UNIVERSITY OF SOUTHAMPTON

DEPARTMENT OF CHEMISTRY

SALINOMYCIN : THE BIS-SPIROACETAL MOIETY

A Thesis Submitted for the
Degree of Doctor of Philosophy

by

Margaret Anne Brimble

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ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Doctor of Philosophy

SALINOMYCIN : THE BIS-SPIROACETAL MOIETY

by Margaret Anne Brimble

The synthesis of (Z)-7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-1-octen-4-one (87) and 7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-octan-4-one (115) are described. In both cases, the key step was the addition of the lithium acetylide prepared from 7-methyl-4-trimethylsilyloxy-7-octen-1-yne (98) to δ-valerolactone (97). The attempted acid catalysed cyclization of (Z)-7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-1-octen-4-one (87) failed to yield the desired 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system (26) found in the salinomycin series of polyether antibiotics. The successful acid catalysed cyclization of 7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-octan-4-one (115) to 1-(2-methyl,1,6,8-trioxadispiro[4.1.5.3]pentadec-2-yl)-methanol (118), however, highlighted a means of constructing the corresponding 1,6,8-trioxadispiro[4.1.5.3]pentadecane ring system. An alternative strategy for the preparation of the required 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system via a Barton-type reaction of an hydroxy-spiroacetal derivative was developed. This was exemplified by the successful synthesis of 2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene (119) from 4-(1,7-dioxaspiro[5.5]undec-4-en-2-yl)-2-methylbutan-2-ol (121). The stereochemistry of 2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene (119) was found to be identical to that found in the analogous ring system of epi-17-deoxy-(O-8)-salinomycin (8) using high field ^{1}H n.m.r. spectroscopy, in particular, nuclear Overhauser effect (NOE) difference and proton homonuclear correlation (COSY) experiments.

The preparation of two key intermediates required for the synthesis of the bis-spiroacetal moiety of epi-17-deoxy-(O-8)-salinomycin (125) namely, (1'S,3R,5S,6S)-(+)-tetrahydro-6-[1-(acetoxymethyl)propyl]-3,5-dimethylpyran-2-one (206) and (3R,4'S)- or (3S,4'S)-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-5-hexyn-3-ol (128), is described. Lactone (206) was prepared enantioselectively from the optically active building block (R)-(-)-methyl 3-hydroxy-2-methylpropionate (177). Acetylene (128) was prepared from levulinic acid (213) incorporating the 'classical' resolution of (±)-(tetrahydro-2-methyl-5-oxofuran-2-yl)carboxylic acid (212) as a key step. An alternative synthesis of 4-(1,7-dioxaspiro[5.5]undec-4-en-2-yl)-2-methylbutan-2-ol (121) from acetylene (128) and δ-valero-lactone (97) demonstrates the potential of the lactone (206) and acetylene (128) to be converted into an hydroxyspiroacetal derivative suitable for the synthesis of the bis-spiroacetal moiety of epi-17-deoxy-(O-8)-salinomycin (125) via a Barton-type cyclization.

CONTENTS

ABBREVIATIONS

ax	=	axial
Bn	=	benzyl
COSY	=	correlation spectroscopy
m-CPBA	=	meta-chloroperoxybenzoic acid
CSA	=	camphorsulphonic acid
DDQ	=	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	=	dihydropyran
DIBAL	=	diisobutylaluminium hydride
DMAP	=	4-dimethylaminopyridine
DMF	=	N,N-dimethylformamide
DMSO	=	dimethyl sulphoxide
eq	=	equatorial
equiv.	=	equivalent
LDA	=	lithium diisopropylamide
Ms	=	methanesulphonyl
NCS	=	N-chlorosuccinimide
NOE	=	nuclear Overhauser effect
PCC	=	pyridinium chlorochromate
PPTS	=	pyridinium p-toluenesulphonate
py	=	pyridine
R.T.	=	room temperature
TBDMS	=	tert-butyldimethylsilyl
Tf	=	trifluoromethanesulphonyl
TFAA	=	trifluoroacetic anhydride
THF	=	tetrahydrofuran
THP	=	tetrahydropyranyl
Ts	=	p-toluenesulphonyl
p-TSA	=	p-toluenesulphonic acid

CHAPTER 1

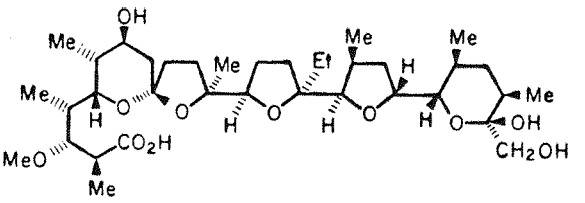
INTRODUCTION

1.1 The Polyether Antibiotics

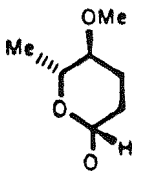
The majority of polyether antibiotics are isolated from the Streptomyces genus of microorganisms, in particular, S.albus and S.hygroscopicus. The polyethers exhibit antimicrobial activity against gram-positive bacteria and mycobacteria but do not inhibit gram-negative microorganisms. Some of the compounds have been reported to be active against phytopathogenic bacteria and fungi. Although the polyethers have not been used as clinical antibacterial agents due to their parenteral toxicity, they have, nevertheless, adopted an important role in veterinary medicine as coccidiostats in poultry and as growth promotants in ruminants such as cattle and sheep. The increasing interest in polyether antibiotics has generated a number of reviews[1-8].

The most characteristic of all the structural features displayed by the polyether antibiotics is the presence of a multiplicity of cyclic ethers. In addition, these antibiotics are also monocarboxylic acids which cannot be extracted from organic solvents by aqueous sodium carbonate or bicarbonate. On the contrary, alkali metal cations like sodium are extracted into the organic phase from which the antibiotic salt complexes can be isolated by evaporation and crystallization. Hence the polyether antibiotics belong to the large family of ionophores which include the synthetic crown ethers and cryptates in addition to antibiotics of the macrotetralide type such as nonactin. The polyethers, being acids yielding neutral salt complexes, are distinguished from many of the other ionophores which are neutral cyclic structures yielding positively charged cation complexes.

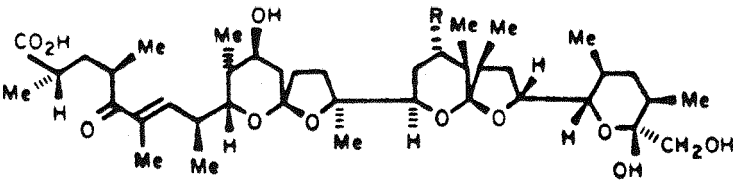
A polyether antibiotic can assume a characteristic cyclic conformation by concentrating all the oxygen functions at the centre of the structure where they are available for complexation of a suitable cation. The many branched alkyl groups are then spread over



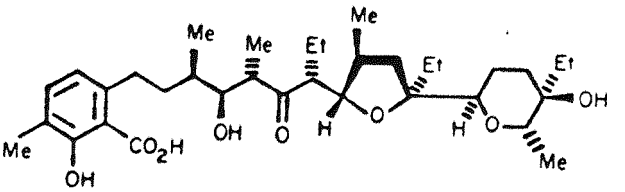
Monensin (1)



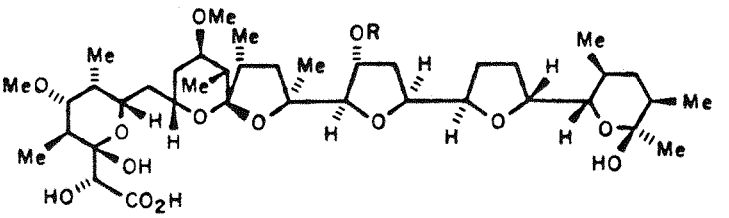
(2)



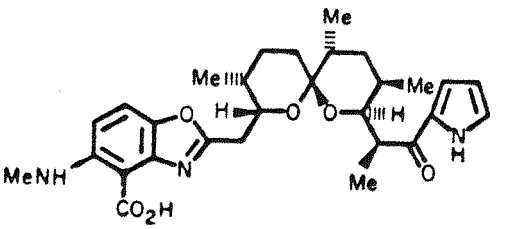
Dianemycin (3):R=(2)



Lasalocid A (4)



Antibiotic-6016 (5):R=(2)



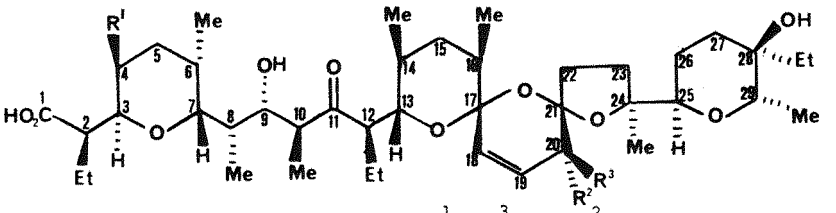
Antibiotic A23187 (6)

the outer surface, rendering the complex lipid soluble. Thus, cations may be conducted across membranes down the concentration gradient by a mechanism known as passive diffusion[9]. The cation selectivity of the polyether antibiotics can be determined using fluorimetric or two phase distribution techniques and provides a basis for a method of classifying the polyether antibiotics.

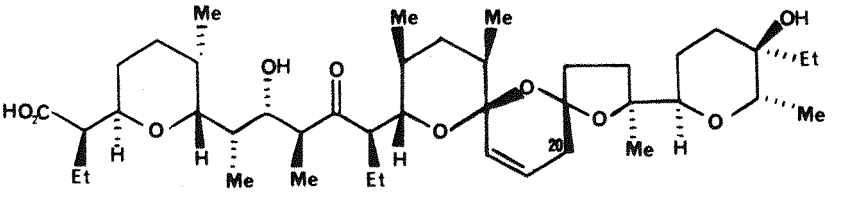
Using this criterion, Westley defined five classes of polyether antibiotics : monovalent, monovalent glycoside, divalent, divalent glycoside and divalent pyrrole ether[4,6]. Thus, a polyether antibiotic is classified as monovalent if it transports monobasic cations into a lipophilic environment more efficiently than basic cations (e.g. monensin (1)). If in addition, it contains the 4-O-methyl-amicetose moiety attached as a glycoside (2), it is classified as a monovalent glycoside (e.g. dianemycin (3)). Similarly, polyether antibiotics which transport dibasic cations more efficiently than monobasic cations are classified as divalent (e.g. lasalocid A (4)). The additional presence of the same sugar-like moiety attached as a glycoside (2), or a pyrrole-2-carbonyl chromophore, necessitates the classifications divalent glycoside (e.g. antibiotic - 6016 (5)), or divalent pyrrole ether (e.g. antibiotic A23187 (6)), respectively. The number of monovalent polyether antibiotics is much higher than the number of divalent polyether antibiotics.

1.2 Polyether Antibiotics containing a Bis-spiroacetal Moiety

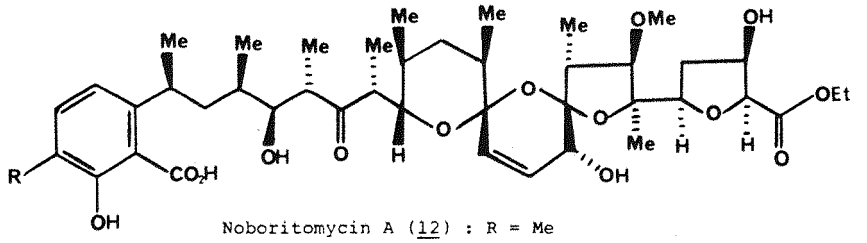
Salinomycin (7) is a member of the monovalent class of polyether antibiotics, elaborated by the strain of Streptomyces albus 80614 and exhibits antimicrobial activity against gram-positive bacteria, mycobacteria and fungi. Furthermore, salinomycin is effective in the treatment of coccidial infections in poultry[10]. The structural elucidation of salinomycin was reported by Kinashi et al[11] in 1973 by X-ray analysis of its p-iodophenacyl ester and revealed the presence of the novel unsaturated tricyclic spiroacetal (or bis-spiroacetal) ring system. Re-examination by Westley et al[12],



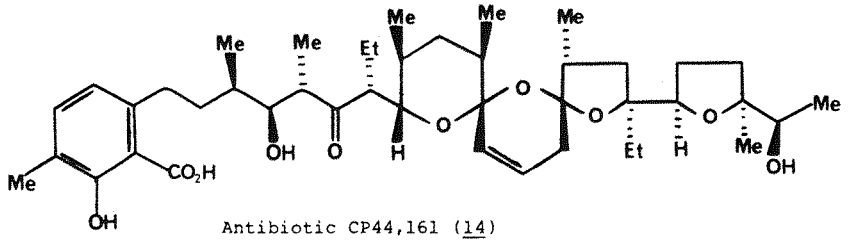
Salinomycin (7) : $R^1 = R^3 = H$, $R^2 = OH$,
Deoxy-(O-8)-salinomycin (9) : $R^1 = R^2 = R^3 = H$
Narasin A (10) : $R^1 = Me$, $R^2 = OH$, $R^3 = H$
Narasin B (11) : $R^1 = Me$, $R^2 = R^3 = O$



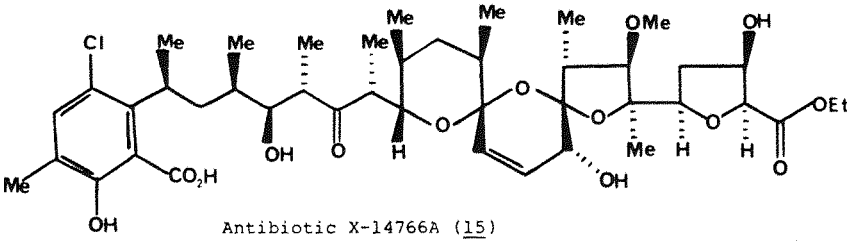
epi-17-Deoxy-(O-8)-salinomycin (8)



Noboritomycin A (12) : R = Me
Noboritomycin B (13) : R = Et



Antibiotic CP44,161 (14)



Antibiotic X-14766A (15)

of the same salinomycin-producing culture of S.albus using a different culture medium led to the isolation of two C-17 epimers of deoxy-(O-8)-salinomycin. The major metabolite, epi-17-deoxy-(O-8)-salinomycin (8),was found to be present at three to four times the level of the other two products, salinomycin (7) and deoxy-(O-8)-salinomycin (9).

The second bis-spiroacetal containing polyether antibiotic to be isolated was narasin A (10)[13] whose structure was confirmed as 4-methylsalinomycin by Occolowitz et al[14] by mass spectral comparison with salinomycin (7). This study also revealed a related component, narasin B (11), containing an allylic ketone function in place of the alcohol function in narasin A.

In the course of their screening for new antibiotics from soil actinomycetes, Keller-Juslén et al[15] isolated the polyether antibiotics noboritomycin A (12) and noboritomycin B (13) from a strain of Streptomyces noboritoensis. X-ray analysis of the silver salt established the presence of the prominent bis-spiroacetal system, thereby establishing the structural relationship with salinomycin (7). In the same year, Tone et al[16] reported the isolation of the polyether antibiotic CP44,161 (14) from a new species of Dactylosporangium. Several years later Westley et al[17] reported the first halogen containing antibiotic X-14766A (15). Both of these also contained the salient bis-spiroacetal moiety.

Several other structural analogues of the previously mentioned bis-spiroacetal containing polyether antibiotics continuing to add to this burgeoning group of compounds include salinomycin A II[18], salinomycin SY-4 (5-hydroxy)[19], salinomycin SY-5 (18,19-dihydro)[20], salinomycin SY-8 (isomer of SY-5)[20], epi-17-deoxy-(O-8)-narasin[21], deoxy-(O-8)-narasin[21] and narasin D[22].

1.3 Biosynthesis of Salinomycin and Narasin

The biosynthetic origin of salinomycin and narasin is probably identical except for the origin of the C-3, C-4, and the C-

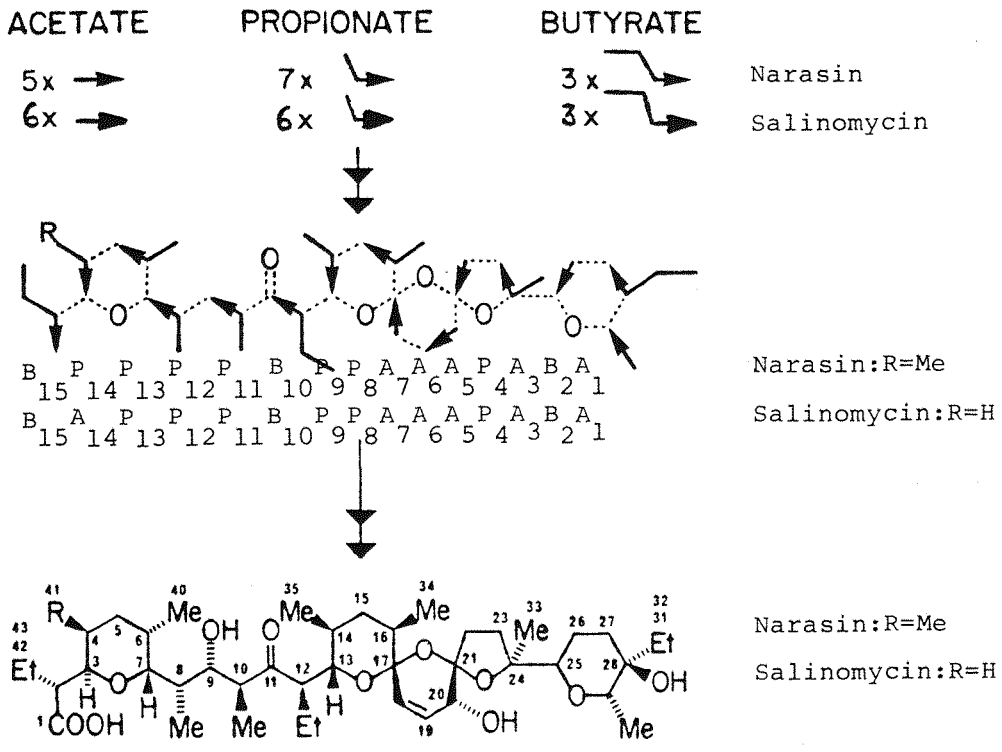
methyl group at C-4 of narasin. They are therefore considered together in this section.

Following their investigation into the biosynthesis of narasin by feeding ^{13}C-labelled acetate, propionate and butyrate to S.aureofaciens and analysing the enrichment pattern by ^{13}C n.m.r. spectroscopy, Dorman et al[23] concluded that three butyrate and seven propionate units were involved in narasin biosynthesis. In addition five acetate units were probably incorporated on the basis of structural analysis. Although the results from the [2-^{13}C]-acetate incorporation study of narasin were inconclusive, an independent study by Seto et al[24] on the biosynthesis of salinomycin using the doubly labelled substrates [1,2-^{13}C]acetate and [1,2-^{13}C]propionate revealed that six acetate and six propionate units are utilized by S.albus to assemble the antibiotic. Replacement of the acetate unit constituting the C-3 and C-4 carbons in salinomycin by a propionate unit during the polyketide assembly would yield narasin. Hence it was inferred that five acetate units are involved in narasin biosynthesis. The labelling patterns of salinomycin and narasin are illustrated (Figure 1).

The first four biogenetic units giving rise to the tetrahydropyran ring at the opposite terminus to the carboxylic acid function are propionate, acetate, butyrate and acetate : $P_4A_3B_2A_1$ or, simply, PABA. Thus, using the Cane-Celmer-Westley model[25] for polyether antibiotic structure and biogenesis, salinomycin is described as a PABA polyether.

Based on recent investigations into the biosynthesis of monensin using [1-^{13}C, ^{18}O] labelled substrates and molecular $^{18}O_2$ experiments, a biosynthetic hypothesis for salinomycin has been proposed by Westley et al[5,25] (Scheme 1). Thus, in a sequence of transformations analogous to, but certainly not identical, with classical saturated fatty acid biosynthesis, the simple precursors acetate, propionate and butyrate are assembled into polyene (16), which would undergo selective epoxidation to give diene diepoxide (17). Stereocontrolled cyclization of the putative diepoxide would thus yield

Figure 1



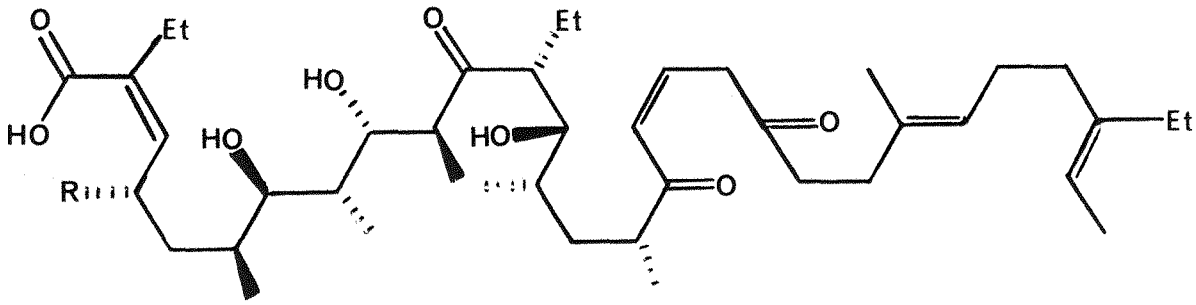
salinomycin (or narasin).

The speculative cyclization was further elaborated by Westley[5] to account for the observation that epi-17-deoxy-(O-8)-salinomycin (8) was found to be present in much higher yield than both salinomycin (7) and deoxy-(O-8)-salinomycin (9)[12]. If the allylic alcohol group, O-8, is present in the hypothetical linear diene diepoxide (17) then these results implicate this hydroxyl group as the key to the stereochemistry at C-17. If O-8 is hydrogen bonded to an oxygen earlier in the backbone (e.g. the carbonyl at C-11) then the linear precursor would assume a U-shaped conformation similar to that found in salinomycin. Cyclization to the hemiacetal (step (a) in Scheme 2) would then be conformationally restricted to a single epimer. In the case of the non-hydroxylated precursor, the less sterically hindered linear conformation can be adopted and cyclization to the hemiacetal can thus result in the opposite stereochemistry at C-17, yielding epi-17-deoxy-(O-8)-salinomycin (8). The formation of the C,D, and E rings must proceed similarly as

Scheme 1

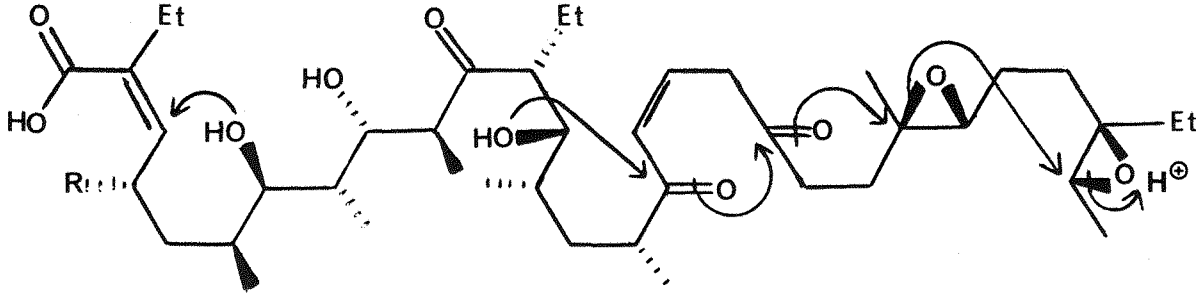
acetate, propionate, butyrate

↓ polyketide assembly



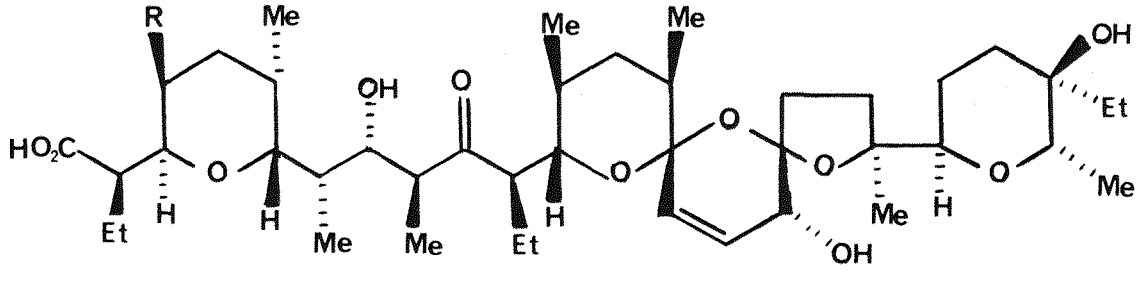
(16)

↓ O_2



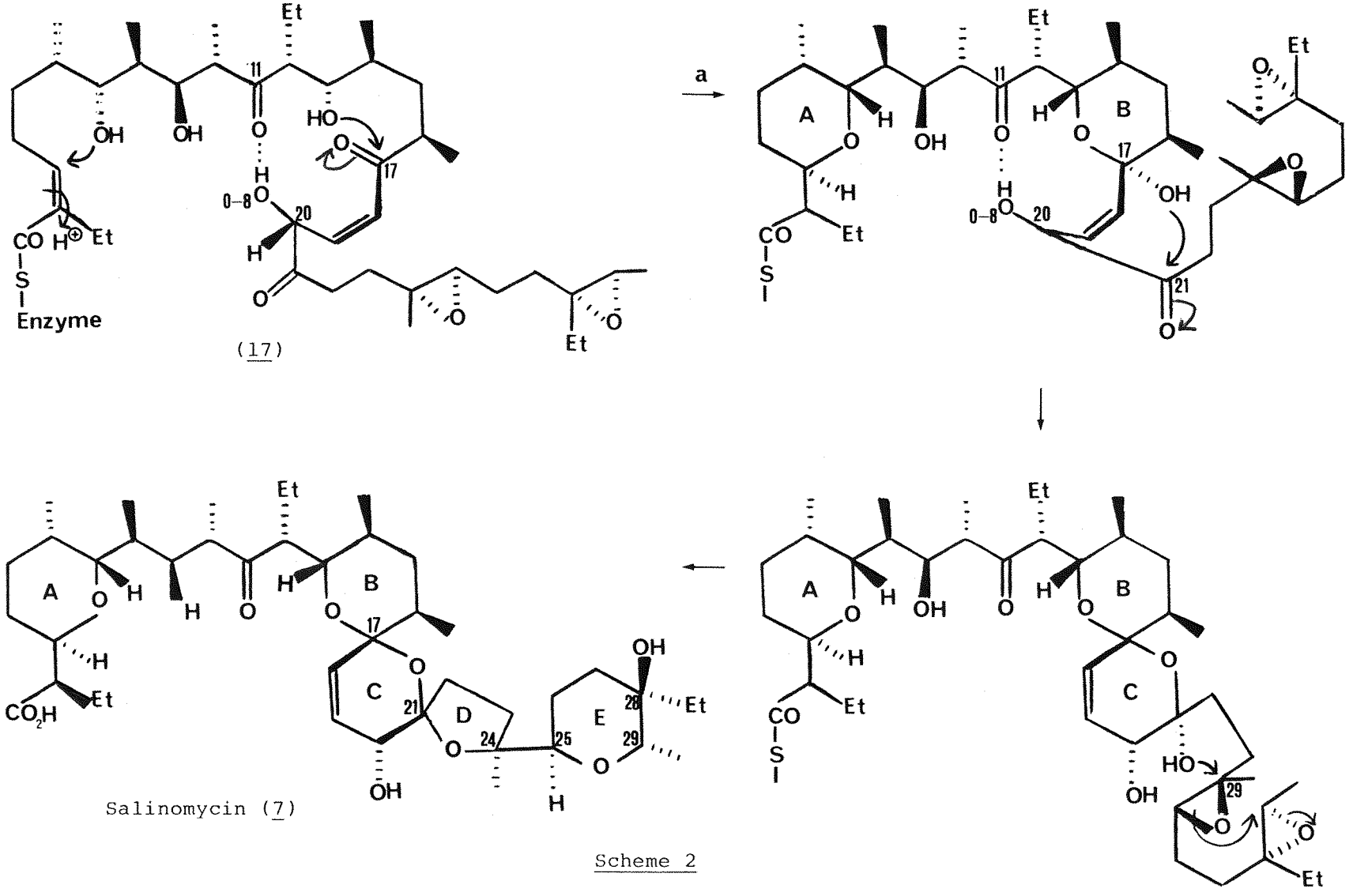
(17)

↓



Salinomycin (7):R=H

Narasin (10):R=Me



(17)

Salinomycin (7)

Scheme 2

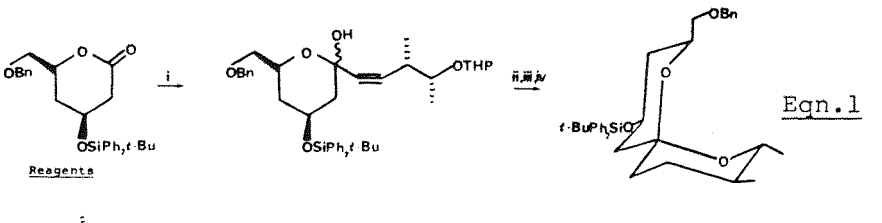
C-21, C-24, C-25, C-28, and C-29 all have the same configuration in both molecules.

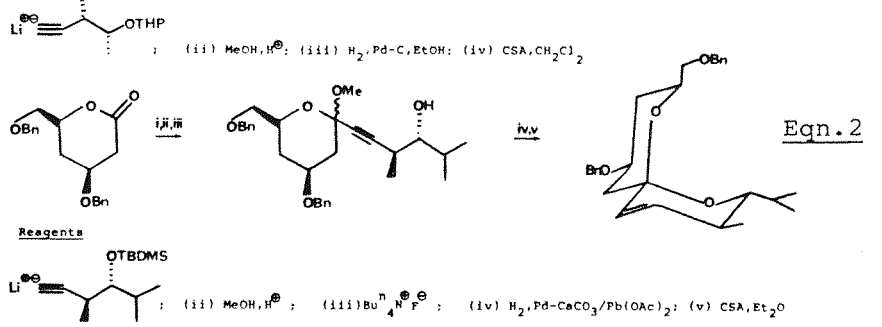
Whilst the precise details of salinomycin biosynthesis remain to be experimentally proven, the basis of the above speculations is sure to be tested in the chemical synthesis.

1.4 Synthesis of Bicyclic and Tricyclic Spiroacetals

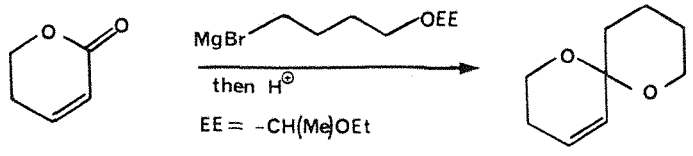
The occurrence of a spiroacetal moiety as a prime structural feature in a host of natural products, particularly, insect pheromones[26], oxygenated terpenoids[27], the potent antiparasitic agents, the milbemycins and avermectins[28,29], and the polyether antibiotics[7], has prompted the development of a range of methods to construct the spiroacetal skeleton. This section commences with a review of bicyclic spiroacetal formation.

The most common method[30-39], the addition of carbanions to δ-valerolactones followed by cyclization of the resultant lactols, is best exemplified by the synthesis of the spiroacetal portions of milbemycin β_1 (Eqn.1)[38] and avermectin B_{1b} (Eqn.2)[39] as reported by Baker et al. As anticipated, the favoured conformation is that in which all the substituents are equatorial and the ring oxygens are axial to the adjacent ring thereby gaining stability from the anomeric effect[40].

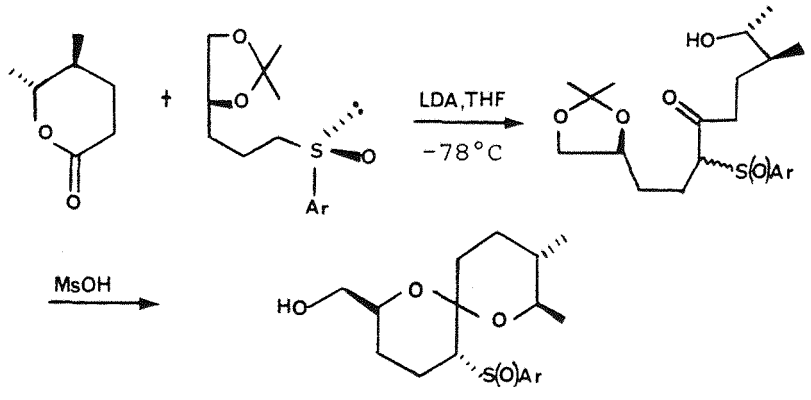




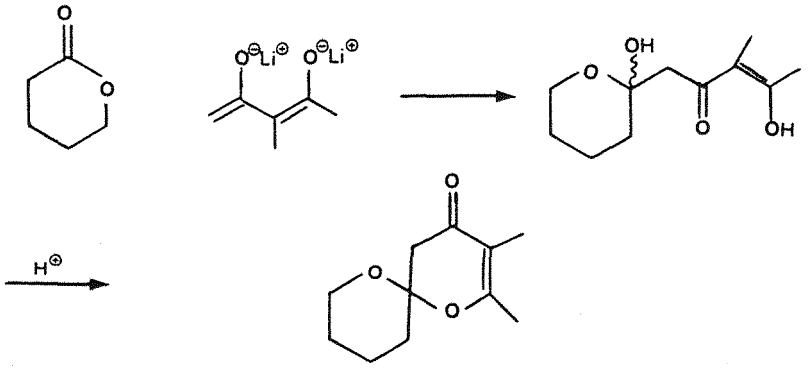
The potential of this strategy for construction of the spiroacetal skeleton is demonstrated not only in the variety of carbanions used in the nucleophilic addition reaction but also in the nature of the subsequent cyclization. Included amongst a host of nucleophiles were a Grignard reagent (Eqn.3)[34], an α-lithiosulphinyl carbanion (Eqn.4)[33] and the dianion of a β-diketone (Eqn.5)[31]. One elegant variation of the subsequent cyclization step conjectured by Smith et al[32] involved Michael addition of the lactol onto an α-β-unsaturated aldehyde (Figure 2). Moreover, the α,β-unsaturated aldehyde was present in masked form as an isoxazoline (18), yielding aminol (19), upon reduction with lithium aluminium hydride. Successive treatment with potassium hydride, benzyl iodide, excess methyl iodide and aqueous p-toluenesulphonic acid yielded the spiroacetal northern hemisphere of milbemycin β_3 (Scheme 3).



Eqn.3.



Eqn.4



Eqn.5.

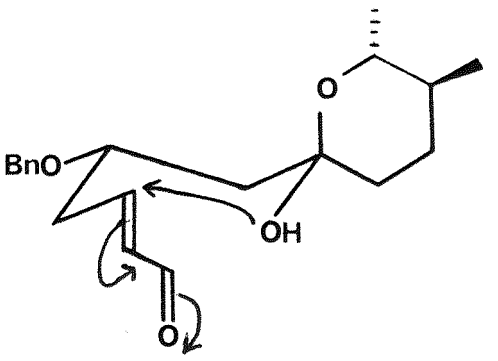
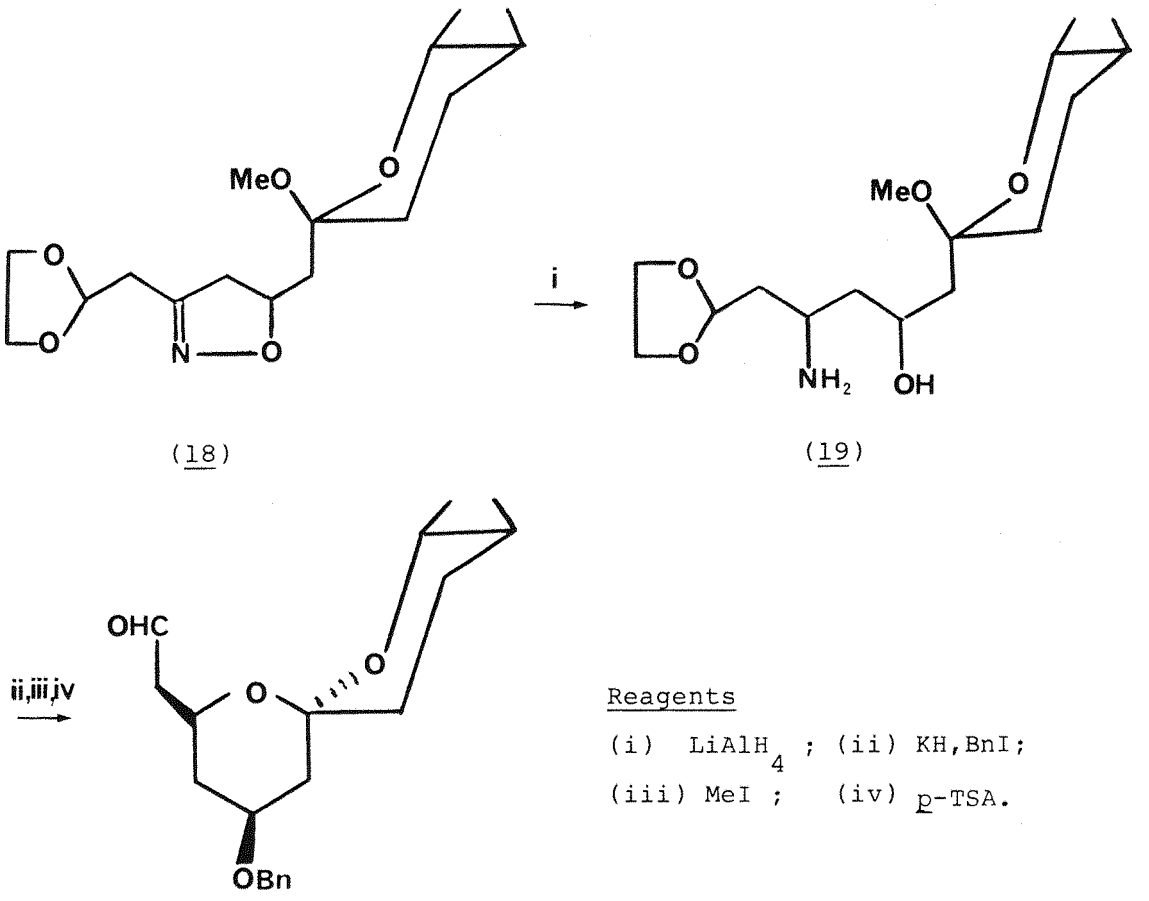


Figure 2



(18) (19)

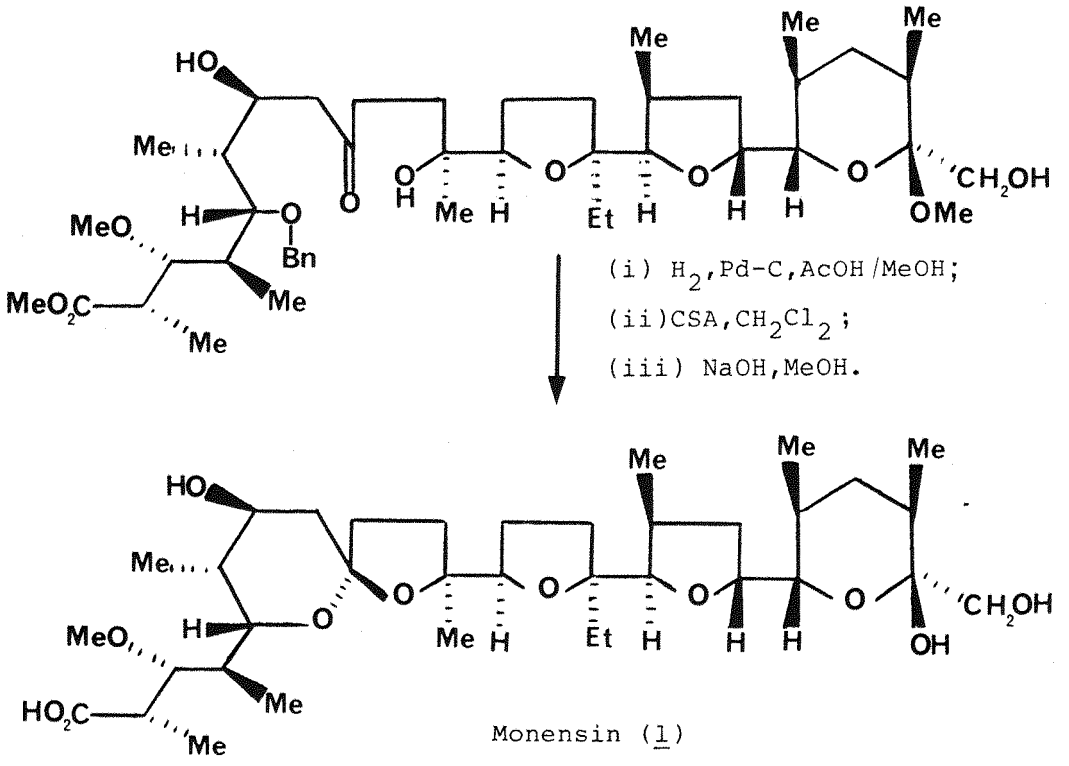
Reagents

(i) $LiAlH_4$; (ii) KH,BnI;

(iii) MeI ; (iv) p-TSA.

Scheme 3

Another approach to spiroacetals where the anomeric effect is used to control the stereochemistry at the spirocentre involves the intramolecular ketalization of a dihydroxyketone under thermodynamically controlled conditions[41-49]. Thus, the successful total synthesis of the polyether antibiotic monensin (1) was achieved by Kishi et al[41] incorporating a stereocontrolled ketalization as the key step (Scheme 4).

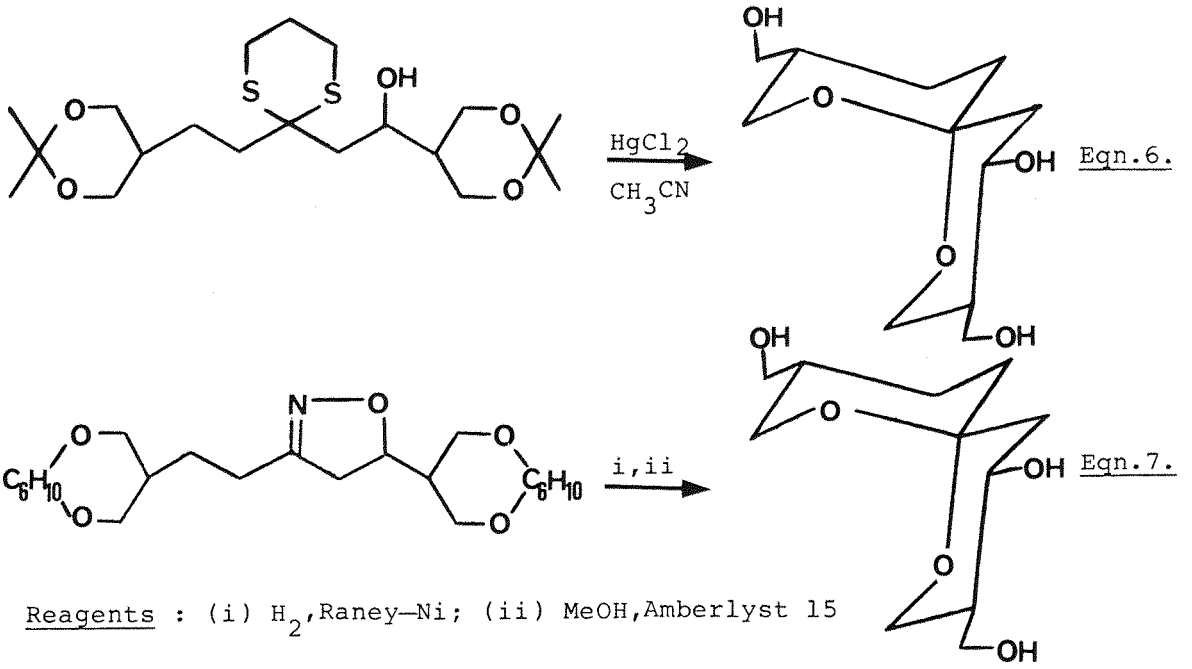


Monensin (1)

Scheme 4

Other systems have been designed to employ this spiroketalization reaction with the modification of a masked carbonyl group which is liberated in situ in the spirocyclization step. Thus, in the synthesis of (±)-talaromycin B using this approach, both a dithiane (Eqn.6)[48] and an isoxazoline (Eqn.7)[49] have been used as the latent carbonyl group.

An alternative route to spiroacetals developed by Ley et al[50,51] for use in the successful synthesis of the spiroacetal moiety of the milbemycins, involves the Horner-Wittig coupling of

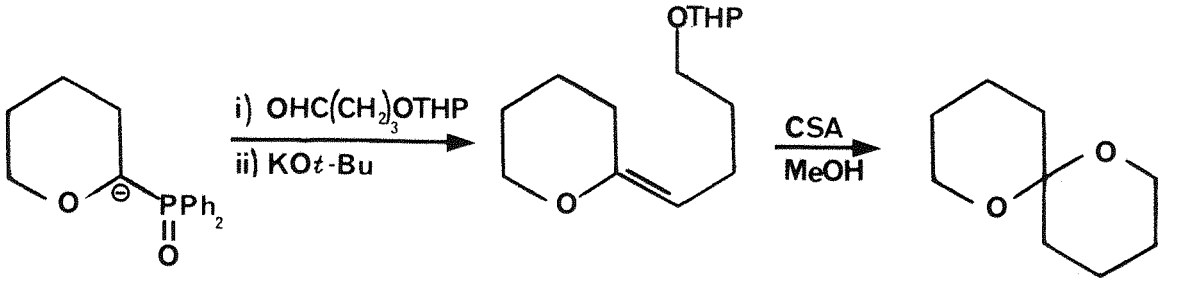


Eqn.6.

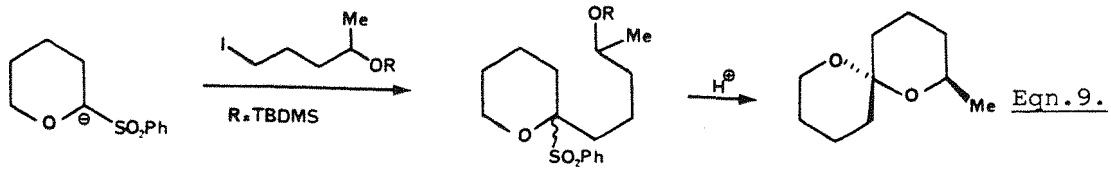
Eqn.7.

Reagents : (i) H_2,Raney—Ni; (ii) MeOH,Amberlyst 15

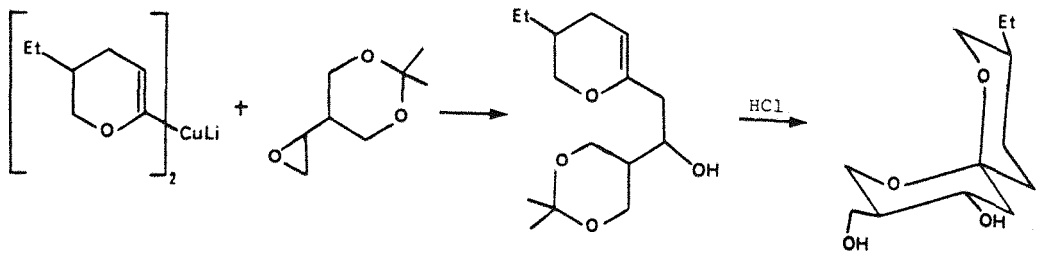
2-phosphinoxy cyclic ethers with either aldehydes or lactols, followed by acid catalysed spiroacetal formation (Eqn.8). Later, Ley and co-workers extended their strategy to include the use of a carbanion stabilized by an adjacent sulphoxide group to form the required carbon-carbon bond prior to cyclization (Eqn.9)[52]. Kocienski and Yeates[53,54] have also made use of a carbanion generated α to the oxygen of a cyclic ether to construct spiroacetals. Their strategy, used in the synthesis of (±)-talaromycin B, involves cleavage of a monosubstituted oxirane by an organocuprate and subsequent cyclization (Eqn.10).



Eqn.8.

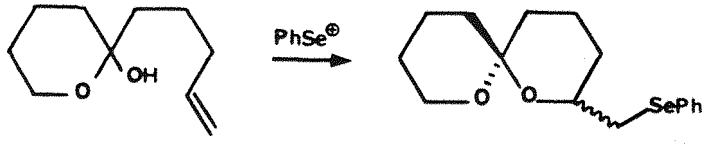


Eqn.9.

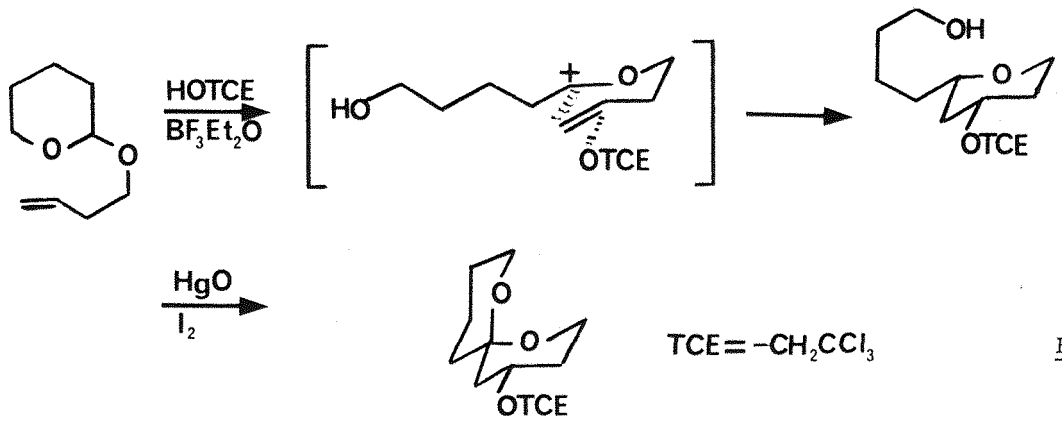


Eqn.10.

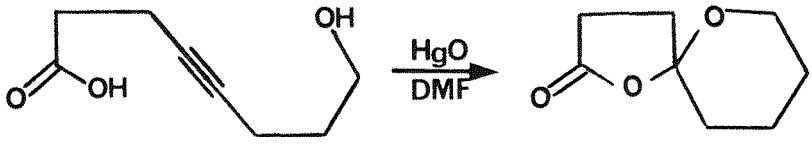
The use of carbon-carbon multiple bonds in the formation of spiroacetals has also been well realized. Thus, Ley et al[55] have developed the use of an organoselenium-mediated cyclization of an alkenyl hydroxyketone via its hemiacetal form (Eqn.11). A fundamentally different approach reported by Kay et al[56,57] proceeds via an intramolecular cation-olefin cyclization to give a substituted hydroxyspiroacetal which undergoes spirocyclization via its hypoiodite (Eqn.12). In addition to olefins, cyclization of alkynes have also provided a valuable path to spiroacetals (Eqn.13)[58].



Eqn.11.



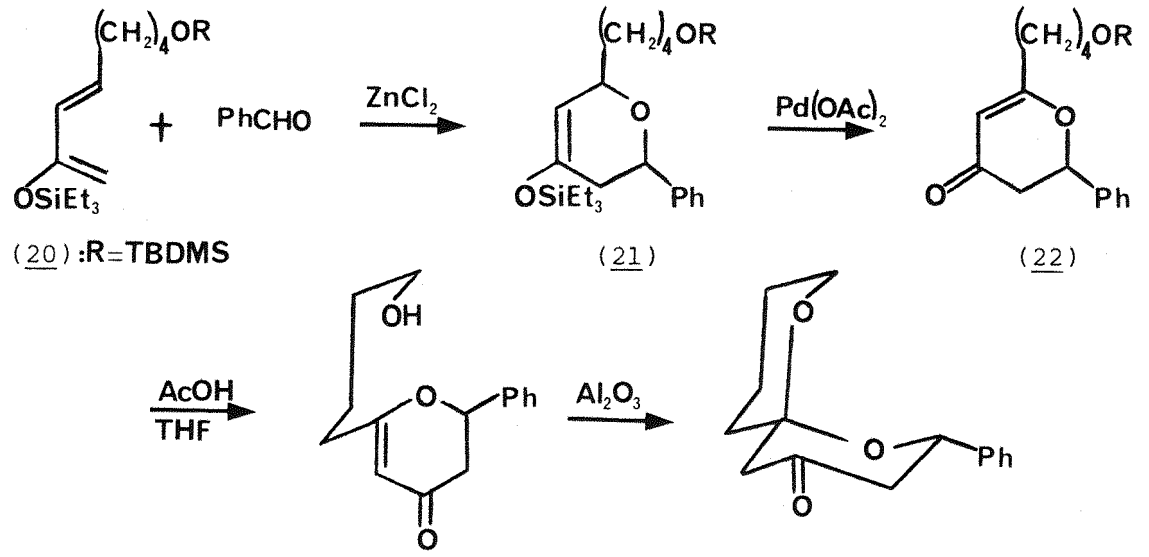
Eqn.12.



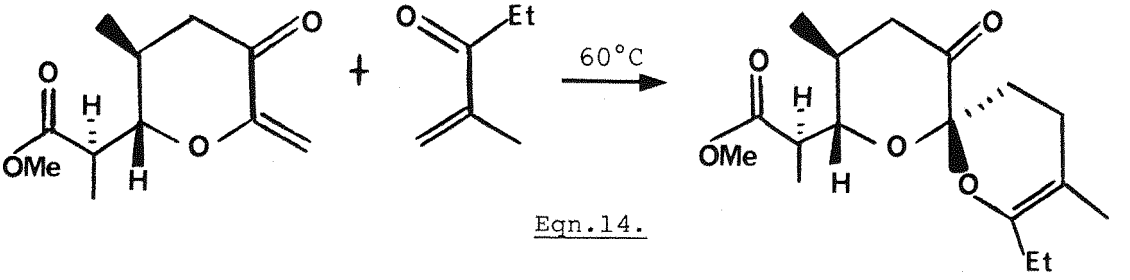
Eqn.13

The Diels-Alder reaction, a powerful synthetic tool in organic synthesis, has also proved most versatile in spiroacetal synthesis. In 1983, Danishefsky and Pearson[59] reported the facile cyclocondensation of the activated conjugated diene (20) with an aldehyde under the influence of a Lewis acid. The adduct (21), thus generated, was oxidized with palladium acetate yielding the dihydro-γ-pyrone (22). After desilylation, exposure to neutral alumina resulted in spiroacetal formation (Scheme 5). In the same year, Ireland *et al*[60,61] published a method for the preparation of spiroacetals *via* the inverse hetero-Diels-Alder cycloaddition of a keto-enol ether to an α,β-unsaturated ketone (Eqn.14). This elegant method provided a useful entry into macrolide total synthesis by thioketal exchange of a key intermediate spiroacetal to the desired open chain derivative and subsequent elaboration to the required macrolide[61].

Whilst this is not a comprehensive review of bicyclic spiroacetal formation, the synthetic methods described above emphasize the increasing interest in a rapidly developing field. Recent developments include the enantioselective synthesis of 1,7-dioxaspiro[5.5]undecane (23) *via* asymmetric induction in an intra-



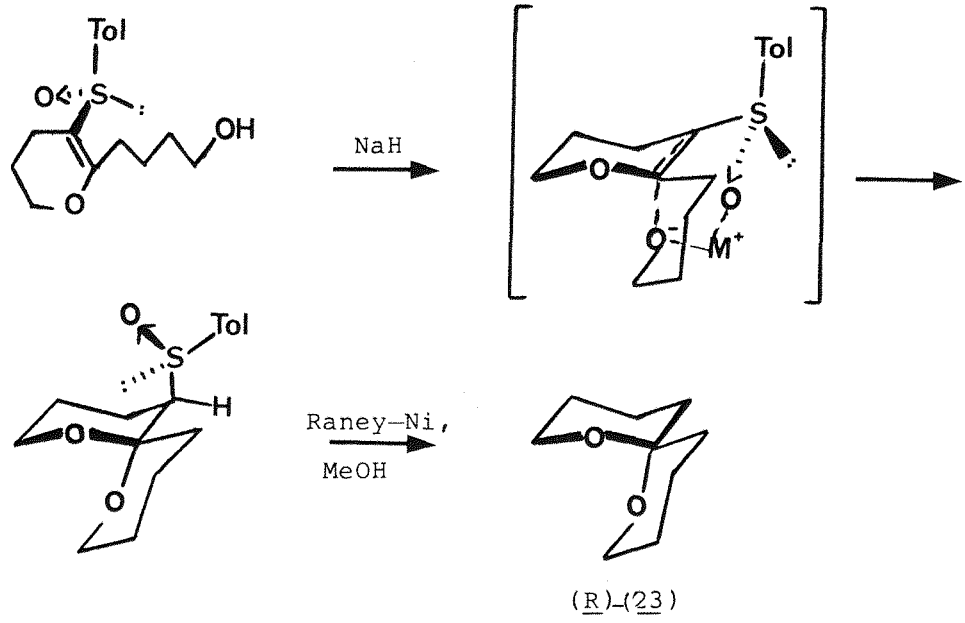
Scheme 5



Eqn.14.

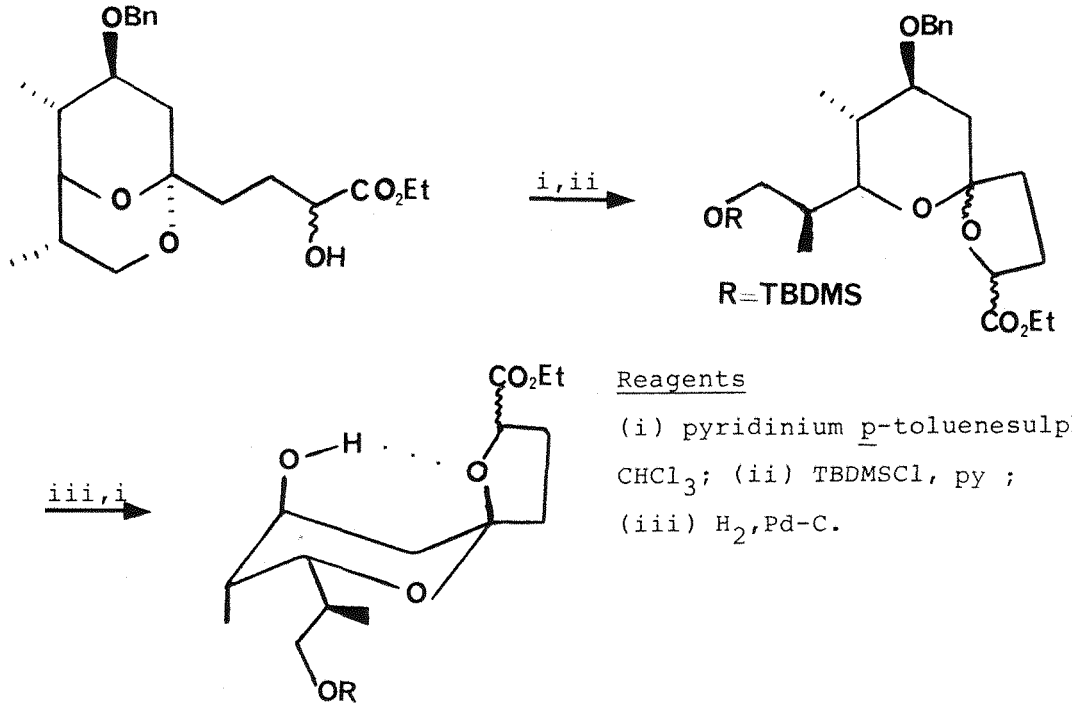
molecular Michael addition of an hydroxyl group to a chiral vinylic sulphoxide (Scheme 6)[62] and the synthesis of the monensin spiroacetal from a bicyclic acetal (Scheme 7)[63]. In contrast to their bicyclic analogues, the tricyclic spiroacetals have generated comparatively little interest to date.

In 1963, Ponomarev and Markushina[64] reported the first preparation of a tricyclic spiroacetal. They constructed the novel 1,6,8-trioxadispiro[4.1.4.2]tridec-13-ene ring system (24) via an electrolytic alkoxylation using a nickel cathode and a carbon anode. (Scheme 8). The reaction was later ascertained to be trans stereoselective based on dipole moment measurements on the unsubstituted bis-spiroacetal[65].



(R)-(23)

Scheme 6

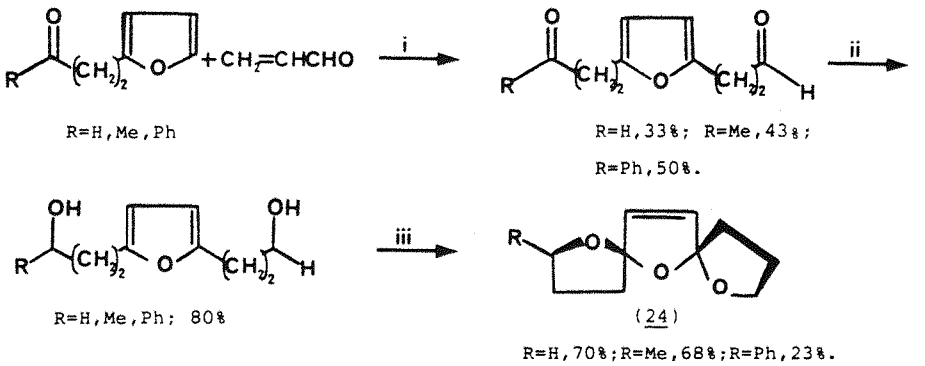


Reagents

(i) pyridinium p-toluenesulphonate, $CHCl_3$; (ii) TBDMSCl, py ;

(iii) H_2,Pd-C.

Scheme 7

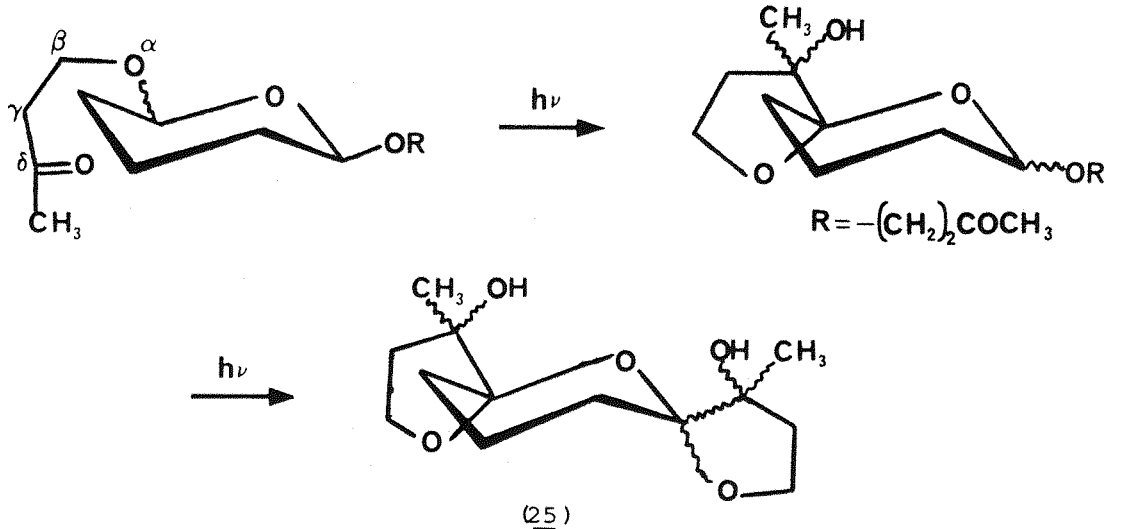


Reagents

(i) $H^{\oplus}$, 100-130°C,2-5h.; (ii) H_2,Cu chromite,120°C/130atm.,EtOH;
(iii) Ni cathode, C anode, $NH_4^{\oplus}\ Br^{\ominus}$, MeOH.

Scheme 8

Over a decade later, Descotes et al[66] described the photolytic preparation of a second bis-spiroacetal, namely, 4,11-dimethyl-1,6,8-trioxadispiro[4.1.4.3]-4,11-tetradecanediol (25). Extension of their existing methodology[67] for construction of bicyclic spiroacetals, using a Norrish type II reaction applied to a tetrahydropyranic keto-acetal bearing a carbonyl group at the position δ to the acetalic hydrogen, enabled them to synthesize the corresponding tricyclic spiroacetals (Eqn.15).



(25)

Eqn.15

Initially no effort was made to improve the stereoselectivity of the reaction and all six possible bis-spiroacetals were isolated (Scheme 9). Note that isomer (25b) is superimposable with isomer (25f) and that isomers (25c) and (25g) are enantiomers. Spectroscopic studies[66,68] combined with X-ray crystallography[69] established that in all six diastereomers the two C-O bonds of the tetrahydrofuran ring adopt an axial position. For isomers (25a), (25b), and (25e) this necessitates the tetrahydropyran ring to adopt a skew boat conformation not only to minimize the unfavourable steric interactions which would occur if a chair conformation were adopted but also to gain stability from a second stabilizing anomeric effect (Figure 3).

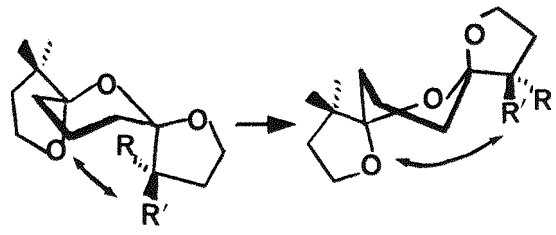
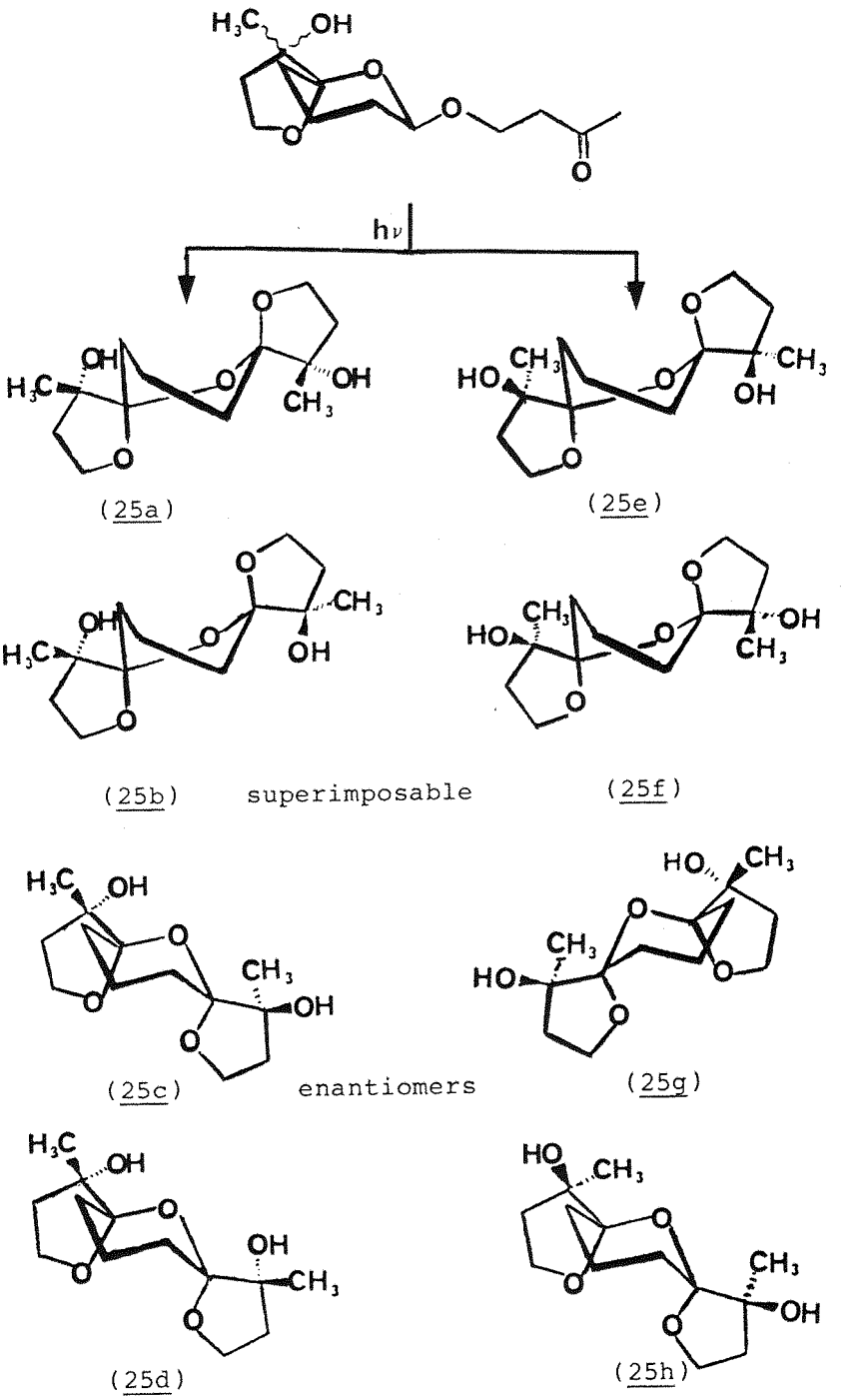


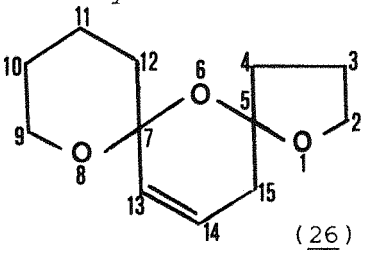
Figure 3

Recently, Cottier and Descotes[70] investigated the improvement of the stereoselectivity of the bis-spiroacetal forming reaction under thermodynamic conditions using acid catalysed isomerisation. Subsequent treatment of isomers (25a), (25c), and (25e) with camphorsulphonic acid in dichloromethane gave mainly isomer (25c) whilst the remaining isomers (25b), (25d), and (25h) yielded a mixture containing mainly isomers (25d) and (25h) in equal quantities. Thus, acid catalysed equilibration of the bis-spiroacetals isolated initially, results in a mixture in which the isomers (25c), (25d), and (25h), wherein the two C-O bonds of the tetrahydrofuran ring occupy axial positions and the tetrahydropyran ring adopts a chair conformation, predominate. On the other hand, treatment of the bis-spiroacetals (25a-h) with a mixture of aluminium chloride and aluminium acetate gave predominantly isomer (25d).


hν
(25a)
(25e)
(25b)
superimposable
(25f)
(25c)
enantiomers
(25g)
(25d)
(25h)

Scheme 9

At the outset of this work, no methodology existed for the construction of the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system (26) incorporated in the polyether antibiotics salinomycin (7), epi-17-deoxy-(O-8)-salinomycin (8), narasin A (10), narasin B (11) noboritomycin A (12), noboritomycin B (13), CP44,161 (14) and X-14766A (15). Furthermore, this novel ring system presented an interesting synthetic target in that the existing syntheses of bis-spiroacetals were not directly applicable. Thus, with a view to achieving the total synthesis of the polyether antibiotics in the salinomycin series, attention was focussed on the synthesis of the novel bis-spiroacetal moiety.

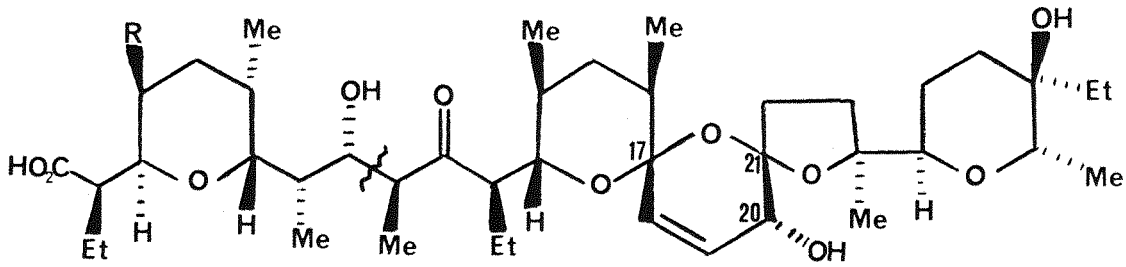


(26)

1.5 The Total Synthesis of Salinomycin and Narasin

During the course of this work, Kishi et al[71] reported the total synthesis of the polyether antibiotics salinomycin and narasin. The first step in their retrosynthesis was the crossed aldol reaction (step (a), Scheme 10), the feasibility of which was well demonstrated in the synthesis of lasalocid A (4)[72,73,74]. The right half (27) was then assumed to be synthetically equivalent to its open form (28) which itself was envisaged to be assembled from the three building blocks (29), (30),and (31).

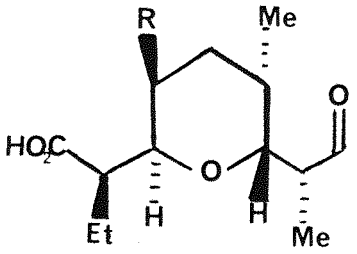
The tetrahydropyran ring of the left half of salinomycin (32) was constructed via cyclization of the monomesylate (34) using potassium hydride (Eqn.16). The analogous cyclization of the monomesylate (35) for the narasin series, however, resulted mainly in elimination to the olefins (36) using a variety of basic and thermal conditions (Eqn.17). This was attributed to steric effects since in both conformations of the tetrahydropyran ring in the narasin series (37A, 37B), two out of the four substituents must adopt axial



Salinomycin (7):R=H

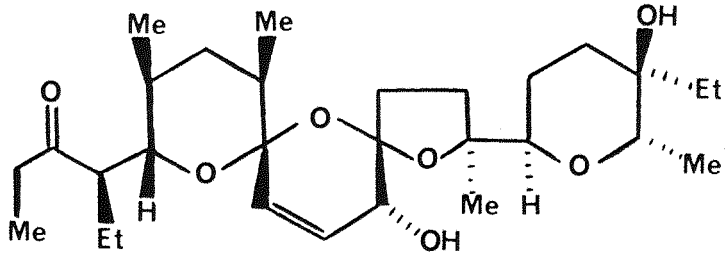
Narasin (10) :R=Me

a

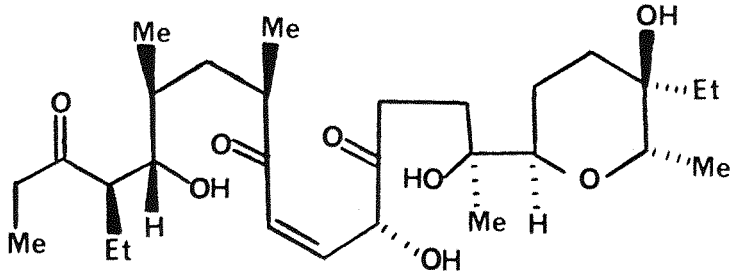


(32):R=H

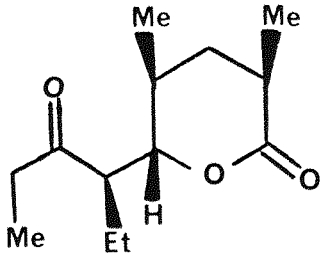
(33):R=Me



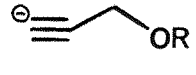
(27)



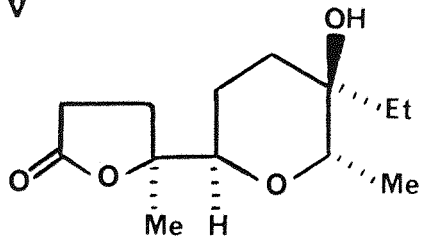
(28)



(29)



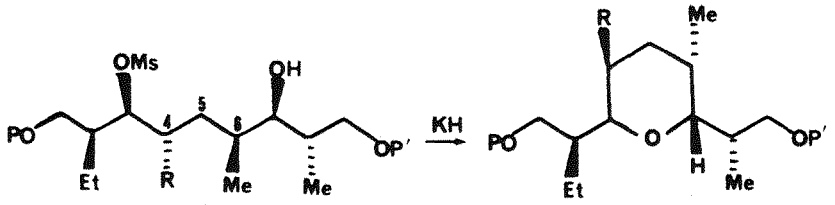
(30)



(31)

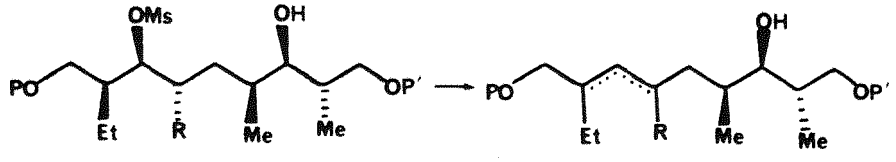
Scheme 10

positions resulting in steric compression whereas in the salinomycin case, one of the conformations,(38B),has only one substituent in an axial position. Thus, the transition state leading to conformation (38B) is sterically less crowded than that leading to conformation (37B) and hence smooth cyclization was observed in this case (Figure 4).



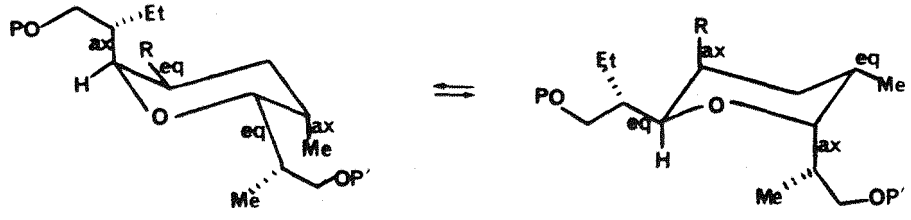
(34):R=H,P=$Me_3CC(O)$,P'=$-CH_2OMe$ (38):R=H

Eqn.16



(35):R=Me (36):R=Me

Eqn.17

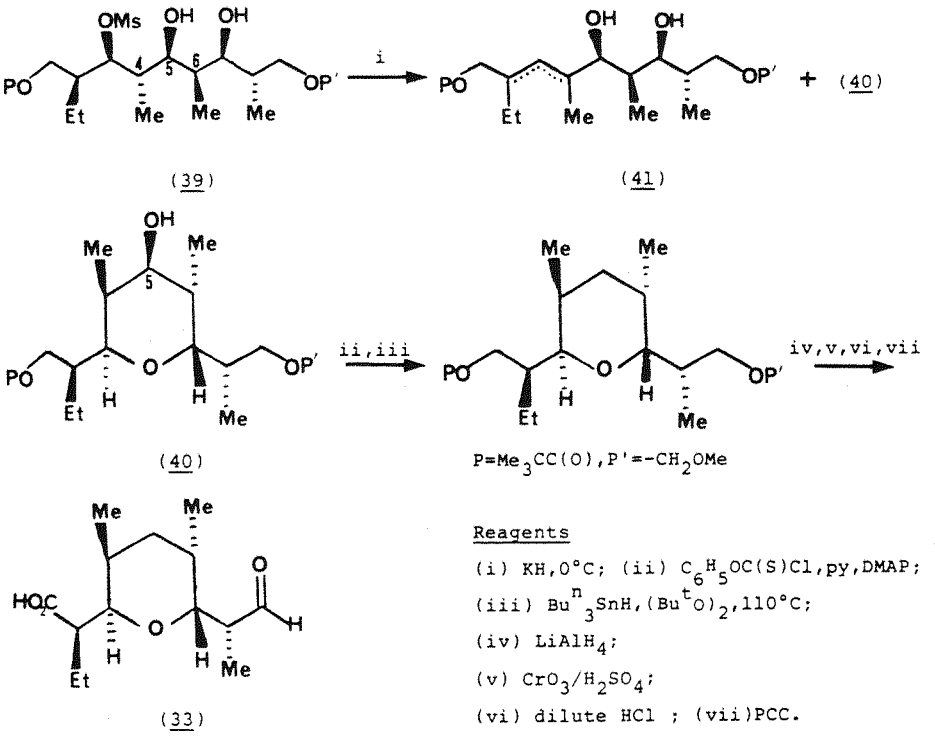


(37A):R=Me;(38A):R=H (37B):R=Me; (38B):R=H

Figure 4

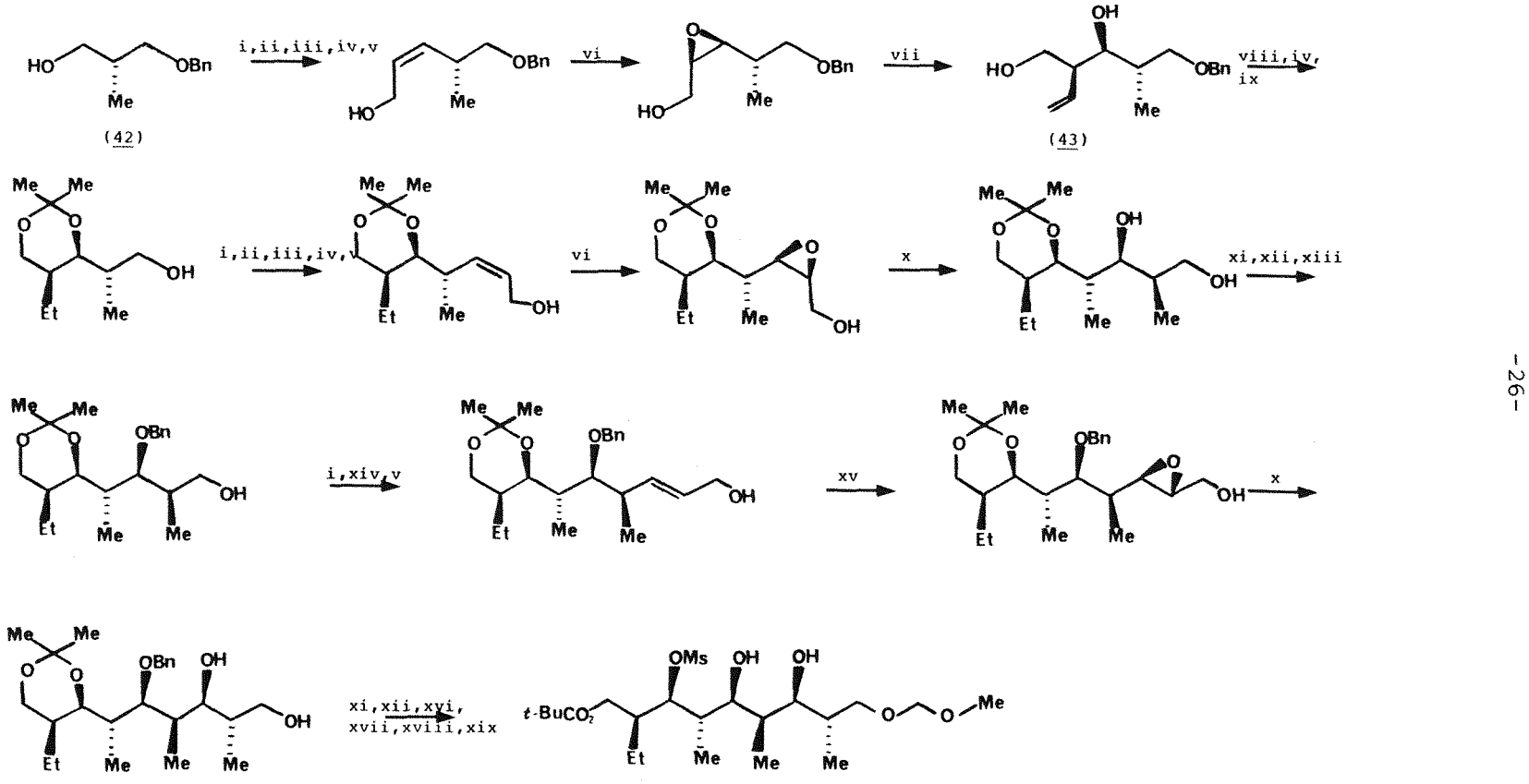
A dramatic improvement in the efficiency of the cyclization for the narasin series was achieved by the introduction of an hydroxyl group at C-5 (Scheme 11). In this case, treatment of the monomesylate (39) with potassium hydride at 0°C gave the required tetrahydropyran

(40) in 45% yield. This improvement was attributed to the C-5 hydroxyl group which existed as an alkoxide group under the reaction conditions thereby discouraging deprotonation at the C-4 position leading to one of the olefins (41). Reductive removal of the C-5 hydroxyl group followed by selective removal of the protecting groups and subsequent oxidation to the required oxidation state yielded the required left half of narasin (33). These latter steps were also used for the conversion of tetrahydropyran (38) into the left half of salinomycin (32).



Scheme 11

The cyclization precursor for the synthesis of the left half of narasin, namely, monomesylate (39), was assembled via a series of chain extension steps (Scheme 12). Thus, repetition of the reactions (with slight modification in each case) used for the conversion of alcohol (42)



Reagents

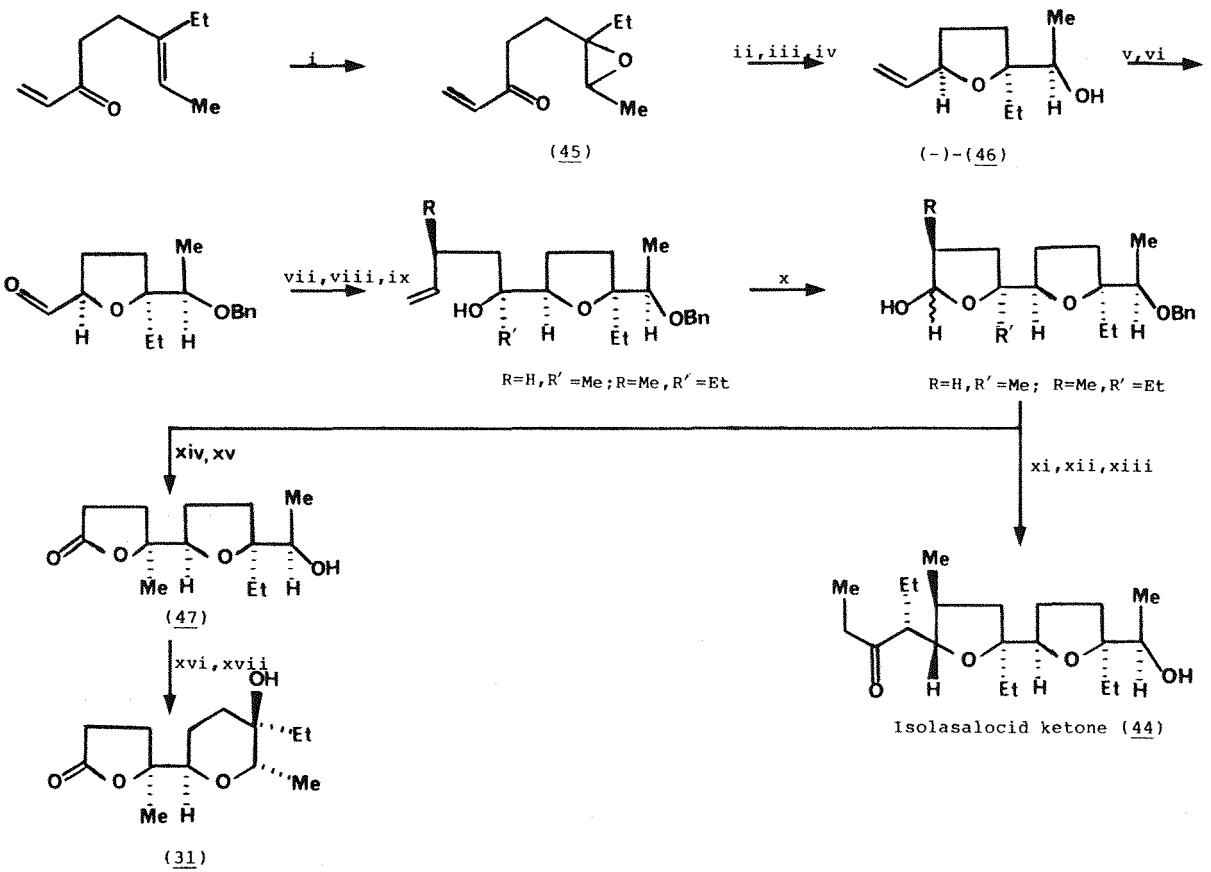
(i) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C, then Et_3N ; (ii) CBr_4, PPh_3, 0°C ; (iii) Bu^nLi, THF, -78°C, then $ClCO_2Me$;
(iv) H_2, Lindlar catalyst ; (v) DIBAL, CH_2Cl_2, -78°C; (vi) m-CPBA, CH_2Cl_2, -78°C ; (vii) CH_2=CHMgBr, CuI, Et_2O, -40°C;
(viii) $MeC(OMe)_2$, acetone, CSA; (ix) Li, liq.NH_3/THF ; (x) $LiCuMe_2$, Et_2O, -40°C ; (xi) $MeOCH_2Br$, Pr^i_2EtN, CH_2Cl_2, 0°C ;
(xii) BnBr, KH, DMF/THF, 0°C ; (xiii) 1% HCl, MeOH, Δ ; (xiv) Ph_3P=$CHCO_2Et$, $ClCH_2CH_2Cl$, Δ ;
(xv) Bu^tOOH, $Ti(OPr^i)_4$, D-(-)-diethyl tartrate , CH_2Cl_2, -23°C ; (xvi) aq.AcOH, THF, 50°C ; (xvii) $Me_3CC(O)Cl$, py ;
(xviii) Ms_2O ,py,DMAP, CH_2Cl_2,R.T., (xix) H_2,Pd-C,MeOH.

Scheme 12

to diol (43) yielded the required unit (39). The new chiral centres in each case were introduced by stereoselective epoxidation of an allylic alcohol followed by nucleophilic opening of the epoxide by an organocuprate reagent. The precise details for the monomesylate precursor (34) to the left half of salinomycin were not reported.

Focussing next on the right half of salinomycin and narasin (27), Kishi assembled the right segment, namely, lactone (31), enantioselectively, using the method adopted for the synthesis of isolasalocid ketone (44)[73] (Scheme 13). The key steps were the stereoselective tandem reduction and cyclization of keto-epoxide (45) to tetrahydrofuran (46) and the ring expansion of the tetrahydrofuran (47) into the tetrahydropyran (31). The lactone (31) was then converted in three steps to the dithiane (48) ready for the critical carbon-carbon bond forming reaction with aldehyde (49) (Scheme 14).

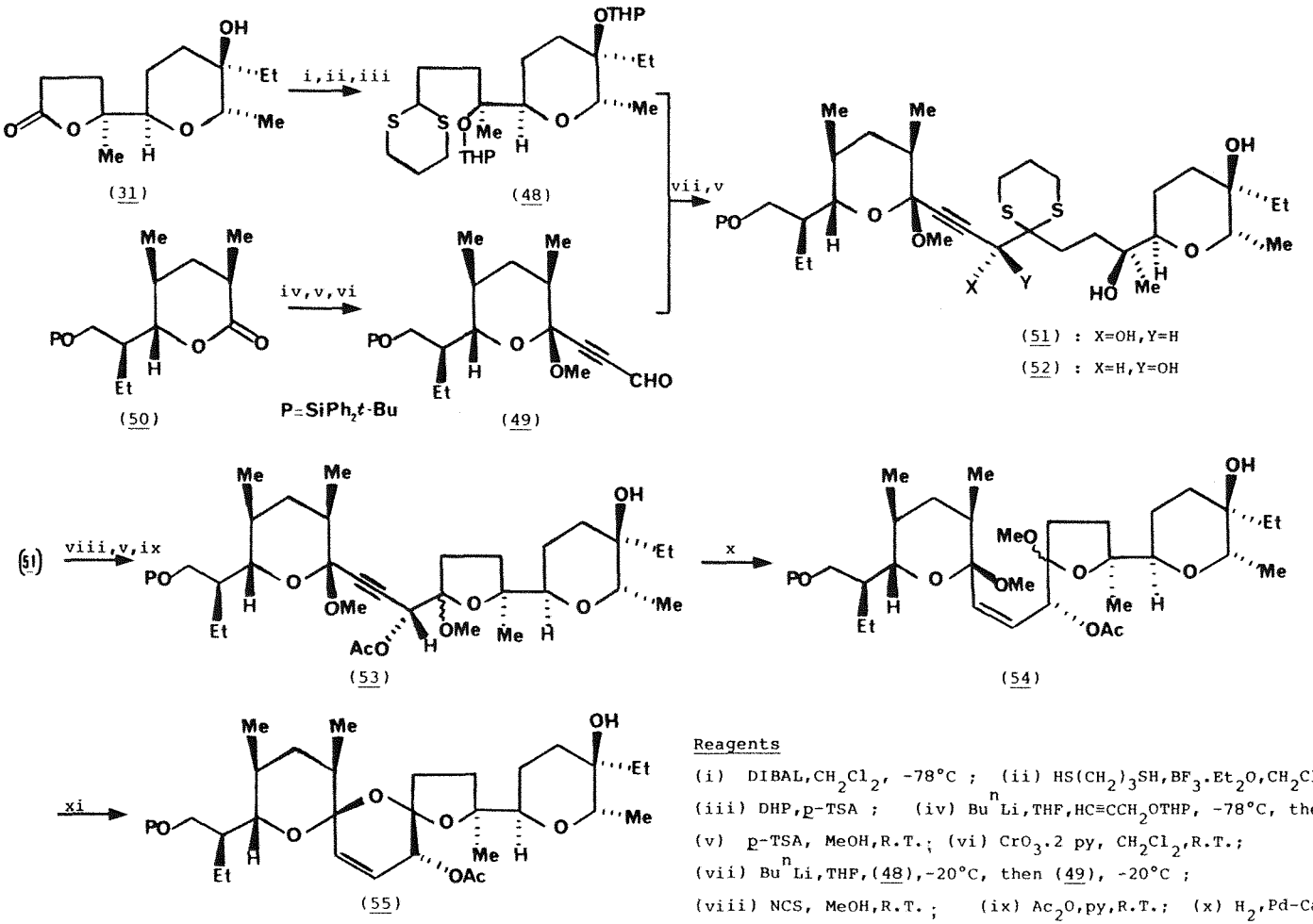
Meanwhile, lithium acetylide (30) was reacted with a synthon for the left hand building block (29), namely, lactone (50), yielding aldehyde (49) after treatment with acid in methanol followed by oxidation. No details for the synthesis of lactone (50) were reported. The C-20~C-21 bond was then formed by reaction of the anion of dithiane (48) with the aldehyde (49) at -20°C. Subsequent hydrolysis of the tetrahydropyranyl group yielded the desired alcohol (51) (37% yield) and the undesired alcohol (52) (48% yield). Dethioketalization of the desired alcohol (51) followed by intramolecular ketalization and acetylation yielded the acetate (53) in 61% yield. Catalytic hydrogenation of the acetylenic bond to the (Z)-olefin (54) followed by intramolecular ketalization in aqueous acetic acid provided the bis-spiroacetal (55) in 45% yield with the same stereochemistry as that found in epi-17-deoxy-(O-8)-salinomycin (8). Bis-spiroacetal (55) was then successfully converted to the protected right half of epi-17-salinomycin (56) in several steps (Scheme 15).



Reagents

(i) epoxidation ; (ii) $LiAlH_4$, dl-2-(o-2-toluidinomethyl)pyrrolidine, Et_2O, -78°C; (iii) AcOH,R.T.; (iv) resolution ; (v) BnBr,NaH ; (vi) O_3 ; (vii)  MgBr,THF ; (viii) CrO_3/H_2SO_4; (ix) RMgBr, Et_2O ; (x) O_3, Me_2S ; (xi) $MeCH_2C(O)CHBrEt$, Mg; (xii) p-TSA, benzene, Δ ; (xiii) H_2, Pd-C ; (xiv) oxidation; (xv) debenzylation ; (xvi) MsCl,py ; (xvii) Ag_2CO_3, acetone, Δ .

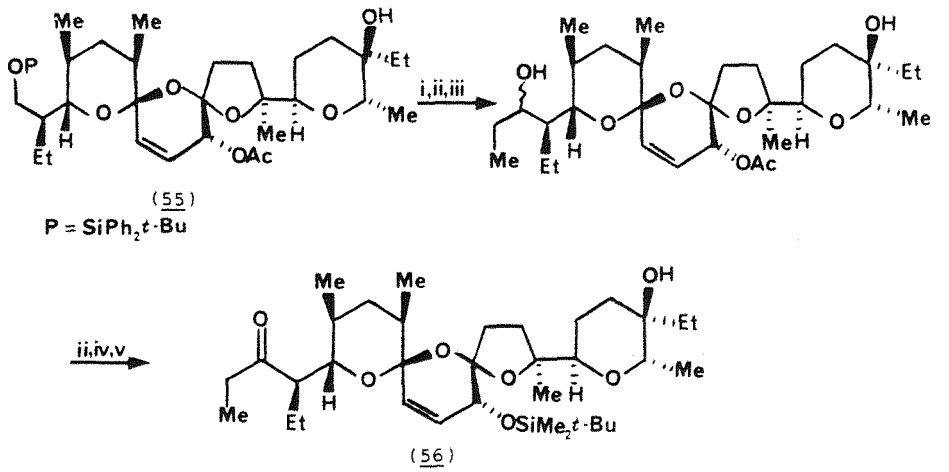
Scheme 13



Reagents

(i) DIBAL,CH_2Cl_2, -78°C ; (ii) $HS(CH_2)_3SH$,$BF_3.Et_2O$,CH_2Cl_2,-10°C;
(iii) DHP,p-TSA ; (iv) Bu^nLi,THF,$HC{\equiv}CCH_2OTHP$, -78°C, then (50),-78°C;
(v) p-TSA, MeOH,R.T.; (vi) CrO_3.2 py, CH_2Cl_2,R.T.;
(vii) Bu^nLi,THF,(48),-20°C, then (49), -20°C ;
(viii) NCS, MeOH,R.T.; (ix) Ac_2O,py,R.T.; (x) H_2,Pd-$CaCO_3$/
$Pb(OAc)_2$,MeOH,R.T.; (xi) 80% aq.AcOH,R.T.

Scheme 14



(56)

Reagents

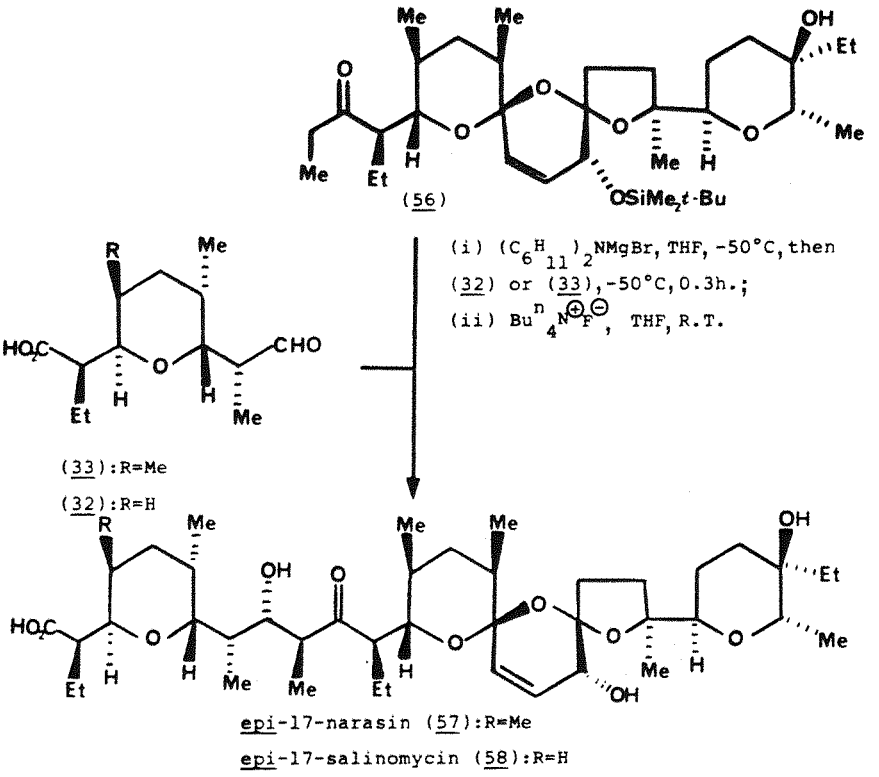
(i) $Bu^n_4N^{\oplus}F^{\ominus}$, THF,R.T.; (ii) CrO_3.2py,CH_2Cl_2,R.T. ; (iii)EtMgBr, Et_2O,-40°C ; (iv) K_2CO_3,MeOH,R.T.; (v) TBDMSCl,DMAP,DMF,80°C.

Scheme 15

With the left and right halves in hand,the crossed aldol condensation was then realized. The optimum conditions, using dicyclohexylamidomagnesium bromide as the base, gave the single required aldol product in 58% yield after desilylation (Scheme 16). Thus, depending on which aldehyde was used, the synthesis of epi-17-narasin (57) or epi-17-salinomycin (58) was complete.

The final step in the synthesis involved isomerization of the bis-spiro system, effected by the treatment of epi-17-narasin (57) or epi-17-salinomycin (58) with a small amount of trifluoroacetic acid in dichloromethane in the presence of molecular sieves at room temperature (Scheme 17) to yield a 7:1 mixture of narasin (10) : epi-17-narasin (57) (or salinomycin (7):epi-17-salinomycin (58)).

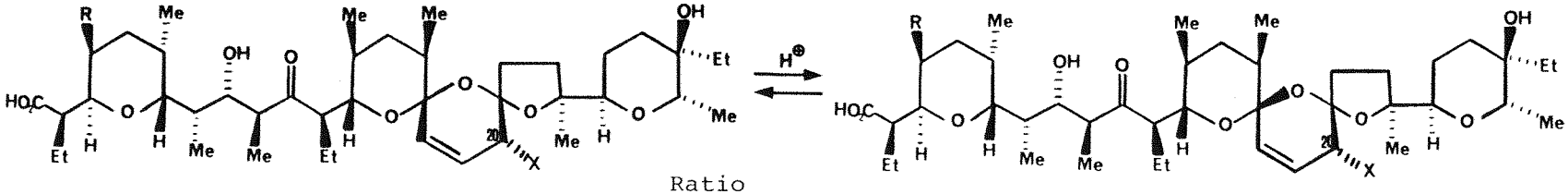
Kishi et al[71] have made an important observation about the thermodynamic stability of the bis-spiro system. Variation in the substituent at the C-20 position was found to influence the stereochemistry at C-17. Thus, in sharp contrast to the results for narasin and salinomycin, narasin acetate (59) and salinomycin



Scheme 16

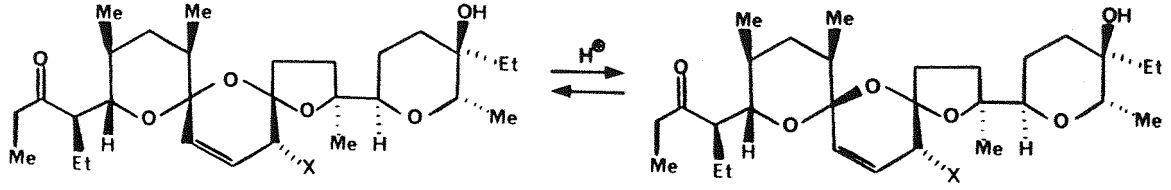
acetate (60) isomerized exclusively upon treatment with camphorsulphonic acid in acetonitrile to epi-17-narasin acetate (61) and epi-17-salinomycin acetate (62), respectively (Scheme 17). These results were attributed to hydrogen bond stabilization in the case of narasin and salinomycin between the hydroxyl group at C-20 and a remote position. Examination of the corresponding ketone series (Scheme 18) supported this hypothesis. Thus, in contrast to the antibiotic series (Scheme 17) both keto-alcohol (27) and keto-acetate (63) equilibrated under acidic conditions to give predominantly the bis-spiro system with the same stereochemistry as that found in epi-17-narasin (57) and epi-17-salinomycin (58).

The only total synthesis of salinomycin to date is that reported by Kishi et al[71]. However, a variation in the construction



	Ratio	
Narasin (10):X=OH,R=Me	7 > 1	epi-17-Narasin (57):X=OH,R=Me
Salinomycin (11):X=OH,R=H	7 > 1	epi-17-Salinomycin (58):X=OH,R=H
Narasin acetate (59):X=OAc,R=Me	0:100	epi-17-Narasin acetate (61),X=OAc,R=Me
Salinomycin acetate (60):X=OAc,R=H	0:100	epi-17-Salinomycin acetate (62):X=OAc,R=H

Scheme 17

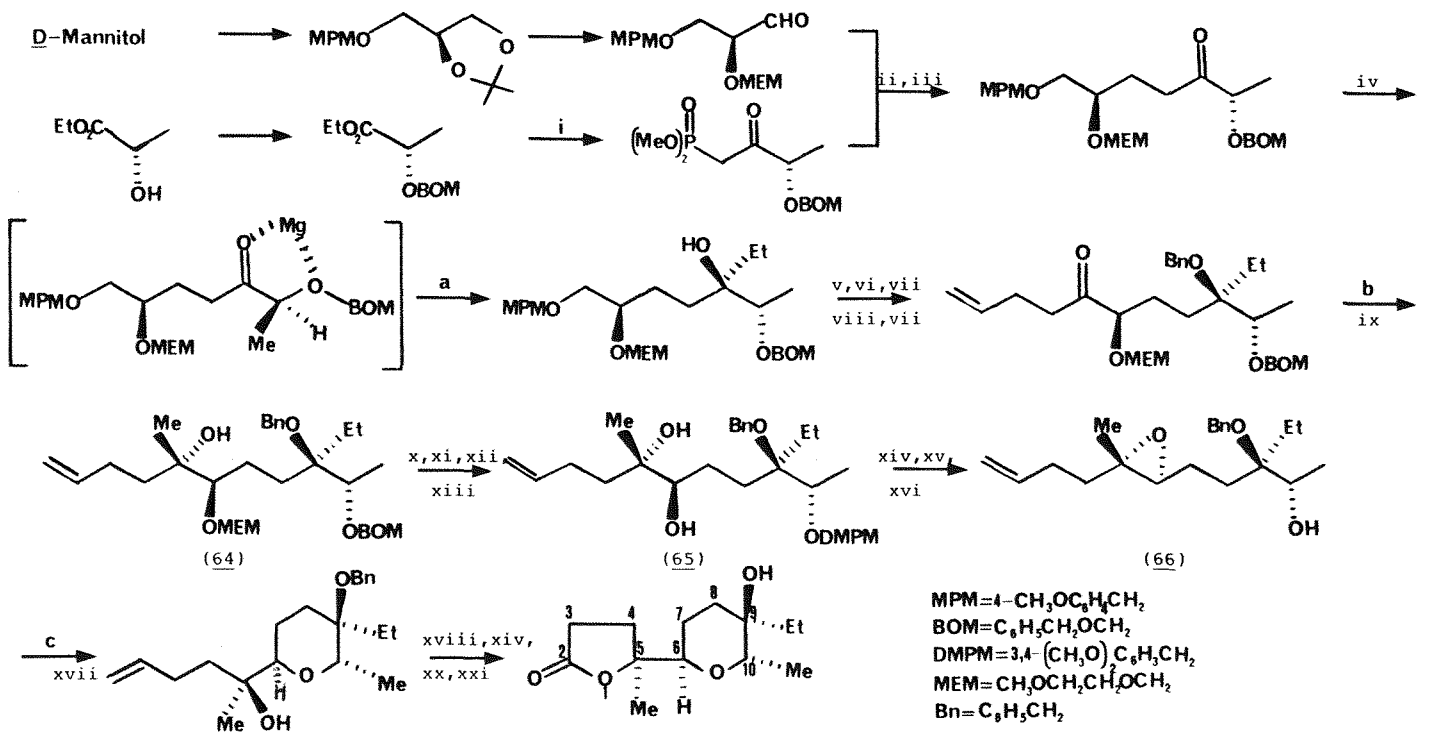


	Ratio
(27):X=OH	1:4
(63):X=OAc	0:10

Scheme 18

of the lactone segment (31) required for the right half of salinomycin has recently been reported by Yonemitsu *et al*[75] starting from D-mannitol and ethyl L-lactate. The synthetic strategy rested on the construction of two 1,2-diol systems at C-5~C-6 and C-9~C-10 using the chelation controlled Grignard reaction of acyclic α-alkoxyketones established by Still and McDonald[76], (steps (a),(b); Scheme 19). The stereoselection observed in both cases was greater than 100:1. Simple manipulation of the protected alcohol (64) to the vicinal diol (65) and hence to the epoxyalcohol (66) set up the introduction of the tetrahydropyran ring *via* acid catalysed cyclization (step (c), Scheme 19). Finally, oxidation of the alkene (67) to the diol, deprotection of the tertiary alcohol, periodate oxidation of the vicinal diol to the lactol and subsequent oxidation, yielded the required lactone (31).

Whilst the disconnection of the right half of salinomycin (27) into the three building blocks (29), (30), and (31) (Scheme 10 page 23) formed the basis for Kishi's synthesis of salinomycin, nevertheless, alternative disconnections may unveil other possibilities for the construction of the bis-spiroacetal system.



Reagents

(i) $(MeO)_2P(O)CH_3$, Bu^nLi, THF, -78°C ; (ii) NaH, THF, 0°C ; (iii) H_2,Pd-C,EtOAc,R.T. ; (iv) EtMgBr,THF,-78°C,1.5h.,100%;
(v) NaH,BnBr,DMF/THF ; (vi) DDQ, R.T., 2h.; (vii) DMSO, $(COCl)_2$, CH_2Cl_2, -60°C, ; (viii) $CH_2=CHCH_2CH_2MgBr$,THF,0°C;
(ix) MeMgBr,THF, -78°C, 94% ; (x) 4M HCl/THF (1:3), 50°C ; (xi) p-$MeOC_6H_4C(Me)(OMe)_2$,CSA,CH_2Cl_2,R.T.;
(xii) NaH, DMPMCl, DMSO/THF (1:3), R.T.; (xiii) 1M HCl/THF (1:3), 50°C ; (xiv) MsCl,Et_3N, 0°C ; (xv) K_2CO_3,MeOH, R.T.;
(xvi) DDQ, CH_2Cl_2/H_2O (20:1), 0°C ; (xvii) CSA, CH_2Cl_2,0°C ; (xviii) OsO_4, acetone/H_2O (2:1), R.T., ;
(xix) H_2,Pd-C,EtOH,R.T.; (xx) $NaIO_4$, THF/H_2O (1:4), R.T. ; (xxi) PCC, CH_2Cl_2, R.T.

Scheme 19

CHAPTER 2

CONSTRUCTION OF THE 1,6,8-TRIOXADISPIRO[4.1.5.3]-PENTADEC-13-ENE RING SYSTEM

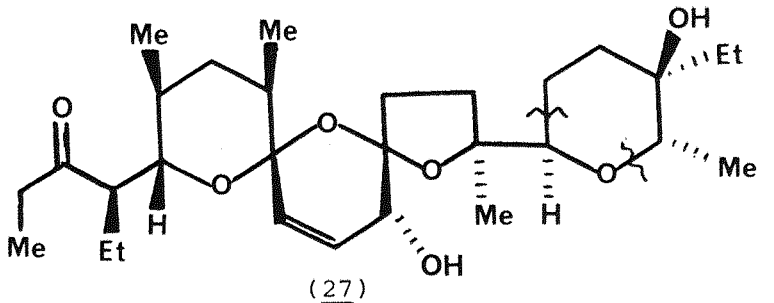
2.1 Retrosynthesis and the Proposed Synthetic Strategy

Kishi's strategy for the synthesis of the right half of salinomycin (27) rested on the stepwise assembly of the three rings of the tricyclic spiroacetal ring system. Adoption of an alternative retrosynthesis for the same right half of salinomycin (27) generated the idea of constructing the bis-spiroacetal system *via* a stereocontrolled intramolecular cyclization (Scheme 20).

Hence the right half of salinomycin (27) can be further disconnected to a bis-spiroacetal moiety (68) and an alkene (69). This was based on the chemistry developed in the synthesis of isolasalocid ketone[72] (Scheme 13, page 28) for the stereocontrolled conversion of a γ-δ-unsaturated ketone to a tetrahydrofuran and subsequent ring expansion to a tetrahydropyran. Thus, nucleophilic addition of the Grignard reagent derived from the alkene (70) to the aldehyde derived from the bis-spiroacetal moiety (71) , followed by oxidation, yields the γ-δ-unsaturated ketone (72) which upon conversion to keto-epoxide (73) may undergo reductive-cyclization to the tetrahydrofuran (74) and finally ring expansion to the tetrahydropyran (75) (Scheme 21).

In turn, the bis-spiroacetal moiety (68) was envisaged to be assembled via a stereocontrolled intramolecular cyclization of the hemiacetal keto-epoxide (76). The cyclization precursor could then be derived from a lactone (77) and a synthon of the acetylene (78).

In order to demonstrate the synthetic feasibility of the proposed intramolecular cyclization, attention was initially directed to the preparation of the model 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system (26) adopting this approach. Thus, it was anticipated that



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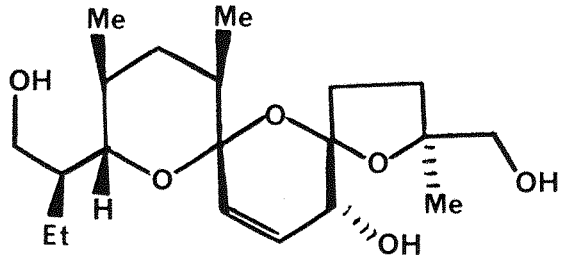
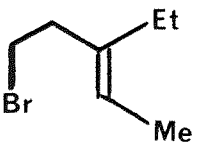
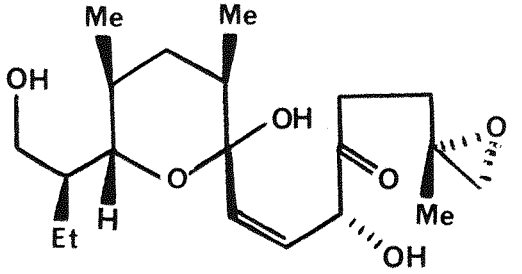


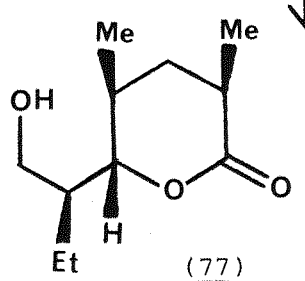
(68)



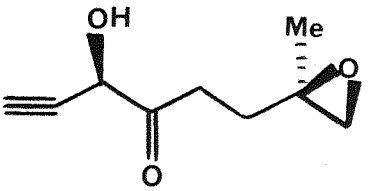
(69)



(76)

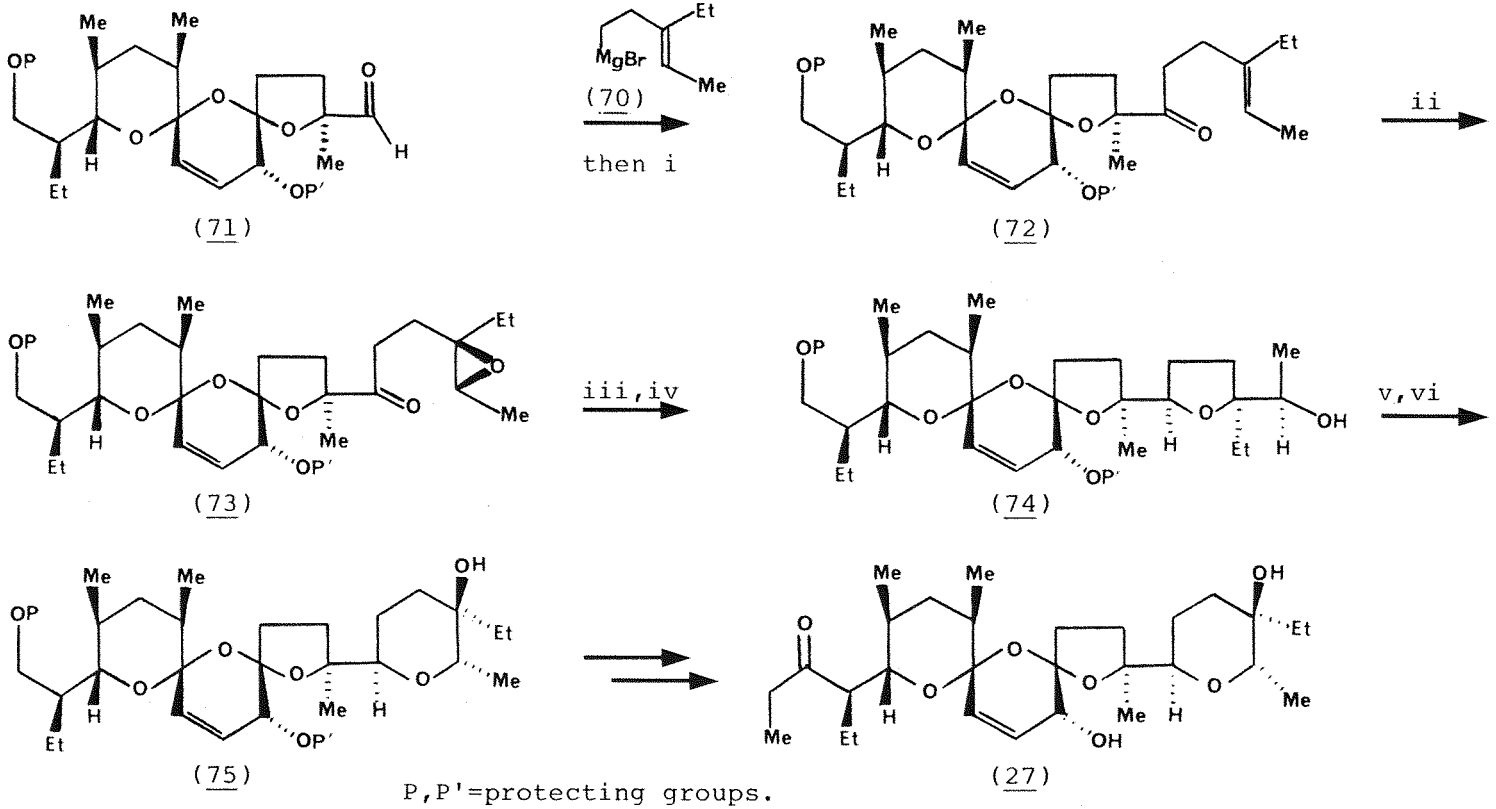


(77)



(78)

Scheme 20



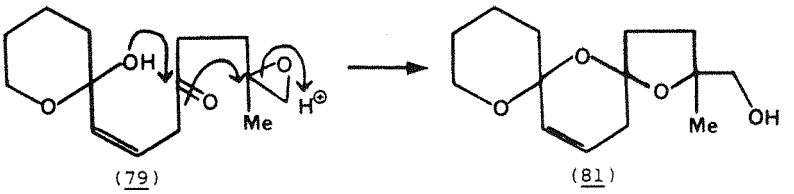
P,P'=protecting groups.

Reagents

(i) oxidation ; (ii) epoxidation ; (iii) $LiAlH_4$,dl-2-(o-2-toluidinomethyl)pyrrolidine,Et_2O,-78°C; (iv) AcOH,R.T.; (v) MsCl,py ; (vi) Ag_2CO_3, acetone, Δ.

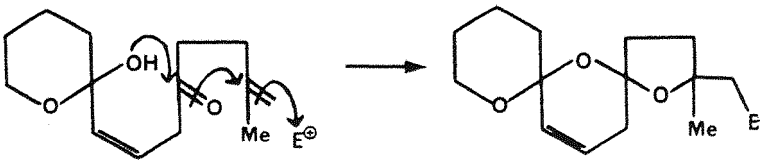
Scheme 21

either acid catalysed cyclization of epoxide (79) (Eqn. 18) or electrophilic cyclization of alkene (80) (Eqn.19) would lead to the required bis-spiroacetals (81, 82).



(79) (81)

Eqn.18

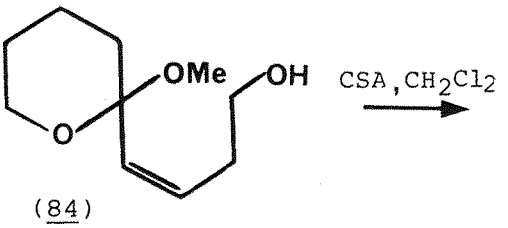


(80) (82)

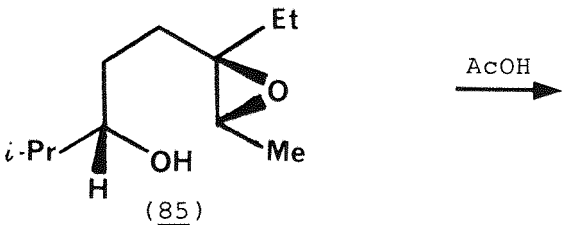
$E^{\oplus}$ = electrophile

Eqn.19

Whilst no syntheses of the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene unit using this approach have been reported, the preparation of the two left hand rings, namely, 1,7-dioxaspiro[5.5]undec-4-ene (83) utilizing a mild cyclization reaction of a methoxyacetal (84) is well known in these laboratories (Eqn.20)[30]. With regards to the formation of the remaining tetrahydrofuran ring, Kishi et al[74] have demonstrated that the analogous acid catalysed cyclization of a γ-hydroxyepoxide (85) results in the formation of the tetrahydrofuran (86) rather than a tetrahydropyran (Eqn.21).

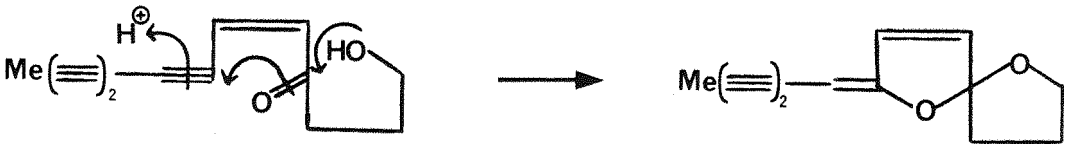


(84) (83) Eqn.20



(85) (86) Eqn.21

Thus, the encouraging results recorded by Baker et al[30] and Kishi et al[74] combined with the observation by Bohlmann et al[77] of the participation of a ketone carbonyl group in an acid catalysed cyclization onto an acetylene (Eqn.22) set a precedent for the proposed cyclizations to construct the required bis-spiroacetals (81,82).
A more recent example of the ability of a carbonyl group to participate in an electrophilic cyclization is that reported by Ley et al (Eqn.11, page 15)[55].

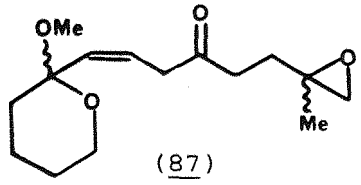


Eqn.22

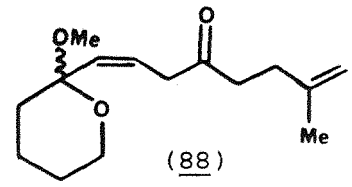
2.2 Synthesis of the Cyclization Precursor (Z)-7,8-Epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)—1-octen-4-one (87)

The electrophilic cyclization of alkene (80) or the acid catalysed cyclization of epoxide (79) was envisaged as a means of constructing the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system. Hence attention was focussed on the synthesis of the cyclization precursors (79,80).

Whilst the hydroxyl group of the hemiacetal is the formal nucleophile in the proposed cyclizations (Eqns. 18 and 19) the preparation of the analogous methoxyacetals (87,88) was initiated with the idea of liberating the free hydroxyl group in situ in the cyclization reaction.

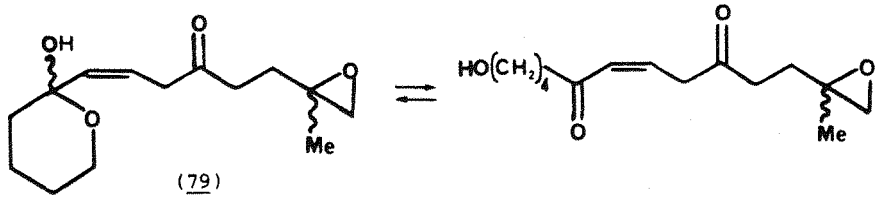


(87)



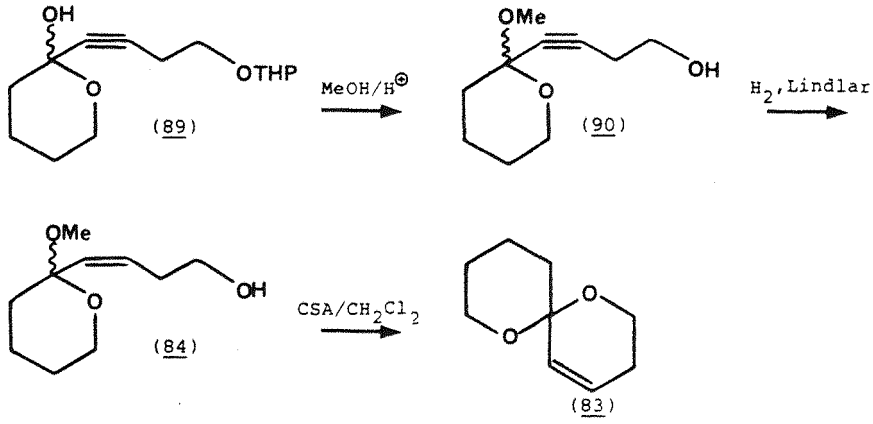
(88)

It was anticipated that the use of the methoxyacetal as a latent hydroxyl group would not only avoid any complications in the synthesis arising from the dynamic equilibrium between the hemiacetal and its open chain form (Eqn.23) but would also overcome the problems experienced by Baker et al[30] in the semi-hydrogenation step. In the synthesis of spiroacetal (83), the initial problems arising from over-hydrogenation of the acetylenic hemiacetal in the semi-hydrogenation step were overcome by conversion of the hemiacetal (89) to the methoxyacetal (90) (Scheme 22).



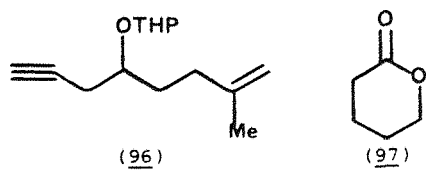
(79)

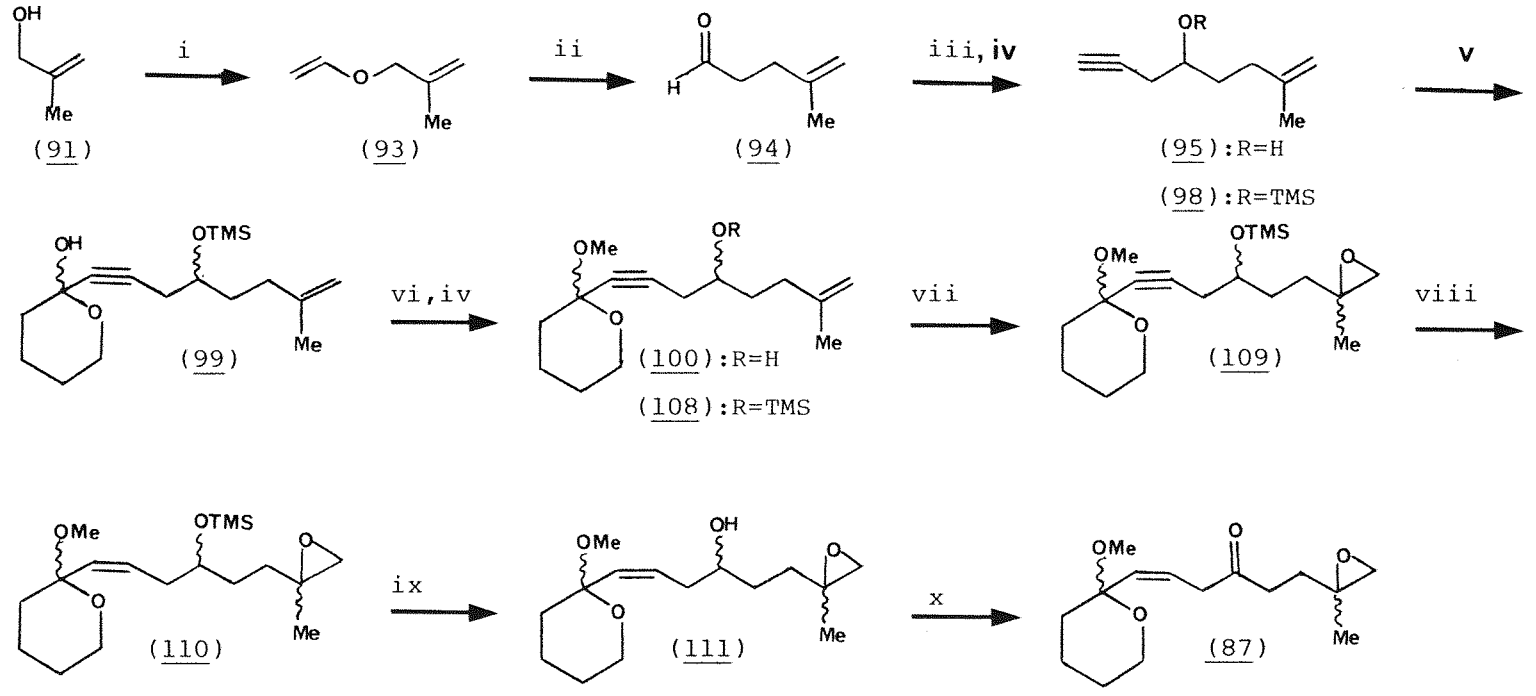
Eqn.23



Scheme 22

The successful synthesis of keto-epoxide (87) is outlined (Scheme 23). The starting point for the synthesis was the mercury(II) trifluoroacetate catalysed transetherification of methallyl alcohol (91) with ethyl vinyl ether (92) which provided the required allyl vinyl ether (93) in 58% yield after distillation. Mercury (II) trifluoroacetate proved to be more expedient than the mercury (II) acetate catalysed reaction reported by Vig et al[78] requiring a reaction time of only 2 hours as opposed to the previously reported reaction time, 9 hours. Claisen rearrangement of the resulting allyl vinyl ether (93) at 120°C in a sealed tube for 24 hours yielded the γ-δ-unsaturated aldehyde (94) in 79% yield after distillation. The crude ^{1}H n.m.r. spectrum indicated an 85% conversion to the aldehyde after this time. Addition of the aldehyde (94) to the organo-zinc reagent (two equivalents) prepared from propargyl bromide and excess activated zinc powder[79], at 0°C in tetrahydrofuran, afforded the acetylenic alcohol (95) in 77% yield. The elemental analysis of the corresponding tetrahydropyranyl ether (96), together with the ^{1}H n.m.r., ^{13}C n.m.r., infra-red and mass spectra were consistent with the assigned structure.





Reagents

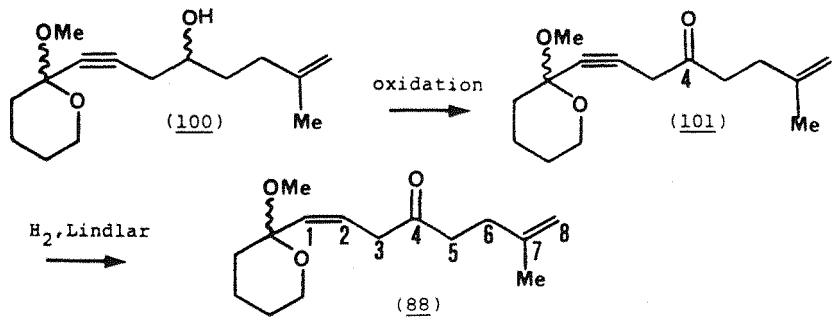
(i) $EtOCH{=}CH_2$ (92), $Hg(O_2CCF_3)_2$, 58%; (ii) 120°C, 24h., 79%; (iii) $HC{\equiv}CCH_2Br$, Zn, THF, 0°C, 77%; (iv) Me_3SiCl, Et_3N, THF, 92%; (v) Bu^nLi, THF, -78°C, 1.5h., then (97), -78°C; (vi) MeOH, Amberlite IR 118, 84% overall; (vii) m-CPBA, CH_2Cl_2, NaOAc, R.T., 8h., 76%; (viii) H_2, 1 atm., 5% Pd on $CaCO_3$-$Pb(OAc)_2$, pentane, R.T., 3h., 95%; (ix) $Bu^n{}_4N^{\oplus}F^{\ominus}$, THF, R.T., 95% ; (x) TFAA, DMSO, Et_3N, CH_2Cl_2, -60°C, 72%.

Scheme 23

The coupling of the acetylene (95) with δ-valerolactone (97) was best achieved in three steps. Thus, the acetylenic alcohol (95) was protected as its trimethylsilyl ether (98) in 92% yield. Generation of the lithium acetylide with butyl-lithium at -78°C for 1.5 hours in tetrahydrofuran, followed by reaction with δ-valerolactone (97) yielded the hemiacetal (99) which was not isolated. The hemiacetal (99) was then stirred overnight with Amberlite IR 118 resin in methanol to effect cleavage of the trimethylsilyl group giving the methoxyacetal (100) in 84% overall yield after purification by 'flash' chromatography.[80] Analysis of the purified product by analytical t.l.c. showed only a single spot. G.l.c. analysis, however, was impeded by decomposition of the product. Attempts to distil the product under reduced pressure also resulted in rapid decomposition with loss of the tertiary methoxyl group. The ^{1}H n.m.r. spectrum exhibited a multiplet at δ_H4.68-4.80, a singlet at δ_H3.40 and a singlet at δ_H1.76, clearly establishing the presence of a methyl-substituted double bond and the methoxyl group. The infra-red spectrum further established the presence of the acetylene group (2260 cm^{-1}) and the hydroxyl group (3600-3200 cm^{-1}). Furthermore, the peak at m/z 221 (13%) in the mass spectrum, assigned to M-OCH_3, is a common fragmentation for methoxyacetals.

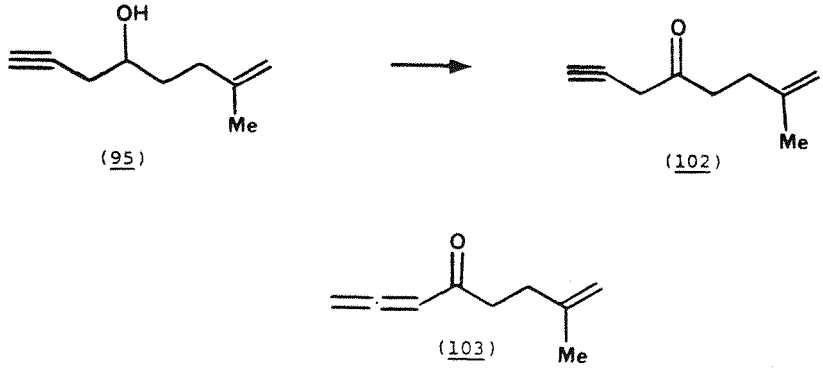
With the methoxyacetal (100) in hand, it was anticipated that oxidation of the secondary alcohol to the ketone (101) followed by semi-hydrogenation of the acetylene to the (Z)-alkene (88) would yield the cyclization precursor required for an electrophilic cyclization to bis-spiroacetal (82) (Scheme 24). However, attempts to oxidize the alcohol (100) to the desired ketone (101) using a variety of oxidizing agents such as pyridinium chlorochromate, dimethyl sulphoxide activated with trifluoroacetic anhydride or oxalyl chloride, silver carbonate on celite, pyridinium dichromate, chromium trioxide in pyridine and pyridine sulphur trioxide, were unsuccessful. (Scheme 24 shown overleaf).

In the light of the disappointing attempts to obtain ketone (101) via direct oxidation of alcohol (100) it was decided to introduce the ketone functionality at position 4 at an earlier stage in the synthesis,



Scheme 24

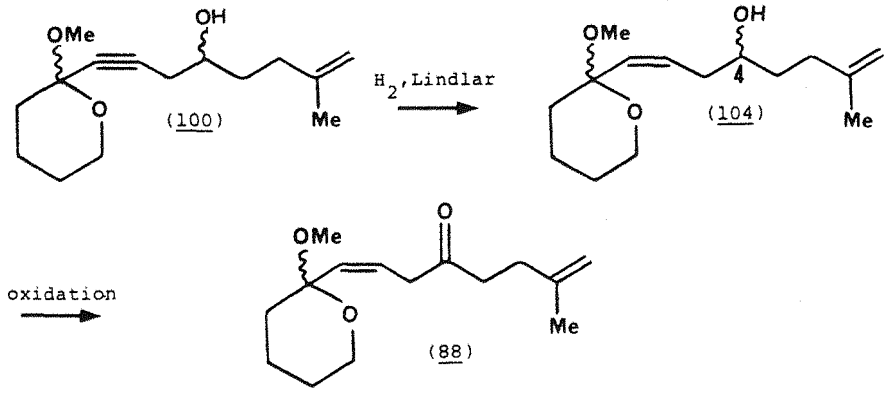
namely, by oxidation of the acetylenic alcohol (95) to the acetylenic ketone (102) (Eqn.24). Protection of the ketone before generation of the lithium acetylide and subsequent deprotection after reaction of the lithium acetylide with δ-valerolactone (97), should provide a route to ketone (101). This approach was thwarted, however, when attempts to oxidize acetylenic alcohol (95) to a ketone using the oxidizing agents pyridinium chlorochromate, dimethyl sulphoxide activated with trifluoroacetic anhydride or oxalyl chloride, silver carbonate on celite and Jones' reagent[81], afforded only moderate yields of allenic ketone (103). This undesired formation of an allenic ketone in preference to an acetylenic ketone in the oxidation of a homo-propargylic alcohol has also posed problems for Salaün and Almirantis[82].



Eqn.24

Since oxidation of acetylenic alcohols (95) and (100) failed to yield the desired acetylenic ketones it was decided that in order to

prepare alkene (88), semi-hydrogenation should precede the oxidation step (Scheme 25).



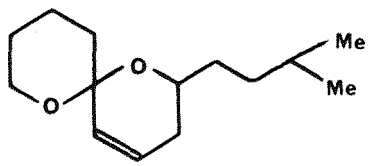
Scheme 25

A summary of the attempts to semi-hydrogenate acetylene (100) to the (Z)-alkene (104) is shown (Table 1). The use of pentane as a solvent eliminated the undesired intramolecular displacement of the methoxyl group by the hydroxyl group at C-4, previously observed using methanol as solvent. The problem of hydrogenation of the terminal double bond in addition to the acetylene, however, was not overcome.

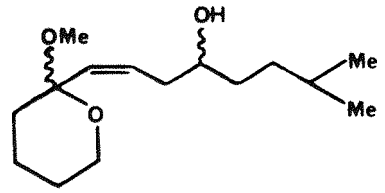
Hindered by the hydrogenation step in the route to alkene (88), attention was redirected to the epoxide (87). Direct epoxidation of alcohol (100) gave mainly the cyclic ether (107). Hence, the alcohol (100) was reprotected as a trimethylsilyl ether (108), before treatment with meta-chloroperoxybenzoic acid for 8 hours at room temperature, to give the epoxide (109), in 76% yield (Scheme 26). In order to minimize the formation of the by-product (107), it was essential to buffer the reaction medium with sodium acetate. Epoxide formation was evident by the disappearance in the ^1H n.m.r. spectrum of the signal at δ_H 4.62-4.79 due to the vinylic protons and the appearance of a resonance at δ_H2.32-2.84 due to the epoxide protons. ^{13}C n.m.r. indicated that the product was in fact a mixture of diastereomers which were not separated.

Table 1. Attempted Semi-hydrogenation of Acetylene (100)

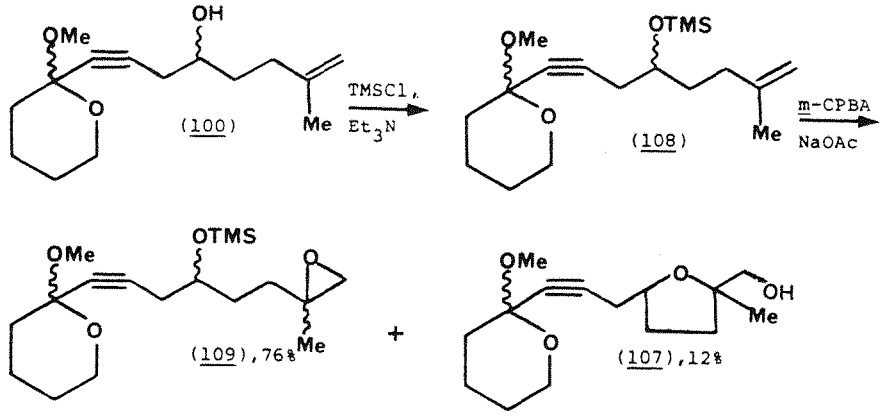
Substrate	Catalyst	Conditions	Product
(100)	5% Pd on $CaCO_3$-$Pb(OAc)_2$	H_2, 1 atm./methanol/quinoline/room temp.	(105)
(100)	5% Pd on $CaCO_3$-$Pb(OAc)_2$	H_2,1 atm./methanol/Et_3N/room temp.	(105)
(100)	5% Pd on $CaCO_3$-$Pb(OAc)_2$	H_2,1 atm./methanol/quinoline/0°C	(105)
(100)	5% Pd on $BaSO_4$	H_2,1 atm./methanol/Et_3N/room temp.	(105)
(100)	5% Pd on $CaCO_3$-$Pb(OAc)_2$	H_2,1 atm./pentane/quinoline/room temp.	(106)
(100)	5% Pd on $CaCO_3$-$Pb(OAc)_2$	H_2,1 atm./pentane/Et_3N/room temp.	(106)
(100)	5% Pd on $BaSO_4$	H_2,1 atm./pentane/room temp.	(106)
(100)	$Ni(OAc)_2.4H_2O$/$H_2N(CH_2)_2NH_2$[83]/$NaBH_4$	H_2, 1 atm./ethanol/room temp.	(106)



(105)

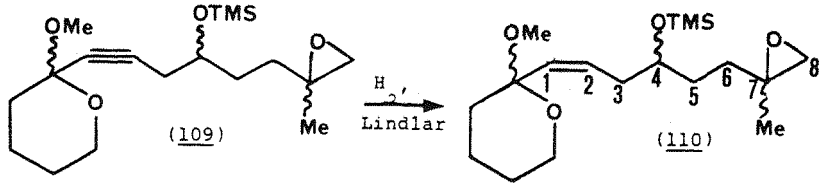


(106)



Scheme 26

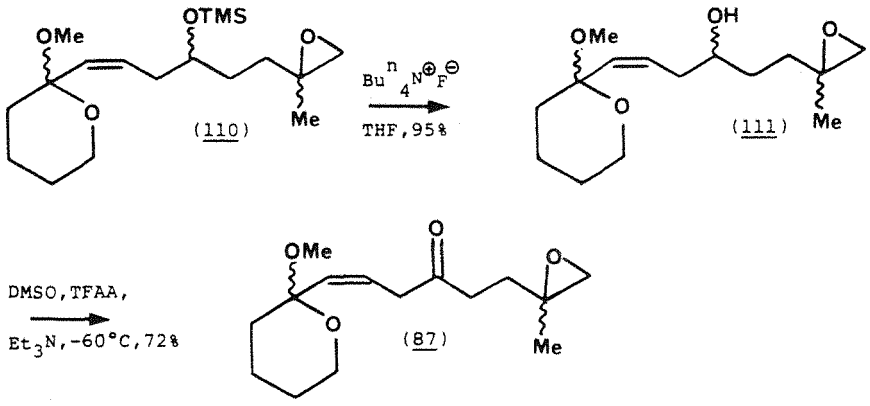
Semi-hydrogenation of epoxide (109) was then effected cleanly using Lindlar catalyst (5% palladium on calcium carbonate poisoned with lead acetate) yielding alkene (110) (Eqn.25). Irradiation at the frequency in the ^{1}H n.m.r. spectrum corresponding to the allylic protons at δ_H2.45 collapsed the multiplet at δ_H5.48-5.61, assigned to the vinylic proton attached to C-2, to a doublet with coupling constant J 10.5 Hz, thereby confirming the (Z)-stereochemistry of the double bond.



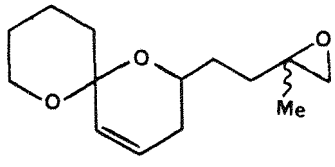
Eqn.25

The remaining step in the preparation of the epoxide cyclization precursor (87) requires the transformation of the trimethylsilyl ether at C-4 to a ketone. Attempts to oxidize trimethylsilyl ether (110) directly to the keto-epoxide (87) using ceric ammonium nitrate, N-bromosuccinimide, triphenylcarbenium tetrafluoroborate and Jones' reagent[81], were unsuccessful. However, cleavage of the trimethylsilyl ether (110) with tetrabutylammonium fluoride in tetrahydrofuran liberated the alcohol (111) which was subsequently oxidized with dimethyl sulphoxide activated with trifluoroacetic anhydride to the desired keto-epoxide (87) (Scheme 27). Use of the chromium reagents, pyridinium

chlorochromate buffered with sodium acetate, pyridinium dichromate and chromium trioxide in pyridine, led only to the spiroacetal (112).



Scheme 27



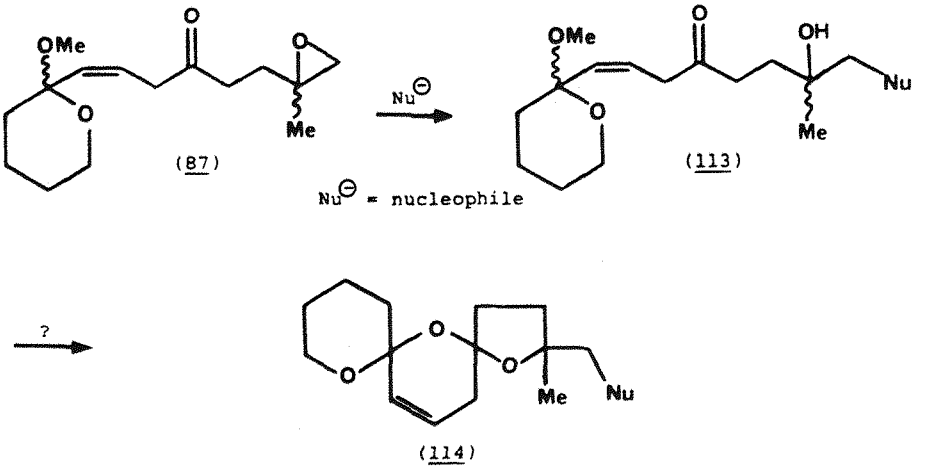
(112)

The successful synthesis of the β-γ-unsaturated ketone (87) was indicated not only by the carbonyl group absorption at 1710 cm^{-1} in the infra-red spectrum but also by the downfield shift of the resonance corresponding to the allylic protons, appearing as a doublet, J 5.9Hz, at δ_H 3.49 in the 360 MHz ^1H n.m.r. spectrum. The ^{13}C n.m.r. and mass spectra were also consistent with the assigned structure. Although the product was unstable, nevertheless, its synthesis enabled attempts to induce an intramolecular cyclization to bis-spiroacetal (81) to be carried out.

2.3 Attempted Cyclization of (Z)-7,8-Epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-1-octen-4-one (87)

A summary of the attempts to cyclize the previously prepared unsaturated keto-epoxide (87) using a variety of protic and Lewis acids is presented (Table 2). In the majority of cases, the starting material either decomposed to give a dark coloured resinous material or yielded an unidentified polar product whose ^{1}H n.m.r. spectrum indicated the presence of a highly polarized double bond as well as substantial skeletal rearrangement. The ^{13}C n.m.r., ^{1}H n.m.r., infra-red and mass spectra of the product were not consistent with the desired bis-spiroacetal (81).

An alternative approach, involving nucleophilic opening of the epoxide (87) followed by attempted cyclization of the resultant tertiary alcohol (113) to a bis-spiroacetal derivative (114) (Scheme 28) also met with disappointing results. This was due to the inability to cleave epoxide (87) cleanly to the desired tertiary alcohol (113) using a variety of nucleophiles including sodium hydroxide, lithium iodide and sodium thiophenolate.

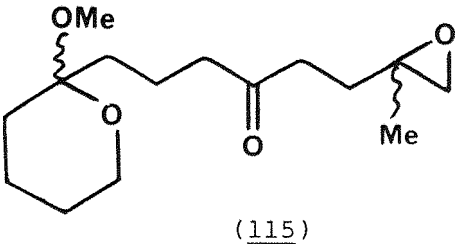


Scheme 28

Table 2. Attempted Cyclization of Keto-Epoxide (87)

Acid	Conditions	Result
CSA	CH_2Cl_2, 0.2h., room temp., 0.1 equiv.	Polar product
CSA	1:1 CH_2Cl_2:H_2O, 0.2h., room temp., 0.1 equiv.	Polar product
Amberlyst	CH_2Cl_2, 48 h., room temp.	No reaction
$BF_3.Et_2O$	CH_2Cl_2, 0.2h., -20°C, 0.1 equiv.	Dark resinous material
$TiCl_4$	CH_2Cl_2, 0.2h., room temp., 0.1 equiv.	Dark resinous material
$TiCl_4$	CH_2Cl_2, 0.2h., -60°C, 0.1 equiv.	Dark resinous material
$SnCl_4$	CH_2Cl_2, 0.2h., 0°C, 1 equiv.	Dark resinous material
$SnCl_4$	CH_2Cl_2, 0.2h., 0°C, 0.1 equiv.	Dark resinous material
Me_3SiI	CH_3CN, 0.5h., room temp., 1 equiv.	Complex mixture by t.l.c. No vinylic protons present.
CSA	MeOH, 0.5h., room temp.	Polar product
CF_3COOH	H_2O, 0.2h., 0°C, 0.1 equiv.	Polar product
K_{10} Montmorillonite	$CHCl_3$, 24h., room temp.	Polar product
BCl_3	CH_2Cl_2, 0.2h., -60°C, 0.1 equiv.	Complex mixture by t.l.c. No vinylic protons present.
$ZnCl_2$	CH_2Cl_2, 24h., room temp., 1.0 equiv.	Polar product
$ZnCl_2$	CH_2Cl_2, 24h., room temp., 0.1 equiv.	Polar product

The isolation of products from the attempted acid catalysed cyclization of keto-epoxide (87) in which reaction of the double bond had clearly occurred, suggested that a study of the analogous saturated keto-epoxide (115) might be informative.

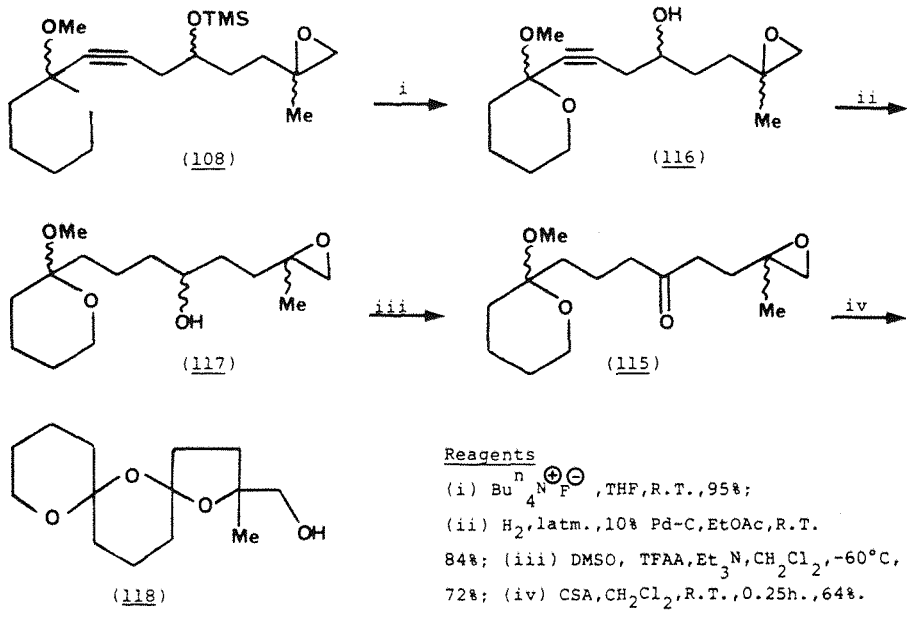


(115)

2.4 Synthesis of 1-(2-Methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-2-yl)methanol (118)

Whilst the cyclization of the unsaturated keto-epoxide (87) to bis-spiroacetal (81) remained to be accomplished, encouraging results were obtained with the analogous saturated keto-epoxide (115). Keto-epoxide (115) was easily prepared in a similar manner to the unsaturated analogue (87). The common intermediate, trimethylsilyl ether (108) after deprotection to the unsaturated alcohol (116) using tetrabutylammonium fluoride, was hydrogenated over 10% palladium on charcoal in ethyl acetate to the saturated alcohol (117). Subsequent oxidation using dimethyl sulphoxide activated with trifluoroacetic anhydride afforded the desired keto-epoxide (115), which when treated with a catalytic amount of camphorsulphonic acid in dichloromethane underwent facile cyclization to the novel bis-spiroacetal (118) (Scheme 29).

The formation of the bis-spiroacetal derivative (118) was indicated in the 360 MHz ^{1}H n.m.r. spectrum by the disappearance of the resonances due to the methoxyl group (δ_H 3.19), the epoxide group (δ_H 2.57-2.62) and the methylene protons α to the carbonyl group (δ_H 2.44, 2.49) of the cyclization precursor (115), together with the appearance of a signal at δ_H 3.38-3.59 due to the hydroxymethyl



Scheme 29

group. The signal due to the methyl group attached to oxygen also shifted upfield from δ_H1.31 to δ_H1.18. The infra-red spectrum exhibited a strong hydroxyl group absorption (3470 cm^{-1}) and no carbonyl group absorption. The mass spectrum with a peak at m/z 225 (M-CH_2OH, 51%) together with the elemental analysis establishing the molecular formula $C_{14}H_{22}O_4$, were also consistent with the formation of bis-spiroacetal (118).

The observation of only one methyl resonance at δ_H1.18 in the 360 MHz ^{1}H n.m.r. spectrum together with 14 carbon resonances in the ^{13}C n.m.r. spectrum suggested that the product isolated was in fact a single diastereomer. Whilst the stereochemistry of the five-membered ring and the hydroxymethyl substituent could not be assigned unambiguously it was assumed that under the thermodynamic conditions used, the two six-membered rings adopted the conformation in which the ring oxygens are axial to the adjacent ring thus gaining stability from the anomeric effect[40]. The signal in the ^{1}H n.m.r. spectrum at δ_H2.51-2.62 results

from the characteristic deshielding of these protons (11' $_{ax}$-H and 14' $_{ax}$-H, Figure 5) owing to the 1,3-diaxial interaction with the oxygen of the adjacent ring.

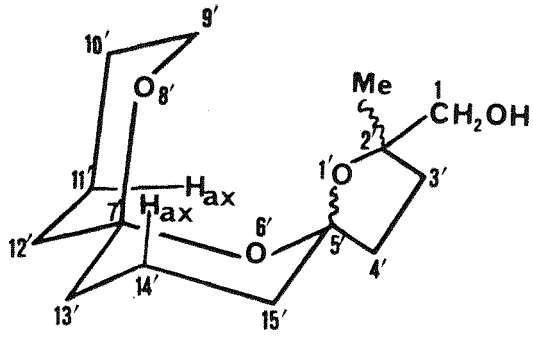


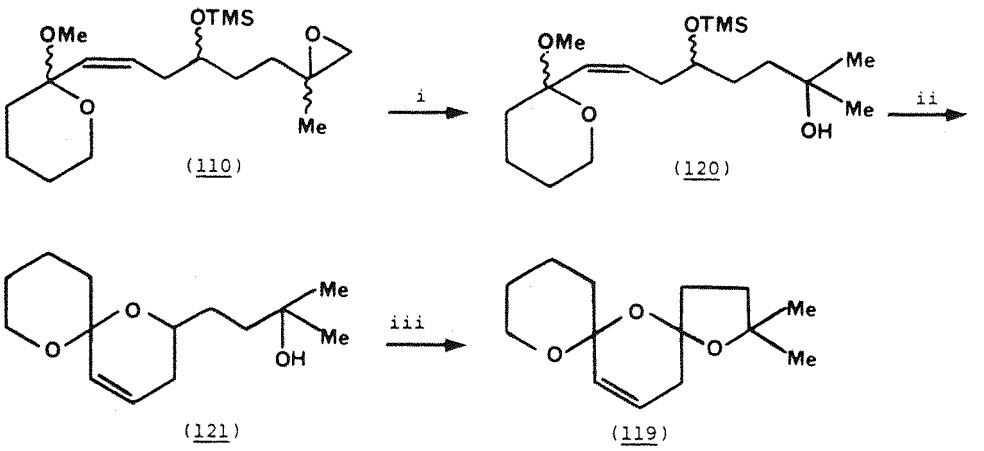
Figure 5

The facile acid catalysed intramolecular cyclization of the saturated keto-epoxide (115) to the bis-spiroacetal (118), in contrast to the disappointing results observed for the unsaturated analogue (87), suggested that an alternative strategy had to be developed to introduce the required unsaturation at C-13'.

2.5 Synthesis of 2,2-Dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene (119)

Methodology for the introduction of unsaturation at position 13 was required in order for the model work to be applicable to the synthesis of salinomycin (7). Thus, whilst the acid catalysed cyclization of keto-epoxide (115) provided a route to the 1,6,8-trioxadispiro[4.1.5.3]pentadecane ring system, entry to the required 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system rested on a somewhat different approach. This involved an initial cyclization to form a spiroacetal derivative which was subsequently converted to a bis-spiroacetal utilizing an oxy-radical generated by photolysis. The successful synthesis of 2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]-pentadec-13-ene (119) (Scheme 30) highlights this approach.

Treatment of the previously prepared (Z)-ene-epoxide (110) with lithium aluminium hydride in diethyl ether for 2 hours yielded the tertiary alcohol (120) in 89% yield. Cyclization of alcohol (120) to spiroacetal (121) was then achieved with a catalytic amount of



Reagents

(i) $LiAlH_4$(0.5eq.),Et_2O,Δ,2h.,89%; (ii) CSA,CH_2Cl_2,0.5h.,R.T.,93%;
(iii) $PhI(OAc)_2$(1eq.),I_2(0.5eq.),cyclohexane,24h.,hν,R.T.,53%.

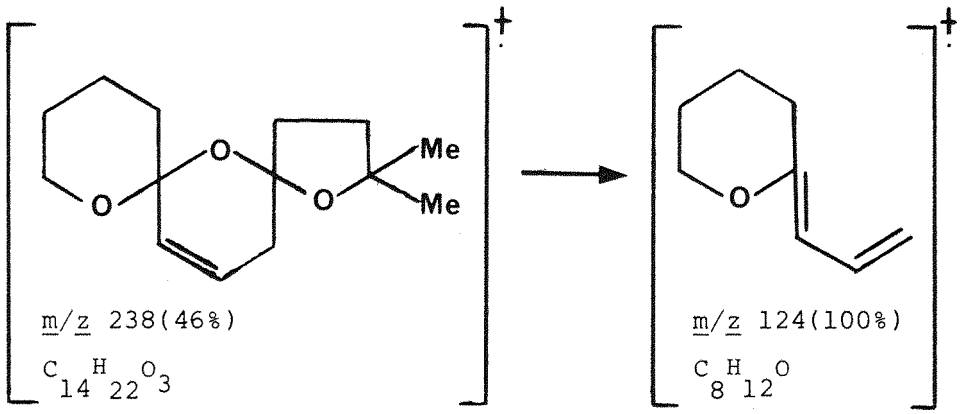
Scheme 30

camphorsulphonic acid in dichloromethane in 93% yield. The ^{13}C n.m.r. spectrum, showing only 14 carbon resonances, combined with t.l.c. and g.l.c. analysis indicated that the product was diastereomerically pure.

Cyclization of spiroacetal (121) to the bis-spiroacetal (119) could not be induced using mercuric oxide and iodine. These conditions were, however, successfully used by Kay et al[56,57] in a similar spirocyclization (Eqn.12,page 16). Nevertheless, irradiation of a solution of spiroacetal (121) in cyclohexane containing iodobenzene diacetate and iodine at room temperature for 24 hours[84] did provide the required unsaturated bis-spiroacetal (119) in 53% yield after purification by 'flash' chromatography[80]. In an analogous fashion to its precursor (121), t.l.c. and g.l.c. analysis combined with the observation of only 14 carbon resonances in the ^{13}C n.m.r. spectrum established that the product was diastereomerically pure.

Bis-spiroacetal formation was indicated not only by the absence of an hydroxyl group absorption in the infra-red spectrum but also by the two diastereotopic methyl groups, resonating at δ_H1.24 and δ_H1.48 in the ^1H n.m.r. spectrum. It is of note that in the precursor (121)

the methyl groups were in fact coincident, resonating at δ_H1.24. Mass spectrometry gave a molecular ion at m/z 238 (46%) consistent with the molecular formula $C_{14}H_{22}O_3$. In addition, the base peak at m/z 124 (100%) consistent with the molecular formula $C_8H_{12}O$, probably arises from a retro-Diels-Alder type fragmentation (Scheme 31). A similar fragmentation is observed in the mass spectrum of epi-17-deoxy-(O-8)-salinomycin (8)[12].



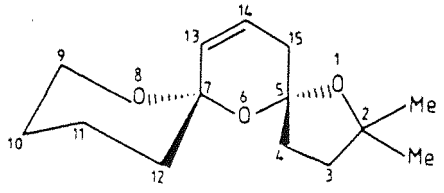
Scheme 31

Hence, the Barton-type reaction of substituted hydroxyspiroacetal (121) to the unsaturated bis-spiroacetal (119) provided a novel route to the preparation of the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system present in the salinomycin series of polyether antibiotics. Details on the stereochemistry of bis-spiroacetal (119) together with the assignment of the 360 MHz ^{1}H n.m.r. spectrum remain to be disclosed.

2.6 Stereochemistry of 2,2-Dimethyl-1,6,8-trioxadispiro[4.1.5.3]-pentadec-13-ene (119)

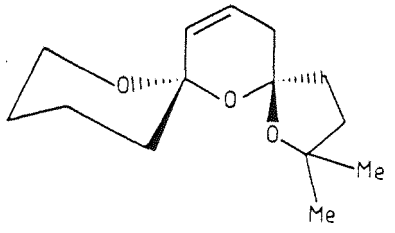
The two possible stereoisomers (A and B) of the unsaturated bis-spiroacetal (119) formed from the sequential cyclization reactions are depicted below (Figure 6) with their respective conformational isomers (D and C). Based on the number of anomeric effects[40,85], B could be predicted to be less thermodynamically stable than the other three. The unfavourable dipole-dipole interaction due to the two syn carbon-oxygen bonds existing in A and D would also render them thermodynamically less favourable. Thus, considering anomeric

effects in conjunction with dipole-dipole interactions C is predicted to be the thermodynamic product.



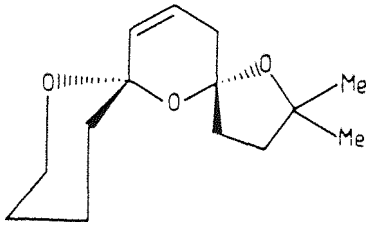
3 Anomeric Effects
Dipole-Dipole interactions unfavourable

(A)



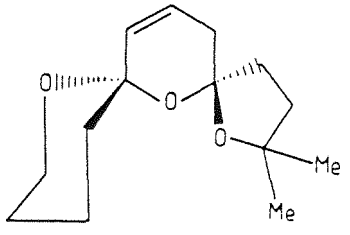
2 Anomeric Effects

(B)



4 Anomeric Effects
Dipole-Dipole interactions unfavourable

(D)



3 Anomeric Effects

(C)

Figure 6

The stereochemistry at C-7, established in the first of the two steps could be predicted to follow that already reported in similar cyclizations by Hanessian *et al*[35] and Baker *et al*[39]. Formation of A or B could therefore be discounted. The second cyclization would establish the relative configuration at C-5 with consequent formation of either C or D. The use of ^{1}H n.m.r. spectroscopy with the aid of proton homonuclear correlation (COSY), and NOE difference experiments, established that the diastereomer isolated was, in fact, C. This is consistent with the observation that the analogous bis-spiroacetal moiety in the natural product, *epi*-17-deoxy-(O-8)-salinomycin (8), has been shown by X-ray analysis to have the same relative configuration at the spirocentres[12].

The 360 MHz ^{1}H n.m.r. spectrum and two-dimensional COSY experiment of the model bis-spiroacetal (119) are depicted (Figures 7,8).

Figure 7

360 MHz ^{1}H n.m.r. spectrum of bis-spiroacetal (119)

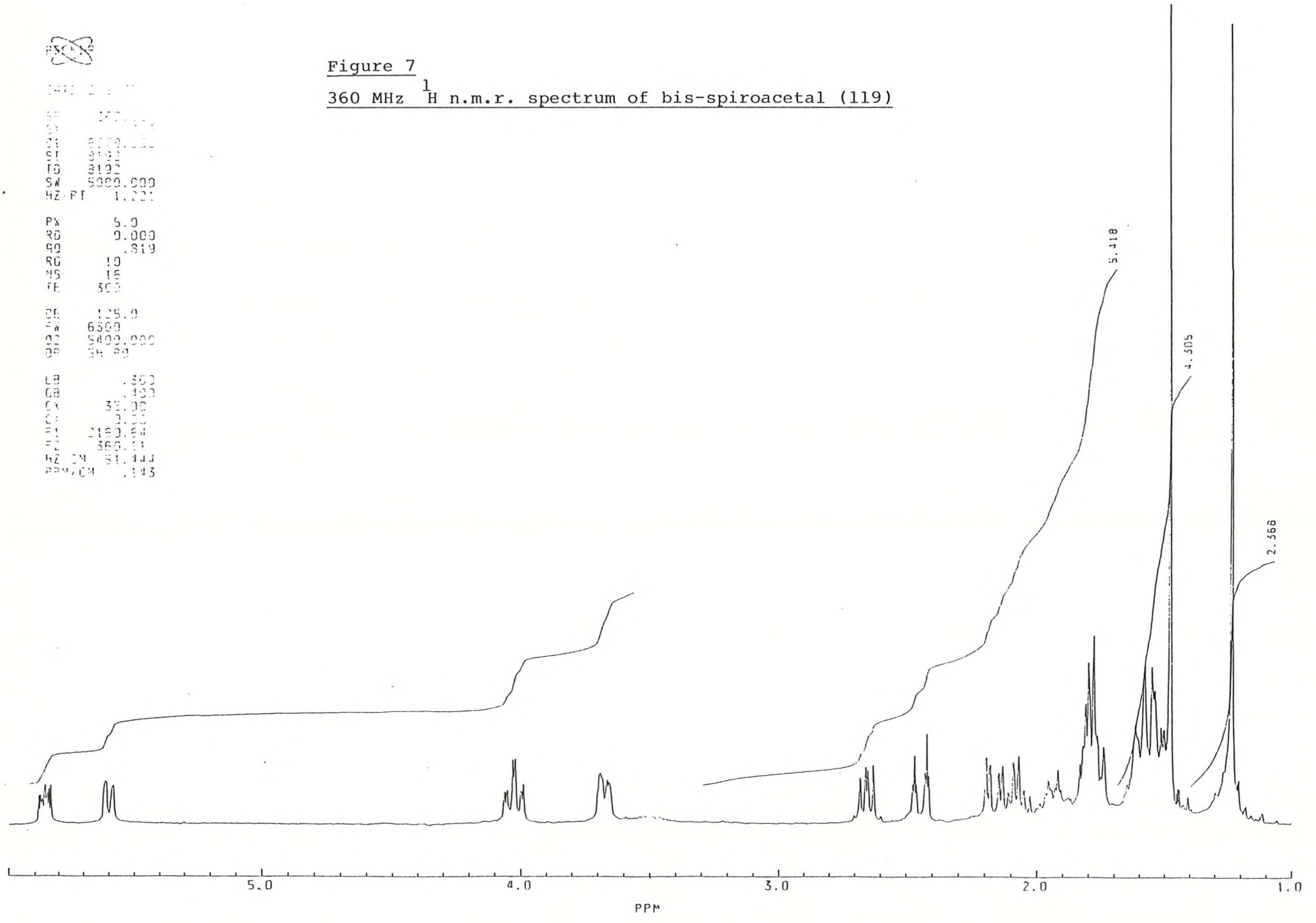
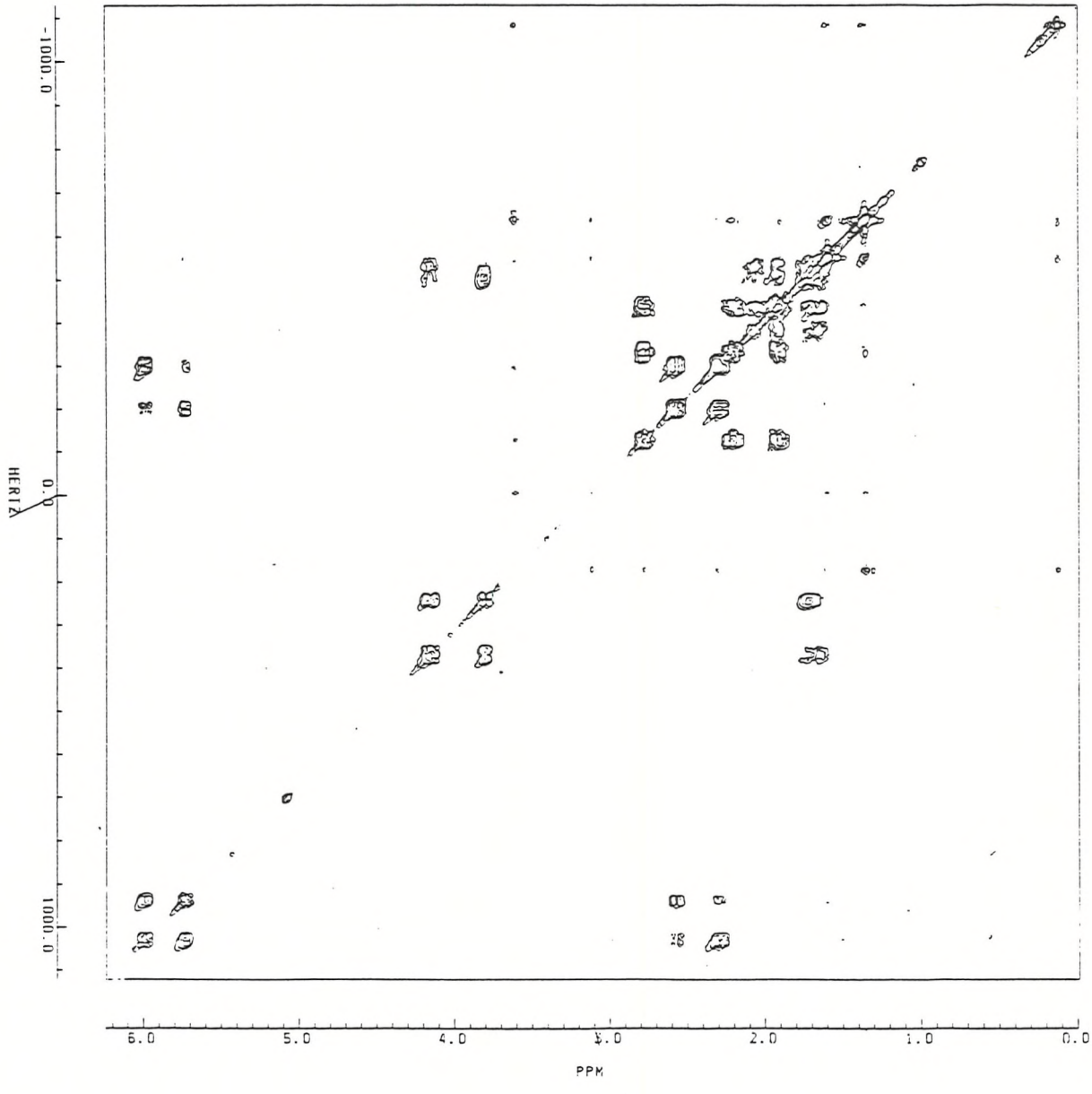


Figure 8

^{1}H- ^{1}H COSY spectrum of bis-spiroacetal (119)

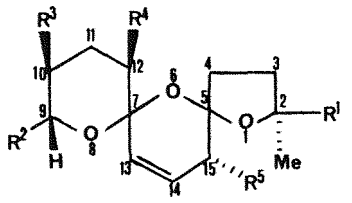


The chemical shifts and coupling constants observed are tabulated (Tables 3,4) along with the analogous data reported for the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system of epi-17-deoxy-(O-8)-salinomycin (8)[86] and salinomycin (7)[86,87]. Using this information the ^{1}H n.m.r. spectrum recorded for bis-spiroacetal (119) was assigned.

The resonance at δ_H4.02 appeared as a double double doublet with two large constants $J_{9ax,9eq}$ 11.3 Hz, $J_{9ax,10ax}$ 11.3 Hz and one smaller coupling constant $J_{9ax,10eq}$ 3.3 Hz, thereby assigning this signal to the axial proton attached to C-9. In the COSY spectrum the signals at δ_H5.59 and δ_H5.86 assigned to the vinylic protons were coupled only to the one proton multiplets which resonated at δ_H2.16 and δ_H2.45. Hence these latter two double double doublets were assigned to the allylic protons attached to C-15. The coupling constants observed (Table 4) were of similar magnitude to the analogous coupling constants in epi-17-deoxy-(O-8)-salinomycin[86]. Similarly, the methylene protons attached to C-9 which were assigned to the multiplets at δ_H3.67 and δ_H4.02 were only coupled to the four proton multiplet at δ_H1.49-1.64. Thus, two of the four protons resonating at δ_H1.49-1.64 were assigned to the methylene protons attached to C-10. The residual resonances, namely, three multiplets, at δ_H1.86-1.99, δ_H2.04-2.12, and δ_H2.59-2.70, each integrating for one proton, the multiplet at δ_H1.72-1.83 integrating for three protons and two protons of the four proton multiplet at δ_H1.49-1.64, remained to be assigned to the eight methylene protons attached to carbons 3,4,11 and 12.

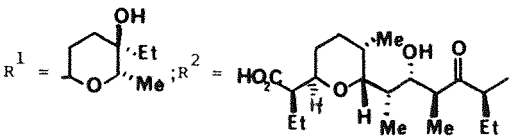
The COSY spectrum showed that the protons appearing as multiplets at δ_H2.59-2.70 and δ_H2.04-2.12 were not only coupled to each other but also to the protons resonating as a multiplet at δ_H1.72-1.83. The proton giving rise to the multiplet at δ_H1.86-1.99, however, was coupled to the protons which gave rise to the multiplets at δ_H1.72-1.83 and δ_H1.49-1.64. Double resonance experiments indicated that the protons occurring as multiplets at δ_H2.04-2.12 and δ_H2.59-2.70 were,

Table 3. Chemical Shifts[a,b] for the 1,6,8-Trioxadispiro[4.1.5.3]pentadec-13-ene Ring System

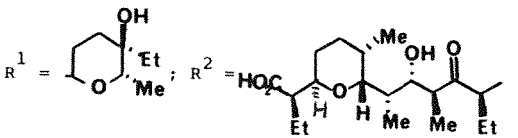


Model Bis-spiroacetal (119) : R^1 = Me; R^2 = R^3 = R^4 = R^5 = H.

epi -(17)-Deoxy-(O-8)-salinomycin (8): R^3 = R^4 = Me ; R^5 = H ;



Salinomycin (7) : R^3 = R^4 = Me ; R^5 = OH ;



Compound	2-Me	2'-Me	12'	11_{eq}	10,10'	12	4'	3'	11_{ax}	3	15'	15	4	9_{eq}	9_{ax}	13	14
(119)	1.24 (s)	1.48 (s)	1.49-1.64 (m)	1.49-1.64 (m)	1.49-1.64 (m)	1.72-1.83 (m)	1.72-1.83 (m)	1.72-1.83 (m)	1.86-1.99 (m)	2.04-2.12 (m)	2.16 (ddd)	2.45 (ddd)	2.59-2.70 (m)	3.67 (m)	4.02 (ddd)	5.59 (ddd)	5.86 (ddd)
(8)[85]	-	1.43	1.54 (ax)	c	1.70 (ax)	-	1.59	1.95	c	2.09	2.03	2.40	3.01	-	3.80	5.46	5.88
(7)[85,86]	-	1.48	1.71 (ax)	1.61	1.72 (ax)	-	2.09	1.84	1.09	2.23	-	3.98[d]	2.40	-	3.89	5.98	6.03

a. Obtained from 360 MHz ^{1}H n.m.r. spectrum in $CDCl_3$.

b. Expressed in parts per million downfield from TMS (δ_H).

c. Not reported.

d. Allylic carbinol proton.

Table 4. Coupling Constants (J Hz)[a] for the 1,6,8-Trioxadispiro[4.1.5.3]pentadec-13-ene Ring System

Compound	$9_{ax}, 9_{eq}$	$9_{ax}, 10_{ax}$	$9_{ax}, 10_{eq}$	13,14	13,15	13,15'	14,15	14,15'	15,15'
(119)	11.3	11.3	3.3	10.0	2.6	1.2	2.6	5.8	16.9
(8)	-	10.2	-	10.0	3.0	1.0	2.0	6.4	16.8
(7)	-	10.2	-	10.9	-	0.6	-	1.7	-

a. Obtained from 360 MHz ^1H n.m.r. spectrum in $CDCl_3$.

in fact, vicinal to each other. Thus, the absence of any coupling between the methylene protons attached to C-10 resonating at δ_H1.49-1.64 and the protons occurring as multiplets at δ_H2.04-2.12 and δ_H2.59-2.70 precluded the possibility of assigning these latter multiplets to the protons attached to C-11 or C-12.

The above observations suggested the assignment of the multiplets at δ_H2.04-2.12 and δ_H2.59-2.70 to two vicinal methylene protons in the five-membered ring and the multiplet at δ_H1.86-1.99 to the axial proton attached to C-11. The observation of an NOE effect between the protons resonating at δ_H1.86-1.99 and δ_H4.02 was consistent with those protons bearing a 1,3-diaxial relationship to each other.

The characteristic deshielding of the axial proton at C-11, δ_H1.86-1.99, relative to the geminal equatorial proton and the vicinal protons at C-10 and C-12 which appear at δ_H1.49-1.83 is attributed to the 1,3-diaxial interaction with the oxygen of the adjacent ring (Figure 9). The observation of an NOE effect between the proton resonating at δ_H2.04-2.12 and the methyl group giving rise to the singlet at δ_H1.48 was consistent with the assignment of this signal to a methylene proton attached to C-3 and the signal at δ_H2.59-2.70 to a methylene proton attached to C-4. The remaining two methylene protons of the five-membered ring were assigned to the multiplet at δ_H1.72-1.83 using the information from the COSY experiment as described above.

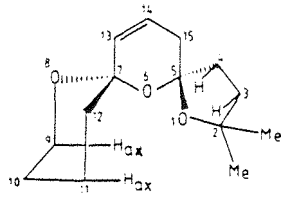
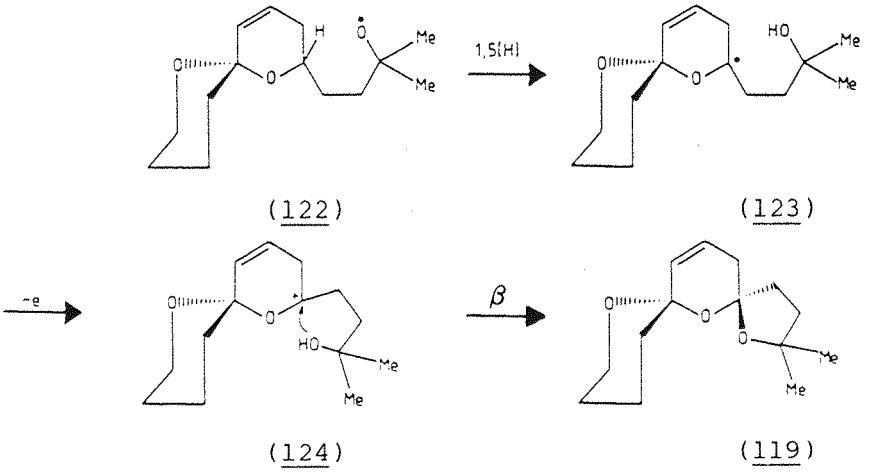


Figure 9

Finally, the most striking feature observed from NOE difference spectra was an NOE effect between the axial proton at C-9 resonating at δ_H4.02 and the methylene protons attached to C-4 and C-3 resonating at δ_H2.59-2.70 and δ_H2.04-2.12, respectively. This observed NOE effect is fully consistent with the assignment of structure C (Figure 6) to bis-spiroacetal (119) in that this diastereomer may readily adopt a conformation in which the axial proton at C-9 and the methylene protons at C-4 and C-3 are in close proximity (Figure 9).

The stereochemistry observed at C-7, established in the initial cyclization to hydroxyspiroacetal (121), is therefore fully consistent with the results obtained by Hanessian et al[35] and Baker et al[39] in their respective syntheses of the spiroacetal moiety of avermectin B_{1a} and avermectin B_{1b}. The stereochemistry at C-5, however, is established in the final free-radical substitution reaction. Thus, the oxy-radical (122), generated by photolysis, undergoes 1,5-hydrogen transfer to give the stabilized radical (123) ; this is subsequently oxidized to cation (124) which is trapped by the hydroxyl substituent from the least hindered β-face thus avoiding the unfavourable 1,3-dipole interactions (Scheme 32).



(122) (123)

(124) (119)

Scheme 32

In summary, the use of the Barton-type reaction of a substituted hydroxyspiroacetal has demonstrated a novel means of constructing the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system required for the synthesis of the salinomycin series of antibiotics. Moreover, the

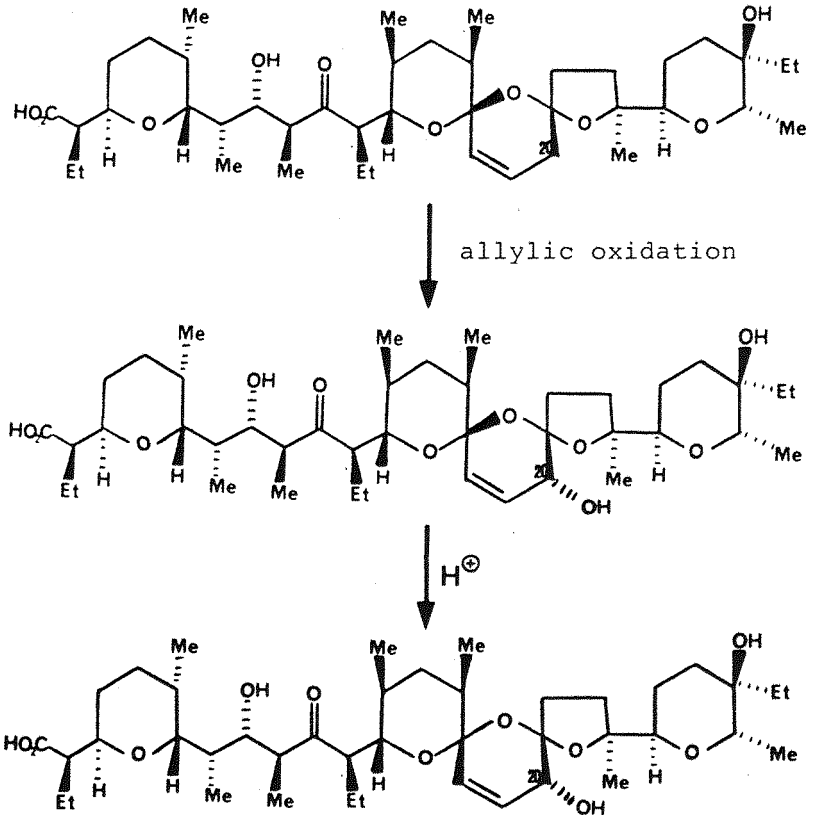
stereochemistry of the model bis-spiroacetal (119) prepared in this manner was shown to be the same as that found in epi-17-deoxy-(O-8)-salinomycin. This is highlighted by comparison of the ^{1}H n.m.r. data for the model compound (119) with epi-17-deoxy-(O-8)-salinomycin (8) (Tables 3,4). Treatment of the bis-spiroacetal (119) isolated from the Barton-type reaction with camphorsulphonic acid at room temperature for 24 hours did not result in epimerization at the spirocentres thus suggesting that the bis-spiroacetal isolated was in fact the thermodynamic product. This observation was in keeping with that reported by Kishi[71] (page 32) wherein it was demonstrated that in the absence of the allylic hydroxyl group equilibration under acidic conditions results predominantly in formation of the bis-spiroacetal system with the same stereochemistry as that found in epi-17-deoxy-(O-8)-salinomycin (8).

CHAPTER 3

SYNTHESIS OF TWO KEY INTERMEDIATES REQUIRED FOR THE SYNTHESIS OF THE BIS-SPIROACETAL MOIETY OF epi-17-DEOXY-(O-8)-SALINOMYCIN (8)

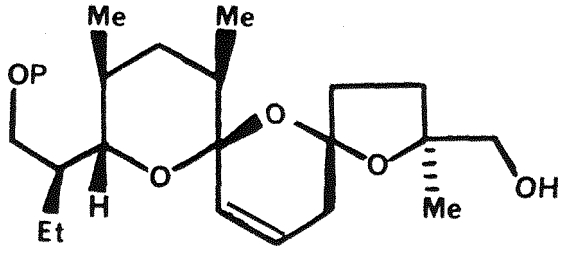
3.1 Application of the Model Work to the Synthesis of epi-17-Deoxy-O-8)-salinomycin (8)

Having developed the methodology for the construction of the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system with the same stereochemistry as that found in epi-17-deoxy-(O-8)-salinomycin (8), attention was initially directed towards the synthesis of this compound. It was envisaged that upon completion of the synthesis of epi-17-deoxy-(O-8)-salinomycin (8), stereoselective allylic oxidation followed by equilibration under acidic conditions would yield salinomycin itself. (Scheme 33).

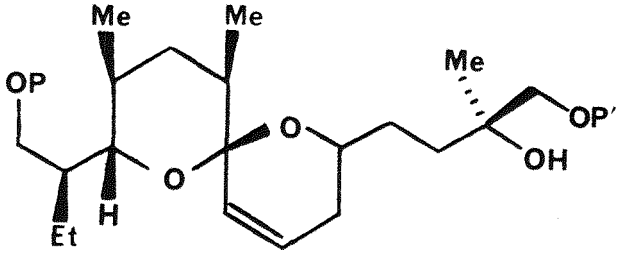


Scheme 33

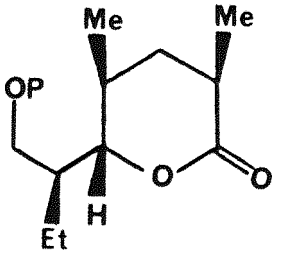
Using the same strategy for the synthesis of the model bis-spiroacetal (119), the bis-spiroacetal moiety of epi-17-deoxy-(O-8)-salinomycin (125) was envisaged to be assembled via a Barton-type reaction of substituted hydroxyspiroacetal (126). Based on the model studies,the hydroxyspiroacetal (126) in turn could be derived from a lactone fragment (127) and an acetylenic fragment (128) (Scheme 34). These latter two intermediates are therefore the building blocks for the construction of the bis-spiroacetal moiety of epi-17-deoxy-(O-8)-salinomycin (125).



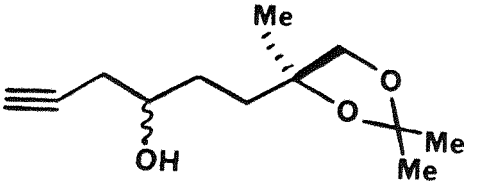
(125)



(126):P,P'=protecting groups



(127)



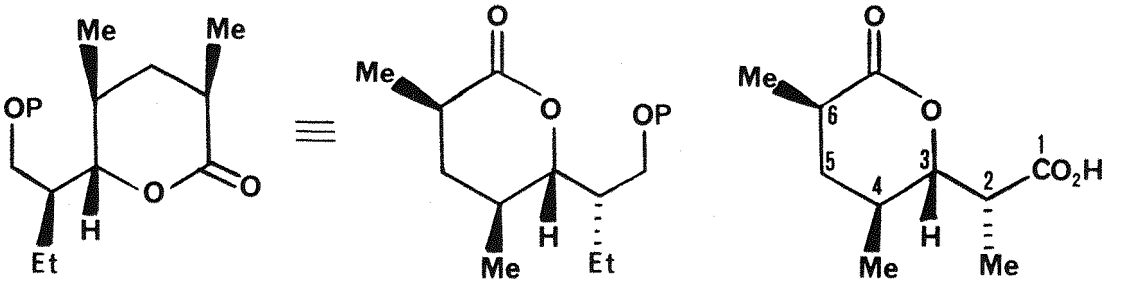
(128)

Scheme 34

3.2 Enantioselective Synthesis of Lactone (127)

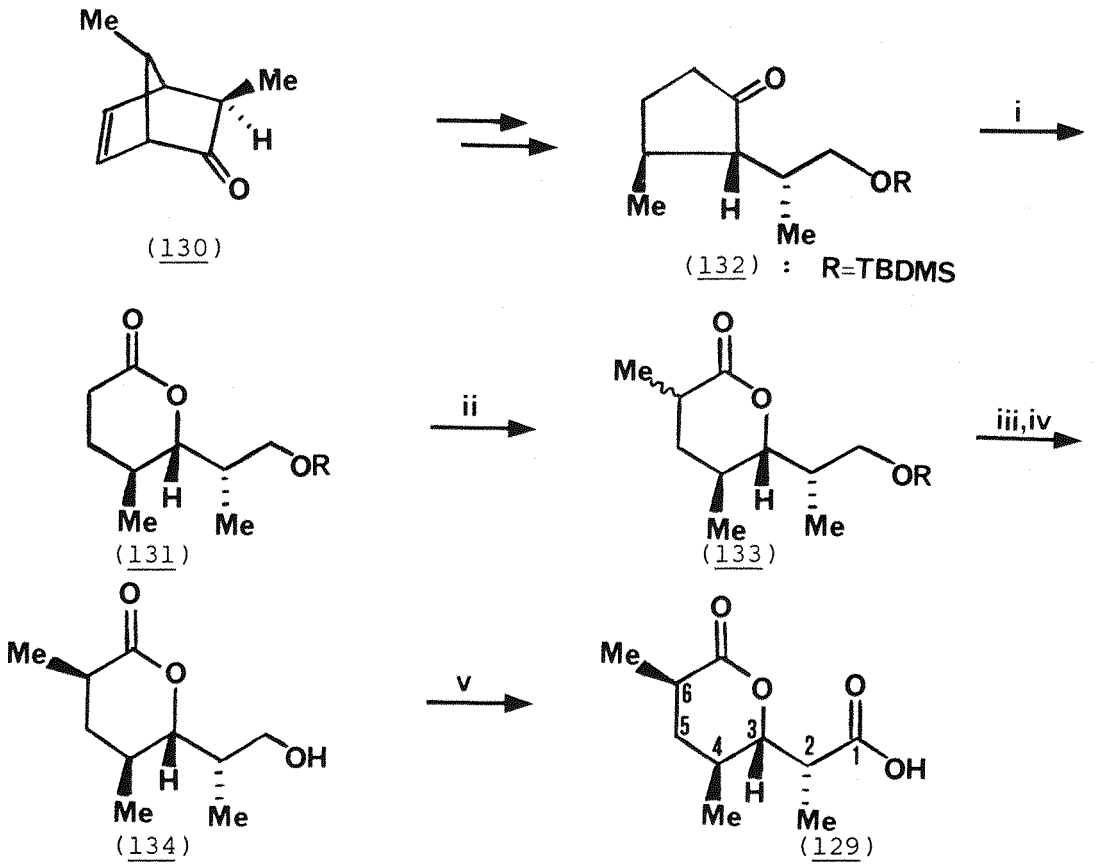
3.2.1 (+)-Prelog-Djerassi Lactonic Acid (129)

In planning the enantioselective synthesis of the required lactone (127) it was noticed that several important architectural features were common to the Prelog-Djerassi lactonic acid (129) derived via degradation of either methymycin or narbomycin[88,89]. Prelog-Djerassi lactone (129) itself, has served as a focal point for the development of a variety of new stereoselective chemical reactions and several syntheses both in racemic[90-100] and optically pure[101-110] form have been reported. These latter enantioselective syntheses, however, were most relevant to the synthesis of the required lactone (127).



(127): P=protecting group (129)

A major drawback in the first synthesis of (+)-Prelog-Djerassi lactone (129)[107] starting from optically pure bicyclo[2.2.1]heptenone (130) (Scheme 35) was the need for an epimerization step to provide the required stereochemistry at C-6. Thus, methylation of lactone (131) obtained from the Baeyer-Villiger oxidation of furanone (132), only provided a 1:1 mixture of the desired alkylated ketone (133) and its C-6 epimer. Although the stereoselectivity in the introduction of the methyl group at C-6 was improved in a later synthesis by Jarosz and Fraser-Reid[106], nevertheless, their synthesis only provided a 3:2 mixture of Prelog-Djerassi lactone (129) and its C-2 epimer.



Reagents

(i) mCPBA, $NaHCO_3$, CH_2Cl_2, 5°C;

(ii) LDA, THF, HMPA, MeI, -78°C;

(iii) LDA, THF, -78°C, 10% citric acid;

(iv) MeOH, p-TSA, 5°C, 12h.;

(v) Jones' reagent.

Scheme 35

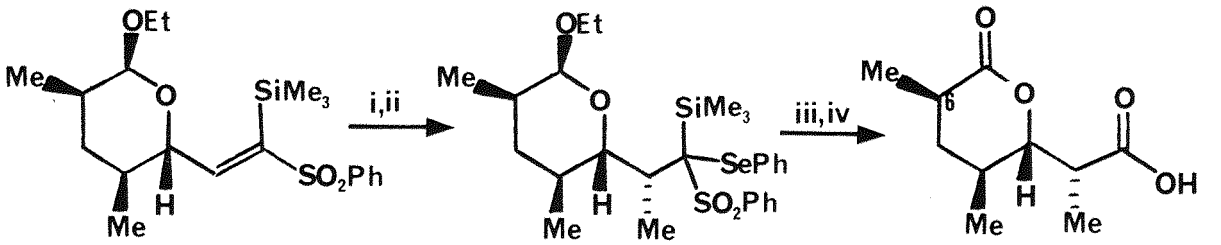
Two other lengthy syntheses of (+)-Prelog-Djerassi lactone (129) based on carbohydrate chemistry were also accomplished. In the first synthesis the side chain configurations were controlled by an Ireland-Claisen rearrangement[104]. In the second synthesis[102], however, elaboration of the carboxylic acid group involved :

(i) asymmetric addition of methyl lithium onto a hetero-olefin (135);

(ii) trapping of the carbanion intermediate to give the adduct (136);

and (iii) oxidative hydrolysis to the lactone acid (129) (Scheme 36).

In both syntheses, the methyl group at C-6 was introduced via stereoselective catalytic hydrogenation.



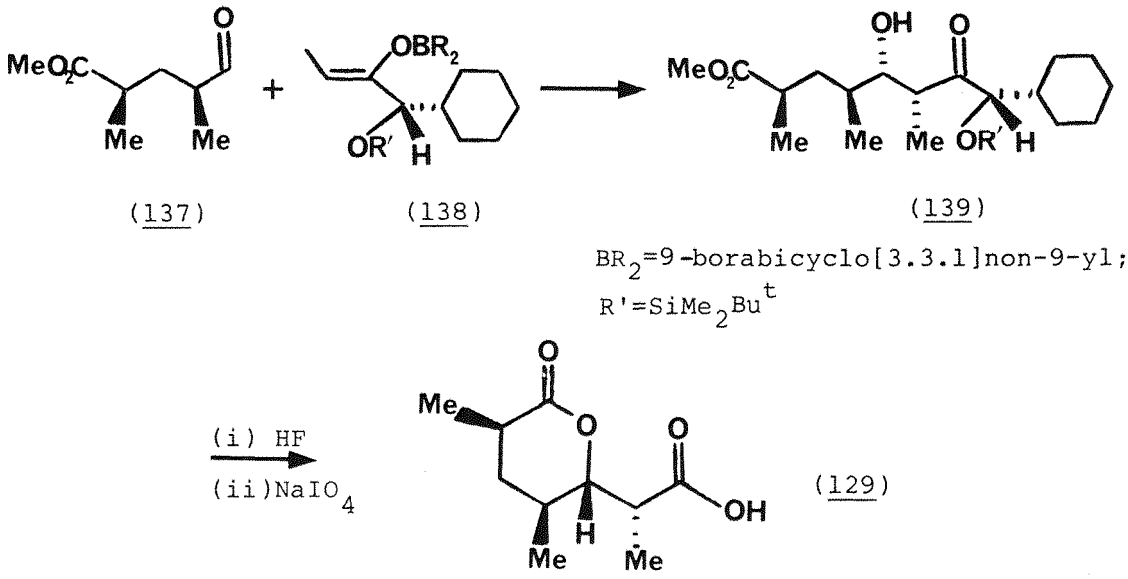
(135) (136) (129)

Reagents: (i) MeLi; (ii) PhSeCl; (iii) H_2O_2/HCl; (iv) Br_2,NaOAc.

Scheme 36

The commonest method[101,103,105,110] to prepare (+)-Prelog-Djerassi lactone (129) was based on the use of a stereoselective aldol condensation to form the C-2∿C-3 bond with the desired stereochemistry. Thus, the aldol condensation between (-)-aldehyde (137) with the (Z)-boron enolate (138) (Scheme 37), reported by Masamune et al[105], not only proceeded smoothly in 85% yield, but also with a diastereoselectivity of 40:1. Successive treatment of the aldol product (139) with hydrogen fluoride and sodium metaperiodate gave the required lactone (129).

Even greater selectivity in the aldol reaction was later achieved by Evans and Bartroli[103] (Scheme 38). Aldol condensation of the (Z)-boron enolate (140) derived from the chiral propionimide (141) with the (S)-aldehyde (142) gave the required aldol adduct (143) in 86% yield. Moreover, the stereochemical control in this process was remarkable. Diastereomer analysis on the unpurified adduct revealed that the total erythro: threo diastereoselection (vide infra) was 400:1 and asymmetric induction within the erythro manifold was 660:1. The final methyl-bearing asymmetric centre was introduced by a hydroboration process. Conversion of the aldol adduct (143) to its

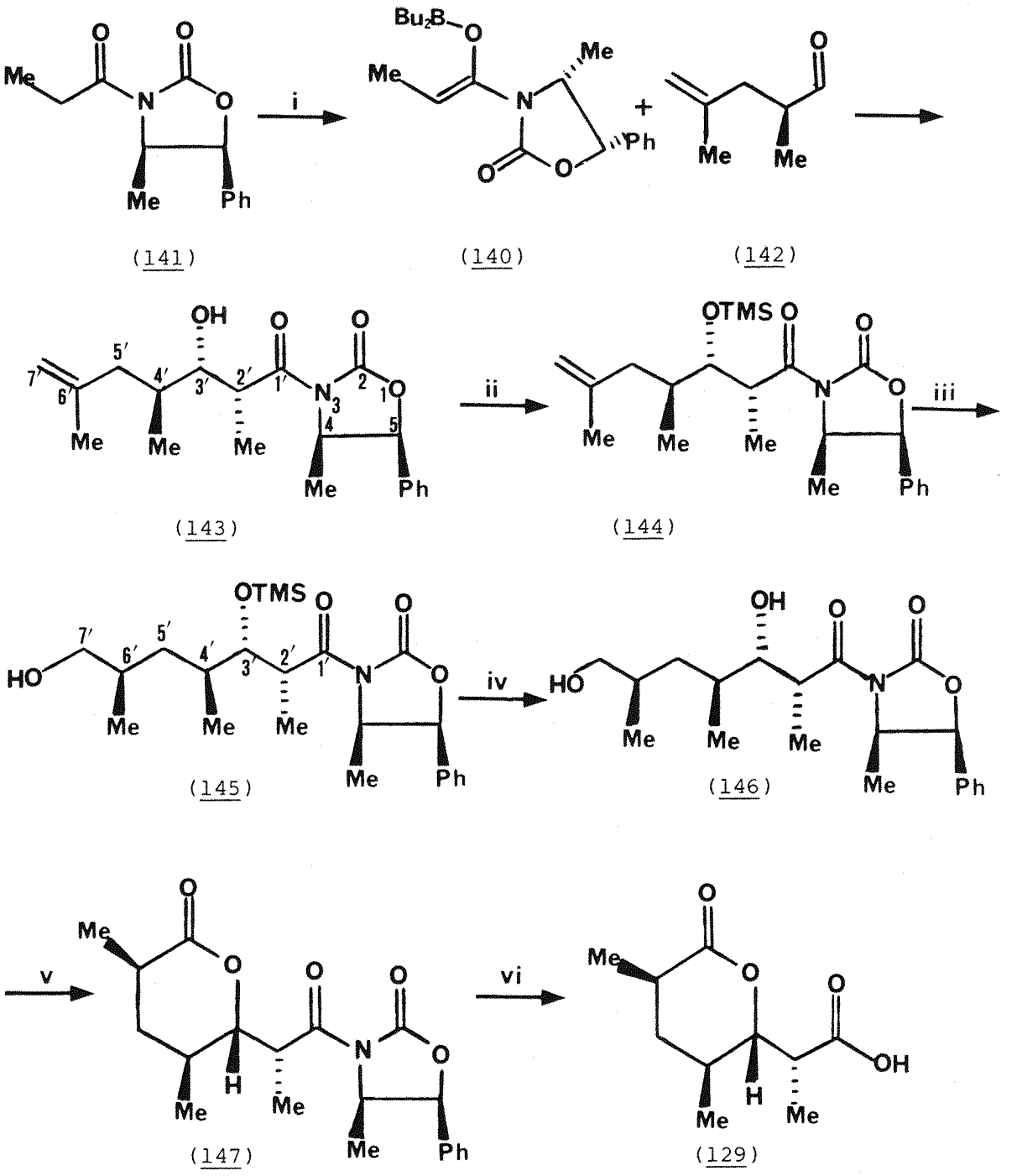


Scheme 37

trimethylsilyl ether (144) followed hydroboration with thexyl-borane with a subsequent bicarbonate peroxide oxidation afforded an 85:15 mixture of the (6'R)-alcohol (145) and its C-6' epimer. Acid hydrolysis to the diol (146) and subsequent ruthenium catalysed oxidation gave the lactone (147), which after removal of the chiral auxiliary with lithium hydroxide, yielded (+)-Prelog-Djerassi lactone (129).

A second synthesis[110] of the methyl ester of (+)-Prelog-Djerassi lactone (148) in which the same (Z)-boron enolate (140) was condensed with furfuraldehyde (149) with greater than 99% diastereoselectivity (Scheme 39) was hampered by a lengthy series of steps required to transform the furan (150) into the required lactone (148) via the hydropyranone (151). Furthermore, the synthesis involved a separation step using high pressure liquid chromatography and was not amenable to large scale preparations.

In light of the higher diastereoselectivity observed by Evans and Bartroli[103] than by Masamune et al[105] in their respective



Reagents

(i) Bu_2BOT_f, Et_3N, 0°C ; (ii) Me_3SiNEt_2, DMAP, CH_2Cl_2, 25°C, 2h;

(iii) $C_6H_{13}BH_2$ (2 equiv.), THF, 0°C, 5h., 79%;

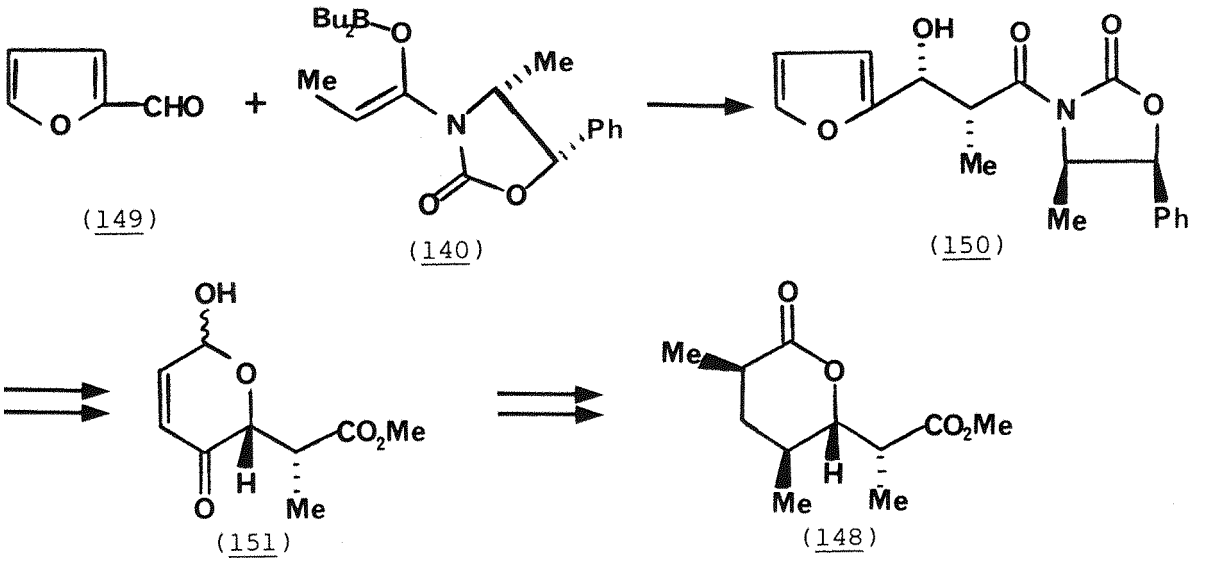
(iv) oxalic acid, MeOH, 25°C, 0.1h.;

(v) N-methylmorpholine-N-oxide, 1% $Ru(PPh_3)_3Cl_2$, acetone, 25°C, 3h., 73%;

(vi) LiOH, MeOH, 0°C, 0.1h.

Scheme 38

Scheme 39

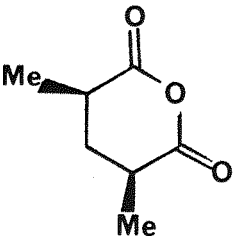


(149) (140) (150) (151) (148)

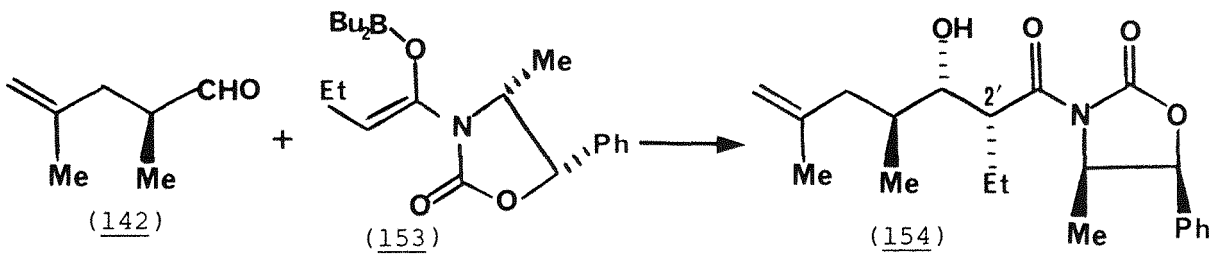
key aldol condensations,it was decided that Evans' synthesis (Scheme 38) be modified to provide a route to the lactone (127) required for the bis-spiroacetal moiety of epi-17-deoxy-(O-8)-salinomycin (125). Moreover, the synthesis of the aldehyde (142) used by Evans in the aldol condensation was prepared in relatively few steps by asymmetric alkylation of the propionimide (141) (vide infra). In contrast, the corresponding aldehyde (137) used by Masamune et al, was obtained from glutaric anhydride (152) in a somewhat lengthy synthesis which included a tedious 'classical' resolution. The necessary modifications were :

(i) the introduction of an ethyl group at C-2' of the aldol product by condensation of the analogous boron enolate (153) with the same aldehyde (142) to give the alcohol (154) (Eqn.26), and

(ii) extension of the synthesis of the analogous lactone acid (155) to the required protected lactone alcohol (127) by selective reduction of the carboxylic acid group (Eqn.27).

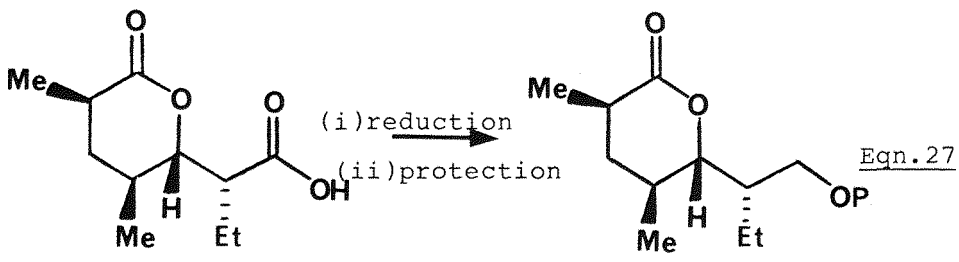


(152)



(142) (153) (154)

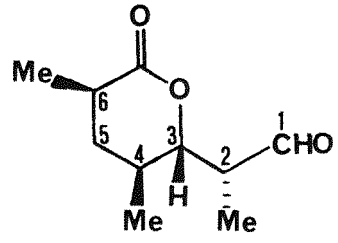
Eqn.26



(155) (127)

Eqn.27

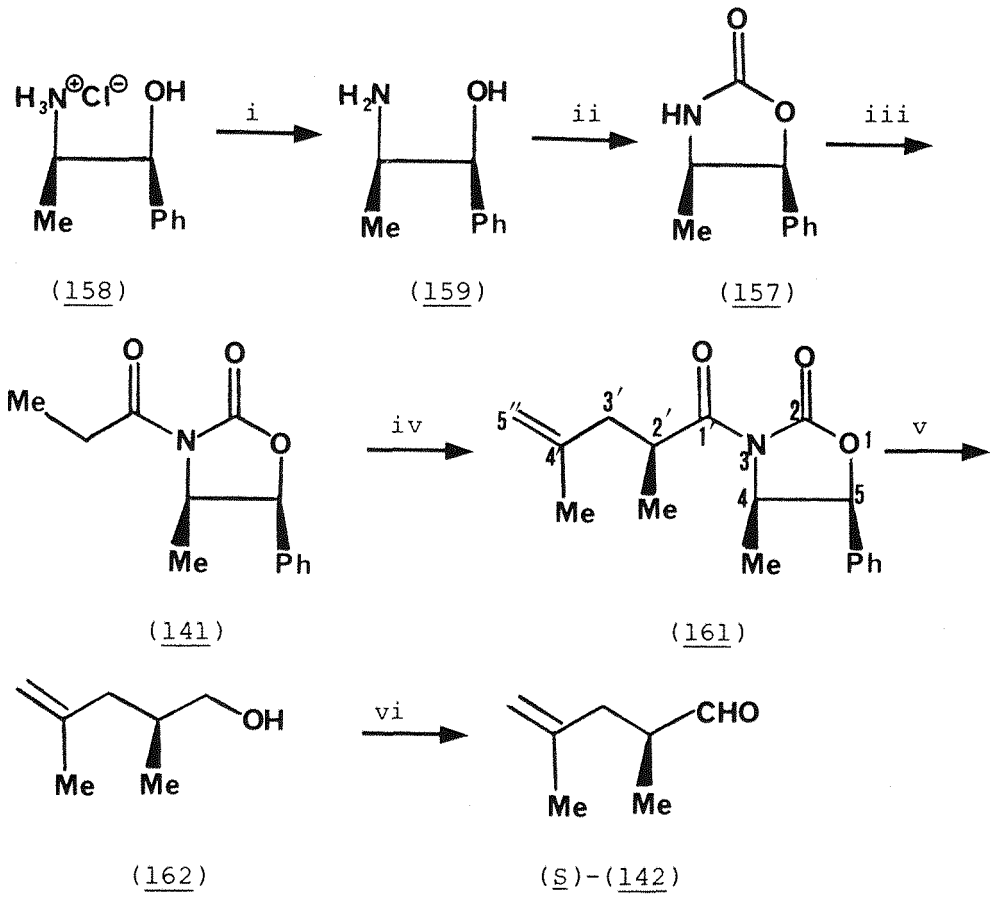
Before the adaptation of Evans' synthesis of (+)-Prelog-Djerassi lactone (129) (Scheme 38) to the synthesis of the required protected alcohol (127) is described, it is of note that an alternative to the use of a stereoselective aldol condensation to control the stereochemistry at C-2 and C-3 of lactone (129) has only recently been published. Thus, Midland and Tsai[108] made use of the high diastereoselectivity of the [2,3]-sigmatropic (Wittig) rearrangement to control the relative and absolute configurations of the two chiral centres at carbons 2 and 3 in their synthesis of (+)-Prelog-Djerassi lactonic aldehyde (156).



(156)

3.2.2 Synthesis of (S)-(+)-2,4-Dimethyl-4-penten-1-al (142)

The optically active aldehyde (142) required for the key aldol condensation with boron enolate (153) (Eqn.26) was first prepared using the synthesis outlined by Evans and Bartroli[103] for which few experimental details were given (Scheme 40).



Reagents

(i) 2M,NaOH,R.T., 2h; (ii) $(EtO)_2CO$,toluene, K_2CO_3, Δ ,15h., 80% overall ; (iii) Bu^nLi, THF,EtCOCl,-78°C,1h.,92%; (iv) Pr^i_2NH, Bu^nLi,-78°C,0.5h., then $CH_2=C(Me)CH_2I$ (160), -50 to -20°C, 3h., 73%; (v) $LiAlH_4$,Et_2O,0°C,0.1h, 82%; (vi) py.SO_3 (3 equiv.), Et_3N (7 equiv.), DMSO, 25°C, 3h., 64%.

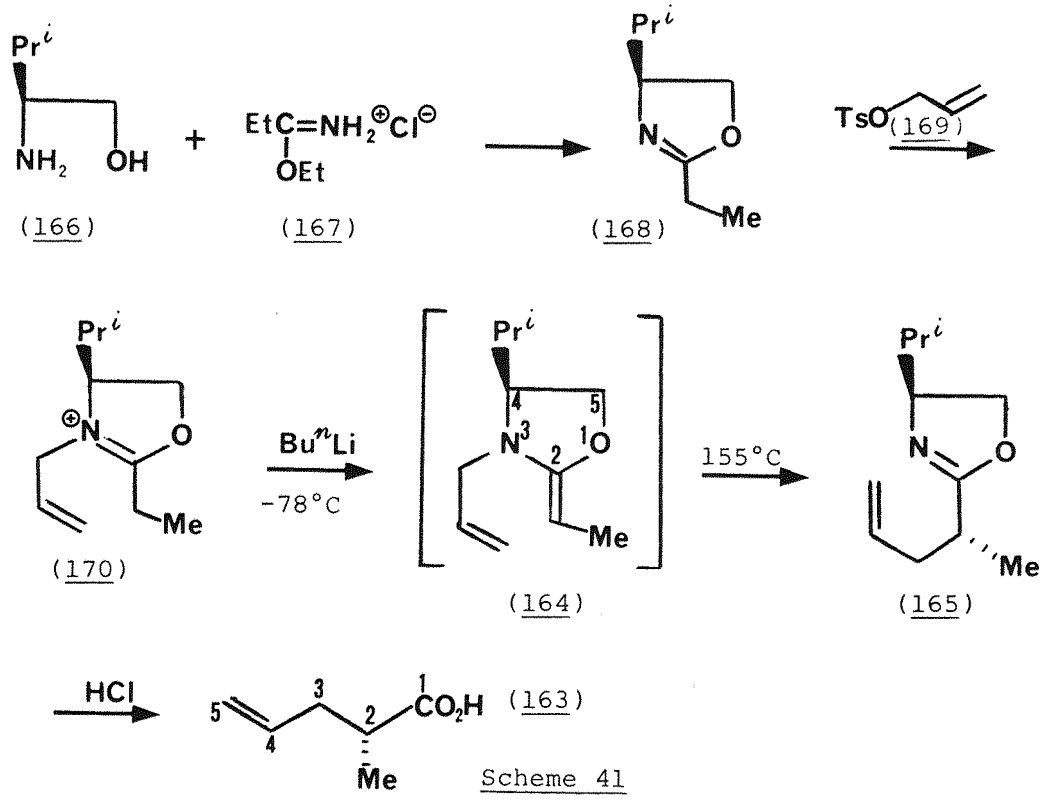
Scheme 40

The chiral auxiliary, oxazolidinone (157)[111], was easily prepared from (1S,2R)-(+)-norephedrine hydrochloride (158). Treatment of the hydrochloride salt (158) with aqueous sodium hydroxide gave the amino-alcohol (159) which after treating overnight in toluene with diethyl carbonate and potassium carbonate afforded the oxazolidinone (157) in 80% yield after recrystallization. Acylation was cleanly effected in 92% yield using butyl-lithium and propanoyl chloride in tetrahydrofuran at -78°C to give the propionimide (141)[111]. The propionimide (141) was then treated successively with lithium diisopropylamide in tetrahydrofuran at -78°C and freshly distilled methallyliodide (160)[112] (two equivalents) at -50°C to -20°C for 3 hours. The major (2'S)-alkylation product (161) was obtained in 73% yield after purification by 'flash' chromatography[80]. The melting point and optical rotation were identical to that reported by Evans and Bartroli[103]. Transformation of the imide (161) to the (S)-aldehyde (142) was then carried out in two steps. Thus, reduction of imide (161) with lithium aluminium hydride in diethyl ether at 0°C afforded the optically active alcohol (162) in 82% yield, which was subsequently oxidized to the required (S)-aldehyde (142) using pyridine-sulphur trioxide in dimethyl sulphoxide[113]. This latter reagent was found by Evans and Bartroli[103] to be exceptional in that no more than 0.1% racemization accompanied the oxidation process. In subsequent passes through the synthesis, material with the same optical rotation was obtained using dimethyl sulphoxide activated with trifluoroacetic anhydride. With both oxidizing agents, however, direct distillation of the crude product resulted in decomposition, thus, purification was effected by 'flash' chromatography[80]. The oxidation in both cases was clean, however, due to the volatility of the aldehyde (142), the yield was only 64%. This problem has also been encountered by Still and Shaw[95] using racemic material.

The low yielding oxidation step was highlighted even more by the low molecular weight of the aldehyde (142) compared with the oxazolidinone precursor (161). Thus, a large amount of the alkylated

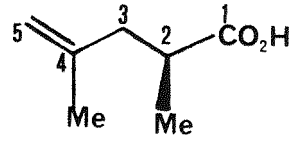
oxazolidinone (161) yielded only a small amount of the aldehyde (142). These later problems combined with the low recovery of the chiral auxiliary (157) from the reduction step meant that Evans' synthesis was not amenable to large scale preparation. Alternative syntheses of the optically active aldehyde (142) were therefore sought.

At this time, Kurth and Decker[114] had reported the synthesis of (R)-2-methyl-4-pentenoic acid (163) using the diastereoselective aza-Claisen rearrangement of N-allylketene N,O-acetal (164) to the oxazole (165) (Scheme 41). The N-allylketene N,O-acetal (164) was readily available from L-valinol (166). Condensation of L-valinol (166) with the imidate hydrochloride (167) gave the oxazole (168) which underwent N-allylation with allyl tosylate (169) to the oxazolinium salt (170). Neutralization of this salt with butyl-lithium afforded the N-allylketene N-O-acetal (164) which underwent thermal rearrangement to the oxazole (165) with a diastereoselectivity of 87:13. Subsequent hydrolysis yielded the (R)-acid (163).

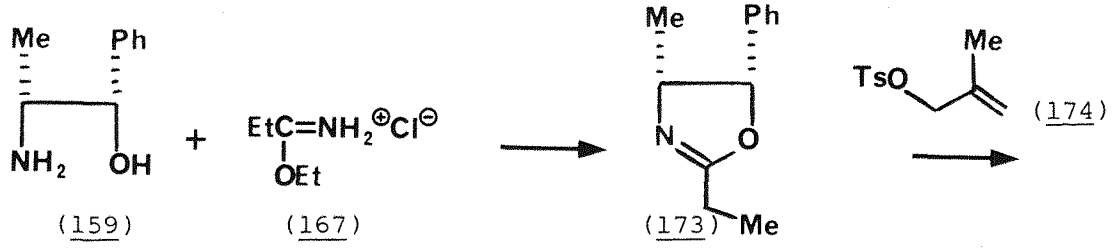


Scheme 41

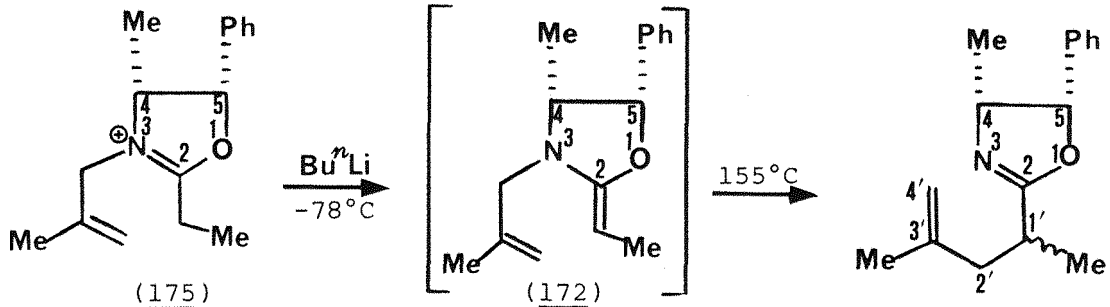
With a view to preparing the required (S)-aldehyde (142) from the (S)-acid (171), it was hoped that Kurth's synthesis of (R)-2-methyl-4-pentenoic acid (163) could be modified to prepare the (S)-acid (171). The requirement for the (S)-configuration at C-2 necessitated that the aza-Claisen rearrangement proceeded with the opposite sense of asymmetric induction to that observed by Kurth. This was envisaged to be effected by use of an N-allylketene N,O-acetal containing a substituent with the opposite stereochemistry at C-4. Examination of the readily available amino-alcohols suggested the N-allylketene N,O-acetal (172) (Scheme 42).



(171)



(159) (167) (173) (174)



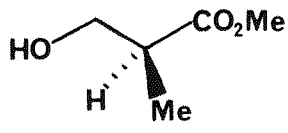
(175) (172) (176)

Scheme 42

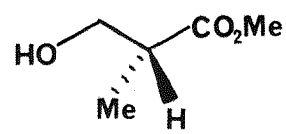
The oxazole (173) required for the preparation of N-allylketene N,O-acetal (172) was readily prepared by condensation of (1S,2R)-(+)-norephedrine (159) with the imidate hydrochloride (167) using the procedure described by Meyers et al[115]. N-allylation of the oxazole (173) with methallyl tosylate (174) at 50°C for 24 hours yielded the oxazolinium salt (175) in 82% yield which was not isolated. After neutralization of the salt (175) with butyl-lithium in tetrahydrofuran at -78°C, the resultant N-allylketene N,O-acetal (172) was heated in situ at 155°C in decalin for 3 hours, yielding the oxazole (176). In contrast to the high diastereoselectivity obtained by Kurth and Decker[114], the oxazole (176) was found to be a 1:1 diastereomeric mixture. This was indicated in the 360 MHz ^{1}H n.m.r. spectrum by the presence of two doublets (J 7 Hz) of equal intensity, resonating at δ_H 1.25 and δ_H1.27, which were assigned to the methyl group attached to C-1'.

The absence of any stereoselectivity in the aza-Claisen rearrangement of N-allylketene N,O-acetal (172) containing only a methyl substituent at C-4 was consistent with the results published by Kurth et al[116] after completion of this work. In this recent paper, the authors established that the steric bulk of the C-4 appendage was an important variable. Clearly, in the present case, the methyl group at C-4 in N-allylketene N,O-acetal (172) was of insufficient steric bulk to influence the stereochemical outcome of the rearrangement.

In light of these disappointing results an alternative synthesis of the required (S)-aldehyde (142) was investigated starting from the optically active building block, methyl 3-hydroxy-2-methylpropionate (177).

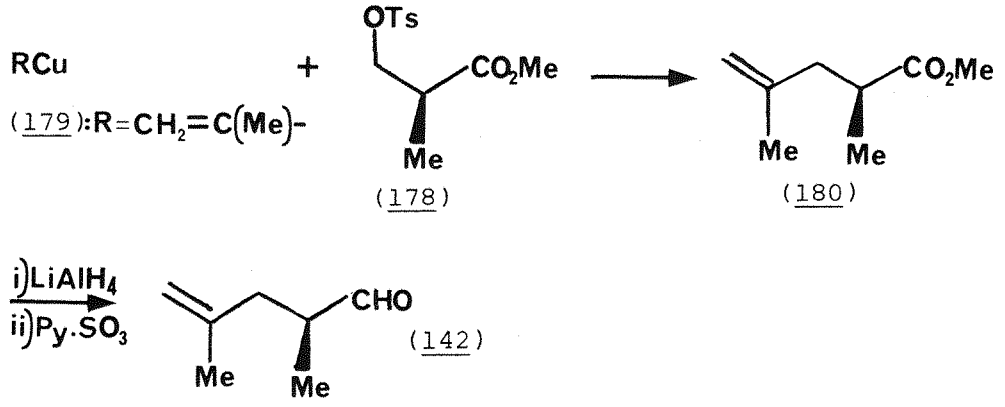


(S)-(177)



(R)-(177)

Initially, the synthetic plan for the synthesis of the (S)-aldehyde (142) entailed the coupling of the tosylate (178) with an isopropenylcopper reagent (179) to give the (S)-ester (180) which could then be easily converted to the (S)-aldehyde (142) (Scheme 43).



Scheme 43

The tosylate (178) was prepared in 83% yield from the (S)-alcohol (177) using p-toluenesulphonyl chloride in pyridine at 0°C for 12 hours. Attempts to couple the tosylate (178) with various isopropenylcopper reagents (179) are summarized (Table 5). Examination of the crude product in several instances revealed that reaction had occurred at the ester group in preference to the tosylate group, thus, suggesting the need for reduction of the ester group before attempting the coupling reaction.

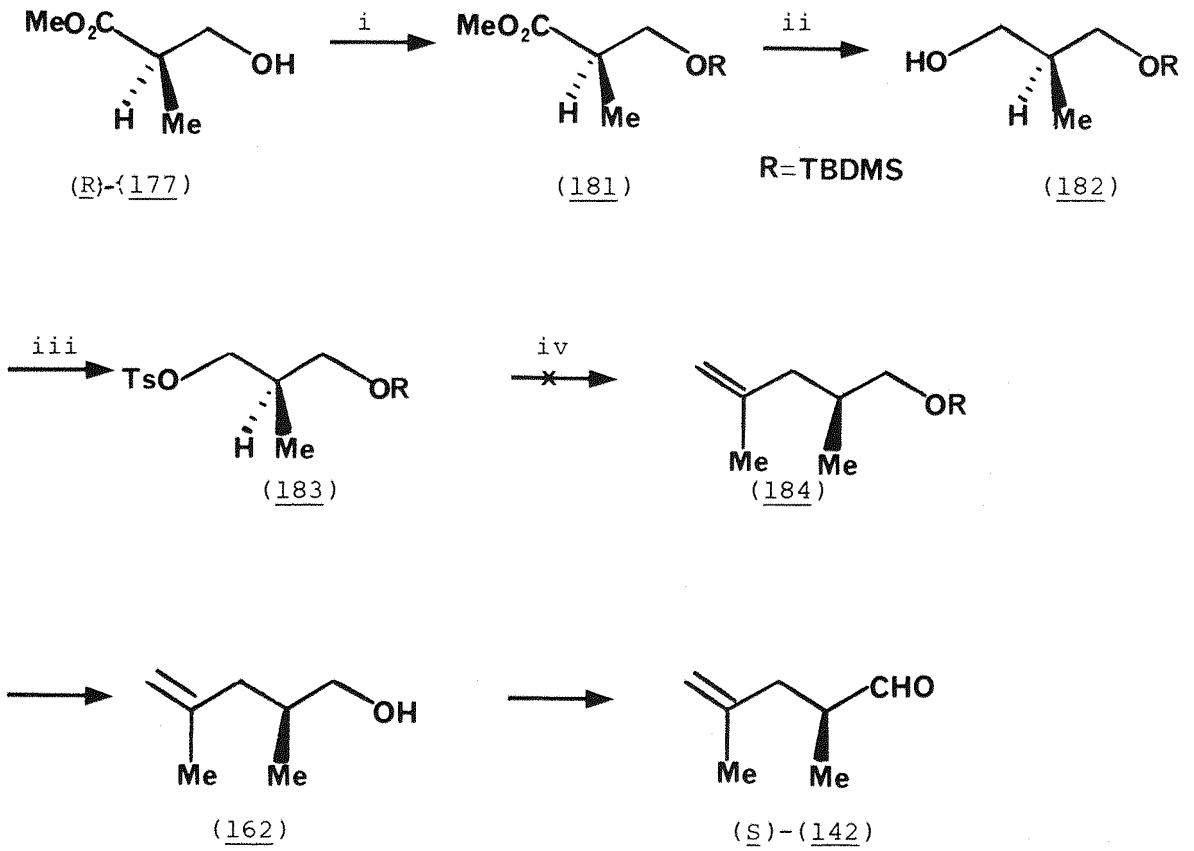
A suitable substrate for the cuprate reaction that did not contain an ester group was prepared from the corresponding (R)-methyl-2-hydroxy-2-methylpropionate (177) (Scheme 44). After protection as its tert-butyldimethylsilyl ether (181), the (R)-ester (177) was reduced in 89% yield with lithium aluminium hydride in diethyl ether at room temperature for 12 hours to the alcohol (182), which formed the required tosylate (183) upon treatment with p-toluenesulphonyl chloride in pyridine at 0°C for 12 hours. Coupling of this latter tosylate (183) with an isopropenyl copper reagent (179) was anticipated to yield the alkene (184), which after deprotection to the alcohol

Table 5. Attempted Coupling of Isopropenylcopper reagents (179) with Tosylate (178)

CUPRATE	CONDITIONS[a]	RESULT
R_2CuLi (1 equiv.)	 (2 equiv.), ^tBuLi (4 equiv.), CuI(1 equiv.), Et_2O -78°C to -60°C, 1h., then (178), -60°C to 0°C, 24h.	Crude ^1H n.m.r. shows no OMe group or OTs group. Complex mixture by t.l.c.
R_2CuLi (1.5 equiv.)	 (3 equiv.), ^tBuLi (6 equiv.), CuBr.DMS (1.5 equiv.), Et_2O, -78°C to -40°C, 3h., then (178), -70°C to -45°C, 12h.	Crude ^1H n.m.r. shows OTs group but no OMe group. Complex mixture by t.l.c.
R_2CuLi (1.5 equiv.)	 (3 equiv.), ^tBuLi (6 equiv.), CuBr.DMS (1.5 equiv.), Et_2O -78°C to -35°C, 4.5h., then (178), -40°C to -35°C, 12h.	Crude ^1H n.m.r. shows OTs group but no OMe group. Complex mixture by t.l.c.
$R_2CuCNLi_2$ (3 equiv.)	 (6 equiv.), ^tBuLi(12 equiv.), CuCN (3 equiv.), Et_2O, -78°C to -45°C, 3h., then (178), -45°C to -25°C, 10h.	Crude ^1H n.m.r. shows OTs group but no OMe group. Complex mixture by t.l.c.
$R_2CuCNLi_2$ (2 equiv.)	 (4 equiv.), ^tBuLi (8 equiv.), CuCN(2 equiv.), Et_2O -78°C to -60°C, 5h., then (178), -60°C to -40°C, 6h.	Crude ^1H n.m.r. shows no OTs group or OMe group Complex mixture by t.l.c.
RCuCNLi (1 equiv.)	 (1 equiv.), ^tBuLi (2 equiv.), CuCN(1 equiv.), Et_2O, -78°C to -40°C, 2h., then (178), -60°C to -30°C, 5h.	Crude ^1H n.m.r. shows OTs group but no OMe group. Complex mixture by t.l.c.

(a) All reactions were carried out under an argon atmosphere.

(162) followed by oxidation should afford the desired (S)-aldehyde (142). However, treatment of the tosylate (183) with the same isopropenylcopper reagents as those used for the attempted coupling with the ester (178) (Table 5) resulted mainly in recovery of starting material using temperatures below -60°C. At higher temperatures -60°C to -25°C recovery of starting material was also accompanied by the formation of isoprene dimers. The apparent inability of the isopropenylcopper reagents used to displace the tosylate (183) prompted the use of an acetylide anion to introduce the required unsaturation.



(R)-(177) (181) (182)

(183) (184)

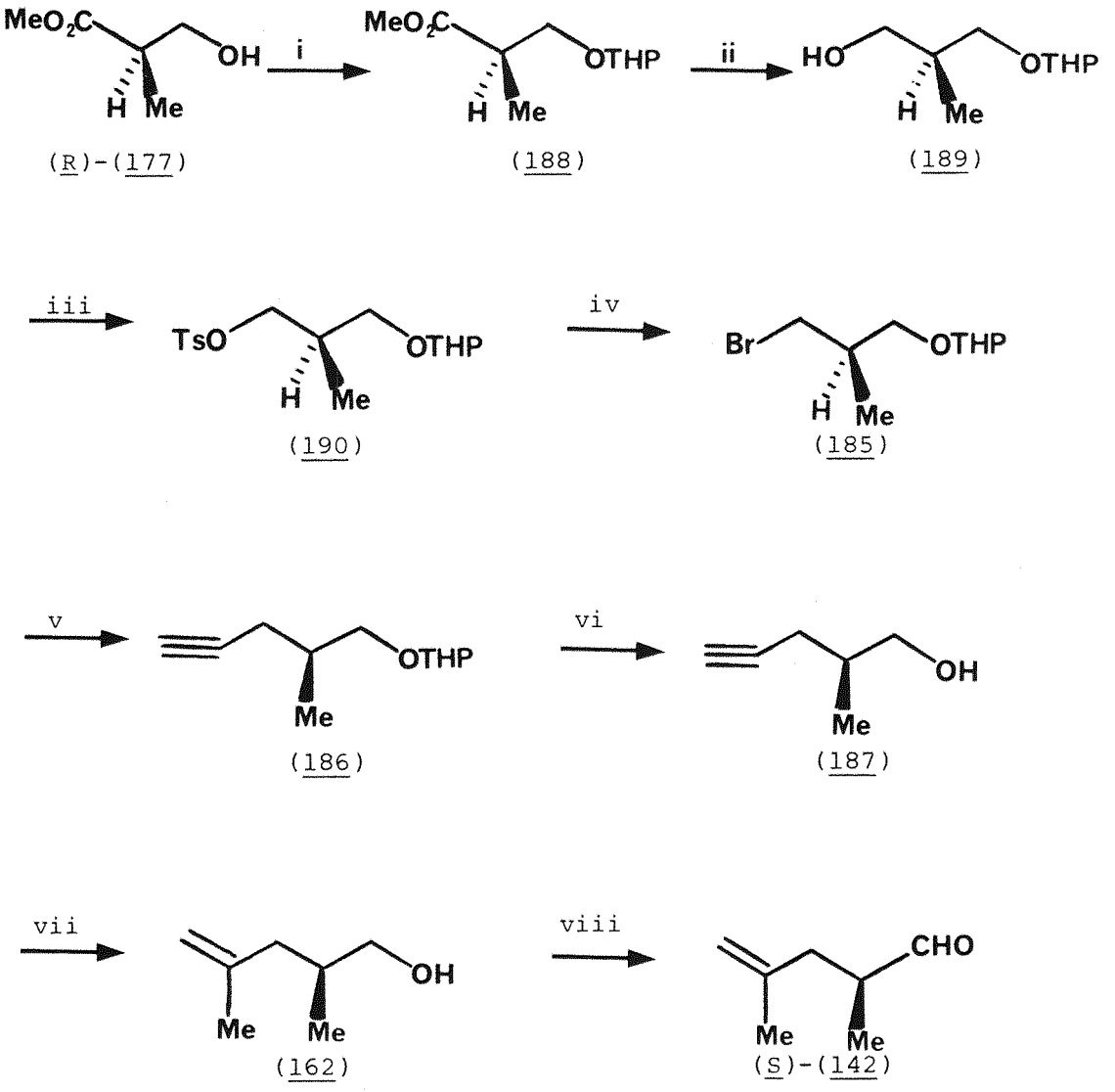
(162) (S)-(142)

Reagents

(i) TBDMSCl, imidazole, DMF, R.T., 91%; (ii) $LiAlH_4$, Et_2O, R.T., 12h., 89%; (iii) TsCl, py, 0°C, 12h., 82%; (iv) RCu(179): R=CH_2=C(Me)-

Scheme 44

In the successful synthesis of the required (S)-aldehyde (142) from the readily available building block, (R)-(177) (Scheme 45), the methyl substituted double bond was introduced by lithium acetylide displacement of bromide (185) to give the acetylene (186), followed by carboalumination of the derived alcohol (187) to the alkene (162) using similar conditions to those described by Negishi et al[117].



(R)-(177) (188) (189)

(190) (185)

(186) (187)

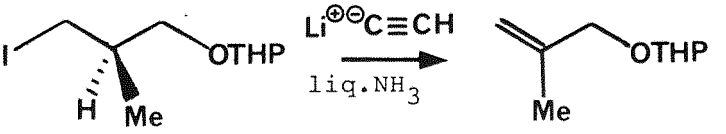
(162) (S)-(142)

Reagents

(i) DHP, p-TSA, R.T., THF, 100%; (ii) $LiAlH_4$, Et_2O, 0°C, 15h., 90%; (iii) TsCl, py, 0°C, 100%; (iv) LiBr (4 equiv.), $NaHCO_3$, THF, Δ, 92%; (v) $Li^{\oplus\ominus}C{\equiv}CH$ (5 equiv.), liq.NH_3, 15h., 60%; (vi) MeOH, Amberlite IR 118, room temp., 15h., 92%. (vii) Me_3Al, Cl_2ZrCp_2, $Cl(CH_2)_2Cl$, R.T., 15h., aqueous work-up, 82%; (viii) py.SO_3, DMSO, Et_3N, 25°C, 3h., 64%.

Scheme 45

The bromide (185) was easily prepared in a series of high yielding steps from the (R)-ester (177). Thus, protection of the alcohol (177) as a tetrahydropyranyl ether (188),followed by reduction of the ester group using the procedure described by Mori and Senda[118] gave the alcohol (189) in 90% yield. Treatment of the alcohol (189) with p-toluenesulphonyl chloride in pyridine at 0°C gave the tosylate (190) in quantitative yield,which was not isolated but converted directly to the bromide (185) in 92% yield by heating overnight with lithium bromide and sodium hydrogen carbonate in tetrahydrofuran. Addition of the bromide (185) to an excess of lithium acetylide, prepared by bubbling acetylene gas through a suspension of lithium amide, gave the acetylene (186) in 60% yield together with the alkene (191). Use of the corresponding iodide (192) in the lithium acetylide displacement reaction resulted in exclusive formation of the elimination product (191) (Eqn.28). Deprotection of the tetrahydropyranyl ether (186) to the alcohol (187) was then effected cleanly in 92% yield by stirring with Amberlite IR 118 in methanol overnight at room temperature. Treatment of this alcohol (187) with trimethylaluminium and zirconocene dichloride at room temperature overnight under argon,followed by aqueous work-up,gave the methyl substituted alkene (162) in 82% yield, which upon oxidation using the conditions described previously (page 75) gave the (S)-aldehyde (142). The optical rotation of the (S)-alcohol (162) prepared by this new route was identical to that recorded for material prepared by Evans' route. More importantly, in this new synthesis of the (S)-alcohol (162) all of the reactions could be conducted on a large scale thus allowing the preparation of the (S)-aldehyde (142) required for the aldol condensation (Eqn.26, page 73), in multigram quantities.



(192) (191) Eqn.28

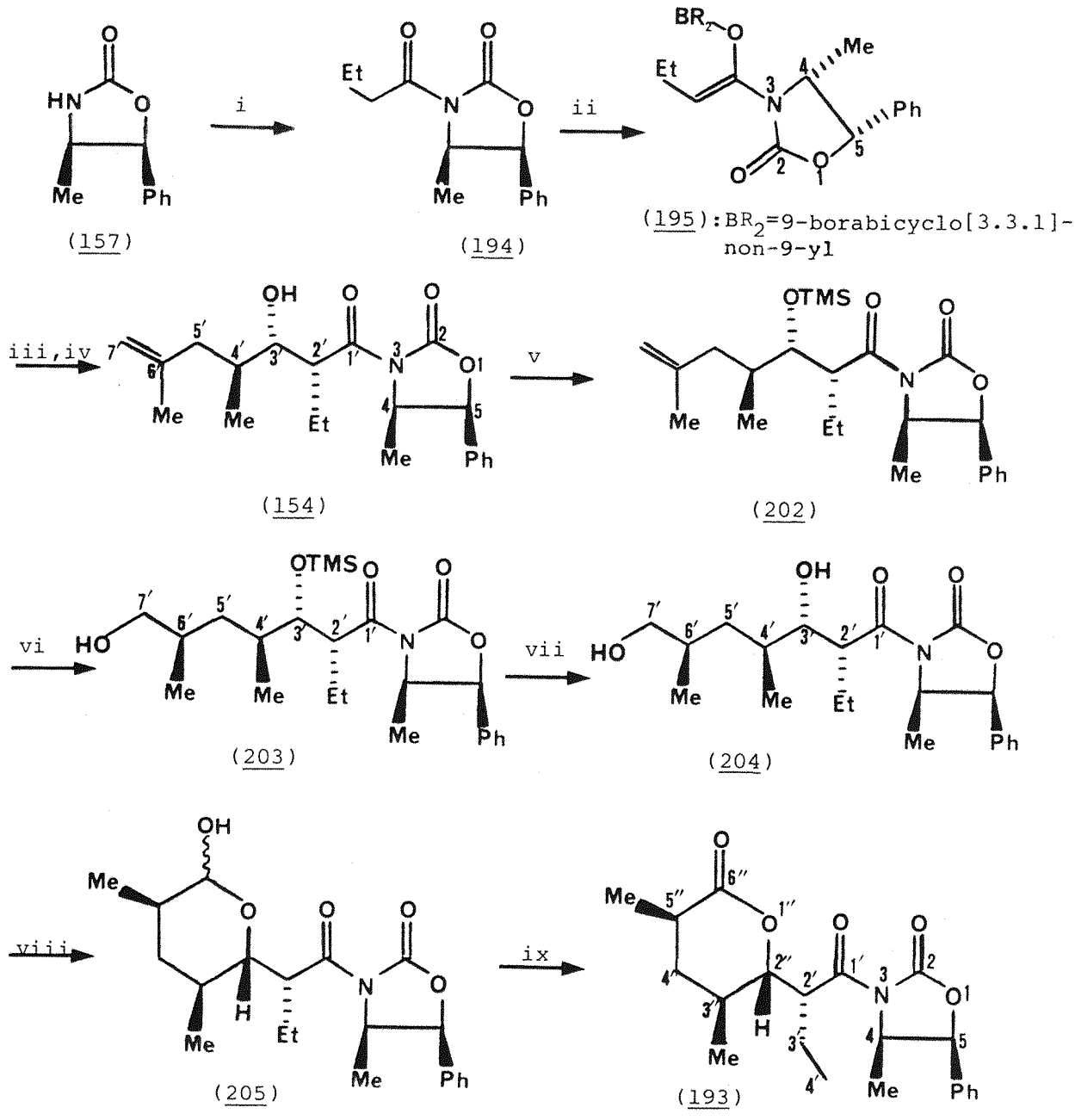
3.2.3 Completion of the Synthesis

Having devised an improved synthesis of the key optically active aldehyde (142), attention was directed to the preparation of the lactone amide (193) by adaptation of Evans' synthesis of (+)-Prelog-Djerassi lactone (129)[103] to the present case (Scheme 46).

Butanoyloxazolidinone (194) was prepared in 91% yield by lithiation of the oxazolidinone (157) with butyl-lithium at -78°C in tetrahydrofuran and subsequent reaction with butanoyl chloride. After purification by 'flash' chromatography[80], enolization of the acylated oxazolidinone (194) was effected by treatment with 9-borabicyclo[3.3.1]nonyl trifluoromethanesulphonate[119] (1.1 equivalents) followed by diisopropylethylamine (1.2 equivalents) at 0°C for 0.5 hour. Condensation of the derived (Z)-boron enolate (195) with the (S)-aldehyde (142) afforded, after oxidative work-up, the diastereomerically homogeneous aldol adduct (154) in 84% yield after purification by 'flash' chromatography[80].

In the crossed aldol condensation between the (4R,5S)-boron enolate (195) and the (S)-aldehyde (142) there are four possible product diastereomers (154), (196), (197),and (198) (Scheme 47). Given the extended or 'zig-zag' conformation of the carbon backbone containing the relevant functional groups (e.g. carbonyl and hydroxyl groups), as illustrated, diastereomers (154) and (196), disposing the ethyl and hydroxyl groups in a gauche relationship are defined as either 2',3'-erythro[120] or 2',3'-syn[121]. Similarly, diastereomers (197) and (198) are defined as either 2',3'-threo, or 2',3'-anti.

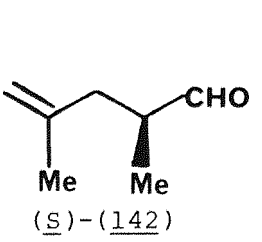
Due to the popularity of the erythro-threo convention in consideration of directed aldol condensations, its use, although not being rigorously correct, is continued in this discussion in the context of the foregoing definition. Hence, the relative stereochemistry at C-3' and C-4' can also be defined as threo or erythro as indicated (Scheme 47).



Reagents

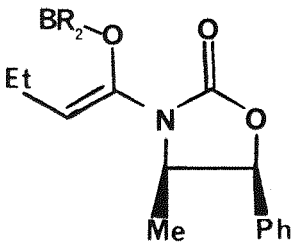
(i) Bu^nLi, THF, -78°C, $CH_3(CH_2)_2COCl$, 91% ; (ii) BR_2OTf (1.1 equiv.), Pr^i_2EtN (1.2 equiv.), CH_2Cl_2, 0°C, 0.5h.; (iii) CH_2=C(Me)CH_2CH(Me)CHO (142) CH_2Cl_2, -78°C, 25°C, 2h. ; (iv) MeOH, H_2O_2, 0°C, 1h., 84% overall,; (v) Me_3SiNEt_2 (1.5 equiv.), DMAP (0.2 equiv.), CH_2Cl_2, room temp., 15h., 85% ; (vi) $C_6H_{13}BH_2$ (2 equiv.), THF, 0°C, 5h., then aq.$NaHCO_3$, H_2O_2, room temp., 12h., 69% ; (vii) MeOH, oxalic acid, room temp., 0.2h., 91%; (viii) N-methylmorpholine-N-oxide (2 equiv.), $RuCl_2(PPh_3)_3$, acetone, room temp., 3h.; (ix) Ag_2CO_3 on celite, toluene, Δ, 1h., 70% overall.

Scheme 46

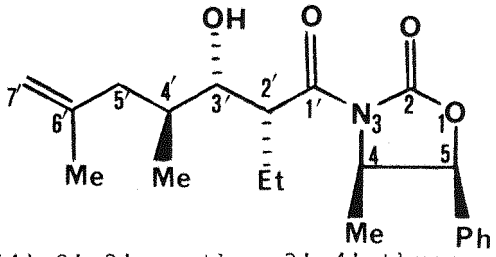


(S)-(142)

+

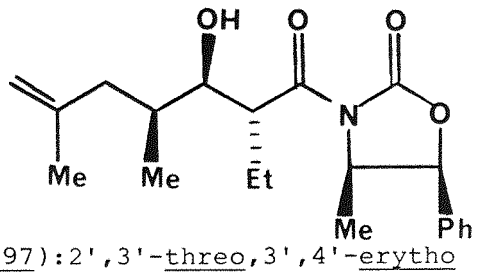


(195):BR_2=9-borabicyclo[3.3.1]non-9-yl



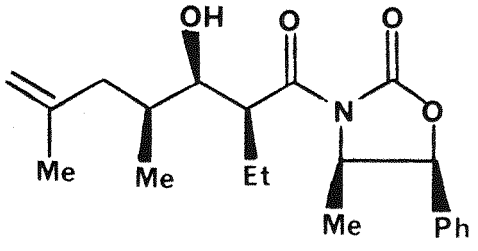
(154):2',3'-erythro,3',4'-threo

$J_{2',3'}$ 3-6 Hz, $J_{3',4'}$ 7-9 Hz.



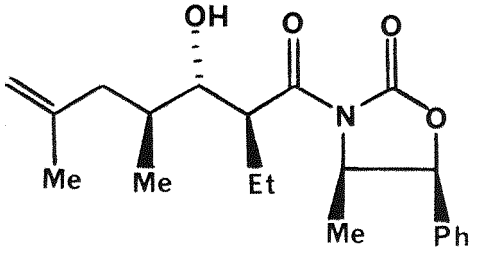
(197):2',3'-threo,3',4'-erytho

$J_{2',3'}$ 7-9 Hz, $J_{3',4'}$ 3-6 Hz



(196):2',3'-erythro,3',4'-erythro

$J_{2',3'}$ 3-6 Hz, $J_{3',4'}$ 3-6 Hz.

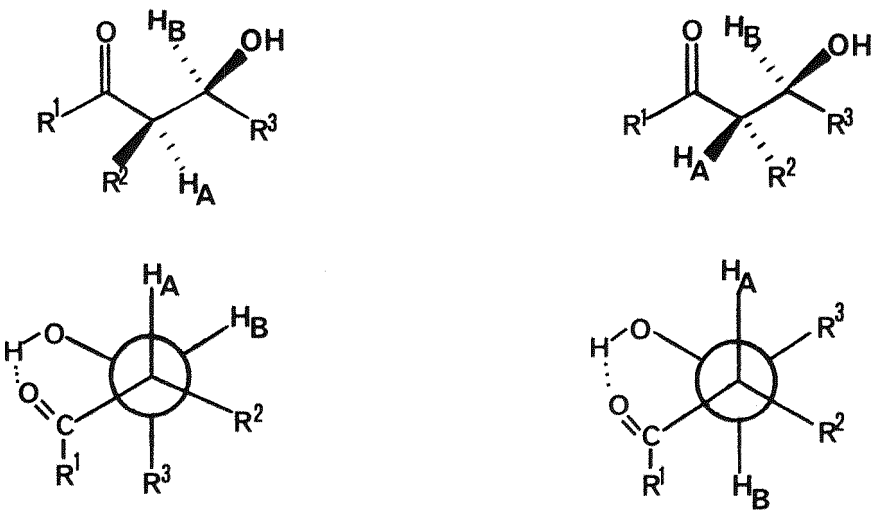


(198):2',3'-threo,3',4'-threo

$J_{2',3'}$ 7-9 Hz, $J_{3',4'}$ 7-9 Hz

Scheme 47

In many instances the erythro-threo stereochemical assignments may be conveniently made from the magnitude of the vicinal coupling constant, J_{AB} [122]. Thus, when intramolecular hydrogen bonding provides the dominant conformational bias, J_{AB}(erythro) falls in the range of 3-6 Hz, and J_{AB}(threo) is about 7-9 Hz (Figure 10).



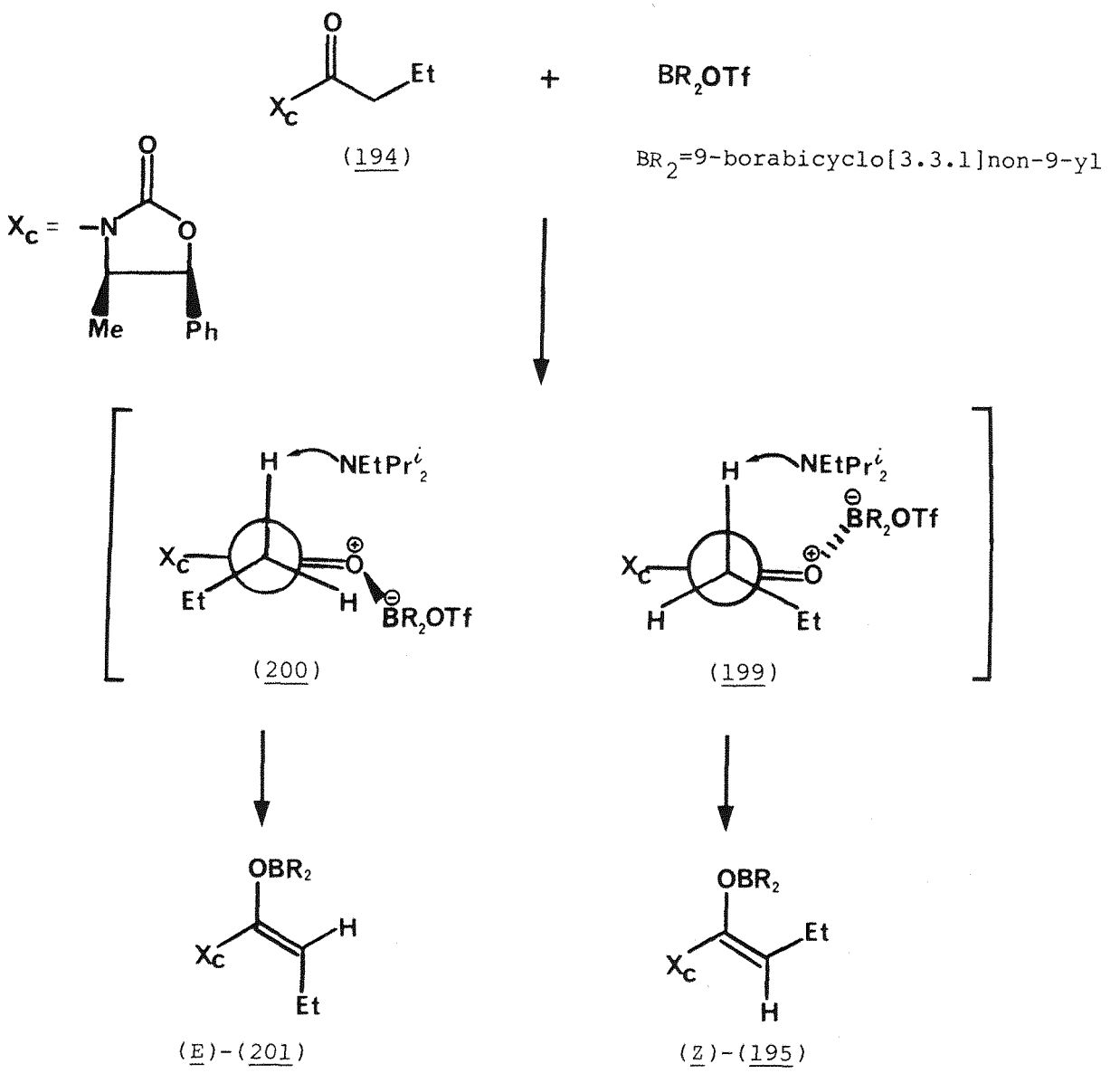
J_{AB} (erythro) 3-6 Hz

J_{AB} (threo) 7-9 Hz

Figure 10

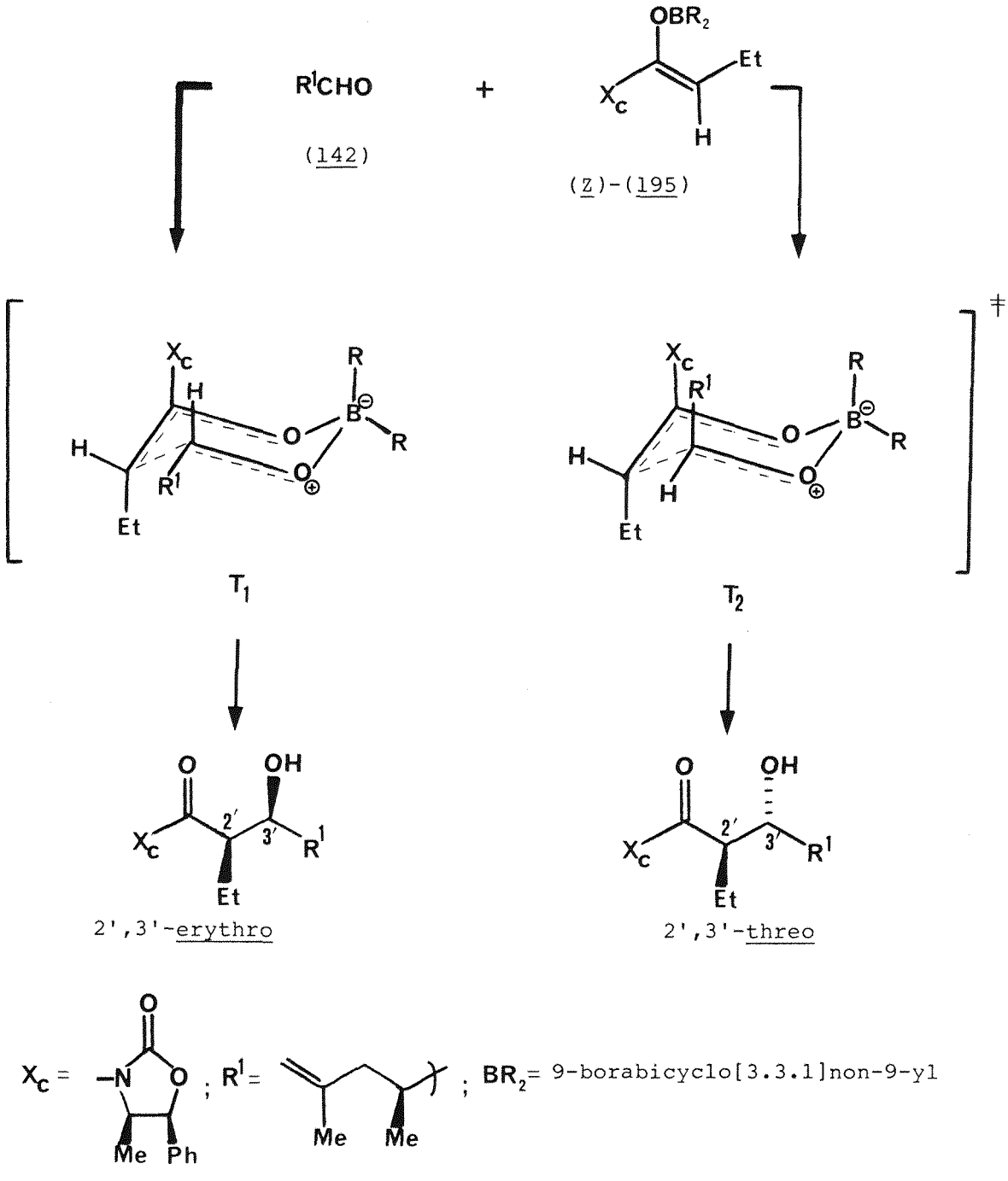
The stereochemistry assigned to the major aldol product (154) although based on literature precedent[103,111] was supported by the magnitude of the vicinal coupling constants obtained from the 360 MHz ^1H n.m.r. spectrum. Thus, the proton attached to C-3' resonated as a double doublet at δ_H 3.61 with coupling constants J 4 Hz and 7 Hz. Irradiation at the frequency corresponding to the proton attached to C-2', resonating at δ_H 4.19, collapsed the double doublet at δ_H 3.61 to a doublet with coupling constant $J_{3',4'}$ 7 Hz. Thus, the magnitude of this latter coupling constant, $J_{3',4'}$ 7 Hz, established the 3',4'-threo stereochemistry. By inference, the former smaller coupling constant $J_{2',3'}$ 4 Hz, established the relative stereochemistry at carbons 2' and 3' to be erythro.

The 2',3'-erythro stereochemistry is readily explained by the condensation of the (Z)-boron enolate (195) with the (S)-aldehyde (142) proceeding via a chair transition state. Firstly, formation of the (Z)-enolate (195) can be accounted for using the proposed mechanistic model (Scheme 48)[123]. Thus, using a hindered base, kinetic deprotonation of the anti-complex (199) leading to the (Z)-enolate (195) is favoured over deprotonation of the syn-complex (200) leading to the corresponding (E)-enolate (201).



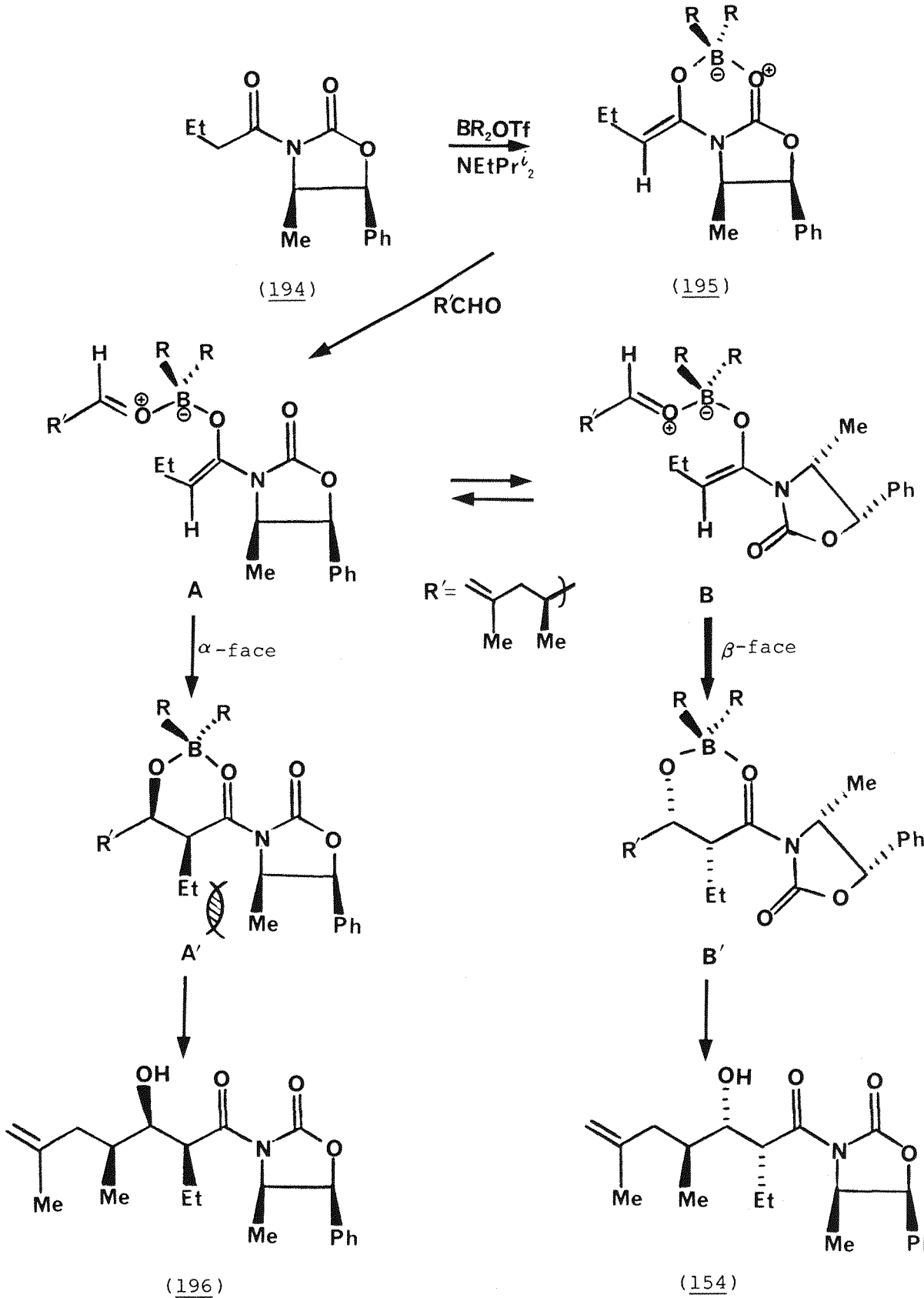
Scheme 48

Thus, the 2',3'-erythro selectivity arising from the use of the (Z)-enolate (195) in the aldol process can be readily accommodated by examination of the steric effects in the diastereomeric chair transition states (Scheme 49)[123,124,125]. Thus, transition state T_1, leading to the 2',3'-erythro product, is favoured over transition state T_2, leading to the 2',3'-threo product, due to the absence of the unfavourable pseudo-1-3-diaxial $R^1 \longleftrightarrow R$ and $X_C \longleftrightarrow R^1$ interactions in transition state T_1.



Scheme 49

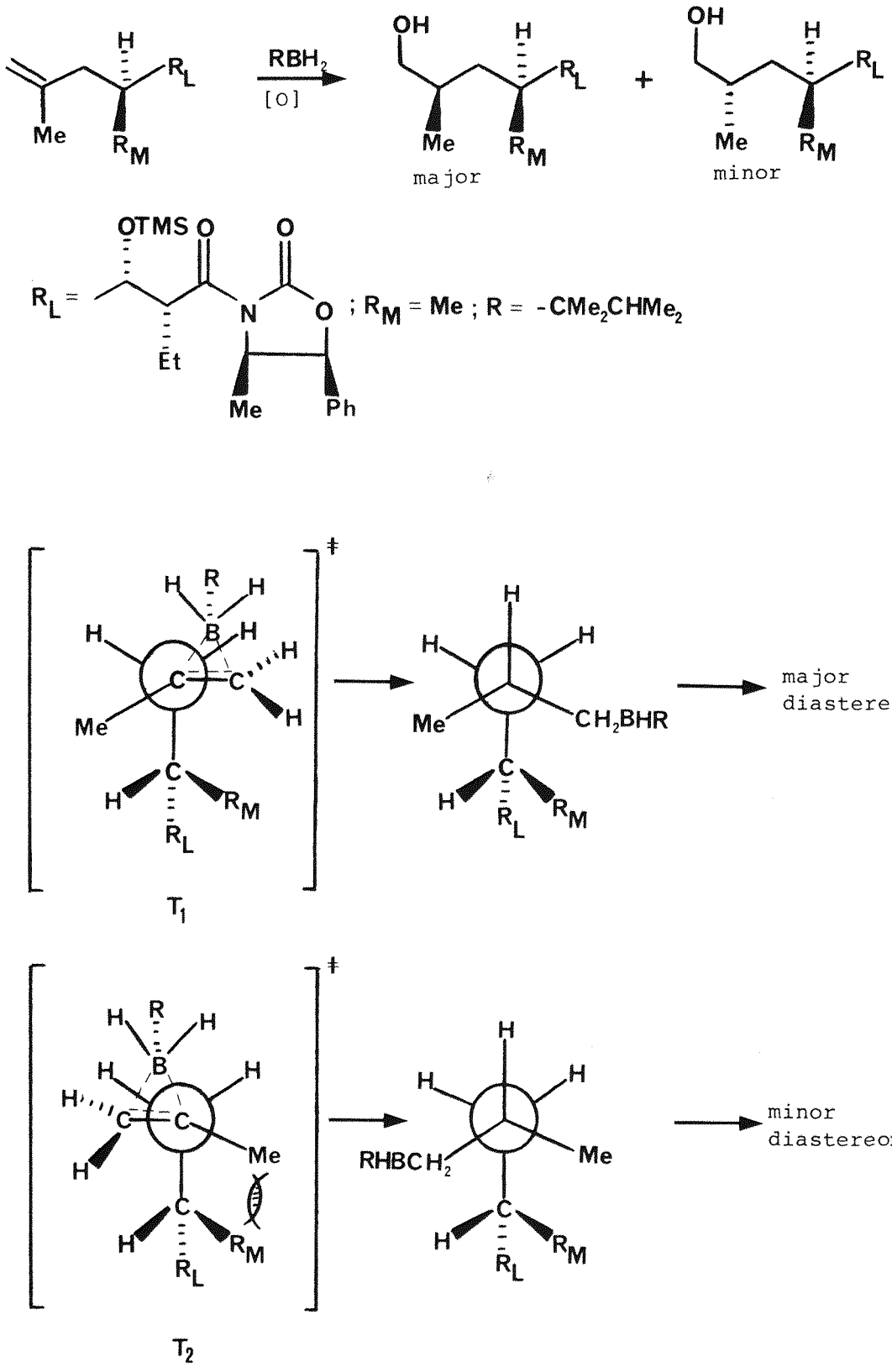
Whilst an explanation has been given for the formation of an aldol product wherein the relative stereochemistry at C-2' and C-3' is erythro the preference for the 2',3'-erythro, 3',4'-threo adduct (154) over the 2',3'-erythro, 3',4'-erythro adduct (196) is due to



Scheme 50

the resident chirality in the (Z)-enolate (195). In order to explain the absolute stereochemistry of the major aldol adduct (154) one must examine the control elements in the condensation process which regulate the sense and degree of chirality transfer. Whilst this is a difficult task, Evans et al have provided an operational model to explain the diastereofacial selectivity (Scheme 50)[124,125]. In the respective aldol transition states derived from conformers A and B leading to the erythro diastereomers A' and B' it was assumed that the developing imide resonance[126] locked the chiral auxiliary in one of the in-plane conformations illustrated in products A' or B'. Based on an examination of models, it was proposed that developing Et⟷Me allylic strain steric interaction[127] disfavoured that transition state leading to A'. These steric considerations were largely attenuated in the transition state leading to the observed erythro adduct B'.

With the aldol adduct in hand, elaboration to the lactone amide (193) proceeded as outlined previously (Scheme 46, page 85). The alcohol (154) was converted in 85% yield to the trimethylsilyl ether (202) using N-N-diethyltrimethylsilylamine in dichloromethane at room temperature with a catalytic amount of 4-dimethylaminopyridine. Subsequent hydroboration with freshly prepared thexylborane (2 equivalents) in tetrahydrofuran at 0°C for 5 hours, followed by bicarbonate peroxide oxidation afforded the alcohol (203) in 69% yield after purification by 'flash' chromatography[80]. The stereochemistry assigned to C-6' was based on the stereochemical outcome of the analogous hydroboration step in Evans' synthesis of (+)-Prelog-Djerassi lactone (129)[103] and was confirmed at a later stage in the synthesis (vide infra). The 1,3-asymmetric induction noted in this hydroboration of the terminal olefin (202) has been found to be rather general in nature and a transition state model has been proposed by Evans et al to account for these observations[128]. Thus, in the general hydroboration reaction where R_L and R_M are sterically dominant and subordinate ligands respectively the model established for the observed π-facial selectivity is illustrated (Scheme 51). In both


RBH2
[O]
major
minor
OTMS
Et
Me
Ph
; RM = Me ; R = -CMe2CHMe2
major diastereomer
minor diastereomer
T1
T2

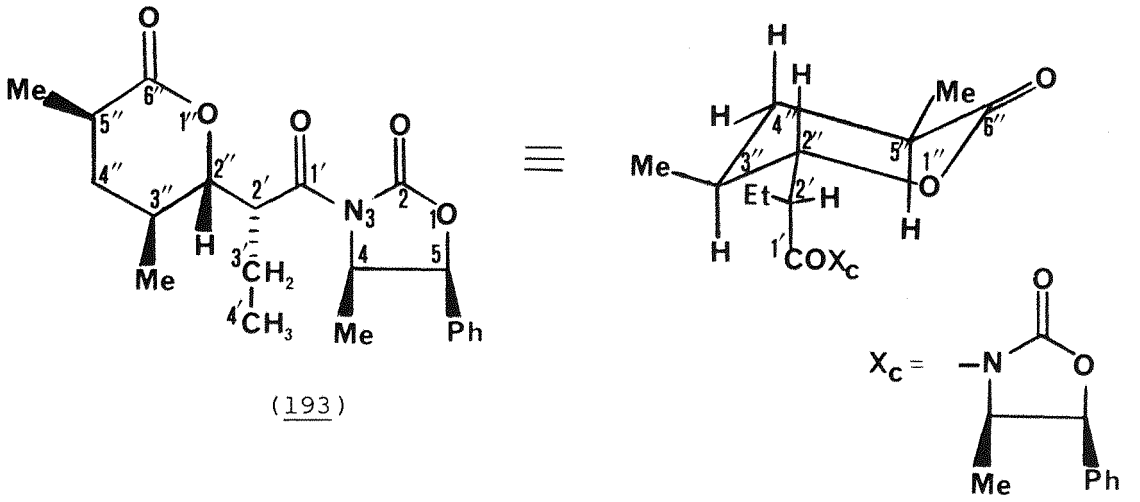
Scheme 51

transitions states T_1 and T_2 the allylic substituent ($-CHR_MR_L$) is ordered anti-periplanar to the partially formed B-C bond in accordance with the theoretical studies in olefin addition reactions[129]. When the sterically dominant ligand R_L adopts the illustrated anti-conformation a subtle olefin diastereofacial bias may be created. Thus, in this orientation it was proposed that the developing Me$\leftrightarrow R_M$ non-bonding interaction destabilizes transition state T_2 relative to transition state T_1.

The synthesis of the lactone amide (193) was completed by mild acid hydrolysis in methanol at room temperature of the alcohol (203), to the diol (204), followed by oxidation. The 2',3'-erythro, 3',4'-threo stereochemistry of the diol (204) was confirmed by the magnitude of the vicinal coupling constants, $J_{2',3'}$ 3.9 Hz and $J_{3',4'}$ 7.1 Hz, respectively. The diastereotopic protons attached to C-7' resonated as double doublets at δ_H3.46 and δ_H3.57, respectively, with coupling constants J_{gem} 10.9 Hz and $J_{6',7'}$ 4.3 Hz. The oxidation of the diol (204) to the lactone (193) was best achieved in two steps. Treatment of the diol (204) with N-methylmorpholine-N-oxide (2 equivalents) catalysed by tris(triphenylphosphine) ruthenium(II)chloride[130] in acetone at room temperature for 3 hours afforded the lactol (205). Direct conversion of the lactol (205) to the lactone (193) was then effected cleanly by treating with Fetizon's reagent[131] (silver carbonate on celite) in toluene for 1 hour. The overall yield for the oxidation was 70% after purification by 'flash' chromatography[80]. Alternatively, direct oxidation of the diol (204) to the lactone (193) using an excess of N-methylmorpholine-N-oxide was possible, however, this required a much longer reaction time.

The 360 MHz ^{1}H n.m.r. data and ^{13}C n.m.r. data were consistent with the assigned structure and, moreover, indicated that the optically active lactone amide (193) prepared, was in fact a single diastereomer. The proton attached to C-2" (Figure 11) resonated as a double doublet at δ_H 4.37 with coupling constants J 3.8 Hz and

9.4 Hz . Irradiation at the frequency corresponding to the resonance at δ_H4.04, assigned to the proton attached to C-2', collapsed the signal at δ_H4.37 to a doublet with coupling constant $\underline{J}$ 9.4 Hz. Hence, this larger coupling constant, 9.4 Hz, was assigned to $\underline{J}_{2",3"}$, consistent with the protons attached to carbons 2" and 3" being diaxial. The smaller coupling constant, 3.8 Hz, assigned as $\underline{J}_{2',2"}$ was consistent with a gauche relationship between the protons attached to C-2" and C-2'.



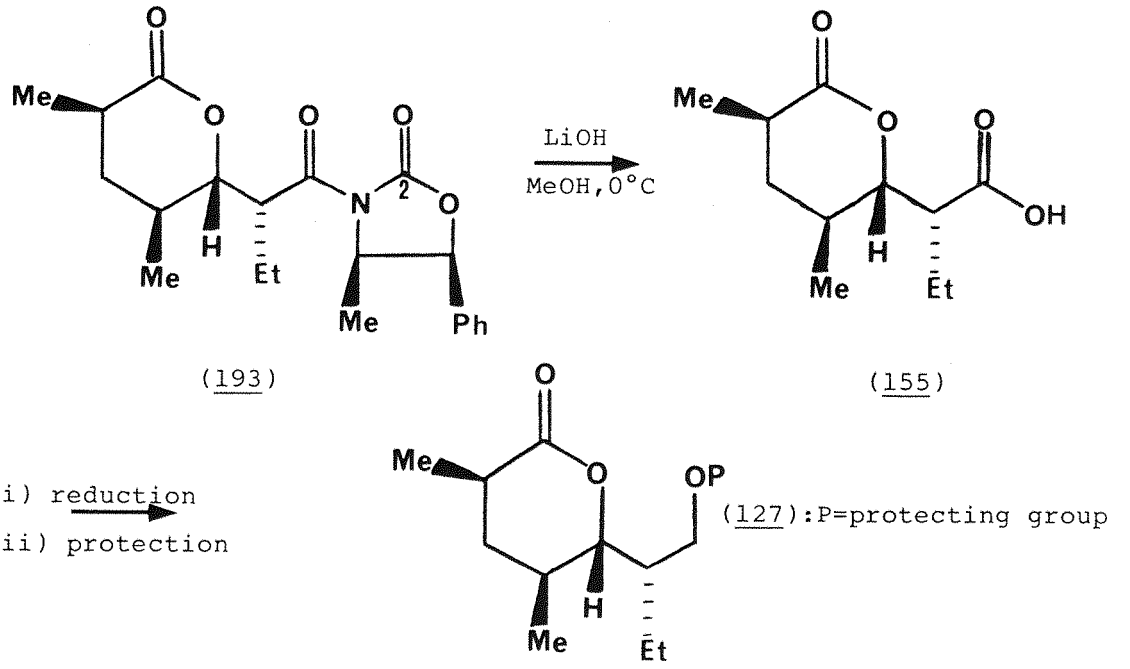
(193)

Figure 11

The appearance of a quartet, $\underline{J}$ 12 Hz, at δ_H1.40 assigned to the axial proton attached to C-4" established that this proton was coupled not only to the geminal equatorial proton but also to the vicinal protons attached to C-3" and C-5". Moreover, the magnitude of the coupling constant, $\underline{J}$ 12 Hz, clearly indicated that this vicinal coupling was due to coupling between axial protons. Hence it was established that the protons attached to C-3" and C-5" were in fact axial and the methyl groups equatorial. Irradiation at the frequency corresponding to the resonance at δ_H2.53, assigned to the axial proton attached to C-5",collapsed the quartet at δ_H1.40 to a triplet, $\underline{J}$ 12 Hz, consistent with assignment of the resonance at δ_H1.40 to the axial proton attached to C-4".

The 360 MHz ^{1}H n.m.r. data clearly established that both the methyl groups at C-3" and C-5" and the substituent at C-2" occupied equatorial positions as required. More importantly, the observation that the methyl group at C-5" occupied an equatorial position confirmed the original assignment of the stereochemistry at C-6' in the hydroboration product (203). If the opposite epimer at C-6' had been formed in the hydroboration step then this would have resulted in formation of a lactone in which the methyl group at C-5" was axial. This is clearly not the case.

At this point, it was anticipated that removal of the chiral auxiliary by basic hydrolysis, followed by selective reduction of the carboxylic acid (155), would provide the lactone (127) required for the synthesis of the bis-spiroacetal moiety of epi-17-deoxy-(O-8)-salinomycin (125) (Scheme 52).

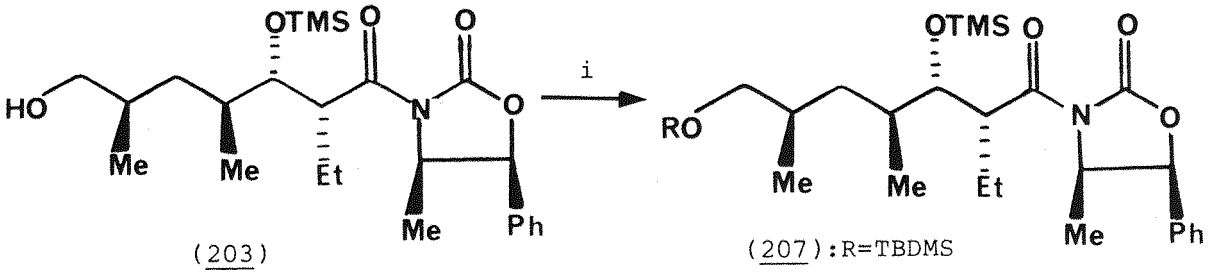


(193) (155)

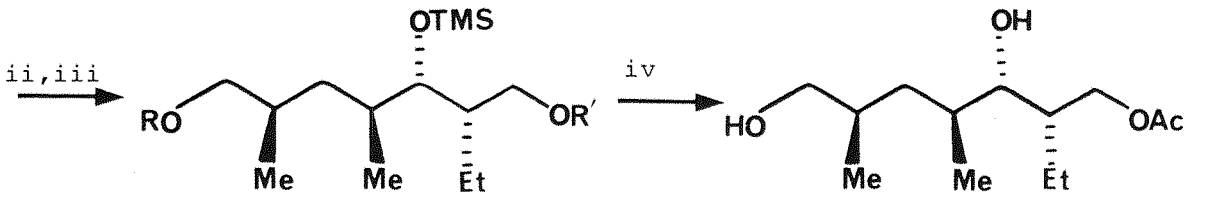
Scheme 52

Attempts, however, to hydrolyse the lactone amide (193) using lithium hydroxide in methanol at 0°C lead to a complex mixture of products. Thus, in contrast to the clean hydrolysis of the analogous lactone amide (147) (Scheme 38, page 71), reported by Evans and Bartroli[103], hydrolysis of lactone amide (193) was complicated by competing hydroxide attack at the C-2 carbonyl group. This problem was further complicated by the difficulties associated with the separation of the required acid (155) from the by-products. In a recent paper, Evans et al[132] allude to the difficulties in the removal of the chiral auxiliary by direct hydrolysis, stating that, "the relative rates of nucleophilic attack at either of the two carbonyl functions of these carboxamides are dictated by subtle interplay of electronic and steric effects". Hence it was decided to reductively remove the chiral auxiliary before the oxidation and cyclization steps.

Adopting this approach, the synthesis of the lactone acetate (206), containing the required oxygen functionality at C-1", was completed (Scheme 53). Thus, the hydroboration product, alcohol (203), was protected as its tert-butyldimethylsilyl ether (207) in 94% yield using tert-butyldimethylsilyl trifluoromethanesulphonate (1.5 equivalents) and 2,6-lutidine (2.2 equivalents) in dichloromethane at 0°C. Removal of the chiral auxiliary was then effected by treatment with lithium borohydride (1 equivalent) at room temperature overnight in tetrahydrofuran affording the alcohol (208) in 71% yield after purification by 'flash' chromatography. Formation of the acetate (209) in 92% yield using acetic anhydride (1 equivalent) and triethylamine (2 equivalents) in dichloromethane, followed by cleavage of the silyl protecting groups by stirring overnight in methanol with Amberlite IR 118 resin, yielded the diol (210) which was not isolated. Direct oxidation of the diol (210) to the lactone (206) was best effected in 68% yield using N-methylmorpholine-N-oxide catalysed by bis(triphenylphosphine)ruthenium(II)chloride followed by Fetizon's reagent[131], as described earlier for the preparation of lactone amide (193) (page 93).



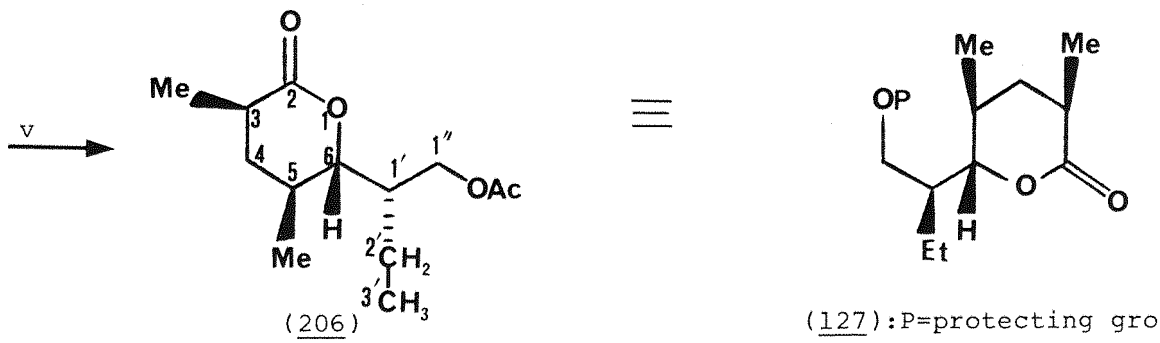
(203) (207):R=TBDMS



(208):R=TBDMS,R'=H

(209):R=TBDMS,R'=Ac

(210)



(206)

(127):P=protecting group

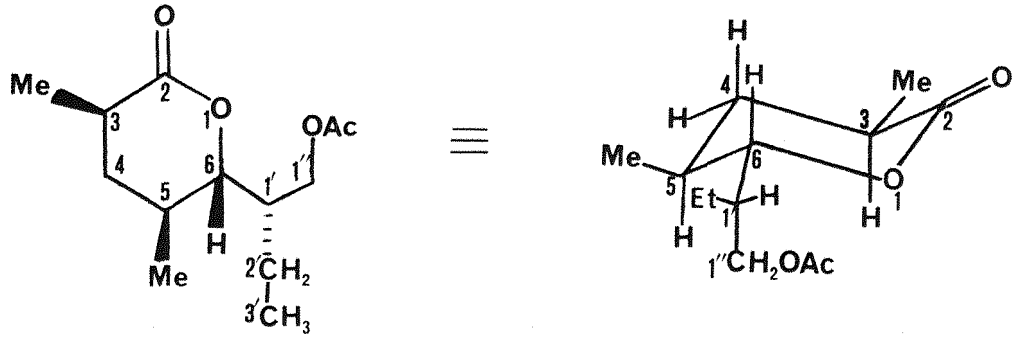
(206):P=Ac.

Reagents

(i) TBDMSOTf(1.5 equiv.), 2,6-lutidine (2.2 equiv.), 0°C, 0.25h., 94%; (ii) $LiBH_4$ (1 equiv.), THF, R.T., 15h., 71%; (iii) Ac_2O (1 equiv.), Et_3N(2 equiv.), DMAP, R.T., 2h., 92% ; (iv) MeOH, Amberlite IR 118, R.T., 1.5 h.; (v) N-methylmorpholine-N-oxide (2 equiv.), $RuCl_2(PPh_3)_3$, acetone, R.T., 3h., then Ag_2CO_3 on celite, toluene, Δ , 1h., 68% overall.

Scheme 53

The lactone acetate (206) thus prepared was optically active, $[\alpha]_D^{21}$ + 77.6° (c, 0.51, CCl_4), and both the high field ^1H n.m.r. and ^{13}C n.m.r. spectra indicated that the product was a single diastereomer. Analogous to the lactone amide (193), the axial proton attached to C-4 resonated as a quartet at δ_H1.39 with coupling constant, J 12 Hz. The magnitude of the coupling constant established that the methyl substituents at C-3 and C-5 occupied equatorial positions (Figure 12). Similarly, the proton attached to C-6 resonated as a double doublet at δ_H4.32 with the coupling constants, $J_{5,6}$ 10.6 Hz and $J_{1',6}$ 5.3 Hz, indicating that the substituent at C-6 also occupied an equatorial position.



(206)

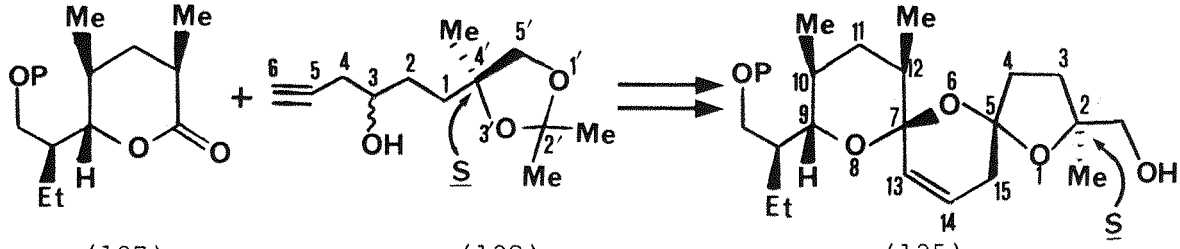
Figure 12

In summary, the successful enantioselective synthesis of the lactone acetate (206) from the optically active building block, (R)-methyl 3-hydroxy-2-methylpropionate (177), has established a viable route to the lactone fragment (127) required for the synthesis of the bis-spiroacetal moiety of epi-17-deoxy-(O-8)-salinomycin (125). The only modification being the simple substitution of the acetate group at C-1″ for a protecting group compatible with a lithium acetylide addition reaction.

3.3 Synthesis of Acetylene (128)

With the preparation of the lactone (127) in hand, plans for the synthesis of the bis-spiroacetal moiety of epi-17-deoxy-(O-8)-salinomycin (125), based on the retrosynthetic analysis outlined

(Scheme 34, page 66) and the model studies discussed in Chapter 2, rested on the synthesis of the acetylenic building block (128). In developing the construction of the required acetylenic fragment (128) it was noted that carbons 2 and 5 of the 1,6,8-trioxadispiro-[4.1.5.3]pentadec-13-ene ring system of epi-17-deoxy-(O-8)-salinomycin (125) would be derived from carbons 4' and 3, respectively, of the acetylene (128) (Scheme 54). The (S)-configuration at C-2 in the bis-spiroacetal moiety of the natural product necessitated the synthesis of the acetylene (128) in which the configuration at C-4' was also S. Since C-3 of the acetylene is to be transformed into a spiro centre it was not necessary to control the stereochemistry at this carbon.



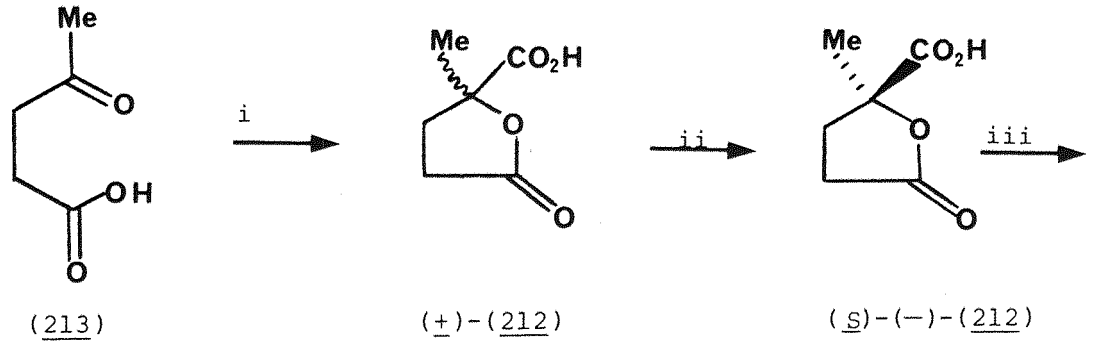
(127) (128) (125)

P=protecting group

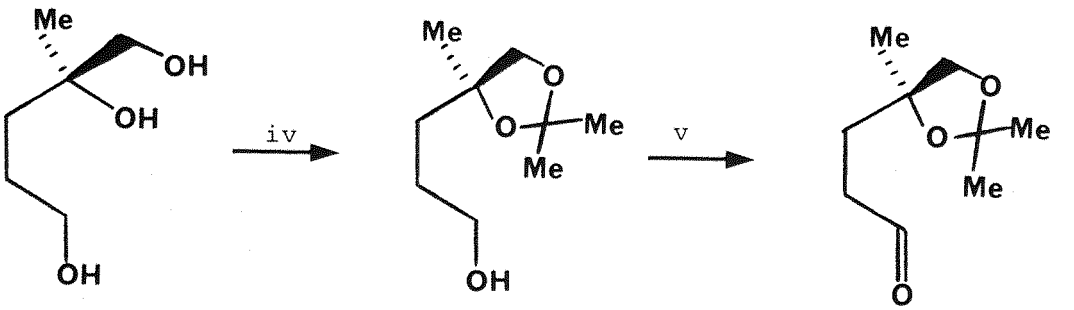
Scheme 54

The successful approach to the (4'S)-acetylene (128) involved the addition of the Grignard reagent of propargyl bromide to the (S)-aldehyde (211). The (S)-aldehyde (211), in turn, was prepared in several steps from the simple intermediate (S)-(-)-lactonic acid (212) which was available via a 'classical' resolution (Scheme 55).

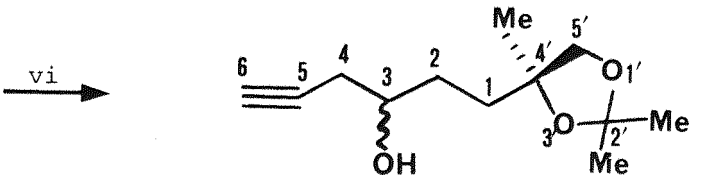
Large quantities of the racemic lactonic acid (212) were prepared from levulinic acid (213) by cyanohydrin formation and acid hydrolysis according to the method of Iwanami and Kawai[133]. The (S)-(-)-lactonic acid (212) was then easily obtained by resolution of its cinchonine salt using the procedure described by Mori[134]. The cinchonine salt of the (-)-acid (212) was highly crystalline while the antipodal (+)-acid



(213) (±)-(212) (S)-(−)-(212)

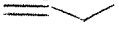


(214) (215) (211)



(128)

Reagents

(i) NaCN, H_2O, 0.5h., R.T., then HCl(conc.), Δ ,4h. 83%; (ii) cinchonine, recrystallization and separation, then 10% HCl, continuous extraction (Et_2O), 48h.; (iii) $LiAlH_4$, R.T., 15h., 53%; (iv) acetone, p-TSA , R.T., 15h., 83%; (v) DMSO, TFAA, Et_3N, -60°C, CH_2Cl_2, 68% ; (vi)  Br, Mg, $HgCl_2$(cat.), 81%.

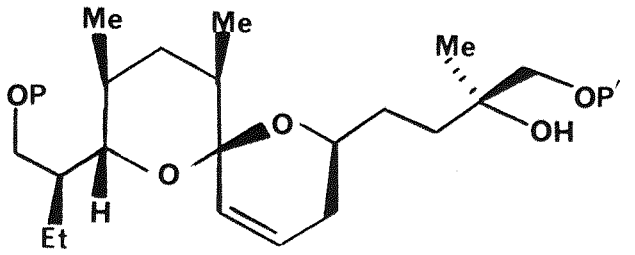
Scheme 55

(212) gave non-crystalline salt. The optical rotation of the (-)-acid (212) obtained after treatment of the crystalline salt with acid was in accordance with the literature value.

The conversion of (S)-(-)-lactonic acid (212) to the (S)-aldehyde (211) was then effected in three steps. The (S)-(-)-lactonic acid (212) was reduced to to the (S)-triol (214) with lithium aluminium hydride in diethyl ether at room temperature for 15 hours. An improved yield (53%) to that reported by Mori[134] was obtained by Soxhlet extraction of the salt residues for 3 days with ethyl acetate. The (S)-triol (214) was dissolved in acetone and treated with p-toluenesulphonic acid at room temperature overnight affording the (S)-acetonide (215) in 83% yield. The optical rotations of these latter two intermediates were also in agreement with the literature values[134].

Oxidation of the (S)-alcohol (215) using dimethylsulphoxide activated with trifluoroacetic anhydride at -60°C in dichloromethane yielded the (S)-aldehyde (211) in 68% yield. Addition of the (S)-aldehyde (211) to the magnesium Grignard reagent of propargyl bromide in the presence of mercuric chloride in diethyl ether at room temperature for 1 hour gave the required (4'S)-acetylene (128) in 81% yield after purification by 'flash' chromatography[80]. The presence of two singlets of equal intensity in the 360 MHz ^1H n.m.r. spectrum at δ_H1.28 and δ_H1.29, which were assigned to the methyl group attached to C-4', established that the product was in fact a 1:1 mixture of the (3R,4'S)- and (3S,4'S)-diastereomers.

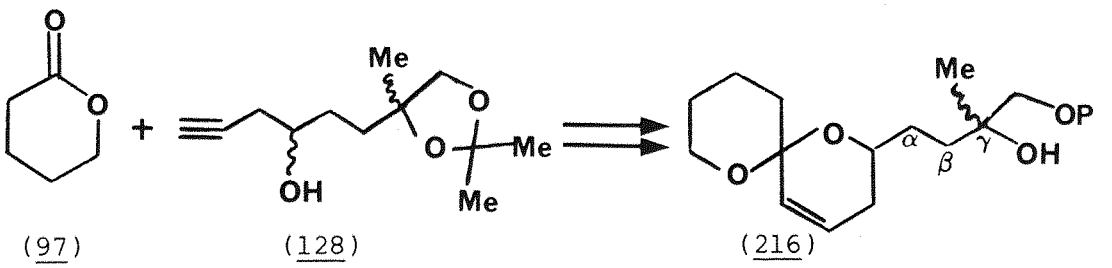
Having designed and implemented the syntheses of the lactone (127) and acetylenic (128) building blocks required for the construction of the bis-spiroacetal moiety of epi-17-deoxy-(O-8)-salinomycin (125), model studies directed towards their conversion into a substituted hydroxyspiroacetal (126) suitable for the Barton-type cyclization were initiated.



(126):P,P'=protecting groups

3.4 Conversion of the Acetylene (128) into suitable γ-Hydroxy-spiroacetal Derivatives for Bis-spiroacetal formation via a Barton-type reaction

Before the acetylenic fragment (128) was coupled with a suitably protected form of the optically active lactone (127), it was advisable to establish the precise conditions for construction of the hydroxy-spiroacetal (126) on a model system. Thus, using δ-valerolactone (97) and the same acetylene (128), although only in racemic form, the synthesis of suitable hydroxyspiroacetal derivatives (216) for use in a Barton-type cyclization, was investigated (Scheme 56).

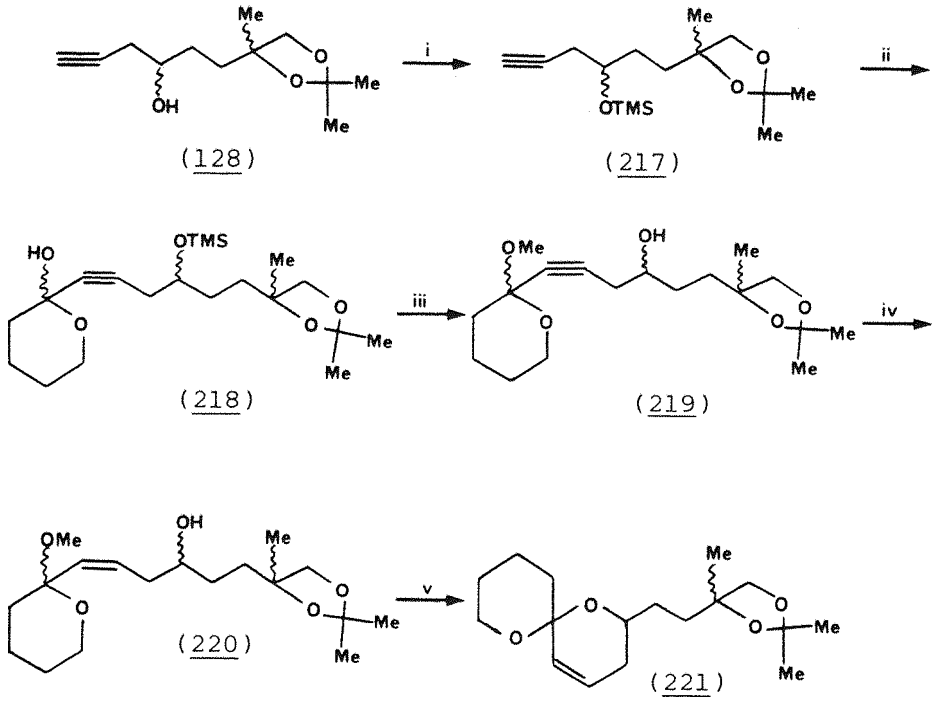


(97) (128) (216)

Scheme 56

Addition of δ -valerolactone (97) to a solution of the lithium acetylide anion prepared from the trimethylsilylether (217) using butyl-lithium at -78°C in tetrahydrofuran, gave the hemiacetal (218), which after stirring overnight in methanol with pyridinium p-toluene-sulphonate afforded the methoxyacetal (219) in 92% yield. Semi-hydrogenation of the acetylene (219) to the alkene (220) in 94% yield

followed by cyclization in dichloromethane with a catalytic amount of camphorsulphonic acid yielded the spiroacetal acetonide (221) in 81% yield (Scheme 57).

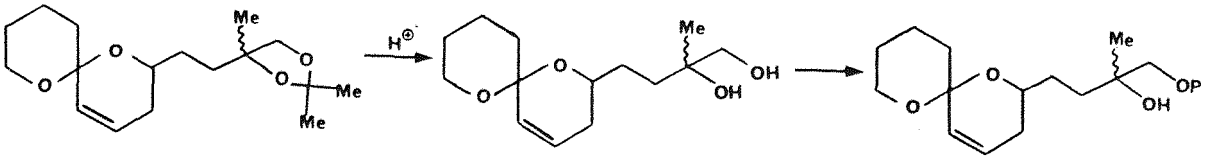


Reagents

(i) TMSCl, Et_3N, THF, 93%; (ii) Bu^nLi, THF, -78°C, then δ-valerolactone (97),-78°C; (iii) MeOH,PPTS, R.T., 15h., 82% ; (iv) H_2,1 atm.,5% Pd on $CaCO_3$-$Pb(OAc_2)$,pentane, R.T., 3h., 94% ; (v) CSA, CH_2Cl_2, R.T., 0.5h., 81%.

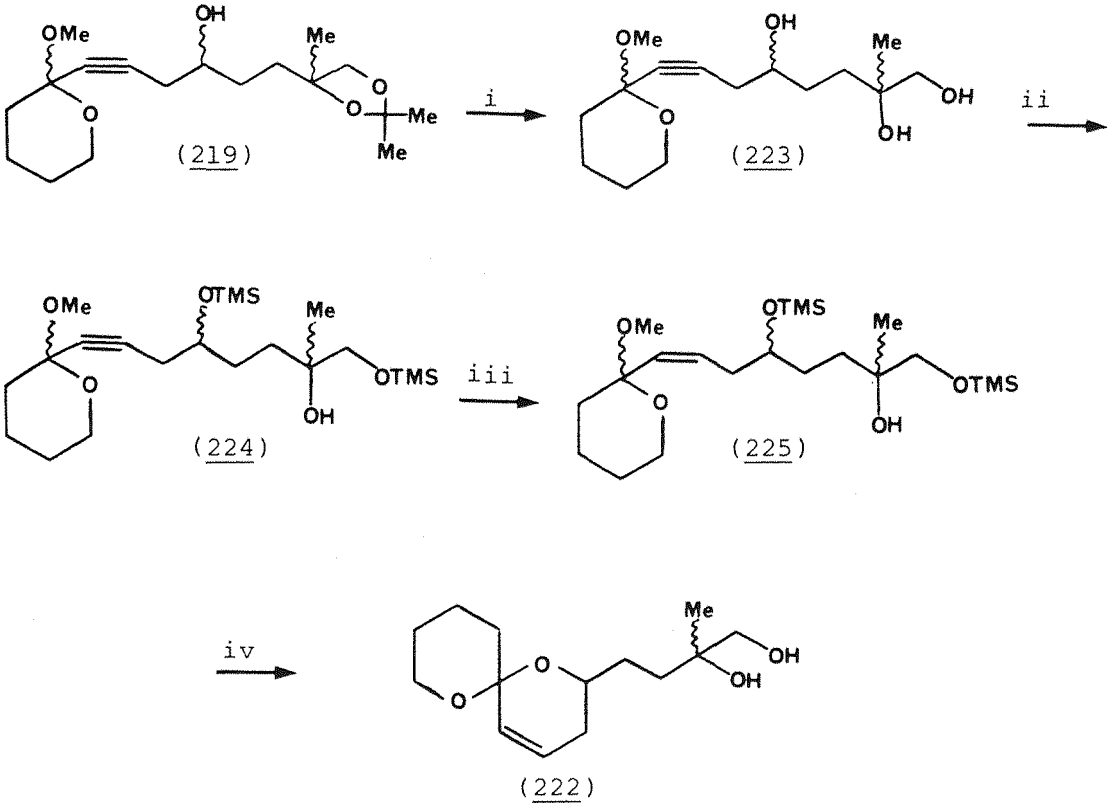
Scheme 57

At this point, it was anticipated that removal of the acetonide protecting group under acidic conditions would yield the diol (222), which after selective protection of the primary hydroxyl group, would give a hydroxyspiroacetal derivative (216) suitable for use in a Barton-type cyclization (Scheme 58). Liberation of the diol (222) from the acetonide (221) under a variety of acidic conditions together with the use of dimethylboron bromide[135] proved to be problematic, hence an alternative route to the diol (222) was found (Scheme 59).



(221) (222) (216):P=protecting group

Scheme 58



(219) (223) (224) (225) (222)

Reagents

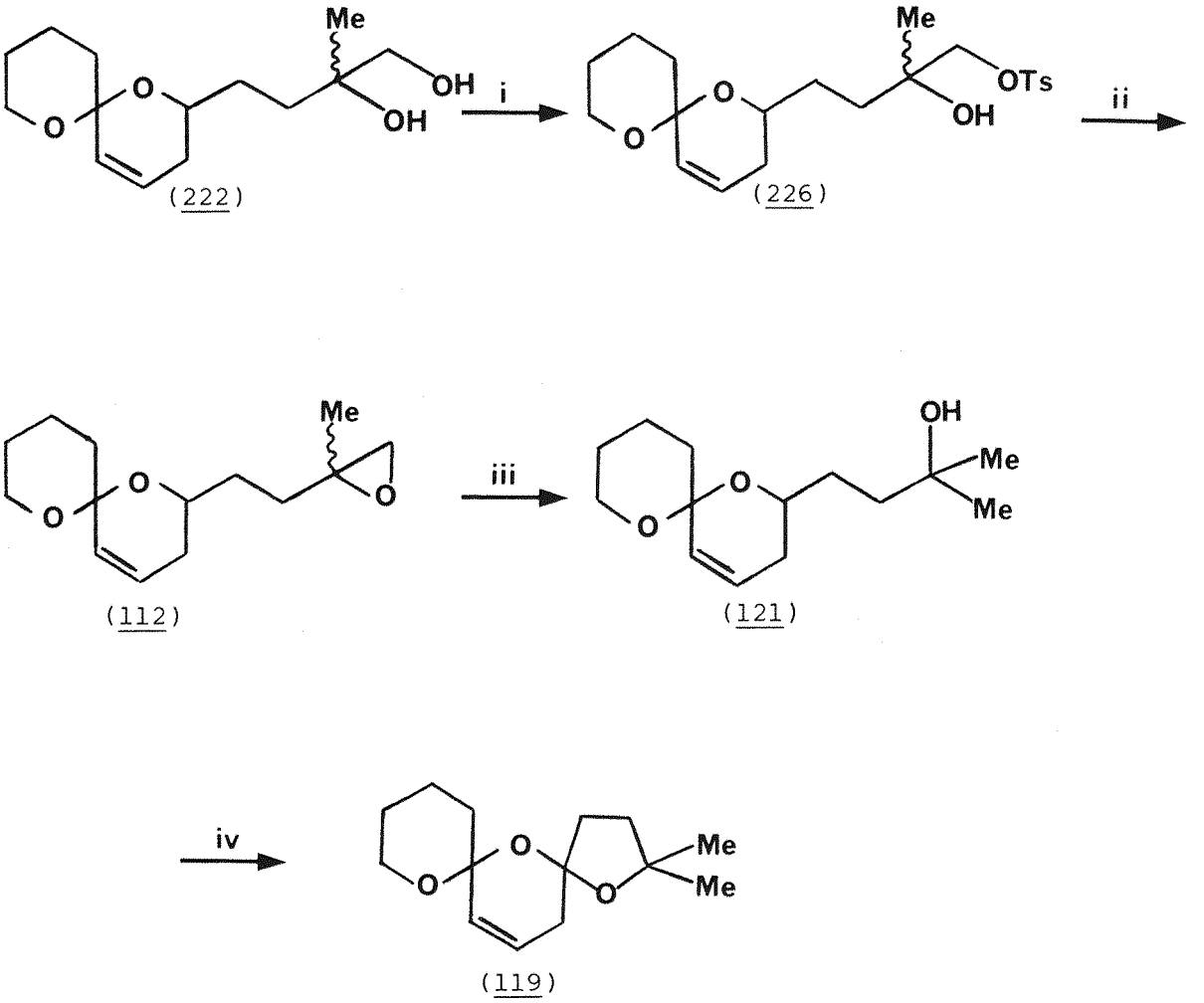
(i) MeOH, Amberlite IR 118, R.T., 15h.; (ii) TMSCl (2 equiv.), Et_3N (4 equiv.), THF, R.T., 1h., 85%; (iii) H_2, 1 atm., 5% Pd on $CaCO_3$-$Pb(OAc)_2$, ethyl acetate, K_2CO_3, R.T., 4h.;
(iv) CSA, CH_2Cl_2, R.T., 14h., 77%.

Scheme 59

The previously prepared methoxyacetal (219) was redissolved in methanol and stirred overnight with Amberlite IR 118 resin at room temperature to give the triol (223) as a viscous colourless oil which was difficult to purify. Successive treatment of the triol (223) with two equivalents of trimethylsilyl chloride in tetrahydrofuran with triethylamine (4 equivalents) at room temperature for 1 hour gave the alcohol (224) in 85% yield which was readily purified by 'flash' chromatography[80]. Furthermore, acetylenic alcohol (224) underwent facile semi-hydrogenation to the alkene (225), which was not isolated but redissolved in dichloromethane yielding the required diol (222) in 77% yield after stirring overnight with a catalytic amount of camphorsulphonic acid at room temperature.

The diol (222) thus prepared, proved to be a versatile intermediate in that addition of p-toluenesulphonyl chloride (1 equivalent) and triethylamine (2 equivalents) at 0°C for 48 hours in dichloromethane yielded the monotosylate (226). Upon addition of sodium hydride (1 equivalent) at room temperature for 3 hours, the monotosylate (226) underwent intramolecular displacement to the epoxide (112) (Scheme 60). Nucleophilic opening of this epoxide (112) with lithium aluminium hydride gave the same hydroxyspiroacetal (121) used earlier to prepare the model bis-spiroacetal (119) (Scheme 30, page 54), thus confirming that the acetylene (128) can be transformed into a hydroxyspiroacetal derivative suitable for bis-spiroacetal formation via a Barton-type reaction.

The synthesis of the bis-spiroacetal moiety of epi-17-deoxy-(O-8)-salinomycin (125) requires the introduction of suitable functionality at C-2 of the bis-spiroacetal ring system which can provide a 'handle' to elaborate the right hand side of the molecule. The three intermediates above, namely, diol (222), monotosylate (226) and epoxide (112) add flexibility to the synthesis. Thus, selective protection of diol (222), nucleophilic displacement of the tosylate (226) or nucleophilic opening of the epoxide (112) (Scheme 61) allow the introduction of various substituents at C-1 of the corresponding hydroxyspiroacetal, which after Barton-type



Reagents

(i) TsCl (1 equiv.), Et_3N (2 equiv.), 0°C, 48h., 81%;

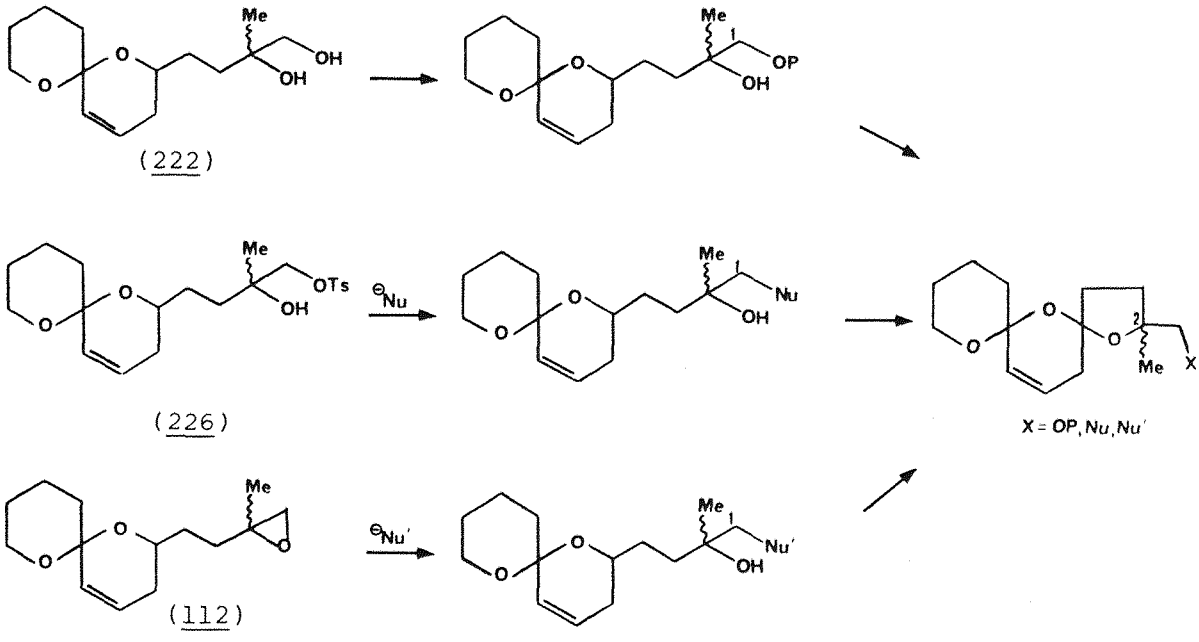
(ii) NaH (1 equiv.), THF, R.T., 3 h., 72% ;

(iii) $LiAlH_4$, Et_2O, R.T., 6h., 78% ;

(iv) $PhI(OAc)_2$, (1 equiv.), I_2(0.5 equiv.), cyclohexane, $h\nu$, R.T., 53%.

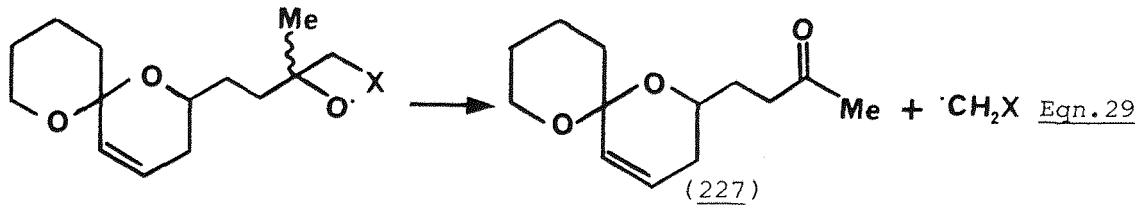
Scheme 60

cyclization to a bis-spiroacetal derivative may provide such a 'handle'.



Scheme 61

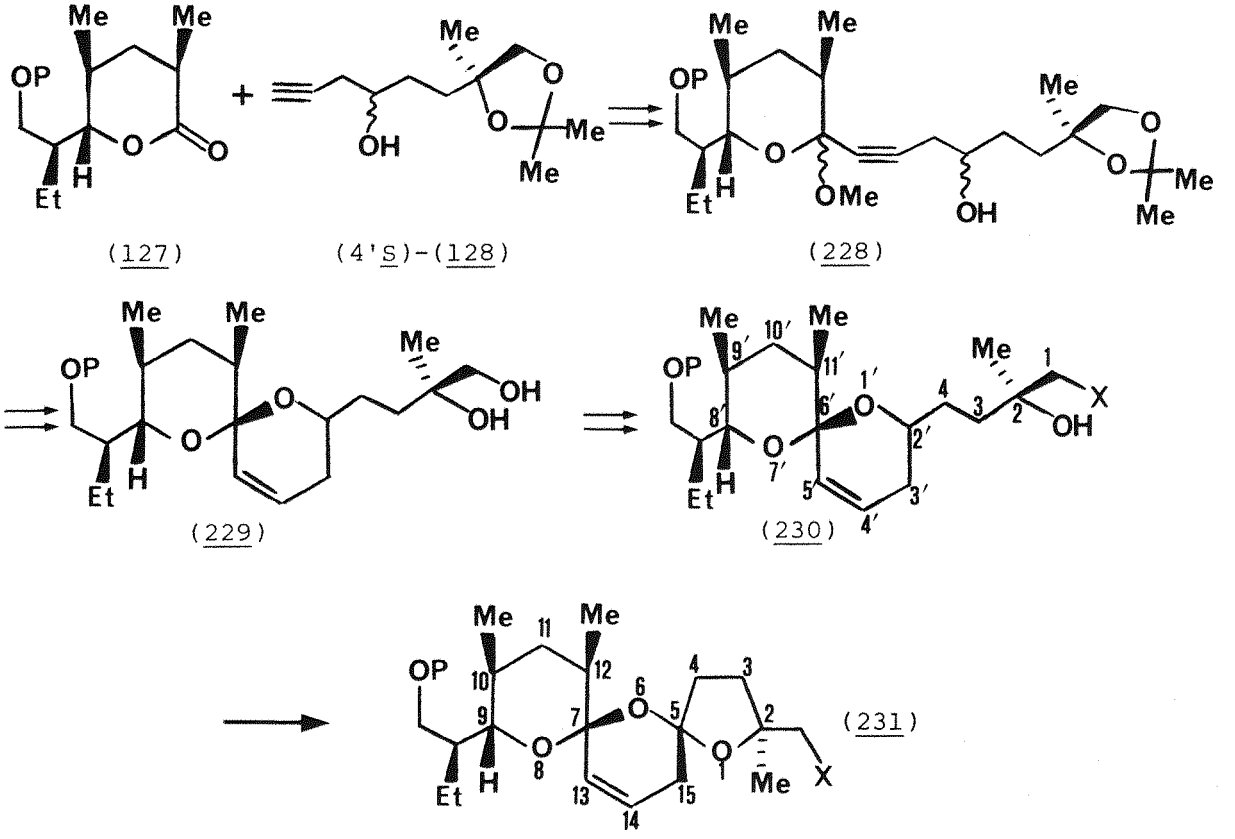
The precise path to be followed to introduce the required functionality remains to be investigated. The choice of substituent introduced at C-1 of the hydroxyspiroacetal, however, is limited by the pre-requisite that it must be compatible with the cyclization reaction and not facilitate the competitive fragmentation to the methyl ketone (227) (Eqn.29).



Eqn.29

Despite the lack of the precise details for the introduction of the required functionality for elaboration of the right hand side

of the model bis-spiroacetal (119), it is possible to apply this latter model work to the synthesis of the bis-spiroacetal moiety of epi-17-deoxy-(O-8)-salinomycin (125). Thus, addition of the (4'S)-acetylene (128) to the optically active lactone (127) should yield the methoxyacetal (228) after treatment with methanol and pyridinium p-toluenesulphonate (Scheme 62). The methoxyacetal (228) may then be converted to the diol (229) in a series of steps analogous to the synthesis of diol (222) from methoxyacetal (219) (Scheme 59). Given that a method for the introduction of a suitable substituent, X, at C-1, is found, hydroxyspiroacetal (230) after Barton-type cyclization should yield the bis-spiroacetal moiety of epi-17-deoxy-(O-8)-salinomycin (231). Moreover, the substituent, X, at C-2 and the protected alcohol at C-9 provide a means for further elaboration of this bis-spiroacetal moiety into epi-17-deoxy-(O-8)-salinomycin (8).



Scheme 62

CHAPTER 4

EXPERIMENTAL

GENERAL DETAILS

Elemental Analyses were carried out at the microanalytical laboratory, University College, London.

Infra-red spectra (IR) were recorded on a Perkin-Elmer 157-G or a Pye-Unicam SP/-100 spectrophotometer, either as thin films or nujol mulls between sodium chloride discs, or as solutions in sodium chloride cells (thickness 0.1 mm). Absorption maxima are given in wavenumbers (cm^{-1}) relative to a polystyrene standard and are described with the following abbreviations :

s = strong,
m = medium,
w = weak,
br. = broad.

^{1}H Nuclear magnetic resonance (n.m.r.) spectra were obtained at 60 MHz using a Hitachi-Perkin-Elmer R-24B spectrometer, at 100 MHz on a Varian Associates XL-100-12 instrument, and at 360 MHz using a Bruker AM360 instrument. ^{1}H n.m.r. data are expressed as parts per million downfield shift from tetramethylsilane as internal reference and are reported as position (δ_H), relative integral, multiplicity (s = singlet, m = multiplet, d = doublet, dd = double doublet, ddd = double double doublet, t = triplet, q = quartet, p = pentet, br. = broad), coupling constant (J Hz), and assignment.

^{13}C n.m.r. spectra were recorded at 25.2 MHz on a Varian Associates XL-100-12 instrument and at 90.6 MHz on a Bruker AM360 instrument. The ^{13}C n.m.r. data are expressed as parts per million

downfield shift from tetramethylsilane as internal reference and are reported as position (δ_C), multiplicity in the single frequency off-resonance decoupled (s.f.o.r.d.) spectrum, and assignment.

Mass spectra (MS) and accurate mass measurements were recorded on a Kratos-AEI MS30 spectrometer with a Digispec DS 50S data system. An ionization potential of 70 eV was used unless otherwise stated and major fragmentations are given as percentages compared to the base peak intensity (100%). Chemical ionization (C.I.) spectra were recorded using methane or ammonia.

Melting points were determined in sealed capillaries on an electrothermal melting point apparatus and are uncorrected.

Optical rotations were measured on an Optical Activity Limited AA100 polarimeter.

'Flash' column chromatography was performed according to the procedure of Still et al[80] using Macherey-Nagel Kieselgel 60 (230-400 mesh) with the solvents described. For gravity column chromatography Aldrich Florisil (100-200 mesh) was used.

Analytical thin layer chromatography (t.l.c.) was carried out on precoated silica gel plates (Merck Kieselgel 60F(254)), and compounds were visualized by UV fluorescence, iodine vapour, aqueous potassium permanganate or vanillin in methanolic sulphuric acid.

Solvents were purified and dried according to the methods of Perrin, Perrin and Armarego[136].

'Petrol' refers to petroleum ether with boiling point in the range 40-60°C.

Ethenyl 2-methyl-2-propenyl ether (93)

Mercuric trifluoroacetate (730 mg, 1.7 mmol) was added to a solution of 2-methyl-2-propen-1-ol (91) (20 g, 280 mmol) in ethenyl ethyl ether (92) (150 ml) and the mixture heated under reflux under a nitrogen atmosphere for 2h. The reaction mixture was cooled in an ice bath and 10% aqueous sodium carbonate solution (100 ml) added. The organic layer was separated, washed with water (2 x 50 ml) and dried over potassium carbonate. Removal of solvent by distillation at atmospheric pressure followed by repeated fractionation of the residue gave ethenyl 2-methyl-2-propenyl ether (93) (16 g, 58%) as a colourless liquid, b.p. 76-80°C/760 mm Hg (lit.[78] b.p. 78-80°C/758 mm Hg).

4-Methyl-4-penten-1-al (94)

Ethenyl 2-methyl-2-propenyl ether (93) (5 g, 51 mmol) was heated in an evacuated sealed tube at 120°C for 24 h. The ^{1}H n.m.r. spectrum of the crude product indicated an 85% conversion to the aldehyde. Direct distillation provided 4-methyl-4-penten-1-al (94) (4 g, 79%) as a colourless liquid, b.p. 99-102°C/760 mm Hg (lit.[78] b.p. 100-103°C/758 mm Hg).

7-Methyl-7-octen-1-yn-4-ol (95)

Activated zinc powder (2.4 g, 37 mmol), prepared according to the method of Vogel[79], was covered with dry tetrahydrofuran (5 ml) and a few drops of a solution of propargyl bromide (3.6 ml of an 80% solution in toluene, 24 mmol) in dry tetrahydrofuran (25 ml) added under nitrogen. The flask was heated gently to induce reaction. After the initial effervescence the reaction mixture was cooled in an ice bath and the remainder of the propargyl bromide added dropwise over 1.5h. 4-Methyl-4-penten-1-al (94) (1.2 g, 12 mmol) in dry tetrahydrofuran (20 ml) was then added. After stirring at 0°C for 2h. the reaction mixture was poured into acidified iced water (100 ml) and extracted with diethyl ether (3 x 75 ml).

The ethereal extract was washed with concentrated ammonium sulphate solution (2 x 50 ml), water (2 x 20 ml), brine (50 ml) and dried over sodium sulphate. Evaporation of the solvent gave an orange oil (2g) which was purified by flash chromatography. Elution with 1:1 petrol:diethyl ether followed by Kugelrohr distillation afforded 7-methyl-7-octen-1-yn-4-ol (95) (1.3 g, 77%) as a colourless oil, b.p. 70-72°C/20 mm Hg. Conversion to the tetrahydropyranyl ether (96), b.p. 67-69°C/20 mm Hg, afforded an analytical sample (Found : C, 75.65 ; H, 9.6. $C_{14}H_{22}O_2$ requires C, 75.6; H, 9.9%); ν_{max} (thin film) 3650-3100 (br.s, OH), 3300 (s, ≡C-H), 3090(m,=C-H), 2140(w,C≡C), 1640 (w,C=C), and 895 cm^{-1}(s, $R_2C=CH_2$) ; δ_H(100 MHz; $CDCl_3$) 1.56-1.85 (2H, m, $-CH_2CHOH$), 1.74(3H, s, Me), 1.98-2.24(3H,m,$-CH_2(Me)C=C$ and -C≡CH), 2.26-2.48(2H, m,$-CH_2C\equiv C$), 3.76(1H,p, J 6 Hz,-CHOH), 3.80-3.98(1H,br.s, exchangeable on deuteration, OH), and 4.74 (2H,m,$-C=CH_2$); δ_C(25.2 MHz; $CDCl_3$) 22.4(q,Me), 27.3(t,C-5), 33.8(t,C-3 or C-6), 33.9(t, C-6 or C-3), 69.6(d,C-4), 70.8(d,C-1), 80.8(s,C-2), 110.3(t,C-8), and 145.3(s,C-7); m/z 123(M-CH_3,3%), 105(M-H_2O-CH_3,28), 82(22), 81(95), 69(C_5H_9,19), 55(89), 43(98), and 41(100).

7-Methyl-4-trimethylsilyloxy-7-octen-1-yne (98)

Chlorotrimethylsilane (200 mg, 1.8 mmol) was added to a mixture of 7-methyl-7-octen-1-yn-4-ol (95) (250 mg, 1.8 mmol) and dry triethylamine (360 mg, 3.6 mmol) in dry tetrahydrofuran (25 ml) at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 2h. whereupon a white precipitate formed. Water (3 ml) was added and the reaction mixture extracted with diethyl ether (3 x 30 ml). The ethereal extract was washed with water (10 ml), brine (10 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure afforded a pale yellow oil (380 mg) which was purified by flash chromatography using 9:1 petrol : diethyl ether as eluant to give 7-methyl-4-trimethylsilyloxy-7-octen-1-yne (98) (350 mg, 92%) as a colourless oil, δ_H(60 MHz; $CDCl_3$) 0.13(9H,s,Me_3Si), 1.54-1.87(2H, m, $-CH_2CHOSi$), 1.75(3H, s, 7-Me), 1.95-2.12(3H, m, $-CH_2(Me)C=C$ and -C≡CH), 2.20-2.43(2H, dd, J 3 and 6 Hz, $-CH_2C\equiv C$), 3.78 (1H, p,J 6 Hz, -CHOSi), and 4.72(2H, m, $-C=CH_2$);

m/z 121(M-C_3H_9OSi, 3%), 95(12), 81(C_6H_9,100), 75(17), 73(C_3H_9Si, 58), 55(13), 43(15), and 41(12).

7-Methyl-1-(tetrahydro-2-methoxypyran-2-yl)-7-octen-1-yn-4-ol (100)

To a solution of 7-methyl-4-trimethylsilyloxy-7-octen-1-yn-4-ol (98) (500 mg, 2.4 mmol) in dry tetrahydrofuran (30 ml) cooled to -78°C, was added butyl-lithium (1.5 ml of a 1.6 mol l^{-1} solution in hexane, 2.4 mmol) dropwise under nitrogen. After stirring at -78°C for 1.5h. a solution of δ-valerolactone (97) (240 mg, 2.4 mmol) in dry tetrahydrofuran (15 ml) was added in one portion. After gradually warming to -40°C over 1.5 h. saturated aqueous sodium dihydrogen phosphate solution (2 ml) was added. The reaction mixture was extracted with diethyl ether (3 x 50 ml), washed with brine (30 ml) and dried over sodium sulphate. Removal of solvent at reduced pressure gave a yellow oil (760 mg) which was redissolved in dry methanol (30 ml) and stirred overnight with Amberlite IR 118 resin. Removal of Amberlite by filtration followed by removal of solvent at reduced pressure yielded an orange oil (770 mg) which was purified by flash chromatography (1:1 petrol:diethyl ether) to give 7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-7-octen-1-yn-4-ol (100) (500 mg, 84%) as a colourless oil, ν_{max} ($CHCl_3$) 3600-3200 (br.s, OH), 3080(m,=C-H), 2260(w, C≡C), 1640(m, C=C), 1030 (s,CO), and 900 cm^{-1}(s, $R_2C{=}CH_2$); δ_H(100 MHz; $CDCl_3$) 1.43-1.98(8H, m, 4 x $-CH_2$), 1.76(3H, s, 7-Me), 2.01-2.29(2H,m,$-CH_2$(Me)C=C), 2.38-2.61(2H, m, $-CH_2C{\equiv}C$), 2.81-2.98(1H, br.d, J 2Hz, exchangeable on deuteration, OH), 3.40(3H, s, OMe), 3.62-3.91(3H, m, -CHOH and $-OCH_2$), and 4.68-4.80(2H, m, $-C{=}CH_2$); δ_c(25.2 MHz; $CDCl_3$) 19.1(t,C-4') 22.5(q,7-Me),24.7(t, C-5'), 27.5(t,C-5), 33.8(t,C-6 or C-3'), 34.2(t, C-3' or C-6), 36.7(t, C-3), 50.5(q,OMe), 62.2(t,C-6'), 69.6(d,C-4), 80.3(s,C-2), 82.2(s,C-1), 95.0(s,C-2'), 110.3(t,C-8), and 145.3(s,C-7); m/z 221 (M-OCH_3,13%), 203(M-OCH_3-H_2O,8), 122($C_8H_{10}O$,84), 81(82), 67(63), 66(48), 55(100), 43(65), and 41(60).

7-Methyl-1-(tetrahydro-2-methoxypyran-2-yl)-4-trimethylsilyloxy-7-octen-1-yne (108)

Using the procedure described for the preparation of 7-methyl-4-trimethylsilyoxy-7-octen-1-yne (98) (page 112), 7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-4-trimethylsilyloxy-7-octen-1-yne (108) was prepared in 91% yield from 7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-7-octen-1-yn-4-ol (100) and chlorotrimethylsilane, δ_H(60 MHz; $CDCl_3$) 0.13(9H, s, Me_3Si), 1.45-1.99(8H, m, 4 x $-CH_2$), 1.74(3H, s, 7-Me), 1.98-2.20(2H, m, $-CH_2$(Me)C=C), 2.31-2.49(2H, m,$-CH_2C{\equiv}C$), 3.40(3H, s, OMe), 3.59-3.92(3H, m, -CHOSi and $-OCH_2$), and 4.62-4.79(2H, m,$-C{=}CH_2$).

7,8 -Epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-4-trimethylsilyloxy-1-octyne (109)

To a solution of 7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-4-trimethylsilyloxy-7-octen-1-yne (108) (580 mg, 1.8 mmol) and sodium acetate (300 mg, 3.7 mmol) in dry dichloromethane (25 ml), cooled to 0°C, was added 80% meta-chloroperoxybenzoic acid (390 mg, 1.8 mmol) in small portions. The resulting suspension was stirred at 0°C for 1h. then left to stand at room temperature for 8h. After filtration to remove the major portion of meta-chlorobenzoic acid, the dichloromethane solution was washed sequentially with saturated aqueous sodium sulphite (2 x 15 ml), 5% aqueous sodium bicarbonate (2 x 15 ml), water (1 x 10 ml), brine (10 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure yielded a pale yellow oil (560 mg) which was purified by flash chromatography. Elution with 7:3 petrol:diethyl ether gave :

(a) 7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-4-trimethylsilyloxy-1-octyne (109) (460 mg, 76%) as a colourless oil, ν_{max}($CHCl_3$) 3600-3200 (br.s,OH), 3080(m,=C-H), 2260(w,C≡C), 1640(m,C=C), 1030(s,CO), and 900 cm^{-1}(s,$R_2C{=}CH_2$); δ_H(100 MHz ; $CDCl_3$), 0.13(9H, s, Me_3Si), 1.32 (3H, s, 7-Me), 1.37-1.98(10H, br.m, 5x $-CH_2$),

2.32-2.84(4H, m, $-CH_2C\equiv C$ and $-CH_2$ epoxide), 3.41(3H, s, OMe), and 3.61-3.92(3H, m, $-OCH_2$ and -CHOSi); δ_c(25.2 MHz;$CDCl_3$) 0.29(q,Me_3Si), 19.3(t,C-4'), 21.0(q,7-Me), 24.8(t,C-5'),27.7,32.2,32.5(t,C-6,C-3' or C-4'), 36.8(t,C-3),50.6(q,OMe), 53.5(t,C-8), 53.8(s,C-7), 62.2(t,C-6'), 70.8(d,C-4), 80.0(s,C-2), 82.3(s, C-1), and 95.1(s, C-2') ; m/z 187 ($C_9H_{19}O_2Si$, 14%), 129(16), 97(C_6H_9O, 12), 89($OSiMe_3$,9), 83(C_5H_7O,10), 73($SiMe_3$,100), 69(20), 55(18), and 43(16).

(b) tetrahydro-2-methyl-5-[3-(tetrahydro-2-methoxypyran-2-yl)prop-2-ynyl] furan-2-ylmethanol (107) (58 mg,12%), as a colourless oil,ν_{max}($CHCl_3$) 3650-3200(s,OH),2260(w,C≡C),1030, and 1060 cm^{-1}(s,CO);δ_H(60 MHz;$CDCl_3$) 1.24 (3H, s, Me), 1.41-2.26 (10H, br.m, 5 x $-CH_2$), 2.31-2.62(2H, m, $-CH_2C\equiv C$), 3.34(3H, s, OMe), 3.39(2H, s, $-CH_2OH$), 3.50-3.82(2H, m, $-OCH_2$), and 3.82-4.32(2H, m, -CHO and OH) ; m/z 236(M $-CH_3OH$, 2%), 205(M $-CH_2OH-CH_3OH$,18), 115($C_6H_{11}O_2$,54), 97(C_6H_9O, 24), 83(C_5H_7O,12), 71(44), 69(44), 57(30), 55(33), and 43(100).

(Z)-7,8-Epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-4-trimethylsilyloxy-1-octene (110)

A solution of 7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-4-trimethylsilyloxy-1-octyne (109) (300 mg, 0.9 mmol) in dry pentane was stirred with activated charcoal (30 mg) for 2h. After the charcoal was removed by filtration through a celite pad, Lindlar catalyst (20 mg) and potassium carbonate (50 mg) were added to the filtrate. The resultant suspension was stirred at room temperature under a balloon of hydrogen for 3h. Removal of the catalyst by filtration and evaporation of solvent afforded (Z)-7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-4-trimethylsilyloxy-1-octene (110) (290 mg, 95%) as a colourless oil,

ν_{max} (CCl_4) 3040 (m,=C-H), 1660(w,C=C), 1250 and 850 cm^{-1} (s, CO epoxide) ; δ_H(360 MHz ; $CDCl_3$) 0.11(9H, s, Me_3Si), 1.31(3H, s, 7-Me), 1.45-1.93(10H, br.m, 5x $-CH_2$), 2.36-2.54(2H, m, $-CH_2C=C$), 2.55-2.64(2H, m, $-CH_2$epoxide), 3.17(3H, s, OMe), 3.61-3.77(3H, m, $-OCH_2$ and -CHOSi), 5.28-5.39,and 5.48-5.61 (2H, m, HC=CH) ; δ_C(90.6 MHz ; $CDCl_3$) 0.3(q, Me_3Si), 19.2(t, C-4'), 21.0(q, 7-Me), 24.7(t, C-5'), 32.4, 35.2, 35.5, 35.6(t, C-3, C-3', C-5 or C-6), 48.3(q, OMe), 53.4(t,C-8), 53.8(s, C-7), 60.8(t,C-6'), 72.2(d,C-4), 98.9(s, C-2'), 129.8(d,C-1), and 132.3(d, C-2) ; m/z 187 ($C_9H_{19}O_2Si$, 19%), 129(35), 75(21), 73($SiMe_3$,100), 69(25), 55(31), 43(15), and 41(17).

(Z)-7,8-Epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-1-octen-4-ol (111)

To a solution of (Z)-7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-4-trimethylsilyloxy-1-octene (110) (240 mg, 0.7 mmol) in dry tetrahydrofuran (20 ml) was added tetrabutylammonium fluoride (0.7 ml of a 1 mol l^{-1} solution in tetrahydrofuran, 0.7 mmol) at room temperature under a nitrogen atmosphere. After stirring at room temperature for 0.25h., saturated aqueous sodium dihydrogen phosphate solution (0.5 ml) was added. The reaction mixture was extracted with diethyl ether (3 x 20 ml), washed with brine (10 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure yielded a pale yellow oil (190 mg) which was purified by passage through a short column of florisil to give (Z)-7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-1-octen-4-ol (111) (180 mg, 95%) as a colourless oil, ν_{max}(thin film) 3600-3150(br.s, OH), 3040(m, =C-H), 1660(w, C=C), 1230, 1030, and 820 cm^{-1} (s,CO) ; δ_H(60 MHz ; $CDCl_3$) 1.31(3H, s, 7-Me), 1.42-2.14(10H, br.m, 5 x $-CH_2$), 2.31-2.73(4H, m, $-CH_2C=C$ and $-CH_2$ epoxide), 3.14(3H, s, OMe),3.28-3.47(1H, br.s, exchangeable on deuteration, OH), 3.47-3.80(3H, m, $-OCH_2$ and -CHOH), and 5.14-5.78 (2H, m, HC=CH).

(Z)-7,8-Epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-1-octen-4-one (87)

To a solution of dry dimethyl sulphoxide (120 mg, 1.4 mmol) in dichloromethane (10 ml) cooled to -60°C, was slowly added a solution of trifluoroacetic anhydride (150 mg, 0.7 mmol) in dichloromethane (5 ml) under nitrogen. A white precipitate quickly formed which was stirred at this temperature for 0.25h. To this was then added a solution of (Z)-7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-1-octen-4-ol (111) (190 mg, 0.7 mmol) in dichloromethane (10 ml) and the mixture stirred at -60°C for 0.5h. Dry triethylamine (210 mg, 2.1 mmol) was added and the reaction mixture gradually warmed to -30°C over 0.75h. After quenching with water (1 ml) the reaction mixture was extracted with dichloromethane (3 x 25 ml), washed with brine (10 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure afforded a pale yellow oil (160 mg) which was purified by flash chromatography. Elution with 1:1 petrol;diethyl ether gave (Z)-7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-1-octen-4-one (87) (136 mg, 72%) as a colourless oil, ν_{max} (thin film) 3040(m, =C-H), 1710(s, C=O), 1660(w,C=C), 1070, 1060, 1030 (s,CO), 890, and 810 cm^{-1} (m, CO epoxide) ; δ_H(360 MHz ; $CDCl_3$) 1.31(3H, s, 7-Me), 1.41-2.02(8H, br.m, 4 x $-CH_2$), 2.51(2H, t, J 7.4 Hz, $-CH_2CO$), 2.58, 2.61(2H, 2xd, J 4 Hz, $-CH_2$ epoxide), 3.13(3H, s, OMe), 3.49(2H, d, J 5.9 Hz, $-C=C-CH_2CO$), 3.64(2H, m, $-OCH_2$), 5.42(2H, d, J 10.8 Hz, HC=C), and 5.75 (2H, dt, $J_{2,3}$ 5.9 and $J_{1,2}$ 10.8 Hz, $-C=C\underline{H}CH_2$) ; δ_C(90.6 MHz ; $CDCl_3$) 18.8(t, C-4'), 21.3(q,7-Me), 24.9(t,C-5'), 29.9, 35.1(t, C-6 or C-3'), 37.6(t, C-5), 41.7(t,C-3), 48.8(q,OMe), 53.6(t,C-8), 56.1(s,C-7), 60.9 (t, C-6'), 99.3(s,C-2'), 124.6(d,C-1), and 134.1(d, C-2) ; m/z 237(M-OCH_3, 2%), 236(M-CH_3OH,4), 151($C_9H_{11}O_2$,14), 123($C_8H_{11}O$,22), 95(22), 85(C_5H_9O,17), 69(28), 55(63), 43(75), and 32(100).

7,8-Epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)octan-4-ol (117)

To a solution of 7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-1-octyn-4-ol (116) (80 mg, 0.3 mmol) in ethyl acetate (25 ml) was added 10% palladium on charcoal (7 mg) and potassium carbonate (25 mg). The resultant suspension was stirred under a balloon of hydrogen for 24h. Removal of the catalyst by filtration and evaporation of the solvent afforded a colourless oil (76 mg) which was purified by passing through a short column of florisil using 1:1 petrol:ethyl acetate as eluant to give 7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)octan-4-ol (117) (68 mg, 84%) as a colourless oil, $\nu_{max}(CCl_4)$ 3650-3300(br.s, OH), 2950(s,CH), 1030, 1060, and 1100 cm^{-1}(s, CO) ; δ_H(360 MHz;$CDCl_3$) 1.32(3H,s,7-Me), 1.38-2.13(16H,br.m,8x-CH_2), 2.59-2.70(2H,m,-CH_2 epoxide), 3.18(3H,s,OMe), and 3.38-3.72(4H,m,-OCH_2,-CHOH and OH); m/z 241(M-OCH_3,8%), 240(M-CH_3OH,2), 209(34), 115($C_6H_{11}O_2$,79),111(37), 98(21), 83(26), 71(29), 55(64), and 43(100).

7,8-Epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)octan-4-one (115)

Using the procedure described for the preparation of 7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-1-octen-4-one (87) (page 117), 7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl) octan-4-ol (115) was prepared in 72% yield from 7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)octan-4-ol (117) as a colourless oil, ν_{max} (thin film) 2940(s,CH), 1710(s,C=O), 1100, 1060, 1040(s,CO), 890 and 810 cm^{-1} (m, CO epoxide) ; δ_H(360 MHz; $CDCl_3$) 1.31(3H, s, 7-Me), 1.40-2.01(12H, br.m, 6 x -CH_2), 2.44(2H,t, J 7.2 Hz, -CH_2CO), 2.49(2H, t, J 7.3 Hz, -CH_2CO), 2.57-2.62(2H,m, -CH_2 epoxide), 3.19(3H, s, OMe), and 3.56-3.72(2H, m, -OCH_2); m/z 239(M-OCH_3,5%), 238(M-CH_3OH,3), 115($C_6H_{11}O_2$,100), 111(45), 110(31), 98(34), 91(81), 55(76), 43(62), and 32(51).

1-(2-Methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-2-yl)methanol (118)

To a solution of 7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)octan-4-one (115) (70 mg, 0.26 mmol) in dichloromethane (25 ml) was added a few crystals of camphorsulphonic acid and the mixture stirred at room temperature for 0.25h. under a nitrogen atmosphere. Removal of solvent at reduced pressure afforded a pale yellow oil (72 mg) which was purified by flash chromatography. Elution with 1:1 petrol:diethyl ether afforded 1-(2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-2-yl)methanol (118) (42 mg, 64%) as a colourless oil (Found : C, 65.2; H, 9.3. $C_{14}H_{22}O_4$ requires C, 65.6 ; H, 9.4%) ; $\nu_{max}(CCl_4)$ 3470(s, OH), 1050, 1070, and 1090 cm^{-1}(s,CO) ; δ_H(360 MHz ; $CDCl_3$) 1.18(3H,s,Me), 1.41-1.98(14H, br.m, $-CH_2$), 2.51-2.62(2H, m, 11'$_{ax}$-H and 14'$_{ax}$-H), 3.38(1H, t,J 11.1 Hz,collapses to a doublet,J 11.1 Hz, upon deuteration, $-CH_AH_BOH$), 3.59(1H, d,J 11.1 Hz, $-CH_AH_BOH$), and 3.62-3.83(3H, m, $-OCH_2$ and OH) ; δ_c(90.6 MHz ; $CDCl_3$) 17.4, 18.7, 25.3 (t, C-10', C-11', or C-14'), 24.3(q, 2'-Me), 30.7, 35.3, 35.9, 36.6, 37.0 (t, C-12', C-4', C-3', C-13', or C-15'), 61.5(t, C-9'), 67.8(t , $-CH_2OH$), 85.9(s, C-2'), 98.5(s, C-7'), and 107.9 (s,C-5') ; m/z 238 (M-H_2O, 5%), 225(M-CH_2OH, 51), 128($C_7H_{12}O_2$,20), 111($C_7H_{11}O$, 100), 98($C_6H_{10}O$, 62), 97(C_6H_9O,39), 55(83), 43(68), and 41(31).

(z)-2-Methyl-8-(tetrahydro-2-methoxypyran-2-yl)-5-trimethylsilyloxy-7-octen-2-ol (120)

To a suspension of lithium aluminium hydride (6 mg, 0.15 mmol), in sodium dried diethyl ether (25 ml) was added a solution of (z)-7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-4-trimethylsilyloxy-1-octene (110) (100 mg, 0.3 mmol) in diethyl ether (3 ml)dropwise under nitrogen. After heating under reflux for 2h., the reaction mixture was quenched with saturated ammonium

chloride solution (2 ml) and extracted with diethyl ether (3 x 50 ml). The ether extract was washed with water (10 ml), brine (10 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure afforded a colourless oil (94 mg) which was purified by flash chromatography using 1:1 petrol:diethyl ether as eluant to give (Z)-2-methyl-8-(tetrahydro-2-methoxypyran-2-yl)-5-trimethylsilyloxy-7-octen-2-ol (120) (89 mg, 89%) as a colourless oil, ν_{max} (CCl_4) 3600-3200(s,OH), 3040(w,=C-H), 1660(w,C=C), 1070, and 1030 cm^{-1}(s,CO); δ_H(360 MHz;$CDCl_3$) 0.12(9H,s,Me_3Si), 1.22(6H, s, 2 x Me), 1.42-2.21(10H, br.m, 5x $-CH_2$), 2.37-2.57(2H,m, $-CH_2C=C$), 3.16(3H, s, OMe), 3.59-3.74(3H, m, $-OCH_2$ and -CHOSi), 5.24-5.33, and 5.44-5.59(2H, m, HC=CH); δ_C(90.6 MHz;$CDCl_3$) 0.4(q,Me_3Si), 18.8(t,C-4'), 25.0(t,C-5'), 29.3,29.6(q,2xMe), 31.7, 35.1, 35.4, 39.5 (t,C-3',C-3,C-4 or C-6), 48.7(q,OMe), 60.9(t,C-6'), 70.4(s,C-2), 72.8(d,C-5), 99.3(s,C-2'), 129.9(d,C-8), and 132.5(d,C-7); m/z 313(M-OCH_3, 0.3%), 172($C_9H_{20}OSi$,12), 171($C_9H_{19}OSi$,83), 156(34), 124($C_8H_{12}O$,55), 83(C_5H_7O,39), 81(C_6H_9,100), 73($SiMe_3$,75), 55(46), 43(59), and 41(36).

4-(1,7-Dioxaspiro[5.5]undec-4-en-2-yl)-2-methylbutan-2-ol (121)

To a solution of 2-methyl-8-(tetrahydro-2-methoxypyran-2-yl)-5-trimethylsilyloxy-7-octen-2-ol (120) (400 mg, 1.2 mmol) in dichloromethane (30 ml) was added a few crystals of camphorsulphonic acid. After stirring at room temperature for 0.5h., the solvent was removed at reduced pressure to give a pale yellow oil (276 mg) which was purified by flash chromatography. Elution with 1:1 petrol:diethyl ether afforded 4-(1,7-dioxaspiro[5.5]undec-4-en-2-yl)-2-methylbutan-2-ol (121) (261 mg, 93%) as a colourless oil (Found : M^+, 240.1706. $C_{14}H_{24}O_3$ requires M, 240.1725) ; ν_{max} (CCl_4) 3640-3260(s,OH), 3040(m, =C-H), 1660(w,C=C), and 1010 cm^{-1}(s,CO) ; δ_H(360 MHz ; $CDCl_3$) 1.24(6H, s, 2 x Me),

1.49-2.34(12H,br.m, 6 x $-CH_2$), 3.58-3.69(1H,m,-CHO), 3.80-3.91(2H,m, $-OCH_2$), 5.58-5.62(1H,m,HC=C), and 5.86-5.92(1H,m,-C=C<u>H</u>CH_2); δ_c(90.6 MHz ; $CDCl_3$) 18.6(t, C-10'), 25.1(t, C-9'), 29.3, 29.5 (q,2 x Me), 30.4, 30.8, 35.1, 39.9 (t, C-3, C-3', C-4 or C-11'), 61.0(t, C-8'), 67.5(d,C-2'), 70.6(s,C-2), 94.1(s,C-6'), 127.6(d,C-5'), and 130.6(d,C-4') ; <u>m/z</u> 240(<u>M</u>$^+$, 1%), 222(<u>M</u>-H_2O,4), 207(<u>M</u>-H_2O-CH_3,9), 184(12), 166(12), 153($C_9H_{13}O_2$,17), 124($C_8H_{12}O$,77), 108(60), 99(60), 95(51), 81(56), 69(57), 59(49), 55(66), and 43(100).

<u>2,2-Dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene (119)</u>

To a solution of 4-(1,7-dioxaspiro[5.5]undec-4-en-2-yl)-2-methylbutan-2-ol (<u>121</u>) (30 mg, 0.13 mmol) in cyclohexane (30 ml) was added iodobenzene diacetate(40 mg, 0.13 mmol) and iodine (16 mg, 0.06 mmol). After irradiating for 24h. at room temperature with a 150W tungsten filament lamp, the reaction mixture was poured into diethyl ether (50 ml), washed with 10% aqueous sodium thiosulphate solution (20 ml), water (10 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure afforded a colourless oil (53 mg) which was purified by flash chromatography using 9:1 petrol:diethyl ether as eluant to give <u>2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene (119)</u> (16 mg, 53%) as a colourless oil (Found : <u>M</u>$^+$, 238.1599. $C_{14}H_{22}O_3$ requires <u>M</u>, 238.1569); ν_{max}(CCl_4) 3040(w,=C-H), 2940(s,CH), and 1050 cm^{-1}(m,CO); δ_H(360 MHz ; $CDCl_3$) 1.24(3H, s, Me), 1.48(3H,s,Me), 1.49-1.64(4H, m, 10-H, 10'-H, 11_{eq}-H,12'-H), 1.72-1.83(3H,m,3'-H,4'-H,12-H), 1.86-1.99(1H,m,11_{ax}-H), 2.04-2.12(1H,m,3-H), 2.16(1H,ddd, $J_{13,15}$,1.2, $J_{14,15}$,5.8, and $J_{15,15'}$16.9Hz, 15'-H), 2.45(1H, ddd, $J_{13,15}$2.6, $J_{14,15}$2.6, and $J_{15,15'}$16.9Hz,15-H), 2.59-2.70(1H,m,4-H), 3.67(1H,m,9_{eq}-H), 4.02(1H, ddd, $J_{9ax,10eq}$3.3, $J_{9ax,10ax}$11.3, and $J_{9ax,9eq}$11.3Hz, 9_{ax}-H), 5.59(1H, ddd, $J_{13,15'}$1.2, $J_{13,15}$2.6, and $J_{13,14}$10.0Hz, 13-H), and 5.86(1H, ddd, $J_{14,15}$2.6, $J_{14,15'}$5.8, and $J_{13,14}$10.0Hz,14-H); δ_c(90.6 MHz;$CDCl_3$) 18.8, 25.3(t,C-10 or C-11), 28.9, 30.1(q,2 x Me),

35.0, 36.4, 36.7, 37.7(t, C-3, C-4, C-12, or C-15), 61.5(t, C-9), 82.7(s, C-2), 99.3(s, C-7), 106.8(s, C-5), 125.1(d, C-13), and 130.1(d, C-14) ; m/z 238(M^+, 46%), 151($C_9H_{11}O_2$, 32), 138(88), 124($C_8H_{12}O$, 100), 75(78), 69(49), 55(44), 43(53), 41(59), and 39(44).

(4R,5S)-(+)-4-Methyl-5-phenyl-2-oxazolidinone (157)

(1S,2R)-(+)-Norephedrine hydrochloride (158) $[\alpha]_D^{23}$ + 33.4° (c, 7.0, H_2O), (10 g, 53 mmol) was added to aqueous sodium hydroxide (150 ml of 2M solution) and the solution stirred at room temperature for 1h. The aqueous mixture was extracted with diethyl ether (3 x 100 ml), and the combined extracts washed with brine (2 x 20 ml), dried over magnesium sulphate and concentrated *in vacuo* to give (4R,5S)-(+)-norephedrine (159) (7.6 g) as a viscous oil after drying at 18°C/1 mm Hg. To this was added diethyl carbonate (130 ml), toluene (20 ml) and potassium carbonate (1.4 g) and the resultant mixture heated under reflux at 130°C overnight using a Dean and Stark apparatus to remove any water. After filtration, the filtrate was concentrated at reduced pressure to give a pale yellow solid (9.1 g) which was recrystallized from 1:1 petrol:dichloromethane to give (4R,5S)-(+)-4-methyl-5-phenyl-2-oxazolidinone (157) (7.5 g, 80%) as a white crystalline solid, m.p. 121-122°C (lit.[111] m.p. 120-121°C) ; $[\alpha]_D$ + 163.4° (c, 11.0, $CHCl_3$) (lit.[111] $[\alpha]_D$ + 163.7° (c, 1.0, $CHCl_3$)).

(4R,5S)-(+)-4-Methyl-3-(1-oxopropyl)-5-phenyl-2-oxazolidinone (141)

To a solution of (4R,5S)-(+)-4-methyl-5-phenyl-2-oxazolidinone (157) (5.6 g, 32 mmol) in dry tetrahydrofuran (60 ml), cooled to -78°C under nitrogen, was added butyl-lithium (16.8 ml of 1.9 mol l^{-1} solution in hexane, 32 mmol) dropwise. After stirring at -78°C for 1h.,

propanoyl chloride (2.8ml, 32 mmol) was added dropwise and the mixture stirred at this temperature for 1h. then warmed to room temperature. The reaction mixture was quenched with saturated ammonium chloride solution (10 ml) and extracted with diethyl ether (3 x 75 ml). The combined extracts were washed with water (2 x 20 ml) brine (2 x 15 ml) and dried over magnesium sulphate. Removal of solvent at reduced pressure gave a pale yellow oil (7.2 g) which was purified by flash chromatography using 1:1 petrol: diethyl ether as eluant to yield (4R,5S)-(+)-4-methyl-3-(1-oxopropyl)-5-phenyl-2-oxazolidinone (141) (6.9 g, 92%) as a colourless viscous oil, $[\alpha]_D^{23}$ + 43.4° (c, 3.0, CH_2Cl_2) (lit.[111] $[\alpha]_D$ + 43.8° (c, 2.0, CH_2Cl_2).

(2'S,4R,5S)-(+)-3-(2,4-Dimethyl-1-oxo-4-pentenyl)-4-methyl-5-phenyl-2-oxazolidinone (161)

To a solution of diisopropylamine (2.2 g, 22 mmol) in dry tetrahydrofuran (50 ml), cooled to -78°C under nitrogen, was added butyl-lithium (11.6 ml of 1.9 mol l^{-1} solution in hexane, 22 mmol). After stirring at -78°C for 0.25h., the reaction mixture was warmed to -30°C then recooled to -78°C, whereupon a solution of (4R,5S)-(+)-4-methyl-3-(1-oxopropyl)-5-phenyl-2-oxazolidinone (141) (5 g, 22 mmol) in dry tetrahydrofuran (25 ml) was added. After stirring at -78°C for 0.5h. the mixture was warmed to -50°C and a solution of freshly distilled methallyl iodide[112] (7.9 g, 44 mmol) in dry tetrahydrofuran (20 ml) added dropwise. The reaction mixture was stirred at -50°C to -20°C for 3h. whereupon a white precipitate formed. After quenching with saturated ammonium chloride solution (10 ml) the reaction mixture was extracted with diethyl ether (3 x 75 ml) and dried over magnesium sulphate. Removal of solvent at reduced pressure afforded a yellow oil (5.1 g) which was purified by flash chromatography using 9:1 petrol:diethyl ether as eluant to give (2'S,4R,5S)-(+)-3-(2,4-dimethyl-1-oxo-4-pentenyl)-4-methyl-5-phenyl-2-oxazolidinone (161) (4.6 g, 73%) as a white crystalline solid,

m.p. 41-43°C (lit.[103] m.p. 42-44°C); $[\alpha]_D$ + 33.1° (c, 1.0, CH_2Cl_2) (lit.[103] $[\alpha]_D$ + 33.7° (c,6.0, CH_2Cl_2)).

(S)-(−)-2,4-Dimethyl-4-penten-1-ol (162)

To a solution of (2S,4R,5S)-(+)-3-(2,4-dimethyl-1-oxo-4-pentenyl)-4-methyl-5-phenyl-2-oxazolidinone (161) (4 g, 13.9 mmol) in dry diethyl ether (50 ml) cooled to 0°C under nitrogen was added lithium aluminium hydride (530 mg, 13.9 mmol). After stirring at 0°C for 0.1h. the reaction mixture was quenched with saturated ammonium chloride solution (2 ml), extracted with diethyl ether (3 x 50 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure afforded a yellow oil which was purified by flash chromatography using 1:1 petrol:diethyl ether as eluant to give :

(a) (S)-(-)-2,4-dimethyl-4-penten-1-ol (162) (1.3 g, 82%), b.p. (Kugelrohr) 76°C/17 mm Hg (lit.[103] b.p. 73°C/15 mm Hg) ; $[\alpha]_D$-3.6° (c, 2.0, CH_2Cl_2) (lit.[103] $[\alpha]_D$-3.9° (c, 4.0, CH_2Cl_2)).

(b) (4R,5S)-(+)-4-methyl-5-phenyl-2-oxazolidinone (157) (920 mg, 37%), m.p. 119-121°C (lit.[111] m.p. 121-122°C).

(S)-(+)-2,4-Dimethyl-4-penten-1-al (142)

To a solution of (S)-(-)-2,4-dimethyl-4-penten-1-ol (162) (1 g, 8.8 mmol) and triethylamine (6.2 g, 61.6 mmol), in dry dimethyl sulphoxide (20 ml) under nitrogen at room temperature was added a solution of pyridine-sulphur trioxide complex (4.2 g, 26.4 mmol) in dry dimethyl sulphoxide (10 ml) dropwise via syringe. After stirring at room temperature for 3h. the reaction mixture was acidified to pH 4.5 with 10% aqueous hydrochloric acid

and extracted with diethyl ether (3 x 20 ml). The ether extract was washed with 10% aqueous sodium bicarbonate solution (2 x 10 ml), brine (10 ml) and dried over magnesium sulphate. After removal of the solvent by distillation at atmospheric pressure the residue was purified by flash chromatography using 9:1 petrol: diethyl ether as eluant to give (S)-(+)-2,4-dimethyl-4-penten-1-al (142) (640 mg, 64%), b.p. 124-128°C/760 mm Hg (lit.[137] b.p. 128°C/760 mm Hg); $[\alpha]_D^+$ 3.2° (c, 2.0, CH_2Cl_2).

Ethyl iminopropionate hydrochloride (167)

Ethyl iminopropionate hydrochloride (167) was prepared in 86% yield from propionitrile using the procedure described[138] for acetamidine hydrochloride, m.p. 96-98°C (lit.[115] m.p. 97-98°C).

(4R,5S)-(+)-4,5-Dihydro-2-ethyl-4-methyl-5-phenyloxazole (173)

(4R,5S)-(+)-4,5-Dihydro-2-ethyl-4-methyl-5-phenyloxazole (173) was prepared in 80% yield from (1S,2R)-(+)-norephedrine (159) and ethyl iminopropionate hydrochloride (167) using the procedure described by Meyers et al[115], b.p. 97-99°C/3 mm Hg. (lit.[115] b.p. 95-97°C/2 mm Hg) ; $[\alpha]_D^{20}$ + 220.6° (c,9.4,ethanol) (lit.[115] $[\alpha]_D^{24}$ + 220.9° (c, 10.48, ethanol)).

(4R,5S)-4,5-Dihydro-2-ethyl-4-methyl-3-(2-methyl-2-propenyl)-5-phenyloxazolinium p-toluenesulphonate (175)

(4R,5S)-(+)-4,5-Dihydro-2-ethyl-4-methyl-5-phenyloxazole (173) (700 mg, 3.7 mmol) and 2-methyl-2-propenyl p-toluenesulphonate (174)[139] (1 g, 4.4 mmol) were stirred together in a dry flask under nitrogen at 50°C for 24h. The resulting yellow viscous oil was triturated with diethyl ether (3 x 10 ml) and dried to constant weight at 21°C /0.5 mm Hg to give (4R,5S)-4,5-dihydro-2-ethyl-4-methyl-3-(2-methyl-2-propenyl)-5-phenyloxazolinium p-toluenesulphonate (175) (1.4 g , 82%)

as a yellow viscous oil, ν_{max} (thin film) 3010 (s,CH), 1640(m,C=C), 1450, 1180(s,-SO_2O), 1040, and 1020 cm^{-1} ; δ_H(60 MHz; $CDCl_3$) 0.95(3H, d, J 7 Hz, -NCHC$\underline{H}_3$), 1.36(3H, t, J 7 Hz,-$CH_2C\underline{H}_3$, 1.81(3H,br.s, CH_3C=C), 2.32(3H,s,Ar-C$\underline{H}_3$), 2.72-3.22(2H,m,-CH_2C=N), 4.26-5.51(5H, m,-C=CH_2,-NC$\underline{H}CH_3$, and -CH_2N), 6.61(1H,d,J 10 Hz,-CHO), and 7.01-7.88 (9H,m,Ar-H).

(4R,5S,1'R)- and (4R,5S,1'S)-4,5-Dihydro-2-(1,3-dimethyl-3-butenyl)-4-methyl-5-phenyloxazole (176)

To a solution of (4R,5S)-4,5-dihydro-2-ethyl-4-methyl-3-(2-methyl-2-propenyl)-5-phenyloxazolinium p-toluenesulphonate (175) (1 g, 2.41 mmol) in dry tetrahydrofuran (20 ml) cooled to -78°C under argon was added butyl-lithium (1.8 ml of 1.7 mol l^{-1} solution in hexane, 3.1 mmol) dropwise over 0.5h. After stirring at -78°C for 0.25h. the reaction mixture was warmed to room temperature over 0.5h. and dry decalin added (40 ml). After removal of the low boiling solvents by rotary evaporation at reduced pressure the resulting decalin mixture was heated under argon at 150°C for 3h., cooled to 0°C, and extracted with cold 10% aqueous hydrochloric acid (3 x 50 ml). The aqueous layer was neutralized with 40% aqueous sodium hydroxide solution and extracted with diethyl ether (3 x 75 ml). The ether extract was washed with brine (2 x 25 ml) and dried over sodium sulphate. Removal of solvent at reduced pressure afforded a yellow oil (726 mg) which was purified by flash chromatography to give :
(4R,5S,1'R)- and (4R,5S,1'S)-4,5-dihydro-2-(1,3-dimethyl-3-butenyl)-4-methyl-5-phenyloxazole (176) (324 mg, 55%) as a 1:1 mixture (^{1}H n.m.r., 360 MHz), colourless oil (Found : M^+,243.1661.$C_{16}H_{21}NO$ requires M, 243.1624); ν_{max} (thin film) 3090(m,=C-H), 2990,2970(s,CH), 1670(s,C=C), and 1450 cm^{-1} ; δ_H(360 MHz;$CDCl_3$) 0.74(3H,d,J 7Hz,-NCHC$\underline{H}_3$), 1.25,1.27(3H,2xd,J 7Hz,-CH_2CHC$\underline{H}_3$), 1.78(3H,s,CH_3C=C), 2.15-2.86(3H,m, -C=C-CH_2 and -CH_2C$\underline{H}$CH_3), 4.34-4.49(1H,m,-NC$\underline{H}CH_3$), 4.93(2H,m,-C=CH_2), 5.54(1H,d,J 9.8Hz,-CHO), and 7.18-7.44(5H,m,Ph); m/z 243(M^+,11%), 122($C_8H_{12}N$,100), 95(83), 77(C_6H_5,47), 55(95), 42(42), 41(76), and 39(41).

(S)-(-)-2-Methyl-3-(tetrahydropyran-2-yloxy)propan-1-ol (189)

(S)-(-)-2-Methyl-3-(tetrahydropyran-2-yloxy)propan-1-ol (189) was prepared in 90% yield in two steps from (R)-(-)-methyl 3-hydroxy-2-methylpropionate (177) ($[\alpha]_D$-26.1°(c,1.5,MeOH)), using the procedure described by Mori and Senda[118], b.p. 95-98°C/4 mm Hg (lit.[118] b.p. 85-89°C/3.5 mm Hg); $[\alpha]_D$-12.0°(c,1.11,$CHCl_3$) (lit.[118] $[\alpha]_D$-12.2° (c,1.08,$CHCl_3$)).

(R)-2-Methyl-3-(tetrahydropyran-2-yloxy)prop-1-yl p-toluenesulphonate (190)

(R)-2-Methyl-3-(tetrahydropyran-2-yloxy)prop-1-yl p-toluenesulphonate (190) was prepared in quantitative yield from (S)-(-)-2-methyl-3-(tetrahydropyran-2-yloxy)propan-1-ol (189) and p-toluenesulphonyl chloride using the procedure described by Mori[118] for the preparation of (S)-2-methyl-3-(tetrahydropyran-2-yloxy)prop-1-yl p-toluenesulphonate (190). This was employed in the next step without further purification.

(R)-(-)-1-Bromo-2-methyl-3-(tetrahydropyran-2-yloxy)propane (185)

A mixture of (R)-2-methyl-3-(tetrahydropyran-2-yloxy)prop-1-yl p-toluenesulphonate (190) (24 g, 73 mmol), lithium bromide (25 g, 293 mmol) and sodium hydrogen carbonate (5 g) in dry tetrahydrofuran (150 ml) was heated at reflux under nitrogen for 15h. After removal of tetrahydrofuran at reduced pressure the residue was diluted with water (25 ml) and extracted with petroleum ether (3 x 100 ml). The petroleum ether extract was washed with water (2 x 10 ml), brine (20 ml) and dried over magnesium sulphate. Removal of solvent at reduced pressure afforded an oil (17.1 g) which was distilled to give (R)-(-)-1-bromo-2-methyl-3-(tetrahydropyran-2-yloxy)propane (185) (15.9 g, 92%) as a colourless liquid, b.p. 78-81°C/3 mm Hg (lit.[118] b.p. 82-85°C/4 mm Hg) ; $[\alpha]_D$-13.2° (c,3.75,$CHCl_3$) (lit[118] $[\alpha]_D^{21}$-13.5°(c,1.037,$CHCl_3$)).

(S)-(-)-2-Methyl-1-(tetrahydropyran-2-yloxy)-4-pentyne (186)

To a solution of ferric nitrate (20 mg) in liquid ammonia (250 ml) was added lithium metal (2.3 g, 327 mmol). After 0.25h. a grey suspension had formed from the initial dark blue solution. Triphenylmethane (20 mg) was then added to give a rose coloured precipitate. Dry acetylene gas was then bubbled through the reaction mixture until a black colour persisted (1h.). A solution of (R)-(-)-1-bromo-2-methyl-3-(tetrahydropyran-2-yloxy)propane (185) (15.5 g, 65.4 mmol) in dry tetrahydrofuran (100 ml) was then added and the reaction mixture stirred overnight with a temperature controlled cryostat set at -60°C. The reaction mixture was diluted with diethyl ether (100 ml) and quenched with the dropwise addition of saturated ammonium chloride solution (30 ml). After evaporation of the ammonia the organic layer was removed and the aqueous layer extracted with diethyl ether (3 x 100 ml). The combined organic extracts were washed with 10% hydrochloric acid solution (3 x 30 ml), brine (2 x 25 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure afforded a brown liquid (11.2 g) which was distilled at reduced pressure to give (S)-(-)-2-methyl-1-(tetrahydropyran-2-yloxy)-4-pentyne (186) (7.1 g, 60%) as a colourless liquid, b.p. 112-114°C/17 mm Hg; $[\alpha]_D^{21}$ -15.1°(c,8.11,$CHCl_3$); ν_{max} (thin film) 3300 (s,≡C-H), 2940(s,CH), and 2100 cm^{-1}(w,C≡C) ; δ_H(360 MHz ; $CDCl_3$) 1.02(3H,d, J 7 Hz,-$CHCH_3$), 1.46-1.88(6H,m,3x-CH_2), 1.95(1H, t, J 2.6 Hz, -C≡CH), 1.98(1H,m,-C<u>H</u>CH_3), 2.12-2.39(2H,m,-CH_2C≡C), 3.25-3.90(4H,m, 2x-OCH_2), and 4.56-4.61(1H,m,-CHO) ; m/z 181(M-H,1%), 101($C_5H_9O_2$,12), 85(C_5H_9O,100), 84(C_5H_8O,11), 81(C_6H_9,11), 57(16), 56(31), 55(31), 43(19), and 41(34).

(S)-(-)-2-Methyl-4-pentyn-1-ol (187)

A solution of (S)-(-)-2-methyl-1-(tetrahydropyran-2-yloxy)-4-pentyne (186) (4 g, 22 mmol) in dry methanol (30 ml) was stirred at room temperature with Amberlite IR 118 resin for 15h.

Removal of Amberlite by filtration followed by evaporation of solvent afforded a colourless liquid (2.4 g) which was purified by distillation at reduced pressure to give (S)-(-)-2-methyl-4-pentyn-1-ol (187) (1.98g, 92%) as a colourless liquid, b.p . 74-77°C/16 mm Hg (lit.[140] b.p. 64-65°C/10 mm Hg) ; $[\alpha]_D^{21}$ -16.2°(c,7.47, $CHCl_3$).

(S)-(-)-2,4-Dimethyl-4-penten-1-ol (162)

To a suspension of zirconocene dichloride (2.5 g, 8.6 mmol) in dry 1,2-dichloroethane (30 ml) cooled to 0°C under argon was added trimethylaluminium (13 ml of a 5.13 mol l^{-1} solution in hexane, 66.7 mmol). The pale yellow solution was stirred at 0°C for 10 minutes then a solution of (S)-(-)-2-methyl-4-pentyn-1-ol (187) (2.2 g, 22.4 mmol) in dry 1,2-dichloroethane (15 ml) added dropwise. A rapid evolution of methane occurs. The reaction mixture was then warmed to room temperature and stirred overnight. After dilution with petroleum ether (30 ml) the reaction mixture was cooled to -30°C and slowly quenched with water (3 ml). Sodium sulphate (2 g) was then added. Filtration through a short column of sodium sulphate followed by removal of solvent at reduced pressure gave a colourless liquid (2.5 g) which was purified by bulb to bulb distillation to give (S)-(-)-2,4-dimethyl-4-penten-1-ol (162) (2.1 g, 82%) as a colourless liquid, b.p. (Kugelrohr) 75-77°C/18 mm Hg. (lit.[103] b.p. 73°C/15 mm Hg); $[\alpha]_D$-3.7°(c,1.8,CH_2Cl_2) (lit.[103] $[\alpha]_D$-3.9°(c,4.0,CH_2Cl_2)).

(4R,5S)-(+)-4-Methyl-3-(1-oxobutyl)-5-phenyl-2-oxazolidinone (194)

Using the procedure described for (4R,5S)-(+)-4-methyl-3-(1-oxopropyl)-5-phenyl-2-oxazolidinone (141), (4R,5S)-(+)-4-methyl 3-(1-oxobutyl)-5-phenyl-2-oxazolidinone (194) was prepared in 91% yield from (4R,5S)-(+)-4-methyl-5-phenyl-2-oxazolidinone (157) and butanoyl chloride. Recrystallization from petroleum ether gave

(4R,5S)-(+)-4-methyl-3-(1-oxobutyl)-5-phenyl-2-oxazolidinone (194) as a white crystalline solid, m.p. 57-58°C ; $[\alpha]_D^+$ 40.2°(c,1.5,CH_2Cl_2) (Found : C, 67.85 ; H,7.0 ; N, 5.7% ; M^+ 247.1230. $C_{14}H_{17}NO_3$ requires C, 68.0 ; H, 6.9 ; N, 5.7% ; M, 247.1208) ; $\nu_{max}(CCl_4)$ 2950(s,CH), 1780(s,-OCON), and 1700 cm^{-1}(s,-NCOC) ; δ_H(360 MHz ; $CDCl_3$) 0.88(3H,d,J 7Hz, $-CHCH_3$), 0.99(3H,t,J 8Hz,$-CH_2CH_3$), 1.64-1.73(2H,m, $-CH_2CH_3$), 2.82-3.03(2H,m,$-CH_2CO$), 4.72-4.82(1H,m,$-NCHCH_3$), 5.68(1H,d, J 8Hz,-CHO), and 7.29-7.47(5H,m,Ph) ; δ_C(90.6 MHz ; $CDCl_3$) 13.6(q,C-4'), 14.5(q,4-Me), 17.9(t,C-3'), 37.5(t,C-2'), 54.8(d, C-4), 79.0(d,C-5), 125.8, 128.8(d,Ar), 133.8(s,Ar), 153.1(s,C-2), and 173.0(s,C-1') ; m/z 247(M^+,4%), 107(C_7H_7O,43), 71(C_4H_7O,100), 70(19), 43(53),42(9), and 41(11).

(2'R,3'S,4'S,4R,5S)-(+)-3-(4,6-Dimethyl-2-ethyl-3-hydroxy-1-oxo-6-heptenyl)-4-methyl-5-phenyl-2-oxazolidinone (154)

To a solution of (4R,5S)-(+)-4-methyl-3-(1-oxobutyl)-5-phenyl-2-oxazolidinone (194) (660 mg, 2.67 mmol) in dry dichloromethane (20 ml) cooled to 0°C under argon, was added a solution of 9-borabicyclo[3.3.1]-nonyl trifluoromethanesulphonate[119] (800 mg, 2.97 mmol) via cannula, followed by diisopropylethylamine (420 mg, 3.2 mmol). After stirring at 0°C for 0.5h. the yellow solution was cooled to -78°C and a solution of (S)-(+)-2,4-dimethyl-4-penten-1-al (142) (300 mg, 2.67 mmol) in dry dichloromethane (5 ml) added. After stirring at this temperature for 0.5h. the reaction mixture was stirred at room temperature for 1.5h. After quenching with saturated aqueous sodium dihydrogen phosphate solution (5 ml) the reaction mixture was extracted with diethyl ether (3 x 75 ml), washed with brine (2 x 10 ml) and concentrated in vacuo. The residue was dissolved in methanol (10 ml), cooled to 0°C and treated with 30% w/v hydrogen peroxide (3 ml) for 1h. After addition of water (5 ml) the methanol was removed at reduced pressure and the residue extracted with diethyl ether (3 x 50 ml). The ether extract was washed with 10% aqueous sodium hydrogen carbonate solution (2 x 15 ml), brine (2 x 10 ml) and dried over magnesium sulphate. Removal of solvent at reduced pressure afforded a viscous oil (1.1g) which was purified by flash chromatography using 1:1 petrol:diethyl

ether as eluant to give (2'R,3'S,4'S,4R,5S)-(+)-3-(4,6-dimethyl-2-ethyl-3-hydroxy-1-oxo-6-heptenyl)-4-methyl-5-phenyl-2-oxazolidinone (154) (803 mg, 84%) as a viscous colourless oil, b.p. (Kugelrohr) 80°C/1.5 mm Hg ; $[\alpha]_D^+$ 7.5°(c,1.9,CCl_4) ; ν_{max} (thin film) 3600-3260 (s,OH), 3080(m,=C-H), 2980-2900(s,CH), 1780(s,-OCON), and 1690 cm^{-1} (s,-NCOC) ; δ_H (360 MHz ; $CDCl_3$) 0.89-1.01 (9H,m,3x $-CH_3$), 1.72(3H,br.s, $CH_3C=C$), 1.74-2.03(3H,m,$-C\underline{H}_2CH_3$ and $-C\underline{H}CH_3$), 2.36-2.61(2H,m,$-CH_2C=C$), 2.94(1H,br.s, OH), 3.61(1H,dd,$J_{2',3'}$ 4 and $J_{3',4'}$ 7 Hz, $-C\underline{H}OH$), 4.19(1H,ddd,J 4, 4,and 8 Hz, $-C\underline{H}(Et)CO$), 4.69-4.89(3H,m,$-C=CH_2$ and $-NC\underline{H}CH_3$), 5.67(1H, d, J 7Hz, -CHOPh), and 7.28-7.47 (5H,m,Ph); δ_c(90.6 MHz;$CDCl_3$) 11.6(q,$-CH_2\underline{C}H_3$), 14.5(q,4-Me), 15.8(q,4'-Me), 19.7(t,$\underline{C}H_2CH_3$), 22.4(t,6'-Me), 34.6(d,C-4'), 41.1(t,C-5'), 46.7(d,C-2'), 55.1(d,C-4), 76.6(d,C-3'), 78.8(d,C-5), 111.7(t, C-7'), 125.7, 128.7(d,Ar), 133.4(s,Ar), 144.6(s,C-6'), 152.7(s,C-2), and 176.5(s,C-1') ; m/z 341(M-H_2O,1%), 247($C_{14}H_{17}NO_3$,11), 118(C_9H_{10},36), 107(C_7H_7O,58), 71(C_4H_7O,56), 55(72), 43(100), and 41(67).

(2'R,3'S,4'S,4R,5S)-(-)-3-(4,6-Dimethyl-2-ethyl-1-oxo-3-trimethylsilyloxy-6-heptenyl)-4-methyl-5-phenyl-2-oxazolidinone (202)

To a solution of (2'R,3'S,4'S,4R,5S)-(+)-3-(4,6-dimethyl-2-ethyl-3-hydroxy-1-oxo-6-heptenyl)-4-methyl-5-phenyl-2-oxazolidinone (154) (200 mg, 0.56 mmol) in dichloromethane (30 ml) was added N,N-diethyltrimethylsilylamine (122 mg, 0.84 mmol) and 4-dimethylaminopyridine (14 mg, 0.11 mmol) at room temperature under nitrogen. After stirring at room temperature overnight the reaction mixture was washed with water (2 x 5 ml), brine (10 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure afforded a yellow oil (262 mg) which was purified by flash chromatography using 9:1 petrol:ethyl acetate as eluant to give (2'R,3'S,4'S,4R,5S)-(-)-3-(4,6-dimethyl-2-ethyl-1-oxo-3-trimethylsilyloxy-6-heptenyl)-4-methyl-5-phenyl-2-oxazolidinone (202) (205 mg, 85%) as a colourless oil,

$[\alpha]_D^{21}$ -9.3°(c,0.99,CCl_4) (Found : C,66.5; H, 8.6; N, 3.3. $C_{24}H_{37}NO_4Si$ requires C, 66.8 ; H,8.6; N,3.2%) ; ν_{max} (thin film) 3080(m,=C-H), 2980(s,CH), 1780(s,-OCON), and 1690cm^{-1}(s,-NCOC); δ_H(360 MHz ; $CDCl_3$) 0.15(9H,s,Me_3Si), 0.82-1.02(9H,m,3x-CH_3), 1.61-2.01(3H,m,-C<u>H</u>$_2$$CH_3$ and -C<u>H</u>CH_3), 1.69(3H,br.s, -CH_3C=C), 2.26-2.32(2H,m,-CH_2C=C), 3.86(1H,dd, $J_{2',3'}$ 3.1 and $J_{3',4'}$ 7.5Hz,-CHOSi), 4.10-4.17(1H,m,-C<u>H</u>(Et)CO), 4.65-4.88(3H,m,-C=CH_2 and -NC<u>H</u>CH_3), 5.60(1H, d, <u>J</u> 7 Hz, -CHOPh), and 7.27-7.48(5H,m,Ph); <u>m/z</u> 416(<u>M</u>-Me,1%), 348($C_{18}H_{26}NO_4Si$,15), 171($C_8H_{15}O_2Si$,100), 118(C_9H_{10},17), 95(92), 75(19), 73($SiMe_3$,88), 55(18), and 43(17).

<u>(2'R,3'S,4'S,6'R,4R,5S)-(-)-3-(4,6-Dimethyl-2-ethyl-7-hydroxy-1-oxo-3-trimethylsilyloxyheptyl)-4-methyl-5-phenyl-2-oxazolidinone (203)</u>

To a solution of borane-tetrahydrofuran (1.0 ml of a 1 mol l^{-1} solution in tetrahydrofuran, 1.0 mmol) in dry tetrahydrofuran (10 ml) cooled to 0°C was added 2,3-dimethyl-2-butene (1.0 ml of a 1 mol l^{-1} solution in tetrahydrofuran, 1.0 mmol) under argon. After stirring at 0°C for 1h. a solution of (2'<u>R</u>,3'<u>S</u>,4'<u>S</u>,4<u>R</u>,5<u>S</u>)-(-)-3-(4,6-dimethyl-2-ethyl-1-oxo-3-trimethylsilyloxy-6-heptenyl)-4-methyl-5 phenyl-2-oxazolidinone (<u>202</u>) (200 mg, 0.46 mmol) in dry tetrahydrofuran (3 ml) was added and the reaction mixture stirred at this temperature for 5h. After the addition of aqueous sodium bicarbonate solution (4 ml of a 1 mol l^{-1} solution) and 30% w/v hydrogen peroxide solution (0.5 ml) the reaction mixture was stirred overnight at room temperature and extracted with diethyl ether (3 x 25 ml). The ether extract was washed with water (2 x 25 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure gave a colourless oil (320 mg) which was purified by flash chromatography using 7:3 petrol:ethyl acetate as eluant to yield <u>(2'R,3'S,4'S,6'R,4R,5S)-(-)-3-(4,6-dimethyl-2-ethyl-7-hydroxy-1-oxo-3-trimethylsilyloxyheptyl)-4-methyl-5-phenyl-2-oxazolidinone (203)</u> (142 mg, 69%) as a colourless oil,

$[\alpha]_D^{21}$-7.2°(c,0.95,CCl_4) (Found : C,63.9;H,8.7 ; N,3.3. $C_{24}H_{39}NO_5Si$ requires C,64.1; H, 8.7; N.3.1%) ; ν_{max} (thin film) 3650-3200(s,OH), 2980(s,CH), 1780(s,-OCON), and 1690 cm^{-1}(s,-NCOC); δ_H(360 MHz ; $CDCl_3$) 0.15(9H,s,Me_3Si), 0.83-1.12(12H,m,4x-CH_3), 1.47-1.92(6H,m,-CH(Me)CH_2CH(Me)- and -CH_2CH_3), 3.46(2H,m, -CH_2OH), 3.89(1H, dd, $J_{2',3'}$ and $J_{3'4'}$ 7 Hz, -CHOSi) , 4.17(1H,m,-CH(Et)CO), 4.78(1H,p,J 7 Hz, -NCHCH_3), 5.69(1H,d, J 7.3Hz, -CHOPh), and 7.26-7.41(5H,m,Ph) ; δ_c(90.6 MHz ; $CDCl_3$) 0.8(q,Me_3Si), 11.1(q,-CH_2CH_3), 14.5(q,4-Me), 18.2,18.5 (q,4'-Me or 6'-Me), 23.8(t,-CH_2CH_3), 33.0(t,C-5'), 34.3(d,C-4'), 35.3(d,C-6'), 47.5(d,C-2'), 55.3(d,C-4), 67.2(t,C-7'),78.7, 78.8 (d,C-5 or C-3'), 125.7,128.8(d,Ar), 133.6(s,Ar), 152.9(s,C-2), and 175.9(s,C-1'); m/z 348($C_{18}H_{26}NO_4Si$, 61%), 304(33), 247($C_{14}H_{17}NO_3$,22), 171($C_8H_{15}O_2Si$,100), 113(42), 73($SiMe_3$,80), 55(34), 43(42), and 31(36).

(2'R,3'S,4'S,6'R,4R,5S)-(+)-3-(3,7-Dihydroxy-4,6-dimethyl-2-ethyl-1-oxoheptyl)-4-methyl-5-phenyl-2-oxazolidinone (204)

To a solution of (2'R,3'S,4'S,6'R,4R,5S)-(-)-3-(4,6-dimethyl-2-ethyl-7-hydroxy-1-oxo-3-trimethylsilyloxyheptyl)-4-methyl-5-phenyl-2-oxazolidinone (203) (55 mg, 0.12 mmol) in methanol (5 ml) was added oxalic acid (2 mg). After stirring at room temperature for 0.2h. the solvent was removed at reduced pressure and the residue passed through a short column of florisil using 1:1 petrol: ethyl acetate as eluant to give (2'R,3'S,4'S,6'R,4R,5S)-(+)-3-(3,7-dihydroxy-4,6-dimethyl-2-ethyl-1-oxoheptyl)-4-methyl-5-phenyl-2-oxazolidinone (204) (41 mg, 91%), $[\alpha]_D$ +3.8°(c,2.1,CCl_4) ; ν_{max} (thin film) 3650-3100(s,OH), 2980, 2960,2880(s,CH), 1780(s,OCON), and 1690 cm^{-1}(s,-NCOC) ; δ_H(360 MHz ; $CDCl_3$) 0.85-1.11(12H,m,4x-CH_3), 1.62-1.94(6H,m,-CH(Me)CH_2CH(Me)- and -CH_2CH_3), 2.52(1H,br.s, OH), 3.06(1H,br.s,OH), 3.46(1H,dd, $J_{6',7'}$ 4.3 and J_{gem} 10.9 Hz, $-CH_AH_BOH$), 3.57(1H,dd,$J_{6',7'}$ 4.3 and

J_{gem} 10.9 Hz,-CH_AH_BOH), 3.60(1H,dd,$J_{2',3'}$ 3.9 and $J_{3',4'}$ 7.1 Hz, -CHOH), 4.18(1H, ddd,J 3.9, 3.9, and 10.1 Hz, -CH(Et)CO), 4.82(1H,p, J 7Hz, -NCHCH$_3$), 5.72(1H,d, J 7Hz,-CHOPh), and 7.26-7.42(5H,m,Ph) ; m/z 276($C_{15}H_{18}NO_4$,5%), 247($C_{14}H_{17}NO_3$,9), 107(C_7H_7O,70), 71(61), 55(65), 43(100), 44(43), 42(51), and 41(69).

(2'R,2"S,3"S,5"R,4R,5S)-(+)-4-Methyl-3-[1-oxo-2-(tetrahydro-3,5-dimethyl-6-oxopyran-2-yl)butyl]-5-phenyl-2-oxazolidinone (193)

To a solution of (2'R,3'S,4'S,6'R,4R,5S)-(+)-3-(3,7-dihydroxy-4,6-dimethyl-2-ethyl-1-oxoheptyl)-4-methyl-5-phenyl-2-oxazolidinone (204) (550 mg, 1.46 mmol) in dry acetone (40 ml) was added N-methylmorpholine-N-oxide (342 mg, 2.92 mmol) and tris(triphenylphosphine)ruthenium (II) chloride (20 mg). The gold solution was stirred at room temperature for 3h. after which time the reaction mixture was dark brown. After removal of solvent at reduced pressure the residue was extracted with dichloromethane (3 x 30 ml), washed with 4% aqueous hydrochloric acid (2 x 10 ml), water (2 x 10 ml), brine (10 ml) and dried over sodium sulphate. Concentration afforded a brown oil (492 mg) which was purified by flash chromatography using 8:2 petrol:ethyl acetate as eluant to give the lactol (205) (390 mg) as a white solid, m.p. 34-37°C (unrecrystallized).

The lactol (205) (390 mg) was subsequently treated with Fetizon's reagent[131] (1.5 g) in toluene (30 ml) and heated under reflux for 1h. Filtration to remove the oxidant and evaporation of the solvent afforded (2'R,2"S,3"S,5"R,4R,5S)-(+)-4-methyl-3-[1-oxo-2-(tetrahydro-3,5-dimethyl-6-oxopyran-2-yl)butyl]-5-phenyl-2-oxazolidinone (193) (379 mg, 70%) as a colourless oil. Further purification by flash chromatography afforded an analytical sample (Found : C, 67.1; H, 7.4 ; N,3.7. $C_{21}H_{27}O_5N$ requires C,67.5 ; H,7.3 ; N,3.7%) ; $[\alpha]_D^+$ 11.5°(c,0.81,CCl_4) ; ν_{max} (thin film) 2980, 2950, 2880 (s,CH), 1780(s,-OCON), 1730(s,-OCOC),

1690(s,-NCOC), and 1600 cm^{-1} (w,C=C) ; δ_H(360 MHz ; $CDCl_3$) 0.93(3H,d, J 6.7Hz,-NCHC$\underline{H}_3$), 0.95(3H,t, J 7.2Hz, -$CH_2C\underline{H}_3$), 1.10(3H,d,J 6.6Hz, 3"-Me), 1.27(3H, d, J 7.1Hz, 5"-Me), 1.40(1H, q, J 12Hz, 4" $_{ax}$-H), 1.59-2.08(4H,m,3" $_{ax}$-H, 4" $_{eq}$-H, and -C$\underline{H}_2CH_3$), 2.46-2.59(1H,m,5" $_{ax}$-H), 4.04(1H,ddd, $J_{2'3'}$ 3.8, $J_{2'2"}$ 3.8, and $J_{2'3'}$ 10.3 Hz,2'-H), 4.37(1H,dd, $J_{2',2"}$ 3.8 and $J_{2"3"}$ 9.4 Hz, 2" $_{ax}$-H), 4.84(1H,p,J 6.7Hz,-NC$\underline{H}$CH$_3$), 5.71(1H,d, J 7.2Hz,-CHOPh), and 7.26-7.43(5H,m,Ph) ; δ_C(90.6 MHz ; $CDCl_3$) 11.9(q,-$CH_2\underline{C}H_3$), 14.4(q,4-Me), 17.2, 17.6(q,3"-Me or 5"-Me), 18.6(t, -$\underline{C}H_2CH_3$), 32.0(t,C-4"), 36.0(d,C-3"), 37.5(d,C-5"), 48.1(d,C-2'), 55.4(d,C-4), 79.1(d,C-5), 85.6(d,C-2"), 125.7, 128.8(d,Ar), 133.3(s,Ar), 153.1(s,C-2), and 171.9,173.7(s,C-1' or C-6") ; m/z 247($C_{14}H_{17}NO_3$,8%), 116(22), 107(C_7H_7O,59), 71(100), 44(20), 43(86), 42(21), and 41(42).

(2'R,3'S,4'S,6'R,4R,5S)-(-)-3-(7-tert-Butyldimethylsilyloxy-4,6-dimethyl-2-ethyl-1-oxo-3-trimethylsilyloxyheptyl)-4-methyl-5-phenyl-2-oxazolidinone (207)

To a solution of (2'R,3'S,4'S,6'R,4R,5S)-(-)-3-(4,6-dimethyl-2-ethyl-7-hydroxy-1-oxo-3-trimethylsilyloxyheptyl)-4-methyl-5-phenyl-2-oxazolidinone (203) (190 mg, 0.42 mmol) in dry dichloromethane (25 ml) cooled to 0°C under nitrogen was added 2,6-lutidine (100 mg, 0.93 mmol) and tert-butyldimethylsilyl trifluoromethanesulphonate (170 mg, 0.64 mmol). After stirring at 0°C for 0.25h. the reaction mixture was quenched with water (2 ml) and extracted with dichloromethane (3 x 25 ml). The dichloromethane extract was washed with brine (5 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure afforded a colourless oil (235 mg) which was purified by flash chromatography using 8:2 petrol:diethyl ether as eluant to give (2'R,3'S,4'S,6'R,4R,5S)-(-)-3-(7-tert-butyldimethylsilyloxy-4,6-dimethyl-2-ethyl-1-oxo-3-trimethylsilyloxyheptyl)-4-methyl-5-phenyl-2-oxazolidinone (207) (221 mg, 94%) as a colourless oil, $[\alpha]_D^{22}$ -8.5°(c,3.02, CCl_4) ; ν_{max} (thin film) 2960, 2940, 2860 (s,CH), 1780(s,-OCON), 1690(s,-NCOC), and 1360 cm^{-1}(s,-CMe_3) ;

δ_H(360 MHz ; $CDCl_3$) 0.04(6H,s,$(C\underline{H}_3)_2Bu^tSi$), 0.14(9H,s,$Me_3Si$), 0.85-1.03(21H,m,4x-$CH_3$,and $(C\underline{H}_3)_3CSiMe_2$), 1.38-1.83(6H,m, -C$\underline{H}$(Me)C$\underline{H}_2C\underline{H}$(Me)- and -C$\underline{H}_2$$CH_3$), 3.22(1H,dd, $\underline{J}_{6',7'}$ 7.8 and $\underline{J}_{gem}$ 9.7 Hz, -C$\underline{H}_A\underline{H}_B$OSiBu^t$Me_2$), 3.54(1H,dd, $\underline{J}_{6',7'}$ 4.6 and $\underline{J}_{gem}$ 9.7 Hz, -$CH_A\underline{H}_B$OSiBu^tMe_2), 3.83(1H, dd, $\underline{J}_{2',3'}$ 3.7 and $\underline{J}_{3',4'}$ 7.3 Hz, -C$\underline{H}$OSiMe_3), 4.03-4.10(1H,m,-C$\underline{H}$(Et)CO), 4.77(1H, p,$\underline{J}$ 6.7 Hz, -NC$\underline{H}$$CH_3$), 5.60(1H, d, $\underline{J}$ 7.1Hz, -CHOPh), and 7.28-7.45(5H, m, Ph) ; $\underline{m/z}$ 548($\underline{M}$-CH_3,3%), 506($\underline{M}$-CMe_3,8), 348($C_{18}H_{26}NO_4Si$,51), 304(53), 171($C_8H_{15}O_2Si$,96), 75(36), 73($SiMe_3$,100), 71(37), 57(CMe_3, 62), and 55(40).

(2S,3S,4S,6R)-(-)-7-tert-butyldimethylsilyloxy-4,6-dimethyl-2-ethyl-3-trimethylsilyloxyheptan-1-ol (208)

To a solution of (2'$\underline{R}$,3'$\underline{S}$,4'$\underline{S}$,6'$\underline{R}$,4$\underline{R}$,5$\underline{S}$)-(-)-3-(7-tert-butyldimethylsilyloxy-4,6-dimethyl-2-ethyl-1-oxo-3-trimethylsilyloxyheptyl)-4-methyl-5-phenyl-2-oxazolidinone (207) (230 mg, 0.41 mmol) in dry tetrahydrofuran (20 ml) cooled to 0°C under nitrogen was added lithium borohydride (9 mg, 0.41 mmol). The reaction mixture was warmed to room temperature and stirred overnight. After quenching with water (1 ml) and extraction with diethyl ether (3 x 25 ml), evaporation of the solvent at reduced pressure yielded a colourless oil (168 mg). Purification by flash chromatography using 8:2 petrol:diethyl ether as eluant afforded (2S,3S,4S,6R)-(-)-7-tert-butyldimethylsilyloxy-4,6-dimethyl-2-ethyl-3-trimethylsilyloxyheptan-1-ol (208) (114 mg, 71%) as a colourless liquid, $[\alpha]_D^{21}$ -1.4°(c, 1.3, CCl_4); ν_{max} (thin film) 3600-3150(s,OH), 2980-2860(s,CH), 1360(m,-CMe_3), and 1250 cm^{-1} (s,CO) ; δ_H(360 MHz ; $CDCl_3$) 0.04(6H,s,$(C\underline{H}_3)_2Bu^tSi$) , 0.13(9H,s,$Me_3Si$), 0.86-0.99(18H,m,3x-$CH_3$ and $(C\underline{H}_3)_3CSiMe_2$), 1.11-2.09(7H,m,-C$\underline{H}$(Me)C$\underline{H}_2C\underline{H}$(Me), -C$\underline{H}_2$$CH_3$, and -C$\underline{H}$(Et)), 3.31-3.52(2H,m,-$CH_2$OSi), and 3.59-3.70(3H,m,-C$\underline{H}_2$OH and -CHOSi); $\underline{m/z}$ 317($\underline{M}$ − $SiMe_3$,7%), 185($\underline{M}$-$C_9H_{25}OSi_2$,11), 175($C_8H_{19}O_2Si$,60), 103($C_4H_{11}OSi$,60), 95(28), 75(C_2H_7OSi,100), 73($SiMe_3$,69), and 57(CMe_3,25).

(2S,3S,4S,6R)-(+)-7-tert-Butyldimethylsilyloxy-4,6-dimethyl-2-ethyl-3-trimethylsilyloxyhept-1-yl acetate (209)

To a solution of (2S,3S,4S,6R)-(-)-7-tert-butyldimethylsilyloxy-4,6-dimethyl-2-ethyl-3-trimethylsilyloxyheptan-1-ol (208) (130 mg, 0.33 mmol) in dichloromethane (10 ml) was added triethylamine (66 mg, 0.66 mmol), acetic anhydride (34 mg, 0.33 mmol) and 4-dimethylaminopyridine (3 mg). After stirring at room temperature for 2h., water (1 ml) was added and the reaction mixture extracted with dichloromethane (3 x 20 ml). The dichloromethane extract was washed with water (2 ml), brine (2 ml) and dried over sodium sulphate. Removal of solvent at reduced pressure afforded a pale yellow oil (146 mg) which was purified by flash chromatography using 9:1 petrol:diethyl ether as eluant to give (2S,3S,4S,6R)-(+)-7-tert-butyldimethylsilyloxy-4,6-dimethyl-2-ethyl-3-trimethylsilyloxyhept-1-yl acetate (209) (132 mg, 92%) as a colourless liquid, $[\alpha]_D$+7.2°(c,3.25,CCl_4); ν_{max} (thin film) 2980-2860(s,CH), 1740(s,C=O), 1380, 1360(s,-$OCOCH_3$, and -CMe_3), and 1250 cm^{-1}(s,CO); δ_H(360 MHz; $CDCl_3$) 0.04(6H,s,(CH_3)$_2$$Bu^tSi$), 0.12(9H,s,$Me_3Si$), 0.82-1.01(18H,m,3x-$CH_3$ and (CH_3)$_3$$CSiMe_2$), 1.16-1.79 (7H,m,-CH(Me)CH_2CH(Me), -CH_2CH_3, and -CH(Et)),2.06(3H,s,-$COCH_3$), 3.31(1H, dd, $J_{6,7}$ 6.6 and J_{gem} 9.9 Hz,-$CH_AH_BOSiBu^tMe_2$), 3.48(1H,dd,$J_{2,3}$ 3.6 and $J_{3,4}$ 6.3 Hz, -CHOSiMe_3), 3.52(1H,dd, $J_{6,7}$ 4.5 and J_{gem} 9.9 Hz, -$CH_AH_BOSiBu^tMe_2$), 3.91(1H,dd, $J_{1,2}$ 7.9 and J_{gem} 11.2 Hz, -CH_AH_BOAc), and 4.12(1H,dd, $J_{1,2}$ 4.9 and J_{gem} 11.2 Hz, -CH_AH_BOAc); m/z 317 (M-$SiBu^tMe_2$,3%), 244(M-$SiBu^tMe_2$-$SiMe_3$,3),243(19), 185(M-$SiBu^tMe_2$-$SiMe_3$ -$OCOCH_3$,17), 157($C_8H_{17}OSi$,85), 117(41), 75(C_2H_7OSi,46), 73($SiMe_3$,100), 57(CMe_3,24), and 43(CH_3CO,34).

(1'S,3R,5S,6S)-(+)-Tetrahydro-6-[1-(acetoxymethyl)propyl]-3,5-dimethyl-pyran-2-one (206)

A solution of (2S,3S,4S,6R)-7-tert-butyldimethylsilyloxy-4,6-dimethyl-2-ethyl-3-trimethylsilyloxyhept-1-yl acetate (209) (56 mg, 0.13 mmol) in methanol (10 ml) was stirred overnight with Amberlite IR 118 resin. Removal of solvent at reduced pressure, after filtration to remove the Amberlite, afforded a colourless oil (31 mg) which was dissolved in acetone (25 ml). To this was then added N-methylmorpholine-N-oxide (30 mg, 0.26 mmol) and tris(triphenylphosphine)ruthenium(II) chloride (3 mg). The resultant gold solution was stirred at room temperature for 3h. After removal of solvent by filtration the brown residue was purified by flash chromatography using 1:1 petrol:ethyl acetate as eluant to give a colourless oil (24 mg). This oil (24 mg) was treated with Fetizon's reagent[131] (1 g) in toluene (20 ml) and heated under reflux for 2 h. Filtration to remove the oxidant and removal of solvent at reduced pressure afforded (1'S,3R,5S,6S)-(+)-tetrahydro-6-[1-(acetoxymethyl)propyl]-3,5-dimethylpyran-2-one (206) (21 mg, 68%) as a colourless oil, $[\alpha]_D^{21}$ + 77.6°(c,0.51,CCl_4) (Found: M+H(CI,CH_4), 243.1596.$C_{13}H_{23}O_4$ requires M,243.1596); ν_{max} (thin film) 2970, 2940, 2880(s,CH), 1740(s,C=O), 1380(s,-$OCOCH_3$), and 1240 cm^{-1}(s,CO); δ_H(360 MHz; $CDCl_3$) 0.93(3H,d,J 6.3 Hz, 5-Me), 0.95(3H, t, J 7.6 Hz, -$CH_2\underline{CH_3}$), 1.24(3H, d, J 7.1 Hz, 3-Me), 1.39(1H,q,J 12 Hz, 4_{ax}-H), 1.48-2.04(5H,m,4_{eq}-H,5_{ax}-H, -C<u>H</u>(Et), and -$\underline{CH_2}CH_3$), 2.06(3H,s,-$COCH_3$), 2.43-2.55(1H, m,3_{ax}-H), 4.06(1H,t, J 11 Hz, -$\underline{CH_A}H_BOAc$), 4.14(1H,d, J 11 Hz, -$CH_A\underline{H_B}OAc$), and 4.32(1H,dd, $J_{1',6}$ 5.3 and $J_{5,6}$ 10.6 Hz, 6_{ax}-H); δ_C(90.6 MHz;$CDCl_3$) 12.4(q,-$CH_2\underline{C}H_3$), 17.3(q,3-Me and 5-Me), 18.1(t, -$\underline{CH_2}CH_3$), 21.0(d,C-1'), 30.7(t,C-4), 36.2(d,C-5). 37.8(d,C-3), 41.1(q,-$OCO\underline{C}H_3$), 64.0(t,C-1''), and 86.1(d,C-6); m/z(CI,CH_4) 243(M+H,5%), 183(M-$OCOCH_3$,10), 127($C_7H_{11}O_2$,75), 99($C_6H_{11}O$,27), 83(12), 57(C_3H_5O,12), 56(C_3H_4O,37), 55(20), 43(CH_3CO,100), and 41(23).

(±)-(Tetrahydro-2-methyl-5-oxofuran-2-yl)carboxylic acid (212)

Acetic acid (40 ml) was dissolved in water (60 ml) and neutralized to pH 6 with sodium hydroxide (20 g). To the ice-cooled buffer solution was added simultaneously levulinic acid (213) (232 g, 2 mol) and a solution of sodium cyanide (100.2 g, 2 mol) in water (140 ml) over 1h. Throughout the addition the pH of the mixture was kept at 6. The pale brown mixture was stirred at room temperature for 0.5h. then concentrated hydrochloric acid (520 ml) added at room temperature. The mixture was heated under reflux for 4h. then concentrated at reduced pressure. The separated sodium chloride and ammonium chloride were removed by filtration and washed with acetone. The washings were added to the filtrate to precipitate the remaining inorganic salts. After filtration, the filtrate was concentrated at reduced pressure to give a brown residue (382 g) which was distilled at reduced pressure to give (±)-(tetrahydro-2-methyl-5-oxofuran-2-yl)carboxylic acid (212) (240 g, 83%) as a viscous colourless liquid which solidified on cooling, b.p. 142-146°C/0.3 mm Hg (lit.[133] b.p. 163-167°C/1.5 mm Hg). Recrystallization from diethyl ether/benzene gave a white crystalline solid, m.p. 72-73°C (lit.[141] m.p. 72-73.5°C).

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

(S)-(-)-(Tetrahydro-2-methyl-5-oxofuran-2-yl)carboxylic acid (212) was prepared from (±)-(tetrahydro-2-methyl-5-oxofuran-2-yl)carboxylic acid (212) via resolution of its cinchonine salt using the procedure described by Mori[134], m.p. 88-89°C (lit.[134] m.p. 88-89°C); $[\alpha]_D^{21}$ -15.9°(c,1.8,H_2O) (lit.[134] $[\alpha]_D^{23}$ -16.2°(c,1.86,H_2O)).

(S)-(+)-2-Methylpentane-1,2,5-triol (214)

(S)-(+)-2-Methylpentane-1,2,5-triol (214) was prepared from (S)-(−)-(tetrahydro-2-methyl-5-oxofuran-2-yl)carboxylic acid (212) using the procedure described by Mori[134]. An improved yield (53%) was obtained by Soxhlet extraction of the salt residues for 3 days with ethyl acetate, b.p. 124-126°C/0.1 mm Hg (lit.[134] b.p.137°C/0.5 mm Hg); $[\alpha]_D^{21}$ +1.8°(c, 1.89, EtOH) (lit.[134] $[\alpha]_D^{23}$ +1.7°(c,1.85, EtOH)).

(S)-(−)-3-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)propan-1-ol (215)

(S)-(−)-3-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)propan-1-ol (215) was prepared from (S)-(+)-2-methylpentane-1,2,5-triol (214) in 83% yield using the procedure described by Mori[134], b.p. 65-66°C/0.15 mm Hg (lit.[134] b.p. 83°C/0.4 mm Hg) ; $[\alpha]_D^{20}$ -0.8°(c, 1.45, acetone) (lit.[134] $[\alpha]_D^{23}$ -0.5°(c, 2.25,acetone)).

(S)-(+)-3-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)propan-1-al (211)

To a solution of dry dimethyl sulphoxide (670 mg, 8 mmol) in dry dichloromethane (15 ml) cooled to -60°C under nitrogen was added trifluoroacetic anhydride (840 mg, 4 mmol) in dry dichloromethane (3 ml) dropwise. A white precipitate formed which was stirred at this temperature for 0.25h. then a solution of (S)-(−)-3-(2,2,4-trimethyl-1,3-dioxolan-4-yl)propan-1-ol (215) (700 mg, 4 mmol)) in dichloromethane (5 ml) was added slowly. The mixture was stirred at -60°C for 0.5h. then dry triethylamine (2.2 ml, 16 mmol) was added and the reaction mixture warmed to 0°C. After quenching with water (2 ml) the reaction mixture was extracted with dichloromethane (3 x 30 ml), washed with water (2 x 5 ml), brine (5 ml) and dried over potassium carbonate.

Removal of solvent at reduced pressure afforded a yellow liquid (702 mg) which was purified by flash chromatography using 1:1 petrol: diethyl ether as eluant to give (S)-(+)-3-(2,2,4-trimethyl-1,3-dioxolan-4-yl)propan-1-al (211) (491 mg, 68%) as a colourless liquid, b.p. (Kugelrohr) 55°C/17 mm Hg ; $[\alpha]_D^{22}$ +1.53°(c,2.48,CCl_4) ; ν_{max} (thin film) 3000, 2940 (s,CH), 2880(m,H-CO), 2720(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,2x2'-Me), 1.79-2.02(2H,m,-CH_2C(Me)O), 2.53-2.59(2H,m,-CH_2CHO), 3.75(1H,d,J 8.6Hz,-CH_AH_BO), 3.79(1H, J 8.6Hz,-CH_AH_BO), and 9.8(1H, t,J 1Hz,HC=O) ; 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-CH_3,1%), 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).

(3R,4'S)- and (3S,4'S)-1-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)-5-hexyn-3-ol (128)

A solution of propargyl bromide (0.5 ml of 80% w/v solution in toluene, 3.4 mmol) in dry diethyl ether (10 ml) was slowly added to a three-necked 50 ml flask charged with mercuric chloride (3 mg), magnesium turnings (83 mg, 3.4 mmol) and diethyl ether (5 ml). After initiation of reaction by gentle heating the reaction mixture was cooled to 0°C and stirred for 0.5h. To the grey suspension was then added a solution of (S)-(+)-3-(2,2,4-trimethyl-1,3-dioxolan-4-yl)propan-1-al (211) (500 mg, 2.91 mmol) in dry diethyl ether (15 ml). The reaction mixture was warmed to room temperature and stirred for 1h. After quenching with saturated aqueous ammonium chloride solution (5 ml), the reaction mixture was extracted with diethyl ether (3 x 30 ml), washed with water (2 x 5 ml), brine (10 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure gave a yellow liquid (802 mg) which was purified by flash chromatography using 1:1 petrol:diethyl ether as eluant to

give (3R,4'S)- and (3S,4'S)-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-5-hexyn-3-ol (128) (502 mg, 81%) as a 1:1 mixture (^{1}H n.m.r., 360 MHz), colourless oil, $[\alpha]_D^{22}$-3.66°(c, 2.68, CCl_4). Conversion to the acetate derivative afforded an analytical sample (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) ; ν_{max} (thin film) 3650-3150(br.s,OH), 3300(s,≡C-H), 2995, 2940, 2880(s,CH), 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,2x2'-Me), 1.52-1.83(4H,m,2x-CH_2), 2.06(1H,m,-C≡CH), 2.36-2.42(2H,m,-CH_2C≡C), 2.59-2.95(1H,br.s, OH), and 3.71-3.81(3H,m,-CHOH and -OCH_2); 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 or C-3), 74.4(t,C-5'), 80.9, 81.0(s,C-4' or C-5), and 109.5(s,C-2') ; m/z 197(M-CH_3,3%), 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).

(3R,4'S)- and (3S,4'S)-1-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)-3-trimethylsilyloxy-5-hexyne (217)

Using the procedure described for the preparation of 7-methyl-4-trimethylsilyloxy-7-octen-1-yne (98) (page 112),(3R,4'S)- and (3S,4'S)-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-3-trimethylsilyloxy-5-hexyne (217) was prepared in 93% yield from (3R,4'S)- and (3S,4'S)-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-5-hexyn-3-ol (128) and chlorotrimethylsilane , δ_H(60 MHz; $CDCl_3$) 0.13(9H,s,Me_3Si), 1.28(3H,s,4'-Me), 1.38(6H,s,2x2'-Me), 1.46-1.82(4H,m,2x-CH_2), 1.89-2.06(1H,m,-C≡CH), 2.21-2.43(2H,m,-CH_2C≡C), and 3.66-3.84(1H,m, -CHOSi); m/z 269(M-CH_3,11%), 211(M-$SiMe_3$,8), 187(34), 115($C_6H_{11}O_2$,57), 97(C_6H_9O,32), 91(31), 75(31), 73($SiMe_3$,100), 72(51), 57(43), and 55(28).

6-(Tetrahydro-2-methoxypyran-2-yl)-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-5-hexyn-3-ol (219)

Using the procedure described for the preparation of 7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-7-octen-1-yn-4-ol (100) (page 113), 6-(tetrahydro-2-methoxypyran-2-yl)-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-5-hexyn-3-ol (219) was prepared in 82% yield from 1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-3-trimethylsilyloxy-5-hexyne (217) and δ-valerolactone (97). In this case, pyridinium p-toluene-sulphonate was used as the acid catalyst to effect formation of the methoxy acetal, ν_{max} (thin film) 3650-3200(br.s,OH), 2940,2880(s,CH), and 2260 cm^{-1}(w,C≡C) ; δ_H(360 MHz ; $CDCl_3$) 1.28,1.29(3H,s,4'-Me), 1.38(6H,s,2x2'-Me), 1.46-1.93(10H ,m,5x-CH_2), 2.45(2H,m,-CH_2C≡C), 3.40(3H,s,OMe), and 3.65-3.81(5H,m,2x-OCH_2 and -CHOH) ; δ_c(90.6 MHz ; $CDCl_3$) 19.2(t,C-4"), 24.7(t,C-5"), 24.8(q,4'-Me), 27.1-27.5(q,2'-Me), 31.1,31.2(t,C-1 or C-3"), 35.8(t,C-2), 36.8(t,C-4), 50.5(q,OMe), 62.2(t,C-6"), 70.1-70.4 (d,C-3), 74.4(t,C-5'), 80.5, 80.9(s,C-5 or C-4'), 82.0(s,C-6), 95.1(s,C-2"), and 109.4(s,C-2') ; m/z 295(M-OCH_3,2%), 280(M-OCH_3 -CH_3,4), 279(M-CH_3OH-CH_3,20), 173($C_9H_{17}O_3$,10), 122($C_8H_{10}O$,21), 115($C_6H_{11}O_2$,100), 97(C_6H_9O,51), 72(33), 69(31), 59(34), 57(35), and 43(66).

(Z)-6-(Tetrahydro-2-methoxypyran-2-yl)-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-5-hexen-3-ol (220)

Using the procedure described for the preparation of (Z)-7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl)-4-trimethylsilyoxy-1-octene (110) (page 115), (Z)-6-(tetrahydro-2-methoxypyran-2-yl)-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-5-hexen-3-ol (220) was prepared from 6-(tetrahydro-2-methoxypyran-2-yl)-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-5-hexyn-3-ol (219) in 94% yield, ν_{max} (thin film) 3650-3200(s,OH), 3040(m,=C-H), 2980, 2940, 2880(s,CH), and 1660 cm^{-1}(w,C=C); δ_H(360 MHz ; $CDCl_3$)

1.28(3H,s,4'-Me), 1.38(6H,s,2x2'-Me), 1.42-1.94(10H,m,5x-CH_2), 2.27-2.68(2H,m,-CH_2C=C), 3.17(3H,s,OMe), 3.43-3.82(5H,m, 2x-OCH_2 and -CHOH), and 5.15-5.76(2H,m,HC=CH); m/z 296(M-CH_3OH, 2%), 281(M-CH_3OH-CH_3,26), 173($C_9H_{17}O_3$,10), 124($C_8H_{12}O$,24), 115($C_6H_{11}O_2$,100), 97(68), 72(39), 69(51), 57(38), 55(40), 43(72), and 41(38).

2-[2-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)ethyl]-1,7-dioxaspiro[5.5]undec-4-ene (221)

Using the procedure described for the preparation of 4-(1,7-dioxaspiro[5.5]undec-4-en-2-yl)-2-methylbutan-2-ol (121) (page 120), 2-[2-(2,2,4-trimethyl-1,3-dioxolan-4-yl)ethyl]-1,7-dioxaspiro[5.5]undec-4-ene (221) was prepared in 81% yield from (Z)-6-(tetrahydro-2-methoxypyran-2-yl)-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-5-hexen-3-ol (220), (Found : M^+, 296.1996. $C_{17}H_{28}O_4$ requires M, 296.1987) ; ν_{max} (thin film) 3040(m,=C-H), 2980, 2940, 2880(s,CH), and 1660 cm^{-1}(w,C=C) ; δ_H(360 MHz ; $CDCl_3$) 1.28,1.29(3H,s,4"-Me), 1.38(6H,s,2x2"-Me), 1.48-2.11(12H,br.m, 6x-CH_2), 3.58-3.90(5H,m,2x-CH_2O and -CHO), 5.57-5.63(1H,m,HC=C), and 5.83-5.92(1H,m,-C=CHCH$_2$) ; m/z 296(M^+, 7%), 281(M-CH_3,72), 124($C_8H_{12}O$,7), 115($C_6H_{11}O_2$,99), 97(C_6H_9O,85), 95(54), 72(75), 57(45), 55(47), 43(100), and 41(45).

1,5-Bis(trimethylsilyloxy)-2-methyl-8-(tetrahydro-2-methoxypyran-2-yl)-7-octyn-2-ol (224)

A solution of 6-(tetrahydro-2-methoxypyran-2-yl)-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-5-hexyn-3-ol (219) (150 mg, 0.46 mmol) in methanol (20 ml) was stirred at room temperature overnight with Amberlite IR 118 resin. After filtration to remove the Amberlite and removal of solvent at reduced pressure, the resultant

colourless oil (127 mg) was redissolved in tetrahydrofuran (25 ml). To this solution was then added triethylamine (180 mg, 1.8 mmol) and chlorotrimethylsilane (100 mg, 0.9 mmol) under nitrogen at room temperature. The reaction mixture was stirred at room temperature for 1h. whereupon a white precipitate formed. Water (2 ml) was added and the reaction mixture extracted with diethyl ether (3 x 30 ml). The ethereal extract was washed with water (5 ml), brine (5 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure afforded a pale yellow liquid (192 mg) which was purified by flash chromatography using 8:2 petrol:diethyl ether as eluant to give 1,5-bis(trimethylsilyloxy)-2-methyl-8-(tetrahydro-2-methoxypyran-2-yl)-7-octyn-2-ol (224) (168 mg, 85%) as a colourless liquid, ν_{max} (thin film) 3500(s,OH), 2960,2880(s,CH), and 2260 cm^{-1} (w,C≡C); δ_H(360 MHz ; $CDCl_3$) 0.13(9H,s,Me_3Si), 0.14(9H,s,Me_3Si), 1.13(3H,s,2-Me), 1.46-1.92(10H,m,5x-CH_2), 2.43(2H,m,-CH_2C≡C), 3.36(2H,m,-CH_2OSi) , 3.41(3H,s,OMe), and 3.67-3.84(3H,m,-OCH_2 and -CHOSi) ; m/z 399(M-OCH_3,0.3%), 295(18), 187($C_9H_{19}O_2Si$,100), 173(38), 143(34), 129(24), 75(29), 73($SiMe_3$, 100), and 69(30).

4-(1,7-Dioxaspiro[5.5]undec-4-en-2-yl)-2-methylbutane-1,2-diol (222)

A solution of 1,5-bis(trimethylsilyloxy)-2-methyl-8-(tetrahydro-2-methoxypyran-2-yl)-7-octyn-2-ol (224) (160 mg, 0.37 mmol) in pentane (25 ml) was stirred with Lindlar catalyst (10 mg) and potassium carbonate (50 mg) at room temperature under a balloon of hydrogen for 4h. Removal of the catalyst by filtration and the solvent at reduced pressure,afforded a colourless oil (156 mg). This was redissolved in dichloromethane and treated with camphor-sulphonic acid (5 mg) at room temperature for 14h. Sodium bicarbonate (10 mg) was added and the reaction mixture filtered through florisil. Evaporation of the filtrate at reduced pressure afforded a pale yellow oil (93 mg) which was purified by flash chromatography using 1:1 petrol:

ethyl acetate as eluant to give 4-(1,7-dioxaspiro[5.5]undec-4-en-2-yl)-2-methylbutane-1,2-diol (222) (73 mg, 77%) as a colourless oil, ν_{max} (thin film) 3650-3100(br.s,OH), 3040(m,=C-H), 2960, 2880 (s,CH), and 1660 cm^{-1}(w,C=C) ; δ_H(60 MHz; $CDCl_3$) 1.12(3H,s, 2-Me), 1.42-2.16(12H,br.m,6x-CH_2), 2.50(2H,br.s, 2xOH), 3.32(2H,s,-$C\underline{H}_2OH$), 3.52-4.12(3H,m,-OCH_2 and -CHO), and 5.41-5.98(2H,m,HC=CH) ; m/z 256(M^+, 1%), 153($C_9H_{13}O_2$,28), 125(49), 124($C_8H_{12}O$), 115(44), 101(55), 95(61), 85(41), 83(41), 69(55), 55(54), and 43(100).

4-(1,7-Dioxaspiro[5.5]undec-4-en-2-yl)-2-hydroxy-2-methylbut-1-yl p-toluenesulphonate (226)

To a solution of 4-(1,7-dioxaspiro[5.5]undec-4-en-2-yl)-2-methylbutane-1,2-diol (222) (100 mg, 0.39 mmol) in dichloromethane (20 ml) cooled to 0°C was added triethylamine (80 mg, 0.8 mmol) and p-toluenesulphonyl chloride (76 mg, 0.4 mmol). After standing in a refridgerator (-10°C) for 48h. the reaction mixture was poured onto ice (5 ml) and extracted with diethyl ether (3 x 30 ml). The ethereal extract was washed with water (10 ml), brine (10 ml) and dried over magnesium sulphate. Removal of solvent at reduced pressure afforded a yellow oil (153 mg) which was purified by flash chromatography using 1:1 petrol:ethyl acetate as eluant to give 4-(1,7-dioxaspiro[5.5]undec-4-en-2-yl)-2-hydroxy-2-methylbut-1-yl p-toluenesulphonate (226) (129 mg, 81%) as a colourless oil, ν_{max} (thin film) 3600-3250(s,OH), 3040(m,=C-H), 2960,2880(s,CH), 1660(w,C=C), 1610(m,C=C aromatic), 1360, and 1180 cm^{-1}(s,-SO_2O); δ_H(60 MHz; $CDCl_3$) 1.11(3H,s,2-Me), 1.28-2.14(12H,br.m,6x-CH_2), 2.33(3H,s,Ar-$C\underline{H}_3$), 3.49-4.14(3H,m,-OCH_2 and -CHO), 3.79(2H,s,-CH_2OS), 5.32-5.97(2H,m,HC=CH), 7.26(2H,d,J 7 Hz, Ar-H), and 7.73(2H,d,J 7 Hz, Ar-H) ; m/z 410 (M^+,1%), 392(M,-H_2O,1), 155($CH_3C_6H_4SO_2$,30), 124($C_8H_{12}O$,84), 97(59), 95(73), 91(71), 69(63), 57(75), 55(87), 43(85), and 41(100).

2-(3,4-Epoxy-3-methylbutyl)-1,7-dioxaspiro[5.5]undec-4-ene (112)

To a solution of 4-(1,7-dioxaspiro[5.5]undec-4-en-2-yl)-2-hydroxy-2-methylbut-1-yl p-toluenesulphonate (226) (100 mg, 0.24 mmol) in dry tetrahydrofuran (25 ml) under nitrogen was added sodium hydride (15 mg of a 40% dispersion in mineral oil, 0.25 mmol). After stirring at room temperature for 3h. the reaction mixture was quenched with saturated aqueous sodium dihydrogen phosphate solution (1 ml) and extracted with diethyl ether (3 x 25 ml). The ethereal extract was washed with brine (10 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure afforded a colourless oil (46 mg) which was purified by flash chromatography using 1:1 petrol: diethyl ether as eluant to give 2-(3,4-epoxy-3-methylbutyl)-1,7-dioxaspiro[5.5]undec-4-ene (112) (41 mg, 72%) as a colourless oil, b.p. (Kugelrohr) 90°C/17 mm Hg (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) ; ν_{max} (thin film) 3040(m,=C-H), 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,br.m,6x-CH_2), 2.57-2.78(2H,m,-CH_2 epoxide), 3.56-3.93(3H,m,-OCH_2 and -CHO), 5.57-5.66(1H,m,HC=C), and 5.82-5.95(1H,m,-C=C<u>H</u>CH_2); 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, or 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).

4-(1,7-Dioxaspiro[5.5]undec-4-en-2-yl)-2-methylbutan-2-ol (121)

Using the procedure described for the preparation of (Z)-2-methyl-8-(tetrahydro-2-methoxypyran-2-yl)-5-trimethylsilyloxy-7-octen-2-ol (120) from (Z)-7,8-epoxy-7-methyl-1-(tetrahydro-2-methoxypyran-2-yl) -4-trimethylsilyloxy-1-octene (110) (page 119)

4-(1,7-dioxaspiro[5.5]undec-4-en-2-yl)-2-methylbutan-2-ol (121) was prepared in 78% yield from 2-(3,4-epoxy-3-methylbutyl)-1,7-dioxaspiro[5.5]undec-4-ene (112) and lithium aluminium hydride. The product isolated had the same R_f as the material previously prepared from (Z)-2-methyl-8-(tetrahydro-2-methoxypyran-2-yl)-5-trimethylsilyloxy-7-octen-2-ol (120). The ^1H n.m.r., infra-red, and mass spectra were also identical.

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