, CH_2Cl_2.

Scheme 92



Reagents and conditions: (i) $HOCH_2CH_2OH$, TSA, benzene, 94%; (ii) $LiAlH_4$, Et_2O, 0°C, 98%; (iii) 100-200M silica gel, 10% oxalic acid, CH_2Cl_2, 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.

$(C_6H_5)_3P{=}CHCO_2Et$ **353**

$(C_2H_5O)_2P(O)CH_2CO_2Et$ **355**

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*[137] 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-oxymetal 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

Scheme 93

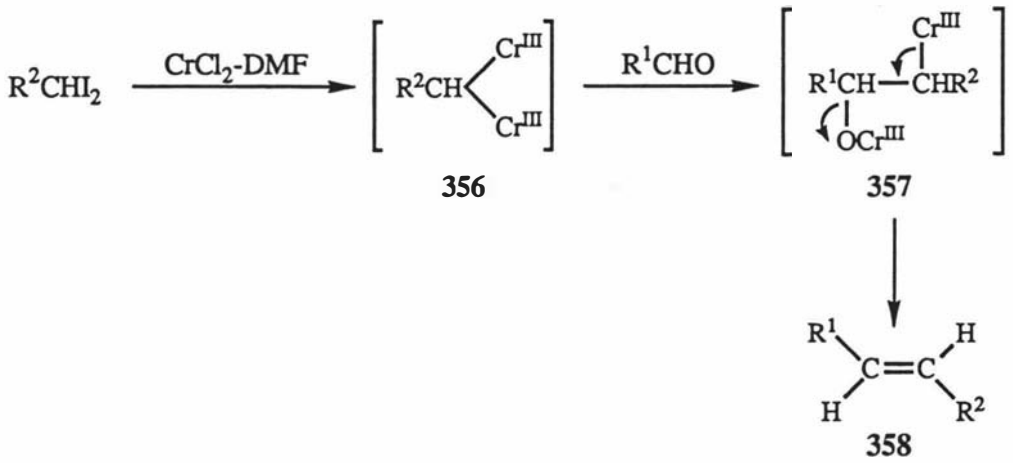


Table 11

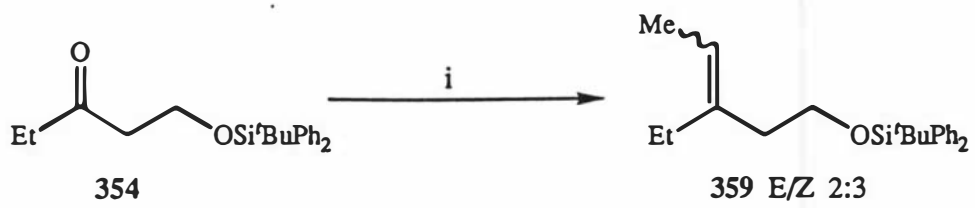
Application of Organochromium Methodology[137] using Various Carbonyl Compounds and 1,1-Diodoalkanes

Carbonyl compound	Diodoalkane	Yield %	E/Z ratio
n-$C_5H_{11}CHO$	CH_3CHI_2	94	96 : 4
n-$C_{11}H_{23}CHO$	CH_3CHI_2	81	95 : 5
Et_2CHCHO	CH_3CHI_2	99	98 : 2
n-$C_8H_{17}CHO$	$PrCHI_2$	85	96 : 4
$(CH_3)_3CCHO$	$PrCHI_2$	96	99 : 1
n-$C_5H_{11}CHO$	$^iPrCHI_2$	79	88 : 12
C_3H_7CHO	$^tBuCHI_2$	90	94 : 6
cyclododecanone	CH_3CHI_2	96	-
dibenzylketone	CH_3CHI_2	88	-
1-tetralone	CH_3CHI_2	85	16 : 84

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*-butyldiphenylsilyloxy)-3-pentanone **354** to afford an unsatisfactory 2:3 mixture of the

Scheme 94



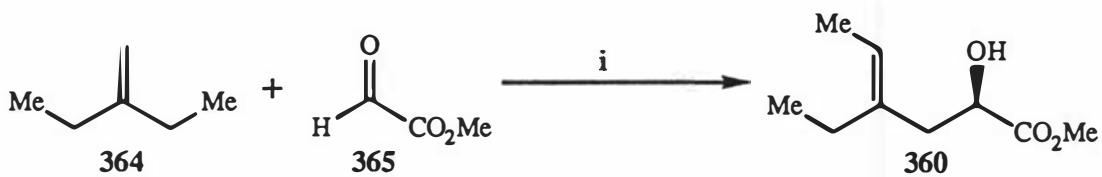
354 359 E/Z 2:3

Reagents and conditions: (i) $CrCl_2$, THF, DMF then $MeCHI_2$ 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*[138,139] 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.

Scheme 95



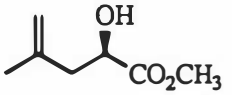
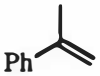
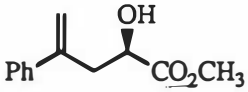
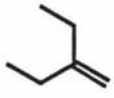
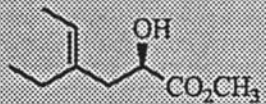
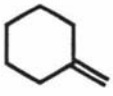
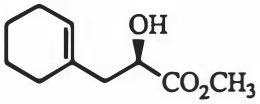
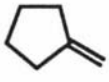
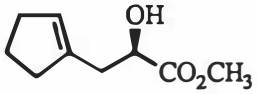
364 365 360

Reagents and conditions: (i) **361**, 4A M.S., CH_2Cl_2 then **364** and **365**, -70 → -30°C, 8h, 89%.

The literature preparation of methyl (E)-4-ethyl-2-hydroxyl-4-hexenoate **360** began with the *in situ* formation of the required chiral titanium catalyst **(R)-361** by the reaction of $(^iPrO)_2TiCl_2$ **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

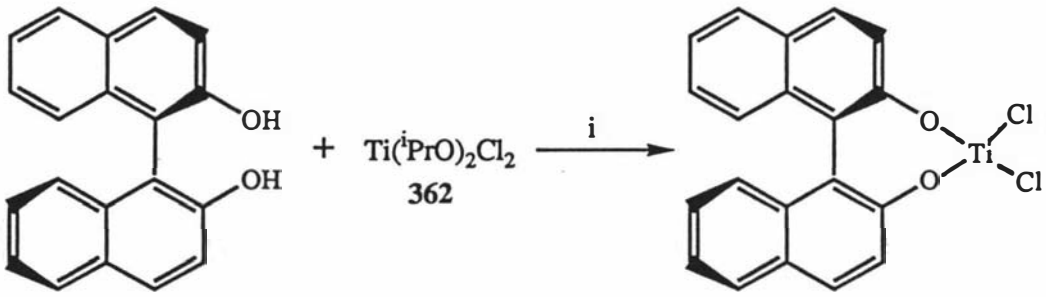
Table 12

Enantio- and Diastereoselective Syntheses using the Asymmetric Glyoxylate-Ene Reaction[138,139]

Alkene	$(^{i}PrO)_2TiX_2$ (X)	Product	Yield %	% enantiomeric excess
	Cl		72 68[a]	95 (R) 95 (S)[a]
	Cl Br		97 98	97 (R) 95 (R)
	Cl Br		89 91	94 (R)[b] 98 (R)[b]
	Cl Br		82 89	97 (R) 98 (R)
	Cl Br		87 92	48 (R) 89 (R)

[a] (S)-Binaphthol was used instead of the (R) counterpart. [b] E/Z ratio = 10 : 1.

Scheme 96

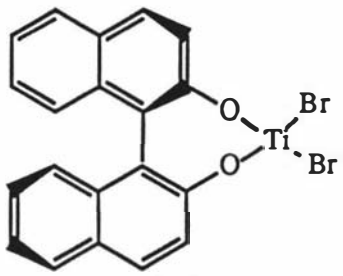


(R)-363 (R)-361

Reagents and conditions: (i) **(R)-(+)-363, 362**, 4A 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 $Ti(^iPrO)_2Br_2$ 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.

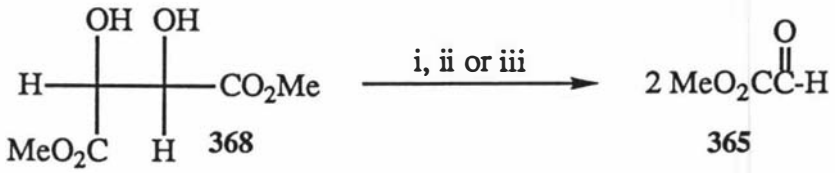
Figure 8



366

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 preparations[140-142]. Mikami *et al*[138,139] 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 al*[140] 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 al*[141] noted that their product contained 5% water. The third procedure described by Thompson *et al*[142] did not include a purification method as the methyl glyoxylate was used in its crude form.

Scheme 97



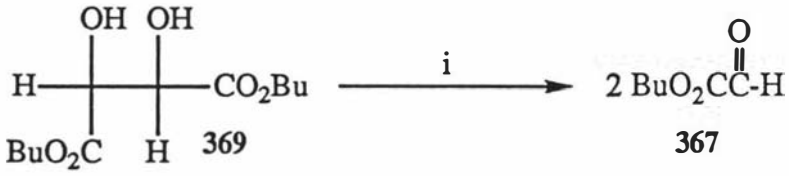
Reagents and conditions: (i) H_5IO_6, THF/Et_2O, 0°C, 86%, crude; (ii) H_5IO_6, Et_2O, 5°C, 35%, crude; (iii) H_5IO_6, Et_2O, 4A MS, 71%, crude.

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*[141]. Attempts to use the crude methyl glyoxylates in the glyoxylate-ene reaction also proved ineffective.

Butyl glyoxylate **367** was prepared[143] by the oxidative cleavage of dibutyl tartrate[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^{-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.

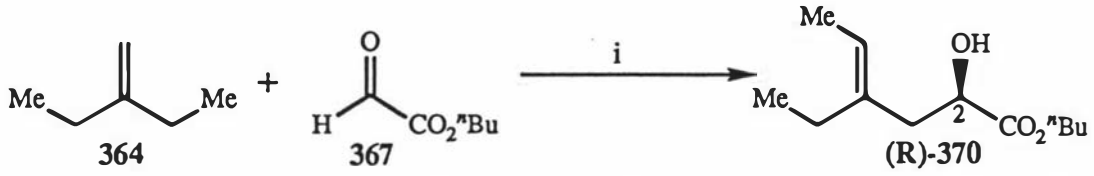
Scheme 98



Reagents and conditions: (i) $NaIO_4$, H_2O, 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 (R)-**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

Scheme 99

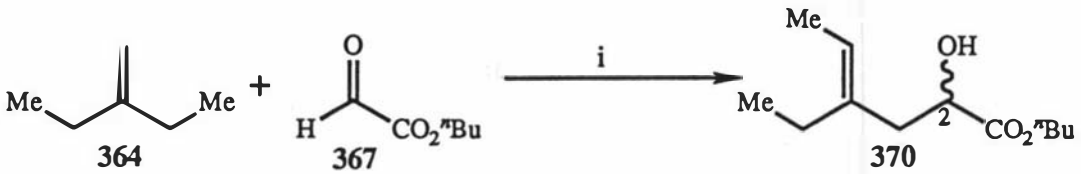


Reagents and conditions: (i) (R)-**363**, **362**, 4A MS, CH_2Cl_2, 1h then **364** and **367**, -70°C to RT, 24h, 57%.

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.

Scheme 100

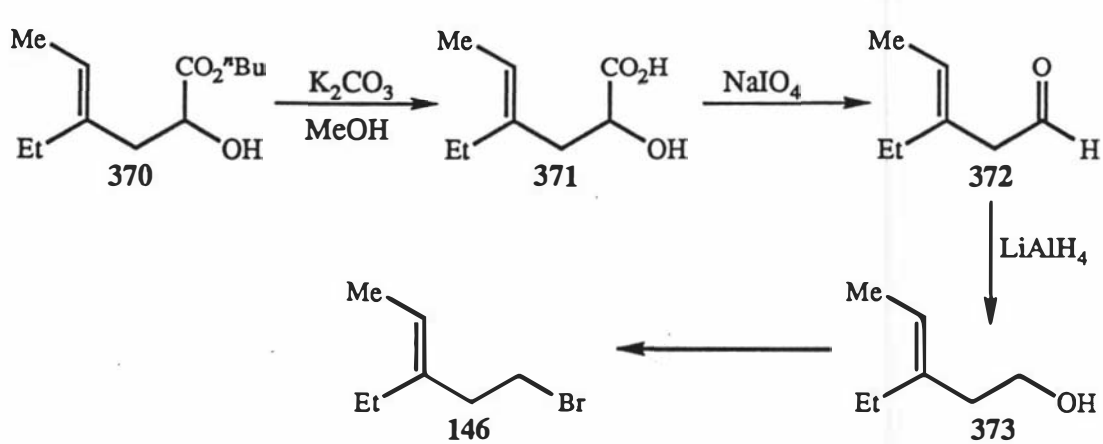


Reagents and conditions: (i) (±)-**363**, **362**, 4A MS, CH_2Cl_2, 1h then **364** and **367**, -70°C to RT, 24h, 57%.

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 α-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].

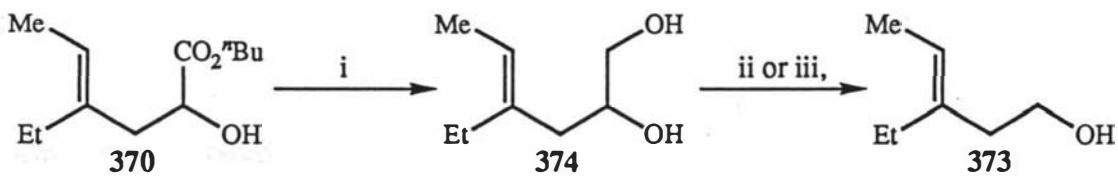
Scheme 101



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 tetrabutyl-ammonium periodate, purported to be a selective oxidant of α-hydroxycarboxylic acids[146]. 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.

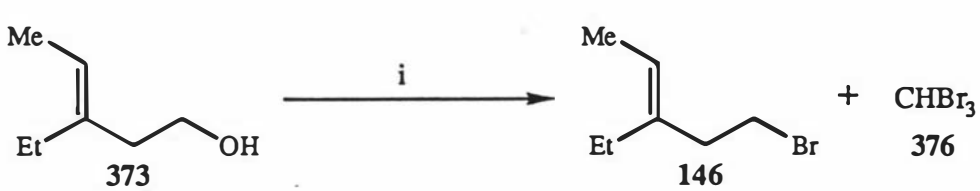
Scheme 102



Reagents and conditions: (i) $LiAlH_4$, Et_2O, 94%; (ii) a: $NaIO_4$, MeOH; b: $LiAlH_4$, Et_2O, 23%; (iii) a: $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, 16h; b: $LiAlH_4$, Et_2O, 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[147] (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

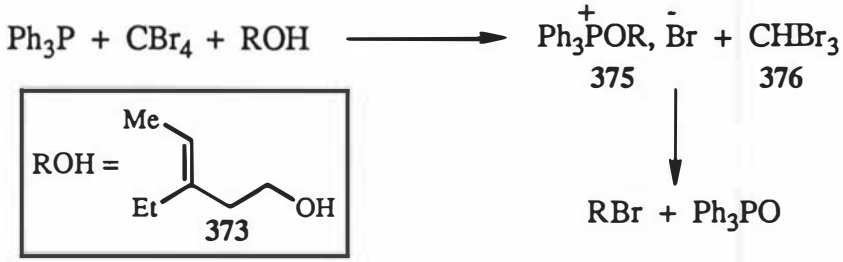
Scheme 103



Reagents and conditions: (i) CBr_4, Ph_3P, 2,6-lutidine, 75%.

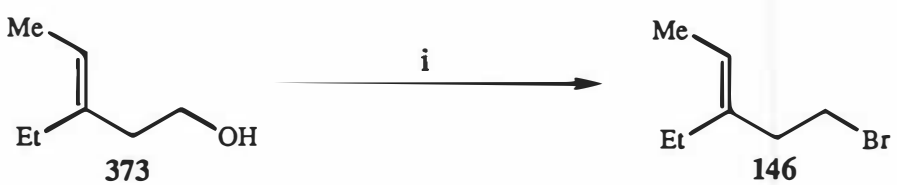
quantities of the bromide **146** were produced, it proved difficult to remove the bromoform by-product **376** by column chromatography or distillation. Consequently, an alternative method for the synthesis of the bromide **146** was pursued.

Scheme 104



Following several unsuccessful attempts to perform a one pot synthesis of the bromide using chlorotrimethylsilane and LiBr[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

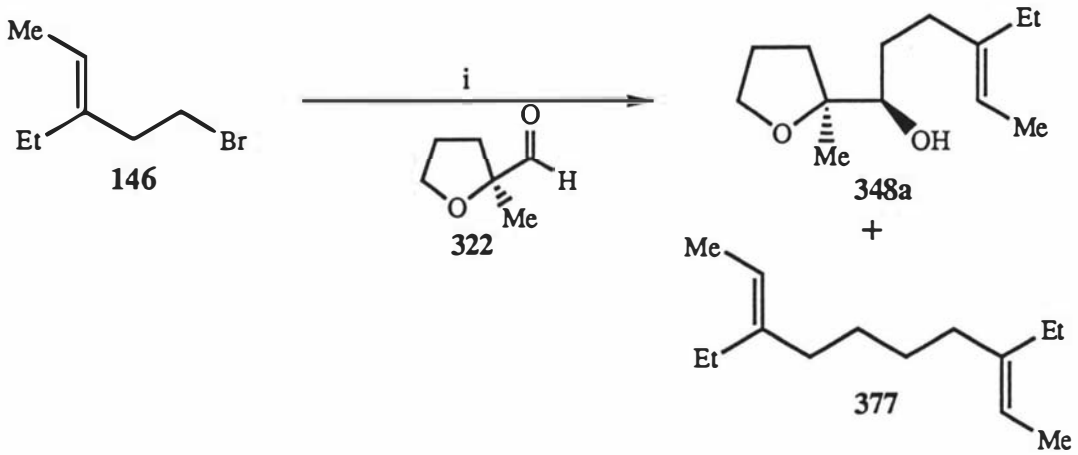


Reagents and conditions: (i) a: MsCl, Et_3N, CH_2Cl_2; b: LiBr, acetone, Δ, 71%.

2.3 Synthesis of (2S*, 3R*, 6R*, 2'S*)-3-Ethyl-3-hydroxy-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran [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

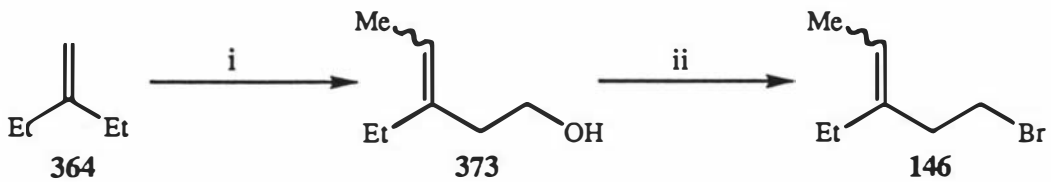
Scheme 106



Reagents and conditions: (i) Mg, THF, **146** then **322**.

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**.

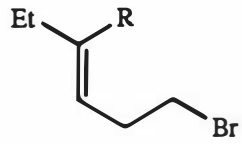
Scheme 107



Reagents and conditions: (i) CH_2O, $SnCl_4$, CH_2Cl_2, 55%; (ii) a: MsCl, Et_3N, CH_2Cl_2; b: LiBr, acetone, Δ, 76%.

In earlier work by Henrick *et al*[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.

Figure 9

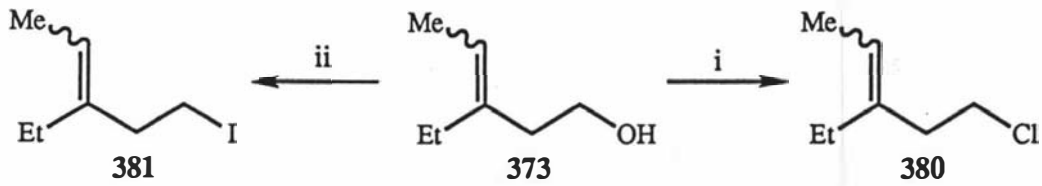


378 R = Me
379 R = Et

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**.

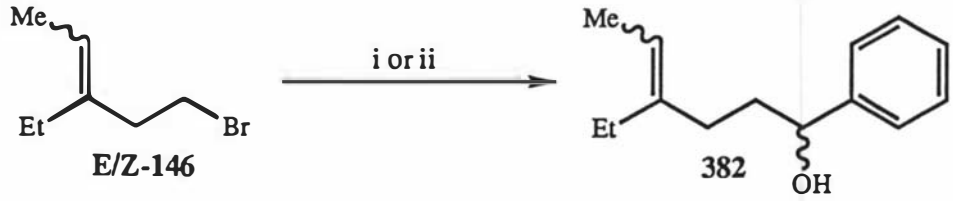
Scheme 108



Reagents and conditions: (i) a: MsCl, Et_3N, CH_2Cl_2; b: LiCl, DMF, Δ, 62%; (ii) a: MsCl, Et_3N, CH_2Cl_2; b: NaI, acetone, Δ, 71%.

When further attempts to improve the yield in the Grignard reaction through the use of chemically activated magnesium[150] or entrainment techniques[151] 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

Scheme 109



Reagents and conditions: (i) Mg, THF, **E/Z-146**, then benzaldehyde, 24%; (ii) ^{t}BuLi, THF, -80°C, **E/Z-146**, 5 min., then benzaldehyde, 66%.

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).

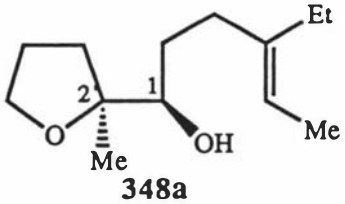
Once the inverse addition technique had been perfected using benzaldehyde, formation of the organolithium reagent and subsequent addition of the model aldehyde **322** resulted in formation of the hydroxyalkene **348** (Scheme 110) as a 3:1 mixture of the *erythro* and *threo* isomers (**348a**, **348b**, 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

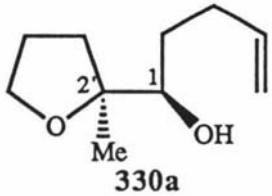
Table 13

Comparison of the ^{1}H and ^{13}C NMR Spectra of the *Erythro* and *Threo* Isomers of Hydroxyalkenes **348** and **330**.

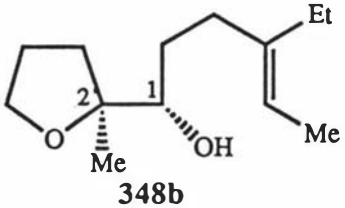
	^{1}H NMR chemical shift		^{13}C NMR chemical shift	
Compound	2'-Me	1-H	2'-Me	C-1
348a (*erythro*)	1.12	3.52	23.8	76.2
348b (*threo*)	1.14	3.38	20.2	76.5
330a (*erythro*)	1.12	3.53	22.9	75.6
330b (*threo*)	1.14	3.40	19.9	75.8



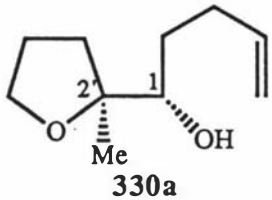
348a



330a

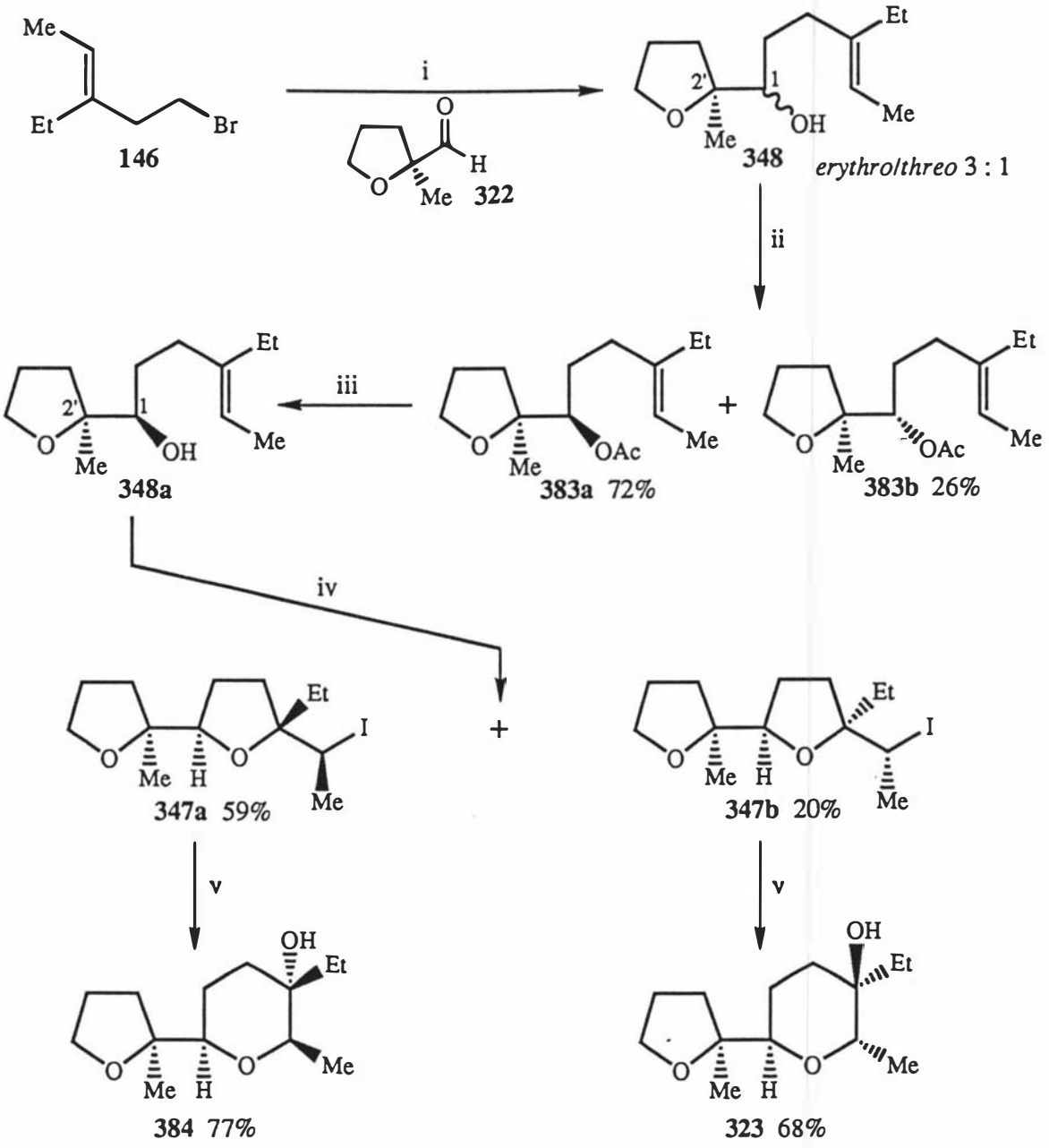


348b



330a

Scheme 110



Reagents and conditions: (i) ^{t}BuLi, THF, -80°C then **146**, 10 min., then **322**, 53%; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 98%; (iii) K_2CO_3, 95% MeOH, 83%; (iv) I_2, Na_2CO_3, MeCN, 79%; (v) Ag_2CO_3, wet acetone, 73%.

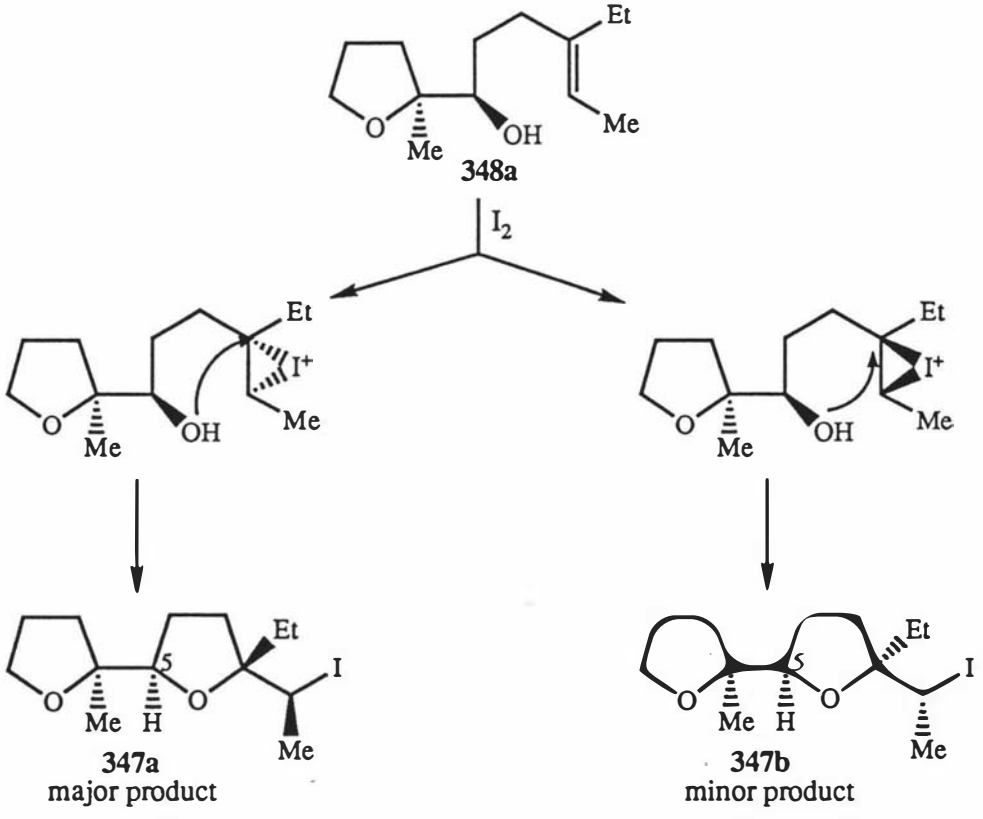
correlations were observed between the two *erythro* alcohols **330a, 348a** and the two *threo* alcohols **330b, 348b** the most significant correlations were observed with the 1-H and 2'-Me groups. The ^{1}H NMR spectra of these alcohols shows that the *erythro* alcohols **330a, 348a** exhibit 1-H 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 $C_{13}H_{23}O_2I$ (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 ^1H and ^1C 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 ^1H NMR spectra of iodide **347a** possessed a 5-H chemical shift of δ 4.02 compared with δ 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*[130] which established

Scheme 111

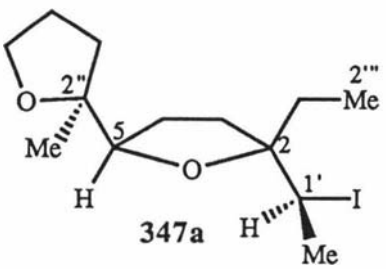


that the chemical shift for the 5-H proton of the *trans* isomer should be in the range δ 4.00 - 4.11 while that of the *cis* isomer should be at δ 3.89 - 3.93. The ^{13}C NMR spectra of iodides **347a** and **347b** (Table 15) reflected the difference in configuration at the C2 and C1' atoms with the 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.

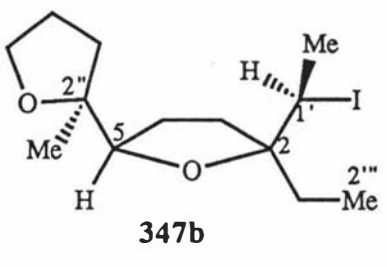
Table 14

^{1}H 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.**

Compound	CH_3 (Et)	2"-CH_3	1'-CH_3	4 × CH_2	CH_2O	5-H	1'-H
347a *trans*	0.92	1.16	1.84	1.59 - 2.07	3.84	4.02	4.52
347b *cis*	0.90	1.14	1.89	1.58 - 2.10	3.84	3.94	4.41



347a



347b

Table 15

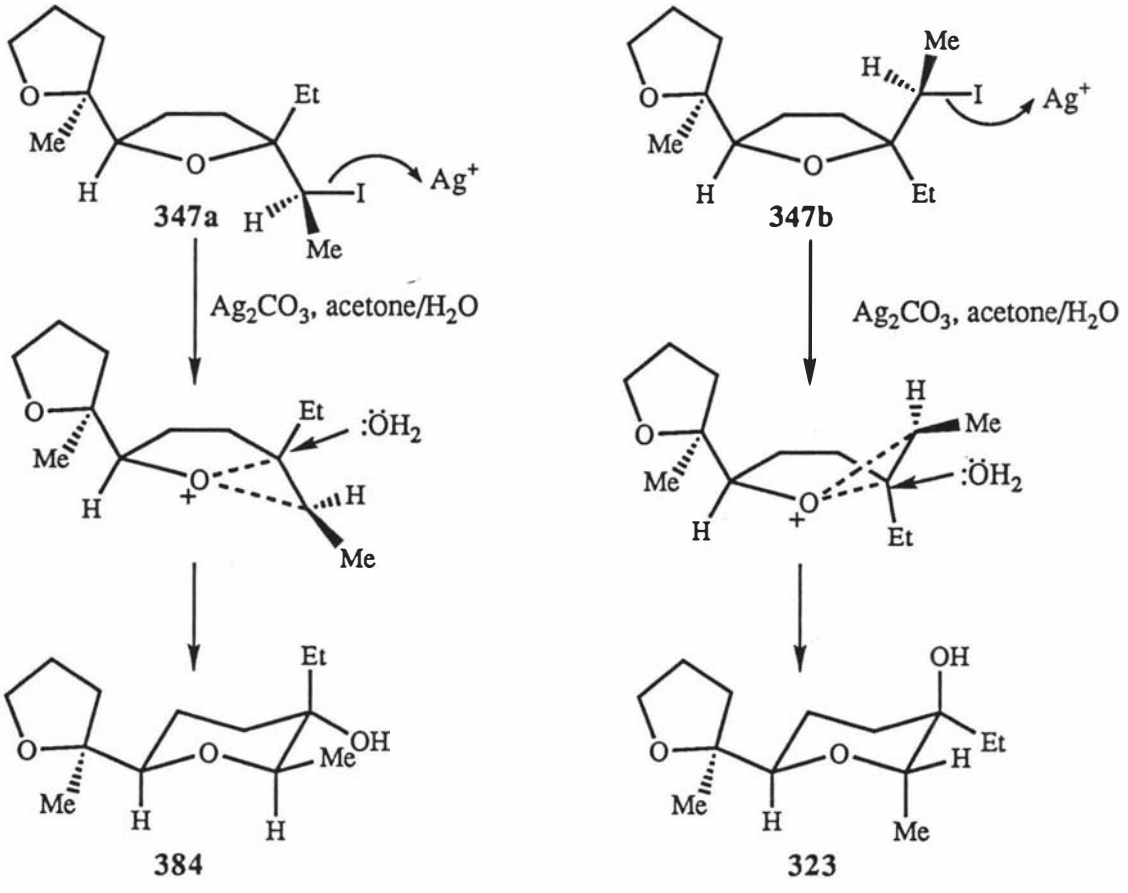
^{13}C NMR Chemical Shifts for (2R*, 5R*, 1'S*, 2"S*)-2-Ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofuran **347a** and (2S*, 5R*, 1'R*, 2"S*)-2-Ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofuran **347b**

Compound	C-2'''	2'-Me	C-2'	C-1'	C-2, C-2"	C-5'	C-5
347a *trans*	7.8	22.5	23.9	40.2	83.5, 86.6	68.2	85.0
347b *cis*	7.5	22.6	22.9	35.6	83.9, 85.6	68.1	86.6

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

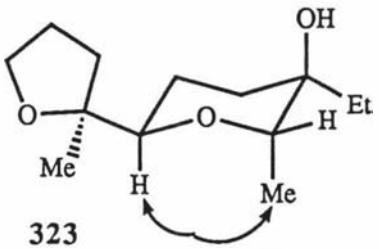
Scheme 112



pyran structure **384** or **323**. Assignment of relative configurations of the ring expanded products **384, 323** was made on the basis of their ^{1}H and ^{13}C NMR spectra. Analysis of the ^{1}H 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 ^{13}C 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



323

NOE effect

Having established that pyran **323** contains the same stereochemistry as that present in the E-ring of salinomycin **1**, a comparison of the ^{1}H and ^{13}C 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 ^{1}H NMR spectra and the chemical shifts of the C2 and C6 atoms in the ^{13}C 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 Rychnovsky[106] 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

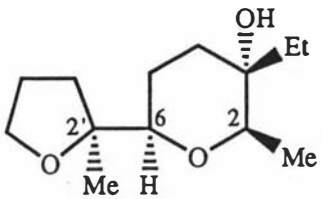
^{1}H NMR Chemical Shifts for (2R*, 3S*, 6R*, 2'S*)-3-Ethyl-3-hydroxyl-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran **384** and (2S*, 3R*, 6R*, 2'S*)-3-Ethyl-3-hydroxyl-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran **323**

Compound	CH_3 (Et)	2-Me	2'-Me	4 × CH_2	6-H	2-H	CH_2O
384	0.90	1.11	1.14	1.16 - 2.10	3.25	3.35	3.82
323	0.92	1.24	1.16	1.16 - 1.92	3.46	3.84	3.75 - 3.89

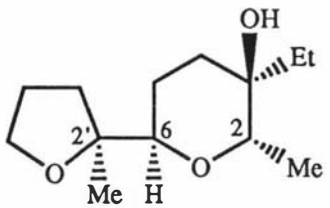
Table 17

^{13}C 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**

Compound	CH_3(Et)	2-Me	2'-Me	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2O	C-3	C-2, C-6	C-2'
384	6.7	14.0	22.3	22.5	24.6	26.2	33.9	34.6	68.3	71.3	80.9, 82.9	83.7
323	7.0	13.0	21.0	22.1	22.8	25.8	29.1	35.5	68.2	71.1	74.0, 74.8	84.5



384

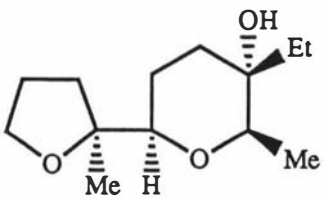


323

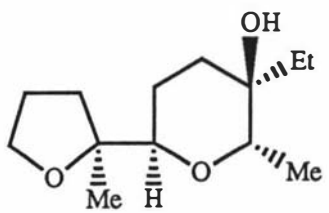
Table 18

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.

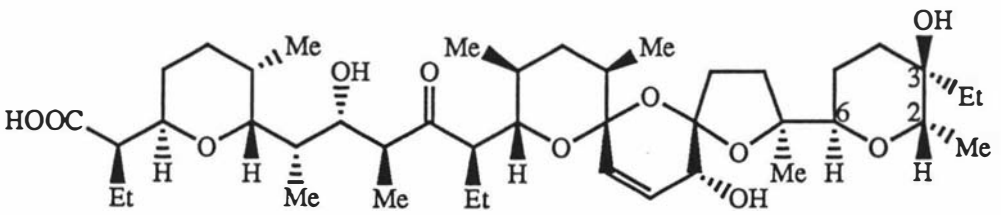
	^{1}H NMR			^{13}C NMR	
Compound	2-H	6-H	2-Me	C-2	C-6
384	3.35	3.25	1.11	80.9, 82.9	
323	3.84	3.46	1.24	74.0, 74.8	
salinomycin **1**	3.83	3.93	1.23	77.2	73.7
lasalocid A **4**	3.76	3.57	1.21	76.9	73.0
47	3.77	3.65	1.22	-	-
61	3.79	3.42	1.23	-	-



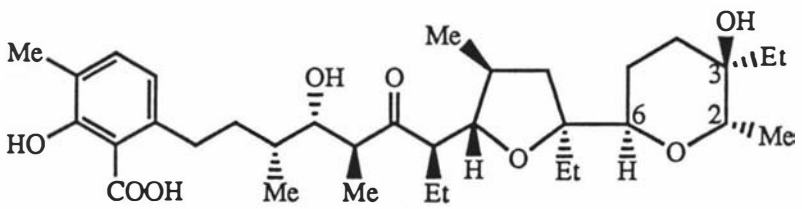
384



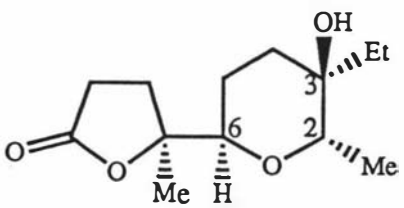
326



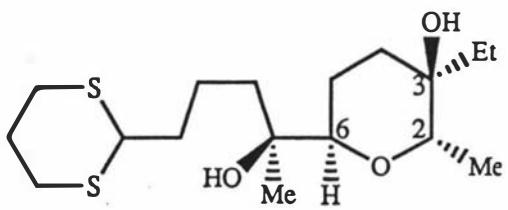
Salinomycin **1**



Lasalocid A **4**



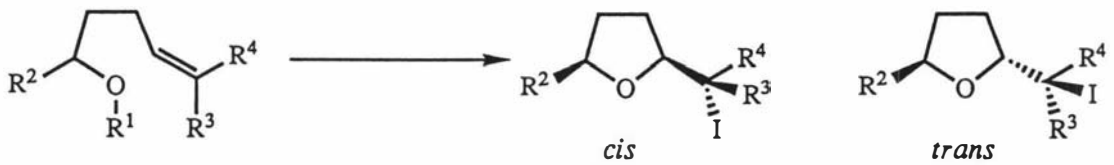
47



61

Table 19

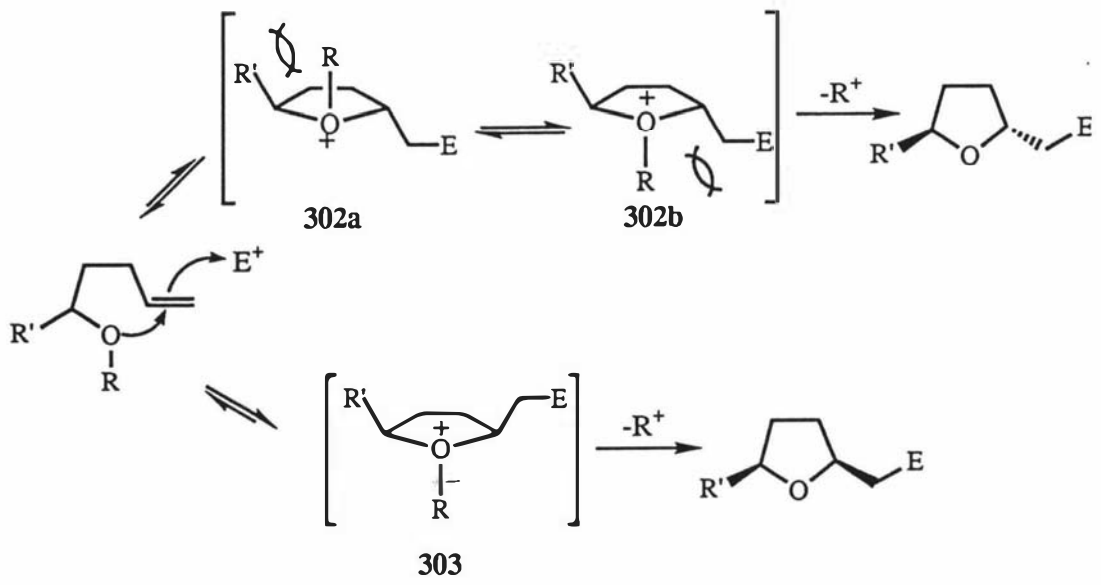
Stereocontrolled Iodoetherification of γ,δ-Unsaturated Alkoxyalkenes



Reagents and conditions: I_2, CH_3CN, 0°C, ($NaHCO_3$ added when R^1=H);

R^1	R^2	R^3	R^4	Ratio *cis*/*trans*	Yield (%)
H	Me	H	H	1 : 2	66
Me	Me	H	H	1 : 2	15
CH_2Ph	Me	H	H	2 : 1	60
Si^tBuPh_2	Me	H	H	3 : 1	43
Si^tBuPh_2	Me	Me	H	8 : 1	30
BB	Me	H	H	3.7 : 1	74
DCB	Me	H	H	21 : 1	63
H	Me_2CH	H	H	1 : 4	88
DCB	Me_2CH	H	H	20 : 1	95
H	Me	Me	H	1 : 2	99
DCB	Me	Me	H	25 : 1	75
H	Me	H	Me	2 : 5	81
DCB	Me	H	Me	12 : 1	47
CH_2Ph	Me	CO_2Me	H	6 : 1	55
DCB	Me	CO_2Me	H	50 : 1	60
BB	Me	CO_2Me	Me	10 : 1	44
^{t}Bu	Me	H	H	28 : 1	91

Scheme 113



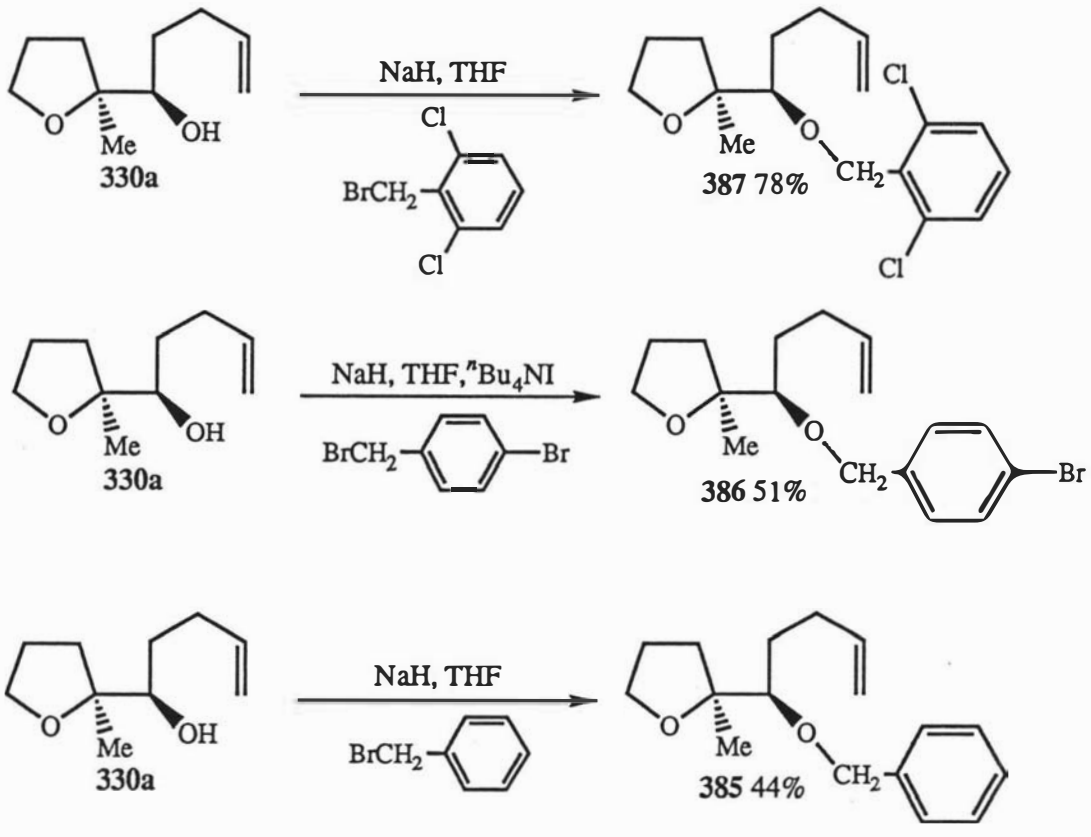
Where R = H, the *trans* intermediates **302a** and **302b** are more stable than the *cis* intermediate **303** therefore the *trans* isomer is favoured. However, if R is a large bulky ether group the resulting steric hindrance (R↔R' or R↔E) destabilises the *trans* intermediates and the *cis* isomer 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 ^{1}H 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 *tert*-butyldimethylsilyl derivative **389** was prepared using *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 *cis* isomer with a 10:1 ratio of the *cis* and *trans* iodides in the case of the 2,6-dichlorobenzyl ether **387**. The inability of the silyl derivatives to effect any *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 *cis* iodide **331b** while the alcohol **330a** shows a greater preference for the *trans* iodide **331a** when compared with the stereoselectivities observed by Bartlett and Rychnovsky[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

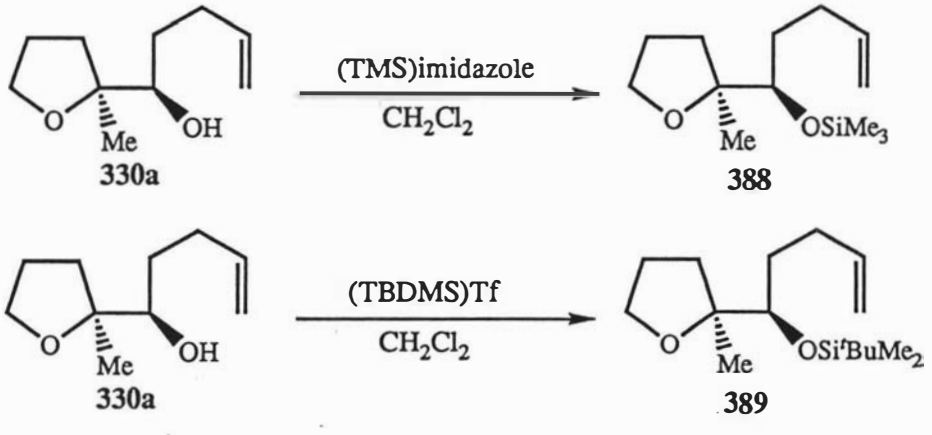
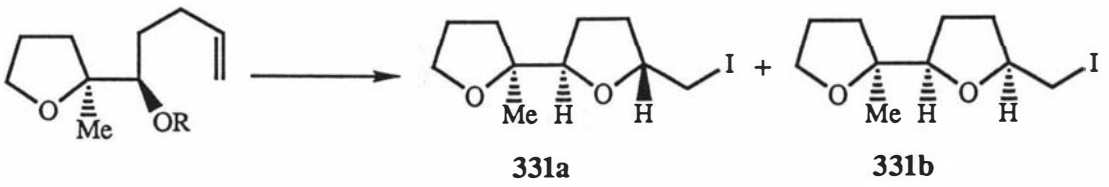


Table 20

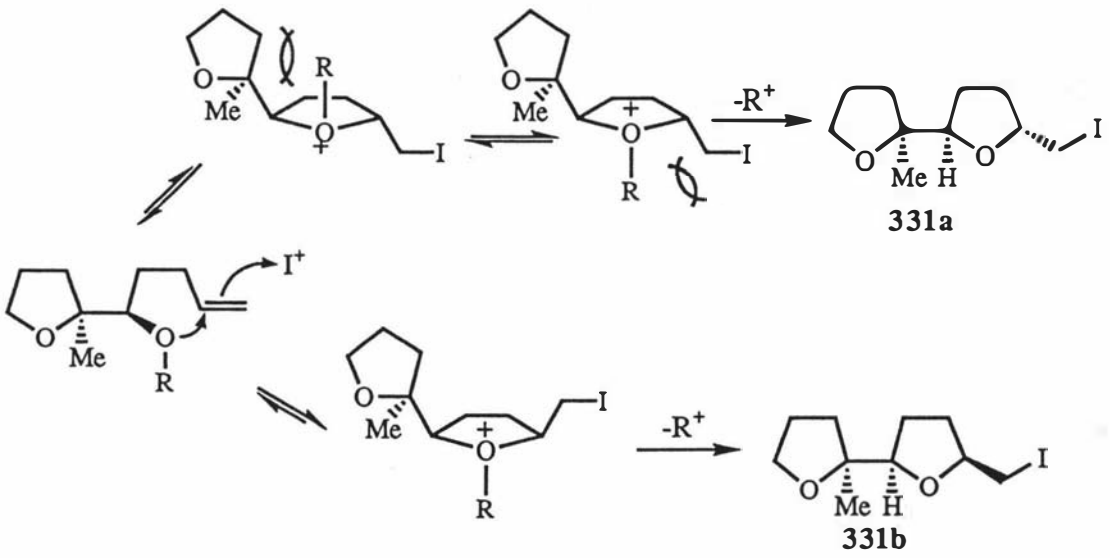
Stereocontrolled Iodoetherification of γ,δ-Unsaturated Alkoxyalkenes derived from Hydroxyalkene **330a**



331a **331b**

Compound	R	Yield %	**331a:331b**	Conditions
330a	H	93	5 : 1	I_2, Na_2CO_3, MeCN, 0°C
338a	Ac	no reaction	-	I_2, MeCN, 0°C
385	Bz	67	5 : 4	I_2, MeCN, 0°C
386	BB	46	2 : 3	I_2, MeCN, 0°C
387	DCB	63	1 : 10	I_2, MeCN, 0°C
388	$SiMe_3$	68	5 : 1	I_2, MeCN, 0°C
389	Si^tBuMe_2	57	5 : 1	I_2, MeCN, 0°C

Scheme 116



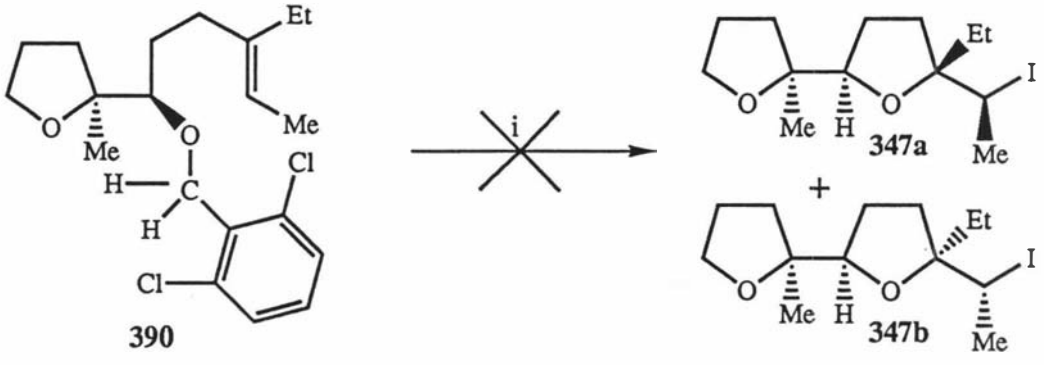
331a

331b

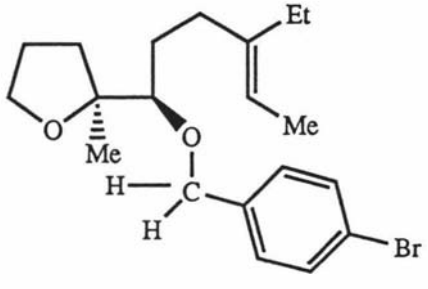
Having established that the dichlorobenzyl ether **387** provides the most effective method for *cis* stereocontrol in the iodoetherification of the monosubstituted hydroxyalkene, this work was extended to the trisubstituted hydroxyalkene system.

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



Reatgents and conditions: (i) I_2, MeCN, 0°C.

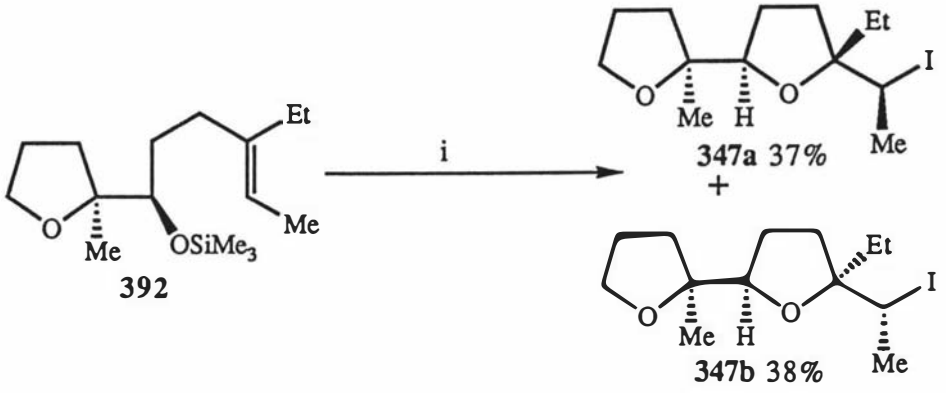


391

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 noticable improvement in the ratio of **347b:347a**, while the yield appeared to decrease significantly.

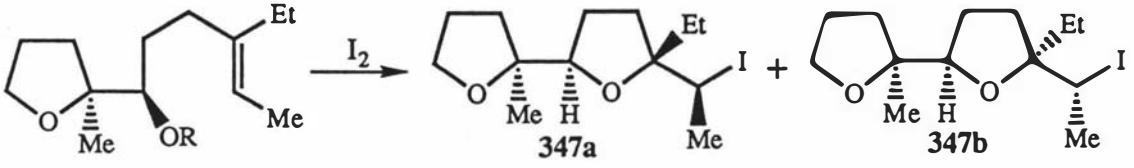
Scheme 116



Reagents and conditions: (i) I_2, MeCN, -5°C, 75%.

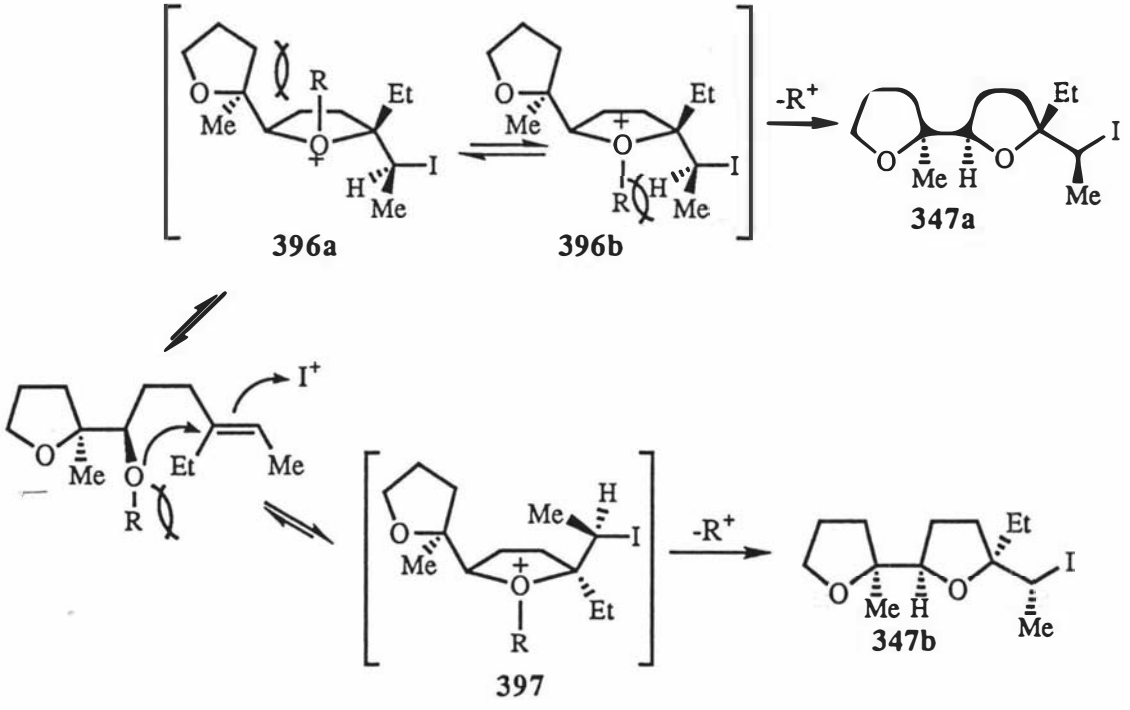
Table 21

Stereocontrolled Iodoetherification of Silyl Derivatives of Trisubstituted Hydroxyalkene **348a**



Compound	R	Prepared from **348a** and:	yield	Iodoetherification conditions	yield	**347a/ 347b**
392	$SiMe_3$	(TMS)imid.	96%	I_2, CH_3CN, -5°C	75%	1:1
393	$SiEt_3$	(TES)Tf	94%	I_2, CH_3CN, 0°C	46%	1:1
394	Si^iPr_3	(TIPS)Tf	93%	I_2, CH_3CN, 0°C	47%	1:1
395	Si^tBuMe_2	(TBDMS)Tf	90%	I_2, CH_3CN, 0°C	27%	1:1

Scheme 119



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 CHIMe 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 CHIMe 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 CHIMe group in intermediate **396b** would become more significant and the reaction occuring *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 (Na_2CO_3, low temperature) and thermodynamic (No Na_2CO_3) 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

Table 22

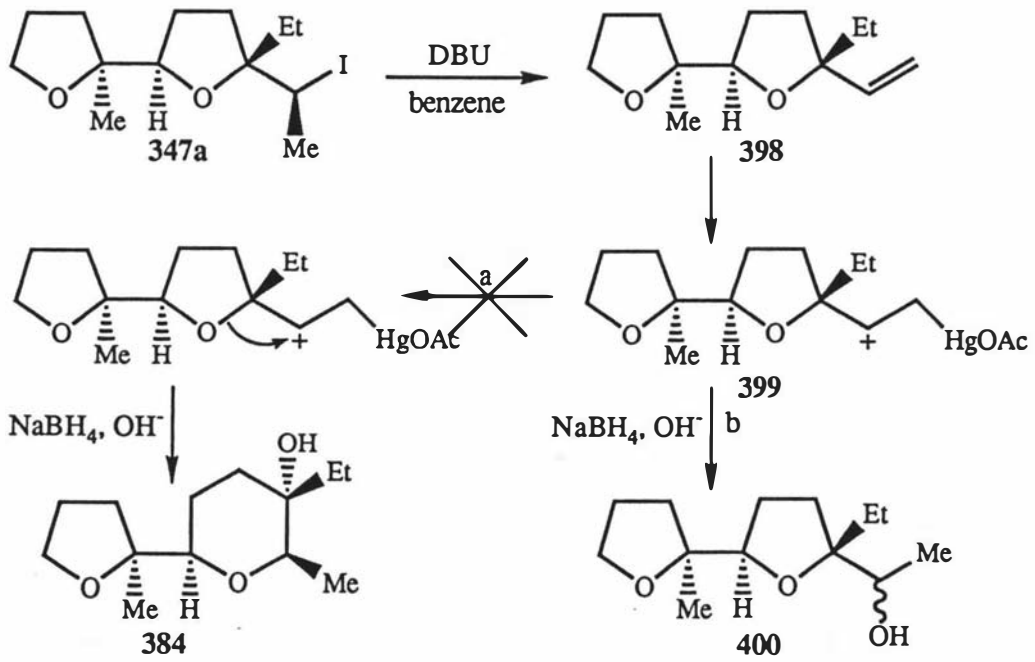
Stereocontrolled Iodoetherification of (4E, 1R*, 2'S*)-4-Ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol **348a** and (4E, 1R*, 2'S*)-4-Ethyl-1-(trimethylsilyloxy)-1-(2'-methyltetrahydrofur-2'-yl)-4-hexene **392**: Kinetic vs Thermodynamic conditions.

Compound	R	**347a:347b**	Yield	Conditions
348a	H	2 : 1	70%	I_2, Na_2CO_3, MeCN, 0°C, 50 min.
348a	H	3.2 : 1	78%	I_2, Na_2CO_3, MeCN, -43°C, 15 min.
348a	H	1.8 : 1	19%	I_2, MeCN, 60°C, 20 min.
348a	H	2.5 : 1	88%	I_2, MeCN, -32°C, 10 min.
392	$SiMe_3$	3 : 4	50%	I_2, MeCN, 0°C, 15 min.
392	$SiMe_3$	1 : 1	75%	I_2, MeCN, -5°C, 5 min.

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 0.5 M NaOH

Scheme 120



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[102] 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 tri-tetrahydrofurans (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 **406**[152] (Scheme 121), Grignard addition of 4-bromo-1-butene **329** affords the hydroxyalkene **407**.

Scheme 121

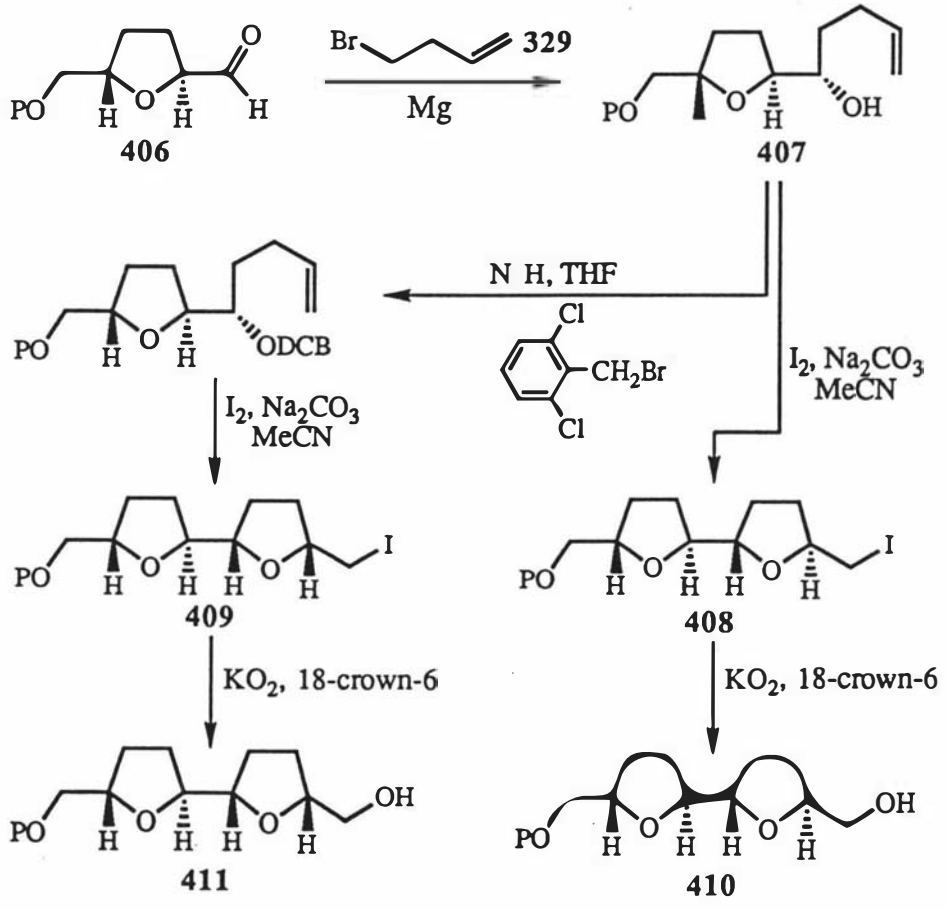
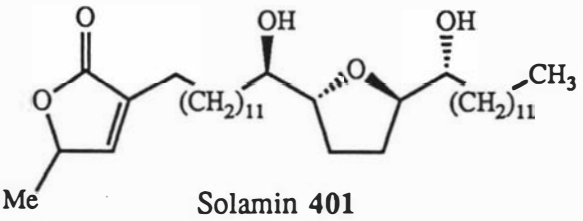
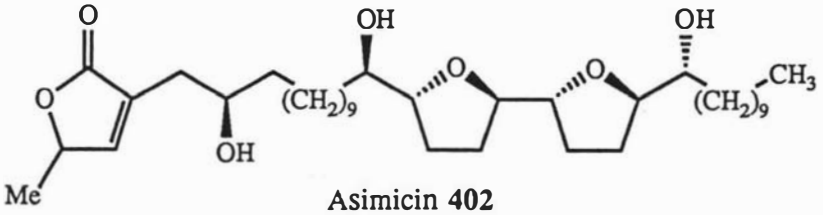


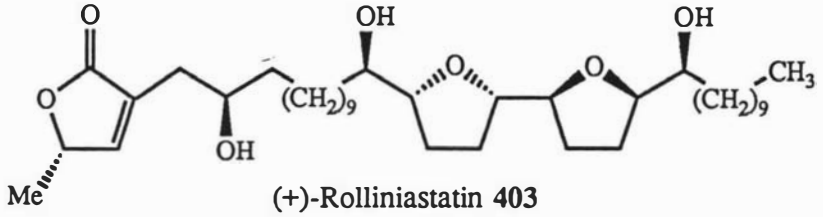
Figure 11



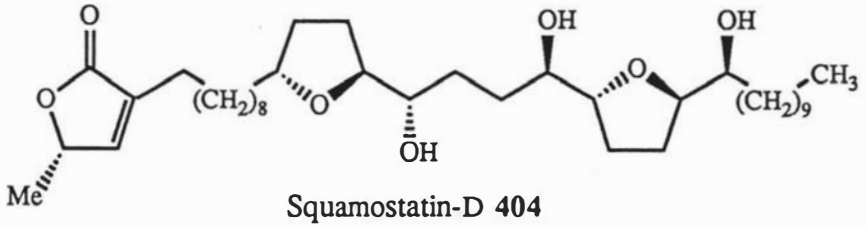
Solamin **401**



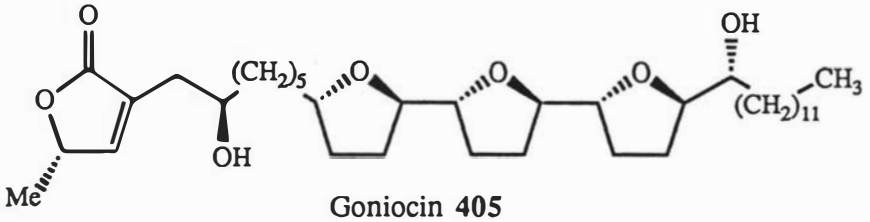
Asimicin **402**



(+)-Rolliniastatin **403**



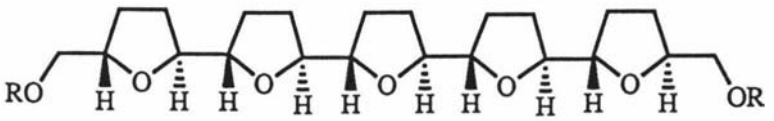
Squamostatin-D **404**



Goniocin **405**

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.

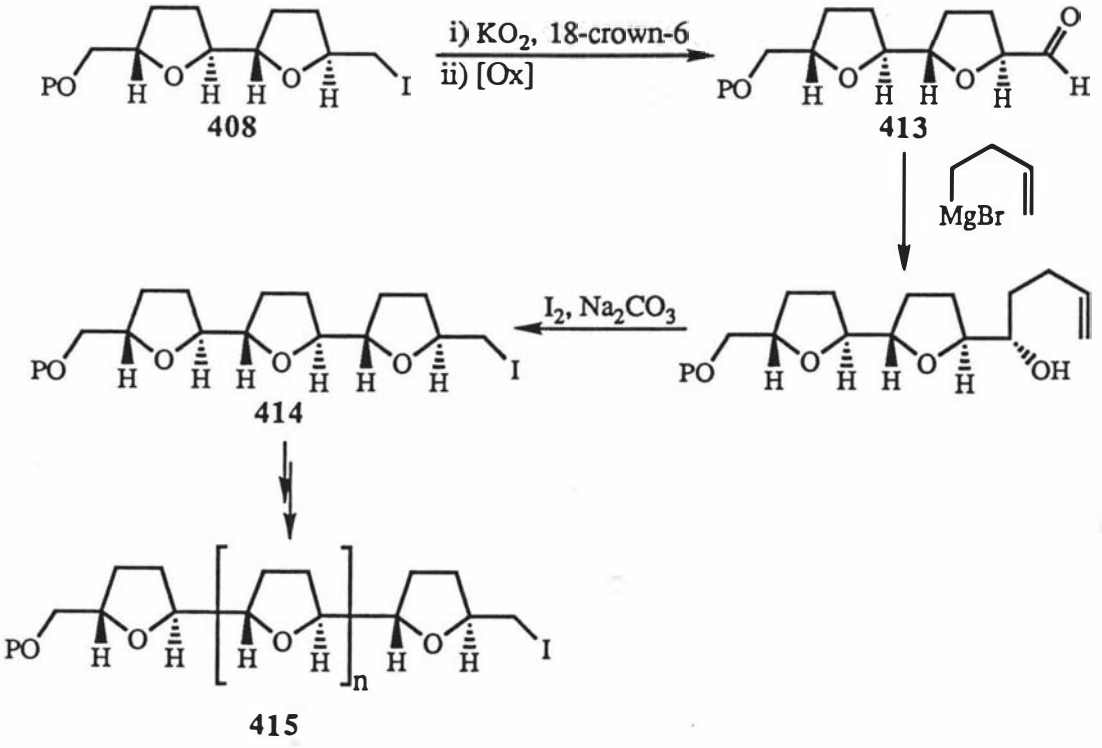
In contrast to the many organic syntheses of natural polyether ionophores (e.g. lasalocid A and salinomycin) which have been reported over the past 15 years, it is only very recently that the construction of "artificial" polyether antibiotics, or podands, has been investigated[156-158]. One such podand which has recently been presented in the literature is the oligo-THF molecule **412**[158]. It is anticipated that the methodology



412

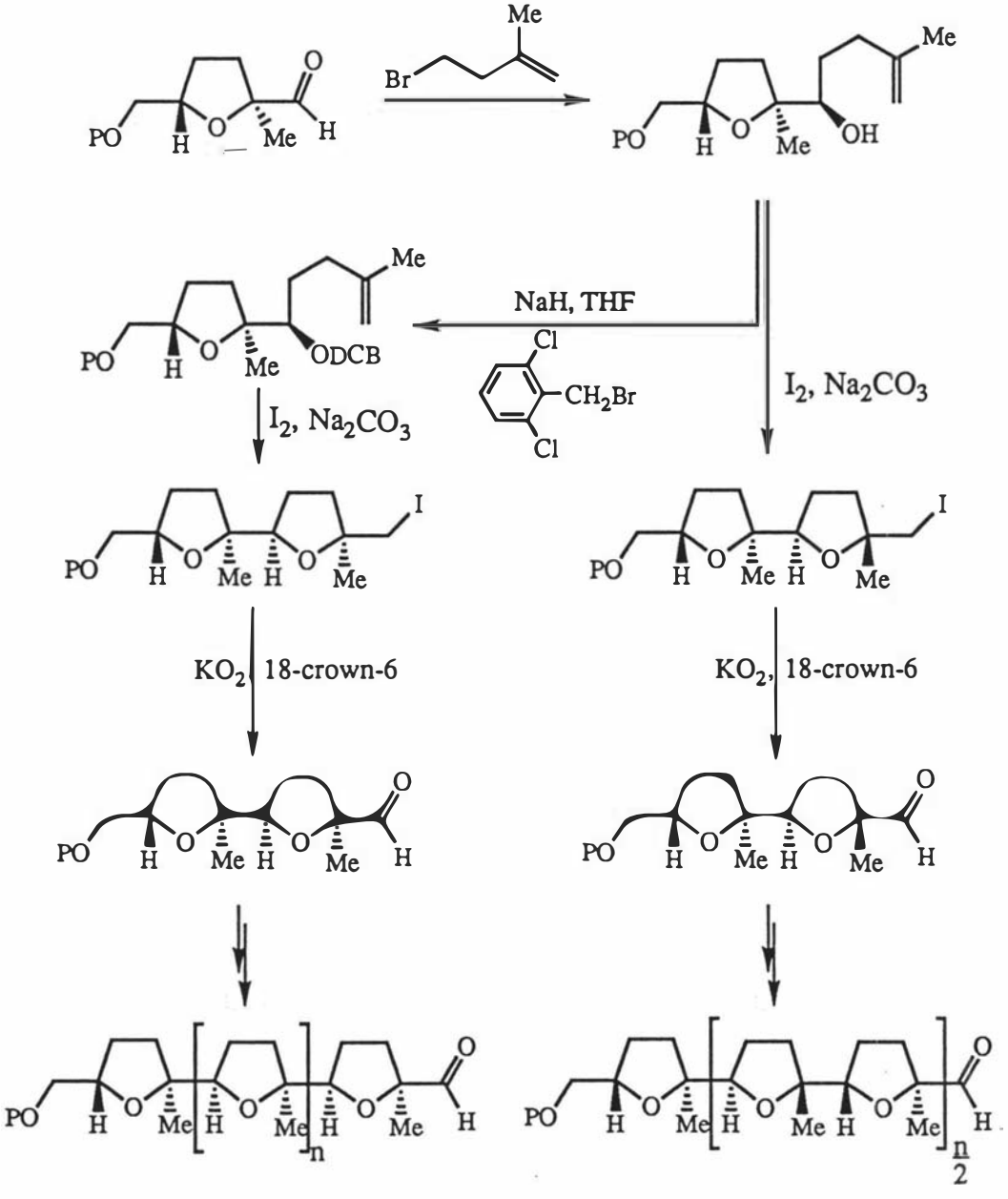
developed for E-ring construction could afford a new and versatile method of synthesising such molecules. Thus, following the formation of iodides such as iodide **408** (Scheme 121), conversion to the corresponding aldehyde **413** (Scheme 122) would then allow the E ring methodology to be applied a second time to form a third tetrahydrofuran ring **414**. This iodide → aldehyde/Grignard reaction/ iodoetherification sequence could then be repeated until the desired number of tetrahydrofuran rings has been produced **415**. This pathway is also quite versatile in that by altering the structure

Scheme 122



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.

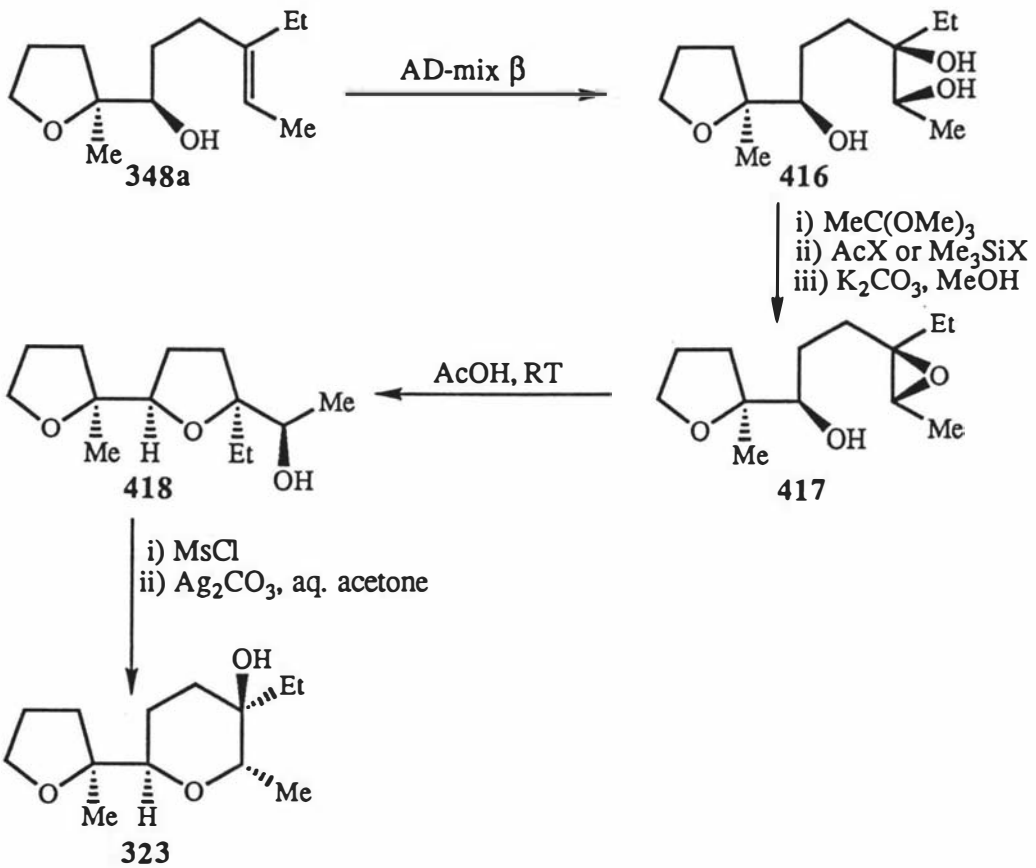
Scheme 123



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[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^+, as previously carried out by Kishi *et al*[8], would then afford the desired E ring **323**.

Scheme 124



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.

^1H nuclear magnetic resonance spectra were obtained at 270 MHz using a JEOL GX270 spectrometer. ^1H nuclear magnetic resonance data are expressed in parts per million downfield shift from tetramethylsilane as an internal reference and are reported as position (δ_H), relative inte. gral, 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 (δ_C) and assignment.

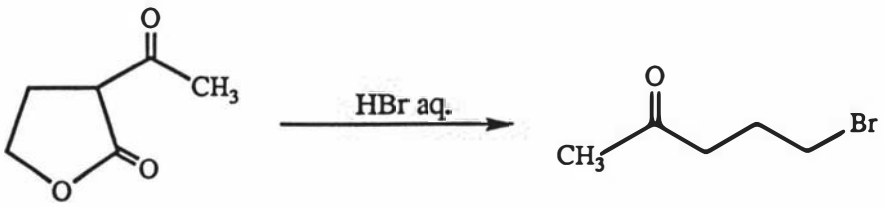
Mass spectra were recorded using a Varian VG70-250S double focusing magnetic sector mass spectrometer with an ionisation potential of 70 eV. Major fragmentations are given as percentages relative to the base peak intensity.

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 fluoresence or by staining with vanillin in methanolic sulphuric acid or phosphomolybdic acid.

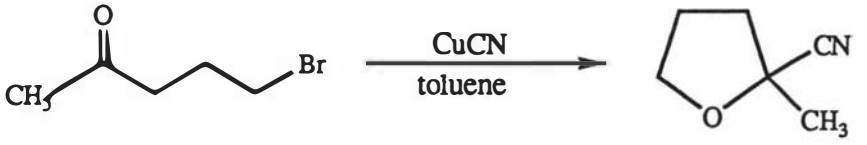
Solvents were dried and purified according to the methods of Perrin, Perrin and Amarego[160].

5-Bromo-2-pentanone 325



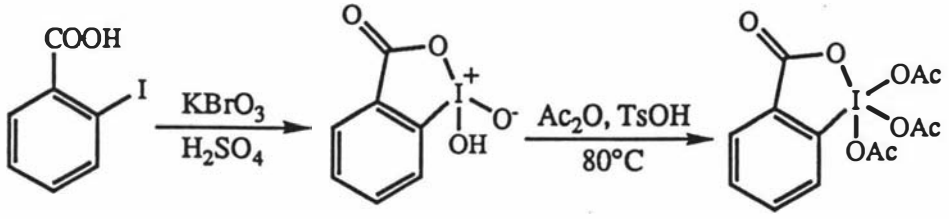
To a solution of hydrobromic acid (48%, 200 ml, 1.77 mol) and distilled water (130 ml) in a distilling flask was added 2-acetylbutyrolactone **324** (131.2 g, 1.02 mol). Carbon dioxide was evolved and the solution began to change colour. Once a red colour was observed the reaction was heated and steam 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 326[124]



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).

Dess-Martin Periodinane[127,128]

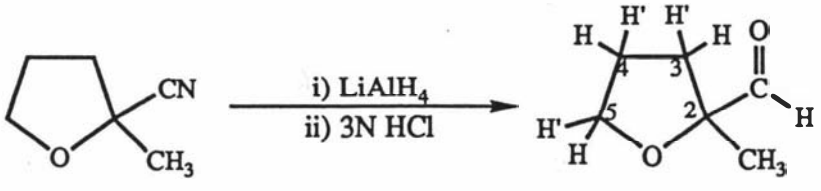


Potassium bromate (18.7 g, 112 mmol) was added over a 90 min. period to a vigorously stirred mixture of 2-iodobenzoic acid (21.0, 84.7 mmol) and 0.73 M sulphuric acid (171 ml). During addition the temperature was maintained below 55°C. The mixture was then warmed to 65°C and stirred for 4 h. Bromine 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 × 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 × 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 322[122]

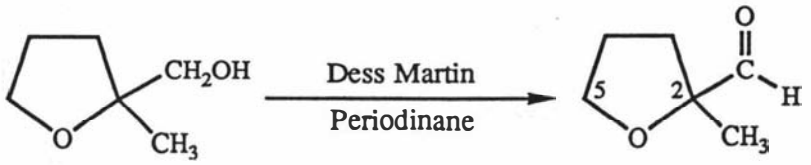
Procedure A



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 **326** (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 × 40 ml) and dichloromethane (2 × 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 **322** as a pungent pale yellow oil (1.04 g, 67%), which was purified by distillation at atmospheric pressure, b.p. 142-143°C; υ_{max}/cm^{-1} 1732 (s, C=O); δ_H (270 MHz; $CDCl_3$) 1.31 (3H, s, CH_3), 1.64-1.75 (1H, m, 3-H'), 1.86-2.02 (2H, m, 4-H, 4-H') 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); δ_C (67.8 MHz; $CDCl_3$) 20.7 (CH_3), 25.8 (CH_2), 32.9 (CH_2), 69.0 (CH_2O), 86.2 (quat., C-2) and 203.0 (C=O).

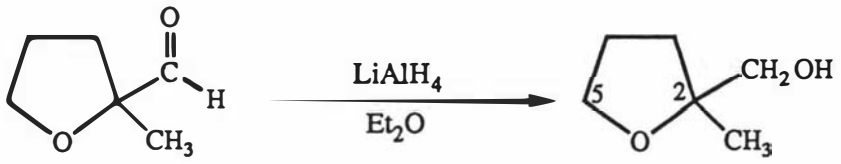
IR and ^1H NMR data were in agreement with that reported in the literature[122].

Procedure B



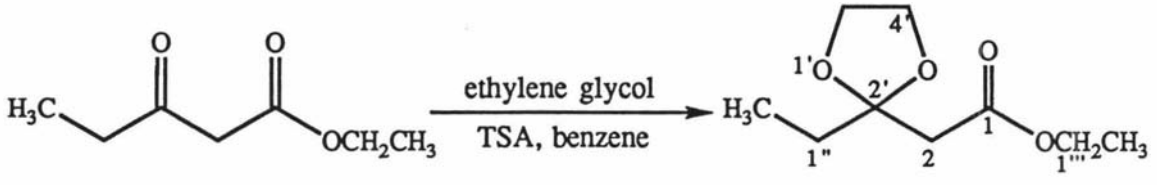
To a solution of 2-methyl-2-tetrahydrofurfuryl alcohol **327** (20 mg, 0.17 mmol) in dry dichloromethane (1.5 ml) was added Dess Martin reagent (*vide supra*) (88 mg, 0.21 mmol). After stirring for 1.5 h the solvent was removed under reduced pressure and the residue was purified by flash chromatography, using pentane/diethyl ether as eluant (1:1), to afford 2-methyl-2-tetrahydrofuraldehyde **322** as a colourless oil (11.2 mg, 58%) for which the IR and ^1H NMR data were in agreement with the literature[122] and that reported for the product using the procedure described above.

2-Methyl-2-tetrahydrofurfuryl alcohol 327



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 × 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-tetrahydrofurfuryl alcohol **327** as a colourless oil (53 mg, 64%) (Found: (CI, NH_3) M + H, 117.0917. $C_6H_{13}O_2$ requires M + H, 117.0916.); υ_{max}/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); δ_H (270 MHz; $CDCl_3$) 1.20 (3H, s, CH_3), 1.64 (1H, s, OH), 1.88-2.00 (4H, m, CH_2), 3.43-3.48 (2H, m, $C\underline{H}_2OH$) and 3.82-3.90 (2H, m, CH_2O); δ_C (67.8 MHz; $CDCl_3$) 23.3 (CH_3), 26.5 (CH_2), 33.5 (CH_2), 68.0 (CH_2, C-5), 68.6 (CH_2, C-1') and 82.9 (quat., C-2); *m/z* 117 (M + H, 100%), 99 (M - OH, 39) and 85 (C_5H_9O, 77).

Ethyl 2-(2'-ethyl-1',3'-dioxolan-2'-yl)acetate 351[134,135]

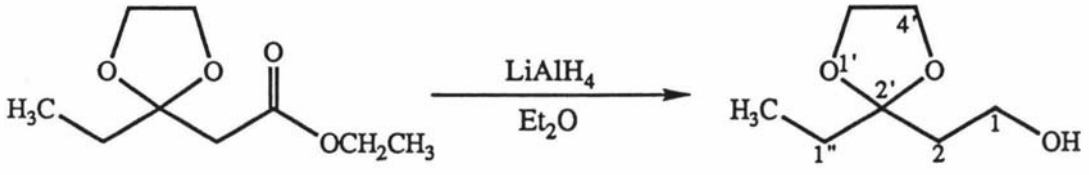


A mixture of ethyl propionylacetate **350** (5.15 g, 35.7 mmol), ethylene glycol (2.00 ml, 35.8 mmol) and a catalytic quantity of *p*-toluenesulphonic acid (~20 mg) in benzene (180 ml) was heated under reflux for 6 h. using Dean-Stark apparatus. The reaction mixture was then dried over magnesium sulphate 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%); υ_{max}/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); δ_H (270 MHz; $CDCl_3$) 0.94 (3H, t, $J_{2'',1''}$ 7.3, CH_3), 1.26 (3H, t, $J_{2''',1'''}$ 7.1, $OCH_2C\underline{H}_3$), 1.83 (2H, q, $J_{1'',2''}$ 7.3, $C\underline{H}_2CH_3$), 2.64 (2H, s, $C\underline{H}_2CO$), 3.96-4.01 (4H, m, $OC\underline{H}_2C\underline{H}_2O$) and 4.15 (2H, q, $J_{1''',2'''}$ 7.1, $OC\underline{H}_2CH_3$); δ_C (67.8 MHz; $CDCl_3$) 7.6 (CH_3, C-2''), 14.0 (CH_3, C-2'''), 30.4 (CH_2, C-1''), 42.1 (CH_2, C-2), 60.3 (CH_2, C-1'''), 65.0 (CH_2, C-4', C-5'), 109.5 (quat., C-2') and 169.4 (quat., C=O).

IR, ^1H and ^{13}C NMR were consistent with that reported in the literature[135].

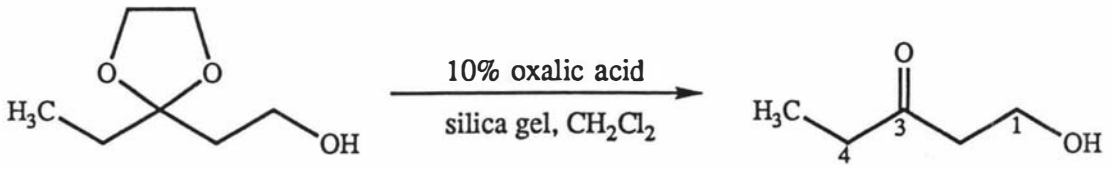
2-(2'-Ethyl-1',3'-dioxolan-2'-yl)ethanol 352[134,135]



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 × 20 ml) and ethyl acetate (2 × 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%); υ_{max}/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); δ_H (270 MHz; $CDCl_3$) 0.92 (3H, t, $J_{2'',1''}$ 7.3, CH_3), 1.67 (2H, q, $J_{1'',2''}$ 7.3, $C\underline{H}_2CH_3$), 1.93 (2H, t, $J_{2,1}$ 5.5, $C\underline{H}_2CH_2OH$), 3.00-3.04 (1H, br, OH), 3.74 (2H, q, $J_{1,2}$ 5.5, $C\underline{H}_2OH$) and 3.98-4.03 (4H, m, OCH_2CH_2O); δ_C (67.8 MHz; $CDCl_3$) 8.1 (CH_3, C-2''), 29.9 (CH_2, C-1''), 37.9 (CH_2, C-2), 58.8 (CH_2, C-1), 64.9 (CH_2, C-4', C-5') and 112.3 (quat., C-2').

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

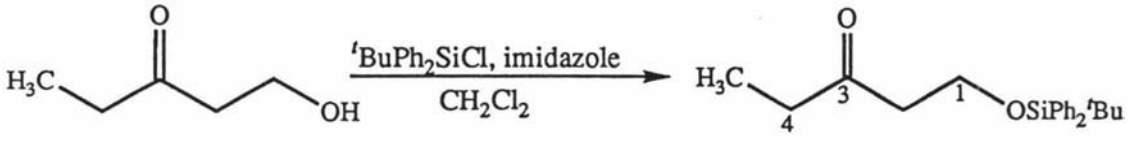
1-Hydroxy-3-pentanone 349[134,135]



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 × 25 ml) and diethyl ether (2 × 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%); υ_{max}/cm^{-1} (film) 3430 (s, br, OH), 2967, 2889 (s, C-H), 1708 (s, C=O), 1457 (s, C-H), 1373 (s, C-H) and 1042 (s, C-O); δ_H (270 MHz; $CDCl_3$) 1.05 (3H, t, $J_{5,4}$ 7.3, CH_3), 2.50 (2H, q, $J_{4,5}$ 7.3, $C\underline{H_2}CH_3$), 2.68 (2H, t, $J_{2,1}$ 6.2, $C\underline{H_2}CH_2OH$), 3.35 (1H, br, OH) and 3.84 (2H, m, $C\underline{H_2}OH$); δ_C (67.8 MHz; $CDCl_3$) 7.1 (CH_3, C-5), 36.1 (CH_2, C-4), 44.0 (CH_2, C-2), 57.1 (CH_2, C-1) and 211.7 (C=O).

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

1-(*tert*-Butyldiphenylsilyloxy)-3-pentanone 354



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*-butylchlorodiphenylsilane (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 × 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. $C_{21}H_{29}O_2Si$ requires M + H, 341.1937.); υ_{max}/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); δ_H (270 MHz; $CDCl_3$) 1.03 (9H, s, Si-$C(CH_3)_3$), 1.05 (3H, t, $J_{5,4}$ 7.3, CH_3), 2.49 (2H, q, $J_{4,5}$ 7.3, CH_2CH_3), 2.62 (2H, t, $J_{2,1}$ 6.2, CH_2CH_2OSi), 3.94 (2H, t, $J_{1,2}$ 6.2, CH_2OSi), 7.36-7.43 (6H, m, Ar-H) and 7.64-7.67 (4H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 7.6 (CH_3, C-5), 19.1 (quat., ^tBu), 26.7 (CH_3, ^tBu), 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 - ^tBu, 100), 253 (38), 199 (34), 139 (12) and 45 (28).

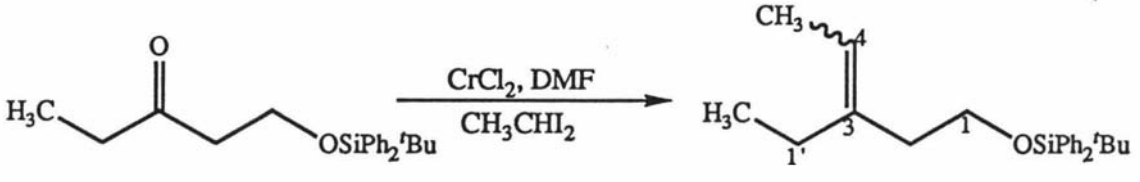
1,1-Diiodoethane[162]

$$CH_3CHCl_2 + 2\,CH_3CH_2I \xrightarrow{AlCl_3} CH_3CHI_2 + 2\,CH_3CH_2Cl$$

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 359

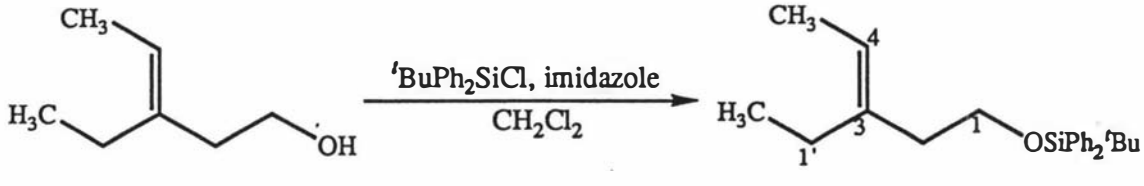
Procedure A



E/Z 2:3

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%); υ_{max}/cm^{-1} (film) 3069 (m, =C-H), 2951, 2924, 2857 (vs, C-H), 1465 (m, C-H), 1424 (m, C-H), 822 (m, =C-H), 735 (s, Si-C) and 702 (vs, Si-C); δ_H (270 MHz; $CDCl_3$) *E-isomer* 0.87 (3H, t, $J_{2',1'}$ 7.3, $CH_2C\underline{H}_3$), 1.03 (9H, s, Si-C$(CH_3)_3$), 1.54 (3H, d, $J_{5,4}$ 6.6, CH_3C=), 1.95 (2H, q, $J_{1',2'}$ 7.3, $C\underline{H}_2CH_3$), 2.21 (2H, t, $J_{2,1}$ 7.3, $C\underline{H}_2CH_2OSi$), 3.69 (2H, t, $J_{1,2}$ 7.3, CH_2O), 5.15 (1H, q, $J_{4,5}$ 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, $J_{2',1'}$ 7.3, $CH_2C\underline{H}_3$), 1.04 (9H, s, Si-C$(CH_3)_3$), 1.48 (3H, d, $J_{5,4}$ 6.6, CH_3C=), 1.89 (2H, q, $J_{1',2'}$ 7.3, $C\underline{H}_2CH_3$), 2.32 (2H, t, $J_{2,1}$ 7.3, $C\underline{H}_2CH_2OSi$), 3.64 (2H, t, $J_{1,2}$ 7.3 CH_2O), 5.22 (1H, q, $J_{4,5}$ 6.6, =CH), 7.34-7.45 (6H, m, Ar-H) and 7.65-7.70 (4H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) *E-isomer* 12.8 (CH_3, C-2'), 13.0 (CH_3, C-5), 19.1 (quat., ^tBu), 22.9 (CH_2, C-1'), 26.8 (CH_3, ^tBu), 39.7 (CH_2, C-2), 63.4 (CH_2OSi), 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 (CH_3, C-2'), 13.2 (CH_3, C-5), 19.1 (quat., ^tBu), 30.1 (CH_2, C-1'), 33.4 (CH_3, ^tBu), 39.7 (CH_2, C-2), 62.5 (CH_2OSi), 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

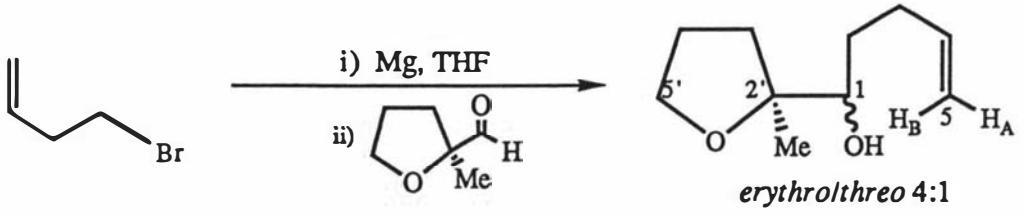


To a solution of (E)-3-ethyl-3-penten-1-ol **373** (50 mg, 0.438 mmol) in dry dichloromethane (2 ml) were added imidazole (59.5 mg, 0.874 mmol) and *tert*-butylchlorodiphenylsilane (120 mg, 0.437 mmol). After stirring for 1 h. at room

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.

^{1}H and ^{13}C 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

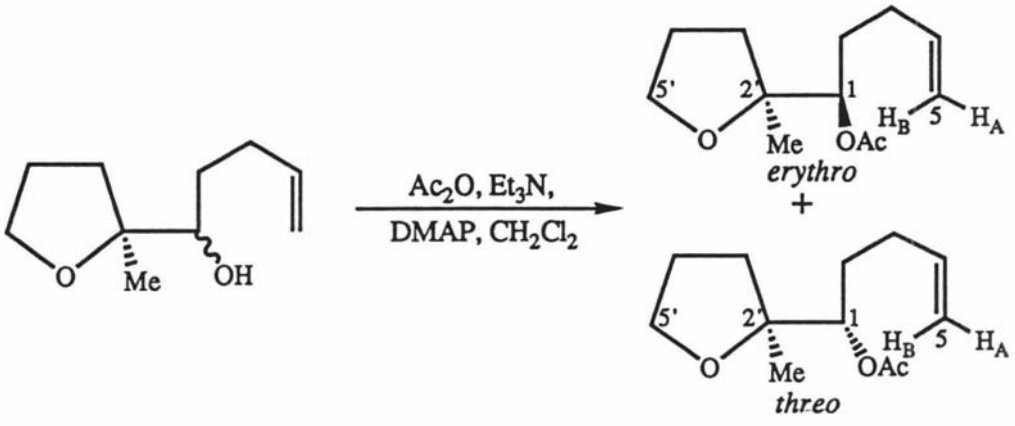


erythro/threo 4:1

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, ^{1}H 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



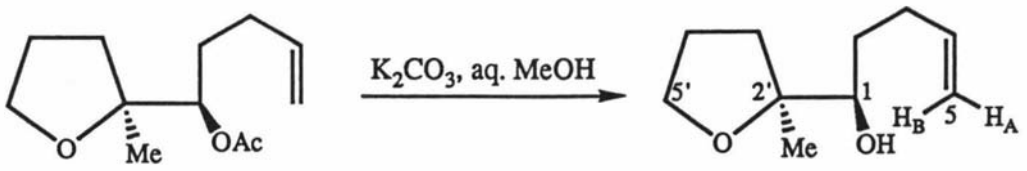
To a solution of (1R*, 2'S*) and (1S*, 2'S)-1-(2-methyltetrahydrofur-2-yl)-4-penten-1-ol (4:1, **330a:330b**) (1.50 g, 8.81 mmol) in dry dichloromethane (110 ml) under nitrogen were added triethylamine (1.62 ml, 11.6 mmol), acetic anhydride (0.91 ml, 9.64 mmol) and a catalytic quantity of 4-dimethylaminopyridine (~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: (CI, NH_3) M + H, 213.1503. $C_{12}H_{21}O_3$ requires M + H, 213.1491.); υ_{max}/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, $=CH_2$); δ_H (270 MHz; $CDCl_3$) 1.10 (3H, s, CH_3), 1.55-1.67 (2H, m, CH_2), 1.68-1.80 (1H, m, CH_2), 1.86-1.92 (3H, m, CH_2), 1.95-2.03 (2H, m, CH_2), 2.08 (3H, s, CH_3CO), 3.80-3.86 (2H, m, CH_2O), 4.83-4.91 (2H, m, CHOAc, 5_A-H), 4.94 (1H, d, $J_{5B,4}$ 17.2, 5_B-H) and 5.81 (1H, ddt, $J_{4,5B}$ 17.2 $J_{4,5A}$ 10.3 $J_{4,3}$ 6.6, 4-H); δ_C (67.8 MHz; $CDCl_3$) 21.1 (CH_3, CH_3CO), 22.4 (CH_3, 2'-Me), 25.9 (CH_2), 29.0 (CH_2), 30.3 (CH_2), 34.5 (CH_2), 68.3 (CH_2O), 77.0 (CHOAc), 83.5 (quat., C-2'), 114.8 ($=CH_2$), 137.8 (=CH) and 170.7 (C=O); *m/z* 213 (M + H, 2%), 153 (M - CH_3COO, 6), 111 (2), 98 (4), 85 (C_5H_9O, 100) and 55(2).

(1S*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-1-pent-4-enyl acetate **338b** [*threo*] (319 mg, 17%) (Found: (CI, NH_3) M + H, 213.1503. $C_{12}H_{21}O_3$ requires M + H, 213.1491); υ_{max}/cm^{-1} (film) 3066 (m, =C-H), 2966, 2862 (s, C-H), 1739 (vs, C=O), 1637 (m,

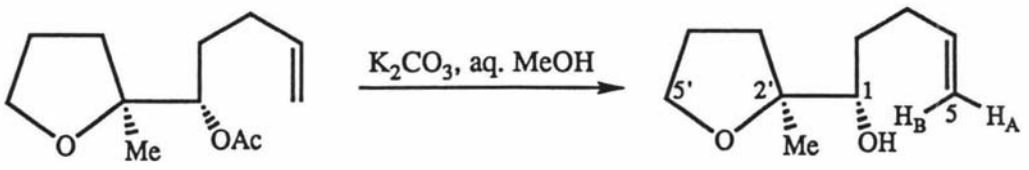
C=C), 1445, 1370 (s, C-H), 1237 (vs, C-O-C) and 915 (vs, $=CH_2$); δ_H (270 MHz; $CDCl_3$) 1.19 (3H, s, CH_3), 1.59-1.69 (3H, m, CH_2), 1.75-1.80 (1H, m, CH_2), 1.85-1.96 (2H, m, CH_2), 1.98-2.09 (2H, m, CH_2), 2.10 (3H, s, CH_3CO), 3.79-3.89 (2H, m, CH_2O), 4.91-4.99 (2H, m, CHOAc, 5_A-H), 5.02 (1H, d, $J_{5B,4}$ 17.2, 5_B-H) and 5.80 (1H, ddt, $J_{4,5B}$ 17.2 $J_{4,5A}$ 10.3 $J_{4,3}$ 6.6, 4-H); δ_C (67.8 MHz; $CDCl_3$) 21.1 (CH_3, Ac), 22.4 (CH_3), 26.2 (CH_2), 29.5 (CH_2), 30.4 (CH_2), 34.6 (CH_2), 67.7 (CH_2O), 77.1 (CHOAc), 83.6 (quat., C-2'), 115.0 ($=CH_2$), 137.8 (=CH) and 170.9 (C=O); *m/z* 213 (M + H, 2%), 153 (M - CH_3COO, 6), 111 (2), 98 (4), 85 (C_5H_9O, 100) and 55(2).

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



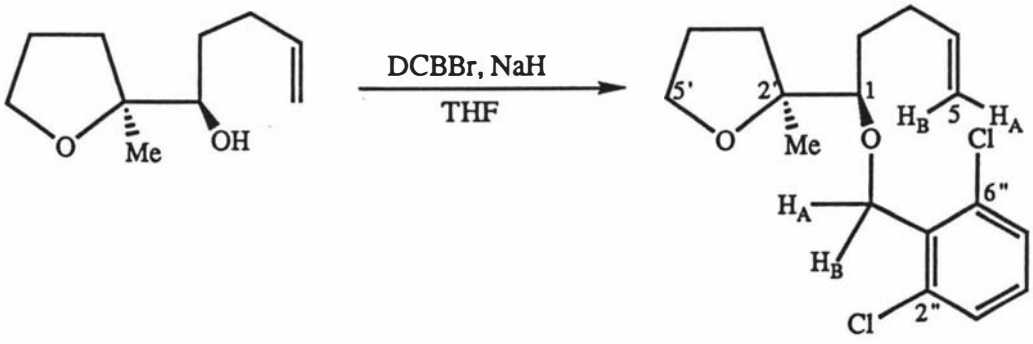
To a solution of (1R*, 2'S*)-1-(2-methyltetrahydrofur-2-yl)-1-pent-4-enyl acetate **338a** (454 mg, 2.14 mmol) in 95% aqueous methanol (40 ml) was added potassium carbonate (1.18 g, 8.54 mmol). After stirring for 16 h. the reaction mixture was filtered and the solvent was removed under reduced pressure. Saturated aqueous sodium chloride solution (5 ml) was added and the mixture was extracted with dichloromethane (6 × 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 eluant, to afford (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol **330a** as a colourless oil (291 mg, 80%); υ_{max}/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, $=CH_2$); δ_H (270 MHz; $CDCl_3$) 1.12 (3H, s, CH_3), 1.31-1.81 (4H, m, CH_2), 1.87-2.05 (2H, m, CH_2), 2.07-2.12 (1H, m, CH_2), 2.30-2.44 (1H, m, CH_2), 2.73 (1H, s, OH), 3.53 (1H, dd, $J_{1,2A}$ 10.3, $J_{1,2B}$ 4.0, C<u>H</u>OH), 3.85 (2H, m, CH_2O), 4.97 (1H, d, $J_{5A,4}$ 10.1, 5_A-H), 5.05 (1H, d, $J_{5B,4}$ 17.2, 5_B-H) and 5.85 (1H, ddt, $J_{4,5B}$ 17.2 $J_{4,5A}$ 10.1 $J_{4,3}$ 6.6, 4-H); δ_C (67.8 MHz; $CDCl_3$) 22.9 (CH_3), 26.2 (CH_2), 30.7 (CH_2), 30.9 (CH_2), 34.3 (CH_2), 67.7 (CH_2O), 75.6 (CHOH), 85.6 (quat., C-2'), 114.5 ($=CH_2$) and 138.4 (=CH); *m/z* 171 (M + H, 4%), 153 (M - OH, 15), 111 (35), 85 (C_5H_9O, 75) and 43 (100).

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



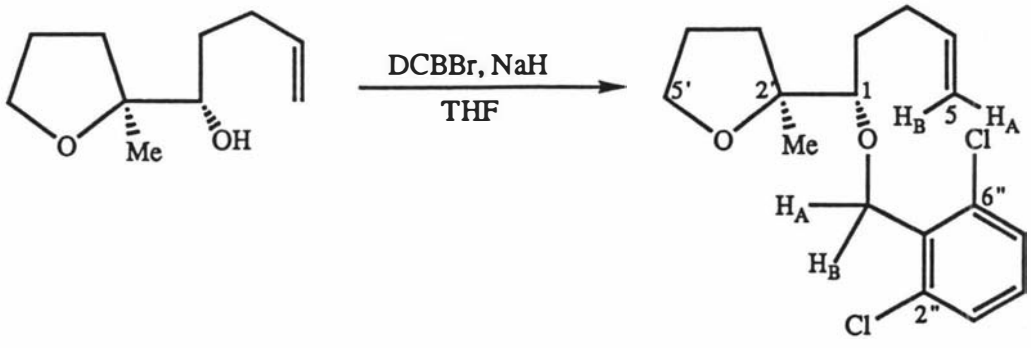
To a solution of (1S*, 2'S*)-1-(2-methyltetrahydrofur-2-yl)-1-pent-4-enyl acetate **338b** (400 mg, 1.88 mmol) in 95% aqueous methanol (30 ml) was added potassium carbonate (1.04 g, 7.53 mmol). After stirring for 18 h. the reaction mixture was filtered and the solvent was removed under reduced pressure. 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%); υ_{max}/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, $=CH_2$); δ_H (270 MHz; $CDCl_3$) 1.14 (3H, s, CH_3), 1.39-1.52 (2H, m, CH_2), 1.57-1.79 (2H, m, CH_2), 1.87-2.05 (2H, m, CH_2), 2.07-2.15 (1H, m, CH_2), 2.32-2.41 (1H, m, CH_2), 2.73 (1H, s, OH), 3.40 (1H, dd, $J_{1,2A}$ 8.4 $J_{1,2B}$ 4.0, C<u>H</u>OH), 3.83 (2H, m, CH_2O), 4.97 (1H, d, $J_{5A,4}$ 10.1, 5_A-H), 5.05 (1H, d, $J_{5B,4}$ 17.0, 5_B-H) and 5.84 (1H, ddt, $J_{4,5B}$ 17.2, $J_{4,5A}$ 10.1, $J_{4,3}$ 6.6, 4-H); δ_C (67.8 MHz; $CDCl_3$) 19.9 (CH_3), 26.3 (CH_2), 30.7 (CH_2), 31.0 (CH_2), 34.4 (CH_2), 67.3 (CH_2O), 75.8 (CHOH), 85.2 (quat., C-2'), 114.6 ($=CH_2$) and 138.4 (=CH); *m/z* 171 (M + H, 4%), 153 (M - OH, 15), 111 (35), 85 (C_5H_9O, 75) and 43 (100).

(1R*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-1-(2",6"-dichlorobenzyloxy)-4-pentene 387



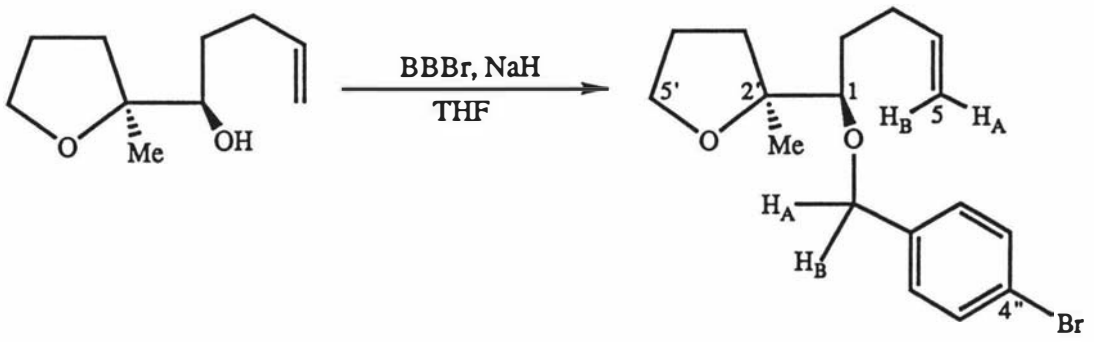
To a solution of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol **330a** (270 mg, 1.59 mmol) in dry tetrahydrofuran (5 ml) at 0°C under nitrogen was added sodium hydride (58 mg, 80% oil dispersion, 1.94 mmol). After stirring for 10 min. 2,6-dichlorobenzyl bromide (400 mg, 1.67 mmol) was added 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. $C_{17}H_{23}O_2{}^{35}Cl_2$ requires M + H, 329.1075.); υ_{max}/cm^{-1} (film) 3073 (m, =C-H), 2972, 2868 (s, C-H), 1581 (m, Ar-H), 1099 (vs, C-O-C), 993 (s, =CH), 911 (s, $=CH_2$), 777 and 765 (vs, Ar); δ_H (270 MHz; $CDCl_3$) 1.15 (3H, s, CH_3), 1.40-1.70 (3H, m, CH_2), 1.85-2.00 (2H, m, CH_2), 2.03-2.18 (2H, m, CH_2), 2.22-2.38 (1H, m, CH_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_2O), 4.85 (1H, d, $J_{HA,HB}$ 10.6, CH_AH_BAr), 4.88-5.03 (2H, m, $=CH_2$), 5.05 (1H, d, $J_{HB,HA}$ 10.6, CH_AH_BAr), 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); δ_C (67.8 MHz; $CDCl_3$) 23.3 (CH_3), 26.2 (CH_2), 30.6 (CH_2), 31.2 (CH_2), 33.2 (CH_2), 67.4 (CH_2O), 68.8 (CH_2Ar), 84.7 (CHO), 86.0 (quat., C-2'), 114.4 ($=CH_2$), 128.4, 129.6 (Ar-H), 134.4, 136.8 (Ar-CH_2, Ar-Cl) and 138.9 (=CH); *m/z* 329 (M + H, 1%), 161 (20), 159 ($C_7H_5{}^{35}Cl_2$, 31), 85 (C_5H_9O, 100) and 43 (48).

(1S*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-1-(2",6"-dichlorobenzyloxy)-4-pentene 340



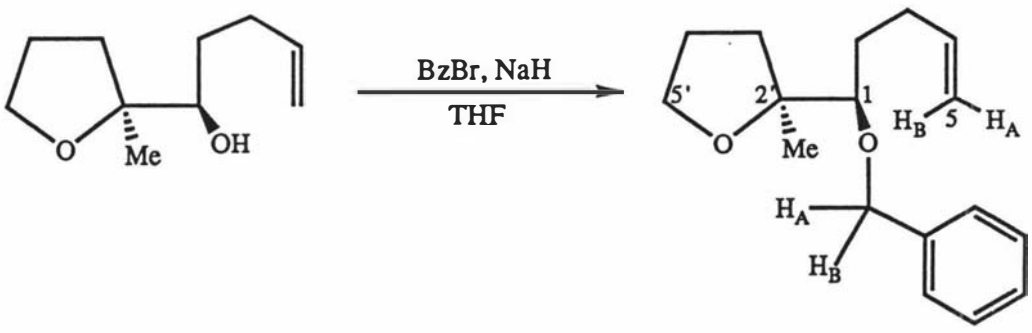
To a solution of (1S*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol **330a** (30 mg, 0.18 mmol) in dry tetrahydrofuran (0.5 ml) at 0°C under nitrogen was added sodium hydride (6 mg, 80% oil dispersion, 0.20 mmol). After stirring for 15 min. 2,6-dichlorobenzyl bromide (46 mg, 0.19 mmol) was added 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. $C_{17}H_{23}O_2{}^{35}Cl_2$ requires M + H, 329.1075.); υ_{max}/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); δ_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_2O), 4.81 (1H, d, $J_{HA,HB}$ 10.6, CH_AH_BAr), 4.86-5.03 (2H, m, $=CH_2$), 5.21 (1H, d, $J_{HB,HA}$ 10.6, CH_AH_BAr), 5.76 (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 7.26-7.32 (2H, m, Ar-H); δ_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_2O), 68.4 (CH_2Ar), 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 ($C_7H_5Cl_2$, 32), 85 (C_5H_9O, 100) and 43 (49).

(1R*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-1-(4"-bromobenzyloxy)-4-pentene 386



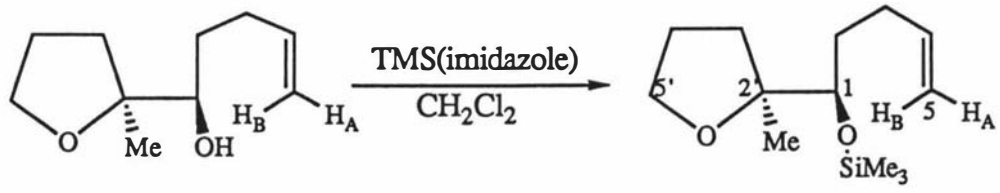
To a stirred solution of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol **330a** (400 mg, 2.35 mmol) in dry tetrahydrofuran (4ml) at 0°C under nitrogen was added sodium hydride (85 mg, 80% oil dispersion, 2.83 mmol). After stirring for 10 min. 4-bromobenzyl bromide (586 mg, 2.34 mmol) and 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. $C_{17}H_{24}O_2{}^{79}Br$, $C_{17}H_{24}O_2{}^{81}Br$ require M + H, 338.0881, 340.0861.); υ_{max}/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, $=CH_2$) and 802 (vs, Ar); δ_H (270 MHz; $CDCl_3$) 1.15 (3H, s, CH_3), 1.45-1.64 (3H, m, CH_2), 1.85-1.95 (2H, m, CH_2), 2.02-2.13 (2H, m, CH_2), 2.24-2.30 (1H, m, CH_2), 3.36 (1H, dd, $J_{1,2A}$ 9.5 $J_{1,2B}$ 2.9, CHO), 3.73-3.91 (2H, m, CH_2O), 4.55 (1H, d, $J_{HA,HB}$ 11.7, CH_AH_BAr), 4.73 (1H, d, $J_{HB,HA}$ 11.7, CH_AH_BAr), 4.95-5.04 (2H, m, $=CH_2$) 5.81 (1H, ddt, $J_{4,5B}$ 16.9 $J_{4,5A}$ 10.3 $J_{4,3}$ 6.6, 4-H), 7.21-7.24 (2H, m, Ar-H) and 7.44-7.47 (2H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 23.9 (CH_3), 26.4 (CH_2), 30.7 (CH_2), 31.1 (CH_2), 32.7 (CH_2), 67.7 (CH_2O, C-5'), 73.8 (CH_2Ar), 84.5 (CHO), 86.1 (quat., C-2'), 114.7 ($=CH_2$), 121.0 (quat., Ar-Br) 129.2, 131.2 (Ar-H) 138.3 (quat., Ar-CH_2) and 138.5 (=CH); *m/z* 340 (M + H, 1%), 338 (M + H, 1), 171 ($C_7H_6{}^{81}Br$, 34), 169 ($C_7H_6{}^{79}Br$, 36), 85 (C_5H_9O, 100) and 43 (69).

(1R*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-1-benzyloxy-4-pentene 385



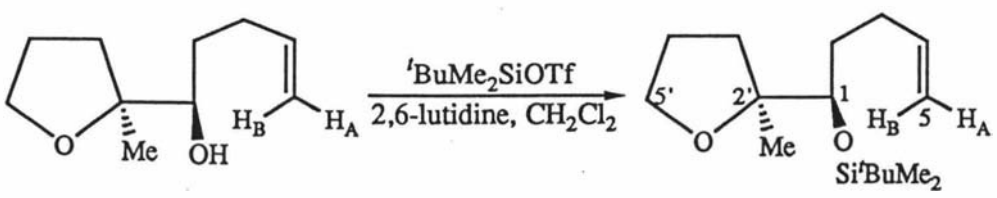
To a solution of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol **330a** (508 mg, 2.98 mmol) in dry tetrahydrofuran (6 ml) at 0°C under nitrogen was added sodium hydride (107 mg, 80% oil dispersion, 3.57 mmol). After stirring for 20 min. benzyl bromide (0.354 ml, 2.98 mmol) and tetrabutylammonium 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. $C_{17}H_{24}O_2$ require M, 260.1776.); υ_{max}/cm^{-1} (film) 3064 (m, =C-H), 2971, 2865 (s, C-H), 1450 (C-H), 1107 (vs, C-O-C), 910 (s, $=CH_2$), 735 and 697 (s, C-H); δ_H (270 MHz; $CDCl_3$) 1.16 (3H, s, CH_3), 1.43-1.67 (3H, m, CH_2), 1.86-1.96 (2H, m, CH_2), 2.04-2.16 (2H, m, CH_2), 2.26-2.31 (1H, m, CH_2), 3.37 (1H, dd, $J_{1,2A}$ 9.5 $J_{1,2B}$ 2.9, CHO), 3.70-3.93 (2H, t, m, CH_2O), 4.59 (1H, d, $J_{HA,HB}$ 11.0, CH_AH_BAr), 4.79 (1H, d, $J_{HB,HA}$ 11.0, CH_AH_BAr), 4.95-5.04 (2H, m, $=CH_2$) 5.80 (1H, ddt, $J_{4,5B}$ 16.9 $J_{4,5A}$ 10.3 $J_{4,3}$ 7.0, 4-H) and 7.26-7.40 (5H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 23.9 (CH_3), 26.5 (CH_2), 30.8 (CH_2), 31.2 (CH_2), 33.0 (CH_2), 67.8 (CH_2O, C-5'), 74.7 (CH_2Ar), 84.4 (CHO), 86.2 (quat., C-2'), 114.6 ($=CH_2$), 127.3, 127.7, 128.3 (C-H, Ar), 138.8 (=CH) and 139.3 (quat., Ar); *m/z* 260 (M^+, 0.5%), 91 (33), 85 (C_5H_9O, 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: (CI, NH_3) M + H, 243.1786. $C_{13}H_{27}O_2Si$ requires M + H, 243.1780.); υ_{max}/cm^{-1} (film) 3069 (m, =C-H), 2962, 2864 (vs, C-H), 1637 (m, C=C), 1447 (s, C-H), 1371 (s, C-H), 1248 (s, Si-CH_3), 1106 (vs, C-O-C), 908 (s, =CH_2) and 838 (vs, Si-CH_3); δ_H (270 MHz, $CDCl_3$) 0.01 (9H, s, CH_3Si), 0.98 (3H, s, CH_3), 1.21-1.55 (4H, m, CH_2), 1.69-1.93 (3H, m, CH_2), 2.07-2.13 (1H, m, CH_2), 3.42 (1H, dd, $J_{1,2A}$ 9.9 $J_{1,2B}$ 2.6, CHO), 3.67 (2H, t, $J_{5',4'}$ 6.6, CH_2O), 4.84 (1H, d, $J_{5A,4}$ 10.3, 5_A-H), 4.91 (1H, d, $J_{5B,4}$ 17.2, 5_B-H) and 5.71 (1H, ddt, $J_{4,5B}$ 17.2 $J_{4,5A}$ 10.3 $J_{4,3}$ 6.6, 4-H); δ_C (67.8 MHz; $CDCl_3$) 0.80 (CH_3, SiMe), 22.8 (CH_3), 26.2 (CH_2), 30.9 (CH_2), 32.4 (CH_2), 32.9 (CH_2), 67.5 (CH_2O), 77.5 (CHO), 85.4 (quat., C-2'), 114.4 (=CH_2) and 138.8 (=CH); *m/z* 243 (M + H, 25%), 207 (29), 171 (32), 153 (M - $OSiMe_3$, 51), 95 (26), 85 (C_5H_9O, 100), 74 (Me_3SiH, 73).

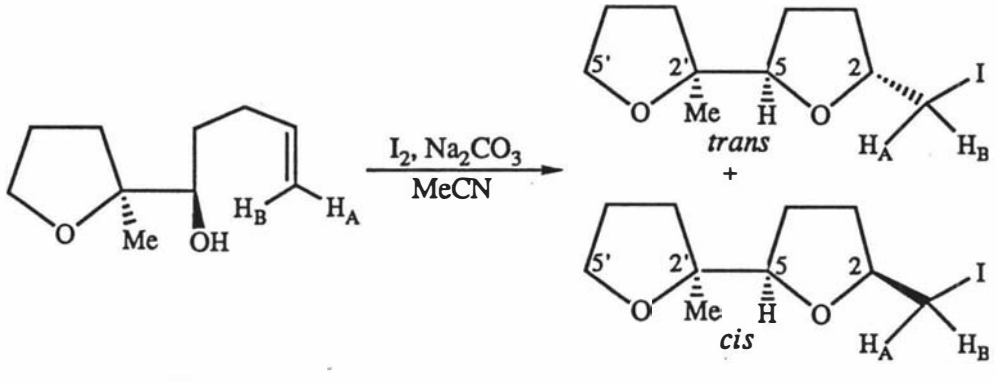
(1R*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-1-(*tert*-butyldimethylsilyloxy)-4-pentene 389



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 × 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: (CI, NH_3) M + H, 285.2259. $C_{16}H_{32}O_2Si$ requires M + H, 285.2250.); υ_{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); δ_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_2O), 4.93 (1H, d, $J_{5A,4}$ 10.3, 5_A-H), 5.00 (1H, dd, $J_{5B,4}$ 17.2 $J_{5B,5A}$ 1.8, 5_B-H) and 5.80 (1H, ddt, $J_{4,5B}$ 17.2 $J_{4,5A}$ 10.3 $J_{4,3}$ 6.6, 4-H); δ_C (67.8 MHz; $CDCl_3$) -4.1 (CH_3, SiMe), 18.2 (quat., ^tBu), 22.3 (CH_3, 2'-Me), 26.0 (CH_3, ^tBu), 26.0 (CH_2), 30.7 (CH_2), 33.1 (CH_2), 33.5 (CH_2), 67.2 (CH_2O), 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_5H_9O).

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

Procedure A

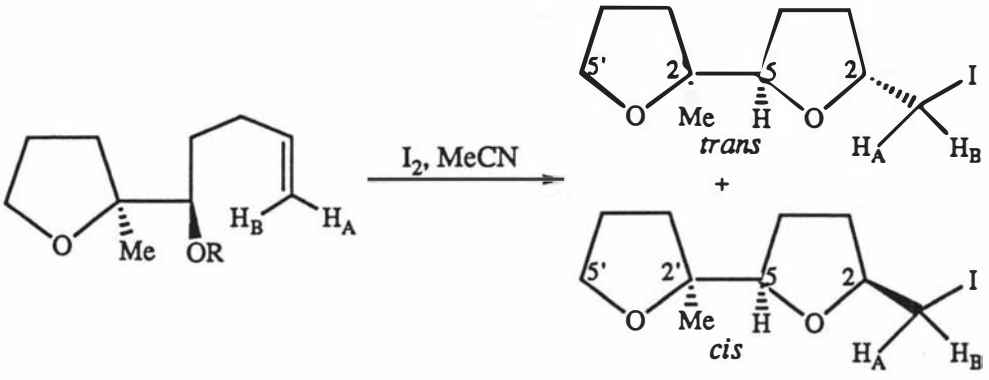


To a solution of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol **330a** (200 mg, 1.17 mmol) in dry acetonitrile (12 ml) were added sodium carbonate (1.24 g, 1.17 mmol) and iodine (1.49 g, 5.87 mmol). After 1 h. the reaction was extracted with diethyl ether (50 ml) and washed with 10% aqueous 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. $C_{10}H_{18}O_2I$ requires M + H, 297.0352.); υ_{max}/cm^{-1} (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); δ_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 $J_{HA,2}$ 8.0, $C\underline{H}_AH_BI$), 3.31 (1H, dd, $J_{HB,HA}$ 9.7 $J_{HB,2}$ 4.4, $CH_A\underline{H}_BI$), 3.85 (2H, t, $J_{5',4'}$ 6.4, CH_2O), 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); δ_C (67.8 MHz; $CDCl_3$) 10.7 (CH_2I), 22.7 (CH_3), 26.1 (CH_2), 28.0 (CH_2), 32.9 (CH_2), 33.4 (CH_2), 68.1 (CH_2O), 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_5H_9O, 100), 55 (13) and 43 (54).

(2S*, 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. $C_{10}H_{18}O_2I$ requires M + H 297.0352.); υ_{max}/cm^{-1} (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); δ_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_2I), 3.86 (2H, t, $J_{5',4'}$ 6.6, CH_2O), 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); δ_C (67.8 MHz; $CDCl_3$) 10.7 (CH_2I), 23.3 (CH_3), 26.3 (CH_2), 27.0 (CH_2), 31.4 (CH_2), 33.2 (CH_2), 68.2 (CH_2O), 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_5H_9O, 100), 55 (12) and 43 (64).

Procedure B

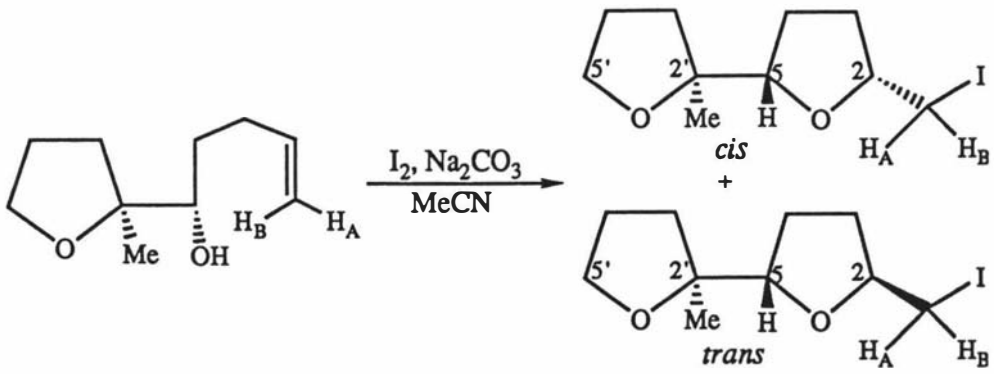


To a solution of each of the protected hydroxyalkenes **385 - 389** (1.0 mmol) in dry acetonitrile (9 ml) at 0°C was added iodine (5.0 mmol). After 10 min. the reaction was extracted with diethyl ether (20 ml) and washed with 10% aqueous sodium sulphite (20 ml). The aqueous layer was extracted with diethyl 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'-methyltetra-hydrofur-2'-yl)tetrahydrofuran **331b** [*cis*].

Compound	protecting group (R)	yield	**331a/331b** ratio
330a	H	93%	5:1
385	benzyl	67%	5:4
386	4-bromobenzyl	46%	2:3
387	2,6-dichlorobenzyl	63%	1:10
388	trimethylsilyl	68%	5:1
389	*tert*-butyldimethylsilyl	57%	5:1
338a	acetate	no reaction	-

(2S*, 5S*, 2'S*) and (2R*, 5S*, 2'S*)-2-(Iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran [*trans* and *cis*] 339a, 339b

Procedure A



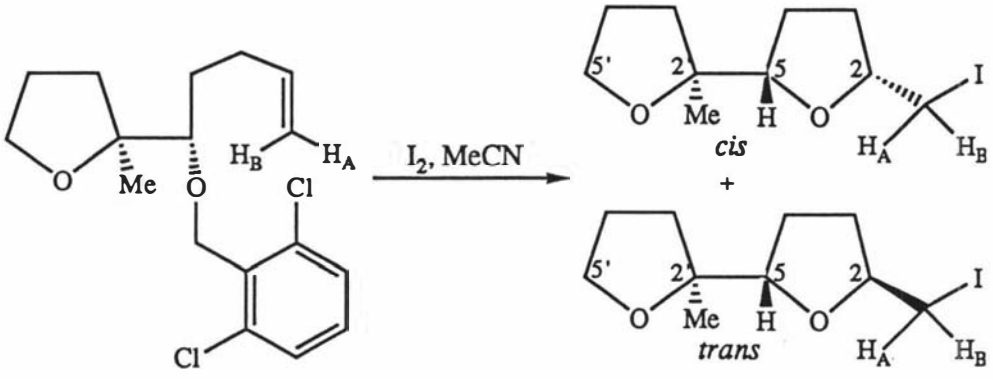
To a solution of (1S*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol **330b** (100 mg, 0.58 mmol) in dry acetonitrile (6 ml) were added sodium carbonate (0.63 g, 0.59 mmol) and iodine (0.75 g, 2.96 mmol). After 1 h. the reaction was extracted with diethyl ether (30 ml) and washed with 10% aqueous 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. $C_{10}H_{18}O_2I$ requires M + H, 297.0352.); υ_{max}/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); δ_H (270 MHz; $CDCl_3$) 1.12 (3H, s, CH_3), 1.57-1.67 (2H, m, CH_2), 1.84-2.04 (5H, m, CH_2), 2.17-2.28 (1H, m, CH_2), 3.18 (1H, dd, $J_{HA,HB}$ 9.9 $J_{HA,2}$ 7.3, CH_AH_BI), 3.28 (1H, dd, $J_{HB,HA}$ 9.9 $J_{HB,2}$ 4.8, CH_AH_BI), 3.77-3.91 (2H, m, CH_2O) and 4.00-4.10 (2H, m, 5-H, 2-H) ; δ_C (67.8 MHz; $CDCl_3$) 10.7 (CH_2I), 22.9 (CH_3), 26.3 (CH_2), 27.4 (CH_2), 33.0 (CH_2), 34.6 (CH_2), 68.4 (CH_2O), 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 (C_5H_9O, 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. $C_{10}H_{18}O_2I$ requires M

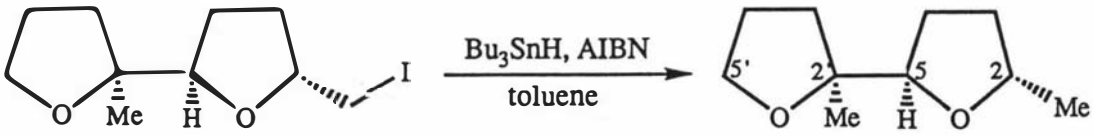
+ H 297.0352.); υ_{max}/cm^{-1} (film) 2968, 2864 (s, C-H), 1454 (m, C-H), 1091 (s, C-O-C), 1053 (vs, C-O-C) and 490 (s, C-I); δ_H (270 MHz; $CDCl_3$) 1.15 (3H, s, CH_3), 1.61-2.06 (8H, m, CH_2), 3.18 (1H, dd, $J_{HA,HB}$ 9.9 $J_{HA,2}$ 5.1, $C\underline{H}_AH_BI$), 3.25 (1H, dd, $J_{HB,HA}$ 9.9 $J_{HB,2}$ 7.7, $CH_A\underline{H}_BI$), 3.83-3.92 (3H, m, CH_2O, 5-H) and 4.02-4.13 (1H, m, 2-H); δ_C (67.8 MHz; $CDCl_3$) 10.2 (CH_2I), 23.2 (CH_3), 26.2 (CH_2), 26.3 (CH_2), 31.4 (CH_2), 34.8 (CH_2), 68.6 (CH_2O), 79.0 (CHO, C-2), 83.1 (quat., C-2') and 86.2 (CHO, C-5); *m/z* 297 (M + H, 1%), 211 (3), 85 (C_5H_9O, 100), 55 (15) and 43 (68).

Procedure B



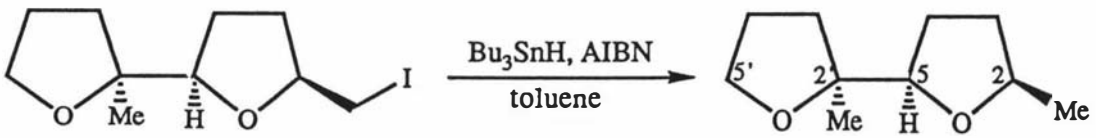
To a solution of (1S*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-1-(2", 6"-dichlorobenzyloxy)-4-pentene (40 mg, 0.12 mmol) in dry acetonitrile (1 ml) at 0°C was added iodine (154 mg, 0.61 mmol). After 10 min. the reaction was extracted with diethyl ether (5 ml) and washed with 10% aqueous sodium sulphite (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'-methyltetra-hydrofur-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: (CI, NH_3) M + H, 171.1390. $C_{10}H_{19}O_2$ requires M + H, 171.1385.); υ_{max}/cm^{-1} (film) 2965, 2864 (vs, C-H), 1454 (s, C-H), 1373 (s, C-H), 1194 (m, C-O-C) and 1086 (vs, C-O-C); δ_H (270 MHz; $CDCl_3$) 1.15 (3H, s, 2'-Me), 1.23 (3H, d, $J_{2\text{-Me},2}$ 5.9, 2-Me), 1.42-1.73 (3H, m, CH_2), 1.86-2.05 (5H, m, CH_2), 3.86 (2H, t, $J_{5',4'}$ 6.4, CH_2O), 3.99 (1H, dd, $J_{5,4A}$ 8.8 $J_{5,4B}$ 6.2, 5-H) and 4.10 (1H, qt, $J_{2,2\text{-Me}}$ 5.9 $J_{2,3}$ 8.8, 2-H); δ_C (67.8 MHz; $CDCl_3$) 21.1 (CH_3, 2-Me), 22.6 (CH_3, 2'-Me), 26.0 (CH_2), 28.1 (CH_2), 33.3 (CH_2), 34.2 (CH_2), 67.9 (CH_2O), 75.9 (CHO, C-2), 83.8 (CHO, C-5) and 84.5 (quat., C-2'); *m/z* 171 (M + H, 1%), 155 (M - CH_3, 18), 131 (9), 111(7), 105 (7), 91 (4), 85 (C_5H_9O, 100), 66 (4) and 55 (3).

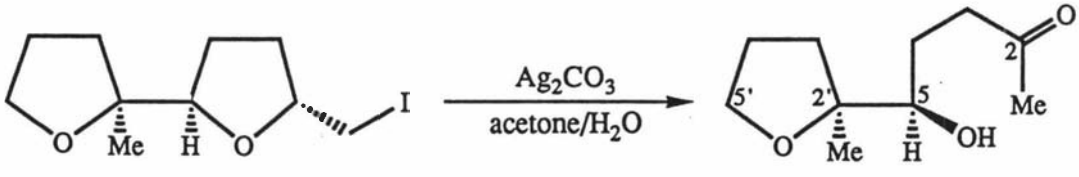
(2R*, 5R*, 2'S*)-2-Methyl-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 341b



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 µl, 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. $C_{10}H_{19}O_2$ requires M + H, 171.1385.); υ_{max}/cm^{-1} (film) 2967, 2865 (s, C-H), 1454 (s, C-H), 1371(s, CH_3), 1194 (m, C-O-C) and 1086 (vs, C-O-C); δ_H (270 MHz; $CDCl_3$) 1.15 (3H, s, 2'-Me), 1.23 (3H, d, $J_{2\text{-}Me,2}$ 6.2, 2-Me), 1.31-1.73 (4H, m, CH_2), 1.87-2.01 (4H, m, CH_2), 3.85 (2H, t, $J_{5',4'}$ 6.4, CH_2O), 3.80-3.85 (1H, m, 5-H) and 4.10 (1H, qd, $J_{2,2\text{-}Me}$ 6.2 $J_{2,3A}$ 1.5, 2-H); δ_C (67.8 MHz; $CDCl_3$) 21.0 (CH_3, 2-Me), 22.7 (CH_3, 2'-Me), 26.3 (CH_2), 27.4 (CH_2), 33.1 (CH_2), 33.5 (CH_2), 68.1 (CH_2O), 75.5 (CH, C-2), 84.0 (quat., C-2') and 84.5 (CH, C-5); *m/z* 171 (M + H, 9%), 85 (C_5H_9O, 100), 66 (26) and 43 (16).

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

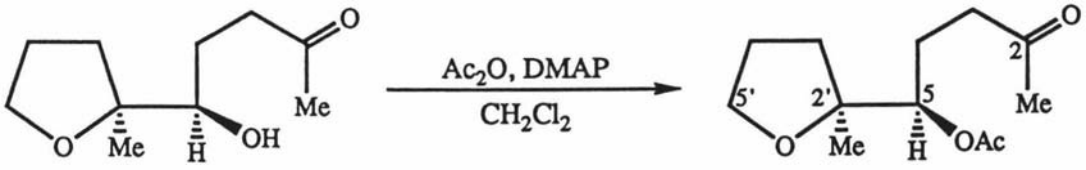


To a solution of (2R*, 5R*, 2'S*)-2-iodomethyl-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran **331a** (118 mg, 0.398 mmol) in acetone (2 ml) and distilled water (2 drops) was added silver carbonate (110 mg, 0.399 mmol). The reaction was heated under reflux for 8 h., during which time additional amounts 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. $C_{12}H_{21}O_4$ requires M + H, 229.1440.); υ_{max}/cm^{-1} (film) 3402 (br, s, OH), 2971, 2872 (s, C-H), 1713 (s, C=O), 1453 (m, C-H) and 1044 (C-O); δ_H (270 MHz; $CDCl_3$) 1.14 (3H, s, 2'-Me), 1.48-2.04 (6H, m, CH_2), 2.17 (3H, s, CH_3CO), 2.52-2.82 (2H, m, CH_2CO), 2.66 (1H, s, OH), 3.48 (1H, dd, $J_{5,4A}$ 11.0 $J_{5,4B}$ 2.0, CHOH) and 3.78-3.97 (2H, m, CH_2O); δ_C (67.8 MHz; $CDCl_3$) 22.9 (CH_3, 2'-Me), 25.5 (CH_2), 26.2 (CH_2), 30.1 (CH_3, C-1), 30.7 (CH_2), 40.9 ($CH_2C=O$), 67.9

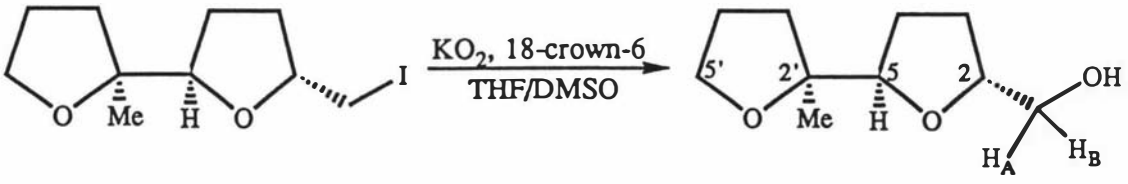
(CH_2O), 75.9 (CHOH), 85.3 (quat., C-2') and 209.4 (C=O); *m/z* 187 (M + H, 3%), 169 (M - OH, 100), 136 (11), 111 (32) and 85 (C_5H_9O) and recovered (2R*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran **331a** (42 mg, 36%)

(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 (22.7mg, 91%) (Found: M + H, 229.1431. $C_{12}H_{21}O_4$ requires M + H, 229.1440.); υ_{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); δ_H (270 MHz; $CDCl_3$) 1.18 (3H, s, 2'-Me), 1.58-2.10 (6H, m, CH_2), 2.08 (3H, s, CH_3COO), 2.13 (3H, s, CH_3CO), 2.43-2.48 (2H, m, CH_2CO), 3.75-3.90 (2H, m, CH_2O) and 4.86 (1H, dd, $J_{5,4A}$ 10.4 $J_{5,4B}$ 2.8, CHOAc); δ_C (67.8 MHz; $CDCl_3$) 21.1 (CH_3, Ac), 22.6 (CH_3, C-2'), 23.8 (CH_2, C-4), 25.9 (CH_2), 30.0 (CH_3, C-1), 34.4 (CH_2), 40.1 ($\underline{C}H_2C=O$), 68.4 (CH_2O), 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 - $OCOCH_3$), 111 (27), 85 (C_5H_9O, 100) and 43 (90).

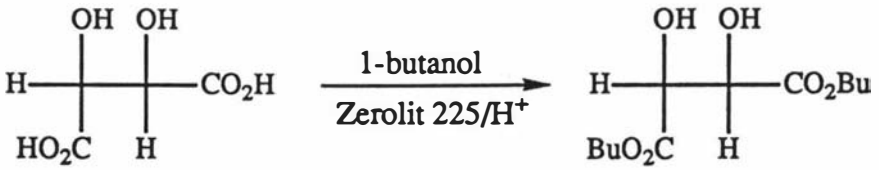
(2R*, 5R*, 2'S*)-2-(Hydroxymethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 343a



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 × 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:

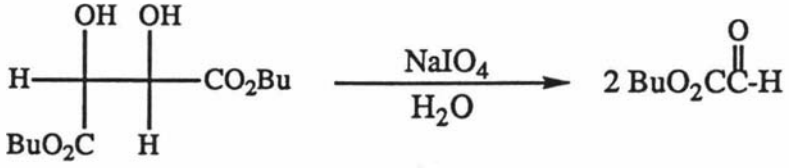
(2R*, 5R*, 2'S*)-2-(hydroxymethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran **343a** as a white crystalline solid (60.4 mg, 23%) m.p. 109-110°C (ethyl acetate) (Found: M + H, 187.1336. $C_{10}H_{19}O_3$ requires M + H, 187.1334.); υ_{max}/cm^{-1} (film) 3434 (s, OH), 2971, 2871 (s, C-H), 1451 (m, C-H) and 1047 (s, C-O); δ_H (270 MHz; $CDCl_3$) 1.15 (3H, s, CH_3), 1.57-2.05 (8H, m, CH_2), 2.13 (1H, s, OH), 3.50 (1H, dd, $J_{HA,HB}$ 11.7, $J_{HA,2}$ 5.9, CH_AH_BOH), 3.69 (1H, dd, $J_{HB,HA}$ 11.7, $J_{HB,2}$ 2.9, CH_AH_BOH), 3.86 (2H, t, $J_{5',4'}$ 6.6, CH_2O), 3.98 (1H, dd, $J_{5,4A}$ 8.8 $J_{5,4B}$ 6.2, 5-H) and 4.07-4.16 (1H, m, 2-H); δ_C (67.8 MHz; $CDCl_3$) 23.0 (CH_3), 26.2 (CH_2), 27.7 (CH_2), 28.3 (CH_2), 33.0 (CH_2), 64.8 (CH_2OH), 68.1 (CH_2O), 80.3 (CHO, C-2) and 84.7 (CHO and quat., C-5 and C-2'); *m/z* 187 (M + H, 2%), 169 (M - OH, 18), 155 (M - CH_2OH, 2), 111 (11), 85 (C_5H_9O, 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[144]



A mixture of (+)-tartaric acid (75 g, 0.50 mol), Zerolit 225/H^+ 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 × 30 ml). The combined organic layer was then washed with saturated aqueous sodium bicarbonate (3 × 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°C/0.3 mm Hg (lit.[144], b.p. 150°C/1.5 mm Hg).

Butyl glyoxylate 367[143]



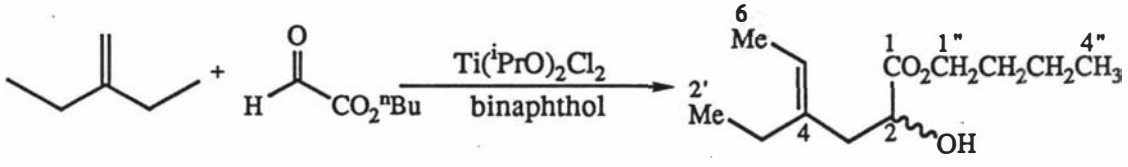
Dibutyl (+)-tartrate **369** (4.33 g, 16.5 mmol) was stirred vigorously with a 0.486 mol/L sodium periodate solution (34 ml, 16.5 mmol) for 40 h. After filtration to remove the white precipitate which had formed, the filtrate was extracted with diethyl ether (3 × 30 ml) and the combined organic layers 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°C/5 mm Hg (lit.[144], b.p. 66-69°C/5 mm Hg).

Diisopropoxytitanium(IV) dichloride 362[139]

$$TiCl_4 + Ti(^iPrO)_4 \longrightarrow 2Ti(^iPrO)_2Cl_2$$

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 × 5 ml) and dried under high vacuum for 12 h. to give diisopropoxytitanium(IV) dichloride **362** as a white solid (958 mg, 20%)

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



To a suspension of activated powdered 4A molecular sieves (6.0 g) in dry dichloromethane (60 ml) were added diisopropoxytitanium(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 × 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. $C_{12}H_{22}O_3$ requires M, 214.1569.); υ_{max}/cm^{-1} (film) 3485 (br, s, OH) 2878, 2937, 2969 (s, C-H) and 1739 (s, C=O); δ_H (270 MHz; $CDCl_3$) 0.92-1.02 (6H, m, 2 × CH_3), 1.35-1.44 (2H, m, CH_2), 1.59-1.67 (2H, m, CH_2), 1.62 (3H, d, $J_{6,5}$ 6.7, CH_3C=), 2.04-2.11 (2H, m,

CH_2), 2.28 (1H, dd, $J_{3A,3B}$ 14.2 and $J_{3A,2}$ 8.4, C$\underline{H}_A$H$_B$CHOH), 2.53 (1H, dd, $J_{3B,3A}$ 14.2 and $J_{3B,2}$ 4.5, CH$_A\underline{H}_B$CHOH), 2.84 (1H, m, OH), 4.17 (2H, t, $J_{1",2"}$ 6.7, CO_2CH_2), 4.25 (1H, m, C$\underline{H}$OH) and 5.31 (1H, q, $J_{5,6}$ 6.7, =CH); δ_C (67.8 MHz; $CDCl_3$) 12.7 (CH_3, C-2'), 13.2 (CH_3, C-6), 13.7 (CH_3, C-4"), 19.1 (CH_2, C-3"), 22.6 (CH_2, C-1'), 30.6 (CH_2, C-2"), 41.7 (CH_2, C-3), 65.3 (CH_2, 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 - H_2O, 33), 140 (M - C_4H_9O, 59), 95 (C_6H_{11}, 64), 83 (C_6H_{11}, 63) and 55 (100).

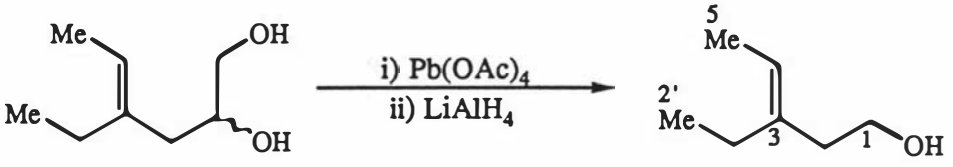
The *Z* isomer gave an additional ^{1}H NMR resonance at δ 5.43 (1/5H, q, $J_{5,6}$ 6.7, =CH).

(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. $C_8H_{16}O_2$ requires M, 144.1150.); υ_{max}/cm^{-1} (film) 3384 (br, vs, OH), 2965, 2934, 2875 (m, CH_2), 1031 (s, C-O primary) and 1067 (s, C-O secondary); δ_H (270 MHz; $CDCl_3$) 0.98 (3H, t, $J_{2',1'}$7.5, $CH_2C\underline{H}_3$), 1.63 (3H, d, $J_{6,5}$ 6.6, CH_3C=), 1.95-2.24 (4H, m, CH_2), 2.37 (1H, s, OH), 2.52 (1H, s, OH), 3.46 (1H, dd, $J_{1A,1B}$ 11.0, $J_{1A,2}$ 6.8, C$\underline{H}_A$H$_B$OH), 3.67 (1H, dd, $J_{1B,1A}$ 11.0, $J_{1B,2}$ 2.9, CH$_A\underline{H}_B$OH), 3.75-3.83 (1H, m, C$\underline{H}$OH) and 5.30 (1H, q, $J_{5,6}$ 6.6, =CH); δ_C (67.8 MHz; $CDCl_3$) 12.6 (CH_3, C-2'), 13.0 (CH_3, C-6), 22.6 (CH_2, C-1'), 40.4 (CH_2, C-3), 66.4 (CH_2O), 69.9 (CHO), 121.8 (=CH) and 137.7 (quat., C-4); *m/z* 144 (M^+, 3%), 126 (M - H_2O, 10), 113 (M -

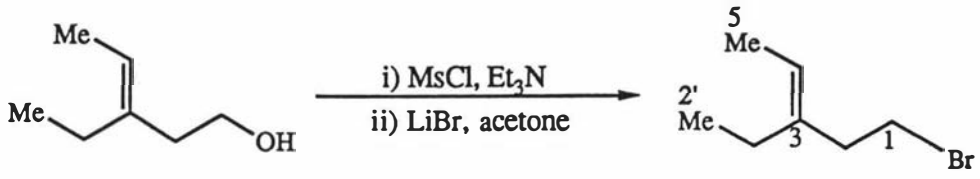
CH_2OH, 11), 95 (M - CH_5O_2), 84 (77), 69 (100), 61 (55), 55 (65), 43 (52) and 41 (60).

(E)-3-Ethyl-3-penten-1-ol 373



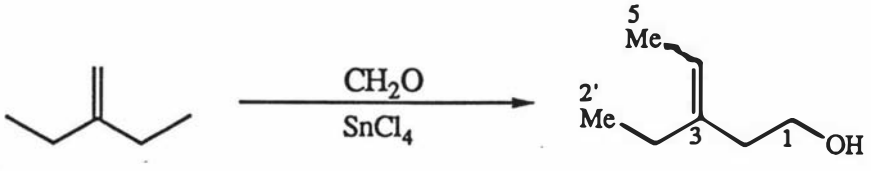
To a solution of (E)-4-penten-1,2-diol **374** (1.06 g, 7.35 mmol) in dry dichloromethane (70 ml) at 0°C under argon was added sodium carbonate (1.63 g, 15.4 mmol) followed by lead tetraacetate (3.91 g, 8.82 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. then 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. $C_7H_{14}O$ requires M, 114.1045.); υ_{max}/cm^{-1} (film) 3342, 3325 (br, s, OH), 3017 (m, =CH), 2955, 2924, 2867 (s, C-H), 1041 (s, CH_2-OH) and 824 (m, =C-H); δ_H (270 MHz; $CDCl_3$) 0.98 (3H, t, $J_{2',1'}$ 7.7, CH_3), 1.62 (3H, d, $J_{5,4}$ 6.6, CH_3C=), 2.05 (2H, q, $J_{1',2'}$ 7.7, $C\underline{H_2}CH_3$), 2.26 (2H, t, $J_{2,1}$ 6.2, 2-CH_2), 3.65 (2H, t, $J_{1,2}$ 6.2, CH_2OH) and 5.29 (1H, q, $J_{4,5}$ 6.6, =CH); δ_C (67.8 MHz; $CDCl_3$) 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_2O), 120.6 (=CH, C-4) and 137.9 (quat., C-3); *m/z* 114 (M^+, 29%), 96 (M - H_2O, 15), 81 (M - CH_5O, 53), 67 (45), 55 (100), 41 (45) and 29 (C_2H_5, 14).

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



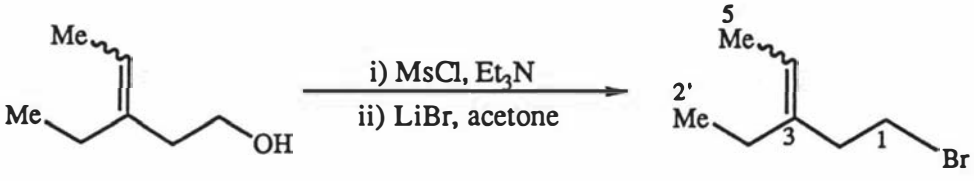
To a stirred solution of (E)-3-ethyl-3-penten-1-ol **373** (200 mg, 1.75 mmol) in dry dichloromethane (10 ml) under argon was added triethylamine (0.37 ml, 2.65 mmol). The reaction mixture was then cooled to -25° C and methanesulphonyl chloride (0.15 ml, 1.94 mmol) was added. After stirring for 30 min. 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. $C_7H_{13}{}^{79}Br$, $C_7H_{13}{}^{81}Br$ require M, 176.0201, 178.0180.); υ_{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; $CDCl_3$) 0.97 (3H, t, $J_{2',1'}$ 7.3, $C\underline{H}_3CH_2$), 1.60 (3H, d, $J_{5,4}$ 6.8, CH_3C=), 2.03 (2H, q, $J_{1',2'}$ 7.3 , $C\underline{H}_2CH_3$), 2.54 (2H, t, $J_{2,1}$ 7.7, CH_2), 3.41 (2H, t, $J_{1,2}$ 7.7, CH_2Br) and 5.27 (1H, q, $J_{4,5}$ 6.8); δ_C (67.8 MHz; $CDCl_3$) 12.8 (CH_3, C-2'), 13.0 (CH_3, C-5), 22.5 (CH_2, C-1'), 31.9 (CH_2, C-1), 40.2 (CH_2, 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



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 × 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%); υ_{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); δ_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_3C=), 2.05 (2H, q, $J_{1',2'}$ 7.5, $C\underline{H}_2CH_3$), 2.25 (2H, t, $J_{2,1}$ 6.6, $C\underline{H}_2CH_2OH$), 3.63 (2H, t, $J_{1,2}$ 6.6, CH_2OH) 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_3C=), 2.02 (2H, q, $J_{1',2'}$ 7.5, $C\underline{H}_2CH_3$), 2.34 (2H, t, $J_{2,1}$ 7.1, $C\underline{H}_2CH_2OH$), 3.61 (2H, t, $J_{1,2}$ 7.1, CH_2OH) and 5.35 (1H, q, $J_{4,5}$ 6.6, =CH); δ_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_2O, 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_2O, C-1), 119.7 (=CH, C-4) and 137.5 (quat., C-3); *m/z* 114 (M^+, 29%), 96 (M - H_2O, 15), 81 (M - CH_5O, 53), 67 (45), 55 (100), 41 (45) and 29 (C_2H_5, 14).

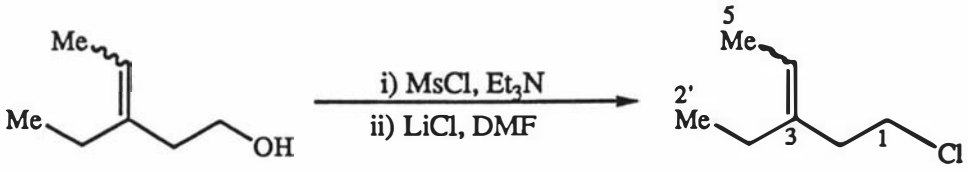
(E)- and (Z)-1-Bromo-3-ethyl-3-pentene 146



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**; υ_{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; $CDCl_3$) *(Z)-isomer* 1.00 (3H, t, $J_{2',1'}$ 7.3 , $C\underline{H}_3CH_2$), 1.62 (3H, d, $J_{5,4}$ 6.8, CH_3C=), 2.06 (2H, q, $J_{1',2'}$ 7.3, $C\underline{H}_2CH_3$), 2.62 (2H, t, $J_{2,1}$ 8.1, CH_2), 3.37 (2H, t, $J_{1,2}$ 8.1, CH_2Br) and 5.36 (1H, q, $J_{4,5}$ 6.8); δ_C (67.8 MHz;

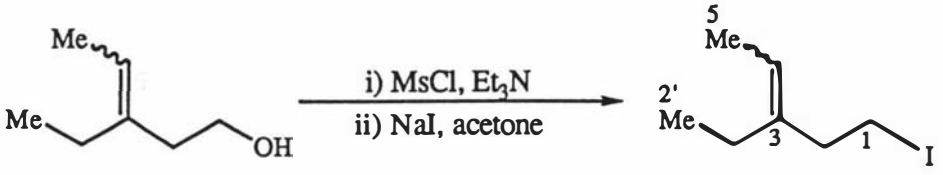
$CDCl_3$) *(Z)-isomer* 12.8 (CH_3, C-2'), 13.3 (CH_3,C-5), 29.4 (CH_2, C-1'), 30.8 (CH_2, C-1), 33.9 (CH_2, C-2), 120.7 (CH, C-4) and 138.5 (quat., C-3); *m/z* 178 (M^+, 20%), 176 (M^+, 20), 97 (M - Br, 44), 69 (27), 55 (100) and 21 (32).

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



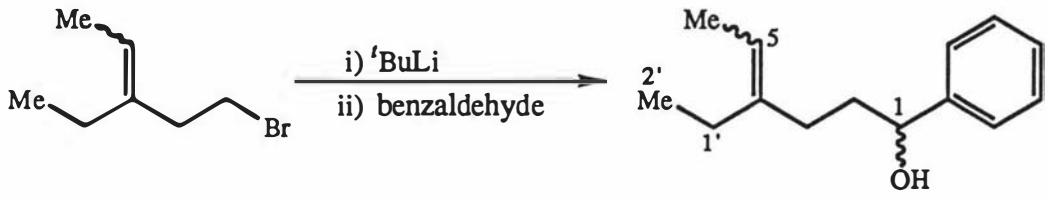
To a solution of a (4:3) mixture of (E)- and (Z)-ethyl-3-penten-1-ol **373** (1.64 g, 14.4 mmol) in dry dichloromethane (60 ml) under argon was added triethylamine (3.00 ml, 21.5 mmol). The reaction mixture was then cooled to -25°C and methanesulphonyl chloride (1.22 ml, 15.8 mmol) was added. After stirring 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. $C_7H_{13}Cl^{35}$, $C_7H_{13}Cl^{37}$ require M, 132.0706, 134.0676.); υ_{max}/cm^{-1} (film) 2967, 2925, 2866 (s, C-H), 1457 (s, C-H), 831 (m, =CH) and 720 (s, C-Cl); δ_H (270 MHz; $CDCl_3$) *(E)-isomer* 0.97 (3H, t, $J_{2',1'}$ 7.5 , $C\underline{H}_3CH_2$), 1.60 (3H, d, $J_{5,4}$ 6.8, CH_3C=), 2.04 (2H, q, $J_{1',2'}$ 7.5, $C\underline{H}_2CH_3$), 2.44 (2H, t, $J_{2,1}$ 7.7, CH_2), 3.55 (2H, t, $J_{1,2}$ 7.7, CH_2Cl) and 5.27 (1H, q, $J_{4,5}$ 6.8) *(Z)-isomer* 1.00 (3H, t, $J_{2',1'}$ 7.5 , $C\underline{H}_3CH_2$), 1.63 (3H, d, $J_{5,4}$ 6.8, CH_3C=), 2.06 (2H, q, $J_{1',2'}$ 7.5 , $C\underline{H}_2CH_3$), 2.53 (2H, t, $J_{2,1}$ 7.7, CH_2), 3.51 (2H, t, $J_{1,2}$ 7.7, CH_2Cl) and 5.36 (1H, q, $J_{4,5}$ 6.8); δ_C (67.8 MHz; $CDCl_3$) *(E)-isomer* 12.8 (CH_3, C-2'), 13.0 (CH_3, C-5), 22.6 (CH_2, C-1'), 39.9 (CH_2, C-2), 43.5 (CH_2, C-1), 121.3 (CH, C-4) and 137.9 (quat., C-3); *(Z)-isomer* 12.7 (CH_3, C-2'), 13.3 (CH_3,C-5), 29.6 (CH_2, C-1'), 33.6 (CH_2, C-2), 42.7 (CH_2, 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).

(E)- and (Z)-1-Iodo-3-ethyl-3-pentene 381



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 × 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 × 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 × 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. $C_7H_{13}I$ requires M, 224.0062.); υ_{max}/cm^{-1} (film) 2956, 2921, 2864 (s, C-H), 1457 (s, C-H) and 827 (m, =CH); δ_H (270 MHz; $CDCl_3$) *(E)-isomer* 0.96 (3H, t, $J_{2',1'}$ 7.7, $C\underline{H}_3CH_2$), 1.59 (3H, d, $J_{5,4}$ 6.8, CH_3C=), 2.02 (2H, q, $J_{1',2'}$ 7.7, $C\underline{H}_2CH_3$), 2.55 (2H, t, $J_{2,1}$ 7.9, CH_2), 3.19 (2H, t, $J_{1,2}$ 7.9, CH_2I) and 5.25 (1H, q, $J_{4,5}$ 6.8) *(Z)-isomer* 0.99 (3H, t, $J_{2',1'}$ 7.5, $C\underline{H}_3CH_2$), 1.59 (3H, d, $J_{5,4}$ 6.8, CH_3C=), 2.04 (2H, q, $J_{1',2'}$ 7.5, $C\underline{H}_2CH_3$), 2.64 (2H, t, $J_{2,1}$ 8.2, CH_2), 3.14 (2H, t, $J_{1,2}$ 8.2, CH_2I) and 5.36 (1H, q, $J_{4,5}$ 6.8); δ_C (67.8 MHz; $CDCl_3$) *(E)-isomer* 5.0 (CH_2, C-1), 12.8 (CH_3, C-2'), 13.0 (CH_3, C-5), 22.2 (CH_2, C-1'), 41.2 (CH_2, C-2), 120.8 (CH, C-4) and 140.4 (quat., C-3); *(Z)-isomer* 3.2 (CH_2, C-1), 12.7 (CH_3, C-2'), 13.3 (CH_3, C-5), 29.0 (CH_2, C-1'), 34.8 (CH_2, 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).

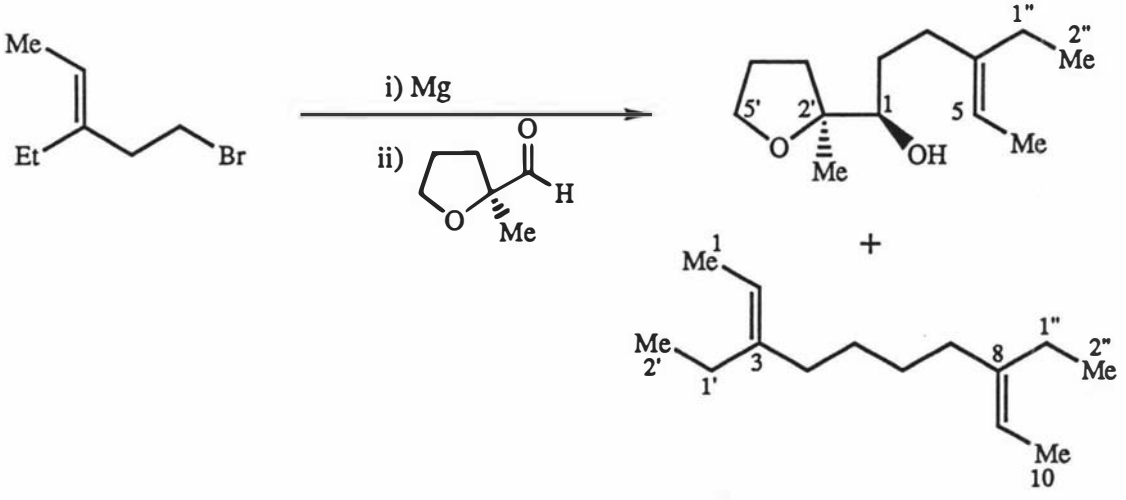
(E)- and (Z)-1-Phenyl-4-ethyl-4-hexen-1-ol 382



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^+, 204.1512. $C_{14}H_{20}O$ requires M, 204.1514.); υ_{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); δ_H (270 MHz; $CDCl_3$) 0.90-0.98 (3H, m, $CH_2C\underline{H}_3$), 1.53 (3/7 × 3H, d, $J_{6,5}$ 6.6, CH_3C=), 1.57 (4/7 × 3H, d, $J_{6,5}$ 6.6, CH_3C=), 1.72-2.15 (6H, m, 3 × CH_2), 2.26 (1H, br, s, OH), 4.59-4.64 (1H, m, C<u>H</u>OH), 5.15-5.24 (1H, m, 5-H) and 7.15-7.37 (5H, m, Ar-H); δ_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_2O, 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

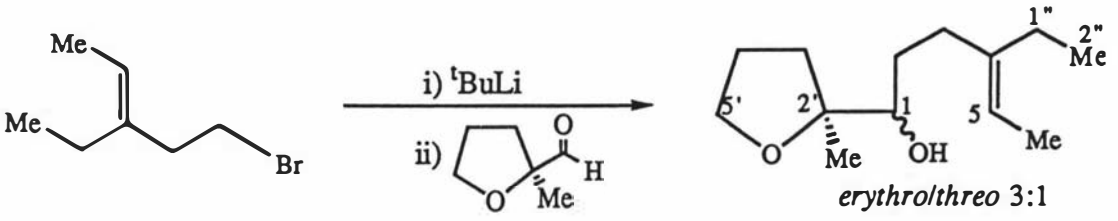


To magnesium filings (83 mg, 3.41 mol) covered with dry tetrahydrofuran (0.5 ml) under argon was added (E)-1-bromo-3-ethyl-3-pentene **146** (90 mg, 0.51 mmol). Heat was evolved and a solution of (E)-1-bromo-3-ethyl-3-pentene **146** (310 mg, 1.76 mmol) in tetrahydrofuran (5 ml) was added slowly over 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 × 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, NH_3) M - H, 193.1957. $C_{14}H_{25}$ requires M - H, 193.1956.); υ_{max}/cm^{-1} (film) 2957, 2923, 1862 (s, C-H), 1660 (m, C=C), 1458 (vs, C-H) and 822 (s, trisub. alkene); δ_H (270 MHz; $CDCl_3$) 0.94 (6H, t, $J_{2',1'}$ 7.3, CH_3CH_2), 1.27-1.40 (4H, m, 5-CH_2, 6-CH_2), 1.57 (6H, d, $J_{1,2}$ 7.0, CH_3-=), 1.94-2.06 (8H, m, 4-CH_2, 7-CH_2, 1'-CH_2, 1"-CH_2) and 5.16 (2H, q, $J_{2,1}$ 7.0, =CH); δ_C (67.8 MHz, $CDCl_3$) 12.8 (CH_3, C-2', C-2"), 13.2 (CH_3, C-1, C-10), 22.7

(CH_2, C-1', C-1"), 28.0 (CH_2, C-5, C-6), 36.6 (CH_2, C-4, C-7), 117.0 (CH_2, C-2, C-9) and 142.0 (quat., C-3, C-8); *m/z* 193 (M - H, 19%), 74 (100) and 58 (66).

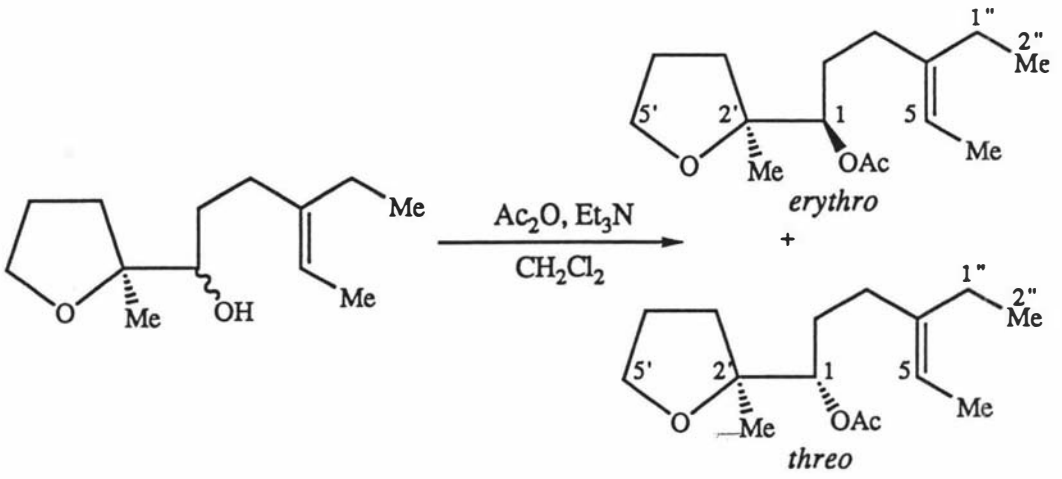
Procedure B



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** (300mg, 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, ^{1}H 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



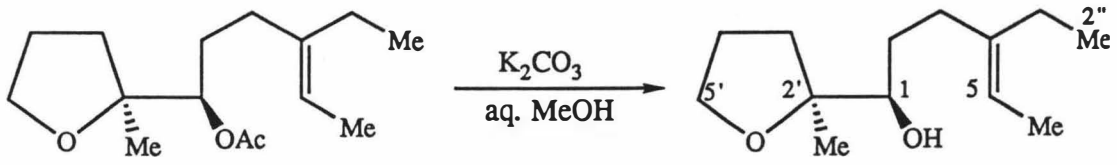
To a solution of (4E, 1R*, 2'S*)- and (4E, 1S*, 2'S*)-4-ethyl-1-(2'-methyltetrahydro-2'-furyl)-4-hexen-1-ol **348** (117 mg, 0.551 mmol) in dry dichloromethane were added triethylamine (92 µl, 0.66 mmol), acetic anhydride (52 µl, 0.55 mmol) and a catalytic quantity of 4-dimethylaminopyridine (~5 mg). 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%); υ_{max}/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); δ_H (270MHz; $CDCl_3$) 0.94 (3H, t, $J_{2",1"}$ 7.7, $CH_2\underline{CH_3}$), 1.17 (3H, s, 2'-Me), 1.57 (3H, d, $J_{6,5}$ 7.0, CH_3-C=), 1.53-1.62 (2H, m, CH_2), 1.69-1.75 (1H, m, CH_2), 1.85-2.10 (7H, m, CH_2), 2.07 (3H, s, CH_3CO), 3.74-3.88 (2H, m, CH_2O), 4.90 (1H, dd, $J_{1,2A}$ 10.4 $J_{1,2B}$ 2.4, CHOAc) and 5.18 (1H, q, $J_{5,6}$ 7.0, =CH); δ_C (67.8 MHz; $CDCl_3$) 12.7 (CH_3, C-2"), 12.9 (CH_3, C-6), 21.1 (CH_3, Ac), 22.5 (CH_3, 2'-Me), 25.9 (CH_2), 28.3 (CH_2), 29.4 (CH_2), 33.0 (CH_2), 34.4 (CH_2), 68.3 (CH_2O), 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%); υ_{max}/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); δ_H (270 MHz; $CDCl_3$) 0.94 (3H, t, $J_{2",1"}$ 7.7, $CH_2\underline{CH_3}$), 1.19 (3H, s, 2'-Me), 1.57 (3H, d, $J_{6,5}$ 7.0, CH_3-C=), 1.53-1.66 (2H, m, CH_2), 1.71-2.21 (8H, m, CH_2), 2.09 (3H, s, CH_3CO), 3.75-3.90 (2H, m, CH_2O), 4.88-4.93 (1H, m, CHOAc) and 5.19 (1H, q, $J_{5,6}$ 7.0,

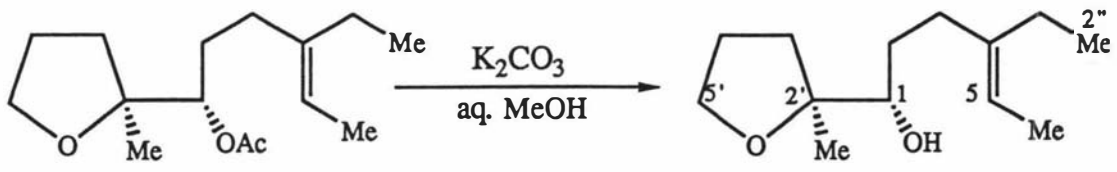
=CH); δ_C (67.8 MHz; $CDCl_3$) 12.8 (CH_3, C-2"), 13.0 (CH_3, C-6), 21.2 (CH_3, Ac), 22.3 (CH_3, 2'-Me), 26.3 (CH_2), 28.5 (CH_2), 28.8 (CH_2), 33.1 (CH_2), 34.7 (CH_2), 67.8 (CH_2O), 77.6 (CHOAc), 83.7 (quat., C-2'), 118.3 (=CH), 140.9 (quat., C-4) and 170.9 (C=O).

(4E, 1R*, 2'S*)-4-Ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol [*erythro*] 348a



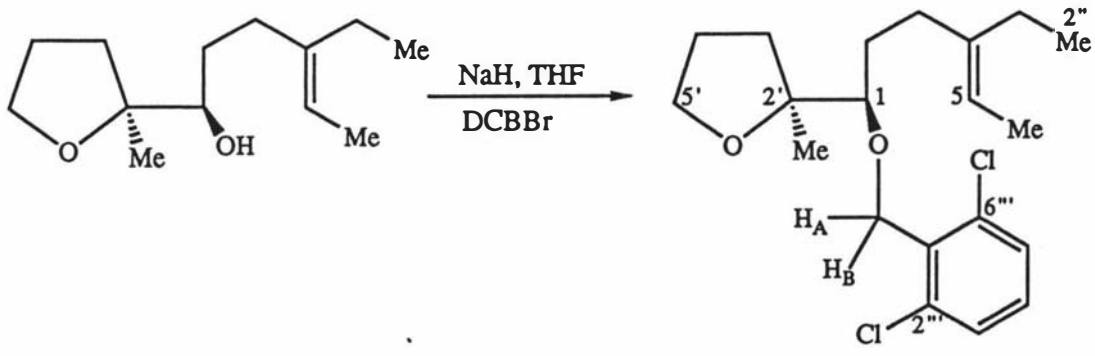
To a solution of (4E, 1R*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-yl acetate **383a** (79.4 mg, 0.312 mmol) in 95% methanol (5 ml) was added potassium carbonate (173 mg, 1.25 mmol). After stirring for 16 h. a saturated solution of sodium chloride (5 ml) was added and extracted with dichloromethane (4 × 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 **348a** as a pale yellow oil (55.2 mg, 83%) (Found: M^+, 212.1776. $C_{13}H_{24}O_2$ requires M, 212.1776.); υ_{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, $CH_2C\underline{H}_3$), 1.12 (3H, s, 2'-Me), 1.28-1.43 (1H, m, CH_2), 1.59 (3H, d, $J_{6,5}$ 6.6, CH_3-C=), 1.44-1.68 (3H, m, CH_2), 1.87-2.12 (5H, m, CH_2), 2.27-2.36 (1H, m, CH_2), 2.38 (1H, s, OH), 3.52 (1H, dd, $J_{1,2A}$ 10.4 $J_{1,2B}$ 2.0, C$\underline{H}$OH), 3.79-3.93 (2H, m, CH_2O) and 5.22 (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), 22.8 (CH_2), 23.0 (CH_3, 2'-Me), 26.3 (CH_2), 30.3 (CH_2), 30.7 (CH_2), 33.6 (CH_2), 67.9 (CH_2O, C-5'), 76.2 (CHO, C-1), 85.8 (quat., C-2'), 118.1 (CH, C-5) and 141.7 (quat., C-4); *m/z* 212 (M^+, 4%), 85 (C_5H_9O, 100), 55 (9) and 43 (26).

(4E, 1S*, 2'S*)-4-Ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol [*threo*] 348b



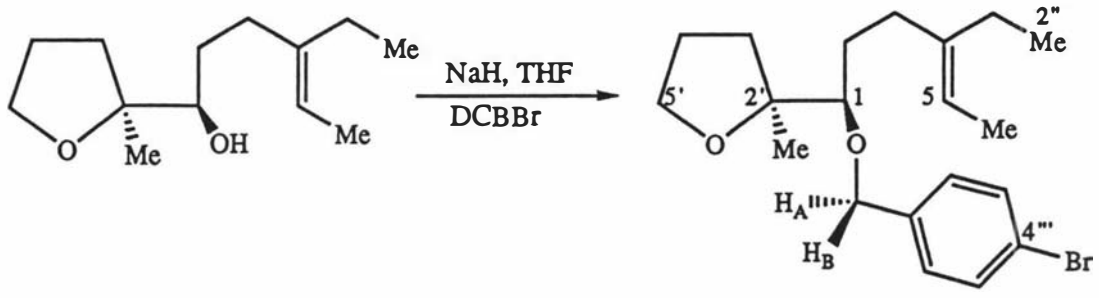
To a solution of (4E, 1S*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-yl acetate **383b** (118 mg 0.464 mmol) in 95% methanol (7 ml) was added potassium carbonate (257 mg, 1.86 mmol). After stirring for 16 h. a saturated solution of sodium chloride (5 ml) was added and extracted with dichloromethane (4 × 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.); υ_{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_2CH_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, CHOH), 3.79 (1H, t, $J_{5'A,4'}$ 7.0, 5'-H_A) 3.86-3.91 (1H, m, 5'-H_B) 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_2O, 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_5H_9O, 100), 55 (9) and 43 (26).

(4E, 1R*, 2'S*)-4-Ethyl-1-(2"',6"'-dichlorobenzyloxy)-1-(2'-methyltetrahydrofur-2'-yl)-4-hexene 390



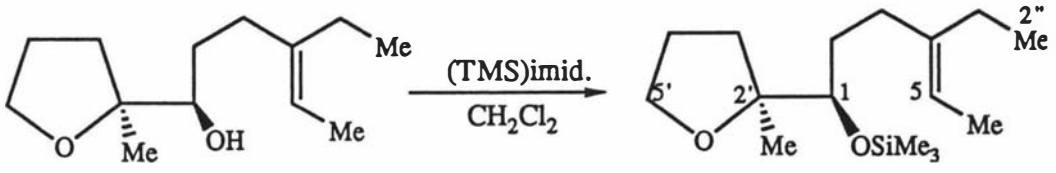
To a solution of (4E ,1R*, 2'S*)-4-ethyl-1-(2'-methyltetrahydro-2'-furyl)-4-hexen-1-ol **348a** (12.8 mg, 60.3 μmol) in dry tetrahydrofuran (0.4 ml) at 0°C was added sodium hydride (2.5 mg, 80% oil dispersion, 83 μmol). After 10 min. 2,6-dichlorobenzyl bromide (15 mg, 63 μmol) was added and the reaction 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. $C_{20}H_{29}O_2{}^{35}Cl_2$ requires M + H, 371.1545.); υ_{max}/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); δ_H (270 MHz; $CDCl_3$) 0.93 (3H, t, $J_{2",1"}$ 7.5, 2"-CH_3), 1.15 (3H, s, 2'-Me), 1.37-1.64 (3H, m, CH_2), 1.56 (3H, d, $J_{6,5}$ 6.8, CH_3C=C), 1.89-2.11 (6H, m, CH_2), 2.28-2.30 (1H, m, CH_2), 3.39 (1H, dd, $J_{1,2A}$ 9.2 $J_{1,2B}$ 2.6, CHO), 3.86 (2H, t, $J_{5',4'}$ 6.8, CH_2O), 4.87 (1H, d, $J_{HA,HB}$ 10.6, $C\underline{H}_AH_BAr$), 5.03 (1H, d, $J_{HB,HA}$ 10.6, $CH_A\underline{H}_BAr$), 5.15 (1H, q, $J_{5,6}$ 6.8, =CH), 7.13-7.19 (1H, m, Ar-H) and 7.26-7.33 (2H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 12.8 (CH_3, C-2"), 13.0 (CH_3, C-6), 22.8 (CH_3, 2'-Me), 23.4 (CH_2), 26.3 (CH_2), 30.7 (CH_2), 33.2 (CH_2), 33.5 (CH_2), 67.5 (CH_2O), 68.8 (OCH_2Ar), 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 - $C_7H_5Cl_2O$, 15), 159 ($C_7H_5{}^{35}Cl_2$, 24), 111 (16), 85 (C_5H_9O, 100) and 43 (16).

(4E, 1R*, 2'S*)-4-Ethyl-1-(4"'-bromobenzyloxy)-1-(2'-methyltetrahydrofur-2'-yl)-4-hexene 391



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. $C_{20}H_{30}O_2{}^{81}Br$ requires M + H, 383.1409.); υ_{max}/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); δ_H (270 MHz; $CDCl_3$) 0.94 (3H, t, $J_{2",1"}$ 7.5, 2"-CH_3), 1.15 (3H, s, 2'-Me), 1.42-1.63 (3H, m, CH_2), 1.57 (3H, d, $J_{6,5}$ 6.6, CH_3), 1.85-2.08 (6H, m, CH_2), 2.19-2.28 (1H, m, CH_2), 3.32 (1H, dd, $J_{1,2A}$ 9.5 $J_{1,2B}$ 2.6, CHO), 3.71-3.87 (2H, m, CH_2O), 4.53 (1H, d, $J_{HA,HB}$ 11.7, CH_AH_BAr), 4.74 (1H, d, $J_{HB,HA}$ 11.7, CH_AH_BAr), 5.15 (1H, q, $J_{5,6}$ 6.6, =CH), 7.22 (2H, d, J 8.4, Ar-H) and 7.45 (2H, d, J 8.4, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 12.8 (CH_3, C-2"), 13.0 (CH_3, C-6), 22.6 (CH_2), 24.1 (CH_3), 26.6 (CH_2), 30.5 (CH_2), 32.7 (CH_2), 33.5 (CH_2), 67.9 (CH_2O, C-5'), 73.9 (CH_2Ar), 85.1 (CH, C-1), 86.3 (quat., C-2'), 118.1 (CH, C-5), 129.7, 131.3 (CH, Ar-H), 121.1 (quat., Ar-Br), 138.5 (quat., Ar-CH_2) and 141.5 (quat., C-4); *m/z* 383 (M + H, 8%), 381 (M + H, 10), 195 (M - C_7H_6OBr, 15), 171 ($C_7H_6{}^{81}Br$, 24), 169 ($C_7H_6{}^{79}Br$, 25) 111 (15), 85 (C_5H_9O, 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. $C_{16}H_{32}O_2Si$ requires M, 284.2172.); υ_{max}/cm^{-1} (film) 2957, 2864 (s, C-H), 1451 (m, C-H), 1369 (m, C-H), 1247 (s, Si-CH_3), 1107 (vs, C-O-C), 863 (s, Si-C) and 838 (vs, Si-CH_3); δ_H (270 MHz; $CDCl_3$) 0.12 (9H, s, $SiMe_3$), 0.96 (3H, t, $J_{2",1"}$ 7.5, CH_3), 1.10 (3H, s, 2'-Me), 1.26-1.62 (3H, m, CH_2), 1.58 (3H, d, $J_{6,5}$ 6.6, CH_3-=), 1.82-2.08 (6H, m, CH_2), 2.17-2.25 (1H, m, CH_2), 3.51 (1H, dd, $J_{1,2A}$ 5.9 $J_{1,2B}$ 3.7, CHOSi), 3.78 (2H, t, $J_{5',4'}$ 6.4, CH_2O) and 5.21 (1H, q, $J_{5,6}$ 6.6, =CH); δ_C (67.8 MHz; $CDCl_3$) 0.80 (CH_3Si), 12.8 (CH_3, C-2"), 13.0 (CH_3, C-6), 22.9 (CH_3, 2'-Me), 26.3 (CH_2), 27.6 (CH_2), 32.0 (CH_2), 33.0 (CH_2), 33.9 (CH_2), 67.5 (CH_2O, 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 - C_5H_9O, 9), 109 (17), 101 (4), 85 (C_5H_9O, 100), 73 ($SiMe_3$, 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); δ_H (270 MHz, $CDCl_3$) 0.53 (6H, q, *J* 7.9, $SiCH_2$), 0.93 (9H, t, *J* 7.9, $SiCH_2CH_3$), 0.97 (3H, t, $J_{2",1"}$ 7.5, CH_3), 1.10 (3H, s, CH_3), 1.20-1.64 (3H, m, CH_2), 1.58 (3H, d, $J_{6,5}$ 6.6, CH_3-=), 1.86-2.06 (6H, m, CH_2), 2.16-2.28 (1H, m, CH_2), 3.53 (1H, m, CHOSi), 3.79-3.84 (2H, m, CH_2O) and 5.18 (1H, q, $J_{5,6}$ 6.6, =CH); δ_C (67.8 MHz; $CDCl_3$) 6.8 ($SiCH_2$), 7.1 ($SiCH_2CH_3$), 12.9 (CH_3, C-2"), 13.0

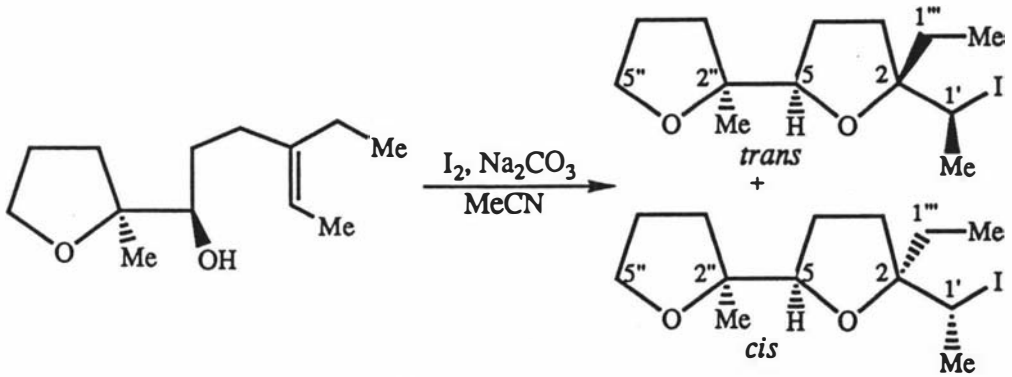
(CH_3, C-6), 22.9 (CH_3, 2'-Me), 26.0 (CH_2), 27.5 (CH_2), 29.7 (CH_2), 32.5 (CH_2), 33.4 (CH_2), 67.4 (CH_2O, C-5'), 78.2 (CHO, C-1), 85.6 (quat., C-2'), 117.5 (CH, C-5) and 142.2 (quat., C-4).

(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); δ_H 0.97 (3H, t, $J_{2'',1''}$ 7.3, CH_3), 1.09 (21H, m, $SiC(CH_3)$, SiCH) 1.20-2.09 (9H, m, CH_2), 1.58 (3H, d, $J_{6,5}$ 6.6, CH_3-=), 1.20-2.09 (9H, m, CH_2), 2.15-2.30 (1H, m, CH_2), 3.70-3.83 (3H, m, CHOSi, CH_2O) and 5.17 (1H, q, $J_{5,6}$ 6.6, =CH); δ_C (67.8 MHz; $CDCl_3$) 12.9 (CH_3, C-2''), 13.0 (CH_3, C-6), 18.1 (quat., ^{t}Bu), 18.2 (CH_3, ^{t}Bu), 22.8 (CH_3, 2'-Me), 25.9 (CH_2), 27.2 (CH_2), 29.6 (CH_2), 33.3 (CH_2), 34.3 (CH_2), 67.2 (CH_2O, 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); δ_H (270 MHz, $CDCl_3$) 0.08 (3H, s, $SiCH_3$), 0.09 (3H, $SiMe_3$), 0.87 (9H, s, ^{t}Bu), 0.96 (3H, t, $J_{2'',1''}$ 7.3, CH_3), 1.11 (3H, s, CH_3), 1.20-2.30 (10H, m, CH_2), 1.58 (3H, d, $J_{6,5}$ 7.0, CH_3-=), 3.51 (1H, dd, $J_{1,2A}$ 5.5 $J_{1,2B}$ 3.3, CHOSi), 3.75-3.82 (2H, m, CH_2O) and 5.18 (1H, q, $J_{5,6}$ 7.0, =CH); δ_C (67.8 MHz; $CDCl_3$) -3.0 ($SiMe_3$), -4.1 ($SiMe_3$), 12.8 (CH_3, C-2''), 13.0 (CH_3, C-6), 18.0 (quat., Si^{t}Bu) 22.7 (CH_3, 2'-Me), 25.7 (CH_2), 26.0 (CH_3, ^{t}Bu), 27.3 (CH_2), 29.7 (CH_2), 32.6 (CH_2), 33.6 (CH_2), 67.3 (CH_2O, 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

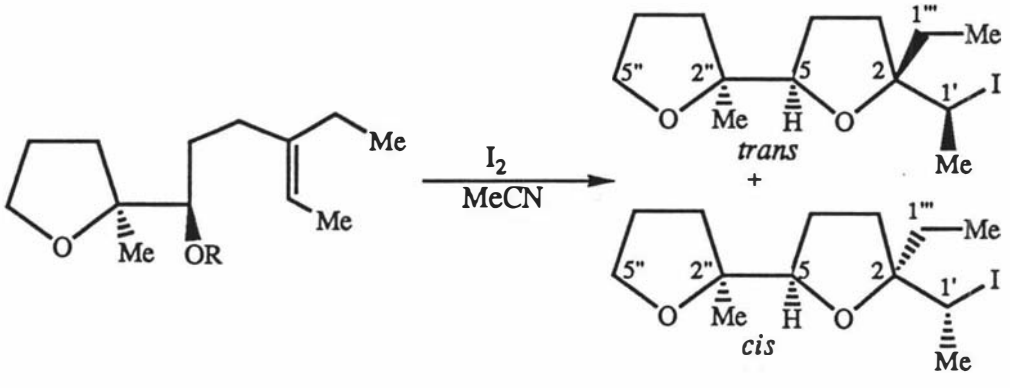


To a solution of (4E, 1R*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol **348a** (17.5 mg, 82.4 μmol) in dry acetonitrile (1 ml) at -43°C under nitrogen was added sodium carbonate (88 mg, 0.830 mmol), followed by iodine (105 mg, 0.414 mmol). After stirring for 15 min. diethyl ether (5 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 × 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. $C_{13}H_{23}O_2I$ requires M, 338.0743.); υ_{max}/cm^{-1} (film) 2966, 2933, 2866 (s, C-H), 1050 (s, C-O), 1458 (m, C-H) and 1370 (m, CH_3); δ_H (270 MHz; $CDCl_3$) 0.92 (3H, t, *J* 7.3, $CH_2\underline{CH_3}$), 1.16 (3H, s, 2"-Me), 1.84 (3H, d, $J_{2',1'}$ 7.3, $\underline{CH_3}CHI$), 1.59-2.07 (10H, m, CH_2), 3.84 (2H, t, $J_{5",4"}$ 6.4, CH_2O), 4.02 (1H, dd, $J_{5,4A}$ 10.6, $J_{5,4B}$ 5.1, CHO) and 4.52 (1H, q, $J_{1',2'}$ 7.3, CHI); δ_C (67.8 MHz; $CDCl_3$) 7.8 (CH_3, C-2'''), 22.5, (CH_3, 2'-Me), 23.9 (CH_3, C-2'), 26.2 (CH_2), 27.9 (CH_2), 28.2 (CH_2), 34.4 (CH_2), 35.2 (CH_2), 40.2 (CH, C-1"), 68.2 (CH_2O), 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 (C_5H_9O, 100) and 43 (28).

(2S*, 5R*, 1'R*, 2"S*)-2-ethyl-2-(1'-iodoethyl)-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.); υ_{max}/cm^{-1} (film) 2966, 2933, 2866 (s, C-H), 1050 (s, C-O), 1458 (m, C-H) and 1370 (m, CH_3); δ_H (270 MHz; $CDCl_3$) 0.90 (3H, t, *J* 7.4, $CH_2C\underline{H}_3$), 1.14 (3H, s, 2"-Me), 1.89 (3H, d, $J_{2',1'}$ 6.9, $C\underline{H}_3CHI$), 1.59-2.10 (10H, m, CH_2), 3.84 (2H, t, $J_{5",4"}$ 6.5, CH_2O), 3.94 (1H, dd, $J_{5,4A}$ 10.3, $J_{5,4B}$ 5.3, CHO) and 4.41 (1H, q, $J_{1',2'}$ 6.9, CHI); δ_C (67.8 MHz; $CDCl_3$) 7.5 (CH_3, C-2'"), 22.6 (CH_3, 2"-Me), 22.9 (CH_3, C-2'), 26.3 (CH_2), 28.5 (CH_2), 31.7 (CH_2), 32.9 (CH_2), 33.8 (CH_2), 35.6 (CH, C-1'), 68.1 (CH_2O), 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 (C_5H_9O, 100) and 43 (28).

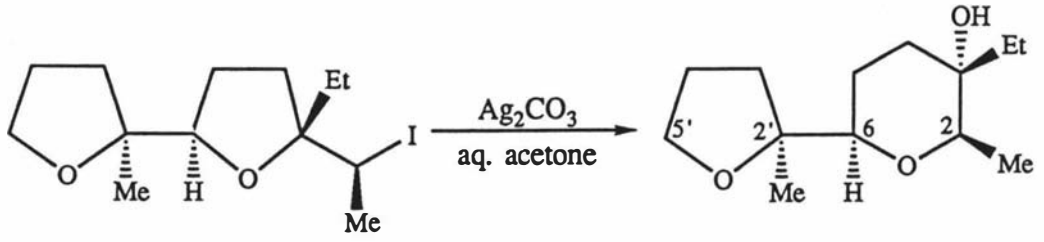
Procedure B



To a solution of each of the silyl protected hydroxyalkenes **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'-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**.

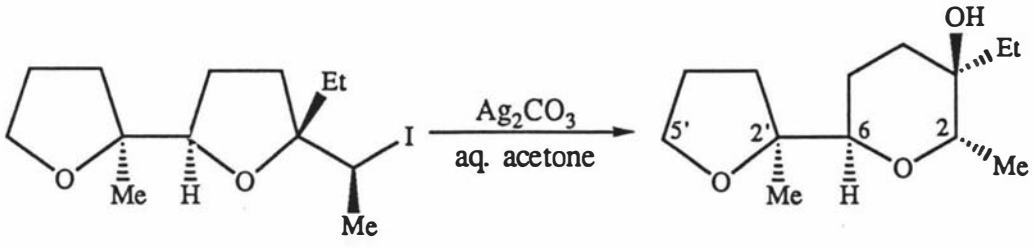
Compound	R	yield	347a/347b
392	$SiMe_3$	75%	1:1
393	$SiEt_3$	46%	1:1
394	Si^iPr_3	47%	1:1
395	Si^tBuMe_2	27%	1:1

(2R*, 3S*, 6R*, 2'S*)-3-Ethyl-3-hydroxy-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran 384



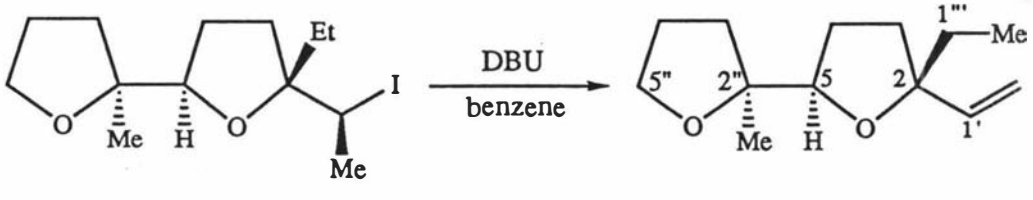
To a solution of (2R*, 5R*, 1'S*, 2"S*)-2-ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofuran **347a** (6.0 mg, 18 μmol) in acetone (0.3 ml) were added silver carbonate (5.0 mg, 18 μmol) and distilled water (4 drops). After stirring for 2 h. the reaction mixture was filtered through 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. $C_{13}H_{24}O_3$ requires M, 228.1725.); υ_{max}/cm^{-1} (film) 3438 (s, OH), 2962, 2863 (s, CH_3), 1100 (s, C-O) and 1452 (s, CH_3); δ_H (270 MHz; $CDCl_3$) 0.90 (3H, t, $J_{2",1"}$ 7.5, $CH_2\underline{CH_3}$), 1.11 (3H, d, $J_{2\text{-Me},2}$ 6.6, 2-Me), 1.14 (3H, s, 2'-Me), 1.16-2.10 (10H, m, CH_2), 3.25 (1H, dd, $J_{6,5A}$ 5.3, $J_{6,5B}$ 11.0, CHO), 3.35 (1H, q, $J_{2,2\text{-Me}}$ 6.6, CHO) and 3.75-3.88 (2H, m, CH_2O); δ_C (67.8 MHz; $CDCl_3$) 6.65 (CH_3, C-2"), 14.0 (CH_3, 2-Me), 22.3 (CH_3, 2'-Me), 22.5 (CH_2), 24.6 (CH_2), 26.2 (CH_2), 33.9 (CH_2), 34.6 (CH_2), 68.3 (CH_2O), 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 (C_5H_9O, 100) and 43 (16).

(2S*, 3R*, 6R*, 2'S*)-3-Ethyl-3-hydroxy-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran 323



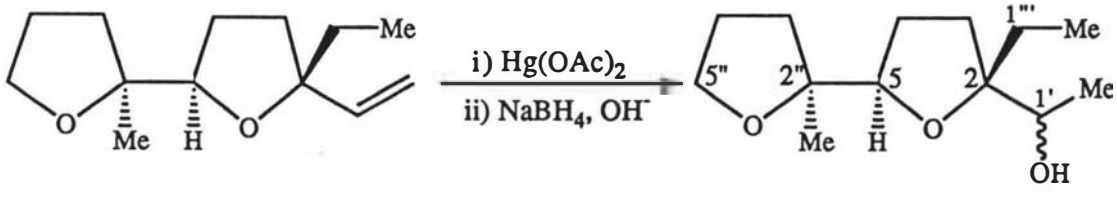
To a solution of (2S*, 5R*, 1'R*, 2"S*)-2-ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofuran **347b** (12.9 mg, 38 μmol) in acetone (0.3 ml) were added silver carbonate (12.7 mg, 46 μmol) and distilled water (5 drops). After stirring for 3 h. the reaction mixture was filtered through 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. $C_{13}H_{25}O_3$ requires M + H, 229.1804.); υ_{max}/cm^{-1} (film) 3432 (s, OH), 2966, 2867 (s, CH_3), 1457 (m, C-H), 1371 (m, C-H), 1102 (s, C-O) and 1046 (s, C-OH); δ_H (270 MHz; $CDCl_3$) 0.92 (3H, t, $J_{2",1"}$ 7.5, CH_2CH_3), 1.24 (3H, d, $J_{2\text{-}Me,2}$ 6.7, 2-Me), 1.16 (3H, s, 2'-Me), 1.42-1.95 (10H, m, CH_2), 3.46 (1H, dd, $J_{6,5A}$ 3.5, $J_{6,5B}$ 9.2, CHO) and 3.75-3.89 (3H, m, CH_2O, 2-CHO); δ_C (67.8 MHz; $CDCl_3$) 7.0 (CH_3, C-2"), 13.0 (CH_3, 2-Me), 21.0 (CH_3, 2'-Me), 22.1 (CH_2), 22.8 (CH_2), 25.8 (CH_2), 29.1 (CH_2), 35.5 (CH_2), 68.2 (CH_2O), 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"-methyltetrahydrofur-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, 211.1707. $C_{13}H_{23}O_2$ requires M + H, 211.1698.); υ_{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_2CH_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_2O), 5.05 (1H, dd, $J_{2'A,1'}$ 10.6 $J_{2'A,2'B}$ 1.8, 2'-H_A), 5.17 (1H, dd, $J_{2'B,1'}$ 17.2 $J_{2'B,2'A}$ 1.8, 2'-H_B) and 5.78 (1H, dd, $J_{1',2'B}$ 17.8 $J_{1',2'A}$ 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_5H_9O, 100).

(2R*, 5R*, 1'RS, 1"S*)-2-Ethyl-2-(1-hydroxyethyl)-5-(2'-methyltetrahydrofur-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"-methyltetrahydrofur-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: (CI, 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,

$CH_2C\underline{H}_3$), 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, C$\underline{H}$OH) 3.82-3.89 (2H, m, CH_2O) and 3.97 (1H, dd, $J_{5,4A}$ 10.6, $J_{5,4B}$ 5.1, CHO); δ_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_2O, 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_5H_9O, 100).

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