A Stereoselective Synthesis of the C_{16}-C_{32} Fragment of Ionomycin

by

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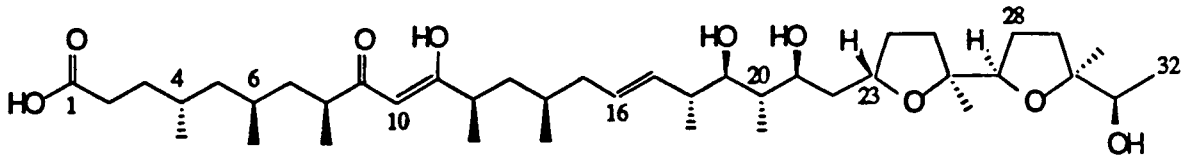
ABSTRACT

This dissertation concerns the stereoselective synthesis of optically pure compound 196, the C_{16}-C_{32} fragment of the polyether antibiotic ionomycin (1).

Fragment 196 was synthesized by preparing and joining the two subunits 172 (C_{16}-C_{22}) and 122 (C_{23}-C_{32}). Compound 172 was synthesized by repetitive asymmetric aldol condensations of optically pure crotonyl imide 69 with aldehydes 129 and 139. The use of 69 allowed for the enantioselective construction of the two propionate units of fragment 172 having the "anti" configuration.

Compound 122 was synthesized using the highly stereospecific oxidative permanganate cyclization of the 1,5-diene 93 to give racemic tetrahydrofuran 94, having the correct relative stereochemistry at the four asymmetric centres. The diene 93 was in turn prepared via the ß-keto ester dianion methodology which allows for the stereospecific introduction of the isoprenoid unit. Diol 103, derived from 94 was resolved as its mono (+)-O-acetylmandelate and was transformed into optically active fragment 122.

Finally, to complete the synthesis of optically active fragment C_{16}-C_{32} of ionomycin, compounds 172 and 122 were coupled via a Wittig reaction to afford the cis olefin 194, and the second tetrahydrofuran ring of 196 was introduced stereoselectively via an internal oxymercuration reaction.



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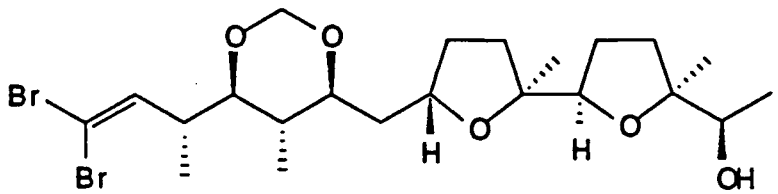

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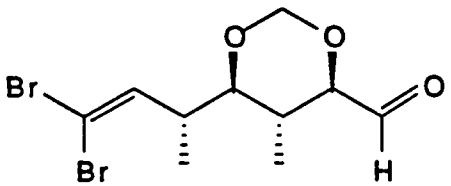

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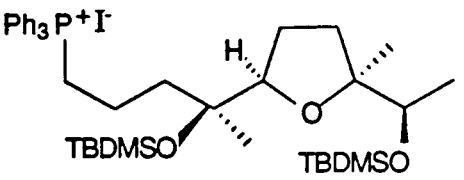

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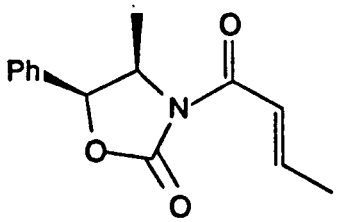

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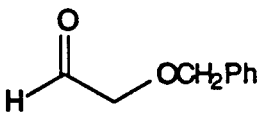

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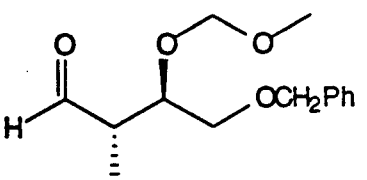

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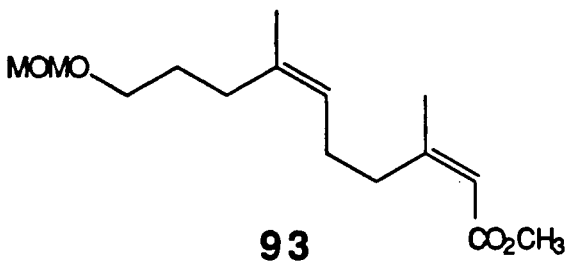
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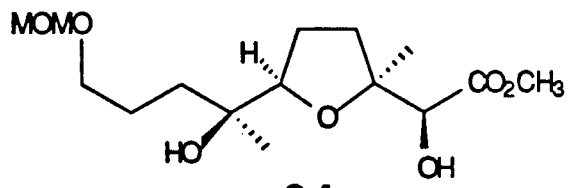
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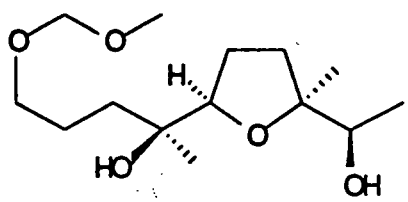
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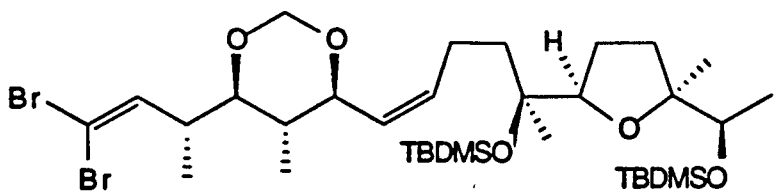
O
O
H
Br
Br
TBDMSO
O
TBDMSO

194

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LIST OF ABBREVIATIONS AND ACRONYMS

Ac	acetyl
acac	acetylacetone
b	broad
Bn	benzyl
bp	boiling point
Bu	butyl
C	charcoal
c	concentration in g of solute per 100 mL of solution
d	doublet (^{1}H NMR data)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DET	diethyl tartrate
DIBAL	diisobutylalumium hydride
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
Et	ethyl
eV	electron volts
ether	diethyl ether
GLC	gas liquid chromatography
h	hour (s)
HMPA	N-hexamethylphosphoramide
Hz	Hertz
IR	infrared

LDA	lithium diisopropylamide
m	medium (IR data) or multiplet (^{1}H NMR data)
m-	meta
Man	O-acetylmandelyl
m-CPBA	m-chloroperbenzoic acid
Me	methyl
MEM	2-methoxyethoxymethyl
MOM	methoxymethyl
MoOPH	oxodiperoxymolybdenum-(pyridine)hexamethylphosphoramide
(Ms)	methanesulfonyl
mesyl	methanesulfonyl
mesylate	methanesulfonate
mass spec	mass spectrum
min	minute (s)
m.p.	melting point
MS	mass spectrometry
NBS	N-bromosuccinimide
NMMO	4-methyl morpholine N-oxide
NMR	nuclear magnetic resonance
NOEDS	nuclear Overhauser effect difference spectroscopy
p-	para
pet. ether	petroleum ether (boiling range 30-60 °C)
Ph	phenyl
PPTS	pyridinium p-toluenesulfonate
py	pyridine
q	quartet (^{1}H NMR data)
qi	quintet (^{1}H NMR data)

s	strong (IR data) or singlet (^{1}H NMR data)
t	triplet (^{1}H NMR data)
TBDMS	tert-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilane (^{1}H NMR reference) or trimethylsilyl
(Ts)	p-toluenesulfonyl
tosyl	p-toluenesulfonyl
tosylate	p-toluenesulfonate
(Tf)	trifluoromethanesulfonate
triflate	trifluoromethanesulfonate
w	weak (IR data)

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to Professor Larry Weiler for his guidance throughout this project and for invaluable advice in the preparation of this thesis. I would also like to thank the "animals" in zoo 320 who made both my stay and my work here so much more enjoyable. Thanks to my three roomates Trisha, Hilo and Donna for their friendship and understanding.

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I dedicate this thesis to my family.

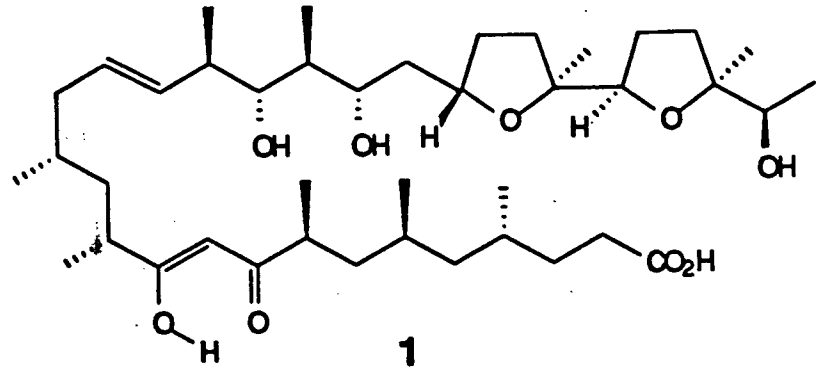
INTRODUCTION

I. Ionomycin

Ionomycin (1), our synthetic target, is an antibiotic of the polyether ionophore family. The first three members of this family were isolated in 1951 from Streptomyces.[1] Ionophores are molecules that have the ability to transport metal cations (iono) across cell membranes (phore from the Greek *pherein* to bear). Monensin (2), lasalocid A (3) and antibiotic A 23187 (4) are typical examples (Figure 1) of polyether ionophores which number over 70 members to date. All display very interesting biological activities including antimicrobial properties, growth promotion in ruminants, and cardiovascular effects.

Ionomycin (1) was isolated in 1975 by extraction of fermentation broths of the fungus Streptomyces conglobatus sp. novo TREJO.[2] Its molecular structure was determined in 1979 by Toeplitz et al. using NMR spectroscopy, mass spectrometry, and X-ray crystallographic analysis of three crystalline forms of its cadmium and calcium salts.[3] The X-ray structure of the calcium salt of ionomycin is shown in Figure 2.

Ionomycin has a high affinity for divalent metal cations ($Ca^{+2} > Cd^{+2} > Mg^{+2} \gg Sr^{+2} \approx Ba^{+2}$), but differs from other members of this family in that it chelates divalent ions as a dibasic acid. Two acidic sites, namely the carboxylic acid and the ß-diketone moieties, confer this dibasic character to the ionophore (Figure 1). As can be seen from the X-ray structure, the molecule wraps around the calcium ion with the oxygen atoms directed towards the inside of the sphere. The alkyl groups, on the other hand, protrude from the shell, providing the ion complex with its hydrophobic properties. The metal ion is transported across cell lipid membranes against concentration gradients in this hydrophobic cage, thus disrupting the natural balance of calcium ions in the cell. Since calcium ions are intricately related to many biochemical processes taking place in the cell, ionomycin and other polyether ionophores have been used extensively to investigate the role of calcium in such processes and the effect of ionophores on them.



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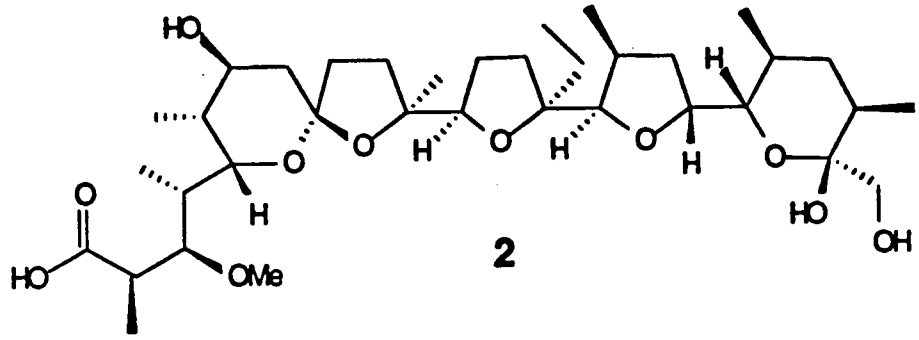

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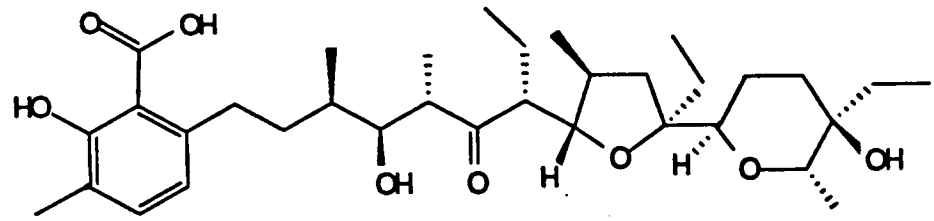

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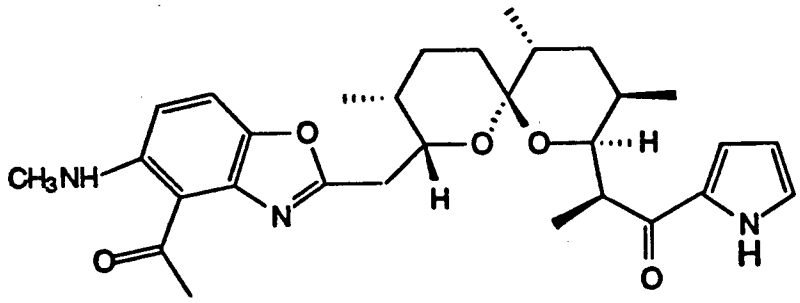

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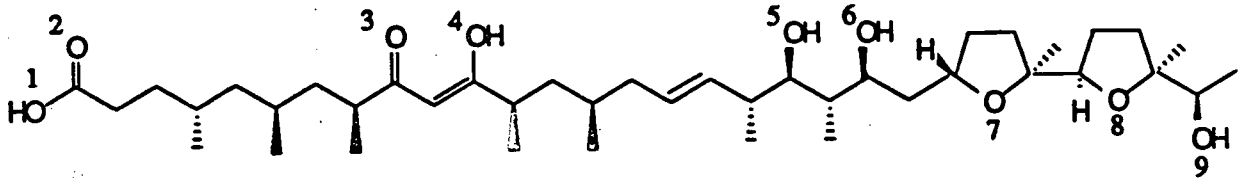
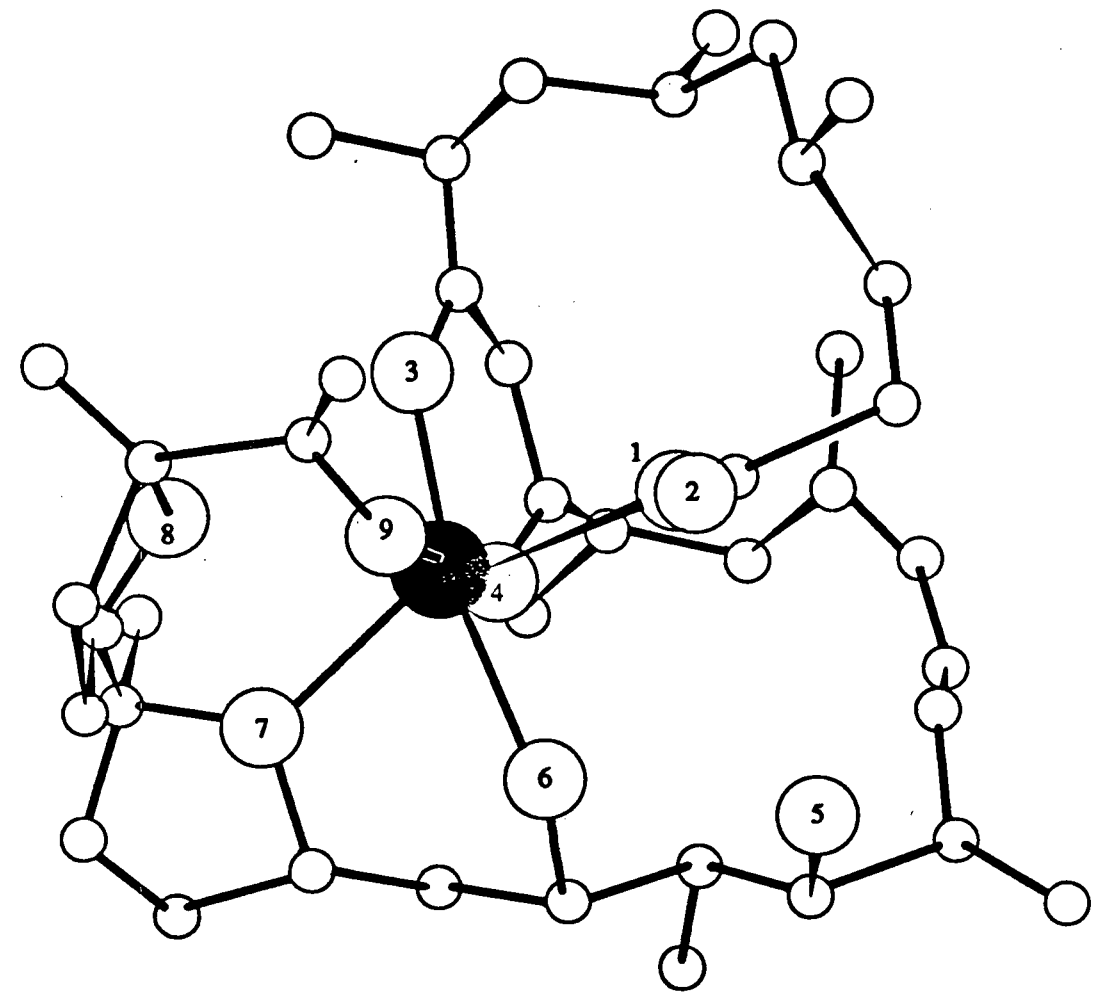
Figure 1. Some typical polyether ionophore antibiotics: ionomycin (1), monensin (2), lasalocid A (3) and antibiotic A 23187 (4).





○ = CARBON ○ = OXYGEN ● = CALCIUM

Figure 2. The X-ray structure of the calcium salt of ionomycin.[3]

In a series of conformational analyses, Brasseur et al. were able to propose a mechanism by which ionomycin could cross lipid membranes and how the lipid-water interface could induce the necessary conformational changes to allow complexation or decomplexation of the calcium ion.[4]

Ionomycin was found to be a potent antimicrobial agent. Like other polyether antibiotics, it is active against Gram-positive bacteria with no demonstrable effect against Gram-negative bacteria.[2] It has been found to stimulate mast cell histamine secretion[5] as well as catecholamines secretion from adrenal gland and spleen[6] by forming a lipid-soluble calcium complex. Ionomycin has also been linked to the activation of human blood platelets.[7] However its rather high toxicity precludes use in human therapy at this time.

The biosynthesis of ionomycin is polyketide in origin and mainly follows the unified model for the biogenesis of polyether antibiotics that Cane et al. recently proposed.[8] A few years ago we embarked on a program to synthesize ionomycin. Its 32-carbon framework and 14 asymmetric centres offer a challenging exercise to the organic chemist. Also contained in the molecule are two trisubstituted tetrahydrofuran rings, a trans double bond, and a 22-carbon acyclic chain with 9 asymmetric centres; clearly good stereochemical control is required for an efficient synthesis of such a natural product.

The polyether ionophores are usually acyclic in nature, but they often contain a number of substituted tetrahydrofurans, tetrahydropyrans and spiroketals (from which they inherited the name "polyether"). Interest in their synthesis spurred renewed effort in the development of stereoselective carbon-carbon bond forming reactions in acyclic systems, such as the aldol condensation and Michael addition. Also, some research groups turned their attention to the construction of cyclic ethers with control over the relative disposition of the substituents.

In the following two sections are described some of the advances made in these respective areas. In the third section, a retrosynthetic analysis of our route to ionomycin is outlined, with special attention given to the guidelines we followed to generate our plan.

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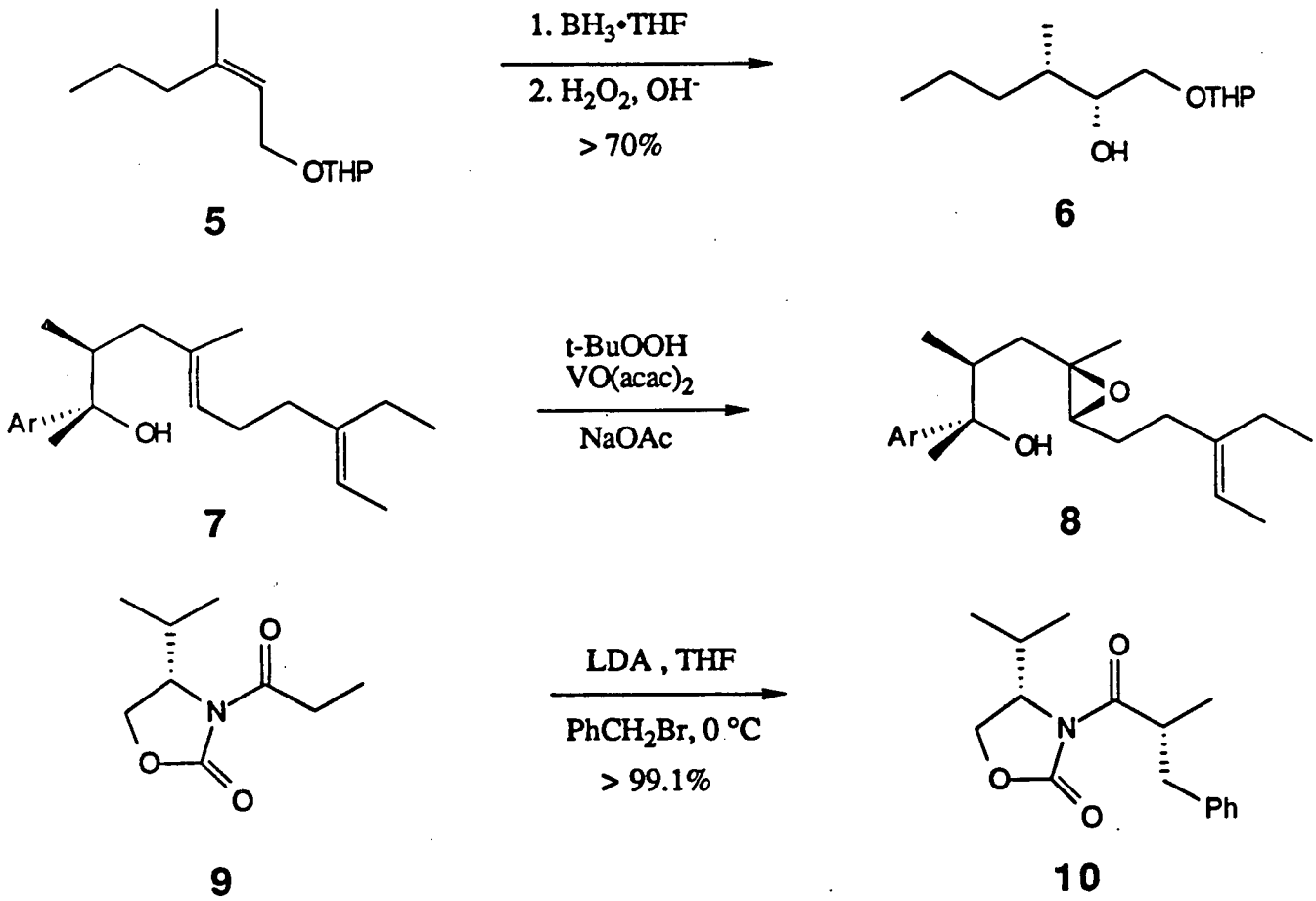
II. Stereocontrol in Acylic Systems: The Propionate Unit

The discovery of the macrolide[9] and polyether antibiotics placed asymmetric synthesis at the forefront of research in organic synthesis. Interest in the synthesis of those natural compounds has created a need for the development of stereoregulated reactions which not only introduce the atoms in a molecule with their correct relative disposition, but also with their correct absolute configuration.

Asymmetric induction falls into two main categories. In the first, the newly formed chiral centres bear a relationship amongst themselves, or to preexisting chiral centres, in an *intra*molecular fashion. The former case has been referred to as internal asymmetric induction and the latter as relative asymmetric induction by Bartlett.[10] The second category deals with *inter*molecular induction where the chirality of a substrate is transferred, through a favored transition state, to a second substrate and has been referred to as absolute asymmetric induction by the same author.[10] Examples for both categories are shown in Scheme 1.

In the first example, the hydration of olefin 5 by hydroboration-oxidation to give alcohol 6, is a case of internal asymmetric induction where the geometry of the double bond and the cis addition of the borane reagent dictate the relative stereochemistry of the methyl and the hydroxyl groups in 6.[11] Relative asymmetric induction is exemplified by the selective epoxidation of the hydroxy alkene 7 to epoxide 8.[12] In this case, the hydroxyl group directs the attack of the epoxidizing reagent to one face of the double bond. Finally, the third reaction is an example of absolute asymmetric induction where the isopropyl group on the oxazolidone ring of 9 forces the alkylating reagent to attack from one face of the enolate intermediate to give compound 10 exclusively.[13]

The task of controlling the absolute stereochemical outcome of a reaction is seldom an easy one and, for a long time, belonged to the domain of rigid and well understood cyclic molecules. Only recently, with the advent of stereochemically complex molecules like the polyether antibiotics, has the need for absolute asymmetric induction in the formation of acyclic molecules been more strongly felt. As a result, many important developments were made, especially in the area of the stereoselective aldol condensation and in reactions dealing with the construction of 1, 3-dioxygenated units.



Scheme 1. The three types of asymmetric induction (from top to bottom): internal, relative, and absolute asymmetric induction.

Some straight chain units, or synthons, frequently encountered in natural products are listed in Figure 3. The polypropionate unit consisting of alternating methyl and hydroxyl groups of all absolute configurations is certainly very common, and indeed often found in the polyether ionophores. The following discussion deals with some of the methods for the enantioselective synthesis of this synthon.

The nomenclature used to describe the stereochemistry of this family of subunits has suffered from a lack of clarity and consistency over the years. Older terms such as erythro and threo are commonly used and can lead to confusion. Seebach and Prelog proposed a new unambiguous method for naming them based on the Cahn-Ingold-Prelog system.[14] But universal acceptance of this proposal has been somewhat slow and many authors continue to use the older nomenclature. We felt that the descriptors syn and anti used with the extended chain formula[15] (Figure 3) create less confusion than the erythro-threo system, while being less cumbersome than the descriptors ul and lk of the Seebach-Prelog system.[14] For these reasons it will be used throughout this thesis. The syn and anti descriptors preceded by the number of the corresponding carbons will describe the relative relationship of the non-hydrogen substituents on those respective carbons. Therefore in Figure 3, unit 11a has the 1,2-syn stereochemistry, unit 11b is 1,2-anti and so on.

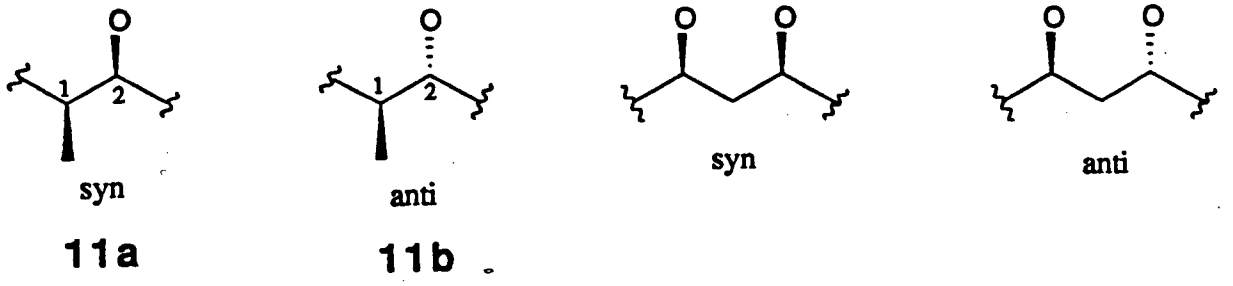
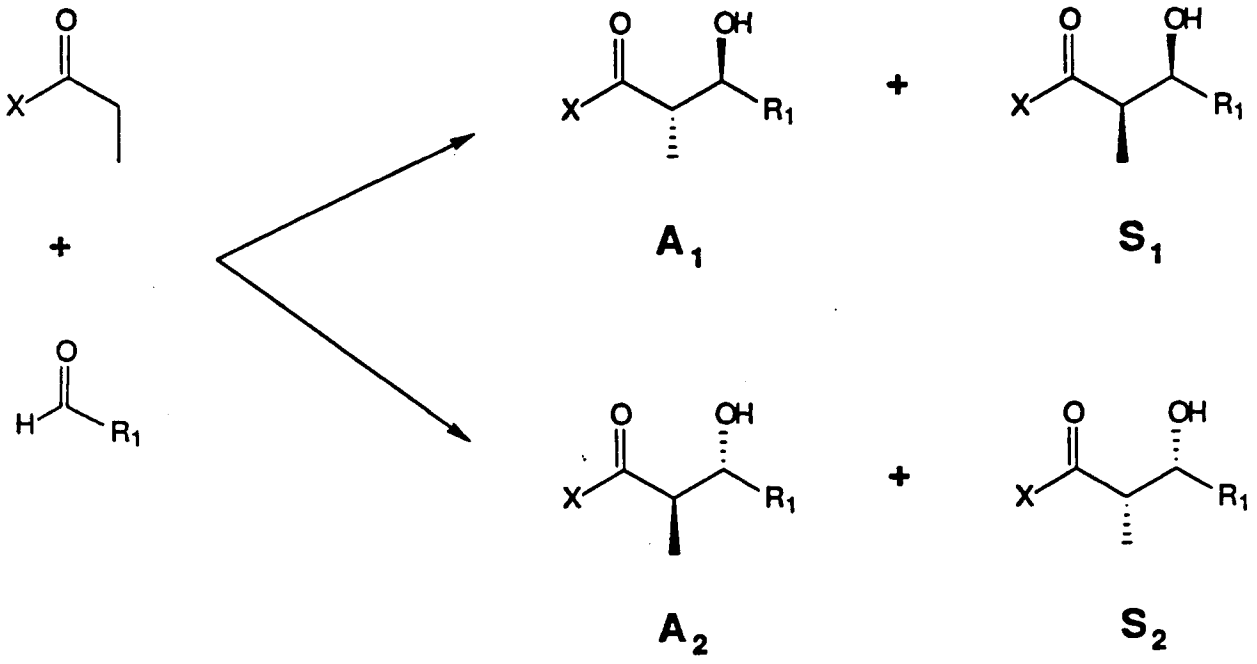


Figure 3. Examples of some straight chain units often encountered in natural products.

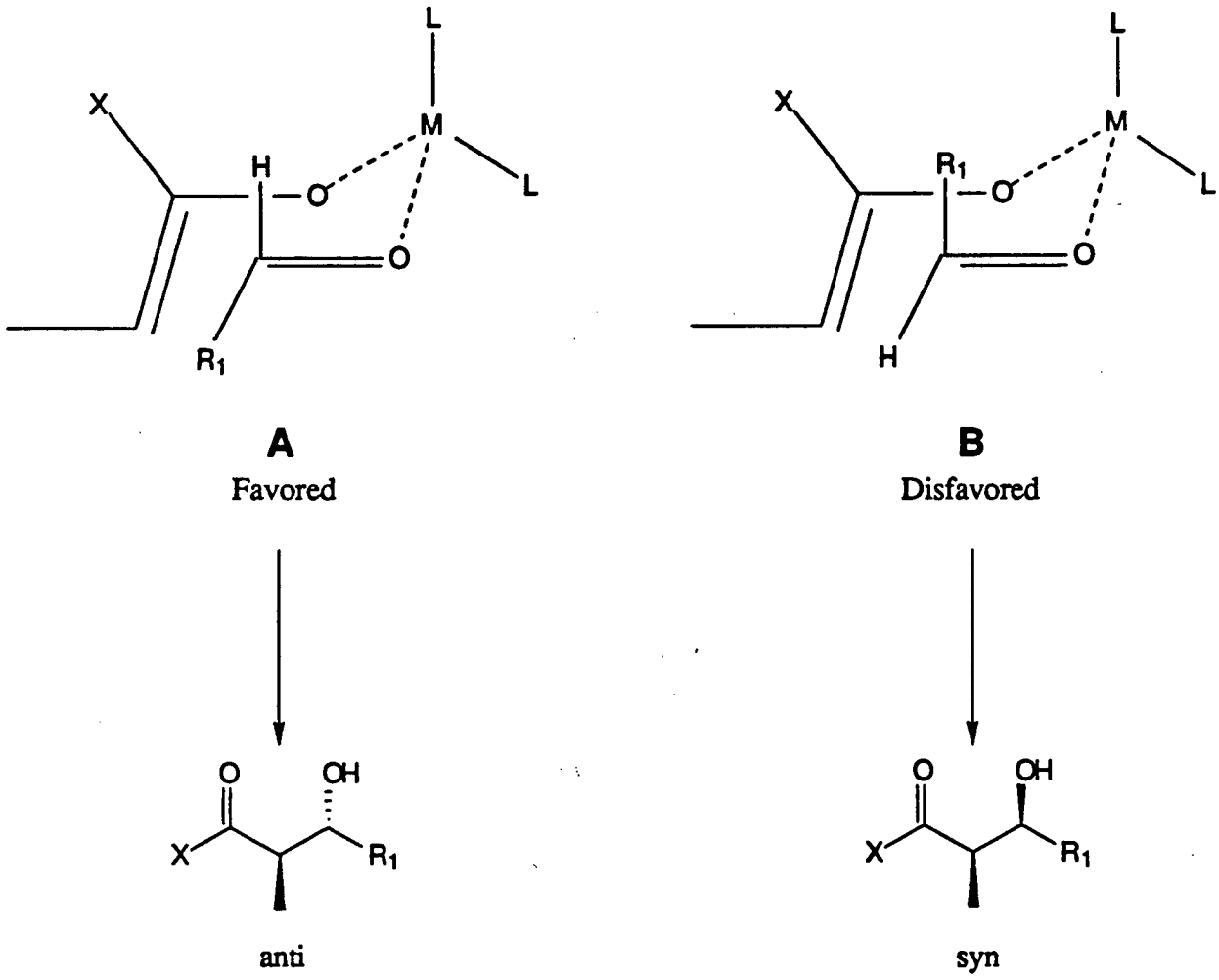
II.A. The Aldol Condensation

The aldol condensation is one of the most fundamental carbon-carbon bond forming reactions in biosynthesis. This reaction is also one of the oldest in organic chemistry and has been used widely in natural products synthesis. In the aldol condensation, two new chiral centres may be introduced producing four possible isomers (A_1, A_2 and S_1, S_2) (Scheme 2).



Scheme 2. The aldol condensation may generate four different isomeric products.

The problem of *diastereoselection* (the selective formation of A_1 or A_2 over S_1 or S_2, respectively) was addressed in the early stages of the work on stereoselective aldol reactions. The *diastereoselectivity* was found to depend on the geometry of the metal enolate, with the Z(O)-enolate leading to syn products (S_1 or S_2) and the E(O)-enolate giving anti products (A_1 or A_2). The descriptors Z(O)- and E(O)- refer to the geometry of the enolate with respect to the carbonyl oxygen.[15] This is shown in Scheme 3 using the Zimmermann-Traxler model for the transition state of the E(O)-enolate.[16] The pioneering work of Dubois and Fellmann[17],



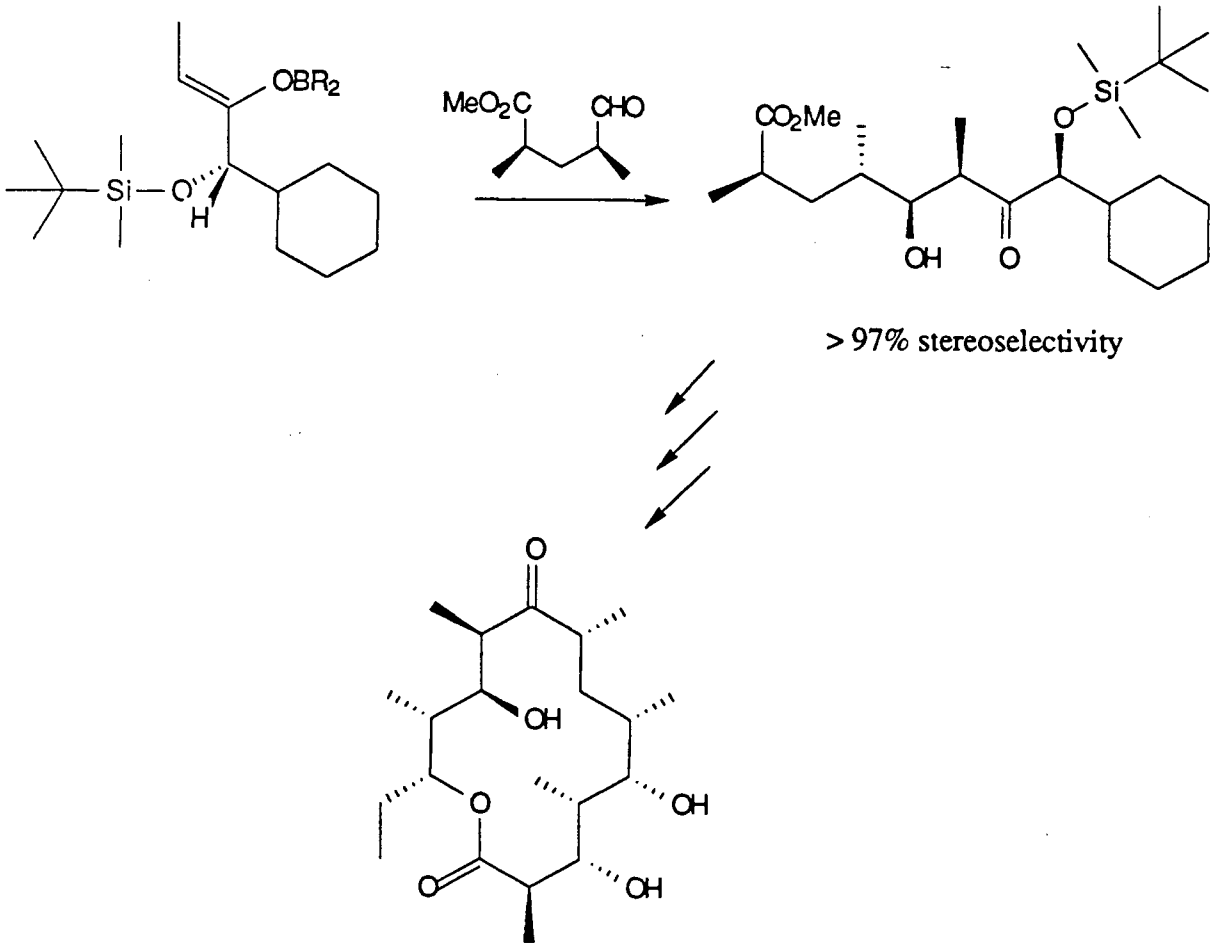
Scheme 3. The Zimmerman-Traxler model for the transition state of the aldol condensation.[16]

as well as the important contributions of Meyers, Heathcock and others[18] on this subject led to a good understanding of the factors mediating the stereoselectivity in the aldol process. Good control over the relative stereochemistry of the newly formed chiral centres can be obtained using a range of different bases and reaction conditions to generate metal enolates of defined geometry. Of a wide repertoire of metals investigated, including aluminium, boron, lithium, magnesium, zinc, zirconium, and others, boron turned out to be the most selective in the metal enolates because of its strong affinity for oxygen as well as the shorter B-O and B-C bond

lengths that in effect "tighten" the transition state. Bulky ligands on the metal centre would further enhance the preference for the aldehyde to adopt the orientation shown in transition state A (Scheme 3).[19]

Resident chirality on either the enolate or the aldehyde can be used to induce asymmetry in the final product. The present discussion will include only the aldol condensation performed with a chiral auxiliary attached to the carbon framework of the enolate. In recent years important advances were made in the development of chiral auxiliaries[20] leading to highly *enantioselective* aldol reactions (the selective formation of $\mathbf{S_1}$ over $\mathbf{S_2}$ or $\mathbf{A_1}$ over $\mathbf{A_2}$, Scheme 2) where the products often had enantiomeric excess exceeding 99%.[13,15,21] However in such asymmetric aldol reactions, because of the bulky chiral auxiliary on the enolate precursor, Z(O)-enolates are formed preferentially, even in conditions normally used to generate E(O)-enolates, leading to syn adducts exclusively.[22] While the transfer of chirality occurs with high selectivity (often > 100 : 1) much effort has been devoted to circumventing this lack of diastereospecificity, without too much success.[23]

Masamune's group found that the boron-mediated aldol condensation of some enolates, prepared with chiral auxiliaries derived from optically active mandelic acids, gave syn aldol adducts with high enantioselectivity.[15,24] They applied their strategy to the total synthesis of 6-deoxyerythronolide B (Scheme 4).[25,26]

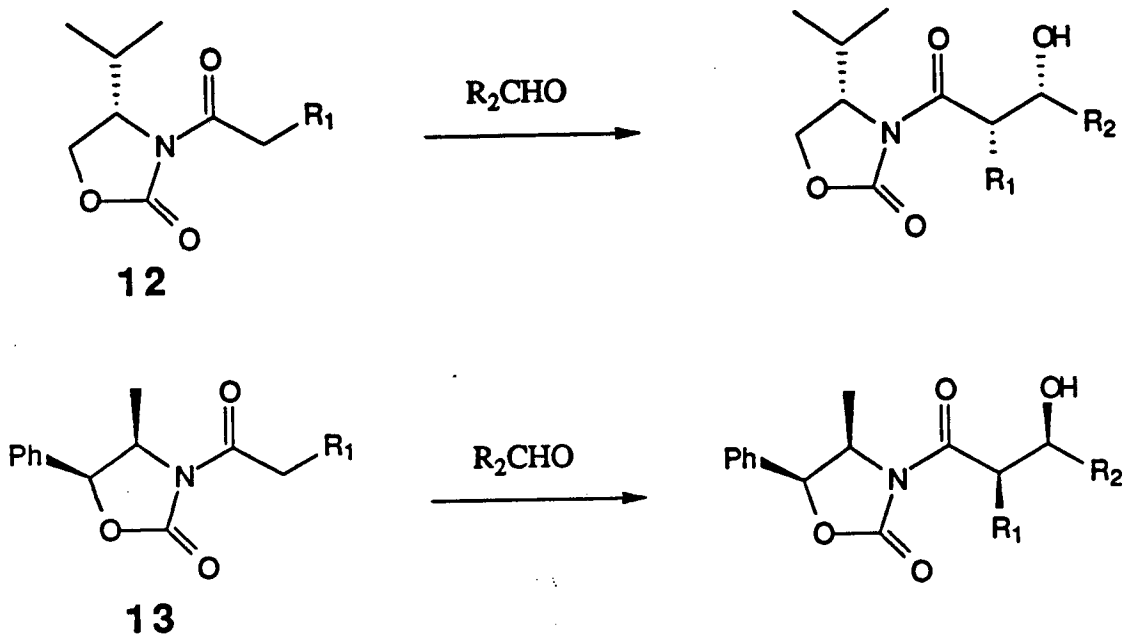


6-deoxyerythronolide B

Scheme 4. Masamune's synthesis of 6-deoxyerythronolide B.[25,26]

Of all chiral auxiliaries developed to date for the aldol condensation reaction, Evans' chiral amide and imide enolates are the most versatile (Scheme 5).[13] The availability, ease of handling and regeneration, and, most important of all, the high topographical bias are the main advantages of this class of chiral auxiliaries. The boron enolates of imides 12a-e and 13a-e invariably gave enantioselectivity ratios > 100 : 1 with a wide variety of aldehydes and these enolates are now commonly used in synthesis as a powerful way to generate the chiral aldol adduct. Moreover, one important feature of these auxiliaries is that the stereochemical outcome of the reaction is controlled by the stereochemistry of the chiral auxiliary and the reaction is unaffected by existing chirality on the substrate aldehyde. This is a particularly useful

characteristic when constructing long chains with alternating alkyl and hydroxyl groups. Usually competitive or additive asymmetric induction between the auxiliary and the chiral centre on the aldehyde (referred to as *double stereodifferentiation*)[15] occurs leading to decreased or increased selectivity in the reaction respectively.[15,26]



a) R_1 = -CH_3 and n-alkyl
b) -CH_2CO_2Me
c) -$CH{=}CH_2$
d) -OMe, OCH_2Ph
e) -SMe

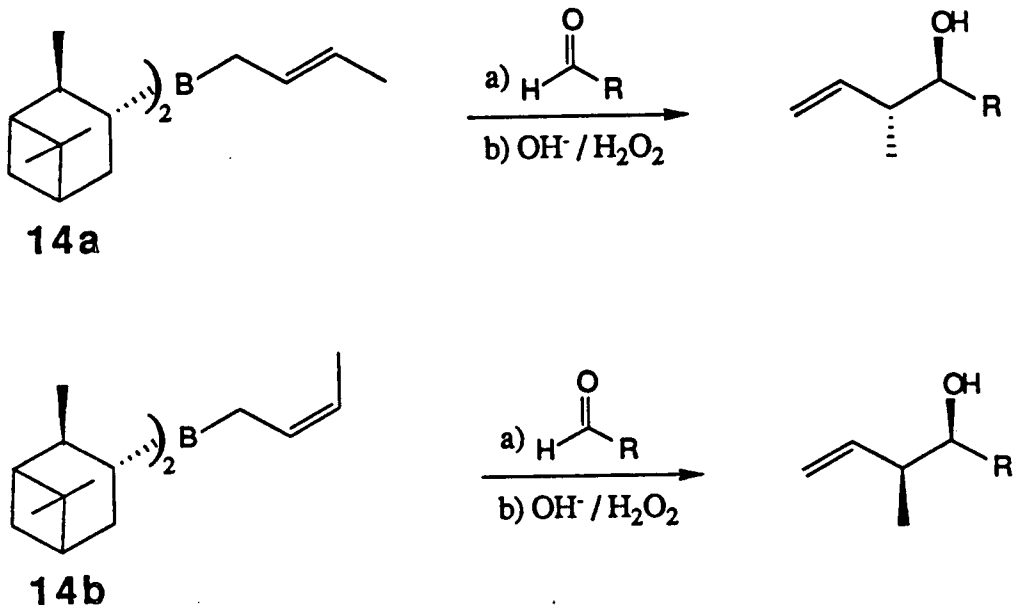
Diastereoselection > 99 %
Enantioselection > 99 %

Scheme 5. The aldol reaction of chiral imide auxiliaries[13]

II.B. Addition of Allyl Metals to Aldehydes

The addition of allylic organometallic reagents to aldehydes is analogous to the aldol condensation in that the homoallylic alcohol produced in the former reaction can easily be transformed into a ß-hydroxy carbonyl moiety (Scheme 7).[27,28] A high degree of control over the *diastereoselectivity* can be achieved with allylic aluminium, tin, chromium, and titanium

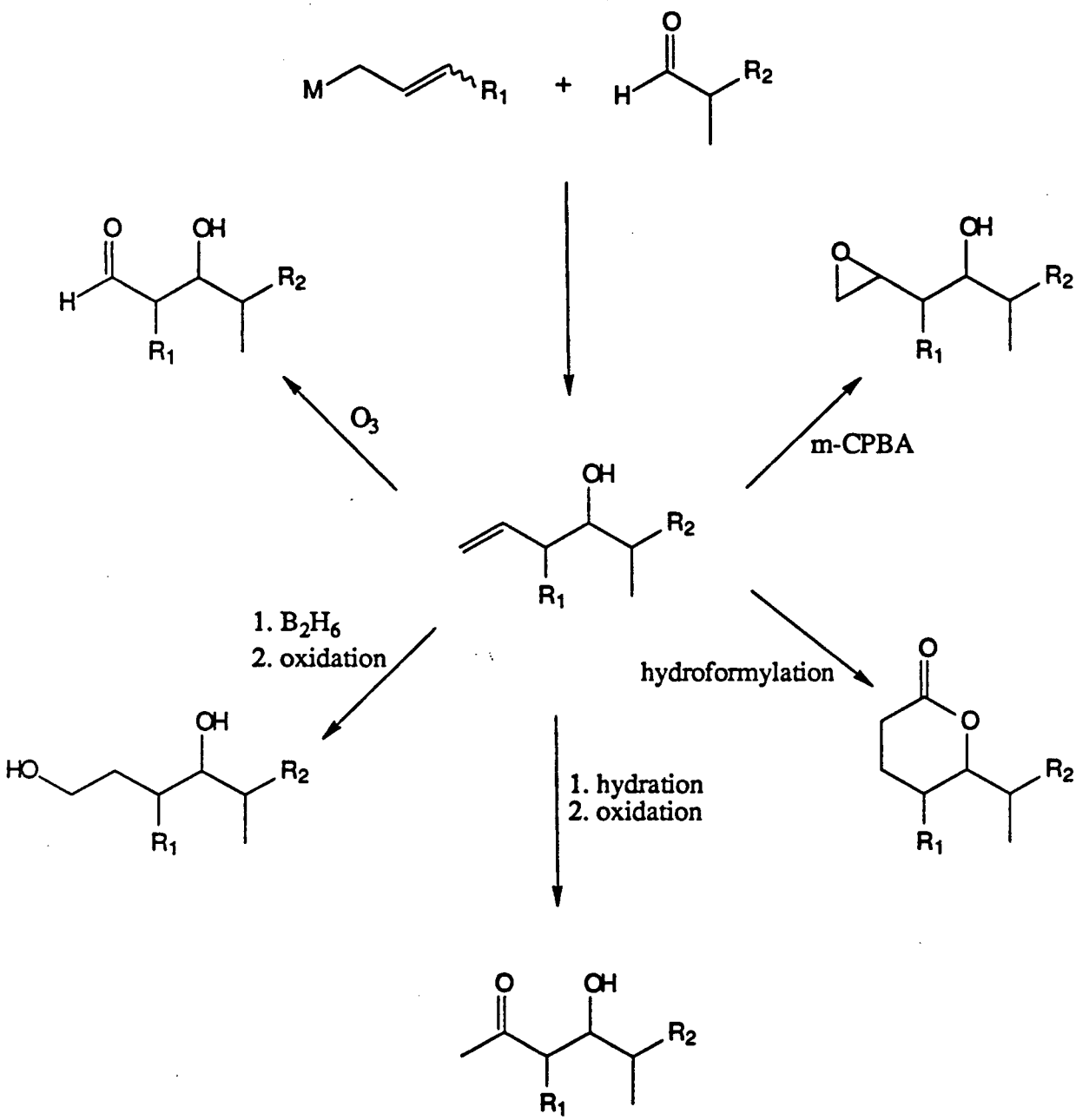
compounds, but again boron was found to be the most selective. The reaction is thought to proceed through a chair-like transition state akin to the aldol reaction. The geometry of the double bond in the organometallic reagent is the major factor controlling the stereochemistry of the products, with the (Z)-olefin giving rise to syn adducts and the (E)-olefin to anti adducts. However the stereoconvergence – both (Z) and (E)-olefin yielding syn products – observed in the case of Lewis acid mediated reactions, such as the addition of allylic tin reagents to aldehydes in the presence of $BF_3 \cdot Et_2O$, was best explained using an acyclic transition state.[28]



Scheme 6. The stereoselective addition of (+)-isopinocampheylborane to aldehydes. In both cases the diastereoselectivity was > 99% and the enantioselectivity was > 95%.

Chirality at the metal centre can be used to induce asymmetry in the addition. The chiral induction achieved so far, occasionally up to 20 : 1 as is the case for the (+)-isopinocampheylborane reagents 14a and 14b developed by Brown and coworkers (Scheme 6), does not quite attain the same level as in the aldol condensation.[29] There are however some

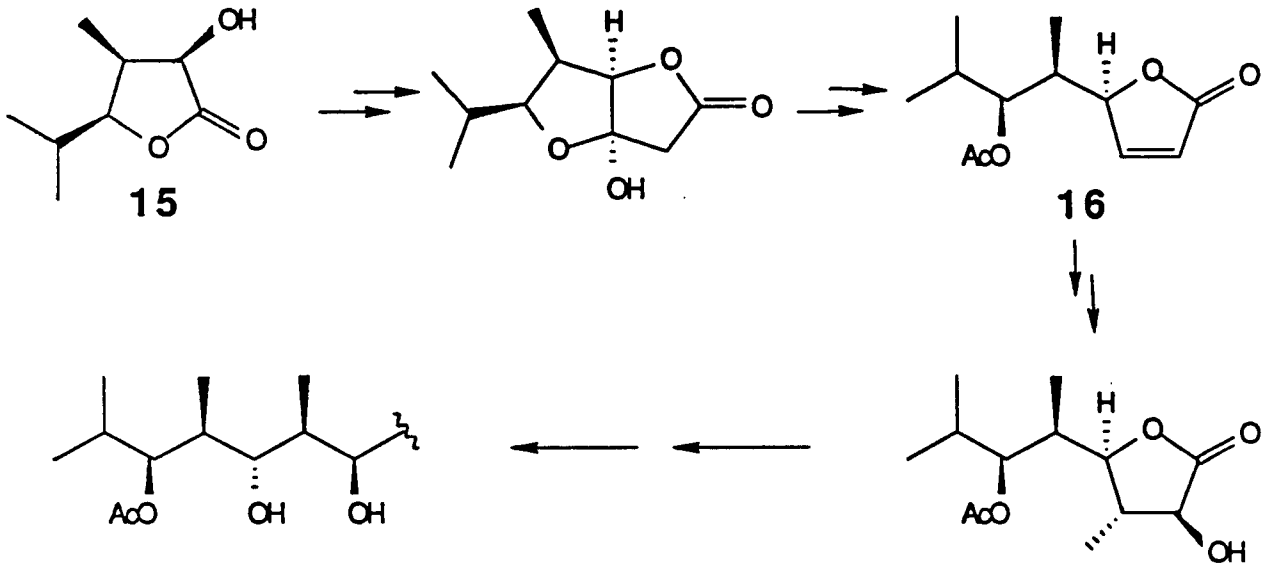
advantages in using this method over the aldol condensation that makes it an extremely useful and versatile tool in organic synthesis. Indeed the homoallylic alcohol generated on the addition of allylic organometallic reagents to aldehydes can be transformed into several useful intermediates, some of which are shown in Scheme 7. However, to date, the method does not offer a good solution to the problem of double stereodifferentiation; the addition of a chiral allyl metal to an asymmetric aldehyde will mainly follow the Cram or anti-Cram rule of addition to aldehydes and the stereochemical outcome of the reaction will not be totally controlled by the chirality on the metal centres. Because of this, the construction of chains of two sequential units or more could not be achieved in a stereocontrolled manner using the allylic organometallic compounds.



Scheme 7. The product of allylic metal addition to aldehydes can be converted into a wide range of synthons.

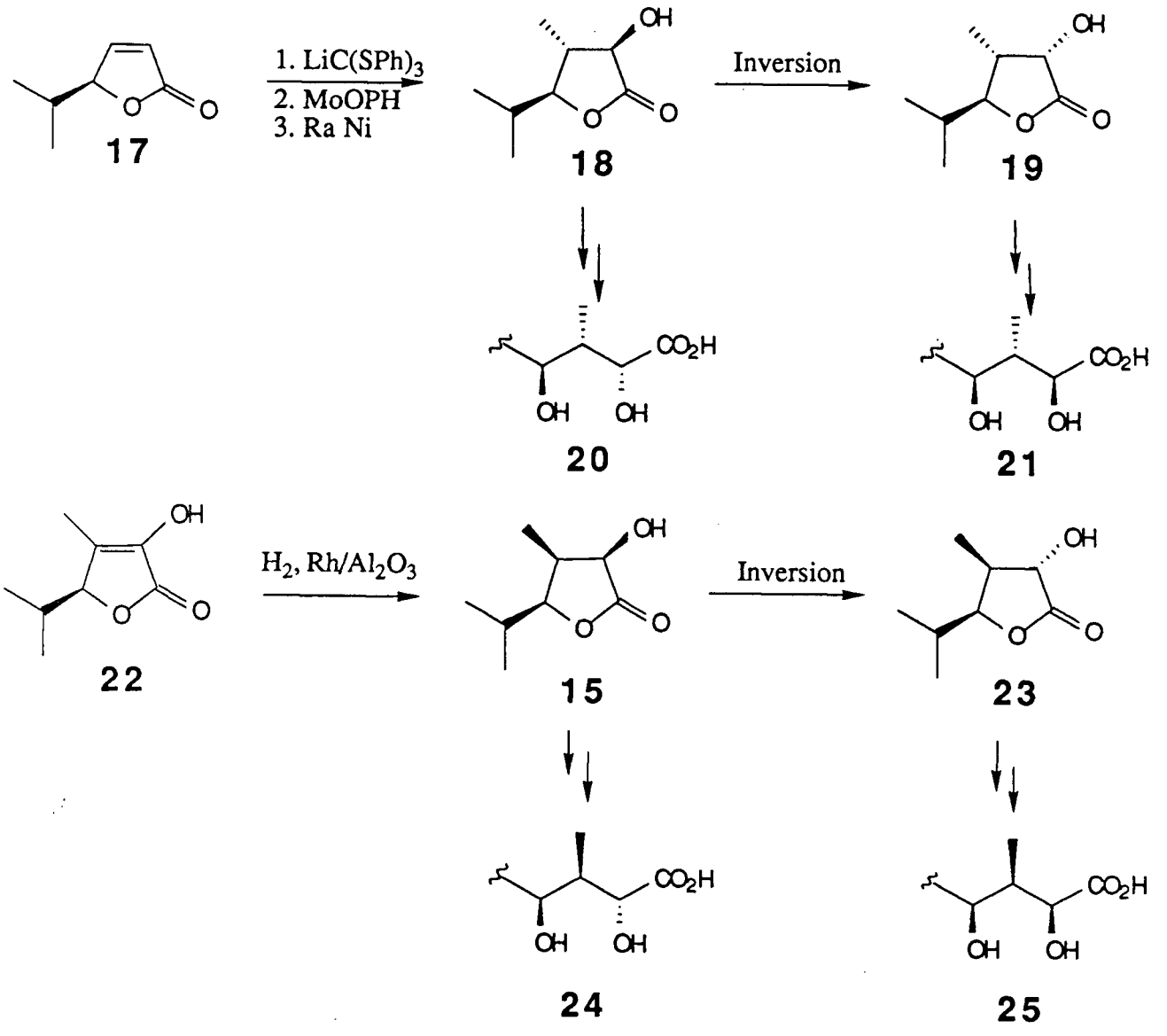
II.C. The Butenolide Template

Stork et al. have recently described a method to control the relative and absolute stereochemistry of each chiral centre in the synthesis of polypropionate units.[30]



Scheme 8. Construction of multiple propionate units by the butenolide template methodology.

This method consists of first adding in a stereoregulated manner a methyl and a hydroxyl group to a chiral 5-substituted butenolide such as 17 (Scheme 9). In a second stage the 3-hydroxy-4-methylbutyrolactone 15, for example, is elaborated into second butenolide 16 (Scheme 8). Subsequently, a methyl and a hydroxyl group can be introduced on this new butenolide and the cycle can be repeated (Scheme 8). The methyl is introduced as a bulky 4-tris(thiophenyl)methyl group (see 17 → 18 in Scheme 9). Oxidation of the enolate intermediate and desulfurization with Raney nickel give the appropriate 2,3-anti adduct 18.



Scheme 9. Stereoselective generation of the propionate unit by the butenolide template methodology.[30]

Inversion of the secondary alcohol using the Mitsunobu procedure[31] leads to the 2,3-syn product 19. Ring opening of the lactones 18 and 19 would lead to 20 and 21 respectively. For the construction of the two isomeric units 24 and 25, butenolide 22 was used. Catalytic hydrogenation of 22 furnished the 2,3-syn product 15 and inversion of the alcohol generated

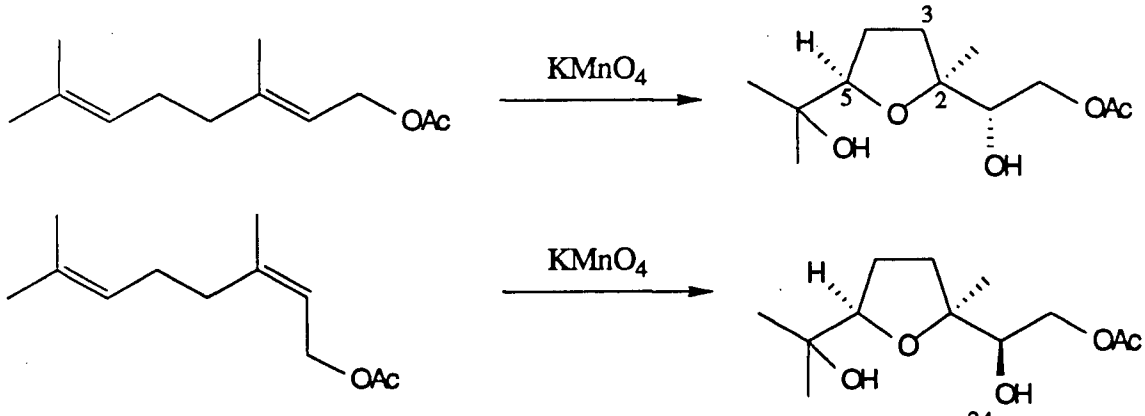
the 2,3-anti adduct 23. The selectivity obtained is quite high in all cases, but only units 20 and 24 can be made directly. A method based on the same principle was also developed by Hanessian and coworkers for the synthesis of the C_2-C_{10} and C_{11}-C_{22} fragments of ionomycin.[32]

III. Stereocontrol in Cyclic Ethers: the Tetrahydrofuran Ring

This section deals only with the stereoselective preparation of tetrahydrofurans.[33]

III.A. The Oxidative Cyclization of 1,5-Dienes

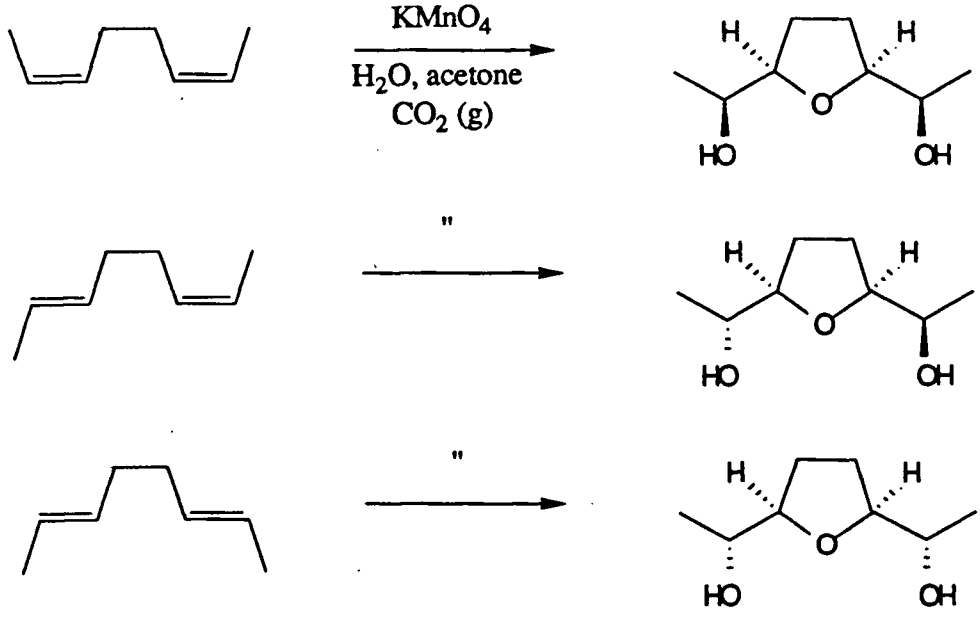
In 1965, Klein and Rhojhan discovered that geranyl and neryl acetate could be oxidatively cyclized to a tetrahydrofuran instead of the expected tetrol.[34] The cyclization was found to give exclusively cis tetrahydrofurans and generated three asymmetric centres in a stereospecific manner. The descriptors cis and trans refer to the relative disposition of the two substituents of higher priority at positions two and five on the tetrahydrofuran (Scheme 10). Scheme 10 shows the products of the $KMnO_4$ cyclization of geranyl and neryl acetate.



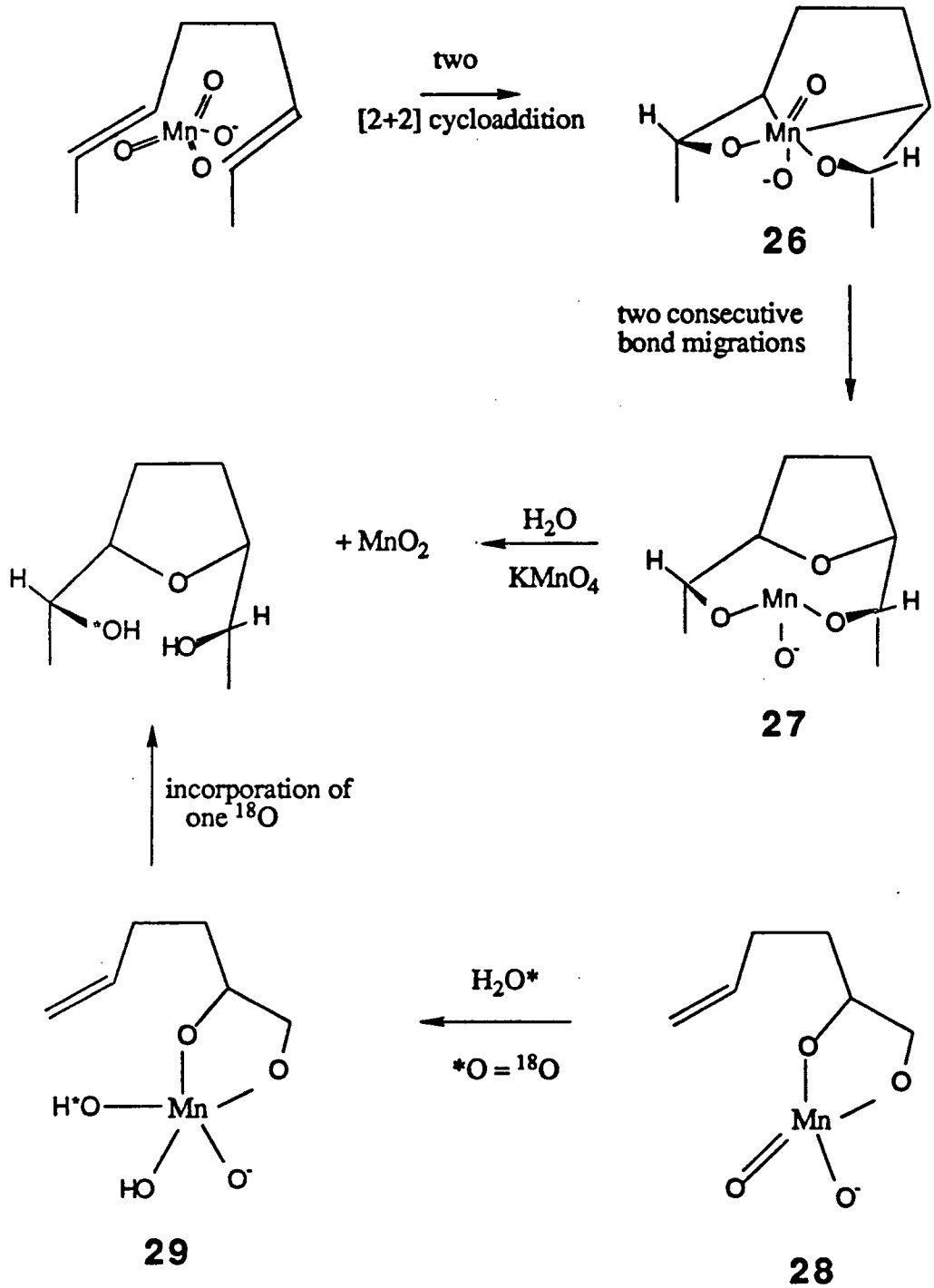
Scheme 10. Oxidation of geranyl and neryl acetate by potassium permanganate.[34]

Later Walba and coworkers correlated the stereochemistry of the tetrahydrofuran products with the geometry of the olefins in the starting diene in a series of studies on the cyclization of octadienes (Scheme 11).[35] They found the cyclization to be > 97% stereospecific and

proposed the mechanism shown in Scheme 12 to account for the high stereoselectivity of the reaction. The first step would involve two Sharpless type [2+2] cycloadditions of the olefinic π bonds and the manganese-oxo bonds to give intermediate 26, which then undergoes bond migration from the metal to the oxygen with retention of configuration followed by a second similar bond migration thus generating the cis-tetrahydrofuran intermediate 27. Then oxidation and hydrolysis of intermediate 27 are required to liberate the diol. Earlier, Sable and coworkers,[36] and also Baldwin et al.[37] suggested that each double bond was oxidized consecutively, and in 1981 Wolfe and Ingold supplied evidence for that mechanism.[38] From ^{18}O labelling experiments they found that at least one of the oxygen atoms of the tetrahydrofuran product came from the solvent, and suggested that a manganese intermediate such as 29 having a coordination number greater than four, was involved. These results were incompatible with Walba's proposal.

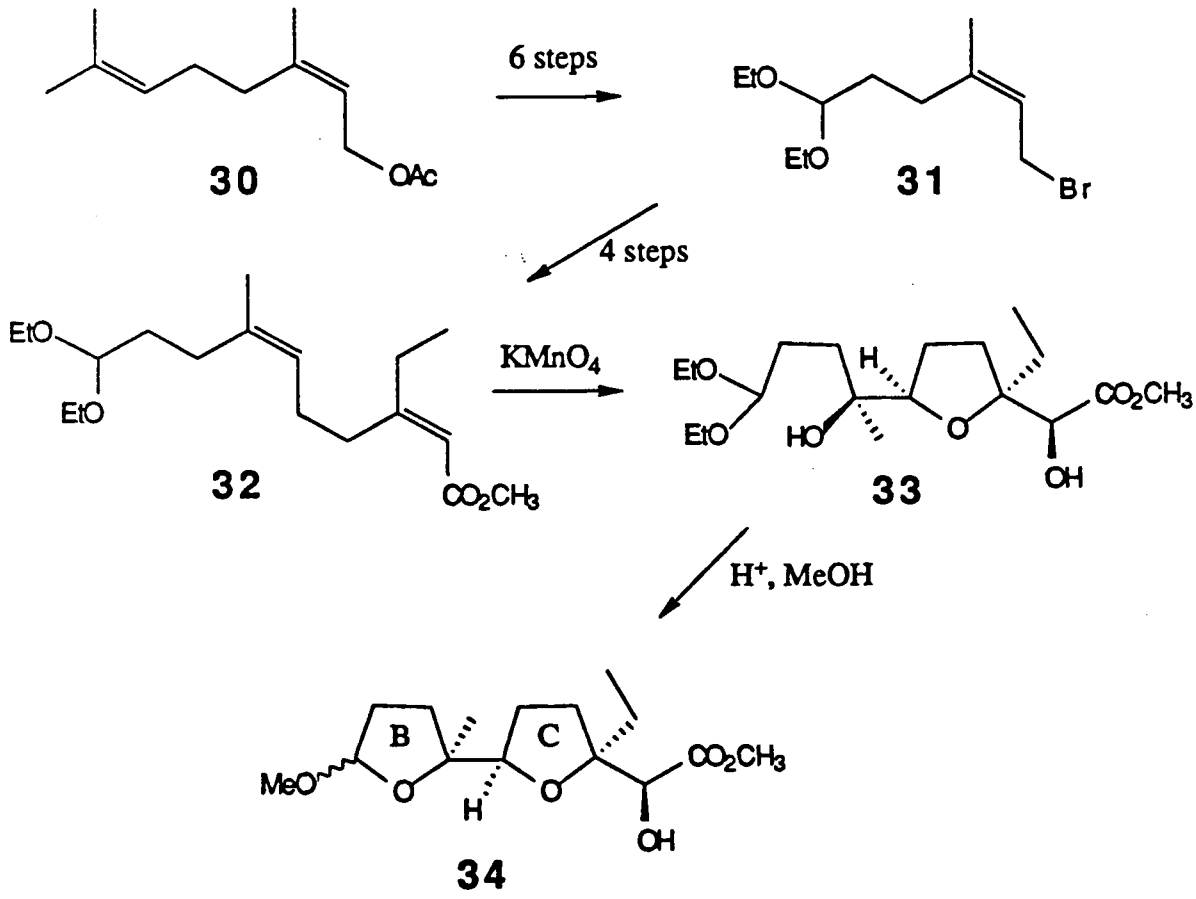


Scheme 11. Correlation between the geometry of the 2,6-octadienes and the stereochemistry of the corresponding tetrahydrofuran in their oxidative cyclization by $KMnO_4$.[35]



Scheme 12. Possible mechanisms for the permanganate cyclization of 1,5-dienes.[35,38]

Walba and Edwards demonstrated the synthetic applicability of the permanganate oxidative cyclization of 1,5-dienes in a synthesis of the central part of monensin (Scheme 13).[39] Starting with neryl acetate (30), they obtained bromide 31 in six steps including a selective cleavage of the double bond at position 6. The second olefin was constructed in four steps using Corey's methodology of addition of cuprate reagents to alkynyl esters to afford 1,5-diene 32 with the desired (Z,Z)-geometry about the double bonds. Cyclization of 32 gave tetrahydrofuran 33 exclusively in 46% yield. Acid catalysed cyclization of 33 gave the cyclic acetal 34 which formally contains rings B and C of monensin.

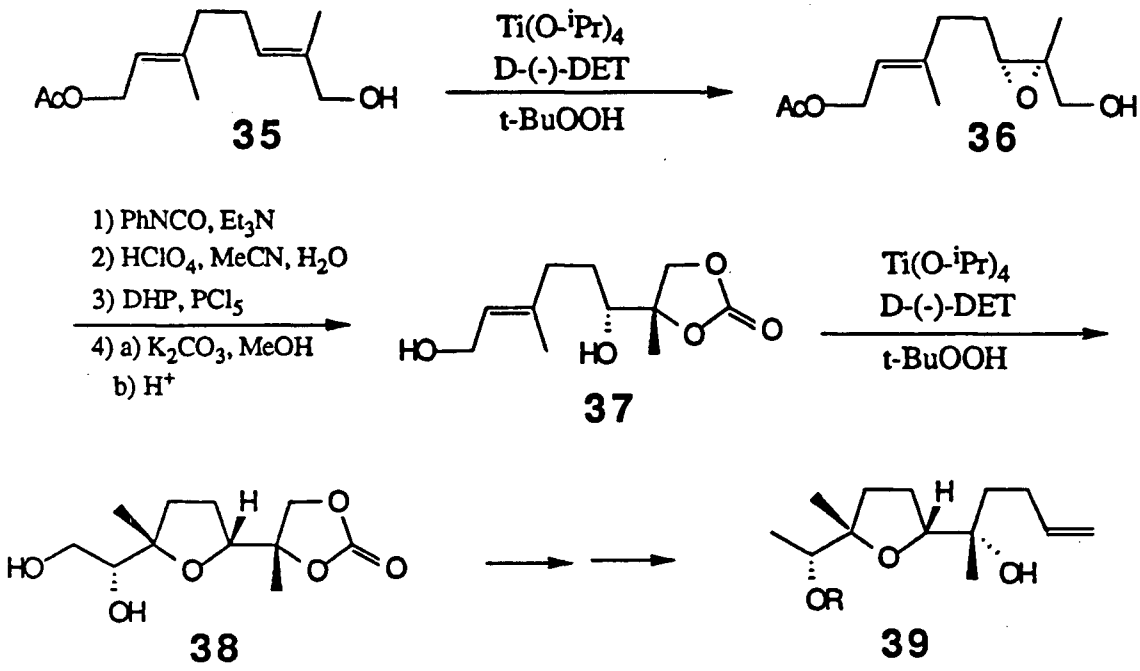


Scheme 13. Synthesis of the central part of monensin using a permanganate cyclization.[39]

Sharpless and coworkers also reported the same oxidation of 1,5-dienes to tetrahydrofurans using ruthenium tetroxide.[40] The oxidation led to tetrahydrofurans with the cis and trans stereochemistry in a ratio of ~ 3:1. Sharpless explained the difference in stereoselectivity between the cyclization with ruthenium tetroxide and the cyclization with permanganate by arguing that the differences in geometry and bond lengths of comparable intermediates allowed for incursion of the pathway leading to the trans-tetrahydrofurans in the oxidation with ruthenium tetroxide.

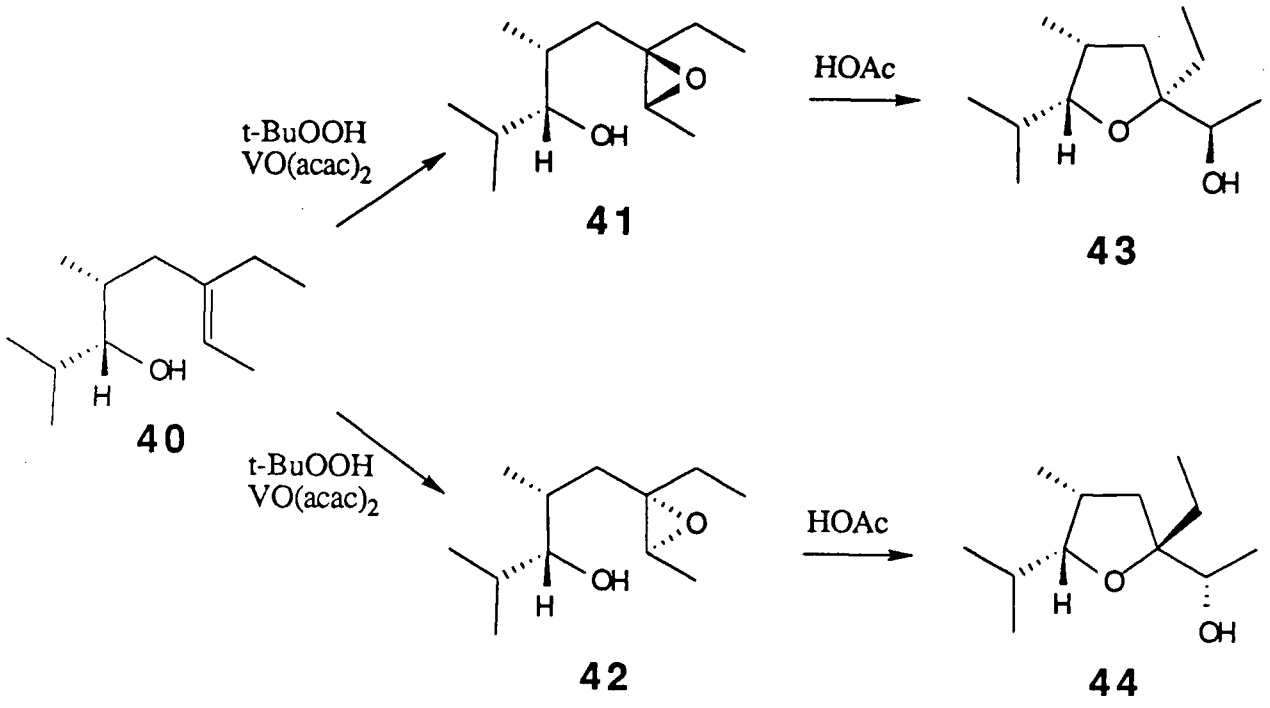
III.B. Hydroxy Epoxide and Polyepoxide Cyclization

Wuts et al. in their effort towards the synthesis of ionomycin constructed the tetrahydrofuran rings by an epoxidation-cyclization sequence.[41] The epoxides were generated with the correct stereochemistry by two Sharpless epoxidations[42] as shown in Scheme 14. Diene 35 was epoxidized to give mainly isomer 36. Opening of the epoxide in the phenylurethane of 36 with perchloric acid, followed by a protection and deprotection, gave cyclic carbonate 37. The second epoxidation was effected on hydroxy alkene 37 and, without isolation of the intermediate epoxide, tetrahydrofuran 38 was obtained. Subsequent functional group manipulations gave fragment 39 of ionomycin.



Scheme 14. Wuts' synthesis of a fragment of ionomycin containing the tetrahydrofuran moiety.[41]

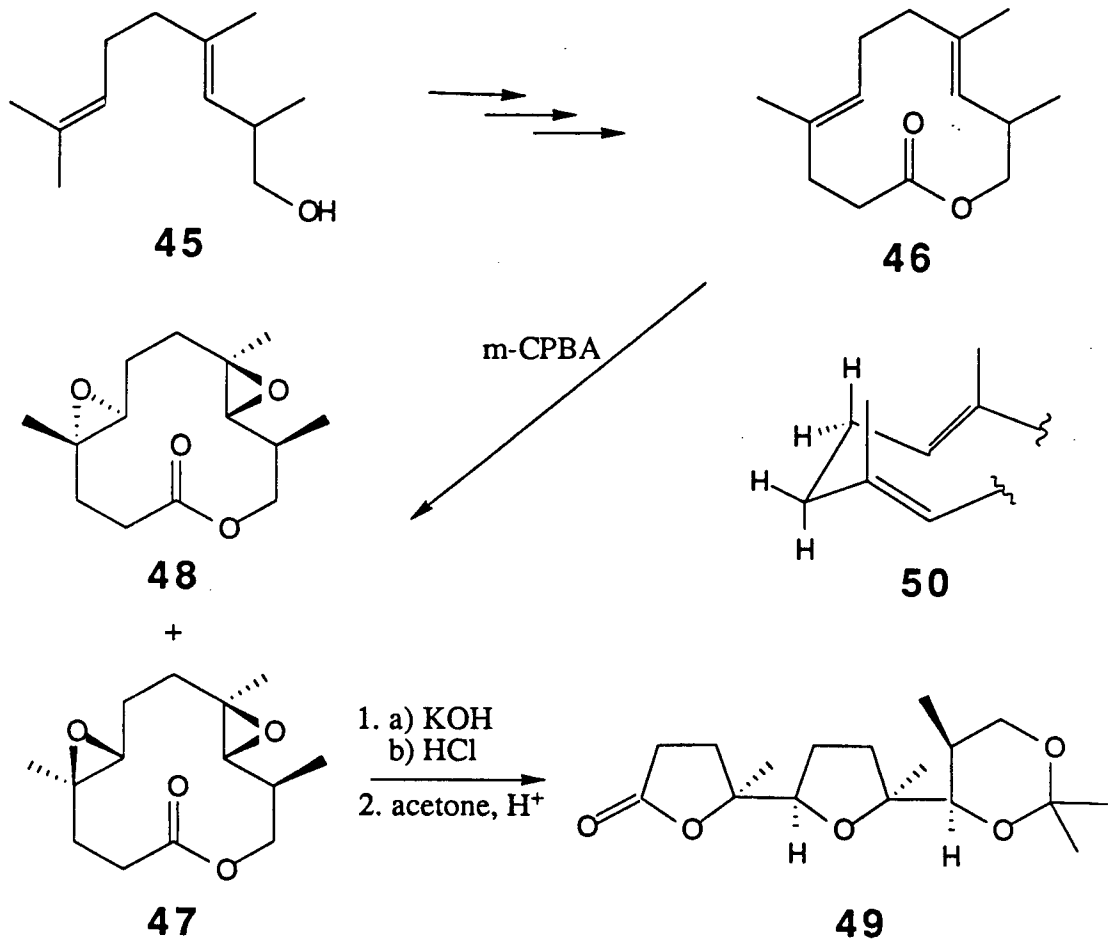
γ,δ-Unsaturated alcohol 40 was epoxidized selectively with t-BuOOH and $VO(acac)_2$ to give a > 20:1 ratio of the epoxides 41 and 42 by Kishi and coworkers (Scheme 15).[43] These hydroxy epoxides were then cyclized to trans-tetrahydrofurans 43 and 44 respectively by the action of acetic acid. The same research group then utilized this methodology for the first synthesis of lasalocid A.[12]



Scheme 15. Hydroxy-directed epoxidation of γ,δ-unsaturated alkenes.[43]

The direct cyclization of polyepoxides to form tetrahydrofurans was ingeniously used by Schreiber et al.,[44] and Still and Romero[45] independently in their syntheses of a subunit of monensin B. Macrolide 46 was constructed in several steps from the racemic diene 45 by Schreiber's group (Scheme 16). This macrolide was expected to adopt the conformation shown in the partial structure 50 and epoxidation should then lead to bisepoxide 47 stereoselectively by peripheral attack of the peracid. This was indeed the case and products 47 and 48 were obtained in a ratio of 9.5 : 1. One-pot hydrolysis and cyclization of the bisepoxide 47 and subsequent acetonization gave compound 49 which constitutes rings B and C of monensin. Still's method involved the stereoselective formation of a trisepoxide from a

14–membered ring triene and its subsequent cyclization gave a tristetrahydrofuran.[45] However the stereochemistry of one of the epoxides on the macrolide was wrong and resulted in the incorrect stereochemistry of ring C of monensin.

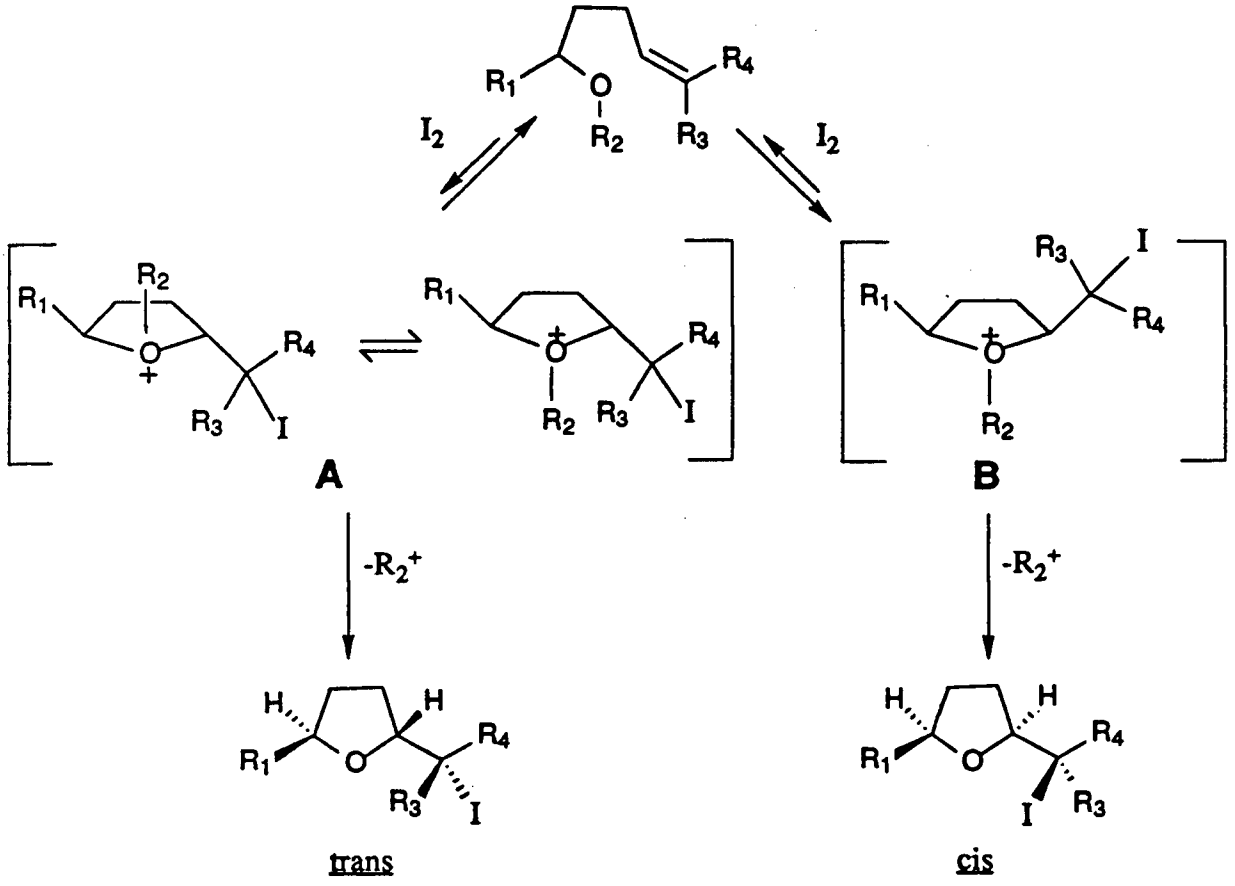


Scheme 16. The stereoselective construction of tetrahydrofurans via a polyepoxide cyclization.[44]

III.C. Electrophilic Cyclization of γ,δ-Unsaturated Ethers or Alcohols

A method involving halocyclization of γ,δ-unsaturated ethers or alcohols was developed by Bartlett's group at Berkeley to stereoselectively form cis or trans tetrahydrofurans.[46-48] Cyclization to cis tetrahydrofurans was effected by treatment of γ,δ-unsaturated ethers with

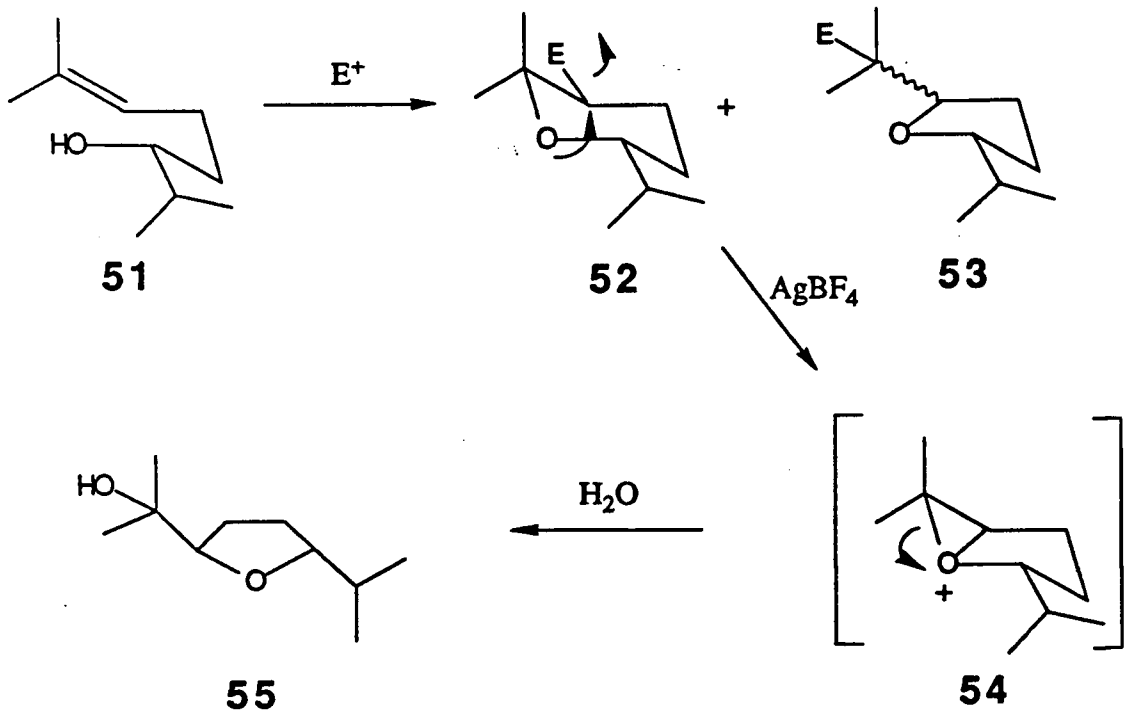
iodine in acetonitrile (Scheme 17).[46] Loss of the alkyl group R_2 from the oxonium ion (Scheme 17) must be slower than its reversible formation so as to allow a thermodynamic differentiation of the intermediates A and B where the latter is favored for steric reasons. Oxonium ion B is also kinetically favored. The alkyl substituents R_2 must be large enough to provide good steric bias, but not too bulky to prevent cyclization. The dichlorobenzyl group was found to have the best balance of steric and electronic properties for the R_2 group.



Scheme 17. Stereoselective formation of cis-tetrahydrofurans by electrophilic cyclization of γ,δ-unsaturated ethers.[46]

As expected, cyclization of the analogous alcohol gives mainly the trans stereochemistry because the steric repulsion between the two substituents on the developing tetrahydrofuran ring favors intermediate A when R_2 = H.

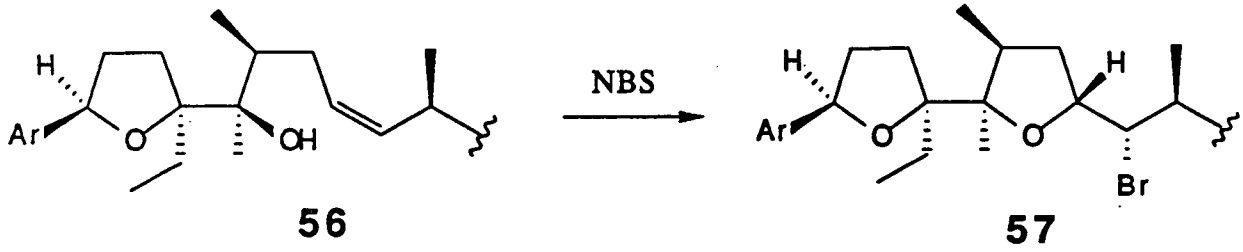
The same group developed a two-step procedure for the stereoselective formation of trans-tetrahydrofurans.[47] The approach is based on the fact that 1,3-asymmetric induction in a six-membered ring is more readily attained than in a five-membered ring. The cyclization of the γ,δ-unsaturated alcohol 51 with 2,4,4,6-tetrabromo-2,5-cyclohexadienone stereoselectively gave tetrahydropyran 52 along with the undesired tetrahydrofuran 53 as a mixture of cis and trans isomers (Scheme 18). A variety of other electrophiles were tried but no improvement over the regioselectivity could be accomplished. Compound 52 was separated from compound 53 and upon ring contraction of 52 with silver tetrafluoroborate the trans-tetrahydrofuran 55 was obtained. The ring contraction presumably proceeds via bicyclic oxonium ion 54 which is then opened to the tetrahydrofuran 55 by a molecule of solvent (Scheme 18).



Scheme 18. Selective formation of trans-tetrahydrofurans by electrophilic cyclization of γ,δ-unsaturated alcohols to tetrahydropyrans and ring contraction, $E^+ = Br^+$ or Tl^{3+}.

This methodology was subsequently greatly improved by the use of thallium (III) as the electrophile in the cyclization.[48] The steric and electronic properties of thallium (III) species confer a better regio and stereochemical control to the cyclization. The thallated intermediate 52 was never isolated and ring contraction occurred immediately to give the desired trans-tetrahydrofuran (Scheme 18).

Direct halocyclization of the complex γ,δ unsaturated alcohol 56 to the trans-tetrahydrofuran 57 was achieved by Kishi and coworkers in their synthesis of monensin (Scheme 19).[49]



56 57

Scheme 19. Halocyclization of a complex γ,δ-unsaturated alcohol in the synthesis of monensin.[49]

Oxymercuration of γ,δ unsaturated alcohols is also a useful technique for the selective formation of trans-tetrahydrofurans. The organomercurial intermediate can be reduced to the alkane with sodium borohydride in the work-up.[50,51] Other electrophiles, such as the halogens, would have to be reduced in a subsequent step.

There are numerous other methods for the stereocontrolled generation of tetrahydrofurans. The catalytic reduction of appropriately substituted furans leads to 2,5-cis-tetrahydrofurans. This approach has been widely exploited in the synthesis of nonactic acid, a monomer of the nactins series of macrolide polyethers.[52] Amongst other methods for the

stereoselective formation of tetrahydrofurans is the intramolecular ester enolate Claisen rearrangement developed by Ireland and coworkers.[53] Collum et al. have used the cyclization of 1,4-diols[54] and there is a case of an allylic oxidative cyclization of a 1,5-hydroxy alkene to stereoselectively generate tetrahydrofurans.[55]

IV. Toward a Stereoselective Synthesis of Ionomycin

The advances made in stereoregulated reactions are pivotal to the success of any synthesis of such complex molecules as the polyether antibiotics. The planning or design of the synthesis also is exceedingly important. The following section describes our plan for the stereoselective synthesis of ionomycin.

Convergence, i.e. the construction of a large and complex molecule from small fragments that are later joined together, is no doubt an important ingredient in a successful synthesis of a molecule the size of the polyethers. A convergent synthesis is usually more efficient than a linear synthesis with an identical number of steps and chemical yields.

The separate fragments should be optically pure prior to coupling to avoid the sometimes tedious task of separating diastereomers, or resolving enantiomers, following the coupling of racemic fragments (eq 1 to 3). In eq 1 both fragments are optically pure prior to coupling which gives rise to a single product. When one of the fragments is racemic as in eq 2, two diastereomeric products are formed. Eq 3 shows the formation of four isomeric products from the coupling of two racemic fragments. The products in eq 3 contain two pairs of enantiomers and a resolution is required for their separation.

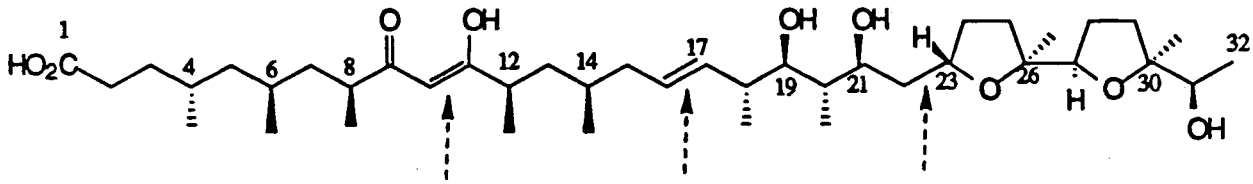
d-A + *d*-B → *d*-A*d*-B (eq 1)

d-A + *dl*-B → *d*-A*d*-B + *d*-A*l*-B (eq 2)

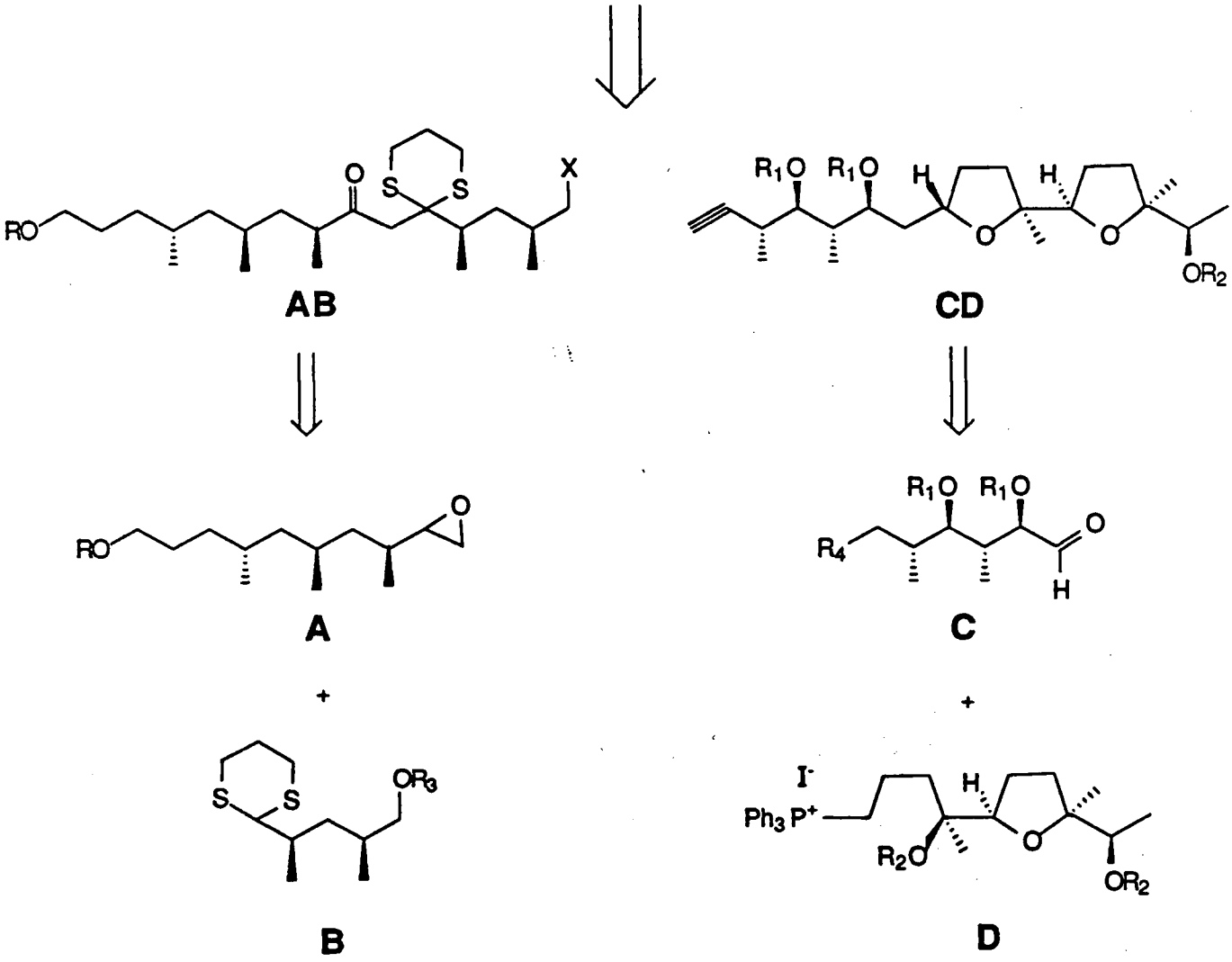
dl-A + *dl*-B → *d*-A*d*-B + *d*-A*l*-B + *l*-A*d*-B + *l*-A*l*-B (eq 3)

IV.A. Synthesis of Fragments A (C_1-C_{10}) and B (C_{11}-C_{15})

We divided ionomycin into four different fragments, A, B, C, and D, as shown in the retrosynthetic analysis in Scheme 20. The A and B fragments would be coupled as well as the

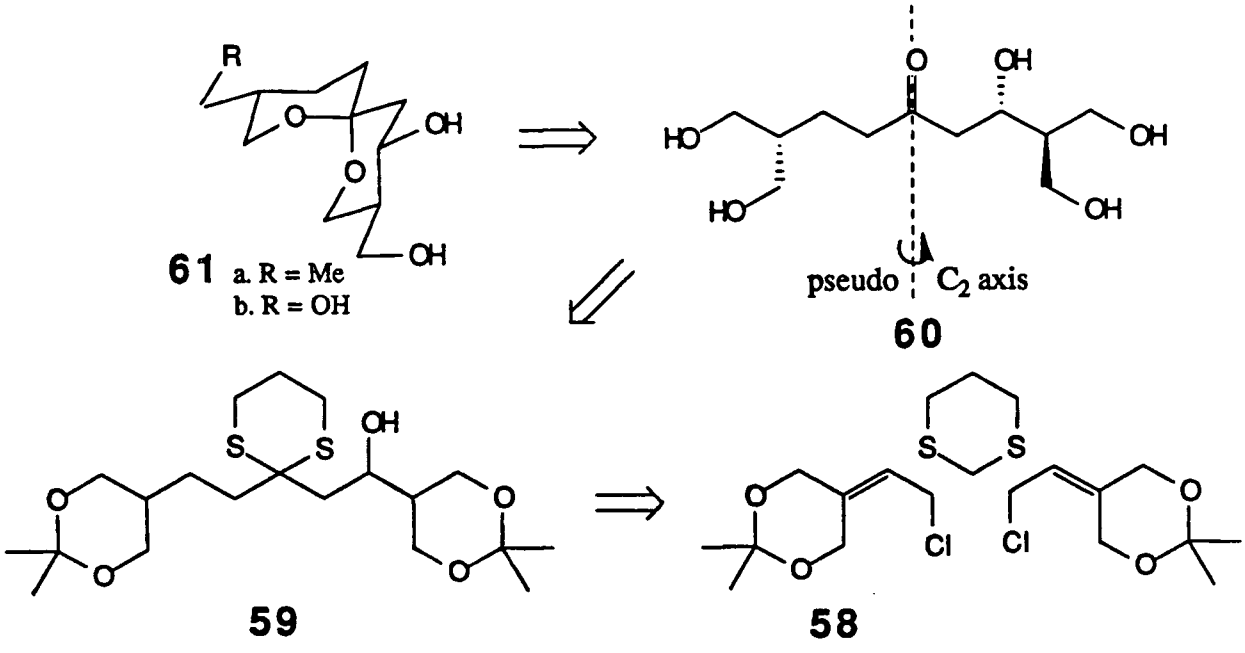


Ionomycin **1**



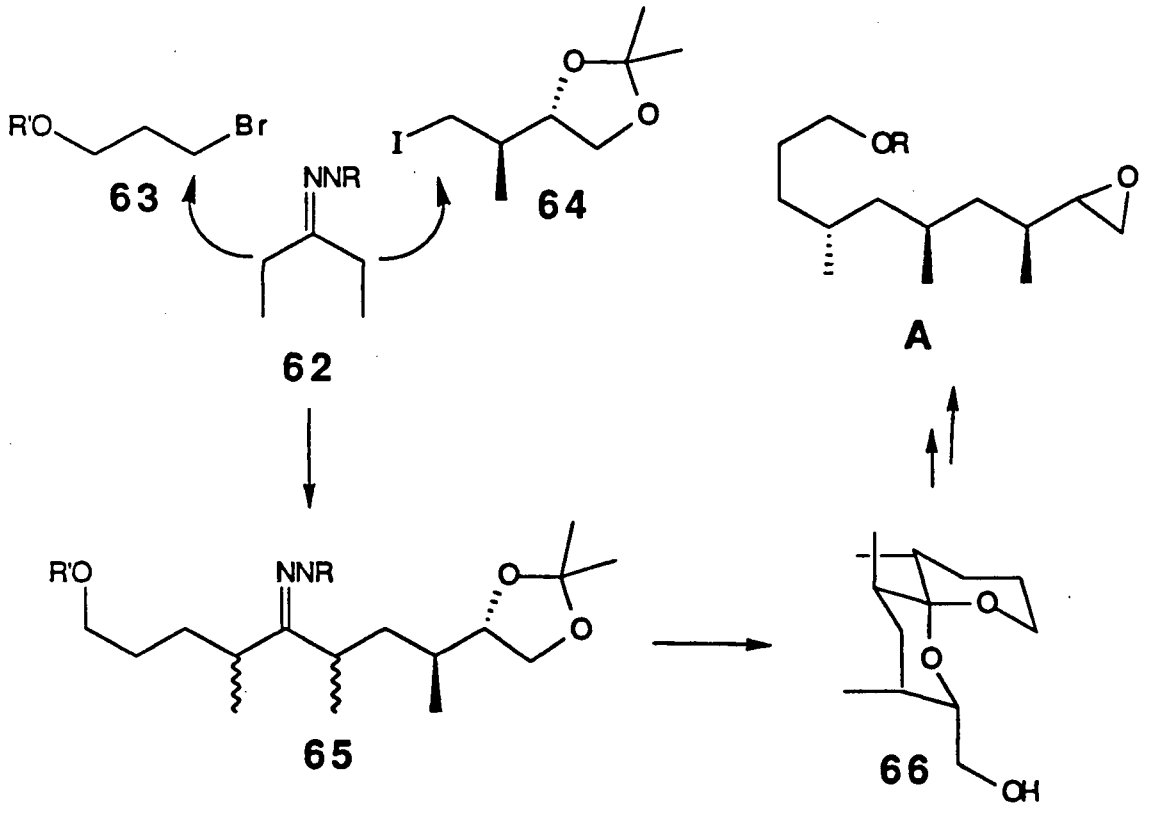
Scheme 20. Retrosynthetic plan for ionomycin.

C and D fragments, and coupling of the AB and CD segments would yield ionomycin's carbon skeleton. During this retrosynthetic analysis we recognized some elements of pseudo-symmetry in fragments A and B. Recognizing elements of symmetry, or pseudo-symmetry in the target molecule can allow one to synthesize two or more fragments via a common intermediate which may greatly reduce the number of steps. An example of this concept is depicted in Scheme 21 for a synthesis of talaromycin B.[56] The authors made elegant use of a pseudo C_2 axis of symmetry in the acyclic structure 60. This led them to join two molecules of a single alkylating agent, chloride 58, via 1,3-dithiane to give the acyclic precursor 59. After cyclization of 60 the two terminal hydroxyl groups were differentiated using the single 1,3-diol relationship found in 61b which was converted into talaromycin B 61a.[57]



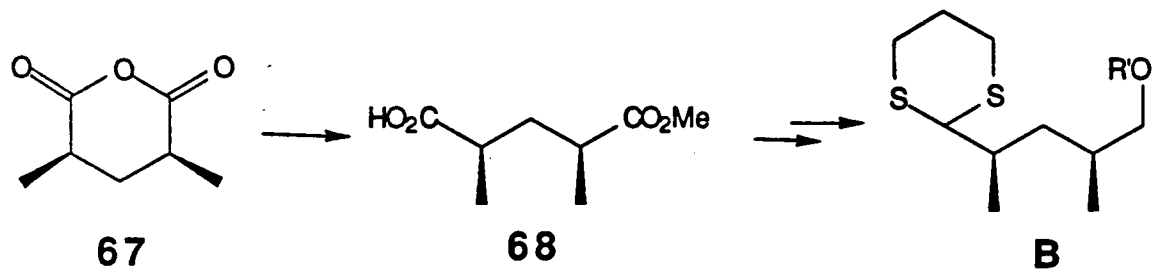
Scheme 21. Synthesis of talaromycin B.[56]

The elements of pseudo-symmetry contained in fragment A (C_1 to C_{10}) of ionomycin would permit us to synthesize it from the imine 62 which could be alkylated with two different alkyl halides (Scheme 22), namely the protected bromopropanol 63 and the iodide 64,[58] to give compound 65 as a mixture of stereoisomers. The stereochemistry at two of the carbons bearing a methyl group, corresponding to C_4 and C_6 in ionomycin, could be controlled by equilibration of the spiroketal 66.[59] Ring opening of 66 and subsequent functional group manipulations would give fragment A of ionomycin.



Scheme 22. Outline of a route to fragment A of ionomycin.

Fragment B (C_{11} to C_{15}) could be constructed from the symmetric meso-2,6-dimethylglutaric anhydride (67).[60] Hydrolysis of the anhydride 67 would give the half acid 68 (Scheme 23), which has been resolved.[61] The half acid 68 could be converted to fragment B by a series of reductions and protections.



67 68 B

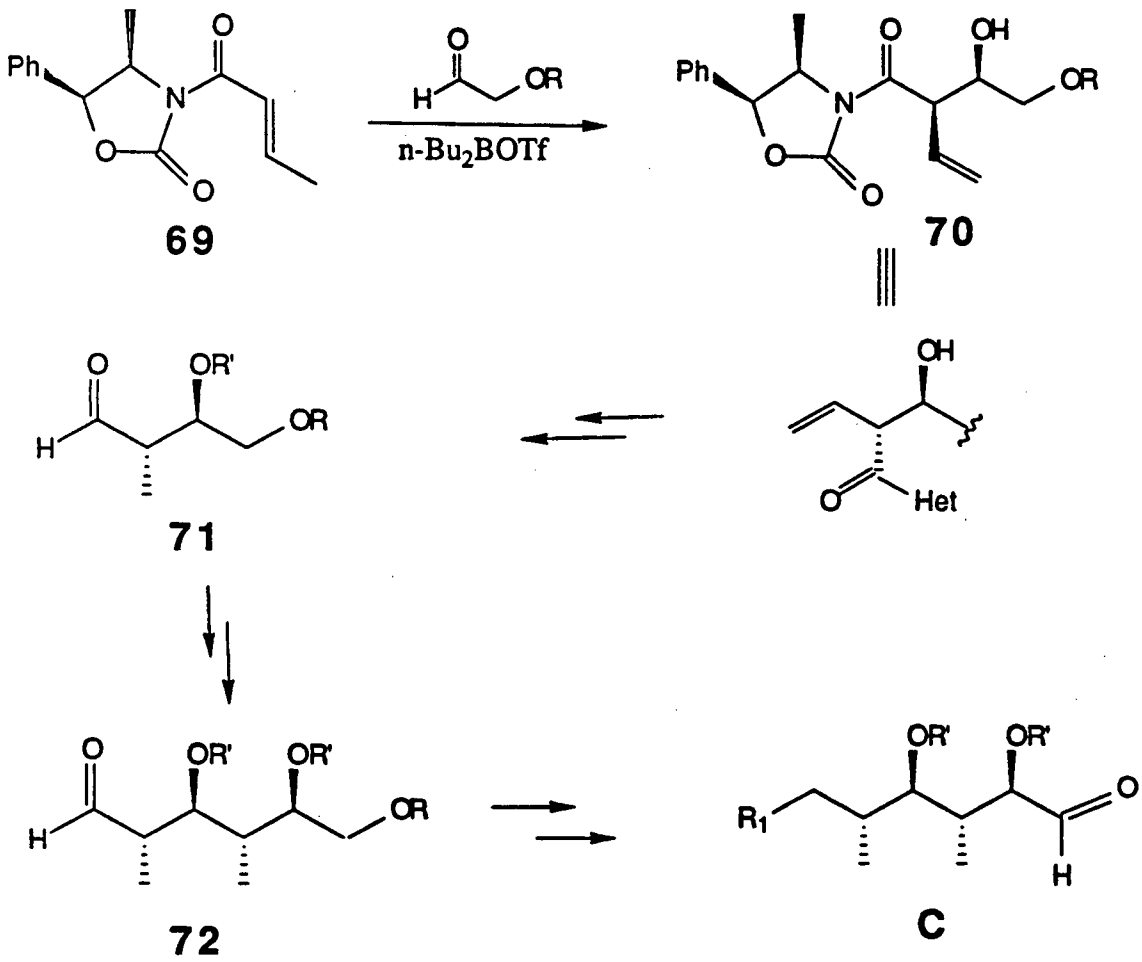
Scheme 23. Outline of a route to fragment B of ionomycin.

IV.B. Synthesis of Fragments C (C_{16}-C_{22}) and D (C_{23}-C_{32})

Repetitive units are occasionally encountered in large natural products. For example, many compounds of polyketide origin contain a series of alternating alkyl and hydroxyl groups or a series of alkyl groups in the 1,3 relationship. These units can be synthesized very effectively by a sequence of repetitive reactions. Such methods greatly reduce the risk of an impasse in the synthetic scheme because of their repetitive nature. Fragments C (C_{16} to C_{22}) and D (C_{23} to C_{32}) could be prepared using repetitive sequences of reactions as will be described in this section.

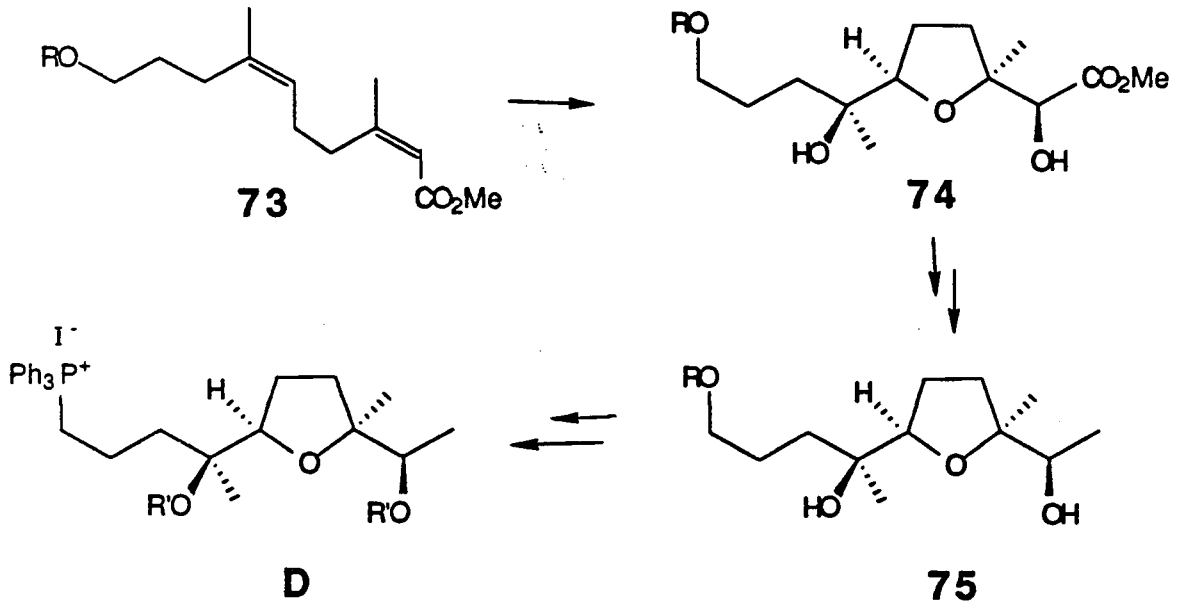
We felt that the uniquely high enantioselectivity of the asymmetric aldol methodology developed by Evans and coworkers[13] could be most effectively employed for the synthesis of fragment C. We planned to circumvent the problem of the syn *diastereoselectivity* by using

chiral crotonyl imide 69 in the condensation to give the aldol adduct 70 (Scheme 24). A rotation of 60° about the newly formed bond reveals the anti relationship between the secondary alcohol and the acyl group. Reduction of the acyl group to the corresponding methyl group followed by oxidative cleavage of the olefin would afford aldehyde 71. A repetition of this sequence of steps would give aldehyde 72. Further functional group manipulations would lead to fragment C.



Scheme 24. Outline of a route to fragment C of ionomycin.

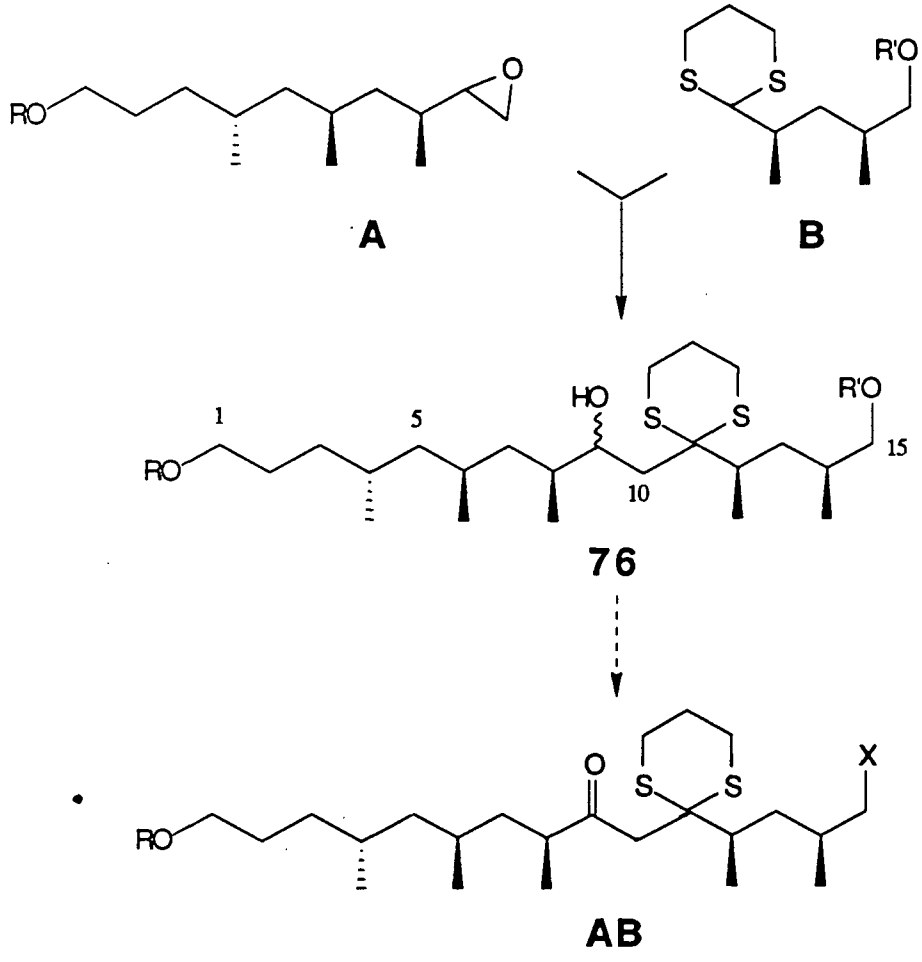
We planned to utilize the oxidative permanganate cyclization of 1,5-dienes to tetrahydrofurans to synthesize fragment D (Scheme 25). The appropriate diene 73 could be constructed by repetition of a sequence of reactions that we developed a few years ago and that allows for the stereospecific introduction of the isoprene unit. This sequence (see Scheme 29, p. 40) was used in our synthesis of two of the three isomeric components of the San Jose scale pheromone.[62] Cyclization of diene 73 (Scheme 25) could provide tetrahydrofuran 74 with all the asymmetric centres having the desired relative stereochemistry. Reduction and protection of 74 would give 75 which could be transformed into fragment D of ionomycin.



Scheme 25. Outline of a route to fragment D of ionomycin.

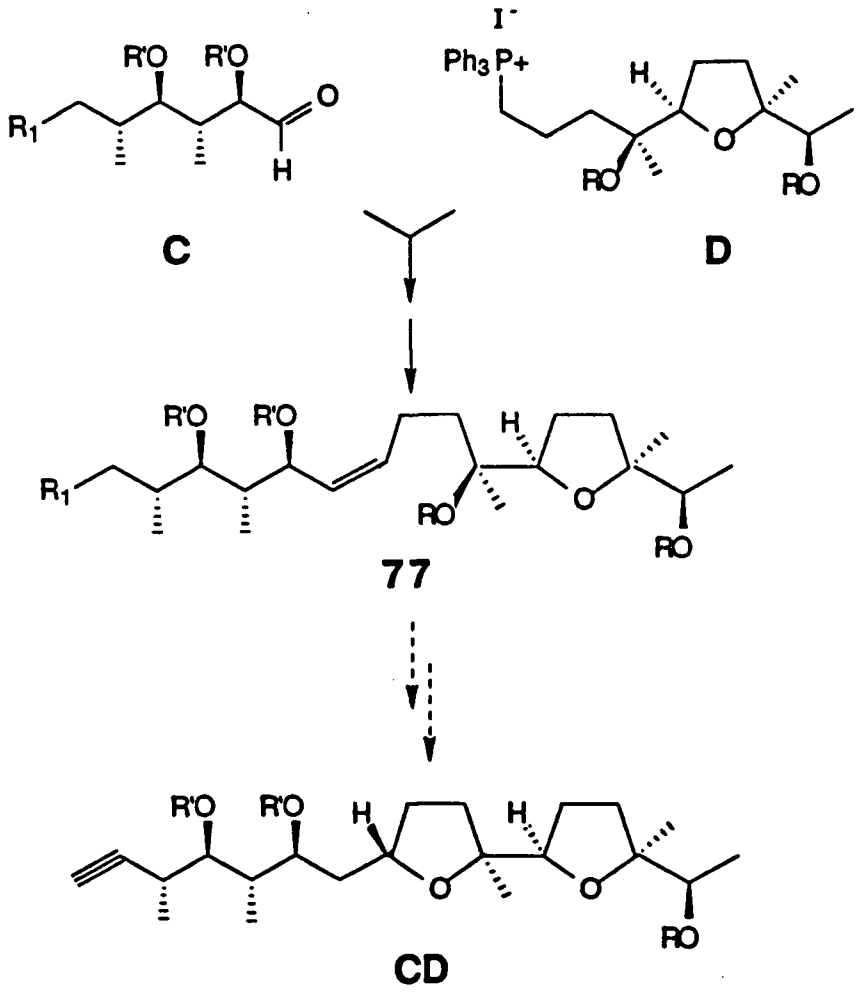
IV.C. Synthesis of Segments AB and CD

After the successful synthesis of the four fragments of ionomycin we would set about the task of assembling them into the final molecule. Fragments A and B would be joined by alkylation of the anion of the dithiane in fragment B with the epoxide in fragment A (Scheme 26) to afford ß-hydroxy dithiane 76. The fragment would then be prepared for its coupling with the CD section by a series of oxidations and protections and by converting the protected alcohol at C_{15} (Scheme 26) into a leaving group such as an iodide.



Scheme 26. Plan for the preparation of segment AB.

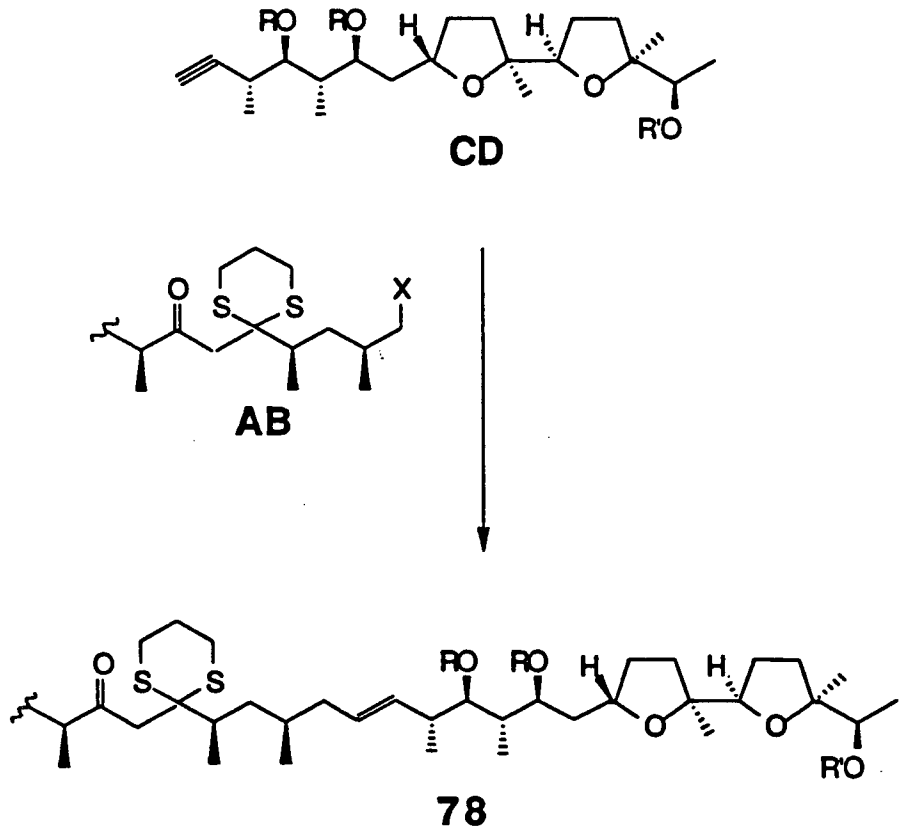
Fragments C and D would be coupled by using the Wittig reaction (Scheme 27) to afford alkene 77. The alcohols in 77 would be deprotected and an oxymercuration or other electrophilic cyclization could be used to introduce the second tetrahydrofuran ring. The segment CD would then be prepared for the final assembly with segment AB by protecting its secondary alcohol and converting the left hand side of the molecule into an acetylene group (Scheme 27).



Scheme 27. Plan for the preparation of segment CD.

IV.D. Coupling of Segments AB and CD

We intended to couple segments AB and CD via the hydrometalation of the acetylene moiety in segment CD and subsequent alkylation of the resulting vinyl aluminate with fragment AB to generate the desired trans double bond in compound 78 (Scheme 28). A series of deprotections would then liberate the ultimate target: ionomycin.



Scheme 28. Plan for the coupling of segments AB and CD.

RESULTS AND DISCUSSION

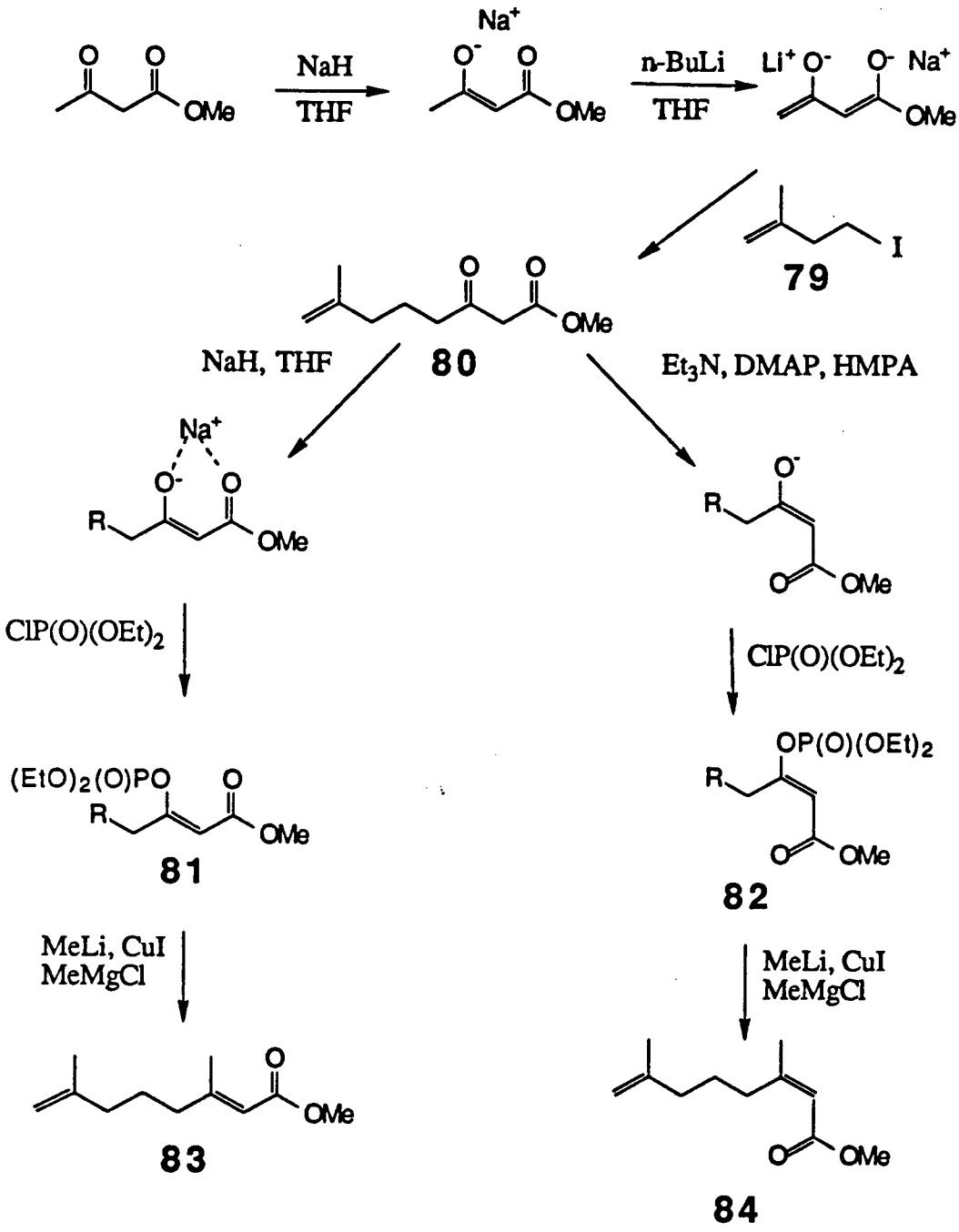
I. Synthesis of the Four Fragments of Ionomycin.

In the following discussion is described our synthesis of the four fragments of ionomycin, starting with fragments D and C which are detailed in this section. The successful coupling of these two fragments, and of the A and B fragments is then described in the following section. The plan for the final union of the CD and AB fragments is described in the last section of this thesis.

I.A. Synthesis of Fragment D (C_{23}-C_{32})

The synthesis of fragment D of ionomycin containing a tetrahydrofuran ring was achieved in a stereoselective manner using an oxidative permanganate cyclization of an appropriately substituted 1,5-diene (Scheme 25).[39] The first task was to prepare a diene such as 73 with good control of the geometry of the double bonds as they are the controlling factor in the stereoselectivity of the cyclization.[35] This was achieved using a sequence of reactions that allows for the stereospecific construction of isoprene units (Scheme 29).[62] The key step involves an addition-elimination reaction of a higher order magnesiocuprate to an enol phosphate with retention of geometry about the double bond. This sequence consists of three reactions. In the first step the dianion of methyl acetoacetate[63] – generated with sodium hydride (1 equiv) followed by n-butyllithium (1 equiv) in tetrahydrofuran – is alkylated with an electrophile, for example iodide 79, exclusively at the more reactive gamma position to give ß-keto ester 80. In tetrahydrofuran as the solvent, no alkylation at the alpha position results. Sodium methoxide in methanol are the usual conditions required for the alpha carbon alkylation of ß-keto esters.

In the second stage the resulting ß-keto ester is selectively converted to either the (E) or the (Z)-enol phosphate. For the preparation of the (Z)-enol phosphate 81, sodium hydride in tetrahydrofuran is used to generate the enolate of 80.[64] It has been proposed that the two



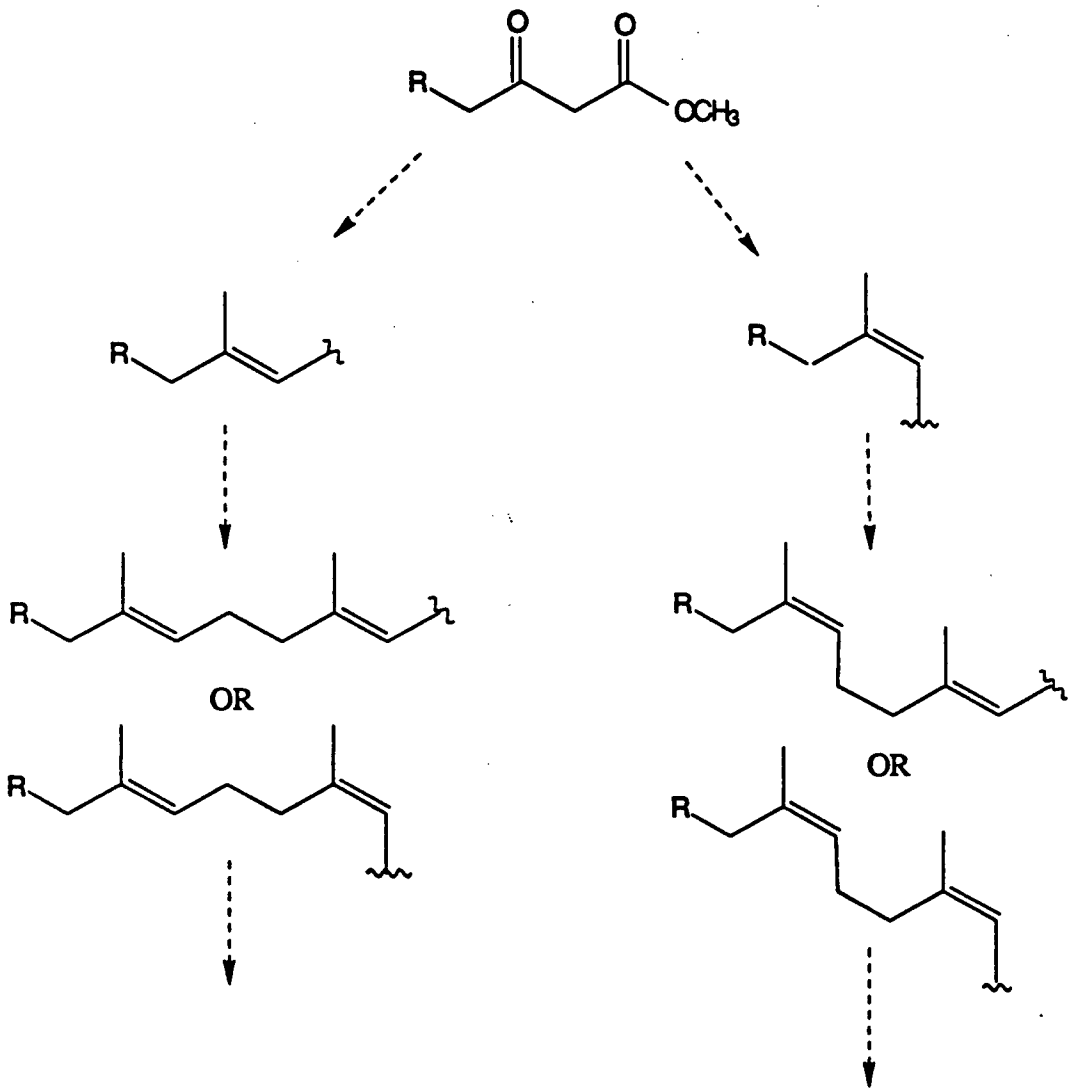
Scheme 29. Synthesis of two of the components of the San Jose scale pheromone.[62]

oxygens of the enolate chelate the sodium ions and hold the enolate in the cis geometry.[65] Trapping of the enolate with diethyl chlorophosphate gives the (Z)-enol phosphate 81. On the other hand, the (E)-enol phosphate 82 is obtained by treating the ß-keto ester 80 with triethylamine as the base in a polar solvent such as N-hexamethylphosphoramide. Trapping of this enolate with diethyl chlorophosphate gives the (E)-enol phosphate 82. In this case it is suggested that the counter ion is solvated and the enolate exists in the trans, or (E), geometry in which the two oxygen dipole moments are opposed.[65]

In the last and key step of this sequence, the two enol phosphates 81 and 82 are separately reacted with a higher order magnesiocuprate generated by treatment of cuprous iodide with 1 equivalent of methyllithium and 1.66 equivalents of methylmagnesium chloride,[66] to yield the methylated products 83 and 84 respectively with retention of the geometry about the double bond (Scheme 29). Mixed magnesiocuprates have been used for the selective 1,4-addition of alkyl groups to α,ß-unsaturated ketones.[67] The higher order magnesiocuprate described above has been found to be an excellent reagent for the selective conversion of a ß-keto ester into the methylated α,ß-unsaturated ester with a high degree of stereospecificity. In some cases, selectivities as high as 49:1 were obtained.[62] Dimethyllithium cuprate also effects this transformation, but with decreased selectivity.[65] The stereoselectivity is temperature dependent and it is also sensitive to the purity of the cuprous iodide used.[68]

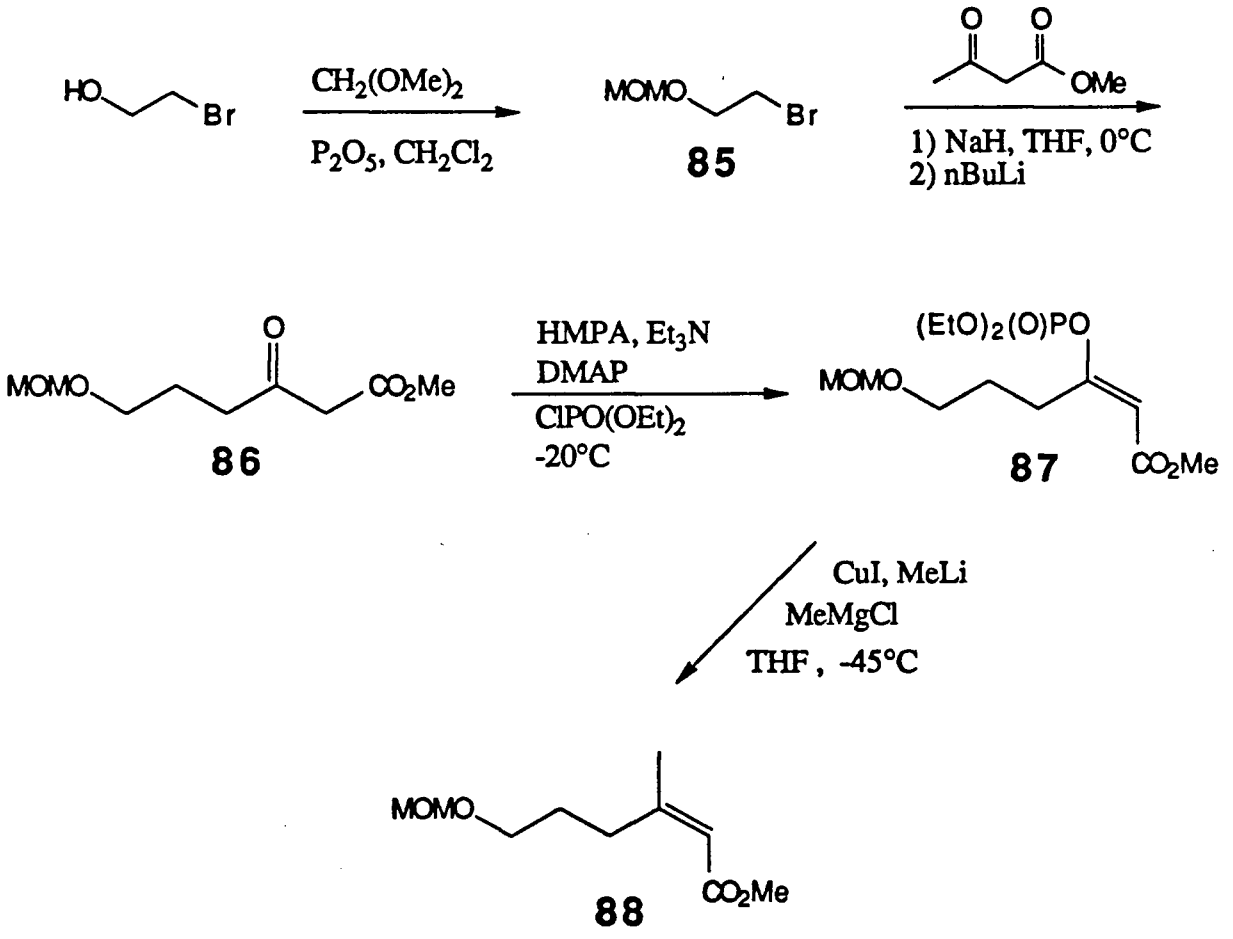
Studies have demonstrated that the ratio of the reagents that constitute the magnesiocuprate reagent, namely cuprous iodide, methyllithium, and methylmagnesium chloride, is important in the selectivity of the reaction.[66] Optimum selectivities were obtained when a ratio of 3:3:5, respectively, of those reagents was used. The structure and composition of the active organometallic species in solution, although not known, must be affected by this ratio. Also interesting is the fact that the use of methylmagnesium chloride gives a better selectivity than the corresponding bromide or iodide.[66] The counter ion possibly affects the size and aggregation of the active species and therefore changes its reactivity and selectivity.

Additional olefinic units can be added to the first one by converting the ester group into a bromide or sulfonate and then repeating the sequence of reactions described above. Note that with this sequence, the stereospecific introduction of an isoprenoid unit is achieved (Scheme 30). This was, to our knowledge, the first time that an isoprene unit was introduced in a stereospecific manner.



Scheme 30. Isoprenoid units can be constructed stereospecifically using the ß-keto ester chemistry.

Using this strategy we set about to prepare the required 1,5-diene. Protection of bromoethanol as its methoxymethyl ether was effected by a trans-acetalization reaction, using dimethoxymethane and P_2O_5 in dichloromethane to give acetal 85 (Scheme 31).[69] This method was used since the conventional method of using chloromethoxymethane and a strong base is precluded in this case because of epoxide formation. Bromide 85 was then used to alkylate the dianion of methyl acetoacetate as described earlier and an 80% yield of ß-keto ester 86 was obtained.



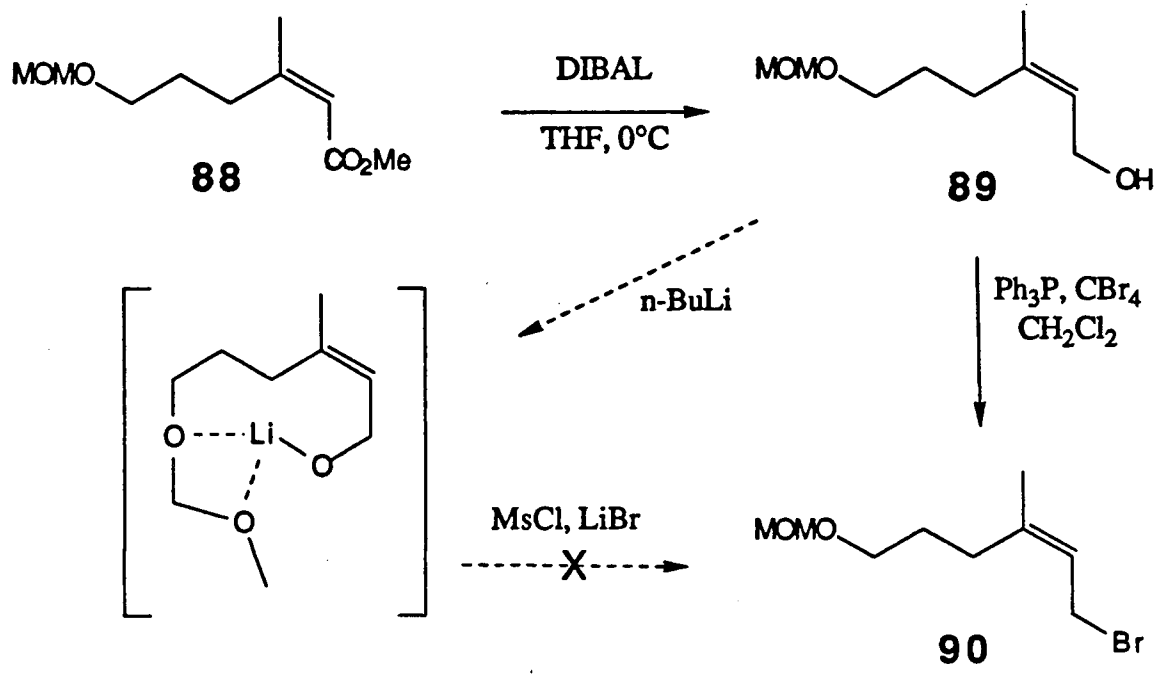
Scheme 31. Synthesis of the first olefinic moiety of the 1,5-diene.

ß-Keto ester 86 was treated under the conditions to generate its (E)-enol phosphate to give a quantitative yield of 87 with no detectable traces of the (Z)-isomer (^{1}H NMR analysis). The two isomers can be readily differentiated by proton NMR spectroscopy; earlier studies with similar compounds showed that the (E)-isomer has the vinylic hydrogen resonance around δ 5.8 whereas the corresponding signal for the (Z)-isomer usually is around δ 5.3 .[65] The vinylic hydrogen in 87 gave a signal at δ 5.90 in the proton NMR spectrum.

When compound 87 was subjected to the magnesiocuprate reaction conditions, the (Z)-methylated α,ß-unsaturated ester 88 was produced in 68% yield, for the last two steps. At -45 °C the reaction was complete in 12 h and gave the desired geometrical isomer 88 in > 96% isomeric purity (GLC analysis).

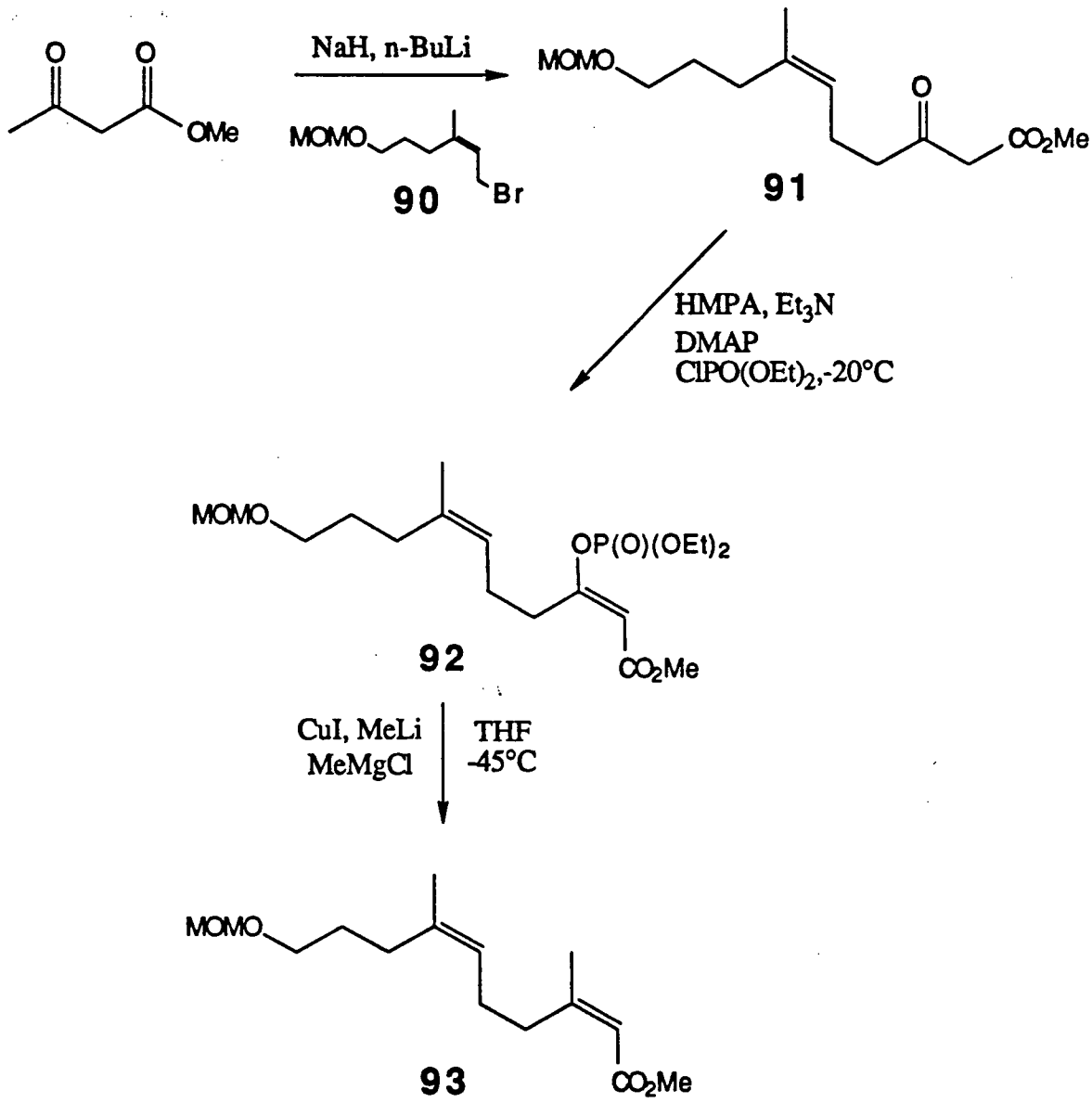
A side product which has a mass spectrum (obtained from a GLC-mass spectrum) very similar to that of starting ß-keto ester 86 was produced in ca. 8% yield. However when co-injected in a GLC capillary column, the side product and ß-keto ester 86 proved to be different compounds. Further characterization of this side product was difficult because it could not be separated from the desired product by normal chromatographic techniques. The side product was removed in the following reduction step.

Ester 88 was reduced to allylic alcohol 89 with diisobutylaluminium hydride in 82% yield (Scheme 32). This alcohol in turn was transformed into the allylic bromide 90 by treatment with triphenylphosphine and carbon tetrabromide in dichloromethane. Similar bromides have been prepared using n-butyllithium, lithium bromide, and methanesulfonyl chloride. However this method seems to have a serious drawback in the case of compound 89, since the reaction never went to completion (typically 5-10% of starting material was recovered). A possible explanation is that the methoxymethyl ether oxygens chelate the lithium salt of the alcohol (Scheme 32) thereby interfering with the mesylation step. It is interesting to note that the tetrahydropyran analogue of 89 did not show this effect.



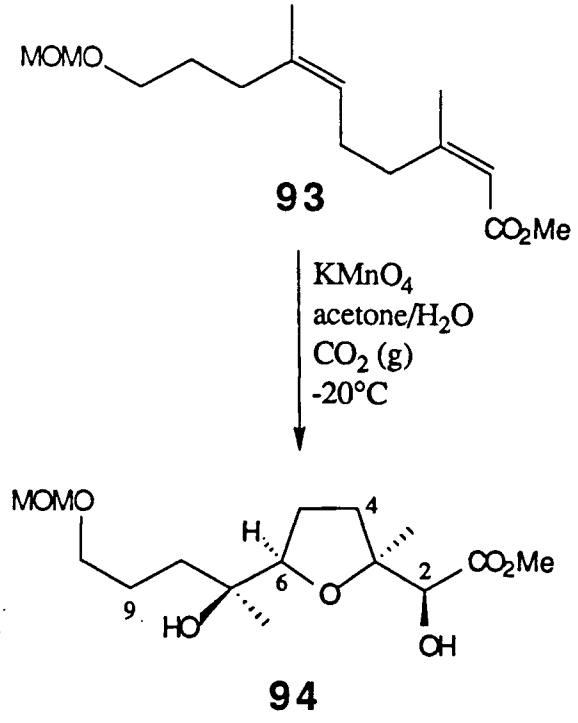
Scheme 32. Conversion of the ester group to a bromide.

To complete the synthesis of 1,5-diene 93, the dianion of methyl acetoacetate was alkylated with bromide 90 to give ß-keto ester 91 in 86% purified yield (Scheme 33). Using the reaction sequence described earlier, ß-keto ester 91 was transformed into the (E)-enol phosphate 92 which was converted to the desired (Z,Z)-1,5-diene 93 in 74% yield for the last two steps. Analysis by capillary GLC revealed the presence of ~ 8% of the combined three possible geometrical isomers of 93. One isomer, presumably the (E,E)-, was present in much smaller amounts than the other two by-products. Normal chromatographic separation of the four geometrical isomers was difficult and for that reason they were carried along in the following cyclization step and were separated at a later stage.



Scheme 33. A repetition of the ß-keto ester sequence of reactions on bromide 90 to yield the 1,5-diene 93.

Based on studies by Walba and Edwards,[39] we anticipated that the permanganate cyclization of diene 93 would proceed to give tetrahydrofuran 94 with the desired stereochemistry at the four asymmetric centres. Only one chiral centre would then remain to be controlled in fragment D of ionomycin. The cyclization of diene 93 with potassium permanganate in a mixture of 10% water in acetone at -20 °C proceeded as expected to give the tetrahydrofuran 94 in 52% yield after chromatography (Scheme 34). Analysis by capillary GLC showed that the product contained > 93% of one isomer. This result was confirmed by high-field proton NMR spectroscopy. Although it was possible to partially separate one of the minor isomers, their complete separation was effected at a later stage. Based on the fact that the starting diene 93 was ca. 92% isomerically pure, we concluded that the cyclization proceeded with complete stereoselectivity as predicted by Walba's results.[39]



Scheme 34. Cyclization of the 1,5-diene 93 to the cis-tetrahydrofuran 94.

Proton NMR spectroscopy was very useful in identifying compound 94. The two characteristic resonances for the methine protons, at positions 2 and 6 (Scheme 34), were readily assigned, namely the singlet at δ 4.10 and the well resolved doublet of doublet at δ 3.86, both integrating for one hydrogen. Two low-field singlet methyl resonances at δ 1.28 and δ 1.24 indicated that these methyls were also attached to a carbinol or an ether carbon. The carbon-13 NMR spectrum confirmed all of the above results and was in agreement with the proposed structure for 94. The high resolution mass spectrum and micro analysis for carbon and hydrogen confirmed that the reaction proceeded to give a tetrahydrofuran and not a tetrol.

A nuclear Overhauser effect difference spectroscopy (NOEDS) experiment showed the cis relationship between the angular methyl and methine proton of the tetrahydrofuran ring in 94. Upon irradiation of the angular methine proton, the two methyl signals were enhanced as well as the signals of some of the methylene protons (Figures 4 and 5). It was difficult in this experiment to selectively irradiate the methine proton at δ 3.86 without irradiating the nearby methyl ester signal at δ 3.81. Thus there was the possibility that it was the irradiation of the methyl ester signal that gave the observed enhancement of the angular methyl resonance.

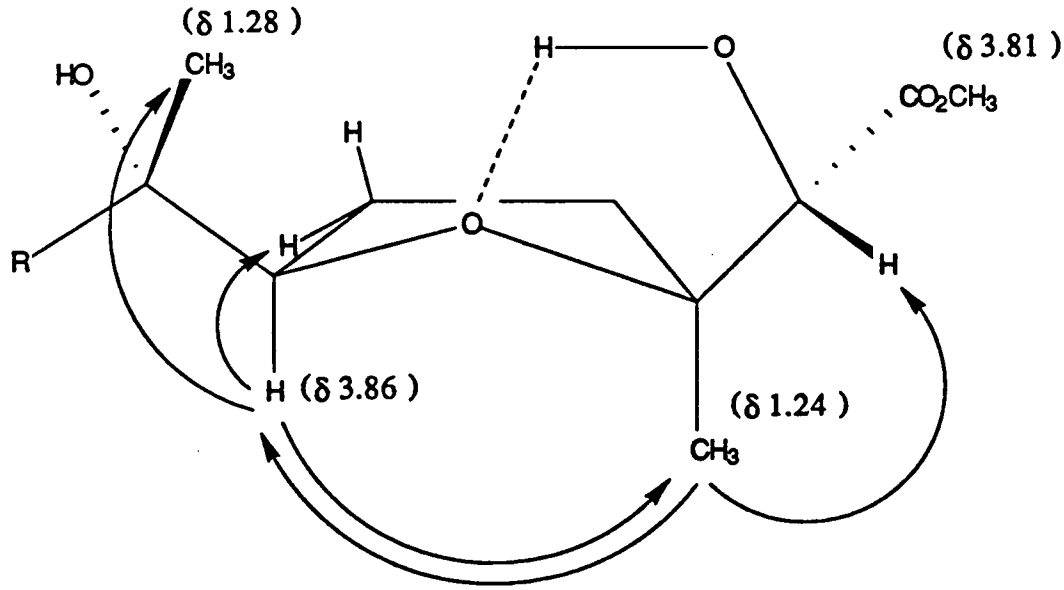


Figure 4. Possible conformation of 94 based on NOEDS experiments. Arrows start at the irradiated protons and show the protons with enhanced NMR signals.

However in a second NOEDS experiment, irradiation of the angular methyl at δ 1.24 (which was accompanied by irradiation of the methyl at δ 1.28) did not give rise to any significant enhancement of the methyl ester signal at δ 3.81, but did give rise to an enhancement of the methine proton signal at δ 3.86. This demonstrated that the enhancement of the angular methyl signal at δ 1.24 in the first NOEDS experiment was indeed caused by irradiation of the methine proton. The tetrahydrofuran 94 could exist in the conformation shown in Figure 4 where hydrogen bonding between the secondary alcohol and the oxygen of the tetrahydrofuran ring holds the methyl ester away from the angular methyl group. Proof of the relative stereochemistry of the other chiral centres at C_2 and C_7 was not possible by direct means in 94 and had to await a later stage.

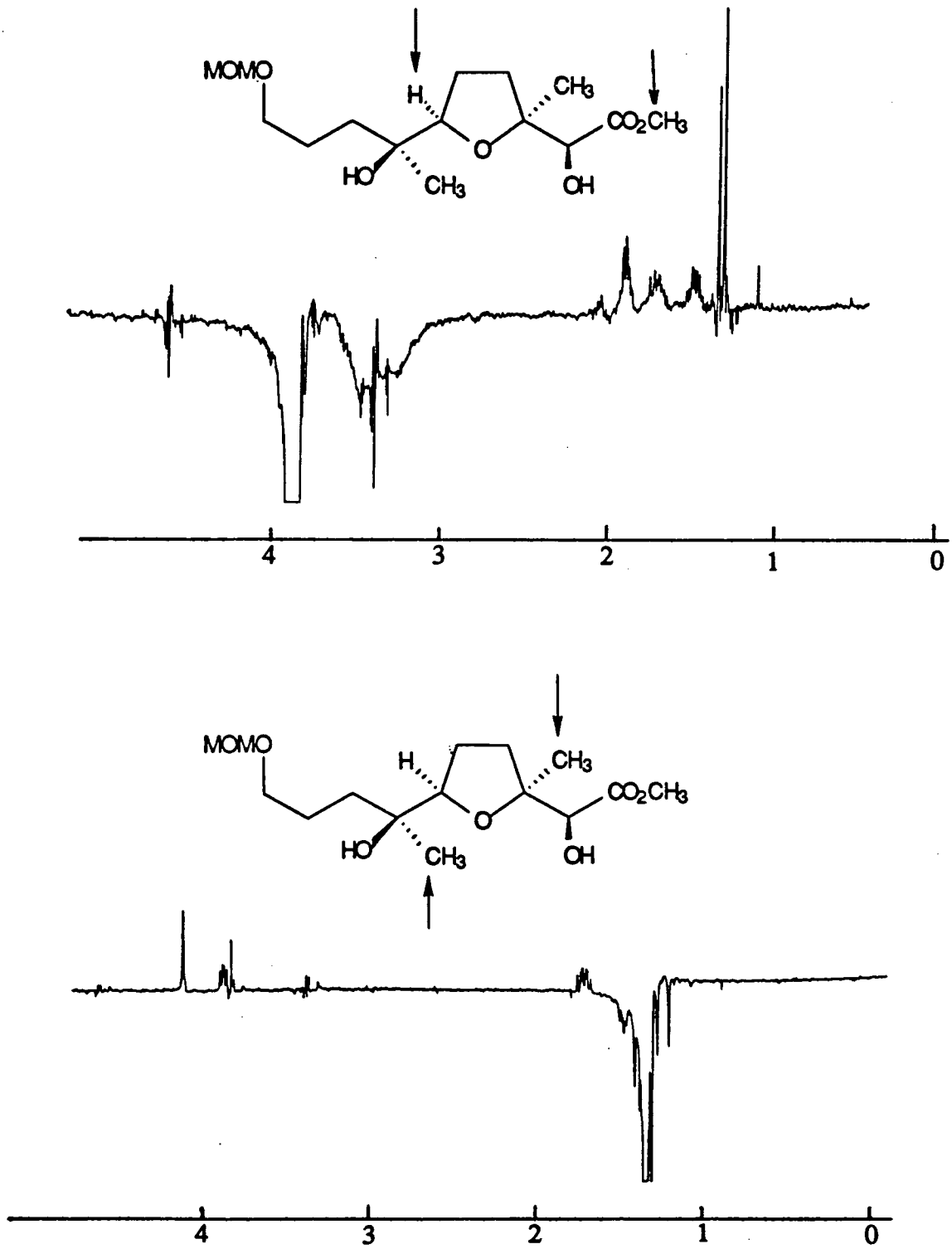
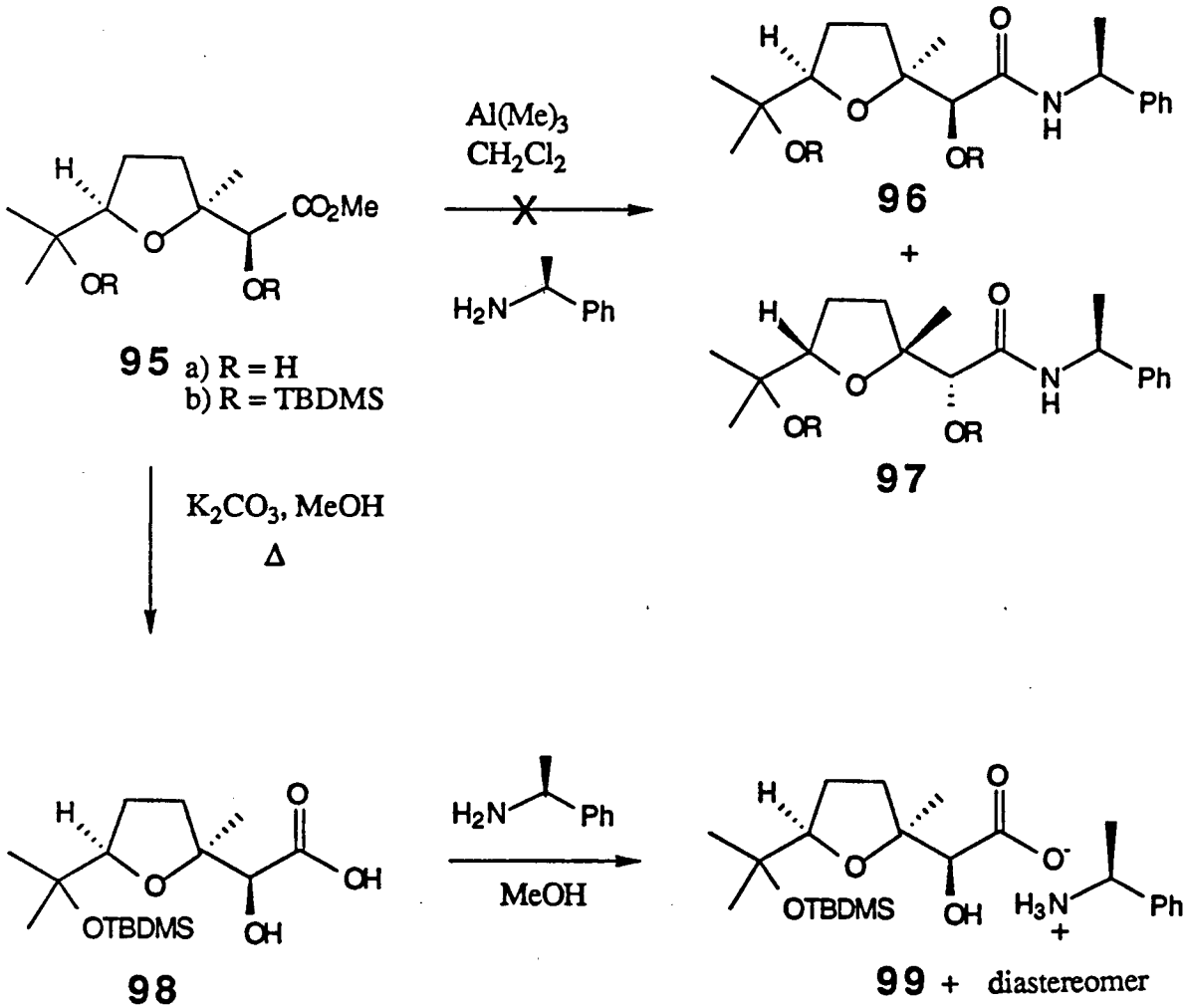


Figure 5. ^{1}H NMR spectra from the NOEDS experiment of 94. The irradiated protons are shown with arrows.

Tetrahydrofuran 94 formed in the permanganate cyclization was a racemic mixture and had to be resolved.[70] The tetrahydrofuran 95a (Scheme 35) was prepared from the permanganate cyclization of the appropriate 1,5-diene ester as a simpler model for the resolution. The required 1,5-diene was in turn prepared by the ß-keto ester dianion reaction sequence described earlier starting from isoprenyl bromide. The tetrahydrofuran 95a could not be converted to the diastereomeric (+)-methylbenzylamides 96a and 97a by the one-step procedure of Weinreb[71] (trimethylaluminium in dichloromethane). Only starting material was recovered from this reaction, even after refluxing for 24 h. The two hydroxyl groups in 95a were protected as their bis-t-butyldimethylsilyl ethers to give compound 95b in excellent yield

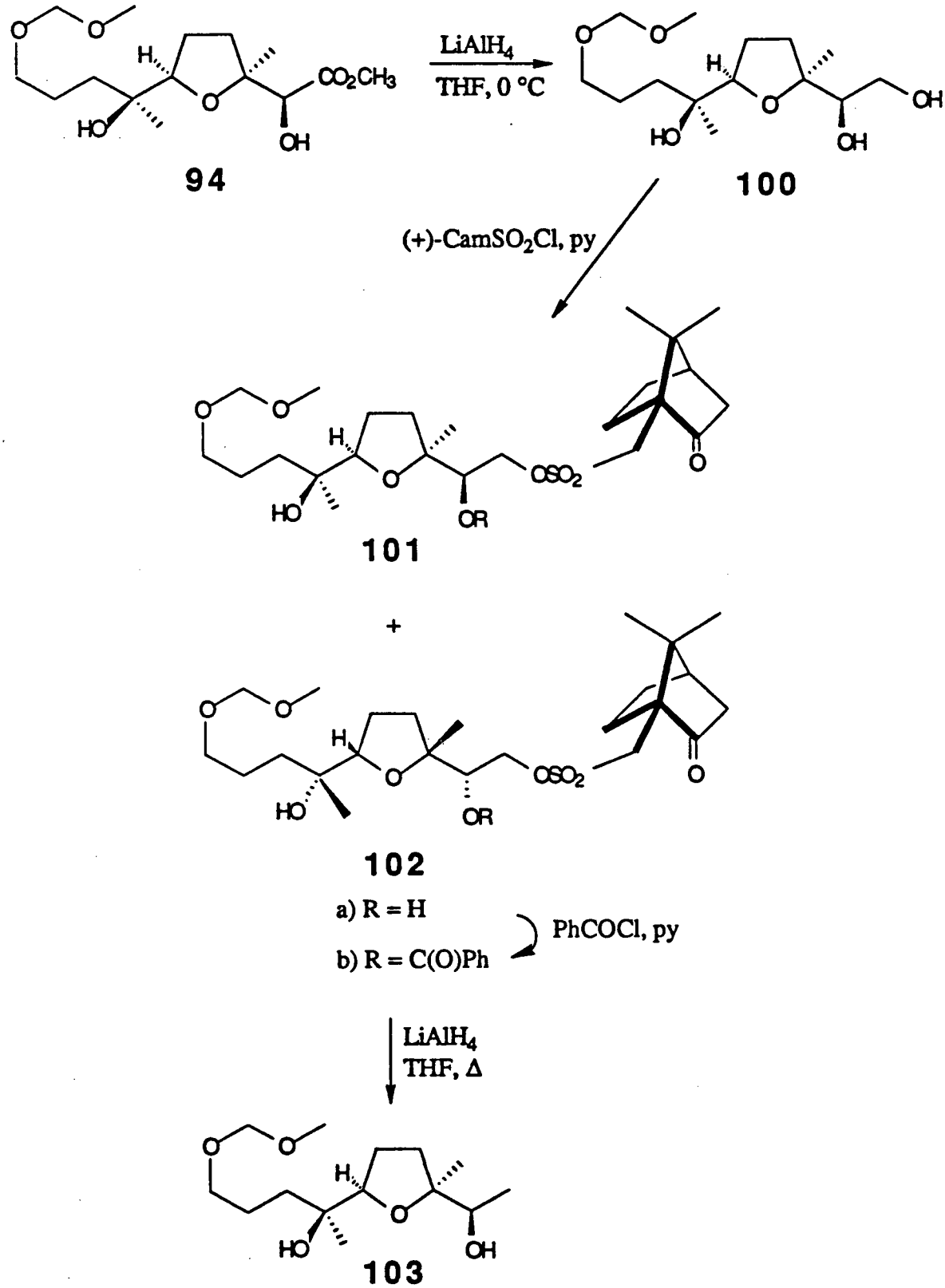


Scheme 35. Model study resolution of tetrahydrofuran 95.

and this was submitted to the same reaction conditions as those for the corresponding diol 95a. Again only starting material was recovered from the reaction.

In a second attempt at resolving tetrahydrofuran 95b, the ester group was hydrolysed with potassium carbonate in refluxing methanol to give 53% of the acid 98. The proton NMR spectrum of 98 indicated the cleavage of one of the silyl protecting groups. Presumably the cleavage occurred to give the secondary alcohol by anchimeric assistance of the neighboring acid group cleaving the silyl ether to form the alcohol and the silyl ester which is in turn hydrolysed in the reaction conditions. Preferential crystallization of the (+)-methylbenzylamine salt of 98 was then attempted; treatment of acid 98 with (+)-methylbenzylamine in methanol at room temperature[72] gave the corresponding salt 99 as a viscous oil and all attempts to crystallize it failed. Hydroxy acid 98 was difficult to obtain in pure form and this could be the reason why the crystallization of the amine salt was not successful. The next obvious step was to try to make the (+)-methylbenzylamide from the acid 98 by standard methods. This was not done because another resolution method that appeared to be more efficient was investigated instead. This method is described in the following paragraphs.

One standard way of reducing an ester to the corresponding alkane is to first reduce it to the primary alcohol, convert the alcohol into a leaving group, usually a sulfonate or halide, and reduce the latter to the methyl group. We investigated the possibility that triol 100 (Scheme 36) would selectively react at the primary hydroxyl group with a chiral leaving group which could then function as a resolving agent and as the leaving group in the subsequent reduction. The (+)-camphorsulfonyl group seemed to be appropriate for this purpose. It has been used in the resolution of a variety of alcohols.[73] In addition alkylsulfonates are often used as leaving groups and can be reduced to the corresponding alkane with hydride reagents. The fact that the resolving agent could not easily be recycled after the resolution and reduction was not of great concern since it can be acquired relatively cheaply. Thus the ester in 94 was reduced to triol 100 with lithium aluminium hydride in tetrahydrofuran at 0 °C and the primary alcohol was selectively reacted with (+)-camphorsulfonyl chloride in pyridine at 0 °C to give

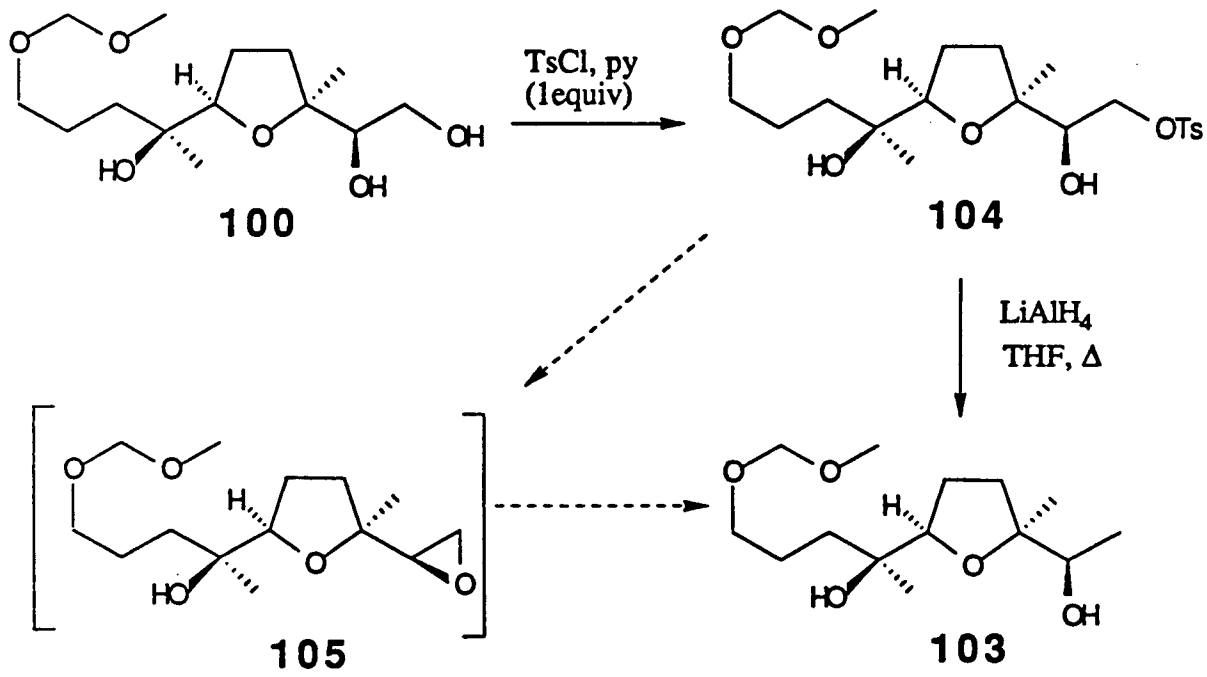


Scheme 36. Attempted resolution–reduction of the triol 100.

sulfonates 101a and 102a. None of the other regioisomers could be detected by ^1H NMR spectroscopy. Although the reduction of the camphorsulfonyl derivatives with lithium aluminium hydride in refluxing tetrahydrofuran proceeded very well to give the methyl compound 103, we were totally unable to separate the two diastereomers 101a and 102a. Chromatography on different supports and solvent systems was tried with no success. The secondary alcohol was derivatized as its chromophoric benzoate (101b and 102b) in order to make it detectable for HPLC separation. We hoped that the bulky benzoate group would enhance the steric interactions between the chiral carbon to which it is attached and the chiral camphorsulfonyl group, thereby increasing the conformational difference between the two diastereomers. Again no separation of the diastereomers 101b and 102b could be obtained. At this stage it appeared that the camphor group, although very bulky, was perhaps too far removed from the chiral centre to fulfill its function as a resolving agent. In retrospect it seemed that the (+)-methylbenzylamides 96 and 97 could suffer the same drawback and hence we decided to continue the synthesis and try to resolve the molecule at a later stage.

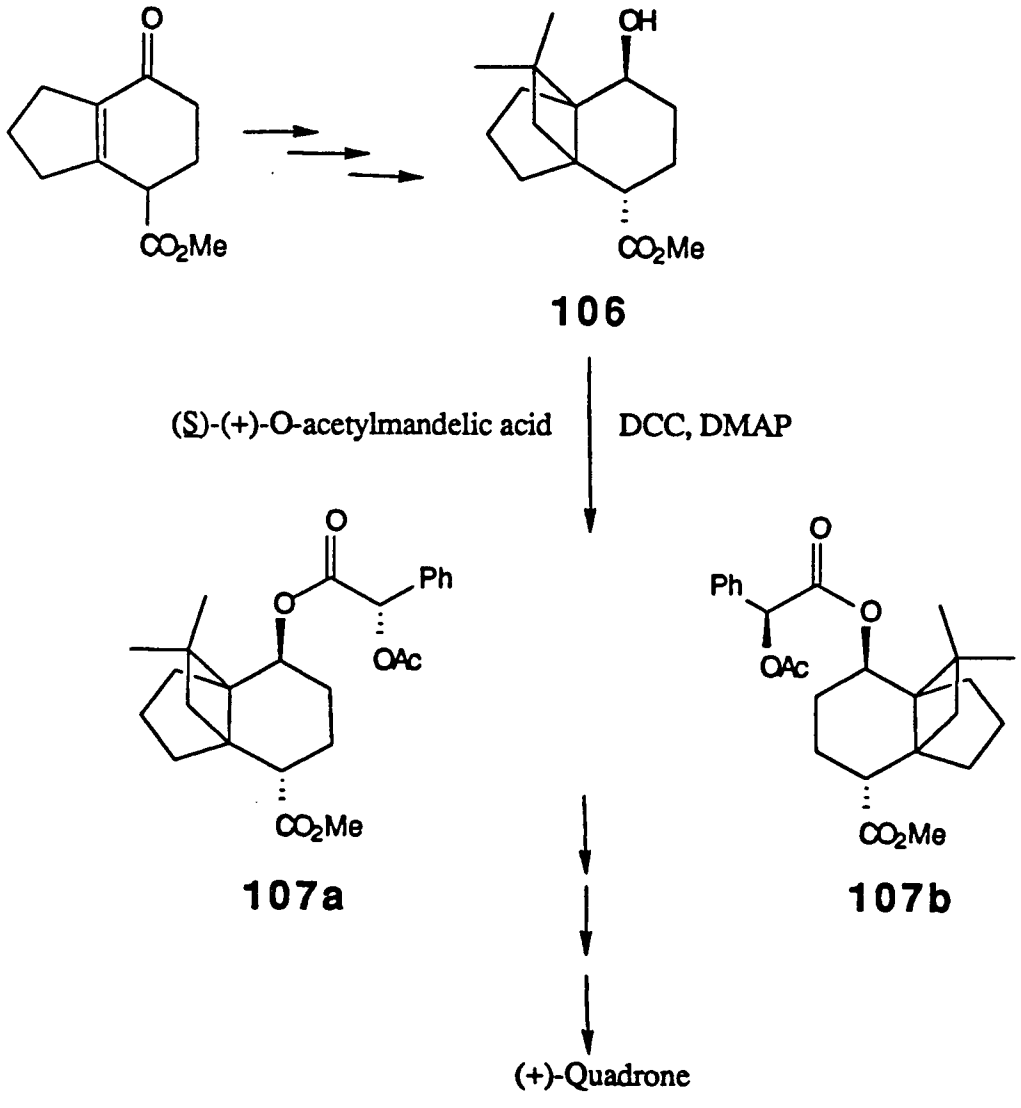
Thus triol 100 was selectively monotosylated at the primary hydroxyl with p-toluenesulfonyl chloride in pyridine to afford toluenesulfonate 104 in quantitative yield (Scheme 37). Reduction of this toluenesulfonate using lithium aluminium hydride in refluxing tetrahydrofuran gave diol 103 in 77% yield. The reduction with lithium aluminium hydride at room temperature was very slow. The reduction may proceed via epoxide 105 and its formation may require refluxing in tetrahydrofuran. Once formed the epoxide is then opened by hydride to give the desired product. Sodium borohydride in refluxing dimethylsulfoxide,[74] as well as lithium triethylborohydride in tetrahydrofuran,[75] were not satisfactory for this reduction.

It was at this stage that we were finally successful in resolving the precursor to fragment D of ionomycin by making the (S)-(+)-O-acetylmandelic ester of the secondary alcohol in 103.



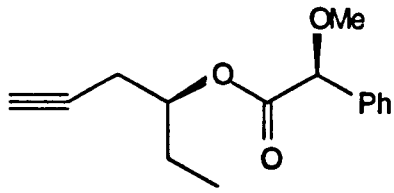
Scheme 37. Reduction of triol 100 to diol 103.

This resolving agent had been previously used by Smith and Konopelski in a synthesis of (+)-quadrone (Scheme 38).[76] Alcohol 106 was resolved with (S)-(+)-O-acetylmandelic acid. The absolute configuration of the diastereomer 107a was assigned by an X-ray crystallographic



Scheme 38. Resolution of 106 with (S)-(+)-O-acetylmandelic acid in a synthesis of (+)-quadrone.[76]

analysis. The closely related O-methylmandelic acid was utilized by Roy and Deslongchamps for the resolution of 5-hexyne-3-ol.[77] The assignment of the absolute configuration of the two diastereomers 108 and 109 was achieved using Mosher's method.[78]



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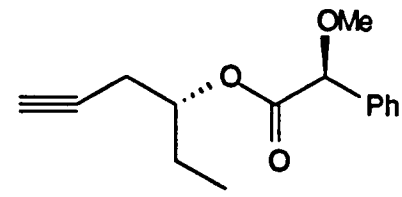
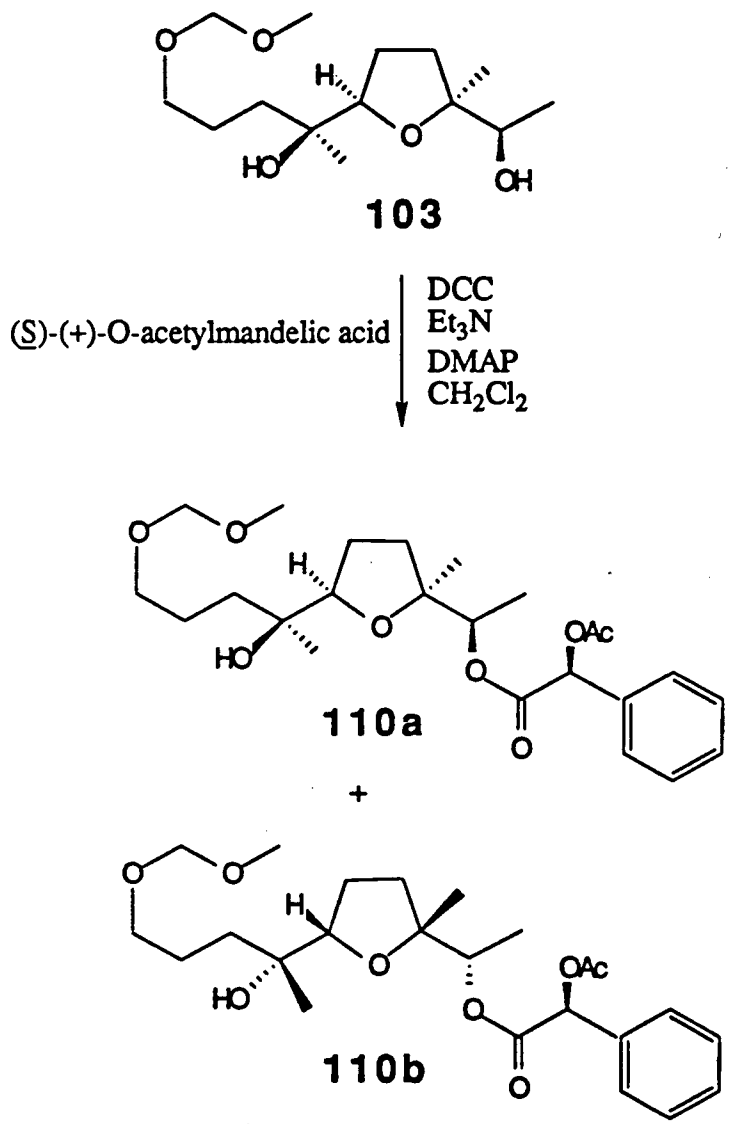


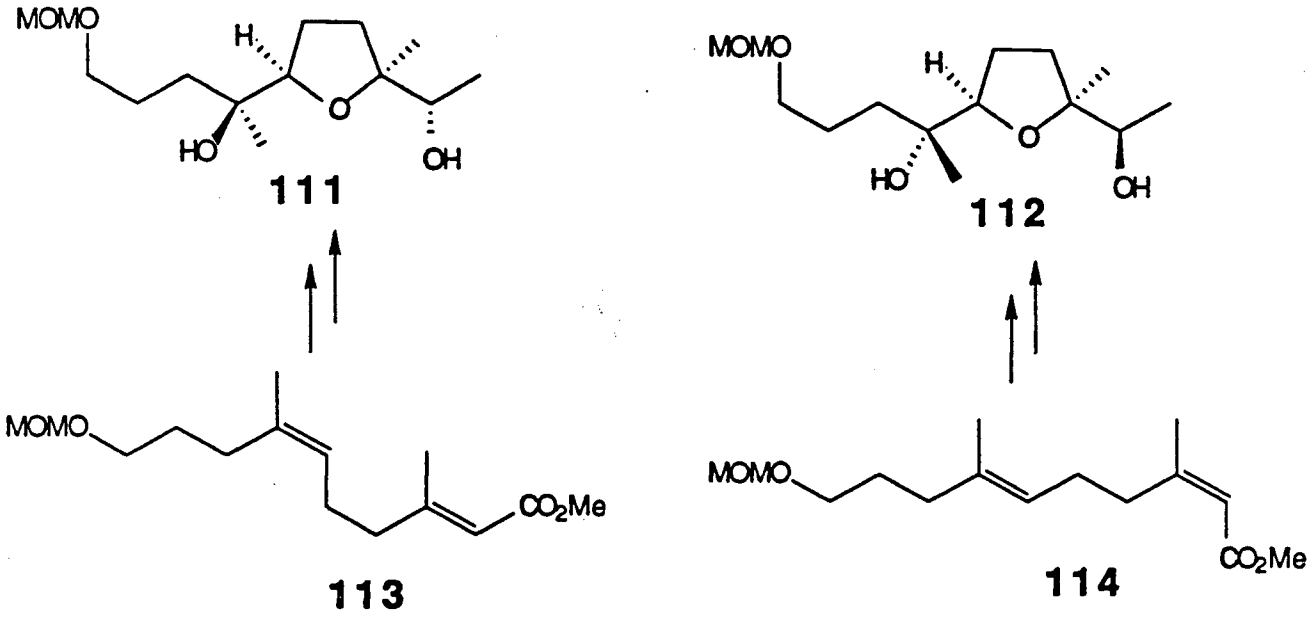
109

Racemic diol 103 was reacted selectively at the secondary alcohol with (S)-(+)-O-acetylmandelic acid[79] in the presence of 1,3-dicyclohexylcarbodiimide and dimethylaminopyridine in dichloromethane at 0 °C to afford the two diastereomers 110a and 110b that were separable by normal column chromatography on silica gel using hexane-acetone 6:1 as eluant (Scheme 39). The GLC trace of the crude mixture showed, in addition to the two main peaks of identical height, two pairs of smaller peaks that were probably due to the mandelic ester of the tetrahydrofuran isomers 111 and 112 (Scheme 40). These isomers would be



Scheme 39. Resolution of diol 103 with (S)-(+)-O-acetylmandelic acid.

formed in the permanganate cyclization step from the two geometrical isomers 113 and 114 respectively. The mandelate derivatives of tetrahydrofurans 111 and 112, formed in the resolution step, were separated from the two main diastereomers 110a and 110b as two separate mixtures of two compounds in a ~ 1:1 ratio. It was rather difficult to assign any stereochemistry to those isomers because they were obtained as mixtures, and no further effort was made towards this goal.



Scheme 40. The isomeric tetrahydrofuran by-products from the permanganate cyclization.

Of the two main diastereomers in the reaction mixture, the diastereomer eluting first could be isolated in > 99% purity (by GLC analysis) and this turned out to be the desired isomer with structure 110a. The second diastereomer was collected in > 98% purity and was assigned

structure 110b. The assignment of the absolute stereochemistry of those two diastereomers was made using Mosher's proton NMR method.[78] This empirical correlation of proton NMR data of diastereomeric esters derived from mandelic acid, O-methylmandelic acid, atrolactic acid, or α-methoxy-α-trifluoromethylphenylacetic acid with their absolute configuration is based on the NMR nonequivalence of diastereotopic groups in these derivatives and has a very good predictive power. It enabled us to assign the absolute configuration to the two diastereomers 110a and 110b with some degree of confidence. Dale and Mosher recorded the proton NMR spectrum from a wide range of esters from the above chiral acids and found that the resonances of the substituents on the carbinol carbon followed a particular pattern common to all but the latter series of esters.[78] The carbinol carbon refers here to the carbon bearing the non-carbonyl oxygen of the ester (shown with an asterisk in Figure 6). This pattern is depicted in Figure 6

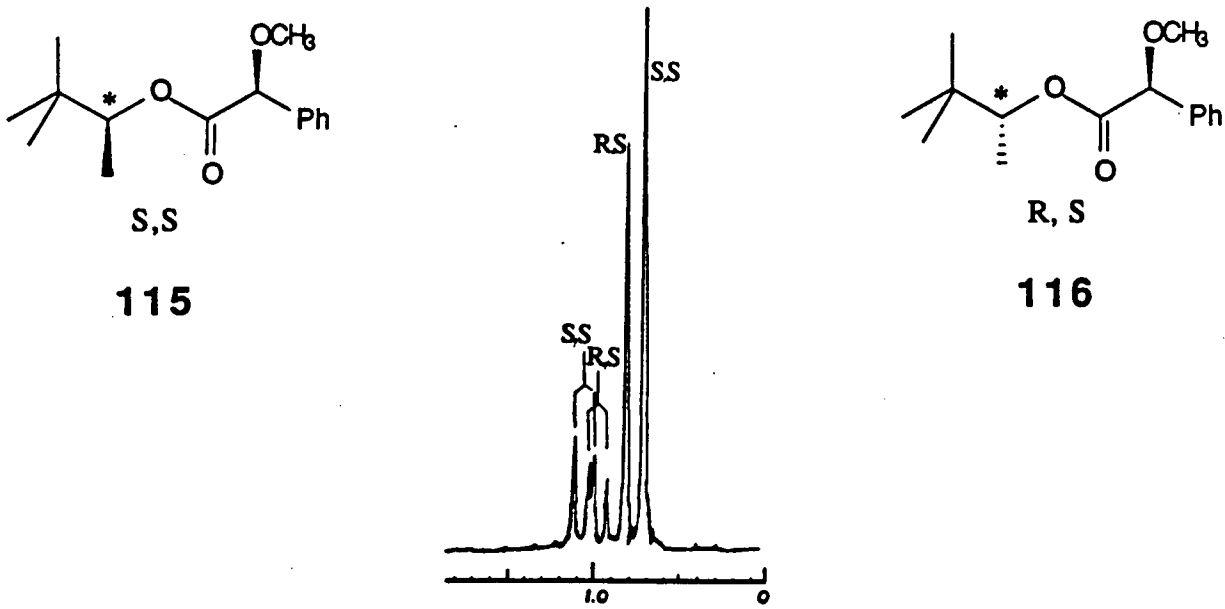


Figure 6. The partial ^1H NMR spectrum of two diastereomeric O-methylmandelate esters.

which shows the ^1H NMR spectrum of a mixture containing a 13% excess of (S)-2,2-dimethylbutyl-(S)-O-methylmandelate 115 over (R)-2,2-dimethylbutyl-(S)-O-methylmandelate 116. The (S,S) diastereomer shows an upfield t-butyl and a downfield methyl signal with respect to the signals for the corresponding groups in the (R,S) diastereomer. No exception was found in this pattern for a wide variety of esters investigated. In the case of α-methoxy-α-trifluoromethylphenylacetates, the pattern was exactly reversed.

The high-field proton NMR spectrum of the two diastereomers 110a and 110b was recorded and showed a pattern that was consistent with the findings of Dale and Mosher (Figure 7). The first-eluting isomer 110a shows a methyl doublet at δ 1.03 and a methyl singlet at δ 1.17 (this angular methyl would correspond to the t-butyl group in the example given in Figure 6) while the last-eluting isomer 110b has the methyl doublet resonance downfield at δ 1.25 and the methyl singlet signal upfield at δ 1.03. Because the O-acetylmandelate moiety used here was of the (S) configuration, diastereomer 110a was assigned the (R) configuration at the secondary carbinol carbon (shown with an asterisk in Figure 7), and diastereomer 110b, the (S) configuration at the same carbon. The other singlet in each partial spectrum was assigned to the tertiary carbinol methyl group. We realized this was only an empirical method of assigning the absolute stereochemistry and was not a proof of it. The synthesis was carried forward with the two diastereomers, waiting for a formal proof to come at a later time. For clarity and economy of space, only the chemistry of the desired isomer will be described in the rest of this synthesis.

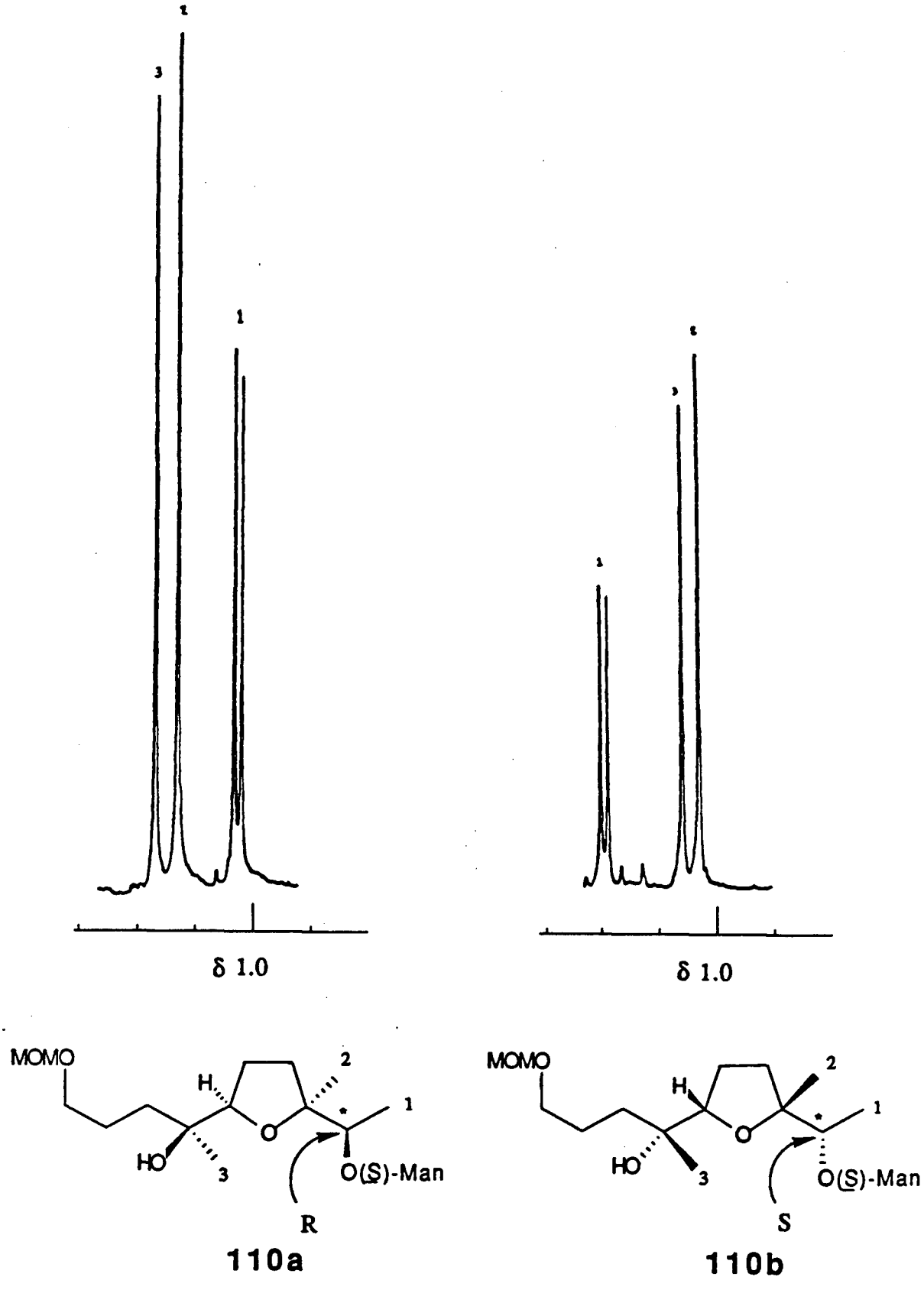
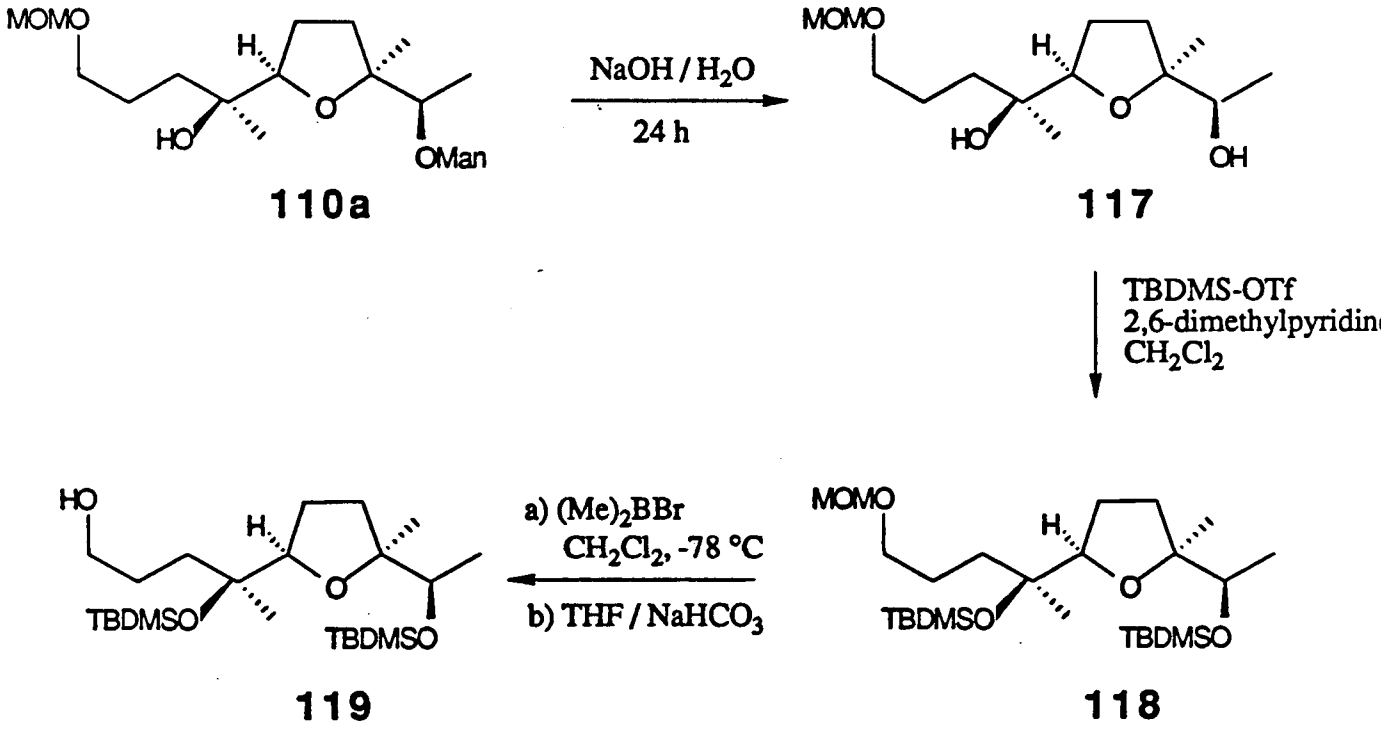


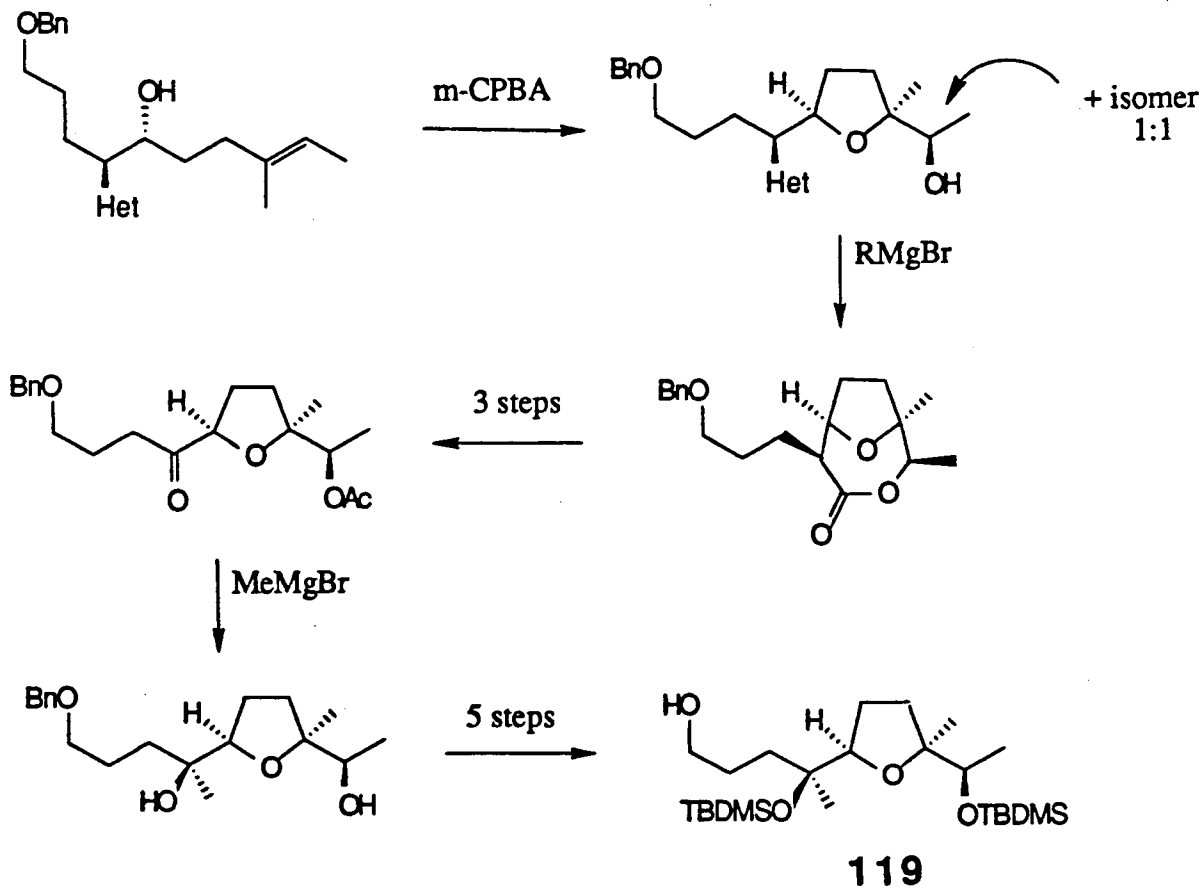
Figure 7. Partial NMR spectrum of diastereomers 110a and 110b.

The O-acetylmandelic ester 110a was hydrolyzed with aqueous sodium hydroxide (Scheme 41). Optically active diol 117 was obtained in excellent yield and all its spectral data were identical to racemic diol 103 with the exception of the optical rotation. Diol 117 was then protected as its bis-t-butyldimethylsilyl ether with t-butyldimethylsilyl triflate and 2,6-dimethylpyridine to afford compound 118 in 90% yield.[80] Cleavage of the methoxymethyl ether was effected with dimethylboron bromide to give the primary alcohol 119. Guindon and coworkers have developed this reagent for the selective removal of acetal protecting groups in the presence of other acid sensitive groups.[81] At 0 °C or higher this reagent has been used to convert ethers into bromo alcohols.[81]



Scheme 41. Conversion of 110a into the optically active alcohol 119.

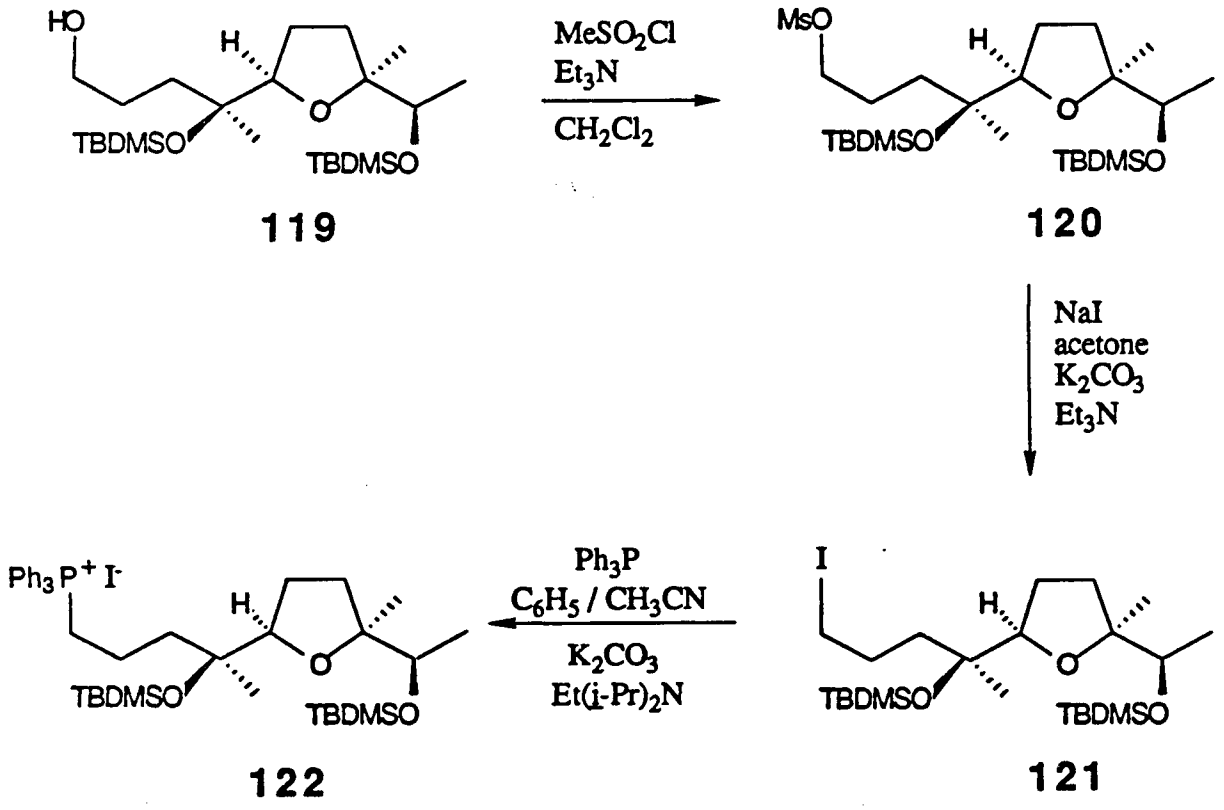
Chiral alcohol 119 has been synthesized by Shih and Evans by a different route.[82] Their synthesis of 119 is summarized in Scheme 42. Both compounds were found to have identical physical and spectral properties including the optical rotation. This reassured us that the permanganate cyclization of the 1,5-diene 93 had proceeded with the expected stereochemical outcome and that the Mosher method of assigning the absolute stereochemistry was valid here.



119

Scheme 42. A synthesis of alcohol 119.[82]

Then alcohol 119 was mesylated using methanesulfonyl chloride and triethylamine (Scheme 43). Without purification methanesulfonate 120 was directly reacted with sodium iodide in acetone containing a trace amount of triethylamine and sodium bicarbonate to give the light sensitive iodide 121. The synthesis of fragment D was completed by treating iodide 121 with triphenylphosphine in a 1:1 mixture of toluene - acetonitrile containing diisopropyl-ethylamine to give the corresponding phosphonium iodide 122. For characterization purposes this salt was isolated once, but normally it was used directly in the next step.



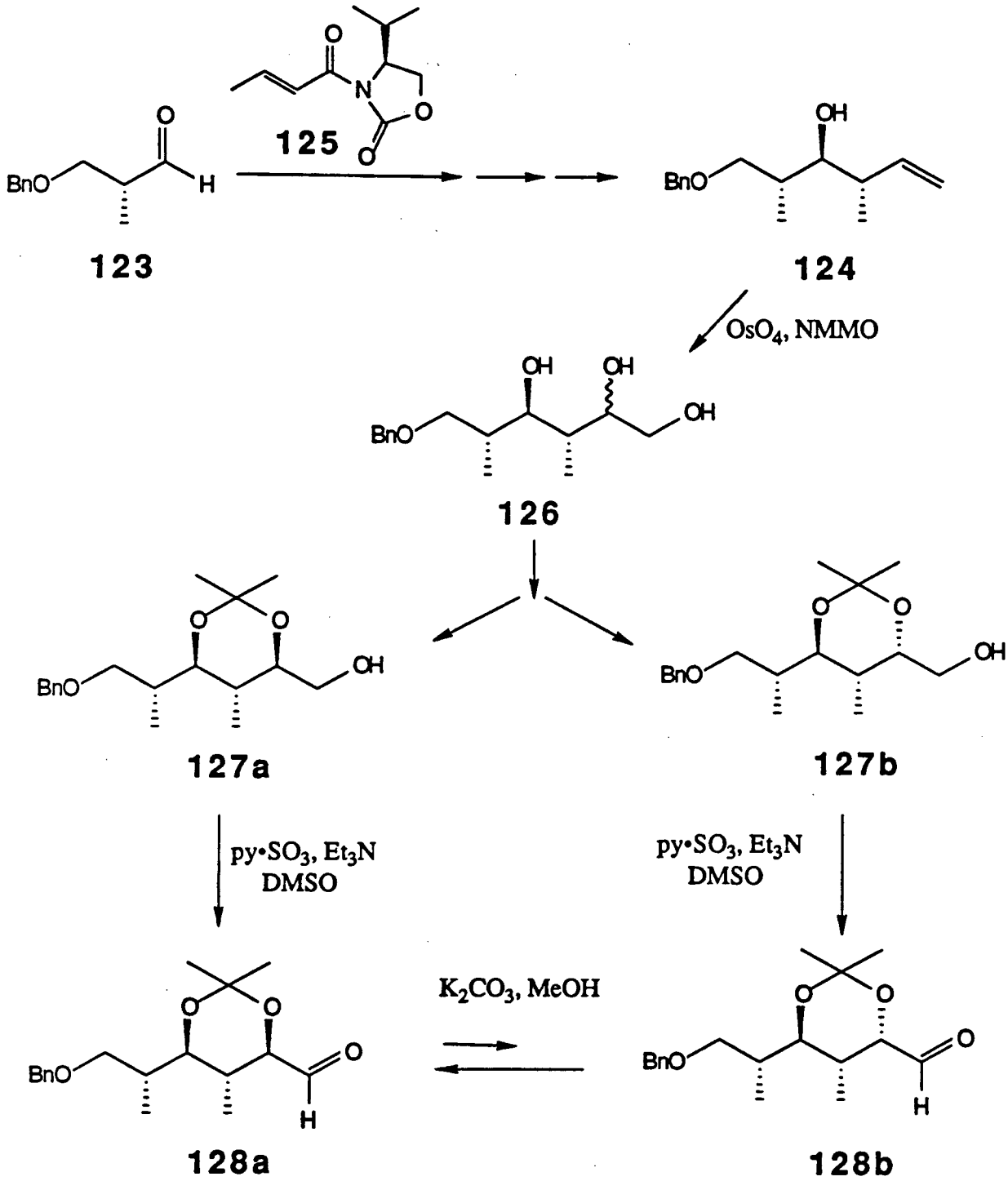
Scheme 43. Completing the synthesis of fragment D from diol 119.

I.B. Synthesis of Fragment C (C_{16}-C_{22})

Our synthesis of the fragment C of ionomycin centred around the asymmetric aldol condensation of the chiral imides developed by Evans and coworkers.[13] A C_{17} to C_{22} fragment of ionomycin was synthesized by Evans and Dow using this methodology (Scheme 44).[83] However, they could only achieve control of three of the four asymmetric centres. Hydroxy alkene 124 was prepared in several steps from the aldol condensation of the boron enolate of crotonyl imide 125 and the aldehyde 123. Hydroxylation of 124 with osmium tetroxide gave diol 126 as a 1:1 mixture of epimers. Further elaboration afforded the alcohols 127a and 127b, which could be separated by chromatography. Alcohols 127a and 127b were oxidized to the aldehydes 128a and 128b respectively. Aldehyde 128b could be equilibrated by treatment with potassium carbonate in methanol into a 92:8 mixture of aldehydes 128a and 128b with the desired aldehyde 128a predominating.

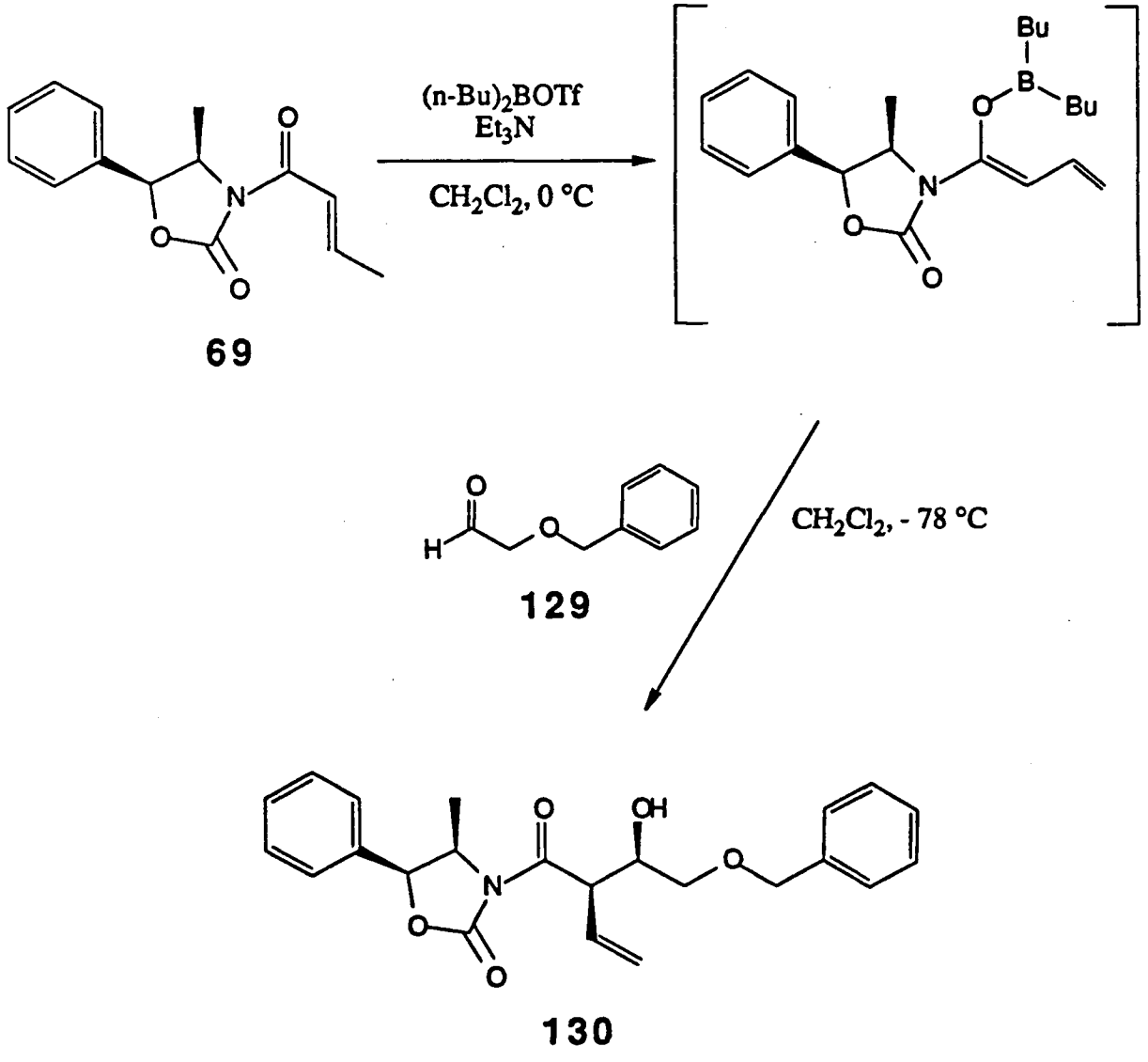
Our synthesis of fragment C, started with α-benzyloxyethanal (129) (Scheme 45) which was prepared as follows: allyl alcohol was treated with sodium hydride and benzyl bromide in tetrahydrofuran in the presence of a catalytic amount of tetrabutylammonium iodide to give allyl benzyl ether, which was oxidatively cleaved with osmium tetroxide and sodium metaperiodate to afford the unstable aldehyde 129. The use of ozone appears to be dangerous for this particular preparation. Indeed when α-benzyloxyethanal was distilled after ozonolysis an explosion resulted despite the fact that all peroxides in the mixture were destroyed by stirring with excess dimethylsulfide for several hours, and the mixture was found to be free of peroxides when checked with peroxide check paper (Peroxid-test, Merck Darmstadt). Aldehyde 129 had previously been prepared by a similar method,[84] and by two other different methods.[85,86]

Crotonyl imide 69 was prepared according to the procedure described by Evans et al.[87] The boron enolate of 69 was generated using the reaction conditions of Inoue et al.[88] namely di-n-butylboron triflate[89] and triethylamine in dichloromethane, and it was condensed with α-benzyloxyethanal (129) at -78 °C (Scheme 45). After chromatography on silica gel, a 60%



Scheme 44. Evans and Dow's synthesis of the C_{17}-C_{22} fragment of ionomycin.[83]

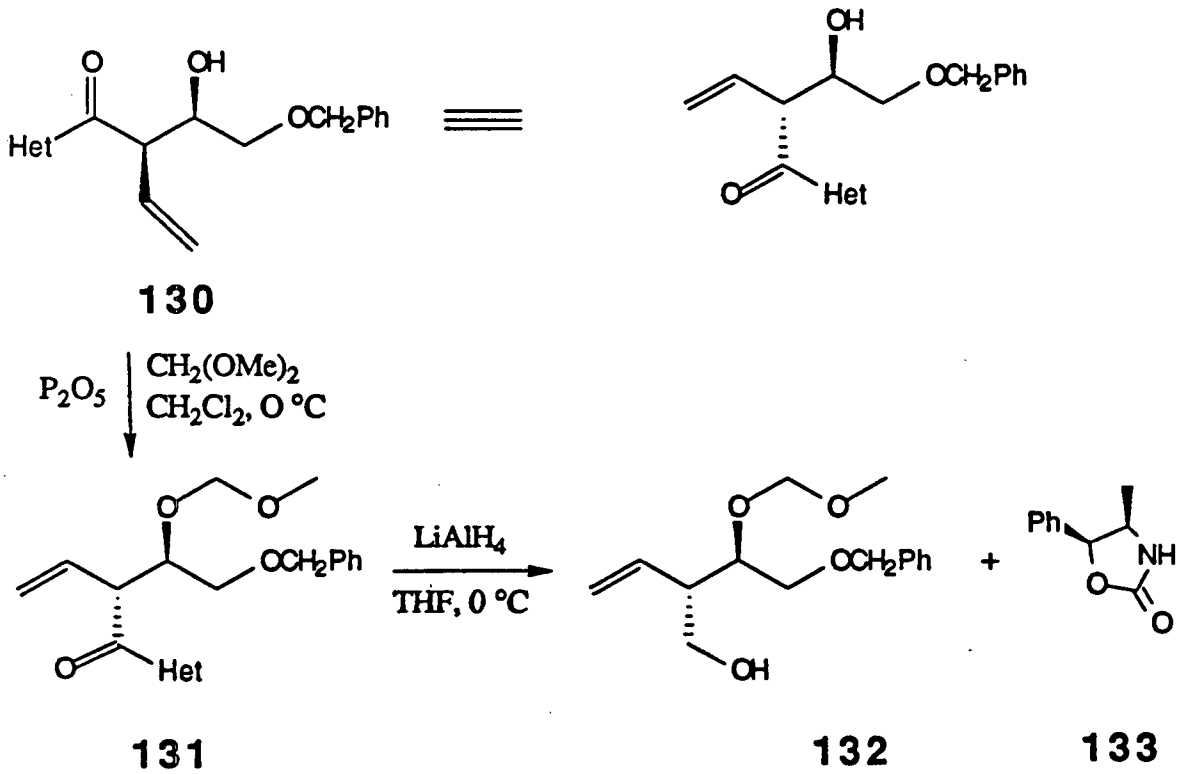
yield of the aldol adduct 130 was isolated as a white crystalline compound. The GLC trace showed only one product peak indicating that only one isomer was formed in the reaction. The proton NMR spectrum confirmed this result and indicated the presence of a terminal olefin with signals of appropriate multiplicity at δ 5.98, 5.38, and 5.35. The allylic hydrogen gave a doublet of doublet at δ 4.74, while the carbinol hydrogen signal was found at δ 4.26. The carbon-13 NMR spectrum also confirmed the generation of only one isomer in the reaction and it was in agreement with the proposed structure for compound 130. The vinyl and hydroxyl



Scheme 45. Aldol condensation between crotonyl imide 69 and aldehyde 129.

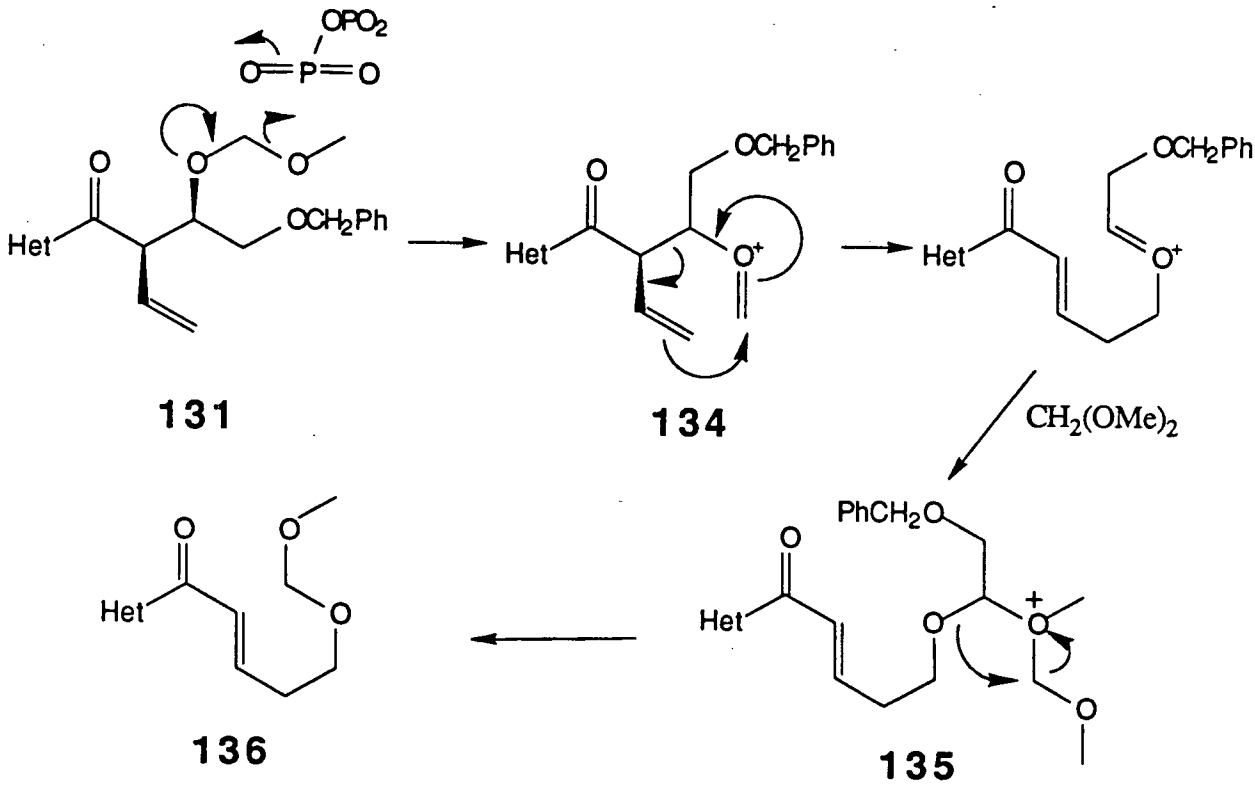
groups in 130 were assumed to have the syn relationship from the results obtained by Evans and coworkers for the aldol condensation of chiral imides. This assumption was verified at a later stage in the synthesis by proton NMR analysis (see this section p 74).

A 60° rotation about the newly formed allylic bond in the reaction illustrates the anti relationship between the alcohol and the imide group (Scheme 46). Reducing the imide to a methyl group would yield the desired product having the anti relationship between the hydroxyl and methyl groups. Thus the alcohol in 130 was protected as its methoxymethyl ether using the transacetalization method to afford compound 131.[69] This reaction had to be conducted at 0 °C to prevent the formation of a side product. The side product was identified by spectroscopic means and was assigned structure 136 (Scheme 47). This product could originate from a [3,3] sigmatropic rearrangement of the intermediate oxonium ion 134 followed by the addition of a molecule of dimethoxymethane to give intermediate 135. The latter can rearrange to give the observed product 136.



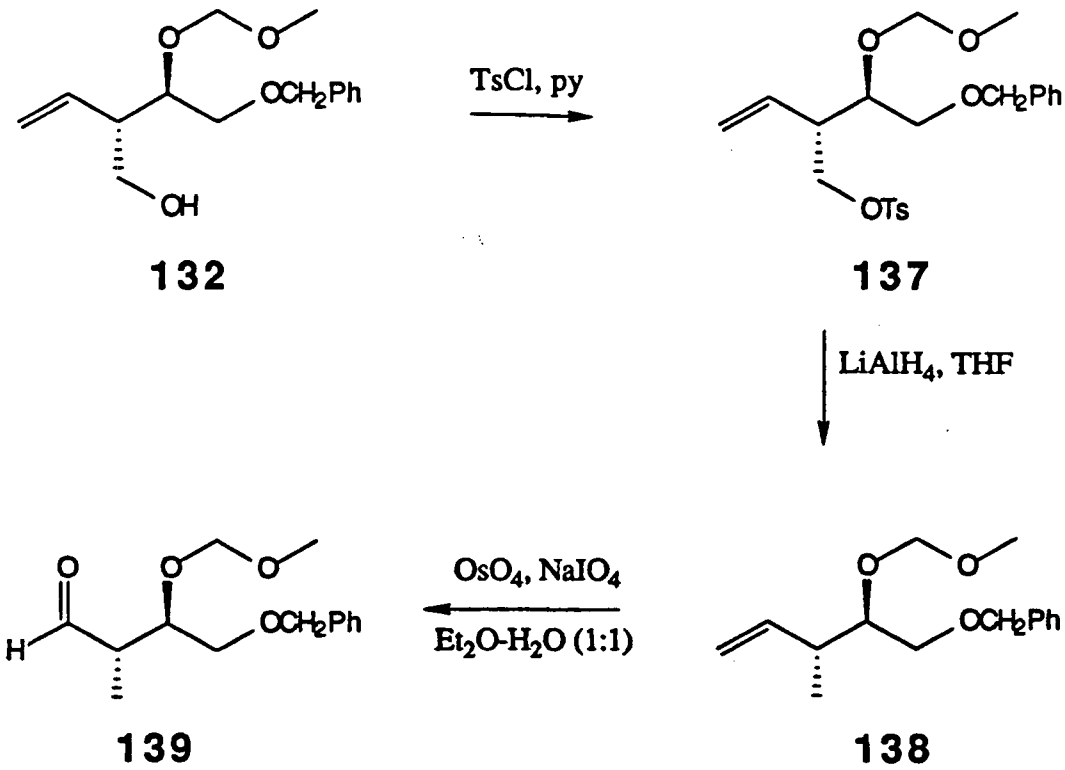
Scheme 46. Protection of the secondary alcohol and reduction of the chiral auxiliary.

Lithium aluminium hydride reduced imide 131 to the primary alcohol 132 (Scheme 46). In the process the oxazolidone ring was not reduced and was recovered as 133. No epimerization at the allylic carbon was detectable by GLC or spectroscopic analyses.



Scheme 47. Proposed mechanism for the formation of the side product in the protection of alcohol 130.

Treatment of the alcohol 132 with p-toluenesulfonyl chloride in pyridine afforded the tosylate 137 in quantitative yield (Scheme 48). Lithium aluminium hydride reduced the latter to the corresponding alkane 138 in excellent yield. Because methoxymethyl ethers are oxidized by ozone,[90] a catalytic amount of osmium tetroxide in the presence of two equivalents of sodium metaperiodate was used to convert alkene 138 to the aldehyde 139. The latter was stable enough to be chromatographed on silica gel and no epimerization could be observed by proton NMR.

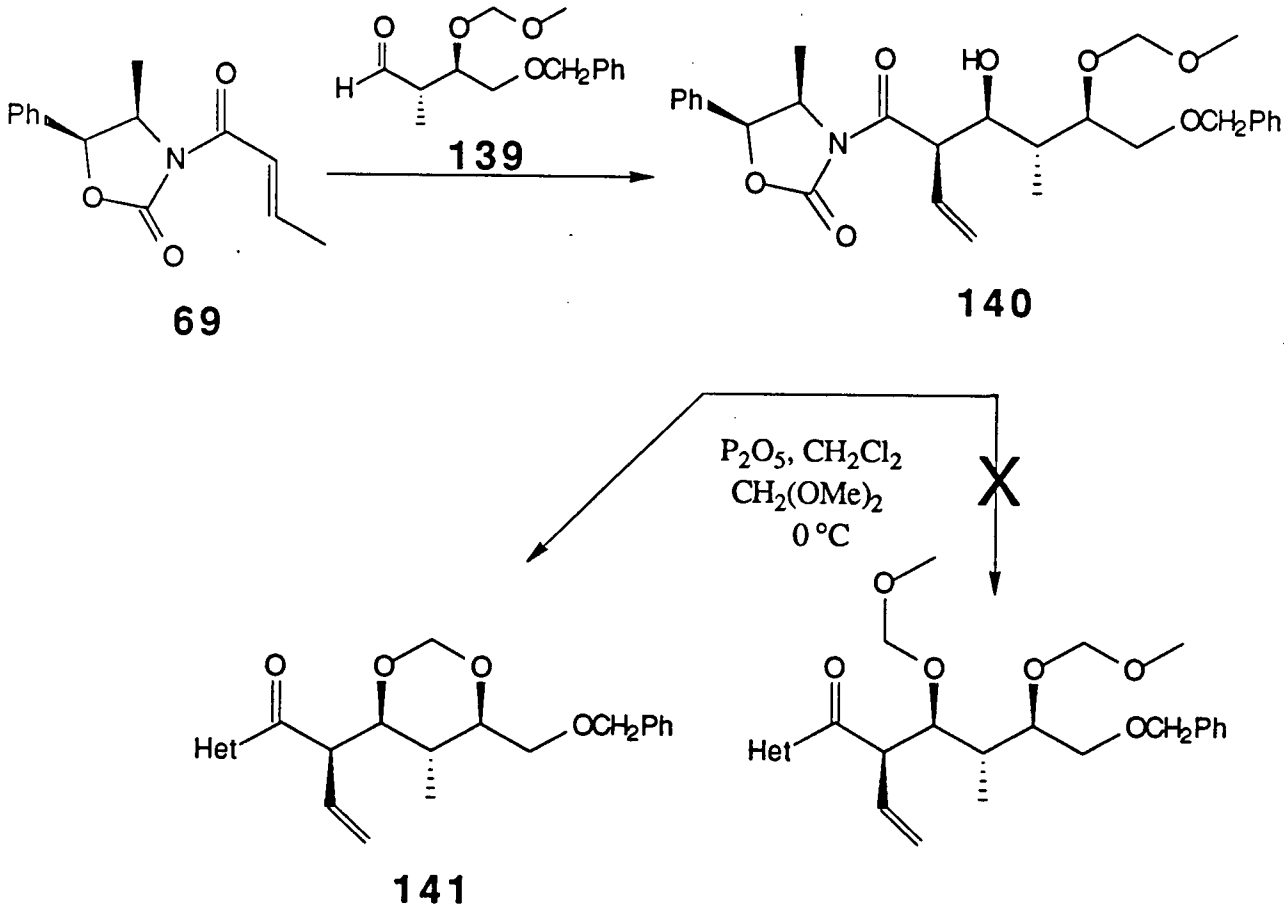


132 137 139 138

Scheme 48. Conversion of the alcohol 132 to 139.

The boron enolate of crotonyl imide 69 was again used in a condensation reaction with aldehyde 139 (Scheme 49). GLC and spectral analyses indicated diastereomer 140 to be the sole product formed in this condensation. The proton and carbon-13 NMR spectra of 140 were consistent with the structure shown. Note the advantage of using chiral imide 69 in the aldol reaction as its asymmetric induction dominates that of the chiral aldehyde 139.[13]

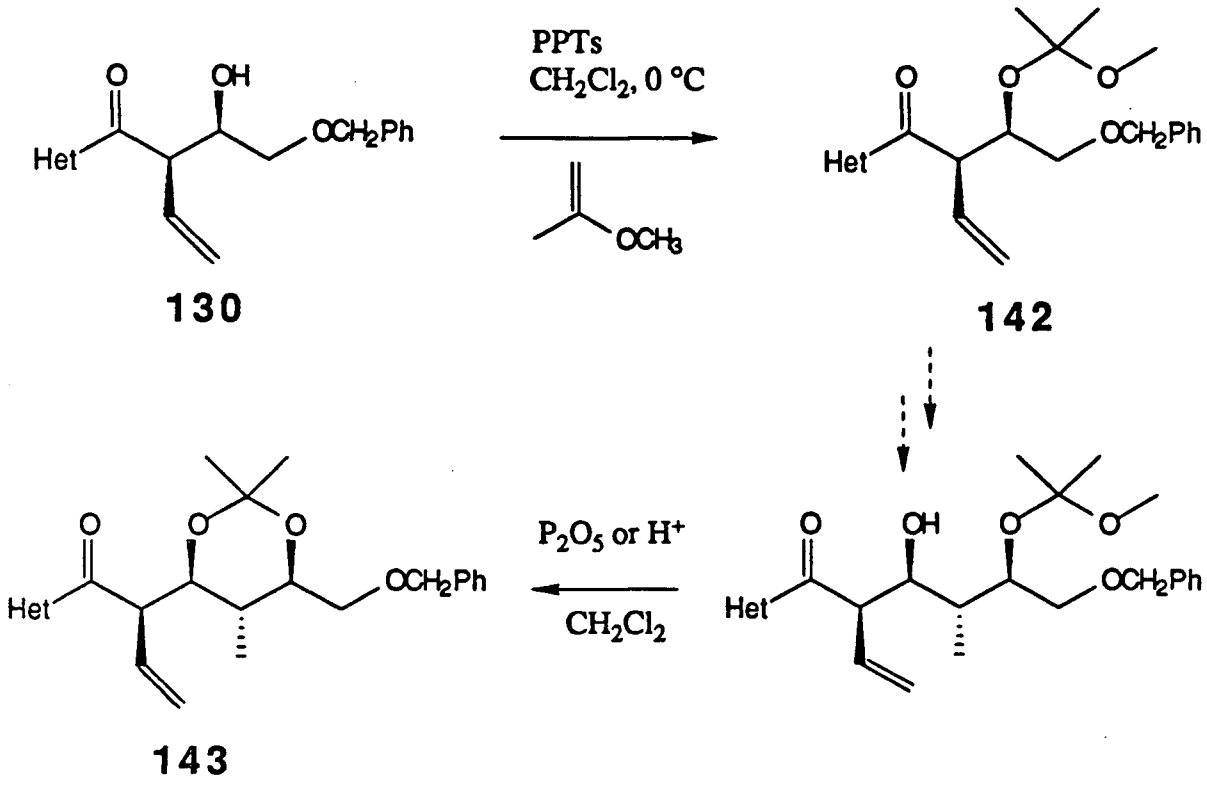
On attempting to protect the secondary alcohol with a second methoxymethyl group using the transacetalization method, cyclic 1,3-dioxane 141 was formed exclusively, even when a large excess of methylal was used (Scheme 49). In retrospect, this result is not too surprising



Scheme 49. Second aldol condensation using crotonyl imide 69 and protection of the resulting alcohol.

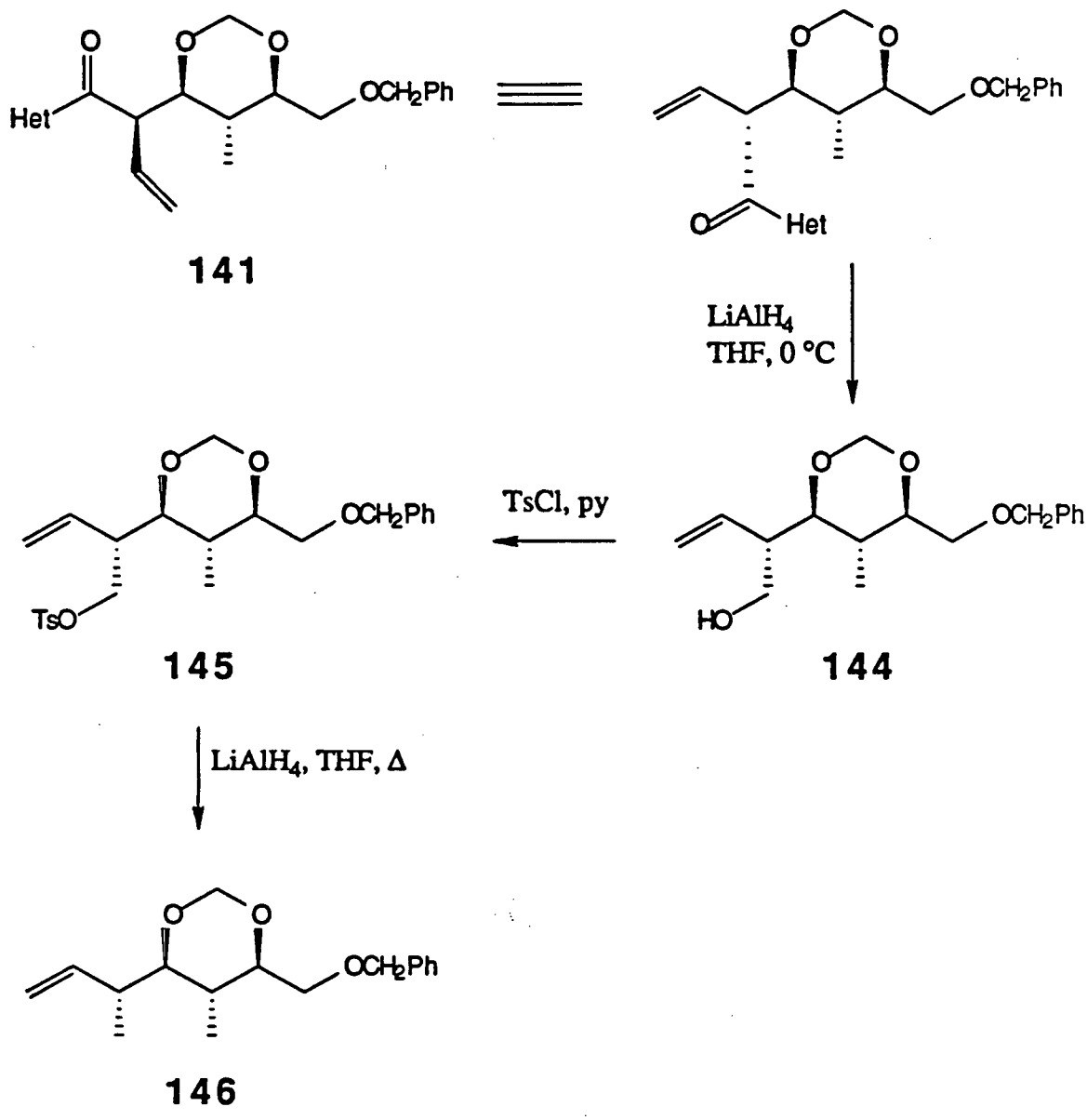
since cyclization processes to small rings are usually much faster than their bimolecular counterparts. It was relatively easy to determine the product's identity. The first evidence was provided by the drastic change in optical rotation from positive (+ 37.7°) for alcohol 140 to negative (- 11.8°) for dioxane 141. This suggested a rather significant difference in the structure of the two molecules. The proton and carbon-13 NMR spectra of 141 were very indicative of a 1,3-dioxane ring. First, the methyl singlets in the ^1H NMR characteristic of methoxymethyl ethers were missing and the two acetal hydrogens of the ring gave two distant doublet resonances near δ 5. The signal at 120 ppm in the carbon-13 NMR spectrum was the only one found in that low-field region. This was assigned to the single acetal carbon of 141. If compound 141 had contained the two methoxymethyl ethers, two of these signals would have been present as well as the two signals for the methyl ether carbons which also were missing in the spectrum.

The methylene acetal was an appropriate protecting group for the two alcohols. It could offer an added bias for the stereoselective formation of the more advance intermediate 196 (see Scheme 67, p 101) at a later stage in the synthesis and in that respect its formation was an added bonus. However we were wary of the stronger conditions that would be required for the removal of the dioxymethylene later in the synthesis of ionomycin. Therefore, we attempted to replace the methoxymethyl group in compound 131 by a 2-methoxypropyl group in hope of cyclizing it later to the isopropylidene 143 under the same reaction conditions (Scheme 50). The isopropylidene would also offer the same stereochemical bias towards the formation of tetrahydrofuran 196 and usually requires much milder reaction conditions for its removal. Compound 142 was prepared by treating alcohol 130 with 2-methoxypropene in the presence of a catalytic amount of pyridinium p-toluenesulfonate. But the 2-methoxypropyl group proved to be too labile to be of any use in the synthesis, as compound 142 was unstable to chromatography on silica gel. It was also cleaved in less than one hour in ether over magnesium sulfate. Faced with this problem, we decided to try to find mild reaction conditions for the removal of the methylene acetal. This is described later in this section (p. 76).



Scheme 50. Attempted preparation of the isopropylidene 143.

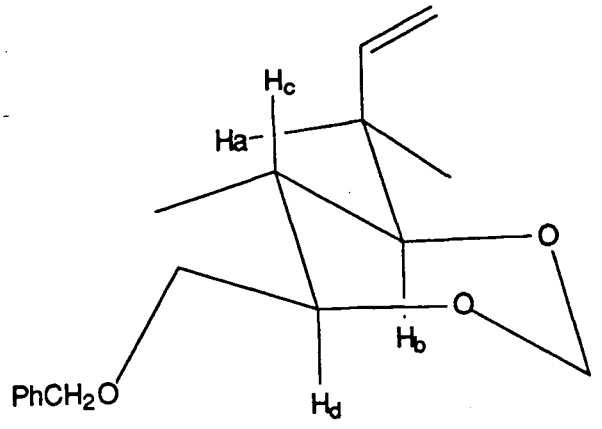
Compound 141 was submitted to the same sequence of reactions as oxazolidone 131, namely reduction to alcohol 144, followed by tosylation to give sulfonate 145, and further reduction to the corresponding methyl product 146 (Scheme 51). That last step required refluxing in tetrahydrofuran since very little product had formed (by TLC analysis) at room temperature in tetrahydrofuran even after 48 h. Similar yields were obtained in this sequence of reactions as in the previous one. Analysis of the coupling constants for the three methine protons on the dioxane ring in the proton NMR of compound 146 enabled us to verify that the relative stereochemistry at three of the four asymmetric centres of the molecule was indeed the



Scheme 51. Repetition of the reduction sequence for the deoxygenation of 132.

one predicted for the two aldol condensations. Figure 8 shows a conformational model of compound 146. The coupling constant between H_b and H_c is 11.0 Hz and the coupling constant between H_c and H_d is also 10.0 Hz. These values are indicative of a 1,2-diaxial relationship in the 6-membered dioxane ring as shown in Figure 8. The coupling constant for axial-axial hydrogens in 6-membered rings is in the range of 10-13 Hz whereas coupling constants for axial-equatorial or equatorial-equatorial hydrogens usually varies between 4 and 7

Hz.[91] It was therefore possible to assign the stereochemistry shown in 146 to the three chiral centres of the dioxane ring which is consistent with that assumed in the aldol condensation. The stereochemistry of the fourth centre could not be verified directly and was assumed to be the one shown in 146 as mentioned previously (p.69).

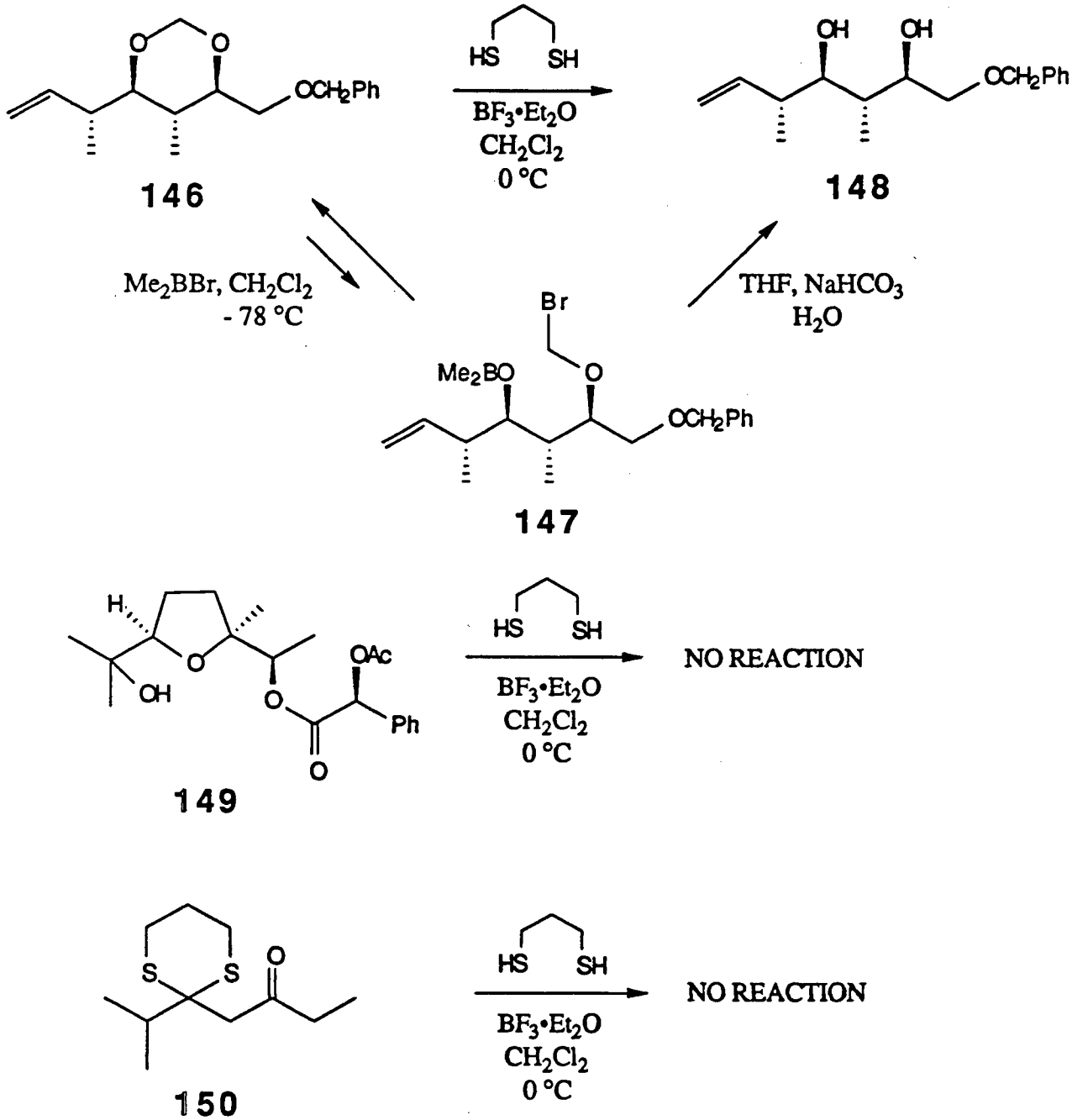


146

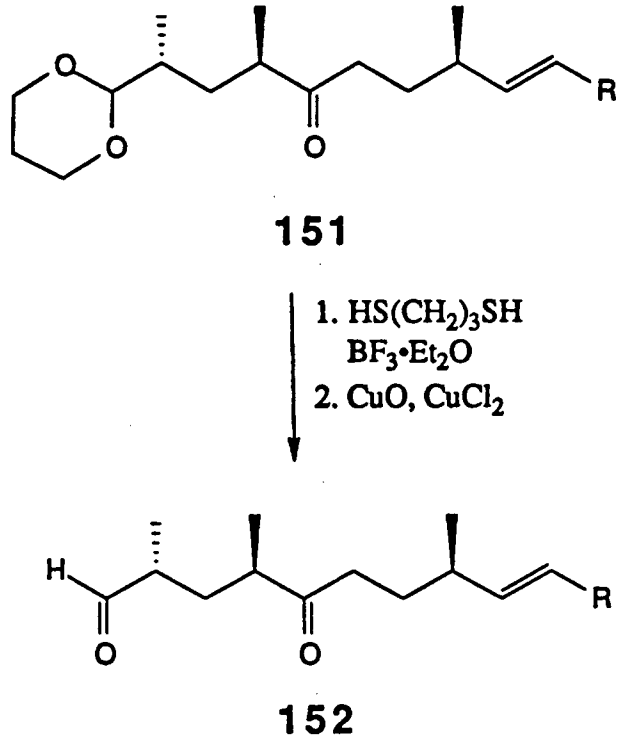
Figure 8. Conformational model of alkene 146 showing the diaxial relationship of the ring protons.

Compound 146 was used as a model to find conditions for the mild removal of the methylene acetal functionality. Dimethylboron bromide in dichloromethane gave a very poor yield of diol 148 because recyclization of the open chain intermediate 147 to the starting acetal 146 competes with its cleavage to give the diol (Scheme 52).[92] Negri and Kishi used propanedithiol with boron trifluoride etherate to cleave the acetal 151 (Scheme 53).[93] They then converted the resulting dithiane to aldehyde 152 with copper oxide. The conditions to cleave the acetal 151 turned out to work quite well in the case of methylene acetal 146 (Scheme 52). Propane dithiol in the presence of 1.5 equivalents of boron trifluoride etherate at 0 °C in dichloromethane cleaved the methylene acetal in 146 in less than two hours (Scheme 52).

When submitted to the same reaction conditions, tetrahydrofuran 149 was left unchanged even after 12 h (Scheme 52). Other model studies demonstrated that these conditions also left the ß-keto dithiane moiety in 150 unchanged (Scheme 52). We therefore extrapolated that these conditions would be appropriate to use in the final deprotection steps in our synthesis of ionomycin.



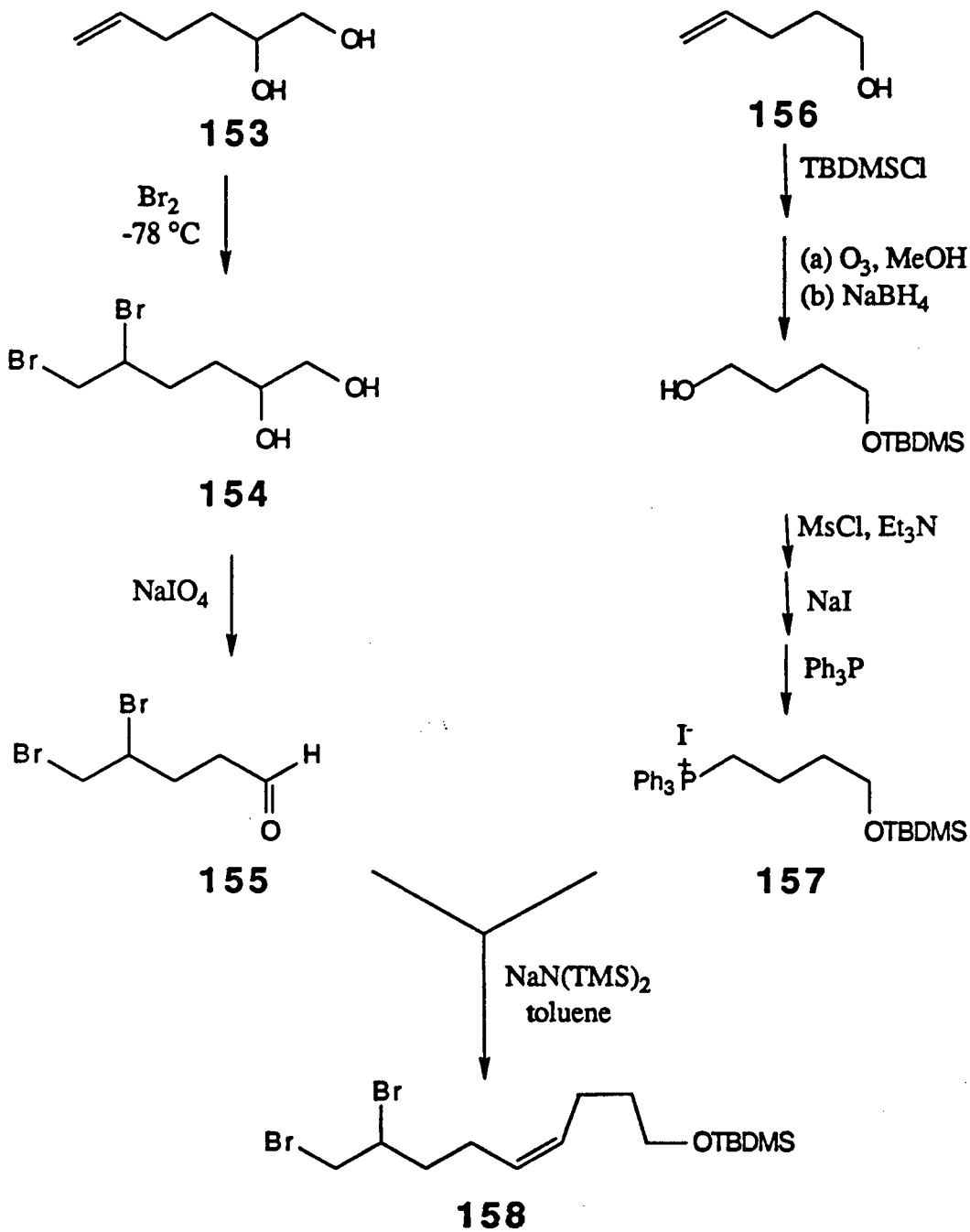
Scheme 52. Model study for the deprotection of the methylene acetal group.



Scheme 53. Cleavage of acetal 151.[93]

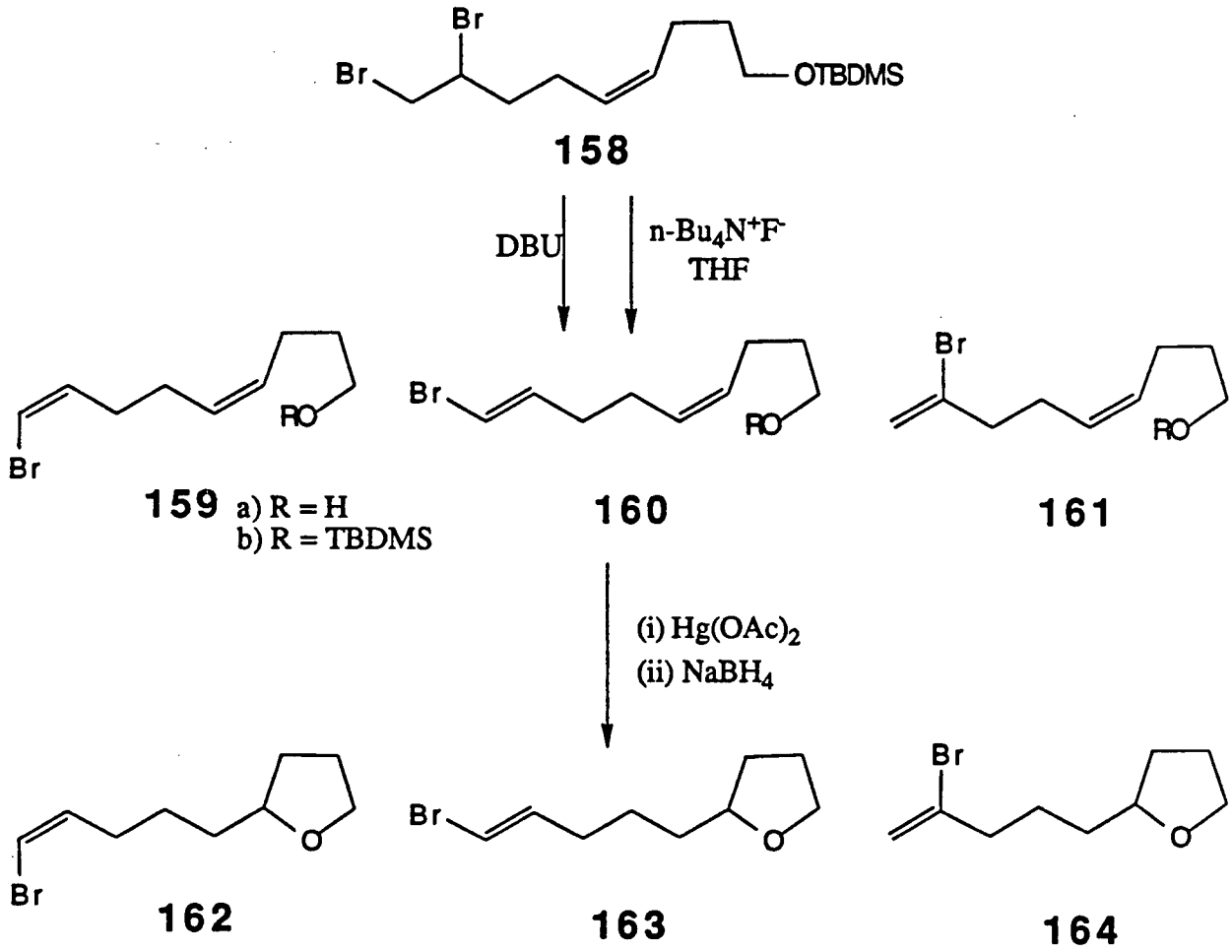
The synthesis of the carbon framework of fragment C was now completed with all the substituents having the correct stereochemistry. An aldehyde functionality was needed at C_{22} of fragment C for its coupling to fragment D (Scheme 20, p.30). Therefore the deprotection and oxidation of the primary alcohol in compound 146 would be needed. Also, we wanted an acetylene group at C_{16}-C_{17} of fragment C for the eventual coupling of segment CD with segment AB. Therefore the alkene in compound 146 would have to be converted to an alkyne. Earlier model studies showed that the acetylenic or the olefinic functional groups are not compatible with one of the reactions planned for the preparation of fragment CD, namely the oxymercuration reaction needed for the formation of the second tetrahydrofuran ring of ionomycin (see 195 → 196 Scheme 67, p. 101). As a result the conversion of the alkene into the alkyne had to be accomplished with a specific sequence of reactions in which one of the intermediates would withstand the coupling reaction. Model studies were thus undertaken to determine which intermediates might be compatible with the reactions involved in the preparation of segment CD (see section II.A, p 96).

One standard way to convert alkenes into alkynes is to halogenate the former and subsequently eliminate two molecules of hydrogen halide. The model alkene diol 153 was brominated with bromine in ether in the presence of sodium bicarbonate to afford dibromide 154 (Scheme 54). Compound 154 was then converted to aldehyde 155 by periodate cleavage. A model phosphonium iodide 157 was prepared in five steps from hydroxy alkene 156 as shown in Scheme 54. The ylid from 157 was generated by treating the phosphonium iodide with sodium bis(trimethylsilyl)amide in toluene and it was then condensed with aldehyde 155 to give the olefin 158 in 66% isolated yield. This demonstrated the compatibility of the dibromo group in the Wittig reaction. The dibromo functionality was expected to also be unreactive toward the oxymercuration reaction conditions.



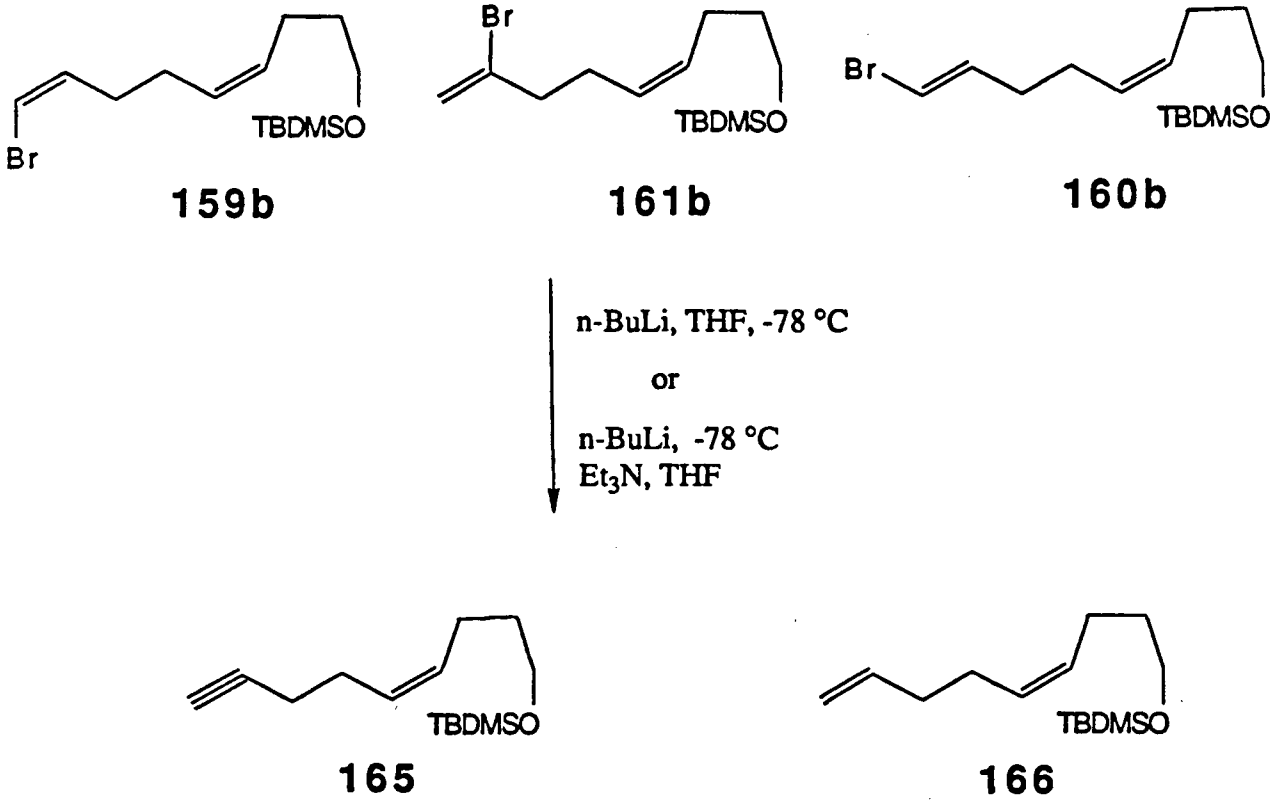
Scheme 54. Preparation and coupling of the model compounds 155 and 157.

However, cleavage of the t-butyldimethylsilyl ether in 158 with tetra-n-butylammonium fluoride also led to the elimination of hydrogen bromide and gave a mixture of isomers 159a, 160a, and 161a in a 1:1:2 ratio (Scheme 55). The elimination of hydrogen bromide seemed rather facile as shorter reaction times led to the formation of the protected alcohols 159b, 160b, and 161b. The elimination of hydrogen bromide in compound 158 was also effected with 1,8-diazabicyclo[5.4.0]undec-7-ene to give the same mixture of the three isomeric vinyl bromides 159b, 160b and 161b. The mixture of γ,δ-hydroxy alkenes 159a, 160a, and 161a was cyclized with mercuric acetate in dichloromethane to give tetrahydrofurans 162, 163 and 164. Under these reaction conditions, the vinyl bromide remained unchanged (Scheme 55). Presumably the electron withdrawing effect of the bromide renders the double bond electron poorer and thus less susceptible to electrophilic attack. Therefore it seemed that this route for the conversion of the olefin in 146 (Scheme 51, p 75) into an acetylene would be appropriate in the synthesis.



Scheme 55. Model studies for the coupling of fragments C and D.

When the second elimination of hydrogen bromide was attempted on vinyl bromides 159b, 160b, and 161b with n-butyllithium, a mixture of alkyne 165 and alkene 166 was obtained in a 3:1 ratio (Scheme 56). Addition of triethylamine (up to 50% v/v) to the reaction mixture increased the ratio to 4:1. It was thought that the alkene 166 was generated from the vinyl bromide 160b because of the cis relationship between the departing bromide and the only available proton for the elimination. The cis elimination of hydrogen halide of this type is known to be slower than the trans elimination.[94] When alkyl metals are used as the base in this

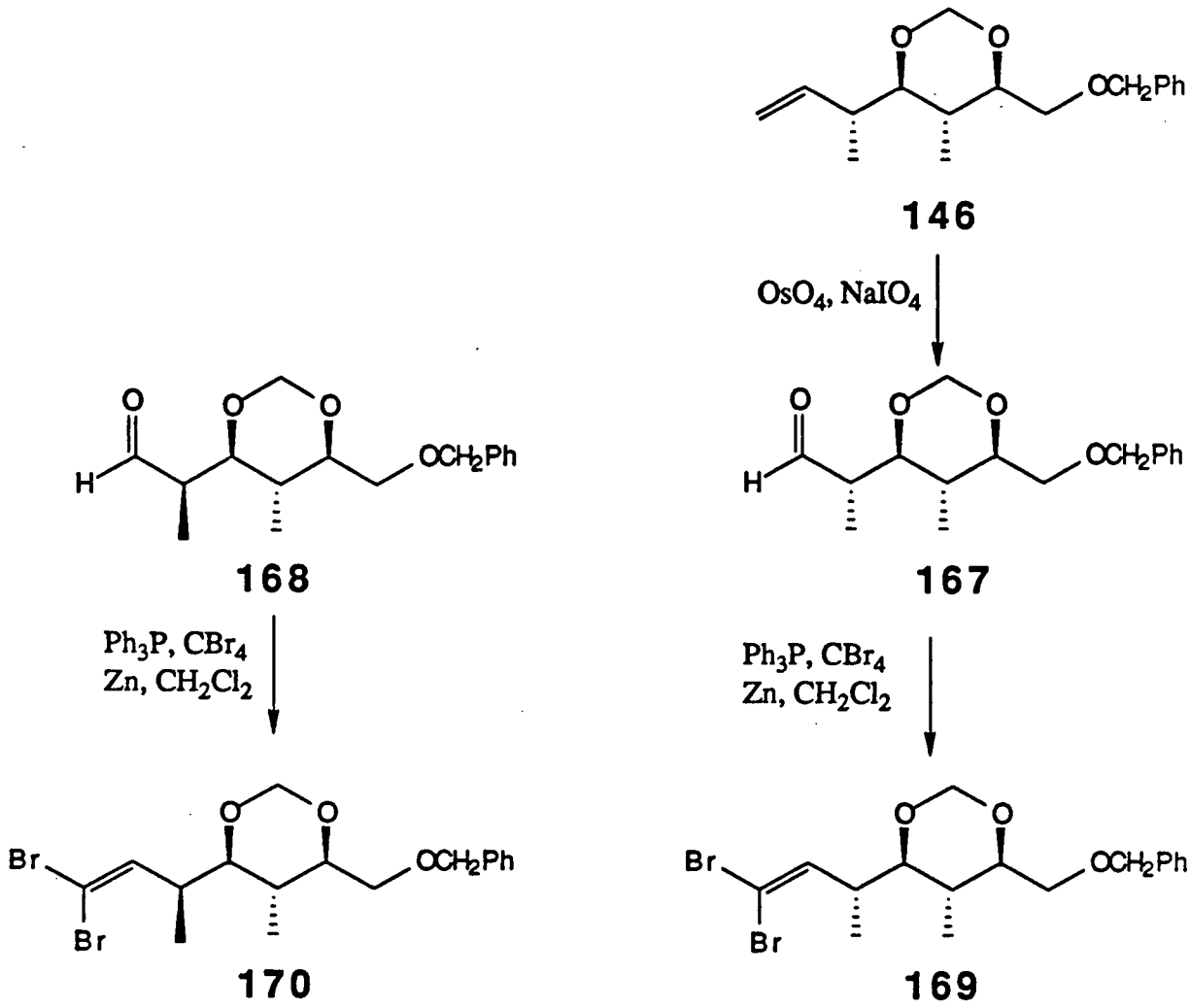


Scheme 56. Elimination reactions of model vinyl bromides.

elimination reaction, transmetallation to give olefinic products is often a competing reaction.[95] In the case of the vinyl bromide 160b, it is possible that elimination is slow enough so as to allow the transmetallation reaction to compete effectively, giving rise to the observed alkene.

Because the formation of isomers was inevitable in the first elimination of hydrogen bromide, we decided to slightly alter the strategy for the conversion of the alkene functionality into the acetylene. Alkene 146 would first be cleaved to the aldehyde 167 (Scheme 57) which could be converted to the vinyl dibromide 169 via a Wittig-type reaction.[96] Compound 169 should be stable to the coupling sequence of reactions and the elimination of terminal vinyl dibromides by an alkyllithium is known to give acetylenes.[96]

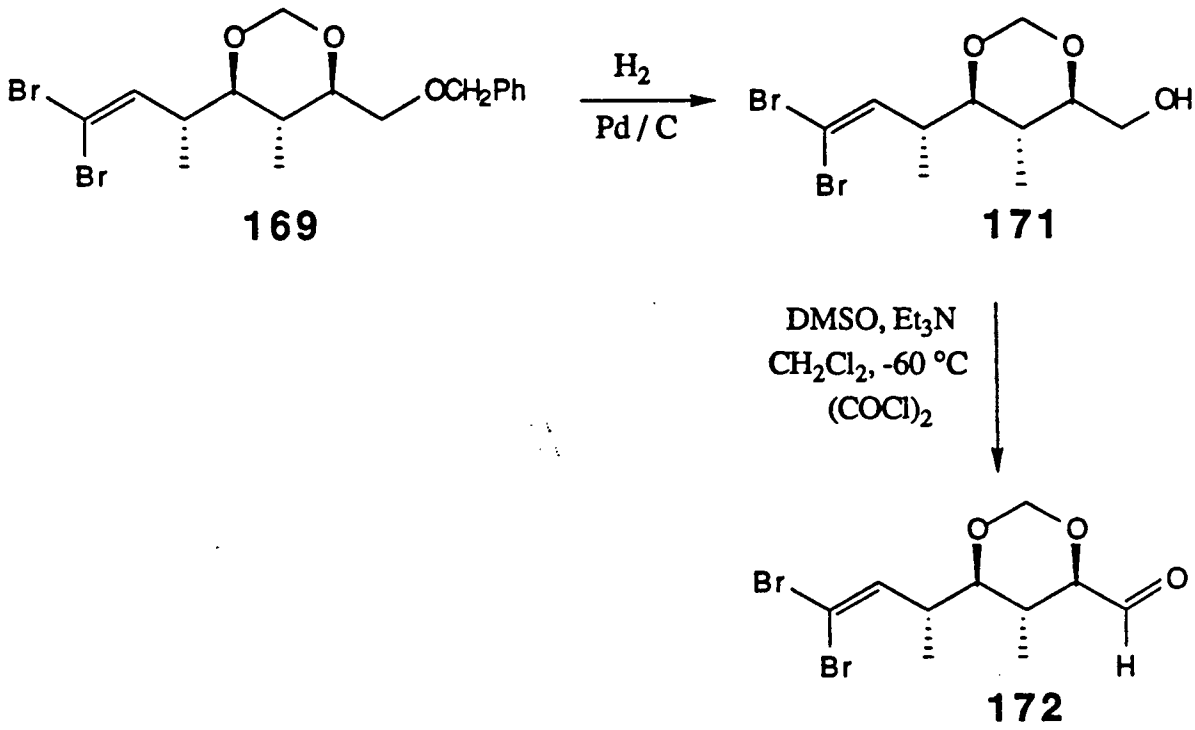
Alkene 146 was converted to aldehyde 167 in quantitative yield using osmium tetroxide and sodium periodate in a mixture of ether and water (Scheme 57). Alkene 146 was less reactive than its homologue 138 (Scheme 48) since this cleavage was completed only after 48 h compared with 36 h for 138. Also aldehyde 167 proved to be less reactive in the Wittig reaction than expected requiring 24 h and 6 equivalents of reagents to achieve complete formation of the vinyl dibromide, compared with 1-2 h and 1.1 equivalents usually required in this reaction. Peculiarly, the aldehyde 167 epimerized upon chromatography on silica gel giving approximately 2-5% of the aldehyde 168 whereas no epimerization could be observed for the more reactive homologue 139 (Scheme 48). Complete separation of the two aldehydes was difficult at this stage and so both isomers were used in the next step. The mixture of aldehydes 167 and 168 was treated, in a Wittig-type reaction, with the ylid derived from carbon tetrabromide and triphenylphosphine in the presence of zinc[96] to give vinyl dibromides 169, and 170 in 61% yield. The two isomeric vinyl dibromides were separable by chromatography on silica gel. Their mass spectrum showed the typical "triplet " of dibromo compounds due to the two isotopes of bromine.



Scheme 57. Preparation of vinyl dibromide 169.

When one equivalent of hydrogen was reacted with benzyl ether 169 in ethanol in the presence of a catalytic amount of palladium on charcoal, alcohol 171 was obtained in 90% yield (Scheme 58). If more than one equivalent of hydrogen was used, olefin reduction occurred, but at a much slower rate. Alcohol 171 was then oxidized using the Swern reaction

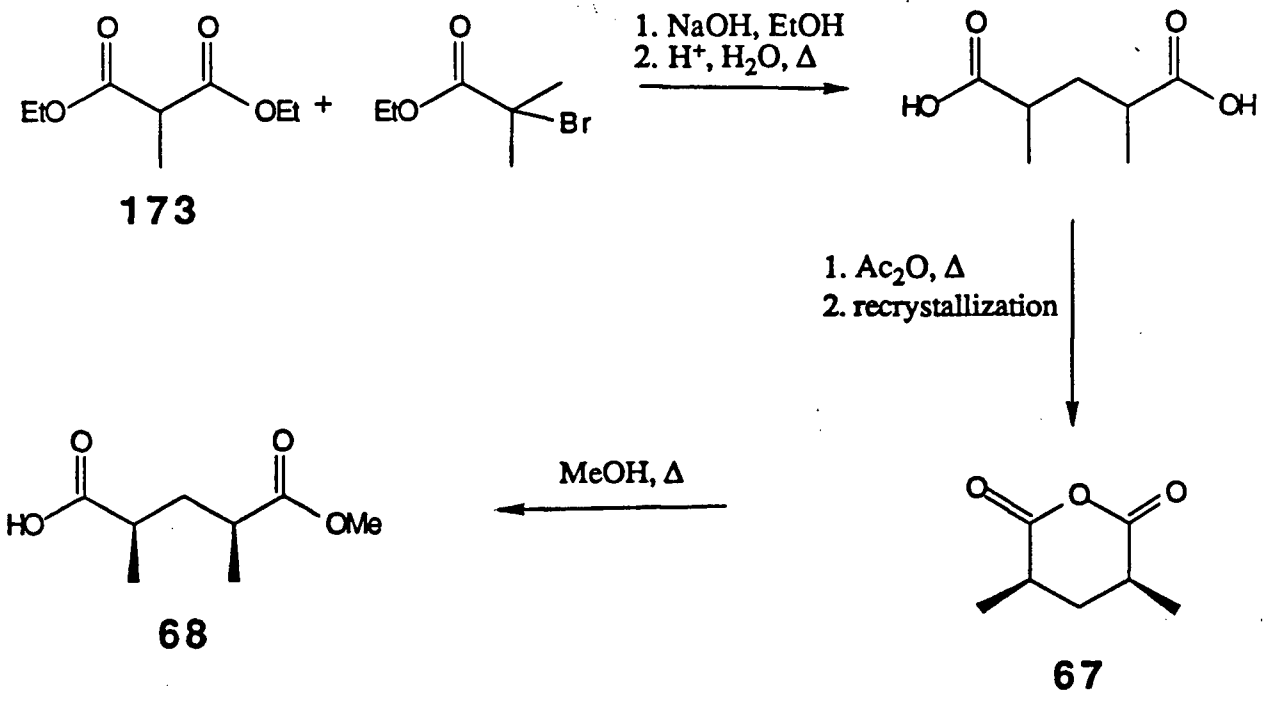
conditions[97] to yield aldehyde 172 in 95% yield, thus completing the synthesis of the C_{17} to C_{22} portion of ionomycin.



Scheme 58. Completion of the synthesis of fragment C of ionomycin.

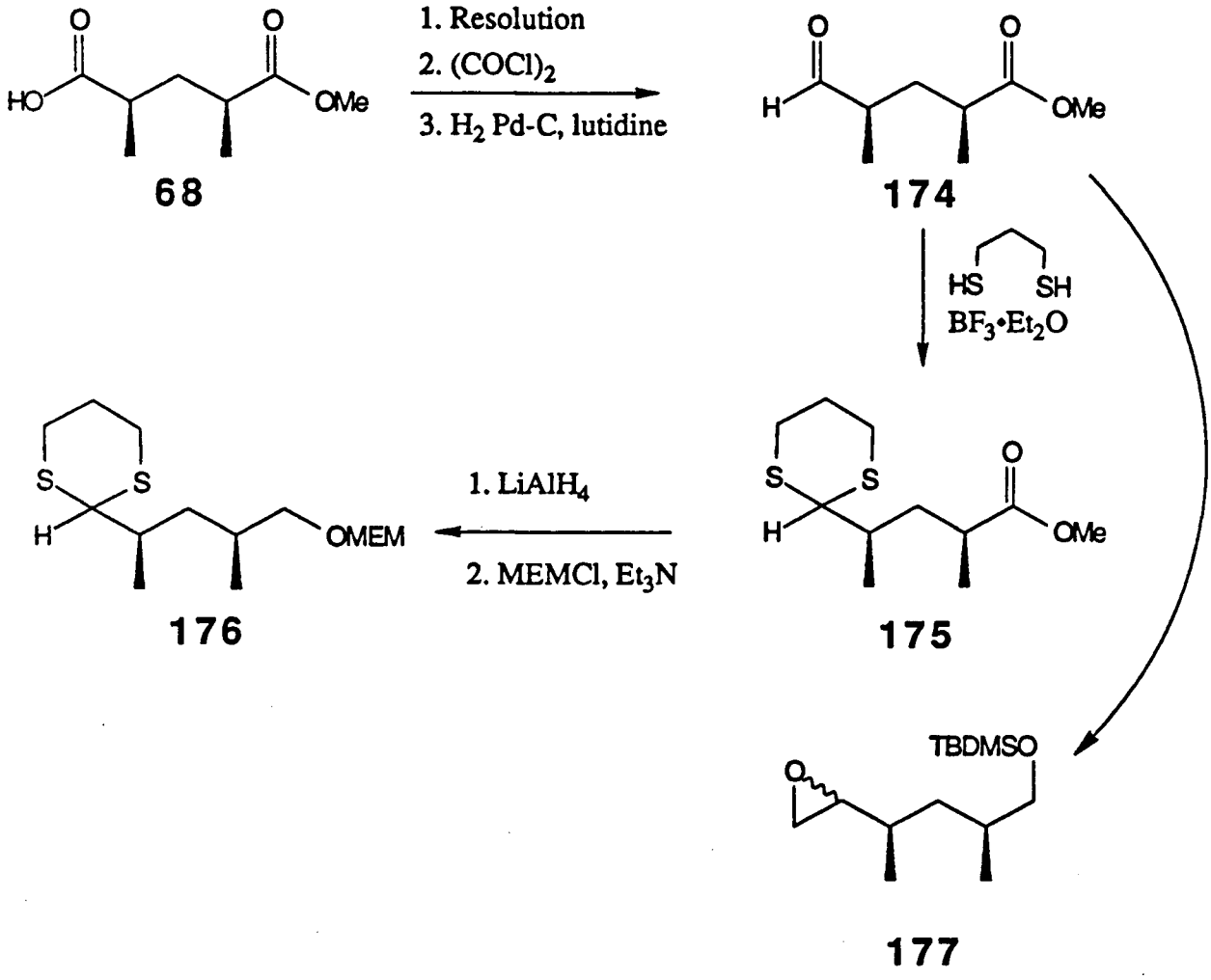
I.C. Synthesis of Fragment B (C_{11}-C_{15})

The synthesis of this fragment was accomplished using meso-(2,4)-dimethylglutaric anhydride (67) (Scheme 59). A mixture of meso and dl-dimethylglutaric anhydride was synthesized in two steps from diethyl methylmalonate (173) in 92% yield as shown in Scheme 59.[98] The meso form of anhydride 67 was preferentially crystallized from the mixture in > 99% purity as analysed by capillary GLC. Methanolysis of meso-dimethylglutaric anhydride gave acid-ester 68 in excellent yield. This acid was resolved by preferential recrystallization of its (+)-α-methylbenzylammonium salt.[61] The acid was subsequently converted into the acyl chloride with oxalyl chloride followed by hydrogenation to afford aldehyde 174 in 55% yield for the two steps (Scheme 60). Treatment of the latter with 1,3-propanedithiol gave dithiane 175 in excellent yield. The aldehyde 174 was also converted to epoxide 177 by m-chloroperoxybenzoic acid epoxidation of the corresponding alkene prepared from the reaction of 174 with Takai's reagent.[99] This epoxide was used as a model in a study of the coupling of fragments A and B.



Scheme 59. Synthesis of dimethylglutaric anhydride and its methanolysis.

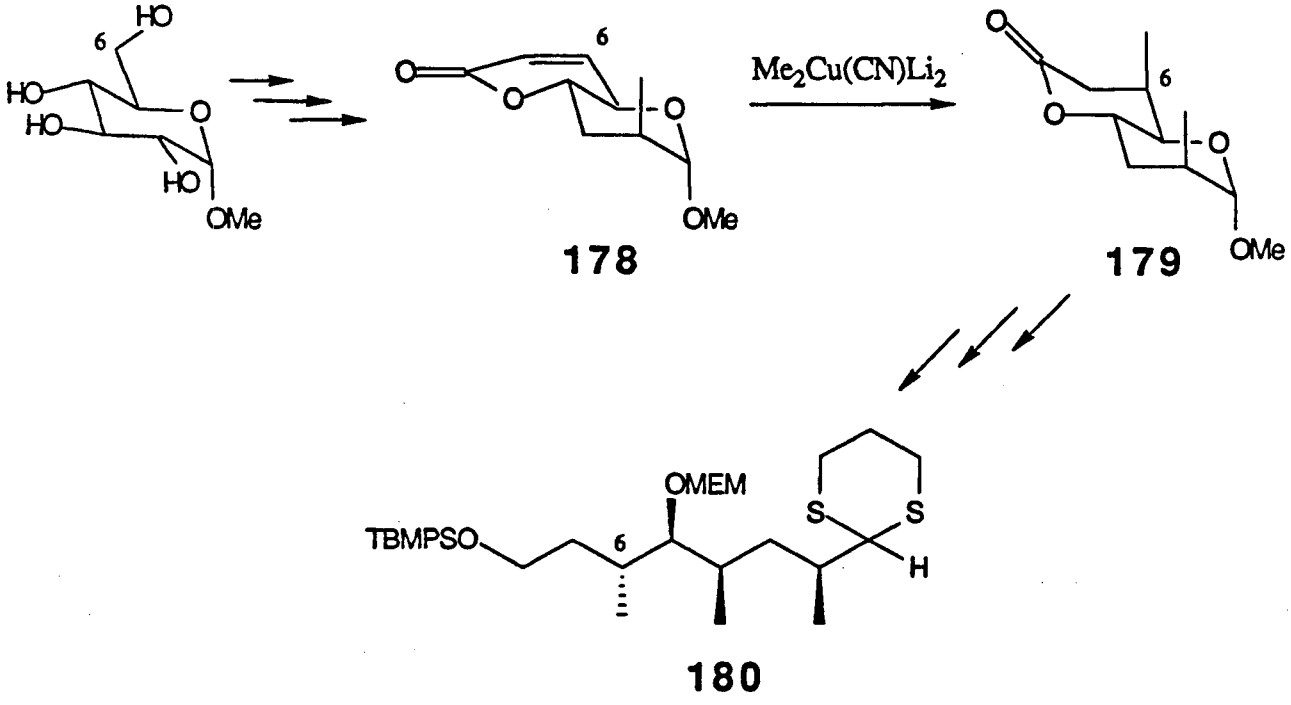
These model studies on the coupling of fragments A and B also demonstrated that the ester moiety interfered with the alkylation of the anion of dithiane 175 with epoxide 173.[98] Hence the ester in 175 was reduced to the alcohol and protected as its methoxyethoxymethyl ether to give fragment B of ionomycin as compound 176. All the work on fragment B was carried out by K.P. Shelly,[98] A. Schwerdtfeger, and P. Giguère.



Scheme 60. Synthesis of fragment B from the resolved acid ester 68.

I.D. Synthesis of Fragment A (C_1-C_{10}).

Originally this fragment was to be constructed from α-D-glucose.[100] This route involved the stereoselective introduction of a methyl group at the C_6 position on the glucose ring by a higher order cuprate addition to the bicyclic lactone 178 to give the axial methyl in product 179 as shown in Scheme 61. This methyl corresponds to the methyl at C_4 in ionomycin. The other two methyl groups were introduced by selective reactions on the glucose ring.[101] This route led to the precursor 180 to fragment A and was carried out by D. Nicoll-Griffith.[100]



Scheme 61. Nicoll-Griffith's synthesis of a precursor to fragment A from methyl α-D-glucopyranoside.[100]

Due to certain difficulties encountered in the synthesis of fragment A by this route it was decided to synthesize fragment A via an alternate route. The new strategy centred around the equilibration of spiroketal 66 (Figure 9).[59,102] The relative energies of the four diastereomers 66, 181, 182, and 183 were obtained from molecular mechanics calculations and are given in the Figure.[103] These diastereomers may be interconverted by epimerization of the methyl groups adjacent to the spiroketal carbon.

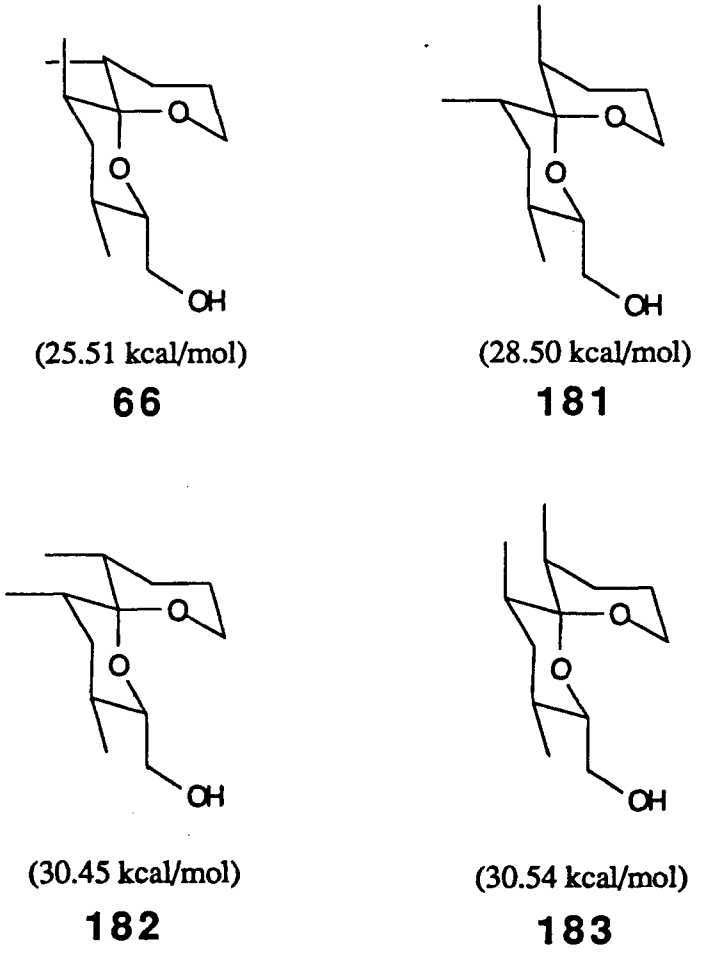
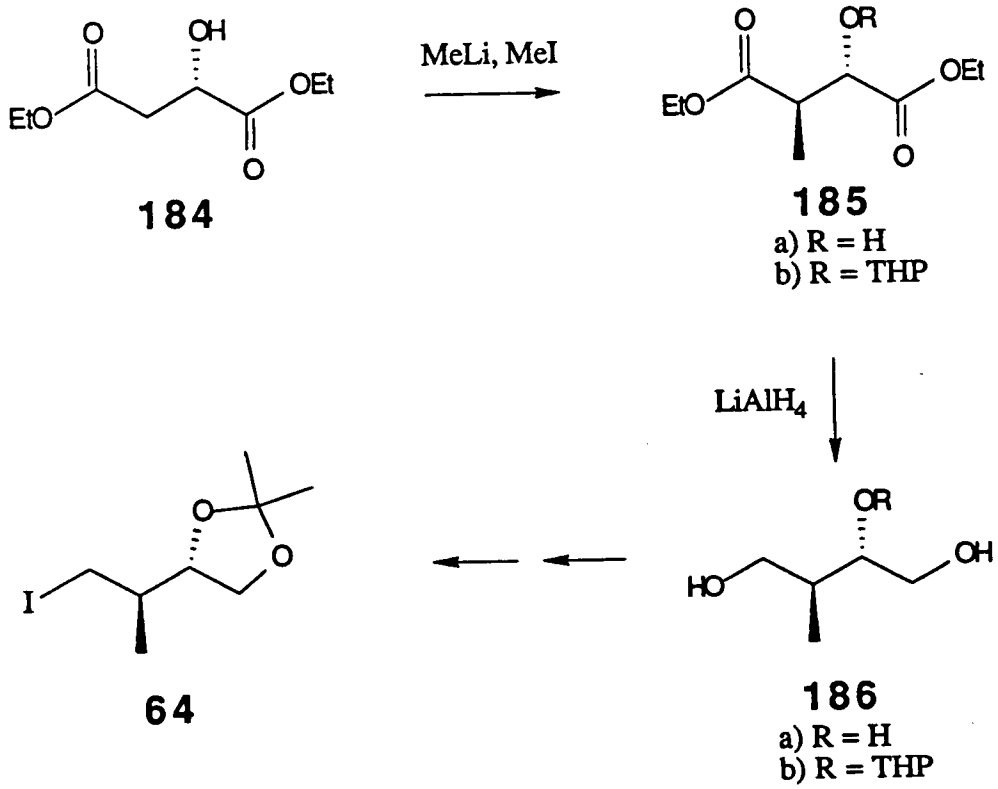


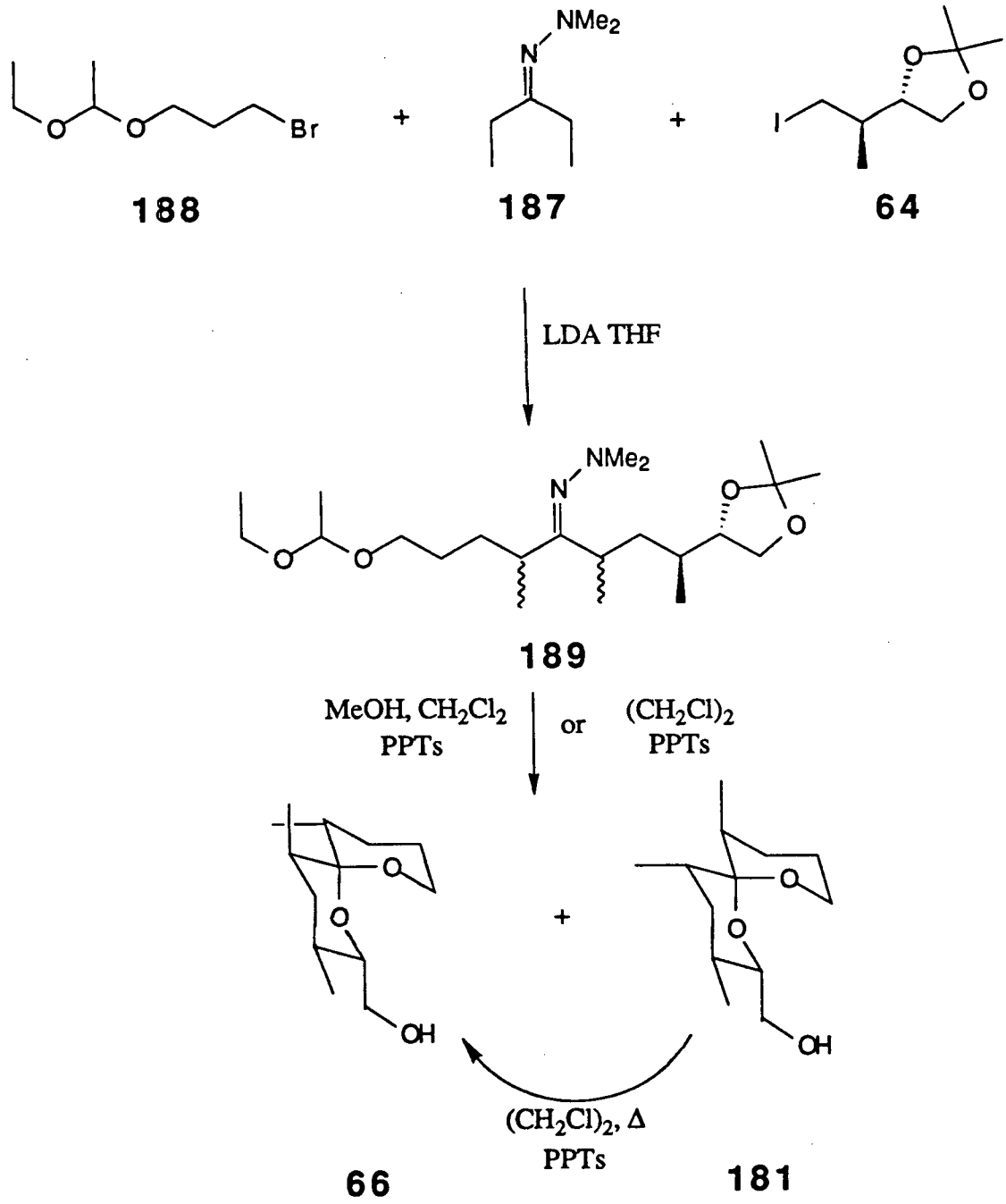
Figure 9. The four isomeric spiroketals and their relative energy (derived from molecular mechanics calculations) in parentheses.

Iodide 64 was prepared from (+)-malic acid in several steps following the procedure of Mori and Iwasawa as shown in Scheme 62.[104] (+)-Malic acid was esterified to give the diester 184 in excellent yield. The dianion of 184 was then alkylated stereoselectively with methyl iodide to give a 72% yield of the methylated diester 185a along with its epimer in a ratio of 9:1. Reduction of diester 185a directly to the triol 186a proved difficult because of the insolubility of the product. Thus the alcohol in 185a was first protected as its tetrahydropyranyl ether 185b followed by reduction with lithium aluminium hydride and subsequent deprotection of the tetrahydropyranyl ether to afford triol 186a in 57% yield for the last three steps. The 1,2-diol in 186a was selectively protected as its isopropylideneketal and the free primary alcohol converted into the iodide by two standard steps to give compound 64 in 69% yield from 186a.



Scheme 62. Preparation of optically active iodide 64.[103]

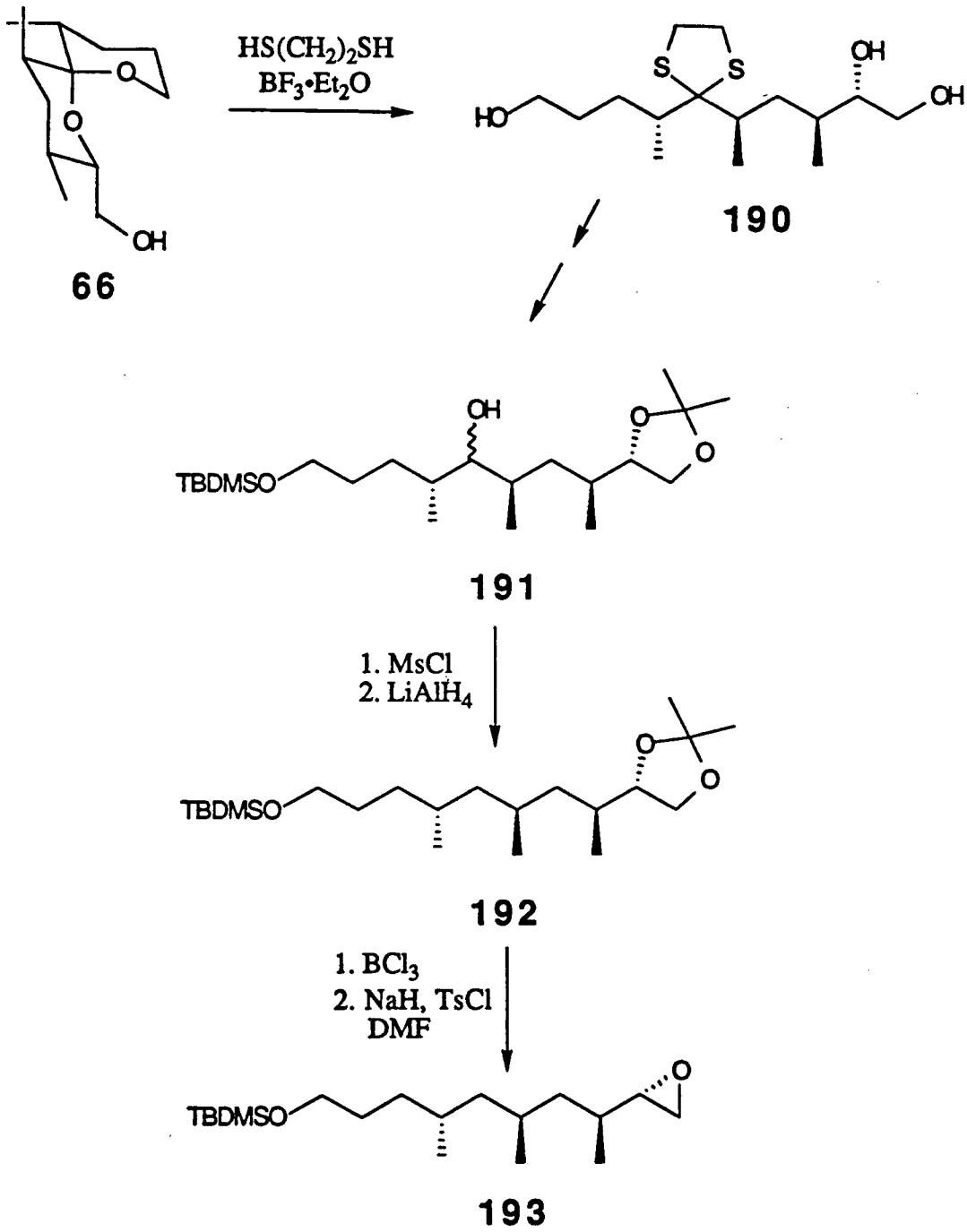
3-(1-Ethoxyethoxy)-1-bromopropanol (188) was then used to alkylate the anion of the hydrazone 187 derived from 3-pentanone (Scheme 63). A second alkylation of 187 with the iodide 64 led to compound 189 in 82% yield from 64. Hydrazone 189 was then directly cyclized to spiroketal 66 with pyridinium p-toluenesulfonate in a 10:1 mixture of dichloromethane and methanol. Under these conditions however **two** of the four possible diastereomers, compounds 66 and 181, were formed in equal amounts. On treatment with pyridinium p-toluenesulfonate in refluxing dichloroethane, the mixture of spiroketals was converted to an equilibrium mixture of the two spiroketals 66 and 181 in a 9:1 ratio, with the desired spiroketal 66 predominating. The same conditions, when used directly on the hydrazone 189, **did not** lead to this equilibrium mixture and again an equal amount of the two compounds was formed (Scheme 63). It would appear that one or more of the by-products from the deprotection–cyclization step interfered with the attainment of the equilibrium.



Scheme 63. Preparation and equilibration of spiroketals 66 and 181.

The spiroketal 66 was cleaved with ethanedithiol and boron trifluoride etherate (Scheme 64) in excellent yield. Then the 1,2-diol in 190 was protected as its isopropylidene ketal and the primary alcohol as its t-butyldimethylsilyl ether. Attempts to reduce the dithiolane 190 directly to the alkane 192 with tributyltin hydride under radical initiation led to epimerization of the adjacent methyl groups as seen by NMR analysis. Raney nickel had been shown to also give epimerization on a similar system.[59] Therefore an indirect route to reduce C_5 was chosen where the dithiolane was hydrolysed and the resulting ketone reduced to alcohol 191 as a 1:1 mixture of epimers at the carbinol carbon. Mesylation of the mixture and further reduction with lithium aluminium hydride in tetrahydrofuran cleanly gave a single alkane 192 in 55% yield for three steps.

To complete the synthesis of fragment A, the protected 1,2-diol was converted into an epoxide in two steps (Scheme 64) by selective cleavage of the isopropylidene protecting group with boron trichloride followed by epoxidation with tosyl chloride and sodium hydride to afford epoxide 193 in 62% yield from 192. The synthesis of fragment A was performed by P. Giguère.



Scheme 64. Synthesis of fragment A from the spiroketal 66.

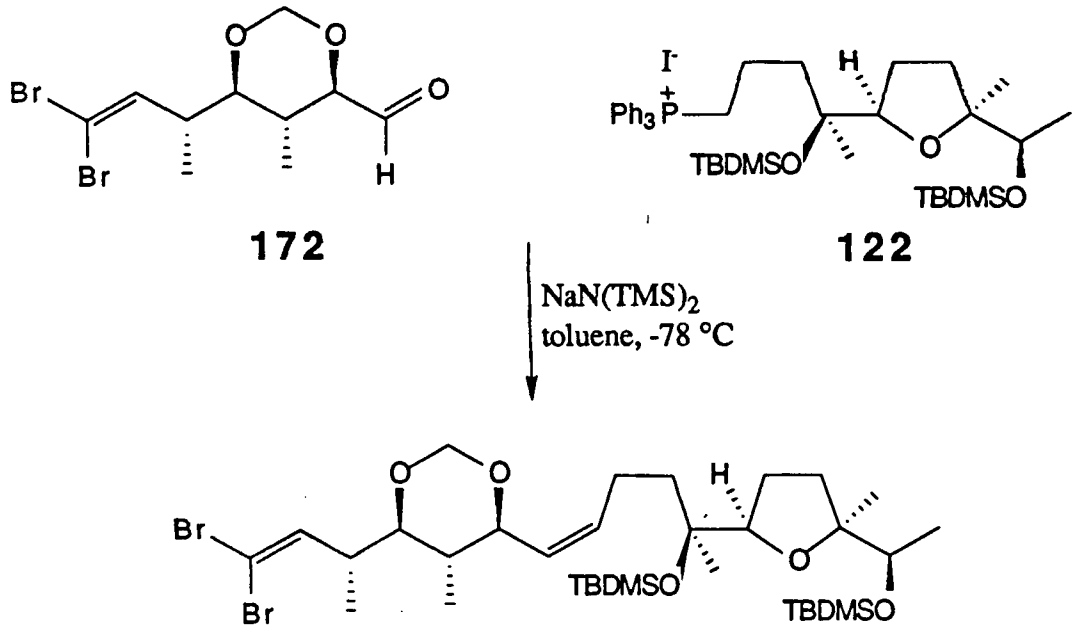
II. Assembly of the Four Fragments of Ionomycin.

This section describes the successful coupling of fragments C and D into a precursor to segment CD and fragments A and B into a precursor to segment AB. The plan for the final assembly of segments AB and CD is then described in section III.

II.A. Coupling of Fragment C (C_{16}-C_{21}) and Fragment D (C_{22}-C_{32}).

Fragments C and D were joined using a Wittig reaction. Under salt-free conditions,[105] the Wittig reaction allows for the generation of predominantly the cis olefin (Scheme 65). The cis geometry of the alkene was required to control the stereochemistry in the subsequent mercury cyclization.

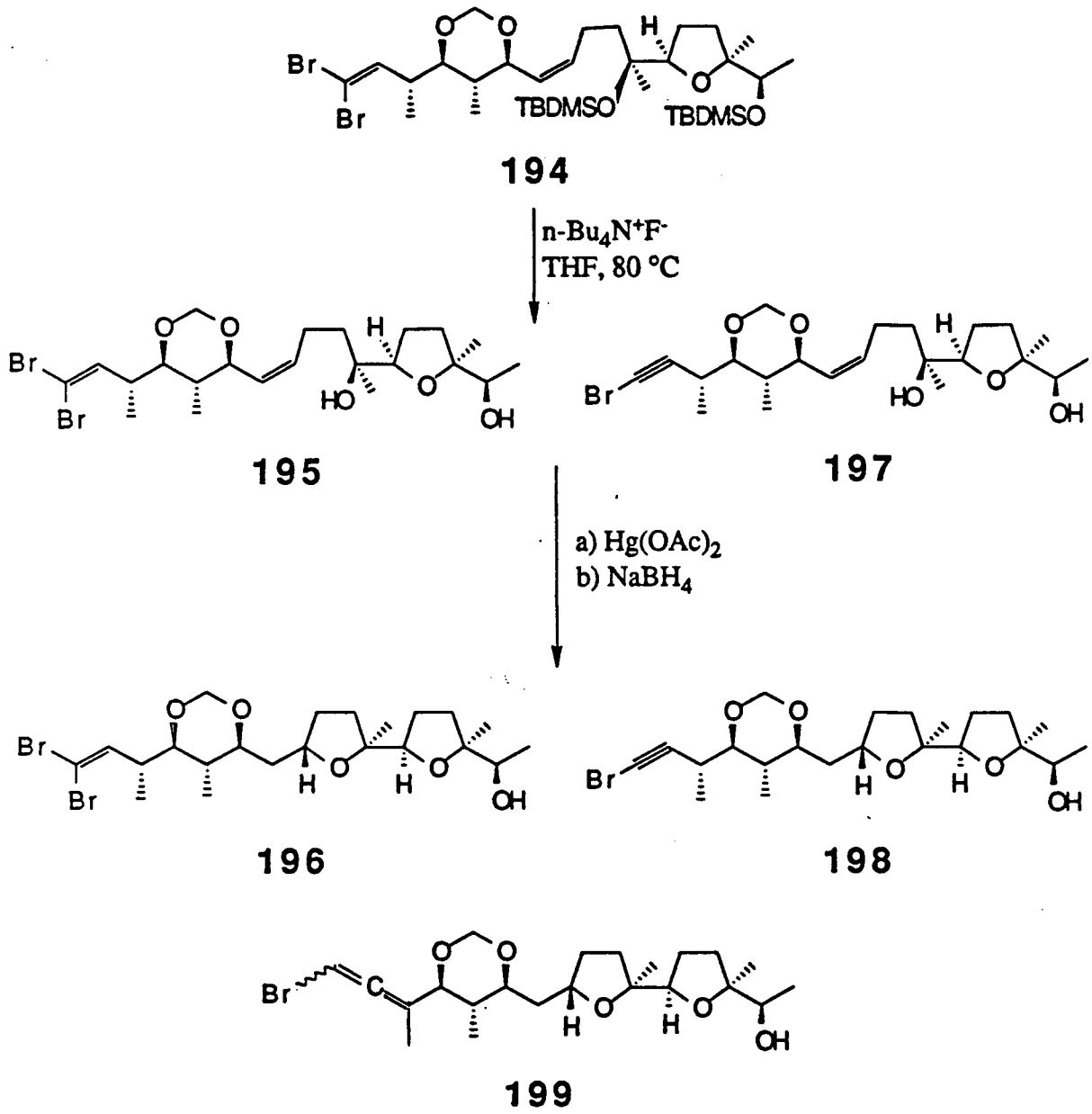
Thus the phosphonium salt 122 was treated with one equivalent of sodium bis(trimethylsilyl)amide in toluene followed by addition of aldehyde 172 to yield the desired olefin 194 in 73% yield along with its geometric isomer in a ratio of 24:1 (Scheme 69). Compound 194 was found to have the cis geometry about the new double bond based on the coupling constant between the two vinylic hydrogens (10.0 Hz) in its proton NMR spectrum. The trans isomer showed the expected larger coupling constant of 15.0 Hz for the corresponding vinylic hydrogens.



Scheme 65. Coupling of fragments C and D via the Wittig reaction.

Deprotection of the alcohols in 194 with n-tetrabutylammonium fluoride in tetrahydrofuran at 80 °C in a sealed tube gave, in 50% chemical yield, a mixture of the desired compound 195 and bromoacetylene 197 in a 1:5 ratio (Scheme 66). This was somewhat surprising, although fluoride ion is a relatively strong base in nonhydroxylic solvents. The t-butyldimethylsilyl groups could not be completely cleaved by the fluoride reagent at room temperature.[82] Previous model studies demonstrated that the acetylene moiety might interfere

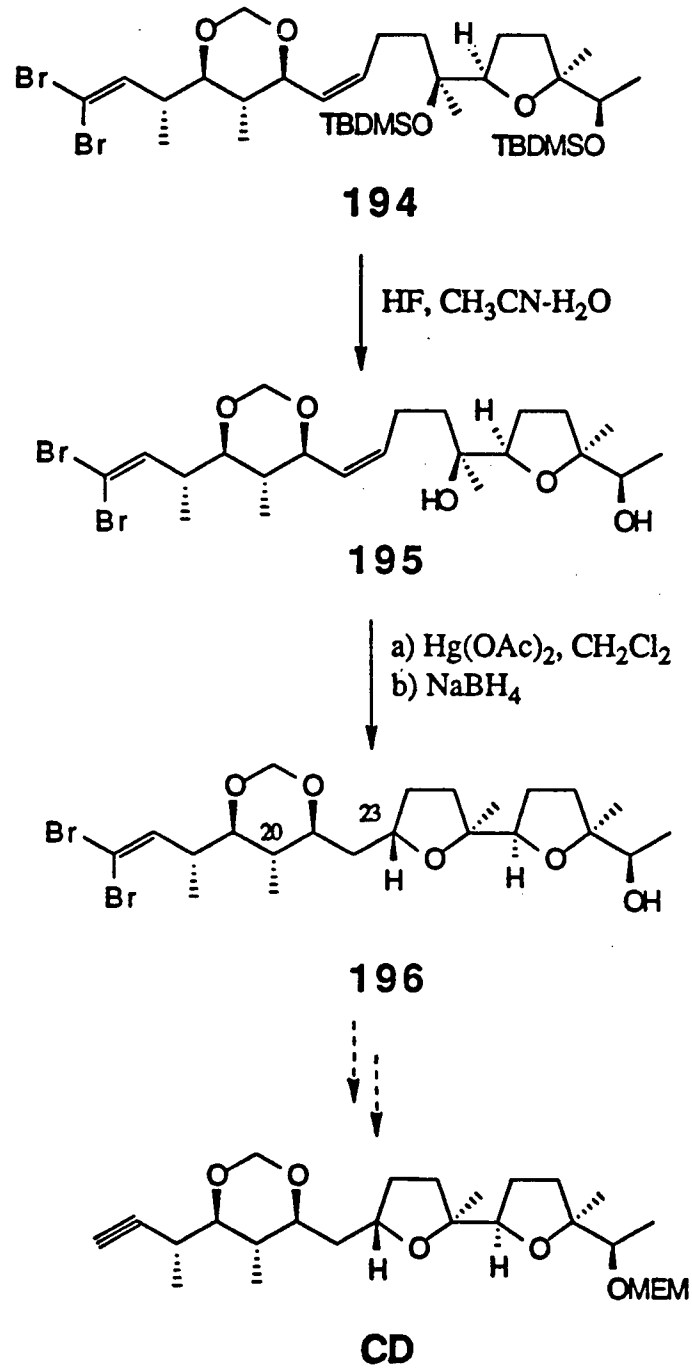
with the oxymercuration step (see section I.B., p. 78). However we hoped that the presence of the bromine atom on the triple bond in 197 could have a strong enough inductive effect on the acetylene to reduce its nucleophilicity, much the same way as it did with olefins 159a, 160a, and 161a (see Scheme 55, p 82), and thereby prevent its reaction in the oxymercuration step. However, treatment of the mixture of γ,δ-unsaturated alcohols 195 and 197 (1:5) with mercuric acetate in dichloromethane, followed by reduction of the organomercurial with sodium borohydride, gave a mixture of three products in a 1:3:2 ratio (Scheme 66). The first two of these products were identified by ^{1}H NMR analysis as the tetrahydrofurans 196 and 198. The third product was tentatively assigned structure 199, containing the allene moiety, on the basis of its proton NMR spectrum. The allene could arise from the mercury catalysed isomerization of the acetylene. It was assumed, in any case, that this product was derived from the reaction of the acetylene group in 197 with the mercury. Therefore another set of reaction conditions was sought for the deprotection of 194.



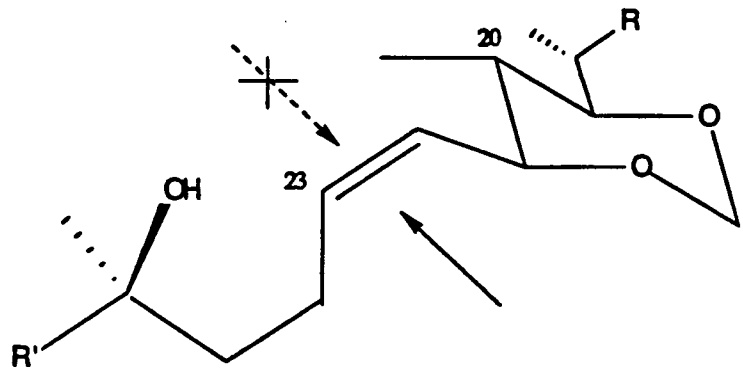
Scheme 66. Deprotection of the bis-t-butyldimethylsilyl ether 194 and oxymercuration of the resulting mixture of 195 and 197.

It was found that aqueous hydrofluoric acid in acetonitrile at room temperature gave in excellent yield diol 195 with no detectable trace of acetylenic products (Scheme 67). The γ,δ-unsaturated alcohol 195 was subsequently subjected to the oxymercuration conditions and after reduction with sodium borohydride, tetrahydrofuran 196 was isolated in 84% yield as the only product (Scheme 67). GLC analysis of the compound obtained did not show any of the tetrahydrofuran epimeric at C_{23}. The ^1H NMR confirmed that result. This type of electrophilic cyclization has been known to give good selectivity and we had predicted that the outcome of the internal oxymercuration reaction, based on examples in the literature,[49,106] would give the desired stereochemistry at C_{23}. The conformational bias that the 1,3-dioxane ring offers to the incoming electrophile is depicted in Scheme 68.[107] Attack of the mercury should come from the more open (re-re) face of the double bond, as shown in the conformation model of 195, away from the methyl substituent at C_{20}. The transition state 201 is further favored over transition state 200 because of the trans relationship between the two bulky substituents on the developing tetrahydrofuran ring. The stereochemistry at C_{23} in 196 was assigned by a nuclear Overhauser effect difference spectroscopy (NOEDS) experiment (Figure 10). When the methine proton at C_{23} in 196 was irradiated, no significant enhancement of the angular methyl at C_{26} was observed, indicating that the stereochemistry shown in 196 for the newly formed tetrahydrofuran was indeed the one obtained in the cyclization reaction.

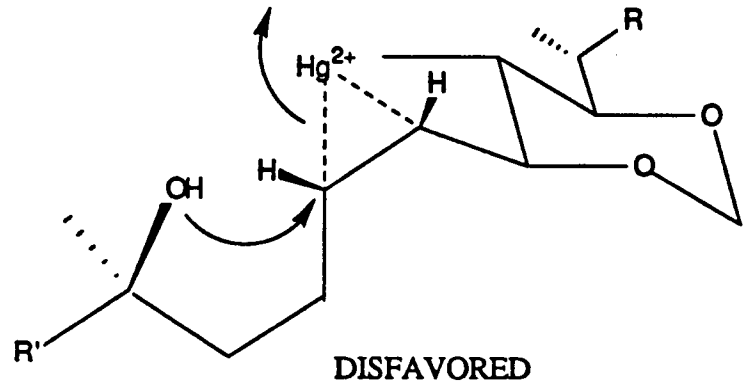
To complete the synthesis of segment CD, the secondary alcohol would be protected as its methoxyethoxymethyl derivative and the vinyldibromide would be converted into an acetylene (Scheme 67). We decided to wait for the results of a model study on the coupling of segments AB and CD before completing these steps.



Scheme 67. Stereocontrolled cyclization of the γ,δ-unsaturated alcohol 195 to bistetrahydrofuran 196.

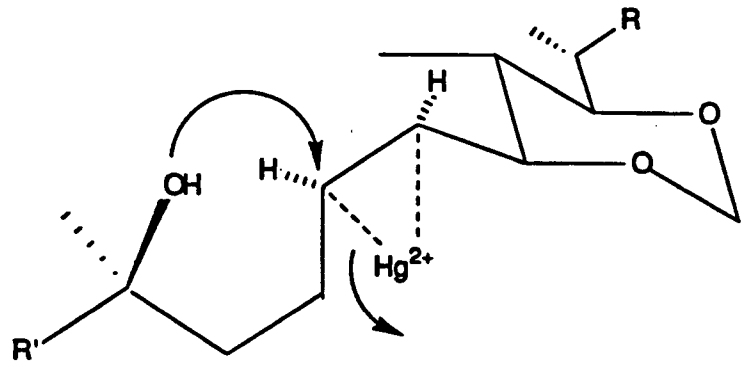


195



DISFAVORED

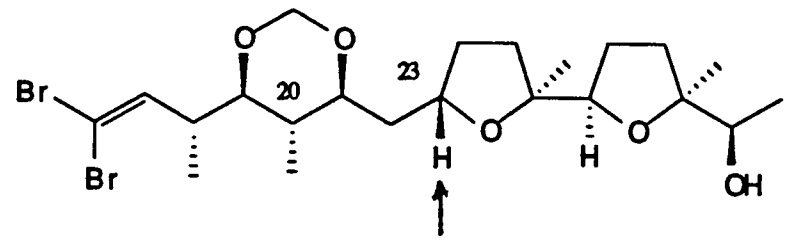
200



FAVORED

201

Scheme 68. Transition states for the oxymercuration of γ,δ-unsaturated alcohol 195.



196

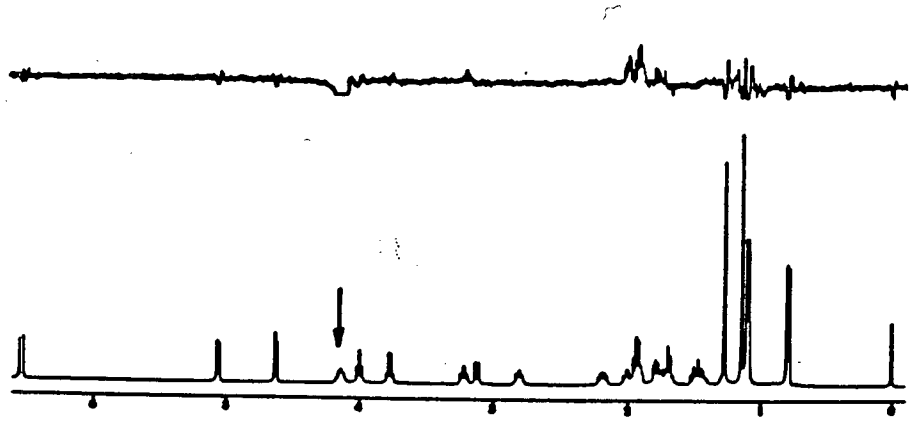
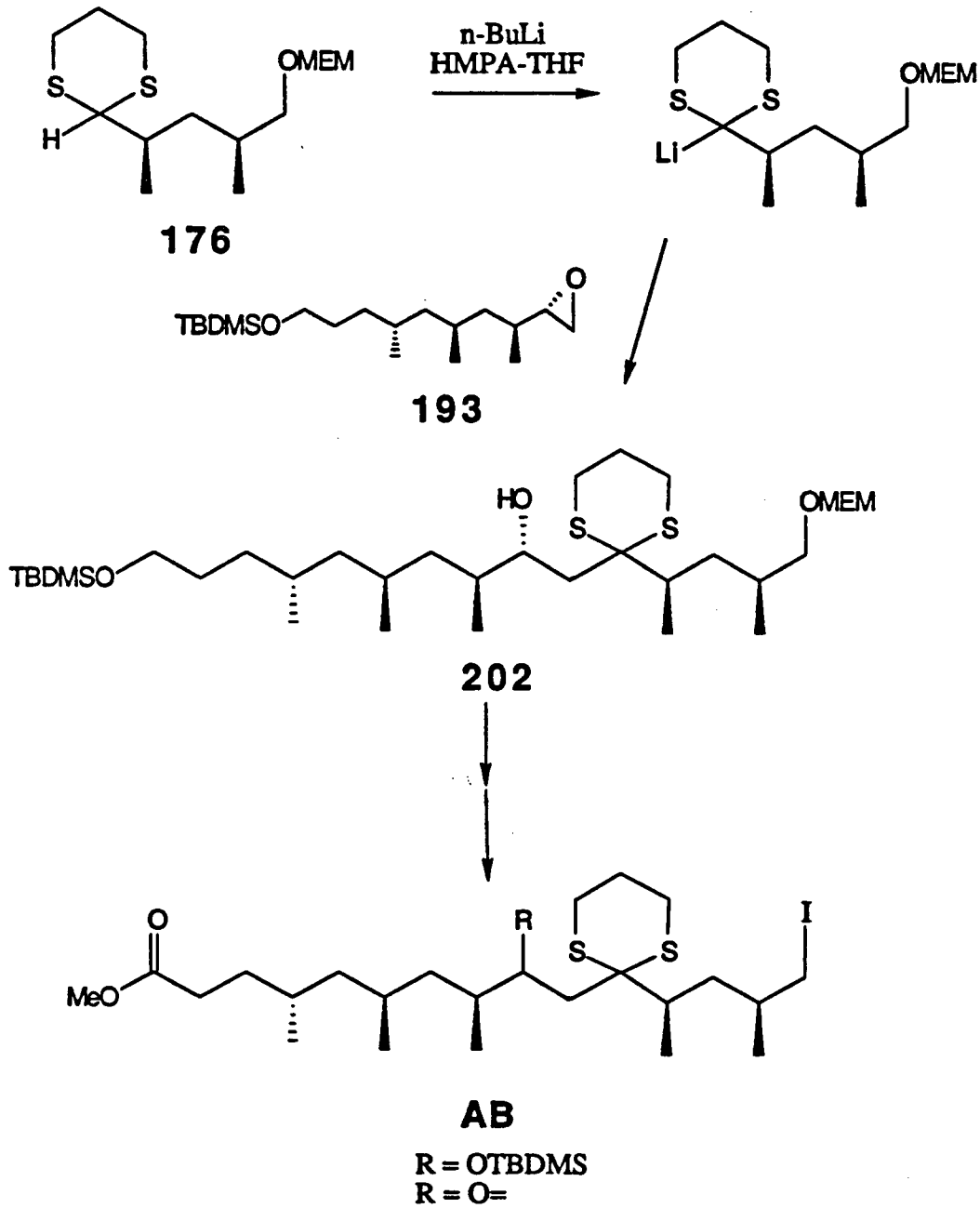


Figure 10. NOEDS experiment on bistetrahydrofuran 196: the irradiated proton is shown with an arrow in the structure.

II.B. Coupling of Fragments A (C_1-C_{10}) and B (C_{11}-C_{15})

The coupling of fragments A and B was achieved by the alkylation of the anion of the dithiane 176 with the epoxide 193 (Scheme 69). Earlier model studies on this coupling showed this route to be viable.[98] However the reaction gave only ~40% yield of the coupled products under a variety of reaction conditions. The deprotonation of dithiane 176 with strong bases such as n-butyllithium and t-butyllithium proved to be difficult.[98,100] This problem was solved by the use of 50% v/v of N-hexamethylphosphoramide in tetrahydrofuran as solvent. Dithiane 176 was metallated with n-butyllithium and was alkylated with epoxide 193 to afford the hydroxy dithiane 202 in > 60% yield. The secondary alcohol would then be oxidized to the ketone or protected with a t-butyldimethylsilyl group, depending on the results of an ongoing model study for the coupling of segments AB and CD.

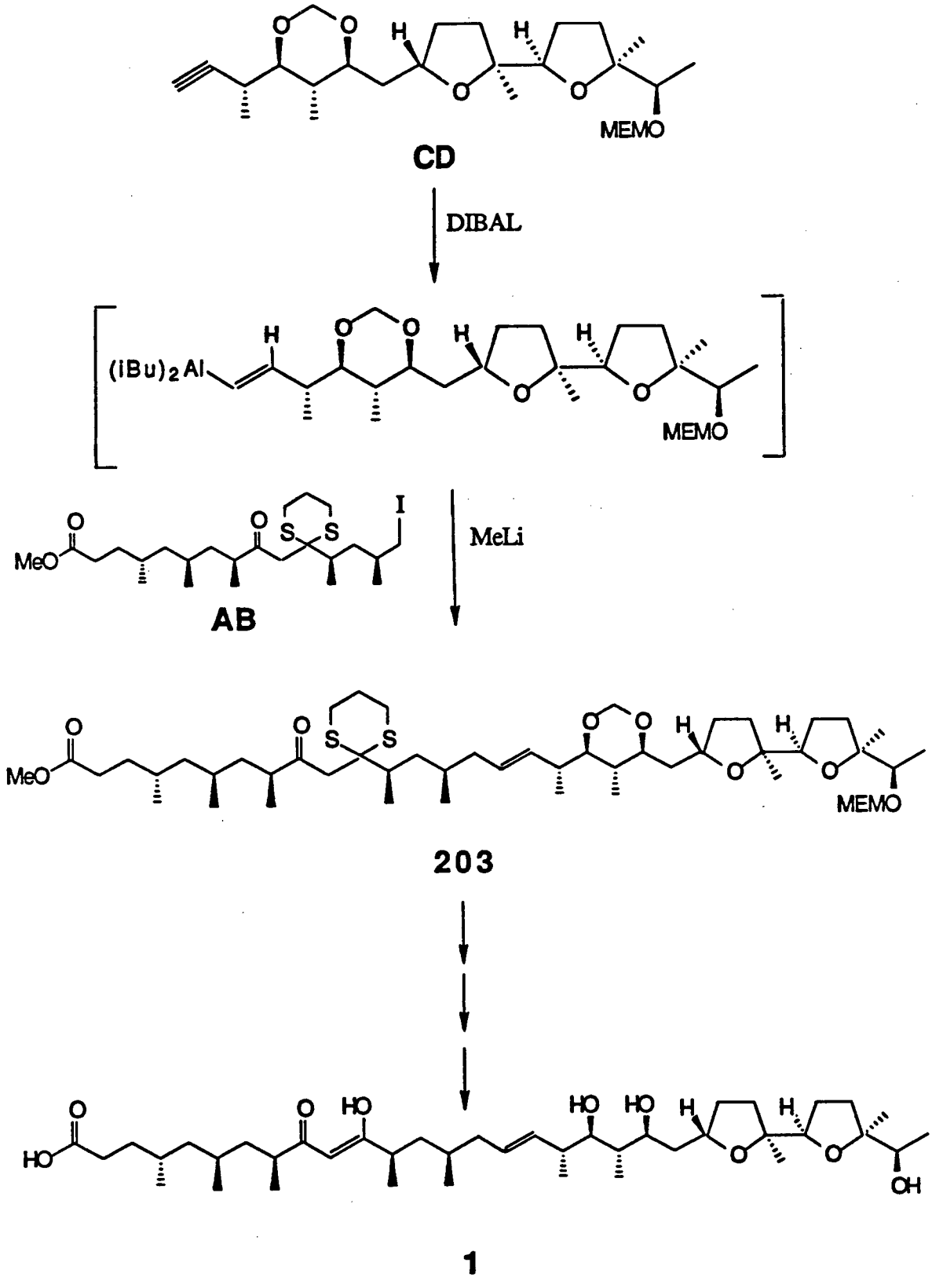
To complete the synthesis of segment AB, the protected alcohol at C_1 (ionomycin numbering) would have to be converted to the corresponding ester and the protected alcohol at C_{15} into the corresponding iodide (Scheme 69). The coupling of fragments A and B was conducted by P. Giguère.



Scheme 69. Coupling of fragments A and B and plan for the completion of segment AB.

III. Plan for the Final Assembly of Segments AB and CD

The hydroalumination of alkynes is known to proceed via the cis addition of the hydrogen and the aluminium.[108] Negishi and coworkers have developed a method for the alkylation of trans alkenyl trialkylaluminates with halides and sulfonates that allows for the stereoselective preparation of trans alkenes.[109] We hoped to use this method in the coupling of segments AB and CD (Scheme 70). Thus segment CD would be treated with the reaction conditions of Negishi and coworkers and alkylated with segment AB to give compound 203 with the desired trans double bond. The simultaneous deprotection of the methylene acetal and the methoxyethoxymethyl would then be achieved using the reaction conditions of Negri and Kishi described in section I.B. (p 76). The consecutive hydrolysis of the dithiane and ester groups would then afford the final target molecule ionomycin (Scheme 70).



Scheme 70. Plan for the eventual coupling of segments AB and CD and the final steps to the ultimate target : ionomycin.

IV. Conclusion

A stereoselective synthesis of the C_{16}-C_{32} segment of ionomycin was achieved by the preparation and coupling of the C_{16}-C_{22} and C_{23}-C_{32} fragments. Fragment C (C_{16}-C_{22}) was synthesized using the asymmetric aldol methodology developed by Evans and coworkers, thus introducing four of the nine asymmetric centres contained in segment CD with the correct absolute stereochemistry. The use of crotonyl imide 69 permitted us to obtain indirectly the anti aldol product in a highly enantioselective fashion.

Fragment D (C_{23}-C_{32}) was prepared using the permanganate oxidative cyclization of 1,5-dienes as the key step. In that reaction, four chiral carbons were created having the correct relative stereochemistry. A resolution of fragment D with (+)-O-acetylmandelic acid was effected before joining it to fragment C.

Finally the two fragments were coupled using the Wittig reaction and the remaining asymmetric centre in segment CD was introduced stereoselectively via the oxymercuration reaction. Colleagues in our laboratory successfully completed the synthesis and the coupling of the C_1-C_{10} and C_{11}-C_{15} fragments. We hope that with these two segments in hand, the successful synthesis of the antibiotic ionophore ionomycin will be completed in the near future.

EXPERIMENTAL

I. General.

Unless otherwise stated, all reactions were performed under nitrogen or argon using oven dried glassware. Cooling of reaction mixtures overnight was effected using a Multi-cool™ cooling apparatus with methanol as cooling fluid.

The purification and source of the reagents and solvents used are listed in Table I. If no comment is made on a specific reagent or solvent, then it was used as received from the supplier.

Alkyllithiums were standardized by titration against 1,3-diphenyl-2-propanone-p-toluenesulfonylhydrazone[110] in THF and were obtained from Aldrich Chemical Co. (either in ether or in hexanes). Cuprous iodide (Aldrich) was purified by dissolving 13.6 g in a solution of 120 g of KI in 100 mL of distilled water and stirring 2 h on 2 g of activated charcoal (Fisher, grade 1) followed by filtration on celite and precipitation with 600 mL of water.[111] Analytical gas-liquid chromatography (GLC) were performed on a Hewlett-Packard model 5880A, equipped with a split mode capillary injection system and a flame ionization detector, using 0.22-mm columns of OV-101, Carbowax-20M, SE-30 or DB-210 and 0.25-mm column of SE-30. The columns were purchased from J.W. Scientific Co. Helium was used as the carrier gas in all cases.

Preparative flash column chromatography[112] was performed with silica gel 60, 230-400 mesh supplied by E. Merck Co. Usually a 60 to 1 ratio of silica gel to compound was used.

Melting points were recorded on a Kofler hot stage apparatus and are uncorrected. In the cases where a Kugelrohr distillation was performed, boiling points are given as the oven temperature. Boiling points are uncorrected.

Optical rotations were determined with a Perkin-Elmer 141 polarimeter at 20°-25 °C. Concentration are in grams of solute per 100 mL of solution. Infrared (IR) spectra were

Table I. Purification of solvents and reagents.

Reagent or solvent	supplier	method of purification
acetone	Aldrich	Distilled from $CaSO_4$
acetonitrile, chloroform, dichloromethane, diisopropylethylamine, hexamethylphosphoramide methanesulfonyl chloride, triethylamine	Fisher, BDH	Distilled from CaH_2
benzene, tetrahydrofuran, toluene,diethyl ether.	Fisher, BDH	Distilled from sodium metal and benzophenone
carbon tetrabromide	BDH	Sublimed 90 °C / 4 torr
crotonyl chloride	Aldrich	Distilled from $CaCl_2$ over molecular sieve at 120 °C
di-n-butylboron triflate	Aldrich	Distilled at 70 °C / 4 torr
2, 6-dimethylpyridine	Aldrich	Distilled from CaH_2
dimethyl sulfoxide	Aldrich	Distilled from CaH_2 at 76 °C/ 12 torr
mercuric acetate	BDH	Recrystallized in AcOH
methyl acetoacetate	Aldrich	Distilled 169 °C / 760 torr
potassium carbonate	BDH	Flamed under vacuum
potassium permanganate	Aldrich	Recrystallized from H_2O
pyridine	Fisher	Distilled from CaH_2
sodium bicarbonate	BDH	Flamed under vacuum
sodium hydride	Aldrich	Washed 3 times with THF
sodium iodide	BDH	Flamed under vacuum
tetra-n-butylammonium fluoride	Aldrich	Dried under vacuum at 75 °C for 12 hr.
p-toluenesulfonyl chloride	BDH	Extracted from a soxlet with high boiling pet. ether
triphenyl phosphine	BDH	Recrystallized from EtOH
zinc metal (dust)	Fisher	Washed with HCl, H_2O, EtOH, and ether

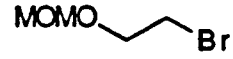
recorded on a Perkin-Elmer model 710B spectrophotometer or on a BOMEM FT-IR Michaelson-100 connected to a IBM compatible microcomputer. IR spectra were taken in a chloroform solution using NaCl cells of 0.2 mm thickness and were calibrated with the 1601 cm^{-1} band of polystyrene except for those spectra recorded on the BOMEM FT-IR instrument. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded in a deuterochloroform solution on a Bruker WP-80 (80 MHz), Bruker HXS-270 (270 MHz), Varian XL-300 (300 MHz), or a Bruker WH-400 (400 MHz) spectrometer. Chemical shifts are given in parts per million on the δ scale versus tetramethylsilane (δ 0) or chloroform (δ 7.27) as internal standards. Signal multiplicity, integration ratios, and coupling constants are indicated in parentheses. Carbon-13 NMR spectra were recorded on a Bruker WH-400 (100 MHz) or a Varian XL-300 (75 MHz) instrument. In cases where a mixture of isomers was obtained, the spectral data are reported only for the major isomer, unless otherwise stated.

Low resolution mass spectra were recorded on either a Varian MAT model CH4B or a Kratos-AEI model MS 50 spectrometer. Only peaks with greater than 20% relative intensity or those which are analytically useful are reported. Gas chromatograph / mass spectra were obtained on a Carlo Erba 4160 gas chromatograph coupled with a Kratos MS 80 RFA mass spectrometer. High resolution mass spectra were carried out on a Kratos-AEI model MS 50 instrument. An ionization potential of 70 eV was used in all measurements.

Microanalyses were carried out at the microanalytical laboratory at the University of British Columbia using a Carlo Erba Elemental Analyzer 1106.

II. Preparation of Fragment D

Preparation of 1-Bromo-2-methoxymethoxyethane (85).



A 500-mL, three-neck, r.b. flask was charged with 300 mL of dry CH_2Cl_2, bromoethanol (14.15 g, 0.113 mole), and 60 mL (0.68 mole) of methylal under nitrogen. The solution was cooled to 0 °C and was allowed to stir for 10 min. Then 1 g of P_2O_5 was added while stirring the mixture vigorously. Every 10 min 1 g of P_2O_5 was added until the reaction was complete (TLC).

The mixture was then carefully added to 1 L of an ice-cold saturated solution of aqueous $NaHCO_3$ and the gummy residue remaining in the flask was also carefully washed with $NaHCO_3$. The aqueous layer was separated and extracted with diethyl ether, the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure to yield a slightly yellow oil. Distillation under reduced pressure (64 °C / 31 torr) gave 15.30 g (80% yield) of bromide 85 as a colorless oil.

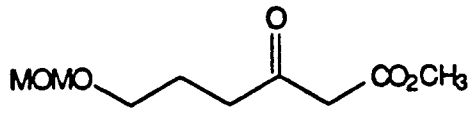
^{1}H NMR (80 MHz), (δ) : 4.73 (s, 2H), 3.90 (t, 2H, J = 5.50 Hz), 3.54 (t, 2H, J = 5.50 Hz), 3.43 (s, 3H).

IR (cm^{-1}) : 3000-2800(m), 1450(w), 1430(w), 1405(w), 1395(w), 1285(m), 1145(s), 1105(s), 1065(s), 1035(s), 990(m), 950(w), 920(m).

MS (m/z) : 169(^{81}Br, M^+-1, 8), 167(^{79}Br, M^+-1,7), 139(9), 137(11), 109(28), 107(25), 75(29), 45(100).

Exact mass calcd for $C_4H_9{}^{79}BrO_2$: 166.9708; found : 166.9703.

Preparation of Methyl 6-methoxymethoxy-3-oxo-hexanoate (86).



A 500-mL, three-neck, r.b. flask was equipped with a stirring bar and two pressure-equalized addition funnels. Sodium hydride (10.1 g, 0.252 mol) was added, followed by 250 mL of dry THF and the resulting suspension was cooled to 0 °C. Methyl acetoacetate (20.9 g, 0.180 mol) in 15 mL of THF was added slowly through one of the addition funnels. The resulting yellowish solution was allowed to stir at 0 °C for 15 min and 146 mL (0.234 mol) of n–butyllithium (1.6 M in hexanes) was added slowly through the second addition funnel. The orange solution was allowed to stir at 0 °C for 15 min. Then 19.0 g (0.112 mol) of 1-bromo-2-methoxymethoxyethane (85) was slowly added through the first addition funnel and the resulting yellow suspension was stirred at 0 °C for 15 min and 1 h at room temperature.

The mixture was then added to 500 mL of an ice-cold saturated solution of aqueous NH_4Cl, acidified with concd HCl to pH 6 and extracted with diethyl ether several times. The combined organic layers were washed twice with saturated aqueous $NaHCO_3$, twice with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to yield 21.02 g of an orange oil. Because of the heat sensitivity of the ß-keto ester, the product was purified by Kugelrohr distillation (90-100 °C / 0.075 torr) in small batches of 3 g giving a total of 18.28 g (80% yield) of ß-keto ester 86 as a slightly yellow oil.

^{1}H NMR (80 MHz), (δ): 4.60 (s, 2H), 3.75 (s, 3H), 3.54 (t, 2H, J = 6.0 Hz), 3.48 (s, 2H), 3.37 (s, 3H), 2.67 (t, 2H, J = 7.0 Hz), 1.90 (q, 2H, J = 7.0 Hz).

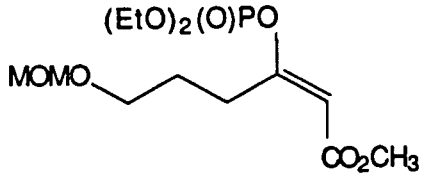
IR (cm^{-1}): 3100-2800(m), 1745(s), 1715(s), 1435(m), 1405(m), 1365(m), 1315(m), 1120(s), 1100(s), 1060(m), 1030(s), 905(m).

MS (m/z): 173 (M^+-OCH_3, 16), 159(16), 143(59), 142(64), 141(100), 129(25), 116(78), 110(13), 101(71), 85(63), 74(22), 6928), 59(41).

Exact mass calcd for $C_8H_{13}O_4$: 173.0814; found: 173.0812.

Anal. calcd for $C_9H_{16}O_5$: C 52.73, H 7.90, O 39.17 ; found : C 52.50, H 7.80.

Preparation of Methyl (E)-3-diethylphosphoryloxy-6-methoxymethoxy-2-hexenoate (87).



To a mixture of 9.95 mL (0.072 mol) of triethylamine, 12.4 mL (0.0724 mol) HMPA , and 793 mg (0.652 mmol) of DMAP at 0 °C was added ß-keto ester 86 (13.2 g, 0.0653 mol). The reaction mixture was then stirred at 0 °C for 0.5 h. Then the mixture was cooled to -20 °C and 10.3 mL (0.0724 mol) of diethyl chlorophosphate was added dropwise. The resulting thick beige slurry was stirred vigorously for 6 h at room temperature. Then the slurry was added to 300 mL of ice-cold 1N HCl. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with a saturated solution of aqueous $CuSO_4$, brine, dried over $MgSO_4$, and evaporated under reduced pressure to afford 21.68 g of a slightly orange oil. Some product was purified by chromatography on silica gel eluting with pet. ether - ethyl acetate (1:1) for analytical purposes, but otherwise the crude enol phosphate 87 was used in the next step without further purification.

^{1}H NMR (80 MHz), (δ) : 5.90 (d, 1H, J = 1.5 Hz), 4.63 (s, 2H), 4.32 (dq, 2H, J_{HH} = 8.0 Hz, J_{PH} = 9.0 Hz), 3.72 (s, 3H), 3.58 (t, 2H, J = 6.5 Hz), 3.38 (s, 3H), 2.90 (t, 2H, J = 8.0 Hz), 1.90 (m, 2H), 1.37 (dt, 3H, J_{HH} = 8.0 Hz, J_{PH} = 2.0 Hz).

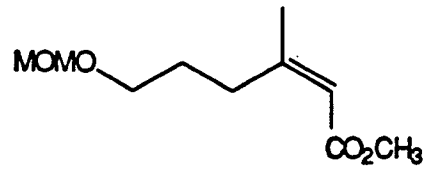
IR (cm^{-1}) : 3050-2800(m), 1720(m), 1650(m), 1445(w), 1380(w), 1280(m), 1150(m), 1135(s), 1115(m), 1030(s), 965(m).

MS (m/z) : 309 (M^+-OCH_3, 3), 295(0.3), 199(44), 169(29), 155(31), 142(20), 111(21), 99(27), 45(100).

Exact mass calcd for $C_{12}H_{22}O_7P$: 309.1103 ; found : 309.1094.

Anal. calcd for $C_9H_{16}O_5$: C 45.88, H 7.40, O 37.61, P 9.10 ; found : C 46.18, H 7.44, O 37.89.

Preparation of Methyl (Z)-6-methoxymethoxy-3-methyl-2-hexenoate (88).



A three-neck, r.b. flask, equipped with a low temperature thermometer and an addition funnel, was charged with 14.9 g (0.0783 mol) of CuI and 260 mL of dry THF. The resulting suspension was cooled to -10 °C and 52.0 mL (0.0783 mol) of methyllithium (1.5 M solution in hexane) was added dropwise. The thick yellow suspension was then cooled to -35 °C and 44.8 mL (0.132 mol) of methylmagnesium chloride (2.9 M solution in diethyl ether) was added dropwise. This light grey-pink suspension was stirred at -45 °C for 15 min and 9.0 g (0.026 mol) of enol phosphate 87 was then added slowly, and the suspension was stirred at -45 °C for 12 h.

The yellow suspension was added to 500 mL an ice-cold saturated solution of aqueous NH_4Cl, and the aqueous phase was extracted with diethyl ether. The combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give 5.08 g of a green oil. Flash chromatography on silica gel using a mixture of pet. ether - ethyl acetate (9:1) as eluant followed by bulb-to-bulb distillation (95-100 °C / .05 torr) yielded the methylated product 88 as a colorless oil (3.45 g, 68% yield).

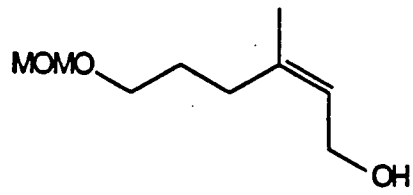
^{1}H NMR (80 MHz), (δ) : 5.70 (bs, 1H), 4.65 (s, 2H), 3.70 (s, 3H), 3.58 (t, 2H, J = 7.0 Hz), 3.40 (s, 3H), 2.70 (bt, 2H, J = 8.0 Hz), 1.91 (d, 3H, J = 1.5 Hz), 1.8 (m, 2H).

IR (cm^{-1}) : 3100-2800(m), 1710(s), 1650(m), 1445(m), 1390(s), 1300(s), 1190(m), 1155(s), 1110(m), 1040(s), 920(w), 865(w).

MS (m/z) : 171(M^+-OCH_3, 8), 170(8), 157(6), 141(16), 140(16), 139(12), 127(16), 126(16), 125(25), 95(21), 81(28), 45(100), 41(22).

Exact mass calcd for $C_9H_{15}O_3$: 171.1021 ; found : 171.1006.

Preparation of (Z)-6-Methoxymethoxy-3-methyl-2-hexen-1-ol (89).



The ester 88 (3.20 g, 15.8 mmol) was added to 40 mL of dry diethyl ether at 0 °C in a dry 100 mL r.b. flask under a nitrogen atmosphere. Then DIBAL (39.5 mL, 39.5 mmol, 1M solution in ether) was added dropwise and the reaction was left to stir at 0 °C for 0.5 h, after which the cooling bath was removed and the reaction mixture was stirred for an additional 1 h.

The mixture was then added to 200 mL of ice-cold 1N HCl and the aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed once with a saturated solution of aqueous $NaHCO_3$ and then with brine, dried over $MgSO_4$ and evaporated under reduced pressure to give 2.35 g of the crude alcohol 89. The product was distilled at 90 °C / 0.2 torr to yield 2.26 g (82% yield) of pure 89 as a colorless oil.

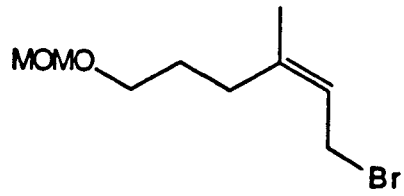
^{1}H NMR (80 MHz), (δ) : 5.52 (bt, 1H, J = 8.0 Hz), 4.63 (s, 2H), 4.12 (d, 2H, J = 8.0 Hz), 3.54 (t, 2H, J = 6.0 Hz), 3.38 (s, 3H), 2.20 (t, 2H, J = 7.0 Hz), 1.75 (d, 3H, J = 1.0 Hz), 1.60 (m, 2H).

IR (cm^{-1}) : 3640(w), 3600-3250(b,w), 3100-2800(m), 1680(w), 1455(m), 1390(m), 1230(b,m), 1150(s), 1110(s), 1040(s), 995(s), 920(m).

MS (m/z) : 142 (M^+-$HOCH_3$, 6), 129(10), 111(10), 97(24), 95(21), 85(27), 83(23), 81(35), 71(21), 69(22), 68(25), 67(21), 55(45), 45(100), 41(36).

Exact mass calcd for $C_8H_{14}O_2$: 142.0994 ; found : 142.0997.

Preparation of (Z)-1-Bromo-6-methoxymethoxy-3-methyl-2-hexene (90).



A dry 200-mL, two-neck, r.b. flask was charged with alcohol 89 (3.43 g, 0.0194 mol) and 100 ml of dry CH_2Cl_2 and the resulting solution was cooled to -78 °C. Then CBr_4 (7.83 g, 0.0242 mol) was added to the mixture followed by of 5.68 g (0.0223 mol) of Ph_3P. The resulting mixture was stirred at -78 °C for 30 min and was then allowed to warm to room temperature.

The solvent was then removed under reduced pressure and 300 mL of pet. ether was added to the residue. The precipitate was filtered and washed several times with pet. ether. The filtrate was evaporated under reduced pressure and the residue treated again with 300 mL of pet. ether. The precipitate was filtered and washed with pet. ether. The filtrate was concentrated under reduced pressure to give a slightly brown oil. This oil was dissolved in 10 mL of pet. ether and filtered through a short column of silica gel. The filtrate was concentrated under reduced pressure to yield 4.43 g (95% yield) of the unstable bromide 90 as a slightly yellow oil. This product was used directly in the next step without further purification.

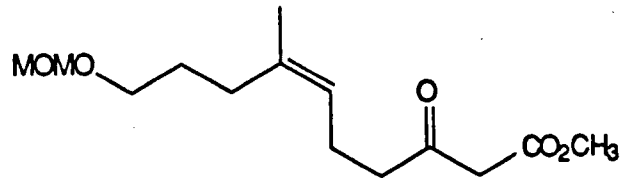
^{1}H NMR (80 MHz), (δ) : 5.58 (t, 1H, J = 9.0 Hz), 4.65 (s, 2H), 4.03 (d, 2H, J = 9.0 Hz), 3.55 (t, 2H, J = 6.0 Hz), 3.40 (s, 3H), 2.25 (bt, 2H, J = 7.0 Hz), 1.80 (bs, 3H), 1.6 (m, 2H).

IR (cm^{-1}) : 3050-2800(s), 1665(w), 1450(m), 1390(m), 1145(s), 1105(s), 1030(vs), 915(m), 850(w).

MS (m/z) : 207(^{81}Br, M^+-OCH_3, 1), 205(^{79}Br, M^+-OCH_3, 1), 157(9), 125(23), 97(24), 95(23), 81(33), 67(22), 55(38), 45(100), 41(23).

Exact mass calcd for $C_8H_{14}{}^{81}BrO$: 207.0209 ; found : 207.0178.

Preparation of Methyl (Z)-10-methoxymethoxy-7-methyl-3-oxo-6-decenoate (91).



The dianion of methyl acetoacetate (5.93 g, 0.0513 mmol) was alkylated as described in the procedure for the preparation of methyl 6-methoxymethoxy-3-oxo-hexanoate (86) (p 113) with 9.30 g (0.0394 mmol) of the bromide 90. The crude ß-keto ester 91 (10.0 g) was purified by chromatography on silica gel eluting with pet. ether - ethyl acetate (6:1) to yield 8.56 g (86% yield) of pure 91.

^{1}H NMR (80 MHz), (δ) : 5.10 (bt, 1H, J = 7.0 Hz), 4.65 (s, 2H), 3.75 (s, 3H), 3.50 (t, 2H, J = 6.0 Hz), 3.45 (s, 2H), 3.38 (s, 3H), 2.6-2.0 (m,6H), 1.65 (d, 3H, J = 1.5 Hz), 1.8-1.5 (m, 2H).

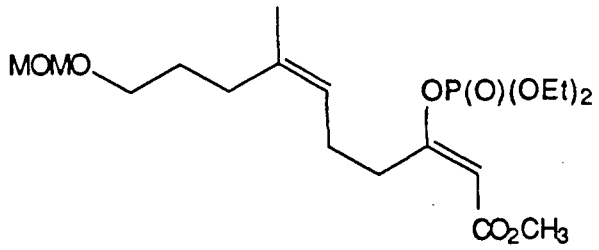
IR (cm^{-1}) : 3100-2800(m), 1745(s), 1715(s), 1630(w), 1440(m), 1405(w), 1395 (w), 1370(w), 1320(m), 1230(m), 1145(s), 1110(s), 1080(m), 1040(s), 920(w).

MS (m/z) : 241(M^+-OCH_3, 0.4), 240(3), 222(3), 209(2), 101(15), 95(14), 45(100).

Exact mass calcd for $C_{13}H_{21}O_4$: 241.1440 ; found : 241.1446.

Anal. calcd for $C_9H_{16}O_5$: C 61.74, H 8.89, O 29.37 ; found : C 61.92, H 8.80.

Preparation of Methyl (2E,6Z)-3-diethylphosphoryloxy-10-methoxymethoxy-7-methyl-2,6-decadienoate (92).



Compound 91 (5.00 g, 0.018 mmol) was treated as described in the procedure for the preparation of methyl (E)-3-diethylphosphoryloxy-6-methoxymethoxy-2-hexenoate (87) (p 114) to afford 7.46 g of crude enol phosphate 92. For analytical purposes a small quantity of the product was purified by chromatography on silica gel eluting with pet. ether - ethyl acetate (1:1). Otherwise the product was used in the next step without purification.

^{1}H NMR (80 MHz), (δ) : 5.85 (d, 1H, J = 1.5 Hz), 5.20 (bt, 1H, J = 7.0 Hz), 4.63 (s, 2H), 4.17 (dq, 2H, J_{HH} = 8.0 Hz, J_{PH} = 9.0 Hz), 3.80 (s, 3H), 3.50 (t, 2H, J = 6.0 Hz), 3.38 (s, 3H), 2.7 (bt, 2H, J = 8 Hz), 2.4-1.9 (m, 4H), 1.7-1.5 (m, 2H), 1.68 (d, 3H, J = 1.5 Hz), 1.34 (dt, 3H, J_{HH} = 8.0 Hz, J_{PH} = 2.0 Hz).

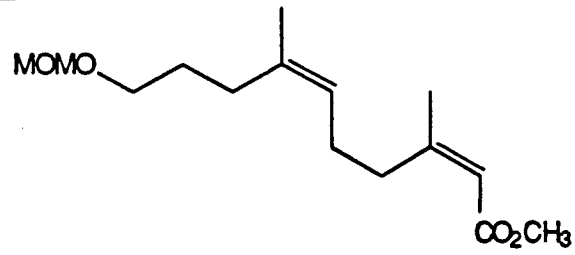
IR (cm^{-1}) : 3050-2800 (m), 1720 (m), 1645 (m), 1440 (s), 1370 (s), 1260 (m), 1150 (m), 1115 (m), 1035 (s), 970 (m), 920 (w), 870 (w).

MS (m/z) : 377 (M^+-OCH_3, 1), 376(4), 346(2), 345(4), 344(4), 314(1), 304(1), 286(1), 285(2), 192(17), 164(10), 155(100), 127(36), 99(36).

Exact mass calcd for $C_{17}H_{30}O_7P$: 377.1729 ; found : 377.1681.

Anal. calcd for $C_9H_{16}O_5$: C 52.93, H 8.14, O 31.34, P (7.58); found : C 52.64, H 8.16, O 31.26.

Preparation of Methyl (2Z,6Z)-10-methoxymethoxy-3,7-dimethyl-2,6-decadienoate (93).



Enol phosphate 92 (5.75 g, 0.0141 mol) was treated according to the procedure described for the preparation of methyl (Z)-6-methoxymethoxy-3-methyl-2-hexenoate (88) (p 115). The crude methylated product 93 (3.78 g) so obtained was purified by chromatography on silica gel eluting with pet. ether - ethyl acetate (9:1) followed by bulb-to-bulb distillation (110 °C / 0.25 torr) to give 2.82 g (74% yield) of pure 93 as a colorless oil.

^{1}H NMR (80 MHz), (δ) : 5.63 (bs, 1H), 5.20 (bt, 1H, J = 7.0 Hz), 4.65 (s, 2H), 3.70 (s, 3H), 3.53 (t, 2H, J = 6.0 Hz), 3.40 (s, 3H), 2.65 (t, 2H, J = 7.0 Hz), 2.3-2.0 (m, 4H), 1.90 (d, 3H, J = 1.5 Hz), 1.70 (d, 3H, J = 1.5 Hz), 1.7-1.5 (m, 2H).

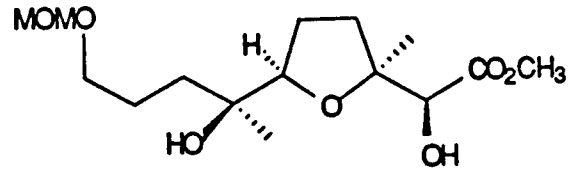
IR (cm^{-1}) : 3050-2800(m), 1710(m), 1650(w), 1440(m), 1385(w), 1295(w), 1160(s), 1110(s), 1040(s), 920(w), 865(w).

MS (m/z) : 239 (M^+-OCH_3, 0.6), 238(2), 225(1), 223(0.1), 220(1), 206(21), 179(14), 147(21), 108(20), 107(26), 97(31), 95(46), 85(53), 82(22), 81(34), 67(25), 55(28), 45(100).

Exact mass calcd for $C_{14}H_{23}O_3$: 239.1644 ; found : 239.1595 .

Anal. calcd for $C_9H_{16}O_5$: C 66.64, H 9.69, O 23.67 ; found : C 65.21, H 9.55.

Preparation of Methyl (S)-hydroxy-{(2R*,5S*)-2-{(2S*)-2-hydroxy-5-methoxymethoxy-2-pentyl}-5-methyl-5-tetrahydrofuranyl}-acetate (94).



Carbon dioxide was bubbled through a solution of 1.17 g (7.40 mmol) of $KMnO_4$ in 30 mL of 10% H_2O in acetone at -25 °C. After the reaction mixture was stirred for 15 min , 1.00 g (3.69 mmol) of methyl (2Z,6Z)-10-methoxymethoxy-3,7-dimethyl-2,6-decadienoate (93) was added slowly through a pressure-equalized addition funnel. The reaction was stirred at -25 °C for 3 h, after which it was added carefully to an ice-cold solution of sodium bisulfite (300 mL). The resulting clear aqueous solution was extracted continuously with ethyl acetate overnight. The organic layer was separated, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give 878 mg of a slightly yellow oil. Chromatography on silica gel eluting with pet. ether - ethyl acetate (1:1) afforded 606 mg (52% yield) of the desired tetrahydrofuran 94 along with 24 mg of a ~ 9:1 mixture of 94 and an isomeric compound 111 or 112 (assignment of stereochemistry was not possible).

^{1}H NMR (400 MHz), (δ) : 4.62 (s, 2H), 4.10 (s, 1H), 3.86 (dd, 1H, J = 6.0, 10.0 Hz), 3.81 (s, 3H), 3.54 (m, 2H), 3.36 (s, 3H), 2.90-2.80 (bs, 2H), 2.30 (ddd, 1H, J = 13.0 , 8.0 , 3.0 Hz), 1.97 (m, 1H), 1.84 (m, 1H), 1.75-1.60 (m, 3H), 1.50-1.35 (m, 2H), 1.28 (s, 3H), 1.24 (s, 3H).

^{13}C NMR (100 MHz), (δ) : 173.48 (s), 96.46 (t) 85.88 (d) 83.92 (s), 75.74 (d) 72.38 (s), 68.34 (t) 55.17 (q) 52.40 (q) 34.92 (t) 34.65 (t) 25.62 (t) 24.75 (q) 23.96 (t) 22.81 (q).

IR (cm^{-1}) : 3600-3200(m), 3000-2800(m), 1735(s), 1440(m), 1375(m), 1270(m), 1140(s), 1100(s), 1075(s), 1030(s), 905(m).

MS (m/z) : 287 (M^+-OCH_3, 4), 271(2), 259(13), 199(41), 181(19), 173(40), 169(79), 155(38), 147(44), 127(45), 115(90), 113(26), 111(83), 99(24),

97(22), 95(27), 85(100), 83(21), 71(44), 69(29), 58(21), 55(25), 45(91), 43(95), 41(26).

Exact mass calcd for $C_{14}H_{25}O_6$: 287.1495 ; found : 287.1503 .

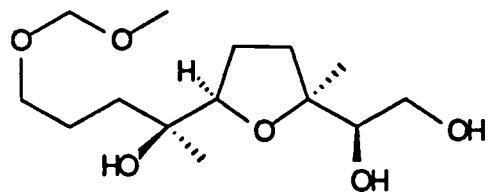
Anal. calcd for $C_9H_{16}O_5$: C 56.23, H 8.81, O 34.96 ; found : C 56.33, H 9.00.

Data for the Isomeric Tetrahydrofuran 111 or 112

^{1}**H NMR** (400 MHz), (δ) : 4.62 (s, 2H), 4.11 (s, 1H), 3.84 (dd, 1H, J = 4.0, 7.0 Hz), 3.79 (s, 3H), 3.54 (m, 2H), 3.37 (s, 3H), 2.22 (ddd, 1H, J = 13.0, 8.0, 3.0 Hz), 2.00 - 1.16 (m, 10H), 1.27 (s, 3H), 1.08 (s, 3H).

MS (m/z) : 287 (M^+-OCH_3, 0.2), 271(1), 259(2), 255(2), 199(8), 181(7), 173(5), 169(19), 155(8), 147(10), 127(10), 115(41), 111(25), 85(100), 83(11), 71(14), 69(6), 58(7), 55(9), 45(79), 43(70), 41(11).

Preparation of (2R*,5S*)-5-{(1R*)-1,2-Dihydroxyethyl}-2-{(2S*)-2-hydroxy-5-methoxymethoxy-2-pentyl}-5-methyltetrahydrofuran (100).



A dry 100-mL, r.b. flask was charged with ester 94 (753 mg, 2.35 mmol). The flask was alternately evacuated and flushed with N_2. Then 20 mL of dry THF was added and the reaction mixture was stirred at 0 °C for 15 min, followed by the addition of 357 mg (9.41 mmol) of $LiAlH_4$. The grey suspension was allowed to warm to room temperature and was stirred for 1 h.

The reaction was then cooled to 0 °C and ice-cold water was added to destroy the excess hydride reagent. The resulting grey suspension was poured into 30 mL of ice-cold 1N HCl, stirred for 1 h, neutralized by adding solid $NaHCO_3$ to the aqueous solution, and extracted

continuously with ethyl acetate for 12 h. The organic solution was dried over $MgSO_4$ and evaporated under reduced pressure to afford 588 mg of triol 100 as a slightly yellow colored oil. A small amount of the compound was purified, for analytical purposes, by column chromatography on silica gel eluting with pet. ether - ethyl acetate (1:1). Otherwise the compound was used in the next step without further purification

^{1}H NMR (270 MHz), (δ) : 4.76 (s, 2H), 3.83 (t, 1H, J = 7.5 Hz), 3.72 (bd, 2H), 3.55 (t, 3H, J = 5.8 Hz), 3.36 (s, 3H), 2.15 (m, 1H), 1.00 (m, 1H), 2.90 (m, 1H), 2.75-1.30 (m, 8H), 1.25 (s, 3H), 1.18 (s, 3H).

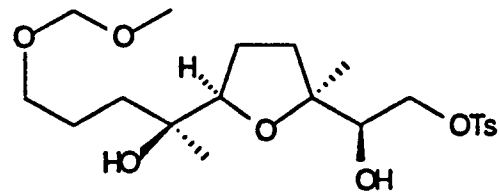
IR (cm^{-1}) : 3600-3200(s), 3000-2800(s), 1450(m), 1370(m), 1140(s), 1100(s), 1025(s), 905(m), 860(w).

MS (m/z) : 293 (M^++1, 0.3), 243(2), 231(17), 211(4), 199(25), 169(85), 147(52), 127(47), 125(27), 115(92), 113(21), 111(89), 109(46), 101(20), 99(44), 97(41), 95(34), 93(22), 86(30), 85(100), 84(51), 83(52), 81(71), 71(84), 69(58), 67(24), 58(40), 57(40), 55(49), 45(80), 43(86), 41(24).

Exact mass calcd for $C_{14}H_{29}O_6$: 293.1964 ; found : 293.1952.

Anal. calcd for $C_9H_{16}O_5$: C 57.51, H 9.65, O 32.83 ; found : C 56.45, H 9.70.

Preparation of (2R*,5S*)-2-{(2S*)-2-Hydroxy-5-methoxymethoxy-2-pentyl}-5-{(1R*)-1-hydroxy-2-(p-toluenesulfonyl)oxy-1-ethyl}-5-methyltetrahydrofuran (104).



Triol 100 (450 mg, 1.54 mmol) dissolved in 5 mL of dry pyridine was added to a 10-mL r.b. flask previously flushed with nitrogen. This solution was cooled to 0 °C and stirred for 0.5 h at that temperature. Then p-toluenesulfonyl chloride (292 mg, 1.54 mmol) was added slowly

over a period of 10 min. The resulting mixture was left to stir at 0 °C for 2.5 h, then allowed to warm slowly to room temperature and stirred for an additional hour.

The mixture was added to 100 mL of ice-cold 1N aqueous HCl and the water layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to yield 598 mg of the desired sulfonate 104 as a slightly yellow oil. The compound was used directly in the next step without purification

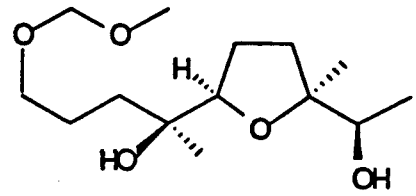
^{1}H NMR (400 MHz), (δ) : 7.80 (d, 2H, J = 10.0 Hz), 7.40 (d, 2H, J = 10.0 Hz), 4.61 (s, 2H), 4.24 (dd, 1H, J = 3.0 , 11.0 Hz), 3.98 (dd, 1H, J = 8.0 , 11.0 Hz), 3.81 (m, 2H), 3.53 (t, 2H, J = 6.0 Hz), 3.36 (s, 3H), 2.45 (s, 3H), 2.15 (m, 1H), 1.95 (m, 1H), 1.85 (m, 1H), 1.75-1.00 (m, 7H), 1.19 (s, 3H), 1.14 (s, 3H).

IR (cm^{-1}) : 3650-3300 (m), 3050-2800(m), 1600(w), 1450(m), 1370(s), 1305(m), 1190(m), 1170(s), 1145(m), 1100(s), 1030(s), 960(s), 915(s).

MS (m/z) : 415 (M^+-OCH_3, 0.3), 397(0.5), 385(0.3), 369(1), 357(1), 343(1), 325(2), 199(37), 172(28), 169(57), 155(23), 127(33), 115(33), 111(66), 109(47), 107(22), 95(22), 91(59), 85(100), 84(20), 83(25), 81(41), 71(24), 69(24), 65(23), 55(20).

Exact mass calcd for $C_{20}H_{31}O_7S$: 415.1790 ; found : 415.1824.

Preparation of (2R*,5S*)-5-{(1R*)-1-Hydroxy-1-ethyl}-2-{(2S*)-2-hydroxy-5-methoxymethoxy-2-pentyl}-5-methyltetrahydrofuran (103).



A 25-mL, two-neck, r.b. flask was fitted with a condenser, flushed with nitrogen, and was charged with 398 mg (0.891 mmol) of tosylate 104 in 10 mL of dry THF. This solution was cooled to 0 °C and 101 mg (2.66 mmol) of $LiAlH_4$ was added to the solution slowly over

a period of 0.5 h. Evolution of gas was observed after each addition. The resulting grey suspension was allowed to warm to room temperature, stirred for 0.5 h, and then heated to reflux for 24 h.

The reaction mixture was cooled to 0 °C and ice-cold water was added to destroy the excess reagent. The mixture was then added to 50 mL of ice-cold 1N HCl and the aqueous phase was continuously extracted with diethyl ether for 36 h. The ether extract was dried over MgSO4 and evaporated under reduced pressure to afford 198 mg of diol 103 as a colorless oil. The product was purified by column chromatography eluting with pet. ether - ethyl acetate (1:1) to give 192 mg (77% yield) of 103 as a colorless oil

^{1}H NMR (400 MHz), (δ) : 4.62 (s, 2H), 3.85 (t, 1H, J = 6.5 Hz), 3.79 (q, 1H, J = 6.5 Hz), 3.54 (t, 2H, J = 6.0 Hz), 3.37 (s, 3H), 2.15 (m, 1H), 1.95 (m, 1H), 1.85 (m, 1H), 1.75-1.40 (m, 7 H), 1.26 (s, 3H), 1.15 (s, 3H), 1.13 (d, 3H, J = 6.5 Hz).

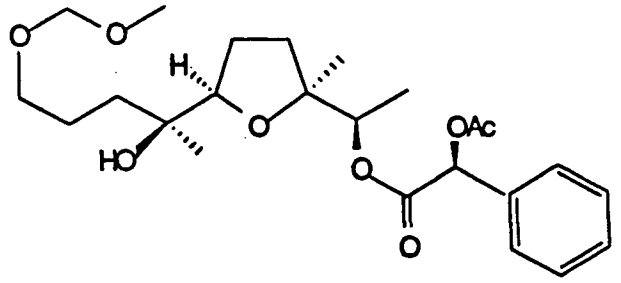
IR (cm^{-1}) : 3650-3200(m), 3050-2800(s), 1450(m), 1380(m), 1220(m), 1150(m), 1110(s), 1070(s), 1030(s), 915(m), 865(w).

MS (m/z) : 277 (M^++1, 0.1), 243(1), 231(3), 215(4), 213(1), 169(40), 147(23), 115(65), 111(61), 85(100), 83(25), 71(26), 69(20).

Exact mass calcd for $C_{14}H_{29}O_5$: 277.2014 ; found : 277.2014.

Anal. calcd for $C_9H_{16}O_5$: C 60.84, H 10.21, O 28.94 ; found : C 60.80, H 10.14.

Preparation of (2R*,5S*)-5-{(1R*)-1-{(S)-O-Acetylmandelyl}oxy-1-ethyl}-2-{(2S*)-2-hydroxy-5-methoxymethoxy-2-pentyl}-5-methyltetrahydrofuran (110a) and its (S,S,R,R,S) isomer (110b).



A 25-mL, r.b flask was flushed with nitrogen and charged with 188 mg (0.682 mmol) of diol 103 in 8 mL of dry CH_2Cl_2. Then 132 mg (0.682 mmol) of (S)-(+)-O-acetylmandelic acid were added along with 8 mg (0.07 mmol) of DMAP. The reaction mixture was cooled to 0 °C and stirred at that temperature for 0.5 h. Then 140 mg (0.682 mmol) of DCC were added in one portion (a white precipitate formed) and the reaction mixture was allowed to warm slowly to room temperature over a period of 2 h.

The suspension was then filtered and the filtrate evaporated under reduced pressure. The residue was redissolved in 1 mL of CH_2Cl_2 and filtered again. The solvent was evaporated under reduced pressure and the resulting oil was purified by chromatography on silica gel eluting with hexane-acetone (6:1). Repeated chromatography was required to separate the mixture of compounds obtained. A mixture of products (10 mg, 7% yield) eluting first was isolated and found to consist of four compounds. The product eluting second (120 mg, 78% yield) was identified as the desired mandelate ester 110a and was obtained in > 99% purity (GLC). The third eluting product (95 mg, 62% yield) was obtained in > 98% purity (GLC) and was determined to be mandelate ester 110b

Data for (110a).

^{1}H NMR (400 MHz), (δ) : 7.53-7.65 (m, 5H), 5.85 (s, 1H), 4.93 (q, 1H, J = 6.0 Hz), 4.62 (s, 2H), 3.82 (dd, 1H, J = 6.0, 8.0 Hz), 3.55 (m, 2H), 3.38 (s, 3H), 2.35 (s, 1H), 2.21 (s, 3H), 2.1-1.4 (m, 8H), 1.22 (s, 3H), 1.17 (s, 3H), 1.03 (d, 3H, J = 6.0 Hz).

IR (cm^{-1}) : 3650-3250(bs), 3050-3000(m), 3000-2850(m), 1746(s), 1497(w), 1452(m), 1374(s), 1227(s), 1181(s), 1153(m), 1105(s), 1050(s), 920(m).

MS (m/z) : 434 (M^+- H_2O, 0.1), 405(1), 391(1), 375(2), 363(1), 169(44), 149(29), 147(30), 118(30), 115(66), 111(75), 107(45), 94(31), 85(100), 84(23), 83(25), 79(22), 71(24), 69(26), 54(33).

Exact mass calcd for $C_{24}H_{34}O_7$: 434.2304 ; found : 434.2304.

Anal. calcd for $C_9H_{16}O_5$: C 63.70, H 8.02, O 28.28 ; found : C 63.54, H 8.13.

$[\alpha]_D$ = + 29.4° (c = 0.83 , acetone).

Data for (110b).

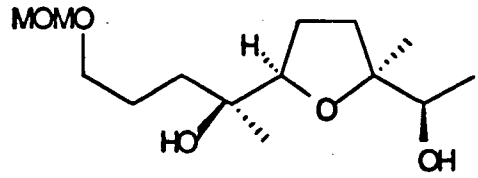
^1H NMR (400 MHz), (δ) : 7.53-7.65 (m,5H), 5.77 (s, 1H), 4.80 (q, 1H, J = 5.0 Hz), 4.58 (s, 2H), 3.72 (t, 1H, J = 5.0 Hz), 3.47 (m, 2H), 3.37 (s, 3H), 2.21 (s, 3H), 1.60 (bs, 1H), 1.75-1.27 (m, 8H), 1.25 (d, 3H, J = 6.0 Hz), 1.06 (s, 3H), 1.03 (s, 3H).

IR (cm^{-1}) : 3650-3250(bs), 3050-3000(m), 3000-2850(m), 1746(s), 1497(w), 1452(m), 1374(s), 1227(s), 1181(s), 1153(m), 1105(s), 1050(s), 920(m).

MS (m/z) : 434 (M^+- H_2O, 0.1), 405(0.4), 391(1), 375(2), 363(1), 169(35), 149(33), 147(22), 118(30), 115(63), 111(54), 107(42), 94(33), 85(100), 83(29), 71(24), 69(29), 54(33).

$[\alpha]_D$ = + 58.25° (c = 0.12, acetone).

Preparation of (2R,5S)-2-{(2S)-2-Hydroxy-5-methoxymethoxy-2-pentyl}-5-{(1R)-1-hydroxy-1-ethyl}-5-methyltetrahydrofuran (117).



The mandelate ester derivative 110a (1.03 g, 2.37 mmol) was weighed into a 50-mL r.b. flask and 20 mL of NaOH 1N was added. The reaction mixture was stirred at room temperature for 24 h and monitored by TLC. When the reaction was over, the mixture was extracted continuously with diethyl ether for 24 h. The ether extract was dried over $MgSO_4$ and evaporated under reduced pressure giving 712 mg of diol 117 as a colorless oil. The product was purified by chromatography on a silica gel column eluting with pet. ether - ethyl acetate (1:1) to afford 625 mg (99% yield) of the desired diol 117 as a colorless oil.

^{1}H NMR (400 MHz), (δ) : 4.62 (s, 2H), 3.85 (t, 1H, J = 6.5 Hz), 3.79 (q, 1H, J = 6.5 Hz), 3.54 (t, 2H, J = 6.0 Hz), 3.37 (s, 3H), 2.15 (m, 1H), 1.95 (m, 1H), 1.85 (m, 1H), 1.75-1.40 (m, 7 H), 1.26 (s, 3H), 1.15 (s, 3H), 1.13 (d, 3H, J = 6.5 Hz).

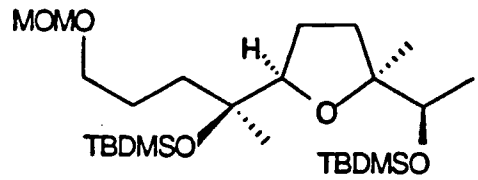
IR (cm^{-1}) : 3650-3200(m), 3050-2800(s), 1450(m), 1380(m), 1220(m), 1150(m), 1110(s), 1070(s), 1030(s), 915(m), 865(w).

MS (m/z) : 277 (M^++1, 0.1), 243(1), 231(4), 215(6), 213(1), 169(47), 147(22), 115(67), 111(59), 85(100), 83(25), 71(28), 69(19).

Exact mass calcd for $C_{14}H_{29}O_5$: 277.2014 ; found : 277.2004.

$[\alpha]_D$ = -9.8° (c = 0.46, $CHCl_3$).

Preparation of (2R,5S)-5-{(1R)-1-(t-Butyldimethylsilyl)oxy-1-ethyl}-2-{(2S)-2-(t-butyldimethylsilyl)oxy-5-methoxymethoxy-2-pentyl}-5-methyltetrahydrofuran (118).



Diol 117 (625 mg, 0.23 mmol) was dissolved in 20 mL of dry CH_2Cl_2 and added to a dry 50-mL r.b. flask under nitrogen. Triethylamine (0.65 mL, 5.6 mmol) was added to the solution followed by 1.14 mL (4.97 mmol) of TBDMS-Tf at 0 °C. The mixture was stirred at 0 °C for 2 h and then was quenched with 70 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted once with CH_2Cl_2, the organic layer dried over $MgSO_4$, and evaporated under reduced pressure to give 1.09 g of compound 118 as a yellow oil. The product was purified by chromatography on silica gel with CH_2Cl_2 as eluant to give 1.01 mg (90% yield) of pure 118 as a colorless oil.

^{1}H NMR (400 MHz), (δ) : 4.78 (s, 2H), 3.84 (t, 1H, J = 6.5 Hz), 3.58 (q, 1H, J = 6.0 Hz), 3.51 (q, 2H, J = 6.0 Hz), 3.36 (s, 3H), 1.88-1.40 (m, 8H), 1.15 (s, 3H), 1.13 (d, 3H, J = 6.0 Hz), 1.07 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H).

IR (cm^{-1}) : 3000-2800(s), 1465(m), 1375(m), 1250(m), 1100(s), 1030(m), 910(w), 830(s).

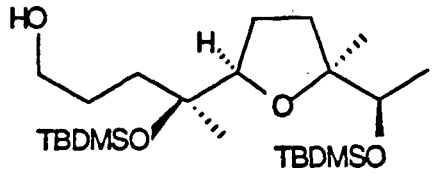
MS (m/z) : 489 (M^+ - CH_3, 0.4), 473(1), 448(3), 447(9), 416(0.3), 401(6), 345(39), 261(71), 229(26), 199(35), 181(27), 115(22), 85(44), 75(57), 73(100).

Exact mass calcd for $C_{25}H_{53}O_5Si_2$: 489.3432 ; found : 489.3427.

Anal. calcd for $C_9H_{16}O_5$: C 61.85, H 11.17, O 15.84, Si 11.13 ; found : C 62.10, H 11.10.

$[\alpha]_D$ = -3.53° (c = 0.43, $CHCl_3$).

Preparation of (2R,5S)-5-{(1R)-1-(t-Butyldimethylsilyl)oxy-1-ethyl}-2-{(2S)-2-(t-butyldimethylsilyl)oxy-5-hydroxy-2-pentyl}-5-methyltetrahydrofuran (119).



The methoxymethyl acetal 118 (46 mg, 0.091 mmol) was dissolved in 2 mL of dry CH_2Cl_2 and added to a 5-mL r.b. flask under nitrogen. The mixture was cooled to -78 °C and dimethylboron bromide (33 mg, 0.27 mmol) was added slowly to the solution. The reaction mixture was stirred at -78 °C for 1 h, then it was cannulated into 15 mL of a vigorously stirred 2:1 mixture of THF and saturated aqueous $NaHCO_3$. The flask and cannula were rinsed with 5 mL of dry CH_2Cl_2 (the flask must be kept at -78 °C at all times). The aqueous phase was extracted with diethyl ether. The organic layers were combined, washed with sodium bisulfate and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give 89 mg of alcohol 119.

The product was then purified by chromatography on silica gel, with pet. ether - ethyl acetate (1:1) as the eluting solvent giving 35 mg (83% yield) of pure 119 as a colorless oil.

^{1}H NMR (400 MHz), (δ) : 3.84 (t, 1H, J = 10.5 Hz), 3.60 (t, 2H, J = 7.0 Hz), 3.56 (q, 1H, J = 6.0 Hz), 1.80 (m, 3H), 1.62 (m,5H), 1.45 (m, 1H), 1.12 (s, 3H), 1.11 (d, 3H, J = 6.0 Hz), 1.06 (s, 3H), 0.86 (s, 9H), 0.84 (s, 9H), 0.065 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H).

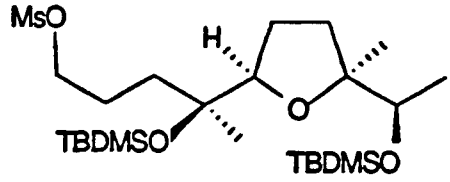
IR (cm^{-1}) : 3650(w), 3600-3300(bw), 3000-2800(s), 1460(m), 1370(m), 1250(m), 1095(s), 1060(s), 1000(m), 980(m), 825(s).

MS (m/z) : 403 (M^+ - $C(CH_3)_3$, 7), 401(5), 383(2), 311(3), 302(3), 301(14), 217(65), 199(30), 179(21), 169(96), 159(22), 125(20), 111(39), 85(100), 75(70), 73(88).

Exact mass calcd for $C_{20}H_{43}Si_2O_4$: 403.2700 ; found : 403.2724.

$[\alpha]_D$ = - 4.7° (c = 0.36, CH_2Cl_2) ; (lit.[81]: - 4.6°, c = 1.77, CH_2Cl_2)

Preparation of (2R,5S)-5-{(1R)-1-(t-Butyldimethylsilyl)oxy-1-ethyl}-2-{(2S)-2-(t-butyldimethylsilyl)oxy-5-(methanesulfonyl)oxy-2-pentyl}-5-methyltetrahydrofuran (120).



The alcohol 119 (57 mg, 0.12 mmol) was dissolved in 1 mL of dry CH_2Cl_2 and added to a dry 5-mL r.b. flask under argon. The solution was cooled to 0 °C and 40 μL of triethylamine (0.31 mmol) followed by 11 μL of methanesulfonyl chloride (0.15 mmol) was added slowly. After the reaction was stirred at that temperature for 3 h the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate, washed with ice-cold water, dried over $MgSO_4$, and evaporated under reduced pressure again to give 66 mg (100% yield) of mesylate 120 as a colorless oil. The compound was used in the next step without further purification.

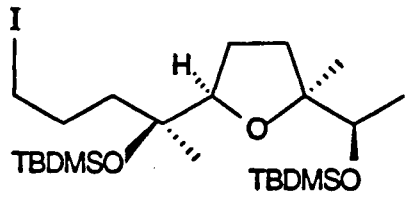
^{1}H NMR (300 MHz), (δ) : 4.21 (t, 2H, J = 6.0 Hz), 3.81 (t, 1H, J = 8.0 Hz), 3.56 (q, 1H, J = 6.0 Hz), 3.00 (s, 3H), 1.90-1.40 (m, 8H), 1.12 (s, 3H), 1.11 (d, 3H, J = 6.0 Hz), 1.06 (s, 3H), 0.86 (s, 9H), 0.84 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H).

IR (cm^{-1}) : 3000-2800(s), 1475(m), 1380(m), 1360(s), 1340(s), 1260(s), 1180(s), 1100(s), 1090(s), 1005(m), 980(s), 960(m), 920(m), 840(s).

MS (m/z) : 442 (M^+- $HOS(O)_2CH_3$, 2), 385(3), 199(20), 153(57), 115(20), 85(27), 75(100), 73(96), 43(32).

Exact mass calcd for $C_{24}H_{50}O_3Si_2$: 442.3298 ; found : 442.3292.

Preparation of (2R,5S)-5-{(1R)-1-(t-butyldimethylsilyl)oxy-1-ethyl}-2-{(2S)-2-(t-butyldimethylsilyl)oxy-5-iodo-2-pentyl}-5-methyltetrahydrofuran (121).



The methanesulfonate 120 (66 mg, 0.12 mmol) was dissolved in 2 mL of dry acetone and added to a 5-mL r.b. flask under argon. Dry sodium iodide (186 mg, 1.22 mmol) was added quickly followed by a catalytic amount of $NaHCO_3$ (~ 5-10 mg) and one drop of triethylamine. The flask was covered with aluminium foil to prevent decomposition from light, and the mixture was stirred at room temperature for 16 h. Then the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate, filtered through Celite and evaporated under reduced pressure to give the light sensitive iodide 121 as a yellow oil. The product was purified by chromatography on silica gel with pet. ether - ethyl acetate (40:1) as the eluting solvent to give 63 mg (93% yield for two steps) of 121 as a colorless oil.

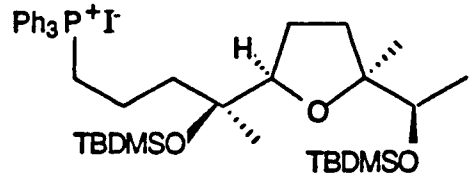
^{1}H NMR (400 MHz), (δ) : 3.83 (t, 1H, J = 10.5 Hz), 3.58 (q, 1H, J = 6.0 Hz), 3.20 (m, 2H), 1.95 (m, 2H), 1.82 (m, 2H), 1.65 (m, 3H), 1.50 (m, 1H), 1.30 (m, 1H), 1.17 (s, 3H), 1.16 (d, 3H, J = 6.0 Hz), 1.10 (s, 3H), 0.90 (s,9H), 0.88 (s,9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H).

IR (cm^{-1}) : 3000-2800(s), 1460(m), 1370(m), 1250(m), 1100(s), 1005(m), 990(w), 905(w), 835(s).

MS (m/z) : 513(M^+ - $C(CH_3)_3$, 1.0), 386(0.2), 329(1), 327(23), 85(37), 75(61), 73(100), 43(25).

Exact mass calcd for $C_{20}H_{42}O_3ISi_2$: 513.1719 ; found : 513.1718.

Preparation of (4S)-4-(t-butyldimethylsilyl)oxy-4-{(2R,5S)-5-methyl-5-{(1R)-1-(t-butyldimethylsilyl)oxy-1-ethyl}-2-tetrahydrofuranyl}-1-pentyltriphenylphosphonium iodide (122).



Iodide 121 (123 mg, 0.226 mmol) was added to a solution of 115 mg (0.44 mmol) of triphenylphosphine and 20 μL (0.13 mmol) of dry diisopropylethylamine in 2.0 mL of a 1:1 mixture of dry toluene and dry acetonitrile. The reaction mixture was heated to 75 °C under an argon atmosphere for 54 h.

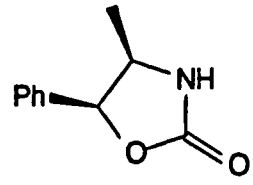
The solution was then cooled to room temperature and the solvents were removed under reduced pressure with care to exclude moisture. The phosphonium salt thus obtained was treated with dry hexanes to remove the excess triphenylphosphine. The resulting white paste was then dried under vacuum for 12 h. The resulting white solid was isolated here for characterization purposes giving 71 mg (80% yield) of the hygroscopic phosphonium iodide 122. Normally the product was used without isolation or purification in the next step.

m.p.: 72-80 °C (lit.[82]: 76-81 °C)

^{1}H NMR (400 MHz), (δ): 7.85-7.40 (m, 15H), 3.85 (m, 1H), 3.63 (t, 1H, J = 10.5 Hz), 3.48 (q, 1H, J = 6.0 Hz), 3.42 (m, 1H), 1.94-1.40 (m, 8H), 1.06 (s, 3H), 1.03 (d, 3H, J = 6.0 Hz), 0.97 (s, 3H), 0.84 (s, 9H), 0.75 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H), -0.01 (s, 3H), -0.05 (s, 3H).

III. Preparation of Fragment C

Preparation of (4R, 5S)-4-Methyl-5-phenyl-2-oxazolidinone (133).



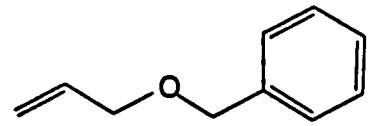
The title compound was prepared according to the procedure below which is a modification of the method described by Evans and Shih.[82] The hydrochloride salt of (1R, 2S)-norephedrine (20 g, 0.13 mol) was dissolved 100 mL of distilled water and 50 mL of 15% NaOH was added. The solution was extracted with $CHCl_3$ several times and the solvent was then removed under reduced pressure. The resulting yellow oil was dried under vacuum over night. The white solid thus obtained was ground into a fine powder and dried under vacuum for an additional 2 hr.

This amino alcohol, 70 mL of diethyl carbonate, and 55 g (0.40 mmol) of potassium carbonate were then added to a 250-mL r.b. flask. The mixture was heated to reflux and stirred for 24 h. The mixture was then cooled to room temperature and the excess diethyl carbonate was removed under reduced pressure to yield 17.11 g of oxazolidinone 133 as a yellow oil which crystallized after it was dried over night under vacuum. The white solid was recrystallized from toluene to yield 16.86 g (89% yield) of product as a white powdery solid.

m.p.: 120-121 °C; (lit.[82]: 120-122 °C).

$[\alpha]_D$: +175° (c = 1.71, $CHCl_3$); (lit.[82]: +177.2°, c = 2.21, $CHCl_3$).

Preparation of 3-Benzyloxy-1-propene.



To a suspension of 6.55 g (0.163 mol) of sodium hydride in 300 mL of dry THF in a dry 500-mL r.b. flask under nitrogen were slowly added 10.3 mL (0.152 mol) of allyl alcohol and the resulting mixture was stirred for 0.5 h. Then 14.0 mL (0.117 mol) of benzyl bromide were added followed by 500 mg (1.34 mmol) of tetrabutylammonium iodide and the resulting white suspension was stirred at room temperature for 20 h.

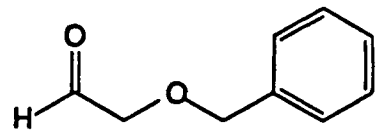
Florisil (20 g) was added and the solvent was evaporated under reduced pressure. The residue was filtered and washed several times with hexanes to yield 19.2 g of the allyl benzyl ether as a slightly yellow oil. The product was distilled at 85 °C (20 torr) to give 15.2 g (88% yield) of the benzyl ether as a colorless oil.

^{1}H NMR (400 MHz), (δ) : 7.40-7.26 (m, 5H), 5.97 (ddt, 1H, J = 5.0) 5.32 (dq, 1H, J = 17.0, 1.5, 1.0 Hz), 5.22 (ddt, 1H, J = 10.0, 1.5, 1.0 Hz), 4.54 (s, 2H), 4.04 (dt, 2H, J = 5.0, 1.0 Hz),

IR (cm^{-1}) : 3081(w), 3000(m), 2950-2800(s), 1954(w), 1874(w), 1814(w), 1645(w), 1495(m), 1453(m), 1355(m), 1078(s), 1020(m), 991(m), 938(m).

MS (m/z) : 148(M^+, 0.6), 147(2), 105(28), 92(55), 91(100), 79(27), 77(37), 65(26), 51(23), 41(21), 39(25).

Preparation of 2-Benzyloxyethanal (129).



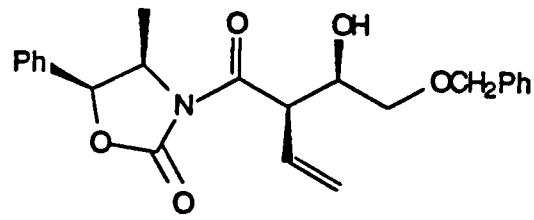
The title compound was prepared by treating 12.0 g (79.9 mmol) of 3-benzyloxy-1-propene with a catalytic amount of osmium tetroxide and 37.5 g (0.175 mol) of sodium metaperiodate in 240 mL of water and an equal volume of diethyl ether. The reaction mixture was vigorously stirred at room temperature for 36 h. Then the two layers were separated and the aqueous phase extracted with diethyl ether. The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure to give 11.1 g of aldehyde 129 as a black oil. The product was distilled at 80-90 °C / 0.1 torr, to yield 10.0 g (83% yield) of aldehyde 129 as a colorless oil.

^{1}H NMR (400 MHz), (δ) : 9.80 (t, 1H, J =) 7.40-7.30 (m, 5H), 4.65 (s, 2H), 4.11(s, 2H).

IR (cm^{-1}) : 3050-3000(w), 3000-2800(s), 1738(s), 1495(w), 1454(m), 1373(m), 1100(s), 992(w), 909(w).

MS (m/z) : 150(M^+, 0.1), 107(27), 91(100).

Preparation of (4R, 5S)-3-{(2R, 3R)-4-Benzyloxy-3-hydroxy-1-oxo-2-vinylbutanoyl}-5-phenyl-4-methyl-2-oxazolidinone (130).



A 100-mL, two-neck, r.b. flask was charged with 1.20 g (4.89 mmol) of (4R, 5S)-3-crotonyl-4-methyl-5-phenyl-2-oxazolidinone (69) in 50 mL of dry CH_2Cl_2. The solution was cooled to -78 °C and stirred for 10 min. Then 0.75 mL (5.4 mmol) of triethylamine was added

to the cold solution followed by 1.47 g (5.38 mmol) of di-n-butylboron triflate and the resulting pale yellow mixture was allowed to warm to 0 °C over 1 h. The pale orange solution was cooled to -78 °C and 807 mg (5.38 mmol) of 3-benzyloxy-1-ethanal (129) were added slowly. The resulting mixture was stirred at -78 °C for 1 h and then for an additional 4 h while allowing it to warm to room temperature.

Then 2 mL of pH 7 phosphate buffer were added to the reaction mixture and the resulting solution was cooled to 0 °C. An ice-cold mixture of 15 mL of the same buffer, 15 mL of 30% aqueous hydrogen peroxide and 30 mL of methanol was added to the solution and the resulting solution was stirred at 0 °C for 1 h. Then 200 mL of a solution of saturated aqueous $NaHCO_3$ were added slowly to the cold mixture while stirring vigorously. After all gas evolution had stopped, the aqueous phase was extracted several times with CH_2Cl_2, and the organic phase was dried over $MgSO_4$. Evaporation under reduced pressure yielded 1.86 g of alcohol 130 as a viscous yellow oil.

This oil was purified by column chromatography on silica gel using pet. ether - ethyl acetate (3:1) as eluant giving 1.12 g (60% yield) of 130 as a colorless oil which crystallized into a white solid upon standing at room temperature for 24 h.

m.p. : 84.5 - 85.5 °C.

^{1}H NMR (400 MHz), (δ) : 7.22-7.43 (m, 10H), 5.98 (ddd, 1H, J = 10.0, 11.0, 17.0 Hz), 5.38 (dd, 1H, J = 17.0, 1.0 Hz), 5.35 (dd, 1H, J = 11.0, 1.0 Hz), 5.31 (d, 1H, J = 8.0 Hz), 4.74 (dd, 1H, J = 7.0, 10.0 Hz), 4.62 (qi, 1H, J = 8.0 Hz), 4.55 (s, 2H), 4.26 (ddd, 1H, J = 3.0, 6.0, 7.0 Hz), 3.60 (AB portion of ABX system, 2H, $J_{AX} = J_{BX} = 6.0$ Hz, $J_{AB} = 10.0$ Hz) 2.71 (d, 1H, J = 3.0 Hz), 1.82 (d, 3H, J = 8.0 Hz).

^{13}C NMR (100 MHz), (δ) : 172.38(s), 152.35(s), 137.88(s), 133.07(d), 131.84(s), 128.50(d), 128.44(s), 128.23(d), 127.57(d), 125.41(s), 120.72(t), 78.40(d), 73.14(t), 71.97(t), 70.31(d), 54.45(d), 50.55(d), 14.08(q).

IR (cm^{-1}) : 3500-3650(w), 3000-3150(w), 2800-3000(w), 1780(s), 1700(m), 1500(w), 1460(m), 1350(s), 1370(s), 1190(m), 1110(m), 1070(m), 1040(w), 1000(w), 980(w), 940(w), 850(w).

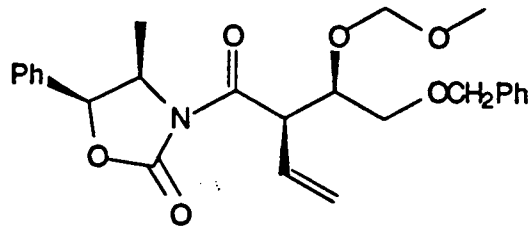
MS (m/z) : 396(M^++1, 0.1), 395(M^+, 0.1), 377(1), 364(1), 347(1), 245(43), 134(27), 118(22), 107(55), 91(100), 69(27).

Exact mass calcd for $C_{23}H_{25}NO_5$: 395.1732 ; found : 395.1750.

Anal. calcd for $C_9H_{16}O_5$: C 69.86, H 6.37, O 20.23, N 3.54 ; found : C 69.57, H 6.53, N 3.54 .

$[\alpha]_D$ = + 73.7 (c =1.24, CH_2Cl_2).

Preparation of (4R, 5S)-3-{(2R, 3R)-4-Benzyloxy-3-methoxymethoxy-1-oxo-2-vinylbutanoyl}-5-phenyl-4-methyl-2-oxazolidinone (131).



A 50-mL, two-neck, r.b flask was charged with 25 mL of dry CH_2Cl_2 and alcohol 130 (1.78 g, 4.50 mmol). Then 4.17 mL (27.0 mmol) of methylal were added in one portion and the reaction mixture was cooled to 0 °C. P_2O_5 was then added in portions of 0.5 g while maintaining the temperature at 0 °C. The addition of P_2O_5 was stopped at completion of the reaction (monitored by TLC).

The mixture was carefully added to 150 mL of ice-cold saturated aqueous $NaHCO_3$ and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give 1.90 g of the crude methoxymethyl ether 131 as a yellow oil. The crude product was purified by chromatography on silica gel with pet. ether - ethyl acetate (5:1) as the eluant to give 1.59 g (80% yield) of 131 as a colorless oil.

^{1}H NMR (400 MHz), (δ) : 7.15-7.40 (m, 10H), 5.99 (ddd, 1H, J = 8.0, 11.0, 17.0 Hz), 5.32 (dd, 1H, J = 17.0, 1.0 Hz), 5.26 (dd, 1H, J = 11.0, 1.0 Hz), 5.04 (d, 1H, J =7.0 Hz), 4.85 (t, 1H, J = 8.0 Hz), 4.76 (d, 1H, J = 7.0 Hz), 4.70 (d, 1H, J = 7.0 Hz), 4.53 (s, 2H), 4.46 (qi, 1H, J = 7.0 Hz), 4.27 (q, 1H, J = 8.0 Hz), 3.75 (dd, 2H, J = 8.0, 10.0 Hz), 3.65 (dd, J = 8.0, 10.0 Hz), 3.38 (s, 3H), 0.78 (,d, 3H, J = 7.0 Hz).

IR (cm^{-1}) : 3050-2800(w), 1780(s), 1700(s), 1642(w), 1500(w), 1460(m), 1365(s), 1350(s), 1190(m), 1120(s), 1030(s), 1000(m), 970(w), 920(w), 840(w).

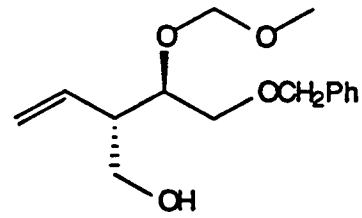
MS (m/z) : 408 (M^+- OCH_3, 1), 394(6), 377(3), 318(10), 289(20), 288(35), 245(20), 91(100).

Exact mass calcd for $C_{24}H_{26}NO_5$: 408.1811 ; found : 408.1804 .

Anal. calcd for $C_9H_{16}O_5$: C 68.32, H 6.65, O 21.84, N 3.19 ; found : C 68.40, H 6.68, N 3.16 .

$[\alpha]_D$ = +31.7 (c = 1.65, CH_2Cl_2).

Preparation of (3S, 4R)-5-Benzyloxy-3-hydroxymethyl-4-methoxymethoxy-1-pentene (132).



$LiAlH_4$ (1.50 g, 39.6 mmol) was added slowly to a solution of 5.80 g (13.2 mmol) of compound 131 in 65 mL of dry THF at 0 °C. The reaction mixture was stirred at that temperature for 3 h. The mixture was quenched with ice-cold water and the resulting grey slurry was added to 200 mL of ice-cold 1N HCl and stirred at 0 °C for 1 h. Then the aqueous layer was extracted with diethyl ether several times and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to give 4.98 g of

crude product as a colorless oil. The product was purified by chromatography on silica gel eluting with pet. ether - ethyl acetate (1:1) to afford 3.10 g (88% yield) of alcohol 132 as a colorless oil along with 1.54 g (66% yield) of recovered (4R, 5S)-4-methyl-5-phenyl-2-oxazolidinone.

^{1}H NMR (400 MHz), (δ) : 7.25-7.40 (m, 5H), 5.75 (ddd, 1H, J = 7.0, 10.0, 17.0 Hz), 5.18 (dd, 1H, J = 10.0, 2.0 Hz), 5.15 (dd, 1H, J = 17.0, 2.0 Hz), 4.83 (dd, 2H, J = 7.0 Hz), 4.67 (dd, 2H, J = 7.0 Hz), 4.51 (AB q, 2H, J = 10.0 Hz), 3.98 (m , 1H), 3.71 (m, 1H), 3.61 (m, 1H), 3.57 (dd, 1H, 6.0, 9.0 Hz), 3.50 (dd, 1H, J = 4.0, 9.0 Hz), 3.42 (s, 3H), 2.53 (m, 1H).

IR (cm^{-1}) : 3600-3400(w), 3050-2800(m), 1645(w), 1500(w), 1460(m), 1370(m), 1120(m), 1100(s), 1030(s), 920(m).

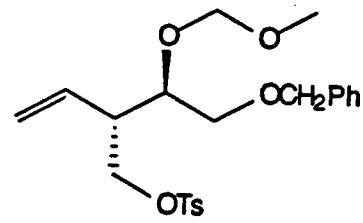
MS (m/z) : 234 (M^+-$HOCH_3$, 0.3), 221(4), 180(1), 174(2), 149(6), 107(25), 91(100), 45(72).

Exact mass calcd for $C_{14}H_{18}O_3$: 234.1256 ; found : 234.1253 .

Anal. calcd for $C_9H_{16}O_5$: C 67.65, H 8.33, O 24.03 ; found : C 67.63, H 8.44.

$[\alpha]_D$ = + 40.5 (c = 1.44, CH_2Cl_2).

Preparation of (3S, 4R)-5-Benzyloxy-4-methoxymethoxy-3-(p-toluene-sulfonyl)oxymethyl-1-pentene (137).



The alcohol 132 (3.10 g, 11.6 mmol) was dissolved in 25 mL of dry pyridine and placed in a 50-mL r.b. flask. The solution was cooled to 0 °C and 2.65 g (14.0 mmol) of p-toluenesulfonyl chloride was added in one portion. The resulting green solution was stirred at 0 °C for 24 h and then added to 100 mL ice-cold 1N HCl. The aqueous phase was extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$,

and evaporated under reduced pressure to give 4.87 g of sulfonate 137 as a slightly yellow oil. The product was used in the next step without further purification.

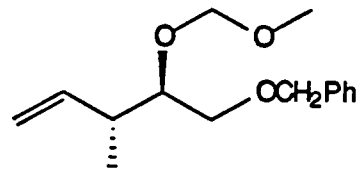
^{1}H NMR (400 MHz), (δ) : 7.77 (d, 2H, 8.0 Hz), 7.38-7.25 (m, 7H), 5.62 (ddd, 1H, J = 9.0, 11.0, 17.0 Hz), 5.16 (dd, 1H, J = 11.0, 2.0 Hz), 5.10 (dd, 1H, J = 17.0, 2.0 Hz), 4.66 (d, 1H, J = 7.0 Hz), 4.57 (d, 1H, J = 7.0 Hz), 4.46 (AB q, 2H, J = 11.5 Hz), 4.16 (dd, 1H, J = 7.0, 9.5 Hz), 4.05 (dd, 1H, J = 7.0, 9.5 Hz), 3.86 (ddd, 1H, J = 3.5, 5.0, 6.0 Hz), 3.52 (dd, 1H, J = 5.0, 10.0 Hz), 3.43 (dd, 1H, J = 6.0, 10.0 Hz), 3.30 (s, 3H), 2.74 (m, 1H), 2.44 (s, 3H).

IR (cm^{-1}) : 3050-2800(m), 1650(w), 1615(m), 1500(w), 1460(m), 1370(s), 1180(s), 1160(m), 1000(s), 1040(s), 970(s).

MS (m/z) : 388 (M^+-$HOCH_3$, 0.1), 375(3), 306(3), 269(0.4), 217(3), 107(47), 106(21), 92(29), 91(100), 65(29), 54(25).

Exact mass calcd for $C_{21}H_{24}O_5S$: 388.1345 ; found : 388.1345 .

Preparation of (3R, 4R)-5-Benzyloxy-4-methoxymethoxy-3-methyl-1-pentene (138).



A 100-mL r.b. flask fitted with a condenser was charged with 4.80 g (11.4 mmol) of tosylate 137 followed by 60 mL of dry THF and the reaction mixture was cooled to 0° C. To that cold mixture was slowly added 1.29 g (34.2 mmol) of $LiAlH_4$ and the resulting mixture was stirred 0.5 h at 0 °C. The mixture was then heated to reflux for 6 h. The work up was identical to the one used in the preparation of (3S,4R)-5-benzyloxy-3-hydroxymethyl-4-methoxymethoxy-1-pentene (132) (p 139) giving 2.90 g of the methyl product 138. The product was purified by chromatography on silica gel eluting with pet. ether - ethyl acetate (15:1) to yield 2.49 g (86% yield) of 138 as a colorless oil.

^{1}H NMR (400 MHz), (δ) : 7.35-7.25 (m, 5H), 5.82 (ddd, 1H, J = 7.0, 11.0, 17.0 Hz), 5.04 (dd, 1H, J = 17.0, 1.0 Hz), 5.03 (dd, 1H, J = 11.0, 1.0 Hz), 4.79 (d, 1H, J = 7.0 Hz), 4.67 (d, 1H, J = 7.0 Hz), 4.52 (s, 2H), 3.68 (q, 1H, J = 6.0 Hz), 3.53 (d, 2H, J = 6.0 Hz), 3.39 (s, 3H), 2.54 (m, 1H), 1.06 (d, 3H, J = 7.0 Hz).

IR (cm^{-1}) : 3100(w), 3050-2800(m), 1645(w), 1500(w), 1455(m), 1370(m), 1140(s), 1100(s), 1030(s), 910(s).

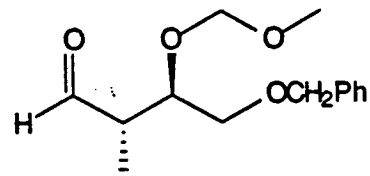
MS (m/z) : 218(M^+-$HOCH_3$, 1), 205(10), 195(1), 188(0.3), 165(13), 91(100).

Exact mass calcd for $C_{14}H_{18}O_2$: 218.1307 ; found : 218.1308 .

Anal. calcd for $C_9H_{16}O_5$: C 71.97, H 8.86, O 19.17 ; found : C 71.70, H 8.80.

$[\alpha]_D$ = +16.6 (c = 0.53, CH_2Cl_2).

Preparation of (2S,3R)-4-Benzyloxy-3-methoxymethoxy-2-methylbutanal (139).



The alkene 138 (2.49 g, 9.95 mmol) was dissolved in 20 mL of diethyl ether and the same volume of water was added. This mixture was stirred vigorously and a catalytic amount (0.50 mmol) of osmium tetroxide was added. A black color developed. Then 4.68 g (21.8 mmol) of sodium metaperiodate were added in small portions over a period of 20 min. The reaction was left to stir at room temperature for 36 h.

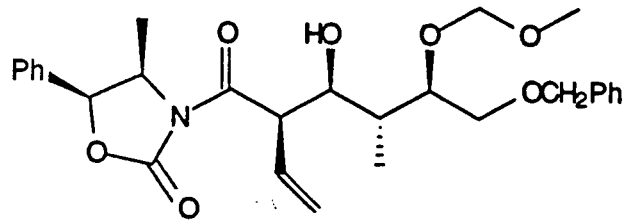
The organic phase was then separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and stirred with 1 g of activated charcoal for 3 h. The black suspension was filtered through Celite and the solvent was evaporated under reduced pressure to yield 2.53 g of a black oil. This oil was purified by chromatography on silica gel eluting with pet. ether - ethyl acetate (3:1) to yield 2.50 g (100%

yield) of aldehyde 139 as a slightly grey oil. The aldehyde thus obtained was suitable for use in the next step without further purification.

^{1}H NMR (400 MHz), (δ) : 10.0 (d, 1H, J = 2.0 Hz), 7.38-7.28 (m, 5H), 4.75 (d, 1H, J = 7.0 Hz), 4.65 (d, 1H, J = 7.0 Hz), 4.53 (AB q, 2H, 12 Hz), 4.03 (q, 1H, J = 5.0 Hz), 3.60 (AB portion of ABX, 2H, $J_{AX} = J_{BX} = 5.0$ Hz, $J_{AB} = 10.0$ Hz), 3.36 (s, 3H), 2.76 (ddq, 1H, J = 2.0, 7.0, 5.0 Hz), 1.11 (d, 3H, J = 7.0 Hz).

IR (cm^{-1}) : 3050-2800(m), 1730(s), 1610(w), 1500(w), 1460(m), 1370(m), 1150(m), 1105(s), 1025(s), 910(m).

Preparation of (4R, 5S)-3-{(2R, 3S, 4R, 5R)-6-Benzyloxy-5-methoxymethoxy-4-methyl-3-hydroxy-1-oxo-2-vinylhexanoyl}-5-phenyl-4-methyl-2-oxazolidinone (140).



The boron enolate of imide 69 (2.92 g (11.8 mmol) was generated as described in the preparation of compound 130 (p 136). To that slightly orange solution at -78 °C was added 2.50 g (9.95 mmol) of the aldehyde 139. The rest of the procedure was identical to the one described in the preparation of compound 130. The crude aldol adduct 140 was isolated (3.40 g) as a yellow oil. The product was purified by chromatography on silica gel eluting with pet. ether-ethyl acetate (3:1) to give 3.25 g (66% yield) of pure 140 as a colorless oil.

^{1}H NMR (400 MHz), (δ) : 7.45-7.25 (m, 10H), 6.07 (ddd, 1H, J = 9.0, 11.0, 17.0 Hz), 5.60 (d, 1H, J = 7.5 Hz), 5.34 (dd, 1H, J = 17.0, 1.0 Hz), 5.33 (dd, 1H, J = 11.0, 1.0 Hz), 4.75 (dd, 1H, J = 7.0 Hz), 4.77-4.65 (m, 2H), 4.69 (d, 1H, J = 7.0 Hz), 4.56 (s, 2H), 4.04 (q, 1H, J = 5.0 Hz), 3.98 (m, 1H), 3.70 (dd, 1H, J =

5.0, 11.0 Hz), 3.59 (dd, 1H, J = 5.0, 11.0 Hz), 3.56 (d, 1H, J = 4.0 Hz), 3.39 (s, 3H), 2.07 (m, 1H), 1.01 (d, 3H, J = 7.0 Hz), 0.88 (d, 3H, J = 7.0 Hz).

IR (cm^{-1}): 3600-3300(bm), 3050-3000(w), 3000-2850(m), 1785(s), 1715(m), 1440(m), 1245(s), 1180(m), 1120(s), 1095(m), 960(s).

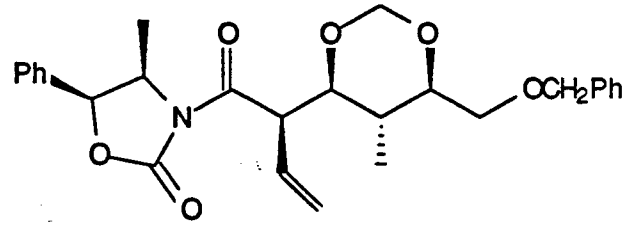
MS (m/z): 466 (M^+-OCH_3, 0.1), 390(0.1), 372(0.2), 344(0.1), 107(32), 101(21), 91(100), 69(24), 45(83), 41(23).

Exact mass calcd for $C_{27}H_{32}NO_6$: 466.1866; found: 466.1852.

Anal. calcd for $C_9H_{16}O_5$: C 67.59, H 7.09, O 22.51, N 2.81; found: C 67.46, H 7.01, N 2.80.

$[\alpha]_D$ = + 37.7 (c = 0.45, CH_2Cl_2).

Preparation of (141) from the cyclization of 140.



A 50-mL, two-neck, r.b flask was charged with 25 mL of dry CH_2Cl_2 and alcohol 140 (590 mg, 1.18 mmol). The reaction mixture was cooled to 0 °C and P_2O_5 was then added in portions of 0.5 g while maintaining the temperature at 0 °C. The addition of P_2O_5 was stopped at completion of the reaction (monitored by TLC).

The mixture was carefully added to 150 mL of ice-cold saturated aqueous $NaHCO_3$ and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give 476 mg of 1,3-dioxane 141 as a yellow oil. The product was then purified by chromatography on silica gel with pet. ether - ethyl acetate (5:1) as the eluant to yield 455 mg (82% yield) of pure 141 as a colorless oil.

^{1}H NMR (400 MHz), (δ): 7.45-7.25 (m, 10H), 6.22 (dt, 1H, J = 11.0, 16.0 Hz), 5.70 (d, 1H, J = 7.5 Hz), 5.34 (dd, 1H, J = 11.0, 1.0 Hz), 5.20 (dd, 1H, J = 16.0, 1.0

Hz), 5.17 (d, 1H, J = 7.0 Hz), 4.75 (qi, 1H, J = 7.0 Hz), 4.71 (d, 1H, J = 7.0 Hz), 4.63 (dd, 1H, J = 3.0, 9.0 Hz), 4.63 (d, 1H, J = 12.0 Hz), 4.56 (d, 1H, J = 12.0 Hz), 3.74 (dd, 1H, J = 10.0, 3.0 Hz), 3.64 (dd, 1H, J = 11.0, 2.0 Hz), 3.56 (dd, 1H, J = 11.0, 6.0 Hz), 3.50 (ddd, 1H, J = 10.0, 6.0, 2.0 Hz), 1.88 (ddq, 1H, J = 3.0, 10.0, 7.0 Hz), 0.92 (d, 3H, J = 7.0 Hz), 0.85 (d, 3H, J = 7.0 Hz).

^{13}C NMR (100 MHz), (δ) : 171.6(s), 152.9(s), 137.9(s), 132.9(s), 131.3(d), 128.74(d), 128.70(d), 128.67(d), 128.3(d), 127.7(d), 127.6(d), 125.56(d), 125.54(d), 125.53(d), 125.51(d), 119.9(t), 93.2(t), 80.9(d), 80.8(d), 79.1(d), 73.4(t), 70.4(t). 55.4(d), 50.7(d), 32.7(d), 14.2(q), 11.3(q).

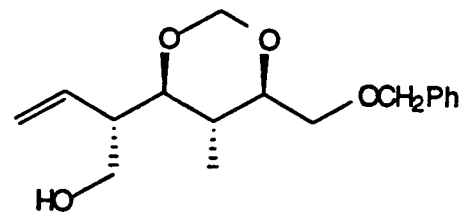
IR (cm^{-1}) : 3050(w), 3000-2800(w), 1785(s), 1715(m), 1465(w), 1355(s), 1190(m), 1170(m), 1150(m), 1130(m), 1095(m), 1040(m), 1010(w), 980(w).

MS (m/z) : 465 (M^+, 0.2), 421(0.1), 344(1), 314(2), 107(47), 91(100), 79(23).

Exact mass calcd for $C_{27}H_{31}NO_6$: 465.2151 ; found : 465.2148 .

$[\alpha]_D$ = - 11.8 °(c = 0.45, $CHCl_3$).

Preparation of (4R, 5R, 6R)-6-Benzyloxymethyl-4-{(3S)-4-hydroxy-1-buten-3-yl}-5-methyl-1,3-dioxane (144).



Compound 141 (1.95 g, 4.19 mmol) was reduced with $LiAlH_4$ (477 mg, 12.6 mmol) according to the procedure described in the preparation of 132 (p 139). The crude product was then purified by chromatography on silica gel using pet. ether - ethyl acetate (1:1) as eluant to give 1.19 g (98% yield) of alcohol 144 as a colorless oil and 519 mg (70% yield) of recovered (4R, 5S)-4-methyl-5-phenyl-2-oxazolidinone.

^{1}H NMR (400 MHz), (δ) : 7.39-7.23 (m, 5H), 5.91 (dt, 1H, J = 10.0, 17.0 Hz), 5.24 (dd, 1H, J = 10.0, 1.0 Hz), 5.16 (dd, 1H, J = 17.0, 1.0 Hz), 5.12 (d, 1H, J = 6.0

Hz), 4.72 (d, 1H, J = 6.0 Hz), 4.62 (d, 1H, 12.0 Hz), 4.56 (d, 1H, 12.0 Hz), 3.71 (bd, 2H, J = 6.0 Hz), 3.62 (dd, 1H, J = 11.0, 2.0 Hz), 3.54 (dd, 1H, J =11.0, 6.0 Hz), 3.46 (m, 2H), 2.50 (m, 1H), 1.89 (bs, 1H), 1.83 (m, 1H), 0.72 (d, 3H, J = 7.0 Hz).

^{13}C NMR (100 MHz), (δ): 137.9(s), 134.3(d), 128.3(d), 127.8(d), 127.6(d), 119.1(t), 93.2(t), 81.7(d), 81.1(d), 73.4(t), 70.6(t), 64.3(t), 47.5(d), 32.7(d), 11.5(q).

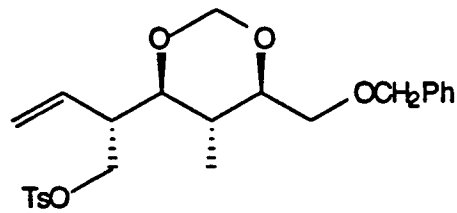
IR (cm^{-1}): 3650-3300(bw), 3050-3000(m), 3000-3800(s), 1650(w), 1500(w), 1470(w), 1455(m), 1405(w), 1385(m), 1365(m), 1180(s), 1150(s), 1100(s), 1080(s), 1025(s), 965(w), 920(m), 845(w).

MS (m/z): 292(M^+, 0.2), 221(2), 128(6), 91(100), 58(23), 41(21).

Exact mass calcd for $C_{17}H_{24}O_4$: 292.1674; found: 292.1670.

$[\alpha]_D$ = + 6.16 (c =3.0, $CHCl_3$).

Preparation of (4S, 5R, 6R)-6-Benzyloxymethyl-5-methyl-4-{(3R)-4-(p-toluenesulfonyl)oxy-1-buten-3-yl}-1,3-dioxane (145).



The alcohol 144 (173 mg, 0.591 mmol) was converted to the tosylate 145 following the procedure in the preparation of (3S,4R)-5-benzyloxy-4-methoxymethoxy-3-(p-toluenesulfonyl)oxymethyl-1-pentene (137) (p 140). Tosylate 145 (263 mg) was obtained as a yellow oil. The product was used directly in the next step without further purification.

^{1}H NMR (400 MHz), (δ): 7.78 (d, 2H, J = 8.0 Hz), 7.38-7.25 (m, 7H), 5.63 (dt, 1H, J = 10.0, 17.0 Hz), 5.20 (dd, 1H, J = 10.0, 1.0 Hz), 5.14 (dd, 1H, J = 17.0, 1.0 Hz), 4.93 (d, 1H, J = 7.0 Hz), 4.60 (d, 1H, J = 12.0 Hz), 4.52 (d, 1H, J = 12.0 Hz), 4.50 (d, 1H, J = 7.0 Hz), 4.14 (t, 1H, J = 9.0 Hz), 3.93 (dd, 1H, J = 7.0,

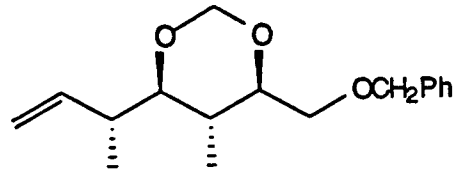
9.0 Hz), 3.58 (dd, 1H, J = 1.0, 11.0 Hz), 3.50 (dd, 1H, J = 11.0, 6.0 Hz), 3.38 (ddd, 1H, J = 9.0, 6.0, 1.0 Hz), 3.33 (dd, 1H, J = 10.0, 1.0 Hz), 2.71 (m, 1H), 2.44 (s, 3H), 1.75 (ddq, 1H, J = 10.0, 9.0, 7.0 Hz), 0.66(d, 3H, J = 7.0 Hz).

IR (cm^{-1}): 3050-3000(w), 3000-2800(m), 1605(m), 1500(w), 1455(w), 1405(w), 1360(s), 1305(w), 1290(w), 1170(s), 1080(s), 1035(s), 1000(m), 955(s), 840(m),

MS (m/z): 446(M^+, 0.2), 349(0.2), 325(1), 295(1), 91(100).

Exact mass calcd for $C_{24}H_{30}O_6S$: 446.1763 ; found : 446.1759 .

Preparation of (4R, 5R, 6R)-6-Benzyloxymethyl-4-{(3R)-1-buten-3-yl}-5-methyl-1,3-dioxane (146).



The tosylate 145 (1.35 g, 3.02 mmol) was reduced into the corresponding alkane with 343 mg (9.06 mmol) $LiAlH_4$ following the procedure described in the preparation (3S, 4R)-5-benzyloxy-4-methoxymethoxy-3-methyl-1-pentene (138) (p 141). The crude oil obtained (829 mg) was purified by chromatography on silica gel eluting with hexanes - ethyl acetate (15:1), to yield 806 mg (96% yield) of alkene 146 as a colorless oil.

^{1}H NMR (400 MHz), (δ) : 7.35-7.25 (m, 5H), 5.86 (ddd, 1H, J = 9.0, 10.0, 17.0 Hz), 5.26 (d, 1H, J = 7.0 Hz), 5.05 (dd, 1H, J = 10.0, 1.0 Hz), 5.01 (dd, 1H, J = 17.0, 1.0 Hz), 4.69 (d, 1H, J =7.0 Hz), 4.61 (d, 1H, J = 12.0 Hz), 4.56 (d, 1H, J = 12.0 Hz), 3.66 (dd, 1H, J = 11.0, 3.0 Hz), 3.53 (dd, 1H, J =11.0, 6.0 Hz), 3.42 (ddd, 1H, J = 10.0, 6.0, 3.0 Hz), 3.12 (dd, 1H, J = 11.0, 2.0 Hz), 2.47 (ddq, 1H, J = 9.0, 7.0, 2.0 Hz), 1.75 (ddq, 1H, J = 11.0, 10.0, 7.0 Hz), 1.11 (d, 3H, J = 7.0 Hz), 0.73 (d, 3H, J = 7.0 Hz).

IR (cm^{-1}): 3050-2800(m), 1452(m), 1277(m), 1093(m), 1046(s).

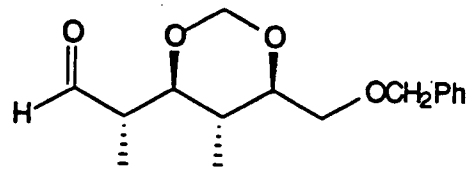
MS (m/z) : 276 (M^+, 1), 221(2), 191(1), 173(2), 155(8), 91(100).

Exact mass calcd for $C_{17}H_{24}O_3$: 276.1725 ; found : 276.1724 .

Anal. calcd for $C_9H_{16}O_5$: C 73.88, H 8.75, O 17.37 ; found : C 74.26, H 8.90.

$[\alpha]_D$ = - 5.5 (c =, $CHCl_3$).

Preparation of (4S, 5R, 6R)-6-Benzyloxymethyl-5-methyl-4-{(2S)-1-oxo-2-propanyl}-1,3-dioxane (167).



The alkene 146 (400 mg, 1.44 mmol) was oxidatively cleaved to the corresponding aldehyde 167 with a catalytic amount of osmium tetroxide and 681 mg (3.18 mmol) of sodium metaperiodate following the same procedure as in the preparation of (2S, 3R)-4-benzyloxy-3-methoxymethoxy-2-methylbutanal (139) (p 142). The reaction had to be stirred for 48 h to achieve completion.

The grey oil thus obtained was purified by chromatography on silica gel eluting with pet. ether - ethyl acetate (8:1) to yield 378 mg (94% yield) of the aldehyde 167 as an unstable, slightly grey oil along with 22 mg (5%) of a mixture containing aldehyde 167 and predominantly (~ 95%) its C_2 methyl epimer 168.

Data for (167).

^{1}H NMR (400 MHz), (δ) : 9.78 (d, 1H, J = 3.0 Hz), 7.40-7.25 (m, 5H), 5.15 (d, 1H, J = 7.0 Hz), 4.70 (d, 1H, J = 7.0 Hz), 4.63 (d, 1H, J = 12.0 Hz), 4.55 (d, 1H, J = 12.0 Hz), 3.64 (dd, 1H, J = 11.0, 3.0 Hz), 3.58 (dd, 1H, J = 11.0, 6.0 Hz), 3.44 (dd, 1H, J = 10.0, 2.0 Hz), 3.42 (m, 1H), 2.61 (ddq, 1H, J = 7.5, 3.0, 2.0 Hz), 1.97 (m, 1H), 1.24 (d, 3H, J = 7.5 Hz), 0.78 (d, 3H, J = 7.5 Hz).

IR (cm^{-1}): 3050-3000(m), 3000-2800(m), 1720(s), 1500(w), 1455(m), 1390(m), 1190(s), 1110(s), 1045(s), 1005(m), 955(w), 895(w).

MS (m/z): 278(M^+,0.2), 247(1), 107(31), 98(20), 92(23), 91(100), 79(22), 77(20), 69(24), 65(26).

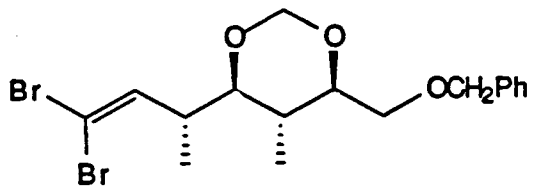
Exact mass calcd for $C_{16}H_{22}O_4$: 278.1518; found: 278.1530.

Data for the Isomeric Aldehyde 168.

^1H NMR (400 MHz), (δ): 9.72 (s, 1H), 7.40-7.27 (m, 5H), 5.16 (d, 1H, J = 7.0 Hz), 4.71 (d, 1H, J = 7.0 Hz), 4.66 (d, 1H, J = 12.0 Hz), 4.58 (d, 1H, J = 12.0 Hz), 3.87 (dd, 1H, J = 10.0, 3.0 Hz), 3.66 (dd, 1H, J =11.0, 3.0 Hz), 3.60 (dd, 1H, J = 11.0, 6.0 Hz), 3.51 (m, 1H), 2.53 (dq, 1H, J = 7.5, 3.0 Hz), 1.97 (m, 1H), 1.19 (d, 3H, J = 7.5 Hz), 0.78 (d, 3H, J = 7.5 Hz).

MS (m/z): 278(M^+,0.2), 247(1), 105(28), 92(23), 91(100), 69(27), 65(20).

Preparation of (4R, 5R, 6R)-6-Benzyloxymethyl-4-{(3R)-1, 1-dibromo-1-buten-3-yl}-5-methyl-1,3-dioxane (169).



Triphenylphosphine (2.28 g, 8.68 mmol) and zinc dust (577 mg, 8.82 mmol) were weighed in a 25-mL, one-neck r.b. flask which was then evacuated and flushed with argon. Then 35 mL of dry CH_2Cl_2 were added followed by 2.88 g (8.68 mmol) of carbon tetrabromide. After stirring for 24 h the solution became red and a white precipitate appeared (absence of these occurrences indicated reaction failure). Then the mixture (20:1) of the two isomeric aldehydes 167 and 168 (400 mg, 1.44 mmol) was added and the solution turned slowly brown. After the mixture was stirred for 12 h, it was added to 300 mL of hexanes and

filtered through Celite. The filtrate was evaporated under reduced pressure to yield 523 mg of vinyl dibromides 169 and 170 as a colorless oil.

The product was purified by chromatography on silica gel eluting with hexanes - ethyl acetate (15:1) to give 378 mg (61% yield) of the vinyl dibromide 169 along with 19 mg (3% yield) of the isomeric vinyl dibromide 170, both as a colorless oils.

Data for 169

^{1}H NMR (400 MHz), (δ) : 7.40-7.25 (m, 5H), 6.57 (d, 1H, J = 9.0 Hz), 5.14 (d, 1H, J = 7.0 Hz), 4.69 (d, 1H, J = 7.0 Hz), 4.63 (d, 1H, J = 12.0 Hz), 4.56 (d, 1H, J = 12.0 Hz), 3.63 (dd, 1H, J = 11.0, 3.0 Hz), 3.54 (dd, 1H, J = 11.0, 5.5 Hz), 3.41 (m, 1H), 3.15 (dd, 1H, J = 10.0, 1.0 Hz), 2.82 (ddq, 1H, J = 9.0, 7.0, 1.0 Hz), 1.64 (m, 1H), 1.11 (d, 3H, J = 7.0 Hz), 0.77 (d, 3H, J = 7.0 Hz).

IR (cm^{-1}) : 3050-3000(w), 3000-2850(m), 2771(w), 1447(w), 1360(w), 1186(s), 1088(s), 1042(s), 952(w), 851(w).

MS (m/z) : 436($^{81}Br^{81}Br$, M^+, 0.2), 434($^{81}Br^{79}Br$, M^+, 1), 432($^{79}Br^{79}Br$, M^+, 0.2), 255(1), 221(2), 215(1), 213(2), 211(1), 91(100).

Exact mass calcd for $C_{17}H_{22}{}^{81}Br_2O_3$: 435.9898 ; found : 435.9909

$C_{17}H_{22}{}^{81}Br^{79}BrO_3$: 433.9917 ; found : 433.9925

$C_{17}H_{22}{}^{79}Br_2O_3$: 431.9937 ; found : 431.9923 .

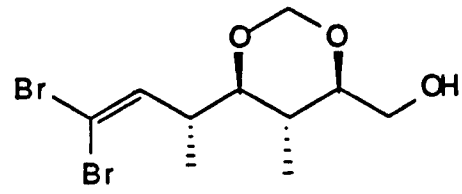
$[\alpha]_D$ = + 9.9 (c = 4.5, $CHCl_3$).

Data for the Isomeric Vinyl Dibromide 170.

^{1}H NMR (400 MHz), (δ) : 7.40-7.25 (m, 5H), 6.55 (d, 1H, J = 9.0 Hz), 5.15 (d, 1H, J = 7.0 Hz), 4.70 (d, 1H, J = 7.0 Hz), 4.64 (d, 1H, J = 12.0 Hz), 4.57 (d, 1H, J = 12.0 Hz), 3.64 (dd, 1H, J = 11.0, 3.0 Hz), 3.58 (dd, 1H, J = 11.0, 6.0 Hz), 3.42 (m, 1H), 3.24 (dd, 1H, J = 10.0, 1.0 Hz), 2.74 (ddq, 1H, J = 9.0, 7.0, 1.0 Hz), 1.87 (m, 1H), 1.05 (d, 3H, J = 7.0 Hz), 0.78 (d, 3H, J = 7.0 Hz).

MS (m/z) : 436($^{81}Br^{81}Br$, M^+, 0.1), 434($^{81}Br^{79}Br$, M^+, 0.4), 432($^{79}Br^{79}Br$, M^+, 0.1), 255(6), 221(2), 215(3), 213(6), 211(3), 91(100).

Preparation of (4R, 5R, 6R)-4-{(3R)-1, 1-Dibromo-1-buten-3-yl}-6-hydroxymethyl-5-methyl-1,3-dioxane (171).



To a 25-mL, two-neck, r.b. flask fitted with a septum was added 10 mL of 95% ethanol followed by a catalytic amount, of palladium on activated charcoal (9% w/w) and two drops of concd HCl. The mixture was prehydrogenated for 30 min. Then 240 mg (0.555 mmol) of benzyl ether 169 dissolved in 2 mL of 95% ethanol was added to the mixture and the resulting solution was stirred under an atmosphere of hydrogen until 12.4 mL (0.555 mmol) of hydrogen were taken up. Then a spatula of solid $NaHCO_3$ was added to neutralize the acid. The suspension was filtered through Celite and evaporated under reduced pressure to give the crude alcohol 171 as a colorless oil. This oil was purified by chromatography on silica gel eluting with hexanes - ethyl acetate (3:1) to give 165 mg (87% yield) of pure alcohol 171 as a colorless oil.

^1H NMR (400 MHz), (δ) : 6.52 (d, 1H, J = 9.0 Hz), 5.13 (d, 1H, J = 6.0 Hz), 4.72 (d, 1H, J = 6.0 Hz), 3.81 (bd, 1H, J = 11.0 Hz), 3.65 (bdd, 1H, J = 11.0, 7.0 Hz), 3.31 (ddd, 1H, J = 9.0, 7.0, 3.0 Hz), 3.16 (dd, 1H, J = 10.0, 1.0 Hz), 2.83 (ddq, 1H, J = 9.0, 7.5, 1.0 Hz), 2.08 (bs, 1H), 1.61 (ddq, 1H, J = 10.0, 9.0, 7.5 Hz), 1.12 (d, 3H, J = 7.5 Hz), 0.83 (d, 3H, J = 7.5 Hz).

IR (cm^{-1}) : 3600-3200 (bs), 3000-2850(s), 2770(w), 1616(w), 1457(m), 1356(m), 1180(s), 1126(m), 1087(s), 1040(s), 957(w), 859(m).

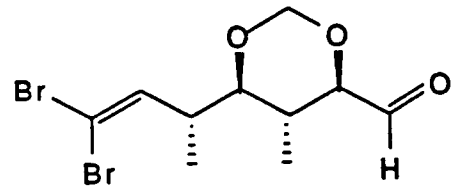
MS (m/z) : 345($^{81}Br^{81}Br$, M^+-1, 0.1), 343($^{81}Br^{79}Br$, M^+-1, 0.1), 341($^{79}Br^{79}Br$, M^+-1, 0.1), 315(0.1), 313(0.1), 311(0.1), 215(2), 213(3), 211(2), 201(0.3), 199(1), 197(1), 131(43), 101(100), 85(48), 83(46), 72(72), 71(26), 69(23), 57(50), 55(89), 43(53).

Exact mass calcd for $C_{10}H_{17}{}^{81}Br^{79}BrO_3$: 342.9369 ; found : 342.9379

$C_{10}H_{17}{}^{79}Br_2O_3$: 340.9389 ; found : 340.9395 .

$[\alpha]_D$ = -11.2 (c = 3.24, $CHCl_3$).

Preparation of (4S, 5R, 6R)-4-{(3R)-1, 1-Dibromo-1-buten-3-yl}-6-formyl-5-methyl-1, 3-dioxane (172).



To a solution of 0.11 mL (1.5 mmol) of DMSO dissolved in 5 mL of dry CH_2Cl_2 cooled to -60 °C was added 67 μL (0.76 mmol) of oxalyl chloride. This solution was stirred for 15 min. Then a solution of 240 mg (0.701 mmol) of alcohol 171 in 2 mL of CH_2Cl_2 was added to the reaction mixture. The resulting solution was stirred for another 15 min, then 0.50 mL (6.82 mmol) of triethylamine was added and the reaction was stirred while allowing it to warm to room temperature. When at room temperature the mixture was poured into saturated aqueous $NaHCO_3$, extracted with diethyl ether several times, washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to yield the crude aldehyde 172 as a slightly yellow oil. The crude compound was purified by chromatography on silica gel eluting with hexanes - ethyl acetate (8:1) to give 226 mg (95% yield) of aldehyde 172 as a colorless oil.

^1H NMR (400 MHz), (δ) : 9.61 (d, 1H, J = 1.0 Hz), 6.51 (d, 1H, J = 9.0 Hz), 5.18 (d, 1H, J = 7.0 Hz), 4.72 (d, 1H, J = 7.0 Hz), 3.60 (dd, 1H, J = 9.0, 1.0 Hz), 3.21 (dd, 1H, 10.0, 1.0 Hz), 2.87 (ddq, 1H, J = 9.0, 7.5, 1.0 Hz), 1.73 (ddq, 1H, J = 9.0, 10.0, 7.5 Hz), 1.13 (d, 3H, J =7.5 Hz), 0.93 (d, 3H, J =7.5 Hz).

IR (cm^{-1}) : 3000-2800(m), 2776(w), 1735(s), 1458(w), 1388(w), 1364(m), 1123(m), 1095(s), 1042(s).

MS (m/z) : 344($^{81}Br^{81}Br$, M^+, 0.1), 343(0.4), 342($^{81}Br^{79}Br$, M^+, 0.4), 341(1), 340($^{79}Br^{79}Br$, M^+, 0.2), 339(0.3), 315(8.3), 313(15), 311(9), 285(6), 283(13), 281(7), 257(18), 255(33), 253(19), 229(10), 227(21), 225(14), 215(43), 213(70), 211(44), 201(18), 199(27), 197(14), 129(100), 101(23), 99(57), 83(47), 73(32), 71(73), 69(26).

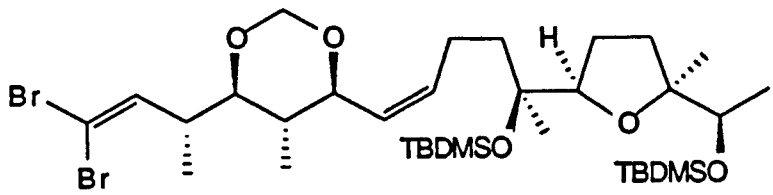
Exact mass calcd for $C_{10}H_{14}{}^{81}Br_2O_3$: 343.9271 ; found : 343.9258

$C_{10}H_{14}{}^{81}Br^{79}BrO_3$: 341.9291 ; found : 341.9286

$C_{10}H_{14}{}^{79}Br_2O_3$: 339.9311 ; found : 339.9305 .

IV. Coupling of Fragments C and D.

Preparation of Olefin 194 from the Wittig Reaction of 122 and 172.



To a solution of 238 mg (0.28 mmol) of phosphonium salt 122 in 1 mL of toluene was added 0.55 mL of sodium bis(trimethylsilyl)amide (0.575 M in toluene). The bright orange solution was stirred for 20 min and then it was cooled to -78 °C. Then 98 mg (0.28 mmol) of aldehyde 172 in 1 mL of toluene was added to the reaction mixture and the cooling bath was removed. The resulting colorless solution was stirred for an additional 12 h.

The white suspension was diluted with 20 mL of hexanes and filtered though Celite. The filtrate was evaporated under reduced pressure to yield 178 mg of a colorless oil. The product was purified by chromatography on silica gel eluting with hexanes - ethyl acetate (40:1) to give

160 mg (73% yield) of the cis-olefin 194 as a colorless oil along with 14 mg of a ~ 1:1 mixture of the cis-olefin 194 and its trans-isomer.

^{1}H NMR (400 MHz), (δ) : 6.55 (d, 1H, J = 9.0 Hz), 5.65(dt, 1H, J = 7.0, 10.0 Hz), 5.31 (dd, 1H, J = 9.0, 10.0 Hz), 5.09 (d, 1H, J = 6.0 Hz), 4.72 (d, 1H, J = 6.0 Hz), 3.95 (t, 1H, J = 9.0 Hz), 3.82 (t, 1H, J = 7.0 Hz), 3.54 (q, 1H, J = 6.0 Hz), 3.15 (dd, 1H, J = 10.0 + 1.0 Hz), 2.80 (ddq, 1H, J = 1.0, 8.0, 9.0 Hz), 2.18 (m, 1H), 1.85 - 1.35 (m, 4H), 1.13 (s, 3H), 1.11(d, 3H, J = 8.0 Hz), 1.10 (d, 3H, J = 6.0 Hz), 1.07 (s, 3H), 0.82 (s, 18H), 0.73 (d, 3H, J = 7.0 Hz), 0.08 (s, 6H), 0.03 (s, 3H), 0.01 (s, 3H).

IR (cm^{-1}) : 3000-2850(s), 1680(w), 1470(m), 1395(m), 1260(m), 1095(s), 1040(s).

MS (m/z) : 713($^{81}Br^{81}Br$, M^+-t-Bu, 1), 711($^{81}Br^{79}Br$, M^+-t-Bu, 1), 709($^{79}Br^{79}Br$, M^+-t-Bu, 0.4), 611(7), 609(11), 607(6), 527(17), 525(33), 523(16), 185(20), 159(24), 81(20), 75(52), 73 (100).

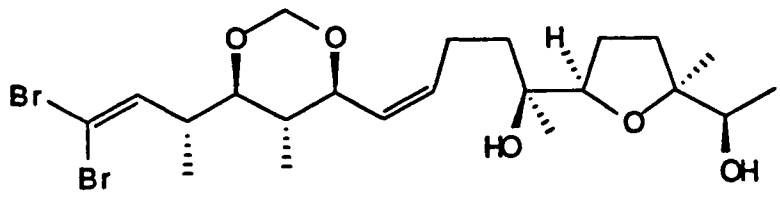
Exact mass calcd for $C_{30}H_{55}{}^{81}Br_2O_5Si_2$: 713.1917 ; found : 713.1956

$C_{30}H_{55}{}^{81}Br^{79}BrO_5Si_2$: 711.1936 ; found : 711.1920

$C_{30}H_{55}{}^{79}Br_2O_5Si_2$: 709.1955 ; found : 709.1981 .

$[\alpha]_D$ = + 46.33 (c = 2.21, $CHCl_3$).

Preparation of Diol 195 from the Deprotection Reaction of 194.



A solution of 10 mL of a 95:5 mixture of acetonitrile and aqueous HF was added to the bis-t-butyldimethylsilyl ether 194 (150 mg, 0.20 mmol) and the resulting solution was stirred for 1 h at room temperature. The reaction mixture was poured in 50 mL of a pH 7 aqueous

phosphate buffer solution. The aqueous phase was extracted several times with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to yield 99 mg of a colorless oil. Purification by chromatography on silica gel eluting with hexanes - ethyl acetate (1:1) gave 91 mg (87% yield) of pure diol 195 as a colorless oil.

^{1}H NMR (400 MHz), (δ) : 6.56 (d, 1H, J = 9.0 Hz), 5.65 (dt, 1H, J = 7.0, 10.5 Hz), 5.37 (dd, 1H, J = 9.0, 10.5 Hz), 5.26 (d, 1H, J = 6.0 Hz), 4.75 (d, 1H, J = 6.0 Hz), 3.97 (t, 1H, J = 9.0 Hz), 3.84 (t, 1H, J = 7.0 Hz), 3.79 (q, 1H, J = 6.0 Hz), 3.21 (dd, 1H, J = 10.0 + 1.0 Hz), 2.81 (ddq, 1H, J = 1.0, 7.0, 9.0 Hz), 2.18 (m, 1H), 2.22 (q, 1H, J = 9.5 Hz), 2.18 - 1.85 (m, 4H), 1.56-1.39 (m, 4H), 1.27 (s, 3H), 1.17 (s, 3H), 1.15 (d, 3H, J = 7.0 Hz), 1.13 (d, 3H, J = 6.0 Hz), 0.77 (d, 3H, J = 7.0 Hz).

IR (cm^{-1}) : 3608(w), 3550-3300(bw), 3050-3000(w), 3000-2800(m), 1595(w), 1451(w), 1246(w), 1181(s), 1118(m), 1072(m), 1035(s), 852(w), 794(w).

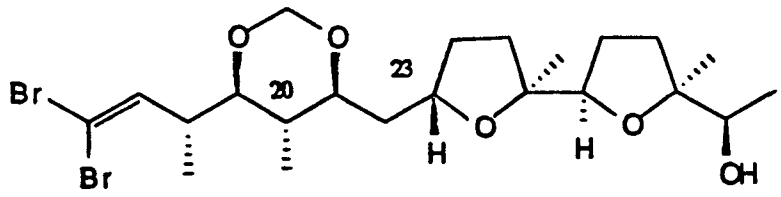
MS (m/z) 497 ($^{81}Br^{81}Br$, M^+-47, 2), 495 ($^{81}Br^{79}Br$, M^+- 47, 5), 493 ($^{79}Br^{79}Br$, M^+-47, 3), 449(1), 447(2), 445(1), 413(7), 411(12), 409(6), 278(52), 277(100), 199(31), 171(26), 139(36), 129(25), 94(27), 85(65), 83(20), 81(40), 77(23), 57(21), 55(24).

Exact mass : $C_{20}H_{31}{}^{81}Br_2O_4$: 497.0850 ; found : 497.0569

$C_{20}H_{31}{}^{81}Br^{79}BrO_4$: 495.0570 ; found : 495.0575

$C_{20}H_{31}{}^{79}Br_2O_4$: 493.0590 ; found : 493.0626 .

Preparation of Tetrahydrofuran 196 From the Oxymercuration of 195.



To a solution of 25 mg (0.05 mmol) of 195 in 1 ml of dry CH_2Cl_2 at -78 °C was added 51 mg (0.16 mmol) of mercuric acetate and the resulting reaction mixture was stirred for 1 h. Then the solution was allowed to warm to room temperature over a period of 4 h and it was stirred for an additional 2 h. Then the solution was cooled to - 78 °C and 17 mg (0.16 mmol) of $NaBH_4$ in a mixture of 6 mL of methanol, 1 mL of water, and 0.5 mL of 15% aqueous NaOH at -78 °C were added in one portion. The resulting mixture was stirred at -78 °C for 15 min and at room temperature for 1 h.

The solution was diluted with 50 mL of water and extracted with diethyl ether. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure to give 25 mg of a slightly grey oil. Tetrahydrofuran 196 was purified by chromatography with hexanes - ethyl acetate (4:1) as eluant to give 21 mg (84% yield) of 196 as a colorless oil.

^{1}H NMR (400 MHz), (δ) 6.53 (d, 1H, J = 10.0 Hz), 5.05 (d, 1H, J = 6.0 Hz), 4.62 (d, 1H, J = 6.0 Hz), 4.13 (m, 1H), 4.00 (t, 1H, J = 9.0 Hz), 3.77 (q, 1H, J = 7.0 Hz), 3.22 (dt, 1H, J = 2.5, 9.0 Hz), 3.12 (dd, 1H, J = 10.0 + 1.0 Hz), 2.80 (ddq, 1H, J = 1.0, 7.0, 9.0 Hz), 2.18 (m, 1H), 2.00 (m, 1H), 1.9 8-1.87 (m, 3H), 1.82-1.64 (m, 4H), 1.53-1.38 (m,2H), 1.26 (s, 3H), 1.13 (s, 3H), 1.14 (d, 3H, J = 8.0 Hz), 1.13 (d, 3H, J = 6.0 Hz), 0.79 (d, 3H, J = 7.0 Hz).

IR (cm^{-1}): 3555-3250(bm) 3000-2800(m), 1456(m), 1376(s), 1306(w), 1122(s), 1090(s), 1070(s), 1039(s), 887(w).

MS (m/z): 497 ($^{81}Br^{81}Br$, M^+- 47,8), 495 ($^{81}Br^{79}Br$, M^+47,16), 493 ($^{79}Br^{79}Br$, M^+- 47, 8), 413(31), 411(60), 409(30), 383(13), 381(24), 379(12), 139(32), 111(24), 99(28), 85(100), 81(23), 43(80), 32(43).

Exact mass calcd for $C_{20}H_{31}{}^{81}Br_2O_4$: 497.0550 ; found : 497.0540

$C_{20}H_{31}{}^{81}Br^{79}BrO_4$: 495.0570 ; found : 495.0565

$C_{20}H_{31}{}^{79}Br_2O_4$: 493.0580 ; found : 493.0568

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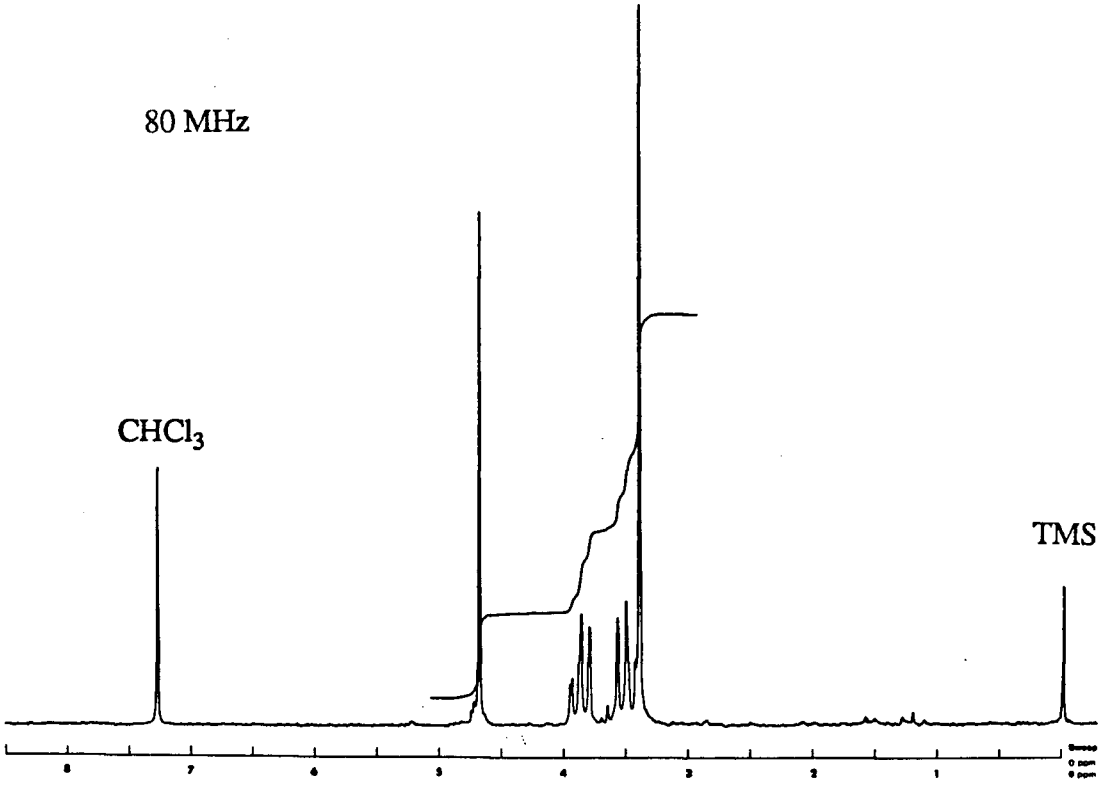
SPECTRAL APPENDIX

The ^{1}H NMR followed by the IR spectra are given below the structure of the corresponding compounds. In the case where diastereomers were obtained, only the spectra for the major isomer are given. ^{13}C NMR spectra are given on the following page when applicable.


MOMO
Br

85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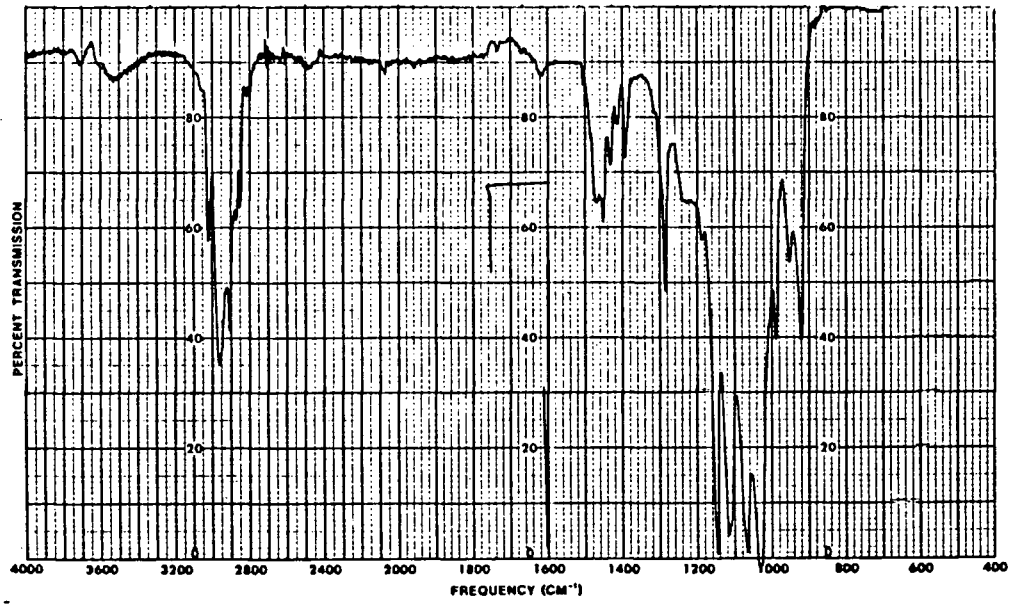
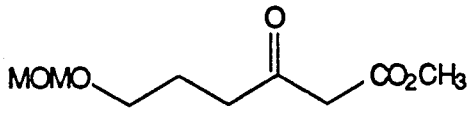
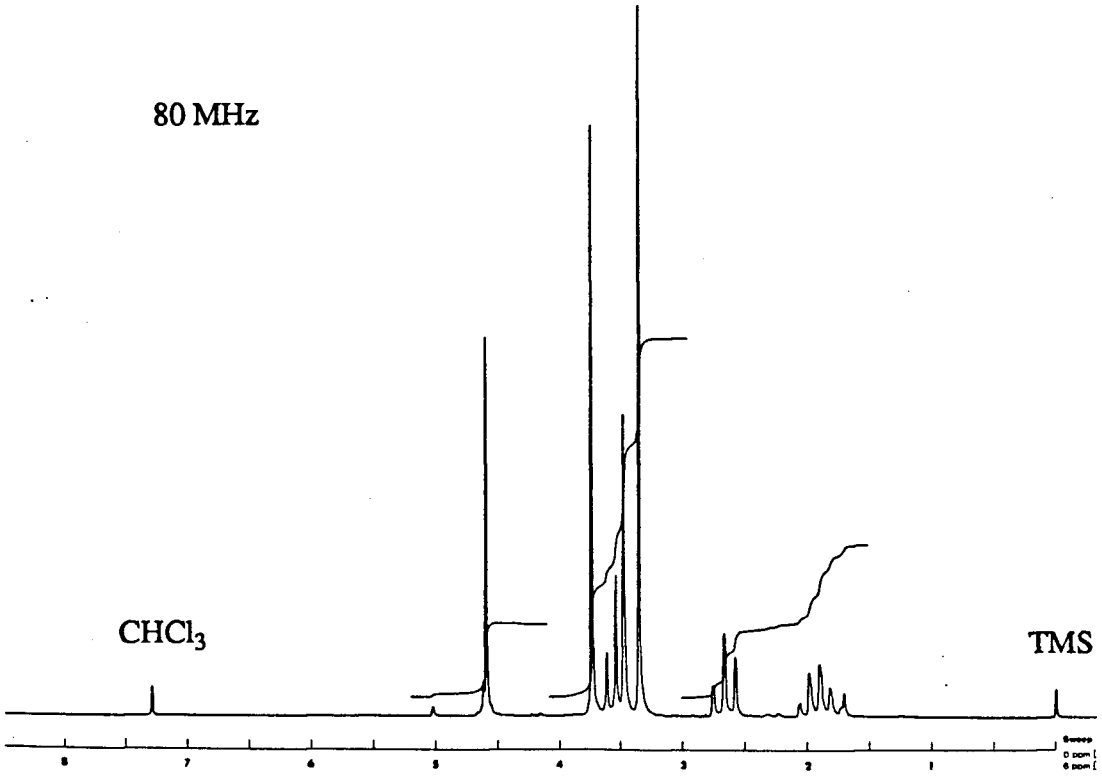
$CHCl_3$
TMS


PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)


O
MOMO
CO_2CH_3

86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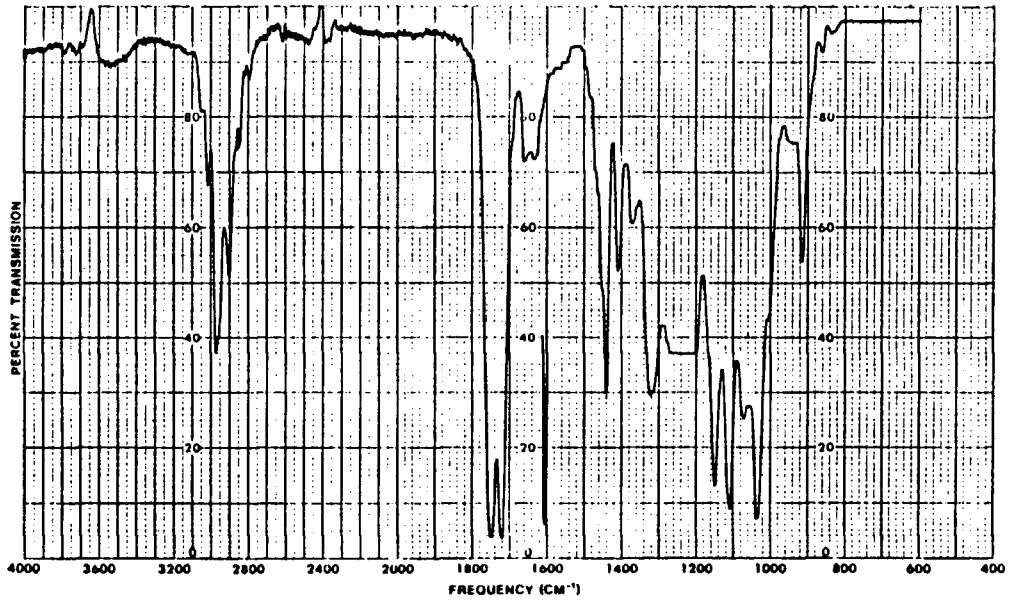
$CHCl_3$
TMS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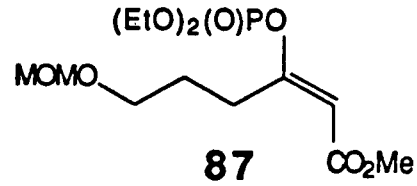
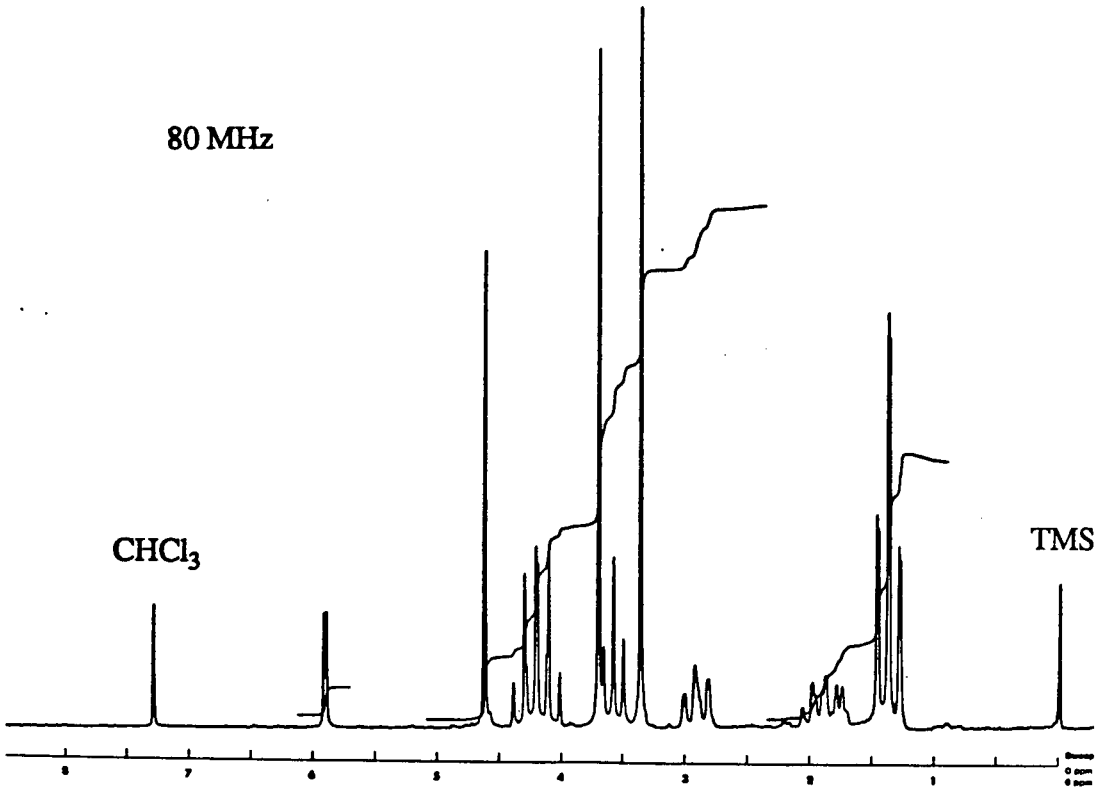
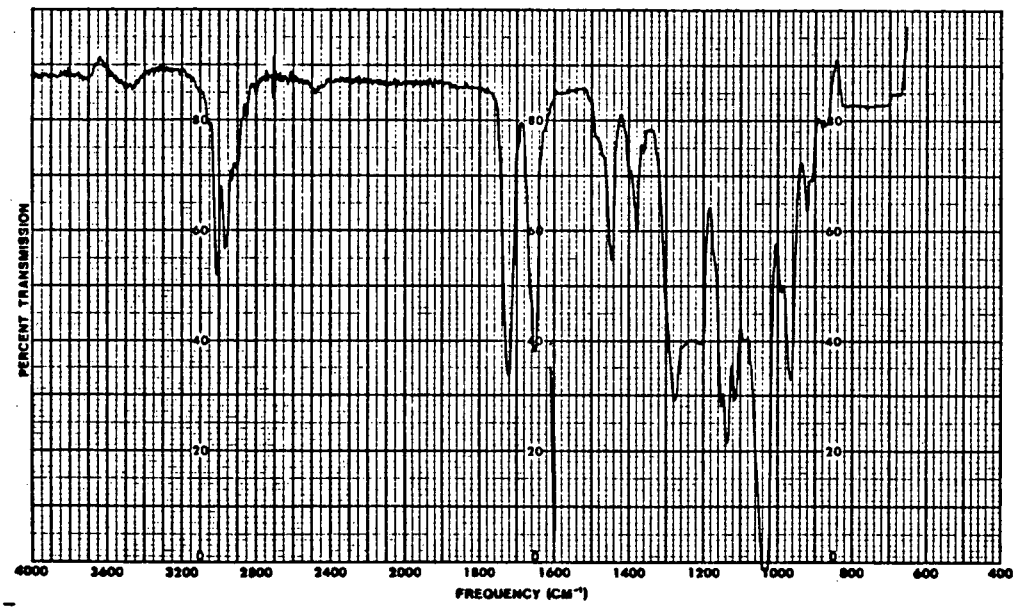
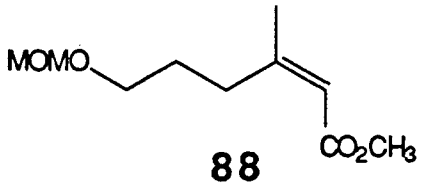
1800
1600
1400
1200
1000
800
600
400


(EtO)2(O)PO
MOMO
CO2Me

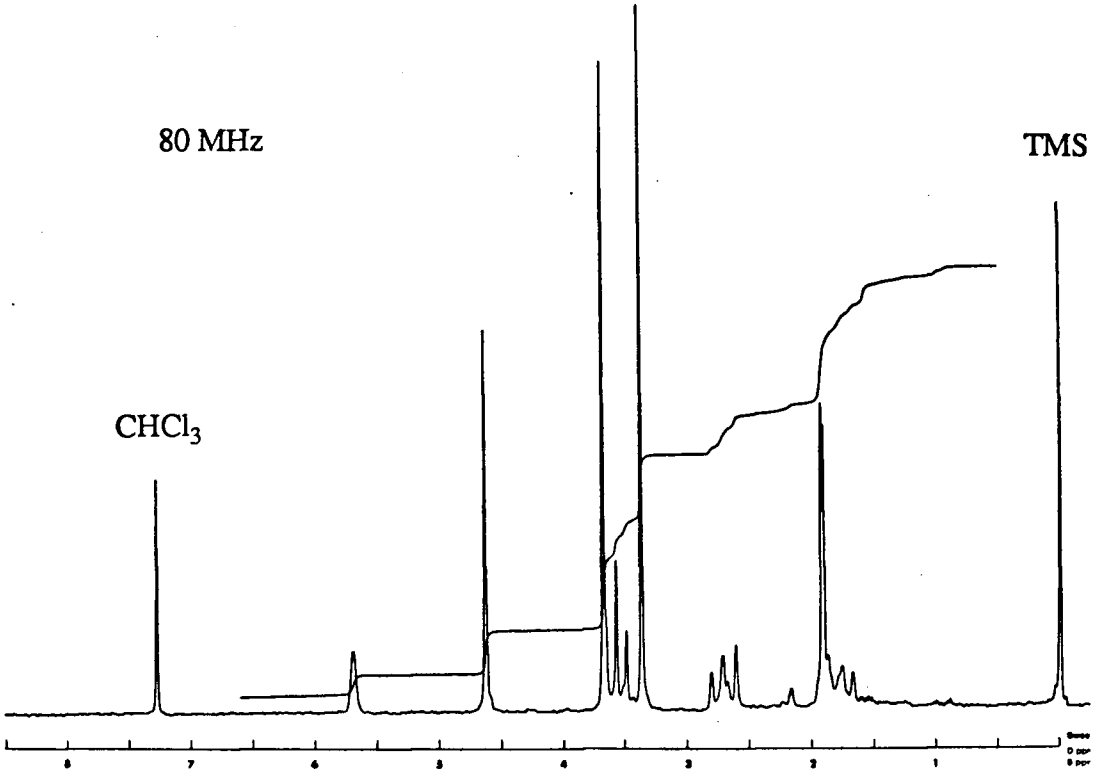
87

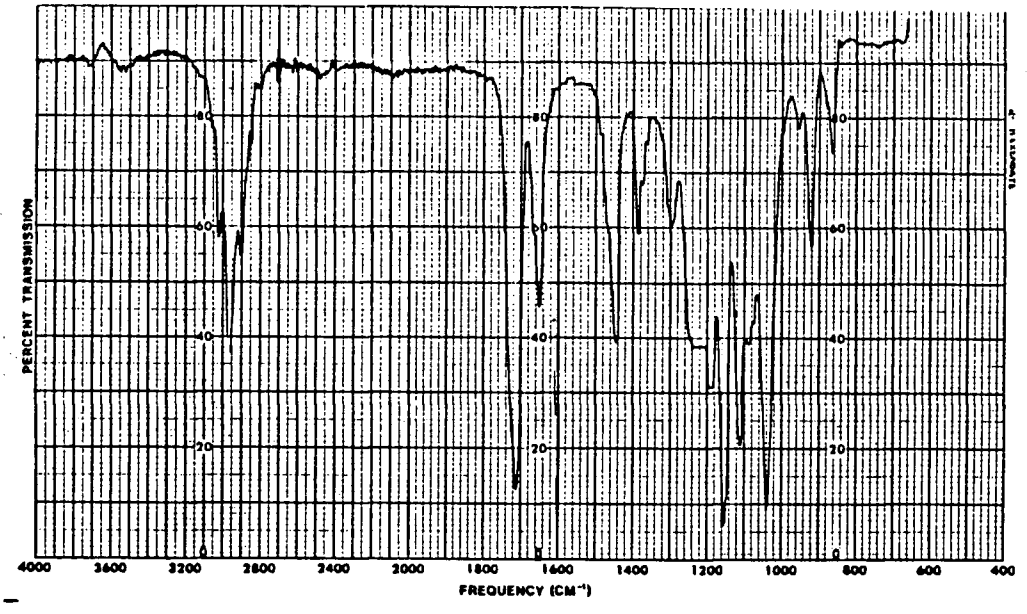

80 MHz
CHCl3
TMS

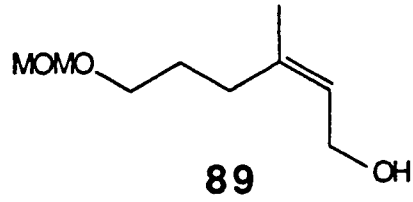

PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)


MOMO
CO_2CH_3

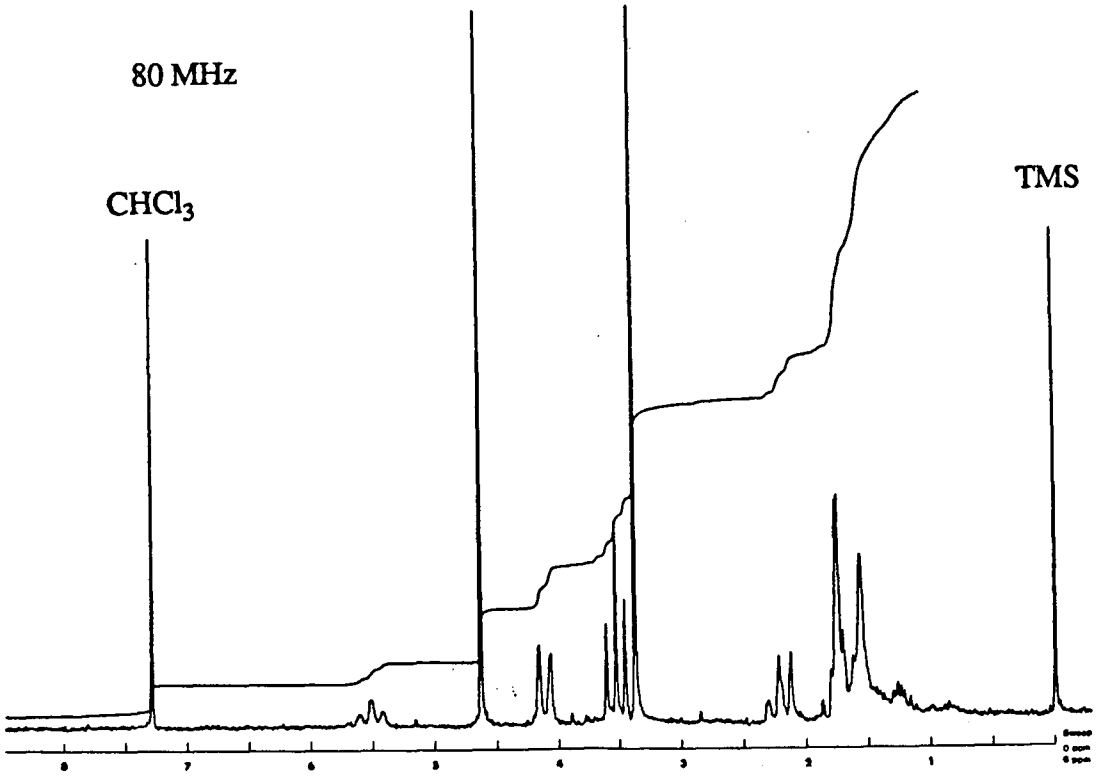
88

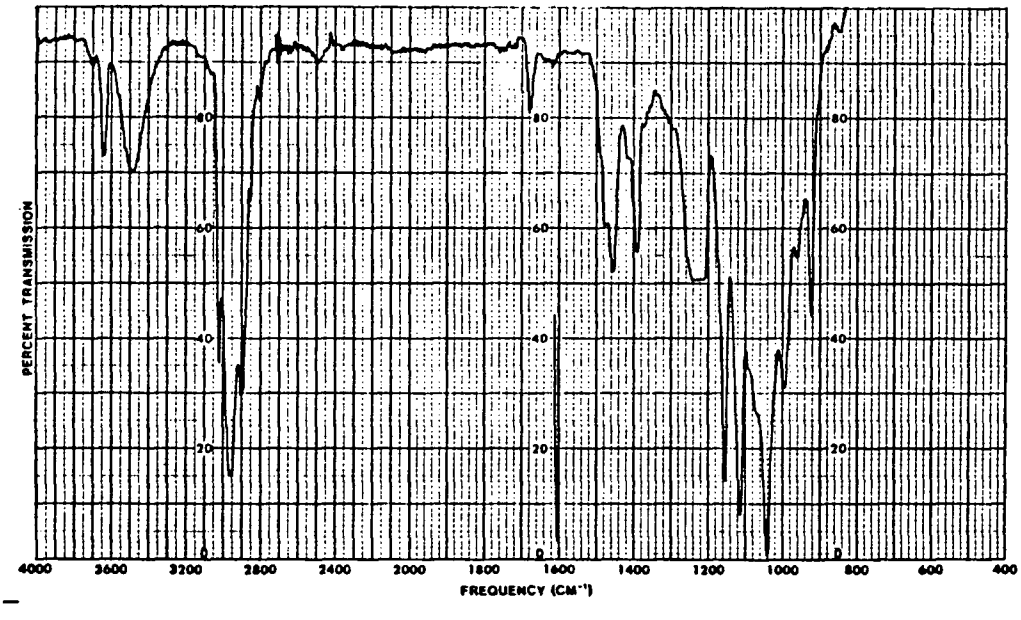

80 MHz
TMS
$CHCl_3$

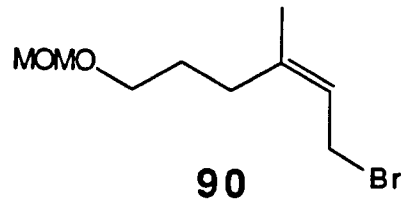

PERCENT TRANSMISSION
FREQUENCY (CM^{-1})
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400


MOMO
OH

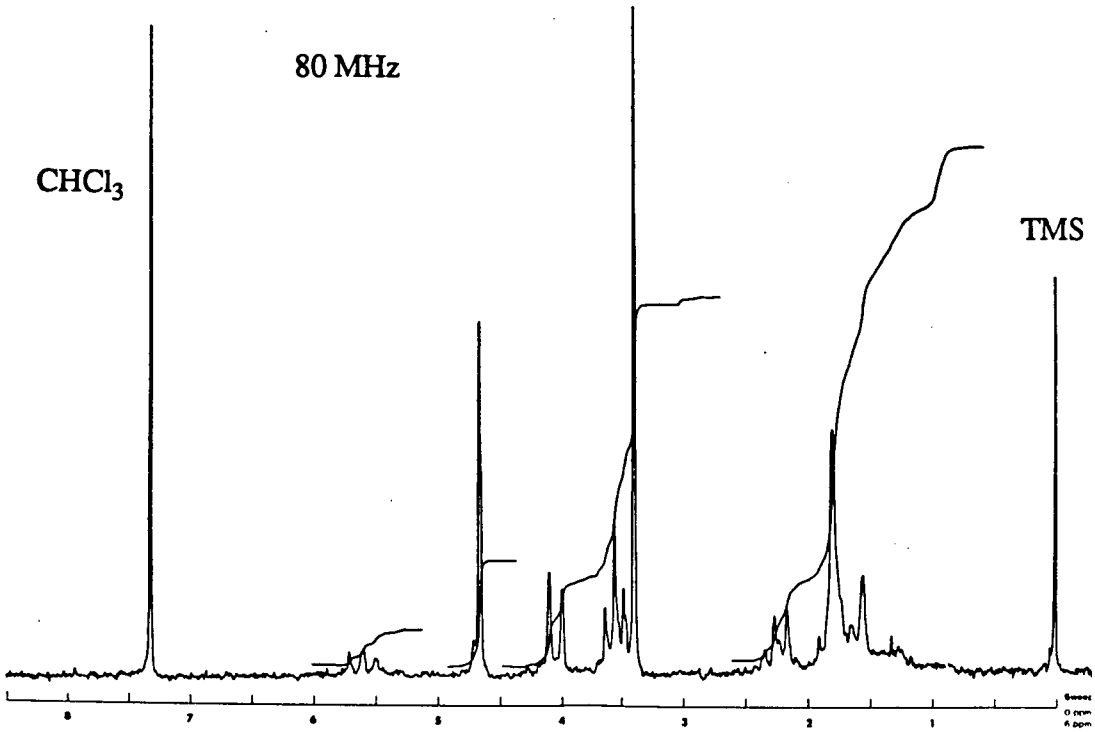
89

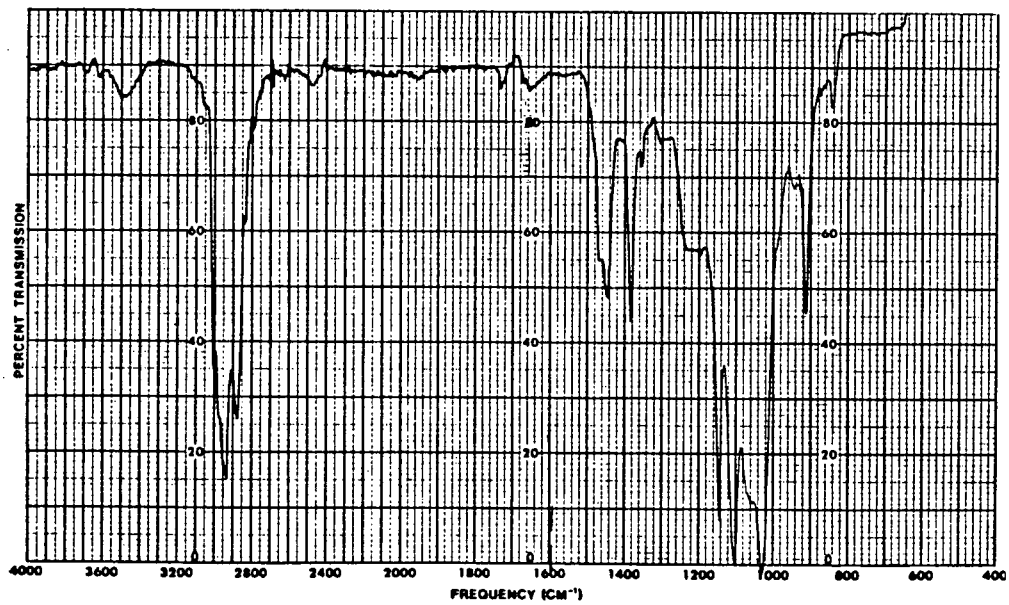

80 MHz
CHCl3
TMS

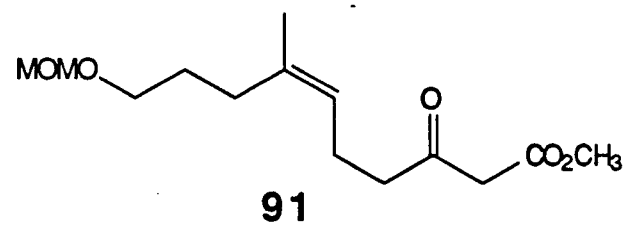

PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)


MOMO
Br

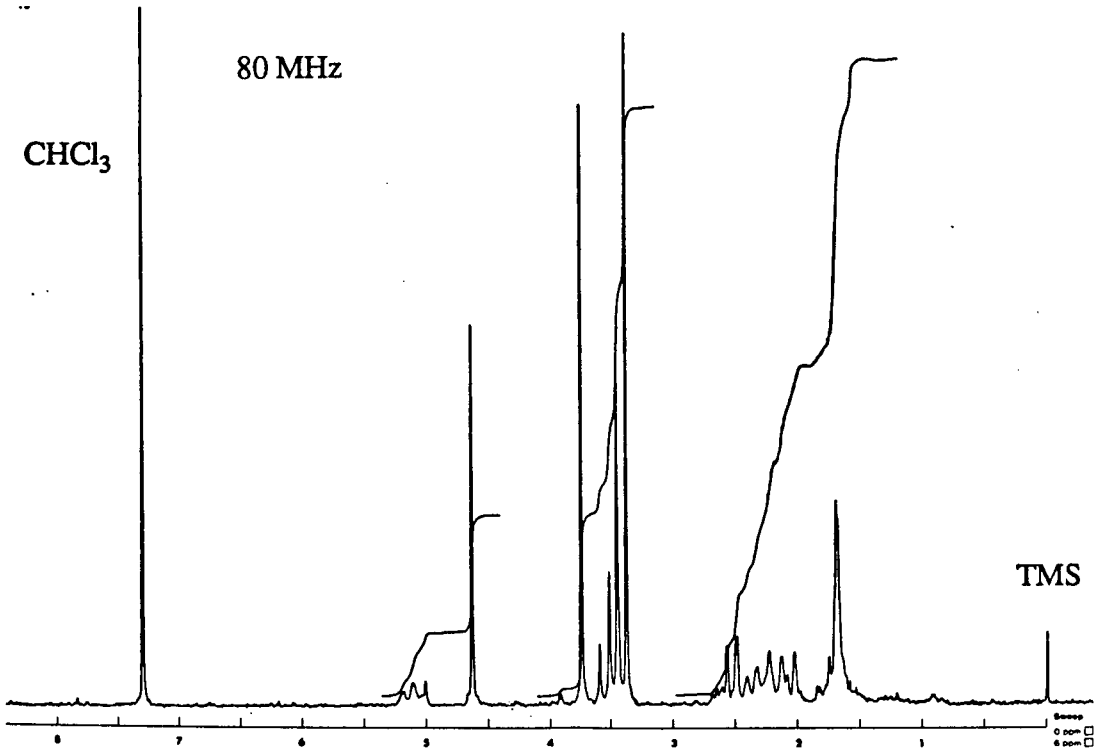
90

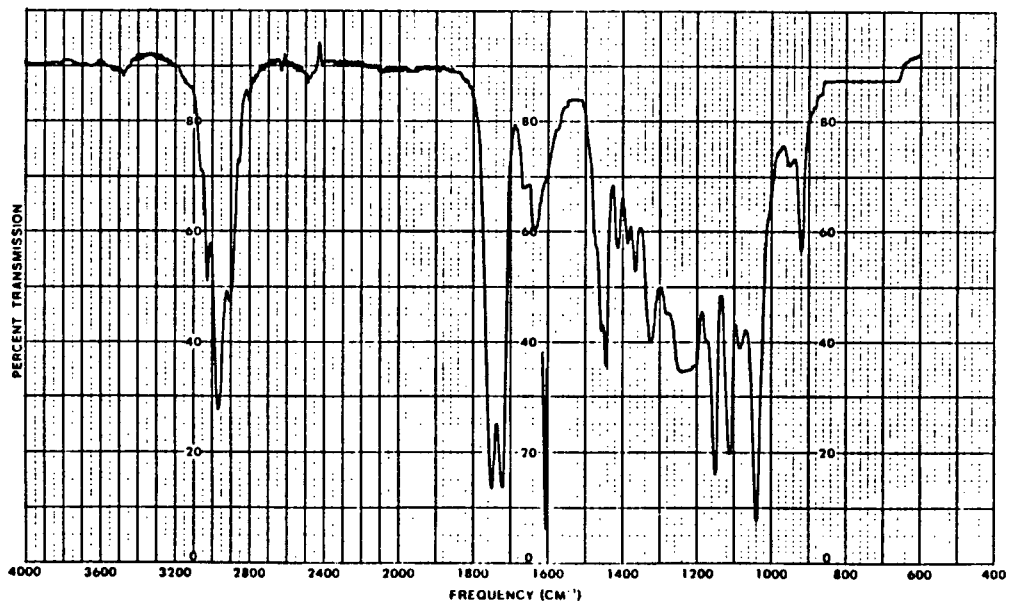

80 MHz
$CHCl_3$
TMS

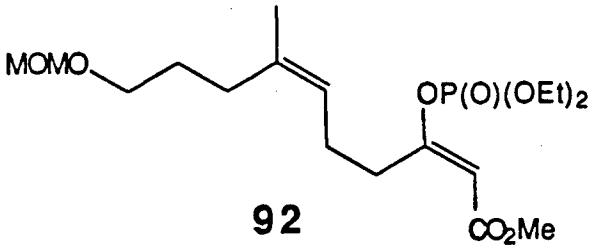

PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)


MOMO
O
CO_2CH_3

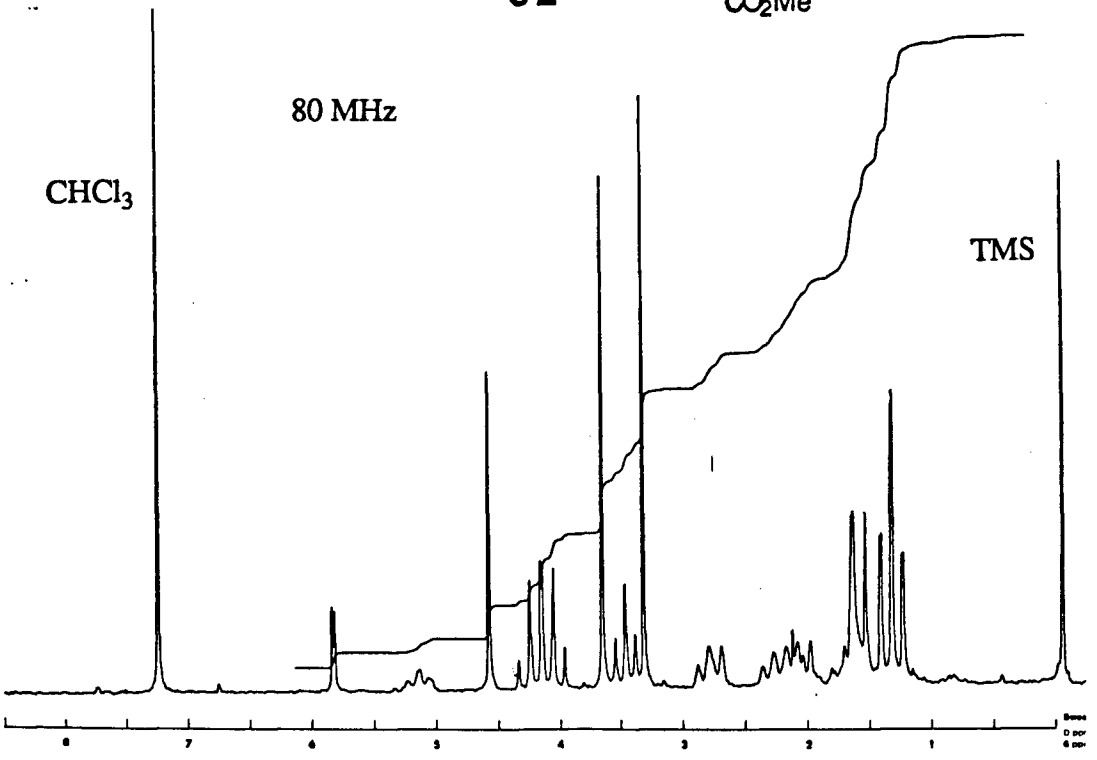
91

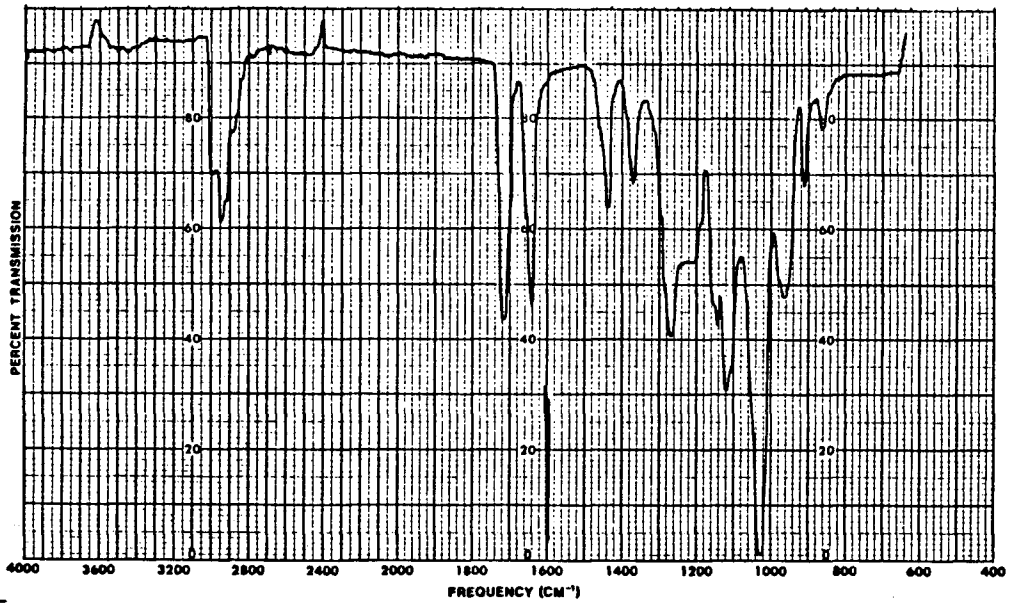

80 MHz
$CHCl_3$
TMS

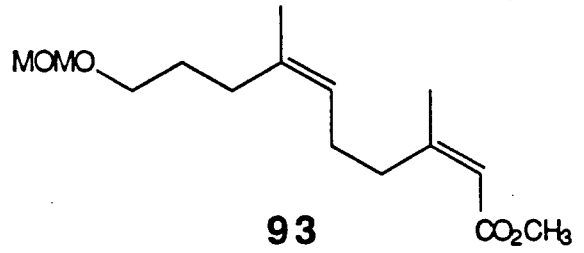

PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400


MOMO
OP(O)(OEt)2
CO2Me

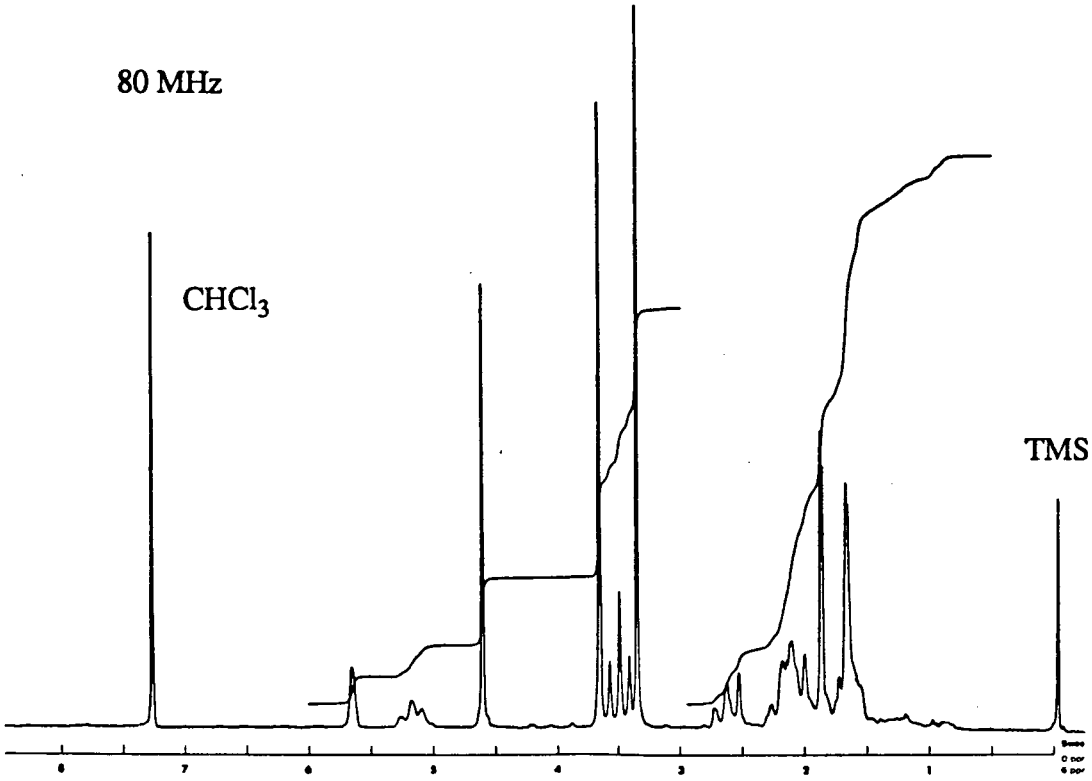
92

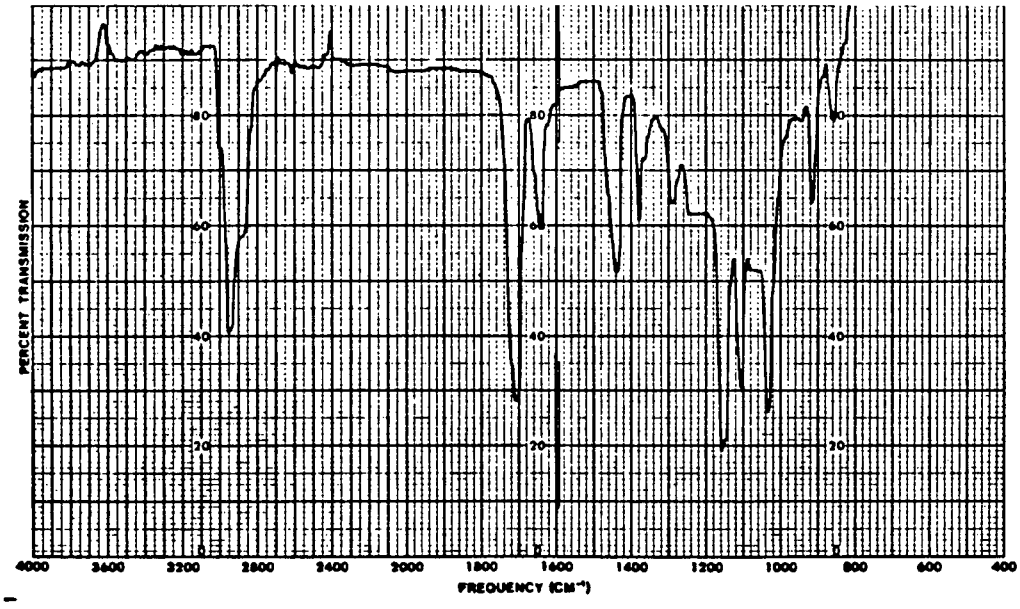

80 MHz
CHCl3
TMS

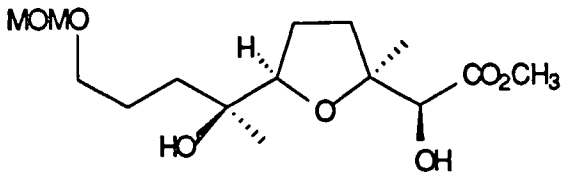

PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)


MOMO
CO2CH3

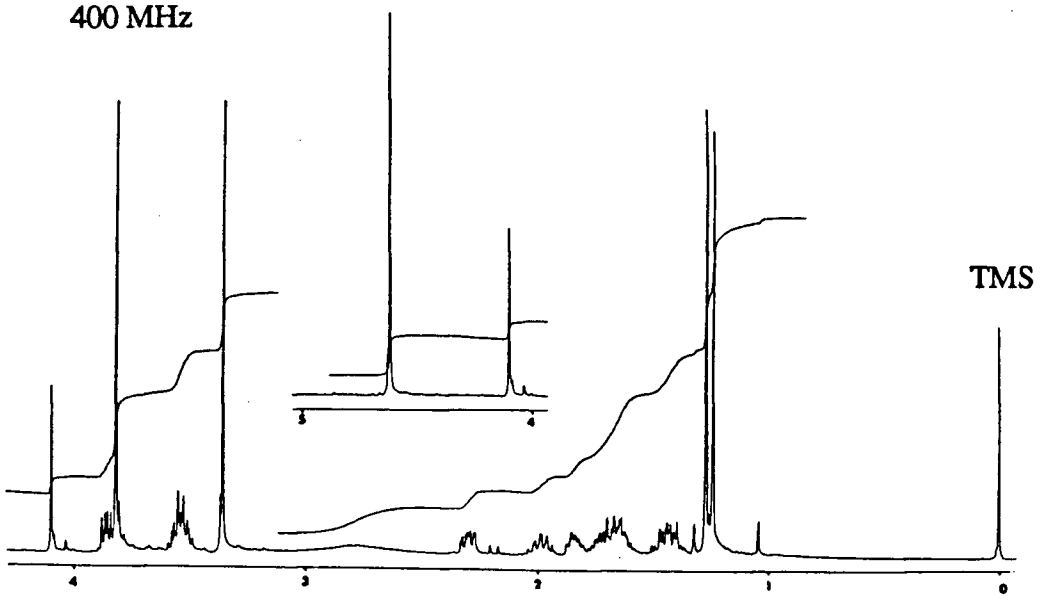
93

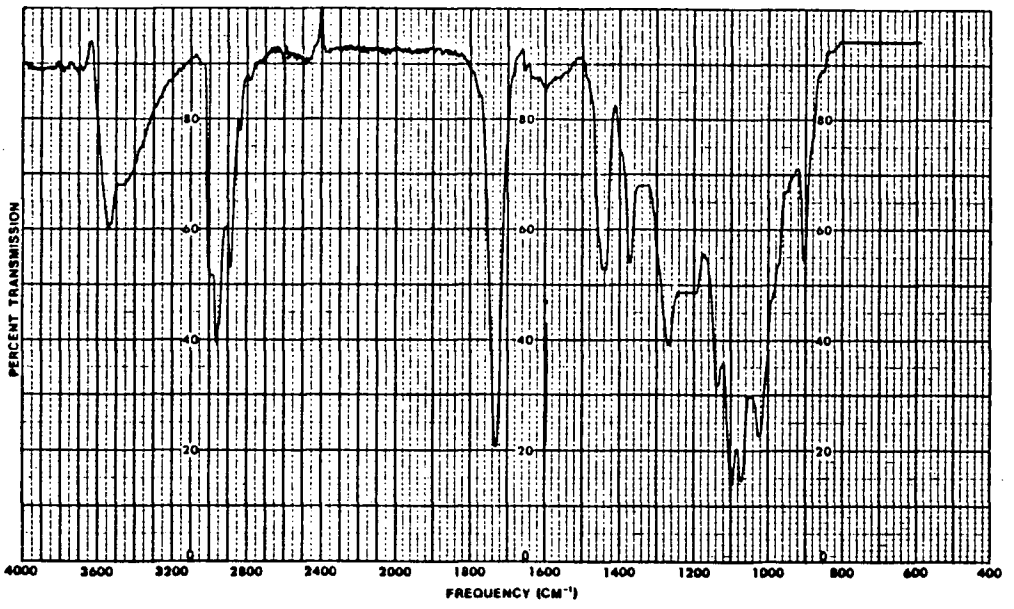

80 MHz
CHCl3
TMS

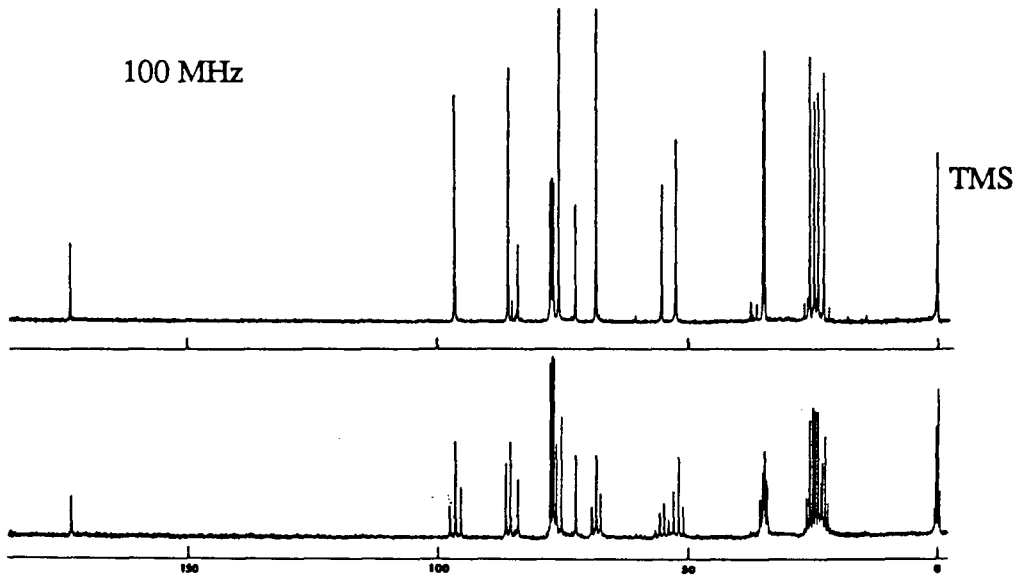

PERCENT TRANSMISSION
FREQUENCY (CM-1)

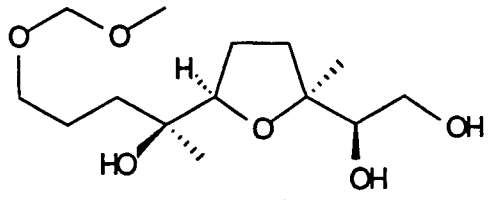

MOMO
H
O
CO_2CH_3
HO
OH

94

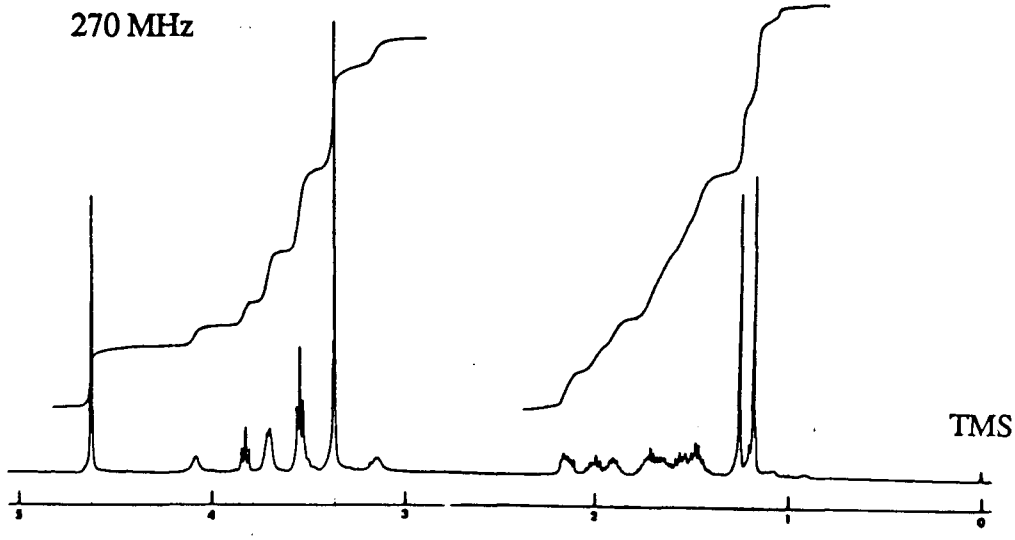

400 MHz
TMS
4
3
2
1
0

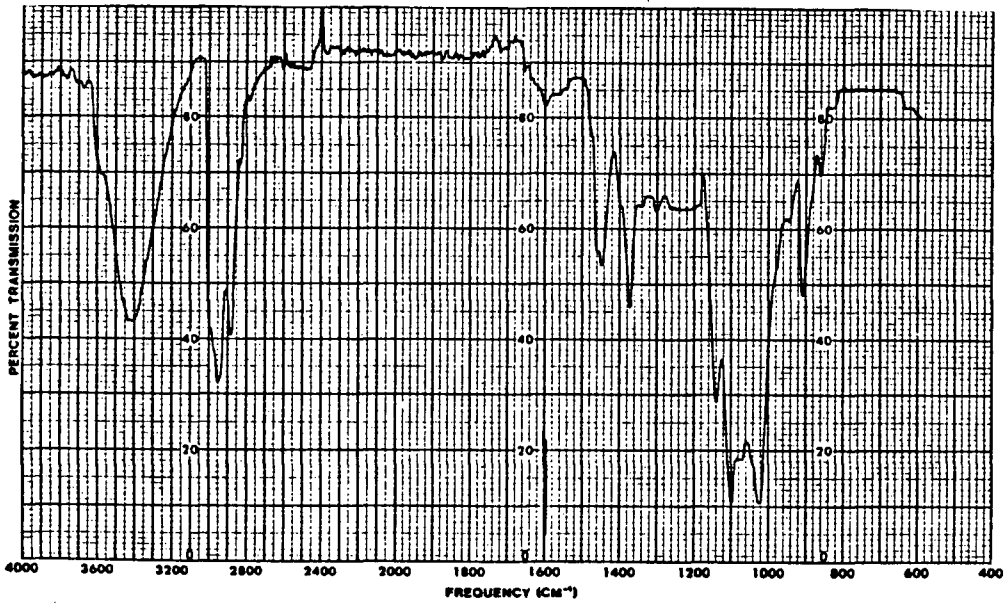

PERCENT TRANSMISSION
100
80
60
40
20
0
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
FREQUENCY (CM^{-1})

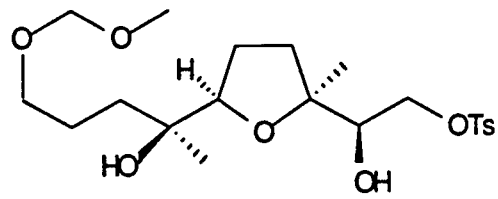

100 MHz
TMS
150
100
50
0


O
O
H
O
OH
HO
OH

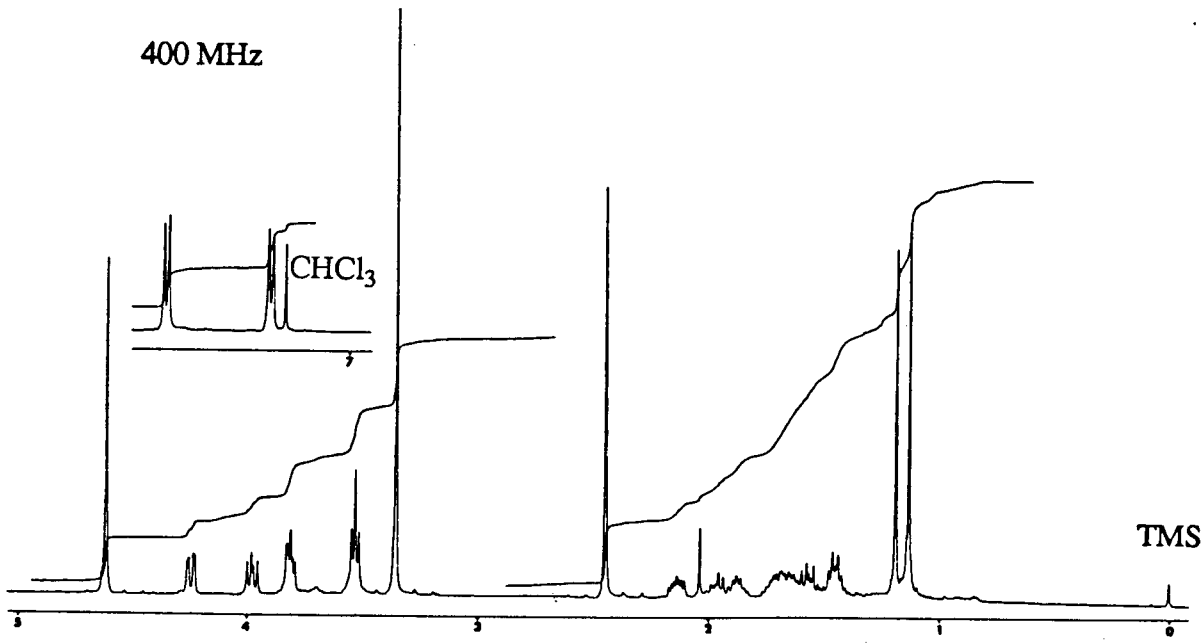
100

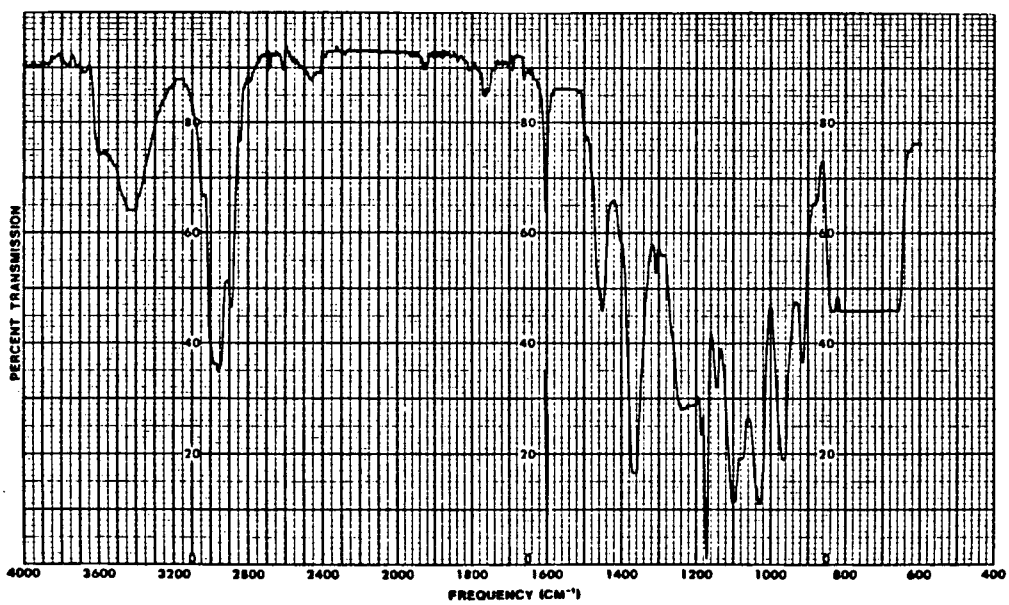

270 MHz
TMS
5
4
3
2
1
0

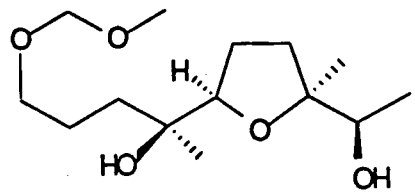

PERCENT TRANSMISSION
100
80
60
40
20
0
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
FREQUENCY (CM⁻¹)


O
O
H
O
OTs
HO
OH

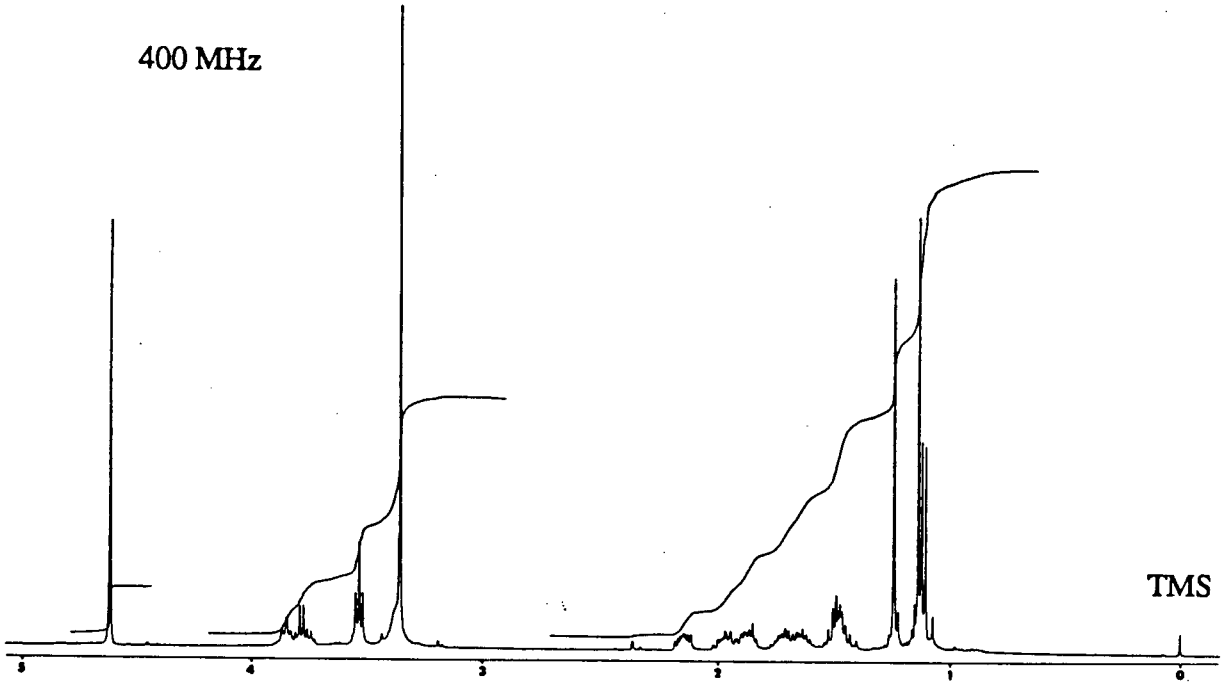
104

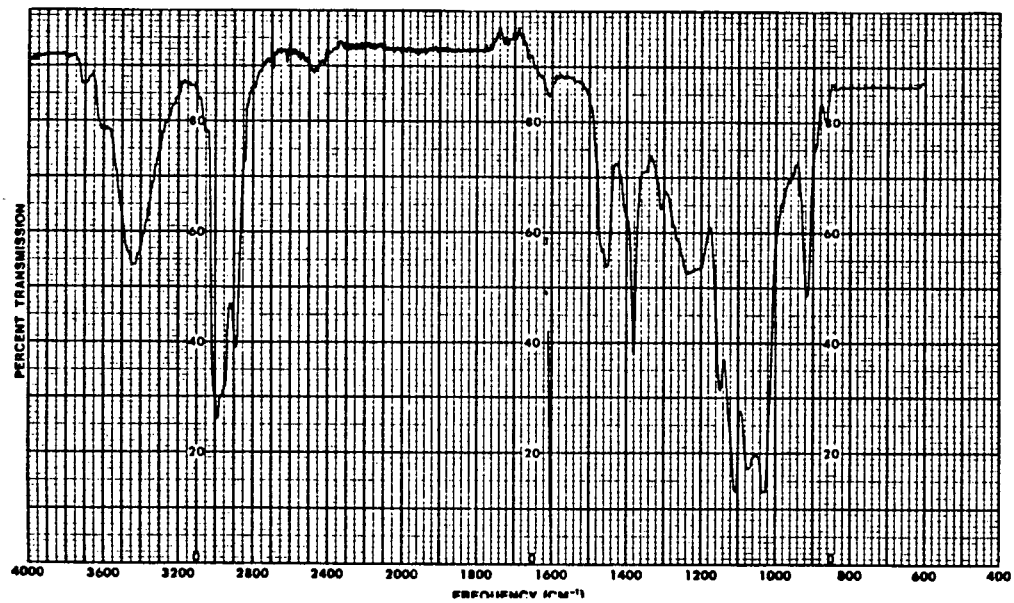

400 MHz
CHCl3
TMS
5
4
3
2
1
0

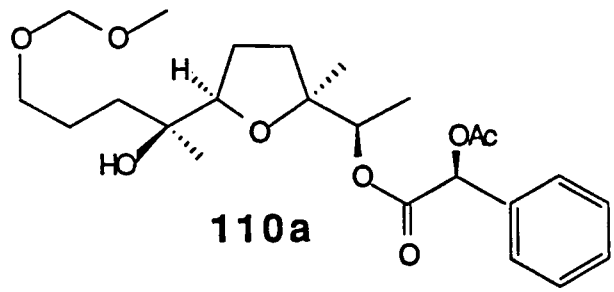

PERCENT TRANSMISSION
100
80
60
40
20
0
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
FREQUENCY (CM⁻¹)


O
O
H
O
HO
OH

103

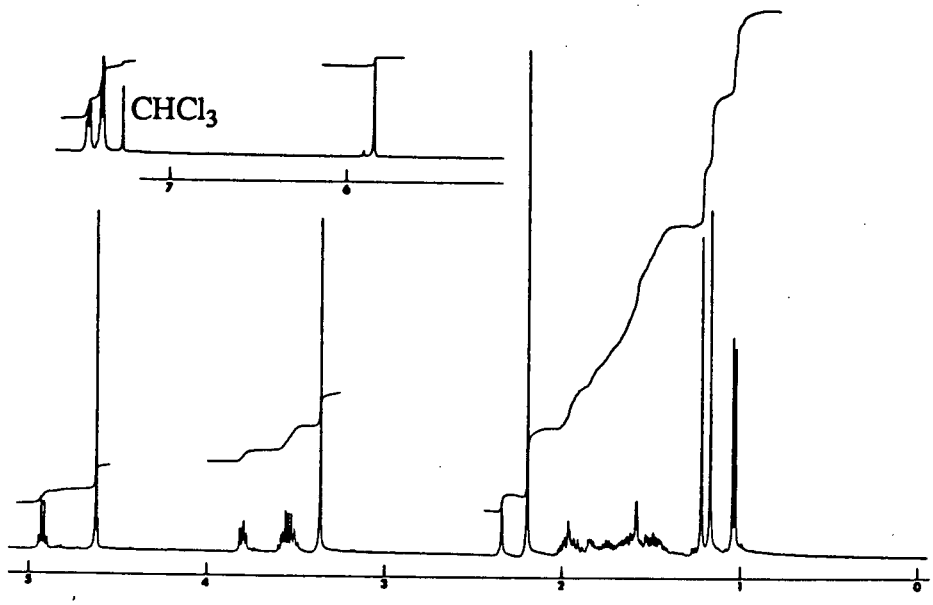

400 MHz
TMS
5
4
3
2
1
0

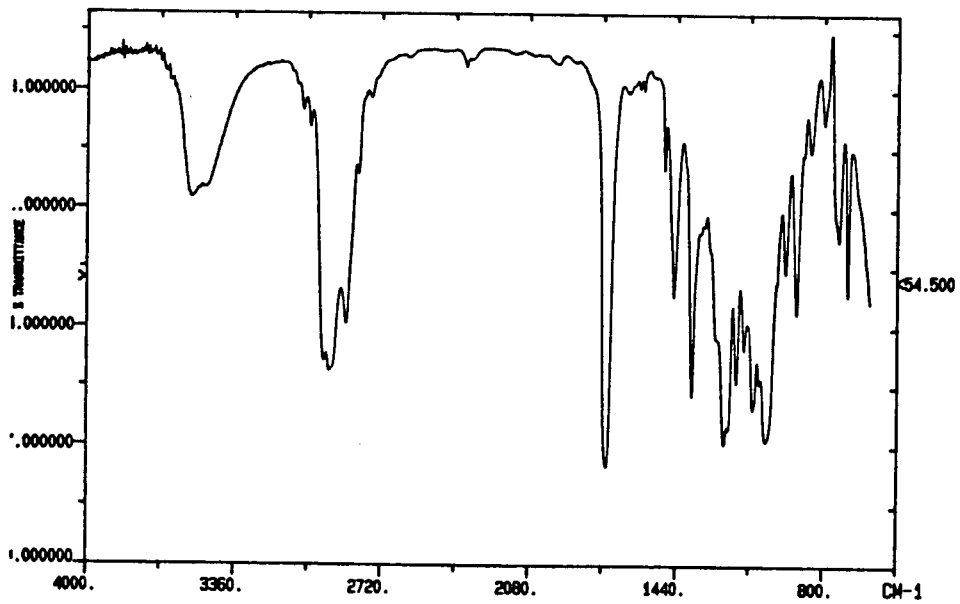

PERCENT TRANSMISSION
100
80
60
40
20
0
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400

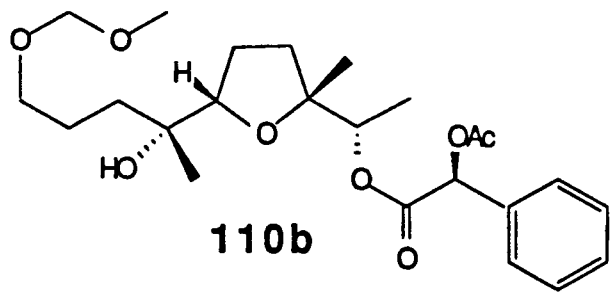

O
O
H
O
HO
OAc
O
O

110a

400 MHz

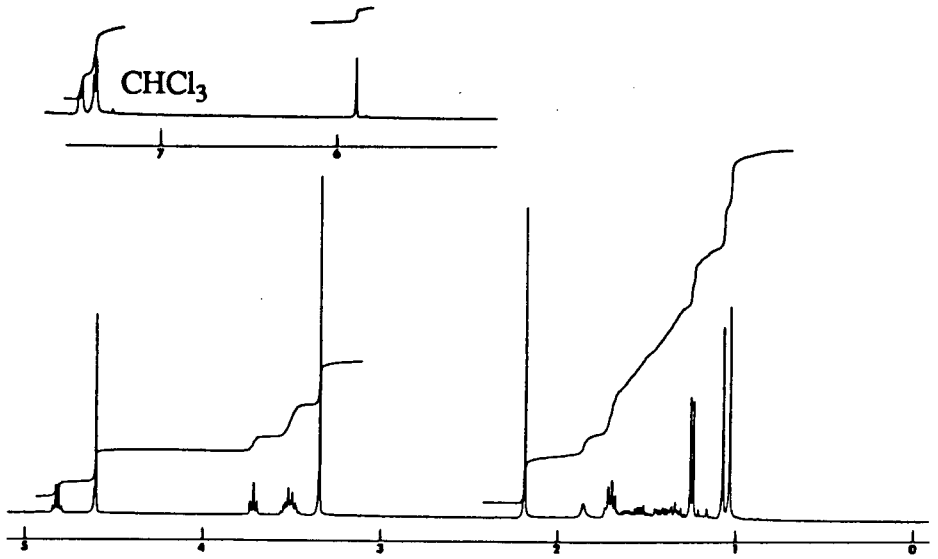

CHCl3
7
6
5
4
3
2
1
0

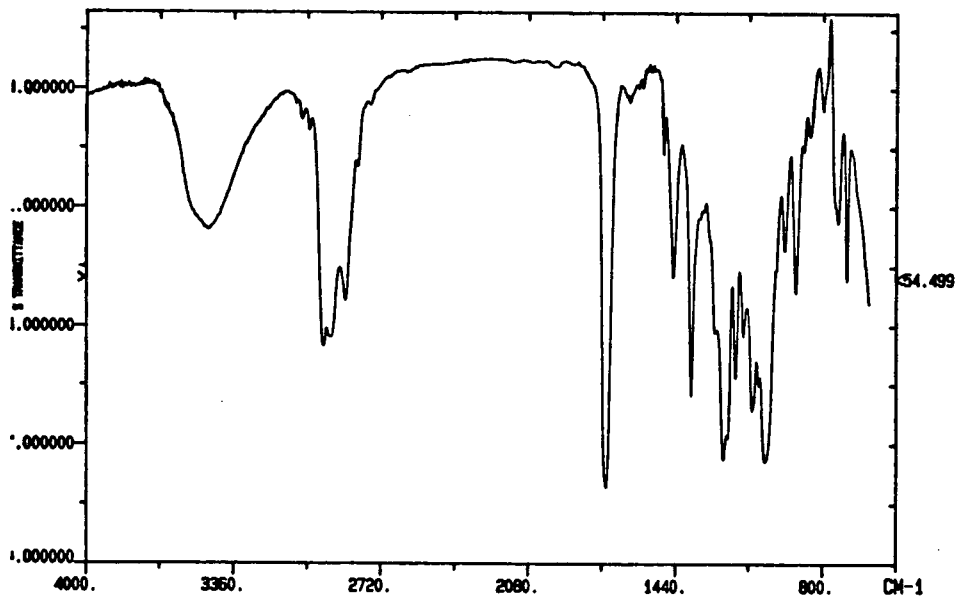

1.000000
.000000
1.000000
.000000
1.000000
4000.
3360.
2720.
2080.
1440.
800.
CM-1
54.500

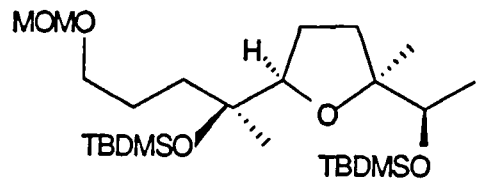

O
O
H
O
HO
OAc
O
O

110b

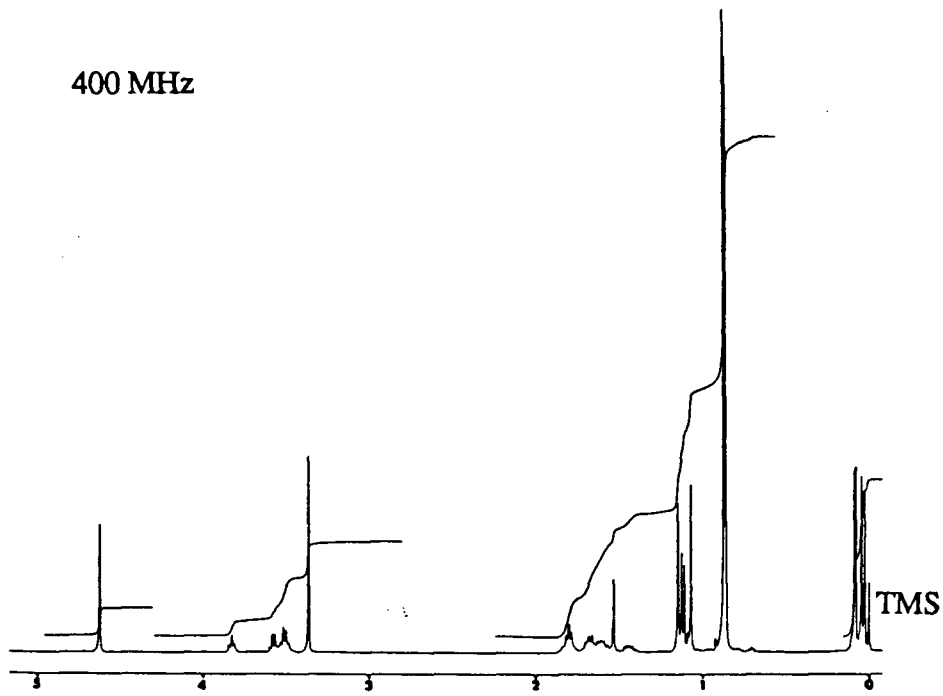
400 MHz

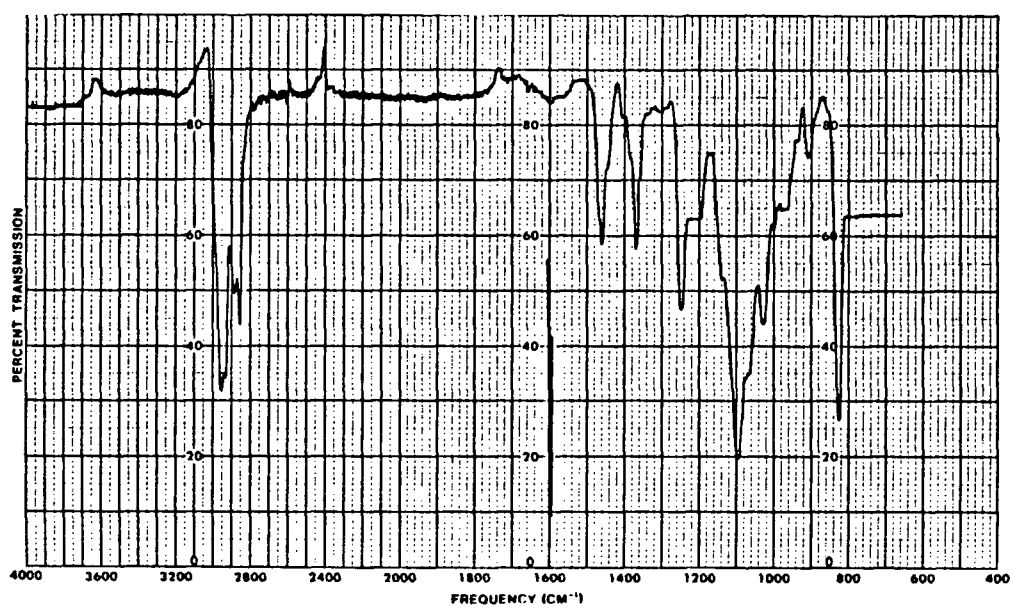

CHCl3
7
6
5
4
3
2
1
0

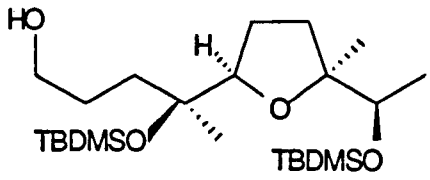

1.000000
.000000
1.000000
.000000
1.000000
4000.
3360.
2720.
2080.
1440.
800.
CM-1
54.499


MOMO
H
O
TBDMSO
TBDMSO

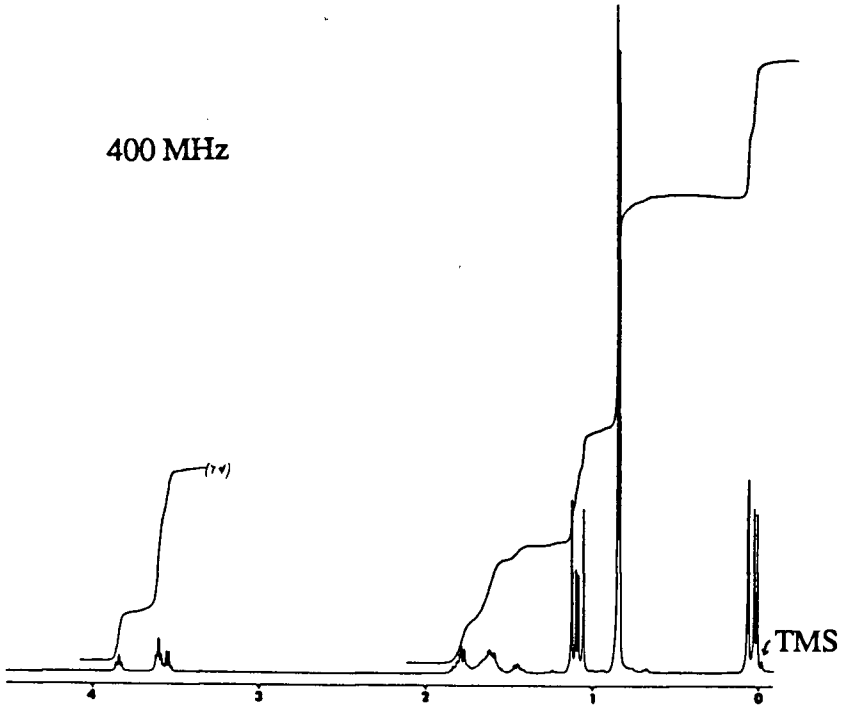
118

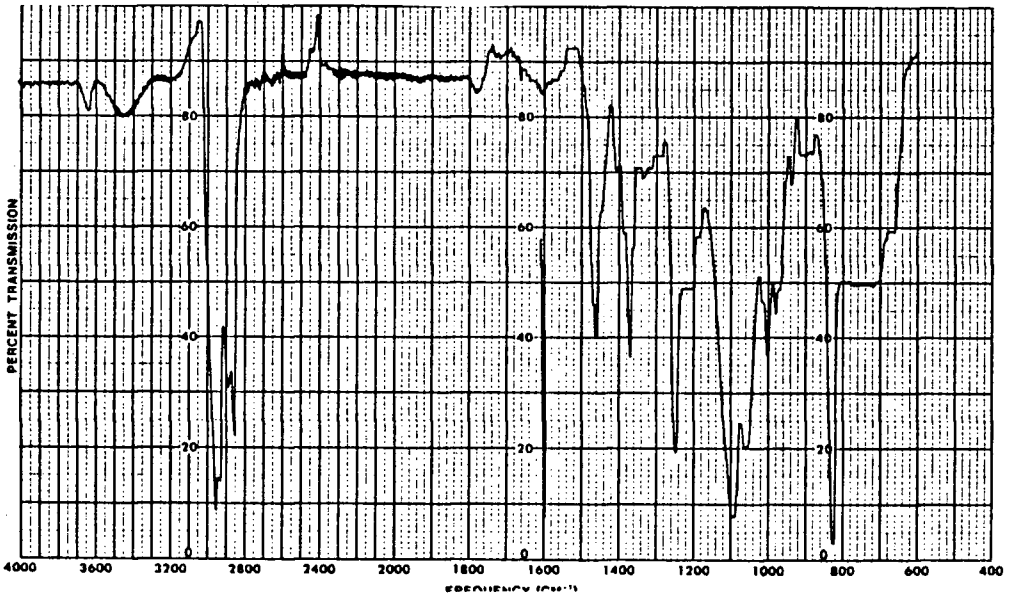

400 MHz
TMS
5
4
3
2
1
0

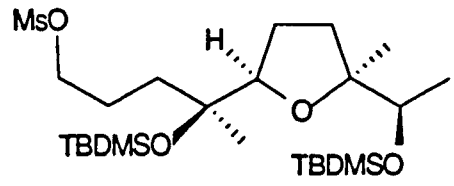

PERCENT TRANSMISSION
100
80
60
40
20
0
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
FREQUENCY (CM⁻¹)


HO
H
O
TBDMSO
TBDMSO

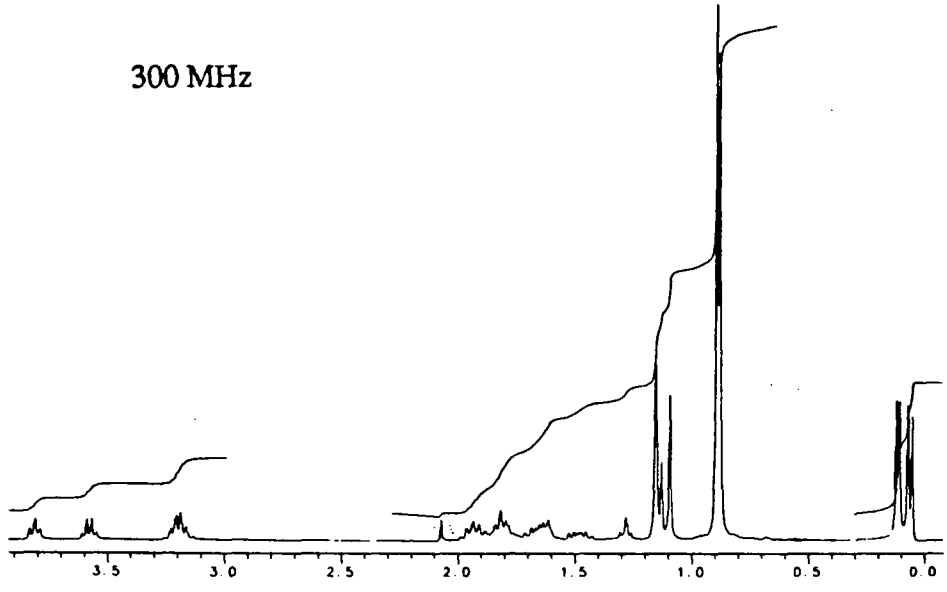
119

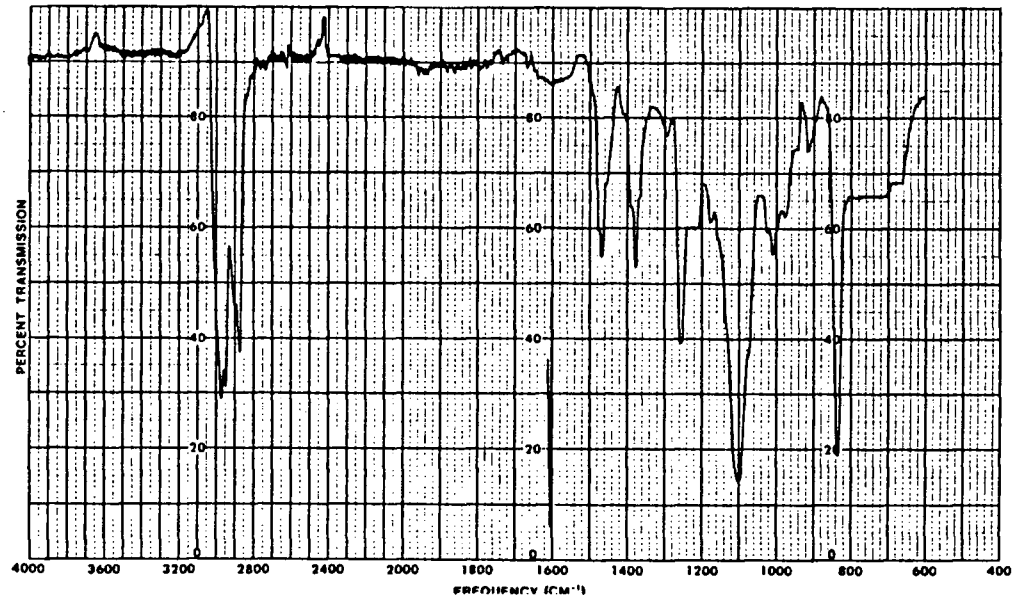

400 MHz
TMS
4
3
2
1
0

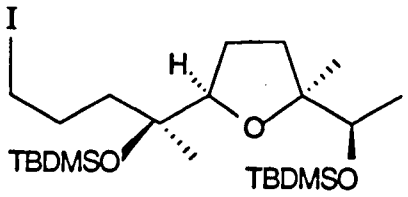

PERCENT TRANSMISSION
100
80
60
40
20
0
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400


MsO
H
O
TBDMSO
TBDMSO

120

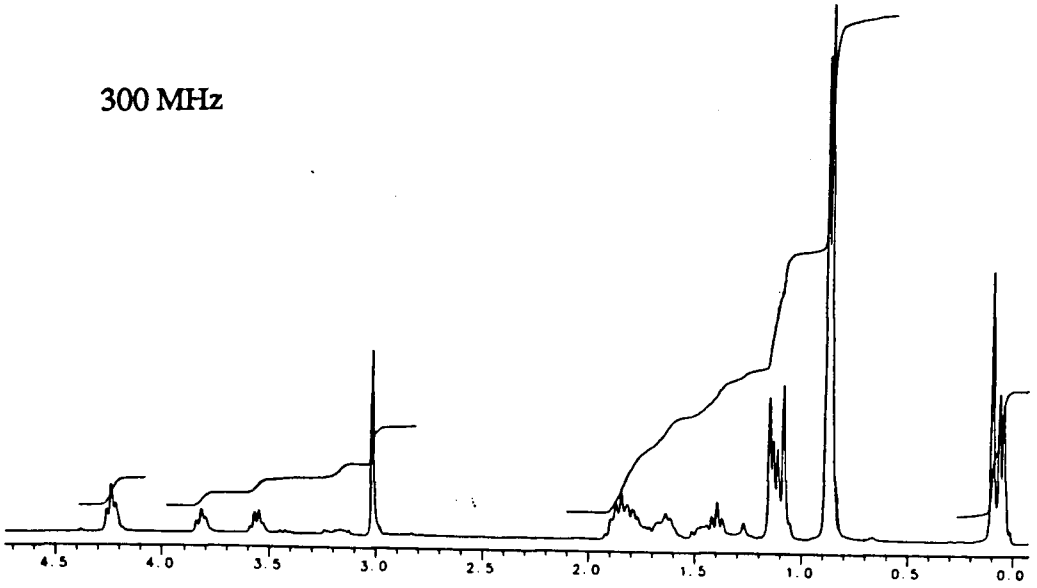

300 MHz
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

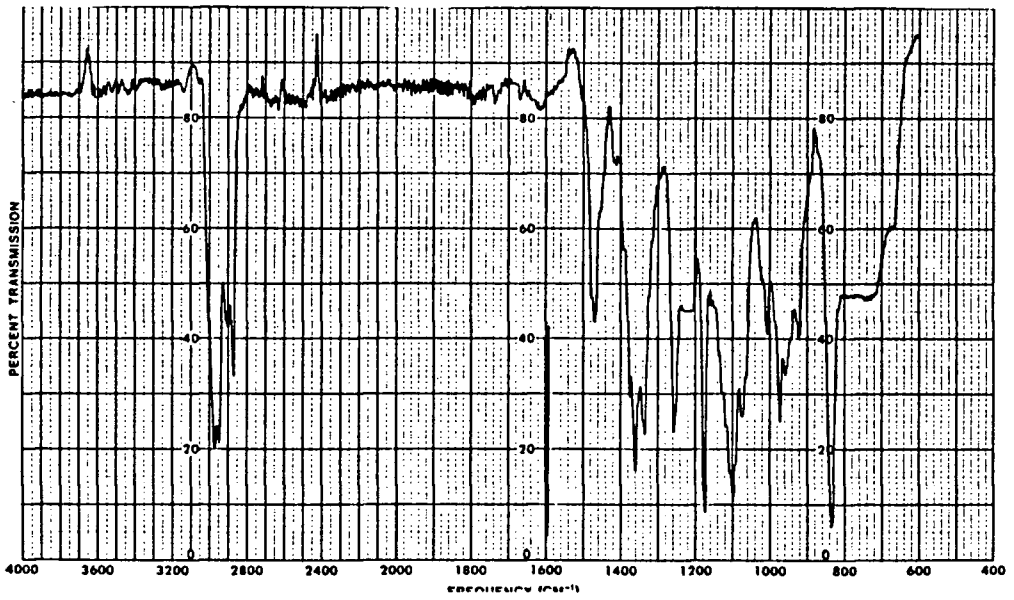

PERCENT TRANSMISSION
100
80
60
40
20
0
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400

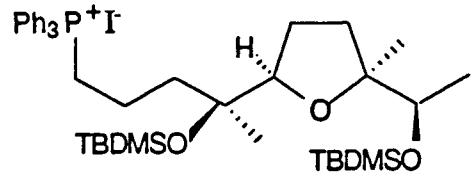

I
H
O
TBDMSO
TBDMSO

121

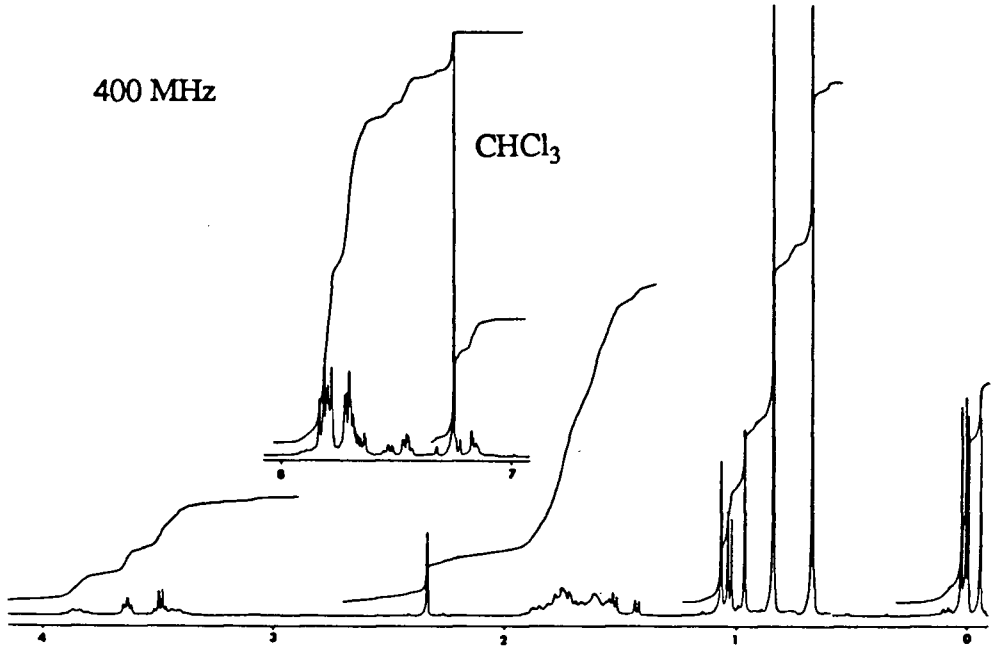
300 MHz

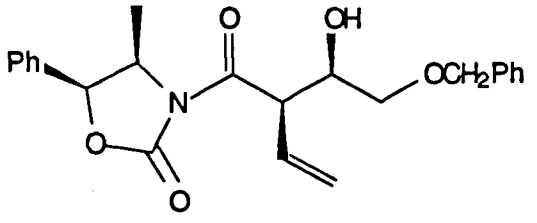

4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


PERCENT TRANSMISSION
100
80
60
40
20
0
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400

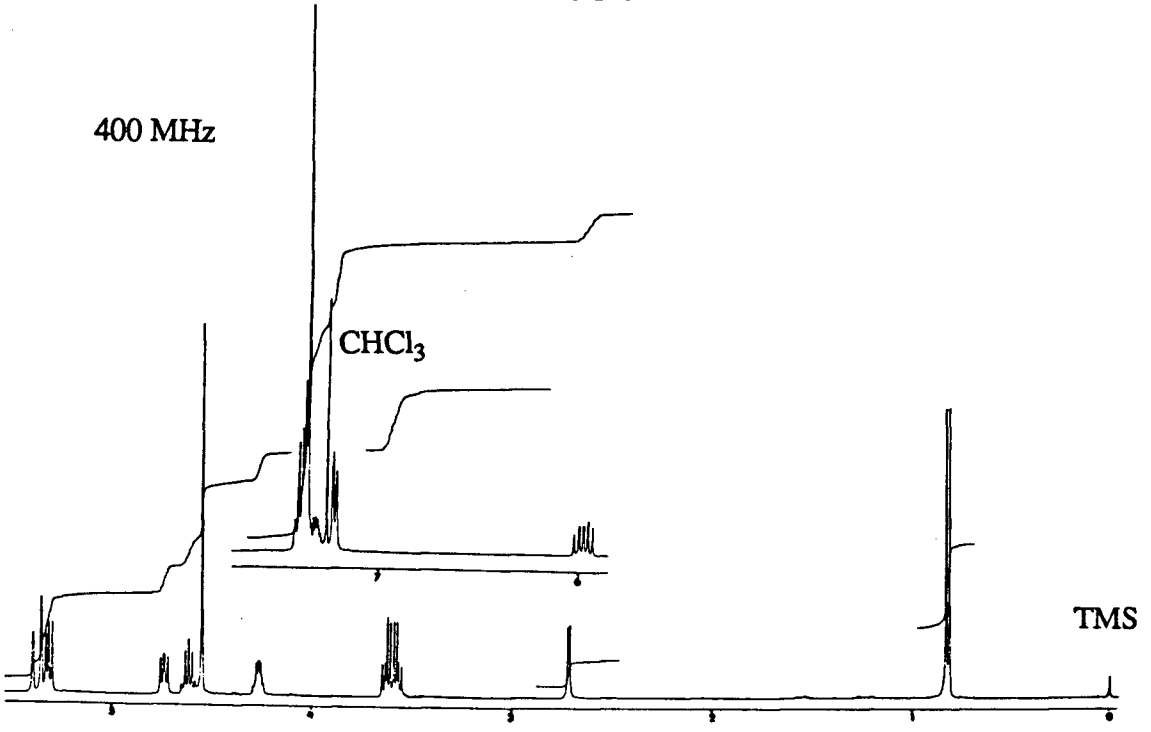


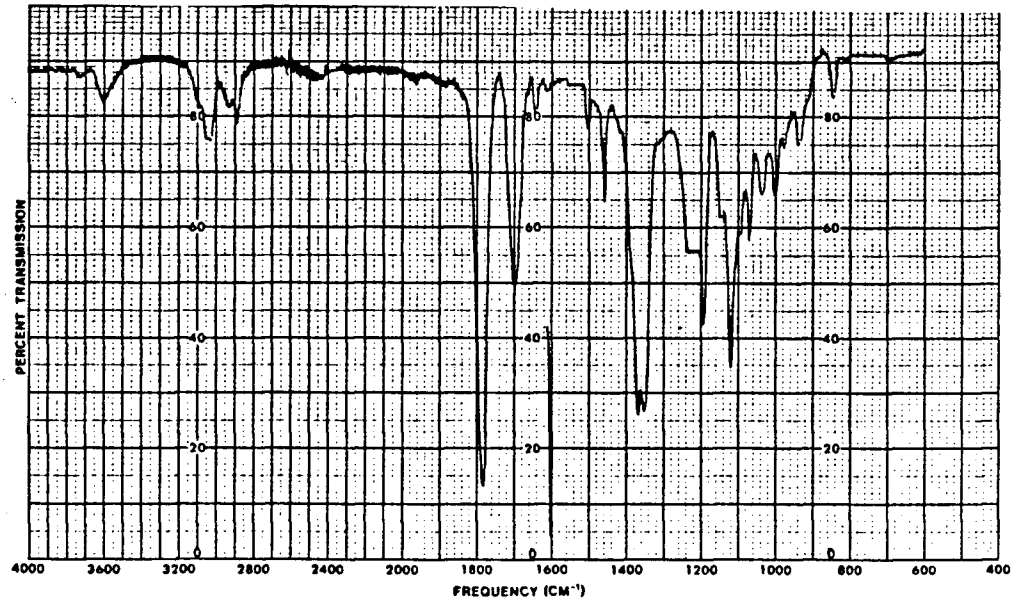
122

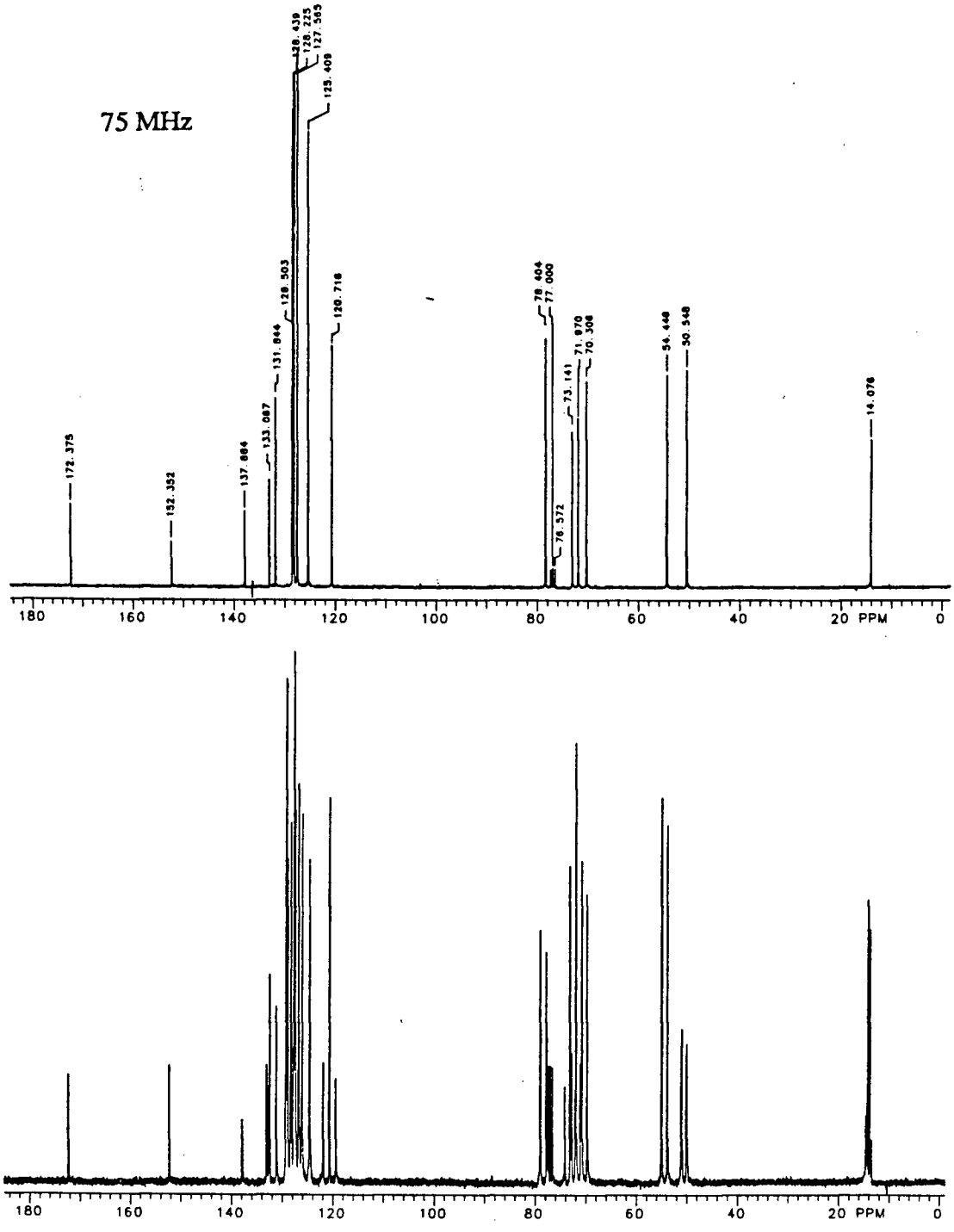


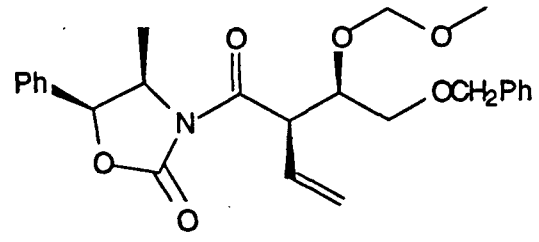

Ph
O
OH
N
O
OCH2Ph
O

130

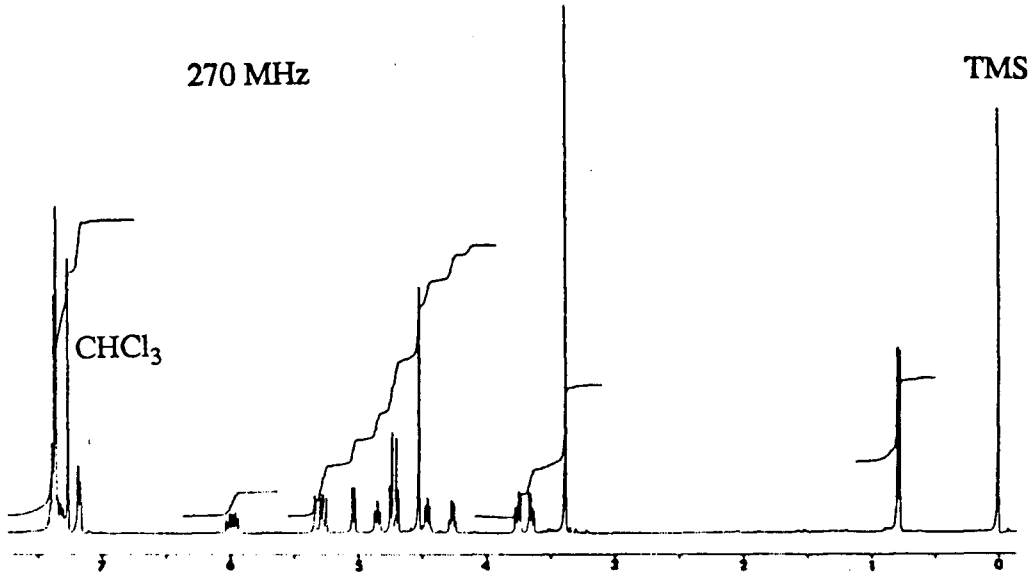

400 MHz
CHCl3
TMS

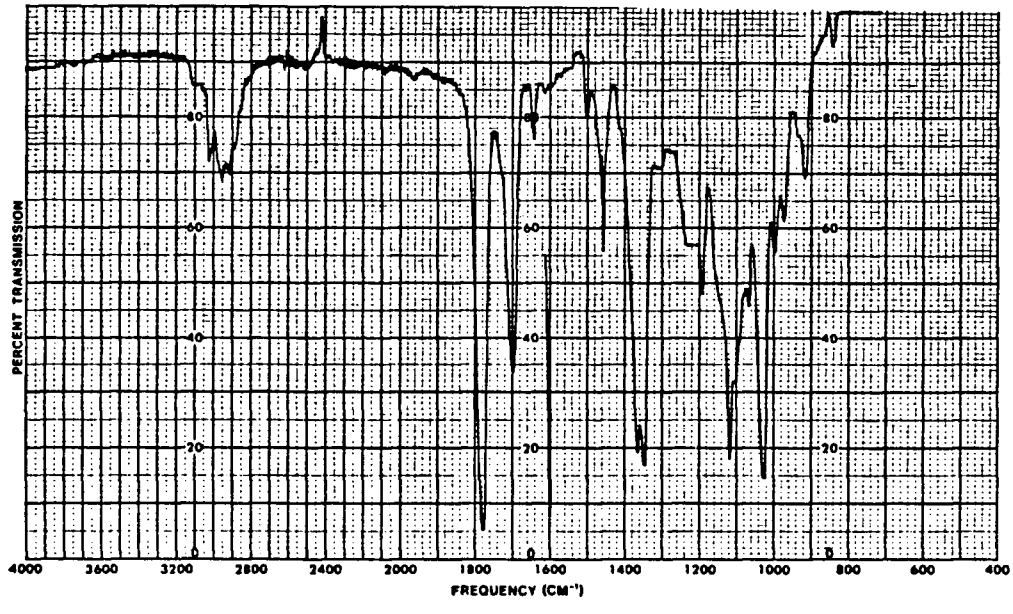

PERCENT TRANSMISSION
100
80
60
40
20
0
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
FREQUENCY (CM-1)

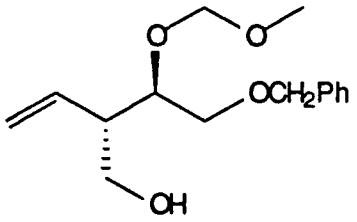

75 MHz
172.375
152.352
137.884
133.087
131.844
128.503
130.439
128.225
127.505
123.409
120.718
78.404
77.000
76.372
73.141
71.870
70.308
54.448
50.548
14.076
180
160
140
120
100
80
60
40
20 PPM
0


Ph
N
O
O
O
O
O
OCH2Ph

131

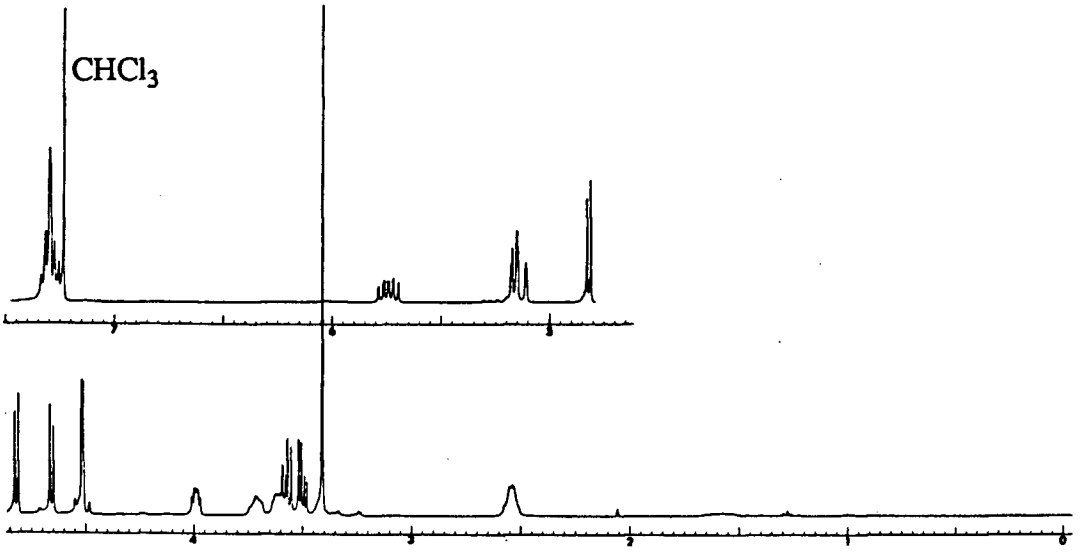

270 MHz
TMS
CHCl3

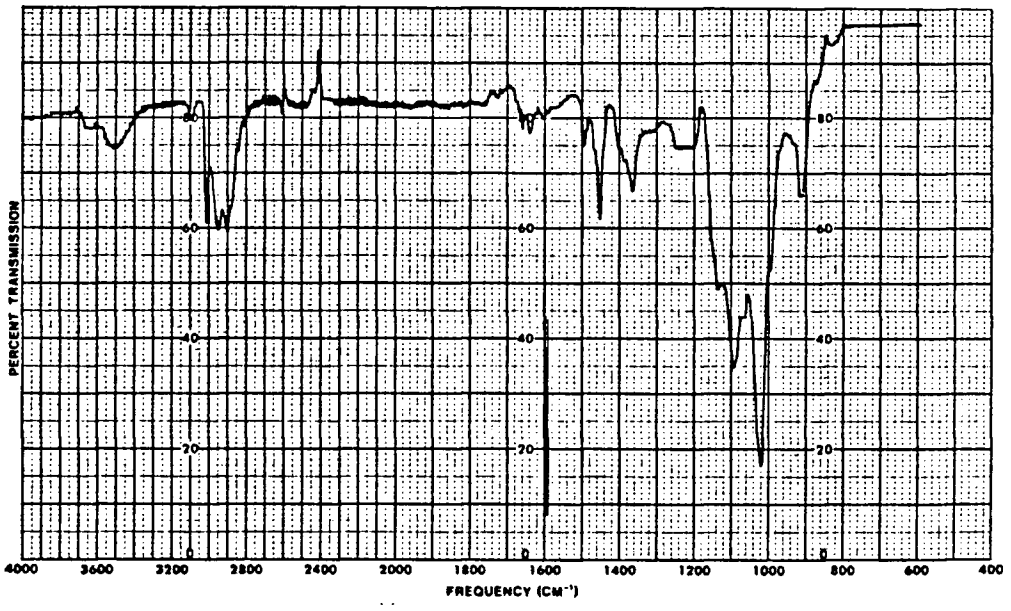

PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400

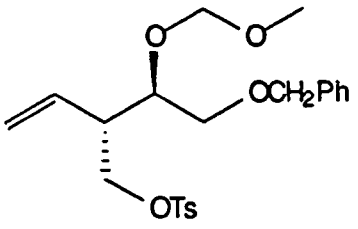

O
O
OCH2Ph
OH

132

270 MHz

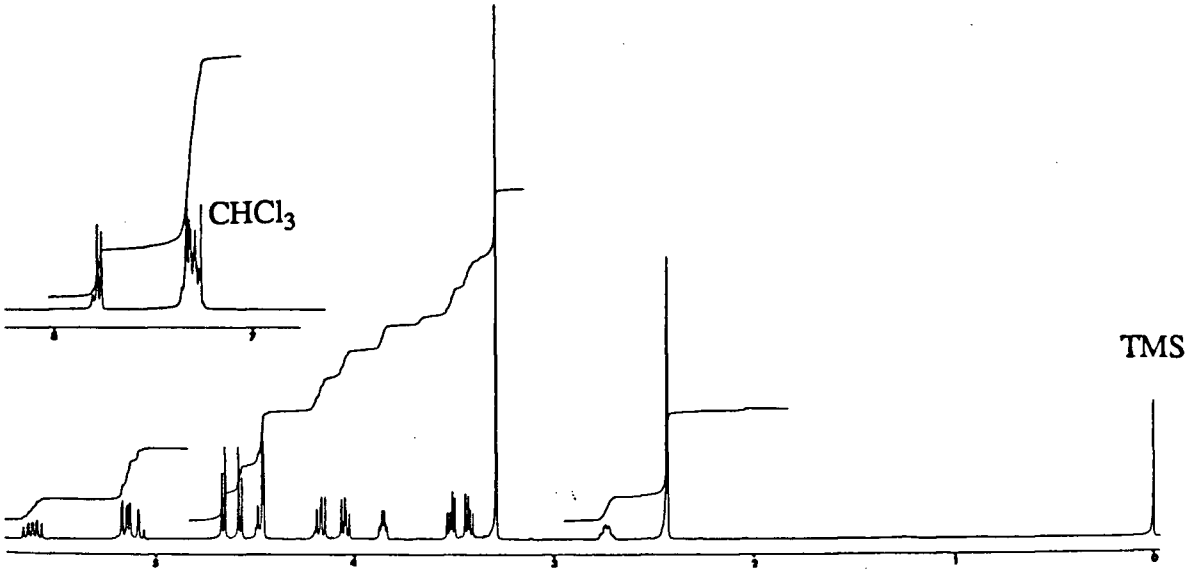

CHCl3
7
6
5
4
3
2
1
0

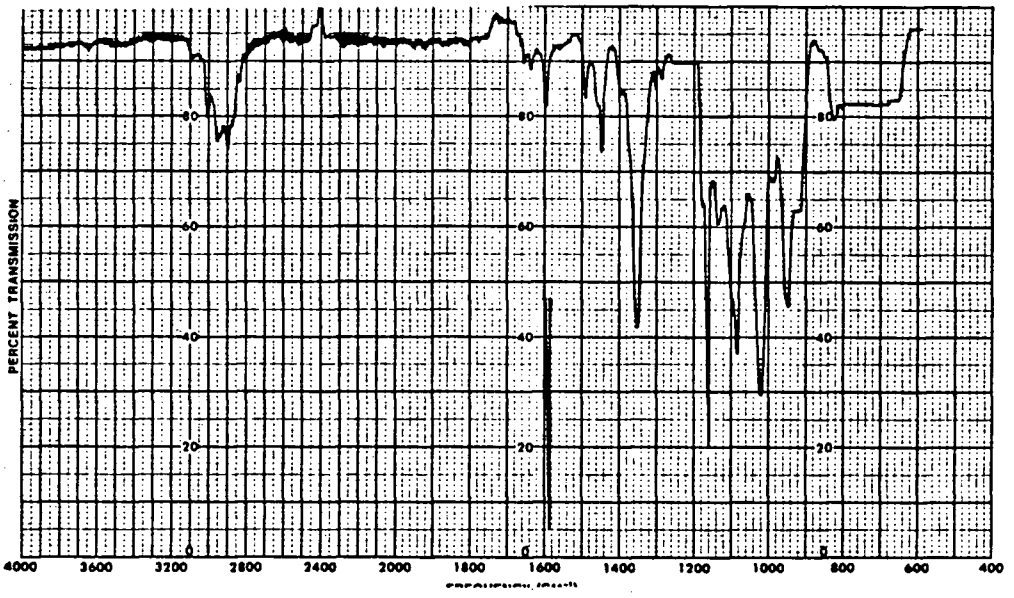

PERCENT TRANSMISSION
100
80
60
40
20
0
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
FREQUENCY (CM⁻¹)

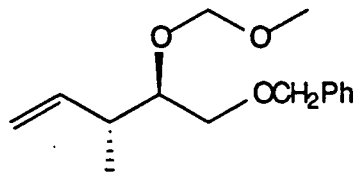

OCH2Ph
OTs

137

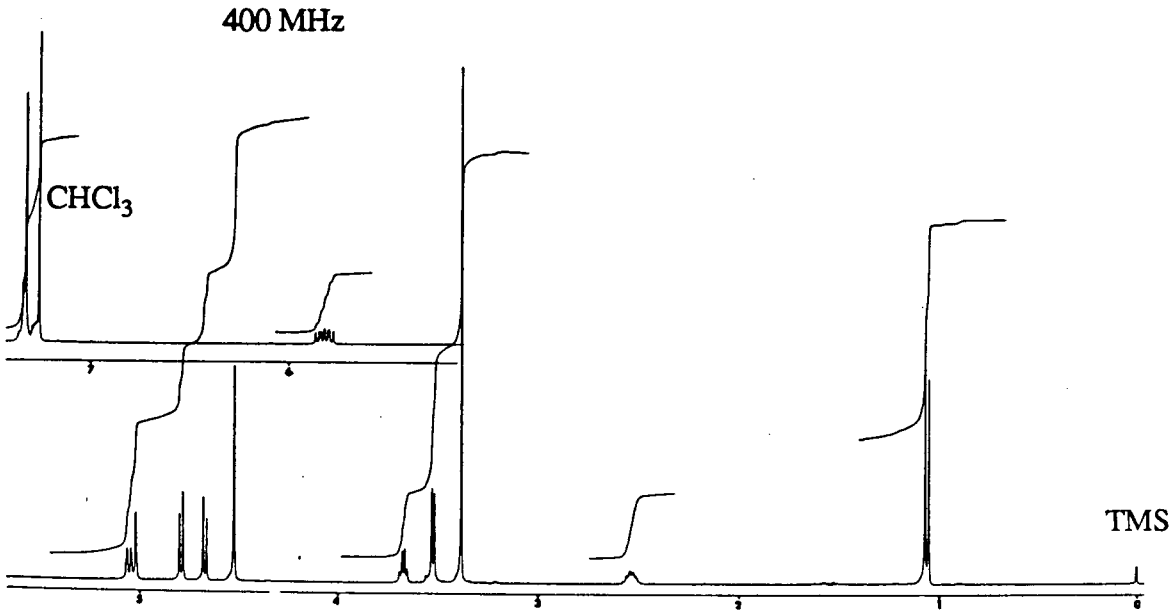
400 MHz

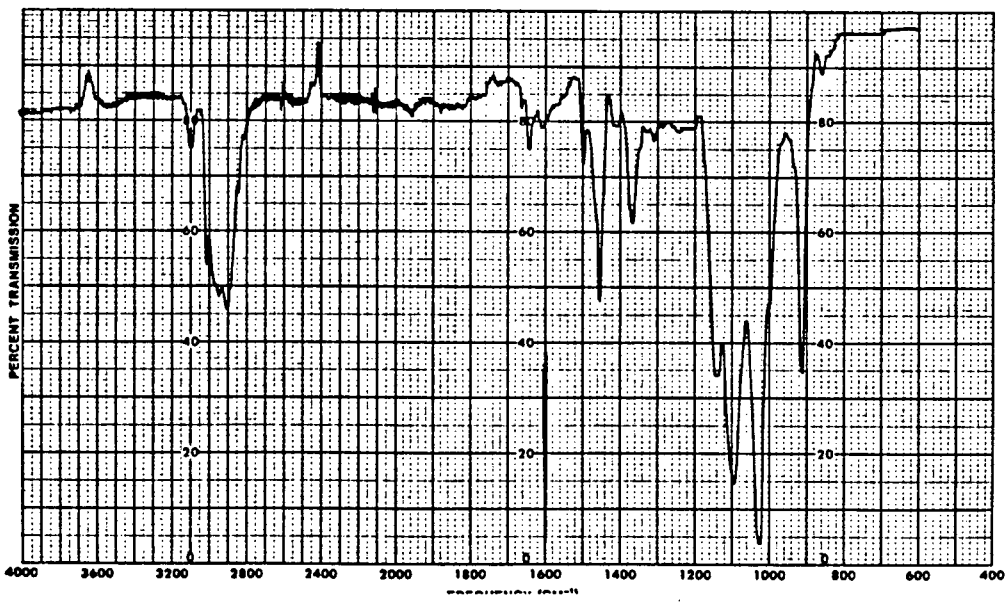

CHCl3
TMS

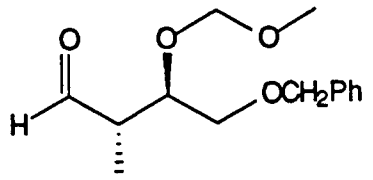

PERCENT TRANSMISSION
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400


OCH2Ph

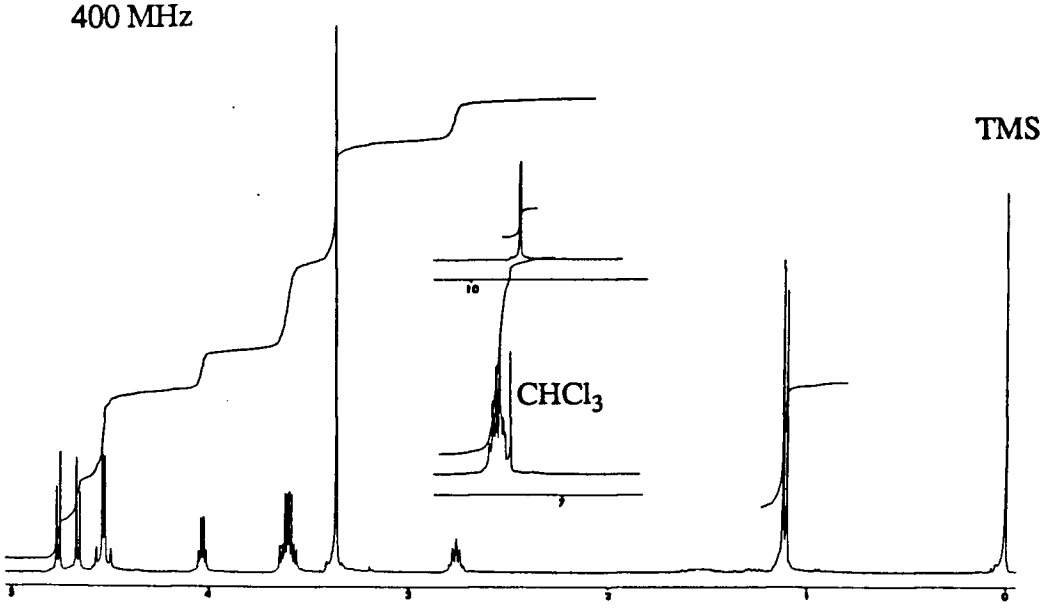
138

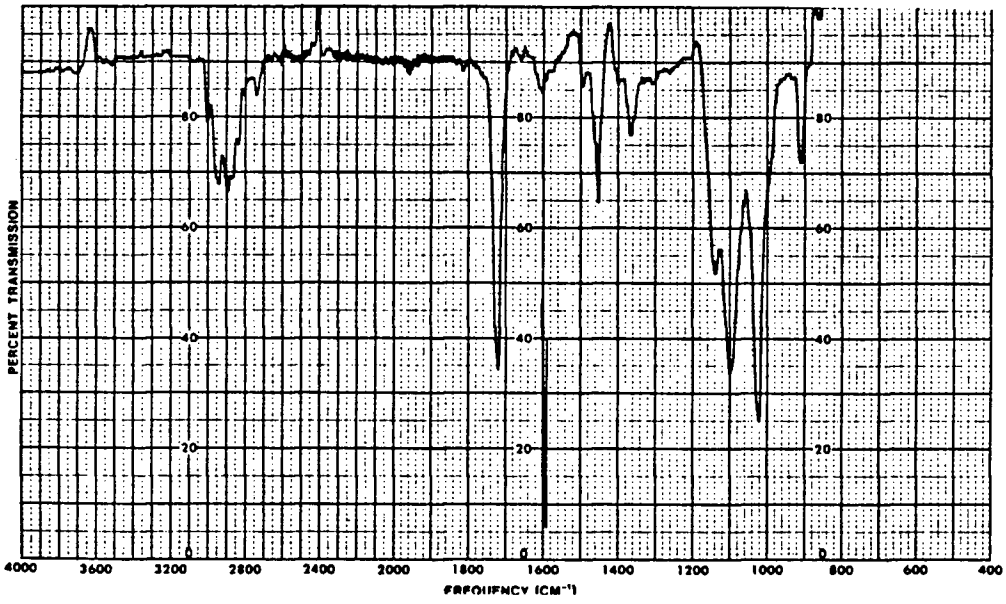

400 MHz
CHCl3
TMS

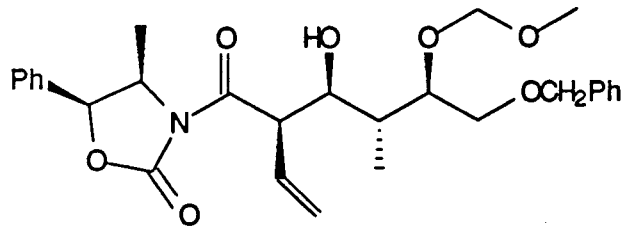

PERCENT TRANSMISSION
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400


O
O
O
H
OCH2Ph

139

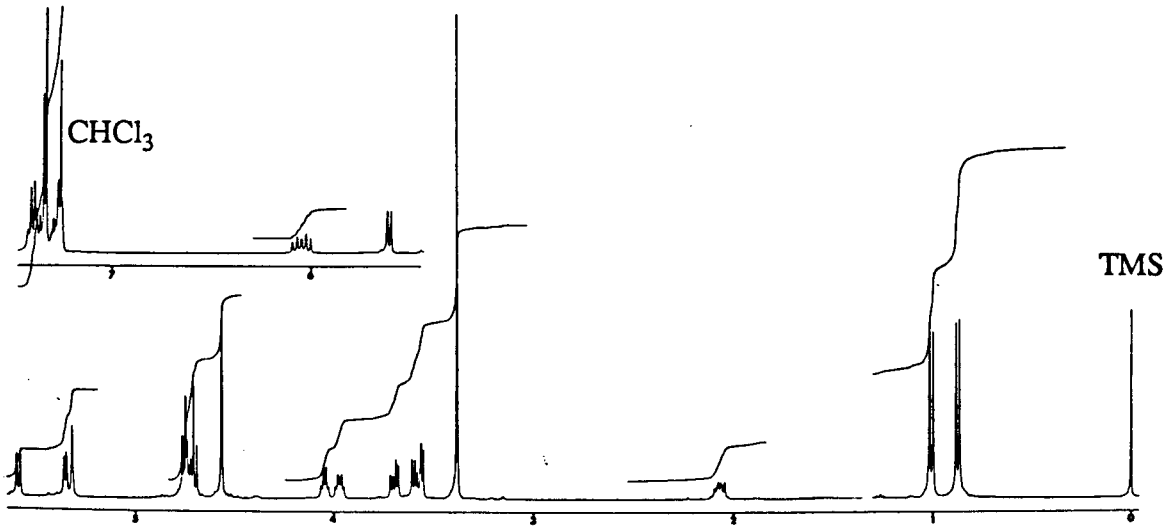

400 MHz
TMS
CHCl3

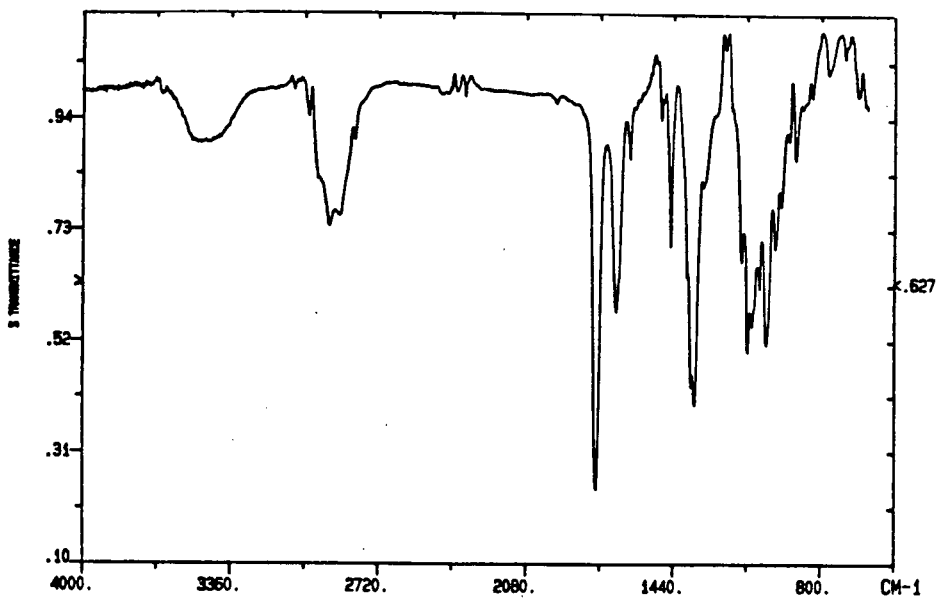

PERCENT TRANSMISSION
100
80
60
40
20
0
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400

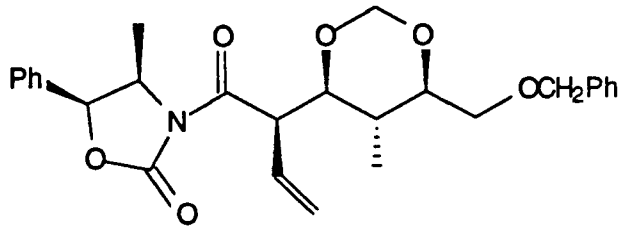

Ph
O
HO
O
O
N
O
O
OCH2Ph

140

400 MHz

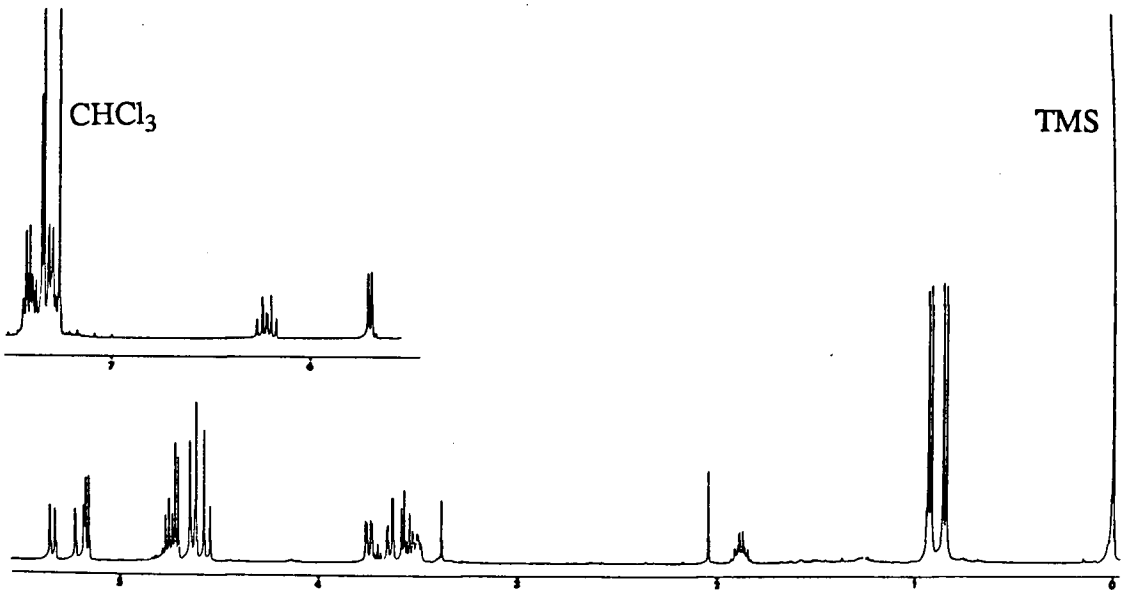

CHCl3
TMS

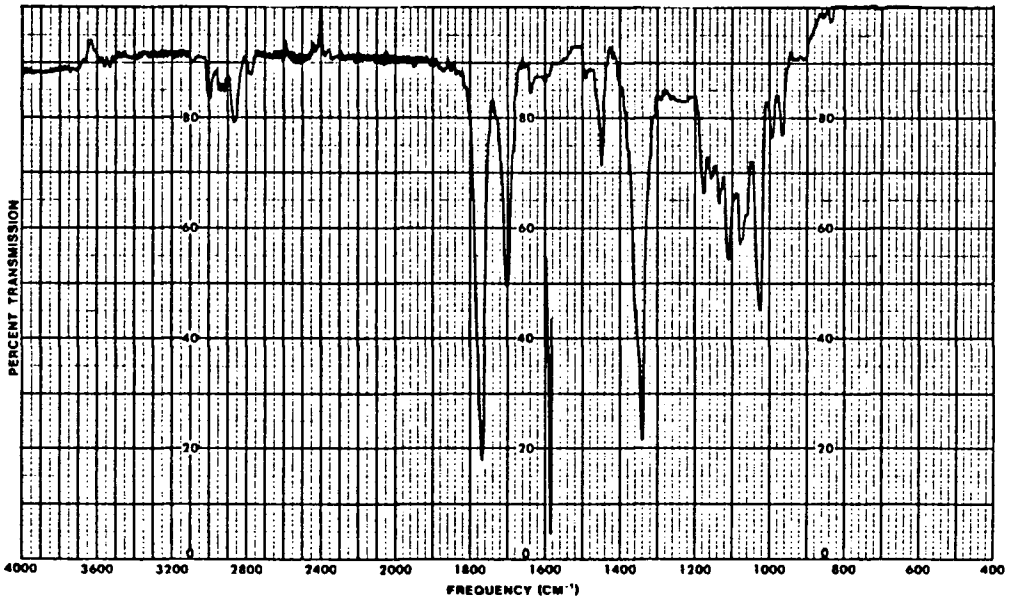

.94
.73
.52
.31
.10
4000.
3360.
2720.
2080.
1440.
800.
CM-1
.627


Ph
N
O
O
O
O
O
OCH2Ph

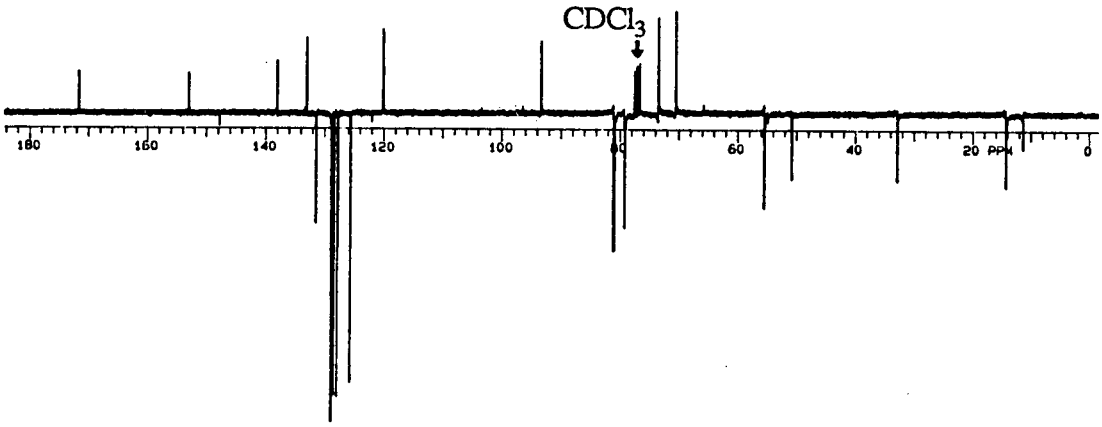
141

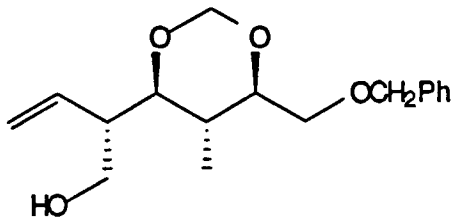
400 MHz


CHCl3
TMS


PERCENT TRANSMISSION
FREQUENCY (CM-1)
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400

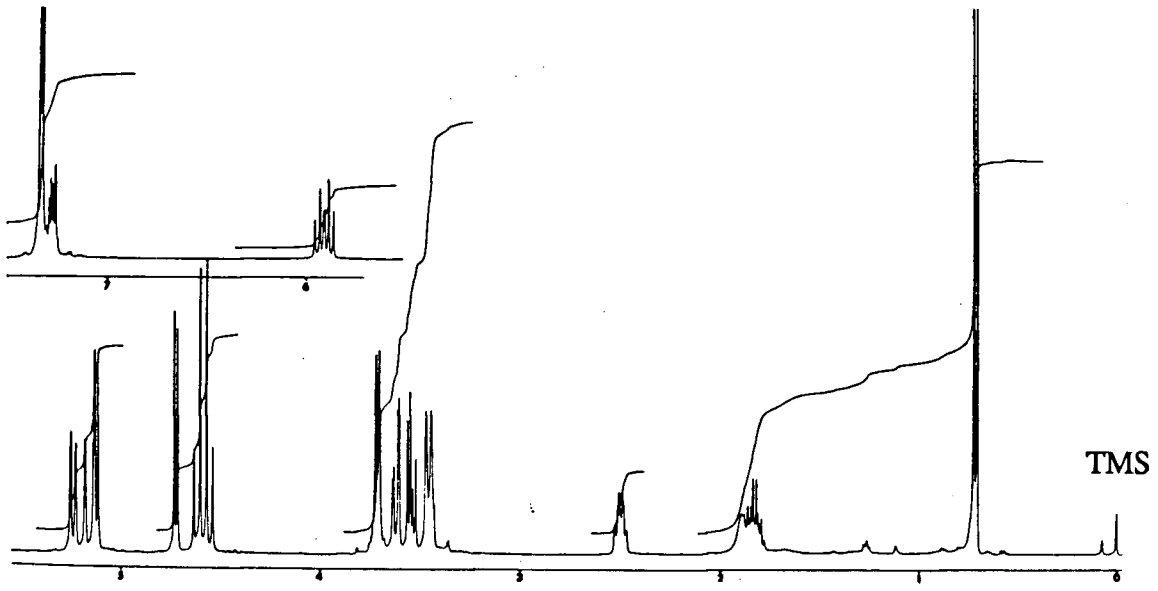
75 MHz

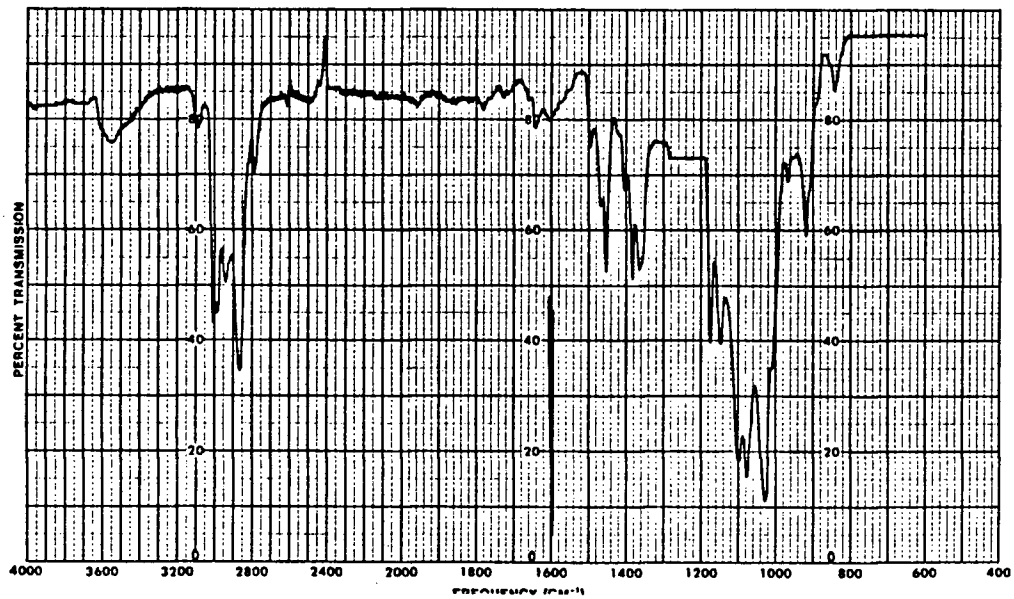



O
O
OCH2Ph
HO

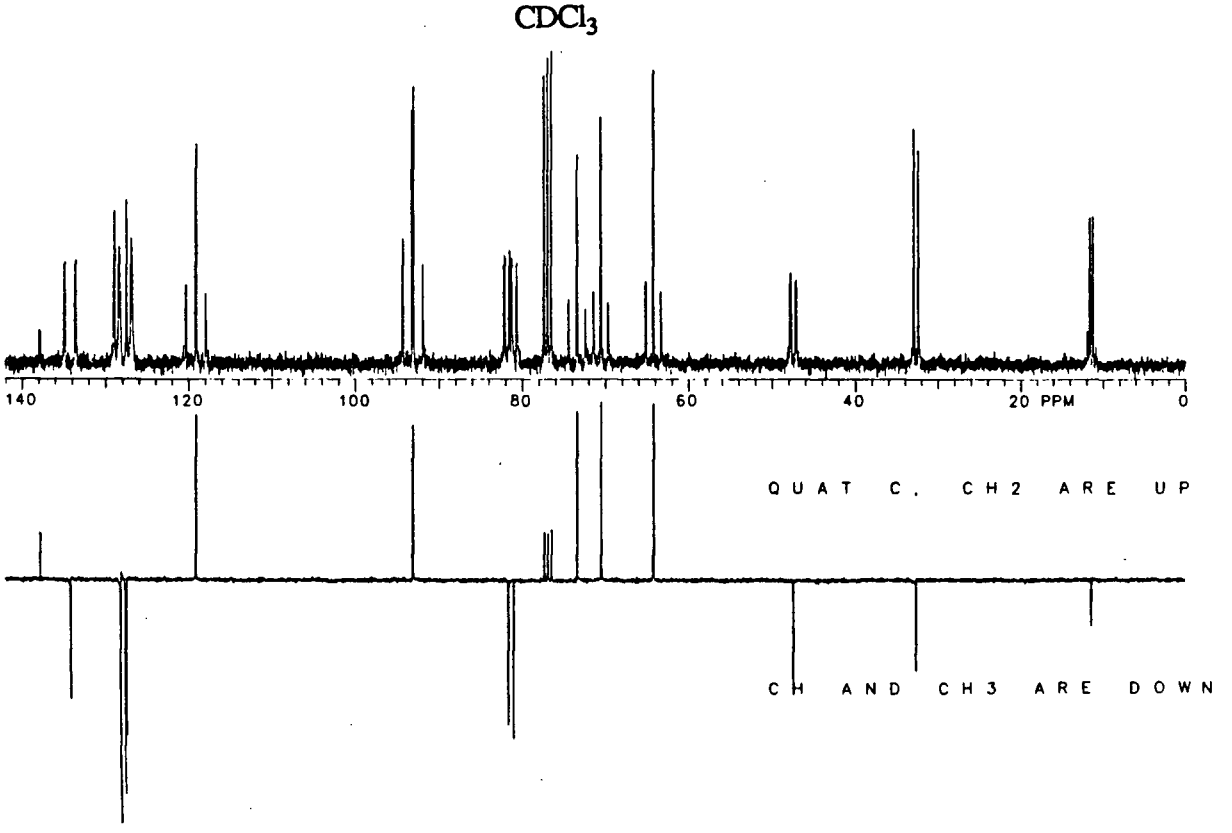
144

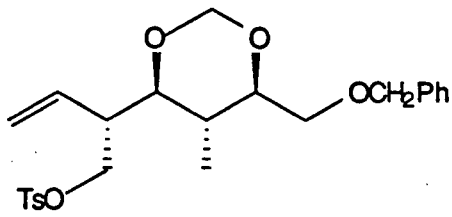
400 MHz


TMS


PERCENT TRANSMISSION
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400

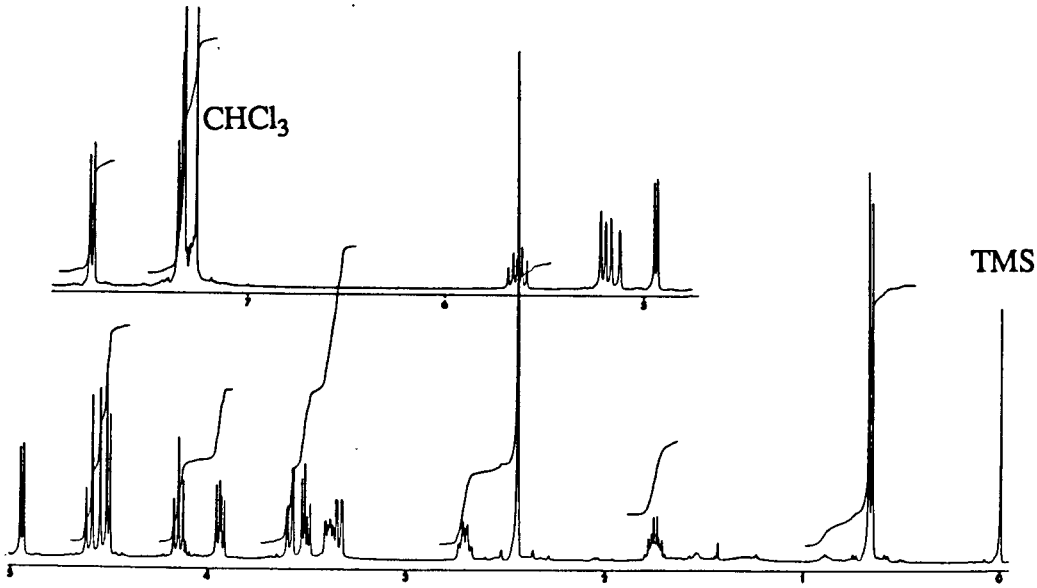
75 MHz

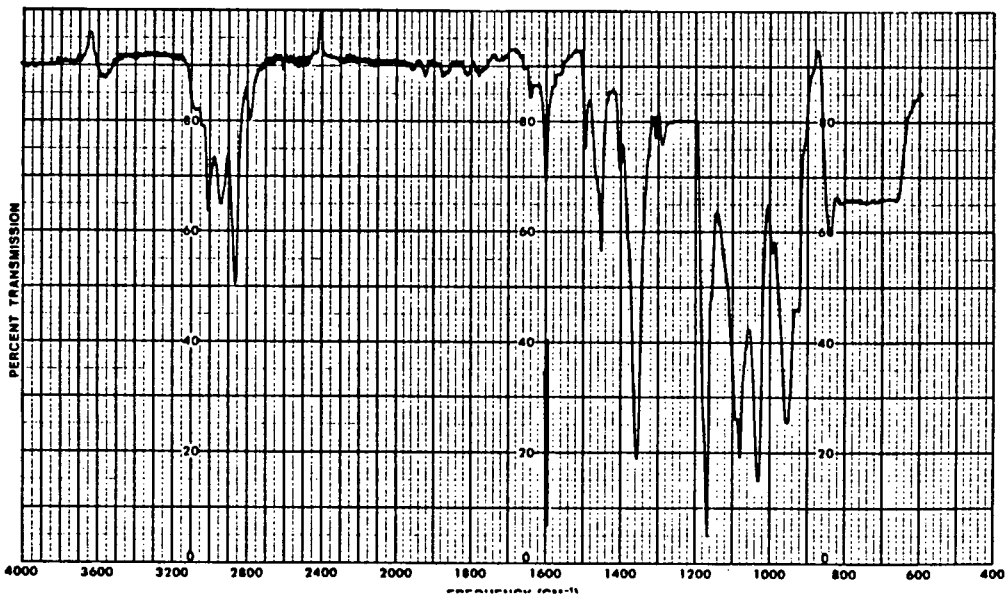

CDCl3
140
120
100
80
60
40
20 PPM
0
QUAT C, CH2 ARE UP
CH AND CH3 ARE DOWN

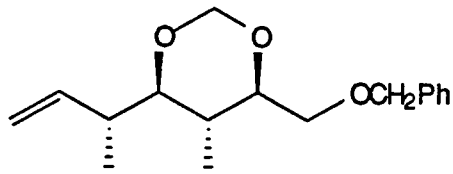

O
O
OCH2Ph
TsO

145

400 MHz

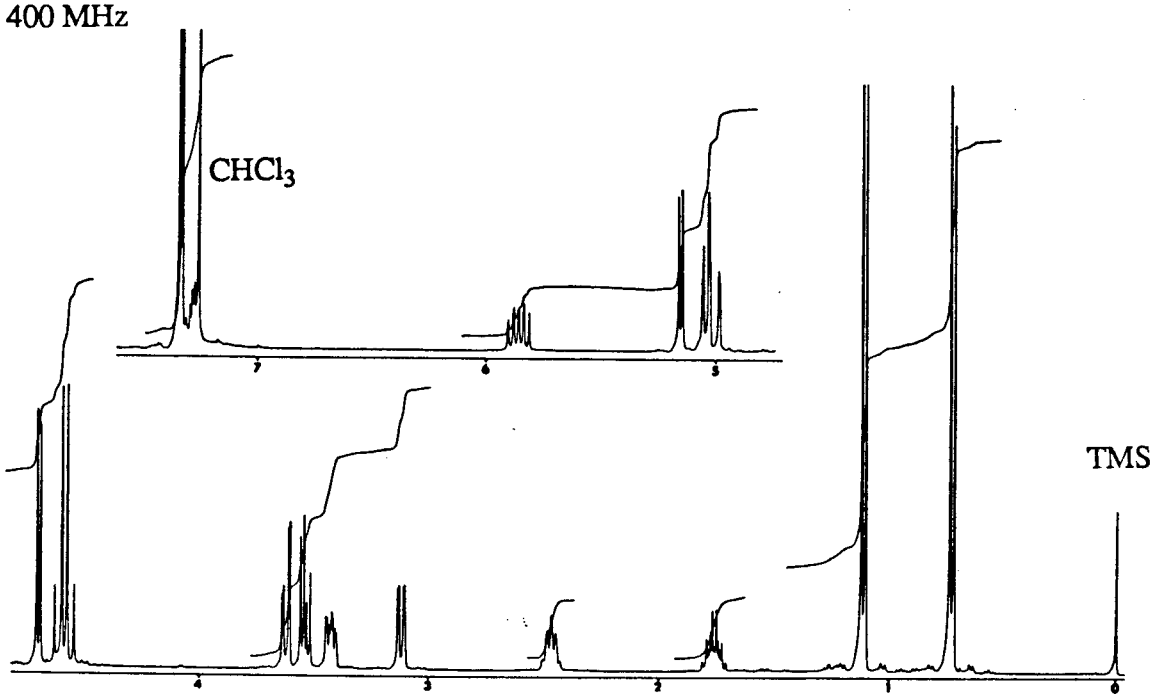

CHCl3
TMS

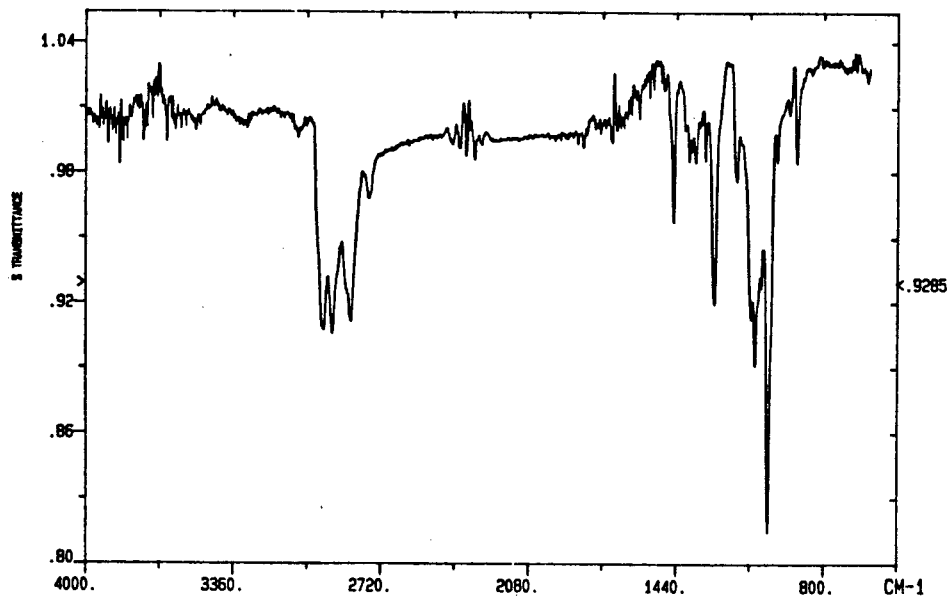

PERCENT TRANSMISSION
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400

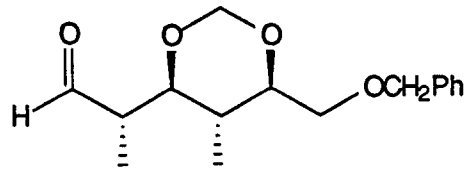

O
O
OCH2Ph

146

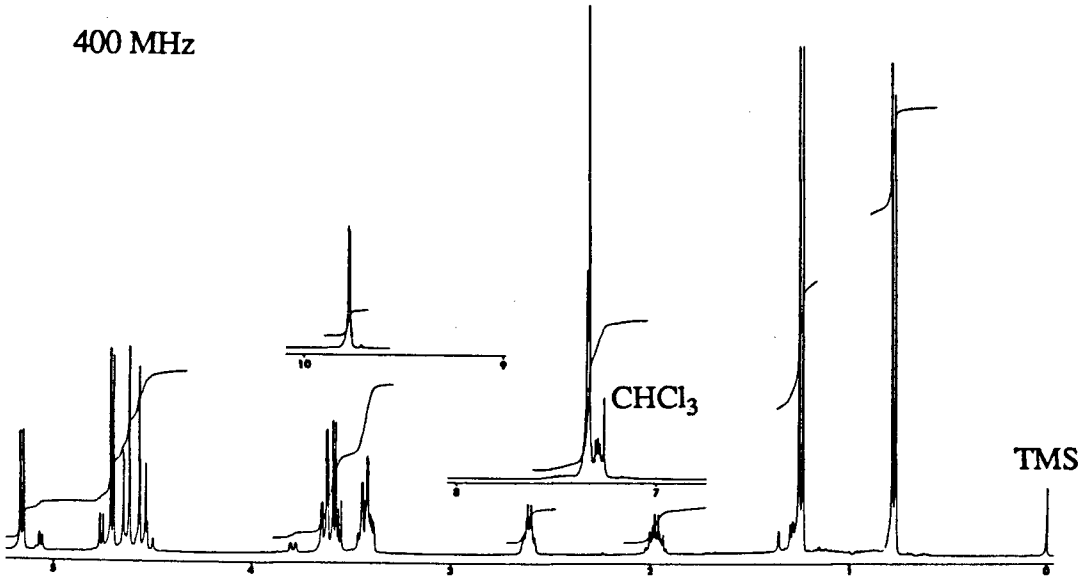
400 MHz

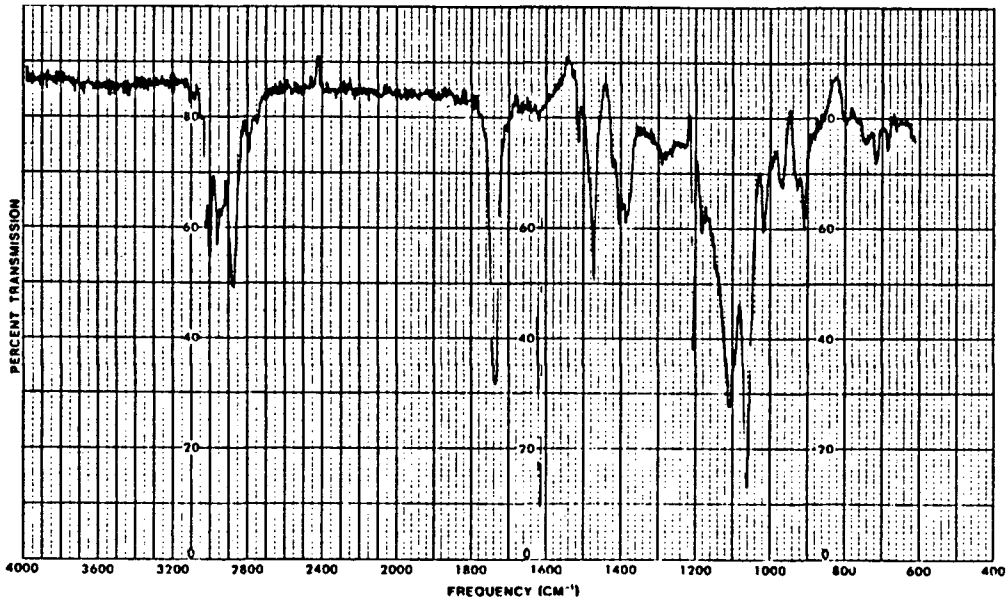

CHCl3
TMS
7
6
5
4
3
2
1
0

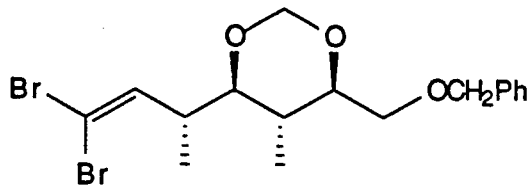

1.04
.98
.92
.86
.80
4000.
3360.
2720.
2080.
1440.
800.
CM-1
.9285


O
O
O
H
OCH2Ph

167

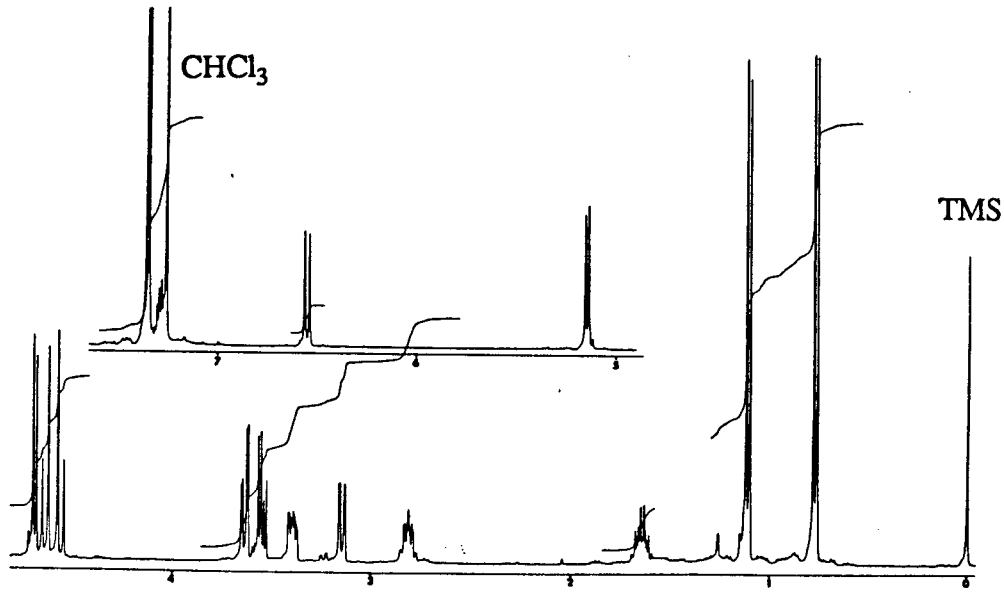

400 MHz
CHCl3
TMS

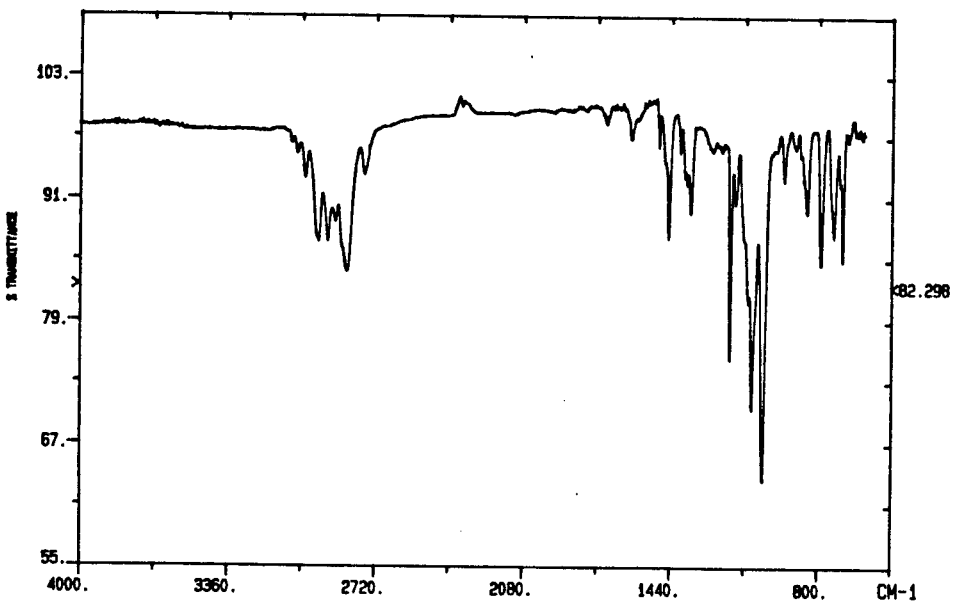

PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)

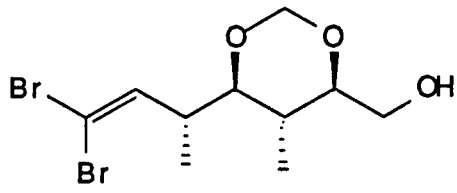

Br
Br
O
O
OCH2Ph

169

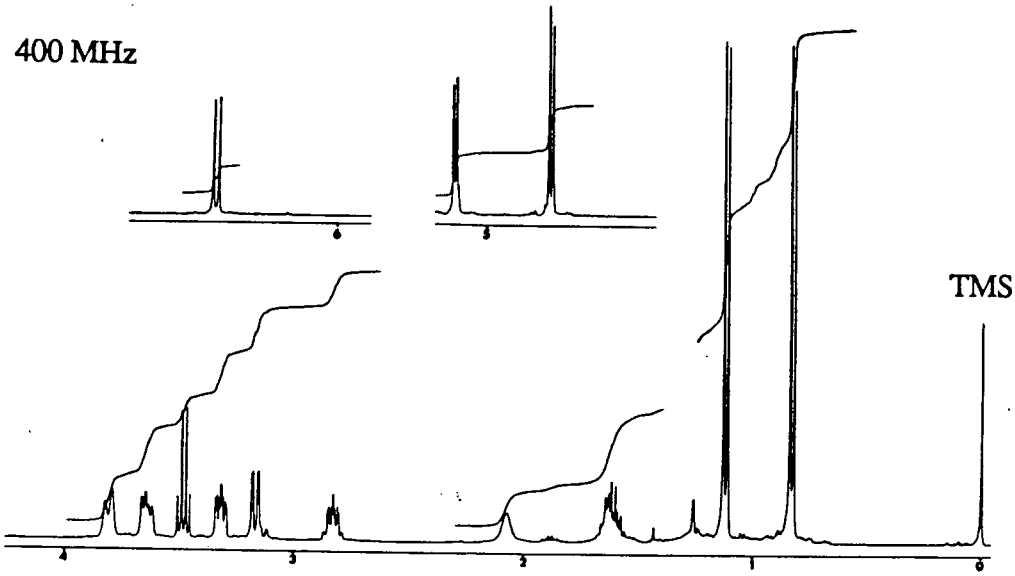
400 MHz

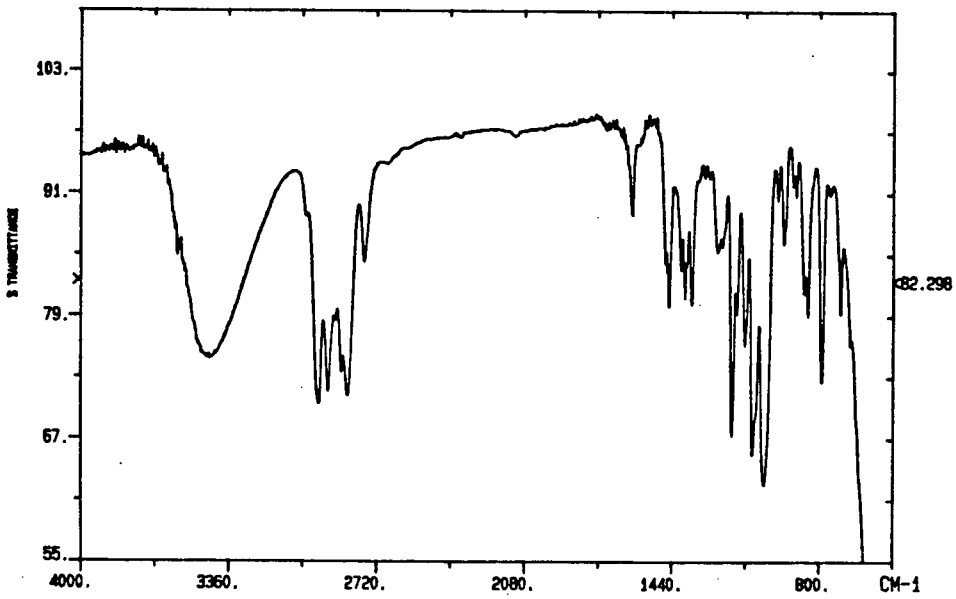

CHCl3
TMS

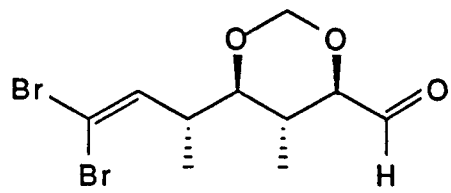

103.
91.
79.
67.
55.
4000.
3360.
2720.
2080.
1440.
800.
CM-1
82.298


Br
Br
O
O
OH

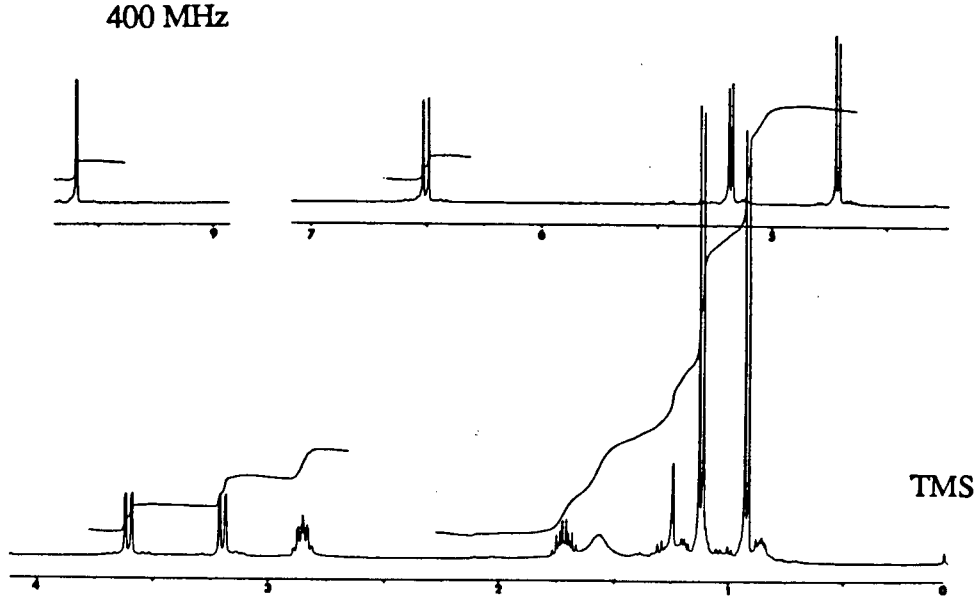
171

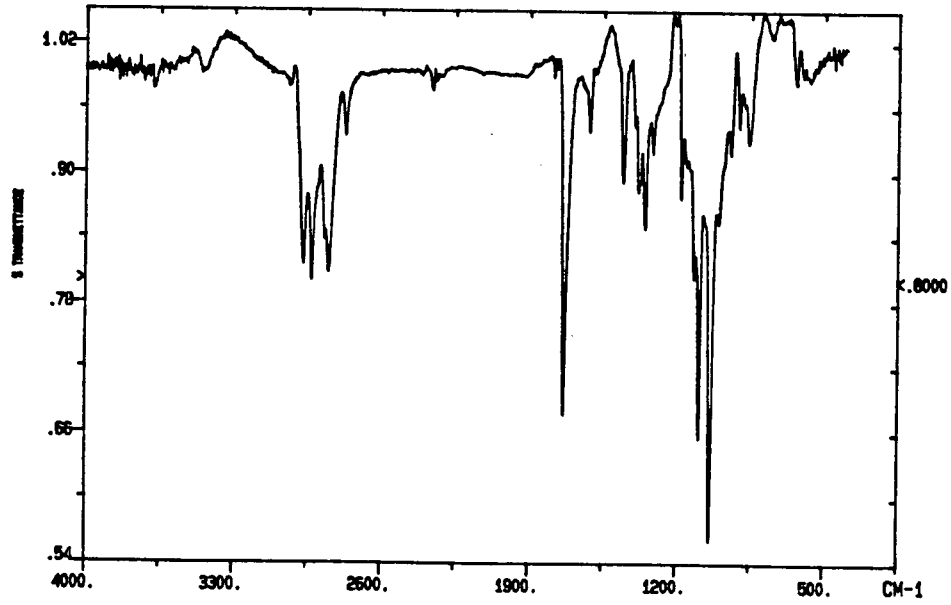

400 MHz
TMS
4
3
2
1
0

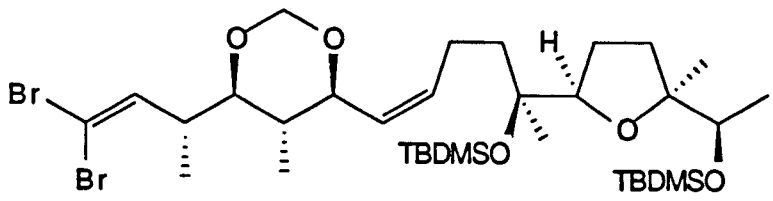

103.
91.
79.
67.
55.
4000.
3360.
2720.
2080.
1440.
800.
CM-1
82.298


Br
Br
O
O
O
H

172

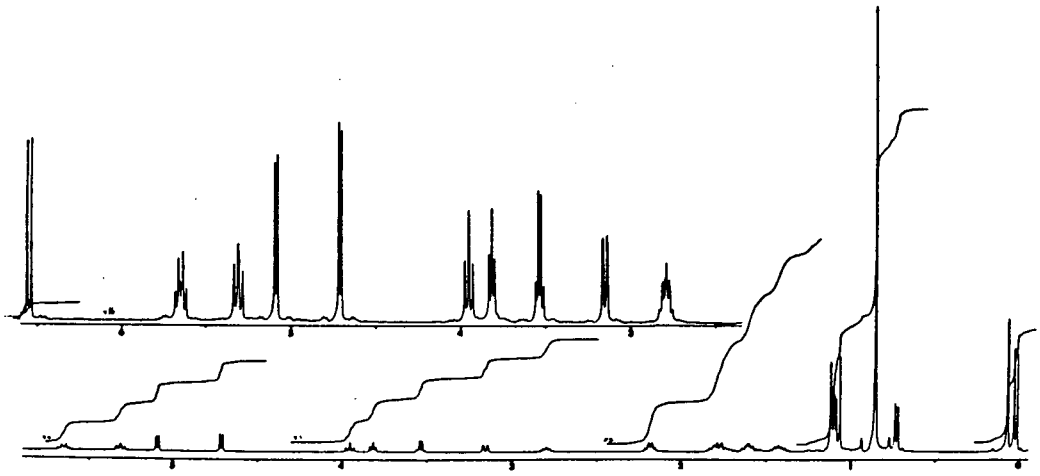

400 MHz
TMS

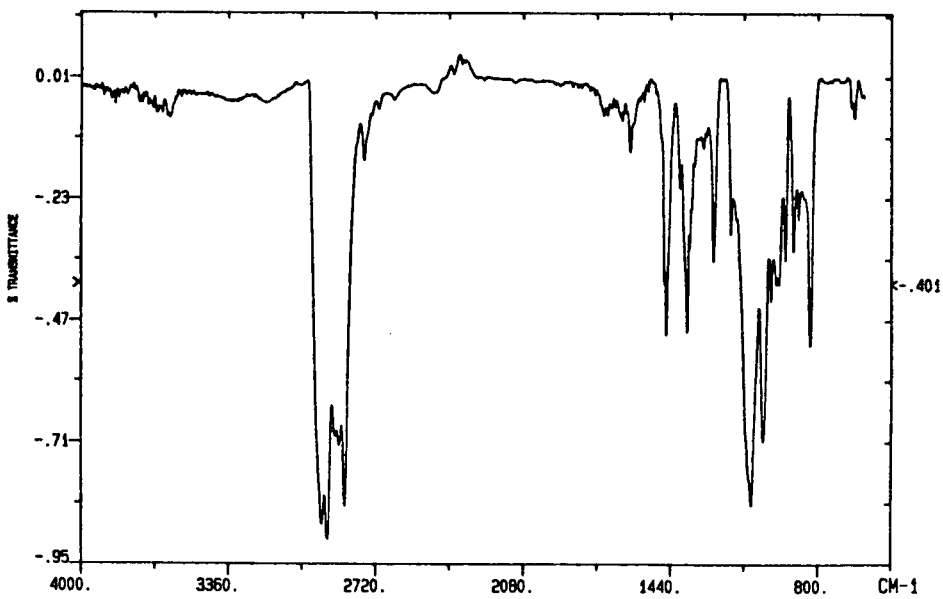

1.02
.90
.78
.66
.54
4000.
3300.
2600.
1900.
1200.
500.
CM-1
.6000

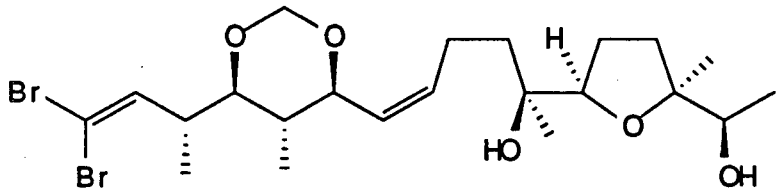

Br
Br
O
O
H
O
TBDMSO
TBDMSO

194

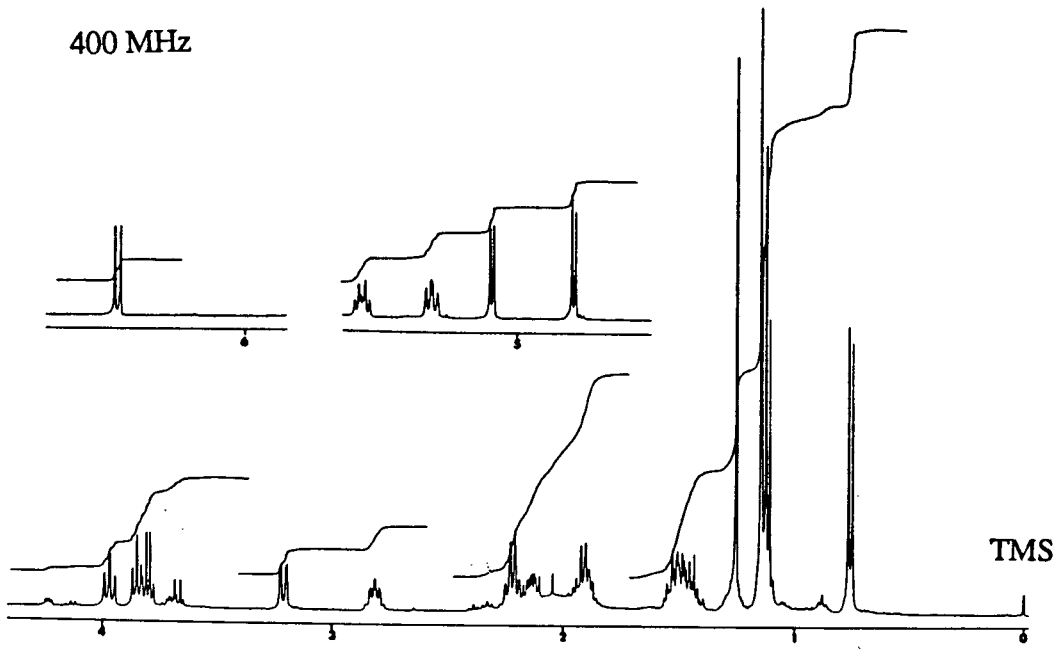
400 MHz

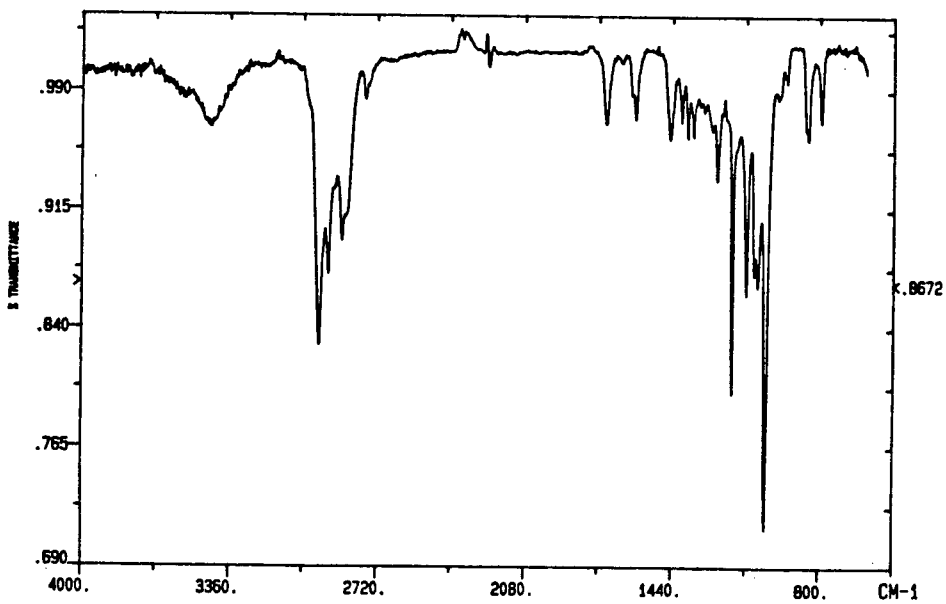


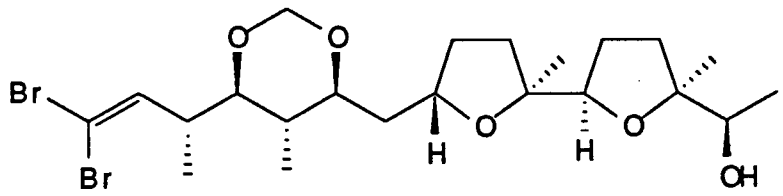

0.01
-.23
-.47
-.71
-.95
4000.
3360.
2720.
2080.
1440.
800.
CM-1
<-.401


Br
Br
O
O
H
HO
O
OH

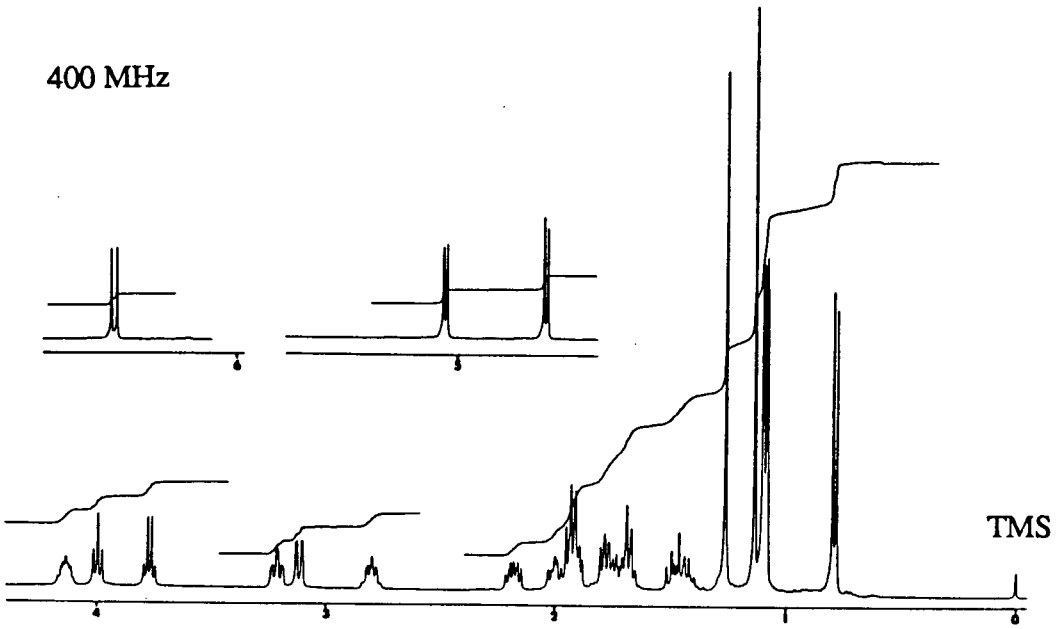
195

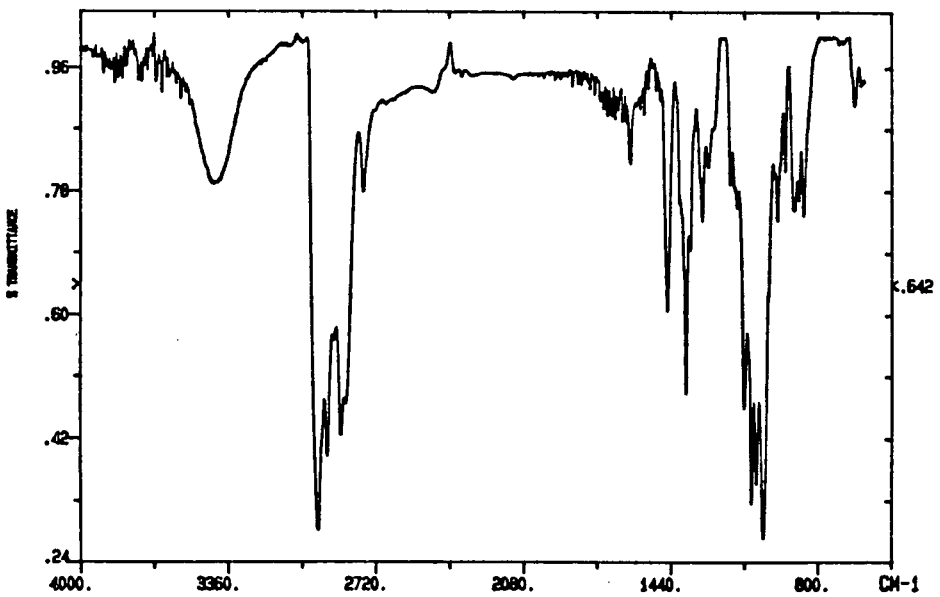

400 MHz
TMS


.990
.915
.840
.765
.690
4000.
3360.
2720.
2080.
1440.
800.
CM-1
.8672


Br
Br
O
O
O
O
H
H
OH

196


400 MHz
TMS


.96
.78
.60
.42
.24
4000.
3360.
2720.
2080.
1440.
800.
CM-1
.642

AWARDS

1988-1989	Postdoctoral fellowship (NSERC)
1984-1987	Postgraduate scholarship (NSERC)
1984-1988	University Graduate Fellowship (UBC, declined)
1986-1988	British Colcumbia Postsecondary Award
1982	Undergraduate University Summer Research Award (NSERC)

BIOGRAPHICAL NOTES

1961 Born, Montréal, Québec
1983 B.Sc., Université de Montréal

PUBLICATIONS

"A Stereoselective Synthesis of the Tetrahydrofuran Unit in Ionomycin", Claude Spino and Larry Weiler, Tetrahedron Letters, Vol. 28, no. 7, pp 731-734, 1987.

"Synthesis of the Three Isomeric Components of San Jose Scale Pheromone", Margot Alderdice, Claude Spino and Larry Weiler, Tetrahedron Letters, Vol. 25, No. 16, pp 1643-1646, 1984.

"Synthesis of spin-labeled analogs of drug molecules with potential action on neuroreceptors", H. Dugas, C. Spino and M. Ouelette, Canadian Journal of Chemistry, Vol. 61, No. 11, pp 2540-2543, 1983.