SYNTHESIS TOWARDS THE ANTIBIOTIC M139603

A thesis presented by

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ABSTRACT

The biological properties and chemical syntheses of a polyether ionophore antibiotic, monensin, are reviewed in chapter one.

The thesis then outlines the biological properties of the ionophore M139603 and its chemical degradation studies undertaken in this laboratory. The main part of chapter two describes our efforts to synthesise the central tetrahydropyranyl fragment of the ionophore.

Firstly an approach is described in which the C15, C16 bond (M139603 numbering) is formed by the union of a C15 sulphone anion with a leaving group on C16. The route was discontinued owing to poor yields in the coupling reaction of 1-benzyloxy-4-(S)-methyl-5-phenylsulphonyl-2-E-pentene (46) with glycerol derivatives (23).

Secondly, the synthesis of a model compound, 2(R)-(2' -^{t}butyldiphenylsilyloxy-1' -acetyl)-6-(S)-(dimethoxymethyl)tetrahydropyran (78) is described from (±)3-benzoyloxy-cyclohexene (68). The allylic benzoate (68) is ozonolysed in methanol with an acid catalyst to afford (±)-5-benzoyloxy-6,6-dimethoxy-hexanal (70). (70) is elaborated to (±) 8,8-dimethoxy-oct-2-(E)-en-1,7-diol (73) which undergoes ring closure in a modified Sharpless epoxidation reaction containing 2.2 equivalents of titanium isopropoxide and (+) diethyl L-tartrate. It is shown that the carbonyl grouping of ketone acetal (78) will react with trimethylsilyl-methylene magnesium chloride in a Peterson olefination reaction, and that the aldehyde group can be liberated using $PdCl_2(CN)_2$ in acetone.

Lastly, a ten step synthesis of a chiral tetrahydropyranyl fragment of M139603, (20), is described from known 4-(R)-methylcyclohexanone, employing the methodology developed for the model ketone (78).

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Professor Steven Ley for his advice and encouragement throughout the past two and a half years.

Thanks are also due to the technical staff of the Chemistry Department for their skilful assistance.

Special thanks go to all my colleagues in the Whiffen Laboratory both past and present, for their enthusiasm and friendship. In particular, I would like to thank Graham Maw for his help on this project, and Dr. Kevin Lawson of ICI Plant Protection and Dr. José Godoy of Geneva for friendship and gifts of chemicals, wine and glassware.

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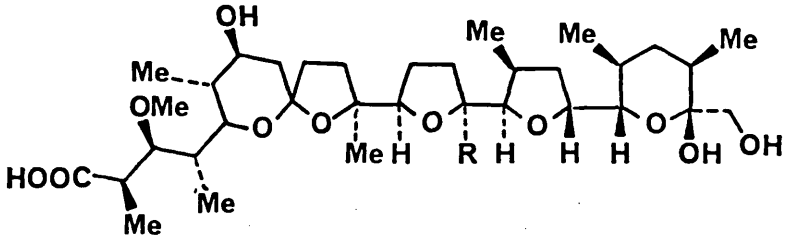
ABBREVIATIONS

Ac	Acetyl
AIBN	α,α -azobisisobutryonitrile
n-BuLi	n-Butyl lithium
9-BBN	9-Borabicyclo [3.3.1]nonane
Bn	Benzyl
CSA	Camphor sulphonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEAD	Diethylazodicarboxylate
DET	Diethyl tartrate
DIBAL-H	Diisobutylaluminium hydride
DMAP	N,N-Dimethyl-4-aminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
HMPA	Hexamethylphosphoramide
h.p.l.c.	High pressure liquid chromatography
LAH	Lithium aluminium hydride
MCPBA	m-Chloroperbenzoic acid
NPSP	N-Phenylselenophthalimide
NPSS	N-Phenylsulphenylsuccinimide
Py	Pyridine
RT	Room temperature
SAMP	(S)-1-amino-2-methoxymethyl-pyrrolidine
TBAF	Tetrabutylammonium fluoride
TBDMS	^{t}Butyldimethylsilyl
TBDPS	^{t}Butyldiphenylsilyl

REVIEW

Introduction

Monensin belongs to the class of antibiotics known as the carboxylic acid polyether ionophores. As their name implies, these compounds are able to form lipid-soluble complexes which provide a vehicle for a variety of cations to cross lipid barriers. Monensin is produced in high titer ~ 5000 μg/ml with three other homologues in the fermentation isolate of *Streptomyces cinnamonensis*.

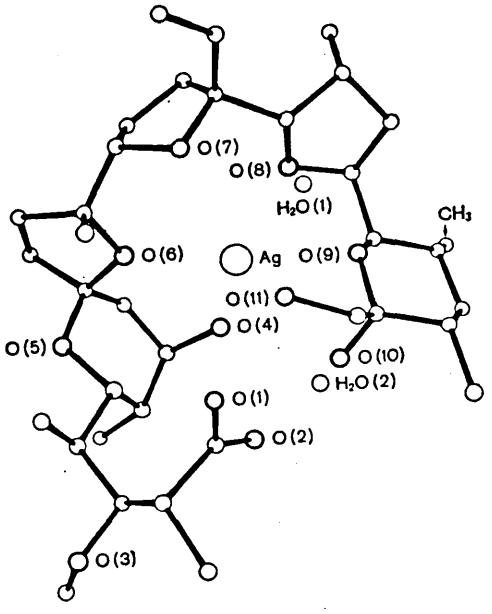


R = Et monensin A

R = Me monensin B

Its structure, shown above, was determined by X-ray crystallographic analysis of its silver salt[1] in 1967. As the crystal structure depicts, monensin exists in a cyclic form with head to tail hydrogen bonding between the carboxylate group and the two hydroxyls of the A-ring. The starred oxygen functions point toward the interior of the complex forming a distorted octahedral array about the silver ion, simultaneously exposing the lipophilic groups of monensin on its outer surface. Comparison of the X-ray structure of the silver salt with those of the sodium[2] and lithium[3] salts show that while the conformation of the B-ring and the D-E spiroketal rings remain little changed from one complex to another, adjustments to the torsional angles of bonds near the C-ring allow cations of various sizes to be accommodated. In the free

Crystal Structure of Ag^{+}Monensin^{-}

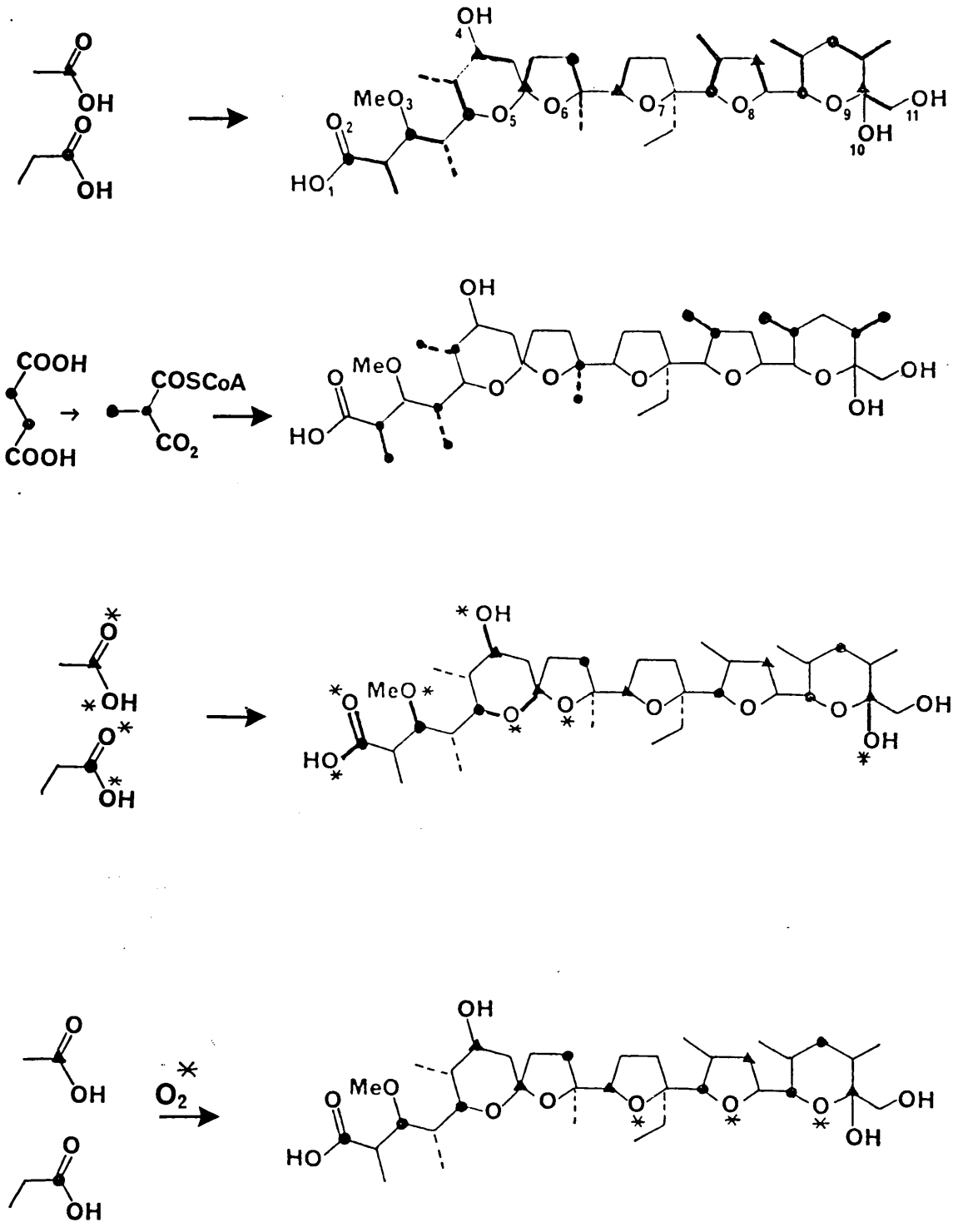


acid a molecule of water replaces the central cation and a hydrogen bond exists between the O(4) hydroxyl and the oxygen O(6) of the spiroketal D ring[4]. Nmr[5] and potentiometric[6] studies have shown that monensin's conformation in solution closely resembles that of the solid state.

Monensin A, the major component of the fermentation isolate, exhibits a large Na^{+}/K^{+} selectivity ratio[7,8], varying from 7 to 13 depending upon the solvent. A fuller selectivity sequence[6] is $Ag^{+} > Na^{+} >> K^{+} > Rb^{+} > Li^{+} \sim NH_4^{+}$. Unlike lasalocid, its complexes with divalent cations such as Ca^{2+} and Mg^{2+} are weak, presumably because it is unable to form 2:1 complexes thereby achieving charge compensation. This has important consequences when considering its pharmacological effects (vide infra).

Using ^{14}C-labelled precursors followed by partial degradation, investigators at Eli Lilly have shown that biosynthetically the carbon chain is assembled from five acetate, seven propionate and one butyrate molecules, while the C-3 O-methyl is derived from methionine.[9] Later, an elegant series of incorporation experiments by Cane and coworkers

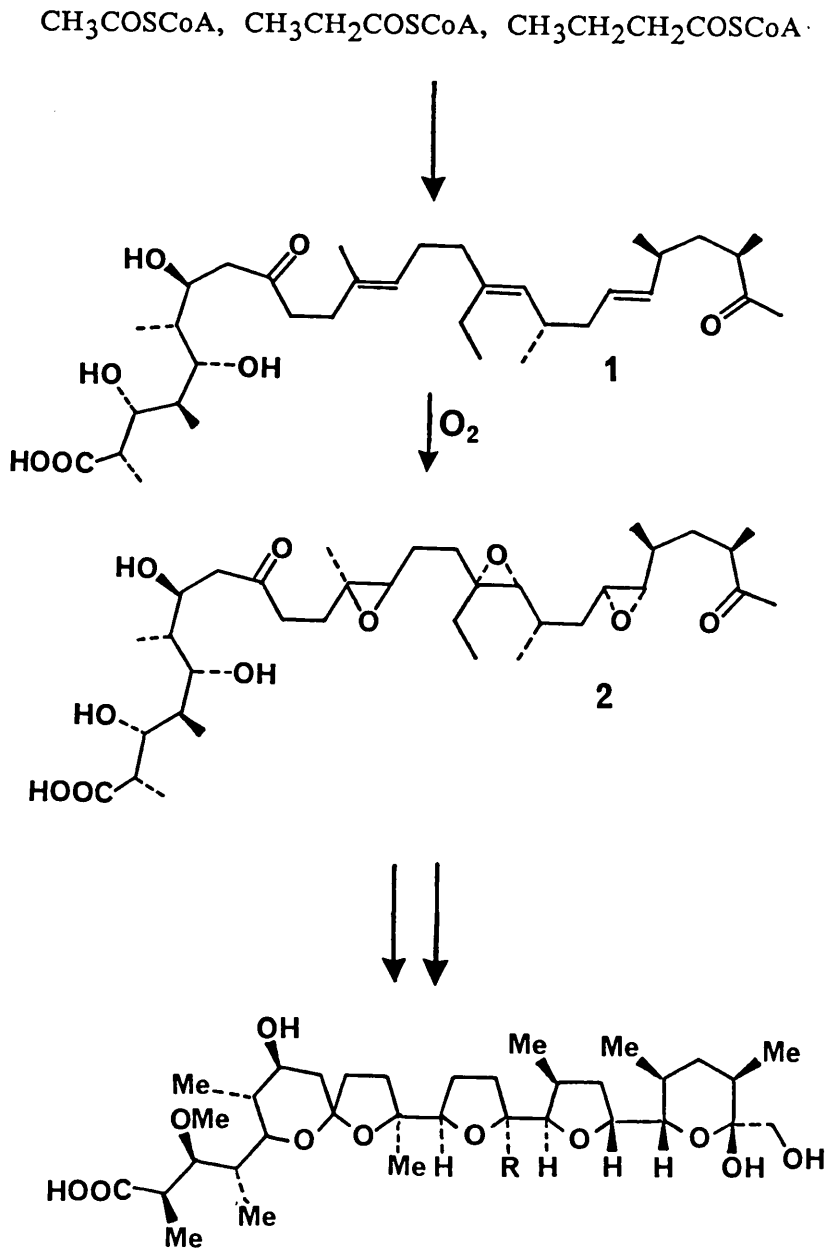
Scheme 1



confirmed these earlier findings.[10] Thus feeding [1-^{13}C] acetate to cultures of *Streptomyces cinnamonensis* gave monensin A labelled at carbons 7, 9, 13 and 25 as established by ^{13}C NMR analysis. Similarly, incorporation of [1-^{13}C] propionate resulted in enrichment of carbons 1, 3, 5, 11, 17, 21 and 23. Further incorporations of [1,2-$^{13}C_2$] acetate, [1,2-$^{13}C_2$] propionate and [2,3-^{13}C] succinate (a biosynthetic equivalent of [2,3-^{13}C] propionate) established the origin of all the carbon atoms of monensin. When [1-^{13}C, 1-$^{18}O_2$] propionate was fed, isotopically shifted peaks indicating the presence of ^{18}O at C-1, C-3 and C-5 were observed, while feeding of [1-^{13}C, 1-$^{18}O_2$] acetate gave rise to excess oxygen-18 at C-7, C-9 and C-25. The three remaining ether oxygens, O(7), O(8) and O(9) were shown to be derived from molecular oxygen by growth of the bacterium in an atmosphere of $^{18}O_2$ and subsequent ^{13}C NMR analysis of the labelled compound (Scheme 1).

These results are consistent with an intriguing suggestion by Cane[11,12] that monensin might be derived from a first formed *all*-E-triene (1) (Scheme 2). Epoxidation at each of its double bonds would give the 12R, 13R, 16R, 17R, 20S, 21S) triepoxide (2) and attack of its C-5 hydroxyl would initiate a cascade of ring closures to generate all five ether rings of monensin. Recently Sih has synthesised the triene (1)[13] and shown that it cannot be converted to monensin by *Streptomyces cinnamonensis*.[14] Although this does not invalidate the proposed biosynthesis, we may conclude either that triene (1) never becomes free of its synthetase enzymes or that (1) is not a substrate for the oxidase-epoxidation enzymes.

Scheme 2


CH3COSCoA, CH3CH2COSCoA, CH3CH2CH2COSCoA
HO
O
HO
OH
HOOC
1
O2
2
OH
Me
Me
Me
Me
OMe
O
Me H
R H
H
H
OH
OH
HOOC
Me
Me

Biological Activity

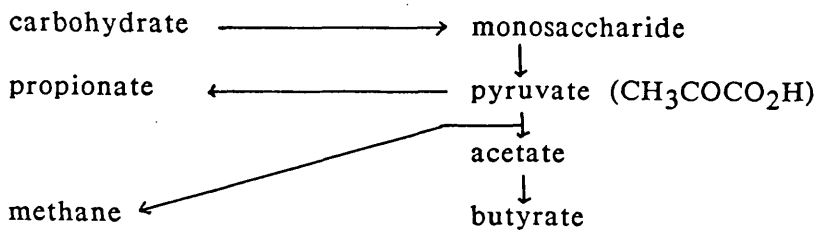
Monensin together with three other ionophores was first reported in 1968 to be orally effective in controlling coccidiosis,[15] a parasitic protozoan infection of the epithelial cells in the internal tracts of poultry. Eli Lilly patented the use of monensin for this purpose in 1970[16] and when the drug was put on the market the following year it quickly acquired the major part of the coccidiostat market. However, even greater sales have been realised as a growth-promoting feed additive for cattle.

In common with other polyether antibiotics, monensin exhibits activity against Gram-positive bacilli, cocci and filamentous organisms. It has been suggested that this microbial inhibition results from losses of essential monovalent ions such as K^+ with resulting uncoupling of oxidative phosphorylation[17]. Evidence to support this assertion comes from the observation that the antibiotic activity of a peptide-based ionophore, valinomycin, was suppressed by the addition of excess K^+ ions to the culture medium[18]. An alternative explanation is provided by Guffanti[19] who has studied the effect of nigericin upon the acidophilic bacterium *Bacillus acidocaldarius*. He established that by Na^+/H^+ exchange the ionophore abolished the pH difference between the cytoplasm (pH 6) and the culture medium (pH 3.5) causing a decline in respiratory activity and death through a drop in ATP content. The effect of nigericin could be reversed by raising the pH of the culture medium.

The precise nature of the effect of monensin upon *Eimeria tenella*, the strain of coccidia causing coccidiosis in poultry, is unknown. However, it has been shown that at a 0.01 ppm level, monensin completely inhibits schizont formation, an asexual stage in the life cycle of that coccidia[19].

The growth promoting properties of monensin as a feed additive for cattle result from an increase in the propionic acid content of the rumen fluid. The chemical degradation of dietary carbohydrate to the volatile fatty acids by rumen microflora is shown in Scheme 3. One of

Scheme 3



the major inefficiencies in rumen fermentation is the production of acetate (and hence butyrate) which is accomplished with the loss of one of the pyruvate carbons as methane. Any agent which directs fermentation in favour of propionate rather than acetate production will increase the nutritional value of cellulose to the cow.[20]

The minimum inhibitory concentrations (MICs) of monensin in the rumen fluid against methanogens such as *Methanobacterium* and butyrate forming organisms such as *Butyrivibrio fibrisolvens* is about 40 μg ml^{-1}. At such concentrations, propionate forming organisms like *Selenomonas ruminantium* are unaffected. Monensin is particularly effective against hydrogen and formate producing organisms; the MICs for the representatives of this class, *Ruminococcus albus* and *R. flavefaciens* is only 2.5 μg ml^{-1}. It has been suggested by Van Nevel and Demeyer[19] that this is the true cause of improved feed utilization.

Monensin also has interesting cardiovascular regulating properties. It is a powerful inotropic agent having a five-fold greater potency than lasalocid[21] despite having only one ten-thousandth of the Ca^{2+} carrying

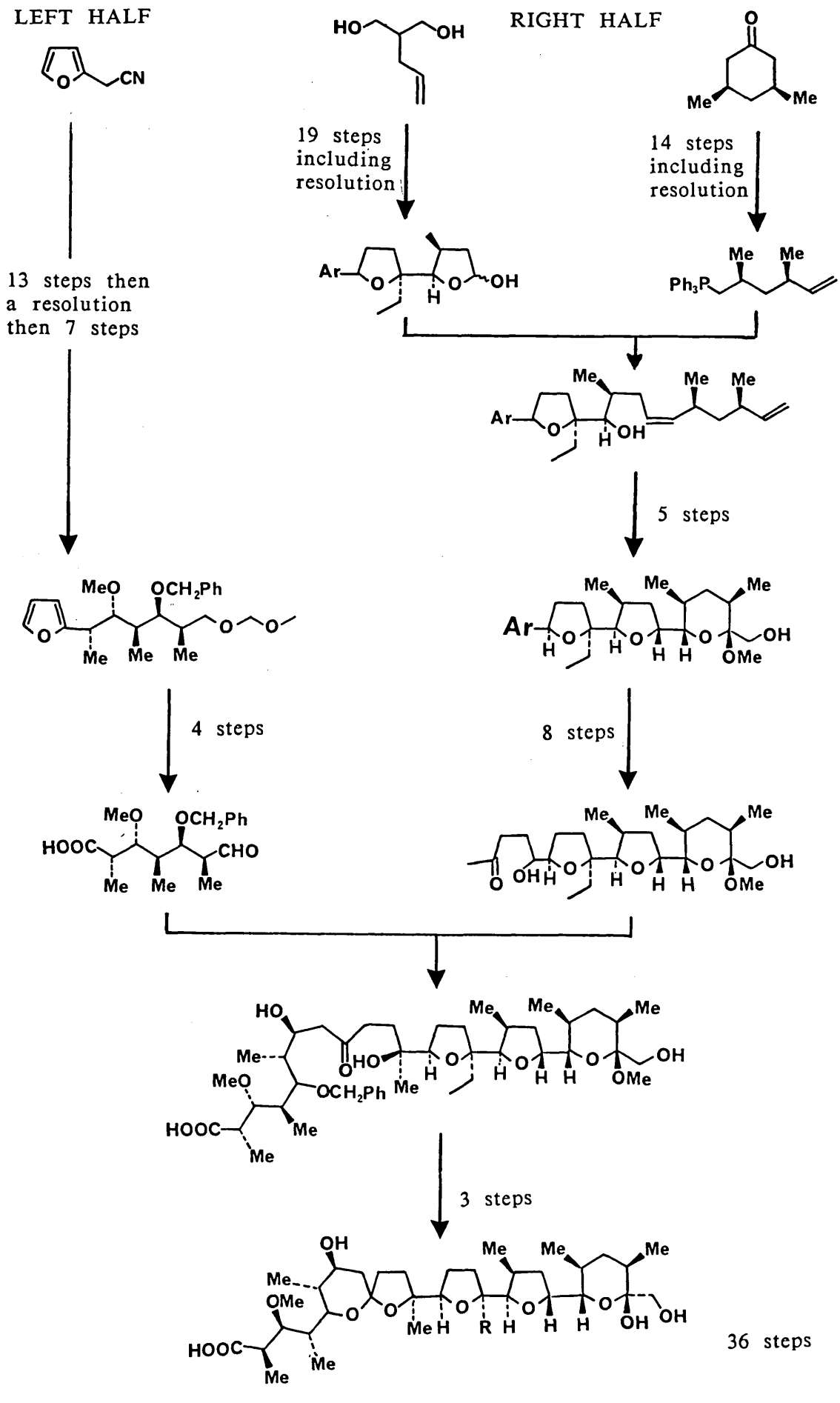
capacity of that ionophore. This is a puzzling result since it was believed that increased heart contractility was due to raised levels of intracellular Ca^{2+} making the metal ion directly available to the troponin of the microfibrils for a stronger contraction.[22] It has therefore been suggested that the increased Na^+ levels inside the cell brought about by ionophore mediated Na^+ for H^+ exchange, activate secondary ion exchanges. Examples of this include $Na^+out - Ca^{2+}in$ exchange between the intra- and intercellular fluid mediated by an endogenous sarcolemmal carrier[23] or direct release of Ca^{2+} from mitochondria.[24] Another indirect effect of monensin brought about by increased intracellular Ca^{2+} levels is the activation of phospholipase A_2 releasing prostaglandins from the renal medulla.[25]

Monensin also inhibits serotonin uptake by platelets since a sodium gradient across the cell membrane is required for this process.[19] This concludes the brief survey of the biological effects of monensin.

Chemical Syntheses of Monensin and its Precursors

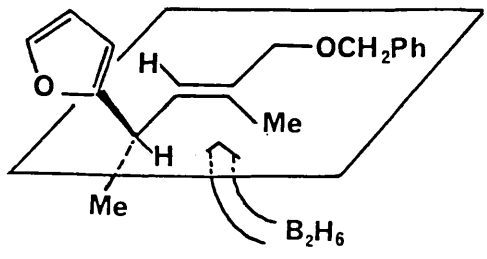
Monensin, possessing seventeen chiral centres along its twenty-six carbon backbone presents a formidable challenge to the synthetic chemist. To date, there have been two complete chiral syntheses by Kishi[26,27,28] (1979) and Still[29,30] (1980), and an, as yet, incomplete one reported by Ireland[31,32,33] (1985). Danishefsky[34] (1985), Bartlett[35] (1985), and Walba[36,37] in two papers (1980) and (1982), have reported racemic syntheses of various monensin subfragments and finally Sih[13] (1985) has completed an elegant synthesis of the proposed biosynthetic monensin precursor. As one would expect, all the total syntheses, for reasons of logistical efficiency, employ convergent approaches. Kishi, Still and Sih all used aldol condensations between a C-9 methyl ketone and a C-7 aldehyde unit with desired Cram-type selectivity to join a right-hand and

Scheme 4 : Kishi's Synthesis



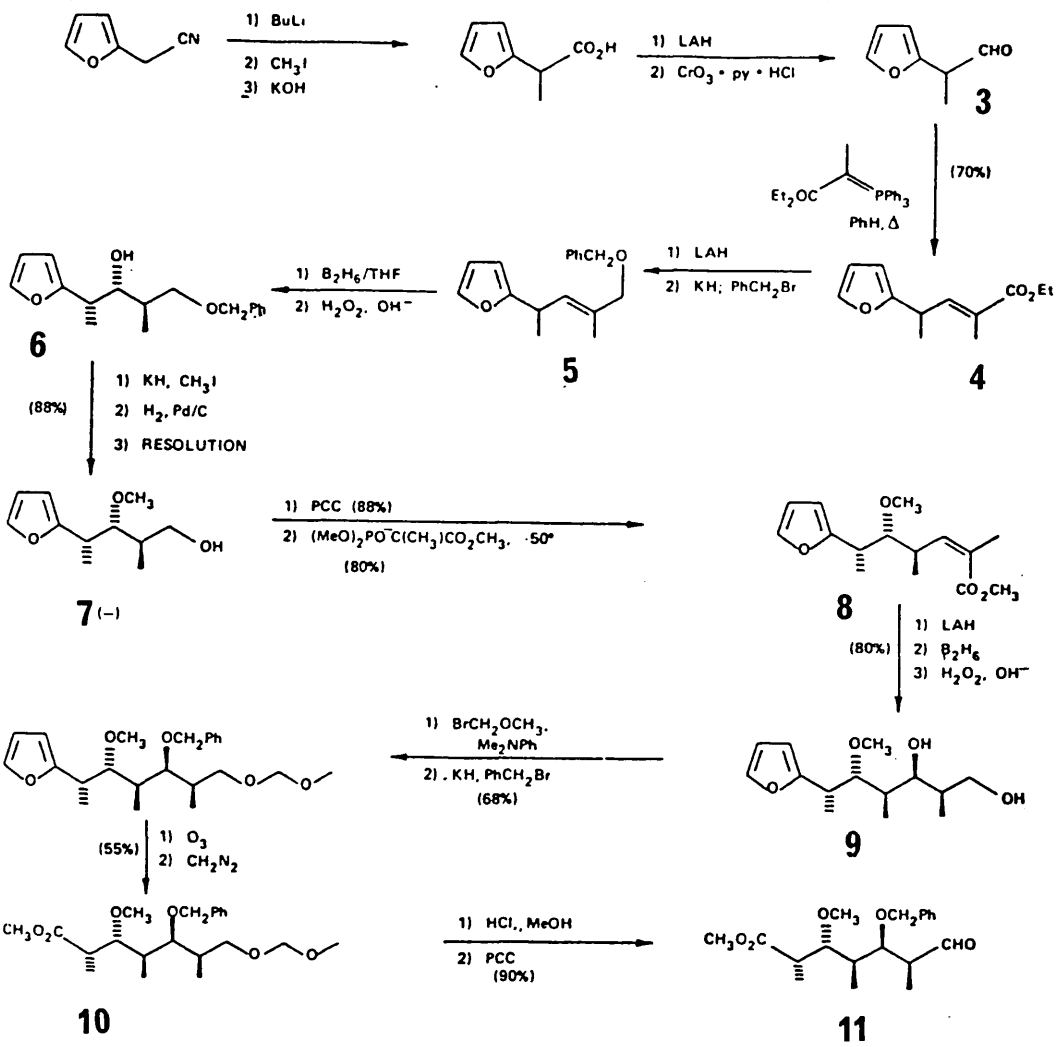
a left hand half of monensin. This is a sensible coupling since from the degradative work of Agtarap *et al*[1] (1967) extended later by Still[38] (1980), it was known that oxidation of monensin by chromium trioxide in acetic acid followed by standard chemical manipulation furnish both the required right- and left-hand advanced chemical intermediates. From the aldol adduct, acid-catalysed equilibration of the spiroketal centre and deprotection steps give monensin.

Kishi's synthetic strategy is shown in Scheme 4. The starting material for the left hand half[26] was 2-(2-furyl)propanal (3) (Scheme 5) prepared in five steps from 2-furylacetonitrile[39]. As we shall see, the furan ring serves as a bulky masked methylcarboxylate group. The Wittig reaction of (3) with carboethoxyethylidene triphenylphosphorane gave 70% of the *trans* (E) ester (4) together with 5% *cis* (Z). Hydride reduction of (4) and benzylation gave the benzyl ether (5). Hydoboration of (5) proceeded with excellent stereoselectivity from the sterically less hindered α face (furyl *vs* methyl) of the double bond to produce alcohol (6) in 85% overall yield from (5) in a ratio of 8:1 relative to the other diastereomer. The structural assignment was based



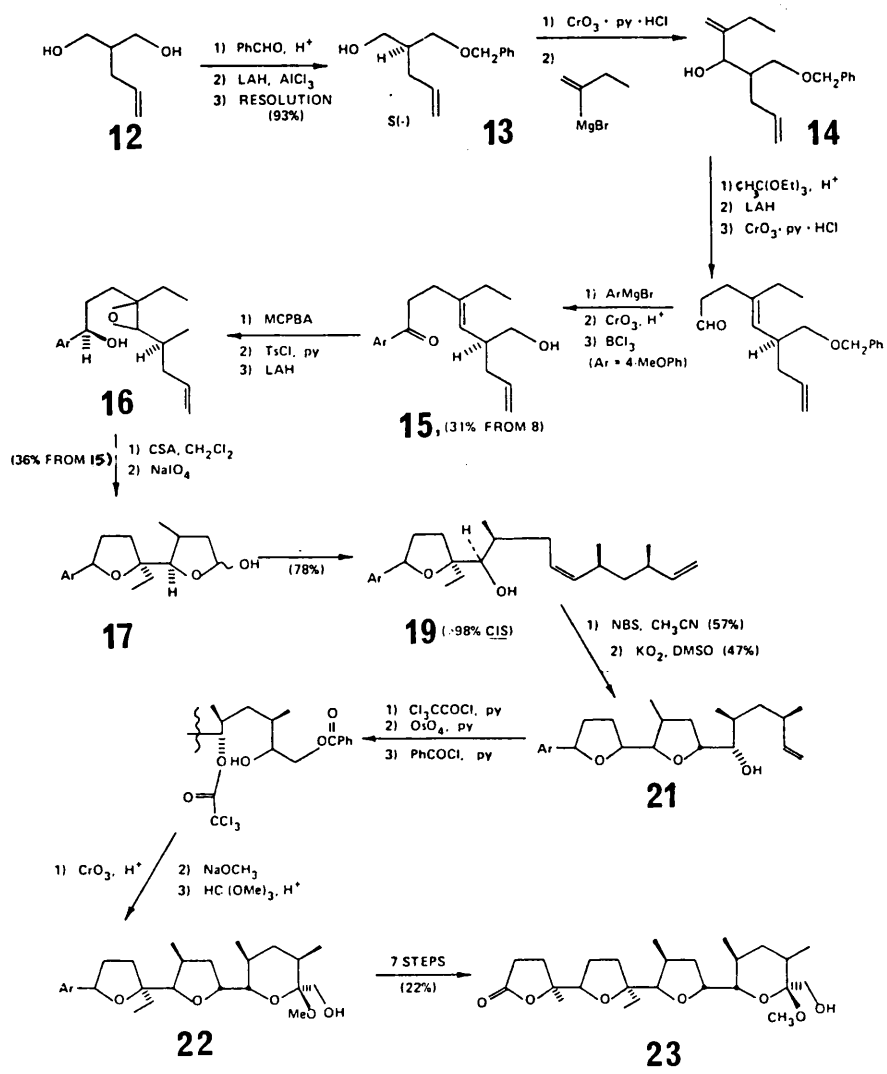
on literature precedent.[40] Alcohol (6) was methylated then debenzylated to give the primary alcohol (7). Optical resolution of (7) was achieved in three steps by formation of the diastereomeric α-methylbenzyl-

Scheme 5



Left half.

Scheme 6

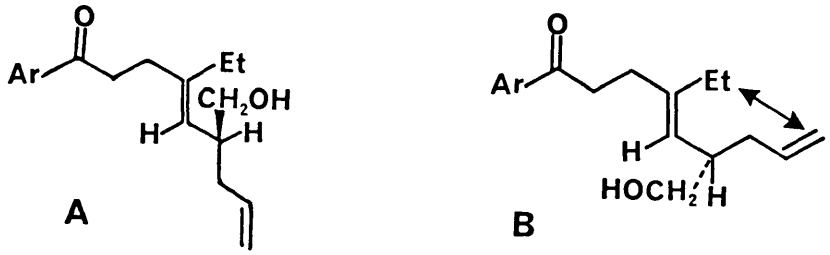


Right half.

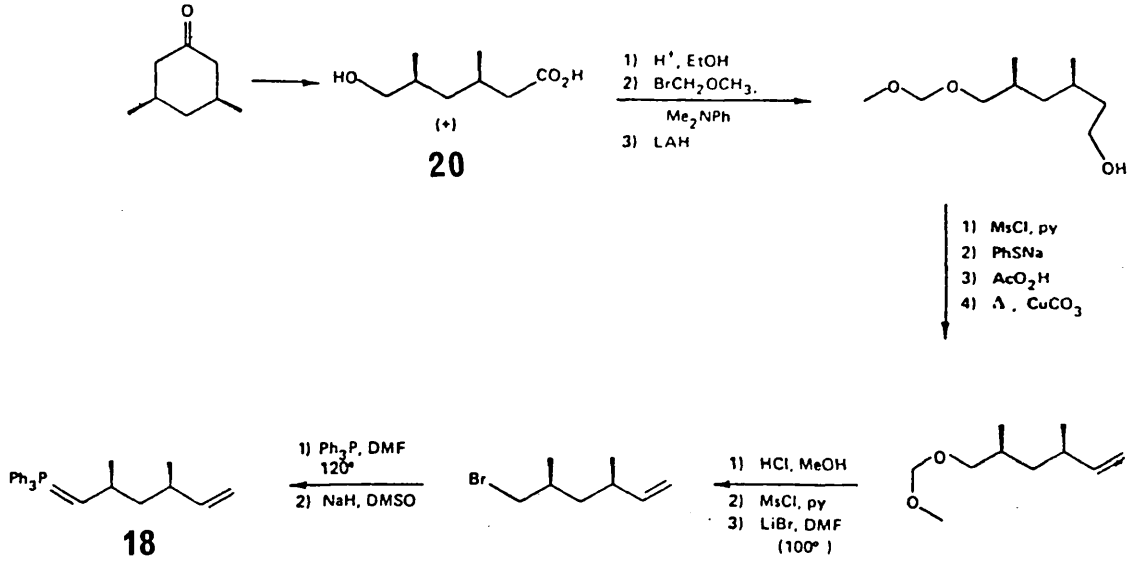
urethanes, separation by medium pressure chromatography and reductive hydride cleavage. The laevorotatory alcohol (7) was converted to the corresponding aldehyde with PCC then condensed with the phosphonate anion derived from $(MeO)_2P(O)CH(CH_3)CO_2CH_3$ to give exclusively the *cis* ester (8). Hydroboration of the analogous alcohol gave a 12:1 ratio of diastereomeric diols (9) in 80% yield from (8). After differential protection of the 1^o and 2^o alcohols the furan was oxidatively cleaved to the carboxylate (10). Removal of the methoxymethyl protecting group and pyridinium chlorochromate oxidation gave the left hand fragment (11).

The starting material for the right hand half[27] (Scheme 6) was 2-allyl-1,3-propandiol[41] (12). This was converted to its monobenzyl ether (13) by acetalization with benzaldehyde and reductive cleavage with $LiAlH_4$-$AlCl_3$. Urethane resolution as for the left hand half gave the S(-) alcohol which was correlated in four steps with (-)2-methylpentanoic acid. (13) was elaborated through Johnson orthoester Claisen chemistry on substrate (14). The resultant ester was converted to the aldehyde in two steps, which was treated with p-methoxyphenylmagnesium bromide, reoxidized to the ketone and debenzylated with boron trichloride to give the homoallylic alcohol (15). Because of its symmetry the R(+) alcohol (13B) could also be converted to (15) by protection as the methoxymethyl ether, debenzylation and then taken through similar chemistry as for the S(-) alcohol (13A). Kishi correctly surmised that (15) existed preferentially in conformer A rather than in conformer B in which there is more steric repulsion betweeen the ethyl and allyl substituents. Thus complexation of m-chloroperbenzoic acid with the homoallylic alcohol directs the epoxidation solely to the β face of the more nucleophilic bond. The homoallylic alcohol is removed by LAH reduction of its tosylate ester to give the benzylic alcohol (16). Camphor sulphonic acid

catalysed ring closure gives the tetrahydrofuran in 7:2 diastereomeric



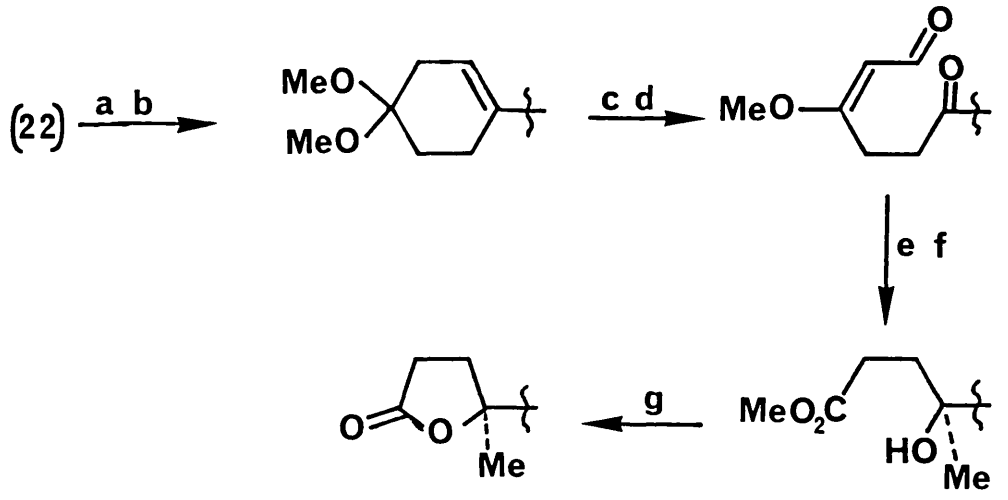
ratio and Lemeiux cleavage of the terminal double bond produced hemiacetal (17). This was reacted with ylid (18) to give the diene (19) ready for elaboration into monensin's A-ring. The required phosphonium salt was prepared from 3,5-dimethylphenol (see below).



Raney nickel hydrogenation followed by sodium dichromate oxidation gave *cis*-3,5-dimethylcyclohexanone. Baeyer-Villiger oxidation followed by hydrolysis and resolution (by fractional crystallization of the α-methyl benzylamine salt eight times from ether-chloroform) gave the (+) hydroxy acid (20). (20) was converted in 10 steps to the phosphonium salt in 36% yield and thence to (18) by treatment with NaH in DMSO.

NBS mediated ring closure of (19) gave a single tetrahydrofuran-bromide in 57% yield. Inversion of the bromide with potassium superoxide in DMSO afforded alcohol (21) in 47% yield. The tetrahydropyran monensin A ring was then formed by protection of the 2° alcohol as its trichloroacetate, osmium tetroxide oxidation of the terminal olefin, monobenzoylation, Jones oxidation and hydrolysis of the trichloroacetal and benzoyl groups with sodium methoxide to give a single hemiacetal (22) in 53% yield from (21).

The p-methoxyphenyl group of (22) was then ingeneously transformed in seven steps to the γ-methylfuranone (23) as shown below.

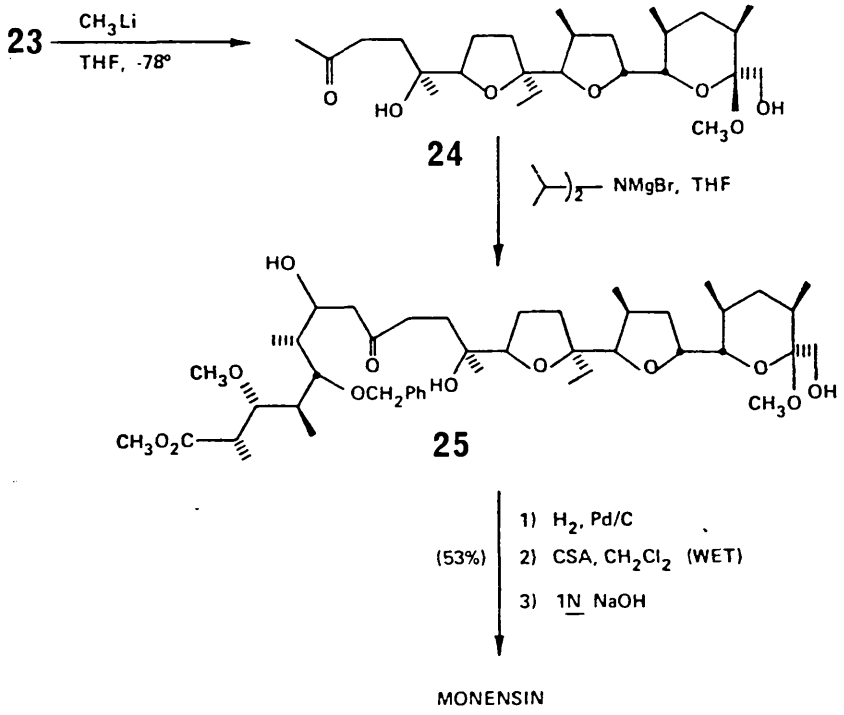


Reagents (a) Li, NH_3; (b) $HC(OMe)_3$, H^+; (c) O_3, -78°C; (d) $MgBr_2$ (wet), CH_2Cl_2; (e) MeMgBr, Et_2O; (f) O_3, -78°C; (g) HCl, MeOH. 22% yield overall.

Birch reduction and treatment with trimethylorthoformate gave a dimethyl acetal. Ozonolysis followed by elimination of methanol with wet magnesium bromide afforded the unsaturated aldehyde. Chelation-controlled stereoselective addition of methylmagnesium bromide to the ketone adjacent to the furan followed by a second ozonolysis and lactonization gave (23). Treatment of (23) with methyl lithium afforded the methyl ketone (24) in quantitative yield, ready for coupling with the

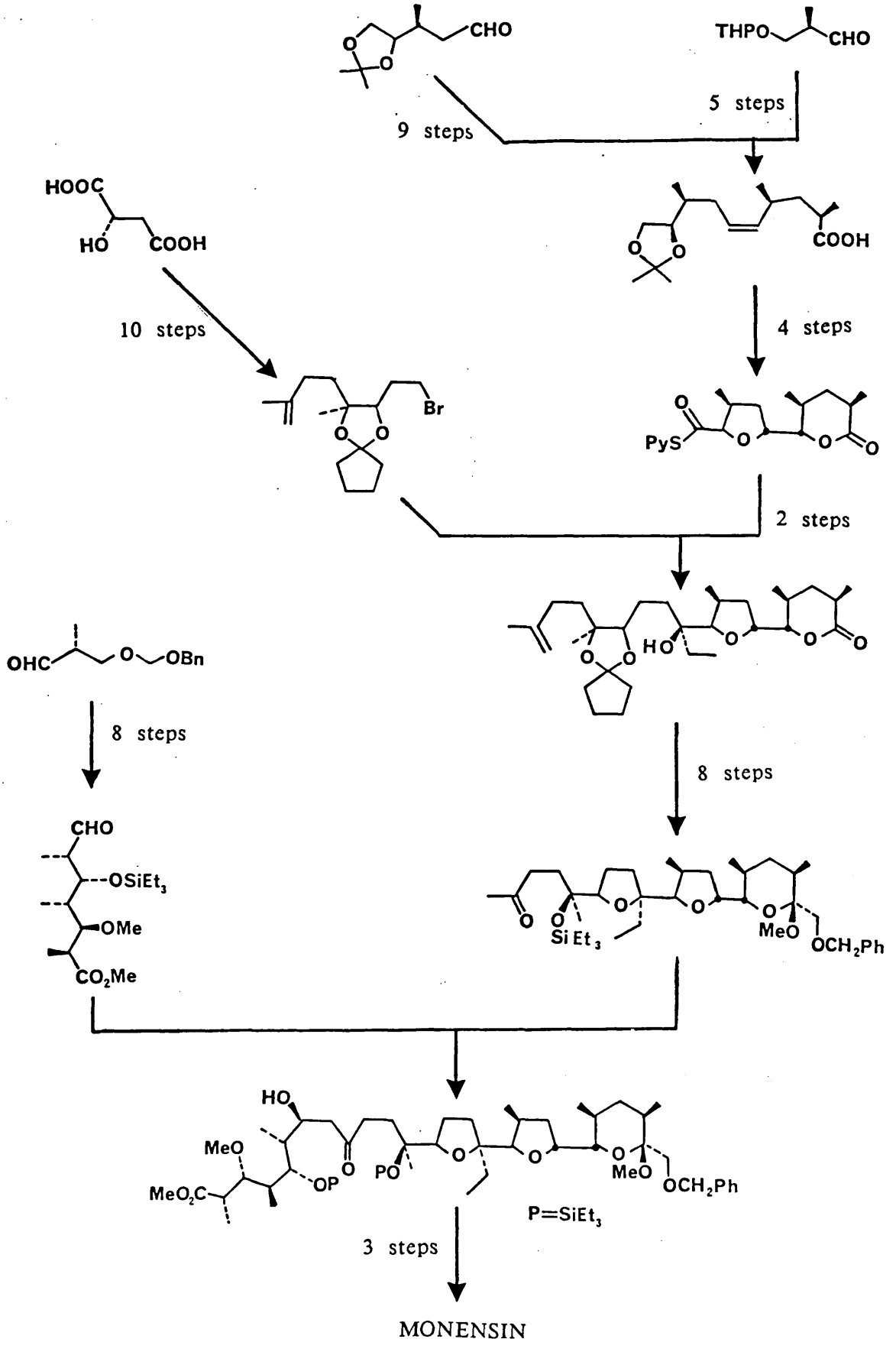
left hand fragment (11). The key coupling reaction (Scheme 7) was accomplished with diisopropylamine magnesium bromide in THF at -78°C in 21% yield giving an 8:1 ratio of the desired Cram to anti-Cram aldol product (25). When the same reaction was conducted at 0°C the yield improved to 71% while the diastereomeric ratio fell to 1:1. Hydrogenolytic debenzoylation of (25) and acidic equilibration of the dioxaspirane gave the thermodynamically more favourable (desired) spiroketal (26) in which the tetrahydrofuran C-O bond (D-ring) is axial. Exposure to acid also hydrolysed the A-ring methoxy ketal. Base hydrolysis of the methyl ester of (26) completed the synthesis of monensin.

Scheme 7



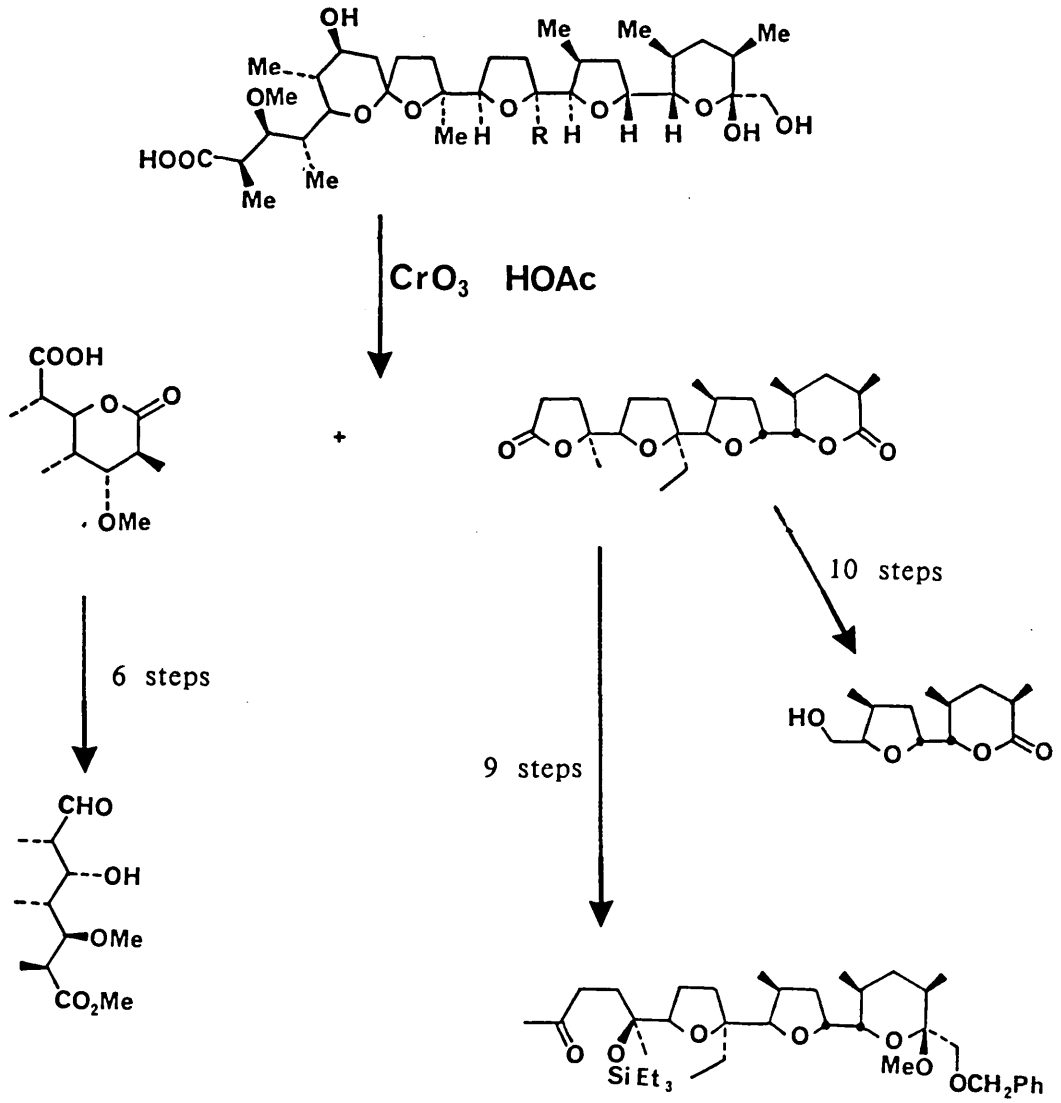
Still's group completed their total synthesis (shown in Scheme 8) in 1980, a year after Kishi's seminal work. They employed a different set of subfragments each of which could be prepared from optically active

Scheme 8 : Still's Synthesis

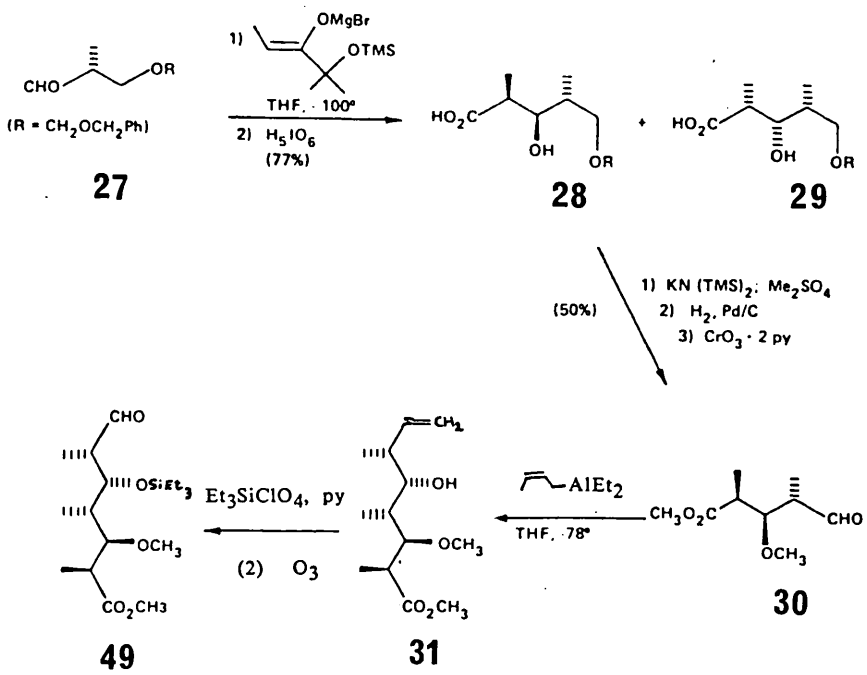


starting materials. This avoided resolution steps and gave a shorter more convergent synthesis. In an accompanying paper[38] Still undertook a multipronged degradation of the natural material to provide structural proof and relay material for his synthetic intermediates. These degradations are summarized in Scheme 9.

Scheme 9 : Still's Degradation

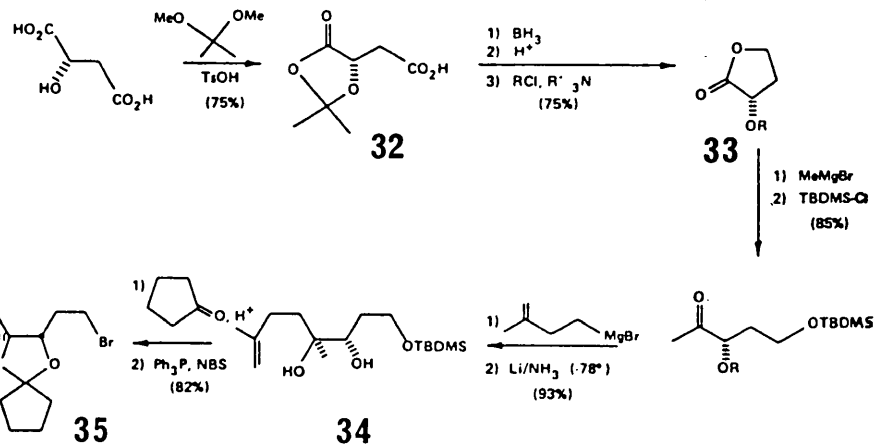


Scheme 10



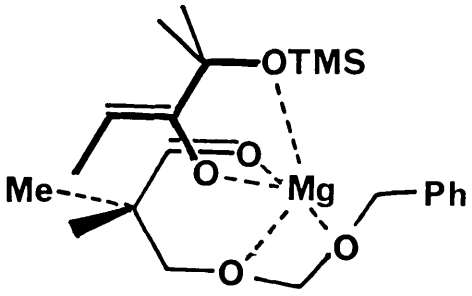
Left fragment.

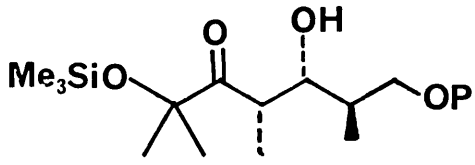
Scheme 11



Central fragment.

Aldehyde (27), derived from β-hydroxyisobutyric acid was the starting material for the left fragment (Scheme 10). Condensation of (27) with Heathcock's enolate gave after oxidative cleavage of the resultant α-hydroxyketones, a 5:1 mixture of (28) to (29). The anti-Cram product predominates (see below) because chelation of the magnesium salt to both the ketone and the β-benzyloxymethoxy group directs the attack of the E-enolate *anti* to the α-methyl group. Another example of chelation-control occurs in the synthesis of the central piece.



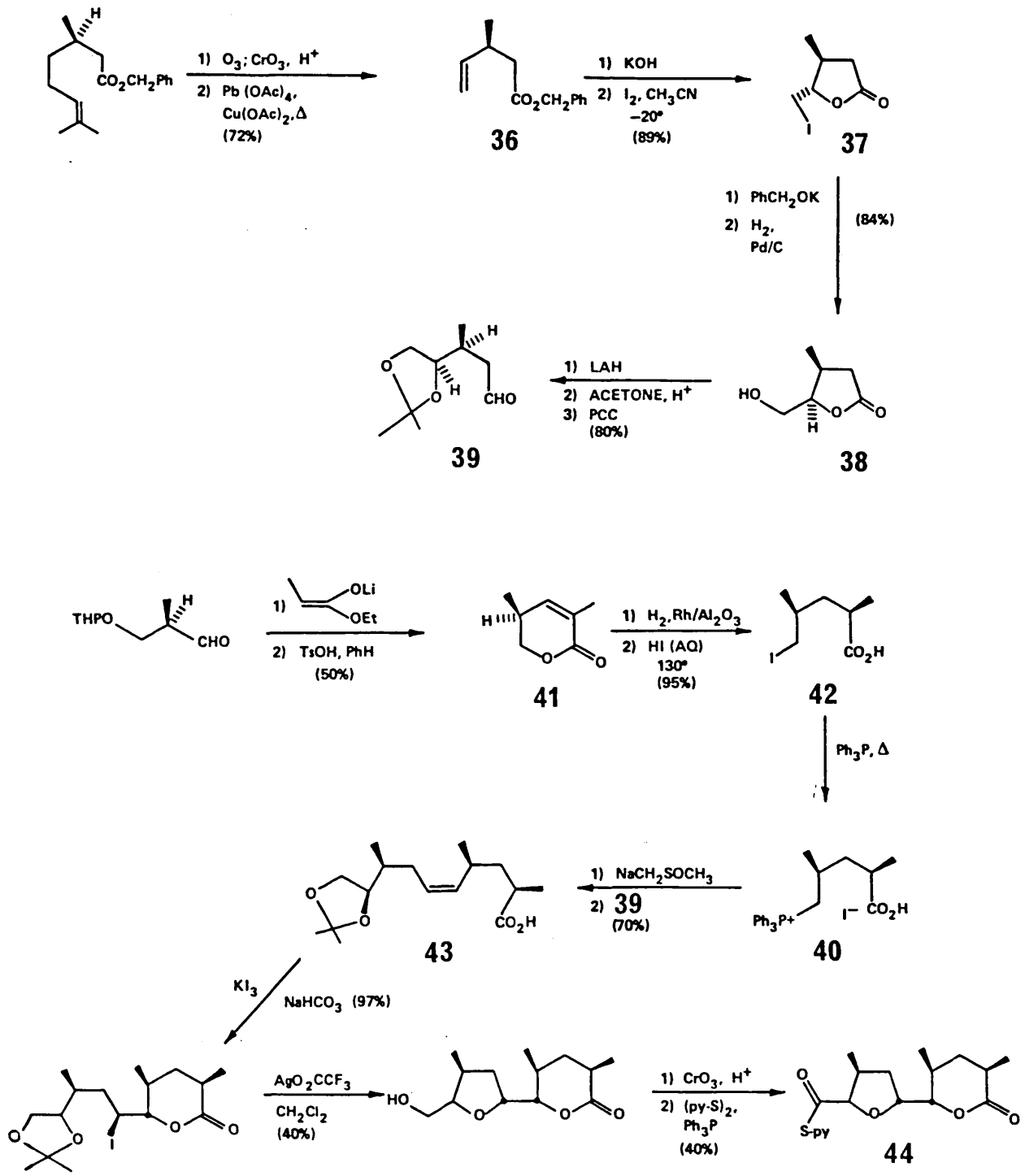


major product

The major isomer (28) was di-O-methylated, deprotected and oxidized to a new aldehyde (30). Treatment of (30) with the propanal enolate equivalent *cis*-2-butenyldiethylaluminium in THF at -78°C gave a 3:1 mixture of isomers in favour of the "Cram" product (31) - here the relatively bulky and branched nature of C-3 overrode the chelating effect of its methoxy group. The major isomer was separated by flash chromatography. (31) was correlated by ozonolysis and Jones oxidation with the lactonic acid prepared by degradation of monensin. (31) was converted into the left hand fragment (49) by saponification, silylation with Et_3SiClO_4 in pyridine and ozonolysis.

The synthesis of the central fragment is shown in Scheme 11. Borane reduction of the acetonide of ℓ-malic acid (32) followed by lactonization and methoxybenzoylation gave the furanone (33). Treatment of (33) with MeMgBr and silylation gave a methyl ketone which was

Scheme 12



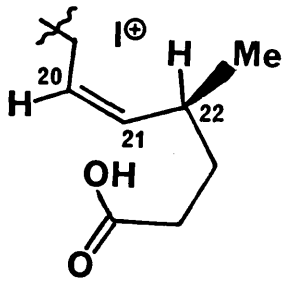
Right fragment.

subjected to a chelation controlled nucleophilic addition of isopentenyl magnesium bromide to the less hindered *Si* face of the carbonyl group. Debenzylation gave diastereomer (34) in a 50:1 ratio over the alternative isomer. The diol was protected as the cyclopentylidene derivative with concomitant desilylation. The primary hydroxyl was converted to the bromide to afford the central fragment (35).

The right hand piece was constructed from two subfragments (see Scheme 12). Benzyl citronellate was ozonolysed with oxidative work up to give an acid which was decarboxylated with lead tetraacetate and copper II acetate to the olefin (36). Saponification and thermodynamic iodolactonization gave a 20:1 excess of the depicted diequatorial iodide (37). The new chiral centre was inverted to (38) *via* an intermediate epoxide-benzol ester. Standard manipulation gave (39).

The fragment (40) that was to be condensed with (39) was derived from the tetrahydropyranyl ether of 3-hydroxy-2-(R)-methylpropanal. Condensation of this with the lithium enolate of ethylpropanoate followed by acid treatment gave the unsaturated lactone (41). Reduction of the double bond gave an 8:1 preponderance of the isomer shown and brief treatment with HI gave iodide (42). The phosphonium salt was formed by heating (42) with triphenylphosphine at 130^{o}C without a and its ylid was condensed with (39) in DMSO to form the *cis*-olefin (43). A second iodolactonization followed by silver (I) mediated loss of acetonide and internal SN-2 displacement of iodide set up the correct asymmetry at C-20 and C-21 (monensin numbering). The reason why the iodolactonization is stereospecific is because the most stable conformer of (43) is where the C-22 H is eclipsed with the cis double bond hence the carboxylate bearing appendage is constrained to the space below the plane of the olefin. Finally, Jones oxidation and conversion of the acid

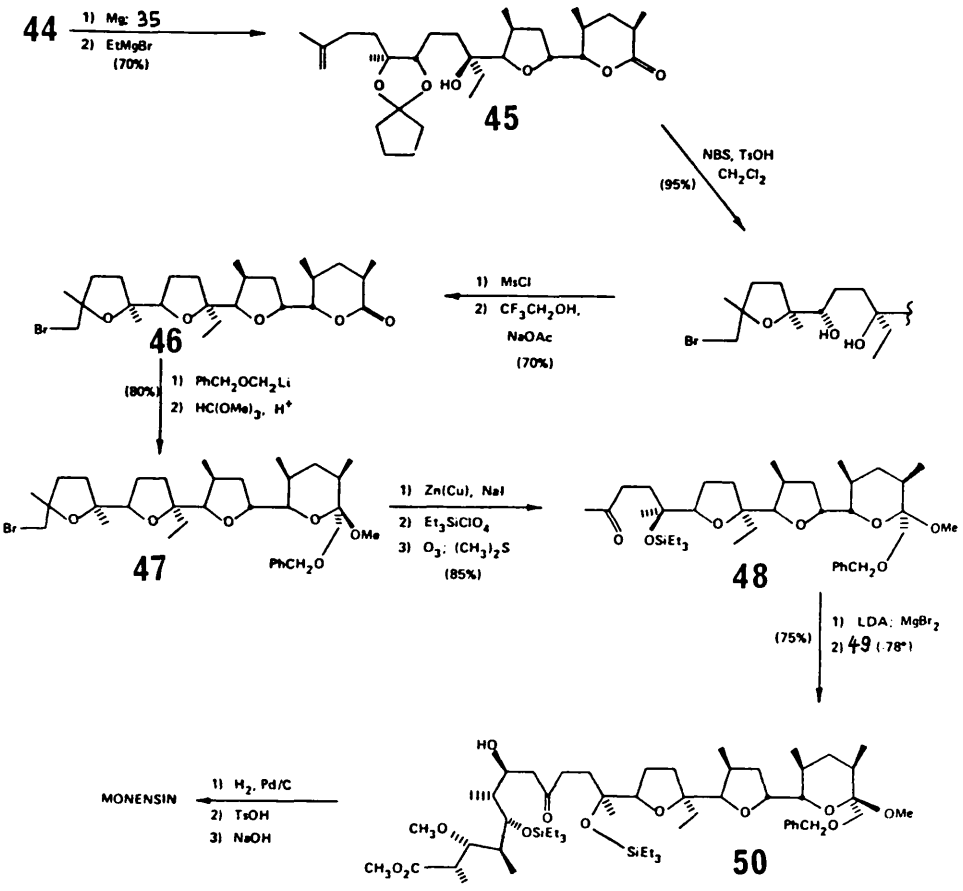
to the corresponding thiopyridyl ester afforded the right hand fragment (44).



Treatment of (44) (Scheme 13) with the Grignard of (35) and then ethylmagnesium bromide gave a single isomer (45), the result of chelation stereocontrol during the second Grignard reaction.

Deketalization with differentiation of the C-12 and C-16 tertiary hydroxyls was achieved by NBS induced bromoetherification of the terminal olefin. Selective mesylation of the secondary C-13 hydroxyl followed by solvolysis in buffered trifluoroethanol afforded (46). Addition of benzyloxymethyllithium followed by trimethylorthoformate gave the thermodynamic methyl ketal (47). The methyl ketone (48) was obtained by reductive elimination of (47), silylation and ozonolysis. Aldol condensation of (48) with (49) using LDA and $MgBr_2$ in THF at -78°C much improved upon Kishi's original coupling, giving a 3:1 ratio of the desired Cram product (50) in 75% yield. Deprotection of (50), acid catalysed spiroketal formation and saponification gave monensin A.

Scheme 13

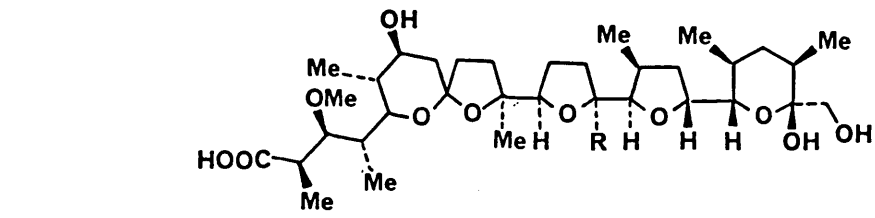


Convergence of fragments.

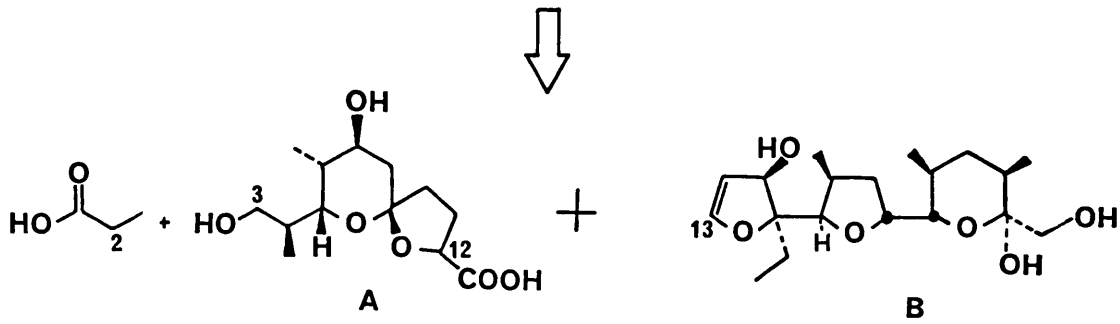
Ireland and coworkers[31,32,33] are currently engaged upon a distinctive but as yet unfinished synthesis of monensin A. The synthetic plan, illustrated in Scheme 14, involves linking sugar-derived tetrahydrofuran and tetrahydropyran rings by a series of Ireland-Claisen e ster enolate rearrangements. This methodology shown at best in his synthesis of the related lasalocid[42] leads to structural determination problems of his advanced intermediates.

The starting material for the spiroketal fragment (Scheme 15) was α-D-glucosaccharinic acid γ-lactone (51) which can be obtained in 10% yield from the treatment of inverted sugar with calcium hydroxide over

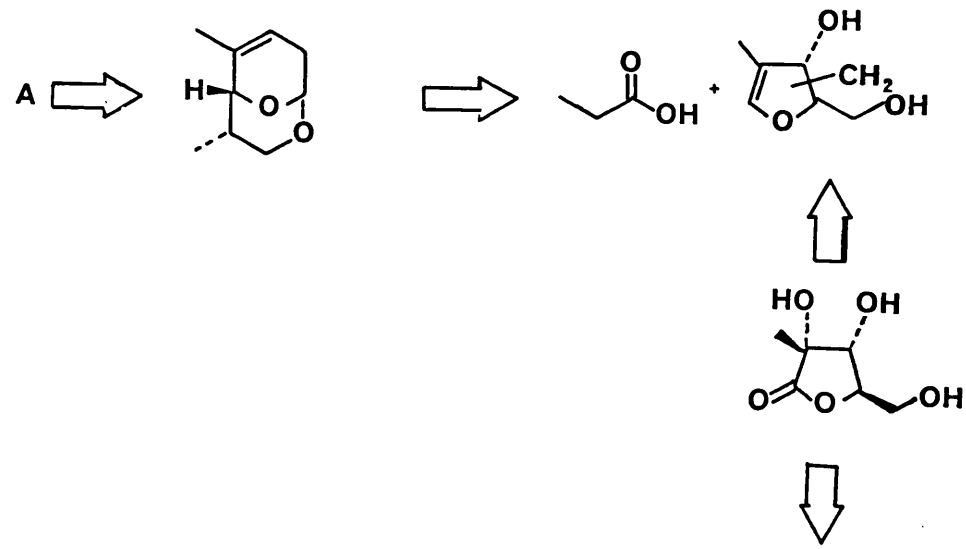
Scheme 14 : Ireland's Strategy

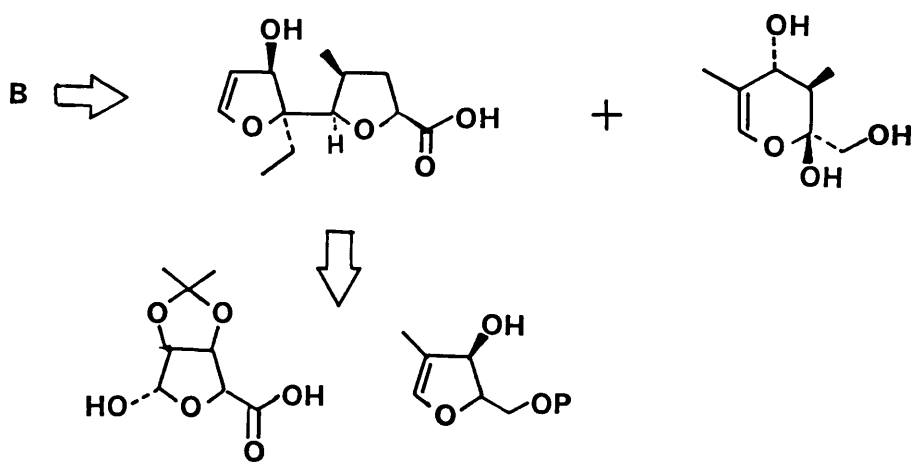


MONENSIN

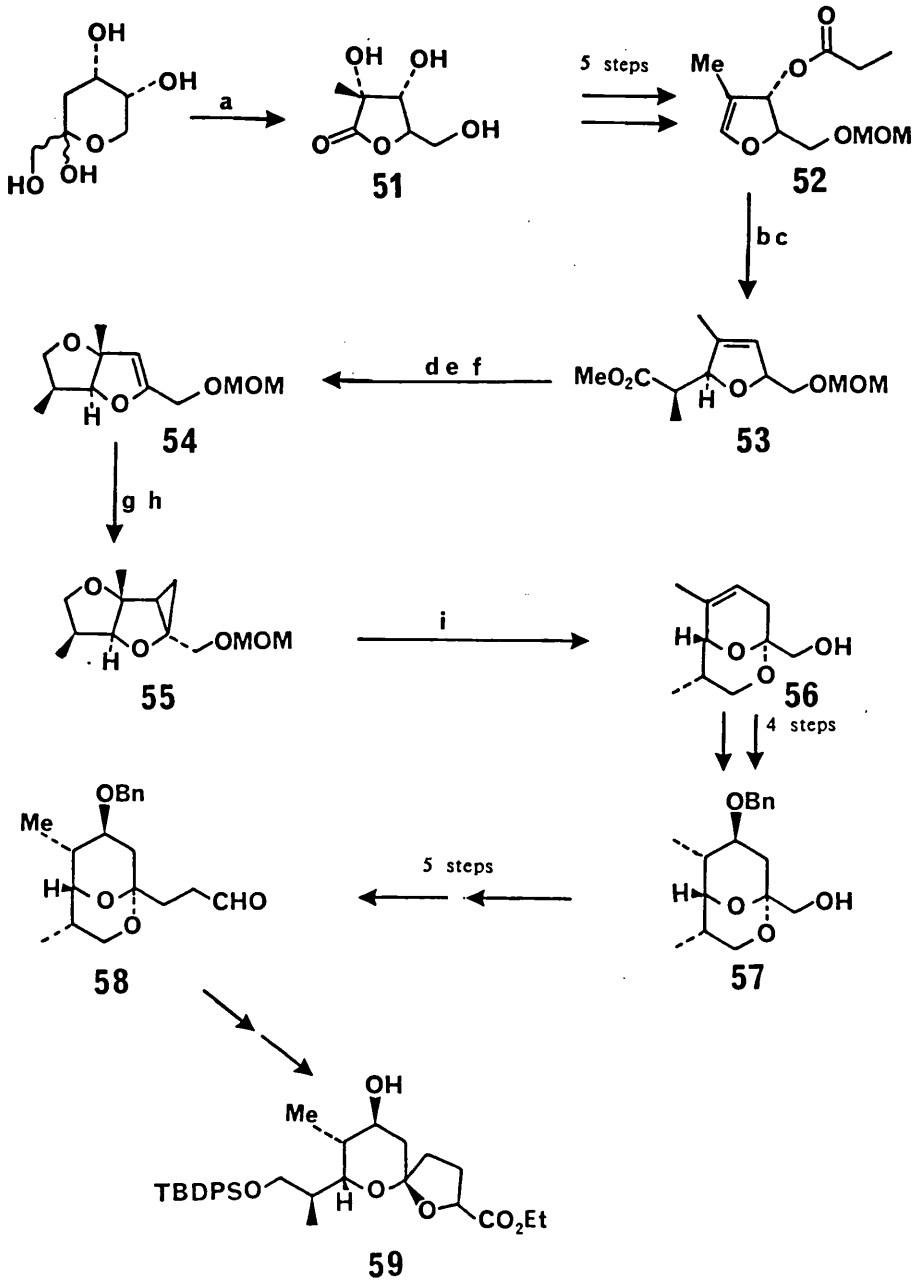


A B





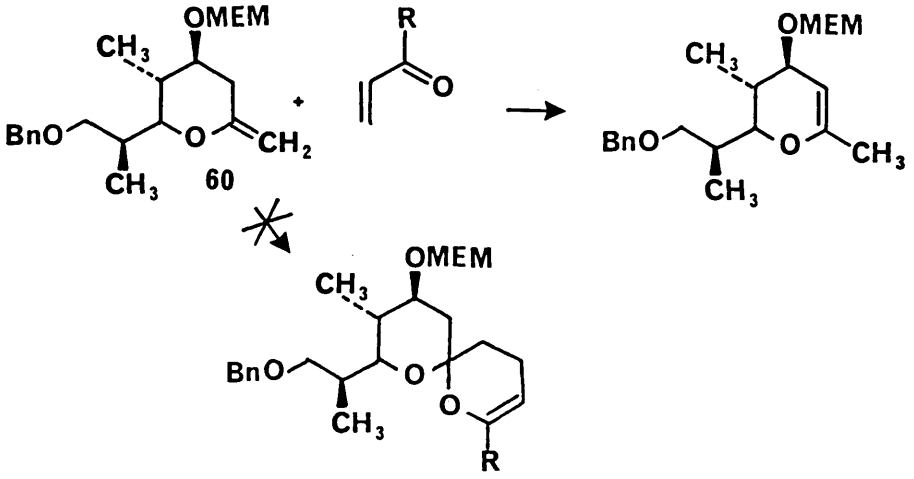
Scheme 15



Reagents (a) $Ca(OH)_2$, 10%; (b) LDA, THF then Me_3SiCl; (c) OH^-; CH_2N_2, Et_2O, 55% for b and c; (d) $LiAlH_4$; (e) I_2, Na_2CO_3, MeCN; (f) DBU, 78% for d, e and F; (g) 50% NaOH, TEBAC, $CHCl_3$; (h) $LiAlH_4$, 74% for g and h; (i) $HClO_4$, MeCN, 95%.

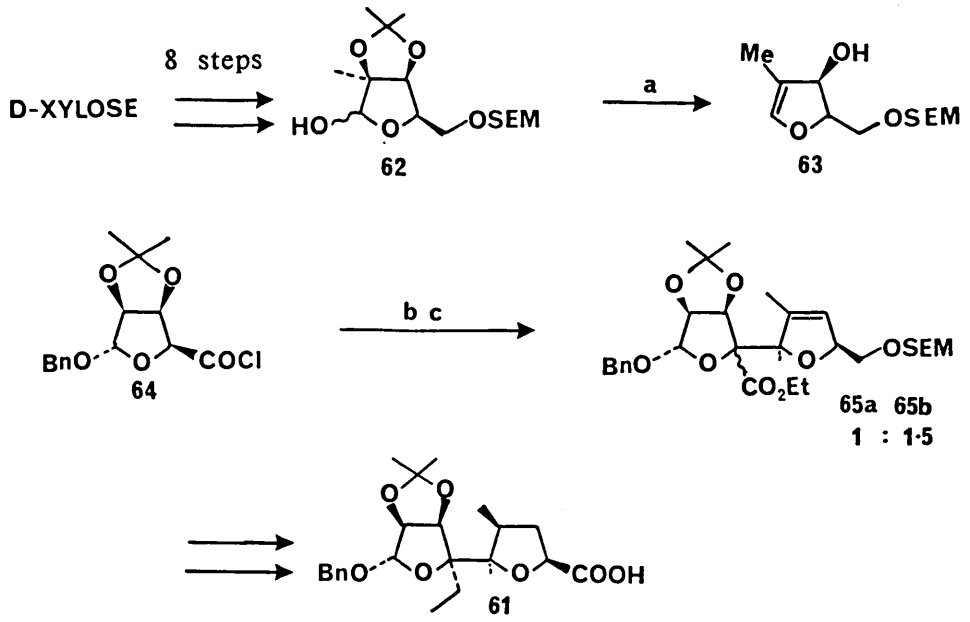
a period of six to eight weeks. Lactone (51) was transformed in a five step sequence to the allylic propionate (52). Claisen ester-enolate rearrangement using LDA in the presence of HMPA gave a 4:2 ratio of isomers (53 a,b) via a boat-like transition state involving the Z-silyl ketene acetal. The major isomer (53a) was converted by reduction, iodoetherification and elimination to the acid-sensitive glycal (54). Dichlorocyclopropanation under Riemer-Tiemann conditions and reduction produced (55) which upon acid catalysed rearrangement afforded (56). Hydroboration of (56) solely from the convex face of the molecule and protection gave (57). The monensin D-ring was then built up in eleven steps via addition of 1-lithiumethoxyvinylether to aldehyde (58) followed by ozonolysis to provide the α-hydroxy ethyl ester group of (59).

Ireland also investigated hetero Diels-Alder additions of enones to olefin (60). No cycloadducts could be obtained because the reaction conditions promoted migration of the *exo*-methylene double bond of (60) into the tetrahydropyran ring.

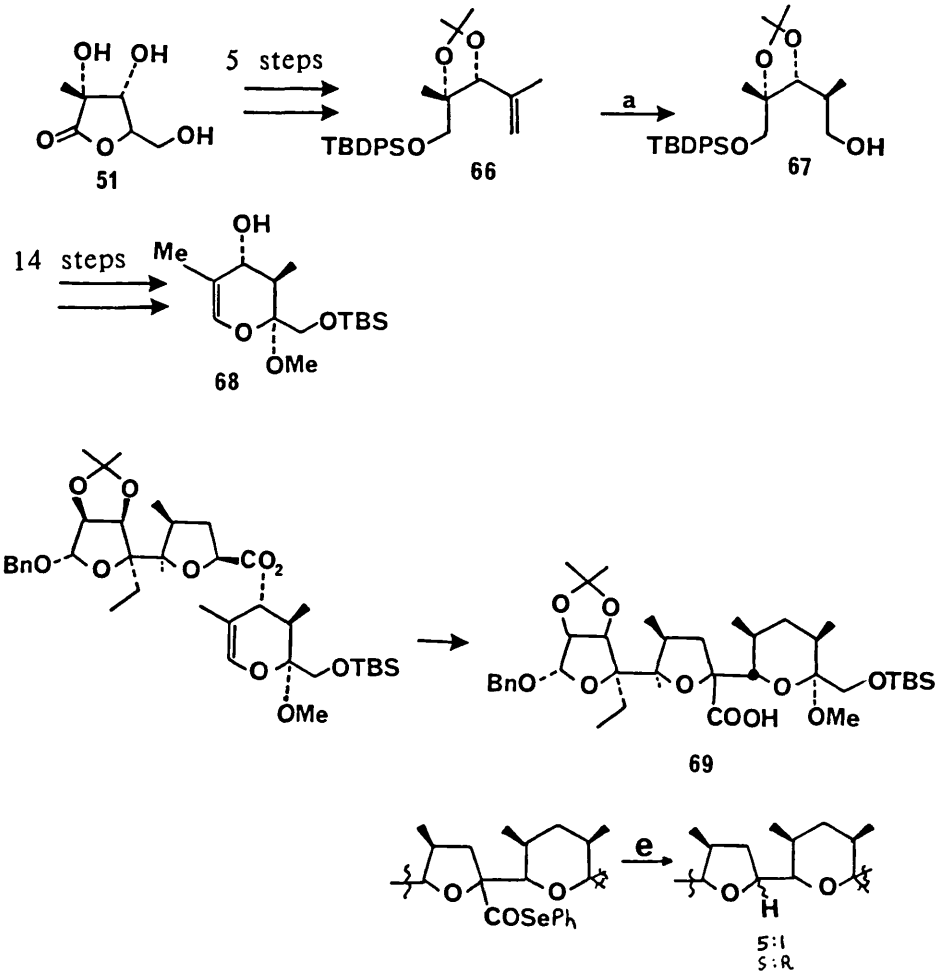


The route to the central fragment (61) is shown in Scheme 16. D-xylose was converted in 8 steps in an overall yield of 35% to lactol (62). Reduction of the corresponding furanosyl chloride by lithium in

Scheme 16a



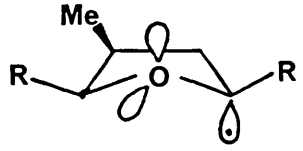
Scheme 16b



Reagents (a) $P(NMe_2)_3$, CCl_4, THF; Li,NH_3;NH_4Cl; (b) n-BuLi, DMAP, 63; (c) LDA, Me_3SiCl, THF, HMPA; (d) BH_3; H_2O_2, OH^-; (e) AIBN.

liquid ammonia or in higher yield using lithium *bis* 4,4′ -t-butylbiphenyl gave the allylic alcohol (63). Esterification with (64) followed by Claisen-ester rearrangement in the presence of HMPA and reesterification gave a 2:3 mixture of (65a) and (65b). The structure of these were determined by X-ray crystallography. (65a) was converted to (61) using standard chemistry in 70% yield.

The starting material for the A-ring was once again α-D-glucosaccharinic acid, γ-lactone (51). This was transformed in five steps (76% yield) to olefin (56) which was hydroborated with only modest (2:1) diastereoface selection to alcohol (67). Unsaturated alcohol (68) was obtained in a further twelve steps in 47% yield from (67). Esterification of (67) with (61) and Claisen ester-enolate rearrangement using $KN(TMS)_2$, TBSCl, THF gave in 45% yield a single crystalline carboxylic acid (69). Decarboxylation of (69) was effected by tri n-butyltin hydride reduction of the analogous phenylselenyl ester. This procedure gives a 5:1 preponderance of the unnatural C-20 epimer in 70% yield. This arises because the most stable transition state conformer (70) has its C-2 radical antiperiplanar to a ring oxygen lone pair, allowing the C-2 and C-5 substituents to be pseudoequatorial. Proton



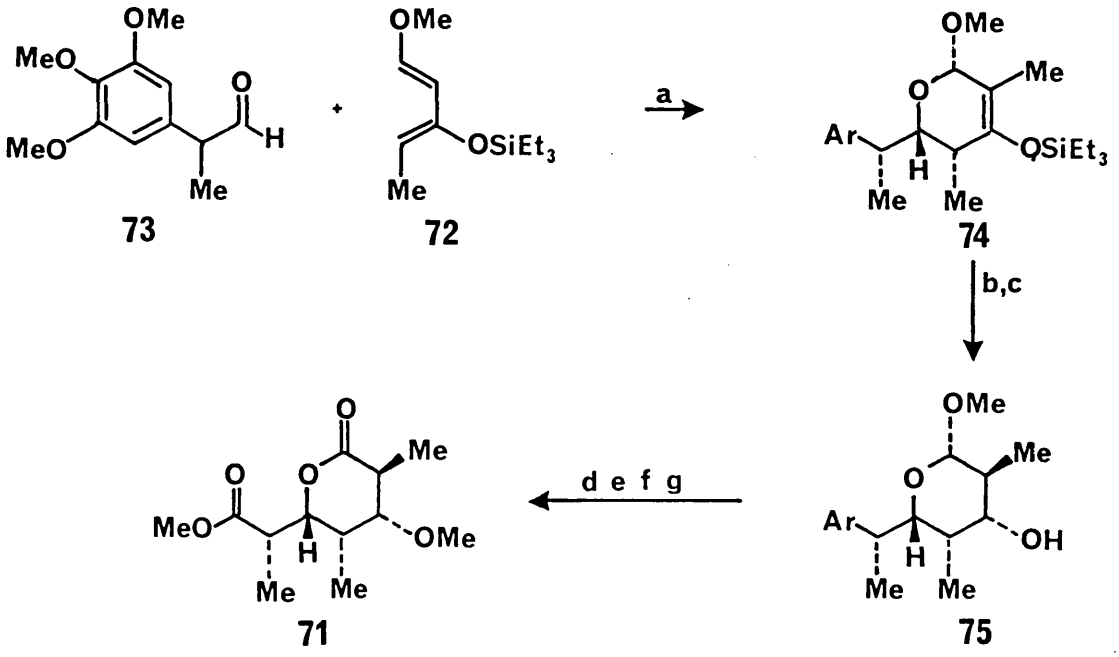
70

abstraction by this radical leads to the undesired epimer. To complete the synthesis this stereochemical problem needs to be overcome, a Claisen rearrangement is required to join the C and D rings and an aldol reaction to append C1 and C2.

Synthesis of Racemic Monensin Subfragments

Danishefsky and Harvey[34] have published a route to racemic monensin lactone (71) using a hetero Diels-Alder approach (Scheme 17). *Cis-endo* addition of diene (72) to the least hindered (methyl) face of the aldehyde (73) under $Yb(Fod)_3$ catalysis gave a single cycloadduct (74) in 56% yield. Treatment of (74) with HF in pyridine-methanol gave a ketone which was reduced to the equatorial alcohol (75) and methoxylated in 70% yield. Hydrolysis of the methyl glucoside, conversion of the lactol to the lactonic acid with a two-phase ruthenium dioxide - sodium metaperiodate system and esterification with diazomethane gave (±) monensin lactone in 56% yield from (71). If the aldehyde (73) were constructed using Enders RAMP or SAMP chemistry this would constitute a chiral synthesis.

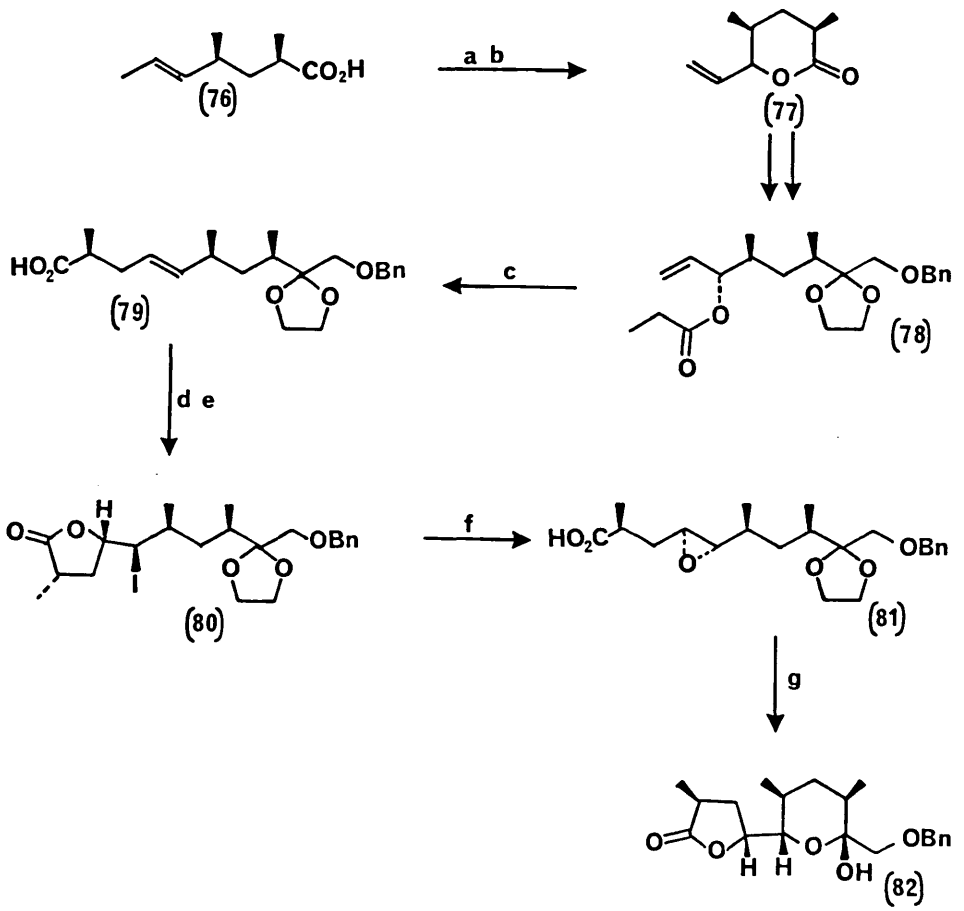
Scheme 17



Reagents (a) $Yb(fod)_3$, 56%; (b) HF, py, MeOH, 86%; (c) $NaBH_4$, MeOH, 81%; (d) NaH, MeI, DMF, 98%; (e) HCl, THF; (f) RuO_2, $NaIO_4$; (g) CH_2N_2, 56% for e, f, g.

Bartlett and coworkers have produced a linear synthesis of a monensin A- and B-ring fragment (Scheme 18). The carboxylic acid (76) available from *meso* glutaric anhydride was phenylselenolactonized and eliminated to give olefin (77) with >95% stereochemical purity olefin (77). Subsequent addition of benzyloxymethyllithium to (77), followed by acetalization and esterification gave ester (78). Ireland-Clais en rearrangement of (78) in the presence of HMPA (which promotes the formation of the Z enol silylether) gave a 10:1 mixture of diastereomeric carboxylic acids (79) in favour of the depicted isomer. Iodolactonization of the *methyl ester* of (79) gave a 9:1 excess of the *cis* iodolactone (80) in 80% yield. By comparison with Still's iodolactonization of the

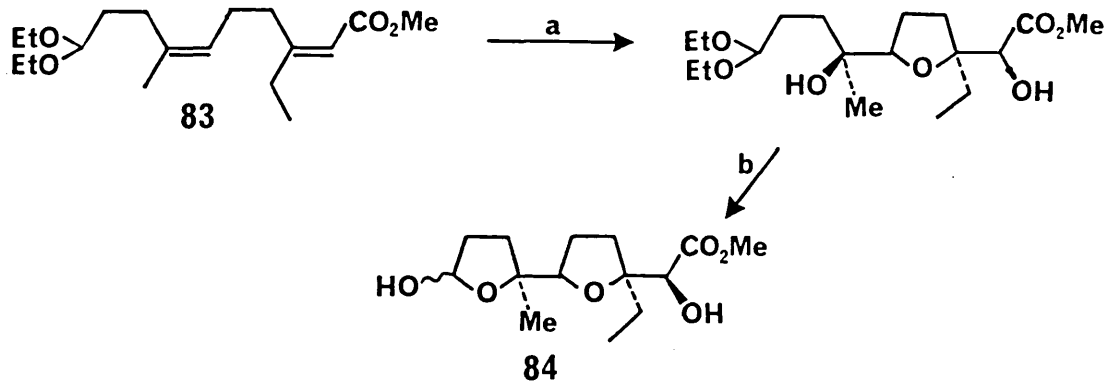
Scheme 18



Reagents (a) PhSeCl; (b) MCPBA; (c) LDA, Me_3SiCl, THF, HMPA, 80%; (d) CH_2N_2, 91%; (e) I_2, MeCN, -15°C; (f) Na_2CO_3, MeOH, 94% for e and f; (g) $HClO_4$, THF, 81%.

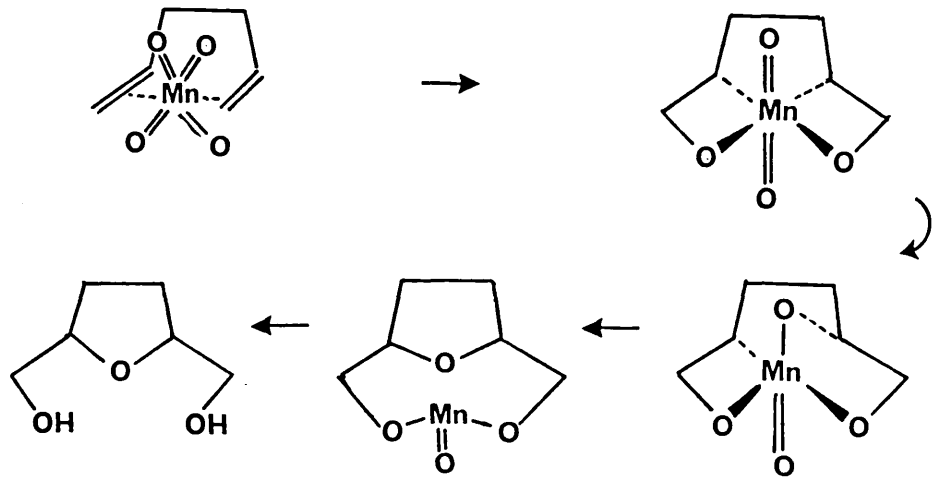
monensin A-ring, the degree of stereocontrol provided by a methyl group α to the carboxylate function is seen to be inferior to that where it is vicinal to the double bond. Transesterification of (80) with concomitant epoxide formation was effected with potassium carbonate in methanol affording (81). The corresponding epoxy-ketone of (81) was neatly converted to monensin fragment (82) with perchloric acid in 78% yield.

Walba and Edwards[36] have published the synthesis of a C,D fragment (84) by an unusual stereospecitic oxidation of 1,5-diene (83) by potassium permanganate wherein the two hydroxyls and the ether oxygen are added to the same face of the diene.



Reagents (a) $KMnO_4$, CO_2, acetone, 47%; (b) $HC(OMe)_3$, TsOH, 50%.

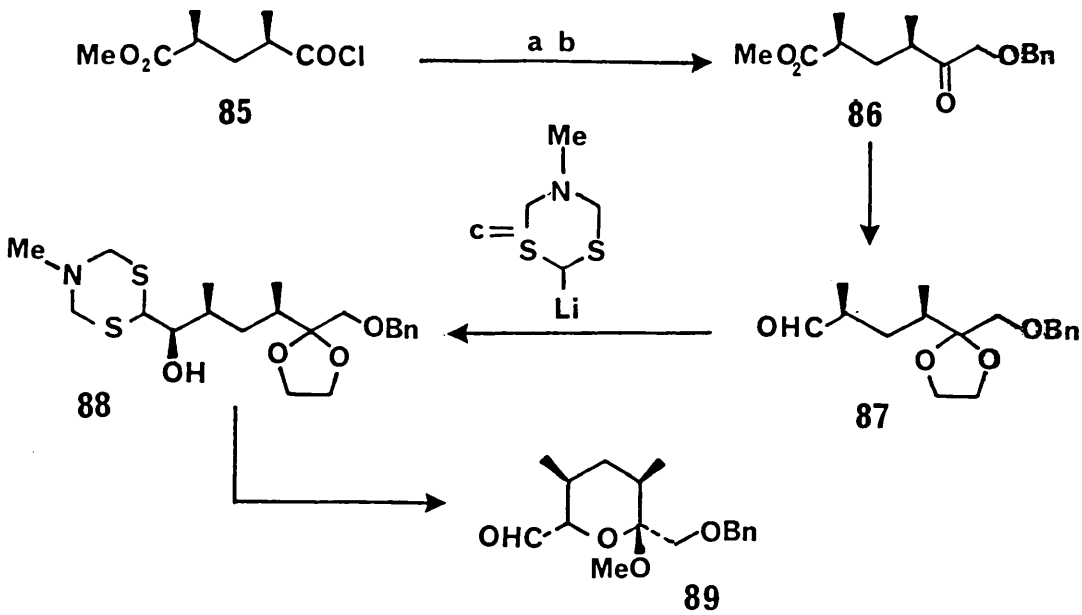
The explanation for the intriguing stereochemistry of this oxidation is given in a previous paper[43] as shown below.



In a third paper Walba[37] describes an alternative synthesis of the Monensin A ring. This is shown in Scheme 19. Treatment of the half acid chloride ester (85) (derived in two steps from *meso*-2,4-dimethyl-glutaric anhydride) with diazomethane and then benzyl alcohol gave (86) in 61% yield. Ketalization, hydride reduction and reoxidation afforded aldehyde (87). Condensation of (87) with a formyl synthon, N-methylthioformaldine (MTF) gave only the *syn* adduct (88) in 92% yield in keeping with Felkin's rules of diastereoselection.

Closure of the tetrahydropyran ring with pyridinium tosylate followed by deprotection of the aldehyde gave the monensin fragment (89).

Scheme 19



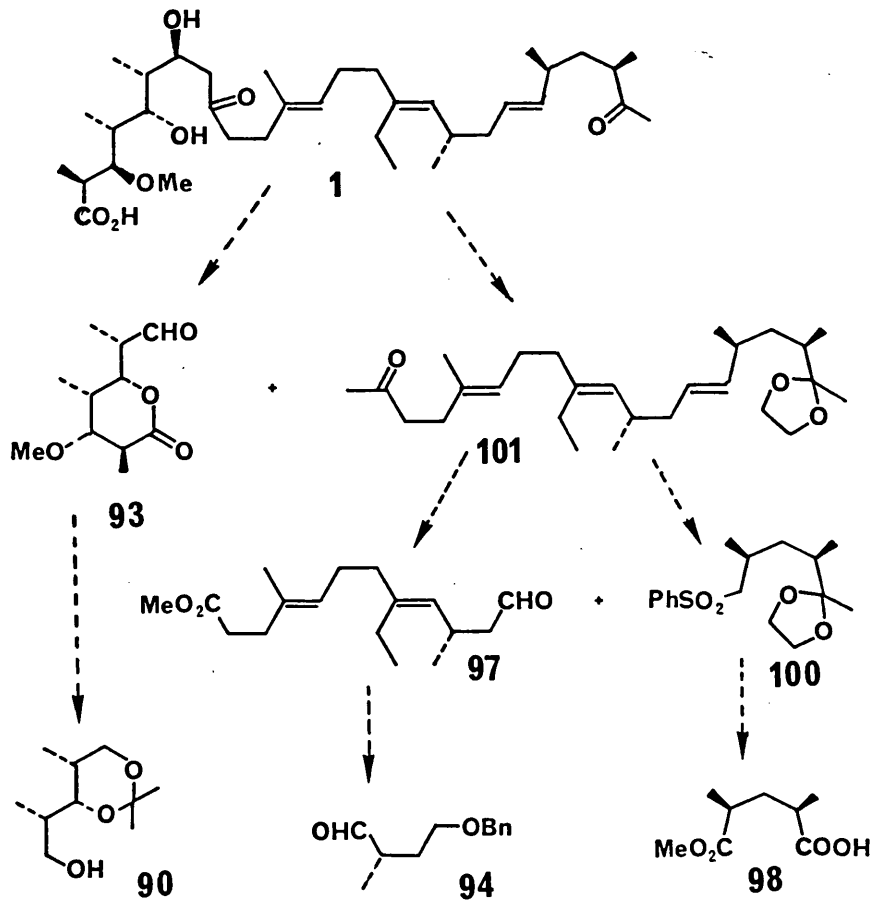
Reagents (a) CH_2N_2; (b) $PhCH_2OH$, 61% for a and b; (c) Li^+ MTF^-, 92%.

Biosynthetic Precursor to Monensin

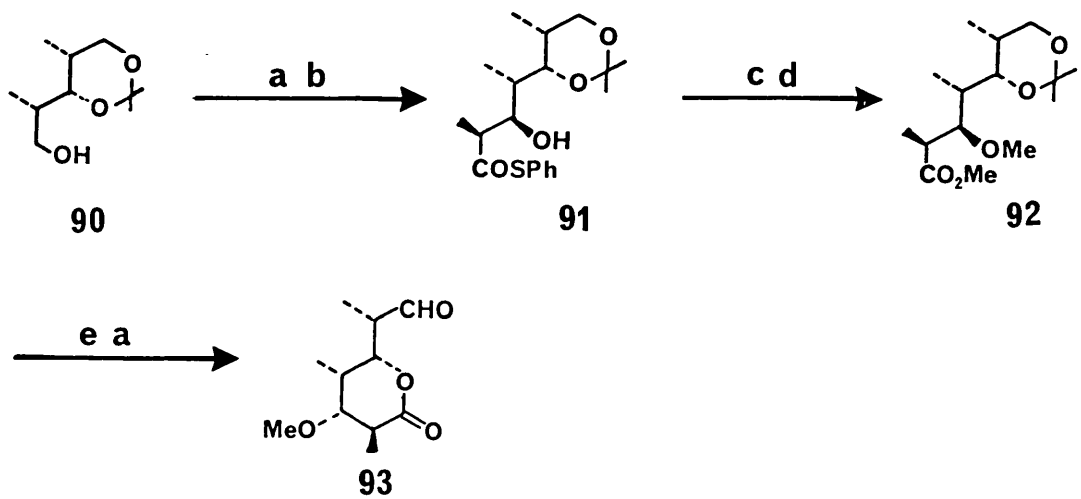
The synthesis of the biosynthetic precursor (1) to monensin A proposed by Cane[11] has been elegantly achieved by Sih.[13] His retrosynthetic plan is shown in Scheme 20. The left hand part (93) was synthesised from (90) obtained by enantioselective hydrolysis of its (±) acetoxy ester by pig pancreatic lipase.[44] (Scheme 21). Condensation of the corresponding aldehyde of (90) with the boron enolate of (S)-phenylthiopropionate gave (91) (65%) as the major product having the desired 2,3-syn and 3,4-anti configuration. Transesterification and methylation of (91) afforded (92) which, upon acid-catalysed deprotection, lactonized spontaneously. Swern oxidation produced the lactone-aldehyde (93) whose stereochemical assignment was confirmed by comparison with naturally degraded material. The starting point for the middle unit was aldehyde (94) derived by enantioselective enzymatic kinetic hydrolysis of its' corresponding (±) ester by Bacillus sp ATCC B-15053[45]. (Scheme 22). Addition of 1-buten-2-yl magnesium bromide to (94) afforded the allylic alcohol which upon ortho-ester Claisen rearrangement produced ester (95) in 83% yield from (94). Repetition of this addition-rearrangement sequence with the aldehyde derived from (95) using 1-propen-2-yl magnesium bromide, gave (96) in 55% yield from (95). To prevent over-reduction, the ester group of (96) was hydrolysed prior to debenzylation. Reesterification and oxidation gave the middle fragment (97) in 68% yield from (96).

Scheme 23 illustrates how the right hand piece was made. The chiral half-ester (98)[46] was converted to the methyl ketone with oxalyl chloride then dimethyl copper lithium, and ketalized to give (99). Reduction of (99) followed by the conversion of the resulting alcohol to the phenyl sulphide with Ph_2S_2 and PPh_3 and buffered oxidation gave (100). The union of (100) with (97) was accomplished by the Julia

Scheme 20

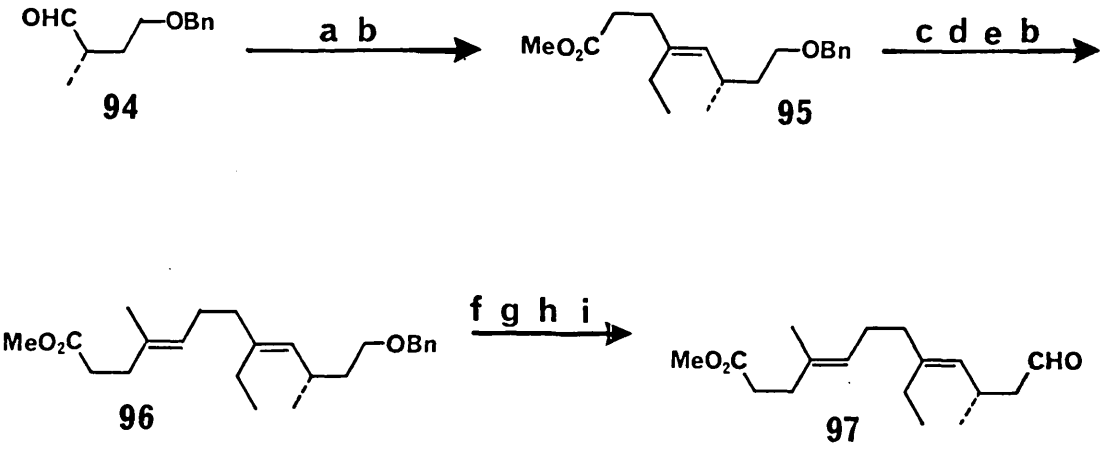


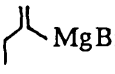
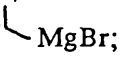
Scheme 21



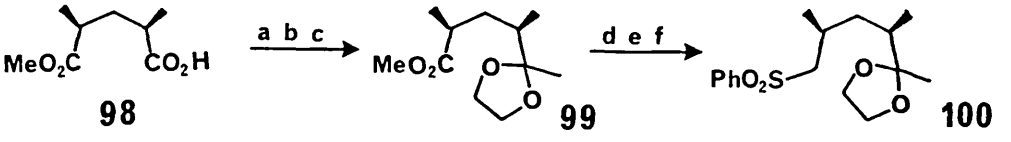
Reagents (a) $(COCl)_2$, DMSO, DCM -78°C; NEt_3; (b) CH_3CH_2COSPh, 9-BBN·OTf, 65%; (c) $HgCl_2$, $CdCO_3$, MeOH, CH_3CN; (d) CH_3I, Ag_2O; (e) TsOH.

Scheme 22



Reagents (a)  MgBr; (b) $MeC(OMe)_3$, H^+, toluene, 110°C; (c) $LiAlH_4$; (d) PCC; (e)  MgBr; (f) LiOH; (g) Na, NH_3; (h) CH_2N_2; (i) $(COCl)_2$, Me_2SO.

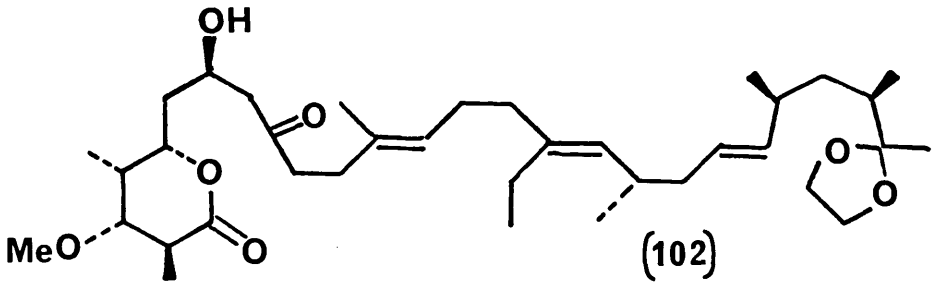
Scheme 23



Reagents (a) $(COCl)_2$; (b) Me_2CuLi; (c) HO OH, TsOH; (d) $LiAlH_4$; (e) PhSSPh, n-Bu_3P, py; (f) MCPBA, $NaHCO_3$.

procedure to give in 35% yield the E olefin (101). The ester grouping of (101) was converted to a methyl ketone by hydrolysis and dimethyl copper lithium addition to its corresponding acid chloride.

Aldol condensation of (101) and (93) (LDA, THF, -78°C) gave a 9:1 preponderance of the desired Cram product (102) in 85% yield. The



(102)

ketal and the lactone of (102) were cleaved with tosic acid and the ester saponified with sodium hydroxide to give the precursor (1).

Concluding Remarks

Monensin, which poses two distinct problems to the synthetic chemist; the generation of multiple linked ether rings and of a branched polyoxygenated acylic chain, is unlikely to be the target of fresh total syntheses, being too large and diverse to effectively show off a single strategy or synthetic method. However, the triepoxide precursor (2) still presents an attractive challenge. While the possibility of its' biological incorporation by *Streptomyces cinnamonensis* must be put in doubt by Sih's failure with the triene (1), if a chemical method could be found to initiate the cascade of ring closures, this would truly be a satisfying way to generate monensin A.

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RESULTS AND DISCUSSION

1. Introduction

The launch by Eli Lilly of monensin as a coccidiostat (1971) and later as a growth promoting feed additive for cattle (1974) stimulated great interest in the polyether ionophores amongst other pharmaceutical firms eager to obtain a share of these important vetinary markets. In the fifteen year period to 1983, seventy-six novel ionophores had been characterized from cultures of *Actinomycetales* predominantly from the genus *Streptomyces.*

In 1981, one of these designated M139603[1] (1) was isolated by workers at ICI from the aerobic fermentation of *Streptomyces longisporoflavus* NCIB 11426. In common with other ionophores, it possesses a tetrahydrofuran and a tetrahydropyran group. However, it also has an unusual six-membered carbocyclic ring and was the first example of an ionophore to have the terminal carboxylic acid grouping replaced by an acyltetronic acid moiety.

Like monensin, M139603 and a number of its derivatives have been shown to increase the proportion of propionic acid produced by rumen fermentation. For this reason, ICI[2] have patented its use as a growth promoter for ruminants.

Shortly after the structure of M139603 had been reported, a Swiss group[3] isolated a closely related ionophore antibiotic called tetronomycin (2), from a culture of *Streptomyces* sp nov (S 53161A). This antibiotic differs structurally by the absence of methyl groups at C-20 and C-22 and the presence of a methylene group at C-34 (numbered according to the convention proposed by Westley)[57]. Astonishingly, the absolute configuration was reported to be opposite to that of M139603 at all of the comparable chiral centres.

Figure 1a

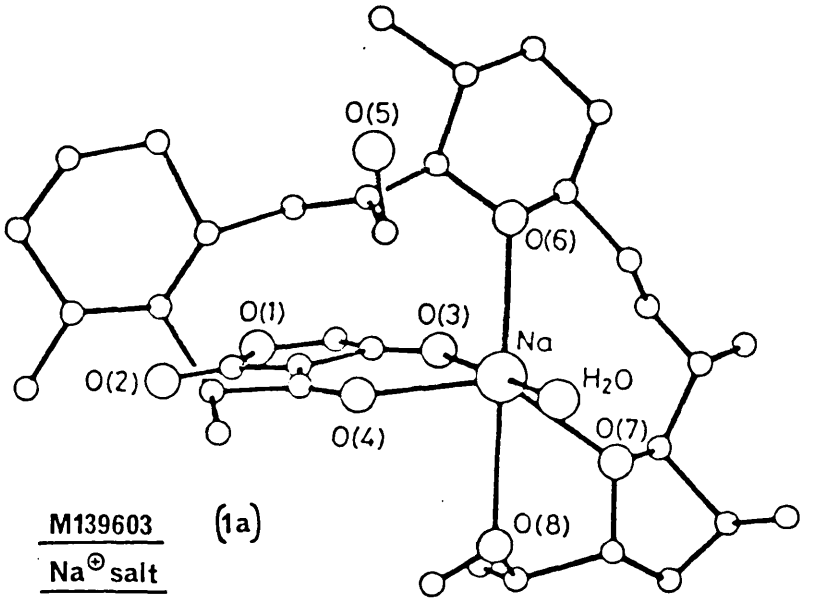
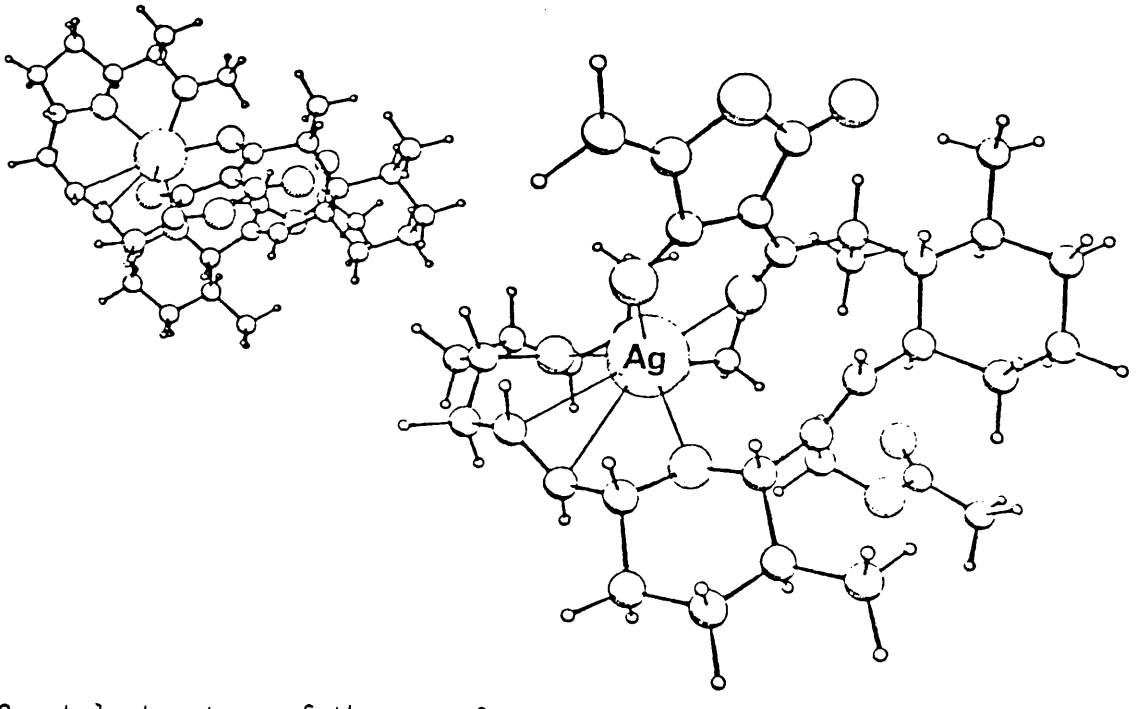
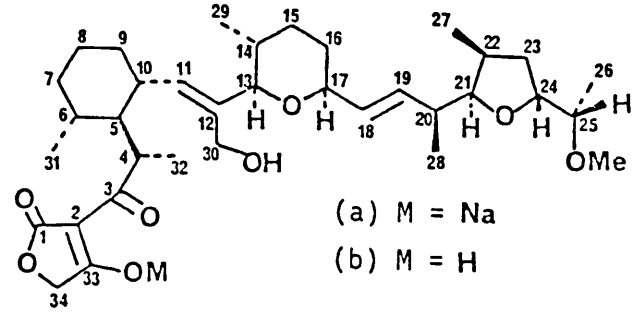


Figure 1b

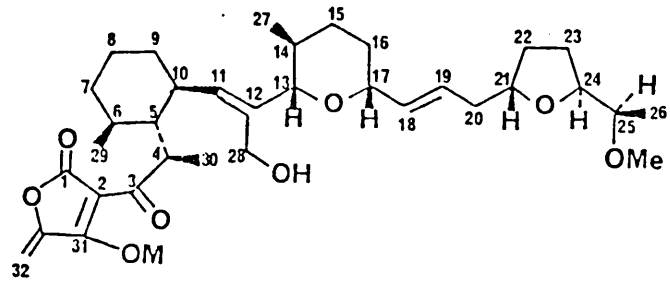


Crystal structure of the mono-O-acetyltetronomycin silver salt.
The upper inset view shows the silver coordination more clearly.



(a) M = Na
(b) M = H

M139603 (1)



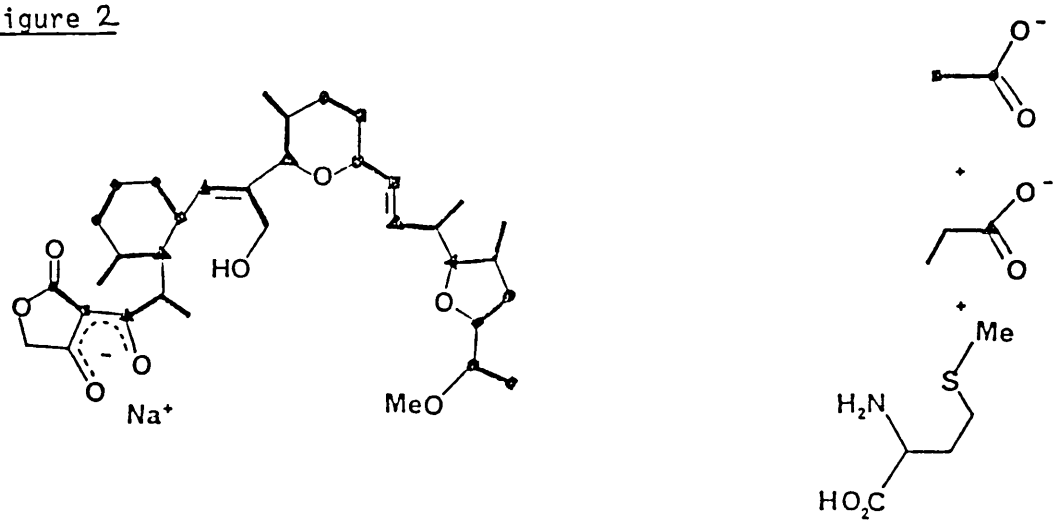
TETRONOMYCIN (2)

The ICI group[1] published the X-ray crystal structure of the 4-bromo-3,5-dinitrobenzoyl derivative of the sodium salt of M139603 in which the metal ion is coordinated by five oxygen atoms of the molecule and by a water molecule in a distorted octahedral array (Figure 1). The non-polar groups exposed upon the complex's exterior explain its lipid solubility. Using COSY 45 and 90 n.m.r. techniques, Grandjean and Laslo[4] have shown that the conformation of both the sodium salt and the free acid in solution is very similar to that of the solid state. In addition, they have shown that M139603 forms 1:1 complexes with both mono and divalent cations, displaying a preference for sodium in the former group and also forming stable complexes with Ca^{2+} and Mg^{2+}.

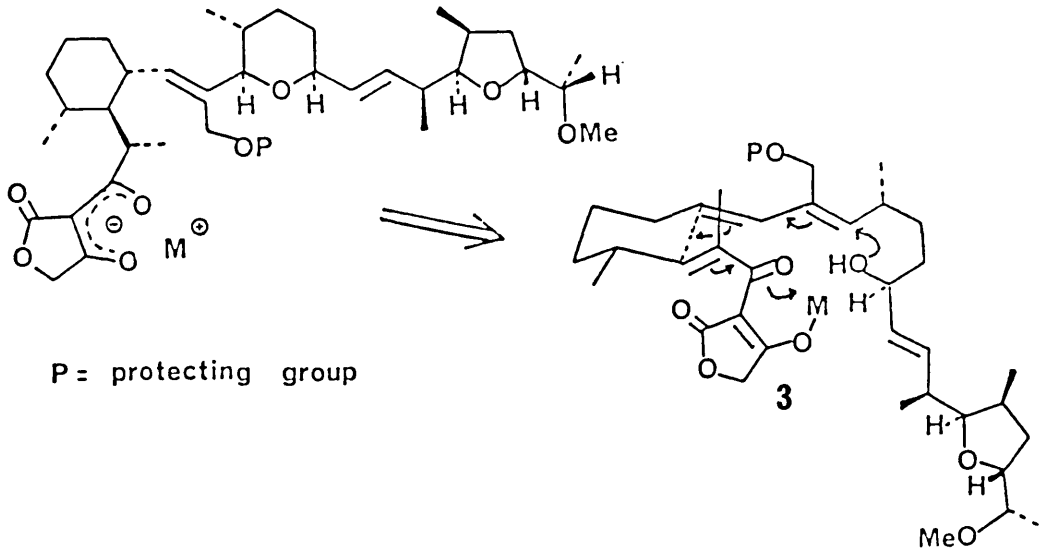
A marked synergistic effect has been demonstrated in the transport of Pr^{3+} across lipid bilayers when used jointly with lasalocid[5].

Biosynthetic studies by Staunton and coworkers[6-8] have shown that the carbon skeleton is assembled from seven acetate units, six propionate units and two carbons of unknown origin (Figure 2) in a manner

Figure 2



inconsistent with the prototypes proposed by Cane *et al*[9]. A range of possibilities exist for the closure of the carbocyclic ring, the most interesting being a polyene cyclization of a tetraene such as (3) wherein both rings would be formed in chair conformations with all groups equatorial.



P = protecting group

It is possible this polyene cyclization could occur without enzymatic catalysis if, as seems likely from model studies, a suitable cation could hold the molecule in the correct conformation.

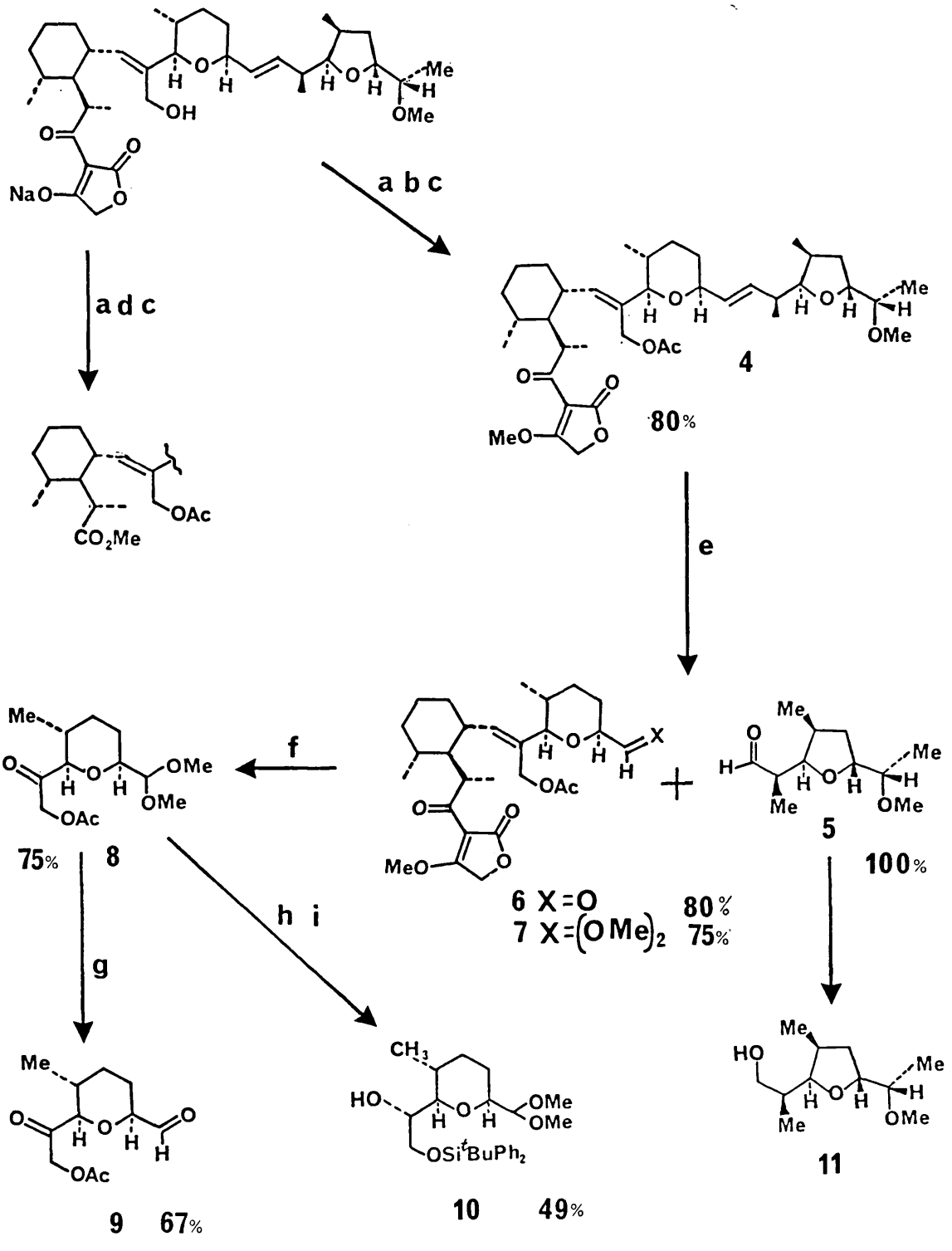
2. Chemical Transformations on M139603

Workers[10,11] in this laboratory have carried out the following degradations on M139603 (Scheme 1).

Direct ozonolysis of the sodium salt (1a) or the free acid (1b) gave only one aldehyde (5). However, ozonolysis at -78°C of its derivative (4) where the C-30 hydroxyl had been acylated and the tetronic acid protected as its methyl ether, selectively cleaved the C18, C19 double bond to give in good yield aldehydes (5) and (6). (5) could be simply separated from (6) by extraction with petrol in which it was soluble and (6) was not. Reduction of (5) gave alcohol (II) which was independently synthesised in 16 steps from (+)-S-methyl-3-hydroxy-2-methylpropionate by Doherty and Ley[12]. Further ozonolysis of (6) at -20°C brought about a Baeyer-Villiger type rearrangement of the aldehyde grouping to a tetrahydropyran lactol. In order to cleave the C11, C12 double bond, (6) was protected as it dimethyl acetal (7) which underwent smooth ozonolysis at -20°C to give ketone (8). No left-hand aldehyde could be isolated; presumably concurrent scission of the tetronic acid moiety to an unstable ester-diketone destroyed this half. Acetal (8) could be converted to aldehyde (9) with boron tribromide, or alternatively in three steps to its silyl derivative (10). The independent synthesis of (10) from pulegone is discussed in section 4 of this chapter.

To allow a fragment containing the carbocyclic ring to be isolated, it seems likely that the unstable tetronic acid group will have to be removed. One possible method might be chromic acid oxidation[13] of the

Scheme 1



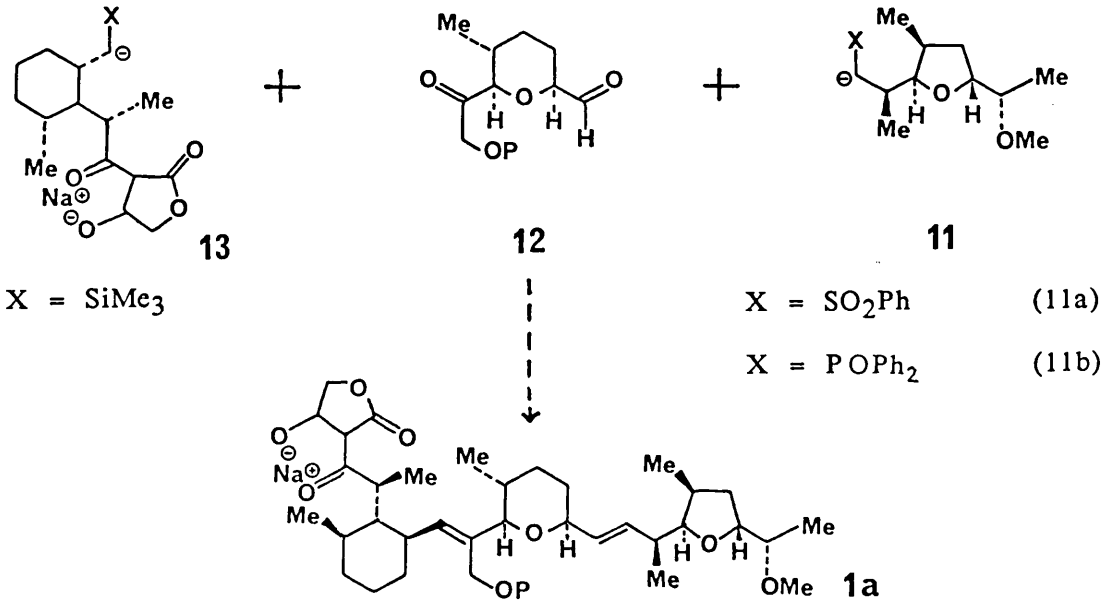
Reagents (a) Ac_2O; (b) H_3PO_4; (c) CH_2N_2; (d) CrO_3, HOAc; (e) O_3, -78°C, Me_2S; (f) O_3, MeOH, -20°C; (g) BBr_3; (h) $LiAlH_4$; TBDPSCl; (j) $(COCl)_2$, DMSO, NEt_3, DCM.

30-O-acetyl derivative of (1) which should give a C-3 carboxylic acid. At the time of writing this reaction has not been tried.

3. Overall Strategies

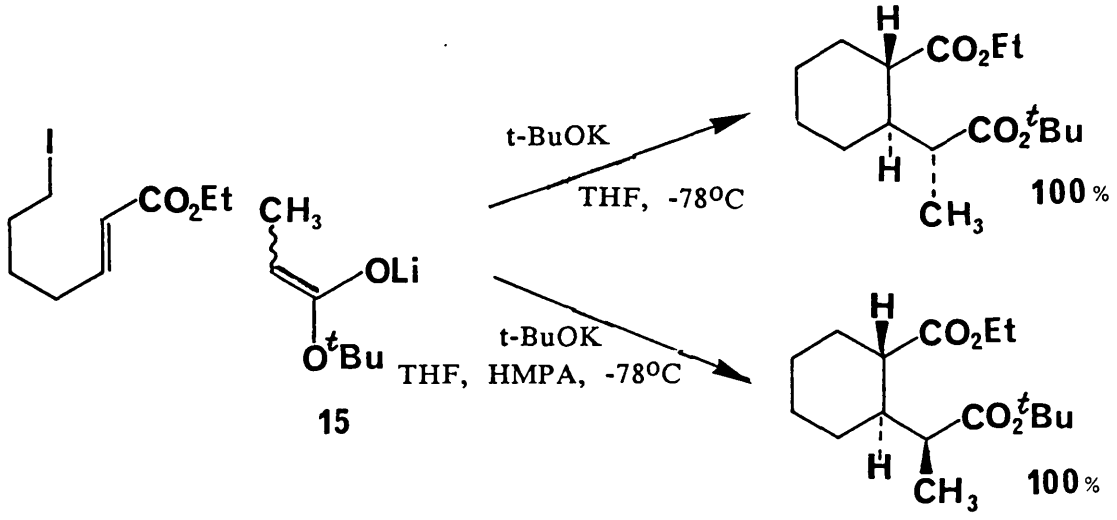
Two synthetic strategies are being pursued towards M139603 in this laboratory. Chronologically the first, shown in Scheme 2, involves the coupling of three advanced fragments (11), (12) and (13). (11) and (12) could be completed either by Julia Sulphone-aldehyde methodology or by a Schlosser-Wittig reaction to give a C18, C19 double bond. The coupling of ketone (12) with an unstabilized fragment (13) is unlikely to proceed stereospecificially. However, if a Peterson reaction were employed, the intermediate trimethylsilyl- alcohols could be separated and eliminated either *syn* or *anti* to give the desired E trisubstituted double bond.

Scheme 2

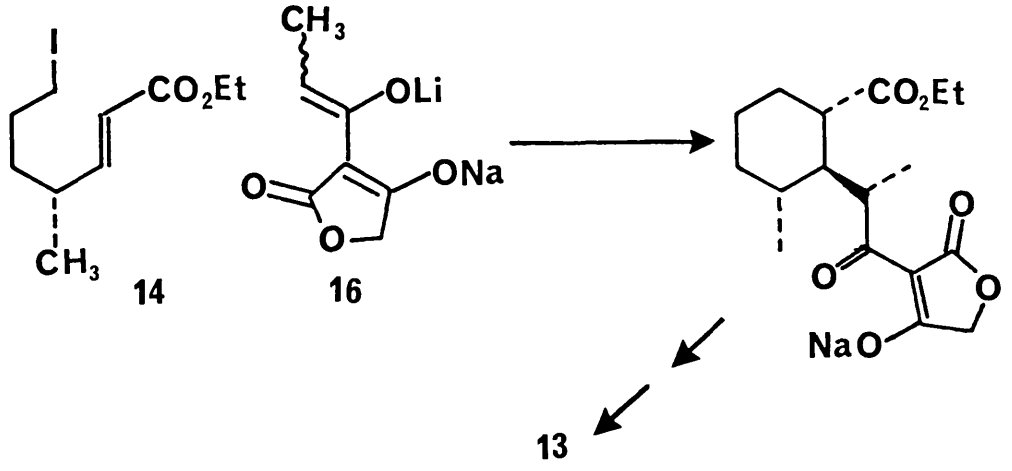


The tetrahydrofuran-sulphone (11a) and diphenylphosphine oxide (11b) have been synthesised in this laboratory by Doherty[10,12], while the synthesis of the central fragment is described in this thesis. Yamaguchi *et al*[14] have reported the stereoselective synthesis of six-membered

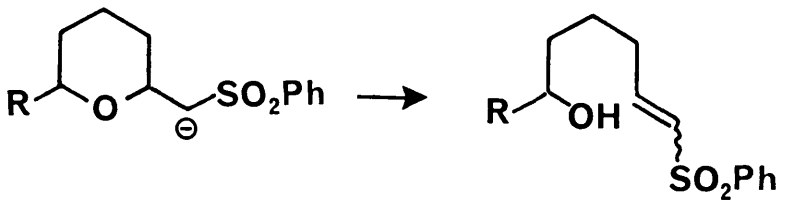
carbocyclic compounds containing an extracyclic chiral centre by Michael induced intramolecular alkylation.



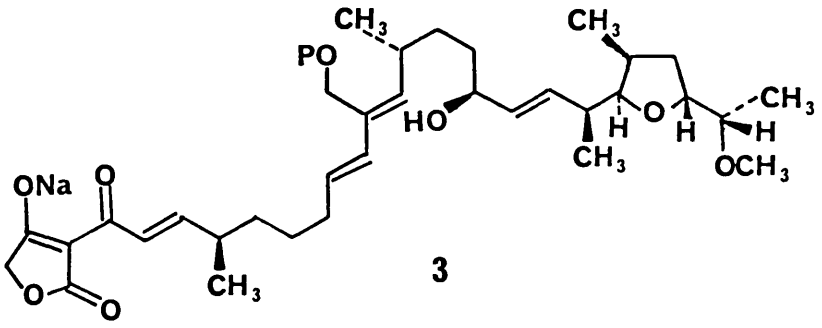
If unsaturated ester (14) were treated with ester enolate (15) or an acyltetronic acid enolate dianion (16) and t-BuOK in THF/HMPA, it might lead to an efficient preparation of the left-hand synthon (13).



We chose not to place the electron-withdrawing groups for the coupling reactions upon the central tetrahydropyranyl fragment since carbanions α to the heterocyclic ring have a tendency to β eliminate[15].



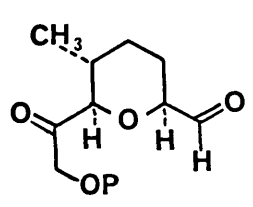
A 'biomimetic' approach proposed independently by Ley and Staunton[8] involving the assembly and polyene cyclization of (3) is also being investigated in the group.



3

4. Synthetic Studies toward the Tetrahydropyran Fragment of M139603

A tetrahydropyran synthon suitable for sequential coupling to first a right-hand tetrahydrofuran fragment, e.g. (11a) and then to a left-hand unit might have structures (17), (18) or (19). If a sulphone-coupling with (11a) showed a preference for addition to an aldehyde over a



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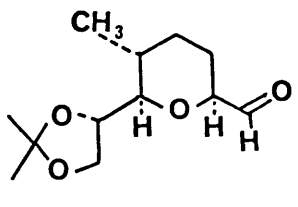

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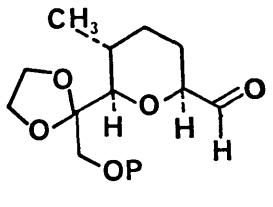
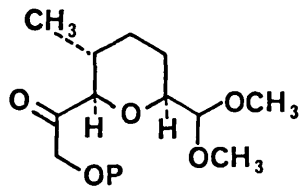


19

ketone (which it might, particularly if the ketone had a bulky protected α-hydroxy substituent) then (17) would be operationally the best synthon

to use. If it did not, then (18) or (19) would be more suitable. (18) is to be preferred over (19) because it requires less steps to make.

If it were planned to couple first with the carbocyclic left-hand fragment, then the synthon should have structures (20) or (21). Since



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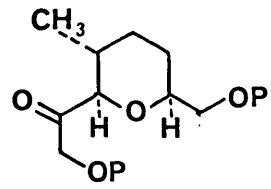
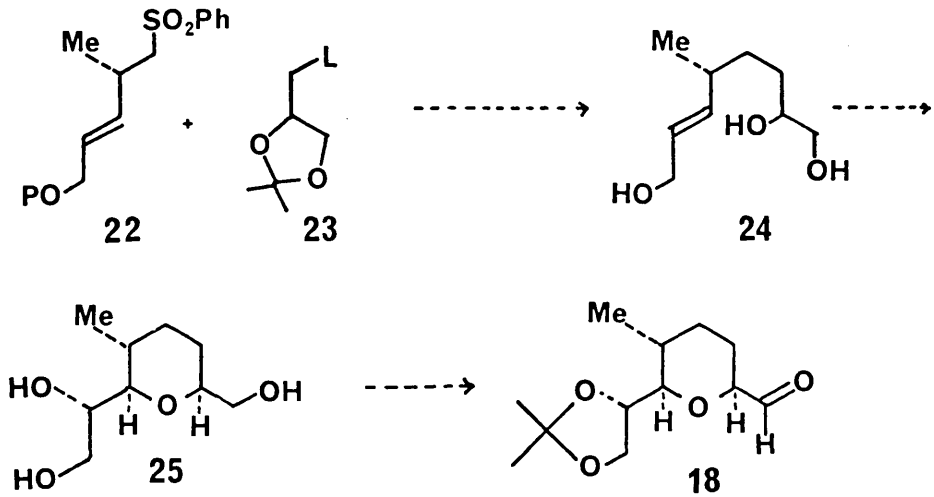


21

no left-hand material was available either by degradation or by total synthesis at the time this work was undertaken, these structures were discounted. It should be noted that both (20) and (18) are easily transformed to (17) in one and three steps respectively.

We chose to synthesise (18) initially, since this is a synthetic precursor to (17). Analysis of the structural features of (18) suggest that it might be constructed by the Sharpless epoxidation with simultaneous ring closure of the allylic alcohol (24) to triol (25). The acetonide of (25) might then be oxidized to aldehyde (18) (Scheme 3).

Scheme 3

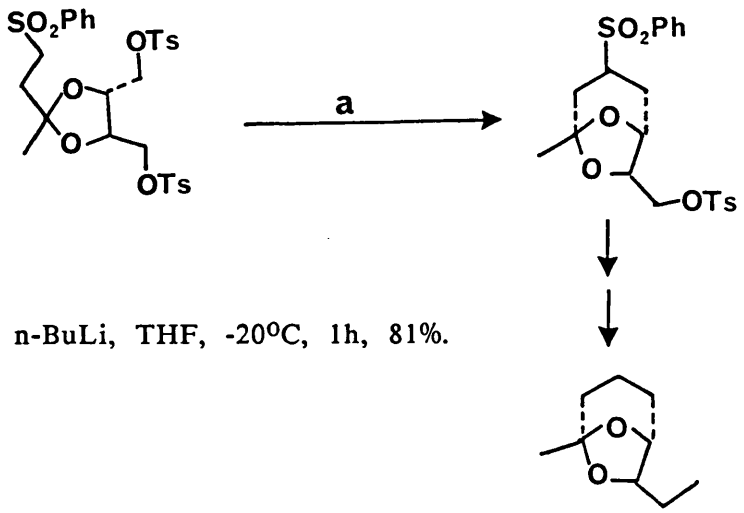


L = leaving group

P = protecting group

The allylic alcohol (24) might be generated by the coupling of a fragment (23) derived from D-mannitol and a sulphone (22). Masaki *et al*[16] used a similar sulphone coupling step in their synthesis of exo-brevicomin (26) (Scheme 4).

Scheme 4

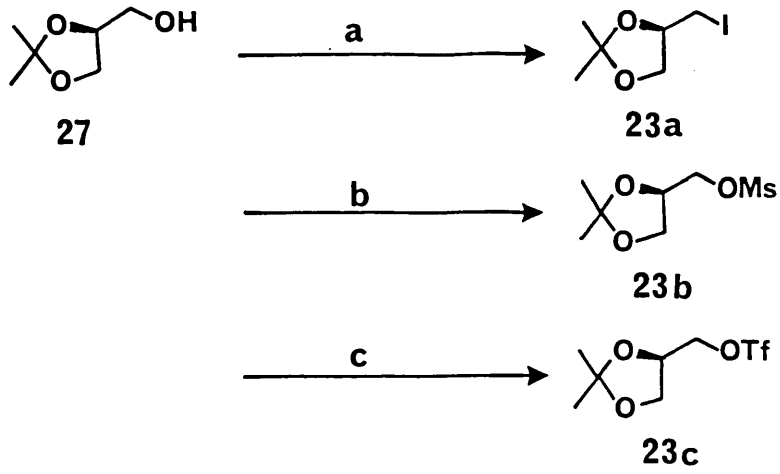


Reagents (a) n-BuLi, THF, -20°C, 1h, 81%.

26

The synthesis of (23) was accomplished as follows: D-mannitol was protected as its 1,2:5,6-diisopropylidene derivative with $ZnCl_2$/acetone in 53% yield. Cleavage of the 3,4-diol with $Pb(OAc)_4$ in benzene followed by reduction of the crude aldehyde with $NaBH_4$/methanol furnished 2-(S),3-O-isopropylidene-glycerol (27) in 81% yield according to the procedure of Fischer *et al*[17]. As shown in Scheme 5, (27) was converted to its iodide (23a) with Ph_3P, I_2 and pyridine in acetonitrile in 23% yield after chromatography (unoptimized). Conversion of (27) to the mesylate (23b) was accomplished in 98% yield with mesyl chloride and triethylamine in dichloromethane. The triflate (23c) was prepared in near quantitative crude yield by treating (27) with triflic anhydride and triethylamine in dichloromethane at -10°C.

Scheme 5

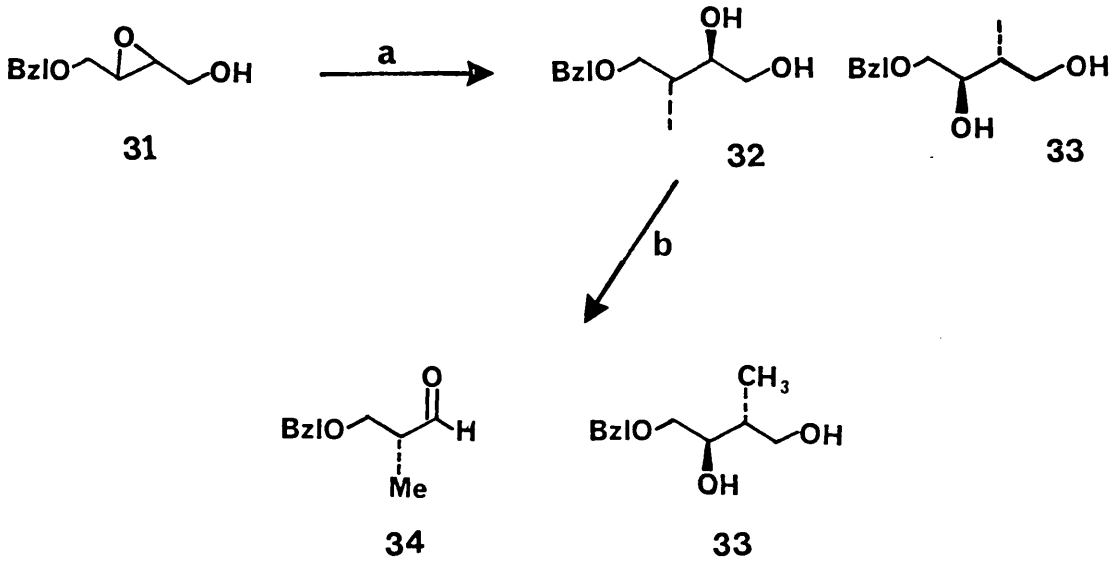


Reagents (a) Ph_3P, I_2, py, MeCN, 23%; (b) MsCl, Et_3N, DCM, -10°C, 98%; (c) $(CF_3SO_2)O$, Et_3N, DCM, -10°C, ~ 100% crude.

The sulphone was prepared by an eleven step route from propargyl alcohol, as shown in Scheme 6. Propargyl alcohol was benzylated with benzyl bromide and powdered sodium hydroxide in DMSO to afford (28) in 95% distilled yield. The anion of (28) was formed with n-BuLi in THF at -30°C and quenched with paraformaldehyde to give the mono protected 2-butyn-1,4-diol (29) in 66% yield. Reduction of the acetylene (29) with two equivalents of lithium aluminium hydride at 0°C in THF gave stereoselectively the *trans* allylic alcohol (30) [J_{23} 16.5 Hz] in 63% yield with 31% overreduction to the saturated alkane. The desired product was purified by chromatography. Sharpless epoxidation[18] of (30) using a 1.2 equivalents of natural (+) diethyl L-tartrate followed by a brine-saturated aqueous sodium hydroxide workup[19] afforded the (S,S)-epoxide (31) in 76% yield. The (S,S)-epoxide (31) had an $[\alpha]_D^{22}$-20.52°, (*c* = 0.78 in DCM) compared with $[\alpha]_D^{21}$ + 21.4° (*c* = 1.40 in $CHCl_3$) observed by Sharpless *et al*[20] for its (R,R)-antipode. They

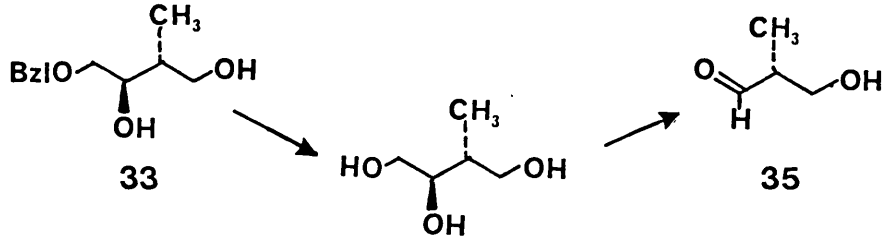
claim an enantiomeric excess of > 95% ee, therefore the (S,S)epoxide (31) must have > 91.5% ee. Treatment of epoxide (31) with trimethyl aluminium in CH_2Cl_2 at 0°C according to the method of Roush *et al*[21], gave an inseparable 5:1 mixture of diols (32) and (33) (Scheme 7). The

Scheme 7



Reagents (a) Me_3Al, DCM, 0°C; (b) $NaIO_4$, THF, H_2O, 67% for a and b.

crude mixture was treated with $NaIO_4$ in (1:1) THF:H_2O which only cleaved with 1,2-diol (32) affording the separable aldehyde (34) in 67% yield over the two steps. Since the aldehyde-alcohol (35)

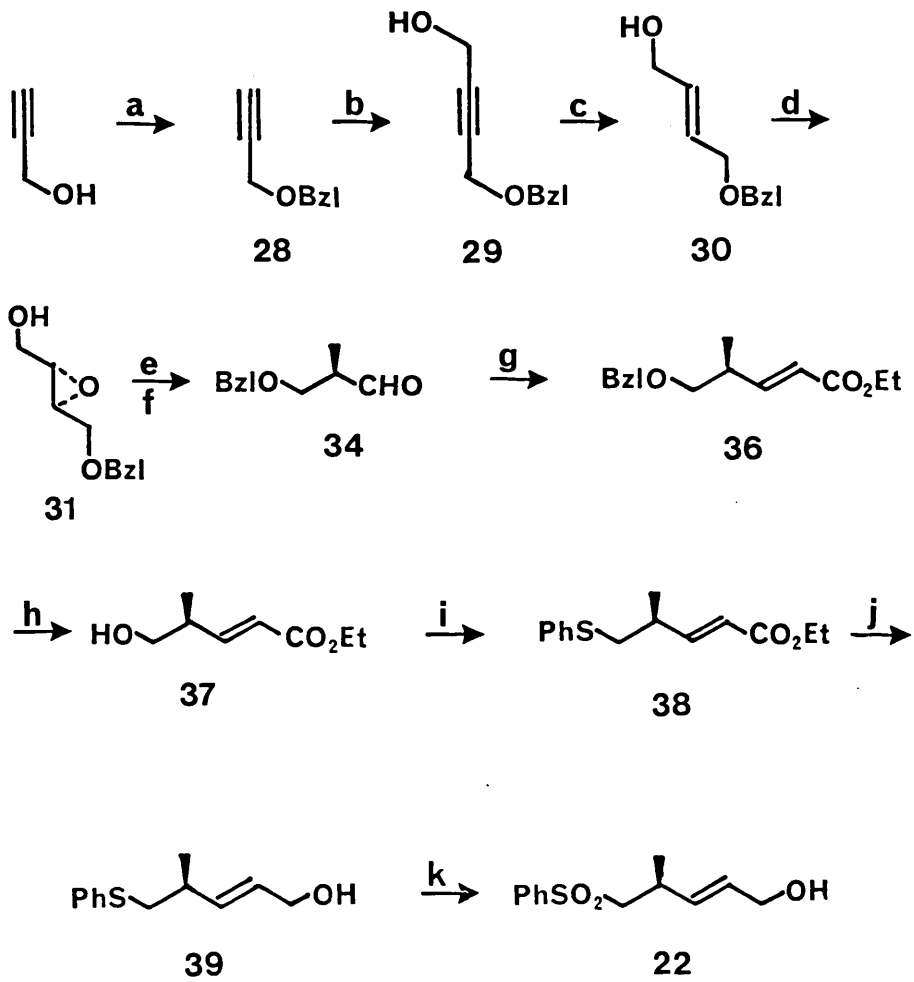


might also be a useful synthetic intermediate, attempts were made to convert the side product (33) to it via debenzylation and diol cleavage.

However, none of the polar triol intermediate could be isolated after treatment of (33) with either H_2,10% Pd/C or $Na,NH_{3(\ell)}$.

Aldehyde (34) was reacted with Ph_3PCHCO_2Et in benzene at 80°C for 2 hr to give a 97% yield of the *trans* unsaturated ester (36). [J_{23} 16 Hz]. Although no *cis* compound could be detected in the chromatographed material, the possibility that a small amount (< 3%) may have been 'columned out' cannot be excluded. (36) was debenzylated with Cl_3SiMe,NaI[22] in dry acetonitrile in 87% yield.

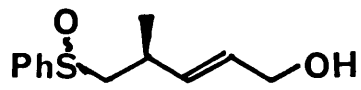
Scheme 6



(a) $PhCH_2Br$, NaOH, DMSO; (b) n-BuLi, $(CH_2O)_n$; (c) $LiAlH_4$; (d) (+) L-DET, $Ti(i\text{-}OPr)_4$, t-BuOOH; (e) Me_3Al; (f) Ph_3PCHCO_2Et; (h) Cl_3SiMe, NaI; (i) NPSS, Bu_3P; (j). DIBAL-H; (k) oxone.

Initial attempts to convert alcohol (37) to sulphide (38) via mesylation and treatment with sodium thiophenylate were unsuccessful, since the thiolate anion underwent concurrent Michael addition to the unsaturated ester grouping, giving a complex mixture of products. The conversion (37) to (38) was effected in 94% yield using tri-n-butylphosphine and N-phenylsulphenylsuccinamide[23] (NPSS) in THF[24] at 0°C. Ester (38) was reduced to alcohol (39) with DIBAL in THF in 75% yield, which was oxidized to sulphone (22) by three equivalents of oxone[25] in 1:1 H_2O:MeOH at 0°C in 81% yield.

Two other methods were tried for the oxidation of the sulphide to the sulphone. These were meta-chloroperbenzoic acid and the combination of hydrogen peroxide and phenyl diselenide[26]. Treatment of (39) with two equivalents of MCPBA in CH_2Cl_2 gave products arising from oxidation of both the sulphide to a sulphoxide or sulphone and epoxidation of the double bond. Treatment of (39) with phenyl diselenide and 30% aqueous hydrogen peroxide in wet ether at 0°C for 6 h did give some sulphone (22) albeit in poorer yield (32%), along with greater amounts of sulphoxide (40) (54%).



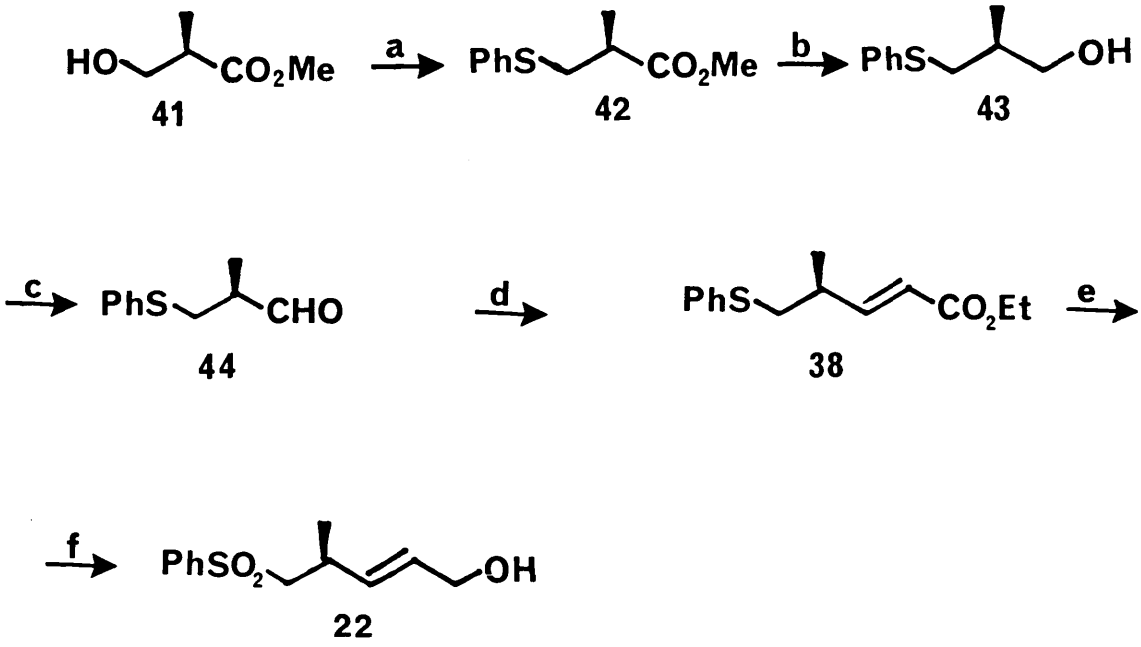
40

This route had yielded 3g of sulphide-alcohol (39) when in May 1984 it was superceded by a second shorter sequence from a new commercial product, methyl-3-hydroxy-2-(R)-methylpropionate (41), obtained by the bacterial oxidation of isobutyric acid followed by esterification[26].

This second route to sulphone (22) is shown in Scheme 8. Methyl-3-hydroxy-2-(R)-methylpropionate (4) was smoothly converted to

its phenylsulphide (42) in 93% yield using 1.5 equivalents of tri-n-butylphosphine and phenyl disulphide in THF[27].

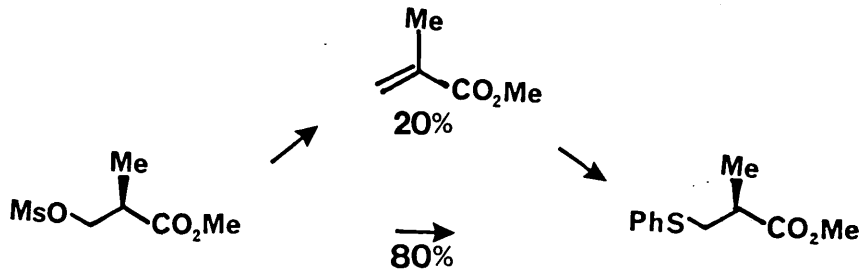
Scheme 8



(a) PhSSPh, n-Bu_3P; (b) $LiAlH_4$; (c) $C_2O_2Cl_2$, DMSO, NEt_3; (d) Ph_3PCHCO_2Et; (c) DIBAL-H, THF; (f) oxone.

This transformation was also effected using a two-step procedure; mesylation followed by displacement with sodium thiophenylate. Comparison of the optical rotations of sulphide (42) obtained from either route $[\alpha]_D^{22}$-67.3° and -54.2°, indicated that 20% racemization had occurred in the mesylation-displacement procedure; presumably owing to

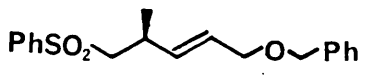
base catalysed elimination of methanesulphonic acid and Michael addition of phenylthiolate anion to the resultant unsaturated ester.



SN2 displacement

In a control experiment it was shown that (42) could not be racemized by NaSPh. Ester (42) was reduced with lithium aluminium hydride in 90% yield to alcohol (43) which was oxidized in a Swern reaction[28] to aldehyde (44) in 73% yield. Treatment of (44) with Ph_3PCHCO_2Et in benzene at RT gave stereospecifically the *trans* unsaturated ester (38) in 87% yield. This was converted in two steps as in the previous route to sulphone-alcohol (22).

In order to avoid the complication of having two sites for alkylation, as in coupling of the dianion of (22) with species (23 a-c), we first protected the hydroxyl function. Treatment of (39) with benzyl bromide and sodium hydroxide in DMSO gave benzyl ether (45) in 82% yield and oxidation with oxone afforded a new sulphone (46) in 53% yield.

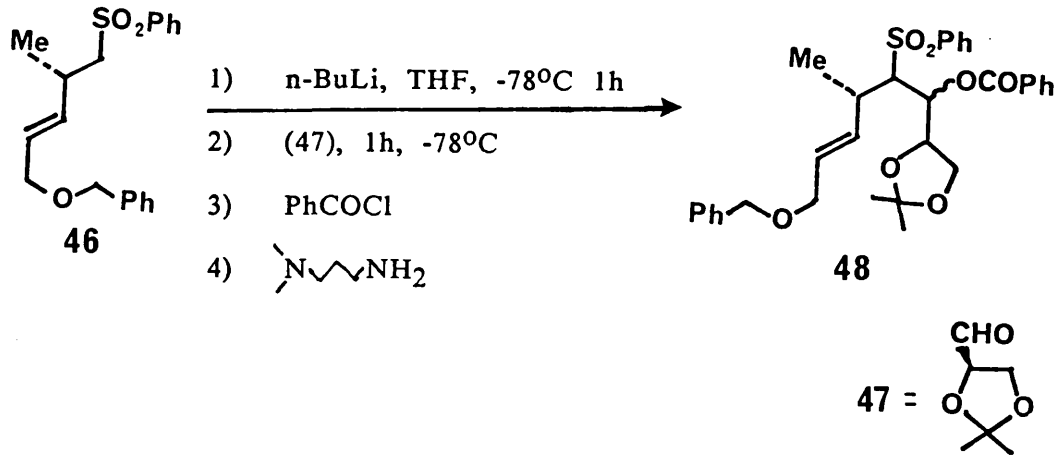


46

To determine if (46) could be deprotonated α to the sulphone group, (46) was treated with 1.1 equivalents of n-butyl lithium at -78°C giving a deep yellow solution. The solution was warmed to -40°C over 15 min and quenched with D_2O. N.m.r. analysis of the recovered sulphone showed a reduced integral for the 5-H_2 proton signal at

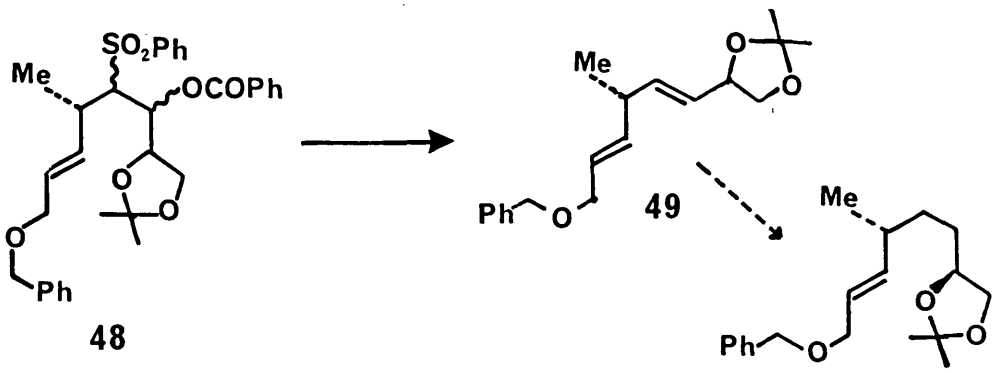
δ 3.04 and δ 3.17 indicating that the anion had formed. However, when (46) was deprotonated with n-BuLi in THF at -78°C and quenched with the mesylate (23b), only starting material was recovered on workup. After this failure, we tried alkylation with a more reactive alkylating agent. No reaction was observed between the anion of (46) with allyl bromide in THF at -78°C → 0°C 3h, in THF with one equivalent of HMPA -78°C → RT, 4h, or in (1:4) HMPA:DME. In addition, (46) could not be alkylated with 1-bromohexane.

Despite being unreactive towards alkyl halides, treatment of (46) with n-BuLi at -78°C in THF followed by addition of 2-(R),3-O-isopropylidene glyceraldehyde (47) and then of benzoyl chloride[29] after 1 h at -78°C, gave a 57% yield of the addition products (48)



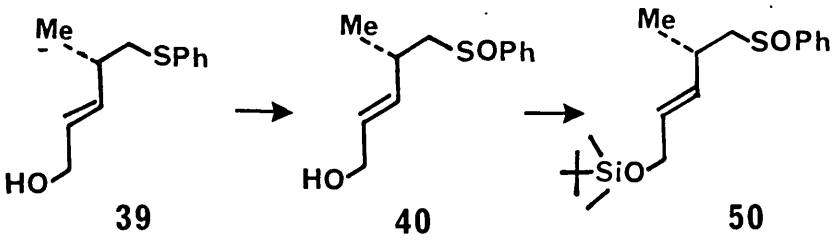
(48): δ(90 MHz) 0.90-1.65 (10H, m, 4-H, 4-Me, acetal Me_2), 3.31 (1H, m, 5-H), 3.7-4.3 (4H, m, 6-H, 7-H, 8-H_2), 4.50 (2H, m, 1-H_2), 5.35 (2H, s, CH_2Ph), 5.5-5.85 (2H, m, 2-H and 3-H), and 7.25-8.3 (15H, m, 3Ph); $\nu_{max.}$ 3062, 2934, 1725 (-OCOPh), 1681 (C=C), 1450, 1308 (-SO_2Ph), 1149 and 713 cm^{-1}; *M/Z* 552 (M^+), 537 (M^+-CH_3), 427 (M^+-3-$PhCO_2H$), 407 (M^+-3-$PhSO_2$), 105 ($PhCO^+$) and 91 ($PhCH_2^+$).

One attempt was made to reduce (48) with 6% sodium amalgam[30] in sodium dihydrogen phosphate buffered methanol to olefin (49), but



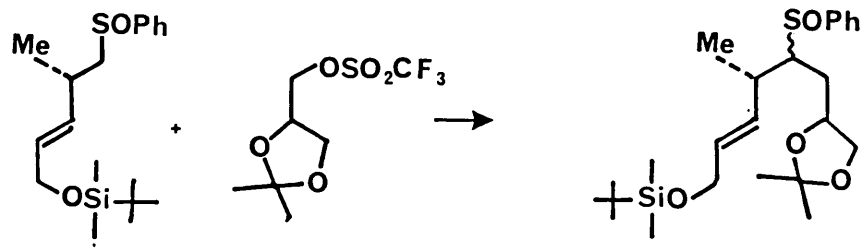
neither starting material nor product could be isolated from the reaction mixture. This experiment was not repeated because (49) would require selective reduction of its C5-C6 double bond to be synthetically useful. While this might be possible by selective deprotection of the C-1 hydroxyl, Sharpless epoxidation and then reduction of the double bond, it adds unnecessary complications to the route. We chose instead to examine alkylation reactions of derivatives of the sulphoxide (40).

Sulphide (39) was converted to sulphoxide (40) using sodium periodate[31] in water:methanol in 97% yield and (40) was silylated to (50) in 98% yield with t-butyldimethylsilylchloride and imidazole in DMF[32].



Deprotonation of (50) with n-BuLi in THF at -78°C gave a deep yellow solution of the anion which was reacted in separate experiments

with the iodide (23a), the mesylate (23b) and the triflate (23c). No apparent reaction was observed by t.l.c. in any of these experiments. The position of one starting material, (50), could be determined on the t.l.c. plate either under a U.V. lamp or by a number of spray reagents. However, the position of the iodide (32a) and the mesylate (23b) could not be identified. Reaction with the triflate (23c) gave rise to much base-line material. However, workup of this reaction and chromatography gave a fraction (corresponding to approximately 20% by weight of the starting materials) coeluting with or marginally less polar than the starting sulphoxide (50). Examination of the n.m.r. of this fraction indicated that the silyl group and the phenyl sulphoxide and isopropylidene groups were all present in the sample. In order to determine if the fraction contained (51) and not an inseparable mixture of (50) and (23c), the mass spectrum was taken. The results looked

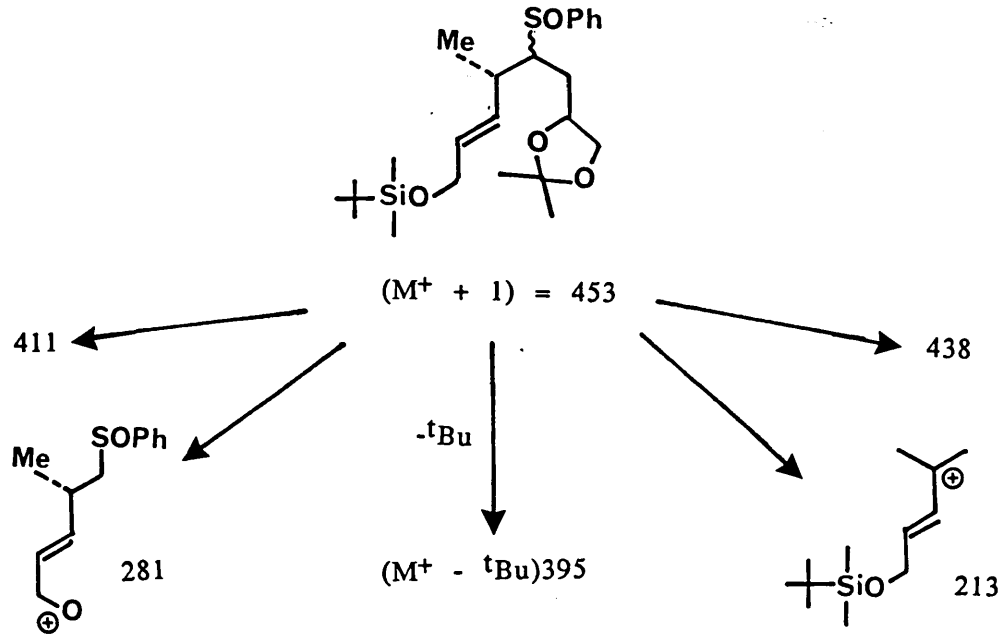


50 **23c** **51**

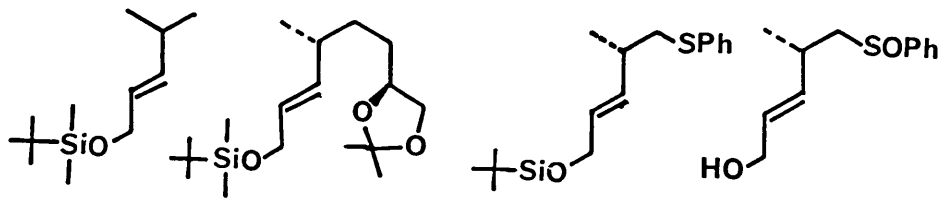
discouraging because although the mass spectrum contained higher mass peaks than 322 (the cation obtained by loss of oxygen from sulphoxide (50)), they were inconsistent with the fragmentation of (51).

Whilst reexamining this spectrum prior to writing up, I discovered that mass-scale had been incorrectly counted up from N_2^+ = 28, resulting in a 23 unit discrepancy in the region 350-500. Introducing this change, the spectrum is now consistent with the fragmentation of (51) (Scheme 9).

Scheme 9



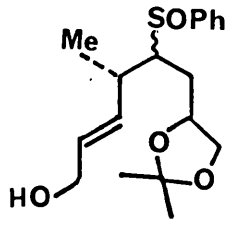
The n.m.r. of a fraction co-eluting with (50) isolated from the reaction of (50) and the mesylate (23b) also contained both phenyl sulphoxide and isopropylidene groups, although the latter's signals were much weaker. In an attempt to separate (50) from (51) we tried sodium-amalgam reduction[30] of the sulphoxide groupings expecting to obtain (52) and (53).



52 **53** **54** **40**

A new non-polar product was formed in this reaction and was subsequently identified as (54), but much of the starting mixture remained. This mixture was treated with tetrabutylammonium fluoride in THF[33] to obtain a 40% yield of (40) and a second less polar alcohol containing both a phenylsulphoxide moiety and an isopropylidene group

in low yield. This would be consistent with (55) although the



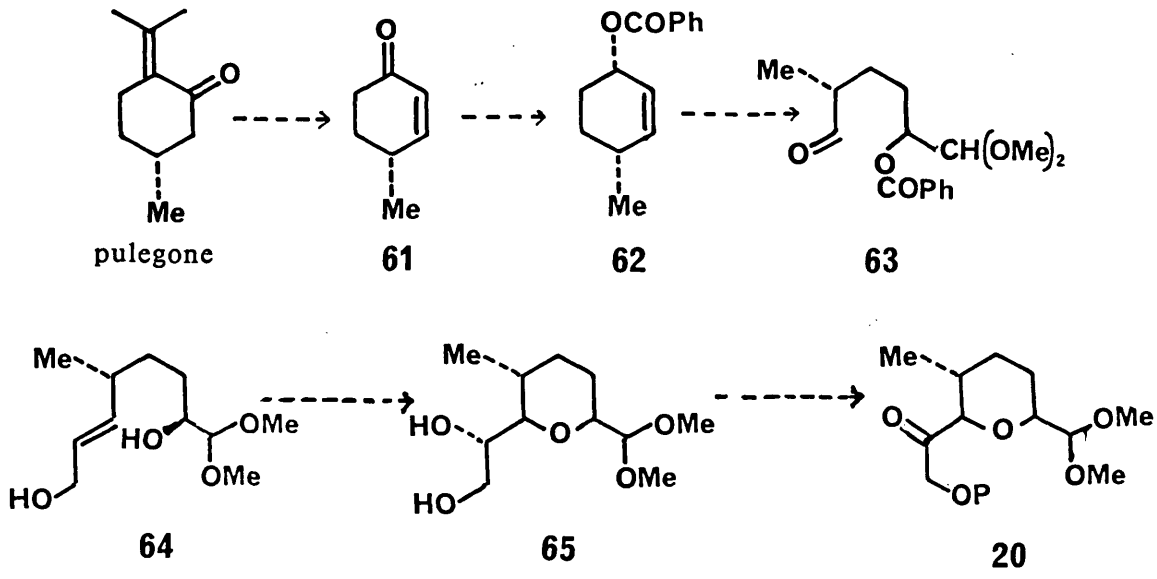
55

materials was not fully characterized. This material was lost in an attempted Sharpless epoxidation. Presumably the products were water-soluble.

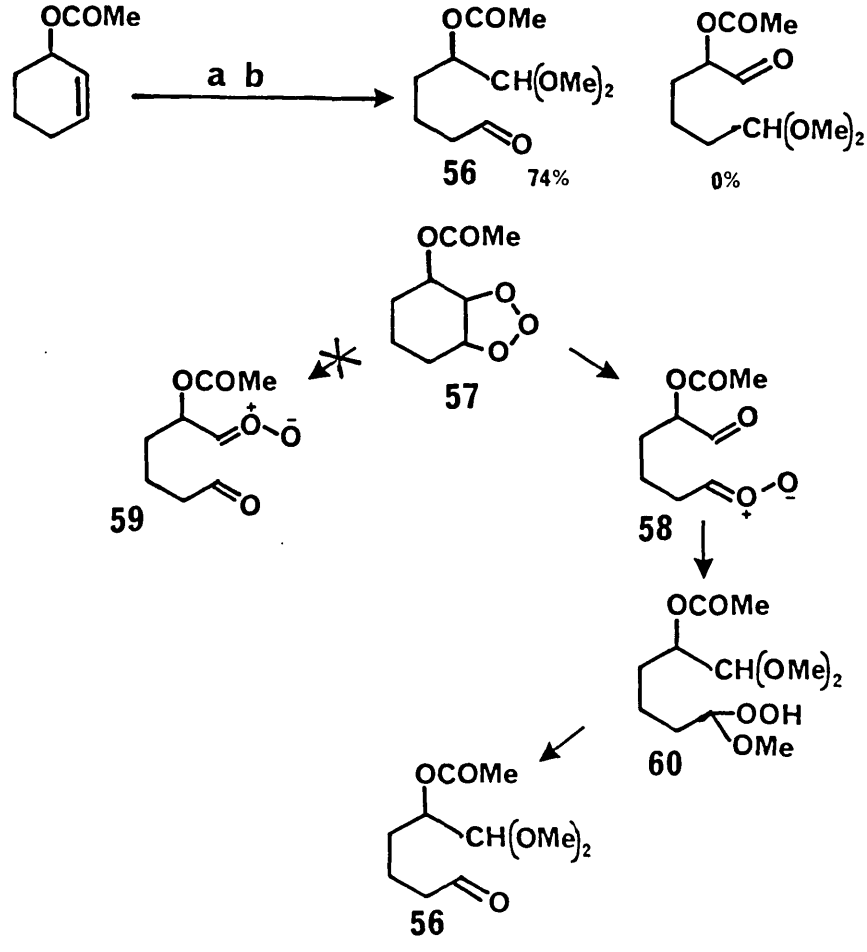
At this point we decided to abandon the route being uncertain as to whether or not the key coupling step had worked. As explained above, it is likely from revised mass spectral evidence that we had synthesised (51) in low yield.

Reexamination of our proposed target molecules (17)-(21) uncovered an attractive approach to synthon (20) employing as its key step an ozonolysis reaction (Scheme 10). Schreiber *et al*[34] have reported that terminally differentiated products can be obtained from the ozonolysis of cycloalkenes in methanol. Moreover, high regioselectivity is observed particularly if the double bond has an electron-withdrawing group α to it. For example, treatment of 3-acetoxycyclohexene with ozone in methanol containing a little *p*-toluenesulphonic acid, followed by sodium carbonate buffered dimethylsulphide work-up, is reported to give a 74% yield of acetal-aldehyde (56)[34] with no regioisomeric material (Scheme 11). This owes to preferential 2+3 retrocycloaddition to (58) and not (59), so that the electron withdrawing acetoxyl substituent is remote from the electrophilic carbon of the carbonyl oxide. 1,3 Addition of the methanol to the carbonyl oxide and acetalization of the aldehyde leads to the α-methoxy hydroperoxide (60) which is reduced to (56).

Scheme 10



Scheme 11



Reagents (a) O_3, MeOH, TsOH, -78°C → RT, 2h; (b) Me_2S

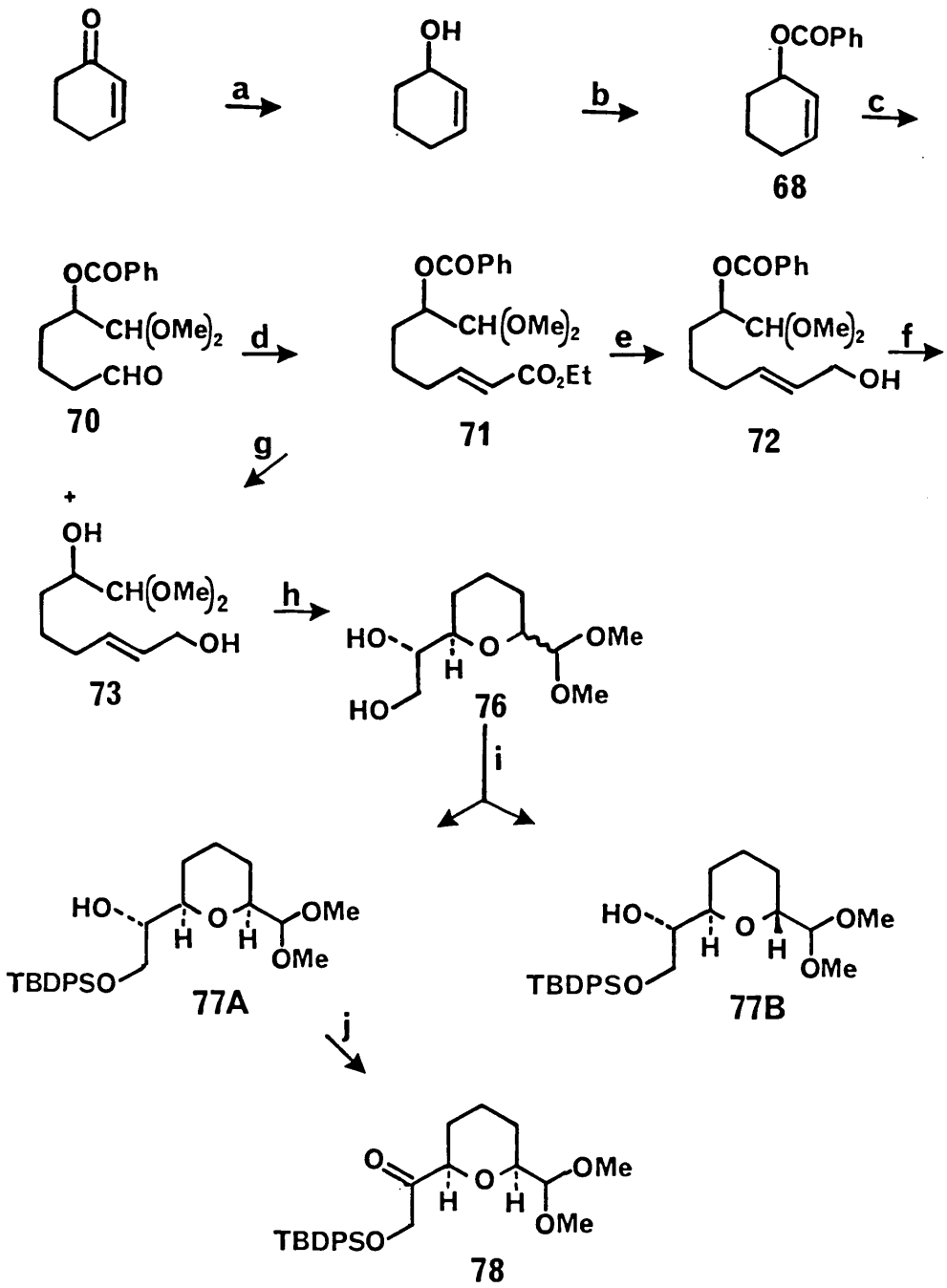
Recalling Scheme 10, treatment of allylic benzoate (62) under identical conditions should give aldehyde-acetal (63) and two steps later, a modified Sharpless reaction[35,36] on (64) should furnish diol (65) leading easily to synthon (20). It was envisaged that the *cis* relationship between the hydroxyl and the methyl groups in (62) might be obtained with equatorial attack of a bulky hydride reducing agent upon enone (61). The synthesis of (61) has been reported by Silvestri[37].

So as to optimise the yield for the key ozonolysis step and also provide a model substrate for coupling reactions with the tetrahydrofuranyl fragments (11a) and (11b), we tried our route on a model compound, 2-cyclohexenone (66) (Scheme 12). Reduction of (66) with lithium aluminium hydride gave a 95% distilled yield of racemic 3-cyclohexenol (67). Treatment of (67) with benzoyl chloride in pyridine gave benzoate (68) in 84% yield. Alternatively, (68) could be produced in 64% yield by a Mitsunobu reaction[38] of (67) with triphenylphosphine, diethylazodicarboxylate and benzoic acid.

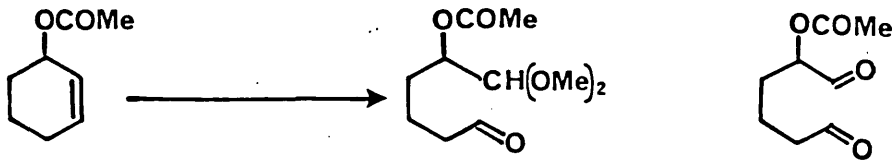
3-Acetoxycyclohexene was also prepared from (67) and acetic anhydride in 90% yield.

Attempts to repeat Schreiber's work[34] on 3-acetoxycyclohexene by ozonolysis in 5:1 dry dichloromethane-methanol at -78°C, followed by stirring the reaction mixture at RT for 2 h with 10% by weight of *p*-toluenesulphonic acid and finally by sodium hydrogen carbonate buffered dimethylsulphide work-up gave low to moderate (15-53%) yields of aldehyde-acetal (56) with no regioisomeric material. The other major product produced in up to 75% yield from these reactions was the dialdehyde (69).

Scheme 12



Reagents (a) $LiAlH_4$, 95%; (b) PhCOCl, py, 84%; (c) O_3, MeOH, -78°C; $(MeO)_3CH$, K10 clay, RT; PPh_3, $NaCO_3$, 58%; (d) Ph_3PCHCO_2Et, 82%; (e) DIBAL, THF, -78°C, 76%; (f) KOH, MeOH, 86%; (g) DIBAL, THF, -78 → 0°C, 84%; (h) 2.2 eq $Ti(OiPr)_4$ (+) L -DET, t-BuOOH, -20°C 12h; Me_2S, 40°C 2h; NaF w.u., 64%; (i) TBDPSCl, imidazole, DMF, 37%; (j) $(COCl)_2$, DMSO, NEt_3, 84%.

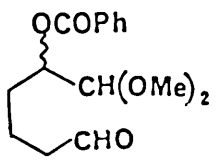


56 69

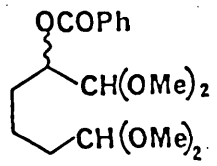
There were two possible reasons for the failure to form the monoacetal intermediate (60) (see Scheme 11). These were either that the ozone supply was introducing water into the reaction mixture, so making acetalization unfavourable under equilibrium conditions, or that the primary ozonide (57) had not decomposed to any great extent during the acetalization process and was reduced directly by dimethylsulphide to dialdehyde (69). To counter the first possibility, the reaction flask was scrupulously dried and charged with dry solvents, substrate and acid catalyst under argon. Ozone was passed through a 1 metre calcium chloride drying tube before being bubbled through the reaction-mixture. Once ozonolysis was complete, evidenced by the blue-violet colour that excess ozone imparts to the reaction-mixture, the solution was warmed to room temperature and stirred for 4-6 h under argon. Reduction as before gave an optimum yield of 53% after several experiments. Replacement of *p*-toluenesulphonic acid by camphorsulphonic acid or amberlyst $4A^{o}$ resin did not give a consistent improvement in yields. Since we knew from our concurrent study of the real system that 4-methyl-1-acetoxy- cyclohex-2-ene was too volatile to be handled easily, we turned our attention to benzoyloxy derivative (58).

Ozonolysis of (68) also gave very variable yields of the desired aldehyde-acetal (70). An optimum yield of 58% was obtained using K10-clay[39] and trimethylorthoformate in place of the acid catalyst. The product distributed from this reaction was quite different from that

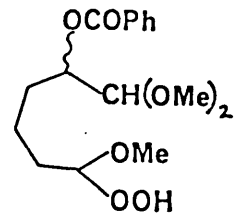
obtained with other acid catalysts. The other major components were the bis – acetal (70A) and the unreduced diastereomeric α-methoxyhydroperoxides (70B). This modification was also capricious



70



70A



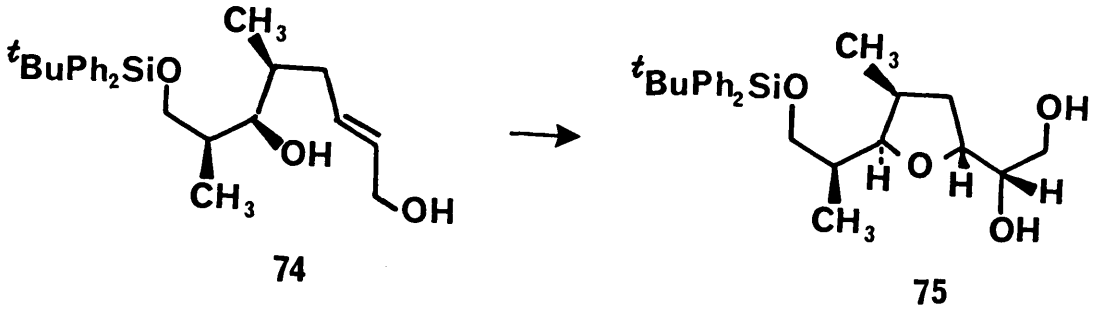
70B

since trimethylorthoformate could replace the hydroperoxide group of the hemimethoxy acetal giving synthetically worthless (70A). Thus stirring the ozonolysed mixture with the K10 reagent for 15-20 min gave optimum yields of (70). The proportion of unreduced peroxides (70B) in the final mixture could be reduced but not eliminated by employing triphenylphosphine rather than dimethylsulphide for the reductive step.

Reaction of (70) with the stabilized ylid Ph_3PCHCO_2Et gave the *trans* unsaturated ester (71) in 82% yield with 1.5% of the *cis* ester. Reduction of (71) in THF with excess DIBAL-H at -78°C gave (72) in 84% yield if quenched at that temperature, or (73) if the reaction mixture was first allowed to warm to RT. Ester (72) was saponified by methanolic potassium hydroxide to alcohol (73) in quantitative yield.

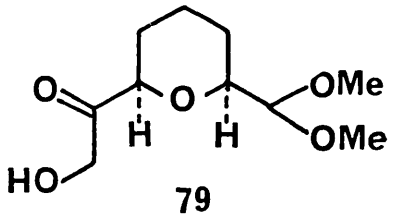
Doherty[12,36] has reported that enantioselective Sharpless epoxidation of (74) with titanium (IV) isopropoxide (2 eq), L-(+)-diethyltartrate (2.4 eq) and t-butylhydroperoxide (5 eq) at -20°C in DCM gave a 75% yield of a watersoluble diol (75) after sodium fluoride work-up[40].

Treatment of (73) under identical conditions gave mixtures of tetrahydropyran diols (76) together with unclosed epoxide diols. However, if after 16 h at -20°C, the excess t-butylhydroperoxide was quenched with dimethylsulphide and the reaction mixtue was refluxed



74 75

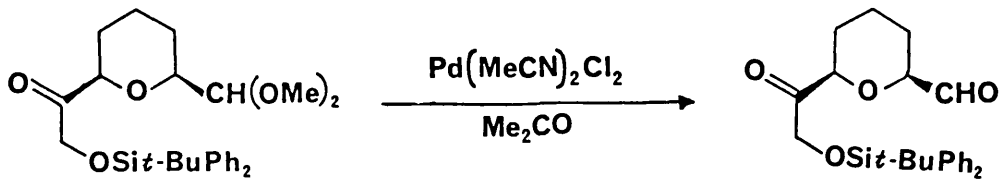
for 1 hr at 40°C, a 64% yield of inseparable diols (76) was obtained upon sodium fluoride work-up. The primary hydroxyls of (76) were selectively protected with TBDPSCl,imidazole,DMF in a surprisingly low 37% yield (100% based on recovered starting material) to afford a separable 1:1 mixture of (77A) and (77B). Swern oxidation of (77A) furnished ketone (78) in 84% yield. An attempt to selectively oxidize the secondary hydroxyl of diol (76) using "Blue Ram Toilet Cleaner" (NaOCl)[56] in acetic acid gave a 21% yield of an unstable hydroxy-ketone (79) which could not be fully characterised .



79

This is in agreement with findings from our degradation studies; treatment of ketone-acetate (8) with LiOH or NaOH in THF-H_2O gave only 15-27% yields of saponified products.

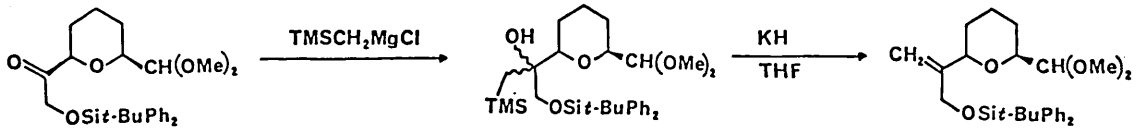
The acetal grouping of (78) proved very stubborn to remove. For example, (78) was recovered unchanged after treatment with 20% sulphuric acid on silica gel[41] or 50% aqueous trifluoroacetic acid[42] for one week. Conversion of (78) to ketone-aldehyde (80) was eventually accomplished in 48% unoptimised yield using $PdCl_2(MeCN)_2$ in acetone.[43]



78 80 35%

Coupling reactions suitable for joining the central and left-hand fragments of M139603 were briefly investigated. Since no left-hand unit has yet been synthesized, the reactions were conducted between (78) and methylene synthons. No reaction was observed between (78) and methylene triphenylphosphine at RT or at reflux, presumably owing to the steric bulk of the silyl protected hydroxyl function.

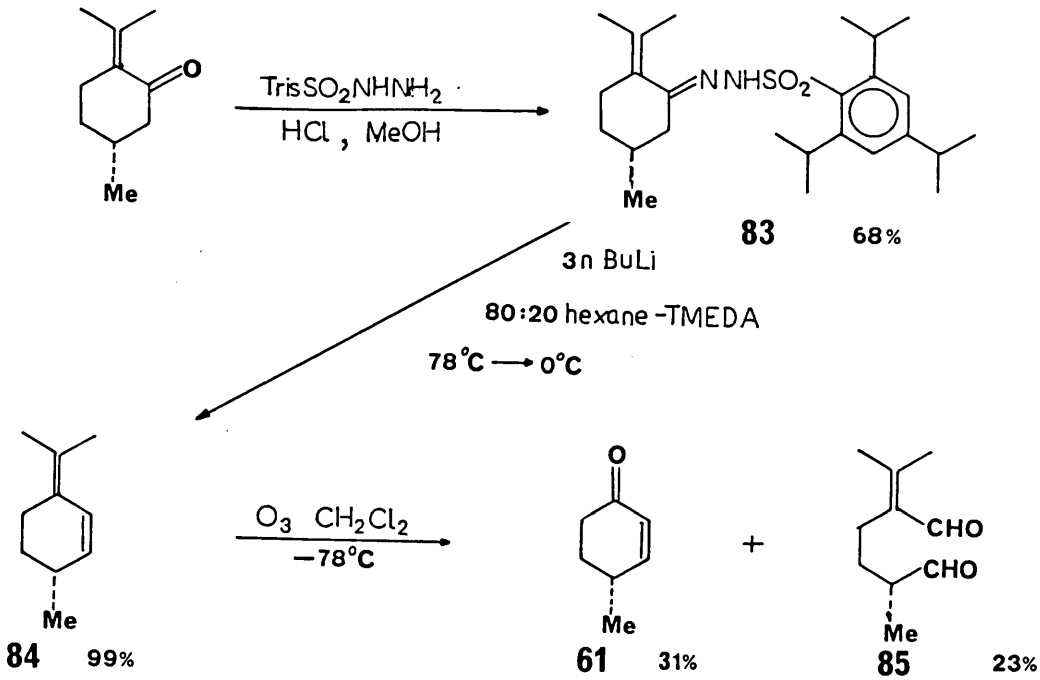
Peterson reaction[44] of ketone (78) with trimethylsilylmethylene magnesium chloride in THF at RT followed by treatment with potassium hydride afforded olefin (81) in 69% yield. Since the 1-hydroxy-2-trimethylsilyl intermediates can be isolated and eliminated either *syn* (with KH) or *anti* (with acid) this offers a method for controlling the geometry of the trisubstituted double bond of M139603.



78 69% 81

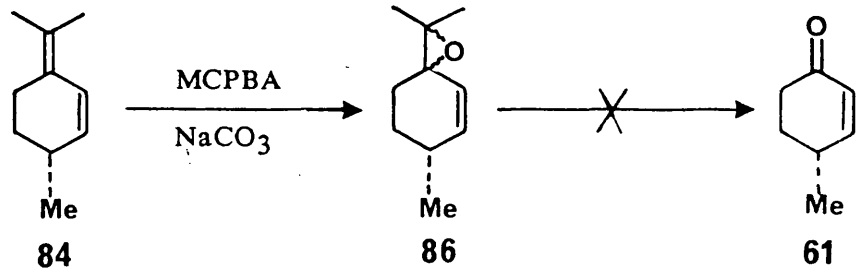
4-(R)-methyl-2-cyclohexenone (61) was prepared in three steps from (+)-pulegone (82) by Silvestri's route[37] (Scheme 13). Treatment of (+)-pulegone (82) with tris lylsulphonylhydr azide in methanol with a trace of acid gave hydrazone (83) in 68% yield. (83) was converted using the

Scheme 13



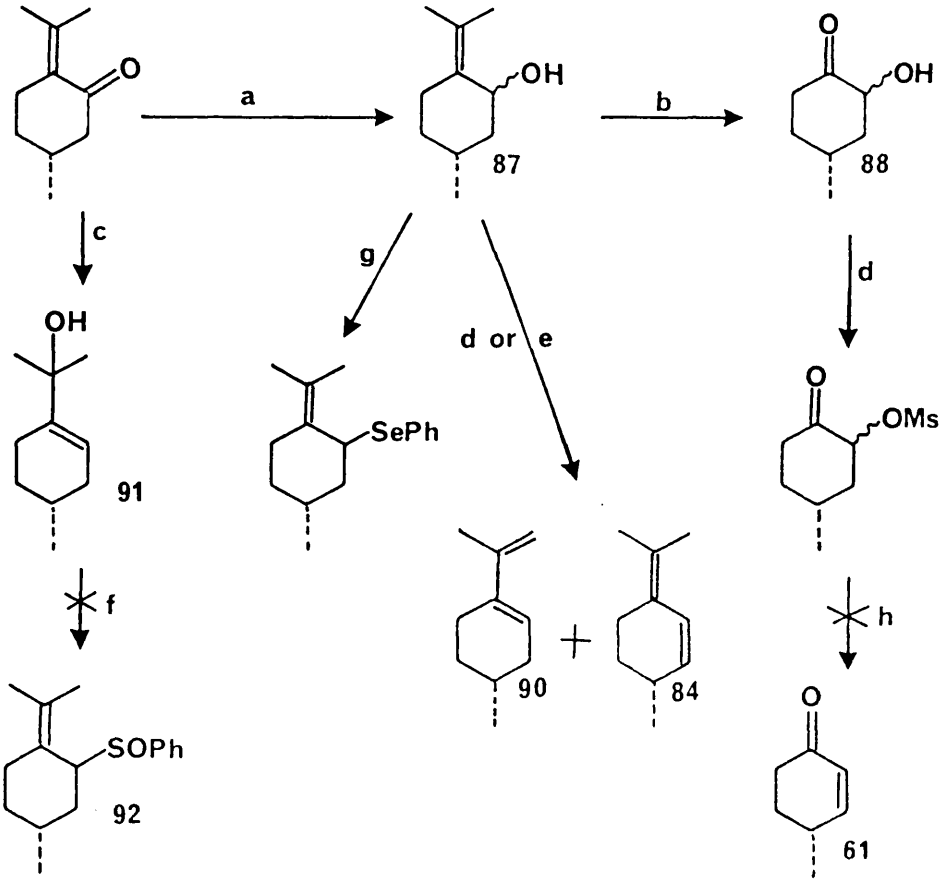
Bond modification[45] of the Shapiro reaction to diene (84) in an excellent 99% yield. Attempted selective ozonolysis of the exocyclic double bond a -78°C in dichloromethane using Sudan red as an indicator, afforded enone (61) in a disappointing 27-31% yield together with comparable quantities of dialdehyde (85). The literature yield[37] for this step was 36%. In general, ozone would be expected to react preferentially with the most electron rich olefin. The unexpected extent of cleavage of the disubstituted cyclic double bond might therefore be a consequence of ring strain. The 60-65% recovery of material from this reaction suggests that a substantial amount of over-oxidation must also be occurring. In an attempt to avoid this, we conducted the ozonolysis in b.p. 30-40°C petrol-ether so that the primary products of ozonolysis would precipitate out of solution and so be protected from further oxidation. A syrupy sludge was indeed formed, but since this coated the ozone inlet-tube, only a 25% yield of enone (61) was obtained after dimethylsulphide work-up.

An alternative to ozonolysis was considered. Sodium carbonate buffered epoxidation of diene (84) with MCPBA gave a 45% yield of diastereomeric epoxides (86). However, periodic acid cleavage of the epoxide was unsuccessful.



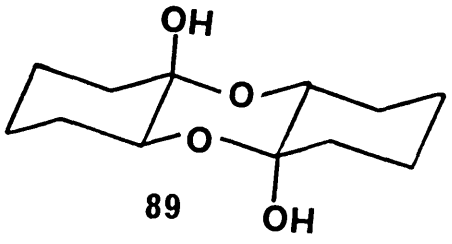
In view of the low yields of our intended starting material, other approaches were considered (Scheme 14).

Scheme 14



(a) DIBAL-H, $NaHCO_3$ w.u.; (b) O_3; c) DIBAL-H, H^+ w.u.; (d) MsCl, NEt_3, DCM; (e) TosCl, NEt_3, DCM; (f) PhSCl; (g) NPSP, $n\text{-}Bu_3P$; (h) DBU.

DIBAL-H reduction of pulegone with sodium bicarbonate work-up gave alcohol (87) in 89% yield which was smoothly ozonolysed to keto-alcohol (88) in 90% yield. Unsuccessful attempts were made to eliminate the alcohol with Burgess' salt[46] or in two steps by mesylation or tosylation followed by treatment with DBU. It is known that 2-hydroxycyclohexanone exists in its solid form as a hemiacetal dimer[47] (89). If a proprtion of its 4-methyl derivative (88) also exists in



89

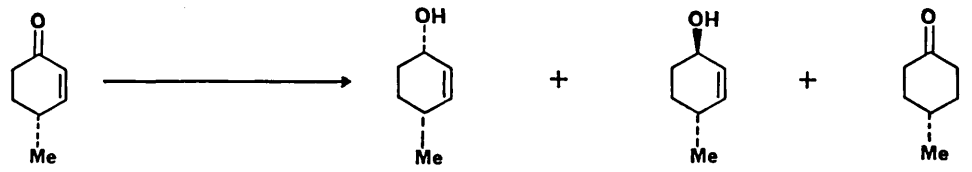
dimeric form in solution it might explain why only starting meterial is recovered from reaction with Burgess' salt. Elimination of a hemiacetal hydroxyl would give an enol ether which would rehydrate upon aqueous work-up. This does not explain why either the mesylate or tosylate (formed in good yield) failed to eliminate since each has a strong carbonyl stretch in the I.R. ($\nu_{max.}$ 1733 and 1729 cm^{-1} respectively). Attempts to prepare the phenylsulphides of (87) and (88) with PhSSPh and n-Bu_3P or the phenyl selenides with N-phenylselenosuccinamide proceeded in low yields.

Mesylation or tosylation of allylic alcohol (87) gave a 5:1 mixture of olefins (84) and (90).

An attempt to convert the rearranged allylic alcohol (91) (formed by DIBAL reduction and acidic workup in 76% yield) to sulphoxide

(92) by treatment with phenylsulphenylchloride[48] gave unidentifiable products. At this point we decided to content ourselves with the literature method.

Table 1



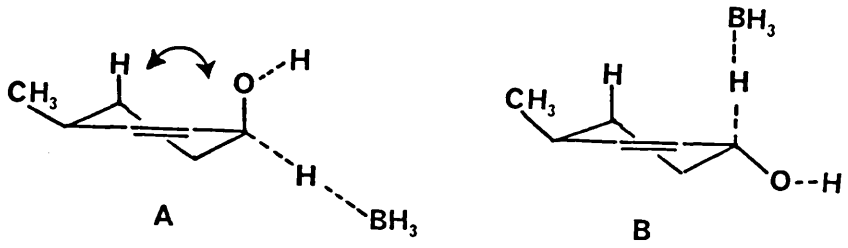
61 **93A** **93B**

Reducing agent	Cis	Trans	Ketone
$NaBH_4$	1	2·5 (50)	
$NaBH_4.CeCl_3$	1	2·2 (34)	
$LiAlH_4$	1	2·3 (37)	
9-BBN	1	7 (41)	
DIBAL	1	7 (74)	
L-Selectride	—	—	(70)
Alpine Borane (R)	—	—	
$LiAlH_4$ (S)PhNH⟨NHMe⟩OH	4	1 (64)	
$LiAlH(t\text{-}BuO)_3$	1	3·2 (43)	

The results of reduction of enone (61) by a selection of hydride reducing agents appear in Table 1. All the reactions were carried out once (except for the reaction with DIBAL) and the moderate yields reflect losses of the volatile product alcohols (93A) and (93B) during work-up. With the exception of L-selectride which gave 1,4 addition[49], Alpine Borane from which no products could be isolated, and the chiral reducing system (vide infra), the other reducing agents gave an excess of the *trans*-methyl-alcohol (93A) varying from 2.2:1 to 7:1. The alcohols could not be adequately separated by flash chromatography but their ratio could be easily determined from their n.m.r. spectra. The 4-methyl doublets were separated; *trans* (93A) δ 0.96 and *cis* (93B) δ 1.02, as were the AB quartets arising from their H-2 and H-3 olefinic protons;

trans (93A) δ 5.63 and *cis* (93B) δ 5.73. A preference for axial attack by hydride reducing agents has been observed for other unhindered steroidal cyclohexenones[56] but no experimentally-based rationalization of these results are reported.

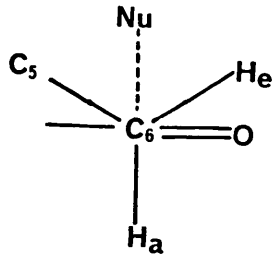
Wigfield's review[51] of cyclohexanone reduction suggests that for $NaBH_4$ reductions in which the transition state is known to be product-like, the stereoselectivity arises from significant steric interaction between the forming axial hydroxyl group and the axial hydrogen at



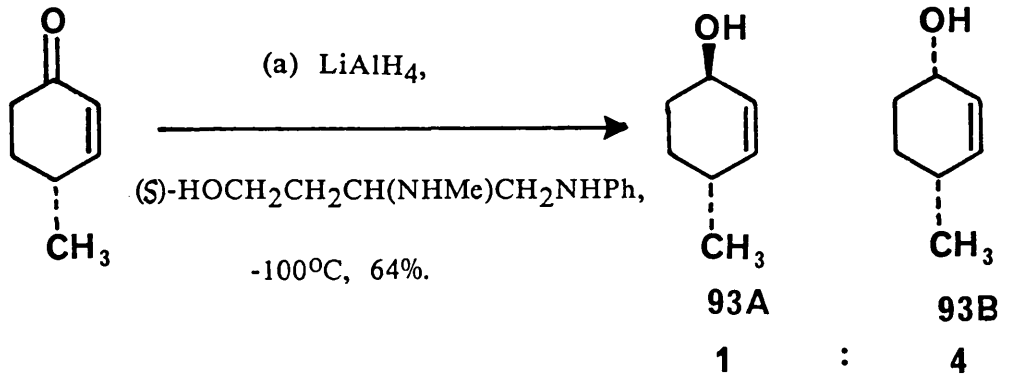
C-5 for equatorial approach of hydride (transition state A). In transition state B, the borohydride molecule is too far away from the C-5 hydrogen for this steric interaction to be important and axial attack is preferred. The BH_4^- anion accounts for only 25% of the reduction, but similar considerations would apply for any $BH_n(OMe)_{4-n}$ species. The sodium cation does not play a complexing role in the reduction. From deuterium kinetic isotope experiments and measurements of Hammett ρ constants for the reduction of aromatic ketones it is believed that the hydride ion is half transferred in the transition-state for the reductions of ketones by $LiAlH(Ot\text{-}Bu)_3$.

An explanation for the predominant axial attack of $LiAlH_4$, 9-BBN and DIBAL-H comes from the ab initio calculations of Anh[52] in which favourable consequences result from the antiperiplanar orientation between the developing C-H bond and the axial C-6 hydrogen. Axial attack allows in phase overlap between the H^- and the σ^*C6-H and avoids

eclipsing the C1-H$^-$ and the C6-H bonds. For equatorial attack this is not possible.



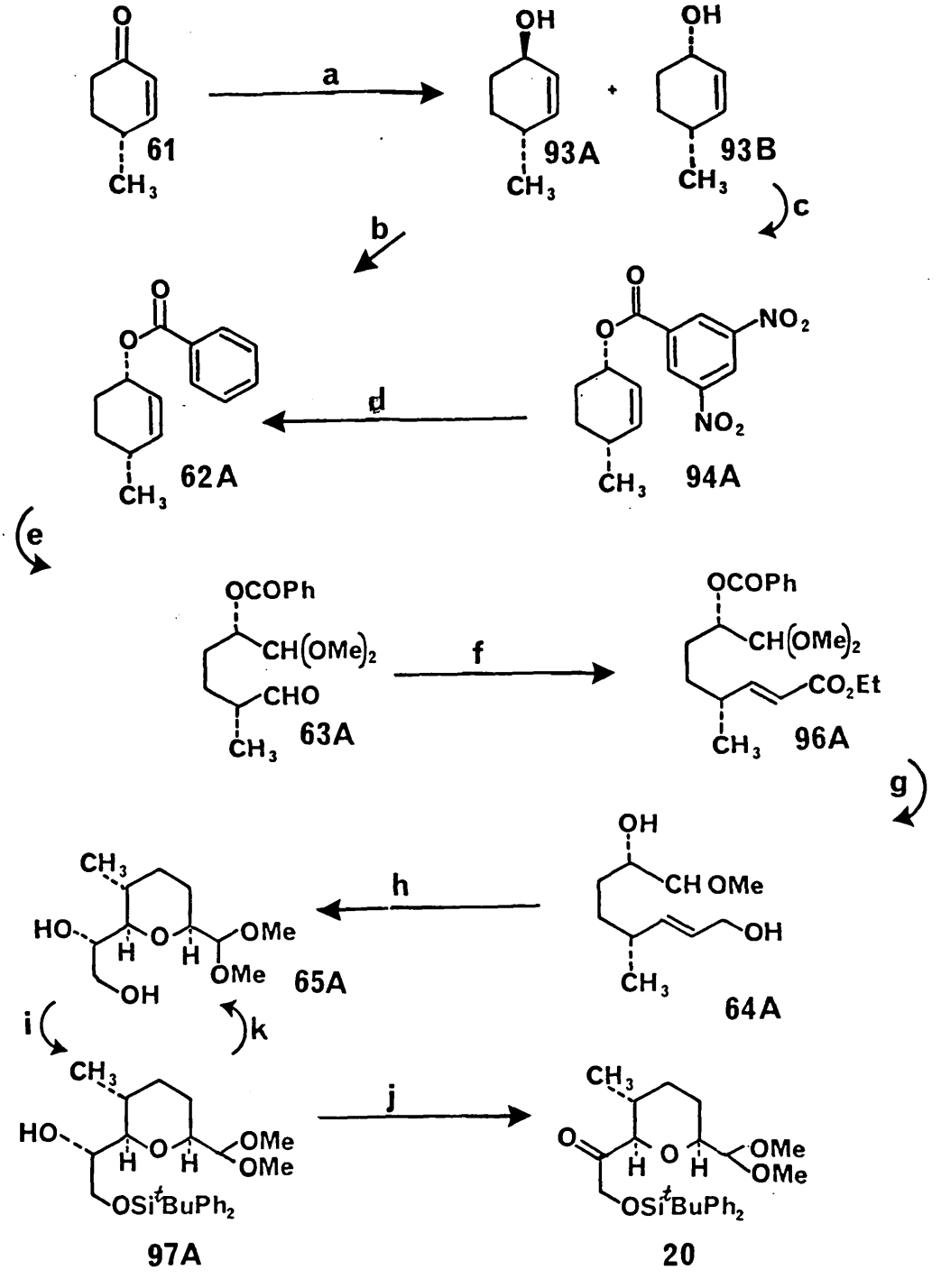
Fujisawa *et al*[53] have recently reported the 100% enantiospecific reduction of cyclohexenone to S-cyclohex-2-en-1-ol using $LiAlH_4$ and a chiral ligand[54] derived from aspartic acid. Reaction of enone (61) with this system gave only a 4:1 ratio of the S-alcohol (93B) to (93A) in 64% yield.



Although (93A) and (93B) could be separated by h.p.l.c. in 50 mg batches, this was time consuming and it was decided to carry a mixture of the alcohols through the sequence shown in Scheme 15 to a point where they could be more easily separated.

Thus reduction of enone (61) with DIBAL-H and chromatographic removal of toluene gave a 7:1 mixture of (93A) and (93B) in 74% yield. Mitsunobu inversion of (93) with DEAD, Ph_3P and benzoic acid gave an inseparable mixture of benzoates (62) in 20-47% yield. The major side product was benzoic anhydride resulting from attack of the benzoate anion (rather than the alcohol) upon the protonated Ph_3P-DEAD complex

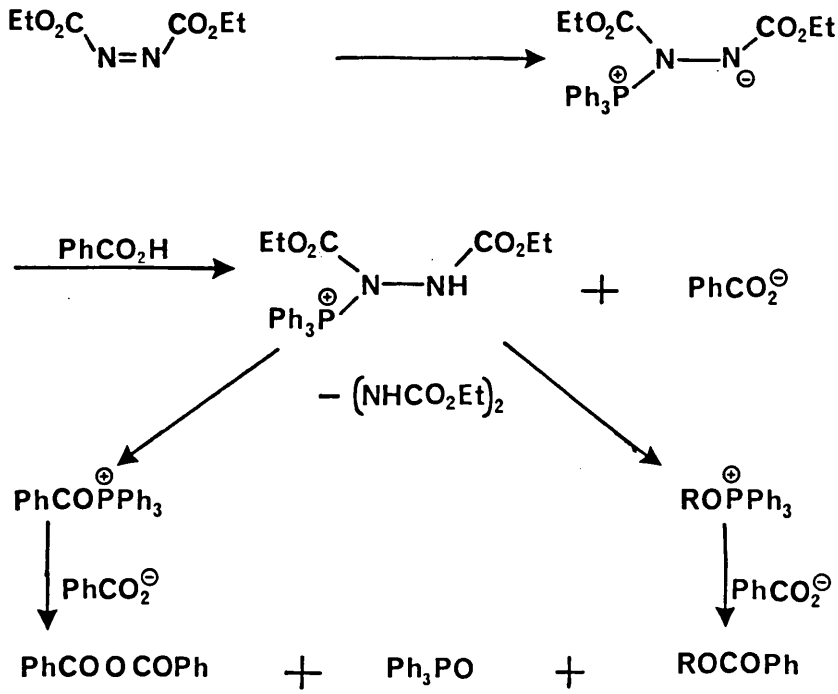
Scheme 15



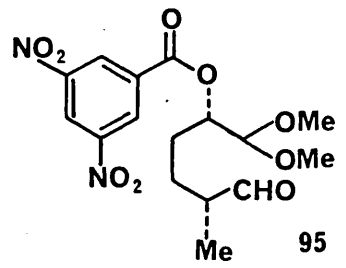
Reagents (a) DIBAL, THF, 74%; (b) DEAD, PPh_3, $PhCO_2H$, 47%; (c) DEAD, PPh_3, 3,5-dinitrobenzoic acid, 0°C, 68%; fractional recrystallization; (d) NaOH; PhCOCl, py, 95%; (e) O_3, MeOH, TsOH; PPh_3, $NaHCO_3$, 36%; (f) $PhPCHCO_2Et$, 97%; (g) DIBAL, THF, -78 → 0°C, 98%; (h) $Ti(Oi\text{-}Pr)_4$, (+) L-DET, ^tBuOOH, -20°C, 12h; Me_2S, 40°C, 2h; NaF work-up, 85%; (i) TBDPSCl, NEt_3, 70%; (j) $(COCl)_2$, DMSO, NEt_3, 90%; (k) TBAF, 100%.

(Scheme 16). The problem was solved by reducing the nucleophilicity of the benzoate anion by placing nitro groups on the aromatic ring. Mitsunobu reaction of (93) with 3,5-dinitrobenzoic acid gave a 68%

Scheme 16

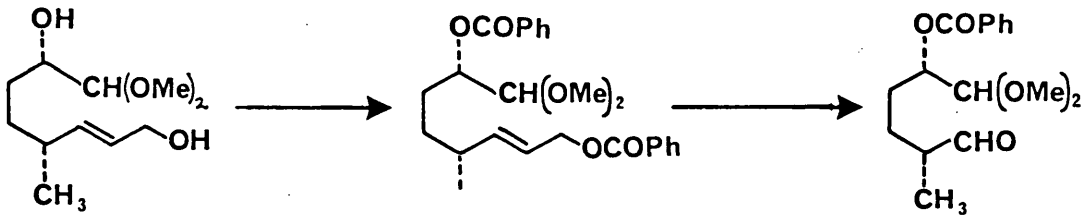


yield of a mixture of dinitrobenzoate esters (94A) and (94B) from which the major isomer (94A) could be fractionally crystallized pure from petrol-dichloromethane. From this point on in the synthesis both enantiomerically pure (94A) and a 60:40 mixture of (94A) and (94B) were carried separately through the sequence of steps towards the target molecule. Two attempts at the ozonolysis of (94) in methanol gave poor yields of the desired aldehyde-acetal (95) together with some material in which the ester group had been lost.



95

(94A) was converted to the phenyl ester (62A) in two steps in 95% yield. The crucial ozonolysis of pure (62A) employing a K10-trimethylorthoformate as the acetal-forming reagent gave a complex mixture of products from which aldehyde-acetal (63A) was obtained crude in 1% yield. Aldehyde (63A) was reacted with Ph_3PCHCO_2Et to give the *trans* unsaturated ester (96A) which was purified by h.p.l.c. Reduction of (96A) to diol (64A) was accomplished in 98% yield with DIBAL-H. Since we did not have sufficient chiral material to complete the synthesis, alcohol (64A) was esterified with benzoylchloride and ozonolysed to afford a pure sample of aldehyde (63A).



64A 63A

The 60:40 mixture of (94A) and (94B) was converted to the inseparable benzoate esters (62A) and (62B) by saponification and reesterification. Ozonolysis of the mixture followed by K10 treatment gave a best yield of 31% while a 36% yield was obtained by Schrieber's method. In each case the inseparable product acetal-aldehyde mixture (63A) and (63B) could be chromatographed free from impurities.

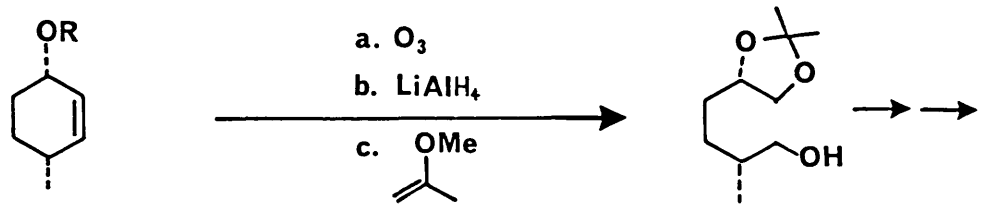
The aldehydes (63A and B) were converted to the *trans* unsaturated esters (96A and B) in 97% yield together with 1.5% of their *cis* isomers. Reduction with DIBAL-H afforded the inseparable allylic diols (64A and B) in 89% yield. Sharpless epoxidation of the mixture (64A and B) with 2.2 equivalents of titanium isopropoxide, 2.6 equivalents of (+)L-diethyl tartrate and 5.2 equivalents of t-butyl hydroperoxide in dichloromethane at -20°C for 12 hr followed by quenching of the peroxides with Me_2S and heating the reaction mixture under reflux at 40°C for 2 hr gave, after fluoride work-up, an excellent 85% yield of the inseparable tetrahydropyran diol mixture (65A and B). Selective primary hydroxyl protection using TBDPSCl, NEt_3 with a catalytic amount of DMAP[55] afforded a separable mixture of the equatorial acetal (97A) and the axial acetal (97B). (97A) was converted by a Swern oxidation to ketone (20) in 90% yield and a small sample of (97A) was deprotected in quantitative yield with TBAF to afford a pure sample of (65A). The synthetic (20) was identical in all respects with material provided by degradation of M139603[11].

20: Colourless oil, $[\alpha]_D^{25}$ +20.8° (*c* 0.75 in $CHCl_3$); δ(250 MHz) 0.73 (3H, d, J 6.3 Hz, 3-Me), 1.1 (9H, s, ^tBu), 1.13-1.40 (3H, m, 5-H_2, 4-H), 1.65 and 1.82 (2H, m, 4-H, 3-H), 3.27 (1H, m, 6-H), 3.28 and 3.30 (6H, 2s, 2 OMe), 3.47 (1H, d, J 9 Hz, 2-H), 4.07 (1H, d, J 6 Hz, 1"-H), 4.51 (1H, d, J 19.8 Hz, 2 -H), 4.63 (1H, d, J 19.8 Hz, 2 -H), 7.38 (6H, m, Ph), and 7.67 (4H, m, Ph); $\nu_{max.}$(neat) 3069, 2954, 2736 (C=O), 1427, 1191, 1112, 921, 824 and 704 cm^{-1}; *m/z* 413 (M^+--^tBu), 381 (M^+-^tBu-MeOH), 199, 141 and 75.

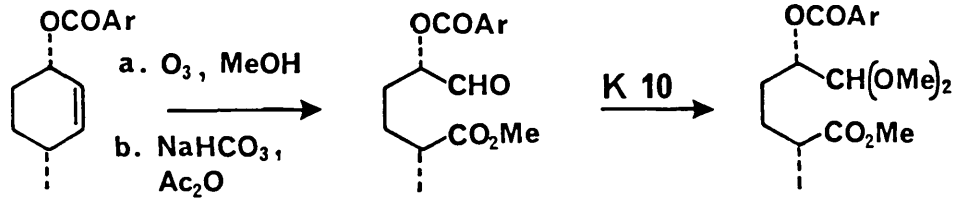
20 (provided by degradation)[11]: colourless oil, $[\alpha]_D^{25}$ +20.5° (c 3.1 in $CHCl_3$); δ(400 MHz) identical; $\nu_{max.}$(neat) 3071, 2954, 1736 (C=O), 1427, 1112, 921, and 704 cm^{-1}; *m/z* 413, 381, 363, 349, 199, 141 and 75.

5. Conclusion

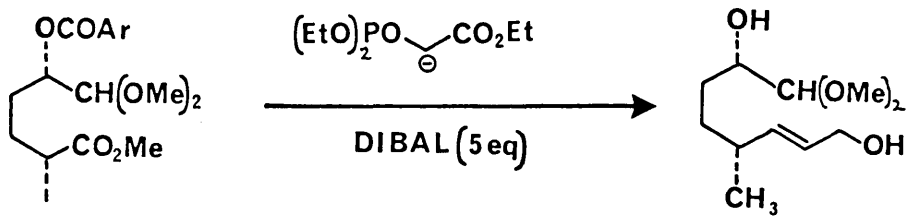
A ten step synthesis of a tetrahydropyran unit for M139603 is described from the known 4-(R)-methyl-2-cyclohexenone[37]. Improvements could be made in two areas. Firstly, the key ozonolysis reaction still needs to be mastered or avoided by two alternatives described below.



In this version the two ends are distinguished by forming an acetonide.

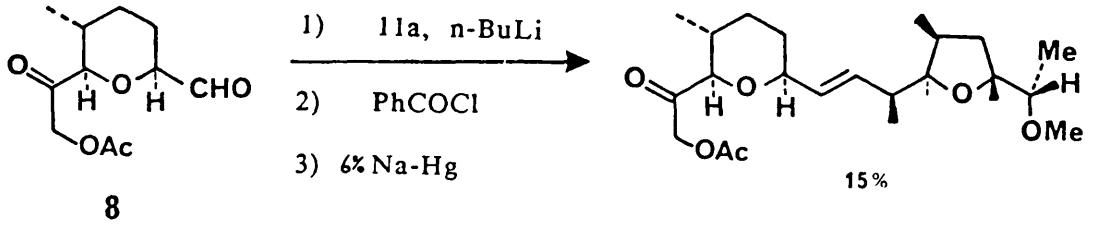


In this version, taking the methoxyhydroperoxide intermediate to the ester oxidation state avoids problems in a second separate acetalization step. The ester may be converted to the E allylic alcohol (64A) in one step using both DIBAL *and* $(EtO)_2POCHLiCO_2Et$.[58]



If this modification worked on the nitrobenzoate (94A), the sequence would be shortened to 7 steps.

Secondly, it has recently been shown that (8) is a suitable substrate for the Julia reaction with (11a). In view of these findings the diol (65A) may need to be converted to the keto-acetate (8) rather than



8

ketosilylether (20). Attempted selective primary acetylation of diol (65A) with Ac_2O and triethylamine at 0°C proved quite indiscriminate, but better methods exist.[59] Work continues in this area.

EXPERIMENTAL

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured using an Optical Acitivity AA-1000 or Perkin-Elmer 151 polarimeter. Infrared spectra were recorded on a Perkin-Elmer 298 grating infrared spectrophotometer using a thin film of KBr disc. ^1H NMR spectra were recorded at 60 MHz on a Varian EM-360A, at 90 MHz on a Jeol FX 90Q or at 250 MHz on a Bruker WM-250 machine and are quoted for $CDCl_3$ solutions with tetramethyl silane as internal standard. Mass spectra were determined with a VG micromass 7070B instrument. Microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory.

Analytical thin layer chromatography (t.l.c.) was performed on Merck precoated silica gel F_{254} plates and flash chromatography was conducted under low pressure using Merck kieselgel 60 (230-400 mesh).

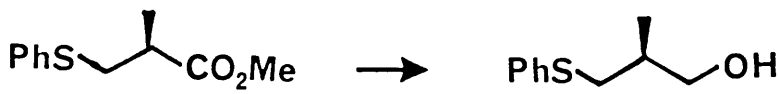
Petrol refers to the fraction with b.p. 40-60°C and was redistilled before use. All solvents were purified and dried by standard techniques. All experiments using dry solvents were carried out under argon unless specifically stated otherwise.

1. Preparation of Methyl-2-(S)-methyl-3-phenylthiopropionate (42)

42

Methyl-3-hydroxy-2-(R)-methyl-propionate (102 mg, 0.86 mmol), diphenyldisulphide (528 mg, 2.54 mmol) and tri-n-butylphosphine (525 mg, 2.54 mmol) were stirred in THF (6 ml) at RT under argon for 26 h. The reaction mixture was poured into saturated ammonium chloride solution (20 ml) and extracted twice with ether (2 x 30 ml). The extracts were dried over $MgSO_4$, concentrated, and flash chromatographed (gradient elution, 0-10% ether-petrol) to afford *methyl-2-(S)-methyl-3-phenylthiopropionate* (42) (169 mg, 93%) as a clear oil; δ = 250 MHz) 1.28 (3H, d, J 7 Hz, Me), 2.70 (1H, tq, J 7 Hz, 2-H), 2.95 (1H, dd, J 10.8 and 7 Hz, 3-H), 3.28 (1H, dd, J 10.8 and 7 Hz, 3-H), 3.68 (3H, s, OMe), and 7.2-7.4 (5H, m, Ph); $\nu_{max.}$ (neat) 2977, 2951, 1735 (CO_2Me), 1436, 1212, 1166, 741 and 690 cm^{-1}; *m/z* 210 (M^+), 150 (M^+-$MeCO_2H$), 123 ($PhSCH_2^+$), 110 $(PhSH)^+$, 77 (Ph^+), and 65; (Found: C, 62.77; H, 6.79; S, 15.08. $C_{11}H_{14}O_2S$ requires C, 62.83; H, 6.71; S, 15.25); $[\alpha]_D^{22}$-67.3° (c 1.70 in $CHCl_3$).

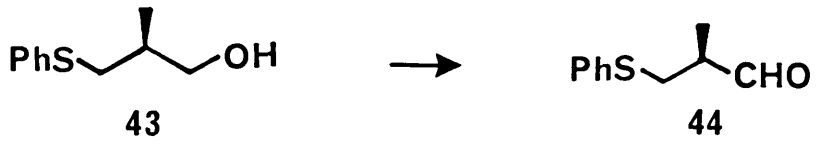
2. Preparation of 2-(S)-Methyl-3-phenylthiopropan-1-ol (43).



42 43

Lithium aluminium hydride (26 mg, 0.67 mmol) was added portion-wise to an ice-cold stirred solution of the ester (42) (165 mg, 0.81 mmol) in dry THF (10 ml) over 1 min. After 20 min, saturated ammonium chloride solution (0.5 ml) was added. The resultant solids were filtered off and extracted once with ether (10 ml). The combined organic layers were dried over $MgSO_4$, concentrated and chromatographed (eluant, ether) to afford *2-(S)-methyl-3-phenyl- thiopropan-1-ol* (42) (133 mg, 90%) as a colourless oil; δ(250 MHz) 1.04 (3H, d, J 6.9 Hz, Me), 1.92 (1H, m, J 5.5, 6.5 and 6.9 Hz, 2-H), 2.08 (1H, br s, OH), 2.82 and 3.06 (2H, 2 dd, J 12.9 and 6.5 Hz, 3-H_2), 3.58 (2H, dd, J 10.8 and 5.5 Hz, 1-H_2), and 7.1-7.4 (5H, m, Ph); $\nu_{max.}$ (neat) 3370, 2959, 2873, 1483, 1091, 1028, 739, and 691 cm^{-1}; *m/z* 182 (M^+), 123 ($PhSCH_2^+$), 77 (Ph^+) and 65; (Found: C, 65.76; H, 7.98; S, 17.87. $C_{10}H_{14}SO$ requires C, 65.89; H, 7.74; S, 17.59%). $[\alpha]_D^{25}$ + 15.56 (*c* 13.3 in CH_2Cl_2).

3. Preparation of 2-(S)-Methyl-3-phenylthiopropan-1-al (44)

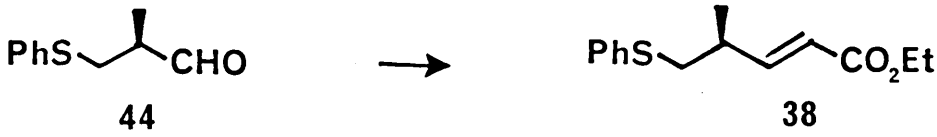


43 44

DMSO (5.14 g, 66 mmol) in dichloromethane (20 ml) was added dropwise to a stirred solution of oxalyl chloride (4.18 g, 33 mmol) in dichloromethane (40 ml) at -78°C. After 5 min the solution was treated with the alcohol (43) (5.00 g, 27.5 mmol) in dichloromethane followed by triethylamine (17 ml, 132 mmol) after 30 min, and then allowed to regain RT over 1 h. The solution was diluted with dichloromethane (100 ml) and washed with 1 M hydrochloric acid (100 ml), water (2 x 100 ml) and dried over $MgSO_4$. Concentration under reduced pressure

and chromatography (gradient elution, 1 → 10% ether-petrol) afforded 2-(S)-methyl3-3phenylthiopropan-1-al (44) (3.68 g, 74%) as a colourless oil; δ(250 MHz) 1.20 (3H, d, J 6.8 Hz, Me), 2.60 (1H, dddq, J 6.8, 6.4, 1.35 and 7.0 Hz, 2-H), 2.90 (1H, dd, J 6.4 and 13.4 Hz, 3-H), 3.30 (1H, dd, J 6.4 and 13.4 Hz, 3-H), 7.3 (5H, m, Ph), and 9.65 (1H, d, J 1.35 Hz, 1-H); $\nu_{max.}$ (neat) 3058, 2970, 1772 (CHO), 1582, 1479, 1438, 1025, 740 and 691 cm^{-1}; *m/z* 180 (M^+), 123 ($PhSCH_2^+$), 110, and 77; $[\alpha]_D^{25}$-6.25° (*c* 0.48 in CH_2Cl_2).

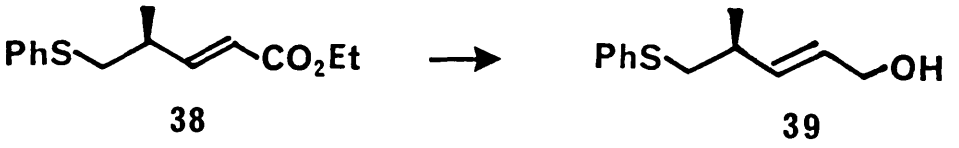
4. Ethyl-4-(S)-methyl-5-phenylthiopent-2-(E)-enoate (38)



44 38

The aldehyde (44) (80 mg, 0.44 mmol) was added to carboethoxymethylenetriphenylphosphorane (170 mg, 0.48 mmol) in dry THF at RT. After 4 h the reaction mixture was preabsorbed on silica (0.5 g) and chromatographed (gradient elution, 2 → 10% ether-petrol) to afford the *trans* unsaturated ester (38) (88 mg 79%) as a colourless oil; δ(250 MHz) 1.17 (3H, d, J 6.8 Hz, Me), 1.26 (3H, t, J 7.2 Hz, OCH_2CH_3), 2.58 (1H, m, J 6.8, 6.8, 7.6, 7.7 and 1.3 Hz, 4-H), 2.82 (1H, dd, J 6.8 and 13.2 Hz, 5-H), 3.03 (1H, dd, J 7.7 and 13.2 Hz, 5-H), 4.17 (2H, q, J 7.2 Hz, OCH_2Me), 5.80 (1H, dd, J 16.1 and 1.3 Hz, 2-H), 6.90 (1H, dd, J 16.1 and 7.4 Hz, 3-H), and 7.30 (5H, m, Ph); $\nu_{max.}$ (neat) 3058, 1718, 1583, 1480, 1154 and 1026 cm^{-1}; *m/z* 250 (M^+), 205 (M^+-OEt), 180, 177, 141, 123 ($PhSCH_2^+$), and 110 ($PhSH^+$); $[\alpha]_D^{25}$-36.8° (*c* 0.8 in CH_2Cl_2).

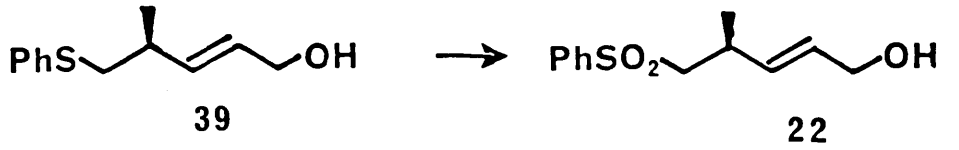
5. Preparation of 4-(S)-Methyl-5-phenylthiopent-2E-en-ol (39)



38 39

DIBAL-H (0.50 ml of a 1.5 M solution in toluene, 0.74 mmol) was added to a stirred solution of the unsaturated ester (38) (86 mg, 0.34 mmol) in dry THF (5 ml) at -78°C. The reaction mixture was allowed to warm to 0°C over 1 h and quenched with 3 M hydrochloric acid (2 ml) and brine (10 ml). The mixture was shaken for 5 min then extracted twice with ether (2 x 20 ml). The extracts were dried over $MgSO_4$, concentrated and flash chromatographed (eluant, 40% ether-petrol) to afford 4-(S)-methyl-5-phenylthiopent-2E-en-1-ol (39) (54 mg, 75%) as a colourless oil; $[\alpha]_D^{25}$-16.3° (c 0.54 in CH_2Cl_3); δ(250 MHz) 1.13 (3H, d, J 6.8 Hz, Me), 1.67 (1H, br s, OH), 2.45 (1H, m, 4-H), 2.86 (1H, dd, J 6.9 and 12.8 Hz, 5-H), 2.95 (1H, dd, J 7.1 and 12.8 Hz, 5-H), 4.08 (2H, m, 1-H_2), 5.62 (2H, m, 2-H and 3-H), and 7.12-7.34 (5H, m, Ph); $\nu_{max.}$ 3357 (OH), 3056, 2961, 2868, 1583, 1437, 1373, 1091, 1006, 971 and 738 cm^{-1}; *m/z* 208 (M^+), 180 (M^+-H_2O), 123 ($PhSCH_2^+$), 110 (PhSH), 98, and 55.

6. Preparation of 4-(S)-methyl-5-phenylsulphonyl-pent-2-E-en-1-ol (22)



39 22

A solution of oxone (1.08 g, 3.53 mmol) in water (12 ml) was added to an ice-cold stirred solution of the sulphide (39) (245 mg, 1.18 mmol) in methanol (10 ml). After 20 min at 0°C and 1 h 10 min at RT, the reaction mixture was diluted with water (40 ml) and extracted with dichloromethane (3 x 15 ml). The organic phase was washed with brine (10 ml), dried over $MgSO_4$, concentrated and chromatographed (eluant, 5% ethanol-chloroform) to afford 4-(S)-methyl-5-phenylsulphonyl-pent-2-E-en-1-ol (22) (232 mg, 82%) as a colourless oil; $[\alpha]_D^{25}$ -7.0° (*c* 0.2 in CH_2Cl_2); δ(60 MHz) 1.20 (3H, d, J 7 Hz, Me), 2.20 (1H, br s, OH), 2.87 (1H, m, 4-H), 3.18 (2H, m, 5-H_2), 4.06 (2H, m, 1-H_2), 5.64 (2H, m, 2-H and 3-H), and 7.5-8.12 (5H, m, Ph); $\nu_{max.}$ 3502 (OH), 2926, 1666, 1583, 1300 and 1147 (-SO_2-), 1086, 973 (C=C), 740, and 688 cm^{-1}.

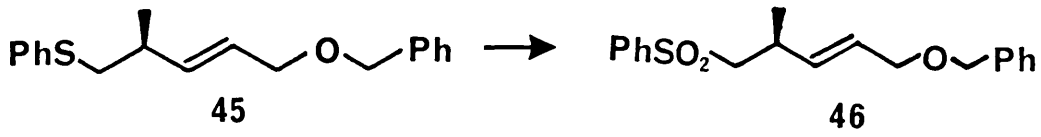
7. Preparation of 1-Benzyloxy-4-(S)-methyl-5-phenylthio-pent-2-E-ene (45)

39 45

A solution of the alcohol (39) (470 mg, 2.26 mmol) and benzyl bromide (405 g, 2.37 mmol) in DMSO (0.5 ml) was added to a stirred suspension of powdered sodium hydroxide (252 mg, 6.3 mmol) in DMSO (0.5 ml) at RT. This resulted in a dark yellow solution after an initially exothermic reaction. After 1 h the reaction mixture was poured into water and extracted with ether (2 x 20 ml). The extracts were dried over $MgSO_4$, concentrated and chromatographed (eluant, 5% ether-petrol) to afford 1-benzyloxy-4-(S)-methyl-5-phenylthio-2-E-pentene (45) (554 mg, 82%) as a colourless oil; δ(90 MHz) 1.14 (3H, d, J 6.5

Hz, Me), 2.46 (1H, m, 4-H), 2.84 (1H, dd, J 7.2 and 12.8 Hz, 5-H), 2.96 (1H, dd, J 7.1 and 12.8 Hz, 5-H), 3.97 (2H, d, J 3.9 Hz, 1-H_2), 4.49 (2H, s, CH_2Ph), 5.61 (1H, dd, J 4.9 and 15.7 Hz, 3-H), 5.69 (1H, dd, J 4 and 15.7 Hz, 2-H), and 7.12-7.45 (10H, m, 2 x Ph); $\nu_{max.}$ 3027, 2958, 2923, 2858, 1664, 1583, 1451, 1437, 1360, 1089, 1071, 971, 737, and 696 cm^{-1}; *m/z* 298 (M^+), 207 (M^+-CH_2Ph), 123 ($PhSCH_2^+$), 110 ($PhSH^+$), and 91 ($PhCH_2^+$); $[\alpha]_D^{25}$-7.0° (*c* 6.0 in $CHCl_3$).

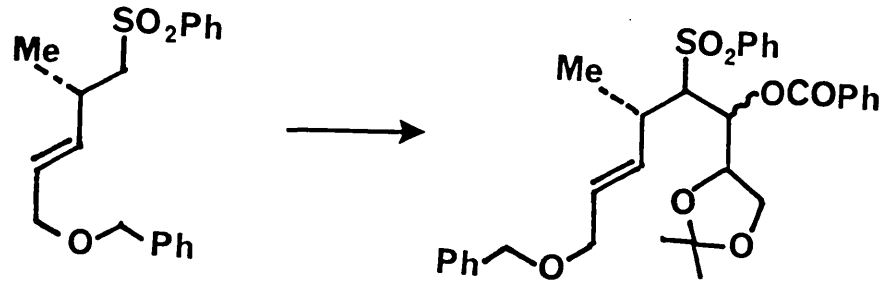
8. Preparation of 1-Benzyloxy-4-(S)-methyl-5-phenylsulphonyl-2-E-pentene (46)



45 46

A solution of the sulphide (45) (554 mg, 1.86 mmol) in methanol (20 ml) was added to a solution of oxone (1.72 g, 2.79 mmol) in water (10 ml) at RT. After stirring for 2 h, the methanol was evaporated under reduced pressure and the aqueous remainder extracted with chloroform (2 x 20 ml). The extracts were dried over $MgSO_4$, concentrated under reduced pressure and chromatographed (eluant, 50% petrol-chloroform) to afford the sulphone (46) (326 mg, 53%) as a colourless oil; δ(90 MHz) 1.16 (3H, d, J 6.5 Hz, Me), 2.84 (1H, m, 4-H), 3.04 (1H, dd, J 6.5 and 12.8 Hz, 5-H), 3.17 (1H, dd, J 6.5 and 12.8 Hz, 5-H), 3.88 (2H, m, 1-H_2), 4.45 (2H, s, CH_2Ph), 5.57 (2H, m, 2-H and 3-H), 7.3 (5H, s, CH_2Ph), 7.5-7.65 (3H, m, SO_2Ph), and 7.8-7.95 (2H, m, SO_2Ph); $\nu_{max.}$ 3030, 2927, 2854, 1668 (C=C), 1585, 1304 and 1148 (SO_2), 738, and 689 cm^{-1}.

9. Preparation of 6-Benzoyloxy-1-benzyloxy-7-(R),8-O-isopropylidene-4-(S)-methyl-5-phenylsulphonyl-oct-2-E-ene (48)

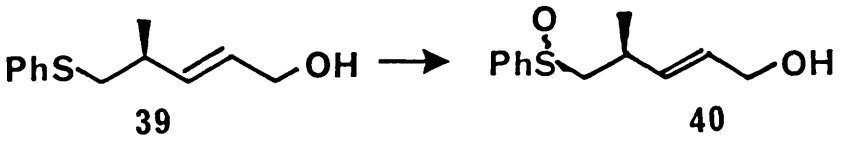


46 48

To a stirred solution of the sulphone (46) (108 mg, 0.33 mmol) in THF (8 ml) was added n-butyl lithium (0.40 ml of a 1.28 M solution in hexane, 0.51 mmol) at -78°C. After 1 h, a solution of 4-(R)-formyl-2,2-dimethyl-1,3-dioxalane (58 mg, 0.45 mmol) in THF (1 ml) was added. The reaction mixture was stirred for 1 h at -78°C then treated with benzoyl chloride (127 mg, 0.9 mmol) in THF (2 ml). After a further 1 h, the solution was warmed to 0°C and treated with 3-dimethylamino-1-propylamine (91 mg, 0.9 mmol). After 20 min saturated ammonium chloride solution (20 ml) was added, the THF layer was separated and the aqueous layer extracted twice with ether (2 x 20 ml). The combined organic layers were dried over $MgSO_4$, evaporated under reduced pressure and chromatographed (gradient elution, 0 → 1% ethanol-dichloromethane) to afford the addition products (48) (103 mg, 57%) as a colourless oil; δ(90 MHz) 0.90-1.65 (10H, m, 4-H, 4-Me, 2 x acetal-Me), 3.31 (1H, m, 5-H), 3.7-4.3 (4H, m, 6-H, 7-H, 8-H_2), 4.50 (2H, m, 1-H_2), 5.35 (2H, s, CH_2Ph), 5.5-5.85 (2H, m, 2-H and 3-H), and 7.25-8.3 (15H, m, 3 x Ph); $\nu_{max.}$ 3062, 2985, 2934, 1725 (OCOPh), 1681 (C=O), 1450, 1371, 1308 (-SO_2Ph), 1217, 1149 (-SO_2Ph), 1071, 1027, 974 and 713 cm^{-1}; *m/z* 552 (M^+), 549 (M^+-3), 537 (M^+-CH_3), 485, 451

(M^+-4-dehydro-2,2-dimethyl-1,3-dioxalane), 427 (M^+-3-$PhCO_2H$), 423, 407 (M^+-3-$PhSO_2$), 365, 343, 329, 293, 278, 260, 187, 143 ($PhSO_2H_2^+$), 105 ($PhCO^+$), 91 ($PhCH_2^+$), 77 (Ph^+), 65, 51, and 43.

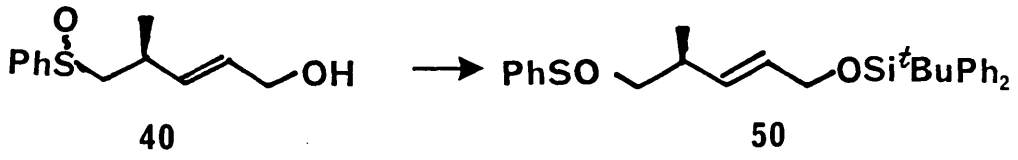
10. Preparation of 4-(S)-Methyl-5-phenylsulphinyl-pent-2-E-en-1-ol (40)



39 40

The sulphide (39) (2.0 g, 9.62 mmol) in methanol (20 ml) was added to a stirred solution of sodium periodate (3.08 g, 14.4 mmol) in water (40 ml) at O^oC. After stirring at 0^oC for 15 min then at RT for 2 h, the cloudy suspension was filtered through celite then extracted with dichloromethane (3 x 70 ml). The extracts were dried over $MgSO_4$, evaporated under reduced pressure and chromatographed (eluant, 1% ethanol-chloroform) to afford the diastereomeric sulphoxides (40) (2.10 g, 97%) as a colourless oil; δ(60 MHz) 1.1 (3H, m, Me), 2.45-3.05 (3H, m, 1-H_2, 4-H), 3.20 (1H, br s, OH), 4.08 (2H, m, 5-H_2), 5.55 (2H, m, 2-H and 3-H), and 7.30-7.62 (5H, m, Ph); $\nu_{max.}$ 3509 (OH), 3064, 2963, 1581, 1444, 1377, 1087, 1019, 973, 751, and 691 cm^{-1}.

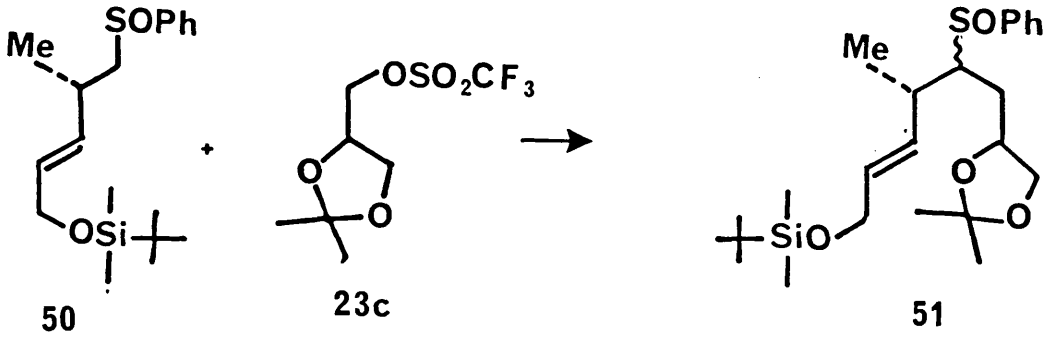
11. Preparation of 5-t-Butyldimethylsilyloxy-2-(S)-methyl-1-phenylsulphinyl-pent-3-E-ene (50)



40 50

A solution of sulphoxide (40) (2.10 g, 9.38 mmol), t-butylchloro-dimethylsilane (1.55 g, 10.3 mmol) and imidazole (1.62 g, 23.4 mmol) in dry DMF (6 ml) was stirred at RT for 2 h. The reaction mixture was poured into water (50 ml) and extracted with dichloromethane (2 x 50 ml). The extracts were dried over $MgSO_4$, concentrated and chromato-graphed (gradient elution, 5 → 50% ether-petrol) to afford the *silyl ether* (50) (3.10 g, 98%) as a colourless oil; δ(60 MHz) 0.00 and 0.03 (6H, 2 s, Me_2Si), 0.84 (9H, s, tBu), 1.18 (3H, m, Me), 2.50-3.0 (3H, m, 1-H_2 and 2-H), 4.13 (2H, m, 5-H_2), 5.61 (2H, m, 3-H and 4-H), and 7.43 (5H, m, Ph); $\nu_{max.}$ 2930, 2857, 1461, 1379, 1254, 1088, 971, 836, 777 and 748 cm^{-1}; *m/z* 322 (M^+-O), 281 (M^+-^{t}Bu), 265 (M^+-^{t}Bu-0), 255, 213 (M^+-PhSO), 183, 167, 155 (M^+^{t}Bu-PhSOH), 123, 110 ($PhSH^+$), and 75; (Found: C, 63.72; H, 9.07; S, 9.34. $C_{18}H_{30}SO_2Si$ requires C, 63.85; H, 8.93; S, 9.47).

12. Attempted preparation of 4-(S)-[6'-t-Butyldimethylsilyloxy-3'-(S)-methyl-2'-phenylsulphinyl-hex-4'-E-enyl]-2,2-dimethyl-1,3-dioxalane (51)

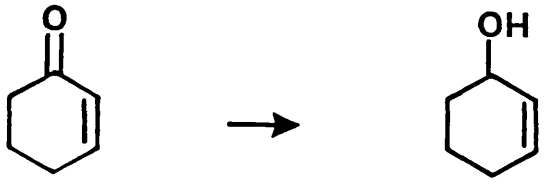


n-Butyl lithium (0.22 ml of a 1.49 M solution in hexane, 0.31 mmol) was added to a stirred solution of the sulphoxide (50) (103 mg, 0.30 mmol) in THF (2 ml) at -78°C. After 30 min, the yellow solution was treated with crude 2,2-dimethyl-4-(R)-trifluoromethylsulphonyl-oxymethyl-1-,3-dioxalane* (82 mg, 0.33 mmol) in THF (1 ml) and stirred at -78°C for 1 h then at RT for 16 h. Despite t.l.c.s. run in ether and 75% ether-petrol indicating no apparent change, the reaction mixture was worked up by quenching with saturated ammonium chloride solution (5 ml), extracting with ether (2 x 25 ml), drying over $MgSO_4$ and evaporating under reduced pressure to give a yellow oil (169 mg). Flash chromatography (gradient elution, 0 → 20% ether-petrol) gave a fraction (45 mg) co-eluting with or marginally less polar than the starting sulphoxide having the following spectral data; δ(250 MHz) 0.03 and 0.08

*2,2-Dimethyl-4-(R)-trifluoromethylsulphonyloxymethyl-1,3-dioxalane was prepared as follows:- A solution of 2-(S),3-O-isopropylidene-glycerol (41 mg, 0.34 mmol) and triethylamine (68 mg, 0.68 mmol) in dichloromethane (1 ml) was added dropwise to a stirred solution of triflic anhydride (115 mg, 0.41 mmol) in dichloromethane (2 ml) at -8°C. The resultant brown solution was stirred for 12 h at -8°C, then diluted with more dichloromethane (5 ml) and washed once with 1 M HCl(aq) (5 ml) and once with water (1 ml). Drying over $MgSO_4$ and evaporation under reduced pressure at 5°C gave a black oil (82 mg, 98%) which was used without further purification in Experiment No. 12.

(6H, 2s, SiMe_2), 0.86 and 0.92 (10.4H, 2s and multiplet, t-Bu plus 1.4 H), 1.26 and 1.35 (1.78H and 1.5H, 2 d, J 7.2 Hz, 3' -Me and (**50**) 4-Me?), 1.35 (2.5H, s, 2-Me), 1.42 (2.5H, s, 2-Me), 2.05 (0.3H, br s, H), 2.4 (0.4H, br s, H), 2.47-2.97 (3.2H, m, 1' -H_2, 2' -H and 3' -H), 3.52-4.25 (3H, m, 4-H and 5-H_2), 4.18 (2H, m, 6' -H_2), 5.62 (1.7 H, dd plus m, J 7.4 and 18.5 Hz, 4' -H plus H), 5.73 (0.6H, dt, J 18.5 and 4.7 Hz, 5' -H), 7.5 (3.1H, m, Ph), and 7.62 (2.0H, m, Ph); *m/z* 465, 453 (M^+ + 1), 438 (M^+ + 1-CH_3), 411, 395 (M^+-^{t}Bu), 351, 311, 281 [(50)$^+$-^{t}Bu], 213 [(50)$^+$-PhSO] 211, 184, 155, 126 ($PhSOH^+$), 109 (PhS^+), and 77 (Ph^+).

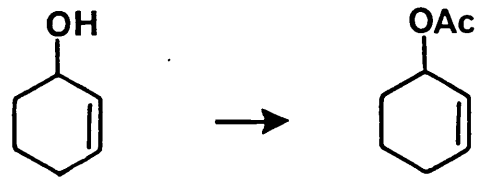
13. Preparation of (±) 2-Cyclohexen-1-ol (67)



67

To a stirred solution of 2-cyclohexenenone (16.40 g, 0.171 mol) in dry THF (50 ml) at 0°C was added lithium aluminium hydride (1.86 g, 49 mmol) portion-wise over 5 min. After stirring for 20 min, saturated ammonium chloride solution (4 ml) was added and the solution was diluted with ether (100 ml). After 5 min, the granular precipitate was filtered off and the filtrate dried over Na_2SO_4 and evaporated to give crude product (15.1 g). Kugelrohr distillation (80°C, 11 mm Hg) afforded racemic 2-cyclohexen-1-ol (67) (14.4 g, 88%) as a colourless liquid. δ(60 MHz) 1.3-2.2 (6H, m, 4-H_2, 5-H_2, 6-H_2), 4.22 (1H, m, 1-H), and 5.80 (2H, br s, 2-H, 3-H); $\nu_{max.}$ (neat) 3342, 2936, 1648, 1434, 1052, 960, and 727 cm^{-1}.

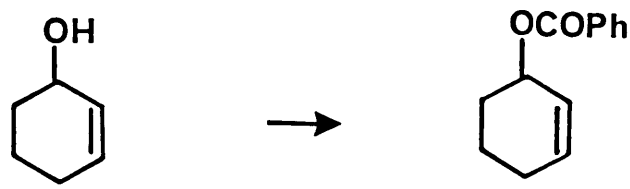
14. Preparation of (±) 1-Acetoxy-2-cyclohexene



67

To a stirred solution of 2-cyclohexen-1-ol (67) (0.50 g, 5.1 mmol), triethylamine (1.0 g, 1 mmol) and DMAP (20 mg) in dry dichloromethane (30 ml) was added acetic anhydride (1.0 g, 1 mmol) dropwise at 0°C under argon. After 5 min the reaction mixture was allowed to warm to RT and was stirred for 1 h. The solution was washed once with saturated sodium bicarbonate solution (30 ml) and brine (30 ml). Drying over $MgSO_4$ and evaporation under reduced pressure below 5°C gave a yellowish oil which was chromatographed (eluant, 10% ether-petrol) to afford (±)acetoxy-2-cyclohexene (0.64 g, 90%) as a colourless volatile aromatic liquid; δ(90 MHz) 1.52-2.1 (6H, m, 4-H_2, 5-H_2, 6-H_2), 2.03 (3H, s, OCO*Me*), 5.26 (1H, m, 1-H), 5.71 (1H, dm, J~10 Hz, 3-H), and 5.95 (1H, dm, J~10 Hz, 2-H); $\nu_{max.}$ (neat) 2939, 1732, 1370, 1240, 1058, 1030, 1009, and 908 cm^{-1}.

15. Preparation of (±)1-Benzoyloxy-2-cyclohexene (68)

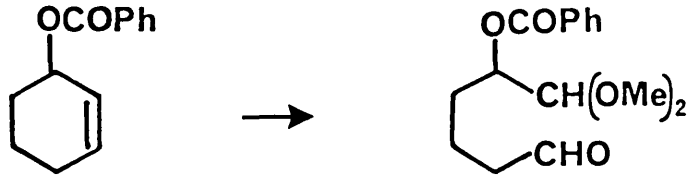


67 68

To a stirred solution of 2-cyclohexen-1-ol (67) (496 mg, 5.1 mmol) in dry pyridine (3 ml) was added benzoyl chloride (0.70 ml, 6 mmol) dropwise at 0°C under argon. After stirring for 1 h, the reaction

mixture was taken up in ether (150 ml), washed with saturated copper(II) sulphate solution (3x50 ml) then brine (50 ml) and dried over $MgSO_4$. Evaporation under reduced pressure and chromatography (eluant, 5% ether-petrol) afforded (±)1-benzoyloxy-2-cyclohexene (68) (860 mg, 84%) as a colourless oil; δ(60 MHz) 1.4-2.3 (6H, m, 4-H_2, 5-H_2, 6-H_2), 5.51 (1H, m, 1-H), 5.9 (1H, dm, J~10 Hz, 3-H), 6.0 (1H, dm, J~10 Hz, 2-H), 7.3-7.65 (3H, m, Ph), and 8.1 (2H, m, Ph); $\nu_{max.}$ (neat) 3032, 2938, 1708 (OCOPh), 1450, 1270, 1112, 1026, 917, and 711 cm^{-1}.

16. Preparation of (±)5-Benzoyloxy-6,6-dimethoxy-hexanal (70)



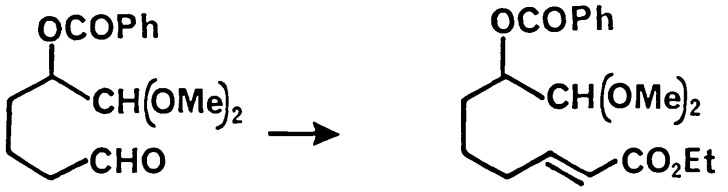
68 70

A solution of 1-benzoyloxy-2-cyclohexene (68) (500 mg, 2.48 mmol) in dry dichloromethane (8 ml) and methanol (2 ml) with a catalytic amount of p-toluenesulphonic acid (50 mg) was ozonized at -78°C until the solution turned violet (*ca.* 15 min). The solution was warmed to RT and after 20 min, was treated with trimethylortho- formate preabsorbed on K-10 montmarillonite clay (2 g). The mixture was stirred for 1 h, filtered and the filtrate washed with sodium bicarbonate solution (2x5 ml), brine (5 ml) and dried over $MgSO_4$. The solvent was evaporated to afford (±)5-benzoyloxy-6,6-dimethoxy- 1-hydroperoxy-1-methoxy-hexane as an oil; δ(90 MHz) 1.5-2.0 (4H, br m, 3-H_2, 4-H_2), 2.35 (2H, m, 2-H_2), 3.45 and 3.49 (7.5H, 2s, 2.5xOMe), 3.63 (1.5 H, s, 1/2xOMe), 4.45 (1H, d, J 5.8 Hz, 6-H), 5.25 (1H, m, 5-H), 7.3-7.65 (3H, m, Ph), and 8.1 (2H, m,

Ph). The peroxy-hemimethoxy-acetal was taken up in dichloromethane (20 ml) and stirred at RT with sodium bicarbonate (3 g) and triphenylphosphine (1.28 g, 4.9 mmol) for 18 h. Filtration, evaporation and chromatography (gradient elution, 5→20% ether-petrol) afforded the *aldehyde-acetal* (70) (406 mg, 58%) as a colourless oil; δ(90 MHz) 1.3-2.1 (4H, m, 3-H_2, 4-H_2), 2.50 (2H, m, 2-H_2), 3.43 and 3.45 (6H, 2s, 2xOMe), 4.49 (1H, d, J 5.3 Hz, 6-H), 5.19 (1H, m, 5-H), 7.3-7.6 (3H, m, Ph), 8.19 (2H, m, Ph), and 9.75 (1H, t, J 1.5 Hz, 1-H); $\nu_{max.}$ (neat) 2942, 1716, 1449, 1362, 1315, 1273, 1114, 1071, 1026, 976 and 848 cm^{-1}; *m/z* 279 (M^+-H), 265 (M^+-CH_3), 249 (M^+-OMe), 175 (M^+-OCPh), 105 $(OCPh)^+$, and 75; (Found: C, 63.94; H, 7.19. $C_{15}H_{20}O_5$ requires C, 64.27; H, 7.19).

The more polar 2-benzoyloxyhexandial (70) (231 mg, 40%) was also isolated as a colourless oil; δ(250 MHz) 1.8-2.1 (4H, m, 3-H_2, 4-H_2), 2.55 (2H, dt, J 1.2 and 7.8 Hz, 5-H_2), 5.22 (1H, dt, J 0.9 and 6.5 Hz, 2-H), 7.4-7.65 (3H, m, Ph), 8.1 (2H, m, Ph), 9.63 (1H, d, J 0.9 Hz, 1-H), and 9.79 (1H, t, J 1.2 Hz, 6-H).

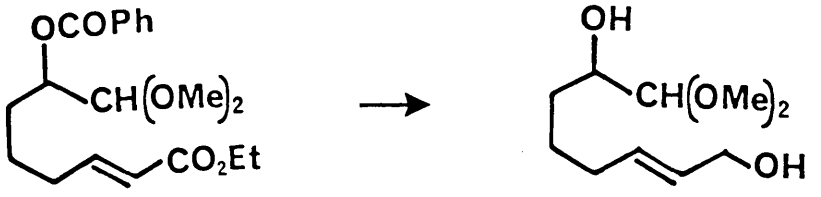
17. Preparation of (±)-Ethyl-7-benzoyloxy-8,8-dimethoxy-2E-octenoate (71)



70 71

The aldehyde (70) (212 mg, 0.76 mmol) and carboethoxymethylene-triphenylphosphorane (394 mg, 1.1 mmol) were stirred in dry benzene (20 ml) under argon at 60°C for 14 h. The solution was evaporated to dryness and chromatographed (eluant, 20% ether-petrol) to give the unsaturated ester (71) (195 mg, 78%; 98% based on recovered starting material) as a colourless oil; δ(250 MHz) 1.25 (3H, t, J 7 Hz, OCH_2CH_3), 1.42-1.95 (4H, m, 5-H_2, 6-H_2), 2.25 (2H, dq, J 1.6 and 6.7 Hz, 4-H_2), 3.43 and 3.46 (6H, 2s, 2xOMe), 4.18 (2H, q, J 7 Hz, OCH_2Me), 4.43 (1H, d, J 5.0 Hz, 8-H), 5.25 (1H, dt, J 5 and 6.7 Hz, 7-H), 5.82 (1H, dt, J 15.5 and 1.6 Hz, 2-H), 6.94 (1H, dt, J 15.5 and 6.7 Hz, 3-H), 7.3-7.6 (3H, m, Ph), and 8.1 (2H, m, Ph); $\nu_{max.}$ (neat) 2935, 1717 (OCOPh), 1649, and 1601 cm^{-1}; *m/z* 319 (M^+-OMe), 305 (M^+-OEt), 241 (M^+-OCOPh), 196, and 75 $[CH(OMe)_2]^+$; (Found: (M^+-OMe), 319.1553. $C_{18}H_{23}O_5$ requires 319.1545).

18. Preparation of (±)8,8-Dimethoxy-oct-2-(E)-en-1,7-diol (73)

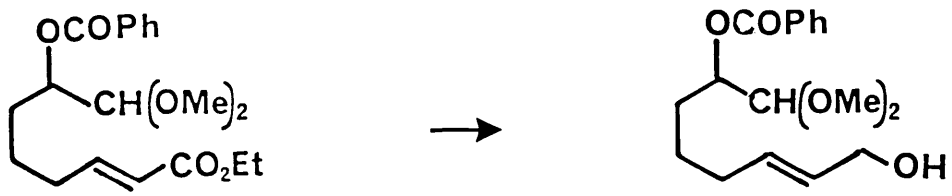


71 73

To a stirred solution of the diester (71) (8.4 g, 24 mmol) in dry THF (50 ml) cooled to -78°C was added DIBAL-H (80 ml of a 1.5 M solution in toluene, 120 mmol). After stirring at -78°C for 15 min then at 0°C for 1 h, the reaction was quenched with water (5 ml). After stirring for 20 min at RT, the mixture gelled. The gel was adsorbed on sodium bicarbonate (20 g) and $MgSO_4$ (15 g) and the wet solid was extracted three times with ethyl acetate (3 x 100 ml) and four times

with 20% ethanol-chloroform (4 x 100 ml) through a small pad of silica. The extracts were evaporated under reduced pressure and flash chromatographed (gradient elution, 0 → 10% ethanol- dichloromethane) to afford the (±)*allylic diol* (73) (3.85g, 80%) as a colourless oil; δ(90 MHz) 1.3-1.8 (4H, m, 5-H_2, 6-H_2), 2.05 (2H, m, 4-H_2), 2.9 (2H, br s, 2 x OH), 3.42 and 3.46 (6H, 2s, 2 x OMe), 3.55 (1H, m, 7-H), 4.05 (2H, m, 1-H_2), 4.12 (1H, d, J 6.4 Hz, 8-H), and 5.67 (2H, m, 2-H and 3-H); $\nu_{max.}$ 3402 (OH), 2938, 1668, 1437, 1303, 1190, 1078, 971 and 723 cm^{-1}; *m/z* 172 (M^+-MeOH), 155 (M^+-MeO-H_2O), 154, 141, 123, 109, 105, and 75; (Found: C, 58.96; H, 10.11. $C_{10}H_{20}O_4$ requires C, 58.81; H, 9.87).

19. Preparation of (±)-7-Benzoyloxy-8,8-dimethoxy-oct-2-(E)-en-1-ol (72)

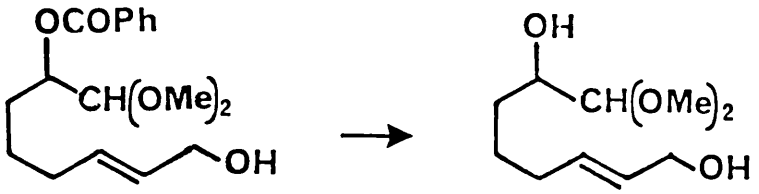


71 72

DIBAL-H (0.62 ml of a 1.5 M solution in toluene, 0.94 mmol) was added to a stirred solution of the diester (71) (149 mg, 0.43 mmol) in dry THF (3 ml) under argon at -78°C. After 2 h, the reaction mixture was quenched with methanol (1 ml) at -78°C and warmed to 0°C. Water (1/2 ml) was added, and after stirring for 20 min, the mixture gelled. The gel was adsorbed on sodium bicarbonate (3 g) and $MgSO_4$ (3 g) and extracted with three portions of ethyl acetate (3 x 30 ml) through a small pad of silica. The extracts were evaporated under reduced pressure and flash-chromatographed (eluant, 30% ether-petrol) to afford the benzoate alcohol (72) (99 mg, 76%) as a colourless oil; δ(90 MHz) 1.3-2.2 (7H, m, 4-H_2, 5-H_2, 6-H_2 and OH), 3.36 and 3.41 (6H, 2s, 2 x OMe), 4.05 (2H, m, 1-H_2), 4.42 (1H, d, J 5.2 Hz, 8-H), 5.23 (1H, dt,

J 5.2 and 6.3 Hz, 7-H), 5.62 (2H, m, 2-H and 3-H), 7.35-7.6 (3H, m, Ph) and 8.05 (2H, m, Ph); $\nu_{max.}$ 3422(OH), 2933, 1716 (OCOPh), 1601, 1315, 1274, 1112, 970 and 712 cm^{-1}.

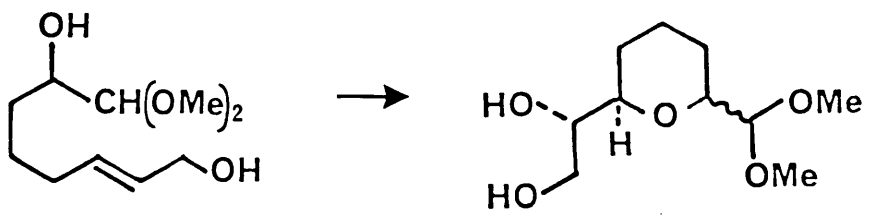
20. Preparation of (±)-8,8-Dimethoxy-oct-2-(E)-en-1,7-diol (73)



72 73

The benzoate alcohol (72) (29 mg, 0.32 mmol) was saponified by stirring in 10% potassium hydroxide in methanol (3 ml) for 20 min. The reaction mixture was poured into brine (15 ml) and extracted with chloroform (3 x 10 ml). The extracts were washed once with sodium bicarbonate solution (5 ml) then brine (5 ml) and dried over $MgSO_4$. Concentration and flash chromatography (gradient elution, chloroform → 10% ethanol-chloroform) gave the diol (73) (61 mg, 86%) as a colourless oil. Spectral data as for Expt. No. 18.

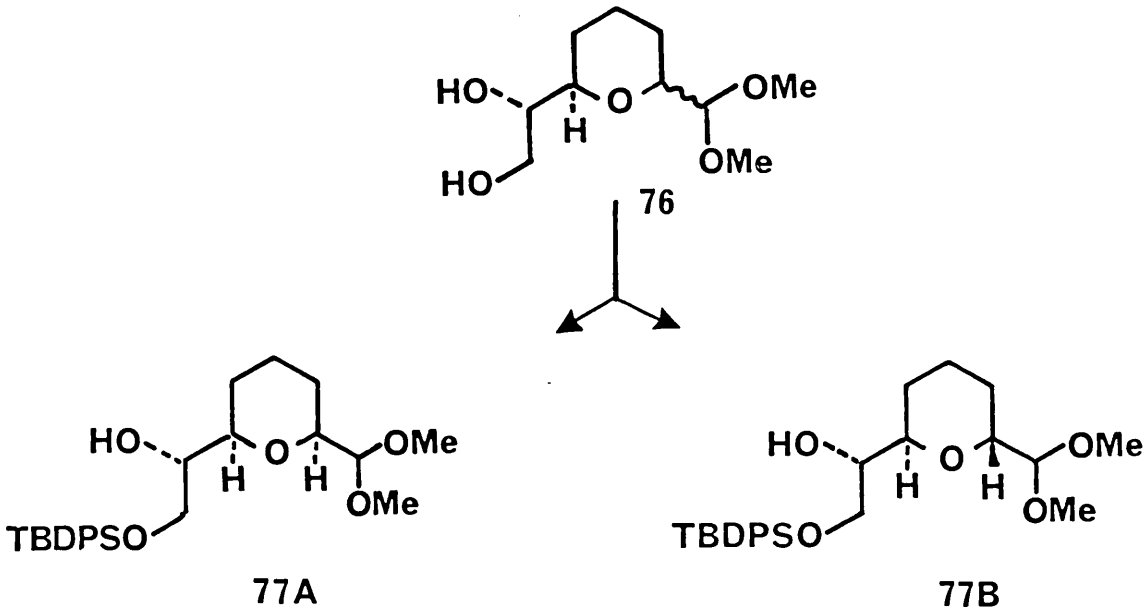
21. Preparation of 2-(R)-[1'-(S),2'-Dihydroxyethyl]-6-dimethoxymethyl-tetrahydropyran (76)



73 76

Titanium (IV) isopropoxide (10.6 ml, 35.5 mmol) was added to a stirred solution of (+)-diethyl L-tartrate (8.77 g, 42.6 mmol) in dry dichloromethane (100 ml) at RT. After 5 min, the solution was cooled to -78°C and treated with the allylic alcohol (73) (3.62 g, 17.7 mmol) in dichloromethane (6 ml) followed by t-butyl hydroperoxide (28.4 ml of a 3 M solution in toluene, 85 mmol). The solution was stirred for 2 min and then allowed to warm to -20°C. After 16 h dimethyl sulphide (6 ml) was added and the reaction mixture was warmed to RT and stirred for 1 h. Acetonitrile (7 ml) and saturated sodium fluoride solution (7 ml) were added and the mixture wa stirred vigorously for 2 h. The resultant gel was filtered through celite and the filter-cake washed with dichloromethane (2 x 50 ml) followed by 10% ethanol-chloroform (4 x 100 ml). The combined filtrates were dried (Na_2SO_4) and chromatographed (gradient elution, 2 → 10% ethanol- chloroform) to afford a 1:1 mixture of the epimeric diols (76) (2.49 g, 64%) as a colourless oil; δ(250 MHz) 1.2-1.95 (6H, m, 3-H_2 4-H_2, 5-H_2), 2.45 (2H, br s, 2 x OH), 3.38 (6H, s, 2 x OMe), 3.37-3.44 (2H, m, 2-H, 6-H), 3.52-3.90 (3H, m, 1'-H, 2'-H_2), 4.17 (0.5H, d, J 6.0 Hz, 1"-H) and 4.57 (0.5 H, d, J 6.2 Hz, 1"-H) $\nu_{max.}$ 3426 (OH), 2938, 1441, 1305, 1197, 1080, 976, and 911 cm^{-1}; *m/z* 201, 199, 189 (M^+-OMe), 185, 159 (M^+-$C_2H_5O_2$), and 75; (Found: M^+-OMe, 189·1130. $C_9H_{17}O_4$ requires 189·1127).

22. Preparation of 2-(R)-[1'-(S)-hydroxy-2'-t-butyldiphenylsilyloxyethyl]-6-(S)-dimethoxymethyltetrahydropyran (77A) and 2(R)-1'-(S)-Hydroxy-2'-t-butyldiphenylsilyloxyethyl]-6-(R)-dimethoxymethyltetrahydropyran (77B)



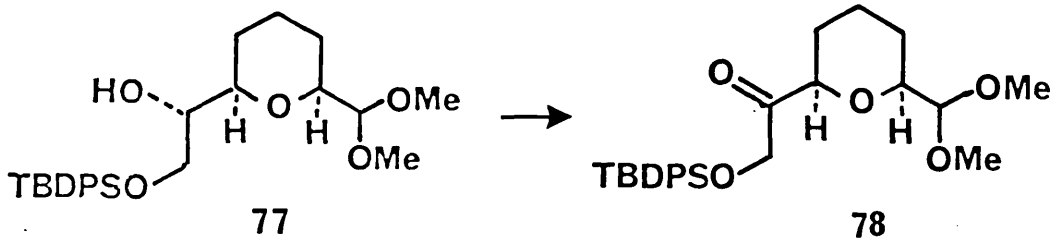
t-Butylchlorodiphenylsilane (2.0 ml, 7.73 mmol) was added to an ice-cold stirred solution of epimeric diols (76A and B, 1:1 mixture) (1.41 g, 6.44 mmol), triethylamine (1.24 ml, 8.84 mmol) and DMAP (50 mg). After 14 h at 0°C, the incomplete reaction mixture was preabsorbed upon silica gel (10 g) and flash chromatographed (gradient elution, 20% ether-petrol and then 10% ethanol chloroform) to obtain (in order of increasing polarity) the 6-(R) alcohol (77B) (0.59 g, 20%), the 6-(S) alcohol (77A) (0.68 g, 23%) both as colourless oils and the recovered starting diol (76) (0.77 g, 54%).

6-(S) alcohol (77A); R_F 0.35 in 40% ether-petrol; δ(90 MHz) 1.09 (9H, s, t-Bu), 1.5-1.9 (6H, m, 3-H_2, 4-H_2, 5-H_2), 2.55 (1H, br s, OH), 3.21 and 3.36 (6H, 2xs, 2xOMe), 3.36-4.00 (5H, m, 1 -H, 2 -H_2, 6-H), 4.31 (1H, d, J 6.9 Hz, 1"-H), 7.31-7.54 (6H, m, Ph), and 7.6-7.8 (4H, m, Ph).

6-(R) alcohol (77B); R_F 0.44 in 40% ether-petrol; δ(90 MHz) 1.09 (9H, s, t-Bu), 1.15-2.03 (6H, m, 3-H_2, 4-H_2, 5-H_2), 2.5 (1H, br s, OH), 3.28 and 3.34 (6H, 2xs, 2xOMe), 3.3-3.49 (2H, m, 2-H, 6-H), 3.54-3.88 (3H, m, 1'-H, 2'-H_2), 4.08 (1H, d, J 5.4 Hz, 1"-H), 7.3-7.48 (6H, m, Ph), and 7.55-7.75 (4H, m, Ph).

Low resolution mass spectrum, infrared and accurate mass data of a ~ 1:1 mixture of (77A) and (77B); $\nu_{max.}$ 3469 (OH), 3069, 3047, 2931, 1460, 1442, 1426, 1338, 1360, 1257, 1194, 1111, 1006, 912, 824, and 704 cm^{-1}; *m/z* 419, 409 (M^+-OMe-H_2O), 387, 369 (M^+-^{t}Bu-MeOH), 351 (369$^+$-^{t}Bu), 337, 319, 281, 259, 199 ($SiPh_2OH^+$), 142 and 75 [$CH(OMe)_2^+$]; (Found: M^+-H_2O-OMe, 409·2202. $C_{25}H_{33}O_3$ requires 409.2199.

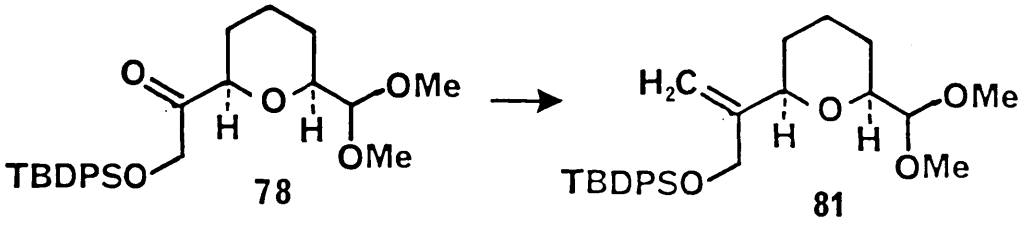
23. Preparation of 2(R)-(2'-t-Butyldiphenylsilyloxy-1'-acetyl)-6-(dimethoxymethyl)tetrahydropyran (78)



To a stirred solution of oxalylchloride (94 mg, 0.74 mmol) in dichloromethane (10 ml) at -78°C was added dropwise a solution of dimethylsulphoxide (115 g, 1.48 mmol) in dichloromethane (2 ml) followed after 5 min by a 1:1 mixture of the alcohols (77A and B) (96 mg, 0.21 mmol) in dichloromethane (0.5 ml). After 30 min, triethylamine (0.36 ml, 2.59 mmol) was added and the mixture was warmed to RT over 1 h. The reaction mixture was washed with water (10 ml), brine (10 ml) and dried over $MgSO_4$. Evaporation under reduced pressure gave an oil which was chromatographed (eluant, dichloromethane) to afford a 1:1 mixture of the epimeric *ketones* (78) (80 mg, 83%) as a colourless oil;

δ(90 MHz) 1.10 (9H, s, t-Bu), 1.15-1.95 (6H, m, 3-H_2, 4-H_2, 5-H_2), 3.38 (6H, s, 2xOMe), 3.32 (1H, m, 6-H), 3.85 and 3.96 (1H total, m, 2-H both isomers), 4.07 and 4.15 (1H total, 2d, J 5.8 Hz each, 1"-H both isomers), 4.40-4.57 (2H, m, 2 '-H_2), 7.3-7.5 (6H, m, Ph) and 7.6-7.8 (4H, m, Ph); ν max. 2930, 2857, 1737 (C=0), 1427, 1111, 917, 823, 741, and 703 cm^{-1}; *m/z* 409, 399 (M^+-^{t}Bu), 381 (M^+-^{t}Bu-H_2O), 367 (M^+-^{t}Bu-MeOH), 199 $(Ph_2SiOH)^+$, 159 $(C_8H_{15}O_3)^+$, 127 $(C_7H_{11}O_2)^+$ and 75; (Found: M^+-^{t}Bu, 399.1628. $C_{22}H_{27}O_5Si$ requires 399·1628); (Found: C, 68.49; H, 7.88. $C_{26}H_{36}O_5Si$ requires C, 68.38; H, 7.95).

24. Preparation of 2-(R)-(1 '-t-Butyldiphenylsilyloxy-prop-2'-en-2'-yl)-6-(dimethoxymethyl)tetrahydropyran (81)



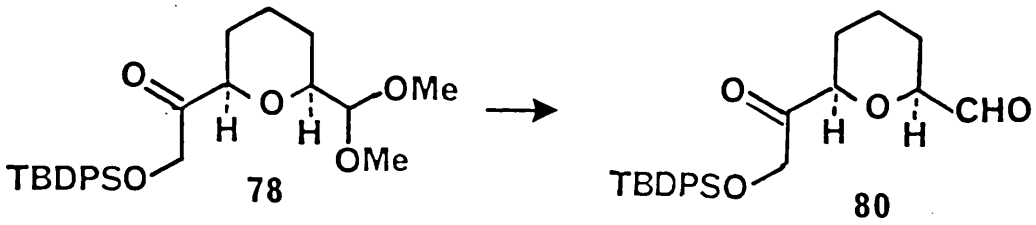
Magnesium turnings (55 mg, 2 mmol), chloromethyltrimethylsilane (244 mg, 2 mmol) and a crystal of iodine (5 mg) in THF (5 ml) were heated under reflux under argon at 65°C until a Grignard reaction commenced. Heating was continued for a further 20 min, then the reaction mixture was cooled to RT, and treated with the ketone (78) (49 mg, 0.1 mmol) in THF (2 ml). After 1/2 h the reaction mixture was quenched with saturated ammonium chloride solution (4 ml) and extracted twice with ether (2 x 15 ml). The extracts were dried over $MgSO_4$, evaporated to dryness and chromatographed (eluant, 20% ether-petrol) to afford (in order of increasing polarity) an inseparable mixture of

TMS-methyl-hydroxy epimers derived from the *cis*-6-(S)-tetrahydropyran ketone (27 mg); δ(90 MHz) - 0.05 (9H, s, Si*Me*$_3$), 0.89 and 0.92 (2H, 2d, J 11.5 and 11Hz, 1'-H_2), 1.08 (9H, s, t-Bu), 1.2-2.05 (6H, m, 3-H_2, 4-H_2, 5-H_2), 2.65 (1H, br s, OH), 3.35-3.40 (6H, 3 lines, 2xOMe, both isomers), 3.35-3.80 (4H, m, 3'-H_2, 2-H, 6-H), 4.11 (1H, d, J 6.0 Hz, 1"-H), 7.3-7.5 (6H, m, Ph), and 7.6-7.8 (4H, m, Ph); R_F 0.77 in 50% ether-petrol. Also isolated were a mixture of the TMS-methyl addition products to the *trans*-6-(R)-tetrahydropyran-ketone (15 mg), R_F 0.71 and 0.67; δ(90 MHz of mixture) -0.05 (9H, s, Si*Me*$_3$), 0.8-1.05 (2H, m, 1'-H_2), 1.8-08 (9H, s, t-Bu), 1.3-1.8 (6H, m,4 3-H_2, 4-H_2, 5-H_2), 2.62 (1H, br s, OH), 3.27 and 3.39 (6H, 2xs, 2xOMe), 3.4 (1H, m, 6-H), 3.58 (2H, m, 3'-H_2, 3.8 (1H, m, 2-H), 4.66 (1H, d, J 7.7 Hz, 1"-H), 7.3-7.5 (6H, m, Ph) and 7.6-7.8 (4H, m, Ph).

A 35% dispersion of potassium hydride in mineral oil (200 mg, ~ 1.7 mmol) was stirred in sodium-dried 30-40°C petrol (5 ml) under argon for 2 min. The suspension was allowed to settle and the petrol was decanted by syringe. The process was repeated twice, the last portion of petrol was replaced by dry THF (5 ml). The combined Peterson intermediates (41 mg) in THF (0.5 ml) were added to the stirred suspension at RT. After 13 h, the mixture was quenched with saturated ammonium chloride solution (5 ml), extracted with ether (2 x 10 ml), dried $MgSO_4$ and evaporated to dryness. The residue was chromatographed (eluant, 10% ether-petrol) to afford an inseparable mixture (1:1) of the methylene diastereomers (81) (34 mg, 69%) as an oil; δ(250 MHz) 1.06 and 1.065 (9H, 2s, t-Bu), 1.2-1.93 (6H, m, 3-H_2, 4-H_2, 5-H_2), 3.24-3.35 (7H, 4 lines, 2xOMe, 6-H), 3.82 (0.8 H, dm, J 10.3 Hz, 2-H), 4.14 (1/2H, d, J 5.2 Hz, 1"-H [6-(S)-epimer]), 4.20 (0.5 H, d, J 5.8 Hz, 1"-H [6-(R)-epimer]), 4.24 (2H, m, *CH*$_2$OTBDMS), 5.15, 5.30 and 5.52

(2H, 3m [ratio 9:5:2], CH_2=CR_1R_2) 7.36-7.46 (6H, m, Ph), and 7.65-7.75 (4H, m, Ph); R_F 0.55 in 20% ether-petrol.

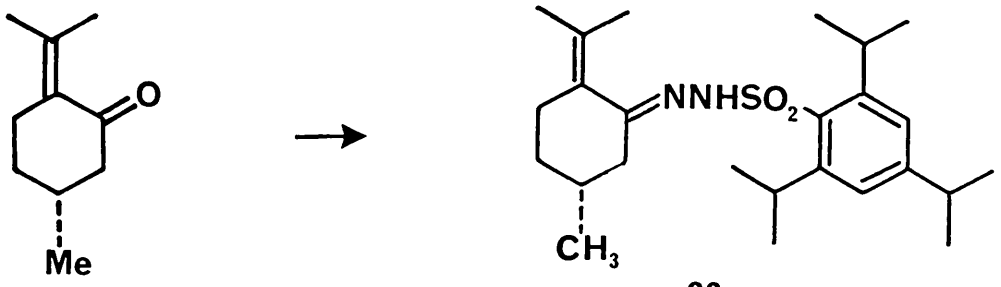
25. Preparation of 2-(R)-2' -t-Butyldiphenylsilyloxy-1'-acetyl)-6-formyltetrahydropyran (80)



The acetal-ketone (*78*) (45 mg, 0.1 mmol) and light sensitive $PdCl_2(MeCN)_2$ (29 mg) were stirred in the dark for 16 h at RT in dry acetone 1 ml) under argon. The incomplete reaction was evaporated to dryness and the red solid residue extracted with ether (2 x 5 ml). The extracts were concentrated and chromatographed (eluant, 40% ether-petrol) to afford in order of increasing polarity: the starting acetal (8 mg), the *trans*-aldehyde (80B) (8 mg, 20%) and the *cis* aldehyde (80A) (8 mg, 20%) as colourless oils; 48% yield based on recovered starting material. (80A): δ(250 MHz) 1.08 (9H, s, t-Bu), 1.2-2.0 (6H, m, 3-H_2, 4-H_2, 5-H_2), 3.75 (1H, dd, J 11.8 and 2.83 Hz, 6-H), 4.08 (1H, dd, J 12.0 and 2.4 Hz, 2-H), 4.58 (2H, m, 2'-H_2), 7.4 (6H, m, Ph), 7.67 (4H, m, Ph), and 9.58 (1H, s, 1"-H); $\nu_{max.}$ 3475 ($CH(OH)_2$), 2930, 1734(C=O), 1427, 1112, 823, and 741 cm^{-1}.

(80B): δ(90 MHz) 1.12(9H, s, t-Bu), 1.2-2.0 (6H, m, 3-H_2, 4-H_2 and 5-H_2), 3.4 (1H, m, 6-H), 4.12 (1H, m, 2-H), 4.5 (2H, m, 2' -H_2), 7.4 (6H, m, Ph), 7.65 (4H, m, Ph), and 9.61 (1H, s, 1"-H).

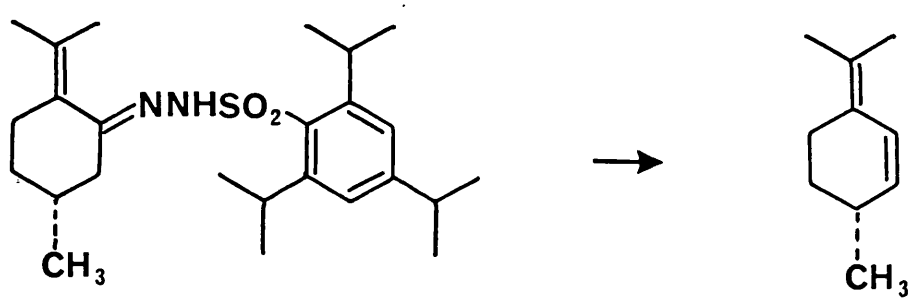
26. Preparation of (+)Pulegone-2,4,6-Triisopropylbenzenesulphonyl-hydrazone (83)



83

To a stirred suspension of 2,4,6-triisopropylbenzenesulphonyl-hydrazide (26.3 g, 88 mmol) and (+)pulegone (13.4 g, 88 mmol) in methanol (88 ml) was added concentrated hydrochloric acid (1 ml) at RT. After 15 min the solution became clear and was cooled to -5°C and stirred at this temperature for 14 h. The crude product was filtered off, washed with ice-cold methanol (3 x 20 ml) and dried under high vacuum over P_2O_5 for 24 h to give the desired *hydrazone*[37] (83) (25.8 g, 68%) as a white crystalline solid. Mp. 128° C; lit.mp., 128°C; $[\alpha]_D^{25}$ +27.3 (*c* 2.3, $CHCl_3$); δ(90 MHz) 0.95 (3H, d, J 6 Hz, 5-Me), 1.25 (18H, d, J 7 Hz, 3 x i-Pr), 1.70 (7H, m, 3-H_2, 4-H_2, 5-H, 6-H_2), 2.90 (1H, septet, J 7 Hz, 4'-C*H*Me_2), 4.30 (2H, septet, J 7 Hz, 2' and 6' -C*H*Me_2), 7.15 (2H, s, 3'-H, 5'-H), and 7.8 (1H, m, N-H); $\nu_{max.}$ ($CHCl_3$) 3221, 2927, 1598, 1457, 1424, 1375, 1324, 1154, 1073, and 939 cm^{-1}; *m/z* 432 (M^+), 267 ($TrisSO_2^+$), and 165 (M^+-Tris SO_2); (Found: C, 63.72; H, 9.07; N, 6.39; S, 7.48. $C_{25}H_{40}N_2SO_2$ requires C, 69.40; H, 9.32; N, 6.47; S, 7.41%).

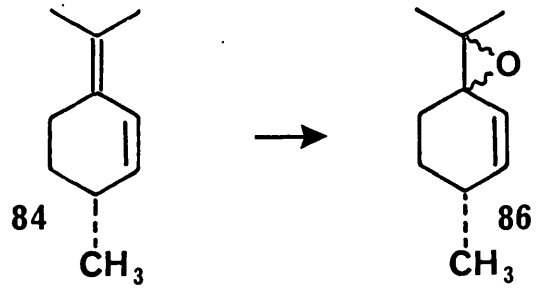
27. Preparation of 1-Isopropylidene-4-(R)-methyl-2-cyclohexene (84)



83 84

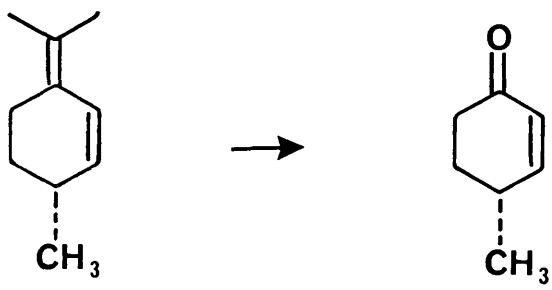
To a stirred suspension of the trislylhydrazone (83) (25.7 g, 60 mmol) in 4:1 petrol:TMEDA (600 ml) under argon at -78°C was added n-butyl lithium (115 ml of a 1.55 M solution in hexane, 0.179 mol) dropwise over 20 min. The yellow solution was stirred at -78°C for a further 20 min and warmed to 0°C at which temperature nitrogen was given off vigorously. After 40 min at 0°C effervescence had ceased and the solution was quenched with water (100 ml). The organic layer was washed with water (4x100 ml) then brine (100 ml) and dried over $MgSO_4$. Concentration gave a yellow oil (10.1 g) which was chromatographed on a short column of silica gel (eluant, petrol) to afford pure diene (84) (8.1 g, 99%) as a colourless oil; δ(250 MHz) 1.00 (3H, d, J 6.8 Hz, 4-Me), 1.20-1.35 (2H, m, 5-H_2), 1.73 and 1.77 (6H, 2xs, 2i-Pr Me_2), 2.1-2.6 (3H, m, 4-H, 6-H_2), 5.54 (1H, dm, J 10 Hz, 3-H), and 6.39 (1H, dd, J 2.3 and 10 Hz, 2-H); $\nu_{max.}$(neat) 3025, 2954, 2923, 1606, 1451, 1371, 881, and 731 cm^{-1}; m/z 136 (M^+).

28. Preparation of 1-Isopropylidene-4-(R)-methyl-2-cyclohexenyl-1,9-(R,S)epoxide (86)



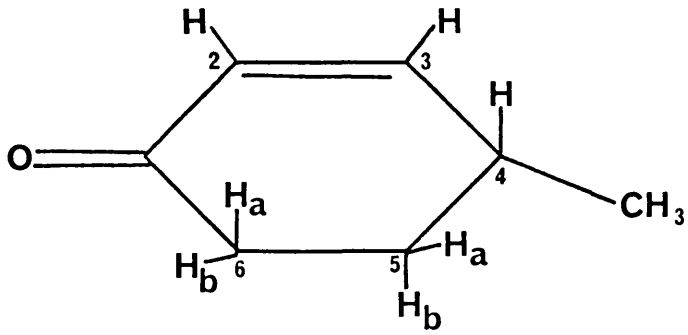
To a stirred suspension of potassium carbonate (305 mg) and and peracetic acid (30%, 186 mg, 0.74 mmol) in dry dichloromethane (10 ml) was added a solution of the diene (84) (101 mg, 0.74 mmol) in dichloromethane (2 ml) under argon at RT. After 1 h, no starting material remained by t.l.c. so the reaction mixture was washed with sodium bicarbonate solution (10 ml) then water (10 ml). Drying over $MgSO_4$ and evaporation under reduced pressure at 5°C gave an aromatic oil which was chromatographed on silica gel doped with 1% triethylamine (eluant, petrol) to afford an inseparable mixture of the diastereomeric epoxides (86) (51 mg, 45%) as a colourless oil; δ(250 MHz) 1.02 (1/3 x 3 H, d, J 7.6 Hz, 4-Me), 1.06 (2/3 x 3H, d, J 7.6 Hz, 4-Me), 1.34 and 1.36 (6H, 2s, i-Pr 2xMe), 1.37-2.4 (5H, m, 4-H, 5-H_2, 6-H_2), 5.5 (1H, m, 3-H), and 5.92 (1H, m, 2-H).

29. Preparation of 4-(R)-Methyl-2-cyclohexenone (61)



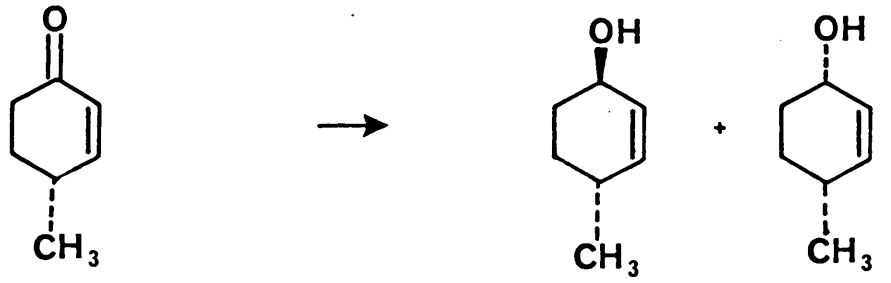
84 61

1-Isopropylidene-4-(R)-methyl-2-cyclohexene (84) (28.5 g, 0.21 mol) in dichloromethane (1700 ml) at -78°C was slowly ozonized until all the starting material had disappeared by t.l.c. Thus after *ca.* 4.5 h, excess dimethylsulphide (60 ml) was added and the solution was allowed to warm to RT overnight. Concentration under reduced pressure gave a residue which was chromatographed (gradient elution, 5 → 15% ether-petrol) to afford *4-(R)-methyl-2-cyclohexenone* (61) (7.16 g, 31%) as a colourless oil, $[\alpha]_D^{25}$ + 124.2° (*c* 2.3 in $CHCl_3$), lit$[\alpha]_D^{22\ 37}$ +105° (*c* 9.2 in $CHCl_3$) δ(250 MHz) (protons labelled as in the diagram below).



1.18 (3H, d, J 7.3 Hz, 7-H_3), 1.68 (1H, dddd, J_{5A5B} 12.8, J_{5B4} 9.3, J_{5B6A} 11.9 and J_{5B6B} 4.9 Hz, 5-H_B), 2.13 (1H, ddt), J_{5A5B} 12.8, J_{5A3} 1.6 and J_{5A6} 5.5 Hz, 5-H_A), 2.36 (1H, ddd, J_{6A6B} 16.4, J_{6A5B} 11.9, and J_{6A5A} 5.1 Hz, 6-H_A), 2.49 (1H, dt, J_{6B6A} 16.4, J_{6B5} 5.1, and J_{6B2} 0.8 Hz, 6-H_B), 2.56 (1H, dtq, J_{45B} 9.3, $J_{42,43}$ 2.5, and J_{47} 7.3 Hz, 4-H), 5.94 (1H, ddd, J_{23} 10.1, J_{24} 2.4, and J_{26} 0.8 Hz, 2-H), and 6.82 (1H, ddd, J_{32} 10.1, J_{34} 2.8, and J_{35} 1.5 Hz, 3-H); ν_{max} (neat) 2959, 2873, 1677, 1251, and 826 cm^{-1}; *m/z* 110 (M^+); (Found: C, 76.34; H, 9.14. $C_7H_{10}O$ requires C, 76.32; H, 9.15%).

30. Preparation of 4-(R)-methyl-1-(R)-cyclohex-2-enol (93A) and 4-(R)-methyl-1-(S)-cyclohex-2-enol (93B)



61 93A 93B

To a stirred solution of the enone (61) (6.79 g, 61.7 mmol) in dry ether (200 ml) was added DIBAL-H (49 mol of a 1.5 M solution in toluene, 74.1 mmol) dropwise under argon at -78°C. After 30 min the reaction was quenched with methanol (3 ml) at -78°C and allowed to warm to 0°C. Water (10 ml) was added and the reaction mixture was stirred for 15 min until a gel formed. The gel was dissolved in 2N hydrochloric acid (100 ml) and extracted with ether (3 x 100 ml). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure at 5°C to *ca.* 50 ml. The concentrate was chromatographed (gradient elution, 5 → 30% ether-petrol) to afford an unseparated mixture of epimeric *allylic alcohols* (93A) (4.51 g, 65%) and (93B) (0.67 g, 10%) as a clear oil; δ(90 MHz) 0.96 (2.6H, d, J 6.9 Hz, 4-Me (93A)), 1.02 (0.4H, d, J 7.5 Hz, 4-Me (93B)), 1.1-2.25 (5H, m, 4-H, 5-H_2, 6-H_2), 4.21 (1H, m, 1-H), 5.63 (1.74 H, m, 2-H (93A) and 3-H (93A)), and 5.73 (0.3H, m, 2-H (93B) and 3-H (93B)); $\nu_{max.}$ (neat) 3340 (OH), 2929, 1453, 1275, 1156, 1058, 991, and 733 cm^{-1}; *m/z* 112 (M^+), 97, 95 (M^+ -OH), 70 (M^+-CH_3CHCH_2), and 43; (Found: C, 75.08; H, 10.94. $C_7H_{10}O$ requires C, 74.96; H, 10.78%).

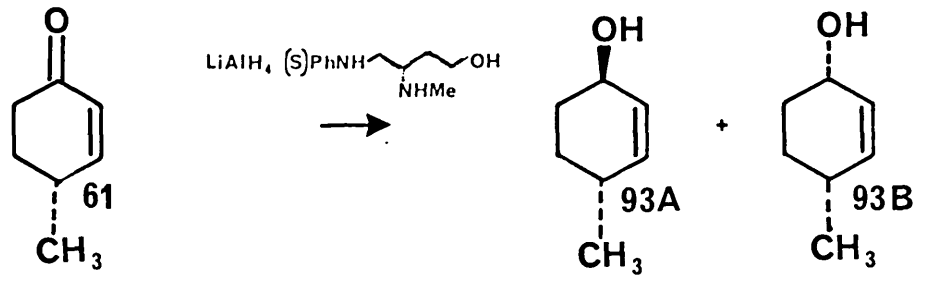
The alcohols (93A) and (93B) could be separated to > 99% purity on a 50 mg scale by h.p.l.c. (eluant, 7% isopropanol-hexane) but owing to

the volatility of (93A and 93B) the overall yield fell to 31% for the reduction.

More polar isomer (93A), $[\alpha]_D^{25}$ +194.1° (*c* 1.12 in $CHCl_3$); ^1H n.m.r. and IR data as above, purity of 99.5+% determined by gas chromatographic analysis using superox column, oven setting 130°C retention time 2.05 min.

Less polar isomer (93B), ^1H n.m.r. and i.r. data as above, g.c. retention time 1.91 min under identical conditions to (93A) above.

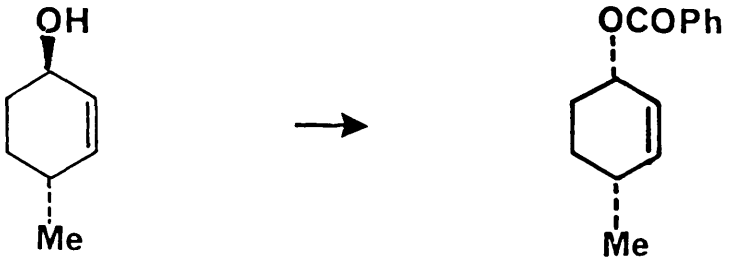
31. Preparation of epimeric (R) and (S)-1-Hydroxy-4-(R)-methyl-2-cyclohexene (93A and 93B) using lithium aluminium hydride and 3-(S)-(N-methylamino)-4-(N -phenylamino)-1-butanol



To a stirred solution of 3-(S)-(N-methylamino) -4-(N -phenylamino)-1-butanol (486 mg, 2.5 mmol) in dry THF (25 ml) was added lithium aluminium hydride (66 mg, 1.74 mmol) portion-wise under argon at RT. After stirring for 1 h the solution was cooled to -100°C in an ether/dry-ice bath. The enone (61) (92 mg, 0.83 mmol) in THF (2 ml) was added dropwise and stirring was continued at -100°C for 4 h. The reaction mixture was quenched with methanol (0.3 ml) and water (0.3 ml), and upon warming to RT gave a granular precipitate. The precipitate was filtered off and extracted once with dichloromethane (5 ml). The combined filtrates were dried over $MgSO_4$, concentrated under reduced pressure at 5°C and chromatographed (eluant, 20% ether-petrol)

to give an 82:18 inseparable mixture of *cis* and *trans* allylic alcohols (93B) and (93A) (60 mg, 64%) as a colourless oil. Physical data as for Expt. No. 30.

32. Preparation of 1-(S)-Benzoyloxy-4-(R)-methyl-2-cyclohexene (62A)

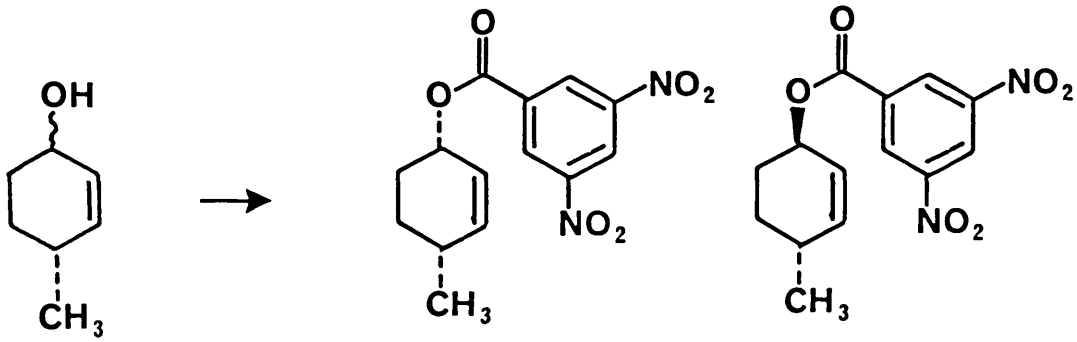


93A 62A

To a solution of the alcohol (93A) (44 mg, 0.39 mmol, > 99% pure by g.l.c.) in dry ether (7 ml) was added triphenylphosphine (206 mg, 0.79 mmol) in ether (3 ml) then diethyl azodicarboxylate (137 mg, 0.79 mmol) dropwise under argon at RT. After 5 min, benzoic acid (96 mg, 0.79 mmol) was added and the reaction mixture was stirred for 2.5 h. Sodium periodate (200 mg) in water (1 ml) was added to remove any remaining triphenylphosphine and the two phase mixture was stirred for 30 min. Ether (30 ml) was added and the organic layer separated, washed with brine (10 ml), dried over $MgSO_4$ and evaporated. The residue was extracted with ether (2 x 10 ml) and the insoluble triphenylphosphine oxide filtered off. The filtrate was concentrated and chromatographed (2% ether-petrol) to afford 1-(S)-benzoyloxy-4-(R)-methyl-2-cyclohexene (62A) (40 mg, 47%) as a colourless oil; $[\alpha]_D^{25}$-167.0° (*c* 1.45 in $CHCl_3$). A purity of > 99% diastereomeric determined by g.c. analysis using a superox column, oven setting 170°C with a retention time of 6.75 min. The retention time for the *trans* compound (62B) was

7.30 min under identical conditions. Physical data for (62) is given in Exp. no. 36.

33. Preparation of 1-(S)-(3',5'-Dinitrobenzoyloxy)-4-(R)-methyl-2-cyclohexene (94A) and 1-(R)-3', 5'-Dinitrobenzoyloxy)-4-(R)-methyl-2-cyclohexene (94B).



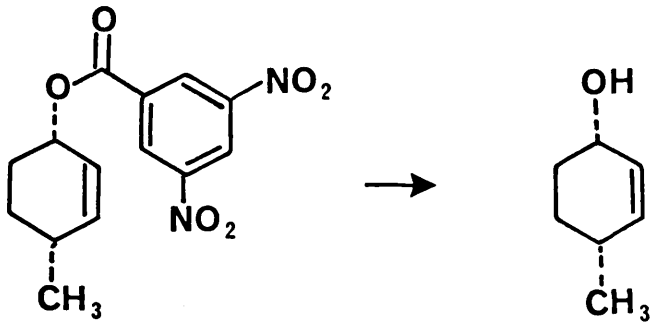
93 94A 94B

To a stirred solution of the alcohols (93A and B) (0.20 g, 1.79 mmol) and triphenylphosphine (0.936 g, 3.57 mmol) in dry benzene (15 ml) at 0°C under argon was added a solution of diethyl azodicarboxylate (0.622 g, 3.57 mmol) and 3,5-dinitrobenzoic acid (0.76 g, 3.57 mmol) in THF (3 ml). The solution was allowed to warm to RT and stirred for 4 h before diluting with ether (50 ml). After 20 min, the precipitate of triphenylphosphine oxide and diethylhydrazido- dicarboxylate was filtered off and the filtrate was evaporated under reduced pressure to give a black solid. Chromatography (gradient elution, 10 → 20% ether-petrol) afforded an inseparable mixture of dinitrobenzoate esters (94A) (317 mg, 59%) and (94B) (48 mg, 9%) as a yellow-white solid. 1-(S)-(3',5'-Dinitrobenzoyloxy)-4-(R)-methyl- 2-cyclohexene (94A) (245 mg) was obtained pure after three recrystallizations from dichloromethane-petrol as fine white needles, mp. 116°C; $[\alpha]_D^{25}$-124.6° (*c* 1.15 in $CHCl_3$); δ(90 MHz) 1.10 (3H, d, J 7.7 Hz, 4-Me), 1.2-2.5 (5H, m, 4-H, 5-H_2, 6-H_2), 5.52 (1H, m, 1-H), 5.82 (1H, dm, J 11.1 Hz, 3-H), 5.96

(1H, dm, J 11.1 Hz, 2-H), and 9.18 (3H, m, Ar); ν_{max} (nujol) 3098, 2954, 1718 (OCOR), 1541 (NO_2) 1342 (NO_2), 1196, and 959 cm^{-1}; *m/z* 306 (M^+), 277 (M^+-C_2H_4-H), 264 (M^+-CH_3CHCH_2), 195 OC-$C_6H_3(NO_2)_2^+$, and 94 (M^+-$O_2CC_6H_3(NO_2)_2$).

A 60:40 mixture of (94A) and (94B) (120 mg) was recovered from the mother liquors of the fractional recrystallization experiments. δ(90 MHz) as for (94A) except that the 4-Me of (94B) appears as a doublet J 7.7 Hz at δ 1.04.

34. Preparation of 4-(R)-Methyl(S)-cyclohex-2-en-1-ol (93B)

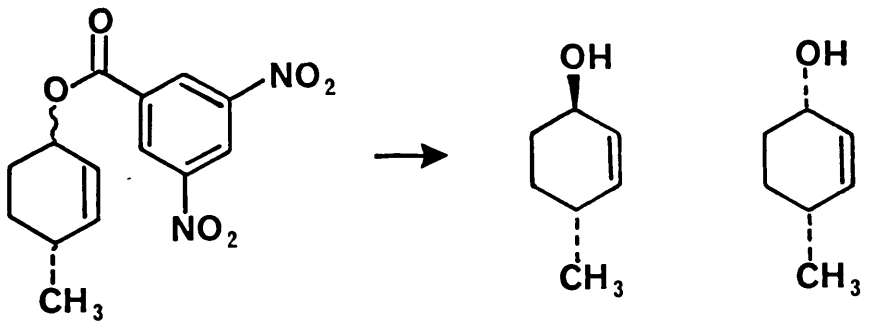


94 A 93 B

A solution of the dinitrobenzoate ester (94A) (6.37 g, 20.8 mmol) in THF (60 ml) was stirred with 3.4 M aqueous sodium hydroxide (30 ml) at RT for 10 h. The THF layer was decanted off and the aqueous layer filtered and extracted with ether (2 x 75 ml). The combined organic layers were washed with brine-saturated sodium bicarbonate solution (20 ml), dried over Na_2SO_4 and concentrated to afford *4-(R)-methyl-(S)-cyclohex-2-en-1-ol* (93B) (2.216 g, 95%) as a slightly yellowed oil; δ(250 MHz) 1.02 (3H, d, 7.2 Hz, Me), 1.25-1.80 (4H, m, 5-H_2, 6-H_2), 2.12 (1H, m, 4-H), 4.13 (1H, m, 1-H), 5.70 (1H, dd, J 1.5

and 8.71 Hz, 3-H), and 5.76 (1H, dd, J 1.5 and 8.7 Hz, 2-H); $\nu_{max.}$ 3340 (OH), 2929, 1646, 1453, 1058, 991, and 733 cm^{-1}; *m/z* 112 (M^+), 95(M^+-OH), 70 (M^+-CH_3CHCH_2), and 43 $(CH_3C{\equiv}O)^+$; (Found: C, 75.08; H, 10.94. $C_7H_{12}O$ requires C, 74.96; H, 10.78%). A purity of 99.5+% was determined by gas chromatographic analysis using superox column, oven setting 130°C with a retention time of 1.91 min. Retention time of the R,R epimer is 2.05 min under identical conditions; $[\alpha]_D^{25}$ + 194.1° (*c* 1.16 in $CHCl_3$).

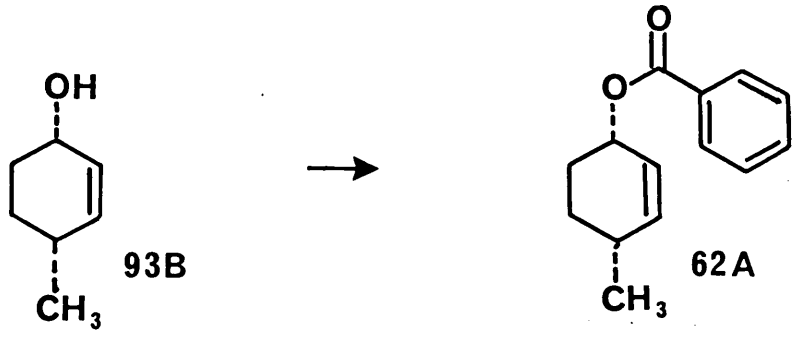
35. Preparation of 4-(R)-Methyl(S)-cyclohex-2-en-1-ol (93A) and 4-(R)-Methyl-(R)-cyclohex-2-en-1-ol (93B)



94 93A 93B

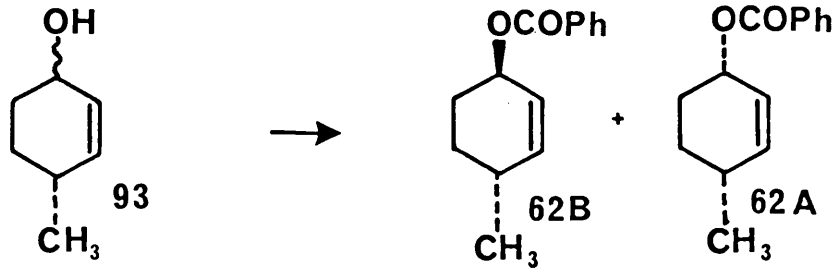
A 3:2 mixture of (94A) and (94B) (13.20 g, 43 mmol) was converted to an inseparable 2:3 mixture of the epimeric alcohols (93 A) and (93B) (4.00 g, 82%) by the procedure described in Expt. No. 34. Physical data was identical except the NMR spectrum; δ(90 MHz) 0.96 (1.2 H, d, J 6.9 Hz, 4-Me (93A)), 1.02 (1.8H, d, J 7.5 Hz, 4-Me (93B), 1.1-2.25 (5H, m, 4-H, 5-H_2, 6-H_2), 4.21 (^{1}H, m, 1-H), 5.63 (0.8H, m, 2 and 3-H_2 (93A)), and 5.73 (1.2H, m, 2 and 3-H_2 (93B)). No rotation was taken.

36. Preparation of 1-(S)-Benzoyloxy-4-(R)-methyl-2-cyclohexene (62A)



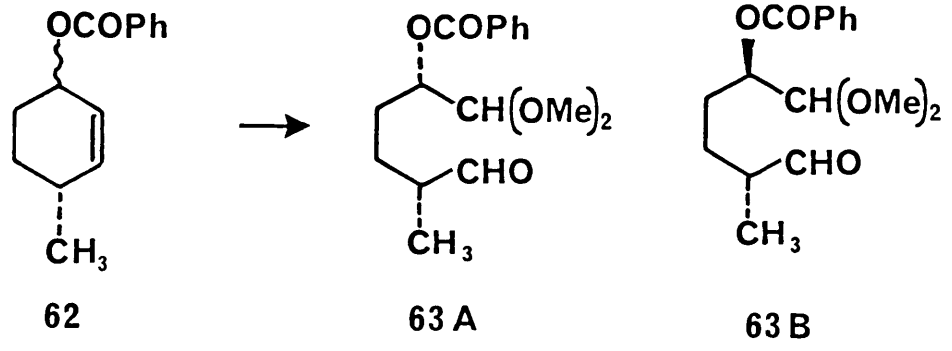
To a stirred solution of the allylic alcohol (93B) (2.216 g, 19.8 mmol) in dry ether (25 ml) and pyridine (5 ml) at 0°C under argon was added dropwise benzoyl chloride (3.34 g, 23.7 mmol). A heavy white precipitate formed immediately and the reaction mixture was warmed to RT. After 1 h, more benzoyl chloride (0.83 g, 5.9 mmol) was added and the solution was stirred at RT for 10 h. The solution was filtered to remove pyridinium hydrogen chloride, diluted with ether (200 ml) and washed with saturated copper (II) sulphate solution (100 ml). The aqueous layer was extracted with ether (100 ml) and the organic layers were combined, dried over Na_2SO_4 and concentrated to give an orange oil (5.6 g). Chromatography (eluant 5% ether-petrol) gave 1-(S)-*benzoyloxy*-4-(R)-*methyl*-2-*cyclohexene* (62A) (4.60 g, 100%) as a clear oil; $[\alpha]_D^{25}$-158.3° (*c*, 1.8 in $CHCl_3$); δ(90 MHz) 0.92 (3H, d, J 7.3 Hz, Me), 1.08-2.2 (5H, m, 4-H, 5-H_2, 6-H_2), 5.32 (1H, m, 1-H), 5.73 (2H, m, 2-H, 3-H), and 7.37 and 7.9 (5H, m, Ph); $\nu_{max.}$ (neat) 2954, 2869, 1713, (OCOPh), 1600 (C=O), 1272, 1111, 965, and 877 cm^{-1}; *m/z* 216 (M^+), 105 ($PhCO^+$); (Found: C, 77.69; H, 7.43. $C_{14}H_{16}O_2$ requires C, 77.75; H, 7.46%).

37. Preparation of 1-(S)-Benzoyloxy-4-(R)-methyl-2-cyclohexene (62A) and 1-(R)-Benzoyloxy-4-(R)-methyl-2-cyclohexene (62B).



A 3:2 mixture of (93B) and (93A) (241 mg) was converted into an inseparable 3:2 mixture of the epimeric allylic benzoates (62A) and (62B) (394 mg, 89%) by the procedure described in Expt. No. 36. The physical data was identical except for the NMR spectrum; δ(90 MHz) 0.90 (1.2 H, d, J 7.3 Hz, 4-Me (62B)), 0.92 (1.8H, d, J 7.3 Hz, 4-Me (62A)), 1.10-2.35 (5H, m, 4-H, 5-H_2, 6-H_2), 5.32 (1H, m, 1-H), 5.67 (0.8H, s, 2-H, 3-H (62B)), 5.73 (1.2 H, s, 2-H, 3-H (62A)), 7.37 (3H, m, Ph), and 7.9 (2H, m, Ph). No rotation was taken.

38. Preparation of 5-(S)-Benzoyloxy-6,6-dimethoxy-2-(R)-methylhexanal (63A) and 5-(R)-Benzoyloxy-6,6-dimethoxy-2-(R)-methylhexanal (63B)



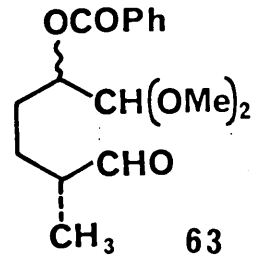
A mixture of the benzoates (62A) and (62B) (56 mg, 0.26 mmol) in dry methanol (15 ml) was ozonized at -78°C for 20 min.

Camphorsulphonic acid (10 mg) was added and the reaction mixture was warmed to RT and stirred for 2 h. Sodium bicarbonate (1g) and dimethyl sulphide (0.3 ml) were added and the suspension was stirred for 4 h, filtered and evaporated under reduced pressure. Chromatography on silica gel (gradient elution, petrol → 5% → 10% ether-petrol) afforded an inseparable mixture of *aldehyde-acetals* (63A) and (63B) (27 mg, 36%) as a colourless oil; R_F 0.83 (ether); δ(250 MHz) 1.10 (3H, d, J 7.6 Hz, 2-Me), 1.30-2.0 (4H, m, 3-H_2, 4-H_2), 2.39 (1H, m, 2-H), 3.41 and 3.60 (6H, 2xs, 2OMe), 4.44 (1H, d, J 5.2 Hz, 6-H), 5.21 (1H, m, 5-H), 7.5 (3H, m, Ph), 8.06 (2H, m, Ph), and 9.60 (1H, d, J 0.75 Hz, 1-H); $\nu_{max.}$ (neat) 2934, 1717 (OCOPh), 1600, 1449, 1315, 1271, 1197, 972 and 712 cm^{-1}; *m/z* 293 (M^+-H), 277, 263 (M^+-OMe), and 75 [$CH(OMe)_2^+$]; (Found: C, 65.02; H, 7.67. $C_{16}H_{22}O_5$ requires C, 65.29; H, 7.53%).

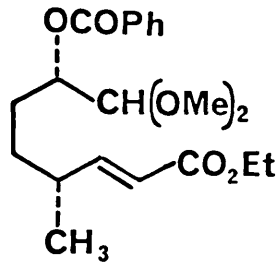
The more polar dialdehyde (63C) (22 mg, 34%) was also isolated as a colourless oil; δ(90 MHz) 1.15 (3H, d, J 7 Hz), 1.36-2.20 (4H, m, 3-H_2, 4-H_2), 2.40 (1H, m, 2-H), 5.22 (1H, m, 5-H), 7.56 (3H, m, Ph), 8.10 (2H, m, Ph) and 9.65 (2H, br s, 1-H, 6-H); R_F 0.66 (ether).

An equally successful variant upon the reaction involved adding K-10 clay and trimethylorthoformate instead of p-toluenesulphonic acid to promote acetalization. Thus following ozonolysis at -78°C the reaction mixture was warmed to RT and stirred for 20 min with trimethylortho-formate absorbed upon K-10 montmarillonite clay (1g per mmol of substrate). The clay was filtered off and the filtrate washed once with sodium bicarbonate solution before treatment with solid sodium bicarbonate and triphenylphosphine as before. The highest yield of the desired acetal-aldehyde (63) by this method was 27%, and the chief side-product was the *bis*-acetal.

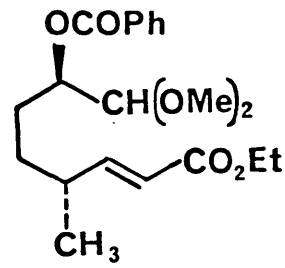
39. Preparation of Ethyl-7-(S)-benzoyloxy-8,8-dimethoxy-4-(R)-methyl-2E-octenoate (96A) and ethyl-7-(R)-benzoyloxy-8,8-dimethoxy-4-(R)-methyl-2E-octenoate (96B).



63



96A

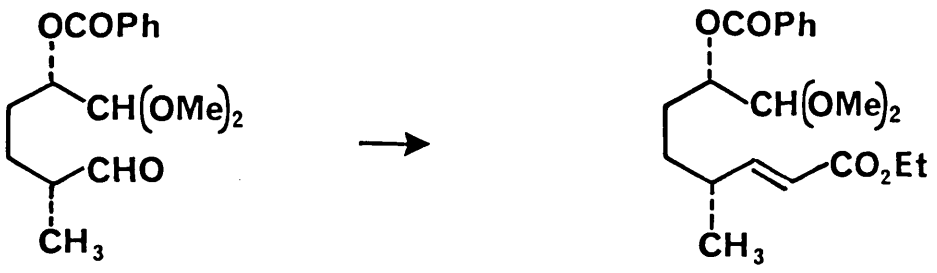


96B

To a stirred solution of carboethoxymethylenetriphenylphosphorane (2.09 g, 6.0 mmol) in dry dichloromethane (25 ml) was added a 2:1 mixture of the aldehydes (63A and 63B) (1.47 g, 5.0 mmol) in dichloromethane (5 ml) at RT under argon. After 3 h, the reaction mixture was preabsorbed on silica gel (12 g) and chromatographed (gradient elution, 20 → 30% ether-petrol) to yield two fractions; the less polar *Z* unsaturated esters (1.4 mg, 14%) and the more polar inseparable mixture (3:2) of *E unsaturated esters* (96A and 96B) (1.754 g, 96.4%) as a colourless oil; δ(250 MHz) 1.05 (0.65 x 3H, d, J 6.9 Hz, 4-CH_3 (96 A)), 1.06 (0.35 x 3H, d, J 6.9 Hz, 4-CH_3 (96B)), 1.28 (3H, t, J 7.5 Hz, O-CH_2CH_3), 1.47 (2H, q, J 7.5 Hz, 5-H_2), 1.76 (2H, m, 6-H_2), 2.32 (1H, d septet, J 1 and 7.1 Hz, 4-H), 3.40 and 3.44 (6H, 2s, 2xOMe), 4.19 (2H,

q, J 7.5 Hz, OCH_2Me), 4.42 (1H, d, J 5 Hz, 8-H), 5.21 (1H, dt, J 5.4 and 7.2 Hz, 7-H), 5.77 (0.35 x 1H, dd, J 15.6 and 1 Hz, 2-H (96B)), 5.79 (0.65 x 1H, dd, J 15.6 and 1 Hz, 2-H (96A)), 6.81 (0.65 x 1H, dd, J 8 and 15.6 Hz, 3-H (96A)), 6.84 (0.35 x 1H, dd, J 8 and 15.6 Hz (96B)), and 7.4-7.6 and 8.1 (5H, m, Ph); $\nu_{max.}$(neat) 2961, 1716 (2 x OCOR), 1647, 1601, 1272, 1178, 1112, 1071, and 983 cm^{-1}; *m/z* 364 (M^+), 363, 333 (M^+-OMe), 105 ($OCPh^+$) and 75; (Found: C, 65.99; H, 7.78. $C_{20}H_{28}O_6$ requires C, 65.91; H, 7.74%).

40. Preparation of Ethyl-7-(S)-benzoyloxy-8,8-dimethoxy-4-(R)-methyl-2E-octenoate (96A).

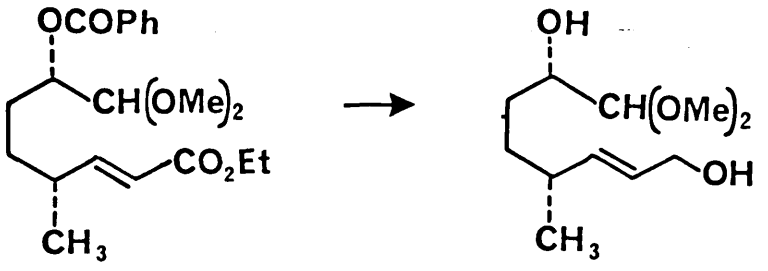


63A 96A

To a crude sample of the aldehyde (63A) (56 mg) containing no 2R-5R epimer in dry dichloromethane (5 ml) was added carboethoxymethylenetriphenylphosphorane (102 mg, 0.29 mmol). The solution was stirred for 3 h, preabsorbed on silica gel (0.25 g) and chromatographed (eluant, 20% ether-petrol) to obtain the crude product (96A) (25 mg) contaminated with a forerunner and a tailing impurity. H.p.l.c. of the crude material on a Dynamex macro Si h.p.l.c. column (internal diameter 21.4 mm) (eluant, 5% isopropanol-hexane) gave pure ethyl-7-(S)-benzoyloxy-8,8-dimethoxy-4-(R)-methyl-2E-octenoate (96A) (30 mg) as a colourless oil; $[\alpha]_D^{25}$-13.2° (*c* 1.3 in $CHCl_3$); δ(90 MHz) 1.05 (3H, d, J 6.9 Hz, 4-Me), 1.28 (3H, t, J 7.5 Hz, OCH_2CH_3), 1.47-1.90

(4H, m, 5-H_2), 2.32 (1H, d septet, J 1 and 7.1 Hz, 4-H), 3.40 and 3.44 (6H, 2s, 2 x OMe), 4.19 (2H, q, J 7.5 Hz, OCH_2Me), 4.42 (1H, d, J 5 Hz, 8-H), 5.21 (1H, dt, J 5.4 and 7.2 Hz, 7-H), 5.79 (1H, dd, J 1 and 15.6 Hz, 2-H), 6.81 (1H, dd, J 8 and 15.6 Hz, 3-H), 7.4-7.6 (3H, m, Ph), and 8.1 (2H, m, Ph); $\nu_{max.}$(neat) 2961, 1716 (2 x OCOR), 1647, 1601, 1272, 1178, 1112, 1071, and 983 cm^{-1}.

41. Preparation of 8,8-Dimethoxy-7-(S)-hydroxy-4-(R)-methyl-oct-2E-en-1-ol (64A)



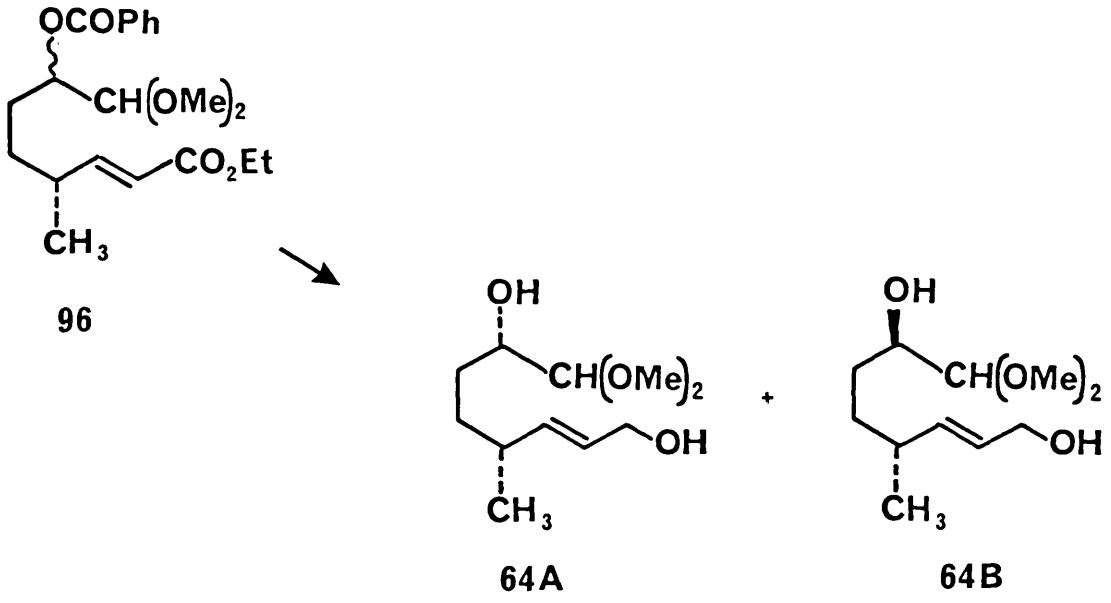
96A 64A

To a stirred solution of the diester (96A) (30 mg, 0.82 mmol) in dry ether (3 ml) cooled to -78°C was added DIBAL-H (275 μl of a 1.5 M solution in toluene, 0.41 mmol).

After stirring at -78°C for 10 min then at 0°C for 40 min, the reaction was quenched with methanol (100 μl). Water (150 μl) was added and after stirring for 20 min at RT, the mixture gelled. The gel was adsorbed on sodium bicarbonate (10 g) and Na_2SO_4 (6 g) and the sticky solid extracted six times with ethyl acetate (6 x 10 ml) and twice with 20% ethanol-chloroform (2 x 15 ml) through a small pad of silica. The extracts were evaporated and flash chromatographed (eluant, 2% ethanol-chloroform then 5% ethanol chloroform) to afford the *diol* (64A) (17.5 mg, 98%) as a clear oil; δ(250 MHz) 1.00 (3H, d, J 6.5 Hz, 9-H_3), 1.3-1.6 (4H, m, 5-H_2, 6-H_2) 2.05 (1H, br s, OH), 2.25 (1H, septet, J ~ 6

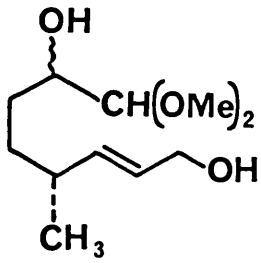
Hz, 3-H), 2.35 (1H, br s, OH), 3.42 (6H, 2s, 2xOMe), 3.56 (1H, m, 7-H), 4.08 (2H, d, J 4.5 Hz, 1-H_2), 4.12 (1H, d, J 6 Hz, 8-H), 5.53 (1H, dd, J 6 and 15 Hz, 3-H), and 5.64 (1H, ddd, J 2, 4 and 15 Hz, 2-H); $\nu_{max.}$ (neat) 3390 (br OH), 2926, 1451, 1193, 1074, and 972 cm^{-1}; *m/z* 186 (M^+-MeOH), 169 (M^+-Me-H_2O), 143 (M^+-$CH_3OCHOCH_3$) and, 75 ($CH(OMe)_2^+$; (Found: C, 60.53; H, 10.06. $C_{11}H_{22}O_4$ requires C, 60.52; H, 10.16). $[\alpha]_D^{25}$-39.6° (c 0.7 in $CHCl_3$).

42. Preparation of 8,8-dimethoxy-7 (S and R)-hydroxy-4-(R)-methyl-oct-2E-en-1-ol (64A) and (64B)

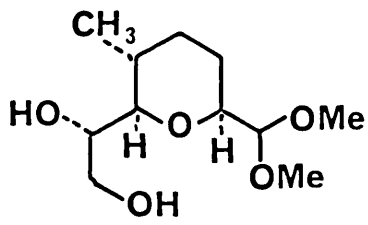


A 3:2 mixture of the diesters (96A) and (96B) (1.73 g) was converted to an inseparable 3:2 mixture of the diols (64A) and (64B) (0.94 g, 01%) on a 4.76 mmol scale by the procedure described in Expt. No. 41. IR, NMR and mass spectral data of the mixture were identical with that of the pure 3-R-7-S-epimer (64A) Expt. No. 41.

42. Preparation of 2-(R)-(1' -(S),2' -Dihydroxyethyl)-3-(R)-methyl-6-(S)-dimethoxymethyltetrahydropyran (65A) and 2-(R)-(1' -(S),2'-Dihydroxy-ethyl)-3-(R)-methyl-6-(R)-dimethoxymethyltetrahydropyran (65B)

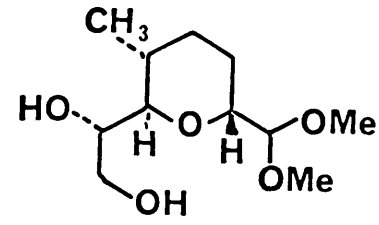


64



65A

+

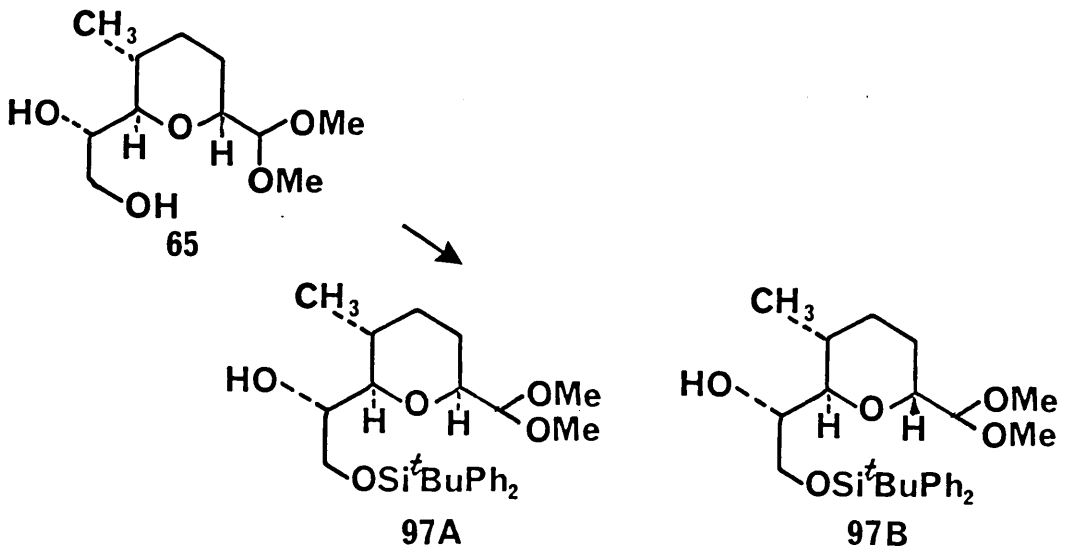


65B

To a stirred solution of titanium (IV) isopropoxide (1.95 g, 2.05 ml, 6.83 mmol) in dry dichloromethane (10 ml) at RT under argon was added a solution of diethyl L-tartrate (1.68 g, 8.20 mmol) in dichloromethane (3 ml). After 5 min the solution was cooled to -78°C and was treated with the mixture of allylic alcohols (64A and 64B) (718 mg, 3.29 mmol) in dichloromethane (3 ml) followed by t-butyl-hydroperoxide (5.46 ml and a 3.0 M solution in toluene, 16.4 mmol). The solution was allowed to reach -20°C over a 2 h period. After 12 h at -20°C dimethylsulphide (1.21 ml, 16.4 mmol) was added and the solution was heated under reflux for 2 h. The solution was cooled to RT, treated with saturated sodium fluoride solution (3 ml) and aceto- nitrile (3 ml) and stirred vigorously for 2 h. The resultant slurry was filtered through a celite pad and the filter-cake eluted with 20% ethanol-chloroform (6 x 30 ml). The combined filtrates were dried

(Na_2SO_4) and concentrated. Chromatography (gradient elution, dichloromethane → 5% ethanol-dichloromethane) gave an inseparable mixture (3:2) of the *diol epimers* (65A and 65B) (651 mg, 84%) as a colourless oil; δ(90 MHz) 0.87 (0.63 x 3H, d, J 7 Hz, Me (65A)), 0.99 (0.37 x 3H, d, 7 Hz, Me (65B)), 1.00-2.00 (5H, m, 3-H, 4-H_2, 5-H_2), 2.7 (2H, br s, 2 x OH), 3.2-3.5 (2H, m, 2-H and 6-H), 3.4 (6H, s, 2xOMe), 3.6-3.9 (3H, m, 1'-H, 2'-H_2), 4.18 (0.63 x 1H, d, J 6.4 Hz, 1"-H (65A)), and 4.50 (0.37 x 1H, d, J 10.3 Hz, 1"-H (65B); $\nu_{max.}$(neat) 3390 (OH), 2925, 1456, 1196, and 1180 cm^{-1}; *m/z* 203 (M^+-OMe), 173 (M^+-OMe-CH_2O), 171, 159, and 75 $(CH_3OCHOCH_3)^+$; (Found: C, 56,24; H, 9.79. $C_{11}H_{22}O_5$ requires C, 56.39; H, 9.47).

43. Preparation of 2-(R)-(2'-t-Butyldiphenylsilyloxy-1'-(S)-hydroxyethyl)-3-(R)-methyl-6-(S)-(dimethoxymethyl)tetrahydropyran (97A) and 2-(R)-(2'-t-Butyldiphenylsilyloxy-1'-(S)-hydroxyethyl)-3-(R)-methyl-6-(R)-(dimethoxymethyl)-tetrahydropyran (97B)



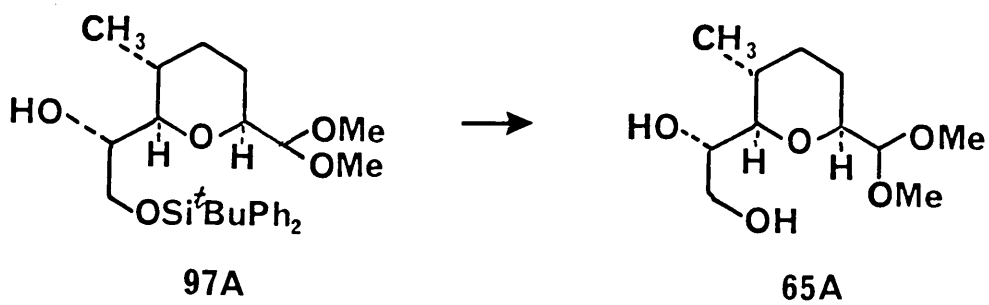
To a stirred solution of imidazole (25 mg, O.356 mmol) and the diol epimers (65A and 65B) (38 mg, 0.162 mmol) in dry DMF (0.6 ml) under argon at RT was added t-butylchlorodiphenylsilane (50 mg, 0.178 mmol) in DMF (0.5 ml). After stirring for 13 h at RT, the solution

was diluted with water (30 ml) and extracted with dichloromethane (3 x 15 ml). The combined extracts were washed with brine (10 ml), dried over Na_2SO_4 and evaporated. Chromatography (gradient elution, 20 → 50% ether-petrol) afforded the 6-(R)-epimer (97B) (10 mg, 25%) and the desired *6-(S)-epimer* (97A) (32 mg, 42%) both as colourless oils.

Less polar 6-(R)-isomer (97B) (R_F 0.38 in 50% ether-petrol); δ(90 MHz) 1.02 (3H, d, J 7.7 Hz, CH_3), 1.08 (9H, s, t-Bu), 1.2-2.1 (5H, m, 3-H, 4-H_2, 5-H_2), 3.65 (1H, br s, OH), 3.22 (3H, s, OMe), 3.34 (3H, s, OMe), 3.25-3.6 (2H, m, 2-H, 6-H), 3.7-4.2 (3H, m, 1' -H, 2' -H_2), 4.25 (1H, d, J 7.8 Hz, 1"-H), 7.35-7.50 and 7.65-7.80 (10H, m, 2 x Ph); $\nu_{max.}$ (neat) 3482 (br OH), 2930, 1588, 1427, 1192, 1112, 823, and 703 cm^{-1}.

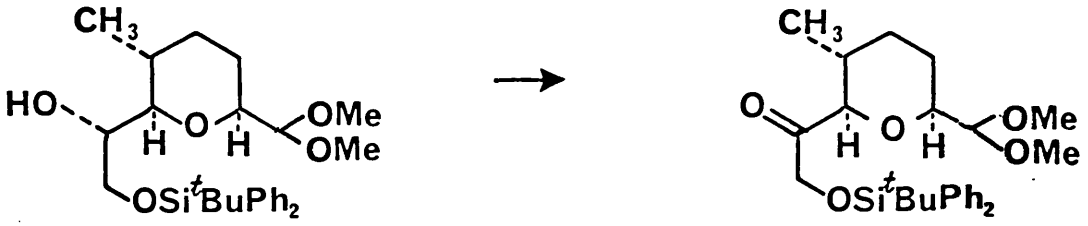
More polar 6-(S)-isomer (97A) R_F 0.18 in 50% ether-petrol); δ(250 MHz) 0.80 (3H, d, J 6.8 Hz, Me), 1.06 (9H, s, t-Bu), 1.1-1.8 (5H, m, 3-H, 4-H_2, 5-H_2), 3.15 (1H, m, 6-H), 3.31 and 3.33 (6H, 2 x s, 2 x OMe), 3.42 (1H, m, 2-H), 3.80 (2H, dd, J 13.5 and 3.9 Hz, 2' -H_2), 3.87 (1H, m, 1' -H), 4.11 (1H, d, J 5.2 Hz, 1"-H), 7.4 and 7.7 (10H, m, 2 x Ph); $\nu_{max.}$ (neat) 3446 (OH), 3069, 3028, 1427, 1192, and 824 cm^{-1}; *m/z* 383 (M^+-^{t}Bu-MeOH), 241, 235, 147, 105, and 76; $[\alpha]_D^{25}$-16.4° (c 2.6 in $CHCl_3$).

44. Preparation of 2-(R)-(1'-(S),2'-Dihydroxyethyl)-3-(R)-methyl-6-(S)-(dimethoxymethyl)-tetrahydropyran (65A)



To a solution of the silylether (97A) (26 mg, 0.055 mmol) in THF (3 ml) was added tetrabutylammonium fluoride (61 μl of a 1.0 M solution in THF, 0.061 mmol). After stirring for 15 minutes the mixture was evaporated and chromatographed (dichloromethane then 5% ethanol-dichloromethane) to yield the *diol* (65A) (13 mg, 100%); δ(90 MHz) 0.87 (3H, d, J 7 Hz, Me), 1.00-2.00 (5H, m, 3-H, 4-H_2, 5-H_2), 2.7 (2H, br s, 2xOH), 3.20-3.50 (2H, m, 2-H, 6-H), 3.4 (6H, s, 2 x OMe), 3.6-3.9 (3H, m, 1'-H, 2'-H_2), and 4.18 (1H, d, J 6.4 Hz, 1"-H); $\nu_{max.}$ (neat) 3390 (OH), 2925, 1456, 1196, and 1080 cm^{-1}; *m/z* 203 (M^+-OMe), 173 (M^+-OMe-CH_2O), 171, 159, and 75 $(CH_3O{=}CHOMe)^+$; $[\alpha]_D$-23.2° (c 2.58 in $CHCl_3$); (Found: C, 56,24; H, 9.79. $C_{11}H_{22}O_5$ requires C, 56.39; H, 9.47).

45 Preparation of 2(R)-(2'-t-Butyldiphenylsilyloxy-1'-acetyl)-3-(R)-methyl-6-(S)-(dimethoxymethyl)-tetrahydropyran (20)



To a stirred solution of oxalyl choride (39 mg, 0.28 mmol) in dry dichloromethane (4 ml) was added dropwise a solution of DMSO (44 mg, 0.56 mmol) in dichloromethane (0.5 ml) under argon at -78°C. After 5 min, the alcohol (97A) (44 mg, 0.093 mmol) in dichloromethane (1.0 ml) was added and the cloudy solution stirred for 20 min at -78°C before treatment with triethylamine (155 μl, 1.12 mmol). The solution was allowed to warm to RT over 1 h and then preabsorbed on silica gel (0.5 g) and chromatographed (gradient elution, 15 → 30% ether- petrol) to afford recovered starting material (97A) (22 mg) and the desired ketone

(20) (20 mg, 91%) as a colourless oil, $[\alpha]_D^{25}$ + 20.8° (c 0.75 in $CHCl_3$); δ(250 MHz), 0.73 (3H, d, J 6.3 Hz, 3-Me), 1.1 (9H, s, t-Bu), 1.13-1.40 (3H, m, 5-H_2, 4-H), 1.65 and 1.82 (2H, m, 4-H, 3-H), 3.27 (1H, m, 6-H), 3.28 and 3.30 (6H, 2s, 2 x OMe), 3.47 (1H, d, J 9 Hz, 2-H), 4.07 (1H, d, J 6 Hz, 1"-H), 4.51 (1H, d, J 19.8 hz, 2' -H), 4.63 (1H, d, J 19.8 Hz, 2' -H), 7.38 (6H, m, Ph), and 7.67 (4H, m, Ph); $\nu_{max.}$ (neat) 3069, 2954, 1736 (C=O), 1427, 1191, 1112, 921, 824 and 704 cm^{-1}; *m/z*: 413 $(M-^tBu)^+$, 381 $(M-^tBu-MeOH)^+$ 199 $(OCCH_2SiPh_2{}^tBu)^+$, 141, and 75. (20) obtained by degradation of M139603 has identical IR, 400 MHz NMR and mass spectra; $[\alpha]_D^{22}$ +20.5° (c 3.1 in $CHCl_3$).

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