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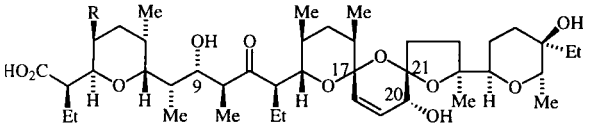
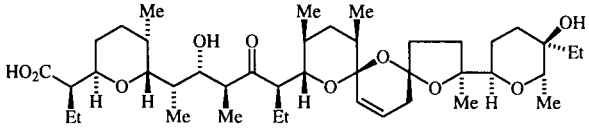
The pharmacological importance of spiroacetal containing compounds is evident from their widespread occurrence as metabolites from insects, microbes, plants, fungi and various marine organisms. The important biological activity of this class of compound has prompted a variety of methods for the synthesis of spiroacetals [1]. In contrast to their bicyclic analogues, the chemistry of tricyclic bis-spiroacetals, in which two acetal carbons are linked in a spiro fashion, has not been fully explored.

In 1973 the polyether antibiotic salinomycin **1**, which contains the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene bis-spiroacetal unit, was isolated from the culture broth of *Streptomyces albus* [2] and was found to exhibit activity against mycobacteria and fungi and acted as a coccidiostat for poultry and as a growth promotant for ruminants. Using the same *S. albus* culture and a different medium, Westley *et al.* [3] established that *epi*-17-deoxy-(*O*-8)-salinomycin **2** was found to be present at much greater levels. Further examples of polyether antibiotics which contain the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system include: narasin A (4-methylsalinomycin) **3** [4] from *S. aureofaciens*, noboritomycins A **4a** and B **4b** from *S. noboritoensis* [5], CP44,161 **5** [6] from a *Dactylsporangium* species and the halogenated polyether antibiotic, antibiotic X-14766A **6** [7].

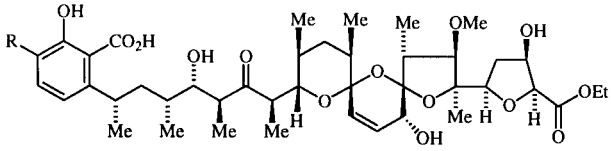
The stereochemistry of the bis-spiroacetal ring system in the above polyether antibiotics needs addressing. The four possible stereoisomers of the bis-spiroacetal ring system are depicted (Figure 1). Diastereomer A depicts the stereochemistry adopted by salinomycin **1** and has three stabilizing anomeric effects but exhibits unfavourable 1,3-dipole-dipole interactions. The 21-*epi*-salinomycin B has only one anomeric effect and is the thermodynamically least stable diastereomer. The 17-*epi*-diastereomer C exhibits three anomeric effects and although it exhibits unfavourable 1,3-diaxial interactions between the C17 oxygen atom and the C21 methylene it lacks the unfavourable 1,3-dipole-dipole interactions exhibited by diastereomer A and 17-*epi*-21-*epi*-diastereomer D.



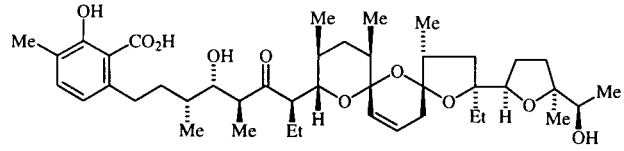
salinomycin **1**: R = H
narasin A **3**: R = Me



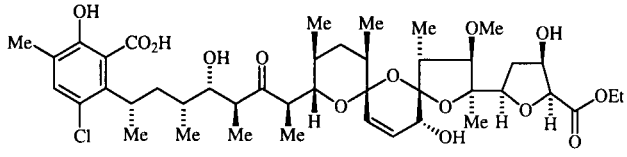
epi-17-deoxy-(*O*-8)-salinomycin **2**



noboritomycin A **4a**: R = Me
noboritomycin B **4b**: R = Et



antibiotic CP44,161 **5**



antibiotic X-14766A **6**

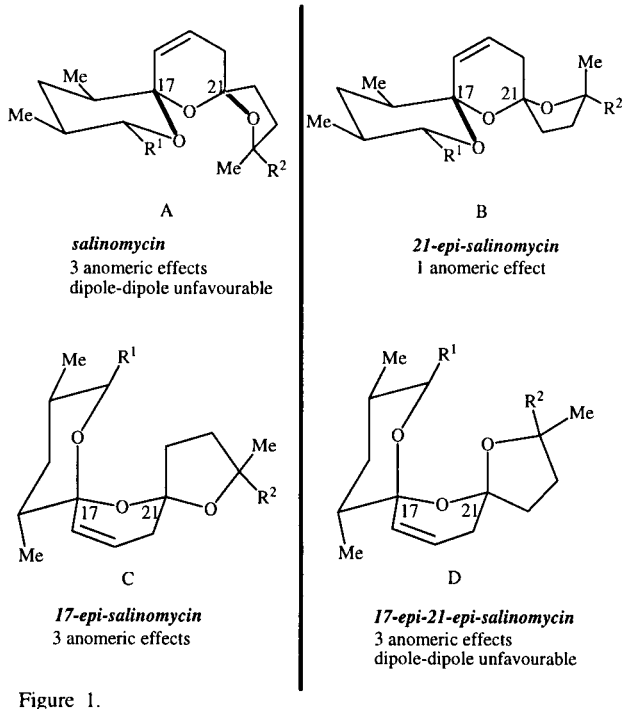
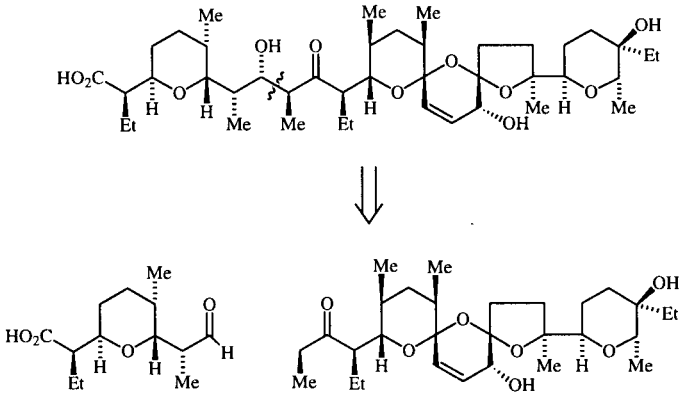


Figure 1.

This qualitative analysis leads to the assumption that 17-*epi*-diastereomer C exhibits the most thermodynamically stable configuration. It transpires that in the cyclic structure that salinomycin **1** adopts, the repulsive 1,3-dipolar interactions in diastereomer A are compensated for by a hydrogen bond between the C9 and C20 hydroxy groups. Bis-spiroacetals whose structures preclude this remote hydrogen bond do not adopt the salinomycin configuration A.

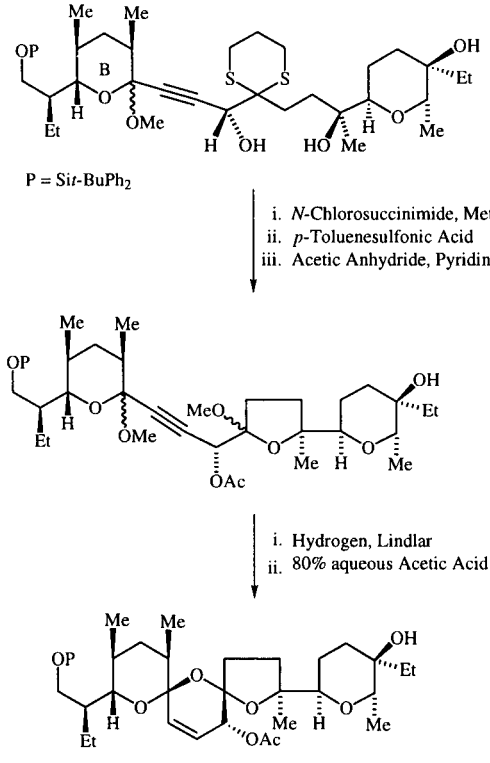
To date there have been three total syntheses of salinomycin **1** [8,9,10] which made use of a stereoselective aldol reaction to construct the C9-C10 bond (Scheme 1). In the first synthesis by Kishi *et al.* [8] the bis-spiroacetal moiety was formed by assembly of a highy functionalised dithiane that was subsequently removed providing the latent carbonyl group for the C21 spiro centre (Scheme 2). Yonemitsu *et al.* [9] used a "chiral pool" approach preparing salinomycin **1** from D-glucose, D-mannitol and (*S*)-lactic

Scheme 1

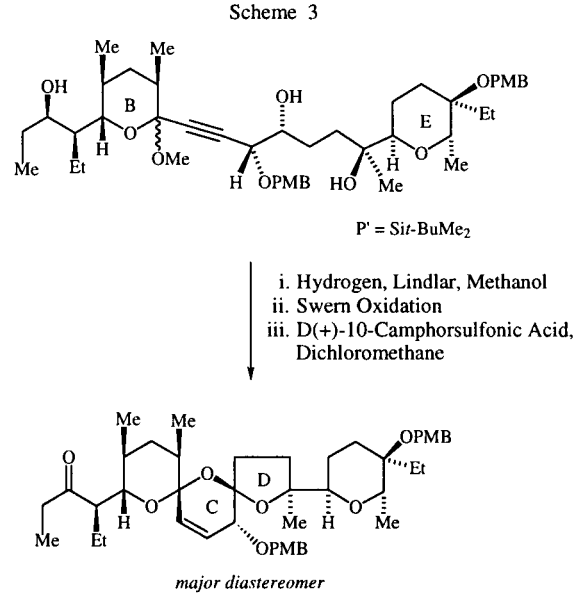


acid using a strategy wherein the B and E rings were assembled prior to construction of the bis-spiroacetal system by an acid catalysed cyclisation (Scheme 3). In the most recent approach to salinomycin **1** by Kocienski *et al.* [10], the bis-spiroacetal core was constructed by an elegant oxidative rearrangement of an acylfuran or by hydrolysis of an allenol ether that was used as an acyl anion equivalent (Scheme 4).

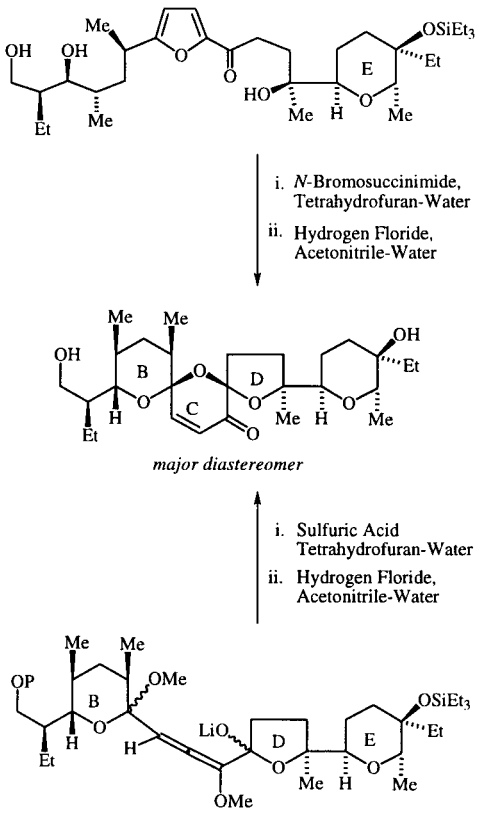
Scheme 2



Scheme 3



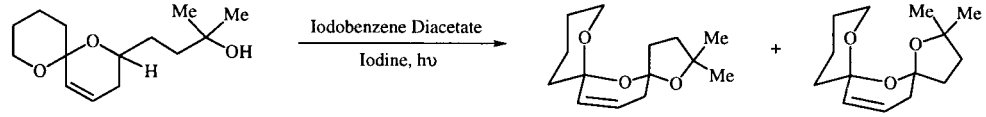
Scheme 4



Whilst the synthetic approaches to salinomycin **1** by Kishi, Yonemitsu and Kocienski, have focused on late assembly of the C ring after appending the D,E rings to the B ring, our synthetic efforts have focused on the construction of a tricyclic bis-spiroacetal core containing the B,C,D rings with the idea of appending the A and E rings at a later stage in the synthesis.

Our initial work in this area focused on the synthesis of the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system *via* oxidative cyclisation of an hydroxyspiroacetal to a bis-spiroacetal [11] (Scheme 5). Treatment of hydroxyspiroacetal **7** with iodobenzene diacetate in iodine under photolytic conditions afforded *trans* bis-spiroacetal **8** and *cis* bis-spiroacetal **9** in a 2.5:1 ratio. The stereochemistry of the major bis-spiroacetal **8** was the same as that present in *epi*-17-deoxysalinomycin **2** hence we embarked on a synthesis of *epi*-17-deoxysalinomycin **2** adopting the retrosynthesis outlined (Scheme 6). The key bis-spiroacetal **10** could be prepared by oxidative cyclisation of iodospiroacetal **11** since extensive model work [12] also established that an iodomethyl group was not only compatible with the key oxidative cyclisation step but was also thought to be readily converted to an aldehyde when elaboration of the E ring was required.

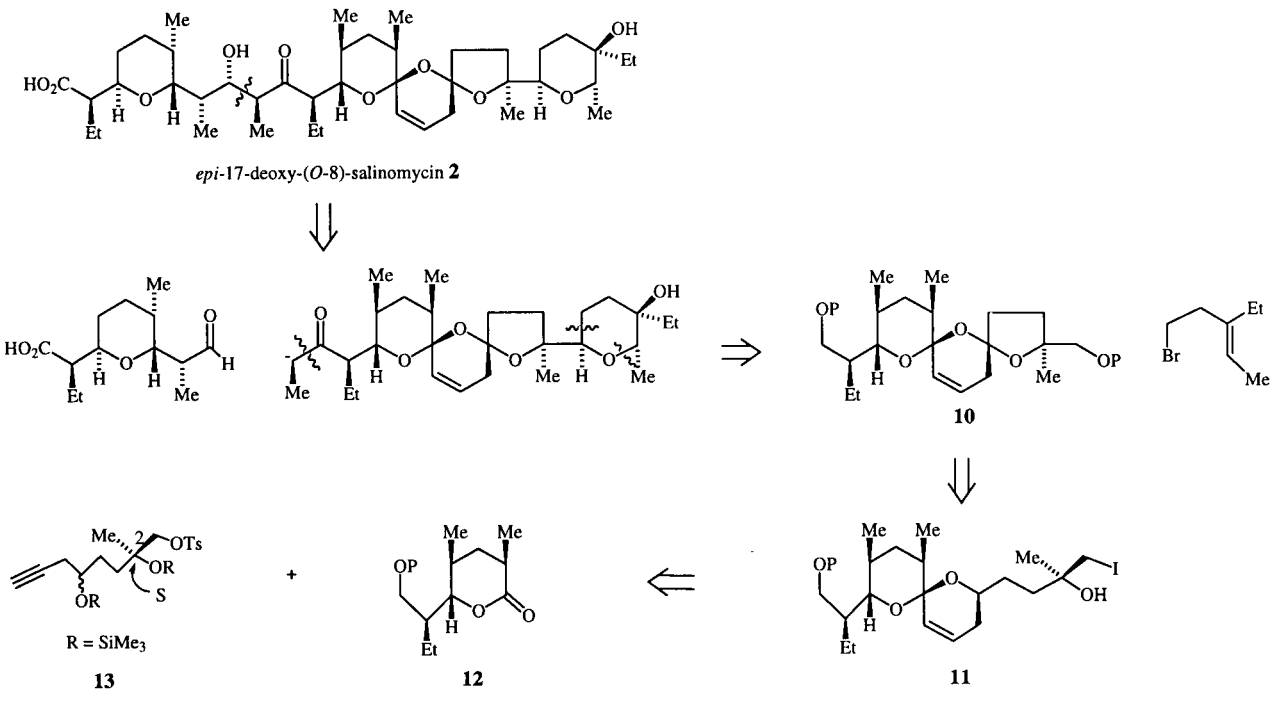
Scheme 5



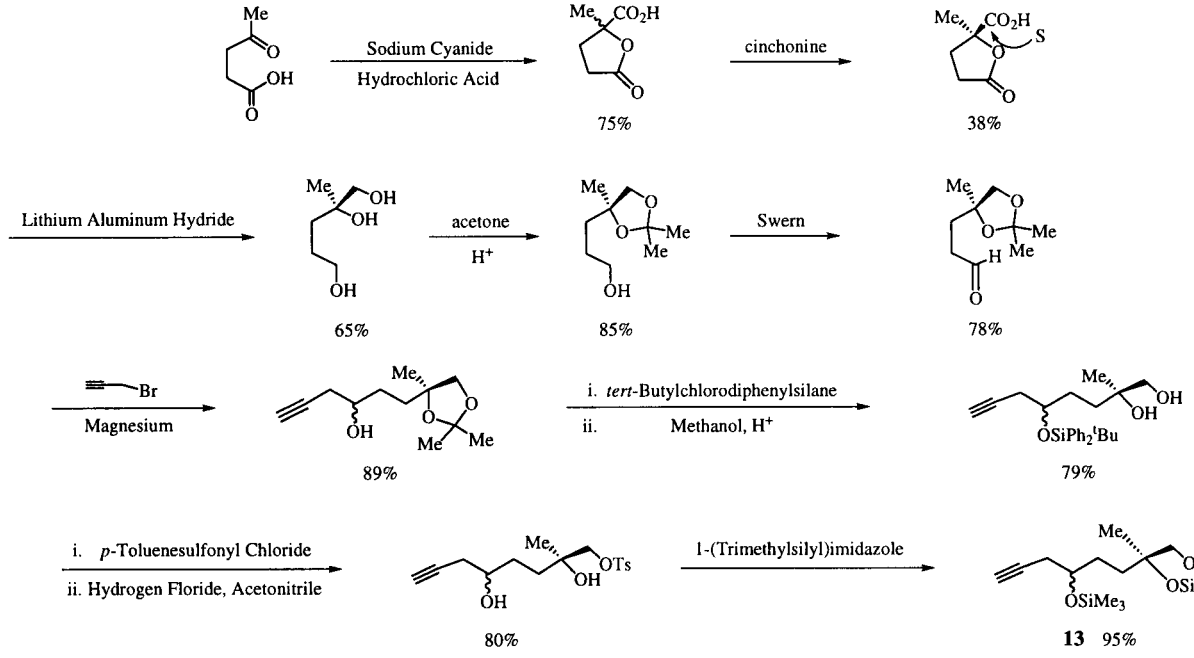
7 **8** 58% *TRANS* **9** 23% *CIS*

The synthesis of the key cyclisation precursor, iodide **11**, initially required the synthesis of optically active lactone **12**, and acetylene **13** with the required *S* configuration at C2. Lactone **12** was prepared [13] using methodology developed by Evans and Bartroli [14] for the synthesis of Prelog-Djerassi lactone. Acetylene **13** was prepared (Scheme 7) from (*S*)-(–)-lactonic acid which in turn was readily available by resolution of racemic lactonic acid using cinchonine.

Scheme 6



Scheme 7



Generation of the acetylide derived from **13** followed by the addition of lactone **12** afforded methyl acetals **14** after *in situ* treatment with acidic methanol (Scheme 8). Semi-hydrogenation of the acetylene to a *cis*-alkene followed by treatment with a catalytic quantity of pyridinium *p*-toluenesulfonate afforded a 1:1 mixture of spiroacetals **15**. This thermodynamically controlled cyclisation affords the most stable configuration at the newly formed spiro centre due to maximum stabilisation by the anomeric effect with the two isomers of spiroacetal **15** differing only in the position that the side chain adopts. With spiroacetals **15a** and **15b** in hand, the neopentyl-like tosylates were converted to the iodides **11a** and **11b** (*via* the intermedicay of an epoxide) in readiness for the key oxidative cyclisation.

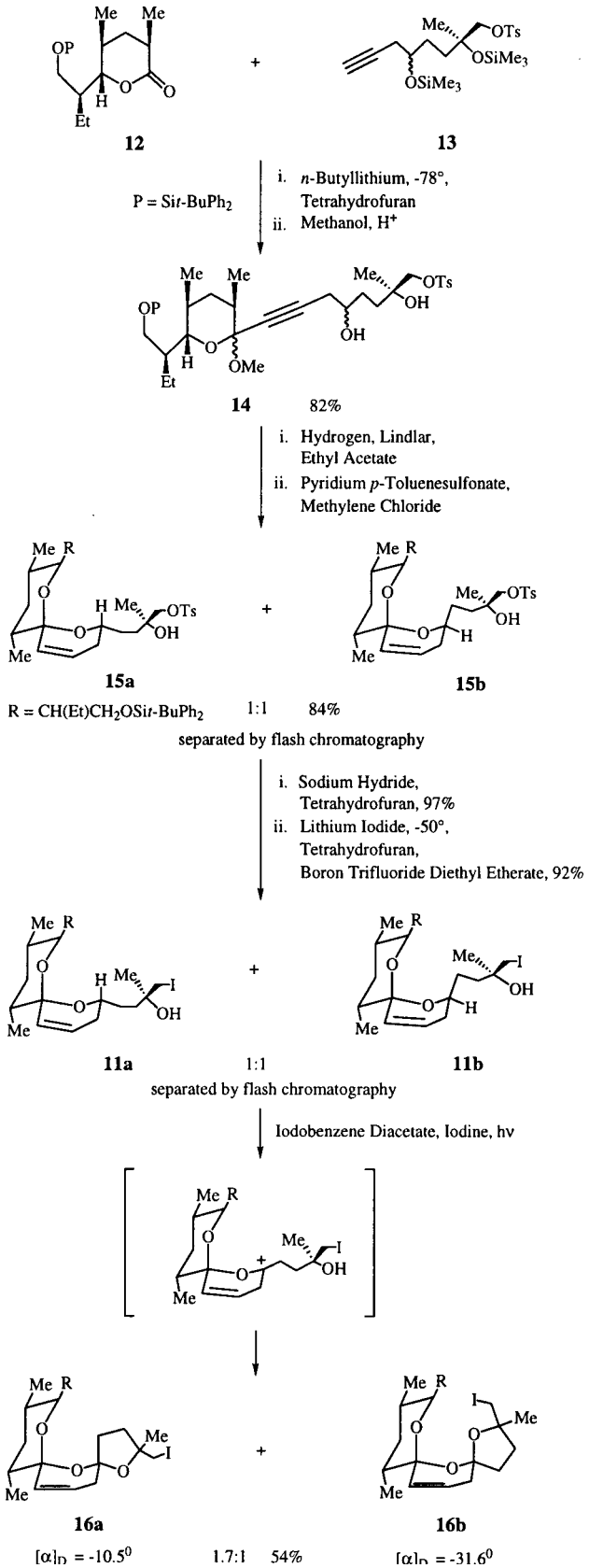
Finally the individual iodides **11a** and **11b** were treated with iodobenzene diacetate and iodine with irradiation from a tungsten filament lamp to afford a 1.7:1 mixture of the *trans* bis-spiroacetal **16a** and the *cis* bis-spiroacetal **16b**. It was pleasing to note that the major isomer had the same stereochemistry as the bis-spiroacetal ring in *epi*-17-deoxy-(*O*-8)-salinomycin **2**.

At this stage we had prepared bis-spiroaetal **16** which was a suitable advanced intermediate for the synthesis of *epi*-17-deoxy-(*O*-8)-salinomycin **2**, however, further elaboration to append the E ring required conversion of the iodide to a hydroxy group. Unfortunately, conversion of the neopentyl-like iodide **16a** into a hydroxy group required the use of potassium superoxide and 18-crown-6 which also deprotected the *tert*-butyldiphenylsilyl ether at the left hand end of the molecule (Scheme 9). This problem was later solved [15] by using an acetate group rather than an iodide in the cyclisation precursor.

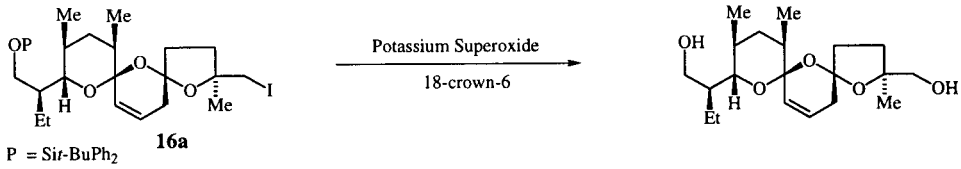
We next addressed the strategy for attachment of the E ring to the BCD fragment. Towards this end, our attention initially focused on a model system, namely, the conversion of the simpler aldehyde **17** and bromide **18** to bicyclic ether **19** (Scheme 10) [16]. Chelation controlled addition of the Grignard reagent derived from bromide **18** to aldehyde **17** afforded predominantly *erythro* alcohol **19**. Treatment of alcohol **19** with iodine in acetonitrile affords predominantly iodoether **20** with the exact ratio of **20**:**21** depending on the temperature used. Individual treatment of each iodide with silver carbonate in wet acetone afforded in each case a single, yet different ring expanded product (**20** gives **22** and **21** gives **23**).

Given that iodoether **21** affords pyran **23** which has the same stereochemistry as the E ring of *epi*-17-deoxy-(*O*-8)-salinomycin **2**, it then remained to alter the stereochemical outcome of the iodoetherification such that the amount of the desired iodoether **21** was increased. Following Bartlett's rationalisation [17] for the synthesis of *cis*-2,5-disubstituted tetrahydrofurans, bulkier ether derivatives

Scheme 8



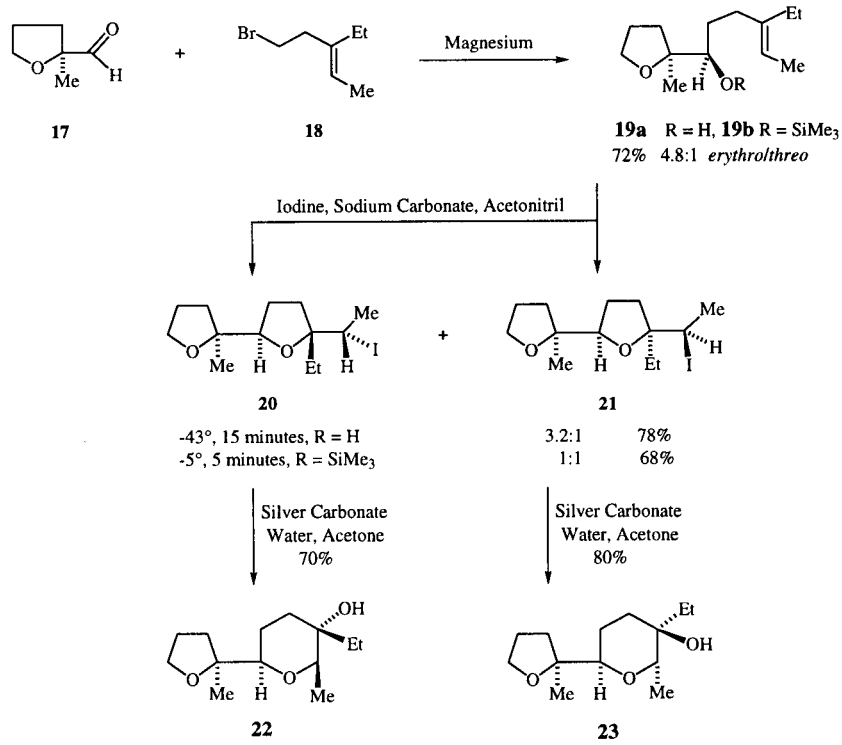
Scheme 9



P = Si*t*-BuPh$_2$

16a

Scheme 10



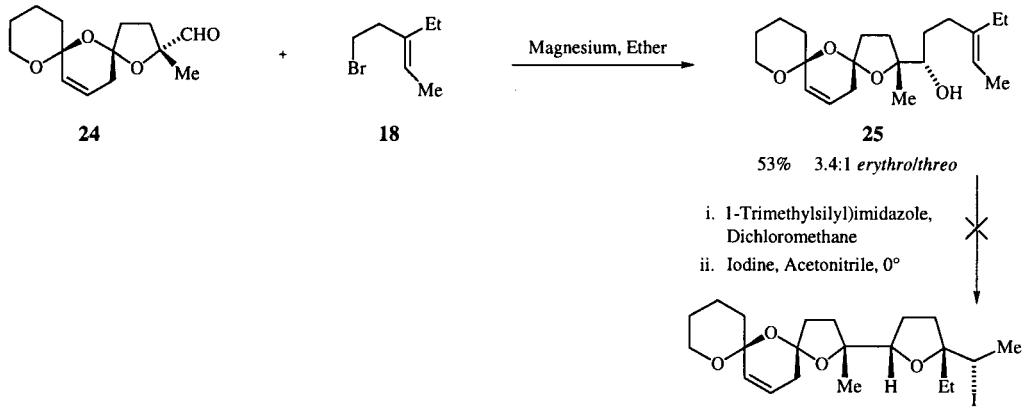
17 **18** **19a** R = H, **19b** R = SiMe$_3$ 72% 4.8:1 *erythro/threo*

20 **21** **22** **23**

were used in the iodoetherification. However, the critical iodoetherification could not be induced to favour the iodoether **21** required for elaboration to the desired bicyclic ether **23**. An alternative approach [18] based on an acid catalysed cyclisation of a hydroxyepoxide and ring expansion of the mesylate derived from the resultant tetrahydrofuranyl alcohol provided little improvement in stereoselectivity for the desired pyran **23**.

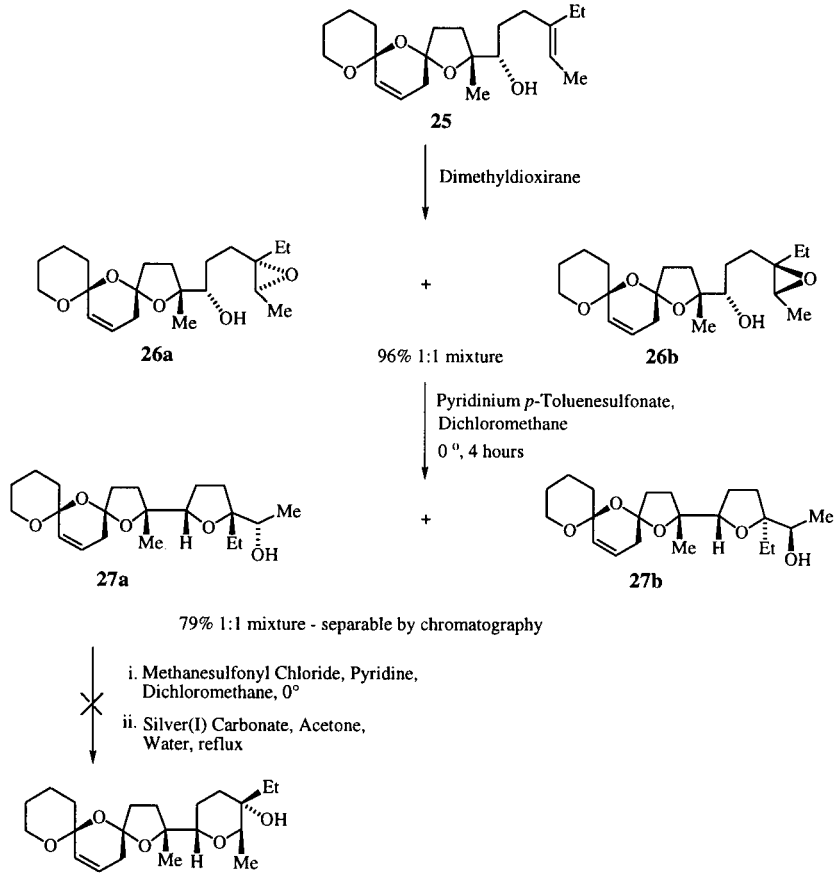
Given that aldehyde **17** had been successfully converted to a bicyclic ether, we then tried to extend our model work to the incorporation of an E ring fragment onto the model bis-spiroacetal aldehyde **24** (Scheme 11). Addition of the Grignard reagent derived from bromide **18** to aldehyde **24** afforded predominantly the *erythro* alcohol **25**, however, it was at this stage that we discovered that the critical iodoetherification step was incompatible with the sensitive bis-spiroacetal ring system.

Scheme 11



An alternative approach was also hampered by the presence of the bis-spiroacetal (Scheme 12). Epoxidation of alcohol **25** afforded a 1:1 mixture of epoxides **26a** and **26b** which then underwent acid catalysed cyclisation to alcohols **27a** and **27b** respectively. Subsequent mesylation and attempted silver assisted ring expansion, however, resulted in destruction of the bis-spiroacetal.

Scheme 12



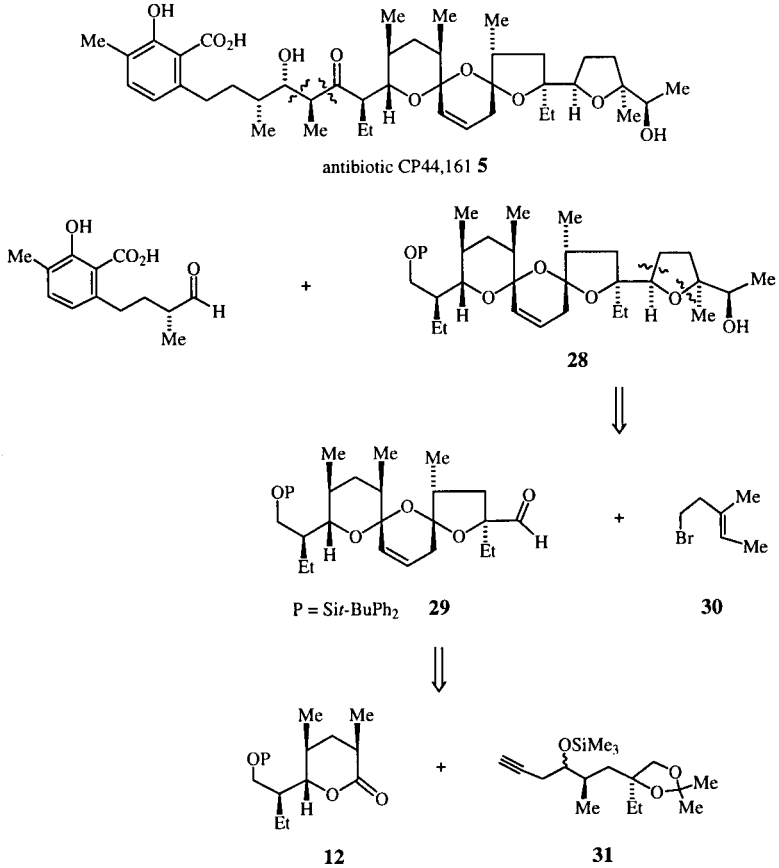
Having committed to the strategy of appending the tetrahydropyran E ring fragment to a BCD bis-spiroacetal it was disappointing to find that the proposed ring expansion was not feasible in the presence of the bis-spiroacetal. Our attention therefore turned to the synthesis of antibiotic CP44,161 **5** which has a substituted tetrahydrofuran as the E ring and thereby avoiding the undesirable ring expansion step [19].

Antibiotic CP44,161 has not been synthesised to date and has the same bis-spiroacetal stereochemistry as salinomycin **1**. Aside from the aromatic A ring and the five membered E ring in CP44,161 **5**, the main differences between the bis-spiroacetal moieties of these two molecules are the presence of an additional methyl group and an ethyl rather than a methyl group in the D ring of CP44,161 **5**. The retrosynthesis adopted for antibiotic CP44,161 (Scheme 13) also uses an aldol disconnection to afford an aromatic left hand portion and the right hand fragment **28** which is further disconnected to the bis-spiroacetal aldehyde **29** and (*E*)-alkene **30**. Finally, use of an oxidative cyclisation to construct bis-spiroacetal **29** affords the same lactone **12** as that used earlier and acetylene **31** which has the requisite ethyl and methyl groups at C2 and C4 respectively.

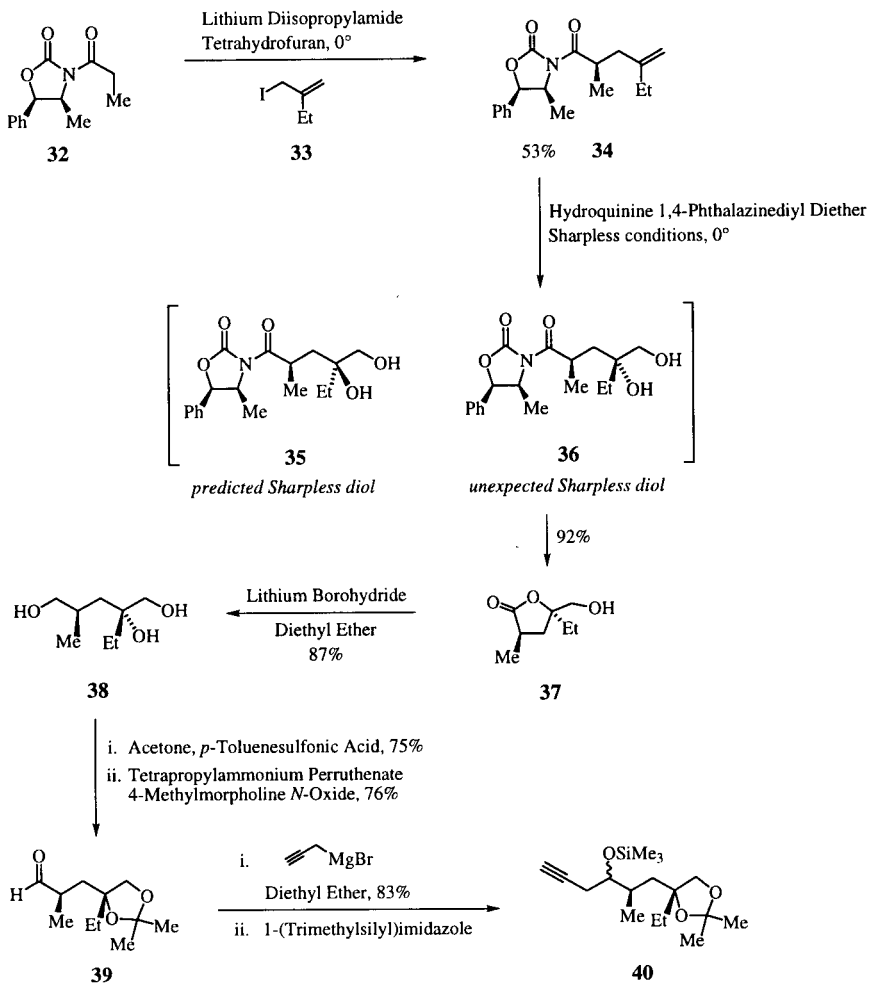
The proposed synthesis of acetylene **31** (Scheme 14) commenced with the alkylation of propanoyloxazolidinone **32** with allyl iodide **33** [20] to form alkene **34**. Based on the Sharpless mnemonic, asymmetric dihydroxylation [21] of the terminal olefin using potassium osmate and hydroquinine 1,4-phthalazinediyl diether, was expected to afford diol **35**, however, in the final stages of this work, X-ray diffraction studies subsequently revealed that lactone **37**, produced by cyclisation of the unexpected diol **36**, was in fact the major product. Lactone **37** contains the incorrect stereochemistry at C4 to that required for the formation of acetylene **31**. It is unclear why the facial selectivity of dihydroquinine ligands did not follow the Sharpless mnemonic, however, the presence of the chiral oxazolidinone moiety may have been a contributing factor.

Lactone **37** was converted to acetylene **40** which was then used to produce a tetracyclic fragment resembling the B,C,D and E rings of antibiotic CP44,161 **5** (Schemes 15 and 16). The synthesis of acetylene **40** was completed by reduction of lactone **37** with lithium borohydride to afford

Scheme 13



Scheme 14



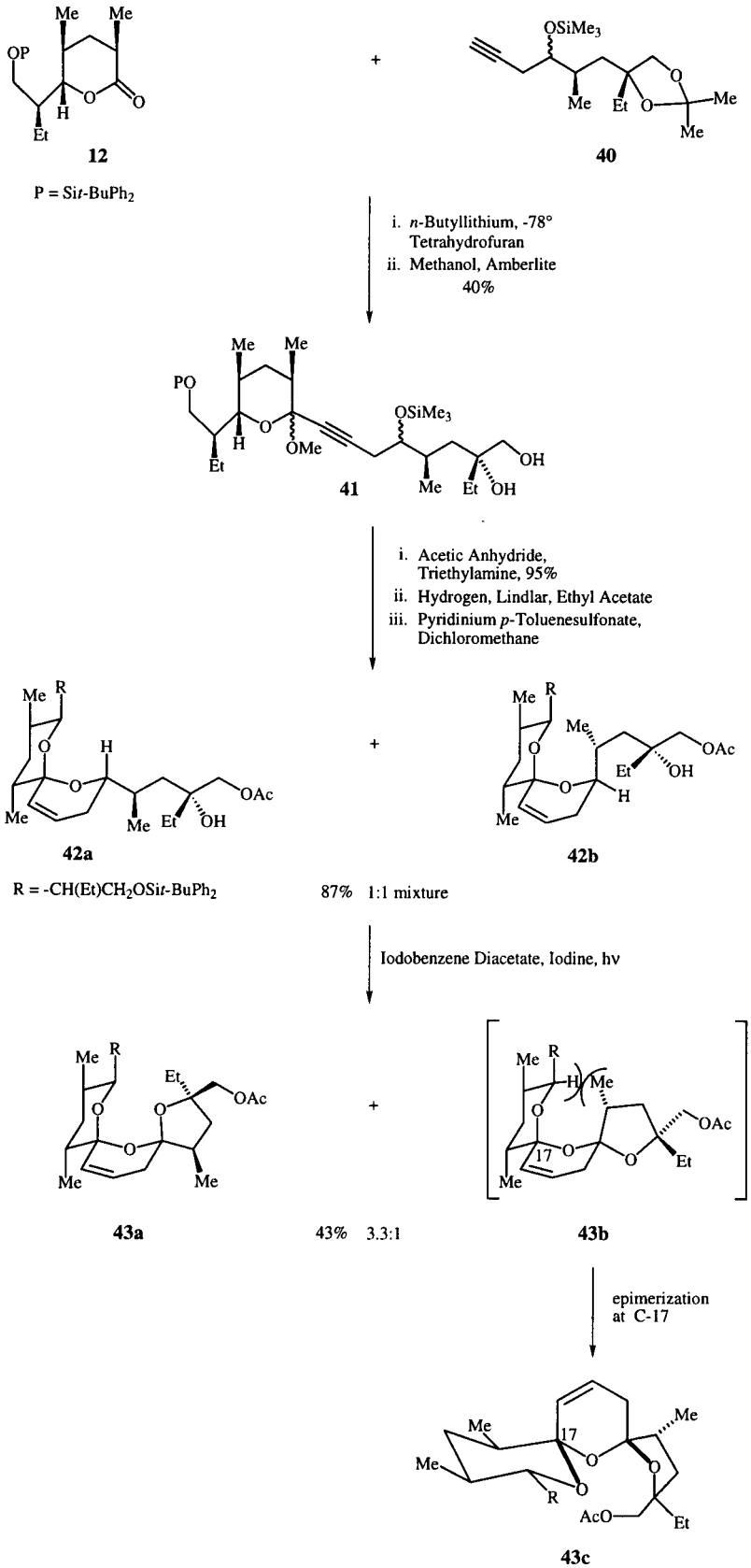
triol **38** which, after protection of the 1,2-diol as an acetonide, was oxidised at the remaining primary alcohol to afford aldehyde **39**. Grignard reaction of aldehyde **39** with propargylmagnesium bromide resulted in the formation of an alcohol which, after protection as a silyl ether afforded acetylene **40** as a 1:1 mixture of diastereomers.

With acetylene **40** and lactone **12** in hand, assembly of the bis-spiroacetal core was effected based on the earlier *epi*-17-deoxy-(*O*-8)-salinomycin **2** work (Scheme 8). Addition of the lithium acetylide derived from acetylene **40** to lactone **12** followed by treatment with acidic methanol afforded methyl acetals **41**. After protection of the primary hydroxyl group as an acetate, partial hydrogenation to a *cis*-olefin followed by acid catalysed cyclisation resulted in a 1:1 mixture of spiroacetals **42a** and **42b**.

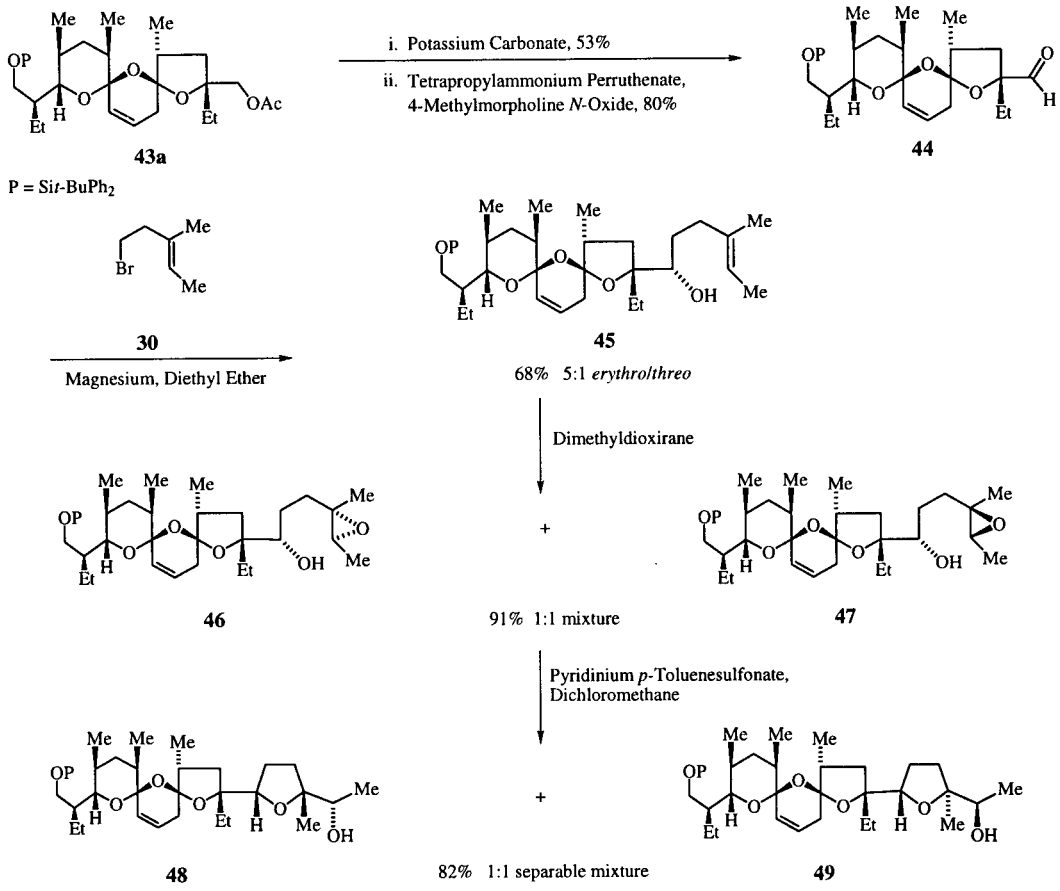
Spiroacetals **42a** and **42b** were treated with iodobenzene diacetate and iodine to afford a 3.3:1 mixture of tricyclic bis-spiroacetals **43a** and **43b**. The preference for *cis* bis-spiroacetal **43a** in this cyclisation reaction can be attributed to the presence of the additional methyl group in the D ring, which causes unfavourable steric interactions upon formation of the minor *trans* bis-spiroacetal **43b**. *trans* Bis-spiroacetal **43b** therefore undergoes rapid epimerisation at the allylic spiro centre to *cis* bis-spiroacetal **43c**. The presence of the additional methyl group exhibited a marked effect on the stereochemical outcome of the oxidative cyclisation in that the oxidative cyclisation of spiroacetal **11** which lacks this methyl group provided the *trans* isomer as the major product (Scheme 8).

The major bis-spiroacetal **43a** isolated from this oxidative cyclisation has the 17-*epi*-21-*epi*-salinomycin stereo-

Scheme 15


12
P = Si-t-BuPh2
40
i. n-Butyllithium, -78°
Tetrahydrofuran
ii. Methanol, Amberlite
40%
41
i. Acetic Anhydride,
Triethylamine, 95%
ii. Hydrogen, Lindlar, Ethyl Acetate
iii. Pyridinium p-Toluenesulfonate,
Dichloromethane
42a
R = -CH(Et)CH2OSi-t-BuPh2
87% 1:1 mixture
42b
Iodobenzene Diacetate, Iodine, hv
43a
43% 3.3:1
43b
epimerization
at C-17
43c

Scheme 16



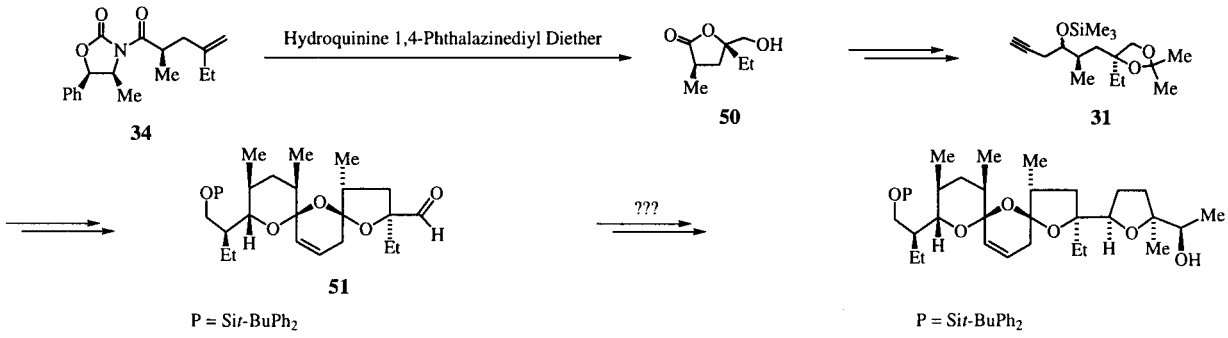
chemistry (Figure 1) whereas the minor *cis* isomer **43c** has the correct bis-spiroacetal stereochemistry for salinomycin **1** and CP44,161 **5**. In view of the fact that in the previous total syntheses of salinomycin **1** the correct stereochemistry for the bis-spiroacetal ring system was obtained *via* a thermodynamically controlled cyclisation after the whole carbon skeleton of the natural product was assembled, it was decided to pursue appendage of the E ring to the major isomer of the BCD fragment **43a**. This approach was justified in that it is well established that long range hydrogen bonding in the final molecule can dramatically alter the position of the bis-spiroacetal equilibrium.

With the bis-spiroacetal ring assembled, hydrolysis of the major *cis* bis-spiroacetal acetate **43a** followed by oxidation using tetrapropylammonium perruthenate afforded aldehyde **44**. Applying methodology established in synthetic approaches to the D and E rings of *epi*-17-deoxy-(*O*-8)-salinomycin **2**, the union of bromide **30** and aldehyde **44** using a Barbier reaction resulted in the successful synthesis of alcohol **45**. Treatment of alcohol **45** with dimethyl dioxirane resulted in a 1:1 mixture of epoxides **46** and **47** which, after treatment with a catalytic quantity of pyridinium *p*-toluenesulfonate underwent cyclisation to afford polyethers **48** and **49** which were separated by hplc.

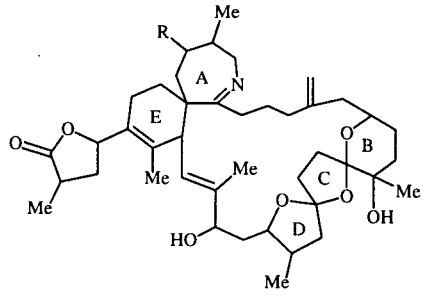
In conclusion, polyethers **48** and **49** were synthesised from aldehyde **44** and bromide **30**. Noteworthy features of the synthetic strategy adopted include the oxidative cyclisation of a bicyclic hydroxyspiroacetal to a bis-spiroacetal which provides *cis* bis-spiroacetal aldehyde **44** preferentially; the addition of a Grignard reagent derived from bis-homoallylic bromide **30** to a neopentyl-like aldehyde **44**; and acid catalysed of a γ-hydroxyepoxide to a disubstituted tetrahydrofuran in the presence of a sensitive bis-spiroacetal.

The synthetic work outlined herein provides a framework on which to synthesise the B,C, D and E rings of antibiotic CP44,161 **5** after synthesising acetylene **31** from lactone **50** (*via* the correct diol **35**) which then provides access to aldehyde **51** (Scheme 17).

Scheme 17

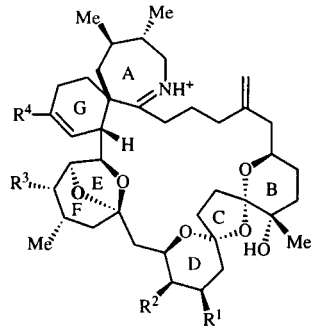


During chemical investigations of polar bioactive molecules from microalgae and shellfish, Wright *et al.* [22] isolated two lipid-soluble macrocycles, spirolides B **52** and D **53**, from the digestive glands of both mussels (*Mytilus edulis*) and scallops (*Placopecten magellanicus*). These macrocycles contain a novel spiro-linked tricyclic ether ring system and an unusual seven-membered spiro-linked cyclic iminium moiety. The spirolides cause potent and characteristic symptoms in the mouse bioassay and their toxicological properties are under investigation. They were also found to be weak activators of type L calcium channels.



spirolide A **52**: R = H
spirolide D **53**: R = Me

In the same year Uemura *et al.* [23] isolated pinnatoxins A **54** and D **55** from the shellfish *Pinna muricato* and proposed a biosynthetic pathway for construction of the G ring. The pinnatoxins are also calcium channel activators and are the principle toxins responsible for outbreaks of *Pinna* shellfish intoxication in China and Japan. The spirolides contain a [6,5,5] bis-spiroacetal system whereas the pinnatoxins contain a [6,5,6] system. The cyclic imine is common to both the spirolides and the pinnatoxins.



pinnatoxin A **54**: $R^1 = R^2 = H$; $R^3 = OH$, $R^4 = COO^-$

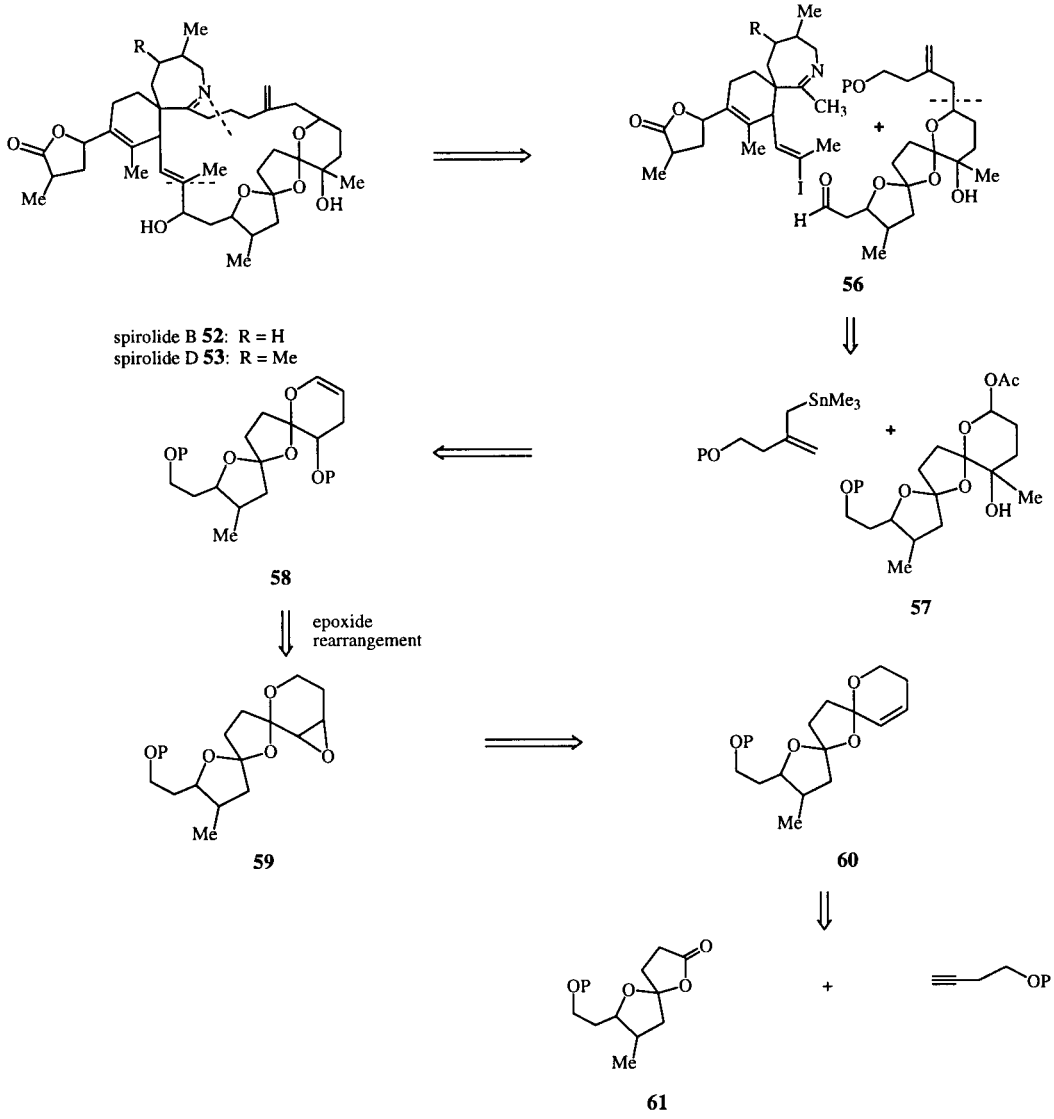
pinnatoxin D **55**: $R^1 = Me$; $R^2 = OH$; $R^3 = H$; $R^4 = CO(CH_2)_2COO^-$

To date there is no synthesis of the spirolides, however Kishi *et al.* [24] have recently reported a total synthesis of pinnatoxin A **54** in which the bis-spiroacetal moiety was assembled by thermodynamically controlled cyclisation of a dihydroxyketone precursor in which the tertiary alcohol in the B ring was constructed using a Sharpless asymmetric dihydroxylation. A similar strategy was used by Hirama *et al.* [25] for the synthesis of the bis-spiroacetal moiety of pinnatoxin A **54** whereas Murai *et al.* [26] introduced the tertiary alcohol by stereoselective methylation of a ketone after assembly of the bis-spiroacetal system.

Kishi's total synthesis of pinnatoxin A **54** has confirmed that the absolute stereochemistry of pinnatoxin A **54** is in fact the antipode of the structure drawn, whereas the relative and absolute stereochemistry of the spirolides has yet to be determined. It is therefore important that any synthetic strategy directed towards the spirolides is flexible in its approach so that the synthesis of synthetic fragments will aid the stereochemical assignment of the natural products. We have therefore embarked on a synthesis of the novel bis-spiroacetal moiety of the spirolides using an approach in which the relative and absolute stereochemistry of the substituents on the B and D rings can be varied.

Key disconnections in our retrosynthesis for the spirolides **52** and **53** (Scheme 18) involve construction of the C27-C26 bond *via* alkylation of a cyclic imine anion and use of a Ni(II)/Cr(II)-mediated coupling of a vinyl iodide with an aldehyde. This latter disconnection was successfully used by Kishi *et al.* [24] in their related synthesis of the pinnatoxins.

Scheme 18



Assembly of bis-spiroacetal **56** which bears a substituted allyl side chain at C22, then makes use of the Lewis acid mediated addition of an allylstannane to a bis-spiroacetal **57** which bears an acetate group at the anomeric position. Bis-spiroacetal acetate **57** can be prepared by hydration of unsaturated bis-spiroacetal **58** which is then available *via* base induced rearrangement of bis-spiroacetal epoxide **59**. Epoxide **59** is derived from unsaturated spiroacetal **60** which can be assembled *via* addition of an acetylide of a protected 3-butyn-1-ol to spirolactone **61** which itself comprises the DC fragment of the spirolides. A synthesis of this latter fragment requires flexibility in the introduction of the substituents such that a number of stereoisomers can be prepared for comparison with the natural product.

The key issue as to whether or not the base induced rearrangement of the epoxide and/or the Lewis acid mediated allylation reactions were compatible with a spiroacetal functionality, needed addressing before embarking on the synthesis of the bis-spiroacetal portions of the spirolides. Towards this end model studies using simpler bicyclic spiroacetals were undertaken to test the feasibility of these two key steps.

Optimism for the proposed base induced rearrangement of epoxide **59** to unsaturated spiroacetal **58** was encouraged by the successful base induced rearrangement of epoxide **63** to allylic alcohol **64** and homoallylic alcohol **65** (Scheme 19) [27]. The nature of the solvent dictated the ratio of these two alcohols with use of a polar solvent favouring formation of the desired homoallylic alcohol **65**. The desired α-epoxide **63** was prepared *via* stereoselective epoxidation of unsaturated spiroacetal **62** using dimethyl dioxirane.

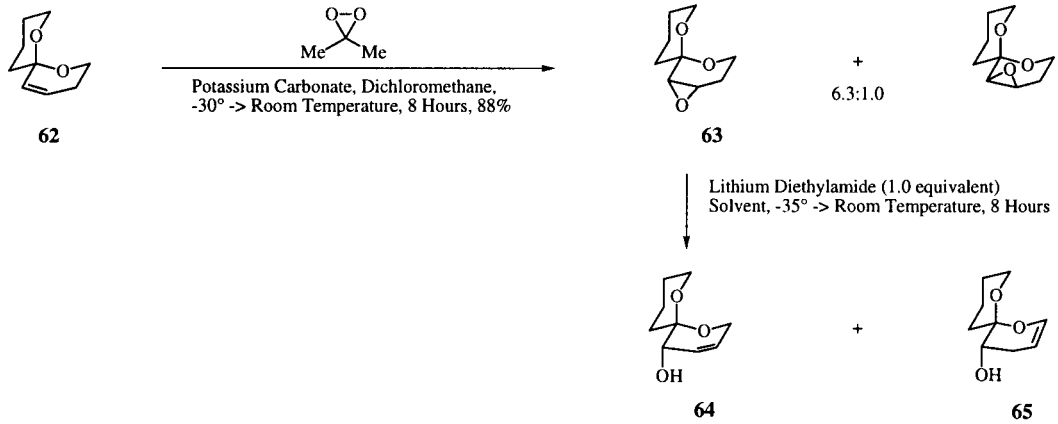
In order to probe the sterochemical course of the second proposed allylation reaction our attention focused on the allylation of spiroacetal **66** which contained an axial benzyloxy substituent at C5 (Scheme 20). Upon treatment with a Lewis acid spiroacetal **66** may undergo thermodynamically controlled ring opening/ring closure to afford a more stable spiroacetal in which the benzyloxy group adopts a more favourable equatorial position. Monitoring the stereochemistry at C5 would therefore provide evidence as to whether addition of the allylstannane to the C2 centered oxocarbenium ion preceded or followed opening of the spiroacetal ring.

Hydration of alkene **65** followed by acetylation afforded 2-acetoxy spiroacetal **66**. The optimum conditions for reaction of spiroacetal **66** with allyltributylstannane involved the use of trimethylsilyl trifluoromethanesulfonate as the Lewis acid in dichloromethane at -78° using 3 equivalents of the allylstannane. Under these conditions the equatorial C2 allylated spiroketal **67** was isolated in 72% yield.

Whilst the ^{1}H nmr data readily assigned the benzyloxy and allyl groups to equatorial positions, the conformation that the spiroacetal ring adopted needed addressing. In order to address this issue spiroacetal **67** underwent hydroboration with diborane providing alcohol **68** which was then converted to its *p*-nitrobenzoate derivative. X-ray analysis then confirmed that not only did the substituents at C5 and C2 adopt equatorial positions, but also the conformation of the spiro centre had changed and did not represent the most stable arrangement of O1 and O7 as predicted by the anomeric effect.

The isolation of allylated spiroacetal **67** as the only product from the addition of allylstannane to spiroacetal

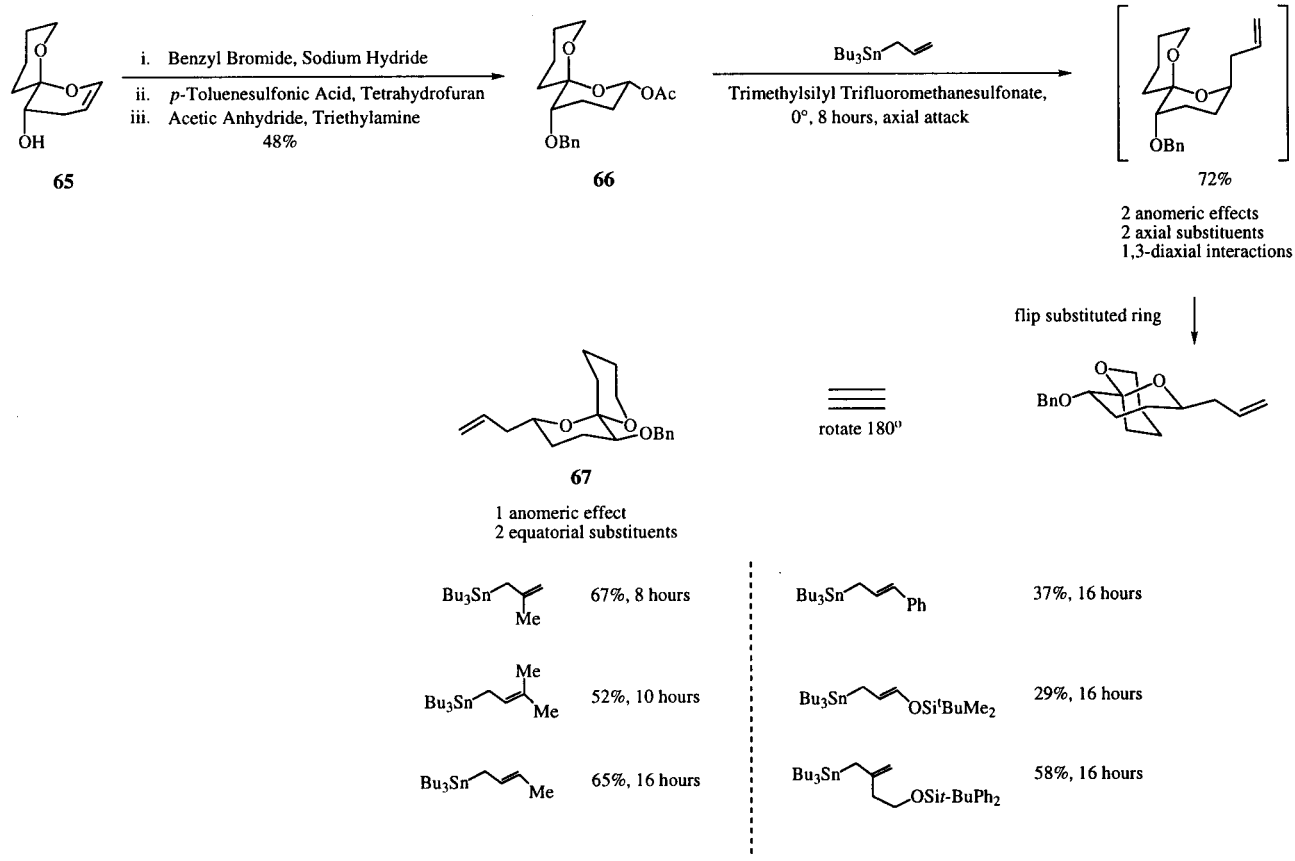
Scheme 19



62 **63** **64** **65**

Tetrahydrofuran	1.0	1.1	(76%)
1:2 Hexane/Diethyl Ether	1.9	1.0	(72%)
Hexane	21.0	1.0	(89%)

Scheme 20

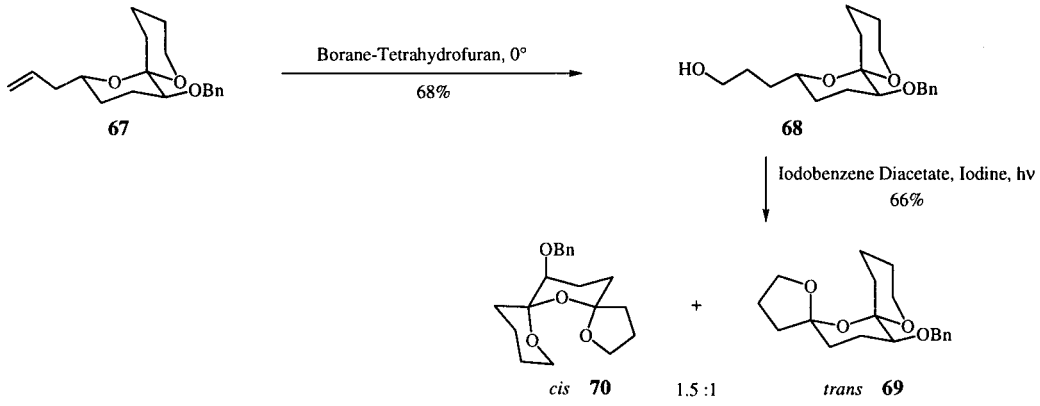


66 can be rationalised by axial approach of the stannane onto the oxycarbenium ion, followed by ring flipping of the disubstituted A ring in order to relieve unfavourable 1,3-diaxial interactions between the allyl group and 8-CH_2. This ring flip proceeds at the expense of a stabilising anomeric effect at the spiro centre.

Reaction of spiroacetal **66** with more functionalised allylstannanes also afforded spiroacetal products in which both the C2 allyl group and the C5 benzyloxy group occupied equatorial positions. It was also of interest that products resulting from addition of the allylstannane to the spirocentre were not observed.

The synthetic utility of the C2 allylated spiroacetal **67** was demonstrated by its conversion to the tricyclic bis-spiroacetals **69** and **70** (Scheme 21). Thus, treatment of alcohol **68** with iodobenzene diacetate and iodine effected oxidative cyclisation to a 1:1.5 mixture of bis-spiroacetals **69** and **70**.

Scheme 21



Having established that the two key reactions required for assembly of the allyl substituted bis-spiroacetal fragment **56** of the spirolides were feasible, (albeit using bicyclic spiroacetal model systems) our focus is now on the synthesis of the natural product itself. This work is only in its early stages and a synthesis of a D ring fragment, namely lactone **71**, has been completed (Scheme 22) which allows variation in the relative and absolute stereochemistry of the substituents. The substituents on lactone **71** were assembled *via* addition of Brown's chiral crotyl borane [29] to a protected aldehyde. This strategy allows for the synthesis of stereoisomers by the appropriate choice of chiral crotyl borane used. Work is currently underway to convert lactone **71** to a bis-spiroacetal fragment of the spirolides based on the synthetic strategy outlined in the retrosynthesis (Scheme 18) armed with the knowledge that the appropriate model work (Schemes 19 and 20) gave cause for optimism.

Acknowledgements.

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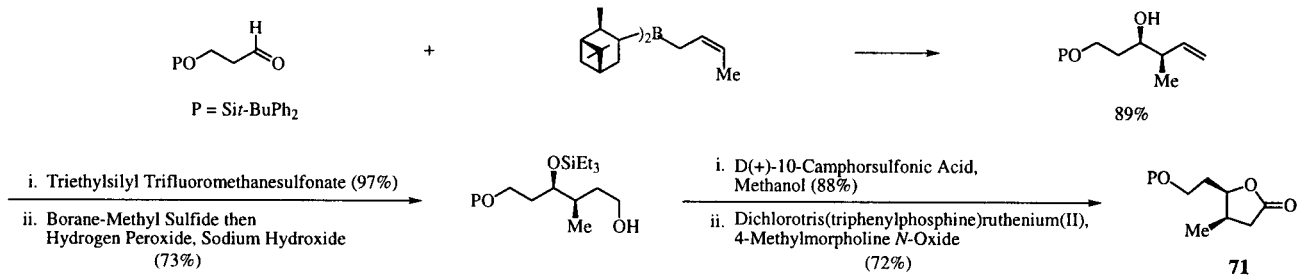
Scheme 22



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