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CYCLIC ACETAL TEMPLATES FOR THE STEREOSELECTIVE SYNTHESIS OF 2,5-DISUBSTITUTED TETRAHYDROFURANS (THF'S)

by

HUIPING ZHANG

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

1997

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.

12/6/96
Date

Dr. David R. Mootoo
Chair of Examining Committee

12/10/96
Date

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Executive Committee

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Dr. Klaus G. Grohmann

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

CYCLIC ACETAL TEMPLATES FOR THE STEREOSELECTIVE SYNTHESIS OF 2,5-DISUBSTITUTED TETRAHYDROFURANS (THF'S)

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HUIPING ZHANG

Adviser: Professor David R. Mootoo

The use of cyclic acetals as templates for the stereoselective synthesis of 2,5-disubstituted tetrahydrofuran (THF) was investigated. The study centered on the iodoetherification of hydroxyalkenes which were embedded in C6 allylated 2,3-dideoxy pyranoside or in 5,6-O-isopropylidene alkene substrates. The reactions were performed in wet CH_2Cl_2 or CH_3CN using iodonium perchlorate (IDCP).

In part II, the reactions of C6 allylated 2,3-dideoxy-gluco and galacto-pyranosides are discussed. The effect of aglycone structure and alkene substitution was evaluated. High *cis* stereoselectivity (>10/1 c/t) was achieved in good yield (78-91%) with trityl pyranoside alkenes. A transition state model was proposed to rationalize the observed stereoselectivity. This assumed a preferred chair like reactive conformation involving the four carbon atoms of the eventual THF ring. More substituted pyranoside substrates (galacto, gluco, and manno) were also investigated. Excellent *cis* stereoselectivity and high yields were obtained in galacto series. The gluco and manno systems also gave good yield but with moderate to low stereoselectivity. The application of these results to the synthesis of complex polyether is discussed.

The iodocyclization of 5,6-O-isopropylidene alkenes is described in Part III. These templates gave the trans 2,5-disubstituted THF's in extremely high stereoselectivity and in excellent yields (88-95%). This stereoselectivity is complementary to results achieved with the trityl pyranosides templates.

The trans 2,5-disubstituted THF methodology was applied to the synthesis of THF containing acetogenins. A chiral building block whose structure is primed for elaboration into a variety of naturally mono and bis-THF acetogenins, was prepared in a concise and straightforward procedure. The synthesis was carried out in 8 steps and in 46% overall yield from 4-benzyloxybutanal. It capitalizes on the enantioselectivity and regioselectivity of the Sharpless asymmetric dihydroxylation and the high *trans* selective iodoetherification of 5,6-O-isopropylidene alkenes.

To

Mom and Dad

ACKNOWLEDGMENTS

The author is particularly indebted to his mentor Dr. David R. Mootoo for his guidance and encouragement throughout the course of graduate studies.

The author would like to extend his sincerest thanks to his committee members Professor Klaus G. Grohmann and Professor Arthur D. Baker for their many suggestions. Thanks are extended to Dr. Micheal Blumenstein, Dr. Clifford Soll, and his fellow graduate students and colleagues.

Finally, thanks are also due to his wife Yuequn for her great patience and understanding.

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PART I

GENERAL INTRODUCTION

I.1. **Background**

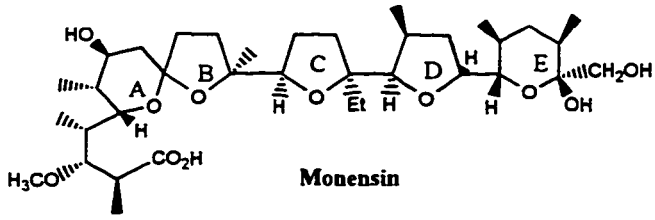
2,5-disubstituted THF rings are found in a wide variety of natural products. Among the well known groups are the ionophore antibiotics which number over 500 natural and unnatural derivatives. In addition to adjacently linked cyclic ethers, they usually contain highly substituted acyclic fragments and intricate spiroketal systems (Fig.1-2). Their biological activity, pharmacology and chemistry have been extensively studied. They are noted for a wide range of biological activities, including ruminant growth promotion[1], coccidiostatic activity[2], mammalian cardiovascular effect[3] and anti-HIV activity[4]. Specifically, monesin (Fig.1) and the ionophore A 204 (Fig 2) inhibit the growth of *Bacillus subtilis* and *Mycobaterium avium* at levels as low as 2.75 and 1.25 μg/ml, respectively[1,5]. It is believed that they promote ion transfer across lipid membranes through cation chelation, and this leads to *trans* membrane ionic imbalances which might be the basis for their activity.[6]

Recently, a number of less complex THF products have been isolated from the genera of *Annonoceae* plants.[7] Over 200 members of this family are now known since the discovery of the first derivatives in 1982. They are characterized by the presence of one, or more than one *cis* or *trans* 2,5-disubstituted THF ring which is usually flanked by a secondary carbinol center. In the case of the mono-THF structures (Fig. 3-4) these positions are attached to hydrocarbon chains, one of which terminates in a butenolide. In the bis-THF derivatives (Fig. 5-7), the chain tethered to the butenolide contains a second THF residue which may be adjacently or non-adjacently linked to the first-THF. In

addition to the number and connectivity of THF rings, structures vary with respect to the length and degree of oxygenation of the hydrocarbon chains and the relative and absolute stereochemistry of the THF subunits.

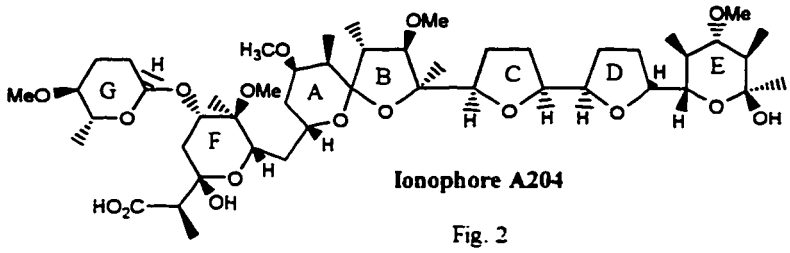
The THF acetogenins have attracted much attention because of their diverse biological effects. Biochemical studies have revealed potent cytotoxic, pesticidal, insect antifeedant, antimalarial, T-cell suppressant, antiparasitic, and antimicrobial activities[7]. For example, *in vivo* antitumour activity shows bullatacin (Fig. 5) to be 300 times as potent as paclitaxol while showing similar positive antileukaemic effects[8]. Studies have shown that biological activity is influenced by the absolute and relative stereochemistry, the degree and the pattern of oxygenation and the number of THF rings.

A major part of the synthesis of the aforementioned groups of natural products is the stereoselective synthesis of 2,5 disubstituted THF's containing highly functionalized branches. Several methodologies have been reported [9-10]. The main aspects of the more noteworthy strategies will be discussed.



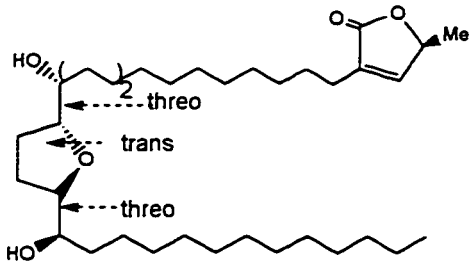
Monensin

Fig. 1



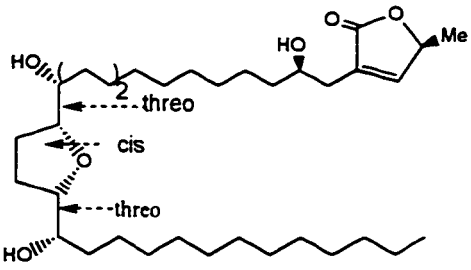
Ionophore A204

Fig. 2



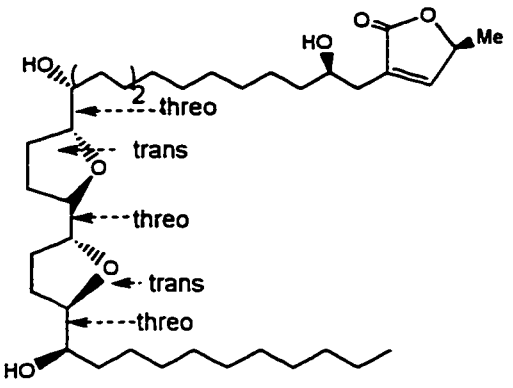
Solamin

Fig. 3



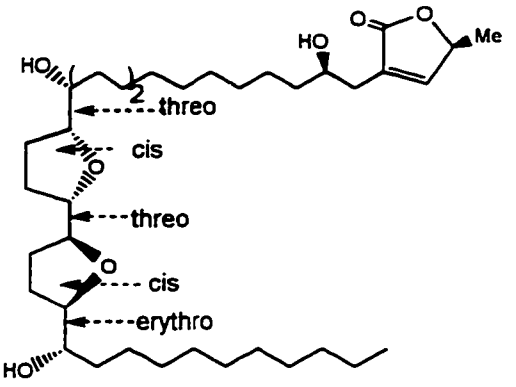
cis-annonacin-10-one

Fig. 4



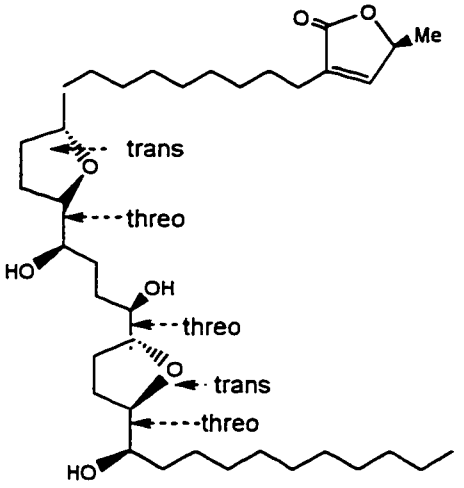
Bullatacin

Fig. 5



Rolliniastatin

Fig. 6



Squamostatins

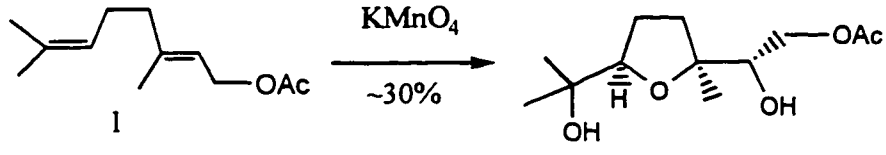
Fig. 7

I.2. Synthetic Routes to 2,5-Disubstituted Tetrahydrofurans

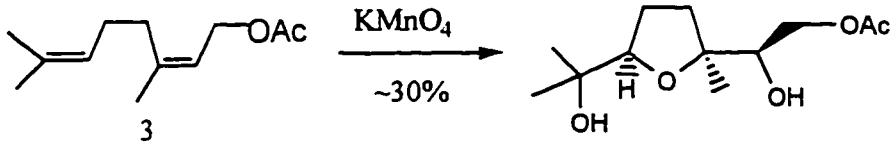
I.2.1 Oxidative Cyclization of Alkenes

1,5-Dienes and 5,6-Dihydroxy alkenes: The pioneering work is due to Klein and Rojahn[11]. In 1965, they reported that 1,5- dienes, geranyl acetate **1** and neryl acetate **3**, when treated with $KMnO_4$ gave stereo-specifically the *cis* 2,5-bis hydroxyl-methyl-tetrahydrofurans **2** and **4** (Scheme 1). The normal tetrol oxidation products were not observed.

Scheme 1:



1 2



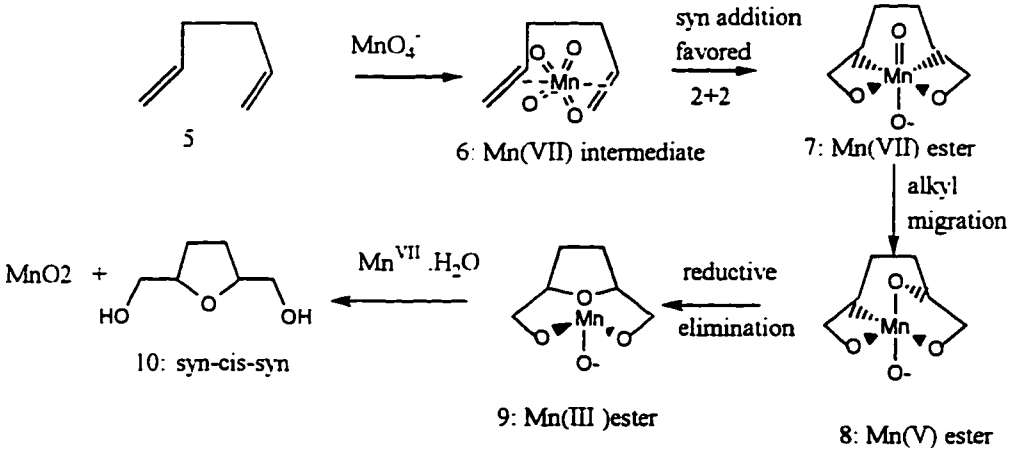
3 4

The stereospecificity of these reaction was mechanistically provocative. Moreover, since four new chiral centers were generated from a prochiral precursor, this methodology had tremendous synthetic potential.

Two possible mechanisms were proposed to account for the high level of stereoselectivity. Both were based on the theory of the oxidation of alkenes by d^0 transition metals.

Walba *et al.* [12] suggested a [2+2] [13] addition mechanism: Initial formation of the bis-π-complex **6** between diene and MnO_4^- was followed by two [2+2] additions giving the unstrained octahedral Mn(VII) intermediate **7**. Alkyl migration with retention to give **8**, followed by the reductive elimination with retention , afforded Mn(III) diester **9**. Oxidation of intermediate **9** and hydrolysis then yielded MnO_2 and diol **10** with correct relative stereochemistry.

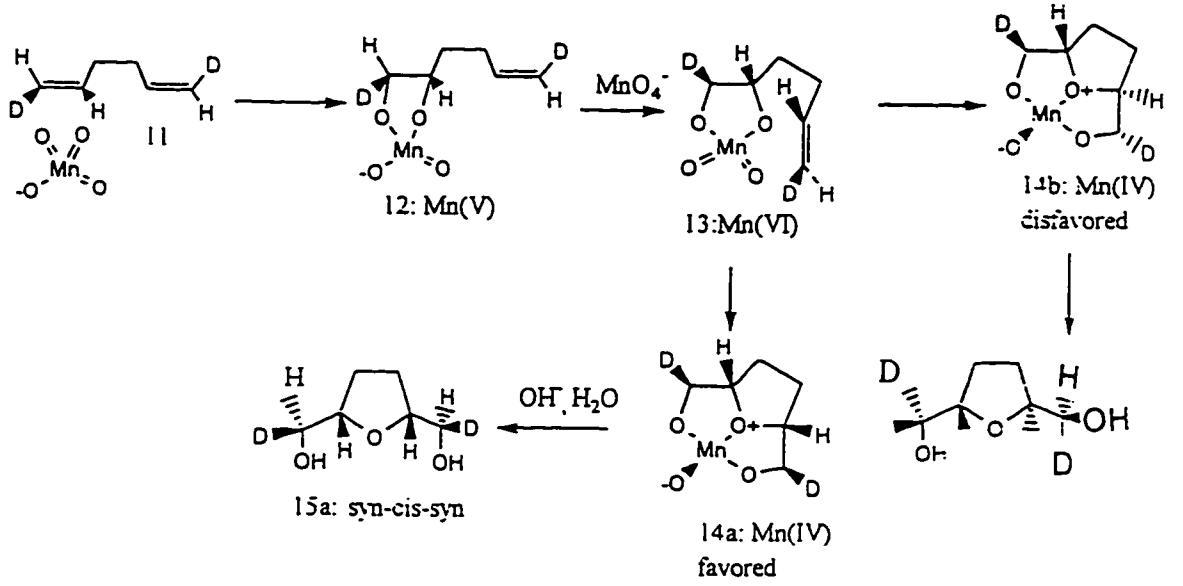
Scheme 2:



The mechanism proposed by Baldwin *et al* [14] (Scheme 3) involved initial [3+2] cycloaddition of MnO_4^- to one of the double bonds to yield Mn(V) ester **12**. Compound **12** then underwent rapid oxidation by another molecular MnO_4^- to afford Mn(VI) diester **13**. Intramolecular [3+2] cycloadditon of the Mn(VI) diester to the remaining olefinic

double bond yielded intermediate **14**, which after hydrolysis produced the observed *cis* product **15**.

Scheme 3:



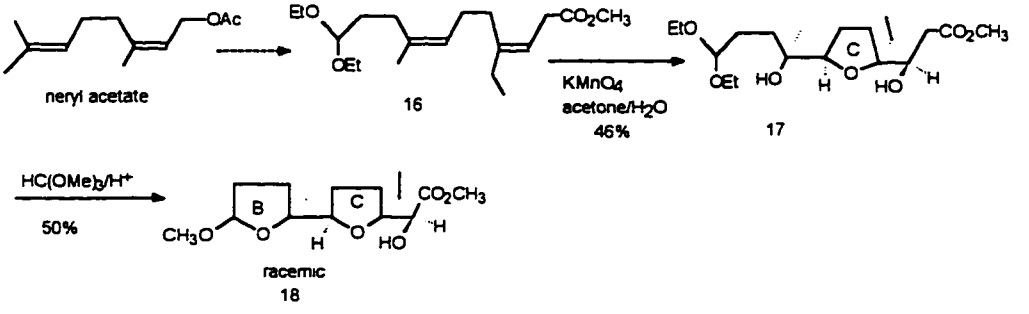
Both mechanisms accounted for the observed *cis* stereoselectivity. They involved the preferred syn addition of the Mn oxo species across double bonds, but differed in the manner in which the THF ring was formed:

In the [3+2] mechanism the rigidity of the intermediate **14** decided the formation of a *cis* rather than *trans* THF ring. This mechanism was supported by Wolf *et al* [15] involving ^{18}O-labeling experiments in which they indicated an intermediate of a cyclic Mn(V) ester analogous to **12**.

In the [2+2] mechanism THF stereoselectivity was determined in the initial double cycloaddition in which a preferred diastereomer of the octahedral intermediate was formed. Rearrangement of Mn(VII) ester **7** via two stereospecific migrations of alkyl from Mn to O with retention gave the product of syn-cis-syn stereochemistry. Ab initia calculation[16] indicated that oxametallocyclobutane intermediate should be substantially less strained than oxacyclobutane derivatives since the longer Mn-C and Mn-O bonds would have the effect of relieving the angle strain in the four-membered ring.

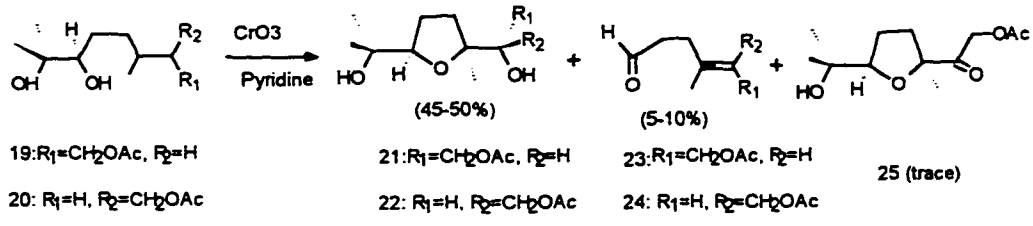
Walba *et al* [17] subsequently applied this method in the construction of the B-C bis-THF ring system of monensin (Scheme 4). The required (Z,Z)-1,5-diene **16** was obtained several steps from the commercially available neryl acetate. Oxidative cyclization of the diene **16** with potassium permanganate in aqueous acetone solution then provided the highly functionalized *cis*-THF **17** in 46% yield. Treatment of **13** with methyl orthoformate in the presence of an acid catalyst then yielded the monensin B-C fragment **18** .

Scheme 4:



γ-δ-Unsaturated Alcohols Further studies by the Walba group led to the discovery that like 1,5-dienes γ-δ-unsaturated alcohols could be converted to *cis*-2,5- substituted THF's[18] . γ-δ-Unsaturated alcohols **19** and **20** were oxidized to **21** and **22** with moderate yields on the treatment of Collin's reagents. The side-products **23** and **25** usually from alcohol oxidation were also obtained (Scheme 5).

Scheme 5:

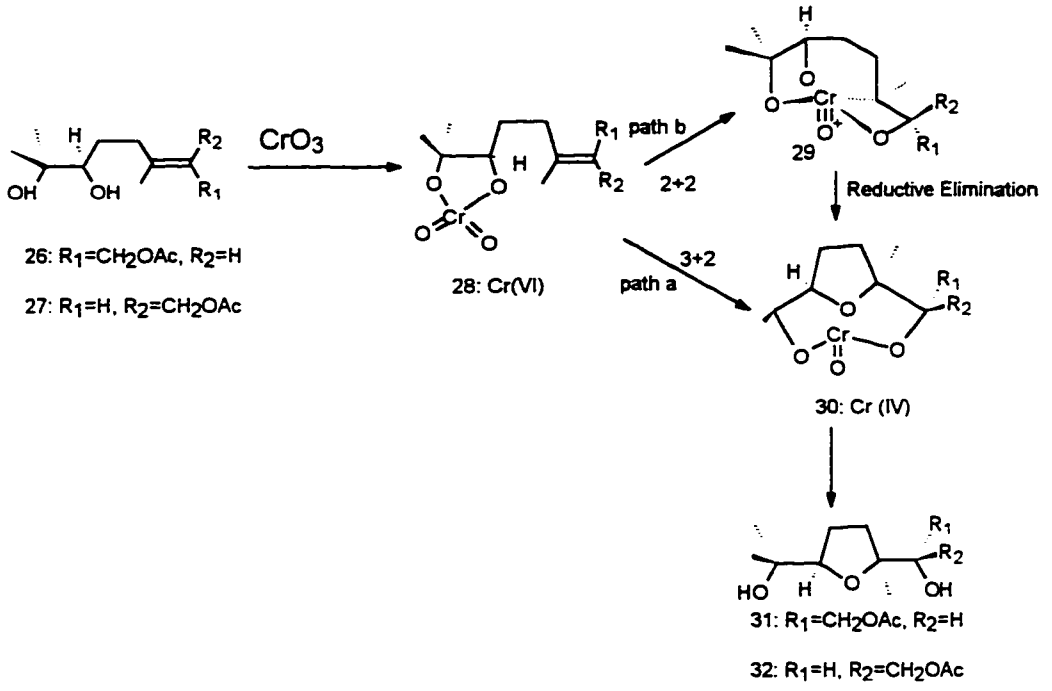


[2+2] and [3+2] mechanisms related to those described for the $KMnO_4$ oxidation of dienes have been used to explain the high stereoselectivity (Scheme 6). The initially formed Cr(VI) ester **28** might be compared to the Mn(VII) ester **12** in the $KMnO_4$ oxidation of dienes.

As proposed by Baldwin *et al* [19], a concerted [3+2] cyclization (path a) led to a preferred *cis* THF Cr(IV) diester **30**. Decomposition of diester **30** afforded the observed *cis*-THF diol product **31** and **32** along with reduced chromium species. On the other hand, a stereoselective [2+2] addition (path b) from **28** gave the oxametallo-cyclobutane **29**[14]. The square pyramidal geometry and novel metal-oxo triple bound of intermediate **29**

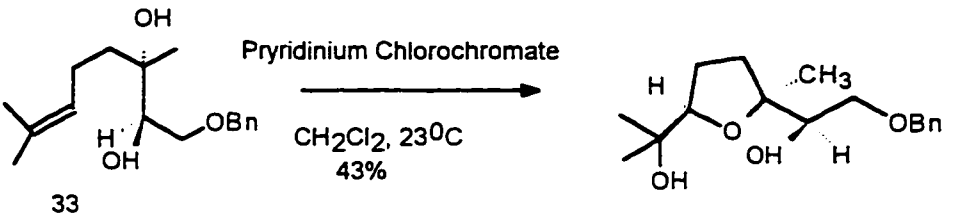
were based upon the calculation of Goddard *et al.* [12] Reductive elimination with retention then afforded **30**, fragmentation of which led to the *cis*-THF diol **31** and **32**.

Scheme 6:



This methodology has been utilized by Corey *et al*[20] in the synthesis of venustatriol. The desired *cis*- THF fragment **34** was prepared in 43% yield by the treatment of diol **33** with PCC in CH_2Cl_2 (Scheme 7).

Scheme 7:

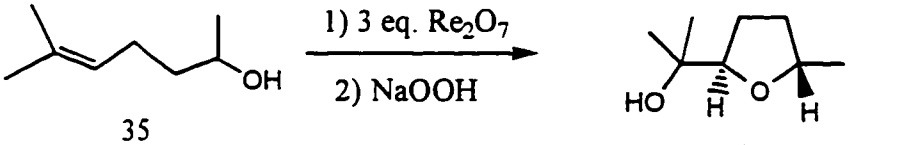


33 34

The high stereoselectivity of Mn(VII) and Cr(III) oxidative cyclization was compromised by the formation of side product arising from alcohol oxidation. This limited the use of these reactions to the synthesis of relatively simple building blocks, and restricted usage at the advanced stage of the complex fragments.

5-hydroxyalkenes: More recently Kennedy *et al* [21] showed that Rhenium (VII) mediated oxidation of 5-hydroxyalkenes **35** gave 2-hydroxymethyltetrahydrofurans **36** (Scheme 8). The stereoselectivity of the THF was *trans*, and as the case for the Mn(VII) and Cr(VI), cyclization addition across the double bond was syn. The two result were therefore complementary.

Scheme 8



35

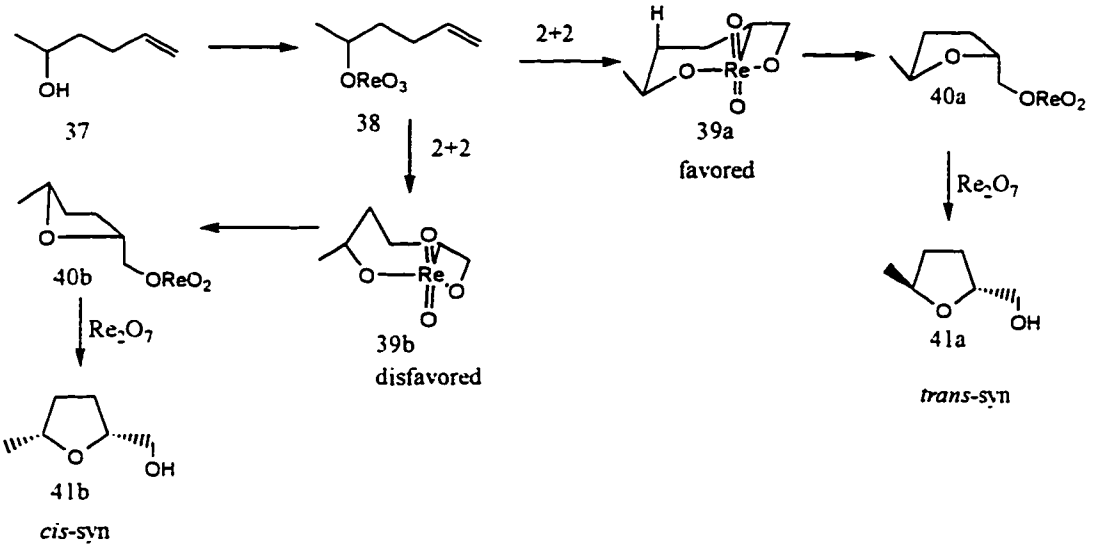
36: trans/cis=32:1, 63%

The first step in this oxidation was presumed to be transesterification producing the perrhenate ester **38** (Scheme 9). Stereoselective [2+2] cycloaddition to the double

bond gave metalloxetane **39a and 39b**. The favored [2+2] adduct was expected to adopt chair-chair conformation as shown in structure **39a**. Reductive elimination of the metalloxetane **39a** would then provided the observed products **41a**.

A key improvement of the Re(VII) cyclization is that the yields were generally higher than those observed in Mn(VII) and Cr(VI) oxidation. The disadvantage of rhenium method was that a 2-3 fold excess of the expensive oxide was required. A variation using co-oxidant H_5IO_6 has been developed [22], but this still required at least 50 mol% rhenium(VII) oxide (Re_2O_7) be used in reactions.

Scheme 9 :

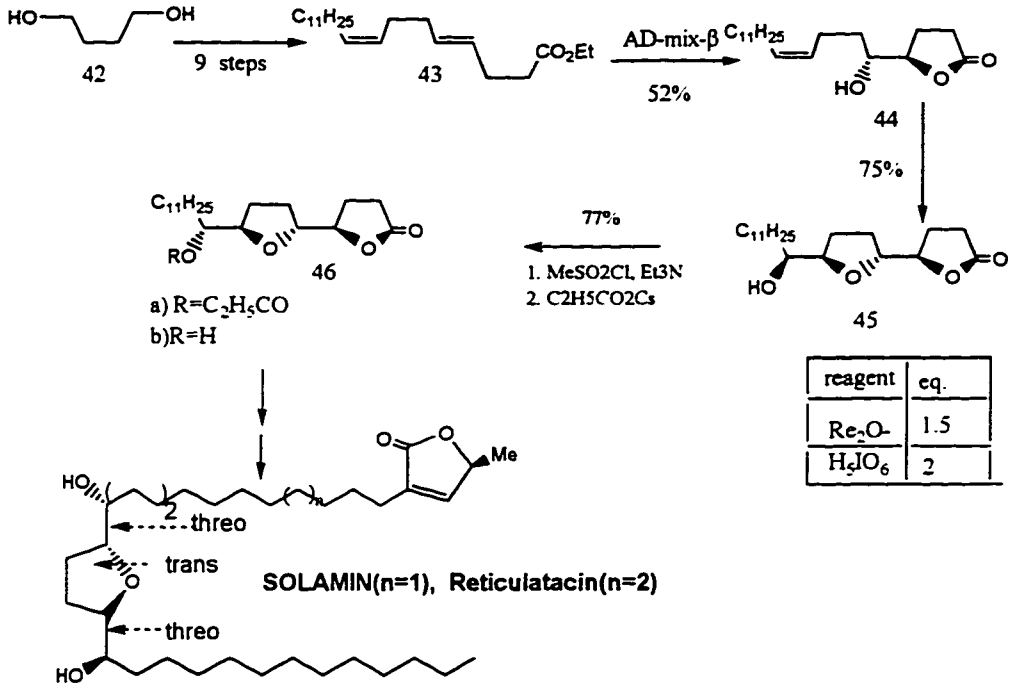


By merging the Sharpless asymmetric dihydroxylation reaction with the rhenium-based oxidative cyclization technique, Keinan *et al.*[23] have recently succeeded in synthesizing a number of THF acetogenin's structures (Scheme 10).

Treatment of the (E,Z)-diene **43** with AD-mix-β resulted in selective oxidation of the E double bond to give hydroxylactone **44**. Oxidative cyclization with 1.5 equivalent of rhenium(VII) oxide and 2 equivalent of periodic acid produced **45** as a single diasteromer

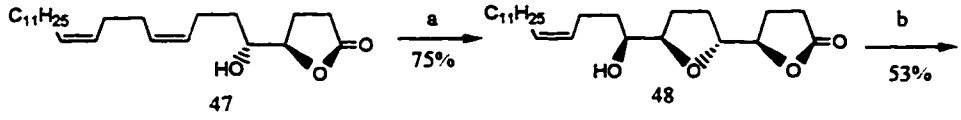
in 75% yield. Inversion of the configuration of the carbinol center in **45** produced alcohol **46b** which was a useful intermediate in the synthesis of monotetrahydrofuranoid acetogenins, such as solamin and reticulatacin.

Scheme 10:

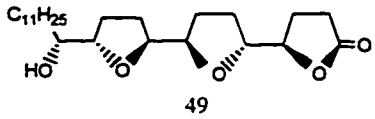


This technology was subsequently extended to the synthesis of adjacently linked bis-THF acetogenins (Scheme 11). A novel aspect of this work was the tandem oxidative cyclization of **47** to produced firstly the mono-THF product **48** in 74% then bis-THF product **49** in 53% yield. Compound **49** are useful intermediate for the synthesis of the naturally occurring bistetrahydrofuranoid acetogenins.

Scheme11:



47 48



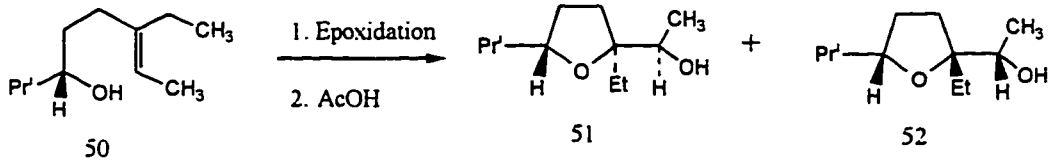
49

reagent	equivalent a	b
Re2O7	2	2
H5IO6	/	3
2, 6-lutidine	4	/

I.2.2 Epoxidation Cyclization of 1,5-Dienes

The application of hydroxy epoxide precursor offers another route to THF's. Since epoxide opening is generally stereospecific, THF's stereoselectivity is determined by the selectivity of the epoxidation step. Kishi *et al.* [24] investigated the overall stereoselectivity of epoxidation of bishomoallylic alcohol **50**, followed by acid-catalyzed cyclization to the THF **51** and **52** (Table 1).

Table 1: Epoxidation of Bishomoallylic Alcohol **50**



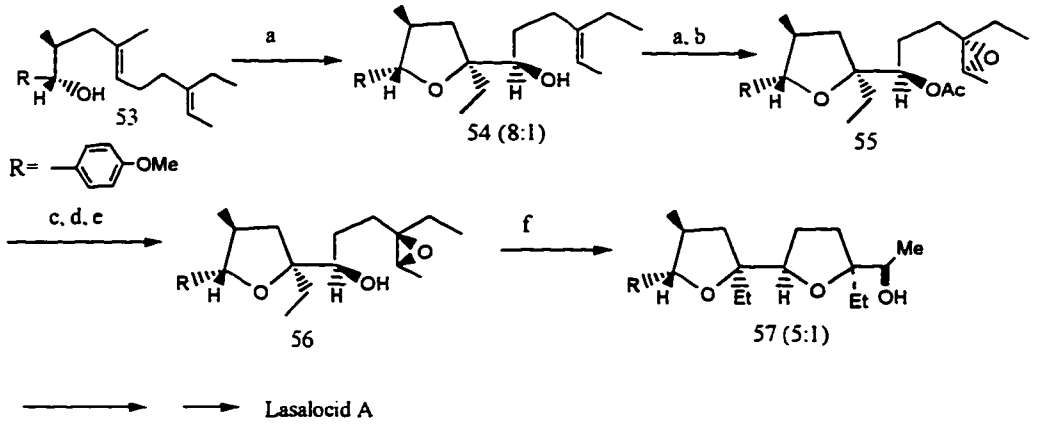
50 51 52

MCPBA	1	:	1
$VO(acac)_2$/t-BuOOH/C_6H_6/RT	9	:	1
$VO(acac)_2$/t-BuOOH/C_6H_6/reflux	7	:	1
$Mo(CO)_6$/t-BuOOH/C_6H_6/reflux	7	:	1

Treatment of the bishomoallylic alcohol **50** with MCPBA led to two isomers of 2,5-disubstituted THF's with no selectivity. However, when **50** was treated with t-BuOOH in the presence of $VO(acac)_2$ or $Mo(CO)_6$, a ratio of 9:1 in favor of *trans* isomer **51** over *cis* isomer **52** was found.

Kishi *et al.* [25] then utilized these results in their first synthesis of lasalocid A (Scheme 12). Epoxidation of the unsaturated alcohol **53** with t-BuOOH in the presence of $VO(acac)_2$, followed by acetic acid work- up afforded THF **54** in 75% yield along with its stereoisomer in a ratio of 8:1. A second epoxidation reaction on **54** under the same condition followed the acetylaction allowed the isolation of the epoxide **53** which was transformed to the THF **57** by 4 steps in 45% overall yield. The overall stereoselectivity from **54** to **57** was 5:1. This methodology has also been used in the total synthesis of the meso-triterpene polyether teurilene [26] .

Scheme 12:



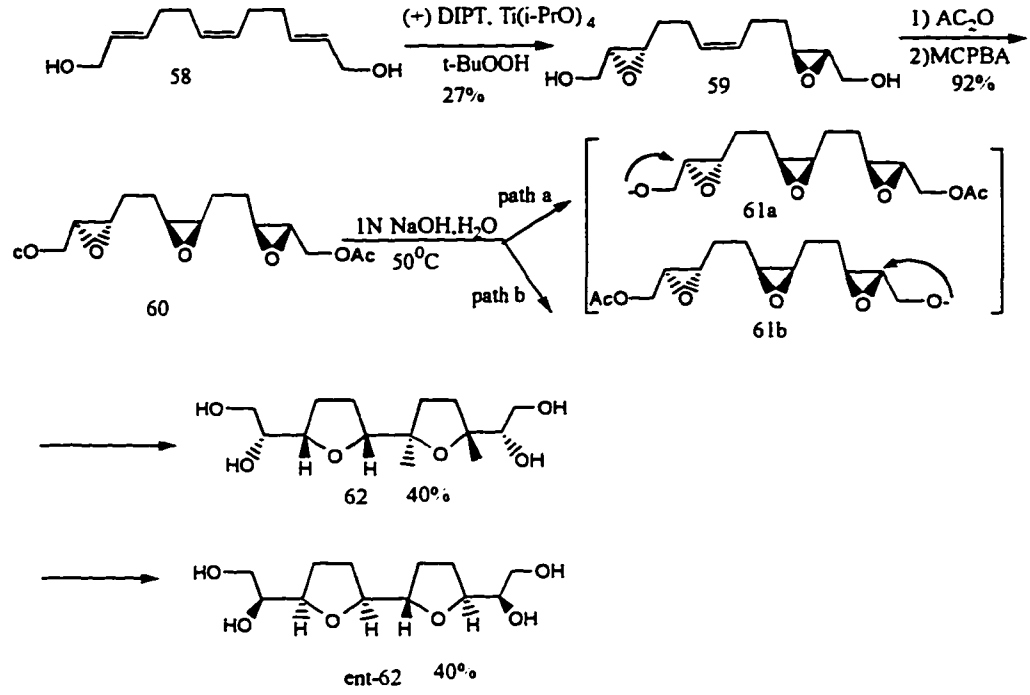
Reaction conditions: a) t-BuOOH/$VO(acac)_2$/NaOAc/C_6H_6, rt; b) Ac_2O/Py; c)0.1N H_2SO4/aq. acetone/KH/THF; d)TsCl/Py; e) K_2CO_3/MeOH; f) AcOH;

The versatility of the Sharpless asymmetric epoxidation has led to the widespread application of the epoxide opening strategy[27]. The tandem epoxide opening cascade sequence is an elegant example of this methodology. In Hoye's work [28] on the bis-THF acetogenins, an triepoxide precursor **58** was converted in a single step to the bis-THF (Scheme 13):

The (E,Z,E)-triene **58** of C_{2v} symmetry was transformed to the diepoxide **59** of C_2 symmetry via a double Sharpless epoxidation. Acetylation followed by epoxidation of the remaining double bond gave the triepoxide **60** as a single stereoisomer. Exposure of the bisepoxide acetate **60** to aqueous NaOH (1N, 50^0C) led to the formation of the enantiomeric bis-THF **62** and ent-**62**. The formation of the racemic mixture could be explained by a fast hydrolysis of the two acetate groups as the first step followed by an epoxide cascade starting from the left side of the molecular (path a, **60→61a→62**) or starting from the right side (path b, **60→61b→ent- 62**).

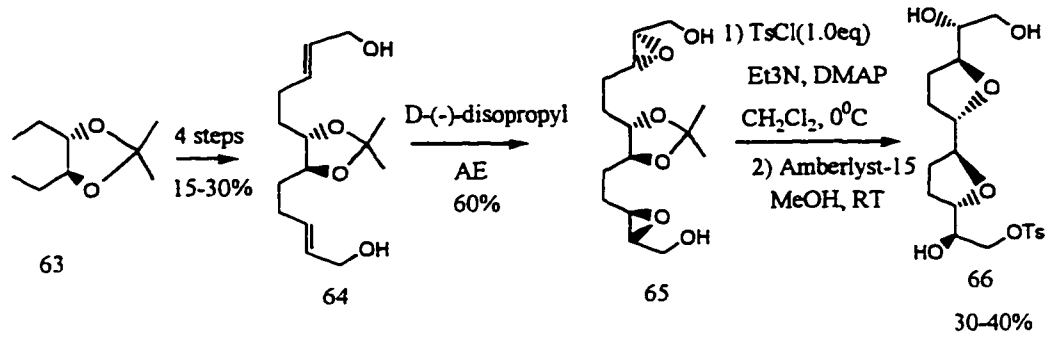
A bi-directional version of this strategy was used by Hoye *et al.* [29] in the synthesis of 15, 16, 19, 20, 23, 24-hexed-uvaricin, a diastereomeric, non-natural bis-THF acetogenins (Scheme 14). The diol **63** was converted to E,E-bisallylalcohol **64** in 15-30% over our steps. Sharpless's asymmetric epoxidation of **64** using D-(-) diisopropyl tartrate as catalyst afforded bisepoxide **65** in 60% yield.

Scheme 13:



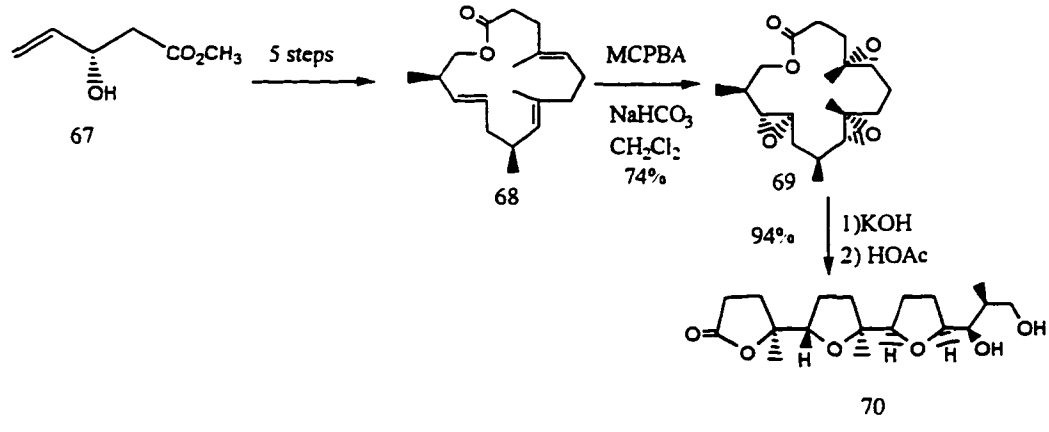
Desymmetrizing the C_2 symmetric bisepoxide diol **65** was achieved by exposure of the diol to 1.0 equiv. of TsCl. The corresponding monotosylate was subjected to acid condition causing simultaneous acetonide cleavage and epoxide opening to produce the erythro/*trans*/threo/*trans*/erythro bis-THF monotosylate **66** in 30-40% yield.

Scheme 14:



Alternatively, the stereoselective preparation of poly epoxide precursor may be substrate controlled as in the case of **68-69** (Scheme 15) [30]. Treatment of **67** with excess HOAc gave 68 in 94% yield. This result demonstrated the feasibility of the polyepoxide cyclization approach for more complex polyethers.

Scheme 15:



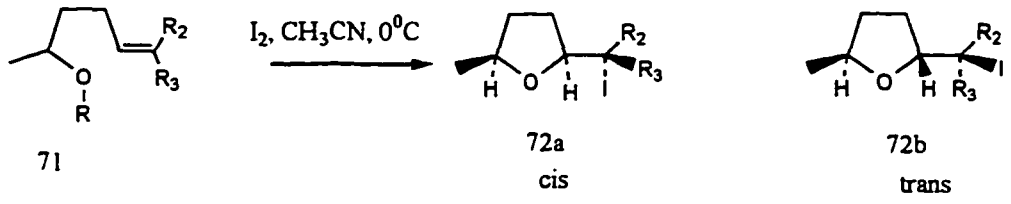
II.2.3 Electrophilic Cyclization of γ,δ-Unsaturated Alcohols

The pioneering work in this area is due mainly to Bartlett and co-workers.[31] They showed that the stereoselectivity of the iodoetherification reaction of 4-alkene-1-yl ethers varied with the alcohol protecting group (Table 2). The free alcohols showed low preference for the *trans* 2,5-disubstituted THF product (entry 1, 3, 5). Bulky protecting groups were formed to favor the *cis* isomer, best results being obtained with 2,6-dichlobenzyl ethers, which gave excellent stereoselectivity.

The results were explained in term of the favored formation of the THF oxonium ion **75** corresponding to *cis* THF **76b**, relative to intermediate **74a** and **74b** which led to the *trans* THF **76a**. *Cis*-THF oxonium **75** was expected to be both kinetically and thermodynamically favored due to the low degree of steric congestion in the transition state leading to its formation, and also in the eventual THF oxonium ion (Scheme 16).

While excellent *cis* stereoselectivity was observed in the Barlett study, it should be pointed out that the substrate were relatively unsubstituted. In light of substrate effects observed for alkene substitution, it was not surprising that subsequent investigation in more complex systems revealed that these reactions were highly dependent on substrate structures. Terminal and vincinal E disubstituted alkenes showed greater preference for the *cis* THF (Table 3, entry 1, 2, 5, 6), compared with the Z-isomers (Table 3, entry 3 and 4). Similar trends have been observed in more substituted systems[32]. There has been several cases of high stereoselectivity in allylic alcohol substrates. But once again, the stereoselectivity was not always predictable. It depended on alkene substitution and substitution at position other than allylic centers[33].

Table 2: Iodoetherification of 4-Alkene-1-yl-Ethers 71



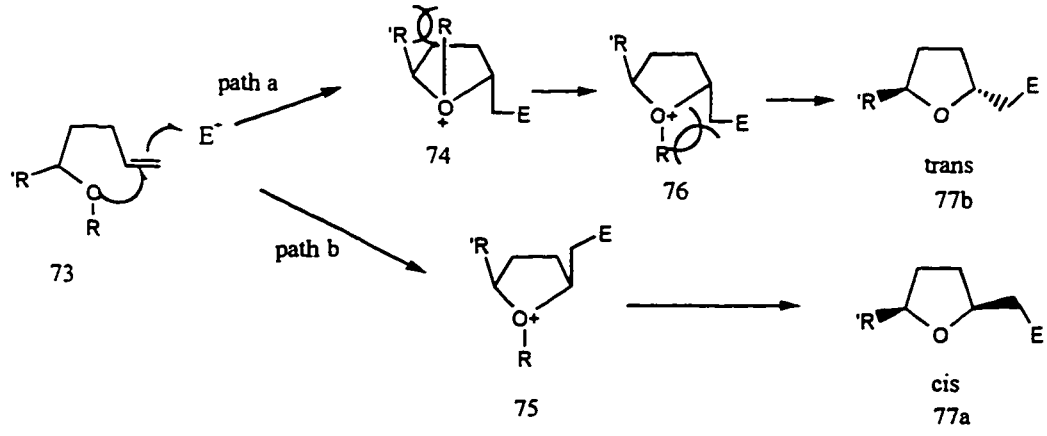
71 72a cis 72b trans

entry	R	R2	R3	cis/trans ratio[a]	yield[b]
1	H	H	H	1/2	66%
2	DCB	H	H	21	63%
3	H	Me	H	0.4	81%
4	DCB	Me	H	12	47%
5	H	H	Me	0.5	99%
6	DCB	H	Me	25	75%

DCB= 2,6-dichlorobenzyl

[a] Ratio determined by ^{13}C or ^{1}H NMR; [b] Isolated yield of purified product

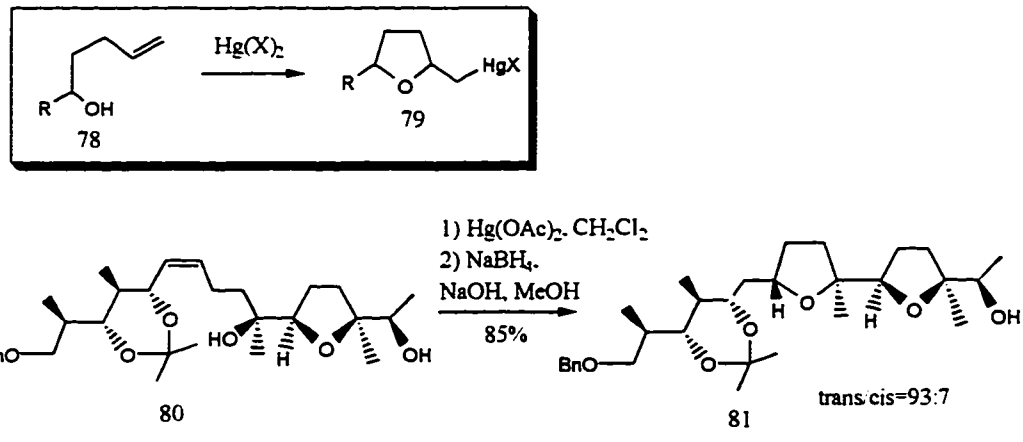
Scheme 16:



The early hypothesis by Barlett suggested that initial oxoniun ion and THF oxonium ion equilibration (Scheme 14) could affect the overall stereoselectivity, therefore

the nature of the electrophile might be important so far as it affected reversibility of oxonium formation. Indeed high stereo control for 2,5-disubstututed THF's have been observed in several of Hg^{+2} promoted cyclization[34] . In these cases, major product formed was the *trans* THF which could be further funtionalized by radical reactions. By using this approach, Evans *et al.*[35] prepared the THF-dimmer **81**, a key intermediate for their synthesis of ionomycin, from the bis(homoallylic alcohol) **80**. The stereoselectivity is 93:7 *trans* to *cis*. (Scheme 17)

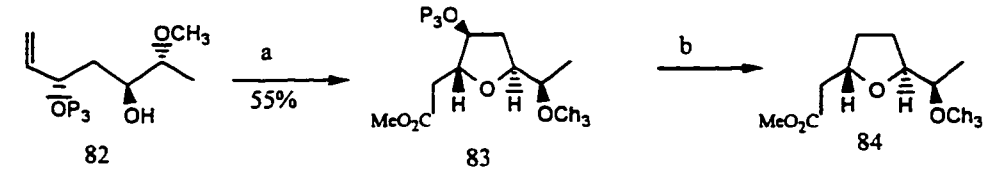
Scheme 17:



Highly stereoselectivities has also been observed with Pd and Se electrophiles [31b, 33-36] . Semmelhack *et al.*[37] applied this approach in the synthesis of ionophore antibiotics (Scheme 18). Pd(II)-promoted cyclization of **82** produced **83** in 55% yield and >98% diastereoselectivity. After desilylation and radical deoxygenation, **85** was isolated (86% yield).

Lipshutz *et al.* [38] showed that β, γ-unsaturated alcohols could lead to 2,5-disubstituted THF. Using I_2 as electrophile gave exclusively *cis* THF but using PhSeCl afforded *trans* isomer (Scheme 19) .

Scheme 18:



82

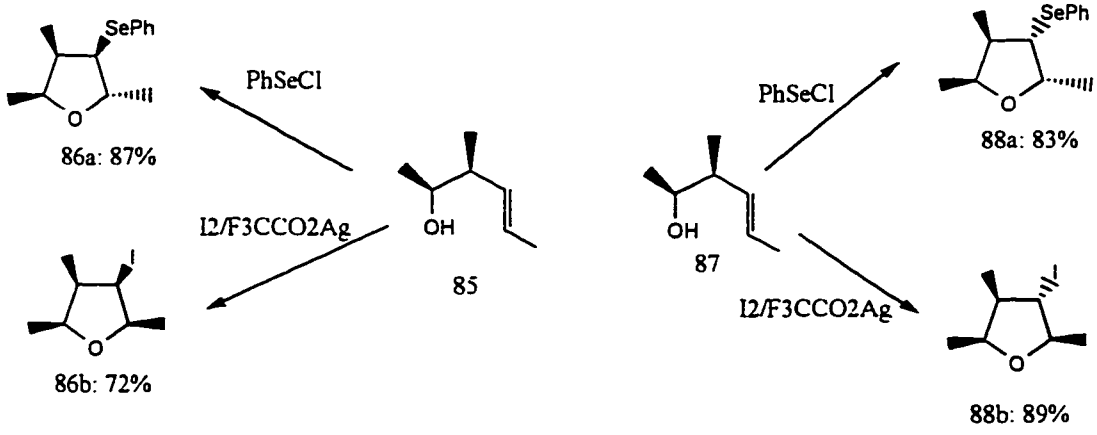
P=Si(tBu)Ph2

83

84

Conditions: a)Pd(OAc)2/CH3OH/CO; b) (i) Bu4NF, THF, 0 ^{0}C (100%), (ii) 2,2'-dibenzothiazoyl disulfide, Bu3P, tolune, reflux, (iii) Bu3SnH, AIBN, benzene, 80 ^{0}C (86%, 2 steps).

Scheme 19:

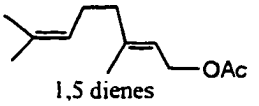
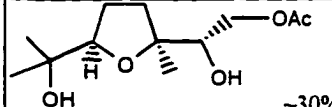
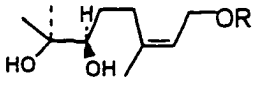
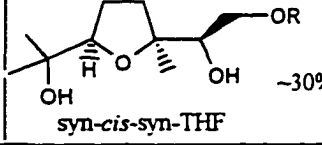
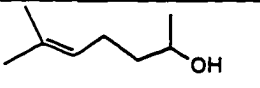
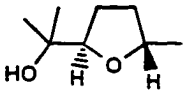


In conclusion, three general approaches in the literature towards the synthesis of 2,5-disubstituted THF have been discussed: (1) oxidative cyclization (Table 3); (2)

epoxidation-cyclization and (3) electrophilic cyclization. They have all been widely used in the synthesis of THF-containing natural products.

Although the oxidative cyclization by $KMnO_4$ and Collin's reagents can provide rapid access to *cis*-2,5-disubstituted from the simple alkene precursors, the yields are generally very low (~40% yield), the reaction conditions are not compatible with the sensitive functional groups, such as primary and secondary alcohols either in the starting material or in the product [39]. The rhenium(VII) mediated cyclization is high yielding but generally requires at least stoichimetric proportion of the expansive Re_2O_7.

Table 3: Oxidative Cyclization of 1,5-Dienes, 5,6-Dihydroxyolefins and 5-Hydroxyalkenes

Method	Substrates	Reagents	THF Products
Oxidative cyclization	 1,5 dienes	$KMnO_4$	 syn-*cis*-syn-THF ~30%
	 5,6-dihydroxyolefins	CrO_3 Pyridine	 syn-*cis*-syn-THF ~30%
	 5-hydroxyalkenes	Re_2O_7/H_5IO_6	 syn-*trans*-THF 63%

Epoxide-cyclization can lead to mono- or oligo-THF's from the appropriate alkenes or polyenes. Although it is less direct than the oxidative cyclization of alkene precursors, the epoxide cyclization methodology is the most versatile due to the availability of procedures for preparation of epoxide of complementary stereochemistry.

The electrophilic cyclization is attractive because of its directness, mildness of reaction conditions, and generally high yielding. Moreover the electrophilic residue is amenable to further elaboration. However this methodology is highly dependent on the substrate structure. This approach has been widely used in simple systems. Stereo-chemistry in more substituted is generally unpredictable.

The design of highly substituted templates in which electrophilic cyclization is highly stereoselective will be relevant to the synthesis of complex natural products. This is the goal of this research.

Part II

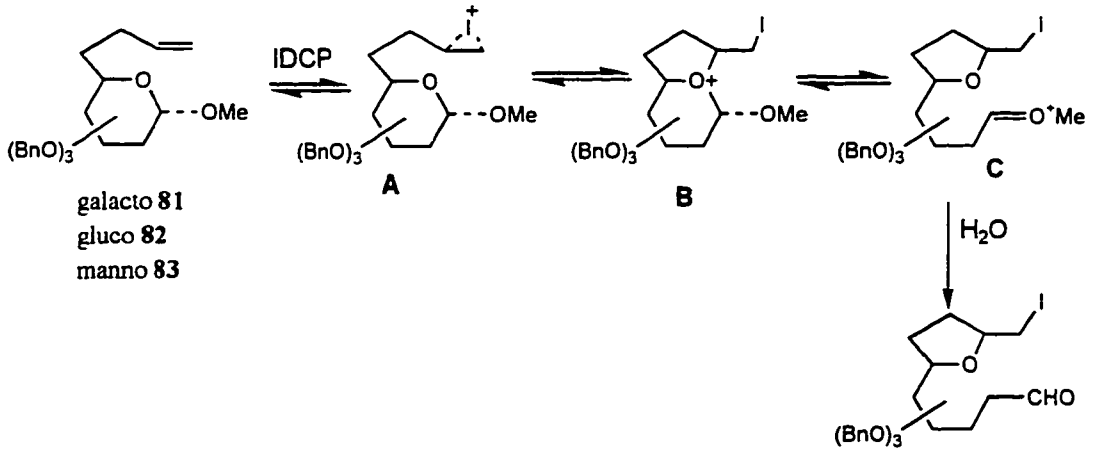
The Synthesis of cis 2,5-Disubstituted Tetrahydrofurans

II.1 Haloetherification of 2,5 Dideoxypyranoside Alkenes

Background

Preliminary studies in this laboratory have shown that monosaccharide alkenes **89-91** on treatment with Iodonium ion in the presence of water, gave 2,5-disubstituted THF's **92-94** (Scheme 20) [40]. The reaction was fast and with good yields (65%-76%), but stereoselectivity was poor (4/5, 5/3 and 5/2 *cis/trans* for gluco, galacto and manno pyranosides, respectively).

Scheme 20:



galacto **81**
gluco **82**
manno **83**

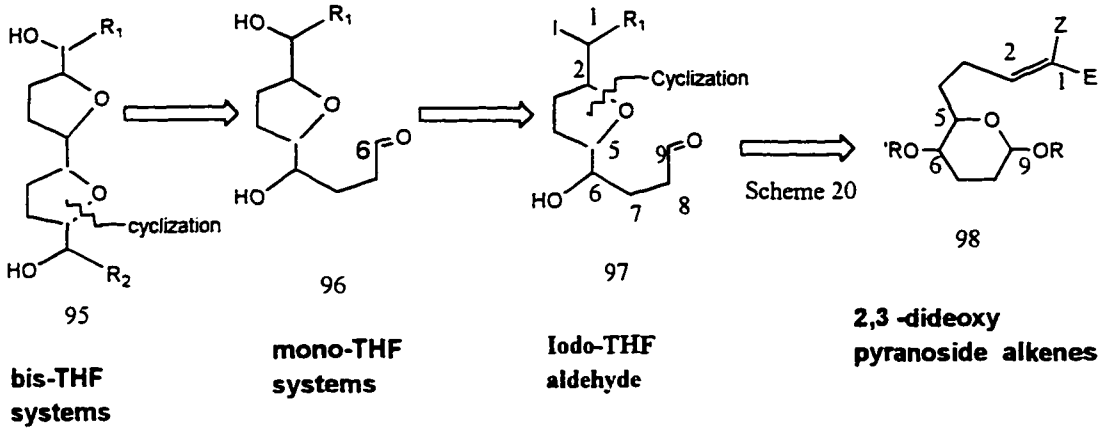
	c/t	yield
galacto **84**	4/5	76%
gluco **85**	5/3	72%
manno **86**	5/2	65%

This transformation provided a way of preparing complex THF's from readily available alkene precursors, in a single, experimentally simple reaction. The reaction was thought to proceed via initial formation of a halonium ion or a charge transfer complex **A**

between the olefin and I_2, then nucleophilic attack by the ring oxygen on the latter to give the oxonium complex **B**, which subsequently underwent fragmentation to yield the oxocabenium ion **C**. Hydrolyis of **C** afforded the THF's **92-94** (Scheme 20).

Specifically we envisioned that a 2,3 dideoxy C-6 allylated pyranoside could be used as a template for the synthesis of mono and bis-THF acetogenins (Scheme 22). Accordingly two stereogenic centers (C_5, C_6) were set in a precursor **98** and two new centers (C_1, C_2) were formed in the iodocyclization reaction. However, before this plan could be implemented, the stereoselectivity of iodocyclization had to be improved.

Scheme 21:

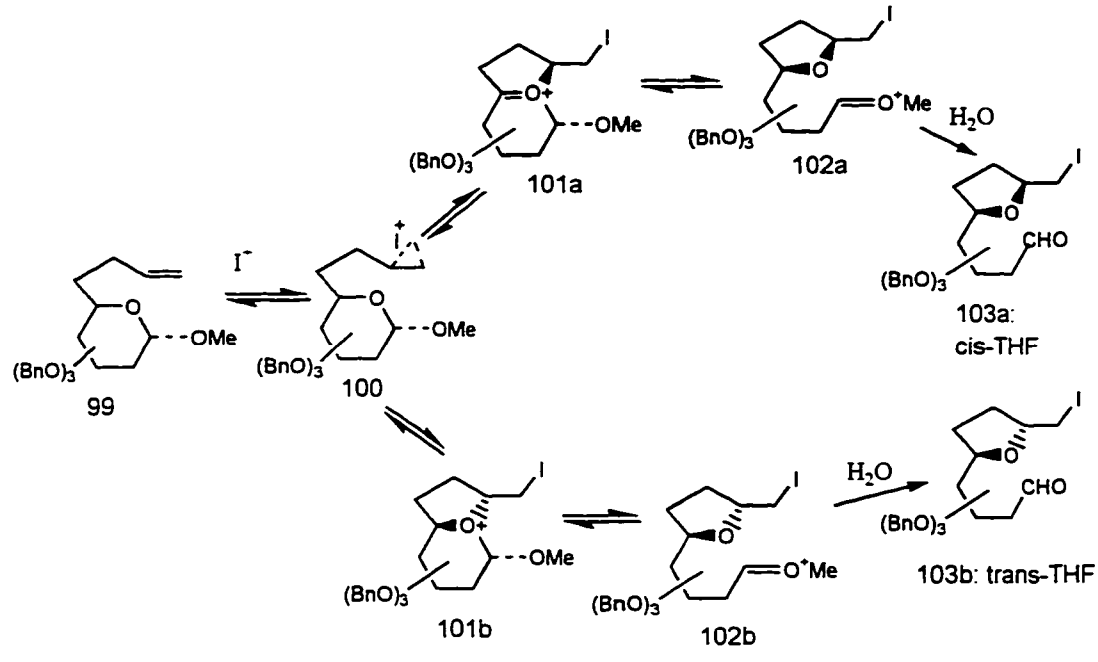


THF Stereoselectivity

In view of the proposed mechanistic, we reasoned that variation of the electronic and steric characteristics of the aglycone in the pyranoside alkenes would affect THF stereoselectivity. Increase in electronegativity of the aglycone might be expected to decrease the rate of fragmentation of the THF-oxonium ion **101** to the oxocarbenium **102**, relative to its reversion to the halonium ion **100**. This would favor formation of the

THF corresponding to the more stable THF oxonium ion **101** (Scheme 21). On the other hand, a sterically demanding, less electronegative aglycone might favor the THF arising from fragmentation of THF-oxonium ion which was kinetically preferred.[41-42]

Scheme 22:

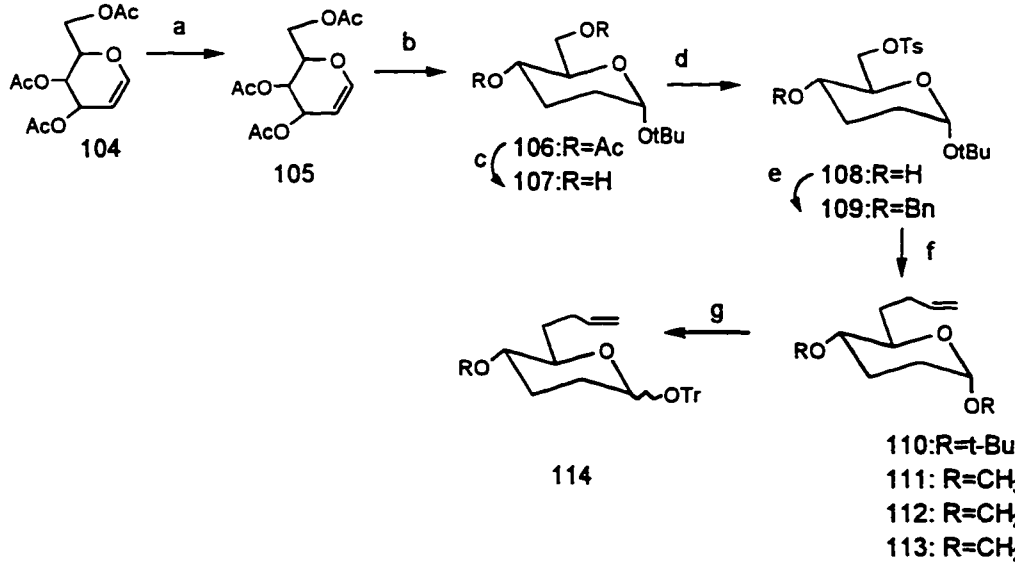


The use of the aglycone as the stereo determining element would be a practical synthetic device, since it can be easily introduced or interchanged by acetal exchange.

Initial Studies on effect of aglycone on stereoselectivity : To test this idea, methyl, ethyl, trifluoroethyl and t-Butyl 2,3 dideoxy C_6-allylated gluco pyranosides were prepared. The synthesis of the t-butyl derivative **110** was illustration of the general procedure (Scheme 23). Commercially available tri-O-acetyl-D-glucal (TAG) **104** on treatment with

BF_3.OEt and t-Butanol in CH_2Cl_2, afforded the unsaturated α-t-Butyl glycoside **105** in 49% yield. Hydrogenolysis of **105** gave the saturated t-Butyl glycoside **106** (75%), which was deacetylated on treatment with NaOMe to the diol **107** (81% yield). Selective tosylation of the primary alcohol in **107** led to **108**, which was converted to the benzyl ether **110**. Treatment of **110** with allylmagnesium bromide in TMEDA-ether led to the allylated pyranoside **110** in 79%.[43] The trityl gluco pyranoside **115** was obtained from the t-butyl glycoside **110** in 51% yield via acetal hydrolysis followed by the AgOTf mediated tritylation of the resulting lactol. This yielded an inseparable 1:1 mixture of α/β anomers, which was used without separation in the iodocyclization. The methyl, ethyl, and trifluoroethyl pyranosides **111**, **112**, **113** were prepared via standard procedure on their respective pyranoside diol precursors[44].

Scheme 23:

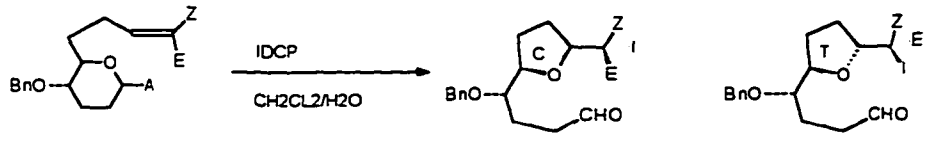


[a]Reagents and conditions: (a) t-BuOH, $BF_3.Et_2O$, rt. AR, 4h, 49%; (b) H_2, 10%Pd/C, overnight, 75%; (c) 1M NaOMe/MeOH, rt., 1h, 81%; (d) 1.2 equiv. of TsCl, pyridine, rt., 2h, 52%; (e) 2 equiv. of NaH, 1.5 equiv. of BnBr, 0.1 equiv. of Bu_4NI, DMF, Ar, rt., 2h, 69%; (f) 2.5 equiv. of

vinylmagnesium bromide, TMEDA, Et_2O, Ar, 1h, 79%; (g) 3 equiv. of Ph_3CCl , 3 equiv. of AgOTf, 3 equiv. of colliding, 4 A M.S., Ar, 10 min., 72%.

Iodoetherification of pyranoside alkenes were effective by treatment with Iodonium dicollidine perchlorate(IDCP) [45] in wet CH_2Cl_2 (Table 4). Aglycone of similar size but different electronic properties ($-OCH_2CH_3$, $-OCH_2CF_3$) were investigated (entry 1, 2). Although the relative reactivity of the substrate did decrease with increasing electronegativity, THF stereoselectivity remained unchanged. Hence, variation of electronic properties of aglycone had apparently little or no effect on THF stereoselectivity. On the other hand, variation of the size of the aglycone was more promising (entry 1, 3, 4). The preference for the *cis* THF was observed to increase with the size of aglycone with very good selectivity for the bulky trityl aglycone (entry 5).

Table 4: Effect of the Aglycone Structures on THF Stereoselectivity



cis/trans THF products

Entry	A	Z	E	THF	c:t[b]
1	α-OCH_2CH_3, **112**	H	H	**115**	1.5/1
2	α-OCH_2CF_3, **113**	H	H	**115**	1.5/1
3	α-OCH_3, **111**	H	H	**115**	1.2/1
4	α-O^{t}Bu, **110**	H	H	**115**	3.5/1
5	α/β-OTr, **114**	H	H	**115**	>10/1

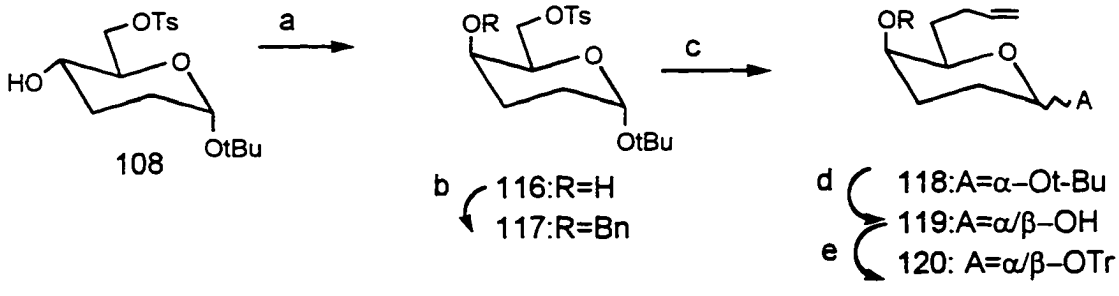
[a] Reaction conditions: 1.5 equiv. of IDCP, wet CH_2Cl_2, rt., 15 minutes;
[b] Ratio determined by ^{13}C or ^1H NMR spectroscopy

Iodocyclization of Trityl Pyranoside Alkenes

Synthesis: In order to evaluate the generality of the apparent steric effect of the aglycone, t-Butyl and trityl glycosides with different α/β C_4 configuration, and variant alkene substitution patterns were prepared.

t-Butyl 2,3-dideoxy C_6 allylated galacto pyranoside **118** was obtained by inversion of the C_4 configuration of the previously described gluco alcohol **108** (Scheme 24). Application of the Mitsunobu reaction,[46] followed by hydrolysis of the remaining benzoate afforded the galacto derivative **117** in 75% yield over two steps. Compound **117** was converted to the desired t-Butyl galacto alkene in two additional steps as previously described for its gluco analog **110**. The trityl glycoside was obtained from the t-Butyl galacto derivative as described earlier.

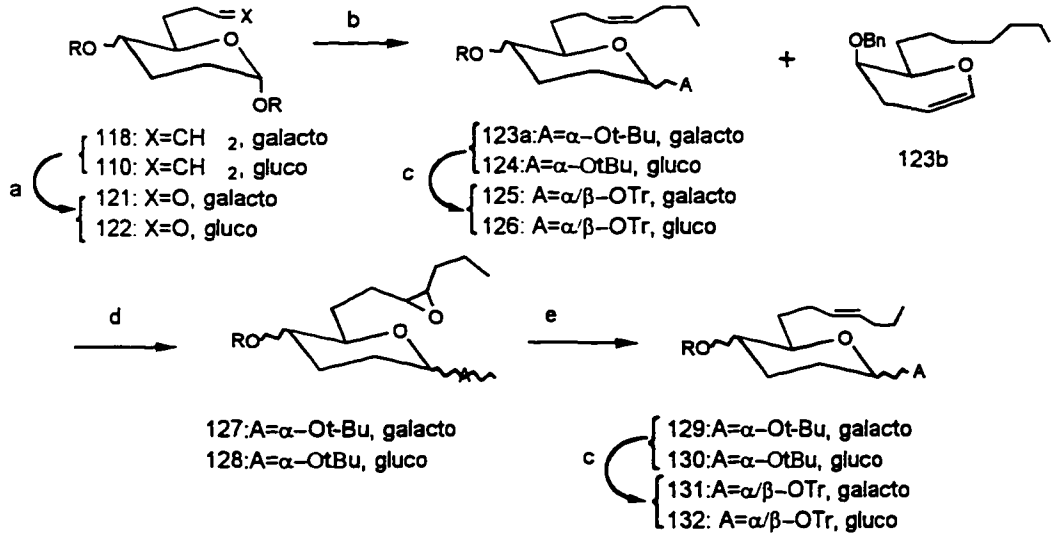
Scheme 24:



Reagents and conditions: (a) i. 4 equiv. of DEAD, 3.5 equiv. of $P(C_6H_5)_3$, 4 equiv. of $PhCO_2H$, toluene, -15°C, 2h; ii. 1N NaOMe/MeOH, 0.5h; 2 steps 75%; (b) 2 equiv. of NaH, 1.5 equiv. of BnBr, 0.1 equiv. of Bu_4NI, DMF, Ar, rt, 2h, 75%; (c) 2.5 equiv. of vinylmagnesium bromide, TMEDA, Et_2O, Ar, 1h, 79%; (d) 1N HCl/THF, rt., 4h, 71%; (e) 3 equiv. of $(C_6H_5)_3CCl$, 3 equiv. of AgOTf, 3 equiv. of collidine, 4 A M.S., Ar, 10 min., 92%.

The Z and E disubstituted alkenes were obtained via straightforward procedures. The protocol would be described for the galacto series. First the alkene **118** was subjected to ozonolysis to give the aldehyde **121**. The t-Butyl-Z-alkene **123** was then obtained in greater than 95% selectivity via the Wittig reaction [47] of butylidenetriphenyl-phosphorane and the aldehyde **121**. Diene **123b** (8%) was also obtained as the byproduct in this reaction. Isomerization of **124** via the Vedjs protocol[48] gave the E isomer **128** in 92%. This involved preparation of the epoxide **127** from the alkene **123**. The Z or E trityl glycosides was obtained from the respective Z or E t-Butyl derivative as previously described (Scheme 24). The Z and E alkene derivatives of the dideoxygluco series were prepared via the similar strategies (Scheme 25).

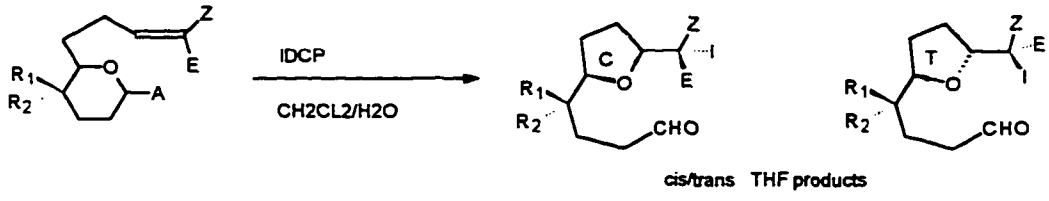
Scheme 25:



[a] Reagents and conditions: (a) O_3, CH_2Cl_2/MeOH, -78°C; then $(CH_3)_2S$, -78°C-rt., 1h, 84%; (b) 5 equiv. of $CH_3CH_2CH_2CH_2P^+Ph_3Br^-$, 5 equiv. of $NaN(SiMe_3)_3$, toluene, -78°C, 87%; (c) i. 1N HCl/THF, rt., 2h, 91%; ii. 3 equiv. of Ph_3CCl , 3 equiv. of AgOTf, 3 equiv. of collidine, 4 A M.S., Ar, 10 min.; (d) 2.5 equiv. of MCPBA, CH_2Cl_2, Na_2HPO_4/NaH_2PO_4, rt., 1.5h, 92%; (e) 3 equiv. of Ph_2PH, 3 equiv. of n-BuLi, dry THF, rt., 2h, then MeI, 1h, 91%.

Cyclization Results : The cyclization reactions were carried out under the standard condition of IDCP in wet dichloromethane (Table 5). The trityl derivative reacted more rapidly than the t-Butyl compounds, and was complete within 10 minutes. As expected from the earlier work, the t-butyl substrates generally showed mediate *cis* selectivity, whereas the trityl derivatives showed good to excellent stereoselectivity.

Table 5: Iodocyclization of the Trityl pyranoside Alkenes



entry	R_1	R_2	A	Z	E	THF's	c/t[a]	yield(%)[b]
1	OBn	H	α-OtBu, **118**	H	H	**133**	7/2	
2	OBn	H	α/β-OTr, **120**	H	H	**133**	c-only	87
3	OBn	H	α-OtBu, **123**	Pr	H	**134**	2/3	
4	OBn	H	α/β-OTr, **125**	Pr	H	**134**	c-only	91
5	OBn	H	α-OtBu, **129**	H	Pr	**135**	7/2	
6	H	OBn	α/β-OTr, **131**	H	Pr	**135**	c-only	79
7	H	OBn	α-OtBu, **110**	H	H	**115**	7/2	
8	H	OBn	α/β-OTr, **114**	H	H	**115**	c-only	80
9	H	OBn	α-OtBu, **125**	Pr	H	**136**	2/3	
10	H	OBn	α/β-OTr, **127**	Pr	H	**136**	8/1	81
11	H	OBn	α-OtBu, **129**	H	Pr	**137**	7/2	
12	H	OBn	α/β-OTr, **131**	H	Pr	**137**	20/1	78

[a] Diasteromer ratios were determined from ^1H and ^{13}C NMR spectra.

[b] Yields are for chromatographically isolated products unless stated otherwise.

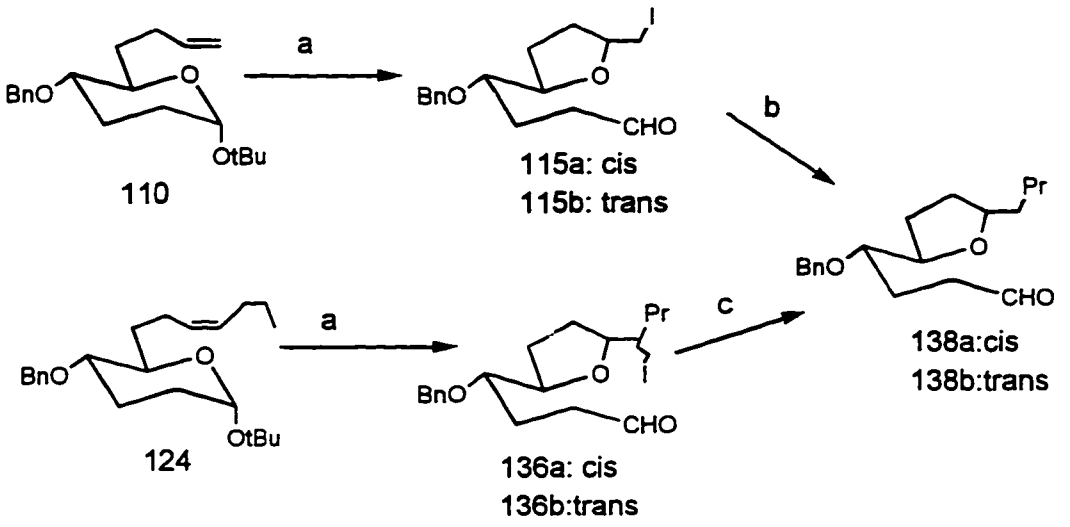
Assignment of the Stereochemistry of the THF Products

The configuration of the new stereogenic centers in the THF products from the terminal alkenes was assigned by comparison of the methylene resonances in the THF ring of *cis* and *trans* isomers. Studies from this laboratory [37] have shown that the resonances for the *cis* THF's methylene carbons consistently occurred upfield compared to those in the corresponding *trans* diastereomer. This will be described in detail later in section B. This trend was found to be the same for the THF **136** from more substituted Z alkenes **124**. Thus the separated *cis* and *trans* THF's **136a** and **136b** obtained from the cyclization of the t-Butyl Z alkene **124** was subjected to n-BuSnH reduction to the deiodo derivative **137**. The product was correlated with the *cis* and *trans* THF's obtained from allylation of the iodo methyl THF **116a** and **116b**. The *cis* and *trans* products matched in agreement with the assignment based on NMR predictions. The correlation between ^{13}C resonance and stereochemistry in related acetogenins THF structure had been observed by other workers. [49]

The configurations of the remaining THF's were deduced by ^{13}C NMR comparison. Accordingly, The THF's products from the trityl pyranosides were subsequently established to be the *cis*-THF's (Table 6).

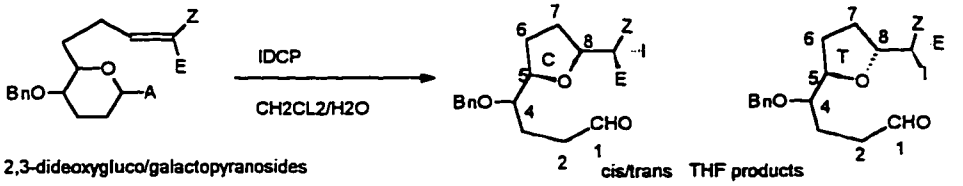
Proposed Model for the Iodoetherification

The iodoetherification results of 2,3 dideoxypyranosides alkenes seem to fit the early transition state model described by Guidon *et al.* [50] for the related haloetherification of 5-alkoxyalkenes. Accordingly, a model has been proposed in which chair like reactive



a) IDCP/CH_2Cl_2/H2O; b)i. $NaBH_4$; ii. Allyltributyltin; iii. H_2, Pd/C; c) i. $NaBH_4$; ii. Bu_3SnH

Table 6: ^{13}C Data of C6 and C7 in the *cis* and *trans* THF Products from 2,3-Dideoxypyranosides

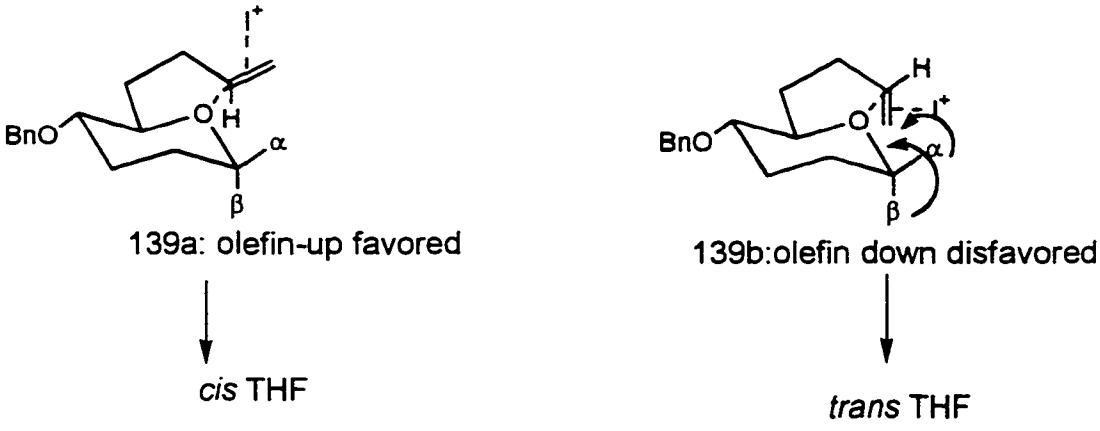


		terminal		Z-alkene		E-alkene	
		cis	trans	cis	trans	cis	trans
Galacto-	C6	27.78	28.83	28.1	28.93	27.29	29.84
	C7	31.12	32.46	30.55	31.55	31.47	32.92
Gluco-	C6	27.12	27.81	27.33	27.67	26.76	27.36
	C7	31.66	32.87	32.87	31.97	31.96	33.25

conformation involving the four carbon atoms of the eventual THF ring is favored. The preferred orientation of the alkene complex or iodonium ion, leading to the formation of *cis* THF, is 'olefin-up' (**139a**) vs. 'olefin down' (**139b**). Due to the distance of the

reacting center to the aglycone, only a very bulky aglycone such as trityl group can induce a significant amount of stereodirecting effect (Scheme 27).

Scheme 27:

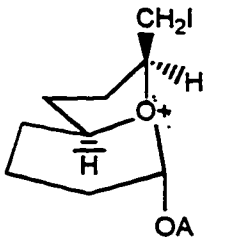


Computation

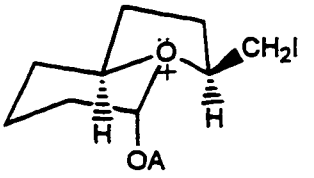
In order to determine whether the relative energies of the bicyclic oxonium ion paralleled the relative transition state energies for their formation, AM1 calculations were performed. This approach which is simpler than the direct calculation of transition state energies was viewed as an initial step in modeling the reaction pathway.

Calculations were carried out by AM1[51] semi empirical method. Simple pyranoside alkenes were used for the study. For a particular aglycone substitutent, two *cis* (A, B) and two *trans* (C, D) THF-oxonium ions corresponding to axial or equatorial attack by the oxygen on the ring substituent were examined (Scheme 28).

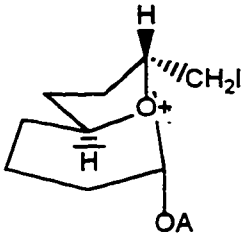
Scheme 28:



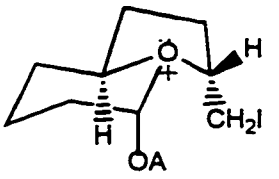
A ⟶ cis product



B ⟶ cis product



C ⟶ trans product

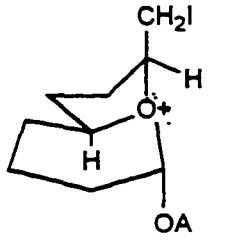


D ⟶ trans produc

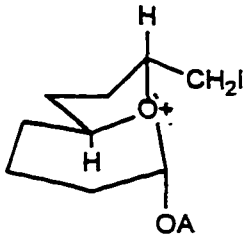
For the minimum energy conformations of the *cis/trans* pair corresponding to axial attack (A and C) the pyranoside ring adopted a boat conformation and THF ring was in the half- chair conformation (scheme 29).

The calculated ΔH difference for the *cis* and *trans* isomers of methyl and t-Butyl glycosides corresponding to A and D followed the same trend as the experimental results. However, calculated results for the key trityl derivative disagreed sharply with the observed selectivity. Hence the model of oxonium ion's A and D was rejected.

Scheme 29:



A ⟶ *cis* product



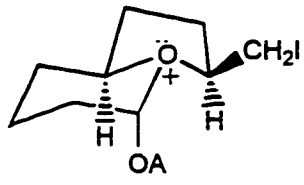
B ⟶ *trans* product

A= Me	79.63 Kcal/mol	83.03 Kcal/mol
A=tBu	66.41 Kcal/mol	72.05Kcal/mol
A=Tr	176.19 Kcal/mol	177.21Kcal/mol

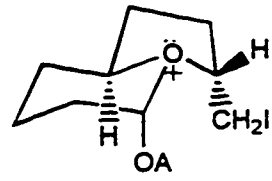
Aglycone	Differences in Heat of Formation Calculated	Observed Stereoselectivity *cis/trans*
A= Me	3.40 Kcal/mol	1.2/1
A=tBu	5.64 Kcal/mol	1.5/1
A=Tr	1.02 Kcal/mol	3.5/1

A similar analysis was carried out for the two oxonium ions corresponding to equatorial attack (Scheme 30). The pyranoside ring adopted chair conformation and the THF ring a half chair conformation which is in agreement with our proposed model (Scheme 27). The variation in *cis/trans* energy difference with the size of aglycone also appeared to be a close fit with the experimental data compared with the axial trajectory. Thus it appeared from the simple study that relative energies of oxonium ion of type B, D (equatorial trajectory) could be useful model for predicting stereoselectivity.

Scheme 30:



B⟶ *cis* product



E⟶ *trans* product

A= Me	77.92 Kcal/mol	80.27 Kcal/mol
A=Et	70.68 Kcal/mol	73.76 Kcal/mol
A=tBu	63.00 Kcal/mol	67.47 Kcal/mol
A=Tr	178.50 Kcal/mol	184.26 Kcal/mol

Aglycone	Differences in Heat of Formation Calculated	Observed Stereoselectivity *cis*/*trans*
A= Me	2.35 Kcal/mol	1.2/1
A= Et	3.08 Kcal/mol	1.5/1
A=tBu	4.47 Kcal/mol	3.5/1
A=Tr	5.76 Kcal/mol	>10/1

II.2 Halocyclization of More Substituted Trityl Pyranosides

Preparation of the Trityl Derivatives

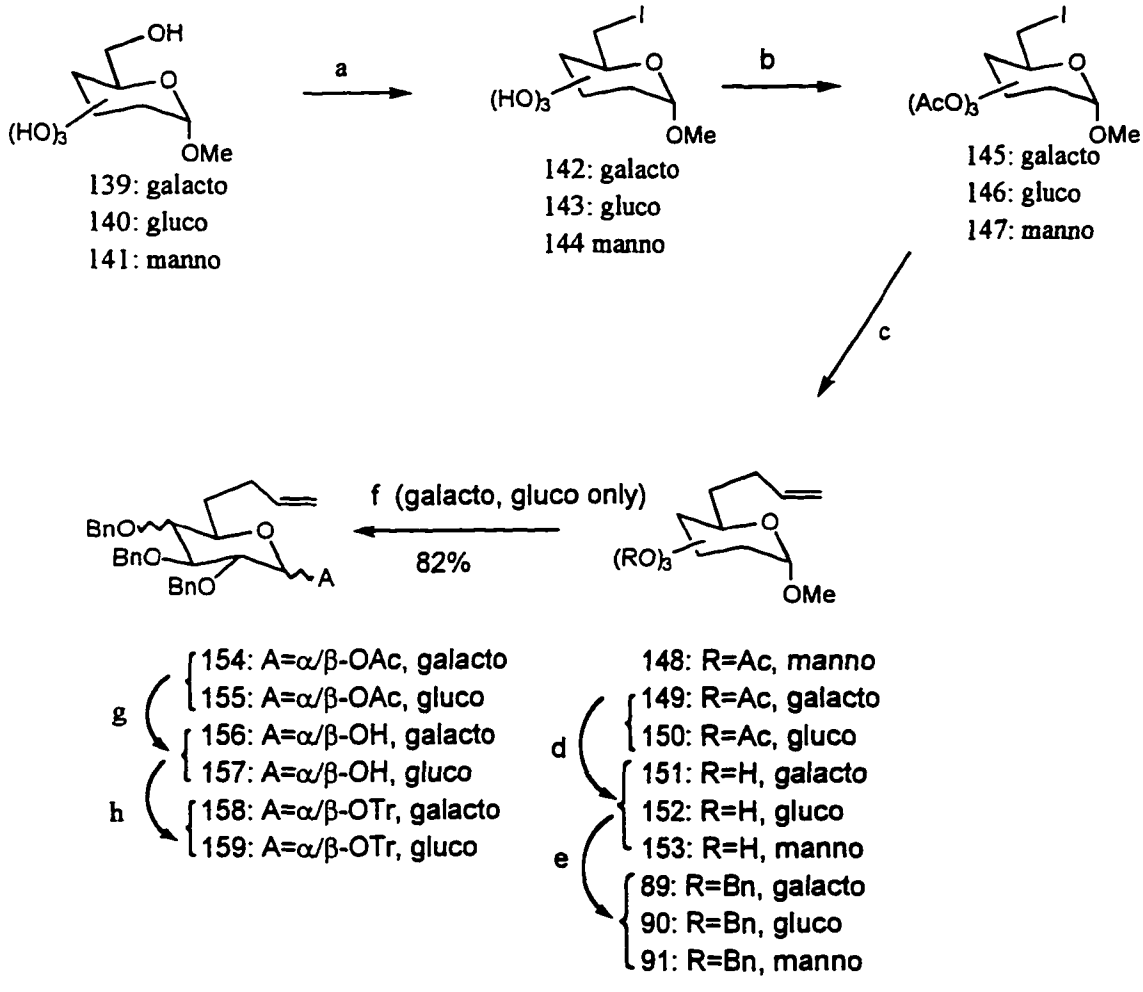
In order to evaluate the stereo directing ability of triphenylmethyl aglycones in more substituted pyranoside, alkene precursors of galacto-, gluco- and manno-pyranosides were examined. The THF products of these cyclizations were similar to the fragments of the ionophore antibiotics.

The methyl tri-O-benzyl pyranoside alkenes **148**, **149** and **150** were prepared via a published protocol which was developed in this laboratory[52]. This involved a five step sequences in which the key steps were an initial selective iodination[53] of the commercially available methyl pyranosides **139**, **140**, and **141**, and the Keck allyl radical coupling reactions[54] of the peracetylated pyranosides (Scheme 31).

The trityl glycosides of **158, 159,** and **163** were next prepared. The first step was the preparation of the corresponding lactols. Attempts to directly hydrolyze methyl glycoside under aqueous acidic conditions were unsuccessful. Treatment of the methyl glycoside with acetic anhydride (Ac_2O) in the presence of $BF_3.Et_2O$ provided the glycosyl acetate **154** and **155** in 82% and 71% yield, respectively. Basic hydrolysis of the acetate **154** and **155** proceeded smoothly to afford the desired lactol **156** and **157** in 97% and 95% yields, respectively. The latter were treated under the standard condition for tritylation to afford an inseparable mixture of α/β (1/1) trityl alkenes **22** and **23** in 84% and 75% yields, respectively.

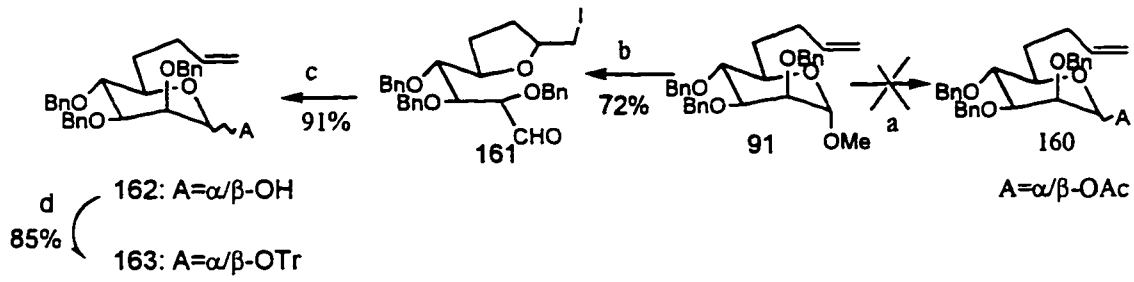
While the acetolysis reaction effective for the galacto and gluco lactols, it proved problematic for the manno derivative, yielding a mixture of several products (Scheme 32). The manno lactol **162** was eventually prepared from the zinc mediated elimination of the THF-iodide **161** obtained from the cyclization of the manno alkene **91**. Tritylation of **162** as described above gave the α/β trityl manno pyranoside mixture **163** in 85% yield.

Scheme 31



[a] Reagents and conditions: (a)2 equiv. of I_2, 2.2 equiv. of Ph_3P, 4.5 equiv. of imidazole, toluene, reflux; (b) Ac_2O, DMAP , EtOAc, rt; (c) 2 equiv. of allyltributyltin, AIBN, PhH, reflux, overnight ;(d)1N NaOMe/MeOH; (e) 1.5 equiv. of BnBr, 2 equiv. of NaH, 0.1 equiv. of Bu_4NI, overnight; (f) Ac_2O, $BF_3.OEt$, rt; (g)1M NaOMe/MeOH, rt., 2h; (h) 3 equiv. of Ph_3CCl , 3 equiv. of AgOTf, 3 equiv. of collidine, 4 A M.S., Ar, 10 min.;

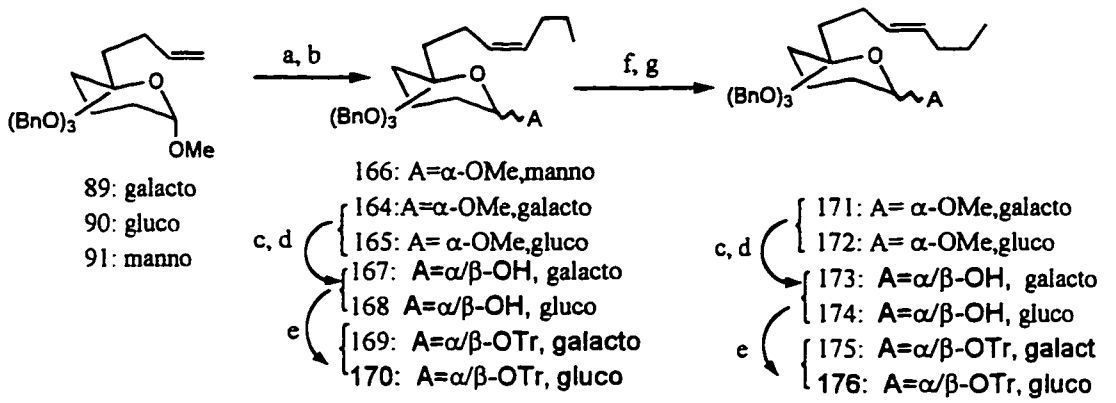
Scheme 32:



[a] Reagents and conditions: (a)BF_3.OEt, Et_2O (b) 2.5 equiv. of IDCP, CH_2Cl_2, rt. , 15 min., 72%; (c)Zn/ 95%EtOH/H_2O, reflux, 30 min., 91%; (d) 3 equiv. of Ph_3CCl , 3 equiv. of AgOTf, 3 equiv. of colliding, 4 A MS, AR, 10 in; 85%.

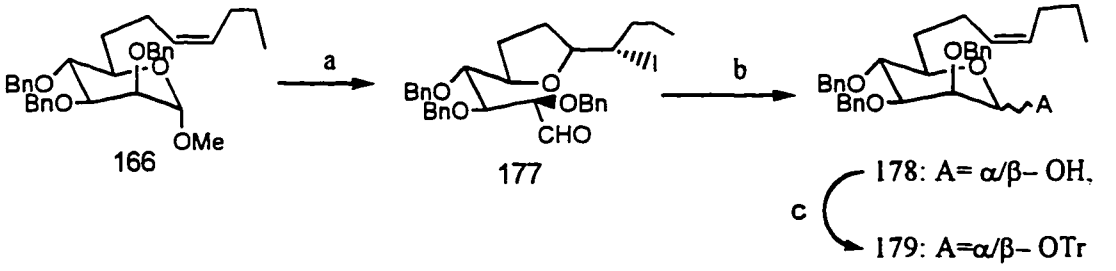
The methyl Z and E vicinal disubstituted alkenes **164**, **165**, and **166** were prepared from the terminal alkene derivatives as was described in 2,3- dideoxy pyranoside substrates (Scheme 25). Wittig olefination on the aldehydes derived from ozonolysis of the terminal alkenes **89**, **90** and **91** gave the Z alkenes **164**, **165**, and **166** respectively. The E alkenes **171** and **172** were obtained by the Vedejs alkene isomerization procedure on the corresponding Z compounds. The trityl Z and E derivatives of galacto and gluco were obtained from the respective methyl substrates via acetolysis, hydrolysis and tritylation as described for the terminal alkenes (Scheme 31). The Z and E manno alkenes were prepared over three steps from the methyl glycosides via iodocyclization, zinc-mediated reduction and tritylation (Scheme 34).

Scheme 33:



[a] Reagents and conditions: (a) O_3, CH_2Cl_2/MeOH, -78°C; then $(CH_3)_2S$, -78°C-rt., 1h; (b) 5 equiv. of $CH_3CH_2CH_2CH_2P^+Ph3Br^-$, 5 equiv. of $NaN(SiMe_3)_3$, toluene, -78°C; (c) 10 equiv. of Ac_2O, 0.1 equiv. of $BF_3.Et_2O$, CH_2Cl_2, Ar, rt 1.5h; (d)1M NaOMe, rt., 2h; (e) 3 equiv. of Ph_3CCl , 3 equiv. of AgOTf, 3 equiv. of collidine, 4 A M.S., Ar, 10 min.; (f) 2.5 equiv. of MCPBA, CH_2Cl_2, Na_2HPO_4/NaH_2PO_4, rt., 1.5h; (g) 3 equiv. of Ph_2PH, 3 equiv. of n-BuLi, dry THF, rt., 2h, then MeI, 1h.

Scheme 34:



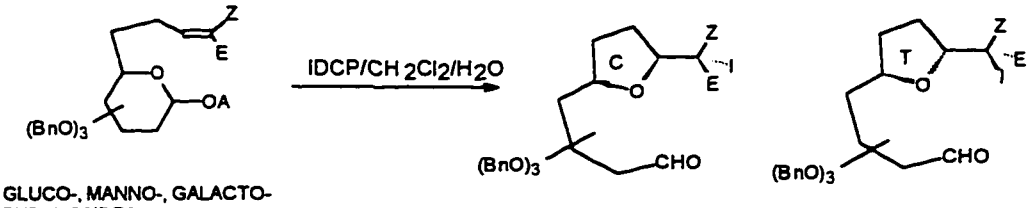
[a] Reagents and conditions: (a) 2.5 equiv. of IDCP, CH_2Cl_2, rt. , 15 min., 87%; (b)Zn/ 95%EtOH/H_2O, 30 min., 92%; (c) 3 equiv. of Ph_3CCl , 3 equiv. of AgOTf, 3 equiv. of collidine, 4 A M.S., Ar, 10 min.; 88%.

Cyclization Studies

The iodocyclization reactions on the trityl alkene substrates were carried out under the standard condition (IDCP/CH_2Cl_2/H_2O). Control cyclizations using the methyl glycosides were also carried out. The trityl glycosides were observed to react at appreciably rate compared with the methyl glycoside (20-30 min. vs 3-4 h). The yields in both cases were good to high (60-80%). As expected, the methyl glycosides showed poor stereoselectivity with no clear correlation between selectivity and the substrate structure. On the other hand, the trityl derivatives, except for the Z-manno alkenes showed an preference for *cis*-THF. The selectivity were low to moderate for the manno terminal alkene and for the gluco series (3/1, 6/1, 7/1, 2/1, respectively) and excellent for the galacto series (*cis* only).

Although the manno Z alkene was *trans* selective (c/t: 2/3), it should be pointed that the proportion of the *cis* isomer was higher than the reaction of the corresponding methyl glycoside (c/t:2/5). The reactions of the manno derivatives were also unusual in that the NMR of the product indicated the presence of two aldehyde signals in addition to those of the expected products. We speculated that these might be due to THF products which were isomerized at the reaction to the aldehyde, and formed as a result of epimerization during the cyclization (Scheme 35):

Table 7: Iodoetherification of Galacto-, Gluco-, and Manno- Pyranoside Alkenes



Alkene structures		THF PRODUCTS								
		Terminal (Z=E=H)			Z-alkene (Z=Pr, E=H)			E-alkene (Z=H, E=Pr)		
		THF	c/t [a]	yield [b]	THF	c/t [a]	yield [b]	THF	c/t [a]	yield [b]
Galacto	A=α-OMe	180	5/3	65%	181	5/3	92%	182	3/1	85%
	A=α/β-OCPh3	180	cis only	82%	181	cis only	87%	182	cis only	83%
Gluco	A=α-OMe	183	4/5	76%	184	1.1/1	87%	185	1/1	86%
	A=α/β-OCPh3	183	6/1	88%	184	7/1	79%	185	2/1	84%
Manno	A=α-OMe	161	5/2	72%	177	2/5	93%			
	A=α/β-OCPh3	161	3/1	65%	177	2/3	62%			

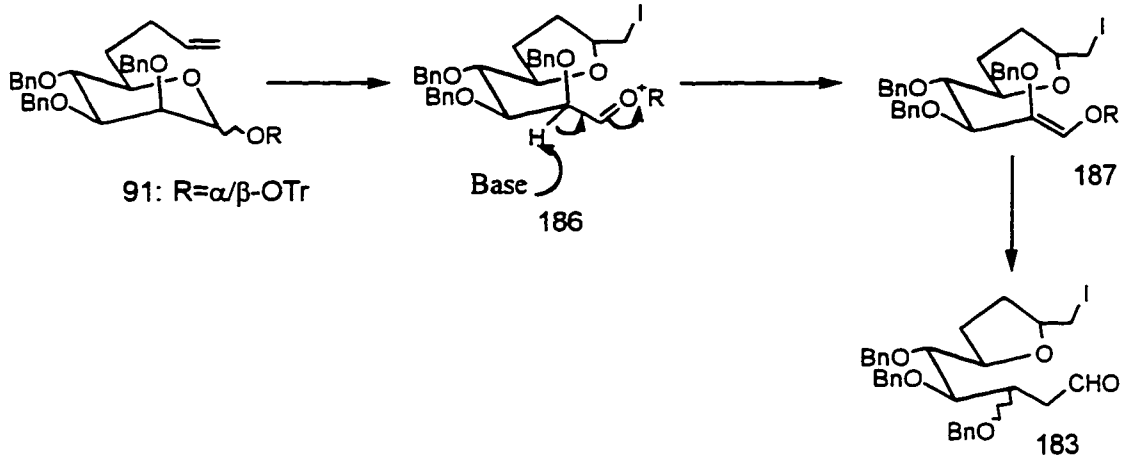
[a] c/t ratio were determined from ^{1}H and ^{13}C NMR.

[b] yields were for chromatographically isolated products unless stated otherwise.

The general increase in the *cis* selectivity from the methyl to trityl pyranosides appeared to fit the stereochemistry described earlier (Scheme 27). That the level of

stereoselectivity varied considerably from gluco to manno to galacto suggested that the stereoselectivity was to some extent substrate dependent

Scheme 35:

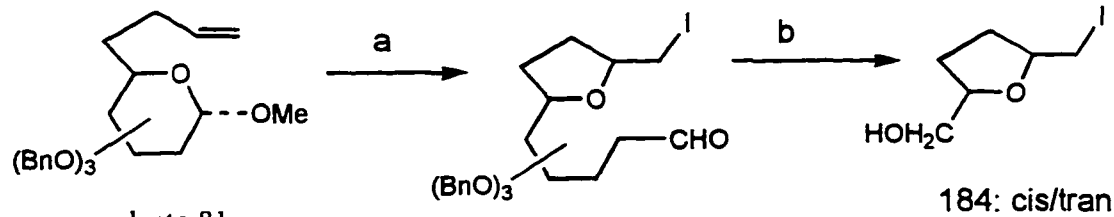


Assignment of THF Stereochemistry

The configuration of the new stereogenic centers in the THF products (**180**, **183**, and **161**) from the terminal alkenes (**89**, **90**, and **91**) were confirmed through degradation[55] to the known 5-methyl tetrahydrofuran-2-methanol isomers[56] (Scheme 35). For the *cis* derivative, the two methylene carbons in the primary iodo-THF's **92**, **93**, **94** were more upfield relative to the trans diastereoisomers. This trend was also observed in related 2,5-bis hydroxy methyl THF's.[57] As mentioned earlier on the section of the 2,3-dideoxy substrate, these correlation was also observed for the secondary iodo-THF's obtained from the cyclization of the Z and E alkenes. Accordingly, examination of the ^{13}C NMR spectra of the THF products from the cyclization of the gluco, glacto, and manno

alkenes revealed two separated signals for C_6 and C_7 and thus allowed assignment of major and minor isomers (Table 8).

Scheme 35:



galacto 81
gluco 82
manno 83

galacto 84
gluco 85
manno 86

Reaction conditions: (a) IDCP/CH_2Cl_2; (b) (I) CH_2Cl_2-MeOH, $BF_3.OEt_2$; (ii) nBu_3SnH, PhH, reflux; (iii) Na/NH_3, ether, -33°C; (iv) $NaIO_4$, THF-H_2O; (v) $NaBH_4$, EtOH.

Application to Polyether Synthesis

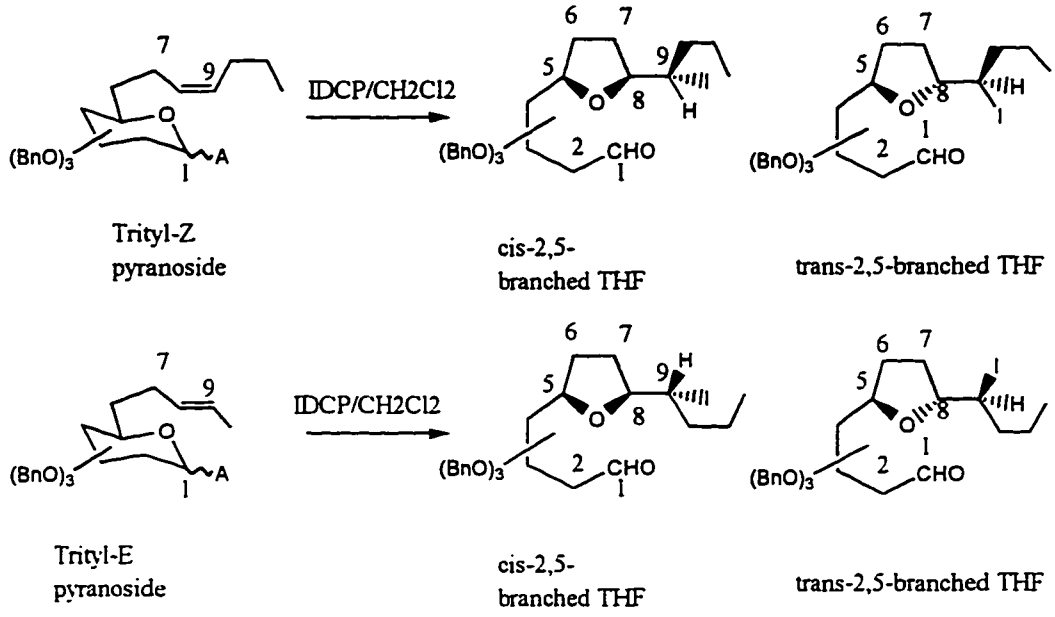
The potential of the pyranoside alkene strategy in the synthesis of highly complex framework found in the polyether antibiotics was illustrated in this section. The haloetherication methodology was suitable for targets containing *cis*-2,5-disubstituted THF with highly substituted branches.

For example, the synthesis of Ionophor A204 could arise from an aldol type coupling of an enolate derived from a CDE-ketone **185** and an F-aldehyde fragment **186**, a strategy which has been successfully used in polyether synthesis (Scheme 36). The CDE fragment contains a *cis*-2,5 disubstituted THF which would come from the intramolecular etherification of a THF iodide **181**. The latter is related to a trityl pyranoside alkene **188**

through key haloetherification reaction. The substrate **188** was structurally very similar to a trityl pyranoside *Z*-alkene **154** which was shown to give the high cis stereoselectivity on our earlier work (II.2.2). The main difference between these two templates was that the C4 position of the pyranoside **188** was disubstituted. According to our stereoselectivity model this difference is not expected to decrease *cis* selectivity (Scheme 37).

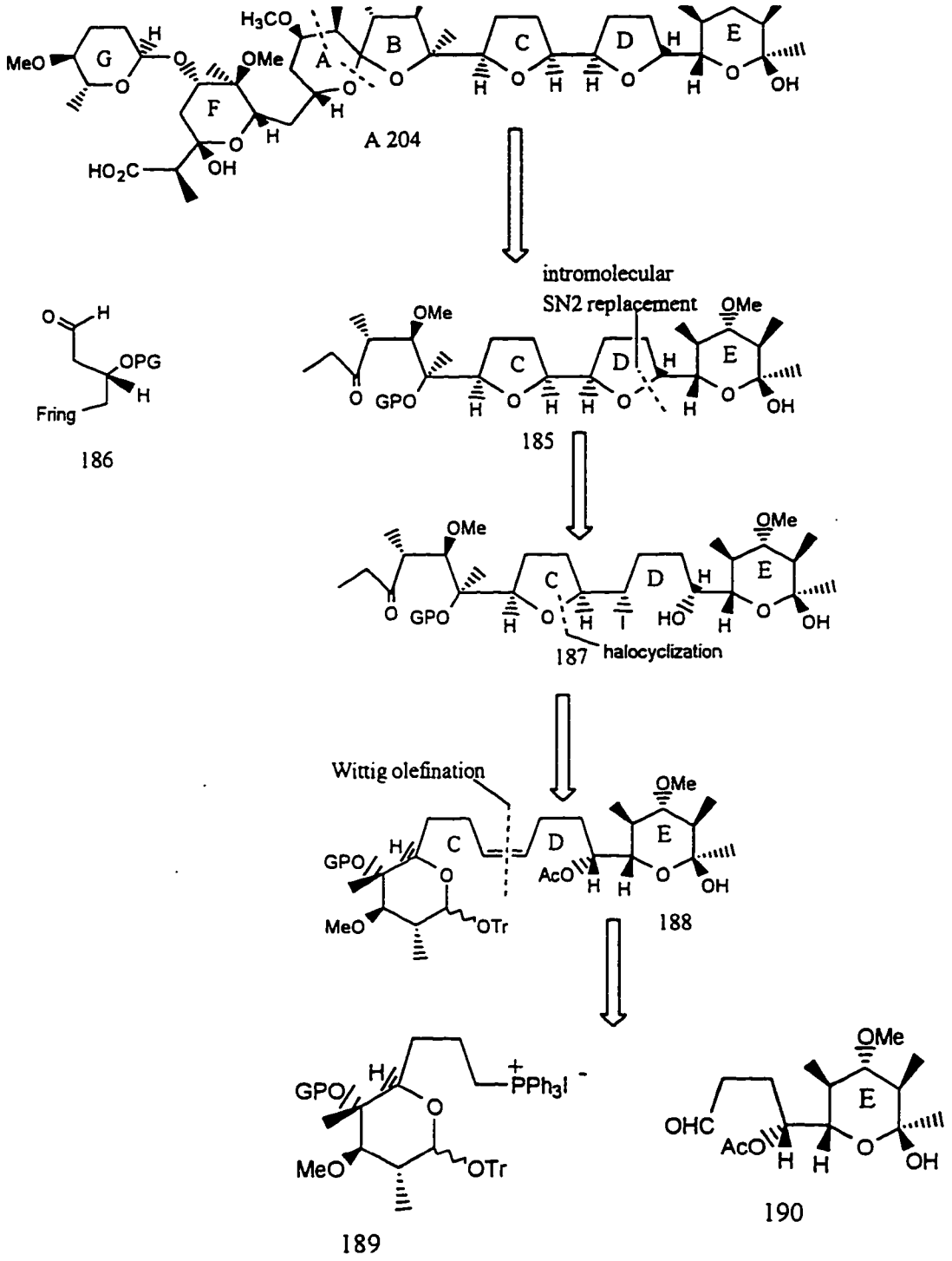
An attractive aspect of this strategy was that the key trityl pyranosides alkene **188** may be prepared in a highly convergent fashion from monosaccharide pyranoside **189** and **190**. The halocyclization reaction then allow rapid progression to a CDE tris cyclic ether which would be a versatile intermediate in the synthesis of several polyether antibiotics.

Table 8: ^{13}C NMR of the C6, C7 in the THF's from Galacto-, Gluco-, and Manno-Pyranoside Alkenes

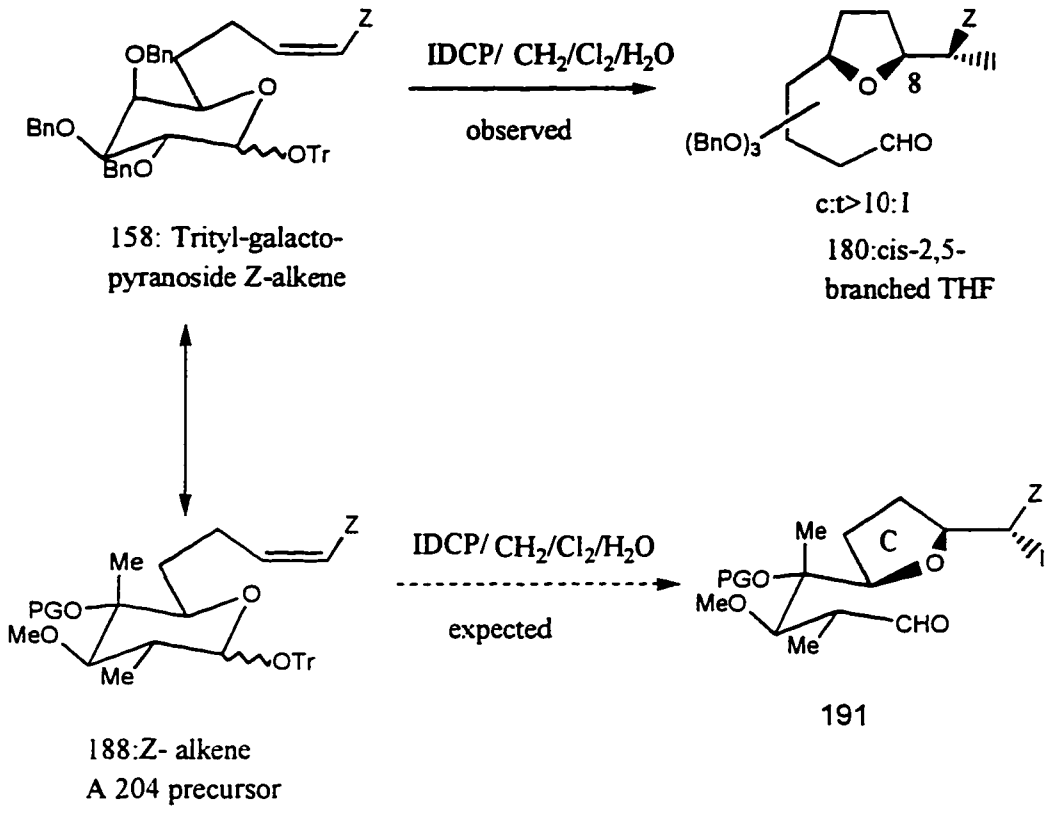


	THF products					
	Z=E=H		Z=Pr, E=H		Z=H, E=Pr	
galacto	cis	trans	cis	trans	cis	trans
C6	27.34	28.07	27.82	28.50	27.49	28.29
C7	31.26	32.61	30.18	30.46	32.51	33.32
gluco						
C6	27.86	29.32	28.09	29.52	27.48	29.13
C7	31.23	32.50	30.61	31.75	31.74	33.05
manno						
C6	27.47	28.43	28.29	29.29		
C7	31.26	31.26	30.80	31.89		

Scheme 36:



Scheme 37:



158: Trityl-galacto-pyranoside Z-alkene

c:t>10:1

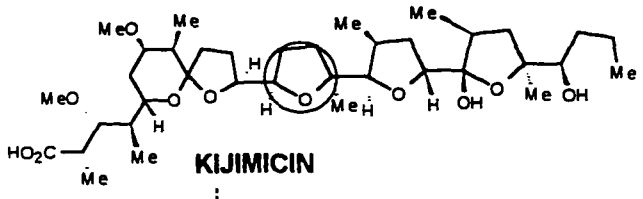
180:cis-2,5-branched THF

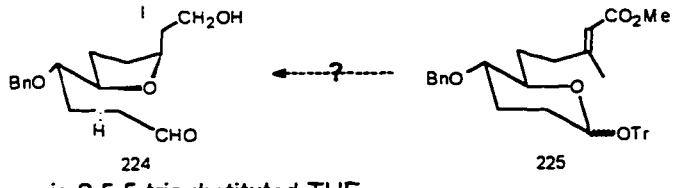
188:Z- alkene
A 204 precursor

II.3 Preparation of 2,5,5-Trisubstituted THF's

The extension of the pyranoside alkene methodology to the synthesis of 2,5,5 trisubstituted THF was next explored. This was also a widely occurring polyether subunit. Model pyranoside alkene subunit **224** was therefore prepared.

Scheme 37:





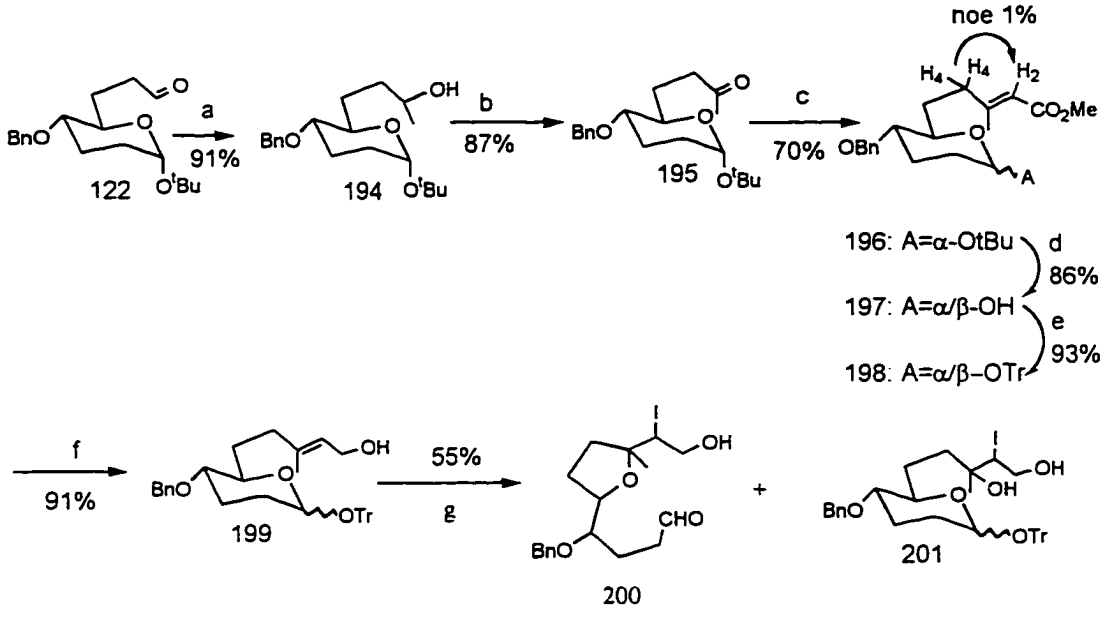
224
cis-2,5,5-trisubstituted THF

225
trityl -trisubstituted alkene precursor

Synthesis: Aldehyde **122** was obtained 8 steps from the commercial available triacetyl glucal in 28% overall yield as described before. Addition of methyl magnesium bromide to the previously obtained aldehyde **122** gave the alcohol **194** in 91% yield. PCC oxidation of **194** provided the methyl ketone **195** in 87% yield. The latter was treated with sodium triethyl phosphonoacetate in anhydrous THF to provide the E alkene **196** in 70% yield, the stereochemistry of which was assigned on the basis of a nOe effect between H_1 and H_3 (Scheme 39)

Carefully hydrolysis of the t-Butyl glycoside with 0.5N HCl/THF provided the lactol **197** in 86% yield with the methyl ester intact. Tritylation of **197** to give trityl pyranoside **198** as described before. DIBAL reduction of compound **198** provided the desired cyclization precursor **199** in 91% yield.

Scheme 38:



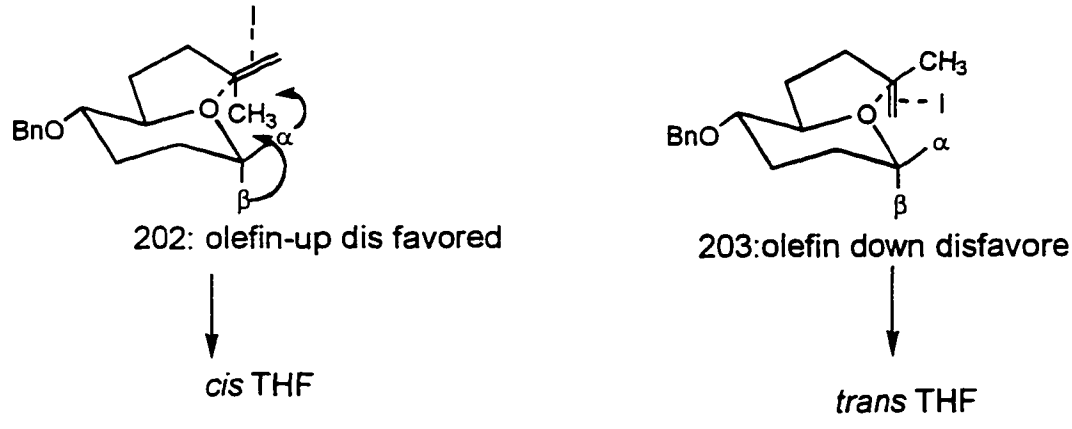
[a] Reagents and conditions: (a)3 equiv. of CH_3MgBr, THF, 0°C, 1h, 91%; (b) 5 equiv. of PCC, CH_2Cl_2, Ar, 1h, 87%; (c) 2 equiv. of NaH, 2.2 equiv. of triethyl phosphonoacetate, THF, 0°C ,70%;(d)0.5N HCl/THF, rt, 2h, 86%; (e) 3 equiv. of Ph_3CCl , 3 equiv. of AgOTf, 3 equiv. of collidine, 4 A M.S., Ar, 10 min; 85%;(f) 5 equiv. of DIBALH, PhH, 30 min, -78°C, 91% (g) 2.5 equiv. of IDCP, CH_2Cl_2, rt. , 45 min., 55%.

Cyclization studies was carried out under the standard condition (IDCP/CH_2Cl_2 /H_2O). Unfortunately, the reaction proceed slowly to give a low 55% yield of an

approximately 1:1 mixture of 2,5,5-trisubstituted THF's. The major other product formed in the reaction was presumed to be the iodohydrin **201**.

The poor stereoselectivity associated with the cyclization of 199 is most likely due to the reaction of two conformer, **202** and **203** of similar energy (Scheme 39).

Scheme 39:



II.4 Experimental

II.4.1 General Procedures

Proton and Carbon Nuclear Magnetic Resonance (^{1}H-NMR and ^{13}C-NMR) were recorded on a GE, QE 300 instrument at 300 and 75.5 MHz respectively. Deutero-chloroform ($CDCl_3$) and deuterobenzene (C_6D_6) were used as solvents with TMS, $CHCl_3$, or $CDCl_3$ as internal standards. Chemical shifts were reported in parts per million (δ) down-field from tetramethylsilane; coupling constants (J) were calculated in Hertz (Hz). The splitting patterns were designated s (single), d (double), dd (double doublet), t (triplet), dt (double triplet), q (quartet), m (multiplet), and br (broad). Hydroxyl protons were identified by exchanged with deuterium oxide. Elemental analysis were performed by Schwarzkopf Microanalysis Laboratory. High resolution Mass Spectroscopy was carried out by Mass Spectrometry Laboratory, University of Illinois at Urbana-Champaign.

The progress of all reactions was monitored by the thin layer chromatography (TLC) on aluminum sheets precoated with silica gel 60 (HF-254, E. Merck) to a thickness of 0.25 mm. The chromatogram were visualized under ultraviolet light, sprayed with a solution of ammonium molybdate VI tetrahydrate (12.5g) and cerium (IV) sulfate tetrahydrate (5.0g) in 10% aqueous sulfuric acid (500ml) and charred by heating on a hot plate. Flash chromatography was performed using Kieselgel 60 (230-400 mesh, E. Merck) and unless otherwise stated employed a stepwise solvent polarity gradient of the solvent mixture reported for TLC.

Solvents were reagent grade and was used without further purification, unless otherwise stated. Anhydrous diethylether and THF were distilled under N_2 from sodium and potassium benzophenone ketyl prior to use. Dichloromethane (CH_2Cl_2) was distilled from phosphoium pentaoxide prior to used. Triethylamine (Et3N) and dimethylformamide (DMF) were distilled from calcium hydride. Benzene and toluene were dried by azeotropic removal of water.

Solvents were evaporated at water aspirator pressure using a Buchi Rotovapor. Anhydrous samples were obtained by azotropic solution in toluene followed by dryings at room temperature (rt) or at 40 ^{0}C by high vacuum (~0.1 mm Hg).

Stock solution of n-butyllithium (BuLi), sodium bis(trimethylsilyl) amide and grinard reagents were purchased from Aldrich Chemical Company and were used directly

II.4.2 Hydrogenation of Alkenes

A solution of alkene in methanol (5ml/ mmol of alkene) was purged with argon. 10% Palladium on activated carbon (20% by weigh of alkene) was then added and the mixture stirred under an atmosphere of hydrogen balloon at rt. for 24h. At that time the mixture was purged with argon, filtrated through Celite and concentrated *in vacuo*. The residue was purified by flash chromatography.

II.4.3 Ozonolysis of Alkenes

The alkene was dissolved in CH_2Cl_2/MeOH (5/1; 5ml/mmol of alkene) and cooled to -78^{0}C. Ozone at 0.6 psi was bubbled through the solution and the reaction was monitored by TLC. Upon completion the solution was purged with argon then MeOH was added so that final was 50% v/v CH_2Cl_2/MeOH. The solution was warmed to rt.,

triphenyl phosphine (1mmol/mmol of alkene) added, stirring continued for 1 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography.

II.4.4 Wittig Olefination with n-Butylidene Triphenylphosphorane

A 1M stock solution of n-Butylidene triphenylphosphorane was prepared by the addition of sodium bis(trimethylsilyl) amide (1.0 eq. of a hexane solution) to a suspension of n-Butyl triphenylphosphonium bromide (1.0eq) in dry toluene (1ml/mmol) at rt. under an argon atmosphere. The yellow-orange suspension were stirred for 1h at rt. then cooled to -78°C. An aliquot (3mmol/mmol of aldehyde) was added dropwise to a solution of the aldehyde in dry toluene (3ml/mmol) over 30 minutes. The reaction was stirred at this temperature for 15 minutes, warmed to rt. and diluted with ether. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography.

II.4.5 Preparation of E-Disubstituted Alkenes

MCPBA (~50% w/w, 2.5mmol/mmol of Z-alkene) was suspended in a mixture of 4M NaH_2PO_4/Na_2HPO_4 buffer (18ml/mmol MCPBA) and CH_2Cl_2 (12 ml/mmol of MCPBA). The suspension was added to a solution of Z-alkene in CH_2Cl_2(10 ml/ mmol of alkene). The reaction was stirred at rt. for 1 h. The organic layer was separated, washed with saturated aqueous solutions of $NaHCO_3$ and $Na_2S_2O_3$, and brine. The combined organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography to afford the epoxide.

A 0.5M stock solution of Ph_2PLi was prepared by the addition of a hexane solution of n-Butyllithium (1.0 eq) to a solution of Ph_2PH (1.05 eq) in dry THF at rt. under an argon atmosphere followed by stirring for 1 h. The red solution of Ph_2PLi (5 mmol/mmol of epoxide) was added to a solution of the above epoxide in dry THF (10ml/mmol) at rt. under an argon atmosphere and stirring continued for an additional 2 hours. At that time freshly distilled MeI (10mmol/mmol epoxide) was added. The mixture was stirred for an additional 1 h. The reaction mixture was diluted with ether, filtered through Celite and the filtrate concentrated *in vacuo*. The residue was subjected to flash chromatography.

II.4.6 Acetylation of Alcohols

A solution of alcohol and 4-dimethylaminopyridine (1.5mmol/mmol alcohol) in dry ethyl acetate (5ml/mmol alcohol) was treated with acetic anhydride (1.5mmol/mmol alcohol) at room temperature. The reaction was monitored by TLC and upon completed, quenched with methanol. The volatile were removed *in vacuo* and the residue purified by flash chromatography.

II.4.7 Benzylation of Alcohols

Sodium hydride (1.5mmol/mmol of alcohol, 60% suspension in mineral oil), was added to a solution of the alcohol in dry DMF (5ml/mmol of alcohol) at 0°C. After stirring at the temperature for 20 minutes, benzyl bromide (1.2 mmol/mmol of alcohol) and tetra-n-Butylammonium iodide (0.1 mmol/mmol of alcohol) were added. The reaction mixture warmed to rt., and stirred for an additional 1h. The mixture was then recooled to 0°C, carefully quenched with methanol, and diluted with water. The resulting suspension

was extracted with ether, the combined organic phase was washed with a saturated solution of sodium chloride, dried over Na_2SO_4, filtered ,and evaporated *in vacuo*. The crude residue was purified by flash chromatography.

II.4.8 Preparation of Trityl Pyranosides

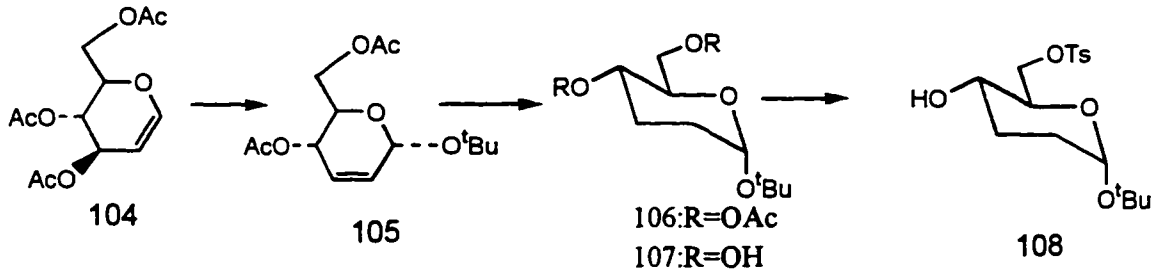
A solution of the pyranoside in dry CH_2Cl_2 (5ml/mmol of alcohol), anhydrous 2,4,6-collidine (3mmol/ mmol of the pyranoside) and freshly activated 4 A molecular sieves was stirred for 15 minutes. Trityl chloride (3mmol/mmol of the alcohol) and silver trifluoromethane sulfonate (3 mmol/ mmol alcohol) were then added. The deep yellow solution was stirred for 5 minutes at which time saturated $Na_2S_2O_3$ solution was added. The mixture was extracted with ether, and the combined organic extract was dried (Na_2SO_4), filtered, concentrated *in vacuo*. The residue was purified by flash chromatography.

II.4.9 Iodoetherification of Pyranoside Alkenes

To a stirred solution of the pyranoside alkene in CH_2Cl_2 (10ml/1mmol of alkene) and water (1% volume of CH_2Cl_2), was added iodonium dicollidine perchlorate (IDCP, 1.2mmol/mmol of the alkene). The reaction mixture was stirred at rt. for 10 min. The light pink solution was then quenched with saturated aqueous $Na_2S_2O_3$ solution, and extracted with diethyl ether. The combined organic extract was dried (Na_2SO_4)and concentrated *in vacuo*. The residue was purified by flash chromatography.

II.4.10 Preparation of 2,3-Dideoxy Pyranoside Alkenes

t-Butyl 2,3-dideoxy-6-O-tosyl-α-D-gluco pyranoside (108)



To a solution of TAG **104** (20g, 0.073mol) in 40 ml anhydrous CH_2Cl_2 was added t-BuOH (14 mL, 0.149 mol) and $BF_3.OEt_2$ (1.0 mL, 8.06 mmol). The solution was stirred for 15 h at rt. then washed by saturated $NaHCO_3$, extracted with CH_2Cl_2 , dried (Na_2SO4) and evaporated *in vacuo*. The residue was purified by flash column chromatography to afford compound **106**[1] (10.3g, 49%) as a light yellow syrup. TLC Rf=0.78 (10% EtOAc/PE). ^{1}HNMR($CDCl_3$): δ 1.24(s, 9H), 2.05(s, 6H), 4.10(m, 3H), 5.20 (m, 2H), 5.80(m, 2H).

Compound **105** (10g, 0.034mol) was subjected to the standard procedure of hydrogenation (II..4.2). Compound **107** [1] (7.8g, 75%) was obtained as light yellow syrup after purification. TLC R_f=0.75 (10% EtOAc/PE). ^{1}HNMR($CDCl_3$): δ 1.22(s, 9H), 2.0(s, 6H), 4.05(m, 2H), 4.22(m, 1H), 4.65(m, 1H), 5.10 (bs, 1H).

To a solution of compound **106** (7.5g, 0.026 mol) in anhydrous MeOH (20 mL) was added 1M NaOMe in MeOH (2 mL). The solution was stirred for 1 h at rt., then neutralized with 10% HCl and evaporated *in vacuo*. The residue was purified by flash column chromatography to afford the desired compound **107** (4.8g, 91%). TLC R_f=0.25(

[1] Isobe. M.; Ichikawa. Y.; Funabashi. Y.; Mio. S.; Goto. T.; *Tetrahedron*. **1986**, 42, 2863

30% EtOAc/ PE). ^{1}HNMR ($CDCl_3$): δ 1.24(s, 9H), 1.80(m, 4H), 3.5-3.85(m, 4H), 5.10 (m, 1H).

To a solution of compound **107** (4.2g, 0.020 mol) in pyridine (50 mL) was added TsCl (4.57g, 0.024 mol). The solution was stirred for 2 h at rt., then quenched by adding MeOH (1 mL). The mixture was washed with saturated Na_2CO_3, extracted with CH_2Cl_2 (3x50 mL), dried (Na_2SO_4) and the filtrate evaporated *in vacuo*. The residue was purified by flash column chromatography to afford the title compound **109** (3.7g, 52%). TLC R_f=0.45(30% EtOAc/ PE). ^{1}HNMR($CDCl_3$): δ 1.24(s, 9H), 1.72(m, 4H), 2.42(s, 3H), 3.52(m, 1H), 3.82(bs, 1H, -OH), 4.02(m, 2H), 4.38(m, 1H), 5.05 (bs, 1H), 7.35(m, 2H), 7.78(m, 2H). ^{13}C NMR($CDCl_3$): 21.77, 27.12, 28.76, 30.91, 66.02, 70.18, 71.45, 74.54, 90.78, 128.09, 128.16, 129.96, 129.89, 133.45, 145.05.

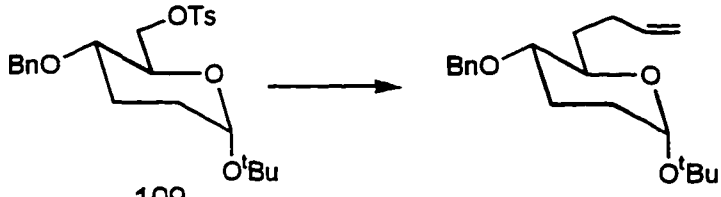
t-Butyl-4-O-benzyl-2,3-dideoxy-6-O-tosyl-α-D-glucopyranoside (109)

108 109

Compound **109** (3.5g, 9.7 mmol) was subjected to the standard procedure for Benzylation of alcohols (2.4.3) . Compound **110** was obtained (3.0g, 69%) as light yellow syrup after purification. TLC R_f=0.70 (10% EtOAc/PE). ^{1}HNMR($CDCl_3$): δ 1.20(s, 9H), 1.65(m, 2H), 1.80(m, 1H), 2.02(m, 1H), 2.40(s, 3H), 3.40(m, 1H), 3.98(m, 1H), 4.18(d,

J=11.94 Hz,1H), 4.32(m, 2H), 4.80(d, J=11.25Hz, 1H), 5.02 (bs, 1H), 7.35(m, 9H), 7.80(m, 2H).

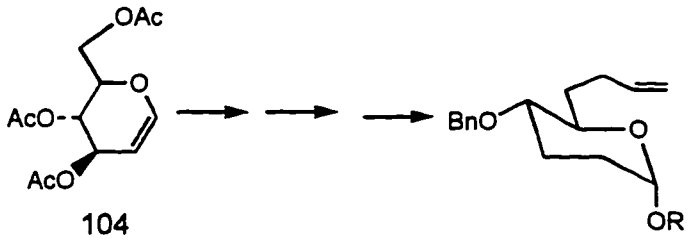
t-Butyl-4-O-benzyl-2,3-dideoxy-α-D-glucopyranoside alkene (110)



109 110

To a solution of compound **109** (2.9g, 6.5mmol) in anhydrous Et_2O (60 mL) was added TMEDA(0.65 mL), and allylmagnesium bromide (5 mL, 32.5 mmol). The solution was stirred for 2 h at rt., then poured into saturated aqueous NH_4Cl and extracted with Et_2O (3x60 mL). The organic extract was dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography to afford alkene **110** (1.0g, 79%). TLC R_f=0.65(10% EtOAc/ PE). ^{1}HNMR(C_6D_6): δ 1.46-2.60(m, 8H, H_2, H_3, H_6, H_7), 1.17(s, 9H, -CMe_3), 3.07(ddd, J=1.2, 4.6, 9.4Hz, 1H, H_4), 4.05(dt, J=1.9, 9.0Hz, 1H, H_5), 4.36(Abq, Δδ=0.20 ppm, J=11.Hz), 5.02(br s, 1H, H1), 5.06(m,2H, H_9), 5.84(m, 1H, H_8), 7.07-7.30 (m, 5H, -ArH). ^{13}C NMR(C_6D_6, 75.5Hz): 24.00, 28.86, 30.17, 31.22, 32.37, 70.43, 71.22, 77.95, 90.57, 114.34, 127.67, 127.77, 127.86, 139.49.

Methyl, Ethyl, Trifloroethyl Pyranoside Alkenes



104

111: R=OCH_3
112: R=OCH_2CH_3
113:R=OCH_2CF_3

Methyl, ethyl and trifluoro ethyl gluco pyranoside alkenes were prepared from tri-O-acetyl-D-gluco as described for the t-butyl derivative.

Methyl-4-O-benzyl-2,3-dideoxy -α-D-glucopyranoside alkene (111)

TLC R_f=0.65 (10% EtOAc/ PE). ^{1}HNMR($CDCl_3$): δ 1.40-2.40(m, 8H), 3.2(m, 1H), 3.4(s, 3H), 3.62(t, J=7.2Hz, 1H), 4.6(m, 2H), 5.06(m, 3H), 5.92(m, 1H), 7.4(m, 5H).

Ethyl-4-O-benzyl-2,3-dideoxy-α-D-glucopyranoside alkene (112)

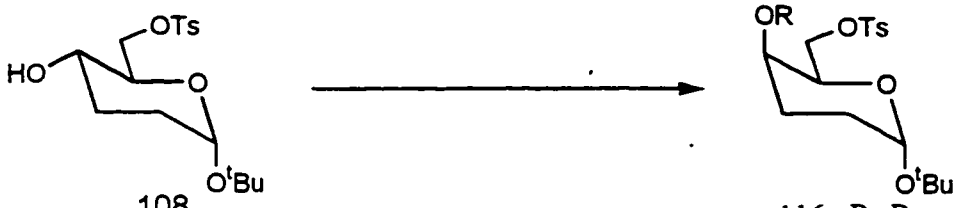
TLC R_f=0.65(10% EtOAc/ PE). ^{1}HNMR($CDCl_3$): δ 1.25(t, J=7.2Hz, 3H), 1.40-2.40(m, 8H), 3.2(m, 1H), 3.45(m, 1H), 3.74(m, 2H), 4.50(d, J=12.05Hz, 1H), 4.74(d, J=12.02 Hz, 1H), 4.80(bs, 1H), 5.06(m, 2H), 5.95(m, 1H), 7.4(m, 5H).

Trifluoroethyl-4-O-benzyl-2,3-dideoxy -α-D-glucopyranoside alkene (113)

TLC R_f=0.62 (10% EtOAc/ PE). ^{1}HNMR($CDCl_3$): δ 1.40-2.40(m, 8H), 3.2(m, 1H), 3.64(t, J=7.1Hz, 1H), 3.94(m, 2H), 4.52(d, J=11.15Hz, 1H), 4.78(d, J=11.10Hz, 1H), 4.90(s, 1H), 5.06(m, 2H), 5.95(m, 1H), 7.4(m, 5H).

2,3-Dideoxy Galacto Pyranoside Terminal Alkenes

t-Butyl-4-O-benzyl-2,3-dideoxy-6-O-tosyl-α-D-galactopyranoside (117)



108

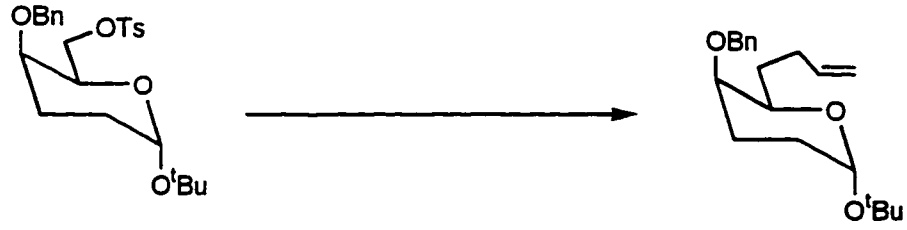
116a:R=Bz
116b:R=H
117 :R=Bn

A solution of $(C_6H_5)_3P$ (1.29 g, 4.9 mmol) in anhydrous toluene (10 mL) was added to a mixture of DEAD (972mg, 5.59mmol), C_6H_5COOH (682.2mg, 5.59mmol) and alcohol **108** (500mg, 1.40 mmol) in anhydrous toluene (25 mL) at -15 ^{0}C under an argon atmosphere. The reaction mixture was slowly warmed to rt, stirred for 2h at this temperature, then concentrated *in vacuo* . For characterization a small amount of the crude residue was purified by flash chromatography. compound **116a**: TLC R_f=0.65(10% EtOAc/PE). ^{1}HNMR($CDCl_3$): δ 1.20 (s, 9H), 1.65 (m, 2H), 1.90 (m, 2H), 2.25 (s, 3H), 3.40(m, 1H), 4.02 (m, 2H), 4.42(m, 1H), 5.02 (bs, 1H), 5.10(bs, 1H), 7.10 (d,J=7.4Hz, 2H), 7.40 (t, J= 6.9Hz, 2H), 7.58 (t, J=6.7Hz, 1H), 7.65 (d, J=7.5Hz, 2H), 7.9 (d, J=7.1Hz, 2H).

The crude compound **116a** was dissolved in MeOH (5 mL) and treated with 1M NaOMe (0.2 mL). The solution was stirred for 1 h at rt, then neutralized with 10% HCl, The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography to afford the galacto alcohol **116b** (375mg, 75% from **108**). TLC R_f=0.25 (30% EtOAc/ PE). ^{1}HNMR($CDCl_3$): δ 1.30(s, 9H), 1.55(m, 1H), 1.80(m, 1H), 2.1(m, 2H), 2.55(s, 3H), 3.82(bs, 1H), 4.05(m, 1H), 4.40(mm, 2H), 5.20 (bs, 1H), 7.45(m, 2H), 7.88(m, 2H). ^{13}C NMR($CDCl_3$): 22.6, 25.2, 28.4, 28.7, 64.8, 67.5, 70.4, 74.8, 91.5, 128.1, 129.2, 132.4, 145.1.

Compound **116b** (5.39g, 15.0mmol) was subjected to the standard procedure for benzylation of alcohol(**II.4.7**). Benzyl ether **117** was obtained (4.83g, 75%) as light yellow syrup after purification. TLC R_f=0.70 (10% EtOAc/PE). ^{1}HNMR($CDCl_3$): δ 1.30(s, 9H), 2.05(m, 4H), 2.50(s, 3H), 3.60(bs, 1H), 4.30(m, 4H), 4.65(d, J=11.20Hz, 1H), 5.12 (bs, 1H), 7.20(m, 9H), 7.85(m, 2H). ^{13}C NMR($CDCl_3$): 21.4, 22.4, 25.8, 28.8, 67.3, 70.2, 71.4, 74.9, 92.5, 127.2, 127.6, 128.1, 130.2, 134.6, 138.2, 145.1.

t-Butyl-4-O-benzyl-2,3-dideoxy -α-D-galactopyranoside alkene (118)

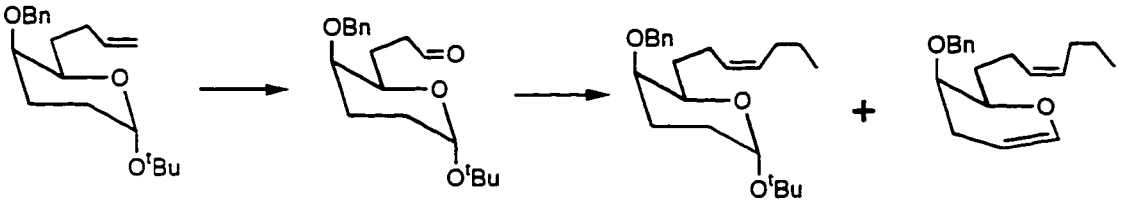


Treatment of compound **117** (4.47g, 9.7mmol) according to the allylation precedure described in the preparation of dideoxy gluco alkenes **110** afforded dideoxy galacto alkene **118** (2.66g, 80%). TLC R_f=0.65 (10% EtOAc/ PE). ^{1}HNMR(C_6D_6): δ

1.22(s, 9H, -C<u>Me</u>$_3$), 1.65-2.28(m, 8H, H_2, H_3, H_6, H_7), 3.10(bs, 1H, H_4), 3.95(m, 1H, H_5), 4.34(Abq, Δδ=0.28 ppm, J=11.9Hz), 5.15(br s, 1H, H_1), 5.05(m, 2H, H_9), 5.82(m, 1H, H_8), 7.07-7.38 (m, 5H, -ArH). ^{13}C NMR(C_6D_6): 20.43, 21.7, 25.68, 28.74, 68.10,69.92, 70.67, 70.74, 74.39, 91.25, 127.68, 127.75, 128.00, 128.39, 129.89, 133.01, 138.31, 144.79.

Z and E Alkene Derivatives

t-Butyl-4-O-benzyl- 2,3-dideoxy- α-D-galactopyranoside-Z-Alkene (123a)



118 121 123a 123b

The terminal alkene **118** (555mg, 1.66 mmol) was converted to the aldehyde according to the general ozonolysis procedure (**II.4.3**). Aldehyde **122** (467mg, 84%) was obtained as a colorless syrup after purification. TLC <u>R_f</u>=0.45 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): 1.16(s, 9H, -C<u>Me</u>$_3$), 1.62- 2.10(m, 8H, H_2, H_3, H_6, H_7), 2.99(bs, 1H, H_4), 3.81(m, 1H, H_5), 4.09(d, J=11.90, 1H, -CH_2Ar), 4.37(d, J=11.90Hz, 1H, -CH_2Ar), 7.21(m, 5H, -C_6H_5), 9.41(s, 1H, H_8). ^{13}C NMR(C_6D_6): δ 20.83, 24.49, 25.89, 28.81, 31.02, 40.18, 69.32, 70.41, 70.50, 73.33, 91.06, 127.39, 127.48, 127.15, 128.03, 128.21, 138.01, 200.79.

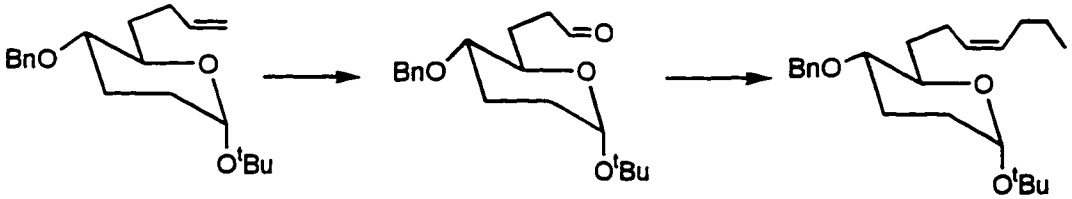
The aldehyde **122** (500mg, 1.56mmol) from the previous step was converted to the Z-alkene according to the general procedure (**II.4.4**). Z-alkene **123a** (488mg, 87%) and

the byproduct diene **123b** (45mg, 8%) was obtained as colorless syrups after purification.

For Z-alkene **123a**: TLC R_f=0.72 (10% EtOAc/PE).^{1}HNMR(C_6D_6): δ 0.92(t, J=7.3Hz, 3H, H_{12}), 1.36-2.36(m, 12H, H_2, H_3, H_6, H_7, H_{10}, H_{11}), 1.27(s, 9H, -C<u>Me</u>$_3$), 3.21(bs, 1H, H_4), 4.06(t, J=6.2Hz, 1H, H_5), 4.36(Abq, Δδ=0.29ppm, J=11.9Hz, -<u>CH2</u>Ar), 5.21(d, J=2.0 Hz, 1H, H1), 5.50(m, 2H, H_8, H_9), 7.05-7.30 (m, 5H, -ArH). ^{13}C NMR(C_6D_6): 13.91, 21.39, 23.18, 24.13, 26.35, 28.95, 29.65, 32.38, 70.30, 70.7, 73.54, 73.64, 127.28, 138.03, 139.65.

For diene **123b**: TLC R_f=0.85 (10% EtOAc/PE).^{1}HNMR(C_6D_6): 0.92(t, J=7.3Hz, 3H, H12), 1.26(m, 3H,), 1.64(m,1H), 1.98-2.14(m, 4H), 2.32(m, 2H), 3.55(m, 1H), 3.98(m, 1H), 4.29(d, J=12.06Hz, 1H), 4.42(d, J=12.09, 1H), 4.52(m, 1H), 5.51(m, 2H), 6.40(d, J=6.09, 1H), 7.2(m, 5H). ^{13}C NMR(C_6D_6): 13.89, 23.18, 23.90, 24.43, 28.97, 29.58, 70.94, 72.64, 75.38, 97.18, 127.26, 127.48, 127.12, 128.10, 128.18, 139.23, 143.05.

t-Butyl-2,3-dideoxy-4-O-benzyl-α-D-glucopyranoside-Z-alkene (124)

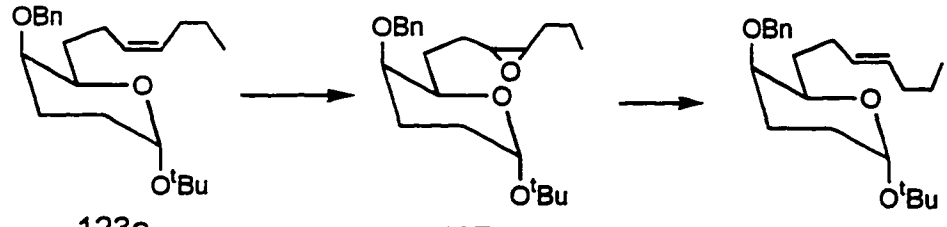


121 122 124

The terminal alkene **111** (4.4g, 13.3 mmol) was converted to the aldehyde according to the general ozonolysis procedure (**2.4.3**). Aldehyde **125a** (2.7g, 61%) was obtained as a colorless syrup after purification. TLC R_f=0.45 (10% EtOAc/PE). ^{1}HNMR(CDCl): δ 1.15(s, 9H, -CMe_3), 1.52-2.52(m, 6H, H_2, H_3, H_6,), 2.68(t, J=7.49 Hz, 1H, H_{7a}), 2.86(t, J=7.52Hz, 1H, H7b), 3.05(m ,1H, H_4), 3.75(dt, J=2.10, 8.76Hz, 1H, H_5), 4.37(d, J=11.49Hz, 1H, -CH_2Ar), 4.58(d, J=11.39Hz, 1H, -CH_2Ar), 4.96(s, 1H, H_1), 7.25 (m, 5H, -ArH), 9.72(s, 1H, H8).

The aldehyde **122** (440mg, 1.3mmol) from the previous step was converted to the Z-alkene **124** according to the general procedure (**II.4.4**). TLC R_f=0.72 (10% EtOAc/PE). ^{1}HNMR($CDCl_3$): δ 0.82(t, J=7.4Hz, 3H, H_{12}), 1.22-2.00(m, 12H, H_2, H_3, H_6, H_7, H_{10}, H_{11}), 1.16(s, 9H, -CMe_3), 3.04(dt, J= 4.7, 10.2 Hz, 1H, H_4), 3.75(dt, J=2.2, 9.1Hz, 1H, H_5), 4.36(Abq, Δδ=0.18ppm, J=11.Hz, -CH2Ar), 4.99(t, J=2.2 Hz, 1H, H1), 5.31(m,2H, H_8, H_9), 7.07-7.27 (m, 5H, -ArH).

t-Butyl-4-O-benzyl -2,3-dideoxy-α-D-galactopyranoside E alkene (129)



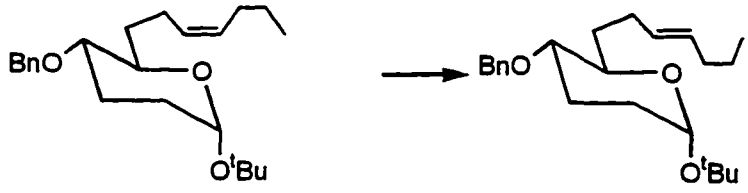
123a 127 129

Treatment of Z alkene **123a** (130mg, 0.36mmol) was subjected to the standard isomerization procedure (II.4.5) to afford a mixture of epoxide **127** (120 mg, 92%) after purification. TLC R_f=0.60(10% EtOAc/PE). ^{1}HNMR(C_6D_6): 0.831(t, 3H, H_{12}), 1.20(s,

9H, -CMe3), 1.28-2.18(m, 12H, H_2, H_3, H_6, H_7, H_{10}, H_{11}), 2.67-2.83(m, 2H, H8, H9), 3.09, 3.15(both bs, 1H, H_4), 3.91(m, 1/2H, H5), 4.04(t, J=5.77Hz, 1/2H, H5), 4.13(t, J=11.54 Hz, 1H, -CH_2Ar), 4.41(d, J=11.87, 1H, -CH_2Ar), 5.14(bs, 1H, H_1)7.26(m, 5H, -C6H5). ^{13}C NMR(C_6D_6): δ 13.82, 19.995, 20.96, 21.06, 24.41, 25.01, 26.00, 28.63, 29.14, 29.92, 56.14, 56.52, 69.85, 70.23, 70.39, 70.57, 73.01, 73.28, 73.62, 91.15, 127.24, 127.39, 127.02, 128.18, 138.1.

The epoxide mixture **127** (110 mg, 0.24mmol) from the previous step was reacted according to the general procedure for olefination (**II.4.5**). E-alkene **129** (78.4mg, 91%) was obtained as a colorless syrup after purification. TLC R_f=0.75 (10% EtOAc/PE). ^{1}HNMR(C6D6): δ 0.94(t, J=7.4Hz, 3H, H_{12}), 1.43-2.50(m, 12H, H_2, H_3, H_6, H_7, H_{10}, H_{11}), 1.28(s, 9H, -CMe3), 3.22(br s, 1H, H_4), 4.05(br t, J=5.8 Hz, 1H, H_5), 4.35(Abq, Δδ=0.29ppm, J=11.9 Hz), 5.21(br s, 1H, H1), 5.56(m,2H, H_8, H_9), 7.15-7.42 (m, 5H, -ArH). ^{13}C NMR(C_6D_6): 13.82, 21.43, 23.08, 26.35, 28.98, 29.42, 32.37, 35.12, 70.19, 70.82, 73.54, 73.76, 98.45, 128.00, 128.32, 128.46, 138.3, 139.71.

t-Butyl-4-O-benzyl -2,3-dideoxy -α-D-glucopyranoside-E-alkene (129)



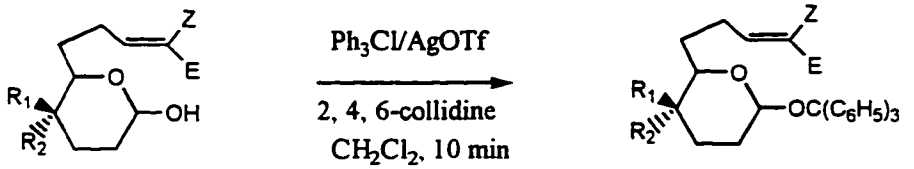
124 130

Treatment of t-Butyl gluco E alkene **124** under two steps Vedjs isomerization procedure(II.4.5) afforded t-Butyl E alkene **130** after purification. TLC R_f=0.72 (10% EtOAc/PE). ^{1}HNMR($CDCl_3$): δ 0.94(t, J=7.2Hz, 3H, H_{12}), 1.24-2.20(m, 12H, H_2, H_3,

H_6, H_7, H_{10}, H_{11}), 1.24(s, 9H, -C<u>Me</u>$_3$), 3.15(dt, J= 5.0, 10.0 Hz, 1H, H_4), 3.82(br t, J=10.0Hz, 1H, H_5), 4.60(Abq, $\Delta\delta$=0.20ppm, J=11.Hz), 5.06(br s, 1H, H1), 5.46(m,2H, H_8, H_9), 7.25-7.45 (m, 5H, -ArH).

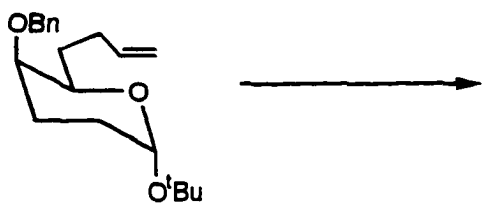
II.4.11 Preparation of Trityl 2,3-Dideoxy Pyranoside Alkenes

Table 9: Reaction Conditions for Tritylation

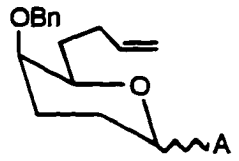


	entry	substrate mg. mmol	Ph_3Cl mg. mmol	AgOTf mg. mmol	collidine mL. mmol	CH_2Cl_2 mL	yield mg.	%
R_1=OBn R_2=H	1	**118**: Z=E=H 30mg. 0.11mol	91mg 0.33mmol	84mg 0.33mmol	0.02mL 0.033 mmol	5 mL	52 mg	92%
	2	**123a**: Z=Pr. E=H 30 mg. 0.115mmol	96mg 0.345mmol	82mg 0.322mmol	0.03mL 0.038mmol	5mL	48mg	89.2%
	3	**129**: Z=H. E=Pr 30 mg. 0.115mmol	96mg 0.345mmol	82mg 0.32mmol	0.03mL 0.038 mmol	5mL	46mg	87%
R_1=H R_2=OBn	4	**110**: Z=E=H 50mg. 0.19mmol	105mg 0.38mmol	87mg 0.34mmol	0.03mL 0.38mmol	10mL	73 mg	75.7%
	5	**124**: Z=Pr. E=H 40mg. 0.26mmol	140mg 0.50mmol	120mg 0.46mmol	0.04 mL 0.50mmol	12 mL	60 mg	76.5%
	6	**130**: Z=H.E=Pr 85mg. 0.28mmol	115mg 0.55mmol	129mg 0.504mmol	0.04 mL 0.55mmol	12 mL	107 mg	70%

Trityl-4-O-benzyl-2,3-dideoxy-α/β-D-galactopyranoside alkene (120)



118



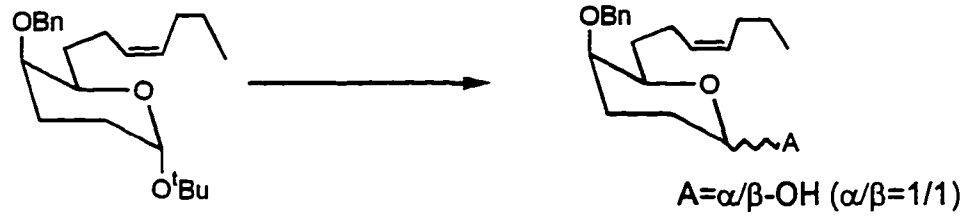
119: A=α/β-OH (α/β=1/1)
120: A=α/β-OTr (α/β=1/1)

To a solution of t-Butyl 2,3-dideoxy galactopyranoside **118** (117mg, 0.36mmol) in THF (3ml) was added 0.5N HCl (1ml). The solution was stirred for 5 h at room temperature then neutralized by aquous saturated $NaHCO_3$ and evaporated *in vacuo*. Flash chromotography gave the pyranoside **119** (72mg, 71%) as an inseparable 1:1 mixture of α/β anomers. TLC Rf=0.25 (20% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 1.05-2.22(m, 8H, H_2, H_3, H_6, H_7), 2.83(bs, 1/2H, $H_{4\beta}$), 3.05(bs, 1/2H, $H_{5\beta}$), 3.16(t, 1/2H, J=5.79, $H_{4\alpha}$), 3.94(t, 1/2H, J=5.79, $H_{5\alpha}$), 4.10, 4.40(both m, 1H each, -$\underline{CH_2}$Ar), 4.58(dd, J=1.8, 9.1 Hz, $H_{1\beta}$), 5.05(m, 2H, H_8), 5.20(bs, 1/2H, $H_{1\alpha}$), 5.90(m, 1H, H_9), 7.18(m, 5H, -$C_6\underline{H_5}$) ^{13}C NMR(C_6D_6): 19.46, 23.54, 24.01, 27.16, 28.93, 29.74, 68.60, 69.38, 69.46, 70.75, 71.92, 76.13, 90.25, 95.41, 113.27, 113.42, 127.24, 127.32, 127.49, 127.65, 137.75, 137.53.

The α/β mixture of anomers **119** (30mg, 0.11mmol) was tritylated according to the general procedure(II.4.8, Table 8: entry 1). An inseparable 1:1 mixture of α/β pyranoside (52mg, 92%) as light yellow syrup after purification. TLC R_f=0.68 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 1.15-2.25(m, 8H, H_2, H_3, H_6, H_7), 2.72(bs, $H_{4\beta}$), 2.80(bt, J=7.8Hz, $H_{5\beta}$), 3.12(bs, $H_{4\alpha}$), 3.96(m, $H_{5\alpha}$), 4.10, 4.40(both m, 2H, -$\underline{CH_2}$Ar), 4.52(dd, J=1.9, 9.3 Hz, $H_{1\beta}$), 5.01 (m, 2H, H_9), 5.25(bs, $H_{1\alpha}$), 5.72(m, 1H, H_8), 7.05-7.75 (m, 5H, -

ArH). ^{13}C NMR(C_6D_6): 25.85, 27.10, 30.29, 31.15, 70.93, 72.34, 77.42, 82.14, 98.22, 102.64, 114.45, 127.27, 127.42, 127.60, 127.72, 129.60, 138.02, 138.04, 139.22. HRFABMS calcd for $C_{35}H_{37}O_3(M+H)^+$ 505.274270, found 505.276147.

Trityl 4-O-benzyl-2,3-dideoxy-α/β-D-galactopyranoside Z-alkene (126)



123a

A=α/β-OH (α/β=1/1)

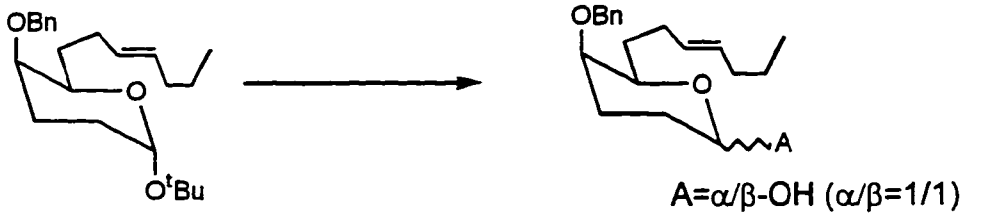
125: A=α/β-OTr (α/β=1/1)

t-Butyl pyranoside Z-alkene **123a** (55mg, 0.132mmol)was treated following the general hydrolysis procedure described for t-Butyl pyranoside **118**. An inseparable 1:1 mixture of α/β anomers lactol (40mg, 91%) was obtained as a colorless syrup after purification. TLC R_f=0.24 (20% EtOAc/PE); ^{1}HNMR(C_6D_6): δ 0.90(m, 3H, H_{12}), 1.00-2.75(m, 12H, H_2, H_3, H_6, H_7, H_{10}, H_{11}), 2.85(bs, 1/2H, $H_{4\beta}$), 3.12(bs, 1/2H, $H_{5\beta}$), 3.23(t, 1/2H, J=5.60, $H_{4\alpha}$), 4.06(m, 3/2H, $H_{5\alpha}$, -$\underline{CH_2}$Ar), 4.14(bs, 1/2H, -OH), 4.39(m, 3/2H, $H_{1\beta}$,-O$\underline{CH_2}$Ar), 4.63(brs, 1/2H, -OH), 5.28(s, 1/2H, $H_{1\alpha}$), 5.46(m, 2H, H_8, H_9), 7.20(m, 5H, -$\underline{C_6H_5}$). ^{13}C NMR(C_6D_6): δ 13.66, 20.49, 22.96, 23.51, 23.58, 24.65, 25.12, 28.311, 29.35, 31.60, 70.00, 70.42, 71.88, 72.94, 77.41, 91.36, 96.68, 127.19, 127.38, 128.13, 128.20, 138.03, 138.92, 139.19.

The pyranoside mixture (30mg, 0.98mmol) was converted to an inseparable 5:1 mixture of α/β trityl Z-alkene **125** (Table8: entry 2). TLC Rf=0.75(10% EtOac/PE). ^{1}HNMR(C_6D_6): 0.90(overlapping t, J=7.2Hz, 3H, H_{12}), 1.24-2.04(m, 12H, H_2, H_3, H_6, H_7,

H_{10}, H_{11}), 2.75(bs, $H_{4\beta}$), 2.82(t, J=5.6Hz, $H_{5\alpha}$), 3.16(bs, $H_{4\alpha}$), 4.00(t, J=6.5 Hz, $H_{5\alpha}$), 4.08, 4.34(both m, -CH2Ar), 4.42(dd, J=1.9, 9.5 Hz, $H_{1\beta}$), 5.28(brs, $H_{1\alpha}$), 5.41(m,2H, H_8, H_9), 7.10-7.80 (m, 5H, -ArH). ^{13}C NMR(C_6D_6) for the major (α anomer): δ 13.96, 23.22, 23.99, 25.88, 27.14, 29.64, 31.97, 70.95, 72.38, 77.79, 87.73, 98.30, 127.15, 127.32, 128.23, 128.30,138.1, 138.3, 146.0. HREIMS calcd for $C_{38}H_{40}O_2$(M-H_2O) 528.302831, found 528.303560.

Trityl-4-O-benzyl-2,3-dideoxy-α/β-D-galactopyranoside E alkene (131)



129

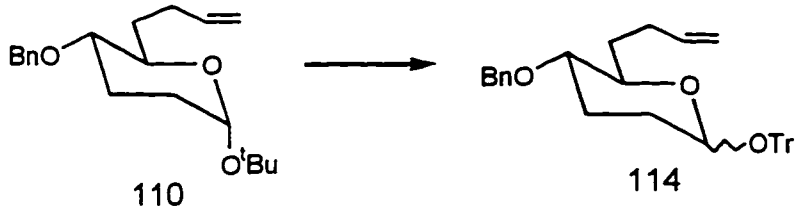
A=α/β-OH (α/β=1/1)

131: A=α/β-OTr (α/β=1/1)

E-alkene **129** (40mg, 0.11mmol) in THF (4ml) was treated according to the general hydrolysis procedure. A mixture of α/β pyranoside lactol (30mg, 92%) was obtained after purification. TLC R_f=0.28 (20% EtOAc/PE); ^{1}HNMR(C_6D_6): 0.94(t, J=7.33Hz, 3H, H12), 1.18-2.28(m, 12H, H_2, H_3, H_6, H_7, H_{10}, H_{11}), 2.94(bs, 2/5H, $H_{4\beta}$), 3.18(bs, 3/5H, $H_{5\beta}$), 3.32(m, 2/5H, $H_{4\alpha}$), 4.09(m, 3/5H, $H_{5\alpha}$), 4.10(m, 1H, -CH_2Ar), 4.46(t, 1H, -CH_2Ar), 4.49(d, J=6.4Hz, 2/5H, $H_{1\beta}$), 5.35(bs, 1/6H, $H_{1\alpha}$), 5.50(m, 2H, H_8, H_9), 7.05-7.78(m, 5H, -C_6H_5). ^{13}C NMR(C_6D_6): 13.83, 20.89, 23.10, 24.95, 25.45, 28.60, 29.19, 31.85, 35.12, 70.13, 70.79, 70.86, 72.19, 73.37, 77.69, 91.66, 96.85, 127.70, 130.65, 130.56, 130.79, 138.1, 139.01, 139.39.

The α/β mixture of pyranosides from above was treated according to the general procedure. An inseparable 1:1 mixture of α/β trityl E-alkene **131** (Table 8: entry 3) was obtained as a light yellow syrup after purification. TLC R_f=0.75 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): 0.95(overlapping t, J=7.0Hz, 3H, H_{12}), 1.25-2.38(m, 12H, H_2, H_3, H_6, H_7, H_{10}, H_{11}), 2.84(bs, $H_{4\beta}$), 2.94(br t, J=6.4 Hz, $H_{5\beta}$), 3.20(bs, $H_{4\alpha}$), 4.18 (m, $H_{5\alpha}$), 4.18, 4.45(both m, 1H each, -CH2Ar), 4.55(dd, J=1.6, 9.8 Hz, $H_{1\beta}$), 5.35(brs, $H_{1\alpha}$), 5.44(m,2H, H_8, H_9), 7.04-7.80 (m, 5H, -ArH). ^{13}C NMR(C_6D_6): 13.53, 22.80, 25.61, 26.85, 28.87, 31.66, 34.82, 70.66, 72.14, 77.32, 92.5, 93.34, 97.98, 102.36, 125.82, 126.86, 126.95, 127.39, 127.45, 127.58, 127.88, 128.22, 128.42, 128.54, 138.02, 138.10, 145.38. HREIMS calcd for $C_{38}H_{41}O_3$(M-H) 545.305571, found 545.306428.

Trityl- 4-O-benzyl -2,3-dideoxy-α/β-D-gluco- pyranoside alkene (121)

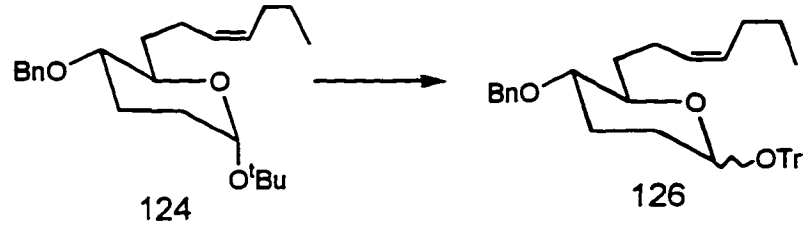


110 114

t-Butyl 2,3-dideoxygluco alkene pyranoside **110** (50mg, 0.19mmol) was tritylated according to the general procedure(II.4.8). TLC R_f=0.68 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 1.46-2.20(m, 8H, H_2, H_3, H_6, H_7), 3.02(m, 1H, $H_{4\alpha}$, $H_{5\beta}$), 3.10(m, 1/2H, $H_{4\beta}$), 4.18(dt, J=2.1, 10.5Hz, 1/2H, $H_{5\alpha}$), 4.25(Abq, Δδ =0.20 ppm, J=11 Hz, 1H, -CH_2Ar), 4.36(Abq, Δδ=0.24 ppm, J=11.Hz, 1H, -CH_2Ar), 5.10(m,2H, H_9), 5.86(m, 1H, H_8), 7.04-7.80 (m, 5H, -ArH). ^{13}C NMR(C_6D_6): 24.94, 27.55, 29.88, 30.84, 32.05,

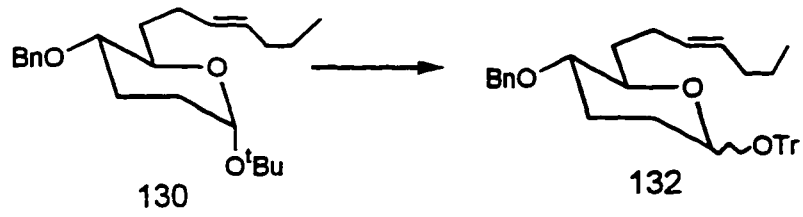
34.45, 70.95, 72.94, 77.88, 78.64, 78.89, 86.75, 87.13, 92.62, 98.54, 114.55, 127.17, 127.38, 127.62, 127.72, 129.50, 139.62. HRFABMS calcd for $C_{35}H_{37}O_3(M+H)^+$ 505.274270, found 505.275249.

Trityl-4-O-benzyl -2,3-dideoxy- α/β-D-glucopyranoside Z-alkene (126)



An inseparable mixture of 1/1 α/β trityl pyranoside **126** (Table 8: entry 5) was obtained as light yellow syrup after purification. TLC Rf=0.75(10% EtOAc/PE). ^{1}HNMR(C_6D_6): 0.90(overlapping t, J=7.0Hz, 3H, H_{12}), 1.25-2.20(m, 12H, H_2, H_3, H_6, H_7, H_{10}, H_{11}), 2.96(m, 1H, $H_{4\beta}$, $H_{5\alpha}$), 3.03(m, $H_{4\alpha}$), 4.19 (dt, J=2.0, 10.0 Hz, $H_{5\alpha}$), 4.18(Abq, Δδ=0.19ppm, J=11.Hz, -CH2Ar), 4.36(Abq, Δδ=0.24ppm, J=11.Hz, -CH2Ar), 4.36(dd, J=2.1, 9.1 Hz, $H_{1\beta}$), 5.18(brs, $H_{1\alpha}$), 5.44(m, 2H, H_8, H_9), 7.03-7.69 (m, 5H, -ArH). ^{13}C NMR(C_6D_6): δ 13.667, 13.912, 22.907, 23.164, 23.283, 24.099, 27.771, 29.324, 30.121, 31.006, 32.604, 32.666, 32.711, 32.818, 70.442, 72.471, 76.464, 77.487, 77.987, 87.52, 92.226, 97.403, 126.964, 127.391, 127.485, 127.714, 128.032, 128.135, 129.147, 129.269, 129.556, 130.180, 130.465, 145.159, 145.271.

Trityl-4-O-Benzyl -2,3-Dideoxy -α/β -D-Glucopyranoside E Alkene (132)

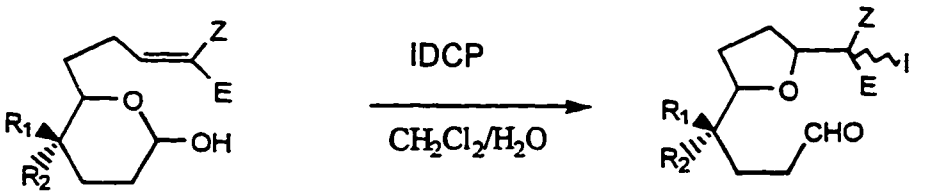


t-Butyl gluco pyranoside E alkene **130** was tritylated according to the general procedure to afford inseparable mixture of 1/1 α/β trityl alkene **132** (Table 8: entry 6) (107mg, 70%) after purification. TLC R_f=0.75 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): 0.90(overlapping t, J=7.0Hz, 3H, H_{12}), 1.30-2.20(m, 12H, H_2, H_3, H_6, H_7, H_{10}, H_{11}), 3.04(m, 2H, $H_{4\beta}$, $H_{4\alpha}$, $H_{5\beta}$), 4.22 (dt, J=2.0, 10.0 Hz, $H_{5\alpha}$), 4.25(Abq, Δδ=0.18ppm, J=11.9Hz, -CH2Ar), 4.43(Abq, Δδ=0.24ppm, J=11.Hz, -CH2Ar), 4.43(dd, J=1.8, 9.1 Hz, $H_{1\beta}$), 5.25(brs, $H_{1\alpha}$), 5.44(m,2H, H_8, H_9), 7.04-7.80 (m, 5H, -ArH). ^{13}C NMR(C_6D_6): δ 13.559, 22.820, 24.07, 27.76, 28.28, 28.36, 30.10, 31.01, 32.70, 34.84, 70.40, 70.44, 72.27, 76.55, 77.58, 77.76, 86.76, 87.23, 92.25, 97.36, 126.93, 127.39, 127.50, 127.73, 128.04, 128.15, 128.33, 129.26, 129.83, 129.99, 130.97, 130.97, 139.04, 145.15, 145.28.

II.4.12 Iodoetherification of C_6 allylated pyranosides

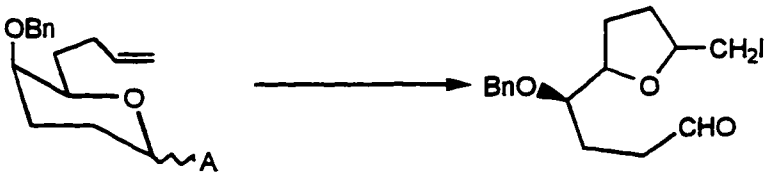
Iodoetherification of alkene precursors were carried out according to the general procedure (II.4.9). The results were summarized in Table 9. Entry 1-6 were conditions for 2,3-dideoxy galacto pyranosides, and entry 7-12 were for gluco pyranosides. The detailed physical properties were listed below.

Table 10: Iodoetherification of 2,3-Dideoxy Pyranoside Alkenes



	entry	compound Substrate	mg	mmol	IDCP mg	mmol	Products THF	c/t	mg	yield(%)
R_1=OBn; R_2=H	1	118: A=α-O'Bu: Z=E=H	22	0.064	109	0.139	133a	7/2	30	84
	2	120:A= αβ-OTr: Z=E=H	50	0.058	109	0.139	133b	cis-only	28	88
	3	123: A=α/β-O'Bu: Z=Pr, E=H		20	109	0.139	134a	7/2	28	84
	4	125: A=α/β-OTr: Z=Pr, E=H	28	0.031	67	0.085	134b	cis -only	20	91
	5	129: A=α-O'Bu: Z= H, E=Pr	18	0.051	33	0.041	135a	7/2	17	80
	6	131: A=α-OTr: Z=H, E=Pr	65	0.044	95	0.121	135b	c-only	25	79
R_1=H; R_2=OBn	7	110: A=α-O'Bu: Z=E=H	65	0.19	357	0.456	115a	7/2	95	89
	8	114:A= αβ-OTr: Z=E=H	36	0.099	185	0.24	115b	cis-only	44	78
	9	124: A=α/β-O'Bu: Z=Pr, E=H					136a	2/3		
	10	126: A=α/β-OTr: Z=Pr, E=H	55	0.063	118	0.151	136b	cis -only	35	81
	11	130: A=α-O'Bu: Z= H, E=Pr					137a	7/2		
	12	132: A=α-OTr: Z=H, E=Pr	109	0.199	374	0.48	137b	c-only	25	79

THF aldehyde 133a and 133b



118: A= α-OtBu
120: A=α/β-OTr

133a: cis/trans(7/2
133b: cis only

THF aldehyde 133b (Table 10: entry 2). TLC R_f =0.30 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 1.20-1.60(m, 6H, H_3, H_6, H_7), 2.10(m, 2H, H_2), 2.70(m, 2H, H_9), 3.10(m, 1H, H_4), 3.65(m, 2H, H_5, H_8), 4.58(Abq, Δδ=0.24 ppm, J=11.6Hz, 2H, -CH2Ar), 7.05-7.38(m, 5H, -C6H5), 9.33(s, 1H, H1). ^{13}C NMR(C_6D_6): 10.49, 24.15, 27.78, 31.12, 40.18, 73.14, 78.90, 80.46, 83.72, 127.27,127.70, 128.04, 138.02, 200.49. HRFABMS calcd for $C_{16}H_{22}O_3I$ (M+H)+ 389.061372, found 389.060583.

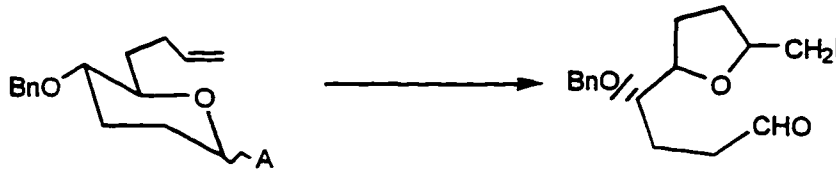
THF aldehyde 133a (Table 10: entry 1). TLC R_f =0.30 (10% EtOAc/PE).

For *cis* isomer: ^{1}HNMR(C_6D_6): δ 1.20-1.60(m, 6H, H_3, H_6, H_7), 2.10(m, 2H, H_2), 2.70(m, 2H, H_9), 3.10(m, 1H, H_4), 3.65(m, 2H, H_5, H_8), 4.58(Abq, Δδ=0.24 ppm, J=11.6Hz, 2H, -CH2Ar), 7.05-7.38(m, 5H, -C6H5), 9.33(s, 1H, H1). ^{13}C NMR(C_6D_6): 10.49, 24.15, 27.78, 31.12, 40.18, 73.14, 78.90, 80.46, 83.72, 127.27,127.70, 128.04, 138.02, 200.49.

For *trans* isomer: ^{1}HNMR(C_6D_6): δ 1.10-1.60(m, 6H, H_3, H_6, H_7), 2.06(m, 2H, H_2), 2.80(m, 2H, H_9), 3.05(m, 1H, H_4), 3.72(m, 1H, H_8), 3.85(m, 1H, H_5), 4.55(Abq, Δδ=0.23 ppm, J=11.6Hz, 2H, -CH2Ar), 7.05-7.38(m, 5H, -C6H5), 9.33(s, 1H, H1). ^{13}C

NMR(C_6D_6): δ 10.80, 23.76, 28.83, 32.47, 40.18, 73.00, 78.80, 80.46, 83.72, 127.27, 127.70, 138.02, 200.49.

THF aldehyde 115a and 115b



110: A= α–OtBu
114: A=α/β-OTr

115a: cis/trans(7/2)
115b: cis only

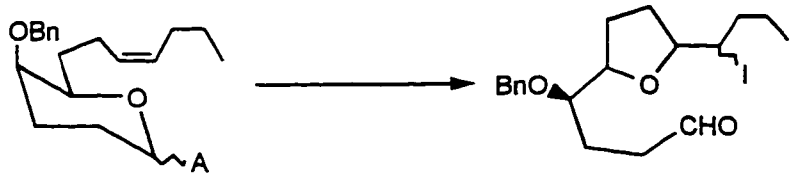
THF aldehyde 115b (Table 10: entry 8). TLC R_f=0.10(10% EtOAc/PE). For *cis* isomer ^{1}HNMR(C_6D_6): δ 1.18-1.70(m, 6H, H_3, H_6, H_7), 2.18(m, 2H, H_2), 2.76(m,2H, H_9), 3.18(m, 1H, H_4), 3.62(m, 1H, H_5), 3.72(m, 1H, H_8), 4.18(Abq, Δδ=0.24 ppm, J=11.6Hz, 2H, -CH2Ar), 7.05-7.15(m, 5H, -C_6H_5), 9.25(s, 1H, H_1). ^{13}C NMR(C_6D_6): 10.49, 24.15, 27.78, 31.12, 40.18, 73.14, 78.90, 80.46, 83.72, 127.27,127.70, , 200.49.

THF aldehyde mixture 115a (Table 10, entry 7): TLC R_f=0.10(10% EtOAc/PE).

For *cis* isomer: ^{1}HNMR(C_6D_6): δ 1.18-1.70(m, 6H, H_3, H_6, H_7), 2.18(m, 2H, H_2), 2.76(m,2H, H_9), 3.18(m, 1H, H_4), 3.62(m, 1H, H_5), 3.72(m, 1H, H_8), 4.18(Abq, Δδ=0.24 ppm, J=11.6Hz, 2H, -CH2Ar), 7.05-7.15(m, 5H, -C_6H_5), 9.25(s, 1H, H_1). ^{13}C NMR(C_6D_6): 10.49, 24.15, 27.78, 31.12, 40.18, 73.14, 78.90, 80.46, 83.72, 127.27,127.70, , 200.49.

For *trans* isomer: ^{1}HNMR(C_6D_6): δ 1.18-1.70(m, 6H, H_3, H_6, H_7), 2.18(m, 2H, H_2), 2.76(m, 2H, H_9), 3.20(q, J=5.8 Hz, 1H, H_4), 3.52(m, 2H, H_8, H_5), 4.18(Abq, Δδ=0.14 ppm, J=11.7Hz, 2H, -CH2Ar), 7.04-7.14(m, 5H, -C6H5), 9.27(s, 1H, H1). ^{13}C NMR(C_6D_6): δ 10.80, 23.76, 28.83, 32.47, 40.18, 73.00, 78.80, 80.46, 83.72, 127.27, 127.70, 200.49.

THF aldehyde 134a and 134b



123: A= α–OtBu
125: A=α/β-OTr

134a: cis/trans(1/1)
134b: cis/trans(cis only

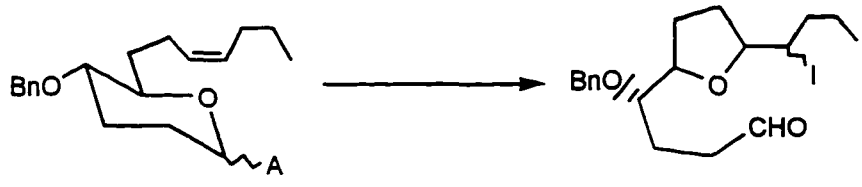
THF aldehyde 134b (Table 10: entry 4): TLC R_f =0.35(10% EtOAc/PE). ^{1}HNMR(C_6D_6): 0.77(t, J=7.12Hz, 3H, H_{12}), 1.25-1.85(m, 10H, H_3, H_6, H_7, H_{10}, H_{11}), 2.12(m, 2H, H_2), 3.32(m, 2H, H_4, H_8), 3.72(m, 1H, H_5), 3.84(m, 1H, H_9), 4.75 (Abq, Δδ=0.25 ppm, J=11.7Hz, 2H, -CH_2Ar), 7.07-7.22(m, 5H, -C_6H_5), 9.35(s, 1H, H_1). ^{13}C NMR(C_6D_6): 13.35, 23.24, 24.44, 28.10, 30.64, 39.17, 40.21, 42.64, 73,27, 80.60, 82.49, 83.46, 127.70, 128.02,128.34, 128.47, 128.65, 200.5. MS: m/e 448 ($M+NH_4$) for $C_{19}H_{27}O_3I$. HRCIMS calcd for $C_{19}H_{28}O_3I(M+H)^+$ 431.108322, found 431.106372. HRCIMS calcd for $C_{19}H_{26}O_3I(M-H)^-$ 429.092672, found 429.092577.

THF aldehyde 134a (Table 10: entry 3): TLC R_f =0.35(10% EtOAc/PE). MS: m/e 448 ($M+NH_4$) for $C_{19}H_{27}O_3I$.

For *cis* isomer : ^{1}HNMR(C_6D_6): 0.77(t, J=7.12Hz, 3H, H_{12}), 1.25-1.85(m, 10H, H_3, H_6, H_7, H_{10}, H_{11}), 2.12(m, 2H, H_2), 3.32(m, 2H, H_4, H_8), 3.72(m, 1H, H_5), 3.84(m, 1H, H_9), 4.75 (Abq, Δδ=0.25 ppm, J=11.7Hz, 2H, -$\underline{CH_2}$Ar), 7.07-7.22(m, 5H, -$C_6\underline{H_5}$), 9.35(s, 1H, H_1). ^{13}C NMR(C_6D_6): 13.35, 23.24, 24.44, 28.10, 30.64, 39.17, 40.21, 42.64, 73.27, 80.60, 82.49, 83.46, 127.70, 128.02,128.34, 128.47, 128.65, 200.5.

For *trans*-THF : ^{1}HNMR(C_6D_6): 0.77(t, J=7.12Hz, 3H, H_{12}), 1.22-1.85(m, 10H, H_3, H_6, H_7, H_{10}, H_{11}), 2.12(m, 2H, H_2), 3.09(m, 1H, H_4), 3.30(m, 1H, H_8), 3.98(m, 1H, H_5), 3.99(m, 1H, H_9), 4.65 (Abq, Δδ=0.23 ppm, J=11.6Hz, 2H, -$\underline{CH_2}$Ar), 7.07-7.22(m, 5H, -$C_6\underline{H_5}$), 9.35(s, 1H, H_1). ^{13}C NMR(C_6D_6): 13.35, 23.32, 23.81, 28.93, 31.55, 38.78, 40.29, 42.76, 73.02, 80.31, 82.79, 83.19, 127.70, 128.02,128.34, 128.47, 128.65, 200.5.

THF aldehyde 136a and 136b



124: A= α-OtBu
126: A=α/β-OTr

136a: cis/trans(2/3)
136b: cis/trans(8/1)

THF aldehyde 136b (Table 10: entry 10):TLC $\underline{R_f}$ =0.35(10% EtOAc/PE). ^{1}HNMR (C_6D_6,) δ 0.71(t, J=7.12Hz, 3H, H_{12}), 1.08-1.80(m, 10H, H_3, H_6, H_7, H_{10}, H_{11}), 2.06(m, 2H, H_2), 3.26(q, J=5.6 Hz, 1H, H_4), 3.43(q, J=6.8 Hz, 1H, H_8), 3.63(q, J=5.3 Hz, 1H, H_5), 3.84(q, J=7.1 Hz, 1H, H_9), 4.37 (Abq, Δδ=0.14 ppm, J=11.7Hz, 2H, -$\underline{CH_2}$Ar), 7.04-7.24(m, 5H, -$C_6\underline{H_5}$), 9.30(s, 1H, H_1). ^{13}C NMR(C_6D_6) δ 13.43, 23.38, 24.55, 27.33, 30.87, 39.21, 39.98, 42.10, 72.97, 82.06, 82.65, 127.84, 128.17,128.49, 128.64, 128.86, 200.69. MS: m/e 448 ($M+NH_4$) for $C_{19}H_{27}O_3I$.

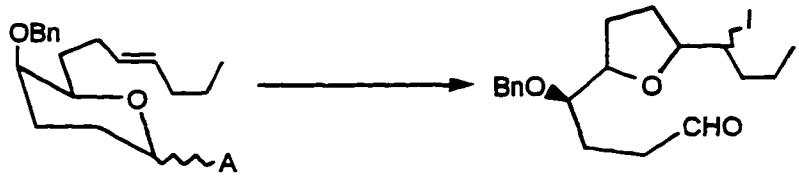
THF aldehyde 136a (Table 10: entry 9): TLC R_f =0.35(10% EtOAc/PE). MS: m/e 448 ($M+NH_4$) for $C_{19}H_{27}O_3I$

For *cis*-THF: ^{1}HNMR(C_6D_6) δ 0.71(t, J=7.12Hz, 3H, H_{12}), 1.08-1.80(m, 10H, H_3, H_6, H_7, H_{10}, H_{11}), 2.06(m, 2H, H_2), 3.26(q, J=5.6 Hz, 1H, H_4), 3.43(q, J=6.8 Hz, 1H, H_8), 3.63(q, J=5.3 Hz, 1H, H_5), 3.84(q, J=7.1 Hz, 1H, H_9), 4.37 (Abq, Δδ=0.14 ppm, J=11.7Hz, 2H, -$\underline{CH_2}$Ar), 7.04-7.24(m, 5H, -$C_6\underline{H_5}$), 9.30(s, 1H, H_1). ^{13}C NMR(C_6D_6) δ13.43, 23.38, 24.55, 27.33, 30.87, 39.21, 39.98, 42.10, 72.97, 82.06, 82.65, 127.84, 128.17,128.49, 128.64, 128.86, 200.69.

For *trans*-THF: ^{1}HNMR(C_6D_6) δ 0.72(t, J=7.12Hz, 3H, H_{12}), 1.20-1.90(m, 10H, H_3, H_6, H_7, H_{10}, H_{11}), 2.05(m, 2H, H_2), 3.26(m, 1H, H_4), 3.45(m, 1H, H_5), 3.80(m, 1H, H_8), 3.84(m, 1H, H_9), 4.42 (Abq, Δδ=0.14 ppm, J=11.7Hz, 2H, -$\underline{CH_2}$Ar), 7.04-7.30(m, 5H, -$C_6\underline{H_5}$), 9.26(s, 1H, H_1). ^{13}C NMR(C_6D_6) δ 13.50, 23.48, 24.40, 27.68, 31.97, 40.23, 39.01, 42.23, 73.16, 79.77, 82.78, 127.86, 128.18,128.49, 128.68, 200.6.

Halocyclization of E alkene

THF aldehyde 135a and 135b



129: A= α–OtBu
131: A=α/β-OTr

135a: cis/trans(8/1)
135b: cis/trans(cis only

THF aldehyde 135b (Table 10: entry 6): TLC R_f =0.35(10%EtOAc/PE). ^{1}HNMR(C_6D_6) δ 0.79(t, J=7.12Hz, 3H, H_{12}), 1.30-1.73(m, 10H, H_3, H_6, H_7, H_{10}, H_{11}), 2.06(m, 2H, H_2), 3.15(m, 1H, H_4), 3.58(q, J=7.5 Hz, 1H, H_8), 3.72(q, J=7.5 Hz, 1H, H_5), 3.99(q, J=7.5 Hz, 1H, H_9), 4.60 (Abq, Δδ=0.25 ppm, J=11.7Hz, 2H, -CH_2Ar), 7.05-7.23(m, 5H, -C_6H_5), 9.35(s, 1H, H_1). ^{13}C NMR(C_6D_6,) δ 13.08, 22.53, 23.94, 27.28, 31.47, 38.60, 39.87, 42.37, 72.85, 80.21, 82.64, 83.44, 127.38, 127.38, 127.70, 128.02,128.19, 200.5. MS: m/e 448 ($M+NH_4$) for $C_{19}H_{27}O_3I$. HRCIMS calcd for $C_{19}H_{28}O_3I$(M+H)+ 431.108322, found 431.106778.

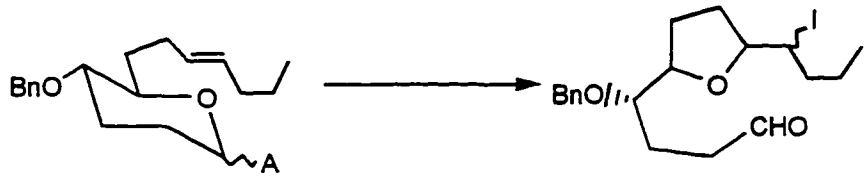
THF aldehyde 135a (Table 10: entry 5):TLC R_f =0.35(10% EtOAc). MS: m/e 448 ($M+NH_4$) for $C_{19}H_{27}O_3I$.

For *cis*-THF: ^{1}HNMR(C_6D_6) δ 0.79(t, J=7.12Hz, 3H, H_{12}), 1.30-1.73(m, 10H, H_3, H_6, H_7, H_{10}, H_{11}), 2.06(m, 2H, H_2), 3.15(m, 1H, H_4), 3.58(q, J=7.5 Hz, 1H, H_8), 3.72(q, J=7.5 Hz, 1H, H_5), 3.99(q, J=7.5 Hz, 1H, H_9), 4.60 (Abq, Δδ=0.25 ppm, J=11.7Hz, 2H, -CH_2Ar), 7.05-7.23(m, 5H, -C_6H_5), 9.35(s, 1H, H_1). ^{13}C NMR(C_6D_6) δ 13.08, 22.53,

23.94, 27.28, 31.47, 38.60, 39.87, 42.37, 72.85, 80.21, 82.64, 83.44, 127.38, 127.38, 127.70, 128.02,128.19, 200.5.

For *trans*-THF : ^{1}HNMR(C_6D_6) δ 0.85(t, J=7.2Hz, 3H, H_{12}), 1.10-1.80(m, 10H, H_3, H_6, H_7, H_{10}, H_{11}), 2.06(m, 2H, H_2), 3.05(m, 1H, H_4), 3.30(m, 2H, H_8,H_5), 3.85(m, 1H, H_9), 4.69 (Abq, Δδ=0.26 ppm, J=11.6Hz, 2H, -$\underline{CH_2}$Ar), 7.05-7.23(m, 5H, -$C_6\underline{H_5}$), 9.34(s, 1H, H_1). ^{13}C NMR(C_6D_6) δ 13.08, 22.53, 23.25, 29.85, 32.92, 38.60, 39.87, 42.37, 72.85, 80.41, 82.64, 83.44, 127.38, 127.38, 127.70, 128.02,128.19, 200.5.

THF aldehyde 137a and 137b



130: A= α–OtBu
132: A=α/β-OTr

137a: cis/trans(8/1)
137b: cis/trans(20/1)

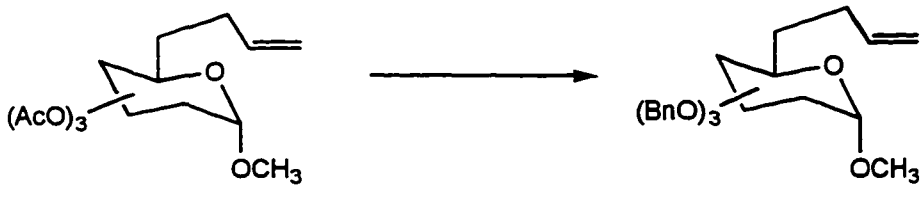
THF aldehyde 137b (Table 10: entry 12):TLC $\underline{R_f}$ =0.35(10% EtOAc/PE). ^{1}HNMR(C_6D_6) δ 0.71(t, J=7.0Hz, 3H, H_{12}), 1.20-1.80(m, 10H, H_3, H_6, H_7, H_{10}, H_{11}), 2.15(m, 2H, H_2), 3.24(q, J=5.5 Hz, 1H, H_4), 3.41(q, J=6.6 Hz, 1H, H_8), 3.61(q, J=5.3 Hz, 1H, H_5), 3.90(q, J=5.7 Hz, 1H, H_9), 4.50 (Abq, Δδ=0.14 ppm, J=11.7Hz, 2H, -$\underline{CH_2}$Ar), 7.08-7.41(m, 5H, -$C_6\underline{H_5}$), 9.27(s, 1H, H_1). ^{13}C NMR(C_6D_6) δ 13.12, 22.23, 23.44, 26.76, 31.96, 38.45, 39.17, 42.07, 72.25, 80.01, 82.76, 83.12, 126.38, 127.18, 127.54, 128.02,128.13, 200.4. MS: m/e 448 ($M+NH_4$) for $C_{19}H_{27}O_3I$.

THF aldehyde 137b (Table 10: entry 11): TLC R_f =0.35 (10% EtOAc/PE). MS: m/e 448 ($M+NH_4$) for $C_{19}H_{27}O_3I$.

For cis-THF: ^{1}HNMR(C_6D_6) δ 0.71(t, J=7.0Hz, 3H, H_{12}), 1.20-1.80(m, 10H, H_3, H_6, H_7, H_{10}, H_{11}), 2.15(m, 2H, H_2), 3.24(q, J=5.5 Hz, 1H, H_4), 3.41(q, J=6.6 Hz, 1H, H_8), 3.61(q, J=5.3 Hz, 1H, H_5), 3.90(q, J=5.7 Hz, 1H, H_9), 4.50 (Abq, Δδ=0.14 ppm, J=11.7Hz, 2H, -CH_2Ar), 7.08-7.41(m, 5H, -C_6H_5), 9.27(s, 1H, H_1). ^{13}C NMR(C_6D_6,) δ 13.12, 22.23, 23.44, 26.76, 31.96, 38.45, 39.17, 42.07, 72.25, 80.01, 82.76, 83.12, 126.38, 127.18, 127.54, 128.02,128.13, 200.4.

For trans-THF: ^{1}HNMR(C_6D_6) δ 0.72(t, J=7.0Hz, 3H, H_{12}), 1.20-1.80(m, 10H, H_3, H_6, H_7, H_{10}, H_{11}), 2.01(m, 2H, H_2), 3.23(m, 1H, H_4), 3.57(m, 1H, H_5), 3.80(m, 1H, H_8), 3.95(m, 1H, H_9), 4.39 (Abq, Δδ=0.14 ppm, J=11.7Hz, 2H, -CH_2Ar), 7.00-7.30(m, 5H, -C_6H_5), 9.26(s, 1H, H_1). ^{13}C NMR(C_6D_6) δ 13.15, 22.20, 23.14, 27.36, 33.25, 38.41, 39.06, 41.07, 72.03, 80.01, 82.86, 83.42, 126.88, 127.34, 127.42, 128.02,128.43, 200.4. MS: m/e 448 ($M+NH_4$) for $C_{19}H_{27}O_3I$.

II.4.14 Preparation of Galacto-, Gluco-and Manno- Pyranoside Alkenes



148: galacto
149: gluco
150: manno

89: galacto
90: gluco
91: manno

Methyl- 2,3, 4-O-tribenzyl-α-D-galacto pyranoside (89)

Methyl tri-O-acetyl galacto alkene **148** [2] (8g, 0.243 mol) in CH_3OH (50 mL) was treated with NaOMe (5 mL) at rt. for 2 h. The reaction mixture was then neutralized with methanolic HCl and the solvent removed *in vacuo*. The crude residue was treated according to the standard procedure for benzylation of alcohol. Tri-O-benzyl alkene **89** (9.3g, 78 % over 2 steps) was obtained after purification. TLC R_f=0.75 (10% EtOAc/PE). ^{1}HNMR($CDCl_3$): δ 1.50-2.30(m, 4H, H6, H7), 3.48(s, 3H, -OMe), 3.75(m, 1H, H5), 3.82(br s, 1H), 4.05(d, J=9.8 Hz, 1H,), 4.18(m, 1H,), 4.64-5.20(m, 7H), 7.26(m, 15H). ^{13}C NMR(C_6D_6): δ 29.87, 31.19, 54.59, 69.56, 72.53, 74.88, 75.30, 80.96, 82.08, 82.21, 97.76, 114.58, 127.25, 129.42, 127.52, 127.67, 127.76, 128.17, 128.21, 128.28, 138.53, 138.59, 139.45. Anal. calcd for $C_{31}H_{36}O_5$: C: 76.23, H:7.38, found C: 76.05, H:7.47.

Methyl- 2,3, 4-O-tribenzyl -α-D-gluco pyranoside (90)

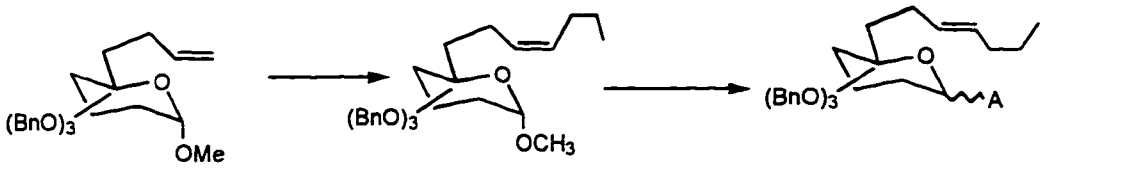
Methyl tri-O-acetyl gluco alkene **149** (7.6g, 0.231 mol) was subjected to the same sequence to provide tri-O-benzyl alkene **90** (7.02g, 62% over 2 steps) after purification. TLC R_f=0.75 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 1.56(m, 1H, H6a), 2.03(mm, 2H, H6b, H7a), 2.30(m, 1H, H7b), 3.14(s, 3H, -OMe), 3.22(t, J=9.16Hz, 1H, H4), 3.53(dd, J=3.51, 9.6 Hz, 1H, H2), 3.75(dt, J=2.12, 9.5Hz, 1H, H5), 4.20(t, J=9.18Hz, 1H, H3), 4.54(m, 4H), 4.61(d, J=3.48Hz, 1H), 4.99(m, 4H), 5.78(m, 1H), 7.26(m, 15H). ^{13}C NMR(C_6D_6, 75.5Hz): δ 29.87, 31.19, 54.59, 69.56, 72.53, 74.88, 75.30, 80.96, 82.08,

[2] Mootoo, D. R.; Wilson, P.; Jammalamadaka, V.; J. Carbohydr. Chem. 1994, 13(6), 841-849.

82.21, 97.76, 114.58, 127.25, 129.42, 127.52, 127.67, 127.76, 128.17, 128.21, 128.28, 138.53, 138.89, 139.45. Anal. calcd for $C_{31}H_{36}O_5$: C: 76.23, H:7.38, found C: 76.35, H:7.41.

Methyl- 2,3, 4-O-tribenzyl-α-D-manno pyranoside (89)

Methyl tri-O-acetyl manno alkene **150** (4.3g, 0.131 mol) was subjected to the same sequence to provide tri-O-benzyl alkene **91** (4.42g, 69% over 2 steps) after purification. TLC R_f=0.75 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 1.65(m, 1H, H_{6a}), 2.05(mm, 2H, H_{6b}, H_{7a}), 2.38(m, 1H, H_{7b}), 3.05(s, 3H, -OMe), 3.62-4.02(m, 4H, H_2, H_3, H_4, H_5), 4.38-4.80(m, 6H, -CH2Ar), 4.98(m, 3H, H1, H_9), 5.78(m, 1H, H_8), 7.26(m, 15H). Anal. calcd for $C_{31}H_{36}O_5$: C: 76.23, H:7.38, found C: 76.29, H:7.42.



89: galacto
90: gluco
91: manno

166: A=α-OMe,manno
164:A=α-OMe,galacto
165: A= α-OMe,gluco

171: A= α-OMe,galacto
172: A= α-OMe,gluco

Methyl-2,3, 4--O- tribenzyl-α-D-galactopyranoside Z alkene (164)

The terminal alkene **89** (1.01g, 0.102mol) was converted to the aldehyde according to the general ozonolysis procedure (II.4.3). The aldehyde (800mg, 79%) was obtained as a colorless syrup after purification. TLC R_f=0.45(10% EtOAc/PE). ^{1}HNMR(C_6D_6): 2.10(m, 4H), 3.2(s, 3H), 3.42(s, 1H), 4.05(dd, J=1.8, 8.9Hz, 1H), 4.3(dd,

J=1.92, 9.1Hz, 1H), 4.65(m, 6H), 4.85(d, J=11.3Hz, 1H), 5.18(d, J=10.3Hz, 1H), 7.3(m, 15H), 9.45(s, 1H).

The aldehyde (700mg, 1.43mmol) was subjected to the general Wittig procedure (II.4.4). Z-alkene **164** (659mg, 87%) was obtained after purification. TLC R_f=0.70 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.87(t, J=7.38Hz, 3H), 1.32(m, 4H), 2.05(m, 3H), 2.22(m, 1H), 3.19(s, 3H), 3.51(bs, 1H), 3.62(m, 1H), 4.03(dd, J=2.74, 10.11Hz, 1H), 4.24(dd, J=3.41, 10.1Hz, 1H), 4.44(d, J=11.9Hz, 1H), 4.60(m, 3H), 4.80(m, 2H), 5.10(d, J=11.32Hz, 1H), 5.44(m, 2H), 7.16(m, 15H). ^{13}C NMR(C_6D_6): 13.709, 22.93, 23.95, 29.39, 31.34, 54.77, 69.99, 72.80, 73.19, 75.02, 77.65, 78.20, 79.16, 98.82, 127.26, 127.63, 127.75, 128.06, 128.13, 128.32, 129.59, 130.09, 139.36.

Methyl-2,3, 4-O-tribenzyl-α-D-galactopyranoside E alkene (171)

Z alkene **164** (500 mg, 0.947mmol) in CH_2Cl_2(20 mL) was subjected to the general epoxidation procedure (II.4.5) using m-CPBA (408.4mg, ~50% w/w, 2.36 mmol) suspended in a mixture of 4M NaH_2PO_4/Na_2HPO_4 buffer(88 mL) and CH_2Cl_2(35 mL). The epoxide derivative (473 mg, 92%) was obtained after purification. TLC R_f=0.50 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.849(t, J=7.05 Hz, 3H, H_{12}), 1.24-1.80(m, 8H, H_6, H_7, H_{10}, H_{11}), 2.74(mm, 2H, H_8, H_9), 3.17(d, J=7.07 Hz, 3H, -O<u>CH$_3$</u>), 3.58(mm, 2H), 4.05(m, 1H), 4.14(m, 1H), 4.4-4.85(m,6H), 5.10(d, J=11.07 Hz, 1H, H_1), 7.35(m, 15H). ^{13}C-NMR(C_6D_6) δ 13.89, 20.05, 24.53, 24.96, 27.98, 28.52, 29.91, 54.78, 54.86, 55.82, 56.11, 56.30, 56.41, 69.92, 70.15, 72.82, 73.17, 73.20, 74.90, 75.11, 77.58, 77.72, 78.46, 79.01, 79.17, 98.81, 98.88, 127.27, 127.43, 127.63, 127.52, 128.32, 139.34, 139.45.

The above epoxide (450mg, 0.83mmol) in anhydrous THF(20 mL) was subjected to the general Vedej isomerization (II.4.5) using Ph_2PLi (4.96 mL, 2.48 mmol) then freshly distilled MeI(0.15 mL, 2.48 mmol). E alkene **168** (371mg, 85%) was afford after purification . TLC R_f=0.6 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.885(t, J=7.36 Hz, 3H, H_{12}), 1.29-1.58(m, 4H, H_6, H_{11}), 1.93-2.24(m, 4H, H_7, H_{10}), 3.20(s, 3H, -OCH_3), 3.51(d, J= 2.02Hz, 1H, H_4), 3.62(m, 1H, H_5), 4.03(dd, J=2.80, 10.08 Hz, 1H, H_3),4.22(dd, J=3.52, 10.06 Hz, 1H, H_2), 4.46(d, J=11.89Hz, 1H), 4.60(m, 3H), 4.78(m, 2H), 5.08(d, J=11.35Hz, 1H, H_1), 5.44(m, 2H, H_8, H_9), 7.15(m, 15H). ^{13}C-NMR(C_6D_6) δ 13.57, 22.79, 29.26, 31.19, 34.82, 54.75, 69.79, 72.77, 73.18, 75.01, 77.62, 78.26, 79.21, 98.80, 127.24, 127.36, 127.43, 127.61, 127.74, 128.13, 130.18, 130.62, 139.38, 139.47.

Methyl-2,3, 4--O- tribenzyl-α-D-gluco pyranoside Z alkene (165)

The terminal alkene **90** (1.87g, 3.99 mmol) was converted to the aldehyde according to the general ozonolysis procedure (II.4.3). The aldehyde (1.35g, 71%) was obtained as a colorless syrup after purification. TLC R_f=0.42(10% EtOAc/PE). ^{1}HNMR(C_6D_6): 2.02(m, 4H), 3.14(s, 3H), 3.20(s, 1H), 3.95(m,1H), 4.1(m, 1H), 4.65(m, 6H), 4.78(d, J=11.2Hz, 1H), 5.09(d, J=10.2Hz, 1H), 7.3 (m, 15H), 9.35(s, 1H).

The aldehyde (1.2g, 2.45 mmol) was subjected to the general Wittig procedure (II.4.4). Z-alkene **165** (1.05mg, 81%) was obtained after purification. TLC R_f=0.70 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.85(t, J=7.24Hz, 3H), 1.28-2.20(m, 8H), 3.14(s, 3H), 3.68(bs, 1H), 3.72(m, 1H), 4.03(dd, J=2.64, 9.98Hz, 1H), 4.24(m, 1H), 4.52(d, J=11.2Hz, 1H), 4.58(m, 3H), 4.75(m, 2H), 4.98(d, J=11.32Hz, 1H), 5.34(m, 2H), 7.16(m,

15H). ^{13}C NMR(C_6D_6): 12.9, 22.83, 23.70, 29.13, 31.34, 54.53, 69.67, 72.80, 73.12, 74.78, 77.55, 78.18, 79.08, 98.82, 127.14, 127.54, 127.76, 128.06, 128.09, 128.28, 129.42, 130.01, 139.32.

Methyl-2,3, 4-O-tribenzyl-α-D-glucopyranoside E alkene (172)

Z alkene **165** (800 mg, 1.52mmol) in CH_2Cl_2(20 mL) was subjected to the general epoxidation procedure (II.4.5). The epoxide derivative (716 mg, 87%) was obtained after purification. TLC R_f=0.50 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.82(t, J=7.02 Hz, 3H, H_{12}), 1.20-1.88(m, 8H, H_6, H_7, H_{10}, H_{11}), 2.56(m, 2H, H_8, H_9), 3.18(s, 3H, -O<u>CH_3</u>), 3.48(m, 2H), 4.00(m, 1H), 4.11-4.85(m,7H), 5.05 (d, J=11.02 Hz, 1H, H_1), 7.35(m, 15H).

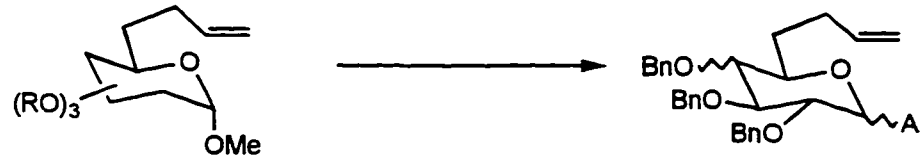
The above epoxide (450mg, 0.83mmol) in anhydrous THF(20 mL) was subjected to the general Vedej isomerization (II.4.5) using Ph_2PLi (4.96 mL, 2.48 mmol) then freshly distilled MeI(0.15 mL, 2.48 mmol). E alkene **169** (331mg, 76%) was afford after purification . TLC <u>R_f</u>=0.6 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.885(t, J=7.36 Hz, 3H, H_{12}), 1.22-2.32 (m, 8H, H_6, H_{11}, 4H, H_7, H_{10}), 3.15 (s, 3H, -O<u>CH_3</u>), 3.45(bs, 1H, H_4), 3.72 (m, 1H, H_5), 4.02(m, 1H, H_3),4.22(m, 1H, H_2), 4.52 (d, J=11.72Hz, 1H), 4.50 (m, 3H), 4.72(m, 2H), 5.02(d, J=11.15Hz, 1H, H_1), 5.32 (m, 2H, H_8, H_9), 7.15(m, 15H). ^{13}C-NMR(C_6D_6) δ 14.07, 21.99, 28.96, 32.09, 35.02, 54.65, 69.83, 72.81, 73.09, 74.98, 77.65, 78.26, 79.11, 98.60, 126.34, 127.36, 127.33, 127.51, 127.84, 128.13, 130.18, 130.73, 139.42, 139.49.

Methyl-2,3, 4--O- tribenzyl-α-D-manno pyranoside Z alkene (166)

The terminal alkene **91** (1.46g, 3.12mol) was converted to the aldehyde according to the general ozonolysis procedure (II.4.3). The aldehyde (1.2g, 83%) was obtained as a colorless syrup after purification. TLC R_f=0.45(10% EtOAc/PE). ^{1}HNMR(C_6D_6): 2.10(m, 4H), 3.18(s, 3H), 3.52(bs, 1H), 4.21(m, 1H), 4.42(m, 1H), 4.58(m, 6H), 4.71(d, J=11.9Hz, 1H), 5.22 (d, J=10.3Hz, 1H), 7.4(m, 15H), 9.31(s, 1H).

The aldehyde (1.1g, 1.53mmol) was subjected to the general Wittig procedure (II.4.4). Z-alkene **166** (902mg, 83%) was obtained after purification. TLC R_f=0.70 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.87(t, J=7.38Hz, 3H), 1.25(m, 4H), 2.20(m, 4H), 3.17(s, 3H), 3.59(m, 2H), 4.03(d, J=10.01Hz, 1H), 4.24(d, J=9.88Hz, 1H), 4.23(d, J=11.5Hz, 1H), 4.75(m, 5H), 5.05(d, J=11.12Hz, 1H), 5.24(m, 2H), 7.16(m, 15H). ^{13}C NMR(C_6D_6): 13.405, 22.98, 23.57, 29.18, 31.56, 54.82, 69.85, 72.75, 73.82, 75.34, 77.81, 78.19, 79.02, 98.16, 127.26, 127.63, 127.82, 128.11, 128.23, 128.32, 129.59, 130.09, 139.42.

II.4.14 Preparation of Trityl Galacto, Gluco, Manno Pyranoside Alkenes



89: R=Bn, galacto
90: R=Bn, gluco

154: A=α/β-OAc, galacto
155: A=α/β-OAc, gluco
156: A=α/β-OH, galacto
157: A=α/β-OH, gluco
158: A=α/β-OTr, galacto
159: A=α/β-OTr, gluco

Trityl- 2,3,4-tri-O-benzyl-α/β-D-galacto pyranoside alkene (161)

To a solution of methyl galactopyranoside alkene **89** (1.0g, 2.11 mmol) in anhydrous CH_2Cl_2 (50 mL) was added $BF_3.OEt_2$(1.34 mL, 0.020 mmol) and Ac_2O (1.97 mL, 20.4 mmol). The reaction was stirred at rt. for 40 min., then diluted with H_2O (5mL) and extracted with Et_2O(3X15 mL). The combined organic phase was dried (Na_2SO_4) , filtered, and the filtrate concentrated *in vacuo*. The residue was subjected to flash chromatographically to afford the acetate **154** (1.06g, 85%), TLC R_f=0.80 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 1.4–2.0(m, 7H), 3.2-4.1(m, 6H), 4.45-5.2(m, 13/2H), 5.78(m, 1H), 6.35(bs, 1/2H), 7.25(m, 15H).

To a solution of acetate **154** (800mg, 1.55 mmol) in MeOH (20ml) was subjected to the standard basic hydrolysis procedure to afford an inseparable 1:1 mixture of α/β lactol **156** (712mg, 97%) after purification. TLC R_f=0.25 (10% EtOAc/PE). ^{1}HNMR(CDCl3): δ 1.25–2.05(m, 4H, H_6, H_7), 2.78(brs, 1/2H), 2.90(d, J=9.2 Hz, 1/2H), 3.28(t, J=9.3Hz, 1/2H), 3.50 (dd, J=1.9, 9.5 Hz, 1/2H), 3.60(d, J=1.9 Hz, 1/2H), 3.65-4.1(m, 3H), 4.5-5.0(m, 7H), 5.12(bs, 1/2H), 5.7(m, 1H), 7.3(m, 15H).

D-galactopyranoside mixture **156** (300mg, 0.63mmol) was tritylated according to the general procedure (II.4.8) using Ph_3Cl (352mg, 1.26mmol), AgOTf (292mg, 1.13mmol) and collidine(0.1mL, 1.26mmol) . An inseparable 1:1 mixture of α/β trityl galacto alkene **158** (403mg, 89%) was obtained as light yellow syrup after purification. TLC R_f=0.68 (10 % EtOAc/PE). ^{1}HNMR(C_6D_6): δ 1.50-1.82(m, 4H, H_6, H_7), 2.50(m, 1/2H, $H_{5\beta}$), 3.10(dd, J=2.1, 9.5Hz, 1/2H, $H_{3\beta}$), 3.18(d, J=1.9 Hz, 1/2H, $H_{4\beta}$), 3.58(m, 1H, $H_{4\alpha}$, $H_{5\alpha}$), 4.08-4.60(m, 6H), 4.72-5.05(m, 4H), 5.38(d, J=4.2 Hz, $H_{1\alpha}$), 5.58(m, 1H,

H_9), 6.8-7.8(m, 30H), ^{13}C NMR(C_6D_6): δ 29.53, 29.68, 29.89, 30.08, 70.83, 73.05, 73.13, 73.33, 74.87, 75.10, 75.21, 76.38, 78.25, 80.16, 81.83, 83.43, 87.42, 89.02, 93.51, 98.72, 98.92, 114.00, 114.14, 127.01, 125.8, 126.2, 126.4, 126.7, 127.0, 127.2, 127.42, 127.75, 128.06, 128.13, 128.85, 128.88, 129.18, 129.36, 129.61, 129.65, 129.69, 130.03, 130.54, 130.73, 130.85, 130.89, 130.99, 138.65, 139.15, 139.19, 139.31, 139.43, 147.38.

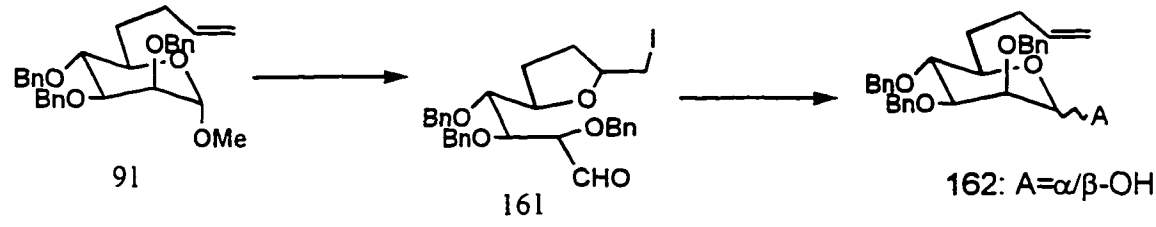
Trityl-2,3, 4-O-tribenzyl-6-allyl-α/β-D-gluco pyranoside (159)

Methyl gluco pyranoside alkene **90** (800mg, 1.69 mmol) was subjected to the same sequence of actolysis and basic hydrolysis procedure to afford an inseparable 1:1 mixture of α/β lactol **157** (667mg, 85% over 2 steps) after purification. TLC R_f=0.25 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 1.44-2.42(m, 4H), 3.09 (s, 3H, -OMe), 3.05(t, J=7.85Hz, 1H, H_4), 3.22(m, 1H, H_2), 3.72(m, 1H, H_5), 4.09(t, J=9.08Hz, 1H, H_3), 4.74(m, 4H), 4.61(d, J=4.08Hz, 1H), 5.02 (m, 4H), 5.78 (m, 1H), 7.26(m, 15H). ^{13}C NMR(C_6D_6): δ 27.52, 30.79, 53.65, 68.42, 71.63, 73.78, 74.56, 80.32, 81.88, 81.87, 96.96, 114.58, 127.21, 129.22, 127.52, 127.47, 127.87, 128.21, 128.34, 138.43, 138.79, 139.25.

Trityl gluco pyranoside was tritylated according to the general procedure (II.4.8) Thus treatment of alcohol **157** (500mg, 1.05 mmol) with Ph_3Cl (585 mg, 2.09 mmol), AgOTf (487mg, 1.88mmol) and collidine (0.17 ml, 2.09mmol) afforded an inseparable 1:1 mixture of α/β trityl alkene **159** (671mg, 89%) was obtained as light yellow syrup after purification. TLC R_f=0.68(10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 1.40-1.90(m, 4H), 2.85(t, J=9.18Hz, 1/2H), 3.30(m, 1H), 3.45(t, J=12.2Hz, 1H), 3.48(dd, J=3.67Hz,

11.02Hz, 1/2H), 3.90(t, J=9.11 Hz, 1/2H), 3.98(m, 1/2H), 4.35(d, 9.18Hz, 1/2H), 4.64(m, 3H), 4.98(m, 4H), 5.25(t, J=11.02Hz, 1H), 5.45(d, J=4.28Hz, 1/2H), 5.70(m, 1H), 7.30(m, 30H). ^{13}C NMR(C_6D_6): δ 28.75, 29.96, 31.14, 70.6, 73.1, 73.6, 74.5, 74.8, 75.0, 75.2, 81.5, 81.6, 82.2, 82.3, 83.2, 85.4, 89.2, 92.7, 98.2, 113.8, 114.3, 127.5, 127.8, 128.0, 128.2, 128.6, 128.8, 129.0, 129.4, 129.5, 129.8, 129.9, 130.0, 130.6, 130.8, 138.4, 138.8, 139.1, 139.4, 139.6,139.8, 145.1.

Trityl- 2,3,4-O-tribenzyl-α/β -D-manno pyranoside (163)



The inseparable mixture of cis and trans (c/t=5/2) THF **161** (250mg, 72%) was obtained after treatment of the methyl alkene **91** to the standard iodoetherification procedure (II.4.9). ^{1}HNMR(C_6D_6): δ 1.25-2.00(m, 4H), 2.90(m, 2H, -CH_2I), 3.62-5.20(m, 11H), 7.25(m, 15H), 9.87(s, 1H). selected ^{13}C NMR(C_6D_6): 9.62, 10.62(-$\underline{C}H_2$I), 27.47, 31.26(C_6, C_7).

A mixture of cis/trans THF **161** (240, 0.434 mmol), freshly activated Zn dust (128mg, 1.95 mmol) and 95% EtOH (10mL) was heated at reflux for 30 min. The reaction mixture was cooled to rt. and filtered through a pad of celite and the filtrate concentrated in vacuo. Flash chromatography of the residue afforded hydroxyl alkene **162**

(188mg, 91%). TLC Rf=0.10 (10% EtOAc/PE) ^{1}HNMR(C_6D_6): δ 1.2–2.4(m, 4H), 2.8-4.2(m, 6H), 4.4-5.2(m, 7H), 5.75(m, 1H), 7.25(m, 15H).

Hydroxyl pyranoside alkene **162** (150mg, 0.32mmol) was tritylated according to the general procedure (II.4.8) using Ph_3Cl (176mg, 0.63mmol), AgOTf (146mg, 0.565mmol) and collidine(0.5mL, 0.63mmol) to afford an inseparable 1:1 mixture of α/β trityl alkene **161** (192.4mg, 85%) as light yellow syrup after purification. TLC R_f=0.65(10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 1.65-2.40(m, 4H), 3.32(m, 1H), 4.05(t, J=9.05Hz, 1H), 4.22-4.72(m, 7H), 4.90-5.20(m,3H), 5.43(d, J=2.01Hz, 1H, H1a), 5.92(m, 1H, H8), 7.22(m, 30H). ^{13}C NMR(C_6D_6): δ 29.78, 31.54, 71.92, 72.39, 72.70, 75.28, 76.86, 78.95, 80.10, 88.5, 94.22, 114.26, 127.20, 127.33, 127.42, 127.53, 127.74, 127.93, 128.05, 128.29, 128.93, 129.27, 129.69, 138.95, 139.4, 144.66.

Preparation of Z and E Trityl Pyranoside Alkenes

164:A=α-OMe,galacto
165: A= α-OMe,gluco

167: A=α/β-OH, galacto
168 A=α/β-OH, gluco
169: A=α/β-OTr, galacto
170: A=α/β-OTr, gluco

Trityl-2,3, 4-O-tribenzyl-α/β -D-galactopyranoside Z alkene (169)

Methyl galacto pyranoside Z alkene **164** (600mg, 1.14mmol) was subjected to the acetolysis procedure described in the preparation of **154** (II.4.16) using $BF_3.OEt_2$(0.72ml,

0.011mmol) and Ac_2O (1.1 mL, 11.4 mmol) in anhydrous CH_2Cl_2(50 mL). Acetate (537mg, 85%;) was afforded after purification. TLC R_f=0.80 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.92(m, 3H), 1.38(m, 2H), 1.70(m, 2H), 1.80(s, 3H, -OC(O)CH3), 2.06(m, 2H), 2.40(m, 2H), 3.29(t, J=9.29Hz, 1H), 3.62(m, 1H), 4.05(m, 1H), 4.55(m, 3H), 4.95(m, 3H), 5.52(m, 2H), 6.68(d, J=3.54Hz, 1H), 7.15(m, 15H). ^{13}C NMR(C_6D_6): δ 13.89, 20.57, 20.54, 23.19, 23.32, 29.56, 30.14, 32.13, 72.49, 73.08, 75.37, 75.53, 79.75, 81.74, 82.24, 85.23, 89.91, 94.58, 127.66, 127.89, 127.98, 128.30, 128.47, 128.59, 129.48, 130.68, 139.02, 139.49, 168.94.

Acetate (100mg, 0.18 mmol) was subjected to base hydrolysis as described. An inseparable 1:1 mixture of α/β anomers **167** (84mg, 91%) was obtained as a colorless syrup after purification. TLC R_f=0.20 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.90(m, 3H), 1.38(m, 4H), 2.20(mm, 4H), 3.10-4.20(m, 5H), 4.40-5.10(m, 6H), 5.60(m, 2H), 7.26(m, 15H). ^{13}C NMR(C_6D_6): δ 13.68, 22.95, 23.33, 23.46, 29.35, 29.91, 31.91, 32.11, 69.91, 72.51, 74.32, 74.87, 74.96, 75.26, 80.93, 81.90, 82.16, 83.85, 90.76, 97.88, 127.41, 127.73, 128.055, 128.20, 128.33, 129.38, 129.86, 130.12, 139.38.

The pyranoside mixture **167** (65mg, 0.13mmol) was tritylated according to the general procedure of tritylation (II.4.8) using Ph_3Cl (72mg, 0.26mmol), AgOTf(60mg, 0.23mmol) and collidine(0.02mL, 0.26mmol) afforded an inseparable 1:1 mixture of α/β trityl alkene (76mg, 78%) was obtained as light yellow syrup after purification. TLC R_f=0.65(10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.78(t, J=7.05Hz, 3H, H12), 1.05-1.95(m, 8H, H_6, H_7, H_{10}, H_{11}), 2.05(t, J=6.4 Hz, 1/2H, $H_{5\beta}$), 3.05(d, J= 9.49Hz, 1/2H, $H_{3\beta}$), 3.15(bs, 1/2H, $H_{4\beta}$), 3.59(bs, 1/2H, $H_{4\alpha}$), 3.65(t, J=6.4 Hz, 1/2H, $H_{5\alpha}$), 4.05-4.54(m,

11/2H), 4.68(d, J=11.99 Hz, 1/2H), 4.82(d, J=10.14 Hz, 1H),4.93(d, J=11.53Hz, 1/2H), 5.01(dd, J=2.34, 11.49 Hz, 1/2H, $H_{1\beta}$), 5.27(m, 2H, H8, H9), 5.32(bs, 1/2H, $H_{1\alpha}$). ^{13}C NMR(C_6D_6, 75.5Hz): δ 13.74, 13.96, 22.89, 22.98, 23.37, 23.66, 29.34, 30.41, 30.83, 70.92, 73.03, 73.08, 73.21, 73.68, 74.83, 74.91, 75.23, 76.34, 77.18, 78.23, 79.41, 80.19, 83.47, 87.44, 88.97, 93.47, 98.77, 126.95, 127.05, 127.20, 127.41, 127.63, 127.74, 128.05, 128.16, 128.35, 128.56, 128.83, 128.89, 129.02, 129.18, 129.31, 129.46, 129.65,130.01, 130.33, 139.02, 139.13, 139.23, 139.31, 139.35, 139.43, 144.92, 145.05, 145.08.

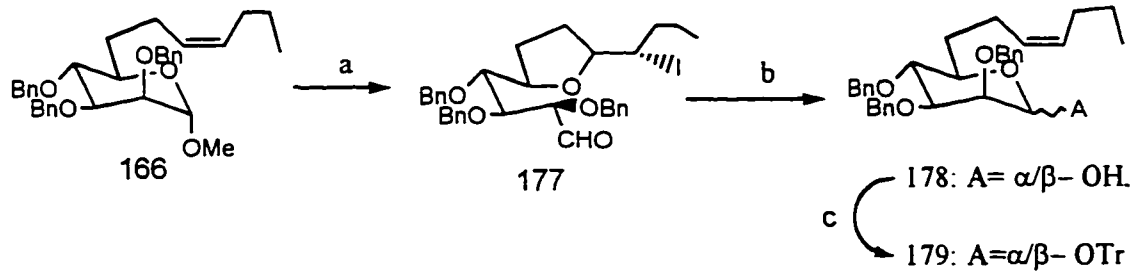
Trityl-2,3, 4-O-tribenzyl-α/β-D-glucopyranoside Z alkene (170)

Methyl gluco pyranoside Z alkene **165** (500mg, 0.95mmol) was subjected to the same sequence of acetolysis and hydrolysis procedure described above to afford an inseparable 1:1 mixture of α/β anomers **167** (65mg, 84% over 2 steps) after purification. TLC R_f=0.20 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.95(m, 3H), 1.36-2.05(m, 8H), 3.00-4.10(m, 5H), 4.40-5.10(m, 6H), 5.75 (m, 2H), 7.26(m, 15H). ^{13}C NMR(C_6D_6): δ 13.42, 22.57, 23.21, 23.21, 29.43, 29.98, 31.87, 32.45, 69.7, 72.87, 74.12, 74.91, 74.65, 75.13, 80.42, 81.83, 82.43, 83.61, 90.51, 97.23, 127.41, 127.82, 128.09, 128.31, 128.42, 129.51, 129.42, 130.81, 139.91.

The pyranoside mixture **168** (55mg, 0.11mmol) was tritylated according to the same procedure to afford an inseparable 1:1 mixture of α/β trityl alkene **170** (57mg, 69%) was obtained as light yellow syrup after purification. TLC R_f=0.70(10% EtOAc/ PE). ^{1}HNMR(C_6D_6): δ 0.92(m, 3H), 1.20-2.20(m, 8H), 2.85(t, J=9.11Hz, 1/2H), 3.40(m, 2H),

3.58(dd, J=4.03, 10.96Hz, 1/2H), 3.75(t, J=9.14Hz, 1/2H), 3.85(m, 1/2H), 4.35(d, J=8.65Hz, 1/2H), 4.80(mm, 5H), 5.25(t, J=10.96Hz, 1/2H), 5.45(m, 2H), 7.25(m, 30H). ^{13}C NMR(C_6D_6): δ 13.71, 13.77, 22.58, 22.86, 23.03, 29.31, 29.35, 31.89, 32.00, 70.72, 73.02, 74.02, 74.59, 75.02, 75.26, 75.33, 81.79, 82.25, 82.33, 83.04, 85.51, 87.87, 89.11, 92.53, 98.26, 127.15, 127.43, 127.48, 127.75, 127.84, 127.93, 128.07, 128.21, 128.29, 128.47, 128.56, 128.95, 129.02, 129.25, 129.33, 129.55, 129.66, 129.79, 130.18, 138.55, 138.97, 139.08, 139.33, 144.79, 144.85.

Trityl-2,3, 4-O-benzyl-α/β-D-mannopyranoside Z alkene (179)



The inseparable mixture of cis and trans (c/t=2/5) THF **213** (820mg, 93%) was obtained after treatment of the methyl alkene **166** to the standard iodoetherification procedure (II.4.9). ^{1}HNMR(C_6D_6): δ 0.82(m, 3H), 1.20-2.0(m, 8H), 3.80-4.38(m, 7H), 4.52-4.80(m, 5H), 7.20(m, 15H), 9.77(bs, 5/7H)(H1 trans), 9.79(s, 2/7 H) (H1 cis). selected ^{13}C NMR(C_6D_6): δ: 28.29(c), 29.29(t), 30.80(c), 31.89(t) (C6, C7), 42.86, 43.09(-CHI)

A mixture of cis/trans THF **177** (500mg, 0.946 mmol) was subjected to the standard Zn-mediated reduction to afford a mixture of hydroxyl alkene **178** (447.8mg,

92%). TLC Rf=0.10 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.90(m, 3H), 1.38(m, 2H),1.65- 2.60(m, 6H), 3.05-4.20(m, 4H), 4.40-5.10(m, 6H), 5.58(m, 2H), 7.26(m, 15H). ^{13}C NMR(C_6D_6): δ 12.45, 12.55, 21.69, 21.84, 22.50, 27.68, 28.27, 31.00, 31.10, 33.72, 70.21, 70.36, 70.88, 71.78, 73.85, 75.10, 77.98, 79.25, 79.28, 91.68, 126.01, 126.35, 126.63, 127.08, 127.25, 128.69, 129.03, 129.24, 129.39, 137.93, 138.23.

The hydroxyl alkene **178** was tritylated according to the general procedure (II.4.8) to afford an inseparable 1:1 mixture of α/β trityl alkene **179** (171.5mg, 88%) after purification. TLC R_f=0.65(10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.94(m, 3H), 1.30-2.40(m, 8H), 3.02-3.32(m, 2H), 3.78-4.65(m, 7H), 5.02(m, 1H), 5.42(m, 3H), 7.30(m, 30H); ^{13}C NMR(C_6D_6): δ13.50, 13.62, 22.91, 22.73, 23.54,28.57, 29.32, 32.30, 32.50, 34.77, 71.09, 71.88, 72.33, 72.71, 73.04, 75.20, 76.93, 78.93, 79.04, 80.05, 81.77, 83.07 , 88.48, 94.23, 97.43, 127.35, 127.54, 127.63, 128.06, 128.01, 128.12, 128.23, 128.35, 128.67, 129.02, 129.25, 129.45, 129.69, 138.4, 138.8, 139.0,144.62, 147.36.

171: A= α-OMe,galacto
172: A= α-OMe,gluco

173: A=α/β-OH, galacto
174: A=α/β-OH, gluco
175: A=α/β-OTr, galacto
176: A=α/β-OTr, gluco

Trityl-2,3, 4-O-tribenzyl-α/β-D-galactopyranoside E alkene (171)

Methyl galacto pyranoside **171** (200 mg, 0.36mmol) was subjected to the standard acetolysis procedure to afford acetate (255mg, 81%). TLC R_f=0.80 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.89(m, 3H, H_{12}), 1.30-2.14(m, 8H, H_6, H_7, H_{10}, H_{11}), 1.77(s, 3H, -OC(O)CH_3), 3.38(m,1H), 3.56(d, J=1.98Hz, 1H), 3.8(m, 1H), 3.90(dd, J=2.7, 8.97Hz, 1H), 4.26-5.12(m, 6H), 5.38(m, 2H), 6.74(d, J=3.72Hz, 1H, H1), 7.25(m, 15H).

Acetate (100mg, 0.18 mmol) was subjected to the basic hydrolysis described above to afford an inseparable 1:1 mixture of α/β anomers **173** (159mg, 86%) after purification. TLC R_f=0.25 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.887 (t, J=7.35Hz, 3H, H_{12}), 1.29-2.19(M, 8H, H_6, H_7, H_{10}, H_{11}), 3.50(m, 2H), 4.10(m, 2H), 4.20-4.90(m, 6H), 5.11(m, 1H). 5.47(2H), 7.25(m, 15H). ^{13}C-NMR(75Hz) δ 12.48, 21.69, 27.88, 28.03, 29.93, 30.00, 33.71, 68.95, 71.77, 71.97, 72.93, 73.62, 73.76, 75.02, 76.27, 76.46, 78.17, 80.63, 81.60, 90.48, 97.30, 126.11, 126.29, 126.35, 126.62, 126.69, 126.94, 127.20, 128.72, 128.95, 129.52, 137.71,137.82, 138.17, 139.02.

The hydroxyl alkene **173** (78mg, 0.16mmol) was tritylated according to the general procedure. An inseparable 1:1 mixture of α/β trityl alkene (97mg, 83%) was obtained after purification. TLC R_f=0.65 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.95(m, 3H, H_{12}), 1.05-1.95(m, 8H, H_6, H_7, H_{10}, H_{11}), 2.40(s, 1/2H, $H_{4\beta}$), 2.58(t, J=6.4 Hz, 1/2H, $H_{5\beta}$), 3.18(dd, J= 4.25, 9.29Hz, 1/2H, $H_{3\beta}$), 3.28(bs, 1/2H, $H_{4\alpha}$), 3.68(bs, 1H), 4.2-4.6(m, 5H), 4.80(d, J=11.32 Hz, 1/2H), 4.95-5.18(m,2H), 5.32(m, 2H, H_8, H_9), 5.50(d, J=5.6Hz, 1/2H, $H_{1\alpha}$), 7.15(m, 30H). ^{13}C NMR(C_6D_6): δ 12.48, 21.71, 27.48, 27.70, 28.78, 28.95, 29.10, 29.76, 33.63, 33.71, 69.73, 71.92, 72.02, 72.26, 72.40, 73.80, 74.10, 75.36, 75.94,

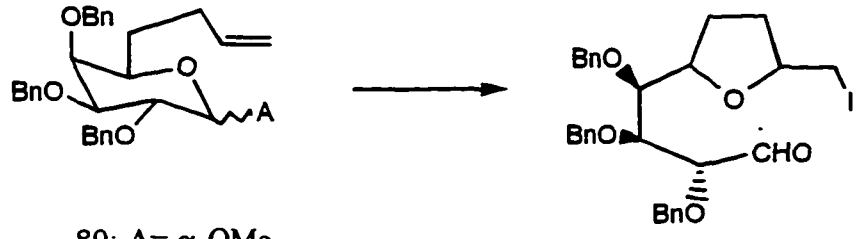
77.19, 78.30, 79.09, 82.43, 86.28, 87.92, 92.44, 97.65, 125.85, 125.90, 126.08, 126.30, 126.44, 126.52, 126.63,126.82, 126.95, 127.04, 127.24, 127.56, 127.78, 128.30, 128.49, 128.61,128.91, 129.23, 137.94, 138.04, 138.16, 138.32, 143.95, 144.03, 146.30.

Trityl-2,3, 4-O-benzyl-α-D-glucopyranoside E alkene (176)

Methyl gluco pyranoside **172** (400 mg, 0.72 mmol) was subjected to the standard acetolysis and basic hydrolysis described above to afford an inseparable 1:1 mixture of α/β anomers **174** (300mg, 61%) after purification. TLC R_f=0.25 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.92 (t, J=7.31Hz, 3H, H_{12}), 1.22-2.25 (M, 8H, H_6, H_7, H_{10}, H_{11}), 3.45 (m, 2H), 4.10-4.80(m, 8H), 5.10(m, 1H), 5.52 (2H), 7.25(m, 15H).

The hydroxyl alkene **174** (78mg, 0.20mmol) was tritylated according to the general procedure. An inseparable 1:1 mixture of α/β trityl alkene (76mg, 51%) was obtained after purification. TLC R_f=0.65 (10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.97(m, 3H), 1.20-2.10(m, 8H), 2.52(m, 8H), 2.52(d, J=3.28Hz, 1/2H), 2.89(t, J=6.08 Hz, 1/2H), 3.47(m, 1/2H), 3.57(dd, J=3.49, 9.91Hz, 1/2H), 4.02(m, 1H), 4.35(d, J=7.76Hz, 1/2H), 4.54(d, J=12.07Hz, 1H), 4.70(m, 2H), 4.92(m, 5/2H), 5.04(dd, J=2.71, 11.2Hz, 1/2H), 5.25(t, J=11.24Hz, 1H), 5.43(m, 2H), 5.46(d, J=3.42Hz, 1/2H), 7.30(m, 30H). ^{13}C-NMR(C_6D_6) δ 12.44, 21.71, 26.57, 26.92, 30.84, 30.94, 33.69, 69.61, 71.99, 72.63, 73.48, 73.69, 73.88, 74.14, 74.21, 80.74, 81.26, 81.99, 84.41, 91.53, 97.10, 125.88, 125.99, 129.29, 126.47, 126.81, 126.94, 127.16, 128.45, 128.57, 128.80, 129.14, 129.74, 130.70, 137.82, 137.90, 138.24, 138.34, 143.72, 143.77.

II.4.15. Iodoetherification of the Galacto, Gluco, and Manno Pyranoside Alkenes



89: A= α-OMe
158: A=α/β -OTr

180a: cis/trans THF
180b: cis-THF

(2R, 3S, 4R, 5R, 8S)-2,3,4-O-tribenzyl-5,8-epoxy-9-iodo-nonane-1-al (180b)

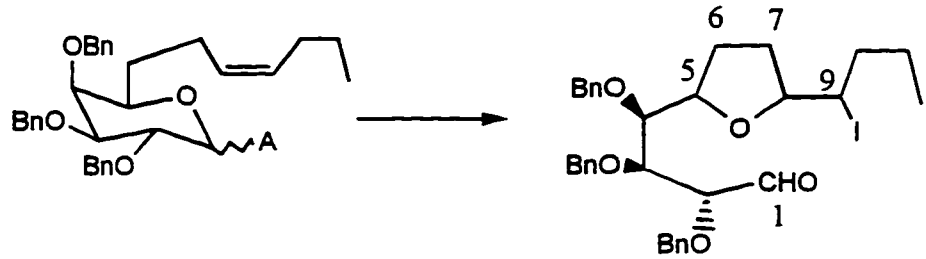
Halocyclization was performed according to the general procedure (II.4.9). Thus , treatment of the trityl alkene **161**(19mg, 0.0265 mmol) with IDCP(30mg, 0.064 mmol) in 5 mL CH_2Cl_2 afforded cis-THF product **180b** (12mg, 82%) as colorless syrup after purification. TLC R_f =0.25(10% EtOAC/PE). ^{1}HNMR(C_6D_6): δ 1.43-1.55(m, 4H, H_6, H_7), 2.89(q, J=6.74, 9.71 Hz, 1H, H_{9a}), 3.00(q, J=5.74, 9.77 Hz, 1H, H_{9b}), 3.69(m, 1H, H_4), 3.82(m, 1H, H_8), 4.11(dd, J=1.31, 1H, H_3), 4.25(m, 3H, H_2, H_5, -CH2Ar), 4.62(m, 5H, -OCH_2Ar), 7.33(m, 15H, -C6H5), 9.74(s, 1H, H_1). ^{13}C NMR(C_6D_6): 9.94, 27.34, 31.26, 72.52, 73.75, 74.31, 78.75, 80.00, 80.18, 80.32, 84.21, 126.86, 127.41, 127.73, 127.84, 128.05, 128.29, 128.80, 128.86, 137.89, 138.3, 139.2, 200.99.

cis/trans-THF 180a

An inseparable mixture of cis and trans (c/t=2/1) THF **180a** (15mg, 65%) was obtained after treatment of the methyl alkene **89** to the standard iodoetherification procedure. ^{1}HNMR(C_6D_6): δ 1.20-1.5585(m, 4H, H_6, H_7), 2.85-3.05(m, 2H, -CH_2I), 3.65-5.25(m, 11H), 7.35(m, 15H, -C6H5), 9.63(s, 1/3H, H1), 9.74(s, 2/3H, H_1). ^{13}C

NMR(C_6D_6): selected δ 9.94 (C_9 cis), 11.63(C_9 trans), 27.34(cis), 28.07(trans), 31.26(cis), 32.61(trans), 200.99(cis), 201.08(trans) .

Haloetherification of the Z-alkene:



164: A= α-OMe
169: A=α/β -OTr

181a: cis/trans THF
181b: cis-THF

(2R, 3S, 4R, 5R, 8S, 9S)-2,3,4-O-tribenzyl-5,8-epoxy-9-iodo -dodecane-1-al (181b)

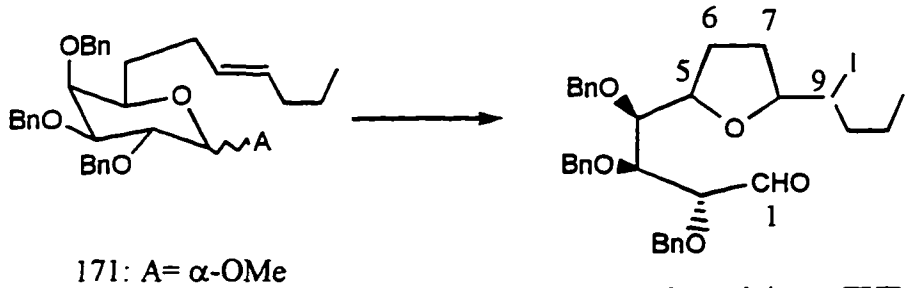
Halocyclization was performed according to the general procedure described in Part 1. Thus , treatment of the trityl alkene **169** (50mg, 0.065 mmol) with IDCP(62mg, 0.13 mmol) in 10 mL CH_2Cl_2 afforded cis-THF product **181b** (37mg, 87%) as colorless syrup after purification. TLC R_f =0.25(10% EtOAC/PE). ^{1}HNMR(C_6D_6): δ 0.78(t, J=7.12 Hz, 3H), 1.20-1.78(m, 8H, H_6, H_7, H_{10}, H_{11}), 3.58(m, 1H), 3.68(m, 1H), 3.88(m, 1H), 4.10(d, J=2.12Hz, 1H), 4.25(m, 3H), 4.62(m, 5H), 7.22(m, 15H), 9.72(s, 1H). ^{13}C NMR(C_6D_6): δ 13.05, 22.95, 27.82, 30.18, 38.01, 42.07, 72.62, 73.64, 74.33, 79.94, 80.11, 80.40, 82.76, 84.20, 126.99, 127.41, 127.73, 127.85, 128.05, 128.21, 128.30, 137.7, 138.4, 139.1, 200.55.

cis/trans THF 181a

An inseparable mixture of cis and trans (c/t=5/3) THF **174** (25mg, 82%) was obtained after treatment of the methyl Z alkene **164** to the standard iodoetherification

procedure. ^{1}HNMR(C_6D_6): δ 0.78(m, 3H), 1.20-2.20(m, 8H), 3.40-5.20(m, 12H), 7.25(m, 15H), 9.70(s, 3/8H), 9.74(s, 5/8H). ^{13}C NMR(C_6D_6): selected δ (C6, C7): 27.82(cis), 28.50(trans), 30.18(cis), 30.46(trans).

Haloetherification of the E-alkene



171: A= α-OMe
175: A=α/β -OTr

182a: cis/trans THF
182b: cis-THF

(2R, 3S, 4R, 5R, 8S, 9R)-2,3,4-O-tribenzyl-5,8-epoxy-9-iodo -dodecane-1-al 182b

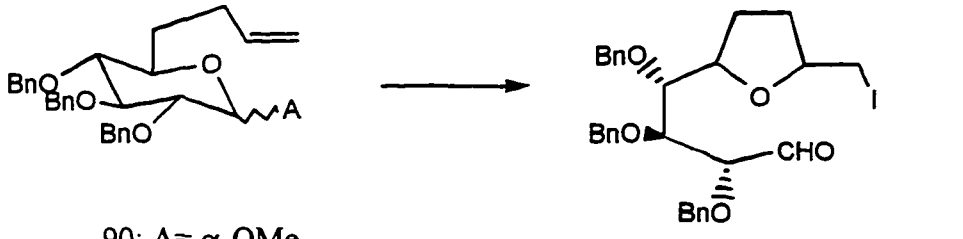
Halocyclization was performed according to the general procedure (II.4.9). Thus , treatment of the trityl alkene **175** (30mg, 0.0395 mmol) with IDCP(37mg, 0.079 mmol) in 5 mL CH_2Cl_2 afforded cis-THF product **182b** (21mg, 83%) as colorless syrup after purification. TLC R_f =0.25(10% EtOAC/PE). ^{1}HNMR(C_6D_6): δ 0.85(t, J=6.8 Hz, 3H), 1.2-1.98(m, 8H), 3.62(m, 1H), 3.75(m, 1H), 4.02(m, 2H), 4.20(mm, 3H), 4.58(m, 5H), 7.25(m, 15H). 9.75(s, 1H), ^{13}C NMR(C_6D_6): δ 13.44, 22.87, 27.57, 32.55, 38.91, 42.58, 72.93, 73.97, 74.71, 80.58, 80.92, 82.96, 84.43, 127.69, 128.01, 128.33, 128.58, 128.91, 129.11, 129.20, 138.08, 138.49, 138.88, 201.14.

cis/trans THF 182a

An inseparable mixture of cis and trans (c/t=2/1) THF **176** (25mg, 85%) was obtained after treatment of the methyl E alkene **171** to the standard iodoetherification procedure. ^{1}HNMR(C_6D_6): δ 0.83(m, 3H), 1.20-1.98(m, 8H), 3.66(m, 2H), 4.20(m, 5H), 7.22(m, 15H), 9.72(bs,1H). ^{13}C NMR(C_6D_6): δ 13.33(t), 13.44, 22.87, 22.96, 27.57, 27.67, 32.55, 38.91, 38.94, 42.58, 43.78, 72.77, 72.93, 73.97, 73.99, 74.71, 74.86, 80.08, 80.58, 80.84, 80.92, 82.52, 82.96, 84.43, 84.84, 127.69, 127.90, 128.01, 128.33, 128.58, 128.91, 129.01, 129.11, 129.20, 138.08, 138.49, 138.88, 201.14, 201.46.

Iodoetherification of Gluco Pyranoside Alkenes

Iodoetherification of the terminal alkenes



90: A= α-OMe
159: A=α/β -OTr

183a: THF(c/t=4/5)
183b: THF(c/t=6/1)

(2R, 3S, 4S,)-2,3,4-O-tribenzyl-5,8-epoxy-9-iodo-nonane-1-al(183b)

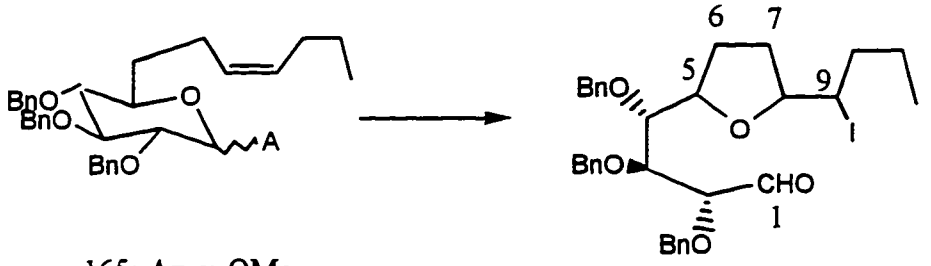
Halocyclization was performed according to the general procedure (II.4.9). Thus , treatment of the trityl alkene **159** (25mg, 0.035 mmol) with IDCP(39.6mg, 0.084 mmol) in 5 mL CH_2Cl_2 afforded an inseparable mixture of 6/1 cis to trans THF product **183b** (17mg, 88%) as colorless syrup after purification. TLC R_f =0.25 (10% EtOAC/PE). ^{1}HNMR (C_6D_6): δ 1.10-1.90(m, 4H), 2.83(m, -CH2I), 3.58(m, 1H),3.92(m, 2H), 4.15(m,

2H), 4.44(d, J=11.82Hz, 1H), 4.53-4.85(m, 5H), 7.15(m, 15H), 10.00(s, 1H), ^{13}C NMR(C_6D_6): δ 10.12(c), 10.93(t), 27.86(c), 29.322(t), 31.23(c), 32.50(t), 72.97, 73.89, 74.01, 75.31, 77.96, 78.15, 78.28, 78.29, 79.36, 79.76, 79.99, 80.13, 81.05, 81.08, 81.47, 81.64, 127.22, 127.44, 127.76, 127.97, 128.08, 128.23, 128.34, 128.42, 128.62, 128.70, 199.61.

cis/trans-THF 183a

An inseparable mixture of cis and trans (c/t=4/5) THF **183a** (22mg, 76%) was obtained after treatment of the methyl alkene **90** to the standard iodoetherification procedure. ^{1}HNMR(C_6D_6): δ 1.10-1.90(m, 4H), 2.83(m, -CH2I), 3.58(m, 1H),3.92(m, 2H), 4.15(m, 2H), 4.44(d, J=11.82Hz, 1H), 4.53-4.85(m, 5H), 7.15(m, 15H), 10.00(s, 1H). ^{13}C NMR(C_6D_6): δ 10.12(c), 10.93(t), 27.86(c), 29.322(t), 31.23(c), 32.50(t), 72.97, 73.89, 74.01, 75.31, 77.96, 78.15, 78.28, 78.29, 79.36, 79.76, 79.99, 80.13, 81.05, 81.08, 81.47, 81.64, 127.22, 127.44, 127.76, 127.97, 128.08, 128.23, 128.34, 128.42, 128.62, 128.70, 199.61.

Haloetherification of the Z-alkene:



165: A= α-OMe
170: A=α/β -OTr

184a: THF(c/t=1/1)
184b: THF(c/t=7/1)

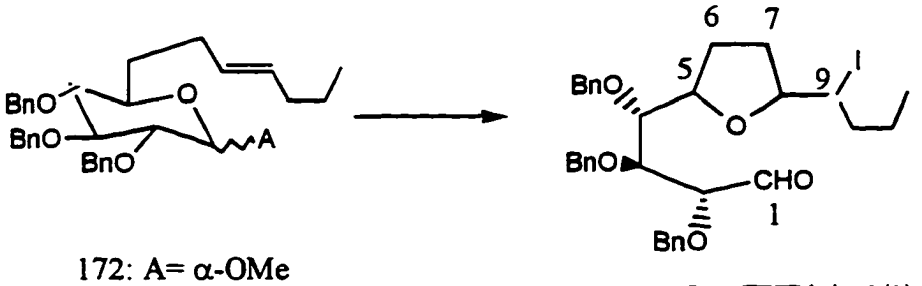
(2R, 3S, 4S)-2,3,4-O-tribenzyl-5,8epoxy-9-iodo -dodecane-1-al (184b)

Halocyclization was performed according to the general procedure. Thus , treatment of the trityl alkene **170** (25mg, 0.032 mmol) with IDCP(31mg, 0.065 mmol) in 5 mL CH_2Cl_2 afforded an inseparable mixture of 7/1 cis to trans THF product **184b** (16.8mg, 79%) as colorless syrup after purification. TLC $\underline{R_f}$ =0.25(10% EtOAC/PE). ^{1}HNMR(C_6D_6): δ 0.78(t, J=7.32Hz, 3H), 1.10-1.90(m, 8H), 3.25(q, J=3.10, 5.79 Hz, 1H, -CHI), 3.85(m, 2H0, 4.20(m, 4H), 4.70(m, 5H), 7.15(m, 15H), 9.98(s, 1H); For the major cis isomer: ^{13}C NMR(C_6D_6): δ 13.06, 22.91, 28.09, 30.61, 38.86, 41.85, 72.97, 73.85, 73.98, 78.99, 79.74, 79.87, 80.28, 81.01, 81.25, 82.00, 82.14, 127.00, 127.41, 127.73, 127.85, 128.05, 128.31, 128.37, 128.59, 129.51, 138.07, 138.49, 138.73, 199.50.

cis/trans THF 184a

An inseparable mixture of cis and trans (c/t=1/1) THF **165** (21mg, 87%) was obtained after treatment of the methyl alkene **184a** to the standard iodoetherification procedure. ^{1}HNMR(C_6D_6): δ 0.78(m, 3H), 1.20-2.20(m, 8H), 3.75-5.08(m, 12H), 7.25(m, 15H), 9.95(s, 1/2H), 9.98(s, 1/2H). ^{13}C NMR(C_6D_6): 13.06, 22.91, 23.02, 28.09, 29.52, 30.61,31.75, 38.58, 38.86, 41.85, 42.78, 72.97, 73.85, 73.98, 74.02, 74.14, 75.28, 78.99, 79.74, 79.87, 80.28, 80.86, 81.01, 81.16, 81.25, 82.00, 82.14, 127.00, 127.41, 127.73, 127.85, 128.05, 128.31, 128.37, 128.59, 129.51, 138.07, 138.49, 138.73, 199.50.

Haloetherification of the E-alkene



172: A= α-OMe
176: A=α/β -OTr

185a: THF(c/t=1/1)
185b: THF(c/t=2/1)

(2R, 3S, 4S)-2,3,4-O-tribenzyl-5,8epoxy-9-iodo -dodecane-1-al (185b)

Halocyclization was performed according to the general procedure. Thus , treatment of the trityl alkene **176** (30mg, 0.0395 mmol) with IDCP(37mg, 0.079 mmol) in 5 mL CH_2Cl_2 afforded cis-THF product **185b** (21.3mg, 83%) as colorless syrup after purification. TLC $\underline{R_f}$ =0.25(10% EtOAC/PE). trityl-E-alkene-THF(c/t=2/1)

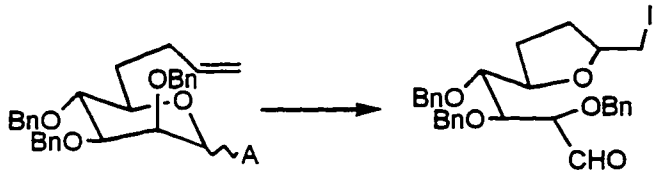
^{1}HNMR(C_6D_6): δ 0.81(m, 3H), 1.35-1.95(m, 8H), 3.55(mm, 1H), 3.82-4.45(m, 6H), 4.52-4.90(m,5H), 7.15(m, 15H), 9.98(s, 1/3H)., 10.02(s, 2/3H). ^{13}C NMR(C_6D_6): δ 13.07, 22.63(c), 22.71(t), 27.47(c), 29.12(t), 31.73(c), 33.05(t), 38.45(t), 38.59(c), 41.91(c), 43.60(t), 72.99, 73.87, 73.94, 74.05, 79.76, 79.86, 80.01, 80.32, 80.92, 81.19, 81.31, 82.09, 82.26, 126.97, 127.10, 127.39, 127.71, 127.87, 128.03, 128.18, 128.35, 138.3, 138.68, 138.88, 199.43(t), 199.47(c).

cis/trans THF 185a

An inseparable mixture of cis and trans (c/t=1/1) THF **185a** (27mg, 86%) was obtained after treatment of the methyl alkene **172** to the standard iodoetherification procedure. ^{1}HNMR(C_6D_6): δ 0.82(m, 3H), 1.35-1.95(m, 8H), 3.58(mm,1H)3.80-4.90(m, 11H), 7.15(m, 15H), 9.98(s, 1/2H), 10.02(s, 1/2H). ^{13}C NMR(C_6D_6): δ 13.07, 22.63(c),

22.71(t), 27.47(c), 29.12(t), 31.73(c), 33.05(t), 38.45(t), 38.59(c), 41.91(c), 43.60(t), 72.99, 73.87, 73.94, 74.05, 79.76, 79.86, 80.01, 80.32, 80.92, 81.19, 81.31, 82.09, 82.26, 126.97, 127.10, 127.39, 127.71, 127.87, 128.03, 128.18, 128.35, 138.3, 138.68, 138.88, 199.43(t), 199.47(c).

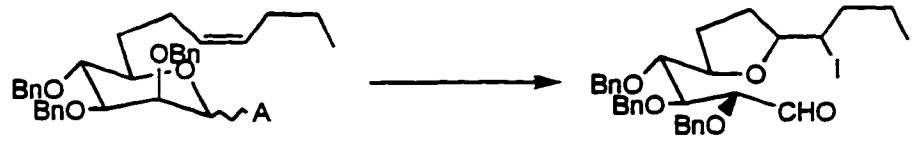
Iodoetherification of Mannopyranoside Alkenes



163: A=α/β-OTr 161b

(2S, 3S, 4S,)-2,3,4-O-tribenzyl-5,8epoxy-9-iodo-nonane-1-al(161b)

Halocyclization was performed according to the general. Thus , treatment of the trityl alkene **163** (50mg, 0.070 mmol) with IDCP(79.2mg, 0.168 mmol) in 10 mL CH_2Cl_2 afforded an unseparable mixture of 7/2 cis to trans THF product **161b** (25.1mg, 65%) as colorless syrup after purification. TLC $\underline{R}_f$ =0.25(10% EtOAC/PE). ^{1}HNMR(C_6D_6): δ 1.25-2.00(m, 4H), 2.90(m, 2H, -CH2I), 3.62-5.20(m, 11H), 7.25(m, 15H), 9.87(s, 1H). ^{13}C NMR(C_6D_6): 9.62, 10.62, 27.47, 28.45, 31.26, 72.38, 74.20, 74.32, 74.47, 78.19, 78.49, 79.65, 79.77, 80.18, 80.95, 81.07, 81.14, 81.26, 83.74, 127.18, 127.57, 127.74, 127.92, 127.96, 128.05, 128.26, 128.36, 128.63, 137.77, 138.40, 200.50, 200.533.



179: A=α/β– OTr

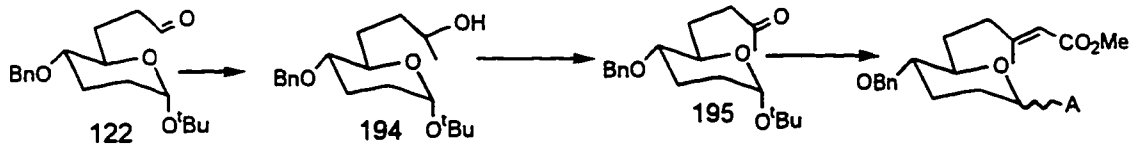
177b

(2S, 3S, 4S)-2,3,4-O-tribenzyl-5,8epoxy-9-iodo -dodecane-1-al (177b)

Halocyclization was performed according to the general procedure. Thus, treatment of the trityl alkene **215** (90mg, 0.118 mmol) with IDCP(111mg, 0.237 mmol) in 10 mL CH_2Cl_2 afforded an inseparable 2/3 cis to trans THF product **223** (48mg, 62%) as colorless syrup after purification. TLC $\underline{R_f}$ =0.25(10% EtOAC/PE).

^{1}HNMR(C_6D_6): δ 0.82(m, 3H), 1.20-2.0(m, 8H), 3.80-4.38(m, 7H), 4.52-4.80(m, 5H), 7.20(m, 15H), 9.77(bs, 3/5H)(H1 trans), 9.79(s, 2/3H)(H1 cis). ^{13}C NMR(C_6D_6): δ 13.31, 23.18, 23.27, 28.29, 29.29, 30.80, 31.89, 32.07, 38.85, 38.90, 42.86, 43.09, 72.72, 73.95, 74.52, 74.67, 79.70, 80.31, 81.07, 81.63, 81.69, 82.31, 84.13, 84.21, 126.8, 127.2, 127.5, 127.7, 127.8, 128.01, 128.2, 128.4, 128.5, 137.8, 138.10 , 200.69, 200.76.

II.4.16 Preparation of Trityl E-Allylic Alcohol **199**



196: A=α-OtBu
197: A=α/β-OH
198: A=α/β-OTr

t-Butyl-4-O-benzyl- 2,3-dideoxy- α-D-glucopyranoside methyl ketone (195)

A solution of the aldehyde **122** (4.4g, 0.013 mol) in THF (20 mL) was added dropwise to a 3.0M THF solution of MgBr (13 ml, 0.039 mmol). The reaction was stirred

for 1 h at that temperature, then warmed to rt. The reaction mixture was poured to saturated aqueous NH4Cl (50mL) and extracted with CH_2Cl_2(3X50 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash Chromatography to afford the alcohol mixture **194** (4.19g, 91%). TLC Rf=0.20(30% EtOAc/PE). ^{1}HNMR($CDCl_3$): δ 1.08(d, J=6.18Hz, 3H, H9), 1.17(s, 9H, -C$\underline{Me_3}$), 1.38-1.98(m, 8H, H_2, H_3, H_6, H_7), 2.18(bs, -OH), 3.05(m, 1H, H_4), 3.75(m, 2H, H_8, H_5), 4.37(d, J=11.47Hz, -$\underline{CH_2}$Ar), 4.57(d, J=11.37Hz, 1H, -$\underline{CH_2}$Ar), 4.98(br s, 1H, H1), 7.07-7.30 (m, 5H, -ArH). ^{13}C NMR($CDCl_3$): 23.77, 28.50, 28.94, 28.97, 31.09, 35.14, 35.21, 68.19, 68.46, 70.83, 71.31, 71.35, 74.29, 77.68, 90.60, 127.82, 128.03, 128.57, 138.2.

To a solution of compound **194** (2.2g, 6.25mmol) indry CH_2Cl_2 (110ml) was sequentially add PCC(6.73g, 31.2 mmol), Celite(6.73g), florisil(673mg) and sodium acetate(6.73g). The reaction mixture was stirred for 30 min at rt. under argon atmosphere, then diluted with Et_2O(200ml) and filtered through florisil. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography to afford methyl ketone (1.9g, 87%). TLC: Rf=0.3 (30% EtOAc/PE), ^{1}H-NMR(C_6D_6) δ 1.61(m, 2H, H_3), 1.97(t, 2H, J=6.98Hz, H_2), 3.11(t, 2H, J=6.07Hz, H_4), 4.20(s, 2H, -O$\underline{CH_2}$Ar), 7.19(m, 5H, ArH) ^{13}C-NMR(C_6D_6) δ 22.791, 40.828, 69.210, 72.874, 127.68, 128.00, 128.32.

t-Butyl-4-O-benzyl-2,3-dideoxy-α-D-glucopyranoside Methyl Ester (196)

To a suspension of sodium hydrid (0 mg of ~60% emulsion in mineral oil) in dry THF (40 mL) was added ditheyl(ethoxycarbonyl)methyl-phosphonate(2.70mL, 13.66

mmol). After the mixture was stirred for 30 min at 0^0C, a solution of methyl ketone **195** (1.20g, 0 mmol) in anhydrous THF(20 mL) was added. The solution was stirred at rt. for 20h, then diluted with water (50 mL) and extracted with CH_2Cl_2(3X50 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatographicaliy to afford E- methyl ester **196** (942mg, 70%,). TLC: Rf=0.35(10% EtOAc/PE) ^{1}HNMR($CDCl_3$): δ 1.14(s, 9H, -C$\underline{Me_3}$), 1.16(m, 3H, -CO$CH_2\underline{CH_3}$), 1.21-2.22(m, 8H, H_2, H_3, H_6, H_7), 2.07(s, 3H, -$\underline{CH_3}$), 3.02(m, 1H, H_4), 3.77(dt, J=2.32, 9.17 Hz, 1H, H_5), 4.05(q, J=7.07Hz, 2H, -CO$\underline{CH_2}CH_3$), 4.35(d, J=11.52Hz, 1H, -$\underline{CH_2}$Ar), 4.57(d, J=11.56Hz, 1H, -$\underline{CH_2}$Ar), 4.96(br s, 1H, H_1), 5.59(s, 1H, H_9), 7.15 (m, 5H, -ArH). ^{13}C NMR($CDCl_3$): 14.44, 18.99, 23.67, 28.86, 30.46, 30.97, 37.03, 59.56, 70.65, 70.82, 74.67, 77.57, 90.45, 115.44, 127.73, 127.89, 128.35, 128.47, 138.57, 160.43.

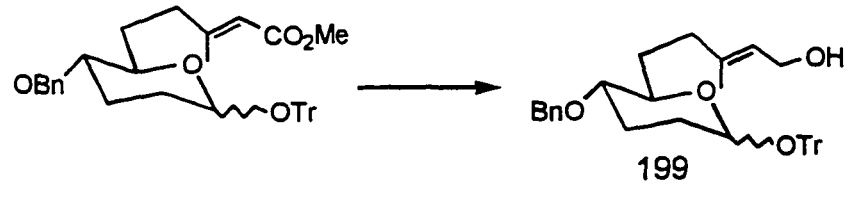
Trity-4-O-benzyl l-2,3-dideoxy -α/β-D-glucopyranoside E-methyl ester (198)

A solution of the compound **196** (550mg, 1.39mmol) in 2ml 0.5N JCL and THF (20ml) was stirred for 10 h at rt. The mixture was then neutralized by saturated Na_2CO_3 , extracted with Et_2O(3X20 mL). The organic phase was dried (Na_2SO_4), filtered and the filtrate and evaporated in vacuo. A inseparable 1:1 mixture of α/β anomers **229** (379mg, 86%) was obtained as a colorless syrup after purification. TLC Rf=0.20(20% EtOAc/PE); ^{1}HNMR($CDCl_3$): δ 1.18(t, J=8.66Hz, 3H, -CO$CH_2\underline{CH_3}$), 1.38-2.25(m, 8H, H_2, H_3, H_6, H_7), 2.07(s, 3H, -$\underline{CH_3}$), 3.05(m, 1H, H_{4a}, $H_{4\beta}$), 3.25(dt, J=2.40, 9.12 Hz, 1/2H, $H_{5\beta}$), 3.75(dt, J=2.54, 9.08Hz, 1/2H, $H_{5\alpha}$), 4.07(q, J=7.08Hz, 2H, -CO$\underline{CH_2}CH_3$), 4.39, 4.59(

both m, 1H each , -$\underline{CH_2}$Ar), 4.75(d, J=7.02Hz, 1/2H, $H_{1\beta}$), 4.96(br s, 1/2H, $H_{1\alpha}$), 5.60(s, 1H, H_9), 7.20 (m, 5H, -ArH). ^{13}C NMR($CDCl_3$): 14.54, 19.01, 19.07, 23.42, 27.66, 29.77, 29.89, 29.44, 31.93, 36.75, 59.73, 76.12, 76.84, 77.01, 77.26, 77.69, 77.89, 90.91, 96.1, 122.64, 122.34, 127.68, 127.75, 128.21, 128.32, 138.36, 160.06.

The pyranoside mixture **197** (395mg, 1.25 mmol) was tritylated according to the general procedure (II.4.8) using Ph_3Cl (692mg, 2.5 mmol), AgOTf (587mg, 2.25mmol) and collidine (0.19mL, 2.5mmol). An inseparable 1:1 mixture of α/β trityl alkene (686mg, 93%) was obtained after purification. TLC R_f=0.70(10% EtOAc/PE). ^{1}HNMR($CDCl_3$): δ 1.22(m, 3H, -$COCH_2\underline{CH_3}$), 1.65(m, 6H, H_2, H_3, $H_{6,}$), 2.02(m, 2H, H_7), 2.08(s, 3H, -$\underline{CH_3}$), 3.05(m, 1H), 4.05(m, 2H, -$CO\underline{CH_2}CH_3$), 4.35-4.62(m, 3H), 5.05(bs, 1H), 5.55(s, 1H, H_9), 7.25 (m, 20H, -ArH). ^{13}C NMR($CDCl_3$): 14.01, 18.65, 18.59, 21.18, 23.74, 27.57, 29.80, 30.00, 30.61, 35.86, 36.04, 59.11, 70.52, 70.63, 75.92, 76.36, 76.97, 87.8, 91.76, 97.02, 114.72, 114.78, 125.03, 126.95, 127.73, 127.93, 127.95, 144.40, 144.60, 146.65, 160.07, 166.72.

Trityl-4-O-benzyl -2,3-dideoxy -α/β-D-glucopyranoside E-Allylic Alcohol (199)

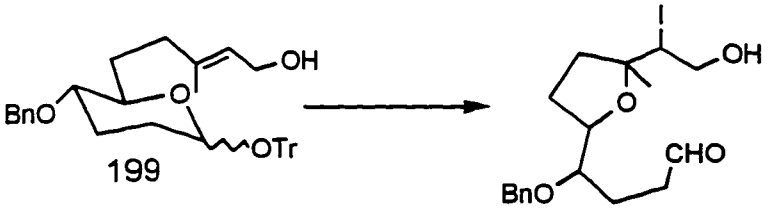


199

To a solution of the ester **198** (370mg, 0.63mmol) in anhydrous CH_2Cl_2(30ml) was slowly added DIBALH (1M in heptane, 1.88ml, 1.88mmol) at ~-42^{0}C. After stirring for 1.5h at that temperature, MeOH(5ml) was added to the solution and the mixture was warmed to

rt. Potassium sodium tartrate (20ml) was added, the mixture was stirred at rt for an additional 1h, then extracted with CH_2Cl_2(20ml, 3X). The organic phase was washed with saturated $NaHCO_3$(15ml), brine(15ml), dried (Na_2SO_4), filtered and *concentrated in Vacuo*. The residue was purified by flash chromatography to afford the E allylic alcohol **199** (313mg, 91%). TLC R_f=0.20 (30% EtOAC/PE,) ^{1}HNMR($CDCl_3$): δ 1.06-2.10(m, 8H, H_2, H_3, H_6, H_7), 2.08(s, 3H, -$\underline{CH_3}$), 2.73(dt, J=2.0, 9.04 Hz, 1/2H, $H_{4\beta}$), 2.95(m, 1H, $H_{4\alpha}$, $H_{5\beta}$), 3.72(t, J=9.12Hz, 1/2H, $H_{5\alpha}$), 4.02(d, J=6.92 Hz, -$\underline{CH_2}$OH), 4.40(m, 5/2H , -$\underline{CH_2}$Ar, $H_{1\beta}$), 5.01(br s, 1/2H, $H_{1\alpha}$), 5.20(m, 1H, H_9), 7.20 (m, 5H, -ArH). ^{13}C NMR($CDCl_3$): δ 16.49, 16.53, 24.19, 28.10, 30.39, 30.64, 31.10, 34.94, 35.14, 59.59, 71.06, 71.16, 72.40, 76.63, 77.64, 77.72, 78.17, 87.8, 92.27, 97.54, 127.18, 127.21, 127.70, 129.17, 140.2, 140.4, 144.88, 145.07.

II.4.17 Iodoetherification of E Allylic Alcohol 199



A solution of E allylic alcohol **199** (80mg, 0.146mmol) in CH_3CN (10mL) was subjected to the standard iodoetherification procedure (II.4.9)using IDCP(171mg, 0.365mmol) at rt for 5 min. THF mixture **200** (33.6mg, 55%) was obtained after purification. TLC R_f=0.20 (30% EtOAc/PE), ^{1}HNMR($CDCl_3$): δ 1.02-2.05(m, 8H, H_2, H_3, H_6, H_7), 2.08(s, 3H, -$\underline{CH_3}$), 3.40(m, 7H), 7.22(m, 7H), 9.64(s, 1H) ^{13}C NMR($CDCl_3$):

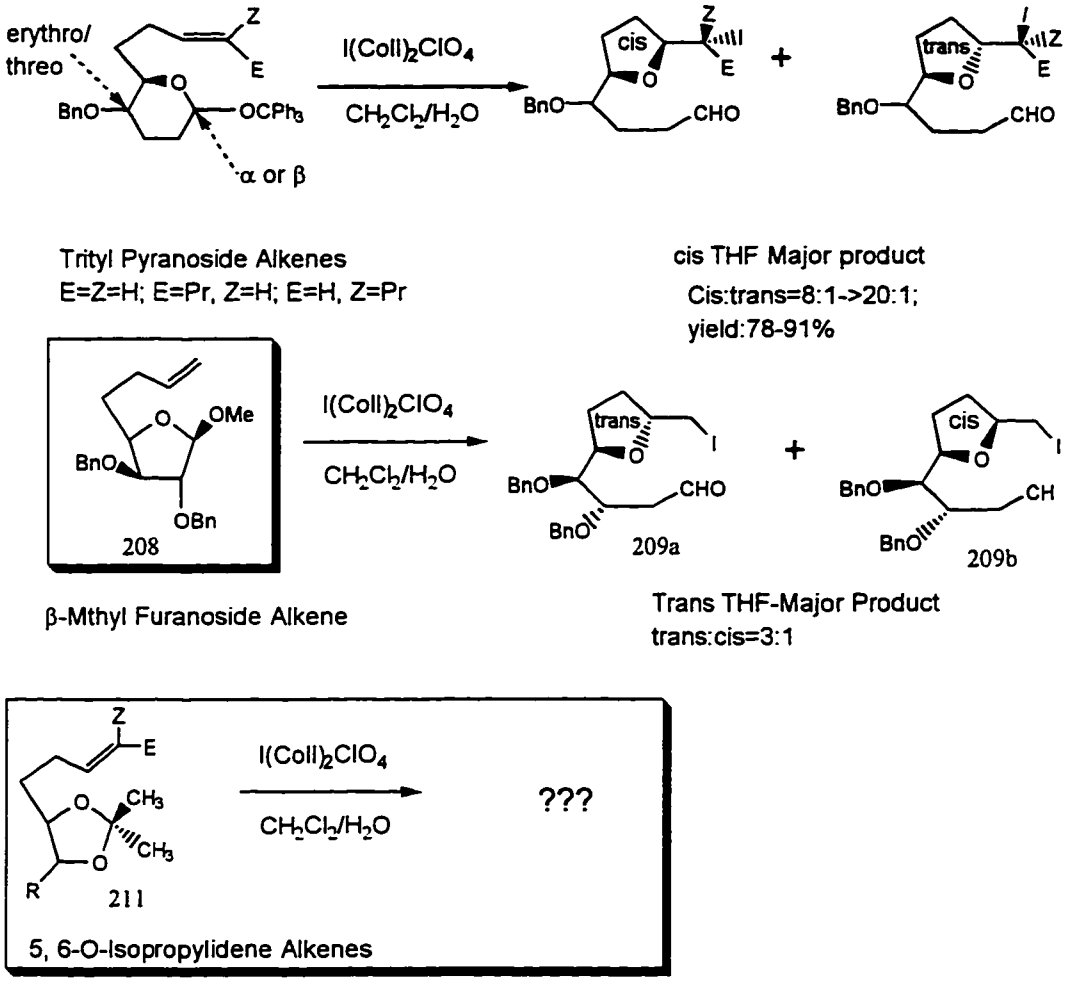
δ 21.31, 23.47, 23.71, 23.96, 26.19, 27.65, 30.65, 39.31, 39.80, 43.63, 66.15, 72.67, 79.23, 81.87, 85.74, 126.84, 127.34, 128.74, 127.69, 128.24, 138.4, 201.69, 201.73.

Part III

Preparation of *trans*-2,5-Disubstituted THF's

III.1 Acetal Templates for the Synthesis of *trans*-2,5-Disubstituted THF's

Scheme 41:



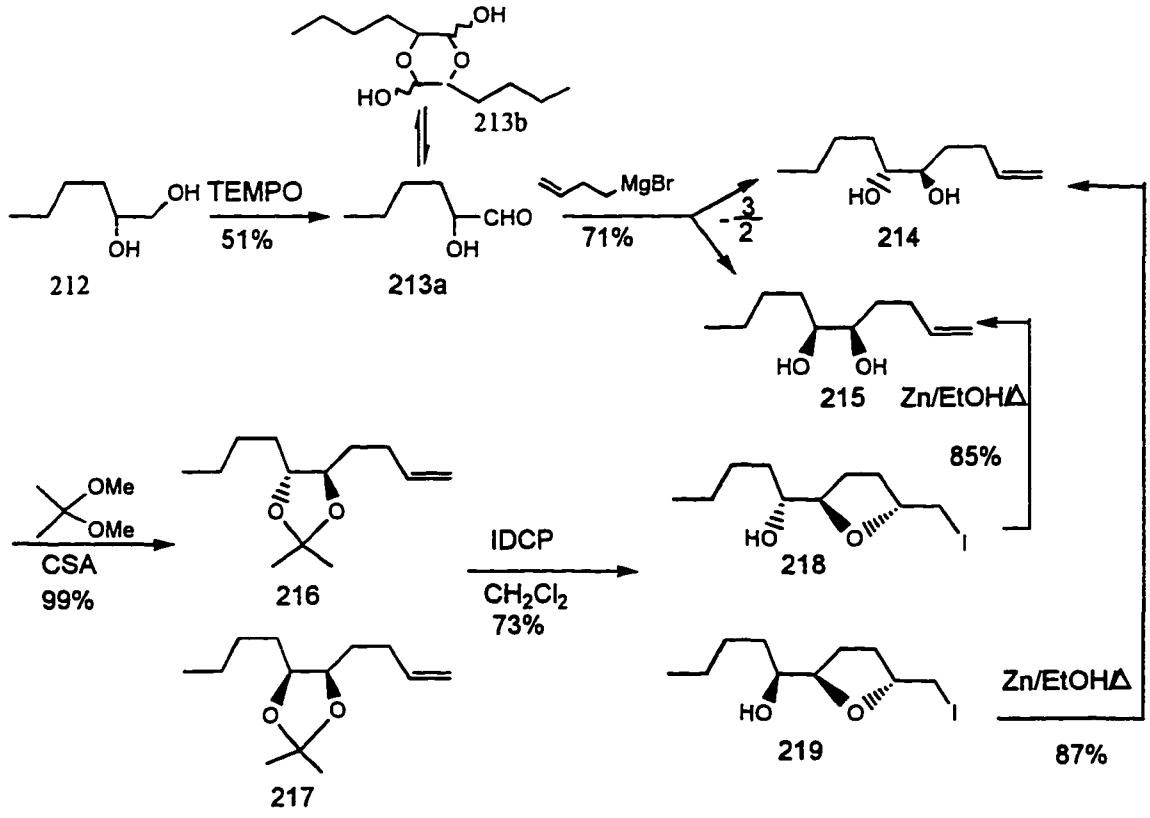
Preparation of *trans*-2,5 disubstituted THF's, also a common subunit in the THF-containing natural products, was next explored. The iodocyclization of substrate in which the 5,6 diol residue was embedded into a pyranoside ring, favored a 2,5-disubstituted *cis*-THF product (Scheme 40). The principle behind this work was the idea that

conformationally restricted acetal alkenes could be used as templates for the stereoselective halocyclizations Interestingly, the furanosides alkene precursor **208** showed a modest preference for the *trans*-2,5 disubstituted THF. Based on this result, we speculated that isopropylidene derivatives of 5,6-dihydroxyalkenes of the type **211** should be *trans* selective, because of its structural similarity to the β-furanoside framework **208** .

Preparation of the Isopropylidene Alkenes

In order to test this hypothesis, terminal, Z and E -alkene derivatives of the erythro and threo1,2- diols were prepared. A divergent strategy centered on the initial preparation of the terminal alkene systems was devised (Scheme 41).

Scheme 41:



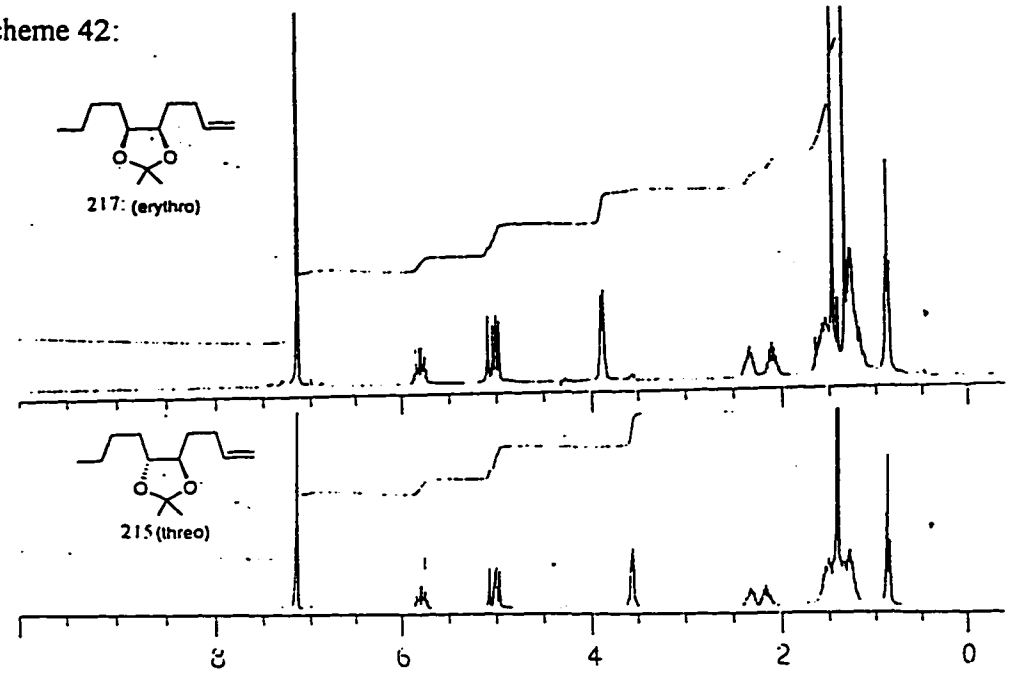
Selective oxidization of the primarily hydroxyl group[58] of commercially available 1,2-hexanediol afforded 2-hydroxyl aldehyde **212** in 55% yield as that drawn as **213b**. Treatment of **213** with 4-butenylmagnesium bromide led to an inseparable 3:2 mixture of diols **214:215**. Acetonation of the diol alkene with 2,3-dimethoxy propane resulted in a mixture of isopropylidenes **216** and **217**, which were also inseparable. The iodocyclization reaction of this mixture was used for its eventual separation. Treatment of the mixture with iodonium dicollidine perchlorate (IDCP) in wet dichloromethane (CH_2Cl_2) led to two single THF's products **218** and **219**, which were chromatographically separable. These THF's were determined to be the *trans* isomers as will be discussed in detail later. Zinc - mediated reductive elimination of each THF **218** and **219** gave the respective diol **214** and **215** which were converted to separate isopropylidenes **216** and **217** .

The relative configurations of the diol residue in **216** and **217** were assigned based on the ^1H NMR signals for the two acetonide methyl groups (Scheme 42) [59-60]. The acetonide methyls in related to threo derivatives shown a single peak in ^1H NMR attributed to the pseudo C_2 symmetrical structures. The methyl signal in corresponding erythro compounds are known to appear as separated signals.

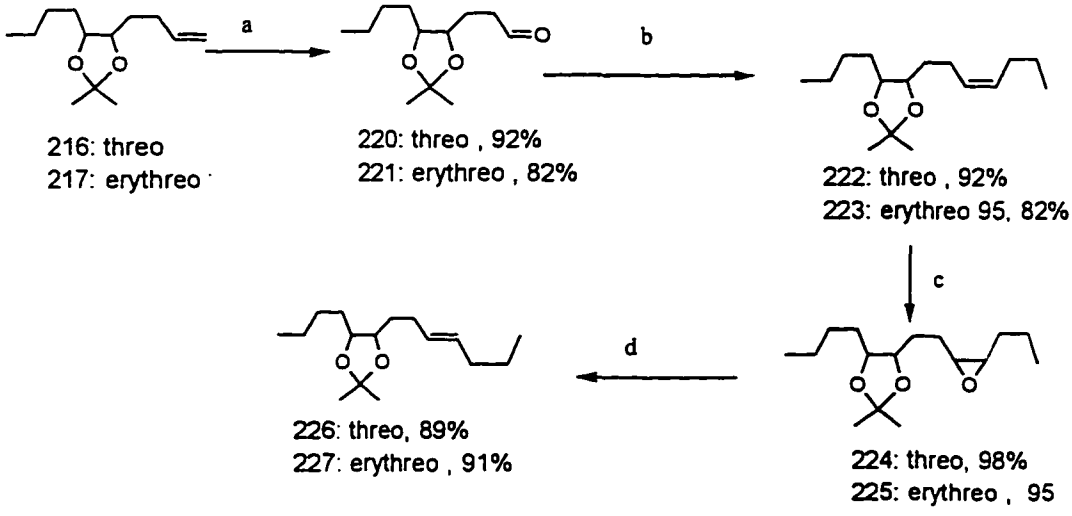
The isopropylidene Z and E alkenes were next prepared (Scheme 43). The Z derivatives were prepared as described earlier by the Wittig olefination of butylidene triphenylphosphone and on the aldehydes **220** and **221** respectively. The E substrates were also obtained as shown before by application of the Vedejs alkene isomerization procedure on the corresponding Z compounds. Thus, threo-Z-alkene **222** and erythro

223 were obtained respectively form the terminal alkene **216** and **217** in 83% and in 77% and greater than 95% stereoselectivity. Erythro and threo-E-alkene **226** and **227** were obtained form from their Z isomers **222** and **223** in 87% and 86% yield respectively.

Scheme 42:



Scheme 43:

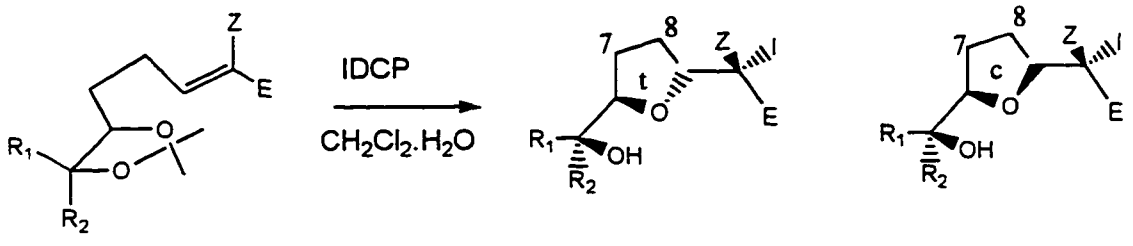


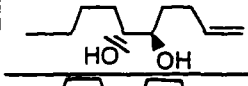
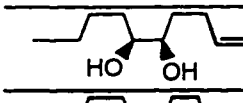
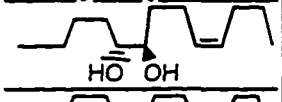
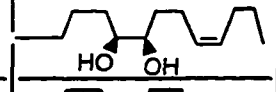
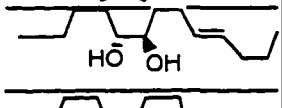
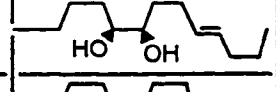
[a] Reagents and conditions: (a) O3, CH_2Cl_2/MeOH, -78°C; then $(CH_3)_2S$, -78°C-rt., 1h; (b) 5 equiv. of $CH_3CH_2CH_2CH_2P^+Ph_3Br^-$, 5 equiv. of $NaN(SiMe_3)_3$, toluene, -78°C; (c) 2.5 equiv. of MCPBA, CH_2Cl_2, Na_2HPO_4/NaH_2PO_4, rt., 1.5h; (d) 3 equiv. of Ph_2PH, 3 equiv. of n-BuLi, dry THF, rt., 2h, then MeI, 1h.

Cyclization studies

Treatment of the isopropylidene terminal, *Z* and E alkene under the standard cyclization procedure afforded in all cases a single *trans* THF in greater than 88% yield. For comparison, the stereoselectivity of the dihydroxyl alkene derivatives were carried out. These results gave approximately equal portion of *cis* and *trans* THF's (Table 11).

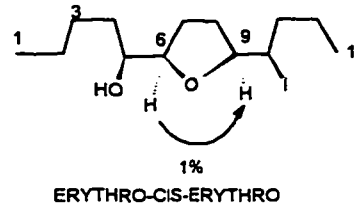
Table 11: Threo and Erythro Isopropylidine Precursors Vs THF's



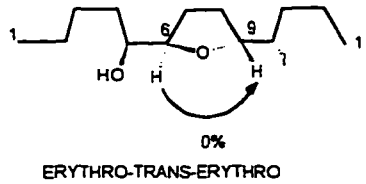
ALKENE PRECURSOR	THF PRODUCTS cis/trans	yield	ALKENE PRECURSOR	cis/trans	yield
	1/1	90%		1/1	92%
	**trans Only**	88%		**trans only**	93%
	3/4	87%		2/5	91%
	**trans only**	91%		**trans only**	95%
	1/1	90%		1/1	89%
	**trans only**	92%		**trans only**	91%

As described earlier, stereochemistry of the THF's products were assigned by the comparison of ^{13}C NMR resonance for the methylene carbons of the THF's ring (Table 12). In the case of the *cis* THF product from the iodocyclization of the dihydroxy erythro-E-alkene, the assignment were confirmed by a strong noe effect between H_6 and H_9, but such interaction was not observed for the *trans* isomer (Scheme 44).

Scheme 44:

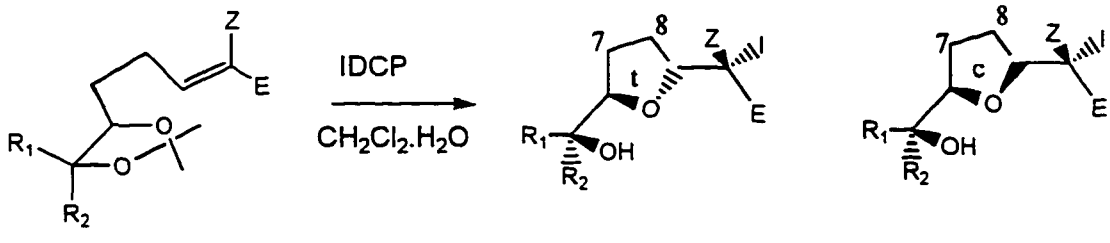


ERYTHRO-CIS-ERYTHRO



ERYTHRO-TRANS-ERYTHRO

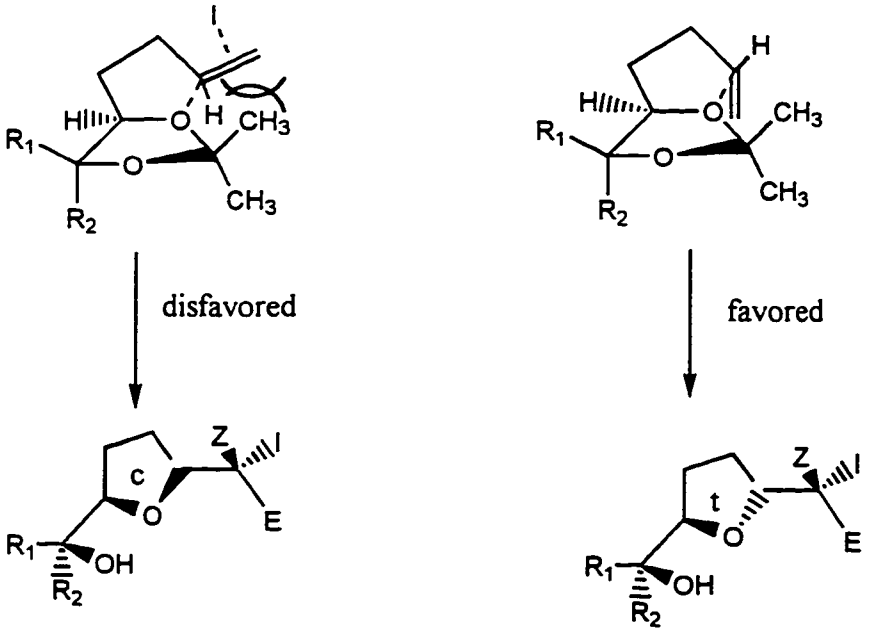
Table 12: ^{13}C NMR Data of the C_7 and C_8 in the THF Products



		terminal Z=E=H		Z-alkene, Z=Pr, E=H		E-alkene, Z=H, E=Pr	
		cis	trans	cis	trans	cis	trans
threo R_1=H, R_2=Pr	C7	27.8	28.54	27.34	27.91	27.08	28.0
	C8	32.0	32.2	31.31	31.35	31.46	33.31
erythro R_1=Pr, R_2=H	C7	28.45	28.48	28.14	28.14	28.45	28.45
	C8	31.69	32.76	29.83	31.5	31.59	32.89

The high stereoselectivity which was observed in the reactions of these isopropylidene systems resulted from the *cis* fused (5,5,0) oxahydrindan type geometry of the THF-oxonium ion intermediate. The *trans* products would be favored because of steric crowding (due to interactions between the C5 iodoalkyl substitutent of the eventual THF and the methyl group of the acetonide) in the concave region of the transition state for the *cis* isomer. The higher selectivity observed for these isopropylidene systems compared to the methyl-β-furanoside **208** might be the consequence of the larger A value of the CH_3 group compared to OCH_3 (Scheme 45).

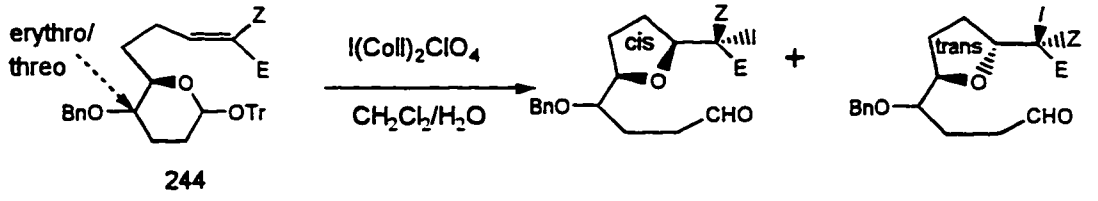
Scheme 45:



In conclusion, an efficient and versatile methodology of preparing 2,5-disubstituted THF's has been achieved. Compared to other methodologies , this approach stands out because of the easy availability of D and L isopropylidene alkene derivatives of these types, the high stereoselectivity in substrates containing all possible combinations of the substitutions patterns with respect to the configuration of the vicinal diols and alkenes, and the inherent advantage in terms of alcohol protecting group chemistry, combine to make this a highly practical and versatile methodology for the preparation of the *trans* 2,5-disubstituted THF's.

III.2 1,3-Dioxane Templates for the Synthesis of 2,5-Disubstituted THF's

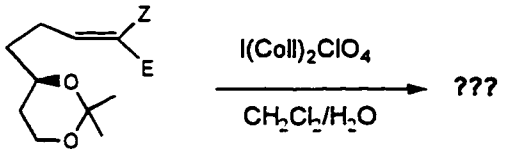
Scheme 46:



244

Trityl Pyranoside Alkenes
E=Z=H; E=Pr, Z=H; E=H, Z=Pr

cis THF Major product
Cis:trans=8:1->20:1;
yield:78-91%



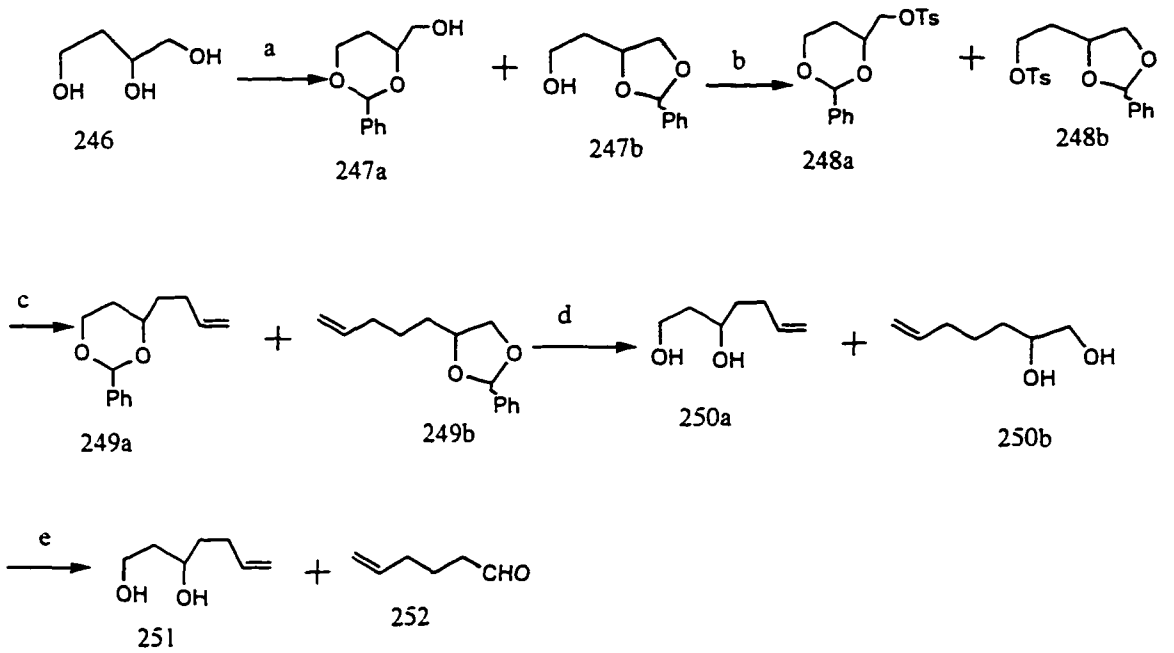
245

1,3-dioxane templates of the type **260** are similar in geometry to the pyranoside substrate **244** used for the preparation of 2,5 disubstituted THF's (Scheme 46) . Hence followed the idea behind the 1,2-O-isopropylidene project, it would be interested to compare stereoselectivity of the iodocyclization of 1,3 dioxane and pyranoside substrates.

Synthesis of 1,3 Dioxane Substrates: Treatment of the commercial available triol **246** with benzyl aldehyde in N, N,-dimethylformamide (DMF) catalyzed by p-toluenesulfonic acid afforded an inseparable 2/1 mixture of 1,3-dioxane **247a** and the α/β 1,3-dioxolanes **247b** in 80% yield[61]. The mixture was tosylated to afford an inseparable mixture of primary tosylates in 76% yield, which was subsequently converted to the

which was subsequently converted to the corresponding alkene derivatives **249a** and **249b** by the addition of the vinyl magnesium bromide in the presence of TMEDA. Hydrolysis of the alkene mixture, and sodium periodate oxidation of the mixture of diols **250a** and **250b** gave the desired 1,3 dioxane precursor **251** and the volatile aldehyde **252** (Scheme 47).

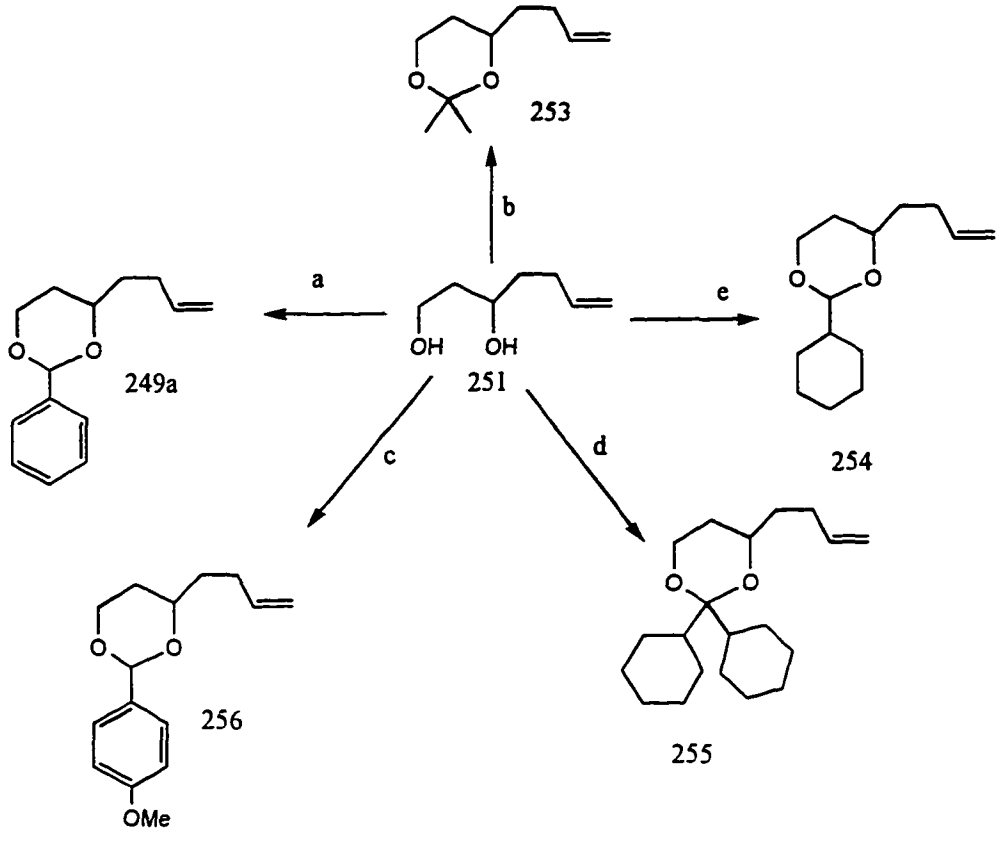
Scheme 47:



[a]Reagents and conditions: (a) 3 equiv. benzaldehyde, 0.01 equiv. p-TsOH, DMF, 80%;(b) 1.2 equiv. TsCl, pyridine, 65%; (c) 2.5 equiv. of allylmagnesium bromide, TMEDA, Et_2O, AR, 1h, 78%; (d) 0.1 N HCl/ THF , 91%; (e) 1.2 equiv. $NaIO_4$, THF/H_2O(v/v= 2/1).

Acetal derivatives **253-256** were prepared by treatment of 1,3 diol **251** with the corresponding aldehyde, ketone or dimethyl acetal in the presence of catalytic camphore sulfonic acid in DMF solution (Scheme 48).

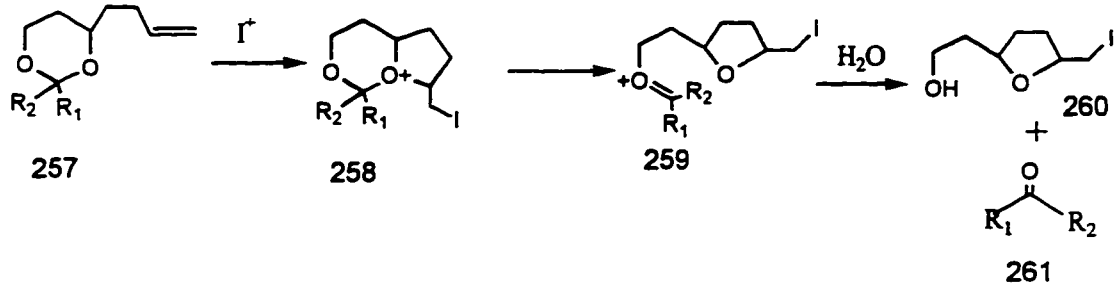
Scheme 48:



[a] Reagents and conditions: (a) 3 equiv. benzyl aldehyde, 0.01 equiv. p-TsOH, DMF, 80%;(b) 2 equiv. 2,3-dimethoxypropane, 0.075 equiv. CAS, CH_2Cl_2; 92%; (c) 3 equiv. p-methoxylbenzyl aldehyde, 0.01 equiv. p-TsOH, DMF, 85%; (d) 3 equiv. biscyclohexyl aldehyde, 0.01 equiv. p-TsOH, DMF, 75%; (e) 3 equiv. cyclohexyl aldehyde, 0.01 equiv. p-TsOH, DMF, 84%.

Substrates **253** (R_1=R_2=CH_3), **254** (R_1=H, R_2=cyclohexyl) and **255** (R_1=R_2= cyclohexyl) were designed to test steric and conformational effects. Benzylidene acetal **249a** (R_1=H, R_2=Benzyl) and **256** (R_1=H, R_2=p-methoxylbenzyl) were included to test electronic effect since fragmentation of the benzylidene THF-oxoium to the oxocarbenium ion was expected to be faster compared with **252-256**. This should lead to a preference for the THF corresponding to the first formed THF oxonium ion (Scheme 49).

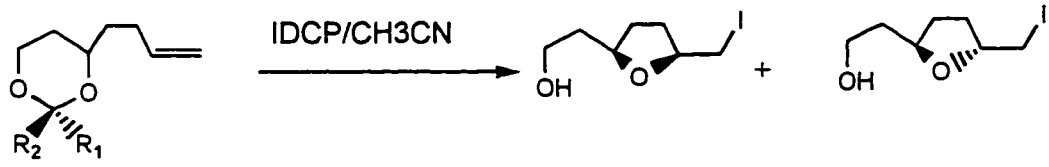
Scheme 49:



Cyclization: Cyclization studies were carried out under the standard conditions with IDCP in wet CH_3CN. Although the yields were high, stereoselectivity was poor (c/t~3/2) and independent of the structures of acetal (Table 13).

The low stereoselectivity of the 1,3 dioxane compared to the trityl pyranoside templates suggest that more subtle factors involving the conformation of the six membered oxacycles might have to be considered.

Table 13: Iodocyclization of 1,3-Dioxane Acetals

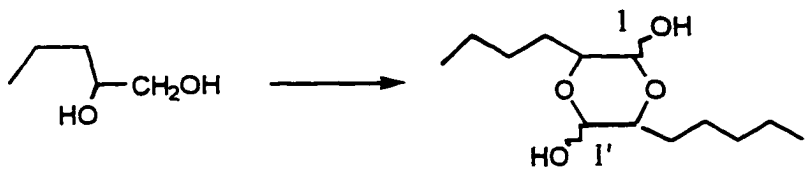


Entry	Alkenes	THF	c/t	yield
1	249a: R_1=H, R_2=Ph	262	~3/2	85%
2	253: R_1=R_2=CH_3	262	~3/2	89%
3	256: R_1=H, R_2=-(p-OMe-)C_6H_5	262	~3/2	88%
4	254: R_1=H, R_2=cyclohexyl	262	~3/2	78%
5	255: R_1=R_2=cyclohexyl	262	~3/2	75%

III.3 Experimental

III.3.1 General (II.4.1)

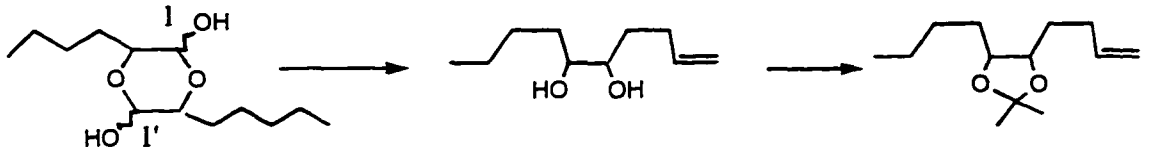
III. 3.2 TEMPO Reaction of Primary Alcohol 212



212 213b

A round bottom flask was charged with a solution of the 1,2-hexanediol **212** (5g, 42.3mmol) in CH_2Cl_2 (112 mL), TEMPO(66mg, 0.42 mmol), saturated aqueous solution $NaHCO_3$ (70.5 mL), potassium bromide(503 mg, 4.23 mol) and tetrabutylammonium chloride(625mg, 4.23mol). To this cooled (0^0C) and well stirred mixture was added dropwise over 45 min. a solution of sodium hypochlorite(> 4%, 93 mL, 55mmol), saturated sodium bicarbonate (42.3 ml) and brine (84.6 mL).. The mixture was stirred for 1 h at 0^0C, then 20 min. at 20 ^0C and the phases was separated. The aqueous phase was extracted with CH_2Cl_2(3X80 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution (30mL), brine(30 Ml), dried(Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography of the residue gave the desired aldehyde as a dimmer **213b** (2.5g, 51%). TLC Rf=0.25 (50% EtOAc/PE). ^{1}H-NMR(C_6D_6) δ 0.95(m, 6H, H_6, $H_{6'}$), 1.02-1.95(m, 12H, H_3, H_4, H_5, $H_{3'}$, $H_{4'}$, H_5), 3.50-4.08(m, 2H, H_2, $H_{2'}$), 5.22(m, 2H, H_1, $H_{1'}$); ^{13}C-NMR(C_6D_6) δ 14.105, 22.859, 27.229, 31.41, 74.51, 105.13, MS: m/e 117 $(M+H)^+$ for $C_6H_{12}O_2$. Anal clacd. for $C_6H_{12}O_2$: C: 62.04, H: 10.41, found: C: 62.08, 10.46.

III.3.3 Grignard Reaction of Aldehyde 213b



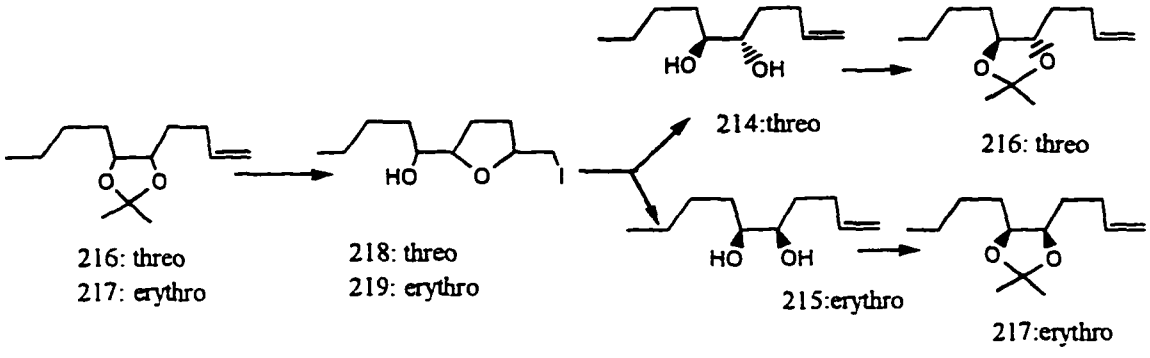
213b

214: threo
215: erythro

216: threo
217: erythro

4-bromo-1-butene(14.98g, 0.111 mol) in 40 ml anhydrous THF was added in 30 min. dropwise to a round bottom flask charged with activated Mg (5.4g, 0.222mol) in 20mL anhydrous THF. The mixture was then stirring for 2 hour to ensure the completion of the reaction. After cooled to -78^{0}C, a solution of the aldehyde **213b** (6g, 0.037 mol) in 20 mL THF was added dropwise to it. The reaction was allowed to stir for 1.5 h, then warmed up to rt. 50mL saturated NH_4Cl was added to it and the reaction mixture was extracted with CH_2Cl_2(3X50 mL). The combined organic phase was dried (anhydrous Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography to afford an inseparable mixture of threo:erythro(3:2) diol alkenes **214** and **215** (6.3g, 71%). TLC Rf=0.20 (30% EtOAc/PE). ^{1}H-NMR(C_6D_6) δ 0.92(m, 3H, H_9), 1.05-1.62(m, 6H, H_4, H_7, H_8), 2.20(m, 2H, H_3), 3.40(m, 2H, H_5, H_6), 5.00(m, 2H, H_1), 5.83(m, 1H, H_2). ^{13}C-NMR(C_6D_6) δ 14.24, 14.57, 23.07, 23.42, 28.51, 28.57, 30.60, 30.69, 30.72, 31.46, 33.53, 33.98, 74.27, 74.38, 74.90, 74.98, 114.99, 115.17, 138.78, 139.16. MS: m/e 190 $(M+NH_4)^+$ for $C_{10}H_{20}O_2$.

III.3.4 Preparation Dihydroxy- and Isopropylidene Terminal Alkenes 216-217



Camphorsulfonic acid (0.25g) was added to a solution of a mixture of threo:erythro(3:2) dihydroxyalkenes **214** and **215** (2.45g, 14.2mmol) and 2,3-dimethoxy-propane (3.52ml, 28.4mmol) in anhydrous CH_2Cl_2(30ml). The reaction mixture was stirred at rt. for 15 min., neutralized by addition of a 1M NaOMe/ MeOH, and concentrated *in vacuo*. The residue was purified by flash chromatography to afford an inseparable mixture of threo:erythro(3:2) isopropylidene alkenes **216** and **217** (3.01g, 99%). TLC Rf= 0.75(10% EtOAc/PE). ^{1}H-NMR(C_6D_6) δ 0.90(m, 3H, H_1), 1.40(S, 6H, -C<u>Me$_2$</u>). 1.45(m, 8H, H_2, H_3, H_4, H_7,), 2.20(mm, 2H, H_8), 3.49(m, 3/5H, H_5, H_6), 3.95(q, J=7.17 Hz, 2/3H, H_5, H_6), 5.02(m, 2H, H_{10}), 5.80(m, 1H, H_9). ^{13}C-NMR(C_6D_6) δ 14.52, 23.44, 27.94, 28.01, 29.14, 31.16, 32.91, 33.26, 77.68, 78.34, 80.96, 81.54, 108.27, 115.22, 138.79. MS: m/e 213 $(M+H)^+$ for $C_{13}H_{24}O_2$.

IDCP (6.42g, 16.7mmol) was added to a mixture(2:3) of **216** and **217** (2.90g, 13.7mmol), CH_2Cl_2(50mL) and H_2O(1 mL). The reaction mixture was stirred at rt. for 45 min., then poured into a 10% aqueous solution of $Na_2S_2O_3$, and extracted with ether. The

combined organic phase was dried(Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography of the residue gave threo-*trans* THF **218** (1.95g, 48%). Rf=0.35(10% acetone/PE) and erythro-*trans* **219** (1.0g, 25%). Rf=0.25(10% acetone/PE).

A mixture of threo-*trans* THF **218** (1.80g, 6.08mmol), freshly activated Zn dust (1.80g, 27.5 mmol) and 95% EtOH(20mL) was heated at reflux for 30 min. The reaction mixture was cooled to rt. and filtered through a pad of celite and the filtrate concentrated *in vacuo*. Flash chromatography of the residue afforded threo dihydroxyalkene **214** (0.91g, 87%). TLC Rf=0.10(10% Aceton/PE) ^{1}H-NMR(C_6D_6) δ 0.91(t, J=7.0 Hz, 3H, H_1), 1.4(m, 8H, H_2, H_3, H_4, H_7,), 2.20(m, 2H, H_8), 2.90(d, J=8.3Hz, 2H, -OH), 3.29(bs, 2H, H_5, H_6), 5.02(m, 2H, H_{10}), 5.83(m, 1H, H_9). ^{13}C-NMR(C_6D_6) δ 14.58, 23.42, 28.57, 30.70, 33.54, 33.98, 74.38, 74.98, 115.17, 139.16. MS: m/e 190 $(M+NH_4)^+$ for $C_{10}H_{20}O_2$.

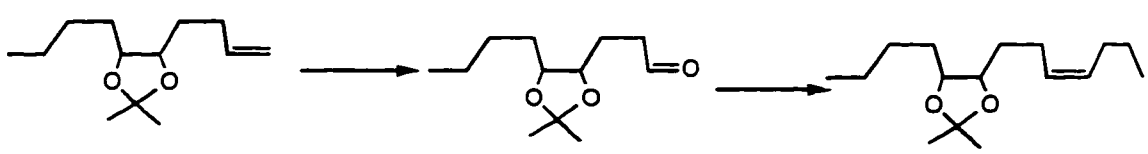
Treatment of the sample of the erythro-trans THF **219** (0.900g, 3.04mmol) under the similar conditions gave the erythro dihydroxyalkene **215** (445.3mg, 83%).TLC R_f=0.10 (10% Aceton/PE); ^{1}H-NMR(C_6D_6) δ 0.87(t, J=7.0 Hz, 3H, H_1), 1.010-1.48(m, 8H, H_2, H_3, H_4, H_7,), 2.03(m,1H, H_8), 2.23(m,1H, H_8), 3.28(m, 2H, H_5, H_6), 5.02(m, 2H, H_{10}), 5.78(m, 1H, H_9). ^{13}C-NMR(C_6D_6) δ 14.25, 23.08, 28.52, 30.06, 30.72, 31.47, 74.27, 74.91, 115.00, 138.79. MS: m/e 190 $(M+NH_4)^+$ for $C_{10}H_{20}O_2$.

Treatment of the individual dihydroxyalkene threo **214** and erythro **215** under the conditions which were used for acetonation of the original mixture of **214** and **215**, gave separated sample of threo and erythro isopropylidene **216** and **217** respectively.

For **216** (threo-terminal alkene): (1.25g, 93%): TLC R_f=0.75 (10% Aceton/PE), ^{1}H-NMR(C_6D_6) δ 0.86(t, J=7.1 Hz, 3H, H_1), 1.19-1.58(m, 8H, H_2, H_3, H_4, H_7,), 1.40(s, 6H, ($\underline{CH_3}$)$_2$C-), 2.20(m,2H, H_8), 3.56(d, J=3.5 Hz, 2H, H_5, H_6), 4.99(m, 2H, H_{10}), 5.76(m, 1H, H_9). ^{13}C-NMR(C_6D_6) δ 14.49, 23.44, 27.98, 29.12, 31.13, 32.29, 80.98, 81.56, 108.29($Me_2\underline{C}$) 115.21, 138.81. MS: m/e 213 $(M+H)^+$ for $C_{13}H_{24}O_2$.

For **217** (erythreo-terminal): (600mg, 88%). TLC R_f=0.75(10% Aceton/PE), ^{1}H-NMR(C_6D_6) δ 0.87(t, J=6.5 Hz, 3H, H_1), 1.10-1.48(m, 8H, H_2, H_3, H_4, H_7,), 1.33, 1.46(both s, 3H each, ($\underline{CH_3}$)$_2$C-), 2.07, 2.34(both m,1H ea., H_8), 3.90(d, J=7.8 Hz, 2H, H_5, H_6), 5.02(m, 2H, H_{10}), 5.81(m, 1H, H_9). ^{13}C-NMR(C_6D_6) δ 13.93, 22.73, 25.81, 28.60, 28.66, 29.41, 29.56, 30.56, 77.08, 77.73, 107.08($Me_2\underline{C}$), 114.59, 138.28 ; MS: m/e 213 $(M+H)^+$ for $C_{13}H_{24}O_2$.

III.3.5 Preparation Z and E Isopropylidene Alkenes



216:threo
217:erythro

220:threo
221:erythro

222:threo
223:erythro

The threo terminal alkene**220** was converted to the aldehyde according to the general procedure of ozonolysis(II.4.3). The aldehyde **220** (1.05g, 90.5%) was obtained as a colorless syrup after purification. TLC R_f=0.35 (10% EtOAc/PE). ^{1}HNMR(C_6D_6,): 0.844(t, J=3.57 Hz, 3H), 1.20-1.6(m, 8H), 1.32, 1.34(both s, each 3H, -C(CH_3)$_2$), 3.4m(2H), 9.32(s, 1H). ^{13}C NMR(C_6D_6): δ 13.78, 22.73, 25.03, 27.12, 27.24, 28.31, 32.45, 40.21, 79.94, 80.73, 107.79, 199.69.

The aldehyde **220** (1.0g, 4.67mmol) was subjected to the standard Wittig reaction procedure (II.4.4) to afford to afford 10(1.08 g, 90%). TLC Rf=0.70(10% EtOAc/PE), ^{1}H-NMR(C_6D_6) δ 0.84(m, 6H, H_1, H_{13}), 1.20-1.60(m, 10H, H_2, H_3, H_4, H_7, H_{12}), 1.41(s, 6H, (CH_3)$_2$C-), 2.00(dd, J=5.9, 7.1Hz, H,), 2.30(m, 2H), 3.60(m, 2H, H_5, H_6), 5.40(apparent t, J=4.7 Hz, 2H, H_9, H_{10}), ^{13}C-NMR(C_6D_6) δ 13.57, 13.84, 22.80, 22.85, 24.19, 27.36, 28.50, 29.28, 32.69, 33.17, 80.44, 80.98, 107.64 (Me_2C) 129.22, 130.31 MS: m/e 255 $(M+H)^+$ for $C_{16}H_{30}O_2$, m/e 272 $(M+NH_4)$ for $C_{16}H_{30}O_2$.

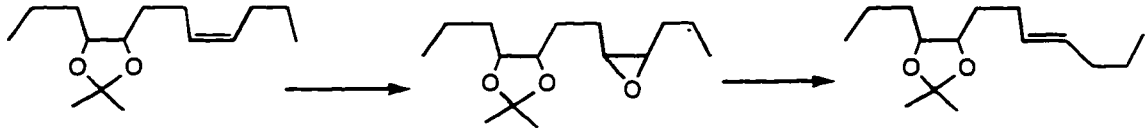
Erythro-Z-alkene:

The erythro terminal alkene **217** was converted to the aldehyde according to the general procedure of ozonolysis(II.4.3). The aldehyde **221** (410mg, 94%) was obtained as a colorless syrup after purification. TLC R_f=0.35(10% EtOAc/PE). ^{1}HNMR(C_6D_6): δ 0.902(m, 3H, H1), 1.02-1.60(m, 8H, H2, H3, H4, H7), 1.25, 1.37(both s, each 3H, -C(CH3)2), 2.10(m, 2H, H8), 3.80(m, 2H, H5, H6), 9.38(s, 1H, H9). ^{13}C-NMR(C_6D_6,) δ 14.49, 23.29, 23.39, 26.22, 28.99, 29.32, 29.91, 41.11, 77.49, 78.28, 107.86, 200.55.

erythro aldehyde **221** (410mg, 1.91mmol) was subjected to the standard Wittig reaction procedure to afford erythro-Z-alkene **223** (420g, 82%). TLC Rf=0.70 (10%

EtOAc/ PE), ^{1}H-NMR(C_6D_6) δ 0.88(t, J=7.4Hz, 6H, H_1, H_{13}), 1.19-1.63(m, 10H, H_2, H_3, H_4, H_7, H_{12}), 1.34, 1.50(both s, 3H each, $(\underline{CH_3})_2C$-), 2.05(q, J=5.4Hz,2H), 2.20, 2.35(both m, 1H each), 3.92(m, 2H, H_5, H_6), 5.49(t, J=4.9 Hz, H_9, H_{10}) ^{13}C-NMR(C_6D_6) δ 13.57, 13.56, 13.88, 22.72, 22.90, 24.16, 25.80, 28.60, 28.66, 29.29, 29.63, 30.19, 77.22, 77.81, 107.07 ($Me_2\underline{C}$) 129.32, 130.24

E -Isopropylidene Alkene 226 and 227



222:threo
223:erythro

224:threo
225:erythro

226:threo
227:erythro

Z alkene **222** (500 mg, 1.97mmol) in CH_2Cl_2(20 mL) was subjected to the standard epoxidation procedure(II.4.5) to afford the epoxide derivative of **224** (525 mg, ~98%) after purification. TLC R_f=0.5 (20% EtOAc/PE); ^{1}H-NMR(C_6D_6) δ 0.79-0.91 (m, 6H, H_1, H_{13}), 1.39(s, 6H, -C($\underline{CH_3}$)$_2$), 1.22-1.86(m, 14H, H_2, H_3, H_4, H_7, H_8, H_{11}, H_{12}), 2.74(m, 2H, H_9, H_{10}), 3.56(m, 2H, H_5, H_6). ^{13}C-NMR(C_6D_6) δ 13.74, 19.91, 22.75, 24.66, 25.38, 27.30, 28.43, 29.88, 30.32, 32.57, 32.63, 56.17, 56.21, 56.36, 55.75, 80.38, 80.95, 81.10, 107.73.

The above epoxide **224** (445mg, 1.6mmol) in dry THF(20 mL) was converted to the E-alkene according to the standard procedure. E alkene 11(370mg, 89%) was

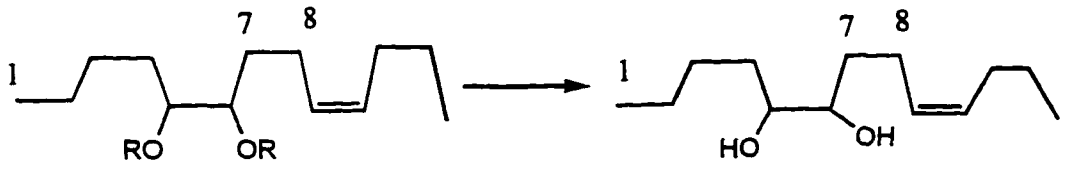
obtained after purification. TLC Rf=0.6 (10% EtOAc/PE) ^{1}H-NMR(C_6D_6) δ 0.86(m, 6H, H_1, H_{13}), 1.20-1.64(m, 10H, H_2, H_3, H_4, H_7, H_{12}), 1.42(s, 6H, ($\underline{CH_3}$)$_2$C-), 1.94(m, Hz,2H,), 2.34(m, 2H), 3.57(m, 2H, H_5, H_6), 5.47(m, 2H, H_9, H_{10}), ^{13}C-NMR() δ 13.57, 13.56, 13.88, 22.72, 22.90, 24.16, 25.80, 28.60, 28.66, 29.29, 29.63, 30.19, 77.22, 77.81, 107.07 (Me$_2\underline{C}$) 129.32, 130.24.

erythro-E Isopropylidene Alkene 227

erythro-Z-isopropylidene alkene **223** was subjected to the standard isomerization procedure to afford the epoxide **225** (203mg, 95%). TLC Rf=0.5 (10% EtOAc/PE). ^{1}H-NMR(C_6D_6) δ 0.86(m, 6H, H_1, H_{13}), 1.10-1.90(m, 14H, H_2, H_3, H_4, H_7, H_8, H_{11}, H_{12}), 1.32, 1.44(both s, 3H each, ($\underline{CH_3}$)$_2$C-), 2.72(m, 2H, H_9, H_{10}), 3.90(m, 2H, H_5, H_6), ^{13}C-NMR(C_6D_6) δ 14.40, 14.52, 20.59, 23.33, 25.34, 26.05, 26.35, 26.40, 27.67, 28.15, 29.17, 29.32, 30.10, 30.14, 30.59, 56.33, 56.90, 57.08, 77.82, 107.82 (Me$_2\underline{C}$) .

The above epoxide **225** (180mg, 0.647mmol) was subjected to the standard isomerization procedure to afford erythro-E-isopropylidene alkene **227** (154mg, 91%) after purification. TLC Rf=0.6(10% EtOAc/PE). ^{1}H-NMR(C_6D_6) δ 0.86(t, J=7.3 Hz, 6H, H_1, H_{13}), 1.16-1.64(m, 10H, H_2, H_3, H_4, H_7, H_{12}), 1.33, 1.46(both s, 3H each, ($\underline{CH_3}$)$_2$C-), 1.96(q, J=7.0 Hz, 2H), 2.11, 2.31(both m, 1H each), 3.95(m, 2H, H_5, H_6), 5.48(m, 2H, H_9, H_{10}), ^{13}C-NMR(C_6D_6) δ 14.11, 14.54, 23.36, 26.46, 29.24, 29.30, 30.08, 30.28, 30.77, 35.41, 77.85, 78.45, 107.69 (Me$_2\underline{C}$) 130.60, 131.24.

III.3.6 Hydrolysis of Isopropylidene Z and E Alkenes



222:R,R=Me2C, threo
223:R,R=Me2C, erythro

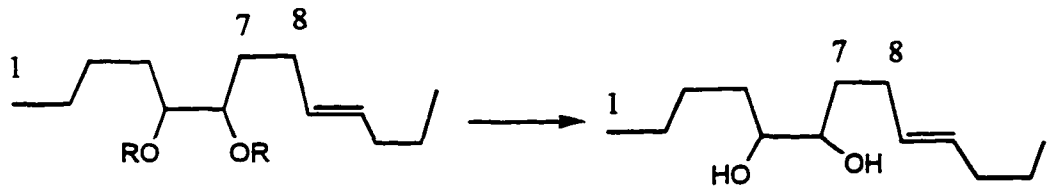
228: threo
229: erythro

hydrolysis of threo-Z-alkene

threo-Z-alkene **222**(75mg, 0.295mmol) was subjected to the general hydrolysis procedure to afford diol **228** (60mg, 95%) as a colorless syrup after purification. TLC Rf=0.20(20% EtOAc/PE); ^{1}H-NMR(C_6D_6) δ 0.87(m, 6H, H_1, H_{13}), 1.22-1.45(m, 10H, H_2, H_3, H_4, H_7, H_{12}), 1.58(d, J=4.25 Hz, 1H, -OH), 1.75(d, J=4.06 Hz, 1H, -OH), 2.05, 2.22(both m, 2H each, H_8, H_{11}), 3.22(mm, 2H, H_5, H_6), 5.45(t, J=4.98 Hz, 2H, H_9, H_{10}), ^{13}C-NMR(C_6D_6) δ 13.597, 13.914, 22.78, 22.88, 23.64, 27.92, 29.32, 33.39, 33.76, 73.89, 74.35, 129.56, 130.19.

Followed the same sequence, erythro-Z-alkene diol **229** (90mg, 97%) was obtained as a colorless syrup after purification. TLC Rf=0.20(20% EtOAc/PE); ^{1}H-NMR(C_6D_6) δ 0.89(t, J=7.30 Hz, 6H, H_1, H_{13}), 1.24-1.56(m, 10H, H_2, H_3, H_4, H_7, H_{12}), 2.02- 2.29(m, 4H, H_8, H_{11}), 3.47(bt, J=8.17, 11.24 Hz, 2H, H_5, H_6), 5.46(m, 2H, H_9, H_{10}), ^{13}C-NMR(C_6D_6) δ 13.59, 13.92, 22.78, 22.88, 23.92, 28.28, 29.31, 31.27, 31.42, 74.60, 74.75, 129.63, 130.19.

Hydrolysis of isopropylidene E- alkenes:



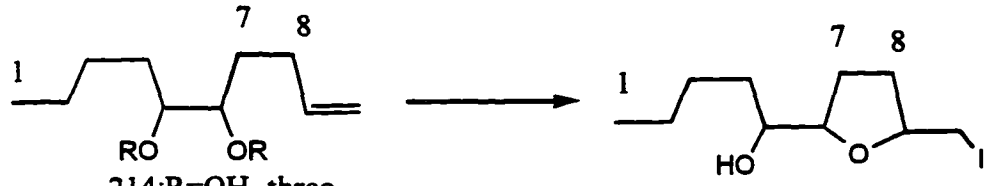
226:R,R=Me2C, threo
227:R,R=Me2C, erythro

230:threo
231:erythro

Threo-E-alkene **226** was subjected to the same condition of hydrolysis mention above and the diol **230** (85mg, 92%) was obtained as a colorless syrup after purification. TLC Rf=0.20(20% EtOAc/PE); ^{1}H-NMR(C_6D_6) δ 0.88(m, 6H, H_1, H_{13}), 1.22-1.52(m, 10H, H_2, H_3, H_4, H_7, H_{12}), 1.58, 1.98 (both m, 1H each, H_8, H_{11}), 2.24(m, 2H, H_8, H_{11}), 3.22(bs, 2H, H_5, H_6), 5.5(m, 2H, H_9, H_{10}), ^{13}C-NMR(C_6D_6) δ 13.49, 13.96, 22.74, 22.83, 28.03, 29.00, 33.40, 33.70, 34.78, 73.99, 74.49, 130.18, 130.57.

erythro-Z-alkene **227** was subjected to the same condition of hydrolysis mention above and the diol **231**(78mg, 93%) was obtained as a colorless syrup after purification. TLC Rf=0.20(20% EtOAc/PE); ^{1}H-NMR(C_6D_6) δ 0.88(m, 6H, H_1, H_{13}), 1.20-1.59(m, 10H, H_2, H_3, H_4, H_7, H_{12}), 1.93- 2.34(m, 4H, H_8, H_{11}), 2.48(bs, 2H, -OH), 3.46(m, 2H, H_5, H_6), 5.48(m, 2H, H_9, H_{10}), ^{13}C-NMR(C_6D_6) δ 14.10, 14.55, 23.42, 23.36, 28.93, 29.87, 31.95, 33.39, 74.76, 75.24, 130.89, 131.24.

III.3.7 Iodoetherfication of Terminal alkenes



214:R=OH, threo
215:R,R=Me2C, threo
216:R=OH, erythro
217:R,R=Me2C, erythro

232:threo , cis/trans THF
233: threo, trans THF
234:erythro, cis/trans THF
235:erythro, trans THF

Iodoetherfication of threo-dihydroxyalkene 214

Threo dihydroxyalkene **214** (40mg, 0.23mmol) was subjected to the general iodoetherification procedure (II.4.9) to give an inseparable mixture of cis/trans THF isomers **232** (71mg, 90%, c/t=~1:1; Rf=0.35).

for trans-THF : ^{1}H-NMR(C_6D_6) δ 0.89(t, J=6.5Hz, 3H, H_1), 1.19-1.92(m, 10H, H_2, H3, H_4, H_7, H_8), 2.05(bs, 1H, -OH), 2.83(m, 2H, H_{10}), 3.18(m, 1H), 3.67(m, 2H), ^{13}C-NMR(C_6D_6) δ 10.7(C_{10}), 14.6, 23.4, 28.5(C_7), 28.8, 33.2(C_8), 33.9, 74.2, 78.9, 83.9.

for cis-THF : ^{1}H-NMR(C_6D_6) δ 0.89(t, J=6.5Hz, 3H, H_1), 1.19-1.92(m, 10H, H_2, H3, H_4, H_7, H_8), 2.05(bs, 1H, -OH), 2.83(m, 2H, H_{10}), 3.28(m, 1H), 3.45(m, 1H), 3.67(m, 1H); ^{13}C-NMR(C_6D_6) δ 11.3(C_{10}), 14.6, 23.4, 27.8(C_7), 28.8, 32.0(C_8), 33.9, 74.2, 78.4, 84.0.

Iodoetherfication of threo-isopropylidene alkene 215

Threo-isopropylidene alkene **215** (25 mg, 0.12 mmol) was subjected to the standard iodoetherification procedure using IDCP(66mg, 0.14 mmol), CH_2Cl_2 (2mL) and water (0.04 mL). A single trans THF **233** (31mg, 88%) was obtained after purification of

the reaction product. TLC Rf=0.35 (10% Aceton/PE). ^{1}H-NMR(C_6D_6) δ 0.89(t, J=6.5Hz, 3H, H_1), 1.19-1.92(m, 10H, H_2, H3, H_4, H_7, H_8), 2.05(bs, 1H, -OH), 2.83(m, 2H, H_{10}), 3.18(m, 1H), 3.67(m, 2H), ^{13}C-NMR(C_6D_6) δ 10.7(C_{10}), 14.6, 23.4, 28.5(C_7), 28.8, 33.2(C_8), 33.9, 74.2, 78.9, 83.9.

Iodoetherfication of erythro-dihydroxyalkene

Erythro-dihydroxy-alkene **216** (40 mg, 0.23 mmol) was subjected to the standard iodoetherification procedure using IDCP (120mg, 0.26 mmol), CH_2Cl_2(3mL) and water(0.03 mL) to give an inseparable mixture of cis/trans THF isomers **234** (71mg, 91%) after purification of the reaction product. TLC Rf=0.20(10% aceton/PE).

for trans-THF : ^{1}H-NMR(C_6D_6) δ 0.87(t, J=7.0Hz, 3H, H_1), 1.21-1.74(m, 10H, H_2, H3, H_4, H_7, H_8), 2.78(dd, J=6.7, 9.8 Hz, 1H), 2.87(dd, J=4.8, 9.9 Hz, 1H), 3.62(m, 3H); ^{13}C-NMR(C_6D_6) δ 11.1(C_{10}), 11.1, 14.2, 23.1, 24.4, 28.5(C_7), 32.8(C_8), 72.0, 28.9, 83.3.

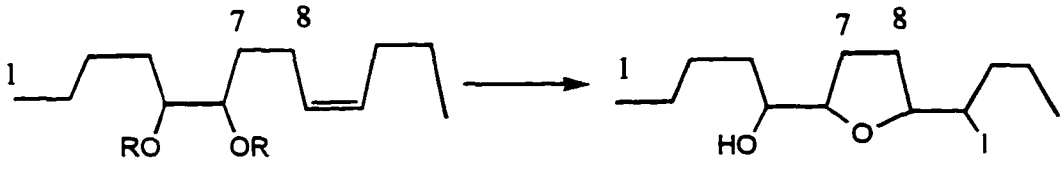
for cis-THF: ^{1}H-NMR(C_6D_6) δ 0.87(t, J=7.0Hz, 3H, H_1), 1.21-1.74(m, 10H, H_2, H3, H_4, H_7, H_8), 2.82(m, 2H, H_{10}), 3.45(t, J=7.7 Hz, 1H), 3.65(m, 2H); ^{13}C-NMR(C_6D_6) δ 11.2(C_{10}), 11.2, 14.2, 23.1, 24.4, 28.5(C_7), 31.7(C_8), 71.9, 77.8, 83.8.

Iodoetherfication of erythro-isopropylidene alkene

Erythro-isopropylidene-alkene **217** (22 mg, 0.104 mmol) was subjected to the standard iodoetherification procedure using IDCP(64mg, 0.125 mmol), CH_2Cl_2(2mL) and water(1 drop) to give a single trans- THF **235** (28mg, 93%)after purification of the reaction product. TLC Rf=0.20(10% Aceton/PE). ^{1}H-NMR(C_6D_6) δ 0.87(t, J=7.0Hz, 3H, H_1), 1.21-1.74(m, 10H, H_2, H3, H_4, H_7, H_8), 2.78(dd, J=6.7, 9.8 Hz, 1H), 2.87(dd,

J=4.8, 9.9 Hz, 1H), 3.62(m, 3H); ^{13}C-NMR(C_6D_6) δ 11.1(C_{10}), 11.1, 14.2, 23.1, 24.4, 28.5(C_7), 32.8(C_8), 72.0, 28.9, 83.3.

III.3.8 Iodoetherfication of Z-Alkenes



228:R=OH, threo
222:R,R=Me2C, threo
229:R=OH, erythro
223:R,R=Me2C, erythro

236:threo , cis/trans THF
237: threo, trans THF
238:erythro, cis/trans THF
239:erythro, trans THF

Iodoetherfication of threo-Z-dihydroxyalkene

threo-Z-dihydroxy-alkene **228** (40 mg, 0.187 mmol) was subjected to the standard iodoetherification procedure using IDCP(175mg, 0.374 mmol), CH_2Cl_2(5mL) and water (0.05 mL) to give an inseparable mixture of 3/4 cis/trans THF isomers **236** (56mg, 87%) after purification. TLC Rf=0.25(10% aceton/PE)

for trans-THF : ^{1}H-NMR(C_6D_6) δ 0.77(t, J=7.3Hz, 3H), 0.90(t, J=7.2Hz, 3H), 1.20-1.75(m, 14H, H_2, H_3, H_4, H_7, H_8, H_{11}, H_{12}), 2.20(bs, 1H, -OH), 3.25(bs, 1H), 3.56(m, 1H), 3.80(m, 2H); ^{13}C-NMR(C_6D_6) δ 13.8, 13.9, 22.8, 23.0, 27.9(C_7), 28.3, 31.4(C_8), 34.0, 41.8(C_{10}), 73.7, 82.2, 83.7.

MS: m/e 358 $(M+NH_4)^+$ for $C_{13}H_{25}O_2I$

for cis-THF : ^{1}H-NMR(C_6D_6) δ 0.77(t, J=7.3Hz, 3H), 0.90(t, J=7.2Hz, 3H), 1.20-1.75(m, 14H, H_2, H_3, H_4, H_7, H_8, H_{11}, H_{12}), 2.20(bs, 1H, -OH), 3.08(m, 1H), 3.42(m, 1H), 3.62(q, J=6.2Hz, 1H); 3.81(m,1H); ^{13}C-NMR(C_6D_6) δ 13.8, 13.9, 22.8, 23.0, 27.3(C_7), 28.1, 31.3(C_8), 33.3, 43.1(C_{10}), 73.7, 81.6, 82.9.

MS: m/e 358 $(M+NH_4)^+$ for $C_{13}H_{25}O_2I$

Iodoetherfication of threo-Z-isopropylidene alkene

Threo-Z-isopropylidene-alkene **222** (100 mg, 0.393 mmol) was subjected to the standard iodoetherification procedure using IDCP(221mg, 0.472 mmol), CH_2Cl_2(5mL) and water(0.05 mL) to give a single *trans*- THF **237** (121mg, 91%) after purification of the reaction product. TLC Rf=0.25(10% Aceton/PE) ^{1}H-NMR(C_6D_6) δ 0.77(t, J=7.3Hz, 3H), 0.90(t, J=7.2Hz, 3H), 1.20-1.75(m, 14H, H_2, H_3, H_4, H_7, H_8, H_{11}, H_{12}), 2.20(bs, 1H, -OH), 3.25(bs, 1H), 3.56(m, 1H), 3.80(m, 2H); ^{13}C-NMR(C_6D_6) δ 13.8, 13.9, 22.8, 23.0, 27.9(C_7), 28.3, 31.4(C_8), 34.0, 41.8(C_{10}), 73.7, 82.2, 83.7.

MS: m/e 358 $(M+NH_4)^+$ for $C_{13}H_{25}O_2I$

Iodoetherfication of erythro-Z-dihydroxyalkene

Erythro-Z-dihydroxy-alkene **229** (40 mg, 0.187 mmol) was subjected to the standard iodoetherification procedure using IDCP(175mg, 0.374 mmol), CH_2Cl_2(5mL) and water (0.05 mL) to give an inseparable mixture of 2/5 cis/trans THF isomers **238** (58mg, 91%) after purification of the reaction product. TLC Rf=0.22 (10% Aceton/PE).

for trans-THF : ^{1}H-NMR(C_6D_6) δ 0.78(t, J=7.3Hz, 3H), 0.88(t, J=7.3Hz, 3H), 1.20-1.85(m, 14H, H_2, H_3, H_4, H_7, H_8, H_{11}, H_{12}), 3.51(bs, 1H), 3.67(m, 1H), 3.86(m, 2H); ^{13}C-NMR(C_6D_6) δ 13.0, 13.8, 22.8, 23.0, 25.6, 28.1(C_7), 31.5(C_8), 32.6, 38.4, 42.6(C_{10}), 71.8, 82.2, 83.6.

MS: m/e 358 $(M+NH_4)^+$ for $C_{13}H_{25}O_2I$

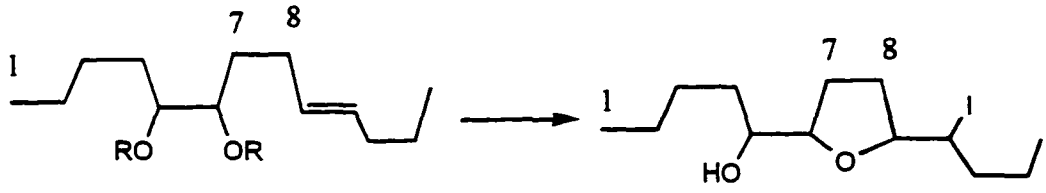
for cis-THF: ^{1}H-NMR(C_6D_6) δ 0.74(t, J=7.2Hz, 3H), 0.88(t, J=7.3Hz, 3H), 1.16-1.98(m, 14H, H_2, H_3, H_4, H_7, H_8, H_{11}, H_{12}), 2.98(m, 1H), 3.66(m, 1H), 3.78(m, 1H); 3.90(m, 1H); ^{13}C-NMR(C_6D_6) δ 13.0, 13.9, 22.8, 23.0, 24.0, 28.1(C_7), 29.8(C_8), 32.8, 39.8, 43.4(C_{10}), 71.8, 81.2, 82.9. MS: m/e 358 $(M+NH_4)^+$ for $C_{13}H_{25}O_2I$.

Iodoetherfication of Erythro-Z-isopropylidene alkene

Erythro-Z-isopropylidene-alkene **223** (60 mg, 0.236 mmol) was subjected to the standard iodoetherification procedure using IDCP(183mg, 0.39 mmol), CH_2Cl_2(5mL) and water (0.05 mL) to give a single trans- THF **239** (76mg, 95%) after purification of the reaction product. TLC Rf=0.22(10% Aceton/PE). ^{1}H-NMR(C_6D_6) δ 0.78(t, J=7.3Hz, 3H), 0.88(t, J=7.3Hz, 3H), 1.20-1.85(m, 14H, H_2, H_3, H_4, H_7, H_8, H_{11}, H_{12}), 3.51(bs, 1H), 3.67(m, 1H), 3.86(m, 2H); ^{13}C-NMR(C_6D_6) δ 13.0, 13.8, 22.8, 23.0, 25.6, 28.1(C_7), 31.5(C_8), 32.6, 38.4, 42.6(C_{10}), 71.8, 82.2, 83.6.

MS: m/e 358 $(M+NH_4)^+$ for $C_{13}H_{25}O_2I$

III.3.9 Iodoetherfication of E-Alkenes



230:R=OH, threo
226:R,R=Me2C, threo
231:R=OH, erythro
227:R,R=Me2C, erythro

240:threo , cis/trans THF
241: threo, trans THF
242:erythro, cis/trans THF
243:erythro, trans THF

Iodoetherfication of threo-E-dihydroxyalkene

threo-E-dihydroxy-alkene **230** (40mg, 0.187 mmol) was subjected to the standard iodoetherification procedure using IDCP (175mg, 0.374 mmol), CH_2Cl_2(5mL) and water(0.05 mL) to give an inseparable mixture of 1/1 cis/trans THF isomers **240** (60mg, 93%) after purification of the reaction product. TLC Rf=0.25 (10% Aceton/PE.)

for trans-THF: ^{1}H-NMR(C_6D_6) δ 0.77(t, J=7.1Hz, 3H), 0.92(t, J=7.2Hz, 3H), 1.21-1.84(m, 14H, H_2, H_3, H_4, H_7, H_8, H_{11}, H_{12}), 3.25(bs, 1H), 3.53(q, J=7.6Hz, 1H), 3.76(q, J=7.4 Hz, 1H), 3.88(q, J=7.2 Hz, 1H); ^{13}C-NMR(C_6D_6) δ 13.0, 13.9, 22.7, 22.8, 27.9, 28.0(C_7), 33.3, 33.3(C_8), 38.6, 43.2(C_{10}), 73.7, 82.3, 83.4. MS: m/e 358 $(M+NH_4)^+$ for $C_{13}H_{25}O_2I$

for cis-THF : ^{1}H-NMR(C_6D_6) δ 0.77(t, J=7.1Hz, 3H), 0.90(t, J=7.2Hz, 3H), 1.21-1.90(m, 14H, H_2, H_3, H_4, H_7, H_8, H_{11}, H_{12}), 3.25(m, 1H), 3.38(m, 1H), 3.68(q, J=5.7Hz, 1H), 4.05(m, 1H); ^{13}C-NMR(C_6D_6) δ 13.0, 13.9, 22.6, 22.8, 27.1(C_7), 27.9, 31.5(C_8), 33.3, 38.6, 43.0(C_{10}), 73.8, 81.6, 83.3. MS: m/e 358 $(M+NH_4)^+$ for $C_{13}H_{25}O_2I$

Iodoetherfication of threo-E-isopropylidene alkene

Threo-E-isopropylidene-alkene **226** (50 mg, 0.196 mmol) was subjected to the standard iodoetherification procedure using IDCP(110.5mg, 0.235 mmol), CH_2Cl_2(5mL) and water(0.05 mL) to give a single trans- THF **241** (61.5mg, 92%) after purification of the reaction product. TLC Rf=0.25(10% Aceton/PE). ^{1}H-NMR(C_6D_6) δ 0.77(t, J=7.1Hz, 3H), 0.92(t, J=7.2Hz, 3H), 1.21-1.84(m, 14H, H_2, H_3, H_4, H_7, H_8, H_{11}, H_{12}), 3.25(bs, 1H), 3.53(q, J=7.6Hz, 1H), 3.76(q, J=7.4 Hz, 1H), 3.88(q, J=7.2 Hz, 1H); ^{13}C-NMR(C_6D_6) δ 13.0, 13.9, 22.7, 22.8, 27.9, 28.0(C_7), 33.3, 33.3(C_8), 38.6, 43.2(C_{10}), 73.7, 82.3, 83.4. MS: m/e 358 $(M+NH_4)^-$ for $C_{13}H_{25}O_2I$

Iodoetherfication of erythro-E-dihydroxyalkene

erythro-E-dihydroxy-alkene **231** (45 mg, 0.21 mmol) was subjected to the standard iodoetherification procedure using IDCP(108.5mg, 0.23 mmol), CH_2Cl_2(8mL) and water (0.08 mL) to give a separable *cis trans* THF isomers **242**.

cis-THF (31mg, 39%) . TLC Rf=0.26 (10% Aceton/PE). ^{1}H-NMR(C_6D_6) δ 0.74(t, J=7.3Hz, 3H), 0.85(t, J=7.3Hz, 3H), 1.10-2.00(m, 14H, H_2, H_3, H_4, H_7, H_8, H_{11}, H_{12}), 2.18(d, J=2.4 Hz, -OH), 3.18(q, J=7.3Hz, 1H), 3.68(m, 1H), 3.80(m, 1H), 4.05(m, 1H); ^{13}C-NMR(C_6D_6) δ 13.4, 14.3, 23.1, 24.3, 25.6, 28.5(C_7), 32.9(C_8), 33.5, 38.9, 44.1(C_{10}), 72.1, 82.3, 83.5. MS: m/e 358 $(M+NH_4)^-$ for $C_{13}H_{25}O_2I$

trans-THF (31mg, 43.6%). TLC Rf=0.22 (10% Aceton/PE). ^{1}H-NMR(C_6D_6) δ 0.76(t, J=7.3Hz, 3H), 0.90(t, J=7.3Hz, 3H), 1.15-1.98(m, 14H, H_2, H_3, H_4, H_7, H_8, H_{11}, H_{12}), 2.45(bs, 1H, -OH), 3.56(q, J=7.3Hz, 1H), 3.66(m, 1H), 3.78(m, 1H), 3.95(q, J=7.3Hz,

1H); ^{13}C-NMR(C_6D_6) δ 13.4, 14.3, 23.1, 24.3, 25.6, 28.5(C_7), 32.9(C_8), 33.5, 38.9, 44.1(C_{10}), 72.1, 82.3, 83.5.

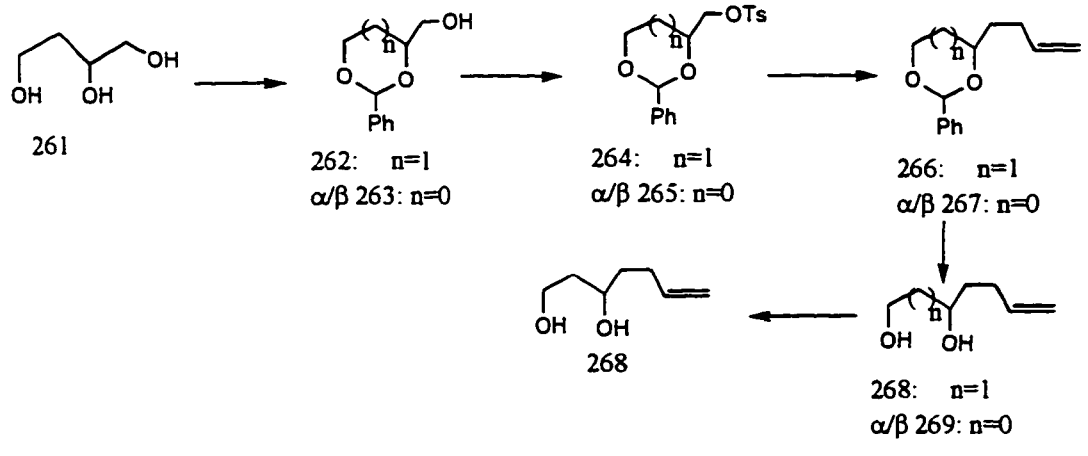
MS: m/e 358 $(M+NH_4)^+$ for $C_{13}H_{25}O_2I$

Iodoetherfication of erythro-E-isopropylidene alkene

erythro-E-isopropylidene-alkene **227**(50 mg, 0.23 mmol) was subjected to the standard iodoetherification procedure using IDCP(219mg, 0.46 mmol), CH_2Cl_2(8mL) and water (0.08 mL) to give a single trans- THF **243** (61mg, 91%) after purification. TLC Rf=0.22(10% Aceton/PE). ^{1}H-NMR(C_6D_6) δ 0.76(t, J=7.3Hz, 3H), 0.90(t, J=7.3Hz, 3H), 1.15-1.98(m, 14H, H_2, H_3, H_4, H_7, H_8, H_{11}, H_{12}), 2.45(bs, 1H, -OH), 3.56(q, J=7.3Hz, 1H), 3.66(m, 1H), 3.78(m, 1H), 3.95(q, J=7.3Hz, 1H); ^{13}C-NMR(C_6D_6) δ 13.4, 14.3, 23.1, 24.3, 25.6, 28.5(C_7), 32.9(C_8), 33.5, 38.9, 44.1(C_{10}), 72.1, 82.3, 83.5.

MS: m/e 358 $(M+NH_4)^+$ for $C_{13}H_{25}O_2I$

III.3.10 Preparation of 1,3-dihydroxyl-6-heptene 268



Alcohol 262 and α/β 263

p-toluensulfonic acid (250mg, 1.31 mmol) was added to a solution of a mixture of triol **261**(3.0g, 28.2mmol) and benzyl aldehyde (8.7ml, 84.6 mmol) in anhydrous DMF (30ml). The reaction mixture was stirred at rt. for 2h, neutralized by addition of a 1M NaOMe/ MeOH, and concentrated *in vacuo*. The residue was purified by flash Chromatography to afford an inseparable mixture of 2:1 **262** and α/β **264** (4.11g, 80%). TLC Rf= 0.75 (10% EtOAc/PE). ^{1}H-NMR(C_6D_6) δ 1.90(m, 2H), 3.40-4.40(m, 5H), 5.52(s, 4/6H), 5.78(s, 1/6H), 5.92(s, 1/6H), 7.20(m, 5H). ^{13}C-NMR(C_6D_6) δ 26.56, 35.28, 59.94, 59.78, 65.40, 66.39, 69.92, 70.57, 75.43, 76.43, 77.36, 101.08, 102.96, 103.87, 125.93, 126.16, 126.39, 128.03, 128.15, 128.72, 129.13, 129.83, 133.12, 138.18.

Tosylate 264 and 265

compound **262** (4.0g, 21.9 mmol) in 50 mL pyridine was treated according to the general tosylation procedure in part 1 . Tosylate **264** and **265** (4.31g, 65%) was obtained after purification. TLC R_f=0.45 (30% EtOAc/ PE). ^{1}H-NMR(C_6D_6) δ 1.95(m, 2H), 2.42(s, 3H), 3.60-4.40(m, 5H), 5.45(s, 4/6H), 5.72(s, 1/6H), 5.84(s, 1/6H), 7.25(m, 7H), 7.80(d, J=4.20, 2H). ^{13}C-NMR(C_6D_6) δ 14.30, 21.72, 27.25, 32.77, 33.25, 66.39, 67.38, 67.41, 69.89, 70.44, 71.67, 72.77, 73.36, 74.21, 101.08, 103.28, 104.12, 126.15, 126.17, 126.42, 126.58, 128.06, 128.22, 127.00, 128.43, 128.63, 128.96, 129.27, 129.43, 129.98, 129.91, 138.08, 144.97.

Alkene 266 and 267

The tosylate **264** and **265** (4.1g, 13.6 mmol) in anhydrous Et_2O(60 mL)was subjected to the general allylation procedure. Alkene **266** and **267** (2.31g, 78%). was obtained after purified by flash column chromatography. TLC R_f=0.68(10% EtOAc/ PE). ^{1}H-NMR(C_6D_6) δ1.20-2.40(m, 6H), 3.6-4.4(m, 3H), 5.05(m, 2H), 5.55(bs, 1H), 5.90(m, 1H), 7.20(m, 5H). ^{13}C-NMR(C_6D_6) δ 24.83, 28.97, 31.09, 34.87, 66.84, 76.25, 100.89, 114.64, 125.81, 127.18, 128.13, 128.41, 138.02.

Triol 268 and 269

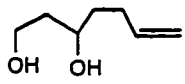
Alkene **266** and **267** (2.2g, 10.1mmol) was hydrolyzed according to the general procedure . An inseparable mixture of **268** and **269** (1.2g, 91%) was obtained as a colorless syrup after purification. TLC Rf=0.25(20% EtOAc/PE). ^{1}H-NMR(C_6D_6) δ 1.40-2.20(m, 6H), 2.85(bs, 2H), 3.40-4.40(m, 3H), 5.05(m, 2H), 5.85(m, 1H). ^{13}C-NMR(C_6D_6) δ 24.58, 29.65, 32.34, 33.39, 36.53, 38.12, 61.31, 66.54, 71.28, 71.91, 114.52, 114.65, 138.10.

1,3-dihydroxyl-6-heptene(268)

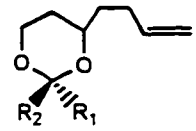
To the solution of the above mixture (1.1g, 9.08 mmol) in THF(24 mL) was added $NaIO_4$ (1.94 g, 9.08 mmol) in H_2O (48 mL). After stirred in rt for 1 h, the mixture was diluted with 40 mL H_2O, extracted with Et_2O (3x 40 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated *in vacuo* and the residue purified by flash column

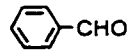
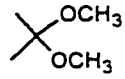
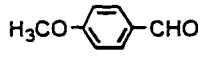
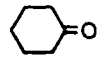
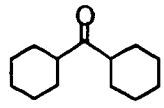
chromatography to afford the triol **268** (300mg). TLC Rf=0.25(20% EtOAc/PE). ^{1}H-NMR($CDCl_3$) δ 1.60(m, 4H, H_2, H_4), 2.15(m, 2H, H_5), 2.80(bs, 2H, -OH), 3.85(m, 3H, H_1, H_3), 5.0(m, 2H, H_6), 5.80(m, 1H, H_7). δ ^{13}C-NMR($CDCl_3$) δ 30.11, 36.96, 38.50, 61.88, 71.87, 115.13, 138.56.

III.3.11 Preparation of alkene precursors 270-274



268



weight(mg)	mmol		weight(mg)	mmol		weight (mg)	yield (%)
57	0.438		139	1.31	270: R_1=H, R_2=Ph	76	80
50	0.38		118	1.14	271: R_1=R_2=CH_3	66	92
55	0.42		171	1.26	272: R_1=H, R_2=-(p-OMe-)C_6H_5	88	85
60	0.46		187	1.38	273: R_1=H, R_2=cyclohexyl	76	84
70	0.53		308	1.59	274: R_1=R_2=cyclohexyl	123	75

The same procedure described above for preparation of the benzylidene from the was applied to diol **268** . The 1,3-dioxlane derivatives were obtained after purification . The NMR data was listed below.

1,3-benzylidene-6-heptene(270)

TLC Rf= 0.75 (10% EtOAc/PE). ^{1}H-NMR($CDCl_3$) δ 1.30-1.85(m, 4H, H_2, H_4), 2.05(m, 2H, H_5), 3.90(m, 2H, H_1), 4.18(dd, J=2.1, 9.5Hz, 1H, H_3), 4.95(m, 2H, H_7), 5.42(s, 1H),

5.80(m, 1H, H_6), 7.22(m, 5H). ^{13}C-NMR($CDCl_3$) δ 29.30, 31.43, 35.21, 67.17, 76.58, 101.22, 114.97, 126.15, 128.74, 128.31, 128.58, 138.35, 139.40.

1,3-isopropylidene-6-heptene(271)

TLC Rf= 0.75 (10% EtOAc/PE). ^{1}H-NMR($CDCl_3$) δ 1.10-1.90(m, 4H, H_2, H_4), 1.38, 1.44(both s, 3H each, -$C(CH_3)_2$), 2.10(m, 2H, H_5), 3.85(m, 3H, H_1, H_3), 5.0(m, 2H, H_7), 5.80(m, 1H, H_6). ^{13}C-NMR($CDCl_3$) δ 19.06, 25.54, 28.42, 28.88, 29.77, 31.06, 35.31, 48.98, 59.75, 67.86, 98.01, 114.43, 138.10.

1,3-(p)-methoxylbenzylidene-6-heptene(272)

TLC Rf= 0.75 (10% EtOAc/PE). ^{1}H-NMR($CDCl_3$) δ 1.40-1.90(m, 4H, H_2, H_4), 2.20(m, 2H, H_5), 3.78(s, 3H, -OCH_3), 3.82(m, 2H, H_1), 4.25(dd, J=2.1, 9.5Hz, 1H, H_3), 5.02(m, 2H, H_7), 5.45(s, 1H), 5.85(m, 1H, H_6), 6.90(m, 2H), 7.24(m, 2H). ^{13}C-NMR($CDCl_3$,) δ 29.33, 31.42, 35.24, 55.46, 67.46, 77.65, 101.20, 113.68, 113.79, 114.97, 127.45, 131.66, 132.15, 138.43.

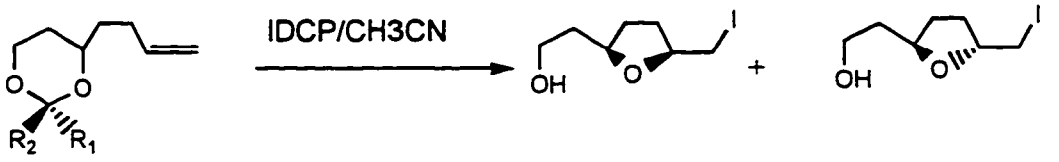
1,3-cyclohexylidene-6-heptene(273)

TLC Rf= 0.75 (10% EtOAc/PE). ^{1}H-NMR($CDCl_3$) δ 1.0-2.45(m, 16H), 3.80(m, 3H, H_1, H_3), 4.90(m, 2H, H_7), 5.75(m, 1H, H_6). ^{13}C-NMR($CDCl_3$) δ 23.00, 23.13, 13.37, 25.39, 25.82, 26.01, 26.38, 27.13, 27.80, 28.18, 28.57, 28.76, 29.19, 29.87, 30.21, 31.28, 32.20, 32.28, 32.36, 36.28, 39.41, 44.00, 59.27, 59.71, 67.61, 77.20, 77.62, 78.04, 98.74, 115.09, 115.15, 138.45, 138.99.

1,3-biscyclohexylidene-6-heptene(274)

TLC Rf= 0.75 (10% EtOAc/PE). ^{1}H-NMR($CDCl_3$) δ 0.90-2.50(m, 28H), 3.85(m, 2H, H_1), 4.25(dd, J=2.1, 9.2Hz, 1H, H_3), 5.00(m, 2H, H_7), 5.85(m, 1H, H_6), 7.22(m, 5H). ^{13}C-NMR($CDCl_3$) δ 28.26, 28.75, 30.97, 34.74, 48.75, 66.59, 77.22, 100.68, 114.32, 137.78.

III.3.12 Iodocyclozation of 1,3 Dioxane Acetals



Entry	Alkenes	THF	c/t	yield
1	249a: R_1=H, R_2=Ph	262	~3/2	85%
2	253: R_1=R_2=CH_3	262	~3/2	89%
3	256: R_1=H, R_2=-(p-OMe-)C_6H_5	262	~3/2	88%
4	254: R_1=H, R_2=cyclohexyl	262	~3/2	78%
5	255: R_1=R_2=cyclohexyl	262	~3/2	75%

TLC Rf= 0.25 (20% EtOAc/PE). ^{1}H-NMR($CDCl_3$) δ 1.0-1.70(m, 6H), 2.20(bs, 1H, -OH), 2.75(m, 2H), 3.40-3.90(m, 4H). ^{13}C-NMR($CDCl_3$) δ 10.65, 31.43, 31.63, 32.42, 32.90, 37.74, 38.00, 61.54, 61.70, 78.54, 78.92, 80.21, 80.66.

Part IV

Synthesis of A Versatile Synthon for Acetogenins Containing 2,5-Disubstituted THF's

IV. 1 Introduction

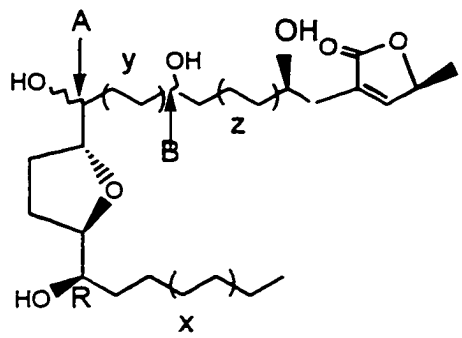
There has been considerable interest in the synthesis of tetrahydrofuran (THF) containing acetogenins analogs for bioactivity studies [62] and in the determination of relative and absolute stereochemistry[63-64]. Significant progress has been made in the design of different strategies, with the majority of these centering on the cyclization of hydroxy olefin and hydroxy epoxide precursors [65, 66, 67]. Our interest in developing versatile and practical methods led to consideration of the mono-THF building block **277**. The epoxide residue permits entry to derivatives with different chain length, and the differentiation of the secondary alcohol positions, facilitates the preparation of analogs in which the configurations at the flanking carbinol centers can be varied (Scheme 50). Furthermore, **277** could be elaborated into both adjacently and non-adjacently linked structures.

As part of our studies on the use of conformationally restricted acetals in stereoselective THF synthesis, we have recently showed that 5,6-O-isopropylidene acetal-alkenes **275** on treatment with iodonium ion gave exclusively the *trans*-2,5-disubstituted THF **276** (Part III) [68]. Notable aspects of this methodology are the use of experimentally straightforward procedures, high THF stereoselectivity, and the dual role of the cyclic acetal as a stereocontrolling element as well as a protecting group. Application to the synthesis of the acetogenin synthon **277** is described herein.

The epoxy-THF **277** was considered to be an attractive synthon since it will allow access to derivatives with different chain length. The differentiation of the secondary alcohols in **277** will facilitate variation of relative configuration of the two secondary

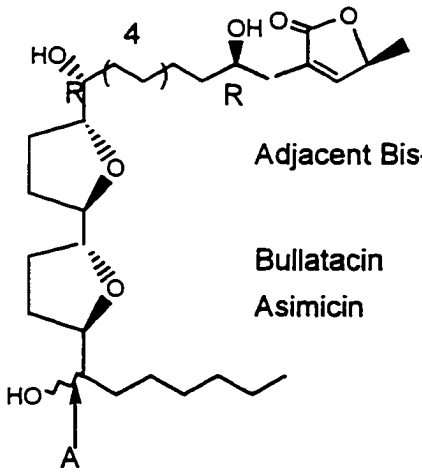
alcohol positions. This will provide the configuration threo/*trans*/threo, erythro/*trans*/ threo or erythro/*trans*/erythro substitution pattern. Furthermore, the 1,4 diol residue is primed for elaboration into bis-THF systems.

Scheme 50:



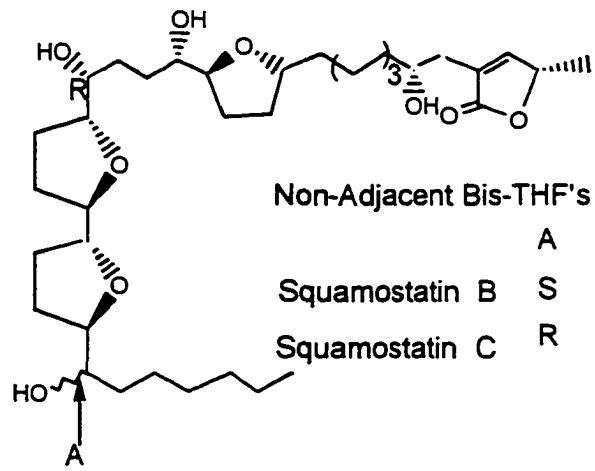
Mono-THF's

Compounds	A	B	x	y	z
Annonacin	S	-	4	2	2
Arianacin	R	S	4	1	2
Javoricin	R	R	4	1	2
Goniothalamicin	R	R	5	1	1



Adjacent Bis-THF's

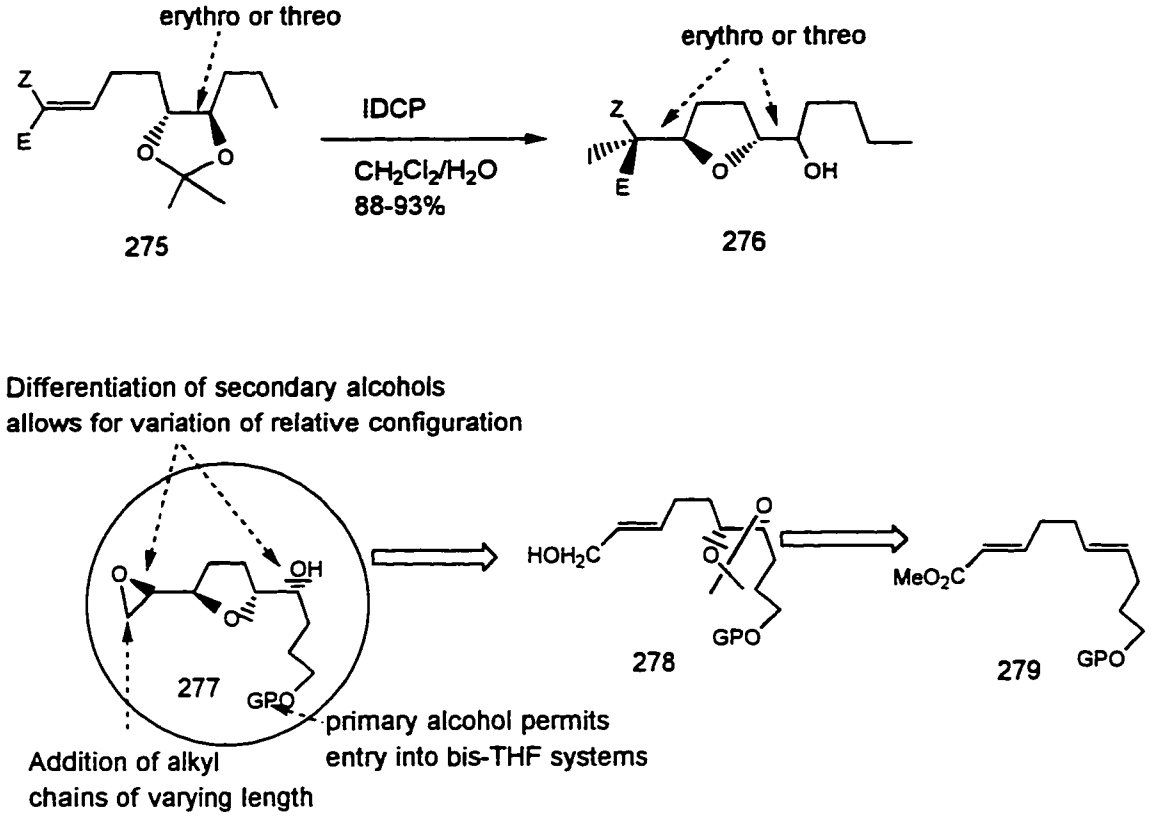
	A
Bullatacin	S
Asimicin	R



Non-Adjacent Bis-THF's

	A
Squamostatin B	S
Squamostatin C	R

Scheme 51:



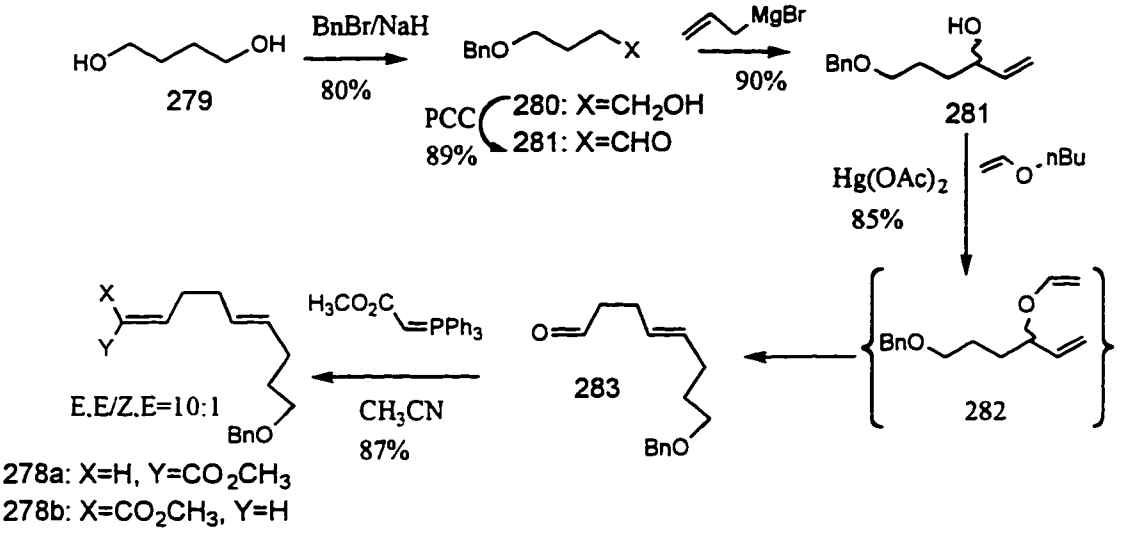
Retrosynthetically the synthon **277** can be obtained from a threo-O-isopropylidene-E-alkene precursor **278**, the latter could be synthesized via the regio- and enantioselective hydroxylation of a diene **279** (Scheme 51). Several examples of related hydroxylation have recently been reported [69].

IV.2 Results and Discussions

Synthesis of 1,2-O-Isopropylidene Alkene Precursor: The synthesis of the alkene precursor **278** started with commercially available 1,4-butane diol **279** (Scheme 52). Selective benzylation afforded alcohol **280** in 80% yield. PCC oxidation of the alcohol

280 provided aldehyde **281** with 89% yield. Addition of vinyl magnesium bromide gave the allylic alcohol **282**. Treatment of **282** with ethyl vinyl ether in the presence of $Hg(OAc)_2$ afforded the vinyl ether **283** together with ~10% of the aldehyde product **284**. When xylene at 105 ^{0}C was used as solvent, the aldehyde **284** was obtained in 80% yield. The use of n-Butyl vinyl ether as reagent and as solvent gave the aldehyde **284** in 90% yield.

Scheme 52:

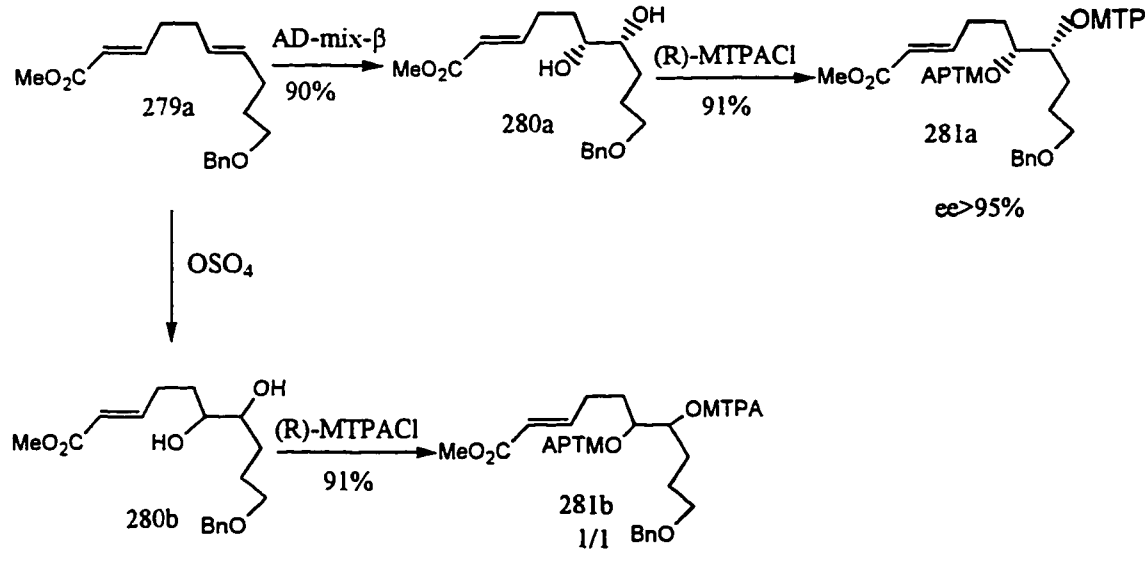


Treatment of the resulting aldehyde **284** with carbomethoxymethylene triphenyl-phosphorane in CH_3CN provided the desired E, E product **278a** in 87% yield together with a minor amount of the Z, E diene **278b** (8.1%). These products were separated by chromatography and their structures assigned by ^{1}HNMR (J_{trans}=15.59 Hz, J_{cis}=9.49Hz).

Diene **278a** was then subjected to the Sharpless's asymmetric dihydroxylation procedure. The diol 12 ($[\alpha]^{25}_D$= +15.47^0(c 0.19, $CHCl_3$)) was obtained in 90% yield. The reaction proceeded slowly (~3 days in 0^{0}C) but with excellent regioselectivity.

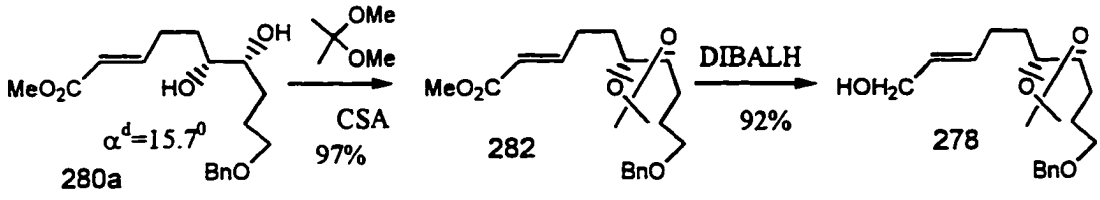
Optical purity of the diol was determined from the ^1H NMR analysis of the bis-Mosher ester[70] of **281a** (Scheme 53). The racemic diol **280b** was obtained from the OsO_4 dihydroxylation of the diene in 95% yield. The reaction was completed within 1h and the regioselectivity was excellent. Racemic diol was converted to the bis-Mosher esters **281b** in 91% yield. ^1H NMR and ^{13}CNMR analysis indicated a 1/1 mixture of two isomers. The bis Mosher ester **281a** of the diol obtained from the Sharpless procedure was found to be a single isomer, thereby establishing the ee to be greater than 95%, within the limits of NMR detection.

Scheme 53:



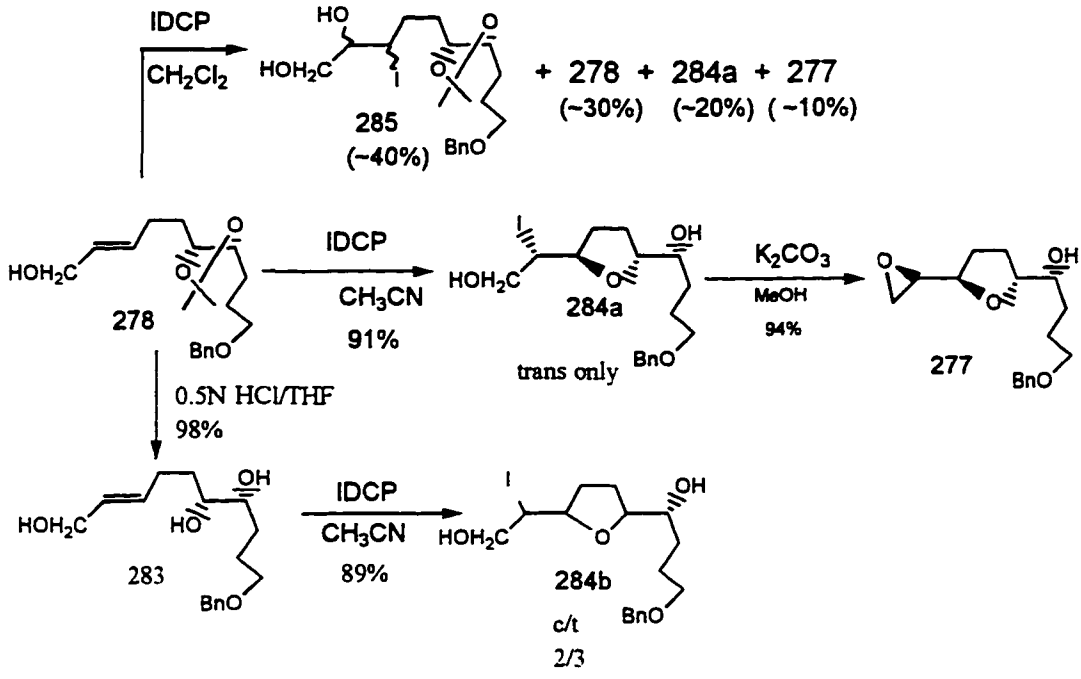
Treatment of the diol **280a** with dimethoxyl propane and camphorsulfonic acid afforded the acetonide **282** in quantitative yield. DIBALH reduction of the ester by led to the key isopropylidene E- alkene substrate **278** in 92 % yield (Scheme 54).

Scheme 54:



Iodocyclization and Preparation of Epoxide Synthon: The initial idea was to obtain the epoxy-THF **277** in a single pot reaction one 'pot' from the isopropylidene alkene **278**. We reasoned that the treatment of **278** with IDCP should lead to form the THF iodohydrin **284a**, which in the presence of collidine should give the desired epoxide **277**. When the reaction was performed in CH_2Cl_2, a mixture of the desired epoxide **277** (~10%), halohydrin **285** (~40%), THF iodide **284** (10%) and starting material **278** (20%) was obtained. Carried out the reaction in acetonitrile (CH_3CN) instead of CH_2Cl_2 led to formation of a single trans-iodide product **284a** in 90% yield. By comparison, the reaction of the triol derivative of 19 led to a 1:2 mixture of *cis:trans* THF's 20. The stereochemistry of the THF product was assigned from the ^{13}C NMR comparison of the *cis* isomer with the related *trans* THF obtained from the cyclization of the diol **284b**. Treatment of the THF-iodohydrin **284a** with K_2CO_3/MeOH gave smoothly the desired epoxy-THF **277** in 94% yield (Scheme 55).

Scheme 55:

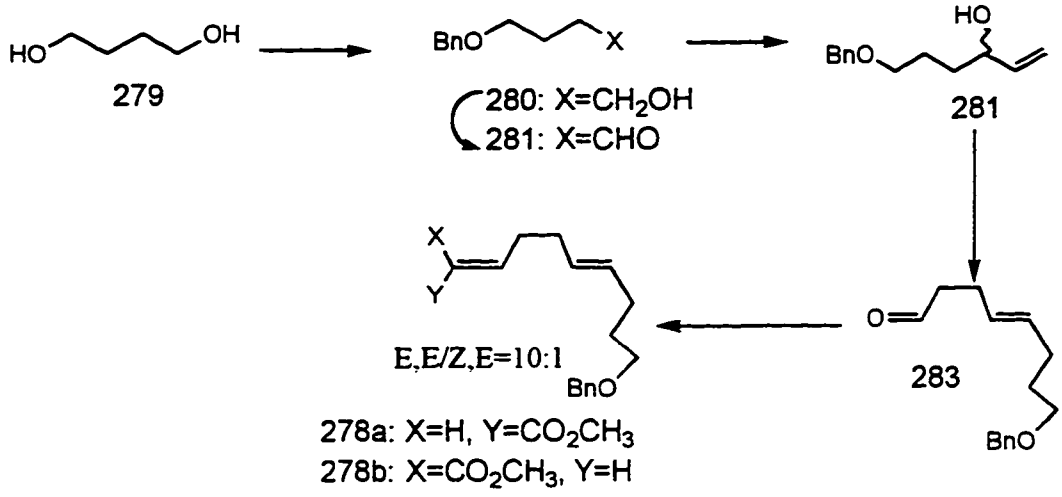


In conclusion, a highly efficient enantioselective synthesis of a chiral building block was achieved. The preparation involved a 10-steps with 32% overall yield. The reactions are straightforward and amenable for large scale work. The key steps are a highly enantio- and regio- selective Sharpless hydroxylation, and the stereoselective iodocyclization of a 1,2-O-isopropylidene-5-alkene. This synthesis illustrated how the acetal alkene methodology can be used for the preparation of more complex THF's.

IV.3 Experimental

IV.3.1 General (I.4.1)

IV.3.2 Synthesis of 1,2-O-Isopropylidene Alkene Precursor 278b



4-benzyl-1-butanol(280)

To a solution of 1,4-butanediol **279** (10g, 0.11 mol) in 40 ml DMF at 0^0C was added NaH(60% weigh, 885mg, 0.037mol), after stirring for 20 minutes, Bu_4NI(1.36g, 0.0037mol) and benzyl bromide(6.32g, 4.39ml, 0.037mol) were added. The solution was then warmed to rt. and sit for 1 hour at this temperature. MeOH (50ml) and H_2O (150ml) was added and the mixture was extracted with Et_2O(~80ml, 3x). The combined organic phase was washed three times with saturated aqueous NaCl (50mL), dried (Na_2SO_4), and contracted *in Vacuo*. The residue was purified by flash chromatography to afford **280** (16.0g, 80%) as light yellow oil: TLC Rf=0.25 (20% EtOAc/PE). ^{1}H-NMR(C_6D_6) δ 1.60(m, 2H, H_2, H_3), 2.95(bs, 1H, -OH), 3.25(t, 2H, J=6.98Hz, H_4), 3.50(t, 2H,

J=4.30Hz, H_1), 4.30(s, 2H, -O$\underline{CH_2}$Ar),7.08-7.30(m, 5H). ^{13}C-NMR(C_6D_6) δ 26.83, 30.18, 62.35, 70.45, 72.97, 127.77, 127.464, 127.68.

4-Benzyl-butanal (281)

To a solution of 4-Benzyl-1-butanol **280** (8g, 0.048mmol) in anhydrous CH_2Cl_2 (500ml) was sequentially added PCC (52.6g, 0.244mol), Celite(52.6g), florisil(5.26g) and sodium acetate (52.6g). The reaction mixture was stirred for 30 minutes at rt. in Ar atmosphere then diluted with Et_2O (800ml) and filtered through Frorisile. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography to afford **281** (7g, 89%). TLC Rf=0.40 (20% EtOAc/PE). ^{1}H-NMR(C_6D_6) δ 1.61(m, 2H, H_3), 1.97(t, 2H, J=6.98Hz, H_2), 3.11(t, 2H, J=6.07Hz, H_4), 4.20(s, 2H, -O$\underline{CH_2}$Ar), 7.19(m, 5H, ArH), 9.34(s, 1H, H_1). ^{13}C-NMR(C_6D_6) δ 22.791, 40.828, 69.210, 72.874, 127.68, 128.00, 128.32, 200.46.

6-benzoloxy-3-hexenol (282)

To a solution of the aldehyde (1.7g, 9.6mmol) in anhydrous THF(30ml) was added dropwise vinyl magnesium bromide(1M in THF, 12.5ml, 12.5mmol) in a period of 20 min. at 0^{0}C. After an additional 30 min., saturated aqueous NH_4Cl (30ml) was added. The mixture was extracted with Et_2O (80ml, x3). The combined organic phase was washed three times with saturated aqueous NaCl solution, dried (Na_2SO_4) and contracted *in Vacuo*. The residue was purified by flash chromatography to afford **282** (1.78g, 90%): TLC R_f=0.20 (20% EtOAC/PE) ^{1}H-NMR(C_6D_6) δ 1.525-1.688 (m, 4H, H_4, H_5), 2.60(bs,

2H, -OH), 3.26(t, 2H, J=5.96Hz, H6), 3.97(q, J_1=4.45Hz, J_2=10.75Hz, 1H, H_3), 4.285(s, 2H, -OCH_2Ar), 4.95(d, 1H, J=10.4Hz, H_1), 5.21(d, 1H, J=17.19Hz, H_1), 5.76(m, 1H, H_2), 7.19(m, 5H). ^{13}C-NMR(C_6D_6) δ 26.156, 34.510, 70.508, 72.552, 72.898, 113.742, 127.78, 127.68, 128.01, 142.129. MS: m/e 207 $(M+H)^+$ for $C_{13}H_{28}O_2$.

8-benzoloxy-4-E-Octenal (284)

A round-bottom flask was charged with the allylic alcohol **282** (1.68g, 8.15mmol), n-butyl vinyl ether (20ml, 17.3mmol) and $Hg(OAc)_2$ (2.54g, 8.15mmol). The reaction mixture was refluxed for 18 h under Argon, then cooled to rt. and diluted with saturated aqueous Na_2CO_3(20ml). The reaction was extracted with CH_2Cl_2 (40ml, 3X) and the combined organic phases dried (Na_2SO_4), filtered and evaporated *in Vacuo*. The residue was purified by flash chromatography to afford **284** (1.60g, 85%): TLC R_f=0.65 (20% EtOAC/PE). ^{1}H-NMR(C_6D_6) δ 1.58(m, 2H, H_7), 1.83(t, 2H, J=6.99Hz, H_2), 2.04(q, 4H, J_1=6.08Hz, J_2=14.58Hz, H_3, H_6), 3.27(t, 3H, J=6.32Hz, H_8), 4.32(s, 2H, -O<u>CH_2</u>Ar), 5.23(m, 2H), 7.18(m, 5H, ArH), 9.28(s, 1H, H1). ^{13}C-NMR(C_6D_6) δ 25.337, 29.440, 29.929, 43.384, 69.651, 72.942, 127.68, 127.66, 128.49, 131.13, 200.211. MS: m/e 250 $(M+NH_4)^+$ for $C_{15}H_{20}O_2$; MS: m/e 233 $(M+H)^+$ for $C_{15}H_{20}O_2$.

Methyl 10-benzyloxy-4E, 8E-decadieneoate (279a).

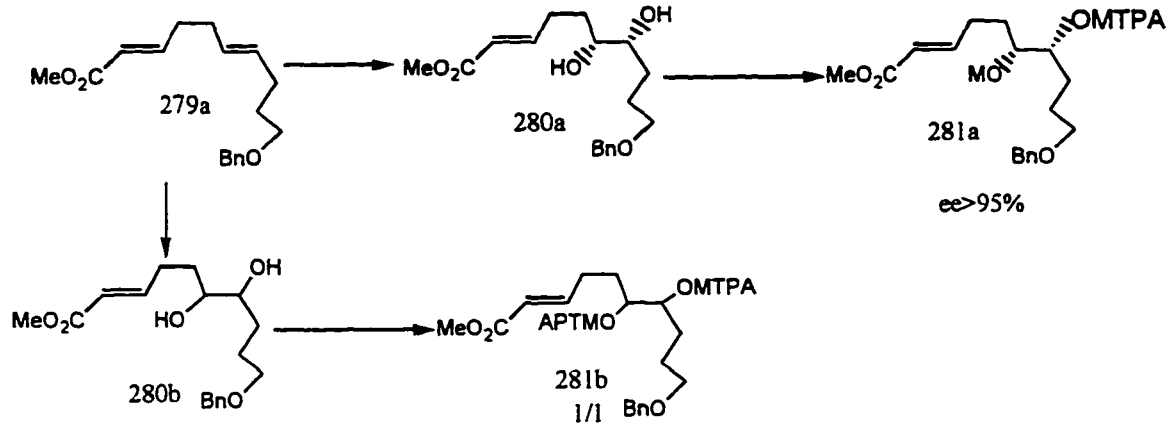
To a solution of aldehyde **284** (1.2g, 8.6 mmol) in CH_3CN (80 ml) was added (Carbomethoxymethyl) triphenyl phosphonium bromide (3.91g, 11.7mmol). The reaction mixture was heated at 60^{0}C for 40 min., then filtered, and the filtrate was concentrated *in*

Vacuo. The residue was purified by flash chromatography to afford **279a** (1.29g, 89%) and **279b** (109mg, 8.1%).

Ester 279a: TLC R_f=0.55 (10% EtOAC/PE), ^{1}H-NMR(C_6D_6) δ 1.55(m, 2H), 1.87(bs, 4H), 2.05(q, 2H, J=6.31Hz), 3.29(t, 2H, J=6.35Hz, H_{10}), 3.42(s, 3H, -O$\underline{CH_3}$), 4.34(s, 2H, -O$\underline{CH_2}$Ar), 5.23(m, 2H, H_6, H_7), 5.82(d, 1H, J=15.59Hz, H_3), 7.00(m, 1H, H_2), 7.18(m, -Ar). ^{13}C-NMR(C_6D_6) δ 29.446, 29.982, 31.206, 32.174, 50.854, 69.674, 72.943, 121.72, 129.158, 131.188, 148.543, 166.428. MS: m/e 306 $(M+NH_4)^+$ for $C_{18}H_{24}O_3$; MS: m/e 289 $(M+H)^+$ for $C_{18}H_{24}O_3$ Anal. calcd. for $C_{18}H_{22}O_3$: C:74.96, H: 8.38. Found: C: 74.83, H: 8.90

Ester 279b: TLC R_f=0.50 (10% EtOAC/PE), ^{1}H-NMR(C_6D_6) δ 1.60(m, 2H, H_9), 2.04(m, 4H, H_5, H_8), 2.78(q, 2H, J=7.21Hz, H_4), 3.28(t, J=6.37Hz, H_{10}), 3.36(s, 3H, -C(O)O$\underline{CH_3}$), 4.32(s, 2H, -O$\underline{CH_2}$Ar) 5.34(m, H6, H7), 5.78(d, J=9.49, 1H), 5.87(m, 1H, H_3), 7.18(m, 5H, -ArH), ^{13}C-NMR (C_6D_6) δ 29.793, 30.182, 30.727, 30.824, 32.870, 51.188, 70.475, 73.642, 120.597, 128.207, 128.689, 129.167, 130.378, 131.684, 140.253, 150.544, 167.003. MS: m/e 306 $(M+NH_4)^+$ for $C_{18}H_{24}O_3$, MS: m/e 289 $(M+H)^+$ for $C_{18}H_{24}O_3$.

IV.3.3 Preparation of bis-MTPA Esters 281a and 281b



(+)-(6R, 7R)-Methyl-10-benzoxoxyl-6,7-dihydroxy-2-E-decenoate 280a

To a solution of diene **279a** (1.0g, 3.46mmol) in t-BuOH (17.3ml), H_2O (17.3 mL) were added AD-mix-β (4.84g) and $MeSO_2NH_2$ (3.29mg). The reaction was stirred at 0^0C for 3 d, at which time $Na_2S_2O_3$ (300mg) was added , followed by extraction with CH_2Cl_2 (3X20mL). The combined organic phase was dried (Na_2SO_4) and contracted *in vacuo*. Purification of the residue by flash chromatography gave the desired diol alkene **280a** (1.0g, 90%). TLC Rf=0.15 (30% EtOAc/PE). $[\alpha]^{25}_D$= +15.47^0(c 0.19, $CHCl_3$); ^{1}H-NMR(C_6D_6) δ1.289-1.80(m, 6H, H_5,H_8, H_9), 2.046-2.23(m, 2H, H_4), 3.15-3.404(m, 2H, H_6, H_7), 3.42(s, 3H. -O<u>CH$_3$</u>), 4.29(s, 2H, -O<u>CH$_2$</u>Ar), 5.88(d, 1H, J=15.64Hz, H_3), 7.033-7.307(m, 6H, H_2, ArH). ^{13}C-NMR(C_6D_6) δ 26.200, 28.363, 30.822, 31.892, 50.632, 70.249, 72.829, 73.465, 74.023, 121.202, 149.123, 166.507. Anal. calcd for $C_{18}H_{26}O_5$: C: 67.05, H: 8.12. Found: C: 66.73, H: 8.38.

(d,l)-Methyl-10-benzoxoxyl-6,7-dihydroxyl-2-E-decenoate 280b

To a solution of diene **279a** (110mg, 0.38 mmol) in acetone (12 mL) was added N-methylmorpholine-N-Oxide (0.066 mL, 60wt% in water) and Osmium tetraoxide(0.28 mL, 2.5 wt% in t-butanol, 0.0228mmol). The reaction mixture was stirred at rt. for 30 min., at which time 1N $Na_2S_2O_3$ (0.06 mL) was added and stirring continued for an additional 30 min., the mixture was diluted with H_2O (5mL), followed by extraction with EtOAc (3X10mL). The organic phase was dried over Na_2SO_4 and contracted *in Vacuo*. Purification of the residue by flash chromatography (4X15 cm silica gel, 30% EtOAC/PE) gave the desired diol alkene **280b** (116mg, 95%). TLC Rf=0.15 (30% EtOAc/PE). ^{1}H-NMR(C_6D_6) δ1.289-1.80 (m, 6H, H_5,H_8, H_9), 2.046-2.23 (m, 2H, H_4), 3.15-3.404(m, 2H, H_6, H_7), 3.42(s, 3H. -O<u>CH_3</u>), 4.29(s, 2H, -O<u>CH_2</u>Ar), 5.88(d, 1H, J=15.64Hz, H_3), 7.033-7.307(m, 6H, H_2, ArH). ^{13}C-NMR(C_6D_6) δ 26.200, 28.363, 30.822, 31.892, 50.632, 70.249, 72.829, 73.465, 74.023, 121.202, 149.123, 166.507.

(+)-(6R, 7R)-Methyl-10-benzoxoxyl-6,7-dihydroxyl-2-E-decenoate 281a -bis-MTPA esters

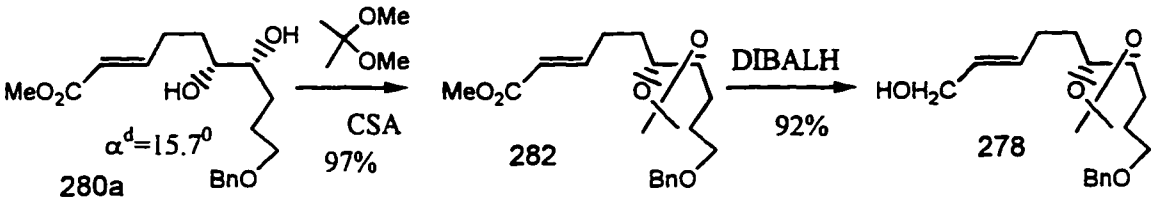
To a stirred solution of diol **280a** (25 mg, 0.077mmol) in anhydrous CH_2Cl_2(10 mL) at rt. was sequentially added anhydrous pyridine(5 mL), 4-(dimethylamino) pyridine (30 mg, 0.19 mmol), and (R)-MTPA-Cl (88 mg, 0.348 mmol). The mixture was allowed to sit for 1 h at rt. , then diluted with saturated $NaHCO_3$(~5 mL) and Et_2O(5 mL). This mixture was stirred for 30 min. to allow for hydrolysis of the excess MTPA-Cl. The organic phase was separated, and the aqueous phase extracted with Et_2O(2X5mL). The

combined organic phase was washed three times with 5% aqueous $NaHSO_4$ and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by flash chromatography gave the desired MTPA ester **281a** (47mg, 82%). TLC R_f=0.20 (30% EtOAc/PE). ^{1}H-NMR($CDCl_3$) δ 0.826-2.08(m, 8H, H4, H5, H_8, H_9), 3.40(m, 2H, H_{10}), 3.47(s, 3H. -O$\underline{CH_3}$), 3.49(s, 3H, -O$\underline{CH_3}$), 3.73(s,3H, -$CO_2\underline{CH_3}$). 4.44(s, 2H, -O$\underline{CH_2}$Ar), 5.16(m, 2H, H_6, H_7), 5.68(d, 1H, J=15.73Hz, H_3), 6.73(m, 1H, H2), 7.25-7.57(m, 5H, -ArH). ^{13}C-NMR(C DCl_3) δ 25.92, 27.00, 27.44, 28.23, 51.24, 55.27, 69.25, 72.83, 74.31, 74.90, 212.84, 126.998, 127.057, 127.458, 127.523, 128.190,128.259, 129.503,131.794,138.110, 146.222, 165.759, 165.828, 166.375. MS: m/e 772 $(M+NH_4)^+$ for $C_{38}H_{40}O_9F_6$.

(d,l)-Methyl-10-benzoxoxyl-6,7-dihydroxyl-2-E-decenoate 281b-bis-MTPA esters

The procedure for the preparation of Mosher ester **281a** was applied to diol **280b** (8 mg, 0.025mmol) in anhydrous CH_2Cl_2(5 mL). Purification of the residue by flash chromatography gave the MTPA ester **281b** (16 mg, 86%). TLC R_f=0.20 (30% EtOAc/PE). ^{1}H-NMR($CDCl_3$) δ 0.826-2.08 (m, 8H, H4, H5, H_8, H_9), 3.40(m, 8H, H_{10}, 2X-O$\underline{CH_3}$), 3.65, 3.66(both s,2/3H ea., -$CO_2\underline{CH_3}$). 4.36, 4.37 (booth s, 1H each, -O$\underline{CH_2}$Ar), 5.16(m, 2H, H_6, H_7), 5.62(d, 1H, J=15.47Hz, H_3), 6.69(m, 1H, H_2), 7.25-7.57(m, 5H, -ArH). MS: m/e 772 $(M+NH_4)^+$ for $C_{38}H_{40}O_9F_6$

IV.3.4 Preparation of Alkene precursor 278



Methyl-10-benzoxoxyl-6R,7R-isopropylidenyloxy-2-E-decenoate 282

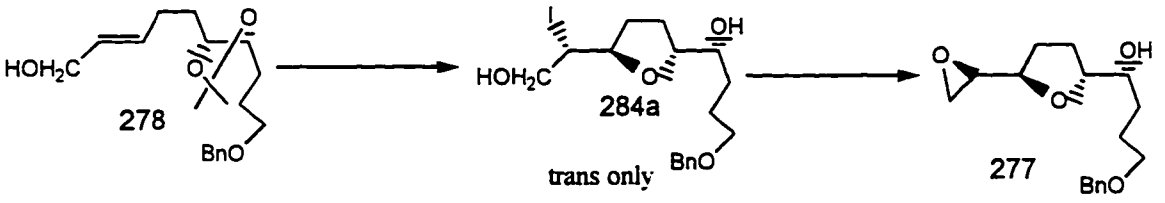
The procedure for the preparation of isopropylidene derivative **216** (Part 3) was applied to the diol **280a** (400mg, 1.24mmol) in anhydrous CH_2Cl_2 (20mL). Isopropylidene **282** (419mg, 97%) was obtained after purification by flash chromatography. TLC R_f=0.80 (10% EtOAC/PE); $[\alpha]^{25}_D$= +23.31^0(c 0.38, $CHCl_3$), ^{1}H-NMR(C_6D_6) δ 1.263-2.105(m, 8H, H4, H5, H8, H9), 1.34(d, 6H, J=2.25Hz, -C($\underline{CH_3}$)$_2$), 3.417(s, 3H, -CO$_2\underline{CH_3}$), 3.22-3.52(m, 4H, H6, H7, H10), 4.318(s, 3H, -O$\underline{CH_2}$Ar),5.84(d, 1H, J=15.64Hz, H3), 6.97(d, 1H, J=15.69Hz, H2), 7.18(m, 5H, ArH). ^{13}C-NMR(C_6D_6) δ 26.616, 27.226, 28.683, 29.508, 31.125, 50.571, 69.818, 72.704, 80.049, 80.580, 107.834,121.371, 148.198, 166.151. MS: m/e 380 $(M+NH_4)^+$ for $C_{21}H_{30}O_5$, MS: m/e 363 $(M+H)^+$ for $C_{21}H_{30}O_5$.

10-benzoxoxyl-6R,7R-isopropylidenyoxyl-2-E-decene-1-ol 278

To a solution of the ester **282** (450mg, 1.29mmol) in anhydrous CH_2Cl_2(20ml) was slowly added DIBALH (1M in heptane, 2.85ml, 2.85mmol) at ~-42^{0}C. After stirring at this temperature for 1.5 h, MeOH (5ml) was added, and the mixture was then warmed

to rt., poured into potassium sodium tartrate (20ml). The mixture was stirred at rt. for an additional 1 h, then extracted with CH_2Cl_2 (20ml, 3X). The combined organic layers was washed with saturated $NaHCO_3$ (15ml), brine(15ml), dried (Na_2SO_4) and concentrated *in Vacuo*. The residue was purified by flash chromatography to afford the isopropylidene alkene **278** (380mg, 92%). $[\alpha]^{25}_D$= +20.4^0(c 0.20, $CHCl_3$), TLC R_f=0.20 (30% EtOAC/PE); ^{1}H-NMR(C_6D_6) δ 0.271-2.271(m, 8H, H_4, H_5, H_8, H_9), 1.393(s, 6H, -C($\underline{CH_3}$)$_2$), 3.35(m, 2H, H_{10}), 3.55(m, 2H, H_6, H_7), 3.86(s, 2H, H_1), 4.312(s, -O$\underline{CH_2}$Ar), 5.53(m, 2H, H_2, H_3), 7.20(m, 5H, -ArH). ^{13}C-NMR(C_6D_6) δ 26.909, 27.599, 29.171, 29.886, 32.809, 63.343, 70.159, 72.964, 80.669, 81.019, 108.057, 130.109. MS: m/e 335 $(M+H)^+$ for $C_{18}H_{24}O_3$. Anal. calcd for $C_{20}H_{30}O_4$: C: 71.81, H:9.05. Found: C: 71.93, H: 9.05.

IV.3.5 Iodocyclization and Preparation of Epoxide Synthon 277



(+)-(2S, 3R, 6R, 7R)-10-benzyloxy-7-hydroxy-2-iodo-3,6-epoxy-1-hydroxy-decane 284a

Isopropylidene alkene **278a** (120mg, 0.359mmol) in CH_3CN (10mL) was subjected to the general iodocyclization procedure (I.4.9) using IDCP (420mg, 0.89mmol). The desired trans-THF **284a** (138mg, 91%) was obtained after purification

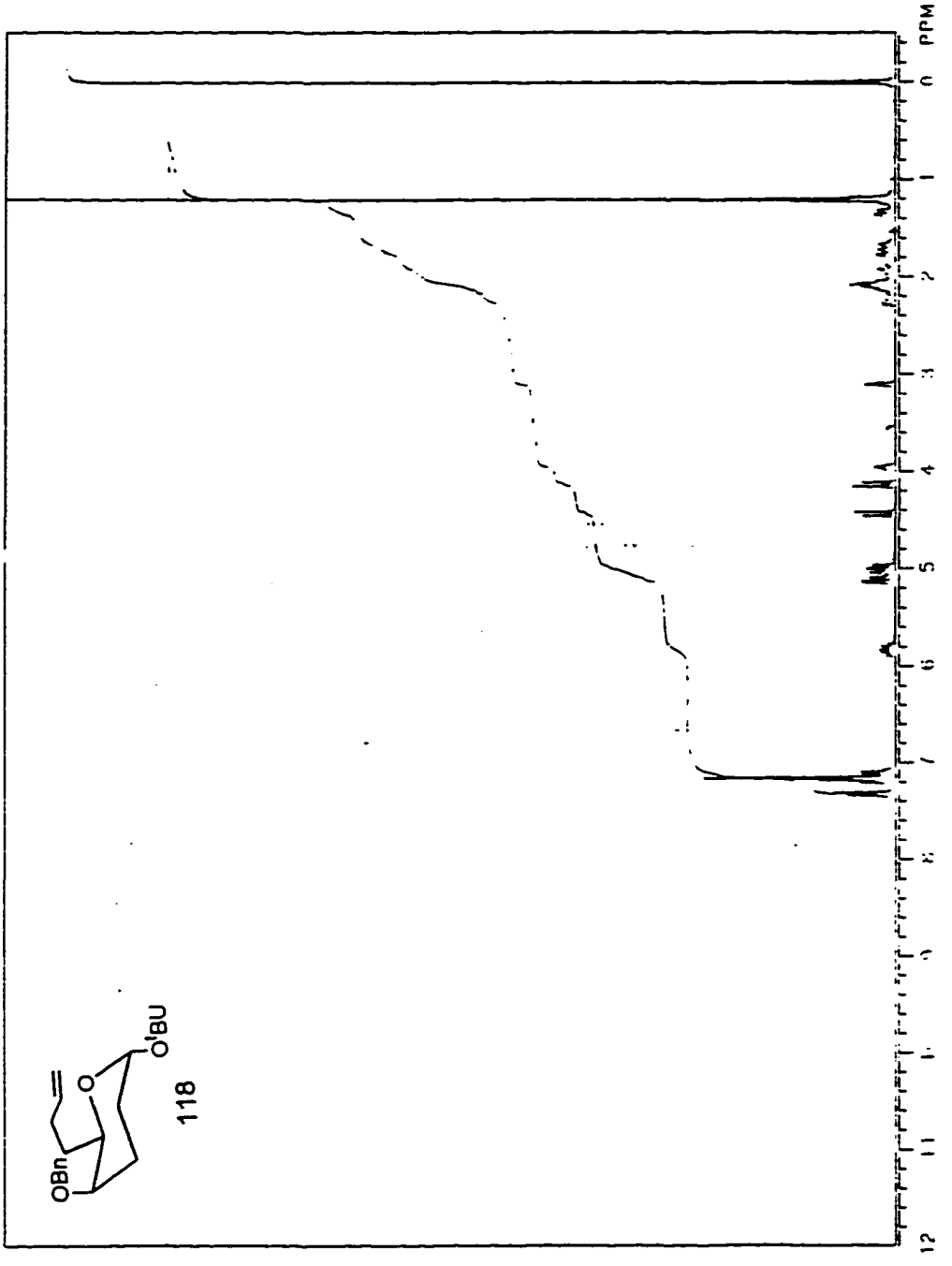
by flash column chromatography. TLC R_f=0.20(30% EtOAc/PE), $[\alpha]^{25}_D$= +11.25°(c 0.16, $CHCl_3$), ^{1}H-NMR(C_6D_6) δ 0.832-2.02 (m, 8H, H_3, H_4, H_8, H_9), 2.94 (bs, 1H, -OH), 3.305(m, 3H, H_7, H_{10}), 3.64-4.03(m, 5H, H_1, H_2, H_3, H_6), 4.32(s, 2H, -O<u>CH_2</u>Ar), 7.25(m, 5H, -ArH). ^{13}C-NMR(C_6D_6) δ 26.440, 27.997, 30.782, 34.013, 40.974, 67.192, 70.429, 73.010, 73.593, 81.712, 84.105. MS: m/e 438 $(M+NH_4)^+$ for $C_{17}H_{25}O_4I$, MS: m/e 421 $(M+H)^+$ for $C_{17}H_{25}O_4I$. Anal. calcd. for $C_{17}H_{25}O_4I$: C: 48.56, H:6.00. Found: C: 48.57, H:6.29.

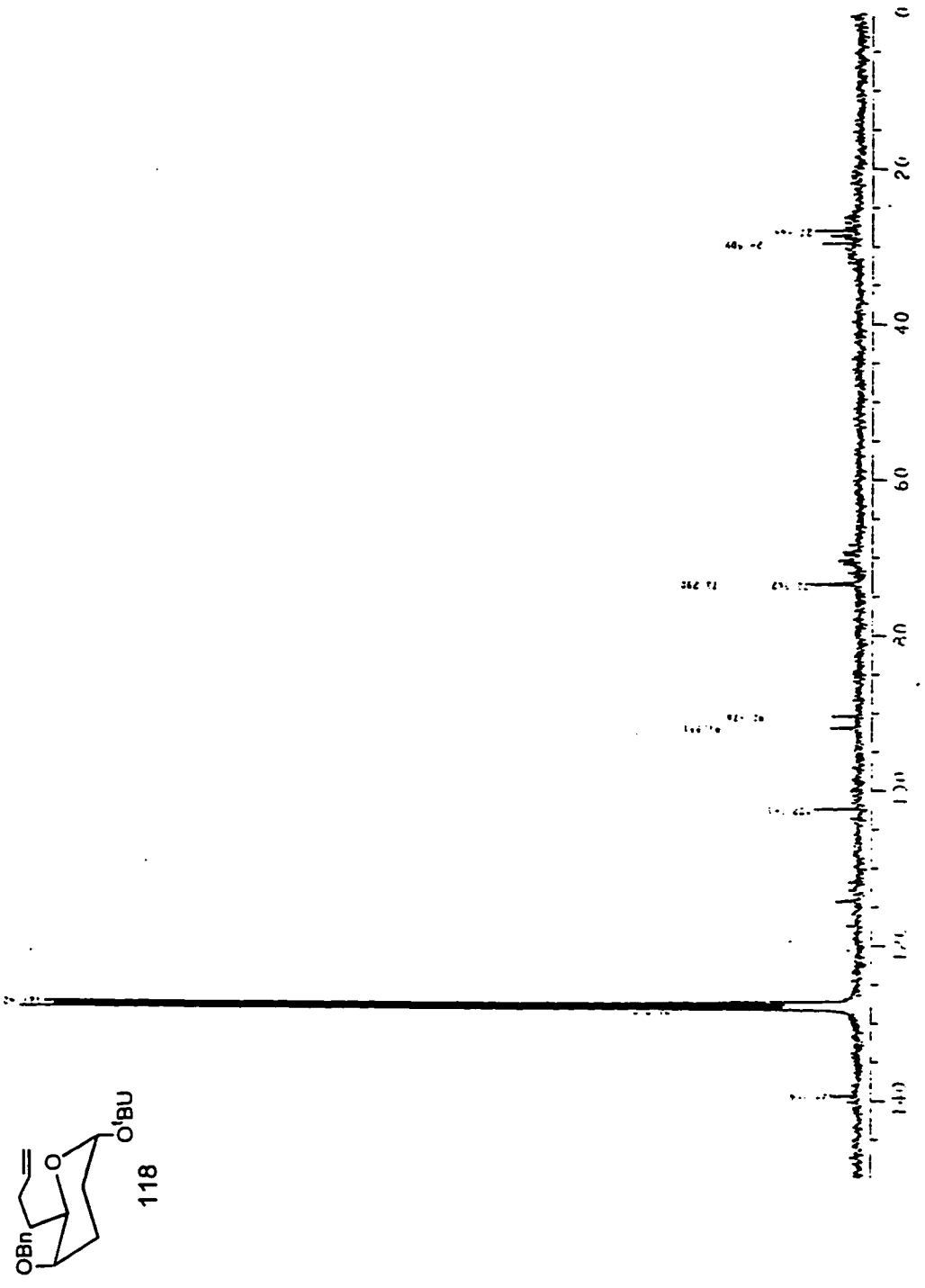
(2R, 3R, 6R, 7R)-10-benzoxyloxy-7-hydroxy-1,2:3,6-diepoxydecane 277

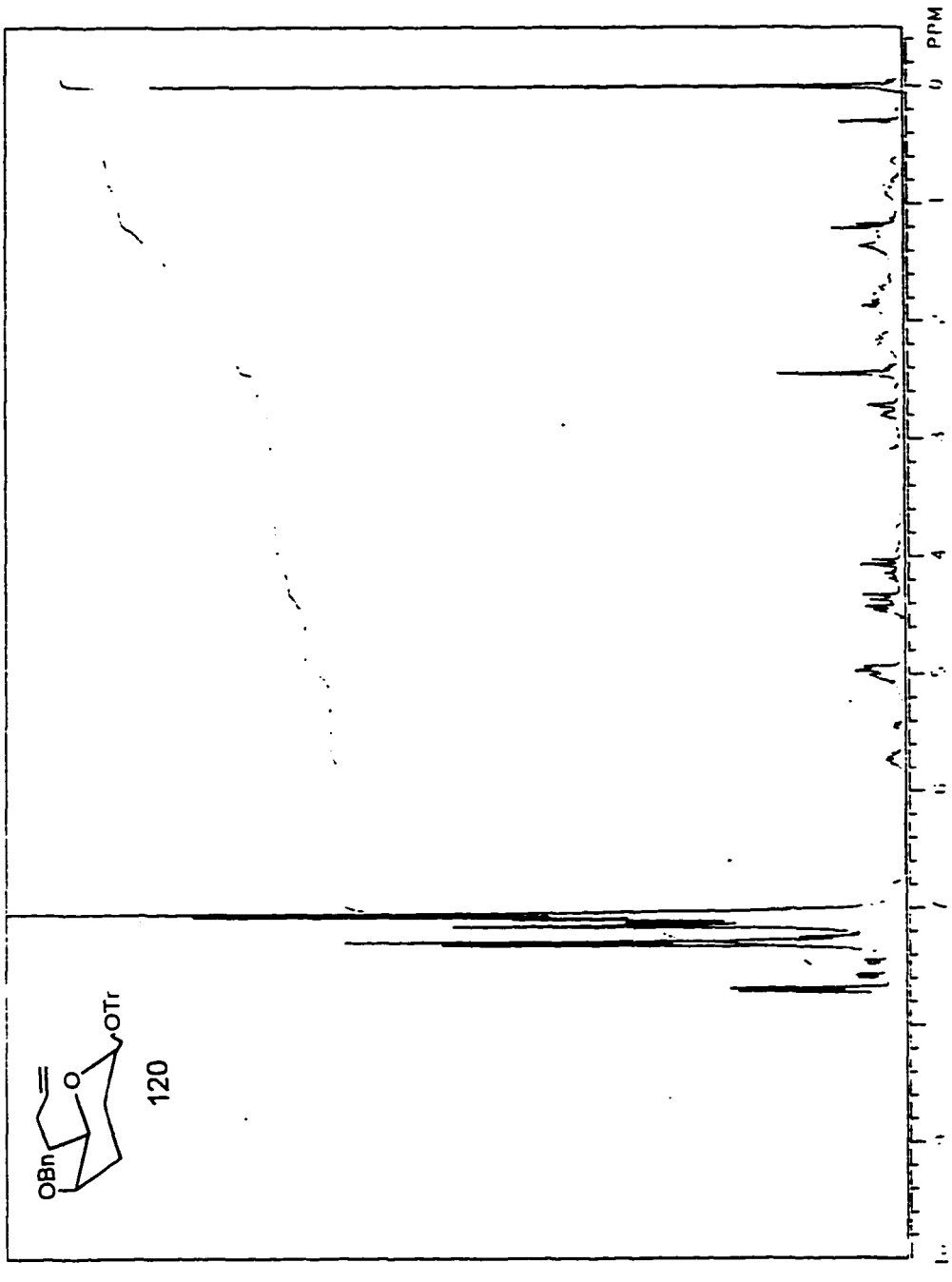
To a solution of compound **284a** (50mg, 0.12mmol) in MeOH (5mL) was added solid K_2CO_3 (500mg). The reaction mixture was stirred for 5 minutes at rt., then diluted with water (5 mL) and extracted with CH_2Cl_2 (3X5mL). The combined organic phase was dried(Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography(2X4cm silica gel, 30%EtOAc/PE) to afford compound **277** (33mg, 94%): TLC R_f=0.25 (30%EtOAc/PE); $[\alpha]^{25}_D$= +13.11°(c 0.18, $CHCl_3$), ^{1}H-NMR(C_6D_6) δ 1.209-1.965 (m, 8H, H_4, H_5, H_8, H_9), 2.38 (m, 2H,, H_1), 2.59 (m, 1H, H_2), 3.26(m, 1H, H_7), 3.38(m, 2H, H_{10}), 3.48(m, 1H, H_3), 3.67(m, 1H, H_6), 4.29(Abq, 2H, δΔ =0.08ppm, J=12.97, -O<u>CH_2</u>Ar), 7.21(m, 5H, ArH). ^{13}C-NMR(C_6D_6) δ 26.511, 28.109, 29.260, 30.848, 43.336, 53.846, 70.493, 73.670, 78.792, 83.555. MS: m/e 310 $(M+NH_4)^+$ for $C_{17}H_{24}O_4$, HRMS calcd for $C_{17}H_{24}O_4$ $(M+H)^+$ 293.175285, found 293.175800. Anal. calcd for $C_{17}H_{24}O_4$: C: 69.84, H: 8.27. Found: C: 68.99, H: 8.27.

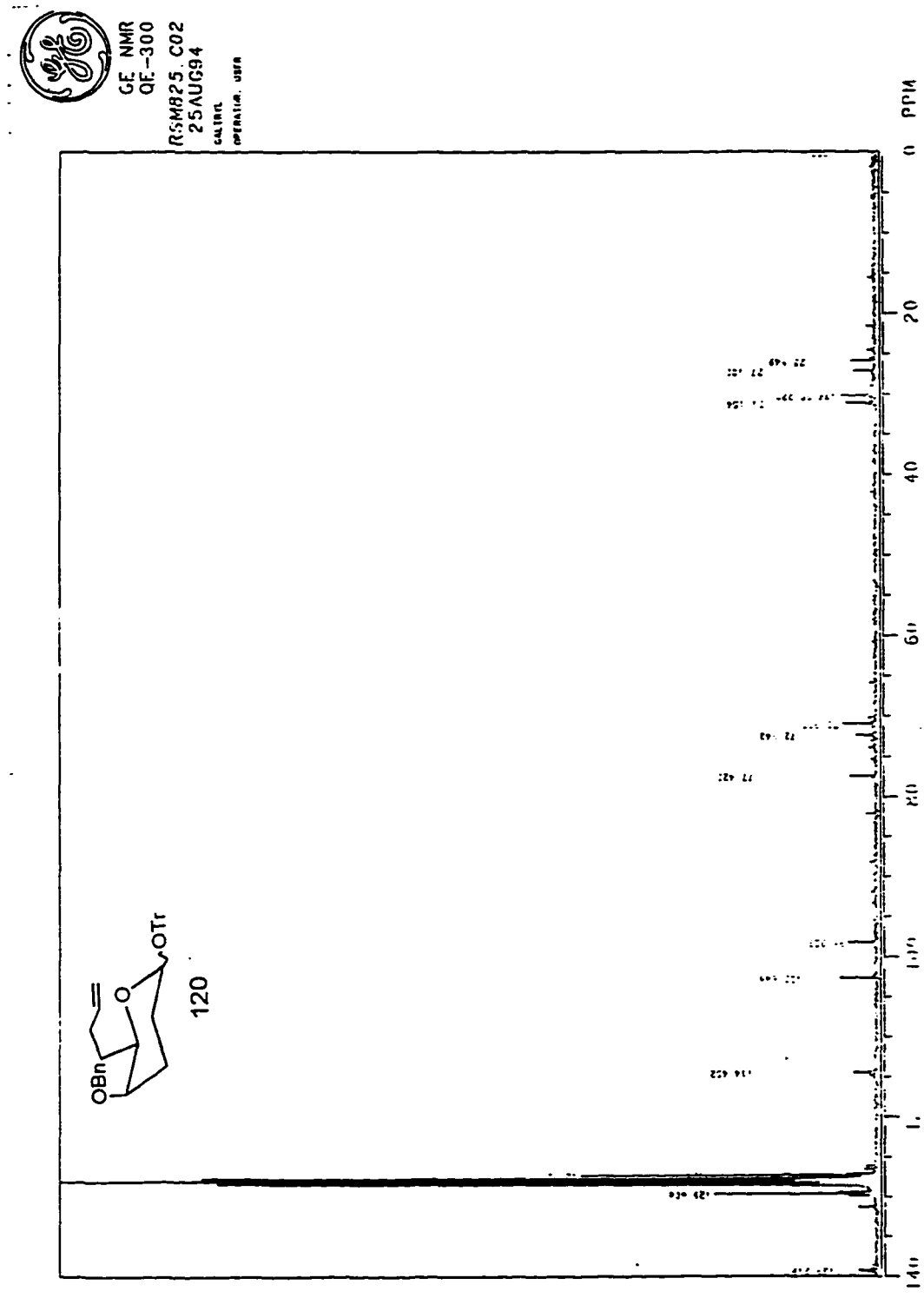
Appendix 1

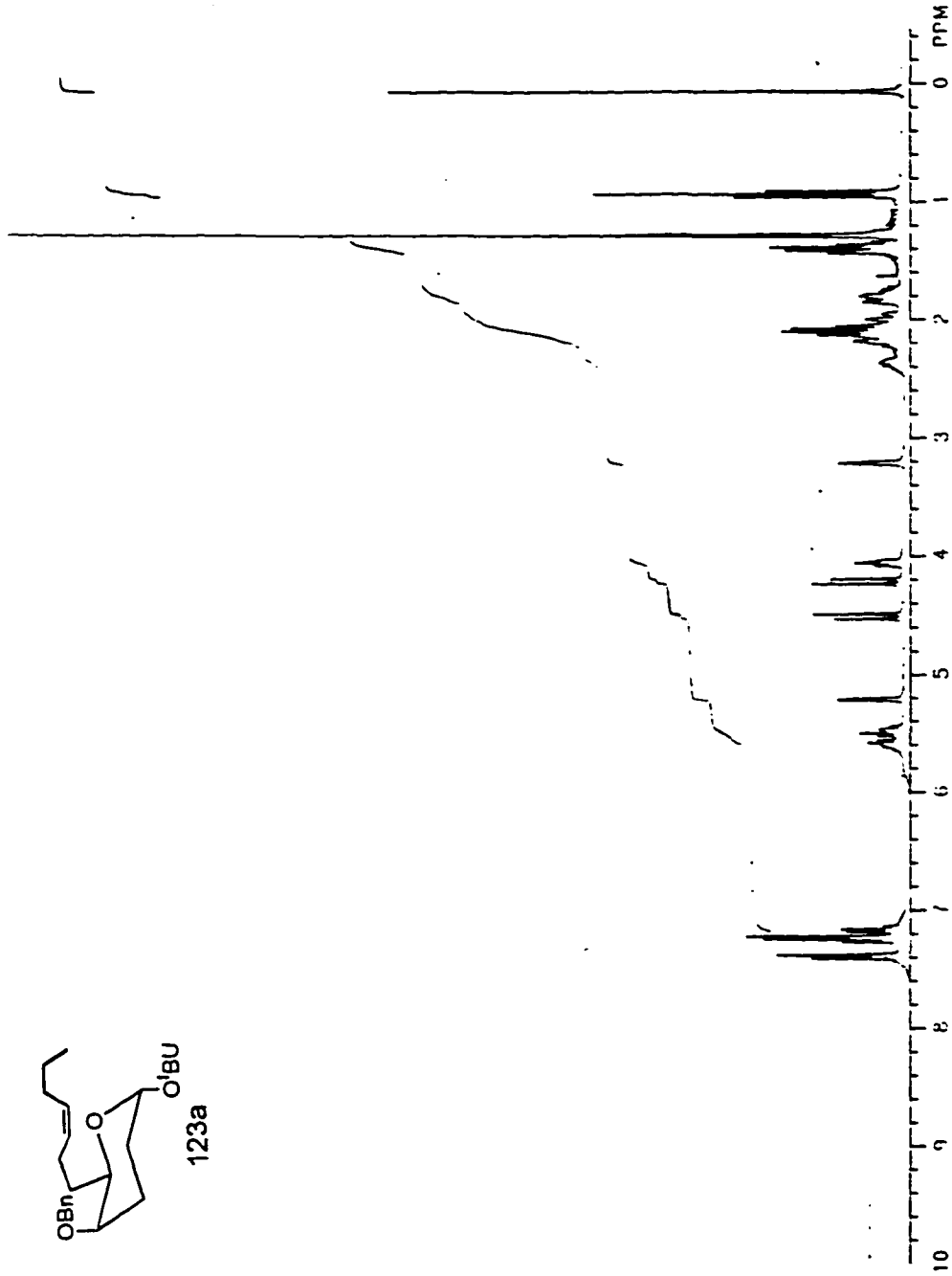
^{1}H and ^{13}C NMR of 2,3-Dideoxy Pyranosides and THF's



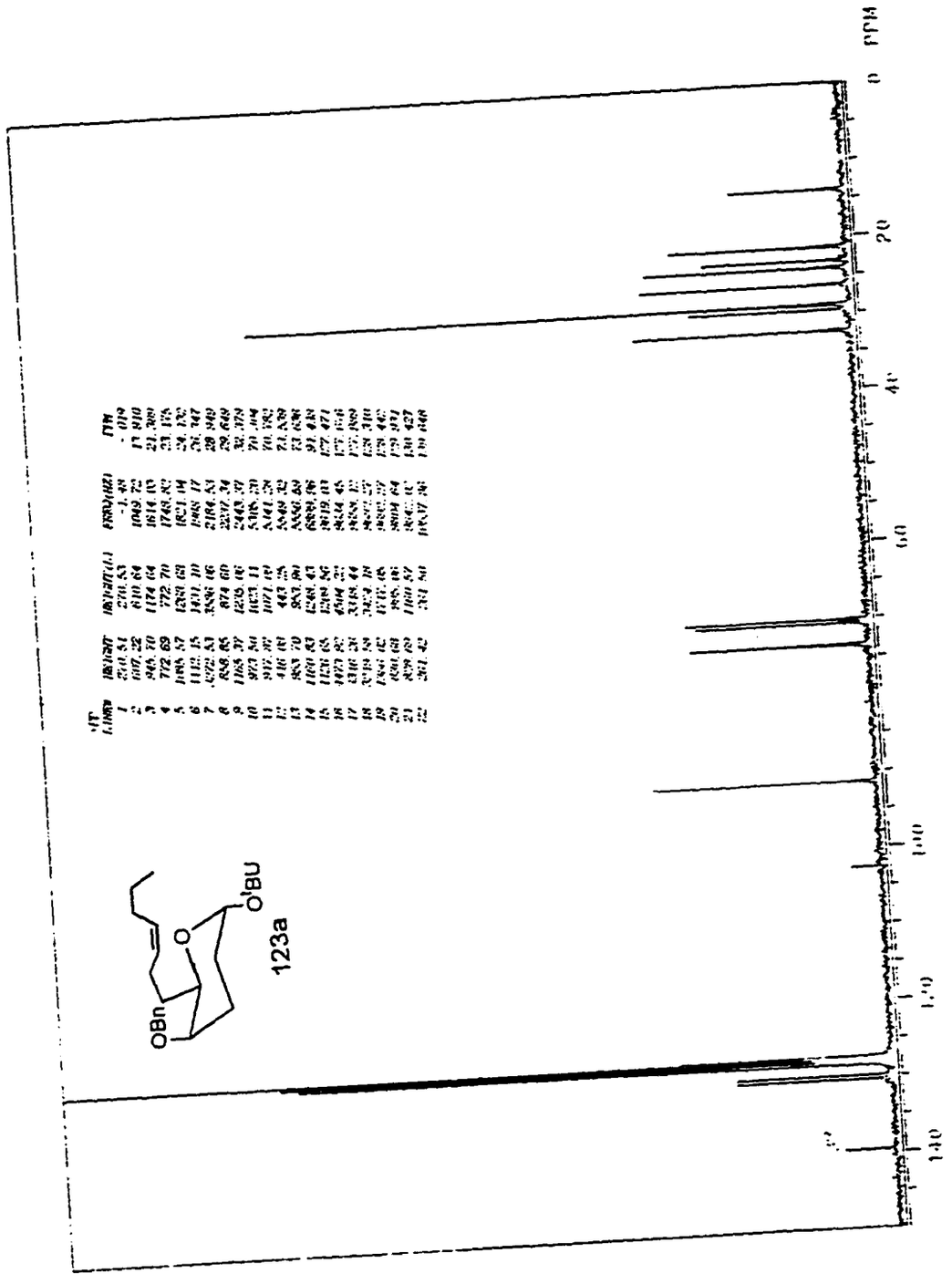


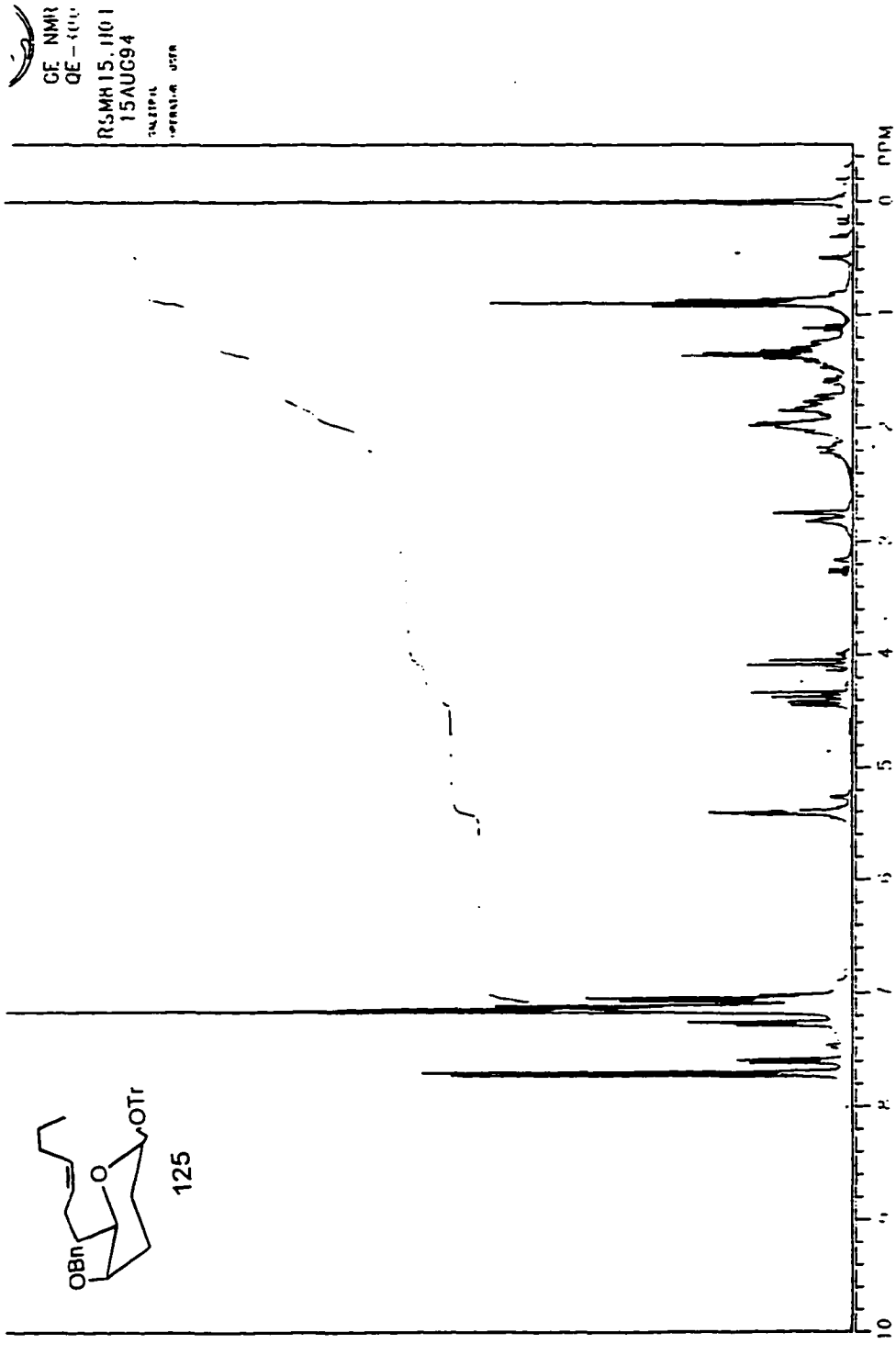


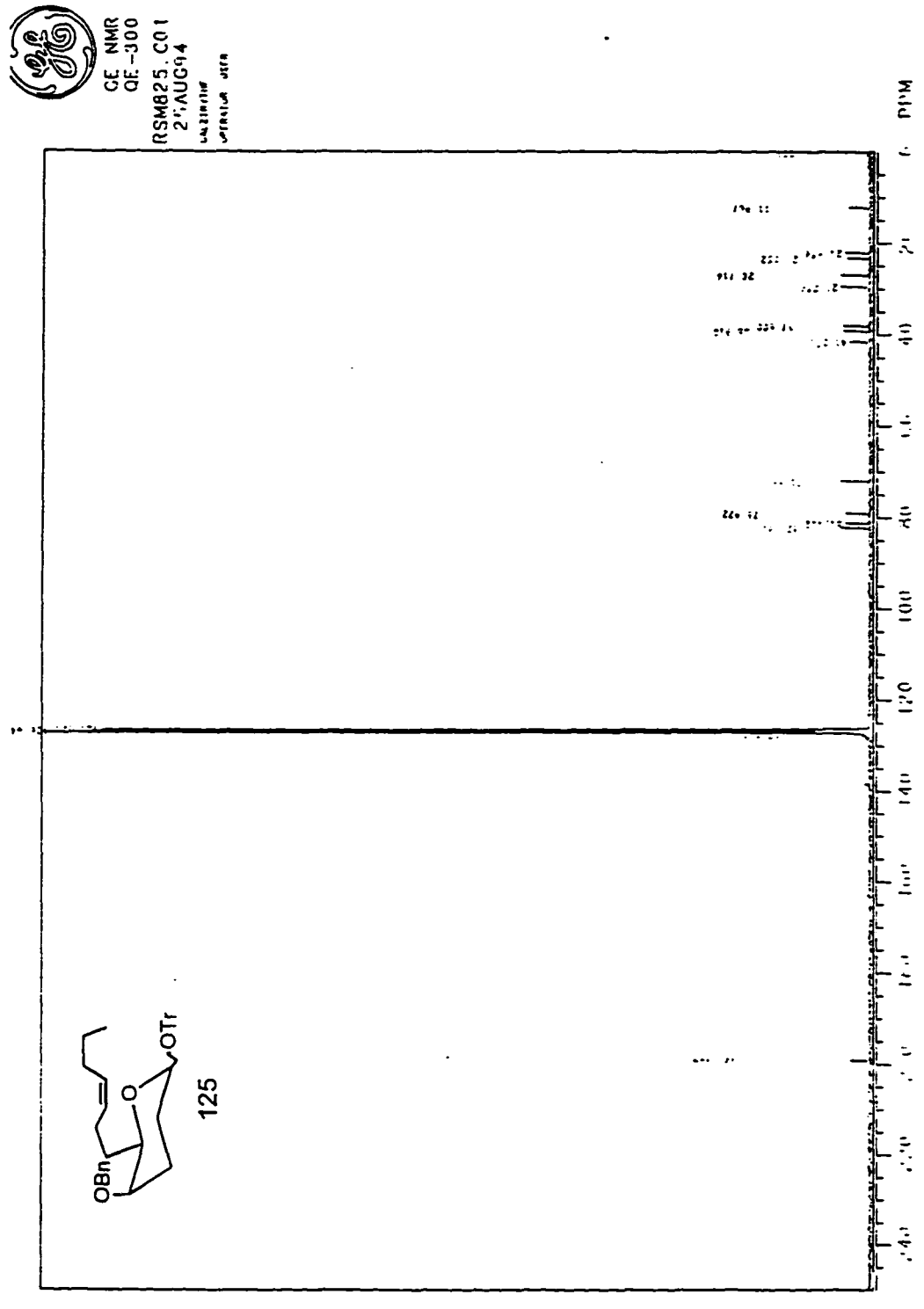


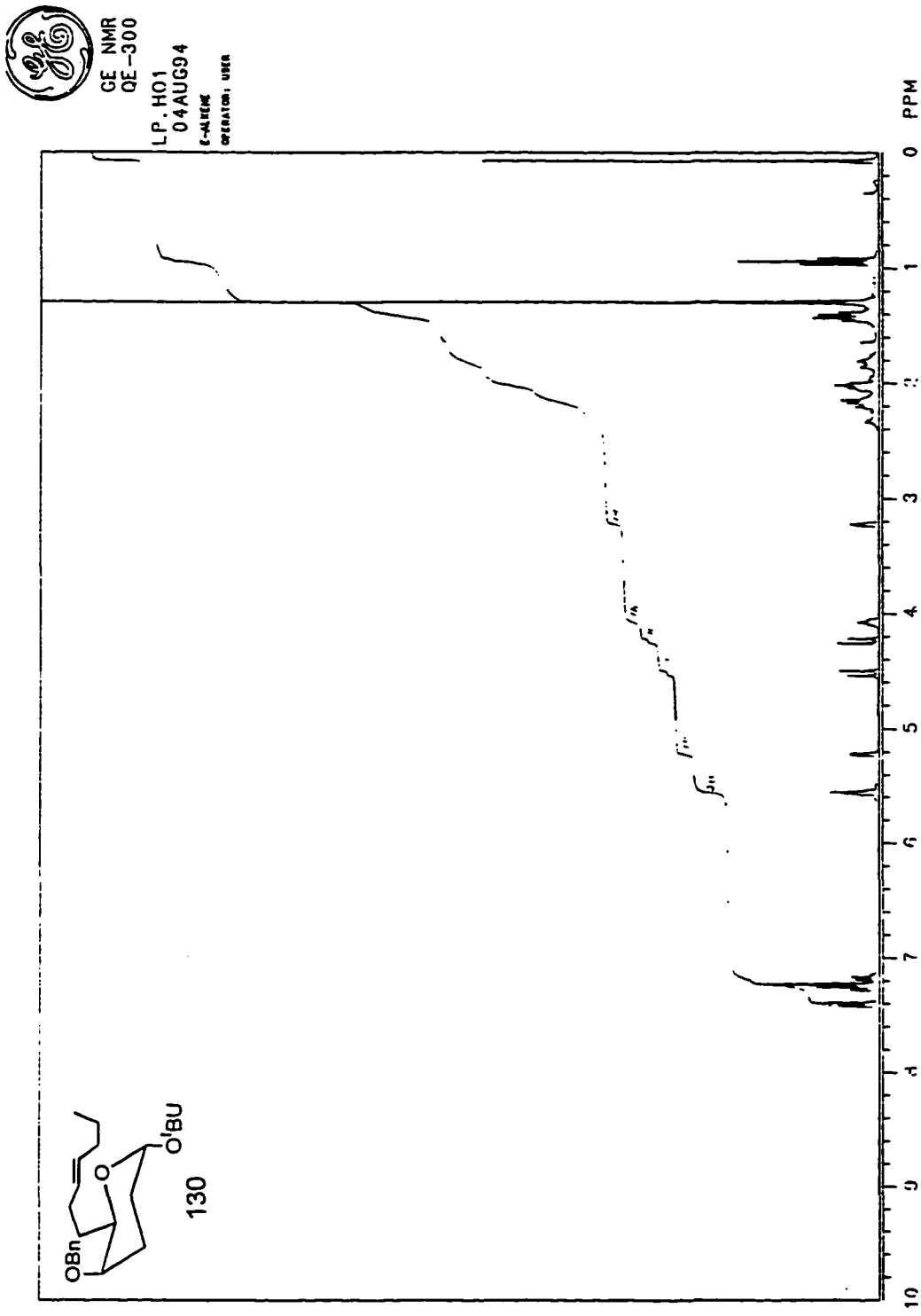


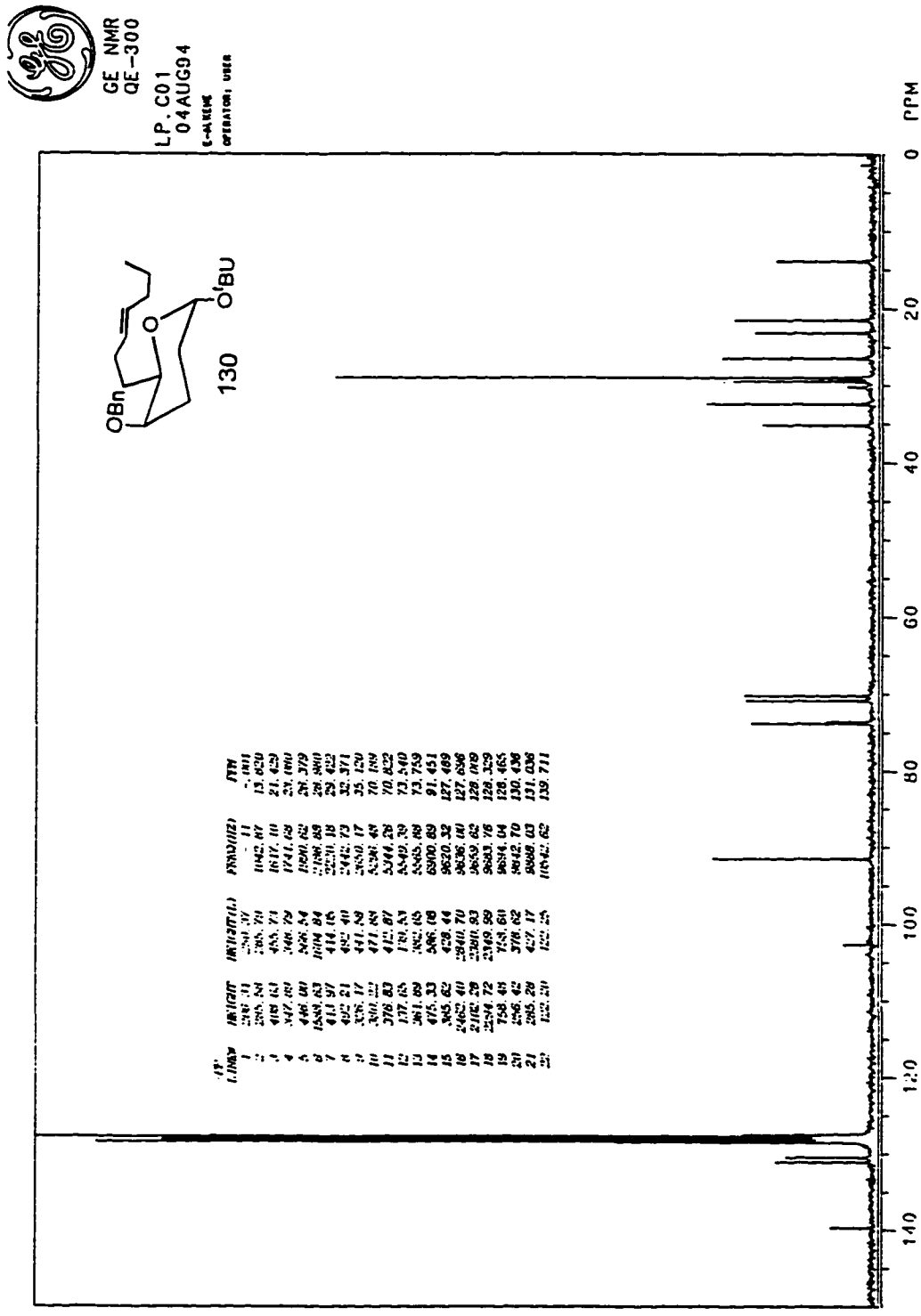
123a

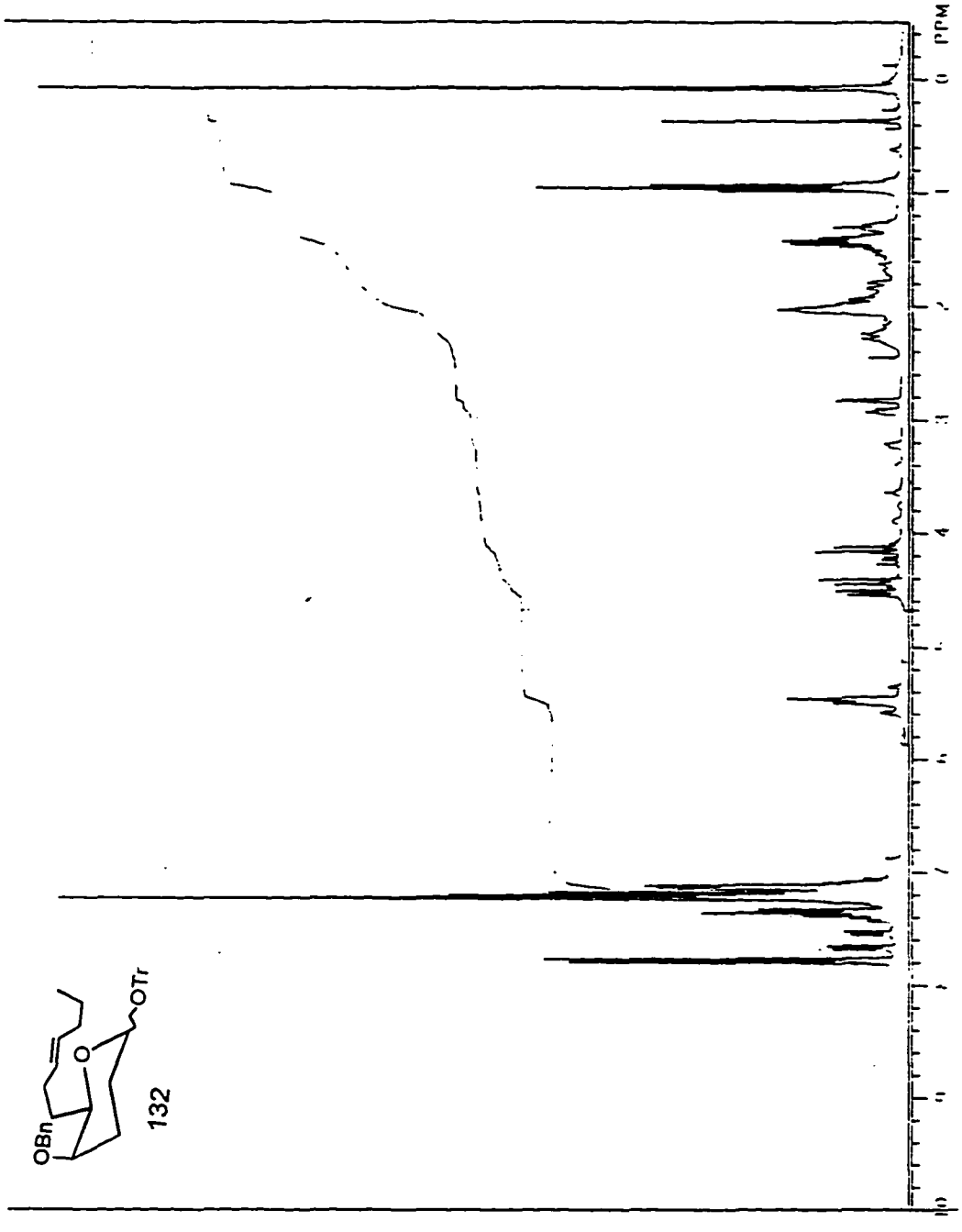


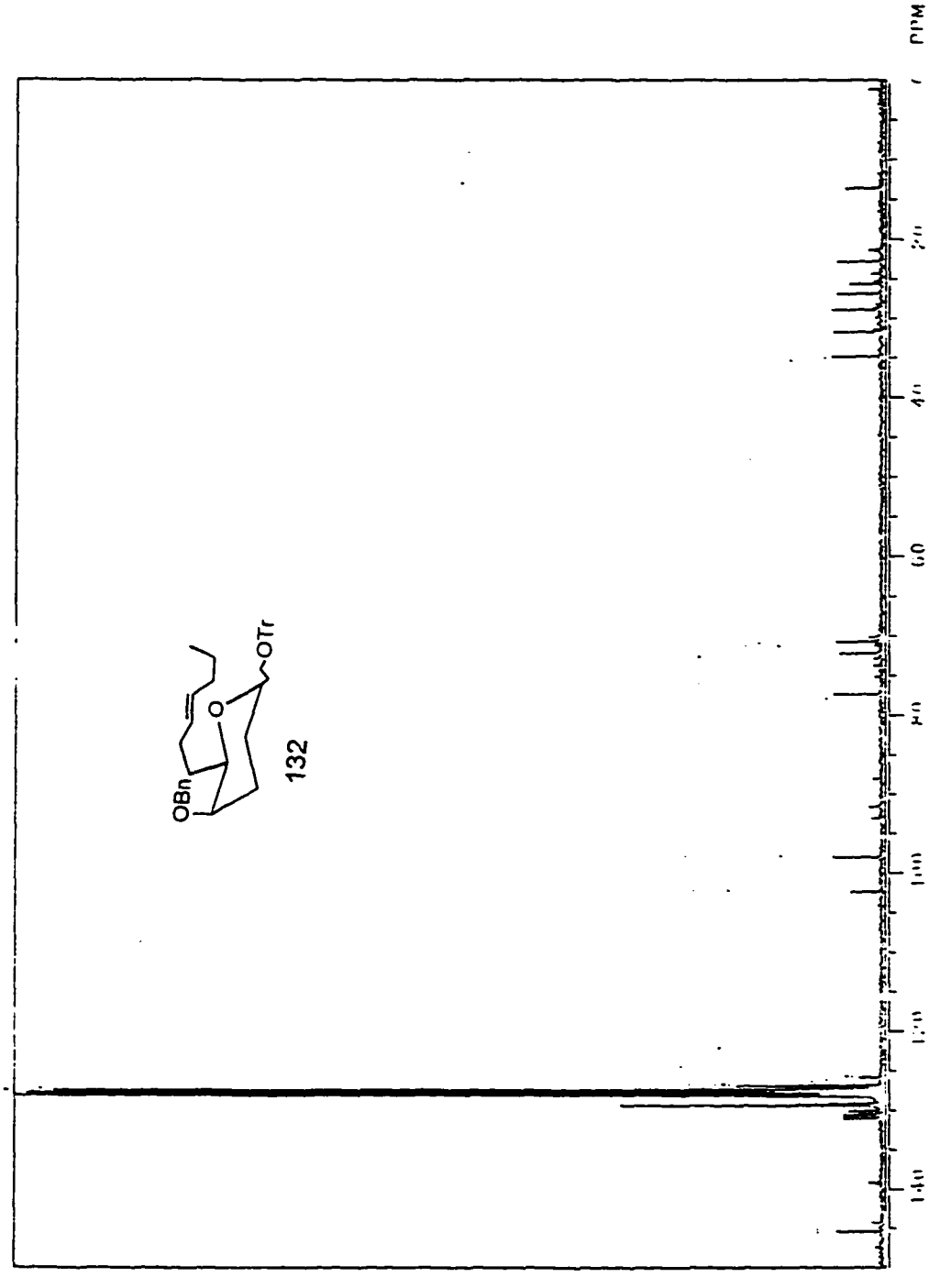


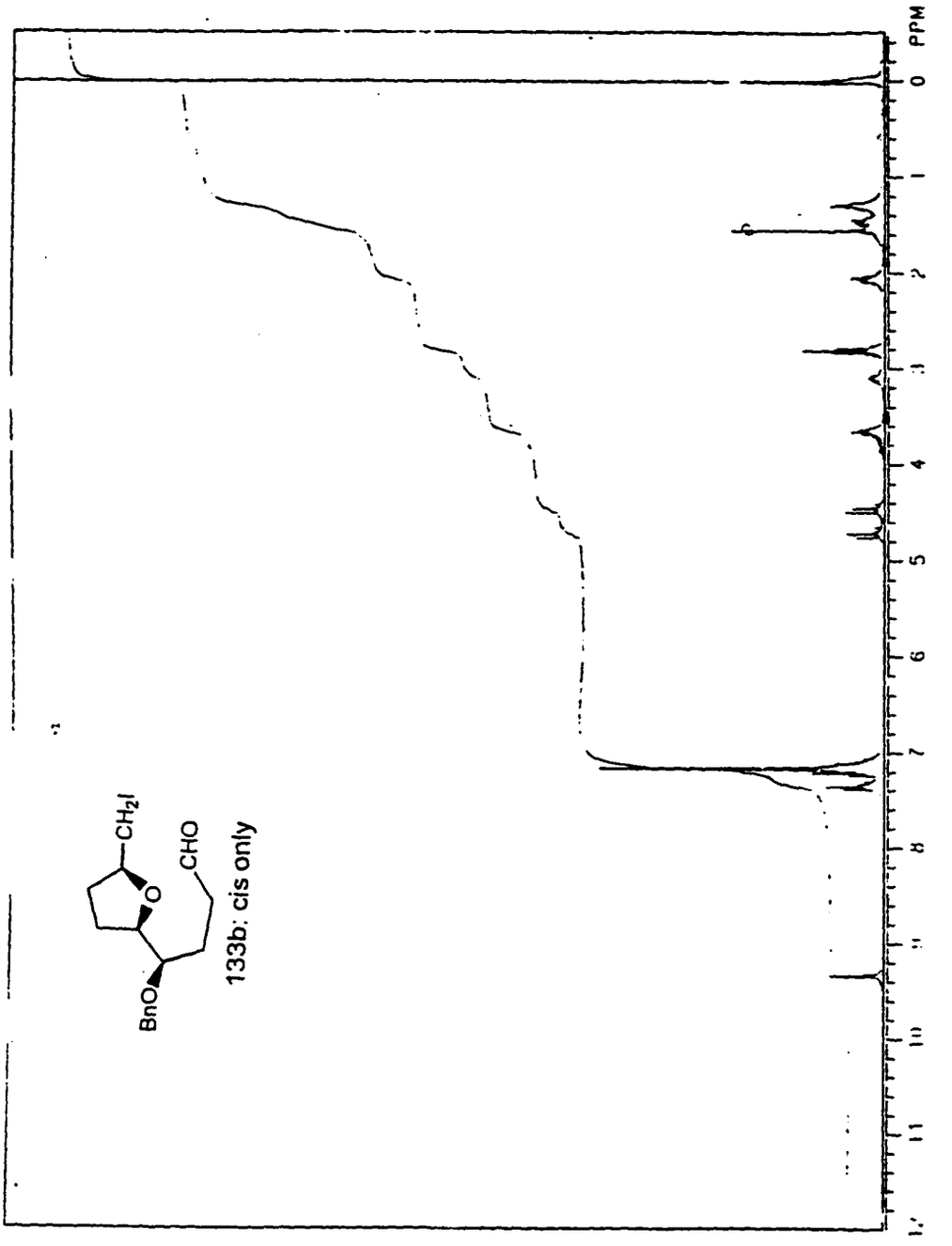


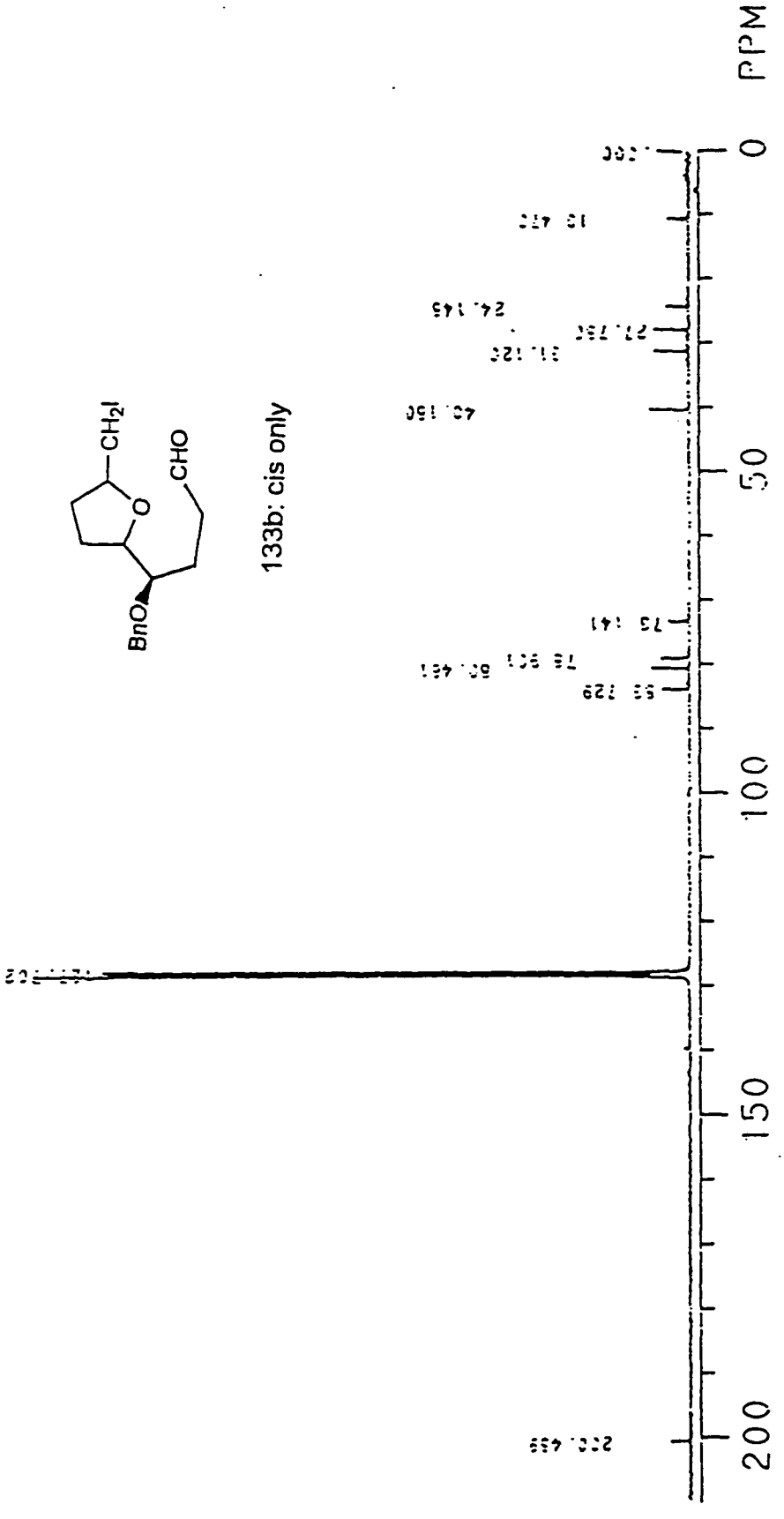


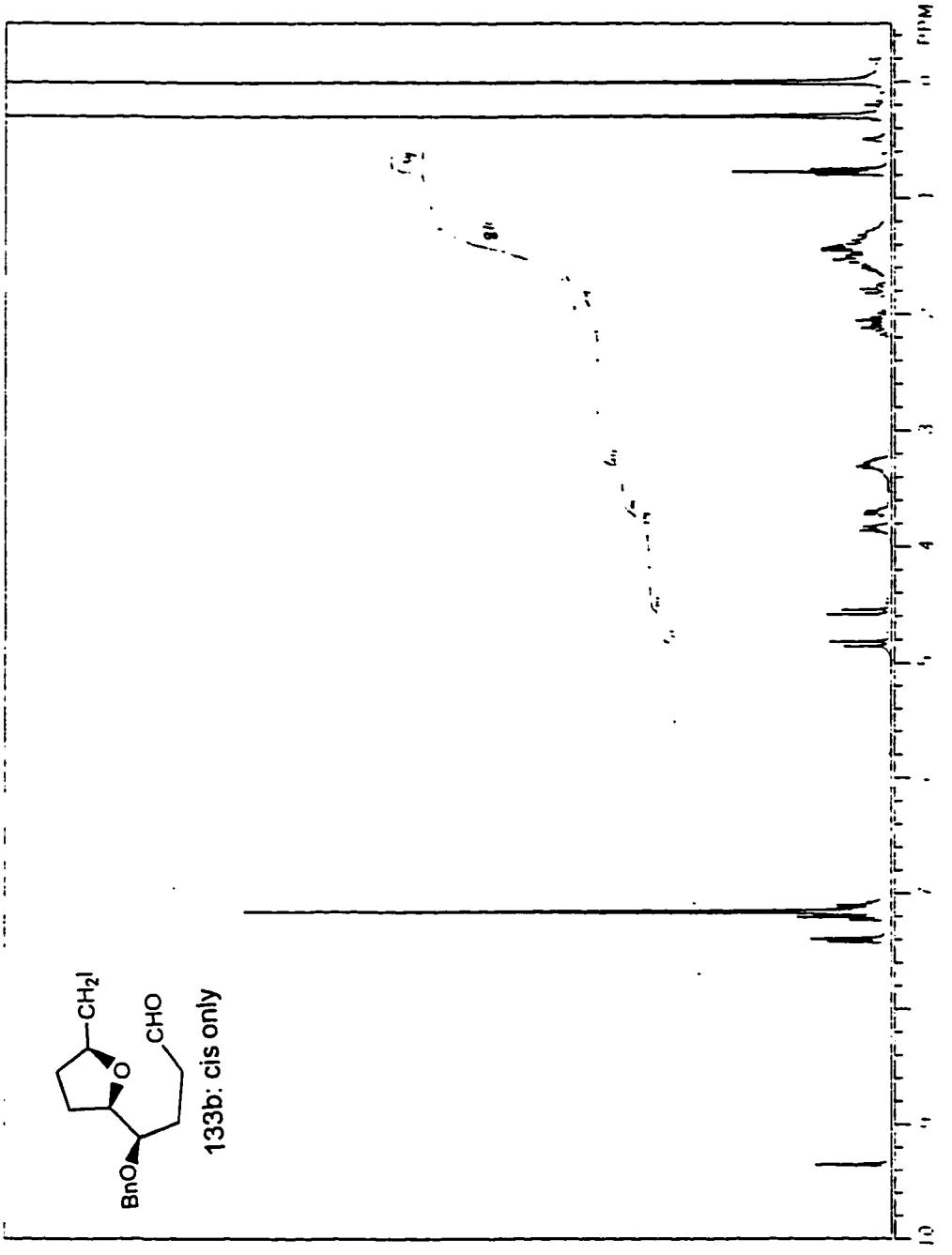


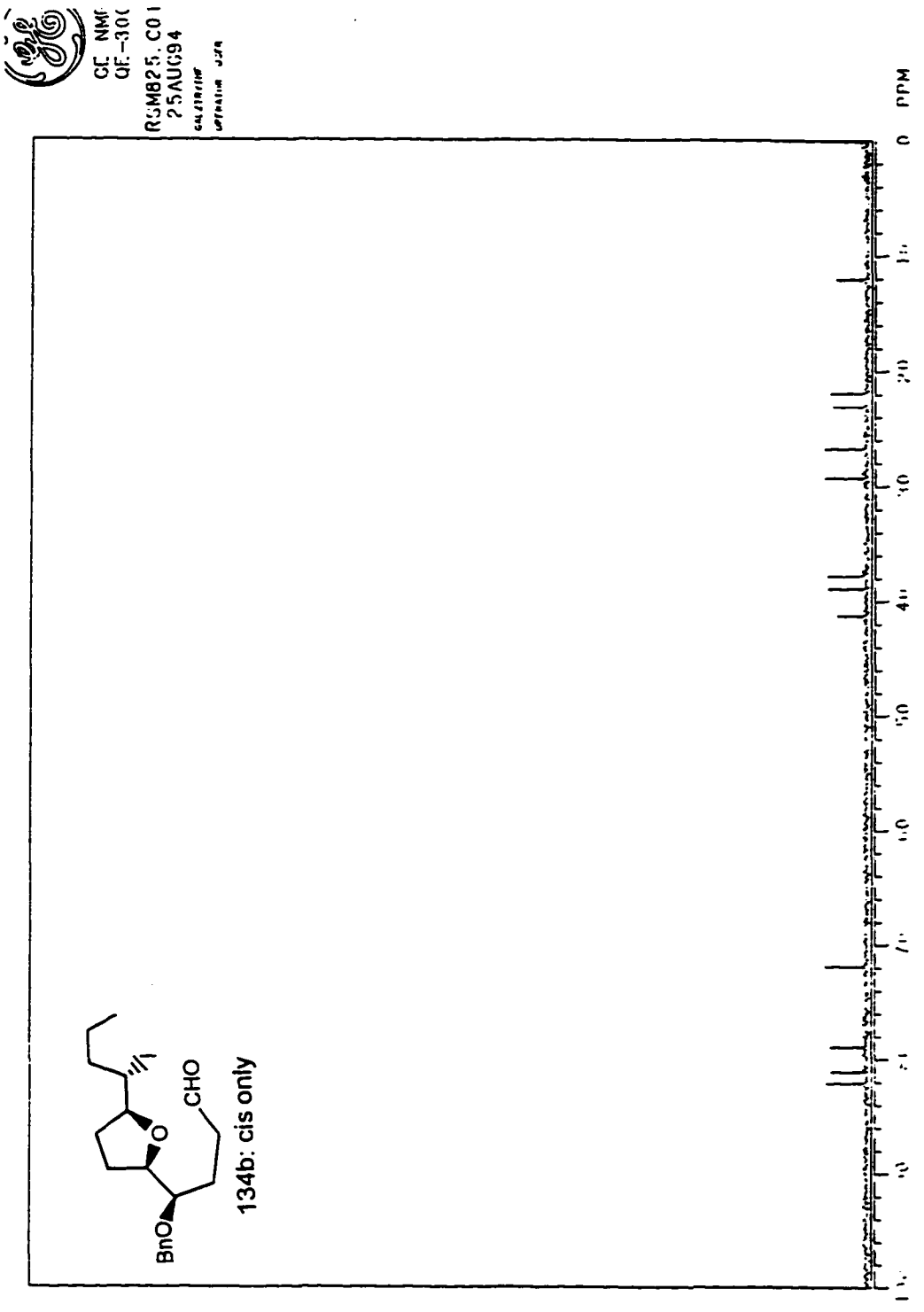


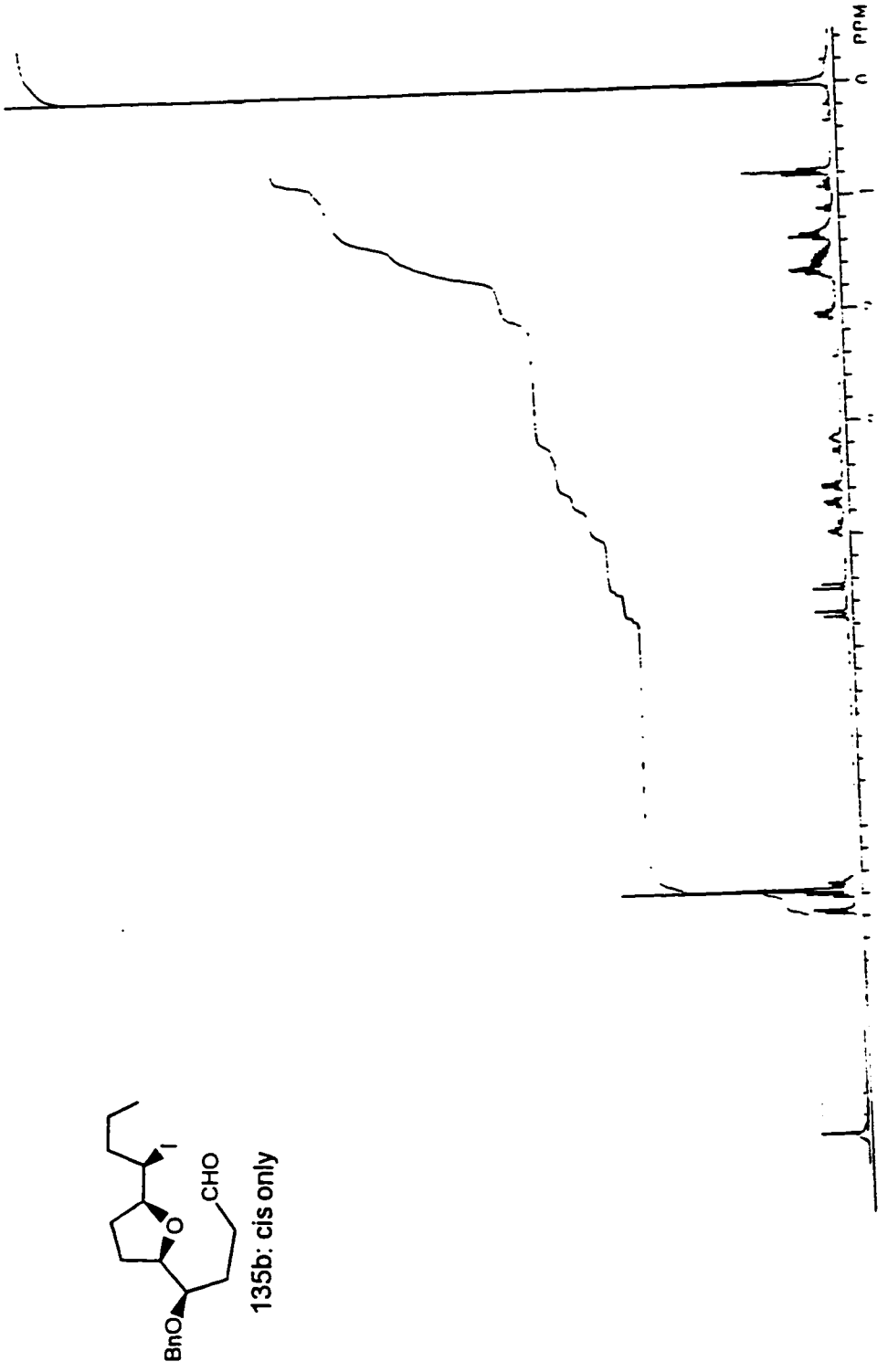


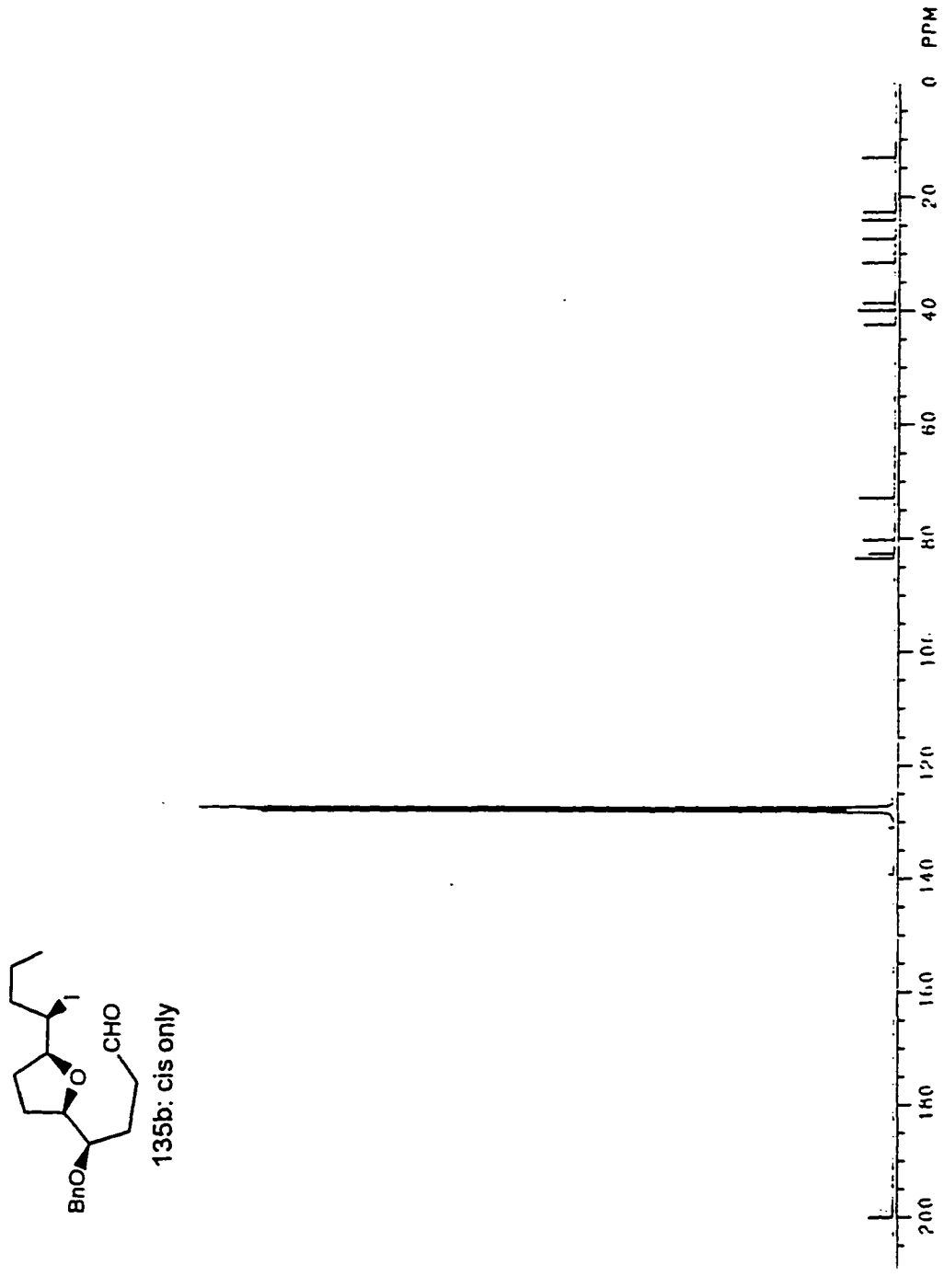






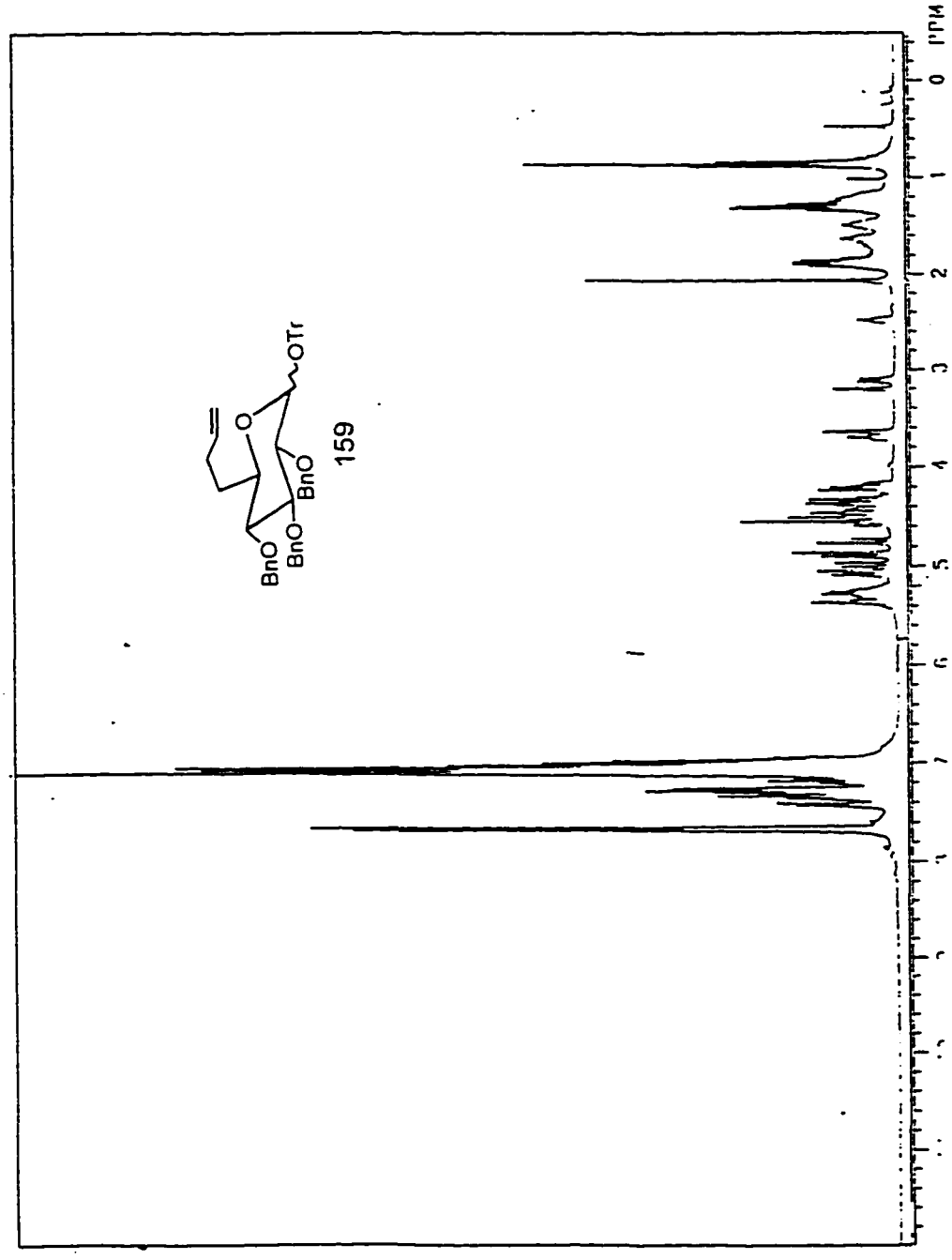


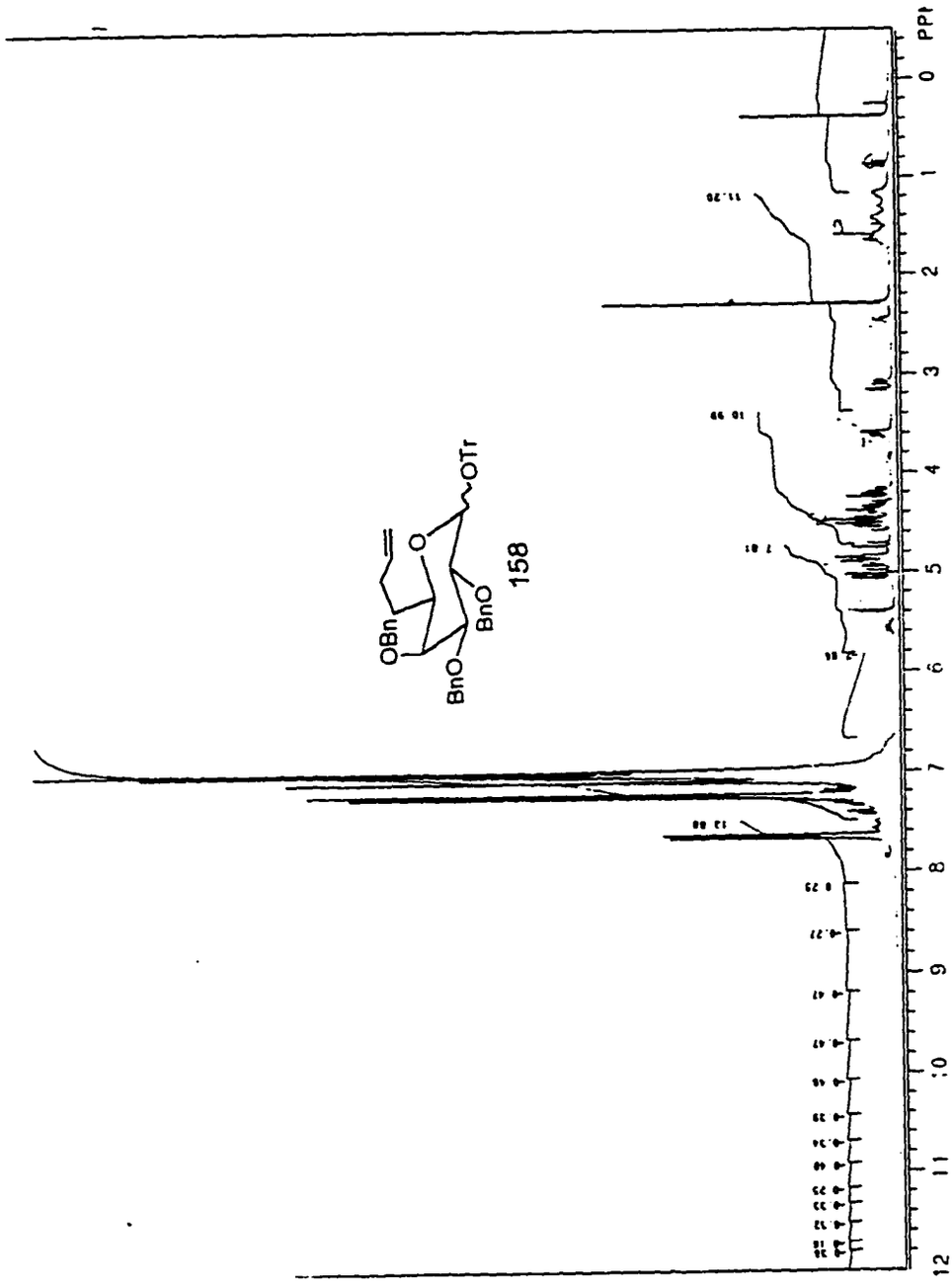


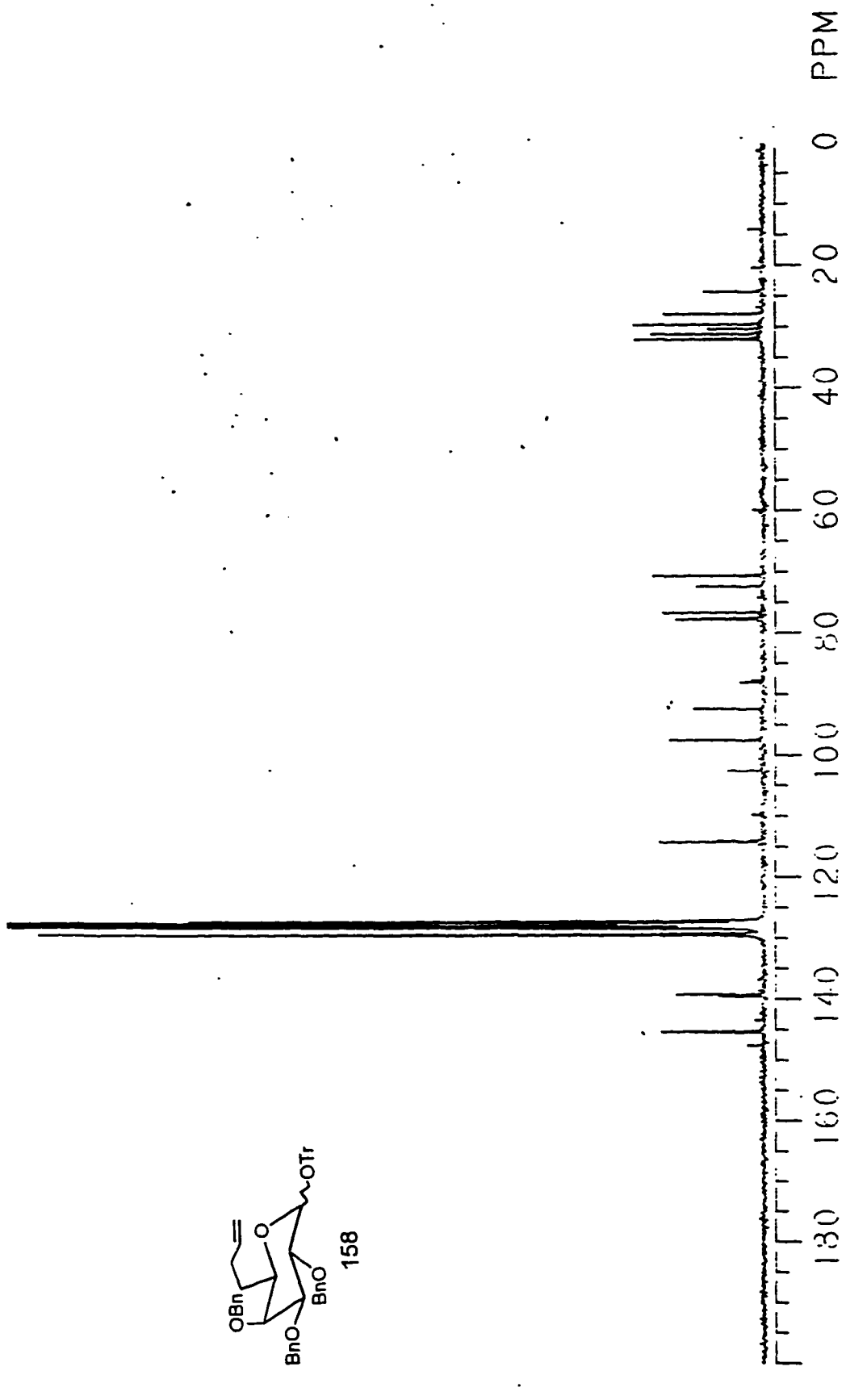


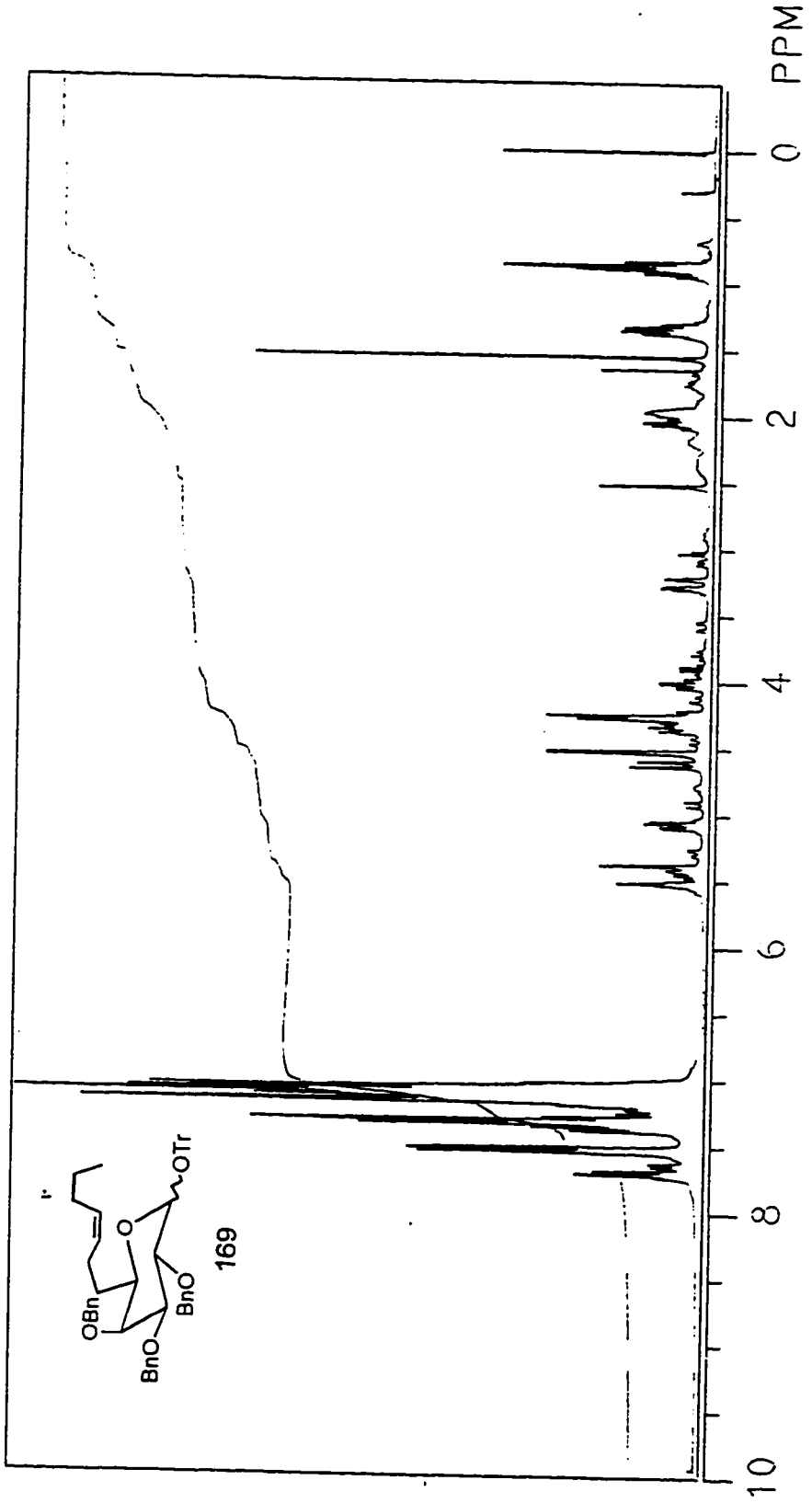
Appendix 2

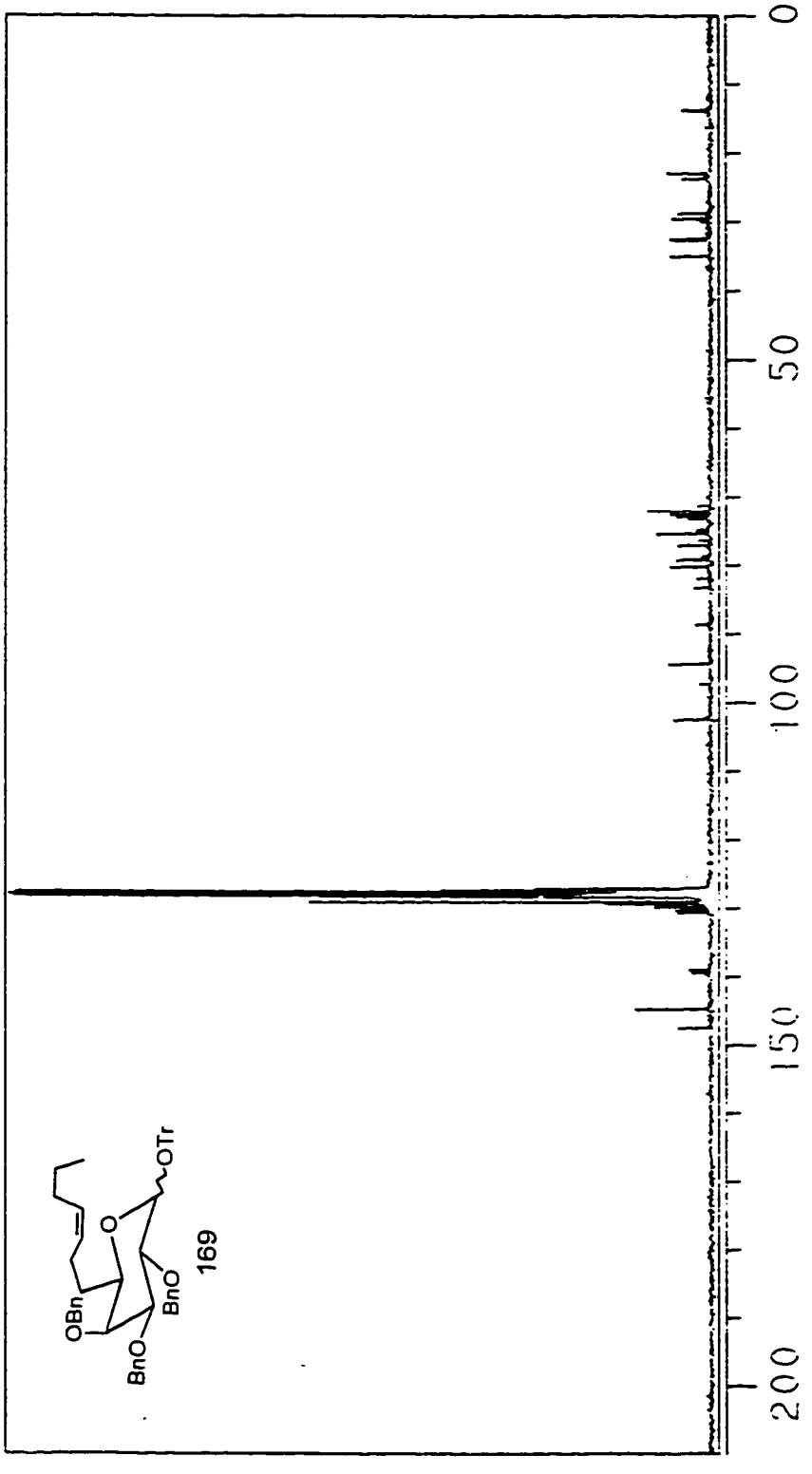
^{1}H and ^{13}C NMR of More Substituted Pyranosides and THF's

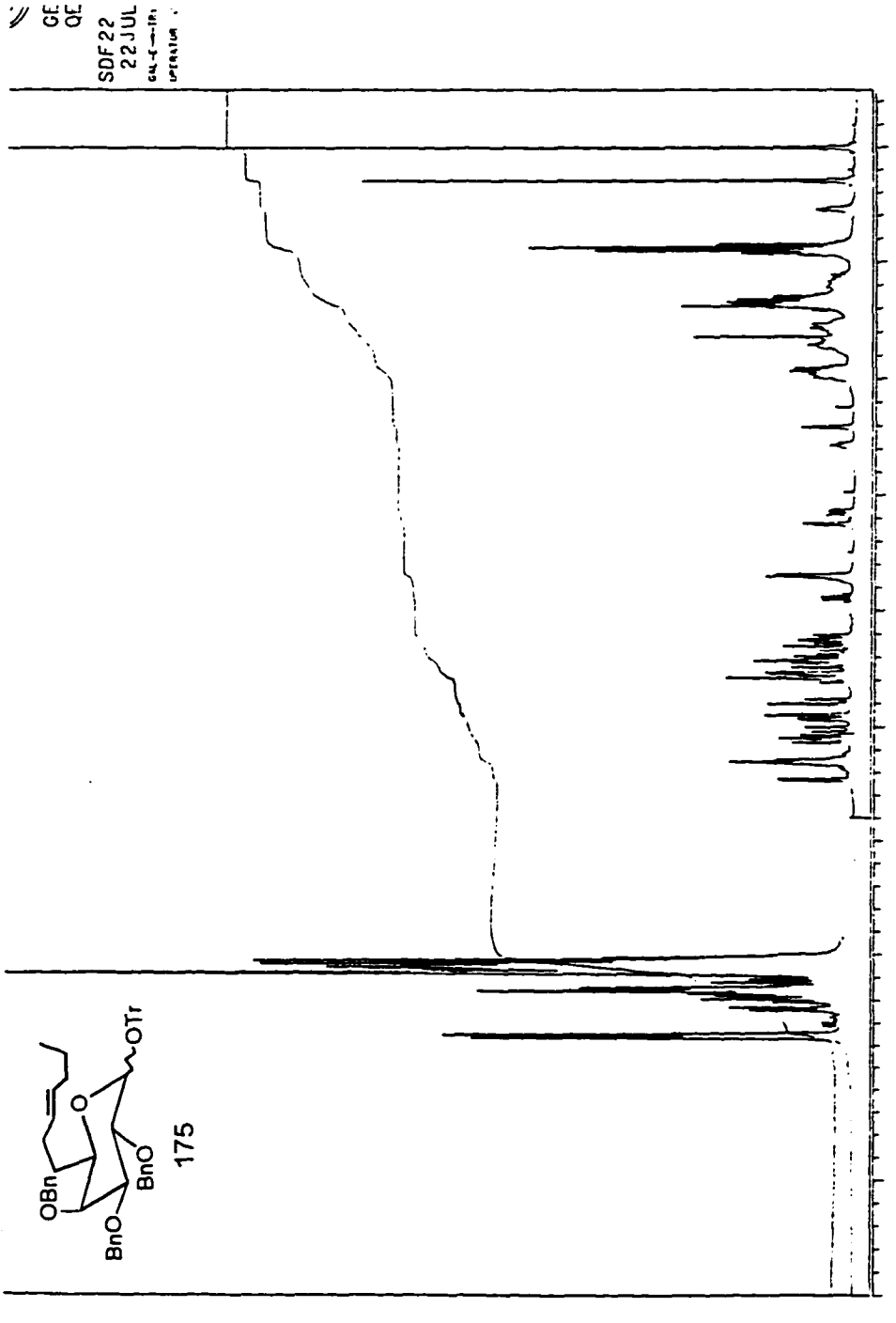


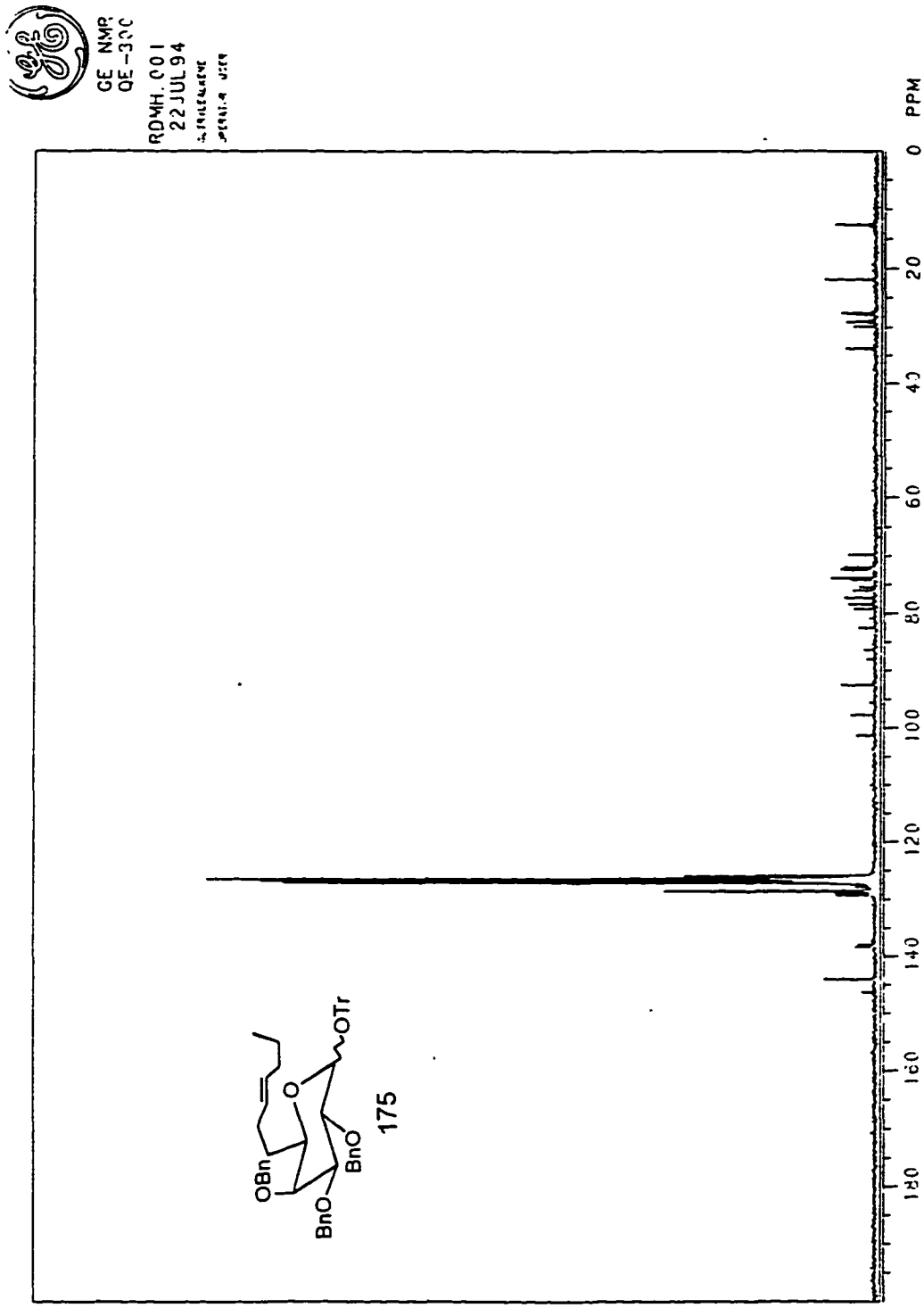


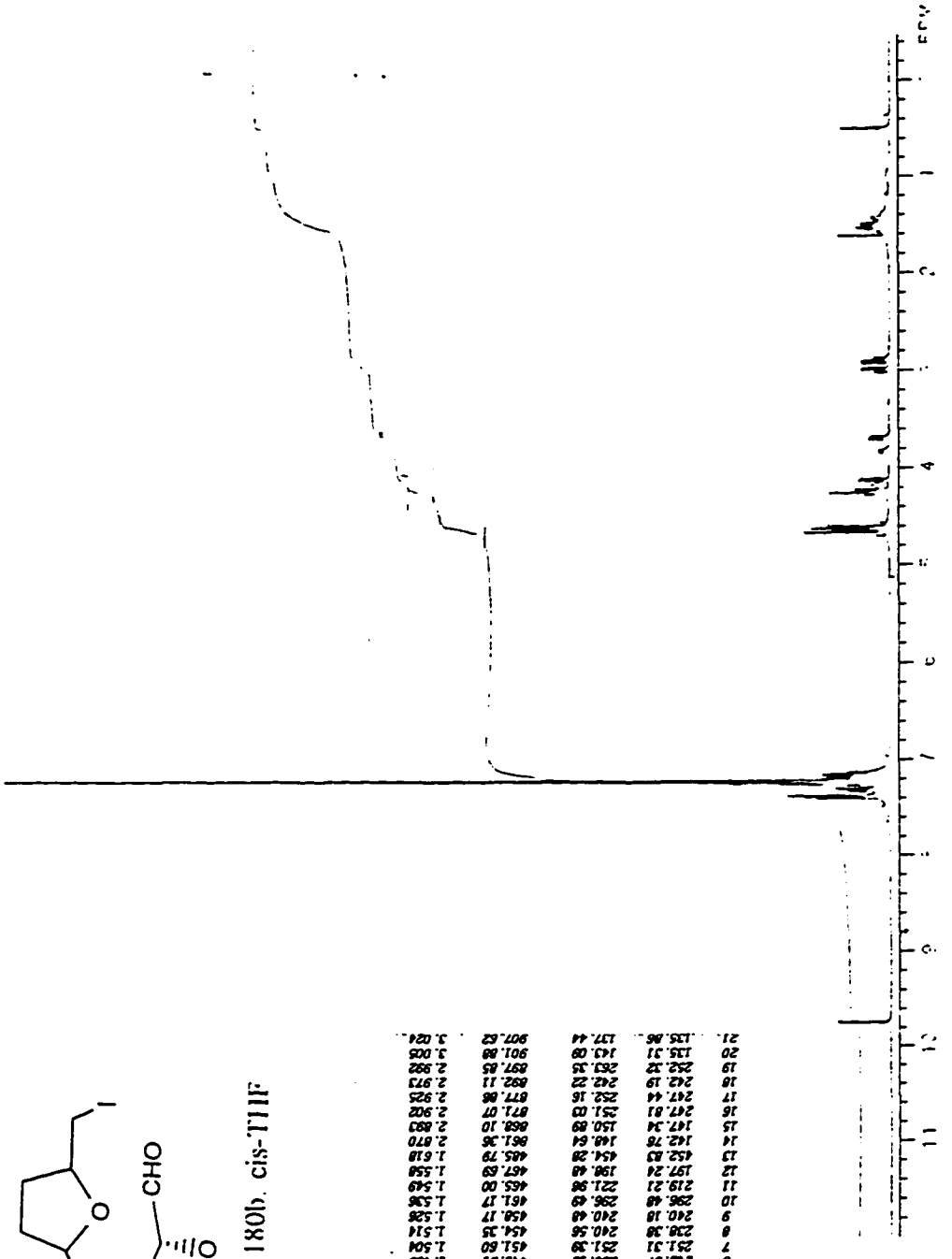




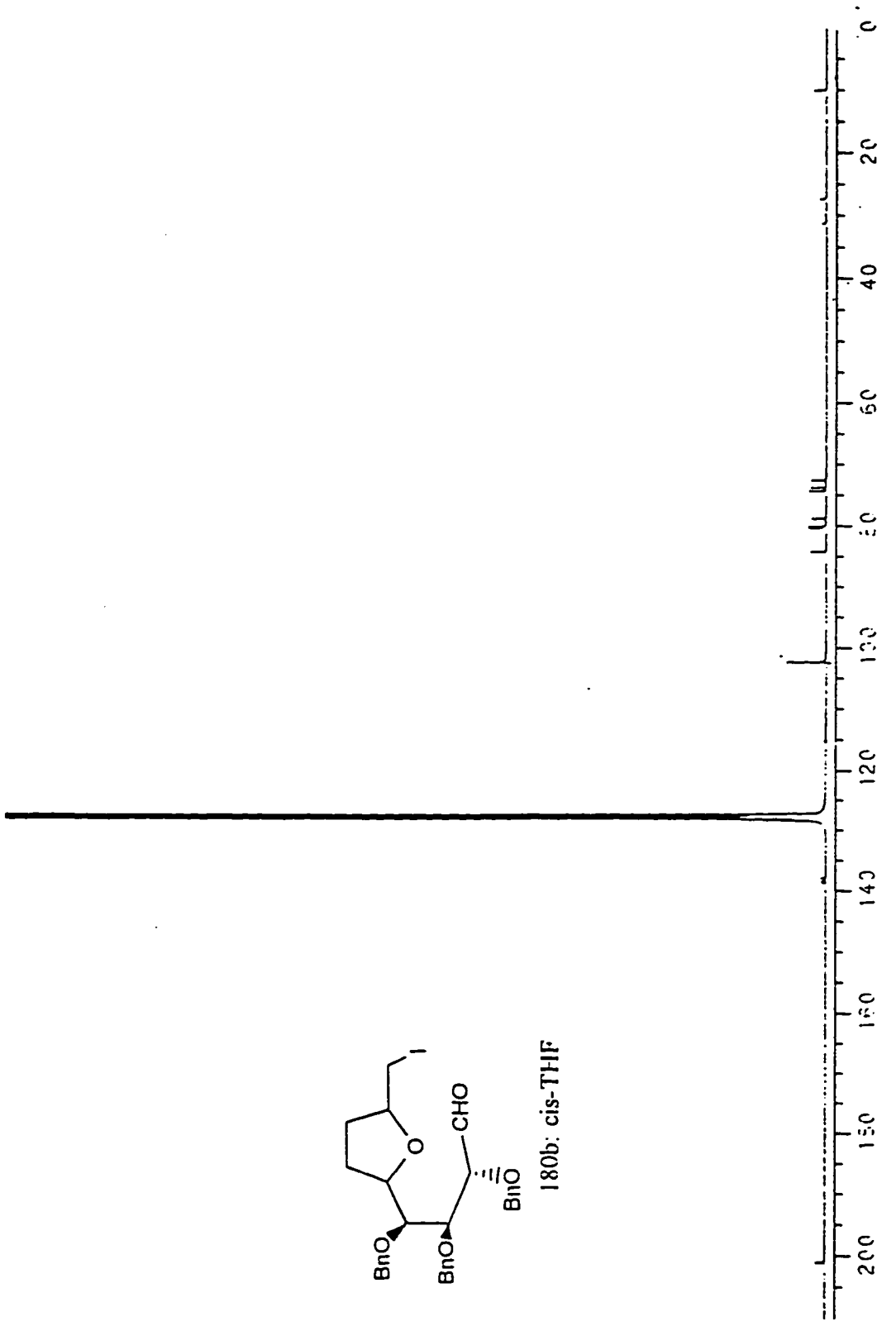








180b. cis-TTIF



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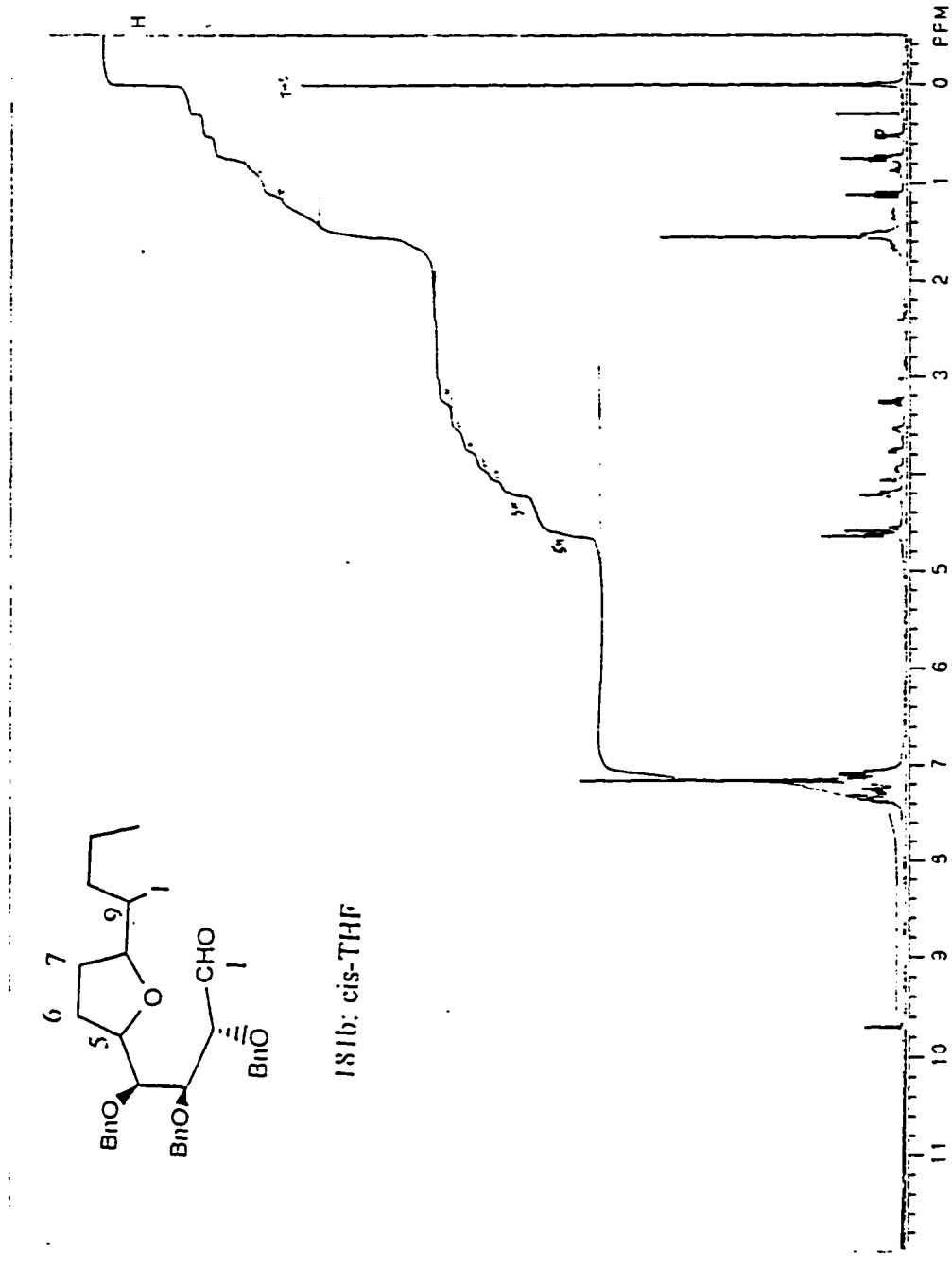
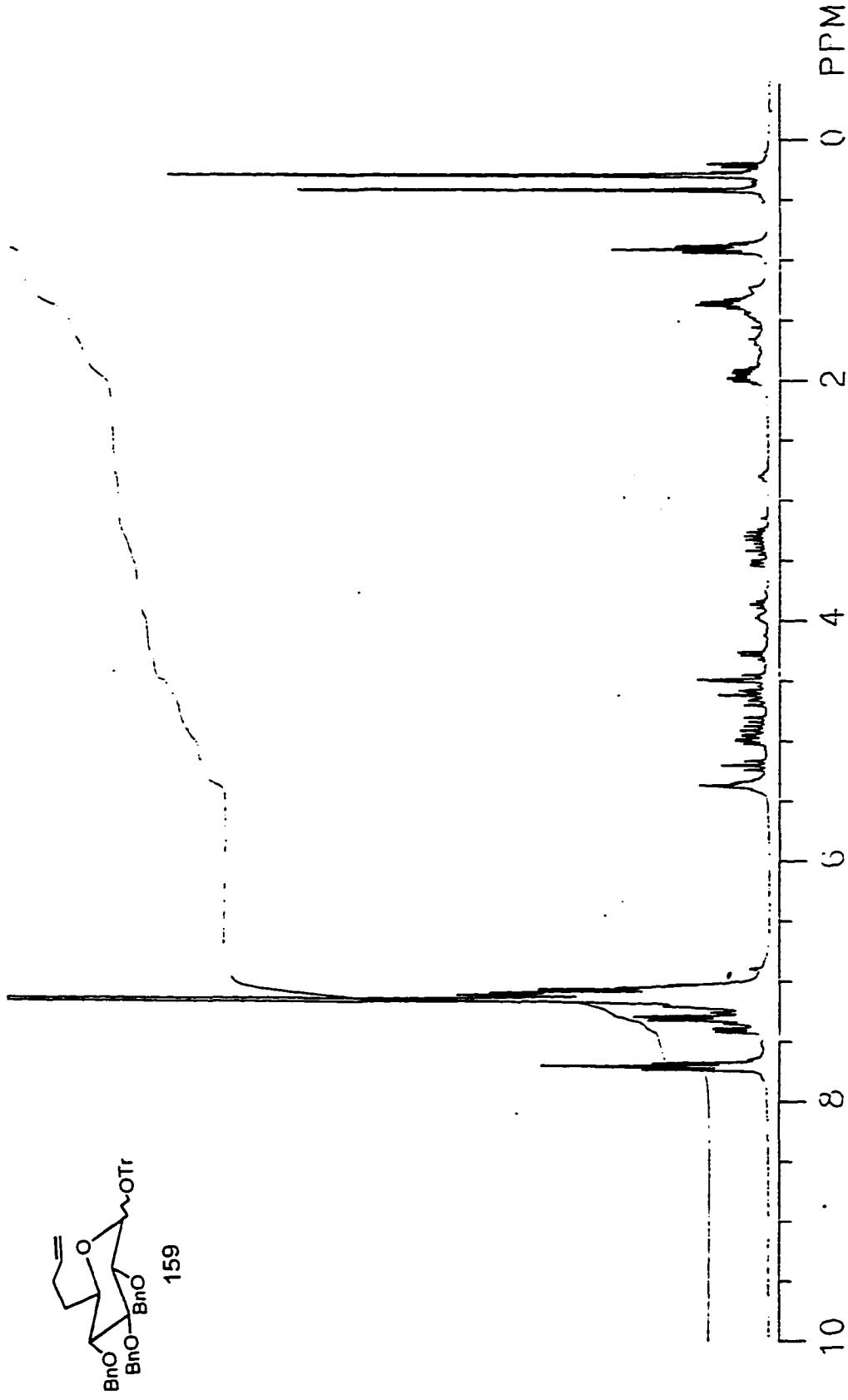
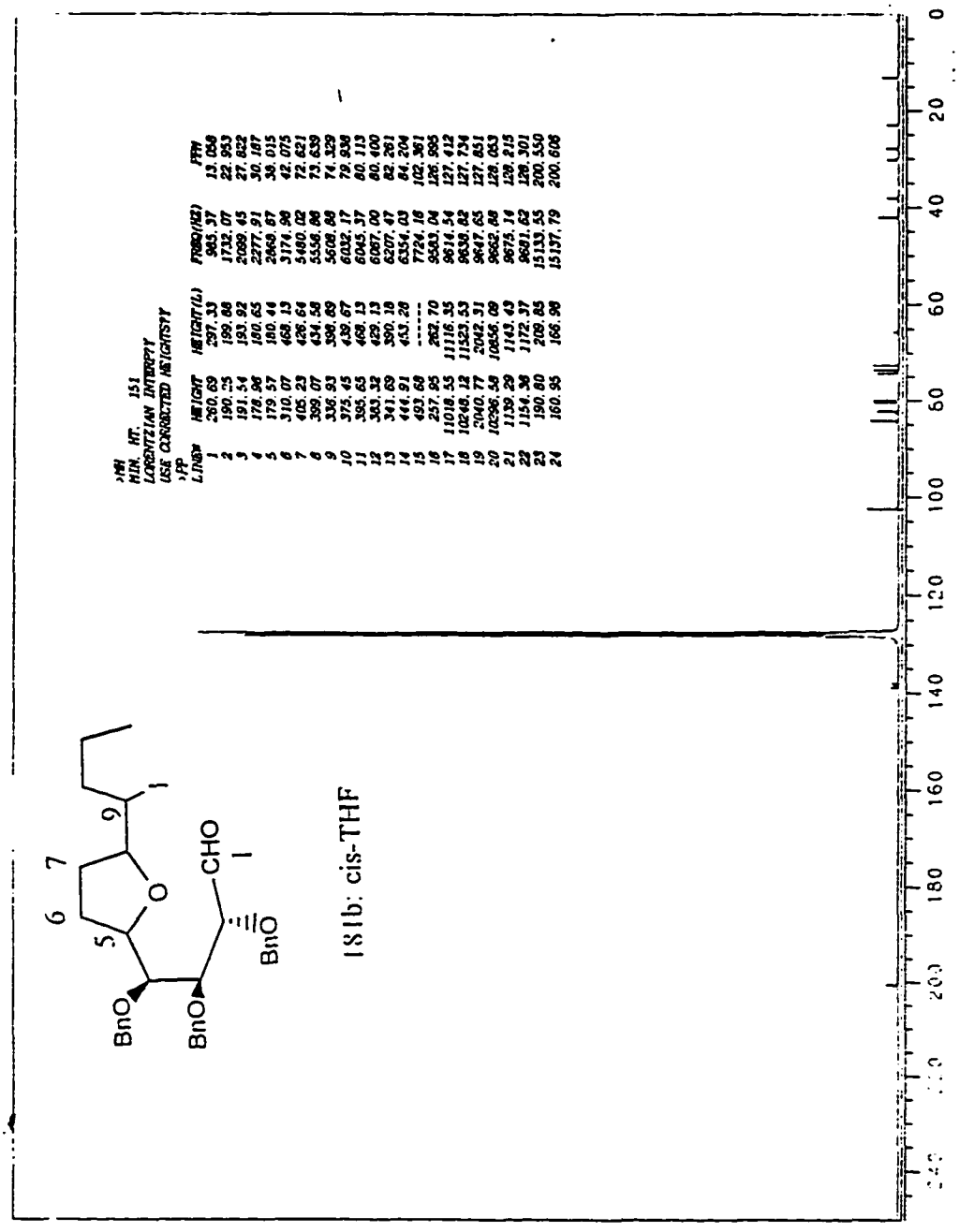
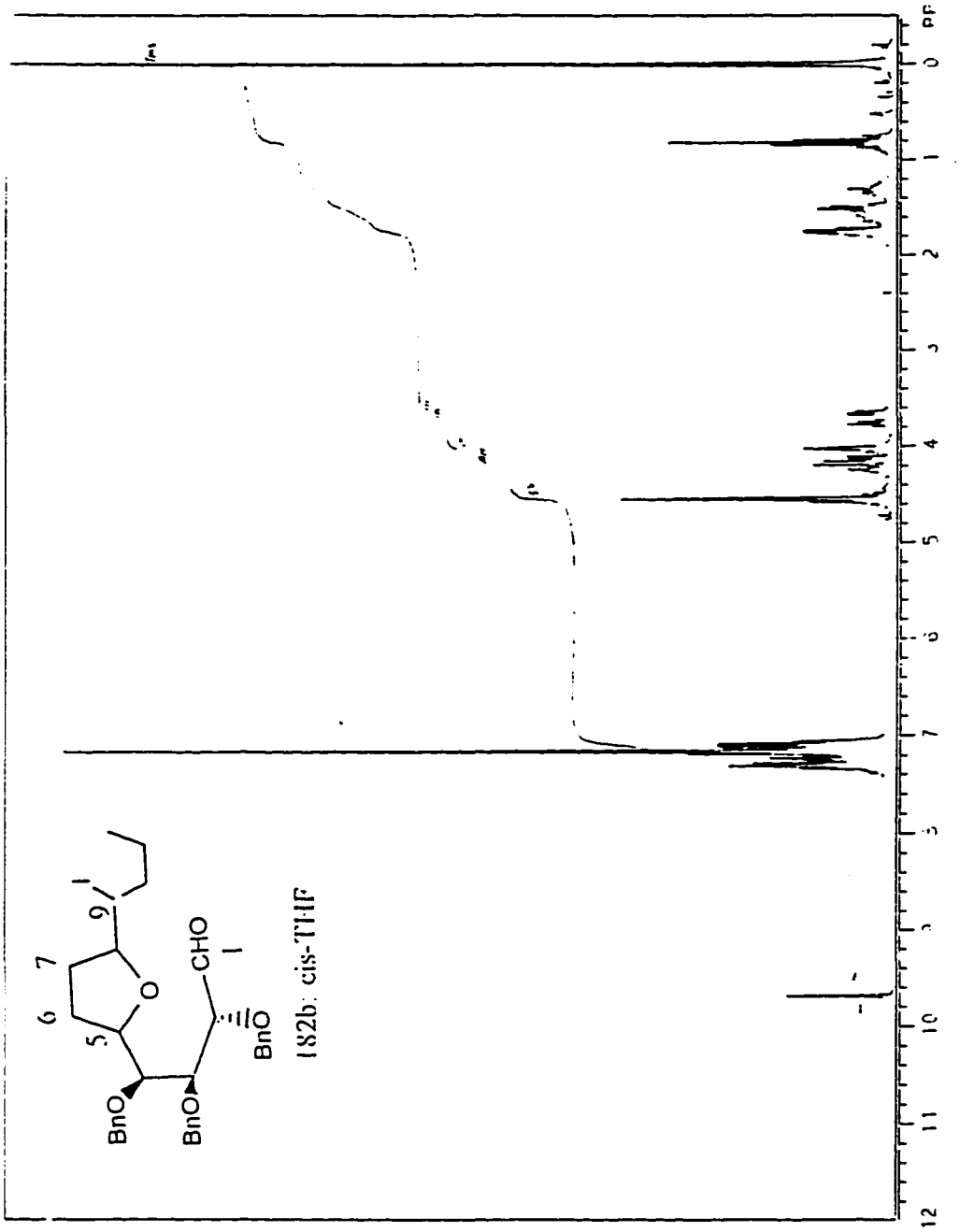


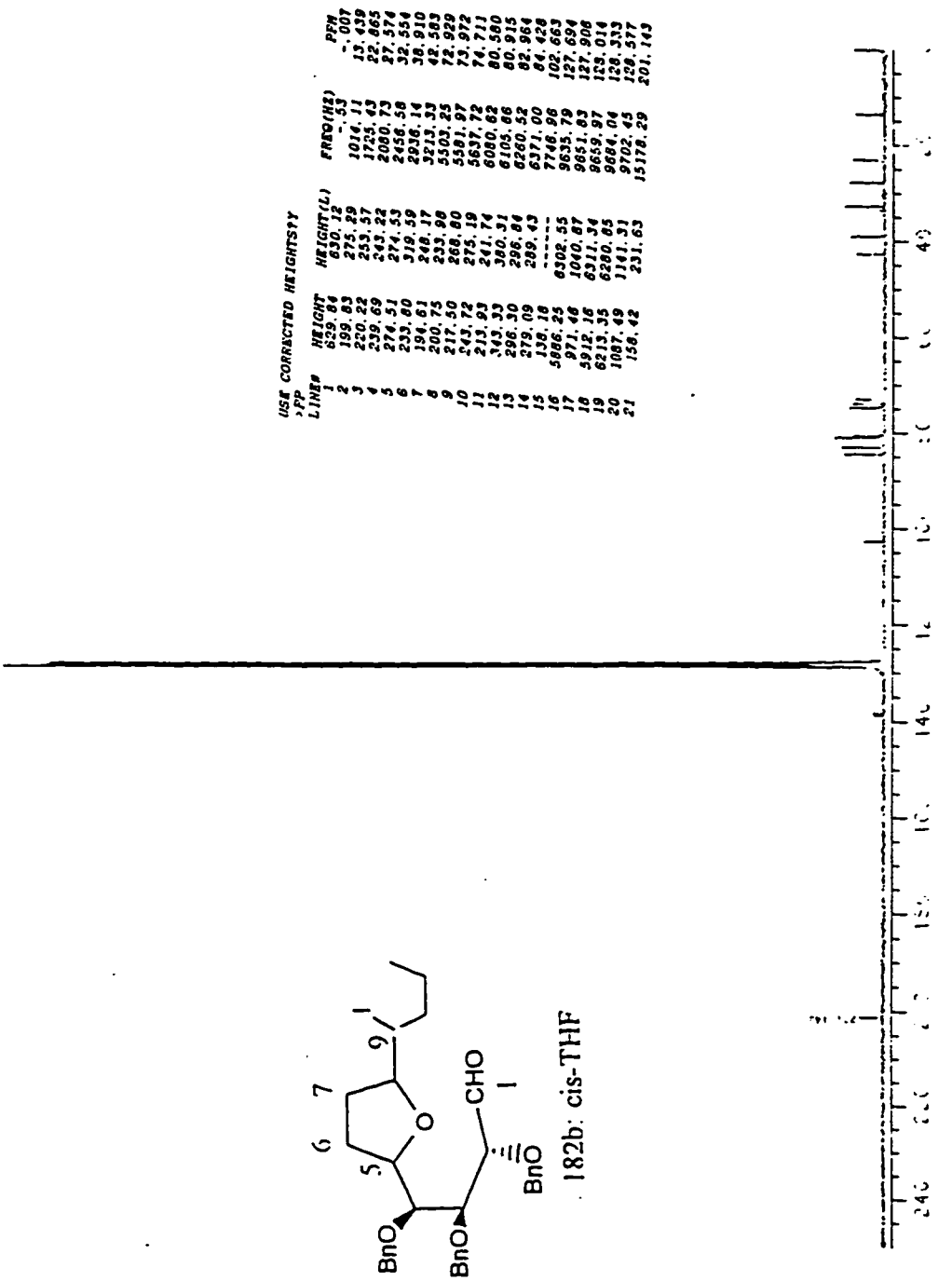
181b: cis-THF



159

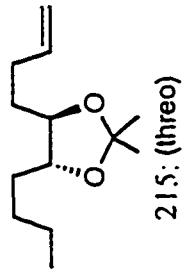




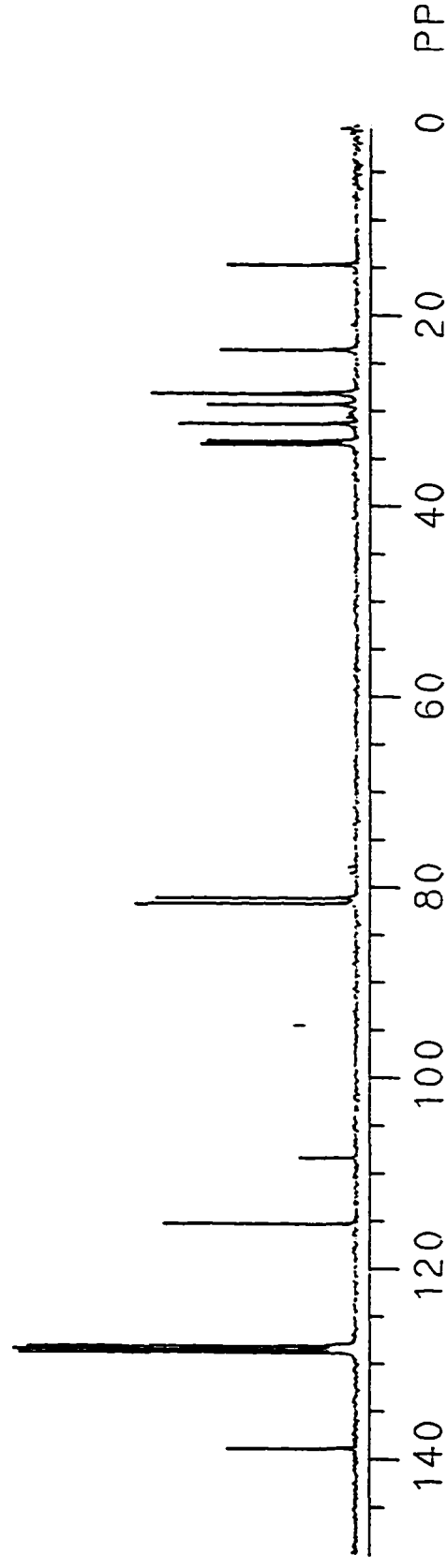


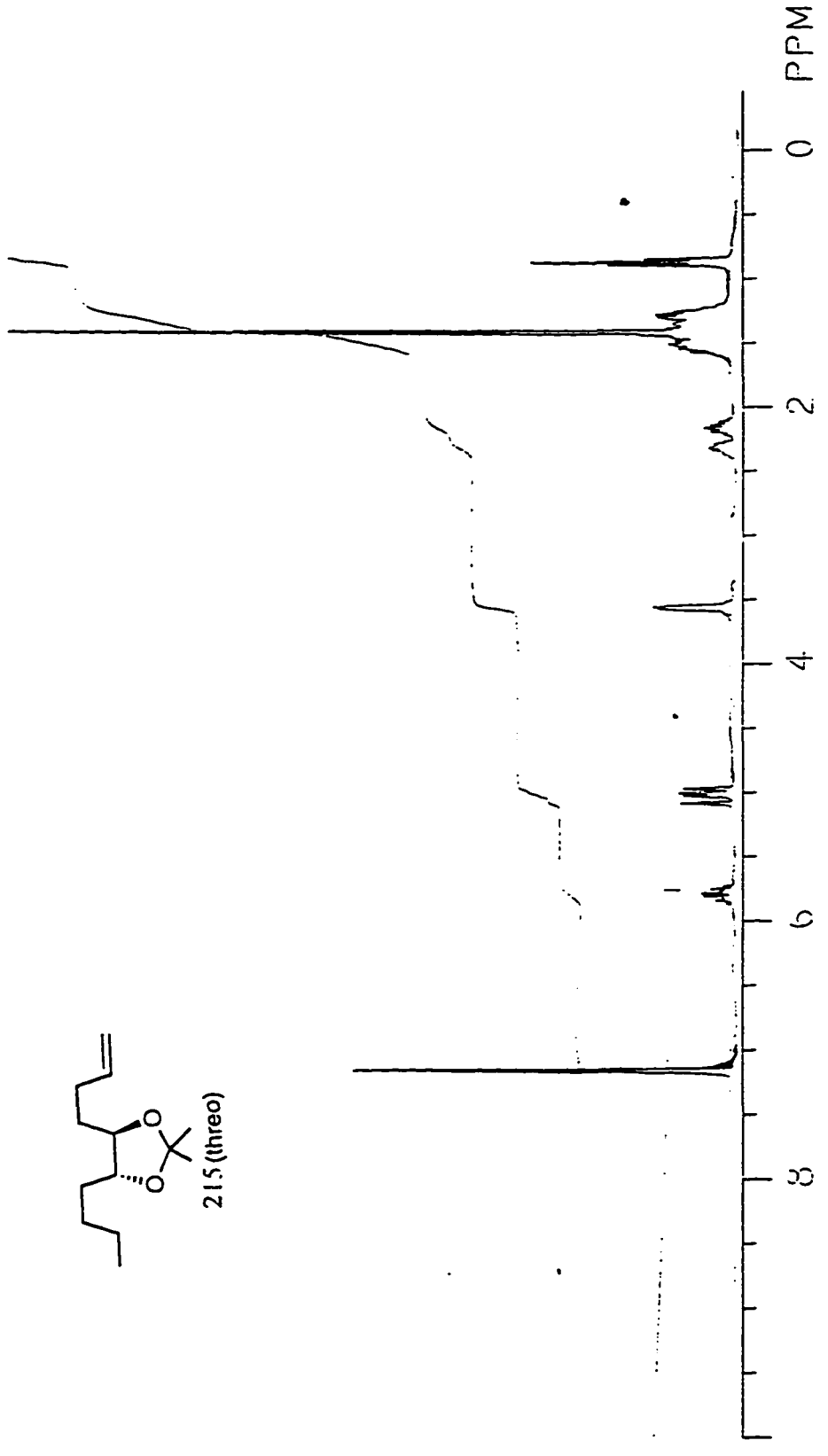
Appendix 3

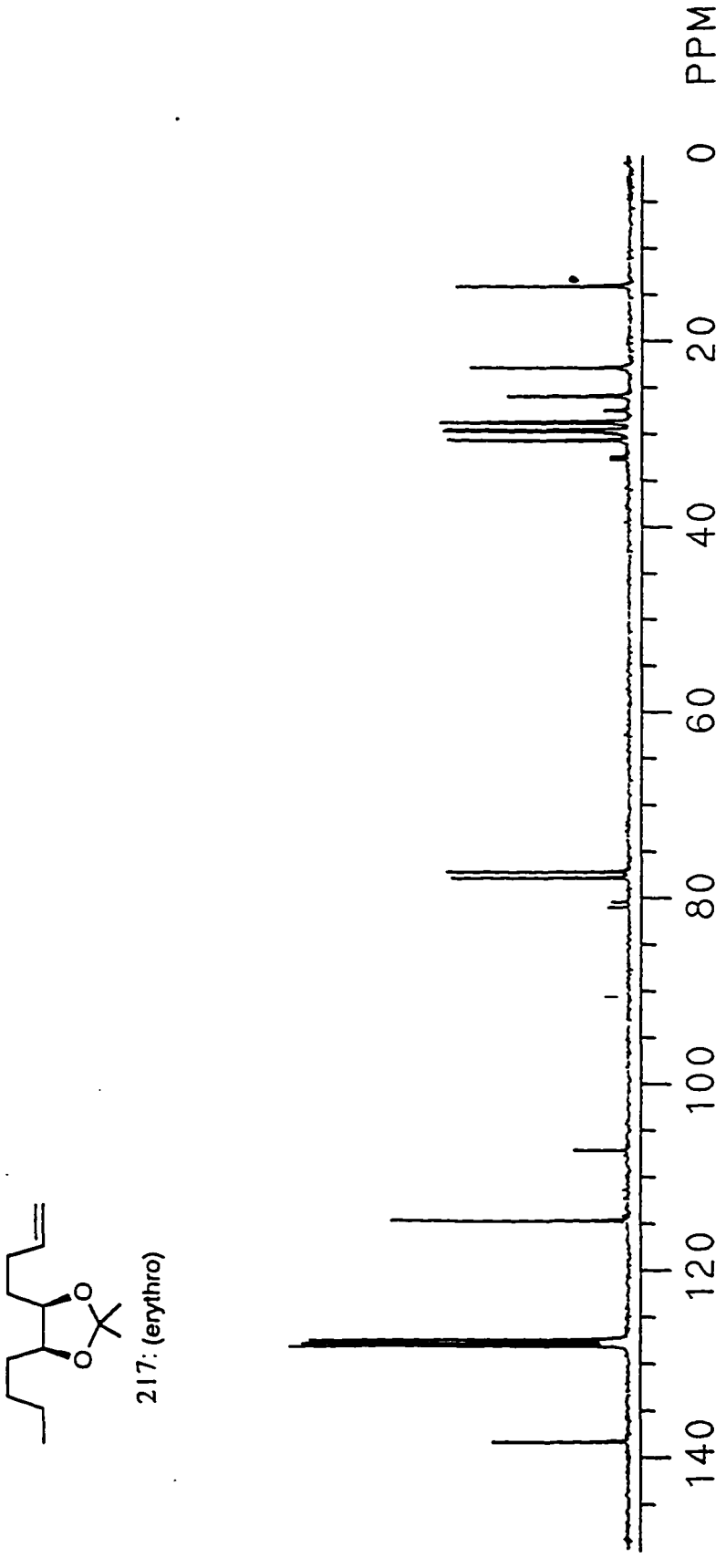
^{1}H and ^{13}C NMR of 5,6-O-Isopropylidene Derivatives and THF's



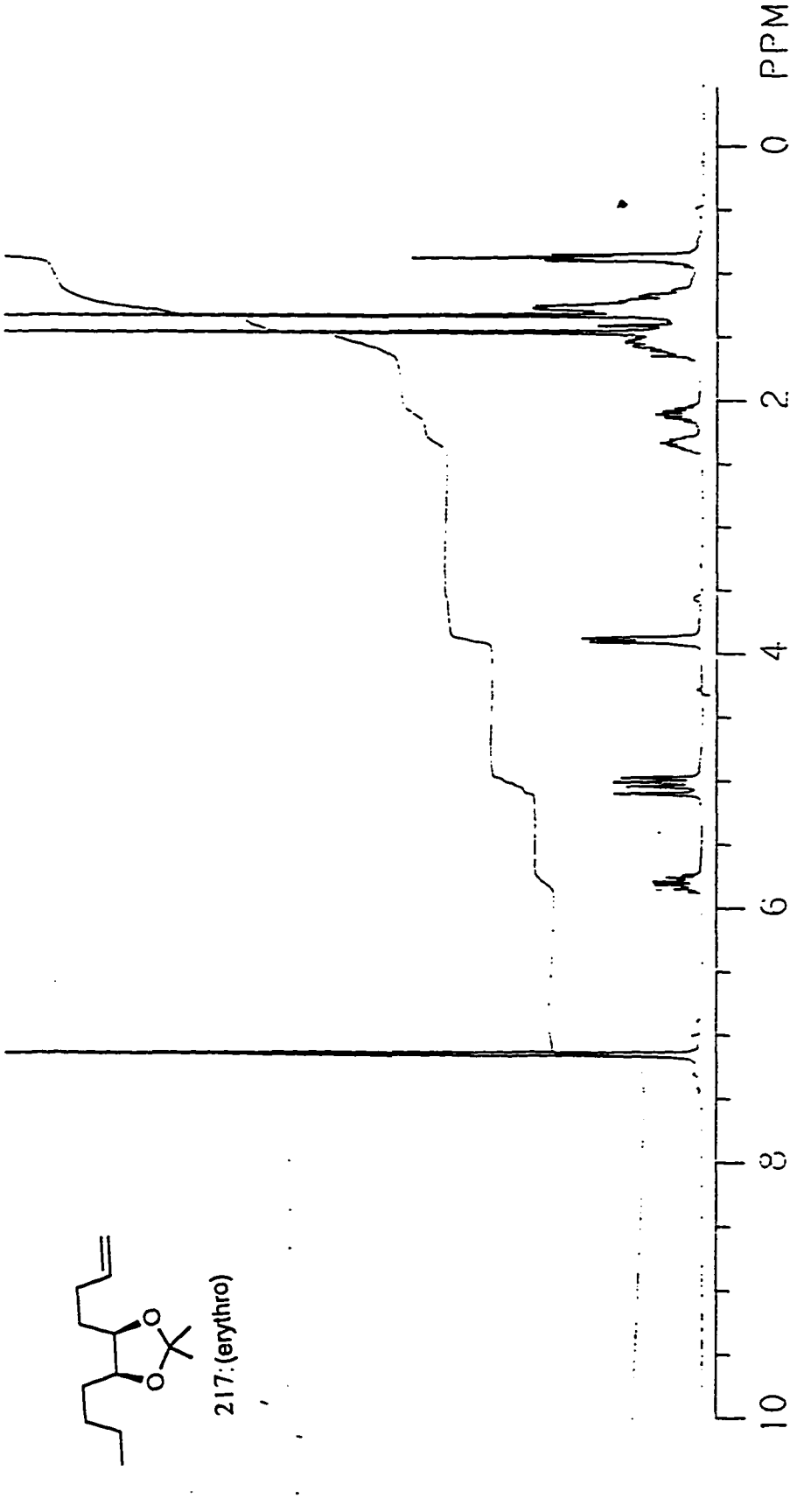
215: (threo)

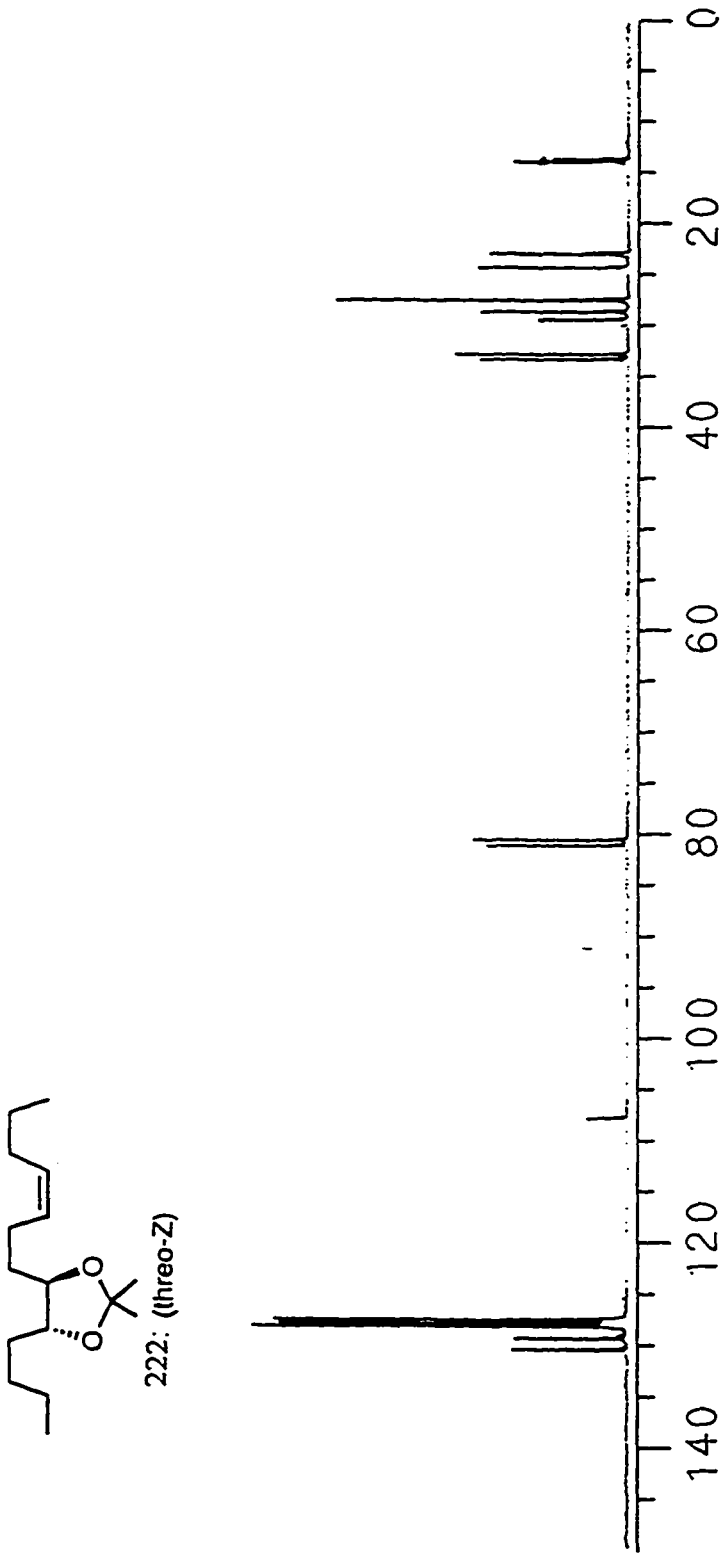


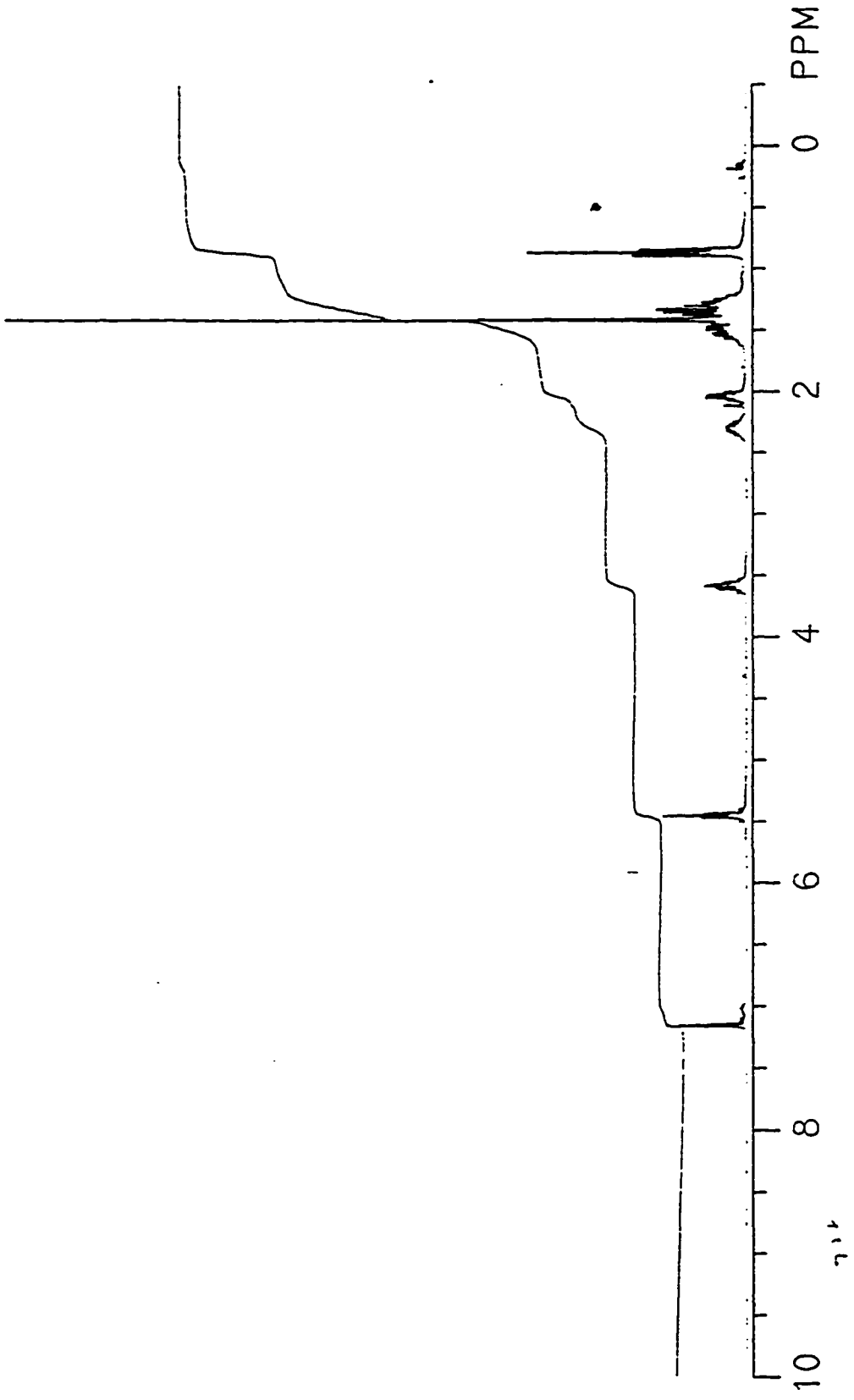


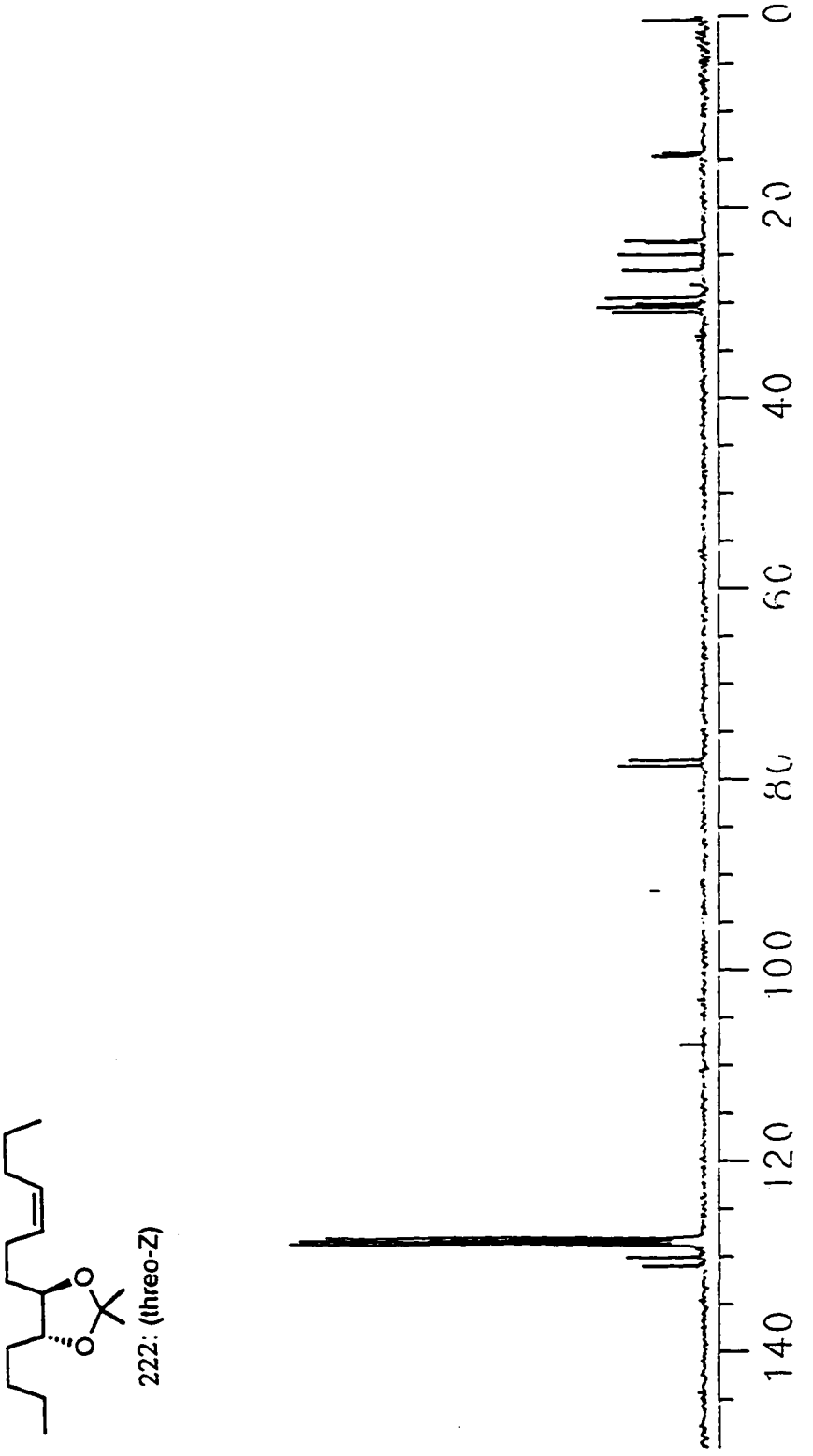


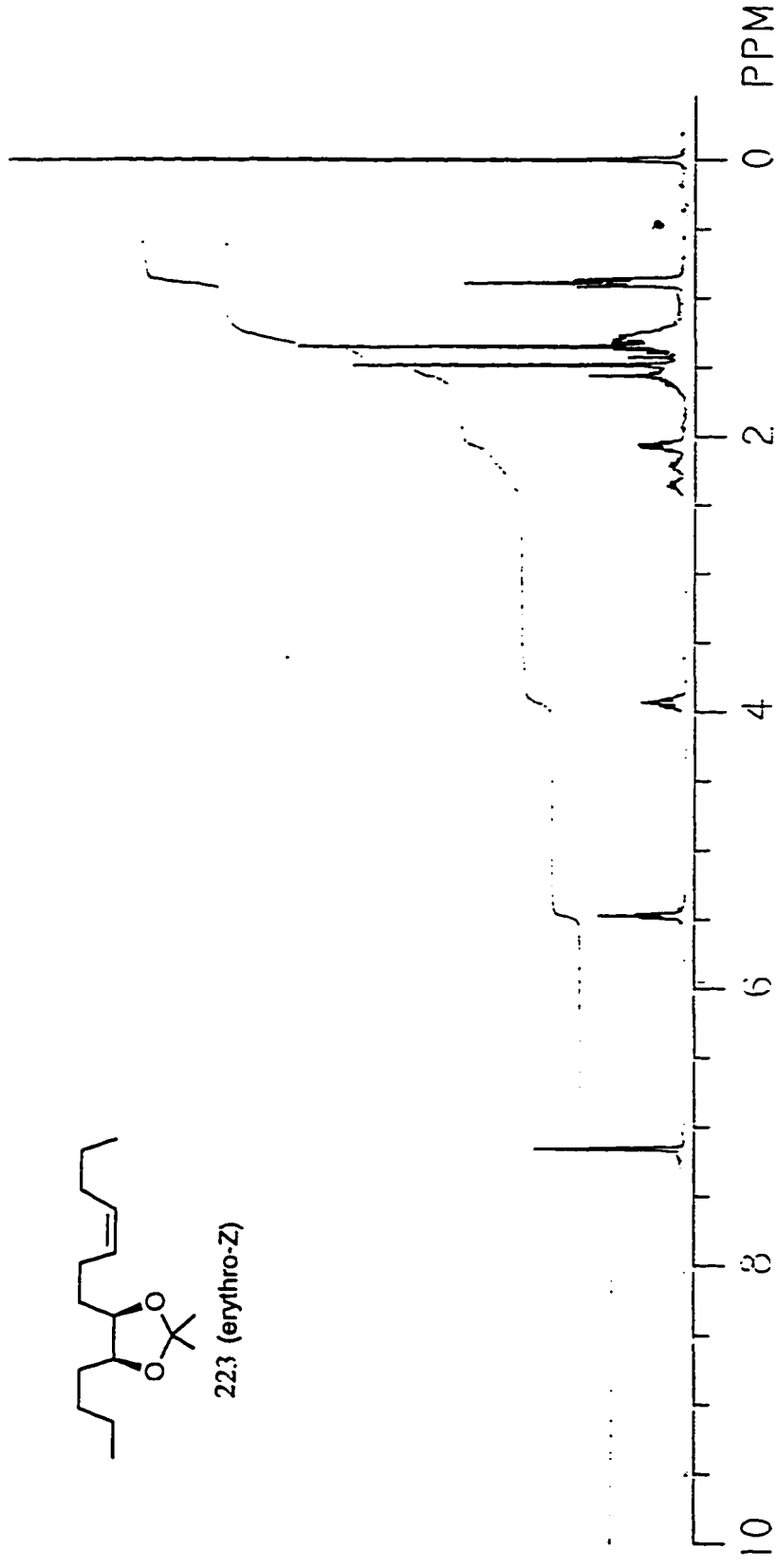
217: (erythro)



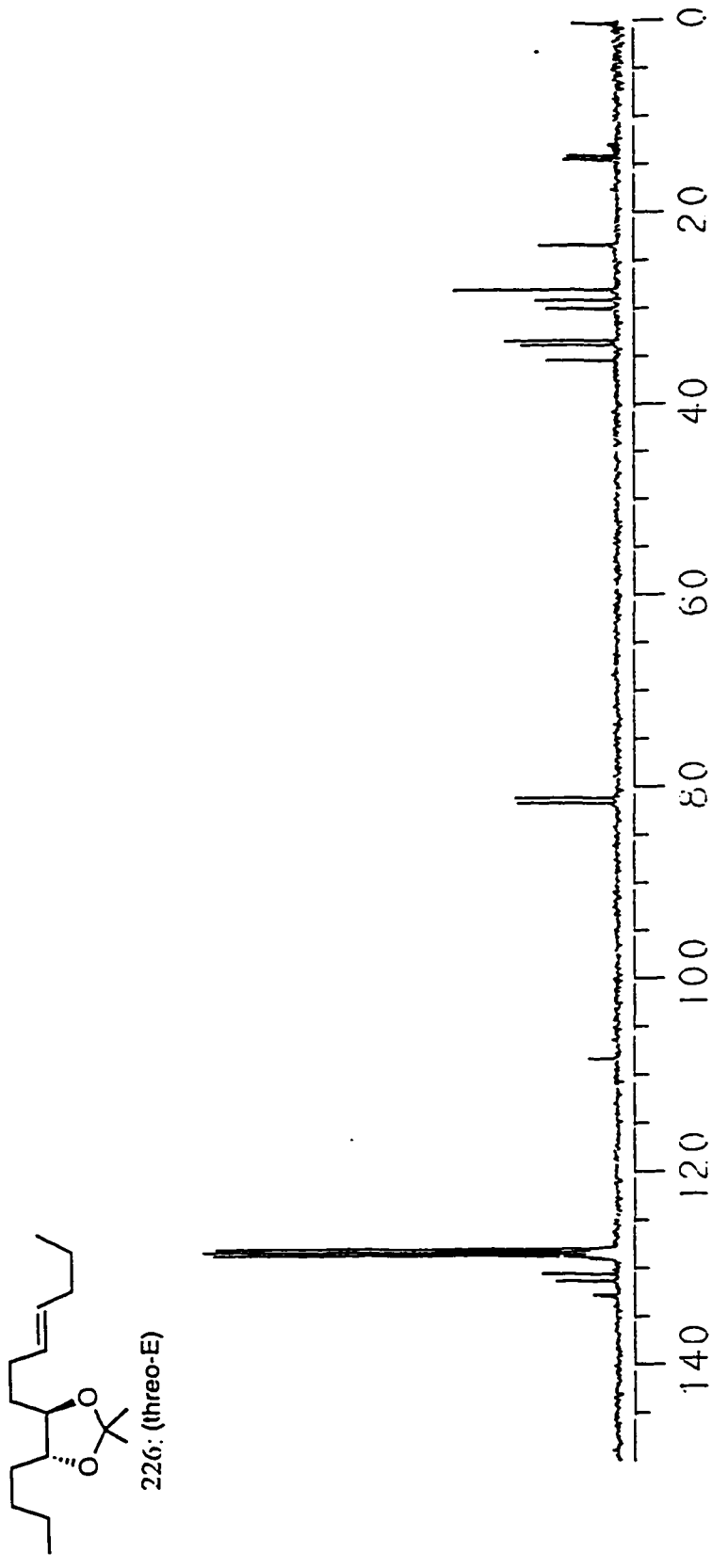




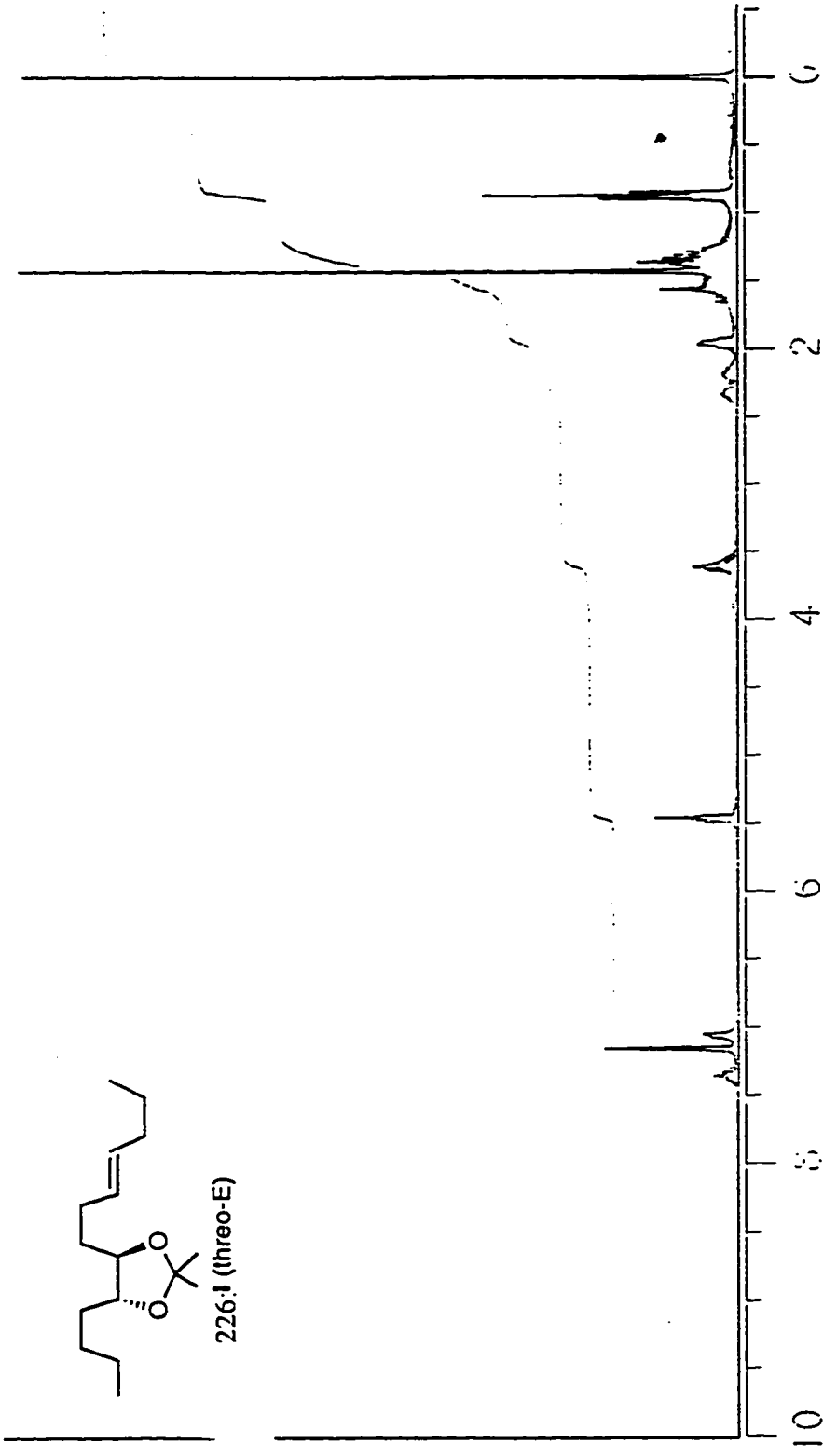


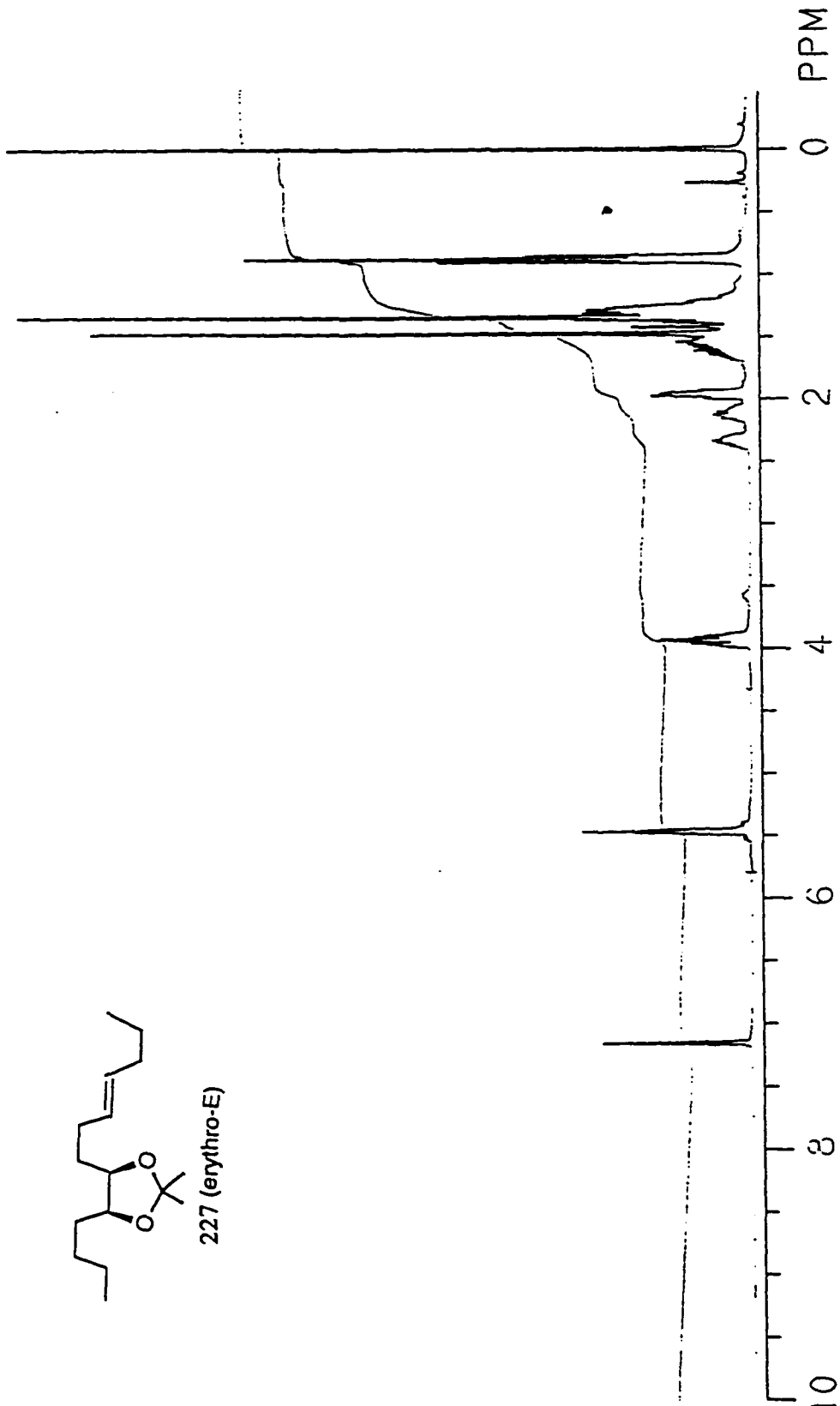


22.3 (erythro-Z)

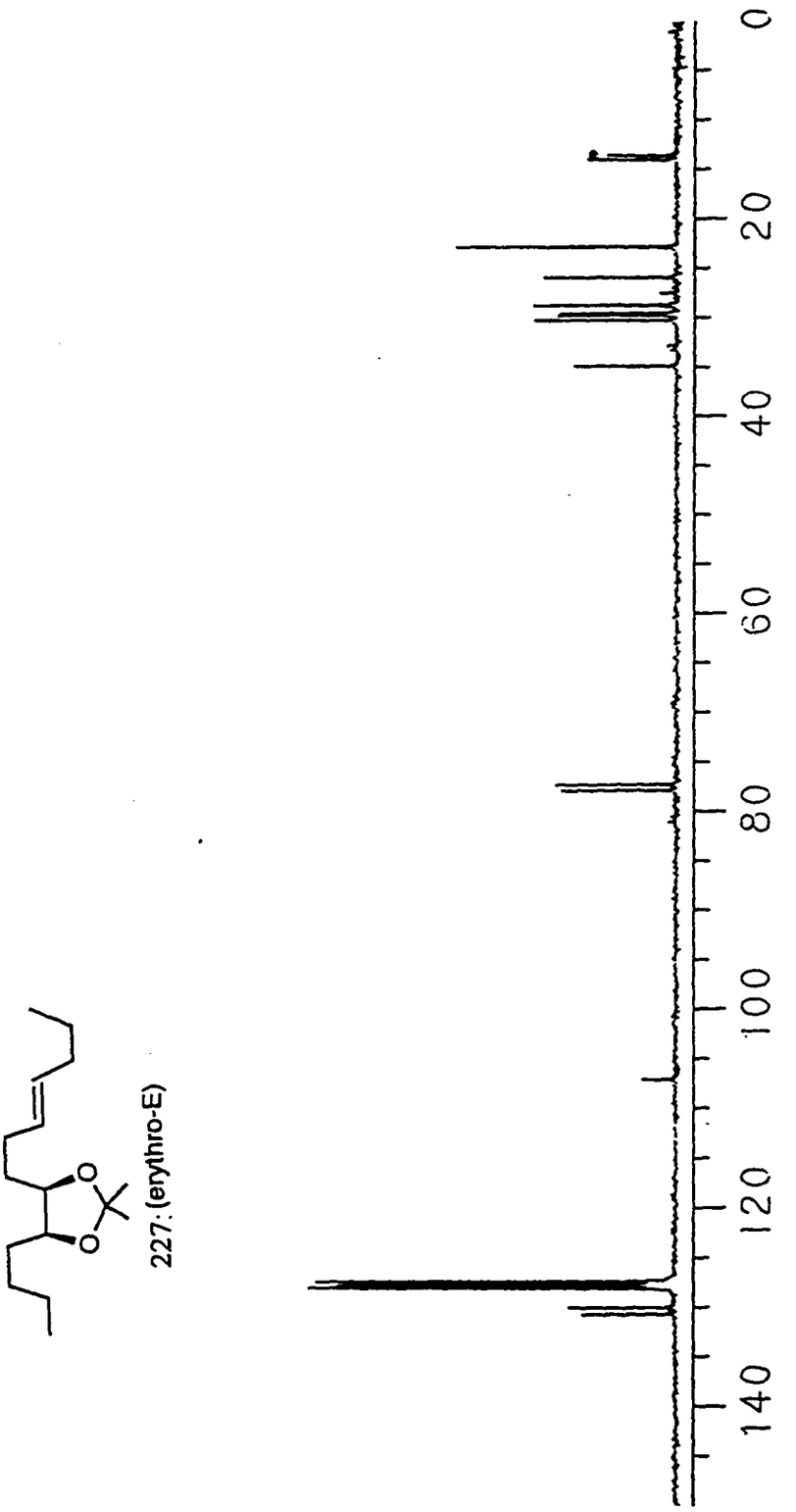


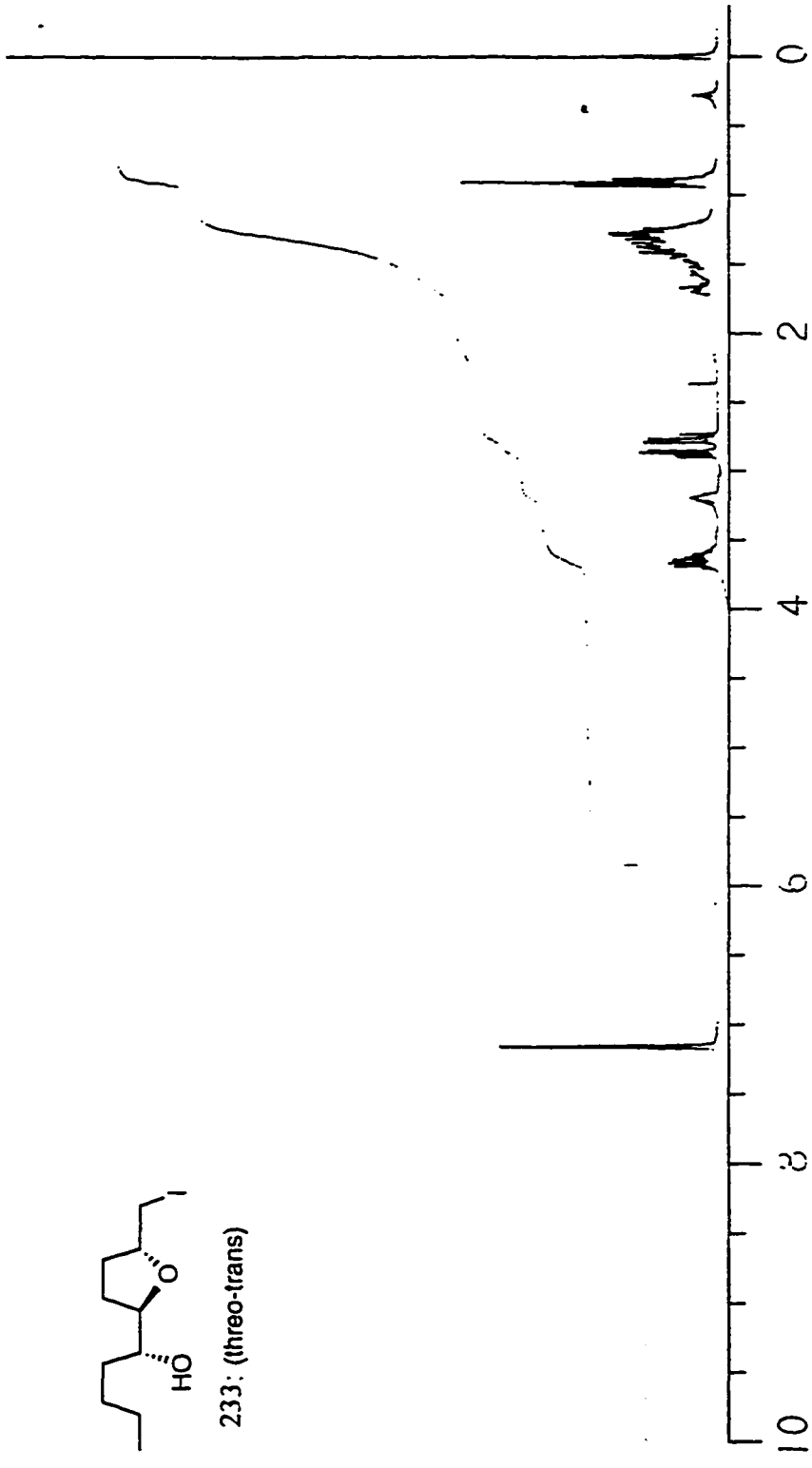
226: (threo-E)



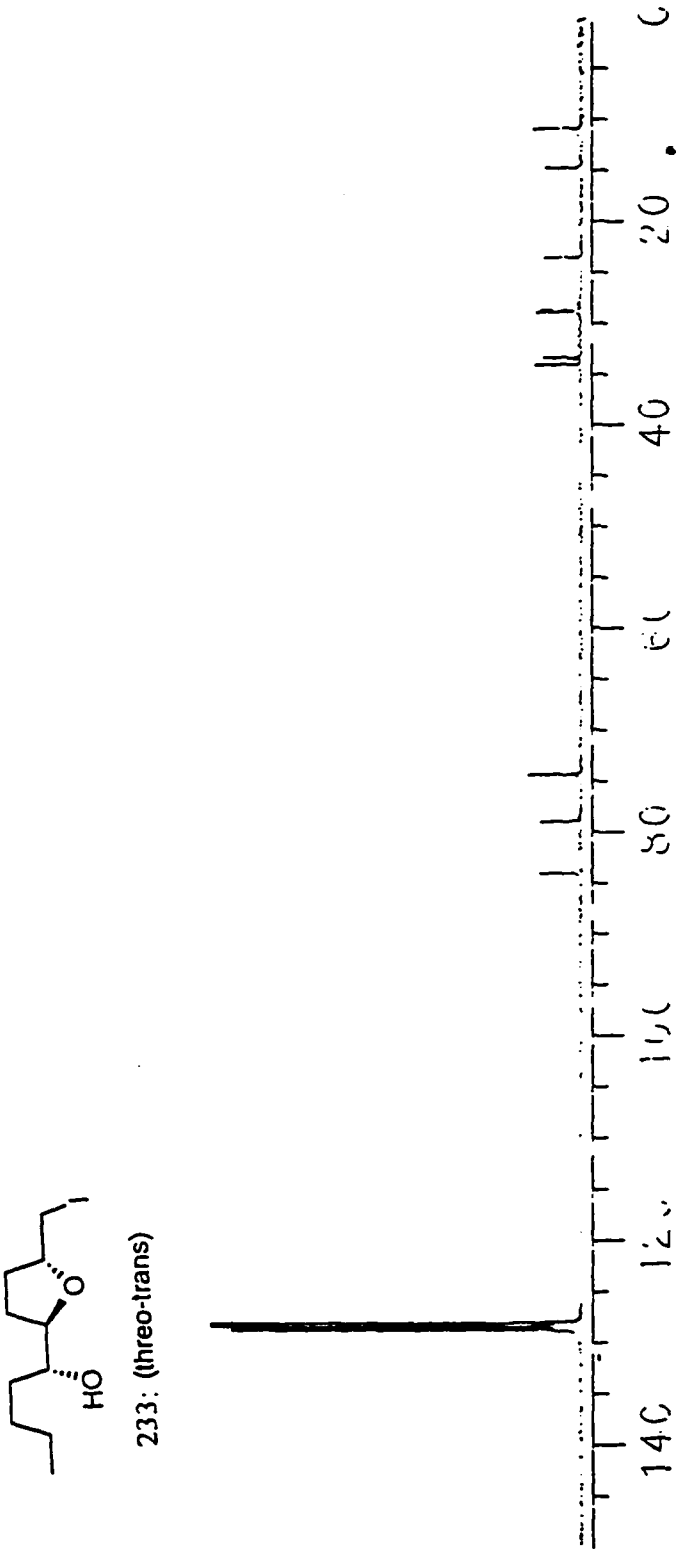


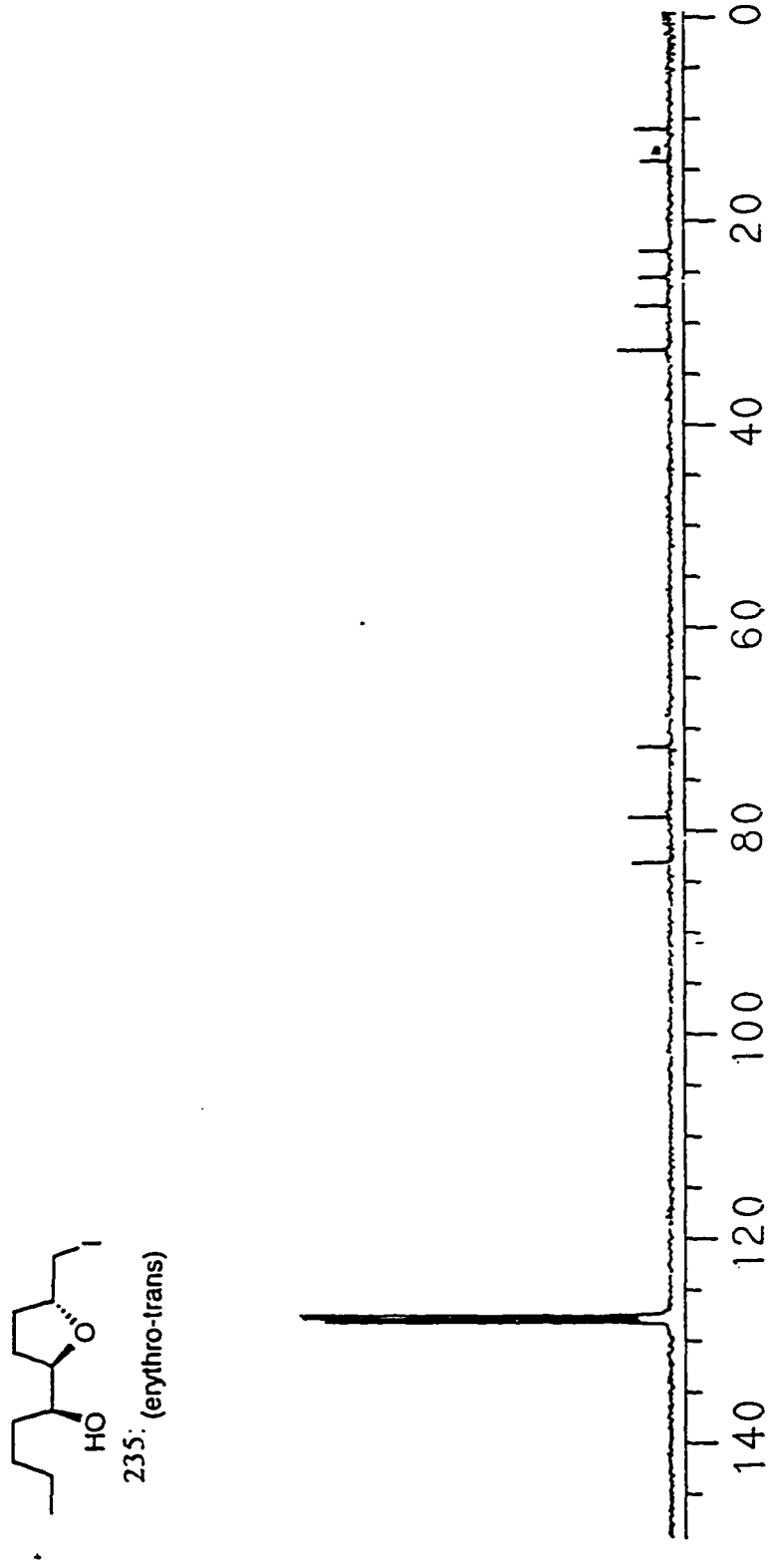
227 (erythro-*E*)

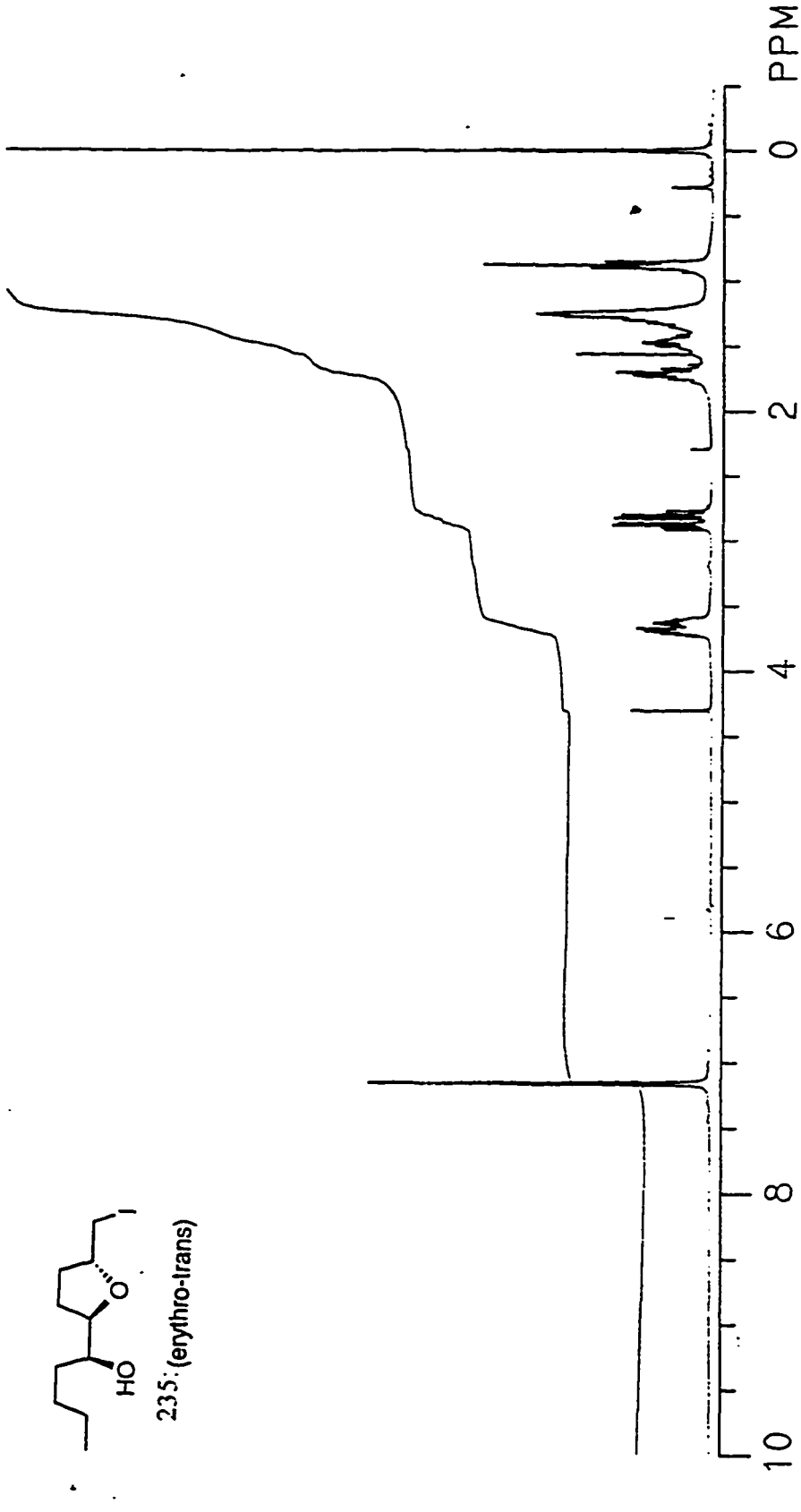




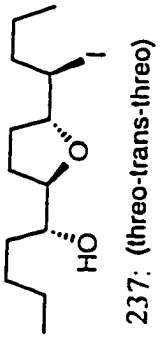
233: (threo-trans)



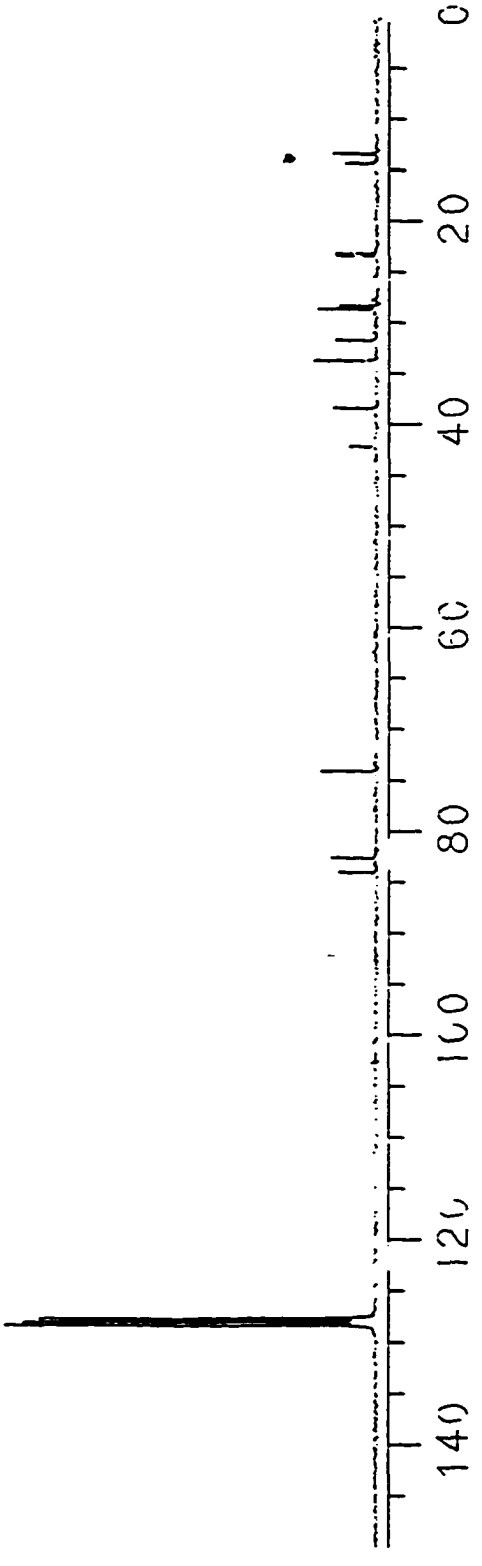


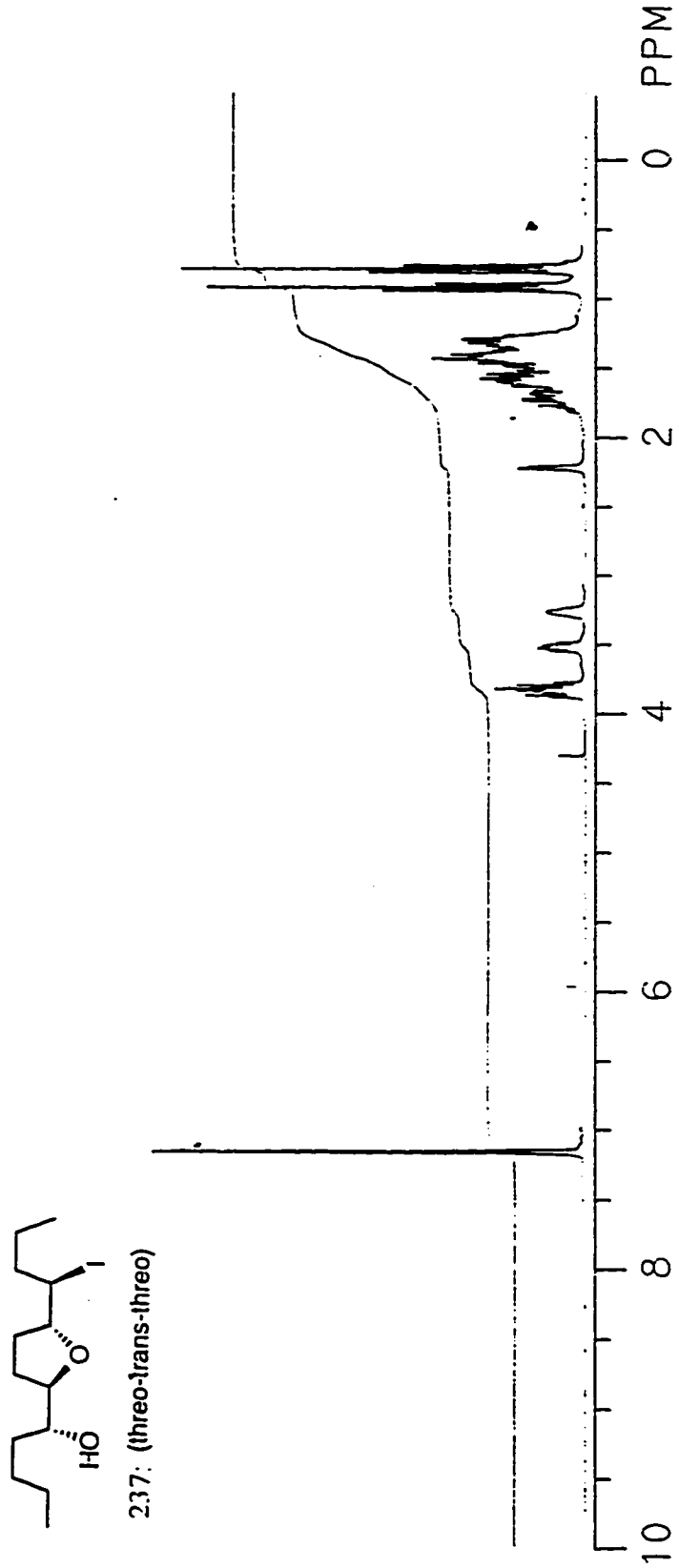


235: (erythro-trans)

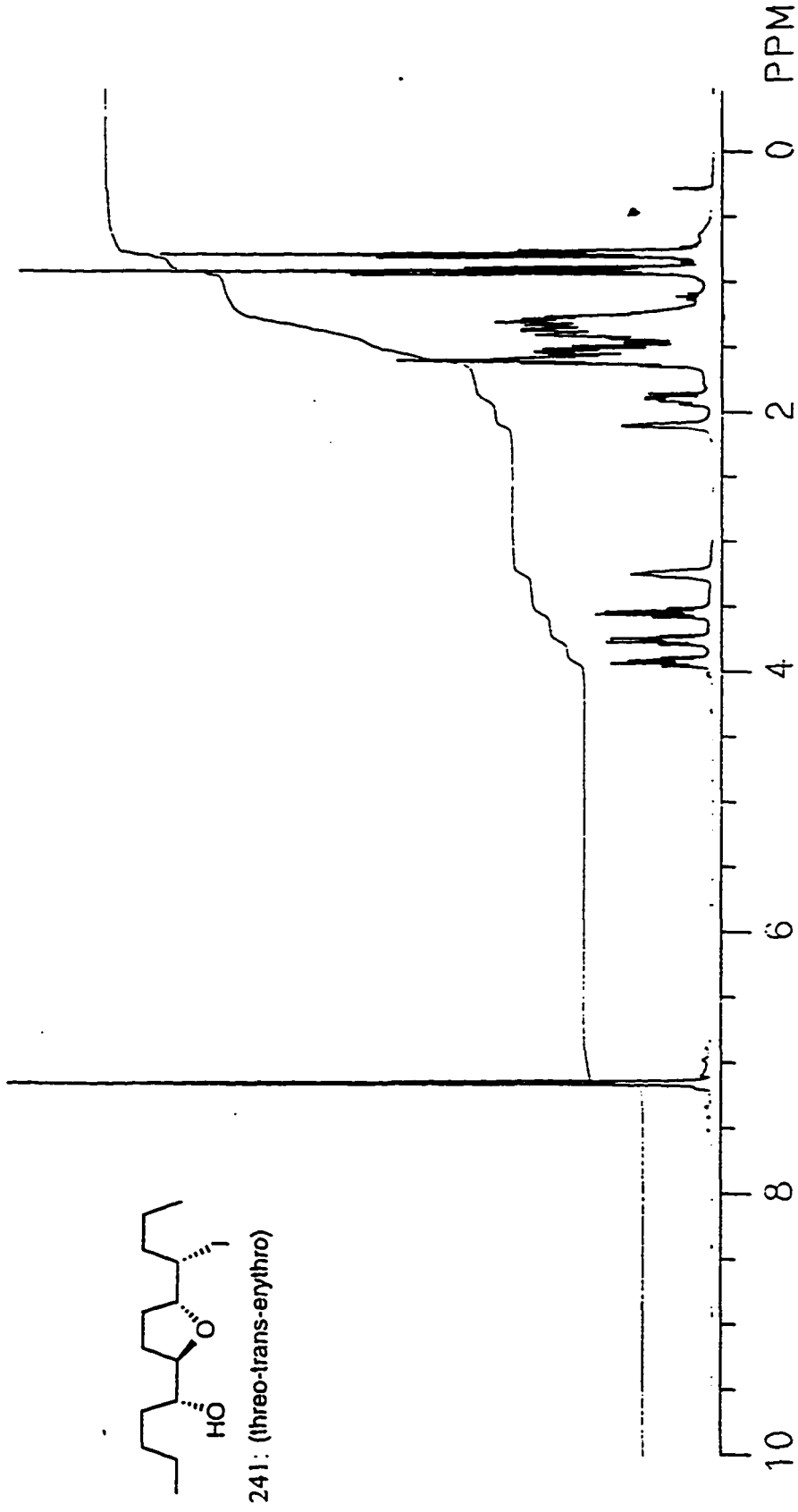


237: (threo-trans-threo)

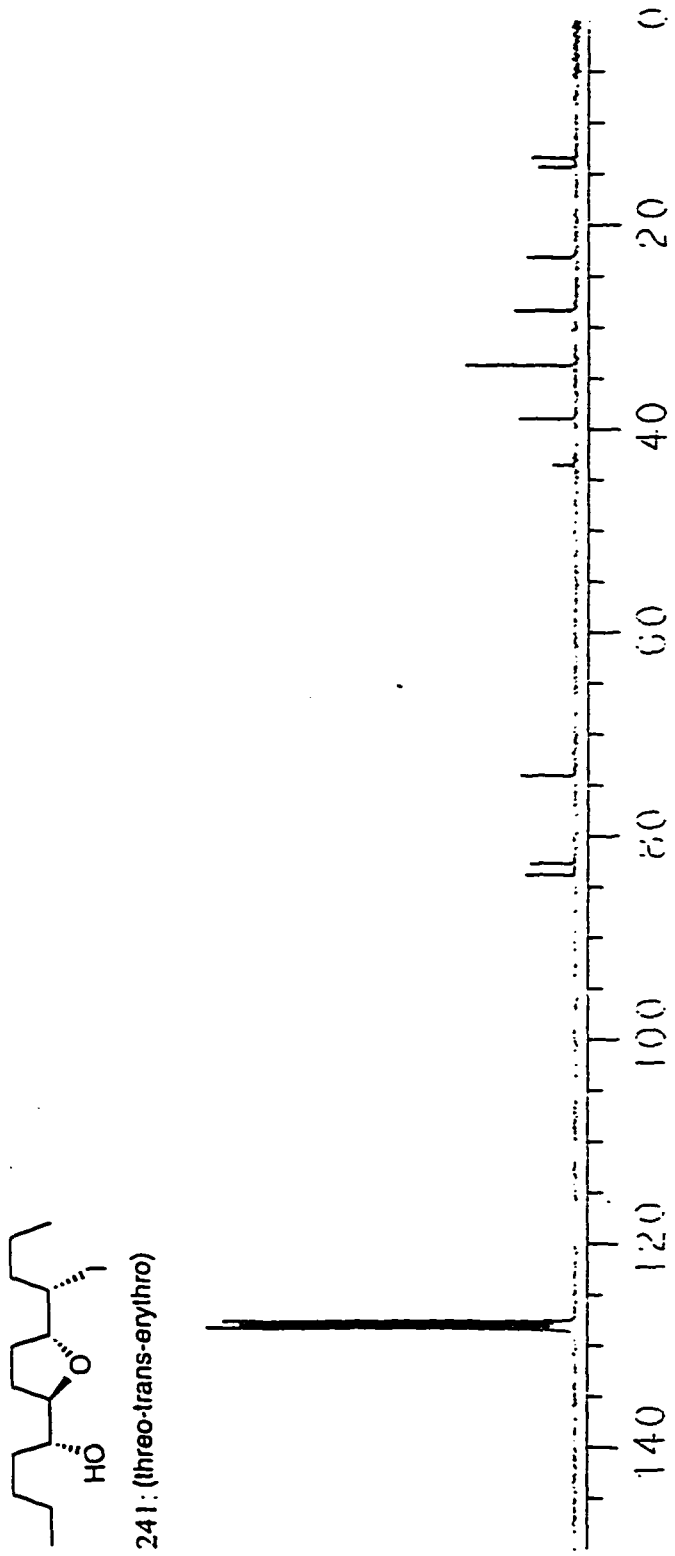


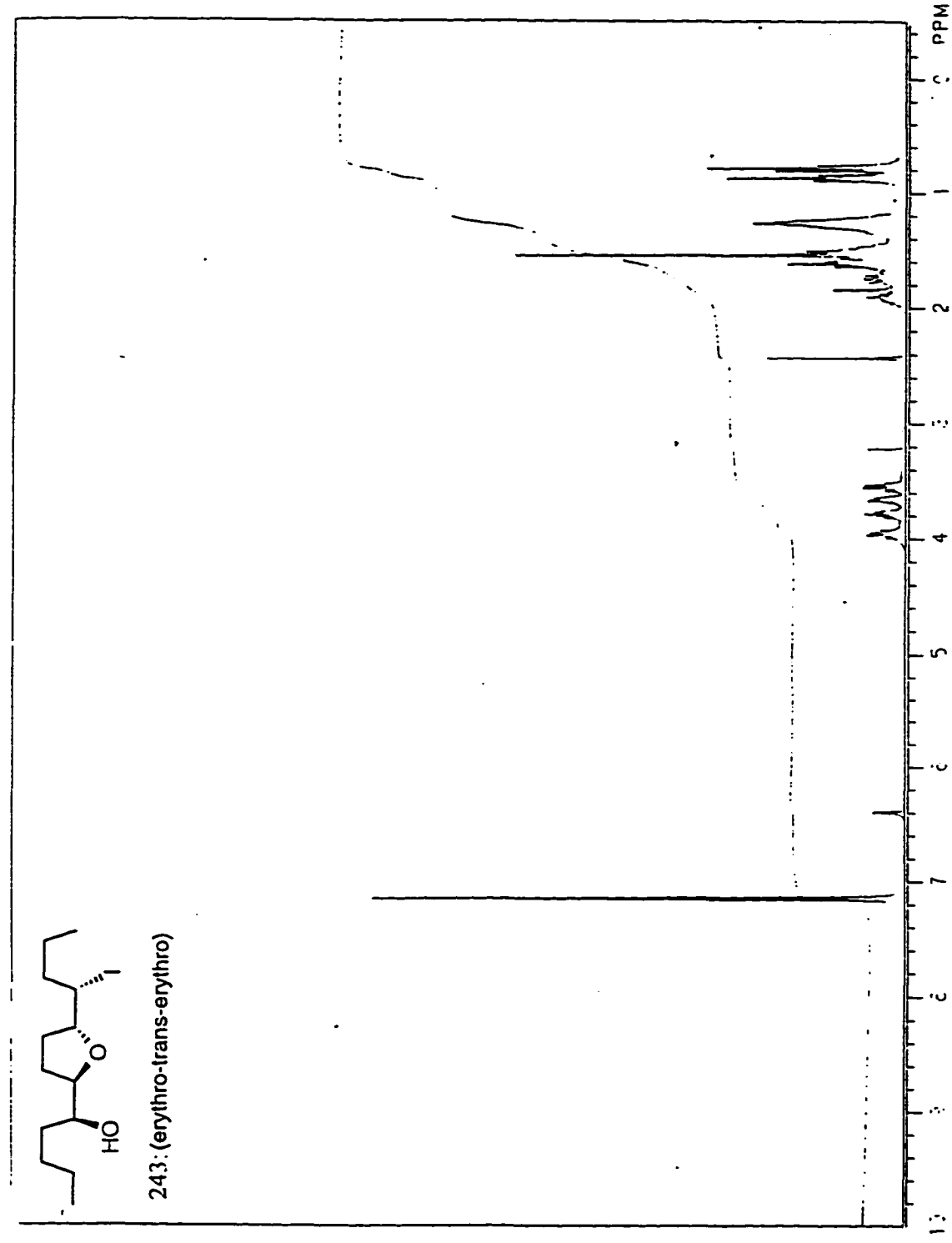


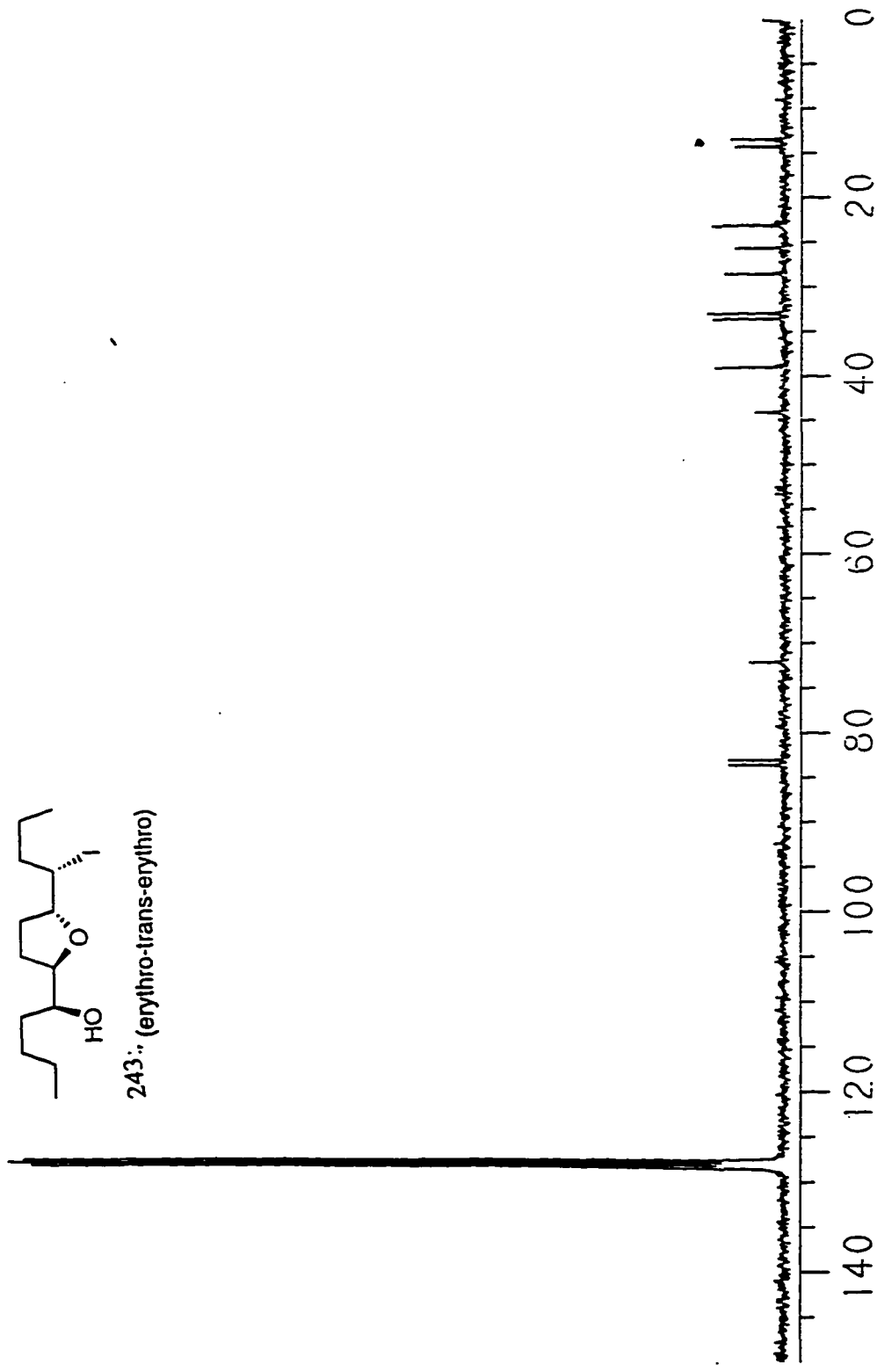
237: (threo-trans-threo)

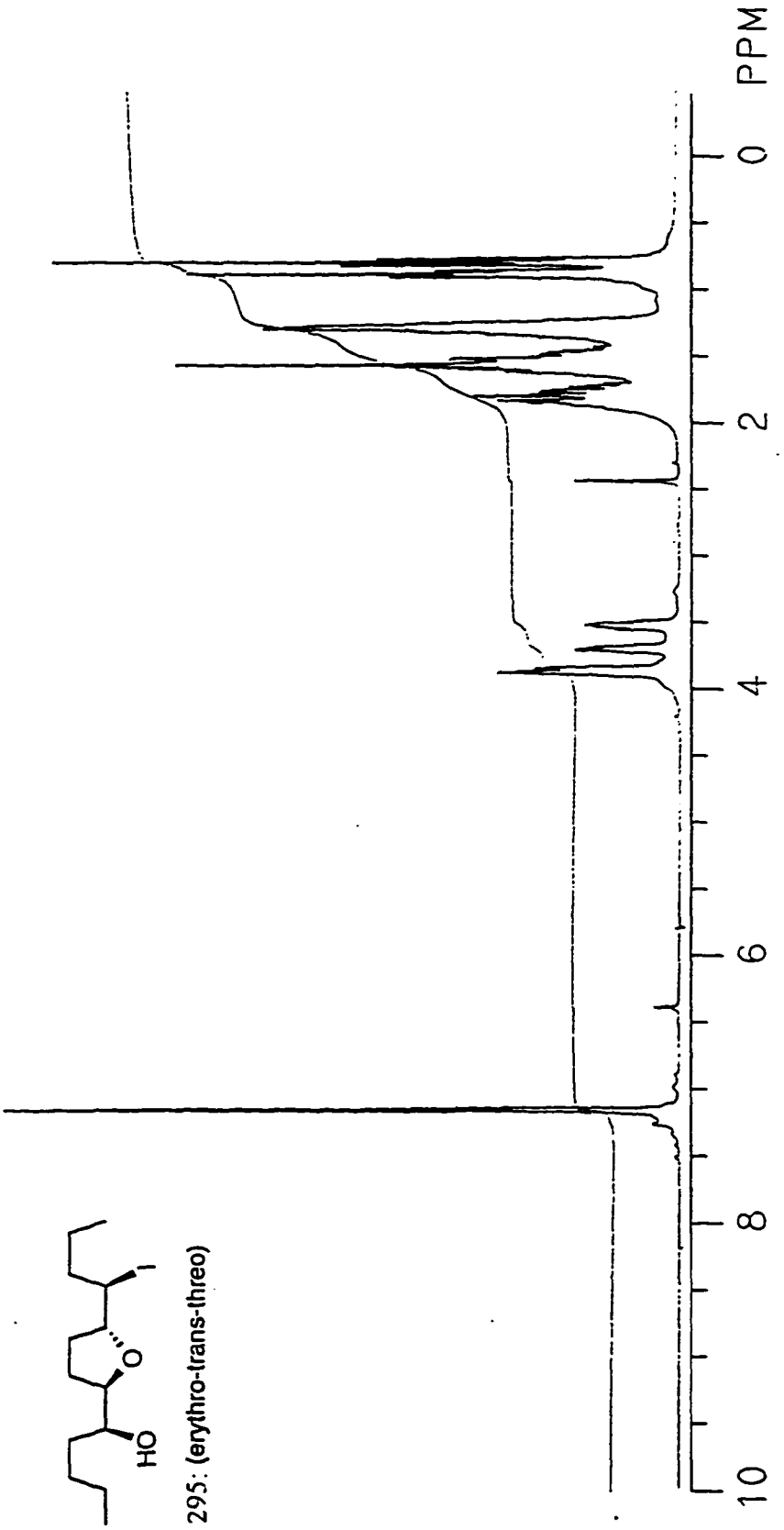


241: (threo-trans-erythro)

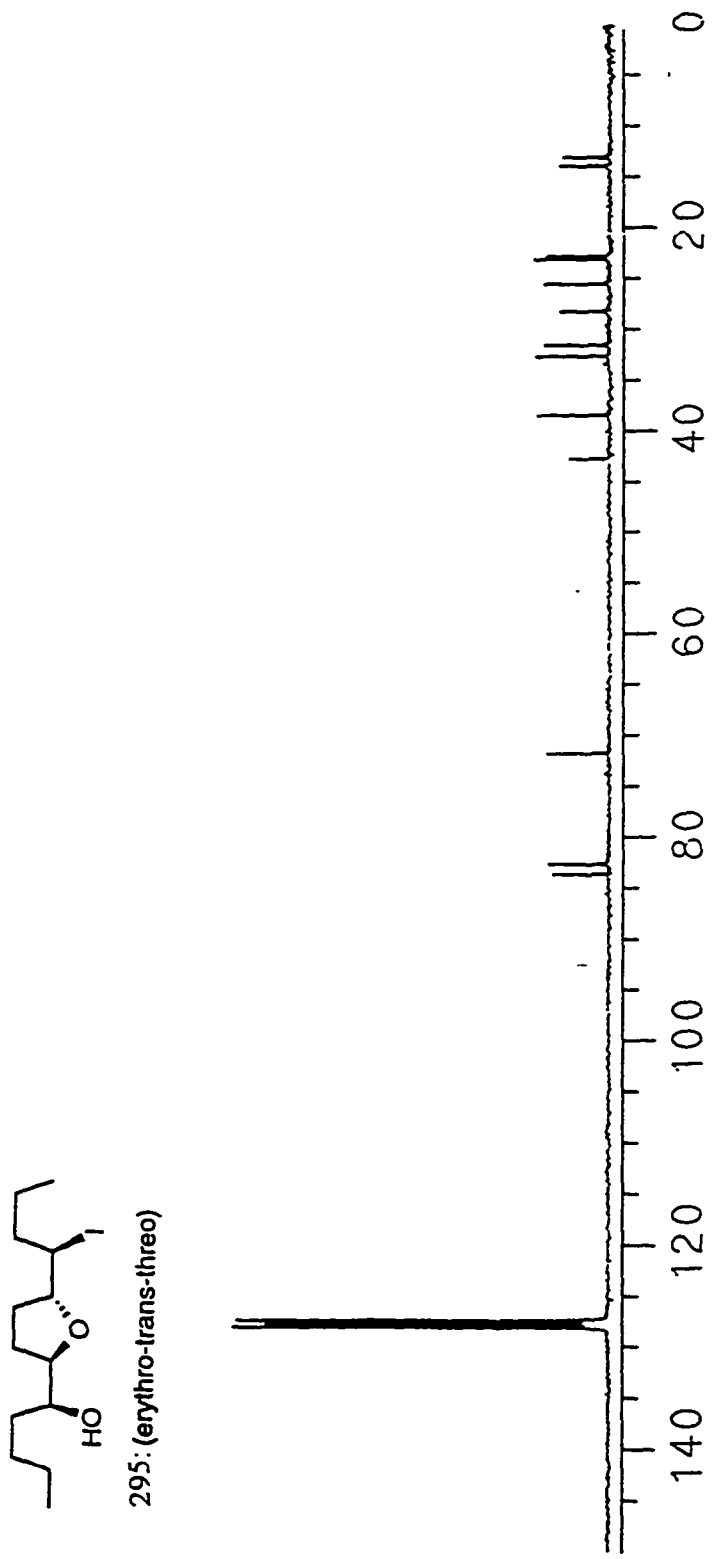


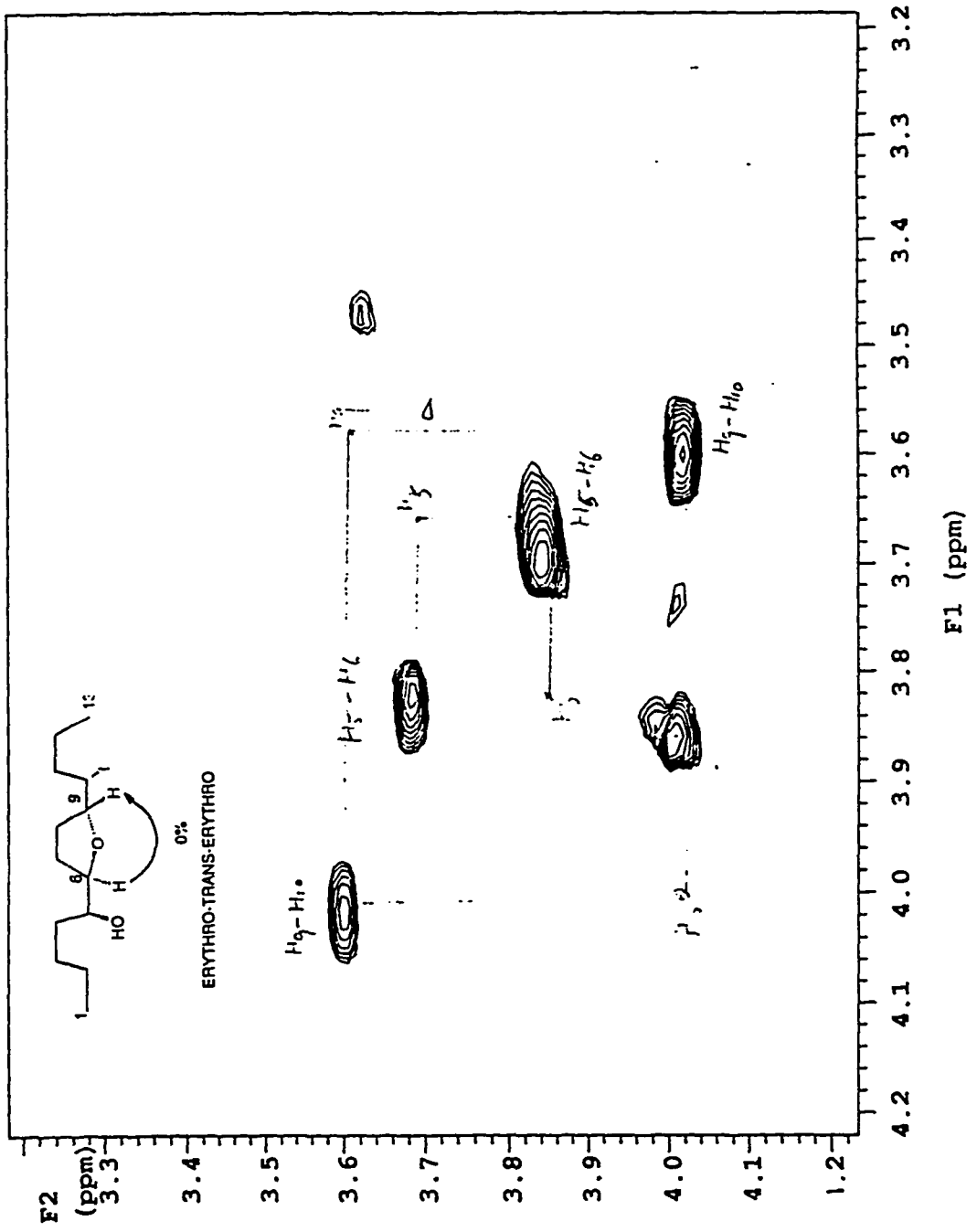


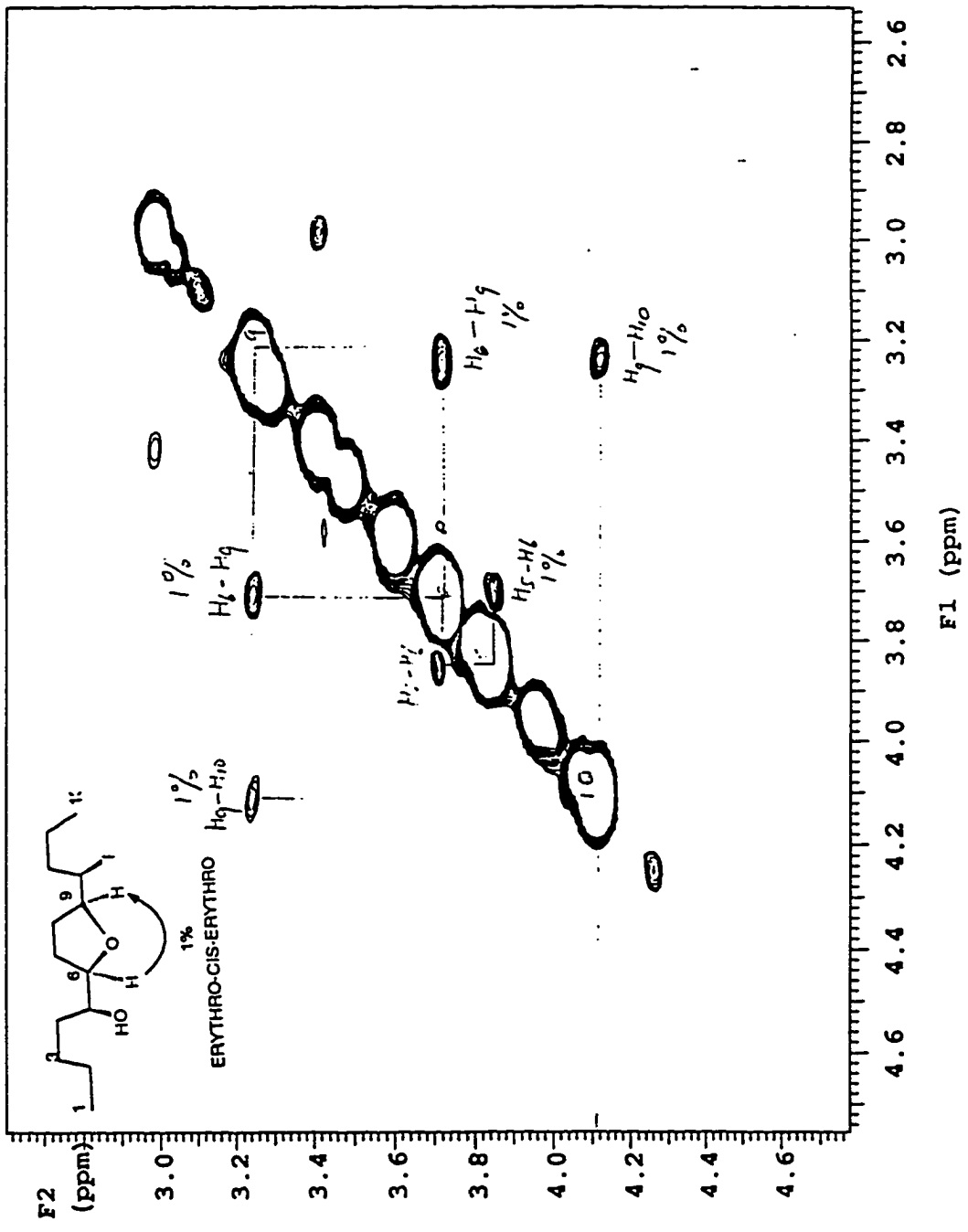




295: (erythro-trans-threo)

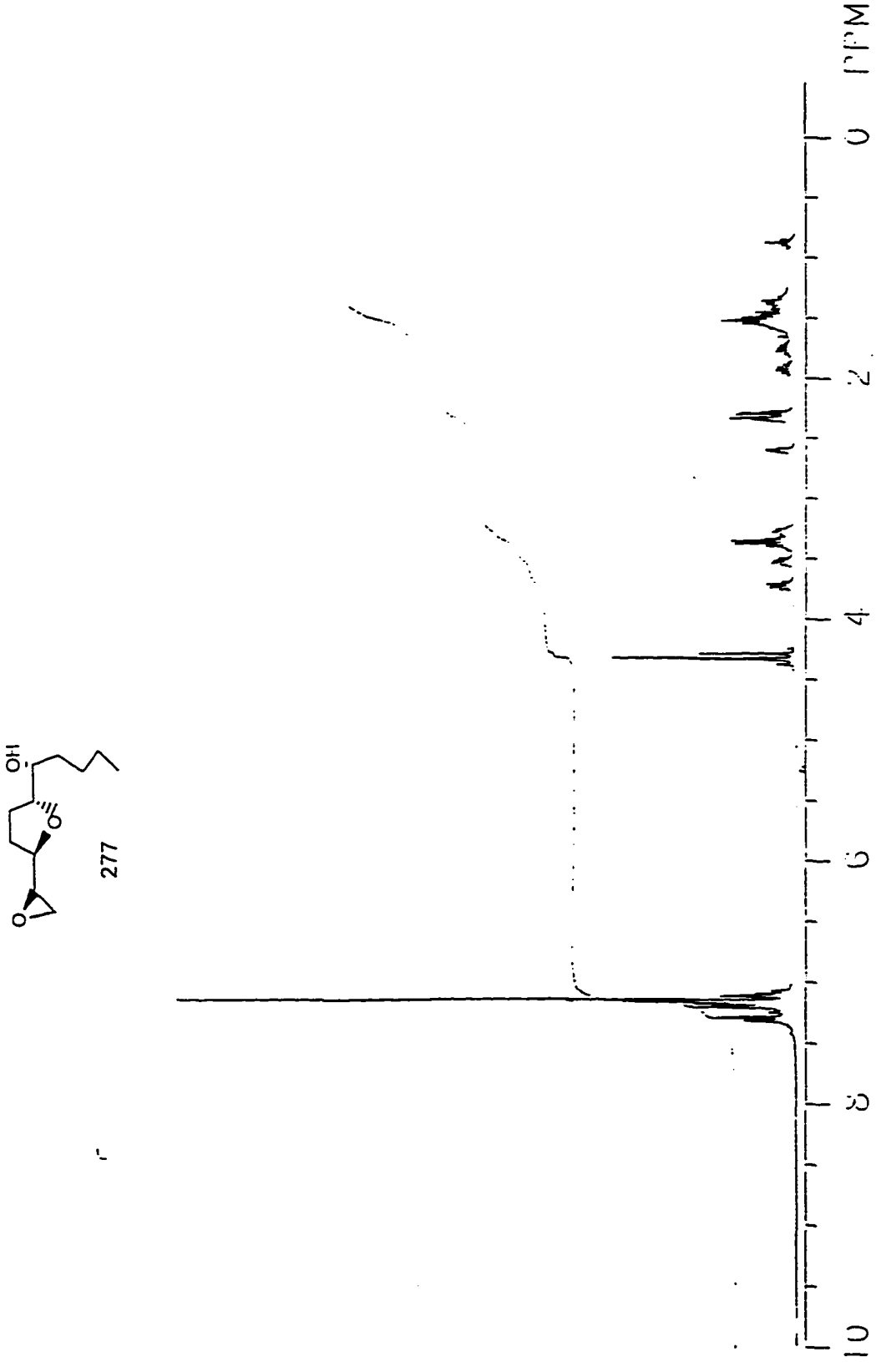


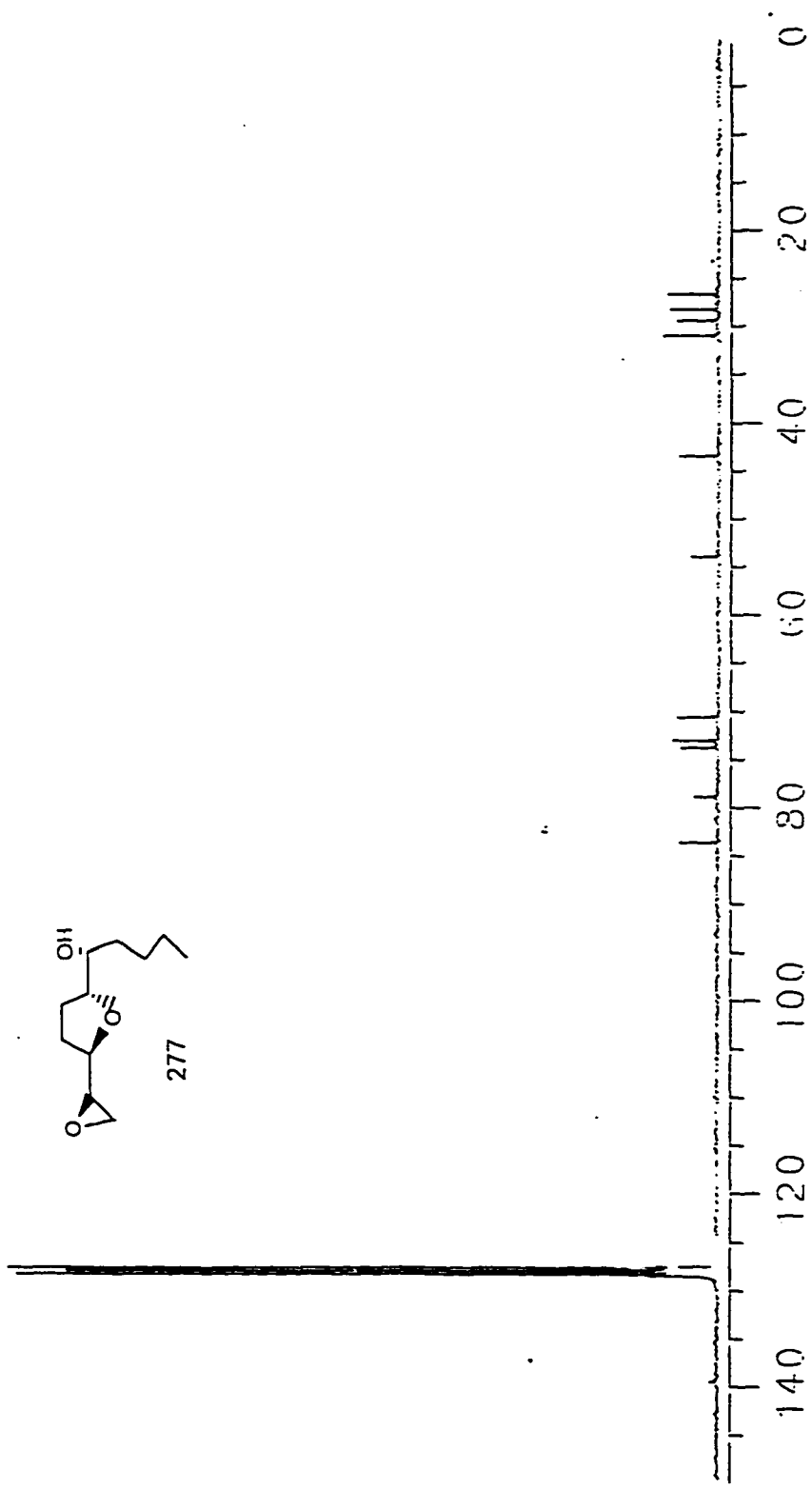


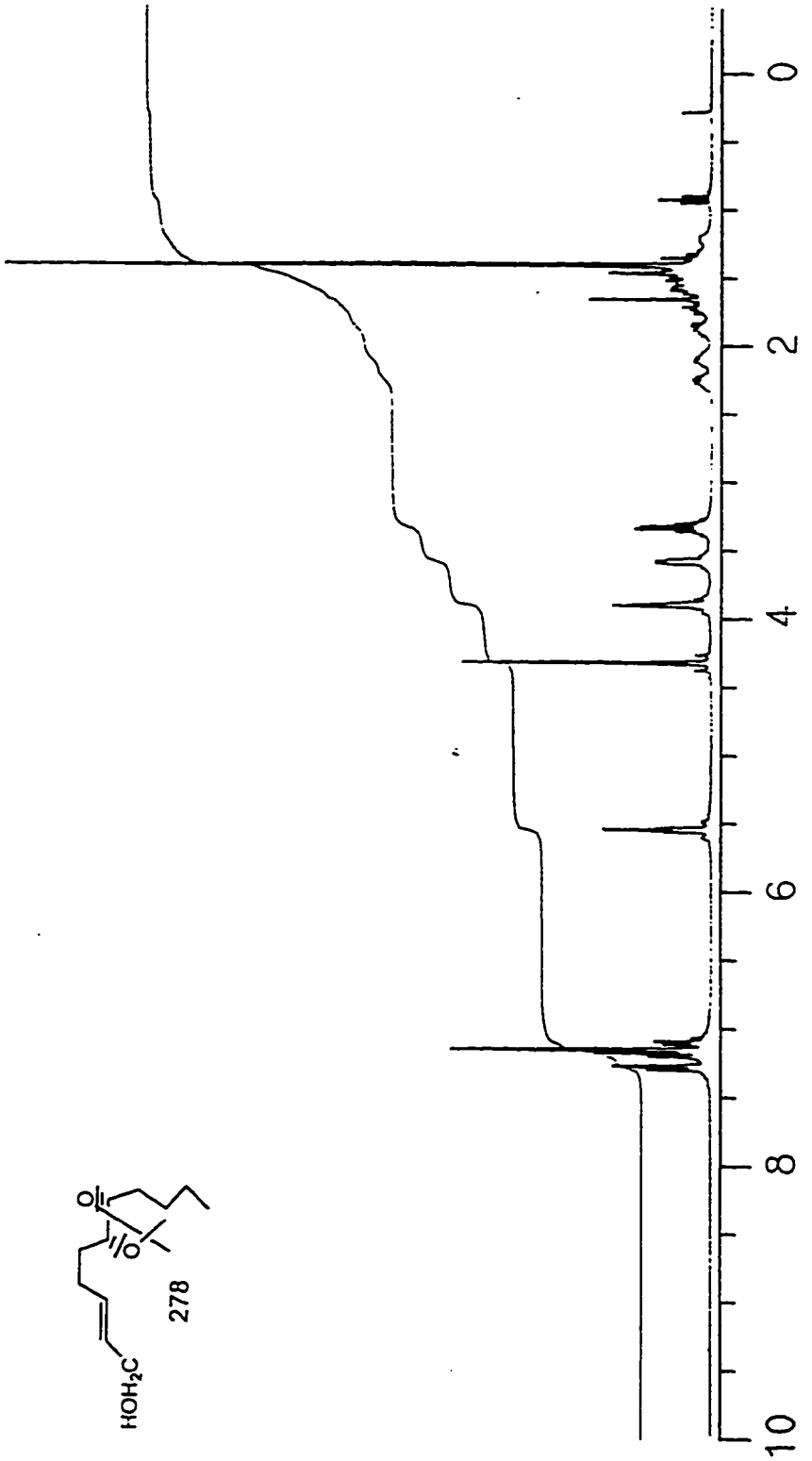


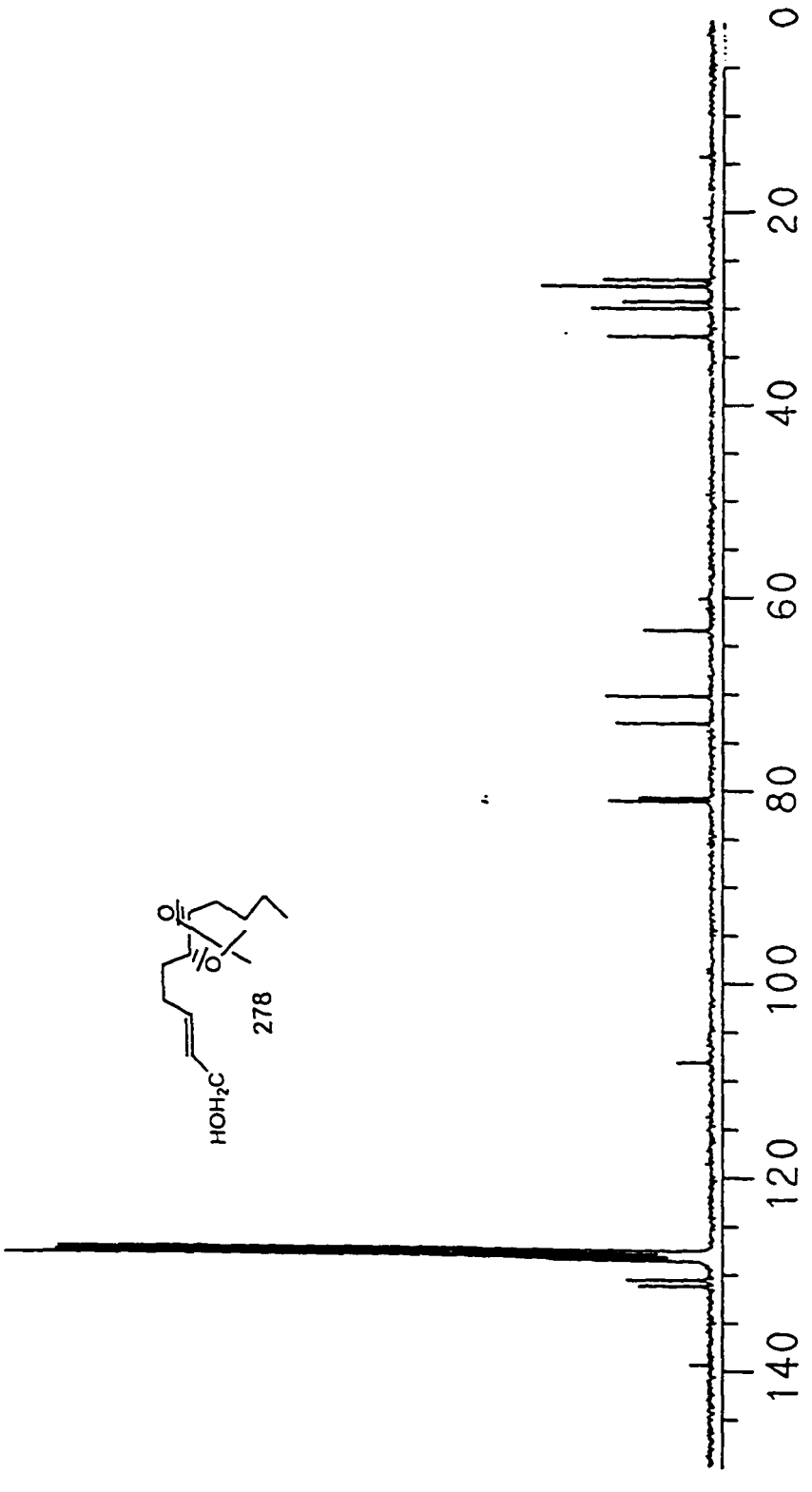
Appendix 4

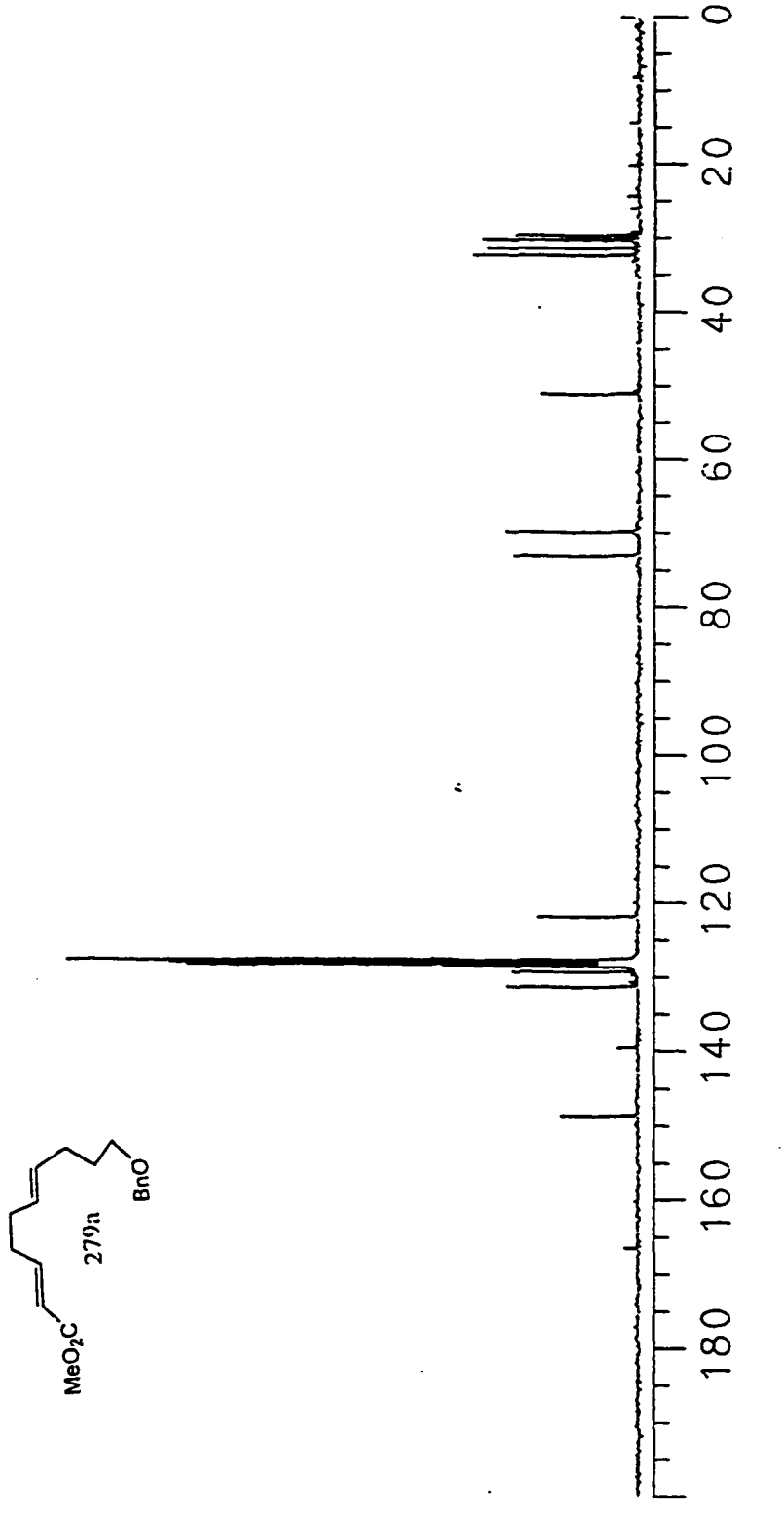
^{1}H and ^{13}C NMR of Compounds in Part IV

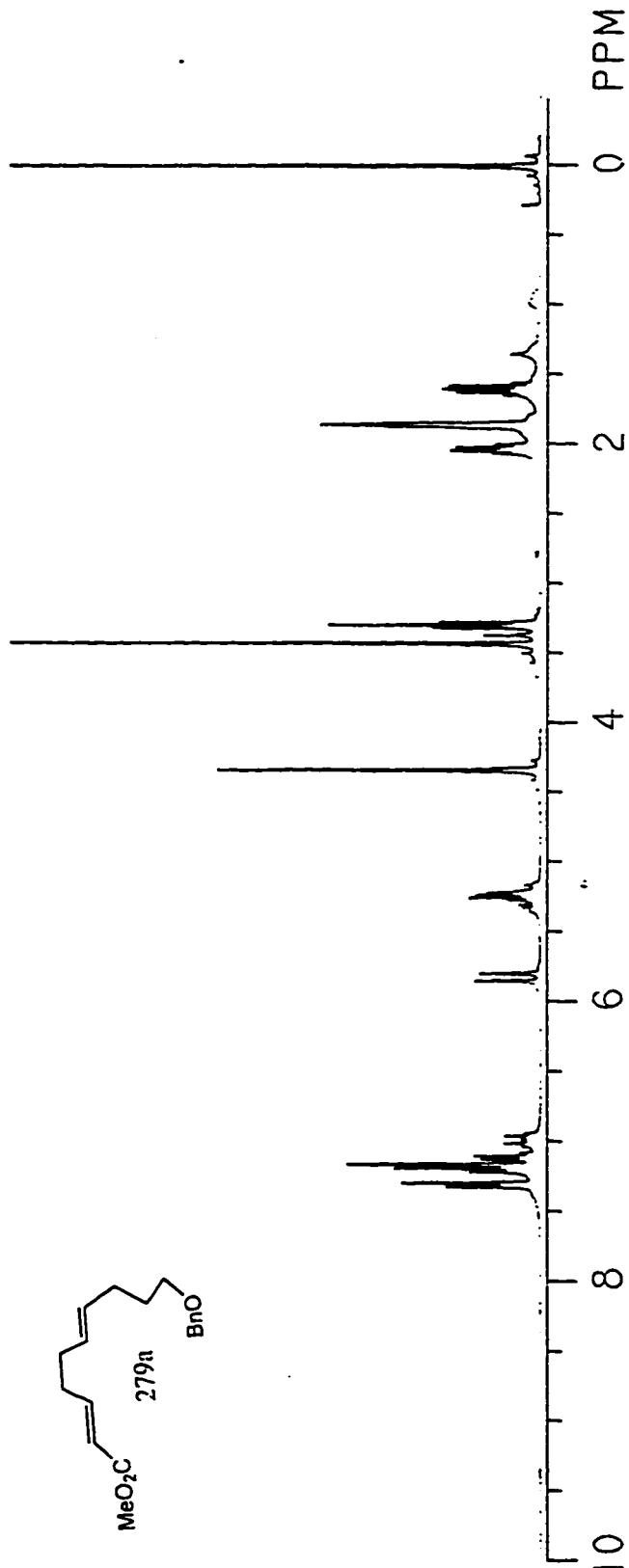


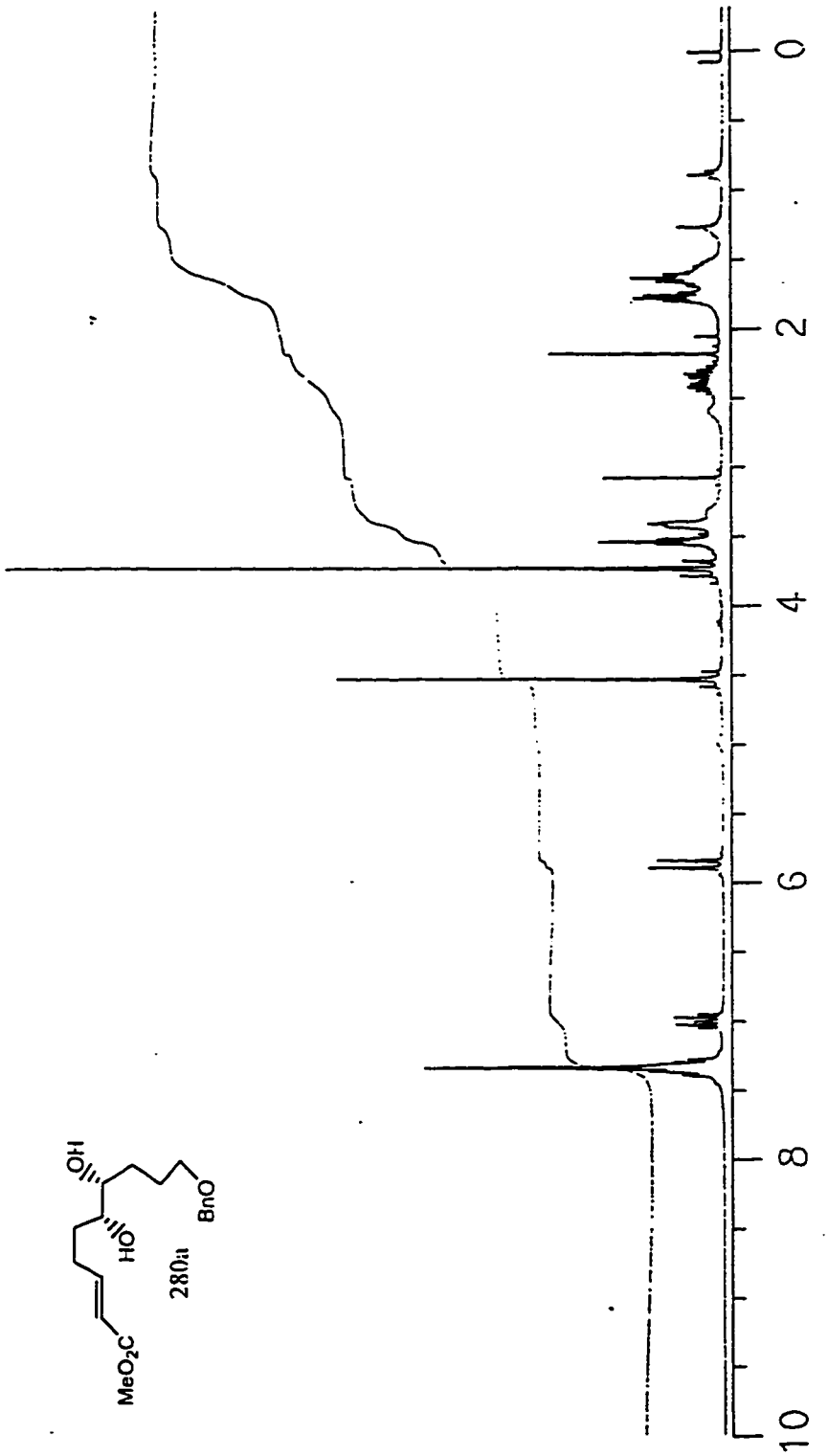


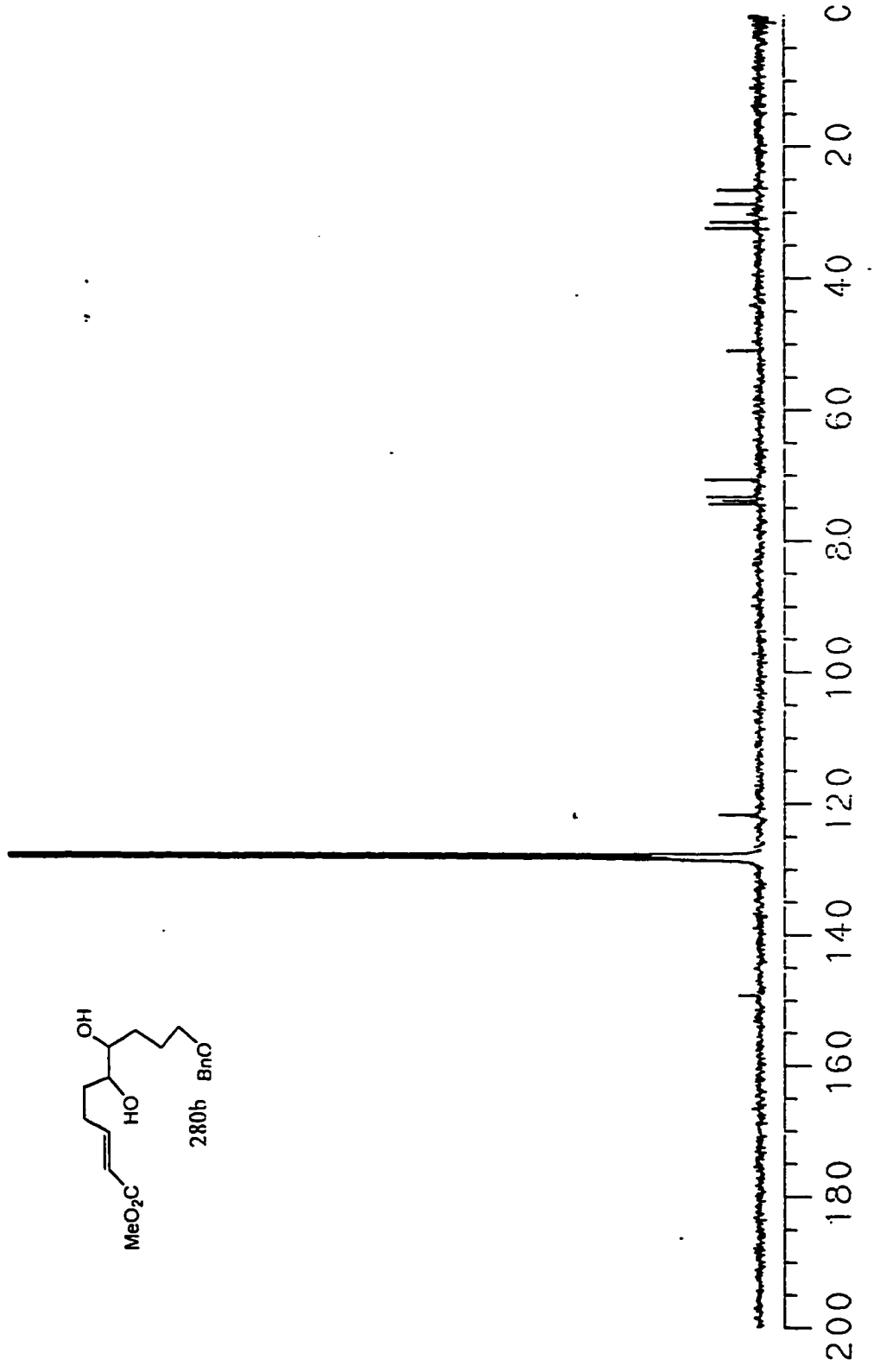


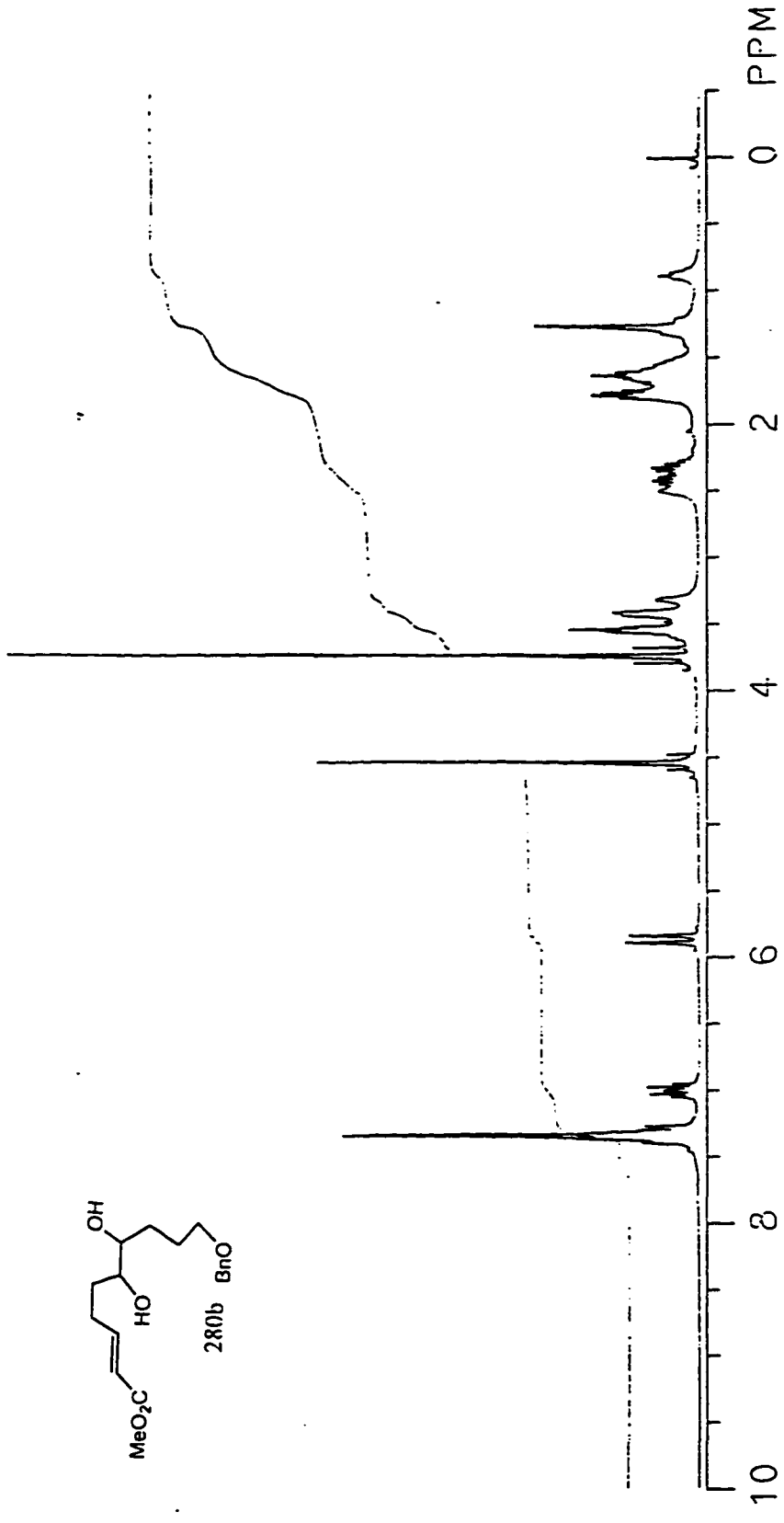


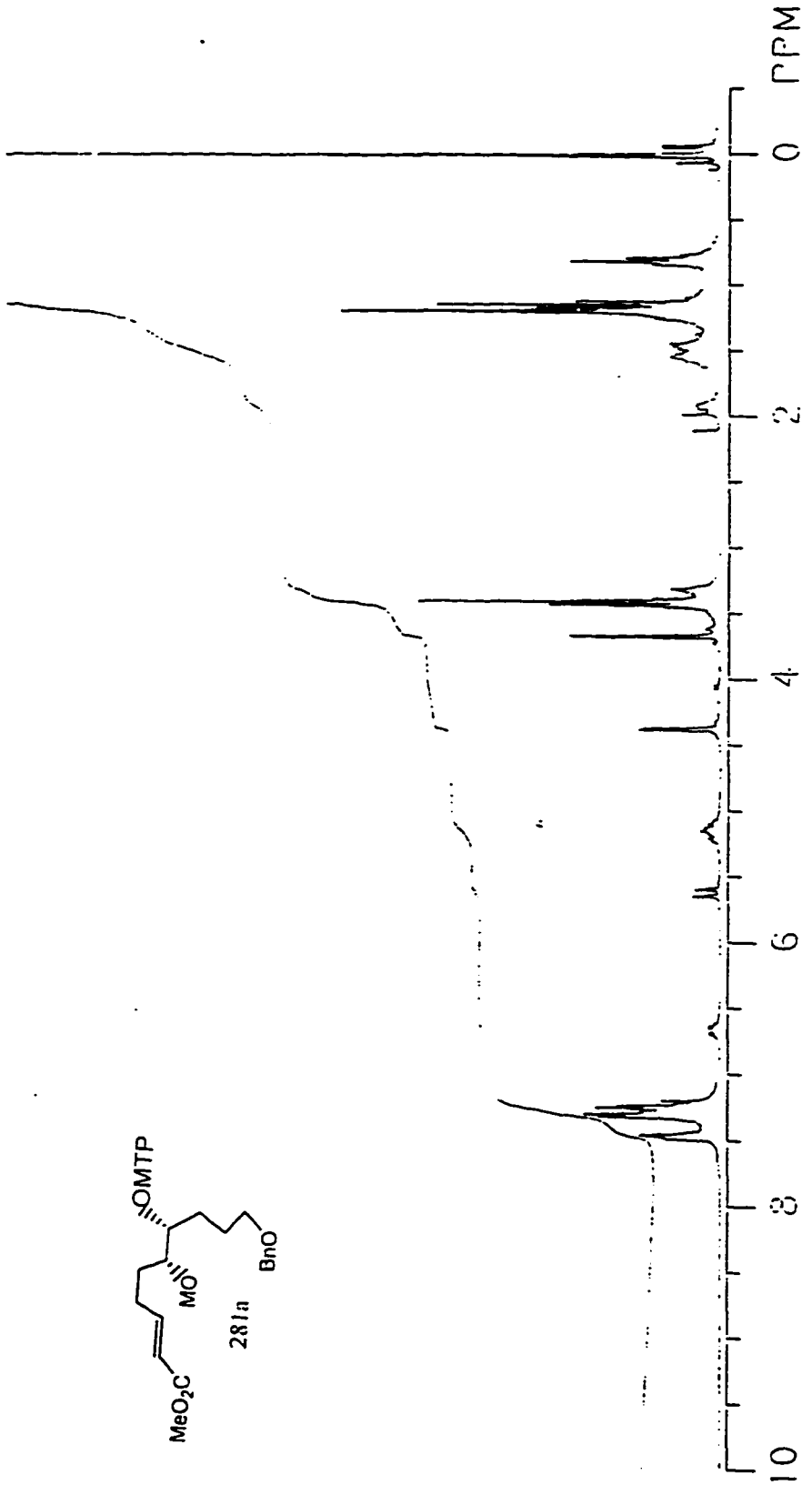


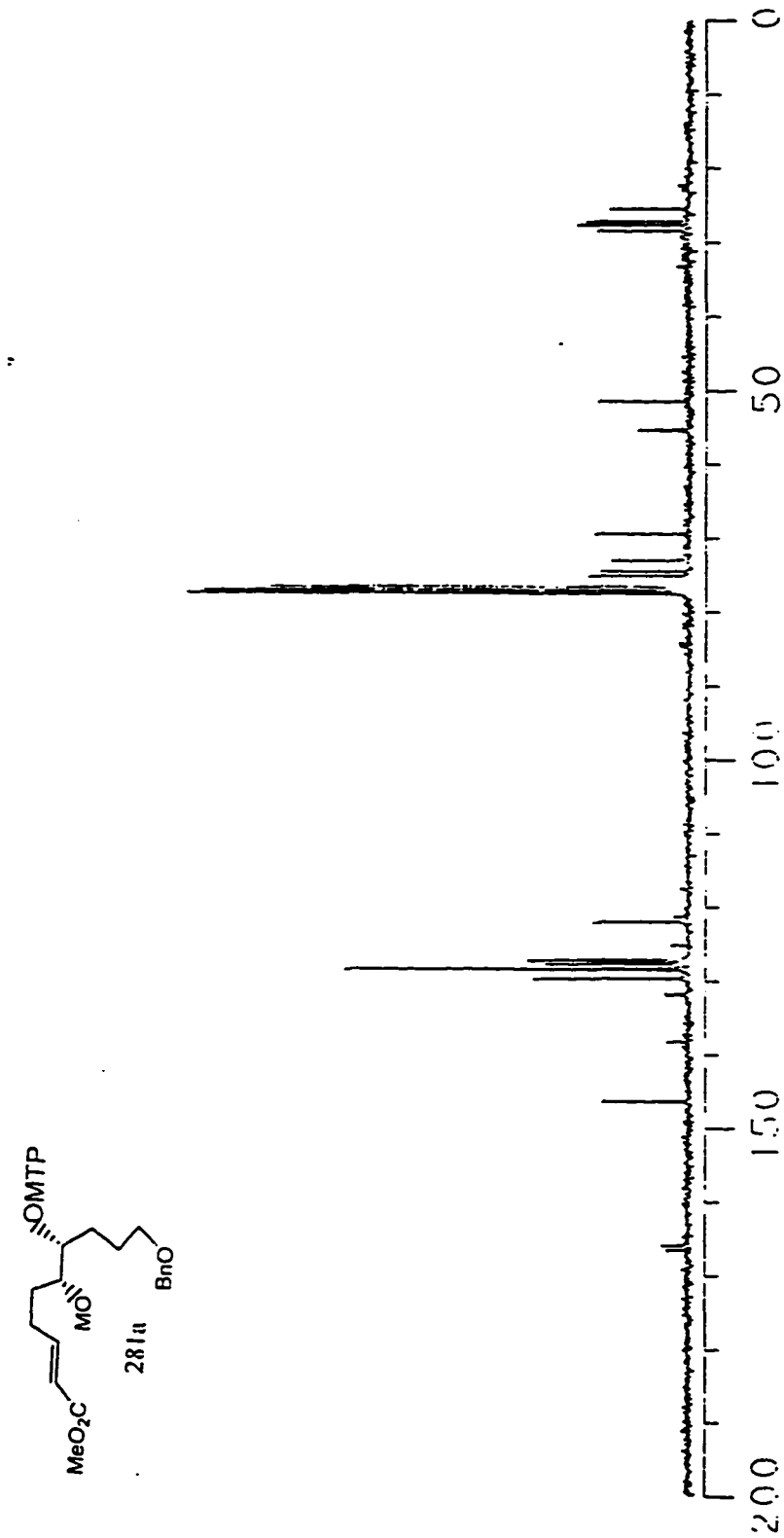


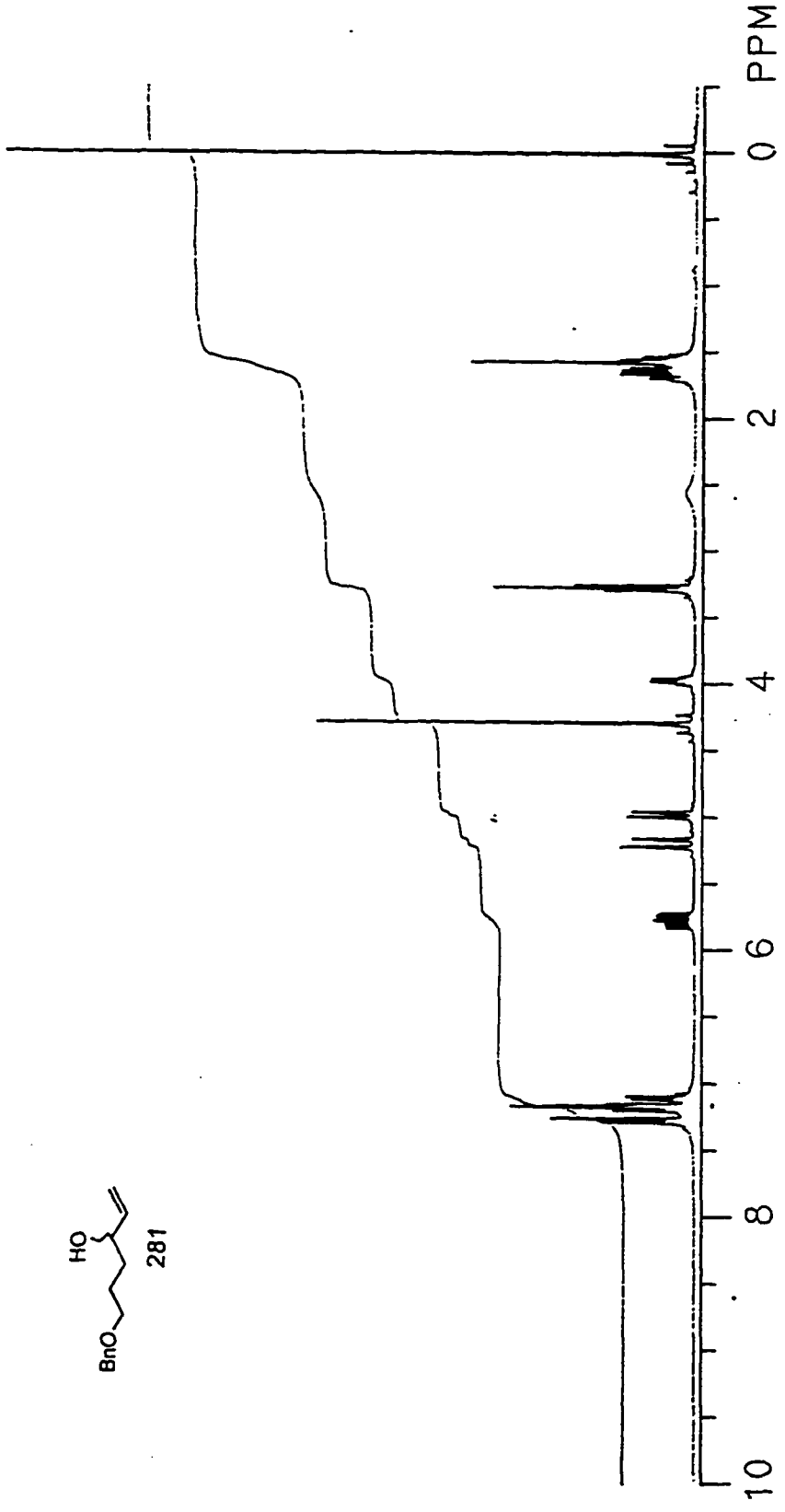


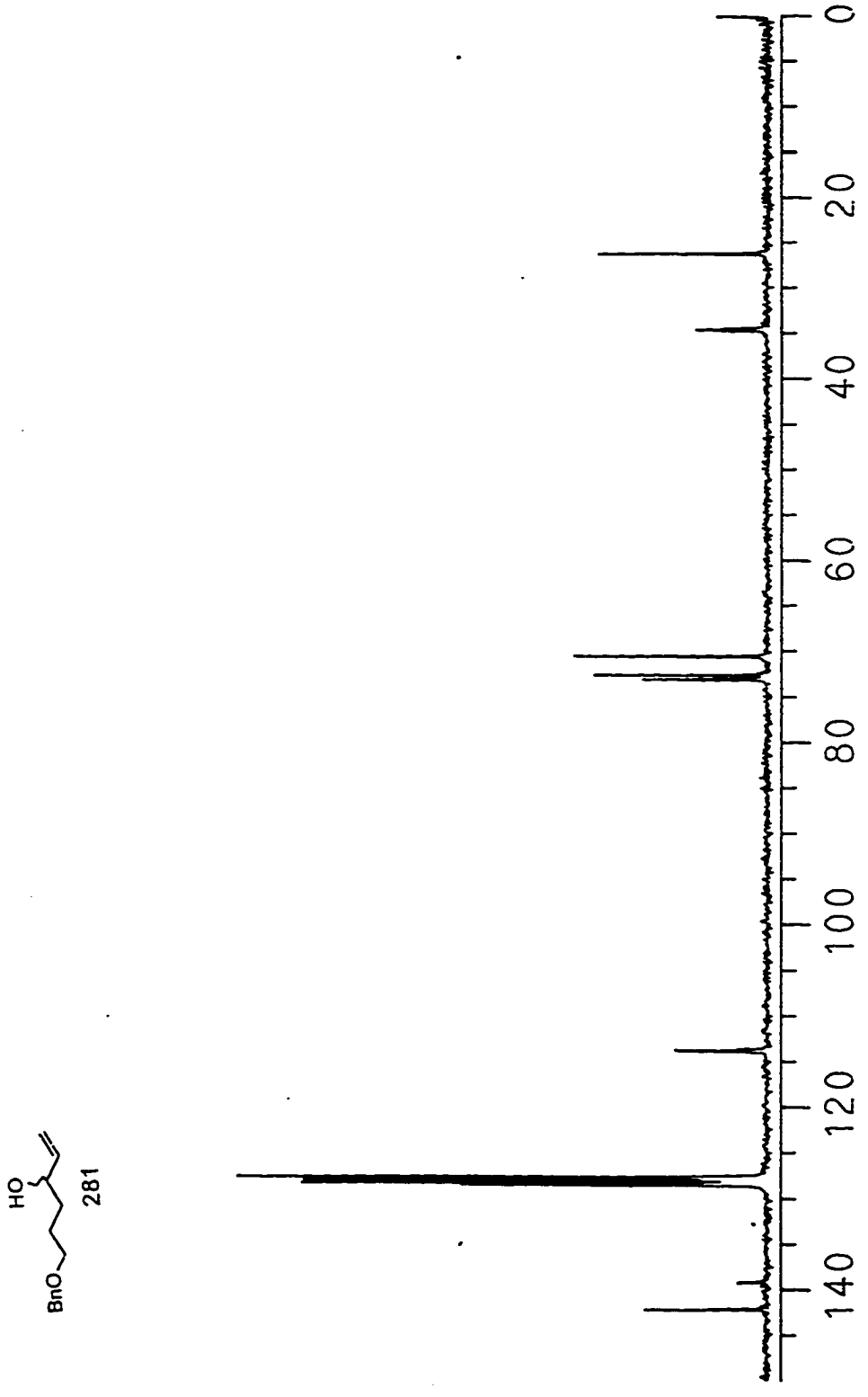


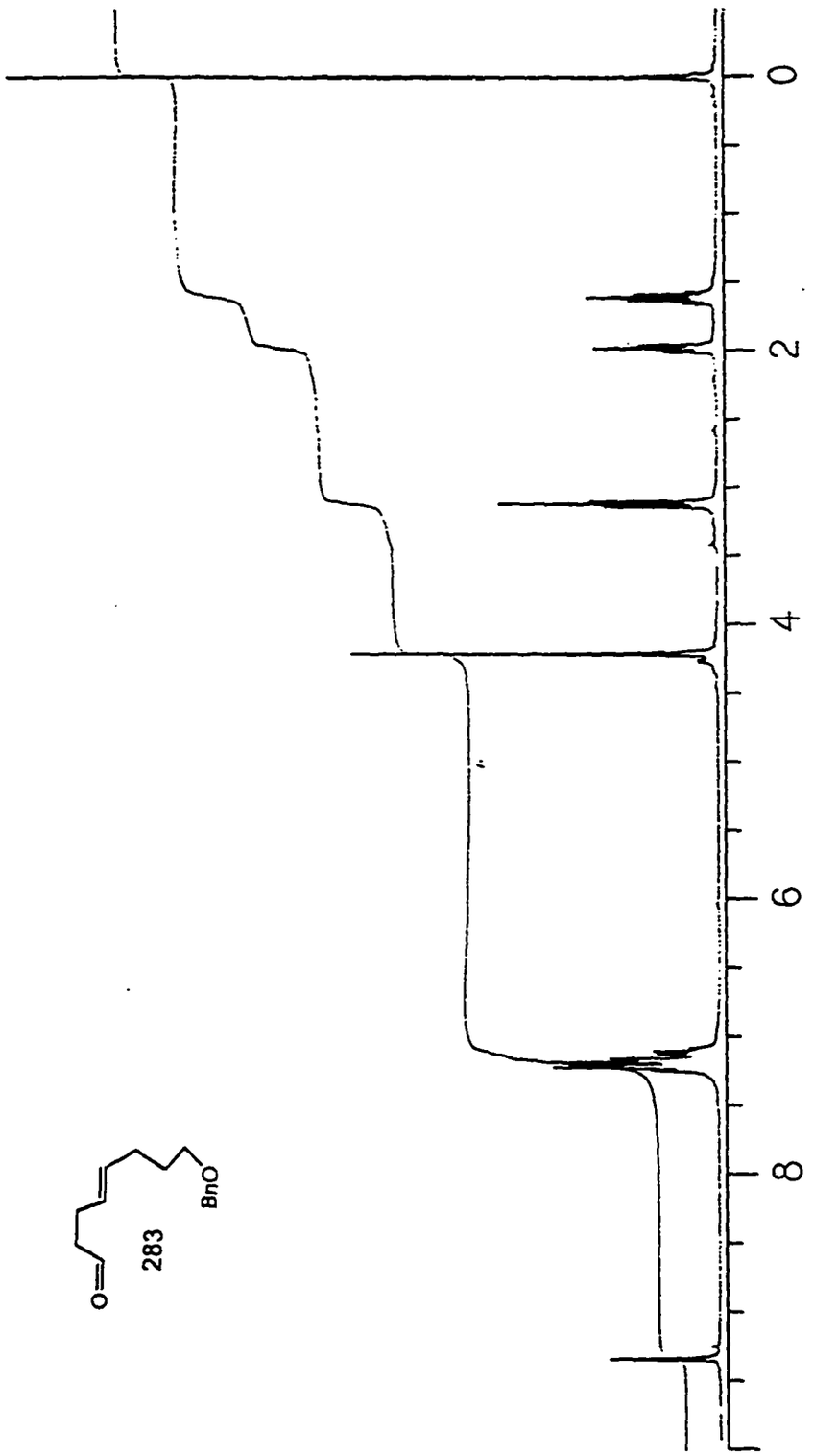












REFERENCES

(1) Westley, J. W. *Annu. Rept. Med. Chem.* **1975**, 10, 246.

(2) Mitrovic, M.; Schildknecht, E.G. *Poult. Sci.* **1974**, 53, 1448.

(3) Pressman, B. C.; *Annu. Rept Med. Chem.* **1976**, 45, 501.

(4) Nakamura, M.; Kunimoto, S.; Takahashi, Y.; Naganawa, H.; Sakaue, M.; Inone, S.; Ohno, T. Y.; Takeuchi, T. *Antimicrob. Agents Chemother.* **1992**, 36, 492.

(5) Polyether Antibiotics in Antibiocs: Isolation, Separation and purification. Hamill, R. L.; Crandall, L. W.; Weinstein, M. J.; Wagman, G. H.N. Y., pp 481, 1978, A204 I derivatives, U.S. Patent, 807832. Hamill, R. L.

(6) (a) Pressman, B. C. *Ann. Rev. Biochem.* **1976**, 45, 925. (b) Pressman, B.C.; Harris, E. J.; Jagger, W. S.; Johnson, J. H. *Proc. Natl. Acad. Sci. U.S.A.* **1967**, 58, 1949. (c) Moore, C.; Pressman, B. C. *Biochem. Biophys. Res. Commun.* **1964**,15, 562.

(7) (a) Rupprecht, J. K.; Hui, Y.-H.; Mclaughlin, J.L. *J. Nat. Prod.* **1990**, 53, 237; (b) Fang, X.; Rieser, M. J.; Gu, Z.; Zhao, G.; McLaughlin, J. L. *Phytochem. Anal.* **1993**, 4, 27. (c) Hopp, D. C.; Zeng, L.; Gu, Z.; Mclaughlin, J. L. *J. Nat. Prod.* **1996**, 59, 97. (d) Rieser, M. J.; Gu, Z.; Fang, X.-P.; Zeng, L.; Wood, K. V.; McLaughlin, J. L. *J. Nat. Prod.* **1996**, 59, 100.

(8) Hui, Y, -H., Rupprecht, J. K., Anderson, J. E., Liu, Y. -M., Wood, K. V. Smith, D. L., Chang, C. -J. and McLaughlin, J. L. *Tetrahedron*, **1989**, 6941-6948.

(9) Bovin, T. L. B.; *Tetrahedron*, **1987**, 43, 3309-3362.

(10) Harmange, Jean-C, and Figadere, B.; *Tetrahedron Asymmetry* **1993**, 4, 1711-1754.

(11) Klein, E. and Rojahn, W., *Tetrahetron* , **1965**, 21, 2353.

(12) Walba D. M., Waud M. D. and Wikes M. C. , *J. Am. Chem. Soc.* **1979**, 101, 4396.

(13) Sharpless, K. B.; Teranishi, A. Y. and Backvall, J. E.. *J. Am. Chem. Soc.*, **1977**, 99, 3120

(14) Baldwin, J. E., Crossley, M. J., and Lehtonen, E. M., *J. Chem. Soc. Chem. Comm.*, **1979**, 918-920.

(15)Wolfe, S. and Ingold, C. F., *J. Am. Chem. Soc.*, **1981**, 103, 940-941.

(16) Rappe, A. K.; Goddard, W. A. III, *J. Am. Chem. Soc.*, **1980**, 102, 5115-5117.

(17) Walba, D. M.; and Edwards P. D., *Tetrahedron lett.*, **1980**, 21, 3531-3534.

(18) Walba, D. M.; and Stoudt, G.S.; *Tetrahedron lett.*, **1982**, 23, 727

(19) Baldwin, J. E.; Crossley, M. J.; and Lehtonen, E.M., *J. Chem. Soc., Chem. Comm.* **1979**, 918-920.

(20) Corey E. J. and Ha, D. C., *Tetrahedron lett.*, **1988**, 29,3171-3174

(21) Tang S. , Kennedy R. M., *Tetrahedron lett.*, **1992**, 33, 3729

(22) Tang S. , Kennedy R. M., *Tetrahedron lett.*, **1992**, 33, 5303

(23) Sinha, S. C..; Sinha-Bagchi, A.; Keinan, E. *J. Am. Chem. Soc.*, **1995**, 1447.

(24) Fukuyama T., Vranesic B.; Negri D. P. and Kishi Y. Tetrahedron Lett., 1978, 31 2741.

(25) Nakata, T., Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer , T.; and Kishi, Y. *J. Am. Chem. Soc.*, **1978**, 2933-2935.

(26) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *J. Org. Chem.* **1991**, 56, 2299.

(27) For a recent review, see Koert, U., *Synthesis*, **1995**, 115-132

(28) (a) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.*, **1985**, 107, 5312. (b) Hoye, T. R.; Suhadolnik, J. C. *Tetrahedron*, **1986**, 42, 2855.

(29) Hoye, T. R.; Hanson, p. r. Kovelesky, A.; Ocain, T. D.; Zhuang, Z. . *J. Am. Chem. Soc.*, **1991**, 113, 9369.

(30) Still, W. C.; Romero, A. G.; *J. Am. Chem. Soc.*, **1986**, 108, 2105.

(31) Rychnovsky, S.D. and Baretlett P. A., *J. Am. Chem. Soc.*, **1981**, 103, 3963-3964.

(32) Freeman, F. and Robarge, K. D., *Tetrahedron lett.* **1985**, 26, 1943-1946.

(33) Tamaru, Y., Hojo, M., Kawamura, S., Sawada, S. and Yoshida Z., *J. Org. Chem.*, **1987**, 52, 4062-4067.

(34) Amouroux, R., Folefoc, G., Chastrette, F., and Chastrette, M., *Tetrahedron Lett.*, **1981**, 22, 2259-2262.

(35) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, 112, 5290.

(36) (a) Walkup, R. D. and Park, G., *Tetrahedro Lett.*, **1987**, 28, 1023-1026. (b) Semmelhack, M. F. and Zhang, N. *J. Org. Chem.* **1989**, 54, 4483.

(37) Semmelhack, M. F., Epa, W. R., Cheung, A. W-H., Gu, Y., Kim, C., Zhang, N., and Lew, W., *J. Am. Chem. Soc.* **1994**, 116, 7455-7456.

(38) Lipshutz B. H. and Barton J. C., *J. Am. Chem. Soc.* **1992**, 114, 1084-1086.

(39) (a) Mcdonald, F. E..; Towne, T. B. *J. Am. Chem. Soc.* **1994**, 116, 7921. (b) Schlecht, M. F.; Kim, H. *Tetrahedron Lett.* **1985**, 26, 551. (c) Schlecht, M. F.; Kim, H. *J. Org. Chem.* **1989**, 54, 583. (d) Waddell, T. G.; Cartler, A. D.; Miller, T. J.; Pagni, R. M. *J. Org. Chem.* **1992**, 57, 381.

(40) Wilson, P.; Shan, W.; Mootoo, D. R. *J. Carbohydr. Chem.* **1994**, 13, 113.

(41) Labelle, M., Morton, H. E.; Guidon, Y.; Springer, J. P., *J. Am. Chem. Soc.*, **1988**, 110, 4533.

(42) (a) Rychnosky, S. D.; Barlett, P. A. *J. Am. Chem. Soc.*, **1981**, 103, 3963. (b) Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S.D.; Hehre, W. J. *J. Am. Chem. Soc.*, **1987**, 109, 672. (c) Label M.; Liotta, D.; Monahan, R. III. *J. Org. Chem.* **1987**, 52, 4191.

(43) Pougry, J. R. *Tetrahedron Lett.* **1984**, 25, 2363.

(44) Isoba, M.; Ichikawa, Y.; Funabashi, Y.; Mio, S.; Goto, T., *Tetrahedron* , **1986**, 42, 2863.

(45) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, 43, 2190.

(46) Hsu, C.-T.; Wang,N. -Y.; Latimer, L. H.; and Sih C. J., *J. Am. Chem. Soc.* **1983**, 105, 593.

(47) For reviews of the Wittig reaction, see (a) Maercker, A., *Org. React.* **1965**, 14, 270. (b) Maryanoff, B. E., and Reitz, A. B.; *Chem. Rev.* **1989**, 89, 863.

(48) Vedejs, E. *J. Org. Chem.* **1973**, 38, 1179.

(49) Fujimoto, Y.; Murasaki, C.; Shimada, H.; Nishioka, S.; Kakinuma, K.; Singh, S.; Singh, M.; Gupta, Y. K.; and Sahai, M.; *Chem. Pharm. Bull.* **1994**, 42, 1175-1185.

(50) (a) Labelle, M.; Morton, H. E.; Guidon, Y.; Springer, J.P. *J. Am. Chem. Soc.* **1987**, 109, 672. (b) Labelle, M.; Guidon, Y. *J. Am. Chem. Soc.* **1989**, 111, 2204.

(51) (a) Dewar, M. J.S..; Zoebich, E. G.; Healy, E. F.; Stewart, J. J. P., *J. Am. Chem. Soc.*, **1985**, 107, 3902. (b) Dewar, M. J.S..; Storch, D. M., *J. Am. Chem. Soc.*, 1985, 107, 3898.

(52) Mootoo, D. R.; Wilson, P.; Jammalamadaka, V.; *J. Carbohydr. Chem.* **1994**, 841-849.

(53) (a) Garegg, P. J. and Samuelsson, B. *J. Chem. Soc. Perkin Trans.* 1, **1980**,2866; (b) Garegg, P. J.; Johansson, R.; Ortega, C.; and Samulsson, B. *J. Chem. Soc., Perkin Trans.* 1, **1982**,681.

(54) Keck, G. E.; Enholem, E. J.; Yates, J. B. and Wiley, M. R.. *Tetrahedron*, **1985**, 41, 4079,

(55) Wilson, P.; Shan, W.; Mootoo, D. R., *J. Carbohydr. Chem.* **1994**, 13, 133.

(56) Brown, H. C. and Lynch, G. T., *J. Org. Chem.*, **1981**, 938)

(57) Jujimoto, Y., Murasaki, C., Shimada, H., Nishioka, S., Kakinuma, K., Singh, S., Singh, M., Gupta, Y., and Sahai, M., *Chem. Phar. Bull.*, **1994**, 1175-1184

(58) Siedlecka, R.; Skarzewski, J.; Miochowski, J. Tetrahedron Lett. 1990, 31, 2177.

(59) Kurosawa, E.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1980**, 21, 2121.

(60) Rieser, J. M.; Fang, X.-P.; Anderson , J.E.; Miesbauer, L.R.; Smith, D. L.; Mclaughlin, J.L. *Helv. Chim. Acta* **1993**, 76, 2433.

(61) Baggett, N.; Duxbury, J. M.; Foster, A. B.; and Webber, J. M.; *Carbohydr. Res.*, **1966**, 216.

(62) Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, 60, 4419-4427.

(63) Reiser, M. J.; Hui, Y.-H.; Rupprecht, J.K.; Kozlowski, J. F.; Wood, K. V.; Mclaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, 114, 10203-10213.

(64) Fujimoto, Y.; Murasaki, C.; Shimada, H.; Nishioka, H.; Nishioka, S.; Kakinuma, K.; Singh, S.; Singh, M.; Gupta, Y. K-.; Sahai, M. *Chem. Phar. Bull.* **1994**, 42, 1175-1184.
(65) Sinha, S.C.; Sinha-Bagchi, A.; Yazbal, A.; Keinan, E. *Tetrahedron Lett.* **1995**, 36, 9257-9260 .

(66) Hoye, T. R.; Ye, Z. Am. Chem. Soc. 1996, 118, 1801-1802.

(67) (a) Harmange, J.-C.; Figadere, B.; Cave, A. *Tetrahedron Lett.* **1992**, 33, 5749-5752; (b) Koert, U. *Tetrahedron Lett.* **1994**, 35,2517-2520. (c) Trost, B. M.; Shi, Z. *J. Am. Chem. Soc.*, **1994**, 116, 7459-7460; (d) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, 61, 4247-4251.

(68) Zhang, H.; Mootoo, D. R. *J. Org. Chem.* **1995**, 60, 8134-8135.

(69).Sharpless, K. B.; Amberg W.; Bennani, Y.; Gerad A.C.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Moeikawa, K.; Wang, Z.-M.; Xu, D.; Zhang X.-L., *J. Org. Chem.*, **1992**, 2768.

(70) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, 512.