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SYNTHETIC STUDIES ON THE TETRAHYDROFURAN CONTAINING ACETOGENINS

BY

ZHEMING RUAN

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

1998

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

9/15/98
Date

Chair of Examining Committee

9/15/98
Date

Executive Officer

David R. Mootoo

Richard W. Franck

William Berkowitz

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

SYNTHETIC STUDIES ON THE TETRAHYDROFURAN CONTAINING ACETOGENINS

by

Zheming Ruan

Adviser: Professor David R. Mootoo

The tetrahydrofuran (THF) containing acetogenins have attracted interest because of their highly potent and diverse bioactivities. They are new candidates for anticancer agents, based on promising antitumor effects in *in vitro* as well as *in vivo* studies. They are C35-C39 compounds which generally contain one or more 2, 5-disubstituted THF's of variable stereochemistry and a α,β-unsaturated γ-lactone subunit. A number of different synthetic approaches have been published.

Two methods for the preparation of 2,5-disubstituted THF's, were previously developed in our laboratory. The first was the synthesis of *cis*-2,5-disubstituted THF's *via* the haloetherification reaction of alkenylated monosaccharides. The second was the synthesis of *trans*-2,5-disubstituted THF's from 5,6-O-isopropylide alkenes.

Based on the first strategy, a highly convergent methodology for adjacently linked bis-THF's containing *cis*-2,5-disubstituted THF's was developed. Using bis-pyranoside alkenes, in which one of the monosaccharide fragment is equipped with an activated *cis* directing aglycone (trityl) and the other with a deactivating aglycone (trifluoroethyl), as precursor, 32/64 possible adjacent bis-THF containing acetogenins may be prepared with this methodology. This convergent strategy is especially well suited to polyether structures which do not have highly symmetrical substitution patterns, as found for example in Ionophore A204.

Based on the second strategy, a bi-directional approach to adjacently linked bis-THF's containing *trans*-2,5-disubstituted THF's was developed. Syntheses of the known trilobacin and asimicin bis-THF cores were accomplished. The use of relatively straightforward and inexpensive reactions should allowe these compounds to be prepared on relatively large scales. 16 of the 64 possible bis hydroxymethyl bis-THF cores can be prepared via this strategy. Together both methodologies allows access to 40 of the 64 possible stereoisomers of the bis hydroxymethyl bis-THF cores.

Finally, application of the bidirectional strategy to more complex polycyclic ether structures was tested. The synthesis of a study of simple polyether analog of Kijimicin and monensin, was performed.

Acknowledgements

A doctorate, although awarded to an individual, is by its very nature the end product of a collaborative involving numerous individuals. I am indebted to the following people who have made my journey through academia an enjoyable one.

My heartfelt thanks go out to my mentor, Dr. David R. Mootoo. I thank him for the knowledge he has given me. His enthusiasm, patience, encouragement and constant support during my studies is deeply appreciated. I gratefully acknowledge Professor Franck Richard, Professor Williams Berkowitz for constituting the thesis committee and reviewing this work. A special thanks to Dr. Qiao-Yun He for so much help that she gave me.

I am indebted to Dr. Michael Blumenstein and Dr. Clifford E. Soll for their expertise in the NMR and MS laboratories. Their advice has been instrumental to the success of this work.

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A special thanks to Dr. R. Michael Lawrence, my boss in BMS, for his support to finish my work in final stage.

To My Wife

Jiafang He

To My Son

Yifeng Ruan

Table of Contents

List of Abbreviations

Ac	Acetate
AD-mix-β	Sharpless asymmetric dihydroxylation reagent
AIBN	2,2'-Azobis(isobutyronitrile)
Bz	Benzoyl
Bn	Benzyl ($PhCH_2$)
Bu	Butyl
c	*cis*
CSA	(1R)-(-)-10-Camphorsulfonic acid
DEAD	Diethyl azodicarboxylate
DIBALH	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMS	Dimethyl sulfide
er	*erythro*
Et_3N	Triethylamine
Hz	Hertz (for coupling constants)
IDCP	Iodonium dicollidine perchlorate
L-(+)-DET	Diethyl L-tartrate
m-CPBA	3-Chloroperbenzoic acid
MHz	Megahertz
Ms	Methanesulfonyl

MsCl	Methanelsulfonyl chloride
NaHMDS	Sodium bis(trimethylsilyl)amide
NIS	N-iodosuccinimide
NMO	4-Methylmorpholine N-Oxide
PNB	4-Nitrobenzoyl
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
Py.	Pyridine
Red Al	Sodium bis(2-methoxyethoxy)aluminum hydride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBAF	Tetrabutylammonium fluoride
t	*trans*
th	*threo*
TFE	Trifluoroethyl
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	*p*-toluenesulfonyl
TsCl	*p*-toluenesulfonyl chloride

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Chapter 1

Review of Synthesis of the THF Containing Acetogenins

More than 230 THF containing acetogenins have been isolated from the family Annonaceae.[1] The Annonaceae family consists of aromatic trees, shrubs or climbers, which occur mainly in tropical and subtropical regions.[2] Since the discovery of *uvaricin* (Figure 1), the first Annonaceous acetogenin, in 1982,[3] THF acetogenins have been found mainly in ***annona, asimina, goniothalamus, rollinia and uvaria*** species. This accounts for 26 out of an estimated number of 2300 Annonaceae species.[2]

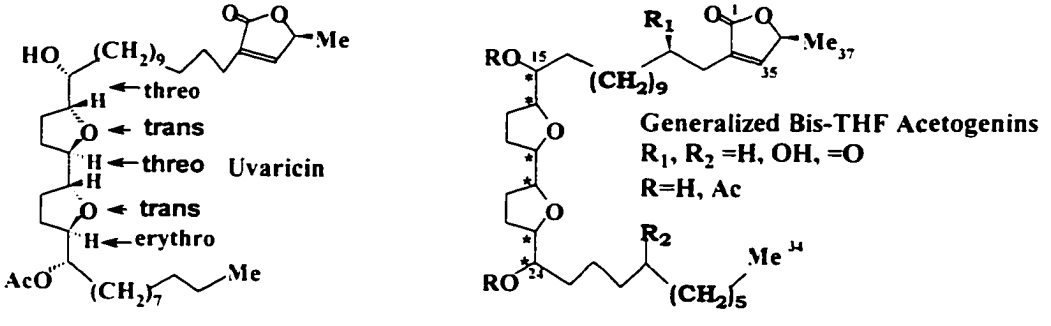
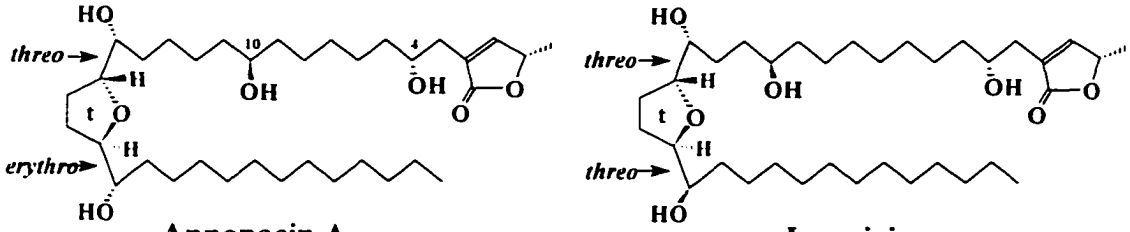


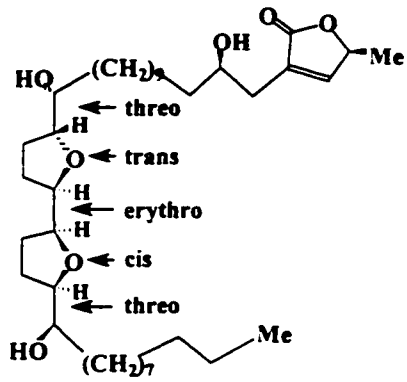
Figure 1

The THF containing acetogenins have attracted interest because of their highly potent and diverse bioactivities. They have exhibited cytotoxic, antitumor, antiprotozoal, antimalarial (superior to tetracycline), T-cell-inhibitory, immunosuppressive, pesticidal and antifeedant activities.[4] They are new candidates for anticancer agents, based on promising antitumor effects in *in vitro* as well as *in vivo* studies.[5]

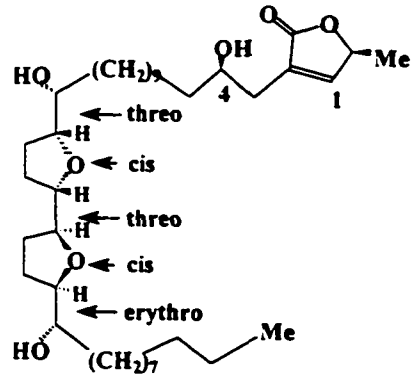
Their structures (C_{35} or C_{37}) are characterized by: (1) one or more THF rings, (2) relatively long unbranched alkyl chains containing usually hydroxyl groups, acetates, or a ketone, and less often an epoxide or olefin. (3) an α,β-unsaturated γ-lactone attached to the end of one of the alkyl chains.[4b] Figure 1 shows a generalized bis-THF acetogenins structure. Derivatives which contain more than one THF ring, may be subdivided into adjacent or non-adjacent linked THF's. Representative structures (Figure 2) are annonacin **1**[6] and javoricin **2**[7] for mono-THF, rolliniastatin **3**[8] and trilobacin **4**[9] for adjacent bis-THF, and squamostatins-E **5**[10] and gigantecin **6**[11] for non-adjacent bis-THF. A small number of tri-THF structures, have also been reported. Recently, a new structural type of acetogenin, mucocin **7**,[12] containing both a THF ring and a tetrahydropyran (THP) ring has been isolated. Coriadienin **8** is an example of the acetogenin, which does not contain a THF ring.[4b]

Figure 2. Representative Structures of Acetogenins

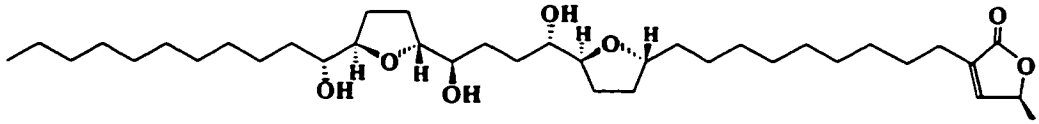




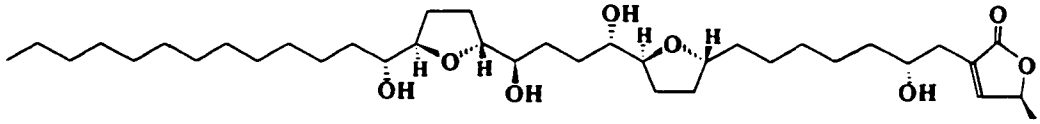
Trilobacin
3



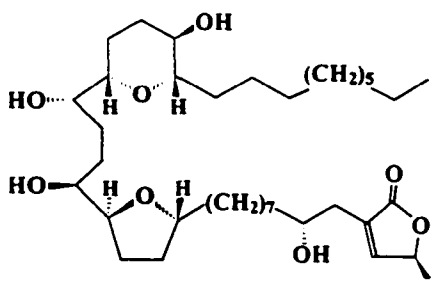
Rolliniastatin
4



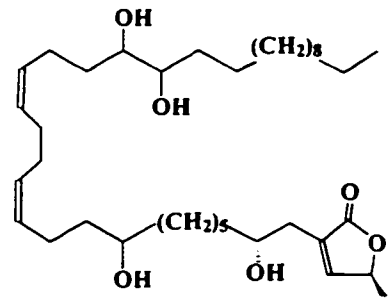
Squamostatins-E
5



Gigantecin
6



Mucocin
7



Coriadienin
8

1. Structure Activity Relationship

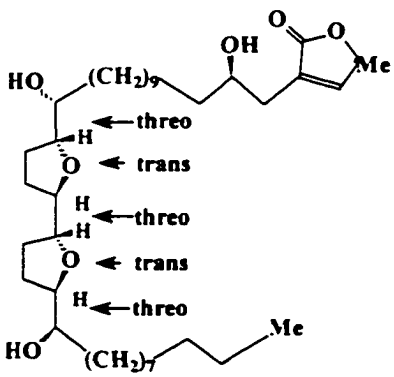
The following structure activity relationships have been identified. (1) activity decreases in the order: adjacent bis-THF's, mono-THF's, non-ring compounds. (2) the α,β-unsaturated γ-lactone is essential for activity. (3) the hydroxyl group at the C-4 /C-10 position are also very important for the enhancement of activity. (4) reduction of the carbonyls to alcohols enhances activity. (5) the presence of double bonds and/or vicinal diols along the hydrocarbon chain enhances activity.[4b] Asimicin **9**,[13, 6a] bullatacin **10**,[6a, 14] trilobin **11**,[9b] and trilobacin **4** are four of the most active (Figure 3).[4b] All are adjacent bis-THF acetogenins and contain a C(4) or C(10)-hydroxyl moiety.

Some acetogenins appear to be selectively cytotoxic to certain cancer types. Altered biological transport or slight variation in receptor geometry in the membranes of such cell lines might explain these selectivities. For example, bullatacin **10** and bullatacinone **12** show significant activity against L1210 murine leukaemia. These represent, respectively, 300 times and 40 times the potency of taxol while showing similar positive antileukaemic effects.[14a] Bullatacin(**10**) and asimicin(**9**) showed potent selectivity (IC_{50}: about 0.35nM) against A2780 human ovarian tumor cells in the 7-day NCI screen.[15] In particular, Annonaceous acetogenins can inhibit the growth of adriamycin resistant tumor cells. For example, asiminocin is nearly one billion times the cytotoxic potency of adriamycin, as measured against several human solid tumor cell lines. Its ED_{50} is 2.9×10^{-12} μg/ML against MCF-7 human breast tumor cells.

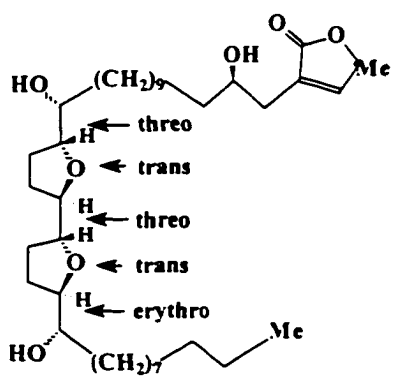
Several reviews have described the sources, isolation, chemistry, biogenesis, and biological activities of these natural products. A number of studies on the mode of

antitumor activities has also been done and it was suggested that the primary mode of action is the inhibition of Complex I (NADH-Ubiqinone Oxidoreductase), which is an essential enzyme of the electron transport system (ETS). The function eventually leads to oxidative phosphorylation in mitochondria and is coupled to energy conservation.[5] They also inhibit the ubiquinone-linked NADH oxidase that is peculiar to the plasma membranes of cancerous cells and functions to permit cytosolic phosphorylation (substrate level phosphorylation) by restoration of NAD^+ levels. The consequence of both mechanisms reduces intracellular ATP levels, which may correlate with the antitumor activity of acetogenins.[5d] There is a demand for combinatorial chemical libraries of such compounds for systematic biological screenings, in order to establish optimal activity relationship.

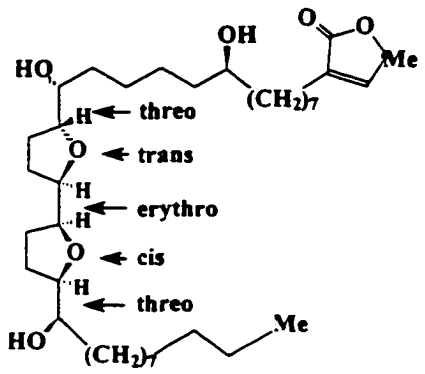
Figure 3



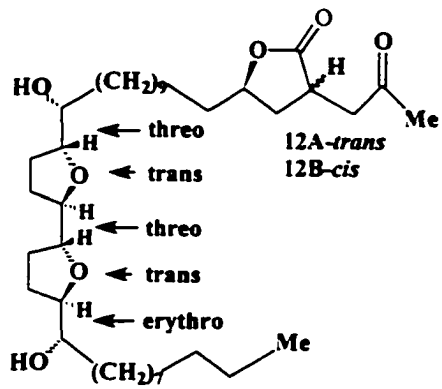
Asimicin
9



Bullatacin
10



Trilobin
11

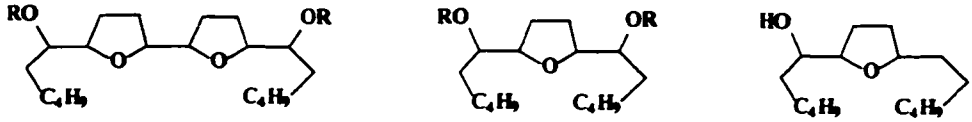


Bullatacinone
12

2. Stereochemistry

Usually, 5-10 chiral carbons are contained in the mono- and bis-THF containing acetogenins. The most potent antitumor derivatives have a ten-carbon subunit comprising two adjacent THF rings flanked by a hydroxyl group as exemplified by the structures of trilobacin **3** and rolliniastatin **4**. With six stereogenic carbinol centers, 64 different stereoisomers of this subunit are possible. Structures are generally unsuitable for direct X-ray crystallographic studies, because of their waxy, amorphous, or microcrystalline nature.[16] General methods for determining relative configuration have been developed by the groups of Hoye and Born. The stereochemistry of the natural compounds has been determined by ^{1}H NMR comparisons with synthetic mono- or bis-THF model compounds of known relative stereochemistry (Figure 4).[17]

Figure 4. Model diols(R=H) and diacetates(R=Ac)



12 isomers 6 isomers 4 isomers

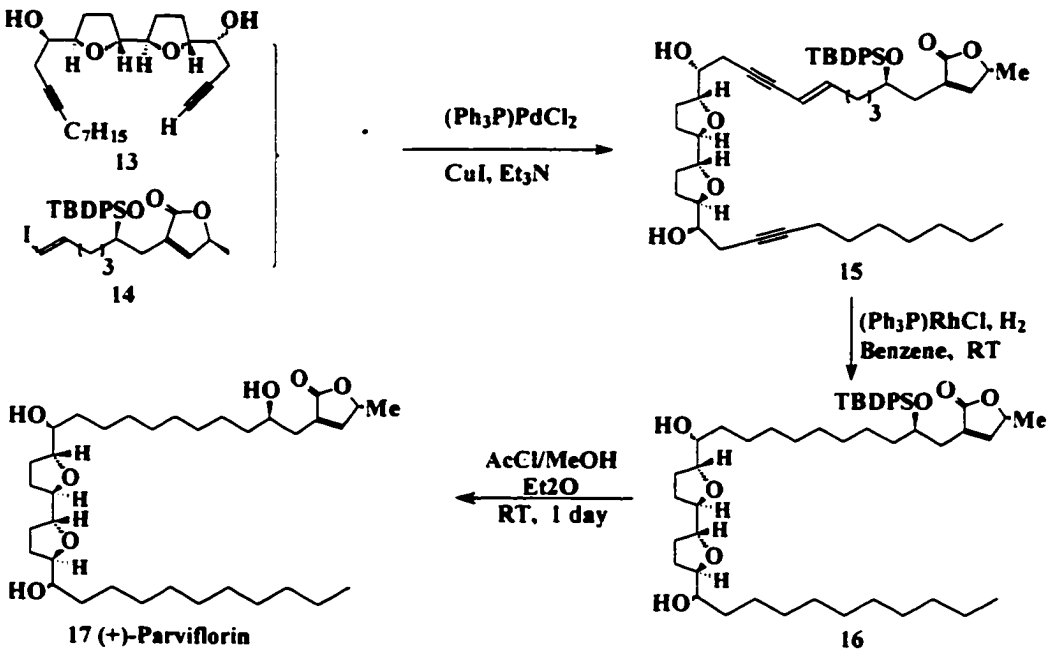
Born's method is used to assign the configurations between the THF ring and the adjacent hydroxyl group. The proton and carbon of the carbinol group attached to the THF ring resonate at δ_H ca. 3.8 and δ_c ca. 71-72 for *erythro* compounds and at δ_H ca. 3.4 and δ_c ca. 74 for *threo* compounds.[16b] For mono THF's, a *cis*-THF is confirmed if the two flanking hydroxyl groups could be bridged to form an acetal.[7] Hoye has assigned absolute configurations by ^1H and ^{19}F-NMR analogs of (R) and (S)-Mosher ester derivatives of alcohol derivatives.[6a] A variation of the Mosher method has been used to determine the C(4)/C(36) relationship of the butenolide subunits.[18] Combinations of these methods has allowed the assignment of the complete stereostructure for several acetogenins.

3. Synthesis

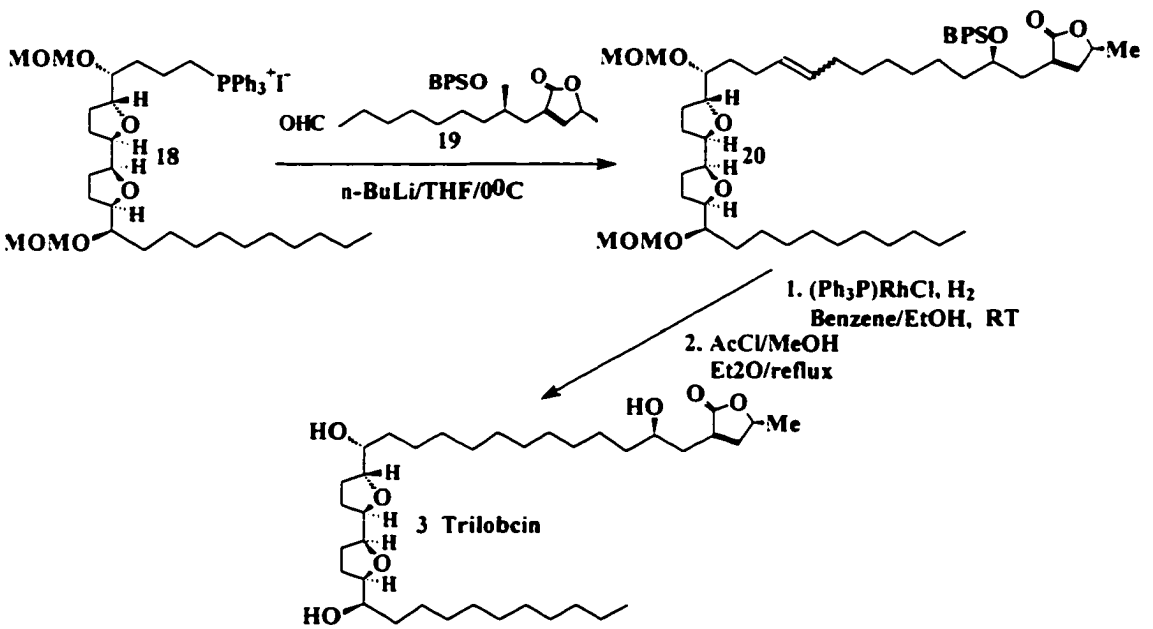
(I) Coupling methods

Retrosynthetically, the THF acetogenins can be disconnected into THF and butenolide subunits. The first methodology for coupling of the two fragments was worked out by the Hoye group.[19] An example is the Pd^0-catalyzed coupling of THF alkyne **13** with the butenolide vinyl iodide **14** to give the enediyne **15** in 82% yield. Selective hydrogenation with Wilkinson's catalyst left the butenolide intact. Desilylation gave **17** (+)-**parviflorin** (Scheme 1).[20]

Scheme 1



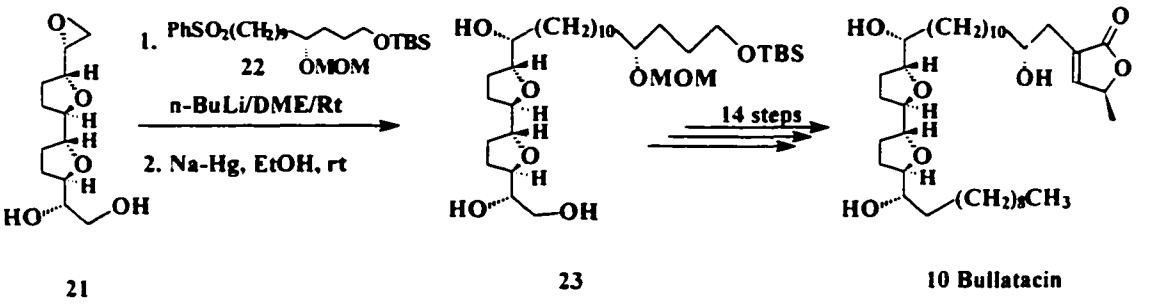
Scheme 2



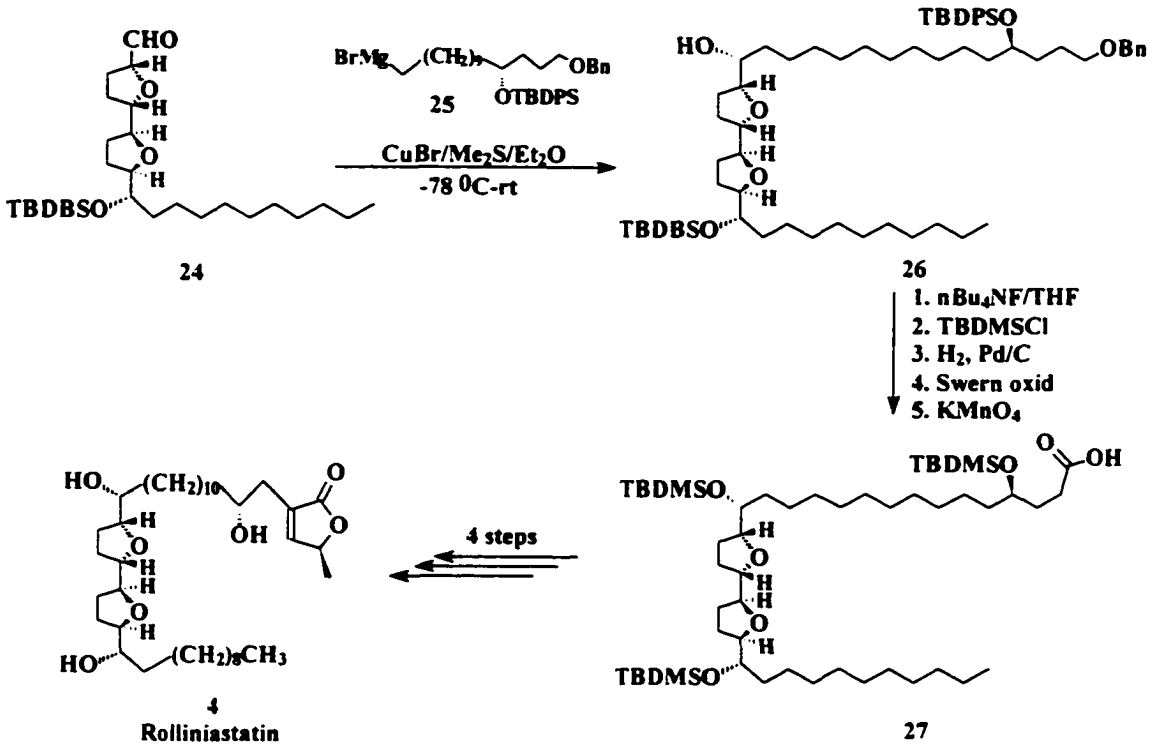
Keinan developed a Wittig coupling strategy. Treatment of the bis-THF core **18** with BuLi and then with butenolide aldehyde **19** followed by selective hydrogenation and deprotection afforded **3, trilobacin** (scheme 2).[21]

Less convergent approaches by Sasaki and Koert used acyclic butenolide synthons, which were converted to the butenolide structure after the coupling reaction. In Sasaki's synthesis of bullatacin, a bis-THF epoxide **21** was coupled with the carbanion derived from sulfone **22**. Reduction and 14 additional steps gave bullatacin (scheme 3).[22] Koert used the Cu(I) catalyzed reaction of the Grignard reagent **25** and the THF aldehyde **24** in his synthesis of rolliniastatin. After 9 additional steps, rolliniastatin was obtained (Scheme 4).[23]

Scheme 3



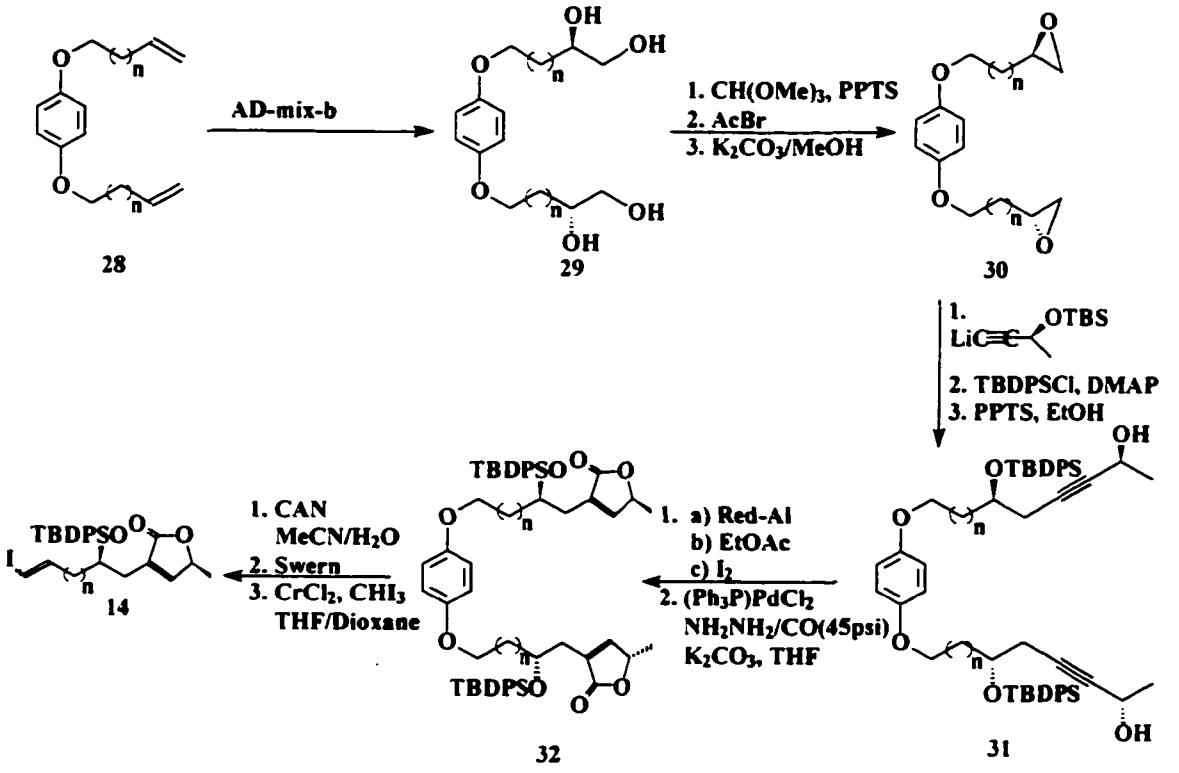
Scheme 4



(II) Butenolide Synthesis

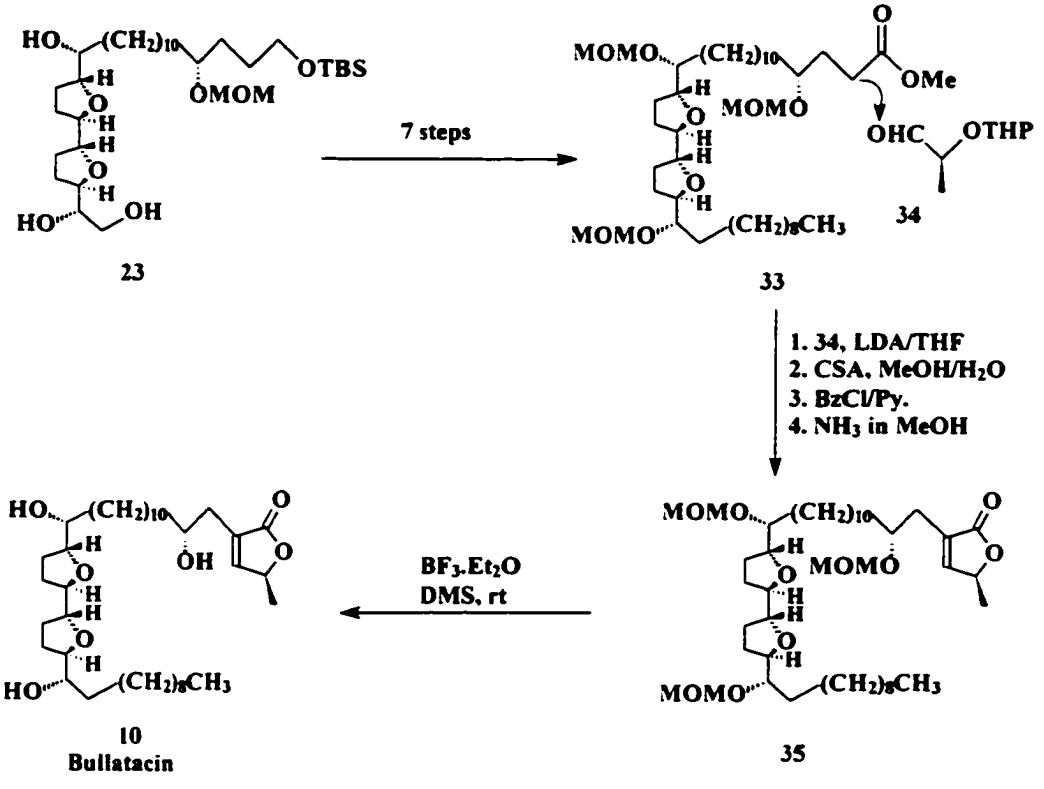
One of the more efficient methods to construct the butenolide subunit was worked out by Hoye's group.[20] 1,4-bis(alkenyloxy)benzene **28** (prepared from bis-alkylation of hydroquinone with 6-iodo-1-hexene) was converted to the corresponding tetraol **29** by double asymmetric dihydroxylation (>99%ee). In a one-pot procedure, **29** was processed into bis-epoxide **30**. Alkylation of **30** followed by protecting group transformation led to the propargylic alcohol **31** in three overall steps. The butenolide **32** was then obtained by Red-Al reduction, iodine treatment, and carbonylation under Stille conditions. Finally, the terminal vinyl iodide **14** (n=3) can be produced with three additional steps: cleavage of the hydroquinone, oxidation of the primary alcohol and olefination (Scheme 5).

Scheme 5



The synthesis by Sasaki involved the aldol addition of the enolate derived from the ester **33** and the chiral aldehyde **34**, which was prepared in two steps from (S)-(-)-methyl lactate. Treatment of the product with CSA in MeOH-H_2O led to THP removal and lactone formation. Benzoylation followed by elimination with ammonia in methanol led to the α, β-unsaturated-γ-lactone **35**. Finally, deprotection of the MOM groups of **35** with $BF_3{\cdot}Et_2O$ in DMS provided **10, (+)-bullatacin** (Scheme 6).[22]

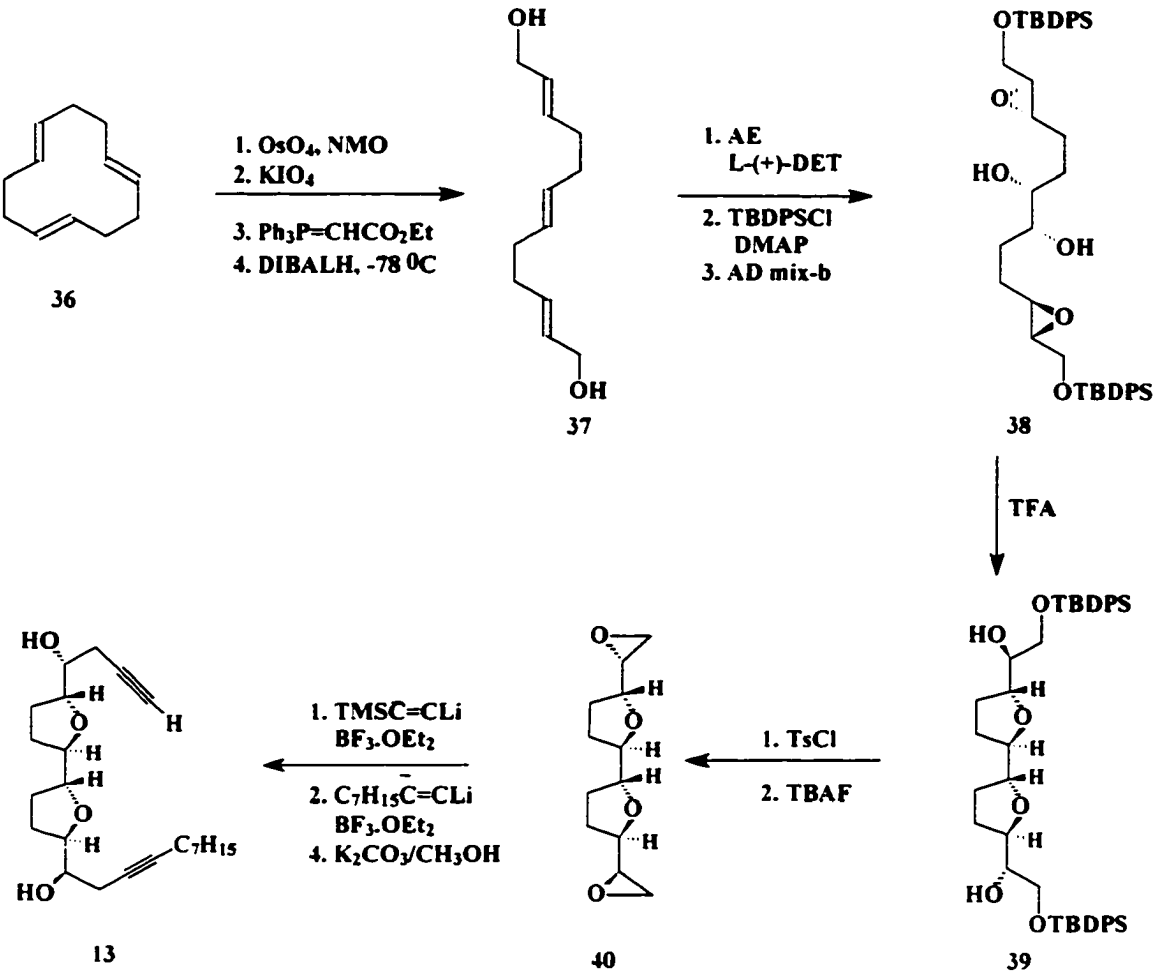
Scheme 6



(III) THF Synthesis

The bidirectional synthesis of a C2 symmetric bis-THF's is an attractive approach. The acid-catalyzed epoxide cascade reaction was the first method to be used for construction of the bis-THF framework.[24] One of the more efficient examples of this strategy involved the bidirectional chain synthesis of the bis-THF synthon alkyne **13**, the intermediate for (+) parviflorin (scheme 7).[20]

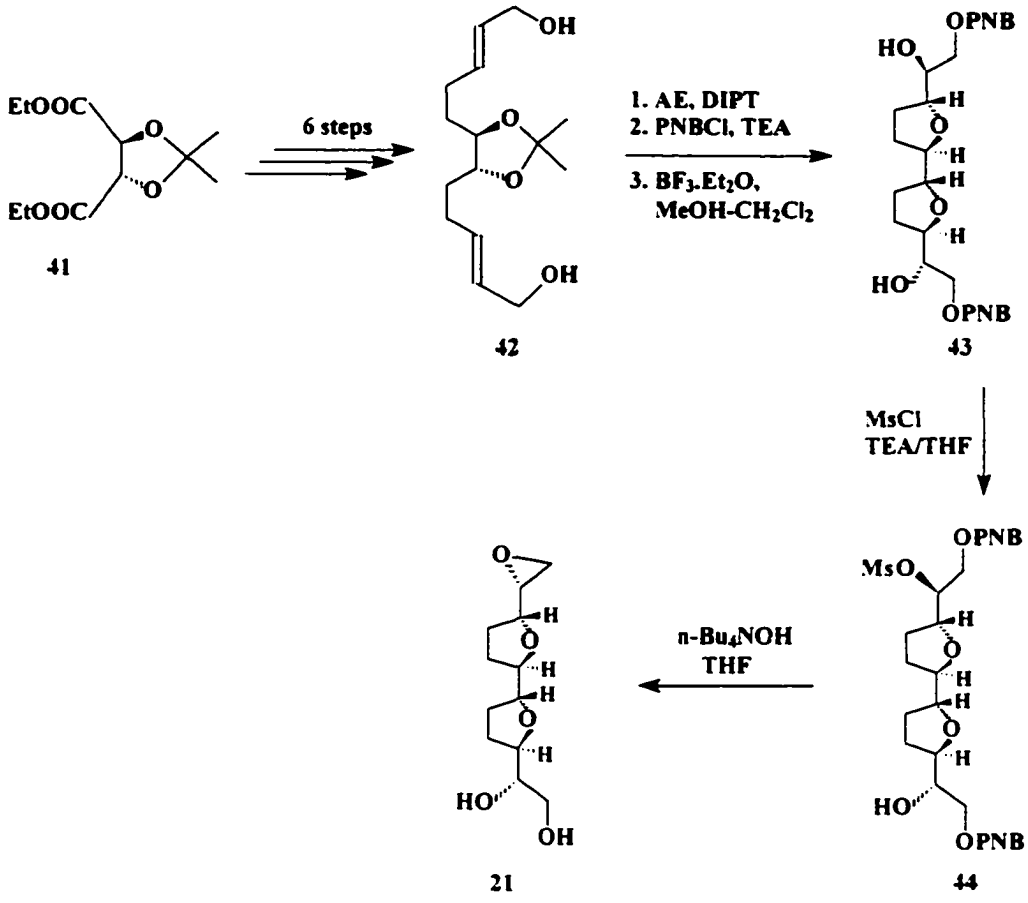
Scheme 7



The first key intermediate, the bis-allylic alcohol **37**, was obtained in four steps from E, E, E-1,5,9-cyclododecatriene **36**. The stereogenic centers in the bis-THF backbone were installed by sequential double Sharpless asymmetric epoxidation/Sharpless asymmetric dihydroxylation to give **38**. Treated with TFA resulted in an "inside-out" epoxide cascade reaction to produce the bis-THF **39**. With another two steps, a C2-symmetric *threo/trans/threo/trans/threo* diepoxide **40** was obtained. Like other bidirectional approachs, a major drawback of this strategy was the desymmetrization of

C2 symmetric intermediate. Treatment of **40** with lithium (trimethylsilyl)acetylide (0.5eq) in the presence of boron trifluoride etherate, provided less than 25% yield of a desymmetrized bis-THF monoepoxide. Opening of this epoxide with $C_7H_5{\equiv}C\text{-}Li$ afforded the bis alkyne **13**. Thirteen steps were required for the preparation of **13** from **36**.

Scheme 8

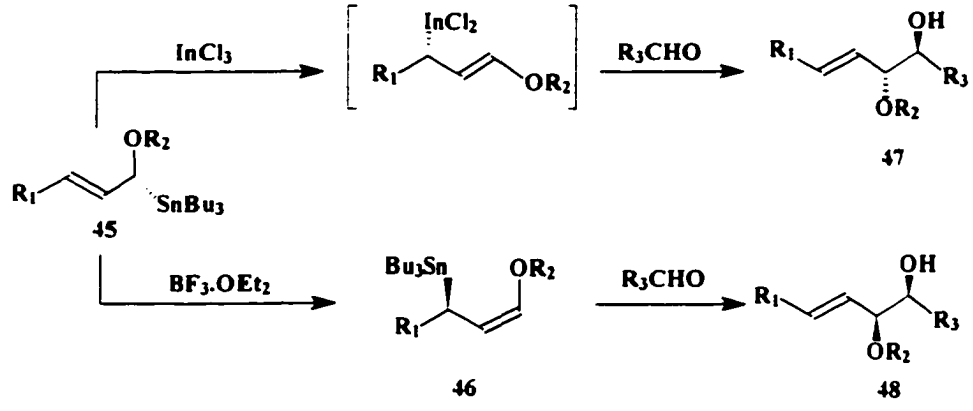


A related epoxide cascade strategy was developed by Sasaki for the synthesis of bullatacin. An intermediate, *trans-trans* diol **42** was obtained from diethyl 2,3-O-isopropylidene-D-tartrate **41** in six steps. Sharpless asymmetric epoxidation and "inside-

out" epoxide cascade strategy resulted in reaction bis-THF framework **43**. Desymmetrization of **43** was performed by monomesylation with 1.5 eq. MsCl to give **44** in 37% yield. Finally, the THF epoxide **21** was obtained by treatment of **44** with n-Bu_4NOH (Scheme 8).[22]

Marshall and co-workers developed a bidirectional approach based on the addition of optically active α-alkoxyallylic stannanes to aldehydes.[25] Chiral nonracemic α-alkoxyallylic stannanes **45** undergo 1,3-isomerization or transmetalation and subsequent S_E2' addition to aldehydes leading to either *syn* or *anti* monoprotected 1,2-diols **47** and **48** stereospecifically and with high diastereoselectivity (Scheme 9).[25a]

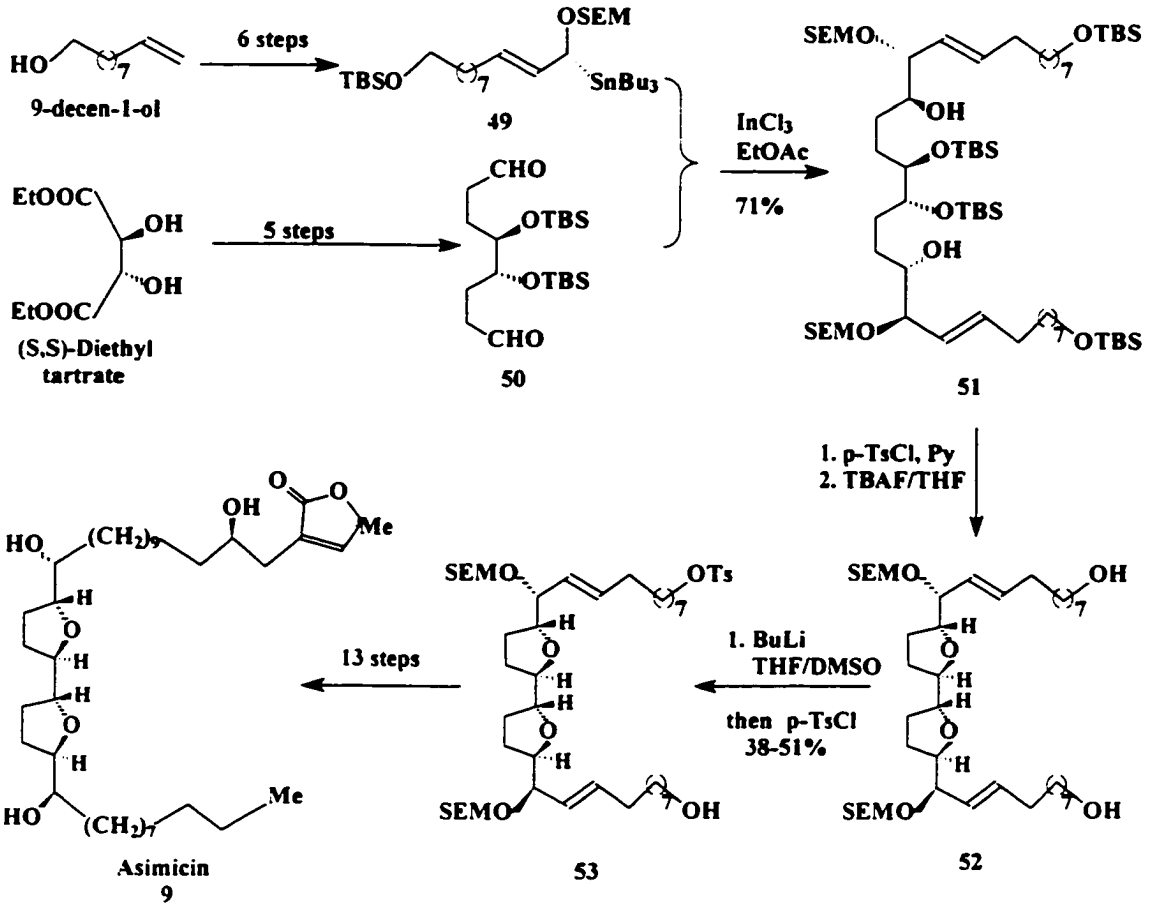
Scheme 9



Addition of the (R)-α-OSEM allylic stannane **49** to the dialdehyde **50** in the presence of $InCl_3$ afforded the bis-adduct **51** in 71% yield. Formation of the bis-tosylate and then treatment with TBAF in THF at 40 °C led to C2-symmetric bis-THF core **52**. In the desymmetrization step, the monotosylate **53** was obtained in 38 ~ 51% yield. The

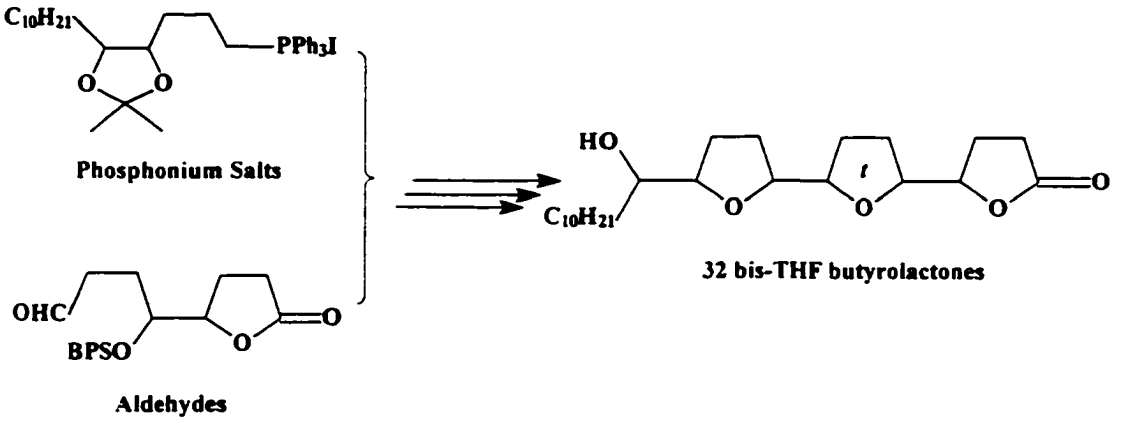
synthesis of **53** from (S,S)-diethyl tartrate and 9-decen-1-ol required 15 steps. Compound **53** was converted to asimicin in 13 additional steps (Scheme 10).[25b]

Scheme 10



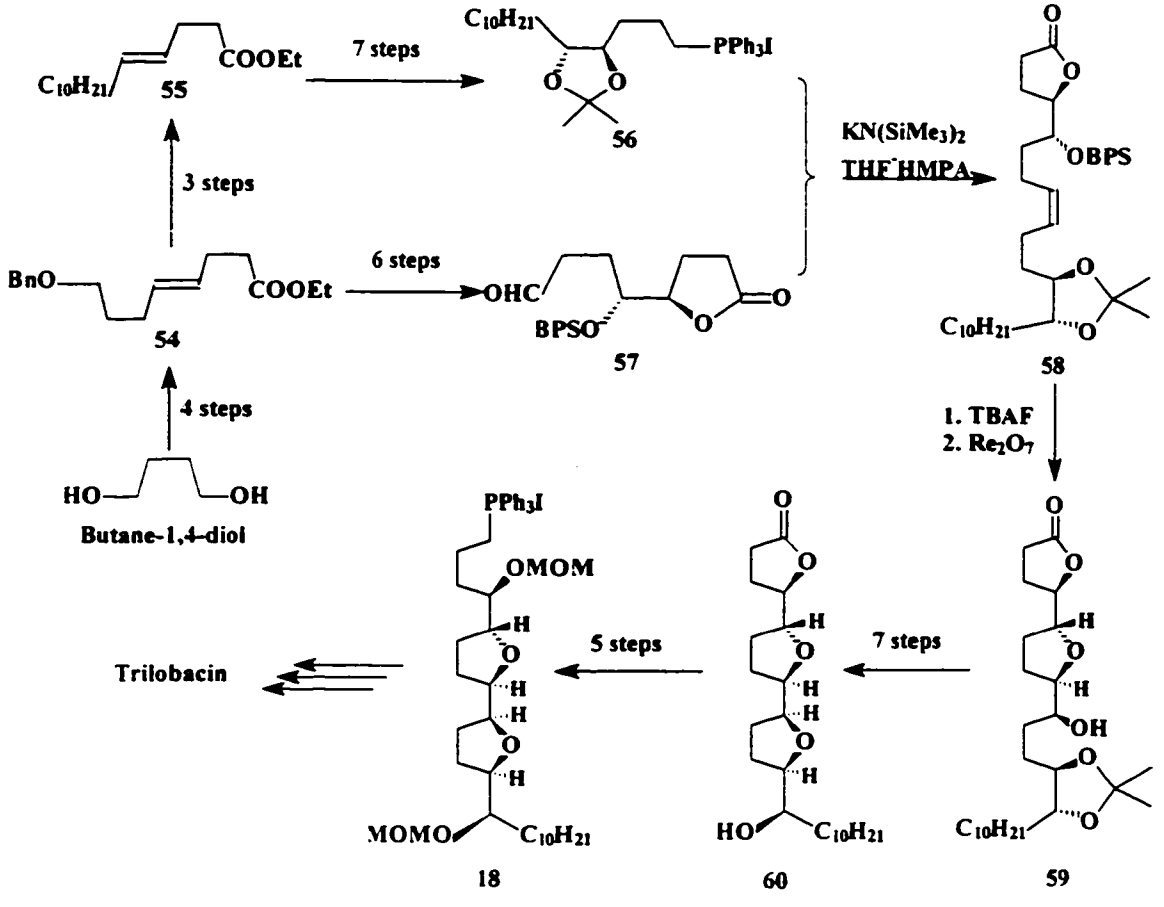
The desymmetrization problem may be avoided by using a convergent type strategy. The convergent approach is also better suited for combinatorial synthesis. The work of the Keinan group is illustrative. The approach combines the Sharpless asymmetric dihydroxylation (AD) reaction and the Rhenium (VII) promoted cyclization of 5-hydroxyl alkenes to *trans* 2,5-disubstituted THF's. In principle, 32/64 stereoisomers of the bis-THF butyrolactone can be synthesized from cross-coupling reactions between phosphonium salts and aldehydes synthons (Scheme 11).[21a]

Scheme 11



The synthesis of trilobacin is an example (Scheme 12). The phosphonium salt **56** and aldehyde **57** were prepared in 13 steps. The key reaction was the AD reaction on intermediates **54** and **55**, respectively. Wittig coupling of **56** and **57** produced Z-alkene **58**. Oxidative cyclization with Re_2O_7/lutidine provided the stereoselective *trans*-THF **59**, which was converted to the bis-THF **60** in seven additional steps. The key reactions in this sequence were the Mitsunobu inversion of the free alcohol, alcohol mesylation and conversion of the hydroxy mesylate to the THF. Compound **60** was converted to the phosphonium salt **18** in five additional steps. The synthesis of **18** from butane-1,4-diol required 34 steps, although the strategy is very convergent, the synthesis of specific compounds is very lengthy.[21a]

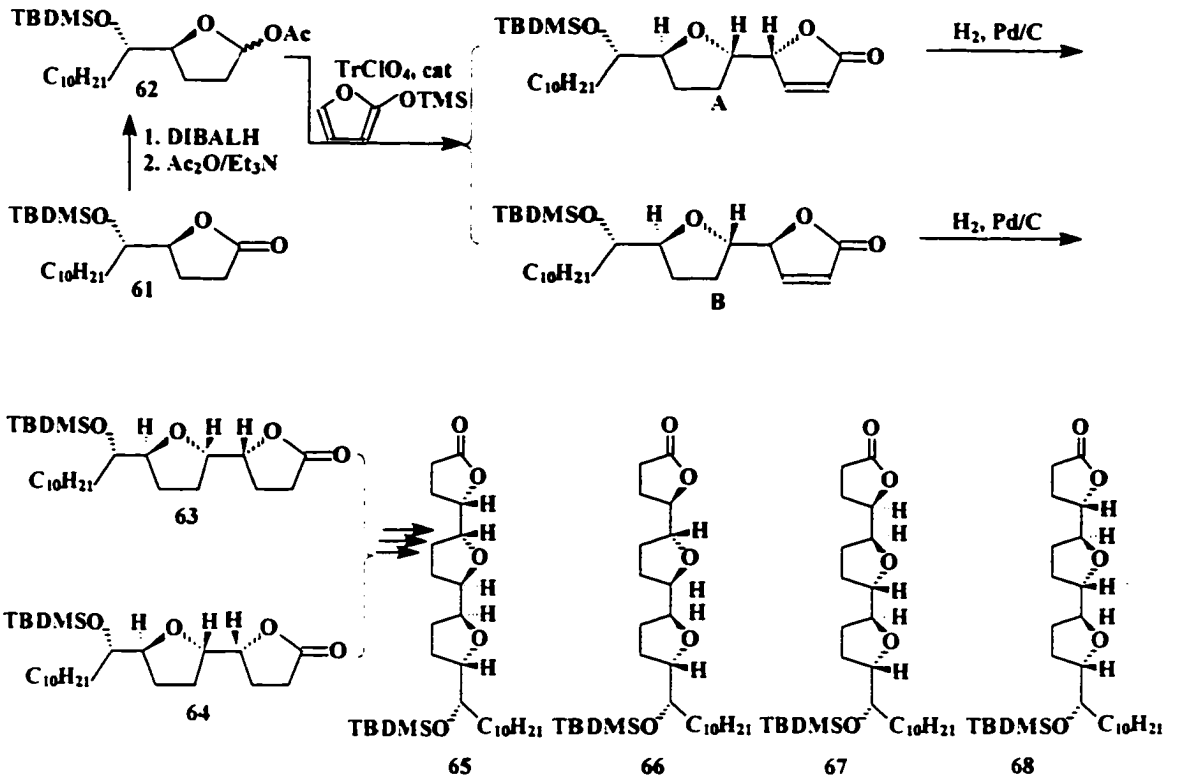
Scheme 12



Figadere developed an efficient iterative approach to oligo-THF's.[26] This involves the replicative C-glycosylation of anomeric acetoxytetrahydrofurans with [(trimethysilyl)oxy]furan (TMSOF). The silyl ether of (-)-muricatacin **61**, prepared in five steps from L-glutamic acid, was treated with DIBALH, followed by acetylation, to provide acetoxy derivative **62**. C-glycosylation of **62** with TMSOF afforded a separable mixture of only two adducts, the *trans-erythro* and *trans-threo* desired butenolides **A** and **B**. Hydrogenation of the products provided the butyrolactones **63** and **64** independently.

A second sequence of the reduction, acetylation, C-glycosylation, and hydrogenation transformation obtained four tricyclic lactones, **65**, **66**, **67**, and **68** (Scheme 13).

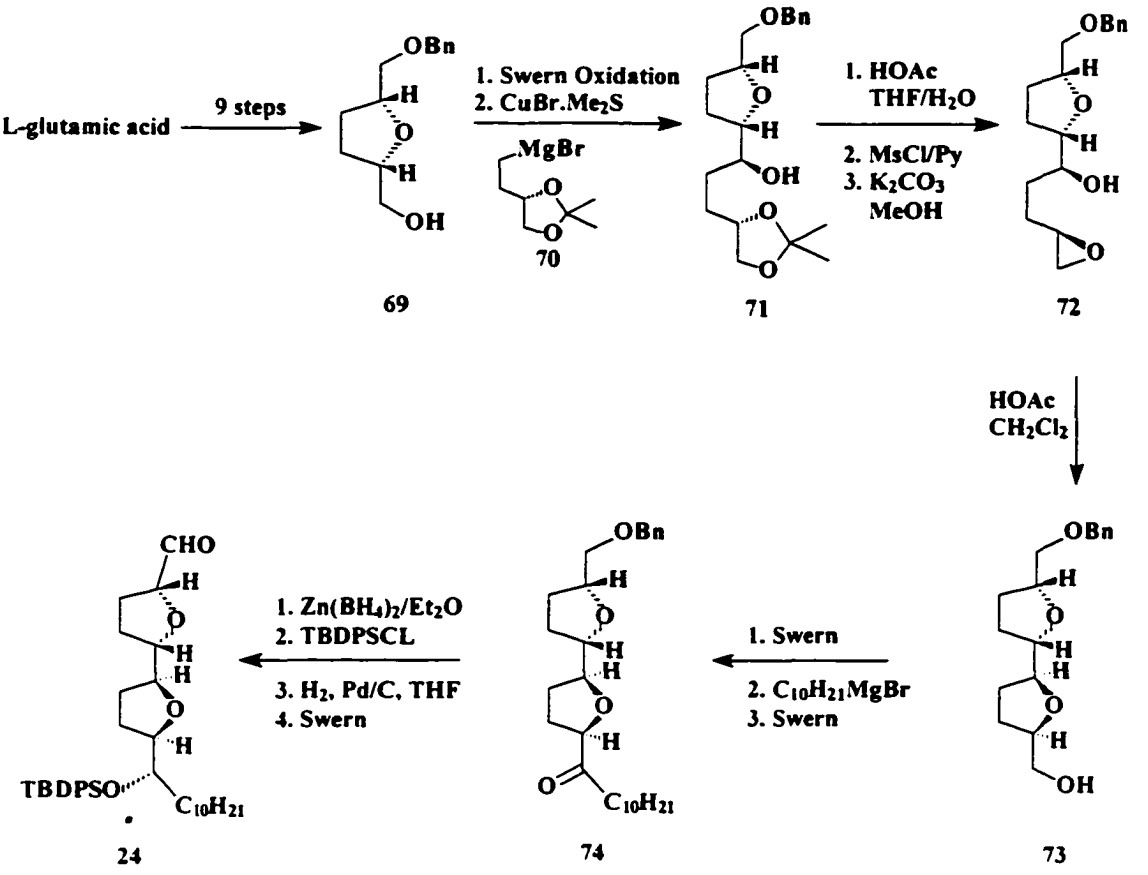
Scheme 13



Koert and co-workers developed a less convergent synthesis of rolliniastatin. The *cis* THF building block **69** was prepared in nine steps from L-glutamic acid (Scheme 14). After Swern oxidation to the corresponding aldehyde, a Cu(I) catalyzed reaction with the Grignard species **70** afforded the alcohol **71** (stereoselectivity: 93/7). The stereochemistry can be rationalized by a chelation controlled reaction pathway. Conversion of the acetonide into an epoxide, and intramolecular epoxide opening gave rolliniastatin bis-THF core **73**. Swern oxidation followed by *in situ* reaction with decyl magnesium bromide and a second Swern oxidation on the resulting alcohol produced the ketone **74**.

The bis-THF synthon **26** was obtained after additional four steps. (total 21 steps from L-glutamic acid).[23]

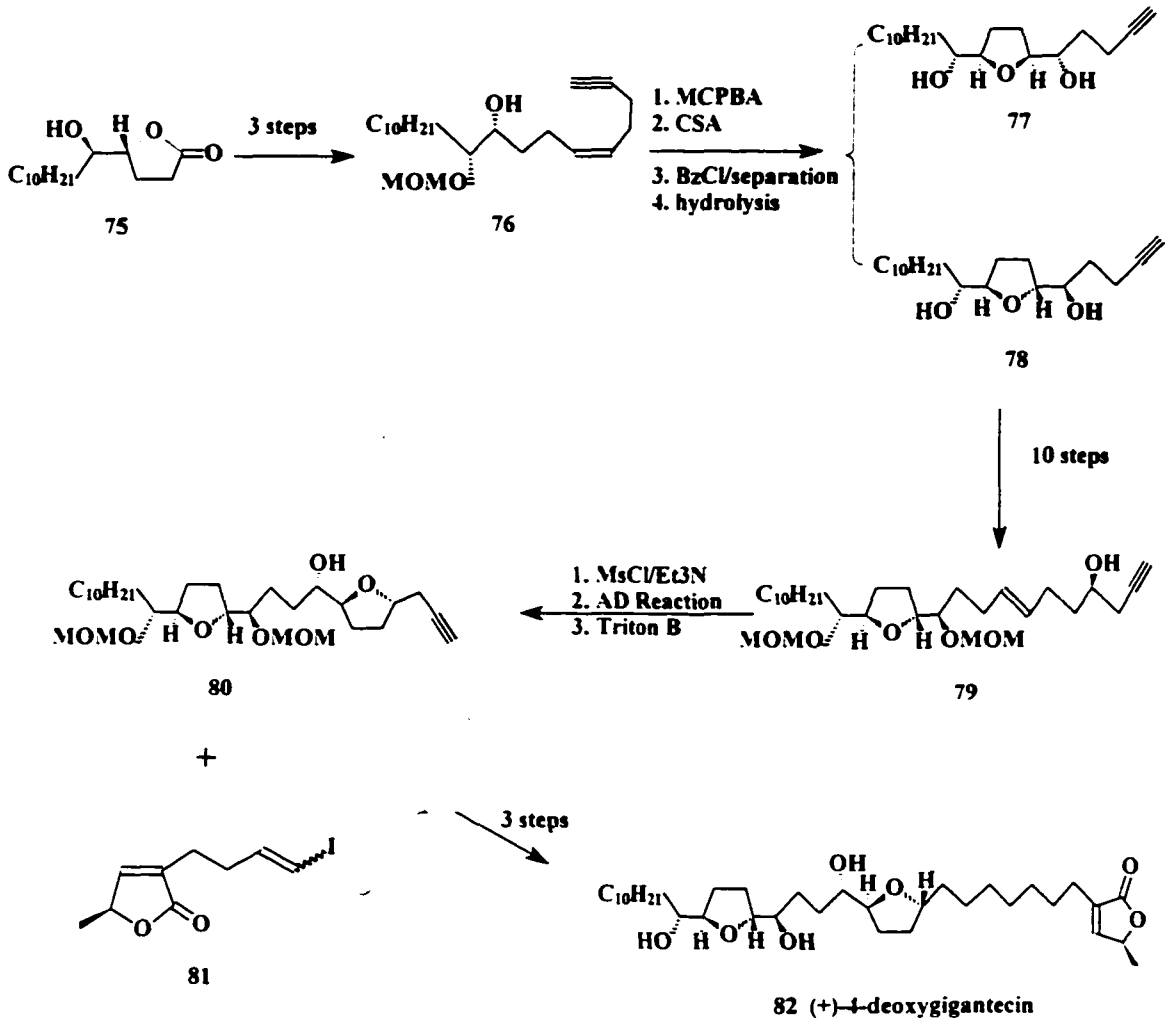
Scheme 14



The first example of the synthesis of an non-adjacent bis-THF type actogenin was recently reported by Tanaka's group.[27] The first THF ring was prepared through a modestlyly stereoselective epoxidation of **76**, and subsequent acid-catalyzed cyclization, giving an inseparable mixture of THF diastereoisomers. The desired mono-THF intermediate **78** was isolated after two additional steps. Ten further steps provided the precursor **79** for the second THF-ring. Mesylation of **79**, followed by AD reaction and cyclization, led to the non-adjacent bis-THF synthon **80**. Application of Hoye's protocol,

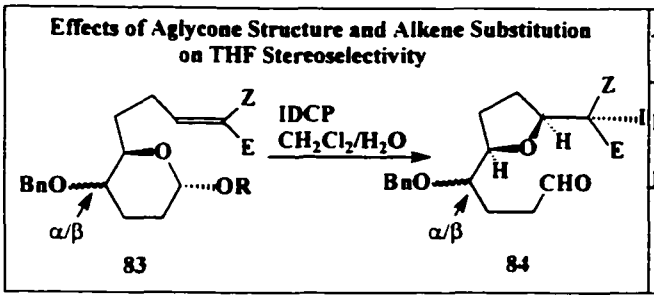
Pd(0)-catalyzed cross coupling reaction of **80** with vinyl iodide **81**, followed by selective hydrogenation and subsequent deprotection of MOM group, gave (+)-4-deoxyigigantecin **82** (Scheme 15).

Scheme 15



Our work in this area started with the development of a strategy for the preparation of 2,5 disubstituted THF's **84**. The method is based on the haloetherification reaction of alkenylated monosaccharides **83** (Scheme 16).

Scheme 16

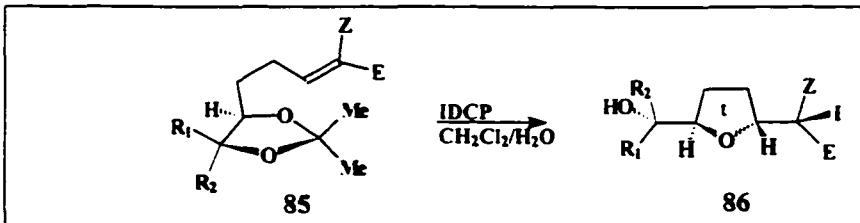


Terminal (E=Z=H) c : t	Z(Z=Pr; E=H) c : t	E(Z=H; E=Pr) c : t
R=C(CH$_3$)$_3$ 3.5 : 1	1 : 2	3.5:1
R=CPh$_3$ 20 : 1	8 : 1	>10:1

IDCP= Iodonium Dicollidine Perchlorate

It has been shown: <i> Both terminal and 1,2-disubstituted E or Z-alkenes, gave high *cis*-selectivity for bulky trityl aglycone substituents. <ii> When the electronegativity of the aglycone increased, the reactivity of the acetal decreased; These results are summarized in scheme 16. It appeared that both stereoselectivity and reactivity could be controlled by varying the aglycone substituent.

Scheme 17



	Terminal(E=Z=H) c : t	Z(Z=Pr; E=H) c : t	E(Z=H; E=Pr) c : t
R_1=Bu, R_2=H	only t	only t	only t
R_1=H, R_2=Bu	only t	only t	only t
Yield	80-90%		

Subsequently a methodology to for *trans*-2, 5 disubstituted THF was developed. Iodoetherfication of the isopropylidene terminal, Z and E alkenes **85** produced the *trans* THF **86** as the only isomer in greater than 88% yield (Scheme 17).

This thesis will deal with the application of these results to the synthesis of the bis-THF subunits of the THF-acetogenins and related structures.

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Chapter 2

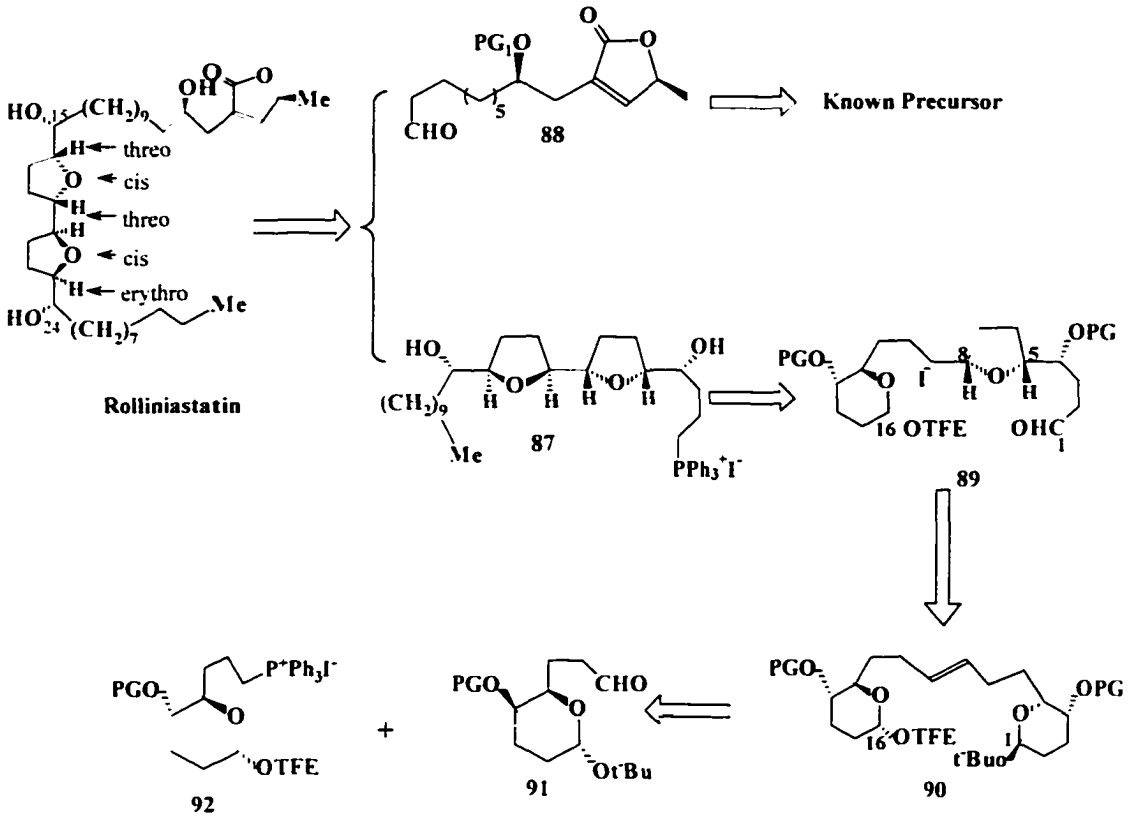
Bis-Pyranoside Alkenes:

Novel Templates for the Synthesis of Adjacently Linked Bis-THF's

The following are important aspects of the haloetherification reaction of C6 allylated pyranosides: (1) obtention of highly functionalized *cis*-2,5-disubstituted THF's which have similar substitution patterns as the THF acetogenins and ionophore antibiotics. (2) the relative reactivity of the pyranoside can be reduced by using an electronegative aglycone. These features allow for a modular synthesis of complex, contiguously linked THF's. Our plan centers on the initial construction of a bis-THF-diol core, which may be converted to bis-THF acetogenins or polyether subunits. Rolliniastatin, a member of the *c/th/c* bis-THF diol core of the acetogenins, was chosen as the initial synthetic target.

Retrosynthetically, rolliniastatin may be disconnected into a bis-THF synthon **87** and a butenolide synthon **88** (Scheme 17). Prefabricated derivatives of **87** and **88** may be coupled *via* established Wittig strategy, which was adopted by Keinan.[21] Our strategy is to use a bis-saccharide-E-alkene **90** as precursor for the *c/th/c* bis-THF core **87**. This precursor may be prepared by the coupling of two monosaccharide components. One of the monosaccharide fragment **91** is equipped with an activating, *cis* directing aglycone (t-butyl or trityl) and the other, **92,** with a deactivating aglycone (trifluoroethyl). Treatment of **90** with IDCP will result in reaction of the t-butyl pyranoside

Scheme 17



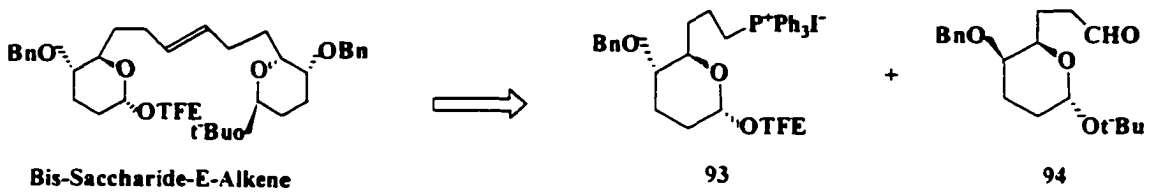
residue, leading to iodo-THF-trifluoroethyl pyranoside **89**. The stereochemistry of this reaction determines the configuration of the second THF, which will be formed by displacement of the halide substituent by the ring oxygen of the deactivated pyranoside. The following should be noted: <i> The bis-saccharide precursor **90** contains the ten carbons (C4-C13) corresponding to the C15-C24 segment of rolliniastatin; <ii> The stereochemistry of C4/C5 (*threo*) and C12/C13 (*erythro*) is identical to C15/C16 and C23/C24 on rollinastatin. The main synthetic steps are: (1) preparation of the D-monosaccharide components; (2) coupling of two D-monosaccharides to give a bis-saccharide-E-alkene **90**; (3) regioselective cyclization of **90** to the mono-THF halopyranoside **89**; (4) formation of the second *cis* THF-ring. In principle, by variation of

the stereochemistry of the pyranoside subunits and that of the connecting alkene, it would be possible to prepare 32 of the 64 possible diastereoisomers of the bishydroxylated bis-THF residue, i.e. the stereoisomers which contain at least one *cis*-THF.

Preparation of Aldehyde and Phosphorane Components

Our initial plan was to assemble the bis-saccharide-E-alkene **90** through the Schlosser variation of the unstabilized Wittig reaction of **93** and **94** (Scheme 18).[28] The D-*erythro* and D-*threo* subunits **93** and **94** were prepared via standard carbohydrate procedures.[29]

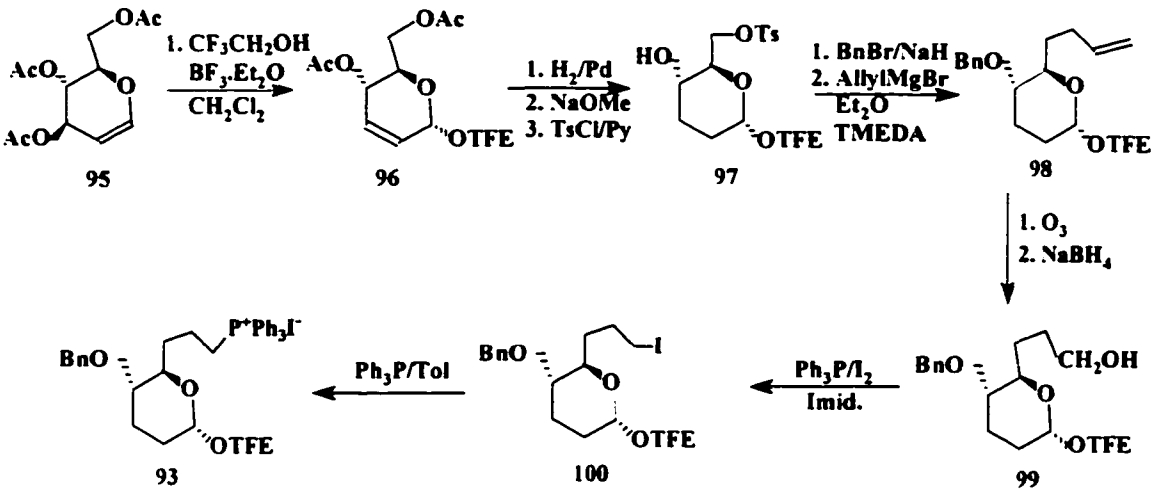
Scheme 18



The synthesis started with the well-known Ferrier reaction on commercially available tri-O-acetyl-D-glucal **95** with trifluoroethanol and BF_3 in dichloromethane.[30] This provided the desired glycoside **96** in 90% yield. A sequence of hydrogenation over Pd(0) on carbon (98%), deacetylation with NaOMe[31] (85%), and selective tosylation of the primary alcohol[32] (83%) furnished the trifluoroethyl-pyranoside **97** on large scale (>5g). The benzyl ether of **97** was prepared under standard conditions and treated with allymagnesium bromide in the presence of TMEDA to give 2,3-dideoxy-glucopyranoside **98** in 82% yield. The use of TMEDA in this reaction was found to give superior results compared with the CuI mediated reaction.[29b] Ozonolysis of **98** followed by sodium

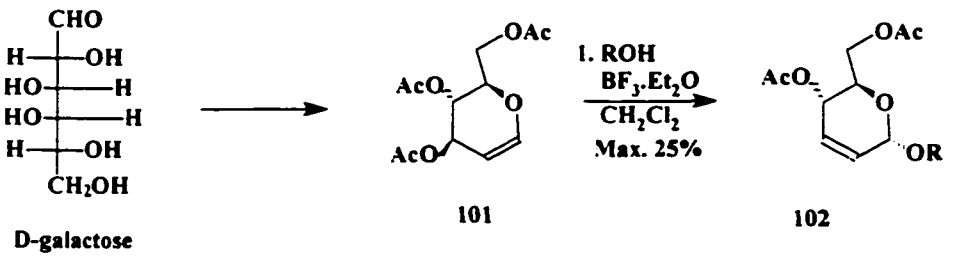
borohydride treatment of the crude aldehyde product led to the alcohol **99** in 85% yield from **98**. Finally, the desired phosphonium salt **93**, was prepared in by iodination of **99**,[33] followed by reaction of the resulting iodide **100** with triphenylphosphine.[34] The overall yield for the two steps was 80% (Scheme 19).

Scheme 19



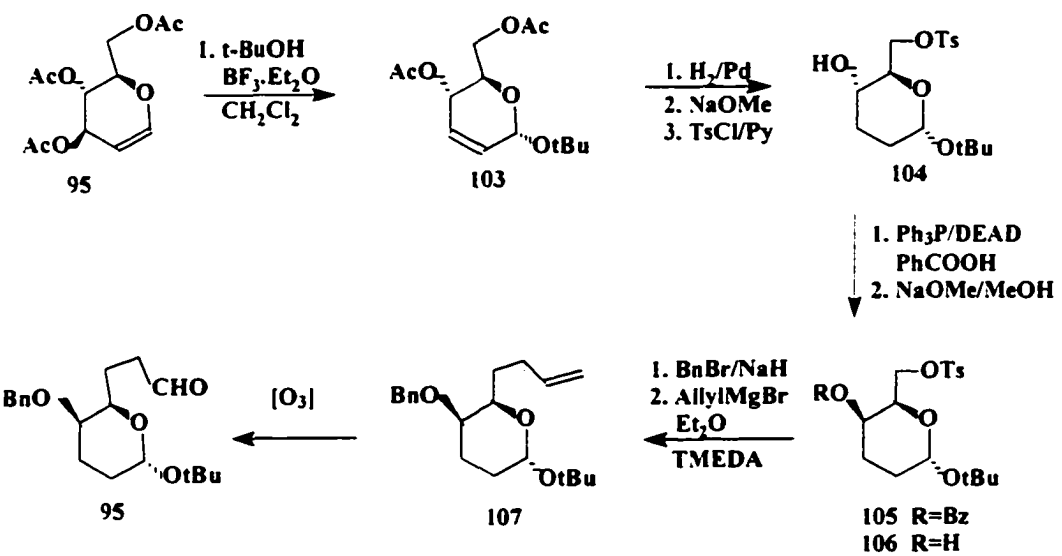
Next we turned to the preparation of the D-*threo*-subunit **94**. The initial plan was to apply the Ferrier strategy to tri-O-acetyl-D-galactal.[28] Tri-O-acetyl-D-galactal **101** is not commercially available and was prepared via a three-step literature procedure from D-galactose. Unfortunately, the Ferrier reaction was not as efficient as for the *gluco* system. Only 25% yield of product **102** was formed (Scheme 20).

Scheme 20



An alternative plan is to invert the C-4 configuration of a D-*erythro* pyranoside. As detailed earlier, a sequence of the Ferrier reaction with t-butyl alcohol, hydrogenation, deacetylation and selective tosylation applied to tri-O-acetyl-D-glucal **95** provided the t-butyl-6-O-tosyl-erythro-D-pyranoside **104**. Treatment of the alcohol **104** under Mitsunobu conditions with benzoic acid as the nucleophile led to the *threo*-D- pyranoside **105**. The benzoyl group was then removed by treatment of **105** with sodium methoxide in methanol to provide **106** in 80% overall yield from the *erythro*-D derivative **104** (Scheme 21). The NMR spectrum for **104** showed a large coupling constant between H-4 and H-5 (J=10.5Hz), indicating that C4 substituent was equatorial. By comparison, the corresponding value in **106** was less than 3 Hz, indicating that the C4 substituent was axial. Using a similar sequence of benzylation, alkylation and ozonolysis as in the *erythro* system, the D-*threo* synthon **94** was obtained in 60% from **106** (Scheme 21).

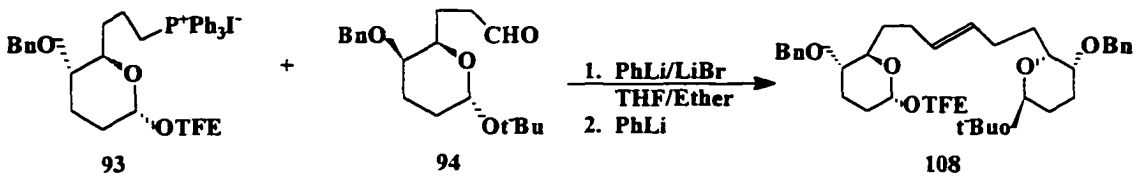
Scheme 21



Assembly of the Bis-Saccharide-E-Alkene Precursor

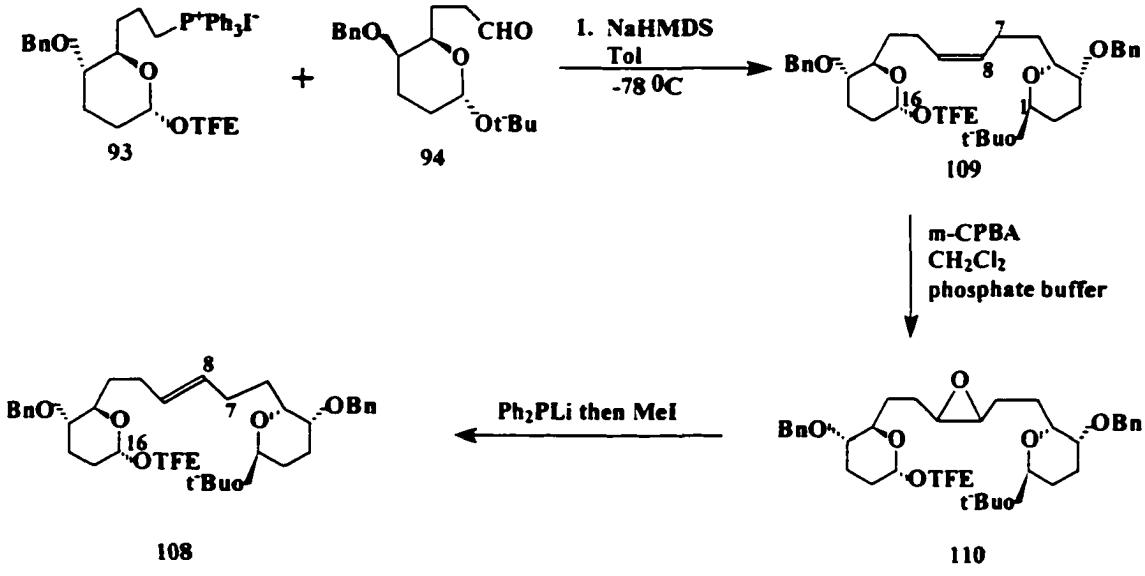
The Schlosser-Wittig procedure was then applied to **93** and **94**.[28] The phosphonium salt **93** was treated with 1 equivalent of PhLi/LiBr in 1:1 THF/ether, followed by addition of aldehyde **94** and then an additional equivalent of PhLi. However, all attempts at this procedure resulted in low yields and poor stereoselectivity (Scheme 22).

Scheme 22



The use of the standard Wittig procedure for unstabilized ylide is experimentally simpler and has been shown to give good yield and high Z-alkene selectivity.[35] Therefore, an alternative plan is to first prepare the Z-alkene, and obtain the E-alkene via stereospecific inversion of the alkene configuration.[36] The Wittig reaction was carried out by treatment of **93** in toluene with sodium bis(trimethylsilyl) amide, followed by addition of aldehyde **94** to the ylide. The t-butyl-Z-trifluoroethyl bis-pyranoside alkene **109** was obtained in 84% yield and greater than 95% stereoselectivity. The E isomer **108** was obtained by conversion of **109** to the epoxide **110** with mCPBA, followed by opening of the epoxide with Ph_2PLi and methylation of the oxido-phosphine with MeI. The overall yield of **108** from **94** was 65% (Scheme 23). The stereochemistry of the Z and E alkenes was established by comparison of ^{13}C chemical shifts: Z alkene, C7 (δ23.62) and C10 (δ23.72), E alkene: C7 (δ28.98) and C10 (δ30.20).[35]

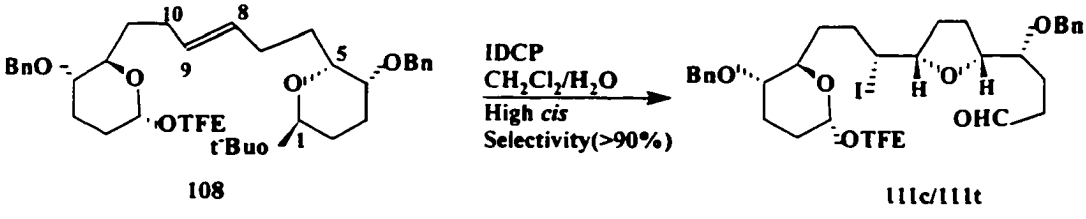
Scheme 23



Iodocyclization of the Bis-pyranoside Alkenes

Treatment of bis-saccharide-E-alkene **108** with IDCP in wet dichloremethane gave a mixture of *cis* and *trans* mono-THF-iodides **111c:111t** in 70% yield (Scheme 24).[37]

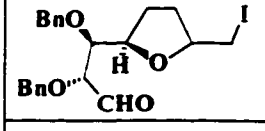
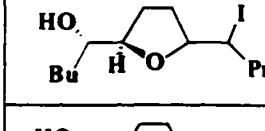
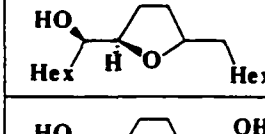
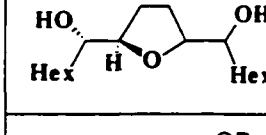
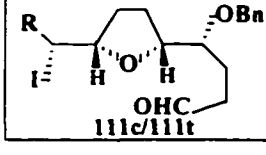
Scheme 24



The mixture was inseparable by chromatography. The *cis* stereochemistry was initially assigned on the basis of our previous results with related pyranoside alkenes.[37, 38] and confirmed by comparison of the ^{13}C NMR data of the mixture with that of known *cis* and *trans* THF's. For these structures at the ^{13}C signals for the methylene carbons in the *trans* isomer occur consistently downfield relative to those of the *cis* isomer (Table 1).[17c, 37, 38, 39]

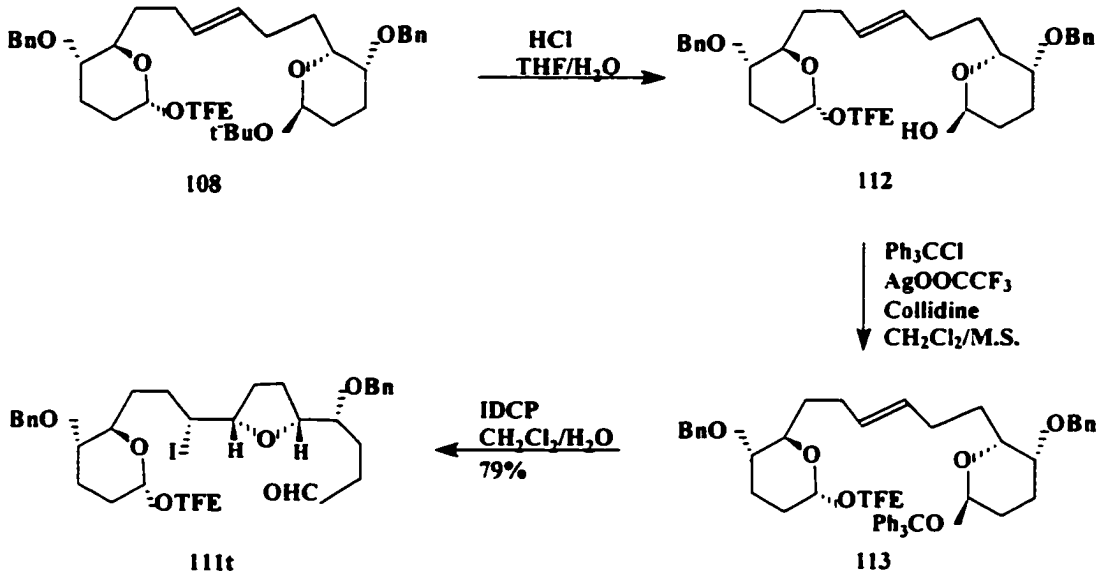
Therefore, the upfield (δ32.2 and δ31.7) resonance for the methylene carbons of the THF ring were assigned to the *cis* isomer, and the downfield (δ33.5 and δ33.0) to the *trans* isomer. The ratio of *cis* and *trans* products was about 9:1 according to ^{13}C NMR spectrum.

Table 1: Methylene Resonances for *trans* and *cis* THF Isomers

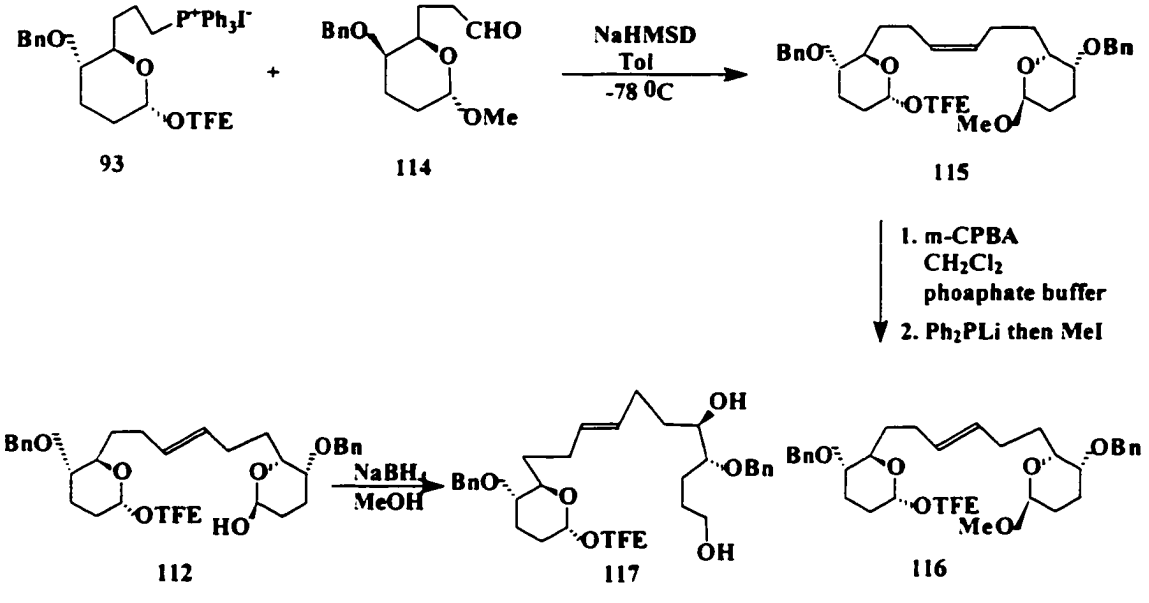
	cis		*trans*		Method of Assignment of Stereochemstry
	a	b	a	b	
	27.32	31.54	27.90	32.58	Degradation to the Known 5-methyl-THF-2-Methanol
	28.45	31.59	28.45	32.89	Observation of an NOE between the carbinol protons in the cis-THF
	27.80	31.40	28.40	32.40	NOE and Synthesis
	24.10	28.40	25.20	28.60	NOE and Synthesis
 111c/111t	31.70	32.20	33.0	33.50	NMR and Comparison

It was expected from the earlier work that the trityl pyranoside should give higher *cis* selectivity. Therefore, the trityl bis-pyranoside E-alkene **113** was prepared. Selective hydrolysis of the t-butyl glycoside gave the lactol **112** which was treated with trityl chloride and silver trifluoroacetate to give **113**.[37] Treatment of **113**, under the standard haloetherification conditions, led exclusively to the *cis*-THF product **111c** in 79% yield (Scheme 25).

Scheme 25



Scheme 26

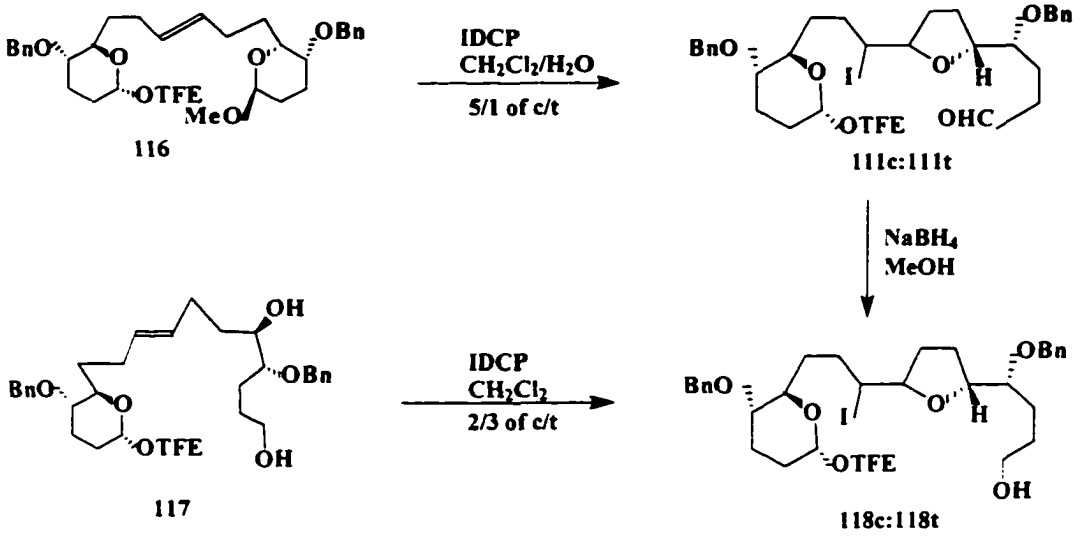


For comparison, methyl E-trifluoroethyl bis-saccharide alkene **116** and hydroxy alkene **117** were prepared, since the iodocyclizations of these substrates were expected to give higher *trans* selectivity. Firstly, the Z-alkene **115** was obtained through a Wittig coupling

reaction of the phosphonium salt **93** and aldehyde **114**. Stereospecific inversion of **115** as described earlier gave the E-alkene **116** in 75% yield. The diol **117** was obtained by reduction of the previously described lactol **112** with sodium borohydride (Scheme 26).

Treatment of **116** under the standard cyclization conditions provided a 5:1 mixture of **111c:111t**. The cyclization of the hydroxy alkene **117** with IDCP in anhydrous dichloromethane gave a 2:3 mixture of **118c:118t**. For comparison, sodium borohydride reduction of the 5:1 mixture of **111c:111t** which was obtained from the cyclization of the methyl bispyranoside **116**, gave a 5:1 mixture of the diol products **118c/118t**. (Scheme27).

Scheme 27

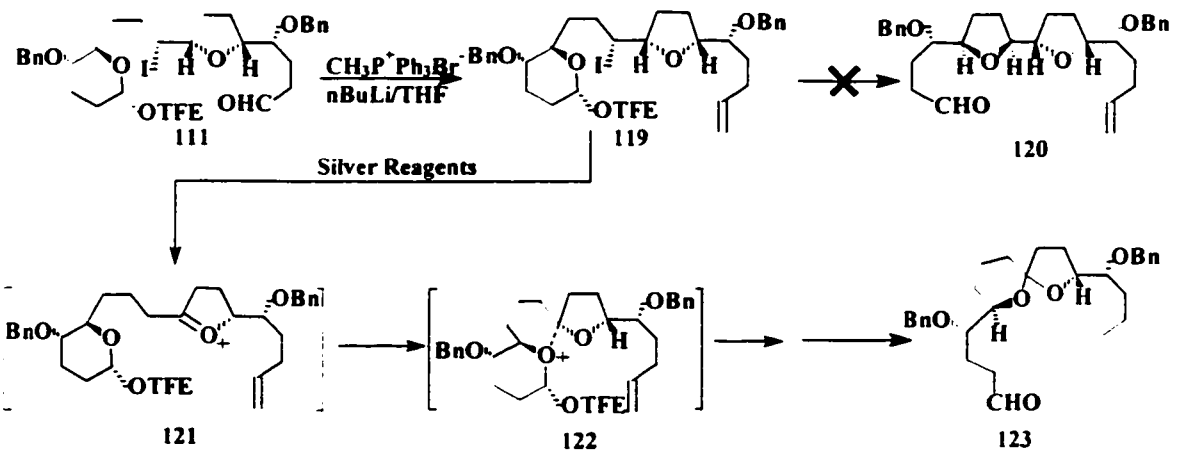


In summary, the results of the cyclization of these more complex alkene substrates were consistent with the results for the simple monosaccharide systems. The pyranoside template showed an intrinsic *cis* selectivity, and the presence of a bulky aglycone led to high selectivity.

Formation of the Second THF Ring

It was our hope that a mono-THF-halopyranoside derivative like **119** could be directly converted to a bis-THF structure, *via* a second neighboring group participation reaction. Therefore, **111c** was elaborated to **119** by reaction with methylene triphenylphosphorane.[40] Compound **119** was treated with several different silver reagents. Unfortunately, in all cases, THF formation to **120** was unsuccessful. The NMR data suggested that the major product was the spiroketal **123** ($^1H/^1H$ COSY, δ9.32: CHO, δ106.50: ketal carbon). It is likely that iodide cleavage occurs with hydride migration to give the oxocarbonium ion **121**. Ring oxygen attack in **121** leads to the tricyclic THP-oxonium **122** which fragments to the spiroketal aldehyde **123**.

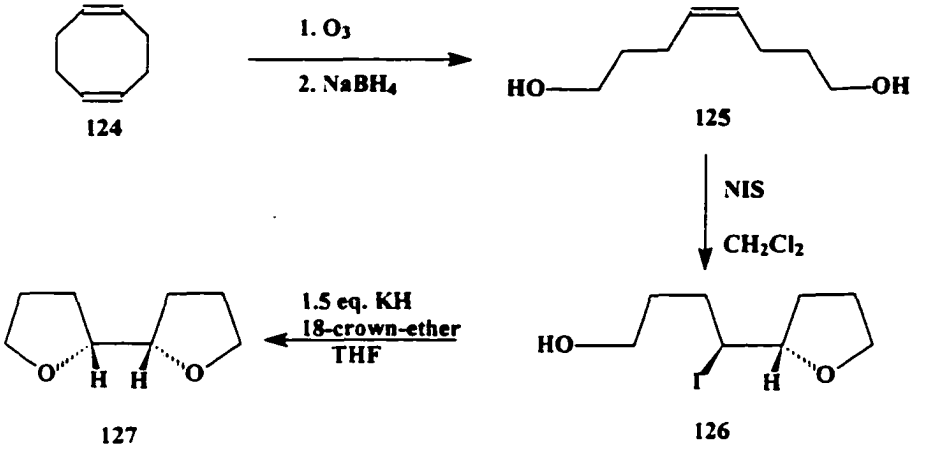
Scheme 28



An alternative plan for formation of the bis-THF is a base mediated cyclization of a hydroxyl halide derivative. In order to develop conditions for this reaction, the model compound **126** was prepared. Ozonolysis of the commercially available 1,5-

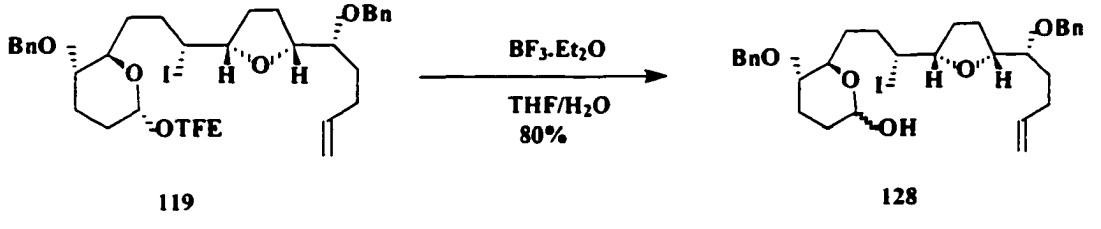
cyclooctadiene **124** followed by aldehyde reduction with sodium borohydride led to Z-4-octene-1, 8-diol **125**.[41] NIS promoted cyclization of **125** in dichloromethane afforded **126** (Scheme 29). Formation of second THF ring was attempted using different bases and solvents. The major side products in these reactions were elimination and formation of the spiroketal related to **123**. Best results were obtained with 1.5eq KH/18-crown-ether/THF which afforded a 61% yield of **127**.

Scheme 29



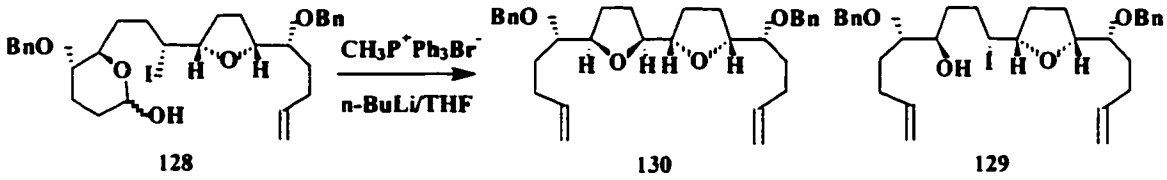
In order to apply these conditions to the rolliniastatin system, the pyranoside **119** was first converted to the lactol **128**. This was accomplished by adding 20eq. $BF_3.Et_2O$ in THF/H_2O to **118** in small portions over three days. The lactol mixture **128** was obtained in 80% yield. (Scheme 30).

Scheme 30



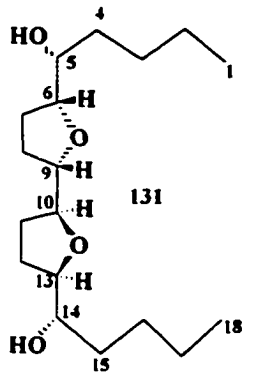
The lactol mixture **128** was then treated with methylene triphenylphosphorane (THF -78°C-rt) in order to obtain hydroxyiodide alkene **129**. Surprisingly, these conditions led directly to the required bis-THF **130** in 70% yield. Evidently, the first formed alkene alkoxide is sufficiently nucleophilic and this results in THF formation. (Scheme 31).

Scheme 31

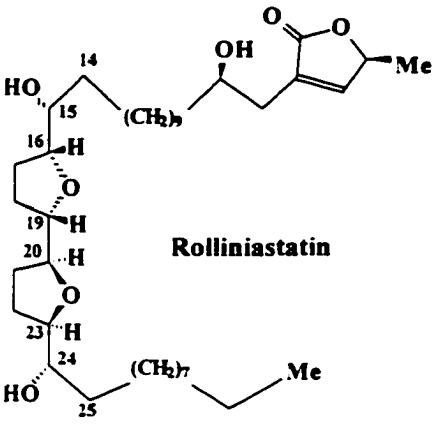


Formation of the second THF with inversion at the iodide carbon leads to the *c/th/c/th* core found in rolliniastatin, whereas retention of configuration would give the *t/th/c/th* core found in trilobacin. Therefore, in order to confirm the stereochemistry of the bis-THF, **130** was hydrogenated to **131** and the ^{1}H and ^{13}C NMR chemical shift data for **131** and natural rolliniastatin and trilobacin were compared (Table 1).[8, 9b] The high degree of correlation with rolliniastatin supports the *c/th/c* structure shown for **131**. The above results provide the groundwork for the total synthesis of rolliniastatin. Reduction of **111c** with sodium borohydride to alcohol derivative **132** followed by acetal hydrolysis to lactol **133**, and then Wittig reaction should give the bis-THF **134** (Scheme 32).

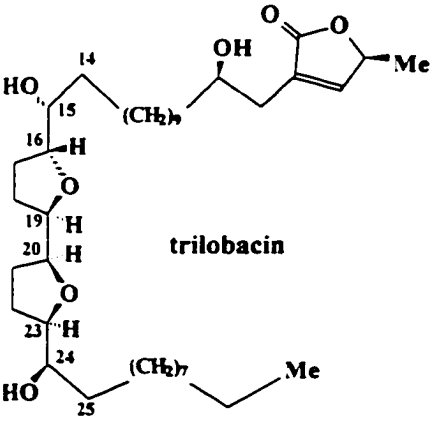
Table 2: Spectral Comparison of Synthetic Bis-THF with Natural Product



	1H NMR (ppm)	13C NMR (ppm)
4	1.48m	34.0
5	3.41m	74.1
*6	3.86m	83.1
7	1.72-1.98m	28.8
8	1.72-1.98m	28.2
*9	3.86m	81.2
*10	3.86m	81.2
11	1.72-1.98m	28.0
12	1.72-1.98m	28.5
13	3.86m	83.0
14	3.86m	71.9
15	1.48m	32.6

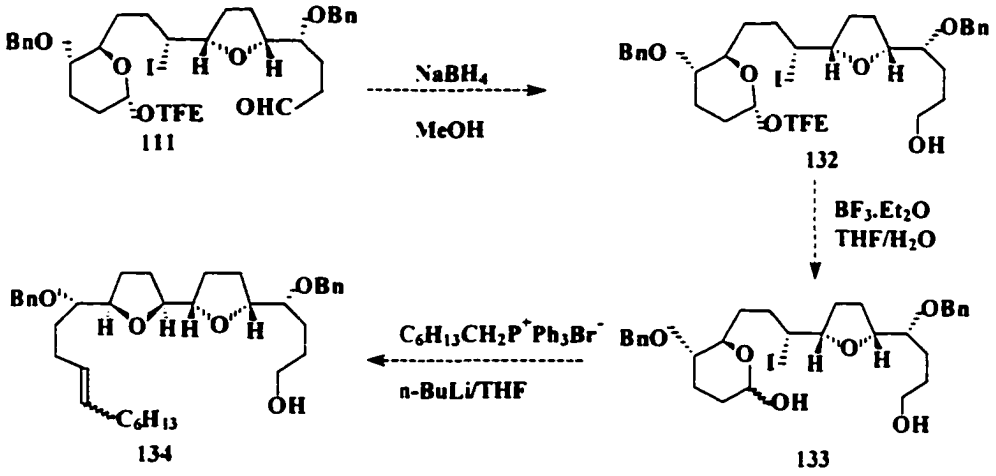


	1H NMR (ppm)	13C NMR (ppm)
14	1.50m	34.1
15	3.38m	74.0
*16	3.85m	83.0
17	1.7-1.9m	28.7
18	1.7-1.9m	27.8
*19	3.85m	81.1
*20	3.85m	81.0
21	1.7-1.9m	27.8
22	1.7-1.9m	28.4
23	3.85m	83.0
24	3.85m	71.8
25	1.45m	32.8



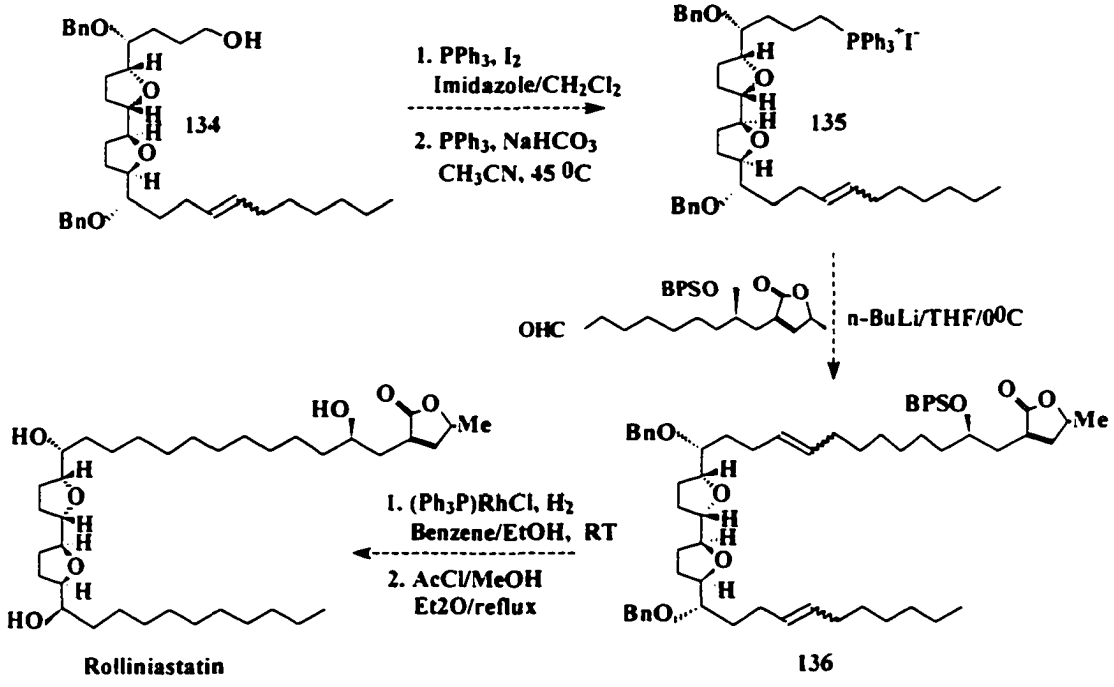
	1H NMR (ppm)	13C NMR (ppm)
14	1.41m	33.6
15	3.36m	74.6
*16	3.83m	83.3
17	1.7-2.0m	28.2
18	1.8-1.9m	29.0
*19	3.97m	81.6
*20	4.05m	80.9
21	1.7-2.0m	29.4
22	1.7-2.0m	29.5
23	3.83m	82.6
24	3.39m	73.9
25	1.41m	34.2

Scheme 32



The bis-THF synthon **134** is closely related to the bis-THF **70** from Keinan's trilobacin synthesis.[21] The same synthetic procedures may be applied for completion of the synthesis of rolliniastatin (Scheme 33).

Scheme 33



Generality of bis-THF Forming Strategy

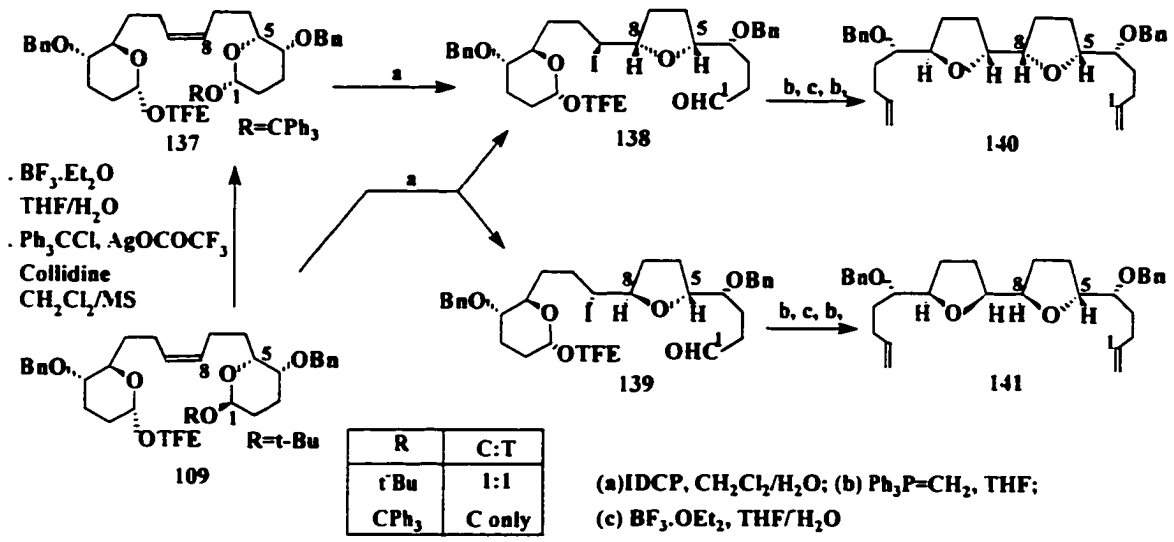
The generality of the bis-THF methodology was uncertain, because the stereoselectivity of the halocyclization could vary with the geometry of alkene, and the ease of halide displacement affected by the stereochemistry of the THF iodide. The bis-THF methodology was therefore tested on bis-pyranoside Z-alkene precursors.

Standard iodoetherification of the t-butyl-Z-trifluoroethyl bis-pyranoside alkene **109** gave a separable 1:1 mixture of *cis:trans* mono-THF iodides **138** and **139** in 73% yield. As before, the *cis* and *trans* configuration of **138** and **139** were distinguished by careful comparison of ^{13}C NMR chemical shifts: C6 (δ32.23) and C7 (δ30.48) for *cis*-THF and C6 (δ32.65) and C7 (δ31.44) for *trans*-THF.

The mixture of trityl-Z-trifluoroethyl pyranoside alkenes **137** was obtained from **109**, over two steps involving selective hydrolysis of the t-butyl glycoside, followed by silver trifluoroacetate promoted tritylation of the resulting lactol. Not surprisingly, based on the superior stereodirecting ability of the trityl aglycone, the trityl-Z-trifluoroethyl pyranoside alkene **137** gave the *cis*-THF iodide **138** exclusively in 86% yield.

The mono-THF iodides **137** and **138** were next individually treated under the identical three step sequence which was applied to the mono-THF-iodide **111**. The desired bis-THF compounds **140** and **141** were obtained in yields of 30 and 40% respectively (Scheme 34).

Scheme 34



Comparisons of NMR spectra for compounds **130** (*er/c/th/c/th*), **140** (*er/t/er/c/th*) and **141** (*er/c/er/t/th*), and the saturated derivatives **131** (*er/c/th/c/th*) and **142** (*er/c/er/t/th*) are shown in Figure 5 and Figure 6. Therefore, the high *cis* stereoselectivity of the halocyclization holds for both E or Z alkene precursors, provided that a trityl aglycone is used. Also the method for halide displacement appears to be general for hydroxyiodide of different stereochemical patterns.

In summary the high *cis* stereoselectivity observed with these bis-pyranoside alkenes provide a synthetic strategy for acetogenins containing *cis*-THF rings. Theoretically, 32/64 possible stereoisomers can be prepared through bis-saccharide-alkenes like **143** in which one of the monosaccharide fragment is equipped with an activated *cis* directing aglycone (trityl) and the other with a deactivating aglycone (trifluoroethyl) (Scheme 35). The convergent strategy is especially well suited to polyether structures which do not have a high degree of symmetry, as found for example in Ionophore A204.[42]

Fig. 5 NMR Spectrum Comparison of Bis-THF's 130, 140 and 141

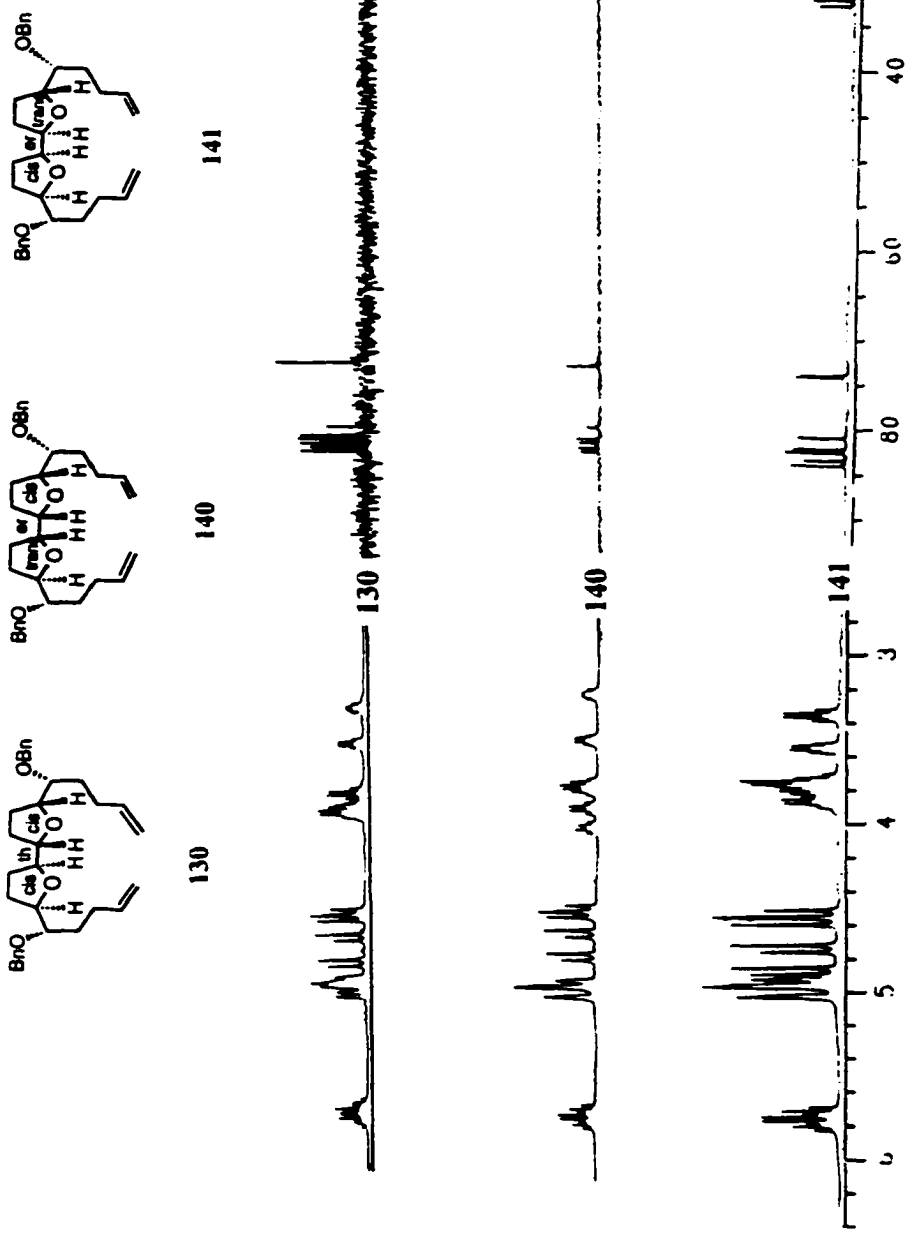
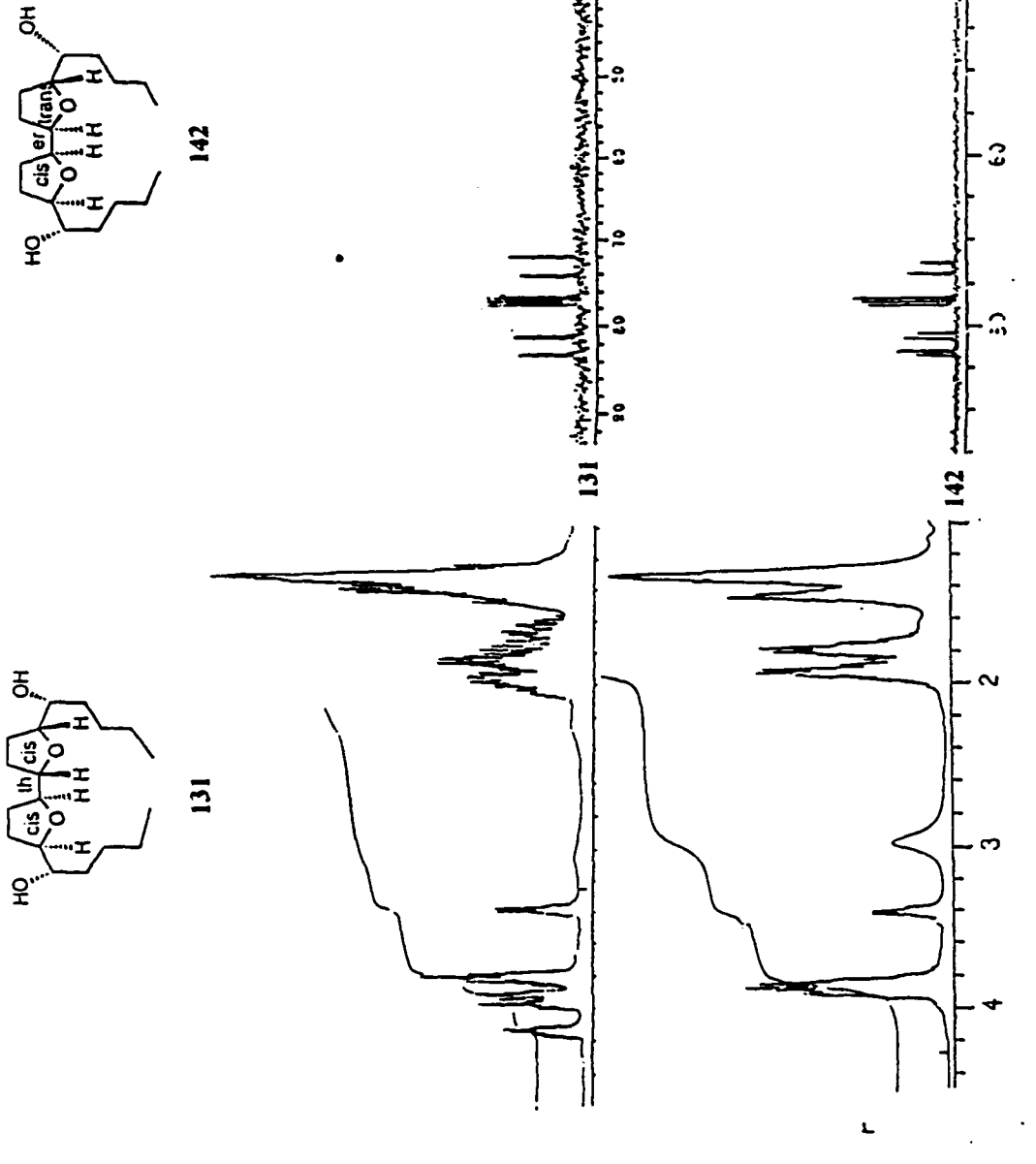
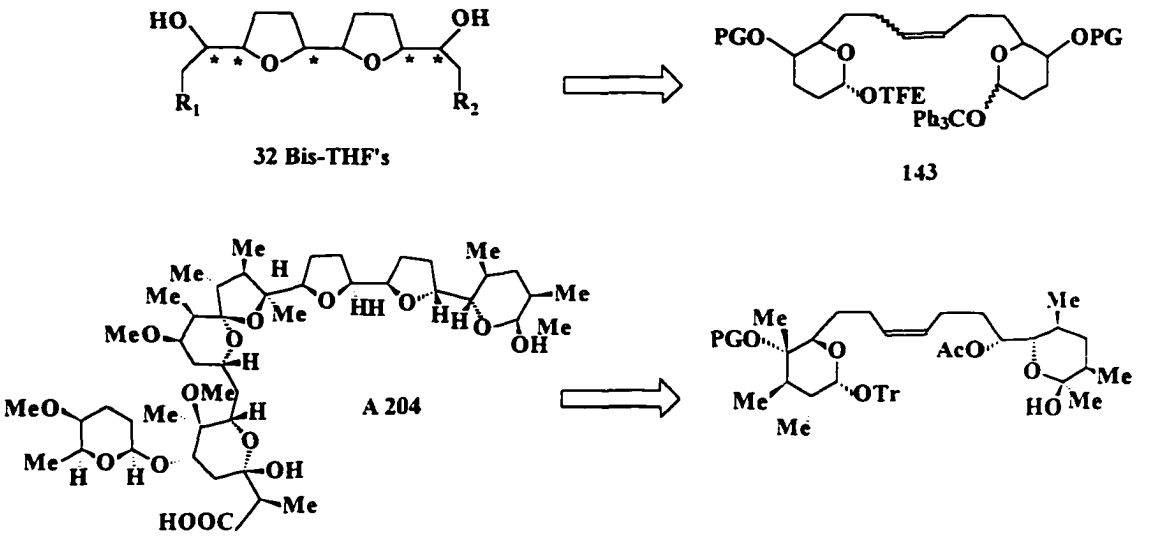


Fig. 6 NMR Spectrum Comparison of Bis-THF's 131 and 142



Scheme 35



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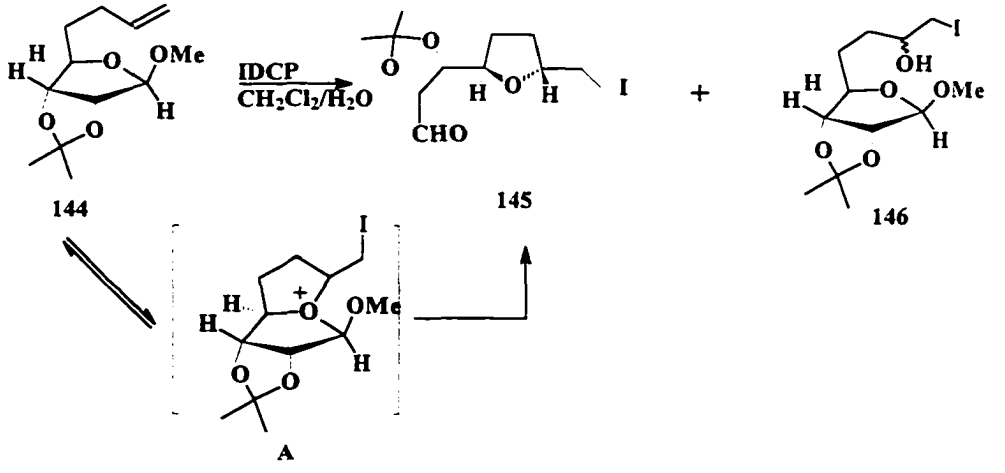
Chapter 3

C5 Allylated Furanosides:

Templates for the Synthesis of Trans-2,5-Disubstituted THF's

In our preliminary investigation of the stereochemical bias of different monosaccharide templates, it was observed that the iodocyclization of methyl 2,3-*ribo*-O-isopropylidenefuranoside alkene **144** provided the *trans*-2, 5-disubstituted THF **145** as the major THF (*trans*:*cis*>8:1). However, an appreciable amount of the halohydrin **146** was also obtained (Scheme 36). For the pyranoside series, increasing the size of the aglycone led to increase in the rate of THF formation. A similar variation in the furanoside**144** was expected to result in a reduced proportion of iodohydrin, although the effect on stereoselectivity was uncertain. The rate effect would presumably result from an increased rate of fragmentation of the intermediate **A** as the size of the aglycone increases.

Scheme 36

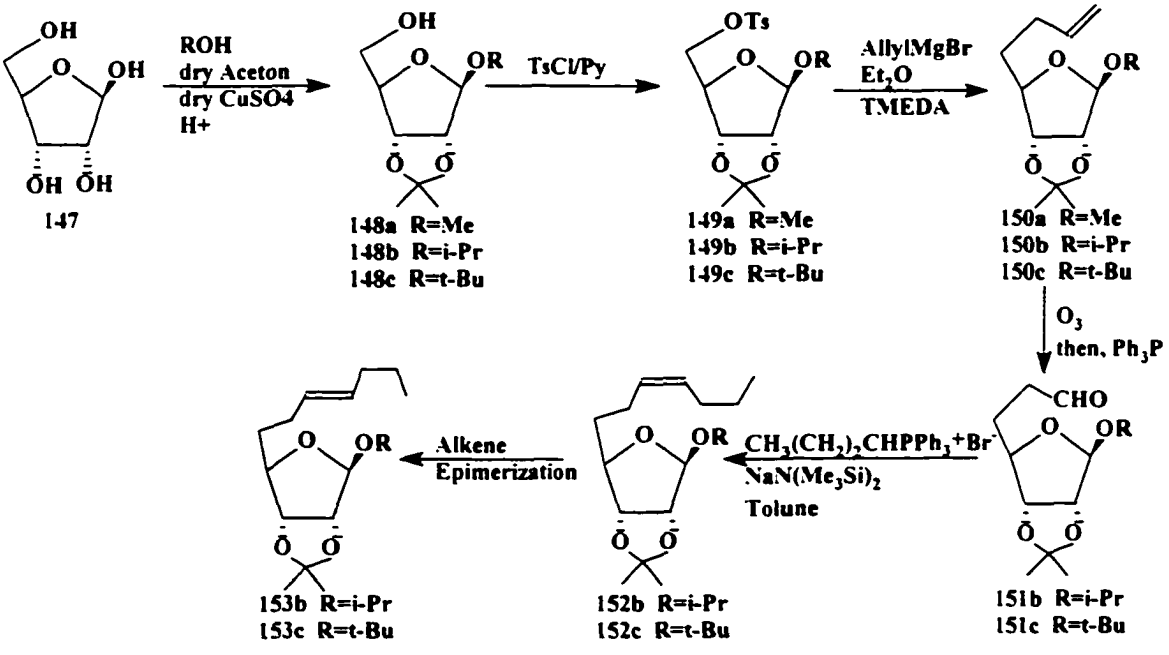


In order to evaluate these effects, C5 allylated derivatives of **144** containing Z and E alkenes with different sizes of aglycones were prepared.

Preparation of Alkene Precursors

The reaction of D-ribose **147** with methanol, isopropanol or t-butanol in acetone, containing H_2SO_4 and dry $CuSO_4$, led to ribofuranosides **148-a,b,c** respectively.[43] Furanosides **148-a,b,c** were converted to tosylates **149-a,b,c** which were transformed to the terminal alkenes **150-a,b,c** by treatment with allylmagnesium bromide. The Z and E alkenes of the methyl and isopropyl furanosides **152-a,b** and **153-a,b** were prepared using reactions identical to those which were used in the *cis*-THF study. The sequence was ozonolysis, Wittig reaction and alkene epimerization (Scheme 37).

Scheme 37

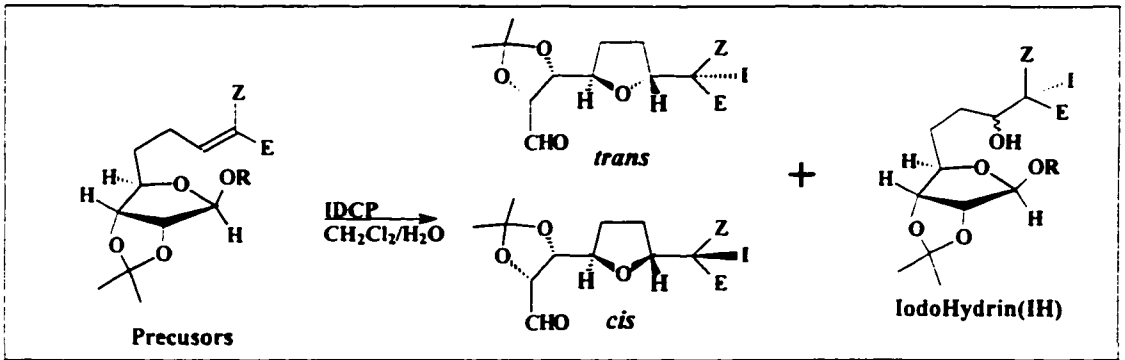


The Z/E alkene geometry was assigned on the basis of the more downfield shift of the allylic carbon in the E isomer (For example, C6 (δ30.41) and C9 (δ25.11) for the Z-alkene **152-b** and C6 (δ35.79) and C9 (δ30.26) for the E-alkene **153-b**).

Halocyclization Studies

The iodocyclizations of the alkenes were carried out under the standard conditions using IDCP in wet dichloromethane. The reactions were complete within 15 min. The stereochemistry of the THF products was assigned by comparison of the methylene resonance in THF ring of the *trans* and *cis* isomers as described previously. In all cases, good to high preference for the *trans* isomer was observed with varying proportion of the iodohydrin product (Scheme 38).

Scheme 38



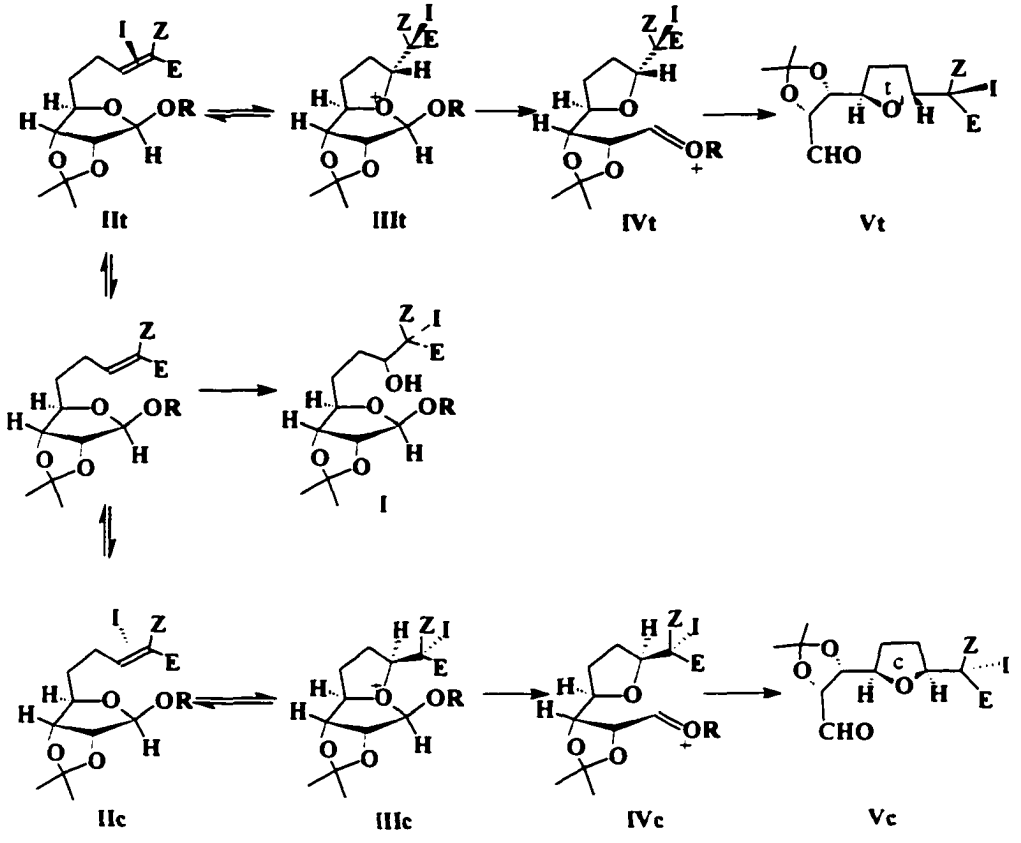
	150a-c		152a-b		153a-b	
	Terminal (E=Z=H)		Z (Z=Pr; E=H)		E (Z=H; E=Pr)	
R	THF c:t	THF:IH	THF c:t	THF:IH	THF c:t	THF:IH
CH_3	145 1:10	2:1	154 <1:40	2:1	155 <1:40	2:1
i-Pr	145 1:9	10:1	154 <1:40	2:1	155 <1:40	10:1
$C(CH_3)_3$	145 1:6	>10:1	———	——	———	———

The following is a summary of the results: <1> For terminal and E alkenes, increasing the size of the aglycone lead to a decreasing proportion of iodohydrin. Regardless of the aglycone, Z-alkenes give considerably lower ratio of THF:iodohydrin, 2:1. <2> The E and Z-alkenes showed very high levels of *trans*-stereoselectivity (>40:1 *trans/cis* ratio) regardless of the size of the aglycone. <3> For terminal alkenes, as the size of the aglycone increases, the selectivity for the *trans*-THF decreases.

In the absence of additional data, the variation of the THF/iodohydrin product, and overall reaction rate with aglycon size appear to fit a reaction mechanism in which fragmentation of THF oxonium ion is the rate determining step (Scheme 39). Increasing the size of aglycone leads to more steric congestion in the THF oxonium ion **III**, and this results in a faster rate of cleavage of the internal acetal bond to give **IV**. This leads to an overall increase in the rate of the THF formation. The formation iodohydrin **I** is not affected by aglycone size and therefore the proportion of **IV** increases as the size of the aglycone increases. Z alkenes give an appreciable proportion of iodohydrin, probably due to a slower rate of THF oxonium ion formation brought about by unfavorable torsional effects in the attack of the ring oxygen on the halonium ion or charge transfer complex **II**. The observed *trans* selectivity seems to fit an oxonium ion **III**, which has a [5,5,0] type geometry. This geometry makes the *cis* transition state **IIIc** disfavored because the concave cavity is more crowded. The higher *trans* preference obtained with more substituted alkenes supports this theory. However, the decrease in *trans* selectivity for the t-butyl terminal alkene **150c** appears to be in disagreement with this model since the increased size of the aglycone would have been expected to give higher *trans* selectivity. This might be due to a subtle conformational distortion of furanoside ring, which lowers

the extent of crowding in **IIIc**, thereby, increasing the proportion of the *cis* THF. For the substituted alkenes, the increasing size of the alkene substituent offsets any subtle effect due to the size of aglycone.

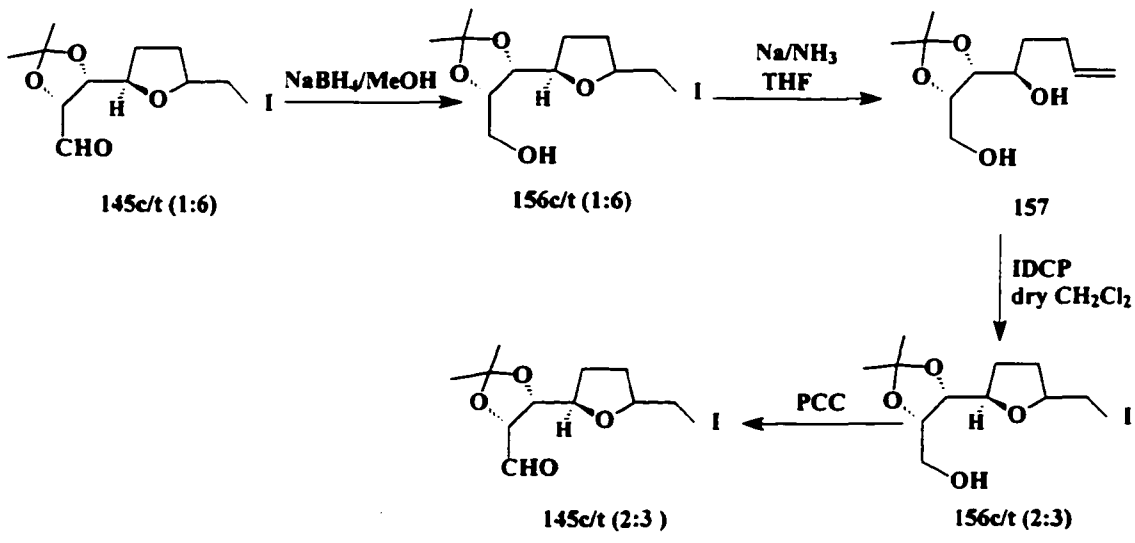
Scheme 39



For comparison, the halocyclization of the diol **157** was carried out. The diol **157** was prepared from THF product **145c/t** (1:6) in two steps: reduction of aldehyde followed by reductive opening of the iodo-THF. Cycling of **157** gave 2:3 mixture of *cis/trans* THF's **156c/t** which was correlated with the THF's (1:6 c/t) derived from the furanosides. After

PCC oxidation, the corresponding 2:3 mixture of *cis/trans* THF products **145c/t** were obtained (Scheme 40).

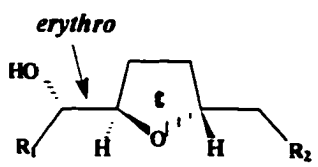
Scheme 40



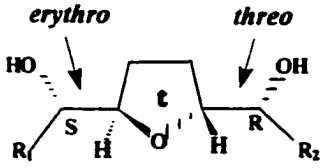
Synthetic Approach to Mono-THF Acetogenins

The result obtained with the isopropyl 2,3-*ribo*-O-isopropylidenefuranoside E-alkene may be applied to the synthesis of *trans*-THF containing acetogenins. First of all, we focused on *erythro-trans* and *erythro-trans-threo* THF subunits as found for example in muricatalin and annonacin A. The abosolute stereochemistry of muricatalin has not been confirmed.[44] The annonacin A type structure is one of the more common acetogenin subunits. The flanking hydroxyls have *R, S*-configuration (Figure 7).

Figure 7



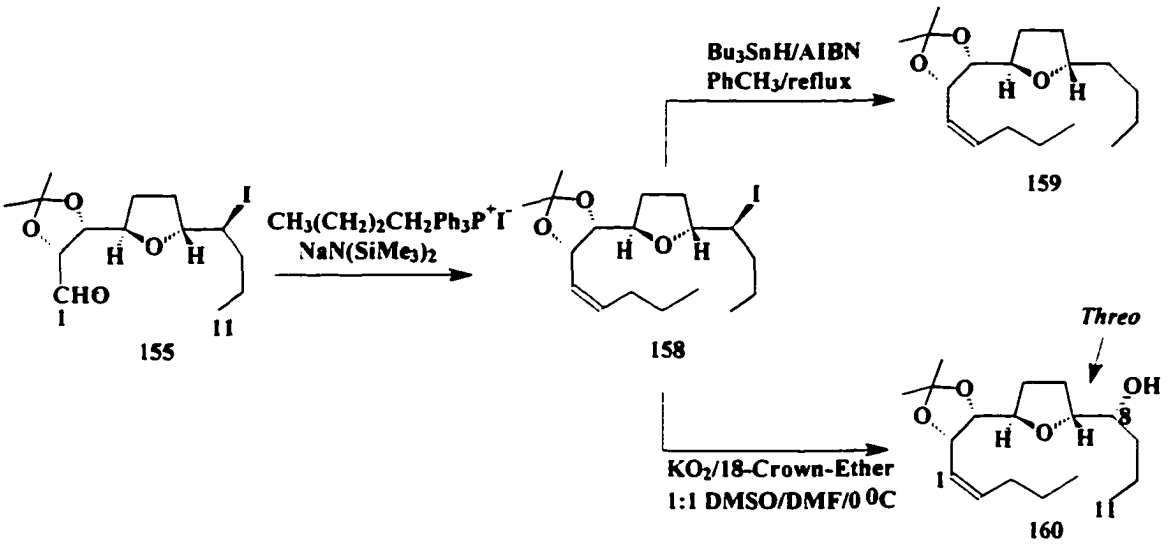
Muricatalin Type



Annonacin A Type

Model compounds **159** and **160,** representative of these two THF motifs, were prepared. The THF aldehyde **155** was obtained from cyclization of E-isopropyl furanoside **153b** as previously described. Compound **155** was converted to **158** by treatment with butylene triphenylphosphorane. Tributyltin hydride reduction of **158** gave **159**.[45] Treatment of **158** with 4eq. KO2/18-crown-ether in 1:1 dry DMSO/DMF solvent afforded compound **160** in 72% yield (Scheme 41).

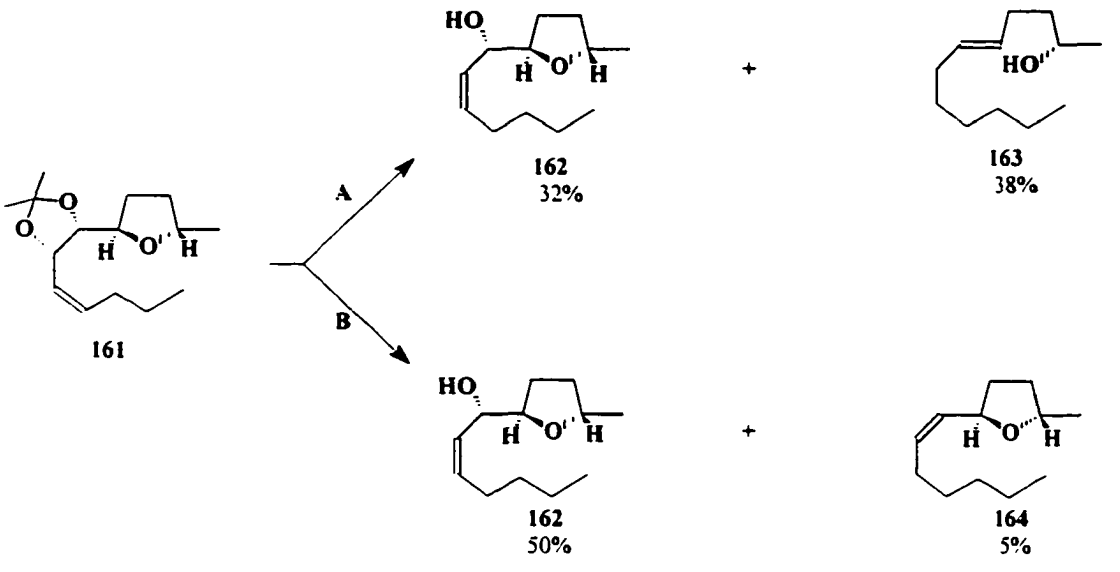
Scheme 41



The *threo* stereochemistry at C7/C8 was confirmed by application of Born's rule (oxymethine proton and carbon alpha to the THF ring resonate at δ_H ca. 3.8 and δ_C ca. 71-72 for *erythro* compounds and at δ_H ca. 3.4 and δ_C ca. 74 for *threo* compounds). δ_H was 3.9 and δ_C, 74.6 for C8.

Selective removal of the allylic oxygen in **159** and **160** is required for the acetogenin structures. Two methods for deoxygenation were tested on **161,** which was synthesized from **145**. The following is a summary of these results.

Scheme 42



(1). Na/NH_3/THF

Two procedures, **A** and **B** were tested.

Procedure **A**: Sodium was slowly added to a solution of the starting material in 1:5 THF/NH_3 solvent at -78 °C under argon atmosphere until the blue color was persistent for

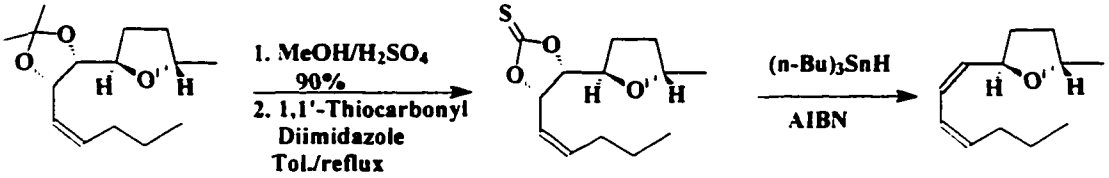
several minutes. After warming to rt, the reaction was quenched with NH_4Cl. The desired product **162** was obtained in 32% yield together with product **163** (38%).

Procedure **B**: The solution of a starting material in THF was added to a prepared solution of excess sodium-ammonia in THF. After the color changed from blue to brown, the reaction was quenched with NH_4Cl as in procedure **A**. The desired product **162** was obtained in 50% yield together with **164** (5%) (Scheme 42).

(2). Stannane-Mediated Reduction

Stannane-mediated reduction of allylic diol derivative **165** was tried (Scheme 43).[46] Hydrolysis of **161**, followed by treatment with 1,1'-thiocarbonyldiimidazole provided the thiocarbonate **165**. However, the selective deoxygenation of **165** with tin hydride was not successful. Diene **166** was obtained as the only product.

Scheme 43



161 **165** **166**

Concurrently, a more efficient methodology for *trans*-2,5 disubstituted THF's was developed. Due to the problem with removal of the allylic oxygen, the construction of the acetogenin THF ring from the *ribo* furanoside precursors was not further pursued. The

new methodology is discussed in the next chapter. These results with the *ribo* furanoside system are more appropriate for more highly oxygenated, unnatural analogs.

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[43] Yadav, J. S.; Barma, D. K. *Tetrahedron*, **1996**, *52*, 4457-4466.

[44] Gui, H.-Q.; Yu, J.-G.; Yu, Z.-L. *Chi. Chem. Lett.* **1995**, *6*, 45.

[45] Zbiral, E.; Brandstetter, H. H.; Schreiner, E. P.; *Monatsh Chem.* **1988**, *119*, 127.

[46] Alpegiaxi, M.; Hanessian, S. J. *J. Org. Chem.* **1987**, *52*, 278.

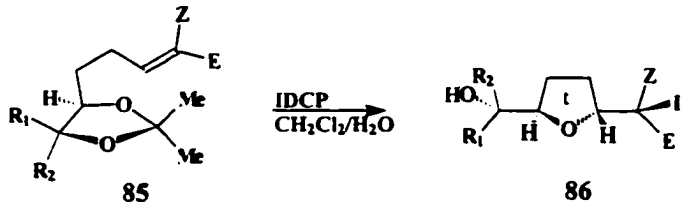
Chapter 4

5, 6-O-Isopropylidene Alkenes:

Synthesis of Acetogenins Containing *trans* THF's

As mentioned earlier, the iodocyclization of 5,6-O-isopropylidene terminal, Z and E alkenes produces the *trans* THF with high stereoselectivity, in greater than 88% yield (Scheme 17). This methodology provides a more efficient way of preparing the less oxygenated structures found in the naturally occurring acetogenins. The application to the systhesis of bis-THF systems was investigated.

Scheme 17

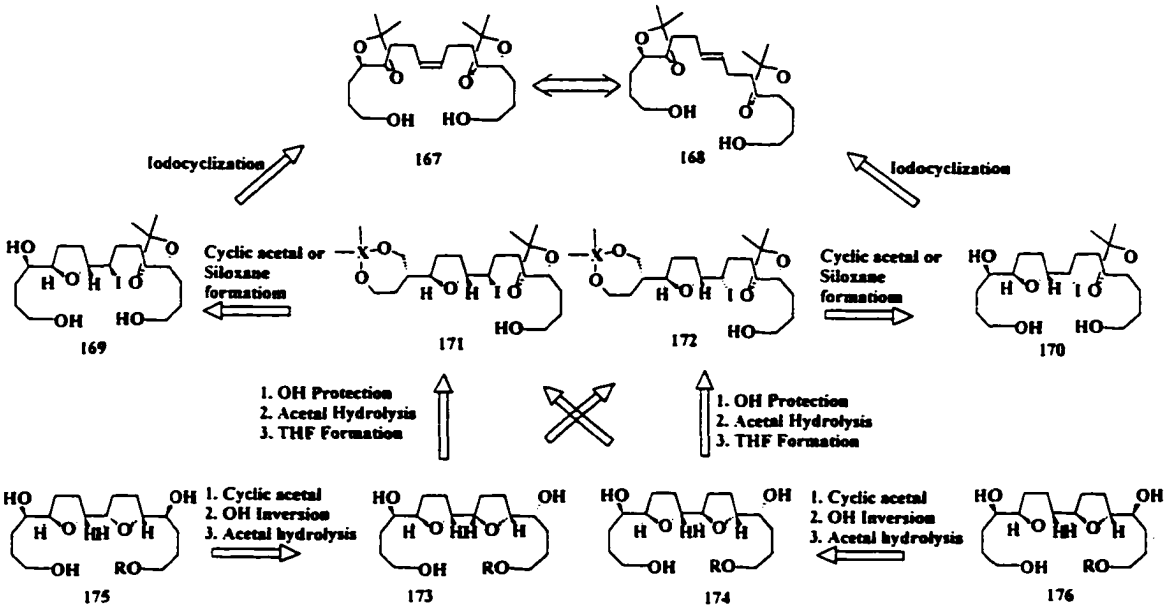


85 86

	Terminal(E=Z=H) c : t	Z(Z=Pr; E=H) c : t	E(Z=H; E=Pr) c : t
R_1=Bu, R_2=H	only t	only t	only t
R_1=H, R_2=Bu	only t	only t	only t
Yield	80-90%		

1. Retrosynthetic Plan

Scheme 44

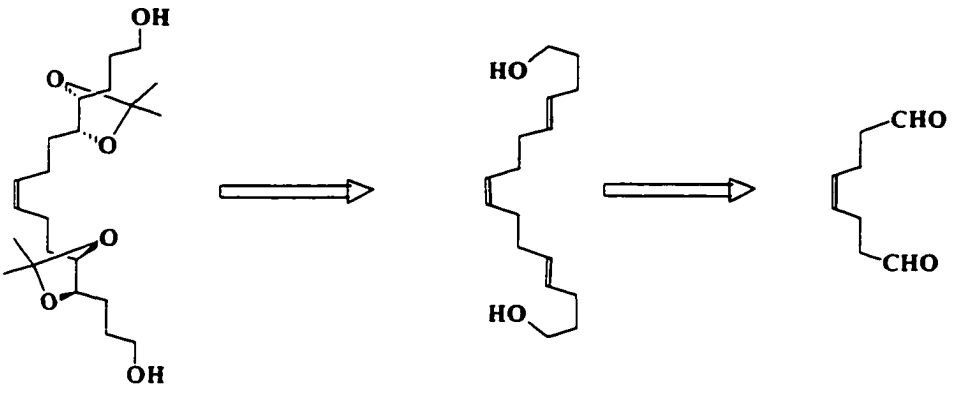


Our plan is based on the use of the iodocyclization reaction of C2 symmetric alkenes like **167** and **168**. The products of these reactions will be the triol derivatives **169** and **170** respectively. Differentiation of the two primary alcohols should be possible by formation of a cyclic acetal or siloxane as in **171** and **172** (X=C or Si) which could be elaborated to different bis-THF targets. Elaboration of the free primary alcohol, followed by acetal hydrolysis and THF formation leads to **173** and **174**. Reintroduction of a cyclic acetal in **173** and **174**, followed by inversion of the secondary alcohol leads to **175** and **176** respectively. In principle, since the precursor alkenes are synthetically interconvertible and the bis-THFs **173** and **174** may be derived from the mono THF iodides of the complementary series, (i.e. from double configurational inversion at the iodide carbons in **172** and **171** respectively), the four diastereomers **173-176** may be derived from a single

E or Z alkene precursor. Using enantiomeric materials, eight of the 64 possible bis-THF-bis hydroxymethyl subunits may be prepared in a straightforward fashion (Scheme 44).

The C2 symmetry of **167** suggested a two directional synthetic approach, based on the selective enantioselective dihydroxylation of a E, Z, E-triene precursor **178**. Recent studies on the Sharpless prtocal with polyene substrate have indicated that disubstituted E alkenes undergo dihydroxylation at an appreciably faster rate than their Z derivatives.[47] Triene **178** should be obtainable from dialdehyde **179** by two directional chain elaboration (Scheme 45).

Scheme 45



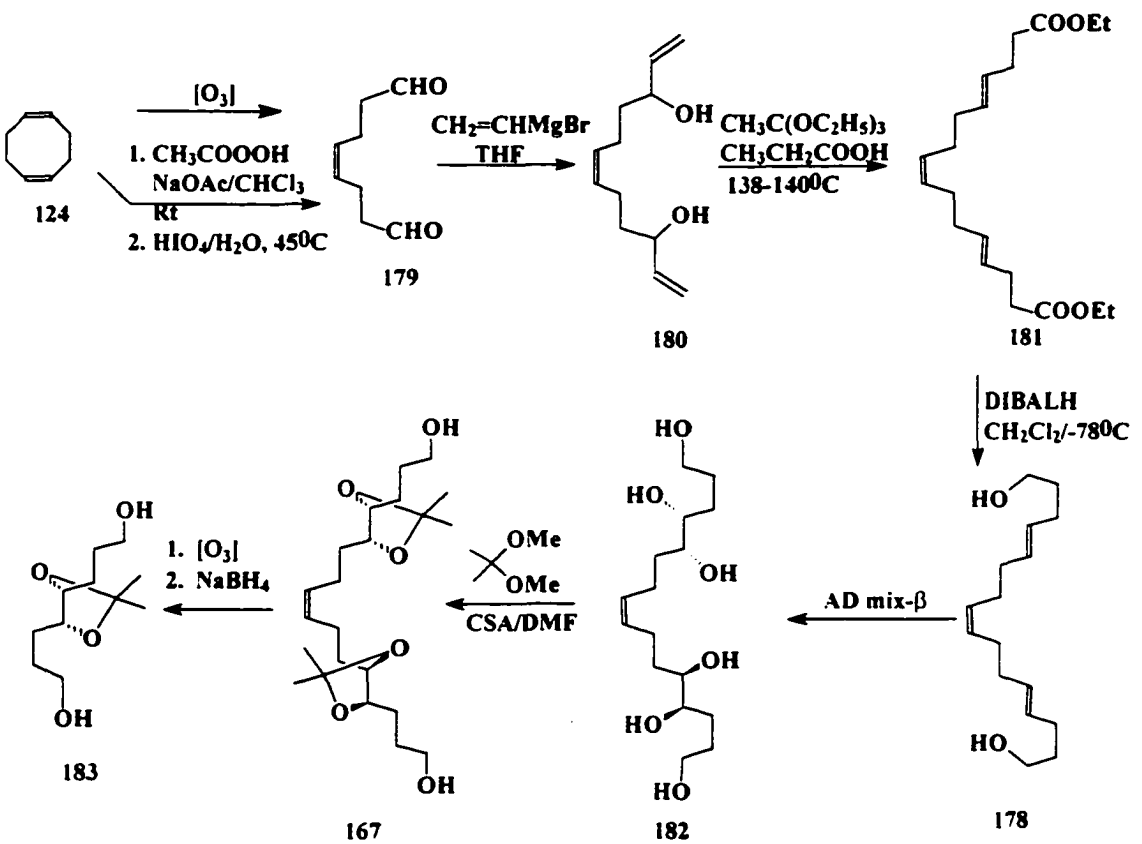
167 178 179

Synthesis of C2- Symmetric Z-alkene 167

Two methods were used for the synthesis of dialdehyde **179** from 1,5-cyclooctadiene. The first was ozonolysis of 1,5-cyclooctadiene **124** directly to **179** in 50-70% yield.[41a] The second was mono-epoxidation, followed by periodic acid oxidation.[41b] The overall yield was about 70-80%. Two step procedure was more practical easy than the ozonolysis

procedure. To ensure the stability of dialdehyde **179**, a small amount of hydroquinone was added after work-up. Reaction of **179** with vinylmagnesium bromide gave the diol **180**. Johnson-Claisen rearrangement on **190** using dry ethyl orthoacetate at 140 °C produced a single triene ester **181**.[48] The E geometry was assumed from the literature procedure on this rearrangement and supported by ^{13}C NMR data. Three signals for alkenes carbons were observed at δ 128.6, 129.5 and 131.2. The two downfield signals compared closely to those for similar E-alkenes.[49] Reduction of **181** with DIBAL-H gave the dihydroxy triene **178** in 70% overall yield from **179** (Scheme 46).

Scheme 46

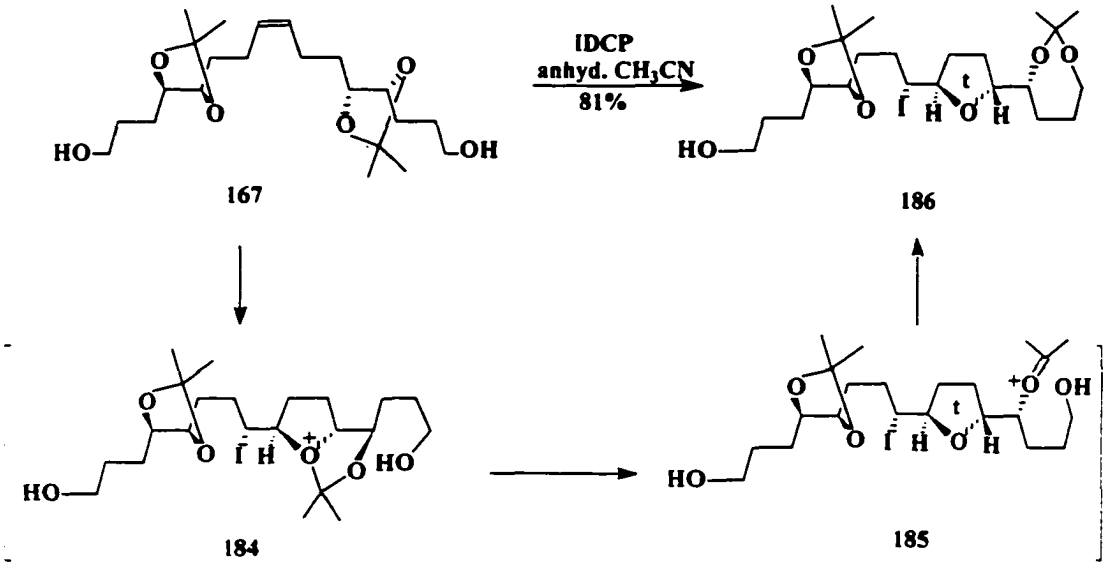


The asymmetric double dihydroxylation of **178** was performed according to the Sharpless protocol, with AD-mix-β. The hexaol **182** was obtained in 62% yield together with 20% mono dihydroxylation material, which could be resubjected to the reaction conditions. The optimal reaction conditions was 1eq. triene **178**, 2.8 g/mmol of AD-mix-β, 5 ml/mmol of t-BuOH, 5 ml/mmol of H_2O, and 95 mg/mmol of $MeSO_2NH_2$. The reaction was stirred at -3 °C and monitored carefully by TLC. Controlling the temperature under -3 °C was very important. Otherwise, appreciable amounts of over dihydroxylation was obtained. NMR analysis greater than 95% of a single product. This high de of the double dihydroxylation suggests that the ee was also very high. Assuming that the hydroxylation of each double bond occurs independently, it can be shown that a de of >95% translates to an ee of >99.9%. Finally, isopropylidene-Z-alkene **167** was obtained in 94% yield by acetalization of **182** with 2,2-dimethoxypropane and camphorsulfonic acid.[50] The high enantioselectivity of the dihydroxylation was confirmed at this stage. This was done by conversion of **167** to the known isopropylidene-1,8-octanediol **183,** $[a]^{26}D$ +29.2 (c 0.51, $CHCl_3$) was isolated that is identical with literature compound.[51] The conversion of **179** to **178** did not require chromatographic purification of the reaction products. Thus, the seven step sequence of **124** to **167** required only four purification steps. This facilitated the routine preparation of **167** on larger than 5g scale.

Halocyclization and Desymmetrization

Treatment of bis-isopropylidene Z alkene **167** with our standard halocyclization condition (IDCP with CH_3CN as solvent) provided the mono-THF iodide **186** in 83% yield. Thus, both desymmetrization and formation of the seven membered cyclic acetal, which was planned as a protecting group, were achieved in a single step. Presumably the formation of the seven membered acetal arises through capture of the intermediate oxocarbenium ion by the proximal promary alcohol (Scheme 47). The next stage was the elaboration of the primary alcohol and formation of the second THF ring.

Scheme 47

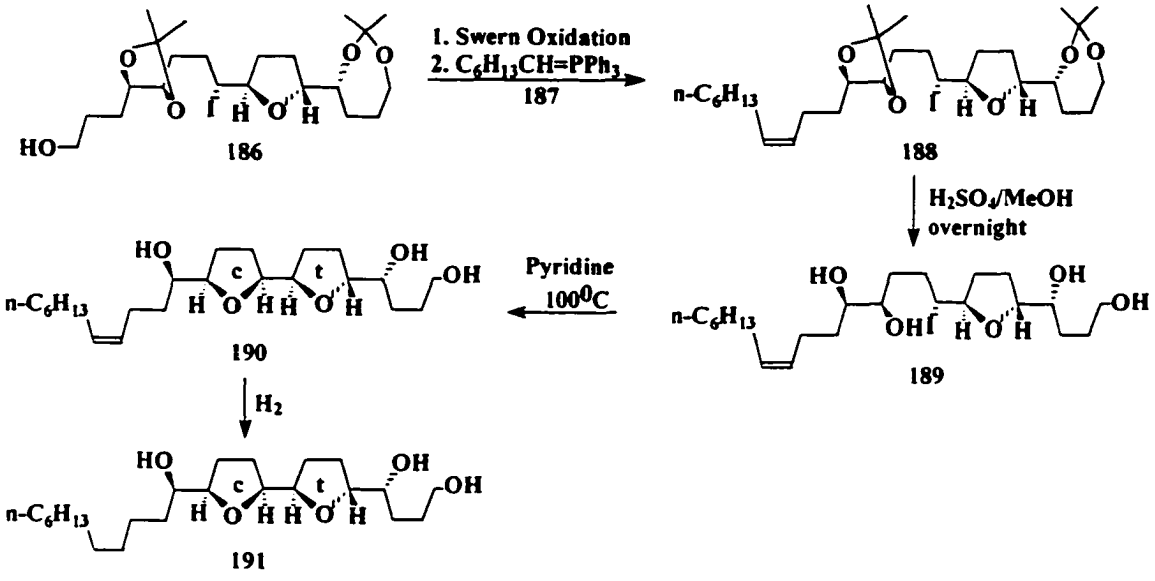


Synthesis of Trilobacin and Asimicin Bis-THF Core

The trilobacin type of acetogenin has a *threo-trans-erythro-cis-threo* stereochemistry with R,R-configuration at the carbinol carbons. Swern's oxidation of **186**, followed by Wittig reaction with the ylide **187** produced the alkene **188** in overall 77% yield. The phosphonium salt precursor of **187** was easily prepared from commercially available 1-

iodoheptane. Hydrolysis of **188** gave tetraol **189** in 89% yield. The second THF-ring was formed in 67% yield from the reaction of **189** in pyridine at 100 °C (Scheme 48). Finally, Keinan's intermediate **191** was synthesized after the hydrogenation of **190**. The obtained compound **191** is identical with Keinan's intermediate, with respect to NMR and MS.[52] Table 3 shows the comparison of ^{1}H and ^{13}C NMR chemical shift data of **191** and natural trilobacin.[8] The high degree of correlation between them further supports the *c/er/t* structure shown for **191**. It culminates in a 12-step synthesis of the trilobacin bis-THF core **191** by comparison with Keinan's 31-step of approach for the same compound.[21]

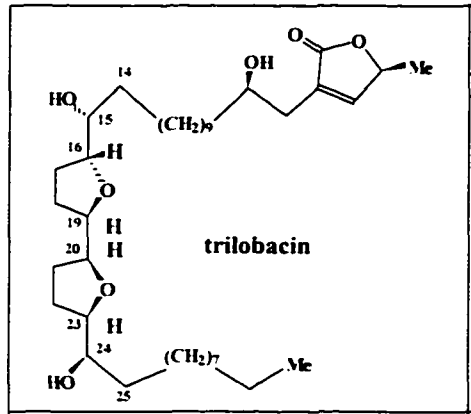
Scheme 48



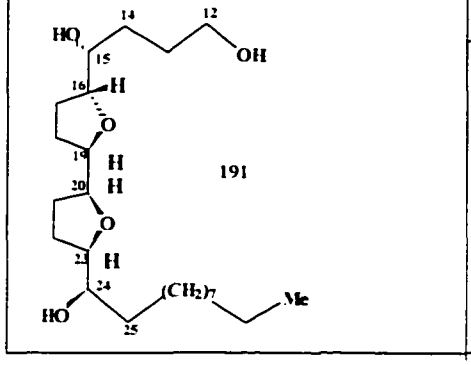
Several other reaction conditions were tested in order to increase the yield of **190**. (1) Collidine/100°C, (2) K_2CO_3/MeOH/reflux, (3) TBAF/THF/50°C, (4) 1:1 Pyridine /Toluene, reflux. However, in all cases, THF formation was accompanied by the formation of a spiroketal **193** (Scheme 49). The ratio of **190** to **193** is normally from 3:1 to 1:1. This side reaction presumably processes through initial dehydroiodonation to the

enol ether **192** which undergo hydrolysis in work up.[53] This is similar to the silver mediated reagent reaction of mono-THF-iodide pyranoside **119** in chapter 2. This reaction is potentially general one for the synthesis of complex spiroketals and remains to be developed.

Table 3 Chemical Shift Data of 191 with Trilobacin

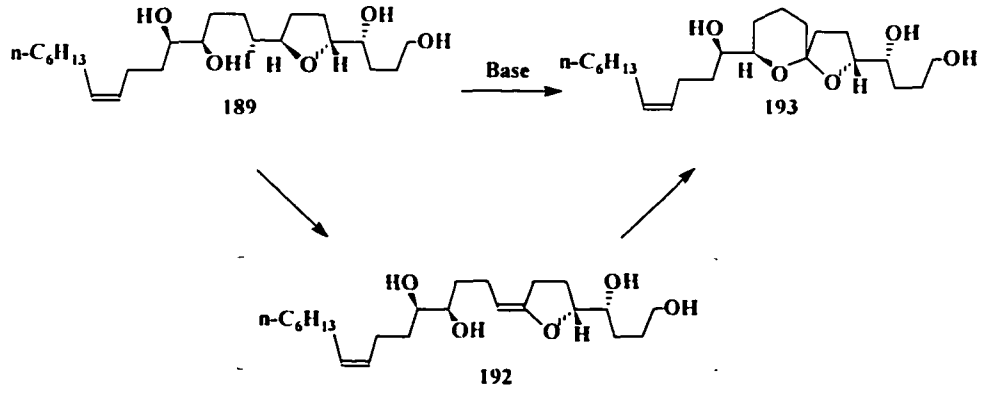


	1H NMR (ppm)	13C NMR (ppm)
14	1.41m	33.6
15	3.36m	74.6
16	3.83m	83.3
17	1.7-2.0m	28.2
18	1.8-1.9m	29.0
19	3.97m	81.6
20	4.05m	80.9
21	1.7-2.0m	29.4
22	1.7-2.0m	29.5
23	3.83m	82.6
24	3.39m	73.9
25	1.41m	34.2



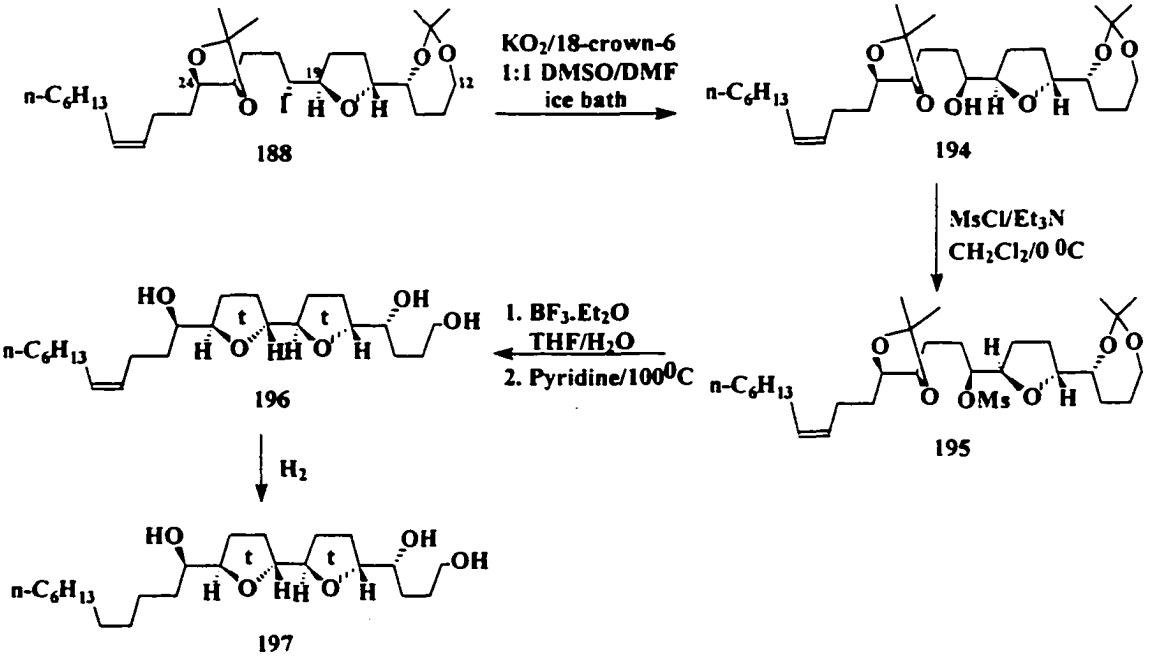
	1H NMR (ppm)	13C NMR (ppm)
12	3.65	62.9
14	1.50m	32.1
15	3.43m	74.7
16	3.83m	83.2
17	1.7-2.0m	28.4
18	1.8-1.9m	29.0
19	3.97m	81.7
20	4.06m	81.0
21	1.7-2.0m	29.4
22	1.7-2.0m	29.5
23	3.83m	82.7
24	3.39m	73.9
25	1.42m	34.5

Scheme 49



The asimicin type of acetogenin has a *threo-trans-threo-trans-threo* stereochemistry with R,R-configuration at the carbinol carbons. In order to get the asimicin bis-THF core, the stereochemistry of the leaving group at C20 in **188** has to be inverted. The iodide **188** was converted to the alcohol **194** via the conditions which were developed in the model study. Treatment of **188** with 4eq KO_2/18-crown-ether, 1:1 dry DMSO/DMF led to **194** in 55% yield.[54] The *threo* stereochemistry at C19/C20 was confirmed by Born's rule. (δ H_{20}, 3.84; C_{20}, 72.10). Subsequent mesylation of **194** yielded intermediate **195** (70% yield). Acetal hydrolysis of **195**, followed by treatment of the resulting tetraol in pyridine at 100 °C provided the asimicin bis-THF Core **196** in 86% yield from **195**. Finally, Keinan's asimicin intermediate **197** was obtained by hydrogenation of **196**. (Scheme 50).

Scheme 50

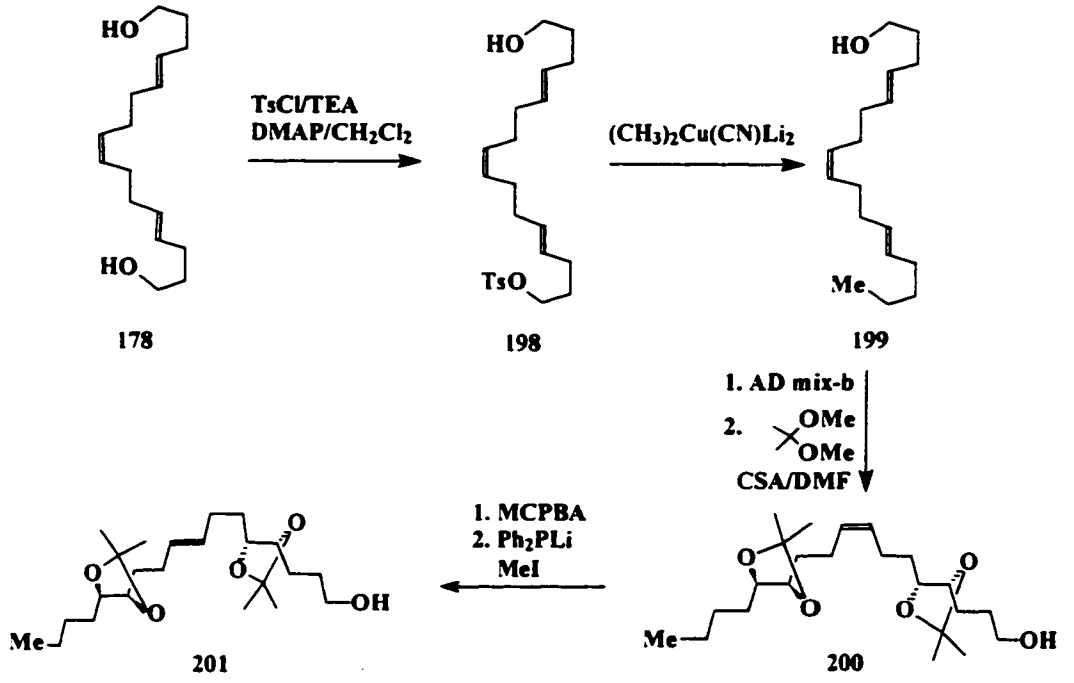


The obtained compound **197** is identical with Keinan's asimicin intermediate, with respect to NMR, and MS.[52]

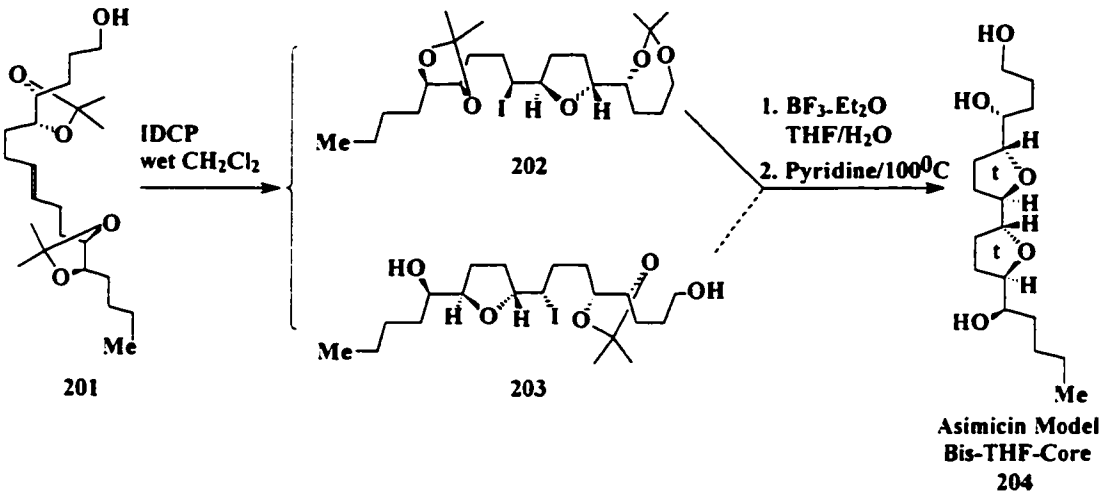
The feasibility of the alternate approach to asimicin type bis-THF core from an E-alkene precursor was tested in a model study using bis-isopropylidene E-alkene **201**. Compound **201** was obtained in five steps from the dihydroxytriene **178**. **178** was desymmetrized by monotosylation with 1eq TsCl and TEA/DMAP in CH_2Cl_2 to give the desired monotosylation compound **198** in 45% yield. Reaction of **198** with lithium dialkylcuprate reagent ($R_2Cu(CN)Li_2$) produced **199** in 87% yield.[55] Sharpless asymmetric double dihydroxylation, followed by acetalization with 2,2-dimethoxypropane, provided a single bis-isopropylidene diastereomer **200** in overall 64% yield. Finally, isomerization of the Z-alkene to the E-alkene **201** was accomplished by the standard Vedejs procedure, which was discussed in Chapter 2. The overall yield for the isomerization was 71% (Scheme 51).

With model compound **201** in hand, the synthesis of asimicin type bis-THF core was pursued. The iodocyclization of **201** produced a 1:1 ratio of **202** and **203** in 70% yield. Hydrolysis of **202** with $BF_3.Et_2O/THF/H_2O$ (93%), followed by heating of the resulting tetraol in pyridine at 100 °C, gave the desired asimicin model bis-THF core **204** in 78% yield (Scheme 52). It should be possible to convert the other iodocyclization product **203** to **204** *via* a similar route.

Scheme 51



Scheme 52

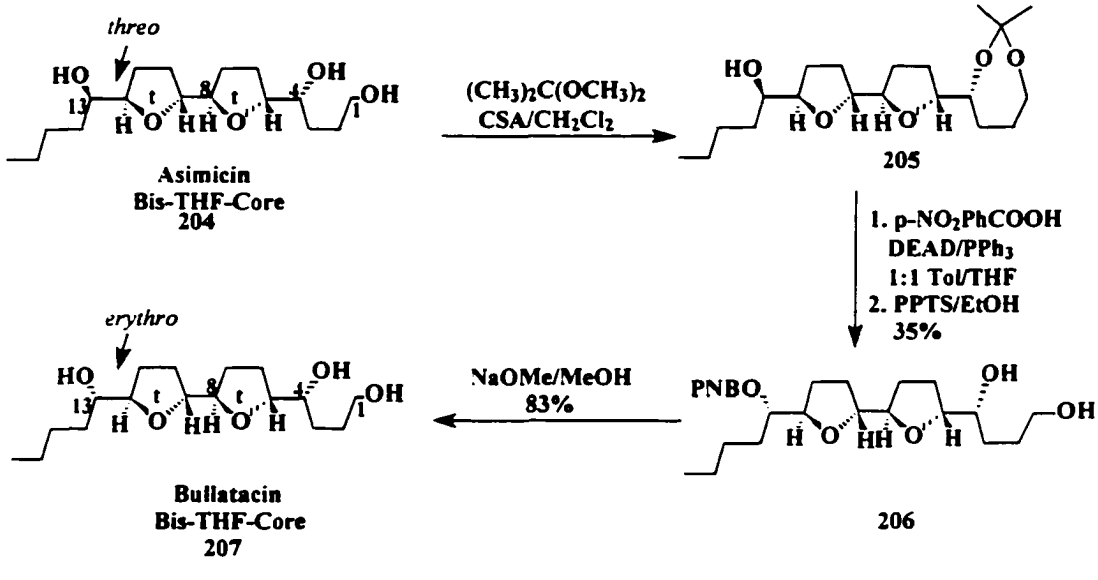


Synthesis of Bullatacin Type Bis-THF Cores

The bullatacin and asimicin bishydroxymethyl bis-THF cores are epimeric at C24. Bullatacin and asimicin differ only that the former is C-24S and the latter is C-24R.

Approximately, 50 compounds with the bullatacin type core have been reported. It is the largest subgroup and contains some of the most active compounds. Inversion of the configuration at C13 of the asimicin model **204** was tested. Treatment of **204** with 2,2-dimethoxypropane gave the isopropylidene **205**. Application of the Mitsunobu reaction on **205**, using 4-nitrobenzoic acid as the nucleophile, followed by acetal hydrolysis of the crude product gave **206** in overall 35% yield from **204**. Those conditions were not optimized. Finally, the bullatacin core **207** was obtained in 83% yield by basic hydrolysis of **206** (Scheme 53).

Scheme 53



The ^{1}H and ^{13}C NMR chemical shift data for asimicin and bullatacin bis-THF cores **204** and **207** were compared with those of natural asimicin and bullatacin (Table 4). The high degree of correlation supports the claim that both of bis-THF cores have correct stereochemistry.

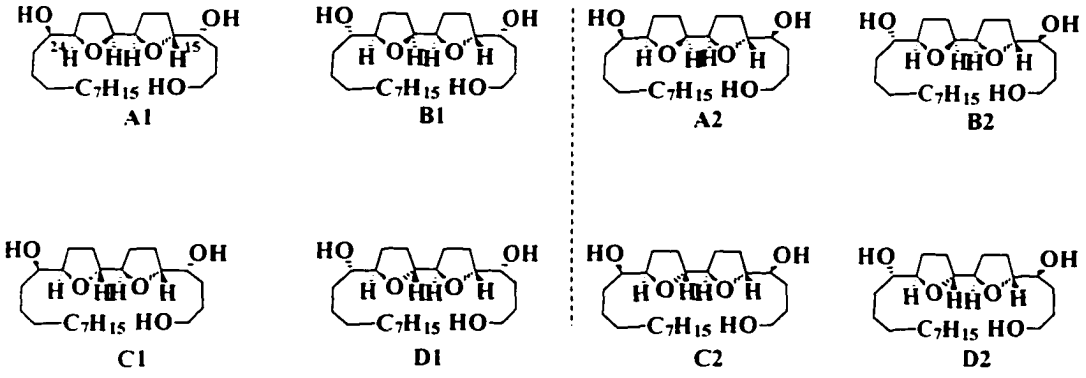
Table 4: NMR Data for Asimicin and Bullatacin bis-THF Cores

13C	13	12	9	8	5	4	1
Asimicin	74.0	83.1	81.8	81.8	83.1	74.0	/
Asimicin Core	74.3	83.1	81.8	81.9	83.3	74.3	63.1
Bullaticin	71.3	82.8	82.2	82.4	83.2	74.1	/
Bullaticin Core	71.8	83.0	82.4	82.6	83.2	74.4	63.1

Summary of Bis-THF Syntheses

Using the chemistry developed in the preceeding sections, the four diastereomer bis-THF cores **A1**, **B1**, **C1**, **D1** with a R configuration at C24 may be obtained from either **167** or **168**. Two of these **A1** and **C1** have already been prepared from **167** and model chemistry was developed for their conversion to **B1** and **D1**. In principle, it is possible through more complicated protecting group sequences to convert **A1-D1** to their C15 epimers **A2-D2** respectively (Figure 8).

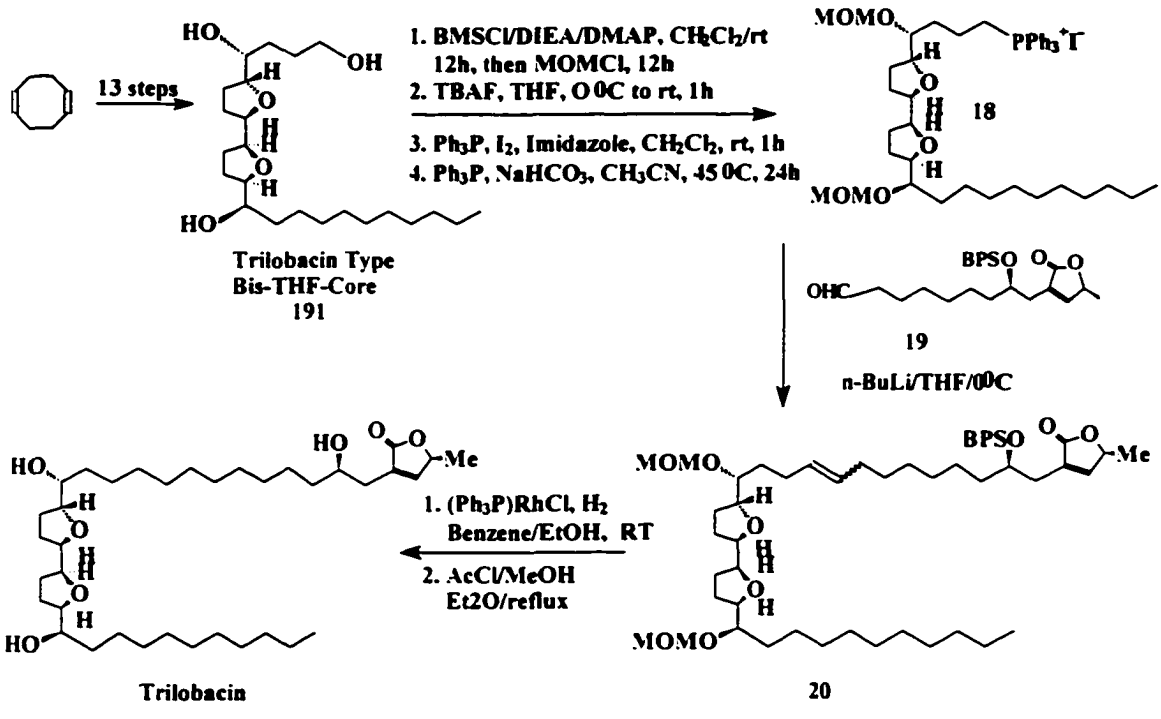
Figure 8



Using materials enantiomeric **167** and **168**, 16 of the 64 possible bis hydroxymethyl bis-THF cores can be prepared. Eight of these (i.e. the *trans-trans* bis-THF's) are not possible via the pyranoside strategy (Chapter 2). Thus, together both methodologies allows access to 40 of the 64 possible stereoisomers of the bis hydroxymethyl bis-THF core.

Existing methodologies for coupling of the butenolide segment may be applied to the bis-THF structures obtained in this study. An example following Keinan's synthesis of trilobacin will be described (Scheme 54).

Scheme 54

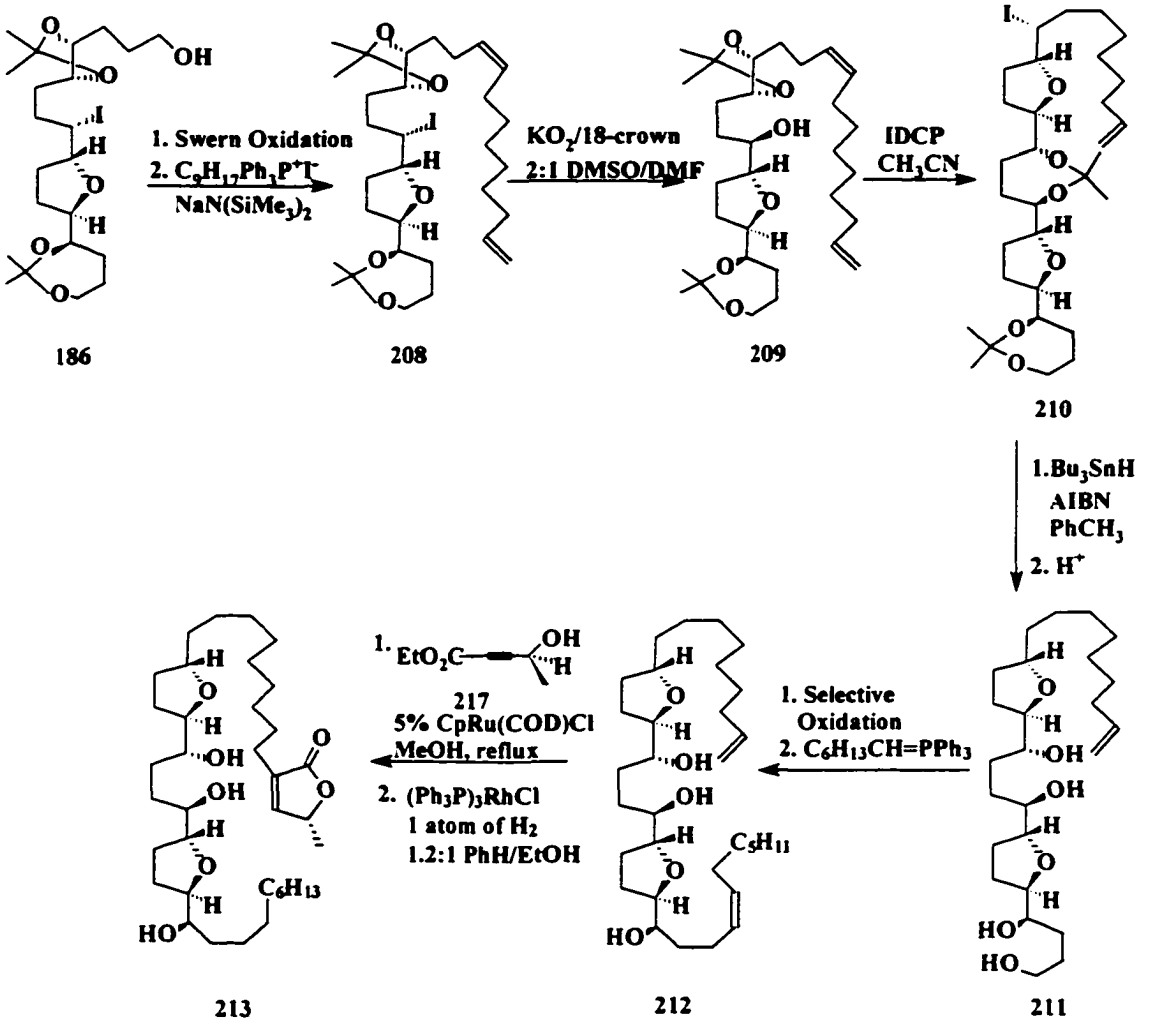


The trilobacin precursor **191** from our synthesis is identical to that prepared by Keinan. Bis-THF **191** was converted to **18** by a sequence involving introduction of alcohol protecting groups, iodination and phosphonium salt formation. Wittig coupling of the ylide derived from **18** and butenolide aldehyde **19** provided **20**. Selective hydrogenation

of **20** followed by removal of alcohol protecting groups afforded trilobacin. Our synthesis of trilobacin will require 18 steps from 1, 5-cyclooctadiene. Keinan's synthesis from butane 1,4-diol required 38 steps.

The mono-THF iodide **186** obtained in our work may also be converted to non-adjacently linked bis-THF structure like **211** (Scheme 55).

Scheme 55



For example, **186** may be transferred to the Z-alkene **208** in two straightforward steps. Iodide substitution will give the isopropylidene alkene **209,** which is set for another *trans*

directed THF cyclization to provide iodide derivative **210**. Iodide reduction and acetal hydrolysis will give **211**. Selective oxidation, followed by another Wittig reaction leads to **212**. Finally, the reaction of **212** and **213**, using the methodology which was developed by Trost in the synthesis of (+)-solamin[56] will provide Squamostatins-E **214**.

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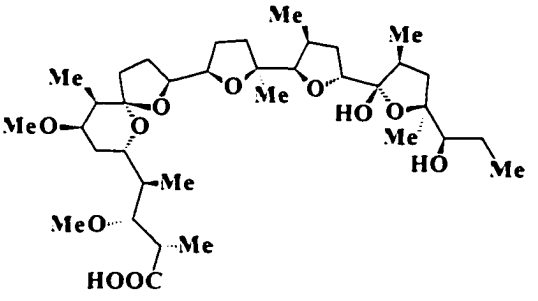
Chapter 5

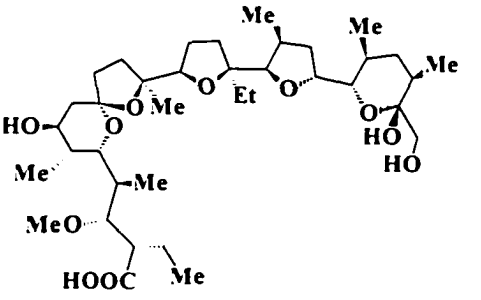
Synthesis of Analogs of Polyether Antibiotics

The ionophore antibiotics are a group of polyether structures which contain highly substituted, adjacently linked THFs connected to a spiroketal.[57] This family exhibits a wide spectrum of biological effects. Two examples are kijimicin (anti-HIV) and monensin (antifeedant) (Figure 10).

Figure 10



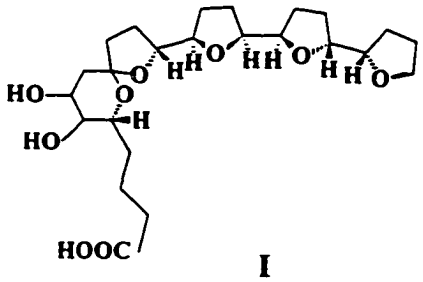
Kijimicin



Monensin

It is believed that their activity is related to the ability to chelate cation and to transport them across lipid membranes. However, detailed structure activity studies have not been worked out, presumably because of their structural complexity. For this reason, there has been interest in less substituted analogs.[58] In this section, as application of our bis-THF methodology, a relatively simple polyther analog **I** will be described (Figure 11). The target structure I was viewed as analog of Kijimicin and monensin.

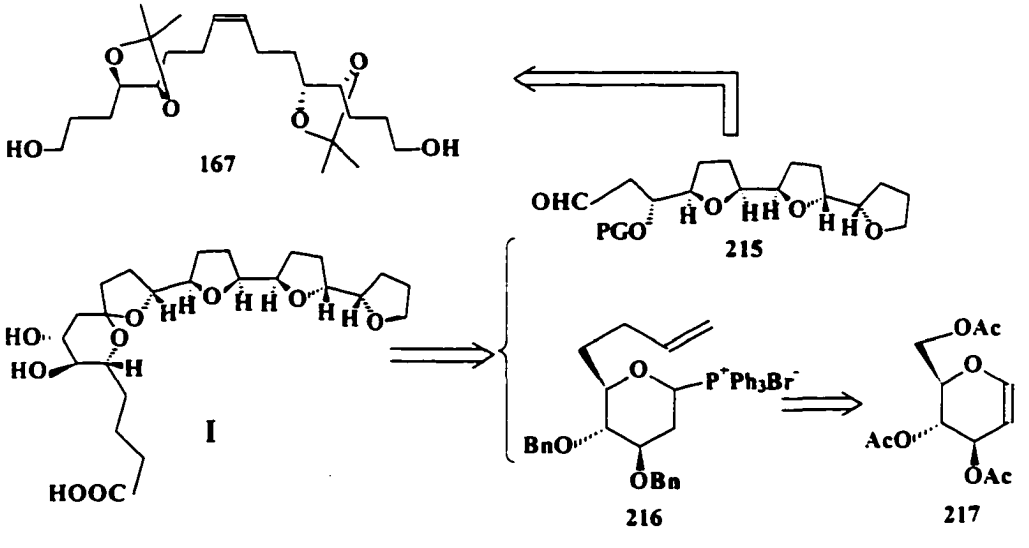
Figure 11



I

Retrosynthetically, Type **I** analog may be constructed from two fragments, oligo-THF aldehyde **215** and Wittig salt **216**, through Wittig reaction, followed by ring closure. The methodology has been previously used for a spiroketal system.[59] Oligo-THF aldehyde **215** may be prepared from bis-isopropylidene alkene **167** with three THF-ring formations. Wittig salt **216** can be synthesized from commercially available tri-O-acetyl-D-glucal **217**. The synthesis of the oligo-THF segment **215** was therefore undertaken (Scheme 56).

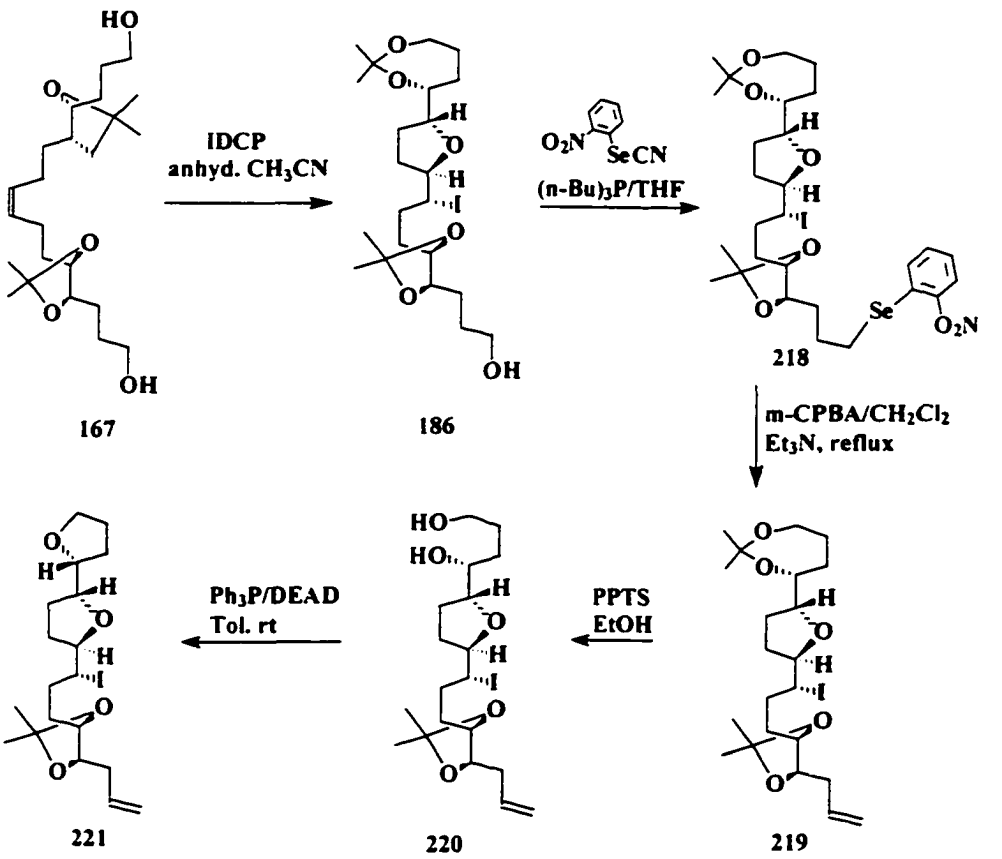
Scheme 56



Synthesis of Oligo-THF Fragment

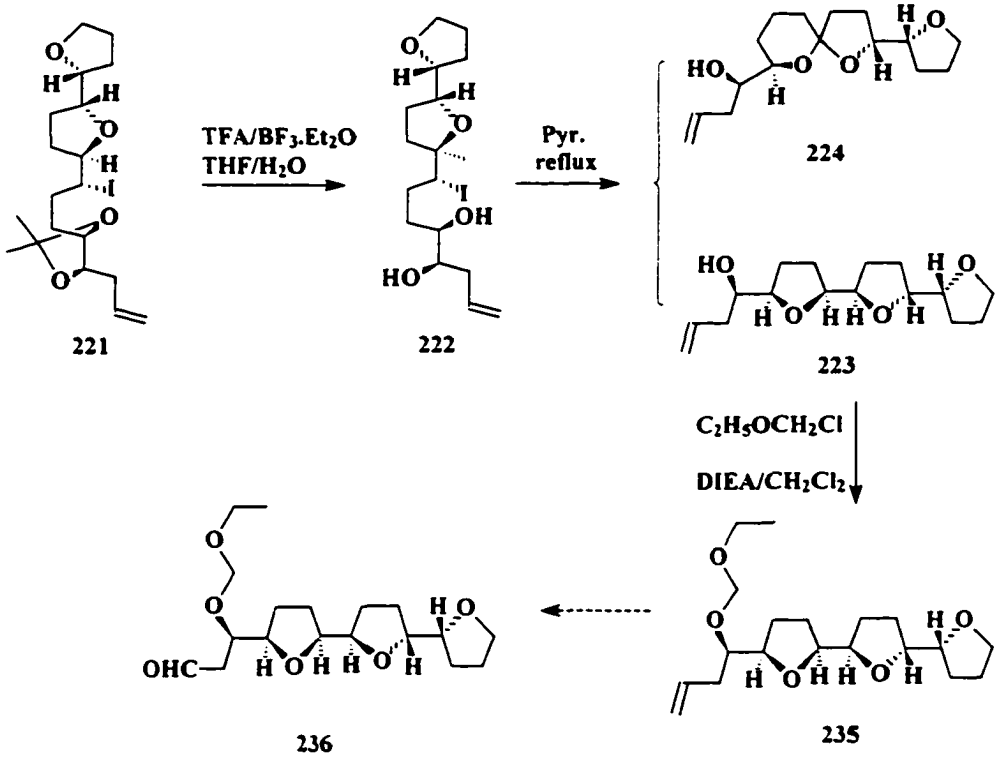
With the C2-Symmetrical bis-isopropylidene Z alkene **167** in hand, THF iodide **186** was obtained with our standard iodocyclization in 81% yield. Compound **186** was converted to the alkene **219** through a two step sequence. Treatment of **186** with 2-nitrophenyl selenocyanate and tri-n-butylphosphine gave **218** in 73% yield.[60] Alkene **219** was then obtained by elimination of **218** with mCPBA in 96% yield.[61] Selective hydrolysis of seven membered ring acetal with PPTS/EtOH provided **220** in 95% yield (Scheme 57).

Scheme 57



Application of Mitsunobu reaction condition to **220** led to the bis-THF **221** in 90% yield. Hydrolysis of the acetal group in **221**, followed by treatment of the resulting dihydroxy iodide in pyridine at 100 °C provided a 1:1 mixture of tri-THF **223** and spiroketal **224** in 59% overall yield. The undesired compound **224** is also a very useful precursor for analog of other polyethers such as dianemycin. Treatment of **233** with chloromethyl ethyl ether provided the alkene **225** which is a precursor to the tris-THF-aldehyde **226** which is segment for coupling with the glycol in the final spiroketalization (Scheme 58).

Scheme 58



221 222 223 224 235 236

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General Methods

List of Important Reactions

General Experimental Methods

Reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen or argon in oven dried flasks. Dry THF and diethyl ether were distilled from potassium and sodium benzophenone ketyl respectively. Dry methylene chloride was distilled from phosphorus pentoxide. Dry DMF and Et_3N were distilled from calcium hydride. Benzene and toluene were dried by azeotropic removal of water.

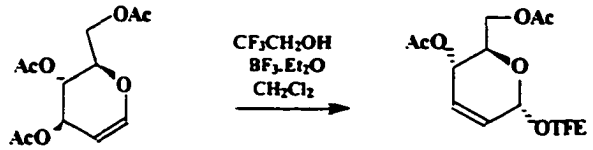
^1H and ^{13}C NMR spectra were obtained using a GE QE 300 (300 MHz) or Unity Plus 500 (500 MHz) spectrometer. Chemical shifts are reported relative to the deuterated solvent peak when noted or otherwise the TMS peak (0.00ppm). The following format was used to report peaks: chemical shifts in ppm (on the δ scale relative to tetramethylsilane), multiplicity (b=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), number of protons, coupling constant (J, in Hz), and proton assignment. Some proton assignments were deduced from $^1H/^1H$ COSY or $^1H/^{13}C$ HETCOR experiments.

Infrared (IR) spectra were obtained on a Perkin-Elmer 710B and reported in cm^{-1}. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory (Woodside, NY). High resolution mass spectrometric data (HRFABMS) was performed on 70-4F spectrometer at University of Illinois, Chicago. LC-MS was performed on Shimadzu-Micromass. Optical rotations were determined using a Rudolph Research AUTOPOL III automatic polarimeter and were determined in solutions of chloroform, otherwise stated. Thin-layer chromatograms were done on precoated TLC sheet of silica

gel 60 HF_{254} (E. Merck) and short and long-wave ultraviolet was used to visualize the spots. Flash chromatography was performed with silica gel 60 (230-400 mesh).). The following format was used to report the amount of silica gel: (Diameter of Column x Height of Silica Gel cm).

Aldehyde and Phosphorane Compounds

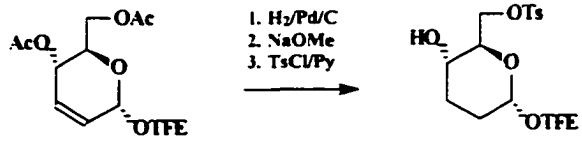
Trifluoroethyl 4-O-acetyl-6-O-acetyl-2,3-dideoxy-α-D-glucopyranoside



95 96

To a solution of tri-O-acetyl-D-gluco **95** (15.0 g, 55.0 mmol) in dry CH_2Cl_2 (400 mL) was added CF_3CH_2OH (11.0 g, 110mmol) and $BF_3.Et_2O$ (1.04 g, 7.3 mmol). The reaction was stirred at rt for 30 min. The solution was then poured into saturated, aqueous $NaHCO_3$ and the mixture extracted with ether (3x). The organic phase was dired (Na_2SO_4), filtered and evaporated in *vacuo*. Flash chromatography of the residue afforded **96** (15.1 g, 90%). TLC R_f = 0.76 (10% EtOAc/PE); ^1H NMR (300 MHz, $CDCl_3$), δ 2.15 (s, 6H, $2xCH_3$), 4.00 (m, 2H, CH_2CF_3), 4.13 (m, 1H, H_5), 4.24 (m, 2H, H_6), 5.15 (bs, 1H, H_1), 5.38 (dd, 1H, H_4), 5.95 (m, 2H, CH=CH).

Trifluoroethyl 6-O-tosyl-2, 3-dideoxy-α-D-glucopyranoside (97)



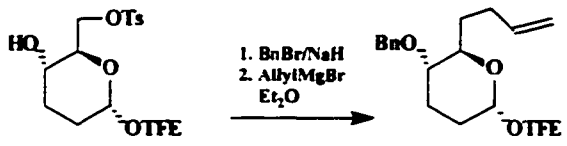
96 97

A mixture of **96** (30.0 g, 0.100mol), 10% w Pd/C in EtOAc (400 mL) was stirred under 1 atm of H_2 overnight. The resulting solution was filtered through a short plug of Celite and concentrated in *vacuo* to give trifluoroethyl 4-O-acetyl-6-O-acetyl-2,3-

dideoxy-α-D-glucopyranoside (29.3 g, 97%). Then, it was dissolved in MeOH (200 mL). A solution of NaOMe in MeOH (20 mL, 1M) was slowly added into the reaction mixture. When the starting material had completely disappeared (ca. 2h), a solution of 10% HCl/MeOH was carefully added to a pH of 8. The solution was concentrated *in vacuo* and the residue was partitioned between ether and saturated aqueous $NaHCO_3$. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification of the residue by flash chromatography (12x15 cm, 30% EtOAc/PE) provided trifluoroethyl 2,3-dideoxy-D-glucopyranoside (18 g, 80%).

To a stirred solution of trifluoroethyl-2,3-dideoxy-D-glucopyranoside (7.45 g, 32.4 mmol) in dry pyridine (35 mL) was added p-toluenesulfonyl chloride (8.00 g, 42.1 mmol) at 0 °C under atmosphere of nitrogen. The reaction mixture was stirred for 2.5 h at rt. then quenched with MeOH. After concentration of the solution, the residue was dissolved in ether and washed with saturated aqueous sodium bicarbonate and brine. The ethereal solution was dried over anhydrous Na_2SO_4. Concentration gave the crude product, which was purified by flash chromatography (10x12 cm, 20% EtOAc:PE) to give product **97** (10.0 g, 83.7%). TLC R_f= 0.3 (20% EtOAc:PE); $[\alpha]^{23}D$: +67° (c = 0.72); IR (neat) 3530, 2949, 1598, 1359, 1279 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 1.68-2.89 (m, 4H, H_2, H_3), 2.43 (s, 3H, Ar-CH_3), 2.70 (s, 1H, OH), 3.62 (m, 2H, H_4, H_5), 3.81 (m, 2H, CH_2CF_3), 4.19-4.36 (m, 2H, H_6), 4.79 (s, 1H, H_1), 7.22-7.83 (m, 4H, Ar-H's); ^{13}C NMR (75MHz, $CDCl_3$), δ 21.66, 26.72, 28.61, 64.01(q), 65.25, 69.60, 72.25, 96.86, 127.98, 129.96, 132.94, 145.14; Anal. Calcd for $C_{15}H_{19}O_{16}SF_3$: C, 46.87; H, 4.98. Found: C, 46.53; H, 5.10.

Trifluoroethyl 4-O-Benzyl-2,3,6,7,8,9-hexadeoxy-



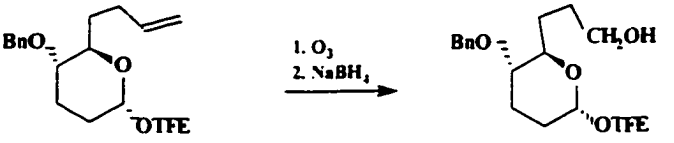
97 98

α-D-*gluco*-non-8-enopyranoside (98)

To a solution of **97** (8.90 g, 23.0 mmol) in dry THF (120 ML) at 0°C was added NaH (1.15 g 60% in mineral oil, 28.8 mmol) and benzyl bromide (3.14 mL, 26.4 mmol), followed by tetrabutylammonium iodide (450 mg, 1.2 mmol). The solution was stirred for 2h at rt under argon atmosphere. The reaction was quenched with H_2O, and extracted with ether (3x). The ether extract was washed with brine, dried (Na_2SO_4) and then concentrated in *vacuo*. The crude product was purified by flash chromatography (10x12 cm, 10% EtOAc/PE) to give product, the 4-O-benzyl ether of **97** (9.3 g, 82%). TLC R_f = 0.2 (10% EtOAc/PE); $[\alpha]^{23}D$: +76.64° (c = 2.74); IR (neat) 2950, 1598, 1362, 1279, 1176, 1087 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ1.79-2.20 (m, 4H, H_2, H_3), 2.54 (s, 3H, Ar-CH_3), 3.52 (ddd, 1H, H_4), 3.85-4.00 (m, 3H, Hs and $\underline{CH_2}CF_3$), 4.42-4.44 (ABX, 2H, H_6), 4.58 (ABq, Δυ = 63.5 Hz, J = 11.1Hz, 2H, $PhCH_2$), 4.92 (s, 1H, H_1), 7.34-7.94 (m, 9H, Ar-H's); ^{13}C NMR (75MHz, $CDCl_3$), δ 21.70, 23.28, 28.19, 64.50 (q), 69.33, 70.52, 70.71, 72.01, 96.86, 127.82, 127.92, 128.06, 128.44, 128.52, 129.85, 137.87; Anal. Calcd for $C_{22}H_{25}O_6SF_3$: C, 55.69; H, 5.31. Found: C, 55.64; H, 5.46.

To a solution of compound obtained in the previous step (7.8g, 16 mmol) in dry ether (85 mL) was added TMEDA (0.85 mL), followed by allylmagnesium bromide (90 mL) under an atmosphere of argon at rt. The reaction was stirred 8h, and quenched with saturated aqueous NH_4Cl. The product was extracted with ether (3x). The ethereal extracts were combined and dried (Na_2SO_4) and then concentrated in *vacuo*. The crude product was purified by flash chromatography (10x12cm, 10% EtOAc: PE) to give product **98** (5.59 g, 99%). TLC R_f = 0.3 (10% EtOAc/PE); IR (neat) 3068, 2974, 2948, 1641, 1496, 1455, 1370, 1279, 1161, 1078, 967 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 1.57-2.47 (m, 8H, H_2, H_3, H_6, H_7), 3.30 (ddd, 1H, H_4), 4.0(m, 2H, CH_2CF_3), 4.70 (AB, q, $\Delta\upsilon$=54.3Hz, J_{AB}=11.7Hz, 2H, $PhCH_2$), 4.97 (s, 1H, H_1), 5.15 (q, 2H, -CH=$\underline{CH_2}$), 5.98 (m, 1H, -$\underline{CH}$=CH_2), 7.4 (m, 5H, Ar-H's); ^{13}C NMR (75MHz, $CDCl_3$), δ 23.58, 28.70, 29.70, 31.21, 63.75 (m), 70.74, 71.79, 76.79, 96.67, 114.74, 127.81, 127.86, 128.29, 138.71. Anal. Calcd for $C_{18}H_{23}O_3F_3$: C, 63.04; H, 7.02. Found: C, 62.78; H, 6.70.

Trifluoroethyl 4-O-benzyl -2,3,6,7-tetradeoxy-α-D-*gluco*-octopyranoside (99)



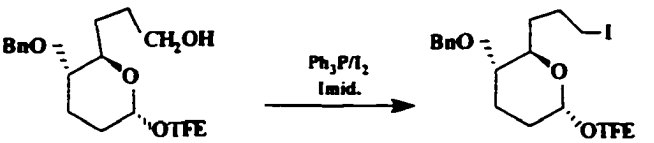
98 **99**

A solution of **98** (7.80 g, 22.7 mmol) in 250 mL of 4:1 CH_2Cl_2 and MeOH was cooled to -78°C. A stream of O_3 in O_2 was bubbled through the solution until **98** was not detectable by TLC analysis (10% EtOAc/PE). The mixture was flushed with N_2 and then

triphenylphosphine (6.60 g, 25.0 mmol) was added. The solution was warmed to rt, stirred for 2h, and concentrated *in vacuo* to give a slurry, which was used directly in the next step. For characterization purpose, a sample of the aldehyde was obtained by flash chromatography (20% EtOAc: PE). TLC R_f= 0.33 (20% EtOAc/PE); $[\alpha]^{23}D$: 127.9° (c = 0.38, CH_2Cl_2); IR (neat) 2943, 2728, 1715, 967 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ1.75-2.60 (m, 8H, H_2, H_3, H_6, H_7), 3.30 (ddd, 1H, H_4), 3.72 (ddd, 1H, H_5), 3.95 (m, 2H, CH_2CF_3) , 4.67 (ABq, Δυ = 58.2 Hz, J = 11.7 Hz, 2H, $PhCH_2$), 4.91 (s, 1H, H_1), 7.46 (m, 5H, Ar-H's), 9.84 (s, 1H, -CHO) ; ^{13}C NMR (75MHz, $CDCl_3$), δ 23.35, 24.83, 28.62, 40.35, 64.0 (m), 70.60, 71.73, 76.43, 96.77(C1), 127.91, 128.55, 138.19, 202.53.

To a solution of the crude mixture from above the containing aldehyde (theoretically 23.0 mmol) in EtOH (100 mL) was added $NaBH_4$ (5.63 mmol, 213 mg) at rt. The reaction mixture was stirred for 1h, and then diluted with 10% HCl in MeOH until the pH was 8. The ethanol was removed under reduced pressure. Flash chromatography of the residue (10x12 cm, 20% EtOAc/PE) gave **99** (6.79 g, 87%). TLC R_f = 0.12 (20% EtOAc/PE); $[\alpha]^{23}D$: 96.76° (c = 0.34, CH_2Cl_2); IR (neat) 3401, 2942, 2872, 1366, 1087, 967 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 1.53-2.2 (m, 8H, H_2, H_3, H_6, H_7), 3.30 (ddd, 1H, H_4), 3.75 (m, 3H, H_5, H_8), 4.06 (m, 2H, CH_2CF_3), 4.67 (ABq, Δυ = 55.85 Hz, J = 11.4 Hz, 2H, $PhCH_2$), 4.96 (s, 1H, H_1), 7.32-7.50 (m, 5H, Ar-H's); ^{13}C NMR (75MHz, $CDCl_3$), δ23.53(C3), 28.27(C2), 28.67 (C6, C7), 62.95 (C8), 63.90 (q), 96.78, 122.27, 125.95, 127.80, 127.91, 128.52, 138.30; Anal. Calcd for $C_{17}H_{23}O_4F_3$: C, 58.61; H, 6.65. Found: C, 58.41; H, 6.79.

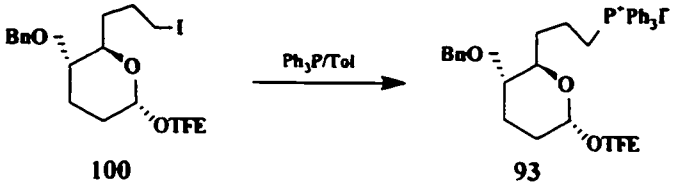
Trifluoroethyl 4-O-benzyl -8-iodo-2,3,6,7,8-pentadeoxy-α-D-*gluco*-octopyranoside (100)



99 100

To a solution of alcohol **99** (6.75 g, 19.5 mmol) in dry benzene (200 mL) were added triphenylphosphine (7.65 g, 29.2 mmol), imidazole (2.78 g, 40.8 mmol), and iodine (5.68 g, 22.4 mmol). The reaction mixture was refluxed for 1h under an atmosphere of argon, then diluted with ether and washed with saturated sodium thiosulfate and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (10x12cm, 10% EtOAc/PE) gave iodide **100** (7.54 g, 85.1%). TLC R_f = 0.60 (20% EtOAc/PE); $[\alpha]^{23}D$: 61.13° (c = 0.68, CH_2Cl_2); ^1H NMR (300MHz, $CDCl_3$) δ 1.59-2.15 (m, 8H, H_2, H_3, H_6, H_7), 3.25 (m, 3H, H_4, H_8), 3.66 (m, 1H, H_5), 3.97 (m, 2H, CH_2CF_3), 4.63 (m, 2H, $PhCH_2$), 4.88 (bs, 1H, H_1), 7.30-7.50 (m, 5H, Ar-H's); ^{13}C NMR (75MHz, $CDCl_3$), δ 6.95 (C8), 23.5 (C3), 28.61 (C6), 29.60 (C2), 32.96 (C7), 63.90 (q), 70.73, 71.66, 76.40, 96.80, 122.24, 125.93, 128.54, 128.72, 138.26. HRMS calcd for $C_{17}H_{22}O_3F_3I$ 458.0589 found 458.0545.

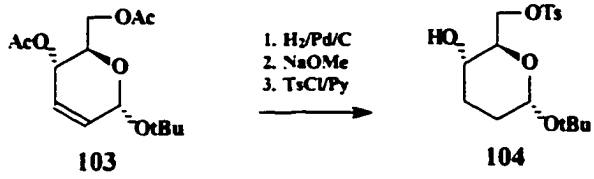
Trifluoroethul pyranoside phosphonium salt (93)



100 93

To a solution containing the iodide **100** (1.16 g, 2.53 mmol) and tripheynlphosphine (1.33 g, 5.06 mmol) in anhydrous toluene (40 mL) and acetonitrile (20 mL) was added diisopropylethylamine (0.7 mL, 3.8 mmol). The reaction mixture was heated at reflux under an atmosphere of argon for 24 h, then most of the solvent was removed under reduced pressure. The resulting syrup was triturated with cold hexane (2x25 mL) and the residual gum was subjected to flash chromatography (4x12cm, 5% MeOH in EtOAc) to give the phosphonium salt **93** (1.59 g, 86.8%). %). TLC R_f = 0.34 (10% MeOH/EtOAc); ^{1}H NMR (300MHz, $CDCl_3$); δ 1.20-2.36 (m, 8H, H_2, H_3, H_6, H_7), 3.25 (ddd, 1H, H_4), 3.52 (ddd, 1H, H_5), 3.73 (m, 2H, CH_2CF_3), 4.55 (ABq, Δυ = 46.9 Hz, J = 11.4 Hz, $PhCH_2$), 4.79 (bs, 1H, H_1), 7.20-7.90 (m, 20H, Ar-H's); ^{13}C NMR (75MHz, $CDCl_3$), δ 19.19, 23.02, 23.73, 23.69, 32.29, 32.50, 64.23 (q), 70.73, 72.13, 76.27, 96.74, 117.49, 118.64, 127.60, 127.89, 128.38. LCMS for **93** m/e 721 $(M+H)^+$ for $C_{35}H_{37}F_3O_3PI$.

t-Butyl 6-O-tosyl-2,3-dideoxy-α-D-glucopyranoside (104)



103 104

Compound **103** (8.50 g, 29.7 mmol), which was prepared from tri-O-acetyl-D-gluco, was subjected to the hydrogenation (98%), deacetylation (87%) and tosylation (83%) three step procedure described in the preparation of trifluoroethyl 6-O-tosyl-2,3-dideoxy-α-D-glucopyranoside **97**. It afforded product **104** (7.38 g, 83%). TLC R_f = 2.5 (30% EtOAc/PE); $[\alpha]^{23}D$: 37° (c = 0.25, CH_2Cl_2); IR (neat) 3533, 2973, 1663, 1598, 1360, 1175, 1054 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 1.19 (s, 9H, t-butyl-H), 1.71-2.20 (m, 5H, OH, H_2, H_3), 2.45 (s, 3H, Ar-CH_3), 3.21 (m, 1H, H_5), 3.86 (d, 1H, J = 10.5 Hz, H_4), 4.05-4.43 (m, 2H, H_6), 5.56 (s, 1H, H_1), 7.32-7.83 (m, 4H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$), δ 21.74, 27.00, 28.56, 28.64, 28.76, 30.84, 65.92, 70.06, 71.36, 74.51, 90.73(C_1), 128.06, 129.89, 133.04, 144.92; Anal. Calcd for $C_{17}H_{26}O_6S$: C, 56.96; H, 7.31. Found: C, 57.08; H, 7.35.

t-Butyl 4-O-benzoyl-6-O-tosyl-2,3-dideoxy-α-D-galactopyranoside (105)

104 105

A mixture of **104** (7.38 g, 20.0 mmol) and triphenylphosphine (6.61 g, 24.0 mmol) was dissolved in dry toluene (120 mL). A solution of benzoic acid (3.68 g, 30 mmol) and DEAD (4.72 mL, 30.0 mmol) in dry toluene (120 mL) was then added slowly at -15°C under an atmosphere of argon. The mixture was allowed to warm to rt, and stirred for 0.5h. After concentration, the mixture was neutralized by addition of saturated aqueous sodium bicarbonate, and then extracted with ether (3x). The ethereal extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (10x12cm, 20% EtOAc/PE) to give product **105** (9.28 g, 98.0%). TLC R_f = 4.5 (20% EtOAc/PE); $[\alpha]^{23}D$: 15.9° (c = 0.39, CH_2Cl_2); $[\alpha]^{23}D$: 15.85°; IR (neat) 3060, 2973, 1720, 1599, 1365, 1270, 1178, 1111, 1010 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$), δ 1.23 (s, 9H, t-butyl-H), 1.39-2.15 (m, 4H, H_2, H_3), 2.25 (s, 3H, Ar-CH_3), 3.94-4.07 (m, 2H, H_6), 4.41 (ddd, 1H, H_5), 5.06 (s, 1H, H_4), 5.18 (s, 1H, H_1), 7.11-7.93 (m, 9H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$), δ 21.62, 22.26, 25.95, 26.05, 28.53, 28.64, 28.78, 28.88, 66.79, 66.90, 67.20, 68.52, 74.72 (t-C), 91.28 (C_1), 127.91, 128.41, 129.65, 130.09, 132.52, 133.16, 144.83, 165.51; Anal. Calcd for $C_{24}H_{30}O_7S$: C, 62.32; H, 6.54. Found: C, 62.04; H, 6.71.

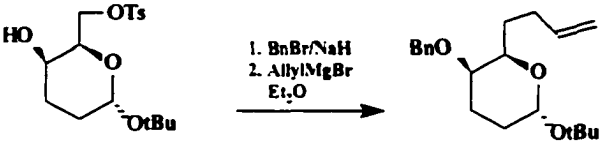
t-Butyl 6-O-tosyl-2,3-dideoxy-α-D-galactopyranoside (106)

105 106

To a solution of **105** (9.20 g, 19.5 mmol) in MeOH (200 mL) was slowly added a 1M solution of NaOMe in MeOH (20 mL) at rt. The reaction was monitored by TLC (20% EtOAc/PE). When the starting material had completely disappeared (*ca.* 2h), a solution of 10% HCl/MeOH was carefully added until a pH of 8 was obtained. The solution was concentrated *in vacuo* and the residue was partitioned between ether and washed with saturated aqueous $NaHCO_3$. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by flash chromatography (10x12cm, 30% EtOAc/PE) provided product **106** (5.4 g, 76%) as a light yellow oil. %). TLC R_f = 0.85 (20% EtOAc/PE); $[\alpha]^{23}D$: 38.98° (c = 0.29, CH_2Cl_2); IR (neat) 3533, 2973, 1663, 1598, 1361, 1177, 1011 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 1.21 (s, 9H, t-butyl-H), 1.35-2.10 (m, 5H, OH, H_2, H_3), 2.45 (s, 3H, Ar-CH_3), 3.75 (s, 1H, H_4), 3.95-4.19 (m, 2H, H_6), 4.22 (ddd, 1H, H_5), 5.10 (s, 1H, H_1), 7.32-7.83 (m, 4H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$), δ 21.72, 25.23, 28.532, 28.63, 28.75, 28.85, 64.29, 67.89, 69.74, 91.34(C_1), 128.05, 129.92, 132.93, 144.92. Anal. Calcd for $C_{17}H_{26}O_6S$: C, 56.96; H, 7.31. Found: C, 56.65; H, 7.42.

t-Butyl 4-O-Benzyl-2,3,6,7,8,9-hexadeoxy-

α-D-*gluco*-non-8-enopyranoside (107)



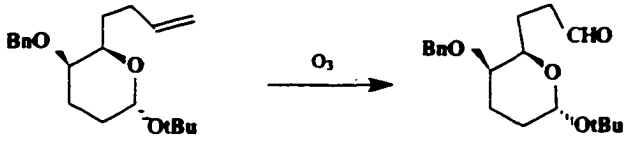
106 107

Compound **106** (5.39 g , 15.2 mmol) was subjected to the procedure described in the preparation of the 4-O-benzyl ether of **97** using NaH (1.20 g, 60% in mineral oil, 30.0 mmol), BnBr (2.8 mL, 26 mmol) and tetrabutylammonium iodide (830 mg, 2.25 mmol). The crude product was purified by flash chromatography (10x12cm, 10% EtOAc/PE) to give the 4-O-benzyl ether of **106** (4.83 g, 71.0%). TLC R_f = 0.75 (20% EtOAc/PE); $[\alpha]^{23}D$: 24.84° (c = 0.32, CH_2Cl_2); IR (neat) 3064, 2972, 1722, 1598, 1362, 1189, 1013 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9H, t-butyl-H), 1.29-2.15 (m, 4H, H_2, H_3), 2.52 (s, 3H, Ar-CH_3), 3.59 (s, 1H, H_4), 4.21 (m, 2H, H_6), 4.29 (ddd, 1H, H_5), 4.54 (ABq, $\Delta\upsilon$ = 82 Hz, J = 12 Hz, 2H, $PhCH_2$), 5.22 (d, 1H, H_1), 7.34-7.88 (m, 9H, Ar-H's); ^{13}C NMR (75 MHz, $CDCl_3$), δ 20.43, 21.70, 25.68, 28.74, 68.10, 69.92, 70.67, 70.74, 74.40, 91.25, 127.68, 127.75, 128.01, 128.40, 129.89, 133.00, 138.31, 144.79; Anal. Calcd for $C_{24}H_{32}O_6S$: C, 64.26; H, 7.19. Found: C, 64.32; H, 7.35.

The compound obtained in the previous step (4.47 g, 9.98 mmol) was subjected to the procedure described in the preparation of compound **97**, using allyl magnesium bromide (100mL). After work-up, the crude product was purified by flash chromatography (4x12cm, 10% EtOAc:PE) to provide product **107** (2.66 g, 84%). TLC R_f = 0.44 (10% EtOAc/PE); IR (neat) 3066, 2974, 2947, 1651, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 9H, t-butyl-H), 1.20-2.20 (m, 8H, H_2, H_3, H_6, H_7), 3.34 (s, 1H, H_4), 3.91(ddd, 1H, H_5), 4.55 (ABq, $\Delta\upsilon$ = 82.8 Hz, J = 12 Hz, 2H, $PhCH_2$), 4.94 (m, 2H, $=CH_2$), 5.16 (s, 1H, H_1), 5.80 (m, 1H, CH=), 7.24-7.38 (m, 5H, Ar-H's); ^{13}C NMR (75 MHz, $CDCl_3$), δ 21.16, 26.10, 28.90, 29.99, 30.95, 69.76, 70.60, 72.73, 73.94, 91.22,

114.40, 127.52, 128.32, 128.39, 128.44, 138.92, 138.99. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.04; H, 9.62.

t-Butyl pyranoside aldehyde (94)

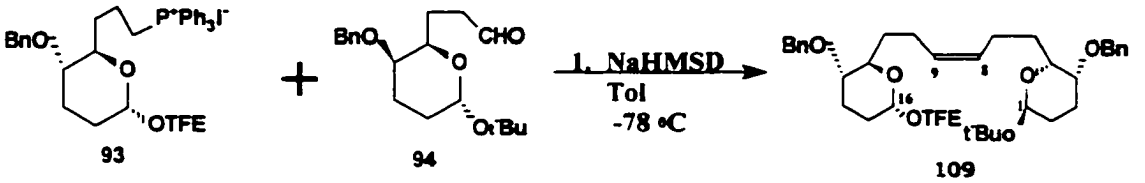


107 94

Compound **107** (555 mg, 1.75 mmol) was subjected to the standard ozonolysis procedure described in the preparation of compound **99**. After work-up, the crude product was purified by flash chromatography (1.5x15cm, 10% EtOAc:PE) to provide t-butyl pyranoside aldehyde **94** (447 mg, 80%). TLC R_f = 0.51 (20% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 9H, t-butyl-H), 1.25-2.20 (m, 6H, H_2, H_3, H_6), 2.45 (m, 2H, H_7), 3.38 (s, 1H, H_4), 3.97 (dd, 1H, H_5), 4.55 (ABq, Δυ = 85.6 Hz, J = 12 Hz, 2H, $PhCH_2$), 5.19 (s, 1H, H_1), 7.31-7.40 (m, 5H, Ar-H's), 9.76 (s, 1H, CHO) ; ^{13}C NMR (75 MHz, CDCl3), δ 21.49, 24.91, 26.50, 29.51, 40.92, 70.01, 71.25, 73.45, 74.51, 91.90, 128 (m, 4C), 139.10, 203.23.

Bis-Saccharide-E-Alkene

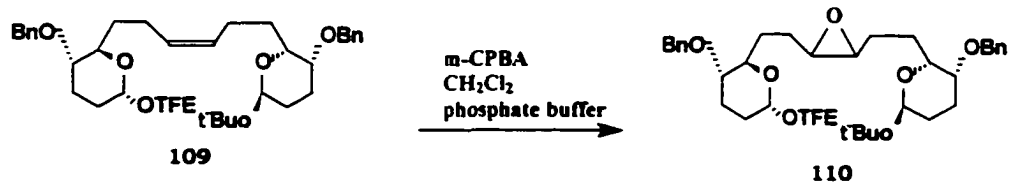
t-Butyl-Z-trifluoroethyl bis-pyranoside alkene (109)



To a solution of phosphonium salt **93** (1.18 g, 1.65 mmol) in dry toluene (25 mL) was added a 1M solution of sodium bis(trimethylsilyl) amide (NaHMDS) in toluene (1.38 mL, 1.38 mmol), under an atmosphere of argon. The yellow-orange suspension was stirred for 1h at rt then cooled to -78°C. A solution of aldehyde **94** (0.44 g, 1.38 mmol) in dry toluene (20 mL) was added dropwise over 30 min. After an additional 15 min, the reaction mixture was warmed to rt, then diluted with ether (100 mL). The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (4x12cm, 10% EtOAc/PE) to afford **109** (732 mg, 84%). TLC R_f: 0.55 (10% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 9H, t-butyl-H), 1.20-2.23 (m, 16H, H_2, H_{15}, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 3.19 (ddd, 1H, H_{13}), 3.37 (bs, 1H, H_4), 3.63 (ddd, 1H, H_{12}), 3.75-4.00 (m, 3H, CF_3CH_2, H_5), 4.58 (ABq, Δυ = 77.7 Hz, J = 12.6 Hz, 2H, $PhCH_2$), 4.58 (ABq, Δυ = 51.9 Hz, J = 11.7 Hz, 2H, $PhCH_2$), 4.67 (bs, 1H, H_{16}), 5.19 (bs, 1H, H_1), 5.42 (m, 2H, CH=CH), 7.28-7.42 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 21.22, 23.21, 23.66 (C7, C10), 26.10, 28.69, 28.88 ($(CH_3)_3C$), 31.63, 31.94, 63.65 (q, J = 34 Hz $\underline{C}H_2CF_3$), 69.93, 70.67, 70.77, 71.99, 72.85, 73.92, 76.81, 91.23, 96.63, 122.35, 126.02, 127.49, 127.84, 128.10, 128.31, 128.50, 129.55

(C9), 130.14 (C8), 138.45. Anal. Calcd for $C_{36}H_{49}O_6F_3$: C, 68.11; H, 7.78. Found: C, 67.85; H, 7.84.

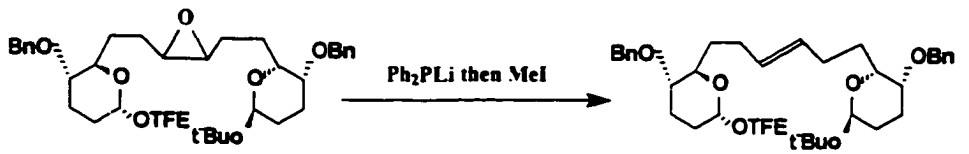
t-Butyl-trifluoroethyl bis-pyranoside epoxide (110)



109 110

m-CPBA (784 mg, 50% w/w, 2.5 mmol) was suspended in a mixture of 4M NaH_2PO_4/Na_2HPO_4 buffer (40 mL) and CH_2Cl_2 (20 mL). The suspension was added to a solution of **109** (635 mg, 0,998 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at rt for 1h. The organic layer was separated, and washed with saturated, aqueous solutions of $NaHCO_3$ and $Na_2S_2O_3$, and brine, dried (Na_2SO_4) and concentrated in *vacuo*. The residue was purified by flash chromatography (2.5x12 cm, 20% EtOAc/PE) to afford epoxide derivative **110** (655 mg, 100%). R_f: 0.45 (20% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 9H, t-butyl-H), 1.20-2.20 (m, 16H, H_2, H_{15}, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 2.98 (m, 2H, H_8, H_9), 3.20 (m, 1H, H_{13}), 3.39 (s, 1H, H_4), 3.69 (m, 1H, H_{12}), 3.79-4.07 (m, 3H, CF_3CH_2, H_5), 4.40-4.75 (m, 2x$PhCH_2$), 4.86 (bs, 1H, H_{16}), 5.20 (bs, 1H, H_1), 7.28-7.42 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.16, 23.54, 23.81, 23.94, 24.06, 24.67, 26.03, 28.33, 28.66, 28.84, 29.09, 56.76, 57.15, 57.60, 63.59 (q), 69.78, 70.17, 70.65, 70.75, 71.86, 72.19, 73.11, 73.94, 76.55, 91.22, 96.73, 127.56, 127.83, 127.90, 128.34, 128.51, 138.50, 139.00.

t-Butyl-E-trifluoroethyl bis-pyranoside alkene (108)



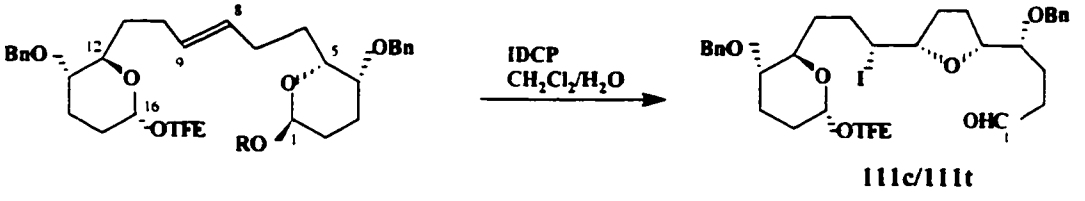
110 108

A 0.5M stock solution of Ph_2PLi was prepared by the addition of a hexane solution of n-butyllithium (6.6 mL,1.55M) to a solution of Ph_2PH (1.74 mL) in dry THF (12 mL) at rt under an argon atmosphere, then stirred for 1h. An aliquot of the red solution of Ph_2PLi (6.0 mL, 3.0 mmol) was added to a solution of **110** (655 mg, 1.01 mmol) in dry THF (10 mL) at rt under an atmosphere of argon, and stirring was continued for an additional 2h. At that time freshly distilled MeI (0.374 mL, 6.0 mmol) was added. The mixture was stirred for another 1h, and n-butyllithium (~0.1mL) was added until a red color persisted. The reaction mixture was diluted with ether (30 mL), filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was subjected to flash chromagraphy (2.5x12 cm, 20% EtOAc/PE) to afford **108** (496 mg, 78%). TLC R_f = 0.54 (20% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 9H, t-butyl-H), 1.20-2.23 (m, 16H, H_2, H_{15}, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 3.19 (ddd, 1H, H_{13}), 3.37 (s, 1H, H_4), 3.63 (ddd, 1H, H_{12}), 3.75-4.00 (m, 3H, CF_3CH_2, H_5), 4.58 (ABq, Δυ = 77.7 Hz, J = 12.6 Hz, 2H, $PhCH_2$), 4.58 (ABq, Δυ = 51.9 Hz, J = 11.7 Hz, 2H, $PhCH_2$), 4.67 (s, 1H, H_{16}), 5.21 (bs, 1H, H_1), 5.39 (m, 2H, CH=CH), 7.28-7.42 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 21.24, 23.62, 26.12, 28.55, 28.70, 28.91 (C7, C10, $(\underline{C}H_3)_3C$), 31.62, 31.95, 63.45 (q, J = 34 Hz, $\underline{C}H_2CF_3$), 69.89, 70.68, 70.79, 71.91, 72.90, 73.91, 76.82, 91.22, 96.62, 127.48-

128.50 (5 peaks, $\underline{C}F_3$), 130.03 (C9), 130.67 (C8), 138.43, 138.98. Anal. Calcd for $C_{36}H_{49}O_6F_3$: C, 68.11; H, 7.78. Found: C, 68.00; H, 7.78.

Formation of First THF Ring

Mono-THF-iodide 111c/111t (from t-butyl-E-alkene, R=t-Bu 108)



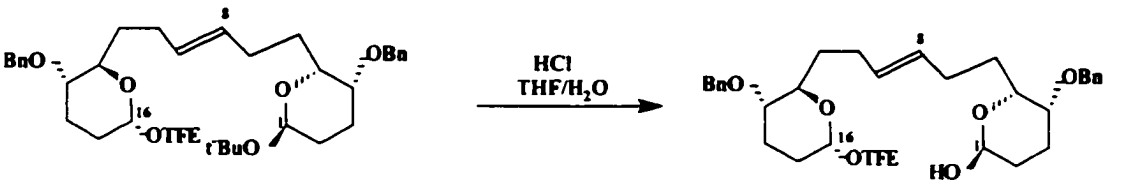
111c/111t

To a solution of t-butyl-E-alkene **108** (496 mg, 0.781 mmol) in a mixture of (CH_2Cl_2, 20 mL) and water (0.5 mL) was added IDCP (549.4 mg, 1.17 mmol). The mixture was stirred at rt for 20 min, then poured into a saturated, aqueous $Na_2S_2O_3$, and extracted with ether (2x). The organic phase was dried (Na_2SO4), filtered and evaporated *in vacuo*. Flush chromatography of the residue (2.5x12 cm, 2% ether/CH_2Cl_2) afforded **111c/t** (~9:1, from ^{13}C NMR) as an inseparable mixture of isomers (406 mg, 70%).

111c R_f: 0.35 (2% ether/CH_2Cl_2); ^1H NMR (300 MHz, C_6D_6), δ 1.04-2.04 (m, 16H, H_2, H_{15}, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 2.90 (m, 1H, H_{13}), 3.06 (m, 1H, H_4), 3.32 (m, 1H, H_8), 3.45-3.70 (m, 4H, CF_3CH_2, H12, H_5), 3.87 (m, 1H, H_9), 4.20-4.43 (m, 3H, H_{16}, $PhCH_2$), 4.38 (ABq, Δυ = 145 Hz, J = 11.8 Hz, 2H, $PhCH_2$), 6.95-7.40 (m, 10H, Ar-H), 9.25 (s, 1H, CHO). ^{13}C NMR (75 MHz, C_6D_6), δ 23.37, 23.88, 27.27, 28.33, 31.60, 31.72 (C7), 32.21 (C6), 39.86, 42.53, 43.32, 63.56 (q, $\underline{C}H_2CF_3$), 70.18, 71.73, 72.82, 76.04, 80.16, 82.78, 83.63, 96.68 (C16), 127-129 (multiple peaks), 138.81, 139.21, 200.23 (CHO). MS (FAB) calcd for $C_{32}H_{40}F_3IO_6$ $(M-H)^-$ 703, found 703.

111t R_f: 0.35 (2 % ether/CH_2Cl_2); ^1H NMR (300 MHz, C_6D_6), δ 1.04-2.04 (m, 16H, H_2, H_{15}, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 2.90 (m, 1H, H_{13}), 3.06 (m, 1H, H_4), 3.32 (m, 1H, H_8), 3.45-3.70 (m, 4H, CF_3CH_2, H12, H_5), 3.79 (m, 1H, H_9), 4.10-4.66 (m, 3H, H_{16}, $PhCH_2$), 6.95-7.40 (m, 10H, Ar-H), 9.25 (s, 1H, CHO). ^{13}C NMR (75 MHz, C_6D_6), δ 23.37, 23.78, 27.34, 28.48, 31.59, 33.02 (C7), 33.46 (C6), 42.80, 43.32, 63.56 (q, $\underline{C}H_2CF_3$), 70.18, 71.73, 72.26, 76.13, 76.30, 80.44, 82.52, 83.29, 83.76, 96.68 (C16), 127-129 (multiple peaks), 138.81, 139.21, 200.23 (CHO).

Trifluoroethyl pyranoside-E-pyranose (112)

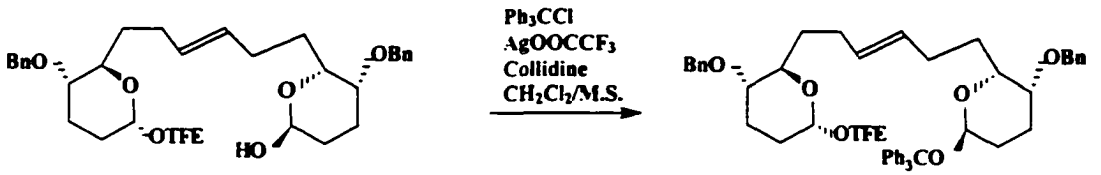


108 **112**

A solution of t-butyl-E-trifluoroethyl bis-pyranoside **108** (140 mg, 0.22 mmol) in a 3:1 mixture of THF-0.5M HCl (12 mL) was stirred at rt for 4h. The solution was then poured into saturated, aqueous $NaHCO_3$ and the mixture was extracted with ether. The organic phase was dried (Na_2SO_4), filtered and evaporated in *vacuo*. Flash chromatography of the residue afforded the trifluoroethyl-E-pyranose **112** (90 mg, 70%). TLC R_f= 0.15 (20% EtOAc/PE); ^1H NMR (300 MHz, $CDCl_3$), δ 1.2-2.4 (m, 16H, H_2, H_{15}, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 2.84 (s, 1H, OH), 3.24 (m, 1H, H_{13}), 3.37 (bs, H4 α-pyranose), 3.45 (bs, H_5 α-pyranose), 3.56 (bs, H_4 β-pyranose), 3.65 (m, 1H H_{12}), 3.80-4.32 (m, 3H,

CF_3CH_2, H_5 β-pyranose); 4.47-4.89 (m, H1 β-pyranose, 2x$PhCH_2$), 4.96 (bs, 1H, H_{16}), 5.40 (bs, H_1 α-pyranose), 5.50 (bs, 2H, CH=CH), 7.08-7.52 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 21.73, 24.02, 24.39, 24.62, 25.63, 26.52, 28.62, 29.71, 31.59, 32.32, 33.10, 33.39, 65.01 (q, J = 33.7 Hz, $\underline{C}H_2CF_3$), 69.93, 71.84, 71.90, 72.98, 73.62, 74.42, 77.76, 92.57 (C1-β-anomer), 99.54 (C1-α-anomer), 97.79, 97.88 (C16 α/β mixture), 128.60-131.40 (multiple peaks), 139.37, 139.70, 146.20.

Trityl-E-trifluoroethyl bis-pyranoside alkene (113)



112 113

A portion of the lactol mixture **112** obtained in the previous step (137 mg, 0.236 mmol), trityl chloride (130 mg, 0.472 mmol), collidine (0.1 mL, 1 mmol), and freshly activated, powdered 4A molecular sieves (100 mg), in anhydrous CH_2Cl_2 (10mL) was stirred at rt for 10 min. At that time $AgOCOCF_3$ (181 mg, 0.7 mmol) was added to the reaction mixture and stirring was continued for an additional 4h. The reaction mixture was then poured into saturated aqueous $Na_2S_2O_3$, and extracted with ether. The combined organic phases were dried (Na_2SO_4), filtered and evaporated in *vacuo*. Flash chromatography of the residual gum afforded **113**α/β (116 mg, 60%) as an in separable mixtuer of anomers. TLC R_f = 0.82 (20% EtOAc/PE); ^1H NMR (300 MHz, $CDCl_3$),

δ 1.00-2.40 (m, 16H, H_2, H_{15}, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 2.96 (bs, H_5 β-pyranose), 3.08 (bs, H_4 β-pyranose), 3.22 (m, 1H H_{13}), 3.42 (bs, H_4 α-pyranose), 3.64 (m, 1H H_{12}), 3.75-4.05 (m, CF_3CH_2, H5 α-pyranose), 4.38-4.75 (m, H_1 β-anomer, 2x$PhCH_2$), 4.88 (bs, 1H, H_{16}) 5.24 (bs, H_1 α-anomer), 5.33 (bs, 2H, CH=CH), 7.20-7.67 (m, 25H, Ar-H). α/β=~1:2 (based on the relative ratio of H4 singlets at 3.42 and 3.08).^{13}C NMR (75 MHz, CDCl3), δ 22.57, 24.19, 24.66, 26.44, 26.90, 27.89, 29.75, 30.82, 31.91, 64.80 (q, J = 33.7 Hz, $\underline{C}H_2CF_3$), 71.89, 72.12, 72.29, 73.10, 73.23, 77.86, 77.91, 78.31, 78.92, 88.27 and 89.00 ($\underline{C}Ph_3$, α/β mixture), 93.98 (C1-β-anomer), 97.73 (C16 α/β mixture), 99.30 (C1-α-anomer), 128.00-131.0 (multiple peaks), 139.55, 139.89, 146.09. MS: m/e 838 $(M+NH_4)^+$ for $C_{51}H_{55}O_6F_3$; m/e 821 $(M+H)^+$ for $C_{51}H_{55}O_6F_3$.

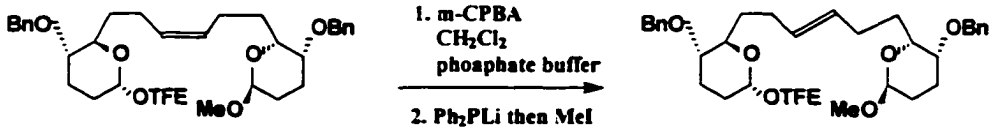
Mono-THF-iodide 111c (from trityl-E-alkene, R=trityl 113)

113 111c

A mixture of trityl-E-trifluororethyl alkenes **113**α/β (600 mg, 0.75 mmol) in CH_2Cl_2 (20 mL) and water (0.5 mL) was treated with IDCP (540 mg, 1.15 mmol) as described for the corresponding reaction of **108**. Processing of the reaction mixture and purification of the crude product as before, afforded the cis-THF-iodide **111c** (406 mg, 79%), which was

identical (TLC, ^1H and ^{13}C NMR) to major peaks of **111** obtained from the reaction of **108.**

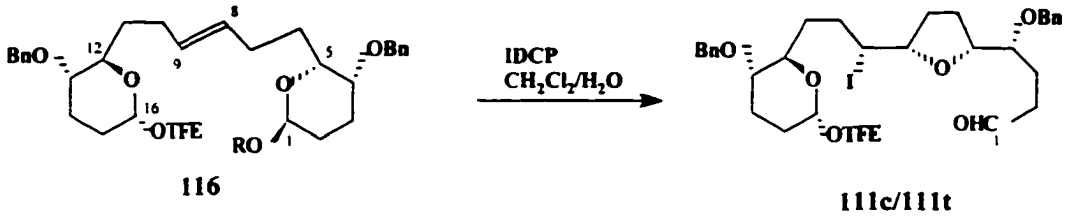
Methyl-E-trifluoroethyl bis-pyranoside Alkene (116)



115 **116**

The procedure for the preparation of **116** was the same as one used for the preparation of **108.** A sample of **115** (320 mg, 0.54 mmol) gave **116** (240 mg, 78%). TLC R_f = 0.35 (20% EtOAc/PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 9H, t-butyl-H), 1.40-2.40 (m, 16H, H_2, H_{15}, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 3.22 (ddd, 1H, H_{13}), 3.38 (s, 1H, H_4), 3.42 (s, 3H, CH_3), 3.66 (ddd, 1H, H_{12}), 3.90 (m, 1H, H_5), 3.99 (m, 2H, CF_3CH_2), 4.62 (m, 4H, 2x$PhCH_2$), 4.81(bs, 1H, H_{16}), 5.89 (bs, 1H, H_1), 5.48 (m, 2H, CH=CH), 7.30-7.44 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 21.27, 23.6, 24.32, 28.57, 28.69, 28.80, 31.56, 31.91, 54.68 (CH3), 63.91 (q, CH_2CF_3), 69.85, 70.78, 71.91, 72.68, 96.62, 98.22, 127.62-128.50 (4 peaks, CF3), 127.61, 127.85, 127.96, 128.37, 128.50, 130.29(C9), 130.40(C8), 138.40, 138.77.

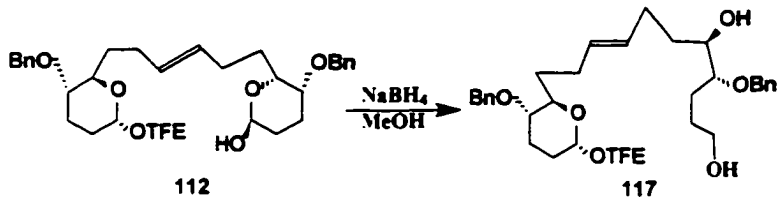
Mono-THF-iodide 111c/111t (from methyl-E-alkene, R=Me 116)



116 111c/111t

To a mixture of methyl-E-trifluororethyl alkenes **116** (240 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) and water (0.25 mL) was added IDCP (281 mg, 0.6 mmol) as described for the corresponding reaction of **108**. Processing of the reaction mixture and purification of the crude product as before, afforded **111c/t** (~5:1, from ^{13}C NMR) as an inseparable mixture of isomers (170 mg, 60%), which was identical (TLC, ^1H and ^{13}C NMR) to the sample of **111c/111t** obtained from the reaction of **108**.

Trifluoroethyl pyranoside-E-dihydroxy alkene (117)

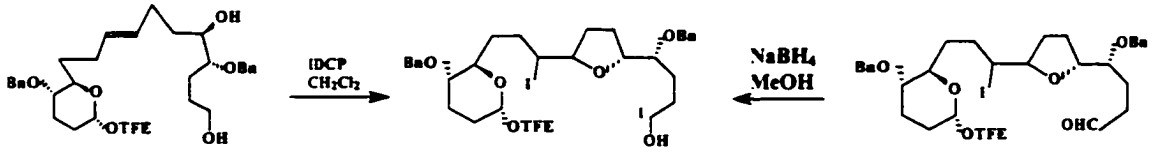


112 117

To a solution of **112** (63.6 mg, 0.10 mmol) in MeOH (2.5 mL) was added $NaBH_4$ (20.0 mg, 0.50 mmol) at rt. The reaction mixture was stirred for 10 min, and then 10% HCl in MeOH was added until the pH = 8. The solvent was removed under reduced pressure. Flash chromatograpy of the residue gave **117** (36 mg, 57%). TLC R_f = 0.13 (30% EtOAc/PE); ^1H NMR (300 MHz, $CDCl_3$), δ 1.2-2.4 (m, 16H, H_2, H_{15}, H_3, H_{14}, H_6,

H_{11}, H_7, H_{10}), 3.15 (ddd, 1H, H_{13}), 3.35 (m, 1H, H_4), 3.6 (m, 4H, H_1, H_{12}, H_5), 3.85 (m, 2H, CF_3CH_2), 4.55 (m, 4H, 2x$PhCH_2$), 4.82 (bs, 1H, H_{16}), 5.45 (m, 2H, CH=CH), 7.20-7.42 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 23.61, 26.50, 28.32, 28.57, 28.69, 28.80, 31.88, 33.24, 54.68 ($\underline{C}H_3$), 63.02, 63.53 (q, $\underline{C}H_2CF_3$), 70.88, 71.82, 72.14, 72.63, 82.17, 96.67, 127.62-128.50 (5 peaks, $\underline{C}F_3$), 127.61, 127.85, 127.96, 128.37, 128.50, 130.14(C9), 130.63(C8), 138.30, 138.67.

Mono-THF-Iodides (118c/118t)



117 118c/118t 111c/111t(5:1)

1. Product from 117

To a solution of **117** (16 mg, 0.030 mmol) in dry CH_2Cl_2 (2 mL) was added IDCP (80 mg, 0.17 mmol). The mixture was stirred at rt for 10 min, then poured into saturated, aqueous $Na_2S_2O_3$, and extracted with ether. The combined organic phases were dried (Na_2SO_4), filtered and evaporated in *vacuo*. Chromatography of the residue afforded **118c/118t** (10 mg, 52%) as an inseparable mixture of isomers (~2:3, calculated from ^1H NMR signal of $PhCH_2$).

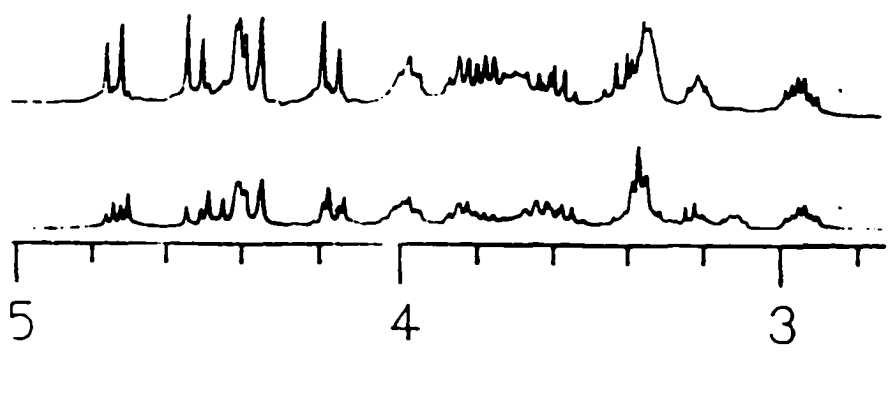
118c/t: TLC R_f = 0.27 (30% EtOAc/PE); ^1H NMR (300 MHz, C_6D_6), δ 1.00-2.20 (m, 16H, H_2, $H_{2'}$, H_3, $H_{3'}$, H_6, $H_{6'}$, H_7, $H_{7'}$), 2.90 (m, 1H, H13), 3.15 (m, H4t), 3.23 (m,

H4c), 3.30-3.90 (m, 5H, CF3CH2, H8, H12, H5), 3.98 (m, 1H, H9), 4.10-4.80 (m, 3H, H16, PhCH2), 6.95-7.40(m, 10H, Ar-H).

2. Product from 111(5:1c/t)

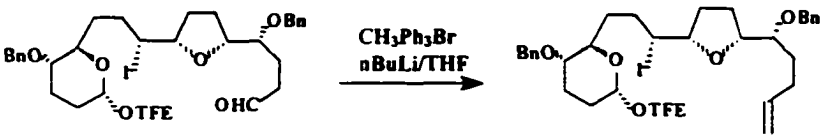
Compound **111**(5:1 c/t, 20 mg, 0.028 mmol) was subjected to the $NaBH_4$ reduction procedure described in the preparation of compound **117**. It gave **118c/t** (15 mg, 75%) (~5:1, calculated from the ^1H NMR signal of $PhCH_2$).

Following is compound **118's** ^1H NMR spectrum comparison from **117** and **111**.



Formation of Second THF Ring

Mono-THF-Iodide Alkene (119)

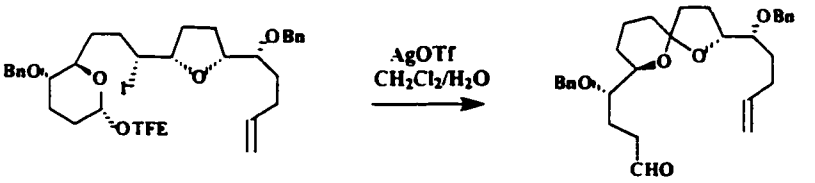


111c 119

A solution of methylenetriphenylphosphorane was prepared by addition of n-BuLi (1.23 mL of 1.55 M solution in hexane, 1.91 mmol) to a suspension of methyltriphenylphosphonium bromide (760 mg, 2.1 mmol) in dry THF (5 mL) at 0 °C, under an atmosphere of argon. The mixture was stirred at this temperature for 1h, then cooled to -78°C, at which time a solution of **111c** (270 mg, 0.383 mmol, prepared from trityl-E-alkene **113**) in dry THF (5 mL) was slowly introduced. The solution was allowed to warm to rt and stirred for an additional 10 min. The reaction mixture was then diluted with ether, filtered through a short column of Celite, and the filtrate was concentrated *in vacuo*. Flash chromatography (2.5x12 cm, 10% EtOAc/PE) of the residue gave **119** (205 mg, 76%). TLC R_f = 0.41 (10% EtOAc/PE); ^{1}H NMR (300 MHz, C_6D_6), δ 1.00-2.35 (m, 16H, H_2, H_{15}, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 2.89 (m, 1H, H_{13}), 3.18 (m, 1H, H_4), 3.34 (m, 1H, H_8), 3.45-3.86 (m, 4H, CF_3CH_2, H_{12}, H_5), 3.95 (m, 1H, H_9), 4.18-4.40 (m, 3H, H_{16}, $PhCH_2$), 4.58 (ABq, Δυ = 90Hz, J = 11.7 Hz, 2H, $PhCH_2$), 4.85 (m, 2H, =$\underline{CH_2}$), 5.60-5.80 (m, 2H, $\underline{CH}$=), 6.80-7.70 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, C_6D_6), δ 23.81, 27.71, 28.76, 30.3, 31.19, 32.14, 32.22, 32.67, 43.14, 63.56 (q, $\underline{CH_2}CF_3$), 70.64, 72.17, 73.30,

76.50, 81.12, 83.17, 84.05, 97.12, 114.98, 127.84, 128.16, 128.48, 128.61, 128.72, 128.90, 139.06, 139.26.

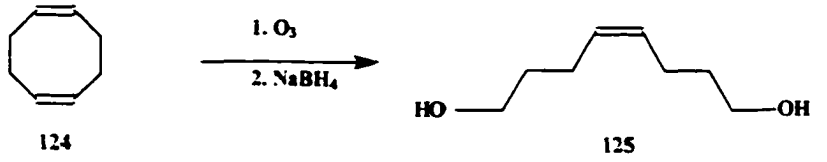
Spiroketal aldehyde (123)



119 123

To a solution of **119** (26 mg, 0.037 mmol) in CH_2Cl_2 (2 mL) was added AgOTf (37 mg, 0.14 mmol). A yellow precipitate was immediately produced. A drop of water was added to the reaction and stirring was continued for 5 min. The solution was then poured into saturated, aqueous $Na_2S_2O_3$ and the mixture was extracted with ether. The organic phase was dried (Na_2SO_4), filtered and evaporated in *vacuo*. Flash chromatography of the residue afforded spiroketal aldehyde **123** (7.4 mg). TLC R_f = 0.55 (20% EtOAc/PE); ^1H NMR (300 MHz, C_6D_6, assignments confirmed by $^1H/^1H$ COSY correlation), δ 1.04-1.6 (m, 12H, H_{14}, H_6, H_{11}, H_7, H_{10}, H_9), 1.75 (m, 1H, H_3), 1.95-2.30 (m, 4H, H_2, H_{15}), 3.17 (m, 1H, H_4), 3.26 (m, 1H, H_{13}), 3.87 (m, 1H, H_{12}), 4.18 (m, 1H, H_5), 4.37 (ABq, $\Delta\upsilon$ = 87 Hz, J = 12 Hz, 2H, $PhCH_2$), 4.60 (ABq, $\Delta\upsilon$ = 90 Hz, J = 11.7 Hz, 2H, $PhCH_2$), 6.95-7.40 (m, 10H, Ar-H), 9.32 (s, 1H, CHO).

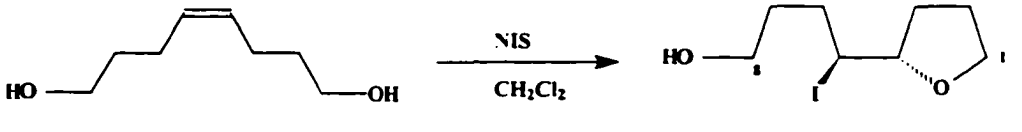
Z-4-octene-1, 8-diol (125)



124 125

A solution of **124** (5.04 g, 50 mmol) in a mixture of cyclohexane (150 mL) and MeOH (2 mL) was treated with a stream of O_3 in O_2 at -5 °C until **124** was not detectable by TLC (50% EtOAc/PE). The mixture was flushed with N_2 to remove residual O_3 and then MeOH (150 mL) and $NaBH_4$ (213 mg, 5.6 mmol) was added at rt. The stirring was continued for 1h, and then 10% HCl in MeOH was carefully added until the pH of the mixture was 8. The solvent was removed under reduced pressure. Chromatographic purification of the residue (10x12 cm, 100% EtOAc) gave **125** (3.5 g, 50%). TLC R_f = 0.35 (10% MeOH/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.63 (m, 4H, 2x$\underline{CH_2}CH_2OH$), 2.20 (q, 1H, 2x allylic CH_2), 3.22 (s, 2H, 2xOH), 3.65 (t, 2x$\underline{CH_2}OH$), 5.42 (m, 2H, CH=CH).

Mono-THF-Iodide (126)

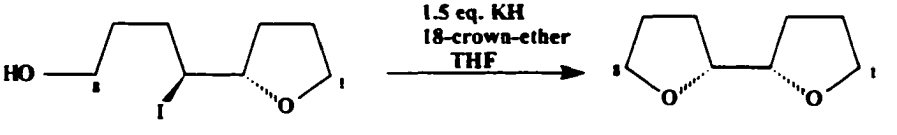


125 126

To a solution of **125** (1.90 g, 13.2 mmol) in dry CH_2Cl_2 (150 mL) was added NIS (3.56 g, 116 mmol). The mixture was stirred at rt for 1h, then poured into saturated,

aqueous $Na_2S_2O_3$, and extracted with ether. The combined organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. Chromatography of the residue (2.5x12 cm, 30% EtOAc/PE) afforded (±) **126** (1.76 g, 50%). TLC R_f = 0.50 (50% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.40-2.2 (m, 8H, H_2, H_3, H_6, H_7), 3.69 (t, 2H, H_8), 3.80 (m, 2H, H_1), 3.96 (m, 1H, H_4), 4.15 (m, 1H, H_5). ^{13}C NMR (75 MHz, $CDCl_3$), δ 24.10.28.69, 30.66, 30.76, 39.68, 59.87, 66.88, 80.34.

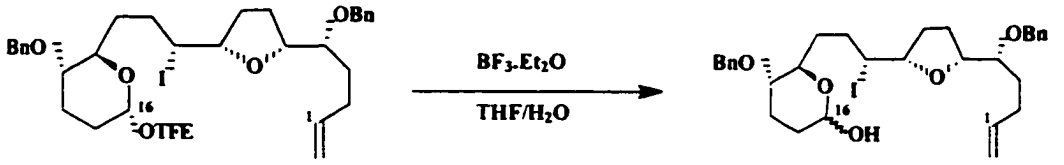
Bis-THF (127)



126 127

To a solution of **126** (269 mg, 1.00 mmol) and 18-crown-ether (264 mg, 1.00 mmol) in dry THF (20 mL) was added KH (200 mg, 30% w/w, 1.50 mmol) slowly at 0 °C. The reaction mixture was stirred for 10 min, and then treated with 10% HCl in MeOH until the pH was 8, followed by extraction with ether. The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Chromatographic purification of the residue gave **127** (86 mg, 61%). TLC R_f = 0.30 (30% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.6-2.2 (m, 8H H_2, H_3, H_6, H_7), 3.8 (m, 6H, other H's). ^{13}C NMR (75 MHz, $CDCl_3$), δ 25.95, 28.46, 68.83, 81.18.

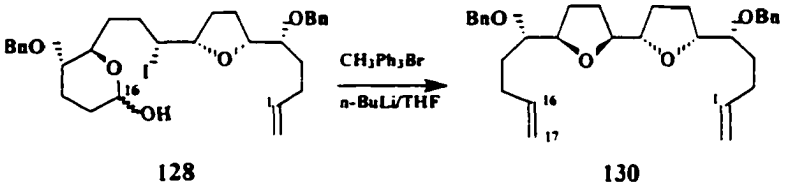
Hydroxyiodide Alkene 128



119 128

To a solution of **119** (160 mg, 0.228 mmol) in a 10:1 mixture of THF/H2O was added 5eq. $BF_3.Et_2O$ (120 µl) initially. After 5h. another 5eq. $BF_3.Et_2O$ (120 µl) was added to the reaction mixture. The mixture was stirred at rt for 2 days. The solution was then poured into saturated, aqueous $NaHCO_3$ and the mixture extracted with ether. The organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography of the residue afforded the hydroxyiodide alkene **128** (119 mg, 80%) as an α/β mixture of anomers. TLC R_f= 0.17 (20% EtOAc/PE); ^{1}H NMR (300 MHz, C_6D_6), δ 1.0-2.3 (m, 16H, H_2, H_{15}, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 2.38 (s, α-OH), 2.58 (d, β-OH), 2.93 (m, 1H, H_{13}), 3.20 (m, 2H, H_4, H_8), 3.75 (m, 2H, H_{12}, H_5), 4.04 (m, 1H, H_9), 4.01-4.75 (m, 5H, H_{16}, 2xPhCH_2), 4.90 (m, 2H, =CH_2), 5.70 (m, 1H, CH=), 6.90-7.50 (m, 10H, Ar-H's).

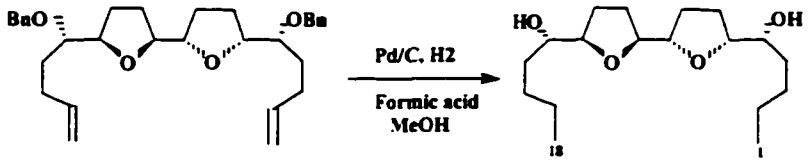
c/th/c **Bis-THF Diene (130)**



128 130

A solution of methylenetriphenylphosphorane was prepared by addition of n-BuLi (1.55 mL of 1.55M solution in hexane, 2.40 mmol) to a suspension of methyltriphenylphosphonium bromide (942 mg, 2.64 mmol) in dry THF (10 mL) at 0 °C, under an atmosphere of argon. The mixture was stirred at this temperature for 1h, then cooled to -78°C, at which time a solution of **128** (155 mg, 0.24 mmol) in dry THF (5 mL) was slowly introduced. After 10 min, the solution was allowed to warm to rt and stirred for an additional 1h at rt. The reaction mixture was then diluted with ether, filtered through a short column of Celite, and the filtrate concentrated *in vacuo*. Flash chromatography (2.5x12 cm, 20% EtOAc/PE) of the residue gave **130** (83 mg, 68%). Rf: 0.65 (20% EtOAc/PE); ^{1}H NMR (300 MHz, C_6D_6, assignments confirmed by ^{1}H/^{1}H COSY correlation), δ 1.20-2.21 (m, 12H, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 2.15-2.43 (m, 4H, H_2, H_{15}), 3.44 (q, 1H, J = 6.0 Hz, H_{13}), 3.54 (m, 1H, H_4), 3.70-3.89 (m, 4H, H_5, H_{12}, H_8, H_9), 4.64 (ABq, Δυ = 59 Hz, J = 12 Hz, 2H, $PhCH_2$), 4.72 (ABq, Δυ = 89 Hz, J =12 Hz, 2H, $PhCH_2$), 4.92-5.03 (m, 4H, 2x $=CH_2$), 5.69-5.83 (m, 2H, 2x CH=), 7.05-7.48 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, C_6D_6), δ 26.74, 27.50, 27.63, 27.86, 29.76, 30.14, 30.78, 31.44, 72.77, 72.94, 79.78, 81.00, 82.24, 82.81, 114.50, 114.56, 127.24, 127.48, 127.48, 127.57, 127.80, 127.89, 128.12, 128.22, 138.86, 139.75, 139.95. MS: (CI/NH3) 508($M+NH_4$, 100%), 491 ($M+H^+$, 2%).

c/th/c **Bis-THF (131)**

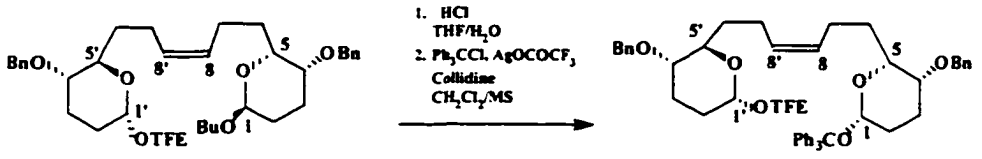


130 **131**

A solution of **131** (47 mg, 0.09 mmol), formic acid (20 µl) and 10% Pd/C (5 mg) in MeOH (4 mL) was stirred under hydrogen (balloon) for 16h. The solution was filtered through a short plug of silica gel (50% EtOAc/PE) and concentrated *in vacuo* to give **131** (20 mg, 70%). Rf: 0.05 (20% EtOAc/PE); ^{1}H NMR (300 MHz, CDCl3, assignments confirmed by ^{1}H/^{1}H COSY correlation), δ 0.89 (t, 6H, 2xCH_3), 1.20-1.60 (m, 12H, H_2, H_{17} H_3, H_{16}, H_4, H_{15}), 1.72-1.98 (m, 8H, H_7, H_{12} H_8, H_{11}), 3.41 (m, 1H, H_5), 3.86 (m, 5H, H_{14}, H_6, H_{13}, H_9, H_{10}). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.08, 22.81, 23.83, 28.01, 28.26, 28.50, 28.81, 32.58, 34.01, 71.94, 74.11, 81.11, 81.22, 83.04, 83.17; HRMS calcd for $C_{18}H_{34}O_4$ 314.2506, Found 314.2435.

Generality of bis-THF Formation Strategy

Trityl-Z-trifluoroethyl bis-pyranoside Alkene (137)



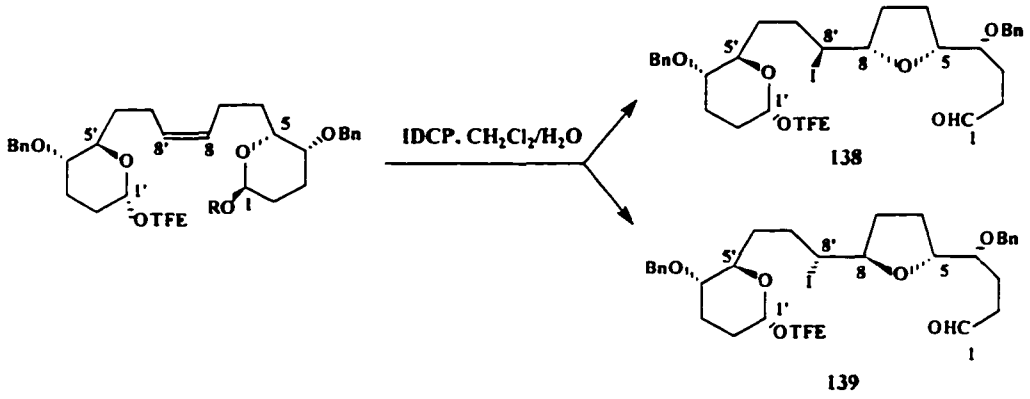
109 137

Compound **109** (200 mg, 0.32 mmol) was subjected to the selective hydrolysis conditions described in the preparation of **112**. Purification of the product afforded trifluoroethyl pyranoside-Z-pyranose (138mg, 80%), which was dried under high vacuum and used directly in the next step. For α/β mixture of pyranoses; TLC R_f = 0.15 (20% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.2-2.6 (m, 16H, H_2, H_{15}, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 3.19 (m, 1H, H_{13}), 3.29 (bs, H_4, α-pyranose), 3.39 (dd, H_5, α-pyranose), 3.56 (bs, H_4, β-pyranose), 3.62 (bt, 1H, H_{12}), 3.75-4.02 (m, 3H, CF_3CH_2, H_5, β-pyranose), 4.39-4.69 (m, H_1 β-pyranose, 2x$PhCH_2$), 4.84 (bs, 1H, H_1), 5.20-5.48 (m, 2H, CH=CH), 7.08-7.52 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 21.73, 24.02, 24.39, 24.62, 25.63, 26.52, 28.62, 29.71, 31.59, 32.32, 33.10, 33.39, 65.01 (q, J = 33.7 Hz, $\underline{C}H_2CF_3$), 69.93, 71.84, 71.90, 72.98, 73.62, 74.42, 77.76, 92.57 (C1-β-anomer), 97.54 (C1-α-anomer), 97.79, 97.88 (C16 α/β mixture), 128.60-131.40 (multiple peaks), 139.37, 139.70, 146.20.

A portion of the lactol mixture (12 mg, 0.020 mmol) obtained in the previous step was subjected to the same procedure described in the preparation of **113**. Purification of the product afforded **137**α/β (12 mg, 70%) as an in separable mixtuer of anomers. TLC R_f

= 0.46 (10% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.00-2.40 (m, 16H, H_2, H_{15}, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 2.96 (bs, H_5, β-pyranose), 3.08 (bs, H_4, β-pyranose), 3.22 (m, 1H, H_{13}), 3.42 (bs, H_4, α-pyranose), 3.64 (m, 1H, H_{12}), 3.75-4.05 (m, CF_3CH_2, H_5, α-pyranose), 4.38-4.75 (m, H_1, β-anomer, 2x$PhCH_2$), 4.88 (bs, 1H, H_{16}) 5.24 (bs, H_1 α-anomer), 5.33 (bs, 2H, CH=CH), 7.20-7.67 (m, 25H, Ar-H). α/β=~1:2 (based on the relative ratio of H_4 singlets at 3.42 and 3.08). ^{13}C NMR (75MHz, $CDCl_3$), δ 22.57, 24.19, 24.66, 26.44, 26.90, 27.89, 29.75, 30.82, 31.91, 64.80 (q, J = 33.7 Hz, $\underline{C}H_2CF_3$), 71.89, 72.12, 72.29, 73.10, 73.23, 77.86, 77.91, 78.31, 78.92, 88.27 and 89.00 ($\underline{C}Ph_3$, α/β mixture), 93.98 (C1-β-anomer), 97.73 (C16 α/β mixture), 99.30 (C1-α-anomer), 128.00-131.0 (multiple peaks), 139.55, 139.89, 146.09; MS (FAB) 819.5 $(M-H)^-$ for $C_{51}H_{55}O_6F_3$.

Mono-THF-Iodides (138/139)



1. ***cis*-THF-iodide (138) and *trans*-THF-iodide (139) (from t-butyl-Z-alkene 109)**

t-Butyl-Z-trifluoroethyl alkene **109** (762 mg, 1.20 mmol) was subjected to the standard halocyclization conditions in the preparation of **111**. Purification of the product

afforded a 1:1 mixture of **138** and **139** (621 mg, 73%). Repeated chromatography (10% EtOAc/toluene) gave samples of **138** and **139**.

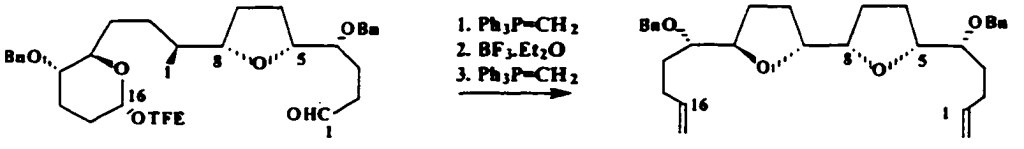
For **138:** R_f: 0.25 (10% EtOAc/toluene); ^{1}H NMR (300 MHz, C_6D_6), δ 1.10-2.32 (m, 16H H_2, H_{15}, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 2.88 (m, 1H, H_{13}), 3.20-3.45 (m, 3H, H_4, H_{12}, H_5), 3.50-3.70 (m, 3H, H_8, CF_3CH_2,), 3.85 (m, 1H, H_9), 4.20 (ABq, Δυ = 67 Hz, J = 11.7 Hz, 2H, $PhCH_2$), 4.39 (bs, 1H, H_{16}), 4.63 (ABq, Δυ = 81 Hz, J = 11.7 Hz, 2H, $PhCH_2$), 7.10-7.50 (m, 10H, Ar-H), 9.42 (s, 1H, CHO). ^{13}C NMR (75 MHz, C_6D_6), δ 23.36, 27.69, 28.32, 30.48 (C7), 32.23 (C6), 33.18, 40.00, 42.83, 63.62 (q, $\underline{C}H_2CF_3$), 70.17, 72.00, 72.93, 76.38, 80.00, 81.81, 83.15, 96.72 (C16), 127-129 (multiple peaks), 138.78, 139.35, 200.36 (CHO);). MS (FAB) calcd for $C_{32}H_{40}F_3IO_6$ $(M-H)^-$ 703, found 703.

For **139:** R_f: 0.37 (10% EtOAc/toluene); ^{1}H NMR (300 MHz, C_6D_6), δ 1.20-2.22 (m, 16H, H_2, H_{15}, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 2.88 and 3.00 (both m, 1H ea, H_4, H_{13}), 3.30 (m, 1H, H_8), 3.40-3.78 (m, 4H, H_{12}, H_5, CF_3CH_2), 3.95 (m, 1H, H_8), 4.35 (ABq, Δυ = 64 Hz, J = 11.7 Hz, 2H, $PhCH_2$), 4.37 (bs, 1H, H_{16}), 4.38 (ABq, Δυ = 63 Hz, J = 11.4 Hz, 2H, $PhCH_2$), 7.00-7.50 (m, 10H, Ar-H), 9.27 (s, 1H, CHO). ^{13}C NMR (75 MHz, C_6D_6), δ 23.39, 23.44, 28.31, 28.58, 31.44 (C7), 32.19, 32.65 (C6), 39.90, 43.20, 63.52 (q, $\underline{C}H_2CF_3$), 70.17, 71.57, 72.69, 76.10, 80.25, 82.59, 82.92, 96.61 (C16), 127-129 (multiple peaks), 138.79, 139.27, 200.45 (CHO).

2. ***cis*-THF-Iodide 138 (from trityl-Z-alkene 137)**

A mixture of trityl-Z-trifluoroethyl alkenes **137** (12 mg, 0.014 mmOl) was subjected to the standard halocyclization reaction conditions, using CH_2Cl_2 (2 mL), water (0.05 mL) and IDCP (34 mg, 0.073 mmol). Processing of the reaction mixture and purification of the crude product as before, afforded the *cis*-THF-Iodide **138** (8.9 mg, 86%), which was identical (TLC, ^1H and ^{13}C NMR) to the sample of **138** obtained from the corresponding reaction of **109.**

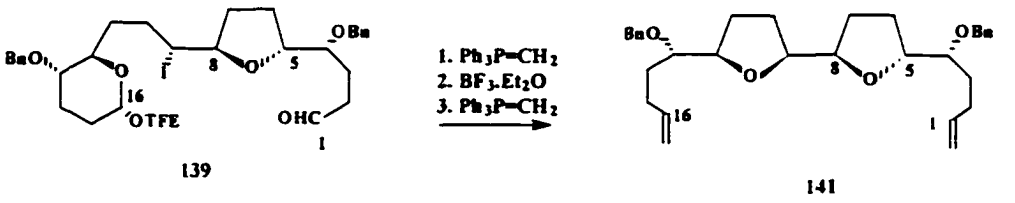
***t/er/c*-Bis-THF (140)**



138 140

cis-THF-iodide **138** (48 mg, 0.070 mmol) was subjected to the identical 3-step sequence which used for the preparation of **130**. *t/er/c*-Bis-THF **140** (10 mg, 30%) was prepared. R_f: 0.82 (20% EtOAc/toluene); ^1H NMR (300 MHz, C_6D_6, assignments confirmed by $^1H/^1H$ COSY correlation), δ 1.19-2.05 (m, 12H, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 2.40 (m, 4H, H_2, H_{15}), 3.32 (m, 1H, H_{13}), 3.52 (m, 1H, H_4), 3.74-4.00 (m, 4H, H_5, H_{12}, H_8, H_9), 4.64 (ABq, Δυ = 45.0 Hz, J = 11.7 Hz, 2H, $PhCH_2$), 4.72 (ABq, Δυ = 85 Hz, J = 11.7 Hz, 2H, $PhCH_2$), 4.92-5.10 (m, 4H, 2x $=CH_2$) , 5.65-5.83 (m, 2H, 2x<u>CH</u>=), 7.05-7.48 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, C_6D_6), δ 26.80, 27.51, 28.20, 29.28, 29.89, 30.02, 30.79, 31.23, 72.94, 80.09, 81.07, 81.44, 81.91, 82.74, 114.45, 127-128 (multiple peaks), 138.77. MS (FAB) calcd for $C_{32}H_{42}O_4$ M^+ 490, found 490.

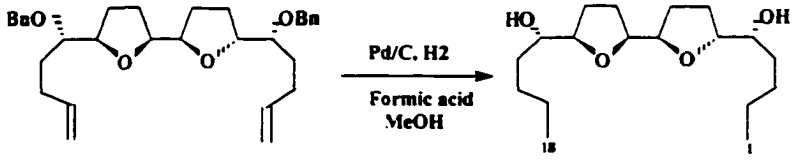
***c/er/t*-Bis-THF (141)**



139 141

trans-THF-Iodide **139** (280 mg, 0.4 mmol) was subjected to the identical 3-step sequence which was used for preparation of **130**. *c/er/t*-Bis-THF **141** (78 mg, 40%) was prepared. R_f: 0.81 (20% EtOAc/toluene); ^1H NMR (300 MHz, C_6D_6, assignments confirmed by $^1H/^1H$ COSY correlation), δ 1.20-1.95 (m, 12H, H_3, H_{14}, H_6, H_{11}, H_7, H_{10}), 2.09-2.40 (m, 4H, H_2, H_{15}), 3.22 (m, 1H, H_{13}), 3.52 (m, 1H, H_4), 3.78, 3.90, 4.04 (all m, 2H, 1H, 1H resp, H_5, H_{12}, H_8, H_9), 4.57 (ABq, $\Delta\upsilon$ = 42.8 Hz, J = 11.7 Hz, 2H, $PhCH_2$), 4.68 (ABq, $\Delta\upsilon$ = 75.9 Hz, J = 11.7 Hz, 2H, $PhCH_2$), 4.92-5.08 (m, 4H, 2x $=CH_2$) , 5.65-5.83 (m, 2H, 2x<u>CH</u>=), 7.05-7.48 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, C_6D_6), δ 26.21, 28.39, 28.44, 29.37, 29.77, 30.02, 30.07, 30.49, 31.36, 72.78, 79.70, 80.96, 81.38, 81.92, 82.29, 82.36, 114.45, 127-128(multiple peaks), 138.72, 138.76.

***c/er/t*-Bis-THF (142)**



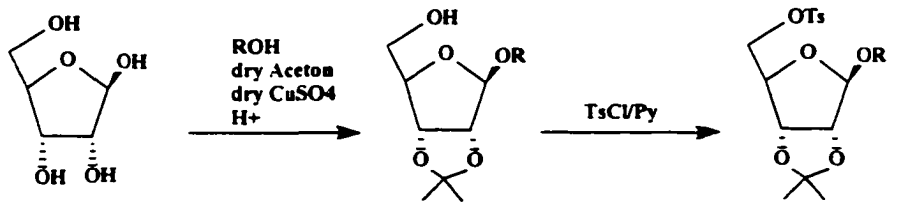
141 142

Compound **141** (70 mg, 0.14 mmol) was subjected to the standard hydrogenation condition described in the preparation of **131**. It gave **142** (35 mg, 80%). Rf: 0.35 (40% EtOAc/PE); ^1H

NMR (300 MHz, CDCl3, assignments confirmed by $^{1}H/^{1}H$ COSY correlation), δ 0.89 (t, 6H, 2xCH_3), 1.00-1.57 (m, 12H, H_2, H_{17} H_3, H_{16}, H_4, H_{15}), 1.57-2.09 (m, 8H, H_7, H_{12} H_8, H_{11}), 3.39 (m, 1H, H_5), 3.81 (m, 2H, H_{14}, H_6), 3.92 (m, 1H, H_{13}), 3.98 (m, 1H, H_9), 4.14 (m, 1H, H_{10}). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.19, 22.90, 22.94, 24.49, 26.94, 27.79, 28.38, 28.36, 28.98, 32.69, 33.42, 72.82, 74.00, 81.01, 81.62, 83.14, 83.64; HRMS calcd for C18H34O4 314.2506, Found 314.2434.

Alkene Precursors

5-O-Tosyl Ribofuranosides (149-a, b, c)



147

148a R=Me
148b R=i-Pr
148c R=t-Bu

149a R=Me
149b R=i-Pr
149c R=t-Bu

Isopropyl-2, 3-O-isopropylidene-5-O-tosyl-β-*ribo*-furanoside (149b)

Ribofuranoside **148b** was prepared from D-ribose **147** according to the literature procedure. Compound **148b** (13.9 g, 60.0 mmol) was then subjected the tosylation procedure described in the prepartion of compound **97**. It afforded product **149b** (14.0 g, 60%). Rf: 0.44 (20% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.07 (d, 6H, $CH(\underline{CH_3})_2$), 1.28, 1.44 (both s, 3H ea. isopropylidene CH_3's), 2.45 (s, 3H, Ar-$\underline{CH_3}$), 3.81 (m, 1H, $\underline{CH}(CH_3)_2$), 4.02 (m, 2H, H_5), 4.27 (t, 1H, H_4), 4.56 (m, 2H, H_2, H_3), 5.14 (s, 1H, H_1), 7.36-7.80 (m, 4H, Ar-H's), ^{13}C NMR (75MHz, $CDCl_3$), δ 22.10, 22.78, 24.23, 25.95, 27.47, 70.36, 70.47, 70.47, 82.78, 84.5, 86.48, 107.12, 113.71, 129.11, 131.04.

The methyl and t-butyl derivatives **149a** and **149c** were prepared by following the aforementioned procedure.

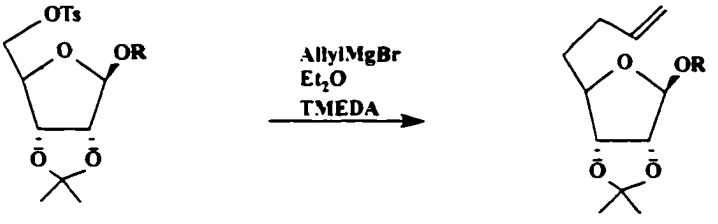
Methyl-2, 3-O-isopropylidene-5-O-tosyl-β-*ribo*-furanoside (149a)

Rf: 0.38 (20% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.28, 1.44 (both s, 3H ea, isopropylidene CH_3's), 2.45 (s, 3H, Ar-CH_3), 3.40 (s, 3H, CH_3), 3.99 (m, 2H, H_5), 4.32 (t, 1H, H_4), 4.56 (m, 2H, H_2, H_3), 5.04 (s, 1H, H_1), 7.36-7.80 (m, 4H, Ar-H's).

t-Butyl-2,3-O-isopropylidene-5-O-tosyl-β-*ribo*-furanoside (149c)

Rf: 0.50 (20% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.18 (s, 9H, $C(CH_3)_3$), 1.28, 1.44 (both s, 3H ea, isopropylidene CH_3's), 2.45 (s, 3H, Ar-CH_3), 4.09 (m, 2H, H_5), 4.24 (t, 1H, H_4), 4.49, 4.61 (both m, 2H, H_2, H_3), 5.31 (s, 1H, H_1), 7.36-7.80 (m, 4H, Ar-H's).

Ribofuranoside Alkenes (150-a, b, c)



149a R=Me
149b R=i-Pr
149c R=t-Bu

150a R=Me
150b R=i-Pr
150c R=t-Bu

Isopropyl 5,6,7,8-tetradeoxy-2,3-O-isopropylidene-β-D-*ribo*-7-enofuranoside (150b)

To a solution of **149b** (9.3 g, 24 mmol) in dry ether (150ml) was added TMEDA (2.4 ml), followed by a 1M solution of allylmagnesium bromide in THF (120 ml) under an atmosphere of argon at rt. The reaction was stirred for 14h, and then quenched with saturated aqueous NH_4Cl. The product was extracted with ether, the combined ethereal extract was dried over (Na_2SO_4) and then concentrated *in vacuo*. The crude product was

purified by flash chromatography (10x12 cm, 20% EtOAc: PE) to give the product **150b** (3.9 g, 63%). Rf: 0.60 (20% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.15 (q, 6H, $CH(\underline{CH_3})_2$), 1.30, 1.47 (both s, 3H ea, isopropylidene CH_3's), 1.54-1.80 (m, 2H, H_5), 2.16 (m, 2H, H_6), 3.93 (m, 1H, $\underline{CH}(CH_3)_2$), 4.13 (t, 1H, H_4), 4.57 (m, 2H, H_2, H_3), 5.00 (m, 2H, CH_2=), 5.15 (s, 1H, H_1), 5.82 (m, 1H, =CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 21.93, 24.22, 26.03, 27.58, 31.38, 35.44, 69.47, 85.47, 87.14, 87.56, 106.84, 113.16, 116.10, 138.75.

The alkenes **150a** and **150c** were prepared from respective 5-O-tosyl ribofuranosides **149a** and **149c,** following the above procedure.

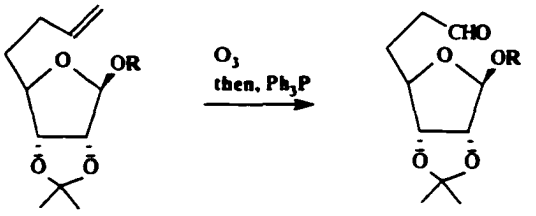
Methyl 5,6,7,8-tetradeoxy-2,3-O-isopropylidene-β-D-*ribo*-7-enofuranoside (150b)

Rf: 0.50 (20% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.27, 1.45 (both s, 3H ea, isopropylidene CH_3's), 1.46-1.72 (m, 2H, H_5), 2.14 (m, 2H, H_6), 3.30 (s, 3H, CH_3), 4.11 (t, 1H, H_4), 4.52 (m, 2H, H_2, H_3), 4.89 (s, 1H, H_1), 4.98 (m, 2H, CH_2=), 5.78 (m, 1H, =CH). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.72; H, 8.84. Found: C, 63.94; H, 9.08.

t-Butyl 5,6,7,8-tetradeoxy-2,3-O-isopropylidene-β-D-*ribo*-7-enofuranoside (150b)

Rf: 0.73 (20% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.27 (s, 9H, $C(CH_3)_3$), 1.36, 1.54 (both s, 3H ea, isopropylidene CH_3's), 1.68, 1.83 (both m, 2H, H_5), 2.22 (m, 2H, H_6), 4.14 (t, 1H, H_4), 4.58 (m, 2H, H_2, H_3), 5.08 (m, 2H, CH_2=), 5.36 (s, 1H, H_1), 5.87 (m, 1H, =CH).

Ribofuranoside Aldehydes (150-a, b)



150a R=Me
150b R=i-Pr

151a R=Me
151b R=i-Pr

Isopropyl ribofuranoside aldehyde (151b)

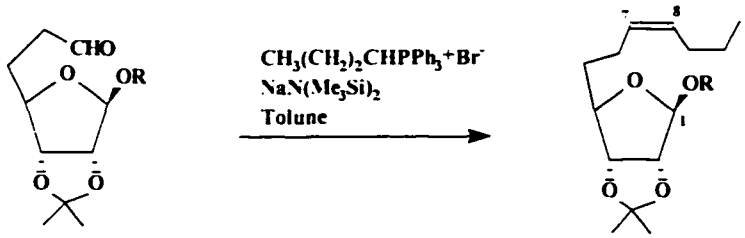
Compound **150b** (3.8 g, 14 mmol) was subjected to the standard ozonolysis procedure described in the preparation of compound **99**. After work-up, the crude product was purified by flash chromatography (6x15 cm, 20% EtOAc/PE) to provide **151b** (3.05 g, 80%). Rf: 0.25 (20% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.11 (d, 6H, $CH(\underline{CH_3})_2$), 1.30, 1.46 (both s, 3H ea, isopropylidene CH_3's), 1.87 (m, 2H, H_5), 2.16 (m, 2H, H_6), 3.89 (m, 1H, $\underline{CH}(CH_3)_2$), 4.11 (t, 1H, H_4), 4.55 (m, 2H, H_2, H_3), 5.14 (s, 1H, H_1), 9.79 (s, 1H, CHO). ^{13}C NMR (75MHz, $CDCl_3$), δ 22.10, 24.28, 26.08, 27.63, 28.65, 41.85, 70.01, 85.35, 87.11, 87.17, 107.20, 113.44, 202.35.

Methyl ribofuranoside aldehydes (151a)

Methyl ribofuranoside aldehyde **151a** was prepared from methyl ribofuranoside alkene**150a**, according to the aforementioned procedure.

Rf: 0.15 (20% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.30, 1.47 (both s, 3H ea, isopropylidene CH_3's), 1.86 (m, 2H, H_5), 2.62 (m, 2H, H_6), 3.35 (s, 3H, CH_3), 4.14 (t, 1H, H_4), 4.60 (m, 2H, H_2, H_3), 4.96 (s, 1H, H_1), 9.81 (s, 1H, CHO).

Ribofuranoside Z-alkenes (152-a, b)



Isopropyl ribofuranoside Z-alkene (152b)

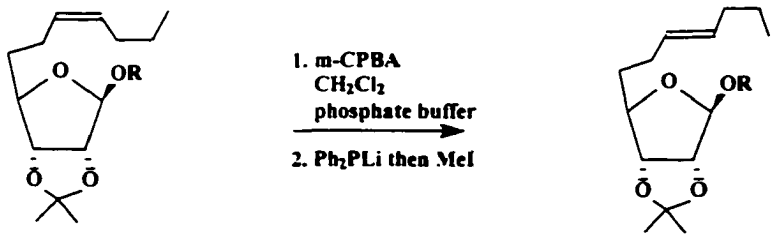
To a solution of butyltriphenylphosphonium bromide (4.83 g, 12.1 mmol) in dry toluene (60 ml) was added a 1M solution of sodium bis(trimethylsilyl) amide in toluene (11ml, 11mmol), under an argon atmosphere. The yellow-orange suspension was stirred for 1h at rt then cooled to -78°C. A solution of aldehyde **151b** (1.5 g, 11 mmol) in dry toluene (20 ml) was added dropwise over 30 min. After an additional 15 min, the reaction mixture was warmed to rt, then diluted with ether (100 ml). The mixture was filtered through *Celite* and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (4x12, 20% EtoAc/PE) to afford **152b** (1.46 g, 83%). Rf: 0.53 (20% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.89 (t, 3H, CH_3), 1.13 (q, 6H, $CH(\underline{CH_3})_2$), 1.30, 1.47 (both s, 3H ea, isopropylidene CH_3's), 1.17-1.80 (m, 4H, H_5, H_{10}), 2.00 (m, 2H, H_9), 2.13 (m, 2H, H_6), 3.93 (m, 1H, $\underline{CH}(CH_3)_2$), 4.11 (dd, 1H, H_4), 4.55 (m, 2H, H_2, H_3), 5.15 (s, 1H, H_1), 5.36 (m, 2H, CH=CH). ^{13}C NMR (75MHz, $CDCl_3$), δ 14.89, 22.00, 23.92,24.30, 25.11, 26.13, 27.65, 30.41, 36.41, 69.5, 85.5, 87.22, 87.82, 106.84, 129.56, 129.64.

Methyl ribofuranoside Z-alkene (152a)

Methyl ribofuranoside Z-alkene **152a** was prepared from methyl ribofuranoside aldehyde**151a**, following the aforementioned procedure.

Rf: 0.46 (20% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.94 (t, 3H, CH_3), 1.37, 1.52 (both s, 3H ea, isopropylidene CH_3's), 1.29-1.80 (m, 4H, H_5, H_{10}), 2.05 (m, 2H, H_9), 2.20 (m, 2H, H_6), 3.39 (m, 3H, CH_3), 4.20 (dd, 1H, H_4), 4.60 (m, 2H, H_2, H_3), 4.98 (s, 1H, H_1), 5.41 (m, 2H, CH=CH). ^{13}C NMR (75MHz, $CDCl_3$), δ 14.28, 23.35, 24.63, 25.66, 27.10, 19.82, 35.72, 55.38, 84.81, 86.22, 87.41, 110.09, 129.05, 131.23.

Ribofuranoside E-alkenes (153a and b)



152a R=Me
152b R=i-Pr

153a R=Me
153b R=i-Pr

Isopropyl ribofuranoside E-alkene (153b)

The Z-alkene **152b** (927 mg, 3.0 mmol) was treated under the two steps Vedjs isomerization procedure which was described in preparation of t-butyl-E-trifluoroethyl bis-pyranoside alkene **108**. It provided isopropyl ribofuranoside E-alkene **153a** (667mg, 72%). Rf: 0.35 (10% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.86 (t, 3H, CH_3), 1.12 (q, 6H, $CH(\underline{CH_3})_2$), 1.29, 1.47 (both s, 3H ea, isopropylidene CH_3's), 1.10-1.80 (m, 4H,

H_5, H_{10}), 1.93 (m, 2H, H_9), 2.09 (m, 2H, H_6), 3.93 (m, 1H, $\underline{CH}(CH_3)_2$), 4.11 (dd, 1H, H_4), 4.55 (m, 2H, H_2, H_3), 5.14 (s, 1H, H_1), 5.40 (m, 2H, CH=CH). ^{13}C NMR (75MHz, $CDCl_3$), δ 14.72, 21.94, 23.75, 24.27, 26.07, 27.62, 30.26, 35.79, 38.23, 69.39, 85.55, 87.20, 87.63, 106.81, 113.14, 130.17, 132.22.

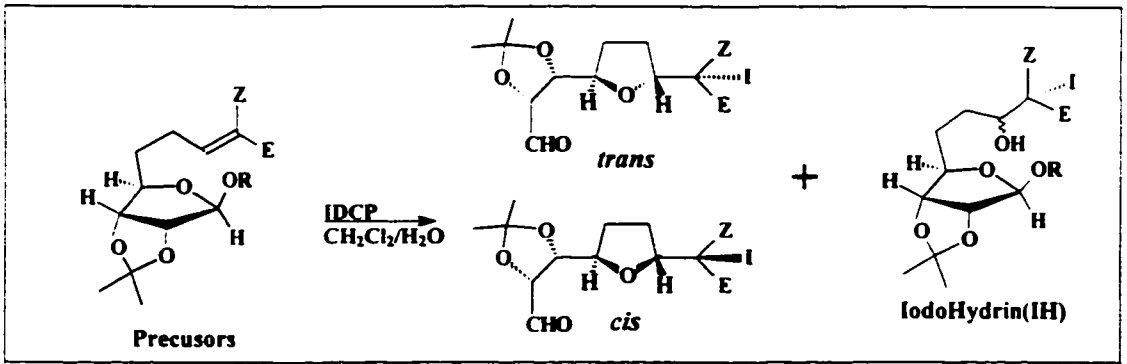
Methyl ribofuranoside E-alkene (153a)

Methyl ribofuranoside Z-alkene **153a** was prepared from methyl ribofuranoside aldehyde**152a**, following the aforementioned procedure.

Rf: 0.45 (20% EtoAc/PE); ^1H NMR (300 MHz, $CDCl_3$), δ 0.93 (t, 3H, CH_3), 1.37, 1.52 (both s, 3H ea, isopropylidene CH_3's), 1.35-1.80 (m, 4H, H_5, H_{10}), 2.00 (m, 2H, H_9), 2.15 (m, 2H, H_6), 3.39 (m, 3H, CH_3), 4.20 (dd, 1H, H_4), 4.60 (m, 2H, H_2, H_3), 4.98 (s, 1H, H_1), 5.45 (m, 2H, CH=CH). ^{13}C NMR (75MHz, $CDCl_3$), δ 14.17, 23.17, 25.60, 27.08, 29.76, 35.21, 35.58, 55.33, 84.79, 86.20, 87.19, 110.04, 112.71, 129.57, 131.74.

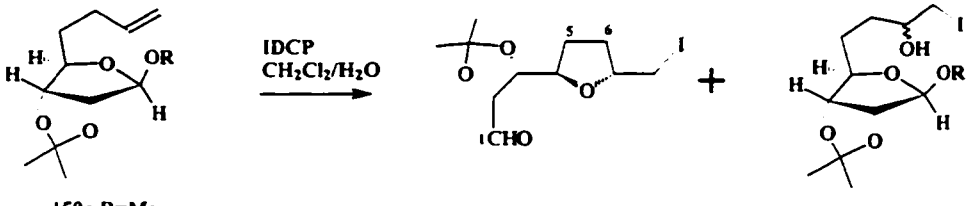
Halocyclization Studies

Iodoetherification of all ribofuranoside alkenes were carried out under the standard halocyclization procedure which was described for the preparation of mono-THF-iodide **111**. They all gave an inseparable mixture of isomers and iodohydrin side product. The results are summarized in following table.



	150a-c Terminal (E=Z=H)		152a-b Z (Z=Pr; E=H)		153a-b E (Z=H; E=Pr)	
R	THF c:t	THF:IH	THF c:t	THF:IH	THF c:t	THF:IH
CH_3	145 1:10	2:1	154 <1:40	2:1	155 <1:40	2:1
i-Pr	145 1:9	10:1	154 <1:40	2:1	155 <1:40	10:1
$C(CH_3)_3$	145 1:6	>10:1	———	—	———	———

1. THF-Iodide (145t/c) from Terminal Alkenes



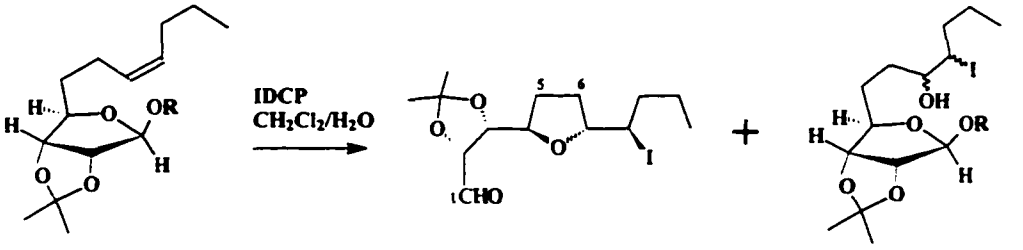
145t: Rf: 0.40 (20% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.39, 1.57 (both s, 3H ea, isopropylidene CH_3's), 1.74 (m, 2H, H_6), 2.15 (m, 2H, H_5), 3.21 (m, 2H, H_8), 4.03 (m, 1H, H_7), 4.21 (t, 1H, H_4), 4.34 (t, 1H, H_3), 4.50 (dd, 1H, H_2), 9.66 (s, 1H, CHO), ^{13}C NMR (75MHz, $CDCl_3$), δ 10.08, 26.36, 28.37, 30.87, 33.19, 78.93, 80.10, 81.96, 82.55, 199.66.

145c: Rf: 0.40 (20% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.39, 1.55 (both s, 3H ea, isopropylidene CH_3's), 1.74 (m, 2H, H_6), 2.15 (m, 2H, H_5), 3.21 (m, 2H, H_8), 3.93 (m, 1H, H_7), 4.20 (t, 1H, H_4), 4.34 (t, 1H, H_3), 4.61 (dd, 1H, H_2), 9.73 (s, 1H, CHO), ^{13}C NMR (75MHz, $CDCl_3$), δ 10.08, 26.49, 28.37, 29.98, 32.15, 79.06, 80.29, 81.45, 82.92, 199.66.

Iodohydrin (R=Me)

Rf: 0.25 (20% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.35, 1.48 (both s, 3H ea, isopropylidene CH_3's), 1.20-2.60 (m, 4H, H_5, H_6), 3.25 (m, 2H, CH_2I), 3.40 (s, 3H, CH_3), 4.20 (t, 2H, H_4, H_7), 4.59 (m, 2H, H_2, H_3), 4.88 (s, 1H, H_1).

2. THF-iodides (154t/c) from Z-Alkenes



152a R=Me
152b R=isopropyl

154t/c

iodohydrin

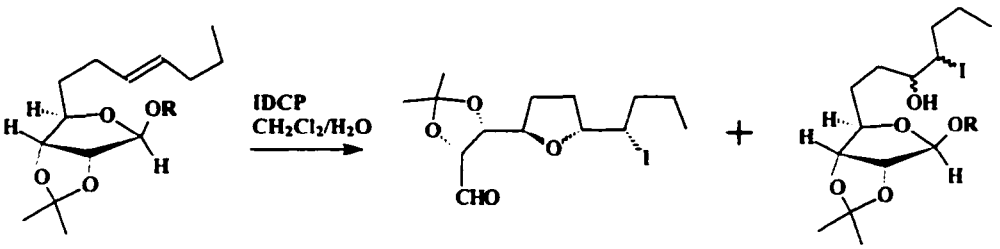
THF iodide **154t**: Rf: 0.51 (10% EtoAc/Tol); ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.96 (t, 3H, CH_3), 1.43, 1.61 (both s, 3H ea, isopropylidene CH_3's), 1.20-2.05 (m, 6H, H_6, H_9, H_{10}), 2.25 (m, 2H, H_5), 3.81 (m, 2H, H_8), 4.10 (m, 1H, H_7), 4.24 (t, 1H, H_4), 4.40 (t, 1H, H_3), 4.55 (dd, 1H, H_2), 9.73 (s, 1H, CHO), ^{13}C NMR (75MHz, $CDCl_3$), δ 14.37, 24.10, 26.52, 28.48, 31.40, 32.32, 39.50, 43.11, 79.26, 82.20, 82.80, 84.01, 112.15, 199.50.

THF iodide **154c**: Rf: 0.51 (10% EtoAc/Tol); ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.96 (t, 3H, CH_3), 1.43, 1.61 (both s, 3H ea, isopropylidene CH_3's), 1.20-2.05 (m, 6H, H_6, H_9, H_{10}), 1.74 (m, 2H, H_6), 2.25 (m, 2H, H_5), 3.81 (m, 2H, H_8), 4.10 (m, 1H, H_7), 4.24 (t, 1H, H_4), 4.40 (t, 1H, H_3), 4.74 (dd, 1H, H_2), 9.81 (s, 1H, CHO).

Iodohydrins (R=i-Pr)

Rf: 0.20 (10% EtoAc/Tol); ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.95 (t, 3H, CH_3), 1.15 (m, 6H, $CH(\underline{CH_3})_2$), 1.30, 1.47 (both s, 3H ea, isopropylidene CH_3's), 1.20-2.20 (m, 8H, H_5, H_6 H_9 H_{10}), 2.90, 3.00 (both m (2:1), 1H, H_7), 3.91 (m, 1H, $\underline{CH}(CH_3)_2$), 4.10 (m, 2H, H_4, H_8), 4.56 (m, 2H, H_2, H_3), 5.17 (s, 1H, H_1).

3. **THF-Iodide (155t/c) from E-Alkenes**



153a R=Me
153b R=isopropyl

155t/c

iodohydrin

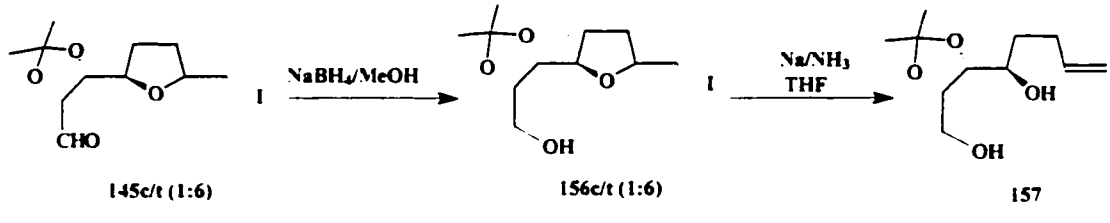
THF iodide **155t**: Rf: 0.48 (10% EtoAc/Tol); ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.90 (t, 3H, CH_3), 1.37, 1.55 (both s, 3H ea, isopropylidene CH_3's), 1.09-1.83 (m, 6H, H_6, H_9, H_{10}), 2.10, 2.22 (both m, 1H/ea, H_5), 3.74 (m, 2H, H_8), 4.06 (m, 1H, H_7), 4.19 (t, 1H, H_4), 4.31 (t, 1H, H_3), 4.46 (dd, 1H, H_2), 9.62 (s, 1H, CHO), ^{13}C NMR (75MHz, $CDCl_3$), δ 14.37, 24.10, 26.52, 28.48, 31.40, 32.32, 39.50, 43.11, 79.26, 82.20, 82.80, 84.01, 112.15, 199.50.

THF iodide **155c**: Rf: 0.48 (10% EtoAc/Tol); ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.90 (t, 3H, CH_3), 1.37, 1.55 (both s, 3H ea, isopropylidene CH_3's), 1.09-1.83 (m, 6H, H_6, H_9, H_{10}), 2.10, 2.22 (both m, 1H/ea, H_5), 3.74 (m, 2H, H_8), 4.06 (m, 1H, H_7), 4.19 (t, 1H, H_4), 4.31 (t, 1H, H_3), 4.61 (dd, 1H, H_2), 9.70 (s, 1H, CHO).

Iodohydrin (R=i-Pr)

Rf: 0.20 (10% EtoAc/Tol); ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.95 (t, 3H, CH_3), 1.15 (dd, 6H, $CH(\underline{CH_3})_2$), 1.30, 1.47 (both s, 3H ea, isopropylidene CH_3's), 1.10-2.20 (m, 8H, H_5, H_6 H_9 H_{10}), 3.42 (m, 1H, H_7), 3.91 (m, 1H, $\underline{CH}(CH_3)_2$), 4.14 (m, 1H, H_4), 4.28 (m, 1H, H_8), 4.56 (m, 2H, H_2, H_3), 5.17 (s, 1H, H_1).

Diol (**162**)



145c/t (1:6) 156c/t (1:6) 157

To a solution of **145** (1:6 c/t, 1.0 g, 0.29 mmol) in MeOH (25 ml) was added $NaBH_4$ (114 mg) at rt. The reaction mixture was stirred for 10 min, and then treated with 10% HCl in MeOH until the pH was 8. The solvent was removed by reduced pressure. Flash chromatography of the residue gave **156c/t** (690 mg, 1:6 c/t).

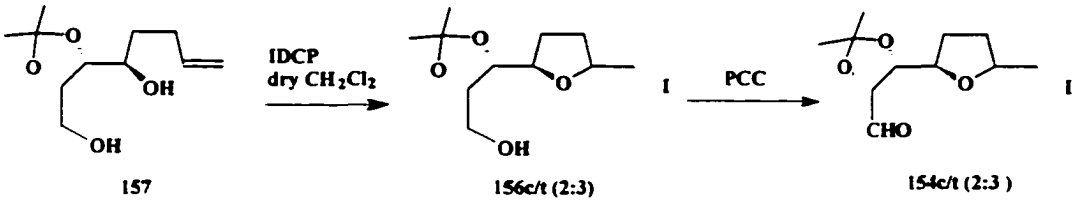
156t: Rf: 0.39 (30% EtoAc/PE); ^1H NMR (300 MHz, $CDCl_3$, assignments confirmed by $^1H/^1H$ COSY correlation) δ 1.35, 1.40 (both s, 3H ea, isopropylidene CH_3's), 1.65, 1.95 (both m, 2H, H_6), 2.20 (m, 2H, H_5), 3.09 (m, H, OH), 3.21 (m, 2H, H_8), 3.75-4.22 (m, 5H, H_1, H_3, H_4, H_7), 4.35 (m, 1H, H_2), ^{13}C NMR (75MHz, $CDCl_3$), δ 9.95, 25.23, 27.85, 30.96, 31.78, 77.65, 79.50, 109.95.

156c: Rf: 0.39 (30% EtoAc/PE); ^1H NMR (300 MHz, $CDCl_3$, assignments confirmed by $^1H/^1H$ COSY correlation) δ 1.35, 1.40 (both s, 3H ea, isopropylidene CH_3's), 1.65, 1.95 (both m, 2H, H_6), 2.20 (m, 2H, H_5), 3.09 (m, H, OH), 3.21 (m, 2H, H_8), 3.75-4.22 (m, 5H, H_1, H_3, H_4, H_7), 4.35 (m, 1H, H_2), ^{13}C NMR (75MHz, $CDCl_3$), δ 9.95, 25.23, 27.85, 29.59, 30.72, 78.00, 79.75, 109.95.

Liquid NH_3 was condensed into a solution of the alcohol mixture **156c/t** (250 mg, 0.72 mmol) in dry ether (2 ml) at -78°C under an atmosphere of argon. Sodium (166 mg, 7.2 mmol) was then added to this solution slowly until the blue color was persistent for several minutes. After warming to rt, the reaction was quenched with solid NH_4Cl, and extracted with ether (3x). The organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography afforded **157** (97mg, 62%). Rf: 0.34 (30% EtoAc/PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.31, 1.36 (both s, 3H ea, isopropylidene CH_3's), 1.53,

1.84 (both m, 2H, H_5), 2.15, 2.67 (both m, 2H, H_6), 3.22, 3.31 (both s, 2H, 2xOH), 3.67 (m, 1H, H_4), 3.80 (t, 2H, H_1), 3.95 (dd, 1H, H_2), 4.26 (m, 1H, H_3), 5.02 (m, 2H, CH_2=), 5.88 (m, 1H, =CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 26.5, 29.08, 30.62, 34.38, 62.09, 70.45, 78.37, 81.12, 109.90, 116.11.

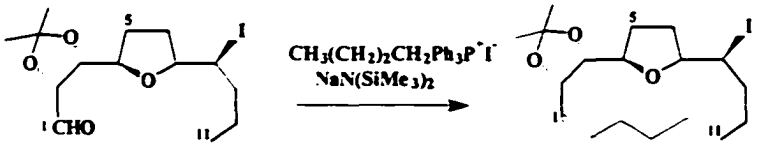
THF-Iodide (154c/t) from Diol 157



Diol **157** (97 mg, 0.453 mmol) was subjected to the standard halocyclization conditions in the preparation of **118**. Purification of the product afforded **156 c/t** (70 mg, 2:3 c/t) as an inseparable mixture of isomers.

Pyridinum chlorochromate (185 mg, 0.85 mmol) was added to a mixture of Celite (185 mg), anhydrous sodium acetate (70 mg), florisil (18.5 mg), and **156c/t** (60 mg, 0.17 mmol) in dry CH_2Cl_2 (5 ml). The reaction was stirred at rt for 14h, then diluted with ether and filtered through a short column of florisil. The column was eluted with additional ether and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography (1.5x15 cm, 30% EtOAc/PE) to afford **154c/t** (43mg, 2:3 c/t) as an inseparable mixture of isomers.

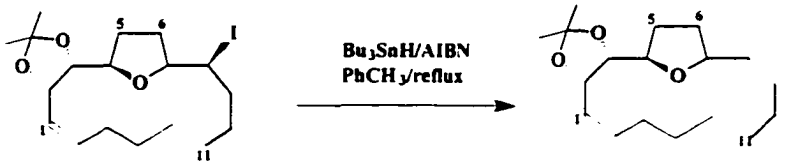
THF-iodide Alkene (165)



155 158

By a similar Wittig procedure to that used for preparation of alkene **152b**, THF-iodide **155** (388 mg, 1 mmol) was converted to THF-iodide alkene **165** (387 mg, 90%). Rf: 0.70 (5% EtoAc/Tol); ^{1}H NMR (300 MHz, C_6D_6), δ 0.82 (m, 6H, 2xCH_3), δ 1.32, 1.48 (both s, 3H ea, isopropylidene CH_3's), 1.2-1.82 (m, 8H, H_6, H_9, H_{10}, =$CH_2CH_2$$\underline{CH_2}$), 1.98 (m, 4H, H_5, =$CH_2$$\underline{CH_2}$), 3.74 (q, 1H, H_8), 3.85 (m, 1H, H_7), 4.00 (m, 1H, H_4), 4.07 (dd, 1H, H_3), 5.01 (m, 1H, H_2), 5.60 (m, 2H, CH=CH). ^{13}C NMR (75MHz, C_6D_6), δ 13.14, 13.63, 22.58, 22.58, 25.33, 25.43, 27.89, 29.66, 29.75, 32.91, 38.63, 43.27, 73.77, 78.17, 80.92, 82.77, 108.02, 126.42, 133.45.

Muricatalin Model (159)

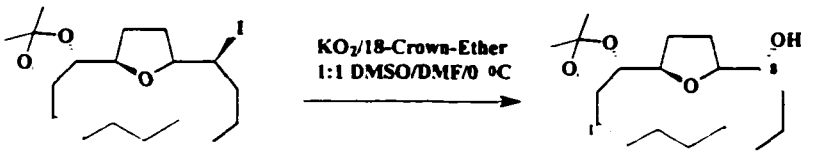


158 159

In a 50ml round-bottom flask equipped with reflux condenser and magnetic stirring bar, were placed **165** (100 mg, 0.23 mmol), Bu_3SnH (185 µl, 0.69 mmol), AIBN (5 mg) and dry toluene (10 ml). The reaction mixture was refluxed for 2h. The toluene was

removed *in vacuo*. The crude product was purified by flash chromatography to **166** (55mg, 60%). Rf: 0.65 (10% EtoAc/Tol); ^{1}H NMR (300 MHz, C_6D_6), δ 0.88 (m, 6H, 2xCH_3), δ 1.35, 1.46 (both s, 3H ea, isopropylidene CH_3's), 1.11-1.82 (m, 10H, H_6, H_8, H_9, H_{10}, =$CH_2CH_2\underline{CH_2}$), 1.98 (m, 4H, H_5, =$CH_2\underline{CH_2}$), 3.98 (m, 1H, H_7), 4.12 (m, 2H, H_3, H_4), 4.98 (m, 1H, H_2), 5.55 (m, 2H, CH=CH). ^{13}C NMR (75MHz, C_6D_6), δ 14.1, 14.88, 22.11, 23.76, 26.1, 28.62, 29.65, 29.7, 30.94, 34.92, 36.1, 74.46, 76.41, 78.12, 81.33, 109.20, 126.67, 135.64.

Annonacin A model (167)

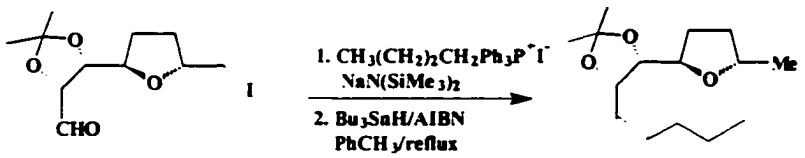


158 160

To a stirring solution of THF-iodide alkene **158** (110 mg, 0.26 mmol) and 18-crown-ether (211 mg, 0.4 mmol) in DMSO/DMF (1:1, 5 ml) was added KO_2 (57 mg, 0.4 mmol) slowly at 0 °C very carefully (*safety* 2,2909D). After stirring 2h at 0 °C, the reaction was quenched with water, followed by extraction with ether. The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Chromatographic purification of the residue afforded compound **160** (58.6 mg, 72%). Rf: 0.25 (10% EtoAc/PE); ^{1}H NMR (300 MHz, C_6D_6, assignments confirmed by ^{1}H/^{1}H COSY correlation), δ 0.91 (m, 6H, 2xCH_3), δ 1.36, 1.45 (both s, 3H ea, isopropylidene CH_3's), 1.02-1.72 (m, 7H, $H_{6\alpha}$, H_9, H_{10}, =$CH_2CH_2\underline{CH_2}$), 1.72-2.20 (m, 5H, $H_{6\beta}$, H_5, =$CH_2\underline{CH_2}$), 2.29 (d, 1H, OH), 3.34 (dd, 1H,

H_8), 3.79 (m, 1H, H_7), 3.89 (m, 1H, H_4), 4.05 (t, 1H, H_3), 4.98 (m, 1H, H_2), 5.46, 5.64 (both m, 2H, CH=CH). ^{13}C NMR (75MHz, C_6D_6), δ 14.90, 15.25, 19.95, 23.84, 23.84, 26.40, 28.84, 29.20, 30.91, 36.62, 74.58, 74.72, 78.18, 81.32, 83.88, 109.46, 126.66, 135.52.

THF Alkene (168)



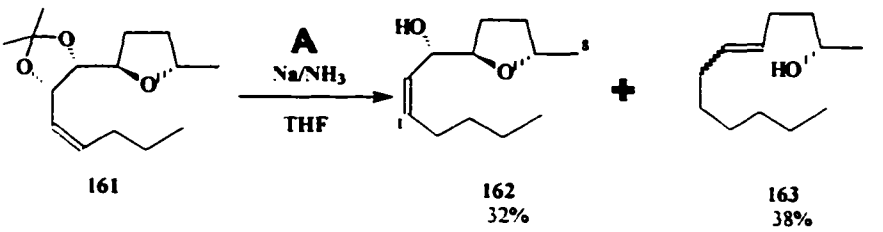
145 161

By a similar Wittig procedure to that used for preparation of alkene **152b**, THF-iodide **145** (968 mg, 2.8 mmol) was converted to THF-iodide alkene (750 mg, 68%). Rf: 0.75 (20% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.87 (m, 6H, 2xCH_3), δ 1.37, 1.45 (both s, 3H ea, isopropylidene CH_3's), 1.20-2.35 (m, 8H, H_5, H_6, =$CH_2$$\underline{CH_2}$, =$CH_2CH_2$$\underline{CH_2}$), 3.19 (q, 2H, H_8), 4.08 (m, 3H, H_7, H_4, H_3), 4.99 (m, 1H, H_2), 5.45, 5.64 (both m, 2H, CH=CH). ^{13}C NMR (75MHz, $CDCl_3$), δ 13.86, 22.75, 25.27, 27.48, 27.56, 27.63, 28.85, 29.91, 64.86, 73.38, 79.61, 80.05, 108.39, 125.56, 134.67.

Following the procedure to that used for preparation of the muricatalin model **159**, THF-iodide **154** alkene (750 mg, 1.9 mmol) was converted to THF alkene **161** (500 mg, 97%). Rf: 0.67 (10% EtoAc/Tol); ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.91 (t, 3H, $CH_2$$\underline{CH_3}$), 1.16 (d, 3H, CH_3), 1.375, 1.46 (both s, 3H ea, isopropylidene CH_3's), 1.25-1.50 (m, 2H, =$CH_2CH_2$$\underline{CH_2}$), 1.80-2.20 (m, 6H, H_5, H_6, =$CH_2$$\underline{CH_2}$), 3.98 (m, 1H, H_7), 4.12 (m, 2H, H_4,

H_3), 4.98 (m, 1H, H_2), 5.46, 5.63 (both m, 2H, CH=CH). ^{13}C NMR (75MHz, $CDCl_3$), δ 14.88, 22.11, 23.76, 26.1, 28.62, 29.65, 30.94, 34.92, 74.46, 76.41, 78.12, 81.33, 109.20, 126.67, 135.64.

Deoxygenation Product (162) from Procedure A



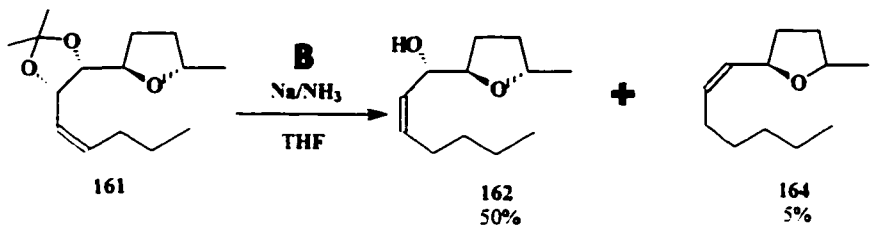
161 162 32% 163 38%

Procedure **A**: Sodium was slowly added to a solution of THF alkene **161** (40 mg, 0.15 mmol) in 1:5 THF/NH_3 solvent at -78 °C under argon atmosphere until the blue color was persistent for several minutes. After warming to rt, the reaction was quenched with solid NH_4Cl and extracted with ether (3x). The organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography afforded the desired product **162** (10 mg, 32%) was obtained together with side product **163** (11 mg, 38%).

162: Rf: 0.37 (20% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$, assignments confirmed by ^{1}H/^{1}H COSY), δ 0.86 (t, 3H, $CH_2\underline{CH_3}$), 1.24 (d, 3H, CH_3), 1.20-1.60 (m, 4H, $\underline{CH_2CH_2}CH_3$), 1.80-2.24 (m, 6H, H_5, H_6, =CH-$\underline{CH_2}$), 4.02 (m, 1H, H_4), 4.15 (m, 1H, H_7), 4.22 (m, 1H, H_3), 4.22, 5.41 (both m, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 15.01, 22.42, 23.30, 23.45, 27.04, 32.39, 33.20, 35.15, 74.82, 77.40, 82.75, 129.11, 134.99.

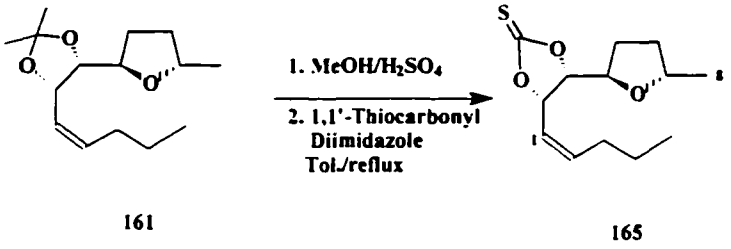
163: R_f: 0.42 (20% EtoAc PE); ^1H NMR (300 MHz, $CDCl_3$, assignments confirmed by $^1H/^1H$ COSY), δ 0.86 (t, 3H, $CH_2\underline{CH_3}$), 1.29 (d, 3H, CH_3), 1.20-1.60 (m, 10H, 5xCH_2), 2.0 (m, 4H, $\underline{CH_2}$-CH=CH-$\underline{CH_2}$), 3.79 (m, 1H, $\underline{CH}$OH), 5.40 (m, 2H, CH=CH).

Deoxygenation Product (162) from Procedure B



Procedure **B**: The solution of THF alkene **161** (50 mg. 0.185) in THF (2 ml) was added to a prepared solution of excess sodium-ammonia in THF. After the color changed from blue to brown, the reaction was then followed by procedure **A**. The desired product **169** (21 mg, 50%) was obtained together with side product **171** (~5%).

Thiocarbonate 172

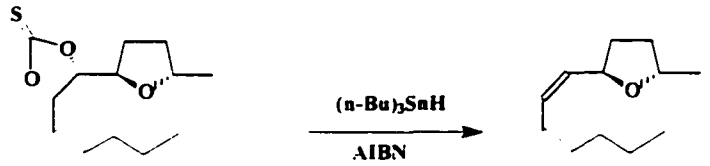


To a stirred solution of **168** (450 mg, 1.77 mmol) in MeOH (6 ml) at rt was added H_2SO_4 (20µl). After 14h, the reaction mixture was partitioned between brine and EtOAc

and separated. After extracting the aqueous phase with EtOAc (3x), the organic phases were combined, washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatographic purification of the residue afforded diol derivative (300 mg, 80%). Rf: 0.21 (20% EtoAc/Tol); ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.85 (m, 3H, CH2$\underline{CH_3}$), 1.20 (d, 3H, CH_3), 1.20-1.60 (m, 2H, =$CH_2CH_2\underline{CH_2}$), 1.80-2.20 (m, 6H, H_5, H_6, =$CH_2\underline{CH_2}$), 3.22 (m, 1H, H_3), 3.40 (m, 1H, H_4), 3.99 (m, 1H, H_7), 4.12 (m, 1H, H_2), 5.50, 5.75 (both m, 2H, CH=CH).

A portion of diol derivative obtained in the previous step (100 mg, 0.467 mmol) was dissolved in toluene (4 ml). 1,1'-thiocarbonyldiimidazole (238 mg, 1.4 mmol) was then added. The reaction mixture was heated at reflux for 24h, then cooled to rt and partitioned between brine and ether. The organic layer was dried (Na_2SO_4) and then concentrated in *vacuo*. Flash chromatography afforded **165** (60 mg, 62%). Rf: 0.64 (20% EtoAc/Tol); ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.90 (m, 3H, CH2$\underline{CH_3}$), 1.22 (d, 3H, CH_3), 1.00-2.20 (m, 8H, =$CH_2CH_2\underline{CH_2}$, H_5, H_6, =$CH_2\underline{CH_2}$), 4.15 (m, 2H, H_4, H_7), 4.47 (m, 2H, H_2, H_3), 5.78, 5.93 (both m, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.85, 22.04, 22.42, 34.03, 34.14, 34.92, 58.36, 58.64, 76.04, 79.50, 125.27, 138.26.

THF-Diene (173)

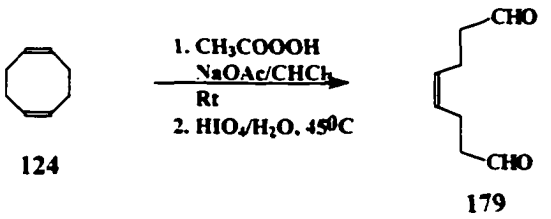


165 166

In a 10ml round-bottom flask equipped with reflux condenser and magnetic stirring bar, were placed **165** (50 mg, 0.186 mmol), Bu_3SnH (100 ul, 0.38 mmol), AIBN (2 mg) and dry toluene (5 ml). The reaction mixture was refluxed for 15 min. The toluene was removed *in vacuo*. The crude product was purified by flash chromatography to give **173** (25 mg, 74%). Rf: 0.83 (20% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.80 (t, 3H, $CH_2\underline{CH_3}$), 1.20 (d, 3H, CH_3), 1.32 (t, 2H, $\underline{CH_2}CH_3$), 1.38, 1.55 (both m, 2H, $\underline{CH_2}$-CH=CH), 2.00 (m, 4H, H_5, H_6), 5.51 (m, 2H, 2x$\underline{CH}$=CH), 5.93 (m, 1H, CH=$\underline{CH}$), 6.10 (m, 1H, CH=$\underline{CH}$). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.10, 20.61, 23.2, 28.82, 29.63, 31.36, 71.40, 73.35, 128.0, 128.1, 131.2, 133.60.

C2-Symmetric Z-Alkene

Cis-4-Octenedial (189)



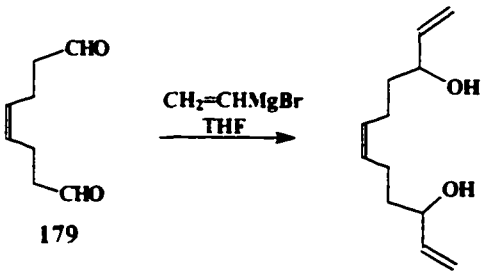
124 179

To a rapidly stirred suspension of 1, 5-cyclooctadiene **124** (10.8 g, 0.10 mol) and NaOAc (8.2 g, 0.1 mol) in $CHCl_3$ (350 ml), was added CH_3COOOH (21 ml, 0.1 mol) slowly. After stirring 1h reaction at rt, the reaction mixture was filtered, and the filtrate was washed with aqueous $NaHCO_3$ and brine. The organic phase was dried (Na_2SO4), and filtered and evaporated *in vacuo*. The crude product 5,6-epoxycyclooctene can be used directly for next step. ^1H NMR (300 MHz, $CDCl_3$), δ 2.00 (m, 4H, $\underline{CH_2}CH=CH\underline{CH_2}$), 2.10, 2.41 (both m, 4H, $\underline{CH_2}CH(O)CH\underline{CH_2}$), 3.01 (m, 2H, CH(O)CH), 5.57 (m, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 23.82, 28.27, 56.84 and 128.99.

To the crude material from the previous step, was added a solution of periodic acid (22.8 g, 0.1 mol) in H_2O (350 ml). The mixture was stirred for 1h at 40 °C. After cooling to 0 °C, the reaction mixture was neutralized with aqueous $NaHCO_3$ and then saturated with NaCl and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and filtered. The filtrate was then be stabilized with a small amount of hydroquinone (10 mg) and evaporated *in vacuo*. Chromatographic purification of the residue gave *cis*-4-octenedial **179** (10.5 g, 76% overall yield). ^1H NMR (300MHz, $CDCl_3$), δ 2.30 (m, 4H,

$\underline{CH_2}CH=CH\underline{CH_2}$), 2.44 (t, 4H, 2x$\underline{CH_2}$CHO), 5.28 (m, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 19.97, 43.51, 128.89 and 201.77.

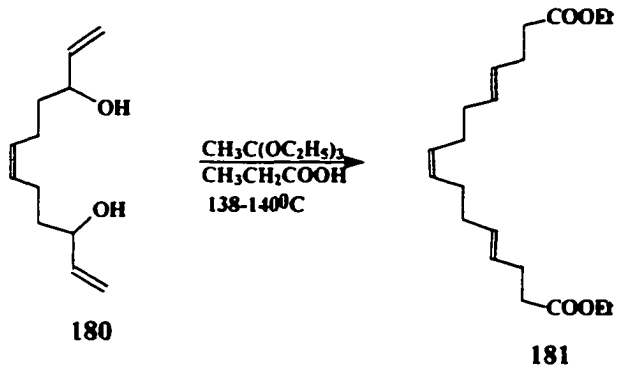
(Z)-1,6,11-dodecantriene-3,10-diol (180)



179 180

To a solution of vinylmagnesium bromide (240 ml, 1M) in dry THF (440 ml) was added dropwise a solution of **179** (12.7 g, 90 mmol) in dry THF (100 ml) at 0 °C. The reaction was stirred 1h, quenched with 1M aqueous HCl and extracted with ether (3x). The ethereal extract was washed with brine, dried (Na_2SO_4) and then concentrated in *vacuo*. The crude (Z)-1,6,11-dodecantriene-3,10-diol **190** was used directly in the next step. A small portion of the crude product was purified by flash chromatography. IR (neat) 3356, 2926, 2858, 1644 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.58 (m, 4H, $\underline{CH_2}CH_2CH=CHCH_2\underline{CH_2}$), 2.16 (m, 4H, $\underline{CH_2}CH=CH\underline{CH_2}$), 2.58 (s, 2H, 2xOH), 4.12 (m, 2H, 2x$\underline{CH}$(OH)), 5.15 (m, 4H, 2xCH_2=), 5.40(m, 2H, CH=CH), 5.87 (m, 2H, 2x=CH). ^{13}C NMR (75MHz, $CDCl_3$), Major compound, δ 23.19, 36.95, 72.25, 114.57, 129.87, 141.34; Minor compound, δ 23.37, 36.84, 72.56, 114.57, 129.95, 141.34; HRMS calcd for $C_{12}H_{20}O_2$ $(M+H)^+$ 197.1542, found 197.1539.

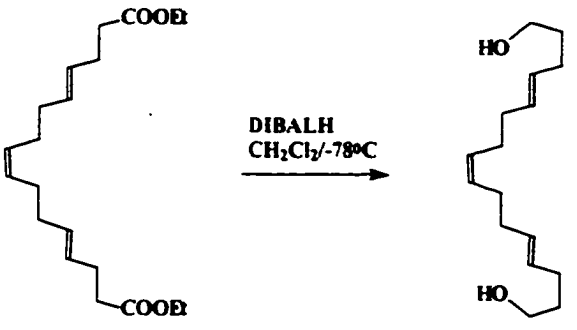
(4E,8Z,12E)-triene-diethyl 1, 16-hexadecadiacetate (191)



180 181

A 100ml, one-necked round-bottomed flask containing a magnetic stirring bar was fitted with a Claisen adaptor, two thermometers and a receiving flask. To the flask was added ethyl orthoacetate (160 ml), diol **180** (17.8 g, 90.0 mmol) and propionic acid (0.8 ml). The mixture was heated with stirring to keep temperature above 138~142 °C. Heating was continuous until the reaction was completed. The reaction mixture was then cooled to rt and excess ortho ester and propionic acid were removed by distillation under reduced presure. The crude triene ester **181** was used in next step. IR (neat) 3356, 2926, 2858, 1644 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.24 (t, 6H, $2xCH_3$), 2.03 (m, 8H, $4xCH_2$), 2.33 (m, 8H, $4xCH_2$), 5.34 (m, 2H, CH=CH), 5.46 (m, 4H, 2xCH=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.45, 27.41, 28.11, 32.72, 34.56, 60.41, 128.64, 129.54, 131.23, 173.39.

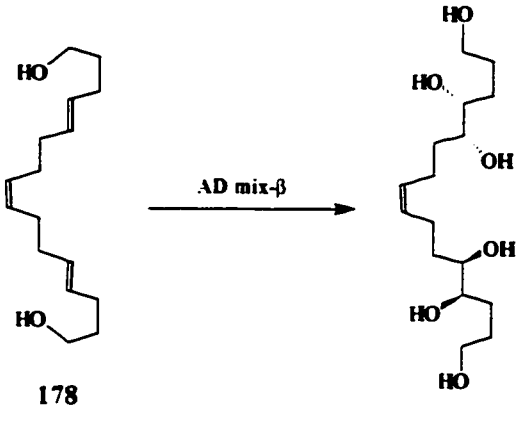
(4E,8Z,12E)-hexadecatriene-1, 16-diol (178)



181 **178**

To a stirred solution of diester **181** (30.3 g, 90mmol) in dry CH_2Cl_2 (300 ml) at -78 °C under N2 was added dropwise a solution of DIBAL (347 ml, 347 mmol, 1M in heptane). The mixture was stirred for 1h at -78 °C and then warmed to rt. The reaction mixture was poured into ice cold of Rochell's salt (saturated $KNaC_4H_4O_6$, 500 ml). The mixture was warmed to rt, and stirred until the aluminum salts had dissolved. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo.* Chromatographic purification of the residue (12x20 cm, 40% EtOAc/PE) gave **178** (16.15 g, 71% overall yield from **179**). IR (neat) 3345, 2933, 2849, 1445, 1350, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 1.59 (m, 4H, 2x$\underline{CH_2}CH_2OH$), 2.03 (m, 12H, 6xCH_2), 2.43 (s, 2H, 2xOH), 3.59 (t, 4H, 2x$\underline{CH_2}OH$), 5.33 (m, 2H, CH=CH), 5.41 (m, 4H, 2xCH=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 27.44, 28.99, 32.46, 32.68, 62.37, 129.56, 130.01, 130.49.

(8Z,4R, 5R, 12R, 13R)- hexadecaene-1,4,5,12,13,16-hexaol (182)



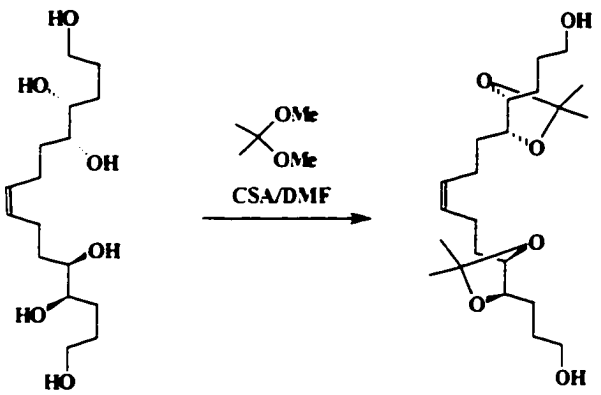
178 182

A 1000ml, round-bottomed flask, equipped with a magnetic stirring bar, was charged with t-butyl alcohol (160 ml), H2O (160 ml), AD-mix-β (44.7 g), and $MeSO_2NH_2$ (3.0 g, 16 mmol). The mixture was stirred at rt until both phases are clear, and then cooled to -3 °C , whereupon the inorganic salts partially precipitated. At this point, triene **178** (4.03 g, 16 mmol) was added, and the heterogeneous slurry was stirred vigorously at -3 °C until TLC revealed complete consumption of the starting material (~40h). The reaction was quenched at -3 °C by addition of sodium sulfite (49 g), warmed to rt and stirred for additional 1h. The t-butyl alcohol layer was separated and the aqueous layer was extracted with t-butyl alcohol (1x) and EtOAc (4x). The combined organic phase was washed with 2N KOH to remove most of $MeSO_2NH_2$, dried (Na_2SO_4) and concentrated *in vacuo*. Chromatographic purification of the residue (10x25 cm, 10% MeOH/EtOAc) gave hexaol **182** (3.15 g, 62%) containing small amounts of diastereomer product (<5%) and mono dihydroxylation derivative (915 mg, 20%).

182: IR (neat) 3356 cm^{-1}; ^1H NMR (300 MHz, CD_3OD), δ 1.56 (m, 12H, 6xCH_2), 2.02 (m, 4H, CH_2CH=$CHCH_2$), 3.40 (m, 4H, 4xCH-OH), 3.57 (t, 4H, 2xCH_2-OH), 5.40(m, 2H, CH=CH). ^{13}C NMR (75 MHz, CD_3OD), δ 25.76, 30.21, 30.49, 34.06, 63.10 (CH_2OH), 74.79 ($CHOH$), 75.19 ($CHOH$), 130.92. MS: calcd for $C_{16}H_{36}O_6$ MW 320.21, found $(M+H)^+$ 321.20.

Diastereomer: 62.52 (CH_2OH), 75.92 ($CHOH$), 76.41 ($CHOH$),

(8Z,4R,5R,12R,13R)-hexadecaene-4,5:12,13-diisopropylidenedioxy-1,16-diol (167)

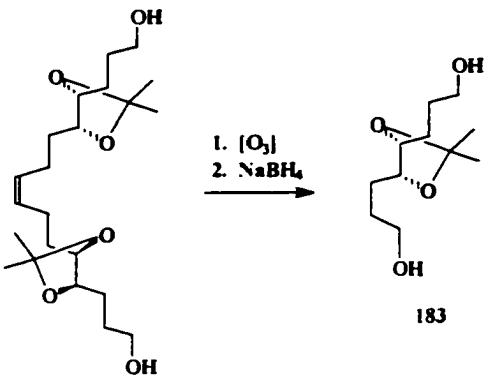


182 **167**

2,2-Dimethoxypropane (2.45 ml, 20 mmol) and (±)-10-camphorsulfonic acid (970 mg, 4.35 mmol) were added to a solution of hexaol **182** (2.78 g, 8.7 mmol) in anhydrous DMF (120 ml) at 0 °C. The reaction mixture was warmed to rt and stirred for 30min. The reaction was quenched with saturated sodium bicarbonate and extracted with ether (3x) and EtOAc (1x). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Chromatographic purification of the residue (4x20 cm, EtOAc) gave **167** (3.28 g, 94%).

IR (neat) 3419, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 1.32 (s, 12H, 4xCH_3), 1.58 (m, 12H, 6xCH_2), 2.14 (m, 4H, $C\underline{H}_2CH=CHC\underline{H}_2$), 3.58 (m, 8H, 4xCH-O, CH, 2x$C\underline{H}_2OH$), 3.82 (bs, 2H, 2xOH), 5.35 (m, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 23.85, 27.33, 27.40, 29.46, 29.54, 32.72, 62.45, 80.36, 80.82, 108.13, 129.27. HRMS calcd for $C_{22}H_{40}O_6$ $(M+H)^+$ 401.2903, found 401.2903.

(4R,5R)-4,5-(isopropylidenedioxy)-1,8-octanediol (183)



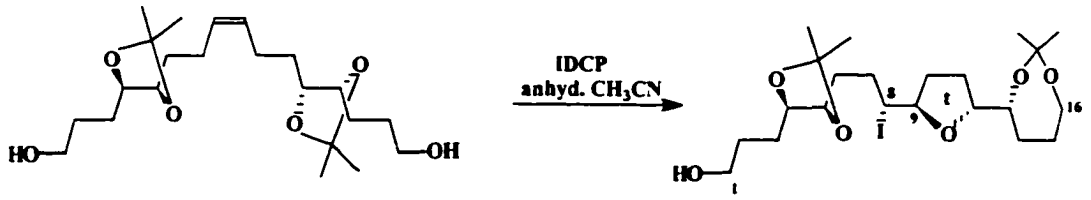
167 183

Compound **167** (40 mg, 0.1 mmol) was subjected to the similar reaction conditions in the preparation of **99**. Purification of the product afforded **183** (25 mg, 57%).

R_f: 0.38 (10% MeOH/EtOAc); $[\alpha]^{26}D$: 29.2 (c 0.52 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$), δ 1.39 (s, 6H, 2xCH_3), 1.50-1.90 (m, 8H, 4xCH_2), 2.42 (s, 2H, 2xOH), 3.67 (m, 6H, 2x$C\underline{H}$-O, 2x$C\underline{H}_2OH$). ^{13}C NMR (75 MHz, $CDCl_3$), δ 27.45, 29.55, 29.65, 62.77, 81.10, 108.44. HRMS cald for $C_{11}H_{22}O_4$ $(M+H)^+$ 219.1596, found 219.1583.

Trilobacin and Asimicin Bis-THF Core

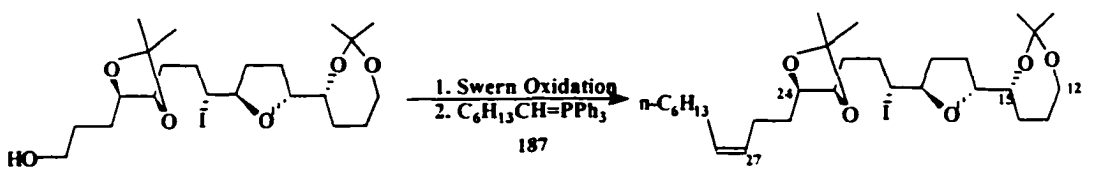
(4R,5R, 8R, 9R, 12R, 13R)-4,5:13,16-diisopropylidenedioxy-9,12-epoxy-8-iodo-1-hexadecaol (186)



167 186

Treatment of **167** (563 mg, 1.4 mmol) with our standard halocyclization conditions (IDCP (985 mg, 2.1 mmol), CH3CN (50 ml)) in the preparation of **117**, provided **186** (616 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.31, 1.32 (both s, 6H, 2xCH_3), 1.36 (s, 6H, 2xCH_3), 1.65 (m, 12H, 6xCH_2), 1.95, 2.05 (both m, 4H, H_{10}, H_{11}), 2.40 (bs, 1H, OH), 3.60 (m, 7H, H_1, H_4, H_5, H_{13}), 3.85 (m, 1H, H_9), 4.01 (m, 2H, H_8, H_{12}). ^{13}C NMR (75 MHz, CDCl3), δ 25.39, 27.45, 28.51, 29.36, 29.67, 30.56, 31.19, 32.11, 33.03, 41.90, 62.12, 62.77, 74.27, 80.01, 80.89, 82.59, 82.77, 100.78, 108.46. HRMS calcd for $C_{22}H_{39}O_6I$ $(M+H)^+$ 527.1870, found 527.1869.

Mono-THF Iodide Alkene (188)



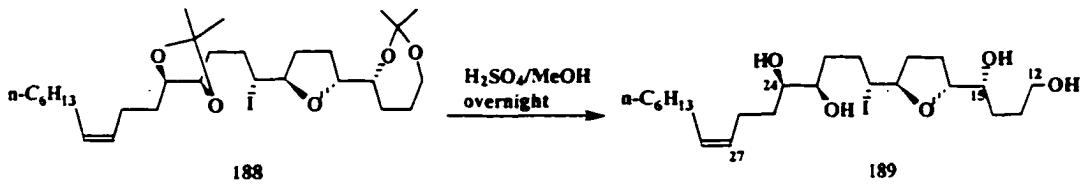
186 188

A 50ml, round-bottomed flask, equipped with a magnetic stirring bar, was charged with oxalyl chloride (0.336 ml, 3.78 mmol) and CH_2Cl_2 (10 ml). The set up was purged with argon and cooled to -78 °C. DMSO (0.54 ml, 7.55 mmol) was added dropwise to the mixture and stirring continued for 20 min. Then a solution of mono-THF iodide **186** (795 mg, 1.51 mmol) in CH_2Cl_2 was added dropwise. The reaction mixture was stirred for 25 min at -78 °C, at which time Et_3N (1.47 ml, 10.57 mmol) was added. After warming to rt, the mixture was stirred for additional 10 min, diluted with ether, washed with saturated sodium bicarbonate, dried (Na_2SO_4) and concentrated *in vacuo.* Chromatographic purification of the residue (2.5x15 cm, 20% EtOAc/PE) gave the aldehyde derivative (710 mg, 90%). ^1H NMR (300 MHz, $CDCl_3$), δ 1.26, 1.30 (both s, 6H, 2xCH_3), 1.33 (s, 6H, 2xCH_3), 1.20-2.22 (m, 14H, 7xCH_2), 2.64 (m, 2H, $\underline{CH_2}CHO$), 3.62 (m, 5H, H_4, H_5, H_{13}), 3.90 (m, 1H, H_9), 4.05 (m, 2H, H_8, H_{12}), 9.78 (s, 1H, CHO). ^{13}C NMR (75 MHz, CDCl3), δ 25.11, 25.36, 25.40, 27.40, 28.45, 29.34, 30.55, 31.19, 32.11, 33.03, 40.47, 41.85, 62.10, 74.18, 79.71, 79.79, 82.57, 82.74, 100.73, 108.61, 201.69.

To a solution of heptyl triphenylphosphonium iodide **187** (988 mg, 2.02 mmol) in dry toluene (50 ml) was added a 1M solution of sodium bis(trimethylsilyl) amide (1.89 ml, 1.89 mmol) in toluene, under an argon atmosphere. The yellow-orange suspension was stirred for 1h at rt then cooled to -78°C. A solution of the aldehyde prepared in previous step (710 mg, 1.35 mmol) in dry toluene (30 ml) was added dropwise over 30 min. After an additional 15 min, the reaction mixture was warmed to rt, then diluted with ether (100 ml). The mixture was filtered through a pad of Celite and the filtrate was

concentrated *in vacuo*. The residue was purified by flash chromatography (2.5x15 cm, 10% EtoAc/PE) to afford **188** (708 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.84 (t, 3H, CH_3), 1.28, 1.30 (both s, 6H, 2xCH_3), δ1.35 (s, 6H, 2xCH_3), 1.20-2.22 (m, 26H, 13xCH_2), 3.63 (m, 5H, H_{24}, H_{23}, H_{15}, H_{12}), 3.90 (m, 1H, H_{19}), 4.06 (m, 2H, H_{20}, H_{16}), 5.35 (m, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.25, 22.79, 23.94, 25.37, 25.40, 27.42, 27.52, 28.45, 29.14, 29.36, 29.82, 30.54, 31.18, 31.93, 32.19, 33.08, 33.17, 41.98, 62.09, 74.19, 79.89, 80.34, 82.60, 82.71, 100.72, 108.23, 128.75, 131.06.

THF-Tetraol (189)

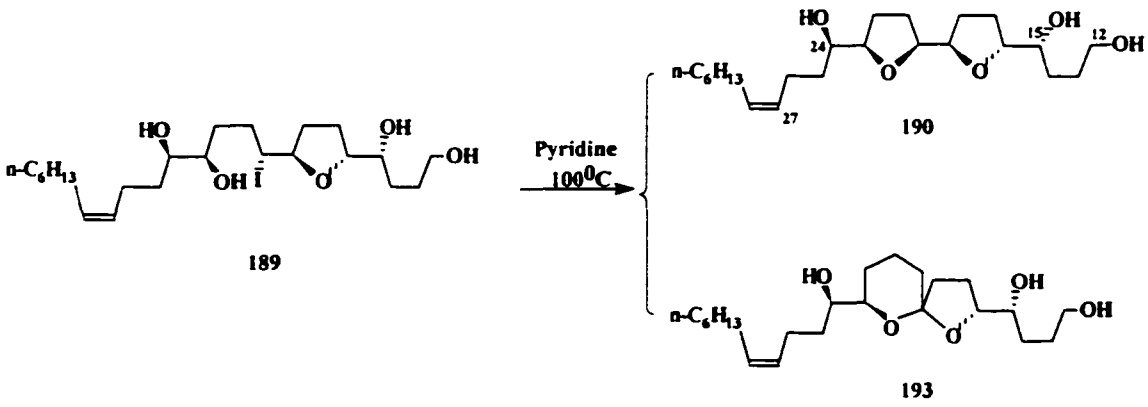


188 189

To a stirred solution of **188** (400 mg, 0.89 mmol) in MeOH (20 ml) at rt was added H_2SO_4 (100 µl). After 14h, the reaction mixture was neutralized with 1M of NaOMe in MeOH and the solvent was removed *in vacuo*. The residue was dissolved in ether and washed with brine. After extracting the aqueous phase with ether (3x), the organic phases were combined, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatographic purification of the residue afforded **196** (307 mg, 89%). IR (neat) 3395, 1455 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.87 (t, 3H, CH_3), 1.00-2.31 (m, 26H, 13xCH_2), 2.57 (s, 1H, OH), 3.05 (s, 1H, OH), 3.41 (bs, 4H, 2xOH, CH_2OH), 3.66 (m, 3H, H_{24}, H_{23}, H_{15}), 3.92 (m, 2H, H_{16}, H_{19}), 4.37 (m, 2H, H_{20}), 5.37 (m, 2H, CH=CH). ^{13}C NMR

(75 MHz, $CDCl_3$), δ 14.30, 22.83, 23.63, 27.48, 28.90, 29.20, 29.87, 30.52, 31.48, 31.83, 31.97, 33.41, 33.59, 41.24, 62.85, 73.18, 74.28, 82.61, 83.89, 129.04, 131.10. HRMS calcd for C23H43O5I $(M+H)^+$ 527.2234, found 527.2234.

Trilobacin type bis-THF alkene (190)



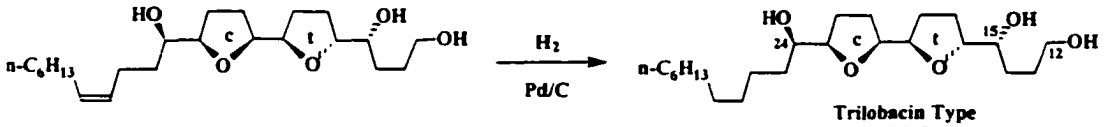
A mixture of THF-tetraol **189** (61 mg, 0.116 mmol) and pyridine (4 ml) was heated at 100 °C for 1h. After cooling to rt, the excess pyridine was removed in *vacuo*. Chromatographic purification of the residue afforded the bis-THF alkene **190** (31 mg, 67%) and spiroketal **193** (9 mg, 19%).

190: IR (neat) 3395 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, assignment confirmed by ^1H /^1H COSY), δ 0.86 (t, 3H, CH_3), 1.28 (m, 8H, H_{30}, H_{31}, H_{32}, H_{33}), 1.55 (m, 4H, H_{25}, H_{14}), 1.70 (m, 5H, $H_{21\alpha}$, $H_{22\alpha}$, $H_{17\alpha}$, H_{13}), 1.90 (m, 1H, $H_{18\alpha}$), 1.98 (m, 6H, $H_{21\beta}$, $H_{22\beta}$, $H_{17\beta}$, $H_{18\beta}$, H_{29}), 2.15 (m, 2H, H_{26}), 3.01 (s, 3H, 3xOH), 3.41 (m, 2H, H_{24}, H_{15}), 3.64 (t, 2H, $\underline{CH_2}OH$), 3.83 (m, 2H, H_{23}, H_{16}), 3.97 (m, 1H, H_{19}), 4.06 (m, 1H, H_{20}), 5.34 (m, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.26, 22.82, 26.93, 27.41, 28.33, 28.40, 29.02, 29.16, 29.37, 29.87,

30.75, 31.96, 34.47, 62.90, 73.99, 74.10, 81.07, 81.80, 82.67, 83.27, 129.29, 130.76. HRMS calcd for $C_{23}H_{42}O_5$ $(M+H)^+$ 399.3111, found 399.3114.

193: ^1H NMR (300 MHz, $CDCl_3$, assignment confirmed by ^1H /^1H COSY correlation), δ 0.86 (t, 3H, CH_3), 1.10-2.25 (m, 28H, 14xCH_2), 2.38 (d, 1H, OH), 2.73 (bs, 2H, 2xOH), 3.38 (m, 1H, H_{11}), 3.45 (m, 1H, H_{20}), 3.64 (m, 3H, H_{12}, CH2OH), 3.93 (m, 1H, H_{19}), 5.36 (m, 2H, CH=CH). ^{13}C NMR (75MHz, $CDCl_3$), δ 14.26, 19.99, 22.81, 23.53, 26.32, 26.77, 27.39, 29.14, 29.56, 29.88, 30.81, 31.95, 33.08, 33.18, 37.84, 62.95, 73.58, 73.79, 74.25, 81.19, 106.62 (tert-C), 129.28, 130.76; HRMS calcd for $C_{23}H_{42}O_5$ $(M+H)^+$ 399.3111, found 399.3112.

Trilobacin type bis-THF core (191)



190

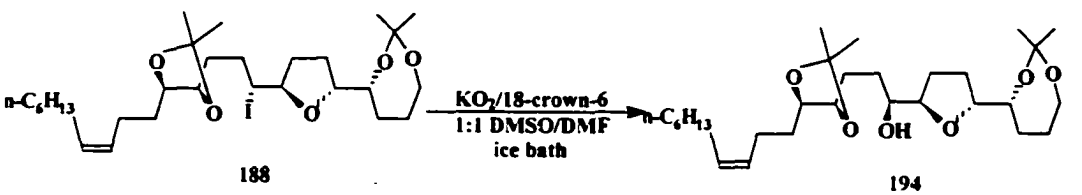
Trilobacin Type Bis-THF-Core

191

A suspension of **190** (24 mg, 0.065 mmol) and 10% w Pd/C in EtOAc (4 ml) was stirred unde H2 balloon overnight. The suspension was filtered through a short plug of Celite and concentrated *in vacuo* to give **191** (22 mg, 92%). $[\alpha]^{23}D$ = +1.4 (C = 0.38, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$, assignment confirmed by ^1H /^1H COSY), δ 0.86 (t, 3H, CH_3), 1.26 (m, 16H, H_{26}, H_{27}, H_{28}, H_{29}, H_{30}, H_{31}, H_{32}, H_{33}), 1.42 (m, 2H, H_{25}), 1.50 (m, 2H, H_{14}), 1.70 (m, 1H, $H_{21\alpha}$), 1.72 (m, 2H, H_{13}), 1.75 (m 2H, $H_{22\alpha}$, $H_{17\alpha}$), 1.86 (m, 1H, $H_{18\alpha}$), 1.93 (m, 1H, $H_{18\beta}$), 1.96 (m, 1H, $H_{22\beta}$, $H_{17\beta}$), 2.05 (m, 1H, $H_{21\beta}$), 2.90 (bd, 3H,

3xOH), 3.39 (m, 2H, H_{24}), 3.43 (m, 2H, H_{15}), 3.65 (t, 2H, $\underline{CH_2}OH$), 3.83 (m, 2H, H_{23}, H_{16}), 3.97 (m, 1H, H_{19}), 4.06 (m, 1H, H_{20}). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.32, 22.88, 26.00, 26.89, 28.40, 29.02, 29.40, 29.53, 29.82, 29.92, 30.81, 32.10, 34.51, 62.93, 73.95, 74.71, 81.07, 81.78, 82.70, 83.22. HRMS calcd for $C_{23}H_{40}O_5$ $(M+H)^+$ 401.32670, found 401.3266.

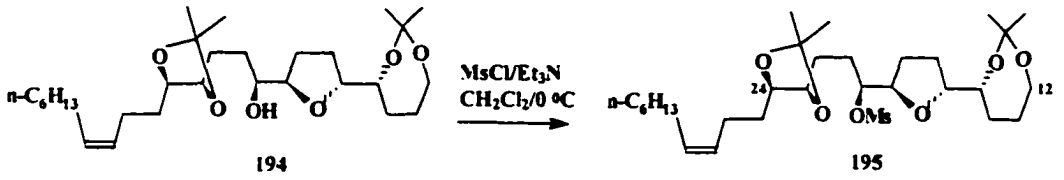
THF-alcohol (194)



188 194

Compound **188** (580 mg, 0.95 mmol) was subjected to the similar reaction conditions in the preparation of **160**. It afforded compound **194** (250 mg, 55%). ^1H NMR (300 MHz, $CDCl_3$), δ 0.86 (t, 3H, CH_3), 1.29, 1.31 (both s, 6H, 2xCH_3), δ1.35 (s, 6H, 2xCH_3), 1.00-2.22 (m, 26H, 13xCH_2), 3.62 (m, 5H, H_{24}, H_{23}, H_{15}, H_{12}), 3.84 (m, 2H, H_{20}), 3.93 (m, 1H, H_{19}), 4.04 (m, 1H, H_{16}), 5.35 (m, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.20, 22.76, 23.98, 25.29, 25.38, 25.71, 27.38, 27.49, 28.68, 29.11, 29.38, 29.67, 29.81, 30.68, 31.91, 33.02, 33.11, 62.07, 72.10, 74.41, 80.62, 81.31, 82.09, 82.34, 100.78, 108.14, 128.80, 130.98.

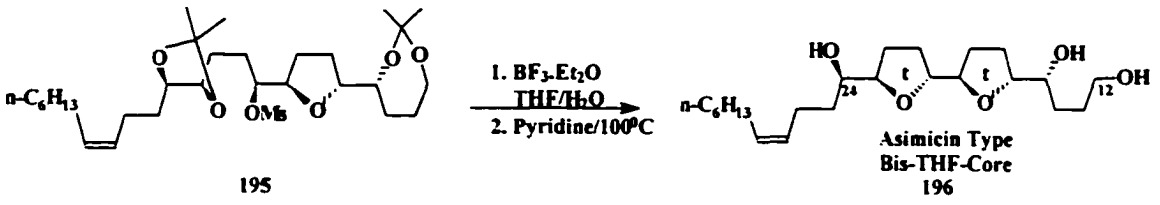
THF-Mesylate (195)



194 195

A stirred solution of **194** (250 mg, 0.5 mmol) and Et_3N (0.2 ml) in CH_2Cl_2 (15 ml) was treated with methylsulfonyl chloride (78 mg, 1.0 mmol) at 0°C under nitrogen atmosphere. The mixture was stirred for 4 h at rt, and then was quenched with MeOH. After concentration, the residue was taken up in ether and washed with sodium bicarbonate and brine. The ethereal solution was dried over (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (2x12 cm, 20% EtOAc: PE) to give product **195** (200 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.86 (t, 3H, CH_3), 1.30 (s, 6H, 2xCH_3), 1.34, 1.35 (both s, 6H, 2xCH_3), 1.00-2.30 (m, 26H, 13xCH_2), 3.08 (s, 1H, CH_3), 3.62 (m, 5H, H_{24}, H_{23}, H_{15}, H_{12}), 3.88 (m, 1H, H_{19}), 4.06 (m, 1H, H_{16}), 4.81 (m, 2H, H_{20}), 5.38 (m, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.22, 22.79, 25.38, 26.45, 27.43, 27.47, 27.52, 28.56, 28.89, 29.16, 29.26, 29.83, 31.03, 31.94, 33.01, 38.56, 62.05, 74.16, 80.02, 80.56, 80.92, 82.58, 84.51, 100.75, 108.27, 128.76, 131.07.

Asimicin type bis-THF alkene (196)



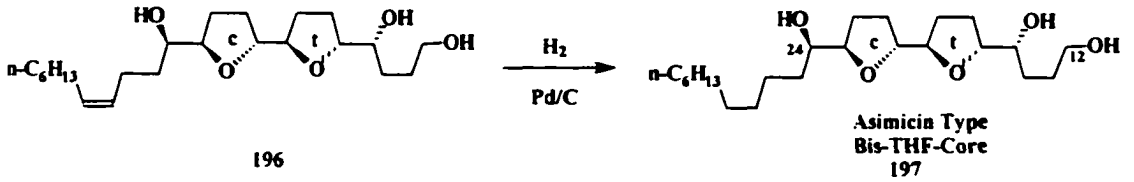
195 196

A solution of **195** (16 mg, 0.028 mmol) in THF (2.5 ml) was treated with $BF_3.Et_2O$ (0.2 ml) at rt for 10 min, and then H_2O (0.2 ml) was added. After stirring for 2h, the reaction mixture was then poured into a saturated, aqueous $NaHCO_3$ and the mixture extracted with ether. The organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography of the residue afforded the tetraol product (14 mg, 100%). ^1H NMR (300 MHz, $CDCl_3$), δ 0.86 (t, 3H, CH_3), 1.00-2.30 (m, 26H, 13xCH_2), 3.08 (s, 1H, CH_3), 3.32 (m, 1H, H_{24}), 3.41 (m, 3H, H_{23}, H_{15}), 3.59 (t, 2H, H_{12}), 3.88 (m, 1H, H_{19}), 4.12 (m, 1H, H_{19}), 4.81 (m, 2H, H_{20}), 5.38 (m, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.55, 23.83, 24.84, 27.56, 28.33, 29.26, 29.70, 30.12, 30.21, 30.28, 30.99, 31.11, 33.07, 34.25, 38.99, 63.12, 74.77, 74.95, 75.28, 81.51, 84.55, 85.97, 130.52, 131.44.

A solution of tetraol (75.0 mg, 0.15 mmol) prepared in previous step in pyridine (5 ml) was heated at 100 °C for 1h. After cooling to rt, the excess pyridine was removed in *vacuo*. Chromatographic purification of the residue afforded **202** (51.7 mg, 86%). ^1H NMR (300 MHz, $CDCl_3$, assignment confirmed by ^1H /^1H COSY), δ 0.86 (t, 3H, CH_3), 1.28 (m, 8H, H_{30}, H_{31}, H_{32}, H_{33}), 1.40-1.80 (m, 10H, $H_{21\alpha}$, $H_{22\alpha}$, $H_{17\alpha}$, $H_{18\alpha}$, H_{25}, H_{13}, H_{14}), 1.98 (m, 6H, $H_{21\beta}$, $H_{22\beta}$, $H_{17\beta}$, $H_{18\beta}$, H_{29}), 2.15 (m, 2H, H_{26}), 2.98 (s, 3H, 3xOH), 3.38 (m, 2H, H_{24}, H_{15}), 3.64 (t, 2H, $\underline{CH_2}OH$), 3.84 (m, 4H, H_{23}, H_{16}, H_{19}, H_{20}), 5.35 (m, 2H,

CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.24. 22.80. 27.42, 28.57, 29.13, 29.41. 29.88, 30.55, 31.96, 33.62, 62.98, 73.68, 74.21, 81.97, 81.97, 83.16. 83.24, 129.26, 130.84. HRMS calcd for $C_{23}H_{42}O_5$ $(M+H)^-$ 399.3111, found 399.3110.

Asimicin type bis-THF core (197)

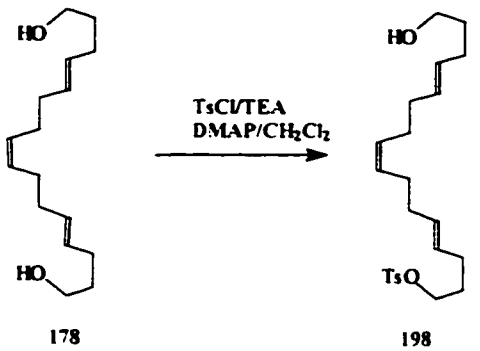


196

Asimicin Type Bis-THF-Core 197

A solution of **196** (4.5 mg, 0.012 mmol), 30% w Pd/C in EtOAc (2 ml) was stirred under 1 atm of H2 gas overnight. The result solution was filtered through a short plug of *Celite* and concentrated in *vacuo* to give **197** (4 mg, 88%). $[\alpha]^{23}D$ = +9.5 (C = 0.4, $CHCl_3$),^{1}H NMR (300 MHz, $CDCl_3$, assignment confirmed by ^{1}H /^{1}H COSY), δ 0.88 (t, 3H, CH_3), 1.26 (m, 16H, H_{26}, H_{27}, H_{28}, H_{29}, H_{30}, H_{31}, H_{32}, H_{33}), 1.39 (m, 2H, H_{25}), 1.50 (m, 2H, H_{14}), 1.65 (m, 4H, $H_{21\alpha}$, $H_{22\alpha}$, $H_{17\alpha}$, $H_{18\alpha}$), 1.72 (m, 2H, H_{13}), 1.97 (m, 4H, $H_{18\beta}$, $H_{22\beta}$, $H_{17\beta}$, $H_{21\beta}$), 2.65 (bd, 3H, 3xOH), 3.38 (m, 2H, H_{24}), 3.45 (m, 2H, H_{15}), 3.67 (t, 2H, $\underline{CH_2}OH$), 3.85 (m, 2H, H_{23}, H_{16}, H_{19}, H_{20}). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.28, 22.87, 25.85, 28.58, 29.13, 29.51, 29.82, 29.93, 30.67, 32.11, 33.68, 63.10, 74.27, 81.89, 82.01, 83.11, 83.39. HRMS calcd for $C_{23}H_{40}O_5$ $(M+H)^-$ 401.3267, found 401.3266.

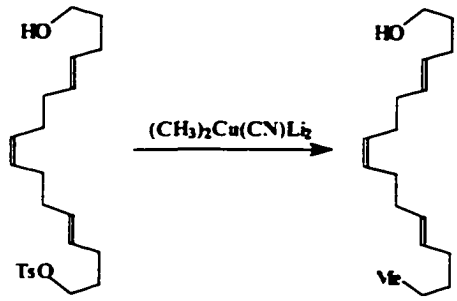
(4E,8Z,12E)-hexadecatriene-1-tosyl-16-ol (198)



178 198

A stirred solution of triene **188** (3.62 g, 14.37 mmol), DMAP (105 mg, 0.86 mmol) and Et3N (3 ml, 21.55 mmol) in CH2Cl2 (100 ml) was treated with p-toluenesulfonyl chloride (2.88 g, 15 mmol) at 0°C under nitrogen atmosphere. The mixture was stirred for 1h at rt, and then was quenched with MeOH. After concentration, the residue was taken up in ether and washed with sodium bicarbonate and brine. The ethereal solution was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (6x12, 30% EtOAc/PE) to give the product **198** (2.65 g, 45%) and recovered **188** (1.32 g, 36%). **198:** ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.65 (m, 4H, $\underline{CH_2}CH_2OH$, $\underline{CH_2}CH_2OTs$), 2.04 (m, 12H, 6xCH_2), 2.44 (s, 3H, CH_3), 3.64 (t, 2H, $\underline{CH_2}OH$), 4.04 (t, 2H, $\underline{CH_2}OTs$), 5.34, 5.45 (both m, 6H, 3xCH=CH), 7.34 (d, 2H, Ar-H's), 7.78 (d, 2H, Ar-H's). ^{13}C NMR (75MHz, $CDCl_3$), δ 21.81, 27.39, 27.50, 28.38, 28.81, 29.12, 32.61, 32.72, 32.76, 62.73, 70.09, 128.09, 128.47, 129.50, 129.68, 129.98, 130.13, 130.13, 131.65.

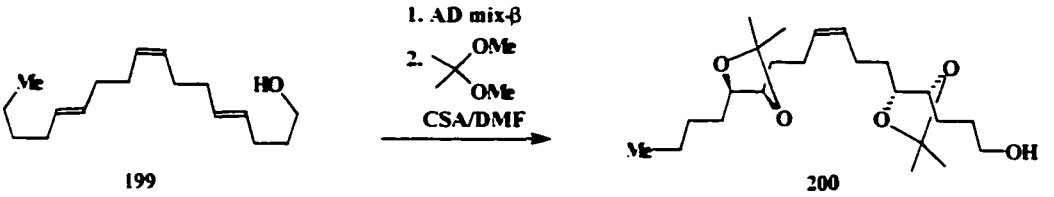
(4E,8Z,12E)-hexadecatriene-1-ol (199)



198 199

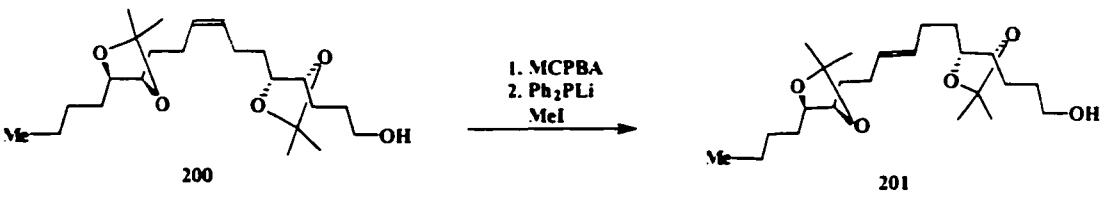
To a stirred solution of CuCN (1.33 g, 15 mmol) in THF (30 ml) at -78 °C was added methyllithium (30 ml, 30 mmol, 1M in THF). The solution was allowed to warm to 0 °C After stirring for 10 min, a solution of **198** (2.03 g, 5 mmol) in THF (20 ml) was added dropwise *via* cannula. After 2h the reaction mixture was allowed to warm to rt and quenched with aqueous NH4Cl/NH4OH (9:1). The heterogeneous mixture was stirred until the copper salts dissolved and then extracted with ether (3x). The combined organic phase was washed with brine, dried (Na2SO4), filtered and evaporated *in vacuo*. Flash chromatography of the residue (6x12 cm, 20% EtOAc/PE) afforded **199** (1.09 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.86 (t, 3H, CH_3), 1.33 (m, 4H, $\underline{CH_2}\underline{CH_2}CH_3$), 1.64 (m, 2H, $\underline{CH_2}CH_2OH$), 2.04 (m, 12H, 6xCH_2), 3.64 (t, 2H, $\underline{CH_2}OH$), 5.4 (m, 6H, 3xCH=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.19, 22.43, 27.54, 27.68, 29.15, 31.99, 32.49, 32.64, 32.85, 62.81, 129.52, 129.83, 130.06, 130.77, 131.03.

(8Z,4R,5R,12R,13R)-hexadecaene-4,5:12,13-diisopropylidenedioxy-1-ol (200)



By a similar procedure to that used for the preparation of the isopropyliden-Z-alkene **167** from dihydroxy triene **178**, Sharpless asymmetric double dihydroxylation of **199** (629 mg, 5 mmol), followed by acetalization with 2,2-dimethoxypropane, provided **200** (740 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.86 (t, 3H, $CH_2\underline{CH_3}$), 1.35 (s, 12H, 4xCH_3), 1.20-1.79 (m, 14H, 7xCH_2), 2.16 (m, 4H, $\underline{CH_2}CH{=}CH\underline{CH_2}$), 3.60 (m, 4H, 4x$\underline{CH}OH$), 3.64 (t, 2H, $\underline{CH_2}OH$), 5.43 (m, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.12, 22.97, 23.96, 24.03, 27.40, 27.47, 28.42, 29.67, 32.79, 33.04, 62.65, 80.47, 80.51, 80.93, 81.03, 107.95, 108.21, 129.64, 129.88

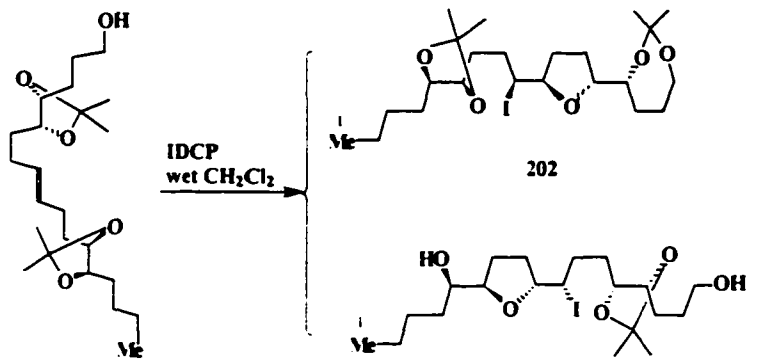
(8E,4R,5R,12R,13R)-hexadecaene-4,5:12,13-diisopropylidenedioxy-1-ol (201)



Treatment of Z-alkene **200** (740 mg, 1.8 mmol) under the two step Vedjs isomerization procedure which have been described in preparation of t-butyl-E-trifluoroethyl bis-pyranoside alkene **108**. E-alkene **201** (520mg, 71%) was obtained. ^{1}H

NMR (300 MHz, $CDCl_3$), δ 0.86 (t, 3H, $CH_2\underline{CH_3}$), 1.35, 1.36 (both s, 12H, 4xCH_3), 1.20-1.79 (m, 14H, 7xCH_2), 2.10, 2.17 (both m, 4H, $\underline{CH_2}CH=CH\underline{CH_2}$), 3.58 (m, 4H, 4x$\underline{CH}OH$), 3.61 (t, 2H, $\underline{CH_2}OH$), 5.35 (m, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.16, 23.02, 27.46, 27.51, 28.48, 29.18, 29.21, 29.80, 32.78, 32.84, 33.04, 62.86, 80.53, 81.01, 81.09, 107.98, 108.28, 130.06, 130.35.

THF-iodides (202 and 203)



201 202 203

Treatment of bis-isopropylidene E-alkene **201** (310 mg, 0.78 mmol) with the standard iodocyclization conditions using IDCP (910 mg, 1.95 mmol) and CH_2Cl_2 (20 ml) provided 1:1 mono-THF iodides **202** and **203** (250 mg, 70%).

(5R,6R, 9S, 10R, 13R, 14R)-5,6:14,17-diisopropylidenedioxy-10,13-epoxy-9-iodo-hexadecane (207)

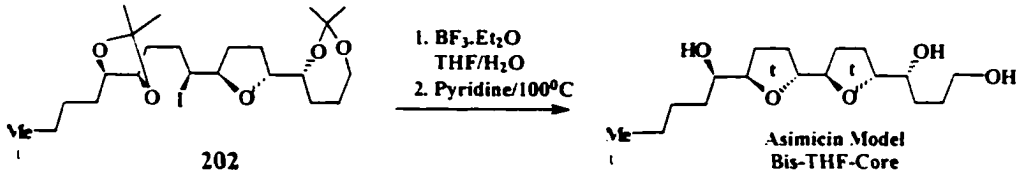
^1H NMR (300 MHz, $CDCl_3$), δ 0.86 (t, 3H, $CH_2\underline{CH_3}$), 1.30, 1.31 (d, 6H, 2xCH_3), 1.34 (s, 6H, 2xCH_3), 1.20-2.25 (m, 18H, 9xCH_2), 3.58 (m, 4H, H_5, H_6, CH_2-O), 3.68 (m, 1H, H_{14}), 3.78 (m, 1H, H_{10}), 4.02 (m, 1H, H_{13}), 4.13 (m, 1H, H_9). ^{13}C NMR (75 MHz,

$CDCl_3$), δ 14.14, 22.97, 25.30, 25.38, 27.50, 28.32, 29.31, 30.62, 32.81, 33.22, 33.76, 44.17, 62.09, 74.05, 80.94, 81.15, 82.36, 82.58, 100.70, 108.11.

(5R,6R, 9R, 10S, 13R, 14R)-13,14-isopropylidenedioxy-6,9-epoxy-10-iodo-5,17-hexadecadiol (208)

^{1}H NMR (300 MHz, $CDCl_3$), δ 0.90 (t, 3H, $CH_2\underline{CH_3}$), 1.36 (s, 6H, 2xCH_3), 1.20-2.30 (m, 18H, 9xCH_2), 3.40 (m, 1H, H_5), 3.62 (m, 4H, H_{13}, H_{14}, $\underline{CH_2}OH$), 3.85 (m, 1H, H_9), 3.95 (m, 1H, H_6), 4.14 (m, 1H, H_{10}). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.18, 22.93, 27.48, 27.90, 28.59, 29.75, 33.13, 33.28, 33.56, 33.73, 43.18, 62.83, 74.39, 80.93, 81.11, 82.51, 83.70, 108.55.

Asimicin model bis-THF core (209)



202

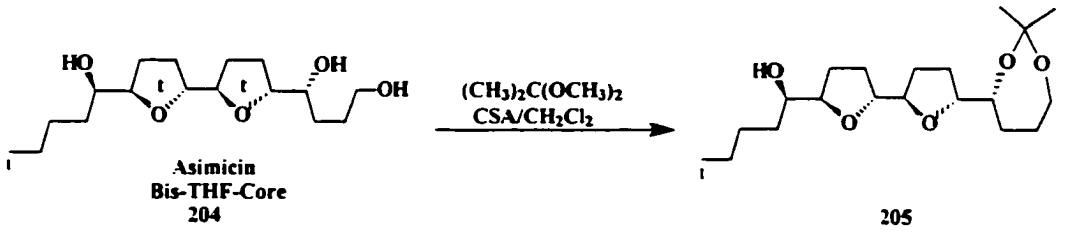
Asimicin Model Bis-THF-Core

204

Compound **202** (120 mg, 0.028 mmol) was subjected to the two step procedure which have been described in preparation of **196**. The asimicin model bis-THF core **204** (45 mg, 78%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.87 (t, 3H, CH_3), 1.19-1.60 (m, 8H, 4xCH_2), 1.70 (m, 6H, $H_7\alpha$, $H_8\alpha$, $H_{11}\alpha$, $H_{12}\alpha$, H_{16}), 1.98 (m, 4H, $H_7\beta$, $H_8\beta$, $H_{11}\beta$, $H_{12}\beta$), 3.01 (s, 3H, 3xOH), 3.40 (m, 1H, H_5), 3.45 (m, 1H, H_{14}), 3.64 (t, 2H, $\underline{CH_2}OH$), 3.84 (m, 4H, H_6, H_9, H_{10}, H_{13}). ^{13}C NMR (75MHz, $CDCl_3$), δ 14.21, 22.98, 28.02, 28.70, 29.02, 29.05, 29.48, 30.75, 33.42, 63.11, 74.30, 74.33, 81.83, 81.95, 83.12, 83.37. MS (EI) calcd for $C_{23}H_{41}IO_5$ $(M+H)^+$ 525, found 525.

Bullatacin Bis-THF Core

(5R,6R, 9R, 10R, 13R, 14R)-14,17-isopropylidenedioxy-6,9:10,13-diepoxy-hexadecane (205)



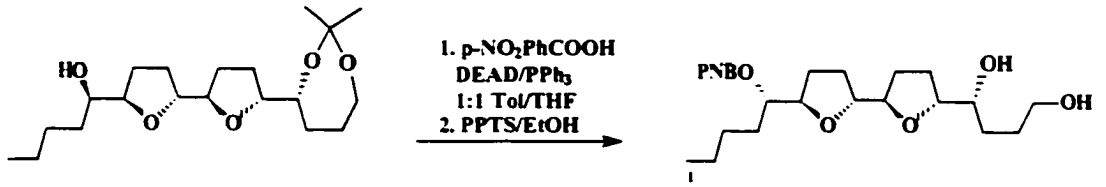
Asimicin Bis-THF-Core 204

205

2,2-Dimethoxypropane (25 µl, 0.2 mmol) and (±)-10-camphorsulfonic acid (23 mg, 0.1 mmol) were added to a solution of **204** (24 mg, 0.1 mmol) in anhydrous CH_2Cl_2 (5 ml) at 0 °C. The reaction mixture was warmed to rt and stirred for 1h, then quenched with saturated sodium bicarbonate and extracted with ether (3x). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatographic purification of the residue (1.5x15 cm, EtOAc) gave **205** (14.3 mg, 50%) and recovered **204** (8 mg, 35%). ^1H NMR (300 MHz, $CDCl_3$), δ 0.88 (t, 3H, CH_3), 1.30, 1.32 (both s, 6H, $C(CH_3)_2$), 1.19-1.80 (m, 14H, 5xCH_2, $H_{7\alpha}$, $H_{8\alpha}$, $H_{11\alpha}$, $H_{12\alpha}$), 1.92 (m, 4H, $H_{7\beta}$, $H_{8\beta}$, $H_{11\beta}$, $H_{12\beta}$), 2.49 (d, 1H, OH), 3.38 (m, 1H, H_5), 3.89 (t, 2H, $\underline{CH_2}OH$), 3.65-4.0 (m, 5H, H_6, H_9, H_{10}, H_{13}, H_{14}). ^{13}C NMR (75MHz, $CDCl_3$), δ 14.19, 22.96, 25.32, 25.42, 27.93, 28.00, 28.56, 28.74, 28.98, 29.42, 30.25, 33.36, 62.18, 73.71, 74.24, 81.68, 81.78, 82.06, 83.13, 100.77.

(5R,6R, 9R, 10R, 13R, 14R)-5-(4-nitrobenzoate)-

6,9:10,13-diepoxy-hexadecane (206)



205 206

A mixture of **205** (14 mg, 0.05 mmol) and triphenylphosphine (54.8 mg, 0.2 mmol) were dissolved in dry 1:1 toluene/THF (2.5 ml) and then a solution of p-NO2-benzoic acid (43.6 mg, 0.25 mmol) and DEAD (0.042 ml, 0.25 mmol) in dry toluene/THF (2.5 ml) was added slowly at -15°C under an atmosphere of argon. Then, this mixture was allowed to warm slowly to rt, and stirred for 30 min. After concentration, the mixture was neutralized by addition of aqueous sodium bicarbonate. The product was isolated from an aqueous work-up by ether extraction (3x). The ethereal extracts were combined and dried (Na_2SO_4) and then concentrated *in vacuo*. The crude product was directly used for next step.

The product from the previous step, was dissolved in EtOH (2 ml). PPTS (25 mg, 0.1 mmol) was then added. The reaction mixture was stirred for 1h. The reaction was quenched with saturated sodium bicarbonate and extracted with ether (3x). The organic phase was dried (Na_2SO_4) and concentrated in *vacuo*. Chromatographic purification of the residue gave compound **206** (6.0 mg, overall 35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 t, 3H, CH_3), 1.19-1.90 (m, 14H, 5xCH_2, $H_{7\alpha}$, $H_{8\alpha}$, $H_{11\alpha}$, $H_{12\alpha}$), 2.00 (m, 4H, $H_{7\beta}$, $H_{8\beta}$, $H_{11\beta}$,

t, 3H, CH_3), 1.19-1.90 (m, 14H, 5xCH_2, $H_{7\alpha}$, $H_{8\alpha}$, $H_{11\alpha}$, $H_{12\alpha}$), 2.00 (m, 4H, $H_{7\beta}$, $H_{8\beta}$, $H_{11\beta}$,

$H_{12\beta}$), 2.80 (s, 2H, 2xOH), 3.44 (m, 1H, H_{14}), 3.68 (t, 2H, $\underline{CH_2}OH$), 3.86 (m, 3H, H_9, H_{10}, H_{13}), 4.20 (m, 1H, H_6), 5.28 (m, 1H, H_5), 8.23 (m, 4H, Ar-H's). ^{13}C NMR (75MHz, $CDCl_3$), δ 14.11, 22.79, 27.85, 27.97, 28.54, 28.64, 29.10, 29.54, 30.69, 31.16, 63.14, 74.37, 80.76, 81.85, 82.23, 83.21, 123.77, 133.93, 136.27, 150.88, 164.52.

Bullatacin model bis-THF-core (207)

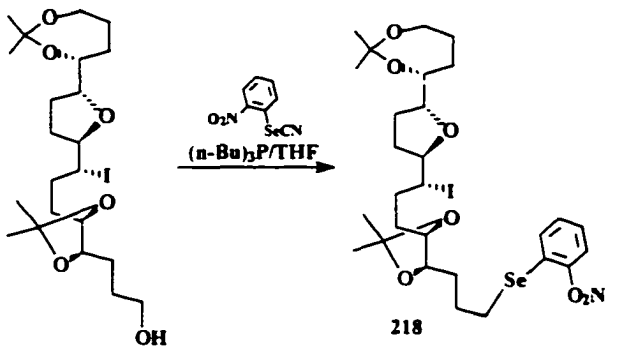
206

Bullatacin
Bis-THF-Core
207

To a solution of **211** (6.0 mg, 0.016 mmol) in MeOH (0.5 ml) was slowly added a 1M solution of NaOMe in MeOH (3 drops) at rt. After stirring for 1h, the reaction was cautiously quenched with a solution of 10% HCl/MeOH to pH=8 and then concentrated in *vacuo*. The residue was taken up in ether and washed with saturated aqueous $NaHCO_3$ and brine. The ethereal solution was dried (Na_2SO_4) and concentrated in *vacuo*. Purification by flash chromatography provided product **207** (3.0mg, 83%). ^1H NMR (300 MHz, $CDCl_3$), δ 0.85 (t, 3H, CH_3), 1.20-2.10 (m, 20H, 10xCH_2), 2.43 (bs, 1H, OH), 2.68 (bs, 1H, OH), 3.20 (bs, 1H, OH), 3.47 (m, 1H, H_{14}), 3.64 (t, 2H, $\underline{CH_2}OH$), 3.86 (m, 3H, H_5, H_9, H_{11}), 3.93 (m, 2H, H_6, H_{10}). ^{13}C NMR (75MHz, $CDCl_3$), δ 14.19, 22.97, 24.94, 28.45, 28.63, 29.10, 29.56, 30.62, 32.49, 63.15, 71.80, 74.37, 82.45, 82.60, 83.10, 83.23. MS (EI) calcd for $C_{23}H_{41}IO_5$ $(M+H)^+$ 525, found 525.

Synthesis of Oligo-THF Fragment

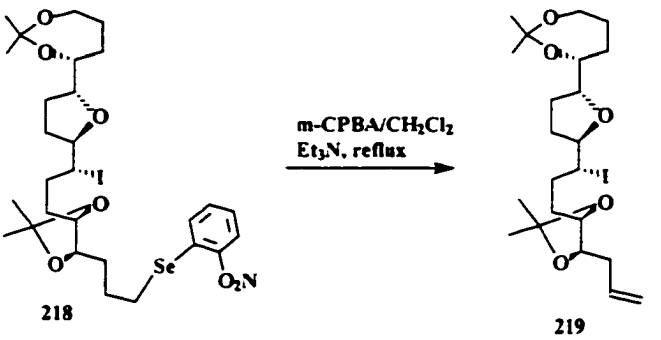
(4R,5R, 8R, 9R, 12R, 13R)-4,5:13,16-diisopropylidenedioxy-9,12-epoxy-8-iodo-1-(2-nitrophenyl seleno)-hexadecane (218)



186 218

To a mixture of **186** (160 mg, 0.30 mmol) and 2-nitrophenyl selenocyanate (198 mg, 0.90 mmol) in dry THF (15 ml) was added tri-*tert*-butylphosphine (0.31 ml, 1.20 mmol) at 0 °C. This mixture was allowed to warm slowly to rt, and stirred for 30 min. The mixture was then diluted with CH_2Cl_2 and washed by aqueous sodium bicarbonate. The organic phase was dried (Na_2SO_4) and concentrated in *vacuo*. Chromatographic purification of the residue (2x12 cm, 20% EtOAc: PE) gave compound **218** (156 mg, 73%). Rf: 0.35 (30% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.33, 1.34 (both s, 6H, 2xCH_3), 1.37 (s, 6H, 2xCH_3), 1.00-2.20 (m, 16H, 8xCH_2), 2.98 (t, 2H, CH_2Se) 3.67 (m, 5H, H_4, H_5, H_{13}), 3.91 (m, 1H, H_9), 4.08 (m, 2H, H_8, H_{12}). ^{13}C NMR (75 MHz, $CDCl_3$), δ 25.38, 26.18, 27.49, 28.51, 29.35, 30.58, 31.16, 32.07, 33.12, 42.03, 62.13, 74.19, 79.87, 80.33, 82.64, 82.77, 100.76, 108.53, 125.52, 126.65, 129.21, 133.72

(4R,5R, 8R, 9R, 12R, 13R)-4,5:13,16-diisopropylidenedioxy-9,12-epoxy-8-iodo-1-hexadecaene (219)

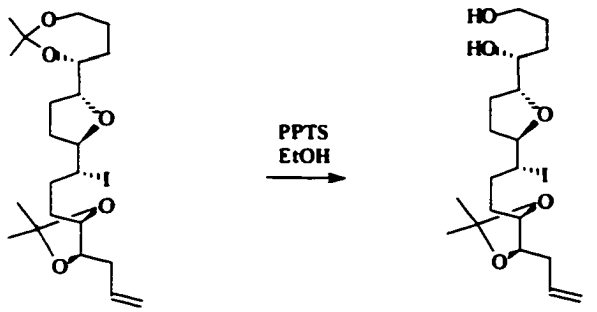


218 219

A stirred solution of **218** (1.0 g, 1.422 mmol) in CH_2Cl_2 (25 ml) was treated with m-CPBA (940 mg, 3.56 mmol) at 0 °C. After 10 min, Et_3N (8 ml, 56 mmol) was added to the solution and the reaction was refluxed for an additional 10 min. The mixture was then diluted with CH_2Cl_2 (100 ml) and washed with 10% aqueous $Na_2S_2O_3$ and $NaHCO_3$. The organic phase was dried (Na_2SO_4) and concentrated in *vacuo*. Chromatographic purification of the residue (5x12 cm, 10% EtOAc: PE) gave compound **218** (697 mg, 96%). Rf: 0.82 (30% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.32, 1.33 (both s, 6H, 2xCH_3), 1.37 (s, 6H, 2xCH_3), 1.00-2.00 (m, 12H, 6xCH_2), 2.33 (t, 2H, $\underline{CH_2}CH=CH_2$) 3.67 (m, 5H, H_4, H_5, H_{13}), 3.91 (m, 1H, H_9), 4.08 (m, 2H, H_8, H_{12}), 5.10 (m, 2H, CH_2=), 5.83 (m, 1H, =CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 25.42, 27.45, 28.49, 29.37, 30.57, 31.16, 32.11, 33.12, 37.21, 41.98, 62.13, 74.21, 79.48, 80.00, 82.64, 82.75, 100.76, 108.42, 117.79, 133.96.

(4R,5R, 8R, 9R, 12R, 13R)-4,5-isopropylidenedioxy-

9,12-epoxy-8-iodo-13, 16-dihydroxy-1-hexadecaene (220)

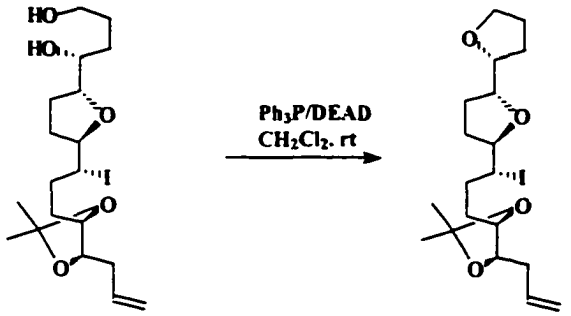


219 220

Compound **219** (227 mg, 0.445 mmol) was dissolved in EtOH (10 ml). PPTS (56 mg, 0.223 mmol) was then added. The reaction mixture was stirred for 1h. The reaction was quenched with saturated sodium bicarbonate and extracted with ether (3x). The organic phase was dried (Na_2SO_4) and concentrated in *vacuo.* Chromatographic purification of the residue gave compound **220** (211 mg, ~100%). Rf: 0.35 (50% EtoAc/PE); ^1H NMR (300 MHz, $CDCl_3$), δ 1.38 (s, 6H, $2xCH_3$), 1.20-2.20 (m, 12H, $6xCH_2$), 2.33 (t, 2H, $\underline{CH_2}CH=CH_2$) 2.45 (bs, 2H, 2xOH), 3.44 (m, 1H, H_{13}) 3.67 (m, 4H, H_4, H_5, H_{16}), 3.87, 3.95 (both m, 2H, H_9, H_{12}) 4.08 (m, 1H, H_8), 5.10 (m, 2H, CH_2=), 5.83 (m, 1H, =CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 27.47, 28.87, 29.42, 30.52, 31.71, 32.47, 33.01, 37.24, 41.37, 63.05, 74.33, 79.39, 80.01, 82.61, 83.58, 108.50, 117.84, 133.93.

(4R,5R, 8R, 9R, 12R, 13R)-4,5-isopropylidenedioxy-

9,12:13,16-diepoxy-8-iodo-1-hexadecaene (221)

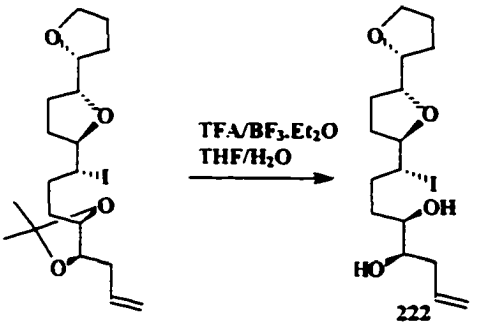


220 221

A mixture of **220** (381 mg, 0.814 mmol) and triphenylphosphine (361 mg, 1.38 mmol) were dissolved in dry CH_2Cl_2 (25 ml) and then DEAD (0.217 ml, 1.38 mmol) in was added. The reaction was stirred for 2h. After concentration, chromatographic purification of the residue gave compound **221** (356 mg, 90%). Rf: 0.83 (50% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.36 (s, 6H, 2xCH_3), 1.20-2.22 (m, 12H, 6xCH_2), 2.33 (t, 2H, $\underline{CH_2}CH=CH_2$) 3.67 (m, 4H, H_4, H_5), 3.76 (m, 2H, H_{16}), 3.85 (m, 1H, H_9) 4.01 (m, 2H, H_{12}, H_{13}), 4.11 (m, 1H, H_8), 5.10 (m, 2H, CH_2=), 5.83 (m, 1H, =CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 26.10, 27.44 (2), 28.27, 29.00, 30.68, 31.64, 33.34, 37.20, 41.31, 68.73, 79.53, 80.05, 82.00, 83.10, 108.42, 117.80, 133.94. HRMS (FAB), calcd for $C_{19}H_{31}O_4I$ (M+H)+ 451.1345, found ??(result will be obtained soon).

(4R,5R, 8R, 9R, 12R, 13R)-4,5-dihydroxy-

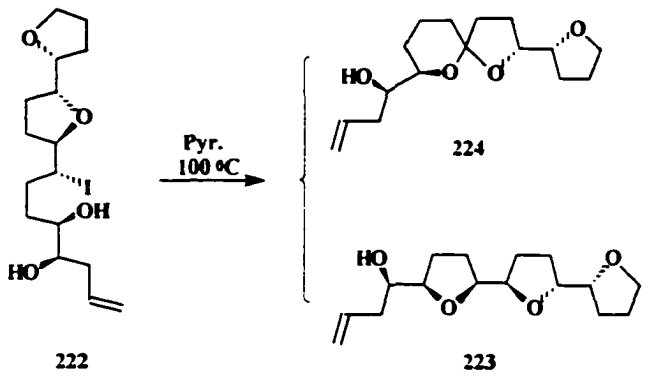
9,12:13,16-diepoxy-8-iodo-1-hexadecaene (222)



221 222

To a stirred solution of **221** (319 mg, 0.71 mmol) in THF (15 ml) and H_2O (3 ml) at rt was added TFA (500 µl) and $BF_3.Et_2O$ (3 ml). After 14h, the reaction mixture was quenched with saturated sodium bicarbonate and extracted with CH2Cl2 (3x). The organic phase was dried (Na_2SO_4) and concentrated in *vacuo*. Chromatographic purification of the residue (4x20 cm, 50%EtOAc/PE) gave **222** (233 mg, 80%). Rf: 0.25 (50% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.40-2.30 (m, 12H, 6xCH_2), 2.34 (t, 2H, $\underline{CH_2}CH{=}CH_2$) 2.55 (s, 2H, 2xOH), 3.49 (bs, 4H, H_4, H_5), 3.76 (m, 2H, H_{16}), 3.85 (m, 1H, H_9) 4.03 (m, 2H, H_{12}, H_{13}), 4.13 (m, 1H, H_8), 5.15 (m, 2H, CH_2=), 5.83 (m, 1H, =CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 26.08, 28.27, 28.98, 30.73, 31.36, 33.73, 38.42, 41.18, 68.70, 72.77, 73.50, 82.00, 83.08, 83.16, 118.39, 134.57.

Tri-THF (223)



A solution of **222** (200 mg, 0.49 mmol) in pyridine (10 ml) was heated at 100 °C for 2h. After cooling to rt, the excess pyridine was removed in *vacuo*. Chromatographic purification of the residue afforded **223** (50 mg, 37%) and spiroketal **224** (50 mg, 37%).

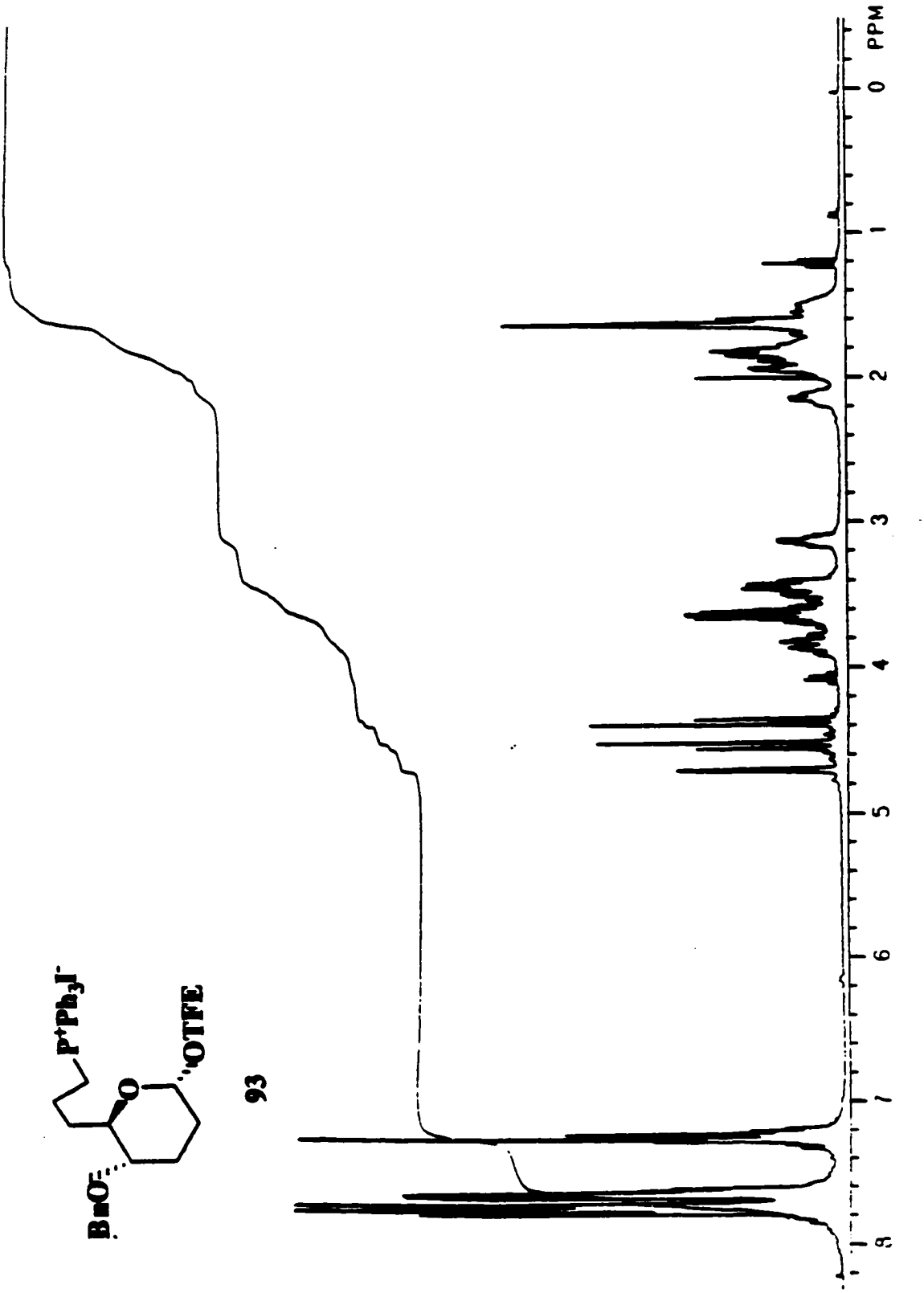
223: Rf: 0.39 (50% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$, assignment confirmed by ^{1}H /^{1}H COSY), δ 1.40-2.18 (m, 12H, 6xCH_2), 2.26 (t, 2H, $\underline{CH_2}CH{=}CH_2$) 2.54 (s, 1H, OH), 3.43 (q, 1H, H_4), 3.77 (m, 2H, H_{16}), 3.85 (m, 2H, H_5, H_{13}), 3.93 (m, 2H, H_8, H_{12}), 4.08 (m, 1H, H_9), 5.15 (m, 2H, CH_2=), 5.87 (m, 1H, =CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 26.14, 27.41, 28.26, 28.30, 28.54, 28.84, 39.04, 68.74, 74.36, 81.42, 81.50, 82.03, 82.32, 117.02, 135.31. HRMS (FAB), calcd for $C_{16}H_{26}O_4$ $(M+H)^+$ 283.1909, found 283.1845.

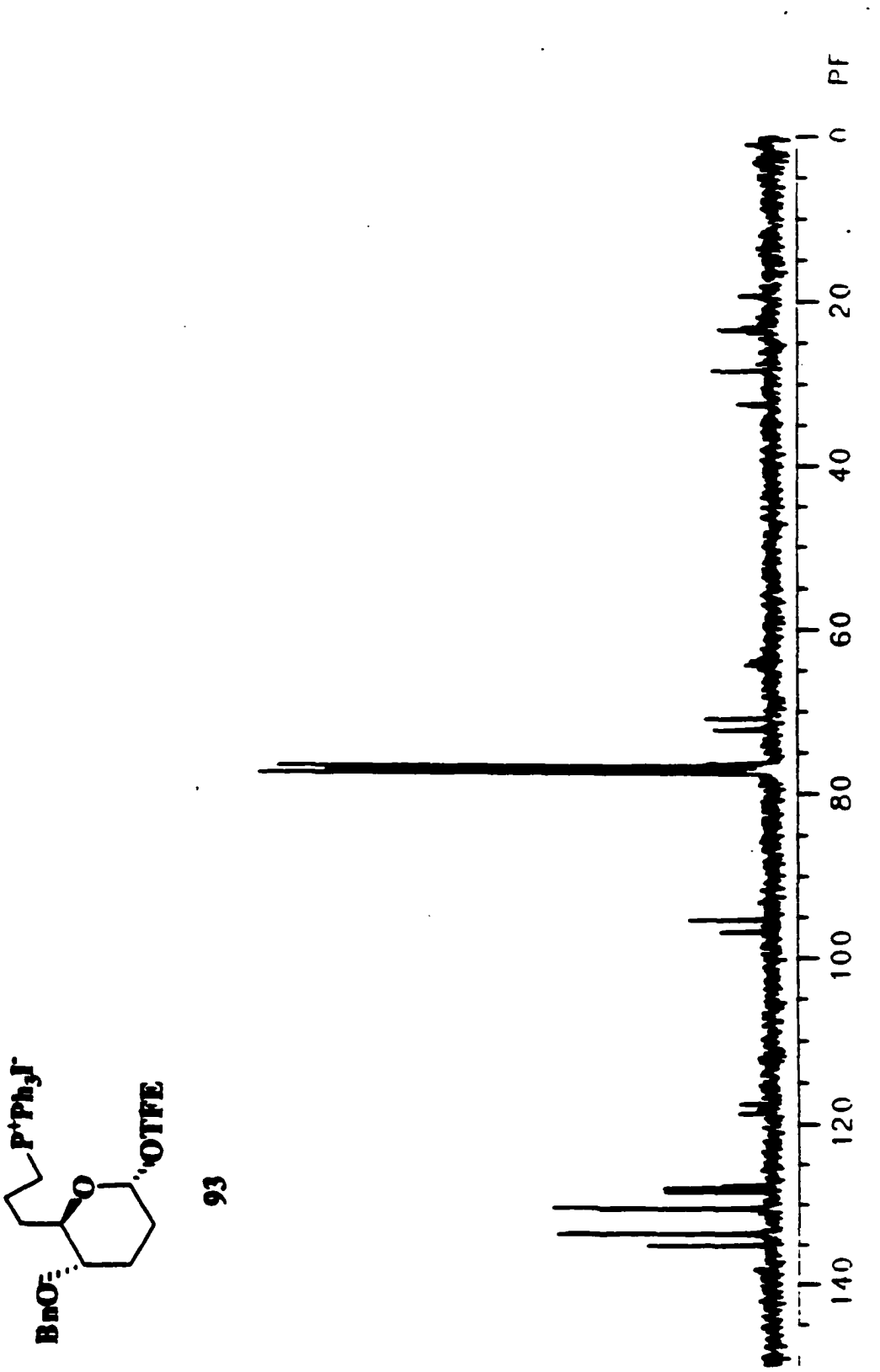
224: Rf: 0.74 (50% EtoAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$, assignment confirmed by ^{1}H /^{1}H COSY), δ 1.20-2.40 (m, 14H, 7xCH_2), 2.26 (m, 2H, $\underline{CH_2}CH{=}CH_2$), 3.43 (m, 1H, H_4), 3.78 (m, 4H, H_{16}, H_5, H_{13}), 3.97 (m, 1H, H_9), 5.07 (m, 2H, CH_2=), 5.87 (m, 1H, =CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 19.93, 26.05, 26.56, 26.87, 28.50, 33.14, 37.66, 38.01, 68.97,

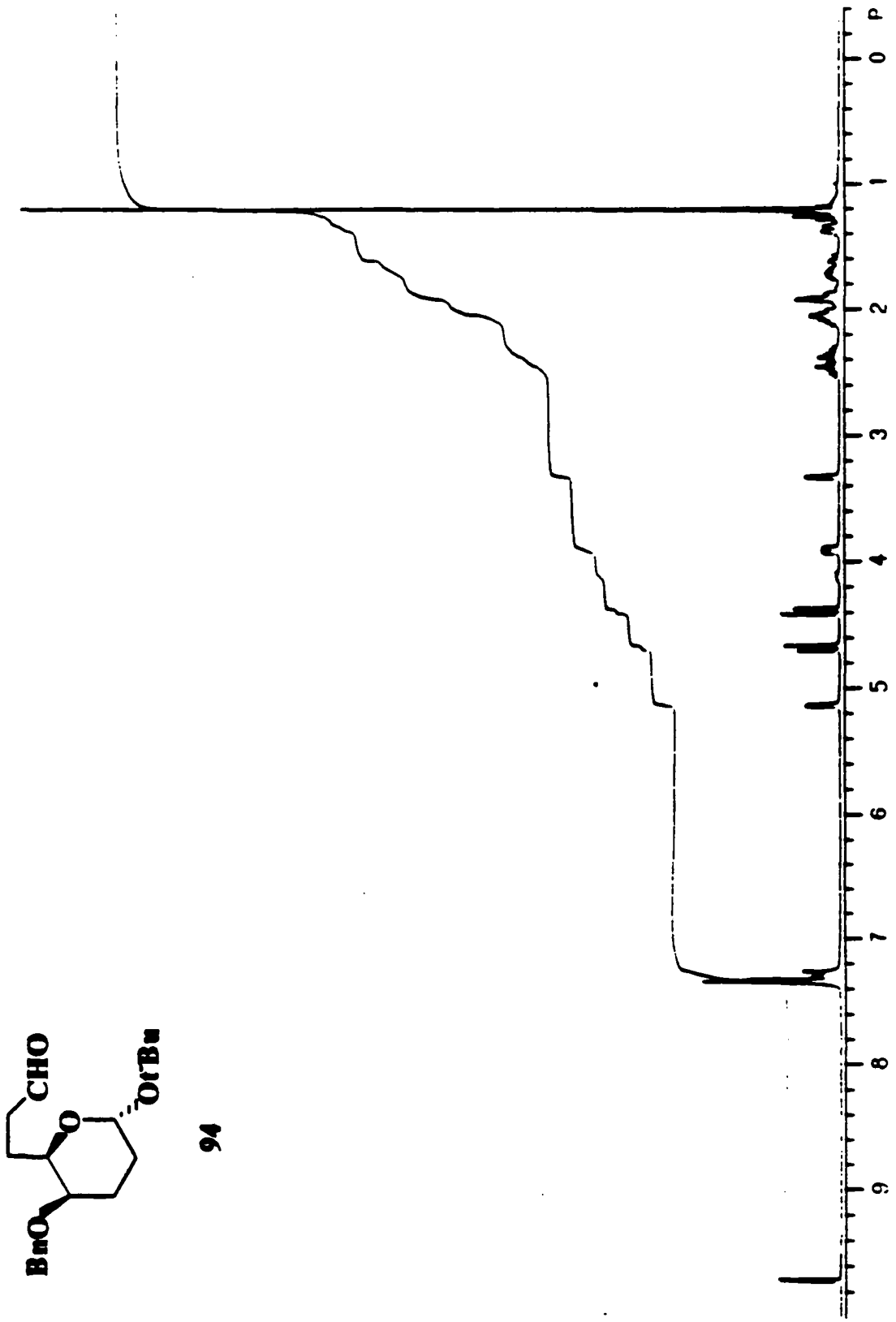
72.64, 73.84, 80.83, 81.53, 106.92, 117.13, 135.31. HRMS (FAB), calcd for $C_{16}H_{26}O_4$ $(M+H)^+$ 283.1909, found 283.1845.

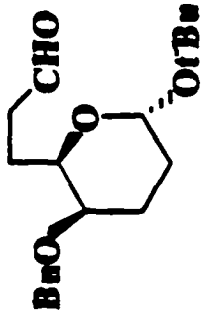
Appendix

^{1}H and ^{13}C NMR of the Important Synthetic Compounds









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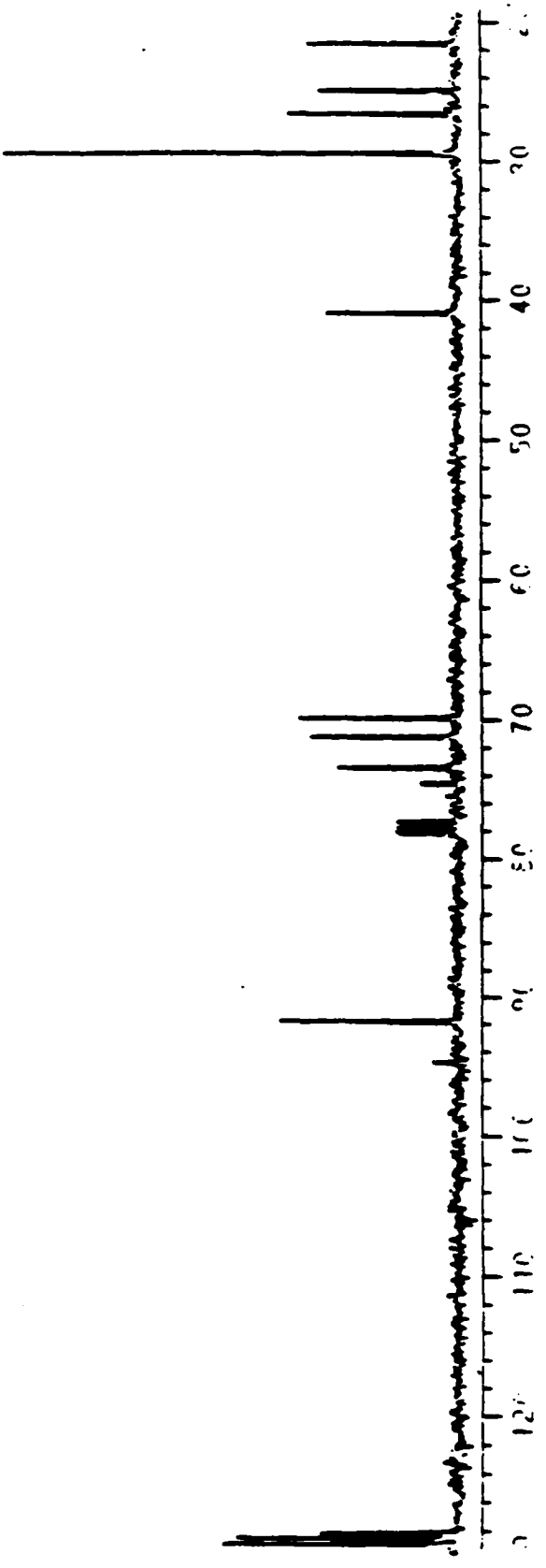

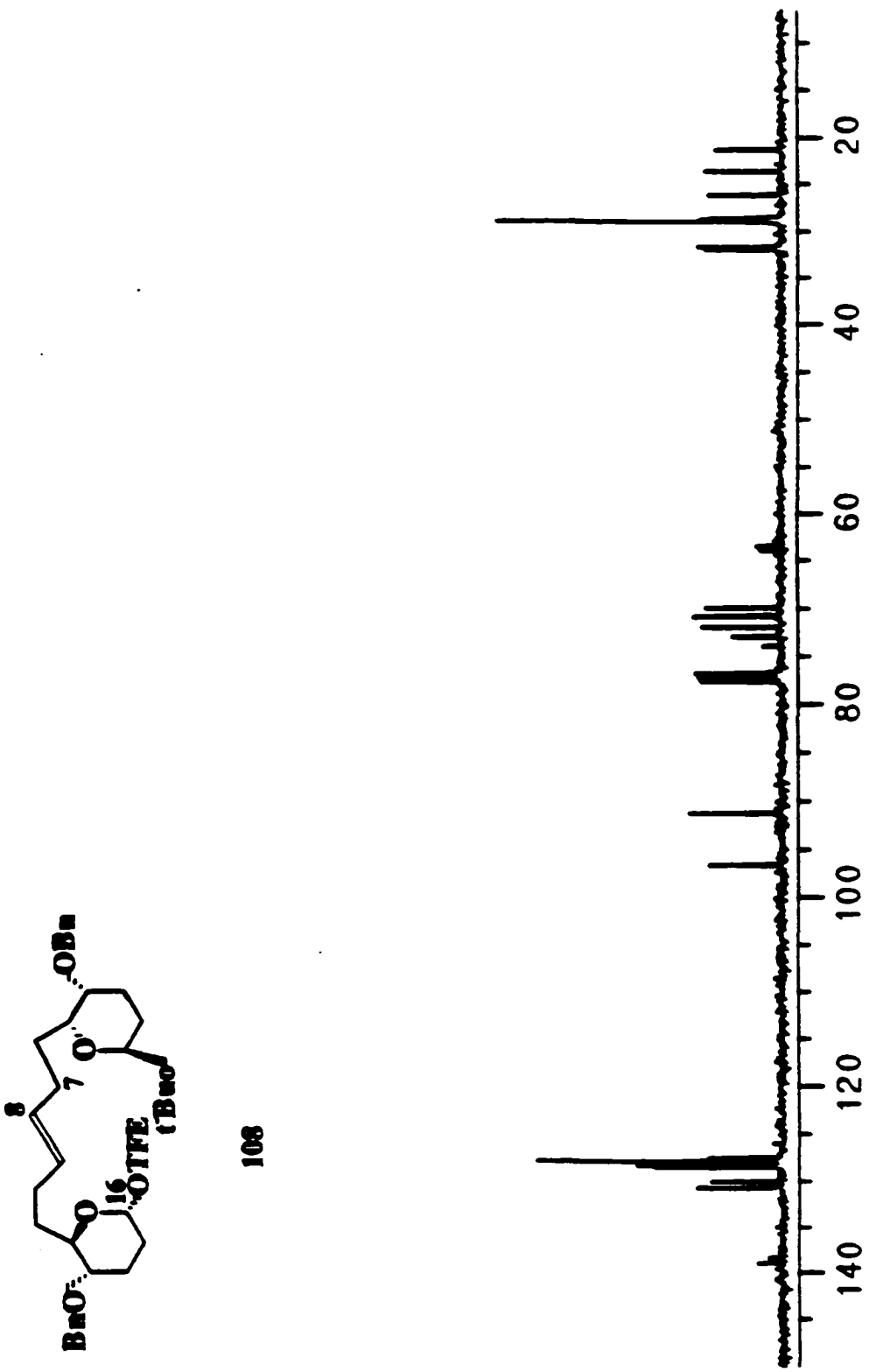

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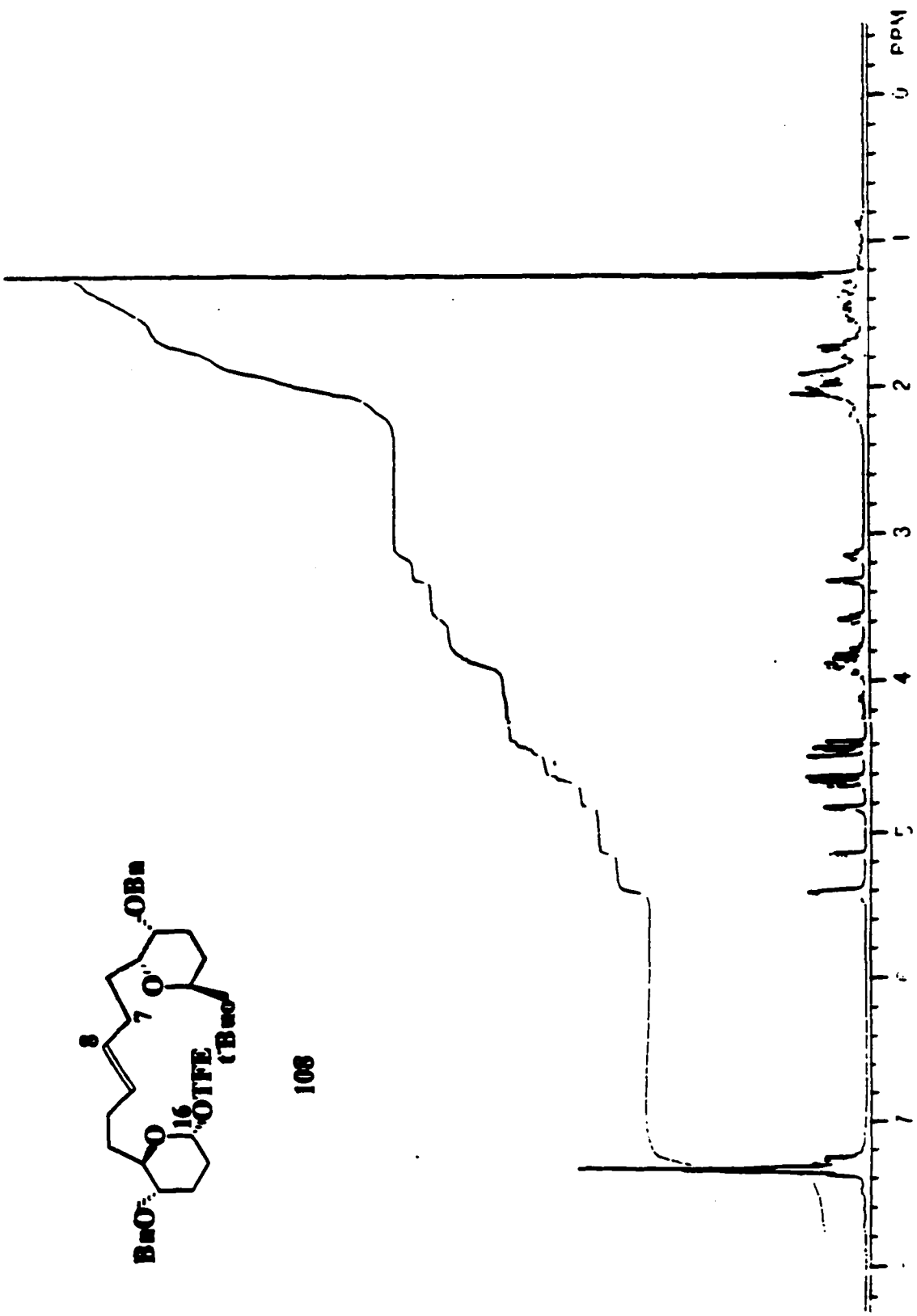

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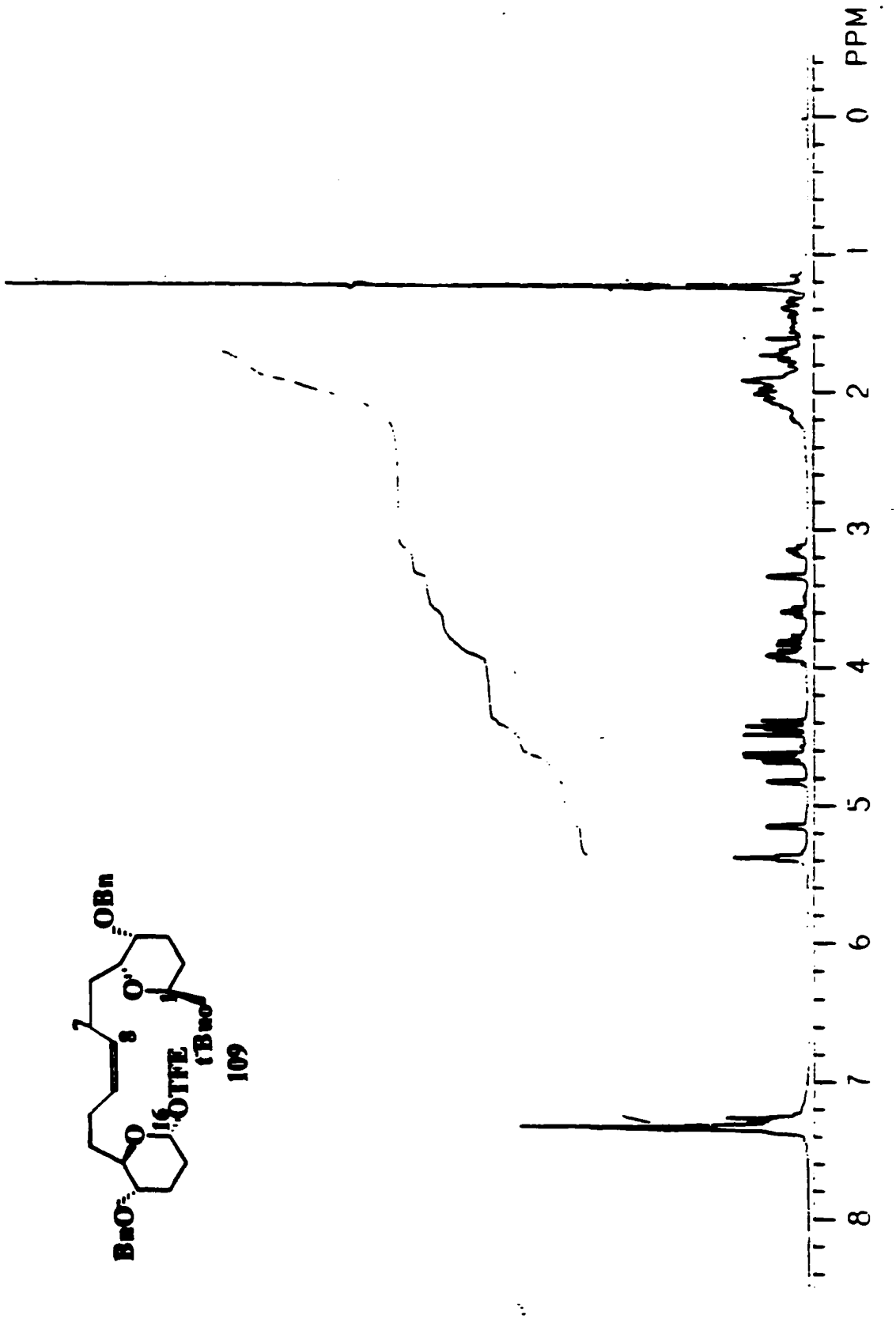

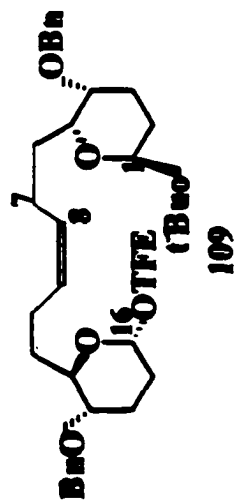

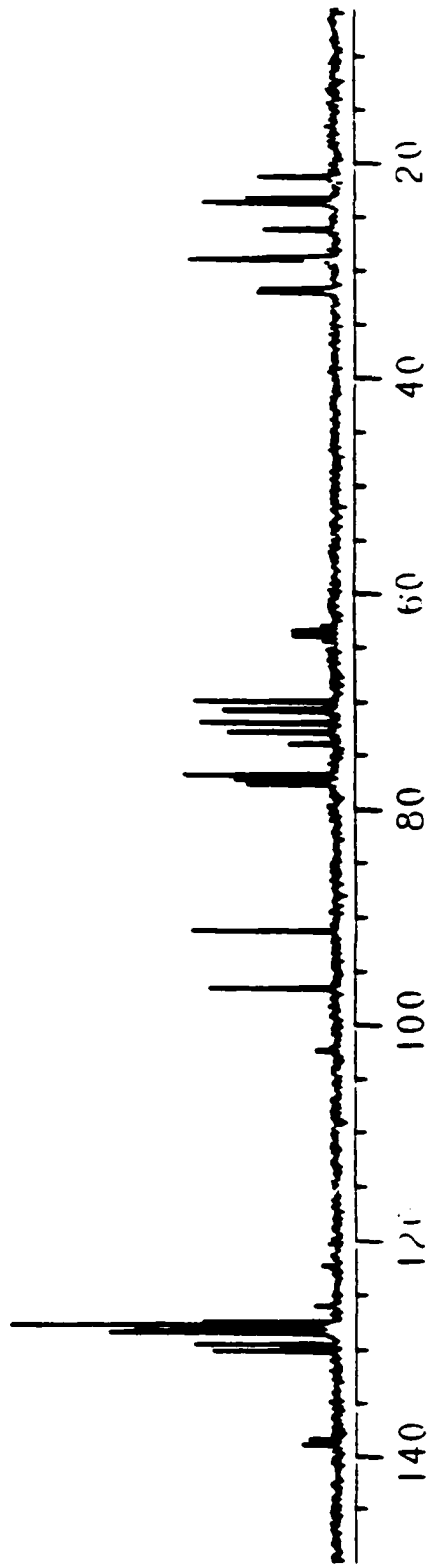

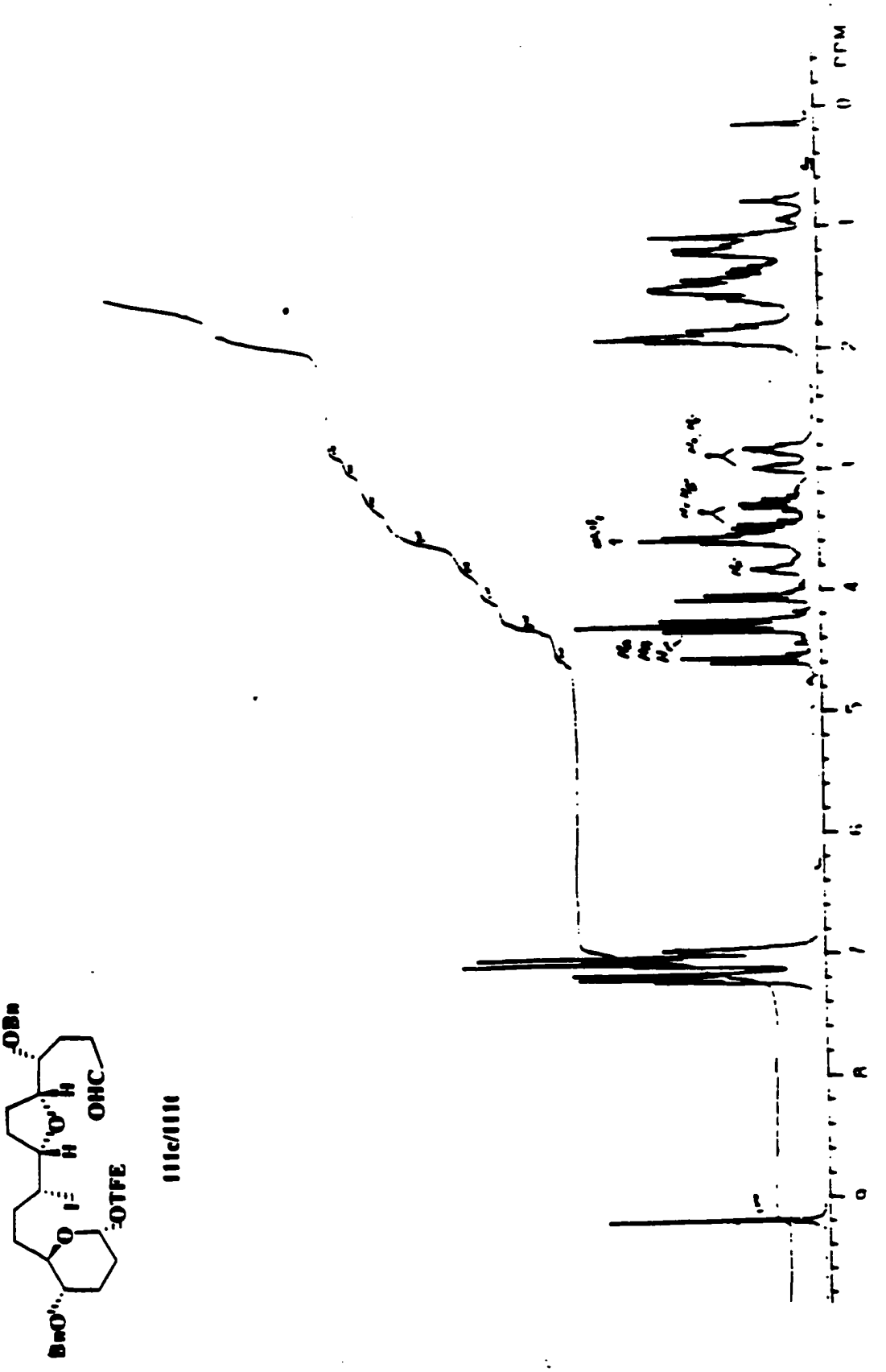

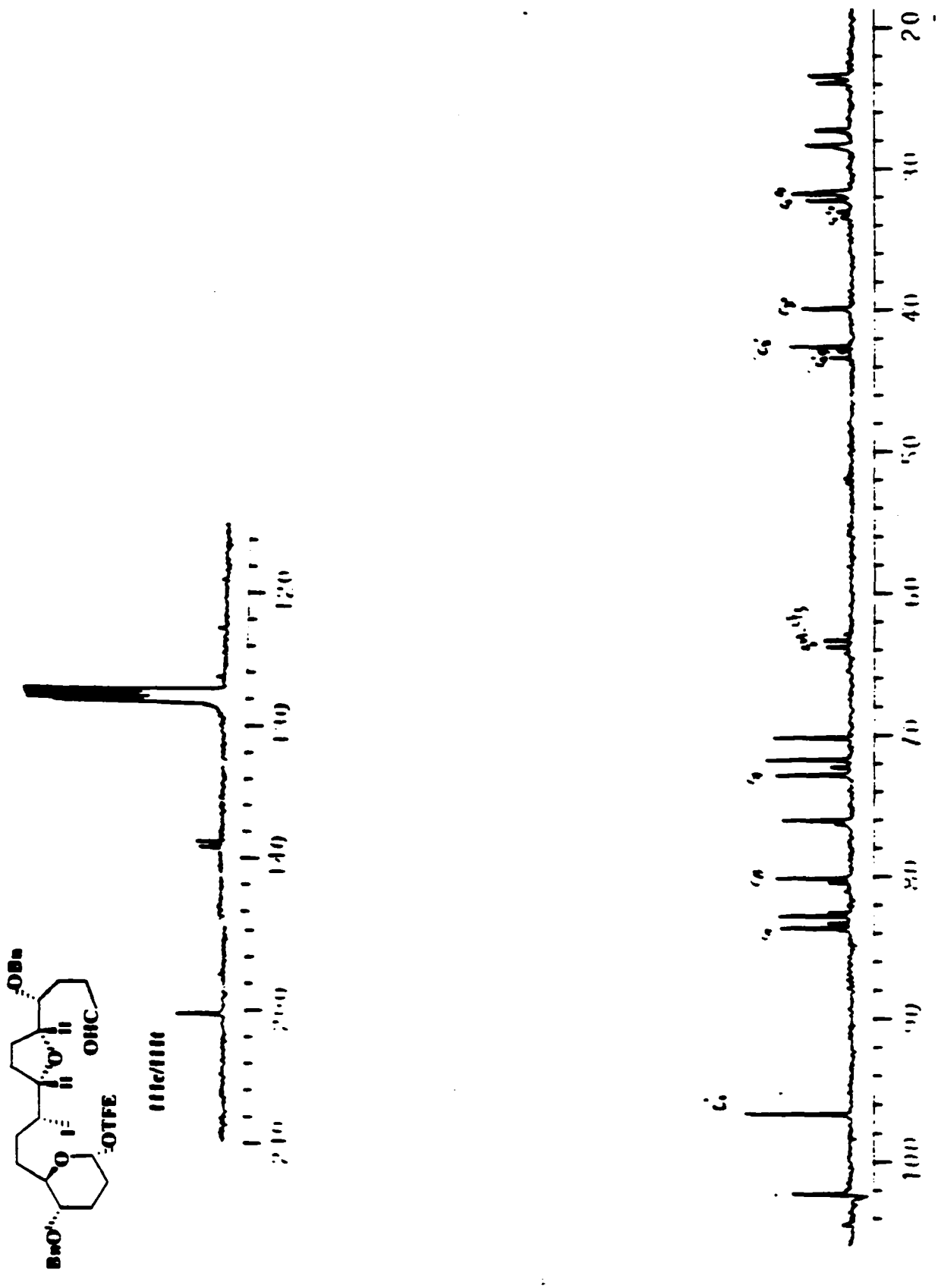

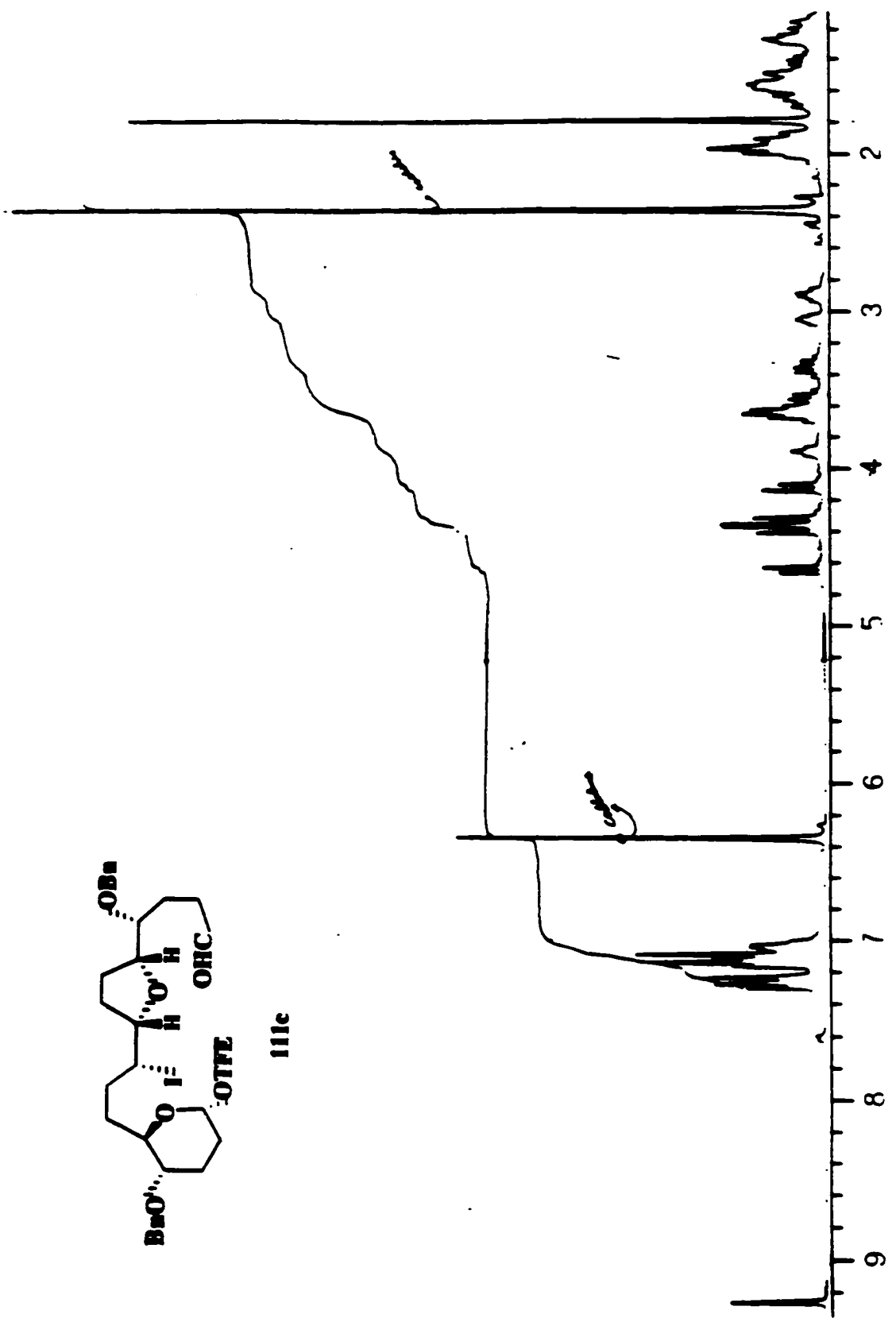

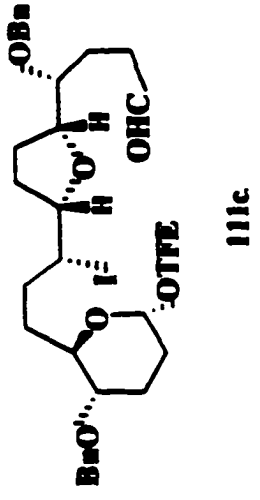

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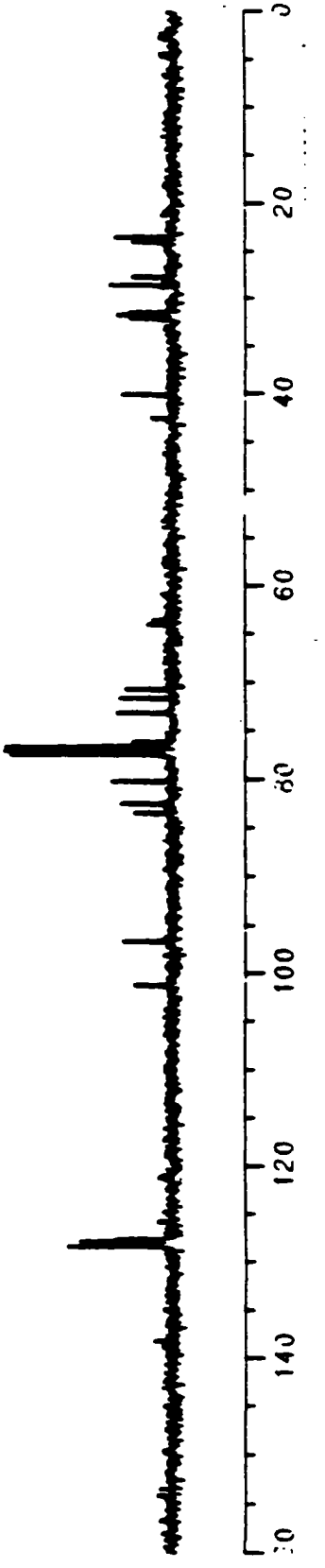

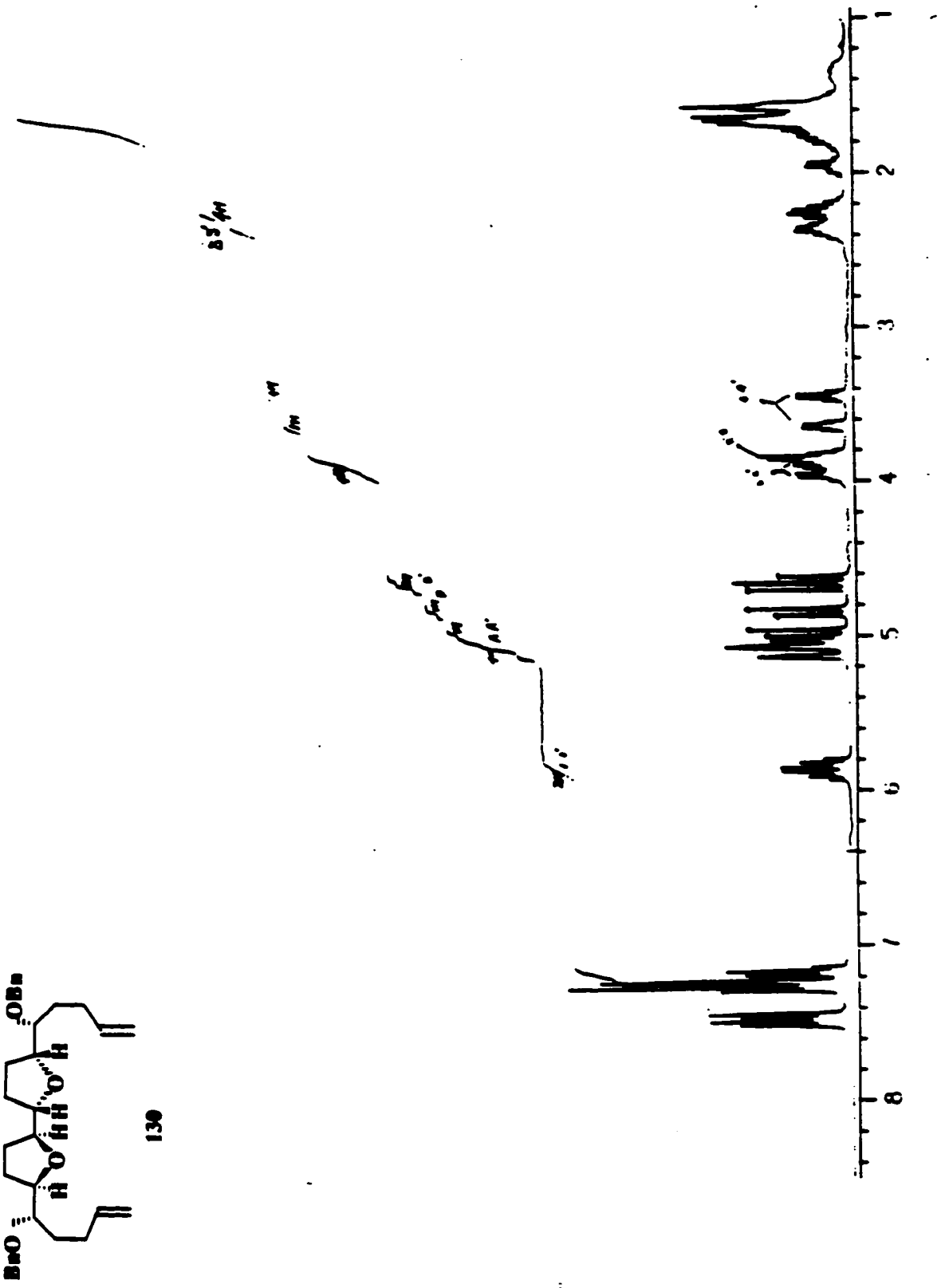

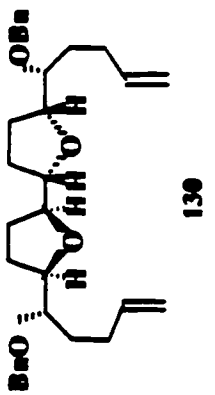

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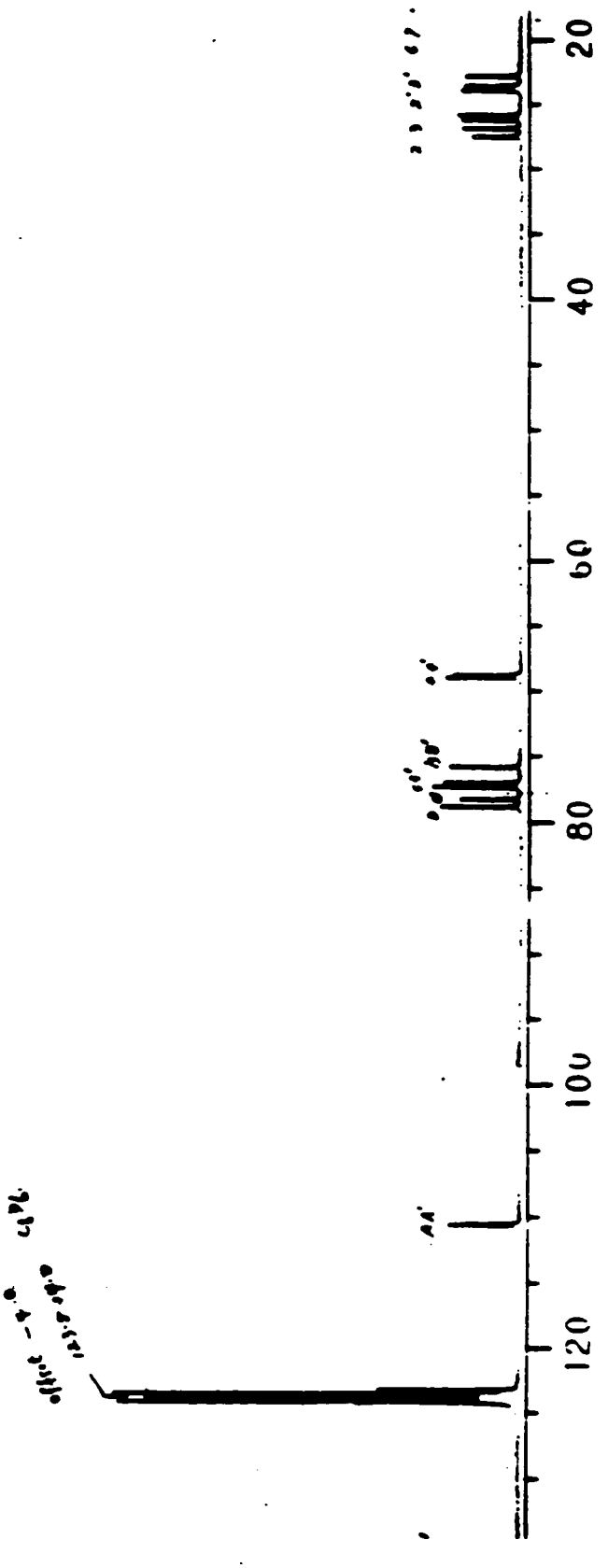

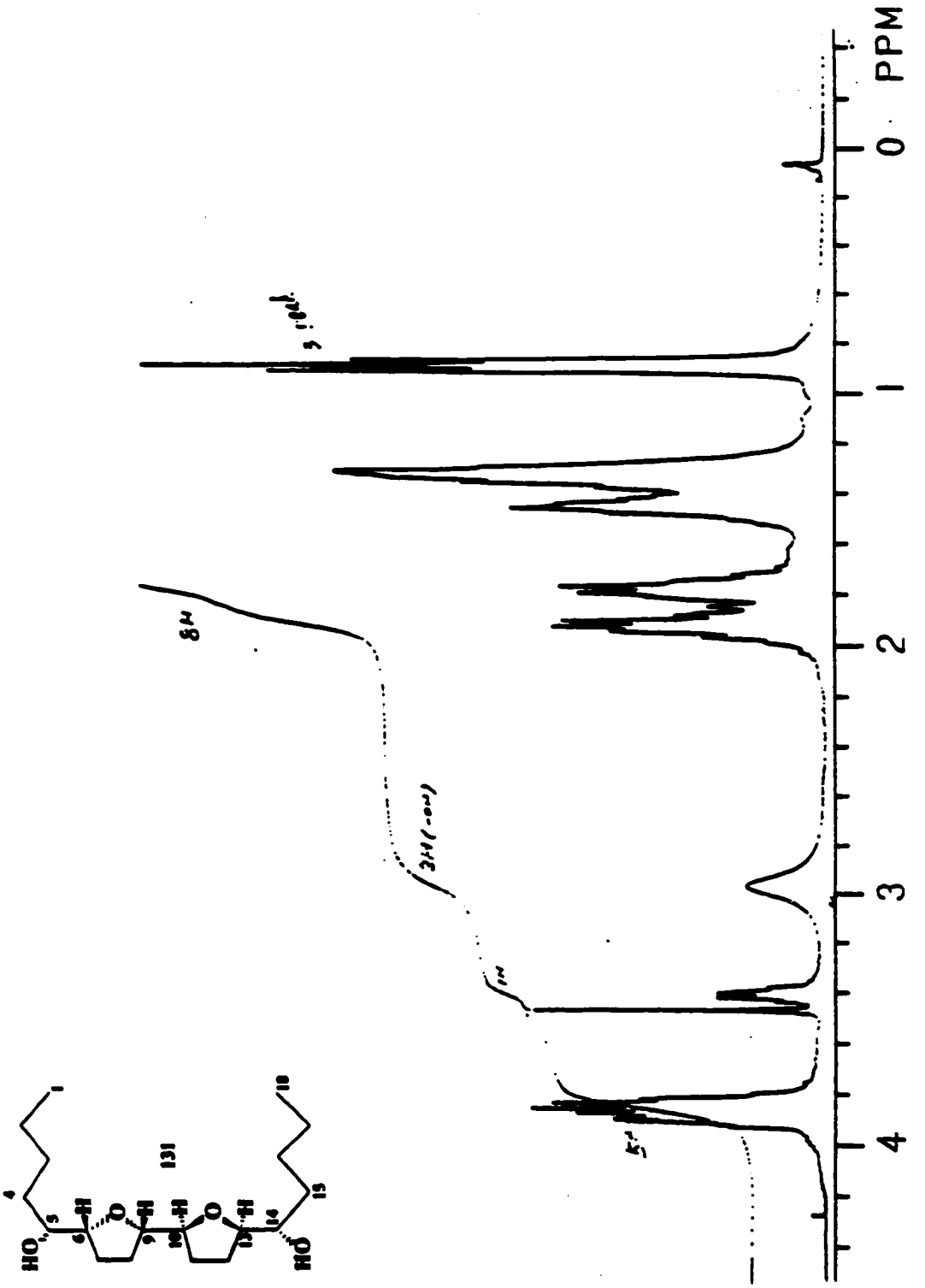

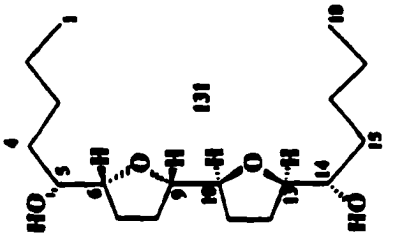

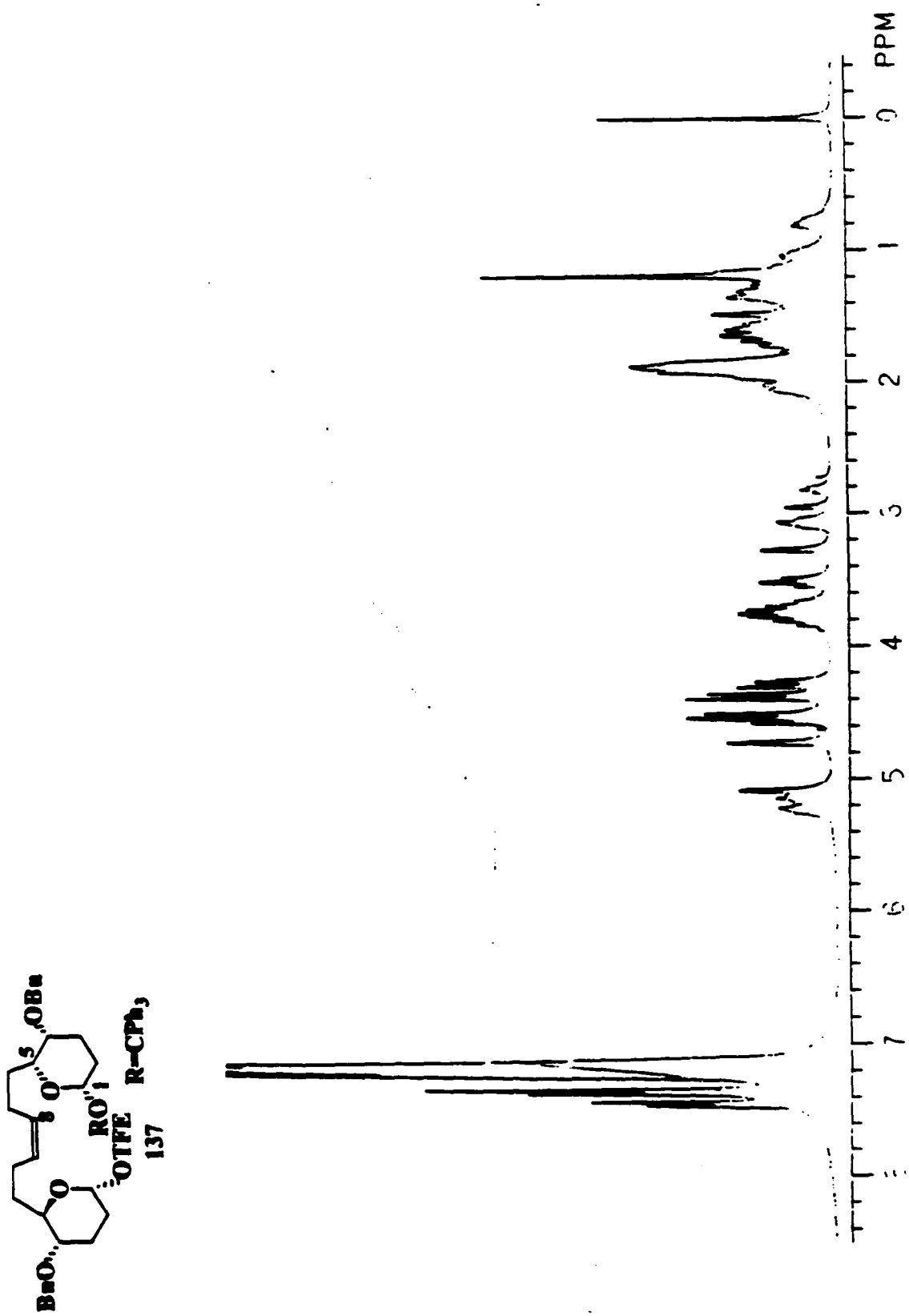

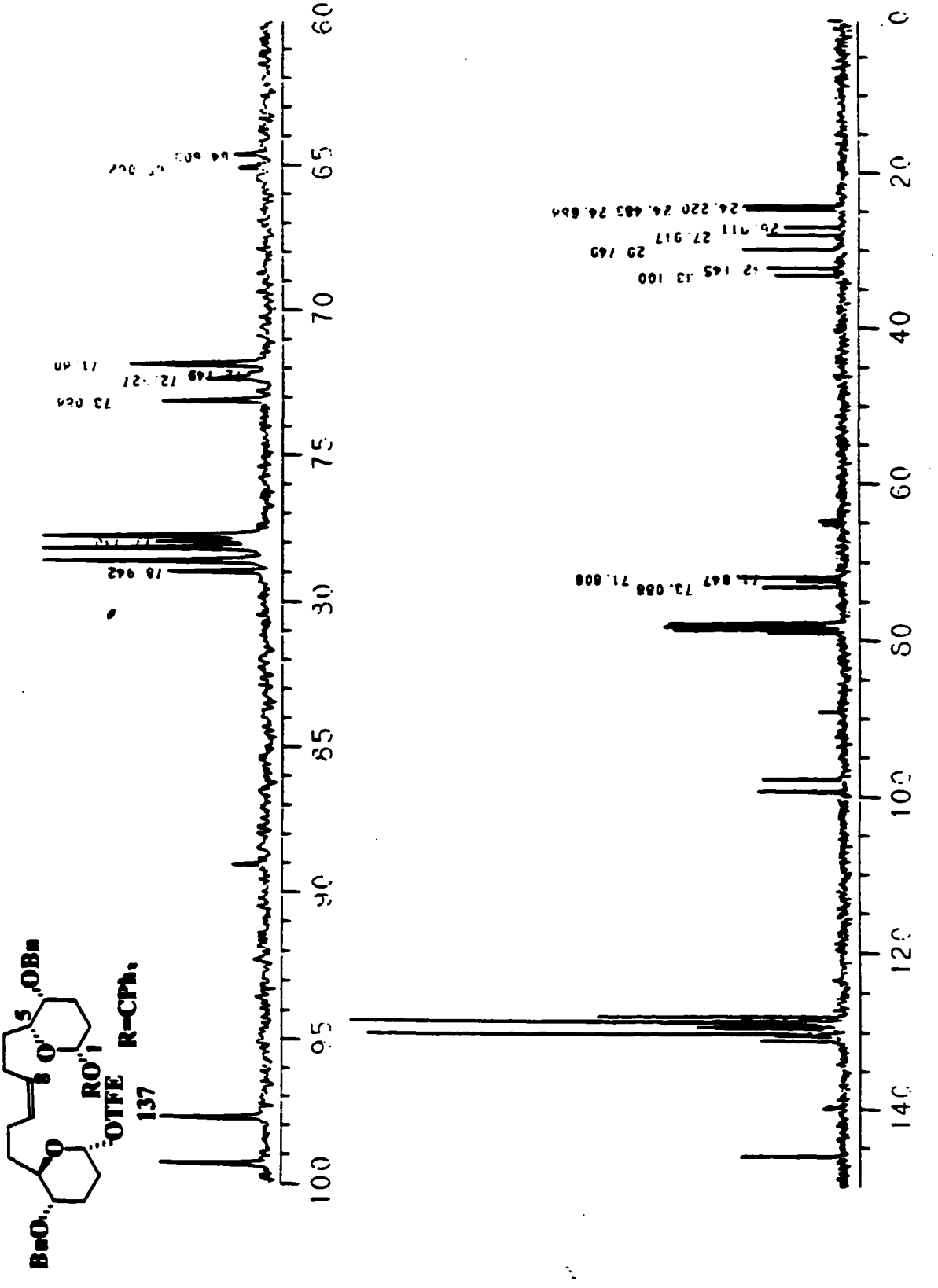

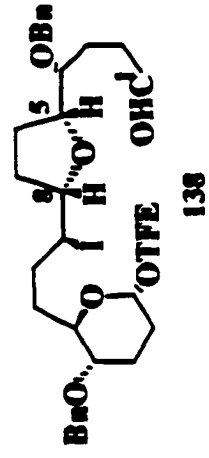

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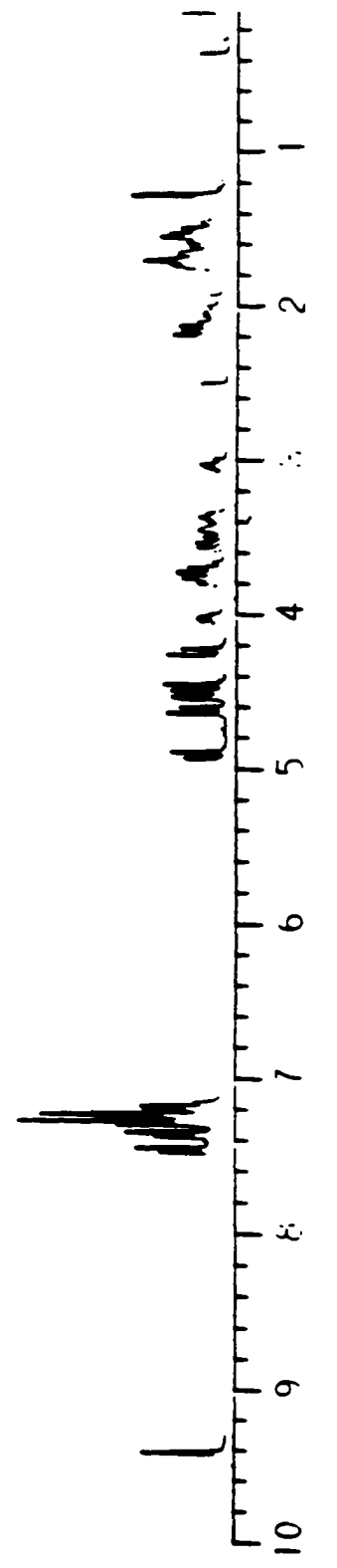

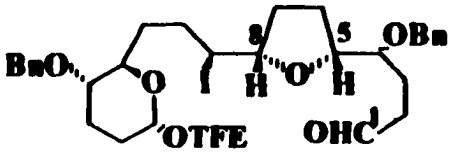

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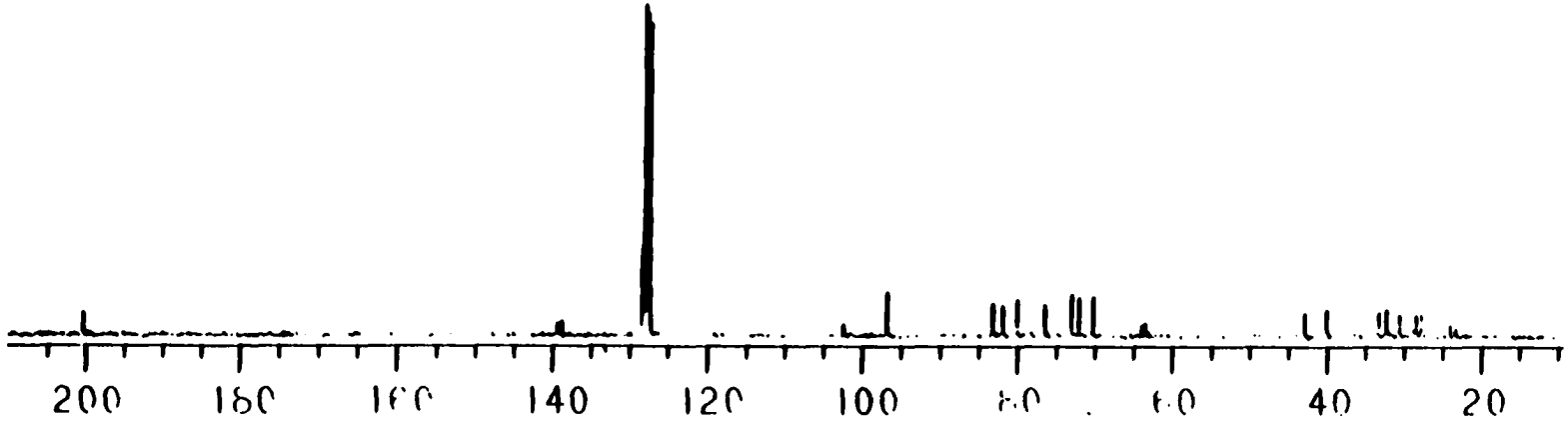

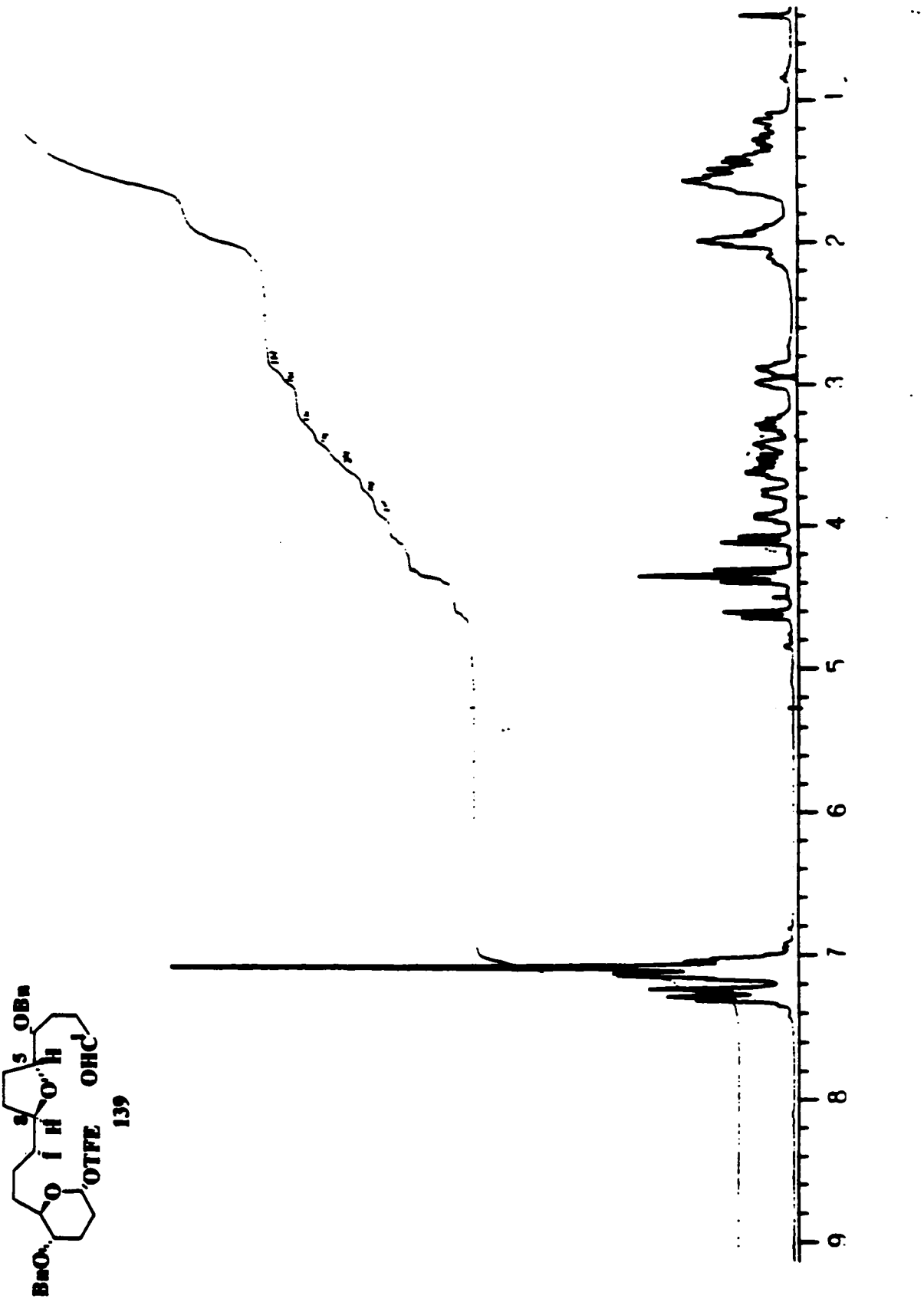

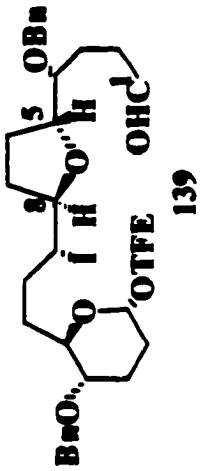

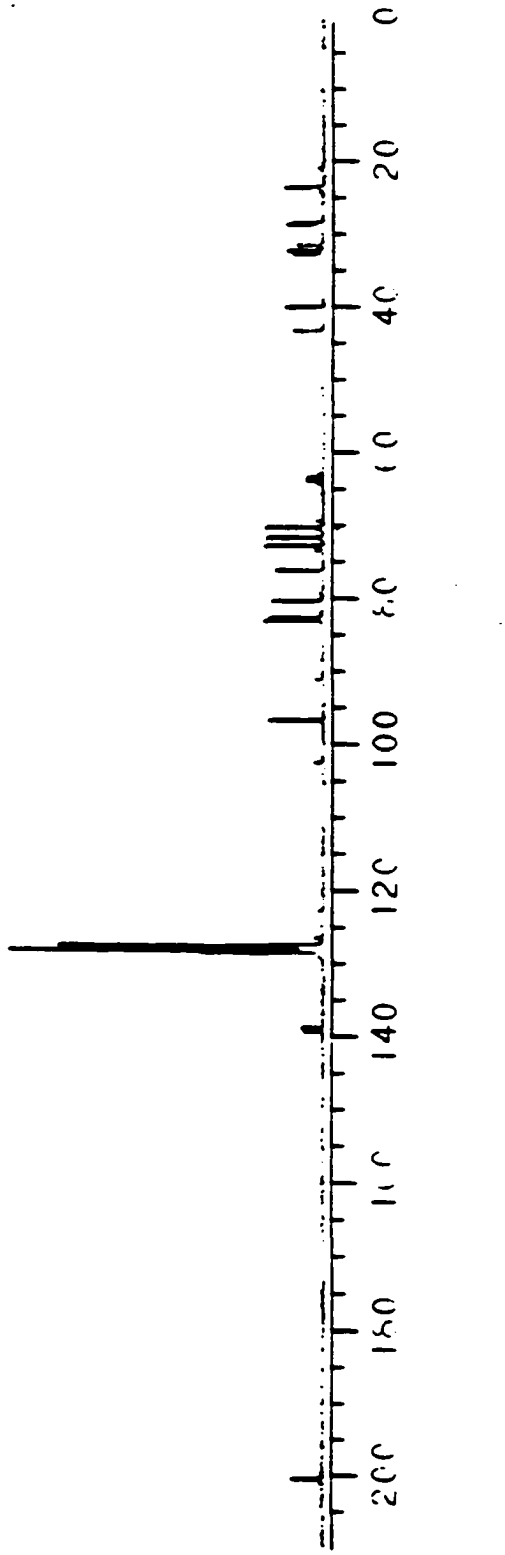

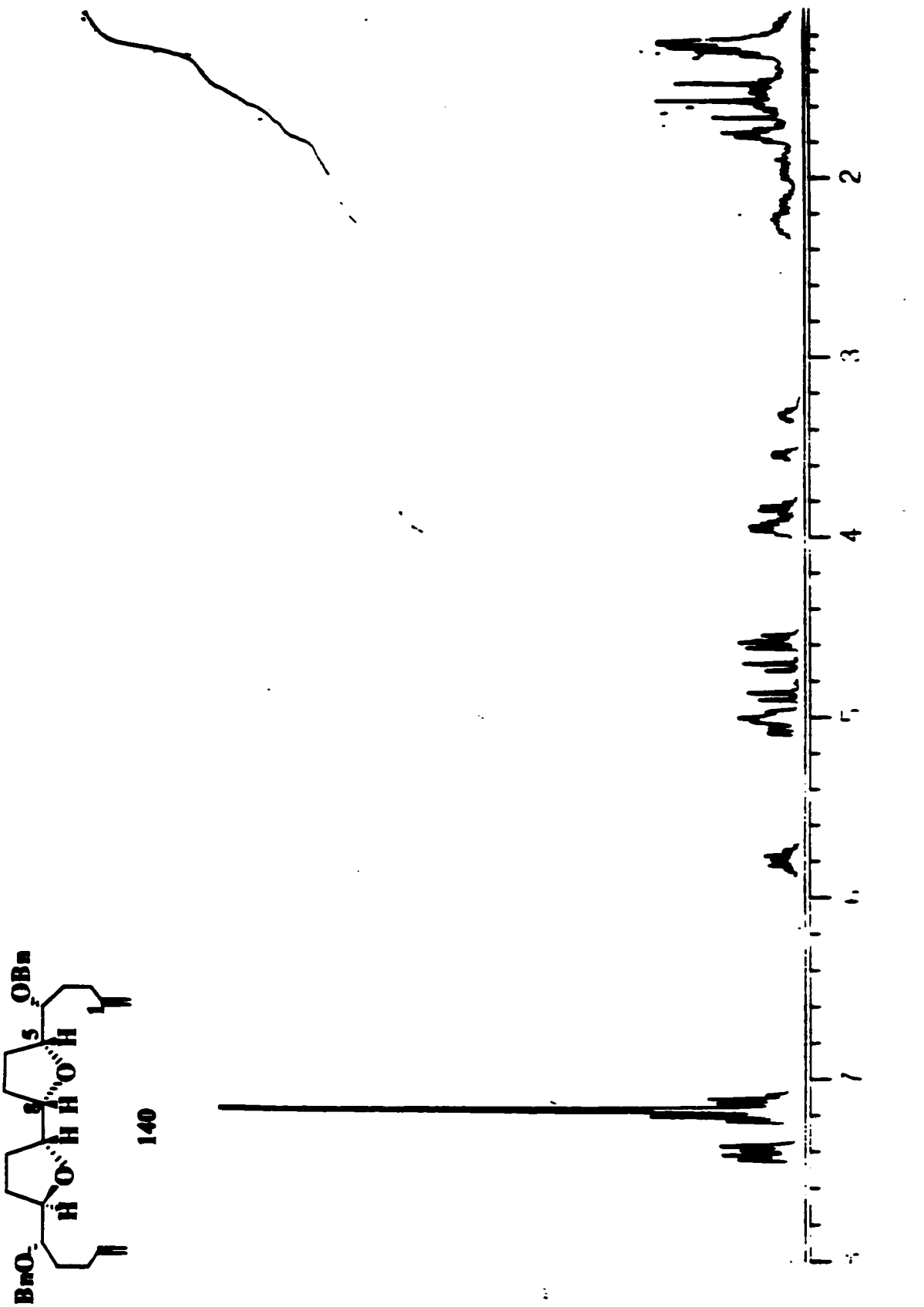

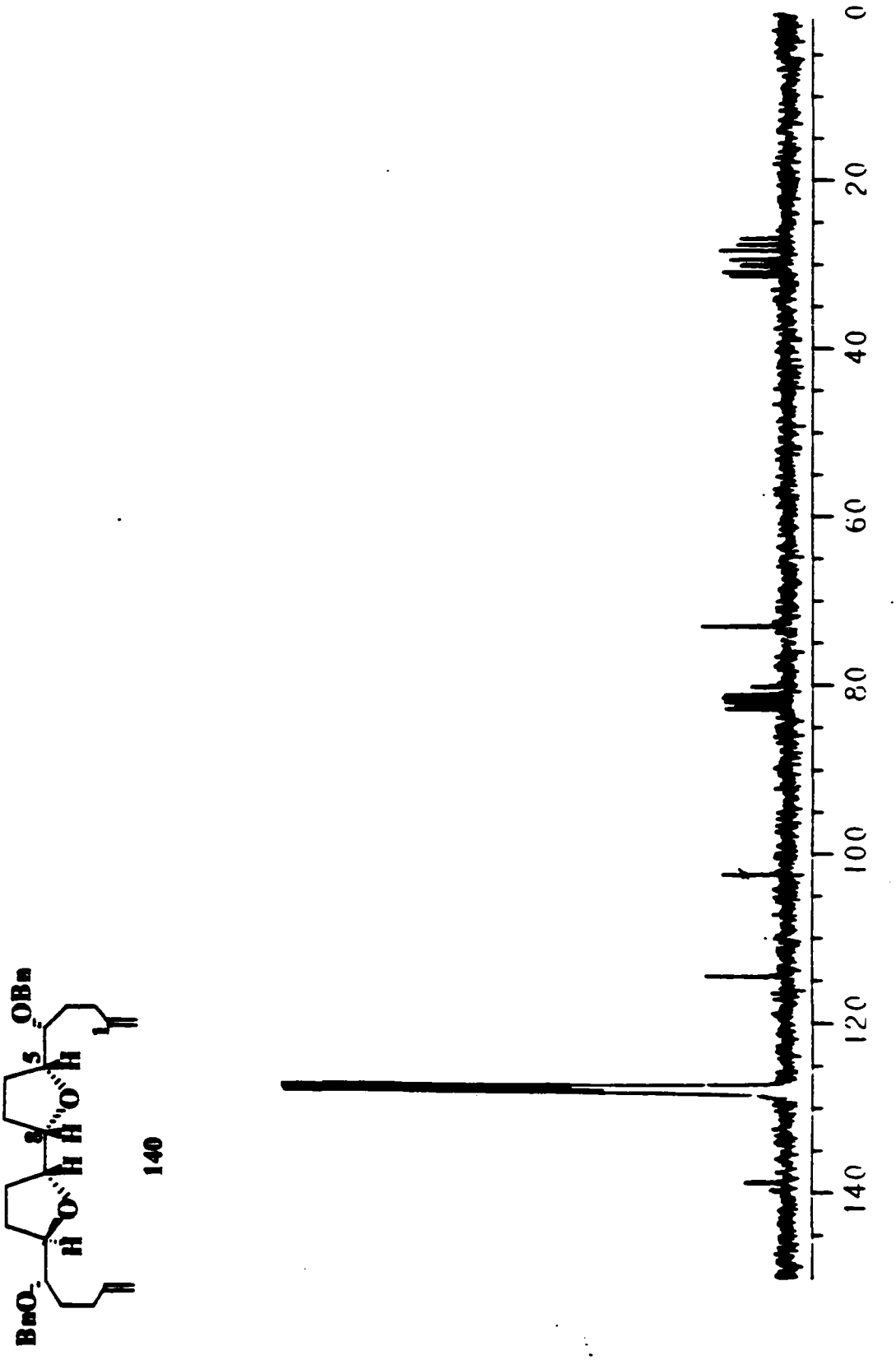

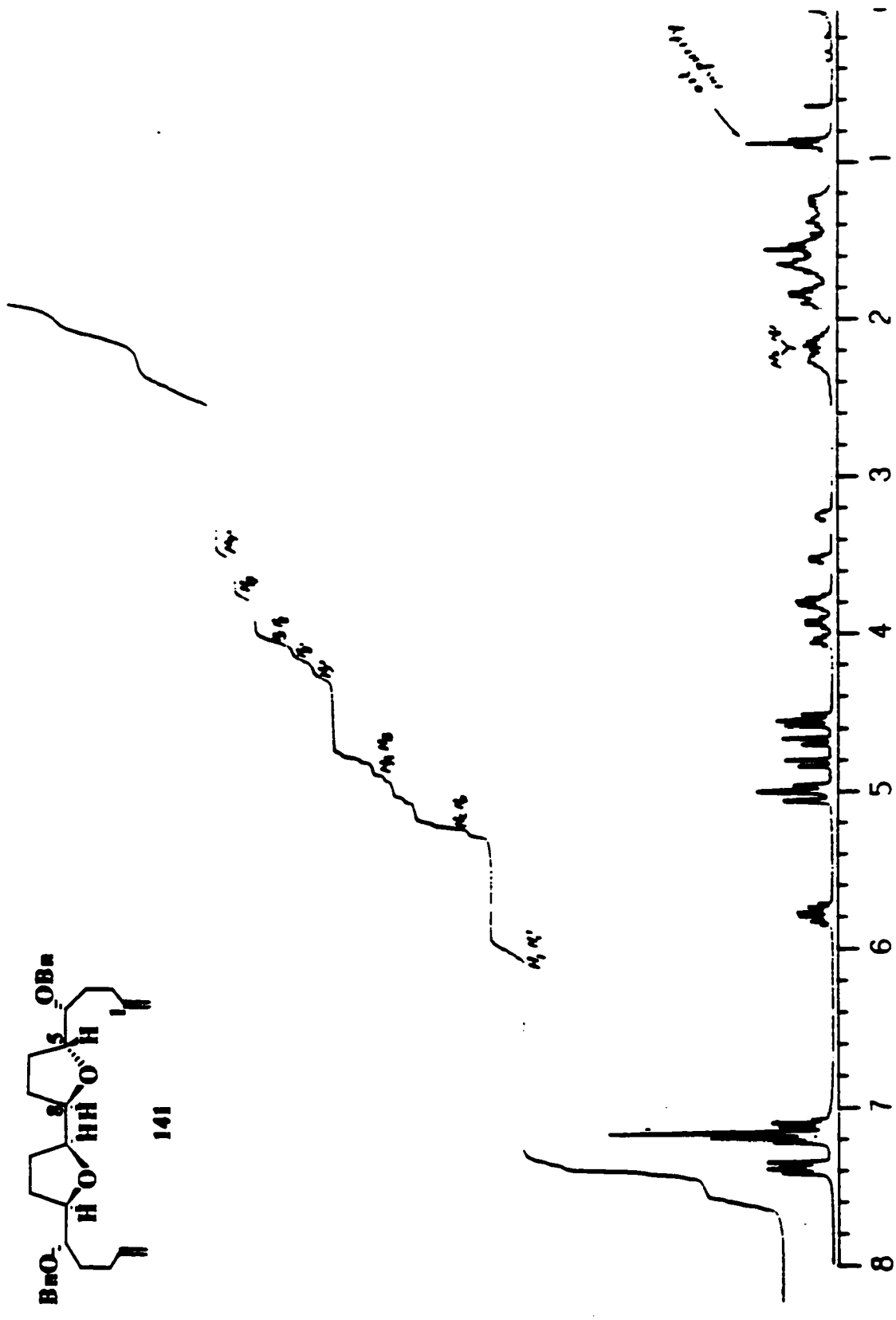

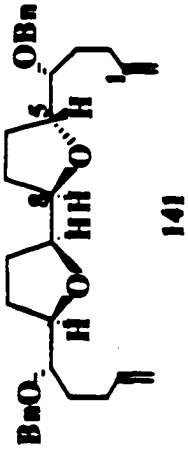

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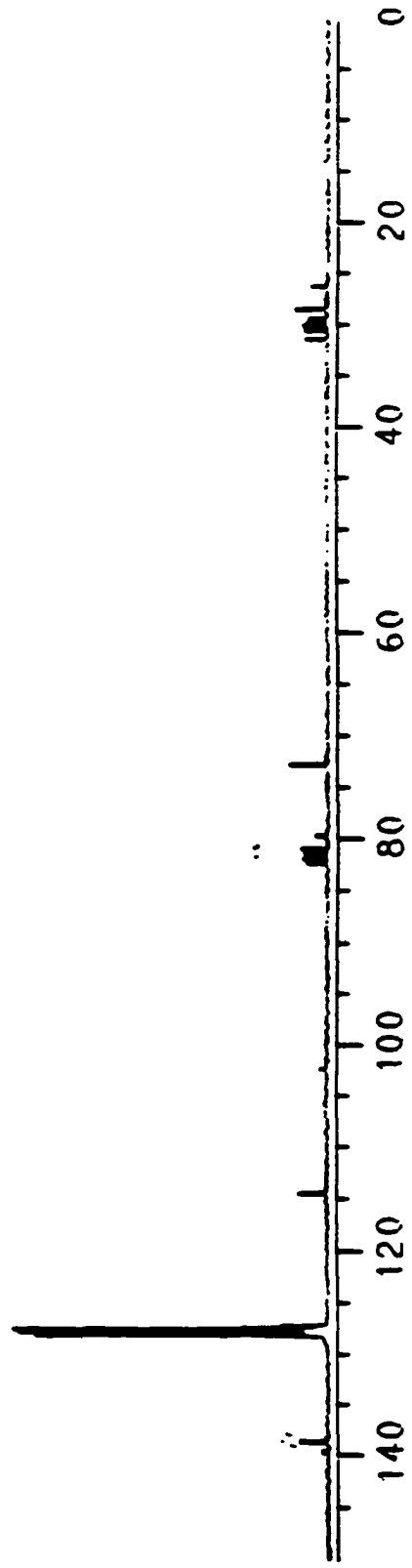

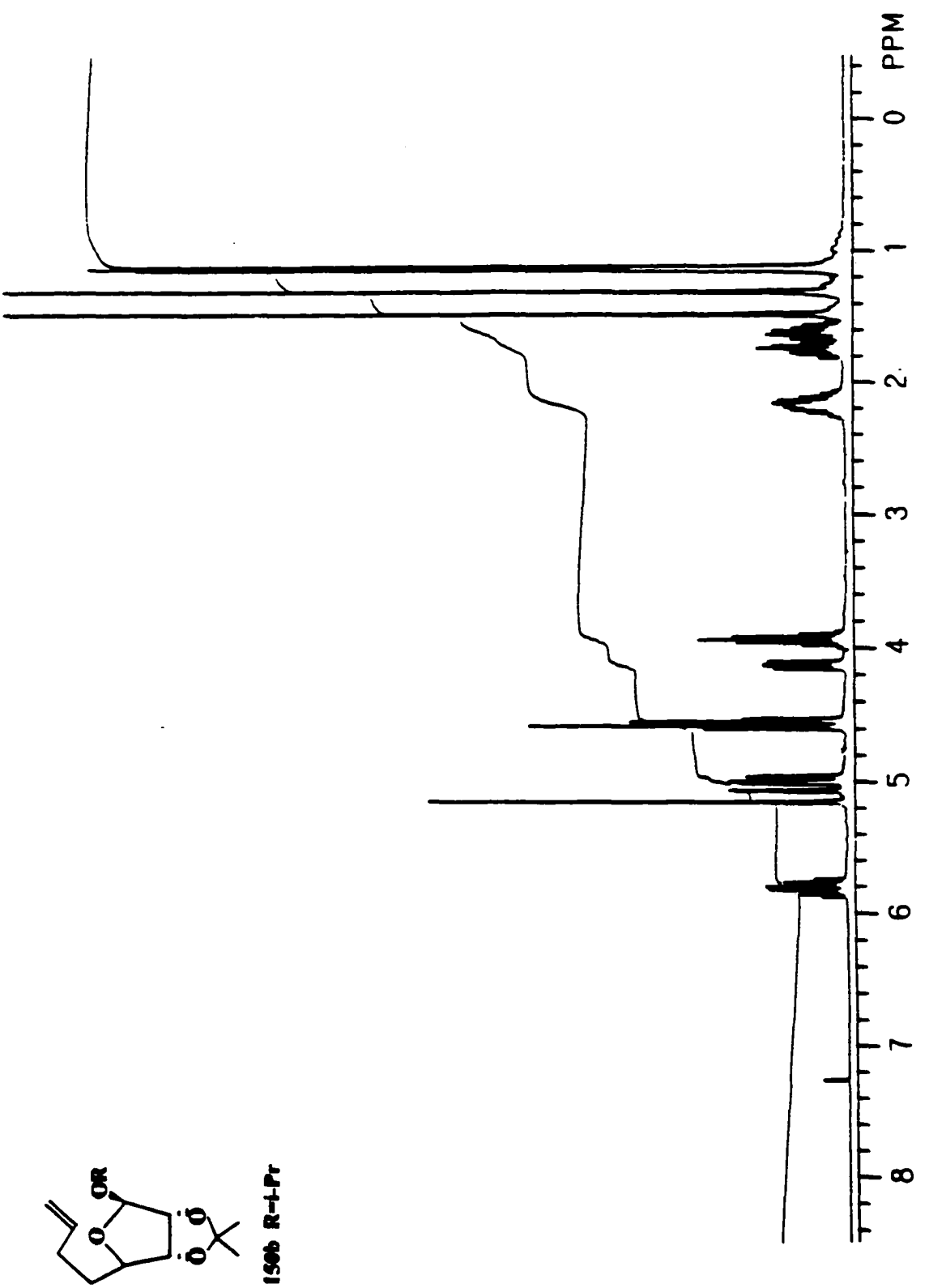

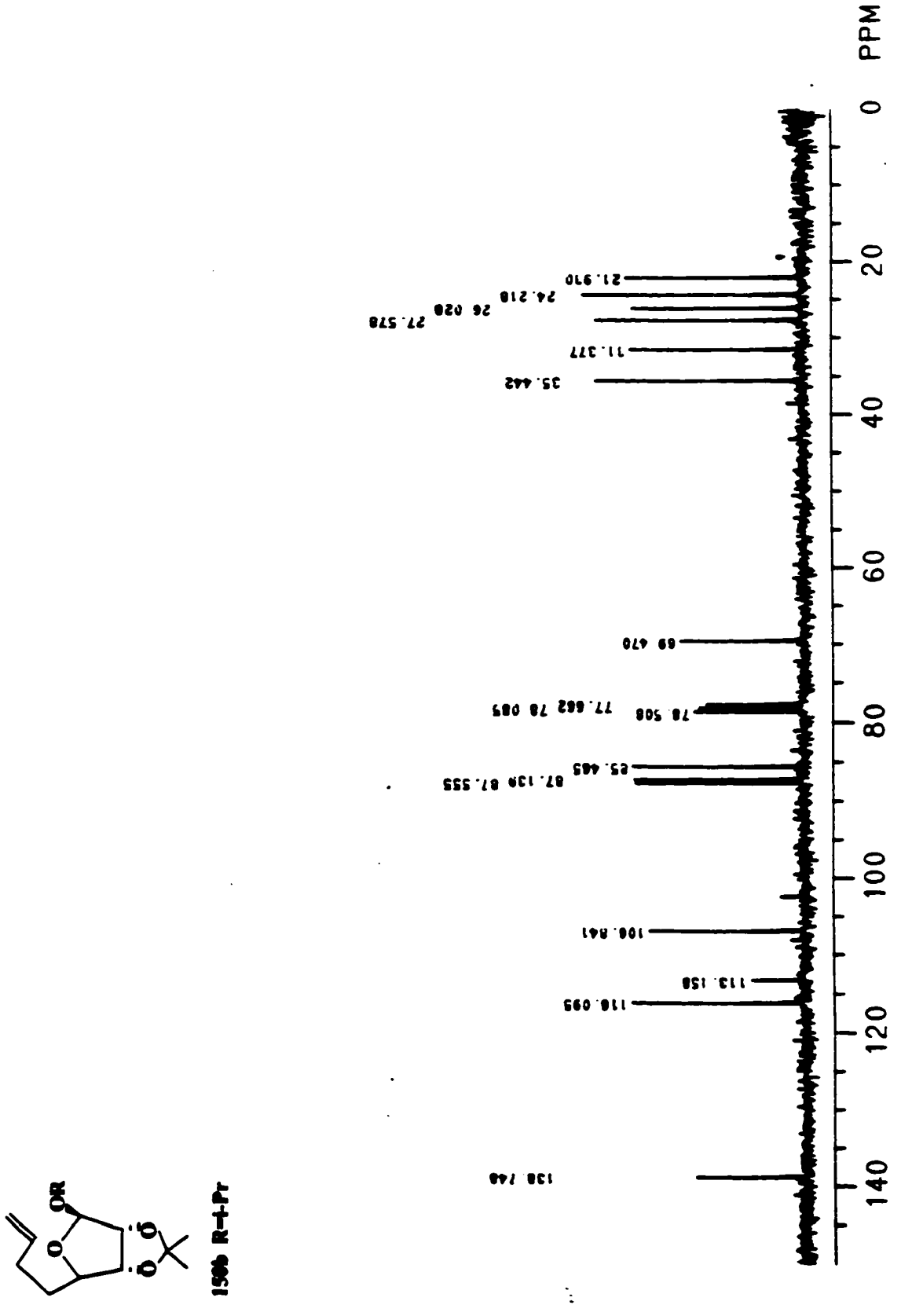

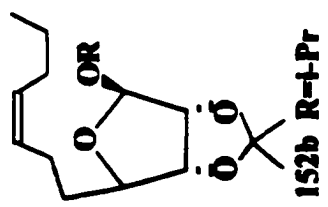

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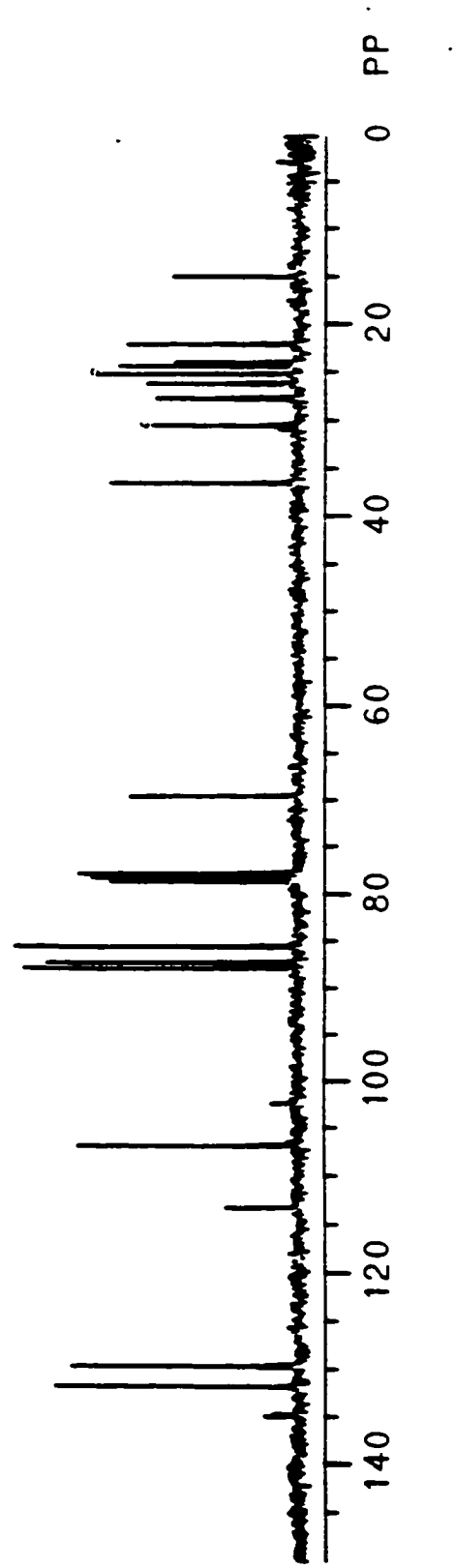

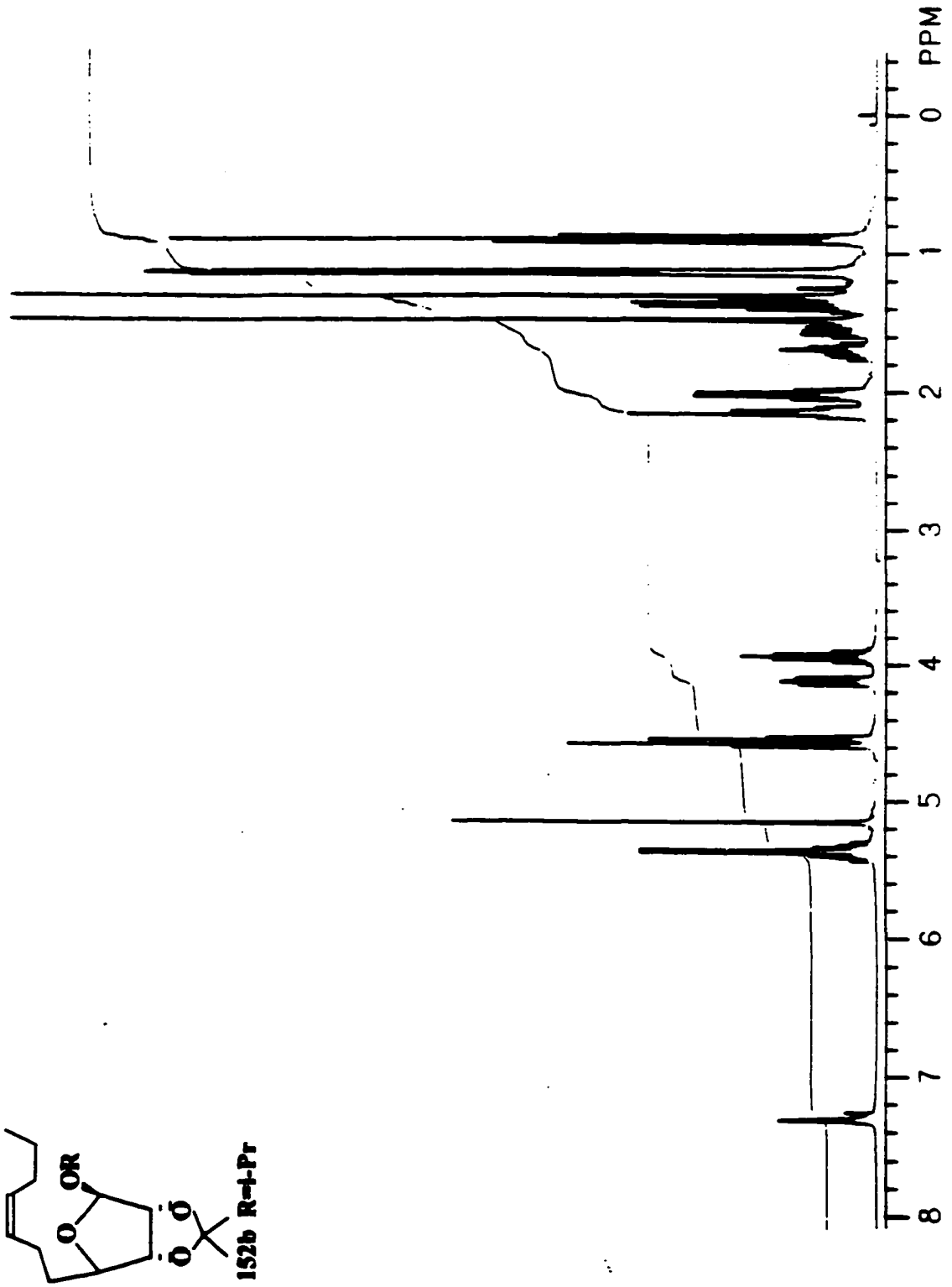

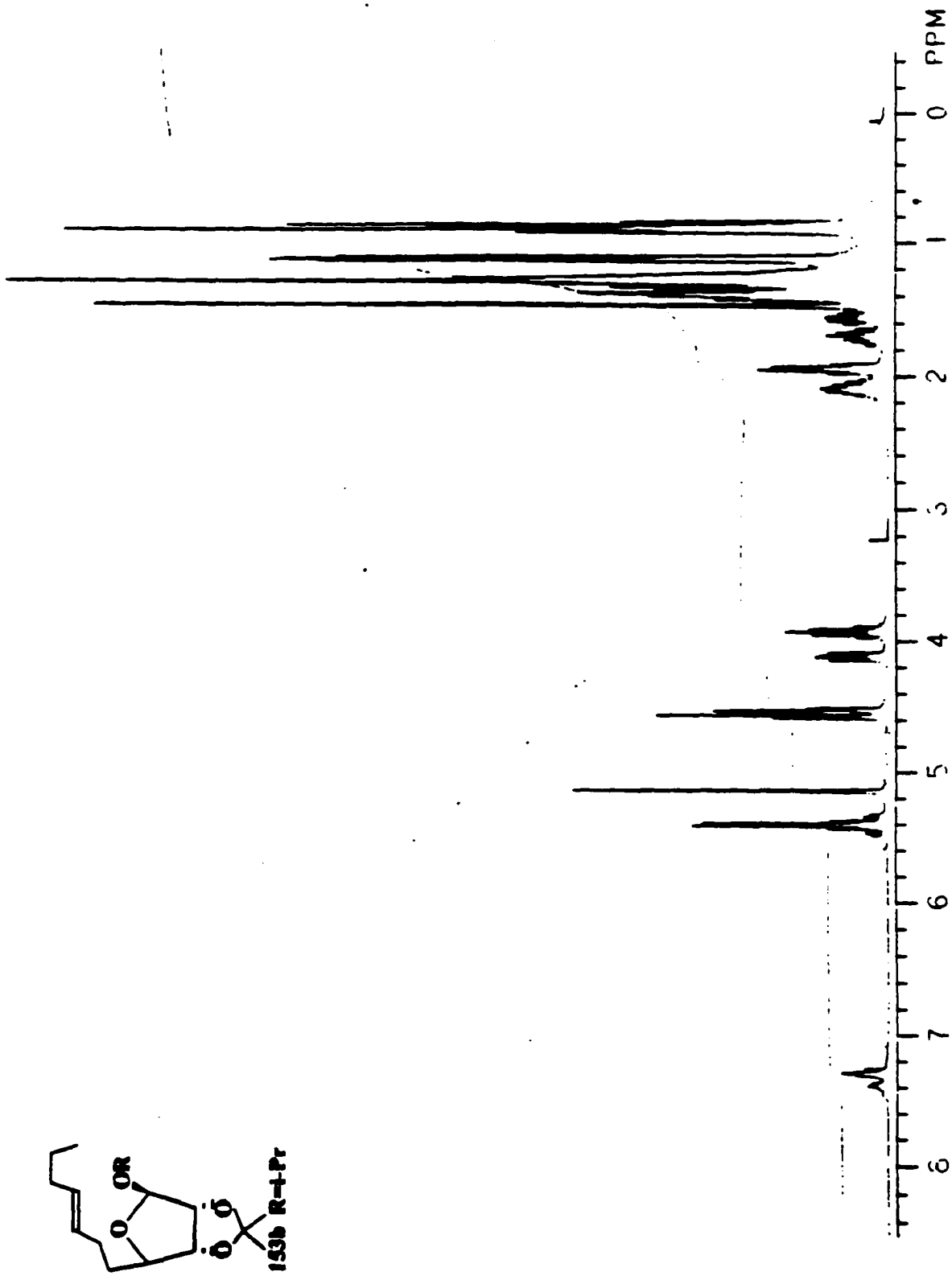

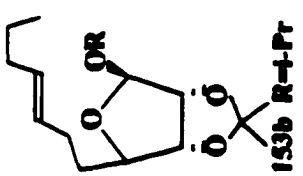

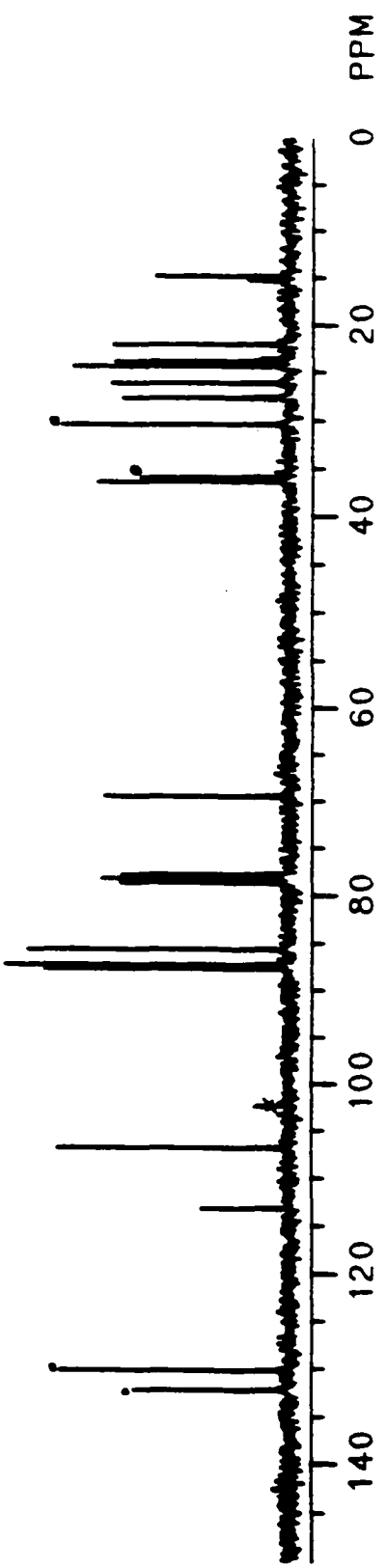

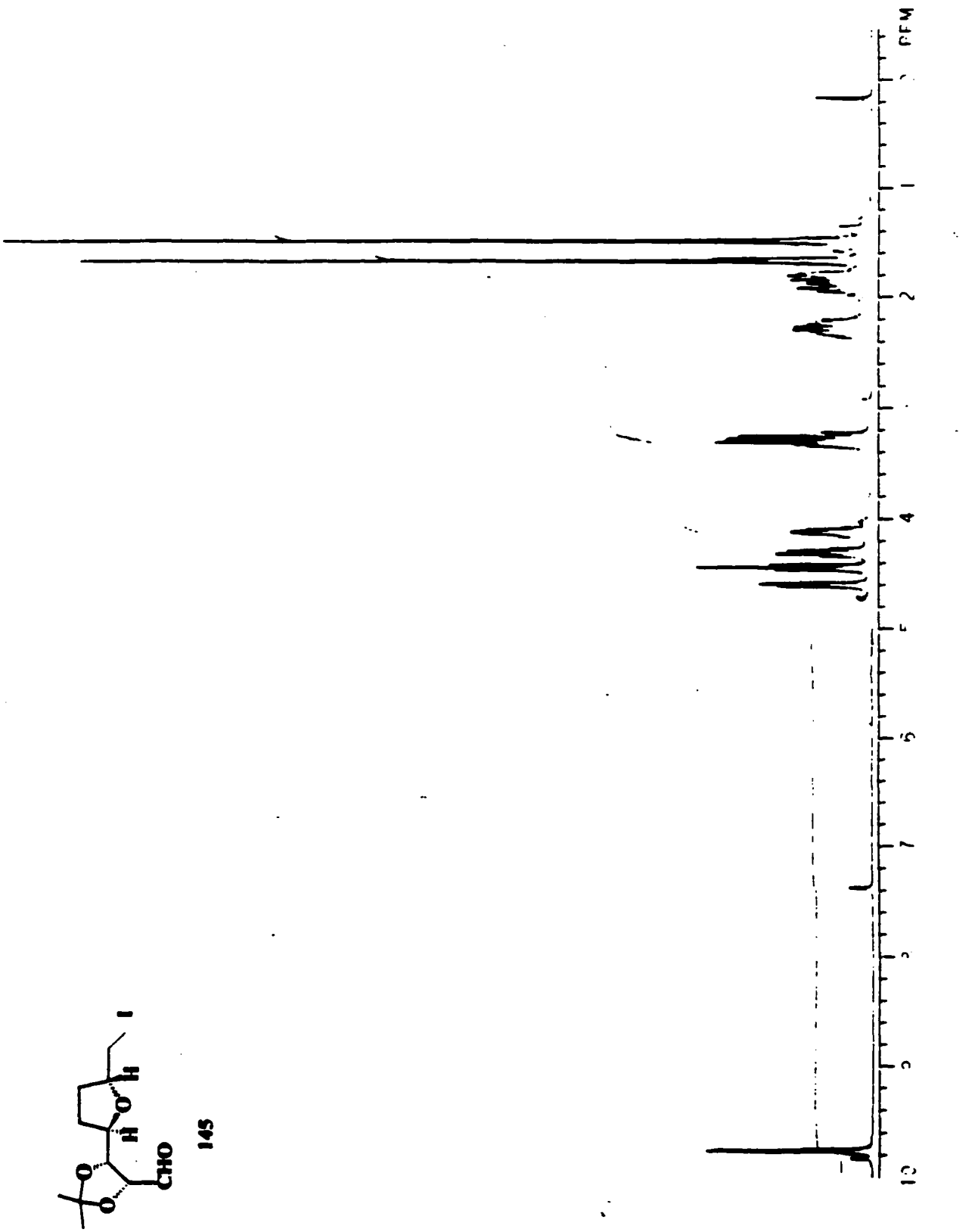

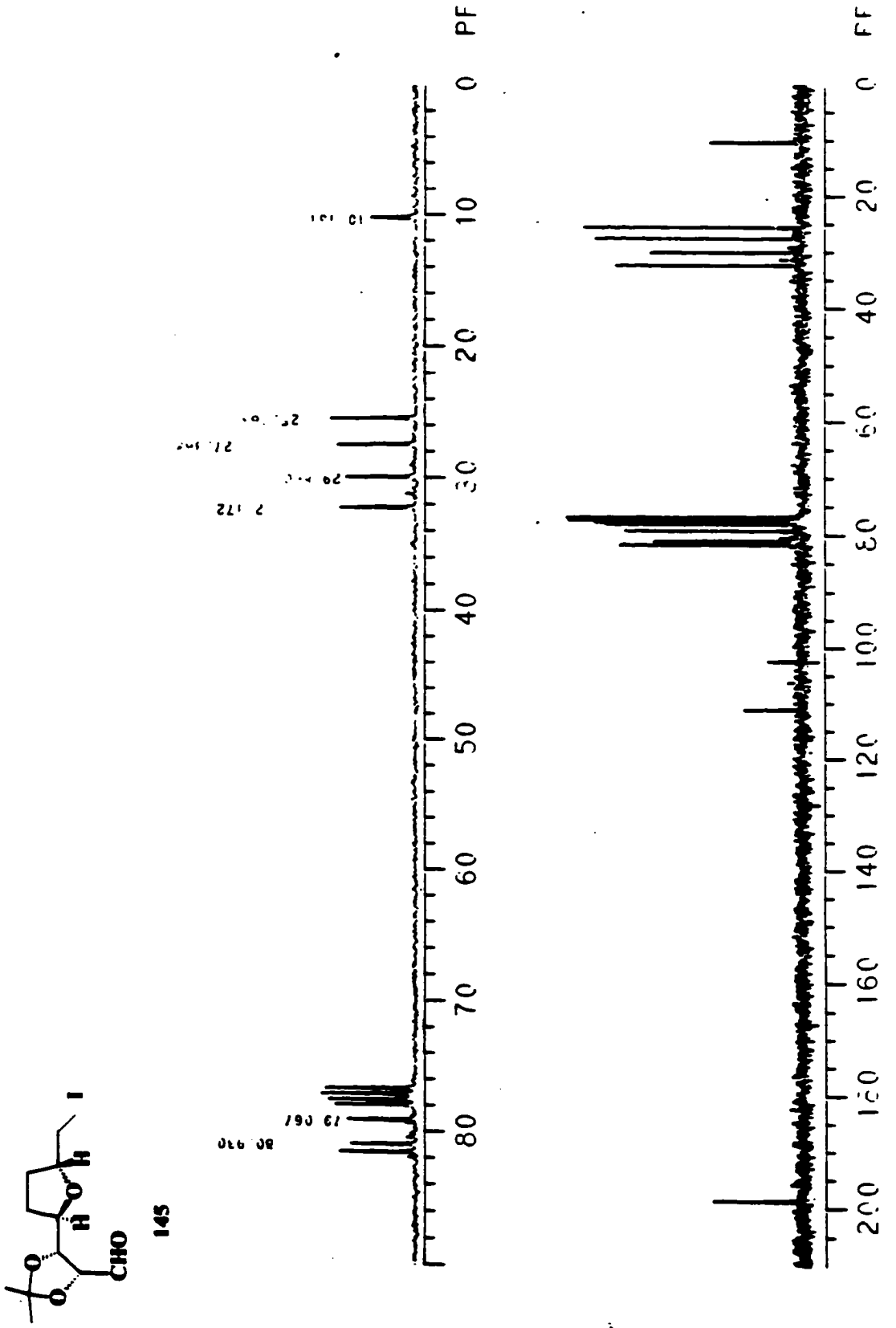

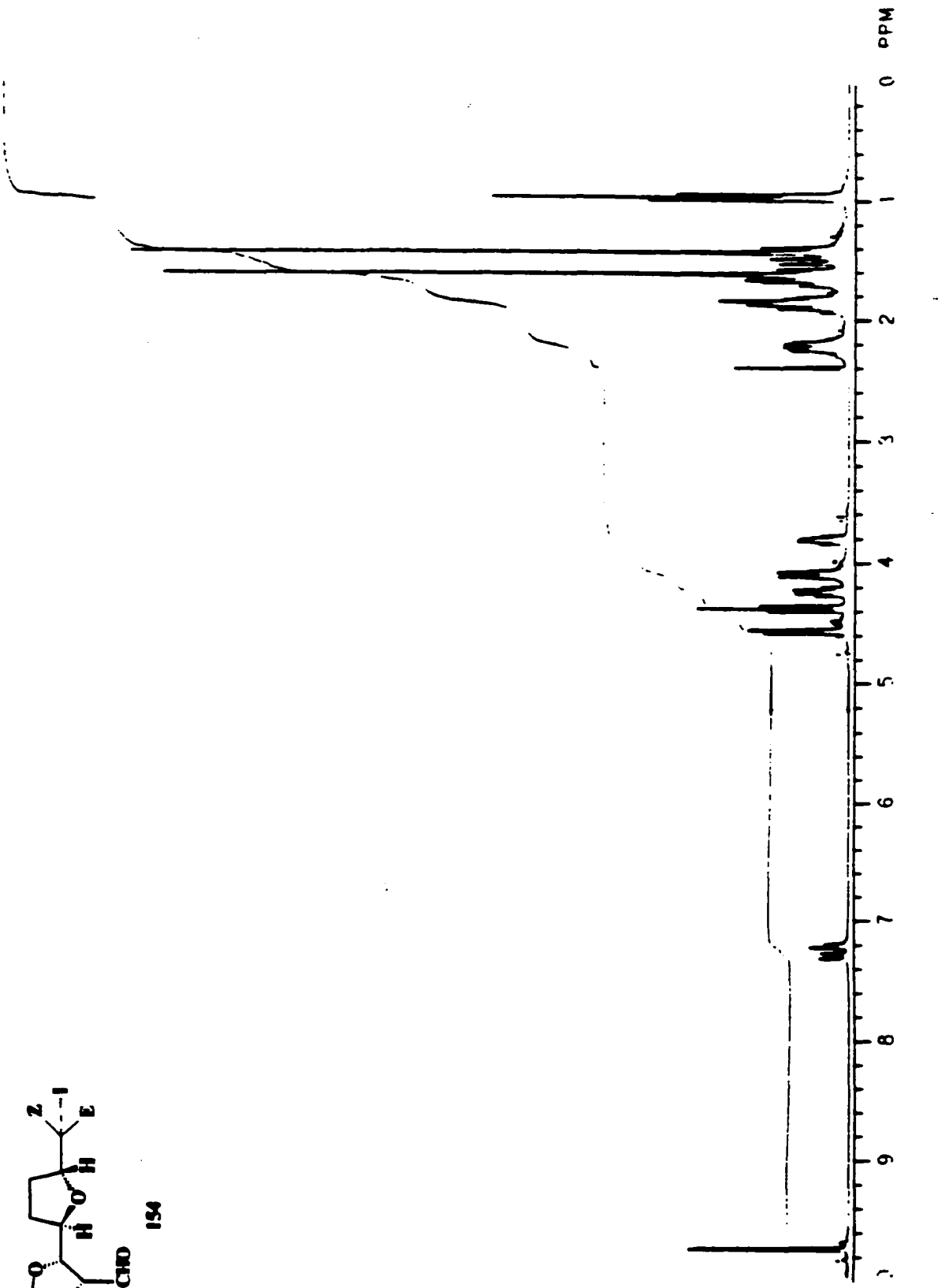

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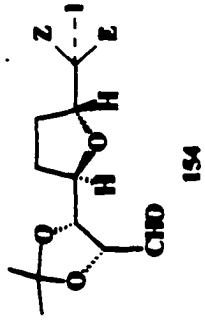

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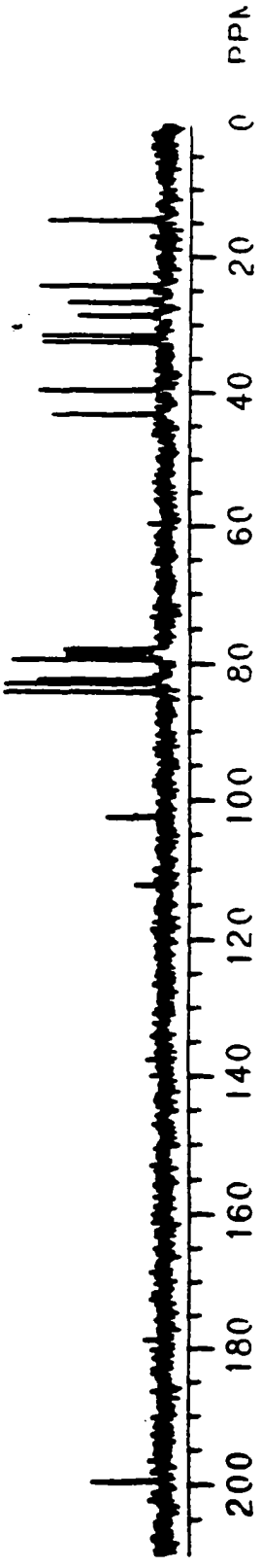

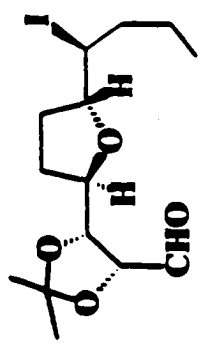

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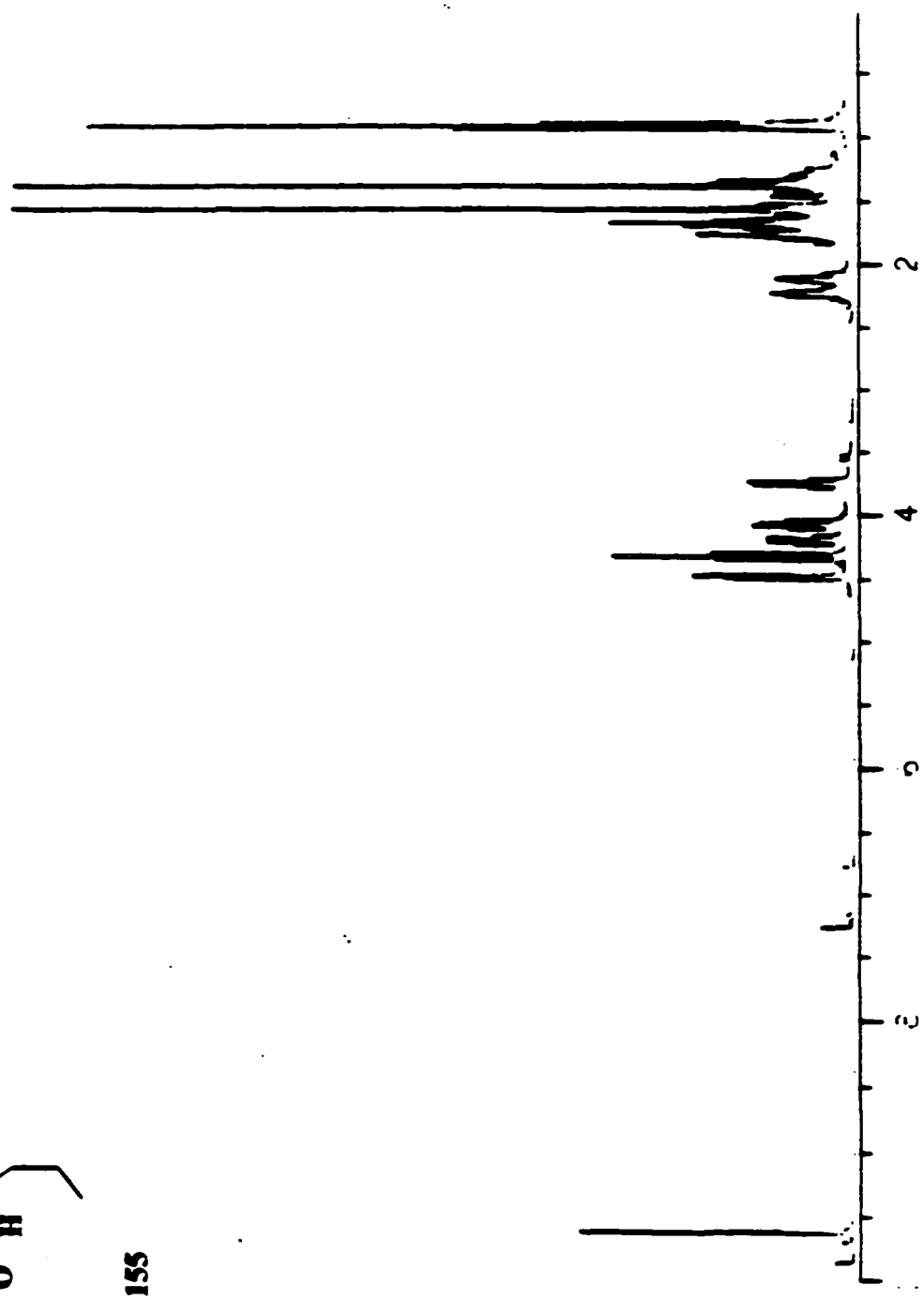

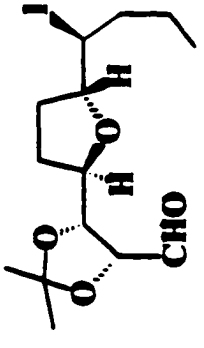

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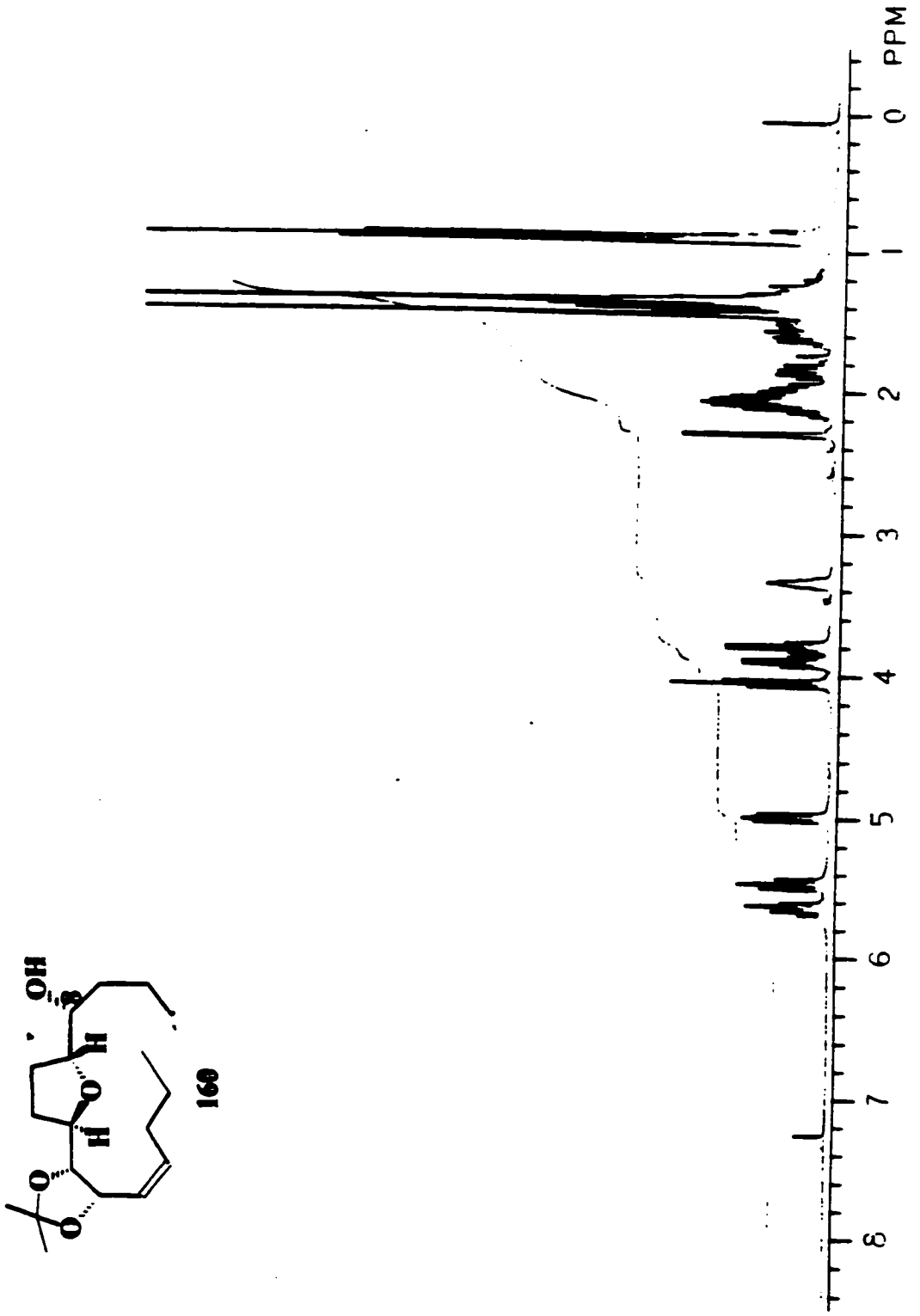

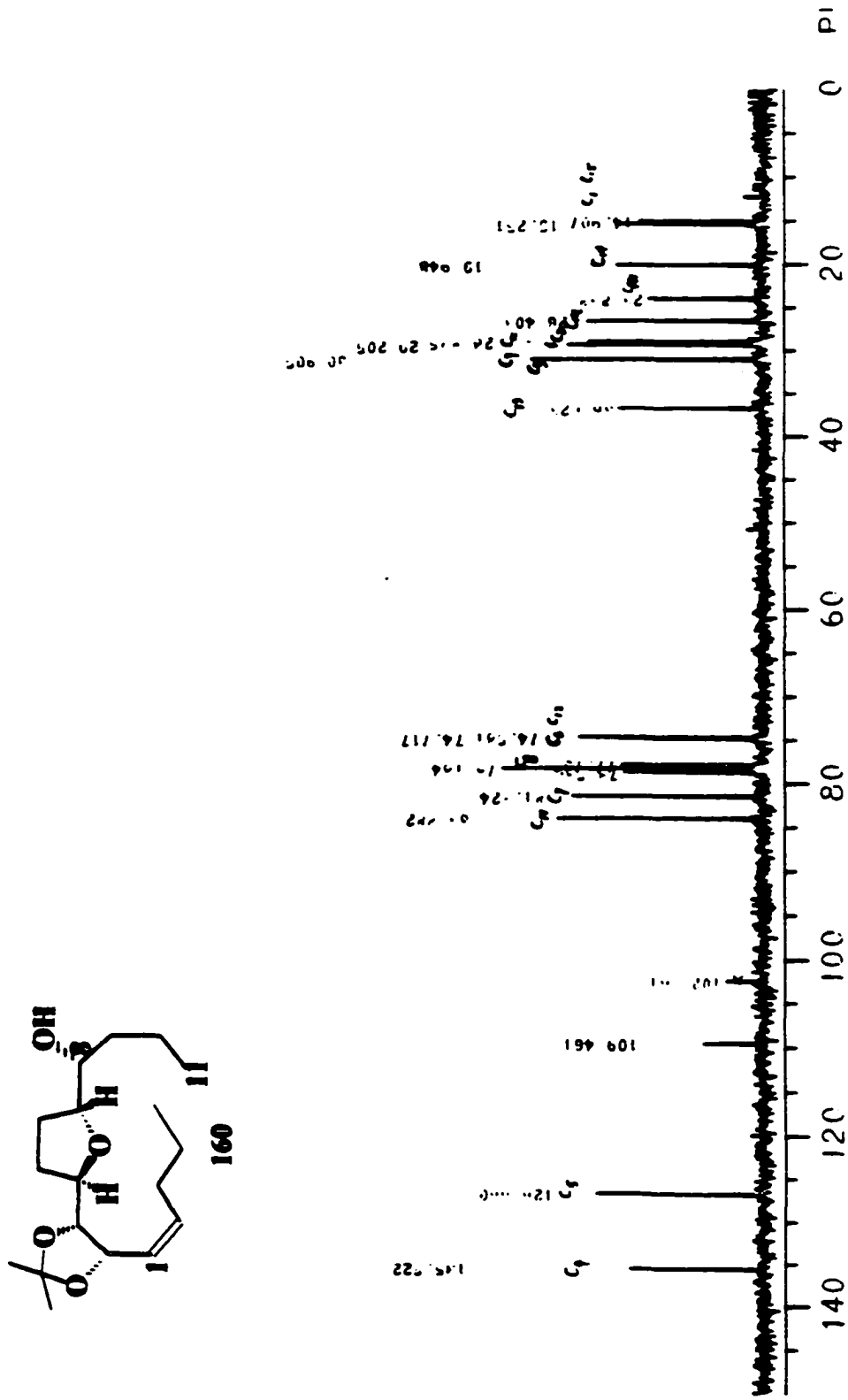

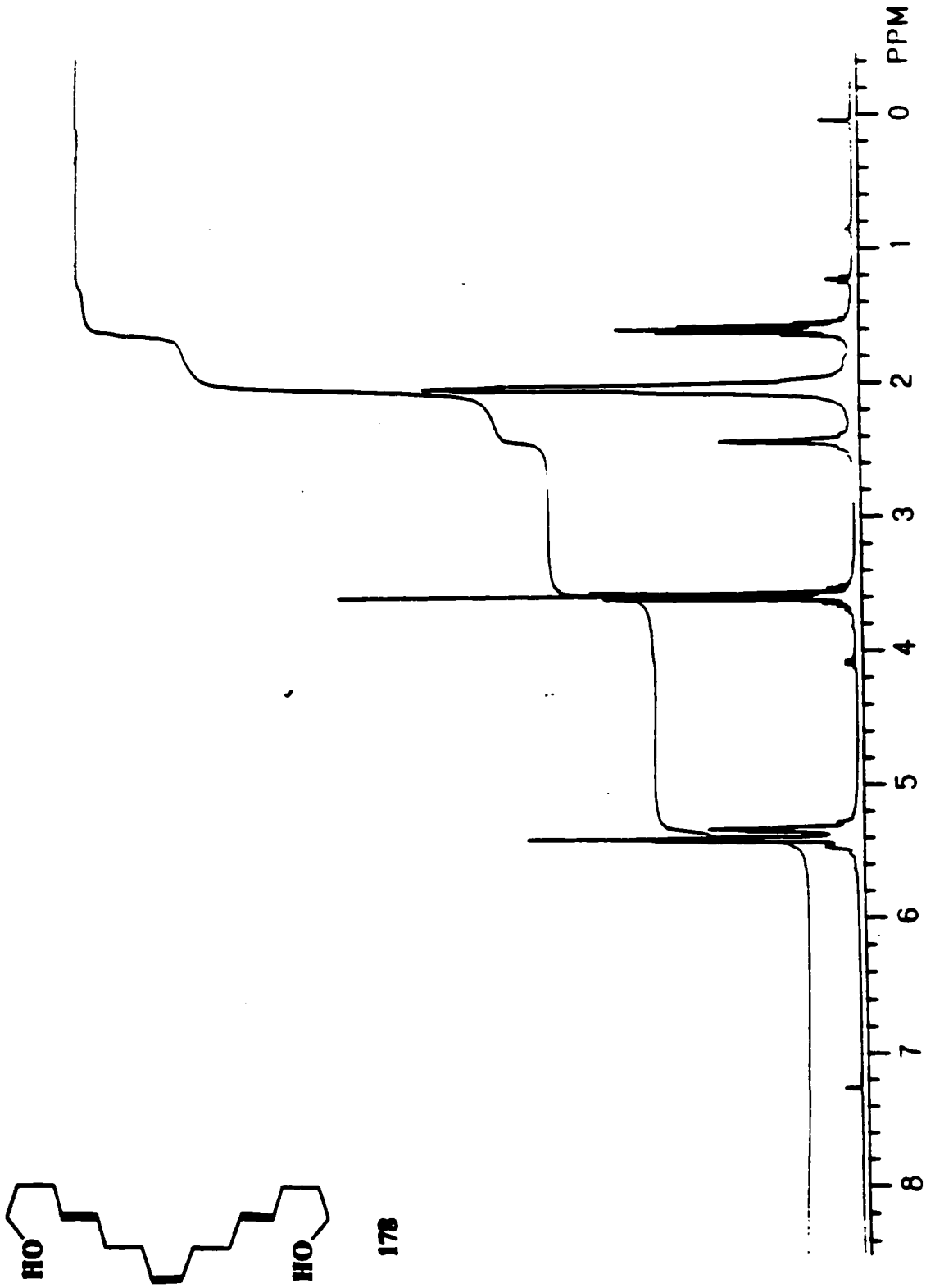

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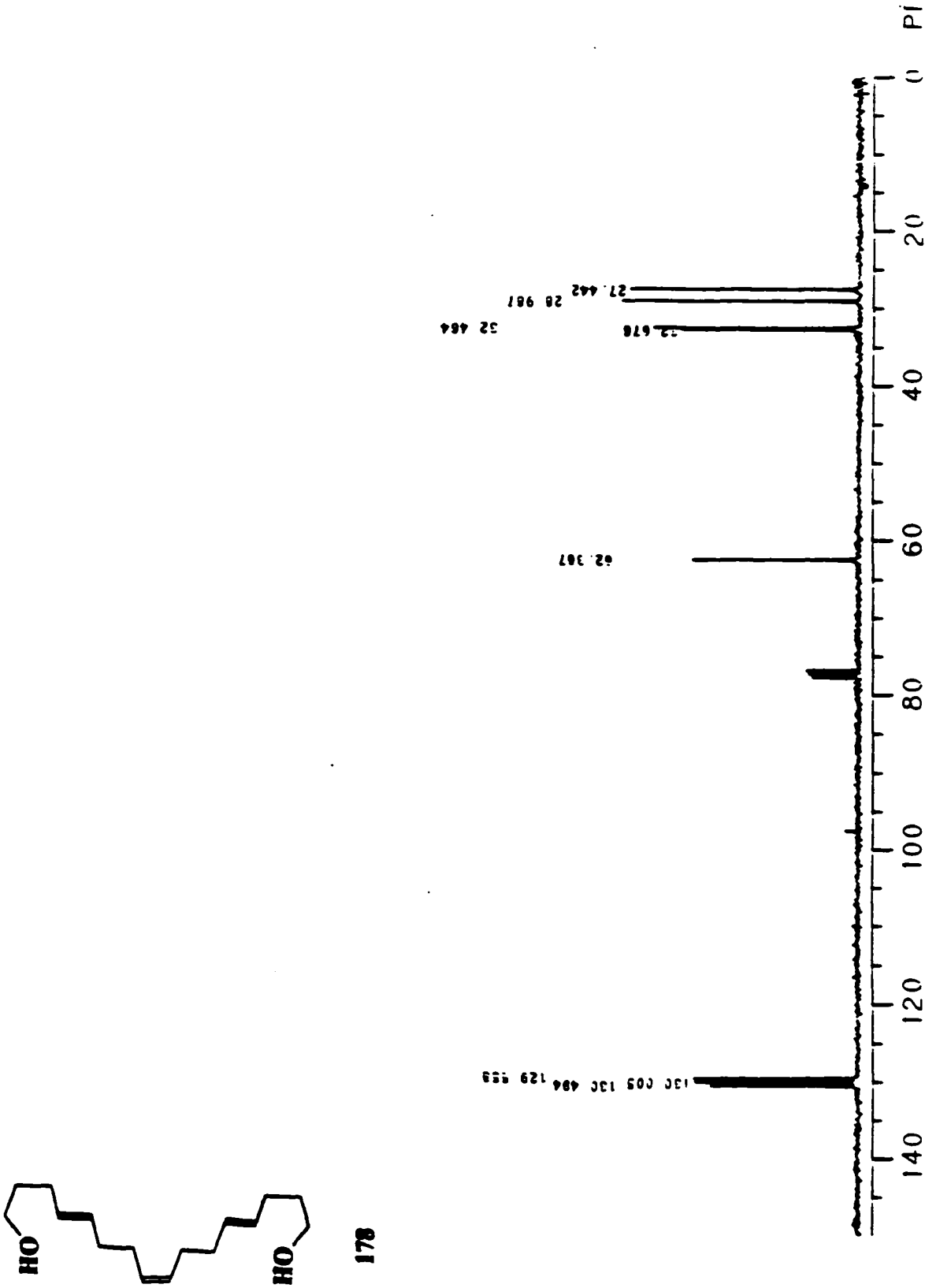

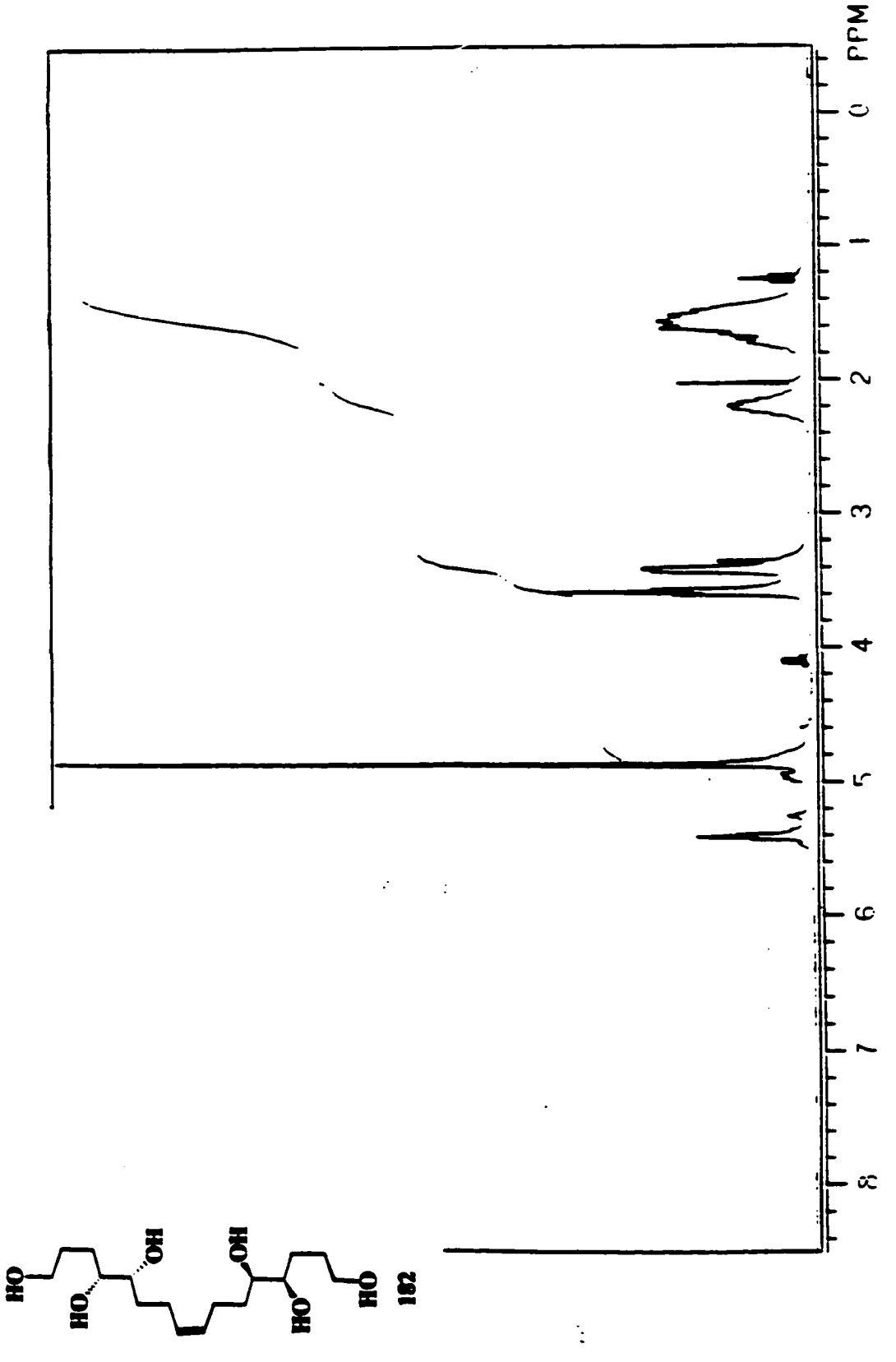

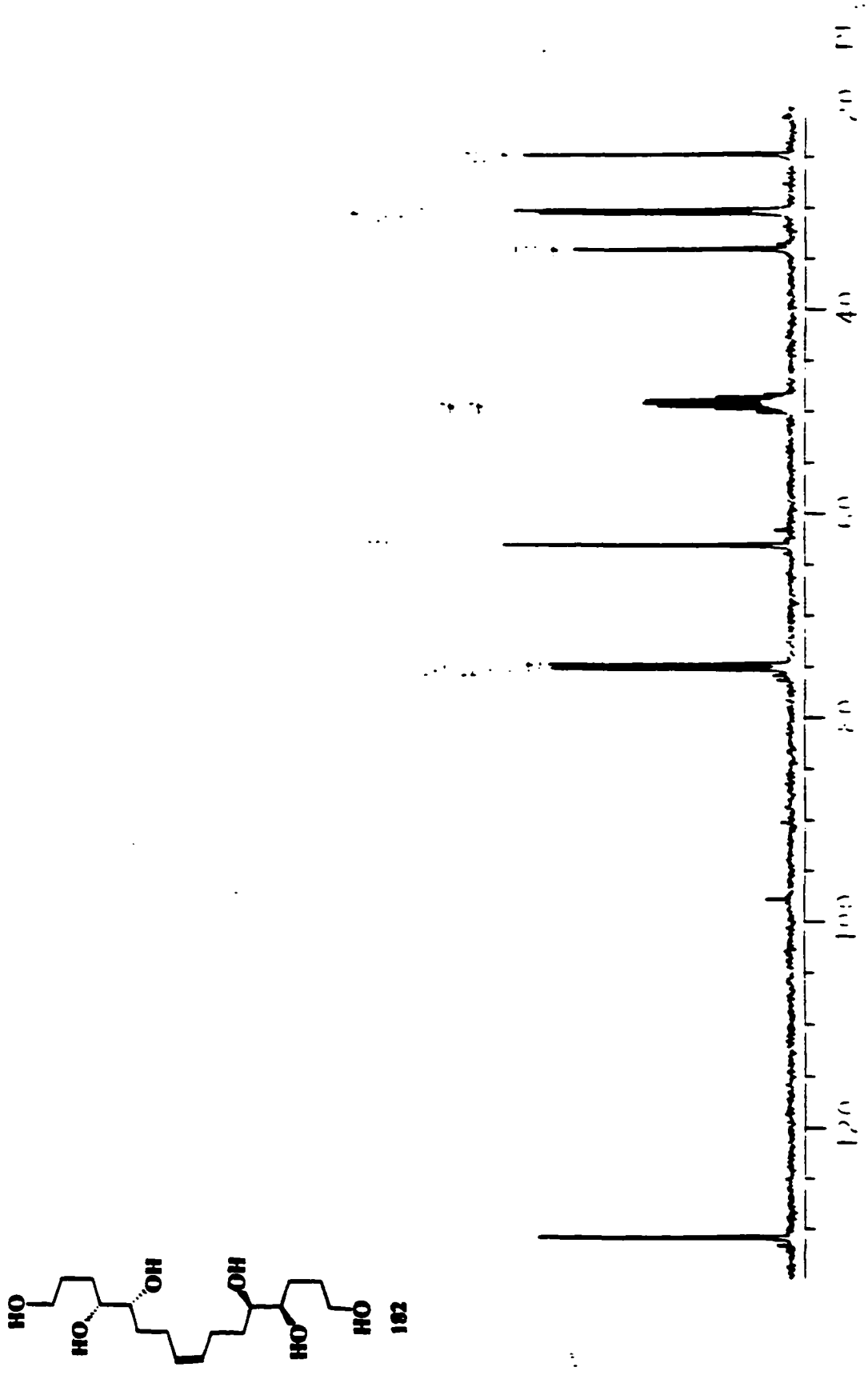

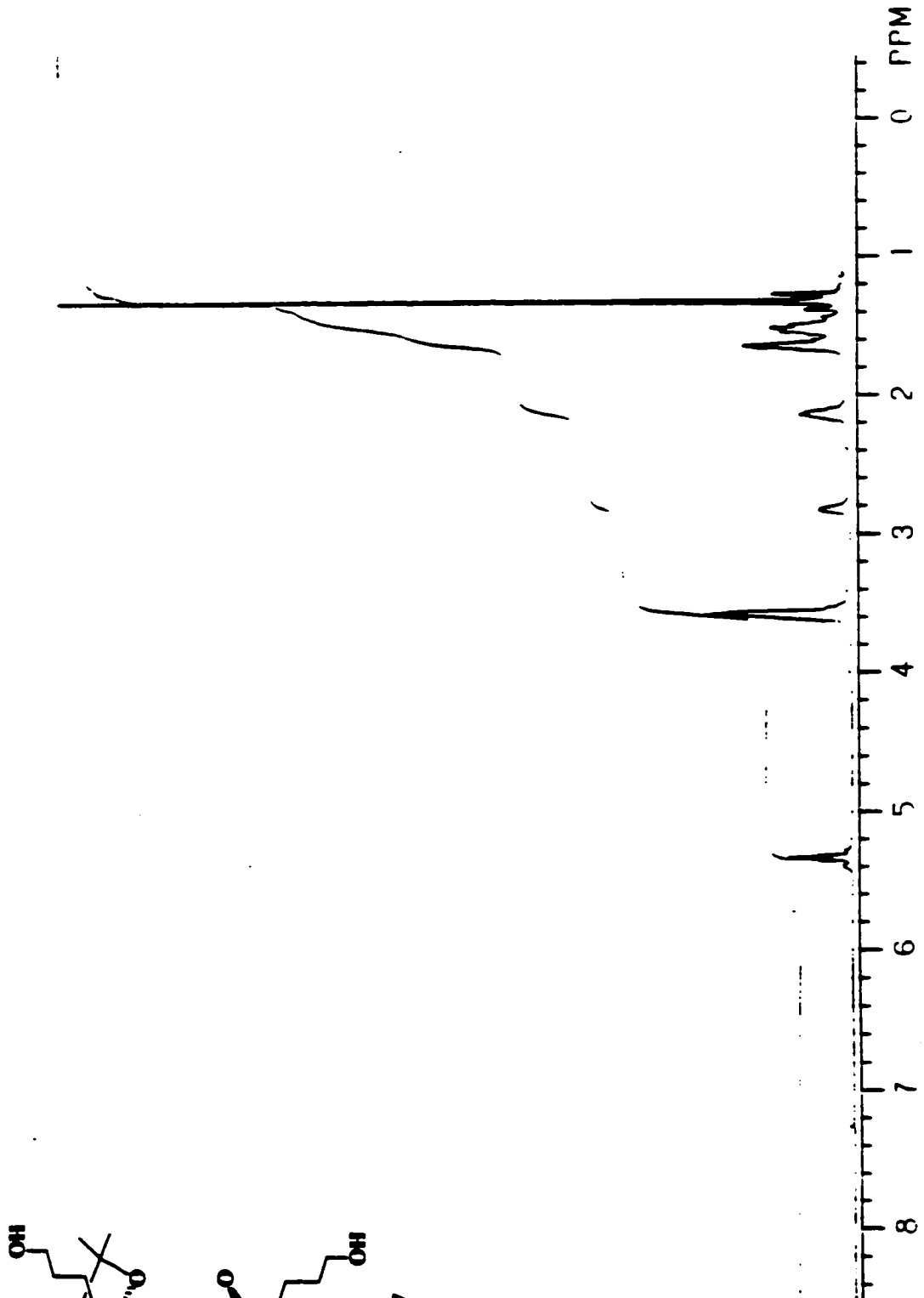

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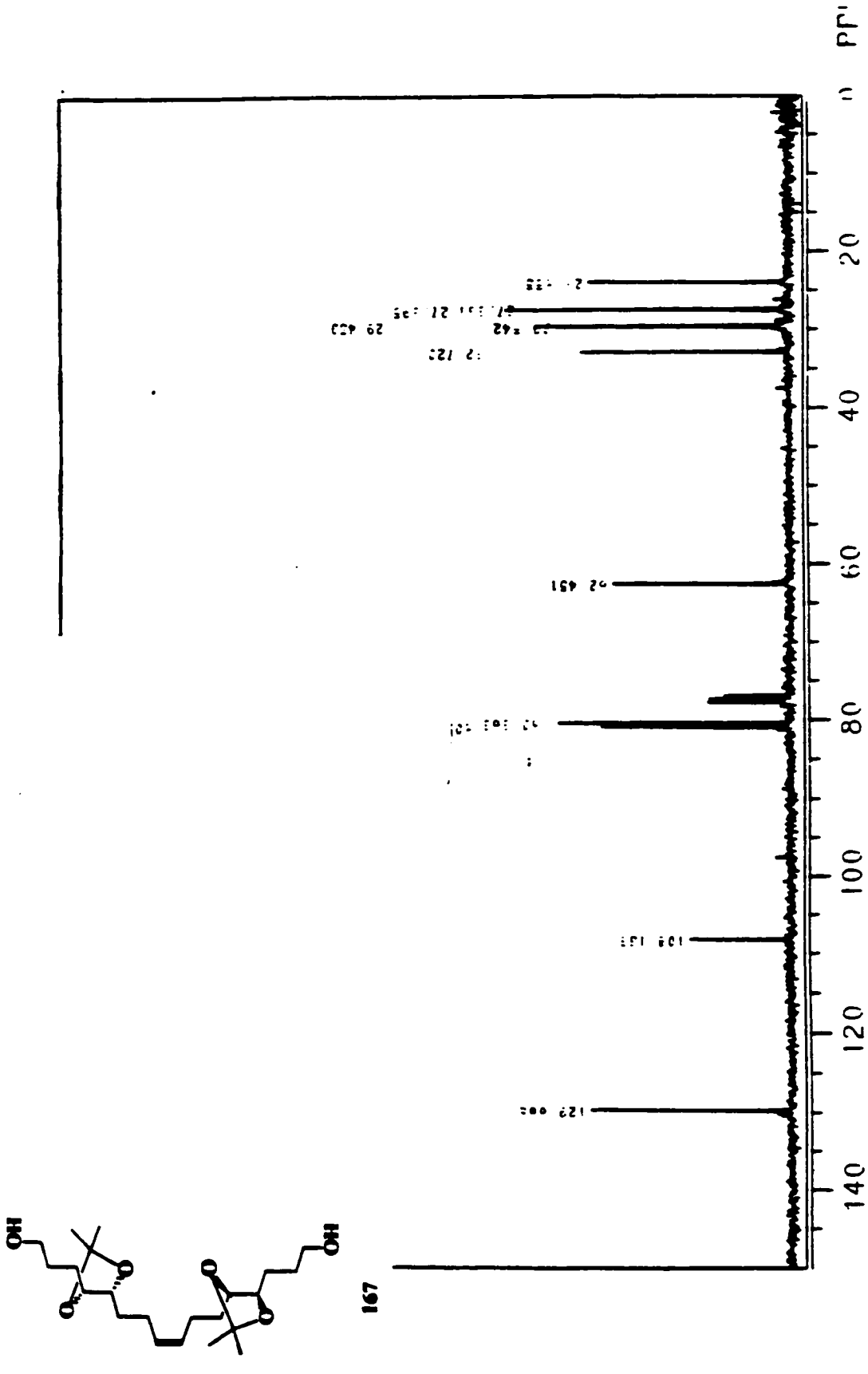

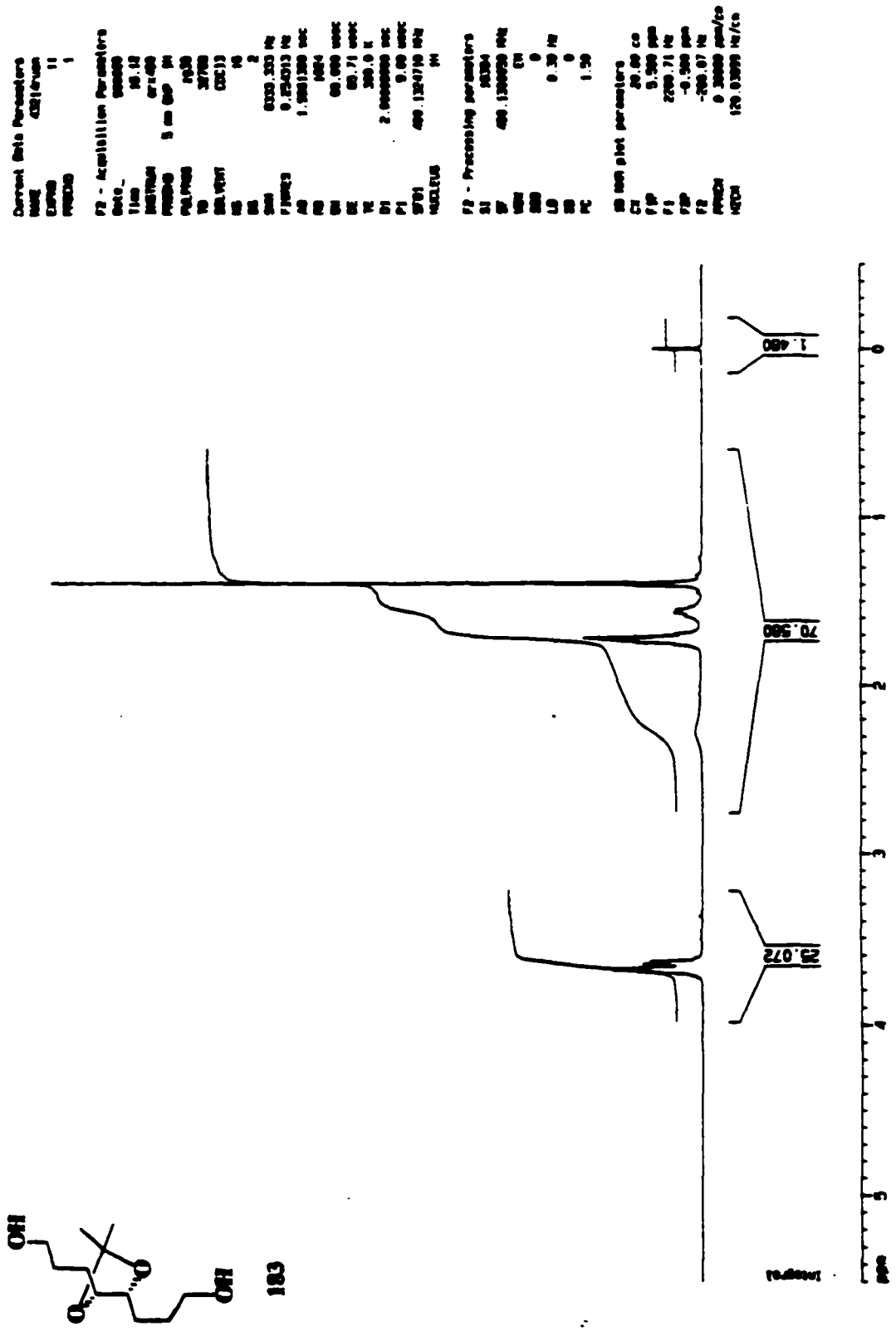

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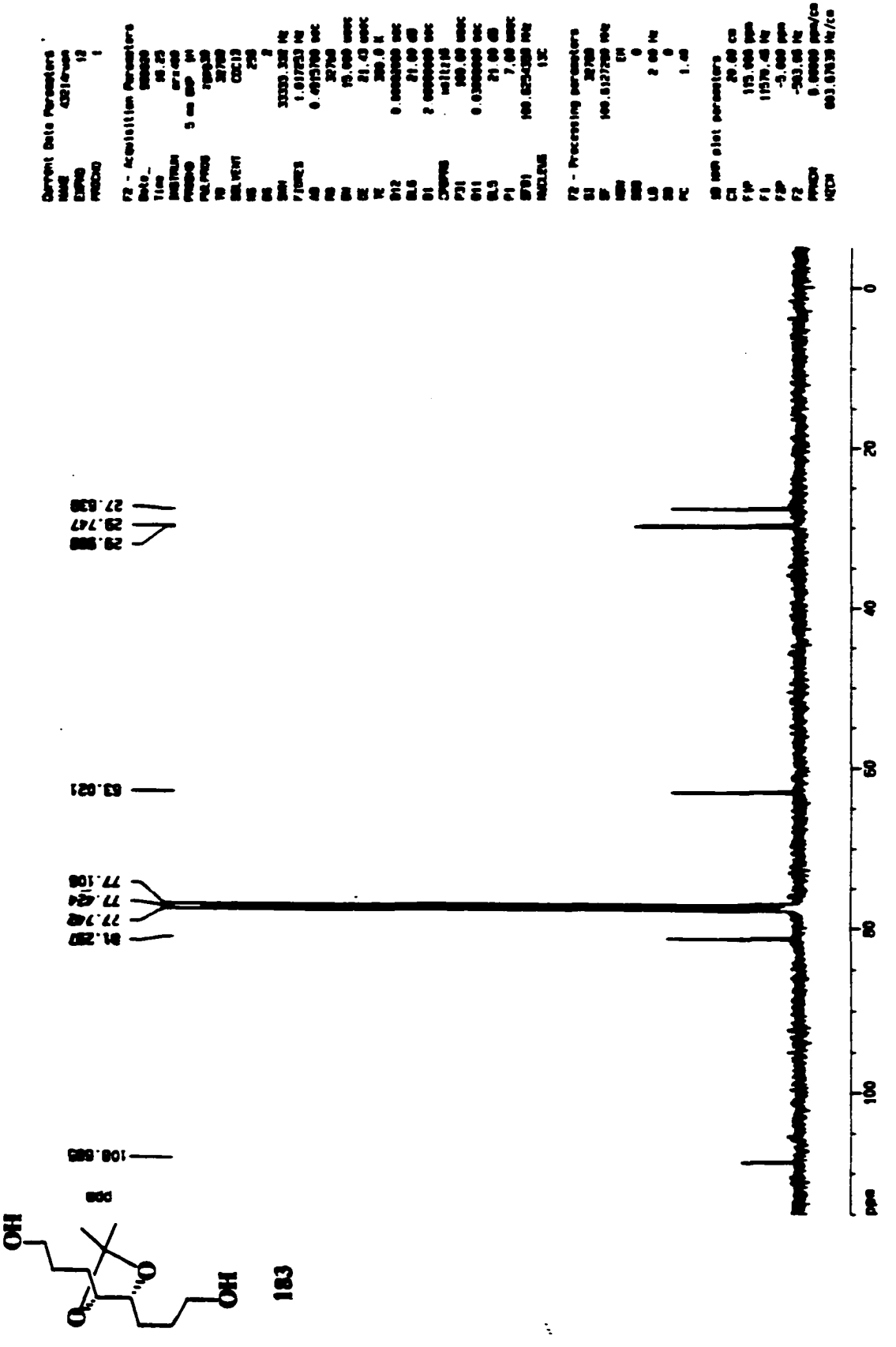

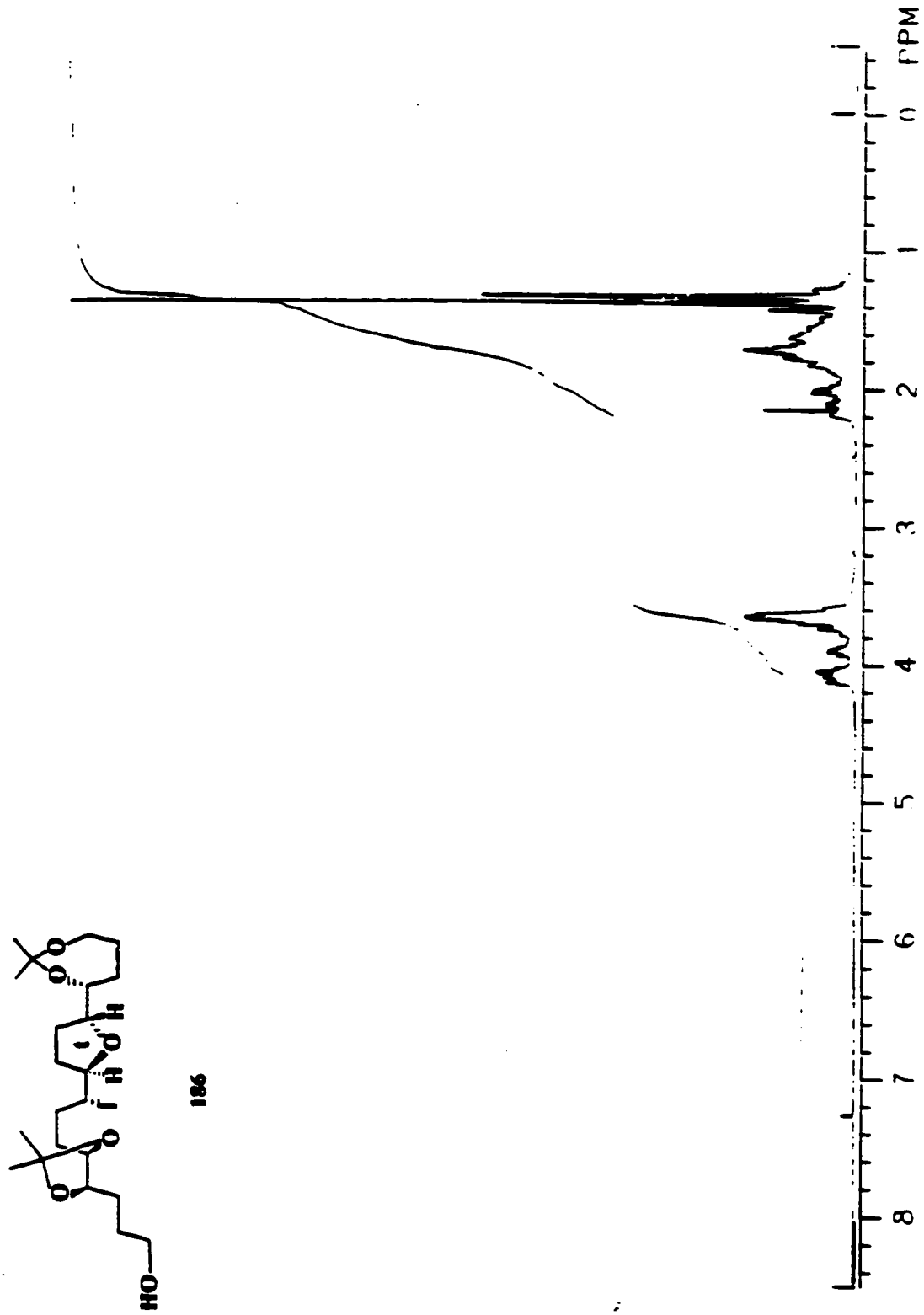

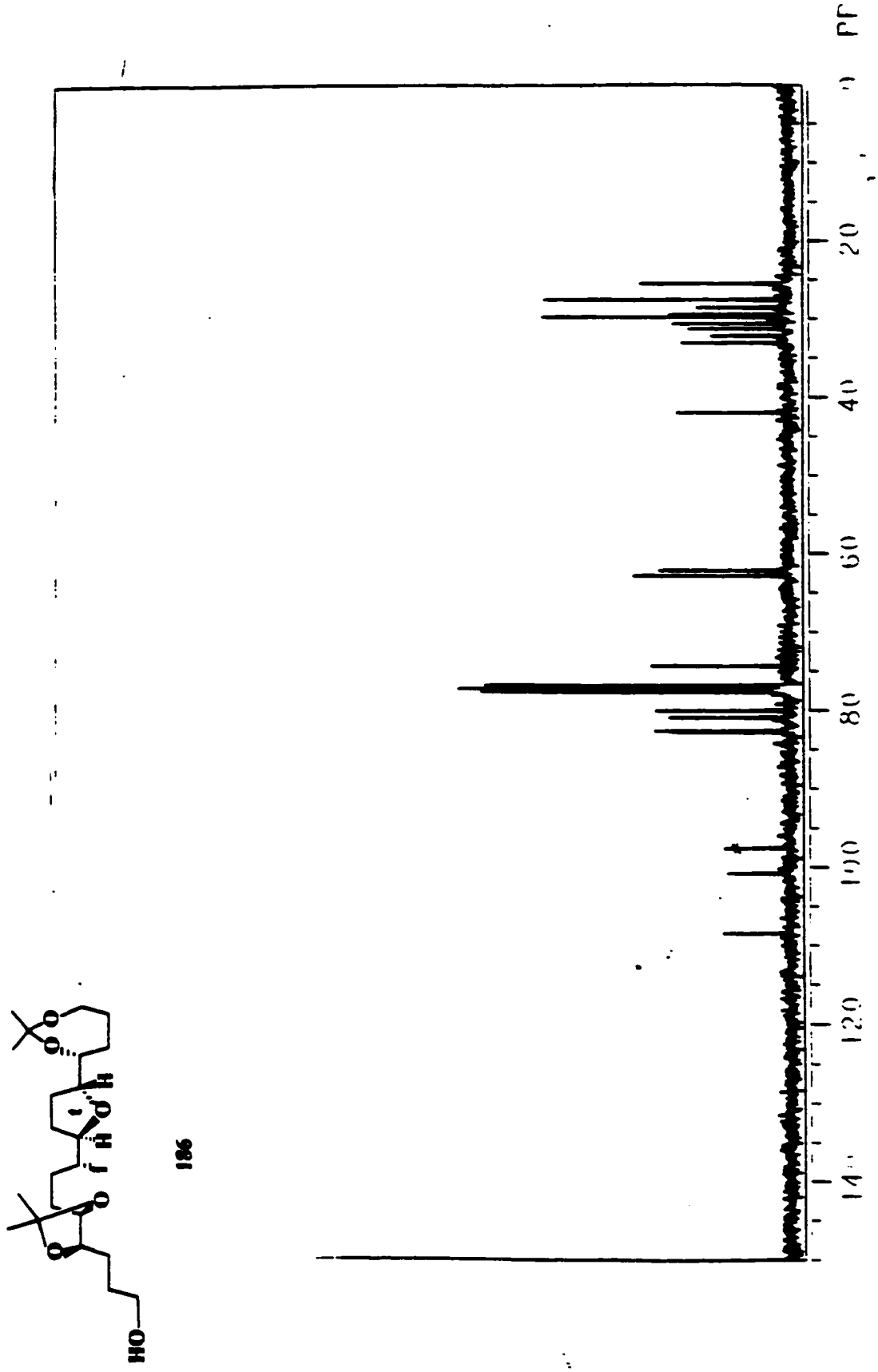

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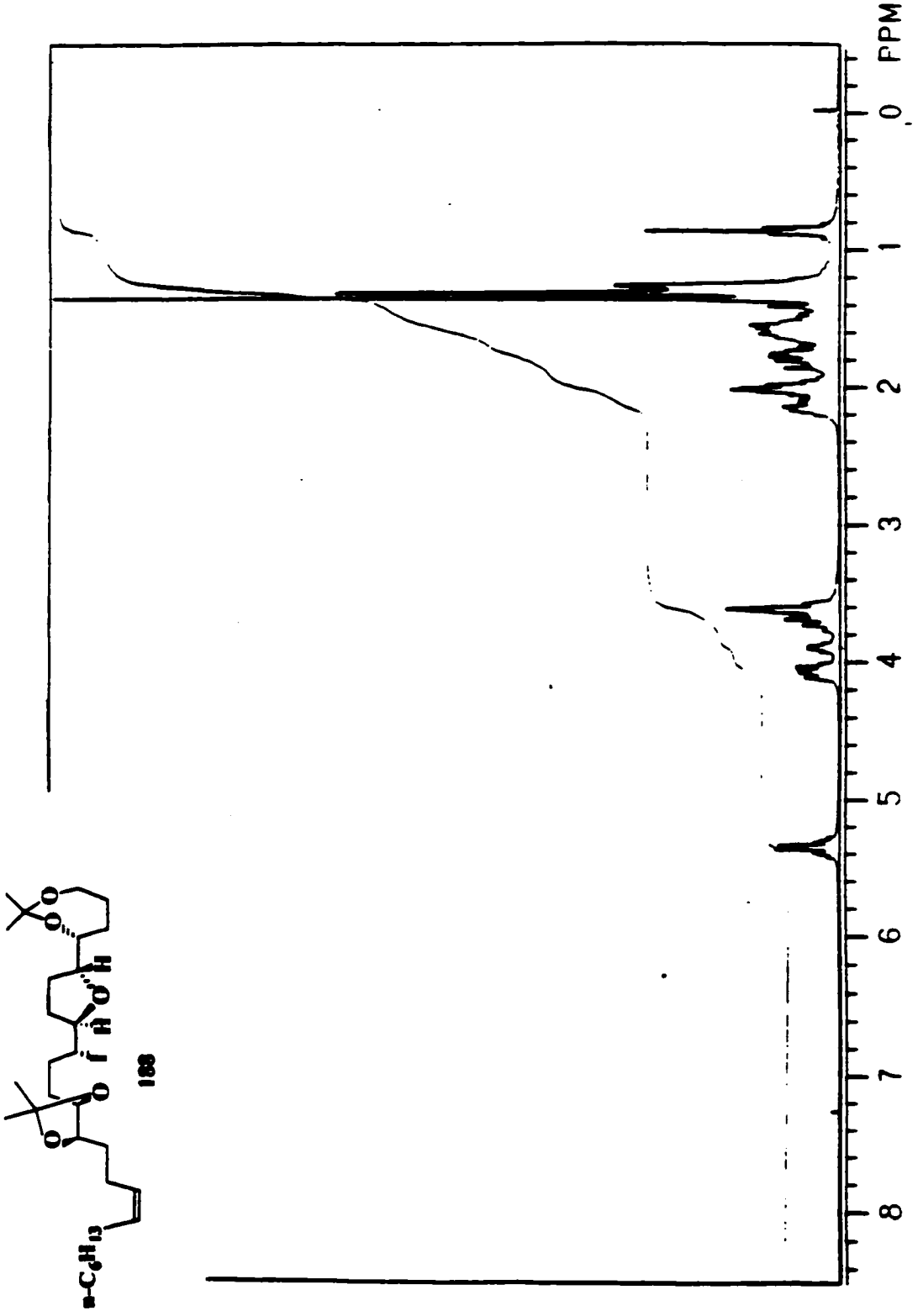

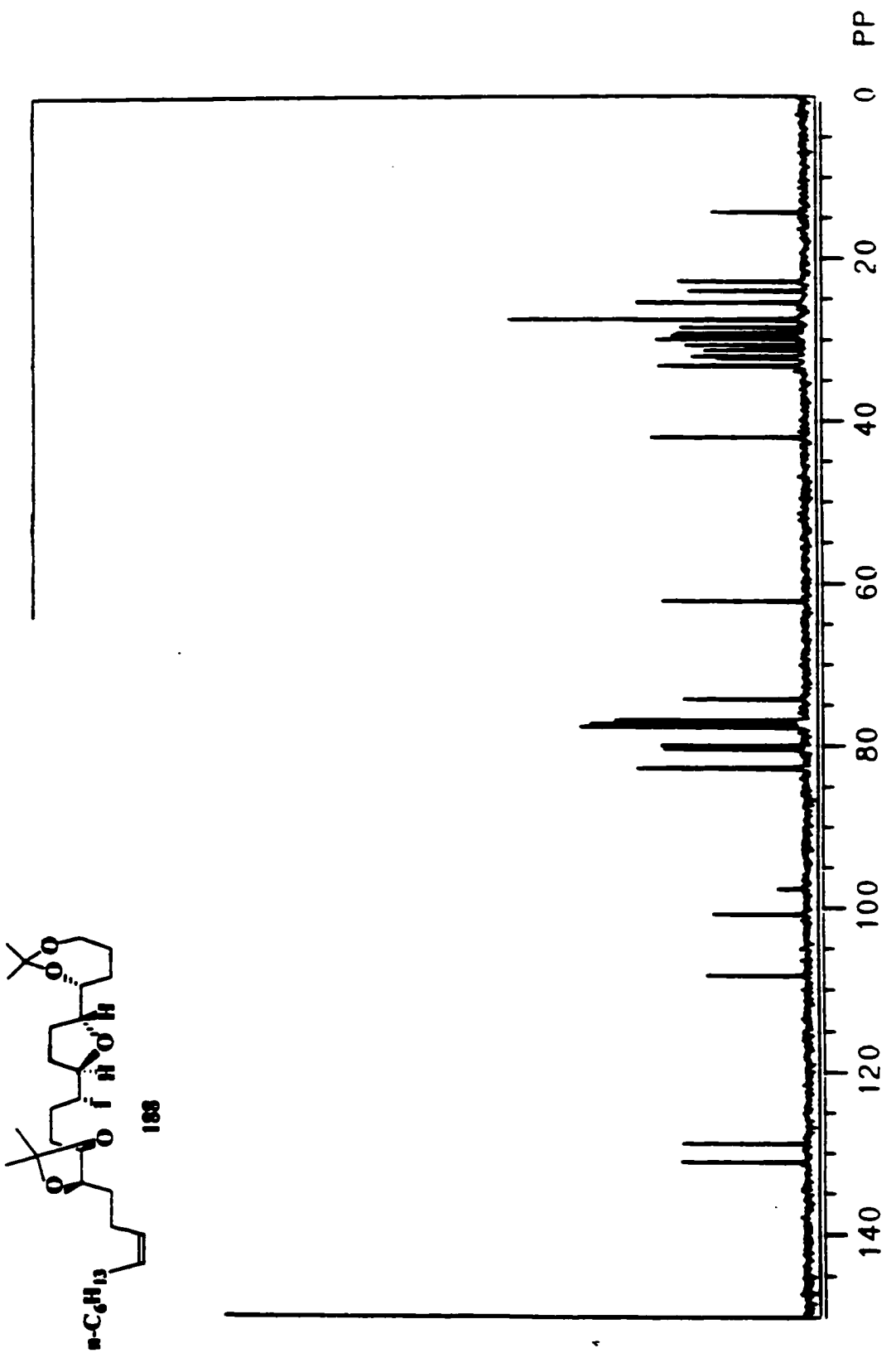

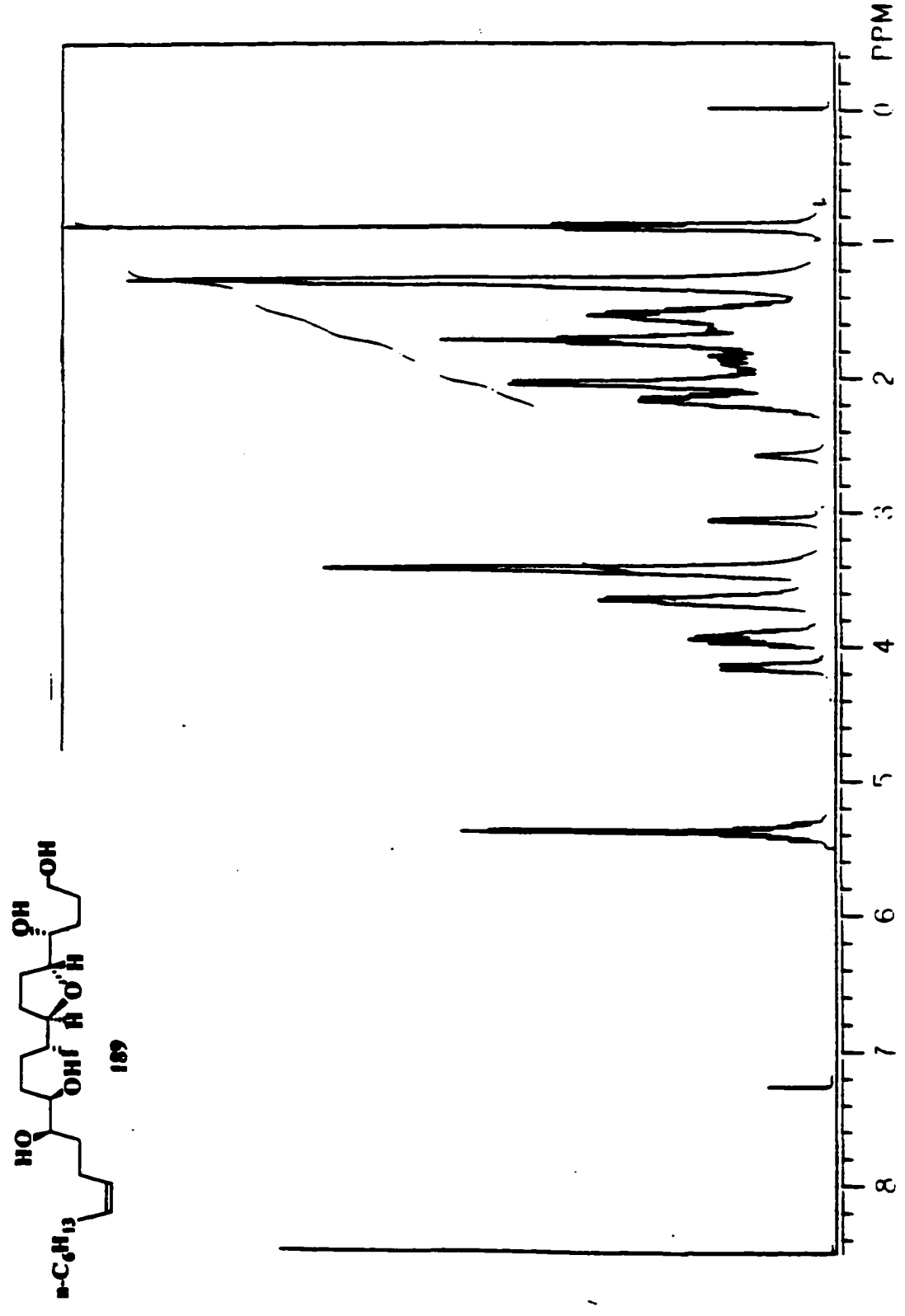

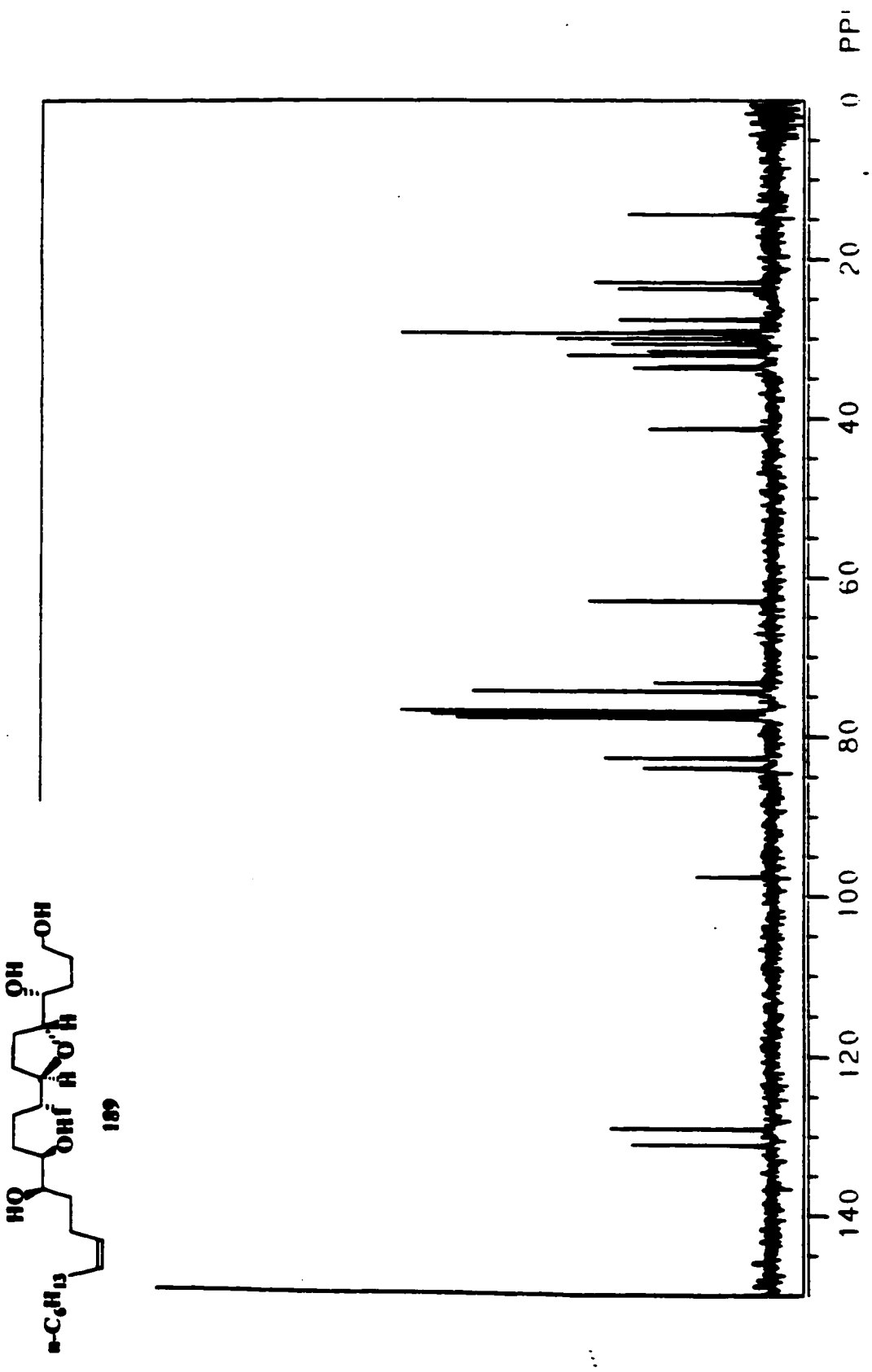

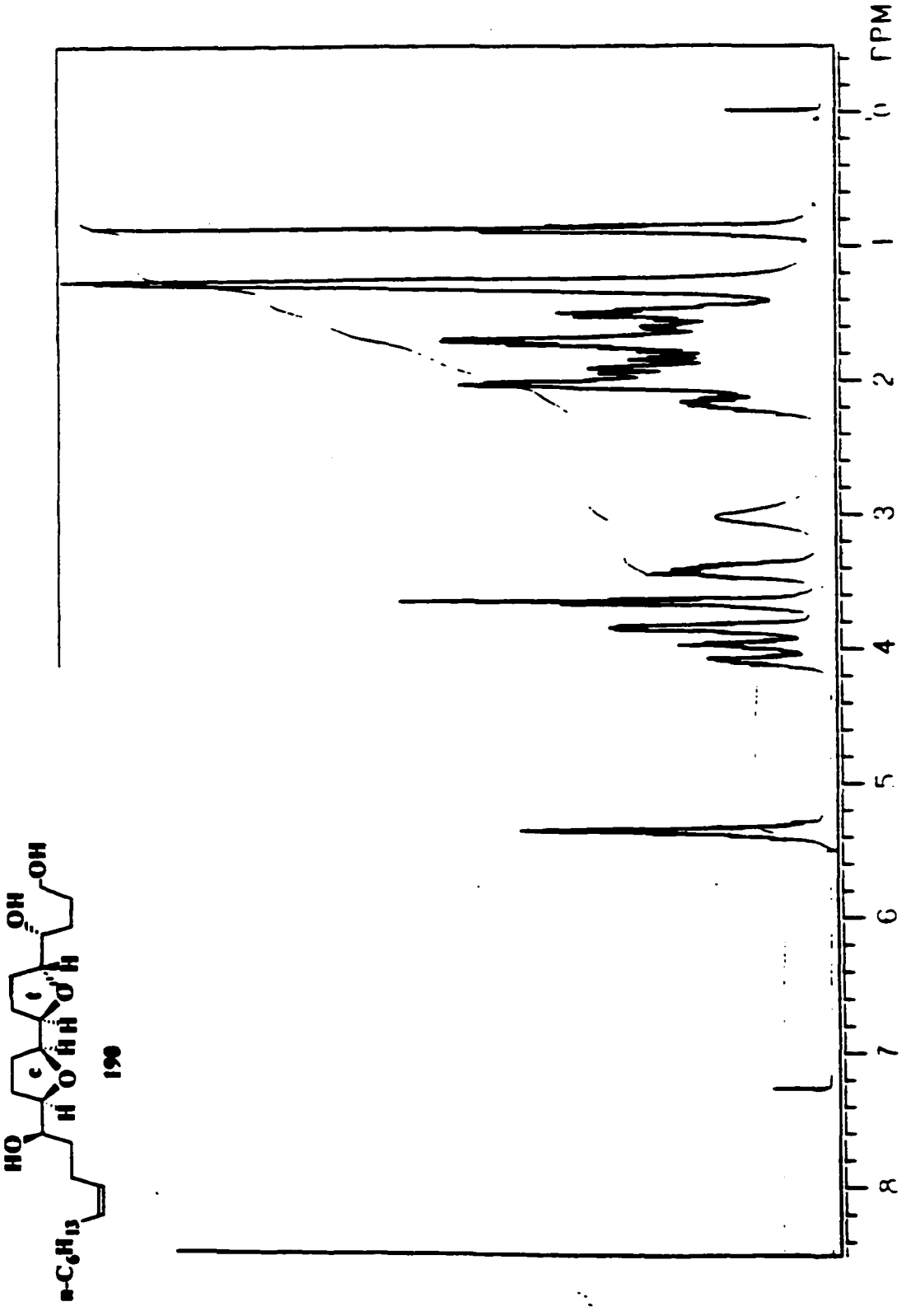

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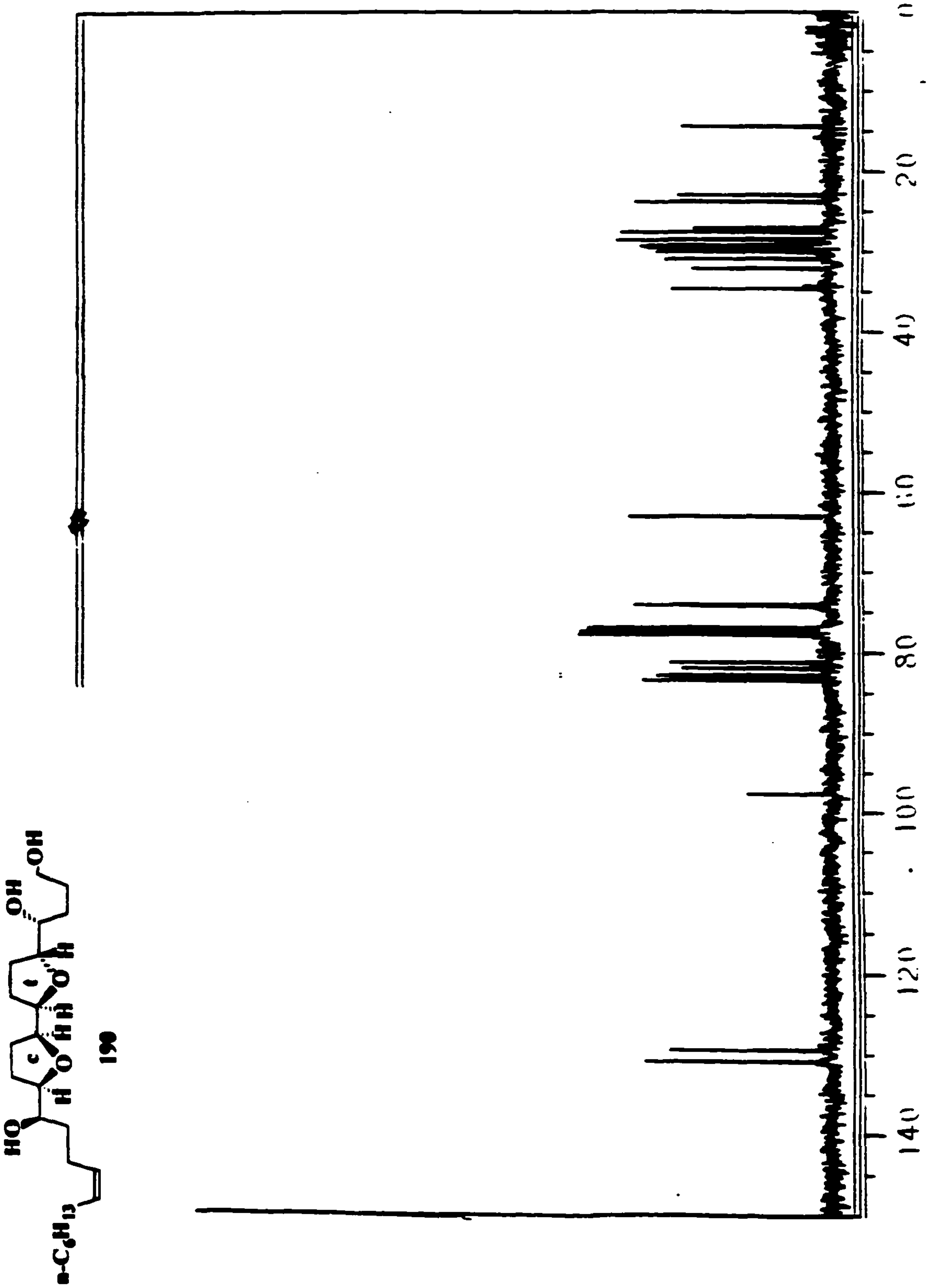

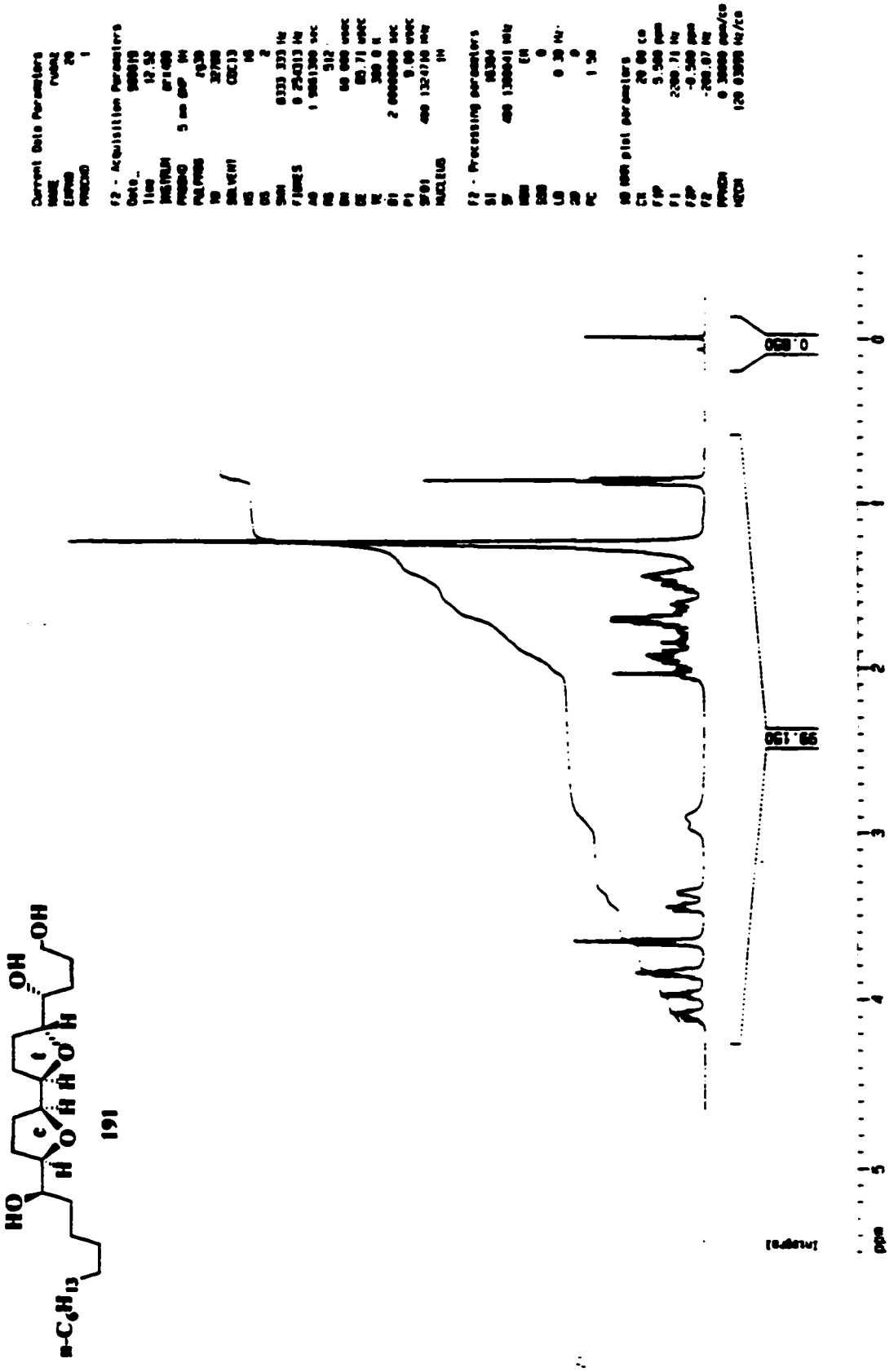

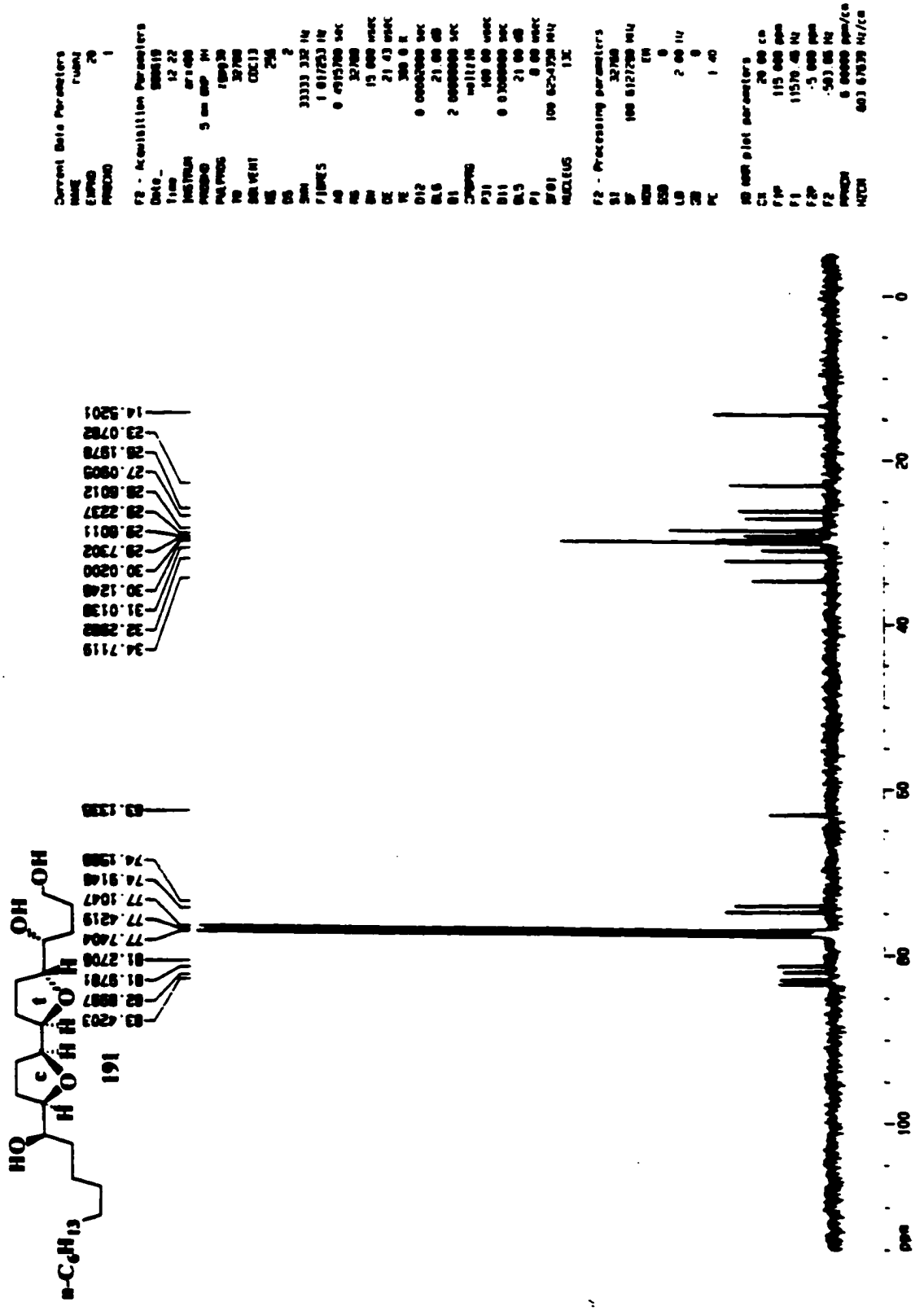

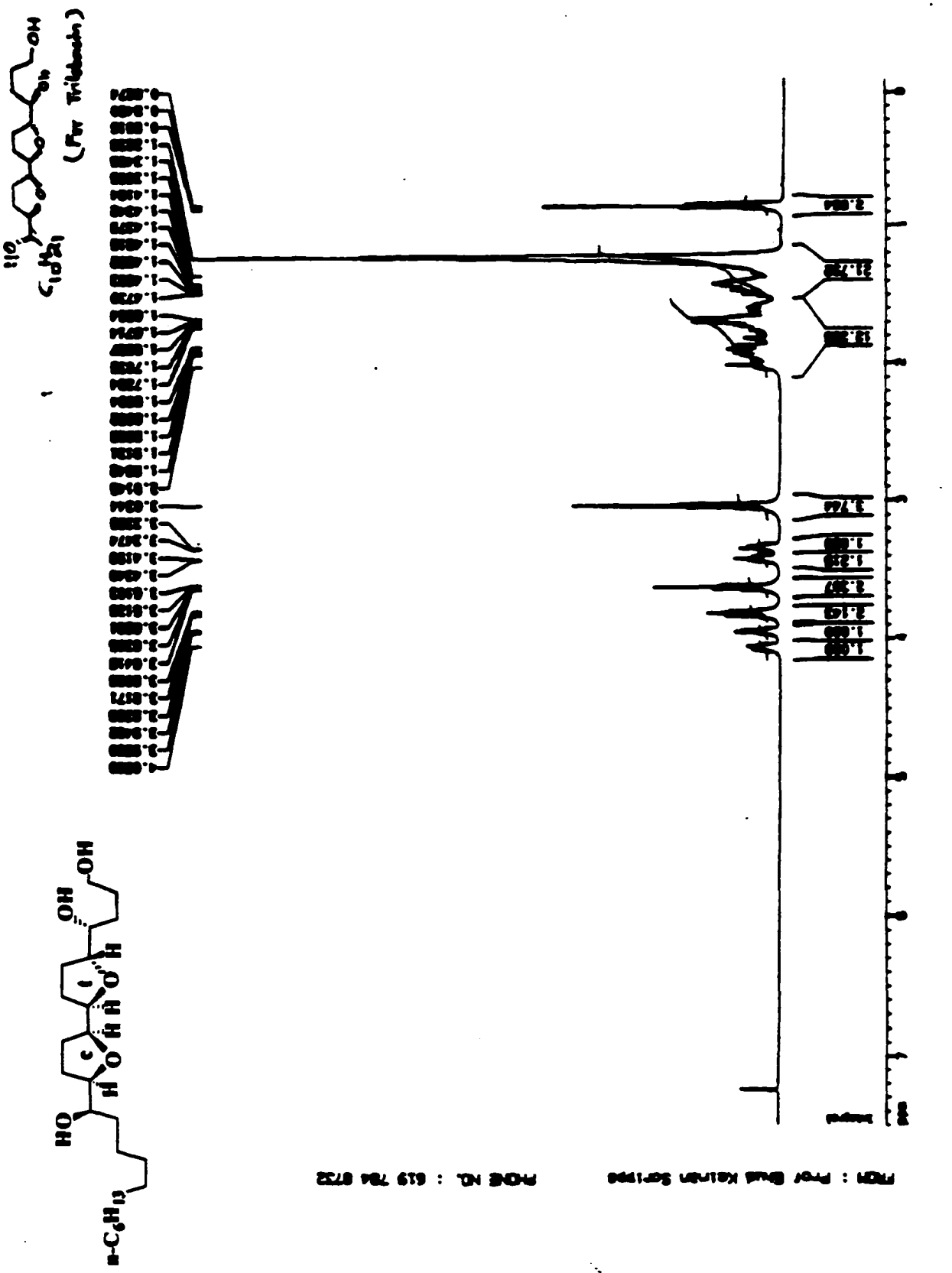

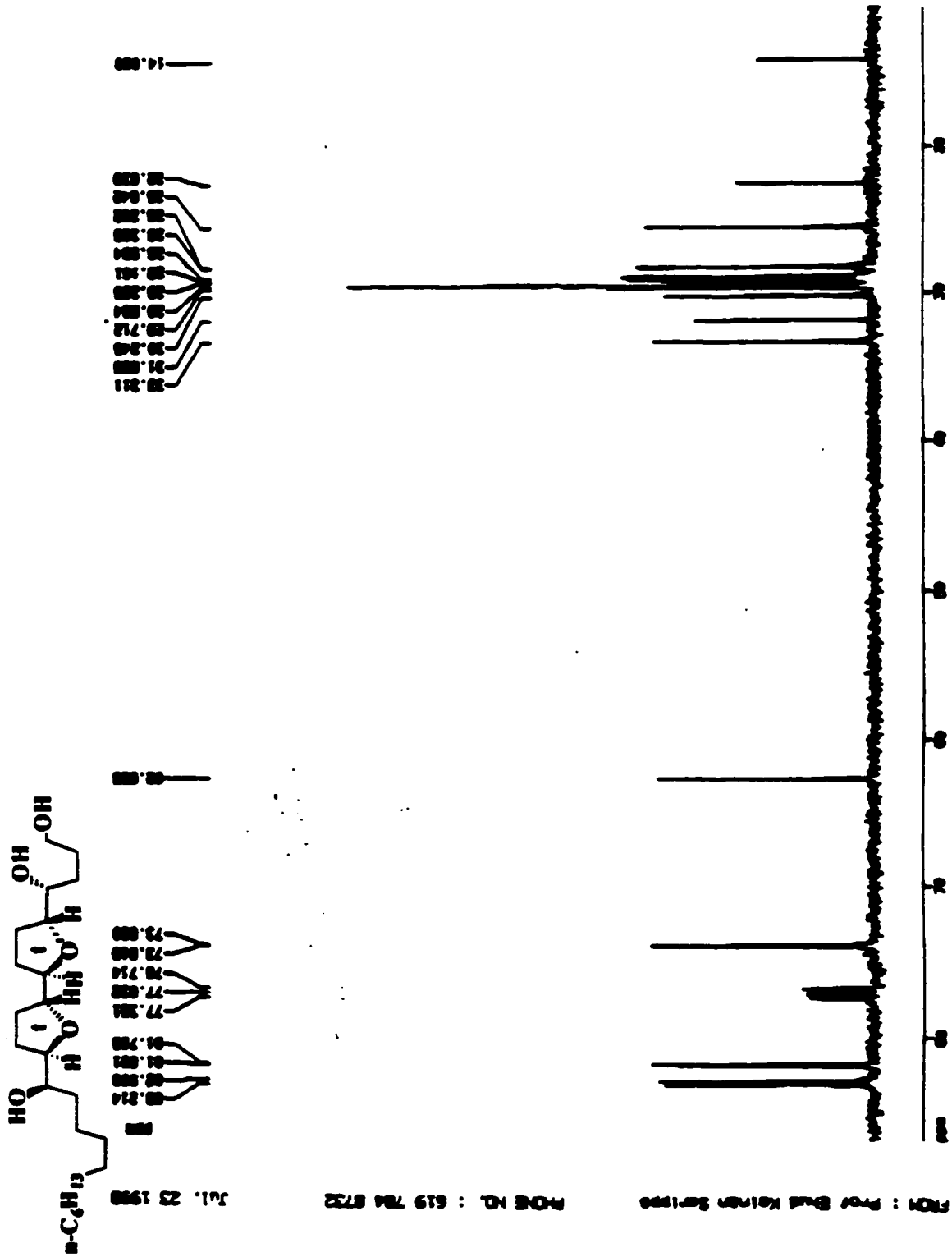

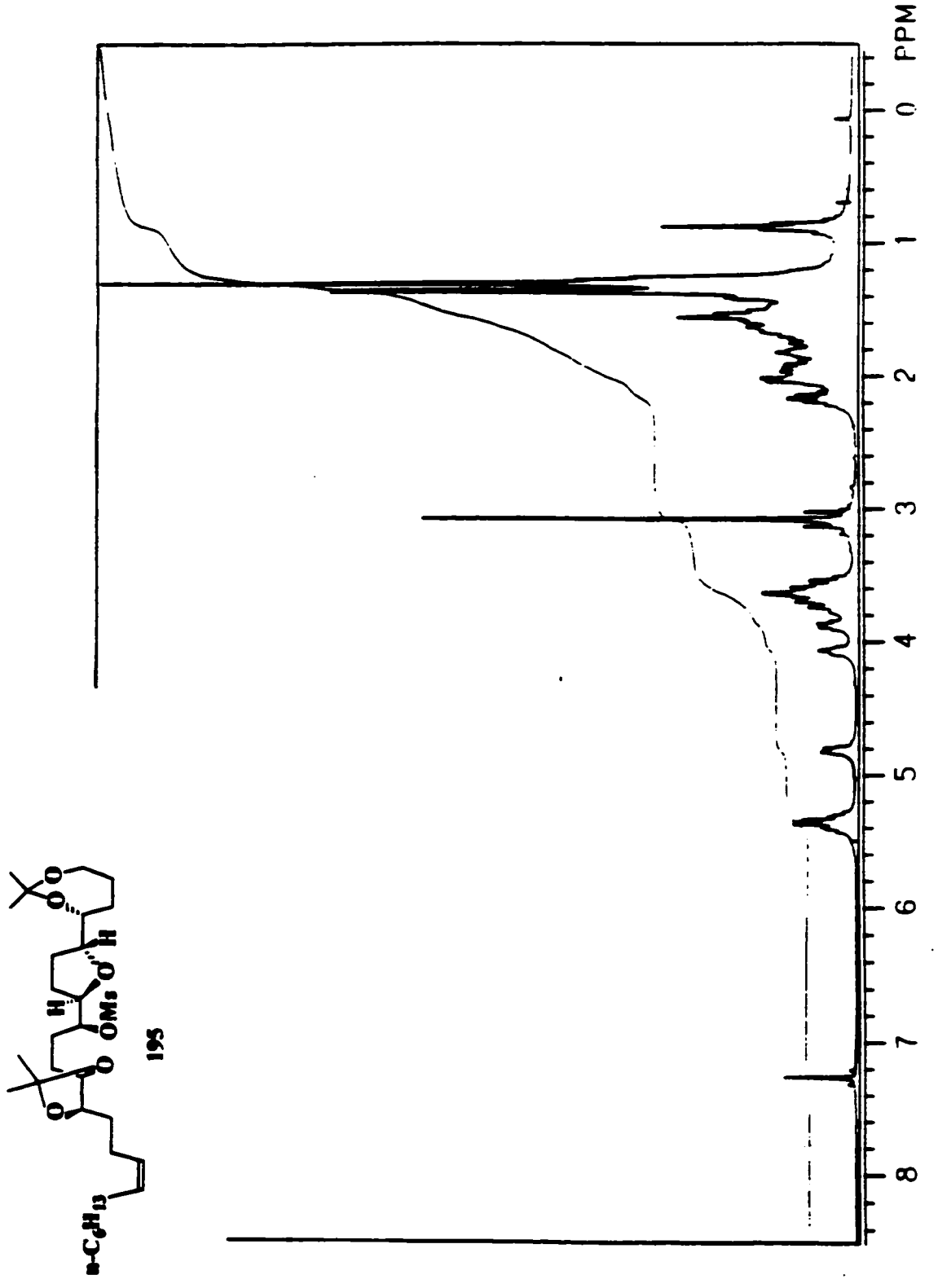

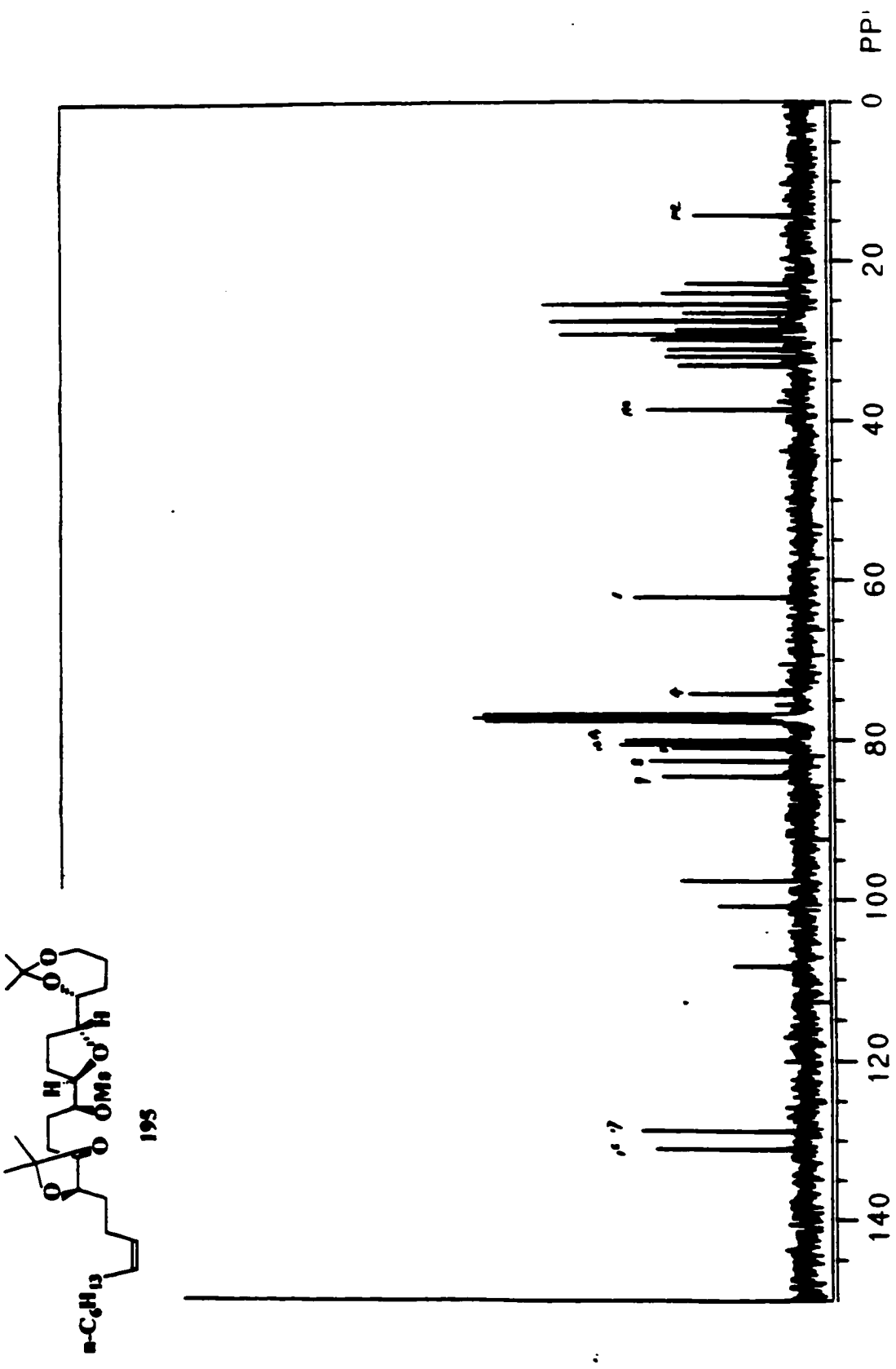

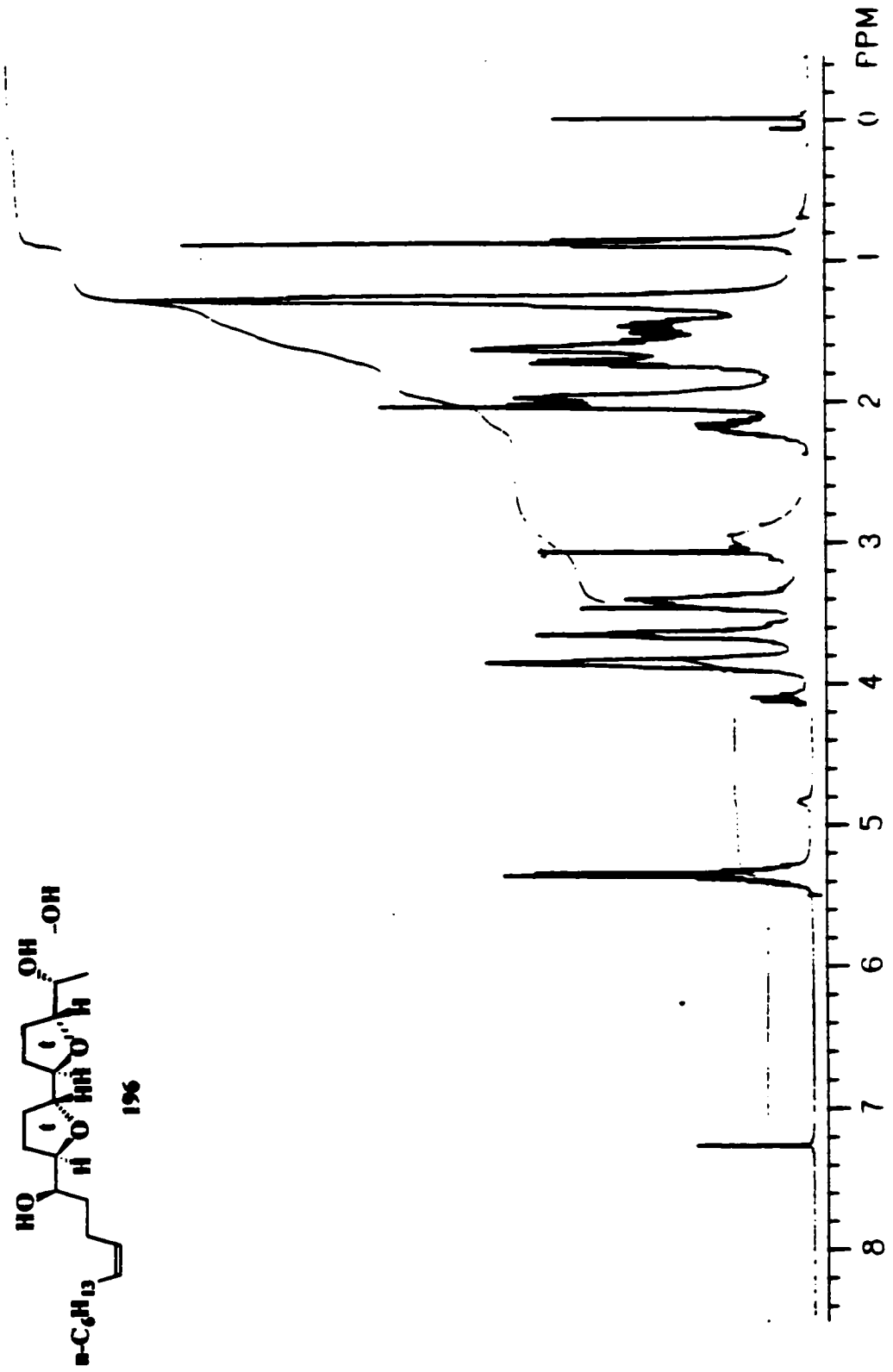

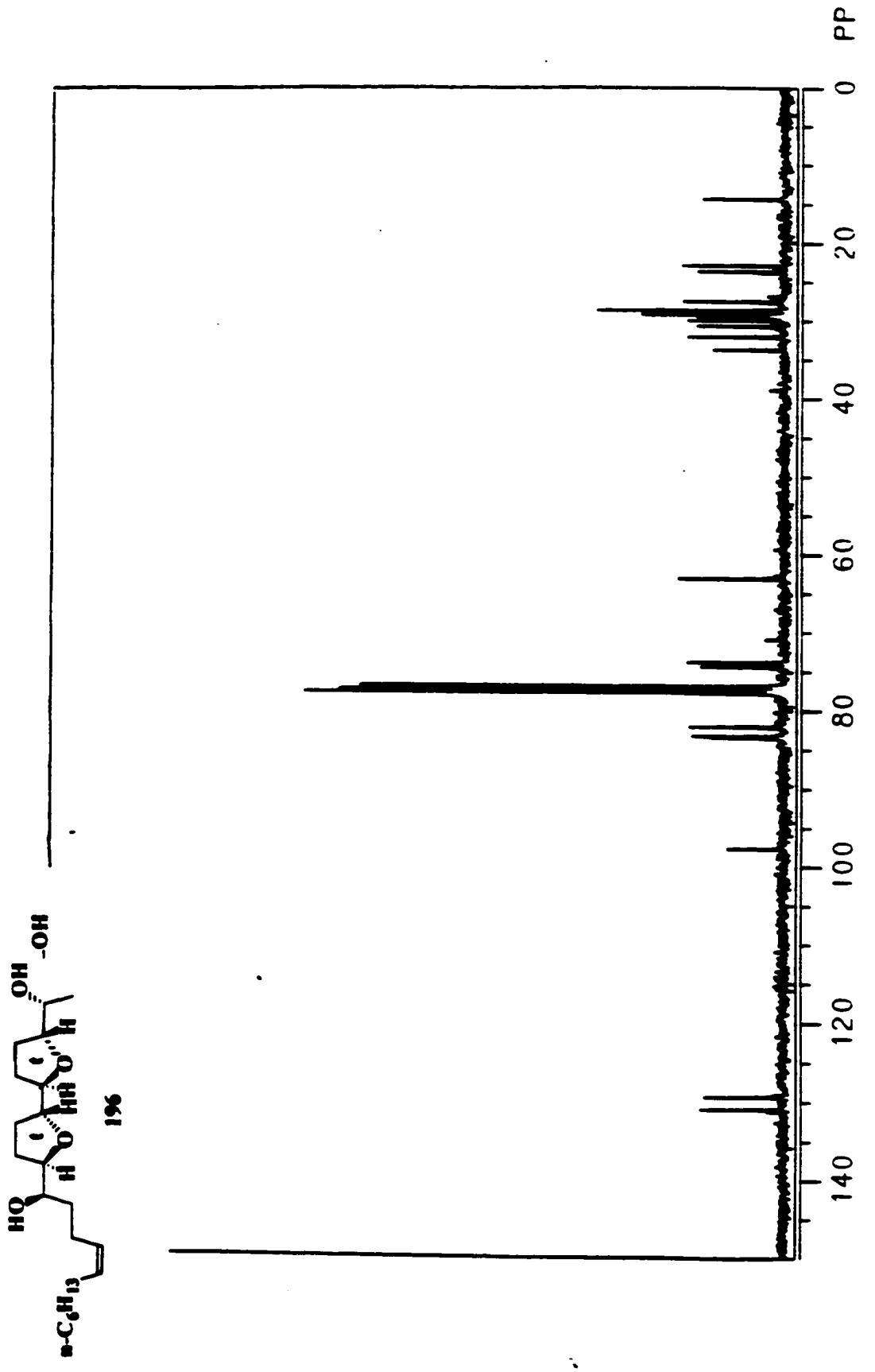

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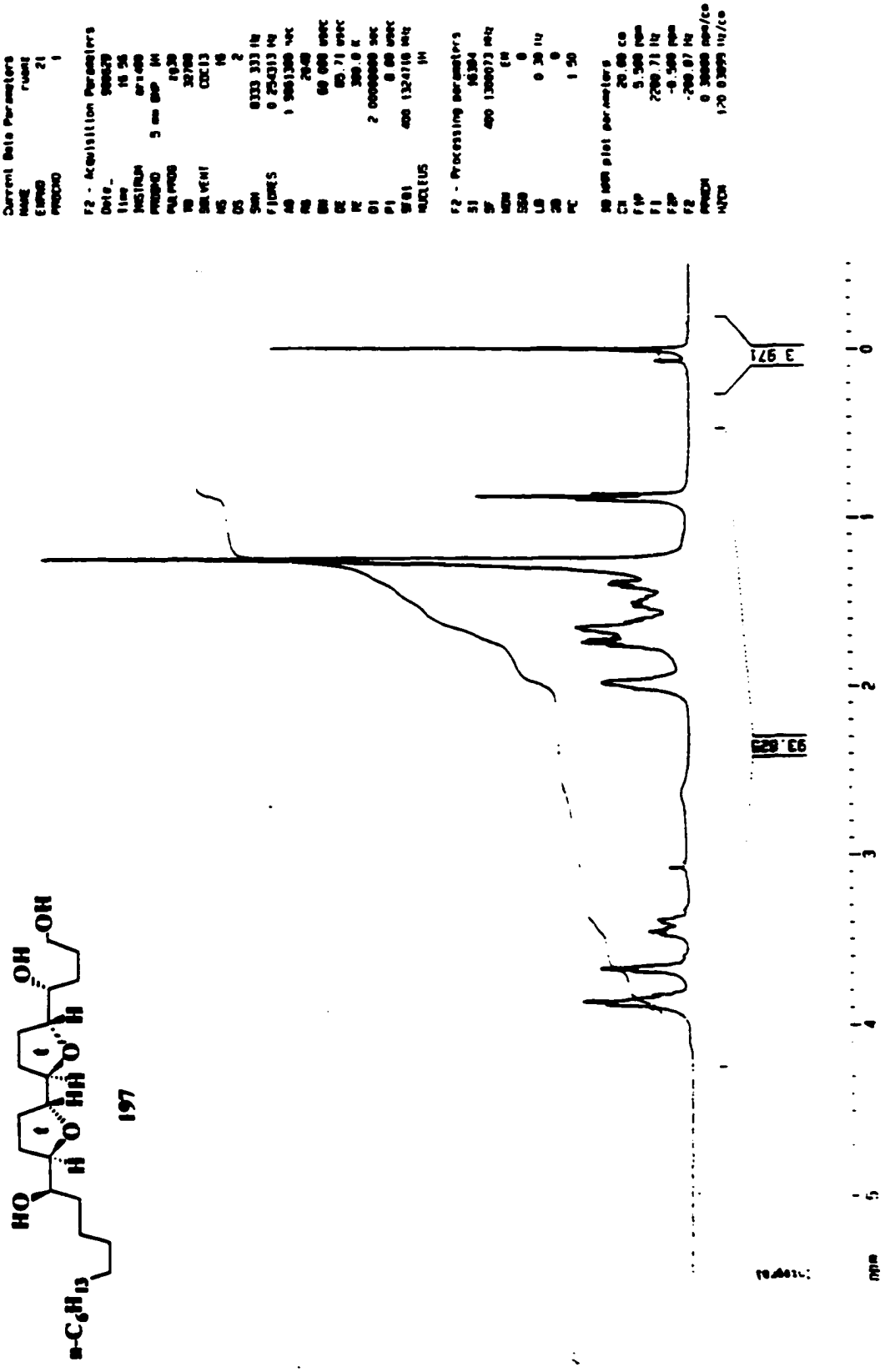

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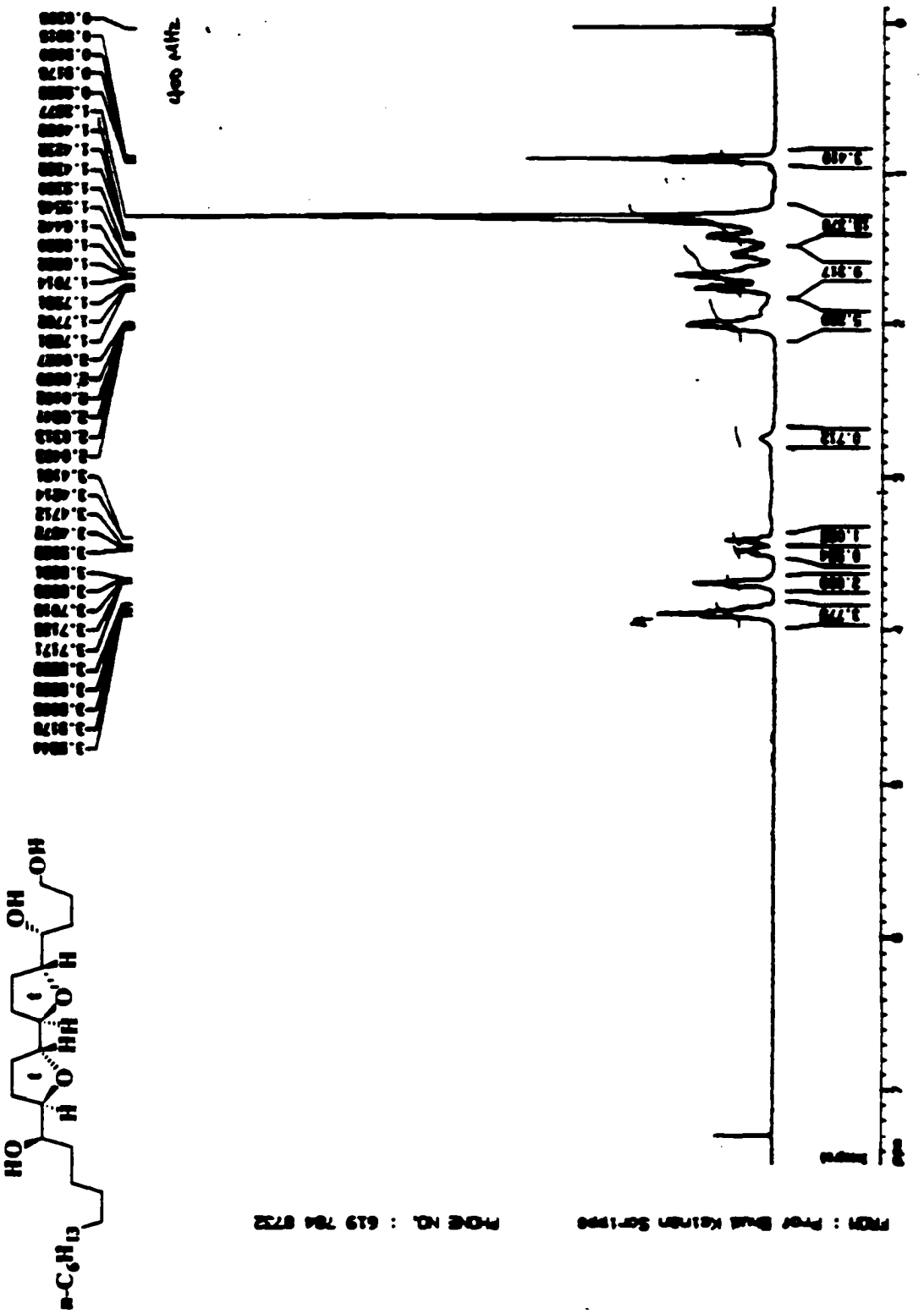

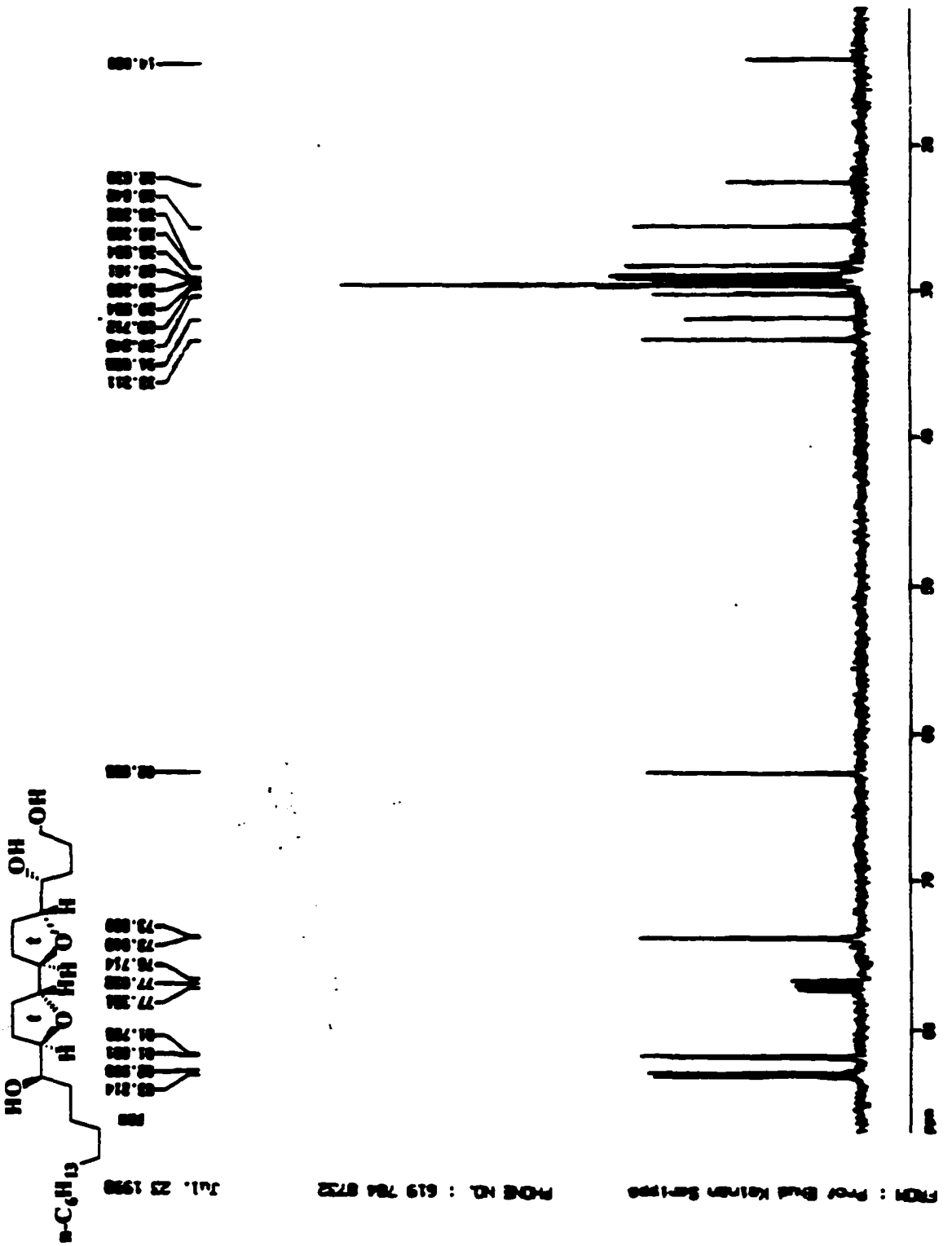

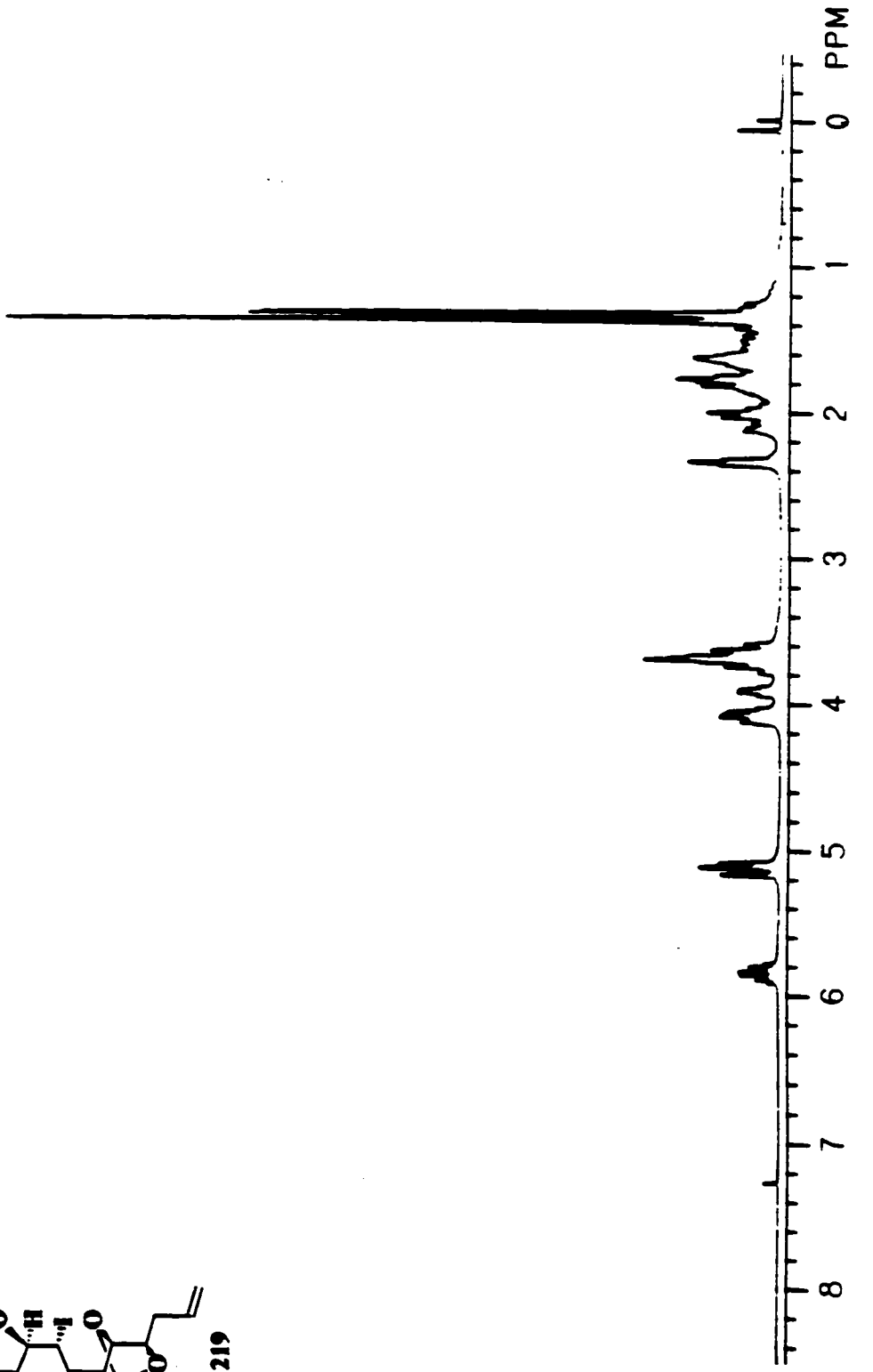

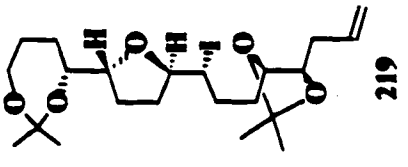

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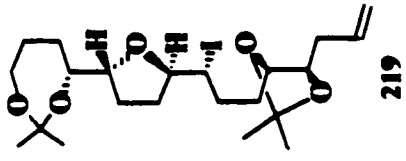

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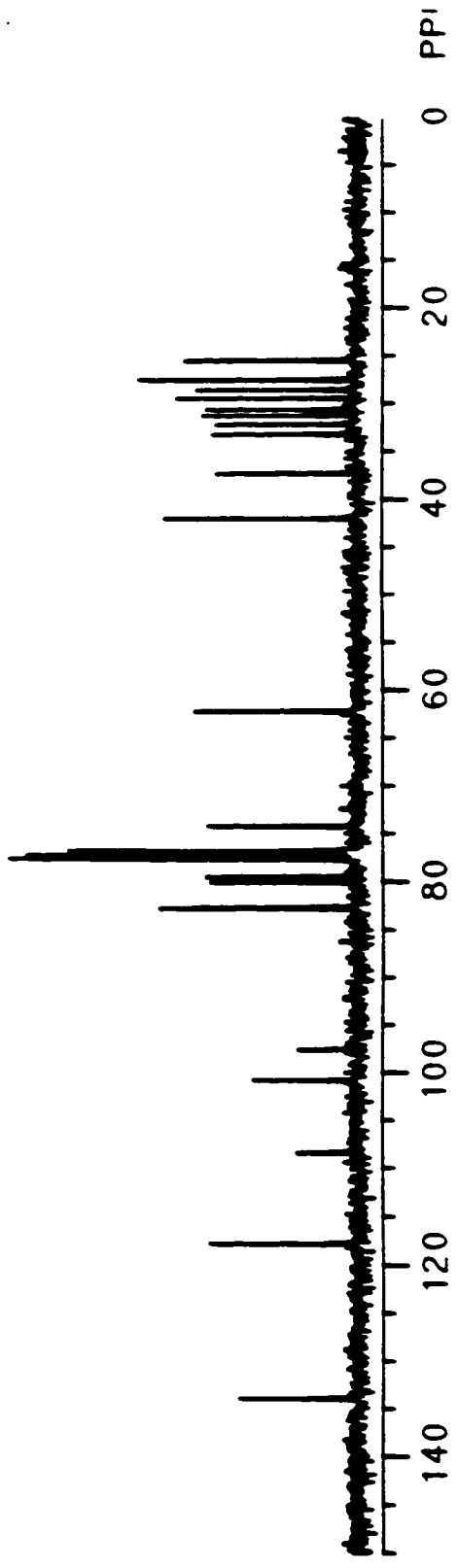

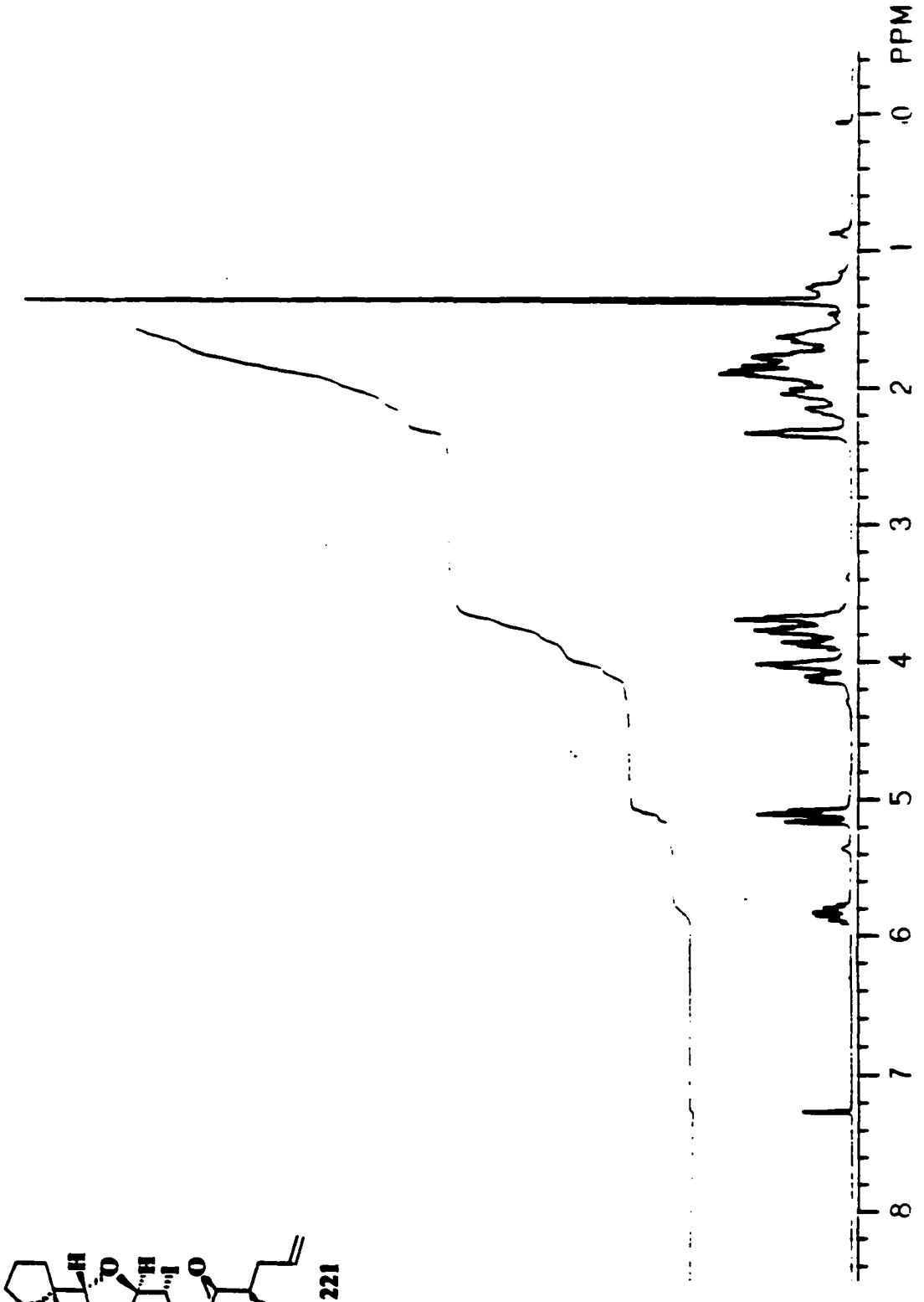

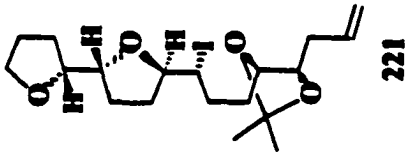

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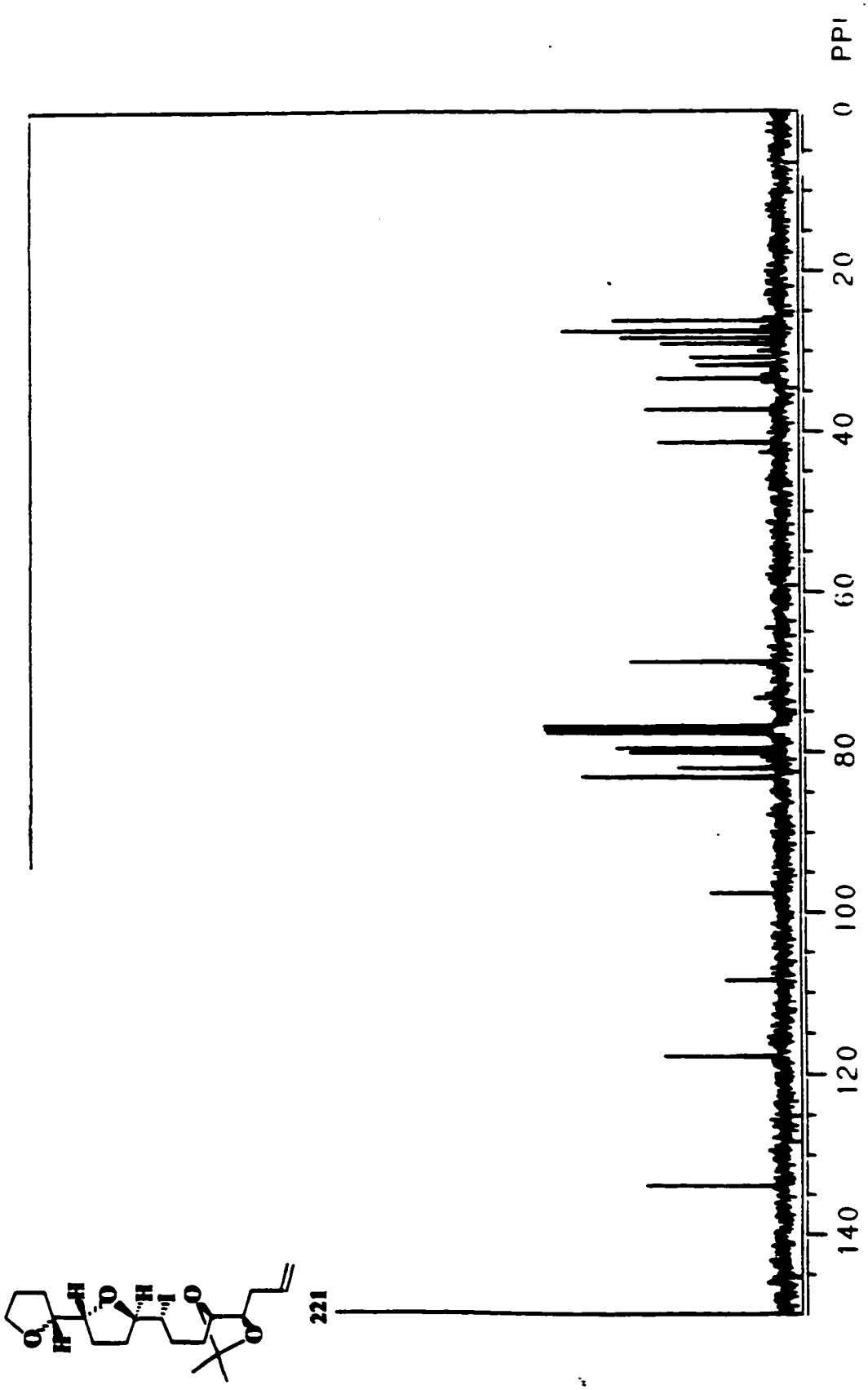

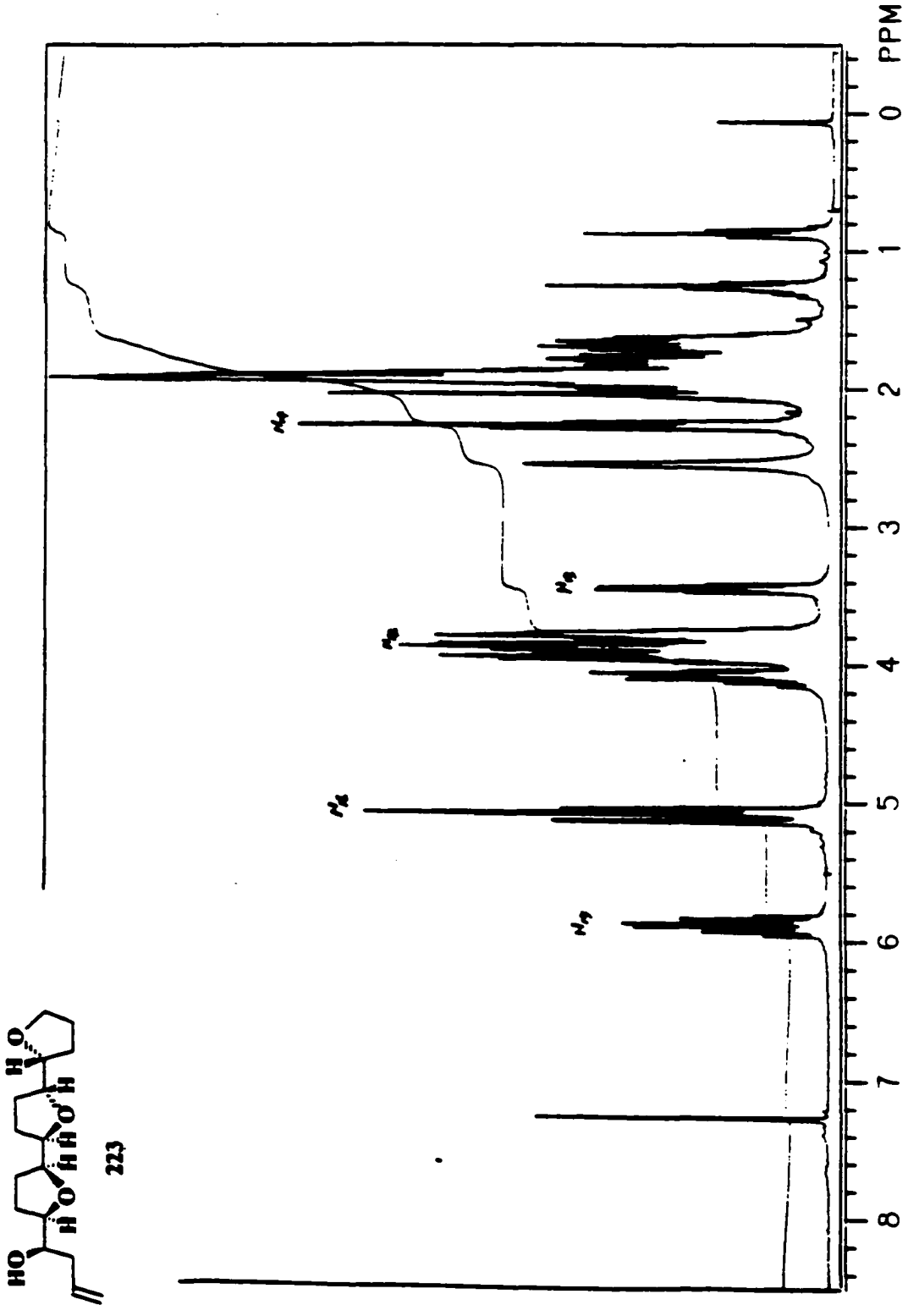

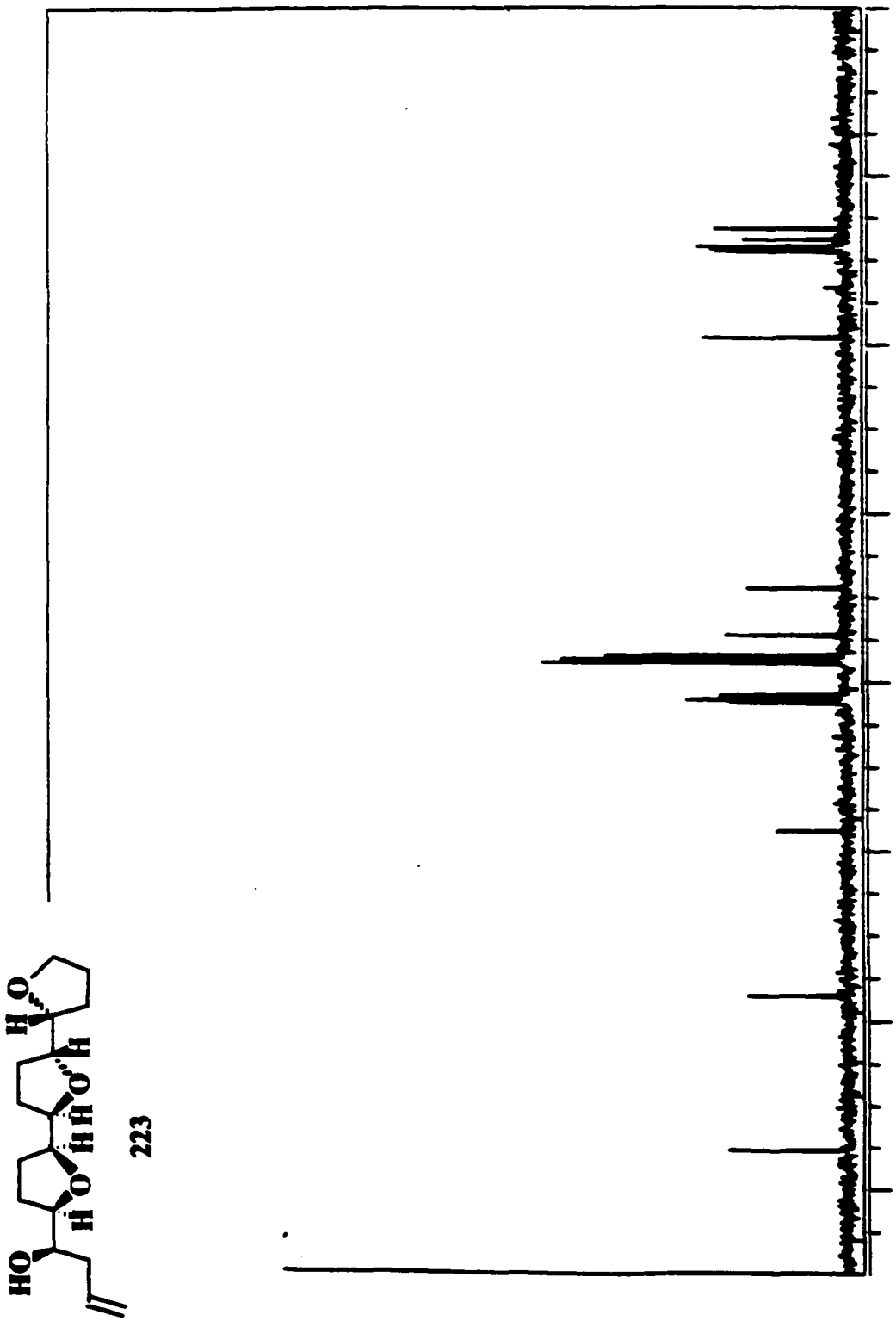

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IMAGE EVALUATION
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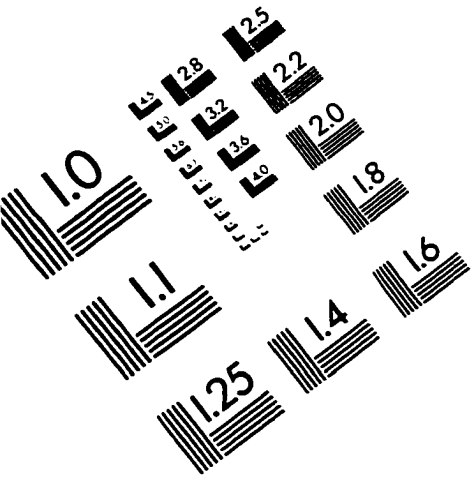

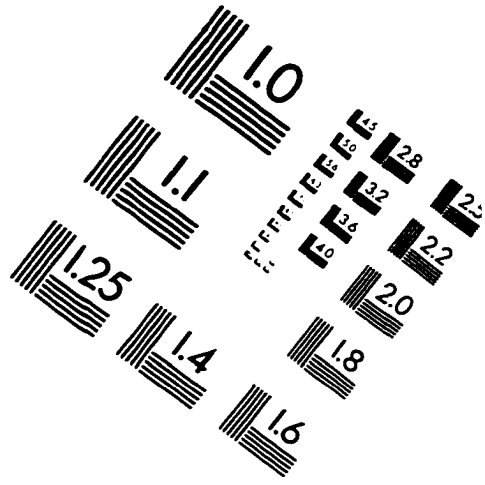

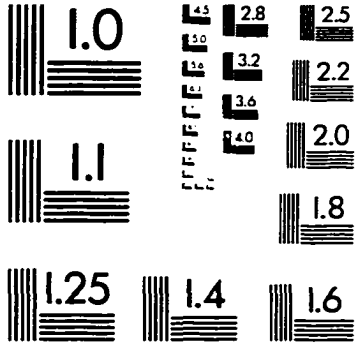

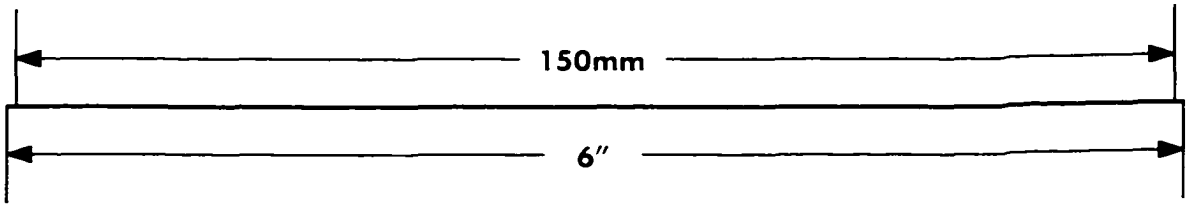

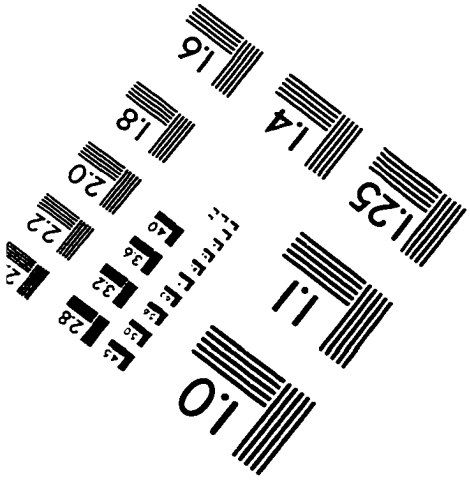

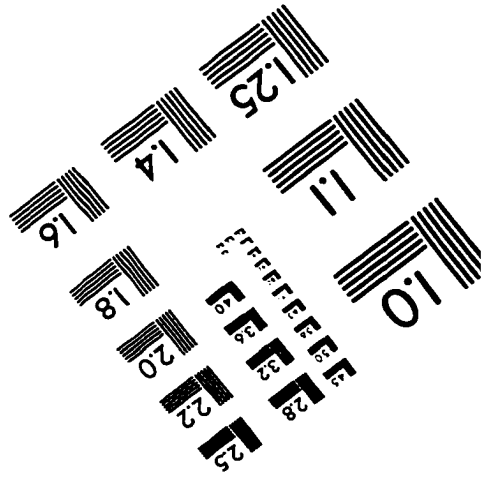

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