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SYNTHETIC ROUTES TO TETRAHYDROFURAN, TETRAHYDROPYRAN, AND SPIROKETAL UNITS OF POLYETHER ANTIBIOTICS AND A SURVEY OF SPIROKETALS OF OTHER NATURAL PRODUCTS

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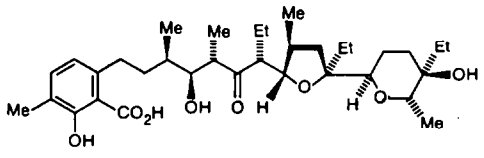
CONTENTS

Abstract—Tetrahydrofuran, tetrahydropyran, and spiroketal units are the main structural features of polyether antibiotics. This review deals with the stereocontrolled methods by which these fragments have been prepared for polyether synthesis and includes a survey of routes to spiroketals of other natural products.

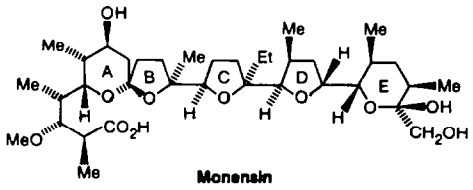
1. INTRODUCTION

The monocarboxylic acid ionophores, such as those shown in Figs 1–7, are a large group of natural products commonly known as polyether antibiotics. They have attracted considerable attention[1] because of their ability to transport metal ions across lipid bilayers,[1,2] a property that is implicated in the biological action of the compounds.[3] They are antimicrobial agents,[4] they cause growth promotion in ruminants,[4] and some are known to produce cardiovascular responses.[5] Several of the polyether antibiotics are commercially important[1] and their value, as well as their elaborate structure, have stimulated the interest of organic chemists. The extreme complexity of the polyethers,



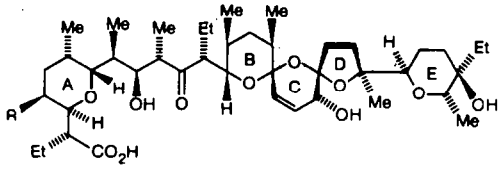
Lasalocid A

Fig. 1.



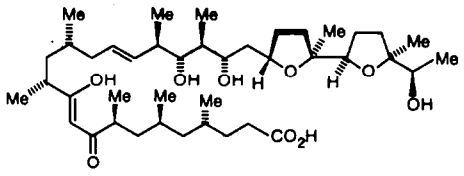
Monensin

Fig. 2.



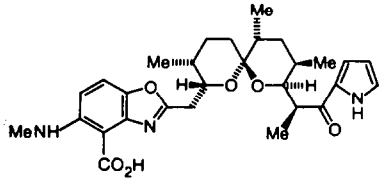
R=H, Salinomycin, R=Me, Narasin

Fig. 3.



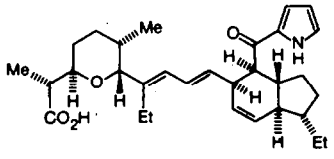
Ionomycin

Fig. 4.



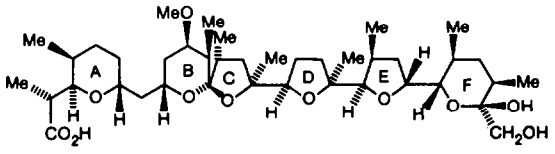
Calcimycin

Fig. 5.



Antibiotic X-14547A

Fig. 6.



Nigericin

Fig. 7.

however, presents a very formidable challenge for synthesis and only a few total syntheses have been reported.[6-12] These clearly represent significant advances in the development of organic chemistry.

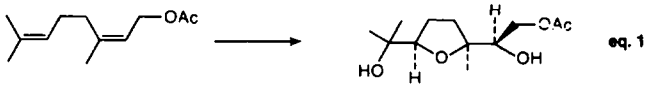
Construction of a polyether antibiotic is, to a large extent, an excercise in the preparation of substituted oxygen heterocycles. As shown in Figs 1–7, the framework of the molecules is dominated by the presence of 2,5-disubstituted tetrahydrofurans, substituted tetrahydropyrans, and spiroketal systems. Hence, considerable attention has been focussed on development of efficient and stereocontrolled routes to these key structural fragments.

The following review deals with the extensive modern synthetic work in this area and the literature covered is based on a CASONLINE search dated 1 May 1986. In order to present a thorough survey from the point of view of *polyether antibiotic* synthesis, some earlier methodology that has formed part of other reviews[13] is also included in the detailed treatment given here. The present work is divided into three sections: the first covers stereo-controlled approaches to *cis*- and *trans*-2,5-disubstituted tetrahydrofurans, the second deals with tetrahydropyrans, and the last section covers approaches to spiroketal systems and includes a survey of routes to spiroketals of other natural products.

2. PREPARATION OF 2,5-DISUBSTITUTED TETRAHYDROFURANS

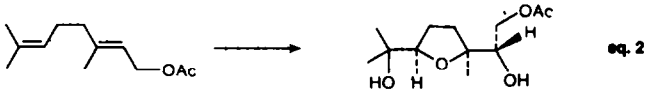
2.1. *Oxidative cyclization of* 1,5-*dienes and* 5,6-*dihydroxyolefins*

In 1965, Klein and Rojahn reported[14] that 1,5-dienes are converted into tetrahydrofurans when treated with potassium permanganate under mildly alkaline conditions. The course of this oxidative cyclization was established as being that which leads specifically to *cis*-2,5-disubstituted heterocycles. Thus, neryl acetate and geranyl acetate reacted as shown [equations (1) and (2)]. Many years later, when interest in polyether antibiotics had developed, the synthetic possibilities of this pioneering work was reexamined[15] and extended: the reaction is general, and *cis*-2,5-bis(hydroxymethyl)-tetrahydrofurans (such as **1** and **2**) can be generated from appropriate dienes with complete stereospecificity. Moreover, *four* new chiral centres are produced in a single reaction.



eq. 1

neryl acetate **1**



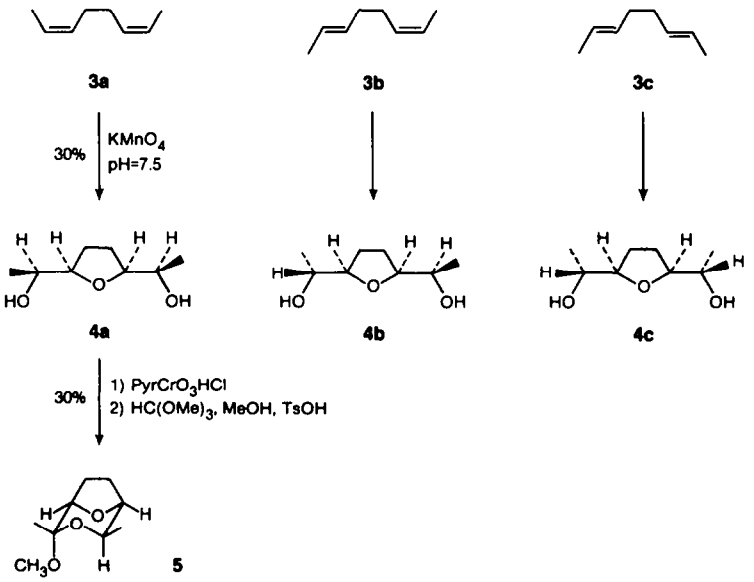
eq. 2

geranyl acetate **2**

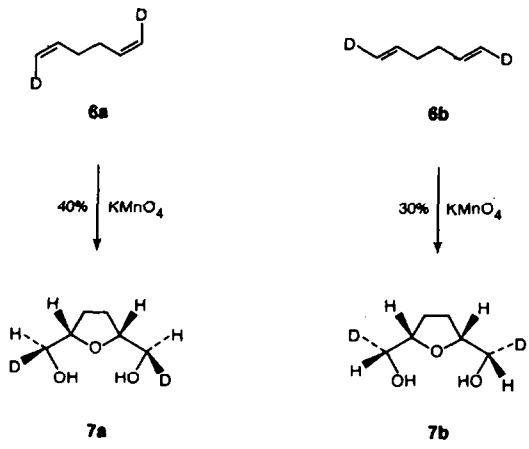
In the course of their study of oxidative cyclization, Walba's group[15a] examined the three isomeric 1,5-dienes **3a–c**, each of which underwent cyclization in the manner shown (Scheme 1) with a very high level (97%) of stereospecificity. The structure of product **4a**, was established rigorously by a single crystal X-ray analysis of the derivative, **5**.

Baldwin's group[15b] probed the stereochemical course of oxidative cyclization by employing deuterated dienes, as summarized in Scheme 2, using NMR techniques to assign relative configurations at each of the stereocentres. Again, the evidence pointed to complete stereospecificity in the cyclization, **7a** being formed from **6a**, and **7b** from **6b**.

Both groups have proposed mechanisms to explain the high level of stereospecificity in this reaction. Walba *et al.*,[15a] basing their pathway on proposals made by Sharpless[16a] concerning the



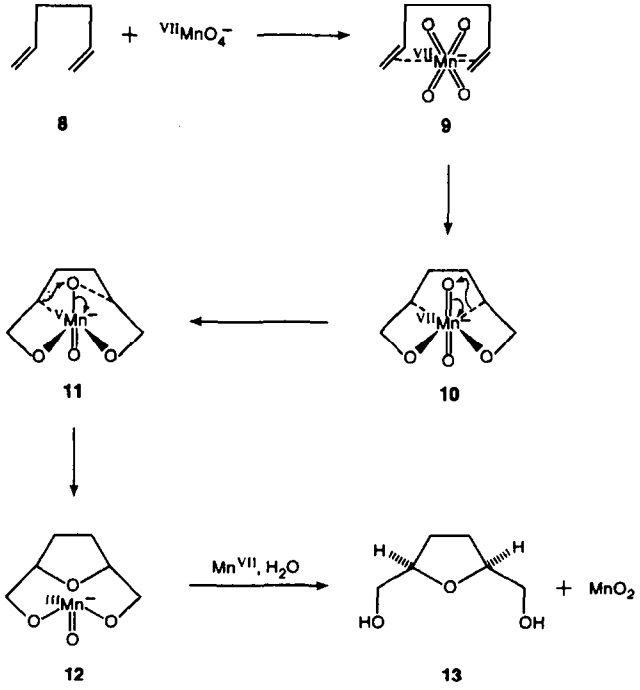
Scheme 1.



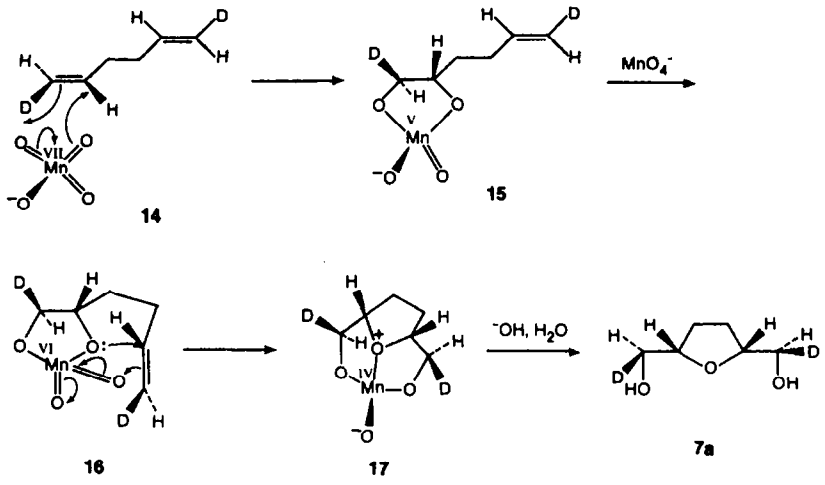
Scheme 2.

mechanism of oxidation of olefins by oxo transition metal species, suggest initial formation of a bis-π-complex **9** between the diene and MnO_4^- (**8** → **9**, Scheme 3). This is followed by two cycloadditions in a [2+2] manner which yield an octahedral Mn(VII) intermediate **10**. Alkyl migration with retention then occurs to give **11** and finally reductive elimination, also with retention, yields the Mn(III) diester **12**. Oxidation of the diester followed by hydrolysis produces the observed diol **13** and MnO_2.

The mechanism suggested by Baldwin *et al.*[15b] (Scheme 4) involves initial [3+2] cycloaddition of MnO_4^- to one of the diene double bonds and the resulting Mn(V) ester **15**, is considered to be rapidly oxidized by another molecule of permanganate to a Mn(VI) diester **16**. This undergoes intramolecular cycloaddition to the remaining double bond to yield intermediate **17** which, on hydrolysis, produces the observed *cis* product **7a**. Support for the pathway of Scheme 4 lies in the fact that there is evidence for the intermediacy of a cyclic Mn(V) ester in reactions of alkenes with permanganate. Additional support is apparent in more recent studies by Wolfe[17] involving ^{18}O-labelling experiments.



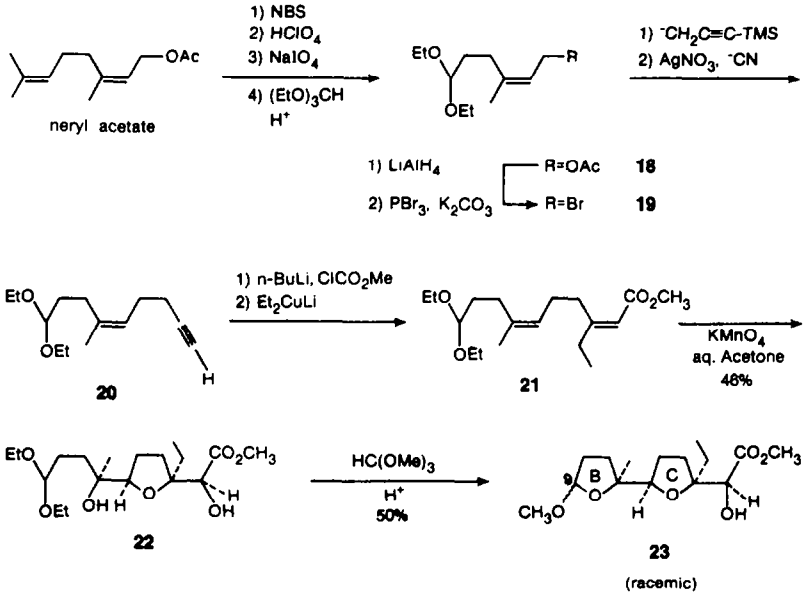
Scheme 3.



Scheme 4.

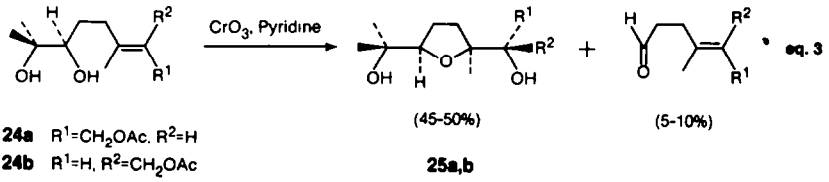
Oxidative cyclization of 1,5-dienes has been used in a synthesis of the (racemic) B–C ring system of monensin (see Fig. 2).[18] As illustrated in Scheme 5, the required (*Z*,*Z*)-1,5-diene **21** was prepared by selective double bond cleavage[19,20] of neryl acetate followed by acetal formation to afford **18**. The acetate group was removed by reduction ($LiAlH_4$) and the resultant alcohol was treated with phosphorus tribromide to yield the labile bromo-compound **19**. Coupling with (trimethylsilyl) propargyllithium,[21] followed by deprotection, gave the acetylene **20**. The (*Z*,*Z*)-1,5-diene **21** was then obtained by methoxycarbonylation followed by conjugate ethylation with lithium diethylcuprate. Oxidative cyclization of the diene **21** with potassium permanganate in aqueous acetone buffered with carbon dioxide produced the highly functionalized compound **22**, as the only isolable (46%) tetrahydrofuran. Exposure of this substance to the action of methyl orthoformate in the presence of an acid catalyst then generated the monensin B–C fragment **23** as a mixture of two substances epimeric at C-9 (monensin numbering).

Walba and Stoudt[22] have extended the scope of oxidative cyclization to include substrates other than 1,5-dienes. Elaborating on much earlier work,[20] they found that 5,6-dihydroxy alkenes could be transformed [equation (3)] directly into *cis*-2,5-disubstituted tetrahydrofurans by treatment with



Scheme 5.

a Cr(VI) oxo species. Thus, when the diols **24a** and **24b**[23] were treated with Collins' reagent,[24] the corresponding heterocycles **25a, b** were produced in a process that was judged to be at least 99.5% stereospecific. Pyridinium chlorochromate[25] oxidation of **24b** gave similar results but bipyridinium chlorochromate[26] was unsuitable.



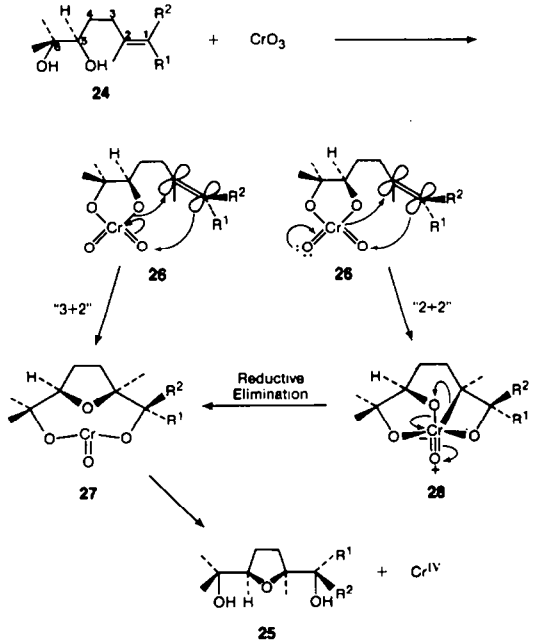
24a R^1=CH_2OAc, R^2=H
24b R^1=H, R^2=CH_2OAc
25a,b

*All compounds are racemic; for clarity, only one enantiomer is shown.

Two pathways were suggested for the reaction of equation (3) and both are related to mechanisms proposed for the cyclization of dienes by permanganate. It was established[22] that the presence of a hydroxyl group at both C-5 and C-6 (numbering with respect to the double bond of compound **24**, Scheme 6) is essential and on this basis a likely first step is formation of a Cr(VI) diester **26**.[17] Concerted [3+2] cycloaddition is envisioned to yield a Cr(IV) species **27** containing two new asymmetric centres. Hydrolysis of **27** should lead directly to the observed organic product. The second possible route involves insertion of the C–C double bond into the chromium oxo bond of diester **26**. The resulting oxametallocyclobutane **28** could give the chromium(IV) diester **27** by reductive elimination with retention (see **28** arrows).[16] At present, both mechanistic schemes are tentative.

2.2. *Halocyclization*

A conceptually different approach to *cis*-2,5-disubstituted tetrahydrofurans has been developed extensively by Bartlett and coworkers.[27] Their method involves use of γ,δ-unsaturated alcohols and the corresponding O-alkylated derivatives which undergo electrophilic cyclization with iodine in acetonitrile at 0°C [equation (4)]. It is found that formation of *trans*-2,5-disubstituted tetrahydrofurans predominates when free alcohols are used, but that *cis* isomers are the major products from the corresponding ethers (Table 1). The steric bulk of the O-alkyl protecting group (R^1 in **29**)



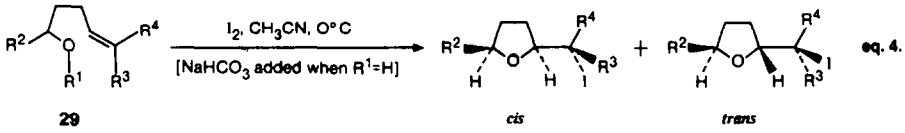
Scheme 6.

Table 1

Example	R^1	R^2	R^3	R^4	Ratio *cis/trans*	Yield (%)
1	H	Me	H	H	1:2	66
2	Me	Me	H	H	1:2	15
3	CH_2Ph	Me	H	H	2:1	60
4	$SiMe_2{}^tBu$	Me	H	H	3:1	43
5	Si^tBuPh_2	Me	H	H	8:1	30
6	BB[a]	Me	H	H	3.7:1	74
7	DCB[b]	Me	H	H	21:1	63
8	H	Me_2CH	H	H	1:4	88
9	DCB	Me_2CH	H	H	20:1	95
10	H	Me	Me	H	1:2	99
11	DCB	Me	Me	H	25:1	75
12	H	Me	H	Me	2:5	81
13	DCB	Me	H	Me	12:1	47
14	CH_2Ph	Me	CO_2Me	H	6:1	55
15	DCB	Me	CO_2Me	H	50:1	60
16	BB	Me	CO_2Me	Me	10:1	44

[a] BB = 4-bromobenzyl.
[b] DCB = 2,6-dichlorobenzyl.

and its electrofugal properties appear to be the main factors which determine the outcome of cyclization. It was observed that 2,6-dichlorobenzyl ethers provide the highest yields of *cis* products; evidently the 2,6-dichlorobenzyl unit has the most appropriate steric and electronic properties.



eq. 4.

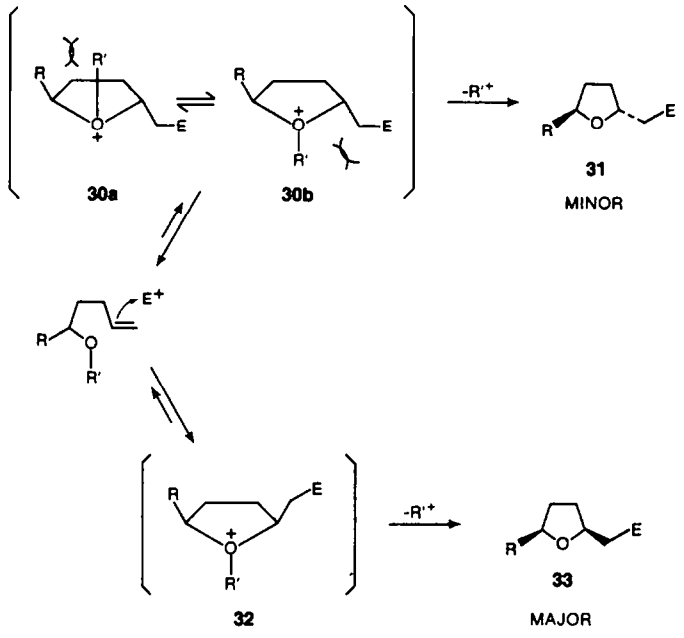
The stereochemical course of iodocyclization can be interpreted in terms of Scheme 7. The transition states **30a** and **30b** leading to *trans*-disubstituted products would be destabilized in the case where R^1 is a bulky group whereas in the isomeric transition state **32** (leading to *cis* products), severe non-bonded interactions are absent. The electrofugal properties of the R^1 group play a critical role in the following way: if loss of R^1 from the oxonium intermediate is too rapid there is insufficient opportunity for equilibration between the oxonium ions **30a, b** and **32**. Hence the extent of thermodynamic control (i.e. preferential formation of **32**) is reduced. However, if loss of R^1 is too slow side reactions, such as cleavage of endocyclic C–O bonds, become significant.

Halocyclization has been also applied, in the present context, to unsaturated acids. It is known that iodolactonization of unsaturated acids with iodine in acetonitrile provides mainly the thermodynamically favoured lactone with high selectivity [equation (5)].[28] Such lactones are convertible into tetrahydrofurans [equation (6)]. Thus, treatment of **34** with $CH_3CHLiCO_2{}^tBu$ provides a route. by way of epoxide **35**, to the *Z* and *E* products **36a** and **36b** in a ratio of 5:1 and these substances have been further manipulated as shown in Scheme 8.[29]†

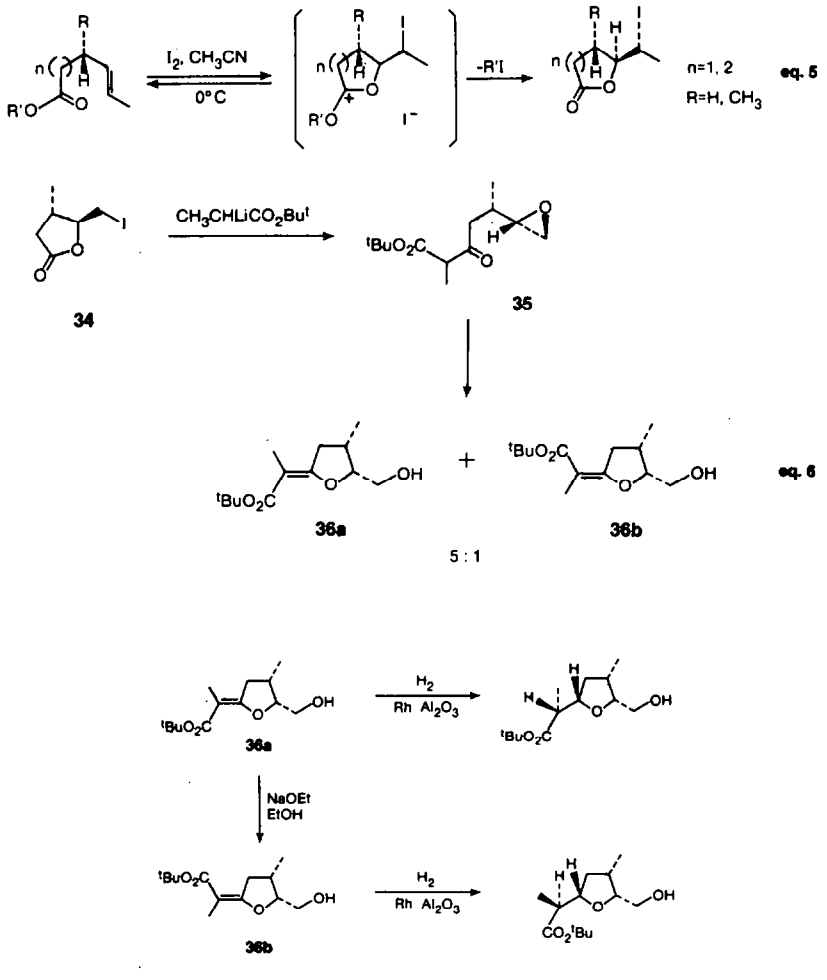
2.3. *Epoxidation–cyclization*

An epoxidation–cyclization approach has been used to generate fragment (Scheme 10) which corresponds to the right-hand portion of ionomycin (Fig. 4).[30] In principle, the method requires a bis-epoxide **38** (Scheme 9) in which acid-catalyzed opening of the right-hand epoxide (**38** → **39**), *followed* by intramolecular hydroxyl participation in opening of the left-hand epoxide, would generate the desired tetrahydrofuran **40**. In practice this overall result was achieved as follows (Scheme 10). Asymmetric epoxidation[31] of **41** gave predominantly the alcohol **42**, which was

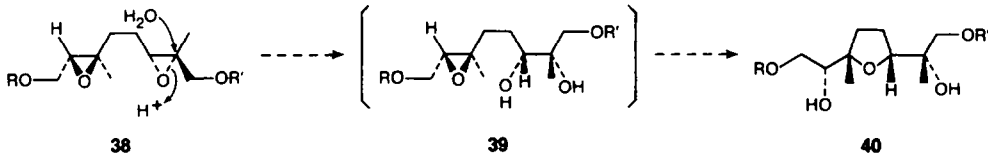
† In a manner analogous to Scheme 8, hydrogenation of α,β-unsaturated esters has been used to make the 2,5-disubstituted tetrahydrofuran units of Nonactin. For example, P. A. Bartlett, J. D. Meadows and E. Ottow, *J. Am. Chem. Soc.* **106**, 5304 (1984). *Cf.* also Ref. 13.



Scheme 7.

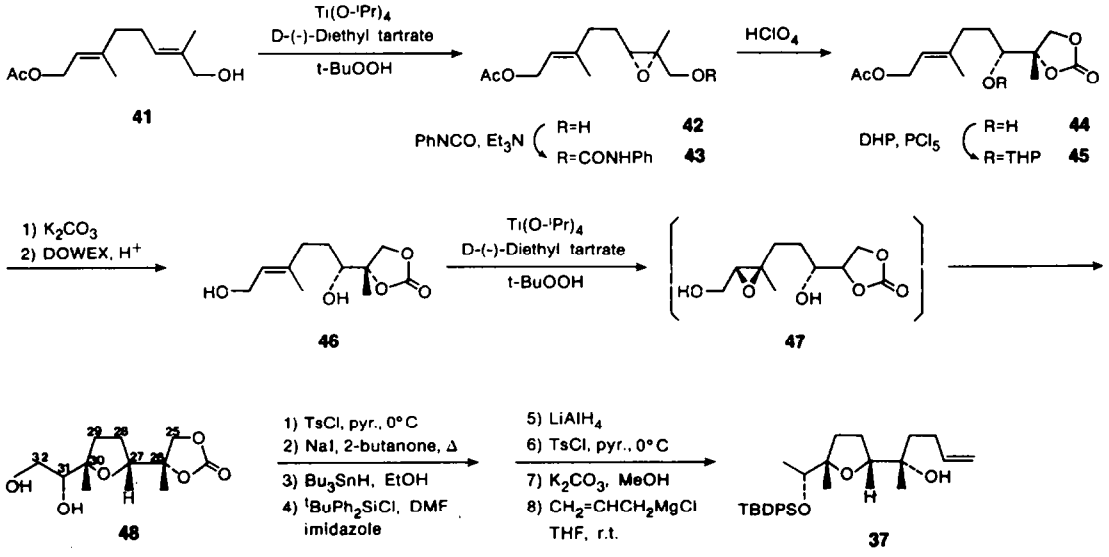


Scheme 8.



Scheme 9.

converted into its phenylurethane **43** and treated with perchloric acid to afford the cyclic carbonate **44**. Hydroxyl protection (**44** → **45**), base-catalyzed hydrolysis of the acetate, and deprotection set the stage for a second asymmetric epoxidation (**46** → **47**). The intermediate epoxide was not isolated since Lewis acid-catalyzed cyclization involving the free hydroxyl (**47**) occurred spontaneously and the desired tetrahydrofuran **48** was formed. Conventional methods were then used to convert **48** into the ionomycin fragment **37**.

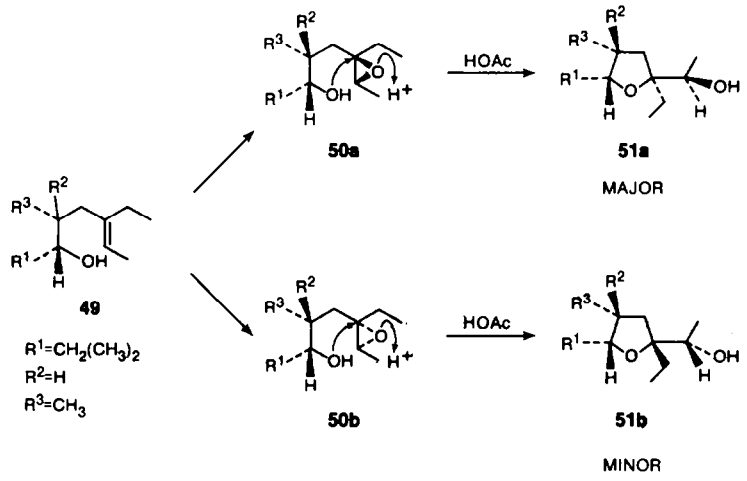


Scheme 10.

A different epoxidation–cyclization methodology was developed by Kishi *et al.*[32] They treated γ,δ-unsaturated alcohols[33] with *t*-BuOOH in the presence of $VO(acac)_2$[34] (Scheme 11). A ratio of more than 20:1 in favour of epoxide **50a** over isomer **50b** was reported using this reagent. The epoxides (without separation) were subsequently converted into *trans*-2,5-disubstituted tetrahydrofurans **51a** and **51b** by treatment with acetic acid at room temperature. The ratio of tetrahydrofurans (and hence of the parent epoxides) was determined by isolation or by VPC measurements.

The observed preference for formation of the β-epoxide **50a** over the α-epoxide **50b** is explained on the basis of two transition state conformations, **A** and **B** (Fig. 8). Destabilizing steric interactions between the ethyl side chain and the bulky R^3 substituent make conformation **B** less favourable than **A** since, in **A**, the bulky side chain is disposed away from R^3. Epoxidation in the manner illustrated, via conformation **A**, leads to the observed β-epoxide.

Kishi utilized these results in the first total synthesis of lasalocid A (Scheme 12).[7a] The optically pure alcohol **52**[35] was converted into the epoxide **53**. On treatment with acetic acid, the tetrahydrofuran **54** was obtained (75% yield from **52**) as an 8:1 mixture of stereoisomers with the major product, as expected,[32] being that shown. A second epoxidation again proceeded in the anticipated[32] fashion (**54** → **55**) but the epoxide stereochemistry of **55** was opposite to that required for lasalocid A synthesis. The desired epoxide **56** had to be generated by a sequence of four additional steps: (1) hydroxyl protection as the acetate, (2) acid-catalyzed opening of the epoxide to the corresponding diol, (3) tosylation of the secondary hydroxyl, and (4) base-induced intramolecular displacement of toluenesulfonate anion. The new epoxide **56** then afforded the bis-tetrahydrofuran unit **57** (45% yield from **55**). This compound represents the tetrahydrofuran ring (C-15 to C-18) and the precursor



Scheme 11.

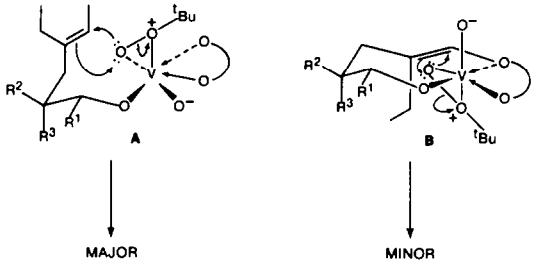
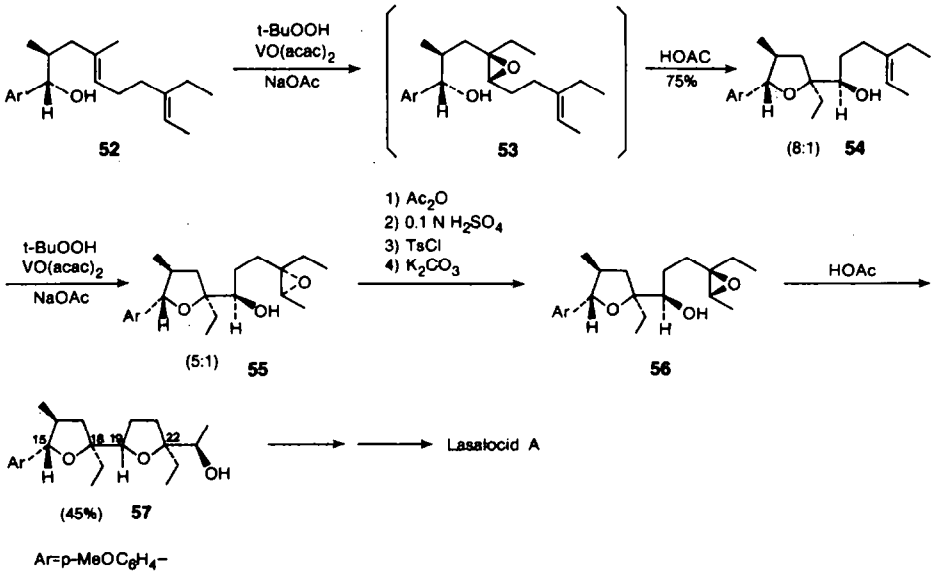


Fig. 8.

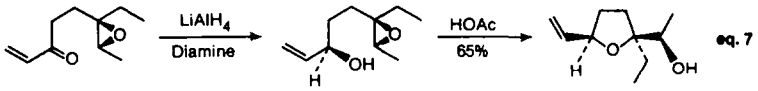
to the tetrahydropyran ring (C-19 to C-22) of lasalocid A with correct relative and absolute stereochemistry. Kishi subsequently transformed this fragment into the natural product.

The epoxide inversion sequence of the above example is obviously cumbersome and therefore, a modified procedure[36] was developed which yields the epoxide of correct stereochemistry for lasalocid A synthesis, directly [equation (7)]. The support studies[32] involved reduction of racemic

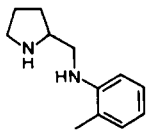


Scheme 12.

keto-epoxides such as **58** (only one isomer shown) with lithium aluminum hydride in the presence of (±)-2-(*o*-toluidinomethyl)pyrrolidine in which two hydroxy-epoxides were formed in a ratio of 10:1 with the required isomer predominating. Cyclization under acidic conditions then proceeded in the expected manner (**59** → **60**). This more concise method was subsequently applied to preparation of isolasalocid ketone,[36] a key intermediate in the synthesis of lasalocid A. The sequence involved optical resolution of compound **60**.



58 **59** (10:1) **60**

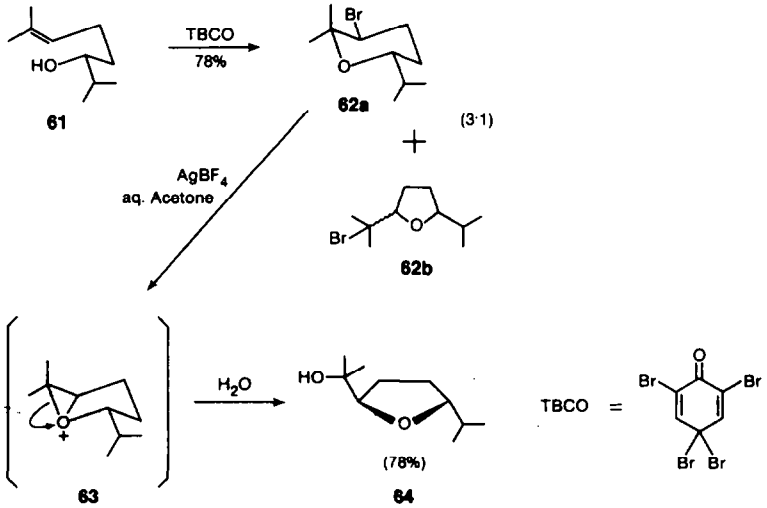


Diamine: dl-2-(o-toluidinomethyl) pyrrolidine

2.4. *Ring contraction of tetrahydropyrans*

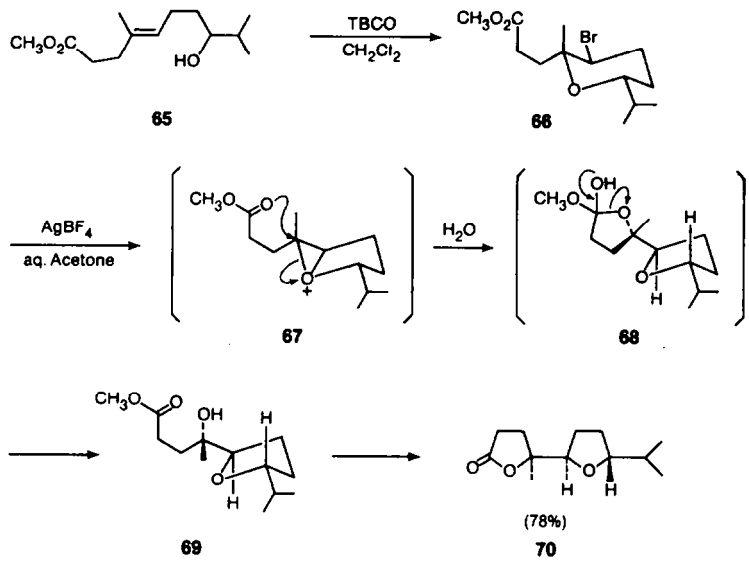
The production of *trans*-2,5-disubstituted tetrahydrofurans by ring contraction of appropriately substitued tetrahydropyrans has been investigated by Bartlett.[37] The approach is based on the fact that relative 1,3-asymmetric induction is more easily attained in a 6- rather than in a 5-membered ring. Advantage was taken of this and, in the event, a high degree of stereocontrol was realized as shown in Scheme 13. The γ,δ-unsaturated alcohol **61** was treated with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO) to generate the desired bromo tetrahydropyran **62a** as the major cyclic ether. Tetrahydropyran **62a** was separated from **62b** and, upon ring contraction induced by silver tetrafluoroborate in acetone, a good yield (78%) of *trans*-2,5-disubstituted tetrahydrofuran **64** was isolated. Presumably, ring contraction takes place via intermediate formation of a bridged oxonium ion **63**. Nucleophilic capture of the incipient carbocation by solvent yields the observed product.

Side chain stereocontrol in this type of process was also examined[37] (Scheme 14) and it was found that clean Walden inversion at the tertiary centre (see **67** → **68**, arrows) did occur, lactone **70** being isolated in 78% yield by the sequence **65** → **70**.



63 **64**

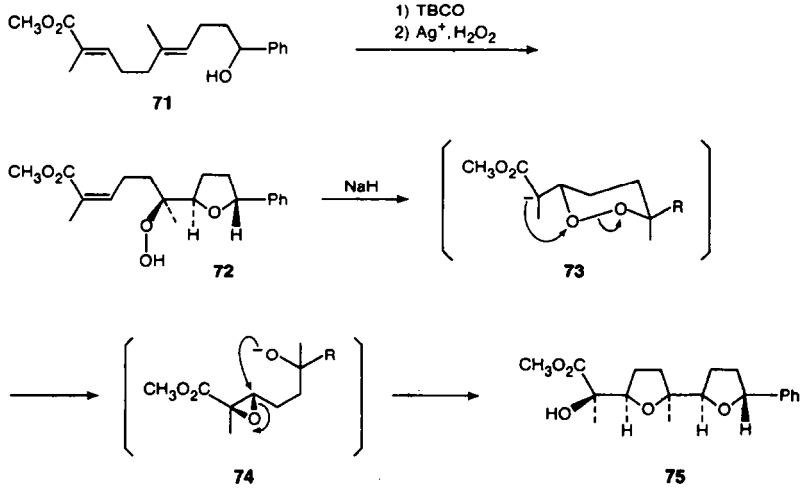
Scheme 13.



Scheme 14.

Modification of the above sequence provides an ingenious route to bis-tetrahydrofurans (Scheme 15).[38] Cyclization of γ,δ-unsaturated alcohol **71** with TBCO, followed by silver ion induced ring contraction *in the presence* of hydrogen peroxide led directly, as shown, to the stereocontrolled generation of five new asymmetric centres in the bis-tetrahydrofuran **75**.

It is possible to improve the ring contraction methodology by using thallium(III) ions as electrophiles instead of positive bromine[39] and a detailed study of alcohol **76**[40] was made [see Table 2 and equation (8)]. Treatment with either of two thallium(III) electrophiles under a variety of mild conditions served to convert **76** into the substituted tetrahydrofurans **79a–79e** in a single operational step. The lifetime of thallated intermediate **77** appears to be extremely short. Presumably, this is due to the well-precedented nucleofugality of thallium(III) and its accompanying counterions and also, of course, to the fact that in the tetrahydropyranyl intermediate the ring oxygen is suitably placed to aid in departure of the electrophile. As shown in equation (8) and Table 2, the substituent X on the tetrahydrofuran results from incorporation of a nucleophile (at the oxonium ion stage) derived from either the solvent or from the thallium salt. Side chain stereocontrol was investigated[39]



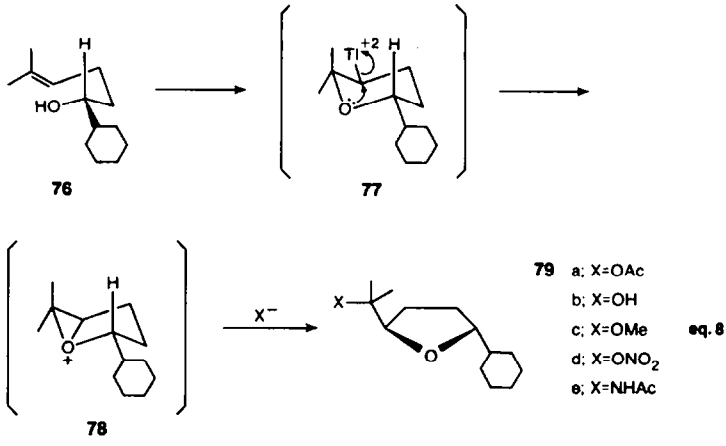
Scheme 15.

Table 2

Entry	Electrophile	Solvent	Conditions	Products (% yield)[a]
1	TTA	CH_3CO_2H	r.t., 1 h	**79a**(72)
2	TTA	acetone/H_2O (4:1), HBF_4	0°C, 25 min	**79b**(73)
3	TTA	CH_3OH	0°C, 30 min	**79a**(11); **79b**(5); **79c**(62)
4	TTN	CH_3OH	0°C, 30 min	**79c**(34); **79d**(29)
5	TTN	$CH_3OH/HC(OMe)_3$ (1:1)	0°C, 45 min	**79c**(33); **79d**(28)
6	TTN	THF	0°C, 30 min	**79b**(6); **79d**(56)
7	TTA	CH_3CN	reflux, 2 h	**79a**(28); **79b**(11); **79e**(40)

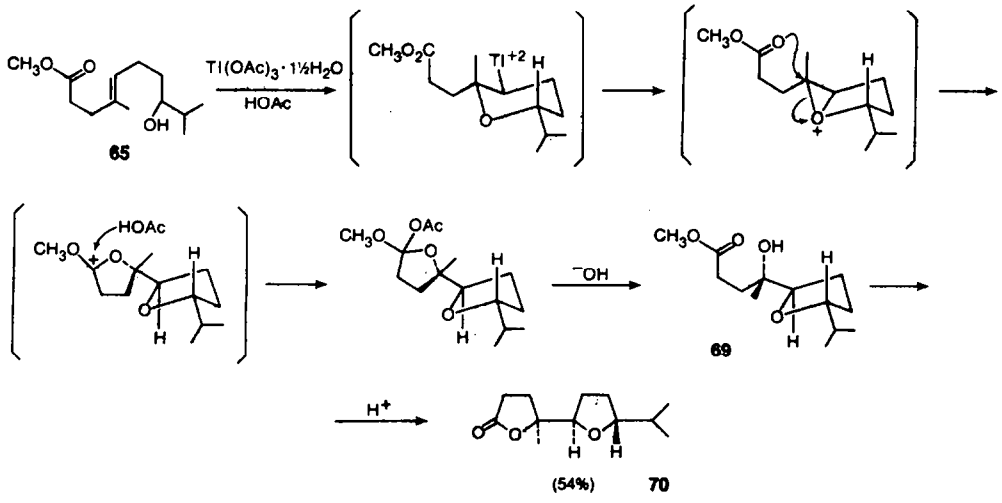
[a] Isolated yields of purified products.
TTA = $Tl(OAc)_3 \cdot 1\frac{1}{2}H_2O$.
TTN = $Tl(NO_3)_3 \cdot 3H_2O$.

and Bartlett found that in the thallium sequence, again, inversion of the tertiary centre takes place (Scheme 16).



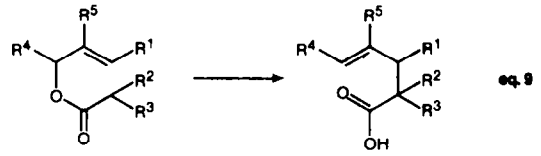
2.5. *Ester enolate Claisen rearrangement*

The Ireland ester enolate rearrangement constitutes an important route to tetrahydrofurans. In 1976, Ireland *et al.* reported[41] that stereochemical control was possible through stereoselective



Scheme 16.

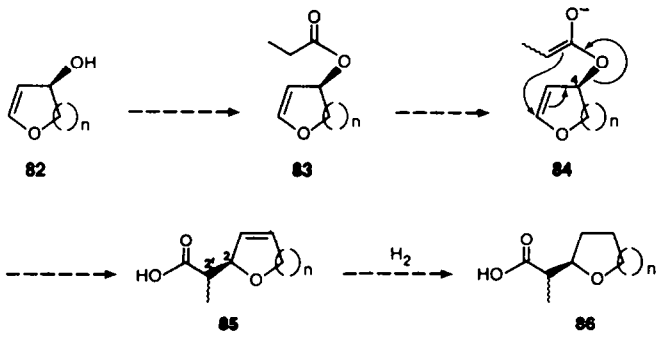
enolate formation. They showed that [3,3]sigmatropic rearrangement of a number of allylic esters **80**, as either the enolate ions or, better, the corresponding silylketene acetals produces γ,δ-unsaturated acids **81** [equation (9)]. It was demonstrated that kinetic enolization with lithium diisopropylamide gives selective formation of enolates in which the geometry is solvent dependent. Use of THF favours formation of a *Z*-enolate (corresponding to *E*-silylketene acetal) while use of THF : 23% HMPA gives mainly the isomeric *E*-enolate (and *Z*-silylketene acetal).



eq. 9

80 **81**

These results have been applied to furanoid and pyranoid chemistry as follows.[42] Scheme 17 illustrates the basis of the method, which involves first preparation of a glycal[43] **82**, then, esterification with the appropriate acid chloride (**82** → **83**) and generation of the corresponding enolate **84**. Upon warming, [3,3]sigmatropic rearrangement of the enolate occurs to afford a substituted dihydrofuran, **85** (in the case of 5-membered glycals), with predictable side-chain stereochemistry at the C-2 and C-2′ centres. Hydrogenation then gives the corresponding substituted tetrahydrofuran **86** ($n = 1$).



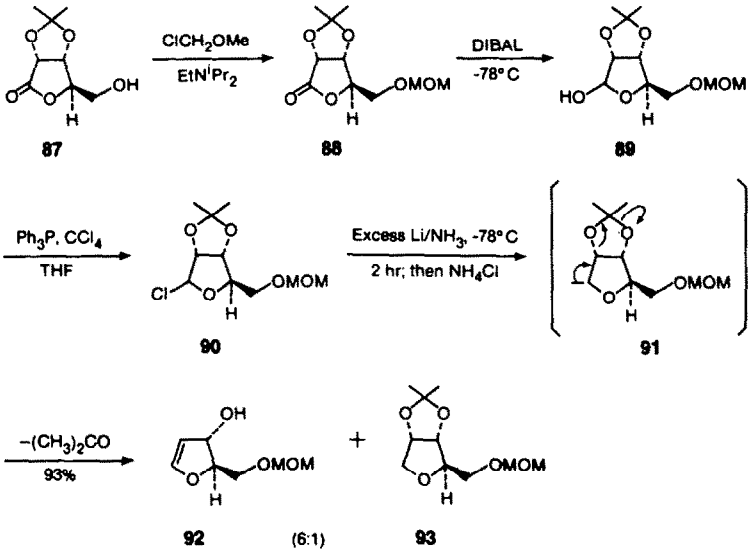
82 **83** **84** **85** **86**

Scheme 17.

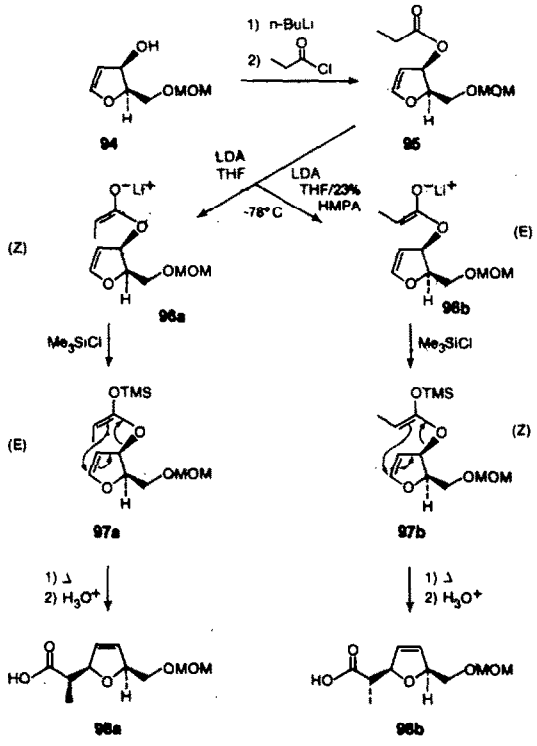
The stereochemistry at C-2 is a direct result of the asymmetry at C-4 of the enolate (**84**), since the entire ester fragment is transferred suprafacially. Similarly, the stereochemistry at C-2′ is controlled by the geometry of the enolate.

An efficient method for preparation of glycals was developed by Ireland[42,43] and Scheme 18 illustrates his procedure for the 5-membered series. Acetonide **87** was prepared directly from ribonic acid γ-lactone and hydroxyl protection was accomplished using chloromethyl methyl ether and diisopropylethylamine at −78°C to yield **88**. Reduction of the lactone with diisobutylaluminum hydride gave lactol **89** and triphenylphosphine-carbon tetrachloride was used to prepare the corresponding chloro-compound **90**. Addition of **90** to an excess of lithium in liquid ammonia at −78°C led, as shown, to the desired glycal **92** and the reduced acetonide **93**, in a ratio of 6 : 1.

Transformation of a glycal to an ester prior to enolate formation is achieved simply by reaction of the lithium alcoholate (see **94** → **95**, Scheme 19) with the requisite acid chloride. Next, an ester enolate of appropriate geometry must be generated. Ireland found that kinetic enolization using lithium diisopropylamide in THF at −78°C affords predominantly (85–90% of the total) the *Z*-enolate **96a**, while use of LDA in THF containing 23 v/v% HMPA gives the *E*-enolate **96b**, again as 85–90% of the total. The stereochemical outcome of the enolization is probably the result of kinetic (THF) and thermodynamic (THF–HMPA) control.[44] Evidence for this is illustrated by the results in Table 3[44a] for enolate generation in 3-pentanone involving both an internal quench[45] with trimethylsilyl chloride, and a two-step generation-quench procedure.[46]



Scheme 18.



Scheme 19.

Table 3

Enolate trapping conditions	Solvent	Ratio $E:Z$
Internal quench (excess TMSCl)	THF	98:2
Internal quench (8 equiv. TMSCl)	HMPA:THF	37:63
Internal quench (17 equiv. TMSCl)	HMPA:THF	46:54
Two-step procedure	HMPA:THF	18:82

LOBA = lithium *t*-octyl-*t*-butylamide; TMSCl = trimethylsilylchloride.

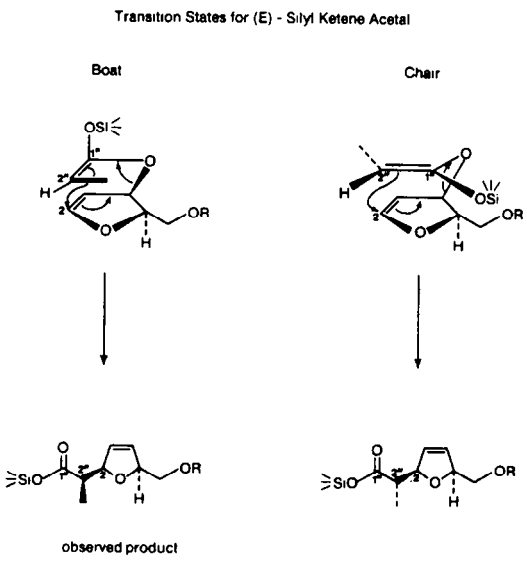


Fig. 9.

[3,3]Sigmatropic rearrangement (**97a, b → 98a, b**) is effected by warming either the enolates **96a, b** or the corresponding silylketene acetals (**97a–b**) (prepared by trapping with either trimethylsilyl chloride or *t*-butyldimethylsilyl chloride) to room temperature or higher. After hydrolysis of the silyl protecting groups, the functionalized dihydrofurans (**98a, b**) are isolated.

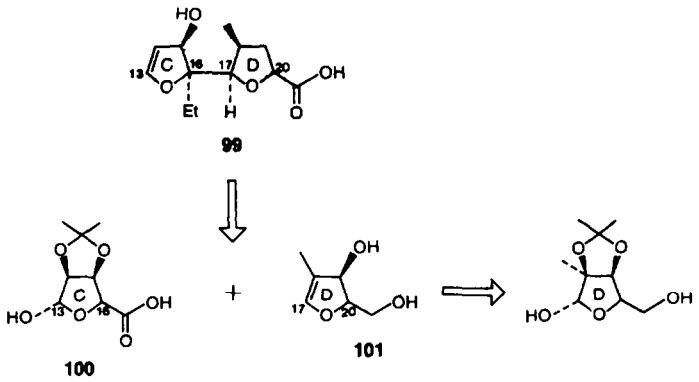
It has been found that in cyclic systems, the ester enolate Claisen rearrangement occurs through a boat-like transition state.[47] This preference together with enolate geometry (which is known from the enolization conditions employed), allows the stereochemistry at both C-2 and C-2′ (see **85**, Scheme 17) to be predicted.

The more favourable nature of the boat over the chair transition state is difficult to understand. Both conformations are illustrated in Fig. 9 for an *E*-silylketene acetal. Non-bonded interactions may play a role and in the two cases they are clearly different. Also inspection of models suggests that the double bond termini C-2″ and C-2 can approach closer to one another without bond angle strain in the boat form than they can in the chair conformation.

The ester enolate rearrangement has been used frequently in the preparation of polyether antibiotic synthesis.† For example, Ireland has employed the methodology in his total synthesis of lasalocid A,[7b] as well as its enantiomer,[8] and in the preparation of the constituent fragments of monensin.[48] Application to the C–D ring fragment of monensin[48b] illustrates the power of the method. The retrosynthetic analysis is shown in Scheme 20. Ireland intended to esterify glycal **101** corresponding to the monensin D-ring, using the second glycal **100**, which would serve as a precursor to the C-ring. Ester enolate Claisen rearrangement would then give the desired C–D fragment **99**, with the requisite stereochemistry at C-16 and C-17. The C-13 ring terminus (**99**) of the resultant fragment would be used in extending the polyether chain to the left, while the D-ring would act as the acyl partner to extend the chain in the opposite direction.

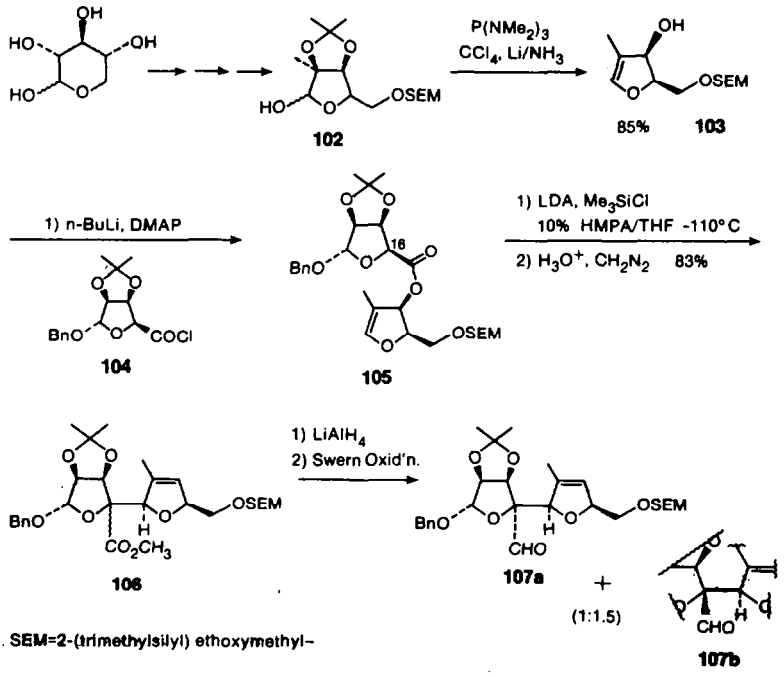
Implementation of this idea is shown in Scheme 21. The acetonide **102** was prepared from D-xylose and converted in 85% yield into the corresponding glycal **103** under the usual conditions. Esterification with the C-ring precursor **104**, prepared from D-mannose, gave ester **105**. Application of the usual procedures for rearrangement to this unique ester proved extremely difficult however, since generation of a negative charge at C-16 in formation of the enolate resulted in β-elimination rather than rearrangement. New conditions were developed, therefore, which allowed O-silylation to occur faster than β-elimination.

† Ireland and Vevert have also employed this methodology for Nonactin synthesis. See R. E. Ireland and J.-P. Vevert, *Can. J. Chem.* **59**, 572 (1981).



Scheme 20.

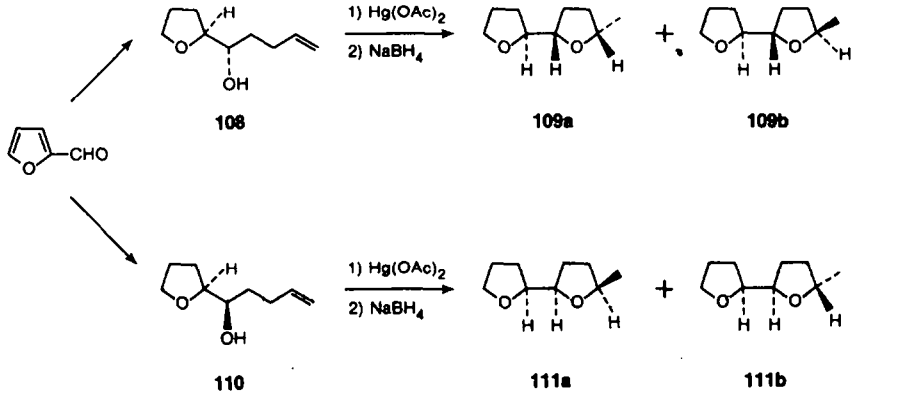
The critical Claisen conditions which were employed were addition of ester **105** to a *pre-mixed* solution of lithium diisopropylamide and trimethylsilyl chloride in 10% HMPA/THF at −110°C. Desilylation and treatment with diazomethane after thermal rearrangement at room temperature afforded a mixture of esters **106**. The ester functionality was reduced with lithium aluminum hydride, and under Swern conditions, a mixture of aldehydes **107a, b**, was obtained. X-ray crystallography on an advanced intermediate derived from the aldehyde **107b** allowed Ireland to determine the stereochemistry of the two aldehydes which were obtained in a ratio of 1 : 1.5. The minor isomer was that required for synthesis of the C-D ring unit. Obviously, these Claisen conditions do not result in only a single geometry for the enolate; however, a sufficient quantity of the desired material was obtained for further elaboration. Other examples of ester enolate rearrangement in polyether synthesis,[6b,11c,49] although not necessarily for substituted THF synthesis, follow similar principles. Application of the methodology to tetrahydropyrans is dealt with in Section 3.



Scheme 21.

2.6. *Mercuricyclization*

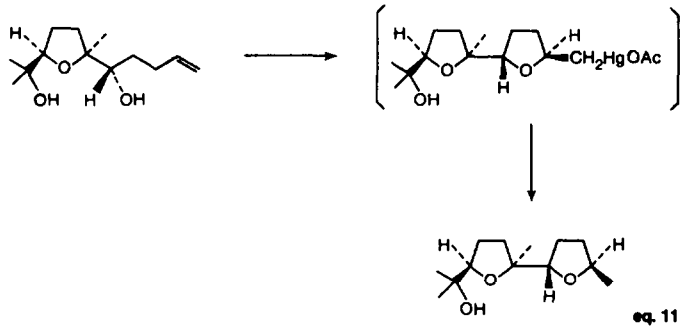
Mercuricyclization of unsaturated alcohols [equation (10)] has been used to generate 2,5-disubstituted tetrahydrofuranyl systems with the stereochemical results (mainly *trans*) shown in Table 4.[50] In the last step of the process the mercury group is removed by borohydride reduction. In principle this reaction could be used for chain extension by free radical methods,[51] however this possibility has not been examined. The mercuricyclization route has been used to make bis-tetrahydrofurans [equations (11) and (12)].[52]



eq. 10

Table 4

Alcohol	% Yield	% *cis* (a)	% *trans* (b)
108	85	16	84
110	85	19	81

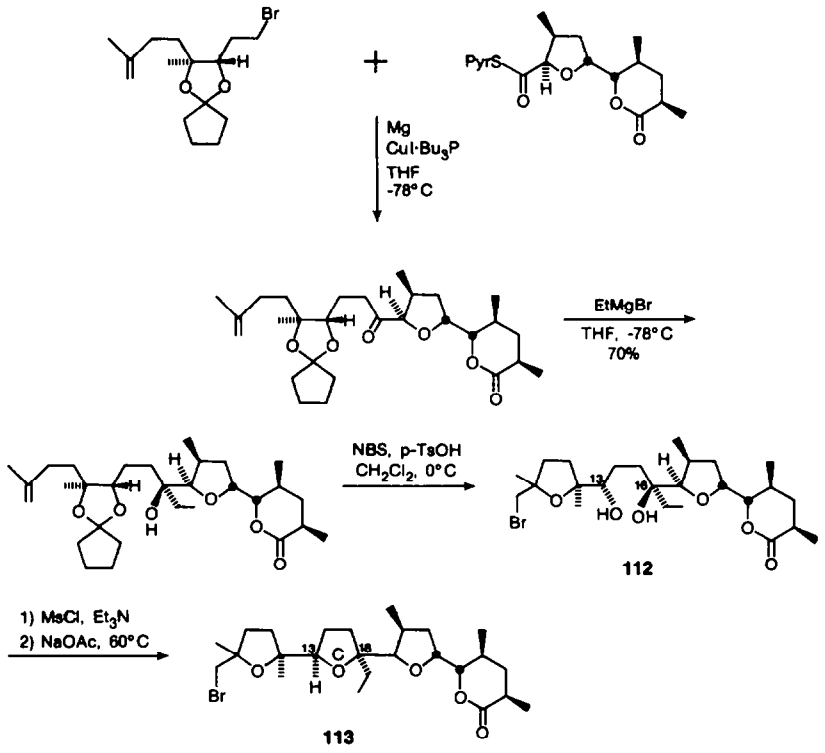


eq. 11

eq. 12

2.7. *Cyclization of* 1,4-*diols*

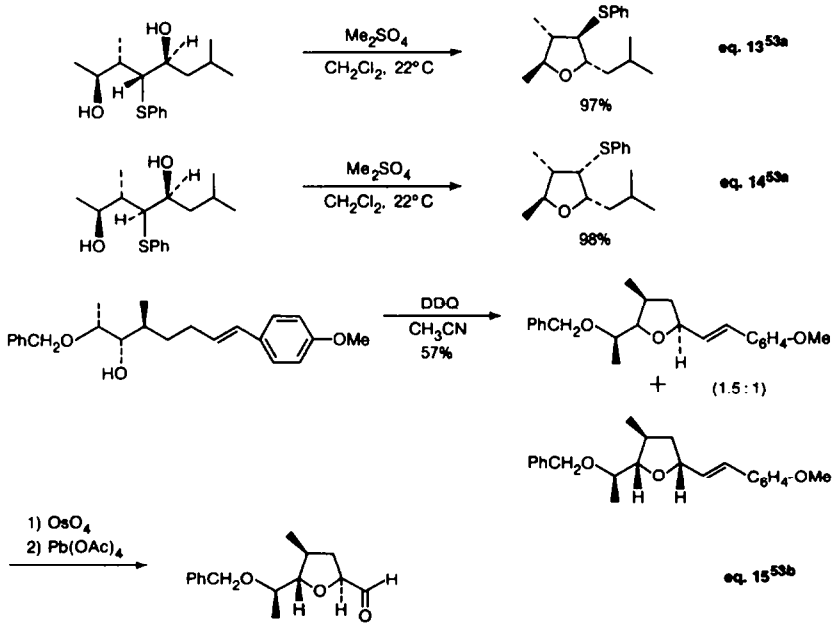
The cyclization of a 1,4-diol system was used by Still *et al.*[9b] in the course of their synthesis of monensin to make the C-13 to C-16 tetrahydrofuran ring in 67% yield (Scheme 22). Thus the diol **111**, assembled as shown, was converted into the monomesylate and then by stereospecific ring closure, into the C-ring of monensin (see **112**).



Scheme 22.

2.8. *Miscellaneous routes to tetrahydrofurans*

Several miscellaneous routes to substituted tetrahydrofurans have been developed recently.[53] These are summarized in equations (13)–(15).



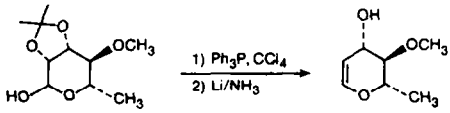
3. PREPARATION OF SUBSTITUTED TETRAHYDROPYRANS

3.1. *Ester enolate Claisen rearrangement*

Ireland's ester enolate Claisen methodology (see Section 2.5) has been applied to preparation of substituted tetrahydropyrans for polyether synthesis.[11c,48c] The procedure is implemented in the

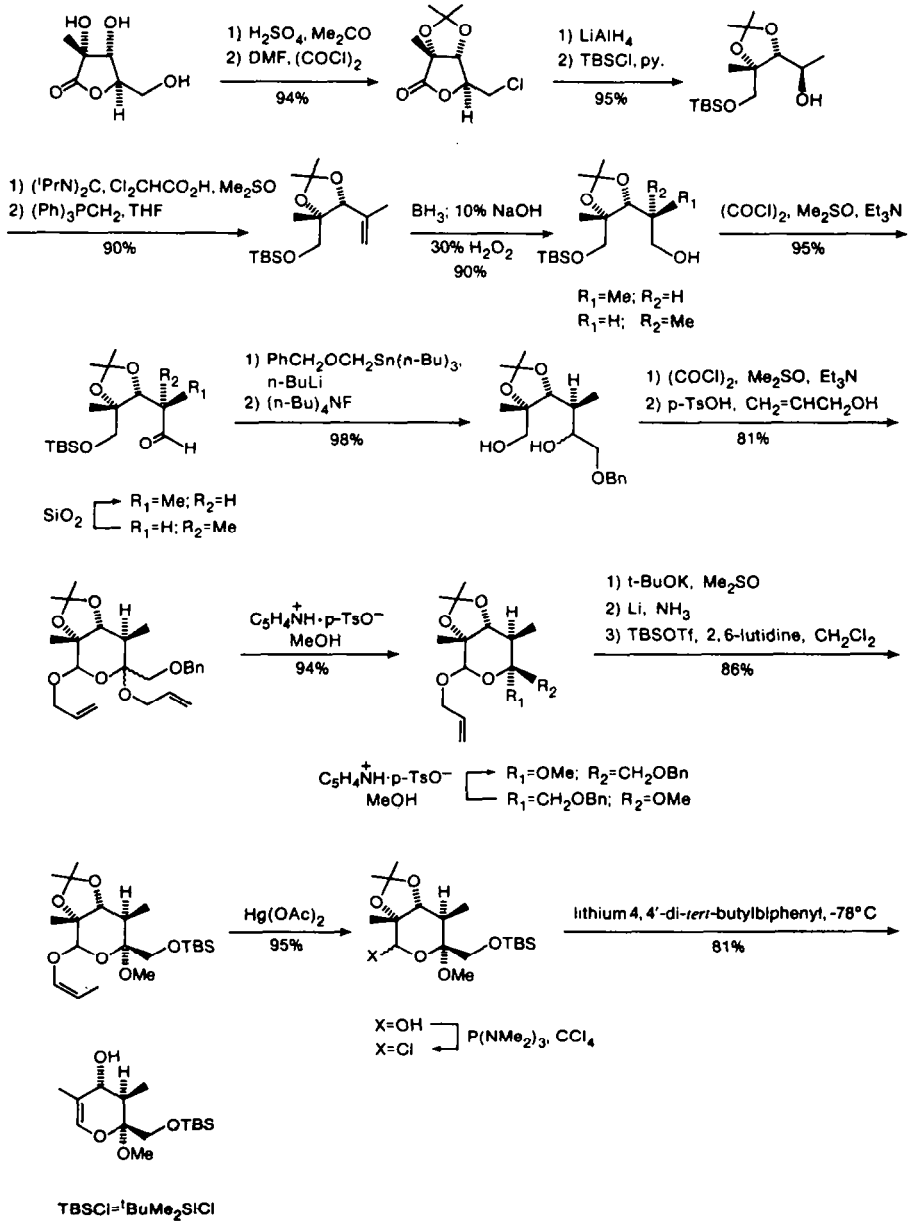
same manner as for 5-membered ring compounds, in that an appropriate glycal is prepared and esterified, the corresponding enolate is generated and trapped, and warming results in rearrangement to afford the Claisen product. Hydrogenation of the resultant dihydropyran gives the corresponding tetrahydropyran.

Formation of a suitable 6-membered glycal is illustrated in equation (16). In this case, the starting carbohydrate **113** was prepared by conventional methods from methyl α-L-rhamnopyranoside.[54]

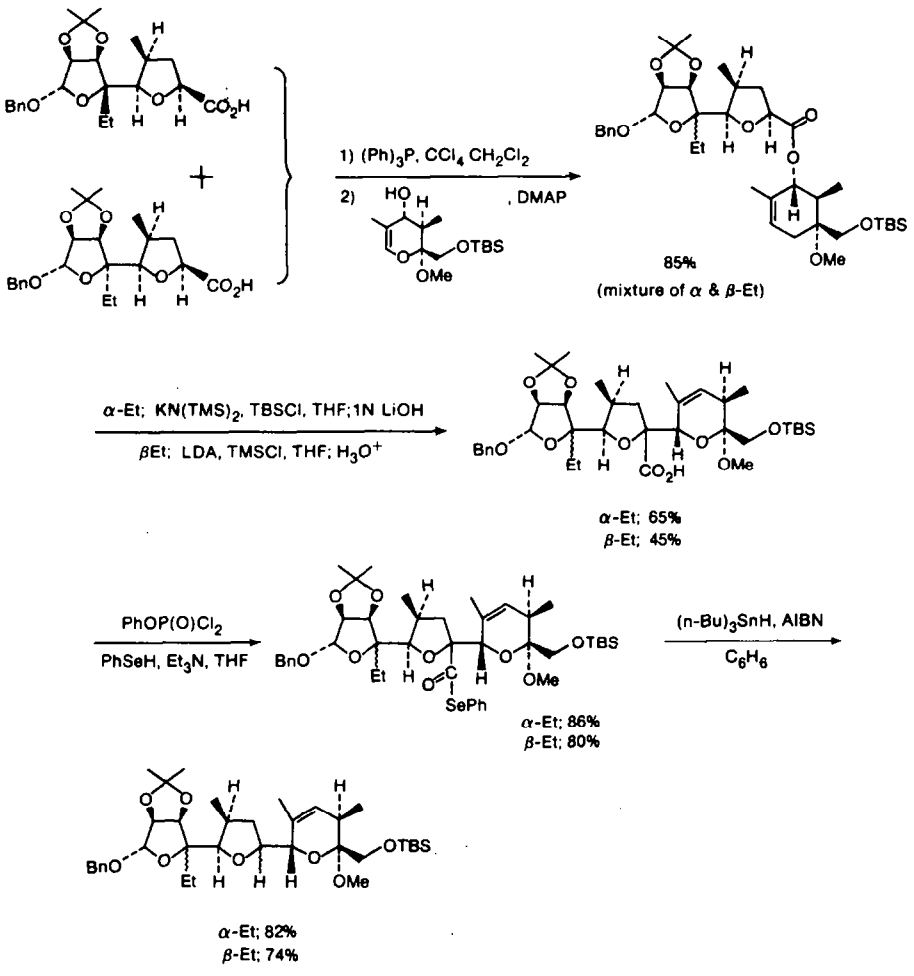


eq. 16

The degree of structural complexity that can be accommodated by an ester enolate route is well illustrated by the example of Schemes 23 and 24 in which the E-ring precursor of monensin is constructed and attached to its C–D ring unit. This is just one of several examples of the methodology from Ireland's laboratory.[48c]

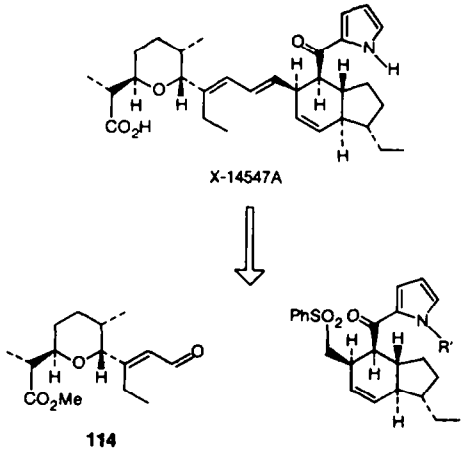


Scheme 23.

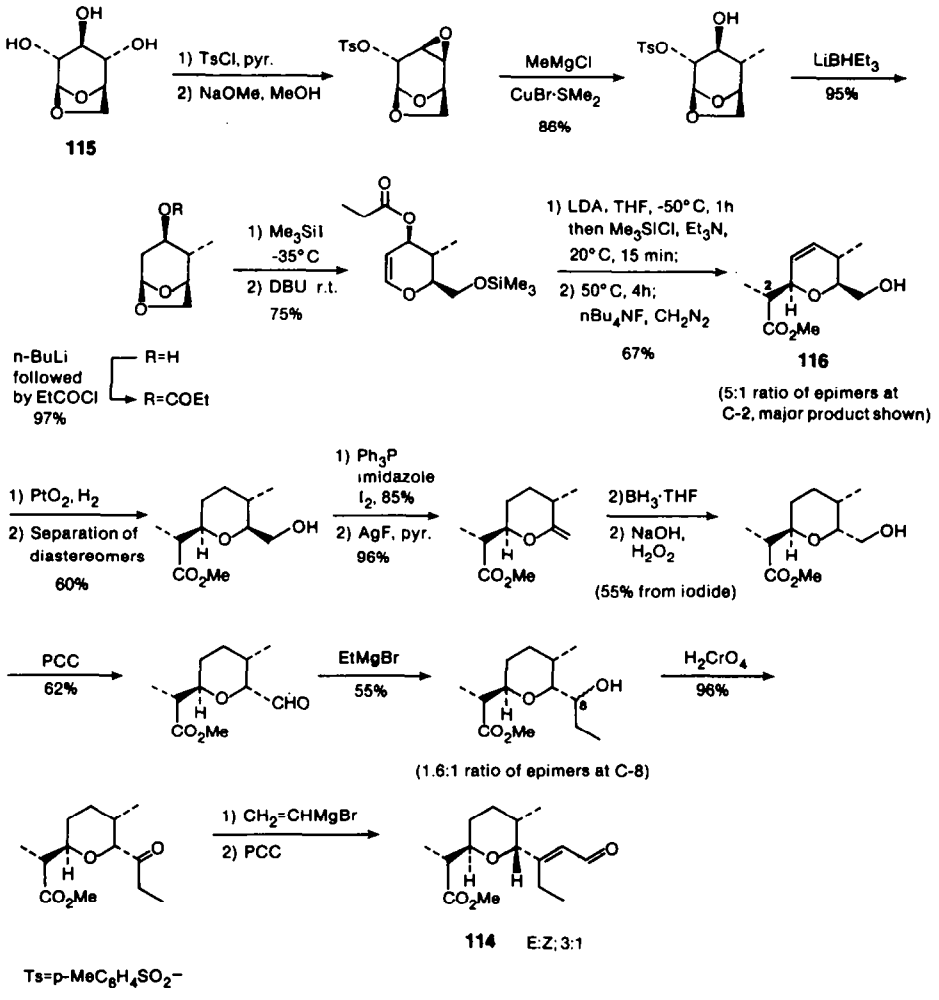


Scheme 24.

Ley *et al.*[11c] have employed the ester enolate technique in their synthesis of polyether antibiotic X-14547A (Fig. 6). In this case the required tetrahydropyran **114** (see Ley's retrosynthesis, Scheme 25), was prepared from a glycal which in turn, was made from 1,6-anhydro-β-D-glucose (laevoglucosan) **115** (Scheme 26). The acyl appendage for the ester enolate rearrangement was the propionyl group. As shown in the scheme, the rearrangement product **116** was subjected to further manipulations in order to convert it into the required unit **114**, which represents the left-hand portion of the antibiotic.



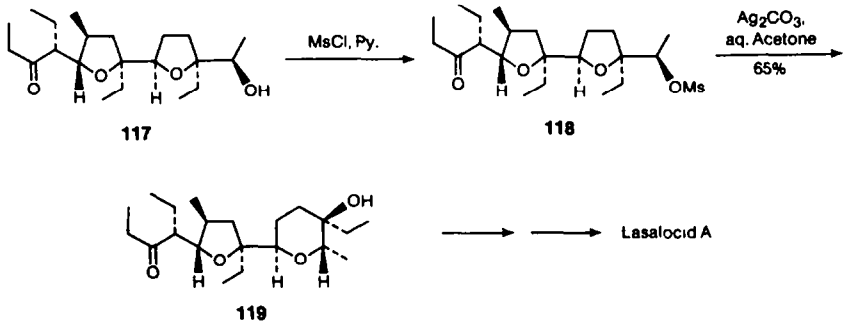
Scheme 25.



Scheme 26.

3.2. *Ring expansion of tetrahydrofurans*

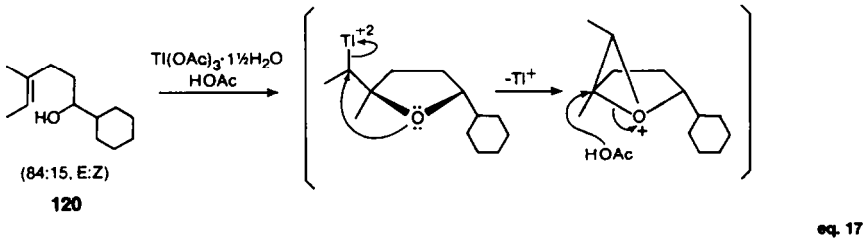
Two methods involving ring expansion of tetrahydrofurans to appropriately substituted tetrahydropyrans have been published in the polyether literature.[7a,39] One procedure was used in a total synthesis of the polyether antibiotic lasalocid A[7a] and the relevant transformations are summarized in Scheme 27. Ketone **117** was prepared by techniques discussed in Section 2.3, and was converted, as shown, into the mesylate **118**. Solvolysis in aqueous acetone, in the presence of silver carbonate, proceeded stereospecifically to give the substituted tetrahydropyran **119**.



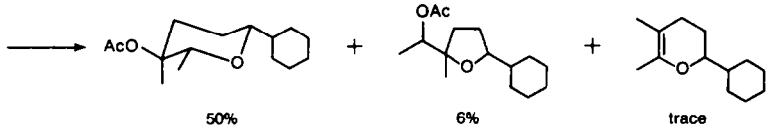
Scheme 27.

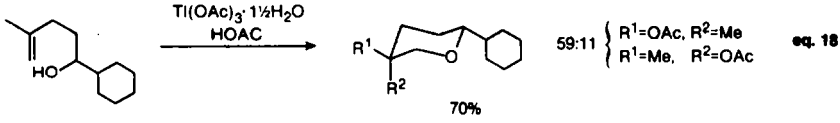
The second example[39] of ring expansion involves thallium-induced cyclization of the hydroxyolefin **120**. In this compound the double bond is polarized such that initial cyclization occurs so as to give a 5-membered heterocycle. Ring-expansion then takes place stereospecifically [equation (17)].

The example of equation (18) proceeds along similar lines, although in higher yields, possibly because the initial competition for cyclization is between a primary and a tertiary incipient carbocation.



eq. 17





eq. 18

3.3. 1,5-*Cyclization*

Intramolecular cyclization by nucleophilic attack on C-5 by an alkoxide at C-1 of a 1,5-diol system (Fig. 10) to yield a tetrahydropyran, has been employed in various approaches to polyether antibiotics.[9a,10,49,55,59] For example, generation of the E-ring tetrahydropyranyl fragment of monensin has been accomplished[9a] by 1,5-cyclization of the δ-hydroxy ketone derived from **123** (Scheme 28). The olefinic alcohol **121** was acylated and hydroxylated (**121** → **122**). Protection of the primary hydroxyl, followed by Jones oxidation gave **123**. Finally, base treatment served to remove the protecting groups and cyclization occurred spontaneously (**123** → **124**) so as to place all of the substituents of ring E equatorial except for the tertiary hydroxyl which is in the anomerically favoured axial conformation.

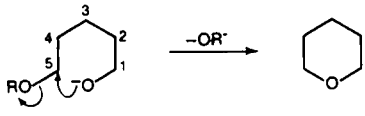
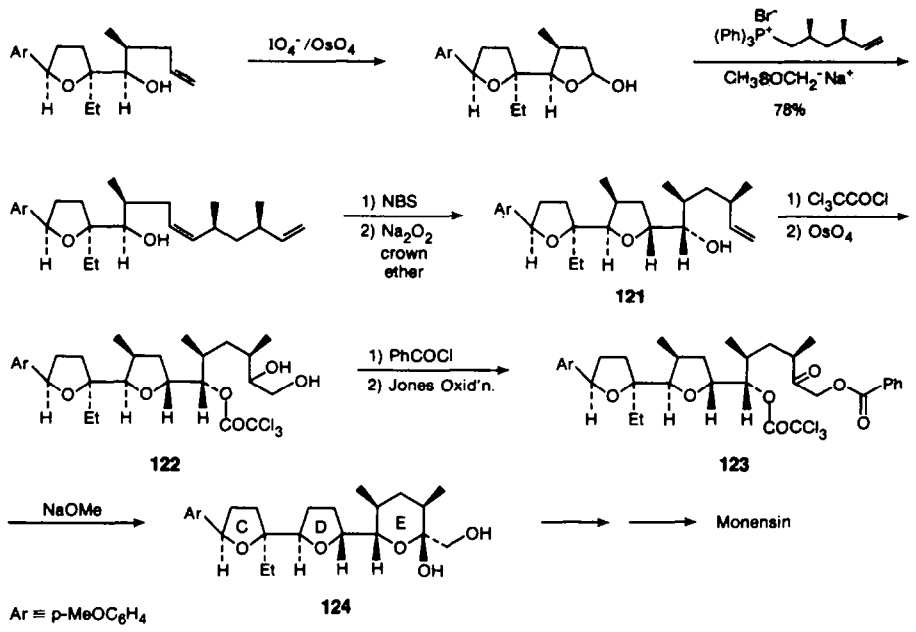


Fig. 10.

Bartlett[49] has used an approach involving 1,5-cyclization of a δ-hydroxy ketone in his synthesis of a polyether fragment representative of the D and E rings of monensin (*cf.* Fig. 2) and the E and F rings of nigericin (*cf.* Fig. 7). Similar methodology has been utilized by others to construct the E-ring fragment of monensin.[55] Bartlett's retrosynthetic plan for preparation of the polyether fragment is shown in Scheme 29 and implementation of the plan in Scheme 30. The key step is acid treatment of **128** to yield **129a, b** (Scheme 30) but, as in the example previously discussed, the route to **129a, b** was of necessity quite involved.

In Scheme 30 the sequence **125** through **128** produces **128** with 77% stereochemical purity, the main loss of stereochemical control apparently having occurred in the iodolactonization of **126** to **127**. Acid catalyzed cyclization of **128** gave the desired tetrahydropyran lactones **129a, b** (93%) as

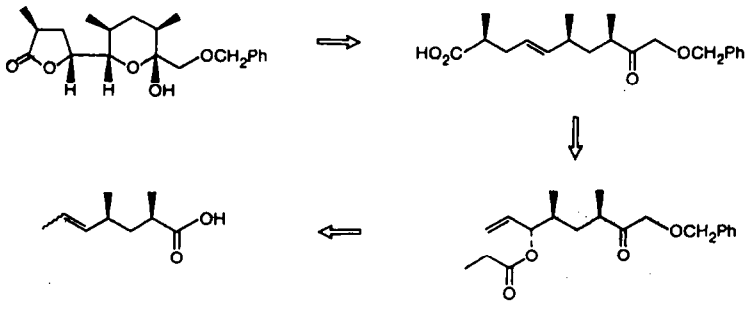


Scheme 28.

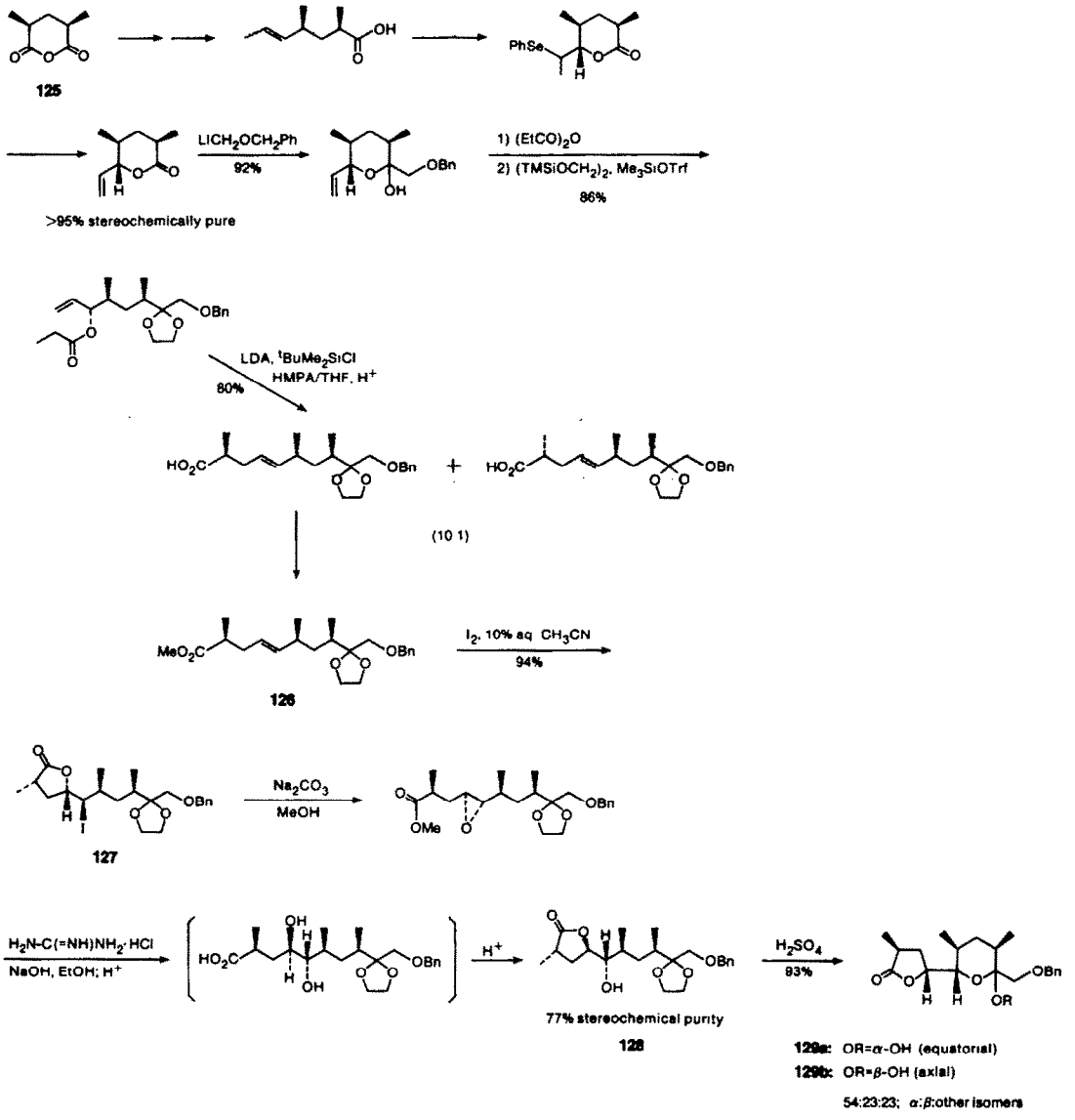
a 54:23:23 mixture of the α- and β-anomers (both isolable by crystallization) and other isomers, respectively.

The A-ring tetrahydropyran fragment of narasin and salinomycin (Fig. 11) was prepared by cyclization of a 1,5-diol.[10a] Here again, preparation of the appropriate starting diol is a complex task. However, the authors introduced a highly repetitive sequence[10a,56] to assemble the requisite tetrahydropyran precursor (Scheme 31). An aldehyde was extended by Horner–Wittig chemistry to an unsaturated ester which was then reduced to the corresponding allylic alcohol. Asymmetric epoxidation[31] set the stage for regioselective cuprate addition[56,57] to the carbon centre adjacent to the hydroxymethyl group. The result of these operations was a branched chain 1,3-diol, with defined stereochemistry at two adjacent asymmetric centres. The secondary alcohol was then protected and the primary one oxidized to an aldehyde. Chain extension by repetition of the sequence afforded the desired 1,5-diol with the appropriate stereochemistry, ready for cyclization.

Scheme 32 illustrates Kishi's use of this methodology to generate the requisite diol **130** for narasin synthesis. In the final stages, the primary hydroxyl of **130** was protected by pivaloylation, the residual secondary hydroxyl was mesylated, and removal of the benzyl protecting groups afforded the key intermediate **131**. In the presence of potassium hydride, the diol **131** cyclized to tetrahydropyran **132** in 45% yield. In the final step, the undesired hydroxyl at C-5 was removed by a variant of the Barton deoxygenation[58] (**132** → **133**). Modification of **133** by literature procedures



Scheme 29.



Scheme 30.

allowed isolation of the desired A-ring of narasin with the correct absolute stereochemistry (**133** → **134**). The A-ring of salinomycin (*cf.* Fig. 11) was prepared by a similar sequence.

Cyclization of a 1,5-hydroxytosylate has been used in synthetic work related to antibiotic X-14547A (Fig. 6) for preparation of the requisite tetrahydropyran ring (see Fig. 12 and Scheme 33).[59]

3.4. *Iodolactonization*

In Still's[9b] synthesis of monensin, iodolactonization was used to produce the E-ring tetrahydropyran system (Scheme 34). The optically active γ,δ-unsaturated acid **138** was assembled by

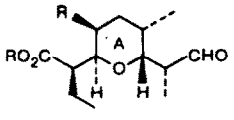
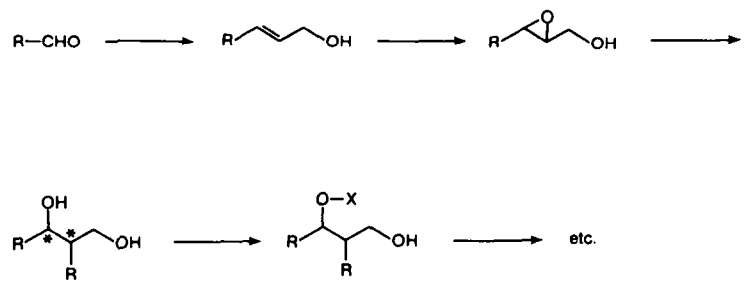
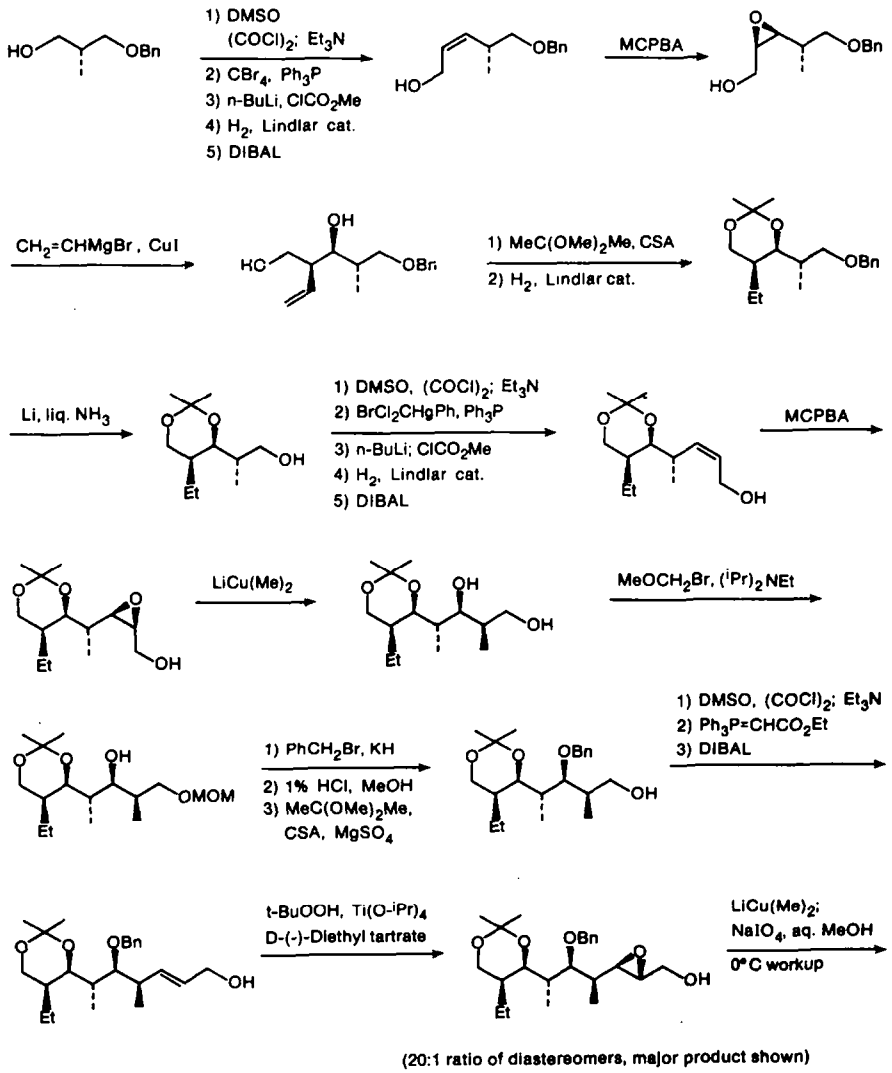


Fig. 11.

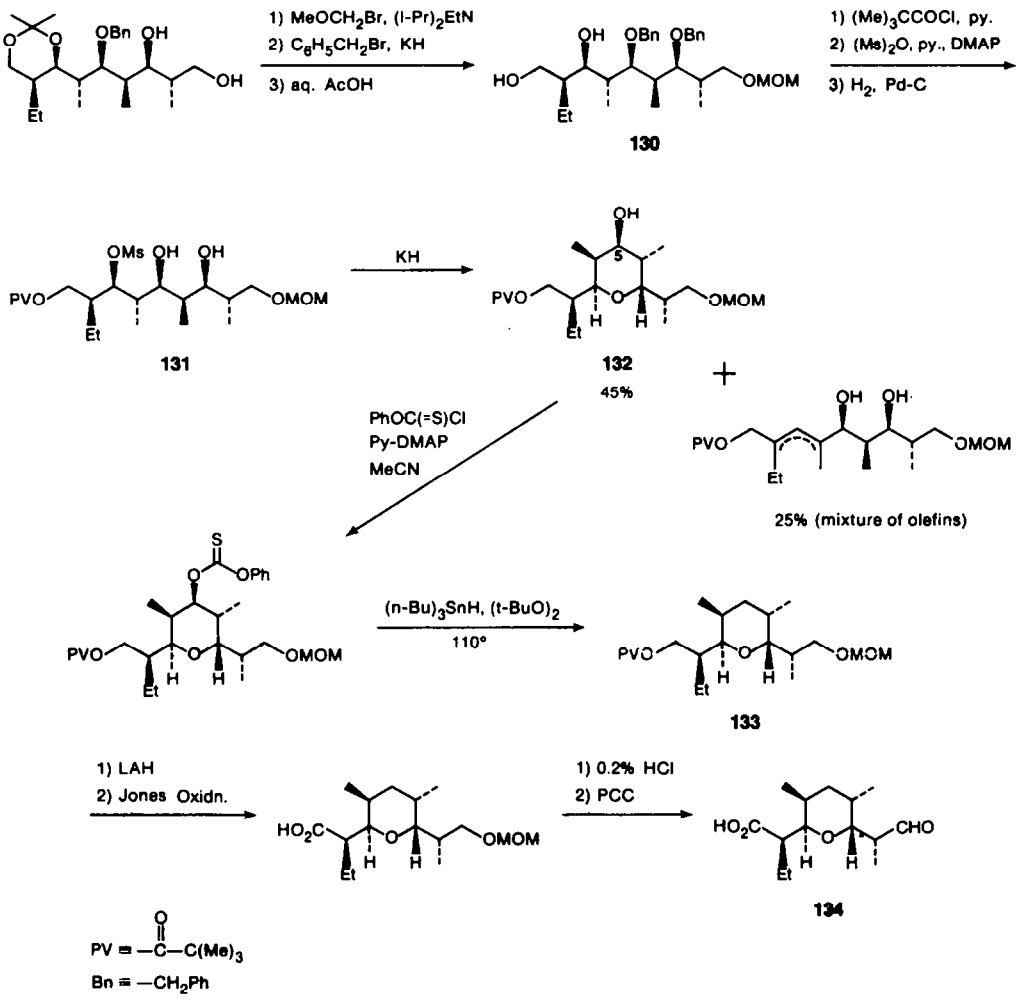


Scheme 31.

Wittig combination of two subfragments, **136** and **137**, derived from (*R*)-citronellic acid and (*R*)-β-hydroxyisobutyraldehyde, respectively. Iodolactonization gave the γ-lactone **139**, as anticipated from steric considerations in which the *cis* olefin and the adjacent asymmetric centre (C-22, monensin numbering) are expected to constrain the carboxylate-bearing appendage below the olefin plane (**138a**).



Scheme 32.



Scheme 32 (cont'd.)

Treatment of **139** with silver trifluoroacetate induced formation of a tetrahydrofuran and resulted in loss of acetone. The bicyclic system **140** was then converted in several stages into the tetracyclic compound **141**, ring C of this fragment being assembled by the method illustrated in section 2.7. With the tetracycle in hand, elaboration of ring E was completed by exposure of **141** first to benzyloxymethyl lithium and then trimethyl orthoformate in the presence of acid. The tetrahydropyran ring (see **142**), with the desired relative and absolute stereochemistry, was thus obtained.

3.5. *Epoxide opening–ring closure reactions*

A high degree of stereocontrol is possible in the synthesis of substituted tetrahydropyrans by simultaneous ring closure and epoxide opening reactions. This fact has been utilized by Nicolaou and co-workers[11a] in synthetic work related to the polyether antibiotic X-14547A. Nicolaou's retrosynthetic analysis is shown in Scheme 35 and the synthesis of the key hydroxy-epoxide **147** in Scheme 36. As shown, diethyl tartrate was converted into **143** and then, by a divergent synthesis,

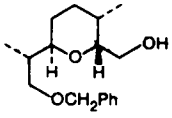
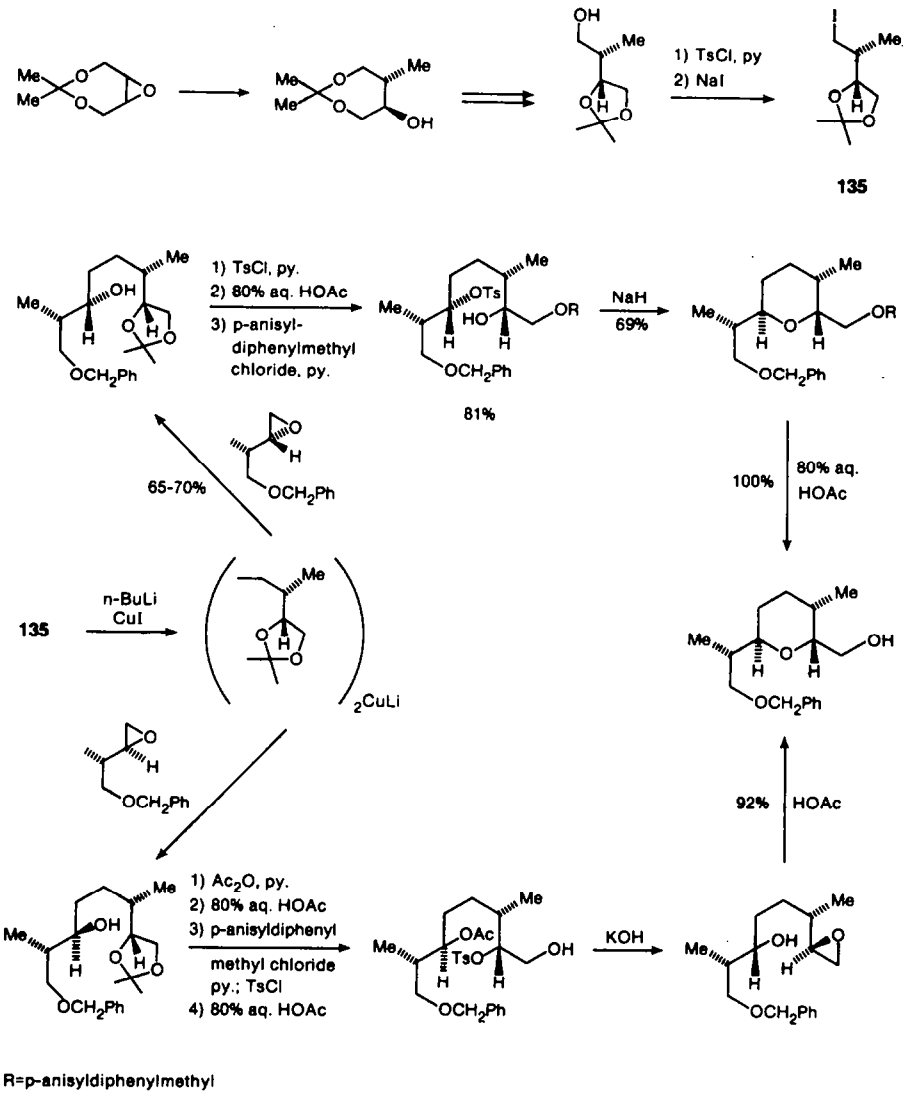


Fig. 12.



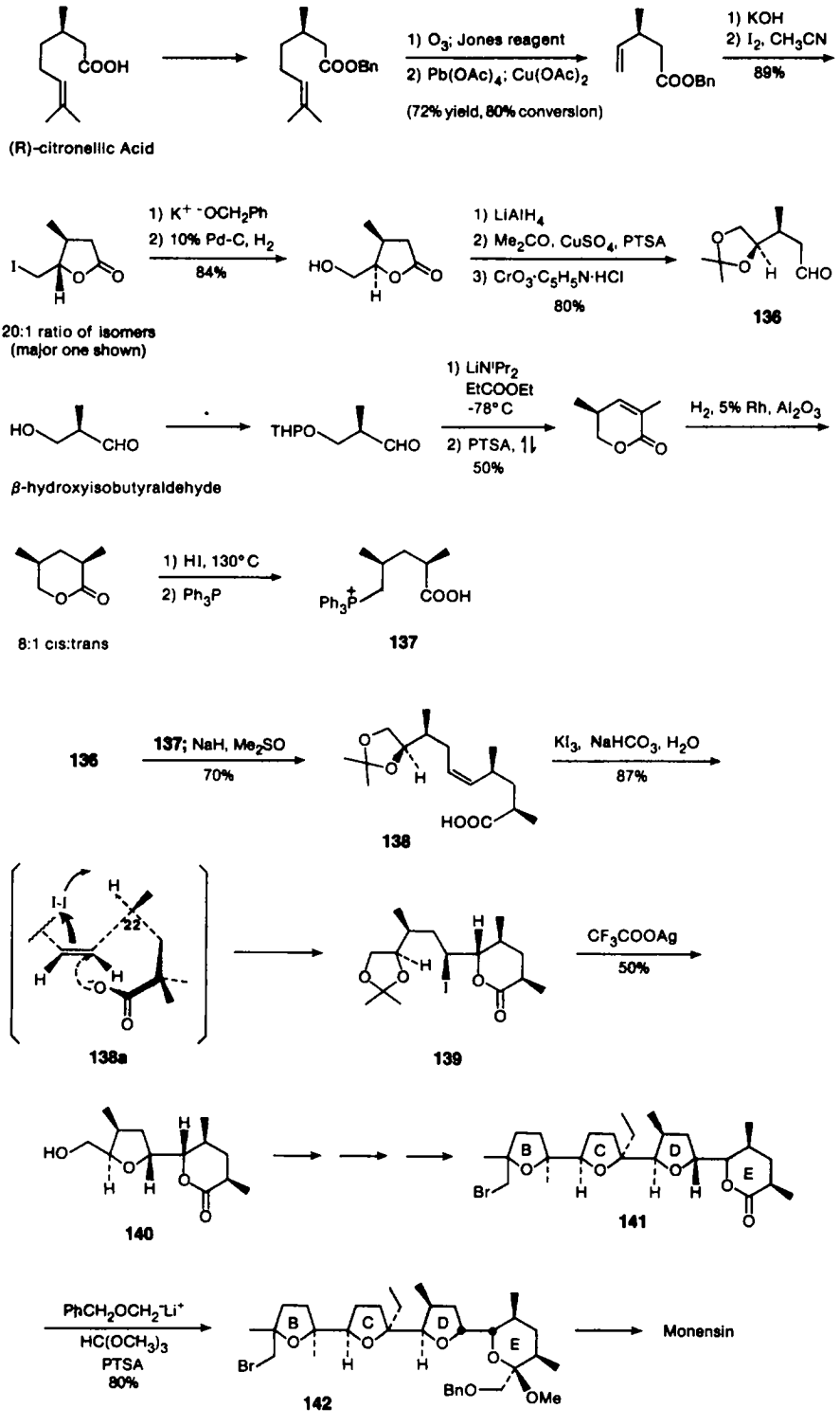
Scheme 33.

into the two sub-fragments **144** and **145**. These were combined and modified to produce hydroxy-epoxide **146**. Cyclization (**146** → **147**) was effected with camphorsulfonic acid, a reaction in which complete regio- and stereoselectivity (inversion at the epoxide carbon) was observed and the resultant tetrahydropyran **147** was subsequently oxidized to ketone **148** for further elaboration to the antibiotic.

The utility of an epoxide opening–ring closure sequence for making substituted tetrahydropyrans was illustrated more recently in Yonemitsu's approach[60] to the D–E ring fragment **149** of the polyether antibiotic, salinomycin (Fig. 3). As indicated in Scheme 37, extensive use was made of chelation controlled Grignard reactions[61] in order to convert optically pure materials derived from the chiral pool into hydroxy-epoxide **151**. Acid treatment proceeded efficiently and stereospecifically to give the expected tetrahydropyran **152**, which was readily converted into the bicyclic unit **149**.

4. SPIROKETALS

As is obvious from the preceding discussion, the modern synthetic literature on disubstituted tetrahydrofurans and -pyrans is largely in the domain of polyethers. A different situation prevails, however, for the synthesis of spiroketal units since considerable novel methodology has also been

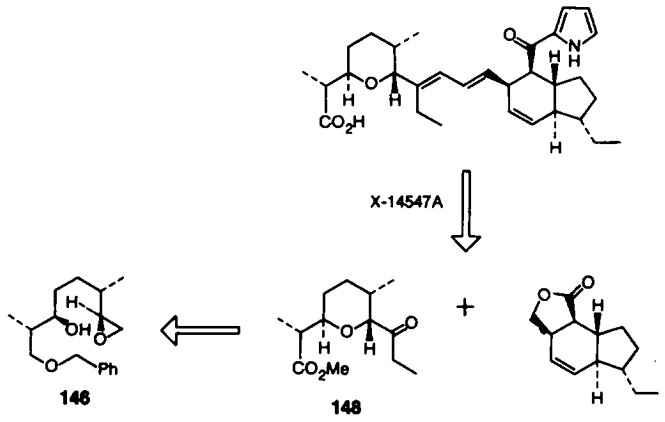


Scheme 34.

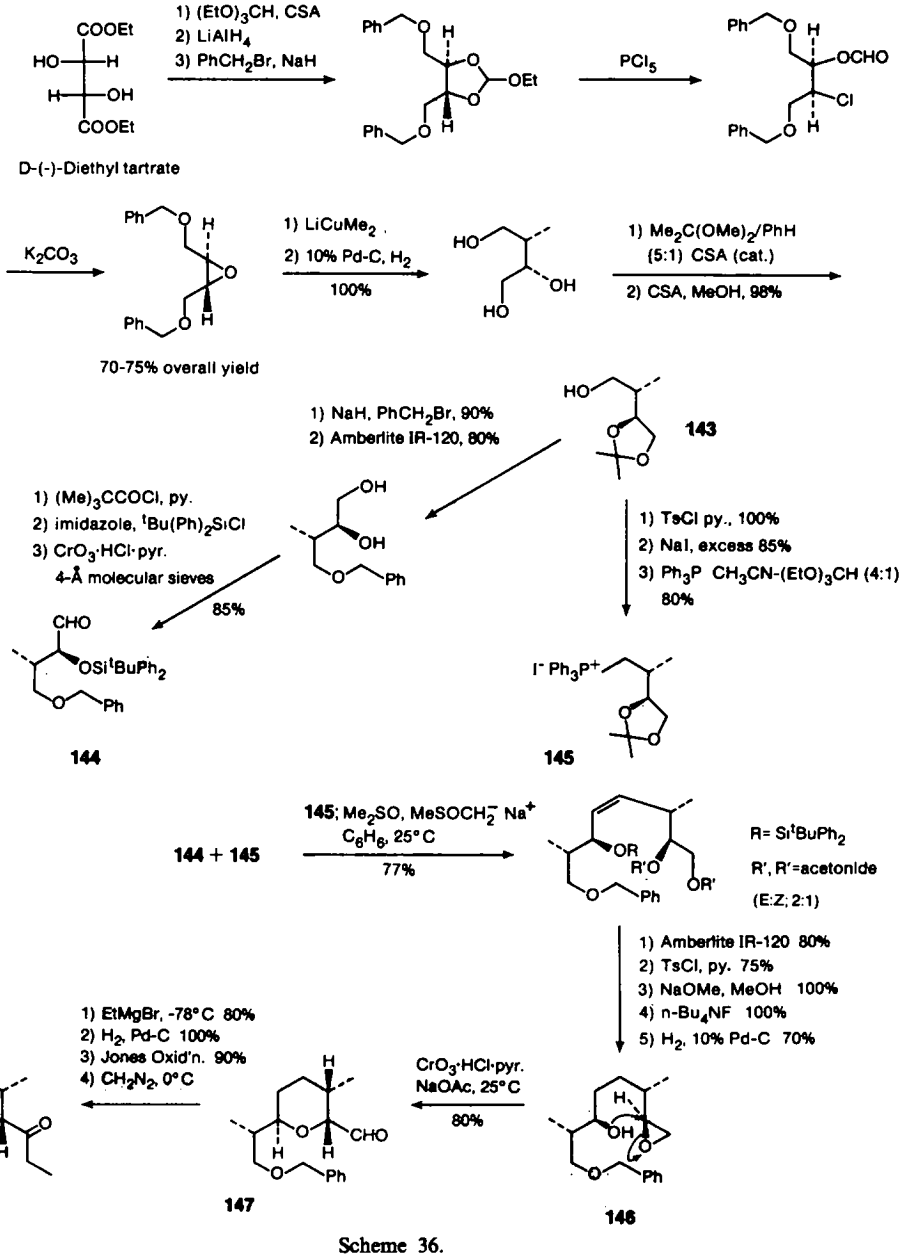
developed outside of the polyether field. For completeness, this other work is surveyed in Section 4.2, which follows the discussion of the *polyether* spiroketals.

4.1. *Spiroketals of polyether antibiotics*

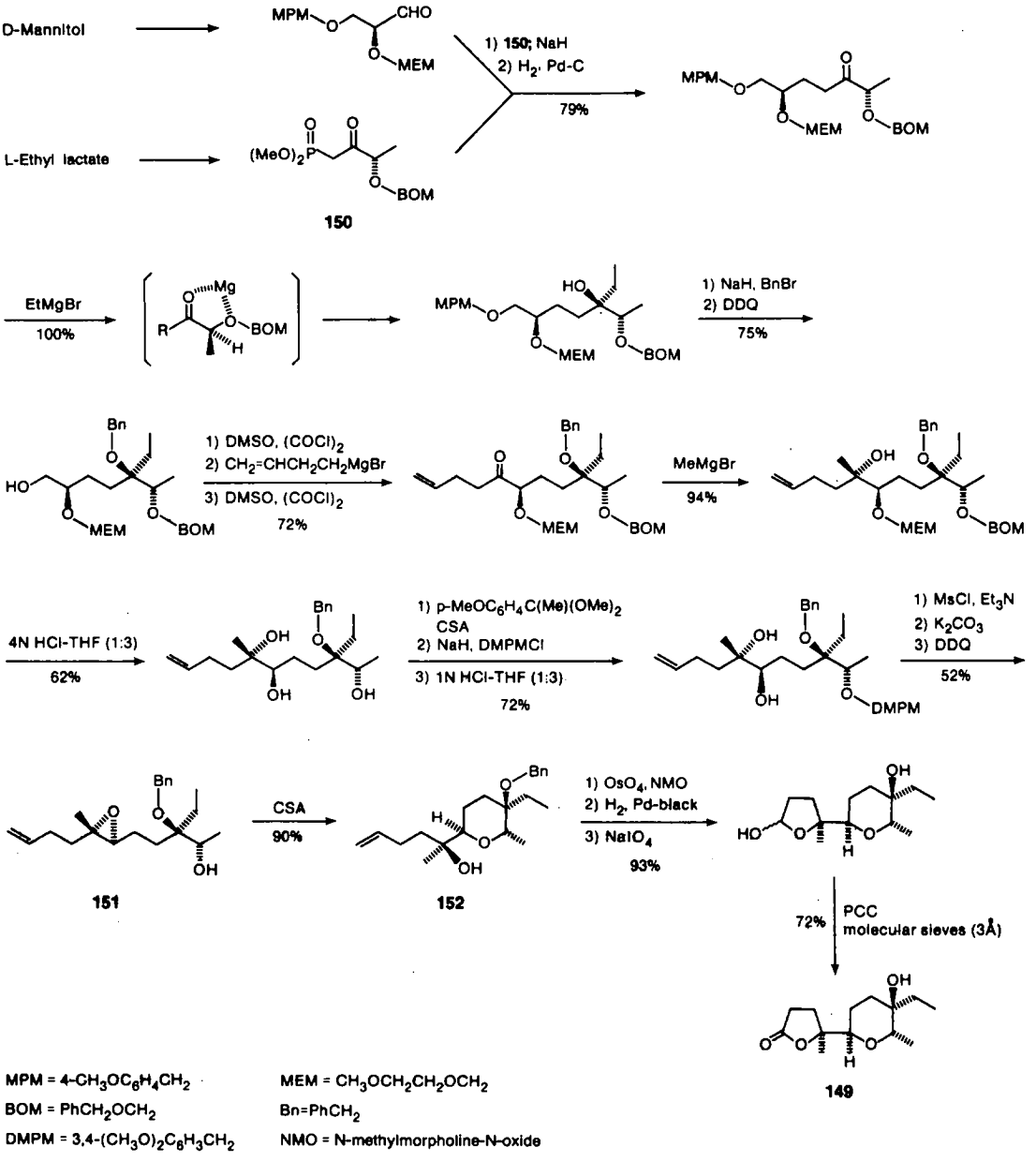
Relatively few different strategies have been used to prepare the spiroketal systems of polyether antibiotics. The most common approach has been formation of a dihydroxyketone equivalent, via



Scheme 35.



Scheme 36.



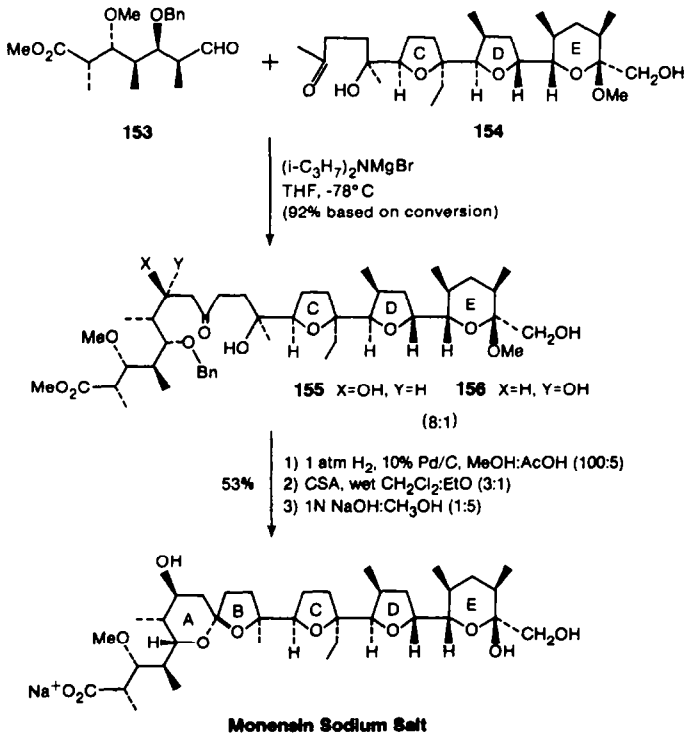
Scheme 37.

aldol chemistry,[62] that undergoes double ring closure.[6,9,63] For example, in Kishi's[9a] synthesis of monensin an aldol reaction was used to join compounds **153** and **154** (Scheme 38) which were prepared by methods previously discussed.[64] The resulting aldols, **155** and **156**, were separated and the former was readily converted by the reactions indicated into the sodium salt of natural monensin.

A comparable sequence, Scheme 39, for preparation of the monensin spiroketal was used in Still's[9b] route to the same polyether antibiotic.

In an alternate approach, Ireland[65] developed a hetero-Diels–Alder route to spiroketals in the sense of equation (19). This method proved useful in the preparation of intermediates for macrolide synthesis[66] and in routes to some spiroketal pheromones.[65b] However, attempts to use it in a model study for the synthesis of monensin[48a] as shown in equation (20) were unsuccessful.

Therefore, Ireland devised a different route to the monensin spiroketal which was based on bicyclic ketal **161**.[48a] The route to **161** is shown in Scheme 40 and its use in preparation of the requisite spiroketal is summarized in Scheme 41. As is obvious from inspection of **161**, the bicyclic

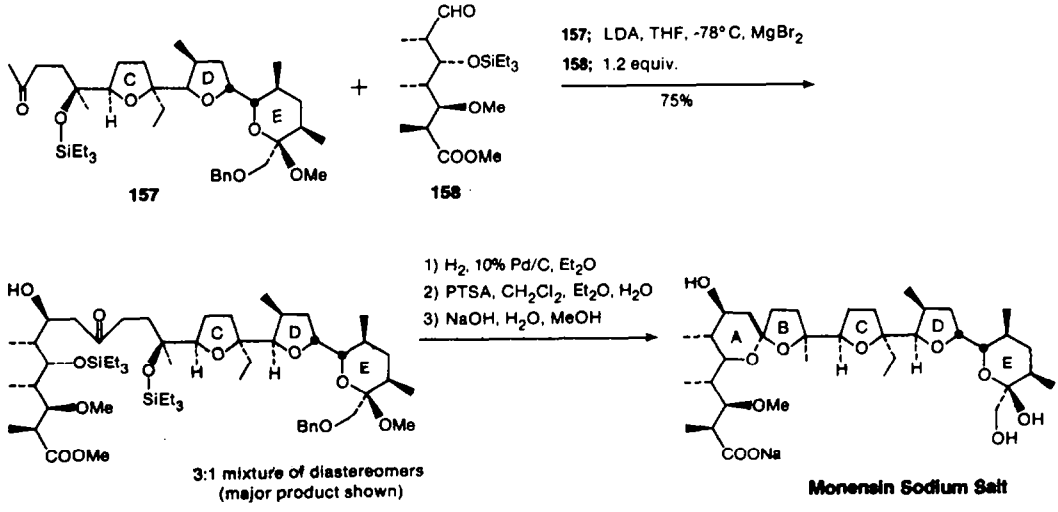


Scheme 38.

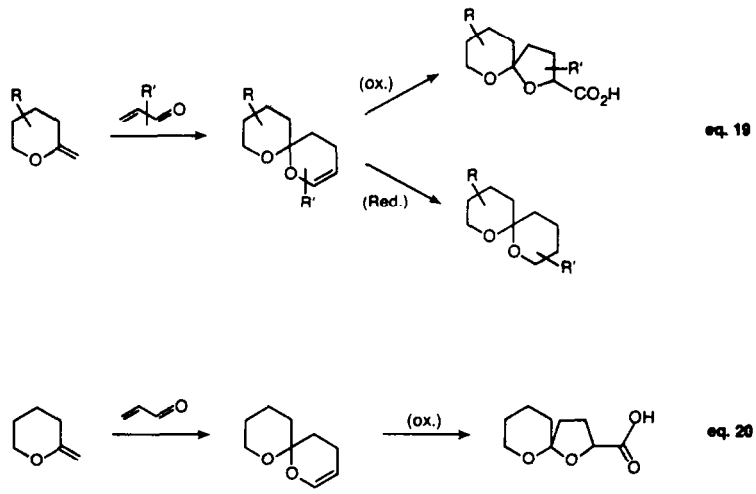
unit represents a masked hydroxy ketone. Hence, the only requirement was to extend the hydroxymethyl group to an appendage carrying a suitably located hydroxyl group. This was achieved by the standard operations shown in Scheme 41 in which the desired spiroketal system **163** resulted from acid-catalyzed equilibration. After debenzylation and re-equilibration, the two desired epimers **164** of the spiro system were obtained (the asymmetry at the carboethoxy centre is not relevant for further elaboration to monensin).

In his synthesis of calcimycin, Evans' route[6a] to the spiro system was based on an aldol approach to obtain the open chain precursor **165** followed by acid catalyzed cyclization. This afforded the requisite spiroketal. Evans' retrosynthetic analysis is shown in Scheme 42.

Grieco[6b,c] made the same polyether antibiotic using technology which avoids aldol chemistry.



Scheme 39.

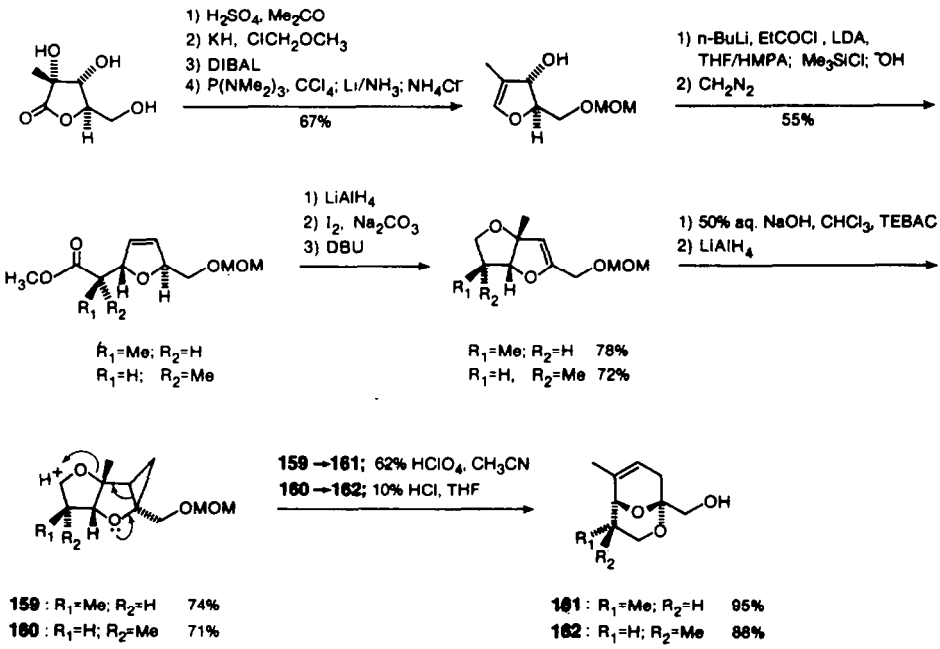


The key intermediate, ketone **166**, was prepared as illustrated in Scheme 43 and functionalized before cyclization to the spiro system in the last step of the synthesis.

The two polyether antibiotics narasin and salinomycin contain identical di-spiroketal systems and Kishi's approach[10a] to narasin is shown retrosynthetically in Scheme 44.

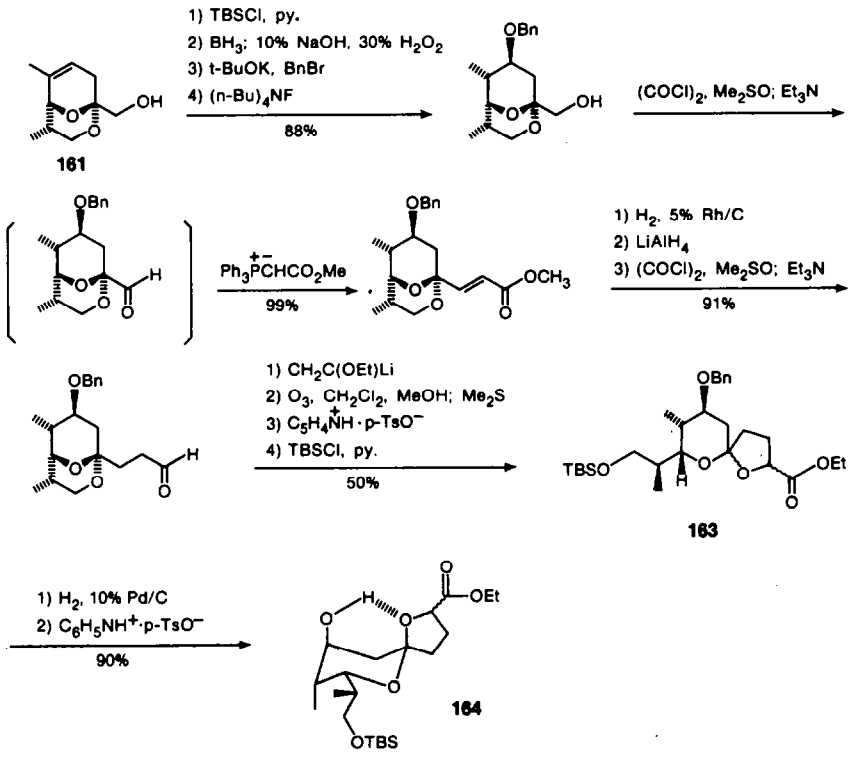
To prepare an open-chain spiroketal precursor corresponding to **167** (Scheme 44) Kishi first synthesized intermediates **168** and **169** (Scheme 45) by methods previously discussed.[67] These were modified and combined as shown in Scheme 45 and the final step in his total synthesis was isomerization of the resultant di-spiroketal system. This was achieved by treatment of the final product with a small amount of camphorsulfonic acid, which induced an equilibration of the C-17 stereocentre to yield a single product of identical configuration to that of the natural polyether.

A related example, containing three spiroketal systems, is provided by the marine toxin polyether, okadaic acid, Fig. 13. A total synthesis of this molecule in which the spiro systems were prepared by acid-catalyzed cyclization of dihydroxyketone equivalents has been published[12] recently.



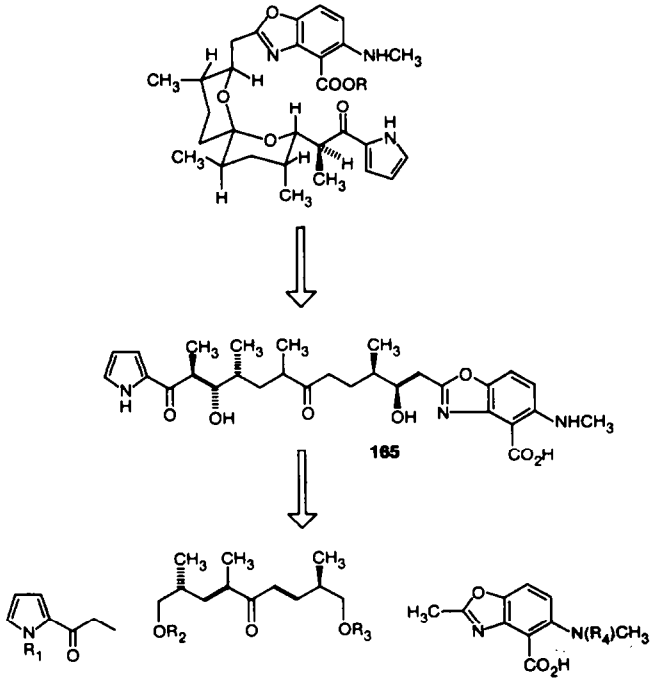
TEBAC=benzyltriethylammonium chloride

Scheme 40.

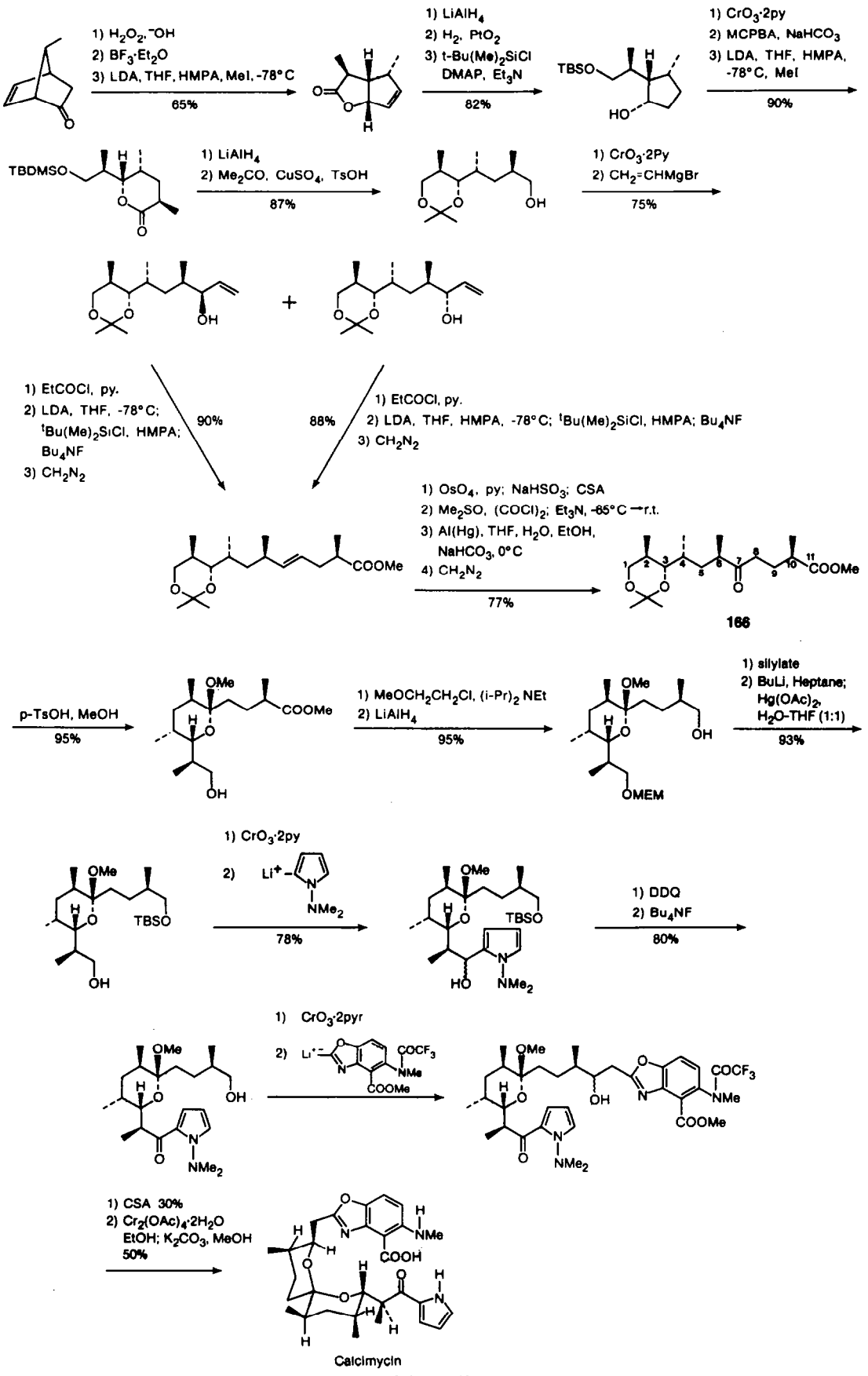


Scheme 41.

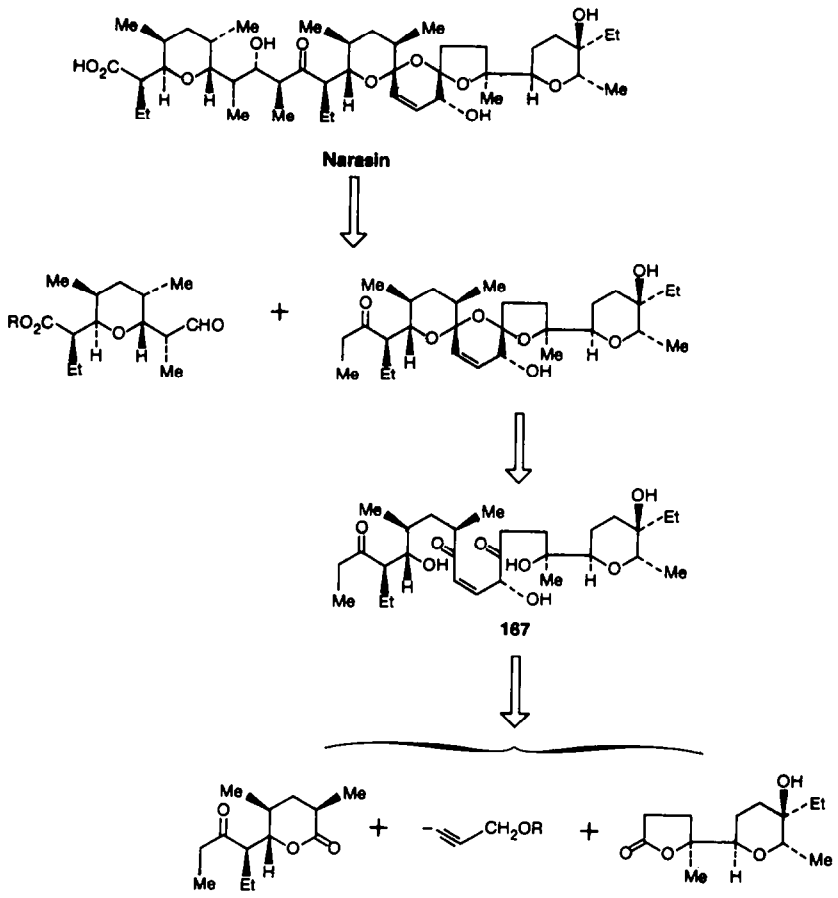
At this point, some comment regarding the configuration of spiroketal centres in the polyether antibiotics is required since this must be taken into account when designing a total synthesis. The natural configuration of spiroketals is due primarily to additive steric and anomeric effects which combine to provide the natural isomer having the most stable configuration about the spiroketal carbon. For example, the 1,7-dioxaspiro[5.5]undecane system is conformationally rigid and it exists



Scheme 42.


1) H_2O_2, ^-OH
2) $BF_3{\cdot}Et_2O$
3) LDA, THF, HMPA, MeI, -78°C
65%
1) $LiAlH_4$
2) H_2, PtO_2
3) t-Bu(Me)$_2$SiCl
DMAP, Et_3N
82%
1) $CrO_3{\cdot}2py$
2) MCPBA, $NaHCO_3$
3) LDA, THF, HMPA, -78°C, MeI
90%
1) $LiAlH_4$
2) Me_2CO, $CuSO_4$, TsOH
87%
1) $CrO_3{\cdot}2Py$
2) CH_2=CHMgBr
75%
1) EtCOCl, py.
2) LDA, THF, -78°C; ^{t}Bu(Me)$_2$SiCl, HMPA; Bu_4NF
3) CH_2N_2
90%
88%
1) EtCOCl, py.
2) LDA, THF, HMPA, -78°C; ^{t}Bu(Me)$_2$SiCl, HMPA; Bu_4NF
3) CH_2N_2
1) OsO_4, py; $NaHSO_3$; CSA
2) Me_2SO, $(COCl)_2$; Et_3N, -65°C → r.t.
3) Al(Hg), THF, H_2O, EtOH, $NaHCO_3$, 0°C
4) CH_2N_2
77%
166
p-TsOH, MeOH
95%
1) $MeOCH_2CH_2Cl$, $(i\text{-}Pr)_2NEt$
2) $LiAlH_4$
95%
1) silylate
2) BuLi, Heptane; $Hg(OAc)_2$, H_2O-THF (1:1)
93%
1) $CrO_3{\cdot}2py$
2)
78%
1) DDQ
2) Bu_4NF
80%
1) $CrO_3{\cdot}2pyr$
2)
1) CSA 30%
2) $Cr_2(OAc)_4{\cdot}2H_2O$
EtOH; K_2CO_3, MeOH
50%
Calcimycin

Scheme 43.



Scheme 44.

only in form **A** (Fig. 14), as opposed to two other possible conformations, **B** and **C**.[68] This is due to the fact that in conformation **A**, steric effects are at a minimum and the ketal function has the maximum number of (stabilizing) anomeric interactions.[69] A review of this subject is presented by Deslongchamps[68] and discussion of possible stereochemistries for the di-spiro systems of narasin, salinomycin, noboritomycin, antibiotic X-14766A, and epi-deoxy salinomycin has been reported by Kishi.[10]

Essentially, Kishi's analysis of conformational possibilities in the di-spiro systems of certain polyethers is based on X-ray data which suggests that the conformation of the di-spiro system in the so-called normal series is most likely **A**, Fig. 15. This has 3 anomeric effects while **A'** has 4. However, **A'** incurs serious steric compressions due to the three axial substituents on ring B. Similarly, for the epi-series, the more stable conformation is **B** which has 3 anomeric effects while **B'** suffers destabilizing steric interactions around the B and D rings. Whether **A** is more stable than **B** then, cannot be based solely on the total number of anomeric and steric interactions since in both, the number of effects is the same. An examination of dipole–dipole interactions due to the carbon–oxygen bonds in **A**, however, appears to make this conformation less favourable than **B**. Kishi

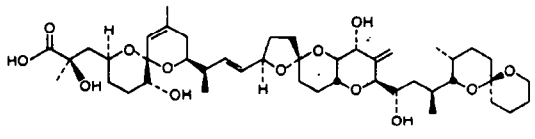
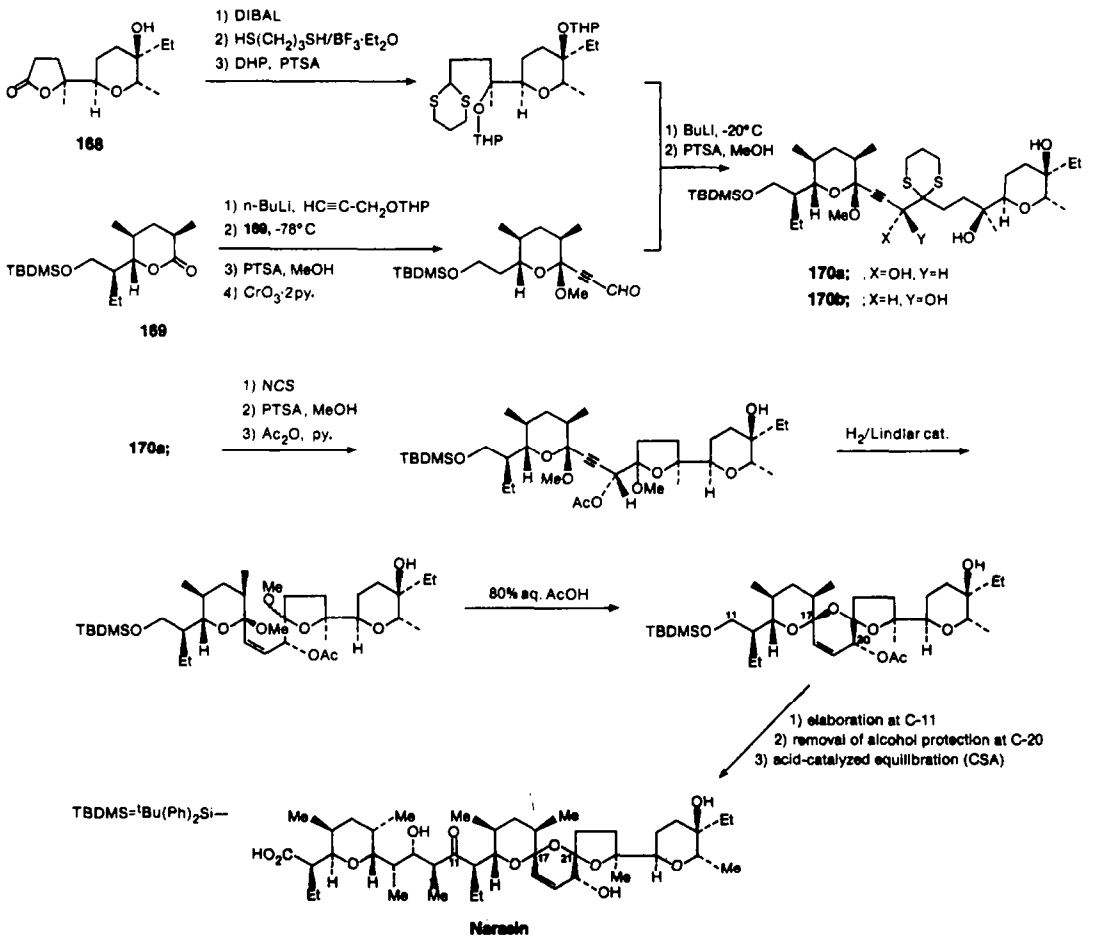


Fig. 13.



Scheme 45.

suggests that this dipole–dipole interaction is overruled by a favourable hydrogen-bond stabilization that occurs in conformation A. Such hydrogen bonding is available in the normal series (since the necessary —OH functionality is present), but is not possible in the epi-deoxy series (similar analyses of possible spiroketal configurations are presented in the review by Deslongchamps[68]). Kishi suggests than in any case where X = OH (see Fig. 15), a stereoisomer belonging to the normal series is thermodynamically more stable, while in any case where X ≠ OH, the epi series is more stable.

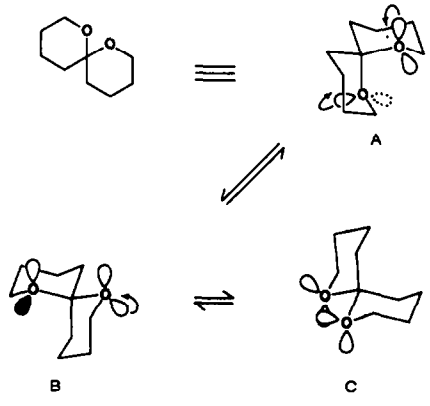
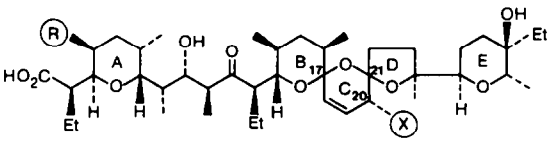
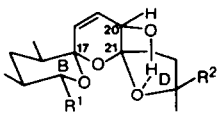


Fig. 14.

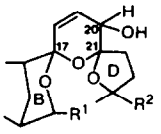


narasin; R=Me, X=OH
salinomycin; R=H, X=OH
epi-deoxysalinomycin; R=H, X=H

normal series
narasin
salinomycin
noboritomycin
antibiotic X-14766A

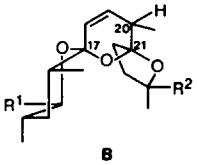


A

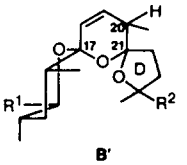


A'

epi series
epi-deoxysalinomycin



B



B'

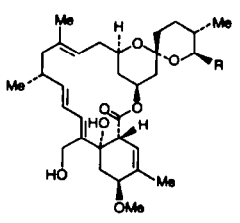
Fig. 15.

4.2. *Spiroketal systems of other natural products*

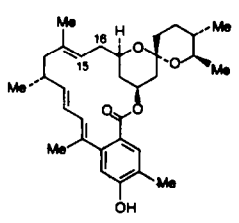
The milbemycins[70] (Fig. 16), avermectins[71] (Fig. 17), and talaromycins[72] (Fig. 18), together with a number of insect pheromones[73] (Fig. 19), contain functionalized spiroketal units. The synthesis of the spiroketal systems of these molecules has attracted much attention and the strategies that have emerged are summarized in the following paragraphs.

4.2.1. *Use of lactones and organometallics.* A recurrent theme in spiroketal synthesis involves reaction of an organometallic unit with a lactone. Such a process preserves the lactone carbonyl carbon which eventually becomes the spiro centre carbon. In those cases where optically pure spiroketals are made, the lactone and the organometallic are often derived from the chiral pool.

An example of the use of lactones with organometallics is the synthesis of (+)-milbemycin β_3 (Scheme 46) by Williams *et al.*[74] (*S*)-Citronellol **171** was elaborated into the *trans*-4,5-dimethyl valerolactone **172** and condensed with the α-lithiosulfinyl carbanion generated from **173**, which, in turn, was derived from (+)-glyceraldehyde. This afforded the open chain keto diols **174** which cyclized readily in wet benzene, in the presence of a catalytic amount of acid, to produce spiroketal **175**. The stereochemistry of the spiro centre was the thermodynamically favoured one in which both ether oxygens are axial to one ring. (Additionally, the stereochemistry of the sulfoxide bearing carbon underwent equilibration.) The spiroketal **175** was subsequently modified further for incorporation into the milbemycin β_3 structure.

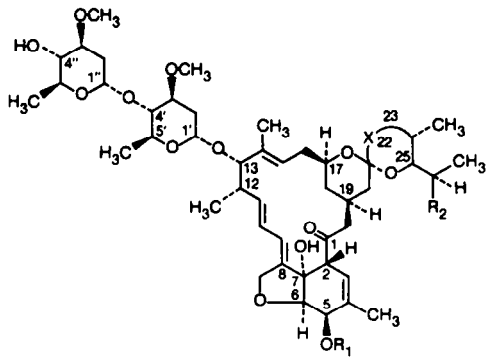


β_1: R = Me
β_2: R = Et



β_3

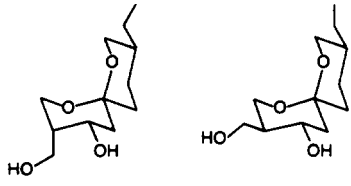
Fig. 16. Some milbemycins.



A : $R_1 = CH_3$
B : $R_1 = H$
a : R_2 = Et
b : R_2 = Me

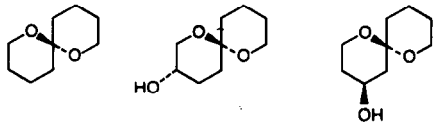
1 : X = —CH=CH—
2 : X = —CH(OH)CH$_2$—

Fig. 17. Some avermectins.



A B

Fig. 18. Talaromycins A and B.



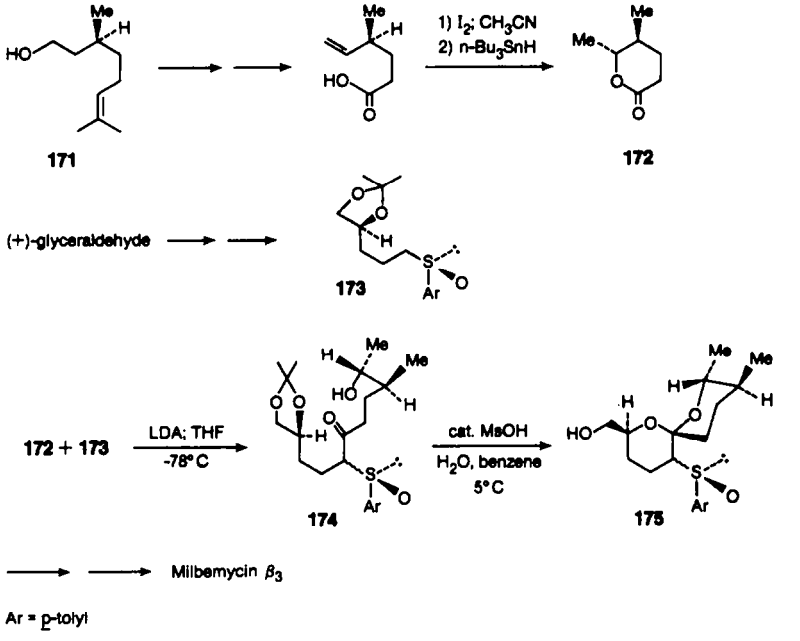
Olive Fruit Fly *Dacus oleae* Pheromone

Chalcogran from the bark beetle,
Pityogenes chalcographus

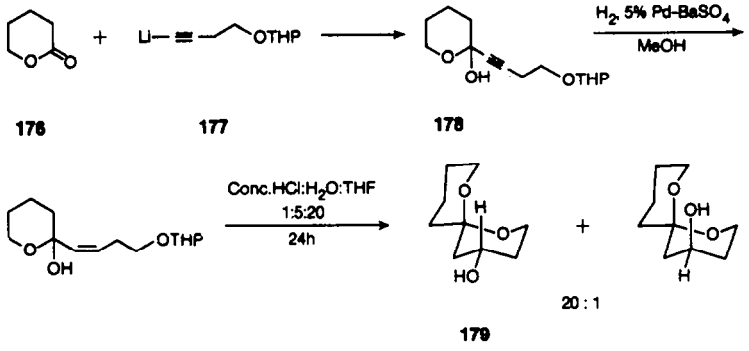
Fig. 19. Some insect pheromones.

Baker *et al.*[73b] employed similar lactone–organometallic methodology in their synthesis of a component of the olive fly pheromone **179** (Scheme 47). This compound was made by addition of the lithium acetylide **177** to α-valerolactone **176**, and semihydrogenation of the resulting acetylene **178** gave a monoene which, on treatment with acid, afforded the desired material **179** as the major product. Transformation of the monoene to **179**, involves Michael addition of water to an intermediate enone.

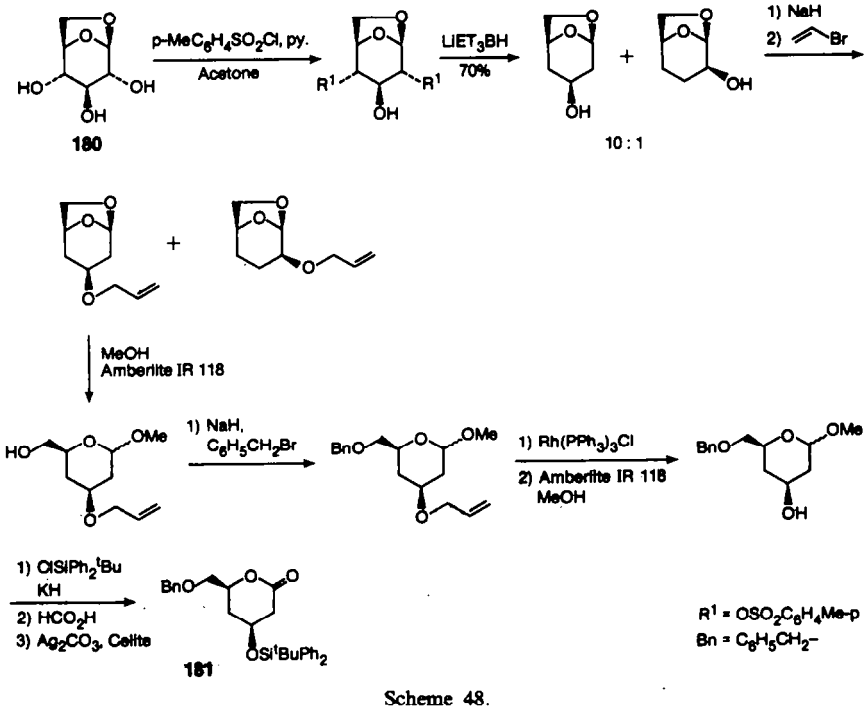
Baker subsequently used this general method in his work on milbemycins β_1 and β_3[75] and on avermectins B_{1b} and B_{2b}.[76] For example, the lactone **181**, prepared as shown from laevoglucosan



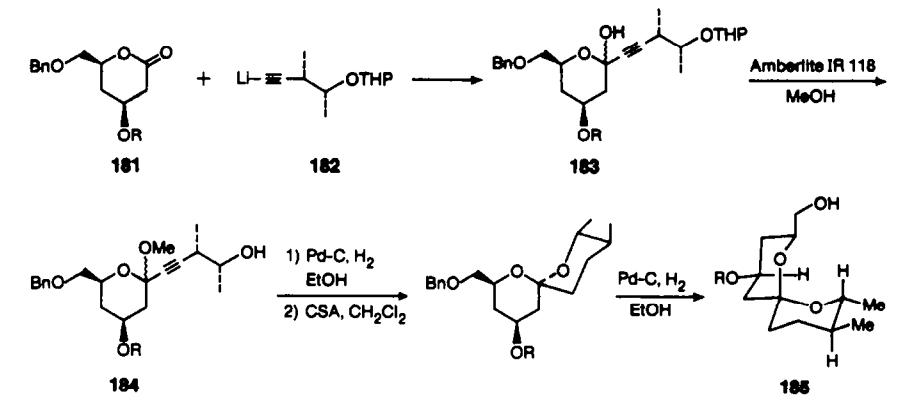
Scheme 46.



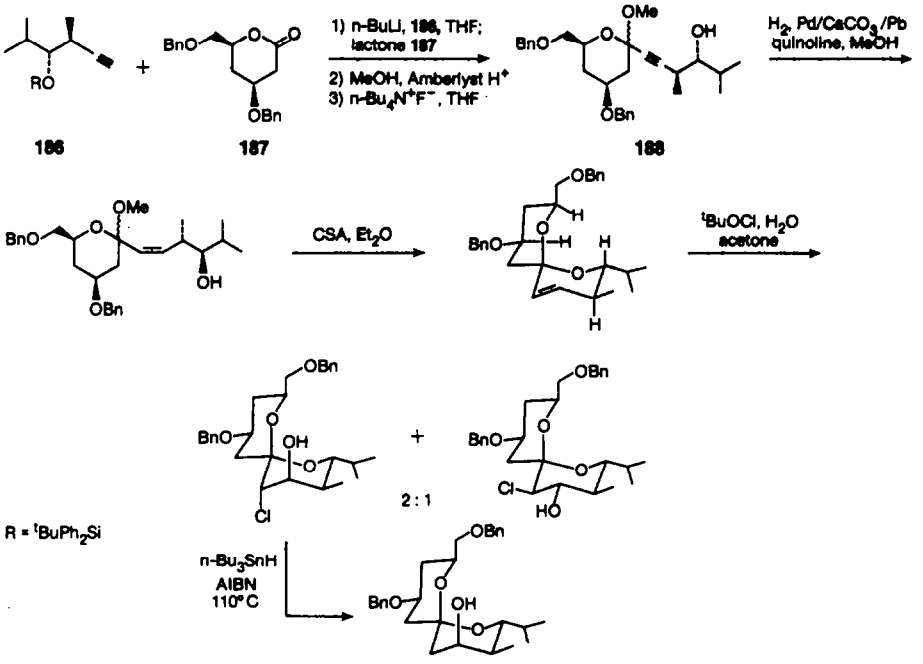
Scheme 47.



Scheme 48.



Scheme 49.



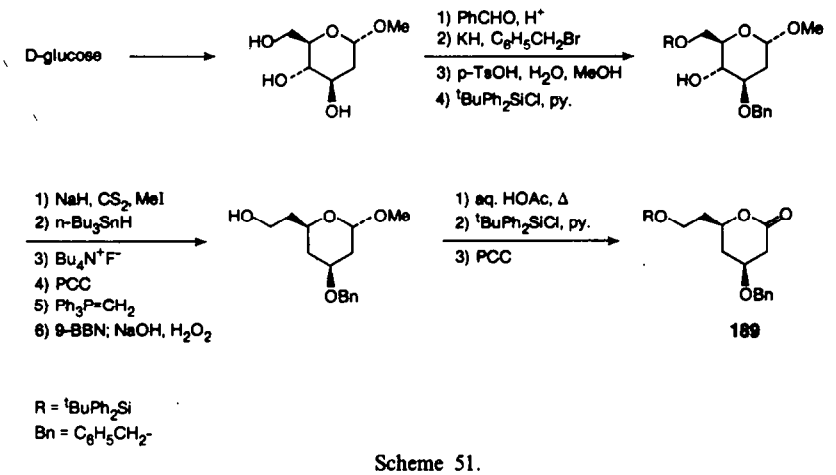
Scheme 50.

180 (Scheme 48), was coupled with the optically pure acetylide **182** (Scheme 49). The adduct **183** was converted into **184** which provided the desired milbemycin spiroketal **185** upon hydrogenation, exposure to acid, and removal of the benzyl protecting group.

In a related sequence[76a] (**186** and **187**; Scheme 50), the lactone–acetylide product **188** was semihydrogenated[76b] so that it could be elaborated into the unsaturated spiroketal system of avermectin B_{1b}, and then into the corresponding saturated spiroketal of avermectin B_{2b} (Fig. 17).

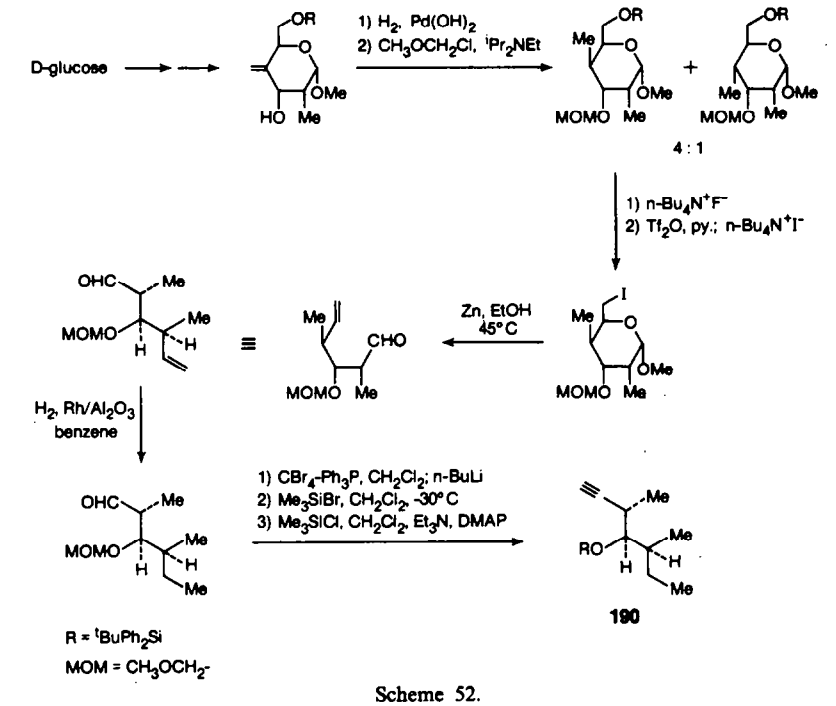
The spiroketal unit of avermectin B_{1a} was prepared in an independent but analogous manner by Hannesian's group.[77] The required fragments **189** and **190** were assembled from D-glucose† (Schemes 51 and 52), and the lactone–acetylide reaction then afforded **191** (Scheme 53). Semireduction and Lewis acid induced closure afforded the desired spiroketal **192**.

† In addition, the lactone **189** was also prepared from (*S*)-malic acid.



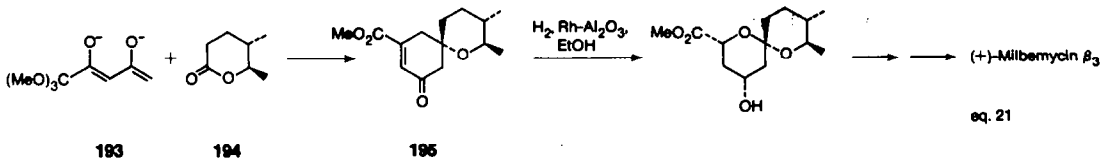
Scheme 51.

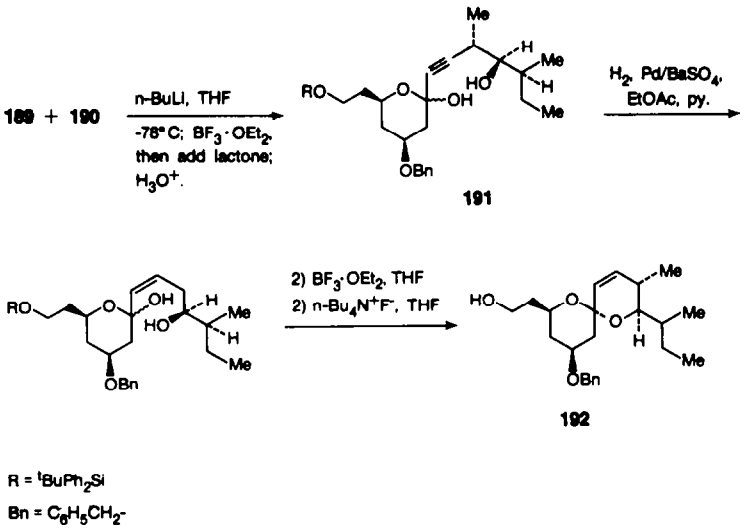
In an alternative route[78] to the (+)-milbemycin β_3 system, optically pure lactone **194** was reacted with the dianion **193** [equation (21)]. Condensation and cyclization occurred to give stereospecifically, and in one step, the spiroketal **195** which was modified to the optically active natural product.



Scheme 52.

An attempt to use the dianion **196** in a similar manner[79] to the above example was unsuccessful but the acetylide **197**, which is synthetically equivalent to the dianion, was used instead as shown in Scheme 54. The last stage of this route involves formation of an α,β-unsaturated carbonyl system **198** which serves as precursor to the spiroketal.

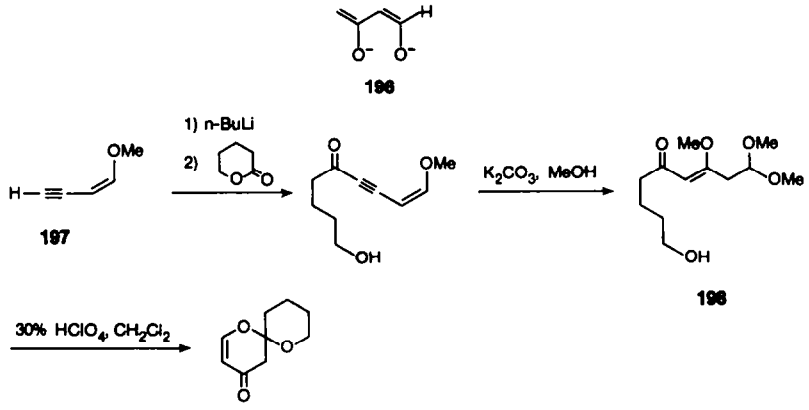




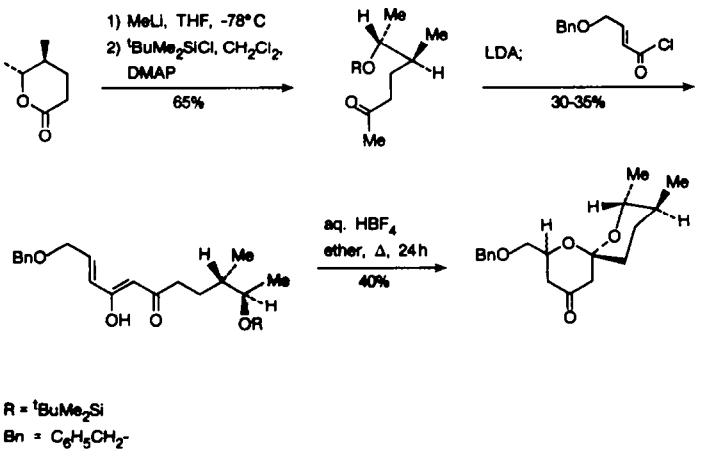
Scheme 53.

In the approach of Williams and Barner[80] to 1,7-dioxaspiro[5.5]undecan-4-ones, an α,β-unsaturated system is also involved as the intermediate which undergoes ring closure by Michael addition (Scheme 55).

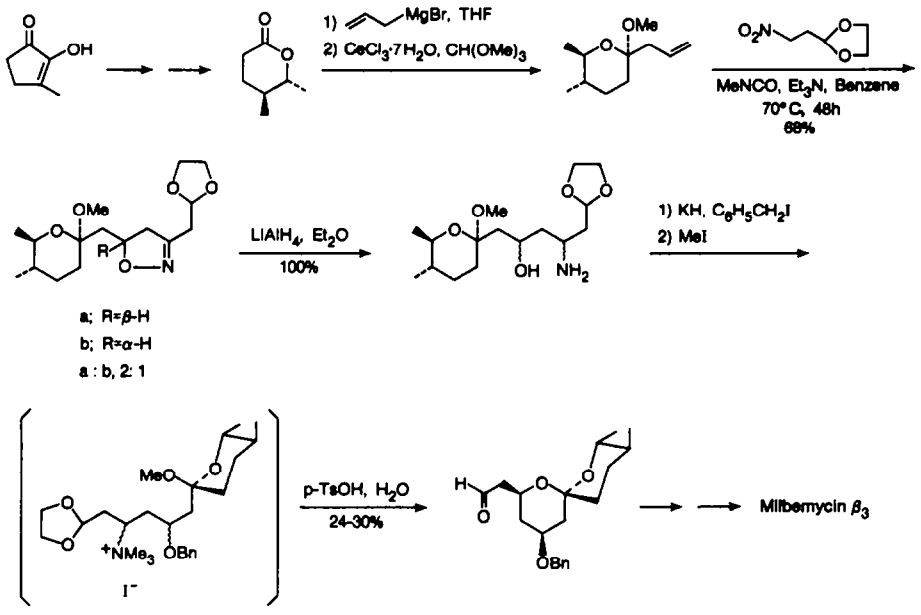
In the milbemycin β_3 synthesis of Smith *et al.*,[81] Michael addition of an anomeric hydroxyl was again used to generate the spiroketal, but the lactol unit was assembled in a different way (Scheme 56).



Scheme 54.



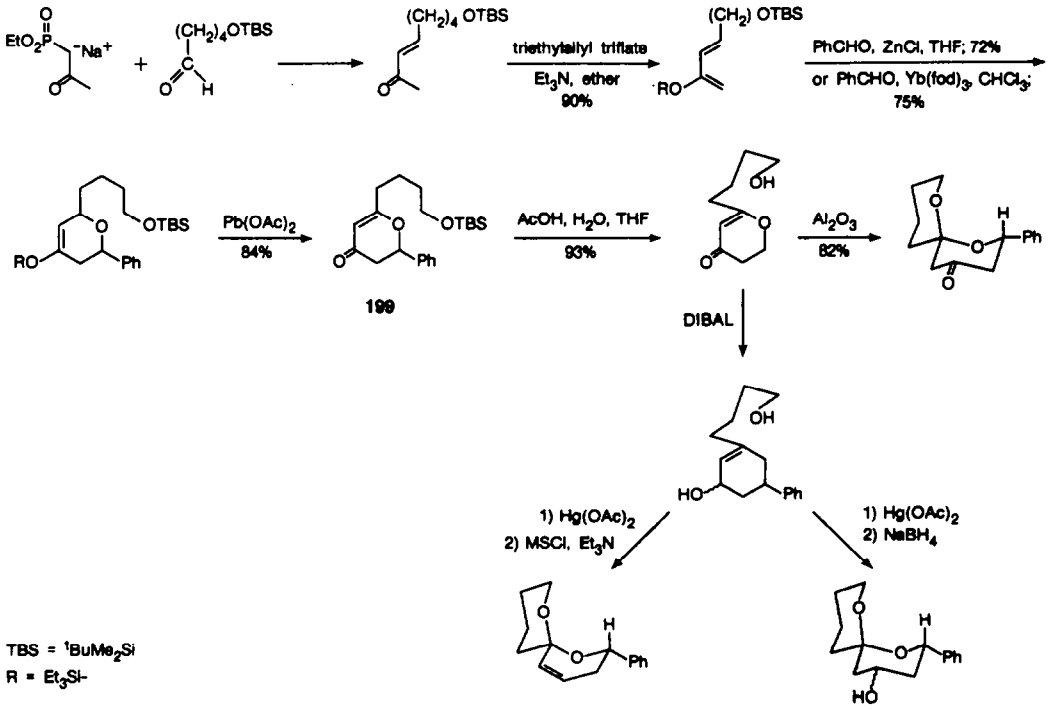
Scheme 55.



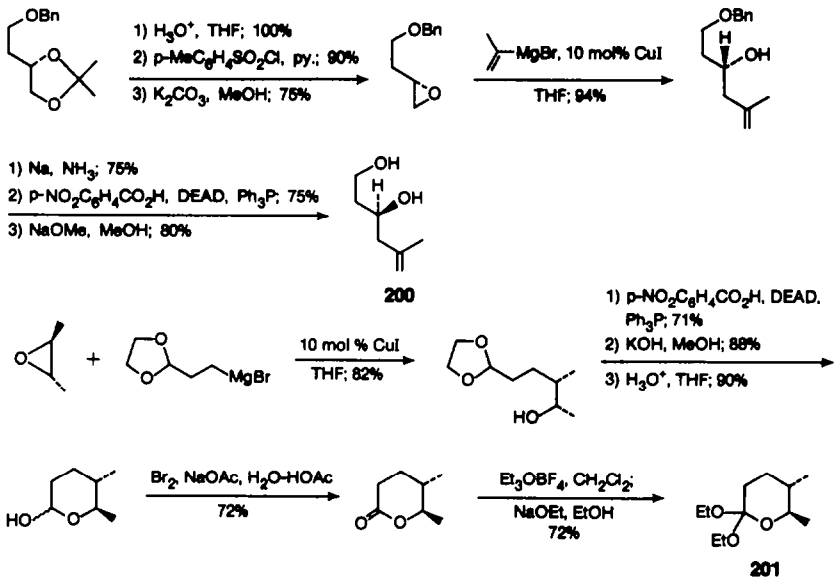
Scheme 56.

Similarly, a substance appropriately functionalized for intramolecular Michael closure to a spiroketal was employed in the methodology of Danishefsky and Pearson[82] (Scheme 57). They used a Diels–Alder approach to the key enone **199**.

An alternative strategy for employing a lactone unit in spiroketal synthesis is represented by Kocienski's[83] route to the (+)-milbemycin β_3 spiroketal. Subunits **200** and **201** were prepared by routine transformations as shown in Scheme 58. These were condensed in the presence of acid to afford a single ortholactone **202** (Scheme 59) which was then converted into an enol silane **203**. In the presence of boron trifluoride etherate at $-78°C$, the enol silane **203** underwent intramolecular



Scheme 57.

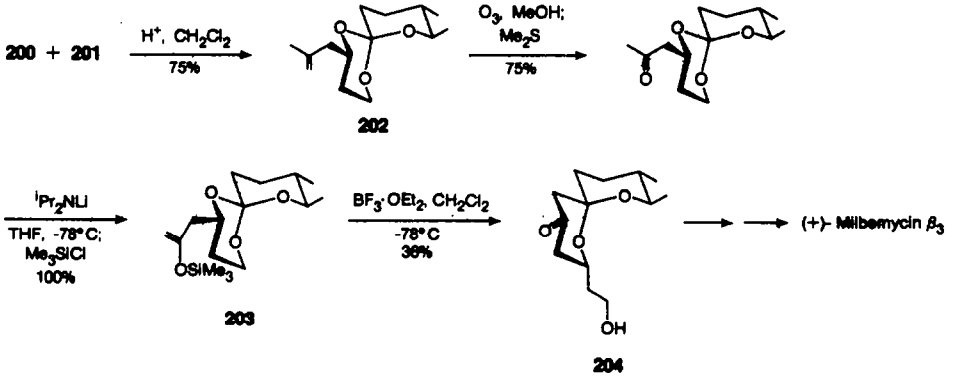


Scheme 58.

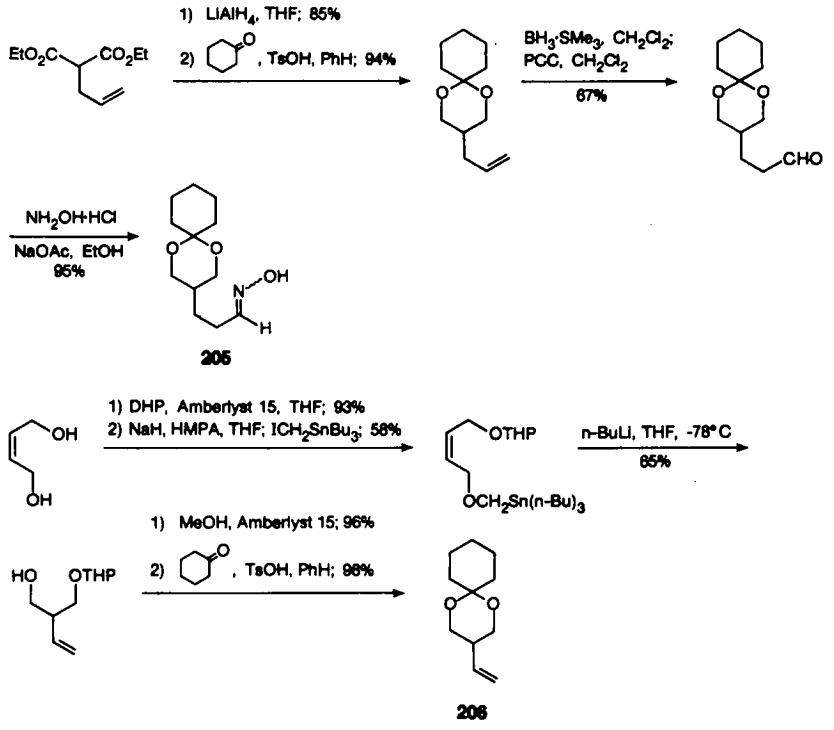
aldol condensation to spiroketal **204**, whose functionality permitted straightforward attachment of other portions of the final target.

The route to the ketal system of (±)-talaromycin B devised by Kozikowski and Scripko[84] uses nitrile oxide cycloaddition to join component units **205** and **206** (Scheme 60). The method illustrates a symmetrization process that permitted assembly of the stereochemically complex product **207** (Scheme 61) from material possessing only one asymmetric centre. The anomeric effect and the equatorial preference of non-anomeric substituents ensured that the desired product was formed.

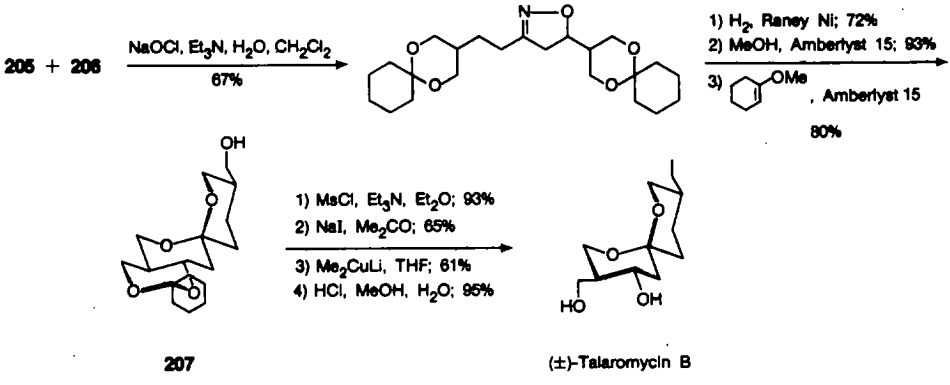
A symmetrization process had earlier been used by Schreiber *et al.* to make (±)-talaromycin B[85] (Scheme 62) and this sequence was subsequently modified so as to lead also to (±)-talaromycin A.[86] The modification allowed the authors to differentiate the pre-talaromycin A and pre-talaromycin B diastereotopic alkoxymethyl groups in the common intermediate **209** (Scheme 62). This was achieved by way of an acetonide migration reaction (Scheme 63). A mixture of products resulted and spiroketalization of the major component **211** (after benzylation of the hydroxyl), using a catalytic amount of camphorsulfonic acid in DMSO, afforded the desired talaromycin A spiro precursor **212C** as the major product of a 4.6 : 1.0 : 17.2 : 3.4 mixture of **212A : 212B : 212C : 212D**. The other spiroketal isomers were re-subjected to the same reaction conditions and the same equilibrium ratio was obtained. Both pre-talaromycin A and pre-talaromycin B spiro compounds **210** and **212C**, respectively, were further elaborated to afford the racemic natural compounds.



Scheme 59.

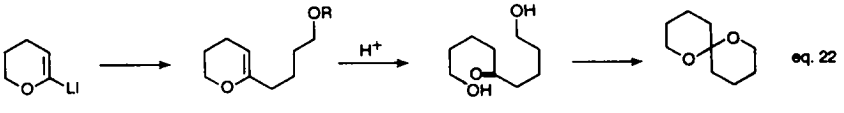


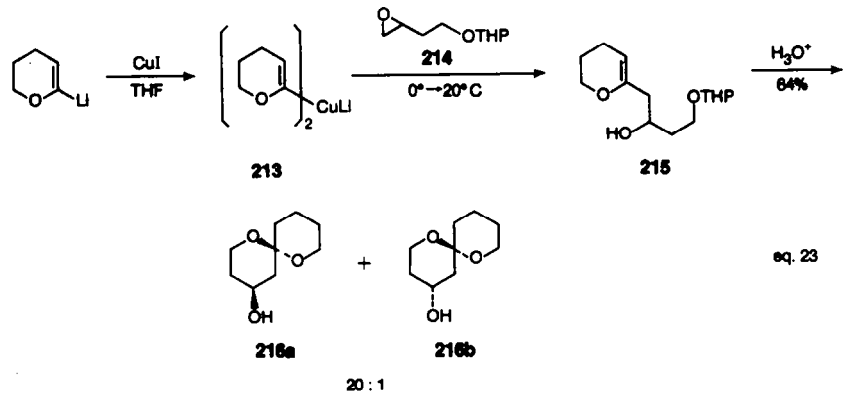
Scheme 60.

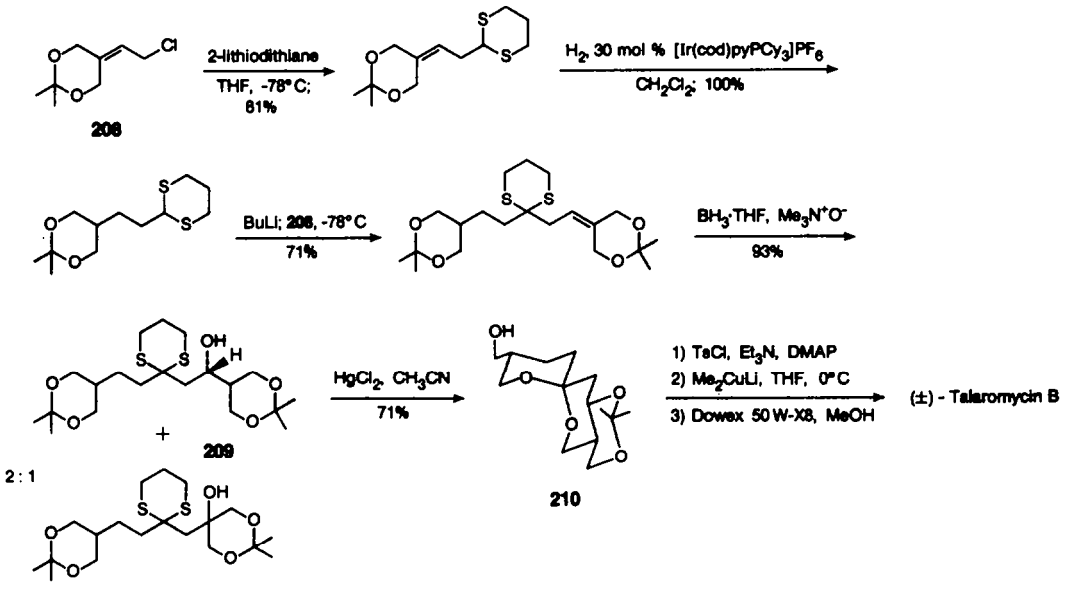


Scheme 61.

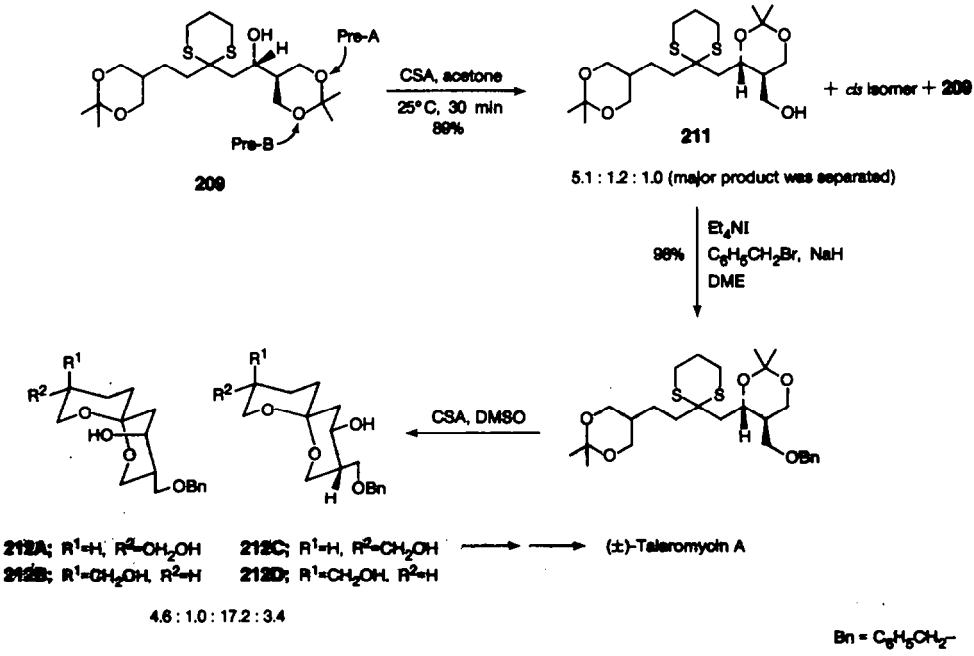
4.2.2. *Use of lithiated vinyl ethers.* A conceptually different approach to spiroketals is shown in equation (22). As indicated, a lithiated vinyl ether serves both as a masked ω-hydroxyketone and as a nucleophile for attachment of the chain destined to become the second ring of the spiroketal. Kocienski[87] used this powerful method in a concise route to the 4-hydroxy-1,7-dioxaspiro[5.5]undecane **216a** [equation (23)], a major component of the olive fly pheromone (Fig. 19). The relatively stable and easily generated organocuprate **213** [equation (23)] reacted smoothly with the epoxide **214** to provide all the required skeletal atoms in the form of the enol ether **215**. Two spiroketals **216a, b** were isolated upon acid hydrolysis of the THP protecting group, the major one being identical to the natural material.



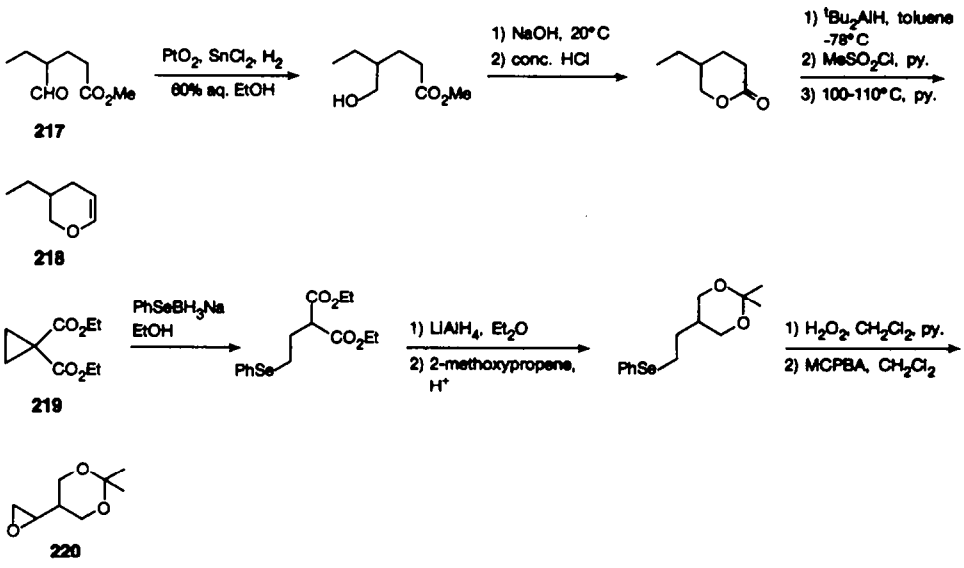




Scheme 62.

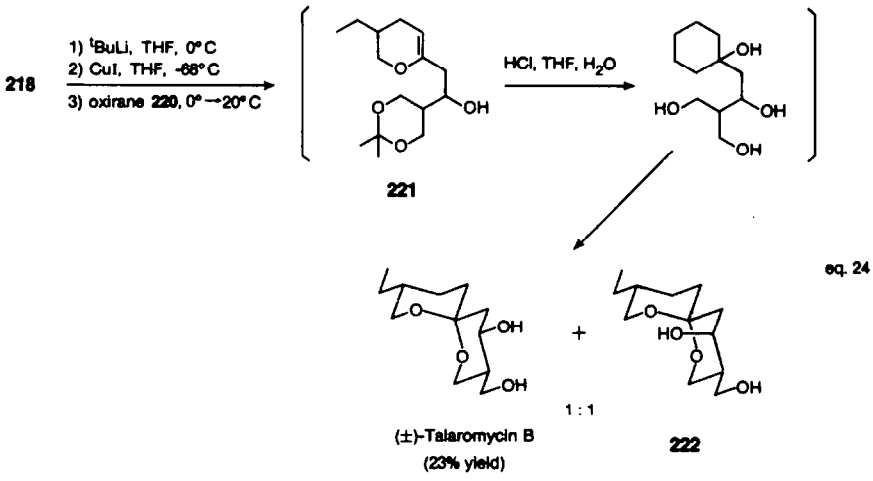


Scheme 63.



Scheme 64.

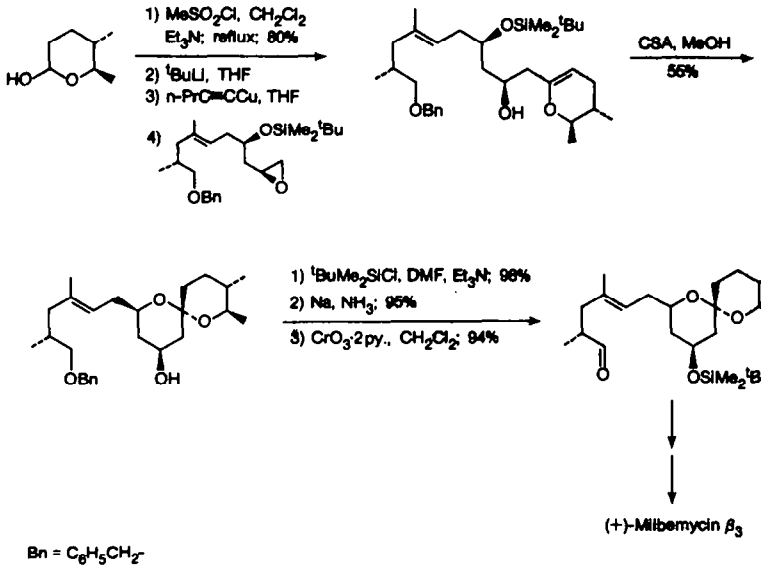
This versatile strategy was also used by Kocienski[88] in the synthesis of racemic talaromycin B from inexpensive and commercially available starting materials. The key dihydropyran **218** was prepared by a short sequence (Scheme 64) from aldehyde **217** in 36% overall yield and the oxirane **220** was made (Scheme 64) from the commercial cyclopropane carboxylic acid **219** (26% overall yield). The two fragments were coupled by the organocuprate procedure that had been used for the olive fly pheromone and the hydrolysis of the resulting intermediate **221** gave (±)-talaromycin B in modest yield, together with the isomer **222** [equation (24)].



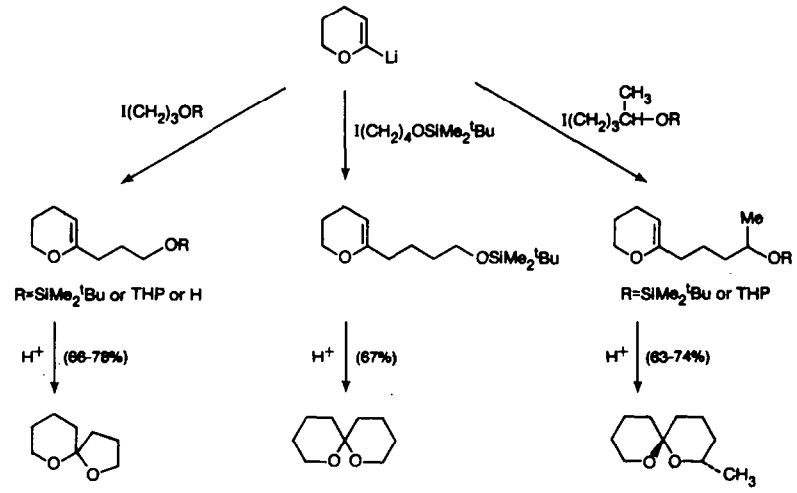
In a closely related sequence, the same group[89] used this vinyl ether methodology to prepare the spiro system of (+)-milbemycin β_3 (Scheme 65).

The use of lithiated vinyl ethers to make spiroketals (Scheme 66) was reported independently by Amouroux.[90]

4.2.3. *Lactol–Wittig route.* Wittig and Horner–Wittig reagents derived from lactols have proved useful in the construction of spiroketals. Again several related processes have been published.[91] The general route is as follows (Scheme 67). Treatment of a lactol with triphenylphosphine and hydrogen chloride (or hydrogen bromide) affords the Wittig salt **223** in good yield. (The same result can also be obtained by use of 2,3-dihydropyran under acidic conditions with the phosphine.) Conversion to a diphenylphosphine oxide **224** follows by treatment with hot aqueous sodium hydroxide although

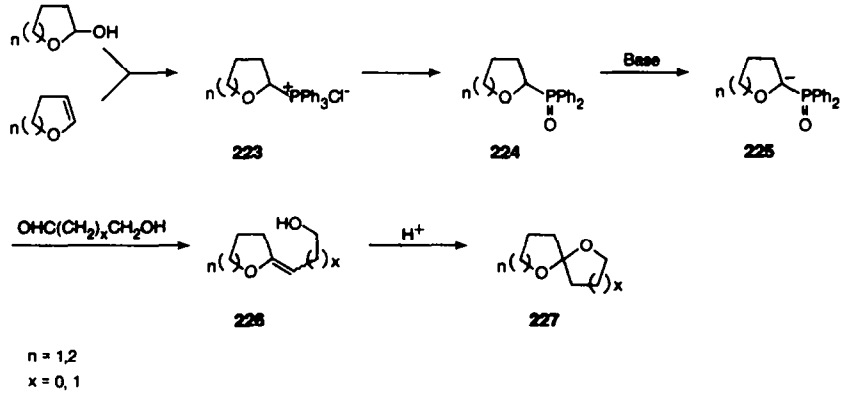


Scheme 65.

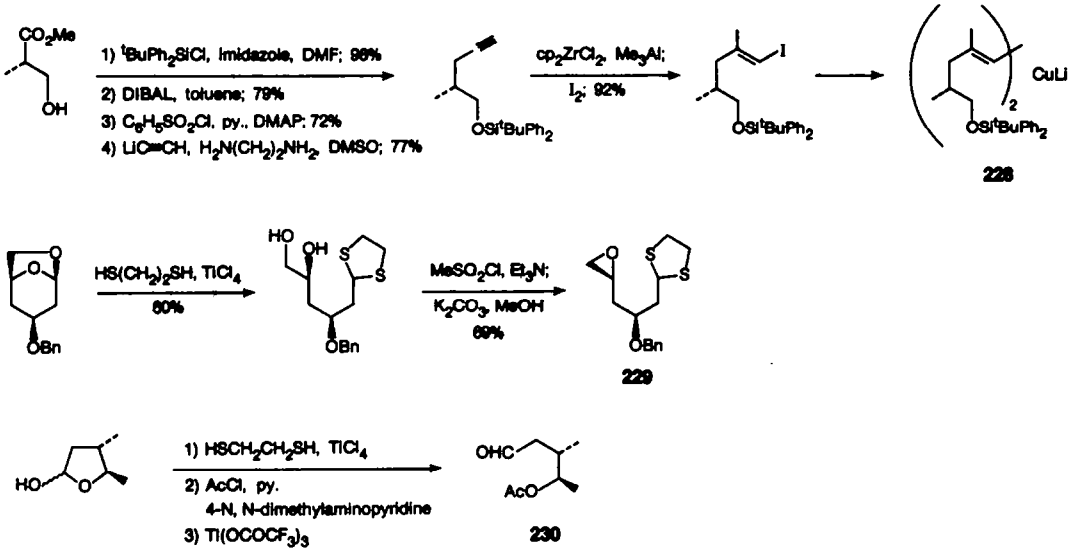


Scheme 66.

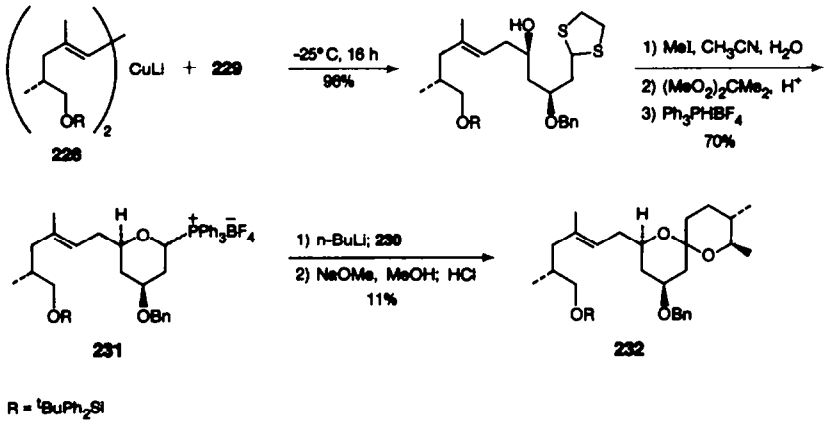
in some examples the phosphonium salt **223** is used directly. Deprotonation (LDA) generates the required phosphorus reagent **225**. Condensation with an appropriate aldehyde or lactol, followed by base treatment to effect elimination of diphenylphosphinic acid, affords a mixture of enol ethers **226**. The corresponding spiroketal **227** is generated by treatment with acid.



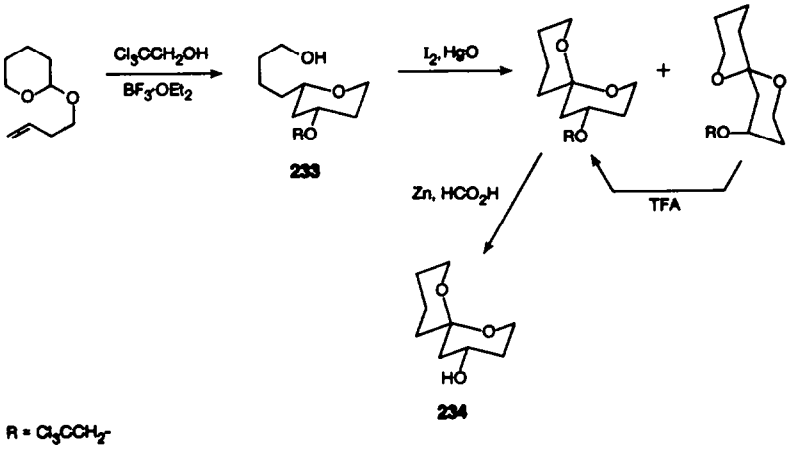
Scheme 67.



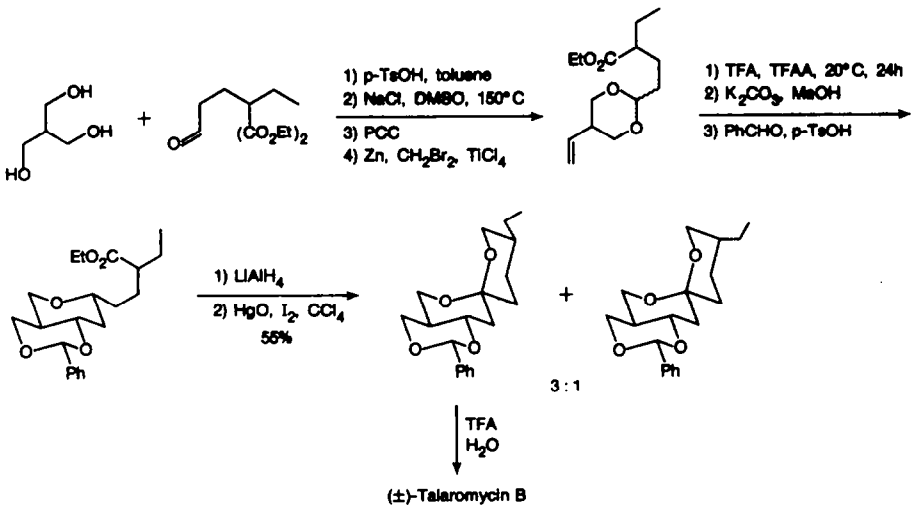
Scheme 68.



Scheme 69.



Scheme 70.

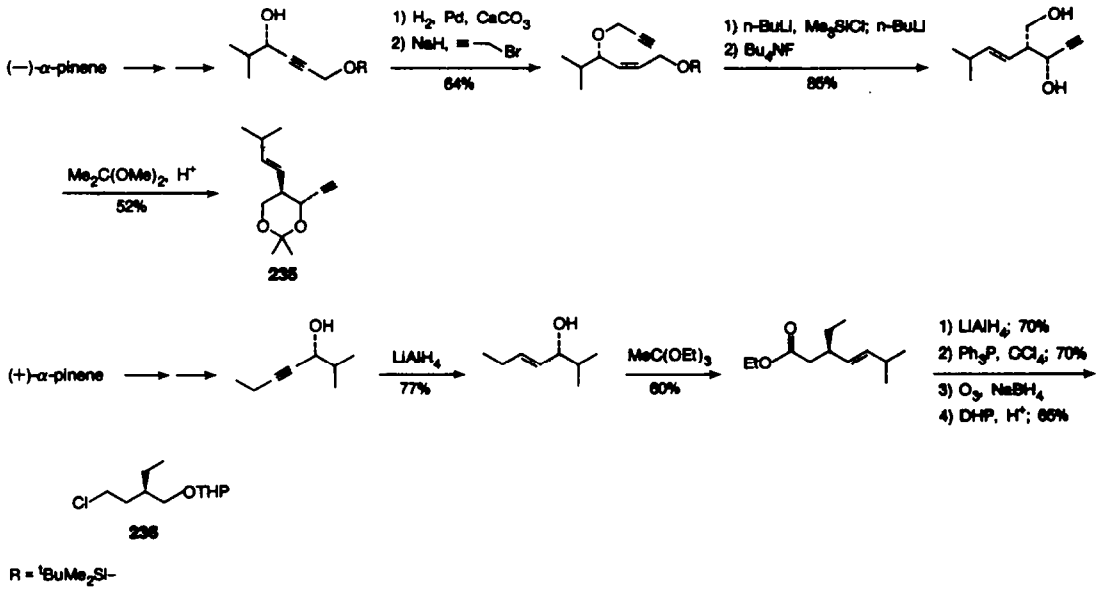


Scheme 71.

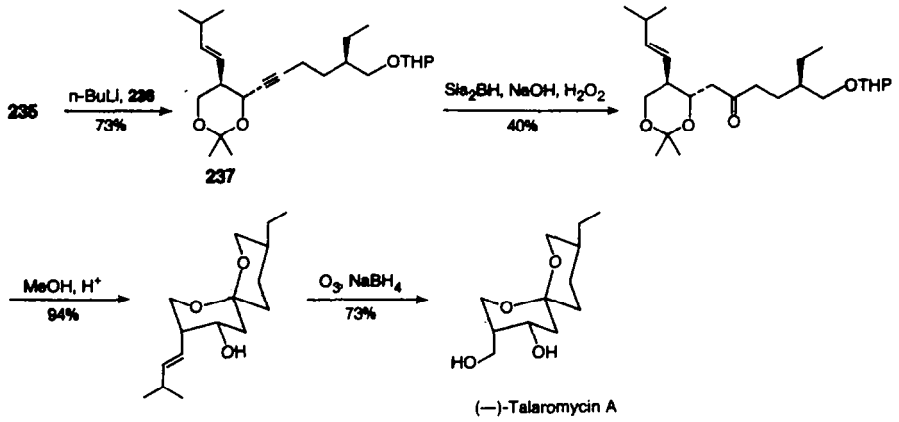
The technique has been applied to the avermectin and milbemycin spiroketal systems.[91c] In the work of Ley's group on the milbemycin series,[91e] the Wittig component was prepared from laevoglucosan. The authors chose to introduce the spiroketal group after formation of the C-15 to C-16 bond (Fig. 16) since previous work suggested that difficulties arise in the formation of this bond when attempts to link the intact spiroketal unit to other portions of the molecule are made. They effectively combined the three fragments **228**, **229**, **230**, which were prepared as shown in Scheme 68. The homocuprate fragment **228** was coupled with the epoxide **229** in very high yield (Scheme 69) and this adduct was then converted to the corresponding phosphonium salt **231**. This was then quenched with fragment **230** and worked up in base. Treatment with acid then afforded the northern portion **232** of milbemycin.

4.2.4. *Intramolecular cation–olefin cyclization.* Kay *et al.*,[92] have used intramolecular cyclization of olefinic cations to afford spiroketals as shown in Scheme 70. A crucial step involves cyclization of **233** via a hypoiodite. Deprotection of the major product affords a component, **234**, of the olive fly pheromone (Fig. 19).

The same procedure has been used to make (±)-talaromycin B (Scheme 71).[93]



Scheme 72.



Scheme 73.

4.2.5. *Acetylene hydration route.* Midland and Gabriel[94] reported a synthesis of (−)-talaromycin A which was prepared in high optical and diastereoisomeric purity by the following route. Chirality transfer was used in preparation of the subunits (Scheme 72) and the optically active fragments **235** and **236** were coupled by acetylide alkylation (Scheme 73). The triple bond in the product **237** served as a precursor of the carbonyl needed for internal ketalization.

4.2.6. *Miscellaneous routes.* A number of miscellaneous routes to pheromone spiroketals have been reported but these methods have not, as yet, been applied to the synthesis of complex natural products.[95]

Acknowledgement—The author wishes to thank Professor D. L. J. Clive for his advice during the preparation of this manuscript.

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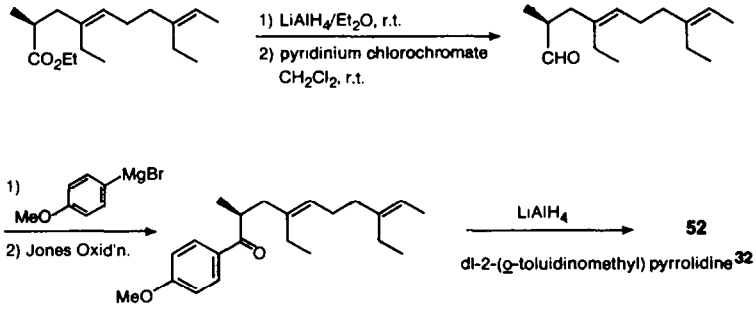

The ratio of **52** and its isomer by this method was at least 10 : 1 (97% yield). Optical resolution of **52** was achieved by preparative HLC separation of the *l*-α-methylbenzylurethane derivative.
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