The Bisspiroketal Moiety of *epi*-17-Deoxy-(O-8)-salinomycin.

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

Doctor of Philosophy

at Massey University.

Geoffrey Martyn Williams.

November 1991

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To my family for their
support and patience.

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Abstract.

The synthesis of 2-(3,4-epoxy-3-methylbutan-1-yl)-1,7-dioxaspiro[5.5]undec-4-ene **188** is described, the key step in it's formation being an addition of the lithium acetylide derivative of 5-*tert*-butyldiphenylsilyloxy-2-methyl-2-trimethylsilyloxy-7-octyn-1-*p*-toluenesulphonate **182** to δ-valerolactone. The epoxide **188** was then converted to the hydroxy spiroketal 4-(1,7-dioxaspiro[5.5]undec-4-en-2-yl)-2-methyl-2-butanol **149** which underwent a Barton-type oxidative cyclisation to afford both the *cis*- and *trans*-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes **192** and **152**. The ring system of this latter compound is analogous to the unsaturated bisspiroketal present in the polyether antibiotic *epi*-17-deoxy-(O-8)-salinomycin **8**.

Subsequently the route was modified to afford the *trans*- and *cis*-(2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-2-yl)methanols **211-214**, since it was expected this terminal hydroxyl group would provide a 'handle' by which these molecules could be further elaborated. This required conversion of the epoxide **188** to 4-(1,7-dioxaspiro[5.5]undec-4-en-2-yl)-1-iodo-2-methyl-2-butanol **200**, which was followed by a Barton-type oxidative cyclisation, to give the *cis*- and *trans*-2-iodomethyl-2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes **201-204**, which were then converted to the alcohols **211-214**.

The techniques used to construct these relatively simple bisspiroketal analogues were then applied to an enantioselective synthesis of the bisspiroketal portion of *epi*-17-deoxy-(O-8)-salinomycin. The two key intermediates required for this were (1'*S*, 3*R*, 5*S*, 6*S*)-(+)-6-[1'-(*tert*-butyldiphenylsilyloxymethyl)propyl]-3,5-dimethyl-tetrahydropyran-2-one **84** and (5*R*, 2*S*)- and (5*S*, 2*S*)-2-methyl-2,5-bis(trimethylsilyloxy)-7-octyn-1-*p*-toluenesulphonate **231**. The lactone **84** was prepared, using Evans' directed aldol methodology, from (4*R*, 5*S*)-(+)-4-methyl-3-(1'-oxobutyl)-5-phenyloxazolidin-2-one **219** and (*S*)-(+)-2,4-dimethyl-4-pentenal **218**. The acetylene **231** was prepared from levulinic acid **174**, and the procedure incorporated a resolution step which enabled the 2*S* configuration of **231** to be introduced. The lactone **84** and the the lithium acetylide derivative of acetylene **231** were combined and subsequently converted to the (1"*S*, 2*S*, 2'*S*, 6'*R*, 8'*S*, 9'*S*, 11'*R*)-(-)- and (1"*S*, 2*S*, 2'*R*, 6'*R*, 8'*S*, 9'*S*, 11'*R*)-(+)-4-{8-[1-(*tert*-butyldiphenylsilyloxymethyl)propyl]-9,11-dimethyl-1,7-dioxaspiro[5.5]undec-4-en-2-yl}-1-iodo-2-methyl-2-butanols **245** and **246**. These hydroxy spiroketals were transformed, again using the Barton-type oxidative cyclisation methodology, to the *cis*-(1'*S*, 2*S*, 5*R*, 7*S*, 9*S*, 10*S*, 12*R*)-(-)- and the *trans*-(1'*S*, 2*S*, 5*S*, 7*S*, 9*S*, 10*S*, 12*R*)-(-)-9-[1-(*tert*-butyldiphenylsilyloxymethyl)propyl]-2-iodomethyl-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **248** and **247**, the latter of which resembles precisely the corresponding portion of *epi*-17-deoxy-(O-8)-salinomycin. In addition, the termini of the bisspiroketal **247** are selectively functionalised, which will allow further elaboration to the entire natural product **8**.

The synthesis of the *cis*- and *trans*-2,2-dimethyl-15-hydroxy-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes **156** and **159**, and of *cis*-2,2-dimethyl-13-hydroxy-1,6,8-trioxadispiro[4.1.5.3]pentadec-14-ene **268** is described. These were formed firstly by allylic bromination of the *cis*- and *trans*-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes **192** and **152** to give the *cis*- and *trans*-15-bromo-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes **262** and **265**, and *cis*-13-bromo-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-14-ene **261**. These bromides were then displaced by an oxygen nucleophile to afford the alcohols **268**, **156**, **159**, a procedure which involved both S_N2 and *anti*-S_N2' processes.

Contents.

Abbreviations.

AIBN	=	2,2'-azobisisobutyronitrile
ax	=	axial
Bzl	=	benzyl
cat.	=	catalytic
COSY	=	correlation spectroscopy
CSA	=	camphorsulphonic acid
DDQ	=	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	=	dihydropyranyl
DIBAL	=	diisobutylaluminium hydride
DMAP	=	4-dimethylaminopyridine
DMF	=	*N, N*-dimethylformamide
DMSO	=	dimethylsulphoxide
eq	=	equatorial
equiv.	=	equivalent
HETCOR	=	heteronuclear correlation spectroscopy
imid	=	imidazole
MCPBA	=	*meta*-chloroperoxybenzoic acid
Ms	=	methanesulphonyl
NBS	=	*N*-bromosuccinimide
NCS	=	*N*-chlorosuccinimide
NMO	=	*N*-methylmorpholine-*N*-oxide
nmr	=	nuclear magnetic resonance
PCC	=	pyridinium chlorochromate
PPTS	=	pyridinium *p*-toluenesulphonate
Py	=	pyridine
RT	=	room temperature
Tf	=	trifluoromethanesulphonyl
TFA	=	trifluoroacetic acid
TFAA	=	trifluoroacetic anhydride
THF	=	tetrahydrofuran
THP	=	tetrahydropyranyl
tlc	=	thin layer chromatography
TMS	=	trimethylsilyl
Ts	=	*p*-toluenesulphonyl
TSA	=	*p*-toluenesulphonic acid

Chapter 1

Introduction

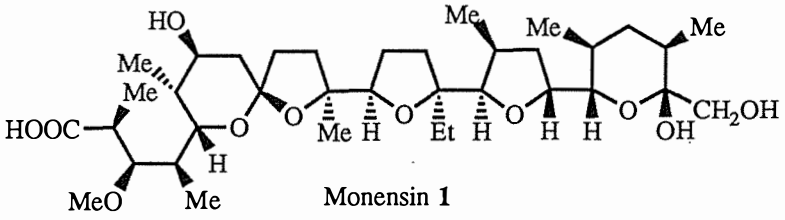
1.1 Polyether Antibiotics.

The class of compounds known as the polyether antibiotics are all microbial in origin, generally being isolated as fermentation products from different strains of the *Streptomyces* genus of microorganism. Representative members of the class appear in figures 1 and 2 and an immediately apparent structural feature is the numerous oxygen atoms distributed along the carbon chain, often as cyclic ethers. This gives rise to a distinguishing chemical characteristic which is the ability to form neutral, lipid soluble complexes with one of a variety of cations. These associations are stabilised by ion induced dipole interactions and a terminal carboxylate often serves to secure the resulting cyclic structure, which presents an exterior array of alkyl groups, thereby imparting solubility in an hydrophobic environment. The ability to extract ions into an organic solvent has been noted since the first isolation[1,2] of the polyethers, and places them in the ever expanding family of ionophores - a group that includes the crown ethers and cryptates. However, the polyethers, being acidic, yield neutral salt complexes and are thus distinguished from these other ionophores which are neutral structures affording charged ion complexes.

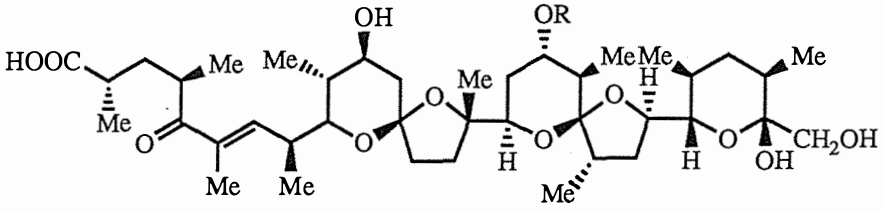
Within the polyether class there exists a certain level of affinity for monovalent ions over divalents, or the reverse, and Westley[3] used this distinction as the basis for a classification system. This resulted in division of the polyethers into four groups, the first of which contains the monovalent and monovalent glycoside polyethers, reflecting an affinity for the transport of monovalent cations, and include monensin **1** and the glycosylated dianemycin **2**. Similarly, the second group, termed the divalents and divalent glycosides, contains those members that transport divalent cations more efficiently, and include lasalocid A **3** and antibiotic 6016 **4**. The remaining classes distinguish those polyethers which possess pyrrole ethers, such as antibiotic A23187 **5**, and those with acyl tetronic acid functionalities.

Historical interest in the polyether antibiotics since their discovery during the 1950s,[1,2] has centred on their inherent pharmacological activity. The strong ion binding and lipophilic transportation properties of the compounds results in disruption of the permeability barriers to ion transport across biological membranes,[3,4] a consequence of which is that they often exhibit potent antimicrobial activity, usually against gram positive bacteria and mycobacteria and some also show significant activity against phytopathogenic bacteria and fungi.[5] Although possessing notable antimicrobial properties *in vitro*, the intrinsic parenteral toxicity of the compounds *in vivo* has precluded their use as clinical antibiotics. However,

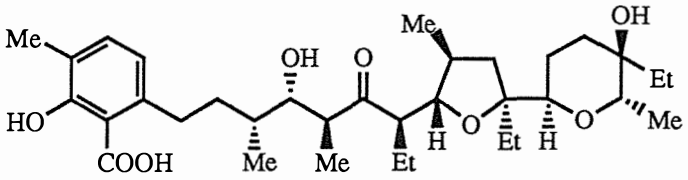
Figure 1



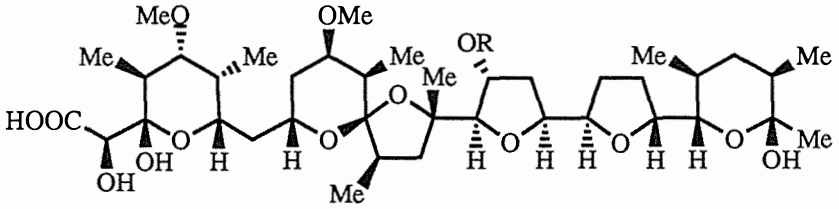
Monensin **1**



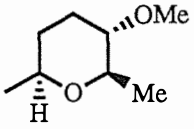
Dianemycin **2** : R=**6**



Lasalocid A **3**



Antibiotic 6016 **4** : R=**6**



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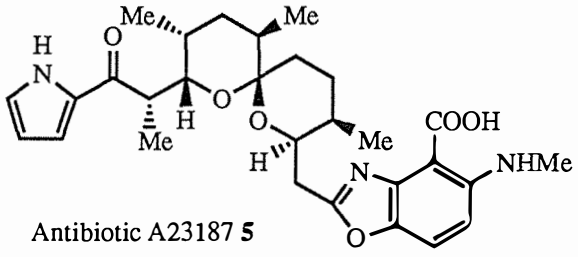


Antibiotic A23187 **5**

certain members, particularly lasalocid A **3**, monensin **1** and salinomycin **7**, have enjoyed considerable commercial success in veterinary medicine - primarily as coccidiostats in poultry[6], due to a fairly specific toxicity against various coccidial parasites of the intestinal tract combined with minimal absorption of the drug by the host, and as growth promotants in ruminant livestock , since a claimed[7] increase in feed efficiency has been observed after administration of the drugs.

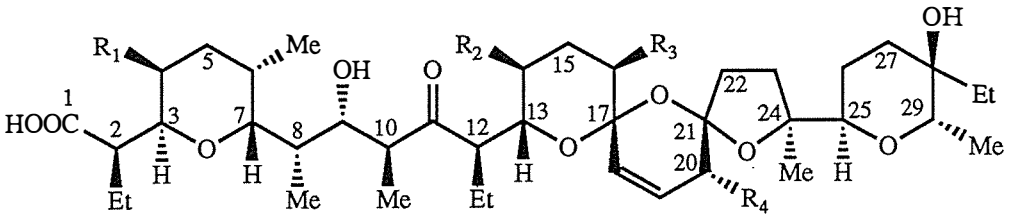
Polyether Antibiotics Containing a Bisspiroketal Ring System.

In 1973 salinomycin **7**, isolated[8,9] from the fermentation medium of *Streptomyces albus*, was found to exhibit marked activity against mycobacteria and fungi in addition to the characteristic antibacterial and anticoccidial properties. X-ray crystallographic analysis of the *p*-iodophenacyl ester derivative of this polyether by Kinashi *et al* [8] in 1973 revealed the presence of a then unique unsaturated tricyclic bisspiroketal ring system. Using the same *S. albus* culture and a different culture medium, Westley *et al* [10] later isolated two C-17 epimers of deoxy-(O-8)-salinomycin. The predominant isomer, *epi*-17-deoxy-(O-8)-salinomycin **8**, the structure of which was confirmed by X-ray crystallographic analysis[10] of the free acid, was found to be present at much greater levels than the corresponding deoxy-(O-8)-salinomycin **9**. Narasin A (or simply 'narasin') **10** was isolated[11] from a culture of *S. aurefaciens* under similar conditions, and was confirmed as being 4-methyl-salinomycin after mass spectral comparison[12] with salinomycin itself. The methyl group was later established to be β on the tetrahydropyran ring by ^{13}C nmr analysis.[13]

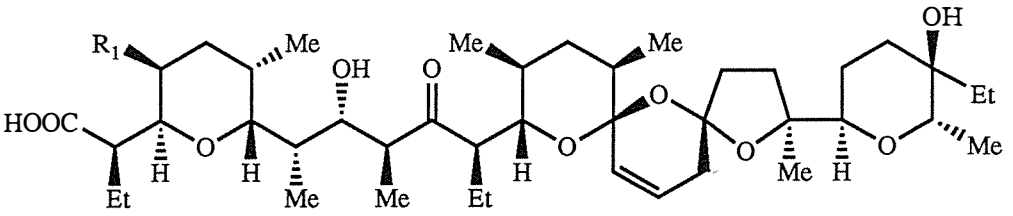
Since then further bisspiroketal containing polyether antibiotics have been reported. Noboritomycins A **11** and B **12** were isolated as fermentation products of the strain *Streptomyces noboritoensis* by Keller-Juslén *et al*,[14] and X-ray crystallographic analysis of the silver salt complexes of **11** and **12** established the presence of this key structural feature. A species of *Dactylosporangium* yielded antibiotic CP44,161[15] **13**, and more recently Westley *et al* [16] reported the first bisspiroketal-containing halogenated polyether X-14766A **14**. The list of structural analogues continues to grow with the addition of such members as *epi*-17-deoxy-(O-8)-narasin **15**,[17] deoxy-(O-8)-narasin **16**[17] and narasins B **17** and D **18**.[18]

With the attributes of structural complexity and unique structural features, this class of compounds will continue to provide a challenge to the synthetic chemist in the quest to design and implement new synthetic strategies and methodologies.

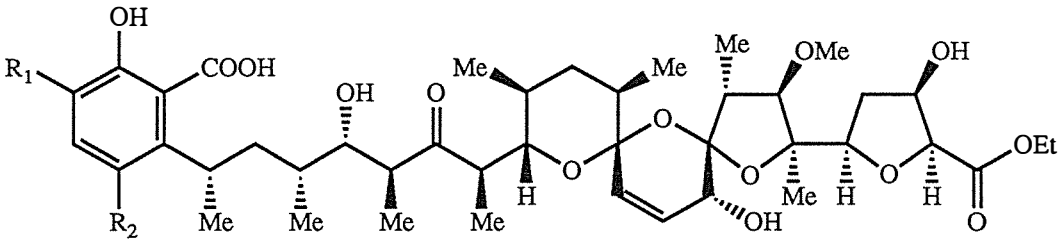
Figure 2



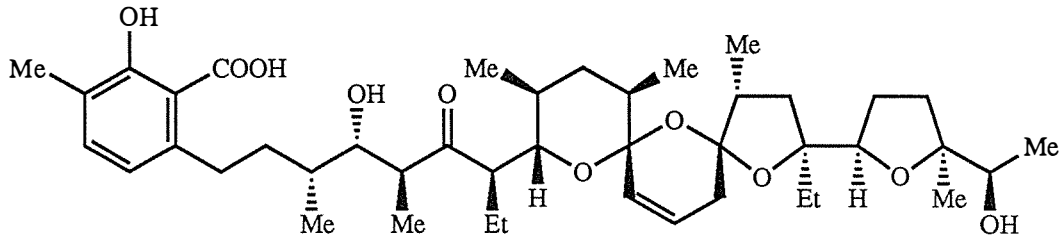
Salinomycin **7**: R_1=H, R_2=R_3=Me, R_4=OH
Deoxy-(O-8)-salinomycin **9**: R_1=H, R_2=R_3=Me, R_4=H
Narasin A **10**: R_1=R_2=R_3=Me, R_4=OH
Deoxy-(O-8)-narasin **16**: R_1=R_2=R_3=Me, R_2=H
Narasin B **17**: R_1=R_2=Me, R_3=Et, R_4=OH
Narasin D **18**: R_1=R_3=Me, R_2=Et, R_4=OH



epi-17-Deoxy-(O-8)-salinomycin **8**: R_1=H
epi-17-Deoxy-(O-8)-narasin **15**: R_1=Me



Noboritomycin A **11**: R_1=Me, R_2=H
Noboritomycin B **12**: R_1=Et, R_2=H
Antiobiotic X-14766A **14**: R_1=Me, R_2=Cl

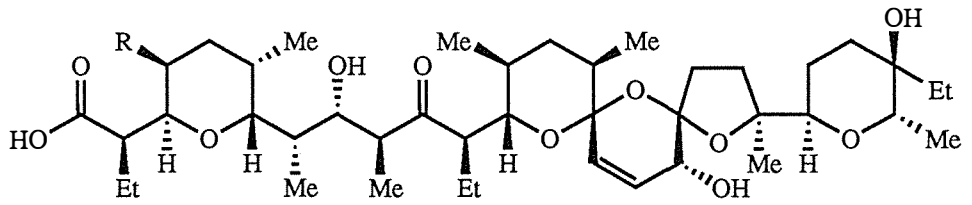


Antibiotic CP44,161 **13**

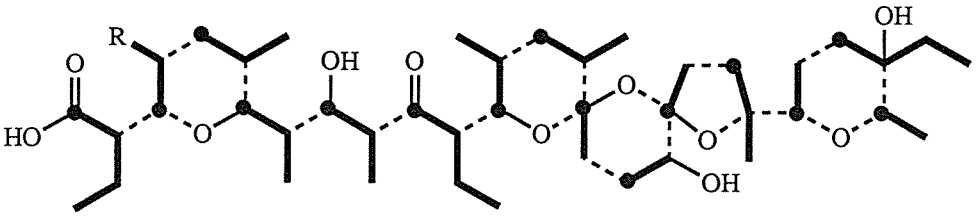
1.2 Biosynthesis of Polyether Antibiotics.

Initial biosynthetic studies into members of the polyether class of compounds indicated that they were constructed predominantly from combinations of acetate, propionate and butyrate units in a manner analogous to the classical biosynthesis of fatty acids.[19] The investigation by Dorman *et al* [20] into the biogenesis of narasin **10**, in which cultures of *S. aureofacies* were grown in media containing ^{13}C labelled precursors and the enrichment pattern in the ^{13}C nmr spectra of the products observed, indicated that five acetate, seven propionate and three butyrate units were required for it s construction (figure 3). However the acetate labelled experiments were inconclusive, probably due to isotope dilution factors.

Figure 3



Salinomycin **7**: R=H
Narasin **10**: R=Me



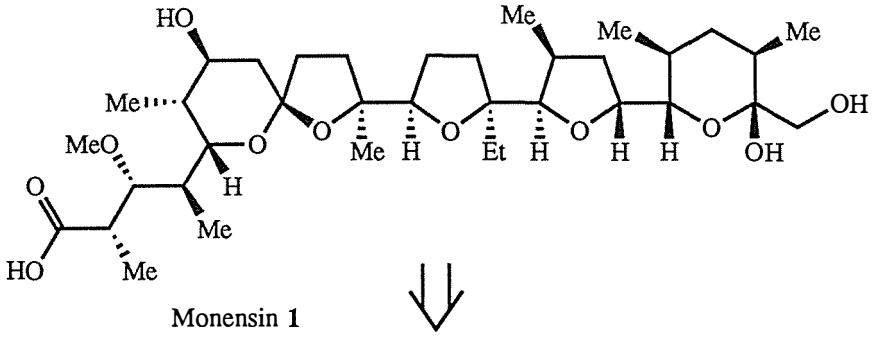
Salinomycin: R=H : $B_{15}A_{14}P_{13}P_{12}P_{11}B_{10}P_9P_8A_7A_6A_5\mathbf{P_4A_3B_2A_1}$
Narasin: R=Me : $B_{15}P_{14}P_{13}P_{12}P_{11}B_{10}P_9P_8A_7A_6A_5\mathbf{P_4A_3B_2A_1}$

A=Acetate; P=Propionate; B=Butyrate.

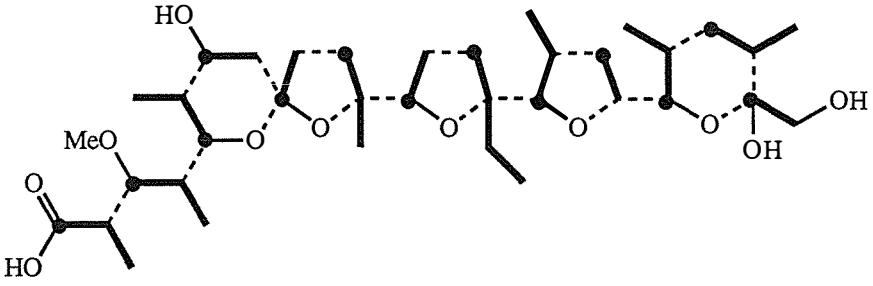
However, subsequent studies by Seto *et al* [21] into the biosynthesis of salinomycin **7**, using doubly labelled [1,2-^{13}C]-acetate and [1,2-^{13}C]-propionate, confirmed that six acetate and six propionate units were required. By simply replacing one of these acetates with a propionate gives rise to the corresponding 4-methyl salinomycin (ie narasin **10**), hence it could be directly inferred that narasin was indeed constructed from five acetate and seven propionate units.

The structural similarities existing within the polyether class of metabolites led Cane, Celmer and Westley[22] to propose a useful grouping system based on these regularities, and also to present a plausible model for the biosynthesis of the compounds. Some members of the monovalent class of antibiotics, for example monesin **1** and dianemycin **2**, were observed to possess identical tetrahydropyran rings at the termini opposite to those bearing the carboxylate functions and that biogenesis of this ring would require acetate, propionate, propionate and acetate units, or APPA, as ordered away from the carboxylate (figure 4). Other members of the class, including the salinomycin and narasin series, require propionate, acetate, butyrate and acetate units for biogenesis of the corresponding terminal portion, and hence are termed PABA polyethers (figure 3).

Figure 4



Monensin **1**

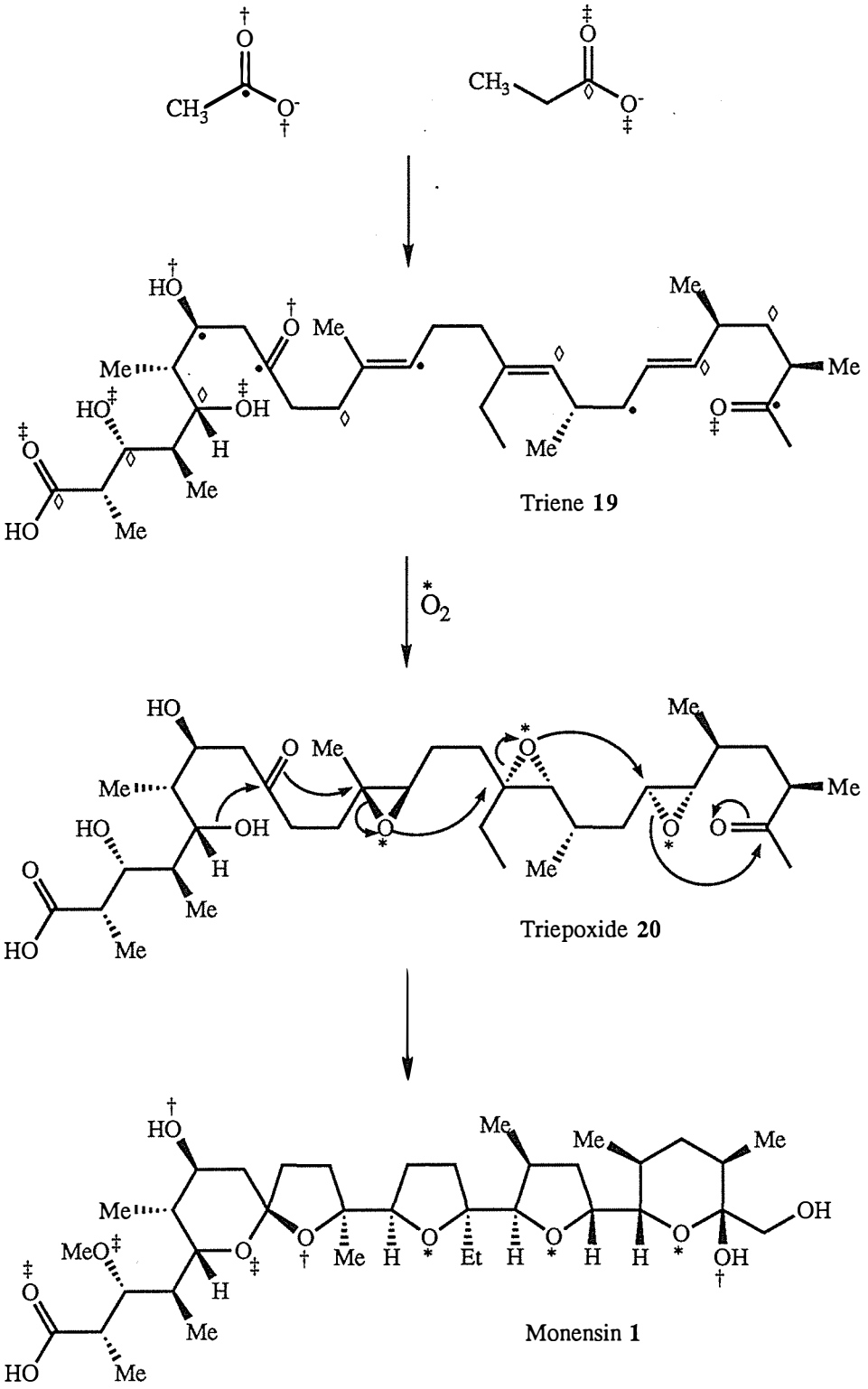


Monensin : $P_{13}P_{12}P_{11}A_{10}A_9P_8A_7B_6P_5A_4P_3P_2A_1$

A=Acetate; P=Propionate; B=Butyrate.

It was proposed that these acetate, butyrate and propionate units combine *in vivo* to give rise to suitably functionalised polyenes which, after selective microbial oxidation, undergo cascade type cyclisations to the polyethers. No such olefin intermediates have yet been isolated but the hypothesis has been tentatively supported in the case of lasalocid A **3**

Scheme 1

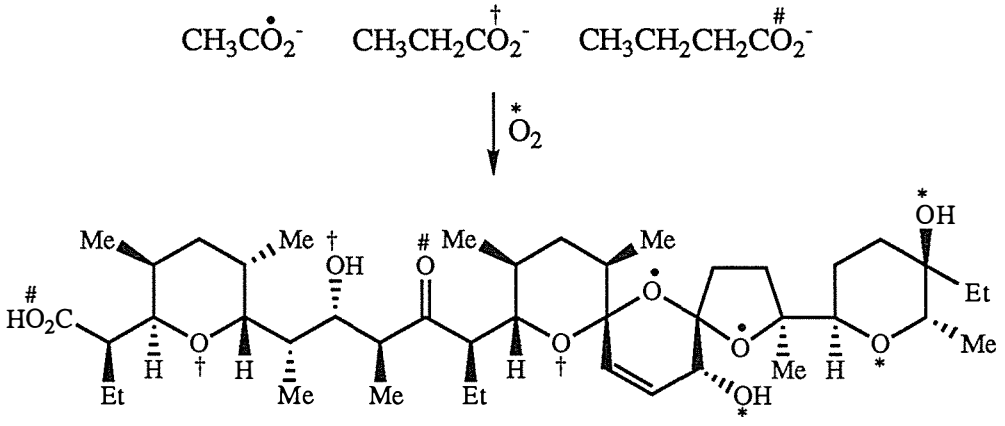


and isolasalocid A using [1-^{13}C,$^{18}O_2$]-acetate, -propionate and -butyrate labelling techniques.[23]

Similar studies on monensin **1**,[24-26] which was the first polyether to be biosynthesised under an atmosphere containing $^{18}O_2$ (scheme 1), showed incorporation of this isotope into three of the ether functions, an observation that could be rationalised in terms of oxidation of a triene precursor **19** to the triepoxide **20** followed by an intramolecular cyclisation to **1** - further reinforcing the Cane-Celmer-Westley hypothesis.[22] Extension of this idea to the biosynthesis of the salinomycin series of polyethers led to a proposed assembly (scheme 2) of acetate, propionate and butyrate into a putative polyene **21**. After selective epoxidation to the diepoxide **22**, a stereocontrolled cyclisation occurs to give the corresponding natural products.

By extending the original investigations of Dorman,[20] Robinson *et al* [27] sought to define the origins of the oxygen atoms of narasin **10** by studying the incorporation of [1-^{13}C,$^{18}O_2$]-acetate, -propionate and -butyrate and $^{18}O_2$, into this polyether by cultures of *S. aurefaciens*. The results (summarised in equation 1) are consistent with the polyene diepoxide model (depicted in scheme 2), and also show that the allylic hydroxyl group is in fact derived from atmospheric oxygen.

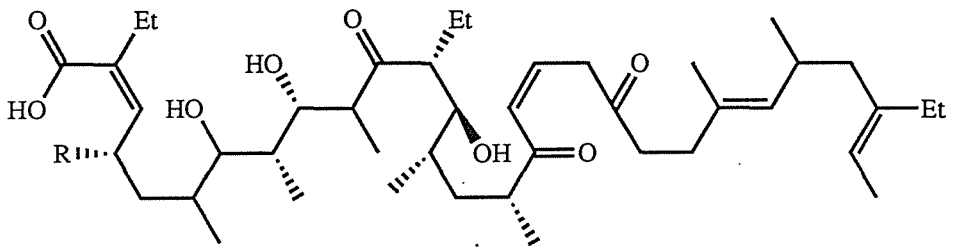
Equation 1



Narasin A **10**

Sih *et al* [28] have synthesised the putative triene precursor **19** for monensin, but a recent elegant study by Robinson *et al* [29] sought to use this to obtain more direct evidence for the Westley model by synthesising suitably labelled analogues **23** and **24** of the biosynthetic triene precursor **19** to monensin (scheme 3) then conducting fermentation experiments with cultures of *S. cinnamonensis*. However, no significant incorporation of

Scheme 2



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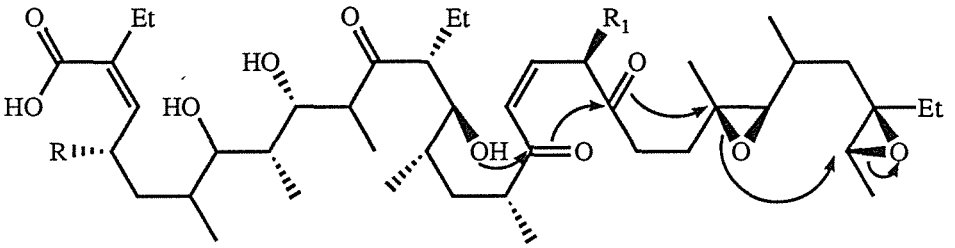

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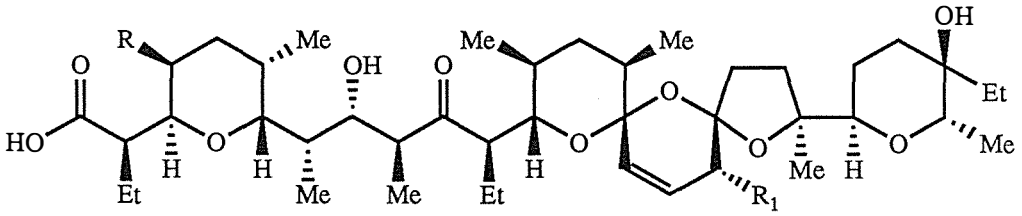
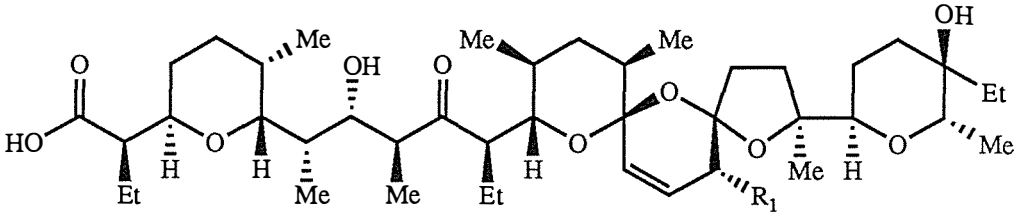
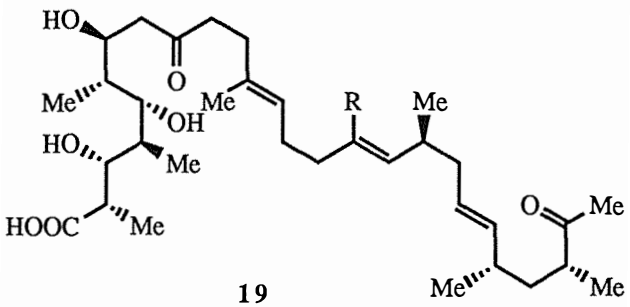


Salinomycin **7**: R=H, R_1=OH
Deoxy-(O-8)-salinomycin **9**: R=R_1=H
Narasin **10**: R=Me, R_1=OH



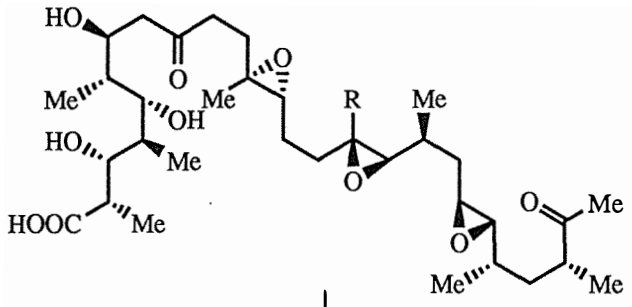
epi-17-Deoxy-(O-8)-salinomycin **8**: R_1=H

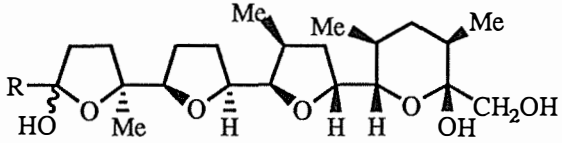
Scheme 3

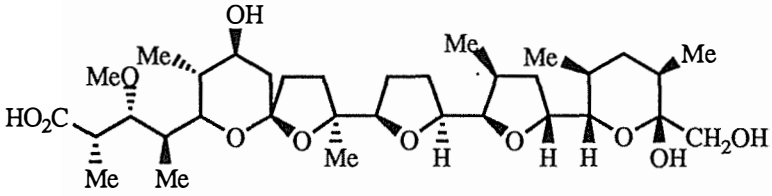


19

S. cinnamonensis

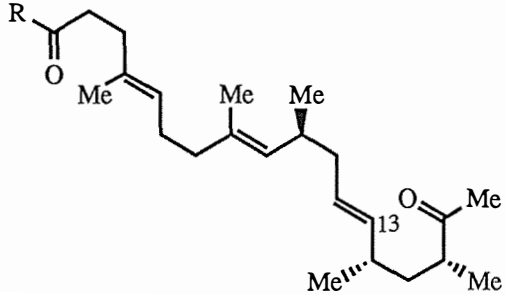






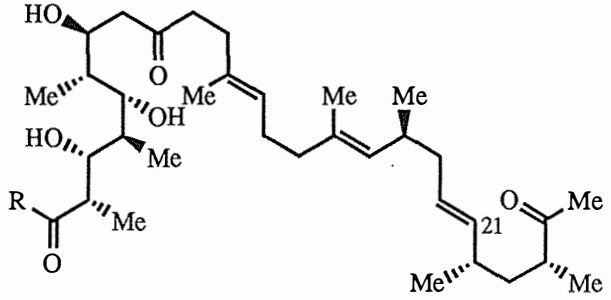
Monensin **1**

S. cinnamonensis



23: R = $C_7H_{15}CONHCH_2CH_2S$

S. cinnamonensis



24: R = $C_7H_{15}CONHCH_2CH_2S$

the trienes **23** and **24** was observed but this was attributed to the inability of the compounds to cross the cell membrane of the microorganism, thereby accessing the biosynthetic pathways. Thus the Cane-Celmer-Westley model, though supported by circumstantial evidence, remains to be conclusively proved.

1.3 Total Syntheses of Salinomycin and Narasin by Kishi *et al.*[30]

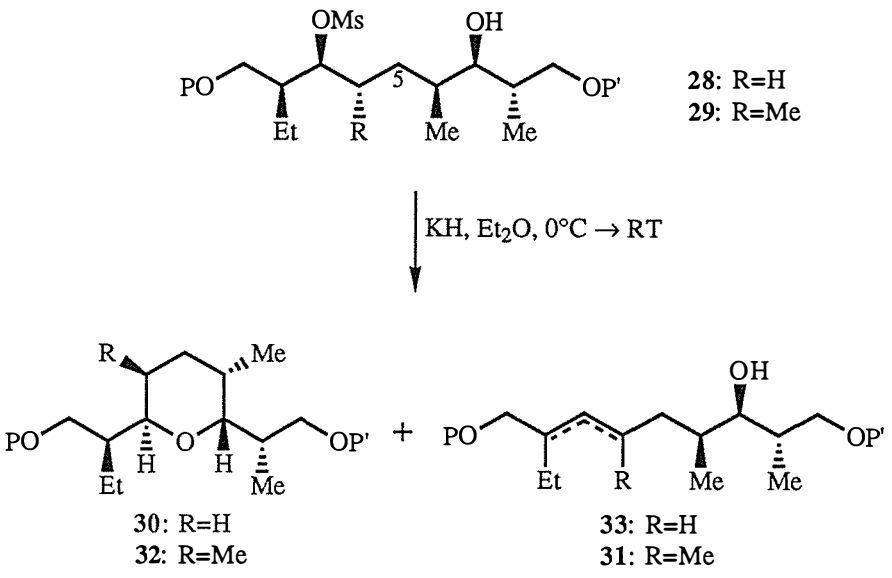
In 1981 Kishi *et al* [30] reported remarkable total syntheses of the polyether antibiotics salinomycin **7** and narasin **10.**

The first disconnection of their retrosynthetic analysis was the bond formed by the stereospecific crossed aldol reaction (step a, scheme 4) which gives rise to the precursors, the tetrahydropyrans **25**, **26** and the bisspiroketal **27**, conventionally termed the left hand and right hand fragments respectively. The efficacy of this step had earlier been well established by Kishi during the synthesis of lasalocid A **3**.[31-33]

The Left Hand Fragments.

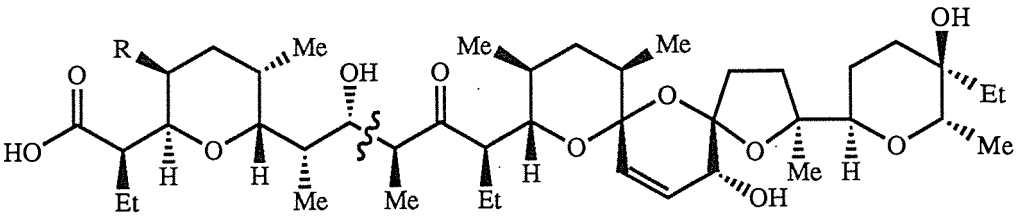
It was proposed that the so called left hand portion of salinomycin **7** (and narasin **10**) could be constructed using a base catalysed cyclisation of suitably functionalised mesylates **28** and **29** (scheme 5).

Scheme 5



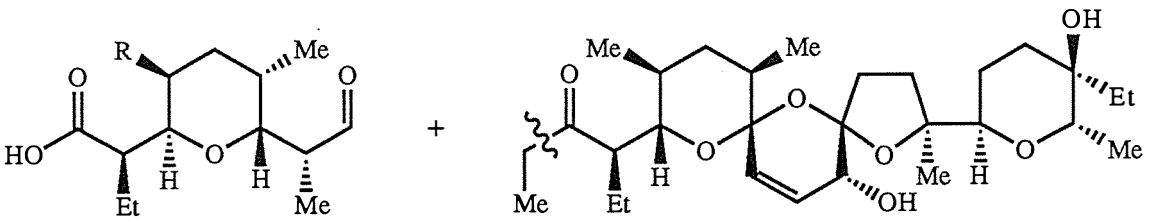
P=$Me_3CC(O)$, P'=$MeOCH_2$

Scheme 4



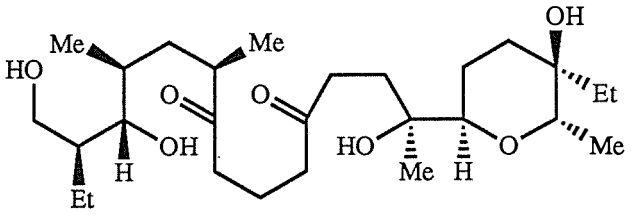
Salinomycin **7**: R=H
Narasin **10**: R=Me

a

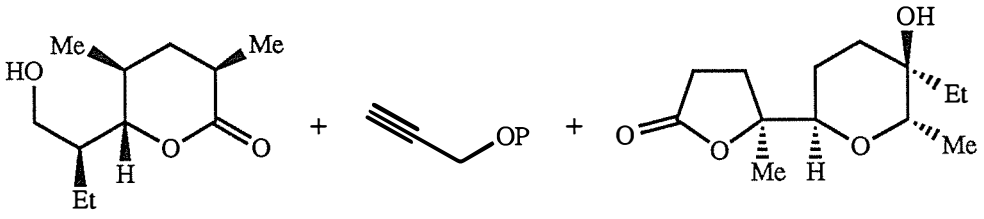


25: R=H
26: R=Me

27



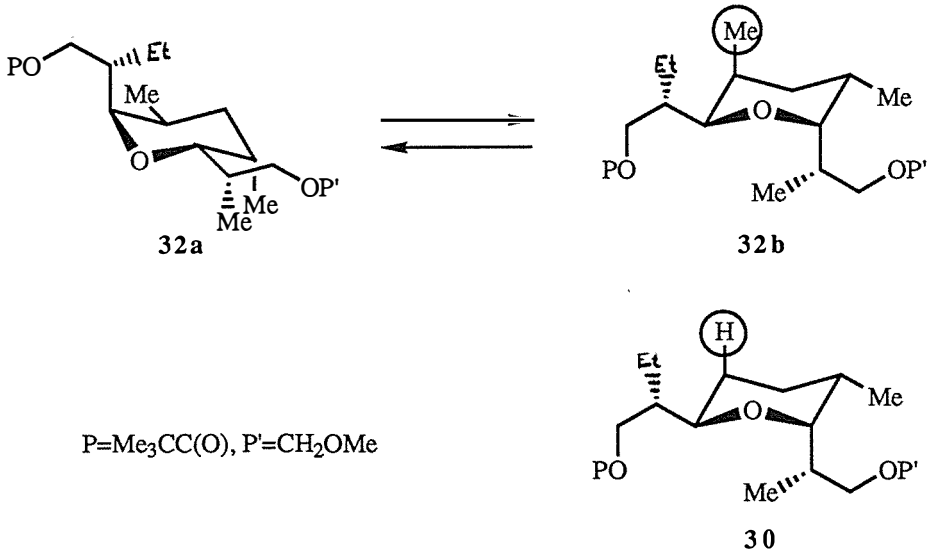
67



68 **69** **70**

For the salinomycin case **28**, cyclisation to the desired tetrahydropyran **30** was readily effected by treatment of the monomesylate **28** with hydride. But when cyclisation of the corresponding narasin precursor **29** was attempted the products were almost exclusively a mixture of the olefins **31**, not the required tetrahydropyran **32**, despite the use of a variety of basic and thermal conditions. The lack of success encountered with this step was attributed to unfavourable steric effects during transformation to the heterocycle. Of the two possible conformations of the narasin fragment **32a** and **32b** (figure 5), two of the four substituents must always adopt axial positions on the ring, and the extent of the resulting steric crowding was such that the elimination products **31** were favoured.

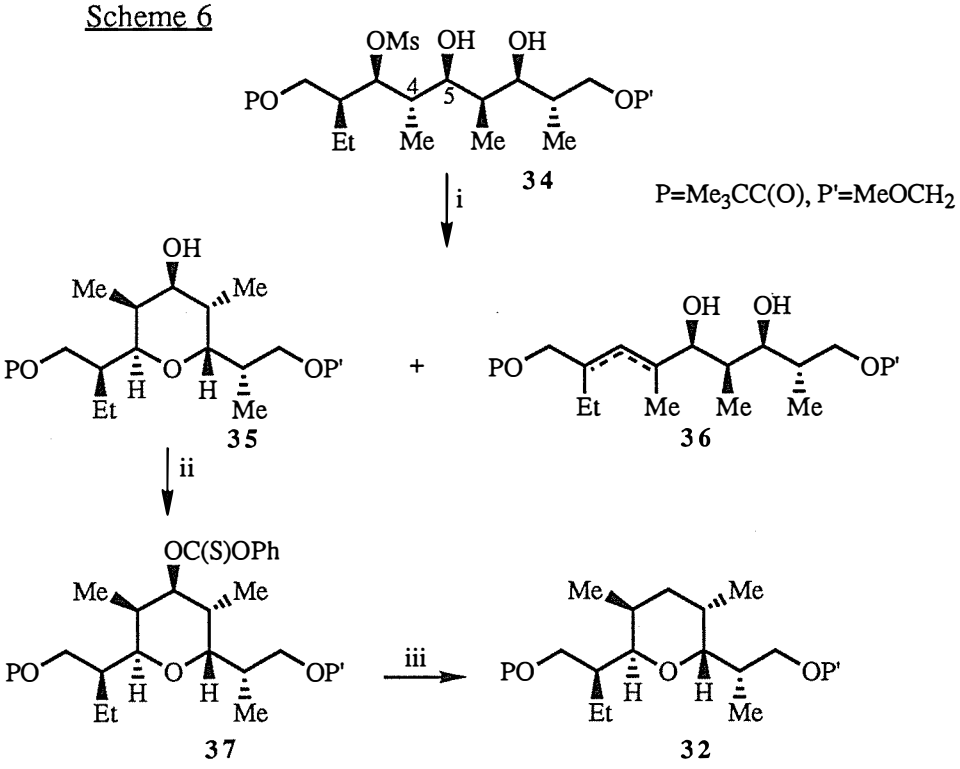
Figure 5



Absence of the indicated methyl group in the salinomycin fragment **30** permits a conformation (figure 5) in which only one substituent need be axial and, as a result of the reduced steric interactions, the desired cyclisation product was observed with minimal formation of the olefin by-products **33**.

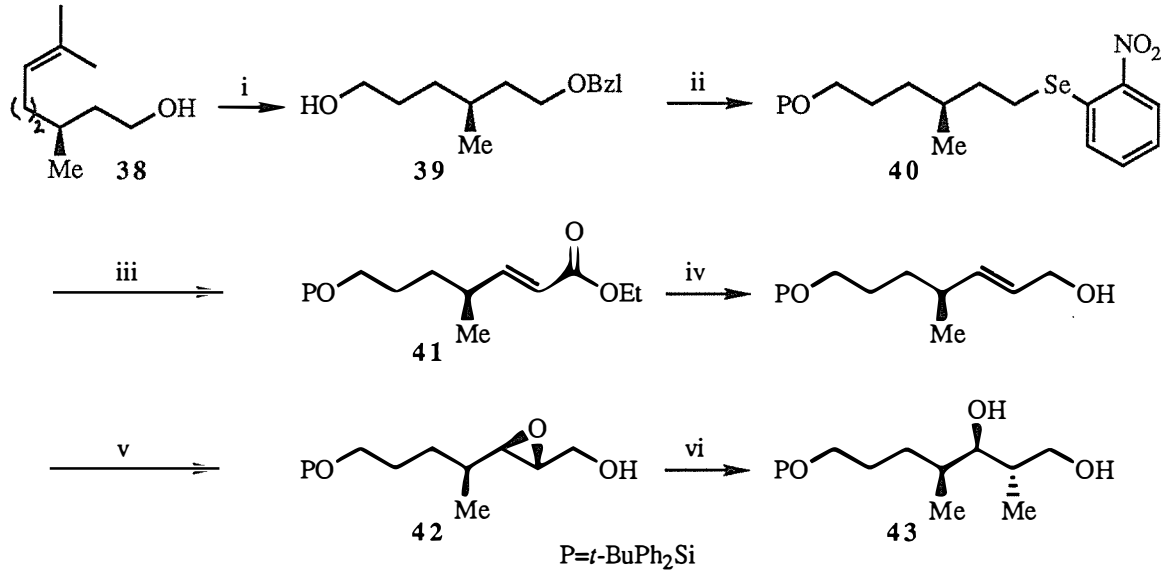
Having established mesylate **28** (see scheme 5) as a suitable intermediate for use in a total synthesis of salinomycin, the analogous narasin precursor **29** was modified to incorporate an hydroxyl group at C5. This caused a marked improvement in the efficiency of the cyclisation step (scheme 6) since treatment of the mesylate **34** with base now afforded the tetrahydropyran **35** in moderate (45%) yield, and the olefins **36** in correspondingly reduced quantities. An explanation offered to account for this effect suggested that the C5

Scheme 6



Reagents and conditions: (i) KH, hexane/toluene, 0°C; (ii) PhOC(=S)Cl, Pyridine, DMAP, MeCN; (iii) *n*-Bu_3SnH, (*t*-BuO)$_2$, toluene, 110°C.

Scheme 7



Reagents and conditions: (i) a: $C_6H_5CH_2Br$, KH, THF, 0°C; b: O_3, MeOH, -78°C; c: $NaBH_4$, MeOH; (ii) a: *t*-$BuPh_2SiCl$, DMF, imida ole; 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; (iv) DIBAL, CH_2Cl_2, -40°C; (v) Ti(O*i*-Pr)$_4$, D-(-)-diethyltartrate, *t*-BuOOH, CH_2Cl_2, -23°C; (vi) $Me_3CuCNLi_2$, THF, -20°C.

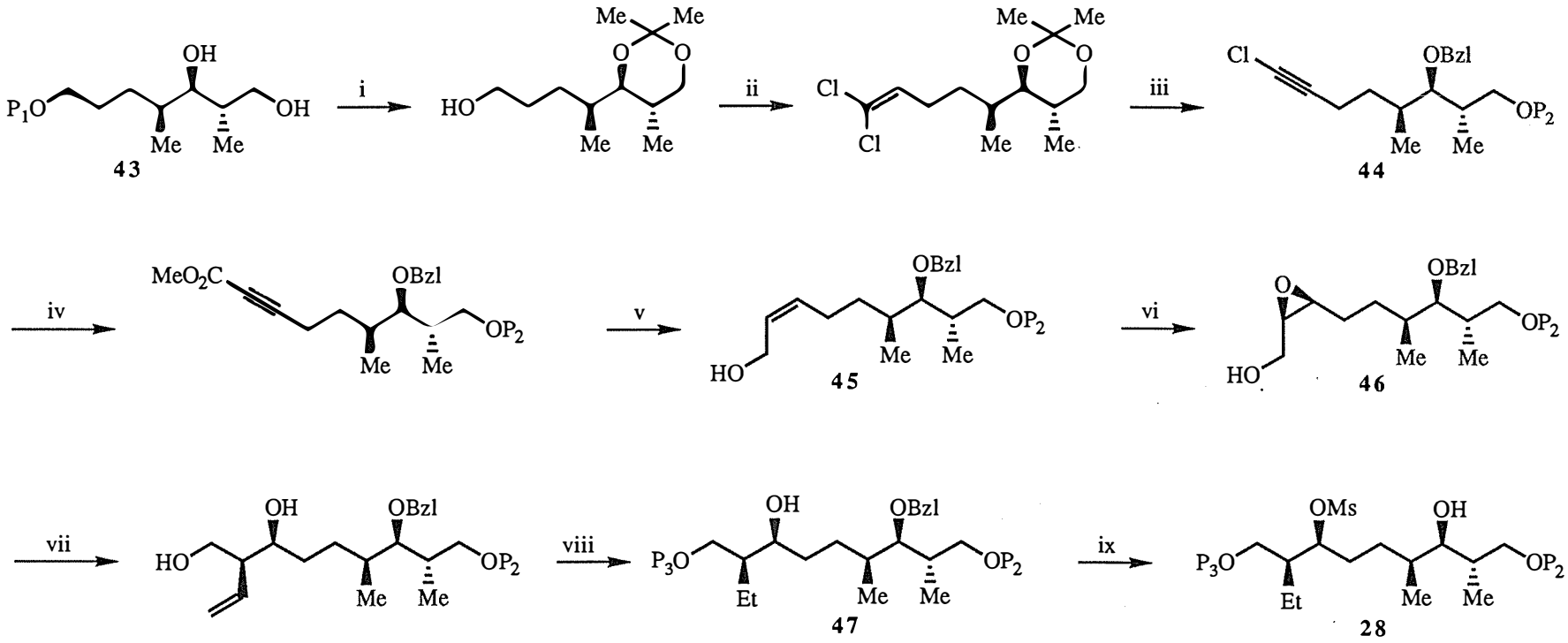
hydroxyl group probably existed as the alkoxide ion under the reaction conditions and this discouraged deprotonation at C4, which leads to the elimination products. However, subsequent reductive removal of this hydroxyl group then became necessary which, though difficult, was achieved by treating the thiocarbonate derivative **37** with tributyltin hydride, affording the desired tetrahydropyran **32**.

The reported[34] procedure for synthesising the mesylate **28**, from which the tetrahydropyran fragment **30** for salinomycin is derived (see scheme 5), required L-(+)-citronellol **38**, as the starting material (scheme 7). This was protected and converted to the alcohol **39**. After selective protection steps **39** was elongated, *via* the selenide **40**, to the olefin **41**. Following a Sharpless epoxidation, the epoxide **42** was opened with an organocuprate to give the alcohol **43** with the desired stereochemistry of the three chiral centres. The carbon chain was further elaborated (scheme 8) by firstly using Seyferth's methodology[35,36] to generate the acetylene **44** which was then converted to the olefin **45**, and thence to the epoxide **46**. After opening this epoxide with an organocuprate and hydrogenation, the alcohol groups of **47** were selectively protected to give **28**, completing this portion of the synthesis.

Assembly of the cyclisation precursor for narasin, mesylate **34** (see scheme 6), was accomplished by a series of chain extension steps from alcohol **48** (scheme 9). Thus conversion of **48** to the *cis* -allylic alcohol **49**, followed by formation of the epoxide **50**, afforded the 1,3-diol **51** after ring opening with an organocuprate. Protection of **51** as the acetonide **52** and cleavage of the benzylic ether, allowed further elaboration to the alcohol **53** by a similar sequence of steps. It is noteworthy that an intermediate from this procedure, alcohol **54**, is in fact used during the synthesis of the right hand fragment (see scheme 15), which demonstrates the efficiency of this synthetic route. The alcohol **53** was then further extended (scheme 10), again in a similar fashion as above, to give the required mesylate **34**.

In view of the difficulties encountered when using **34** in the construction of the tetrahydropyran fragment for use in the narasin synthesis (see scheme 6), an alternative route was suggested by Kishi *et al.*[37] Since cyclisation to the fully substituted tetrahydropyran ring had proved difficult, it was envisaged that a stereocontrolled introduction of an alkyl group on to the preformed ring would prove to be a viable alternative strategy. Precedent[38] indicated that nucleophilic attack on a cyclic oxonium anion intermediate would occur at predominantly the axial position, this being dictated partly by stereoelectronic effects, since the newly formed carbon-nucleophile bond would be antiperiplanar to a lone electron pair of the ring oxygen, and partly by the steric influence of other ring substituents. Thus nucleophilic attack on the oxonium ion **55** (scheme 11) would be expected to occur axially and also at the least hindered face of the ring, giving tetrahydropyran **56**. Attack at the other face is restricted by unfavourable interactions with the large R_1 group, which otherwise gives the 1,3-diaxially substituted tetrahydropyran **57**.

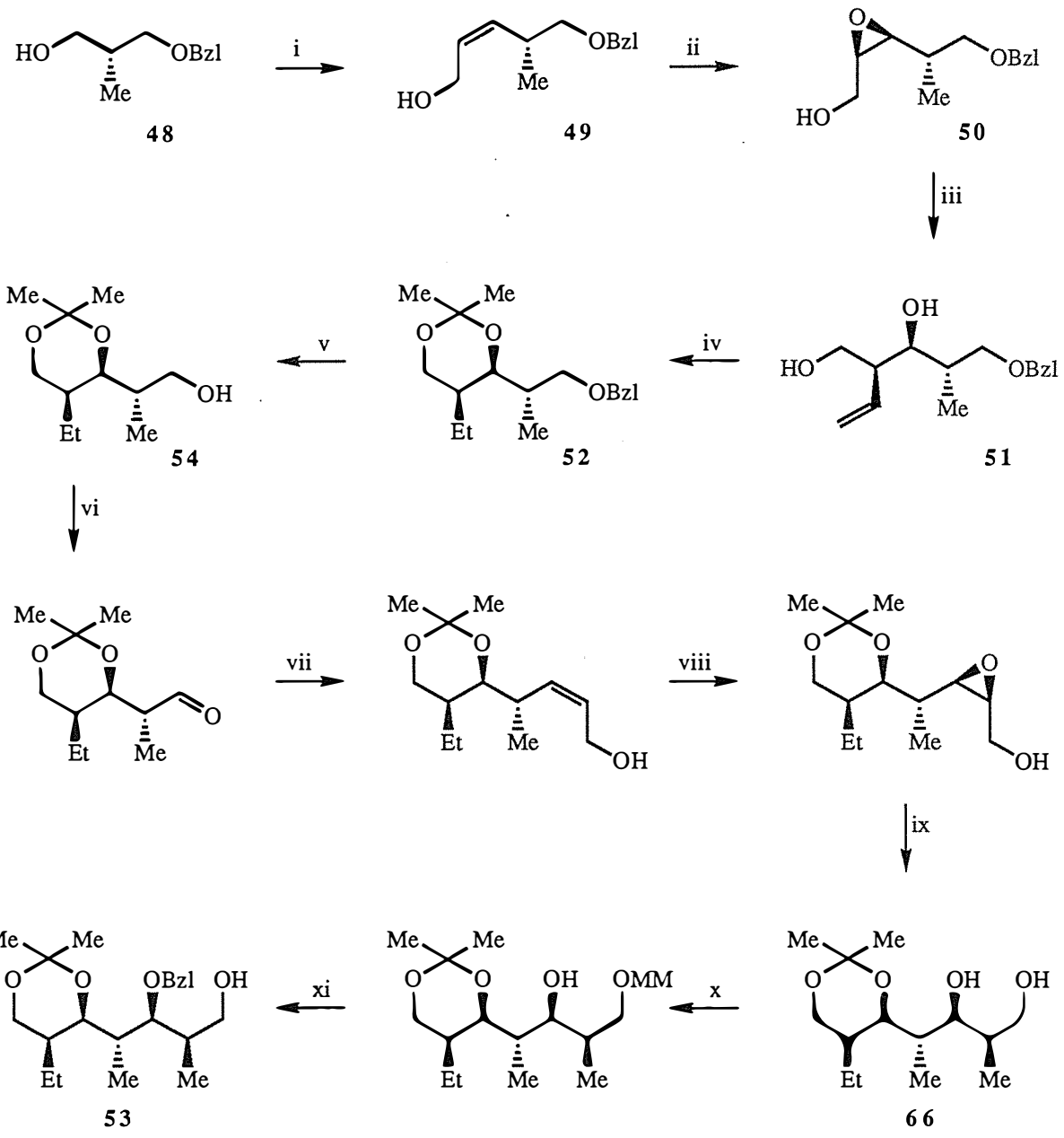
Scheme 8



P_1=*t*-$BuPh_2Si$, P_2=$MeOCH_2$, P_3=$Me_3CC(O)$

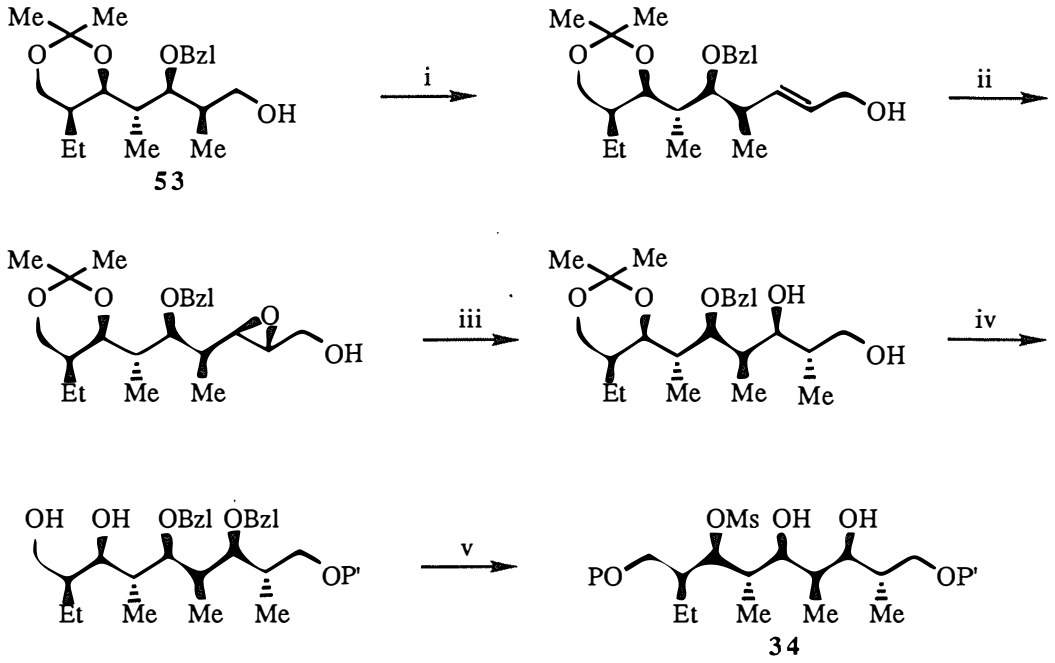
Reagents and conditions: (i) a: $Me_2C(OMe)_2$, CSA, acetone, RT; b: *n*-Bu_4NF, THF; (ii) a: DMSO, $(COCl)_2$, CH_2Cl_2, -60°C then NEt_3; b: $PhHgCCl_2Br$, PPh_3, benzene, Δ; (iii) a: AcOH, H_2O, RT; b: NaH, $MeOCH_2Br$, THF, -12°C; c: KH, $C_6H_5CH_2Br$, THF/DMF, 0°C; (iv) *n*-BuLi, THF, -78°C then $ClCO_2Me$; (v) a: H_2, Lindlar catalyst, quinoline, hexane, RT; b: DIBAL, CH_2Cl_2, -40°C; (vi) Ti(O*i*-Pr)$_4$, D-(-)-diethyltartrate, *t*-BuOOH, CH_2Cl_2, -23°C; (vii) CH_2=$CHMgBr$, CuI, Et_2O, -24°C; (viii) a: H_2, Lindlar catalyst, Et_2O, RT; b: $Me_3CC(O)Cl$, pyridine, RT; (ix) a: Ms_2O, DMAP, pyridine, CH_2Cl_2, 0°C; b: H_2, Pd/C, MeOH.

Scheme 9



Reagents and conditions: (i) a: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then NEt_3; b: CBr_4, PPh_3, CH_2Cl_2, 0°C; c: *n*-BuLi, THF, -78°C then $ClCO_2Me$; d: H_2, Lindlar catalyst, quinoline, hexane; e: DIBAL, CH_2Cl_2, -78°C; (ii) MCPBA, CH_2Cl_2, -78°C; (iii) CH_2=CHMgBr, CuI, Et_2O, -40°C; (iv) a: $MeC(OMe)_2$, acetone, CSA; b: H_2, Lindlar catalyst, Et_2O; (v) Li, THF/NH_3 (liquid); (vi) a: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then NEt_3; (vii) a: $PhHgCl_2Br$, PPh_3, benzene, reflux; b: *n*-BuLi, THF, -78°C then $ClCO_2Me$; c: H_2, Lindlar catalyst, hexane; d: DIBAL, CH_2Cl_2, -78°C; (viii) MCPBA, CH_2Cl_2, 0°C; (ix) $LiCu(Me)_2$, Et_2O, -40°C; (x) $MeOCH_2Br$, $NEt(i\text{-}Pr)_2$, CH_2Cl_2, 0°C; (xi) a: $C_6H_5CH_2Br$, KH, DMF/ THF, 0°C; b: 1% HCl, MeOH, reflux; c: $Me_2C(OMe)_2$, acetone, CSA, $MgSO_4$.

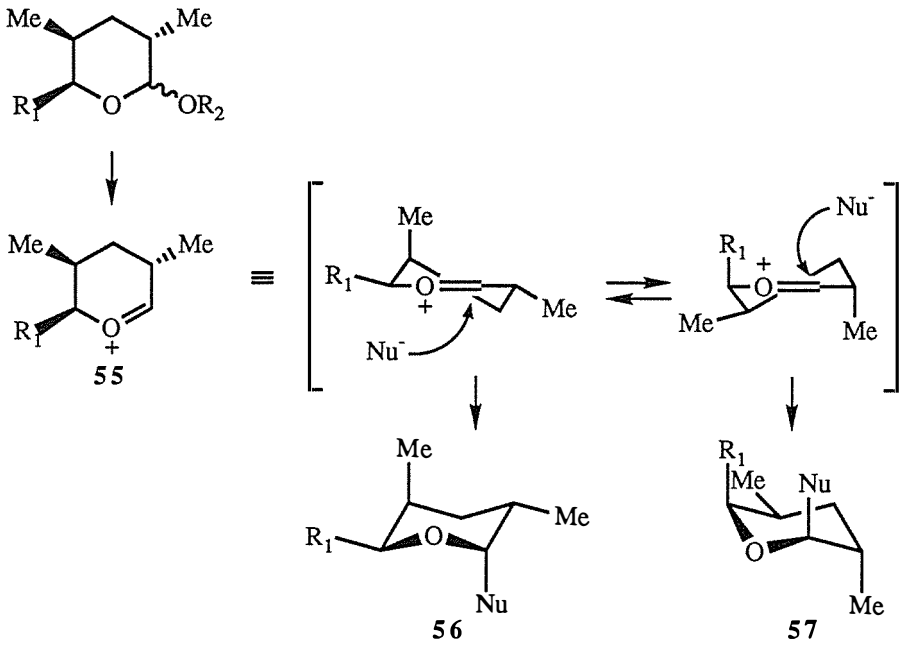
Scheme 10



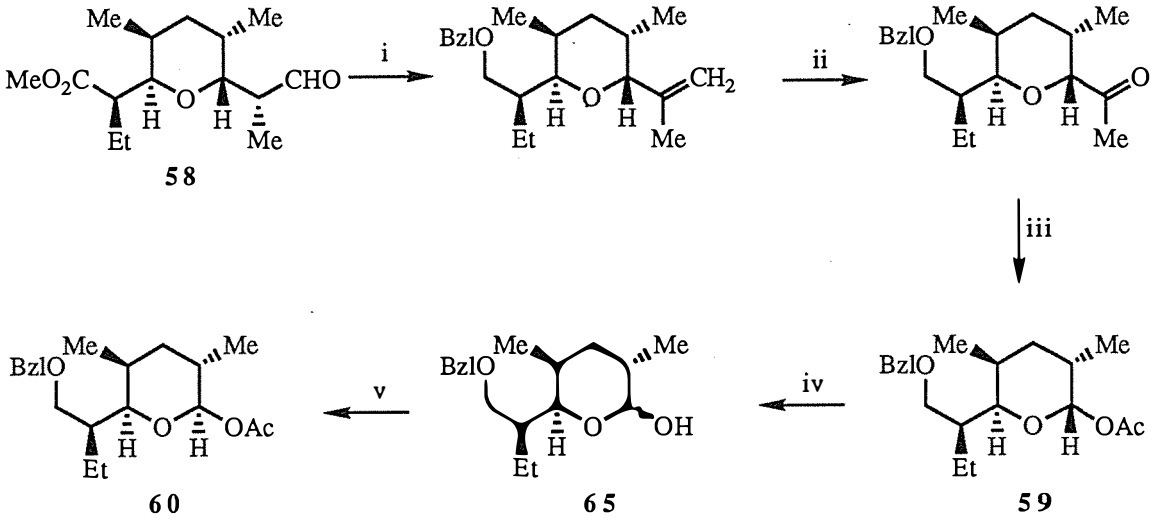
P=$Me_3CC(O)$, P'=$MeOCH_2$

Reagents and conditions: (i) a: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then NEt_3; b: $(Ph)_3P{=}CHCO_2Et$, $ClCH_2CH_2Cl$, Reflux; c: DIBAL, CH_2Cl_2, -78°C; (ii) *t*-BuOOH, Ti(*i*-PrO)$_4$, D-(-)-diethyltartrate, CH_2Cl_2, -23°C; (iii) $LiCuMe_2$, Et_2O, -40°C then $NaIO_4$, aq. MeOH, 0°C workup; (iv) a: $MeOCH_2Br$, $NEt(i\text{-}Pr)_2$, CH_2Cl_2, 0°C; b: $C_6H_5CH_2Br$, KH, DMF/THF; c: aq. AcOH, THF, 50°C;
(v) a: $(Me)_3CC(O)Cl$, pyridine; b: $(Ms)_2O$, pyridine, DMAP, CH_2Cl_2; c: H_2, Pd/C, MeOH.

Scheme 11



Scheme 12

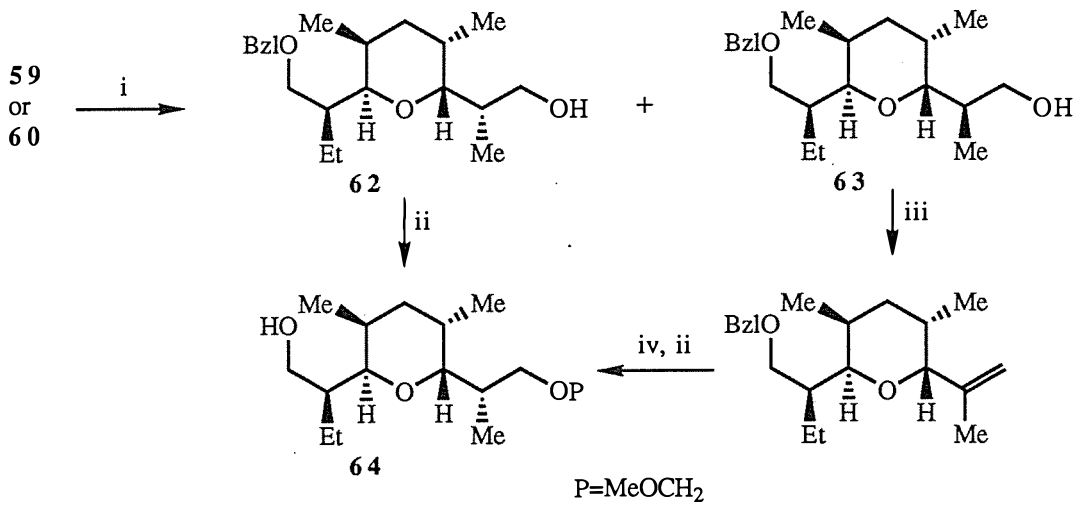


Reagents and conditions: (i) a: $NaBH_4$, MeOH, 0°C; b: *o*-$NO_2C_6H_4SeCN$, PBu_3, THF then H_2O_2, 0°C; c: $LiAlH_4$, Et_2O, 0°C; d: $C_6H_5CH_2Br$, KH, THF/DMF, 0°C; (ii) O_3, MeOH, -78°C then Me_2S workup; (iii) MCPBA, Na_2HPO_4, CH_2Cl_2; (iv) NaOMe, MeOH; (v) Ac_2O, pyridine.

In order to investigate this alternative strategy, natural narasin was degraded to the aldehyde **58** which was then converted (scheme 12) to both the axial and equatorial acetates **59** and **60**. These individual acetates were reacted with a mixture of the *E*- and *Z*-enol silyl ethers **61**[39] (scheme 13) to give, after sodium borohydride reduction, a mixture of alcohols **62** and **63**. Both diastereomers were then converted to the single tetrahydropyran **64**, analysis of which showed that, as anticipated, exclusively axial nucleophilic attack had occurred on the ring to give the product **64** with a configuration that corresponds to the fragment required for the left hand portion of the natural product (narasin).

An alternative synthetic route to the lactol **65**, which had been derived directly from natural narasin for the purpose of this study, was not detailed, but an assertion was made that it could be derived from an intermediate occurring in their previous synthesis[30] of narasin (probably the 1,3-diol **66**, scheme 9).

Scheme 13

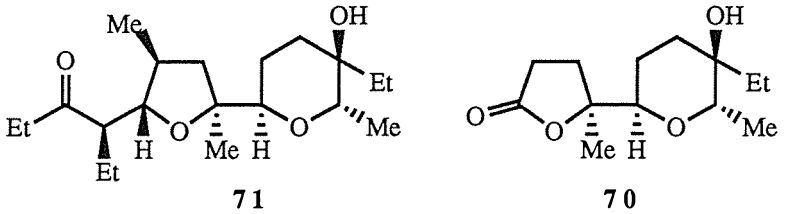


Reagents and conditions: (i) (*Z*)-,(*E*)- MeCH=CHOSiMe$_3$ **61** (ca. 4.5 eq), $ZnCl_2$ (excess), CH_2Cl_2, 0°C then $NaBH_4$, MeOH, 0°C; (ii) a: $MeOCH_2Br$, *i*-Pr_2N t, CH_2Cl_2, RT; b: H_2, Pd/C, MeOH; (iii) *o*-$CNSeC_6H_4NO_2$, Bu_3P, THF, RT then H_2O_2, 0°C; (iv) a: thexylborane, THF, 0°C then H_2O_2/OH^- workup.

The Right Hand Fragment

The right hand portion **27** of salinomycin **7** and narasin **10** was deemed to be synthetically equivalent to the open chain diketone **67** (scheme 4) which was then further disconnected to three key subunits **68**, **69** and **70**.

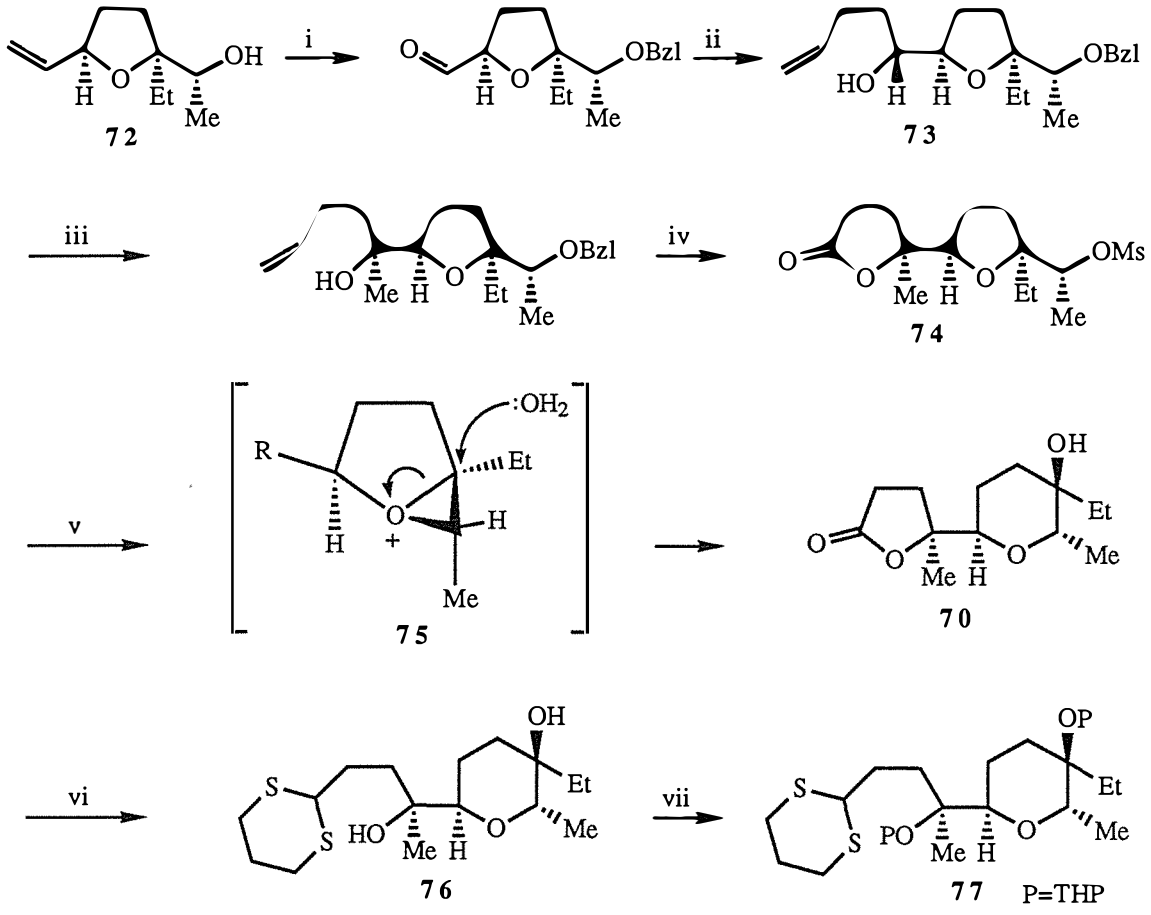
Figure 6



Structural comparison of an intermediate **71** used in the synthesis of lasalocid A and an intermediate **70** required for synthesis of the right hand fragment of salinomycin.

The obvious structural resemblance between the required tetrahydropyranyl γ-lactone **70** and the tetrahydropyranyl ketone **71** (figure 6) used in the synthesis of lasalocid A **3**[31,32] led to essentially the direct application of that methodology to this synthesis (scheme 14). Thus, tetrahydrofuran **72**[31] was extended to the olefin **73** which was subsequently oxidised to the lactone **74**. The tetrahydrofuran portion was then converted to the tetrahydropyran **70** by an elegant ring expansion of the mesylate **74**. Under thermal conditions an oxonium ion intermediate **75** is generated which undergoes nucleophilic attack by a molecule of water to give the observed six membered ring with the desired stereochemistry. Finally, reduction of the lactone **70**, followed by formation of the thioacetal **76** and protection of the remaining hydroxyl groups, afforded **77**, a synthon of the lactone **70** that is suitable for use in the synthetic route.

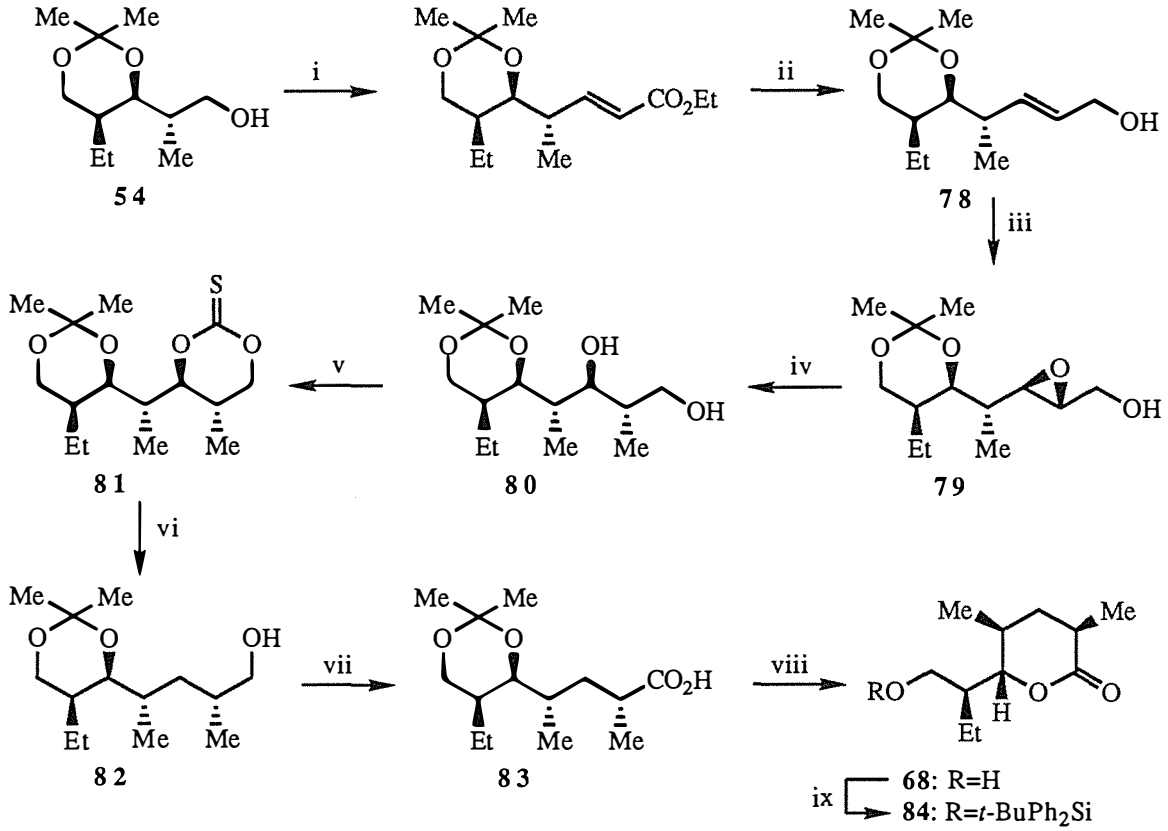
Scheme 14



Reagents and conditions: (i) a: KH, $C_6H_5CH_2Br$, THF/DMF; b: O_3, MeOH, -70°C; (ii) CH_2=$CHCH_2MgBr$, THF; (iii) a: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then NEt_3; b: MeMgBr, Et_2O; (iv) a: O_3, Me_2S; b: PCC, CH_2Cl_2; c: H_2, Pd/C, MeOH; d: MsCl, pyridine; (v) Ag_2CO_3, acetone, Δ; (vi) a: DIBAL, CH_2Cl_2, -78°C; b: $HS(CH_2)_3SH$, $BF_3.Et_2O$, CH_2Cl_2, -12°C; (vii) DHP, TSA, CH_2Cl_2.

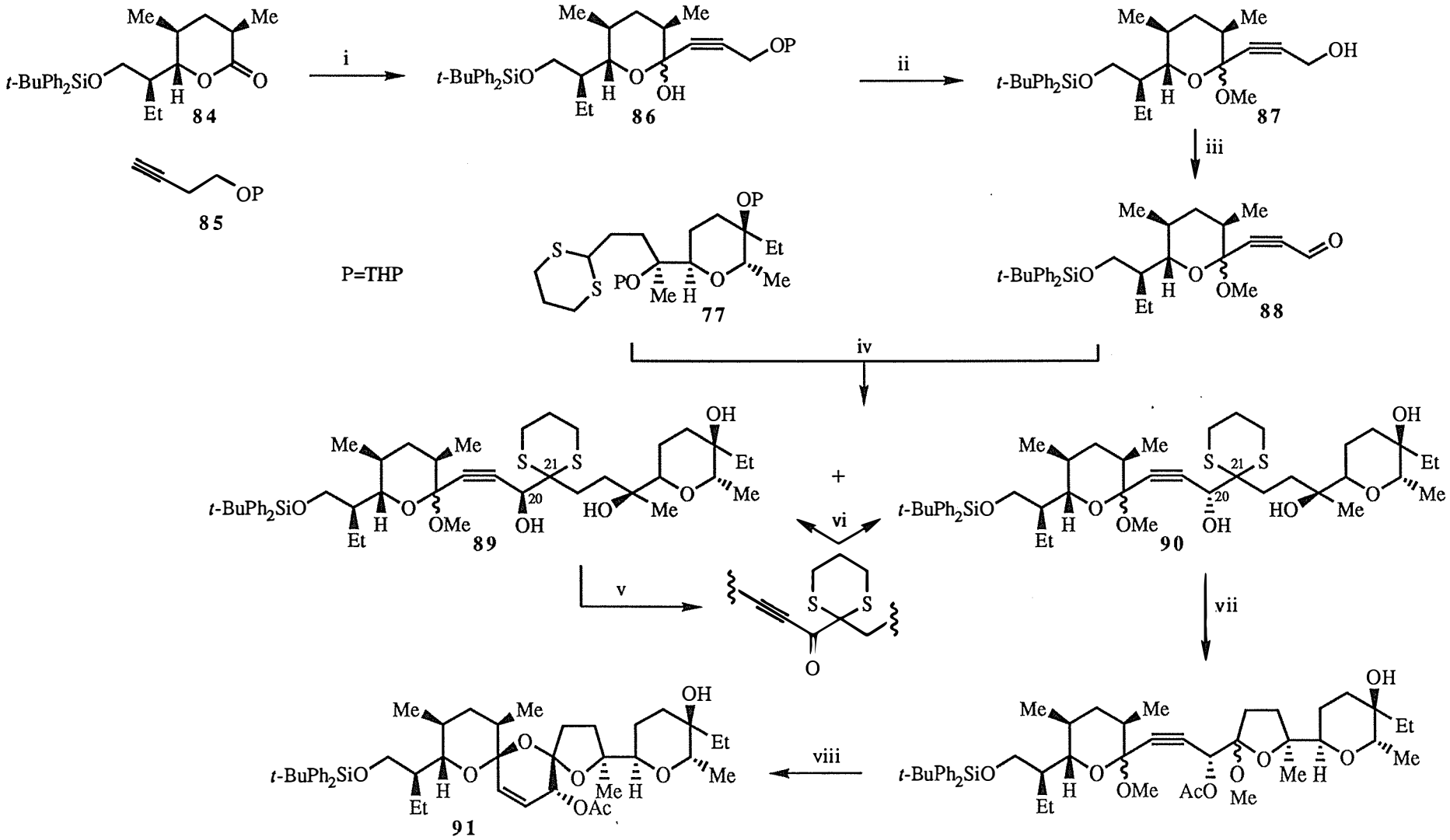
The lactone **68** (from scheme 4), required for contructing the right hand fragment, was reportedly[34] built up (scheme 15) from an intermediate obtained during the synthesis of the left hand portion of narasin, namely alcohol **54** (see scheme 9). Following oxidation of **54**, the aldehyde was extended *via* a Wittig reaction to the *trans* olefin **78** which was epoxidised and the epoxide **79** opened by an organocuprate to give the alcohol **80** with the required stereochemistry of the methyl groups. The resulting secondary hydroxyl group of **80** was removed by firstly converting the 1,3-diol to the thiocarbonate derivative[40] **81** then treating with tributyltin hydride. The alcohol **82** was oxidised to the somewhat unstable acid **83** under mild, buffered, conditions using a RuO_4 catalyst[41] formed *in situ*, and subsequent cyclisation afforded the lactone **68**, which was protected as **84**.

Scheme 15



Reagents and conditions: (i) a: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then NEt_3; b: $EtO_2CCH{=}PPh_3$, $ClCH_2CH_2Cl$, Δ; (ii) DIBAL, CH_2Cl_2, -40°C; (iii) $Ti(O\textit{i}\text{-}Pr)_4$, D-(-)-diethyltartrate, *t*-BuOOH, CH_2Cl_2, -23°C; (iv) $Me_3CuCNLi_2$, THF, -24°C; (v) $(imid)_2CS$, xylene, Δ; (vi) a: Bu_3SnH, AIBN, toluene; b: CSA, $Me_2C(OMe)_2$; c: NaOH, H_2O, RT; (vii) RuO_2-$NaIO_4$ (cat), $NaHCO_3$, acetone/H_2O, RT; (viii) AcOH, acetone; (ix) *t*-$BuPh_2SiCl$, imidazole, DMF.

Scheme 16



Reagents and conditions: (i) *n*-BuLi, THF, -78°C then **84**; (ii) MeOH, TSA, RT; (iii) $CrO_3.2Py$, CH_2Cl_2, RT; (iv) a: *n*-BuLi, THF, -20°C then **88**; b: TSA, MeOH; (v) MnO_2, CH_2Cl_2; (vi) $NaBH_4$, MeOH, -10°C; (vii) a: NCS, MeOH, RT; b: TSA, MeOH, RT; c: Ac_2O, pyridine; (viii) a: H_2, Lindlar catalyst, MeOH; b: 80% aq AcOH.

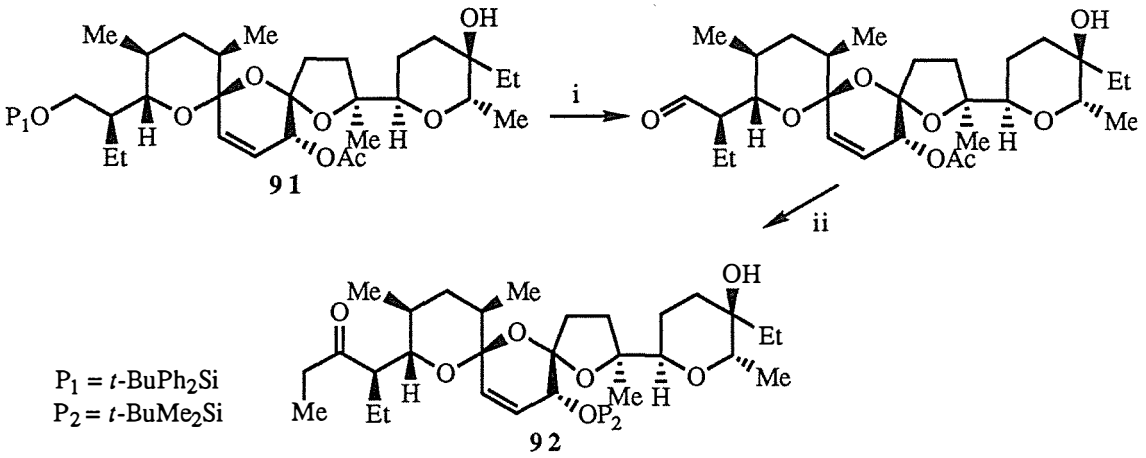
Assembly of the bisspiroketal from the above precursors **68**, **69** and **70** proceeded firstly by reaction of the lithium acetylide derivative of propargyl alcohol, protected as the tetrahydropyranyl ether **85**, with the lactone **84** (scheme 16). The resulting crude hemiketal **86** was treated with acidic methanol to remove the tetrahydropyranyl groups and to form a mixture of the α and β methyl ketals **87** in a 1:3 ratio. It ultimately proved unnecessary to control the stereochemical outcome of this reaction since the ketal carbon was destined to become a spiro centre, the configuration of which is determined by anomeric, steric and hydrogen bonding effects.

Oxidation of the alcohol **87** to the aldehyde **88** enabled formation of the C-20, C-21 bond by a low temperature coupling between **88** and the anion of dithiane **77**, affording a separable 1:1 mixture of acetylenic alcohols **89** and **90**. The alcohol **89** with the undesired configuration of the hydroxyl group could be recycled *via* an oxidation/reduction procedure to provide more of the material **90** with the correct stereochemistry at C20.

The highly functionalised alcohol **90** was finally converted, by a sequence of steps culminating in an acid catalysed intramolecular ketalisation, to the bisspiroketal **91**. It is important to note that the ring conformation adopted under these conditions resembles that of *epi*-17-deoxy-(O-8)-salinomycin **8**, and it was later established[30] that not until the entire molecule had been assembled and the allylic alcohol liberated, was the salinomycin **7** conformation observed under thermodynamic conditions.

The bisspiroketal **91** was then converted to the ketone **92** (scheme 17), in preparation for the crossed aldol reaction that was to follow.

Scheme 17

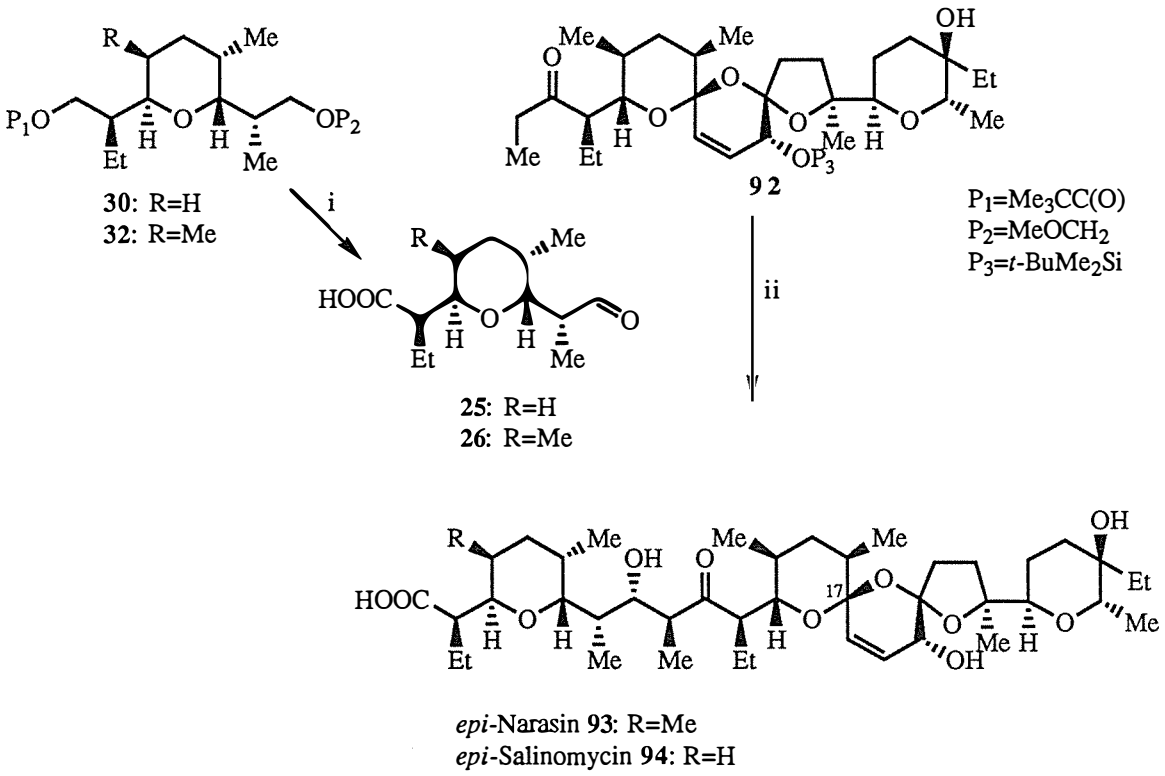


Reagents and conditions: (i) a: *n*-Bu_4NF, THF, RT; b: CrO_3.2Py, CH_2Cl_2, RT; (ii) a: EtMgBr, Et_2O, -40°C; b: CrO_3.2Py, CH_2Cl_2, RT; c: K_2CO_3, MeOH, RT; d: *t*-$BuMe_2SiCl$, DMAP, DMF, 80°C.

Completion of the Synthesis.

On converting the tetrahydropyrans **30** (see scheme 5) and **32** (see scheme 6) to the corresponding aldehydes **25** and **26** (scheme 18), the crossed aldol condensation with the right hand fragment, bisspiroketal **92**, was then investigated (scheme 18). It was found that the optimum conditions, requiring dicyclohexylamidomagnesium bromide as the base to generate the enolate of **92**, afforded a single isomer of the aldol products **93** and **94** in 58% yield after desilylation, which exhibited identical properties to *epi*-narasin and *epi*-salinomycin respectively.

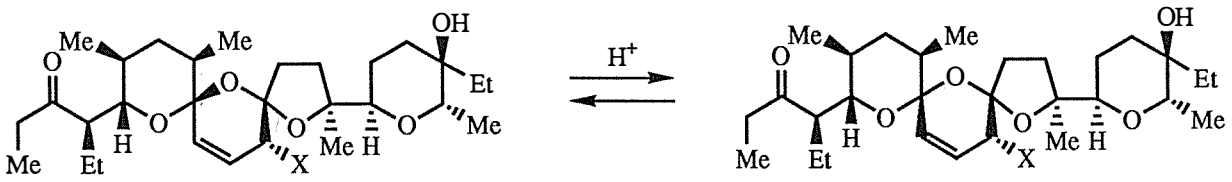
Scheme 18



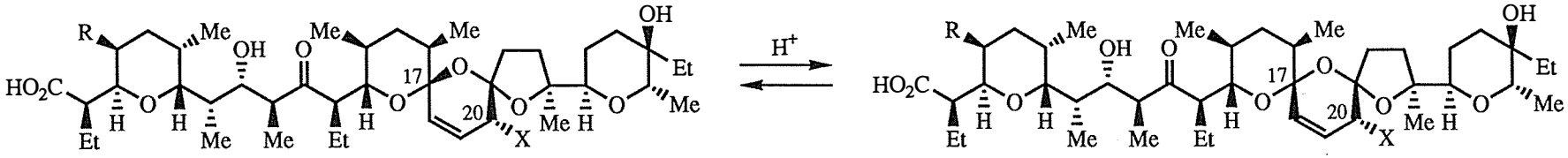
Reagents and conditions: (i) a: $LiAlH_4$, Et_2O, 0°C; b: Jones oxidation; c: 0.2% HCl, MeOH, Δ; d: PCC, CH_2Cl_2, RT; (ii) a: $(C_6H_{11})_2NMgBr$, THF, -50°C then **25** or **26**, -50°C, 20 min; b: *n*-Bu_4NF, THF, RT.

Thermodynamic isomerisation of the bisspiroketal centre of **93** or **94** under acidic conditions (scheme 19) afforded at least a 7:1 ratio of narasin **10**:*epi*-narasin **93** or salinomycin **7**:*epi*-salinomycin **94**, clearly demonstrating a thermodynamic preference for the conformation of the natural products over that of the C17 epimers. It was further noted

Scheme 19



	Ratio	
99: X=OH	4 : 1	**27**: X=OH
100: X=OAc	100 : 0	**101**: X=OAc



	Ratio	
epi-Narasin **93**: R=Me, X=OH *epi*-Salinomycin **94**: R=H, X=OH	1 : <7	Narasin **10**: R=Me, X=OH Salinomycin **7**: R=H, X=OH
epi-Narasin acetate **97**: R=Me, X=OAc *epi*-Salinomycin acetate **98**: R=H, X=OAc	100 : 0	Narasin acetate **95**: R=Me, X=OAc Salinomycin acetate **96**: R=H, X=OAc

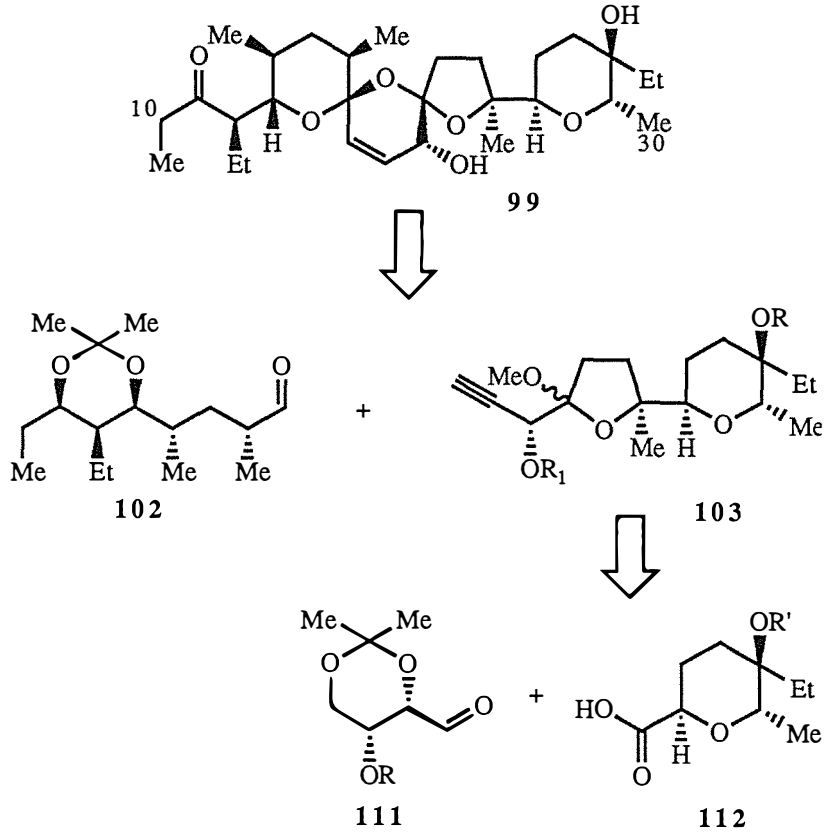
that, on acetylation of the C20 hydroxyl group to give narasin acetate **95** and salinomycin acetate **96**, the C17 epimeric products **97** and **98** were exclusively favoured under thermodynamic conditions. This, coupled with the fact that the corresponding epimeric bisspiroketal ketones **99** and **100** were also favoured[30] over the conformations of **27** and **101**, implies that this allylic hydroxyl serves to stabilise the observed conformations of the natural products by participating in *remote* hydrogen bonding.

1.4 The Total Synthesis of Salinomycin by Yonemitsu *et al.*[42]

The Right Hand Fragment.

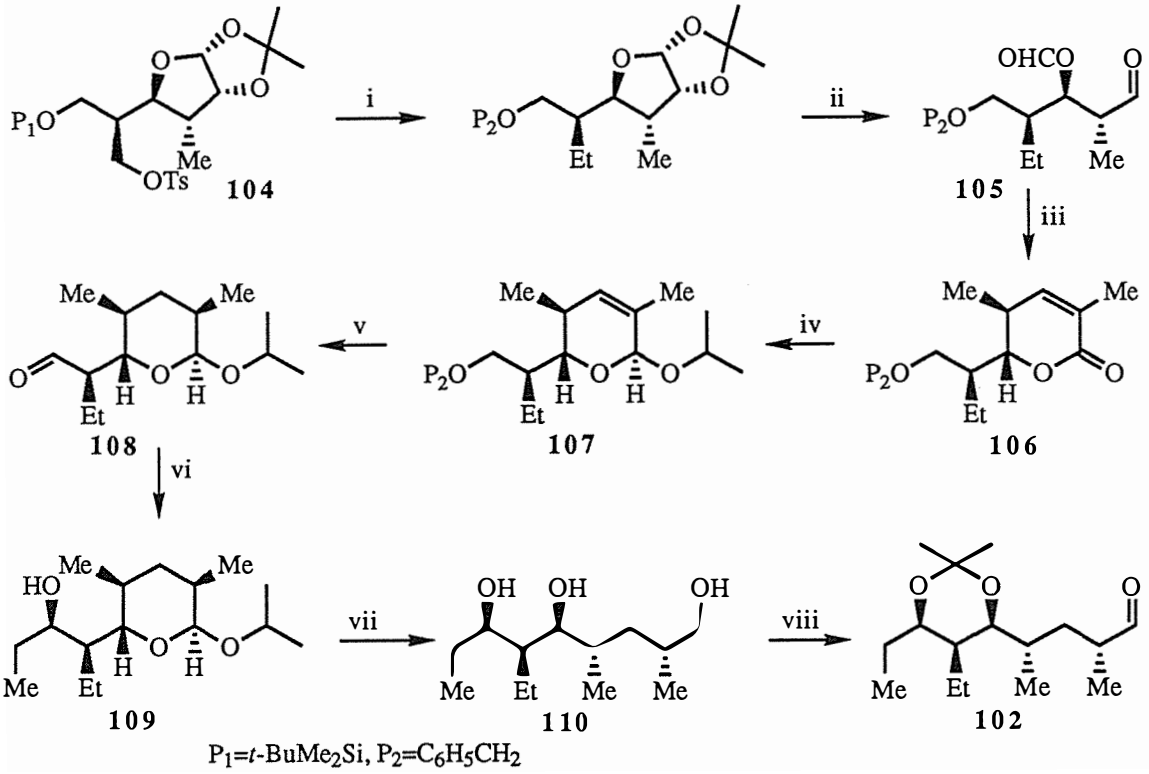
In 1987 Yonemitsu *et al* reported[42] a stereoselective synthesis of the C10-C30 segment, or right hand portion, of salinomycin. In their retrosynthetic strategy (scheme 20) it was envisaged that this bisspiroketal **99** could be constructed from the aldehyde **102** and acetylene **103**.

Scheme 20



Synthesis of the required aldehyde **102** was accomplished from **104**, a D-glucose derivative[43] (scheme 21). Cleavage of the acetonide, followed by reaction with periodate, afforded the aldehyde **105** through which the molecule was extended *via* a Wittig reaction, this product giving the α,β-unsaturated lactone **106** in base. Reduction and conversion to the acetal **107** allowed hydrogenation of the ring with Raney nickel with 13:1 selectivity for the correct isomer which was then oxidised to the aldehyde **108**. Cram addition of ethylmagnesium bromide to **108**, followed by hydrolysis of the cyclic acetal **109**, protection of the resulting 1,3-diol **110**, and oxidation of the terminal hydroxyl group completed the synthesis of the required subunit **102**.

Scheme 21

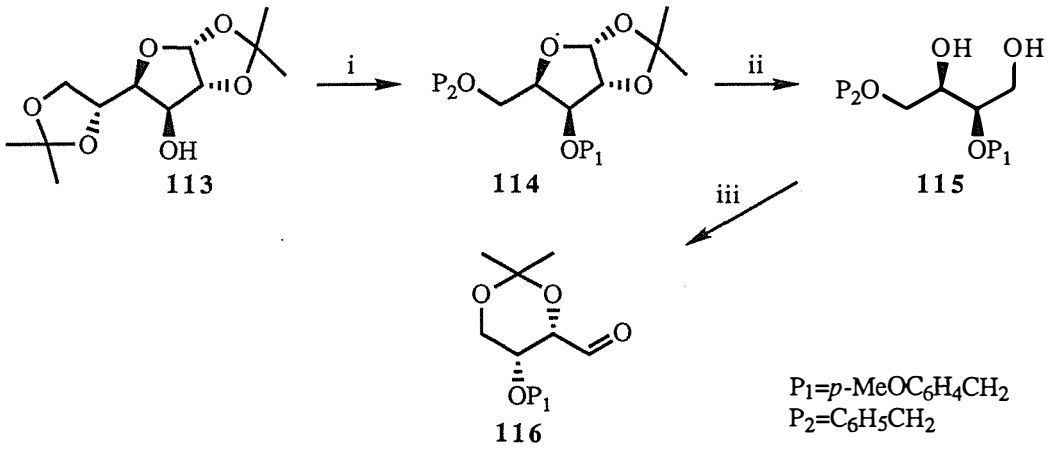


Reagents and conditions: (i) a: CuI, MeLi, Et_2O, -25°C; b: 1M HCl, MeOH, RT; c: $C_6H_5CH_2Cl$, DMSO/THF, NaH; (ii) a: 4M HCl, THF, 45°C; b: $NaIO_4$, THF/MeOH, RT; (iii) a: $(MeO)_2P(O)CHMeCO_2Me$, NaH, THF, -78°C; b: K_2CO_3, MeOH, RT; (iv) a: DIBAH, toluene, -80°C; b: CSA, Me_2CHOH, RT; (v) a: Raney Ni (W-2), EtOH; b: Rh-Al_2O_3, EtOH, RT; c: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then NEt_3; (vi) EtMgBr, Et_2O, -50°C; (vii) a: 1M HCl, THF, 50°C; b: $LiAlH_4$, THF; (viii) a: CSA, $Me_2C(OMe)_2$, acetone; b: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then NEt_3.

The acetylene unit **103** was further simplified (scheme 20) into two components, an aldehyde **111** and a carboxylic acid **112** bearing a tetrahydropyran ring. The first of these components was derived from (*D*)-1,2:5,6-bis-*O*-(1-methylethylidene)-glucofuranose **113**

(scheme 22). The key steps required selective acetonide removal and periodate cleavage of the resulting diol followed by a protection step to give **114**. The remaining acetonide was removed from **114** which was converted to a 1,3-diol **115** and then protected and oxidised to the aldehyde **116**.

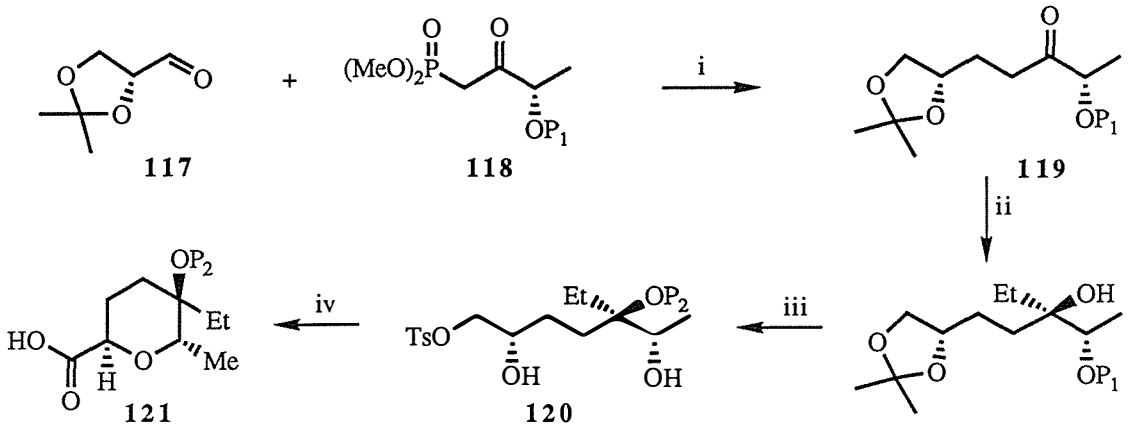
Scheme 22



Reagents and conditions: (i) a: *p*-$MeOC_6H_4CH_2Cl$, NaH, DMSO/THF, RT; b: 2% H_2SO_4, MeOH, RT; c: $NaIO_4$, $MeOH/H_2O$, RT; d: $NaBH_4$; e: $C_6H_5CH_2Cl$, NaH, THF/DMSO; (ii) a: 4M HCl, THF, 55°C; b: $NaIO_4$, THF, $MeOH/H_2O$, RT; c: THF, $LiAlH_4$, 0°C; (iii) $(MeO)_2CMe_2$, acetone, CSA; b: Raney Ni (W-2), EtOH, RT; c: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then NEt_3.

Two precursors were required for construction of the carboxylic acid component **121** (a protected form of **112**, see scheme 20), the aldehyde **117** (scheme 23), obtained from L-glyceraldehyde,[44] and a β-ketophosphonate **118**, prepared from L-lactate.[45]

Scheme 23



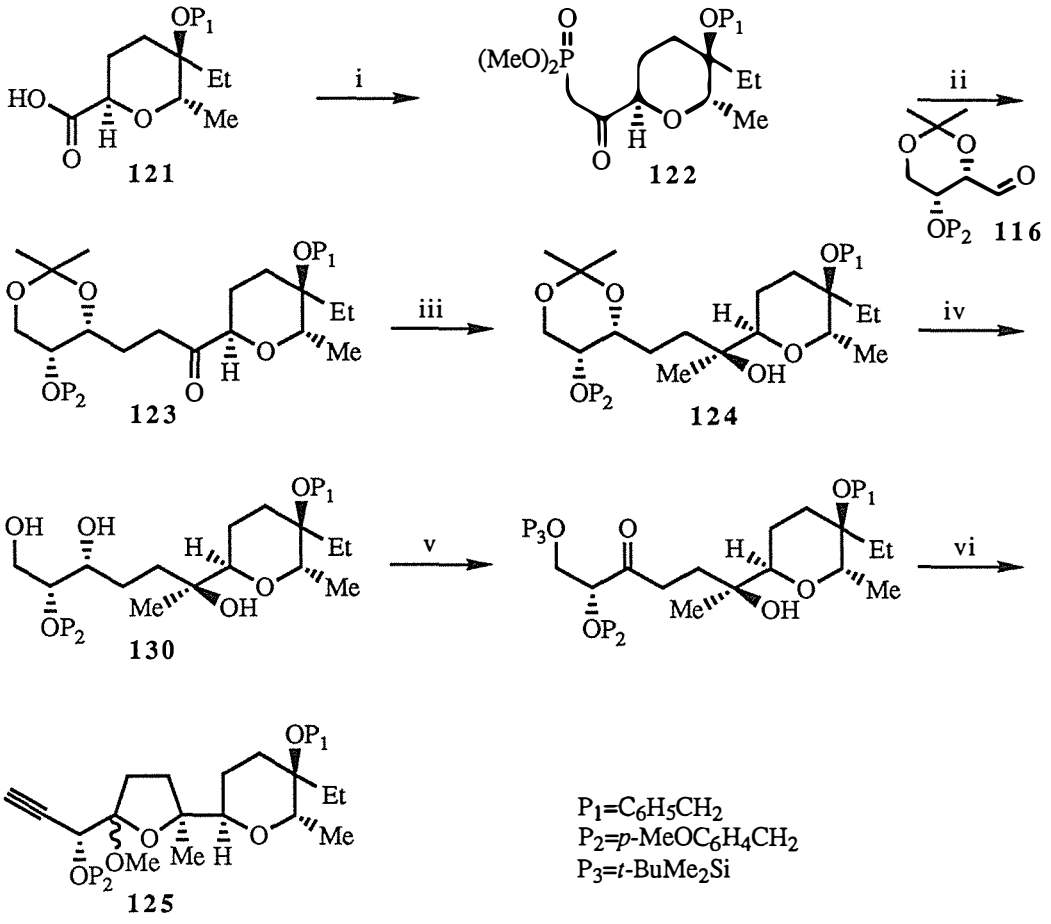
P_1=$C_6H_5CH_2OCH_2$, P_2=$C_6H_5CH_2$

Reagents and conditions: (i) a: NaH, DMSO/THF, 0°C then **118**; b: Pd/C, H_2, EtOAc; (ii) EtMgBr, THF, -93°C; (iii) a: $C_6H_5CH_2Br$, NaH, DMF; b: 4M HCl, THF, 50°C; c: TsCl, Pyridine, RT; (iv) a: NaH, DMSO/THF; b: CrO_3, H_2SO_4, acetone, 0°C.

After combining **117** and **118**, alkylation at the carbonyl group of the resulting ketone **119** introduced an ethyl group with the appropriate stereochemistry, the product then being converted to the tosylate **120**. Base catalysed epoxidation of **120** was accompanied by an intramolecular cyclisation to form a tetrahydropyran ring, which was followed by oxidation of the resulting hydroxyl group to the acid **121**.

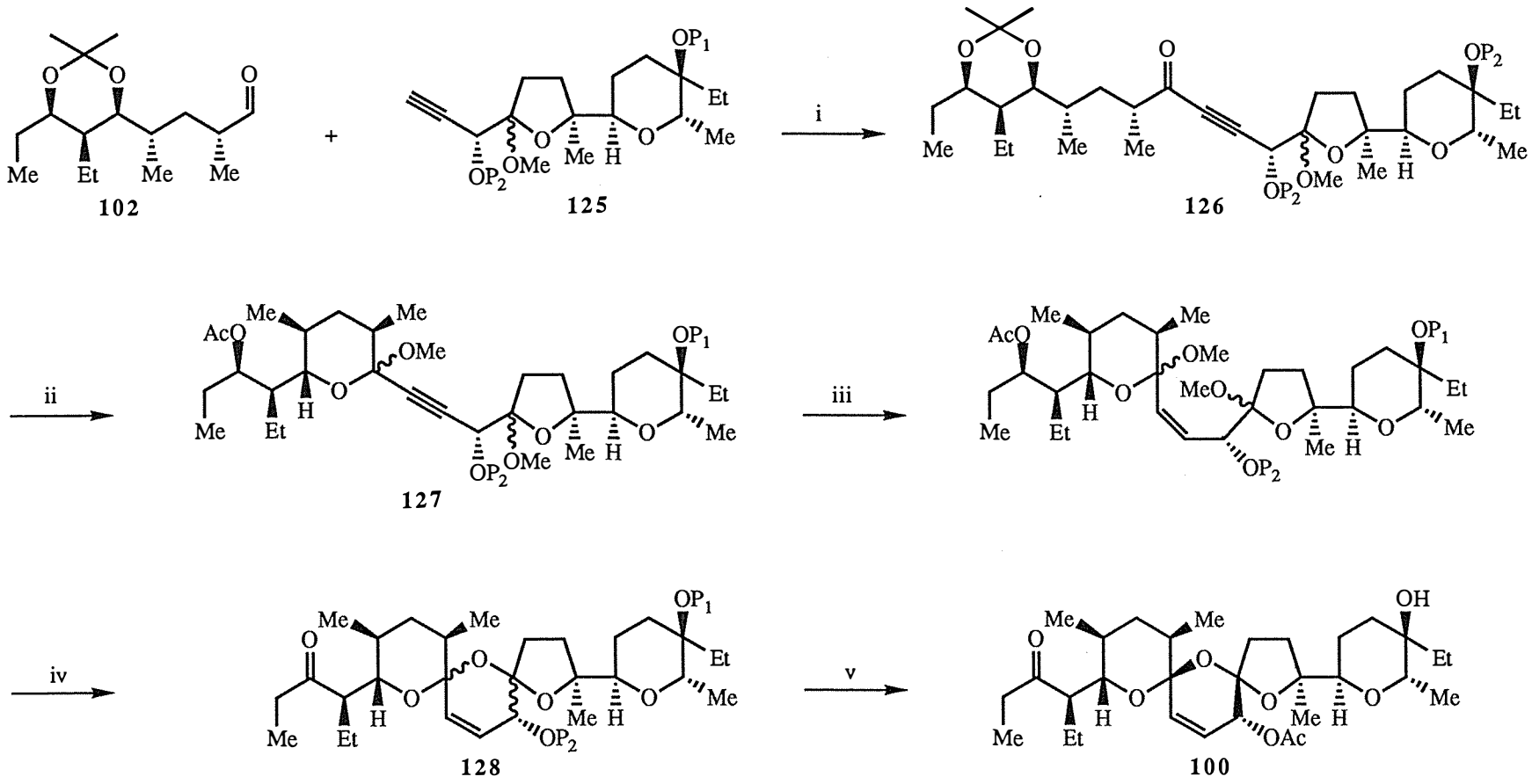
This was converted (scheme 24) to the phosphonate derivative **122** and combined with the aldehyde **116** to afford the ketone **123** after hydrogenation. Following treatment of **123** with methyllithium, the resulting alcohol **124** could be selectively protected and converted to the acetylene **125** using Seyferth's method. [35,36]

Scheme 24



Reagents and conditions: (i) a: CH_2N_2; b: $(MeO)_2P(O)Me$, *n*-BuLi, THF, -93°C; (ii) a: NaH, DMSO/THF, 0°C then **116**; b: Pd/C, H_2, EtOAc; (iii) MeLi, Et_2O, -93°C; (iv) 1M HCl, THF, RT; (v) a: *t*-$BuMe_2SiCl$, imidazole, CH_2Cl_2, RT; b: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then NEt_3; (vi) a: MeOH, CSA; b: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then NEt_3; c: $PhHgCCl_2Br$, PPh_3, benzene, 80°C; d: *n*-BuLi, THF, -78°C.

Scheme 25

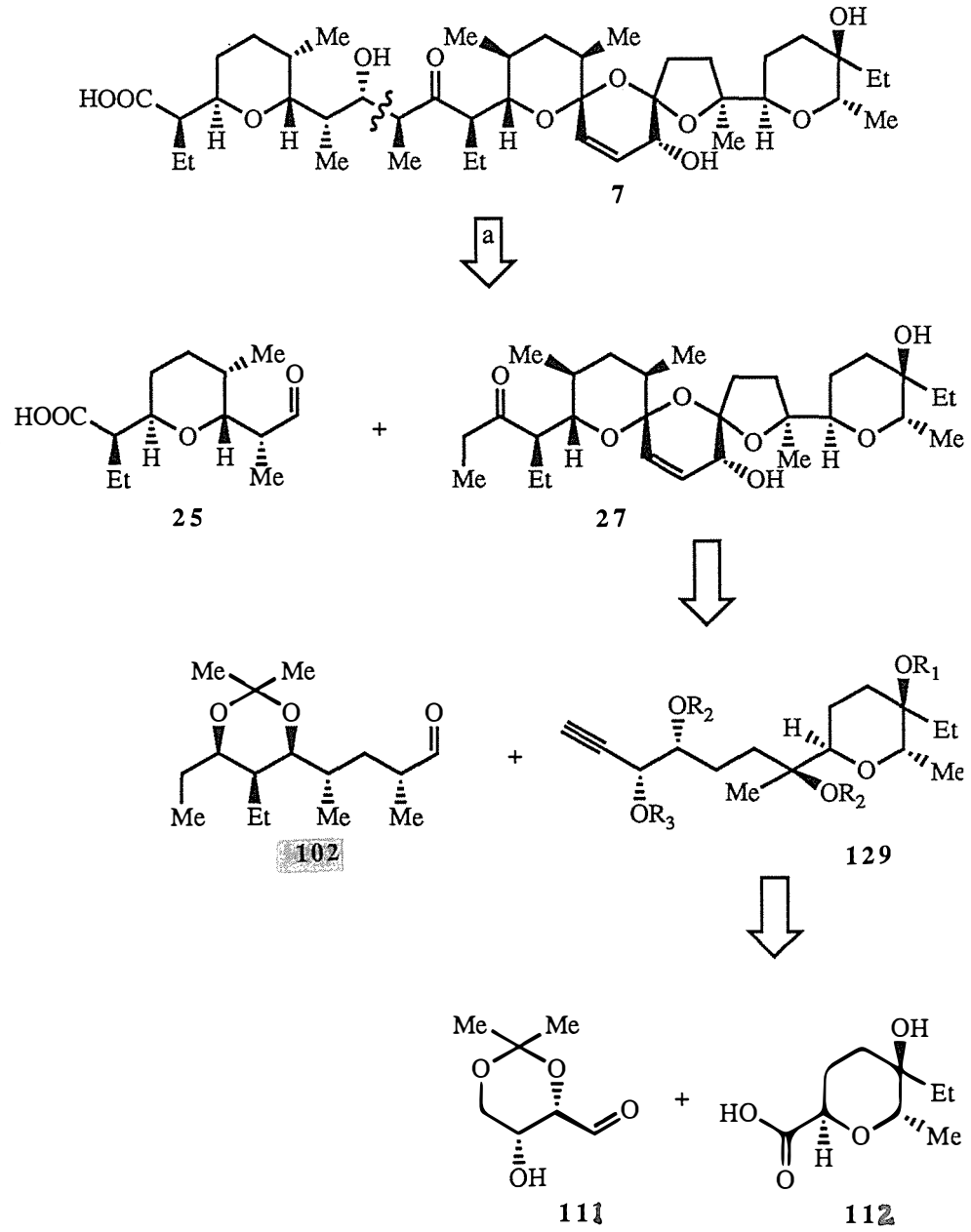


Reagents and conditions: (i) a: *n*-BuLi, THF, -78°C then **103**; b: MnO_2, CH_2Cl_2; (ii) a: CSA, MeOH; b: Ac_2O, NEt_3, DMAP, CH_2Cl_2; (iii) H_2, Lindlar catalyst, MeOH/AcOH; (iv) a: 80% AcOH; b: KOH, aq. MeOH, 60°C; c: PCC, CH_2Cl_2; (v) a: DDQ, H_2O/CH_2Cl_2 (1:10); b: Ac_2O, NEt_3, DMAP, CH_2Cl_2; c: CSA, CH_2Cl_2.

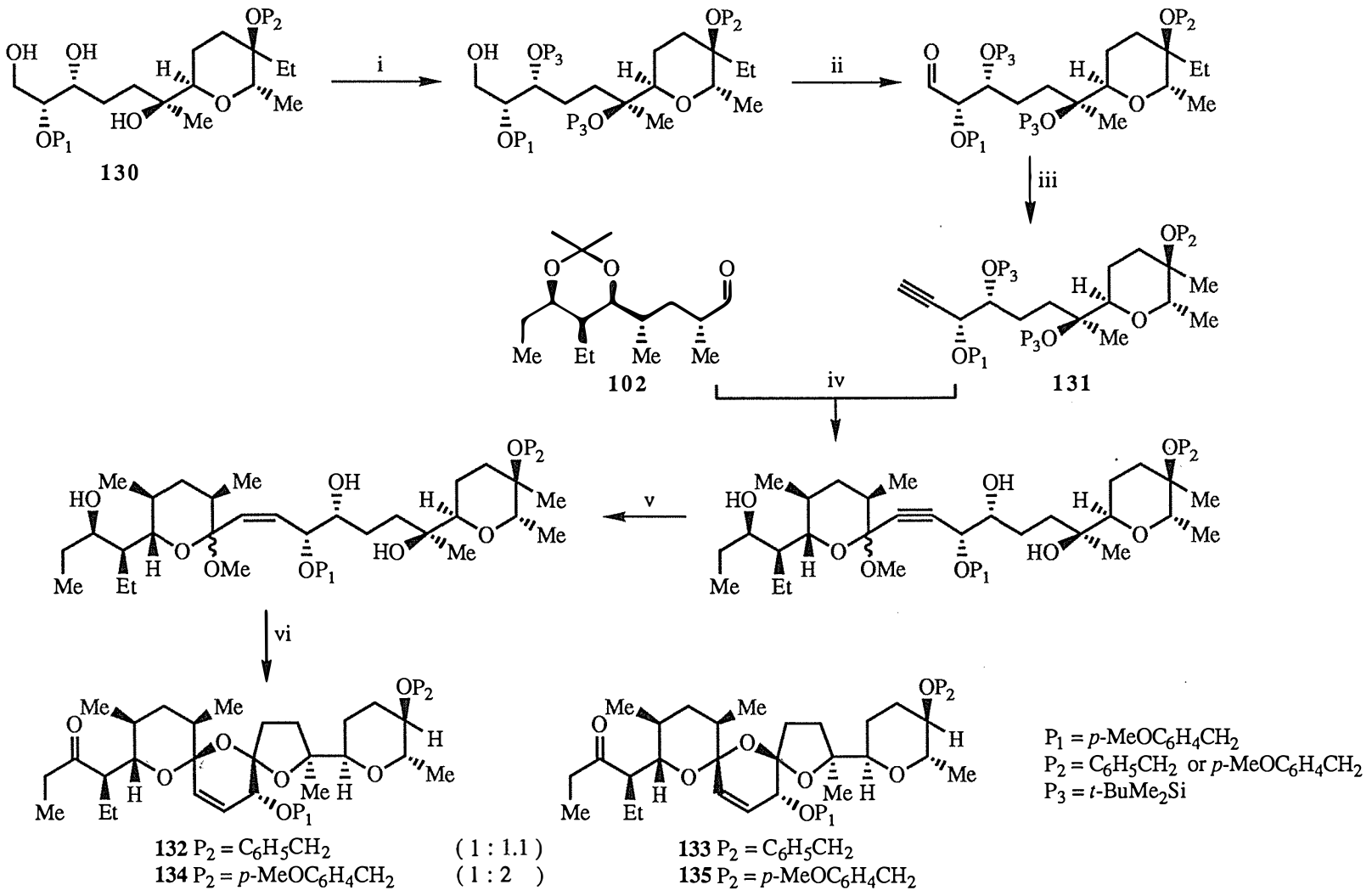
Formation of the bisspiroketal **100** (scheme 25) was achieved by low temperature coupling of the aldehyde **102** with the lithium acetylide derivative of **125**. Subsequent oxidation to the acetylenic ketone **126** and removal of the acetonide enabled formation of the bis-ketal **127**, which, after *cis*-hydrogenation, underwent further intramolecular ketalisation to a mixture of diastereomeric bisspiroketals **128**. These were equilibrated to a single acetylated isomer **100** of the target compound **99** (see scheme 20).

Subsequently, Yonemitsu *et al* published[46] a total synthesis of salinomycin **7**, based partly on their former work.

Scheme 26



Scheme 27



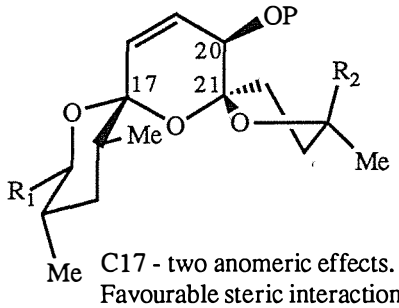
Reagents and conditions: (i) a: $C_6H_5CH_2Cl$, Pyridine, CH_2Cl_2, 0°C; b: *t*-$BuMe_2SiOTf$, NEt_3, CH_2Cl_2, 0°C; c: KOH, MeOH, 55°C; (ii) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then NEt_3; (iii) a: $PhHgCl_2Br$, PPh_3, benzene, 80°C; b: *n*-BuLi, THF, -78°C; (iv) a: *n*-BuLi, THF, -78°C then **102**; b: CSA, MeOH, RT; c: *n*-Bu_4NF, THF/dioxane, 65°C; (v) Lindlar catalyst, H_2, MeOH; (vi) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then NEt_3; b: CSA, CH_2Cl_2, RT.

Their retrosynthesis (scheme 26), like that of Kishi (see scheme 4) required disconnection of the crossed aldol (step a) to give the left and right hand fragments **25** and **27**. The right hand portion was in turn constructed from the aldehyde **102** and acetylene **129** which could be derived from the aldehyde **111** and acid **112**. The resemblance of this portion of the strategy to the synthesis described previously (see scheme 20) is immediately apparent, but the key modification was that the intramolecular ketalisation steps were postponed until after the coupling of **102** and **129**. This amended procedure was to afford both improved yields and a simpler diastereomeric mixture, which proved easier to characterise.

The tetrahydropyran **130**, an intermediate common to the previous synthesis (from scheme 24), was converted (scheme 27) to the tetrahydropyranyl acetylene **131**. The lithium acetylide derivative was then combined with the aldehyde **102** (from scheme 21) and the product transformed into an isomeric mixture of bisspiroketals **132** and **133** or **134** and **135**, the ratios of which were dependent to an extent on the nature of the protecting groups.

However, the ratios themselves appeared somewhat incongruous when compared with the results of Kishi[30] (see Scheme 19), because what appears to be the least thermodynamically stable of these isomers is favoured.

Figure 7

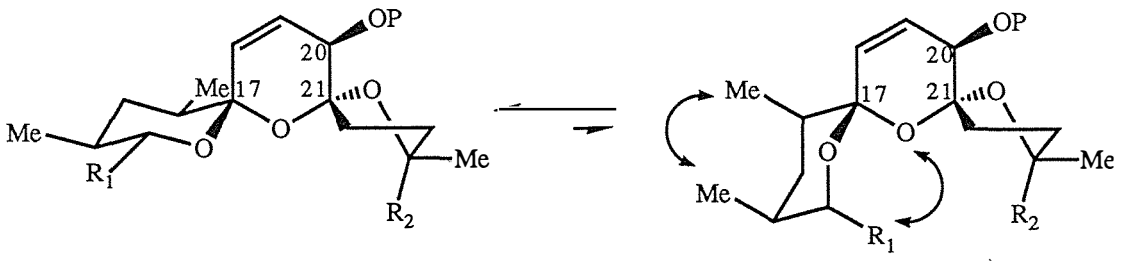


C17 - two anomeric effects.
Favourable steric interactions.

Kishi's *trans* bisspiroketal **100**: P=OAc

Yonemitsu's less-favoured *trans* bisspiroketal **132** or **134**: P=*p*-$MeOC_6H_4CH_2$

Yonemitsu's favoured *trans* bisspiroketal **133** or **135**: P=*p*-$MeOC_6H_4CH_2$

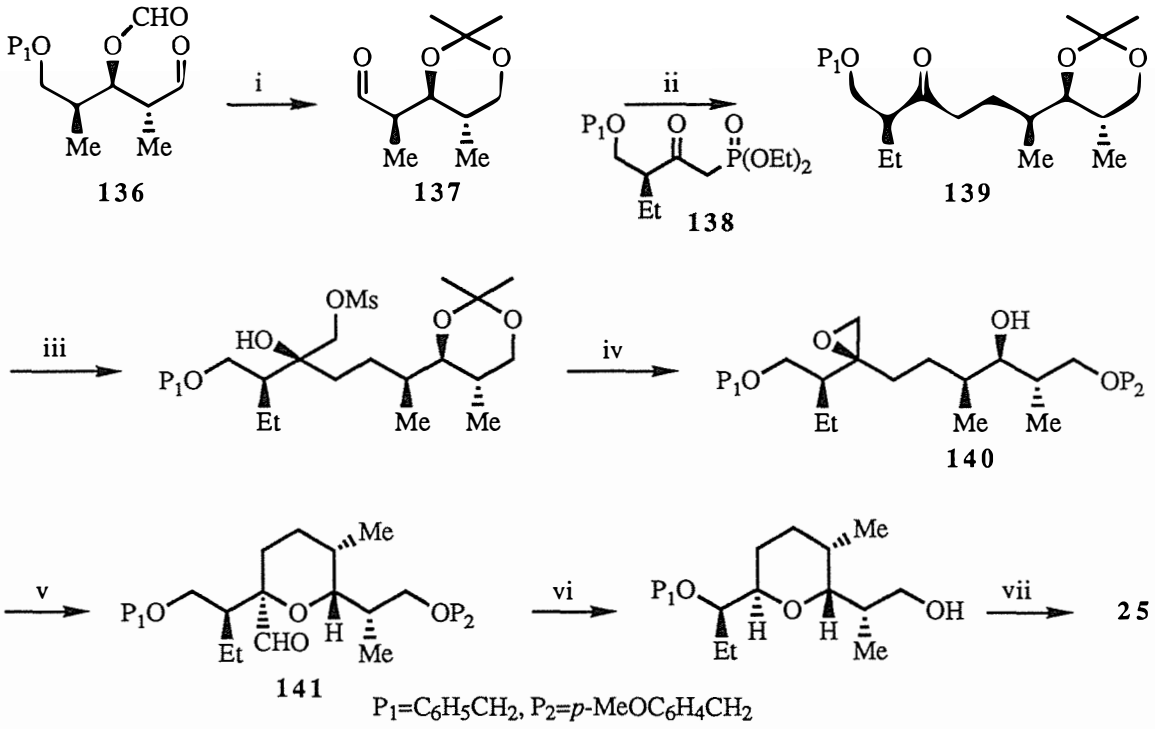


C17 - one anomeric effect.
Favourable steric interactions.

C17 - two anomeric effects.
Unfavourable steric interactions.

Analysis of the conformations (figure 7) shows that for Kishi's *trans* bisspiroketal **100**, the C17-O bond of the central ring adopts an *axial* position with respect to it's neighbouring ring, giving rise to two stabilising anomeric effects[47-50] at that spiro centre. Conversely, for the Yonemitsu case, the corresponding C17-O bond of the central ring in the favoured isomer **133** or **135** adopts an *equatorial* position, giving only one stabilising anomeric effect at that same C17 spiro centre (a conformational change to give two such effects results in prohibitive 1,3 diaxial interactions (figure 7)), and yet the other isomer **132** or **134**, corresponding to that of Kishi and which possesses an apparently more stable configuration, is less favoured under these thermodynamic conditions. No explanation was offered for this apparent anomaly although the nature of the protecting groups may play a role in this outcome.

Scheme 28



Reagents and conditions: (i) a: $LiAlH_4$, Et_2O, 0°C; b: $Me_2C(OMe)_2$, CSA, RT; c: Pd/C, H_2, EtOH, RT; d: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then NEt_3; (ii) a: NaH, DMF/THF, 0°C; b: Pd/C, EtOAc, H_2, RT; (iii) a: CH_2=CHMgBr, THF, -78°C; b: O_3, CH_2Cl_2, -78°C, $NaBH_4$; c: MsCl, NEt_3, CH_2Cl_2, 0°C; (iv) a: 1M HCl, THF, RT; b: K_2CO_3, MeOH, RT; c: *p*-$MeOC_6H_4CH_2Cl$, NaH, THF, RT; (v) a: CSA, CH_2Cl_2, 0°C; b: DMSO, $(COCl)_2$,CH_2Cl_2, NEt_3; (vi) $(Ph_3P)_3RhCl$ (Wilkinson's catalyst), MeCN, 160°C; (vii) a: DDQ, CH_2Cl_2/H_2O, RT; b: DMSO, $(COCl)_2$, CH_2Cl_2 -78°C then NEt_3; c: $(CH_2OH)_2$, TsOH, benzene; d: Pd/C, H_2, EtOAc; e: CrO_3, H_2SO_4, acetone; f: 2M HCl, THF.

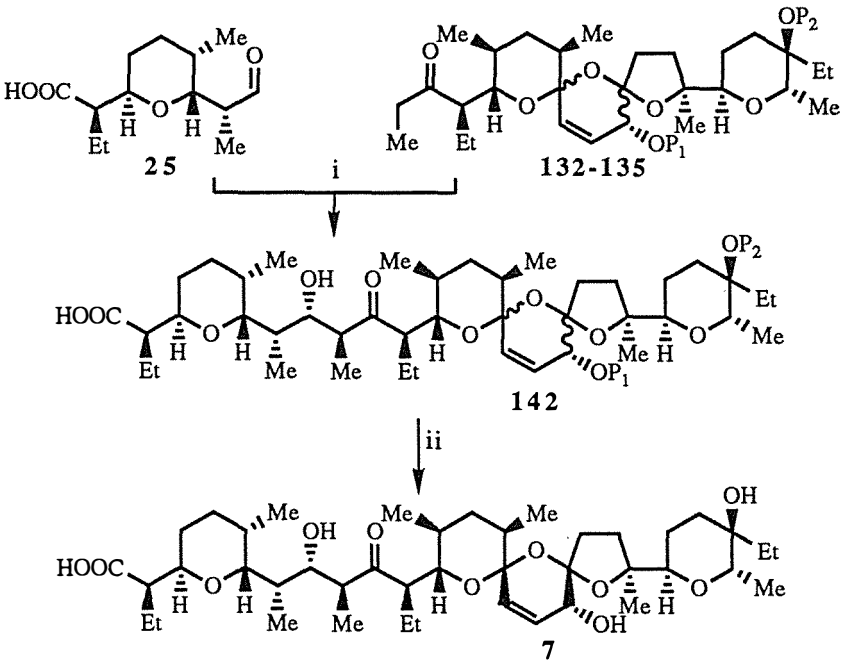
The Left Hand Fragment.

The left hand fragment **25** (see scheme 26) was synthesised (scheme 28) from the aldehyde **136**. Precise details for the synthesis of this precursor have not been reported, but it's construction from D-glucose has been alluded to in previous work by Oikawa *et al.*[51]. Chain extension by conversion of **136** to the aldehyde **137** followed by coupling with the β-ketophosphonate **138**, the preparation of which has, again, yet to be detailed, afforded the ketone **139** which was stereoselectively converted to the epoxide **140**. This allowed generation of the tetrahydropyran ring of **141** under acid catalysed conditions, and the product was subsequently converted to the desired intermediate **25**.

Completion of the Synthesis.

Having obtained the two fragments **25** and **132-135**,which constitute the left and right hand portions of salinomycin, they were combined (scheme 29) in a crossed aldol reaction in precisely the same fashion that Kishi carried out this step.[30] Deprotection of the aldol product **142**, followed by equilibration in acid, afforded a single isomer of the natural product, salinomycin **7**.

Scheme 29



P_1=*p*-$MeOC_6H_4CH_2$, P_2=$C_6H_5CH_2$ or *p*-$MeOC_6H_4CH_2$

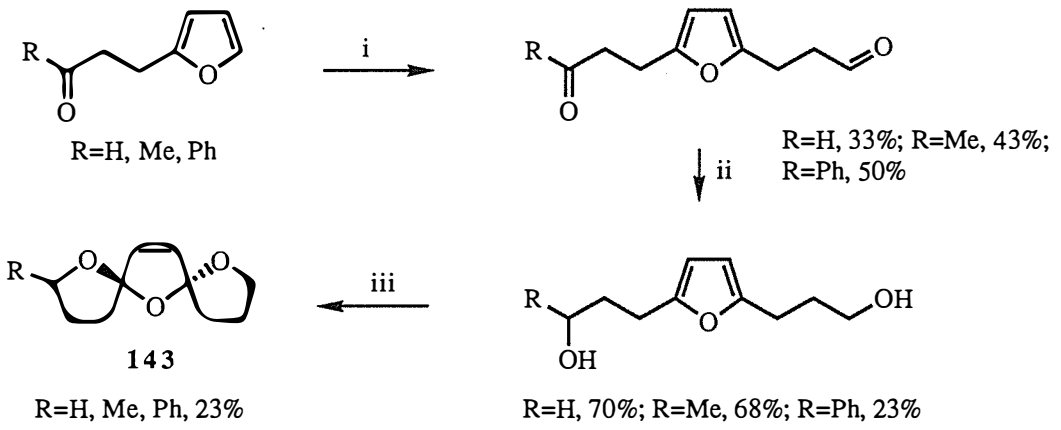
Reagents and conditions: (i) $(C_6H_{11})_2NMgBr$, THF, -55°C; (ii) (For $P_2 = C_6H_5CH_2$) DDQ, CH_2Cl_2, buffer (pH 6.86), RT, 1.5 h., 15%; (ii) (For P_2 = *p*-$MeOC_6H_4CH_2$) a: DDQ, CH_2Cl_2/H_2O (10:1), RT, 10 min., 95%; b: TFA, CH_2Cl_2, 70%,

1.5 Synthesis of Tricyclic Bisspiroketals.

A large number and variety of methods now exist to construct bicyclic spiroketals,[52] but relatively few methods have been developed for synthesising bisspiroketals.

The first of these was reported in 1963 by Ponomarev and Markushina[53] who described a preparation of substituted 1,6,8-trioxadispiro[4.1.4.2]tridec-13-enes **143** *via* an electrolytic alkoxidation using a nickel cathode and carbon anode (scheme 30). The cyclisation was later established to be *trans* stereoselective based on dipole measurements.[54]

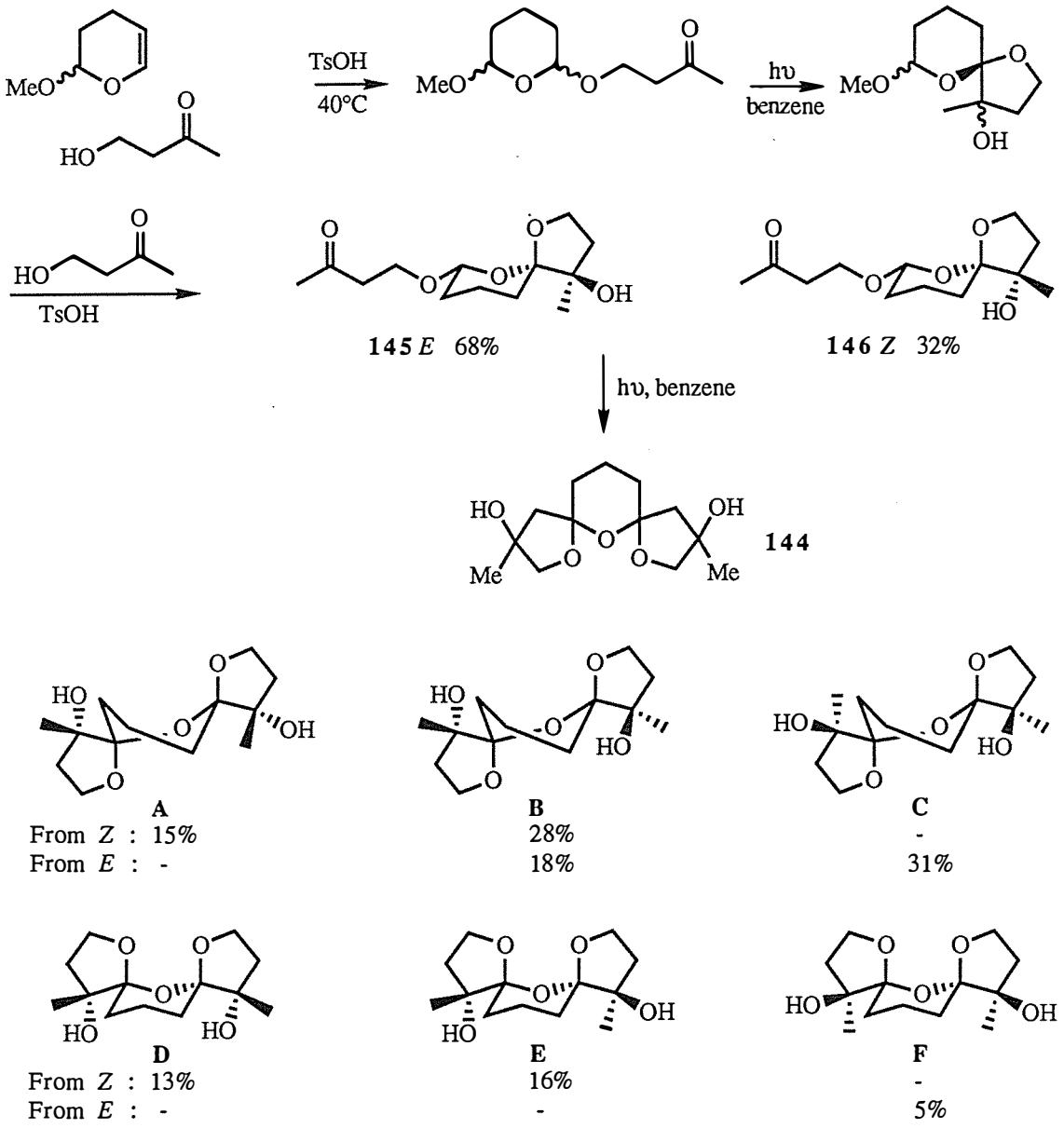
Scheme 30



Reagents and conditions: (i) H^+, CH_2=CHCHO, 100°C, 2-5 h.; (ii) H_2, copper chromite, 120°C/130 atm, EtOH; (iii) Ni cathode, C anode, NH_4Br, MeOH.

Some time was to elapse before Descotes *et al* [55] described the photolytic generation of 4,11-dihydroxy-4,11-dimethyl-1,6,8-trioxadispiro[4.1.4.3]tetradecane **144** employing a Norrish type II reaction (scheme 31). Irradiation of compounds such as **145** and **146**, in which there is an acetal hydrogen δ to the carbonyl and no hydrogen atoms in the γ position,[56] results in hydrogen abstraction and spirocyclisation of the intermediate biradical.[57] The non-stereoselective nature of this cyclisation gave rise to varying ratios of all six possible stereoisomers, each of which was isolated and characterised.[55,58] The diastereoselectivity of these compounds was subsequently investigated under thermodynamic conditions.[59] After treating isomers **A**, **C** and **E** with camphorsulphonic acid and examining the product ratios, predominantly the *cis* isomer **E** was observed with trace quantities of **C**, and, similarly, equilibration of isomers **B**, **D** and **F** afforded equimolar mixtures of the *cis* isomers **D** and **F**. Thus, thermodynamic equilibration of a given isomer gave the *cis* arrangement of the bisspiroketal, in which the C-O bonds of the terminal rings

Scheme 31

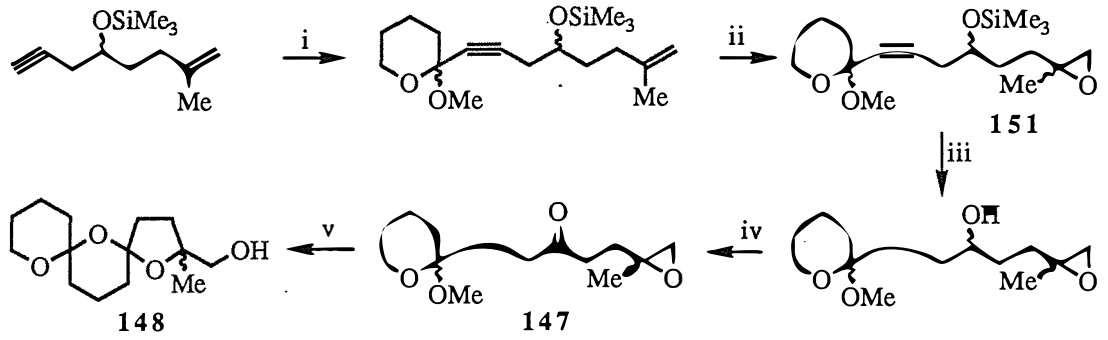


occupy axial positions on the tetrahydropyran ring, which itself adopts a chair conformation. This maximises the number of stabilising anomeric effects[47-50] and relieves the steric interactions between terminal ring oxygen atoms and opposing methyl groups - effects which are pronounced in the *trans* isomers and force the central rings to adopt unfavourable skew boat configurations.

Studies by Baker and Brimble,[60] directed at modelling the unsaturated bisspiroketal moiety of salinomycin **7**, focused firstly on an acid catalysed cascade ring closure of keto epoxide **147** (scheme 32). This afforded 1-(2-methyl-1,6,8-trioxadispiro[4.1.5.3]

pentadecan-2-yl)methanol **148**, the conformation of which was not definitively assigned. However, attempts to construct the unsaturated ring system, which corresponds to that present in the natural product, by the same acid catalysed procedure were unsuccessful.

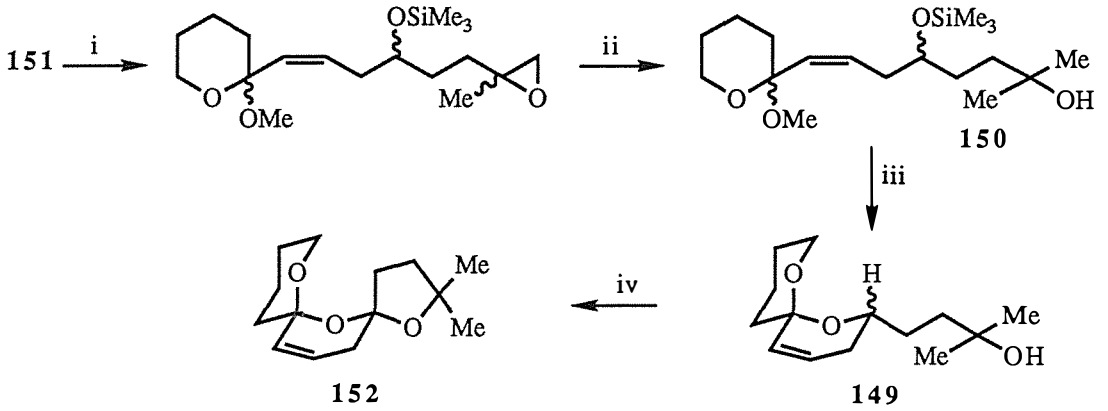
Scheme 32



Reagents and conditions: (i) a: *n*-BuLi, THF, -78°C, δ-valerolactone; b: MeOH, Amberlite IR 118 resin; c: Me_3SiCl, NEt_3, THF; (ii) a: MCPBA, CH_2Cl_2, NaOAc; (iii) a: *n*-Bu_4NF, THF; b: H_2, Pd/C, EtOAc; (iv) DMSO, TFAA, CH_2Cl_2, -60°C then NEt_3; (v) CSA, CH_2Cl_2.

An alternative approach was therefore undertaken, which involved construction of 2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene *via* a photolytically induced free radical process (scheme 33). The spiroketal **149** was formed by an acid catalysed cyclisation of the ketal **150**, derived from an intermediate **151** of the previous route (see scheme 32).

Scheme 33

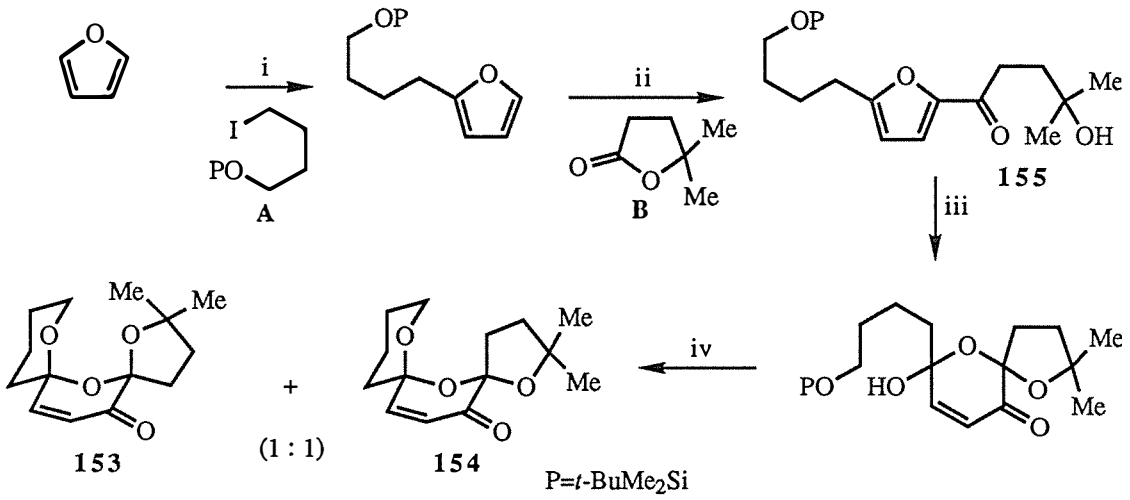


Reagents and conditions: (i) H_2, $Pd/CaCO_3$-$Pb(OAc)_2$, pentane; (ii) $LiAlH_4$ (0.5 eq.), Et_2O; (iii) CSA, CH_2Cl_2; (iv) $PhI(OAc)_2$ (1 eq.), I_2 (0.5 eq.), cyclohexane, hυ.

The conformation of the spiro centre of **149** is one in which the C-O bonds of that centre adopt axial positions with respect to their respective neighbouring rings, thereby deriving maximum stability from anomeric effects.[47-50] A Barton-type oxidative cyclisation, employing iodobenzenediacetate, afforded the bisspiroketal **152**, the stereochemistry of which was assigned by spectroscopic means. Elaboration of this work[61,62] forms part of the basis for this thesis.

During the course of this work, Albizati and Perron[63] and Kocienski *et al* [64] independently reported an elegant procedure to construct the 15-oxo-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes **153** and **154** *via* the oxidation and rearrangement of a 2-furyl ketone **155** (scheme 34).

Scheme 34

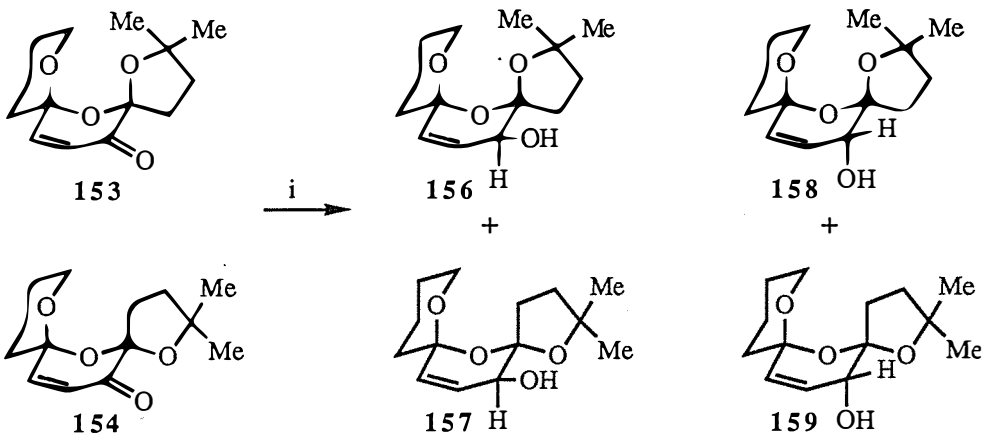


Reagents and conditions: (i) *n*-BuLi, THF, -23°C then **A**; (ii) *n*-BuLi, Et_2O, TMEDA, -23°C then **B**; (iii) NBS, THF/H_2O, 0°C; (iv) HF, CH_3CN, 0°C.

A 1:1 ratio of the diastereomeric bisspiroketals **153** and **154** was obtained in both instances and although the *cis* isomer **153** derives maximum stabilisation from anomeric effects, it did not predominate in the product mixture, probably due to unfavourable dipole interactions which are largely obviated in the *trans* isomer **154**. At this point it was envisaged that facile reduction of the carbonyl group (scheme 35) would afford, from the *cis* isomer, the allylic alcohol with stereochemistry resembling that of salinomycin and narasin. Indeed, Albizati reported this to be the case, obtaining compounds **156** and **157** - in direct contrast to the results of similar experiments performed by Kocienski, in which predominantly the alternative configurations **158** and **159** were obtained. The more

comprehensive nature of these latter experiments coupled with findings reported[65] later in this thesis serve to support Kocienski's results on this point.

Scheme 35

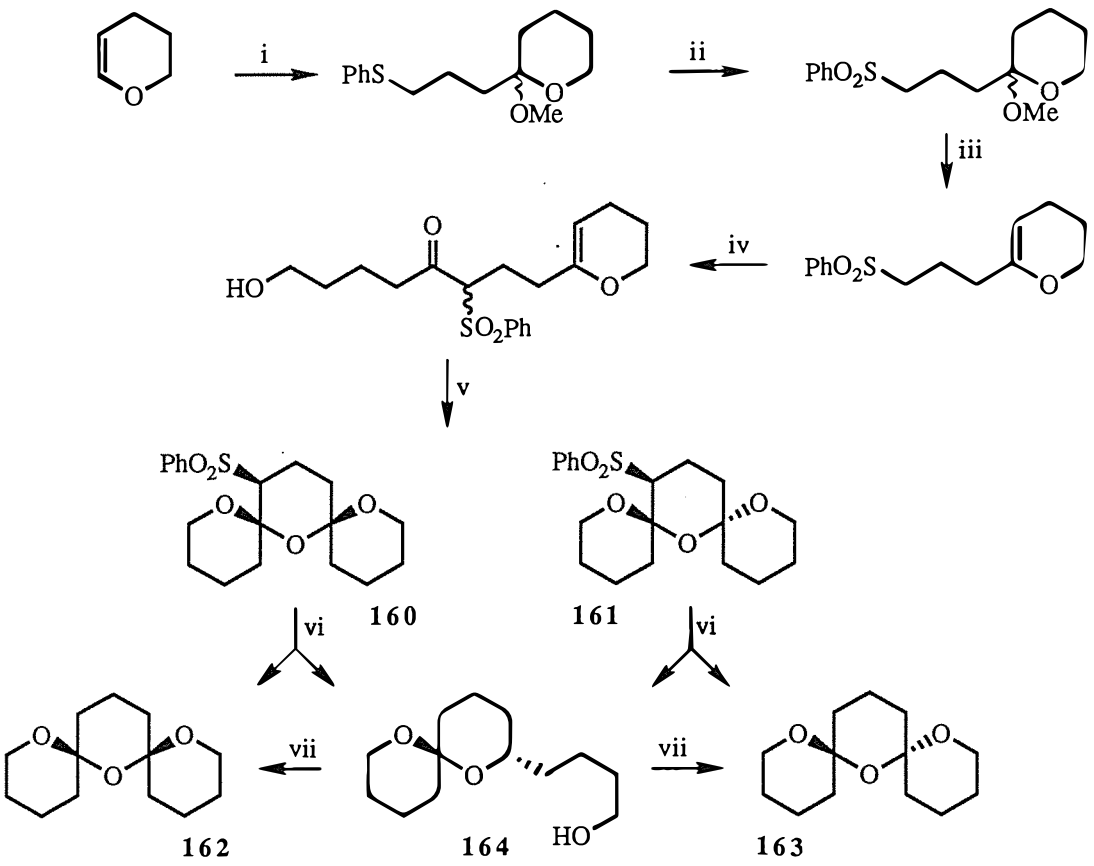


Brimble *et al* [66] recently reported a method for constructing a bisspiroketal ring system which involved a low temperature nucleophilic attack of an α-sulphonyl anion on a lactone (scheme 36). 14-Phenylsulphonyl-1,7,9-trioxadispiro[5.1.5.3]hexadecane was obtained as a 1:1 mixture of isomers **160** and **161**, the structures of which were assigned by X-ray crystallographic analysis in the case of **161** and nmr spectroscopy in the case of **160**.

Reduction of the phenylsulphonyl group of the individual isomers afforded the corresponding *cis* and *trans* 1,7,9-trioxadispiro[5.1.5.3]hexadecanes, **162** and **163**, along with the spiroketal **164** as the major product. This was found to readily undergo oxidative cyclisation, using conditions alluded to previously,[60] to afford a separable mixture of **162** and **163**.

Further work, which will be discussed in this thesis, will extend the application of the methodology originally employed by Baker and Brimble[60] (see scheme 33) to the synthesis of more highly functionalised bisspiroketals, and ultimately to a synthesis of the bisspiroketal moiety of *epi*-17-deoxy-(O-8)-salinomycin **8**.

Scheme 36



Reagents and conditions: (i) a : *n*-BuLi, THF, 55°C then $PhS(CH_2)_3Br$; b: Amberlite IR 120 resin, MeOH; (ii) a: $NaBO_3.4H_2O$, KOH, MeOH; b: Amberlite IR 120 resin, MeOH, Δ; (iii) *n*-BuLi, THF, -78°C then δ-valerolactone; (v) CSA, CH_2Cl_2; (vi) Raney nickel; (vii) Iodobenzenediacetate, I_2, cyclohexane, hυ.

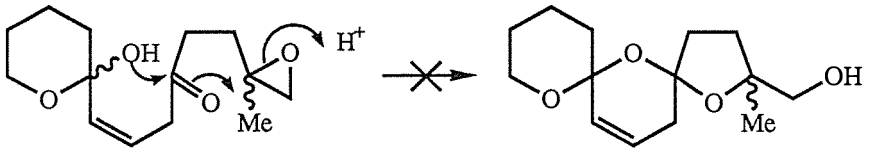
Chapter 2

Synthesis of 1,6,8-Trioxadispiro[4.1.5.3]pentadec-13-ene Ring Systems.

2.1 Retrosynthesis and Synthetic Strategy

The synthetic strategies of Yonemitsu *et al* [42,46] and Kishi *et al*,[30] by which the bisspiroketal fragment **27** of salinomycin **7** or narasin **10** was synthesised, possessed certain similar characteristics. Key aspects of both were that the terminal tetrahydropyran ring was constructed, with appropriate stereochemical features, prior to assembly of the bisspiroketal moiety itself. This tricyclic unit was in turn built up in a stepwise fashion requiring, in the case of both syntheses, acid catalysed intramolecular ketalisation steps to form both spiro centres. A proposed extension of this to an acid catalysed cascade ring closure of an epoxide **165** (equation 2),to form an unsaturated bisspiroketal ring system had been shown to be ineffective,[60] and therefore an alternative route was proposed by which those polyether antibiotics containing a bisspiroketal such as salinomycin **7** might be synthesised.

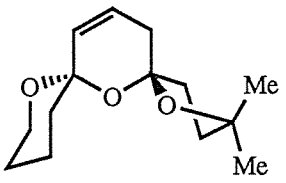
Equation 2



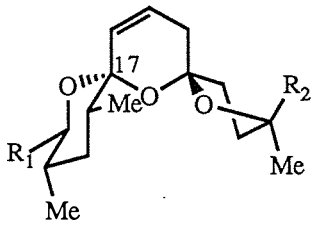
165

Based on the precedent set by the work of Baker and Brimble[60] (see scheme 33), in which an unsaturated bisspiroketal **152** was generated under photolytic conditions, it was envisaged this methodology could be extended to a synthesis of the natural products themselves. In that instance, the spiro centre joining the six membered rings of **149** was formed under thermodynamic acid catalysed conditions, giving the conformation in which the C-O bonds adjoining the rings adopt axial positions, in accordance with the anomeric effect.[47-50] The stereochemistry of that centre is retained throughout the remainder of the procedure, affording a product with a ring system resembling that of *epi*-17-deoxy-(O-8)-salinomycin **8** and *not* that of salinomycin **7**, which is epimeric at that corresponding C17 centre (figure 8). Accordingly the synthetic target is **8**.

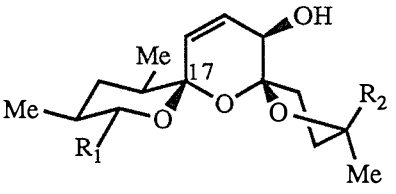
Figure 8



trans-2,2-Dimethyl-1,6,8-trioxadispiro [4.1.5.3]pentadec-13-ene **152**



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



Salinomycin **7**

A comparison between the bisspiroketal conformations of the model compound **152**, obtained by Baker and Brimble, *epi*-deoxy-(O-8)-salinomycin **8** and salinomycin **7** (or narasin **10**) shows which of these natural products is the approriate synthetic target.

A proposed retrosynthesis of this natural product (scheme 37) which incorporates this alternative methodology makes use of the same retro-aldol disconnection, previously employed by both Yonemitsu (see scheme 26) and Kishi (see scheme 4), to afford the left and right hand fragments **25** and **166** respectively. The right hand portion is then further simplified to the bisspiroketal **167**, which is selectively functionalised at the termini to permit subsequent elaboration. **167** is generated *via* an oxidative cyclisation of the spiroketal **168**, it in turn being derived from the epoxide **169**. The synthetic precursors for **169** are the optically active lactone **84** and functionalised acetylene **170**.

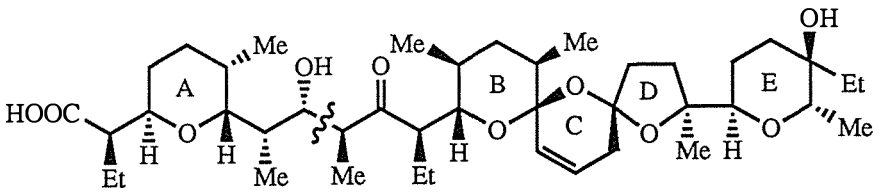
Before embarking on such a synthetically demanding undertaking, it was decided that the feasibility of the procedure should be established using as comprehensive a model system as possible, which allows for circumvention of some of the pitfalls that inevitably arise in the course of any lengthy synthesis. Additionally, such a model permits a full investigation, in a stepwise manner, into the pertinent stereochemical attributes of these bisspiroketals formed under the proposed conditions.

2.2 Synthesis of the Cyclisation Precursor 4-(1',7'-Dioxaspiro[5.5]undec-4'-en-2'-yl)-2-Methyl-2-Butanol. **149**

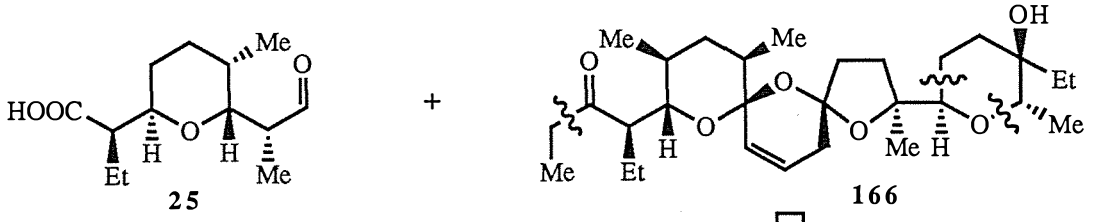
trans-2,2-Dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **152** is a simple analogue of the tricyclic system of *epi*-17-deoxy-(O-8)-salinomycin **8** and was formed, as described earlier[60] (see scheme 33), from the spiroketal **149** under photolytic conditions.

For the purpose of that investigation, the cyclisation precursor, spiroketal **149**, was synthesised[60] from methallyl alcohol (scheme 38). This alcohol was firstly elaborated to the acetylene **171**, the lithium acetylide derivative of which was coupled with δ-valerolactone.

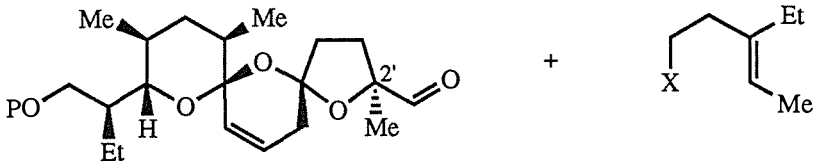
Scheme 37



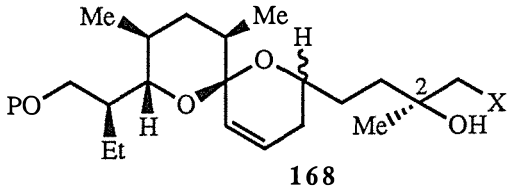
epi-17-Deoxy-(O-8)-salinomycin **7**



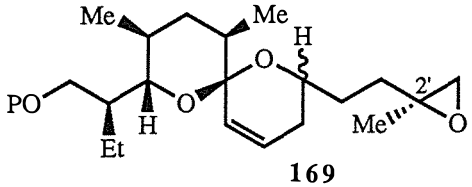
25 **166**



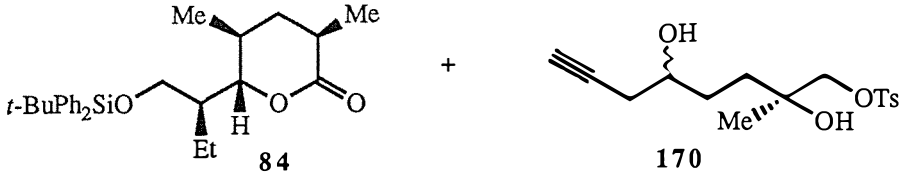
167



168

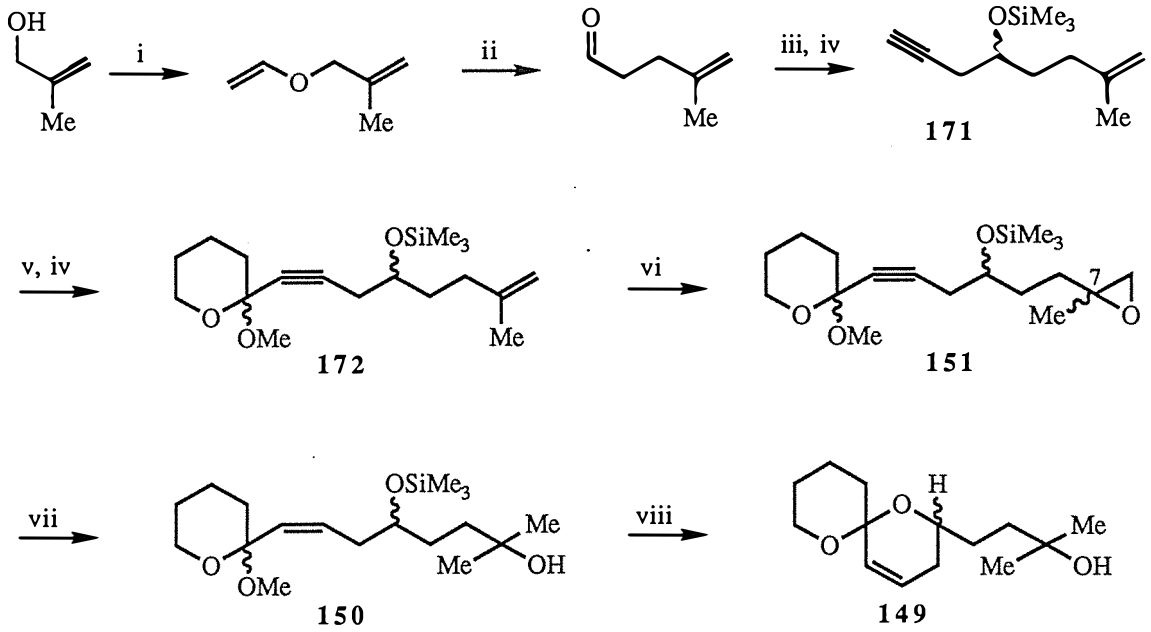


169



84 **170**

Scheme 38



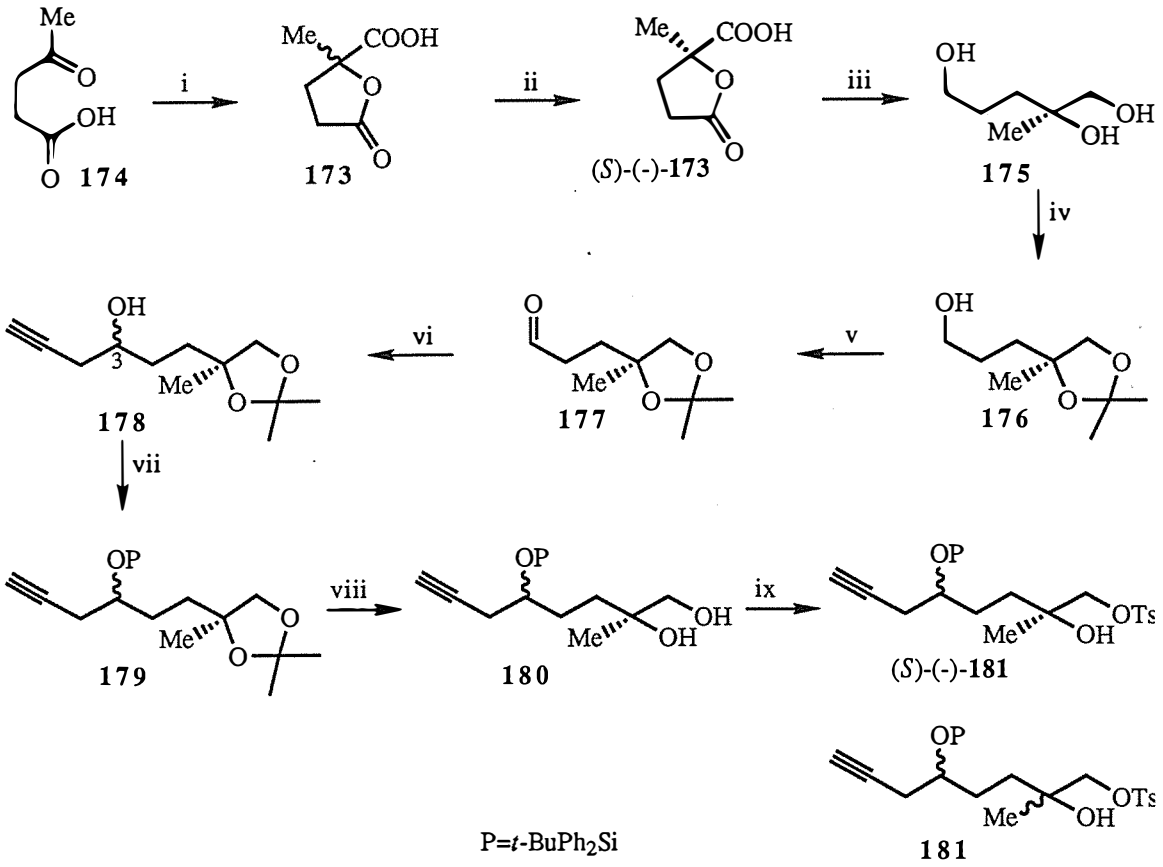
Reagents and conditions: (i) $EtOCH{=}CH_2$, $Hg(O_2CCF_3)_2$; (ii) 120°C, 24 h.; (iii) $HC{\equiv}CCH_2Br$, Zn, THF, 0°C; (iv) Me_3SiCl, NEt_3, THF; (v) a: *n*-BuLi, THF, -78°C then δ-valerolactone, -78°C; b: MeOH, Amberlite IR 118 resin; (vi) MCPBA, CH_2Cl_2, NaOAc; (vii) a: H_2, Lindlar catalyst, pentane; b: $LiAlH_4$, Et_2O; (viii) CSA, CH_2Cl_2.

Further steps, involving ketalisation, epoxidation and hydrogenation, followed, culminating in an acid catalysed intramolecular cyclisation of **150** to generate the spiro centre of **149**.

Although not a consideration for the original study, the sequence could not be amended to resolve C7 of the epoxide **151**, coming as it did from the olefin **172**. This is an important factor if the scheme is to be extended to an enantioselective synthesis since, with reference to the proposed retrosynthetic procedure (see scheme 37), this centre will give rise to C2' of the bisspiroketal **167**, the *S* configuration of which is essential.

A synthesis was therefore adopted which would enable the construction of a related acetylene which possessed the required stereochemistry at this centre. This was achieved (scheme 39) from the racemic lactonic acid **173**, which could be prepared on a large scale using the procedure of Iwami and Kawai[67] in which levulinic acid **174** was treated with sodium cyanide and the resulting cyanohydrin hydrolysed and esterified with hydrochloric acid. The acid was resolved using Mori's method[68] in which the salt of the (-)-acid, formed with the vegetable alkaloid 'cinchonine', being highly crystalline, could be separated from the non crystalline antipodal salt of the (+)-acid. Acidic hydrolysis of the resolved crystalline

Scheme 39



Reagents and conditions: (i) NaCN, NaOAc, H_2O then HCl conc Δ, 75%; (ii) Cinchonine, EtOH, crystallisation then HCl, 39%; (iii) $LiAlH_4$, Et_2O, RT, 12 h., 65%; (iv) Acetone, TsOH, RT 12 h., 85%; (v) DMSO, TFAA, CH_2Cl_2, -65°C, NEt_3, 78%; (vi) $HC{\equiv}CCH_2MgBr$, Et_2O, RT, 89%; (vii) *t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2, 8 h., 96%; (viii) MeOH, Amberlite IR 120 resin, 36 h., 81%; (ix) TsCl, pyridine, 22 h., 82%.

salt then afforded the pure (*S*)-(-)-acid **173** with an optical rotation in agreement with the reported value.[68]

Reduction of the (*S*)-(-)-acid **173** with lithium aluminium hydride in ether afforded the (*S*)-triol **175**. An improved yield over that previously reported[68] was obtained by repeatedly refluxing the salt residues in tetrahydrofuran, then filtering and evaporating the solvent. Subsequent treatment of the crude triol with *p*-toluenesulphonic acid in acetone gave the more manageable (*S*)-acetonide **176**, again with a literature[68] optical rotation, which was purified by flash chromatography.[69] Oxidation of the alcohol **176** using dimethylsulphoxide activated[70] by trifluoroacetic anhydride in dichloromethane at -65°C afforded the (*S*)-aldehyde[71] **177** in satisfactory (78%) yield after purification. Addition of **177** to the Grignard reagent, generated over one hour from propargyl bromide and magnesium turnings in ether, to which a small amount of mercuric chloride had been added, afforded the

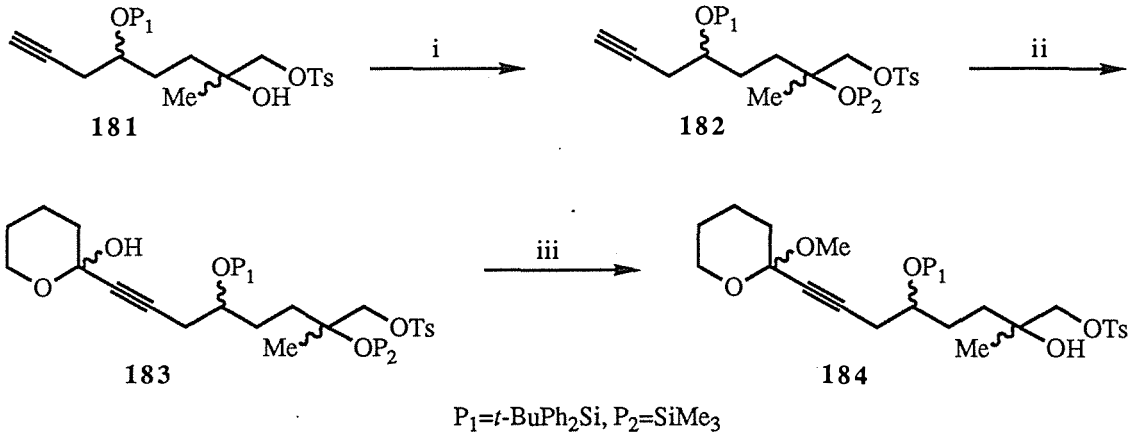
previously reported[71] (*S*)-acetylene **178** in 89% yield. The 270 MHz ^{1}H nmr spectrum of **178** exhibited two resonances of equal intensity at δ_H 1.28 and δ_H 1.29, assigned to the 4'-methyl group, indicating the product mixture was, expectedly, an equimolar mixture of the (3*R*, 4'*S*)- and (3*S*, 4'*S*)- diastereomers. Controlling the stereochemical outcome of this reaction was unnecessary because C3 of the acetylene was destined to eventually become a spiro centre, the stereochemistry of which is determined by other factors.

Completion of this portion of the synthesis was accomplished by a series of selective protection steps. A solution of the (*S*)-alcohol **178** in dichloromethane was stirred with imidazole and *tert*-butyldiphenylsilyl chloride under nitrogen at room temperature to afford the (*S*)-silyl ether **179** in high (96%) yield - a marked improvement than when the more usual solvent, dimethylformamide, was used (~80% yield). Cleavage of the acetonide by stirring a methanolic solution of **179** with acidic Amberlite IR 120 resin, gave the diol **180**, leaving the silyl ether unscathed. This enabled conversion of the resulting primary hydroxyl group to the tosylate derivative **181** by stirring **180** with an excess of *p*-toluenesulphonyl chloride in pyridine for 24 hours. The products obtained from each of these protection steps were purified by column chromatography[69] using an hexane/ethyl acetate mixture as eluant.

Although this procedure describes a synthesis of the (*S*)-acetylene **181**, for the purpose of investigating the model systems the corresponding racemic acetylene sufficed, and was obtained by simply omitting the resolution steps from the procedure.

With the racemic acetylene **181** in hand, a low temperature coupling of this with δ-valerolactone could then be investigated (scheme 40), to assess the lability of the tosyl group under the prescribed basic conditions. Firstly, the tertiary hydroxyl group of the (±)-acetylene **181** was protected as the trimethylsilyl ether **182**, in near quantitative yield, using a slight excess of 1-(trimethylsilyl)imidazole in dichloromethane. Treating a solution of **182** in tetrahydrofuran at -78°C with *n*-butyllithium for 0.5 h., followed by slow addition of a solution δ-valerolactone, afforded the hemiketal **183** (the cyclic form is depicted for clarity) which was not isolated but treated directly with acidic methanol at room temperature for several hours. This had the combined effect of removing the trimethylsilyl ether and forming the methyl ketal **184** in 71% overall yield. It was anticipated that **184** would prove more conducive to further manipulation since the possibility of complications arising in later steps due to the dynamic equilibrium between the closed and open chain forms of the hemiketal **183** is eliminated. Since a semi-hydrogenation step will follow in this synthesis, generating a ketal in this fashion is also in line with the experience of Baker *et al*[72] who found that, during synthesis of the spiroketal **185** (scheme 41), the problem of partial hydrogenation conditions saturating the hemiketal **186** could be effectively circumvented by firstly forming the ketal **187**.

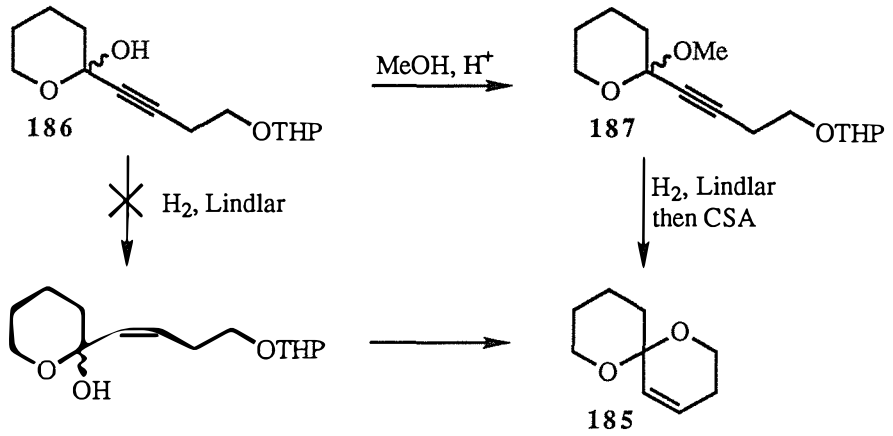
Scheme 40



P_1=*t*-$BuPh_2Si$, P_2=$SiMe_3$

Reagents and conditions: (i) 1-(Me_3Si)imidazole (1 equiv.), CH_2Cl_2, RT, 98%; (ii) *n*-BuLi (1 equiv.), THF, -78°C then δ-valerolactone; (iii) MeOH, H^+, RT, 71% from **182**.

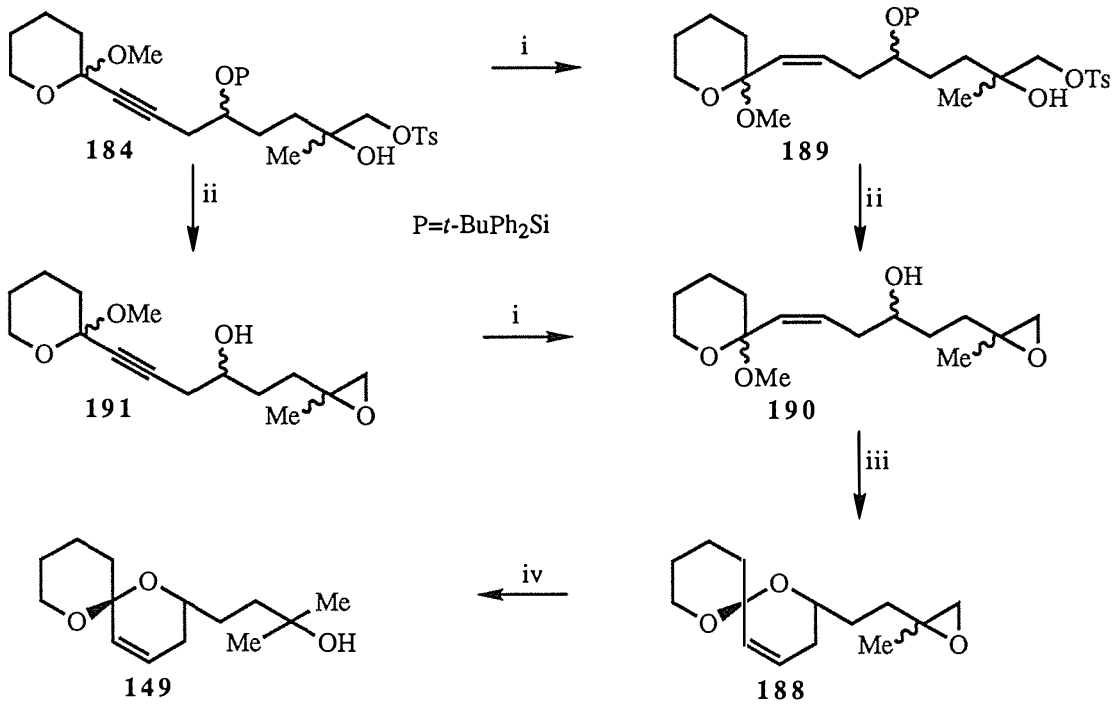
Scheme 41



A number of spectroscopic data indicated successful formation of the ketal **184.** The disappearance from the infra-red spectrum of the strong terminal acetylene absorbance at 3305 cm^{-1} and the appearance in the ^1H nmr spectrum, despite it's complexity due to the number of diastereomers, of a methoxy resonance at δ_H 3.35 confirmed successful coupling of the acetylene **181** and δ-valerolactone. In addition, the infra-red spectrum exhibited characteristic sulphonate absorbances at 1365 and 1178 cm^{-1} and the para-substituted aromatic ring pattern in the ^1H nmr spectrum was also evident, which confirmed the tosylate group was indeed retained under the reaction conditions. This was later supported by mass spectrometry which, under chemical ionisation (NH_3) conditions, gave a parent ion at *m/z* 679 which is consistent with the desired molecular formula $C_{38}H_{50}O_7SSi$ + H. Attempts to obtain satisfactory elemental analysis data for the compound were unsuccessful, probably due to the somewhat labile nature of this ketal function over extended periods of time.

Having successfully achieved this step, the way was now clear to a synthesis of the spiroketal-alcohol **149** (from scheme 38) *via* the spiroketal epoxide **188**, and was achieved in two ways (scheme 42).

Scheme 42



Reagents and conditions: (i) Lindlar catalyst, H_2, hexane/EtOAc, RT; (ii) *n*-Bu_4NF (excess), THF, RT; (iii) PPTS (cat), CH_2Cl_2, RT, 67% from **183**; (iv) $LiAlH_4$ (2 equiv.), Et_2O, RT, 0.1 h., 92%.

Firstly, a solution of the acetylene **184** in hexane and ethyl acetate, containing a trace of triethylamine to ensure a slightly basic medium, was stirred with Lindlar catalyst under hydrogen to give the *cis* olefin **189**, the vinyl protons of which were immediately apparent in the ^{1}H nmr spectrum, resonating at δ_H 5.23-5.62. Upon treatment of this olefin with tetra-*n*-butylammonium fluoride in tetrahydrofuran, two changes were observed; firstly, instantaneous epoxidation, due to the strongly basic conditions, then slower removal of the *tert*-butyldiphenylsilyl group[73] to afford the epoxy alcohol **190**. This compound was not isolated and characterised owing to it s propensity to cyclise to the spiroketal **188** under the mildest of conditions. Hence a solution of **190** in dichloromethane was treated directly with pyridinium *p*-toluenesulphonate to facilitate cyclisation to **188**. Alternatively, the acetylene **184** was firstly treated with tetra-*n*-butylammonium fluoride to afford the epoxy alcohol **191**, then partially hydrogenated to the *cis* olefin **190** which was not isolated but treated with pyridinium *p*-toluenesulphonate in dichloromethane to again afford the spiroketal **188**. Both routes were equally effective, affording the spiroketal in 65-67% yield overall. The spiroketal-alcohol[60] **149** was then formed by simply treating an ethereal solution of **188**, at room temperature, with lithium aluminium hydride.

At this point satisfactory syntheses of the epoxide **188**, which can be resolved at C2', a prequisite for extending the method to an enantioselective synthesis (compare epoxide **169**, scheme 37), and the spiroketal alcohol **149**, required for the preliminary model studies, was achieved. The next stage required a re-examination of the method used by Baker and Brimble[60] to generate a bisspiroketal during their synthesis of 2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **152**.

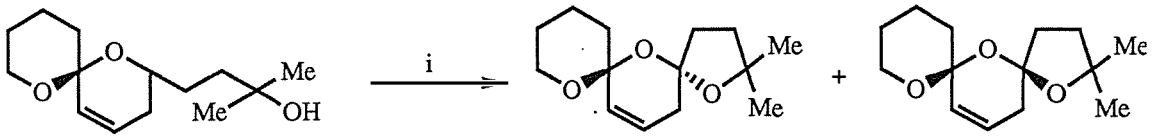
2.3 Synthesis of 2,2-Dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene. **152**, **192**

A stirred solution of the precursor **149** in cyclohexane under nitrogen, also containing two equivalents of iodine and three equivalents of iodobenzenediacetate, was irradiated (scheme 43) with a tungsten filament lamp for several hours. In order to avoid thermal decomposition of the reaction mixture the reaction vessel was partially immersed in a water bath maintained at about room temperature (15-18°C) during the irradiation. Under these conditions two products were cleanly formed and were easily separated by flash chromatography.[69]

The least polar of the two compounds was determined, by spectroscopic comparison, to be the 2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **152**, obtained previously,[60] for which the stereochemistry had been assigned as *trans*, or

resembling that of *epi*-17-deoxy-(O-8)-salinomycin **8**. This product, the major component, was isolated in 54% yield.

Scheme 43

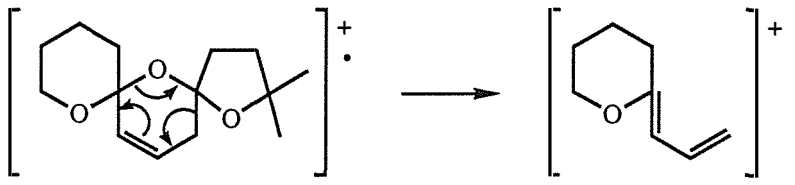


149 **152** 54% **192** 26%

Reagents and conditions: (i) $PhI(OAc)_2$ (3 equiv.), I_2 (2 equiv.), cyclohexane, 15°C.

The second, more polar component **192** was established as being a stereoisomer of **152**. The evidence for this was derived firstly by comparison of the mass spectra of the products since the spectrum of the novel compound resembled precisely that of the reported isomer, exhibiting a molecular ion at *m/z* 238, which is consistent with a molecular formula $C_{14}H_{22}O_3$. Additionally, the base peak at *m/z* 124 is consistent with the formula $C_8H_{12}O$ and corresponds to a retro-Diels-Alder fragmentation (equation 3), a phenomenon also observed in the mass spectrum of *epi*-17-deoxy-(O-8)-salinomycin.[10] This isomer **192** was isolated in 26% yield and tentatively assigned a *cis* stereochemistry (which is analogous to deoxy-(O-8)-salinomycin **9**), an assumption later justified by analysis of the ^1H nmr spectrum.

Equation 3



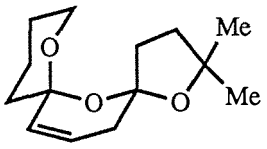
$C_{14}H_{22}O_3$ *m/z* 238 $C_8H_{12}O$ *m/z* 124

The fourteen resonances appearing in the ^{13}C nmr spectrum established the diastereomeric purity of the new product, and furthermore the two quaternary resonances at δ_C 93.6 and 104.2 were characteristic of spiroketal carbon atoms (compare δ_C 99.3 and 106.8 for the known isomer.[60] Other evidence, apart from the disappearance of an hydroxyl group absorbance from the infra-red spectrum of the cyclisation precursor **149**, was that the ^1H nmr resonances of the methyl groups, coincident in the ^1H nmr spectrum of **149** (at δ_H 1.24), now had separate shifts at δ_H 1.15 and 1.39 - suggesting they were attached to a ring.

Stereochemistry.

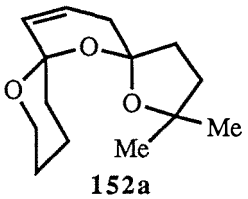
For the 2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring systems the two possible stereoisomers **192** and **152**, formed from the given sequence of cyclisation steps, are depicted (figure 9) along with their respective conformational isomers **192a** and **152a**. Taking into account the number of stabilising anomeric effects exhibited by the *cis* conformations **192** and **192a**, that adopted by **192**, which exhibits the maximum of four, would be deemed the more favourable. Although it exhibits apparently unfavourable dipolar interactions, evidence from other work[74] indicates that this is not an overriding factor in favour of **192a**.

Figure 9



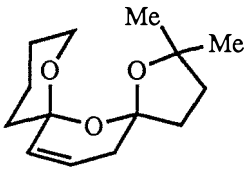
152

3 anomeric effects



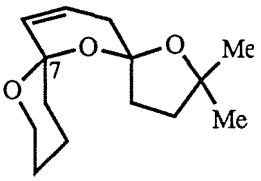
152a

3 anomeric effects



192

4 anomeric effects
Unfavourable dipole interactions



192a

2 anomeric effects

The dipole interactions are alleviated in the *trans* conformations **152** and **152a** both of which exhibit three anomeric effects. However, conformation **152a** possesses relatively unfavourable steric interactions between a methyl group and a methylene group of the saturated ring and hence **152**, in which the C-O bonds adjoining the six membered rings occupy axial or pseudo-axial positions, would be the favoured *trans* arrangement.

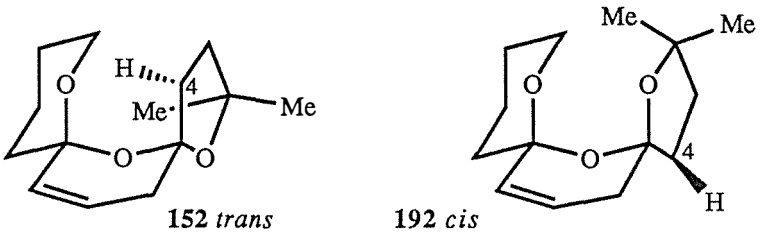
Taking into account the result of Westley's isolation of deoxy-(O-8)-salinomycin[10] in which the 17-*epi* or *trans* isomer was favoured, the conclusion which must be drawn regarding the relative stabilities of the *cis* isomer **192**, with four anomeric effects and unfavourable dipole interactions, and the *trans* isomer **152**, with three anomeric effects, is that the latter would be the preferred conformation. Equilibration of either **192** or **152** (pyridinium-*p*-toluenesulphonate in dichloromethane) gives rise to a product ratio of 2:1

trans:cis, thereby establishing that **152** is indeed the thermodynamically favoured conformation.

The 270 MHz ^{1}H nmr spectrum of each isomer is reproduced (figure 10) since comparative analysis of the spectra highlights a key difference which provides an indicator for distinguishing the ring conformation of each isomer. Additionally, the pertinent chemical shifts of both model compounds are given (table 1) along with the relevant ^{1}H nmr data reported for *epi*-17-deoxy-(O-8)-salinomycin **8**,[75] as this possesses a *trans* arrangement of the bisspiroketal unit. The ^{1}H nmr data reported for salinomycin **7**[76] is also included as it contains a *cis* bisspiroketal moiety, albeit with an allylic hydroxyl group.

It should be noted that for each isomer of the model bisspiroketals, the distinct difference between the two methyl resonances for each isomer (δ_H 1.48 and 1.24 in the *trans* **152**, and δ_H 1.39 and 1.15 in the *cis* **192**) occurs because one methyl group is 1,3-*syn* to a C-O bond of the central ring and is therefore somewhat deshielded (figure 11). The corresponding methyl groups of the natural products are also 1,3-*syn* to a C-O bond and hence experience a similar deshielding effect (see table 1).

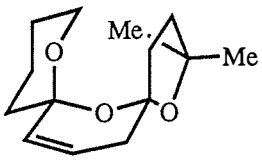
Figure 11



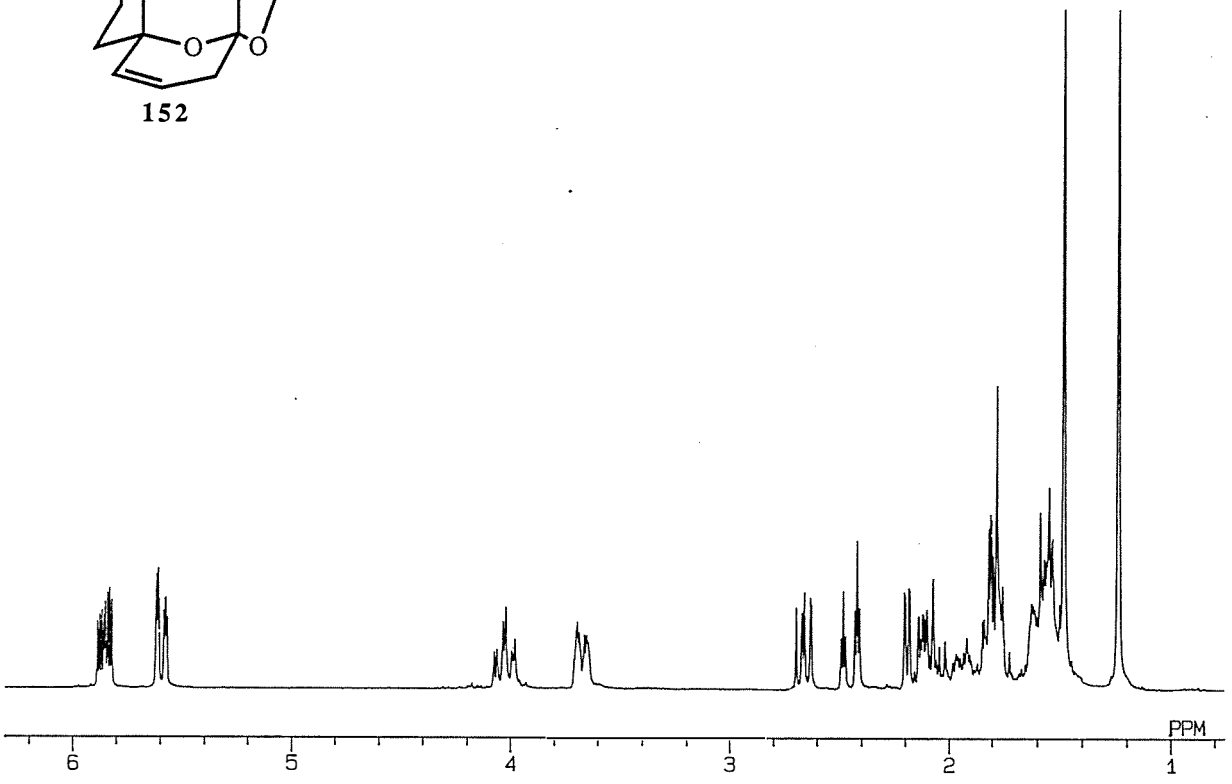
A comparison between the two 2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes shows that in both isomers one methyl group occupies a position 1,3-*syn* to a C-O bond of the central ring and is therefore relatively deshielded. However, for the *trans* isomer, one 4-H occupies a position close to the oxygen atomof the terminal 6 membered ring. This results in a marked deshielding of the 4-H resonance in the ^{1}H nmr spectrum, relative to the corresponding resonance for the *cis* isomer, and is indicative of *trans* isomerism in this ring system.

The obvious and most dramatic difference between the chemical shifts for the *cis* and *trans* isomers **192** and **152** occurs in the location of the 4-H resonance. For the *cis* isomer (and salinomycin **7**) this resonance appears in the range δ_H 1.98-2.12 whereas for the *trans* isomer and *epi*-17-deoxy-(O-8)-salinomycin **8** the resonance now appears downfield at δ_H 2.66 and at δ_H 3.01 respectively. The reason for this becomes obvious on examination of the spatial arrangement of **152** and **192** (figure 11). For the *trans* isomer the proximity of the 4-H proton to the oxygen atom of the terminal six membered ring causes a significant

Figure 10



152



192

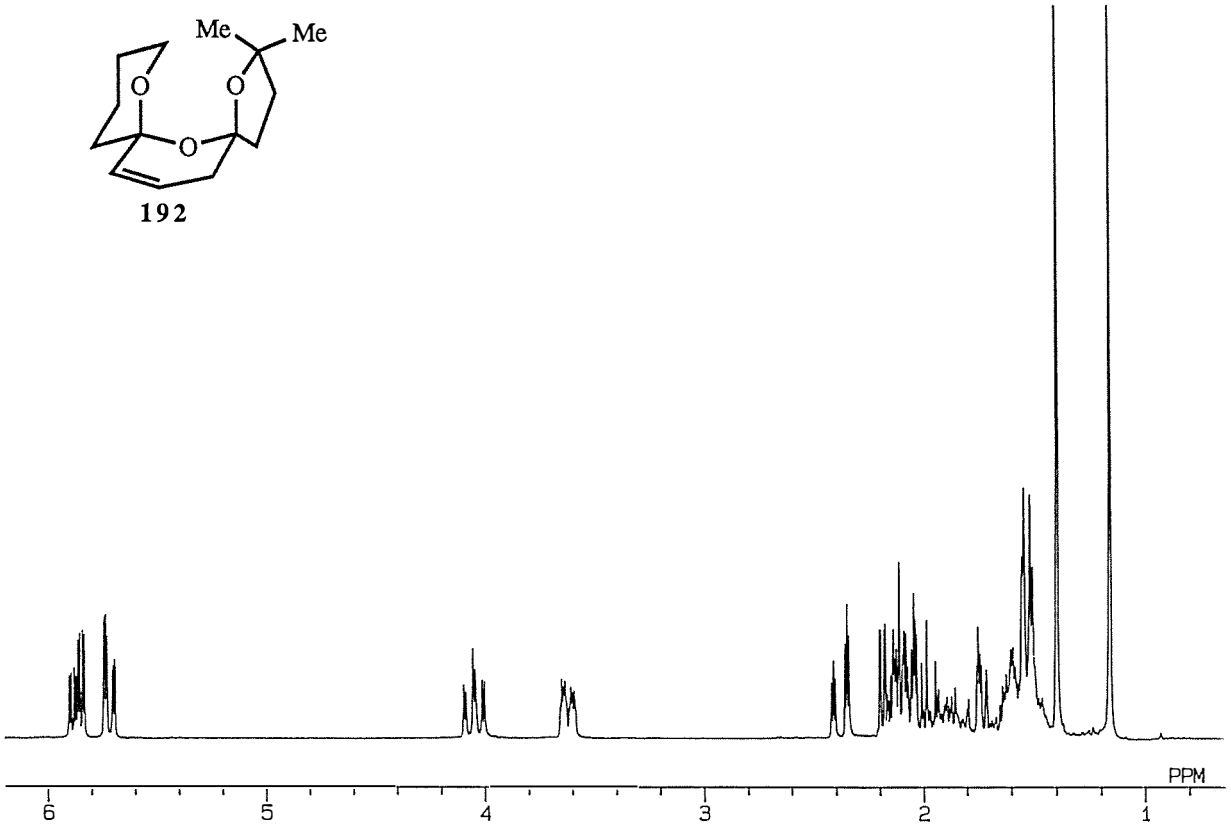
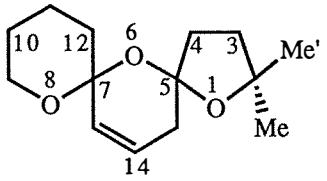


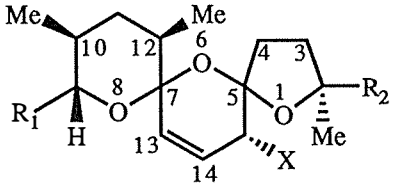
Table 1

^{1}H NMR Chemical Shift Values for 1,6,8-Trioxadispiro[4.1.5.3]pentadec-13-ene Ring Systems.



trans-2,2-Dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **152**[a]

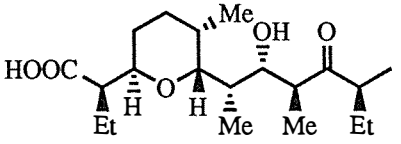
cis-2,2-Dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **192**[a]



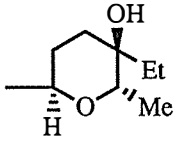
epi-17-Deoxy-(O-8)-salinomycin **8**[b] : X=H

Salinomycin **7**[b] : X=OH

R_1 =



R_2 =



Compound	2-Me	2-Me'	4-H'	3-H'	3-H	15-H'	15-H	4-H	13-H	14-H
8	1.43	-	1.59	1.95	2.09	2.03	2.40	3.01	5.46	5.88
152	1.48	1.24	1.75-1.83	1.75-1.83	2.04-2.13	2.16	2.45	2.66	5.59	5.86
192	1.15	1.39	1.96-2.12	1.70-1.75	1.96-2.12	2.37	2.10-2.20	1.98-2.12	5.71	5.86
7	1.48	-	2.40	1.84	2.23	-	-	2.09	5.98	6.03

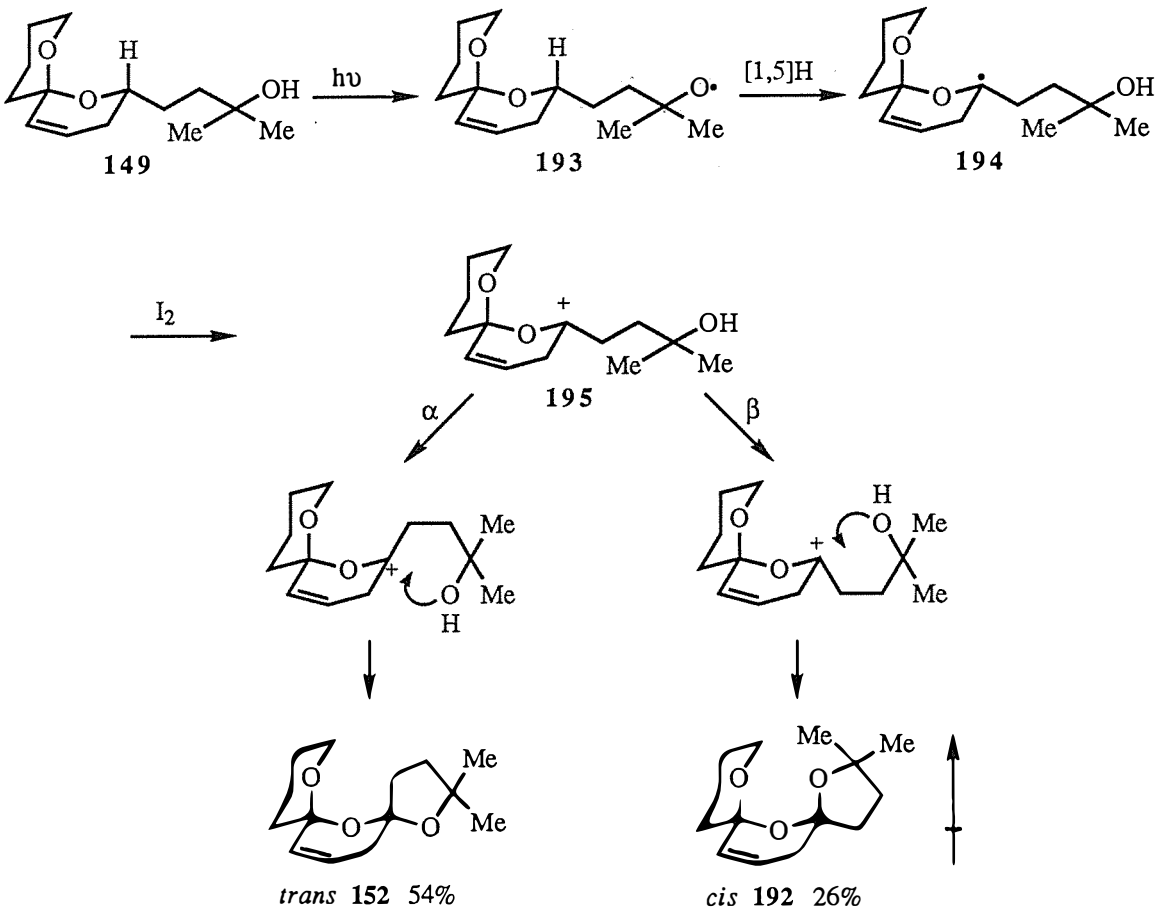
[a] Recorded at 270 MHz in $CDCl_3$ relative to $SiMe_4$

[b] Recorded at 360 MHz in $CDCl_3$ relative to $SiMe_4$

deshielding effect, whereas the corresponding proton of the *cis* isomer is remote from that ring oxygen and therefore resonates considerably further upfield. This phenomenon is characteristic of the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system and will be used consistently as an indicator to distinguish between *cis* and *trans* isomers.

Formation of the diastereomeric bisspiroketals **192** and **152** during the photolytic spirocyclisation process may be rationalised in terms the depicted mechanism (scheme 44).

Scheme 44



The spiroketal centre of the cyclisation precursor **149** is formed under acid catalysed conditions (see scheme 42) giving the most thermodynamically favourable arrangement, in which the ring oxygen atoms adopt axial positions with respect to their neighbouring rings. This affords maximum stabilisation from the anomeric effect[47-50] and is consistent with similar such cyclisations reported by Hanessian *et al* [77] and Baker *et al.*[78] The oxy-radical **193**, generated photolytically from **149**, undergoes a 1,5-hydrogen transfer to give the stabilised carbon centered radical **194**. This species is subsequently oxidised by iodine to

the carbocation **195** which is then trapped by the hydroxyl group, predominantly at the less hindered α face - avoiding pseudo-1,3 diaxial dipolar interactions - giving rise to the *trans* isomer **152**. Competitive trapping of the carbocation from the more sterically demanding β face of the unsaturated ring also occurs to a lesser extent and affords the *cis* isomer **192** as the minor product.

The net dipole of the minor (in this case) *cis* isomer **192** is significantly greater than that of the *trans* isomer **152**, which facilitates separation of the two by flash chromatography. This polarity difference may be used as a preliminary indicator to distinguish formation of these isomeric types in other similar reactions, since the *cis* arrangement should usually be more polar.

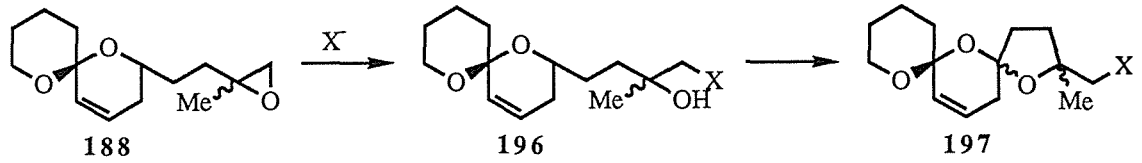
2.4 Synthesis of the Cyclisation Precursor 4-(1',7'-Dioxaspiro[5.5]undec-4'-en-2'-yl)-1-iodo-2-methyl-2-butanol. **200**

Having re-examined the synthesis of 2,2-dimethyl-1,6,8-trioxadispiro [4.1.5.3]pentadec-13-ene, the *trans* isomer **152** of which is analogous to the bisspiroketal moiety of *epi*-deoxy-(O-8)-salinomycin **8**, the existing model scheme was modified in order to incorporate a suitable functionality 'X' (equation 4) which would permit further elaboration of the molecule. This corresponds to a requirement in the proposed synthetic strategy of the natural product (see scheme 37) for some 'handle' on the bisspiroketal **167** which would enable subsequent construction of the terminal tetrahydropyran, or E ring, portion of *epi*--17-deoxy-(O-8)-salinomycin **8**.

Equation 4

The spiroketal epoxide **188** is admirably suited to forming, by an S_N2 opening of the epoxide functionality with an appropriate nucleophile (equation 5), any one of a variety of cyclisation precursors **196** which would then give rise to a functionalised bisspiroketal **197**.

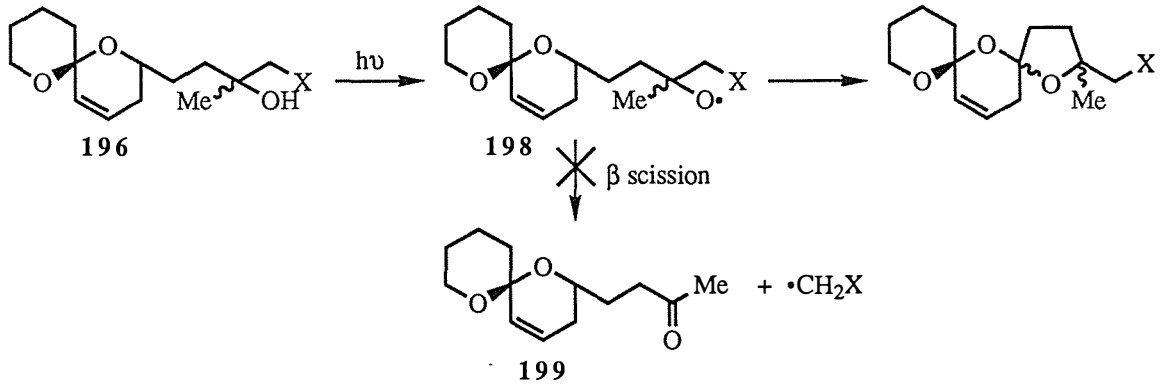
Equation 5



188 196 197

However, a requirement of this group, or handle, is that it be compatible with the Barton-type oxidative cyclisation methodology, which has a pivotal role in the overall synthetic strategy. Hence, two key considerations are that formation of the oxy-radical intermediates **198** (scheme 45) should not be inhibited, and the competitive fragmentation process, which gives rise to the methyl ketone **199**, is not facilitated.

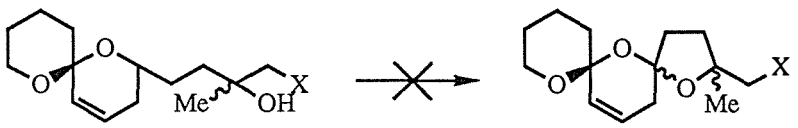
Scheme 45



196 198 199

Attempts by Brimble[79] to effect spirocyclistion of hydroxy spiroketals bearing either a tosylate, alcohol, chloride or bromide group at C1 (equation 6) using the same conditions previously used for **149**, in which X=H (see scheme 43), were unsuccessful, giving either no reaction, or complex product mixtures. However, successful cyclisation to the required bisspiroketal was observed for X=iodide, moreover in reasonable yield.

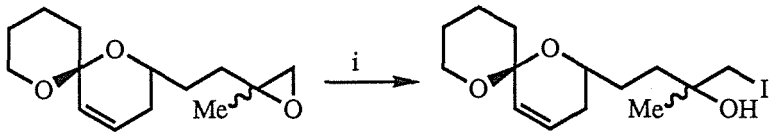
Equation 6



X=OMs, OTs, Cl, Br

To obtain the iodohydrin precursor, a solution of the epoxide **188** in tetrahydrofuran was cooled to -50°C and an excess of lithium iodide in tetrahydrofuran added[80] (scheme 46). After treating the solution with a small quantity of boron trifluoride diethyl etherate, a gradual formation of the iodohydrin **200** was observed which, after completion of the reaction, was isolated and purified in 90% yield.

Scheme 46



188 **200**

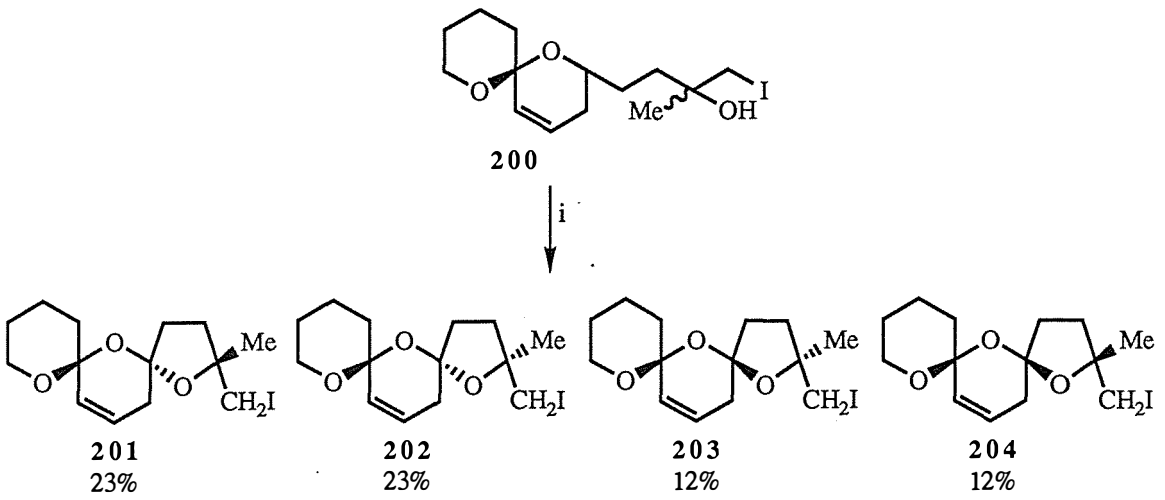
Reagents and conditions: (i) LiI (1.2 equiv.), THF, -50°C, $BF_3.Et_2O$ (cat), 90%.

The appearance of an hydroxyl group absorbance at 3600-3313 cm^{-1} in the infra-red spectrum was the preliminary evidence for formation of the iodohydrin **200**, and this was confirmed by mass spectrometry, which afforded a molecular ion at *m/z* 366 corresponding to a formula of $C_{14}H_{23}O_3I$. A satisfactory elemental analysis for the same formula was also obtained. This iodohydrin was obtained as a 1:1 mixture of diastereomers due to the functionality at C1 and although inseparable, they could be distinguished in the ^1H nmr spectrum since two methyl resonances of equal intensity were evident at δ_H 1.38 and 1.39, as were two very distinct hydroxyl group resonances at δ_H 2.40 and 2.53.

2.5 Synthesis of the (2'-Methyl-1',6',8'-trioxadispiro[4.1.5.3]pentadec-13'-en-2'-yl) methanols. **211-214**

The iodohydrin **200** was subjected to the photolytic conditions required to induce spirocyclisation. A solution of **200**, iodobenzenediacetate (3 equivalents) and iodine (2 equivalents) was irradiated (scheme 47) for several hours with a tungsten lamp whilst rigorously excluding oxygen from the reaction vessel. Again it was necessary to maintain temperatures at or below about 20°C using a controlled water bath to avoid thermal decomposition.

Scheme 47

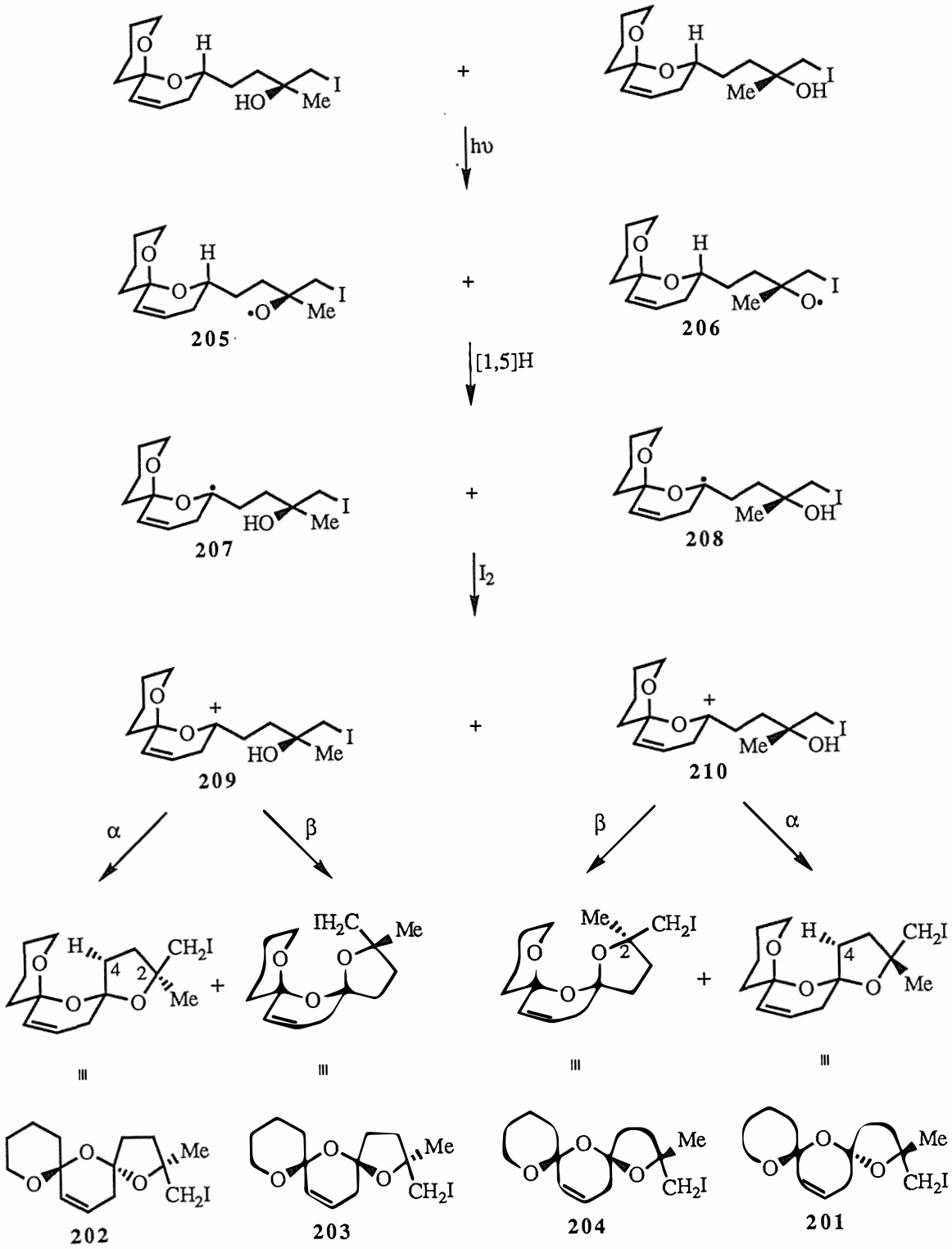


Reagents and conditions: (i) Iodine (2 equiv.), Iodobenzenediacetate (3 equiv.), cyclohexane, hυ, 70%.

Four diastereomers of 2-iodomethyl-2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec -13-ene **201-204** were generated under these conditions, an outcome which can be explained by examining the proposed reaction mechanism (scheme 48). The cyclisation precursor **200** was obtained as a 1:1 mixture of diastereomers in which the spiroketal centre adopts the most thermodynamically favourable arrangement, with the ring oxygen atoms occupying axial positions and the side chain in a sterically favourable pseudo-equatorial orientation. Upon irradiation of this mixture, the oxy-radicals **205** and **206** are formed which then undergo a [1,5]H shift to afford the carbon radicals **207** and **208**. In the presence of iodine **207** and **208** are oxidised to the carbocations **209** and **210**, each of which is trapped by the hydroxyl group. This occurs at the more accessible α face of the unsaturated ring to give a 1:1 mixture of the *trans* isomers **201** and **202**, but trapping also occurs at the more sterically demanding β face to afford the *cis* isomers **203** and **204**, again in a 1:1 ratio. The overall ratio of isomers **201:202:203:204** was 2:2:1:1, which reflected a preference for formation of the *trans* bisspiroketals over the *cis* under these reaction conditions - an effect observed previously for the 2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3] pentadec-13-enes **152** and **192** (see scheme 43).

The two *cis* diastereomers **203** and **204**, being slightly more polar due to the enhanced dipole of this bisspiroketal configuration, were separated by flash chromatography[69] from the *trans* isomers **201** and **202**. However, the individual *trans* isomers were inseparable as were the individual *cis* isomers and therefore were characterised as mixtures. Both configurations afforded, expectedly, identical mass spectra with a

Scheme 48



Ratio **202:203:204:201** = 2 : 1 : 1 : 2

molecular ion at *m/z* 364, consistent with the formula $C_{14}H_{21}O_3I$, and the characteristic retro-Diels-Alder fragment at *m/z* 124 ($C_8H_{12}O$) (see equation 3, p. 52). However, these iodides, unlike the iodohydrin precursor **200**, proved to be somewhat unstable at room temperature and particularly photosensitive, hence satisfactory elemental analyses were not obtained.

The 28 resonances of the complex ^{13}C nmr spectrum recorded for the mixture of *trans* isomers were impossible to assign individually to either **201** or **202**, but the four quaternary resonances at δ_C 96.3, 96.4, 107.4 and 107.7 were indicative of spiroketal centres. The ^1H nmr spectrum, in addition to confirming the mixture was indeed a 1:1 mixture of diastereomers, afforded the key conformational information. The multiplet resonating at δ_H 2.66-2.75, integrating for two protons, was assigned to the 4-H protons of each *trans* isomer. This deshielding effect, due to the proximity of these protons to the opposing ring oxygen atoms, is not observed for the *cis* isomers **203** and **204** since for these the corresponding resonances occur in the multiplet at δ_H 1.52-2.30. This confirms the *trans* arrangement of the bisspiroketals **201** and **202**. Of the two methyl resonances in the spectrum of the *trans* mixture, at δ_H 1.44 and 1.67, the latter can be attributed to the C2 configuration of isomer **202**, since in this case the methyl group occupies a position 1,3-*syn* to a C-O bond of the central ring, and is therefore deshielded relative to the methyl resonance of *trans* isomer **201** (the same effect as that depicted in figure 11, p. 54).

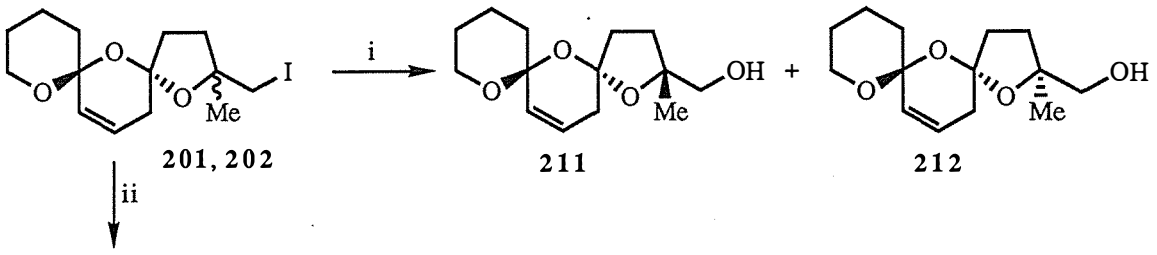
Similar conclusions may be drawn for the minor product, the mixture of *cis* diastereomers **203** and **204**. Of the 28 resonances in the ^{13}C nmr, the four quaternary peaks at δ_C 93.8, 93.9, 105.3 and 105.5 are due to the spiroketal centres of the two isomers. The ^1H nmr spectrum confirmed they were were formed in equal amounts and also showed the lack of deshielded 4-H resonances (occurring in the multiplet at δ_H 1.52-2.30 compared with δ_H 2.66-2.75 in the *trans*), confirming a *cis* arrangement of the bisspiroketal. The two methyl resonances at δ_H 1.39 and 1.63, of which the latter, deshielded by a 1,3-*syn* orientation to a C-O bond (the same effect as that depicted in figure 11, p. 56), can be assigned to C2 of **204** and hence the less deshielded methyl resonance to **203**.

Conversion to the alcohols **211-214**

It was originally envisaged in the retrosynthesis (scheme 37) that the bisspiroketal **167** would be extended *via* a terminal aldehyde group, obtained from the corresponding alcohol. Extension of this to the model system required conversion of the iodide functionality to the synthetically more useful alcohol group, and it was expected this could most readily be achieved by direct S_N2 displacement of the iodide group by an oxygen nucleophile. However, this process proved difficult due to the steric demands of the neopentyl-like configuration of the primary iodide, a problem encountered by Moffatt *et al* [81]

for a similarly disposed iodide group. Hence an attempted conversion of the mixture of *trans* iodides **201** and **202** to the alcohols **211** and **212** by hydroxide in an aprotic solvent was ineffective (scheme 49), despite using elevated temperatures and 18-crown-6 to enhance the nucleophilicity of the anion.

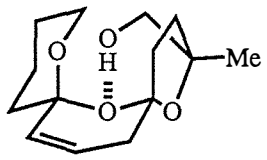
Scheme 49



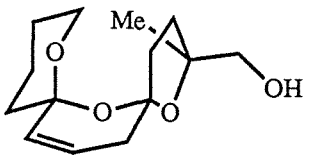
Reagents and conditions: (i) KO_2 (excess), DMSO/THF, 18-crown-6 (excess), RT, 81%; (ii) KOH, DMSO, 18-crown-6, Δ.

Success was achieved by treating a solution of **201** and **202** and 18-crown-6, dissolved in a mixture of dimethyl sulphoxide and tetrahydrofuran at room temperature, with potassium superoxide (scheme 49), as described by Corey *et al.*[82] These *trans* alcohols **211** and **212** were obtained in 81% yield and were separated by flash chromatography. The polarity difference which enabled them to be separated was attributed to the extent of intramolecular hydrogen bonding between the hydroxyl group and the spiroketal ring oxygens (figure 12). The effect is more pronounced in isomer **211**, thereby rendering it markedly less polar than **212**.

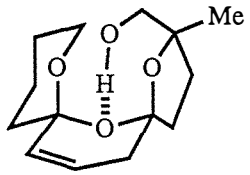
Figure 12



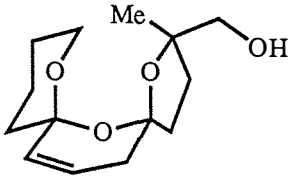
211 *trans*, hydrogen bonded.



212 *trans*, non-hydrogen bonded.



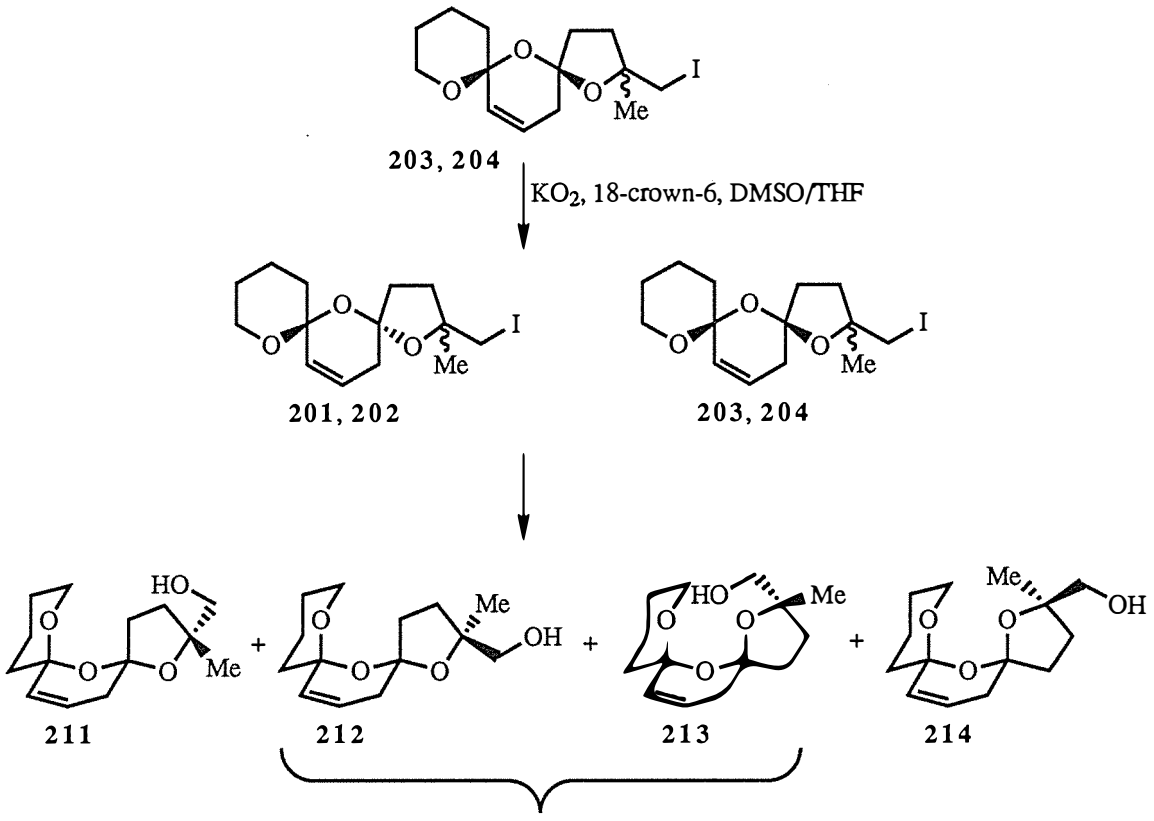
213 *cis*, hydrogen bonded, very unfavourable dipole effects.



214 *cis*, non-hydrogen bonded.

Subjecting the more delicate *cis* iodides to the same reaction conditions was invariably accompanied by rapid equilibration (scheme 50) to give an approximately 1:2 mixture of the *cis* and *trans* iodides **201-204.** This was then followed by slower conversion of these iodides to a mixture of the corresponding four alcohols **211-214** - the two distinct *trans* alcohols **211** and **212** and, by virtue of similar intramolecular hydrogen bonding effects (figure 12), the distinct *cis* alcohols **213** (less polar) and **214.**

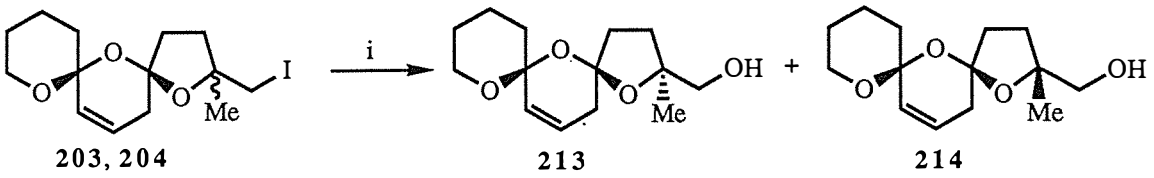
Scheme 50



However, a frustrating consequence of obtaining these alcohols as a mixture was that, although the less polar *trans* isomer **211** and more polar *cis* isomer **214** could be separated and purified, the more polar *trans* **212** and the less polar *cis* **213** isomers could not since the hydrogen bonding effect in **213** exactly compensated for the enhanced polarity of the *cis* conformation of the bisspiroketal. In order to obtain a sample of **213** it was necessary to modify the reaction conditions and, by omitting the tetrahydrofuran component from the solvent mixture (scheme 51), the initial equilibration of **203** and **204** was avoided and the individual *cis* alcohols **213** and **214** could be isolated. However, the *cis* alcohol

213 proved to be very unstable, possibly due to the number of dipole interactions (see figure 12, p. 64), and could not be isolated with a high degree of purity.

Scheme 51

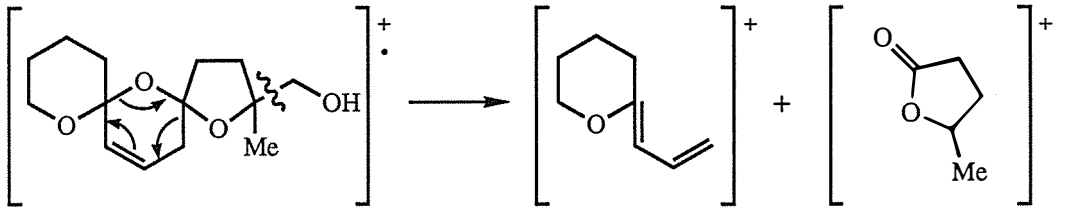


203, 204 **213** **214**

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

All four isomers **211-214** afforded identical mass spectra, giving a parent ion at *m/z* 254, which is consistent with a molecular formula of $C_{14}H_{22}O_4$. Base peaks were observed at *m/z* 223, corresponding to M-CH_2OH, and also at *m/z* 99, corresponding to a formula of $C_5H_7O_2$. This latter peak and that at *m/z* 124 ($C_8H_{12}O$) arise from a retro-Diels-Alder fragmentation process (equation 7).

Equation 7



$C_{14}H_{22}O_4$, *m/z* 254 $C_8H_{12}O$, *m/z* 124 $C_5H_7O_2$, *m/z* 99

^{13}C nmr spectroscopy established each isomer to be diastereomerically pure, except **213** which, as mentioned previously, was not isolated in a pure form. The ^1H nmr spectra of **211**, **212** and **214** are reproduced (figures 13, 14 and 15 respectively) and some of the chemical shifts of the four alcohols **211-214** (table 2) provide confirmation of the assigned stereochemistry for each isomer. The deshielded 4'-H resonances of **211** and **212**, at δ_H 2.79 and 2.70 respectively, are indicative of the *trans* conformation of these bisspiroketals. The corresponding resonances for isomers **213** and **214** occur upfield as part of the multiplets at δ_H 1.53-2.15 and 1.80-2.09, which establishes a *cis* arrangement of the bisspiroketals. The stereochemistry at C-2' of each isomer is inferred by the chemical shifts of the methyl groups; for *trans* isomer **212** the methyl resonance at δ_H 1.47 indicates it is 1,3-*syn* to a C-O bond of the neighbouring ring, whereas for *trans* isomer **211** the

Figure 13

211

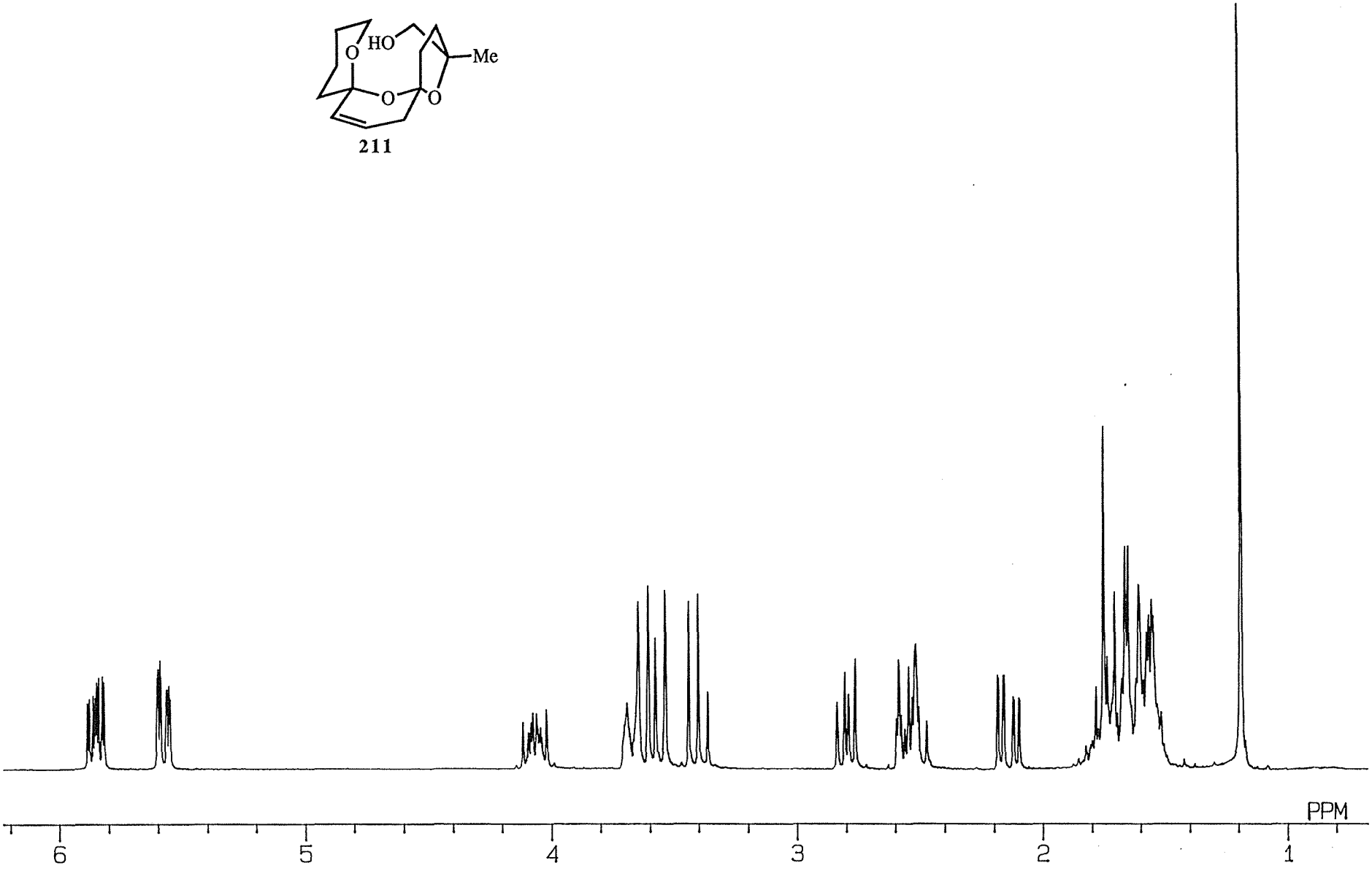


Figure 14

212

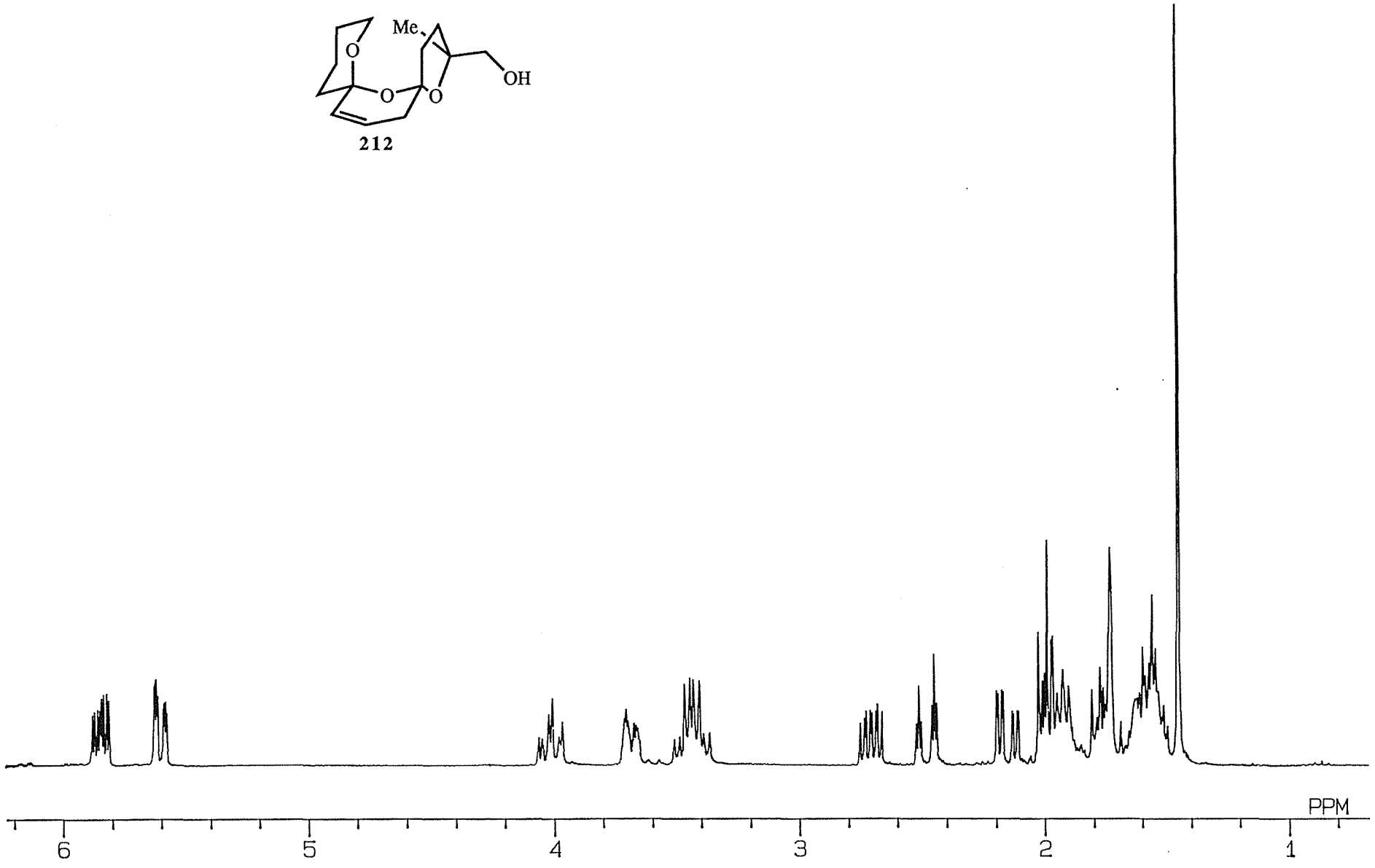


Figure 15

214

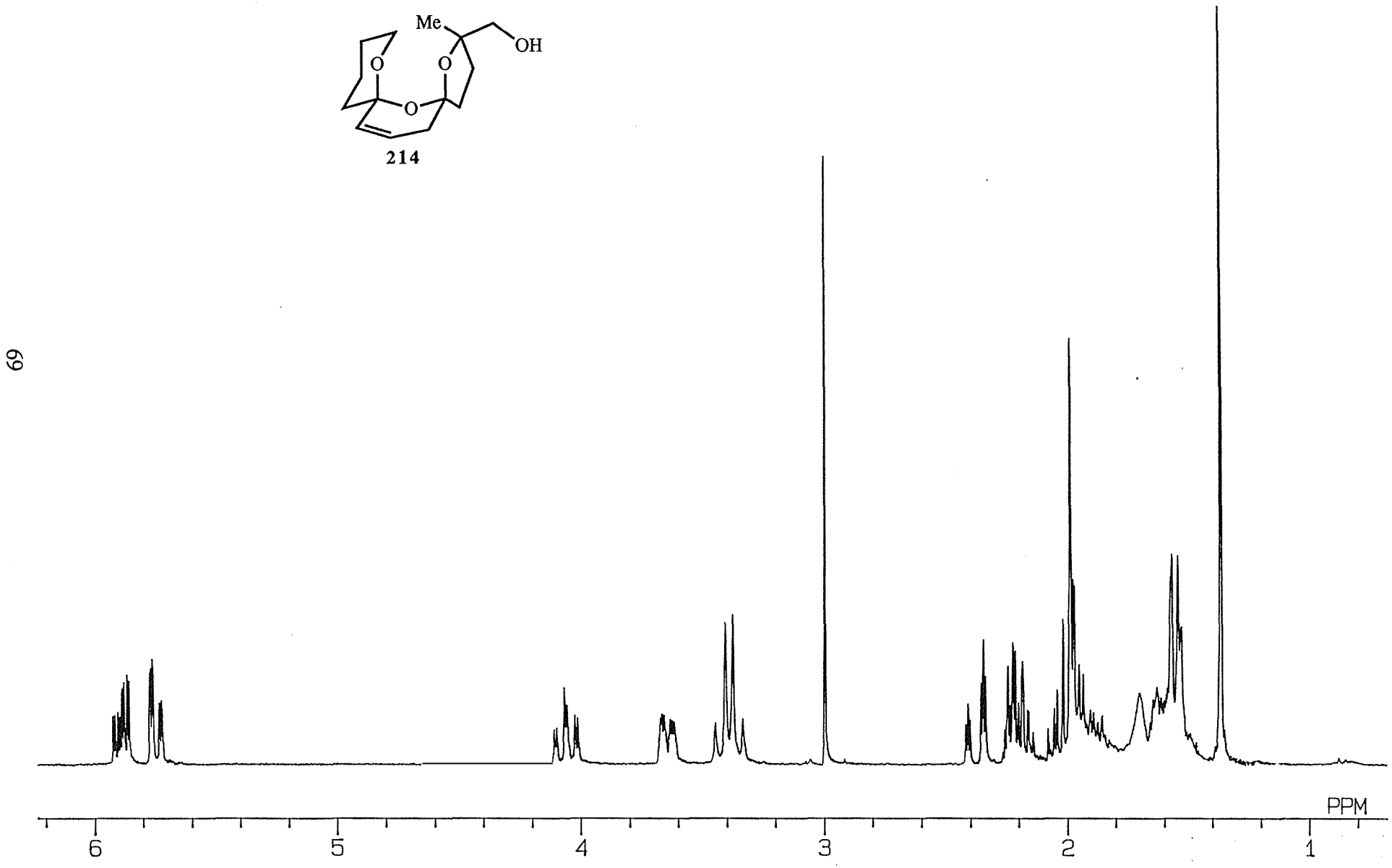
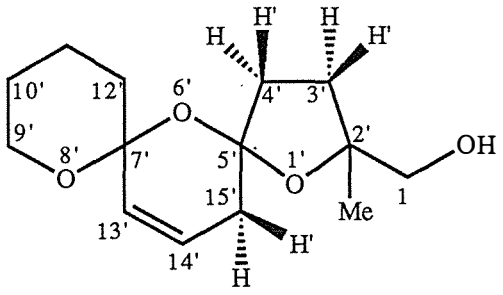
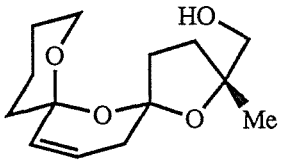


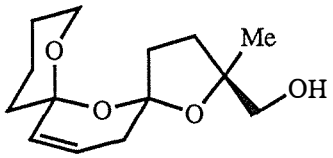
Table 2

^{1}H NMR Chemical Shifts of (2'-Methyl-1',6',8'-trioxadispiro[4.1.5.3] pentadec-13'-en-2'yl)-methanols.[a]

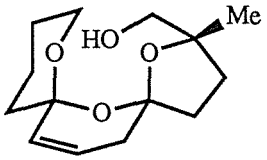




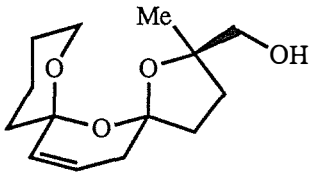
211



212



213



214

Compound	1-H	2'-Me	3'-H'	3-H	4'-H'	4'-H	9'-H_{ax}
211	3.56, 3.60	1.20	1.53-1.80	2.52-2.61	1.53-1.80	2.79	4.06
212	3.37, 3.61	1.47	1.86-2.05	1.86-2.05	1.74-1.82	2.70	4.01
213	3.37, 3.61	1.11	1.53-2.15	1.53-2.15	1.53-2.15	1.53-2.15	3.95
214	3.35, 3.42	1.37	1.80-2.09	1.80-2.09	2.16-2.27	1.80-2.09	4.06

Compound	9'-H_{eq}	13'-H	14'-H	15'-H'	15'-H	OH
211	3.70	5.57	5.85	2.13	2.52-2.61	3.56 (d)
212	3.68	5.60	5.84	2.48	2.15	1.53-2.05
213	3.71	6.17	5.97	2.23	2.47	4.26 (d)
214	3.65	5.74	5.89	2.38	2.16-2.27	2.99 (s)

[a] Recorded at 270 MHz in $CDCl_3$ relative to $SiMe_4$

corresponding methyl resonance appears upfield at δ_H 1.20 implying that it is not in the same 1,3 *syn* arrangement. Similar conclusions may be drawn for the *cis* isomers, of which **214**, possessing a correspondingly deshielded methyl resonance (at δ_H 1.37 compared with δ_H 1.11 for **213**), must possess the indicated stereochemistry at C2', which positions the group 1,3-*syn* to a C-O bond of the central ring.

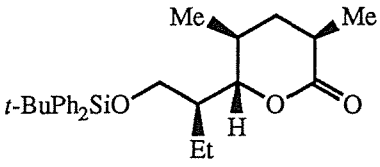
Chapter 3

Synthesis of the Bisspiroketal moiety of *epi*-17-Deoxy-(O-8)-salinomycin **8**

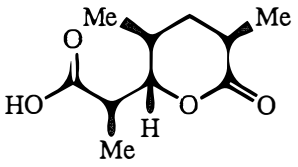
3.1 The Optically Active Lactone **84**

With the synthesis of a suitable model system for the bisspiroketal moiety of *epi*-17-deoxy-(O-8)-salinomycin **8** well in hand, attention was turned to the task of extending the methodology to a synthesis of the natural product. As outlined in the retrosynthetic analysis (see scheme 37), the two necessary precursors are the optically active lactone **84** and the acetylene **170**.

Figure 16



Required synt etic precursor **84**

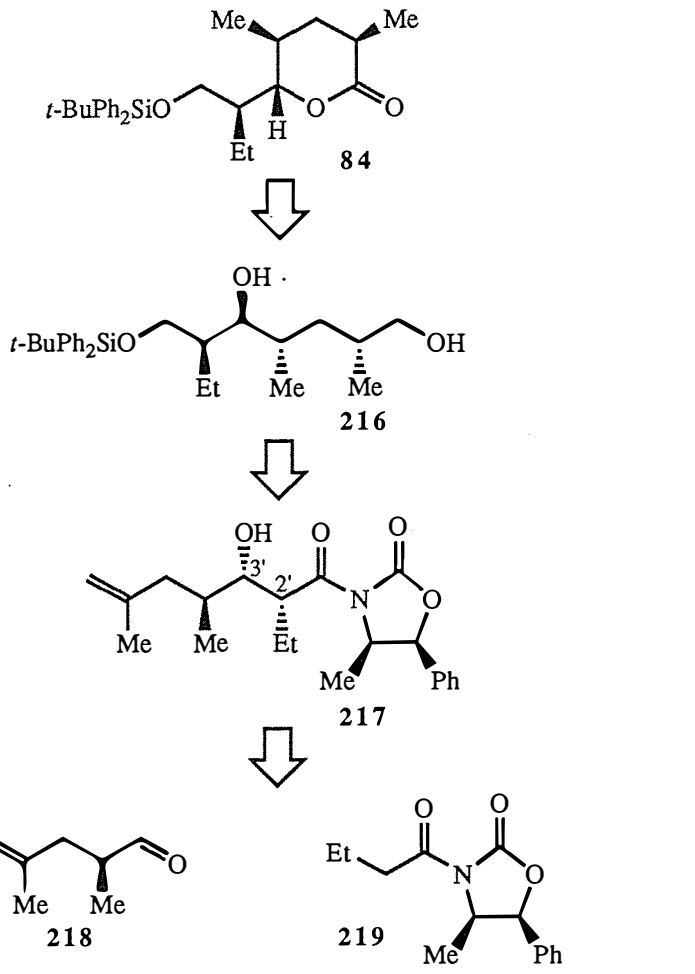


Prelog-Djerassi lactone **215**

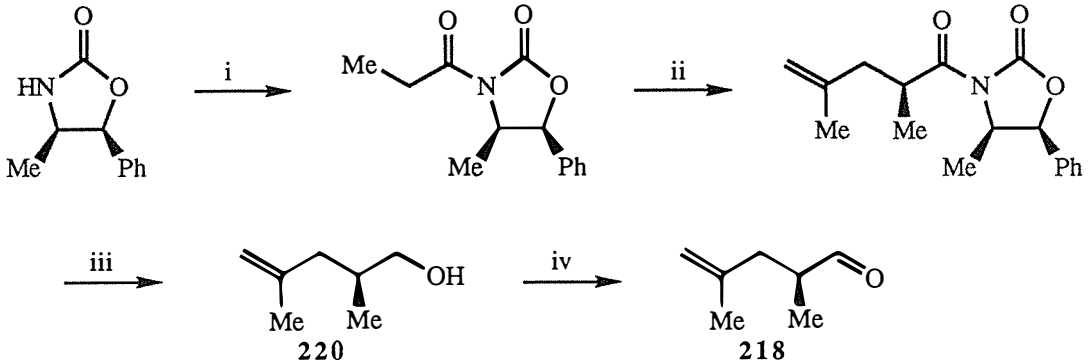
A synthesis of the lactone was detailed previously since it was an intermediate in the synthesis of salinomycin carried out by Kishi *et al* [30] (see scheme 15). However, the methodology developed by Evans and Bartroli[83] in their synthesis of the structurally similar Prelog Djerassi lactone[84] **215** (figure 16) was recently employed by Brimble[85] in a synthesis of **84**. In this procedure the lactone was formed (scheme 52) by a catalytic oxidation of the diol **216**. This was in turn obtained from the oxazolidinone **217** in which the stereochemistry at C2' and C3' had been constructed *via* a directed aldol condensation between the aldehyde **218** and butanoyloxazolidinone **219**.

The aldehyde **218** was initially prepared according to the literature procedure[85] (scheme 53), the final step of which used the Parikh[86] modification of the Moffatt oxidation (pyridine-sulphur trioxide) to oxidise the alcohol **220**. It had been established that this reagent was exceptional in that only a minimal degree (0.1%) of racemisation occurred in the course of reaction, but other shortcomings were noteworthy. The procedure was characterised by incomplete reaction even after extended periods, and the volatility of the product, as noted by Still and Shaw[87] was such as to make workup and subsequent purification steps difficult, further contributing to a reduced yield.

Scheme 52



Scheme 53

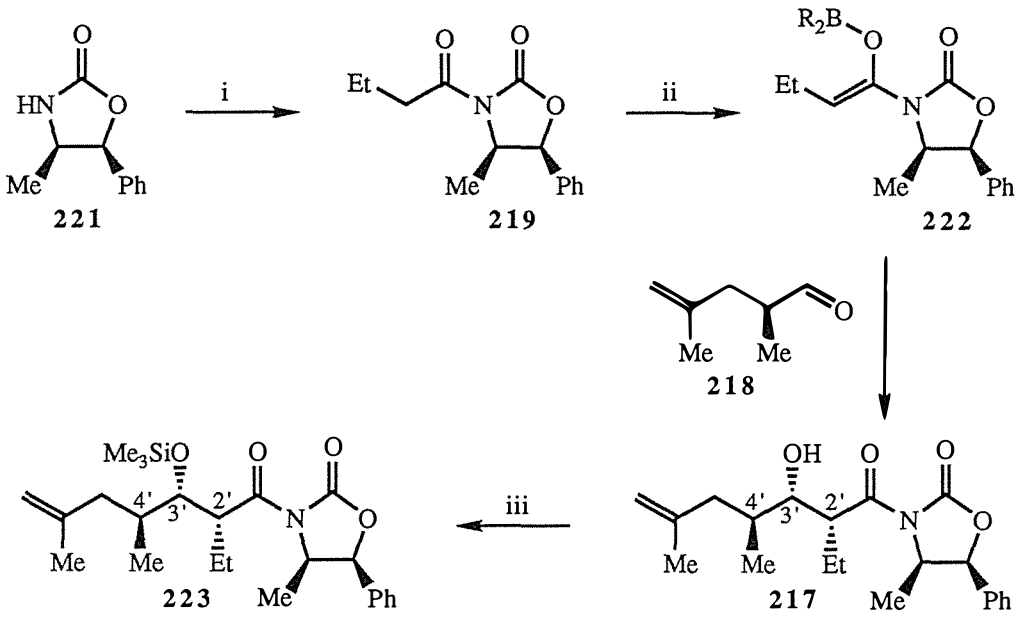


Reagents and conditions: (i) *n*-BuLi (1 equiv.), THF, -78°C, CH_3CH_2COCl, 96%; (ii) $Li(i\text{-}Pr)_2$, -78°C, 0.5 h. then $H_2C{=}C(CH_3)CH_2I$, -50°C to -20°C, 3h. 82%; (iii) $LiAlH_4$, Et_2O, 0°C, 1 h.; (iv) $Py.SO_3$ (3 equiv), NEt_3 (7equiv.), DMSO, RT, 3 h., 64% **OR** (iv) *tetra-n*-propylammonium perruthenate (cat), NMO (1.5 equiv.), CH_2Cl_2, 4Å molecular sieves (powder), 5 h., 80%.

A more expedient means of oxidising **220** employed the tetra-*n*-propylammonium perruthenate catalyst[88] and *N*-methylmorpholine-*N*-oxide, conditions also shown not to cause appreciable racemisation. Oxidation was near quantitative by tlc and the subsequent workup very straightforward, and although the volatility of the product remained a problem the yields were nevertheless improved (80-85%).

The second precursor required for a synthesis of the lactone, butanoyloxazolidinone **219**, was prepared[85] (scheme 54) in 91% yield by lithiation of the oxazolidinone **221** with *n*-butyllithium followed by treatment with butanoyl chloride. Reacting **219** with a slight excess (1.1 equiv.) of 9-borabicyclo[3.3.1]nonyl trifluoromethanesulphonate[89] in the presence of triethylamine (1.2 equiv), afforded the *Z*-boron enolate[90] **222**, which condensed with the aldehyde **218** to give the crossed aldol product **217**, with the required stereoselectivity,[90-92] in 76% yield. Under these conditions the desired 2', 3'-*erythro*- 3', 4'-*threo* product **217** was formed with the 2', 3'-*threo*- 3', 4'-*threo* product in a ratio of 6:1, an improvement on the reported[85] ratio of 3:1. Protection of the resulting hydroxyl group as the trimethylsilyl ether to give **223** was more effectively achieved using 1-(trimethylsilyl)imidazole in dichloromethane (94%) than with trimethylsilyl diethylamine[85] (85%).

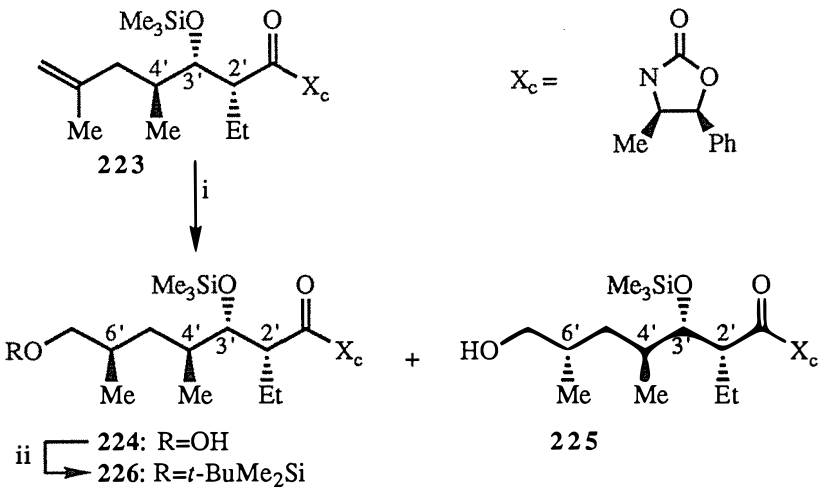
Scheme 54



Reagents and conditions: *n*-BuLi (1 equiv.), $CH_3CH_2CH_2COCl$, 96%; (ii) $R_2BOSO_2CF_3$ (1.1 equiv.)(R_2B=9-borabicyclo[3.3.1]non-9-yl), NEt_3 (1.2 equiv.), CH_2Cl_2, 0°C, 1 h. then -78°C, **218**, RT, 2 h., 76%; (iii) 1-(Me_3Si)imidazole, CH_2Cl_2, RT, 94%.

Hydroboration of the olefin **223** was carried out (scheme 55) using freshly prepared thexylborane in tetrahydrofuran at 0°C. This was followed by a bicarbonate-peroxide workup to afford a separable mixture of the 6'*R*- and 6'*S*- alcohols **224** and **225** in a ratio of 2:1. Modifying this procedure so that the thexylborane solution was cooled to -40°C prior to adding the olefin **223**, then slowly warming the reaction mixture to 0°C, resulted in an improved diastereoselectivity of 3.6:1 in favour of the desired isomer **224**, in 93% overall yield. The resulting hydroxyl group was then protected as a *tert*-butyldimethylsilyl ether **226**, using *tert*-butyldimethylsilyl triflate in dichloromethane, in very high yield (98%).

Scheme 55



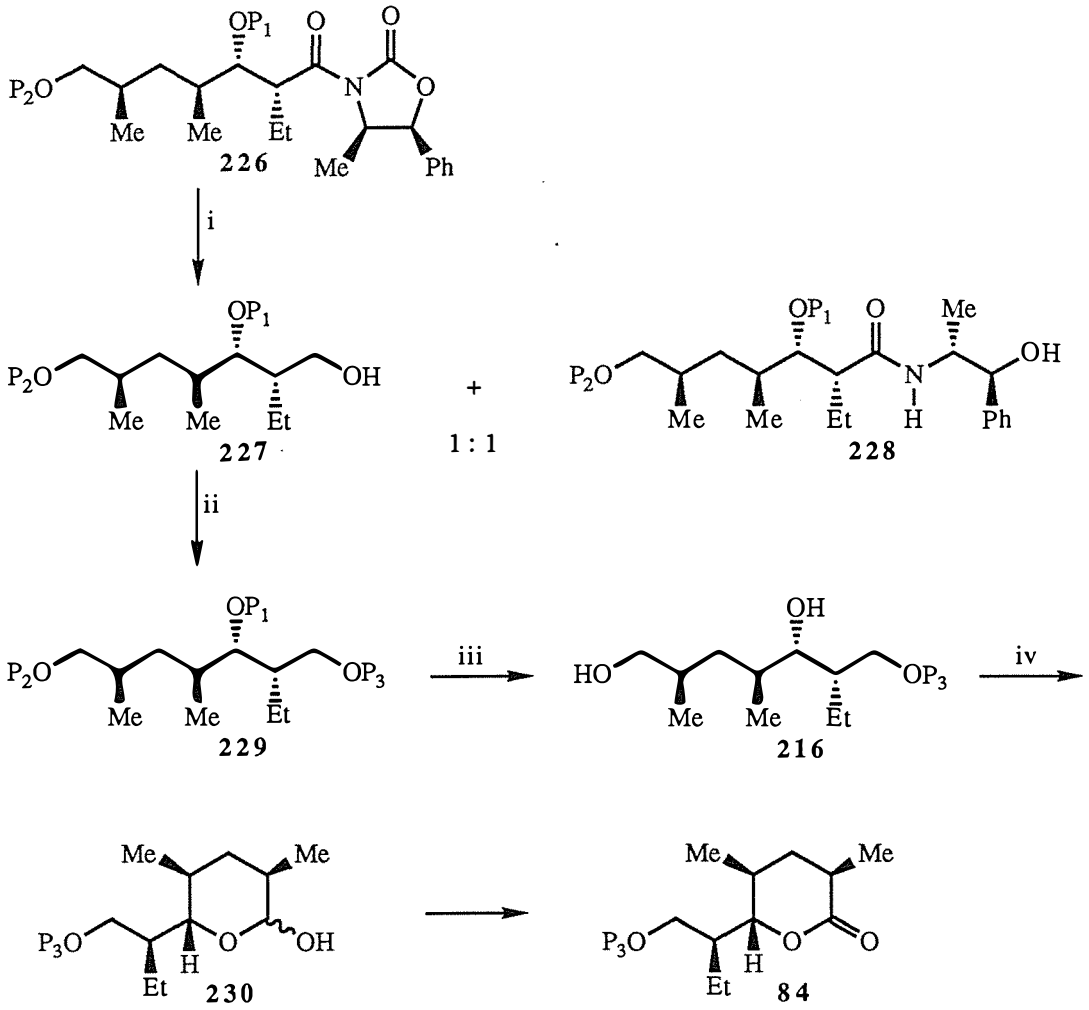
0°C ratio **224** : **225** = 2 : 1
-40 → 0°C ratio **224** : **225** = 3.7 : 1

Reagents and conditions: (i) BH_3 (2 equiv.), $(CH_3)_2C{=}C(CH_3)_2$ (2 equiv.), 0°C, 1 h. then, -40°C, **223** → 0°C over 1.5 h., 93%; (ii) *t*-$BuMe_2SiOTf$ (1.2 equiv.), 2,6-lutidine (2.5 equiv.), CH_2Cl_2, 0°C, 98%;

Attempted removal of the chiral auxiliary by treating **226** with lithium borohydride in tetrahydrofuran[93] (scheme 56) afforded nearly equal quantities of the alcohol **227** and the undesired amide **228**.

This occurred because the site of nucleophilic cleavage of *N*-acyloxazolidinones is subject to both steric and electronic factors and, in the absence of significant steric crowding, the exocyclic carbonyl group is more susceptible to nucleophilic attack. However, as the steric interactions in the vicinity of this carbonyl group increase, competitive attack at the endocyclic carbonyl group is observed, affording the amide, in this case **228**, in increasing quantities. This problem may possibly be circumvented by using lithium hydro peroxide,

Scheme 56



P_1=Me_3Si, P_2=*t*-$BuMe_2Si$, P_3=*t*-$BuPh_2Si$

Reagents and conditions: (i) $LiBH_4$ (1 equiv.), THF, 24 h., RT, 48% **227**; (ii) imidazole (5 equiv.), *t*-$BuPh_2SiCl$ (1.3 equiv.), NEt_3 (5 equiv.), CH_2Cl_2, RT, 96%; (iii) PPTS (cat), EtOH, 82%; (iv) NMO (2 equiv.), $Ru(PPh_3)_3Cl_2$, 4Å molecular sieves (powder), acetone, 87% from **229**.

since this reagent has been shown[94] to effectively remove this chiral auxiliary from imides in which the reactivity of the exocyclic carbonyl group has been suppressed by steric factors. An alternative method for excising the auxiliary may lie in the use of a lithium benzyloxide transesterification,[95] which gives the alcohol after reduction of the resulting ester with lithium aluminium hydride. Recently Evans *et al*[96] employed an effective technique which relied on enhancing the nucleophilic susceptibility of the exocyclic carbonyl group by firstly generating the boron aldolate of that group which was then reduced in high yield to the

alcohol using lithium borohydride. Thus, alternative methods exist whereby an improved yield for removing the chiral auxiliary might be achieved.

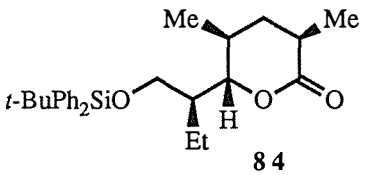
Having obtained the alcohol **227** the hydroxyl group was protected as the *tert*-butyldiphenylsilyl ether to give **229**, which enabled selective removal of the trimethylsilyl and *tert*-butyldiphenyl ether groups, in mildly acidic conditions[97] (pyridinium-*p*-toluenesulphonate in ethanol), to give the diol **216**. This was finally oxidised, using tris(triphenylphosphine)ruthenium(II) chloride as catalyst and *N*-methylmorpholine-*N*-oxide as oxidant in acetone, to the lactol **230** and then to the lactone **84**.

All intermediates in this synthesis of the lactone **84**, from the aldehyde **218** and butanoyloxazolidinone **219**, afforded spectroscopic data and optical rotations which were in agreement with those previously reported.[85]

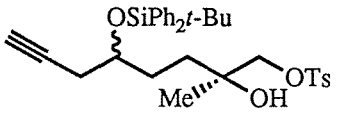
3.2 Enantioselective Synthesis of the Cyclisation Precursors **245, 246**

Enantioselective syntheses of the optically active lactone **84** and (*S*)-(-)-acetylene **181** were now achieved (figure 16), as part of the requirements of the proposed retrosynthesis (see scheme 37) of *epi*-17-deoxy-(O-8)-salinomycin **8**.

Figure 16



84



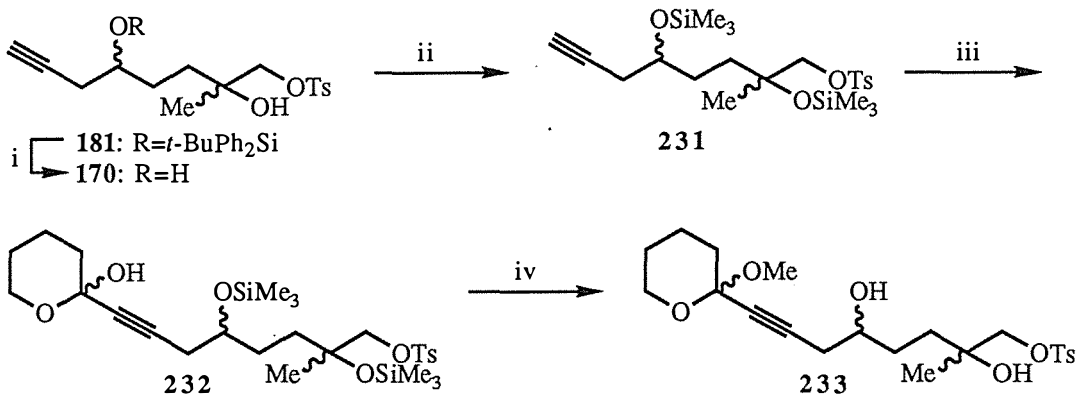
181

However, prior to utilising these precursors to construct the bisspiroketal **167**, a decision was made to retain the large *tert*-butyldiphenylsilyl ether of the lactone component throughout the remainder of the procedure to facilitate manipulation of the small molar quantities of material. In order to distinguish the silyl ether group of **84** from the protected secondary alcohol of the acetylene **181**, the *tert*-butyldiphenylsilyl ether of **181** was reprotected as the more labile trimethylsilyl ether.

Incorporating this modification, firstly into the model procedure (scheme 57), required removal of the *tert*-butyldiphenylsilyl ether from the (±)-acetylene **181** using a 2% solution of hydrofluoric acid in acetonitrile[73] (the use of tetra-*n*-butylammonium fluoride would cause immediate and undesired epoxidation of **181**). This gave the diol **170**, which was reprotected as the bis-trimethylsilyl ether **231** using 1-(trimethylsilyl)imidazole. Since

the secondary silyl ether was somewhat labile, considerable care was required during purification, using florisil for column chromatography.

Scheme 57



Reagents and conditions: (i) a: 2% HF (excess), CH_3CN, RT, 95%; (ii) 1-(Me_3Si)imidazole (2.2 equiv.), CH_2Cl_2, 95%; (iii) *n*-BuLi (1 equiv.), THF, -78°C, then δ-valerolactone (1.1 equiv.); (iv) Amberlite IR 120 resin, MeOH, 75% from **231**.

Treatment of **231** with *n*-butyllithium at -78°C followed by addition of δ-valerolactone gave the hemiketal **232** which was not isolated and purified but immediately dissolved in methanol and stirred with acidic Amberlite IR 120 resin. This effectively removed the trimethylsilyl protecting groups and generated the ketal **233** in 75% yield. From this coupling step, a synthesis of of the model spiroketal epoxide **188** (see scheme 42) was now possible (scheme 58).

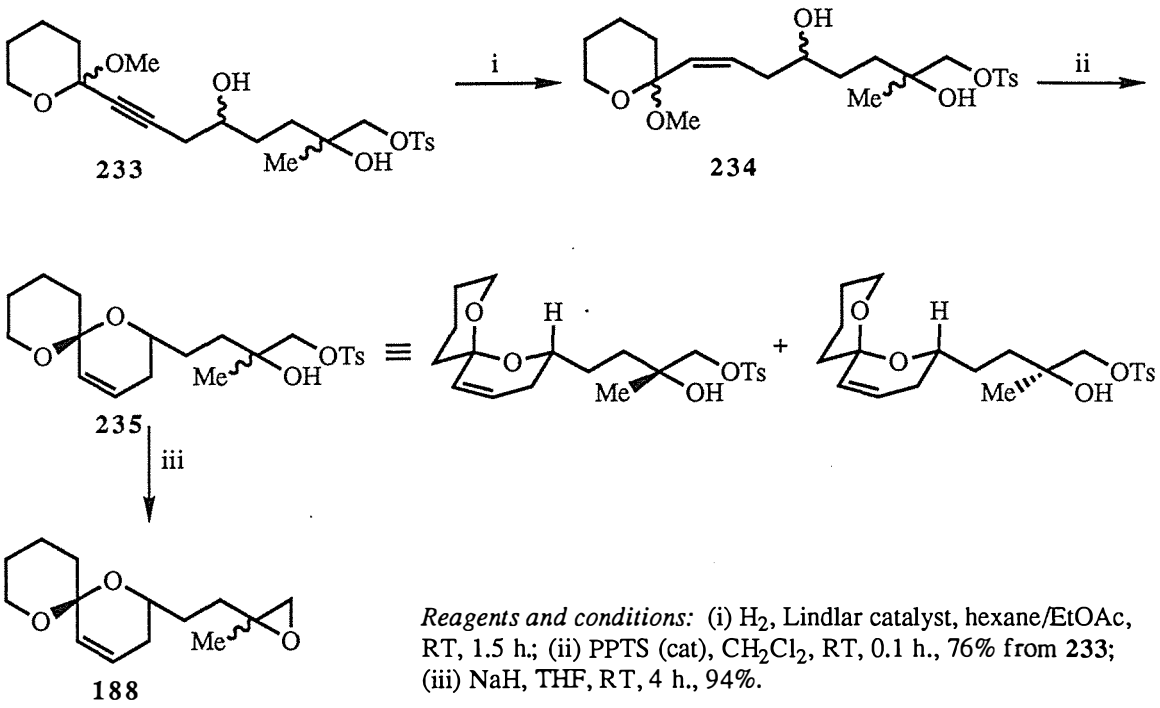
Firstly, the acetylene **233** was partially hydrogenated to the *cis* olefin **234** using Lindlar catalyst. No attempt was made to isolate the product, but by directly treating a solution of **234** in dichloromethane with pyridinium-*p*-toluenesulphonate the spiroketal tosylate **235** was formed as an inseparable 1:1 mixture of diastereomers. This was clearly evident from the ^1H nmr spectrum which showed two methyl resonances at δ_H 1.18 and 1.20 and two hydroxyl group resonances of equal intensity at δ_H 2.66 and 2.86.

The stereochemistry of the spiro centre was assumed to be that in which the C-O bonds adjoining the spiro centre adopt axial positions on their respective neighbouring rings, as determined by the anomeric effect,[47-50] and the side chain is assumed to adopt the more sterically favourable pseudo-equatorial position on the unsaturated ring.

Treatment of the tosylate **235** with sodium hydride in tetrahydrofuran afforded the previously obtained epoxide **188** in 94% yield.

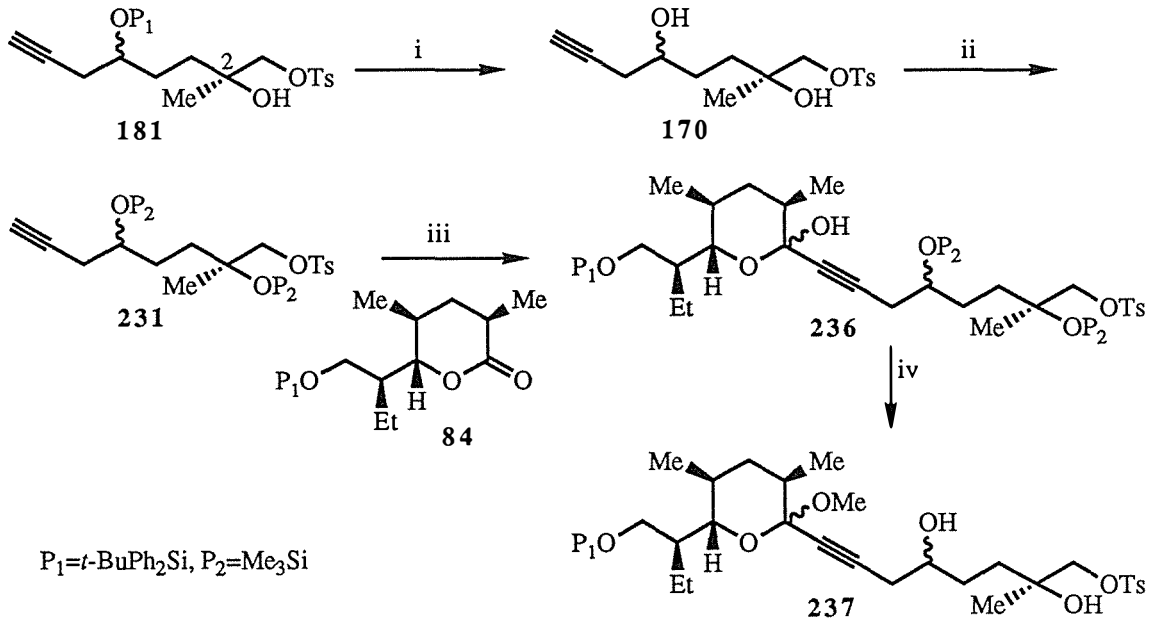
Having satisfactorily modified the model procedure whereby the protected secondary alcohol group of acetylene **181** was reprotected as a trimethylsilyl ether, the stage

Scheme 58



Reagents and conditions: (i) H_2, Lindlar catalyst, hexane/EtOAc, RT, 1.5 h.; (ii) PPTS (cat), CH_2Cl_2, RT, 0.1 h., 76% from **233**; (iii) NaH, THF, RT, 4 h., 94%.

Scheme 59



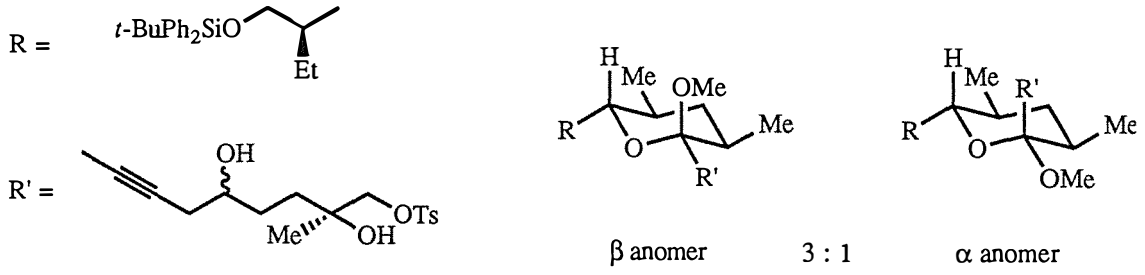
P_1=*t*-$BuPh_2Si$, P_2=Me_3Si

Reagents and conditions: (i) 2% HF (excess), CH_3CN, RT, 95%; (ii) 1-(Me_3Si)imidazole (2.2 equiv.), CH_2Cl_2, 95%; (iii) *n*-BuLi (1 equiv.), THF, -78°C, 0.5 h. then **84**; (iv) MeOH, Amberlite IR 120 resin, 1 h., RT, 84% from **84**.

had now been reached at which the information and insight gathered during the course of the model studies could be applied to an enantioselective construction of the bisspiroketal moiety of *epi*-17-deoxy-(O-8)-salinomycin **8**.

Firstly the (*S*)-(-)-acetylene **181** (see scheme 39) was converted (scheme 59), *via* the diol **170**, to the corresponding (*S*)-bis-trimethylsilyl ether **231**. Treatment of **231** with *n*-butyllithium at -78°C afforded the lithium acetylide derivative which reacted with the optically active lactone **84** to give the hemiketal **236**. Due to the small scale of this reaction, a very slight excess of the acetylene **231** was used, which precluded competitive attack on the lactone by any residual butyllithium. The unreacted acetylene could later be recovered from the reaction mixture by flash chromatography.[69] After quenching with water, drying and evaporating the solvent, hemiketal **236** was quickly filtered through a short column of florisil to remove inorganic salts, then dissolved in methanol and stirred with acidic Amberlite IR 120 resin for one hour to afford the moderately unstable ketal-diol **237** in 84% yield. The ^{1}H nmr spectrum of **237** showed it to be a mixture of two diastereomers since two resonances were evident at δ_H 3.35 due to the β (axial) methoxy group and at δ_H 3.43 due to the α (equatorial) methoxy group, occurring in a 3:1 ratio[98] (figure 17). Assignment of this stereochemistry is based on the stability of each isomer due to the anomeric effect, which favours an axial orientation of the C-O bond of the methoxy group on the ring.

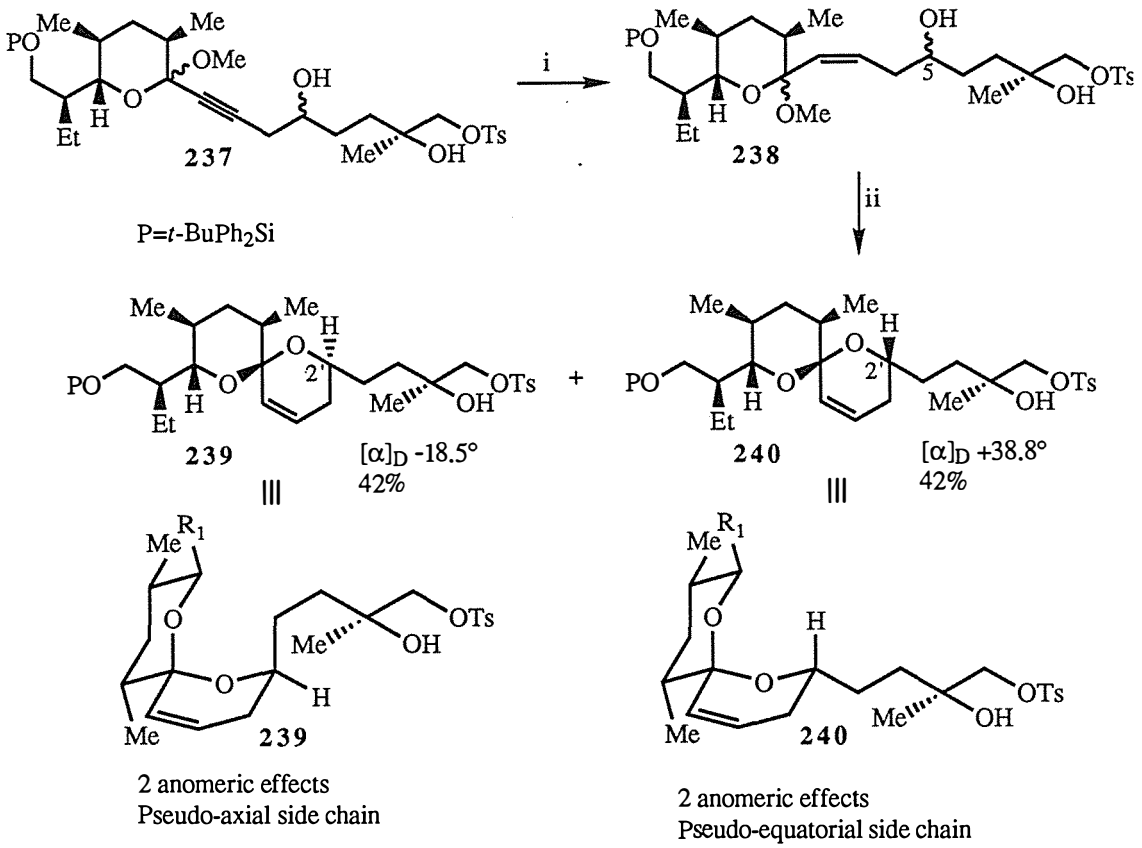
Figure 17



A solution of **237** in ethyl acetate and hexane was partially hydrogenated (scheme 60) using Lindlar catalyst, to afford the *cis* olefin **238** which was not purified but directly dissolved in dichloromethane and treated with pyridinium-*p*-toluenesulphonate. This gave a 1:1 mixture of the less polar spiroketal tosylate **239** and the more polar diastereomer **240**, which were separated by flash chromatography.[69] The optical rotations of each product were surprisingly different when the structural similarity of the two is considered - $[\alpha]_D^{22}$ -18.5°, (c, 1.090, Et_2O) for **239** and $[\alpha]_D^{22}$ +38.8°, (c, 1.034, Et_2O) for **240**, but the mass

spectrum of each diastereomer was identical, affording, under chemical ionisation (NH_3)

Scheme 60



Reagents and conditions: (i) H_2, Lindlar catalyst, hexane/EtOAc;
(ii) pyridinium-*p*-toluenesulphonate, CH_2Cl_2, RT, 84% from **237**.

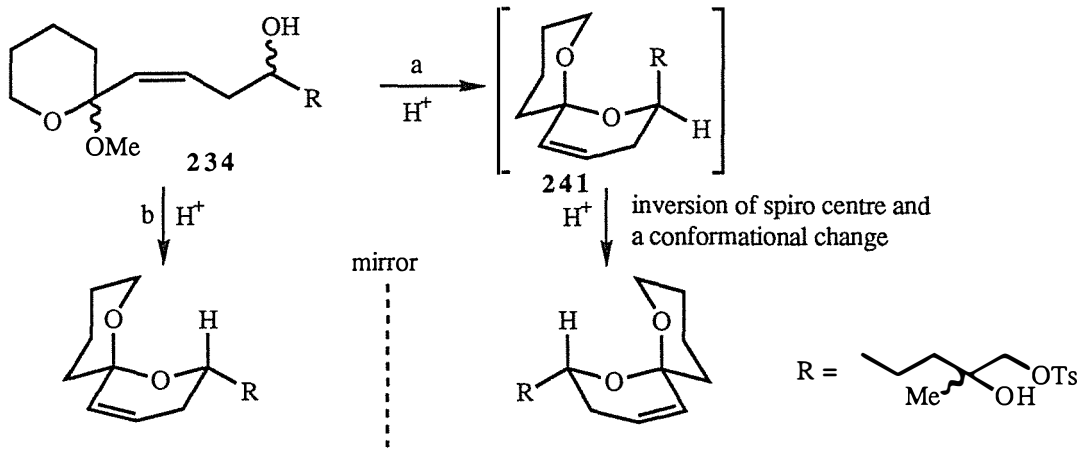
conditions, a molecular ion at *m/z* 749, consistent with the molecular formula $C_{43}H_{60}O_7SSi$ +H. ^{13}C nmr spectroscopy confirmed the diastereomeric purity of each product, with most resonances being assigned on the basis of 2D ^1H-^1H COSY and ^{13}C-^1H HETCOR nmr experiments. The key resonances at δ_C 96.8 for **239** and at δ_C 98.3 for **240** were indicative of spiroketal centres of six membered rings.

The structures of **239** and **240** were ascertained by considering both steric and anomeric effects. The favoured conformation of the spiroketal centre of both isomers is that in which the C-O bonds adopt axial or psuedo-axial positions on their respective neighbouring rings, as dictated by the anomeric effect.[47-50] The difference between the isomers arises from the unresolved C5 of the cyclisation precursor **238**. On spirocyclisation 50% of the mixture will afford that isomer **240** with a pseudo-equatorial side chain, and the remaining 50% that isomer **239** with the side chain placed in the relatively unfavourable

pseudo-axial position. Each can be distinguished by comparing the ^1H nmr spectra, since the 2'-H of **240** possesses a pseudo-1,3 diaxial relationship to a C-O bond and it's resonance is therefore deshielded - occurring as a multiplet at δ_H 3.94-4.05, relative to the resonance for the same proton of isomer **239** which occurs upfield, in the multiplet at δ_H 3.65-3.78.

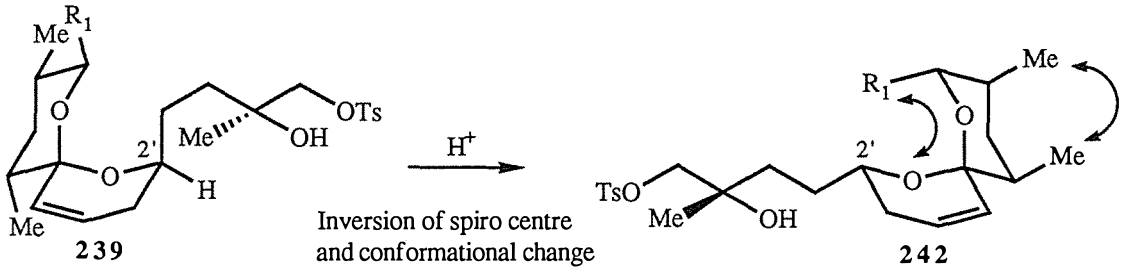
This contrasts with the corresponding model system, the products from which were obtained exclusively with the side chain in the pseudo-equatorial position. This is because the spiro centre of that half of the mixture which would be expected to give the product **241**, bearing a pseudo-axial substituent (step a, scheme 61), can invert in the acidic medium and, when accompanied by a conformational change of the rings to restore two anomeric effects, shift the orientation of the side chain to the pseudo-equatorial position. Since these compounds are racemic this product is simply the mirror image of that half of the mixture which gives the pseudo-equatorial side chain directly (step b).

Scheme 61



However, this scenario cannot apply to the tosylate **239** as it possesses a number of chiral substituents on the saturated ring. If the spiroketal centre was to invert, then undergo a conformational change to restore two anomeric effects (scheme 62) to give **242**,

Scheme 62



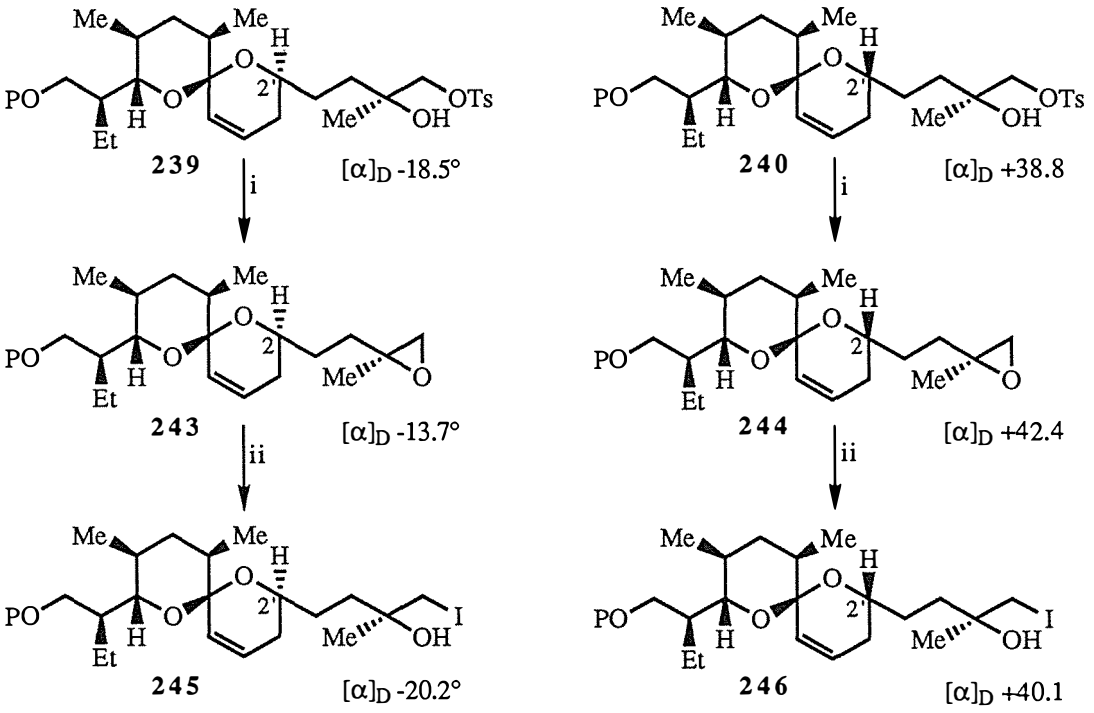
2 anomeric effects
Unfavourable pseudo-1,3-diaxial interactions

2 anomeric effects
Extremely unfavourable 1,3-diaxial interactions

then a pseudo-equatorial side chain at C2'would indeed result, relieving this steric tension. But in addition, that conformational change of the rings would also force the substituents of the unsaturated ring, normally equatorial, into the indicated unfavourable 1,3-diaxial relationships. So, when this steric effect is taken into account, the favoured conformation of the tosylate is that of **239**, for which the side chain occupies a pseudo-axial position at C2'.

Having separated the diastereomeric tosylates **239** and **240**, the remainder of the synthetic procedure was conducted on the individual isomers, each being treated in precisely the same fashion.

Scheme 63



Reagents and conditions: (i) NaH, THF, RT, 97%; (ii) LiI, THF, $BF_3.Et_2O$, -50°C, 91%.

Thus, **239** was converted to the epoxide **243** (scheme 63) in high yield (97%) using sodium hydride in tetrahydrofuran, and similarly the other diastereomeric epoxide **244** was obtained from **240** under the same conditions. The stereochemistry of each epoxide resembles that of the tosylate from which it is derived, since a relatively deshielded resonance, at δ_H 3.98-4.07 is observed in the ^1H nmr spectrum of **244**, due to a pseudo-1,3-diaxial interaction of 2-H with a C-O bond, whereas the corresponding resonance for the other epoxide **243** occurs upfield at δ_H 3.65-3.71. The methylene group of the terminal epoxide was also apparent, the protons resonating as as two doublets at δ_H 2.37 and 2.43 for isomer **243** and at δ_H 2.49 and 2.70 for **244**. The ^{13}C nmr spectrum exhibited

distinctive epoxide resonances, at δ_C 53.7 and 57.0 for **243** and at δ_C 53.9 and 56.8 for **244**. The optical rotations of each isomer were similar to the respective tosylate precursors **239** and **240**, $[\alpha]_D^{22}$ -13.7° (c, 0.766, Et_2O) for **243** and $[\alpha]_D^{22}$ +42.4° (c, 0.752, Et_2O) for **244**.

The iodohydrins **245** and **246** were obtained by a nucleophilic ring opening of the epoxide functionality by lithium iodide[80] in tetrahydrofuran at low temperature, catalysed by boron trifluoride etherate. Hence each diastereomer, **245** and **246**, possessed a stereochemistry analogous to the epoxide from which it was derived. The appearance of an hydroxyl group absorbance in the infra-red spectrum confirmed a ring opening of the epoxide, and the mass spectrum afforded a molecular ion at *m/z* 704, consistent with a molecular formula of $C_{36}H_{53}O_4ISi$. Satisfactory ^1H and ^{13}C nmr data were also obtained for both isomers. The optical rotations were again similar to those of the corresponding precursors, $[\alpha]_D^{22}$ -20.2° (c, 0.60, Et_2O) for **245** and $[\alpha]_D^{22}$ +40.1° (c, 0.51, Et_2O) for **246**.

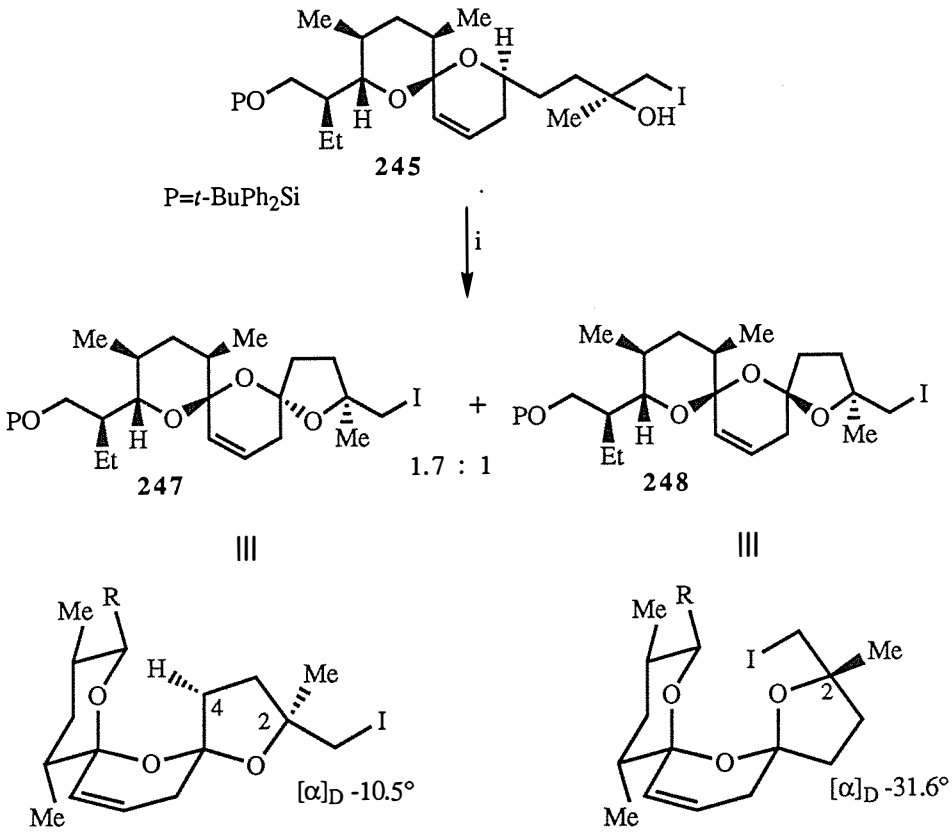
3.3 Assembly of the Bisspiroketal Moiety of *epi*-17-Deoxy-O(-8)-salinomycin.

Having obtained the iodohydrins **245** and **246**, spirocyclisation to the bisspiroketal was then attempted using the same controlled photolytic conditions developed for the model systems (see scheme 47).

Irradiation of a solution of iodohydrin **245** (scheme 64) in cyclohexane, containing iodine and iodobenzenediacetate under nitrogen, with a tungsten filament lamp afforded two less polar products. Although the R_f values differed only very slightly, they could nevertheless be separated by careful flash chromatography[69] to afford the *trans*-bisspiroketal **247** and the more polar *cis*-bisspiroketal **248** in a ratio of 1.7:1, in 54 % overall yield. The mass spectrum of each product was identical, giving a parent ion at *m/z* 702, consistent with the molecular formula $C_{36}H_{51}O_4ISi$. The yield of this cyclisation step was somewhat lower than that of the corresponding model systems, which may be due in part to the steric influence of the chiral substituents during cyclisation. If this is the case then replacing the *tert*-butyldiphenylsilyl ether by a less bulky protecting group would be appropriate. However, it was noted, in contrast to this step for the model experiments, that the reaction did not proceed as cleanly by tlc and hence it would appear that the increased structural complexity of these compounds may also be promoting competitive side reactions.

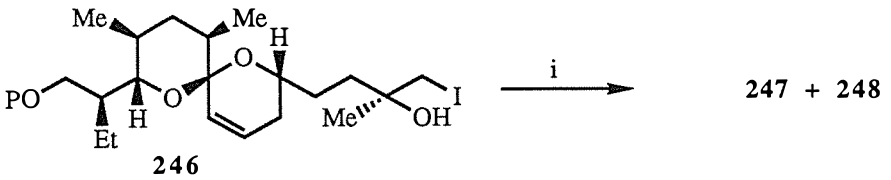
Both isomers exhibited two quaternary resonances in the ^{13}C nmr spectrum, at δ_C 99.1 and 107.4 for **247** and at δ_C 96.6 and 106.3 for the *cis* isomer **248**, resonances characteristic of spiroketal centres. ^1H nmr spectroscopy readily distinguished the *trans* isomer since the spectrum (figure 18) exhibited the characteristic resonance at δ_H 2.57 due to the 4-H proton which is deshielded, owing to it's proximity to a ring oxygen, relative to that in the spectrum of the *cis* isomer (figure 19) in which 4-H occurs at δ_H 2.02-2.11.

Scheme 64



Reagents and conditions: (i) Iodine (2 equiv.), iodobenzenediacetate (2 equiv.), 18°C, hυ, 54%.

Scheme 65



P=*t*-$BuPh_2Si$

Reagents and conditions: (i) Iodine (2 equiv.), iodobenzenediacetate (2 equiv.), 18°C, hυ, ratio **247:248**, 1.7:1.

Figure 18

247

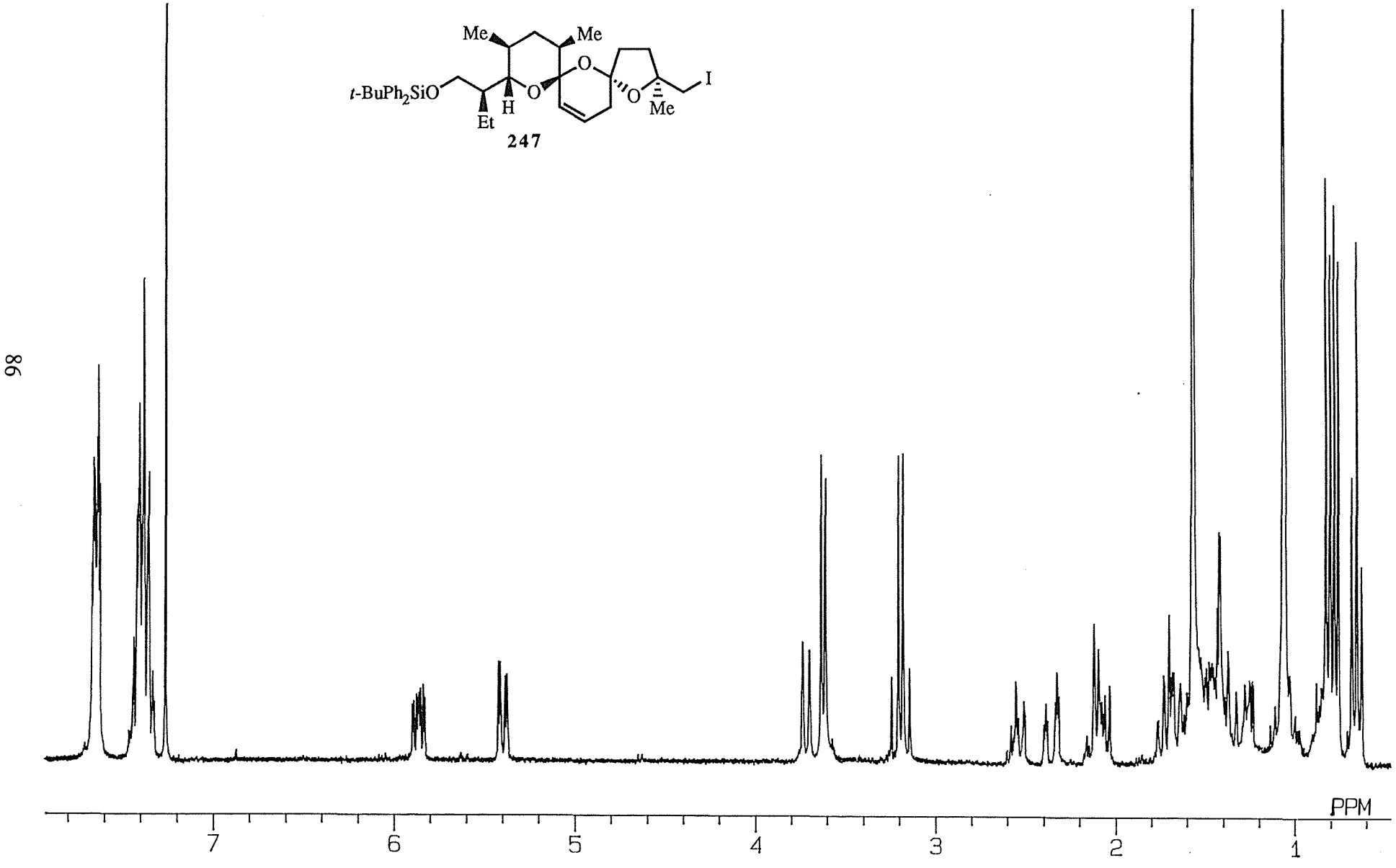
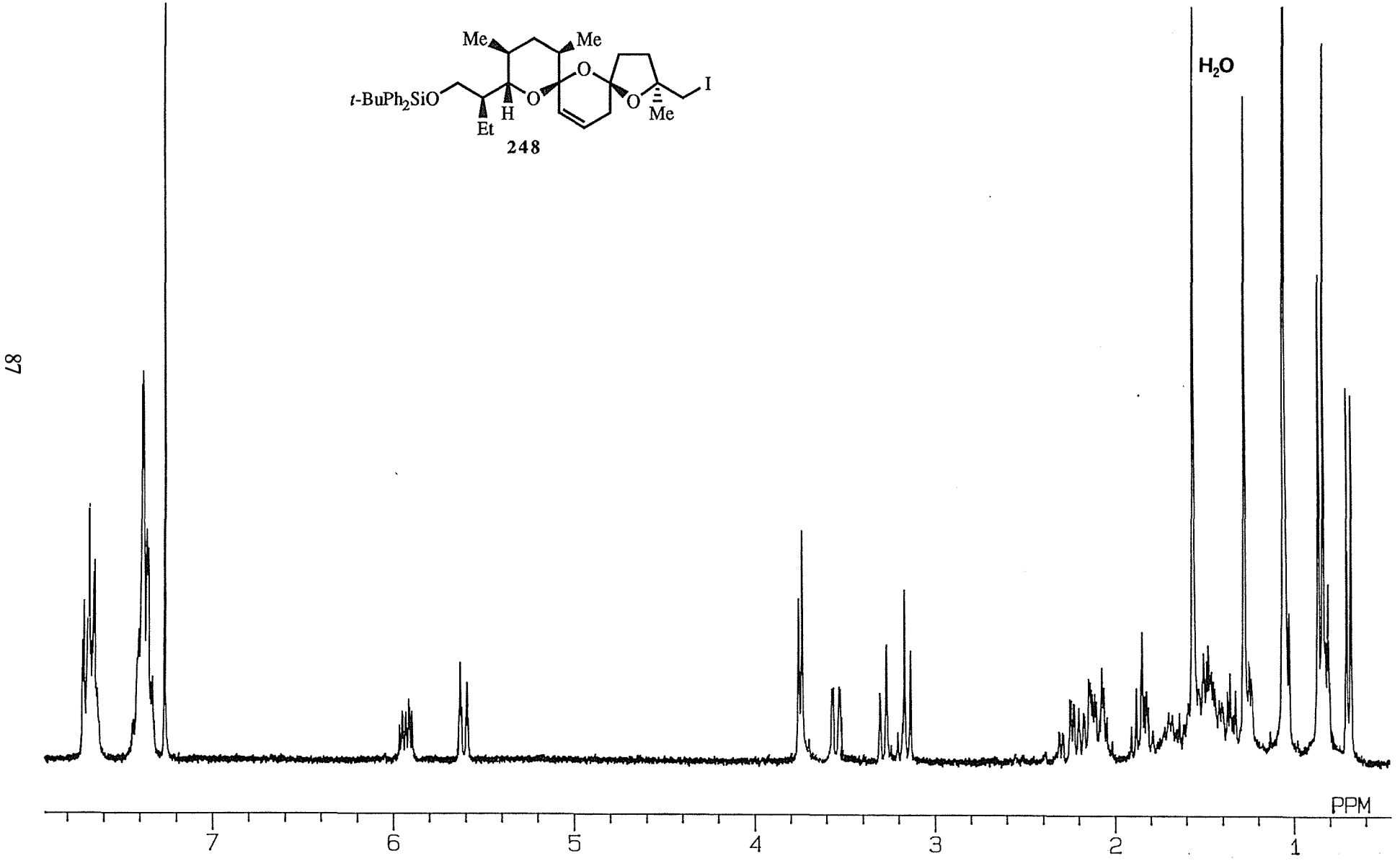


Figure 19

248



87

The stereochemistry of C2 is inferred by examining the chemical shifts of the 2-Me group. Since the C2 centre possesses an *S* configuration then, after spirocyclisation, the methyl group on the five membered ring of the *trans* isomer **247** *must* adopt a 1,3-*syn* orientation with a C-O bond of the central ring (see scheme 64) and therefore be somewhat deshielded relative to the corresponding methyl group of the *cis* isomer, which cannot adopt the same 1,3-*syn* orientation to that C-O bond. This is indeed the case as spectrum of the *trans* isomer **247** exhibits the C2 methyl resonance as a singlet at δ_H 1.57 compared to δ_H 1.28 for the *cis* isomer **248**.

Subjecting the the second iodohydrin **246** to the same photolytic conditions (scheme 65) used above gave rise to precisely the same mixture of products in exactly the same ratio (1:1.7 *cis:trans*) in similar overall yield, an outcome which may be explained by the proposed reaction mechanism (scheme 66). The oxygen radicals **249** and **250**, formed photolytically from the iodohydrins **245** and **246**, undergo a 1,5-hydrogen shift to give the stabilised carbon radical **251**. An important consequence of forming this intermediate is that because radicals of this type are considered[99,100] to be almost planar and freely inverting, the distinction between the diastereomeric precursors **245** and **246** is now lost. The radical species **251** is then assumed to be oxidised by iodine to the planar carbocation **252** which is subsequently trapped, predominantly from the least hindered α face to give the *trans* bisspiroketal **247**, and from the more hindered β face of the unsaturated ring to give the *cis* isomer **248** as the minor product. Thus, according to this mechanism, regardless of which iodohydrin, **245** or **246**, is subjected to these photolytic conditions, indistinguishable radical and carbocation intermediates are formed and hence the same product mixture results.

The *trans*-bisspiroketal **247** obtained by this procedure resembles exactly the bisspiroketal moiety of *epi*-17-deoxy-(O-8)-salinomycin **8**, and a comparison of key ^{1}H nmr chemical shifts and coupling constants with those of the natural product[75] and this fragment (table 3) serves to highlight the similarities. Although 4-H is more deshielded in the natural product, the coupling constants are remarkably similar to those of the synthetic analogue **247**, ($J_{4,4}$ 12.5, $J_{4,3}$ 7.5, $J_{4,3}$ 1.0 Hz for **8** and $J_{4,4}$ 12.6, $J_{4,3}$ 8.1, $J_{4,3}$ 0.4 for **247**). The chemical shifts of the 2-methyl resonances are similar (1.43 for **8** and 1.57 for **247**), in accordance with the stereochemistry of this centre (compare δ_H 1.28 for the *cis* isomer **248** which has the opposite relative stereochemistry of C2), as are those shifts of the chiral substituents which are not greatly influenced by R and R', notably the 10-methyl and 12-methyl groups - which also possess the same coupling constants. Examination of the vinylic (13-H and 14-H) and allylic (15-H) regions show them to be almost identical with respect to both chemical shifts the coupling constants of the resonances (compare $J_{13,14}$ 10.0, $J_{13,15}$ 1.0, $J_{13,15}$ 3.0 and $J_{15,15}$ 16.8 Hz for **8** and $J_{13,14}$ 10.1, $J_{13,15}$ 0, $J_{13,15}$ 2.4 and $J_{15,15}$ 16.8Hz for **247**.

Scheme 66

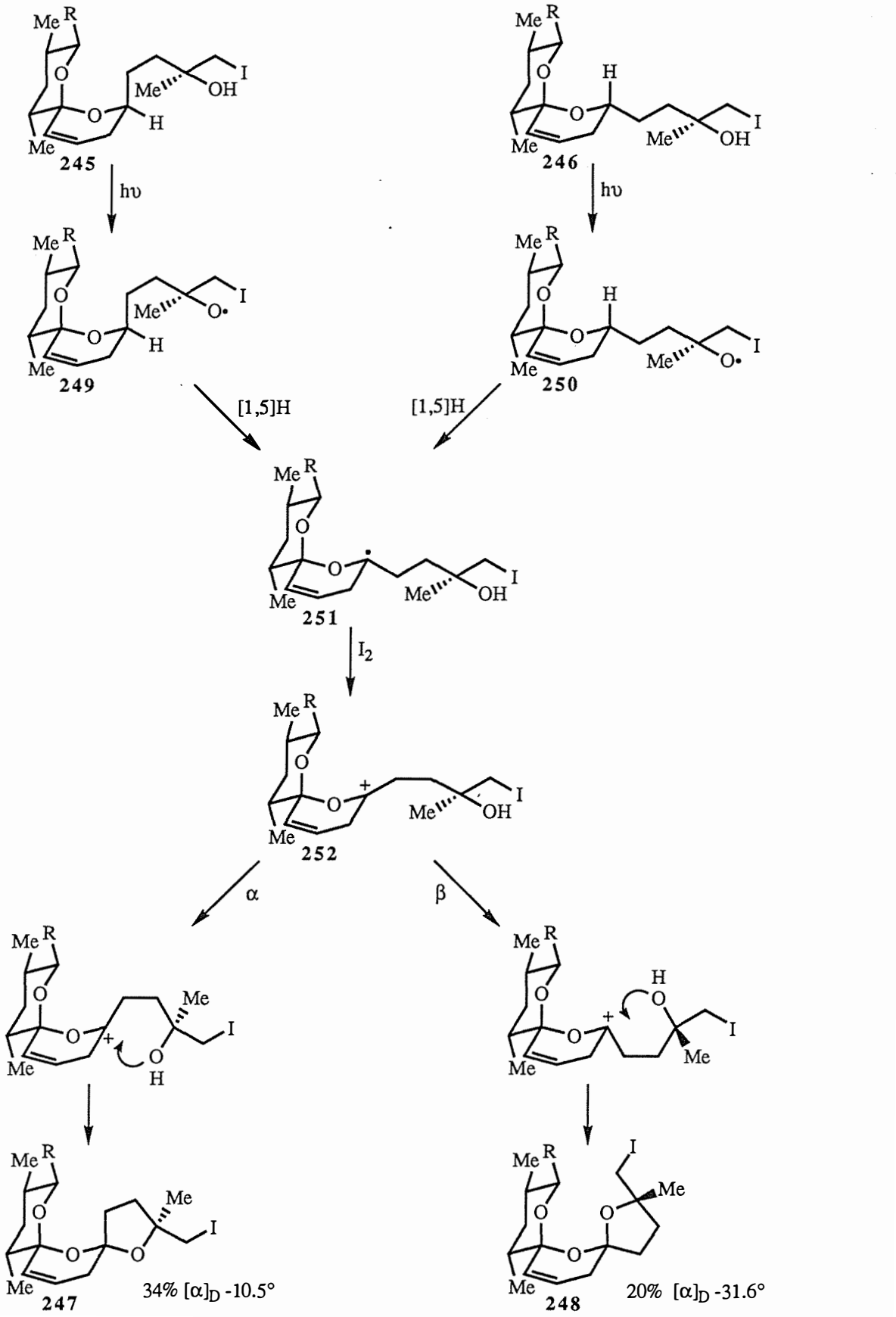
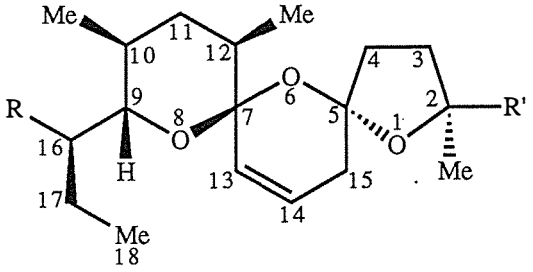
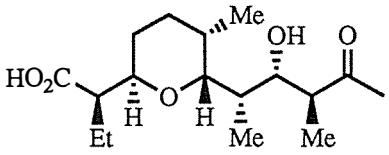
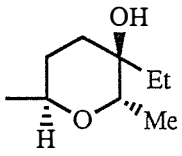

245
246
hυ
249
250
[1,5]H
[1,5]H
251
I2
252
α
β
247
34% [α]D -10.5°
248
20% [α]D -31.6°

Table 3

Key ^{1}H NMR Chemical Shift Values and Coupling Constants for *epi*-17-Deoxy-(O-8)-salinomycin and Synthetic *trans*-1,6,8-Trioxadispiro[4.1.5.3]pentadec-13-ene Analogues.



8 *epi* -17-Deoxy-(O-8)-salinomycin : R =  ; R' = 

247 : R = *t*-$BuPh_2SiOCH_2$; R' = CH_2I
255 : R = $HOCH_2$; R' = CH_2I

Chemical Shifts[a]

Compound	2-Me	3-H	3-H'	4-H	9-H	10-Me
8	1.43 (s)	2.09	1.95	3.01 (ddd)	3.80 (dd)	0.86 (d)
247	1.57 (s)	2.03-2.14	1.75	2.57 (ddd)	3.72 (dd)	0.82 (d)
255	1.89 (s)	2.14-2.23	2.14-2.23	2.57 (ddd)	3.83 (dd)	0.81 (d)

Compound	12-Me	13-H	14-H	15-H	15-H'	18-H
8	0.76 (d)	5.47 (ddd)	5.88 (ddd)	2.40 (ddd)	2.03	0.91 (t)
247	0.77 (d)	5.40 (dd)	5.86 (ddd)	2.36 (ddd)	2.03-2.14	0.66 (t)
255	0.80 (d)	5.48 (ddd)	5.94 (ddd)	2.41 (ddd)	2.14-2.23	0.98 (t)

Coupling Constants (Hz)

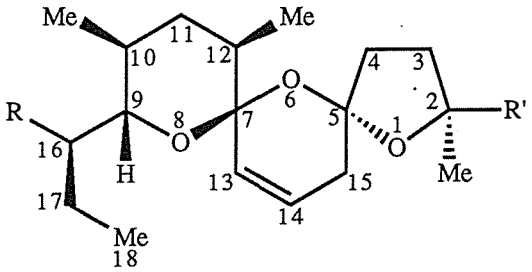
Compound	9, 16	9, 10	10-Me	12-Me	13, 14	13, 15	13, 15'
8	1.2	10.2	6.4	6.5	10.0	1.0	3.0
247	0.6	10.1	6.4	6.2	10.1	0.0	2.4
255	1.6	10.4	6.6	6.6	10.1	0.8	3.0

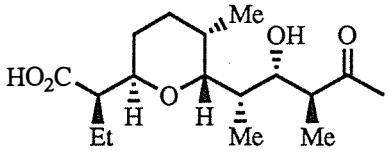
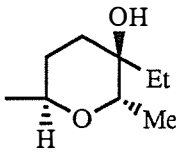
Compound	14, 15	14,1 5'	15, 15'	4, 4	4, 3'	4, 3	18, 17
8	6.4	2.0	16.8	12.5	7.5	1.0	7.5
247	6.4	2.1	16.8	12.6	8.1	0.4	7.5
255	6.2	2.4	16.8	12.6	5.1	5.1	7.1

[a] The spectrum of **8** was recorded at 360 MHz in $CDCl_3$ relative to $SiMe_4$; the spectra of **247** and **255** were recorded at 270 MHz in $CDCl_3$ relative to $SiMe_4$

Table 4

Key ^{13}C NMR Chemical Shift Values for *epi*-17-Deoxy-(O-8)-salinomycin and Synthetic *trans*-1,6,8-Trioxadispiro[4.1.5.3]pentadec-13-ene Analogues.



8 *epi* -17-Deoxy-(O-8)-salinomycin : R =  ; R' = 

247 : R = *t*-$BuPh_2SiOCH_2$; R' = CH_2I
255 : R = $HOCH_2$; R' = CH_2I

Chemical Shifts[a]

Compound	2	5	7	9	13	14
8	88.5	105.0	99.0	71.6	121.8	125.6
247	82.8	107.4	99.1	75.6	125.2	129.6
255	82.8	107.5	99.3	81.1	126.2	128.7

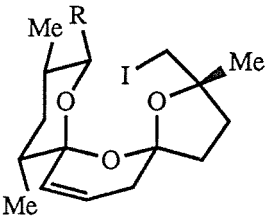
Compound	17	18	2-Me	10-Me	12-Me
8	22.7	11.9	25.8	15.7	17.9
247	17.8	12.9	28.4	16.0	18.3
255	17.5	12.3	28.4	15.9	17.6

[a] The spectrum of **8** was recorded at 25.1 MHz in $CDCl_3$ relative to $SiMe_4$; the spectra of **247** and **255** were recorded at 67.8 MHz in $CDCl_3$ relative to $SiMe_4$

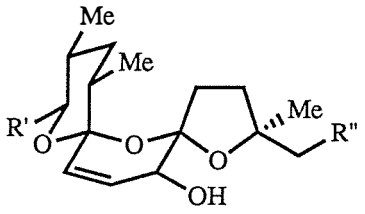
Some of the distinctive chemical shifts in the ^{13}C nmr spectrum of the natural product[101] also correspond closely to those of the synthetic product **247** (table 4). Very important are the two quaternary spiro resonances, occurring at δ_C 105.0 and 99.0 for C5 and C7 respectively for the natural product **8**, and at δ_C 107.4 and 99.1 for **247**. The remaining deshielded resonances, for C2 and C9 and for the vinylic carbons C13 and C14, of both **8** and **247** correspond well, as do the methyl group resonances 10-Me, 12-Me and C18. Such regularities in the nmr data leave little room for doubt that the structure and conformation of the synthetic bisspiroketal **247** does indeed resemble that of corresponding portion of *epi*-17-deoxy-(O-8)-salinomycin **8**.

The more polar diastereomer **248** possesses a *cis* arrangement of the bisspiroketal but the ring system does not resemble that present in salinomycin **7**. For **7** the spiro junction of the six membered rings adopts a relatively unfavourable configuration (figure 20), since only one anomeric effect is exhibited, to give a *cis* bisspiroketal with the opposite stereochemistry, with respect to the chiral substituents of the tetrahydropyran ring, to that of **248**.

Figure 20



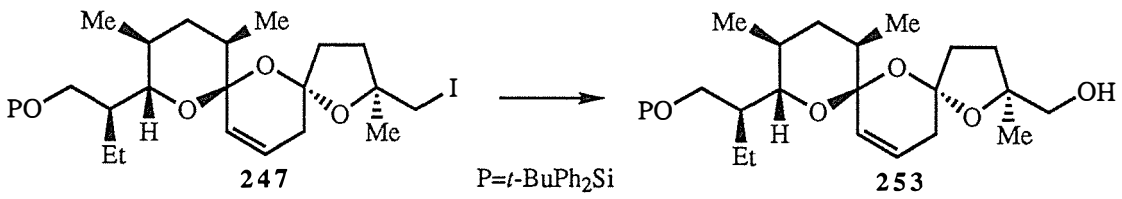
The bisspiroketal conformation of **248**.



The bisspiroketal conformation of salinomycin **7**.

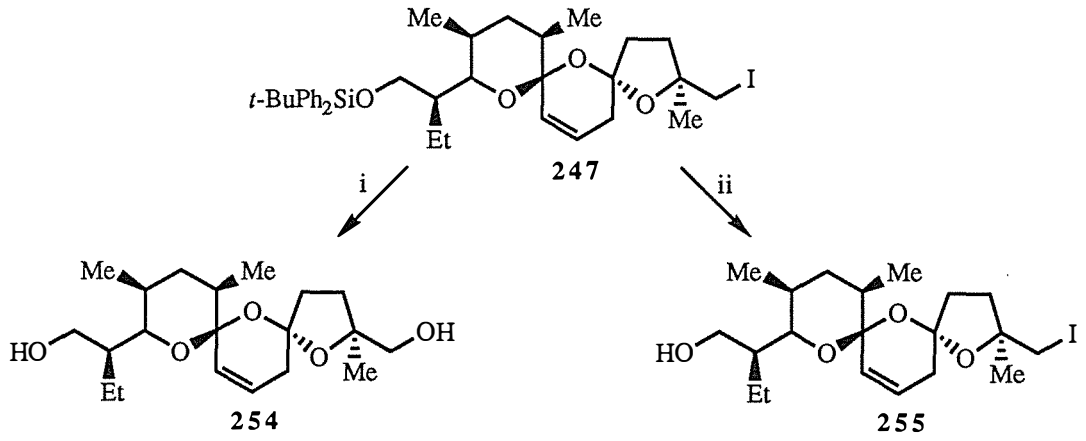
Hence this synthetic route cannot be applied to a synthesis of the deoxy-salinomycin series of compounds. However it can, on the basis of Kishi's work,[30] reasonably be asserted that should an allylic hydroxyl group be introduced with the appropriate stereochemistry and the remainder of the synthesis completed, then salinomycin would be obtained on thermodynamic equilibration of that product.

Equation 8



The next stage in the procedure required conversion of the iodide group of the *trans* bisspiroketal **247** to the alcohol **253** (equation 8), which would then enable subsequent construction of the terminal tetrahydropyran ring to give the right hand fragment **166** (see scheme 37) of the natural product **8**. This, however, presented certain difficulties because treatment of **247** with potassium superoxide in dimethylsulphoxide containing 18-crown-6 (scheme 67) for an extended period (12 h.), conditions[82] applied successfully in the model systems, not only caused displacement of the halogen but also removed the silyl ether to give the spiroketal-diol **254**. This is not a useful outcome since both alcohol groups are primary and virtually indistinguishable, rendering further synthetic manipulation difficult. Shorter reaction times under the same conditions (< 2 h.) exclusively resulted in formation of the iodo-alcohol **255**, which confirmed the *tert*-butyldiphenylsilyl ether to be, unexpectedly, the more labile of the terminal groups.

Scheme 67

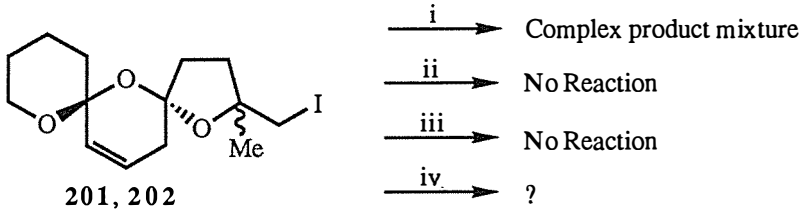


(i) KO_2, DMSO, 18-crown-6, ~12 h.
(ii) KO_2, DMSO, 18-crown-6, <2 h.

Milder reagents and conditions were then used in an attempt to remove the iodide whilst leaving the silyl ether intact. Ganem and Boeckman[102] successfully employed silver tetrafluoroborate to assist with an S_N2 displacement of alkyl halides by dimethylsulphoxide, the resulting intermediate then fragmenting to the aldehyde. Extending this method firstly to the model *trans* bisspiroketal iodides **201, 202** (scheme 68), however, resulted in a complex product mixture and therefore was not be applied to the case of the iodide **247**.

This does not, of course, preclude the possibility of using other silver salts to facilitate an S_N2 removal of the iodide group of **247**.

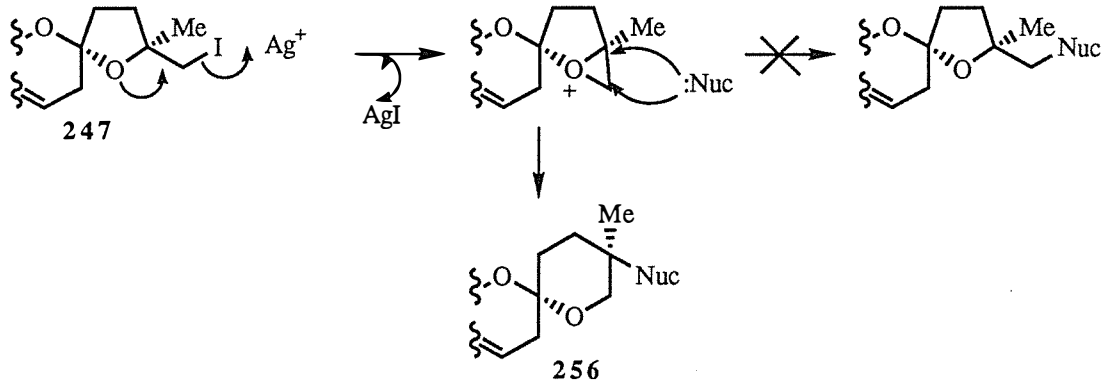
Scheme 68



(i) $AgBF_4$ (2 equiv.), DMSO, NEt_3 (excess).
(ii) KOH (2 equiv.), DMSO, 18-crown-6 (1 equiv.), Δ.
(iii) Me_3NO (excess), DMSO, Δ.
(iv) Tetraphenylphosphoniumdiacetatodioxodichlororuthenate, NMO, CH_2Cl_2.

However, using S_N1 conditions to remove the iodide would most probably be inappropriate when the precedent of Kishi *et al* [30] is considered (see scheme 14), since S_N1 conditions were used to effect a ring expansion of the tetrahydrofuran **74** to the tetrahydropyran **70**. Since the iodomethyl tetrahydrofuran portion of **247** is structurally similar, an analogous ring expansion to the tetrahydropyran **256** is also likely to occur in the same fashion (scheme 69).

Scheme 69



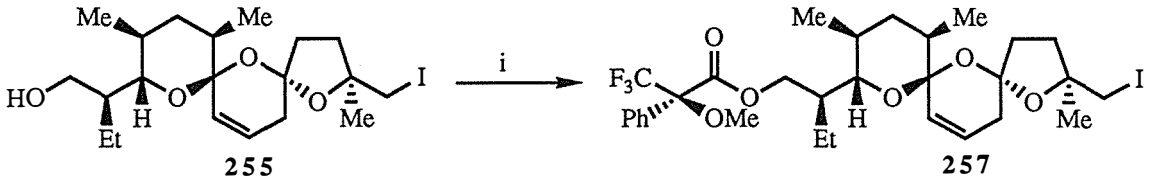
Another method used to convert a halide directly to an aldehyde, employing trimethylamine-*N*-oxide in dimethylsulphoxide[103] at elevated temperatures (scheme 68), gave no reaction when applied to the model iodide system, emphasising the extremely hindered nature of what is otherwise a good leaving group.

The recently reported tetraphenylphosphoniumacetatodichlorodioxoruthenate[104] catalyst and *N*-methylmorpholine-*N*-oxide has been shown to convert alkyl halides directly to the corresponding aldehydes in reasonable yield, and therefore may find an application in resolving the present difficulty.

Failing this, the obvious way to circumvent the problem of selectively removing the iodide group is to reprotect the iodo alcohol **255** with another group which is more compatible with the potassium superoxide reaction conditions. Having already speculated that the large *tert*-butyldiphenylsilyl group may be adversely influencing the photolytic spirocyclisation process (see page 84) it would seem appropriate to introduce this alternative protecting group, possibly a benzyl ether, earlier in the synthesis (step iii, scheme 70).

Having prepared the iodo-alcohol **255**, the optical purity of the product was assessed. It would be expected that after conversion of **255** to the Mosher ester derivative **257**, using (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[105,106] (scheme 71), an examination of the ^1H nmr spectrum of this ester would reveal any resulting diastereomeric resonances.

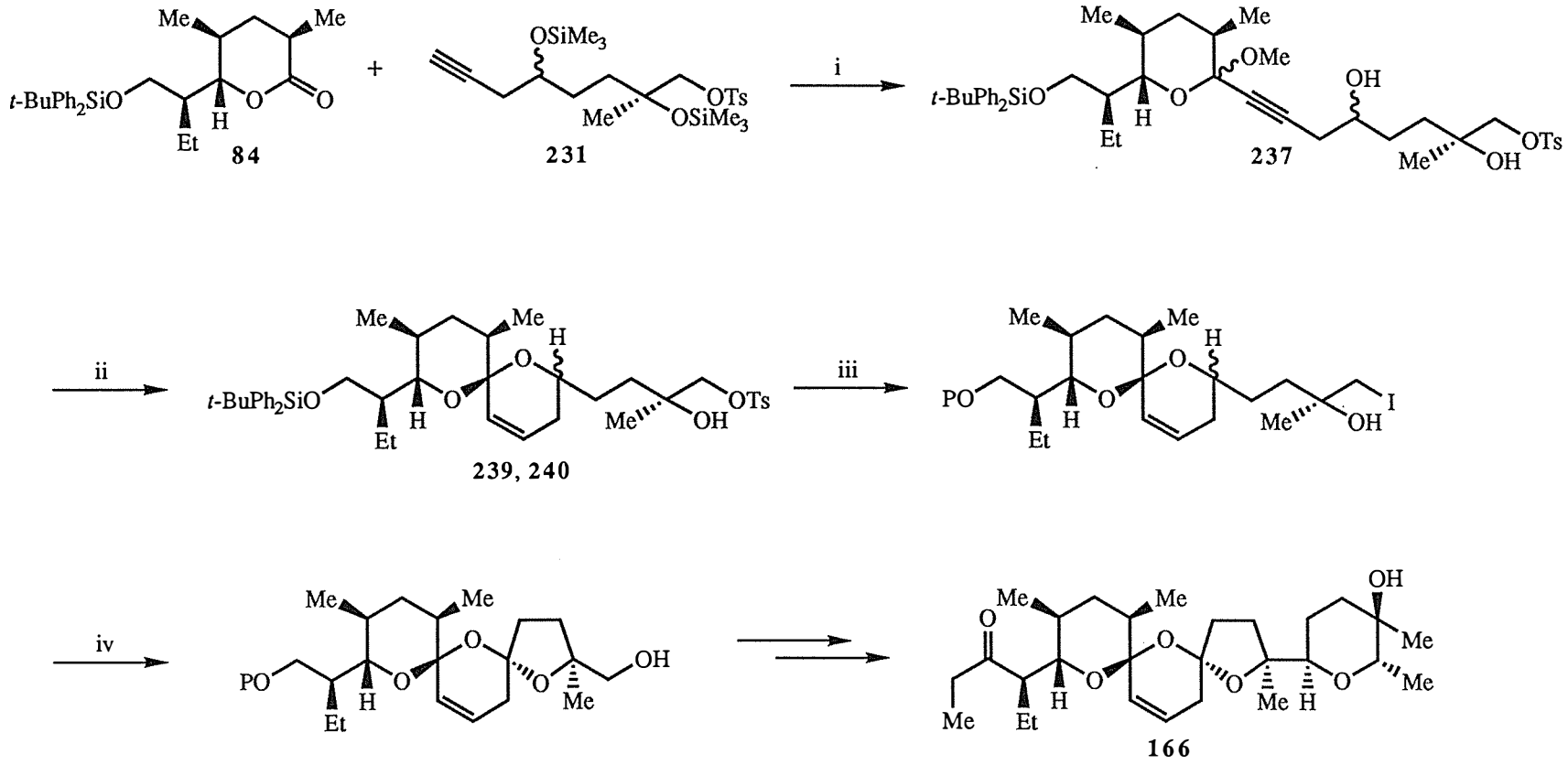
Scheme 71



Reagents and conditions: (i) (*R*)-(+)-α-methoxy-α-(trifluoromethyl) phenylacetyl chloride (slight excess), CCl_4, pyridine, RT, 12 h.

By comparing the spectrum of the alcohol **255** (figure 21) with that of the ester **257** (excluding the aromatic region) (figure 22), the optical purity of the indicated enantiomer of **255** was established to be in excess of 96% e.e. (the multiplicity of the methoxy resonance at δ_H 3.57 in the spectrum of **257** (figure 22) is due to long range coupling with fluorine). Furthermore, the ^{19}F nmr spectrum[107] of **257** exhibited a single broad peak (due to coupling with the methoxy group) at δ_F -104.1 (relative to C_6F_6 at δ_F -163.0), and also implied an enantiomeric excess greater than 96%.

Scheme 70



P=protecting group (eg. $C_6H_5CH_2$)

Reagents and conditions: (i) a: *n*-BuLi, THF, -78°C, 0.5 h. then **84**; b: MeOH, Amberlite IR 120 resin, 1 h.; (ii) a: H_2, Lindlar catalyst, hexane; b: PPTS, CH_2Cl_2; (iii) a: *n*-Bu_4NF, THF, RT; b: Protect (eg. $C_6H_5CH_2$); c: LiI, THF, -50°C, $BF_3.Et_2O$; (iv) a: $PhI(OAc)_2$, I_2, cyclohexane, 15°C, hυ; b: KO_2, DMSO/THF, 18-crown-6.

Figure 21

255

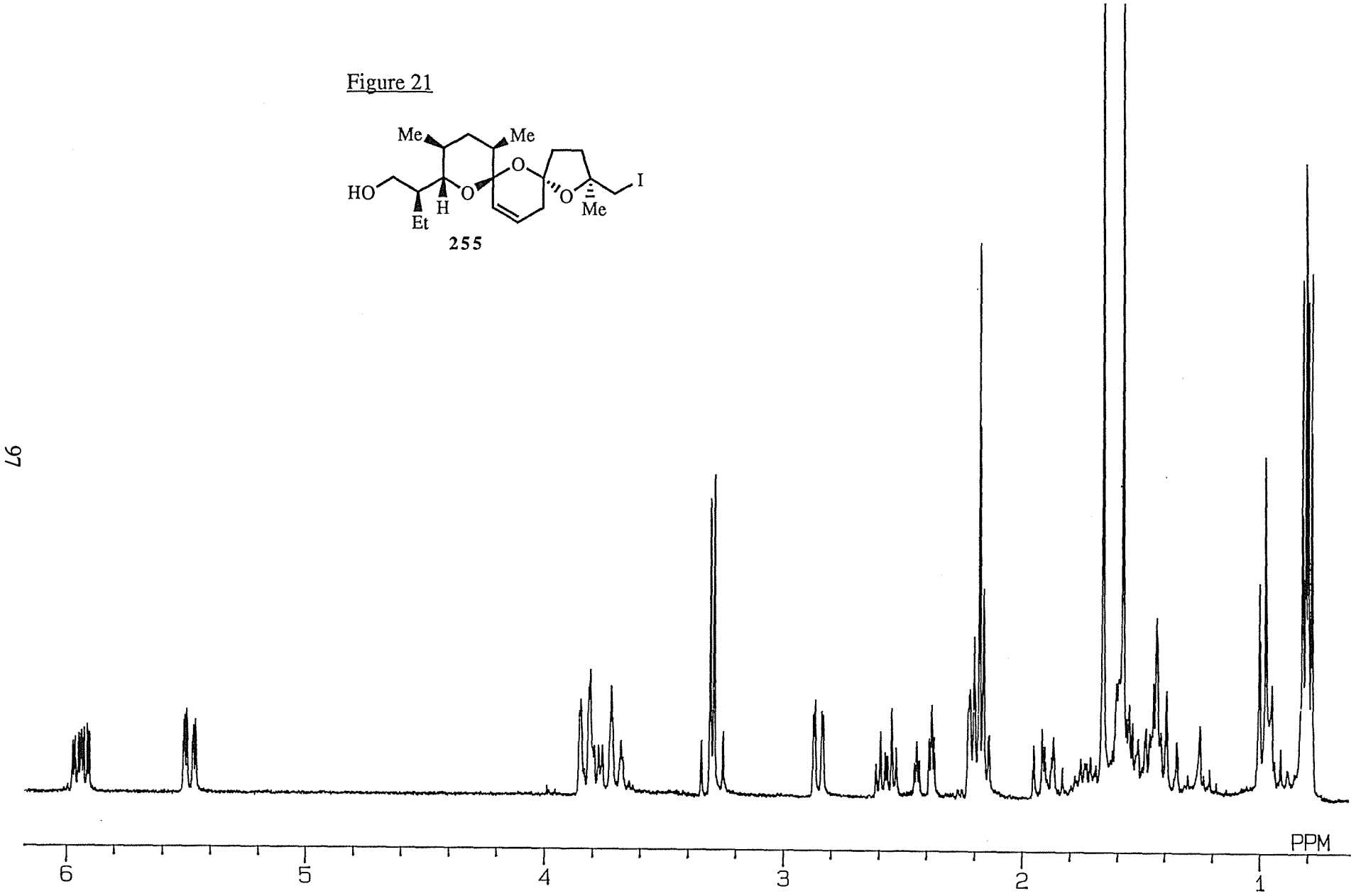
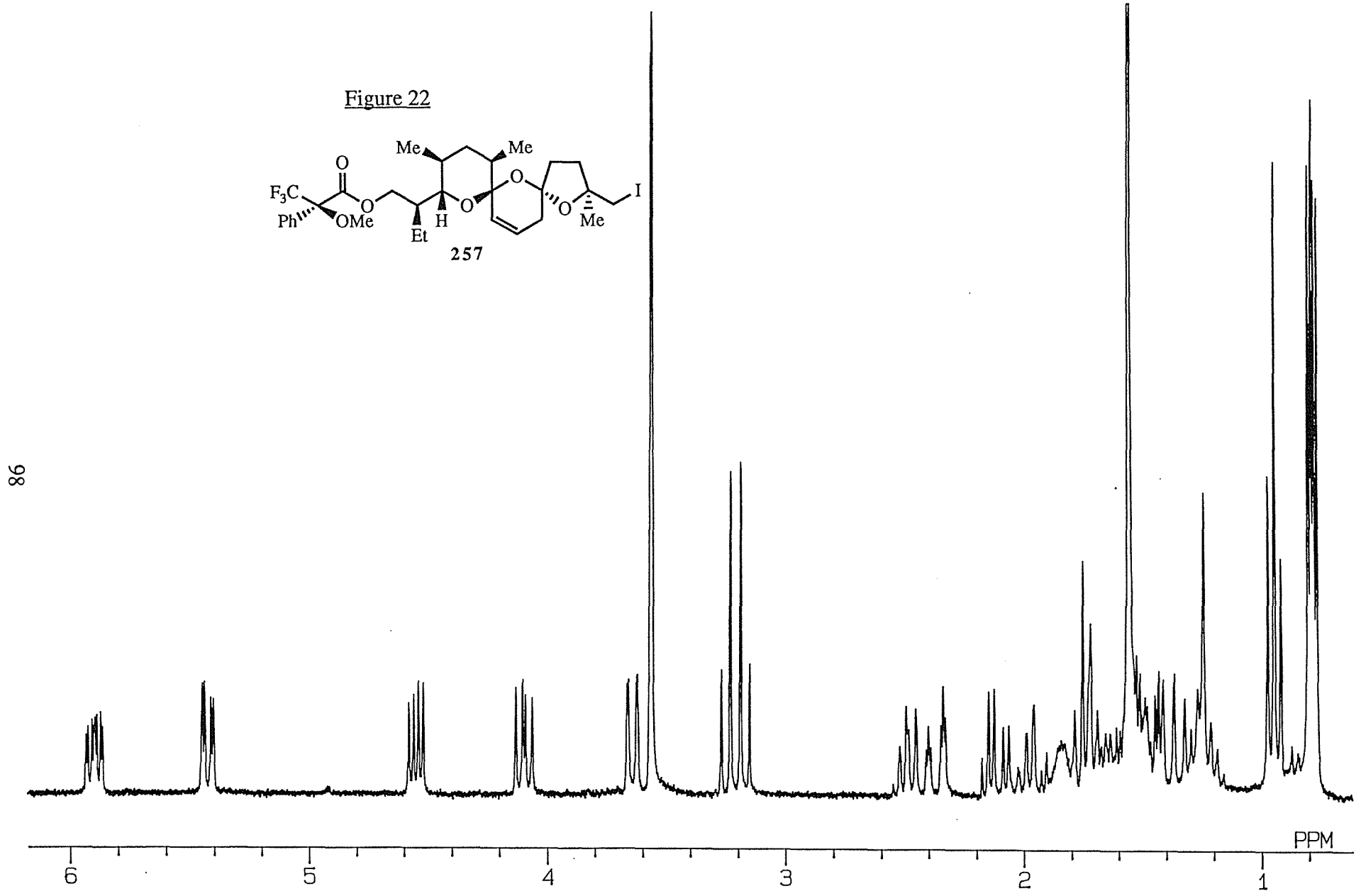


Figure 22

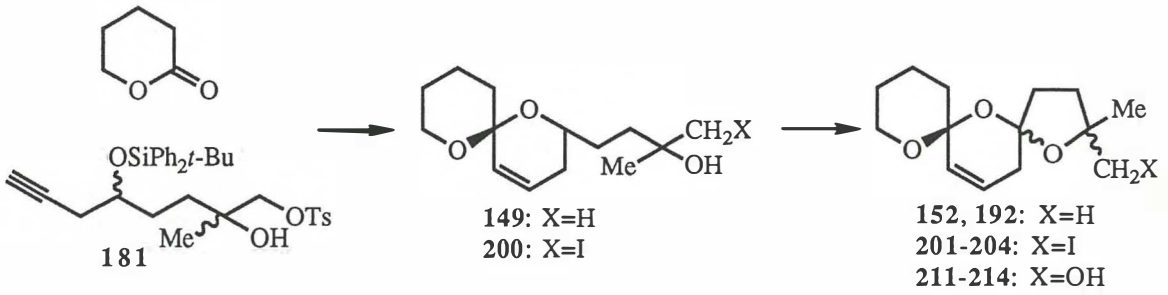
257



3.4 Summary.

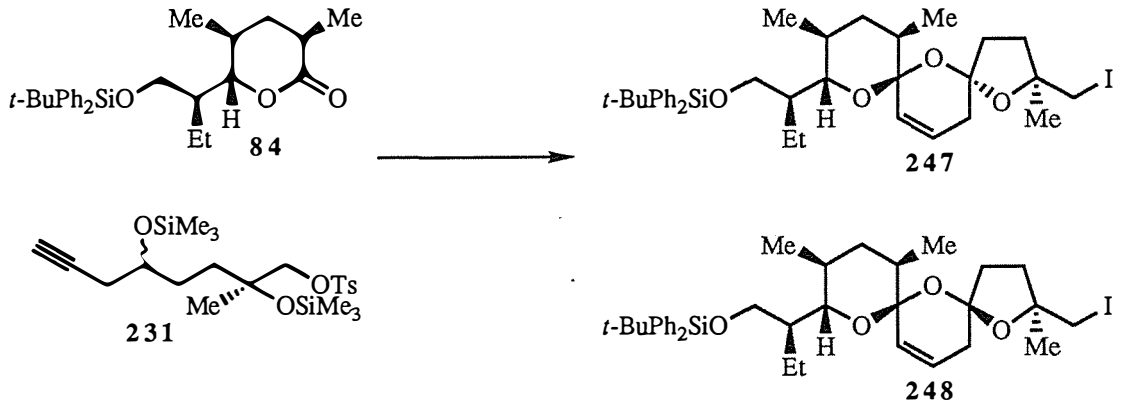
The feasibility of the chosen route for constructing the unsaturated bisspiroketal ring system present in *epi*-17-deoxy-(O-8)-salinomycin **8** has now been reasonably established. The essence of the final enantioselective synthesis was initially mapped out using a relatively simple model (equation 9) which allowed an investigation into the stereochemistry of these ring systems. In the first instance, the original work of Baker and Brimble[60] (see scheme 33) was modified and extended so that δ-valerolactone and the acetylene **181** could be combined to afford both the known *trans* and the novel *cis* 2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes **152** and **192**.

Equation 9



Subsequently the route was modified to incorporate an appropriate terminal functionality, an iodide group, (equation 9) which was both compatible with the critical Barton-type oxidative cyclisation reaction, which generates the bisspiroketal, and also provided a 'handle' by which the resulting *cis* and *trans* 2-iodomethyl-2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes **201-204** might be further elaborated after conversion to the corresponding alcohols **211-214**. When the methodology was extended to the enantioselective portion of the synthesis, the optically active lactone **84** and acetylene **231** were combined (equation 10) to generate the *trans* and *cis* bisspiroketals **247** and **248**, the former of which possesses a stereochemistry corresponding to that of the natural product *epi*-17-deoxy-(O-8)-salinomycin **8**, and is functionalised at the termini to selectively permit further elaboration of the fragment.

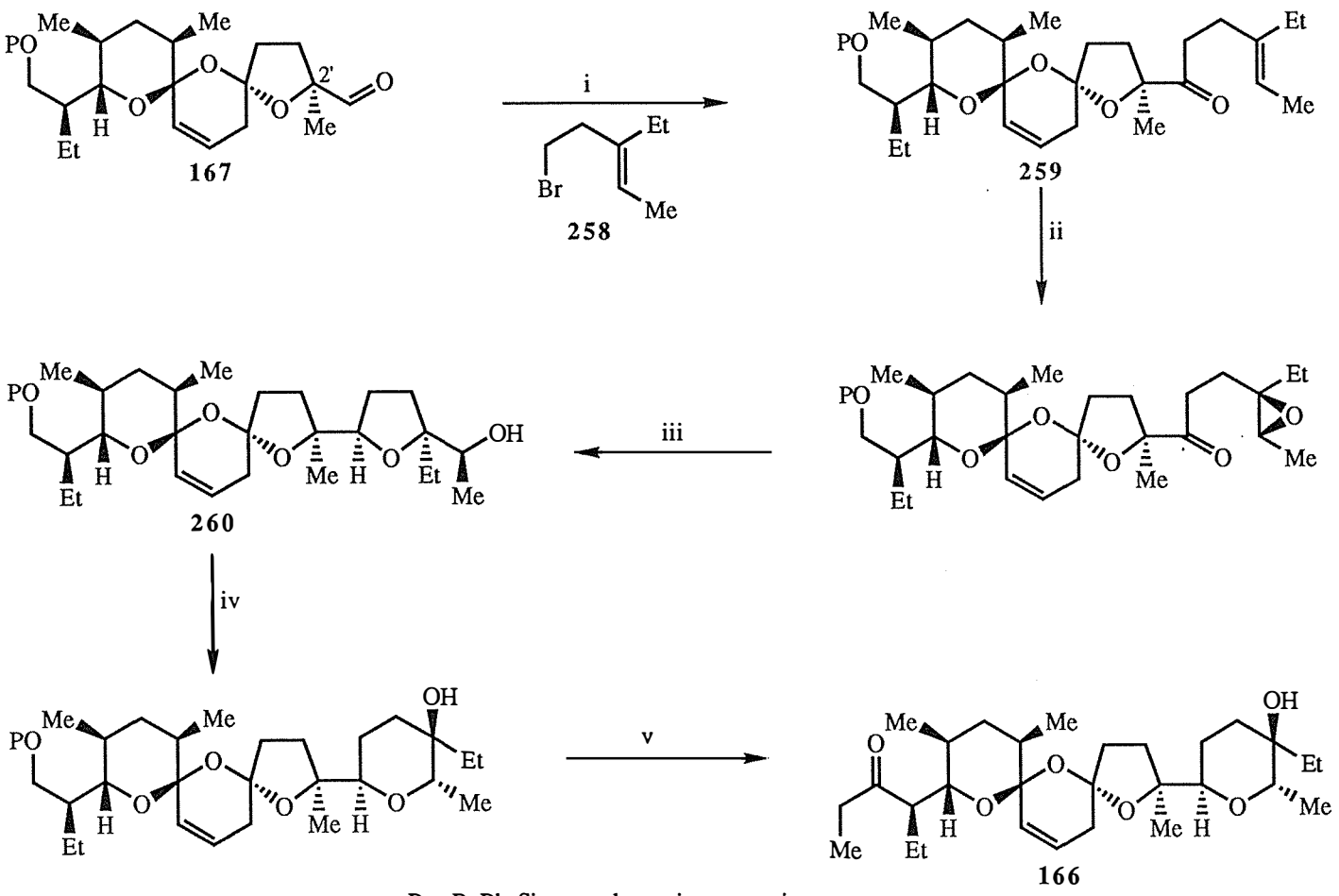
Equation 10



In addition to improving certain steps of the existing pathway, it now remains to convert the *trans* bisspiroketal fragment **247** into the right hand portion of *epi*-17-deoxy-(O-8)-salinomycin, and thence into the entire natural product **8**. Two syntheses of the left hand portion **25** (see pages 11 and 36) have already been described, but a possible means of achieving a synthesis of the novel right hand fragment **166** may be gleaned by analysing the total synthesis of lasalocid A **3** carried out by Kishi *et al* .[31-33] Application of the methodology used in that synthesis to the case in question (scheme 72) would require Grignard addition of the bromo-olefin **258** to the spiroketal aldehyde **167** which could then be stereoselectively converted to the γ, δ-unsaturated ketone **259**. A sequence of steps requiring selective epoxidation, cyclisation to the tetrahydrofuran **260** and a ring expansion would then ensue, affording the right hand fragment of *epi*-17-deoxy-(O-8)-salinomycin **8**.

However, a disadvantage of this synthetic sequence lies in the number of steps performed following formation of the bisspiroketal fragment **167** since, due to the length of the synthesis, the quantities of this material will undoubtedly be small. Hence it would be appropriate to develop an alternative strategy which makes use of a more synthetically advanced form of the tetrahydropyran unit prior to a coupling with **167**.

Scheme 72



P=*t*-$BuPh_2Si$ or an alternative protecting group

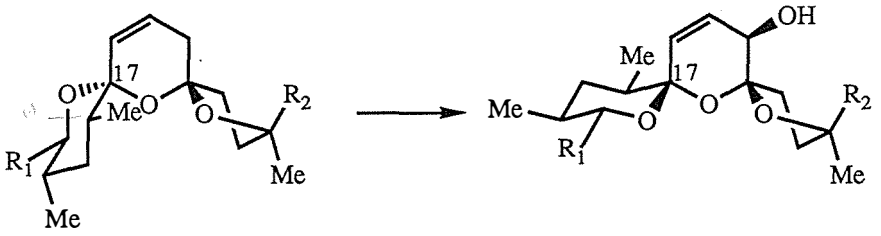
(i) a: Mg turnings, Et_2O then **167**; b: oxidation; (ii) epoxidation; (iii) a: $LiAlH_4$, *dl* -2-(*o*-2-toluidinomethyl)pyrrolidine, Et_2O, -78°C;b: AcOH; (iv) a: MsCl, Pyridine; b: Ag_2CO_3, acetone; (v) a: deprotection; b: oxidation; c: EtMgBr.

Chapter 4

4.1 Allylic Oxidation of 2,2-Dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene.

In line with the search for novel synthetic strategies for constructing the salinomycin-related polyether antibiotics, an investigation was undertaken into the possibility that allylic functionalisation of the bisspiroketal moiety of *epi*-17-deoxy-(O-8)-salinomycin **8** would provide a method of entry into the salinomycin **7** ring system (equation 11).

Equation 11



epi -17-Deoxy-(O-8)-salinomycin **8**
3 anomeric effects
Favourable arrangement of dipoles

Salinomycin **7**
3 anomeric effects
Unfavourable arrangement of dipoles

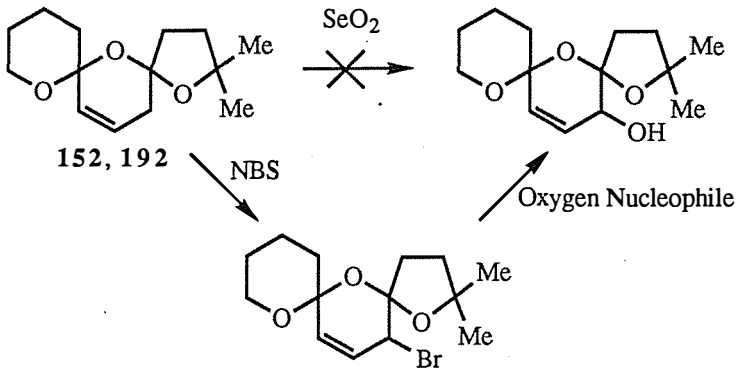
In addition to the obvious functionality difference at the allylic position, the conformations of the tricyclic ring systems of the natural products **7** and **8** also differ. Salinomycin **7** possesses a *cis* arrangement of the bisspiroketal whereas that of *epi*-17-deoxy-(O-8)-salinomycin **8** adopts an apparently more favourable *trans* arrangement, alleviating dipolar interactions. However, experiments carried out by Kishi *et al* [30] showed that the allylic hydroxyl group of salinomycin **7** participated in long range intramolecular hydrogen bonding, and these interactions served to stabilise the observed conformation of this natural product. The implication of this work, therefore, is that if an allylic hydroxyl group were to be introduced onto the spiroketal of *epi*-17-deoxy-(O-8)-salinomycin **8** with the appropriate stereochemistry, then thermodynamic equilibration of this product would afford salinomycin **7**.

An investigation was undertaken into an allylic oxidation of the 2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes **152** and **192** with a view to designing a methodology whereby *epi*-17-deoxy-(O-8)-salinomycin **8** might be converted directly into salinomycin **7**.

Although Deslongchamps *et al* [108] successfully oxidised a bicyclic spiroketal at the allylic position using selenium dioxide, a common reagent for this purpose, the method

proved to be ineffective when extended to the tricyclic bisspiroketals **152** and **192** (scheme 73).

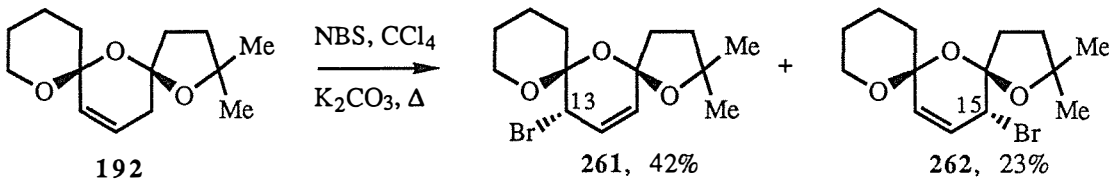
Scheme 73



Owing to the scarcity of other satisfactory mild allylic oxidation procedures a more indirect approach was adopted in which an allylic bromide would firstly be generated and subsequently displaced by an oxygen nucleophile to afford the required alcohol (scheme 73), a procedure which required careful evaluation of regio- and stereochemical outcomes.

Heating a solution of the *cis*-2,2-dimethyl-1,6,8-trioxadis piro[4.1.5.3]pentadec-13-ene **192** in carbon tetrachloride with a slight excess of *N*-bromosuccinimide and anhydrous potassium carbonate (scheme 74) resulted in the formation of two diastereomeric products, crystalline *cis*-13-bromo-2,2-dimethyl-1,6,8-trioxa-dis piro[4.1.5.3]pentadec-14-ene **261** in 42% yield, and the more polar *cis*-15-bromo-2,2-dimethyl-1,6,8-trioxa-dis piro[4.1.5.3] pentadec-13-ene **262** in 23% yield.

Scheme 74



Both products exhibited similar ^1H nmr spectra, the resonances at δ_H 4.29 for **262** and δ_H 4.27 for **261** being attributed to an allylic CHBr proton (table 5) in each case. The mass spectrum of both products exhibited a molecular ion at *m/z* 316, 318, which is consistent with a molecular formula of $C_{14}H_{21}O_3Br$, and a base peak at *m/z* 237 which corresponds to M-Br. Assignment of the regiochemistry for the allylic bromides **261** and **262** was made on the basis of the fragmentation pattern in the mass spectrum of each. The

spectrum of **262** exhibited peaks at *m/z* 202 and 204, corresponding to a formula of $C_8H_{11}OBr$, which arises from a retro-Diels-Alder fragmentation (equation 12) of the unsaturated bisspiroketal substituted at C15.

Equation 12

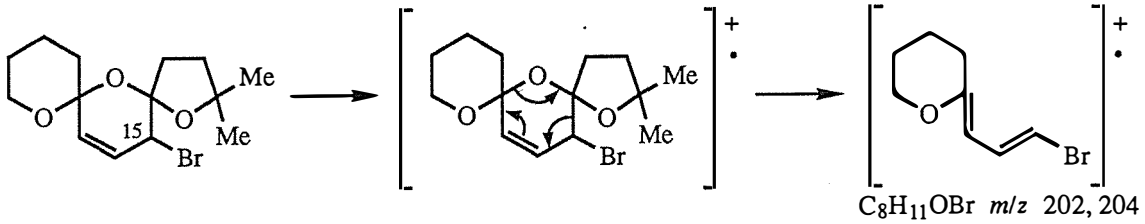
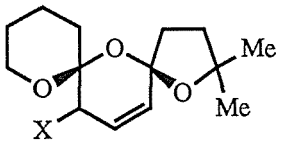
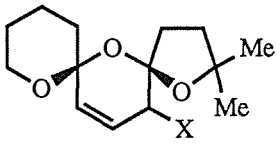


Table 5

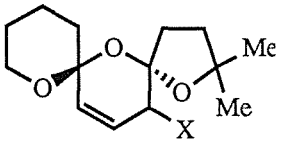
Vinyl and Allyl Chemical Shifts of 2,2-Dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadecenes Substituted at the Allylic Position.



261: X=Br
268: X=OH
269: X=OAc



262: X=Br
156: X=OH
270: X=OAc



265: X=Br
159: X=OH

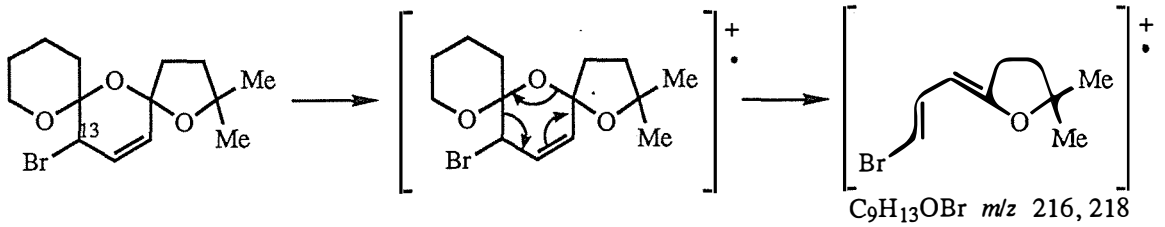
Chemical shifts[a]

Compound	CHX	CH=CH-CHX	CH=CH-CHX
261	4.27 (d)	5.68 (d)	6.10 (dd)
262	4.29 (d)	5.81 (d)	6.13 (dd)
265	4.55 (dd)	5.62 (dd)	6.03 (dd)
268	3.57-3.66	5.78 (d)	6.08 (dd)
156	3.57-3.66	5.88 (d)	6.11 (dd)
159	4.15 (ddd)	5.62 (dd)	5.88 (dd)
269	4.89 (d)	5.87 (d)	5.99 (dd)
270	4.86 (d)	5.97 (d)	6.05 (dd)

[a] Recorded at 270 MHz in $CDCl_3$ relative to $SiMe_4$

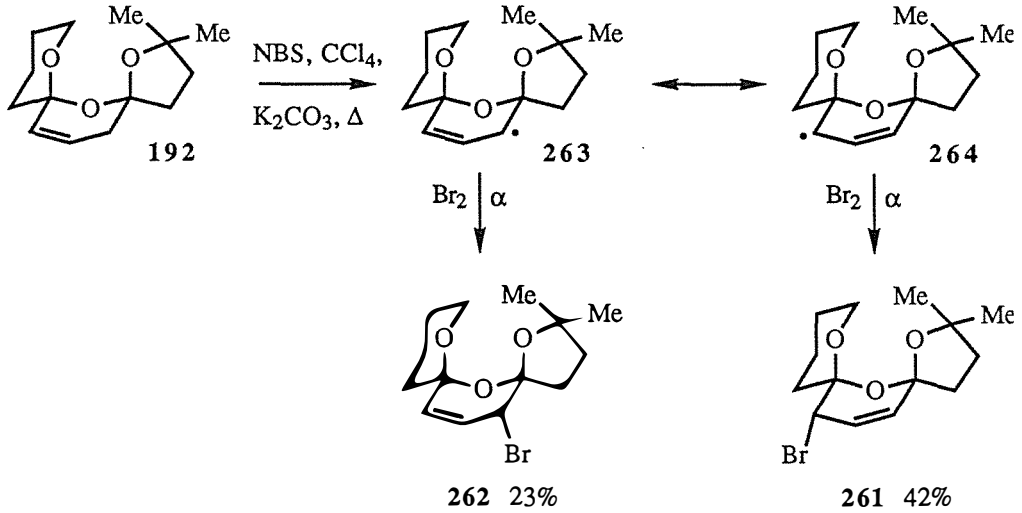
The mass spectrum of the other bromide **261** also showed a similar pair of peaks, but at *m/z* 216 and 218, corresponding to the formula $C_9H_{13}OBr$, a fragment consistent with a retro-Diels-Alder fragmentation of the allylic bromide substituted at C13 (equation 13).

Equation 13



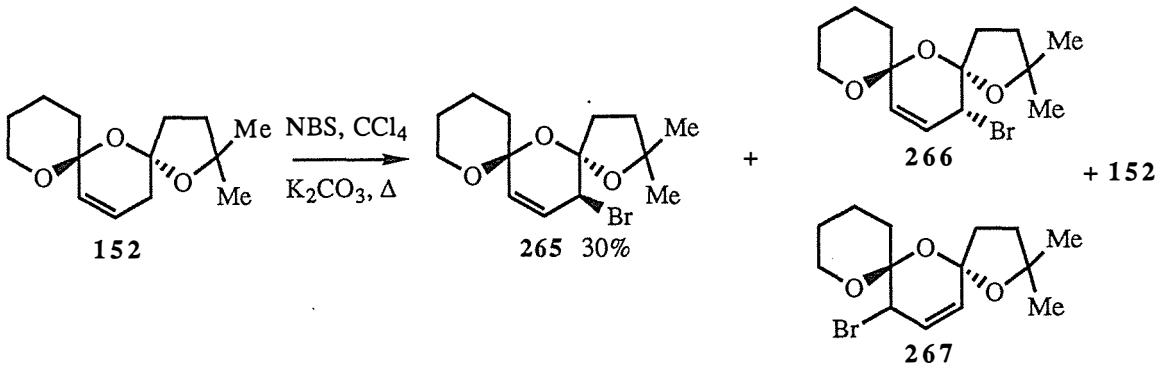
Formation of these two products is easily rationalised by considering the reaction mechanism (scheme 75). On heating **192** with *N*-bromosuccinimide an allylic radical intermediate is generated which undergoes a rearrangement to give a mixture of the two radicals **263** and **264**. These are then trapped by bromine to afford the bromides **261** and **262** in the ratio 2:1.[109] The allylic radicals are assumed to be trapped at the α face of the ring, it being less hindered due to the steric influence of the oxygen atoms of the adjacent terminal rings. This assignment of the stereochemistry, which cannot be supported at this stage, will later be confirmed (*vide infra*).

Scheme 75



The *trans*-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **152** was also treated with *N*-bromosuccinimide under the same conditions (scheme 76) as above to afford the unrearranged allylic bromide **265** in 30% yield.

Scheme 76



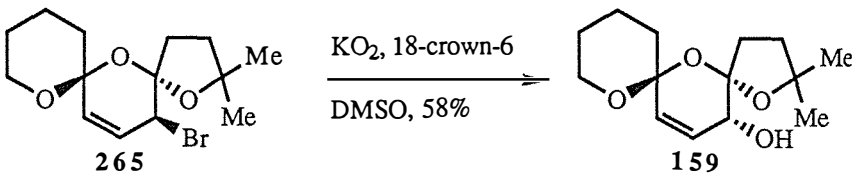
152 **265** 30% **266** **267**

The ^1H nmr spectrum exhibited an allylic CHBr resonance at δ_H 4.55 (table 5, page 104) and the mass spectrum exhibited a molecular ion at *m/z* 318 and 316, corresponding to the formula $C_{14}H_{21}O_3Br$, a base peak at *m/z* 237 (M-Br) and a retro-Diels-Alder fragmentation at *m/z* 202, 204 indicating an introduction of bromine at C15 (see equation 12, p. 104). The steric considerations are such that trapping of the radical intermediate was assumed to occur from above, or β, on the central ring, an assignment which will later be confirmed (*vide infra*).

A second fraction from this reaction was isolated by flash chromatography[69] and ^1H nmr spectroscopy showed it to be a complex mixture, comprising starting material **152**, and the *trans* bromides **266** and **267**. However, since these products could not be individually isolated, further experimentation with this fraction was not pursued.

Having obtained the one *trans* **265** and two *cis* **261**, **262** bromides, an S_N2 displacement of the halogen was attempted using an oxygen nucleophile. The *trans* bromide **265** was treated with potassium superoxide in dimethylsulphoxide containing 18-crown-6 (scheme 77) to afford the 15-hydroxy-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **159**.

Scheme 77

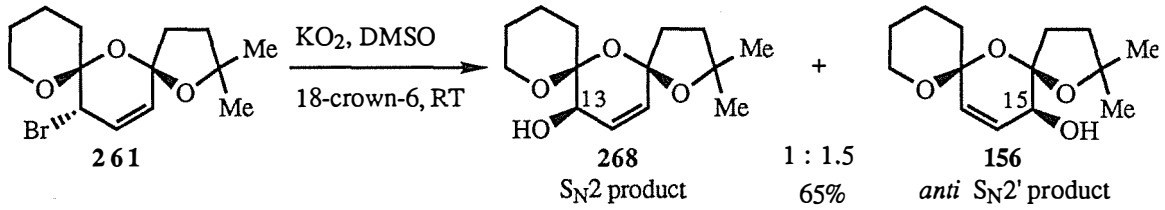


265 **159**

The stereochemistry of this product was confirmed by comparing it's ^1H nmr spectroscopic data with those obtained by Kocienski *et al* for the same product,[110] which had been derived from the ketone **154**[64] (see scheme 35). Also, by implication of an S_N2 process having occurred, the stereochemistry of the bromide group of **265**, previously uncertain, was now established to have been β on the central ring.

Treatment of the *cis*-13-bromo-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-14-ene **261** with potassium superoxide and 18-crown-6 in dimethylsulphoxide (scheme 78), in the same way as above, afforded an inseparable mixture of the 13-hydroxy-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]penta-dec-14-ene **268** and the 15-hydroxy-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]penta-dec-13-ene **156** in the ratio 1:1.5, in 65% overall yield.

Scheme 78



261

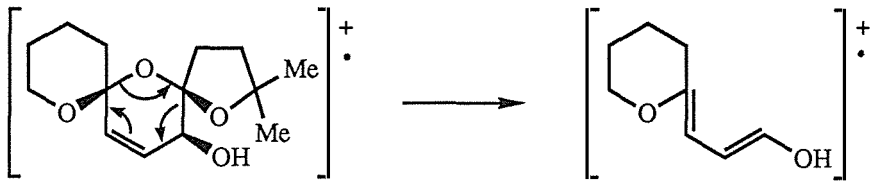
268
S_N2 product

1 : 1.5
65%

156
anti S_N2' product

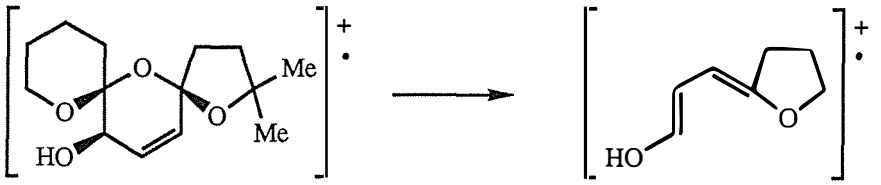
The presence of both diastereomers in the mixture was apparent after examining the mass spectrum, which exhibited a single molecular ion at *m/z* 254 - corresponding to the molecular formula $C_{14}H_{22}O_4$ - but two base peaks at *m/z* 154 ($C_9H_{14}O_2$) and 140 ($C_8H_{12}O_2$). If a retro-Diels-Alder process is invoked to account for these fragments (equations 14 and 15) then both the 15- and 13- hydroxy compounds must be present in the mixture.

Equation 14



$C_8H_{12}O_2$ *m/z* 140

Equation 15

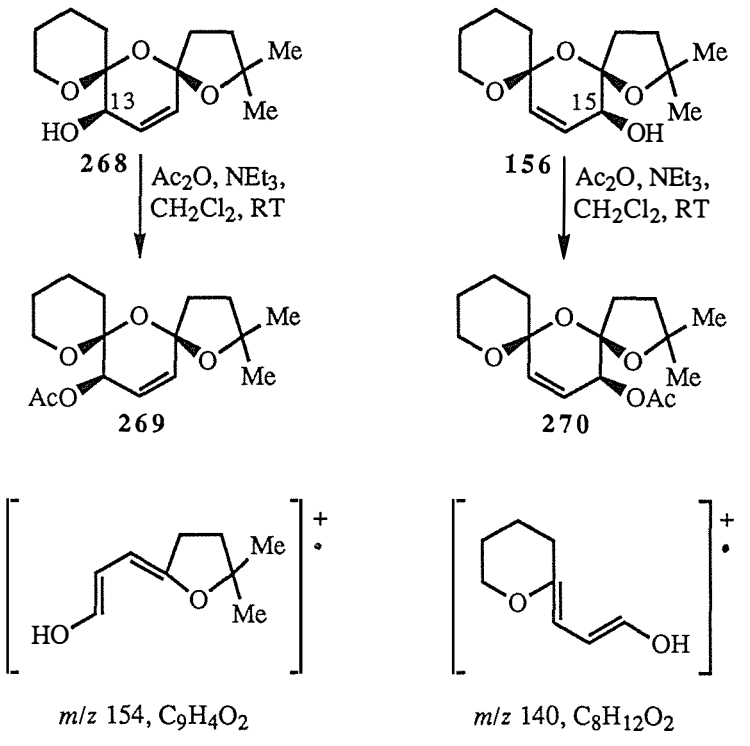


$C_9H_{14}O_2$ *m/z* 154

Formation of the two products **268** and **156** from the single bromide isomer **261** may be accounted for by considering both S_N2 and competitive S_N2' processes. Thus, the 13-hydroxy product **268** arises from direct S_N2 displacement of the bromide, and the 15-hydroxy product **156** from S_N2' displacement. Furthermore, the fact that the ^1H nmr chemical shifts of the CHOH protons of each isomer are coincident (table 5, page 104), resonating as part of a multiplet at δ_H 3.57-3.66, implies that the orientation of these protons on their respective ring systems is the same - both are up (β), or both are down (α). If the relative orientations differed then the resulting 1,2-*syn* relationship of one CHOH proton with a C-O bond of a neighbouring ring would cause a significant deshielding effect and the resonances would no longer be coincident.[111] Since both protons possess the same relative orientations on the ring then the S_N2' process must also have occurred *anti* to the leaving group.[112]

Further analysis of the ^1H nmr spectrum showed that the two alcohols **268** and **156** were not formed in equal quantities and therefore either the S_N2 or S_N2' process was favoured. Conversion of the mixture of alcohols to the now separable acetate derivatives **269** and **270** (scheme 79) established the stereochemistry of the hydroxyl groups of **268** and **156** and also determined which displacement process was favoured.

Scheme 79

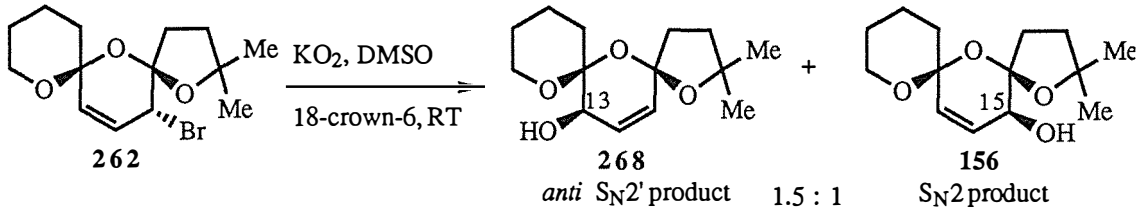


The acetate **270**, derived from the major component of the alcohol mixture, gave the same ^{1}H nmr data as that previously reported by Kocienski *et al.*[64] This established that the acetoxy group of this isomer was attached to C15, further confirmed by the retro-Diels-Alder in the mass spectrum giving a base peak at *m/z* 140, and that the stereochemistry of the group was β, or 1,2-*syn*, to the C-O bond of the five membered ring. Therefore, the hydroxyl group of the alcohol **156** must also have possessed the same stereochemistry and, because of the S_N2 process, the bromide precursor **261** the inverse stereochemistry, placing it 1,2-*anti* to the C-O bond of the neighbouring ring as originally assumed (see page 105).

The acetate **269**, derived from the minor alcohol of the mixture, is therefore the isomer with an acetoxy group attached to C13. This is confirmed by a base peak in the mass spectrum at *m/z* 154 from a retro-Diels-Alder fragmentation (scheme 79). Furthermore, the similarity between the chemical shifts of the CHOAc resonance in the ^{1}H nmr spectrum of **269** (table 5, page 104), occuring at δ_H 4.89, and that of the major acetate **270**, at δ_H 4.86, indicates the acetoxy groups of both have the same orientation on the central ring, and therefore that of **269** is also β on the ring.

Finally, having assessed the regio- and stereochemistry of the acetate derivatives **269** and **270**, the ^{1}H nmr resonances in the spectrum of the mixture of alcohols **268** and **156** were then assigned to the individual diastereomers. This established that the 15-hydroxy-spiroketal **156** was preferentially formed from the 13-bromo-spiroketal **261** (as indicated in scheme 78), and hence the *anti*-S_N2' process must have been favoured under the given reaction conditions.

Scheme 80



262 → **268** (*anti* S_N2' product) + **156** (S_N2 product), 1.5 : 1

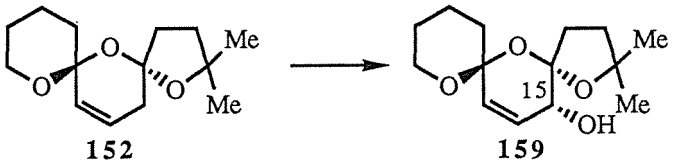
The 15-bromo-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **262** was also treated with potassium superoxide and 18-crown-6 (scheme **80**) in dimethylsulphoxide and an inseparable mixture of the alcohols **268** and **156** was again obtained. Since the stereochemistry of the hydroxyl group of these alcohols has been shown to be β on the central ring, then the bromide group of the precursor **262** is confirmed to have been α, or down, on the ring, and that the S_N2' process has occurred *anti* to the leaving group. In this instance the 13-hydroxy compound **268** predominated in the product mixture, it being

formed with the 15-hydroxy product **156** in the ratio 1.5:1, which demonstrates that the S_N2' process is again favoured.

4.2 Summary.

In summary, an hydroxyl group has now been introduced at C15 (the allylic position) of the model *trans*-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **152** (equation 16) with the indicated stereochemistry.

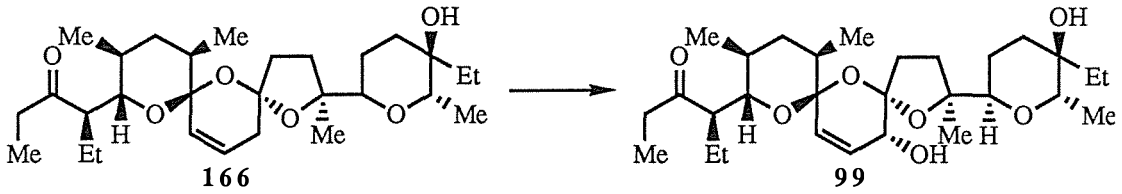
Equation 16



152 **159**

If this synthetic method were to be incorporated into the existing enantioselective synthesis then the right hand portion **166** of *epi*-17-deoxy-(O-8)-salinomycin (see scheme 72) could conceivably be converted into the previously reported[30,42,46] right hand fragment of salinomycin (equation 17). However, the feasibility of this methodology is marred by poor yields and a variety of regiochemical and stereochemical outcomes.

Equation 17

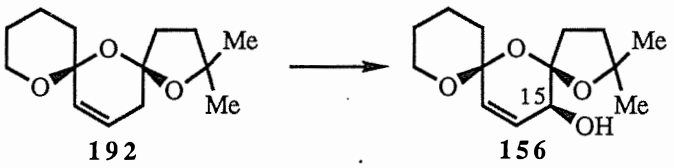


166 **99**

An hydroxyl group has also been introduced at the allylic position of the model *cis*-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **192** with the indicated stereochemistry (equation 18). Incorporation of the methodology into an enantioselective synthesis utilising the chiral bisspiroketal **248** should introduce an allylic hydroxyl group (equation 19), with a similar stereochemistry at C15, to give **271**. However, the consideration of yields and regiochemical outcomes aside, this stereochemistry of the allylic hydroxyl group of **271** renders it unsuitable for use in a total synthesis of salinomycin since

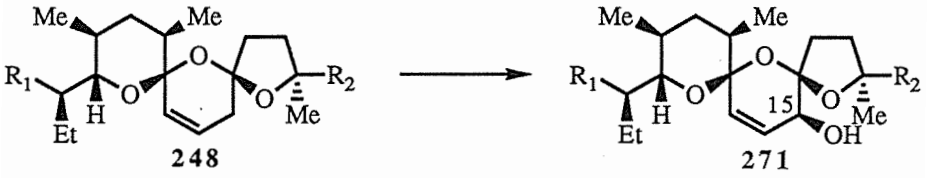
the relative orientation of the hydroxyl group at C15 with respect to the chiral substituents of the terminal rings is opposite to that required for the natural product **7**.

Equation 18

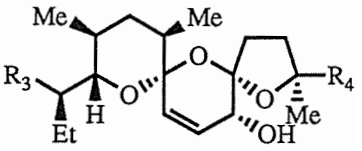


192 **156**

Equation 19



248 **271**



Salinomycin **7**

Chapter 5

Experimental.

General Details

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

Infra-red spectra were recorded using a BIO-RAD FTS-7 or a BIO-RAD FTS-40 spectrophotometer as nujol mulls or thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}) with the following abbreviations: s = strong, m = medium, w = weak and br = broad.

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

^{13}C nuclear magnetic resonance 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), multiplicity in the single frequency off-resonance decoupled spectrum and assignment.

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

Elemental Analyses were performed at the microanalytical laboratory, University of Otago, Dunedin.

Flash chromatography was performed according to the procedure of Still *et al* [69] using Merck Kieselgel 60 (230-400 mesh) with the indicated solvents.

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

Solvents were dried and purified according to the methods of Perrin, Perrin and Amarego.[113]

(±)-(Tetrahydro-2-methyl-5-oxofuran-2-yl)carboxylic acid **173**

Acetic acid (43 ml) was dissolved in water (65 ml) neutralised to pH 6 with sodium hydroxide (21.5 g) and cooled to 0°C. Levulinic acid **174** (250 g, 2.2 mol) and a solution of sodium cyanide (108 g, 2.2 mol) in water (150 ml) were added separately and simultaneously over a period of 1 h. The resulting brown solution was stirred at room temperature for 0.5 h. and concentrated hydrochloric acid (560 ml) was added followed by heating at reflux for 4 h. After concentration by distillation at reduced pressure the precipitated salts were removed by filtration, the filter cake washed with acetone and the washings added to the filtrate to further precipitate inorganic salts. The procedure was repeated several times then the solvent was removed at reduced pressure to afford a brown oil which was distilled under vacuum to give (±)-(tetrahydro-2-methyl-5-oxofuran-2-yl)carboxylic acid **173** (220 g, 75%) as a colourless, viscous oil which solidified on cooling, b.p. 148-150°C/0.02 mm Hg (lit.[67], b.p. 163-167°C/1.5 mm Hg). Recrystallisation from hexane/ether gave a colourless crystalline solid, m.p. 72-73°C (lit.[114] m.p. 72-73.5°C).

(*S*)-(-)-(Tetrahydro-2-methyl-5-oxofuran-2-yl)carboxylic acid **173**

S-(-)-(Tetrahydro-2-methyl-5-oxofuran-2-yl)carboxylic acid **173** was prepared from (±)-(tetrahydro-2-methyl-5-oxofuran-2-yl)carboxylic acid **173** by resolving the cinchonine salt, according to the procedure described by Mori, to give colourless elongated prisms m.p. 88-89°C (lit.[68], m.p. 88-89°C); $[\alpha]_D^{22}$, -16.0° (c, 1.78, H_2O) (lit.[68] $[\alpha]_D^{23}$ -16.2° (c, 1.86, H_2O)).

(*S*)-(+)-2-Methylpentane-1,2,5-triol **175**

The title compound was prepared from (*S*)-(-)-(tetrahydro-2-methyl-5-oxofuran-2-yl)carboxylic acid **173** according to the procedure described by Mori.[68] An improved yield (65%) was obtained by repeatedly refluxing the salt residues in tetrahydrofuran for 3 h., filtering, and evaporating the solvent, b.p. 118-120°C/0.1 mm Hg (lit.[68], b.p. 137°C/0.5 mm Hg); $[\alpha]_D^{22}$ 2.2° (c, 2.40, EtOH) (lit.[68], $[\alpha]_D^{23}$ 1.7° (c, 1.85, EtOH)).

(*S*)-(-)-3-(2',2',4'-Trimethyl-1',3'-dioxolan-4'-yl)propan-1-ol **176**

The title compound was prepared from (*S*)-(+)-2-methylpentane-1,2,5-triol **175** according to the procedure described by Mori,[68] in 85% yield as a colourless oil, b.p. 72-74°C/0.2 mm Hg (lit.[68], b.p. 83°C/0.4 mm Hg); $[\alpha]_D^{22}$ -0.75° (c, 1.38, acetone) (lit.,[68] $[\alpha]_D^{23}$ -0.5° (c, 2.25, acetone).

(*S*)-(+)-3-(2',2',4'-Trimethyl-1',3'-dioxolan-4'-yl)propan-1-al **177**

A solution of dry dimethylsulphoxide (1.88g, 24 mmol) in dry dichloromethane (12 ml) was cooled to -65°C under nitrogen and trifluoroacetic anhydride (3.8 g, 18 mmol) dissolved in dry dichloromethane (6 ml) was added in a dropwise fashion, not allowing the temperature to exceed -60°C. The resulting white slurry was stirred 10 min at this temperature and to it was slowly added a solution of S-(-)-3-(2,2,4-trimethyl-1,3-dioxolan-4-yl)propan-1-ol **176** (2.09 g, 12 mmol) in dry dichloromethane (6 ml). After stirring for 0.25 h. the solution was warmed to -20°C, dry triethylamine (3 g, 30 mmol) carefully introduced, and the reaction vessel brought to room temperature. Water (5 ml) was added and the mixture extracted with dichloromethane (2x 80 ml) which was washed with water (2x30 ml) and brine (50 ml), and dried over potassium carbonate. Evaporation of the solvent at reduced pressure and purification of the residue by flash chromatography, using an hexane/ethyl acetate eluant (9:1), afforded the title compound[71] **177** (1.61 g, 78%) as a colourless oil $[\alpha]_D^{22}$ +1.65° (c, 2.55, $CHCl_3$) (Found: C, 62.8; H, 9.4%. $C_9H_{16}O_3$ requires C, 62.6; H, 9.1%); υ_{max} (film) 3005, 2940 (s, C-H), 2880 (m, H-CO), 2723 (w, H-CO) and 1730 cm^{-1} (s, C=O); δ_H (360 MHz; $CDCl_3$) 1.28 (3H, s, 4'-Me), 1.38 (6H, s, 2x 2'-Me), 1.79-2.02 (2H, m, $C\underline{H}_2CMeO$), 2.53-2.59 2H, m, $C\underline{H}_2CHO$), 3.75 (1H, d, *J* 8.6 Hz, $C\underline{H}_AH_BO$), 3.79 (1H, d, *J* 8.6 Hz, $CH_A\underline{H}_BO$) and 9.80 (1H, t, *J* 1 Hz, CHO); δ_C (90.6 MHz; $CDCl_3$) 25.0 (q, 4'-Me), 27.1 (q, 2'-Me), 27.2 (q, 2'Me), 32.0 (t, C-3), 39.2 (t, C-2), 74.3 (t, c-5'), 80.2 (s, C-4'), 109.6 (s, C-2') and 201.7 (d, C-1); *m/z* 157 (M-Me, 1%), 115 ($C_6H_{11}O_2$, 3), 97 (C_6H_9O, 3), 72 (C_4H_8O, 4), 57 (5), 44 (5), 43 (100), 42 (17) and 41 (19).

(3*R*, 4'*S*)- and (3*S*, 4'*S*)-(-)-1-(2',2',4'-Trimethyl-1',3'-dioxolan-4'-yl)-5-hexyn-3-ol **178**

Activated magnesium turnings (430 mg, 17.5 mmol) and mercuric chloride (~5 mg) were covered with dry ether (15 ml) and cooled to 0°C under nitrogen. A solution of

propargyl bromide (1.95 ml of 80% w/v solution in toluene, 13 mmol) was slowly added over 1 h. with appropriate heating of the vessel to initiate the reaction. After a further 0.5 h. a solution of (*S*)-(+)-3-(2,2,4-trimethyl-1,3-dioxolan-4-yl)propan-1-al[71] **177** in dry ether (30 ml) was added in a dropwise fashion to the grey suspension and stirring continued for 0.25 h. The reaction was quenched with saturated aqueous ammonium chloride (10 ml) and the mixture extracted with ethyl acetate (80 ml) which was washed with water (2x 20 ml) and brine (50 ml), and dried over potassium carbonate. The solvent was evaporated at reduced pressure and the residue purified by flash chromatography, using an hexane/ethyl acetate eluant (1:1), to afford a 1:1 mixture of (3*R*, 4'*S*)- and (3*S*, 4'*S*)-1-(2',2',4'-trimethyl-1',3'-dioxolan-4'-yl)-5-hexyn-3-ol[71] **178** (1.71 g, 89%) $[\alpha]_D^{22}$ -3.66° (c, 2.68, CCl_4) (Found: C, 65.8; H, 8.5%; M^+H (CI, CH_4), 255.1593. $C_{14}H_{22}O_4$ requires C, 66.1; H, 8.7%; M^+H, 255.1596); υ_{max} (film) 3650-3150 (br, s, OH), 3300 (s, ≡CH), 2995, 2940, 2880 (s, C-H) and 2120 cm^{-1} (w, C≡C); δ_H (360 MHz; $CDCl_3$) 1.28, 1.29 (3H, s, 4'-Me), 1.38 (6H, s, 2x 2'-Me), 1.52-1.83 (4H, m, 2x CH_2), 2.06 (1H, m, ≡CH), 2.36-2.42 2H, m, ≡CCH_2), 2.59-2.95 (1H, br., s, OH) and 3.71-3.81 (3H, m, CH_2O and CHO); δ_C (90.6 MHz; $CDCl_3$) 24.8 (q, 4'-Me), 27.1-27.4 (q, 2'-Me), 31.0 (t, C-1), 35.7 (t, C-2), 36.3 (t, C-4), 69.9-70.8 (d, C-6 and C-3), 74.4 (t, C-5'), 80.9, 81.0 (s, C-4' and C-5) and 109.5 (s, C-2'); *m/z* 197 (M-Me, 3%), 115 ($C_6H_{11}O_2$, 18), 97 (C_6H_9O, 12), 72 (C_4H_8O, 27), 69 (15), 59 (23), 57 (26), 43 (100) and 41 (24).

(3*R*, 4'*S*) and (3*S*, 4'*S*)-(-)-3-*tert*-Butyldiphenylsilyloxy-1-(2',2',4'-trimethyl-1',3'-dioxolan-4'-yl)-5-hexyne **179**

A solution of (3*R*, 4'*S*)- and (3*S*, 4'*S*)-1-(2',2',4'-trimethyl-1',3'-dioxolan-4'-yl)-5-hexyn-3-ol[71] **178** (720 mg, 3.4 mmol), imidazole (360 mg, 5.3 mmol) and *tert*-butyldiphenylsilyl chloride (1.02 g, 3.7 mmol) in dry dichloromethane (10 ml) under nitrogen was stirred for 8 h. at room temperature. Water (0.2 ml) was then added and, after stirring a further one hour, the solvent was removed at reduced pressure. The residue was purified by flash chromatography, using an hexane/ethyl acetate eluant (9:1), to afford the title compound **179** (1.38 g, 96%) as a colourless oil $[\alpha]_D^{22}$ -2.76° (c, 3.40, $CHCl_3$); υ_{max} (film) 3315 (m, ≡CH), 3074 (w, Ar-H), 2930, 2855 (s, –CH), 2120 (w, -C≡) and 1390, 1372 cm^{-1} (s, CMe_2); δ_H (270 MHz; $CDCl_3$) 1.06 (9H, s, *t*-Bu), 1.18, 1.20 (3H, s, 4'-Me), 1.33, 1.38 (3H, s, 2'-Me), 1.54-1.64 (4H, m, 2x CH_2), 1.92 (1H, m, ≡CH), 2.30-2.33 (2H, m, CH_2-C≡), 3.61-3.70 (2H, m, CH_2O), 3.82-3.91 (1H, m, CHO), 7.25-7.43 (6H, m, Ar-H) and 7.66-7.69 (4H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 19.3 (s, $\underline{C}Me_3$), 24.7 (q, 4'-Me), 26.3 (t, C-1), 27.0 (q, $C\underline{Me}_3$ and 2'-Me), 30.5 (t, C-2), 34.7 (t, C-4), 70.2 (d,

C-6), 71.3 (d, C-3), 73.9 (t, C-5'), 77.2 (s, C-4'), 80.9 (s, C-5), 109.0 (s, C-2'), 127.6 (d, C-2''), 129.8 (d, C-4''), 133.9 (s, C-1'') and 135.7 (d, C-3''); *m/z* 435 (M-Me, 2%), 335 ($C_{22}H_{27}OSi$, 73), 239 ($C_{16}H_{19}Si$, 5), 221 (56), 199 ($C_{12}H_{11}OSi$, 100), 139 (11), 135 (19) and 119 (19).

(5*R*, 2*S*) and (5*S*, 2*S*)-(-)-5-*tert*-Butyldiphenylsilyloxy-2-methyl-7-octyn-1,2-diol **180**

A solution of (3*R*, 4'*S*) and (3*S*, 4'*S*)-(-)-3-*tert*-butyldiphenylsilyloxy-1-(2',2',4'-trimethyl-1',3'-dioxolan-4'-yl)-5-hexyne **179** (650 mg, 1.44 mmol) in methanol (30 ml) was stirred with Amberlite IR 120 resin for 36 h. Subsequent filtration and evaporation of the solvent at reduced pressure gave a yellow oil which was purified by flash chromatography, using an hexane/ethyl acetate eluant (1:1), to afford the title compound **180** (480 mg, 81%) as a colourless oil, $[\alpha]_D^{22}$ -1.36° (c, 1.41, $CHCl_3$) (Found: C, 72.8; H, 8.45%. $C_{25}H_{34}O_3Si$ requires C, 73.1; H, 8.45%); υ_{max} (film) 3590-3210 (br, s, OH), 3309 (m, ≡CH), 2935. 2235 (s, -CH) and 2115 cm^{-1} (w, -C≡); δ_H (270 MHz; $CDCl_3$) 1.07 (9H, s, *t*-Bu), 1.08 (3H, s, Me), 1.46-1.72 (4H, m, 2x CH_2), 1.94 (1H, m, ≡CH), 2.34 (2H, dd, $J_{6,8}$ 2.2 and $J_{6,5}$ 5.1 Hz, CH_2C≡), 3.33-3.37 (2H, m, CH_2O), 3.87-3.94 (1H, m, CHO), 7.26-7.44 (6H, m, Ar-H) and 7.66-7.70 (4H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 19.3 (s, $\underline{C}Me_3$), 22.9 (q, 2-Me), 26.2 (t, C-3), 27.0 (q, $C\underline{Me}_3$), 29.6 (t, C-4), 33.1 (t, C-6), 69.6 (t, C-1), 70.3 (d, C-8), 71.3 (d, C-5), 72.6 (s, C-2), 81.0 (s, C-7), 127.6 (d, C-2'), 129.8 (d, C-4'), 133.8 (s, C-1') and 135.9 (d, C-3'); *m/z* 353 (M-*t*Bu, 1%), 335 (M-*t*Bu-H_2O, 19), 222 ($C_{16}H_{14}OSi$, 6), 199 ($C_{12}H_{11}OSi$), 139 (18), 135 (19), 123 (10), 105 (22) and 77 (C_6H_5, 10).

(5*R*, 2*S*) and (5*S*, 2*S*)-(-)-5-*tert*-Butyldiphenylsilyloxy-2-hydroxy-2-methyl-7-octyn-1-*p*-toluenesulphonate **181**

A solution of (5*R*, 2*S*) and (5*S*, 2*S*)-(-)-5-*tert*-butyldiphenylsilyloxy-2-methyl-7-octyn-1,2-diol **180** (533 mg, 1.3 mmol) and *p*-tolunesulphonyl chloride (323 mg, 1.7 mmol) in dry pyridine (6 ml) under nitrogen was stirred at room temperature for 22 h. This solution was then diluted with ethyl acetate (100 ml) and the organic phase washed with 5% hydrochloric acid (2x 15 ml), water (20 ml) and brine (30 ml), and dried over magnesium sulphate. Evaporation of the solvent at reduced pressure followed by purification of the residue by flash chromatography, using an hexane/ethyl acetate eluant (4:1), afforded the

title compound **181** (630 mg, 82%) as a colourless oil $[\alpha]_D^{22}$ -2.05° (c, 2.50, $CHCl_3$) (Found: C, 67.95; H, 7.3; S, 5.7%. $C_{32}H_{40}O_5SSi$ requires C, 68.05; H, 7.1; S, 5.7%.); υ_{max} (film) 3605-3280 (br, s, OH), 3285 (m, ≡CH), 2960 2921, 2848 (s, CH), 2124 (w, -C≡) and 1367, 1178 cm^{-1} (s, SO_2O); δ_H (270 MHz; $CDCl_3$) 1.05 (9H, s, *t*-Bu), 1.07 (3H, s, 2-Me), 1.43-1.61 (4H, m, 2x CH_2), 1.92 (1H, t, *J* 2.6 Hz, ≡CH), 2.27 (2H, dd, $J_{6,8}$ 2.6 and $J_{6,5}$ 5.9 Hz, CH_2C≡), 2.44 (3H, s, Ar-Me), 3.75-3.77 (2H, m, CH_2O), 3.77-3.86 (1H, m, CHO), 7.32-7.46 (8H, m, Ar-H), 7.75-7.77 (4H, m, Ar-H) and 7.79 (2H, d, *J* 8.4 Hz, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 19.3 (s, $\underline{C}Me_3$), 21.7 (q, 4'-Me), 23.1 (q, 2-Me), 26.2 (t, C-3), 27.0 (q, $C\underline{Me}_3$), 29.2 (t, C-4), 33.0 (t, C-6), 70.4 (d, C-8), 71.1 (d, C-5), 76.2 (t, C-1), 80.8 (s, C-7), 127.6 (d, C-2''), 128.0 (d, C-2'), 129.8, 129.9 (d, C-3' and C-4''), 132.7 (s, C-4'), 133.8 (s, C-1''), 135.9 (d, C-3'') and 145.0 (s, C-1'); *m/z* 489 (M-*t*Bu-H_2O, 2%), 335 (M-*t*Bu-TsOH, 34) and 199 ($C_{12}H_{11}OSi$, 100).

5-*tert*-Butyldiphenylsilyloxy-2-methyl-2-trimethylsilyloxy-7-octyn-1-*p*-toluenesulphonate **182**

A solution of (±)-5-*tert*-butyldiphenylsilyloxy-2-hydroxy-2-methyl-7-octyn-1-*p*-toluenesulphonate **181** (625 mg, 1.12 mmol) and 1-(trimethylsilyl)imidazole (628 mg, 4.5 mmol) was stirred in dry dichloromethane (10 ml) under argon for 16 h. The solvent was evaporated and the residue purified by flash chromatography, using an hexane-ethyl acetate eluant (4:1), to give the title compound **182** (692 mg, 98%) as a colourless oil; υ_{max} (film) 3305 (s, ≡CH), 2955, 2917, 2850 (s, -CH), 2118 (w, -C≡) and 1364, 1173 (s, SO_2O); δ_H (270 MHz; $CDCl_3$) 0.1, 0.2 (3H, s, $SiMe_3$), 1.05 (9H, s, *t*-Bu), 1.11, 1.13 (3H, s, 2-Me), 1.26-1.59 (4H, 2x CH_2), 1.91 (1H, t, *J* 2.6 Hz, ≡CH), 2.23 (2H, dd, $J_{6,8}$ 2.6 and $J_{6,5}$ 5.5 Hz, CH_2C≡), 2.44 (3H, s, Ar-Me), 3.69 (2H, d, *J* 2.6 Hz, CH_2O), 3.71-3.83 (1H, m, CHO), 7.32-7.45 (8H, m, Ar-H), 7.64-7.67 (4H, m, Ar-H) and 7.77 (2H, d, *J* 1.8 Hz, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 2.33 (q, $SiMe_3$), 19.3 (s, $\underline{C}Me_3$), 21.6 (q, 4'-Me), 24.4 (q, 2-Me), 26.4 (t, C-6), 27.0 (q, $C\underline{Me}_3$), 29.5 (t, C-4), 34.6 (t, C-3), 70.3 (d, C-8), 71.4 (d, C-5), 74.0 (s, C-2), 75.6 (t, C-1), 80.9 (s, C-7), 127.6 (d, C-2''), 129.7 (d, C-2'), 129.7 (d, C-3'), 129.8 (d, C-4''), 133.0 (s, C-4'), 133.8 (s, C-1''), 135.9 (d, C-3'') and 144.7 (s, C-1').

5-*tert*-Butyldiphenylsilyloxy-2-hydroxy-8-(tetrahydro-2'-methoxypyran-2'-yl)-2-methyl-7-octyn-1-*p*-toluenesulphonate **184**

A solution of 5-*tert*-butyldiphenylsilyloxy-2-methyl-2-trimethylsilyloxy-7-octyn-1-*p*-toluenesulphonate **182** (1.59 g, 2.5 mmol) in dry tetrahydrofuran (30 ml) was cooled to -78°C under nitrogen and *n*-butyllithium (1.6 ml of a 1.6 M solution in hexane, 2.6 mmol) was added. After stirring for 0.5 h. A solution of δ-valerolactone (300 mg, 3 mmol) in dry tetrahydrofuran (8 ml) was slowly added and the reaction brought to -50°C over 1 h. On quenching with 10% water in tetrahydrofuran (5 ml) the mixture was warmed to room temperature and extracted with ether (150 ml), washed with water (25 ml) and brine (30 ml), and dried over potassium carbonate. The solvent was evaporated at reduced pressure and the residue dissolved in methanol (30 ml) and stirred 2 h. with Amberlite IR 120 resin. After filtering, the solvent was removed and the residue purified by flash chromatography, using an hexane/ethyl acetate eluant (1:1), to afford the title compound **184** (1.21 g, 71%) as a colourless oil (Found: (CI, NH_3) M^+H, 679.3120. $C_{38}H_{50}O_7SSi$ requires M^+H 679.3125); υ_{max} (film) 3620-3220 (br, s, OH), 2956, 2835 (s, C-H), 2220 (m, C≡C) and 1365, 1178 cm^{-1} (s, SO_2O); δ_H (270 MHz; $CDCl_3$) 1.04 (12H, s, *t*-Bu and 2-Me), 1.25-1.90 (13H, m, 6x CH_2 and OH), 2.34-2.37 (2H, m, $CH_2C\equiv$), 2.45 (3H, s, Ar-Me), 3.35 (3H, s, OMe), 3.64-3.89 (5H, m, 2x CH_2O and CHO), 7.33-7.43 (8H, m, Ar-H) and 7.65-7.79 (6H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 19.2 (t, C-4' or C-5'), 19.2 (s, $\underline{C}Me_3$), 21.7 (q, 4''-Me), 22.9, 23.1 (q, 2-Me), 24.6 (t, C-4' or C-5'), 26.3 (t, C-3), 27.0 (q, $C\underline{Me}_3$), 29.3 (t, C-4), 33.0 (t, C-6), 36.6 (t, C-3'), 50.6 (q, OMe), 62.2 (t, C-6'), 70.7 (s, C-2), 71.0 (d, C-5), 76.2 (t, C-1), 80.0, 81.8 (s, C-7 and C-8), 95.0 (s, C-2'), 127.6 (d, C-2'''), 127.9 (d, C-2''), 129.8, 129.9 (d, C-3'' and C-4'''), 132.6 (s, C-4''), 133.6 (s, C-1'''), 135.8 (d, C-3''') and 145.0 (s, C-1''); *m/z* (CI, NH_3) 679 (M+H, 3%), 647 (M-OMe, 100), 589 (M-*t*Bu-MeOH, 14), 492 (44), 475 (M-OMe-TsOH, 88), 417 (M-*t*Bu-MeOH-TsOH, 27), 219 (66) and 192 (41).

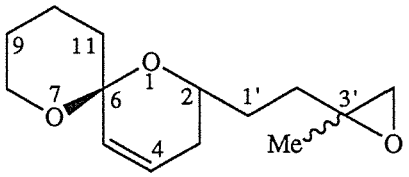
5-*tert*-Butyldiphenylsilyloxy-2-hydroxy-8-(tetrahydro-2'-methoxypyran-2'-yl)-2-methyl-7-octen-1-*p*-toluenesulphonate **189**

5-*tert*-Butyldiphenylsilyloxy-2-hydroxy-8-(tetrahydro-2'-methoxypyran-2'-yl)-2-methyl-7-octyn-1-*p*-toluenesulphonate **184** (257 mg, 0.38 mmol) was dissolved in 1:1 hexane:ethyl acetate (100 ml), and stirred vigorously with a small quantity of Lindlar catalyst (~3 mg) under an hydrogen atmosphere. After 15 h. the solution was filtered, the solvent evaporated, and the residue purified by flash chromatography, using an hexane/ethyl acetate

eluant (2:1), to afford the title compound **189** (220 mg, 85%) as a colourless oil (Found: (CI, NH_3) M-H, 679.3114. $C_{38}H_{52}O_7SSi$ requires M-H 679.3125); υ_{max} (film) 3625-3230 (br. s, OH), 3035 (w, C=CH), 2970, 2965, 2845 (s, C-H), 1655 (w, C=C) and 1365, 1177 cm^{-1} (s, SO_2O); δ_H (270 MHz; $CDCl_3$) 0.98-1.0 (3H, s, 2-Me), 1.05 (9H, s, *t*-Bu), 1.25-2.10 (11H, m, 5x CH_2 and OH), 2.44 (3H, s, Ar-Me), 3.07 (3H, s, OMe), 3.57-3.74 (5H, m, 2x CH_2O and CHO), 5.23-5.62 (2H, m, CH=CH), 7.32-7.41 (8H, m, Ar-H) and 7.65-7.78 (6H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 18.8 (t, C-4' or C-5'), 19.2 (s, $\underline{C}Me_3$), 21.7 (q, 4''-Me), 22.9-23.4 (q, 2-Me), 24.9 (t, C-4' or C-5'), 25.6 (t, C-3), 27.1 (q, $C\underline{Me}_3$), 29.7 (t, C-4), 33.1 (t, C-6), 34.7 (t, C-3'), 48.7 (q, OMe), 60.8 (t, C-6'), 70.9 (s, C-2), 72.9 (d, C-5), 76.3, 76.5 (t, C-1), 99.1 (s, C-2'), 127.5 (d, C-7 and C-2'''), 127.9 (d, C-2''), 129.2 (d, C-8), 129.6 (d, C-4'''), 129.9 (d, C-3''), 132.6 (s, C-4''), 134.2 (s, C-1'''), 135.9 (d, C-3''') and 144.9 (s, C-1''); *m/z* (CI, NH_3) 679 (M-H, 4%), 649 (M-OMe, 3), 477 (M-OMe-TsOH, 10), 428 (73), 274 (100) and 196 (61).

2-(3,4-Epoxy-3-methylbutan-1-yl)-1,7-dioxaspiro[5.5]undec-4-ene **188**

Tetra-*n*-butylammonium fluoride (1.5 ml of a 1.1 M solution in tetrahydrofuran, 1.6 mmol) was added to a solution of 5-*tert*-butyldiphenylsilyloxy-2-hydroxy-8-(tetrahydro-2'-methoxypyran-2'-yl)-2-methyl-7-octen-1-*p*-toluenesulphonate **189** (680 mg, 0.29 mmol) in dry tetrahydrofuran (15 ml) at room temperature under nitrogen. After stirring for 2 h., the solvent was evaporated and the residue columned on silica gel, using an hexane/ethyl acetate eluant (2:1). The resulting oil was then dissolved in dichloromethane and a catalytic quantity (~5 mg) pyridinium-*p*-toluenesulphonate added. After stirring for 0.25 h. the solvent was removed and the residue purified by flash chromatography, using an hexane/ethyl acetate eluant (9:1) to afford the title compound **188** (56 mg, 80%) as a colourless oil (Found: C, 70.2; H, 9.2%; M^+, 238.1536. $C_{14}H_{22}O_3$ requires C, 70.5; H, 9.3%; M^+, 238.1568); υ_{max} (film) 3040 (m, =CH), 1660 (w, C=C), 1270 (m, CO (epoxide)), 1010 (s, CO), 900 and 820 cm^{-1} (s, CO (epoxide)); δ_H (360 MHz; $CDCl_3$) 1.35 (3H, s, 3'-Me), 1.48-2.24 (12H, m, 6x CH_2), 2.57-2.78 (2H, m, CH_2 (epoxide)), 3.56-3.93 (3H, m, CH_2O and CHO), 5.57 -5.66 (1H, m , 5-H) and 5.82-5.95 (1H, m, 4-H); δ_C (90.6 MHz; $CDCl_3$) 18.6 (t, C-10), 21.1 (q, 3'-Me), 25.2 (t, C-9), 30.8, 31.3, 33.1, 35.1 (t, C-1', C-2', C-3 and C-11), 53.6 (t, C-4'), 54.0 (s, C-3'), 60.9 (t, C-8), 66.9 (d, C-2), 93.9 (s, C-6), 127.4 (d, C-5) and 130.7 (d, C-4); *m/z* 238 (M^+, 4%), 124 ($C_8H_{12}O$, 100), 114 ($C_6H_{10}O_2$, 35), 95 (91), 69 (59), 68 (61), 55 (93), 43 (76) and 41 (97).



188

7,8-Epoxy-7-methyl-1-(tetrahydro-2'-methoxypyran-2'-yl)-1-octyn-4-ol **191**

Tetra-*n*-butylammonium fluoride (0.5 ml of a 1.1 M solution in tetrahydrofuran, 0.55 mmol) was added to a solution of 5-*tert*-butyldiphenylsilyloxy-2-hydroxy-8-(tetrahydro-2'-methoxypyran-2'-yl)-2-methyl-7-octyn-1-*p*-toluenesulphonate **184** (81 mg, 0.12 mmol) in dry tetrahydrofuran (8 ml) at room temperature under nitrogen. After stirring for 2 h., the solvent was evaporated and the oily residue purified by flash chromatography, using an hexane/ethyl acetate eluant (1:1) to afford the title compound **191** (32 mg, 99%) as a colourless oil (Found: M^+, 268.1674. $C_{15}H_{24}O_4$ requires M^+, 268.1765); υ_{max} (film) 3690-3200 (br, s, OH), 2944, 2868, 2830 (s, C-H); 2246 (w. C≡C); δ_H (270 MHz; $CDCl_3$) 1.21 (3H, s, Me), 1.47-1.90 (10H, m, 5x CH_2), 2.43 (2H, d, *J* 6.23 Hz, $CH_2C\equiv$), 2.59-2.67 (2H, m, CH_2O(epoxide)), 3.17-3.27 (1H, m, OH), 3.40 (3H, s, OMe), 3.67-3.82 (3H, m, CH_2O (ring) and CHOH); δ_C (67.8 MHz; $CDCl_3$) 18.8 (t, C-4' or C-5'), 20.5, 20.7 (q, 7-Me), 24.3 (t, C-4' or C-5'), 27.2, 31.2, 32.2 (t, C-3, C-5 and C-6), 36.3 (t, C-3'), 50.2 (q, OMe), 53.6 (t, C-8), 56.6, 56.7 (s, C-7), 61.8 (t, C-6'), 69.1, 69.3 (d, C-4), 79.9, 80.0, 81.6, 81.7 (s, C-1 and C-2) and 94.6 (s, C-2'); *m/z* 268 (M^+, 2%), 237 (M-OMe, 20), 154 ($C_9H_{14}O_2$, 74), 122, ($C_8H_{10}O$, 54), 115 ($C_6H_{11}O_2$, 100) and 97 (C_6H_9O, 44).

2-(3',4'-Epoxy-3'-methylbutan-1'-yl)-1,7-dioxaspiro[5.5]undec-4-ene **188**

A solution of 7,8-epoxy-7-methyl-1-(tetrahydro-2'-methoxypyran-2'-yl)-1-octyn-4-ol **191** (230 mg, 0.86 mmol) was dissolved in 1:1 hexane:ethyl acetate (100 ml), and stirred vigorously with a small quantity of Lindlar catalyst (~3 mg) under an hydrogen atmosphere. After 1.5 h. the solution was filtered, the solvent evaporated, and the residue dissolved in dichloromethane and a catalytic quantity (~5 mg) pyridinium-*p*-toluenesulphonate added. After stirring for 0.5 h. the solvent was removed and the residue purified by flash chromatography, using an hexane/ethyl acetate eluant (9:1) to afford a

product (175 mg, 77%) with identical properties to that compound **188** prepared from 5-*tert*-butyldiphenylsilyloxy-2-hydroxy-8-(tetrahydro-2'-methoxypyran-2'-yl)-2-methyl-7-octen-1-*p*-toluenesulphonate **189**.

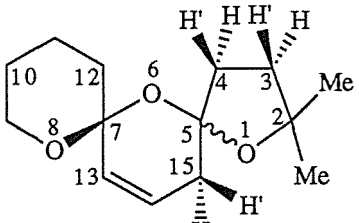
4-(1',7'-Dioxaspiro[5.5]undec-4'-en-2'-yl)-2-methyl-2-butanol **149**

A solution of 2-(3',4'-epoxy-3'-methylbutan-1'-yl)-1,7-dioxaspiro[5.5]undec-4-ene **188** (410 mg, 1.72 mmol) in dry ether (50 ml) was cooled to 0°C under nitrogen and lithium aluminium hydride (30 mg, 0.8 mmol) added. After stirring for 1 h. the reaction was quenched with water (0.1 ml) and extracted with ether (100 ml) which was washed with water (2x 20 ml) and brine (25 ml), and dried over magnesium sulphate. Removal of the solvent at reduced pressure and purification of the residue by flash chromatography, using an hexane/ethyl acetate eluant, afforded the title compound[60] **149** (380 mg, 92%) as a colourless oil with spectroscopic data identical to those previously reported.[60]

2,2-Dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **152, 192**

A solution of 4-(1',7'-dioxaspiro[5.5]undec-4'-en-2'-yl)-2-methyl-2-butanol **149** (700 mg, 2.9 mmol), ground iodine (1.48 g, 5.8 mmol) and iodobenzenediacetate (1.86 g, 5.8 mmol) in cyclohexane (350 ml) was purged with nitrogen and irradiated with two 250 watt tungsten filament lamps. After 12 h., during which the temperature was not allowed to exceed 20°C, the reaction mixture was diluted with ether (200 ml) which was washed with 10% aqueous sodium thiosulphate (50 ml), water (50 ml) and brine (50 ml), and dried over potassium carbonate. The solvent was removed at reduced pressure to afford crude 2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene as a mixture of diastereomers. These were separated and purified by flash chromatography, using an hexane/ethylacetate eluant (9:1), to give the previously reported *trans* isomer[60] **152** (375 mg, 54%) as a colourless oil; δ_H (360 MHz; $CDCl_3$) 1.24 (3H, s, Me), 1.48 (3H, s, Me), 1.49-2.12 (9H, m, 3-H, 3-H', 4-H', 10_{ax}-H, 10_{eq}-H, 11_{ax}-H, 11_{eq}-H, 12_{ax}-H and 12_{eq}-H), 2.16 (1H, ddd, $J_{15,15}$ 16.9, $J_{15,14}$ 5.8 and $J_{15,13}$ 1.2 Hz, 15-H'), 2.45 (1H, ddd, $J_{15,15}$ 16.9, $J_{15,14}$ 2.6 and $J_{15,13}$ 2.6 Hz, 15-H), 2.65 (1H, dd, $J_{4,4}$ 10.2 and $J_{4,3}$ 7.2 Hz, 4-H), 3.67 (1H, m, 9_{eq}-H), 4.02 (1H, ddd, $J_{9ax,9eq}$ 11.3, $J_{9ax,10ax}$ 11.3 and $J_{9ax,10eq}$ 3.3 Hz, 9_{ax}-H), 5.59 (1H, ddd, $J_{13,14}$ 10.0, $J_{13,15}$ 2.6 and $J_{13,15}$ 1.2 Hz, 13-H) and 5.86 (1H, ddd, $J_{14,13}$ 10.0, $J_{14,15}$ 5.8 and $J_{14,15}$ 2.6 Hz, 14-H), and the *cis* isomer **192** (175 mg, 25%) also as a colourless oil (Found: M^+,

238.1578. $C_{14}H_{22}O_3$ requires M^+, 238.1569); υ_{max} (film) 3035 (w, =C-H), 2943, 2875 (s, C-H) and 1655 cm^{-1} (w, C=C); δ_H (270 MHz; $CDCl_3$) 1.15 (3H, s, Me), 1.39 (3H, s, Me), 1.48-2.19 (11H, m, 3-H, 3-H', 4-H, 4-H', 10_{ax}-H, 10_{eq}-H, 11_{ax}-H, 11_{eq}-H, 12_{ax}-H, 12_{eq}-H and 15-H), 2.37 (1H, ddd, $J_{15,15}$ 16.9, $J_{15,14}$ 2.8 and $J_{15,13}$ 2.3 Hz, 15-H'), 3.61 (1H, m, 9_{eq}-H), 4.03 (1H, ddd, $J_{9ax,9eq}$ 11.5, $J_{9ax,10ax}$ 11.5 and $J_{9ax,10eq}$ 2.8 Hz, 9_{ax}-H), 5.71 (1H, ddd, $J_{13,14}$ 10.2, $J_{13,15}$ 2.8 and $J_{13,15}$ 1.1 Hz, 13-H) and 5.86 (1H, ddd, $J_{14,13}$ 10.2, $J_{14,15}$ 5.9 and $J_{14,15}$ 2.2 Hz, 14-H); δ_C (67.8 MHz; $CDCl_3$) 18.7, 25.2 (t, C-10 and C-11), 28.1 (q, Me), 28.9 (q, Me), 35.1, 36.5, 37.1, 39.0 (t, C-3, C-4, C-12 and C-15), 61.3 (t, C-9), 82.9 (s, C-2), 93.6 (s, C-7), 104.2 (s, C-5), 124.1 (d, C-13) and 130.2 (d, C-14); *m/z* 238 (M^+, 42%), 151 ($C_9H_{11}O_2$, 29), 124 ($C_8H_{12}O$, 100) and 75 (70).

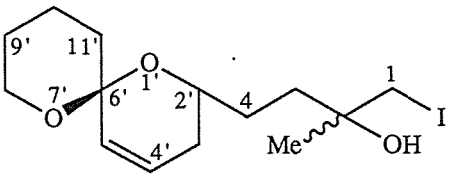


152, 192

4-(1',7'-Dioxaspiro[5.5]undec-4'-en-2'-yl)-1-iodo-2-methyl-2-butanol **200**

A solution of 2-(3',4'-epoxy-3'-methylbutan-1'-yl)-1,7-dioxaspiro[5.5]undec-4-ene **188** (100 mg, 0.42 mmol) in dry tetrahydrofuran (25 ml) was cooled to -50°C under nitrogen and to it was added anhydrous lithium iodide (72 mg, 0.54 mmol) in dry tetrahydrofuran (1.5 ml) and boron trifluoride etherate (0.1 ml). After stirring at this temperature for 5 h. the reaction was quenched with saturated aqueous ammonium chloride (1.5 ml) and the mixture diluted with ether (80 ml). The ethereal solution was washed with water (15 ml) and brine (15 ml), then dried over magnesium sulphate. Removal of the solvent at reduced pressure and purification of the residue by flash chromatography, using an hexane/ethyl acetate eluant (1:1), afforded the title compound **200** (145 mg, 90%) as an inseparable 1:1 mixture of diastereomers in the form of a colourless oil (Found: C, 45.88; H, 6.17; I, 34.48%; M^+, 366.0673. $C_{14}H_{23}O_3I$ requires C, 45.91; H, 6.33; I, 34.65%; M^+, 366.0692); υ_{max} (film) 3600-3315 (br, s, OH), 3030 (w, =CH), 2943, 2880, 2830 (s, C-H) and 1655 cm^{-1} (w, C=C); δ_H (270 MHz; $CDCl_3$) 1.38, 1.39 (3H, s, Me), 1.54-2.17 (12H, m, 6x CH_2), 2.40 (0.5H, s, OH), 2.53 (0.5H, s, OH), 3.38, 3.39 (2H, s, CH_2I), 3.61-3.66 (1H, m, CHO), 3.80-3.94 (2H, m, CH_2O), 5.61 (1H, ddd, $J_{5',4'}$ 9.9, $J_{5',3'}$ 2 and $J_{5',3'}$ 2 Hz, =CH) and 5.90 (1H, ddd, $J_{4',5'}$ 9.9, $J_{4',3'}$ 3.6 and $J_{4',3'}$ 3.6 Hz, =C<u>H</u>CH_2); δ_C

(67.8 MHz; $CDCl_3$) 18.5 (t, C-9' or C-10'), 22.4, 22.5 (t, C-1), 25.0 (t, C-9' or C-10'), 25.9 (q, 2-Me), 30.0, 30.5, 34.9, 36.6 (t, C-3, C-3', C-4 and C-11'), 61.1 (t, C-8'), 67.1 (d, C-2'), 70.3, 70.4 (s, C-2), 94.0 (s, C-6'), 127.4 (d, C-5') and 130.3 (d, C-4'); *m/z* 366 (M^+, 4%), 349 (M-OH, 4), 239 (M-I, 17), 225 (M-CH_2I, 33), 221 (M-I-H_2O, 33), 183 (C_4H_8I, 78) and 124 ($C_8H_{12}O$, 100).



200

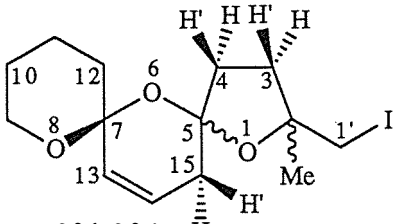
2-Iodomethyl-2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **201-204**

A solution of 4-(1',7'-dioxaspiro[5.5]undec-4'-en-2'-yl)-1-iodo-2-methyl-2-butanol **200** (450 mg, 1.23 mmol), finely ground iodine (630 mg, 2.5 mmol) and iodobenzenediacetate (780 mg, 2.45 mmol) in cyclohexane (230 ml) was purged with nitrogen and irradiated with two 250 watt tungsten filament lamps. After 18 h., during which the temperature was maintained below 20°C, the mixture was diluted with ether (150 ml) which was washed with 10% aqueous sodium thiosulphate (30 ml), water (30 ml) and brine (50 ml), and dried over magnesium sulphate. The solvent was evaporated at reduced pressure and the residue purified by flash chromatography to afford:

(i) the *trans* iodides **201** and **202** (*) (215 mg, 47%) as an inseparable 1:1 mixture of diastereomers in the form of a colourless oil (Found: M^+, 364.0533. $C_{14}H_{21}O_3I$ requires M^+, 364.0533); υ_{max} (film) 3035 (w, =CH), 2945, 2885, 2840 (s, C-H) and 1655 cm^{-1} (w, C=C); δ_H (270 MHz; $CDCl_3$) 1.44 (3H, s, Me), 1.67 (3H, s, Me*), 1.49-1.64 (10H, m, 10_{ax}-H, 10_{ax}-H*, 10_{eq}-H, 10_{eq}-H*, 11_{eq}-H, 11_{eq}-H*, 12_{ax}-H, 12_{ax}-H*, 12_{eq}-H and 12_{eq}-H*), 1.72-1.94 (6H, m, 3-H', 3-H'*, 4-H', 4-H'*, 11_{ax}-H and 11_{ax}-H*), 2.11-2.20 (3H, m, 3-H, 15-H' and 15-H'*), 2.33 (1H, m, 3-H*), 2.42-2.56 (2H, m, 15-H and 15-H*), 2.66-2.75 (2H, m, 4-H and 4-H*), 3.27 (1H, d, *J* 10.1 Hz, $C\underline{H}_AH_BI$*), 3.30 (1H, d, *J* 10.1 Hz, $CH_A\underline{H}_BI$*), 3.45 (1H, d, *J* 9.5 Hz, $C\underline{H}_AH_BI$), 3.55 (1H, d, *J* 9.5 Hz, $CH_A\underline{H}_BI$), 3.66-3.72 (2H, m, 9_{eq}-H and 9_{eq}-H*), 3.96-4.06 (2H, m, 9_{ax}-H and 9_{ax}-H*), 5.58-5.63 (2H, m, 13-H and 13-H*) and 5.82-5.89 (2H, m, 14-H and 14-H*); *m/z* 364 (M^+, 72%), 237 (M-I, 46), 223 (M-CH_2I, 16), 124 ($C_8H_{12}O$, 100) and 113 ($C_6H_9O_2$, 21);

(ii) the *cis* iodides **203** and **204** (*) (102 mg, 23%) as an inseparable 1:1 mixture of two diastereomers in the form of a colourless oil (Found: M^+, 364.0535. $C_{14}H_{21}O_3I$

requires M^+, 364.0533); υ_{max} (film) 3035 (w, =CH), 2945, 2885, 2840 (s, C-H) and 1655 cm^{-1} (w, C=C); δ_H (270 MHZ; $CDCl_3$) 1.39 (3H, s, Me), 1.63 (3H, s, Me*), 1.52-2.42 (24H, m, 3-H, 3-H*, 3-H', 3-H'*, 4-H, 4-H*, 4-H', 4-H'*, 10_{ax}-H, 10_{ax}-H*, 10_{eq}-H, 10_{eq}-H*, 11_{eq}-H, 11_{eq}-H*, 12_{ax}-H, 12_{ax}-H*, 12_{eq}-H and 12_{eq}-H*, 15-H, 15-H*, 15-H' and 15-H'*), 3.21 (2H, d, *J* 2.2 Hz, CH_2I*), 3.36 (1H, d, *J* 9.5 Hz, $C\underline{H}_AH_BI$), 3.46 (1H, d, *J* 9.5 Hz, $CH_A\underline{H}_BI$), 3.62-3.70 (2H, m, 9_{eq}-H and 9_{eq}-H*), 3.92-4.07 (2H, m, 9_{ax}-H and 9_{ax}-H*), 5.71-5.78 (2H, m, 13-H and 13-H*) and 5.86-5.94 (2H, m, 14-H and 14-H*); *m/z* 364 (M^+, 72%), 237 (M-I, 52), 223 (M-CH_2I, 18), 124 ($C_8H_{12}O$, 100) and 113 ($C_6H_9O_2$, 18).



201-204

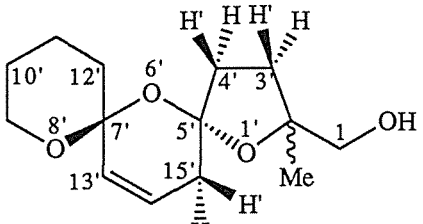
trans-(2'-methyl-1',6',8'-trioxadispiro[4.1.5.3]pentadec-13'-en-2'-yl)methanol **211**, **212**

A solution of the *trans*-iodomethyl-2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes **201** and **202** (70 mg, 0.2 mmol) in dry tetrahydrofuran (7 ml) was added to a solution of potassium superoxide (55 mg, 0.8 mmol) and 18-crown-6 (203 mg, 0.8 mmol) in dry dimethylsulphoxide (5 ml) under argon. After stirring for 18 h. saturated aqueous sodium chloride (2 ml) was added, the tetrahydrofuran evaporated from the mixture and the residue extracted with ether (2x 30 ml). The ethereal solution was then washed with brine (20 ml) and dried over potassium carbonate. The solvent was evaporated at reduced pressure and the residual colourless oil was purified by flash chromatography, using an hexane/ethyl acetate eluant (1:1), to afford:

(i) The *trans* alcohol **211** (17 mg, 36%) as a colourless oil (Found: C, 66.29; H, 8.68%; M^+, 254.1534. $C_{14}H_{22}O_4$ requires C, 66.12; H, 8.72%; M^+, 254.1518); υ_{max} (film) 3600-3115 (br, s, OH), 3042 (w, =CH) and 1643 cm^{-1} (w, C=C); δ_H (270 MHz; $CDCl_3$) 1.20 (3H, s, Me, 1.53-1.80 (8H, m, 3'-H', 4'-H', $10'_{ax}$-H, $10'_{eq}$-H, $11'_{ax}$-H, $11'_{eq}$-H, $12'_{ax}$-H and $12'_{eq}$-H), 2.13 (1H, ddd, $J_{15,15}$ 17.2, $J_{15.14}$ 6.2 and $J_{15,13}$ 1 Hz, 15'-H'), 2.52-2.61 (2H, m, 3'-H and 15'-H), 2.79 (1H, dd, $J_{4,4}$ 12.1 and $J_{4,3}$ 7.7 Hz, 4'-H), 3.40 (1H, t, *J* 10.6 Hz, $C\underline{H}_AH_BOH$), 3.56 (1H, d, *J* 10.6 Hz, OH), 3.64 (1H, d, *J* 10.6 Hz, $CH_A\underline{H}_BOH$), 3.63-3.70 (1H, m, $9'_{eq}$-H), 4.06 (1H, ddd, $J_{9ax,9eq}$ 11.9, $J_{9ax,10ax}$ 9.2 and

$J_{9ax,10eq}$ 6.1 Hz, $9'_{ax}$-H), 5.57 (1H, ddd, $J_{13,14}$ 10.1, $J_{13,15}$ 3.1 and $J_{13,15}$ 1 Hz, 13'-H) and 5.85 (1H, ddd, $J_{14,13}$ 10.1, $J_{14,15}$ 6.2 and $J_{14,15}$ 2.2 Hz, 14'-H); δ_C (67.8 MHz; $CDCl_3$) 24.2 (q, Me), 18.6, 24.9, 30.3, 34.3, 35.9, 36.2 (t, C-3', C-4', C-10', C-11', C-12' and C-15'), 61.8 (t, C-9'), 67.7 (t, C-1), 86.3 (s, C-2'), 97.1 (s, C-7'), 106.4 (s, C-5'), 124.9 (d, C-13') and 129.8 (d, C-14'); *m/z* 254 (M^+, 26%), 237 (M-OH, 10), 223 (M-CH_2OH, 96), 124 ($C_8H_{12}O$, 55) and 99 ($C_5H_7O_2$, 100).

(ii) The *trans* alcohol **212** (17 mg, 36%) as a colourless oil (Found: C, 66.12; H, 8.90%; M^+, 254.1537. $C_{14}H_{22}O_4$ requires C, 66.12; H, 8.72%; M^+, 254.1518); υ_{max} (film) 3600-3120 (br, s, OH), 3045 (w, =CH) and 1641 cm^{-1} (w, C=C); δ_H (270 MHz; $CDCl_3$) 1.47 (3H, s, Me), 1.53-2.05 (10H, m, 3'-H, 3'-H', 4'-H, $10'_{ax}$-H, $10'_{eq}$-H, $11'_{ax}$-H, $11'_{eq}$-H, $12'_{ax}$-H, $12'_{eq}$-H and OH), 2.15 (1H, ddd, $J_{15,15}$ 17.0, $J_{15,14}$ 5.7 and $J_{15,13}$ 1.3 Hz, 15'-H'), 2.48 (1H, ddd, $J_{15,15}$ 17.0, $J_{15,14}$ 2.8 and $J_{15,13}$ 2.8 Hz, 15'-H), 2.70 (1H, ddd, $J_{4,4}$ 12.6, $J_{4,3}$ 6.3 and $J_{4,3}$ 4.7 Hz, 4'-H), 3.39 (1H, dd, $J_{HA,HB}$ 11.4 and $J_{HA,OH}$ 6.0 Hz, $C\underline{H}_AH_BOH$), 3.47 (1H, dd, $J_{HA,HB}$ 11.4 and $J_{HB,OH}$ 6.0 Hz, $CH_A\underline{H}_BOH$), 3.65-3.71 (1H, m, $9'_{eq}$-H), 4.01 (1H, ddd, $J_{9ax,9eq}$ 11.1, $J_{9ax,10ax}$ 3.8 and $J_{9ax,10eq}$ 3.8 Hz, $9'_{ax}$-H), 5.60 (1H, ddd, $J_{13,14}$ 10.1, $J_{13,15}$ 2.8 and $J_{13,15}$ 1.3 Hz, 13'-H) and 5.84 (1H, ddd, $J_{14,13}$ 10.1, $J_{14,15}$ 5.7 and $J_{14,15}$ 2.8 Hz, 14'-H); δ_C (67.8 MHz; $CDCl_3$) 25.2 (q, Me), 18.8, 25.2, 33.2, 34.3, 36.3, 36.9 (t, C-3', C-4', C-10', C-11', C-12' and C-15'), 61.8 (t, C-9), 69.3 (t, C-1), 85.1 (s, C-2'), 96.4 (s, C-7'), 107.4 (s, C-5'), 124.8 (d, C-13'), 129.9 (d, C-14'; *m/z* 254 (M^+, 25), 237 (M-OH, 7), 223 (M-CH_2OH, 100), 124 ($C_8H_{12}O$, 51) and 99 ($C_5H_7O_2$, 100).



211, 212

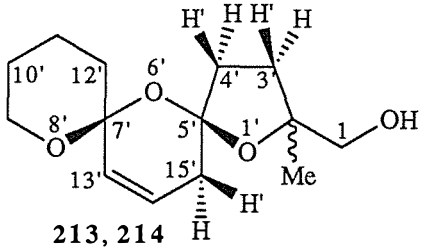
cis-(2'-Methyl-1',6',8'-trioxadispiro[4.1.5.3]pentadec-13'-en-2'yl)methanol **213, 214**

Conversion of the *cis*-2-iodomethyl-2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes **203, 204** to the corresponding alcohols employed a modified procedure to that described above. The tetrahydrofuran component of the solvent mixture was omitted and the

iodides were dissolved in dry dimethylsulphoxide before being introduced into the KO_2/18-crown-6 solution. This afforded:

(i) the *cis* alcohol **213** (19 mg, 40%) as a colourless oil (Found: M^+, 254.1534. $C_{14}H_{22}O_4$ requires M^+, 254.1518); υ_{max} (film) 3600-3115 (br, s, OH), 3042 (w, =CH) and 1643 cm^{-1} (w, C=C); δ_H (270 MHz; $CDCl_3$) 1.11 (3H, s, Me), 1.46-2.16 (10H, m, 3'-H, 3'-H',4'-H, 4'-H', $10'_{ax}$-H, $10'_{eq}$-H, $11'_{ax}$-H, $11'_{eq}$-H, $12'_{ax}$-H and $12'_{eq}$-H), 2.12 (1H, ddd, $J_{15,15}$ 17.0, $J_{15,14}$ 6.2 and $J_{15,13}$ 0.5 Hz, 15'-H), 2.47 (1H, ddd, $J_{15,15}$ 17.0, $J_{15,14}$ 2.6 and $J_{15,13}$ 2.6 Hz, 15'-H'), 3.37 (1H, dd, $J_{HA,HB}$ 10.8 and $J_{HA.OH}$ 10.8 Hz, $C\underline{H}_AH_BOH$), 3.61 (1H, d, J 10.8 Hz, $CH_A\underline{H}_BOH$), 3.66-3.75 (1H, m, $9'_{eq}$-H), 3.89-4.05 (1H, m, $9'_{ax}$-H), 4.26 (H, br., d, J 10.8 Hz, OH), 5.97 (1H, ddd, $J_{13,14}$ 10.3, $J_{13,15}$ 5.9 and $J_{13,15}$ 2.4 Hz, 14'-H) and 6.17 (1H, ddd, $J_{14,13}$ 10.3, $J_{14,15}$ 2.8 and $J_{14,15}$ 1.1 Hz, 13'-H); *m/z* 254 (M^+, 26%), 237 (M-OH, 10), 223 (M-CH_2OH, 96), 124 ($C_8H_{12}O$, 55) and 99 ($C_5H_7O_2$, 100).

(ii) the *cis* alcohol **214** (20 mg, 41%) as colourless prisms, m.p. 80-81°C (Found: C, 66.15; H, 8.82%; M^+, 254.1530. $C_{14}H_{22}O_4$ requires C, 66.12; H, 8.72%; M^+, 254.1518); υ_{max} (film) 3600-3120 (br, s, OH), 3045 (w, =CH) and 1640 cm^{-1} (w, C=C); δ_H (270 MHz; $CDCl_3$) 1.37 (3H, s, Me), 1.53-2.18 (9H, m, 3'-H, 3'-H', 4'-H, $10'_{ax}$-H, $10'_{eq}$-H, $11'_{ax}$-H, $11'_{eq}$-H, $12'_{ax}$-H and $12'_{eq}$-H), 2.16-2.27 (2H, m, 4'-H' and 15'-H), 2.38 (1H, ddd, $J_{15,15}$ 17.0, $J_{15,14}$ 2.5 and $J_{15.13}$ 2.5 Hz, 15'-H'), 2.99 (1H, s, OH), 3.35 (1H, d, J 11.3 Hz, $C\underline{H}_AH_BOH$), 3.42 (1H, d, J 11.3 Hz, $CH_A\underline{H}_BOH$), 3.61-3.68 (1H, m, $9'_{eq}$-H), 4.06 (1H, ddd, $J_{9ax,9eq}$ 11.4, $J_{9ax,10ax}$ 2.9 and $J_{9ax,10eq}$ 2.9 Hz, $9'_{ax}$-H), 5.74 (1H, ddd, $J_{13,14}$ 10.3, $J_{13,15}$ 2.5 and $J_{13,15}$ 0.9 Hz, 13'-H) and 5.89 (1H, ddd, $J_{14,13}$ 10.3, $J_{14,15}$ 5.7 and $J_{14,15}$ 2.5 Hz, 14'-H); δ_C (67.8 MHz; $CDCl_3$) 24.0 (q, Me), 18.7, 25.1, 32.6, 34.6, 36.4, 39.3 (t, C-3', C-4', C-10', C-11', C-12' and C-15'), 61.5 (t, C-9'), 68.6 (t, C-1), 85.1 (s, C-2'), 93.8 (s, C-7'), 105.0 (s, C-5'), 123.9 (d, C-13') and 130.2 (d, C-14'); *m/z* 254 (M^+, 26%), 237 (M-OH, 10), 223 (M-CH_2OH, 96), 124 ($C_8H_{12}O$, 55) and 99 ($C_5H_7O_2$, 100).



213, 214

(5*R*, 2*S*) and (5*S*, 2*S*)-(-)-2,5-Dihydroxy-2-methyl-7-octyn-1-*p*-toluenesulphonate **170**

40% aqueous hydrofluoric acid (5 ml) was added to a solution of (5*R*, 2*S*) and (5*S*, 2*S*)-(-)-5-*tert*-butyldiphenylsilyloxy-2-hydroxy-2-methyl-7-octyn-1-*p*-toluenesulphonate **181** (4 g, 7.1 mmol) in acetonitrile (80 ml) and the mixture stirred for 24 h. The solvent was then evaporated at reduced pressure and the residue purified by flash chromatography, using an hexane/ethyl acetate eluant (1:1), to afford the title compound **170** (2.21 g, 96%) as a colourless oil $[\alpha]_D^{22}$ -2.4° (c, 3.16, $CHCl_3$) (Found: (CI, NH_3) M^+H, 327.1367; $C_{18}H_{24}O_6S$ requires M^+H, 327.1266); υ_{max} (film) 3678-3290 (br, s, OH), 3305 (s, C≡H), 2983, 2961, 2920 (s, C-H), 2120 (w, -C≡) and 1355, 1173 cm^{-1} (s, SO_2O); δ_H (270 MHz; $CDCl_3$) 1.14 (3H, s, 2-Me), 1.45-1.76 (4H, m, 2x CH_2), 2.04 (1H, t, *J* 2.7 Hz, ≡CH), 2.31-2.39 (3H, m, CH_2C≡ and OH), 2.43 (3H, s, Ar-Me), 3.71-3.82 (4H, m, CH_2O, CHO and OH), 7.33 (2H, d, *J* 8.4 Hz, Ar-H) and 7.77 (2H, d, *J* 8.4 Hz, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 21.6 (q, 4'-Me), 23.2, 23.8 (q, 2-Me), 27.2 (t, C-3), 29.5 (t, C-4), 34.1, 34.2 (t, C-6), 70.0, 70.1 (d, C-5 and C-8), 70.9 (s, C-2), 75.6, 76.2 (t, C-1), 80.6 (s, C-7), 127.9 (d, C-2'), 129.9 (d, C-3'), 132.4 (s, C-4') and 145.1 (s, C-1'); *m/z* (CI, NH_3) 327 (M^+H, 100%), 309 (M-OH, 41), 269 ($C_{13}H_{17}O_4S$, 43), 155 (M-OTs, 40) and 137 (M-OTs-H_2O, 95). Conversion of the diol to the monoacetate derivative afforded an analytical sample (Found: C, 58.48; H, 6.52; S, 8.85%. $C_{18}H_{24}O_6S$ requires C, 58.68; H, 6.57; S, 8.70%);

(5*R*, 2*S*) and (5*S*, 2*S*)-2-Methyl-2,5-bis(trimethylsilyloxy)-7-octyn-1-*p*-toluenesulphonate **231**

A solution of (5*R*, 2*S*) and (5*S*, 2*S*)-(-)-2,5-dihydroxy-2-methyl-7-octyn-1-*p*-toluenesulphonate **170** (150 mg, 2.4 mmol) and 1-(trimethylsilyl)imidazole (258 mg, 9.6 mmol) in dry dichloromethane (15 ml) was stirred for 7 h. under nitrogen. The solvent was evaporated at reduced pressure and the residue purified by rapid column chromatography on florisil, using an hexane/ethylacetate eluant (9:1), to afford the title compound **231** (205 mg, 95%) as a colourless oil; υ_{max} (film) 3305 (s, C≡H), 2985, 2950, 2920 (s, C-H), 2120 (w, -C≡) and 1355, 1173 cm^{-1} (s, SO_2O); δ_H (270 MHz; $CDCl_3$) 0.14 (18H, s, 2x $SiMe_3$), 1.17 (3H, s, 2-Me), 1.45-1.76 (4H, m, 2x CH_2), 2.01 (1H, t, *J* 2.8 Hz, ≡CH), 2.44-2.47 (2H, m, CH_2C≡), 2.46 (3H, s, Ar-Me), 3.83 (2H, s, CH_2O), 4.87-4.90 (1H, m, CHO), 7.37 (2H, d, *J* 8.4 Hz, Ar-H) and 7.80 (2H, d, *J* 8.4 Hz, Ar-H).

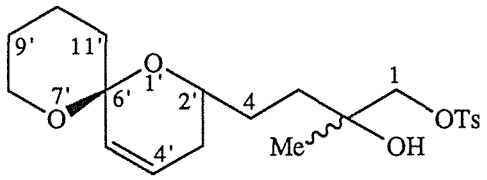
2,5-Dihydroxy-8-(tetrahydro-2'-methoxypyran-2'-yl)-2-methyl-7-octyn-1-*p* toluenesulphonate **233**

A solution of (±)-2-methyl-2,5-bis(trimethylsilyloxy)-7-octyn-1-*p*-toluenesulphonate **231** (450 mg, 0.96 mmol) in dry tetrahydrofuran (20 ml) was cooled to -78°C under nitrogen and to it was added was added *n*-butyllithium (0.72 ml of a 1.6 M solution in hexane, 1.15 mmol). After 0.5 h. a solution of δ-valerolactone (120mg, 1.2 mmol) in dry tetrahydrofuran (1 ml) was introduced followed by stirring a further 0.5 h. at this temperature. After the addition of 10% water in tetrahydrofuran (1 ml), the mixture was brought to room temperature and the solution dried over potassium carbonate. The solvent was then removed at reduced pressure and the residue purified by rapid column chromatography on florisil, using an hexane/ethyl acetate eluant (1:1). The lactol thus obtained was dissolved in methanol (80 ml) and stirred overnight with Amberlite IR 120 resin. The solution was filtered, triethylamine (0.1 ml) added and the solvent evaporated at reduced pressure with the residue being quickly purified by flash chromatography, using an hexane/ethyl acetate eluant (1:1), to afford the title compound **233** (320 mg, 76%) as an unstable colourless oil; υ_{max} (film) 3690-3285 (br, s, OH), 2983, 2961, 2920 (s, C-H), 2120 (w, -C≡) and 1355, 1173 cm^{-1} (s, SO_2O); δ_H (270 MHz; $CDCl_3$) 1.15 (3H, s, 2-Me), 1.46-1.86 (10H, m, 5x CH_2), 2.35-2.45 (3H, s, $CH_2C\equiv$ and OH), 2.45 (3H, s, Ar-Me), 3.37 (3H, s, OMe), 3.35-3.83 (6H, m, CHO, 2x CH_2O and OH), 7.36 (2H, d, *J* 8.4 Hz, Ar-H) and 7.79 (2H, d, *J* 8.4 Hz, Ar-H); δ_C (67.8 MHz; $CDCl_3$), 19.0, 24.6 (t, C-4' and C-5'), 21.7 (q, 4"-Me), 23.4, 24.0 (q, 2-Me), 27.5 (t, C-3), 29.7 (t, C-4), 34.2 (t, C-6), 36.6 (t, C-3'), 50.5 (q, OMe), 62.1 (t, C-6'), 70.0 (d, CHO), 70.8 (s, C-2), 75.7, 76.4 (t, C-1), 80.4 (s, C-7), 81.7 (s, C-8), 94.9 (s, C-2'), 128.0 (d, C-2"), 130.0 (d, C-3"), 132.6 (s, C-4") and 145.0 (s, C-1"); *m/z* 269 (M-OTs, 12%), 236 (M-OTs-OMe, 12), 205 (M-OTs-OMe-H_2O, 56), 172 (TsOH, 79) and 115 ($C_6H_{11}O_2$, 100).

4-(1',7'-Dioxaspiro[5.5]undec-4'-ene-2'-yl)-2-hydroxy-2-methylbutan-1-*p*-toluenesulphonate **235**

A solution of 2,5-dihydroxy-8-(tetrahydro-2'-methoxypyran-2'-yl)-2-methyl-7-octyn-1-*p*-toluenesulphonate **233** (300 mg, 0.68 mmol) in 1:1 hexane:ethyl acetate (150 ml) was stirred vigorously with Lindlar catalyst (~5mg) under an hydrogen atmosphere. After 1.5 h. the solution was filtered and the solvent evaporated at reduced pressure to give an oil that was dissolved in dichloromethane (10 ml) and stirred with a trace amount of pyridinium-p-toluenesulphonate for 0.25 h. The solvent was then removed and the residue purified by

flash chromatography, using an hexane/ethyl acetate eluant (4:1), to afford the title compound **235** (212 mg, 71%) as an inseparable 1:1 mixture of diastereomers in the form of a colourless oil (Found: C, 61.29; H, 7.31; S, 7.74%; M^+, 410.1761. $C_{21}H_{30}O_6S$ requires C, 61.44; H, 7.37; S, 7.81%; M^+, 410.1763); δ_H (270 MHz; $CDCl_3$) 1.17, 1.18 (3H, s, 2-Me), 1.52-1.94 (12H, m, 6x CH_2), 2.45 (3H, s, Ar-Me), 2.66 (0.5H, s, OH), 2.86 (0.5H, s, OH), 3.60-3.92 (5H, m, 2x CH_2O and CHO), 5.60 (1H, d, *J* 9.9 Hz, 5'-H), 5.87 (1H, ddd, $J_{4',5'}$ 9.9, $J_{4',3'}$ 3.6 and $J_{4',3'}$ 3.6 Hz, 4'-H), 7.36 (2H, d, *J* 8.4 Hz, Ar-H) and 7.81 (2H, d, *J* 8.4 Hz, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 18.5 (t, C-9' or C-10'), 21.7 (q, 4''-Me), 23.7, 23.8 (q, 2-Me), 24.9, 25.0 (t, C-9' or C-10'), 28.9, 29.0, 30.5, 34.2, 34.4, 34.8 (t, C-3, C-4, C-3' and C-11'), 61.1 (t, C-8'), 67.2 (d, C-2'), 70.8, 70.9 (s, C-2), 76.0 (t, C-1), 94.0, 94.1 (s, C-6'), 127.4 (d, C-5'), 128.0 (d, C-2''), 129.9 (d, C-3''), 130.3 (d, C-4'), 132.7 (s, C-4'') and 145.0 (s, C-1''); *m/z* 410 (M^+, 5%), 392 (M-H_2O, 9), 269 ($C_{13}H_{17}O_4S$, 24), 238 (M-TsOH, 8) and 124 ($C_8H_{12}O$, 100).



235

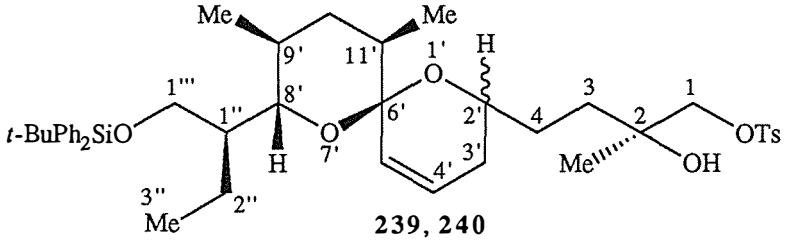
2-(3',4'-Epoxy-3'-methylbutan-1'-yl)-1,7-dioxaspiro[5.5]undec-4-ene **188**

Sodium hydride (15 mg of a 40% dispersion in oil, 0.25 mmol) was added to a solution of 4-(1',7'-dioxaspiro[5.5]undec-4'-ene-2'-yl)-2-hydroxy-2-methylbutan-1-*p*-toluenesulphonate **235** (100 mg, 0.24 mmol) in dry tetrahydrofuran (25 ml) under nitrogen. After stirring at room temperature for 3 h., reaction was quenched with saturated aqueous sodium dihydrogen phosphate solution and the mixture extracted with ether (3x 25 ml) which was washed with water and dried over potassium carbonate. Evaporation of the solvent under reduced pressure and purification of the residue by flash chromatography, using an hexane/ethylacetate eluant (9:1) to afford a product (54 mg, 94%) with identical physical properties to that compound **188** prepared from 5-*tert*-butyldiphenylsilyloxy-2-hydroxy-8-(tetrahydro-2'-methoxypyran-2'-yl)-2-methyl-7-octen-1-*p*-toluenesulphonate **189**.

4-{8'-[1"-(*tert*-Butyldiphenylsilyloxymethyl)propyl]-9',11'-dimethyl-1',7'-dioxaspiro [5.5]undec-4'-en-2'-yl}-2-hydroxy-2-methylbutan-1-*p*-toluenesulphonate **239**, **240**

The acetylene **231** (71 mg, 0.15 mmol) was dissolved in dry tetrahydrofuran (4 ml) and cooled to -75°C under nitrogen. *n*-Butyllithium (0.094 ml of a 1.6 M solution in hexane, 0.15 mmol) was added and the reaction stirred at this temperature for 1 h. whereupon a solution of the lactone **84** (52 mg, 0.12 mmol) in dry tetrahydrofuran (1 ml) was introduced in a dropwise fashion. After stirring for a futher 0.5 h. the reaction was quenched with 10% water in tetrahydrofuran (0.5 ml), the solution brought to room temperature and dried over anhydrous potassium carbonate. The solvent was evaporated at reduced pressure and the residue columned on florisil to afford an oil which was dissolved in methanol and stirred with Amberlite IR 120 resin for 1 h. This solution was filtered and the methanol evaporated under reduced pressure to give a yellow residue which was purified by flash chromatography to afford the ketal **237** (73 mg, 82%). This colourless, somewhat unstable oil was quickly dissolved in 1:1 hexane:ethyl acetate (20 ml) and stirred vigorously with Lindlar catalyst (~2 mg) under an hydrogen atmosphere for 5 h. The solution was filtered and the solvent evaporated to afford a residue which was dissolved in dichloromethane (10 ml) and stirred with a catalytic quantity of pyridinium-*p*-toluenesulphonate for 0.2 h. The solvent was removed and the resulting diastereomers separated and purified by flash chromatography, using an hexane/ethyl acetate eluant (4:1), to afford the less polar (1"*S*, 2*S*, 2'*S*, 6'*R*, 8'*S*, 9'*S*, 11'*R*) tosylate **239** (30 mg, 42% from **84**) as a colourless oil $[\alpha]_D^{22}$ -18.5° (c, 1.09, Et_2O) (Found: (CI, NH_3) M^+H, 749.3900. $C_{43}H_{60}O_7SSi$ requires M^+H, 749.3907); υ_{max} (film) 3670-3290 (br, s, OH), 3035 (m, =CH), 2945, 2870 (s, C-H), (1635, C=C) and 1362, 1175 cm^{-1} (s, SO_2O); δ_H (270 MHz; $CDCl_3$) 0.74 (3H, t, *J* 7.6 Hz, CH_2CH_3), 0.745 (3H, d, *J* 6.8 Hz, 9'-Me), 0.79 (3H, d, *J* 6.6 Hz, 11'-Me), 1.03 (3H, s, 2-Me), 1.04 (9H, s, *t*-Bu), 1.07-1.68 (11H, m, CHEt, CH_2CH_3, 3x CH_2 and 2x CHMe), 1.79-1.87 (2H, m, $=CCH_2$), 2.43 (3H, s, Ar-Me), 2.97 (1H, s, OH), 3.59 (1H, dd, $J_{8'ax,9'ax}$ 10.4 and $J_{8'ax,1''}$ 1.3 Hz, $8'_{ax}$-H), 3.65-3.78 (5H, m, 2x CH_2O and 2'-H), 5.42 (1H, ddd, $J_{5',4'}$ 10.1, $J_{5',3'}$ 2.8 and $J_{5',3'}$ 2.8 Hz, 5'-H), 5.87 (1H, ddd, $J_{4',5'}$ 10.1, $J_{4',3'}$ 5.1 and $J_{4',3'}$ 2.4 Hz, 4'-H), 7.31-7.41 (8H, m, Ar-H) 7.63-7.67 (4H, m, Ar-H) and 7.78 (2H, d, *J* 8.3 Hz, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 13.0 (q, C-3''), 16.0 (q, 9'-Me), 17.8 (q, 11'-Me), 18.1 (t, C-2''), 19.2 (s, CMe_3), 21.6 (q, Ar-Me), 24.3 (q, 2-Me), 27.0 (q, CMe_3), 29.8 (t, C-3'), 28.3, 33.0, 36.3 (t, C-3, C-4 and C-10'), 31.7, 38.6, 43.7 (d, C-1'', C-9' and C-11'), 65.4 (t, C-1'''), 66.3 (d, C-2'), 70.4 (s, C-2), 74.9 (d, C-8'), 75.7 (t, C-1), 96.8 (s, C-6'), 127.5, 127.6 (d, C-2''''), 127.6 (d, C-4'), 128.0 (d, C-2''''), 129.4 (d, C-4''''), 129.8 (d, C-3''''), 129.9 (d, C-5'), 132.8 (s, C-4''''), 134.0, 134.2 (s, C-1''''), 135.5, 135.6 (d, C-3'''') and 144.8 (s, C-1''''); *m/z* (CI, NH_3) 749 (M^+H, 25%), 730 (M-H_2O, 15), 691 (M-*t*Bu, 9), 673 (M-*t*Bu-H_2O, 16), 577 (M-OTs, 8), 559 (M-

OTs-H_2O, 17), 519 (M-OTs-*t*Bu, 12) and 199 ($C_{12}H_{11}OSi$, 100), and (1"*S*, 2*S*, 2'*R*, 6'*R*, 8'*S*, 9'*S*, 11'*R*) tosylate **240** (30 mg, 42% from **84**) as a colourless oil $[\alpha]_D^{22}$ +38.8° (c, 1.034, Et_2O) (Found: (CI, NH_3) M^+H, 749.3901. $C_{43}H_{60}O_7SSi$ requires M^+H, 749.3907); υ_{max} (film) 3670-3290 (br, s, OH), 3035 (m, =CH), 2945, 2870 (s, C-H), 1634 (w, C=C) and 1362, 1175 cm^{-1} (s, SO_2O); δ_H (270 MHz; $CDCl_3$) 0.75 (3H, d, *J* 6.4 Hz, 9'-Me), 0.76 (3H, t, *J* 7.4 Hz, CH_2CH_3), 0.81 (3H, d, *J* 6.4 Hz, 11'-Me), 1.02 (9H, s, *t*-Bu), 1.14 (3H , s, 2-Me), 1.07-1.85 (11H, m, CHEt, CH_2CH_3, 3x CH_2 and 2x CHMe), 1.89-1.95 (2H, m, $=CCH_2$), 2.41 (3H, s, Ar-Me), 2.43 (1H, s, OH), 3.54-3.80 (5H, m, 2x CH_2O and $8'_{ax}$-H), 3.94-4.05 (1H, m, 2'-H), 5.95 (1H, ddd, $J_{4',5'}$ 10.4, $J_{4',3'}$ 3.6 and $J_{4',3'}$ 3.6 Hz, 4'-H), 6.08 (1H, d, *J* 10.4 Hz, 5'-H), 7.30-7.41 (8H, m, Ar-H), 7.63-7.67 (4H, m, Ar-H) and 7.78 (2H, d, *J* 8.4 Hz, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 13.0 (q, C-3"), 15.7 (q, 9'-Me), 17.0 (t, C-2"), 17.1 (q, 11'-Me), 19.1 (s, CMe_3), 21.6 (q, Ar-Me), 23.6 (q, 2-Me), 26.8 (q, CMe_3), 31.2 (t, C-3'), 29.2, 34.6, 38.8 (t, C-3, C-4 and C-10'), 31.6, 39.2, 43.8 (d, C-1", C-9' and C-11'), 63.3 (t, C-1'"), 68.8 (d, C-2'), 70.4 (s, C-2), 76.3 (d, C-8'), 76.8 (t, C-1), 98.3 (s, C-6'), 123.8 (d, C-5'), 127.4, 127.5 (d, C-2'''''), 128.0 (d, C-2''''), 128.7 (d, C-4'), 129.4, 129.5 (d, C-4'''''), 129.8 (d, C-3''''), 132.7 (s, C-4''''), 134.0, 134.1 (s, C-1'''''), 135.5, 135.6 (d, C-3''''') and 144.7 (s, C-1''''); *m/z* (CI, NH_3) 749 (M^+H, 25%), 730 (M-H_2O, 15), 691 (M-*t*Bu, 9), 673 (M-*t*Bu-H_2O, 16), 577 (M-OTs, 8), 559 (M-OTs-H_2O, 17), 519 (M-OTs-*t*Bu, 12) and 199 ($C_{12}H_{11}OSi$, 100).

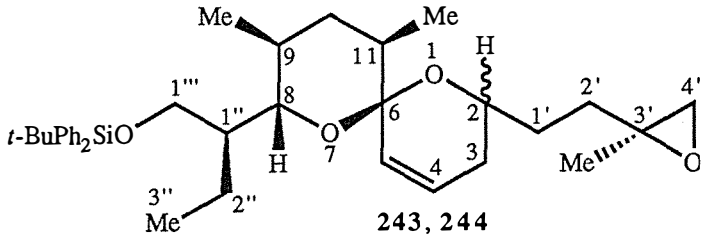


239, 240

8-[1"-(*tert*-Butyldiphenylsilyloxymethyl)propyl]-9,11-dimethyl-2-(3',4'-epoxy-3'-methyl-1-butyl)-1,7-dioxaspiro[5.5]undec-4-ene **243, 244**

To a solution of the (-)-tosylate **239** (52 mg, 0.07 mmol) in dry tetrahydrofuran (20 ml) under a drying tube was added sodium hydride (15 mg of a 40% dispersion in oil, 0.25 mmol) and the supension stirred overnight at room temperature. After quenching with water (0.05 ml) the solvent was evaporated at reduced pressure and the oily solid residue purified by flash chromatography, using an hexane/ethyl acetate eluant (4:1), to afford the (1"*S*, 2*S*,

3'*S*, 6*R*, 8*S*, 9*S*, 11*R*) epoxide **243** (39 mg, 97%) as a colourless oil $[\alpha]_D^{22}$ -13.7° (c, 0.766, Et_2O) (Found: M^+, 576.3640. $C_{36}H_{52}O_4Si$ requires M^+, 576.3635); υ_{max} (film) 3070 (w, Ar-H), 3039 (w, =CH), 2958, 2928, 2856 (s, C-H) and 1656 (w, C=C); δ_H (270 MHz; $CDCl_3$) 0.74 (3H, t, *J* 7.5 Hz, CH_2CH_3), 0.76 (3H, d, *J* 6.6 Hz, 9-Me), 0.80 (3H, d, *J* 6.4 Hz, 11-Me), 1.06 (9H, s, *t*-Bu), 1.19 (3H, s, 3'-Me), 1.05-1.70 (11H, m, CHEt, CH_2CH_3, 3x CH_2 and 2x CHMe), 1.80-1.85 (2H, m, $=CCH_2$), 2.37 (1H, d, *J* 4.9 Hz, CH_AH_BO (epoxide)), 2.43 (1H, d, *J* 4.9 Hz, CH_AH_BO (epoxide)), 3.59 (1H, dd, $J_{8ax,9ax}$ 10.4 and $J_{8ax,1''}$ 1.5 Hz, 8_{ax}-H), 3.65-3.71 (3H, m, CH_2OSi and 2-H), 5.43 (1H, ddd, $J_{5,4}$ 10.1, $J_{5,3}$ 2.0 and $J_{5,3}$ 2.0 Hz, 5-H), 5.88 (1H, ddd, $J_{4,5}$ 10.1, $J_{4,3}$ 4.5 and $J_{4,3}$ 3.0 Hz, 4-H), 7.34-7.42 (6H, m, Ar-H) and 7.64-7.69 (4H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 13.1 (q, C-3''), 16.1 (q, 9-Me), 17.9 (q, 11-Me), 18.2 (t, C-2''), 19.2 (s, CMe_3), 21.0 (q, 3'-Me), 27.0 (q, CMe_3), 30.3 (t, C-3), 38.7, 43.8 (d, C-1'' and C-11), 53.7 (t, C-4'), 57.0 (s, C-3'), 65.6 (t, C-1'''), 66.1 (s, C-2), 74.8 (d, C-8), 96.2 (s, C-6), 127.5, 127.6 (d, C-2''''), 127.6 (d, C-4), 129.5 (d, C-4''''), 130.2 (d, C-5), 134.1, 134.3 (s, C-1'''') and 135.5, 135.7 (d, C-3''''); *m/z* 576 (M^+, 2%), 519 (M-*t*Bu, 23), 337 (6), 323 (5), 295 (7), 207 ($C_{14}H_{23}O$, 10) and 199 ($C_{12}H_{11}OSi$, 100). Repetition of this procedure using the corresponding (+)-tosylate **240** (52 mg, 0.07 mmol) afforded the (1''*S*, 2*R*, 3'*S*, 6*R*, 8*S*, 9*S*, 11*R*) epoxide **244** (38 mg, 95%) also as a colourless oil $[\alpha]_D^{22}$ +42.4° (c, 0.752, Et_2O) (Found: M^+, 576.3629. $C_{36}H_{52}O_4Si$ requires M^+, 576.3635); υ_{max} (film) 3070 (w, Ar-H), 3039 (w, =CH), 2958, 2928, 2856 (s, C-H) and 1656 (w, C=C); δ_H (270 MHz; $CDCl_3$) 0.76 (3H, d, *J* 6.6 Hz, 9-Me), 0.79 (3H, t, *J* 7.5 Hz, CH_2CH_3), 0.83 (3H, d, *J* 6.4 Hz, 11-Me), 1.02 (9H, s, *t*-Bu), 1.30 (3H, s, 3'-Me), 0.97-1.80 (11H, m, CHEt, CH_2CH_3, 3x CH_2 and 2x CHMe), 1.89-1.95 (2H, m, $=CCH_2$), 2.49 (1H, d, *J* 5.0 Hz, CH_AH_BO (epoxide)), 2.70 (1H, d, *J* 5.0 Hz, CH_AH_BO (epoxide)), 3.56-3.69 (3H, m, CH_2OSi and 8_{ax}-H), 3.98-4.07 (1H, m, 2-H), 5.94 (1H, ddd, $J_{4,5}$ 10.4, $J_{4,3}$ 3.8 and $J_{4,3}$ 3.8 Hz, 4-H), 6.11 (1H, ddd, $J_{5,4}$ 10.1, $J_{5,3}$ 1.8 and $J_{5,3}$ 1.8 Hz, 5-H), 7.33-7.43 (6H, m, Ar-H) and 7.64-7.70 (4H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 13.1 (q, C-3''), 15.9 (q, 9-Me), 17.2 (q, 11-Me), 17.3 (t, C-2''), 19.2 (s, CMe_3), 21.1 (q, 3'-Me), 26.8 (q, CMe_3), 31.1, 31.2, 31.9, 39.0 (t, C-1', C-2', C-3 and C-10), 31.7, 39.2, 43.9 (d, C-1'', C-9 and C-11), 53.9 (t, C-4'), 56.8 (s, C-3'), 63.3 (t, C-1'''), 67.0 (d, C-2), 76.1 (d, C-8), 98.1 (s, C-6), 124.4 (d, C-5), 127.4, 127.5 (d, C-2''''), 128.5 (d, C-4), 129.4, 129.5 (d, C-4''''), 134.0, 134.2 (s, C-1'''') and 135.5, 135.6 (d, C-3''''); *m/z* 576 (M^+, 2%), 519 (M-*t*Bu, 36), 477 ($C_{29}H_{37}O_4Si$, 7), 405 ($C_{26}H_{33}O_2Si$, 4), 337 (16), 323 (27), 295 (10), 207 ($C_{14}H_{23}O$, 35) and 199 ($C_{12}H_{11}OSi$, 100).

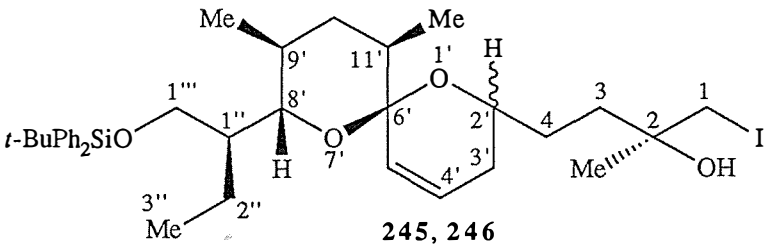


243, 244

4-{8'-[1''-(*tert*-Butyldiphenylsilyloxymethyl)propyl]-9',11'-dimethyl-1',7'-dioxaspiro[5.5]undec-4'-en-2'-yl}-1-iodo-2-methyl-2-butanol **245, 246**

A solution of the (-)-epoxide **243** (37 mg, 0.064 mmol) in dry tetrahydrofuran (9 ml) was cooled to -50°C under nitrogen. Lithium iodide (17 mg, 0.13 mmol), dissolved in dry tetrahydrofuran (1 ml), was then introduced followed with boron trifluoride etherate (0.02 ml). The reaction was stirred at this temperature for 1 h., quenched with 5% water in tetrahydrofuran (0.5 ml) and brought to room temperature. The solution was dried over anhydrous potassium carbonate, the solvent evaporated, and the residue purified by flash chromatography, using an hexane/ethyl acetate eluant (4:1), to afford the (1''*S*, 2*S*, 2'*S*, 6'*R*, 8'*S*, 9'*S*, 11'*R*) iodohydrin **245** (41 mg, 91%) as a colourless oil $[\alpha]_D^{22}$ -20.2° (c, 0.6, Et_2O) (Found: M^+, 704.2744. $C_{36}H_{53}O_4SiI$ requires M^+, 704.2756); υ_{max} (film) 3570-3200 (br, s, OH), 3069 (w, Ar-H), 3047 (w, =CH), 2958. 2923, 2856, (s, C-H) and 1653 (w, C=C); δ_H (270 MHz; $CDCl_3$) 0.77 (3H, d, *J* 6.6 Hz, 9'-Me), 0.79 (3H, t, *J* 8.2 Hz, CH_2CH_3), 0.81 (3H, d, *J* 6.2 Hz, 11'-Me), 1.05 (9H, s, *t*-Bu), 1.20 (3H, s, 2-Me), 1.06-1.71 (11H, m, CHEt, CH_2CH_3, 3x CH_2 and 2x CHMe), 1.82-1.90 (2H, m, $=CCH_2$), 2.25 (1H, s, OH), 3.14 (2H, s, CH_2I), 3.59 (1H, dd, $J_{8'ax,9'ax}$ 10.3 and $J_{8'ax,1''}$ 1.5 Hz, $8'_{ax}$-H), 3.71-3.74 (3H, m, CH_2O and 2'-H), 5.45 (1H, ddd, $J_{5',4'}$ 10.0, $J_{5',3'}$ 2.4 and $J_{5',3'}$ 1.5 Hz, 5'-H), 5.89 (1H, ddd, $J_{4',5'}$ 10.0, $J_{4',3'}$ 4.8 and $J_{4',3'}$ 2.6 Hz, 4'-H), 7.32-7.45 (6H, m, Ar-H) and 7.65-7.70 (4H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 13.2 (C-3''), 16.1 (q, 9'-Me), 17.8 (q, 11'-Me), 18.3 (t, C-2''), 19.3 (s, CMe_3), 22.0 (t, C-1), 25.9 (q, 2-Me), 27.0 (q, CMe_3), 29.6 (t, C-3'), 30.0, 35.6, 36.4 (t, C-3, C-4 and C-10'), 31.8, 38.7, 43.7 (d, C-1'', C-9' and C-11'), 65.8 (t, C-1'''), 66.2 (d, C-2'), 70.2 (s, C-2), 75.0 (d, C-8'), 96.6 (s, C-6'), 127.5, 127.6 (d, C-2''''), 127.7 (d, C-4'), 129.5, 129.6 (d, C-4''''), 130.1 (d, C-5'), 134.2, 134.4 (s, C-1'''') and 135.5, 135.7 (d, C-3''''); *m/z* 704 (M^+, 1%), 647 (M-*t*Bu, 34), 629 (m-*t*Bu-H_2O, 7), 577 (M-I, 3), 519 (M-*t*Bu-I, 7), 431 (9), 337 (21), 323 (12), 225 ($C_6H_{10}OI$, 37) and 199 ($C_{12}H_{11}OSi$, 100). Repetition of this procedure, using the corresponding (+)-epoxide **244** (33 mg, 0.057 mmol) afforded the (1''*S*, 2*S*, 2'*R*, 6'*R*, 8'*S*, 9'*S*, 11'*R*) iodohydrin **246** (37 mg, 92%) also as a colourless oil $[\alpha]_D^{22}$ +40.1° (c, 0.51, Et_2O) (Found: M^+, 704.2744. $C_{36}H_{53}O_4SiI$ requires M^+,

704.2756); υ_{max} (film) 3570-3200 (br, s, OH), 3069 (w, Ar-H), 3047 (w, =CH), 2958. 2923, 2856, (s, C-H) and 1653 (w, C=C); δ_H (270 MHz; $CDCl_3$) 0.77 (3H, d, *J* 6.6 Hz, 9'-Me), 0.78 (3H, t, *J* 8.4 Hz, $CH_2\underline{CH_3}$), 0.82 (3H, d, *J* 6.6 Hz, 11'-Me), 1.02 (9-H, s, *t*-Bu), 1.33 (3H, s, 2-Me), 1.08-1.80 (11H, m, $\underline{CH}Et$, $\underline{CH_2}CH_3$, 3x CH_2 and 2x $\underline{CH}Me$), 1.92-1.98 (1H, m, $=CCH_2$), 3.27 (H, s, OH), 3.32 (2H, s, CH_2I), 3.54-3.78 (3H, m, CH_2O and $8'_{ax}$-H), 4.00-4.10 (1H, m, 2'-H), 5.95 (1H, ddd, $J_{4',5'}$ 10.3, $J_{4',3'}$ 3.3 and $J_{4',3'}$ 3.3 Hz, 4'-H), 6.10 (1H, d, *J* 10.3 Hz, 5'-H), 7.34-7.42 (6H, m, Ar-H) and 7.64-7.68 (4H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 13.0 (q, C-3''), 15.8 (q, 9'-Me), 17.1 (t, C-2''), 17.2 (q, 11'-Me), 19.2 (s, $\underline{C}Me_3$), 22.7 (t, C-1), 26.2 (q, 2-Me), 26.8 (q, $C\underline{Me}_3$), 31.1 (t, C-3'), 30.0, 36.5, 38.9 (t, C-3, C-4 and C-10'), 31.6, 39.1, 43.9 (d, C-1'', C-9' and C-11'), 63.3 (t, C-1'''), 68.5 (d, C-2'), 69.9 (s, C-2), 77.2 (d, C-8'), 98.3 (s, C-6'), 124.1 (d, C-5'), 127.4, 127.5 (d, C-2''''), 128.6 (d, C-4'), 129.4, 129.5 (d, C-4''''), 134.0 (s, C-1'''') and 135.5, 135.6 (d, C-3''''); *m/z* 704 (M^+, 1%), 647 (M-*t*Bu, 34), 629 (M-*t*Bu-H_2O, 7), 577 (M-I, 3), 519 (M-*t*Bu-I, 7), 431 (9), 337 (21), 323 (12), 225 ($C_6H_{10}OI$, 37) and 199 ($C_{12}H_{11}OSi$, 100).



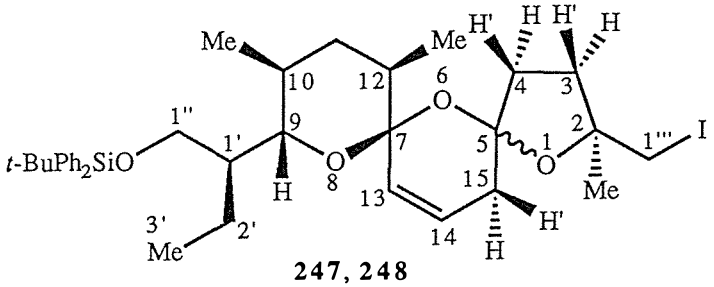
245, 246

<u>9-[1'-(*tert*-Butyldiphenylsilyloxymethyl)propyl]-2-iodomethyl-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene</u> **247, 248**

A solution of the (-)-iodohydrin **245** (42 mg, 0.06 mmol), iodine (32 mg, 0.13 mmol) and iodobenzenediacetate (42 mg, 0.13 mmol) in cyclohexane (10 ml) was purged with nitrogen and irradiated with a 270 watt tungsten filament lamp. After 1.5 h., during which time the temperature was maintained at about 18°C, the solution was diluted with ether (50 ml) then washed with 10% aqueous sodium thiosulphate (10 ml), water (10 ml) and brine (20 ml), and dried over potassium carbonate. The solvent was evaporated under reduced pressure and the mixture of two diastereomers were separated and purified by flash chromatography, using an hexane/ethyl acetate eluant (95:5), to afford the <u>(1'*S*, 2*S*, 5*S*, 7*S*, 9*S*, 10*S*, 12*R*) *trans* iodide</u> **247** (15.1 mg, 36%) as a colourless oil $[\alpha]_D^{22}$ -10.5° (c, 0.39, $CHCl_3$) (Found: M^+, 702.2603. $C_{36}H_{51}O_4SiI$ requires M^+, 702.2601);

υ_{max} (film) 3070 (w, Ar-H), 3040 (w, =CH), 2951, 2927, 2860 (s, C-H) and 1654 (w, C=C); δ_H (270 MHz; $CDCl_3$) 0.66 (3H, t, *J* 7.5 Hz, $CH_2C\underline{H}_3$), 0.77 (3H, d, *J* 6.2 Hz, 12-Me), 0.82 (3H, d, *J* 6.4 Hz, 10-Me), 1.06 (9H, s, *t*-Bu) 1.57, (3H, s, 2-Me), 1.17-1.88 (9H, m, 3-H', 4-H', 2x C<u>H</u>Me, C<u>H</u>Et, $C\underline{H}_2CH_3$, 11_{ax}-H and 11_{eq}-H), 2.03-2.17 (2H, m, 3-H and 15-H'), 2.36 (1H, ddd, $J_{15,15}$ 16.8, $J_{15,14}$ 2.1 and $J_{15,13}$ 2.4 Hz, 15-H), 2.51-2.61 (1H, m, 4-H), 3.16 (1H, d, *J* 10.1 Hz, $C\underline{H}_AH_BI$), 3.22 (1H, d, *J* 10.1 Hz, $CH_A\underline{H}_BI$), 3.62 (2H, d, *J* 6.6 Hz, CH_2O), 3.72 (1H, dd, $J_{9ax,10ax}$ 10.1 and $J_{9ax,1'}$ 0.6 Hz, 9_{ax}-H), 5.40 (1H, dd, $J_{13,14}$ 10.1 and $J_{13,15}$ 2.4 Hz, 13-H), 5.86 (1H, ddd, $J_{14,13}$ 10.1, $J_{14,15}$ 6.4 and $J_{14,15}$ 2.1 Hz, 14-H), 7.32-7.43 (6H, m, Ar-H) and 7.63-7.68 (4H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 12.9 (q, C-3'), 16.0 (q, 10-Me), 17.8 (t, C-2'), 18.2 (t, C-1'''), 18.3 (q, 12-Me), 19.1 (s, $\underline{C}Me_3$), 27.0 (q, $C\underline{Me}_3$), 28.4 (q, 2-Me), 33.9, 35.6, 35.9, 36.7 (t, C-3, C-4 C-11 and C-15), 31.8, 39.4, 44.1 (d, C-1', C-10 and C-12), 65.0 (t, C-1''), 75.6 (d, C-9), 82.8 (s, C-2), 99.1 (s, C-7), 107.4 (s, C-5), 125.2 (d, C-13), 127.5, 127.6 (d, C-2''''), 129.4, 129.5, 129.6 (d, C-4'''' and C-14), 133.9, 134.2 (s, C-1'''') and 135.5, 135.8 (d, C-3''''), and the more polar <u>(1'*S*, 2*S*, 5*R*, 7*S*, 9*S*, 10*S*, 12*R*) *cis* iodide</u> **248** (8.9 mg, 21%) as a colourless oil $[\alpha]_D^{22}$ -31.6° (c, 0.215, $CHCl_3$) (Found: M^+, 702.2603. $C_{36}H_{51}O_4SiI$ requires M^+, 702.2601); υ_{max} (film) 3070 (w, Ar-H), 3040 (w, =CH), 2951, 2927, 2860 (s, C-H) and 1654 (w, C=C); δ_H (270 MHz; $CDCl_3$) 0.70 (3H, d, *J* 6.6 Hz, 12-Me), 0.84 (3H, t, *J* 7.3 Hz, $CH_2C\underline{H}_3$), 0.86 (3H, d, *J* 6.5 Hz., 10-Me), 1.06 (9H, s, *t*-Bu), 1.28 (3H, s, 2-Me), 1.03-1.92 (9H, m, 3-H', 4-H', 2x C<u>H</u>Me, C<u>H</u>Et, $C\underline{H}_2CH_3$, 11_{ax}-H and 11_{eq}-H), 2.02-2.11 (3H, m, 3-H, 4-H and 15-H), 2.27 (1H, ddd, $J_{15,15}$ 16.5, $J_{15,14}$ 5.1 and $J_{15,13}$ 1.6 Hz, 15-H'), 3.15 (1H, d, *J* 9.3 Hz, $C\underline{H}_AH_BI$), 3.29 (1H, d, *J* 9.3 Hz, $CH_A\underline{H}_BI$), 3.55 (1H, dd, $J_{9ax,10ax}$ 10.4 and $J_{9ax,1'}$ 1.8 Hz, 9_{ax}-H), 5.61 (1H, ddd, $J_{13,14}$ 9.9, $J_{13,15}$ 1.6 and $J_{13,15}$ 1.6 Hz, 13-H), 5.93 (1H, ddd, $J_{14,13}$ 9.9, $J_{14,15}$ 5.1 and $J_{14,15}$ 3.7 Hz, 14-H), 7.32-7.43 (6H, m, Ar-H) and 7.63-7.68 (4H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 13.6 (q, C-3'), 15.8 (q, 10-Me), 17.4 (t, C-2'), 18.4 (q, 12-Me), 19.2 (s, $\underline{C}Me_3$), 20.6 (t, C-1'''), 25.6 (q, 2-Me), 27.0 (q, $C\underline{Me}_3$), 34.5, 36.0, 36.5, 39.1 (t, C-3, C-4 C-11 and C-15), 32.5, 39.3, 45.6 (d, C-1', C-10 and C-12), 64.9 (t, C-1''), 77.2 (d, C-9), 83.5 (s, C-2), 96.6 (s, C-7), 106.3 (s, C-5), 125.3 (d, C-13), 127.5, 127.6 (d, C-2''''), 129.4 (d, C-4''''), 130.5 (d, C-14), 134.2 (s, C-1'''') and 135.7, 135.8 (d, C-3''''); *m/z* 702 (M^+, 6%), 645 (M-*t*Bu, 100), 567 (7), 391 ($C_{16}H_{24}O_3I$, 12), 320 ($C_{20}H_{32}O_3$, 16), 303 (12), 200 (12), 199 ($C_{12}H_{11}OSi$, 66), 183 (18, 135 (26), 111 (12) and 97 (12).

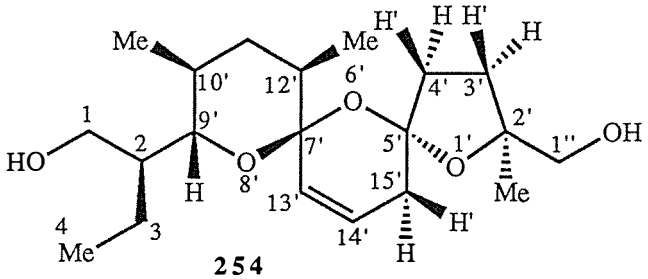
The procedure was repeated, irradiating a solution of the (+)-iodohydrin **246**, iodine and iodobenzenediacetate in cyclohexane, to again form a diastereomeric mixture of bisspiroketals **247, 248** which, on separation, exhibited identical spectroscopic properties to those isomers already described.



247, 248

(2*S*, 2'*S*, 5'*S*, 7'*S*, 9'*S*, 10'*S*, 12'*R*)-2-(2'-Hydroxymethyl-2',10',12'-trimethyl-1',6',8'-trioxadispiro[4.1.5.3]pentadec-13'-en-9'-yl)butan-1-ol **254**

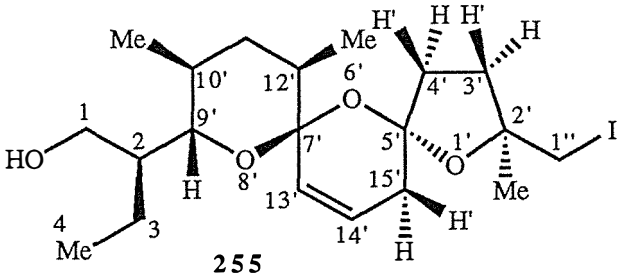
A solution of the (-)-iodide **247** (4 mg), 18-crown-6 (5 mg) and potassium superoxide (5 mg) in dry dimethylsulphoxide (1 ml) under nitrogen was stirred ovenight at room temperature. Water (0.05 ml) was added and the mixture extracted with ethyl acetate (50 ml) which was washed with water (10 ml) and brine (10 ml), then dried over potassium carbonate. The solvent was removed under reduced pressure and the residue purified by flash chromatography, using an hexane/ethyl acetate eluant (1:2) to afford the title compound **254** (~1 mg) as a colourless oil (Found: M^+, 354.2375. $C_{20}H_{34}O_5$ requires M^+, 324.2406), δ_H (270 MHz; $CDCl_3$) 0.81 (3H, d, *J* 6.6 Hz, 10'-Me or 12'-Me), 0.82 (3H, d, *J* 6.6 Hz, 10'-Me or 12'-Me), 0.98 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.44 (3H, s, 2'-Me), 1.30-1.86 (8H, m, CHEt, 2x CHMe, CH_2CH_3, $11'_{ax}$-H, $11'_{eq}$-H and 4'H'), 2.04-2.15 (3H, m, 15'-H', 3'-H and 3'-H'), 2.41 (1H, ddd, $J_{15',15'}$ 16.7, $J_{15',14'}$ 2.4 and $J_{15',13'}$ 3.0 Hz, 15'-H), 2.59 (1H, ddd, $J_{4',4'}$ 12.8, $J_{4',3'}$ 6.3 and $J_{4',3'}$ 4.4 Hz, 4'-H), 2.89 (1H, dd, $J_{HA,OH}$ 9.2 and $J_{HB,OH}$ 0.7 Hz, 1-OH), 3.38-3.55 (2H, m, 2x 1''-H), 3.69-3.82 (2H, m, 2x 1-H), 3.87 (1H, dd, $J_{9'ax,10'ax}$ 10.4 and $J_{9'ax,2}$ 1.8 Hz, 9'-H), 5.49 (1H, ddd, $J_{13',14'}$ 10.1, $J_{13',15'}$ 3.1 and $J_{13',15'}$ 0.9 Hz, 13'-H) and 5.93 (1H, ddd, $J_{14',13'}$ 10.1, $J_{14',15'}$ 6.4 and $J_{14',15'}$ 2.2 Hz, 14'-H); *m/z* 354 (M^+, 36%), 323 (M-CH_2OH, 73), 281 (M-C_4H_8OH, 58), 210 ($C_{12}H_{18}O_3$, 100), 199 (100), 198 (82), 181 (65), 162 (69) and 99 ($C_5H_7O_2$, 55).



254

(2*S*, 2'*S*, 5'*S*, 7'*S*, 9'*S*, 10'*S*, 12'*R*)-2-(2'-Iodomethyl-2',10',12'-trimethyl-1',6',8'-trioxadispiro[4.1.5.3]pentadec-13'-en-9'-yl)butan-1-ol **255**

To a solution of the *trans* iodide (4 mg) in dry tetrahydrofuran (1 ml) under nitrogen was added tetra-*n*-butylammonium fluoride (0.5 ml of a 1 molar solution in tetrahydrofuran, 0.5 mmol) and the mixture stirred overnight. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography, using an hexane/ethyl acetate eluant (2:1), to afford the title compound **255** (~2.5 mg) as colourless prisms, m.p. 83-84.5°C (Found: M^+, 464.1457. $C_{20}H_{33}O_4I$ requires M^+, 464.1424); δ_H (270 MHz; $CDCl_3$) 0.80 (3H, d, *J* 6.6 Hz, 10'-Me or 12'-Me), 0.81 (3H, d, *J* 6.6 Hz, 10'-Me or 12'-Me), 0.98 (3H, t, *J* 7.1 Hz, $CH_2C\underline{H}_3$), 1.66 (3H, s, 2'-Me),1.25-1.79 (7H, m, C<u>H</u>Et, 2x C<u>H</u>Me, $C\underline{H}_2CH_3$, $11'_{ax}$-H and $11'_{eq}$-H, 1.89 (1H, dd, $J_{4',4'}$ 12.6, $J_{4',3'}$ 10 and $J_{4',3'}$ 10 Hz, 4'-H'), 2.14-2.23 (3H, m, 3'-H, 3'-H' and 15'-H'), 2.41 (1H, ddd, $J_{15',15'}$ 16.8, $J_{15',14'}$ 2.4 and $J_{15',13'}$ 3.0 Hz, 15'-H), 2.57 (1H, ddd, $J_{4',4'}$ 12.6, $J_{4',3'}$ 5.1 and $J_{4',3'}$ 5.1 Hz, 4'-H), 2.85 (1H, dd, $J_{HA,OH}$ 10.5 and $J_{HB,OH}$ 1.7 Hz, OH), 3.27 (1H, d, *J* 10.3 Hz, $C\underline{H}_AH_BI$), 3.32 (1H, d, *J* 10.3 Hz, $CH_A\underline{H}_BI$), 3.67-3.78 (2H, m, CH_2O), 3.83 (1H, dd, $J_{9',10'}$ 10.4 and $J_{9',2}$ 1.6 Hz, 9'-H), 5.48 (1H, ddd, $J_{13',14'}$ 10.1, $J_{13',15'}$ 3.0 and $J_{13',15'}$ 0.8 Hz, 13'-H) and 5.94 (1H, ddd, $J_{14',13'}$ 10.1, $J_{14',15'}$ 6.2 and $J_{14',15'}$ 2.4 Hz, 14'-H); δ_C (67.8 MHz; $CDCl_3$) 12.3 (q, C-4), 15.9 (q, 10'-Me), 16.1 (t, C-1''), 17.5 (t, C-3), 17.6 (q, 12'-Me), 28.4 (q, 2'-Me), 31.8, 39.5, 41.7 (d, C-2, C-10' and C-12'), 33.8 (t, C-15'), 35.5, 36.3, 37.0 (t, C-3', C-4' and C-11'), 64.8 (t, C-1), 81.1 (d, C-9'), 82.8 (s, C-2'), 99.3 (s, C-7'), 107.5 (s, C-5'), 126.2 (d, C-13') and 128.7 (d, C-14'); *m/z* 464 (M^+, 22%), 446 ($M-H_2O$, 6), 391 ($M-C_4H_8OH$, 29), 337 (M-I, 5), 320 (M-OH-I, 37), 309 (100), 308 (46), 291 (30), 224 ($C_{14}H_{24}O_2$, 19), 163 (26), 113 ($C_6H_9O_2$, 14), 99 ($C_5H_7O_2$, 8) and 97 (25).



255

Conversion of *trans* alcohol **255** to the Mosher Ester derivative[105] **257** was performed as follows: To a solution of the alcohol **255** (2 mg) and pyridine (0.1 ml) in carbon tetrachloride (1 ml) under nitrogen was added a solution of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[105] (5 mg) in carbon tetrachloride (0.5 ml) and the

reaction stirred overnight at room temperature. Water (1 ml) was added and the mixture extracted with ether (50 ml) which was washed with water (15 ml) and dried over potassium carbonate. Evaporation of the solvent under reduced pressure and purification of the residue by flash chromatography, using an hexane/ethyl acetate eluant (9:1), afforded the Mosher ester **257**; δ_H (270 MHz; $CDCl_3$) 0.77 (3H, d, *J* 6.4 Hz, 10'-Me or 12'-Me), 0.80 (3H, d, *J* 6.4 Hz, 10'-Me or 12'-Me), 0.95 (3H, t, *J* 7.5 Hz, $CH_2C\underline{H}_3$), 1.56 (3H, s, 2'-Me), 1.17-2.02 (10H, m, 2x C<u>H</u>Me, C<u>H</u>Et, 3'-H', 3'-H, 4'-H', C<u>H</u>$_2$CH$_3$, 11$^{'}_{ax}$-H and 11$^{'}_{eq}$-H), 2.11 (1H, dd, $J_{15',15'}$ 16.7 and $J_{15',14'}$ 6.4 Hz, 15'-H'), 2.37 (1H, ddd, $J_{15',15'}$ 16.7, $J_{15',14'}$ 2.6 and $J_{15',13'}$ 2.6 Hz, 15'-H), 2.45-2.52 (1H, m, 4'-H), 3.17 (1H, d, *J* 10.3 Hz, C<u>H</u>$_A$H$_B$I), 3.25 (1H, d, *J* 10.3 Hz, CH$_A$C<u>H</u>$_B$I), 3.57 (3H, q, *J* 1.3 Hz, OMe), 3.64 (1H, dd, $J_{9'ax,10'ax}$ 10.7 and $J_{9'ax,2}$ 1.2 Hz, 9$^{'}_{ax}$-H), 4.10 (1H, dd, $J_{HA,HB}$ 10.8 and $J_{HA,2}$ 7.7 Hz, C<u>H</u>$_A$H$_B$O), 4.55 (1H, dd, $J_{HB,HA}$ 10.8 and $J_{HB,2}$ 5.5 Hz, CH$_A$<u>H</u>$_B$O), 5.43 (1H, dd, $J_{13',14'}$ 10.1 and $J_{13',15'}$ 2.6 Hz, 13'-H) and 5.90 (1H, ddd, $J_{14',13'}$ 10.1, $J_{14',15'}$ 6.4 Hz and $J_{14',15'}$ 2.6 Hz, 14'-H).

<u>13-Bromo-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-14-ene</u> **261** and <u>15-bromo-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene</u> **262**

Potassium carbonate (83 mg, 0.6 mmol) and *N*-bromosuccinimide (35 mg, 0.2 mmol) were suspended in a solution of the *cis*-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3] pentadec-13-ene **192** (36 mg, 0.15 mmol) in carbon tetrachloride (3 ml) under nitrogen. The mixture was heated under reflux for 5.5 h. then poured into ether (30 ml) which was washed with water (10 ml) and brine (10 ml), and dried over potassium carbonate. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography, using an hexane/ethyl acetate eluant (9:1), to give the less polar <u>*cis*-13-bromo-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-14-ene</u> **261** (20 mg, 42%) as colourless prisms m.p. 62-63°C (Found: M$^+$, 318.0655 and 316.0673. $C_{14}H_{21}O_3Br$ requires M$^+$, 318.0654 and 316.0674); δ_H (270 MHz; $CDCl_3$) 1.22 3H, s, Me), 1.48 (3H, s, Me), 1.37-2.26 (10H, m, 5x CH_2), 3.64 (1H, m, 9$_{eq}$-H), 4.18 (1H, ddd, $J_{9ax,9eq}$ 11.7, $J_{9ax,8ax}$ 11.7 and $J_{9ax,8eq}$ 3.8 Hz, 9$_{ax}$-H), 4.27 (1H, d, *J* 5.9 Hz, CHBr), 5.68 (1H, d, *J* 9.9 Hz, 15-H) and 6.10 (1H, dd, $J_{14,15}$ 9.9 and $J_{14,13}$ 5.9 Hz, 14-H); *m/z* 318 (M$^+$, 30%), 316 (M$^+$, 30), 237 (M-Br, 100), 218 ($C_9H_{13}OBr$, 35) and 216 ($C_9H_{13}OBr$, 34), and <u>*cis*-15-bromo-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene</u> **262** (11 mg, 23%) as a colourless oil (Found: M$^+$, 318.0655 and 316.0673. $C_{14}H_{21}O_3Br$ requires M$^+$, 318.0654 and 316.0674); δ_H (270 MHz; $CDCl_3$) 1.17 (3H, s, Me), 1.38 (3H, s, Me), 1.47-2.15 (8H, m, 3-H, 4-H and 4x CH_2), 3.65 (1H, m, 9$_{eq}$-H), 4.05 (1H, ddd, $J_{9ax,9eq}$ 11.4, $J_{9ax,8ax}$ 11.4 and $J_{9ax,8eq}$ 3.2 Hz, 9$_{ax}$-H), 4.29 (1H, d, *J* 5.9 Hz, CHBr), 5.81 (1H, d, *J* 9.9 Hz, 13-H) and 6.13 (1H,

dd, $J_{14,13}$ 9.9 and $J_{14,15}$ 5.9 Hz, 14-H); *m/z* 318 (M^+, 32%), 316 (M^+, 32), 237 (M-Br, 100), 204 ($C_8H_{11}OBr$, 32) and 202 ($C_8H_{11}OBr$, 31).

15-bromo-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **265**

Potassium carbonate (47 mg, 0.35 mmol) and *N*-bromosuccinimide (15 mg, 0.1 mmol) were suspended in a solution of *trans*-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3] pentadec-13-ene **152** (20 mg, 0.085 mmol) in carbon tetrachloride (2 ml) under nitrogen and the mixture heated under gentle reflux for 8 h. The solution was diluted with ether (30 ml) which was washed with water (10 ml) and brine (10 ml), and dried over potassium carbonate. The solvent was removed under reduced pressure and the residue purified by flash chromatography, using an hexane/ethyl acetate eluant (9:1), to afford *trans*-15-bromo-2,2-dimethyl-1,6,8-trioxadispiro[5.1.5.3]pentadec-13-ene **265** (10 mg, 37%) as a colourless oil (Found: M^+, 318.0662 and 316.0663. $C_{14}H_{21}O_3Br$ requires M^+, 318.0654 and 316.0674); δ_H (270 MHz; $CDCl_3$) 1.26 (3H, s, Me), 1.43 (3H, s, Me), 1.45-2.42 (9H, m, 3-H, 3-H', 4-H' and 3x CH_2), 2.54 (1H, ddd, $J_{4,4}$ 13.4, $J_{4,3}$ 7.8 and $J_{4,3}$ 3.8 Hz, 4-H), 3.74 (1H, m, 9_{eq}-H), 4.02 (1H, ddd, $J_{9,9}$ 11.0, $J_{9,8}$ 11.0 and $J_{9,8}$ 3.8 Hz, 9_{ax}-H), 4.55 (1H, dd, $J_{15,14}$ 3.5 and $J_{15,13}$ 1.7 Hz, CHBr), 5.62 (1H, dd, $J_{13,14}$ 10.1 and $J_{13,15}$ 1.7 Hz, 13-H) and 6.03 (1H, dd, $J_{14,13}$ 10.1 and $J_{14,15}$ 3.5 Hz, 14-H); *m/z* 318 (M^+, 38%), 316 (M^+, 38), 237 (M-Br, 100), 204 ($C_8H_{11}OBr$, 69) and 202 ($C_8H_{11}OBr$, 74).

2,2-Dimethyl-15-hydroxy-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **159**

A solution of 18-crown-6 (10 mg, 0.04 mmol) and *trans*-15-bromo-2,2-dimethyl-1,6,8-trioxadispiro[5.1.5.3]pentadec-13-ene **265** (12 mg, 0.038 mmol) in dry dimethylsulphoxide (1 ml) was stirred with potassium superoxide (15 mg, 0.2 mmol) for 8 h. under nitrogen. Water (1 ml) was added and the mixture extracted with ether (30 ml) which was washed with water (2x 10 ml) and brine (10 ml), and dried over potassium carbonate. The solvent was evaporated at reduced pressure and the residue purified by flash chromatography, using an hexane/ethyl acetate eluant (1:2), to give *trans*-2,2-dimethyl-15-hydroxy-1,6,8-trioxadispiro[5.1.5.3]pentadec-13-ene[63,64] **159** as a colourless oil (7 mg, 65%) (Found: M^+, 254.9525. $C_{14}H_{22}O_4$ requires M^+, 254.9518); δ_H (270 MHz; $CDCl_3$) 1.25 (3H, s, Me), 1.48 (3H, s, Me), 1.45-2.23 (9H, m, 3-H, 3-H', 4-H' and 3x CH_2), 2.41 (1H, ddd, $J_{4,4}$ 13.0, $J_{4,3}$ 7.4 and $J_{4,3}$ 3.1 Hz, 4-H), 3.70 (1H, m, 9_{eq}-H), 4.01 (1H,

m, 9_{ax}-H), 4.15 (1H, ddd, $J_{15,OH}$ 4.9, $J_{15,14}$ 2.4 and $J_{15,13}$ 2.4 Hz, CHOH), 5.62 (1H, dd, $J_{13,14}$ 10.1 and $J_{13,15}$ 2.4 Hz, 13-H) and 5.88 (1H, dd, $J_{14,13}$ 10.1 and $J_{14,15}$ 2.4 Hz, 14-H); *m/z* 254 (M^+, 5%), 236 (M-H_2O, 10) and 140 ($C_9H_{14}O_2$, 100).

2,2-Dimethyl-13-hydroxy-1,6,8-trioxadispiro[4.1.5.3]pentadec-14-ene **268** and
2,2-dimethyl-15-hydroxy-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **156**

A solution of 18-crown-6 (16 mg, 0.06 mmol) and *cis*-13-bromo-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-14-ene **261** (18 mg, 0.056 mmol) in dry dimethylsulphoxide (1 ml) was stirred with potassium superoxide (15 mg, 0.2 mmol) for 8 h. under nitrogen. Water (1 ml) was added and the mixture extracted with ether (30 ml) which was washed with water (2x 10 ml) and brine (10 ml), and dried over potassium carbonate. The solvent was evaporated at reduced pressure and the residue purified by flash chromatography, using an hexane/ethyl acetate eluant (1:2), to give an inseparable mixture of *cis*-2,2-dimethyl-15-hydroxy-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene[63,64] **156** and *cis*-2,2-dimethyl-13-hydroxy-1,6,8-trioxadispiro[4.1.5.3]pentadec-14-ene **268** (*) in the ratio of 1.5:1 and in the form of a colourless oil (11 mg, 65%) (Found: M^+, 254.9525. $C_{14}H_{22}O_4$ requires M^+, 254.9518); δ_H (270 MHz; $CDCl_3$) 1.17 (3H, s, 2-Me), 1.23 (3H, s, 2-Me*), 1.40 (3H, s, 2-Me), 1.48 (3H, s, 2-Me*), 1.46-2.18 (19H, m, 3-H, 3-H', 3-H*, 3-H'*, 4-H', 4-H*, 4-H'*, 3x CH_2 and 3x CH_2*), 2.27-2.40 (1H, m, 4-H), 3.57-3.66 (4H, m, 2x CHOH and 2x 9_{eq}-H), 4.05 (1H, ddd, $J_{9ax,9eq}$ 11.5, $J_{9ax,8ax}$ 11.5 and $J_{9ax,8eq}$ 3.2 Hz, 9_{ax}-H), 4.19 (1H, ddd, $J_{9ax,9eq}$ 11.5, $J_{9ax,8ax}$ 11.5 and $J_{9ax,8eq}$ 3.2 Hz, 9_{ax}-H*), 5.78 (1H, d, *J* 10.1 Hz, 15-H*), 5.88 (1H, d, *J* 10.1 Hz, 13-H), 6.08 (1H, dd, $J_{14,15}$ 10.1 and $J_{14,13}$ 5.8 Hz, 14-H*) and 6.11 (1H, dd, $J_{14,13}$ 10.1 and $J_{14,15}$ 5.5 Hz, 14-H); *m/z* 254 (M^+, 4%), 236 (M-H_2O, 8), 154 ($C_9H_{14}O_2$, 98) and 140 ($C_9H_{14}O_2$, 100). Repetition of the above procedure, using the corresponding *cis*-15-bromo-2,2-dimethyl-1,6,8-trioxadispiro[5.1.5.3]pentadec-13-ene **262** afforded the same alcohols **156** and **268** in the ratio 1:1.5.

13-Acetoxy-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-14-ene **269** and
15-acetoxy-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **270**

A solution of the mixture of the *cis*-2,2-dimethyl-15-hydroxy-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **156** and the *cis*-2,2-dimethyl-13-hydroxy-1,6,8-trioxadispiro[4.1.5.3]pentadec-14-ene **268**, triethylamine (5 drops), acetic anhydride (2 drops) and a catalytic quantity of dimethylaminopyridine in dichloromethane (2 ml) was

stirred at room temperature for 2 h. The solution was diluted with ether (20 ml) which was washed with water (5 ml) and dried over potassium carbonate. the solvent was removed under reduced pressure to afford a separable mixture of the acetates **269** and **270**, which were purified by flash chromatography, using an hexane/ethyl acetate eluant (4:1), to afford the less polar *cis*-13-acetoxy-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-14-ene **269** as a colourless oil (Found: M^+, 296.1588. $C_{16}H_{24}O_5$ requires M^+, 296.1624); δ_H (270 MHz; $CDCl_3$ 1.23 (3H, s, 2-Me), 1.48 (3H, s, 2-Me), 1.24-2.15 (10H, m, 5x CH_2), 2.05 3H, s, OAc), 3.62 (1H, m, 9_{eq}-H), 4.18 (1H, m, 9_{ax}-H), 4.89 (1H, d, *J* 5.7 Hz, C<u>H</u>OAc), 5.87 (1H, d, *J* 10.1 Hz, 15-H) and 5.99 (1H, dd, $J_{14,15}$ 10.1 Hz and $J_{14,13}$ 5.7 Hz); *m/z* 296 (M^+, 3%), 254 (M-AcOH, 7), 196 ($C_{11}H_{16}O_3$, 38) and 154 ($C_9H_{14}O_2$, 100), and *cis*-15-acetoxy-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene[64] **270** as a colourless oil (Found: M^+, 296.1613. $C_{16}H_{24}O_5$ requires M^+, 296.1624); δ_H (270 MHz; $CDCl_3$) 1.18 (3H, s, 2-Me), 1.40 (3H, s, 2-Me), 1.48-2.17 (10H, m, 5x CH_2), 2.07 (3H, s, OAc), 3.65 (1H, m, 9_{eq}-H), 4.04 (1H, ddd, $J_{9ax,9eq}$ 11.5, $J_{9ax,8ax}$ 11.5 and $J_{9ax.8eq}$ 3.1 Hz, 9_{ax}-H), 4.86 (1H, d, *J* 5.5 Hz, C<u>H</u>OAc), 5.97 (1H, d, *J* 10.1 Hz, 13-H) and 6.05 (1H, dd, $J_{14,13}$ 10.1 and $J_{14,15}$ 5.5 Hz, 14-H); *m/z* 296 (M^+, 3%), 254 (M-Ac, 23), 236 (M-AcOH, 15), 182 ($C_{10}H_{14}O_3$, 10) and 140 ($C_8H_{12}O_4$, 100).

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