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PYRANOSIDES AS TEMPLATES FOR THE SYNTHESIS OF OXYGENATED TETRAHYDROFURANS

by

Mohindra Seepersaud

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

1999

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.

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date

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1/21/99

date

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THE CITY UNIVERSITY OF NEW YORK

Abstract

USE OF PYRANOSIDES AS TEMPLATES FOR THE SYNTHESIS OF OXYGENATED TETRAHYDROFURANS

by

Mohindra Seepersaud

Advisor: Professor David R. Mootoo

The synthesis of 3-oxygenated-2,5-dialkyl-tetrahydrofurans (THF's) has received interest because of their use as precursors for the synthesis of complex THF containing natural products such as the eunecellin and kumausyne groups and certain polyethers. A common strategy for the synthesis of these THF's is electrophillic cyclization of penten-3,5-diols, wherein the allylic alcohol substituent provides a stereocontrolling element.

Our contribution to the area involves the use of C-6 allylated pyranosides as precursors for these 3-oxygenated THF ring systems. Specifically, R and S allylic alcohol pyranosides were prepared from tri-O-acetyl-D-glucal in 6 steps. These substrates were then subjected to halocyclization using iodonium dicollidine perchlorate (IDCP). For the R series high selectivity for the *cis*-2,5-substituted THF was observed while the S substrates showed poor selectivity. Trityl pyranosides led to higher selectivity than substrates with less bulky aglycones.

The study was then extended to a racemic series of syn and anti homoallylic pyranosides which were prepared in 4 steps from acrolein. Halocyclization of t-butyl glcosides of both the syn (corresponding to R) and anti (corresponding to S) gave moderate selectivity (65-70%) for the *cis*-2,5-THF. The corresponding trityl glycoside gave higher (85-90%) *cis*-2,5-THF selectivity. These results are unlike the allylic case where high selectivity was observed for only the R substrate. A stereochemical model which is based on previous results by Houk and Guindon, was postulated.

The allylic pyranoside methodology was applied to the synthesis of a THF precursor of the eunecellin group of natural products. The pyranoside alkene was prepared from nerol in 11 steps. Cyclization of this precursor gave the key functionalized THF precursor with high selectivity. However, attempts at converting this intermediate to the macrocyclic skeleton of the eunecellin was not sucessful. The iodocyclization of a model Z-alkene pyranoside for the kumausyne framework was carried out as part of this study. High selectivity for the *cis*-2,5-disubstituted THF was observed.

In summary a novel synthesis of complex, oxygenated THF's from carbohydrate alkene precursors was demonstrated. This methodology was applied to the construction of THF subunits of the eunecellin and kumausyne groups of natural products.

This Thesis is dedicated to my mother, brothers and sisters

for their tremendous support and encouragement throughout these years

Acknowledgements

I wish to express my deep sense of gratitude to Prof. D. R. Mootoo for his invaluable guidance, patience and encouragement throughout this work. I am also grateful to Prof. K. Grohmann for his support. I thank Dr. M. Blumenstein for his help in NMR experiments and Dr. C. Soll for his help with mass spectrometry.

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I am also thankful to the MBRS program for their support throughout the years.

Finally I wish to acknowledge my wife Sheila for her love and support over the long years.

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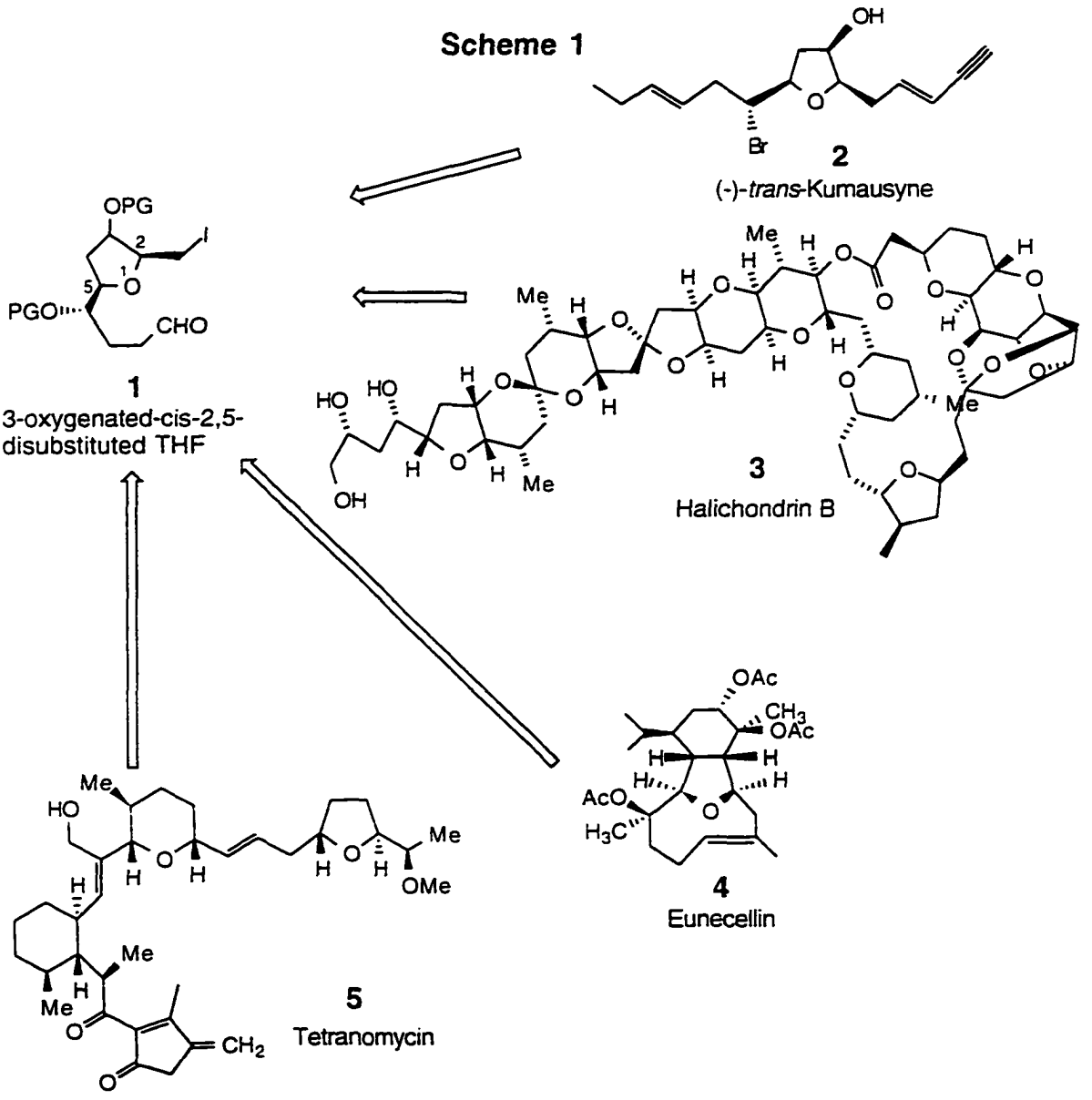
(I) Naturally Occuring Macrocycle and monocyclic ethers

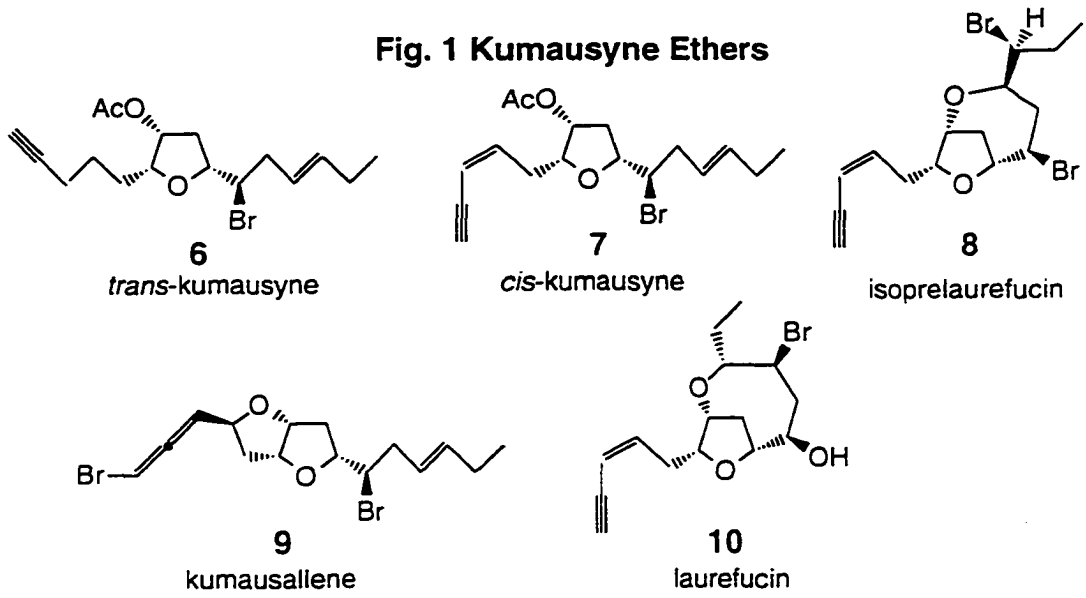
The synthesis of 2,5-dialkyl-3-oxygenated tetrahydrofurans (THF's) **1** has received considerable attention because of their occurrence in a number of marine natural products such as kumausyne **2**[1-7] and halichondrin **3**.[8] They are also precursors to the 2,5-dialkyl-3-C-substituted THF's subunits contained in the eunecellins **4**,[9-12] and to the 2,5-dialkylated THF's found in complex polyethers such as tetranomycin **5** (Scheme 1).[13]

Scheme 1



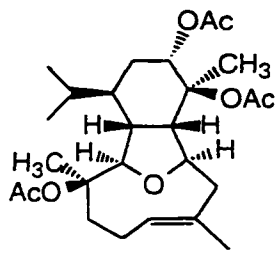
Kumausyne[1] is a structurally diverse nonisoprenoid sesquiterpene isolated from red algae of the genus *Laurencia.* The common structural feature of this family is an all-*cis*. 3-oxygenated-2,5-dialkyl-THF unit containing one or more bromine atoms. A representative selection of these structures are shown in figure 1.[3-7] The majority of these metabolites are believed to arise from the halocyclization of various 6,7-dihydroxypentadeca-3,9-12-trien-1-ynes (laurediols).[2] The bioactivity of these sesquiterpenods has been related with the polyether antibiotics and the annonaceous acetogenins.[14]

Fig. 1 Kumausyne Ethers



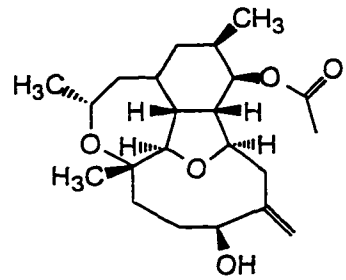
The eunecellin diterpenes are found in gorgonian and soft corals. Eunecellin **11**, the first member of this family to be described, was isolated in 1968 by Djerassi and co-workers[8] from the coral *Eunicella stricta* . To date over 50 eunecellin diterpenoids have been isolated.[9-11] These compounds have a unique tricyclic ring system comprising of a fused cyclohexane-THF core which is bridged across the carbinol carbons of the THF by a nine membered (Fig. 2). Other groups of compounds possessing the cis-oxygenated THF core are the asbestinins **12** and the briarellins **13**. Minor variations in substituents on the macrocycle C-6/C-7 and cyclohexane C-11/C-14 differentiate the three classes of compounds. All three groups show in-vitro bioactivity which range from cytotoxic and antibacterial to anti-inflammatory. For example the eunecellin selerophytin A is active against L1210 cell line at 1 ug/mL and lytophynin A exhibits 50% growth inhibition of chinese silkworm at 12 ppm. [15,16]

Fig. 2 Macrocyclic Ethers



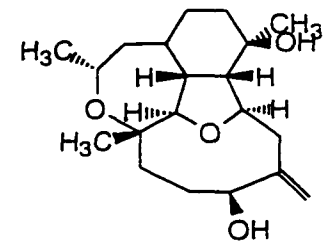
11

Eunecellin



12

Asbestinin-7



13

Briarellin-D

(II) General Approach to 3-Oxygenated THF

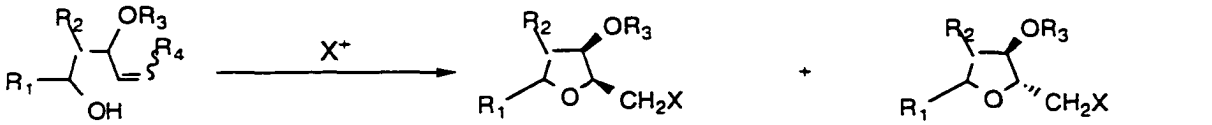
There are three major routes to the synthesis of oxgenated THF's (i) Electrophilic cyclization of 4-penten-1,3-diol derivatives (ii) Intramolecular cyclization of hydroxy epoxides and (iii) Prin's cyclization-pinacol rearrangement of an alkene-diol and aldehyde.

(i) Electrophilic cyclization of 4-penten-1,3-diol derivatives

The electrophilic cyclization of 4-penten-1,3-diol derivatives **14** has been investigated by a number of groups with different electrophiles. In general good to excellent selectivity has been observed for the product in which the CH_2E substituent is cis to the alkoxy group **15** (Scheme 2).

The halocyclization of the hydroxy olefin **14** with different electrophiles was investigated by Maryanoff.[17] Iodoetherification of heavily substituted 4-penten-1,3-diol's were examined by Yoshida.[18] Irrespective of the substitution pattern high selectivity for the *cis*-2-(iodomethyl)-3-hydroxyTHF was observed. Similar results were obtained by Cha[19]. Guindon[20] demonstrated the haloetherification reaction of ethyl(S,E)-4,6-dihydroxy-2-hexenoate. The reaction favors the formation of the cis-THF (*cis*/*trans*:7.3/1). Semmelhack[13] in his preparation of the homochiral tetrahydrofuran portion of tetranomycin utilized an allylic alcohol in a palladium promoted cyclization to give the key oxygenated THF (Scheme 2).

Scheme 2



14
syn or *anti*
4-alken-1,3-diols

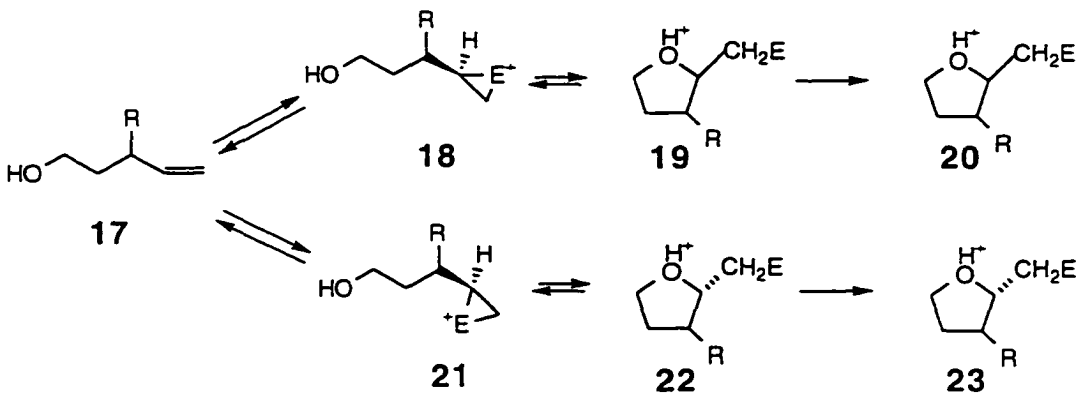
15
cis- 3-hydroxy-2-Xmethyl THF

16
trans- 3-hydroxy-2-Xmethyl THF

R_1	R_2	R_3	R_4	Electrophile/ Conditions	Author
H	OBn	OBn	H	NBS or Br_2/ $Hg(OAc)_2$ etc.	Maraynoff et al[17]
H-^{t}Bu	$(CH_2)_5$	H	CH_3	I_2,$NaHCO_3$	Yoshida et al[18]
CH_3	H	OBzl	H	I_2,THF/Et_2O $NaHCO_3$0^{0}C	Cha et al[19]
H	H	H	COOEt	I_2,Et_2O/ $NaHCO_3$0^{0}C	Guindon et al[20]
-CH_2OMe	H	OSi(tBu)Ph_2	H	$Pd(OAc)_2$,CH_3OH,/ CO,23^{0}C	Semmelhack et al[13]

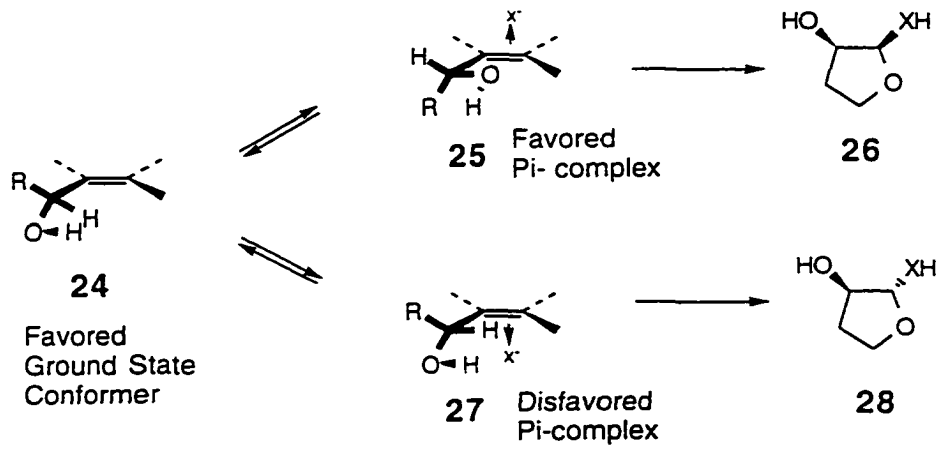
Reitz and Marayanoff[21] proposed a mechanistic pathway for the cyclization of 4-penten-1-ols 17 (Scheme 3). The first step is the formation of three-centered onium species **18**, **21**. Halogen addition to the alkene is assumed to be freely reversible and there may be a kinetic preference for formation of one of the resulting diastereomeric ions (or pi complexes). Halonium ion **18** and **21** then cyclizes to tetrahydrofuranonium intermediates **19** and **22** which fragment to the THF's **20** and **23** respectively. According to the mechanism the ratio of THF's depends on the relative rate of competing reactions in each of these different steps. For example in a simple case, assuming that the relative concentration of initial halonium ions is the same, the favored THF would be a result of the relative rates of cyclization of the diastereomeric species **18** or **21**.

Scheme 3



Allylic asymmetric induction in the iodolactonization reaction was studied by the group of Chamberlin.[22] Stereoselectivity was explained in terms of differences in the facial selectivity in the formation of the pi complexes corresponding to halonium ions **18** and **21** (Scheme 3). Two pi complexes **25** and **27**, may be formed. The complex **25** is predicted to be the favored one according to the Houk's model.[23] The C-C bond is parallel to the π bond and the E^+ comes in the anti orientation. This leads to two transition states which places the H or OH on the inside or outside position with respect to the double bond. The favored one in which the OH is on the inside position, leads to the *cis* -THF product.

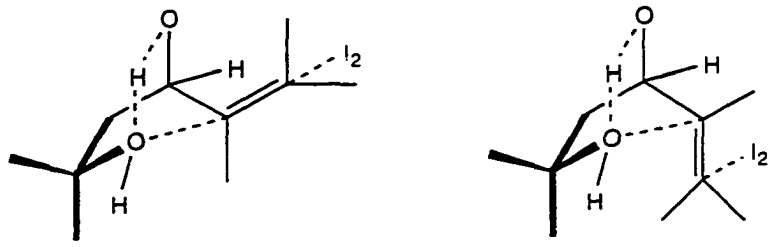
Scheme 4



Yoshida[18] showed that the *cis*-substituted THF was the major product for the reactions of terminal and E-disubstituted alkenes. The selectivity was explained by internal hydrogen bonding between the allylic alcohol (H-bond donor) to the nucleophilic oxygen (H-bond

acceptor) (Scheme 5). This model has been questioned on several grounds: (1) substituents without a hydrogen donor such as OAc, $OSiR_3$ and OBn are as efficient as OH in inducing a cis arrangement; (2) the proposed hydrogen bond would deactivate the nucleophillic oxygen in the transition state; (3) this model does not exclude formation of **29b**. Interestingly **29a** matches up with the preferred Houk conformation.

Scheme 5



29a **29b**

Guindon[20] proposed that there is a rapid pre-equilibrium of iodine-olefin pi complexes, followed by a rate limiting cyclization step. Deprotonation of this complex renders the reaction irreversible, trapping the kinetic product. This implies that the cyclization step of the reaction will dictate the stereochemical outcome. More precisely, only the relative energy of the transition states for this step will determine the product ratio of THF products.[24,25] Reactant-like transition states were assumed (**30-33**). The geometry of the halonium ion or charge transfer complex and the conformation of the forming THF ring were considered in determining relative energies (Fig. 3). The model used was the iodonium ion of the olefin, which features a planar positively charged electrophile carbon and an iodine atom above the plane of the olefin. The five atoms forming the THF adopted a chair-like geometry. Four possible transition structures were considered and minimized via AM1 calculations (Fig 4).

Fig. 3 Reactant like Transition States 30-33

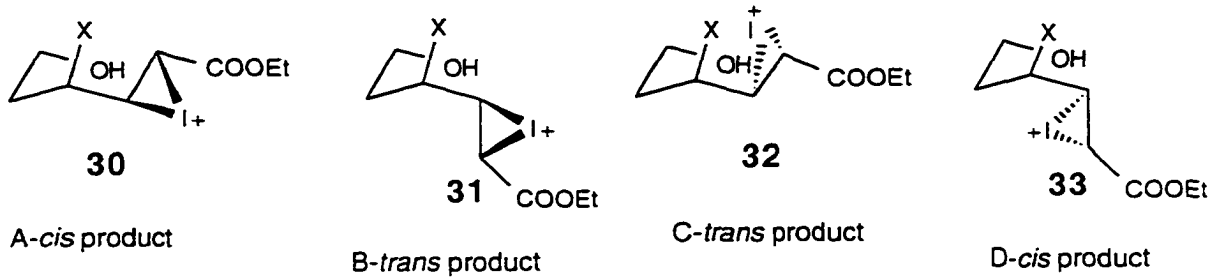
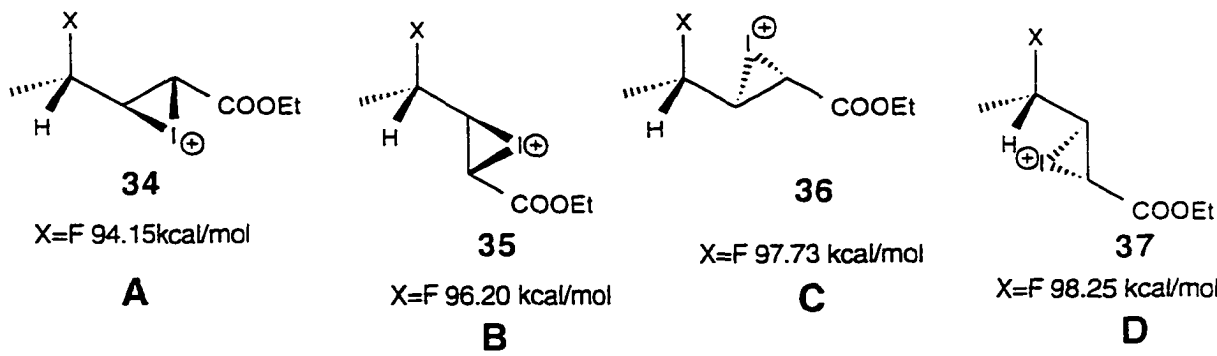


Fig.4 Transition State A-D

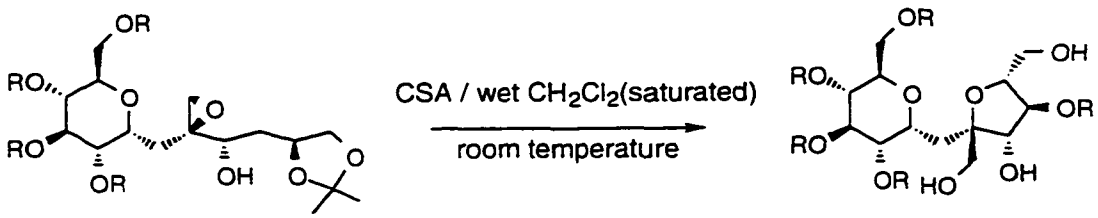


Conformation **A** was favored. This gives rise to the *cis*-product. Comparison of structures **A** and **C** reveals a preference for **A** since the system is in a conformation where the C-F LUMO and the pi system are orthogonal. The "inside alkoxy effect" which is only possible when the fluoride is axial. Finally, the preference for the olefin up over the olefin-down conformation (**A** and **B**) is due to torsional reasons, $A^{1,3}$ strain, since the former is actually staggered whereas the latter is an eclipsed conformation.

(ii) Intramolecular epoxide ring opening

First and epoxide would be prepared using Sharpless's conditions. This would then be treated under acidic conditions to induce intramolecular attack of the alkoxy group on the epoxide. Kishi[26] used this strategy in the synthesis of C-Sucrose **39** (Scheme 6).

Scheme 6

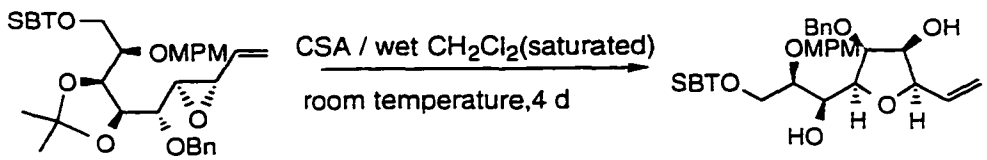


38 **39**

C-Sucrose Analog

Also Murai et al[27] has demonstrated the epoxy opening to give the substituted THF **41** (Scheme 7).

Scheme 7



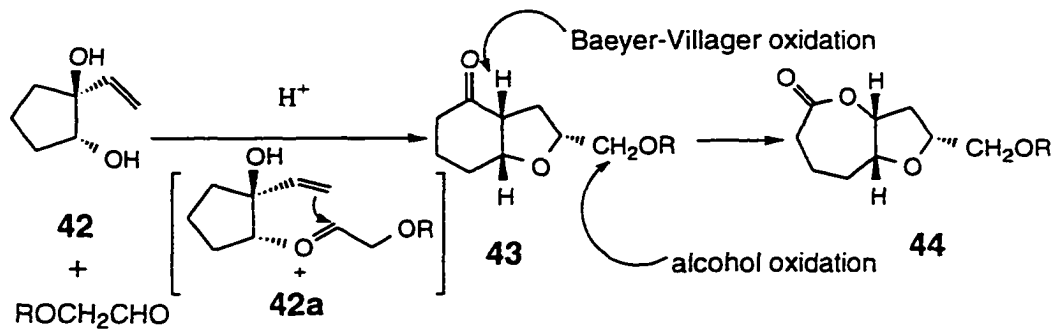
40 **41**

While there are numerous reports on the ring opening of epoxides to give simple 2,5-dialkyl THF's.[28,29] There are only a few reports of ring opening to produce oxgenated THF's.

. (iii) Prin's cyclization -pinacol rearrangement of an alkene-diol and aldehyde

Overman [30,31] demonstrated that cyclopentane diol **42** may be transformed in a single step to the THF **43** (Scheme 8). The reaction proceeds through the initial formation of the oxo-carbenium ion **42a**. Pinacol rearrangement of **42a** gives **43**. Baeyer-Villager oxidation of **43** provides the 2,5-dialkyl-3-oxy THF **44**.

Scheme 8

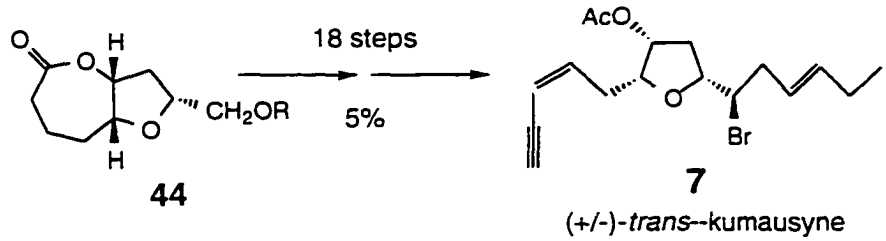


(III) Application to Natural Product Synthesis

(i) Kumausyne Group

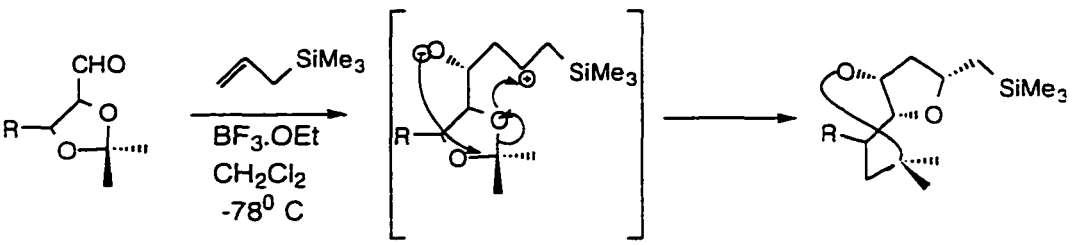
The kumausyne group have been the object of considerable synthetic effort.[32] Overman's group accomplished the landmark total synthesis of (+/-)-**7** in 18 steps (5% yield) from 2-cyclopentylidenecyclopentanone utilizing the Prins cyclization-pinacol rearrarangement discussed earlier (Scheme 9).[30]

Scheme 9



Sugimura[33] prepared (-)-*trans*-kumausyne in an enantiospecific fashion starting from an L-arabinose derivative. The key step was the stereoselective formation of the substituted THF via a novel cyclization of the β-silyl cation intermediate **46**.[34] This was generated by the addition of allylsilane to di-O-isopropylidene-aldehydo-arabinose **45** in the presence of boran trifluoride etherate (Scheme 10). The synthesis involved 19 steps with an overall yield of 1.1%.

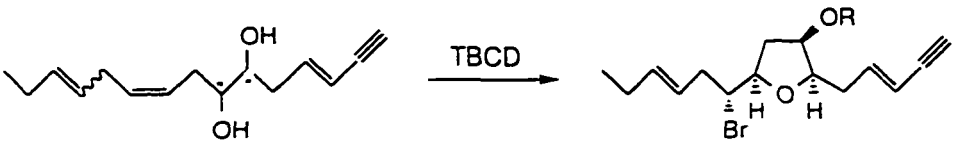
Scheme 10



45 46 47

More recently, Martin disclosed a 22-step stereocontrolled synthesis of (-)-7 (10 % yield) from propargyl alcohol that employs brominative cyclization using 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCD) as the key step[35] (Scheme 11). This type of halocyclization is considered to be the biogenetic origin of *Laurencia* cyclic lipids.

Scheme 11

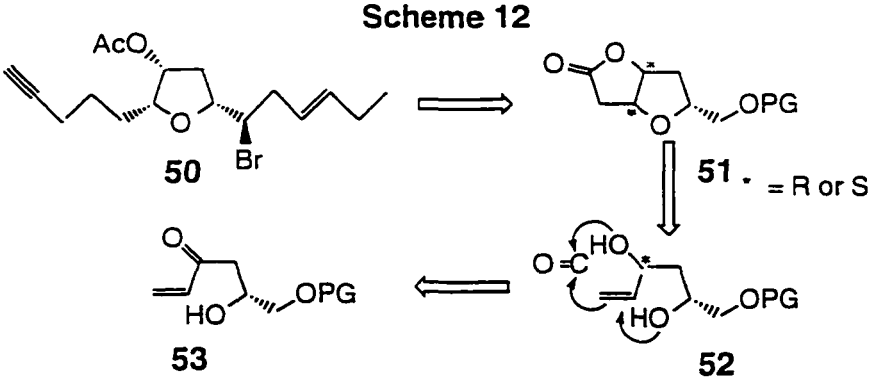


48 49

Laurendiols

Boukouvalas and co-workers[36] demonstrated an exceptionally concise synthesis of (-)-*trans* -kumausyne from dimethyl (R)-malate in 13 steps, 6.2% overall yield). This was done by a unified strategy based upon tandem intramolecular alkoxycarbonylation-lactonization[37] for assemblage of the THF unit **51** (Scheme 12). This strategy is the shortest and simplest synthesis of (-)-*trans* -kumausyne.

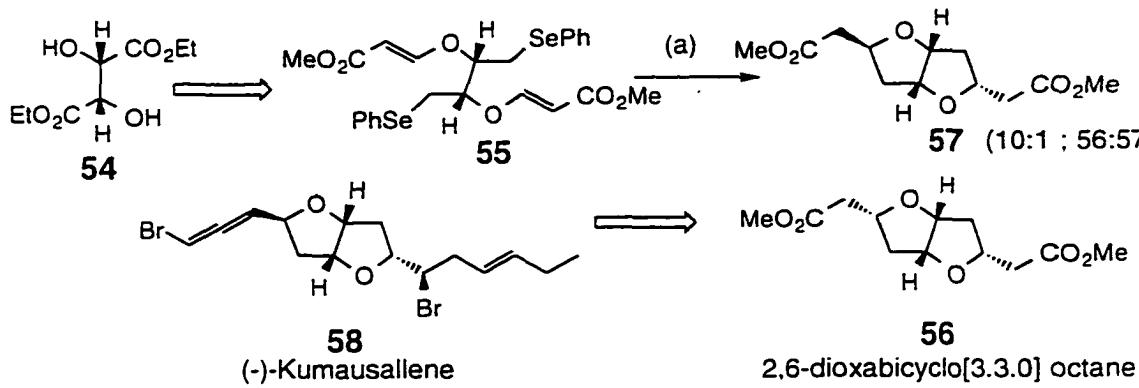
Scheme 12



50 53 52

Lee and co-workers[38] used a radical cyclization reaction of a bis(β-alkoxyacrylate) intermediate **55** to give the 2,6-dioxabicyclo[3.3.0] octane product **56, 57** (Scheme 13). Elaboration of the major isomer gave (-)-Kumausallene. The synthesis is very long (25 steps) and has a low overall yield.

Scheme 13

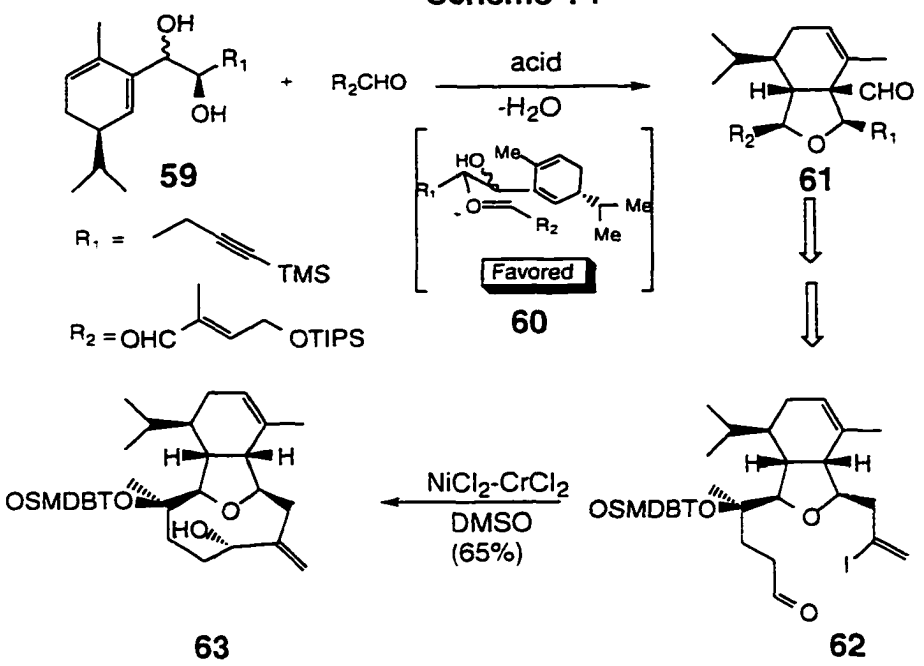


(a) 2.5 eq. Bu_3SnH, 0.25 eq. AIBN
Benzene (0.02 M), Reflux

(ii) Eunecellin

Only one synthesis Eunecellin has been reported.[39] This is a reflection of the high degree of structural complexity. The key reaction in this synthesis was the stereoselective Prins-pinacol condensation-rearrangement[40] of a dienyl diol **59** with an aldehyde to assemble the 2-oxabicyclo-[4.3.0]non-4-ene. This reaction deals with all the stereochemical and structural issues posed by the bicyclic core of the eunecellin diterpenes. The stereochemical outcome of this condensation-rearrangement can be anticipated from the analysis depicted in Scheme 14.

Scheme 14



Prins cyclization of the more stable (E)-oxocarbenium ion intermediate **60**[41] should occur preferentially in a chair topography from the diene face opposite the isopropyl substituent: this transition structure moreover places the R^1 substituent in a favored equitorial orientation.[37] Nozaki-Kishi[42] $NiCl_2$-$CrCl_2$ free radical cyclization of **62** furnished the macrocycle **63** in 65% yield.

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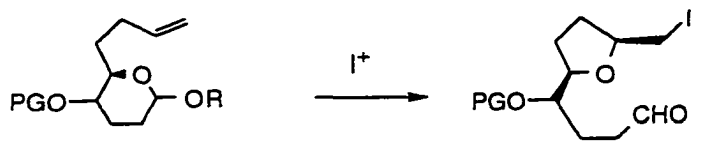
Chapter 2 : Halocyclization of C-6 allylated Pyranosides ; Allylic substrates

(I) Introduction

Earlier work in our laboratory has demonstrated[1] the use of C6-allylated pyranosides **63** as templates for the synthesis of *cis*-2,5-dialkyl THF's **64** (Scheme 15).

Scheme 15

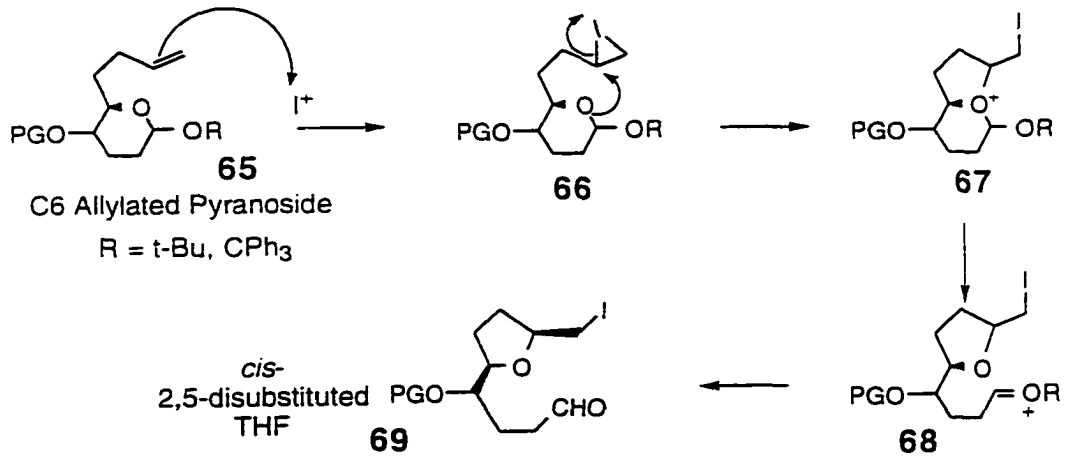


63 — C6 Allylated Pyranoside, R = t-Bu. CPh_3

64 — *cis*-2,5-disubstituted THF

The reaction is thought to proceed via an initially formed iodonium ion **66**. Attack of the pyranoside oxygen gives rise to a bicyclic type intermediate **67** followed by subsequent fragmentation to give mixture of *cis/trans* THF's. Stereoselectivity could be varied by increasing the size of the anomeric substituent. High selectivity was obtained with trityl glycosides (Scheme 16).

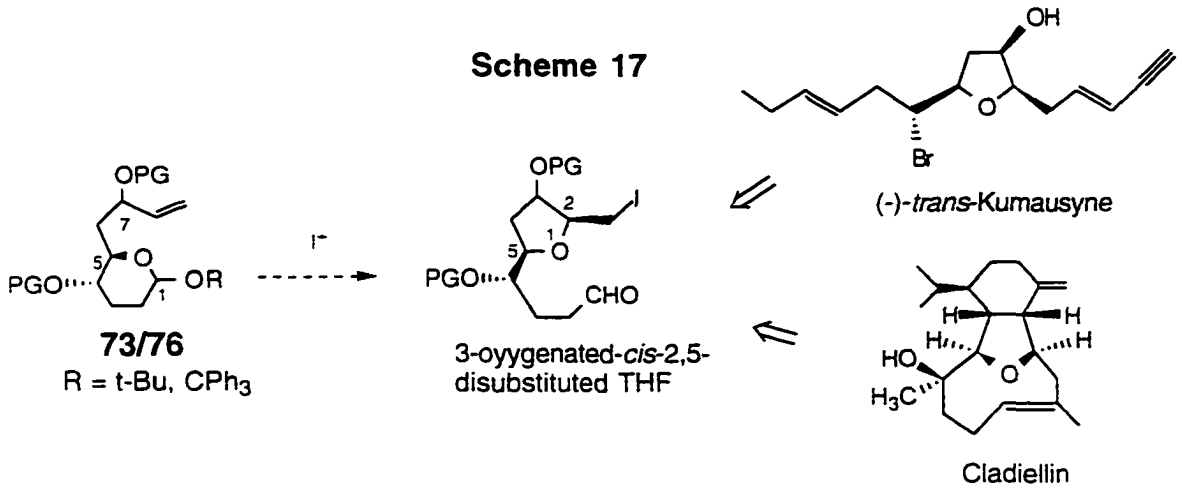
Scheme 16



An allylic alcohol pyranoside **73/76**(R:S) should give rise to an 2,5-dialkyl-3-oxy-THF skeleton (Scheme 17). This THF core can be used as a precursor for the synthesis of

the Eunecellin and Laurencia natural products (as discussed earlier). Synthesis and cyclization of model allylic alcohol pyranosides were therefore investigated.

Scheme 17

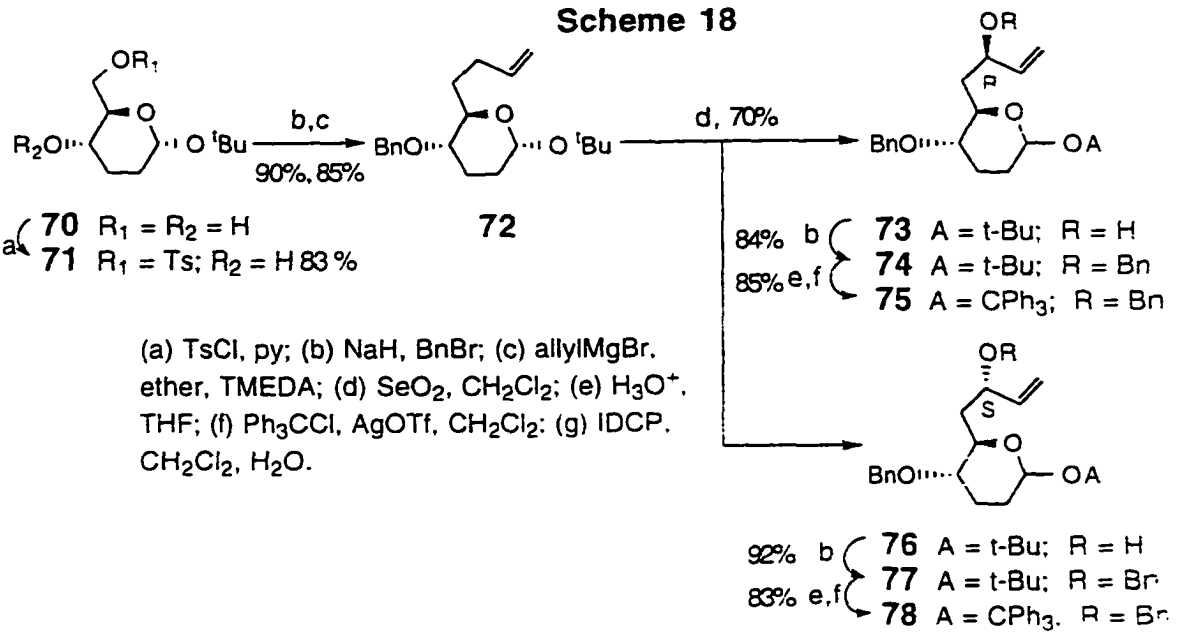


(II) Model Pyranoside

(i) Pyranoside preparation

The pyranoside intermediate was synthesised from tri-O-acetyl-D-glucal. Addition of t-butyl alcohol across the glycal double bond, hydrogenation, tosylation and benzylation followed by allyl grignard addition gave the key C-6 allylated pyranoside **72**.[1,2] Oxidation at the allylic carbon was done with SeO_2/TBHP which gave a 1:1 mixture of allylic alcohols in 79% yield. These alcohols had very similar tlc mobilities and were carefully separated by Flash Column Chromatography (FCC). The hydroxyl groups were protected as benzyl ethers. To prepare the trityl glycosides, cleavage of the t-Butyl group was done via acid hydrolysis followed by silver mediated tritylation of the lactols (Scheme 18).

Scheme 18

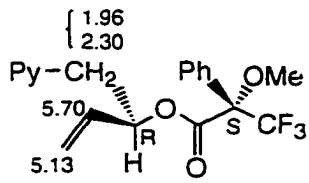


The mixtures of α,β-trityl glycosides were chromatographically inseparable and used without purification in the subsequent iodocyclization since previous studies suggested that both anomers should exhibit high cis 2,5 stereoselectivity.[1]

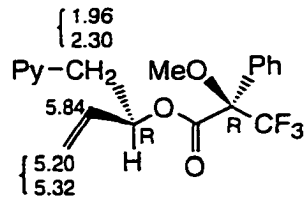
(ii) Alcohol Stereochemistry

For **73** the R and S Mosher esters were prepared. The same was done for the **76** (Fig. 5). Examination of the ^{1}H NMR spectra of the esters for alcohol **73** showed an upfield shift of the vinyl protons for the **73**-(S)-MPTA ester [δ 5.13 (m,2H) and 5.70 (m, 1H)] compared to the **73**-(R)-MPTA derivative[δ 5.20, 5.32 (both dd, 1H ea.) and 5.84 (m, 1H)] indicating the R configuration. Similarly, application of the Mosher analysis to the (R)- and (S)-MPTA esters of **76** led to the independent assignment of the S allylic alcohol epimer.

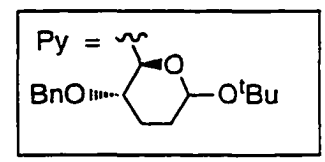
Fig. 5 Mosher Ester NMR Analysis 73-76

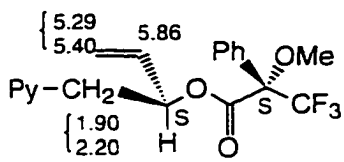


73 -(S)-MTPA ester

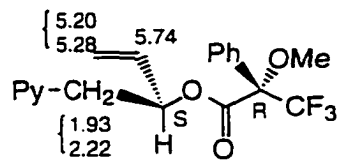


73 -(R)-MTPA ester





76 -(S)-MTPA ester

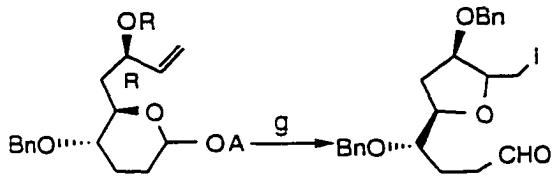


76 -(R)-MTPA ester

(iii) Halocyclization

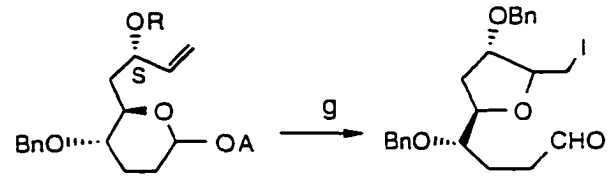
The pyranosides were then subjected to halocyclization using iodonium dicollidine perchlorate (IDCP) in wet dichloromethane[4] (Scheme 19). For the R-allylic alcohol pyranoside **74** and α,β mixture of **75**, halocyclization gave the *cis*-2,5-THF. The corresponding S substrates **77** and α,β mixture of **78** gave cis:trans mixtures. A small preference for the trans 2,5-THF was observed for the t-butyl pyranoside (c:t 40:60) whereas there was an opposite preference for the *cis*-2,5-THF for the trityl pyranoside (c:t 60:40).

Scheme 19



79

74 A = t-Bu; R = Bn A = t-Bu 83%
75 A = CPh_3; R = Bn A = CPh_3 83%



80

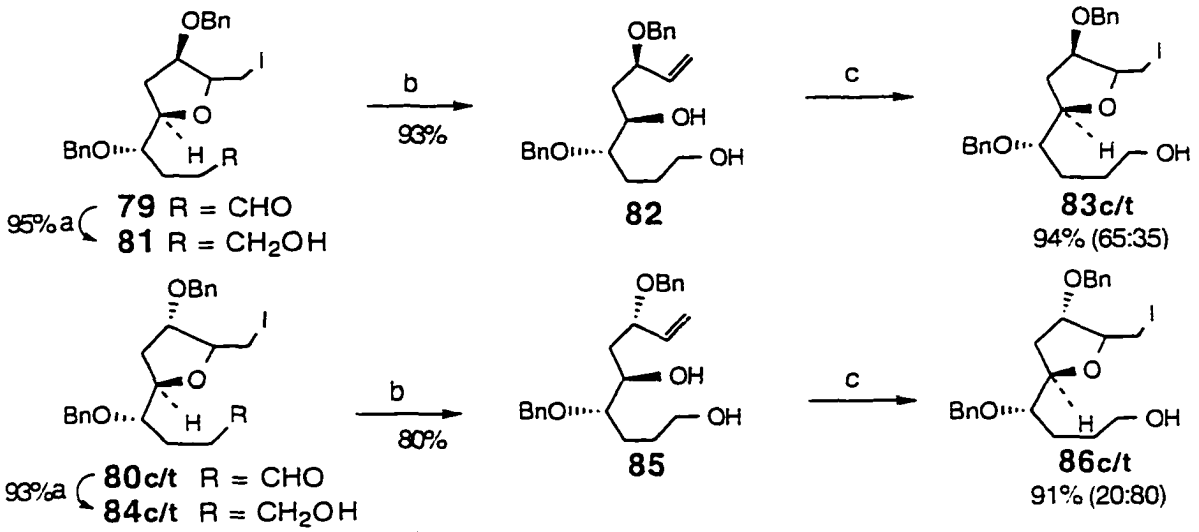
77 A = t-Bu; R = Bn A = t-Bu 89% (40:60)
78 A = CPh_3; R = Bn A = CPh_3 83% (60:40)

(g) IDCP,CH_2Cl_2, H_2O.

(iv) Importance of the pyranoside framework

In order to assess the importance of the pyranoside framework on the stereoselectivity of the halocyclization a model acyclic precursor was prepared. The acyclic 5-hexen-1,2,4-triol derivatives **82** and **85** were prepared as follows: $NaBH_4$ reduction of the THF aldehydes followed by a zinc mediated reductive elimination of the resulting alcohol (Scheme 20).

Scheme 20



(a) $NaBH_4$, EtOH; (b) Zn, 95% EtOH, reflux; (c) IDCP, CH_2Cl_2, H_2O.

Halocyclization on the R acyclic alcohol gave a mixture of cis:trans isomers (65:35) and the S acyclic alcohol afforded a mixture as well (20:80). These results were very different from the high selectivities observed for the R allylic pyranoside observed earlier as well as the high selectivities observed with the less substituted 4-penten-1,3-diol substrates.[5a,b]

(v) Stereochemistry of THF

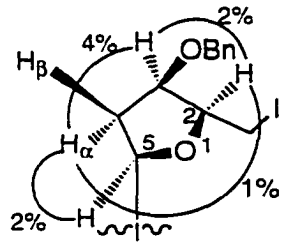
The stereochemistry of the products were assigned by comparison of the ^1H and ^{13}C NMR for the cis and trans isomeric pairs with the data for known 2,5-dialkyl THF's[5a,b]. Here the iodomethyl protons are more upfield for the trans 2,5 THF as compared to the cis THF. Also the iodomethyl carbons resonance for the cis isomer is more upfield compared to the trans. These trends hold regardless of the configuration at C5.

These analyses were carried out for C_6D_6 solutions rather than $CDCl_3$, because of higher signal resolution. This was especially important for determination of product ratios from the proton spectra. Thus, the *cis*-2,5-THF **80c** (i.e. *trans*-2-3-THF) was associated with signals a δ_H 2.80 and δ_C 8.0 ppm whereas the corresponding resonances of the *trans*-2,5 isomer **80t** (i.e. cis-2,3-THF) occured at 3.17 and 3.4 ppm respectively. Since only a single THF isomer **79c** was produced in the cyclization of the **74/75** R pyranosides. the stereochemistry of the THF's in this series were determined by spectral analysis of the mixture of isomers **83c/t** produced from the reaction of the dihydroxyalkene **82**. Accordingly, **83c** (δ_H 3.19 and d_C 2.7 ppm) and **83t** (δ_H 2.90 and δ_C 9.0)ppm were assigned. These assignments meant that the THF-aldehyde **79c**, the $NaBH_4$ reduction precursor of **81c** was also cis.

nOe Study

The signals for #2, 3, 4 and 5 protons were assigned from analysis of 1D and 2D spectrum. Having done that, NOESY spectrum was then performed (Fig. 6). First $H4_\alpha$ and $H4_\beta$ were distinguished where $H4_\alpha$ showed a crosspeak in the NOESY with H3 (4%) and H5 (2%). The other H4 signal (δ 1.93) showed no nOe with either H3 or H5. The other lowfield signal was assigned to H_α. $H4_\alpha$ and $H4_\beta$ could be independently assigned from their relative chemical shift positions. In closely related *syn,syn*-2,5-dialkyl-3-oxy-THF's, the H4 proton syn to the protons at H3 and H5 resonates more downfield, relative to the anti proton.[6] Second, H3 showed a nOe of 1.75% with H2. Having already established the stereochemistry of the H3 position then we can conclude that this data is consistent with an all syn arrangement of substituents on the THF ring. Third, a 1% nOe between $H4_\alpha$ and H2 indicated a cis relationship between these protons, and therefore that H5 and H2 were also cis.

Fig. 6 nOe of 79



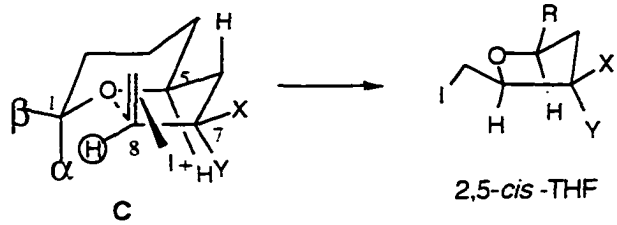
79

(vi) Mechanistic Explanation

The different levels of THF stereoselectivity obtained for substrates in which the allylic alcohol residue is virtually identical (i.e. R substrates:**74**, **75**α/β, **82** or S systems: **77**, **78**α/β, **85**) substantiates the notion that THF stereoselectivity is not controlled solely by allylic sterecontrol in the initial halonium ion (or charge transfer) formation step, but also depends on the cyclization of the diastereomeric species to the THF-oxonium ions. The change in stereoselectivity is especially pronounced in going from the acyclic to the pyranoside templates, i.e. 65:35 to cis only for the R substrates and 20:80 to 60:40 for the S systems. Implicit in this argument is the generally held theory that the initial halonium ion or charge transfer formation step is reversible.[7]

The higher selectivities obtained for the R compared with the S allylic alcohol pyranosides templates might represent a case of matched and mismatched diastereoselection,[8] arising as a result of two stereodirecting elements allylic alcohol configuration, which induces the *cis*-2-iodomethyl-3-oxy product, and a bulky aglycone which favors the *cis*-2,5 disubstituted THF. These results appear to fit a chair-like transition state model which has previously been used to explain the stereoselectivity of these reactions[9,1](Scheme 21). Accordingly, the *cis*-2,5 is formed from transition state C and the *trans*-2,5-THF is formed from **T**. For the R pyranoside, the directing effects of the allylic alcohol and the aglycone act in the same sense. The transition state C, is favored over **T** because the alkoxy group adopts a stereoelectronically preferred, 'inside' (vs. 'outside')[10] position relative to the alkene, and the 'olefin-up' (vs 'olefin-down')[9] orientation is less sterically congested relative to the bulky aglycone. For the S pyranoside substrates, these effects are opposed. **C** correspond to the case of favored aglycone effect and disfavored allylic effect, and the reverse is the case for **T**. Thus for the S pyranoside **77**, the stereodirecting effect of allylic alcohol is apparently greater than that of the t-butyl aglycone, resulting in a predominance of the *trans*-2,5 disubstituted THF. In the trityl, S pyranoside **78**α/β, the aglycone effect is increased due to the increased steric demands of the trityl group, and this presumably outweighs the effect of the allylic alcohol.

Scheme 21



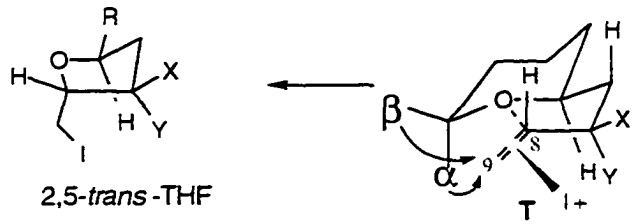
C

2,5-*cis*-THF

smaller H-8 subst. closer to bulky aglycone: Fav

Matched - 7R : X = OBn, Y = H; Alkoxy 'inside': Fav

Mismatched - 7S : X = H, Y = OBn; Alkoxy 'outside': Disfav



2,5-*trans*-THF

T

larger C-9 subst. closer to bulky aglycone : Disfav

Matched - 7R : X = OBn, Y = H; Alkoxy 'outside': Disav

Mismatched - 7S : X = H, Y = OBn; Alkoxy 'inside': Fav

These results illustrate that the stereoselectivity obtained is highly dependent on the nature of the substrate. In the case of the 4-penten-1,3-diols, high stereoselectivity was observed in the cyclizations. Such was not the case for the 5-hexen-1,2,4-triol substrates **82** and **85**. For the R allylic alcohol pyranoside, high selectivities were observed owing to the confomational rigidity imposed by the pyranoside framework that acted in synergy with the stereodirecting effect of the allylic alcohol. For the S allylic pyranoside the pyranoside group did influence the cis selectivity as was observed for the more bulky anomeric group however, this acted only in opposition to the stereodirecting effect of the allylic alcohol.

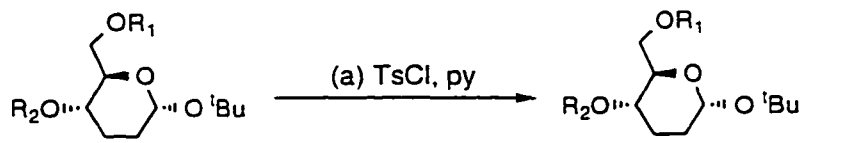
Extension of this methodology to homoallylic alcohol pyranosides was next investigated (see chapter 1).

(III) General Experimental

TLC was carried out on aluminum sheets precoated with silica gel 60 (HF-254, E. Merck) to a thickness of 0.25 mm. Flash column chromatography (FCC) was performed using Kieselgel 60 (230-400 mesh, E. Merck) and usually employed a stepwise solvent polarity gradient, correlated with TLC mobility. ^{1}H and ^{13}C NMR spectra were obtained on GE-QE 300 and Varian UnityPlus 500 instruments. Unless otherwise noted, spectra were recorded at 300 and 75 MHz respectively. Optical rotations were determined on a Rudolph Research AUTOPOL III automatic polarimeter. Elemental analysis were performed by Swarzkopf microanalytical laboratory, Queens, N.Y. Dry THF was obtained by distillation, under nitrogen from potassium-benzophenon ketyl. Dry ether was obtained by distillation under nitrogen from sodium-benzophenon ketyl. Methanol was distilled from Mg and stored over 3A MS. Dichloromethane was distilled from P_2O_5. Other solvents were purified and dried by using standard procedures.

(IV) Experimental

tert-Butyl 6-O-tosyl-2,3-dideoxy-α-D-gluco-pyranoside (71)

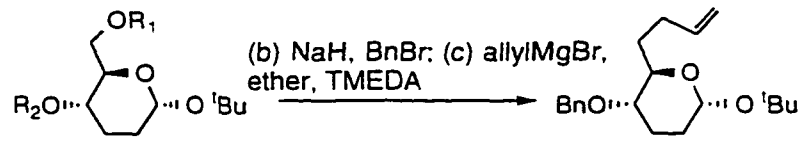


70 $R_1 = R_2 = H$ **71** $R_1 = Ts$; $R_2 = H$

p-Toluenesulfonyl chloride (5.95 g, 31.0 mmol) was added at 0 °C to a solution of of t-butyl 2,3-dideoxy-a-D-gluco-pyranoside **70** (5.27 g, 26.0 mmol) in dry pyridine (30 mL). The reaction mixture was warmed to rt and stirred for an additional 4 h, at which time methanol (1 mL) was added. Most of the solvent was removed in vacuo and the residue diluted with ether. The mixture was washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4), filtered and the filtrate concentrated under reduced pressure. The crude product was purified by flash chromatograpy to give **71** (7.38 g, 83%): Rf = 0.50 (20% EtOAc:P.E.); $[\alpha]^{23}_D$ 37° (c 0.25, $CHCl_3$); IR (neat) 3533, 2973, 1663, 1598, 1360, 1175, 1054 cm-1; ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 9H),

1.71-2.20 (m, 5H), 2.45 (s, 3H), 3.21 (m, 1H), 3.86 (d, 1H, J = 10.5 Hz), 4.05-4.43 (m, 2H), 5.56 (s, 1H), 7.32-7.83 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.7, 27.0, 28.5, 28.6, 28.8, 30.8, 65.9, 70.1, 71.4, 74.5, 90.7, 128.1, 129.9, 133.0, 144.9. Anal. Calcd for $C_{17}H_{26}O_6S$: C, 56.96; H, 7.31. Found: C, 57.08; H, 7.35.

tert-Butyl 4-O-benzyl-2,3-dideoxy-α-D-gluco- non-8-enopyranoside (72)



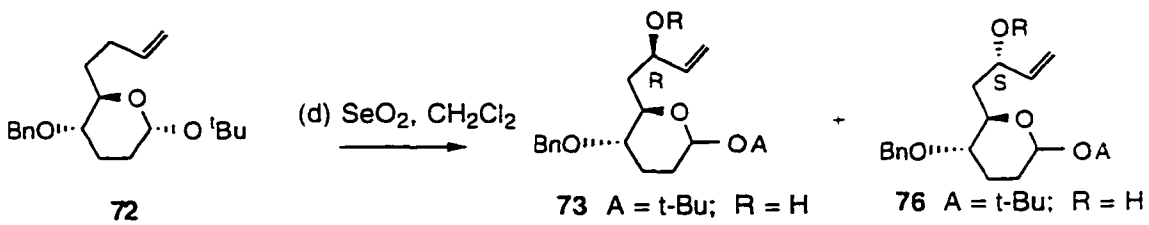
71 R_1 = Ts; R_2 = H **72**

To a solution of **71** (10.0 g, 28.0 mmol) in dry DMF (60 mL) at 0 °C was added NaH (1.34 g, 56.0 mmol), tetrabutylammonium iodide (0.52 g, 1.40 mmol), and benzyl bromide (3.67 mL, 30.8 mmol). The solution was warmed to rt and stirred for an additional 2 h. The reaction was then quenched by the addition of methanol (1 mL), and extracted with ether (3 x 100 mL). The ether extract was washed with brine, dried (Na_2SO_4), filtered and the filtrate concentrated in vacuo. The residue was purified by flash chromatograpy to give the 4-O-benzyl ether derivative (11.2 g, 90%): Rf = 0.8 (20% EtOAc:P.E.); ^1H NMR ($CDCl_3$) δ 1.19 (s, 9H), 1.65 (m, 2H), 1.81 (m, 1H), 2.0 (m, 1H), 2.45 (s, 3H), 3.40 (m, 1H), 3.98 (m, 1H), 4.2 (d, 1H, J = 12.0 Hz), 4.3 (m, 1H), 4.47 (ABq, Δδ = 0.25 ppm, 2H, J = 11.8 Hz), 5.1 (s, 1H), 7.3 (m, 7H), 7.8 (d, 2H, J = 8.0 Hz).

Allylmagnesium bromide (90.0 mL of a 1M solution in ether, 90.0 mmol) was added under argon at rt, to a solution of the benzyl ether-tosylate which was obtained in the previous step (8.0 g, 17.9 mmol), in a mixture of dry ether (90 mL) and TMEDA (0.90 mL). The reaction was stirred for 16 h, then carefully poured into saturated aqueous NH_4Cl (150 mL) at 0 °C. The resulting slurry was extracted with ether (3 x 100 mL), and the combined extract dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo and the crude product purified by flash chromatography to give **72** (4.8 g, 85%): Rf = 0.8 (10% EtOAc:P.E.); $[\alpha]^{25}_D$ 140° (c 2.6, EtOH); IR (neat) 1640, 910, 735 cm-1; ^1H NMR ($CDCl_3$) δ 1.15 (s, 9H), 1.45 (m, 2H), 1.60 (m, 2H), 1.80 (m, 1H), 1.92 (m, 2H), 1.97 (m, 2H), 3.03 (m, 1H), 3.74 (m, 1H), 4.50 (ABq, Δδ = 0.19 ppm, 2H, J = 11.5 Hz), 4.97 (s, 1H), 4.90 (m, 2H), 5.76 (m, 1H), 7.20 (m, 5H); ^{13}C NMR ($CDCl_3$) δ

23.8, 28.9, 30.0, 31.0, 32.0, 70.8, 70.9, 74.0, 78.0, 90.5, 114.3, 127.7, 127.9, 128.5, 138.7, 139.3. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.56; H, 9.29.

t-Butyl Pyranoside-73R Alcohol and 76S Alcohol



72

73 A = t-Bu; R = H

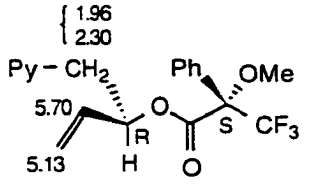
76 A = t-Bu; R = H

A 250 mL flask was charged with SeO_2 (0.261 g, 2.35 mmol), 90% TBHP (0.69 mL, 6.28 mmol) and CH_2Cl_2 (15 mL). After the mixture had been stirred for 0.5 h at rt, a solution of alkene 4 (1.00 g, 3.14 mmol) in CH_2Cl_2 (4 mL) was added over several minutes, and stirring continued for an additional 72 h. At that time 1M NaOMe in MeOH was added to adjust the pH to 7, and the mixture was diluted with water (50 mL), and extracted with ether (3 x 15 mL). The ether extract was washed with saturated aqueous $NaHCO_3$ (2 x 15 mL) and brine (2 x 15 mL), then dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure and the crude residue purified by flash chromatography to yield allylic alcohols **73** (402 mg, 39%) and **76** (329 mg, 31%).

For **73**: Rf = 0.60 (15% EtOAc:P.E.); ^{1}H NMR ($CDCl_3$) δ 1.3 (s, 9H), 1.6 (m, 2H), 1.8 (m, 2H), 1.95 (m, 2H) 3.18 (m, 2H), 3.25 (m, 1H), 4.1 (m, 1H), 4.25 (bm, 6H), 4.50 (ABq, Δδ = 0.30 ppm, 2H, J = 11.8 Hz), 5.0 (t, 1H), 5.1 (s, 1H), 5.25 (d, 1H, J = 15.5 Hz), 5.8 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.4, 28.6, 30.8, 38.5, 69.6, 70.3, 74.2, 76.3, 77.5, 90.3, 113.6, 127.6, 127.8, 128.2, 128.3, 138.2, 141.3. Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.81; H, 9.04. Found: C, 71.43; H, 8.92.

For **76**: Rf = 0.55 (15% EtOAc:P.E.); ^{1}H NMR ($CDCl_3$) δ 1.2 (s, 9H), 1.5 (m, 2H), 1.75 (m, 3H), 2.2 (m, 1H), 3.70 (s, 1H), 4.10 (m, 1H), 4.45 (ABq, Δδ = 0.3 ppm, 2H, J = 11.8 Hz), 5.00 (s, 1H), 5.10 (s, 1H), 5.25 (d, 1H, J = 15.5 Hz), 5.8 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.1, 28.6, 30.6, 39.5, 70.6, 72.0, 72.2, 77.8, 90.2, 113.6, 127.6, 127.7, 128.3, 138.2, 141.7.

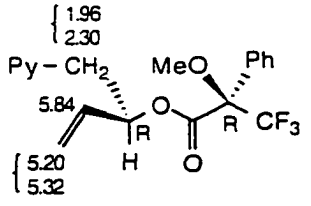
73-(S)-MTPA ester



73 -(S)-MTPA ester

To a stirred solution of allylic alcohol 5 (5.0 mg, 0.015 mmol) in CH_2Cl_2 (1.5 mL) at rt, was added anhydrous pyridine (0.8 mL, 10 mmol), 4-(dimethylamino)pyridine (7 mg, 0.06 mmol) and R-MTPA-Cl (0.06 mL, 0.15 mmol). The solution was stirred at this temperature for 3 h, then diluted with saturated aqueous $NaHCO_3$ and ether (4 mL) and stirring continued for 30 min. The organic phase was then seperated and the aqueous layer extracted with ether (3 x 10 mL). The organic phase was washed with 5% aqueous $NaHSO_4$ (3 x 3 mL) and brine (10 mL), dried ($MgSO_4$) and filtered. Evaporation of the filtrate was concentrated under reduced pressure and flash chromatography of the residual oil gave **73-(S)-MTPA ester** (7.2 mg, 88%): Rf = 0.75 (10% EtOAc:P.E.): ^1H NMR ($CDCl_3$) δ 1.15 (s, 9H), 1.55 (m, 4H), 1.96 (m, 1H), 2.30 (m, 1H), 3.10 (m, 1H), 3.56 (s, 3H), 3.85 (m, 1H), 4.49 (ABq, Δδ = 0.21 ppm, 2H, J = 11.8 Hz), 4.97 (m, 1H), 5.13 (m, 2H), 5.64 (m, 1H), 5.70 (m, 1H), 7.30 (m, 10H). HRMS (CI-CH_4) calcd for $C_{30}H_{38}O_6F_3$ $(M+H)^+$ 551.2621, found 551.2619.

73-(R)-MTPA ester

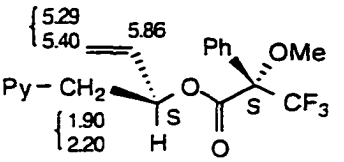


73 -(R)-MTPA ester

Rf = 0.75 (10% EtOAc:P.E.); ^1H NMR ($CDCl_3$) δ 1.20 (s, 9H), 1.60 (m, 4H), 1.96 (m, 1H), 2.30 (m, 1H), 3.1 (m, 1H), 3.51 (s, 3H), 3.82 (m, 1H), 4.48 (ABq, Δδ = 0.19 ppm, 2H, J = 11.8 Hz) 4.98 (m, 1H), 5.20 (dd, 1H, J = 10.4, 2.0 Hz), 5.32 (dd,

1H, J = 17.1, 2.0 Hz), 5.65 (m, 1H), 5.84 (m, 1H), 7.30 (m, 10H). HRMS (CI-CH_4) calcd for $C_{30}H_{38}O_6F_3$ $(M+H)^+$ 551.2621, found 551.2623.

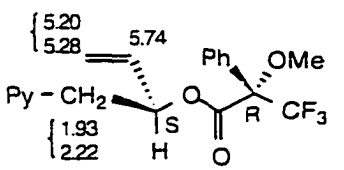
76-(S)-MTPA ester



76 -(S)-MTPA ester

Rf = 0.70 (10% EtOAc:P.E.); ^1H NMR ($CDCl_3$) δ 1.17 (s, 9H), 1.70 (m, 4H), 1.90 (m, 1H), 2.20 (m, 1H), 3.09 (m, 1H), 3.50 (s, 3H), 3.79 (m, 1H), 4.43 (ABq, Δδ = 0.19 ppm, 2H, J = 11.6 Hz), 4.96 (m, 1H), 5.29 (dd, 1H, J = 10.5, 2.0 Hz), 5.40 (dd, 1H, J = 17.2, 2.0 Hz), 5.66 (m, 1H), 5.86 (m, 1H), 7.40 (m, 10H). HRMS (CI-CH_4) calcd for $C_{30}H_{38}O_6F_3$ $(M+H)^+$ 551.2621, found 551.2616.

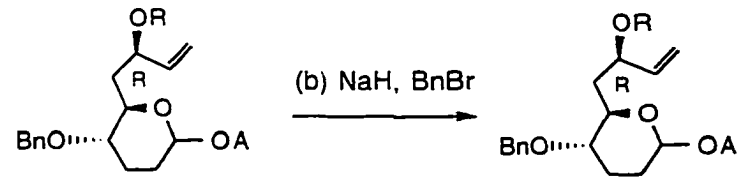
76-(R)-MTPA ester



76 -(R)-MTPA ester

Rf = 0.70 (10% EtOAc:P.E.); ^1H NMR ($CDCl_3$) δ 1.15 (s, 9H), 1.70 (m, 4H), 1.93 (m, 1H), 2.22 (m, 1H), 3.09 (m, 1H), 3.51 (s, 3H), 3.81 (m, 1H), 4.48 (ABq, Δδ = 0.19 ppm, 2H, J = 11.7 Hz), 4.98 (m, 1H), 5.20 (dd, 1H, J = 10.7, 2.0 Hz), 5.28 (dd, 1H, J = 16.7, 2.0 Hz), 5.64 (m, 1H), 5.74 (m, 1H), 7.38 (m, 10H). HRMS (CI-CH_4) calcd for $C_{30}H_{38}O_6F_3$ $(M+H)^+$ 551.2621, found 551.2621.

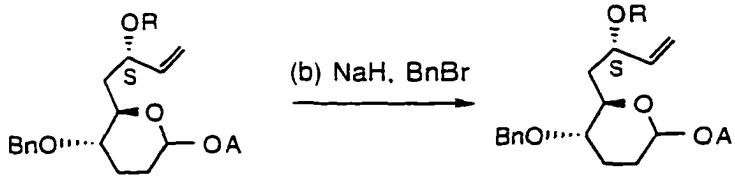
t-Butyl Pyranoside-Benzyl Ether (74)



73 A = t-Bu; R = H **74** A = t-Bu; R = Bn

NaH (45 mg, 1.1 mmol, 60% suspension in mineral oil) and nBu_4NI (17 mg, 0.05 mmol) was added at 0 °C to a solution of alcohol **73** (150 mg, 0.45 mmol) in anhydrous DMF (4 mL). The suspension was stirred at this temperature for 15 min at which time benzyl bromide (0.12 mL, 1.0 mmol) was added. The reaction was warmed to rt, stirred for an additional 16 h, then recooled to 0 °C and quenched by addition of MeOH (0.1 mL). Water (25 mL) was added and the mixture extracted with ether (4 x 20 mL). The ether extract was washed with $NaHCO_3$, and brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure and the crude brown residue purified by flash chromatography to give **74** (162 mg, 84%): Rf = 0.60 (5% EtOAc:P.E.): ^1H NMR ($CDCl_3$) δ 1.25 (s, 9H), 1.5 (m, 1H), 1.75 (m, 3H), 2.0 (m, 2H), 2.39 (m, 1H), 3.16 (m, 1H), 4.20 (m, 2H), 4.49 (ABq, Δδ = 0.29 ppm, 2H, J = 11.7 Hz), 4.6(ABq, Δδ = 0.18 ppm, 2H, J = 11.7 Hz), 4.63 (s, 1H), 5.11 (t, 1H), 5.3 (m, 2H), 5.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 26.6, 29.0, 37.6, 30.6, 65.8, 67.8, 68.4, 71.9, 75.2, 76.2, 88.3, 114.5, 125.1, 125.3, 125.4, 125.6, 126.1, 126.2, 126.3, 136.7,137.0, 137.8. Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.54; H, 8.81.

t-Butyl Pyranoside-Benzyl Ether (77)

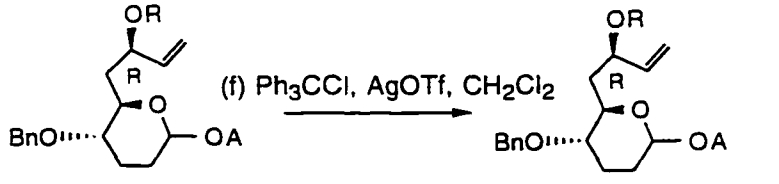


76 A = t-Bu; R = H **77** A = t-Bu; R = Bn

Benzylation of **76** (100 mg, 0.30 mmol) under the conditions described for the preparation of **74**, gave **77** (113 mg, 92%): Rf = 0.55 (5% EtOAc:P.E.); ^1H NMR ($CDCl_3$) δ 1.11 (s, 9H), 1.60 (m, 2H), 1.80 (m, 3H), 1.90 (m, 1H), 2.15 (m, 1H), 3.20 (m, 1H), 3.82 (m, 1H), 4.03 (m, 1H), 4.42 (ABq, Δδ = 0.25 ppm, 2H, J = 10.3 Hz),

4.48 (ABq, $\Delta\delta$ = 0.23 ppm, 2H, J = 14.0 Hz), 4.95 (t, 1H), 5.15 (m, 2H), 5.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5 26.6, 28.8, 36.7, 66.4, 68.0, 68.6, 71.8, 75.7 75.8, 88.2, 115.9, 125.2, 125.3, 125.4, 125.6, 125.8, 126.1, 126.2, 136.5, 136.7. Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.01; H, 8.34.

Trityl Pyranoside-Benzyl Ether (75 α/β)

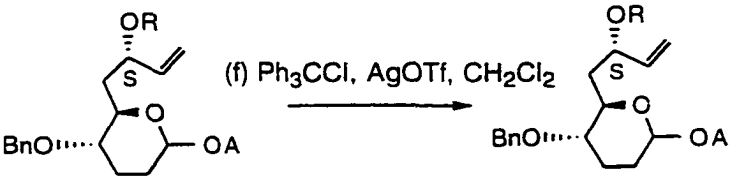


74 A = t-Bu; R = Bn **75** A = CPh_3; R = Bn

A solution of **74** (100 mg, 0.30 mmol) in a mixture of THF (7 mL) and 0.5 N HCl (2 mL) was stirred at rt for 20 h. The mixture was poured into saturated aqueous $NaHCO_3$ (20 mL) and extracted with ether (4 x 15 mL). The ether extract was dried ($MgSO_4$), filtered and the filtrate concentrated under reduced pressure. Purification of the residue by flash chromatography (Rf = 0.10; 5% EtOAc:P.E.) gave the presumed lactol derivative (87.2 mg, 80%) which was dried under high vacuum and used directly in the next step.

Freshly activated, powdered 4A molecular sieves (100 mg) was added to a solution of the material obtained in the previous step (85 mg, 0.23 mmol), 2,4,6-collidine (0.07 mL, 0.506 mmol) and trityl chloride (141 mg, 0.51) in CH_2Cl_2 (3 mL). The mixture was stirred for 15 min, at which time AgOTf (118 mg, 0.46 mmol) was added. After stirring for an additional 15 min, the solution was diluted with 10% aqueous $Na_2S_2O_3$, (10 ml) and extracted with ether (4 x 10 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and filtered. Evaporation of the filtrate under reduced pressure and flash chromatography of the residue gave **75** α/β (119 mg, 85%): Rf = 0.60 (5% EtOAc:P.E.); ^1H NMR ($CDCl_3$) δ 1.40-2.20 (m, 6H), 3.15 (m, 1H), 3.40 (m, 1H), 3.45 (m, 1H), 4.10 (d, J = 10.3 Hz, 1H), 4.50, 5.15 (both m, 6H), 5.7 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (major isomer) 27.8, 31.1, 39.8, 69.8, 71.0, 74.4, 77.5, 79.0, 87.9, 97.2, 116.7, 126.5-129.6 (several lines), 138.6, 139.6, 139.9, 144.8; (minor isomer, selected peaks) 23.8, 29.9, 39.5, 87.9, 92.6, 116.7, 138.6, 139.6, 139.9, 145.0. HRMS (CI-NH_4) calcd for $C_{42}H_{43}O_4$ $(M+H)^+$ 611.3161, found 611.3162.

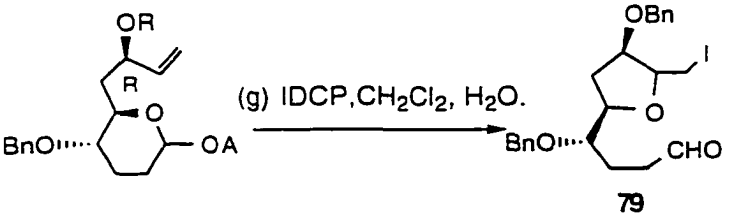
Trityl Pyranoside-Benzyl Ether 78α/β



77 A = t-Bu; R = Bn **78** A = CPh_3; R = Bn

Application of the identical two-step procedure described for the preparation of 75α/β, to the t-butyl pyranoside **77** (100 mg, 0.30 mmol) afforded the trityl glycoside 78α/β (110 mg, 60%): Rf = 0.60 (5% EtOAc:P.E.); ^1H NMR ($CDCl_3$) δ 1.4-2.1 (m, 6H), 2.9, 3.6, 3.8, 4.0 (all m, 2H), 3.2 (m, 1H), 4.2-4.6, 4.9-5.2 (both m, 7H), 5.6 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (major isomer) 28.1, 31.3, 38.1, 70.4, 71.3, 75.4, 76.7, 77.1, 77.4, 88.1, 97.5, 117.6, 127.0-129.0 (several lines), 138.7, 139.0, 139.1, 145.1; (minor isomer, selected peaks) 24.3, 31.1, 38.3, 87.8, 92.6, 117.7, 127.0-129.0 (several lines), 138.7, 139.1, 139.2, 144.9. HRMS (CI-NH_4) calcd for $C_{42}H_{43}O_4$ $(M+H)^+$ 611.3161, found 611.3162.

***cis*-2,5-THF-aldehyde (79c)**



79

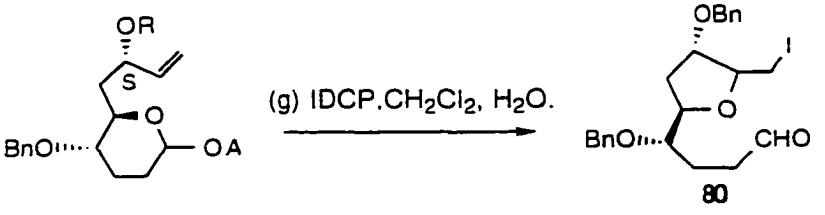
74 A = t-Bu; R = Bn A = t-Bu 83%
75 A = CPh_3; R = Bn A = CPh_3 83%

IDCP (132 mg, 2.82 mmol) was added to a solution of alkene **74** (100 mg, 0.24 mmol) in CH_2Cl_2:H_2O (20:1, 5 mL). The solution was stirred at rt for 5 min, then diluted with 10% aqueous $Na_2S_2O_3$ (10 mL) and extracted with ether (4 x 20 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography yielded the aldehyde **79c** (96 mg, 83%): Rf = 0.30 (10% EtOAc:P.E.); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.82 (m, 1H), 1.93 (m, 1H), 2.20 (m, 2H), 2.78 (m, 2H), 3.31 (dd, 1H, J = 6.3, 10 Hz), 3.38 (dd, 1H, J = 7.9, 10 Hz),

3.64 (m, 1H), 4.02 (m, 1H), 4.10 (m, 1H), 4.18 (m, 1H), 4.51 (ABq, $\Delta\delta$ = 0.23 ppm, 2H, J = 10 Hz), 4.53 (m, 2H), 7.25 (m, 10H), 9.7 (s, 1H); ^{1}H NMR (C_6D_6) δ 1.6 (m, 3H), 2.0 (m, 3H), 3.1 (dd, 1H, J = 6.4, 9.5 Hz), 3.22 (dd, 1H, J = 7.7, 9.5 Hz), 3.35 (q, 1H, J = 5.3 Hz), 3.6 (m, 2H), 3.65 (m, 1H), 4.07 (ABq, $\Delta\delta$ = 0.16 ppm, 2H, J = 11.1 Hz), 4.39 (ABq, $\Delta\delta$ = 0.18 ppm, 2H, J = 12.1 Hz), 7.1 (m, 10H), 9.35 (s, 1H); ^{13}C NMR (C_6D_6) δ 2.6 (CH_2I-cis-2,5), 24.6, 33.3, 40.1, 71.8, 73.0, 79.2, 79.5, 81.5, 83.6, 128.1, 128.4, 128.8, 129.0, 138.9, 139.7, 201.0. MS (CI) m/z 512 ($M+NH_4^+$), 495 ($M+H^+$). Anal. Calcd for $C_{23}H_{27}O_4I$: C, 55.88; H, 5.51. Found: C, 55.70; H, 5.50.

Application of the above procedure to trityl pyranoside **75**α/β (139 mg, 0.228 mmol) afforded aldehyde **79c** (94 mg, 83%).

cis/trans -2,5-THF-aldehyde (80 c/t)

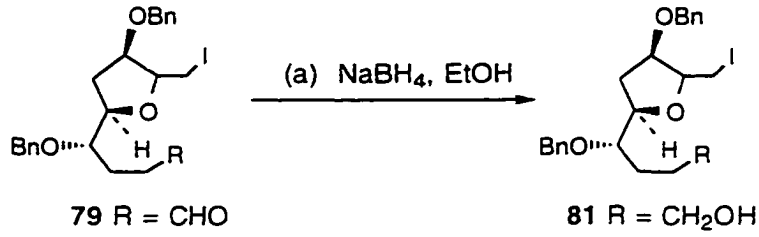


80

77 A = t-Bu; R = Bn A = t-Bu 89 % (40:60)
78 A = CPh_3; R = Bn A = CPh_3 83 % (60:40)

Application of the standard iodoetherification procedure individually, to t-butyl pyranoside **77** (100 mg, 0.236 mmol) and trityl pyranoside **78**α/β (80 mg, 0.13 mmol) afforded *cis/trans* -2,5-THF-aldehydes **80c/t** as inseparable mixtures in yields of (104 mg, 89%) and (54 mg, 83%) respectively. The c:t ratios as determined by the integration of the 1H NMR signals at d 2.80 and 3.17 were 40:60 and 60:40. For **80c/t**: Rf = 0.30 (10% EtOAc:P.E.); ^{1}H NMR (C_6D_6) δ 1.40-2.20 (m, 6H), 2.80 (CH_2I-*cis*-2,5), 3.17 (CH_2I-*trans*-2,5), 3.34, 3.75, and 4.18, (all m, 6H), 4.20-4.60 (m, 4H), 7.20 (m, 10H), 9.25 (s, 1H); ^{13}C NMR (C_6D_6) δ 3.4 (CH_2I-*trans*-2,5), 8.0 (CH_2I-*cis*-2,5), 24.7, 24.8, 33.1, 33.6, 40.3, 40.5, 71.6, 72.3, 73.7, 73.8, 79.4, 80.0, 80.1, 82.1, 82.6, 83.6, 84.4, 121.4, 127.9, 128.4, 128.6, 128.8, 129.0, 139.0, 139.8, 200.8. HRMS (CI-NH_4) calcd for $C_{23}H_{28}O_4I$ $(M+H)^+$ 495.1032, found 495.1021.

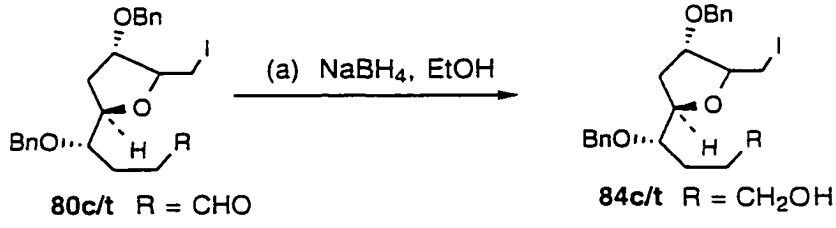
***cis*-2,5-THF-alcohol (81c)**



79 R = CHO **81** R = CH_2OH

$NaBH_4$ (15 mg, 0.40 mmol) was added to a solution of the aldehyde **79c** (100 mg, 0.202 mmol) in ethanol (5 mL), under an atmosphere of argon at rt. The solution was stirred at this temperature for 10 min, then cooled to 0 °C and quenched by addition of 10% methanolic HCl to pH 7. The mixture was then filtered through a bed of celite and the filtrate concentrated under reduced pressure. Flash chromatography of the residue afforded THF-alcohol **81c** (95 mg, 95%): Rf = 0.65 (15% EtOAc:P.E.); ^{1}HNMR (C_6D_6) δ 1.5 (m, 5H), 2.05 (m, 1H), 3.18 (dd, 1H, J = 6.5, 9.5 Hz, CH_2I-*cis*-2,5), 3.3 (m, 3H), 3.50 (m, 1H), 3.70 (m, 3H), 4.1 (ABq, Δδ = 0.17 ppm, 2H, J = 11.6 Hz), 4.5 (ABq, Δδ = 0.17 ppm, 2H, J = 11.5 Hz), 7.2 (m, 10H); ^{13}C NMR (C_6D_6) δ 2.7 (CH_2I-*cis*-2,5), 28.7, 29.1, 33.3, 63.1, 71.8, 73.2, 79.3, 80.3, 81.8, 83.5, 128.5-129.2 (several lines), 138.7, 140.0. MS (CI) m/z 514 ($M+NH_4^+$), 497 ($M+H^+$). Anal. Calcd for $C_{23}H_{29}O_4I$: C, 55.65; H, 5.89. Found: C, 55.59; H, 5.91.

***cis/trans*-2,5-THF-alcohol (84c/t)**

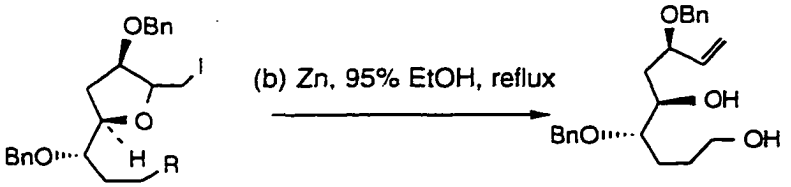


80c/t R = CHO **84c/t** R = CH_2OH

Treatment of aldehyde **80c/t** (100mg, 0.202 mmol), which was obtained from the iodoetherification of t-butyl pyranoside **78**α/β, under the NaBH4 reduction procedure described for the preparation of **81c**, gave **84c/t** (93 mg, 93%). A c:t ratio of 40:60 was determined from the relative integrals of the signals at d 2.9 and 3.22 ppm. For **84c/t**: Rf = 0.65 (15% EtOAc:P.E.); ^{1}H NMR (C_6D_6) δ 1.5 (m, 4H), 1.85 (m, 2H), 2.79 (CH_2I-*cis*-2,5), 2.90 (CH_2I-*cis*-2,5), 3.22 (CH_2I-*trans*-2,5-) and 3.30 (dd, J = 6.9, 9.8 Hz, dd, J = 5.2, 9.8 Hz, dd, J = 6.9, 9.3 Hz, and m, resp., 4H), 3.50 (m, 1H), 3.69 (m, 1H),

4.2 (m, 4H), 4.60 (m, 2H), 7.20 (m, 10H). ^{13}C NMR (C_6D_6) δ 3.5 (CH_2I-*trans*-2,5), 8.1 (CH_2I-*cis*-2,5), 28.7, 29.0, 29.4, 29.5, 32.8, 33.2, 63.0, 71.6, 72.3, 73.8, 73.9, 80.1, 80.9, 82.5, 83.0, 83.5, 83.7, 84.4, 128.1-129.2 (several lines), 139.1, 140.0. MS (CI) m/z 514 ($M+NH_4^+$) (base peak), 497 ($M+H^+$). Anal. (mixture) Calcd for $C_{23}H_{29}O_4I$: C, 55.65; H, 5.89. Found: C, 55.59; H, 5.82.

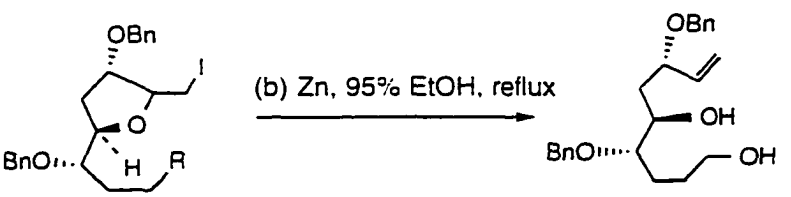
Dihydroxyalkene (82)



81 R = CH_2OH **82**

A mixture of **81c** (45mg, 0.091 mmol), freshly activated zinc dust (100 mg) and 95% ethanol (2 mL) was heated at reflux for 1 h. The mixture was cooled to rt, diluted with ether and filtered through a bed of celite. Evaporation of the filtrate under reduced pressure, followed by purification of the residue by flash chromatography afforded **82** (31 mg, 93%): Rf = 0.40 (30% EtOAc:P.E.); ^1H NMR ($CDCl_3$) δ 1.58-1.90 (m, 6H), 2.81 (d, 1H, J = 3.6 Hz), 3.40 (m, 1H), 3.60 (m, 1H), 4.1 (m, 1H), 4.5 (ABq, Δδ = 0.27 ppm, 2H, J = 11.7 Hz), 4.6 (m, 2H), 5.3 (m, 2H), 5.32 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.6, 28.5, 37.7, 62.8, 68.9, 70.5, 71.9, 77.8, 81.8, 117.1, 127.6, 127.8, 128.4, 138.1, 138.2; HRMS (CI-NH_4) calcd for $C_{23}H_{31}O_4$ $(M+H)^+$ 371.2222, found 371.2208.

Dihydroxyalkene (85c/t)

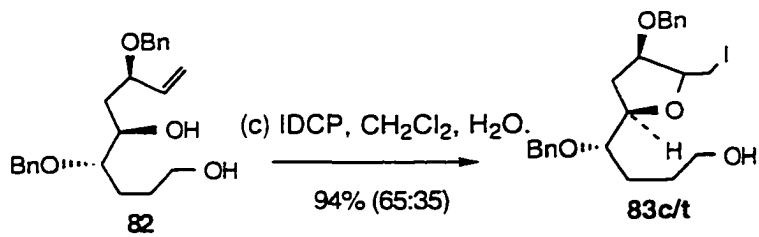


84c/t R = CH_2OH **85**

Treatment of alcohol **84c/t** (50 mg, 0.10 mmol) under the conditions described for the preparation of 15, afforded **85** (32 mg, 80%): Rf = 0.38 (30% EtOAc:P.E.); ^1H NMR ($CDCl_3$) δ 1.40-2.00 (m, 6H), 3.30 (q, 1H, J = 4.8 Hz), 3.55 (d, 2H, J = 5.1 Hz), 3.8

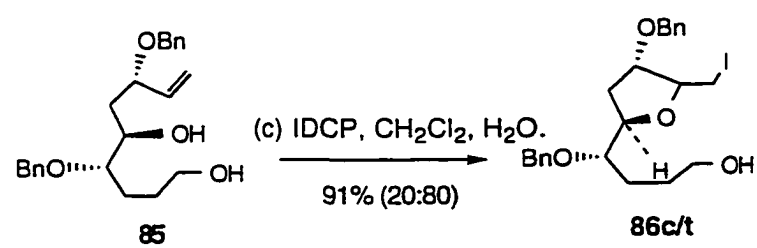
(q, 1H, J = 6.3 Hz), 3.98 (q, 1H, J = 6.6 Hz), 4.43 (ABq, Δδ = 0.27 ppm, 2H, J = 11.6 Hz), 4.53 (ABq, Δδ = 0.08 ppm, 2H, J = 11.5 Hz), 5.3 (m, 2H), 5.70 (m, 1H): ^{13}C NMR ($CDCl_3$) δ 24.9, 27.0, 36.8, 64.2, 70.4, 72.8, 73.5, 80.0 80.7, 119.4, 128.2, 128.5, 128.6, 128.7, 128.8, 128.9, 129.2, 135.9, 136.5, 136.7; HRMS (CI-NH_4) calcd for $C_{23}H_{31}O_4$ $(M+H)^+$ 371.2222, found 371.2223.

Iodoetherification of Dihydroxyalkene (82)



Application of the standard iodoetherification procedure to diol alkene **82** (31 mg, 0.084 mmol) afforded **83c/t** as an inseparable mixture (39 mg, 94%). The major component was identical to previously obtained **79c** (TLC, ^1H and ^{13}C NMR). A *cis:trans* -2,5 ratio of 65:35 was determined from comparison of the proton integrals at δ 3.19 and 2.90 ppm respectively. For **83c/t:** Rf = 0.65 (30% EtOAc:P.E.); ^1H NMR (C_6D_6) δ 1.50 (m, 4H), 1.90 (m, 1H), 2.05 (m, 1H), 2.90 (CH_2I-trans-2,5) and 3.19 (CH_2I-cis-2,5) and 3.30 (ABq, Δδ = 0.02 ppm, J = 10.1 Hz, dd, 6.5, 9.5 Hz and m, resp., 4H), 3.55, 3.70, 3.95 (all m, 4H), 4.20 (m, 2H), 4.55 (m, 2H), 7.2 (m, 10H): ^{13}C NMR (C_6D_6) δ 2.7 (CH_2I-cis-2,5), 9.0 (CH_2I-trans-2,5), 28.5, 28.7, 29.1, 29.2, 33.3, 33.9, 63.1, 71.8, 72.2, 73.2, 73.4, 79.3, 80.3, 80.7, 81.7, 81.8, 82.7, 83.5, 83.7, 127.5-129.6 (several lines), 138.7, 140.0. MS (CI) m/z 514 ($M+NH4^+$) (base peak), 497 ($M+H^+$).

Iodoetherification of Dihydroxyalkene (85)



Application of the standard iodoetherification procedure to diol alkene **85** (30 mg. 0.081 mmol) afforded **86c/t** as an inseparable mixture (37 mg, 91%). The mixture showed identical TLC, ^{1}H and ^{13}CNMR to previously obtained **84c/t**. A *cis*:*trans*-2.5 ratio of 80:20 was determined by comparisons of the proton integrals at δ 2.90 and 3.22 ppm respectively.

(V) References

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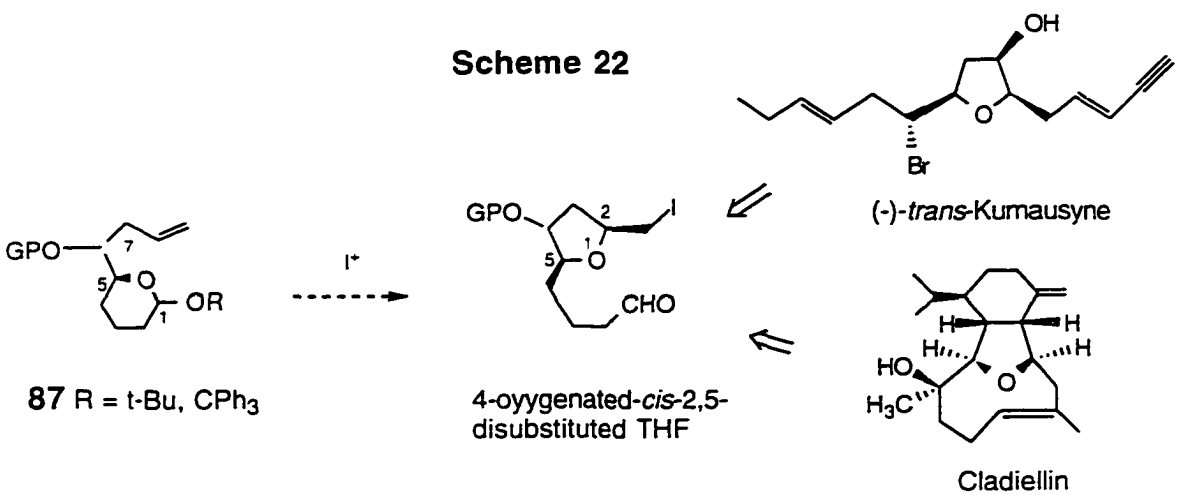
Chapter 3 : Halocyclization of C-6 allylated pyranosides Homoallylic substrates

(I) Terminal Alkenes

(i) Preparation of pyranoside

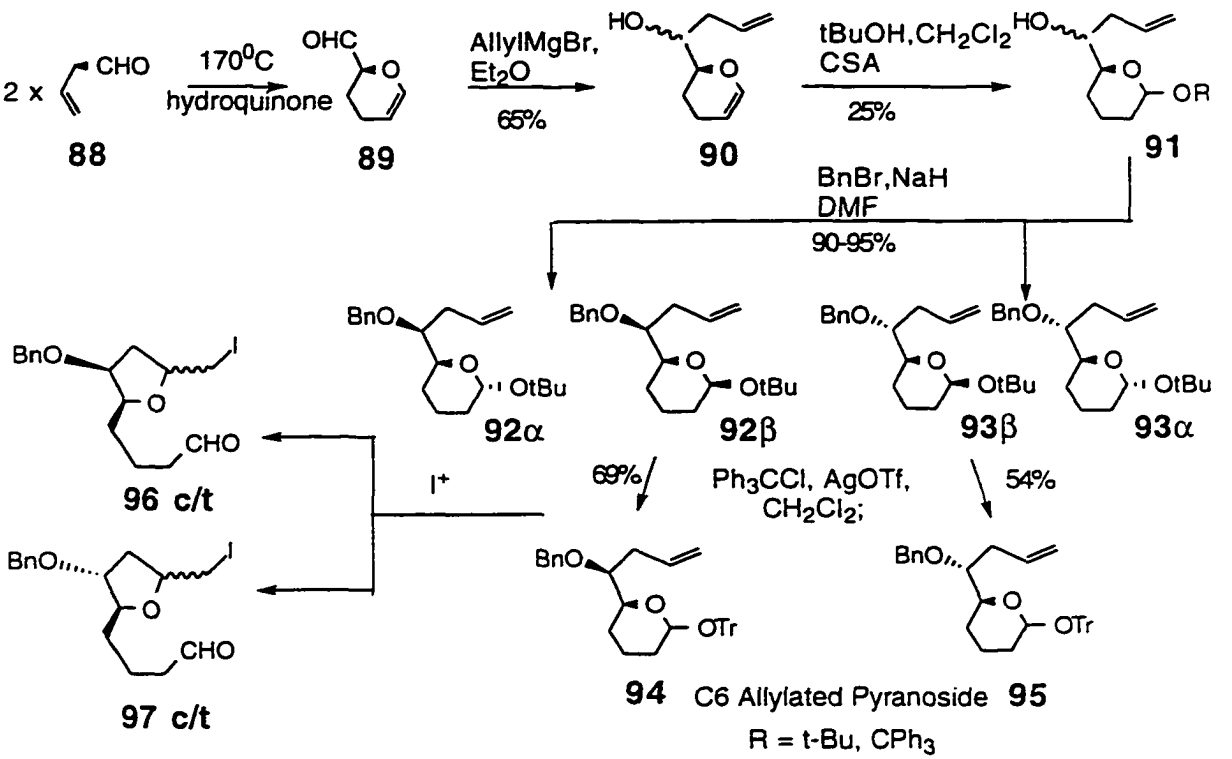
The question was whether the homoallylic substitution would exert any significant directing effect as observed for the allylic case (Scheme 22).

Scheme 22



Our model system chosen for these studies was the pyranoside **87** (Scheme 23). Preparation of **87** began from commercially available acrolein. Heating at 170 ^{o}C in the presence of Hydroquinone gave the Diel's Alder adduct[1] **89**. Addition of the Allylgrignard reagent allylmagnesiumbromide afforded an inseparable mixture of two alcohols (65% yield). Acetalization using tBuOH/CSA afforded the α,β mixture of chromatographically separable t-butyl pyranosides in 25% yield. Acid hydrolysis of the t-butyl followed by a siver mediated tritylation afforded the trityl pyranosides **94** and **95** in 68 and 53% respectively (Scheme 23).

Scheme 23

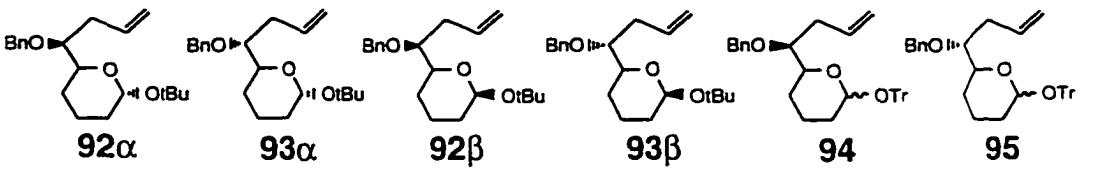


The free homoallylic alcohol was protected under benzylation conditions. The benzyl pyranosides were then treated with IDCP in the presence of wet dichloromethane to yield the desired THF's **96** and **97**.

(ii) Halocyclisation results

Each of the four t-butyl glycosides **92α/β** and **93α/β** was treated with IDCP to produce a mixture of the THF's **96c/t** and **97c/t**. In each series, the β anomer gave a slightly greater proportion of *cis* isomer. Both Trityl pyranosides **94** and **95** yielded high *cis* THF selectivity when treated with IDCP (Scheme 24).

Scheme 24

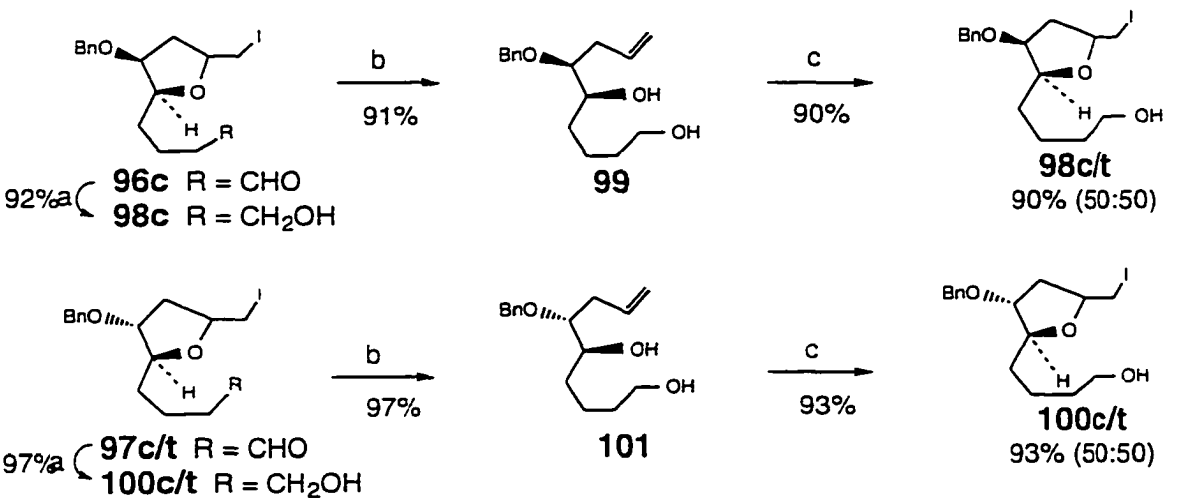


	92α	93α	92β	93β	94	95
YIELDS/%	91	90	94	90	89	91
CIS/TRANS THF	63:37	65:35	73:27	71:29	85:15	85:15

(iii) Importance of pyranoside framework

In order to evaluate the importance of the pyranoside framework on the stereoselectivity of the halocyclisation reaction the acyclic alkenes **99** and **101** were prepared (Scheme 25). These were obtained by $NaBH_4$ reduction of the THF aldehydes **96** and **97** obtained from the halocyclisation reaction. Zinc mediated reductive elimination of the resulting primary alcohols **98** and **100** gave the alkenes. Iodocyclisation of **99** and **101** under the standard conditions gave a 50:50 *cis*:*trans* ratio (Scheme 25). These results were indeed very different from the 4-penten-1,2-diol substrates[2].

Scheme 25



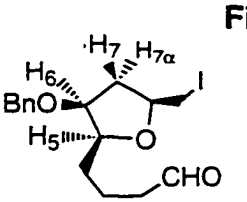
(a) $NaBH_4$, EtOH; (b) Zn, 95% EtOH, reflux; (c) IDCP, CH_2Cl_2, H_2O.

(iv) Stereochemistry

Once again the stereochemistry of the products were assigned by comparison of the ^{1}H and ^{13}C NMR for the *cis* and *trans* isomeric pairs with the data for known 2,5-dialkyl THF's.[3] As before similar patterns in the ^{1}H NMR and ^{13}C NMR was observed.

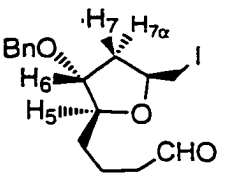
The relative stereochemistry of **96** and **97** was established by their NOESY spectrum (Fig. 7). The CH_2I signal was first identified. This showed an 2% nOe with the H-8 signal as expected. H-8 showed and nOe of 1.75% with one of the H-7 signals (H-7α downfield). This downfield H-7α signal showed and nOe with H-6 of 0.75%. H-6 showed an nOe with H-5 of 2% strongly suggesting an all syn arrangement of substituents.

Fig. 7 nOe of 96 and 97



96

protons	%/nOe obs'd
H_5/H_6	2.0
$H_6/H_7\alpha$	0.5 - 1.0
$H_7\alpha/H_8$	1.5 - 2.0
CH_2I/H_8	2.0



97

protons	%/nOe obs'd
H_5/H_6	0.25
H_5/H_8	0.5
$H_7\alpha/H_8$	
H_6/H_7	0.66

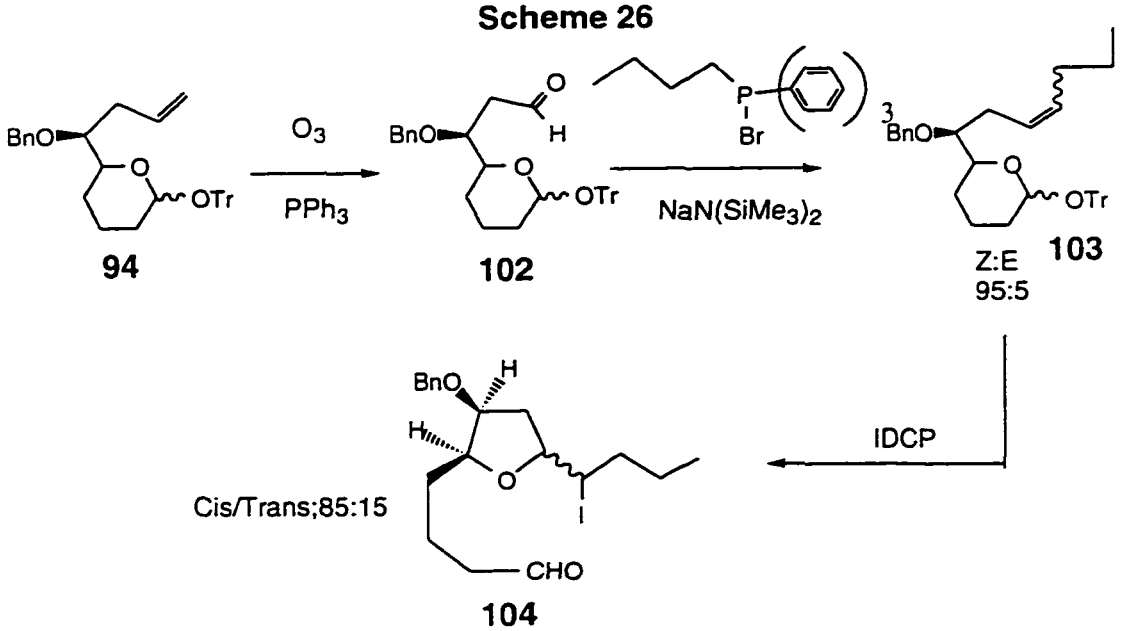
For the other isomer **97** the most convincing data was a direct nOe observed between H-5 and H-8 suggesting a syn arrangement on the THF. The stereochemistry at the H-6 was thought to be the opposite to the other isomer of the Homoallylic alcohol.

(II) Vicinal Disubstituted Alkenes

(i) Preparation and Halocyclisation

Since the halocyclizations of related Z-alkenes are noted for poor cis selectivity, it was of interest to examine the cyclization of the Z-alkene pyranoside **103**. The Z alkene was prepared via ozonolysis of the tritylated pyranoside followed by Wittig addition to furnish the alkene in 68% yield (Scheme 26). Iodoetherification of **103** afforded an 85:15 *cis*:*trans* mixture of chromatographically separable THF's (80% yield).

Scheme 26

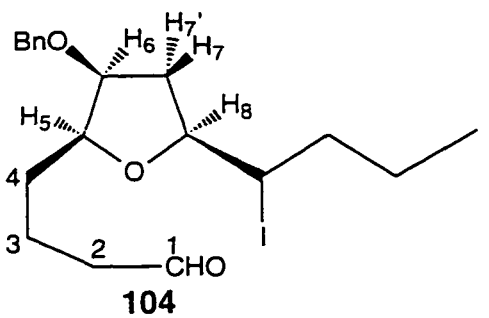


94 102 103 104

(ii) Stereochemical assignment of **104**

Having established the identity of the downfield protons in the ^1H NMR spectra using a COSY analysis, we determined the relative stereochemistry by nOe analysis (Fig. 8). Direct support for a *cis* 2,5-substituted THF came from the strong nOe observed between H-5/H-8 of 1%. H-5/H-6 showed a strong nOe of 2% suggesting an all syn arrangement. A 0.1% nOe between H-6 and H-8 gave support for the syn stereochemistry. nOe's between H-9/H-8, H-6/OBn of 1% were also observed.

Fig. 8 nOe of 104



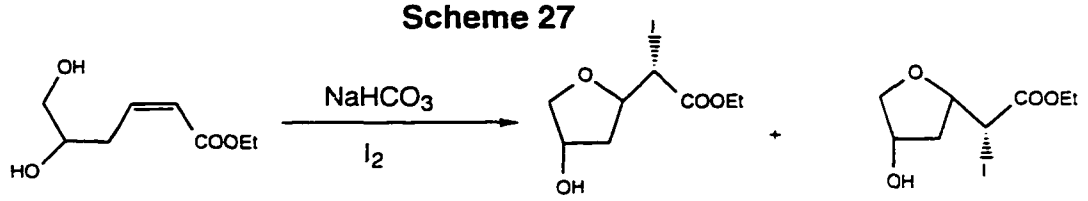
104

protons	%/nOe obs'd
H_5/H_6	2.0
H_6/H_8	0.1
H_6/OBn	1.0
H_5/H_8	1.0
H_9/H_8	1.0

(III) Mechanistic explanation

Presumably, the remoteness of the chiral and prochiral centers in homoallylic induction results in much weaker effects. Guindon et al[2] investigated the homoallylic induction in the iodocyclisation of α,β-unsaturated esters (Scheme 27). The *trans* THF **106** was the major product observed.

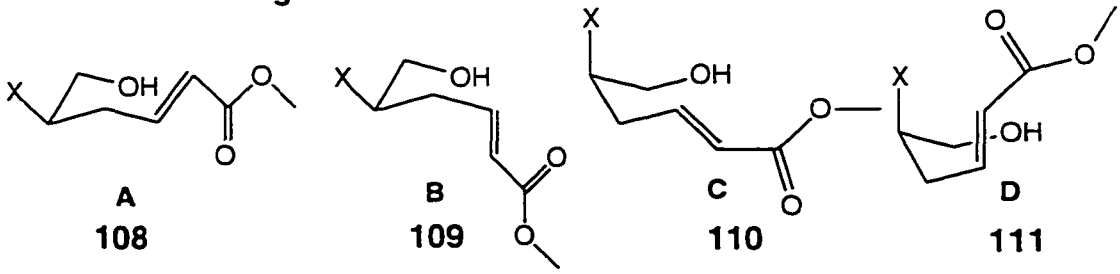
Scheme 27



trans-major **106** *cis*-minor **107**

The results were rationalized by comparing the activation energies of the four low energy conformation of the reactant (Fig. 9). AM1 calculations indicate a energy differnce of 1.6 Kcal/mol favoring the β-orientation of the olefinic carbons in the transition-state model, thus indicating that **A** and **C** should be favored over **B** and **D**. Since **A** and **C** are chair conformations, one might expect that **A** would be the least energetic orientation since X is equatorial. This would lead to the *cis* product. However, closer examination of the nucleophilic end of the molecule revealed its 1,2-disubstituted ethane nature. Several compounds such as 1,2-difluoroethane[11] and 2-fluorethanol[12] have been shown to prefer a gauche arrangement of the heteroatomic substituents (as in **C**) which could overide the preference for the equatorial group. Thus **C** is favored (based on AM1 calculations) giving the *trans* THF product.

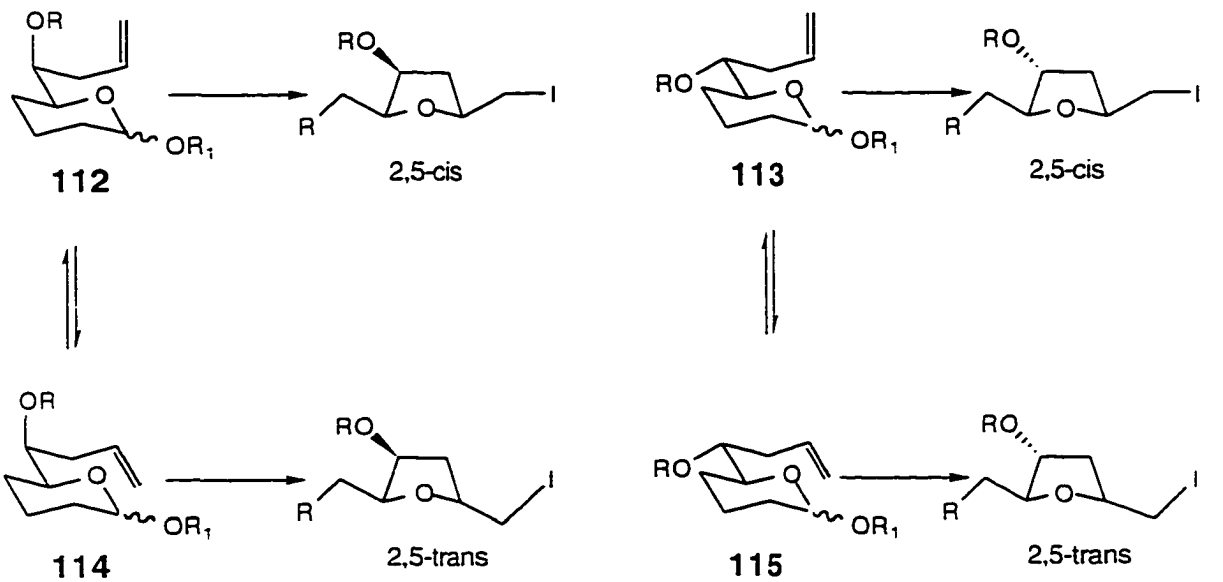
Fig. 9 Reactant like Transition States 108-111



A **108** **B** **109** **C** **110** **D** **111**

The conformational rigidity of the pyranoside ring limits the number of reactive configurations to only two (i.e. about the alkene). For either the axial or equitorial alkoxy group there are two possible olefin configurations. In the first comparison (Scheme 28) **114** (compares to **C** better than **D**) is preferred over **112** due to it's chair shape. However it is disfavored by the pyranoside model and this represents a mismatched case. In the second comparison **115** (chair compares to **A** better than **B**) is preferred over **113** boat. This is also disfavored by the pyranoside model (Scheme 21) and it represents a mismatched case. Since both of these models are mismatched, there is no synergy as observed in the allylic case and the high *cis* selectivity observed can be explained by the strong aglycone effect overiding the weaker Guindon effect ($A^{1,3}$ strain).

Scheme 28



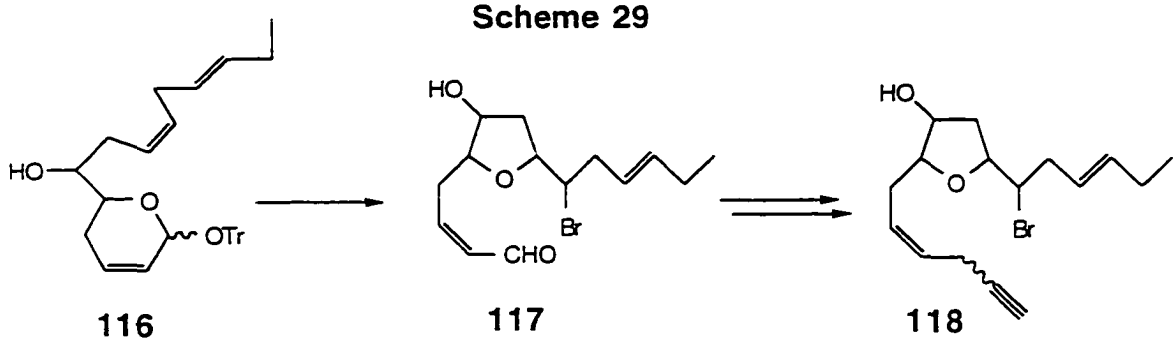
The acyclic substrates **99** and **101** both gave 50:50 mixtures of *cis* : *trans* 2,5-THF derivatives. These results are not in agreement with the pyranoside model system discussed earlier. This suggested that the reaction is heavily substrate dependent and while the model proposed earlier worked for simple systems, as substitution increases the selectivity of cyclization varies. Overall for the homoallylic alcohol pyranosides studied the high *cis*

selectivity observed is presumed to arise as a result of the conformational rigidity imposed by the pyranoside framework.

(IV) Application to Kamausyne Synthesis

The synthesis of Kamausyne can be thought to arise from some pyranoside precursor (Scheme 29). This would then be treated under halocyclisation conditions to yield the key THF intermediate **117** bearing an all syn arrangement of the 2,4 and 5 positions. Further elaboration of the aldehyde side arm via Corey's methodology would enable easy acess to Kamausyne **118**. A recent example of this work was demonstrated by Martin et al.[13] Here cyclizations on a acyclic diene precusor was done to yield the THF intermediate.

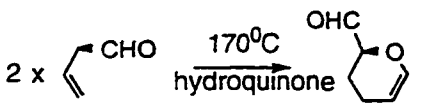
Scheme 29



116 **117** **118**

(V) Experimental

Aldehyde (89)

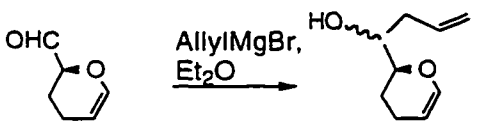


88 89

Prepared according to Alder et al[1]

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (m, 4H), 4.31(m, H-5, 1H), 4.79 (m, H-2.1H). 6.50 (d, 1H , H-1, J = 6.52 Hz). 9.53 (s, 1H).

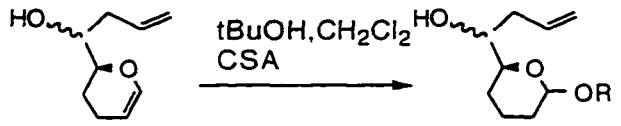
Homoallylic alcohol (90)



89 90

Aldehyde **89** (80 mg. 0.70 mmol) was dissolved in THF (2 mL) and the solution cooled to - 78 °C. Allylmagnesium bromide (3.5 mL, 3.5 mmol, 1.0 M in THF) was added. The reaction was allowed to proceed for 10 min after which time the solution was diluted with Et_2O (15 mL) at 0 °C. Saturated aqueous NH_4Cl (5 mL) was added and the organic phase separated .The aqueous layer was extracted with Et_2O (3 x 5 mL), then the combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL) and dried (Na_2SO_4). Excess solvent was evaporated under reduced pressure to give the crude which was purified by FCC (10-30% EtOAc:PE) to give the homoallylic alcohol **90** (70 mg, 65 %) : Rf 0.6 (10 % EtOAc:PE). ^{1}H NMR(300 MHz) δ 2.00 (m, 3H), 2.30 (m, 3H), 3.69 (m, 1H), 3.85 (m, 1H) (H-5, H-6), 4.80 (m, H-2, 1H), 5.18 (m, H-9, 2H), 5.90 (m, H-8, 1H), 6.40 (m, H-1, 1H).

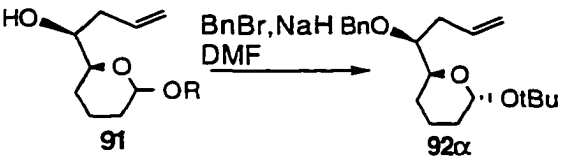
Homoallylic Pyranosides (91)



90 91

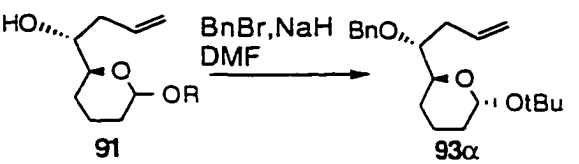
Alcohol **90** (2.2g, 14.40 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL). t-BuOH (6.87 mL, 72 mmol) and CSA (334 mg, 1.44 mmol) was then added. The solution was allowed to stir for 30 min and then quenched by dilution with CH_2Cl_2 (100 mL). After washing with saturated $NaHCO_3$ (20 mL), brine (20 mL) the excess solvent evaporated in vacuo followed by FCC to give 4 fractions of **91** Fr **# 1 OH** α (227 mg, 6.9%) : Rf 0.9 (7% EtOAc/PE). ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 9H),1.60 (m, 4H), 1.89 (m, 2H), 2.28 (m, 2H), 2.40 (m,1H, D_2O exch.), 3.25 (m, 1H), 3.80 (m, 1H), 5.10 (m, 2H), 5.15 (m, 1H), 5.91 (m, 1H); MS (ES) m/z 251 [base peak (M + Na^+)] . Fr **# 2 OH** α (237 mg, 7.2%) : Rf 0.83 (7% EtOAc/PE). ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 9H),1.60 (m, 4H), 1.82 (m, 2H), 2.03(m,1H, D_2O exch.), 2.21 (m, 2H), 3.59 (m, 1H), 3.84 (m, 1H), 5.12 (m, 3H), 5.85 (m, 1H); MS (ES) m/z 251 [base peak (M + Na^+)], Fr **# 3 OH** β (120 mg, 3.6%) : Rf 0.80 (7% EtOAc/PE). ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 9H), 1.50 (m, 4H), 1.90 (m, 2H), 2.30 (m, 2H), 2.58 (m, 1H, D_2O exch.), 3.30 (m, 1H), 3.65 (m, 1H), 4.60 (dd, 1H, J = 1.85, 8.33 Hz), 5.10 (m, 2H), 5.90 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 26.3, 28.9, 32.5, 37.6, 73.1, 75.0, 78.5, 96.9, 117.0, 134.8; MS (ES) m/z 251 [base peak (M + Na^+)]. Fr **# 4 OH** β (240 mg, 7%) : Rf 0.75 (7% EtOAc:PE) δ 1.27 (s, 9H), 1.50 (m, 5H), 1.90 (m, 1H), 2.05 (m,1H, D_2O exch.), 2.20 (m, 1H), 2.39 (m, 1H), 3.30 (m, H), 3.65 (m, 1H), 4.60 (d,1H, J = 9.3 Hz), 5.10(m, 2H), 5.84 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 22.1, 25.1, 28.6, 32.5, 37.3, 72.7, 74.7, 78.3, 96.7, 117.5, 134.8; MS (ES) m/z 251 [base peak (M + Na^+)].

Benzyl pyranoside (92α)



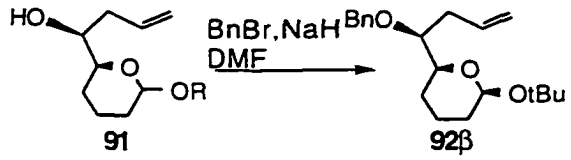
Pyranoside **91(Fr 1)** (227 mg, 1.00 mmol was dissolved in anhydrous DMF (4 mL). To this stirred solution at 0 °C was added NaH (200 mg, 5.00 mmol) and 5 min later Bu_4NI (37 mg, 0.100 mmol) and BnBr (0.69 g, 4.00 mmol) was added. The reaction was stirred for a further 2 h and then quenched by addition of MeOH (2 mL) at 0 °C. The solution was then diluted with H_2O (10 mL) and extracted with ether (4 x 20mL). The combined ether extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL) and the solvent evaporated in vacuo to furnish the crude brown product. F.C.C (5-10% EtOAc:PE) yielded the benzyl adduct **92α** (302 mg, 95%). Rf 0.6 (5% EtOAc:PE) ; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 9H), 1.40-1.90 (brm, 6H), 2.38 (m, 2H), 3.30 (m, 1H), 4.04 (m, 1H), 4.58 (s, 2H), 5.07 (m, 2H), 5.18 (d, 1H, J = 13.0 Hz), 5.89 (m, 1H), 7.30 (m, 5H); MS (ES) m/z 341 ($M + Na^+$), 245 (base peak), 227, 209.

Benzyl pyranoside (93α)



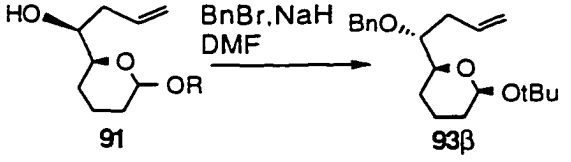
Pyranoside **91(Fr 2)** Alcohol (215 mg, 0.94 mmol) was treated as before to yield the benzyl adduct **93α** (269 mg, 90%). Rf 0.57 (5 % EtOAc:PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 9H), 1.40-1.90 (brm, 6H), 2.39 (m, 2H), 3.35 (m, 1H), 3.98 (m, 1H), 4.57 (s, 2H), 5.05 (m, 2H), 5.15 (m, 1H), 5.90 (m,1H), 7.30 (m, 5H); MS (ES) m/z 341 ($M + Na^+$), 245 (base peak), 227, 209.

Benzyl pyranoside (92α)



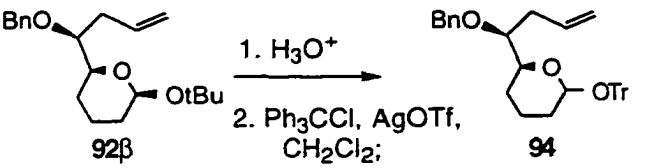
Pyranoside **91(Fr 3)** (110 mg, 0.48 mmol) was treated as before to yield the benzyl adduct **92β** (140 mg, 92 %). Rf 0.50 (5% EtOAc:PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 9H), 1.49 (m, 5H), 1.88 (m, 1H), 2.30 (m, 1H), 2.41 (m, 1H), 3.45 (m, 2H), 4.57 (m, 1H), 4.64 (ABq, Δδ = 0.07 ppm, 2H, J = 10.7 Hz), 5.06 (d, 1H, =9.3 Hz), 5.11 (d, 1H, J = 15.74), 5.83 (m, 1H), 7.34 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 26.1, 29.0, 32.7, 35.2, 73.0, 74.8, 78.1, 81.1, 97.0, 117.0, 127.5, 128.0, 128.3, 135.3, 139.2 MS (ES) m/z 341 ($M + Na^+$), 245 (base peak), 227, 209.

Benzyl pyranoside (93β)



Pyranoside **91(Fr 4)** (240 mg, 0.94 mmol) was treated as before to yield the benzyl adduct **93β** (253 mg,.91 %). Rf 0.45 (5% EtOAc:PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H), 1.4-1.69 (m, 4H), 1.85 (m, 1H), 2.41 (m, 1H), 2.56 (m, 1H), 3.10 (m, 2H), 4.60 (ABq, Δδ = 0.07 ppm, 2H, J = 10.2 Hz), 5.10 (d, 1H, J = 8.24 Hz), 5.14 (d, 1H, J=13.9 Hz), 5.95 (m, 1H), 7.35 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 26.7, 28.4, 32.3, 34.5, 71.9, 74.2, 76.5, 80.4, 96.3, 116.6, 127.4, 127.5, 127.9, 134.3, 138.1; MS (ES) m/z 341 ($M + Na^+$), 245 (base peak), 227, 209.

Trityl Pyranoside (94)

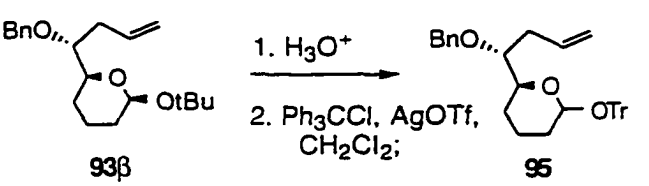


92β 94

Pyranoside **92β** (120mg, 0.377 mmol) was dissolved in THF (10 mL). 0.5N HCl was added until the pH was approximately 2-3. The solution was stirred at rt for 16 h. The reaction was then quenched by addition of saturated aqueous $NaHCO_3$ (10 mL). The aqueous mixture was extracted with ether (4 x 15mL) washed with brine (10 mL) and dried ($MgSO_4$). Evaporation of the solvent gave the crude glycoside **94-OH** (75 mg, 76%) which was used directly in the next step. ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (m, 4H), 1.85 (m, 2H), 2.40 (m, 2H), 3.43 (m, 2H), 4.08 (m, 0.5H), 4.63 (m, 2H), 5.08 (d, 1H, J = 10.2 Hz), 5.14 (d, 1H, J = 16.7 Hz), 5.87 (m, 1H), 7.38 (m, 5H).

The acetal **94-OH** (75mg, 0.20 mmol) was dissolved in anhydrous CH_2Cl_2 (3mL). To this was added crushed molecular sieves (150 mg) and 2,4,6-collidine (77 mg, 0.64 mmol) followed by recrystallised trityl chloride (167 mg, 0.60 mmol). The solution was allowed to stir for 10 min after which AgOTf (154 mg, 0.60 mmol) was added. TLC of the reaction after 10 min indicated a higher Rf component showing that the reaction was complete. The reaction was quenched by addition of 10% aqueous $Na_2S_2O_3$ (5 mL) and extracted with ether (4 x 20mL). Evaporation of excess solvent followed by FCC (5-20% EtOAc:PE) yielded tritylated pyranoside **94** (90 mg, 90.4 %). Rf 0.9 (10 % EtOAc:PE): ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (m, 2H), 1.53 (m, 2H), 1.70 (m, 2H), 2.00 (m, 2H), 2.95 (m, 2H), 4.21 (m, 2.8H), 4.93 (m, 2.2H), 5.62 (m, 1H), 7.20 (m, 15H), 7.50 (m, 5H); MS (ES) m/z 527 ($M + Na^+$), 243 (base peak).

Trityl Pyranoside (95)



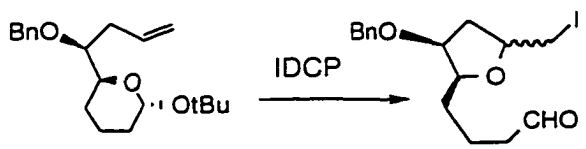
93β 95

Pyranoside **93β** (70 mgs,0.220 mmol) was treated as before to yield crude

glycoside **95-OH**(35 mg, 61 %) which was used directly in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10-1.80 (m, 6H), 2.30 (m, 2H), 3.30 (m, 1H), 3.40 (m, 1H), 3.98 (m, 0.5H), 4.52 (m, 2H), 5.00 (d, 1H, J = 10.1 Hz), 5.03 (d, 1H, J = 16.8 Hz), 5.80 (m, 1H), 7.20 (m, 5H).

To a cooled flame dried 50 mL RBF under Ar was added the acetal **95-OH** (35 mgs, 0.114 mmol) and treated similarly as before to yield the tritylated pyranoside **95** (50 mg, 88.1 %). Rf 0.9 (10 % EtOAc:PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (m, 3H), 1.59 (m, 3H), 1.88 (m, 2H), 2.79 (m, 1H), 3.1 (m, 1H), 4.15 (m, 0.9H), 4.35 (ABq, Δδ = 0.22 ppm, 1.8H, J = 10.2 Hz), 4.51 (m, 0.2H), 4.90 (m, 2.1H), 5.61 (m, 1H), 7.20 (m, 15H), 7.40 (m, 5H); MS (ES) m/z 527 ($M + Na^+$), 243 (base peak).

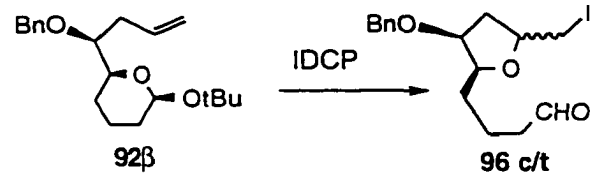
Tetrahydrofuran (96c/t)



92α 96 c/t

To a 50 mL flask containing the alkene **92α** (10 mg , 0.031 mmol), CH_2Cl_2 : H_2O (20:1, 4 mL) was added . IDCP (Iodonium Dicollidine Perchlorate) (19.2 mg, 0.041 mmol) was then added . The solution was stirred at 25 °C for 5 min and checked by TLC. The reaction was quenched by addition of 10% $Na_2S_2O_3$ (5 mL) and stirred for 5 min until the disappearence of the iodine colour. The solution was then extracted with ether (4 x 20 mL). The ether extract dried and concentrated in vacuo and purified by FCC (5-20% EtOAc:PE) to yield an inseparable mixture of aldehydes **96 c/t** (c:t 63:37, 11 mg, 90%). Rf 0.3 (10% EtOAc:Pe); ^{1}H NMR (300 MHz, C_6D_6) δ 1.3-1.8 (br m, 6H), 1.85 (t, 2H, J = 13.9 Hz), 2.88 (m, 0.74H), 3.07 (m, 1.26H), 3.39 (m, 1.26H), 3.46 (m, 0.74H), 3.67 (m, 0.74H), 3.85 (m, 1.26H), 4.08 (ABq, Δδ = 0.23 ppm, 1.26H, J = 10.2 Hz), 4.10 (ABq, Δδ = 0.23 ppm, 0.74H, J = 10.2 Hz), 7.19 (m, 5H), 9.30 (s, 1H). ^{13}C NMR (75 MHz, C_6D_6) δ 8.9, 10.9, 17.7, 17.8, 27.5, 28.0, 35.7, 36.9, 42.3, 69.8, 74.8, 76.6, 77.8, 78.8, 81.4, 82.1, 137.4, 137.6, 199.2; MS (ES) m/z 411 ($M + Na^+$), 281 (base peak).

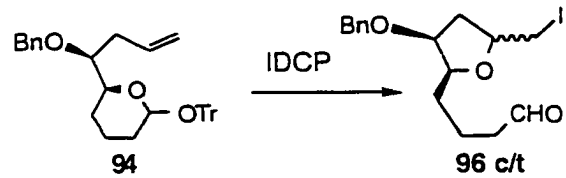
Tetrahydrofuran (96c/t)



92β 96 c/t

The alkene **92β** (50 mg, 0.157 mmol) was treated under similar halocyclization as **92α** to yield an inseparable mixture of aldehydes **96 c/t** (c:t 73:27, 57.3 mg, 94 %).

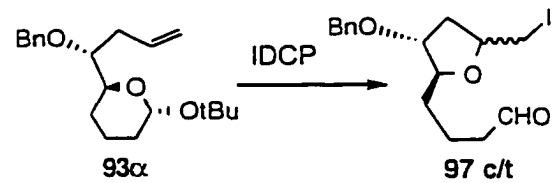
Tetrahydrofuran (96c/t)



94 96 c/t

The trityl pyranoside **94** (50 mg, 0.100 mmol) was treated under similar halocyclization as **92α** to yield an inseparable mixture of aldehydes **96c/t** (c:t 90:10, 35.3 mg, 91%). Rf 0.3 (10 % EtOAc:Pe).

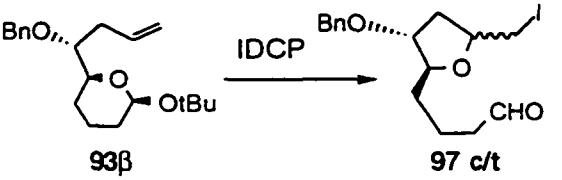
Tetrahydrofuran (97c/t)



93α 97 c/t

The alkene **93α** (10 mg, 0.031 mmol), was treated under similar halocyclization as **92α** to yield an inseperable mixture of aldehydes **97c/t** (c:t 65:35, 11.2 mg, 92 %). Rf 0.31 (10% EtOAc:Pe); ^{1}H NMR (300 MHz, C_6D_6) δ 1.10-1.60 (m, 5H), 1.80 (m, 3H), 2.87(m, 1.3H), 3.08 (m, 0.7H), 3.38 (m, 0.35H), 3.45 (m, 0.65H), 3.85 (m, 0.65H), 3.90 (m, 0.35H), 4.09 (m, 0.7H), 4.14 (ABq, Δδ = 0.07 ppm, 1.3H, J = 10.3 Hz), 9.28 (s, 0.35H), 9.30 (s, 0.65H). ^{13}C NMR (75 MHz, C_6D_6) δ 9.3, 17.2, 17.3, 31.9, 32.5, 35.7, 37.0, 42.0, 42.1, 69.8, 70.3, 75.7, 77.1, 82.1, 82.2, 83.3, 137.3, 137.4, 199.1; MS (ES) m/z 411 ($M + Na^+$), 281 (base peak).

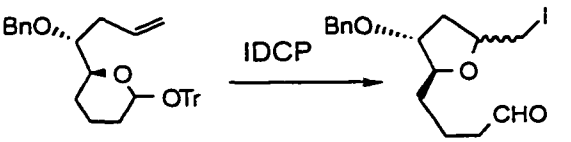
Tetrahydrofuran (97c/t)



93β 97 c/t

The alkene **93β** (50 mg, 0.157 mmol) was treated under similar halocyclization as **92α** to yield an inseparable mixture of aldehydes **97c/t** (c:t 71:29, 54.8 mg, 90 %).

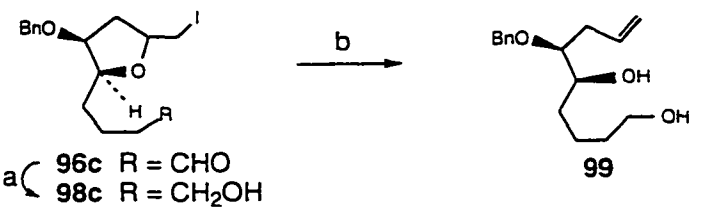
Tetrahydrofuran (97c/t)



95 97 c/t

The trityl pyranoside **95** (50 mg, 0.100 mmol) was treated under similar halocyclization as **92α** to yield an inseparable mixture of aldehydes **97c/t** (c:t 85:15, 37 mg, 95%).

Acyclic Pyranoside (99)

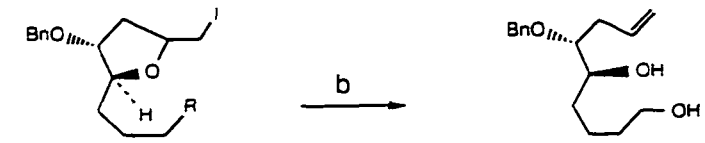


(a) $NaBH_4$, EtOH; (b) Zn, 95% EtOH, reflux;

The aldehyde **96c/t** (25 mg, 0.064 mmol) was dissolved in absolute EtOH (3 mL). To this solution was added $NaBH_4$ (6.1 mg, 0.161 mmol). The reaction was stirred for 10 min then quenched by addition of HCl/MeOH(1:10) until the pH was neutral. The solution was filtered through a bed of celite. Evaporation of the filtrate furnished the alcohol **98 c/t** (23mg, 92 %). Rf 0.2 (15% EtOAc:PE).

The above mixture **98c/t** (23mg, 0.059 mmol) was dissolved in 95% EtOH/H_2O (3 mL). To this solution was added freshly activated Zn powder (77 mg, 1.18 mmol). The mixture was heated at reflux for one h at which time a more polar product was observed on tlc. The solution was to cooled then filtered though a bed of celite. The residue was washed three times with 10mL portions of EtOH. Excess solvent was evaporated and FCC(20-50 % EtoAc:PE) afforded the alkene **99** (14.3 mg, 91 %). Rf 0.3 (30 % EtOAc:PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (m, 6H), 1.97 (m, 1H, D_2O exch.), 2.30 (m, 1H), 2.40 (m, 1H), 2.48 (m, 1H, D_2O exch.), 3.25 (ABq, Δδ = 0.03ppm, 1H, J = 4.6 Hz), 3.52 (m, 3H), 4.51 (ABq, Δδ = 0.22 ppm, 2H, J = 10.2 Hz), 5.02 (d, 1H, J = 8.4 Hz), 5.04 (d, 1H, J = 15.8 Hz), 5.80 (m, 1H), 7.25 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 32.7, 33.0, 35.0, 62.8, 72.5, 72.6, 81.7, 117.7, 128.0, 128.1, 128.6, 134.5, 138.4; MS (ES) m/z 287 [base peak ($M + Na^+$)], 229.

Acyclic Pyranoside (101)



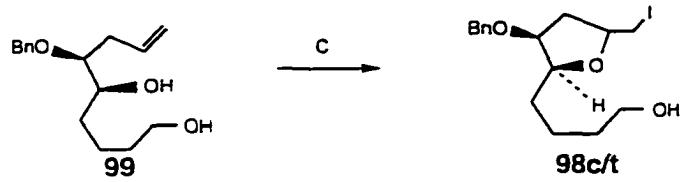
a (**97c/t** R = CHO
100c/t R = CH_2OH

101

(a) $NaBH_4$, EtOH; (b) Zn, 95% EtOH, reflux;

Aldehyde **97c/t** (25 mg, 0.064 mmol) was treated under the conditions described for the preparation of **99**. The alkene **101** (15.8 mg, 94 %) was obtained. Rf 0.3 (30% EtOAc:PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (m, 6H), 1.79 (m, 1H, D_2O exch.), 2.31 (m, 3H), 3.35 (m, 1H) 3.54 (m, 2H), 3.70 (m, 1H), 4.51 (ABq, Δδ = 0.01ppm, 2H, J = 10.3 Hz), 5.01 (d, 1H, J= 10.3 Hz), 5.07 (d, 1H, J = 19.6 Hz), 5.80 (m, 1H), 7.25 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 31.9, 32.7, 34.0, 62.8, 72.2, 72.3, 82.1, 117.1, 128.0, 128.1, 128.6, 135.4, 138.6; MS (ES) m/z 287 [base peak ($M + Na^+$)], 229.

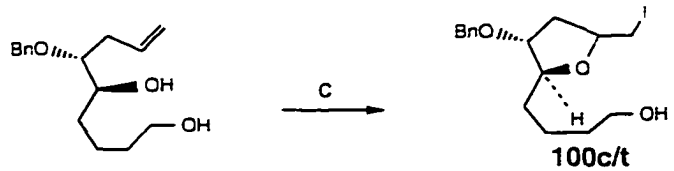
Tetrahydrofuran (98c/t)



(c) IDCP, CH_2Cl_2, H_2O. 90% (50:50)

The alkene **99** (14 mg, 0.053 mmol) was treated according to the typical halocyclization procedure which was described for the preparation of **96c/t**. An inseparable mixture of alcohols **98c/t** (c:t 50:50, 18.5 mg, 90 %) was obtained. Rf 0.4 (30% EtOAc:PE); ^1H NMR (300 MHz, C_6D_6) δ 1.40 (m, 5H), 1.69 (m, 2H), 1.80 (m, 1.5H), 1.95 (m, 0.5H), 2.92 (d, J = 4.7 Hz, 1H), 3.12 (m, 1H), 3.38 (m, 1H), 3.45 (m, 0.5H), 3.7 (m, 0.5H), 3.78 (m, 0.5H), 3.91 (m, 0.5H), 4.10 (ABq, Δδ = 0.26 ppm, 1H, J = 12.1 Hz), 4.13 (ABq, δδ = 0.19 ppm, 1H, J = 10.2 Hz), 7.20 (m, 5H). ^{13}C NMR (75 MHz, CDCl3) δ 1.2, 10.5, 11.9, 22.6, 29.0, 29.5, 29.9, 32.9, 37.1, 38.5, 62.8, 71.3, 72.3, 76.3, 78.1, 79.0, 79.9, 83.3, 84.1, 127.1, 127.5, 127.9, 128.4, 128.6, 138.2, 138.5; MS (ES) m/z 413 [base peak ($M + Na^+$)], 281.

Tetrahydrofuran (100c/t)

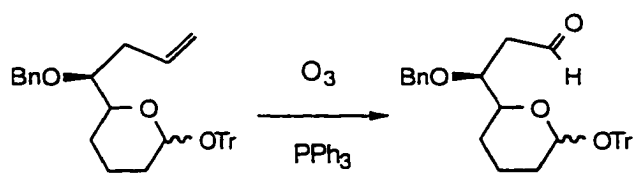


(c) IDCP, CH_2Cl_2, H_2O. 93% (50:50)

The alkene **101** (15 mg, 0.057 mmol) was treated according to the typical halocyclization procedure which was described for the preparation of **96c/t**. An inseparable mixture of aldehydes **100c/t** (c:t 50:50, 20.6 mg, 93%) was obtained. Rf 0.4 (30% EtOAc:PE); ^1H NMR (300 MHz, C_6D_6) δ 1.39 (m, 7H), 2.22 (m, 2H), 2.91 (d, 1H, J = 5.1 Hz), 3.12 (m, 1H), 3.38 (m, 2H), 3.45 (m, 0.5H), 3.50 (m, 0.5H), 3.84 (m, 0.5H), 4.02 (m, 1.5H), 4.20 (m, 2H), 7.20 (m, 5H). ^{13}C NMR (75 MHz, CDCl3) δ 1.2, 10.5, 22.2, 22.3, 29.8, 31.6, 34.4, 34.5, 37.1, 38.6, 63.2, 71.4, 71.7, 72.3, 78.4, 83.5,

83.6, 85.1, 85.2, 127.7, 127.8, 128.0, 138.4, 138.5; MS (ES) m/z 413 [base peak (M + Na^+)], 283.

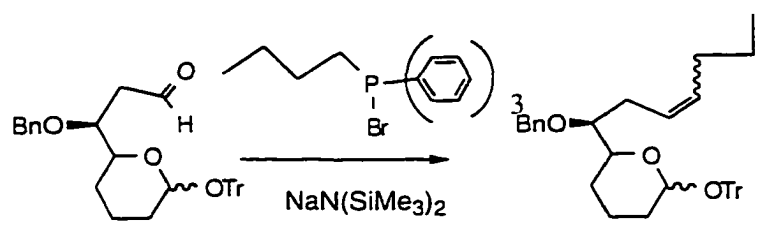
Aldehyde (102)



94 102

The alkene pyranoside **94** (200 mg, 0.40 mmol) was dissolved in CH_2Cl_2: MeOH (8 mL, 4:1). The solution was cooled to -78 °C and O_3 bubbed through for 20 seconds. N_2 was then bubbled through the solution to remove any traces of O_3. PPh_3 (115 mg, 0.44 mmol) was added and the reaction was allowed to stir for 2 h at rt. The solvent was then evaporated under vacuo and purified by FCC (10-20% EtOAc:PE) to furnish aldehyde **102** (164 mg, 85%). Rf 0.2 (10 % EtOAc:PE): ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (m, 3M), 1.71 (m, 3H), 2.39 (m, 2H), 3.10 (m, 1H), 3.51 (m, 1H), 4.40 (m, 2.8H), 5.23 (m, 0.2H), 7.30 (m 15H), 7.50 (m, 5H), 9.50 (m, 1H).

Pyranoside (103)

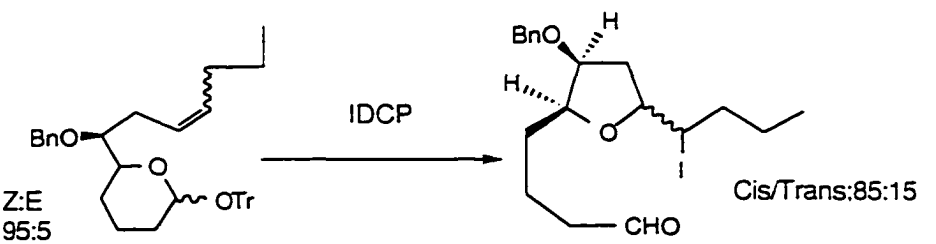


102 Z:E 95:5 103

Butyltriphenyphosphonium bromide (1.35 g, 3.4 mmol) was dissolved in dry toluene (10 mL) and the mixture cooled to rt under N_2. $NaN(SiMe_3)_2$ (1.0M, 2.72 mL, 2.72 mmol) was added dropwise for 10 min and the mixture was allowed to stir for 1 h.

The aldehyde **102** (164 mg, 0.34 mmol) was dissolved in dry toluene (10 mL) and then added to the cooled suspension (-78 ^{o}C) suspension above over 10 min. The flask was allowed to warm to rt and the reaction quenched by addition of Et_2O (30 mL) followed by filtration through celite. Evaporation of excess solvent and FCC (10-30 % EtOAC/PE) gave a mixture of Alkenes **103** (Z:E 95:5, 142 mg, 80%). Rf 0.4 (10% EtOAc:PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 14.0 Hz), 1.40 (m, 5H), 1.64 (m, 3H), 2.10 (m, 4H), 3.09 (m, 1H), 4.24 (m, 0.7H), 4.40 (ABq, Δδ = 0.7 ppm, 1.6H, J = 10.3 Hz), 4.52 (s, 0.4H), 5.24 (m, 2H), 7.30 (m, 15H), 7.55 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.3, 22.7, 25.0, 28.0, 29.4, 31.8, 72.1, 77.1, 80.6, 87.6, 98.2, 126.5, 126.8, 127.2, 127.4, 129.0, 129.1, 130.6, 131.0, 139.2, 145.0; MS (ES) m/z 569 (M + Na^+), 243 (base peak).

Tetrahydrofuran (104c/t)



103 104

The alkene **103** (45 mg, 0.080mmol) was treated under halocyclization conditions to yield a separable mixture (by FCC on Silica) of aldehydes **104c/t** (c:t 85:15, 23.9, 4.13 mg, 80%). Rf 0.35, 0.30 (10% EtOAc:Pe); **104c** ^{1}H NMR (300 MHz, C_6D_6) δ 0.90 (t, 3H, J = 14.0 Hz), 1.30 (m, 2H), 1.71 (m, 8H), 1.89 (m, 2H), 3.40 (m, H-5, 1H), 3.51 (m, H-6, 1H), 3.73 (m, H-8, 1H), 4.07 (m, H-9, 1H), 4.12 (ABq, Δδ = 0.25 ppm, 2H, J = 10.3 Hz), 7.20 (m, 5H), 9.31 (s, 1H). ^{13}C NMR (75 MHz, C_6D_6) δ 11.9, 17.8, 21.8, 27.5, 34.5, 35.8, 42.4, 69.6, 77.9, 80.0, 81.2, 126.9, 127.1, 137.5, 199.2; MS (ES) m/z 453 (M + Na^+), 323, 213 (base peak), 195.

104t ^{1}H NMR (300 MHz, C_6D_6) δ 0.76 (t, 3H, J = 14.0 Hz), 1.30 (m, 2H), 1.55 (m, 8H), 1.90 (m, 2H), 3.53 (, 0.8H), 3.70 (m, 0.4H), 3.85 (m, 1.2H), 4.19 (ABq, Δδ = 0.22 ppm, 2H, J = 10.3 Hz), 4.25 (m, 0.6H), 7.20 (m, 5H), 9.30 (s, 1H). ^{13}C NMR (75 MHz, C_6D_6) δ 11.8, 17.8, 21.9, 27.6, 36.3, 38.0, 42.1, 69.9, 78.7, 78.8, 81.8, 127.1, 129.5, 142.4, 199.1; MS (ES) m/z 453 ($M + Na^+$), 323, 213 (base peak), 195.

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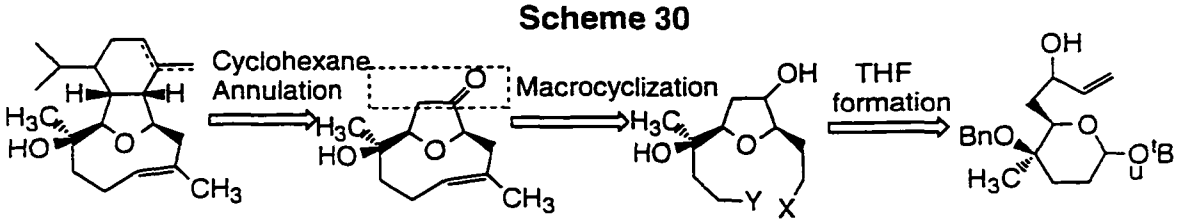
Chapter 4 : THF subunit of the Eunecellins

(I) Retrosynthesis

A synthetic route to the eunecellin series may be devised around the initial synthesis of a complex 3-oxy-*cis*-2,5-dialkyl THF **121**. Subsequent macrocyclisation and annulation of the six membered ring on to the THF would give the eunecellin skeleton (Scheme 30). The results of the iodocyclization of the allylic alcohol pyranosides suggest the alkene pyranoside precursor **122** with a methyl substituent at C-4, and an R allylic ether. The preparation of **122** and its conversion to the required THF is described in the following section.

Scheme 30



119 EUNECELLIN

120 BICYCLIC CORE

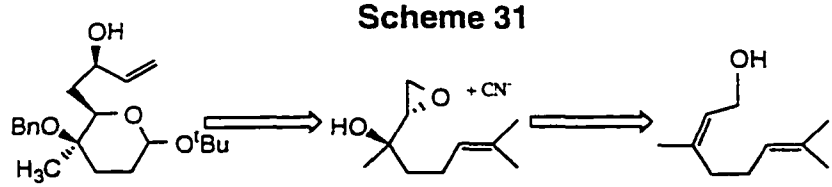
121 MONOCYCLIC THF INTERMEDIATE

122 KEY CARBOHYDRATE PRECURSOR

(II) Synthesis of the Pyranoside alkene precursor 123R

A strategy based on the initial preparation of the chiral epoxy alcohol **124** was devised (Scheme 31).

Scheme 31

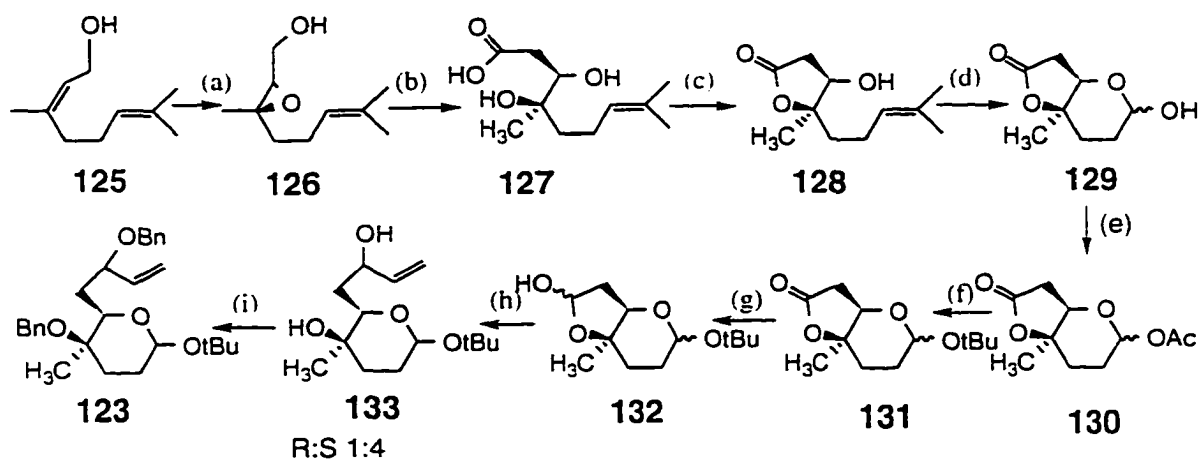


123 **124** **125**

Sharpless asymmetric epoxidation[1] of commercially available nerol **125** using L-tartrate led to epoxide **126**. Treatment of **126** with NaCN[2] followed by acid hydrolysis gave the lactone **128** in 35% yield. Ozonolysis of **128** yielded the hemiacetal **129**.

Acetylation and acid catalyzed acetalization, with t-butanol provided **131** which was reduced to lactol **132**. Reaction of **132** with vinylmagnesium bromide gave a mixture of allylic alcohols, R/S = 1/4. Benzylation of the alcohols furnished the benzyl ethers **123R/S** which were readily separated by flash chromatography (Scheme 32). The configuration of the allylic alcohols was assigned in the subsequent THF products (*vide infra*).

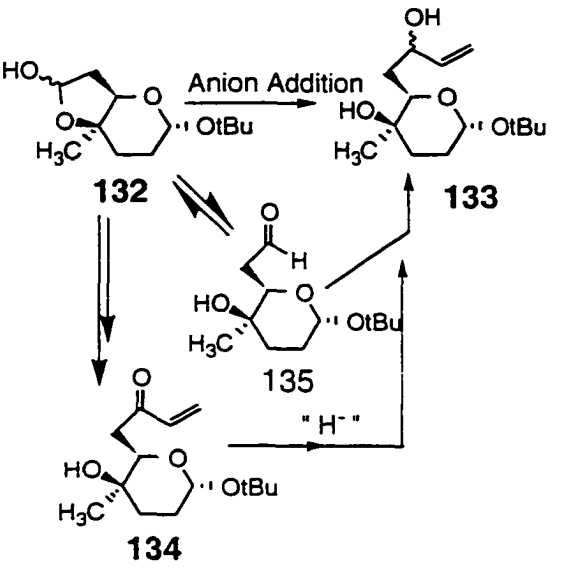
Scheme 32



(a) SAE L-(+) Tartrate,70%(b) NaCN (c) H^+,35% (d) O_3/PPh_3,88% (e) Ac_2O,DMAP, 95% (f) tBuOH,$SnCl_4$, 93% (g) DIBALH, 85% (h) Vinylmagnesium Bromid ,85% (i) BnBr/NaH, 60%

Reaction of different vinyl anion equivalents with the lactol **132** were carried out in an attempt to improve the stereoselectivity. Reaction of vinyllithium resulted in even lower selectivity of **133R**. Interestingly, addition of the acetylene anion gave only the S- isomer (Scheme 33). These results suggested that the preferred facial attack of these reagents is from the "si" of the aldehyde, thus giving rise to the S-allylic alcohol as the major product. We argued that hydride addition to the α,β- unsaturated ketone should give the opposite stereochemistry.

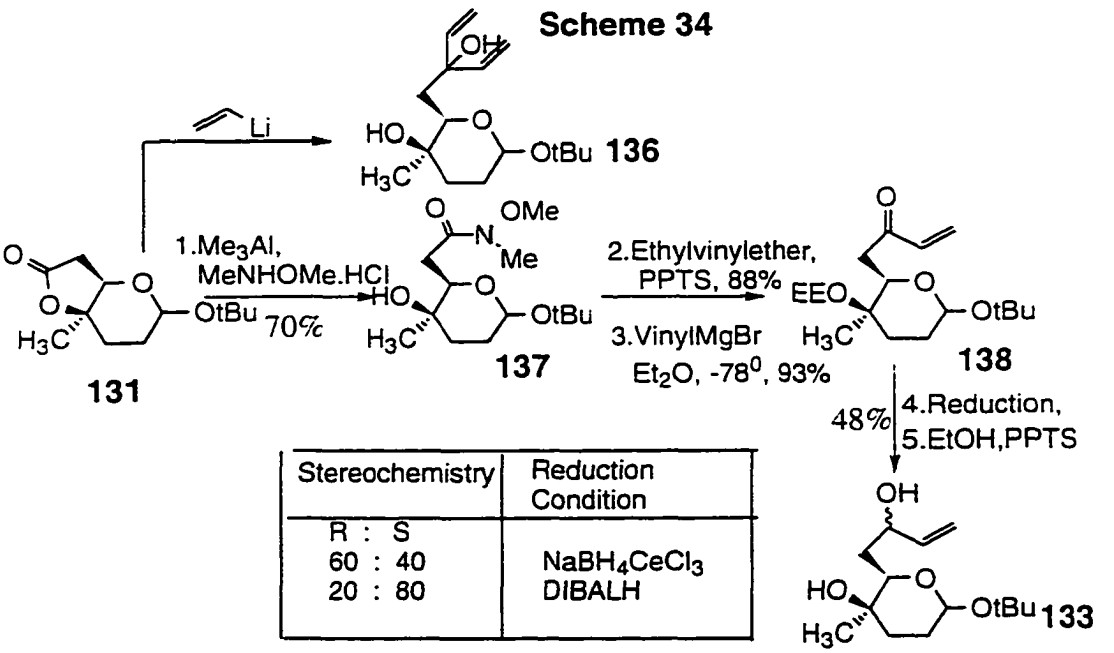
Scheme 33



Stereochemistry R : S	Anion
1 : 4	vinylMgBr
1 : 7	vinyllithium
0 : 100	acetyleneTMS

Attempts to obtain **134** through controlled addition of vinylithium to the lactone **131** were unsucessful (Scheme 34). An indirect procedure via preparation of the Weinreb amide[6] **137** was carried out. This was done by adding N,O -dimethylhydroxylamide to the lactone **131** followed by reaction of the free hydroxyl group with ethyl vinyl ether and addition of vinyl magnesium bromide to the amide (Scheme 34).

Scheme 34

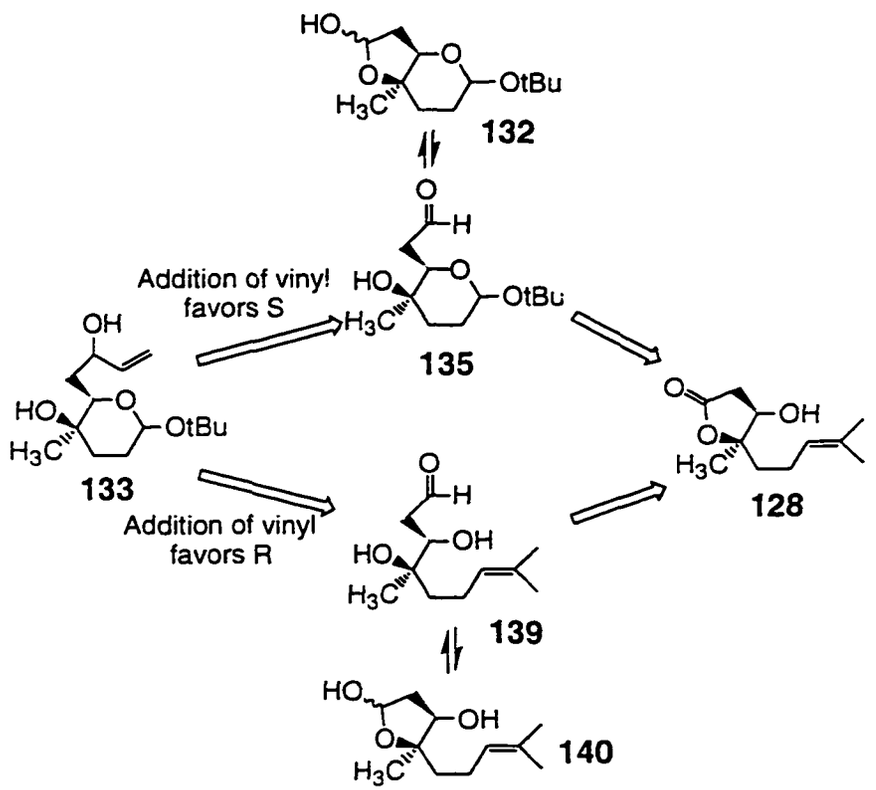


Stereochemistry R : S	Reduction Condition
60 : 40	$NaBH_4CeCl_3$
20 : 80	DIBALH

Reduction of **138** using $NaBH_4/CeCl_3$ (at different temperatures) and DIBALH gave a modest preference for **133R**, or mainly **133S** respectively. Attempted reduction with Corey's chiral catalyst,[7] gave no reaction.

Since the pyranoside template showed the undesired bias for addition to the aldehyde, the reaction of different vinyl anion equivalents to a non pyranoside aldehyde template was next examined. Indeed, addition of TMS-acetylide to the lactol **140** afforded predominantly the R allylic alcohol **133**. This suggested a modified synthesis of the pyranoside alkene template (Scheme 35).

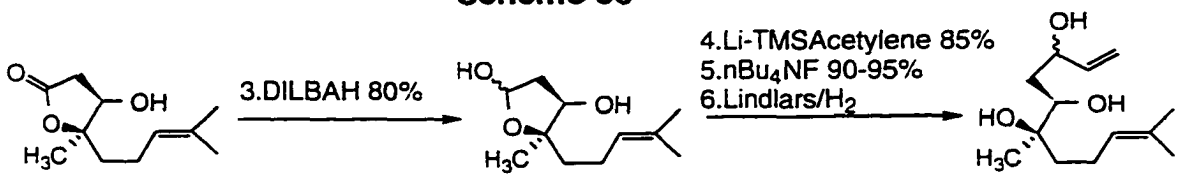
Scheme 35



(III) Alternative Synthesis of the Pyranoside Alkene Template

DIBALH reduction of the lactone **139** obtained earlier followed by acetylide addition resulted in an R:S propargylic alcohol ; ratio of 87:13. Desilyation and Lindlar reduction afforded the triol **141** (Scheme 36).

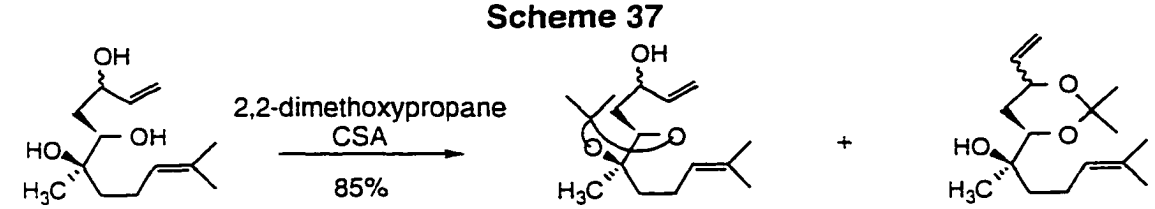
Scheme 36



139 **140** R:S 87:13 **141**

The stereochemistry at the allylic position was assigned through NMR analysis of the acetonides **142** and **143** prepared by acetonation of **141R/S** with 2,2-dimethoxypropane. This resulted in a mixture of 1,2- and 1,3 acetonide products which were separated by chromatography. Analysis of ^{13}C NMR chemical shifts at key position of the 1,3-acetonide products **143** was done using the Rychnovsky method.[8] In this analysis the C-2 signal of the acetonide of a syn isomer is at δ 98.5 and the anti is at δ 100.4, the methyl signals of the syn isomer are at δ 19 ppm(axial) and δ 30 ppm(equatorial) and the anti shows both methyl groups at δ 25 ppm. Comparison of this data indicates the major triol formed is the Anti 1,3 diol i.e. the R allylic alcohol (Scheme 37).

Scheme 37



R:S 87:13 **141**

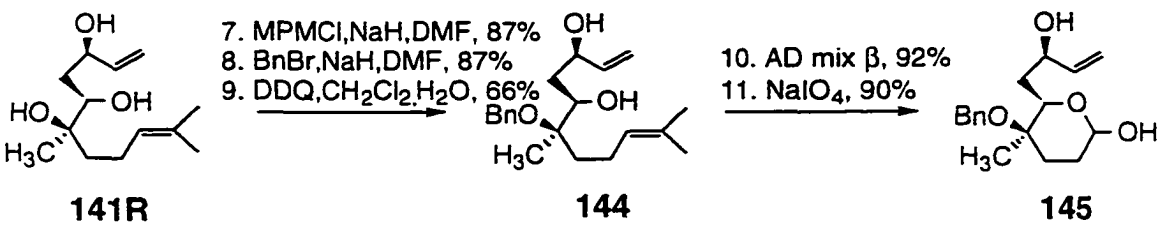
142 1,2 acetonide Thermodynamic product

143 1,3 acetonide Kinetic product

The allylic alcohol **141R** was next converted to the pyranoside **145**. Selective protection of the tertiary alcohol in **141R** was done via a protection/deprotection sequence. The two secondary hydroxy groups were protected as the methoxybenzy ethers (MPM). The tertiary hydroxy was protected as the benzyl ether and the secondary MPM ethers were then deprotected by DDQ. Selective cleavage of the tri-substituted alkene was done by

treatment with AD mix[9] followed by $NaIO_4$ cleavage of the diol (Scheme 38). This led to the pyranoside alkene **145**.

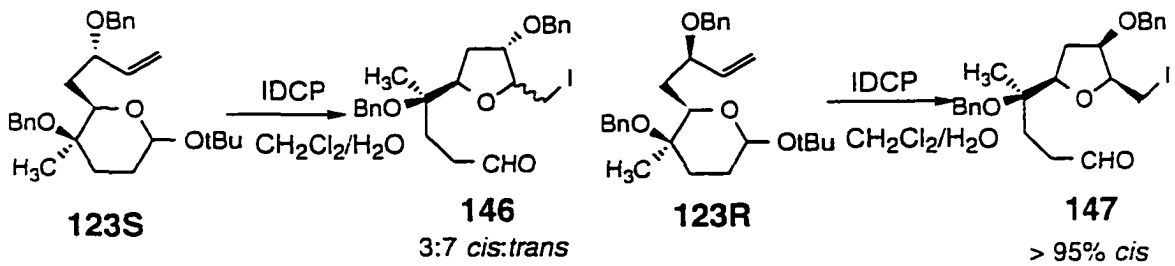
Scheme 38



(IV) Iodocyclization of Pyranose Alkene Templates

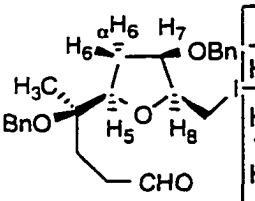
The halocyclization reactions of pyranosides **123R** and **123S** were investigated. Treatment of the R isomer under iodonium collidine perchlorate (IDCP)/CH_2Cl_2/H_2O conditions gave only the *cis* product **147**. Treatment S-derivative **123S** gave a 3:7 *cis:trans* 2,5 disubstituted THF **146** (Scheme 39)

Scheme 39



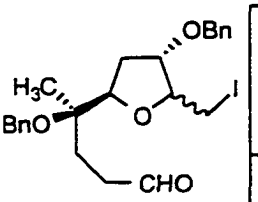
For the THF **147** H-5, H-7, H-8, H-9 and CH_2-6 were assigned by 2D analysis and the stereochemistry was determined from the NOESY spectrum. Here a 1.0% nOe was observed between H-5 and H-6α proton at δ 2.61 ppm. The absence of an nOe between H-5 and H-6 at δ 2.61 ppm allowed assignment of H-6 and H-6α. A 1% nOe was also observed between H-6α and H-7. A 2% nOe was found between H-7 and H-8. Based on these nOe's and previous results we assigned the relative stereochemistry of the THF ring to be an all syn arrangement (Fig. 10).

Fig. 10 nOe of 146 and 147



147

protons	%/nOe obs'd
$H_5/H_{6\beta}$	0.5
$H_5/H_{6\alpha}$	1.0
$H_7/H_{6\beta}$	0.5
$H_7/H_{6\alpha}$	1.0
H_7/H_8	2.0



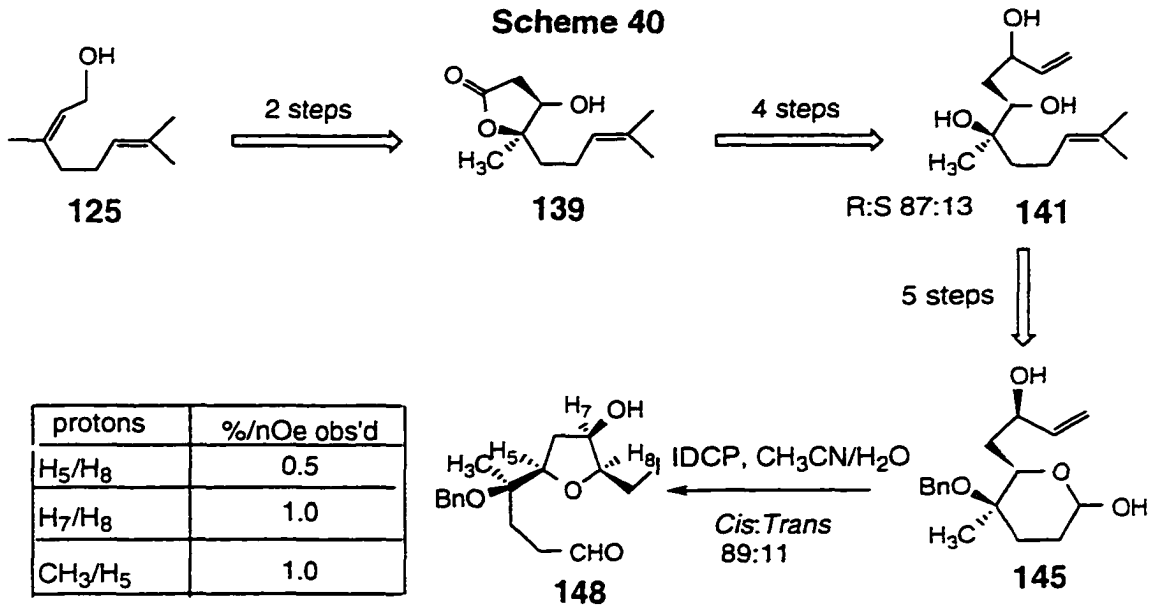
146

C's	^{13}C NMR/ppm	
	cis	trans
C-9	1.2	6.2

The *cis/trans* mixture which was obtained from the S-allylic system, **146S** was inseparable by chromatography. This prevented NOESY analysis. THF stereochemistry was assigned by comparison of the ^{13}C NMR with related oxygenated THF structures.[3-5] The iodomethyl carbon of the THF in which the iodomethyl is cis to the 3-oxygen appears at higher field to the corresponding carbon for the *trans* isomer (Fig. 10). In addition, the proton chemical shift of the iodomethyl protons were observed downfield in the *cis* isomers compared to the corresponding *trans* isomer. This data is also in agreement with the data for known compounds.

Halocyclisation of pyranoside alkene **145** under different conditions showed acetonitrile/water to be the best solvent giving a modest selectivity of 89 : 11 *cis / trans* of THF iodide (Scheme 40). Thus the desired THF **148** was obtained in 6% yield in 12 steps from nerol.

Scheme 40



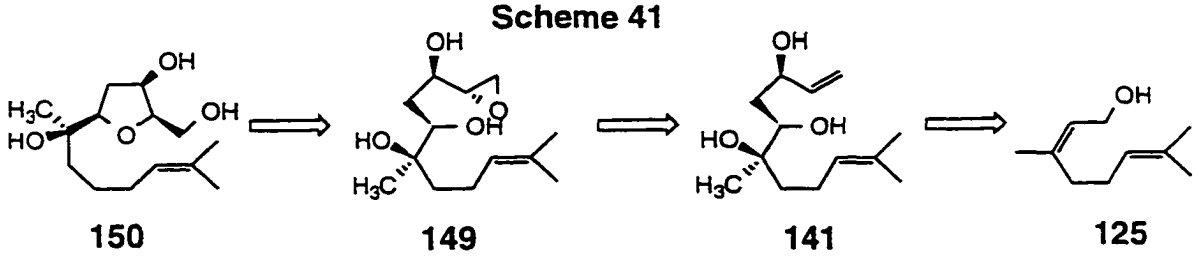
protons	%/nOe obs'd
H_5/H_8	0.5
H_7/H_8	1.0
CH_3/H_5	1.0

The THF stereochemistry was established by nOe analysis (Scheme 40). As before the key signals were identified by 1D COSY and Decoupling experiments. A direct nOe was observed between the H-5 and H-8 signal, also observed were nOe's between H-7/H-8 and CH3/H-5 of 1 and 0.5% respectively. These results suggest an all syn arrangement of the THF.

(V) Epoxide Approach to Synthesis of THF intermediate

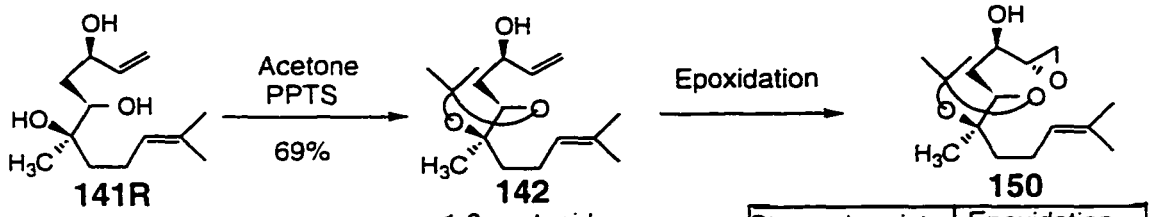
The cyclisation of hydroxy epoxides to produce cyclic THF's has been shown to work in excellent yields.[10,11] Therefore, an epoxide opening strategy was examined as an alternative to our halocyclization route. The synthesis of the epoxide would start from the same starting materials as the previous route. The epoxide can be prepared via an alkene **141**. Ring opening of this epoxide would give the THF (Scheme 41).

Scheme 41



Direct epoxidation of previously described triol **141** by the Sharpless method[1] resulted in no epoxide and decomposition of starting material. Treatment of triol **141R** with acetone and PPTS afforded the 1,2-acetonide **142**. Sharpless epoxidation using L-(+) DIPT yielded a single epoxide . Vanadium acetylacetonate yielded a mixture of two epoxides 35:65 (R:S). The mixture of epoxides were used in the ring opening step (Scheme 42).

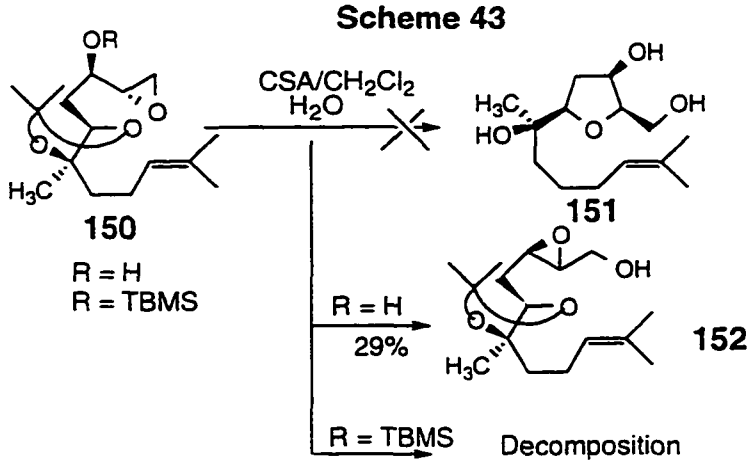
Scheme 42



Stereochemistry	Epoxidation condition
R : S	
0 : 100 74%	Sharpless
35 : 65 57%	V^{5+}

Treatment of a hydroxy epoxide **150** under acid catalysed conditions[10] ($CSA/CH_2Cl_2/H_2O$) did not give the desired product (Scheme 43). NMR of recovered material revealed changes in both the ^1H and ^{13}C spectra. Signals for primary alcohol and internal epoxy ring were observed suggesting that the starting material may have undergone a Payne rearrangement. It was thought that protection of free OH group should disfavor Payne rearrangement and this was subsequently done using TBDMS. However, treatment under the same conditions gave decomposition of starting material and no product formation.

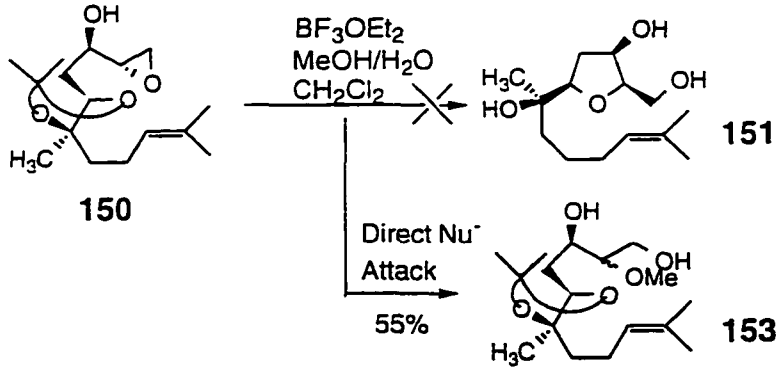
Scheme 43



150 was also treated under conditions developed by Sasaki[11] for cyclization of related hydroxy epoxides (Scheme 44). Upon addition of the BF_3OEt_2 an immediate disappearence of starting material was observed. Isolation of the product and analysis by ^1H NMR and mass spectrometry showed direct incorporation of OMe into the product with cleavage of acetonide. 1,4 -Dioxane containing varying concentrations of methanol and water was used, however under this modified condition direct incorporation of the external nucleophile (OMe, OH) was observed in addition to starting material was recovered.

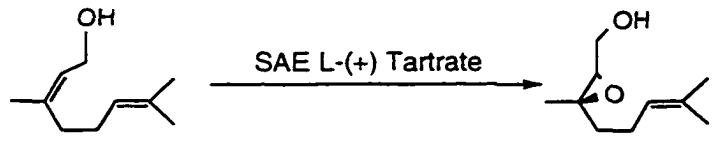
Based on these results, it was decided to pursue the halocyclization strategy as the source of our key THF intermediate.

Scheme 44



(VI) Experimental

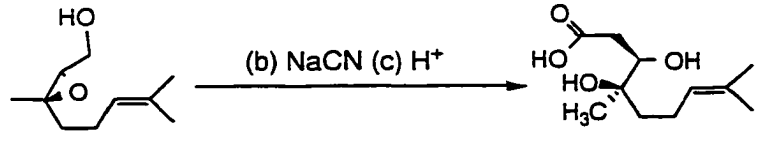
Epoxide (126)



125 126

Titanium tetraisopropoxide (4.6g, 16 mmol) and TBHP (4.2 M in CH_2Cl_2, 120 mL, 500 mmol) were added, successively, to a suspension of L-(+)-DIPT (5.6g, 24mmol) and molecular sieves 4A (30g) in CH_2Cl_2 (500mL) at -10 °C under Ar atmosphere. After being stirred at -10 °C for 20 min, the mixture was cooled to -23 °C and freshly distilled nerol **125** (50g, 320 mmol) was added. The mixture was stirred at -23 °C for an additional 2 h, and then water (50 mL) was added, with vigorous stirring. The mixture was allowed to warm to rt. After 30 min 3M aqueous NaOH (30mL) was added, the mixture was stirred at rt for an additional 30 min and then filtered through a celite pad. The filtrate was stirred vigorously with 10% aqueous citric acid (150mL) at rt for 1 h. After the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (100 mL x 3). The combined organic layer was washed with brine (300mL), dried (Na_2SO_4) and concentrated in vacuo. Distillation of the crude product (78 °C at 7-8 mmHg), followed by FCC (10-50% EtoAC:PE) afforded a clear yellow oil **126** (35g, 70%). Rf 0.2 (10% EtOAc:PE); $[\alpha]^{25}D$ -15.4° (c = 3.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.46 (m, 1H), 1.58 (s, 3H), 1.66 (s, 3H), 1.70 (m, 1H), 2.14 (m, 2H), 2.92 (dd, 1H, J = 4.6 , 6.8 Hz) , 3.76 (m, 1H), 3.81 (m, 1H) , 5.08 (t, 1H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 22.5, 24.5, 26.0, 33.5, 61.5, 62.0, 65.0, 123.7, 132.7.

Acid (127)

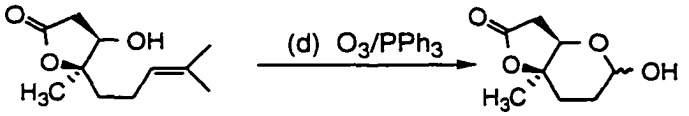


126 127

To a stirred solution of (2R),(3R)- nerol 2,3- epoxide **126** (3.56 g, 20.9 mmol) in 2:3 ethanol:water (45 mL) at rt was added NaCN (14.0 g, 0.29 mol), and the resulting

solution was heated at reflux for 6 h. The ethanol was removed in vacuo, the aqueous residue was cooled to 0 °C and the white precipitate was filtered under suction. The solid was dissolved in CH_2Cl_2 and carefully acidified to pH 3-4 with concentrated H_2SO_4 at 0 °C. The acidification was performed in an efficient fume hood and the discharged HCN was passed through a 3N NaOH solution (300 mL). The aqueous phase was then saturated with NaCl(s) and extracted with ether (6 x 80mL). The combined ether extracts were dried ($MgSO_4$) and concentrated followed by FCC(40-80% EtoAc:PE) to give the lactone **127** (1.45 g, 35%). Rf 0.70 (50% EtOAc:PE); ^1H NMR (300 MHz, CDCl3) δ 1.33 (s, 3H), 1.62 (s, 3H), 1.68 (s, 3H), 1.80 (m, 2H), 2.10 (m, 2H), 2.50 (dd, 1H, J = 2.3, 18.1 Hz), 2.93 (dd, 1H, J = 6.1, 18.1 Hz), 5.14 (t, 1H, J = 6.8 Hz). ^{13}C NMR (75 MHz, CDCl3) δ 17.9, 22.6, 23.3, 25.8, 34.3, 38.6, 73.7, 89.9, 123.6, 133.1, 173.2.

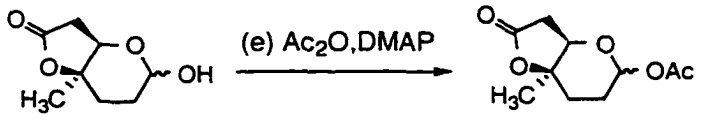
Pyranoside (129)



128 **129**

Lactone **128** (50 mg, 0.25 mmol) was dissolved in 5mL of CH_2CL_2: MeOH (4:1). The solution cooled to -78 °C and O_3 bubbled through for 20 seconds. N_2 was then bubbled through the solution to remove any traces of O_3. PPh_3 (79 mg, 0.30mmol) was added and the reaction stirred for 2 h at rt. The solvent was then evaporated under vacuo and purified by FCC(40-80% EtoAc:PE) to furnish lactol pyranoside **129** (37.84 mgs, 88%). Rf 0.4 (50 % EtOAc : PE); ^1H NMR (300 MHz, CDCl3) δ 1.23 (s, 0.6H), 1.24 (s, 2.4H), 1.57 (m, 1H), 1.90 (m, 2H), 2.05 m, 1H), 2.35 (d, 1H, J = 17.6 Hz), 2.79 (dd, 1H, J = 4.9, 17.6 Hz), 4.05 (d, 0.2H, J = 4.87 Hz), 4.22 (d, 0.8H, J = 4.9 Hz), 4.72 (m, 0.2H), 5.19 (t, 0.8H, J = 6.9 Hz).

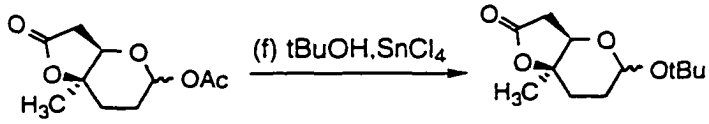
Acetyl Pyranoside (130)



129 **130**

Lactol **129** (790 mg, 4.5 mmol) was disolved in EtOAc (26 mL), Ac_2O (0.51 mL, 5.4 mmol) and DMAP (27 mg,0.225 mmol) was added and the mixture allowed to stir for 1 h. The excess solvent was then evaporated under reduced pressure. FCC (40-50% EtOAc : PE) gave Acetyl Pyranoside **130** (915 mg, 95%). Rf 0.6 (50 % EtOAc : PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.31(s, 0.6H), 1.33 (s, 2.4H), 1.40-2.00 (m, 4H), 2.09 (s, 0.6H), 2.10 (s, 2.4H), 2.45 (d, 1H, J=17.9 Hz), 2.81 (dd, 1H, J = 17.9 Hz), 4.14 (d, 0.8H, J = 4.7 Hz), 4.19 (d, 0.2H, J = 4.7 Hz), 5.60 (m, 0.2H), 6.02 (m, 0.8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 26.4, 26.7, 28.7, 37.3, 70.6, 74.4, 83.4, 90.5, 175.9.

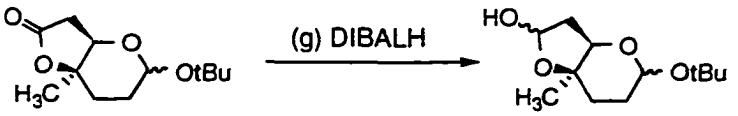
t-Butyl Pyranoside (131)



130 **131**

Acetylpyranoside **130** (600 mg, 3.0 mmol) was dissolved in CH_2Cl_2 (40 mL), t-BuOH (0.576 mL, 6.0 mmol) was added and the solution cooled to 0 °C. $SnCl_4$ (1.5 mL, 0.75 mmol) was added dropwise over 10 min. The reaction mixture was allowed to warm up to rt. Et_2O (100 mL) followed by saturated aqueous $NaHCO_3$ (30 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 50 mL). Evaporation of combined organic layers followed by FCC (20-40% EtOAc:PE) gave the t-Butyl pyranoside **131** (770 mg, 93%). Rf 0.8 (30% EtOAc : PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.23 (s, 3H), 1.40 (m, 1H), 1.80 (m, 3H), 2.36 (d, 1H, J = 17.6 Hz), 2.83 (dd, 1H, J = 4.8, 17.6 Hz), 4.19 (d, 1H, J = 4.9 Hz), 5.05 (t, 1H, J = 6.9 Hz). ^{13}C NMR (75 MHz, CDCl3) δ 24.7, 26.5, 26.8, 28.8, 37.3, 70.7, 74.5, 83.5, 90.5, 90.6, 175.9.

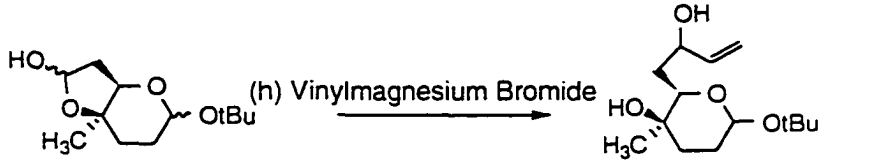
Lactol (132)



131 132

Lactone **131** (300 mg, 1.086 mmol) was dissolved in dry toluene (70 mL). This was then cooled to -78 °C under N_2. DIBALH (2.28 mL, 2.281 mmol) was added dropwise over a 10 min interval and solution allowed to warm up to rt. Na_2SO_4(s) was added and the solution diluted with Et_2O (200 mL). This organic mixture was washed with saturated aqueous $NaHCO_3$ (30 mL) and excess solvent evaporated followed by FCC (20-40% EtOAc:PE) to give a clear colorless oil **132** (257mg, 85%). Rf 0.75 (30% EtOAc:PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 5.8H), 1.24 (s, 3.2H), 1.62 (m, 1H), 1.89 (s, 3H), 1.91 (m, 3H), 2.19 (m, 2H), 3.90 (m, 0.33H, D_2O ex.), 4.10 (m, 1H), 4.40 (m, 0.64H, D_2O ex.), 5.04 (t, 0.64H, J = 5.1 Hz), 5.1 (m, 0.36H), 5.35 (m, 0.36H), 5.73 (m, 0.64H). ^{13}C NMR (75 MHz, CDCl3) δ 26.1, 26.8, 27.0, 27.4, 27.8, 28.3, 28.8, 40.2, 41.2, 73.7, 74.0, 74.4, 75.0, 81.4, 90.9, 91.3, 99.0, 99.3.

Allylic Alcohol Pyranoside (133R/S)

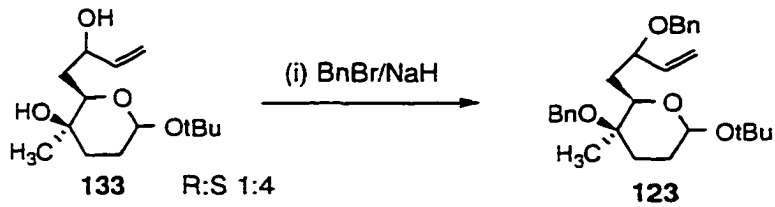


132 133 R:S 1:4

A solution of vinylmagnesium bromide was prepared by dilution of 4.46 mL of stock 1 M solution (THF) in 4.8 mL anhydrous Et_2O. This solution was then cooled to -78 °C under N_2. The lactol (240 mg, 0.892 mmol) dissolved in 7 mL Et_2O was added dropwise over a 10 min period. The reaction was quenched by addition to saturated NH_4Cl (20 mL) solution . The aqueous mixture was extracted with Et_2O (3 x 30 mL), and the organic layers combined and washed with saturated aqueous $NaHCO_3$ (20 mL), brine (20 mL) and then excess solvent evaporated. FCC (10-50% EtOAc:PE) afforded alkene pyranoside **133R/S** (196 mg, 85%) in a 1:4 ratio of diols Rf 0.4, 0.35 R:S mixture (20%

EtOAc : PE); **133R** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.23 (s, 9H), 1.50 (m, 2H), 1.68 (m, 1H), 1.80 (m, 1H), 1.95 (m, 1H), 2.20 (m, 1H), 4.15 (dd, 1H, J = 3.8, 8.5 Hz), 4.35 (m, 1H), 5.10 (m, 2H), 5.25 (d, 1H, J = 17.2 Hz), 5.90 (m, 1H). **133S** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.50 (m, 2H), 1.78 (m, 2H), 1.91 (m, 2H), 4.13 (dd, 1H, J = 4.6, 9.3 Hz), 4.31 (m, 1H), 5.10 (m, 2H), 5.28 (d, 1H, J = 17.6 Hz), 5.85 (m, 1H).

Benzylated Pyranoside (123R/S)



133 R:S 1:4 **123**

Dibenzyl Pyranoside (123S)

Diol **133S** (150 mg s, 0.58 mmol) was disolved in DMF (3 mL, anhydrous) and the solution was cooled to 0 °C and NaH (118 mg, 2.9 mmol) was added. Bu_4NI (22mg, 0.058 mmol) followed by BnBr (0.28 mL, 2.32 mmol) was added and the reaction mixture allowed to stir for 30 min. The reaction was quenched by dropwise addition of MeOH (2mL), then water (25 mL) and the aqueous mixture was extracted with Et_2O (3 x 25 mL). The combined Et_2O extract was washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL) and excess solvent evaporated to give monobenzylated product **133S** (150 mg, 74%). Rf 0.3 (10% EtOAc:PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.18 (s, 9H), 1.42 (m, 2H), 1.90 (m, 4H), 3.82 (dd, 1H, J = 4.6, 8.3 Hz), 3.96 (m, 1H), 4.45 (ABq, Δδ = 0.19 ppm, 2H, J = 11.1 Hz), 5.04 m, 1H), 5.24 (m, 2H), 5.73 (m, 2H), 7.30 (m, 5H).

Alcohol **133S** (150 mg, 0.431 mmol) was disolved in anhydrous DMF (3 mL). The solution was cooled to 0 °C and NaH (118 mg, 2.9 mmol) was added. Bu_4NI (22mg, 0.058 mmol) followed by BnBr (0.280mL, 2.32 mmol) was added and reaction mixture allowed to stir for 30 min. The reaction was quenched by dropwise addition of MeOH (2mL), then water (25 mL), the aqueous mixture was extracted with Et_2O (3 x 25 mL). The combined Et_2O extract was washed with saturated aqueous $NaHCO_3$ (10 mL), brine

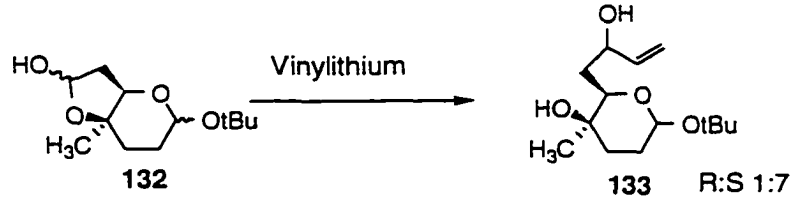
(5 mL) and the excess solvent evaporated in vacuo followed by FCC (5-30% EtOAc:PE) to afford the dibenzylated product **123S** (150 mg, 79%). Rf 0.65 (10% EtOAc :PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, H), 1.19 (s, 9H), 1.35 (m, 1H), 1.90 (m, 4H), 2.19 (m, 1H), 3.74 (d, 1H, J = 8.9 Hz), 3.89 (m, 1H), 4.42 (s, 2H), 4.45 (ABq, Δδ = 0.19 ppm, 2H, = 11.1 Hz), 5.10 (m, 1H), 5.30 (d, 1H, J = 13.3 Hz), 5.33 (d, 1H, J = 4.4 Hz), 5.78 (m, 1H), 7.30 (m, 10H).

Dibenzyl Pyranoside (123R)

Alcohol **133R** (40 mg, 0.115 mmol) was treated under similar benzylation conditions as **133S** to give **133R** (47 mg, 93%). Rf 0.63 (10% EtOAc:PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.20 (s, 9H), 1.40-1.70 (br m, 3H), 1.80-2.10 (br m, 3H), 4.05 (m, 1H), 4.18 (dd, 1H, J = 3.8, 8.5 Hz), 4.25 (ABq, Δδ = 0.28 ppm, 2H, J = 12.1 Hz), 5.13 (m, 1H), 5.20 (d, 1H, J = 10.3 Hz), 5.27 (d, 1H, J = 17.2 Hz), 5.80 (m, 1H), 7.30 (m, 5H).

Alcohol **133R** (40 mg , 0.155 mmol) was treated under similar benzylation conditions as **133S** to give **123R** (50.5 mg, 74%). Rf 0.67 (10% EtOAc:PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (s, 3H), 1.21 (s, 9H), 1.30 (m, 2H), 1.90 (m, 4H), 4.05 (m, 1H), 4.15 (m, 1H), 4.43 (m, 2H), 4.44 (ABq, Δδ = 0.28 ppm, 2H, J = 12.1 Hz), 5.18 (m, 2H), 5.27 (d, 1H, J = 17.2 Hz), 5.80 (m, 1H), 7.30 (m, 2H).

Vinyllithium adduct (133R/S)

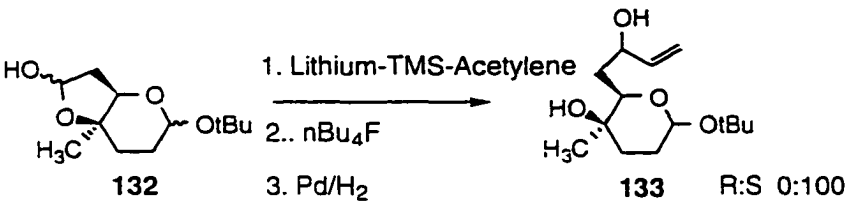


132 **133** R:S 1:7

MeLi (7.14 mL, 10 mmol 1.4 M in Et_2O) was added dropwise with stirring at rt to a solution of tetravinyltin (0.45 mL, 2.5 mmol) in Et_2O (15 mL) and stirring was continued for one h.

A solution of vinyllithium (5mL, 0.55mmol, 0.11mmol/ mL) was added dropwise to the lactol **132** (40 mg, 0.175 mmol) dissolved in Et_2O (3mL) at -78 °C. The reaction was allowed to warm up to rt and quenched by addition to saturated aqueous NH_4Cl (15 mL) then extraction with Et_2O (3 x 15 mL) the organic combined and washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL) and dried ($MgSO_4$). FCC (10-50 % EtOAc:PE) of the evaporated crude furnished the diol mixture **133R/S** [1:7 R:S] (35 mg, 78%) Rf 0.4, 0.35 (20 % EtOAc:PE).

Pyranoside (133)



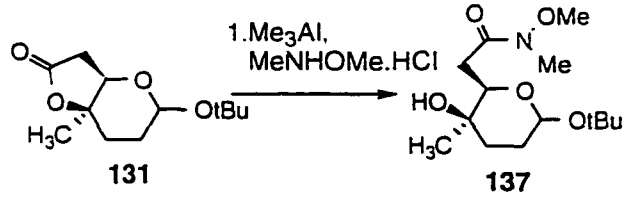
132 **133** R:S 0:100

Lactol **132** (55 mg, 0.20 mmol) was dissolved in Et_2O (5 mL) and cooled to -43 °C under N_2 . Lithium trimethylsilyl acetylide (1.97 mL, 0.989 mmol) of 0.5M solution was added and solution allowed to warm to rt. The reaction was quenched by addition to saturated aqueous NH_4Cl (10 mL) solution . The aqueous layer was extracted with Et_2O (3 x 15 mL), the organic layers combined and washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL) then excess solvent was evaporated. FCC (10-50% EtOAc:PE) afforded alkyne (56 mg, 89%). Rf 0.6 (20% EtOAc:PE); ^1H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 9H), 1.26 (s, 3H), 1.25 (s, 9H), 1.50 (m, 2H), 1.98 (m, 4H), 4.08 (dd, 1H, J = 3.8, 8.5 Hz), 4.57 (m, 1H), 5.12 (m, 1H).

To the Alkyne (56 mg, 0.179 mmol) dissolved in 10 mL THF was added nBu_4NF (0.18 mL, 0.179 mmol). The reaction was allowed to to proceed for 1 h after which excess solvent was evaporated to give the crude alkyne (45 mg, 0.175 mmol). Rf 0.50 (20% EtOAc:PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.25 (s, 9H), 1.50 (m, 2H), 1.98 (m, 4H), 2.48 (s, 1H), 4.08 (dd, 1H, J = 3.8, 8.5 Hz), 4.57 (m, 1H), 5.12 (m, 1H). ^{13}C NMR (75 MHz, CDCl3) δ 23.1, 25.8, 26.7, 30.1, 35.2, 59.2, 66.8, 70.8, 71.3, 72.7, 82.9, 89.0. FT-IR 3412.8, 3307.1, 2966.2, 2355.1, 1443.1, 1366.7, 1302.0, 1255.0, 1190.4, 1108.1, 996.5, 755.6 cm^{-1}.

Alkyne (45 mg, 0.175 mmol) was dissolved in EtOAc (5 mL). The flask was purged several times with Argon. 10% by weight of Lindlar's catalyst (4.5 mg) was then added and the Argon evacuated and replaced with H_2. The reaction was allowed to proceed for 30 min - 1 h after dissapearance of starting material as monitored by tlc. The solution was filtered through a celite pad and the residue was washed with excess EtOAc (30 mL). The EtOAc extract was evaporated and purified by FCC (30%-50% EtOAc:PE) to afford the S allylic alkene pyranoside **133S** (37 mg, 80%). Rf 0.4 (20% EtOAc:PE); whose NMR spectrum matched those of a previous sample.

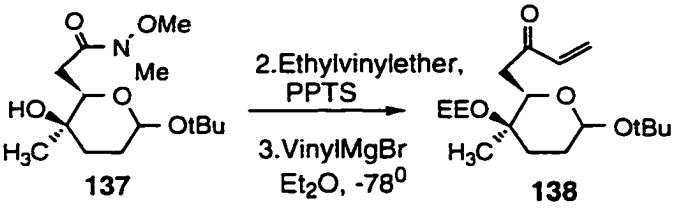
Weinreb's Amide (137)



131 **137**

Dimethylaluminum N, O- dimethylhydroxylamide (4.0 mL of a 1.0M soution, 5.1 mmol) was added to a solution of lactone **131** (110 mg, 0.50 mmol) in dry methylene chloride (4 mL) at rt under argon atmosphere. The reaction mixture was stirred at rt for 16 h, then slowly added to saturated aqueous NH_4Cl (15 mL) at 0 °C. The mixture was then extracted with methylene chloride (4 x 20 mL), the combined organics were washed with saturated aqueous $NaHCO_3$ (20 mL), dried (Na_2SO_4), and the evaporated was evaporated in vacuo.The crude residue **137** (10 mg, 70%) was used directly in the next step. ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.14 (s, 9H), 1.40 (m, 2H), 1.90 (m, 2H), 2.60 (m, 2H), 3.12 (s, 3H), 3.65 (s, 3H), 4.32 (dd, 1H, J = 3.8, 8.5 Hz), 5.02 (m, 1H). ^{13}C NMR (75 MHz, CDCl3) δ 25.3, 27.8, 28.6, 32.0, 32.4, 61.4, 68.7, 71.7, 74.3, 91.1, 197.1.

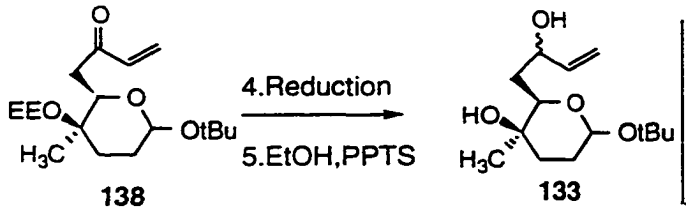
α,β-unsaturated ketone (138)



A solution of hydroxyamide **137** (100 mg, 0.35 mmol), ethyl vinyl ether (0.70 mL, 0.70 mmol), and pyridinium p- toluenesulfonate (8.75 mg, 0.035 mmol) in anhydrous dichloromethane (10 mL) was strirred at rt for 17 h. At this time, the reaction mixture was diluted with dichloromethane (50 mL) and washed with saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated in vacuo to give a pale yellow syrup. This was purified by FCC (40-75% EtOAc:PE) to give the protected tertiary hydroxyl methoxyamide (100 mg, 88%). Rf 0.55 (50% EtOAc:PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 m, 3H), 1.20 (s, 12H), 1.37 (m, 3H), 1.80 (m, 4H), 2.60 (m, 2H), 3.18 (s, 3H), 3.50 (m, 3H), 3.70 (s, 3H), 4.30 (m, 1H), 4.85 (m, 1H), 5.08 (m, 1H).

Protected amide (39 mg, 0.12 mmol) was dissolved in anhydrous THF (4 mL). The mixture was placed under Argon and cooled to 0 °C. Vinylmagnesium bromide (0.615 mL, 0.6 mmol) was added and the reaction was allowed to proceed for 30 min then diluted with Et_2O (30 mL) and poured into saturated aqueous NH_4Cl (15 mL). The aqueous layer was extracted with Et_2O (3 x 15 mL) and combined organic were then washed with saturated aqueous $NaHCO_3$ (15 mL), brine (15 mL) and then concentrated in vacuo. FCC (30-60% EtOAc:PE) gave the unsaturated ketone **138** (35 mg, 93%). Rf 0.75 (40% EtOAc:PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (m, 15H), 1.30 (m, 4H), 1.60 (m, 2H), 2.60 m, 1H), 3.00 (m, 1H), 3.50 (m, 1H), 4.29 (m, 1H), 4.90 (m, 1H), 5.05 (m, 1H), 5.79 (m, 1H), 6.20 (m, 1H), 6.39 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.6, 21.3, 21.4, 22.6, 23.8, 27.6, 27.8, 28.8, 29.5, 39.8, 40.0, 58.0, 58.9, 73.0, 73.1, 73.6, 90.8, 91.1, 93.6, 94.6, 97.6, 128.1, 128.2, 137.7, 137.8, 199.8.

Alkene (133)



138 133

Stereochemistry	Reduction Condition
R : S	
60 : 40	$NaBH_4CeCl_3$
20 : 80	DIBALH

α,β-Unsaturated ketone **138** (10 mg,0.320) was dissolved in EtOH (2 mL) and $CeCl_3.7H_2O$ (33 mg, 0.096 mmol) plus $NaBH_4$ (3.6 mg, 0.096 mmol) was added slowly at 0 °C. The reaction was followed by TLC (15 % EtOAc:PE) and determined complete within 10 min. The reaction was quenched by addition to saturated aqueous $NaHCO_3$ (10 mL) and extraction of the mixture with Et_2O (3 x 10 mL), followed by washing with brine (10 mL), dry ($MgSO_4$) and evaporation of solvent gave a crude product which was deprotected as follows.

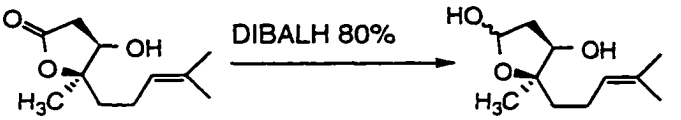
The crude material was dissolved in EtOH (3 mL), and PPTS (0.8 mg, .0032 mmol) was added. The solution allowed to stir for one h and the reaction was quenched by neutralization with NaOMe/MeOH to pH 7. The excess solvent was evaporated and the crude purified by FCC (20-50% EtOAC:PE) to give two diols **133R/S** (4mg, 48%) : R:S (65:35) : Rf 0.4, 0.35 (20% EtOAc:PE).

α,β- Unsaturated ketone **138** (40 mg, 0.128 mmol) was dissolved in anhydrous toluene (10 mL). The solution was cooled under N_2 to -78 °C. DIBALH (0.128 mL, 0.128 mmol, 1M in Heptane) was added and TLC showed disappearence of ketone. Et_2O (20 mL) was added at 0 °C and the suspension was added to saturated aqueous $NaHCO_3$ (5 mL). The aqueous was then extracted with Et_2O (3 x 10 mL) washed with brine (5 mL) and dried ($MgSO_4$). Evaporation of the ether gave a crude material which was deprotected as follows.

The crude pyranoside was dissolved in EtOH (3 mL), and PPTS (3.0 mg, 0.012 mmol) was added. The solution was allowed to stir for one h and the reaction was quenched by neutralization with NaOMe/MeOH to pH 7. The solvent was evaporated and

the crude purified by FCC (20-50% EtOAC:PE) to give two diols **133R/S** (25 mg, 76%) : R:S (20:80). Rf 0.4, 0.35 (20% EtOAc:PE).

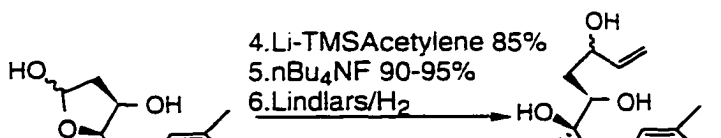
Lactol (140)



139 140

The lactone **139** (2.3g, 11.63mmol) was dissolved in dry toluene (90 mL). The solution was cooled to -78 °C under N_2. DIBALH (16.3mL, 16.28mmol, 1M in Heptane) was added dropwise over a 10 min interval. The solution was allowed to warm to rt. Na_2SO_4 was added and the solution was diluted with Et_2O (150 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (30 mL) and dried (Na_2SO_4). The excess solvent was removed in vacuo to furnish a crude yellow oil. FCC (40-75% EtOAc:PE) afforded a clear colorless liquid lactol **140** (1.978g, 85%). Rf 0.62 (50% EtOAc:PE): ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (s, 3H), 1.60 (s, 3H), 1.67 (s, 3H), 1.77 (m, 2H), 2.05 (m, 2H), 2.30 (m, 2H), 3.0 (m, 1H, D_2O exch.), 3.86 (m, 1H), 4.19 (m, 1H), 5.15 (m, 1H), 5.45 (m, 0.75H), 5.60 (m, 0.25H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 17.7, 21.1, 22.8, 23.5, 24.5, 25.1, 25.7, 35.6, 37.2, 41.1, 42.5, 60.6, 76.7, 77.4, 86.2, 88.3, 97.1, 98.0, 124.6, 131.7. HRMS (CI- CH_4) calculated for $C_{11}H_{20}O_3$ ($M+H^+$) 201.149070, found 201.149706.

Alkene (141)



140 141

To a flame dried 50mL RBF was added Et_2O (7.6mL). The solvent was cooled to -5 °C and nBuLi (3.94 mL, 0.3 mmol, 1.6M in Hexane) was added. To this cooled

solution was added TMS-Acetylene (0.98 mL, 6.93 mmol). The solution was allowed to stir at -5 ^{o}C for 30 min, then gradually warmed up to rt.

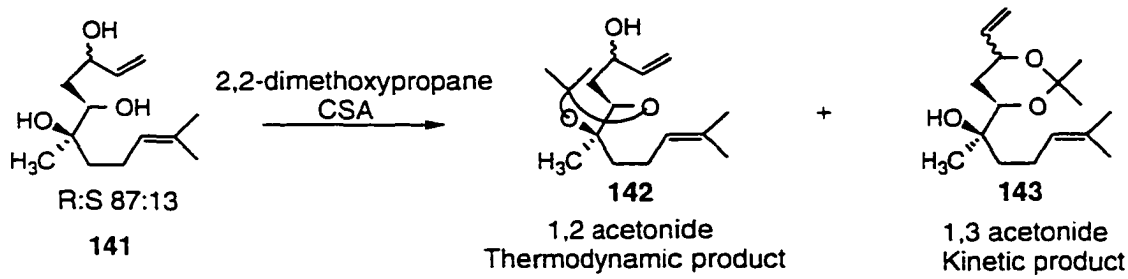
The azeotropically dried lactol (63 mg, 0.315mmol) intermediate was dissolved in Et_2O (2 mL), then cooled to 0 ^{o}C. The Lithium TMS acetylene anion solution was added dropwise. The solution was allowed to stir and then warmed up to rt and the reaction stopped 4 h later by addition to cold saturated saturated NH_4Cl (15 mL). The mixture was extracted with Et_2O (3 x 20mL), washed with saturated aqueous $NaHCO_3$ (30 mL), brine (30 mL) and dried ($MgSO_4$). The Et_2O extract was concentrated in vacuo and purified by FCC (20-60% EtOAc:PE), to give a mixture of alcohols (79 mg, 85%) R:S (85:15). Rf 0.7.0.66 (30% EtOAc:PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.5 (s, 9H), 0.8 (s, 3H), 1.47 (m, 2H), 1.62 (s, 3H), 1.7 (s, 3H), 1.80 (m, 2H), 2.1 (m, 2H), 4.05 (dd, 1H, J = 2.3, 9.5 Hz), 4.17 (t, 1H, J = 4.7 Hz), 5.13 (t, 1H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.0, 17.9, 21.4, 22.2, 25.9, 37.6, 39.0, 61.5, 74.1, 74.8, 90.1, 106.0, 124.3, 135.0. HRMS (CI- CH_4) Calculated for $C_{16}H_{30}O_3Si$ (M+ H^+) 299.204249, found 299.204465.

The alkyne (3.0g, 10.07mmol) was dissolved in THF (350 mL) and nBu_4NF (25mL, 25.17mmol) was added. The reaction was allowed to proceed for 1 h after which excess solvent was evaporated and the crude purified via FCC (15-50% EtOAc:PE) to give the alkyne (2.16g, 95%). Rf 0.6 (30% EtOAc:PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.8 (s, 3H), 1.47 (m, 2H), 1.62 (s, 3H), 1.7 (s, 3H), 1.80 (m, 2H), 2.1 (m, 2H), 4.05 (dd, 1H, J = 2.3, 9.5 Hz), 4.17 (t, 1H, J = 4.7 Hz), 5.13 (t, 1H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 21.3, 22.2, 25.9, 37.3, 38.9, 60.9, 73.5, 74.3, 90.1, 124.3, 135.0. HRMS (CI-CH_4) Calculated for $C_{13}H_{22}O_3$ (M+H^+) 227.164720, found 227.163871.

Alkyne (2.16g, 9.55mmol) was dissolved in EtOAc (150mL). The flask was purged several times with Argon. 10% by weight of Lindlar's catalyst was then added and the argon was evacuated and replaced with H_2. The reaction allowed to proceed for 30 min - 1 h after disapearance of starting material. The solution was filtered through a celite pad and the solid was washed with excess EtOAc (300 mL). The EtOAc extract was evaporated and purified by FCC (30% EtOAc: PE- 50%) to yield a colorless oil **141** (1.97g, 90%). Rf : 0.55 (30% EtOAc:PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (s, 3H), 1.50 (m, 4H),

1.60 (s, 3H), 1.70 (s, 3H) 2.15 (m, 2H), 3.79 (m, 1H), 4.50 (m, 1H), 5.10 (t, 1H, J = 6.8 Hz), 5.18 (d, 1H, J = 13.0 Hz), 5.30 (d, 1H,J = 16.8 Hz), 5.93 (m,1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 21.1, 22.2, 25.8, 37.4, 38.8, 70.2, 73.6, 75.0, 114.5, 124.5, 132.0, 140.9. HRMS (CI-CH_4) Calculated for $C_{13}H_{24}O_3$ ($M+H^+$) 229.180370, found 229.180159.

1,3 acetonide (143)



Triol **141** (100 mg, 0.500 mmol) was dissolved in CH_2Cl_2 (10 mL), 2,2-dimethoxypropane (0.60 mL, 10.00 mmol), Camphorsulfonic acid (11.6 mg, 0.05 mmol) was added and the reaction was allowed to stir for 10 min. The solution was neutralized by addition of NaOMe/MeOH (1M) and the excess solvent evaporated. FCC (5-30% EtOAC:PE) gave 2 fractions #1 of 1,3-acetonide **143** (87.5 mg, 85%) and #2 of 1,2-acetonide **142** (15.5 mg, 15%): Rf 0.6, 0.4 (7% EtOAc:PE).

Fraction # 1 **143** (45 mg, 0.197 mmol) was then subjected to further chromatography by FCC (5-30% EtOAc:CH_2Cl_2) too furnish 2 separable 1,3-acetonide products 1" (51 mg) and 2" (12.9 mg) : Rf 0.30, 0.25 (3 % EtOAc:CH_2Cl_2).

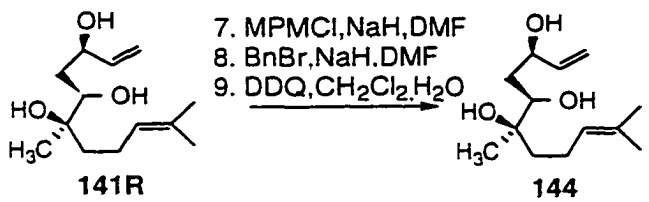
^{13}C NMR spectral comparison for the C-2-Acetonide and methyl shifts indicate that Fraction 1" is Anti (R-Allylic alcohol) and Fraction 2" is Syn (S-Allylic alcohol).

Fraction 1" **143** (S-Allylic Alcohol) ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.40 (s, 6H), 1.50 (m, 3H), 1.61 (s, 3H), 1.70 (s, 3H), 2.05 (m, 3H), 3.70 (dd,1H, J = 5.6, 10.3 Hz), 4.28 (dd, 1H, J = 6.5, 13.1 Hz), 5.10 (m, 1H), 5.13 (d, 1H, J = 10.2 Hz), 5.25 (d,1H, J = 16.8 Hz), 5.83(m,1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 20.6, 21.7, 23.1, 26.4, 30.8, 31.3, 39.6, 70.9, 73.8, 74.2 89.4, 116.3, 125.4, 132.2, 139.6.

Fraction 2" **143** (R-Allylic Alcohol) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.40 (s, 6H), 1.50 (m, 3H), 1.61 (s, 3H), 1.70 (s, 3H), 2.05 (m, 3H), 3.61 (dd, 1H, J = 5.6, 10.2 Hz), 4.20 (dd, 1H, J = 4.7, 9.3 Hz), 5.04 (m, 1H), 5.08 (d, 1H, J = 11.2 Hz), 5.16 (d, 1H, J = 17.7 Hz), 5.80 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 21.0, 22.6, 25.0, 25.4, 26.0, 32.6, 39.2, 68.6, 71.2, 73.8, 100.9, 115.5, 131.8, 134.6.

Fraction # 2 **142** (15.5 mg, 0.07 mmol) was purified by FCC (5-30 % EtOAc: CH_2Cl_2) to furnish an inseparable mixture of 1,2-acetonide products whose signals were indistinguishable by NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.32 (s, 3H), 1.40 (s, 3H), 1.50 (m, 3H), 1.59 (s, 3H), 1.68 (s, 3H), 1.80 (m, 1H), 2.05 (m, 2H), 2.38 (m, 1H, D_2O exch.), 4.05 (d, 1H, J = 11.1 Hz), 4.39 (m, 1H), 5.08 (t, 1H, J = 5.6 Hz), 5.12 (d, 1H, J = 10.2 Hz), 5.30 (d, 1H, J = 17.7 Hz), 5.90 (m, 1H).

Triol (144)



141R **144**

Triol **141R** (240 mgs 1.053mmoles) was dissolved in anhydrous DMF (5mL). The solution was cooled to 0 °C and NaH (155mgs, 3.896mmol) was added. The solution was allowed to stir for 5 min and Bu_4NI (39mg, 0.105 mmol) was added followed by p-methoxybenzychloride (0.58g, 3.684mmoles). The solution was allowed to stir at rt for 2 h. The reaction was quenched by addition of MeOH (2mL), followed by water (30mL). The solution was extracted with Et_2O (3 x 30mL) and washed with saturated aqueous $NaHCO_3$ (50mL), brine (50mL) then dried ($MgSO_4$) . The solvent was evaporated and the residue purified by FCC to yield bismethoxybenzylated alcohol (0.318g, 87%). Rf 0.3 (10% EtOAc:PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.50 (m, 2H), 1.61 (m, 3H) 1,68(s, 3H), 1.74(m, 1H), 2.10 (m, 3H), 3.58 (m, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 3.80 (m, 1H), 4.39 (ABq, Δδ = 0.33 ppm, 2H, J = 11.4 Hz), 4.41 (ABq, Δδ = 0.07 ppm, 2H, J = 11 Hz), 5.10 (t, 2H, J = 6.8 Hz), 5.23 (d, 1H, J = 3.1 Hz), 5.28 (d,1H, J = 10.5 Hz), 5.78 (m, 1H), 6.86 (d, 4H, J = 8.5 Hz), 7.17 (d, 2H, J = 8.5 Hz), 7.27 (d,

2H, J = 7.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 22.3, 22.4, 25.9, 38.3, 39.2, 55.5, 69.8, 74.7, 75.2, 77.4, 82.1, 114.1, 117.1, 125.0, 129.2, 129.8, 131.0, 139.5, 159.5. HRMS (CI-CH_4) calc'd for $C_{36}H_{46}O_5$ ($M+H^+$) 559.342350, found 559.342522.

Alcohol (500mg, 1.064mmoles) was dissolved in anhydrous DMF (5mL). The solution cooled to 0 °C and NaH (89mg, 2.234mmol) was added. The solution was allowed to stir for 5 min and Bu_4NI (39mg, 0.106 mmol) was added followed by benzyl bromide (0.36g, 2.128mmol).The solution was allowed to stir at rt for 2 h. The reaction was quenched by addition of MeOH (2mL), followed by water (30mL). The solution was extracted with Et_2O (3 x 40 mL) and washed with saturated aqueous $NaHCO_3$ (50mL), brine (50mL) then dried ($MgSO_4$). The solvent evaporated and purified by FCC to yield monobenzylbismethoxybenzylated alcohol (0.565mg, 87%). Rf 0.5 (10% EtOAc :PE): ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.52 (s, 3H), 1.57 (m, 2H), 1.61 (s, 3H), 1.72 (m, 1H), 2.10 (m, 3H), 3.68 (s, 3H), 3.69 (s, 3H), 3.80 (m, 1H), 4.04 (m, 1H), 4.12 (m, 1H), 4.20 (m, 1H), 4.42 (ABq, Δδ = 0.40 ppm, 2H, J = 10.8 Hz), 4.45 (m, 3H), 5.05 (m, 1H), 5.31 (d, 1H, J = 10.3 Hz), 5.36 (d, 1H, J = 17.5 Hz), 5.69 (m, 1H), 6.95 (m, 4H), 7.21 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 19.7, 21.7, 25.9, 35.4, 38.3, 55.4, 64.0, 69.8, 74.6, 80.4, 80.8, 113.8, 116.6, 125.0, 127.2, 127.5, 127.9, 128.4, 128.6, 129.2, 129.5, 131.2, 139.7, 159.1, 159.2. HRMS (CI-CH_4) calc'd for $C_{36}H_{46}O_5$ ($M+H^+$) 559.342350, found 559.342522.

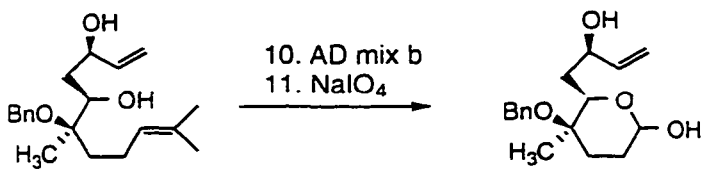
The triply blocked alkene alkene (330 mg, 0.590mmol) was dissolved in CH_2Cl_2:H_2O (1:18, 10 mL:0.5 mL) and cooled to 0 °C. DDQ (335 mg, 1.476 mmol) was added and the reaction was complete within 30 min and quenched by addition of saturated aqueous $NaHCO_3$ (30 mL), brine (30 mL) and finally dried ($MgSO_4$). Excess solvent was evaporated and crude yellow oil was subjected to FCC (10 % -50% EtOAc:PE) to yield 3 compounds. Fraction 1 (60 mgs): Rf 0.8 (10% EtOAc:PE) Fraction 2 (50 mg) :Rf 0.5 (10% EtOAc:PE) and Fraction 3 (50 mg): Rf 0.25 (10% EtOAc:PE).

Treatment of fraction 1 with MeOH (5 mL), 2M HCl (0.5 mL) gave 45 mg of Fraction #3

Treatment of fraction 2 with MeOH (5 mL), NaOMe (pH 12) gave 30 mg of Fraction #3.

Fraction 1, 2 and 3 were combined to afford the monobenzyl triol **144** (125mg, 66%) : Rf 0.25 (10% EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.61 (s, 3H), 1.66 (m, 4H), 1.69 (s, 3H), 2.05 (m, 2H), 2.80 (m, 2H, D_2O exch.), 4.06 (m, 1H), 4.43 m, 3H), 5.14 (m, 2H), 5.34 (d, 1H, J = 17.2 Hz), 5.95 (m, 1H), 7.34 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 18.3, 21.8, 25.9, 34.4, 37.0, 63.6, 70.5, 71.6, 79.9, 114.4, 124.3, 127.7, 128.6, 132.0, 139.1, 141.1. HRMS (CI-CH_4) calc'd for $C_{20}H_{30}O_3$ ($M+H^+$) 319.225977, found 319.225983.

Pyranoside (145)

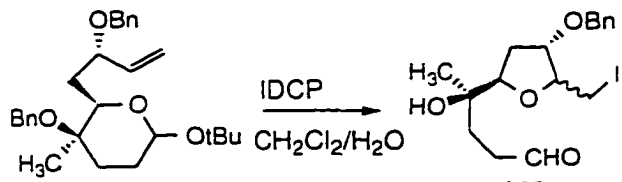


144 **145**

A 25 mL round bottom flask, equipped with a magnetic stirrer, was charged with t-butyl alcohol (5 mL), water (5 mL), AD - mix - β (1.4g) and $MeSO_2NH_2$ (95 mg, 1 equivalent, based on 1 mmol of olefin). The mixture was stirred at rt (1h) until both phases were clear, and then cooled to 0 °C, whereupon the inorganic salts partially precipitate. Diol **144** (319mg, 1.0mmol) dissolved in tBuOH:H_2O (2mL, 1:1) was added at once, and the heterogeneous slurry is stirred vigorously at 0 °C until TLC reveal the absence of the starting olefin (Ca. 48 hours). The reaction was quenched at 0 °C by addition of sodium sulfite (1.5 g) and then warmed to rt and stirred for 30-60 min. The reaction mixture is extracted three times with ethyl acetate (25mL) and then dried ($MgSO_4$) and concentrated to give a mixture of the crude diol. FCC (10-80% EtOAc:PE; the ligand does not elute under these conditions) gives the pure diol (323mg, 92%). Rf = 0.20 (50% EtOAc:PE): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 3H), 1.09 (s, 3H), 1.13 (s, 3H), 1.3 (m, 1H), 1.5 (brm, 4H), 2.0 (m, 1H), 2.70 (m, 4H, D_2O exch.), 3.20 (m, 1H), 4.00 (m, 1H), 4.37 (m, 3H), 5.05 (m, 1H), 5.20 (m, 1H), 5.84 (m, 1H), 7.24 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 18.7, 23.7, 24.9, 25.3, 26.7, 31.5, 37.3, 37.5, 63.9, 63.9, 70.4, 70.5, 71.6, 71.7, 73.4, 79.0, 79.3, 80.0, 80.1, 114.4, 127.8, 128.7, 139.1, 141.2, 141.3.

A solution of $NaIO_4$ (18.22 mg , 0.082 mmol) in water (3mL) was added at 0 °C to a solution of the triol obtained in the previous step (25 mg, 0.071 mmol) in THF (1.5mL). The reaction was warmed to rt and stirred at this temperature for an additonal 30 min. The reacton mixture was diluted with water (5mL) and the resulting solution was extracted with ether (3 x 10 mL) . The combined organic layer was washed with brine (10 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated at rt and 25mmHg FCC (40-90% EtOAc:PE) afforded the pyranoside **145** (22mg, 90%). Rf 0.50 (50% EtOAc:PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 1H), 1.06 (s, 2H), 1.60 (m, 2H), 1.91 (m, 2H), 2.17 (m, 2H), 3.61 (m, 0.33H), 4.19 (m, 0.66H), 4.42 (m, 3H), 4.79 (m, 0.33H), 5.10 (m, 1H), 5.30 (m, 1.66H), 5.90 (m, 1H), 7.30 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 21.4, 22.1, 26.1, 26.2, 31.2, 34.8, 60.6, 63.6, 69.7, 69.8, 72.1, 72.2, 73.1, 79.6, 91.2, 96.5, 114.2, 127.3, 128.4, 139.8, 141.4. HRMS (CI-CH_4) calc'd for $C_{17}H_{24}O_4$ ($M+H^+$) 293.175285, found 293.173679.

Tetrahydrofuran (146)



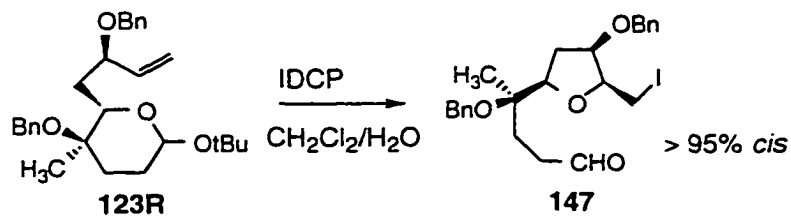
123S **146**

3:7 cis:trans

To a 50 mL flask containing alkene **123S** (118 mg, 0.268 mmol), CH_2Cl_2:H_2O (6 mL, 20:1) was added. Then IDCP (Iodonium Dicollidine Perchlorate, 150 mg, 0.321mmol) was added. The solution was stirred at 25 °C for 5 min and checked by TLC. Saturated aqueous $Na_2S_2O_3$ (5mL) was added and allowed to stir until the Iodine colour disappeared. The solution was then extracted with ether (4 x 20 mL). The ether extract dried and concentrated in vacuo to yield aldehydes **146** (125 mg, 91.6%) *cis:trans* (3:7). Rf 0.23 (10% EtOAc:PE); ^1H NMR (300 MHz, C_6D_6) δ 0.84 (s, 1.9H), 0.92 (s, 1.1H), 1.70 (m, 4H), 2.15 (m, 2H), 2.70 (dd, 0.64H, J = 7.0, 9.3 Hz), 2.82 (dd, 0.64H, J = 4.7, 9.3 Hz), 3.13 (dd, 0.72H, J = 5.1, 8.4 Hz), 3.65 (m, 0.34H), 3.74 (m, 0.64H), 4.02 (m, 1H), 4.20 (m, 2H), 7.30 (m, 10H), 9.39 (s, 1H). ^{13}C NMR (75 MHz, C_6D_6) δ 1.2, 6.2, 17.6, 17.8, 26.7, 31.6, 31.7, 37.3, 63.5, 63.6, 69.7, 70.6, 75.2, 76.2, 77.8,

81.3, 82.1, 82.6, 83.3, 83.8, 95.3, 125-127.1(9 signals), 137.1, 138.6, 139.0, 199.1. MS (CI) m/z (M^+), 526 (base peak), 509, 418, 401.

Tetrahydrofuran (147)

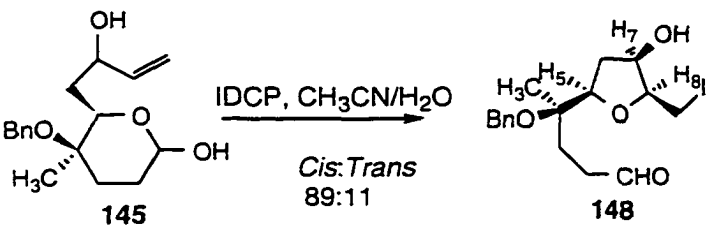


123R **147**

The alkene **123R** (40 mg,.109 mmol) was treated under similar condition to **123S** to yield the aldehyde **147** (45 mg, 97.2%). Rf 0.22 (10% EtOAc:PE); ^{1}H NMR (300 MHz, C_6D_6) δ 0.97 (s, 3H), 1.50 (m, 1H), 1.7 (m, 1H), 1.81 (m, 1H), 1.97 (m, 1H), 2.18 (m, 2H), 3.17 (dd, 1H, J = 6.5, 9.3 Hz), 3.27 (dd, 1H, J = 6.5, 9.3 Hz), 3.51 (t, 1H, J = 17.6 Hz), 3.61 (m, 2H), 4.12 (ABq, Δδ = 0.61 ppm, 2H, J = 11.4 Hz), 4.47 (ABq, Δδ = 0.13 ppm, 2H, J = 10.7 Hz), 7.20 (m, 10H), 9.39 (s, 1H). ^{13}C NMR (75 MHz, C_6D_6) δ 0.7, 18.4, 26.5, 31.6, 37.2, 63.8, 70.0, 75.3, 76.9, 81.4, 82.8, 125.9-127.3(8-signals), 138.8, 199.1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.90 (m, 1H), 2.10 (m, 3H), 2.61 (m, 2H), 3.32 (dd, 1H, J = 8.4 Hz, H-9), 3.44 (dd, 1H, J = 5.6, 8.4 Hz, H-9), 3.99 (m, 1H, H-5), 4.02 (m, 1H, H-8), 4.18 (m, 1H, H-7), 4.50 (ABq, Δδ = 0.20 ppm, 2H, J = 13.0 Hz), 4.58 (ABq, Δδ = 0.19 ppm, 2H, J = 13.0 Hz), 7.30 (m, 10H), 9.75 (s, 1H). MS (CI) m/z (M^+), 526 (base peak), 508, 418, 350, 292, 196.

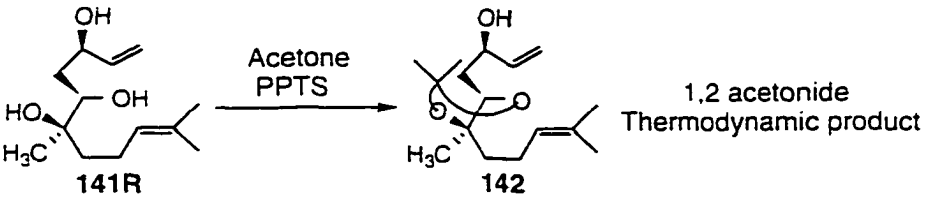
Tetrahydrofuran (148)



protons	%/nOe obs'd
H_5/H_8	0.5
H_7/H_8	1.0
CH_3/H_5	1.0

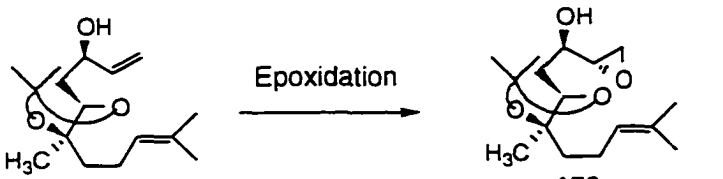
The alkene **145** (29.2 mg, 0.062 mmol) was treated under conditions similar to **123S** to yield the aldehydes **148** (24 mg, 93%) cis:trans(86:14). Rf 0.3 (10% EtOAc:PE): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3H), 2.20 (m, 2H), 2.60 (m, 3H), 3.21 (m, 2H), 3.67 (m, 1H, D_2O exch.), 3.90 (m, 1H), 4.05 (m, 1H), 4.12 (m, 1H), 4.50 (s, 2H), 7.34 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.3, 21.4, 28.4, 36.5, 40.0, 65.5, 71.3, 78.4, 84.2, 84.5, 128.4, 128.7, 129.4, 137.8, 202.7. HRMS (CI-CH_4) calc'd for $C_{17}H_{23}O_4I$ $(M+H)^+$ 418.064111, found 418.064769.

1,2 Acetonide (142)



Triol **141R** (250 mg, 1.097 mmol) was dissolved in acetone (75 mL) and PPTS (28 mg, 0.1097 mmol) added. The solution was allowed to stir for 48 h and then neutralized by addition of NaOMe/MeOH (1M) until pH 7. Excess solvent evaporated followed by FCC (5-30 % EtOAc:PE) to yield 1,2-acetonide **142** (200 mg, 69 %). Rf 0.4 (7% EtOAc:PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.32 (s, 3H), 1.40 (s, 3H), 1.50 (m, 3H), 1.59 (s, 3H), 1.68 (s, 3H), 1.80 (m, 1H), 2.05 (m, 2H), 2.38 (m, 1H, D_2O exch.), 4.05 (d, 1H, J = 11.1 Hz), 4.39 (m, 1H), 5.08 (t, 1H, J = 5.6 Hz), 5.12 (d, 1H, J = 10.2 Hz), 5.30 (d, 1H, J = 17.7 Hz), 5.90 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 21.6, 22.8, 25.8, 27.1, 28.9, 36.2, 39.3, 70.4, 78.1, 82.4, 107.3, 114.5, 124.4, 131.9, 141.0.

Epoxide (150)



142
1,2 acetonide
Thermodynamic product

150

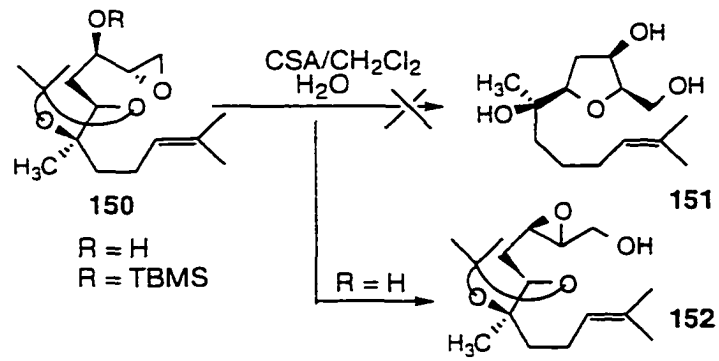
Stereochemistry	Epoxidation condition
R : S	
0 : 100	Sharpless
35 : 65	V^{5+}

Titanium tetraisopropoxide (0.19 mL, 0.625 mmol) and TBHP (4.2M in CH_2Cl_2, 0.24 mL, 1.041 mmol) were added, successively, to a suspension of L-(+)-DIPT (0.15 mL, 0.694 mmol) and molecular sieves 4A (30 mg) in CH_2Cl_2 (1.5 mL) at -10 °C under Ar atmosphere. After being stirred at -10 °C for 20 min, the mixture was cooled to -23 °C and **142** (93 mg, 0.347 mmol) was added at such a rate that the temperature remains under -20 °C. The mixture was stirred at -23 °C for an additional 2 h, and then water (5mL) was added, with vigorous stirring, to stop the reaction. The mixture was allowed to warm to rt and the aqueous extracted with CH_2Cl_2 (3 x 15 mL) . The organic layer was washed with saturated aqueous $NaHCO_3$ (5 mL), saturated aqueous $Na_2S_2O_3$ (5 mL), saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL) and was dried (Na_2SO_4) and finally concentrated in vacuo. FCC (10-80 % EtOAc:PE) afforded a single epoxide **150** (70 mg, 74 %). Rf 0.80 (50 % EtOAC:PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.30 (m, 2H), 1.35 (s, 3H), 1.43 (s, 3H), 1.55 (m, 2H), 1.62 (s, 3H), 1.69 (s, 3H), 1.80 (m, 2H), 2.10 (m, 2H), 2.80 (m, 2H), 3.10 (m, 1H), 4.02 (m, 1H), 4.10 (dd, 1H, J = 1.9, 10.6 Hz), 5.09 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 21.5, 22.9, 25.9, 27.2, 28.9, 33.5, 39.4, 44.0, 54.4, 67.2, 78.3, 82.5, 107.3, 124.4, 132.0.

1,2-Acetonide **142** (21 mg, 0.078 mmol) was dissolved in Benzene (2 mL). Vanadium acetylacetonate (5.45 mg, 0.016 mmol) was added. To this green solution was added TBHP (4.2M, 0.040 mL, 0.157mmol) . A dark red color was observed and the reaction was allowed to stir for 5 h (a yellow/green colour was observed). EtOAc (20mL)

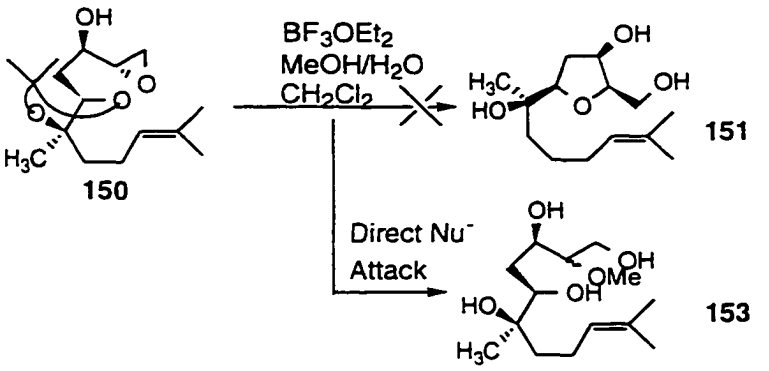
was added then the solution washed with saturated aqueous Sodium bisulfite (5 mL), brine (5 mL) and the excess solvent was evaporated. FCC (10-70 % EtOAC:PE) afforded an inseparable mixture of epoxides **150(syn and anti)** (10 mg, 57%) : Rf 0.80 (50 % EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.30 (m, 2H), 1.35 (s, 3H), 1.43 (s, 3H), 1.55 (m, 2H), 1.62 (s, 3H), 1.69 (s, 3H), 1.80 (m, 2H), 2.10 (m, 2H), 2.80 (m, 2H), 3.05 (m, 0.26H), 3.10 (m, 0.74H), 4.02 (m, 1H), 4.10 (dd, 1H, J = 1.9, 10.6 Hz), 5.09 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 21.5, 22.9, 25.9, 27.2, 28.9, 33.5, 34.9, 39.4, 44.0, 45.0, 54.4, 67.2, 69.1, 77.4, 78.3, 82.5, 107.3, 124.4, 132.0.

Payne product (152)



Epoxide **150** (34 mg, 0.125 mmol) was dissolved in CH_2Cl_2:H_2O (18mL, 18:1). CSA (2.9 mg, 0.0125 mmol) was added and the reaction stirred for 24 h. TLC revealed disappearence of SM and the reaction mixture was carefully neutralised by addition of NaOMe/MeOH (1M) until pH 7. Excess solvent was evaporated in vacuo and purified by FCC (50 % EtOAc:PE) to give epoxide **150** (10 mg, 29%) : Rf 0.8 and epoxide **152** (15 mg, 55%) : Rf 0.4 (50 % EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.60 (s, 3H), 1.70 (s, 3H), 2.05 (m, 2H), 2.40 (m, 2H), 3.04 (dd, 1H, J = 3.7, 13.9 Hz), 3.65 (dd, 1H, J = 3.7, 13.9 Hz), 3.90 (m, 1H, D_2O exch.), 4.10 (m, 2H), 4.58 (m, 1H), 5.10 (m, 1H). MS (CI) m/z ($M+NH_4^+$) 302 (base peak), ($M+H^+$) 285, 227, 209.

Methanol adduct (153)



Epoxide **150** (18 mg, 0.0662 mmol) was dissolved in CH_2Cl_2 (1 mL). MeOH/H_2O (0.43 mL,1:18) was added. BF_3OEt (0.04 mL,0.2647 mmol) was added and the reaction was allowed to stir for 30 min until disappearance of **150**. EtOAc (20 mL) was added and solution was washed with saturated aqueous $NaHCO_3$ (3 mL), brine (3 mL) and then dried (Na_2SO_4). Excess solvent was evaporated and the crude was purified via FCC (50-80% EtOAc:PE) to yield **153** (10 mg, 55%) : Rf 0.1 (30% EtOAc:PE). ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.55 (m, 2H), 1.63 (s, 3H), 1.70 (s, 3H), 2.10 (m, 8H), 3.21 (s, 3H), 3.59 (m, 1H), 3.80 (m, 1H), 3.96 (m, 1H), 5.12 (m, 1H). MS (CI) m/z ($M+NH_4^+$) 294, ($M+H^+$) 277, 241, 224, 196 (base peak).

(VII) References

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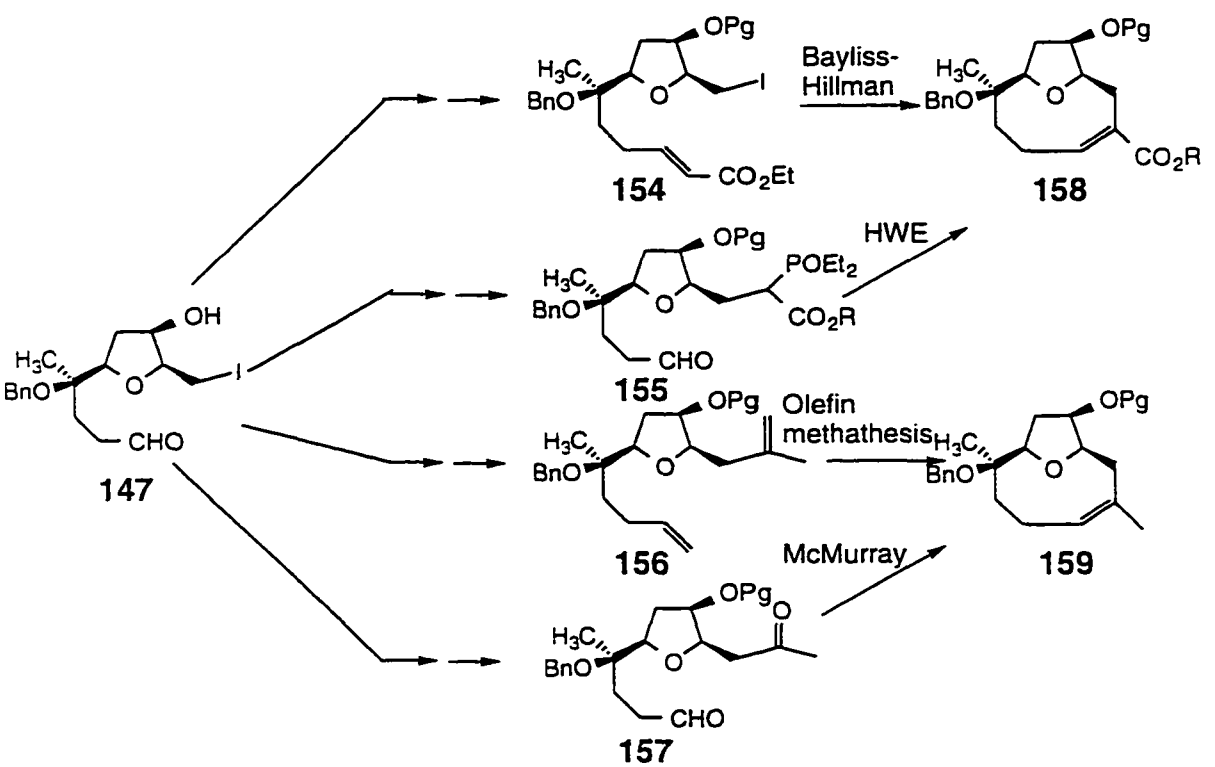
Chapter 5 : Macrocyclization Studies on the Eunecellin

Introduction

Four different strategies were explored for transformation of the THF-iodo-aldehyde **147** to the macrocyclic ring system found in the eunecellins (Scheme 45). These were based on (1) A modified Bayliss-Hillman (2) Horner-Wadsworth-Emmons (3) Olefin methathesis and (4) McMurray coupling methodologies.

Scheme 45

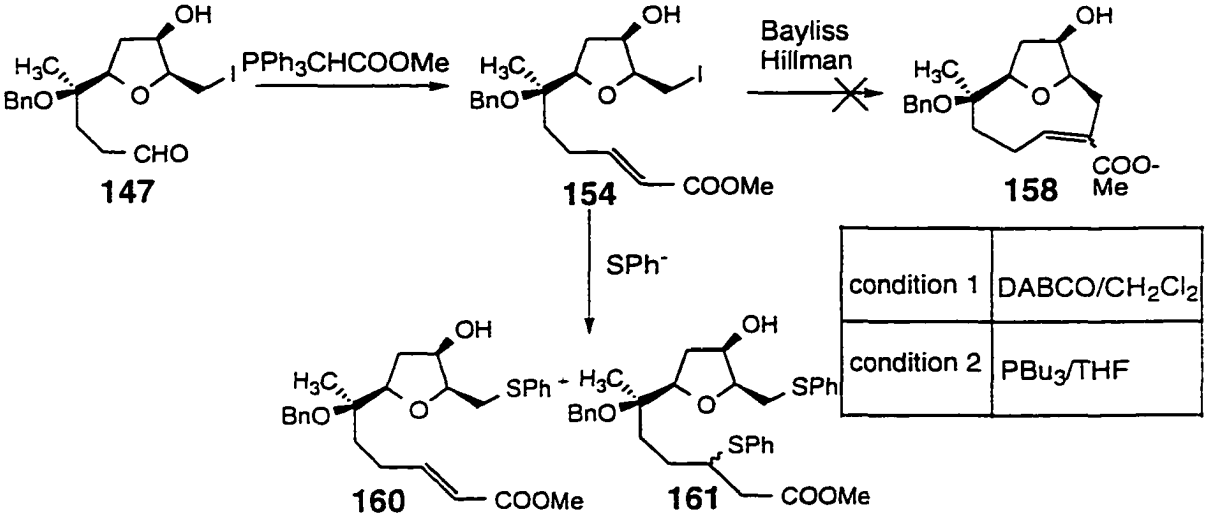


(I) Bayliss-Hillman

The Bayliss-Hillman (B-H) reaction involves the coupling of α,β-usaturated esters with aldehydes and ketones in the presence of a tertiary amine.[1-3] Although there are no examples with alkyl halides as the electrophile, presumably because of their low reactivity compared to aldehydes or ketones, we examined the reaction of the iodo alkene **154**. It was assumed that the C-C bond formation would benefit from the intramolecularity of the reaction.

The required precursor was prepared by reaction of **147** with $PPh_3CH_2CO_2Me$. However treatment of **154** under B-H conditions using either DABCO or PBu_3 resulted in no product formation. The starting material was recovered in 90% yield (Scheme 46).

Scheme 46

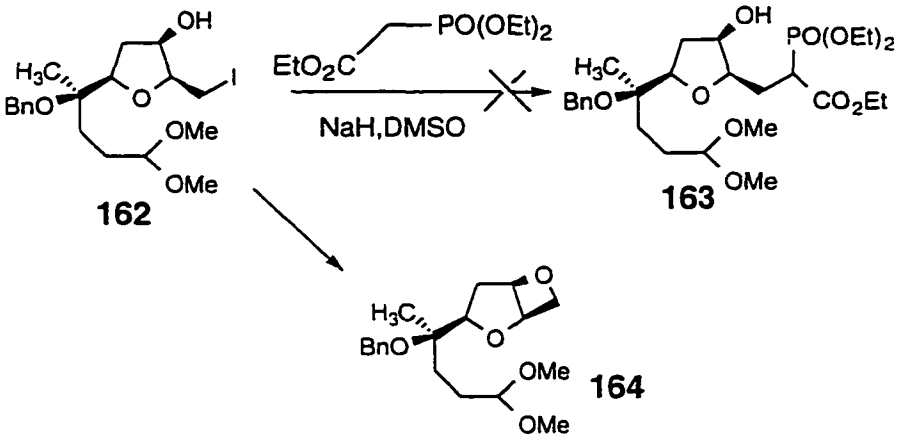


The more nucleophillic thiophenoxide anion was also tested. However. this resulted in direct displacement of the iodide by the anion giving **160** and addition of anion to the α,β- unsaturated system furnishing **161** (Scheme 46). Apparently the rate of intermolecular displacement and addition is faster than intramolecular anionic cyclization. Both products were confirmed by NMR (^1H and ^{13}C, COSY) and low resolution mass spectral analysis.

(II) Horner-Wadsworth-Emmons

The Horner-Wadsworth-Emmons (HWE) alkylation of the oxygenated THF **162** was used as a macrocyclization strategy[4] . The THF aldehyde was first protected as the dimethyl acetal. The triethyl phosphonacetate anion was generated in situ and the iodide added. The reaction was allowed to proceed for 24 h. NMR of the product obtained proved to be the oxetane **164** obtained from intramolecular displacement of the hydroxy anion on the iodide. Both ^1H,^{13}C NMR and mass spectral analysis confirms this. Protection of the hydroxyl group and treatment of the product gave none of the desired product, only starting material was recovered (Scheme 47).

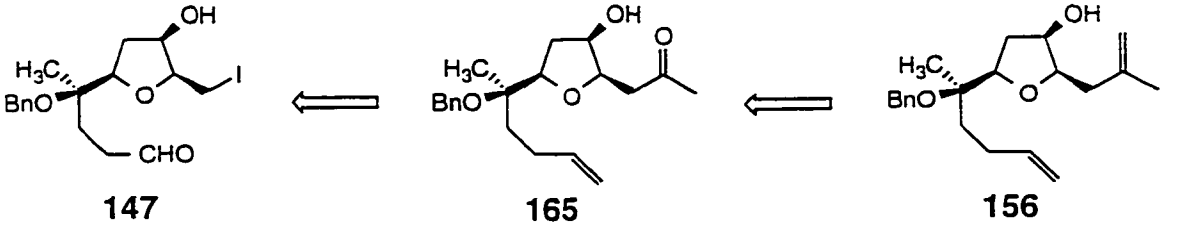
Scheme 47



(III) Olefin Methathesis

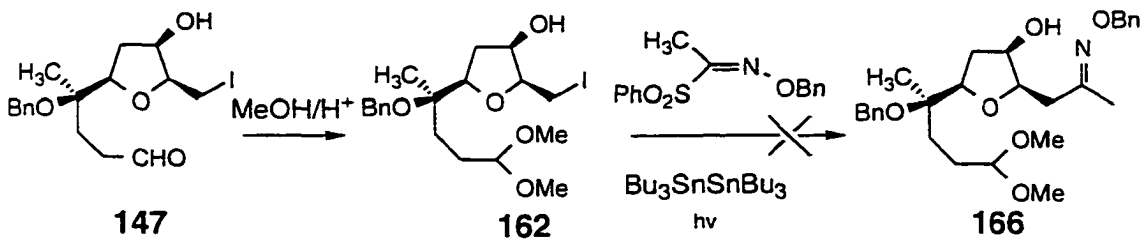
The key precursor required for olefin methathesis is the diene **156** (Scheme 48). This can be prepared from the methyl ketone **165** which can be obtained from a acylation of the iodide moiety and protection of the aldehyde as the terminal alkene. Several approaches to **165** were attempted.

Scheme 48



A recent study showed that phenyl sulfonyl oxime ethers to be highly effective for free radical-mediated acylations[6]. O-benzyl-α-(phenylsulfonyl)-acetalaldoxime was prepared in four steps. The THF iodide **162**, oxime and hexadimethyltin was irradiated at 300 nm for 4 h (Scheme 49).

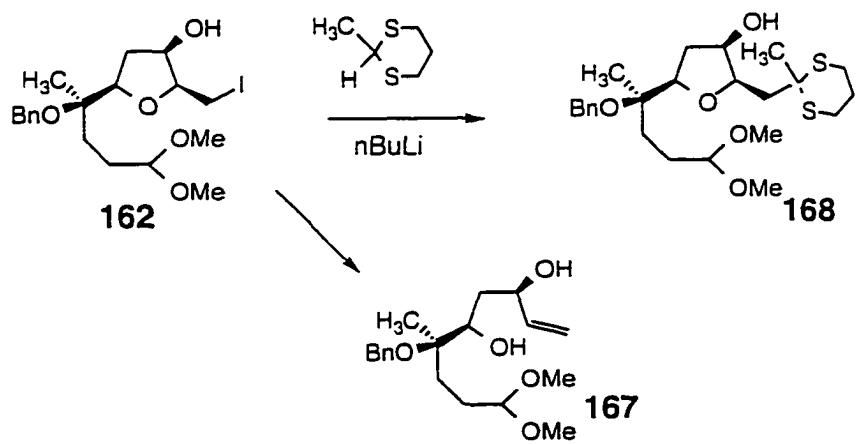
Scheme 49



NMR analysis showed a mixture of unidentifiable products. None of the signals were consistent with product formation.

There are numerous reports on the use of 1,3-dithianes as equivalent acyl anion equivalents.[7] Reactions with common electrophiles such as alkyl, allyl and benzyl halides have been carried out. For our synthesis we required the methyl-1,3-dithiane which was prepared in two steps from acetaldehyde. Addition of the 2-lithio-1,3-dithiane to the iodide gave a mixture of two products. The first was unidentifiable by NMR(containing none of the key THF signals) and the other corresponded to the reductive elimination product, **167** (Scheme 50).

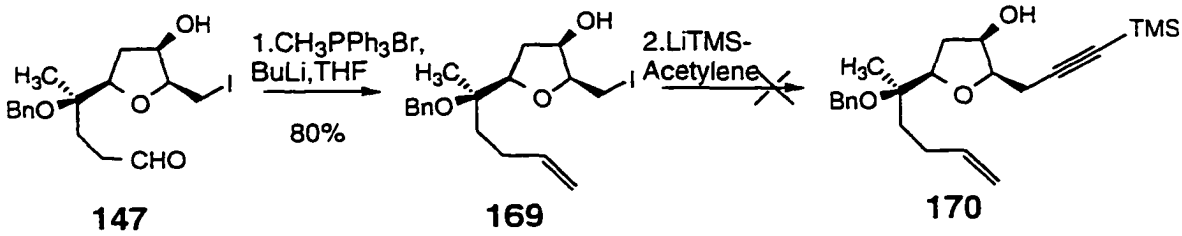
Scheme 50



The acetylide **170** would be convertible to the required methyl ketone. The aldehyde **147** was first converted to the terminal alkene. A freshly prepared batch of TMS acetylene anion was added to the iodide **169** (Scheme 51). Neither iodide displacement or

elimination occured under the reaction conditions. The starting material was recovered in high yield.

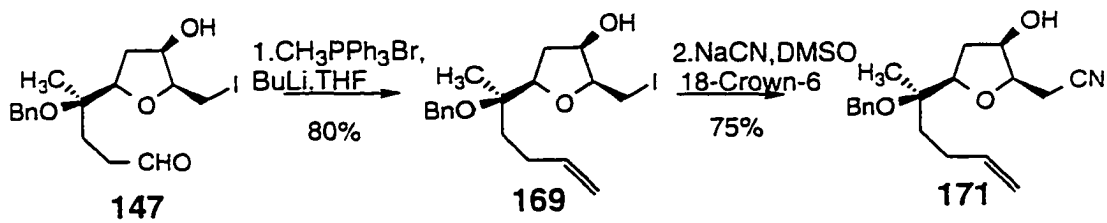
Scheme 51



147 169 170

In view of the problem with direct introduction of an acetyl anion equivalent, we examined an alternative approach via a nitrile precursor. As before the aldehyde was converted to the terminal alkene. Treatment of the iodide THF **169** with NaCN in DMSO at 50-60 ^{o}C furnished the nitrile **171** in 70% yield (Scheme 52). Two methods were attempted for conversion of CN to desired methyl ketone (i) direct nucleophillic attack using methyl anions and (ii) Nitrile hydrolysis followed by conversion to methyl ketone.

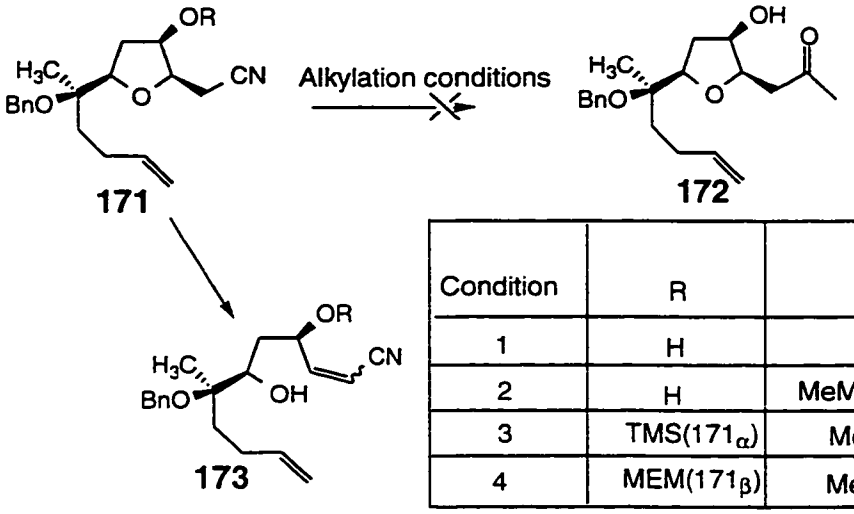
Scheme 52



147 169 171

The addition of methylithium to nitriles has been demonstrated for simple aliphatic and aromatic nitriles[9]. MeLi was added to **171** at -78 ^{o}C. NMR analysis of the crude material indicated signals for starting material as well as downfield signals in the region δ 5-6 indicative of elimination. A variation of this reaction using vinylmagnesium bromide was also attempted. These conditions have been sucessfully applied to base sensitive nitriles.[10] Only a mixture of the alkene elimination product and starting material was observed (Scheme 53). Similar results were obtained with the protected alcohols **171**α and **171**β.

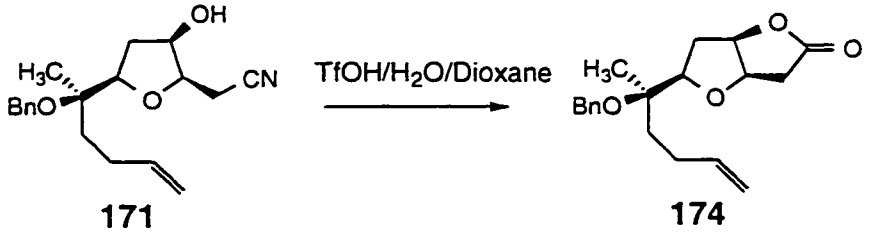
Scheme 53



Condition	R	Nu-
1	H	MeLi/THF
2	H	MeMgBr/TMSCl/THF
3	TMS(171_α)	MeLi/-78^{0}C/Et_2O
4	MEM(171_β)	MeLi/-78^{0}C/Et_2O

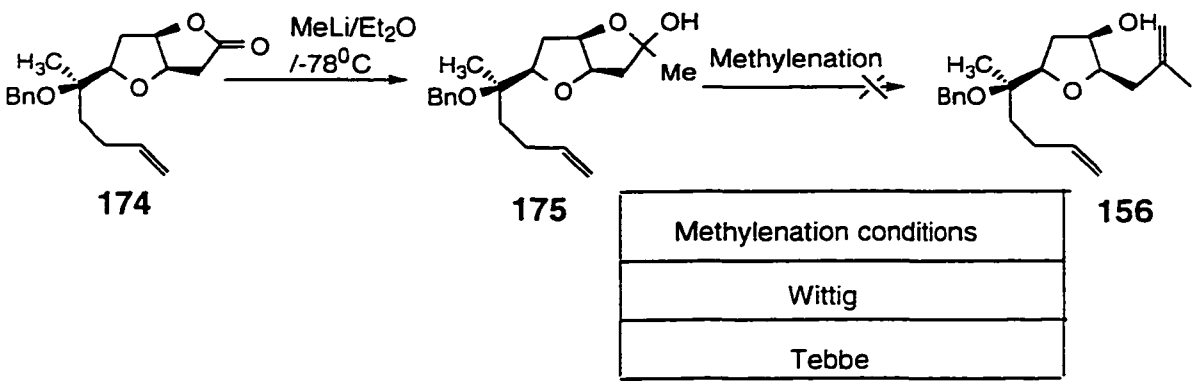
The nitrile was then subjected to acidic hydrolysis. Treatment of cyano alkene **171** with triflic acid in dioxane/H_2O afforded the lactone **174** in 70% yield (Scheme 54).[11]

Scheme 54



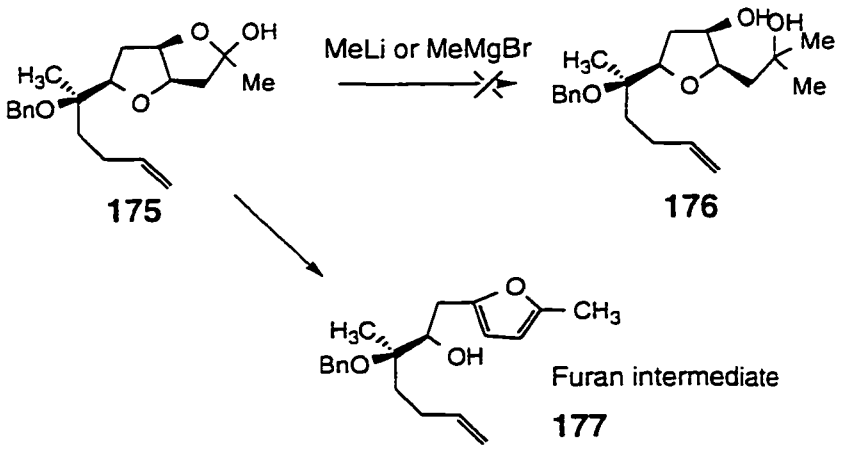
Addition of one mole of MeLi gave the lactol precursor. This is presumed to exist in equilibrium with the required methyl ketone. However, the NMR only showed evidence of the lactol. Reaction of **175** under Wittig, Tebbe,[12] and Nysted[13] conditions (Scheme 55) failed to give the desired alkene. Unidentifiable mixtures of products were obtained.

Scheme 55



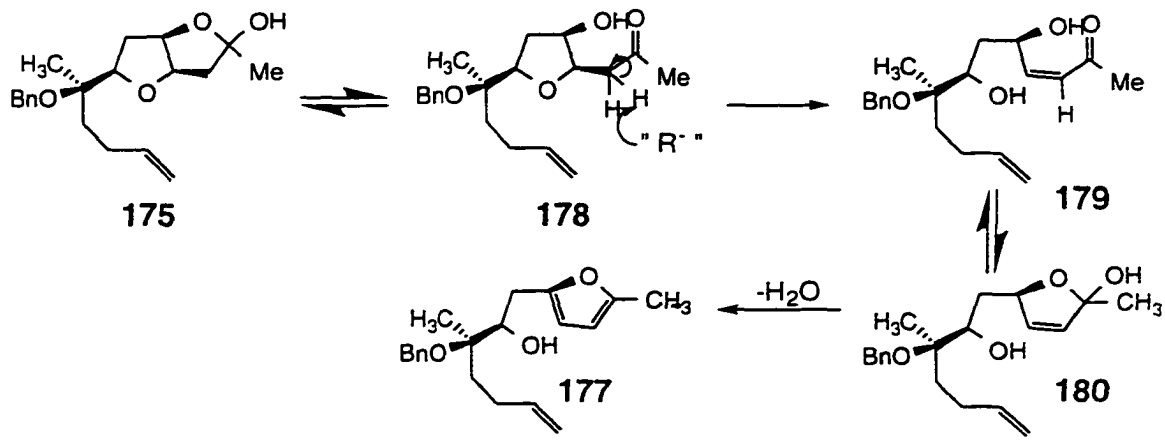
The conversion of **175** to the tertiary alcohol **176** was also attempted, since elimination of **176** could give rise to the desired alkene. Addition of MeLi or MeMgBr under various conditions were not sucessful. In all cases the furan **177** was obtained as the major product (Scheme 56).

Scheme 56



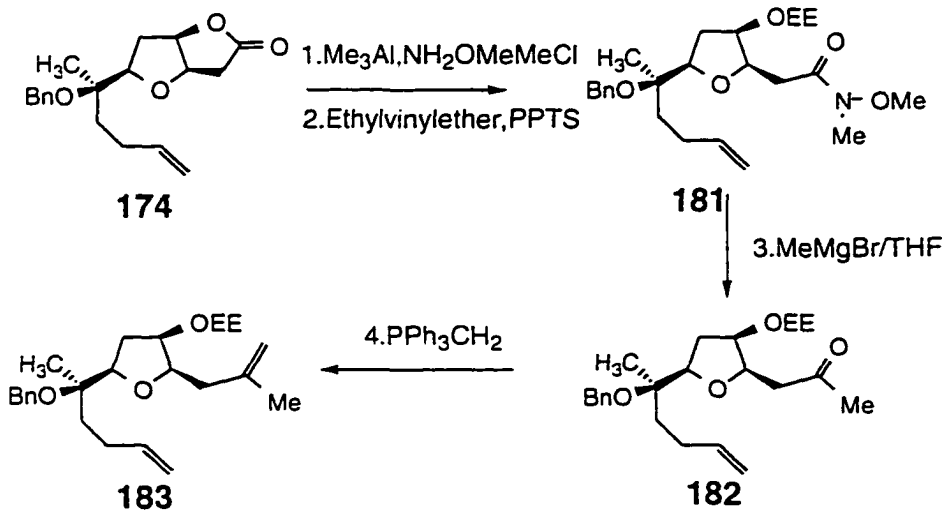
This is thought to arise by ring opening via β-elimination of the methyl ketone **178** and rearrangement with elimination of H_2O to the furan. The structure of the furan was assigned by ^1H and ^{13}C NMR and mass spectral analysis (Scheme 57).

Scheme 57



The precursor for the olefin methathesis was finally obtained through elaboration of the Weinreb amide[14] derived from lactone **174** (Scheme 58). The lactone was treated with a fresh batch of N,O-methylhydroxylamide reagent. The reaction proceeded smoothly to afford the amide in 80% yield. Protection of the free hydroxyl with ethyl vinyl ether and Grignard addition to the amide gave the methyl ketone **182**. Wittig methylenation conditions on **182** afforded the key alkene precursor **183**.

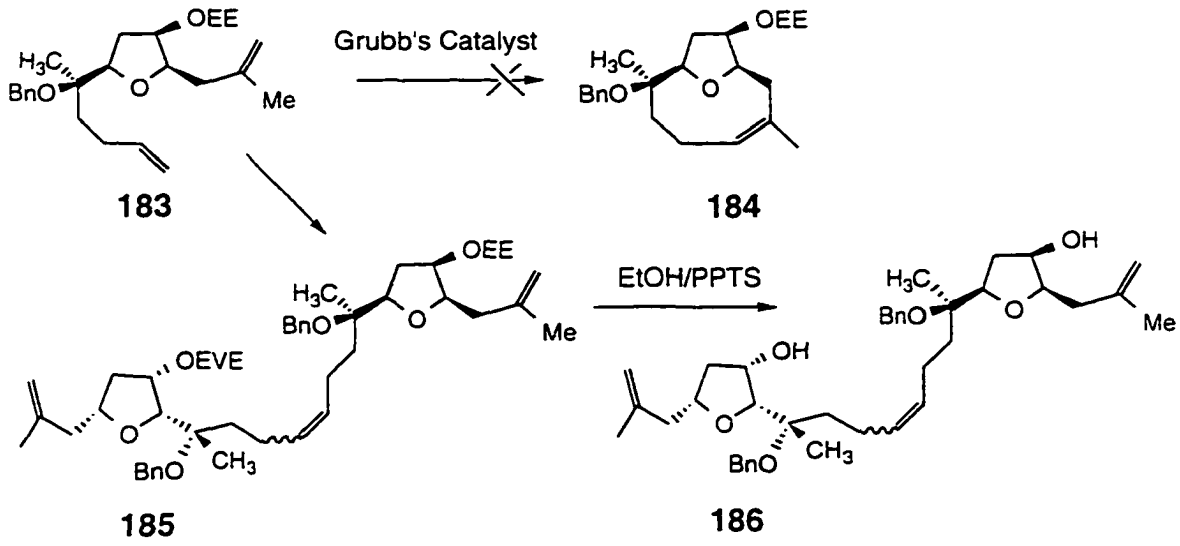
Scheme 58



Treatment of diene **183** with catalytic (0.4 eqs) Grubbs' Ruthenium catalyst[15] bis(tricyclopentylphosphine)benzylidine ruthenium dichloride in toluene at 20 °C for 12 h led to formation of a more polar product. However, NMR and mass spectral analysis of the product was consistent with the dimer **185** resulting from intermolecular methathesis (Scheme 59). The distinctive data for the dimer i.e $[M + NH_4]^+$ of 794.5 was observed.

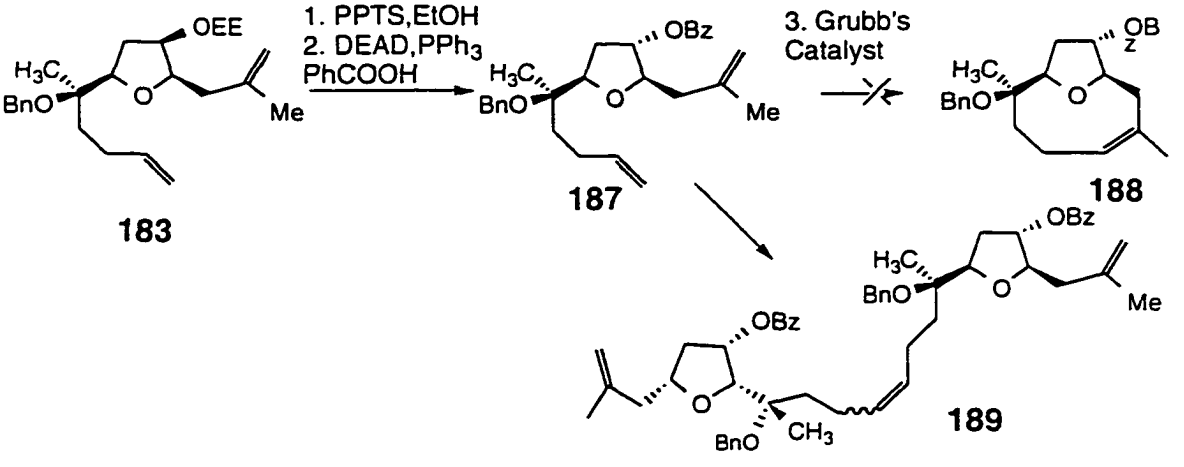
Also the disappearence of the terminal (C-2) and terminal (C-1) alkene ^1H signals and the appearence of new signals at δ 5.39 and 5.42 indicates Z/E olefin formation as a result of dimerization. The NMR analysis on the hydroxy compound was also in agreement with the structure.

Scheme 59



Examination of the model for the diene system suggests that the all syn arrangement of substituents on the THF ring might be unfavorable for thermodynamic formation of the macrocycle. The hydroxy substituent was then inverted via a Mitsunobu reaction to give the benzoate **187** of opposite configuration. Compound **187** was then treated under the Grubbs' conditions. However, the dimer was obtained as the major product (Scheme 60).

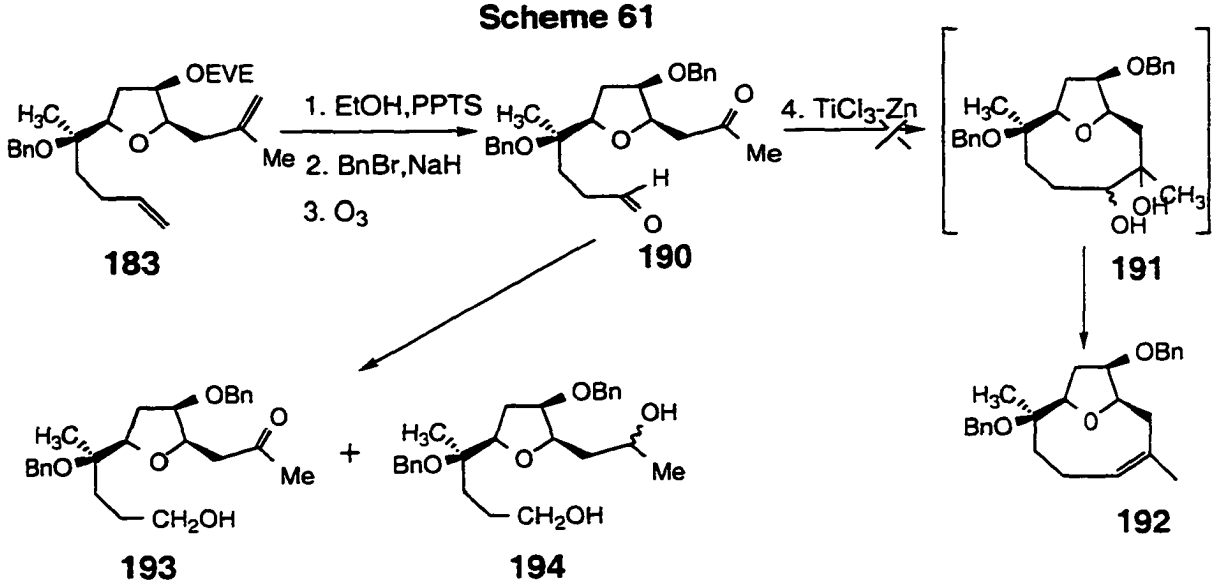
Scheme 60



(IV) McMurry coupling

Since the methathesis reaction is equilibrium controlled, we next turned our attention to a McMurry protocol, with the idea that the macrocycle might be favored under kinetic conditions. The dicarbonyl substrate was prepared by conversion of **183** to the benzyl ether derivative, followed by ozonolysis of the diene (Scheme 61). The ketoaldehyde **190** species was then treated under McMurray Ti-Zn coupling conditions.[16,17] The reaction mixture was heated until there was disapparence of starting material. Two products, the primary alcohol **193** resulting from reduction of the aldehyde and the diol **194** from reduction of both carbonyl groups were obtained. LRMS confirms both of these products.

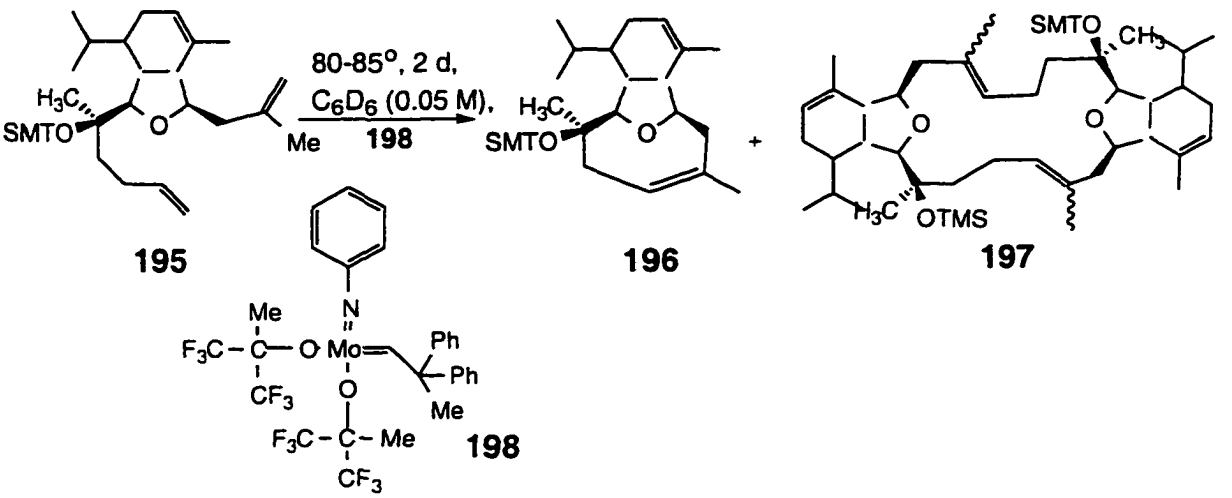
Scheme 61



(V) Summary/Conclusion

Interestingly, there has been a recent attempt[18] to close the 9 membered macrocyclic ring using the Grubb's protocol. Using the Schrock's catalyst a 8 membered ring **196** and macrocycle **197** was obtained (Scheme 62). The former is predicted to occur via a isomerization of the terminal double bond.

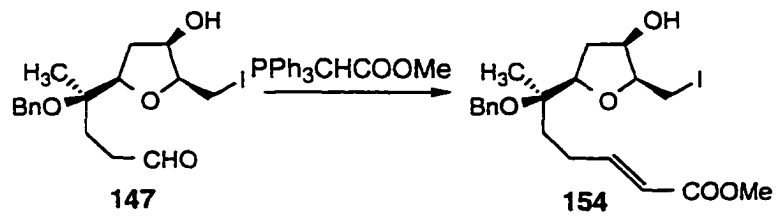
Scheme 62



Our attempts to prepare the THF macrocyclic system of the eunecellin family from the closure of the 9 membered ring on a 2,5-disubstituted THF template were unsuccessful. Bayliss-Hillman, olefin methathesis and McMurry approaches were hampered by competing intermolecular processes. This is probably a reflection of unfavorable kinetic and thermodynamic factors in the individual cyclization reactions. The evaluation of other annulation strategies such as the HWE protocol was limited by difficulty in the alkylation of the THF iodide starting material to the required cyclization precursor.

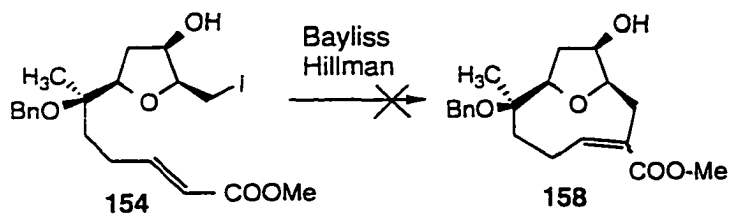
(VI) Experimental

α,β-unsaturated Ester (154)



Aldehyde **147** (200 mg, 0.480 mmol) was dissolved in CH_3CN (5 mL). Methyl(triphenylphosphoranylidene)acetate (320 mg, 0.959 mmol) was added to the solution and the reaction was heated at 60 °C for 2 h. Excess solvent was evaporated in vacuo and the crude subjected to FCC (20-40% EtOAc:PE) to furnish **154** (148 mg, 65%). Rf 0.5 (20% EtOAc/PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.81 (m, 1H), 2.05 (m, 2H), 2.30 (m, 3H), 3.18 (m, 2H), 3.68 (s, 3H), 3.84 (m, 1H), 4.03 (m, 2H), 4.44 (s, 2H), 5.83 (d, 1H, J = 15.6 Hz), 6.96 (m, 1H), 7.23 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.8, 20.6, 27.8, 34.2, 36.1, 51.5, 64.9, 71.1, 78.5, 83.4, 84.4, 121.2, 128.0, 128.1, 128.7, 128.8, 132.2, 137.9, 149.3.

Bayliss-Hillman reaction (158)



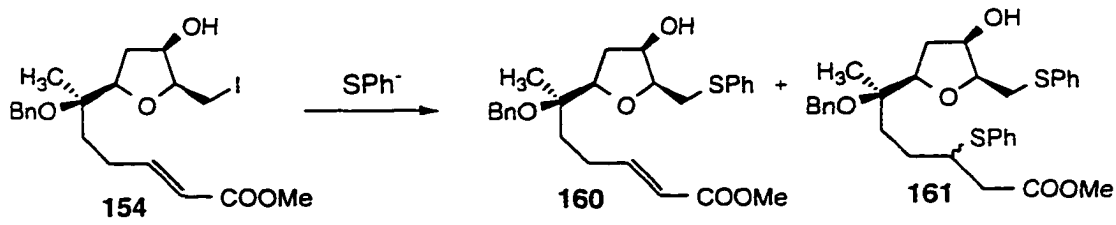
condition 1	DABCO/CH_2Cl_2
condition 2	PBu_3/THF

The ester **154** (29 mg, 0.060 mmol) was dissolved in THF (2 mL), DABCO (1.7 mg, 0.015 mmol), was added and reaction stirred for 24 hrs. EtOAc (5 mL), KF (75 mg, 1.200 mmol) was added and solvent evaporated. NMR analysis indicated that the recovered material was identical to the starting material.

The ester **154** (12 mg, 0.025 mmol) was dissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C and freshly distilled PBu_3 (5 mg, 0.025 mmol) was added and the reaction warmed

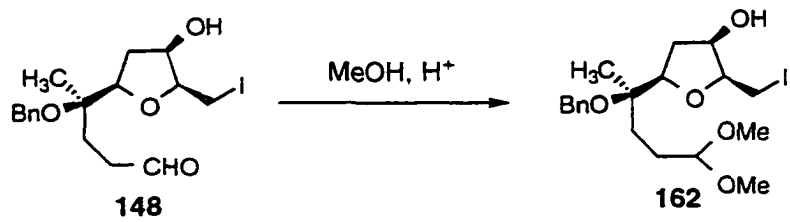
to rt and stirred for 48 h. The solvent was evaporated and NMR indicated that the recovered material was identical to the starting material.

Thiophenoxide adducts (160), (161)



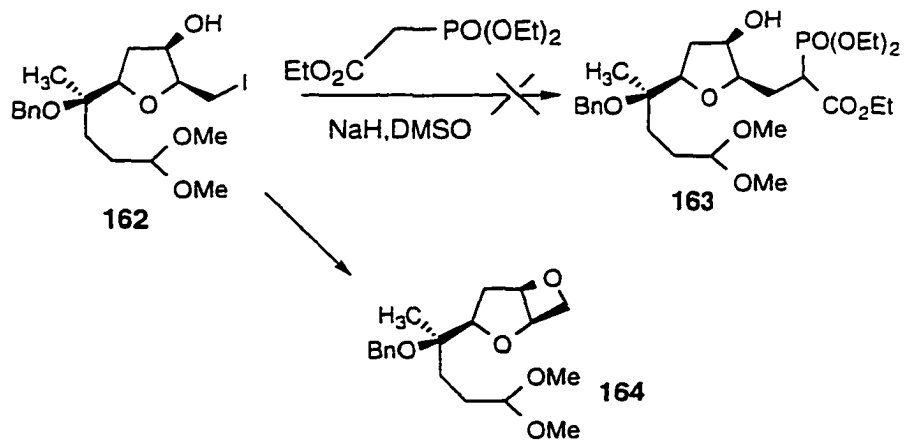
Thiophenol (0.167 g. 1.52 mmol) was dissolved in anhydrous THF (4 mL) and cooled to 0 °C. NaH (55 mg, 1.38 mmol) was added to the solution and the mixture stirred for 30 mins at 0 °C then warmed down to rt. A portion of the sodium thiophenoxide (1.5 mL etc.) was added to a solution of the ester **154** (36 mg, 0.075 mmol) in THF (1.5 mL) at 0 °C. The reaction was allowed to stir at 0 °C for 5 min, and quenched by addition to cold saturated NH_4Cl (5 mL). The mixture was extracted with Et_2O (3 x 10mL), washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL) and dried ($MgSO_4$). The organic extract was concentrated in vacuo and purified by FCC (20% - 50% EtOAc:PE), to give two compounds **160** (14 mg, 33%) Rf 0.55 (20% EtOAc : PE) and **161** (15 mg, 44%) Rf 0.50 (20% EtOAc : PE). **160** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.79 (m, 2H), 2.05 (m, 2H), 2.20 (m, 2H), 2.60 (m, 2H), 3.18 (m, 2H), 3.50 (m, 1H), 3.65 (m, 3H), 3.76 (m, 1H), 3.90 (m, 1H), 4.04 (m, 1H), 4.50 (m, 2H), 7.30 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 20.8, 29.6, 32.5, 32.8, 35.9, 40.2, 40.7, 45.9, 46.4, 52.1, 64.9, 71.4, 78.8, 82.7, 82.8, 126.1, 127.6, 128.1, 128.9, 130.0, 130.1, 133.4, 133.5. MS (CI) m/z ($M+NH_4^+$) 584, ($M+H^+$) 567, 474 (base peak). **161** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.81 (m, 1H), 2.00 (m, 1H), 2.21 (m, 2H), 2.59 (m, 1H), 3.18 (m, 2H), 3.75 (s, 3H), 3.97 (m, 1H), 4.05 (m, 1H), 4.50 (m, 2H), 5.85 (d, 1H, J = 13.9 Hz), 7.00 (m, 1H), 7.30 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 28.0, 32.5, 34.1, 36.0, 41.8, 65.1, 71.5, 78.8, 82.9, 83.2, 121.4, 125.9, 128.2, 128.9, 133.4, 138.4, 149.4. MS (CI) m/z ($M+NH_4^+$) 474, ($M+H^+$) 457, 174 (base peak).

Dimethyl acetal (162)



Aldehyde **148** (60 mg, 0.144 mmol) was dissolved in anhydrous MeOH (7 mL). HCl (1.0M in diethyl ether) was added until the pH was 2-3 and the reaction then allowed to stir for 1 h. The solution was neutralized by an addition of NaOMe/MeOH (1M). FCC (20-40% EtOAc/PE) furnished the dimethyl acetal **162** (60 mg, 90%). Rf 0.55 (20% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.80 (m, 2H), 1.91 (m, 2H), 2.20 (m, 2H), 3.27 (m, 2H), 3.36 (s, 6H), 3.79 (m,1H, D_2O exch.), 3.90 (m, 1H), 4.09 (m, 2H), 4.42 (t, 1H, J = 4.7 Hz), 4.61 (ABq, Δδ = 0.08 ppm, 1H, J = 10.3 Hz), 7.33 (m, 5H).

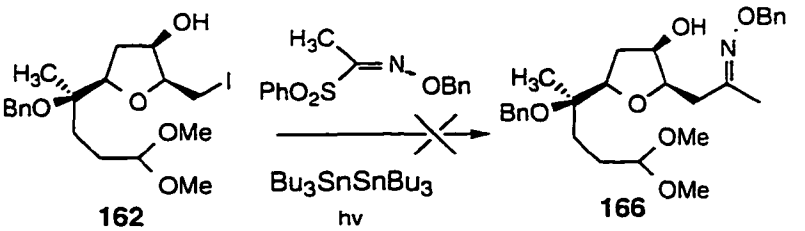
Horner Wadsworth Emmons (164)



To anhydrous DMF (2 mL) was added triethylphosphonoacetate (96 mg, 0.431 mmol), NaH (13.6 mg, 0.345 mmol) and 18-Crown-6 (4.4 mg, 0.017 mmol). The solution was stirred for 30 min at which time a solution of the iodide **162** (20 mg, 0.043 mmol), was added dropwise. The reaction mixture was heated at 50-60 °C for 24 h. The reaction was quenched by addition of H_2O (5 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL), washed with saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL) and dried ($MgSO_4$). The ether extract was concentrated in vacuo and purified by FCC (20% -

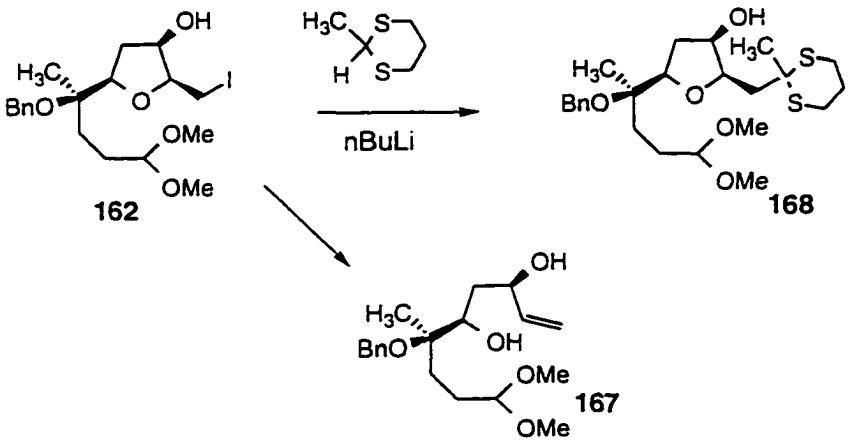
75% EtOAc:PE), to give a single product **164** (6.7 mg, 47%). Rf 0.2 (30% EtOAc:PE): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.79 (m, 4H), 2.29 (m, 2H), 3.35 (s, 6H), 4.21 (t, 1H, J = 8.3 Hz), 4.35 (m, 2H), 4.68 (m, 2H), 4.82 (m, 1H), 5.39 (m, 1H), 7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 26.8, 30.7, 37.4, 53.1, 64.9, 75.3, 77.8, 78.6, 87.0, 89.2, 105.2, 127.3, 127.5, 128.4, 140.0. MS (CI) m/z ($M+NH_4^+$) 354, 305, 200 (base peak).

Reaction of 162 with oximimo sulfone



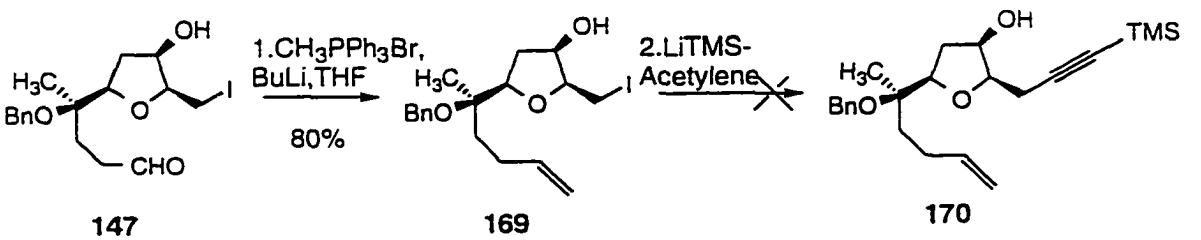
A benzene solution (0.34 mL, 0.3M in iodide) of THF iodide **162** (43 mg, 0.10 mmol), oxime (60 mg, 0.21 mmol), and hexadimethylditin (71 mg, 0.12 mmol), was degassed for 30 min. To the reaction mixture was added acetone (0.04 mL, 0.05 mmol), which was then irradiated with a photoreactor (300 nm) for 4 h. The reaction mixture was concentrated under reduced pressure. Ethyl acetate (0.5 mL), water (0.1 mL), and potassium fluoride (60 mg, 1.0 mmol), were then added and the mixture stirred at rt for 1 h. Anhydrous K_2CO_3 was added and the mixture was filtered though silica gel. The residue was purified by FCC (ethyl acetate : hexane 5-20%) to give the starting material and a mixture of unidentifiable compounds.

Reaction of 162 with Lithium methyl dithiane anion



To dithiane (144 mg, 1.07 mmol) in THF (5.4 mL) at -43 °C was added nBuLi (0.47 mL, 0.78 mmol of 1.6M soln.) slowly at a rate of 3-5 mL/min. The mixture was allowed to stir at this temperature for 1.5-2.5 h then slowly warmed to -15 °C. The mixture was then cooled to -78 °C and substrate (50 mg, 0.10 mmol) added over a 10 min period. The reaction was stirred at this temperature for 1 h, and then quenched by addition to to cold saturated aqueous NH_4CL (5 mL). The mixture was extracted with Et_2O (3 x 10mL), washed with saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL) and dried ($MgSO_4$). The ether extract was concentrated in vacuo and purified by FCC (20% - 50% EtOAc:PE), to give the iodide **162** (30 mg) and alkene **167** (10 mg, 27%). Rf 0.2 (30 EtOAc:PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 3H), 2.30-2.50 (m, 6H), 3.29 (s, 6H), 4.00 (m, 1H), 4.29 (m, 1H), 4.42 (m, 2H), 5.12 (d, 1H, J = 10.2 Hz), 5.30 (d, 1H, J = 16.7 Hz), 5.91 (m, 1H), 7.30 (m, 5H).

Reaction of 169 with Lithium-TMS-acetylene



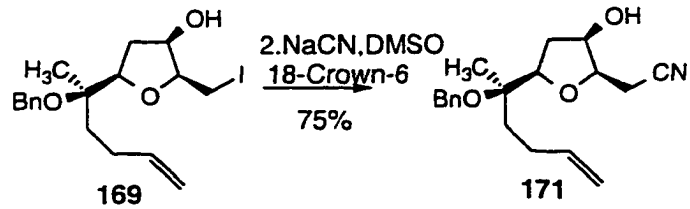
nBuLi (10.79 mmole, 1.6 M in Hexane) is added to a suspension of methyl triphenylphosphonium bromide (4.28g, 11.99mmol) in dry THF (50 mL) at 0 °C under N_2. The suspension was allowed to stir for 30 min at 0 °C then warmed up to rt (1 h).

31 mL of the clear yellow solution (5 mmol) was transferred by syringe to a flame dried R.B.F. and cooled to -78 °C. The THF iodide **147** (1.199mmol) was dissolved in THF (20mL) and transferred by cannula dropwise over 10 min. The reaction mixture was allowed to warm up 0 °C, followed by addition of Et_2O (100 mLs). The suspension was filtered through celite and excess solvent evaporated. FCC (10% - 30% EtOAc :PE) furnished a clear oil **169** (0.42g, 85%). Rf 0.8 (10% EtOAc :PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.21(s, 3H), 1.80 (m, 1H), 2.00-2.19 (m, 5H), 3.24 (m, 2H), 3.80(m, 1H, D_2O exch.), 3.96 (m, 1H), 4.07 (m, 2H), 4.51 (ABq, Δδ = 0.07ppm, 2H, J = 10.8 Hz), 5.05 (m, 2H), 5.90 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.1, 20.5, 29.4, 34.7, 35.8, 64.7, 71.1, 78.9, 83.1, 84.2, 114.6, 128.0, 128.7, 138.1, 138.9. MS (CI) m/z ($M+NH_4^+$) 434 (base peak), ($M+H^+$) 417, 289, 183.

To a flame dried 50mL RBF was added Et_2O (7.6mL). The solvent was cooled to -5 °C and nBuLi (3.94 mL, 6.3 mmol, 1.6M in Hexane) was added. To this solution was added TMS-Acetylene (0.98 mL, 6.93 mmol) and this was allowed to stir at -5 °C for 30 min, then gradually warmed up to rt.

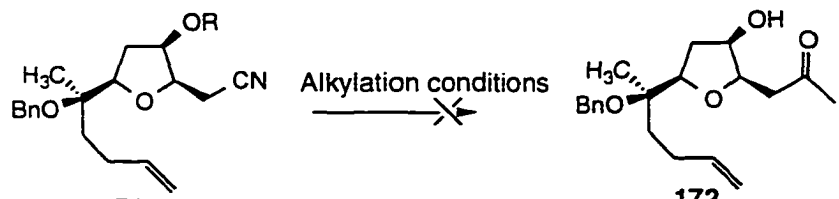
To a solution of the iodide **169** (63 mg,0.315mmol) in Et_2O (2 mL) at 0 °C, the Lithium TMS acetylene anion was added dropwise. The reaction mixture was warmed to rt and stirred for an additional 4 h. At that time the solution was poured into cold saturated aqueous NH_4Cl (15 mL). The mixture extracted with Et_2O (2 x 10mL), washed with saturated aqueous $NaHCO_3$ (30 mL), brine (30 mL) and dried ($MgSO_4$). The Et_2O extract was concentrated in vacuo and the NMR of the crude product showed only starting material **169**.

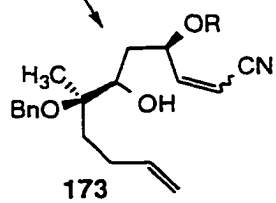
Nitrile (171)



Iodide **169** (9.5 mg, 0.023 mmol), NaCN (3.4 mg, 0.068 mmol) and 18 crown-6 (1.20 mgs, 0.005 mmol) was dissolved in DMSO (1.5mL) and then heated at 50-60 ^{o}C for 24 h. The solution was then added to cold saturated aqueous $NaHCO_3$ (5 mL). The aqueous mixture was extracted with Et_2O (3 x 20 mL), and washed with brine (5 mL) and dried ($MgSO_4$). FCC (50% EtOAc : PE) afforded nitrile **171** (5.04 mg, 70%). Rf 0.3 (50% EtOAc:PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.82 (m, 1H), 2.10 (m, 3H), 2.23 (m, 2H), 2.59 (d, 2H, J = 6.5 Hz), 3.89 (m, 1H), 3.98 (s, 2H), 4.06 (dd, 1H, J = 3.1, 6.7 Hz), 4.49 (ABq, $\Delta\delta$ = 0.08 ppm, 1H, J = 10.4 Hz), 5.00 (d, 1H, J = 10.13 Hz), 5.08 (dd, 1H, J = 1.4, 17.1 Hz), 5.86 (m, 1H), 7.32 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 20.4, 29.3, 34.6, 35.3, 64.7, 71.3, 78.8, 79.1, 82.8, 114.7, 118.2, 128.2, 128.8, 137.8, 138.7. HRMS (CI-CH_4) calc'd for $C_{19}H_{25}NO_3$ $(M+H)^+$ 316.191269, found 316.190604.

Nitrile alkylation





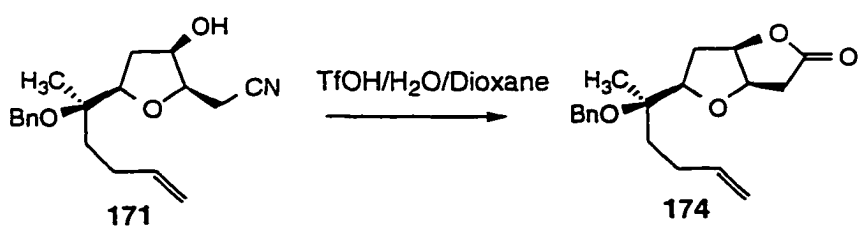
Condition	R	Nu-
1	H	MeLi/THF
2	H	MeMgBr/TMSCl/THF
3	TMS(171_a)	MeLi/-78^{0}C/Et_2O
4	MEM(171_b)	MeLi/-78^{0}C/Et_2O

Nitrile (25 mg, 0.069 mmol), was dissolved in Et_2O (3 mL), and the solution was cooled to -78 ^oC. MeLi (0.20 mL, 0.28 mmol) was added dropwise. 10 min later the reaction mixture was poured in sataurated aqueous NH_4Cl (5 mL) and the aqueous layer was extracted with Et_2O (3 x 10mL), which was washed with saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL) and dried ($MgSO_4$). The Et_2O extract was concentrated in vacuo to give an inseparable mixture of nitrile and alkene Rf 0.2 (30 EtOAc:PE).

^1H NMR analysis of crude mixture indicated signals for starting material as well as downfield signals at δ 5.75 (dd, 1H, J = 2.8, 17.5 Hz) and δ 6.79 (dd, 1H, J = 3.7, 17.5 Hz) indicative of an elimination of the a H to give an alkene.

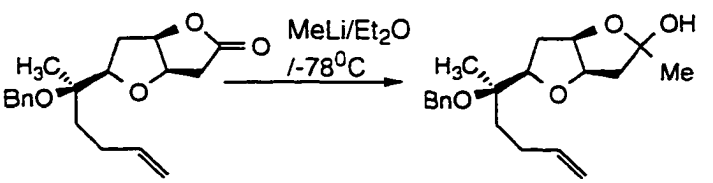
The same procedure was attempted on the silylated nitrile however only a mixture of starting material and elimination product was obtained.

Lactone (174)



Nitrile **171** (50 mg, 0.1587 mmol) was dissolved in Dioxane : water (3 mL, 18:1). Triflic acid (0.03mL, 0.317 mmoles) was added and the mixture was heated at 60-70 °C for 24 hours. The solution was added to water (10mL), extracted with ether (3 x 20 mL), the ether washed with brine (10 mL) dried ($MgSO_4$), and excess solvent evaporated. FCC (1%-10% Acetone : CH_2Cl_2) yielded the lactone **174** (35 mgs, 70%). Rf 0.5 (3% acetone:CH_2CL_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.65 (m, 2H), 2.10 (m, 3H), 2.28 (m, 1H), 2.68 (dd, 2H, J = 1.4, 4.8 Hz), 3.98 (t, 1H, J = 7.6 Hz), 4.45 (m, 3H), 4.89 (d, 1H, J = 10.2 Hz), 4.93 (m, 2H), 5.78 (m, 1H), 7.30 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 27.7, 34.1, 34.8, 36.2, 65.0, 77.4, 78.8, 84.1, 85.7, 114.7, 127.3, 127.4, 128.4, 138.8, 139.6, 175.3.

Lactol (175)



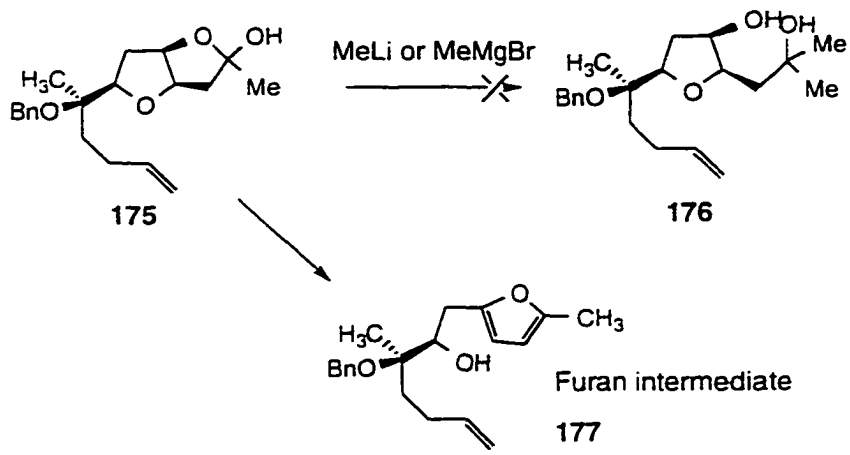
174 **175**

Lactone **175** (57 mgs, 0.180 moles) was dissolved in Et_2O (5mL) and cooled to -78 °C. MeLi (0.27 mL, 0.270 mmoles) was added dropwise over a 5-10 min period. The solution was allowed to stir at this temperature for 5 min. TLC showed complete dissappearance of starting material. The reaction was quenched by addition of Et_2O (10 mL) to saturated aqueous NH_4Cl (10 mL) solution. The aqueous layer was extracted with Et_2O (3 x 15 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL) then dried ($MgSO_4$).

TLC of "work up" material showed a ratio of 40 : 10 : 40 of (starting material : elimination product: lactol) FCC (1%- 10% Acetone:CH_2Cl_2) afforded the lactone **174** (24 mgs), alkene (4 mgs) and lactol **175** (25 mgs) RF (0.8; 0.7 ; and 0.5) respectively (4% Acetone:CH_2Cl_2).

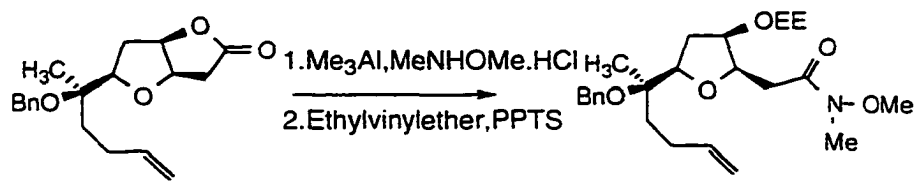
175 ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (s, 3H), 1.20 (m, 2H), 1.25 (s, 2H), 1.60-2.40 (m, 7H), 2.18 (s, 1H), 2.79 (m, 1H), 3.62 (m, 0.5H), 3.99 (m, 1.5H), 4.50 (m, 3H), 5.00 (m, 2H), 5.85 (m, 1H), 7.30 (m, 5H). MS (CI) m/z ($M+NH_4^+$) 350, 332 (base peak), 224.

Furan intermediate (177)



Lactol **175** (11 mg, 0.033 mmol), was dissolved in Et_2O (3 mL) and cooled to -78 °C. MeLi (0.07 mL, 0.068 mmol) was added dropwise and the reaction was stirred for 5 min then quenched by pouring into saturated aqueous NH_4Cl (5 mL), the aqueous layer was extracted with Et_2O (3 x 10mL), washed with saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL) and dried ($MgSO_4$). The ether extract was concentrated in vacuo and purified by FCC (20% - 50% EtOAc:PE), to give the furan product **177** (10 mg, 71%). Rf 0.80 (4% CH_2Cl_2:$(CH_3)_2CO$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.79 (m, 2H), 2.19 (m, 2H), 2.27 (s, 3H), 2.72 (m, 1H), 2.80 (m, 1H), 4.02 (m, 1H), 4.48 (s, 2H), 4.97 (d, 1H, J = 10.1 Hz), 5.04 (dd, 1H, J = 1.6, 17.1 Hz), 5.82 (m, 1H), 5.83 (s, 1H), 6.01 (d, 1H, J = 2.9 Hz), 7.3 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 18.8, 27.7, 30.9, 33.8, 63.8, 73.8, 79.5, 106.4, 107.5, 114.7, 127.6, 127.8, 128.3, 128.6, 138.8, 139.2, 151.1, 151.6. MS (CI) m/z ($M+NH_4^+$) 332 (base peak), ($M+H^+$) 315, 224, 207.

Weinreb amide (181)



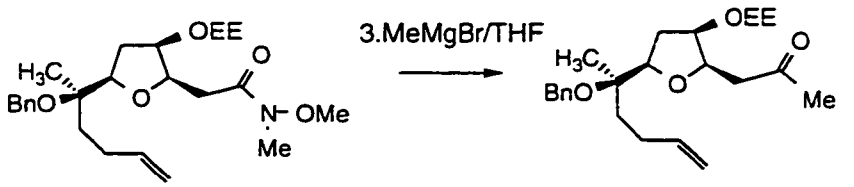
174 181

Dimethylaluminium N, O- dimethylhydroxylamide (0.40 mL of a 1.0M solution, 0.40 mmol) was added to a solution of lactone **174** (25 mg, 0.08 mmol) in dry methylene chloride (2 mL) at rt under argon atmosphere. The reaction mixture was stirred at rt for 4 h, then slowly added to saturated aqueous NH_4Cl (15 mL) at 0 °C. The mixture was then extracted with methylene chloride (4 x 10 mL), the combined organics washed with saturated aqueous $NaHCO_3$ (10 mL), dried ($NaSO_4$), filtered, and evaporated in vacuo. The crude residue was purified by FCC (10-40% EtOAc:PE) to afford the hydroxyamide (29 mg, 98%). Rf 0.1 (40% EtOAc:PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3H), 2.20 (m, 2H), 2.02 (m, 2H), 2.27 (m, 2H), 2.73 (m, 1H), 2.86 (m, 1H), 3.17 (s, 3H), 3.66 (s, 3H), 3.80 (d, 1H, J = 9.9 Hz), 3.98 (dd, 1H, J = 4.2, 9.5 Hz), 4.09 (m, 2H), 4.52 (ABq, Δδ = 0.07 ppm, 2H, J = 10.8 Hz), 4.97 (d, 1H, J = 10.1 Hz), 5.05 (dd, 1H, J = 1.6, 17.2 Hz), 5.84 (m, 1H), 7.30 (m, 5H).

A solution of hydroxyamide (30 mg, 0.08 mmol), ethyl vinyl ether (0.15 mL, 0.16 mmol), and pyridinium p-toluenesulfonate (2 mg, 0.008 mmol) in anhydrous dichloromethane (5 mL) was stirred at rt for 17 h. At this time, the reaction mixture was diluted with dichloromethane (20 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated in vacuo to give a pale yellow oil. This was purified by FCC (10-50% EtOAc:PE) to give the protected hydroxyamide **181** (24 mgs, 67%). Rf 0.30 (20% EtOAc:PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (m, 6H), 1.65 (m, 1H), 1.90 (m, 2H), 2.21 (m, 3H), 2.88 (m, 2H), 3.20 (m, 1H), 3.40 (m, 1H), 3.58 (m, 1H), 3.68 (m, 3H), 3.83 (m, 1H), 4.21 (m, 1H), 4.32 (m, 0.5H), 4.41 (m, 0.5H), 4.60 (m, 3H), 4.97 (d, 1H, J = 10.1 Hz), 5.05 (d, 1H, J = 17.2 Hz), 5.85 (m, 1H), 7.30 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 20.3, 20.6, 20.7, 27.9, 28.1, 32.4, 34.1, 34.5, 34.7, 35.7, 60.0, 60.7, 61.4, 64.9, 65.0, 74.5,

77.9, 78.5, 78.8, 83.2, 83.3, 97.6, 98.0, 101.2, 114.3, 127.1, 127.4, 127.6, 128.3, 139.3, 140.0, 197.1.

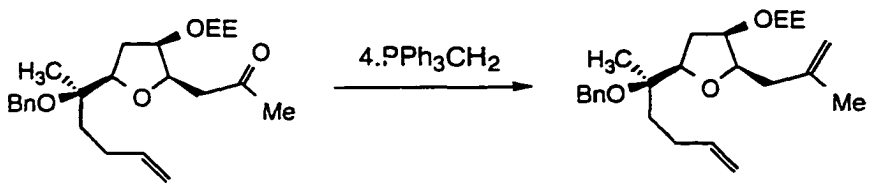
Methyl ketone (182)



181 **182**

Protected amide **181** (24 mg, 0.053 mmol) was dissolved in anhydrous THF (2 mL). The mixture was placed under Argon and cooled to 0 °C. Methylmagnesium bromide (0.05 mL, 0.16 mmol) was added and the reaction allowed to proceed for 10 minutes then diluted with Et_2O (10 mL) and poured into saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL) and the organic were combined, then washed with saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL) then concentrated in vacuo. FCC (EtOAc : PE 10-20%) gave the ketone **182** (15 mg, 85%). Rf 0.8 (10% EtOAc:PE). ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (m, 9H), 1.65 (m, 2H), 1.81 (m, 1H), 1.96 (m, 1H), 2.20 (m, 5H), 2.82 (m, 2H), 3.40 (m, 1H), 3.52 (m, 1H), 4.17 (m, 1H), 4.26 (m, 0.5H), 4.38 (m, 0.5H), 4.60 (m, 3H), 4.94 (d, 1H, J = 10.2 Hz), 5.02 (d, 1H, J = 15.6 Hz), 5.84 (m, 1H), 7.30 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.5, 20.2, 20.4, 20.5, 28.0, 30.9, 31.0, 33.6, 34.6, 34.8, 35.1, 43.7, 44.0, 60.2, 60.6, 65.0, 74.3, 76.5, 77.3, 77.4, 78.0, 83.1, 83.3, 98.1, 100.8, 114.3, 127.1, 127.4, 127.5, 128.3, 139.2, 140.2, 207.6.

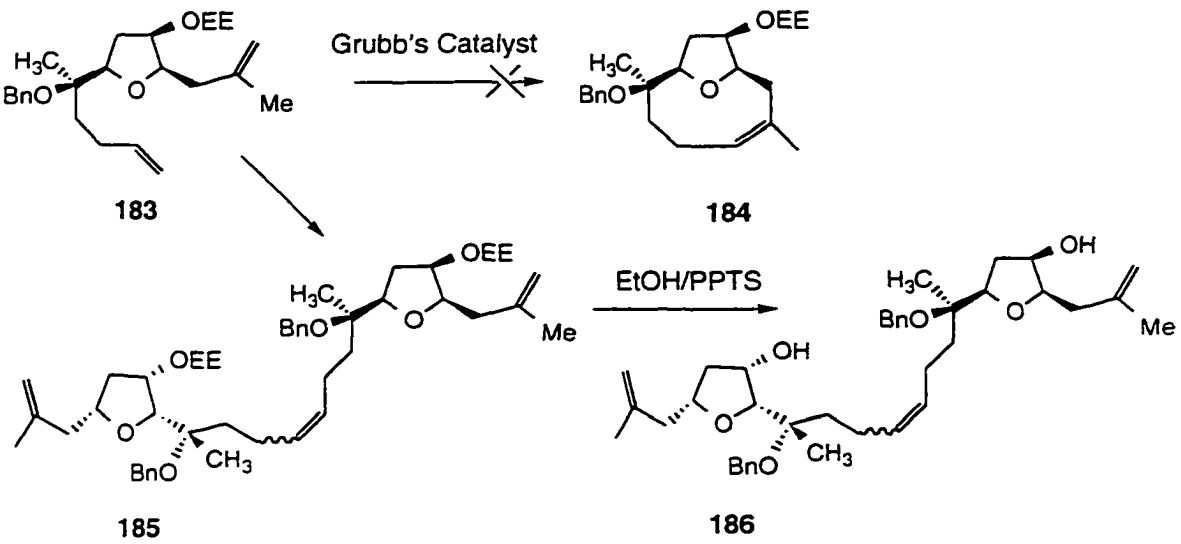
Diene (183)



182 **183**

nBuLi (0.75 mmole, 1.6 M in Hexane) was added to a suspension of methyl triphenylphosphorium bromide (0.313 g, 0.88 mmol) in dry THF (5 mL) at 0 °C under N_2. The suspension was allowed to stir for 30 min at 0 °C then warmed up to rt (1h). 1.62 mL of this clear yellow solution (0.31 mmol) was transferred by syringe to a flame dried R.B.F. and cooled to -78 °C . The ketone **182** (17 mg, 0.04 mmol) was dissolved in THF (2mL) and transferred by cannula dropwise over 10 min. The reaction mixture was allowed to warm up 0 °C, at which time, Et_2O (20 mLs) was added. The suspension was filtered through celite and excess solvent evaporated. FCC (10%-30% EtOAc:PE) furnished the diene **183** (15 mg, 85%). Rf 0.8 (10% EtOAc:PE); ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (m, 9H), 1.60 (m, 1H), 1.72 (m, 3H), 1.80 (m, 1h), 2.10 (m, 3H), 2.30 (m, 1H), 3.39 (m, 1H), 3.48 (m, 1H), 3.71 (m, 2H), 4.10 (m, 0.5H), 4.22 (m, 1H), 4.50 (m, 1H), 4.62 (m, 4H), 4.85 (d, 1H, J = 10.2 Hz), 4.94 (dd, 1H, J = 1.5, 15.6 Hz), 5.76 (m, 1H), 7.30 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.5, 20.2, 20.3, 20.4, 20.5, 23.5, 28.0, 29.9, 33.8, 34.9, 35.0, 35.7, 37.3, 37.4, 59.7, 60.0, 65.1, 65.2, 74.7, 76.6, 77.4, 77.5, 80.9, 81.1, 83.4, 97.7, 100.5, 111.3, 111.3, 114.2, 127.0, 127.4, 127.6, 128.3, 139.5, 140.6, 143.8, 144.1. MS (ES) m/z ($M+NH_4^+$) 425, ($M+Na^+$) 420, 249 (base peak).

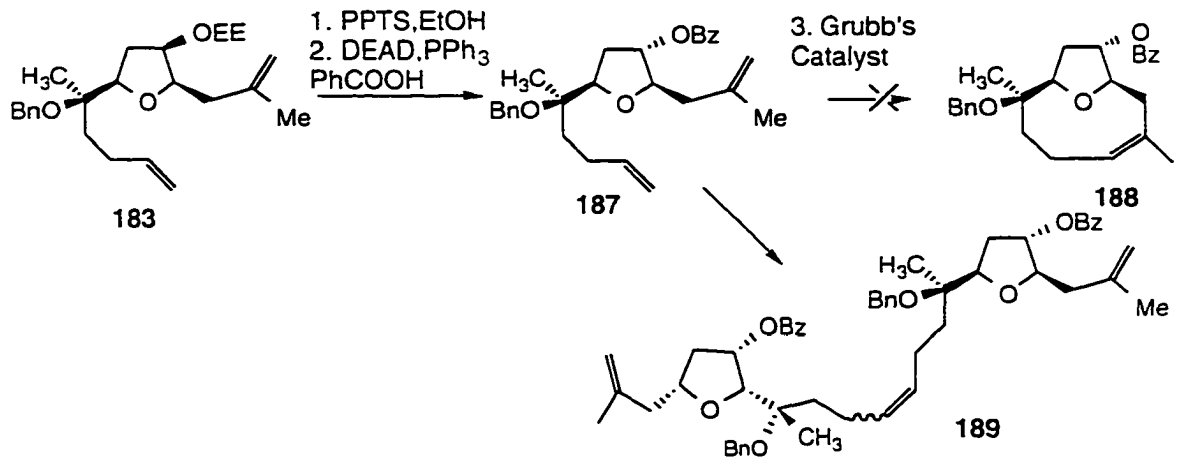
Grubb's cyclization I



The diene **183** (15 mg, 0.037 mmol) dissolved in anhydrous benzene (1.0 mL) was added to a homogeneous orange-red solution of Bis(tricyclopentylphosphine)benzylidine ruthenium dichloride (11.45 mg, 0.015 mmol) in anhydrous benzene (1.5 mL) under N_2. The resulting mixture was stirred at 20 °C for 12 h, at which time TLC showed formation of new material. The reaction mixture was quenched by exposure to air for 1 h then excess solvent evaporated in vacuo. The black residue was purified by FCC (5-20% EtOAc:PE) to give the diene **183** (5 mg) and the dimer **185** (5 mg, 17.3%). Rf 0.3 (5% EtOAc:PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.2 (m, 16H), 1.6 - 2.4 (m, 24 H), 3.50 (m, 2H), 3.8 (m, 2H), 4.27 (m, 4H), 5.39 (m, 1H), 5.45 (m, 1H), 7.3 (m, 10H). MS (ES) m/z ($M+Na^+$) 799, ($M+NH_4^+$) 794 (base peak).

The dimer **185** (5 mg, 0.006 mmol) was dissolved in EtOH (5 mL), and PPTS (15 mg, 0.0006 mmol) added. The reaction stirred for 30 min and quenched by addition of NaOMe (1M) until the pH is 7. The solvent then evaporated in vacuo followed by FCC (5-20% EtOAC:PE) to yield **186** (3 mg, 79%). Rf 0.5 (10% EtOAc:PE), ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (m, 8H), 1.80 (m, 6H), 2.01 - 2.40 (m, 14H), 3.52 (m, 2H), 3.70 (m, 2H), 3.98 (m, 4H), 4.79 (m, 4H), 5.22 (m, 1H), 5.29 (m, 1H), 7.30 (m, 10H).

Grubb's cyclization II



Benzoate (187)

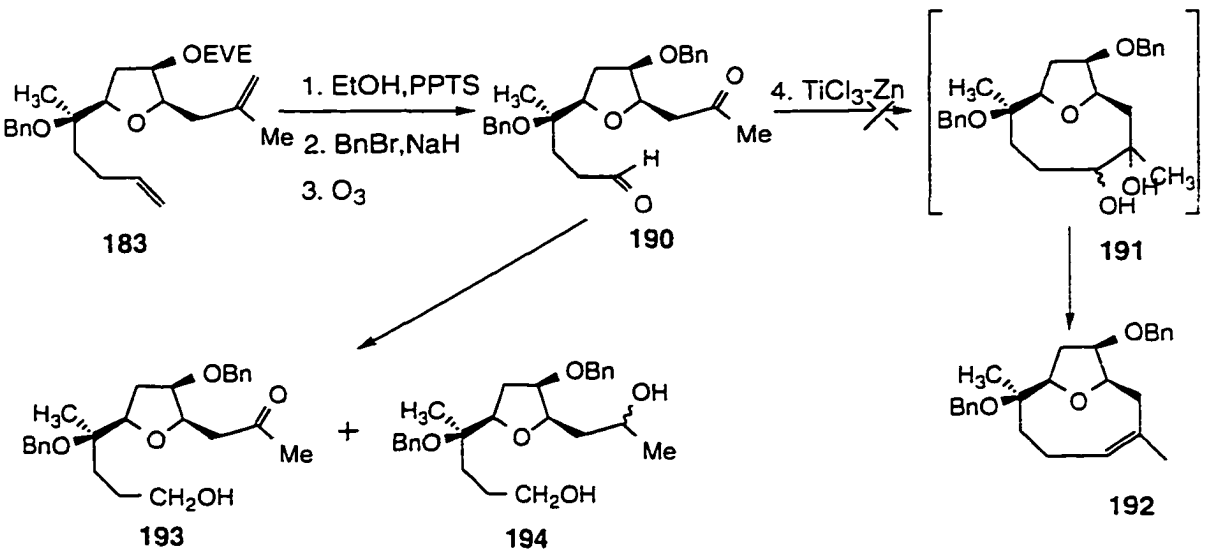
A solution of the alcohol **183 (OH)** (12 mg, 0.037 mmol) and PPh_3 (86 mg, 0.33 mmol) in toluene (1 mL) at -15 °C was treated with 2 mls of a THF solution of DEAD (0.06 mL, 0.36 mmol) and benzoic acid (44.6 mg, 0.36 mmol). The solution was allowed to warm up to rt. The solvent was then evaporated and FCC (5-10% EtOAC : PE) furnished the benzoate **187** (12 mg, 76%) Rf 0.8 (5% EtOAc:PE): ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.69 (m, 2H), 1.73 (s, 3H), 1.98 (m, 1H), 2.20 (m, 5H), 4.19 (m, 2H), 4.56 (ABq, Δδ = 0.06 ppm, 2H, J = 11.7 Hz), 4.73 (d, 2H, J = 8.7 Hz), 4.89 (d, 1H, J = 10.2 Hz), 4.98 (dd, 1H, J = 1.5, 17.1 Hz), 5.15 (m, 1H), 5.80 (m, 1H), 7.30 (m, 5H), 7.43 (m, 2H), 7.55 (m, 1H), 8.00 (d, 2H, J = 7.3 Hz).

The diene **187** (8 mg, 0.018 mmol) dissolved in anhydrous benzene (0.75 mL) was added to a homogeneous orange-red solution of Bis(tricyclopentylphosphine)benzylidine ruthenium dichloride (2.7 mg, 0.004 mmol) in 1.0 mL dry benzene under N_2. The resulting mixture was stirred at 20 °C for 12 h, at which time TLC showed formation of new material. The reaction mixture was then warmed for 1 h at 35 °C then quenched by exposure to air for 1 h, then excess solvent evaporated in vacuo. The black residue was purified by FCC (10-30% EtOAc:PE) to give the diene

187 (2 mg) and the dimer **189** (6 mg, 51.7%). Rf 0.6 (20% EtOAc:PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.2 (m, 6H), 1.62 (m, 4H), 1.77 (s, 6H), 1.77 (s, 6H), 2.0-2.4 (m, 6H), 4.24 (m, 4H), 4.61 (m, 4H), 4.79 (m, 4H), 5.21 (m, 2H), 5.39 (m, 1H), 5.45 (m, 1H), 7.2-7.4 (m, 20H), 8.05 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 21.7, 23.1, 26.9, 29.9, 33.6, 33.7, 36.2, 42.6, 65.1, 77.4, 77.5, 78.2, 79.1, 82.8, 84.4, 112.9, 127.2, 127.3, 127.4, 128.4, 128.6, 129.9, 130.0, 130.1, 130.2, 130.4, 130.5, 133.3, 140.3, 166.3.

McMurry

Ketoaldehyde (190)



The alcohol (26 mg , 0.08 mmol) prepared via hydrolysis of Ethyl vinyl ether **183** was dissolved in DMF (3 mL) and solution was cooled to 0 °C and NaH (12.6 mg, 0.3 mmol) was added. The solution was allowed to stir for 5 min and Bu_4NI (2.9 mg, 0.008 mmol) followed by BnBr (0.04mL, 0.3 mmol) was added and the reaction mixture was allowed to stir for 30 min. The reaction was quenched by dropwise addition of MeOH (0.5 mL), then water (15 mL) and the aqueous layer extracted with Et_2O (3 x 15 mL). The ether extract was washed with saturated aqueous $NaHCO_3$ (5 mL), NaCl (5 mL) and excess solvent was evaporated to give benzylated product (29.8 mg, 90%); Rf 0.6 (5% EtOAc

:PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.60 (m, 1H), 1.72 (s, 3H), 1.79 (m, 1H), 2.10 (m, 4H), 2.41 (m, 2H), 3.78 (m, 2H), 3.93 (m, 1H), 4.36 (ABq, Δδ = 0.20 ppm, 2H, J = 10.9 Hz), 4.55 (ABq, Δδ = 0.18 ppm, 2H, J = 11.6 Hz), 4.71 (s, 2H), 4.85 (d, 1H, J=10.1 Hz), 4.94 (dd, 1H, J = 1.7, 17.1 Hz), 5.76 (m, 1H), 7.21 (m, 10H).

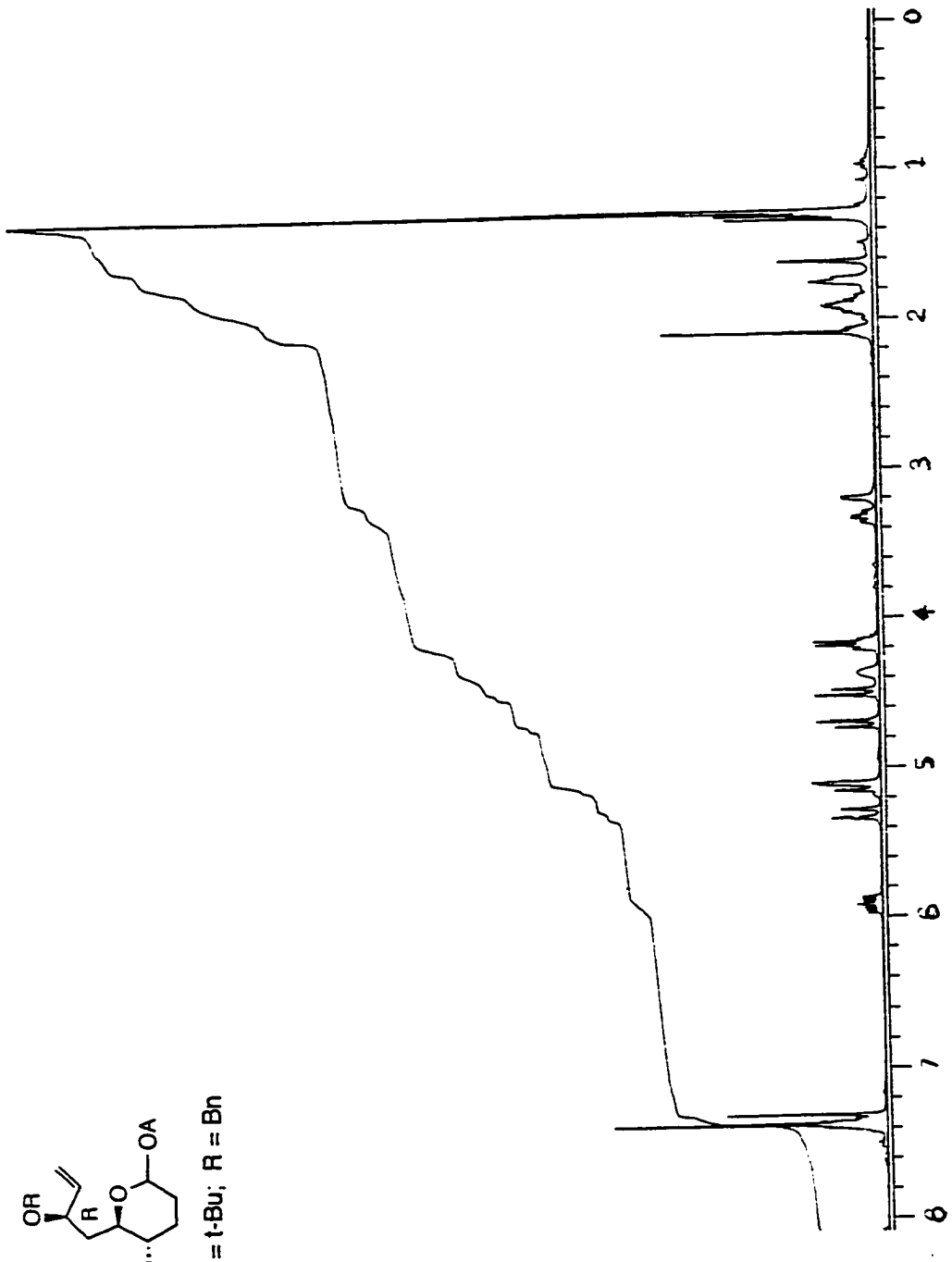
The protected alkene (29.8 mg, 0.07 mmol) was dissolved in CH_2Cl_2 : MeOH (5mL, 4:1). The solution was cooled to -78 °C and O_3 bubbed through for 10 min. N_2 was then bubbled through the solution for 10 min to remove any traces of O_3. PPh_3 (75 mgs, 0.29 mmol) was added and the reaction stirred for 2 h at rt. The solvent was then evaporated under vacuo and purified by FCC (5-20%; EtOAc : PE) to furnish ketoaldehyde **190** (17 mgs, 57%) Rf 0.2 (10 % EtOAc : PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.90 (m, 1H), 2.00-2.20 (m, 3H), 2.10 (s, 3H), 2.56 (t, 2H, J = 7.6 Hz), 2.86 (m, 2H), 3.87 (t, 1H, J = 7.9 Hz), 4.23 (m, 2H), 4.43 (ABq, Δδ = 0.04 ppm, 2H, J = 2.3 Hz), 7.27 (m, 10H), 9.72 (s, 1H).

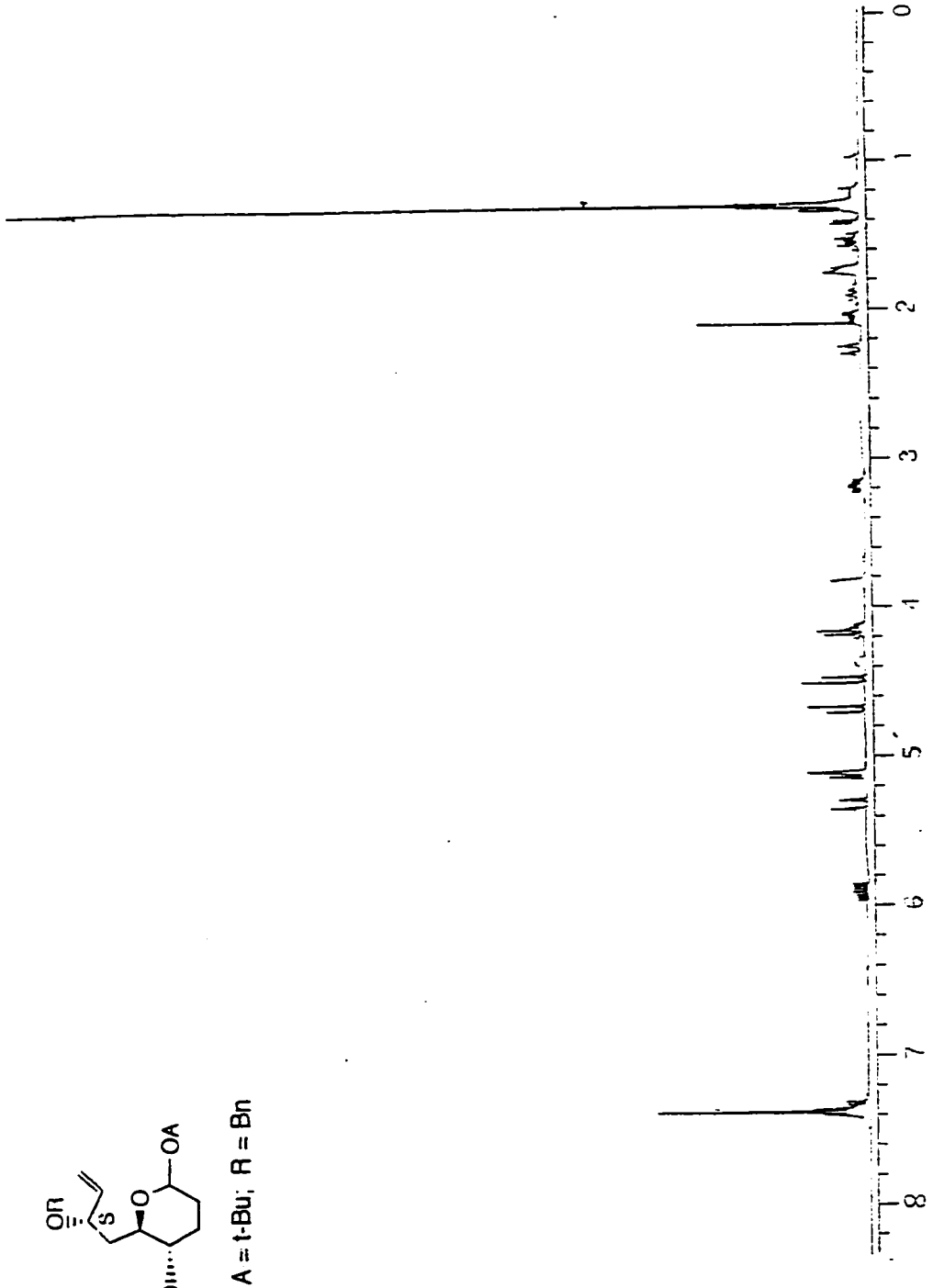
$TiCl_3$-Zn coupling.

A 50 mL three-necked flask fitted with a reflux condenser was charged with dry THF (10 mL) and cooled to -78 °C. $TiCl_4$ (0.08mL,0.40 mmol) was then added slowly, followed by zinc powder (106 mg, 0.81 mmol) and dry pyridine (0.02 mL). The resultant black mixture was refluxed under N_2 for 1 hr and a solution of ketoaldehyde **190** in dry THF (6 mL) was then added dropwise to the stirred mixture over 24 h. After reflux for 6 h, the reaction mixture was ice cooled and quenched (10% aqueous K_2CO_3). The grey precipitate was filtered off and both filter-cake and filtrate were extracted thoroughly with dichloromethane (3 x 10 mL). The combined organic phases were washed with water (5 mL), dried ($MgSO_4$) and the solvent evaporated to give a solid. FCC (50-80% EtOAc:PE) yielded **193** (2 mg, 11.6%) and **194** (1.5 mg, 8.7%) Rf 0.4 and 0.2 (50% EtOAc:PE) respectively. **193** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.69 (m, 4H), 2.05 (m, 1H), 2.12 (s, 3H), 2.20 (m, 1H), 2.89 (m, 2H), 3.64 (m, 2H), 3.91 (t, 1H, J = 8.9 Hz), 4.17 (m, 2H), 4.39 (ABq, Δδ = 0.21 ppm, 2H, J = 11.6 Hz), 4.60 (ABq, Δδ = 0.12 ppm, 2H, J = 11.4 Hz), 7.30 (m, 10H). MS (ES) m/z ($M+Na^+$) 449 (base peak). **194** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (m, 6H), 1.60-2.20 (m, 8H), 3.64 (m, 2H), 3.90 (m, 2H), 4.08 (m, 2H), 5.46 (ABq, Δδ = 0.18 ppm, 2H, 11.9 Hz), 4.62 (ABq, Δδ =

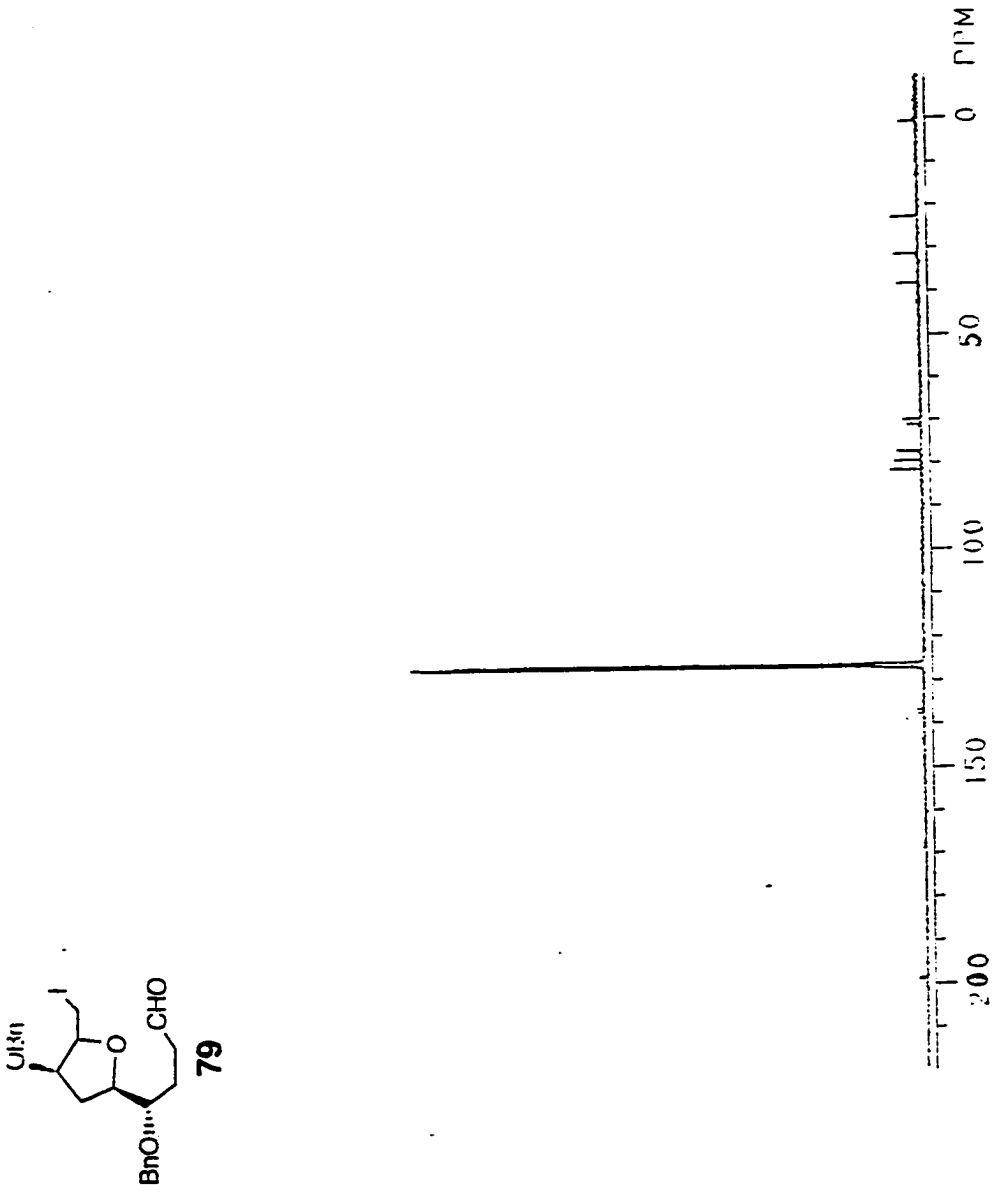
0.11 ppm, 2H, J = 12.0 Hz), 7.30 (m, 10H). MS (ES) m/z ($M+Na^+$) 451 (base peak), ($M+H^+$) 429.

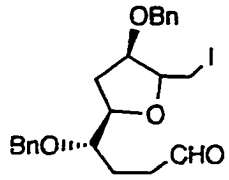
(VII) Appendix



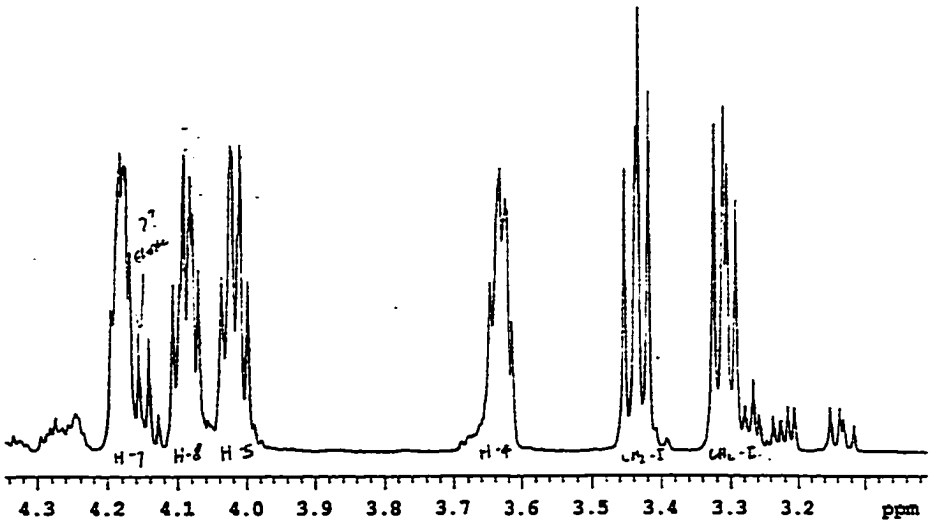


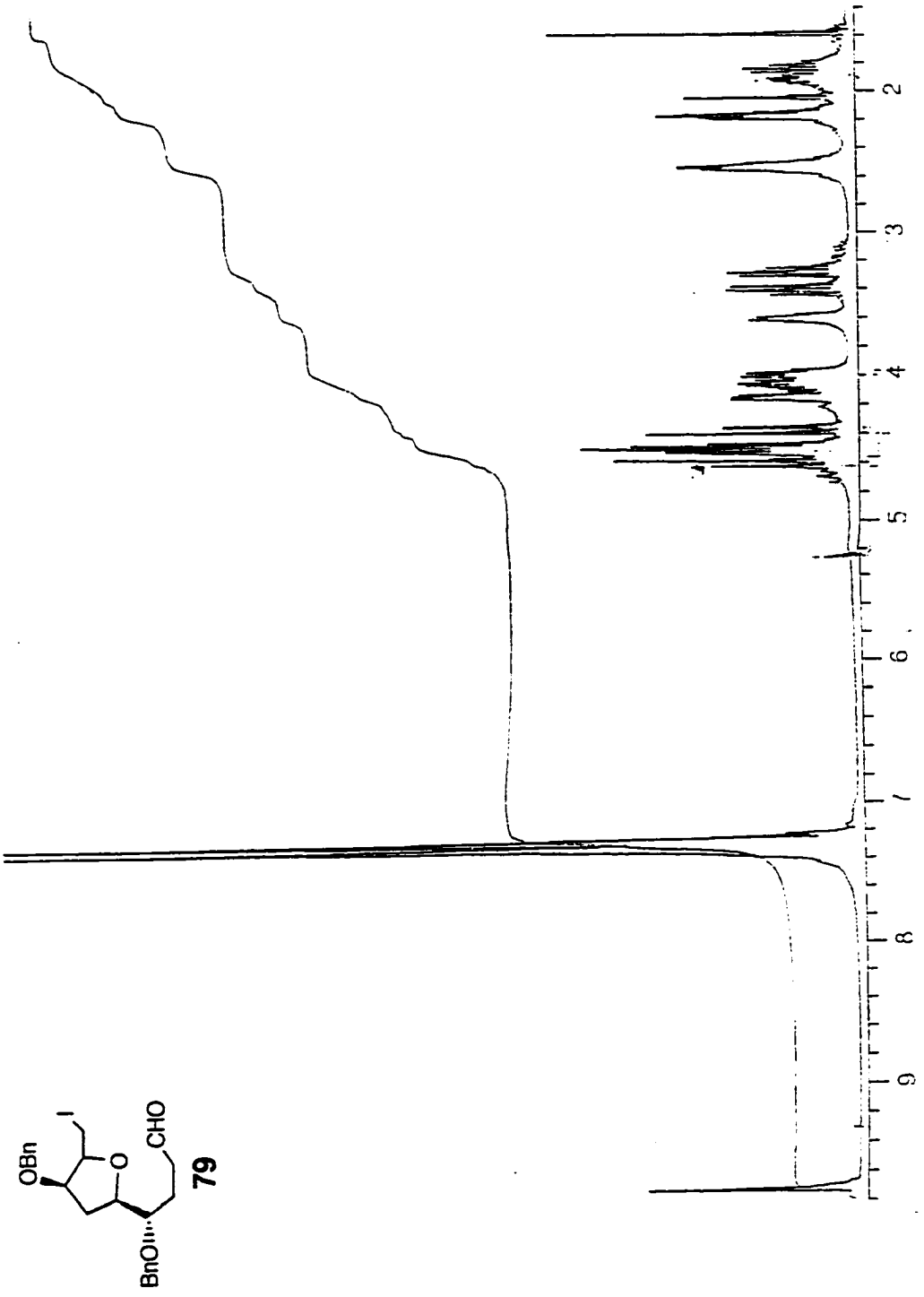
77 A = t-Bu; R = Bn

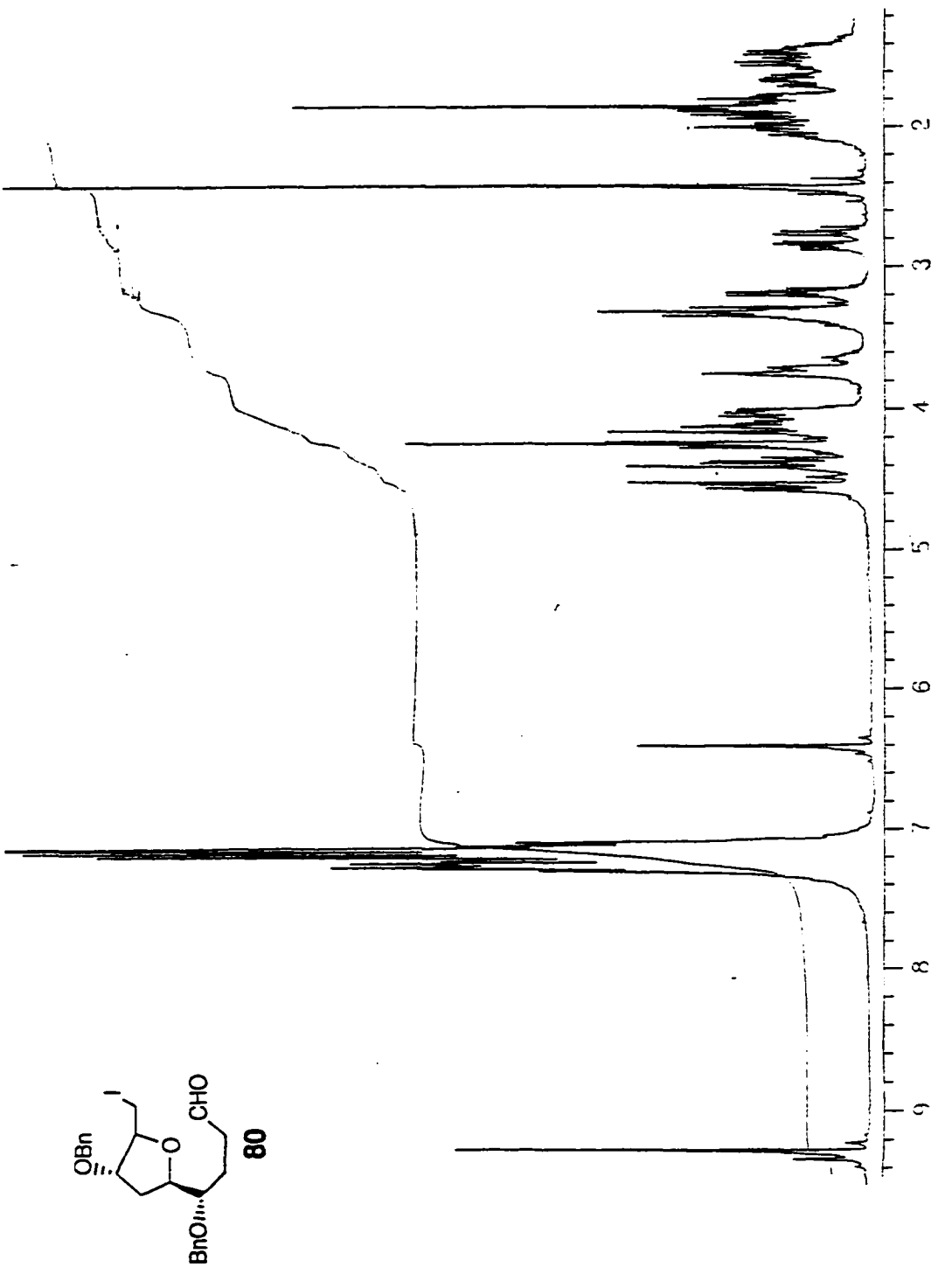


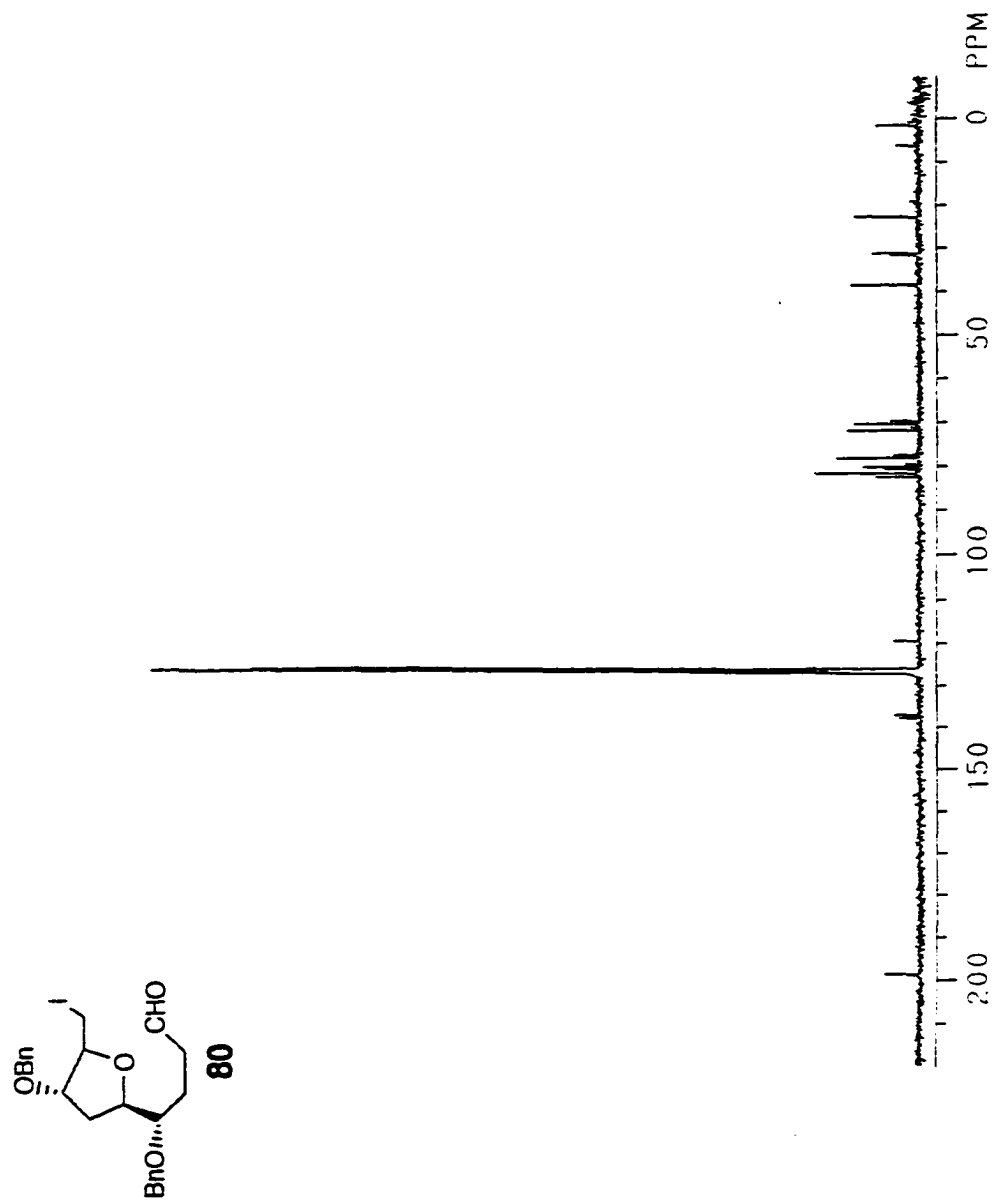


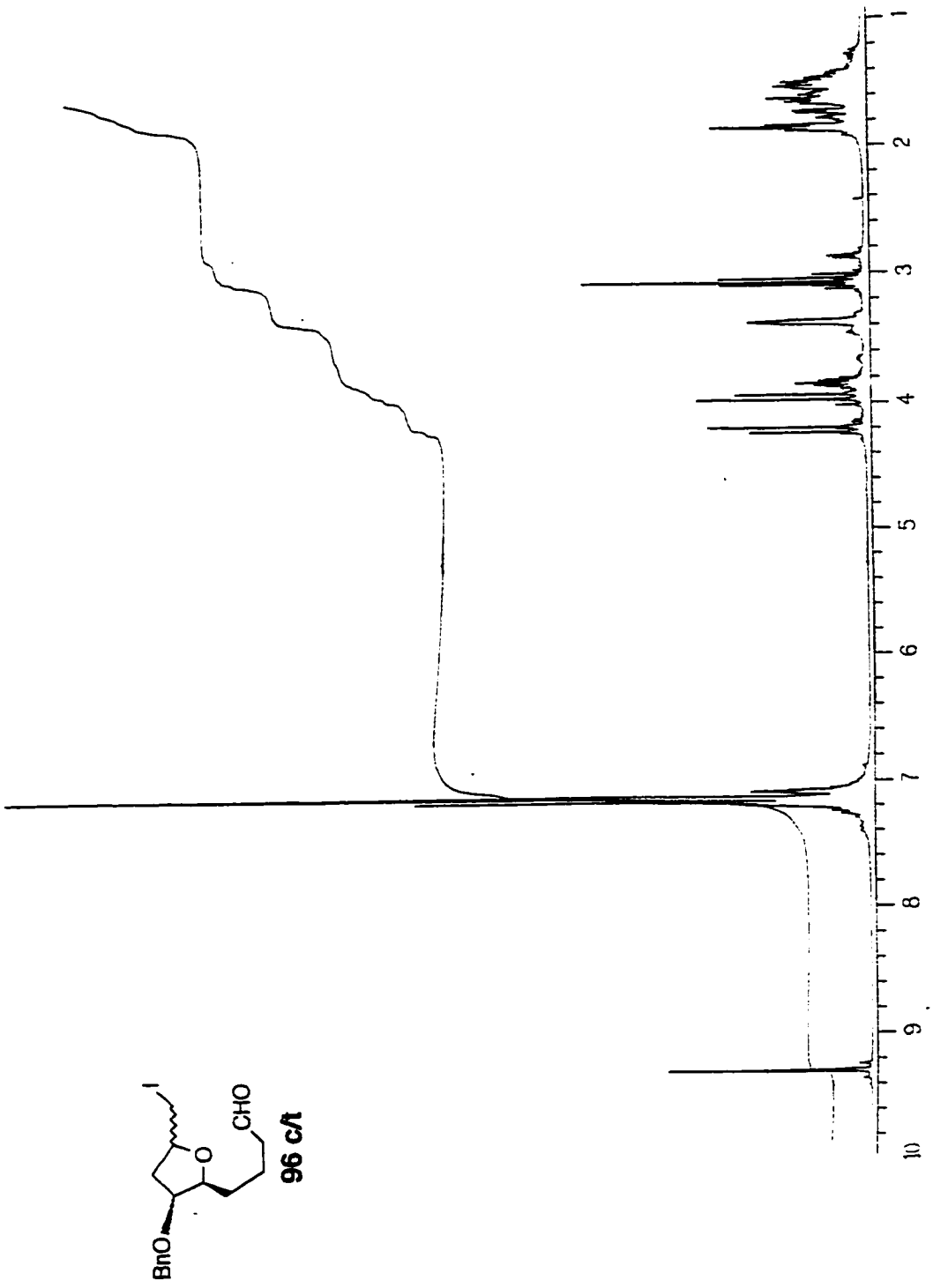
79

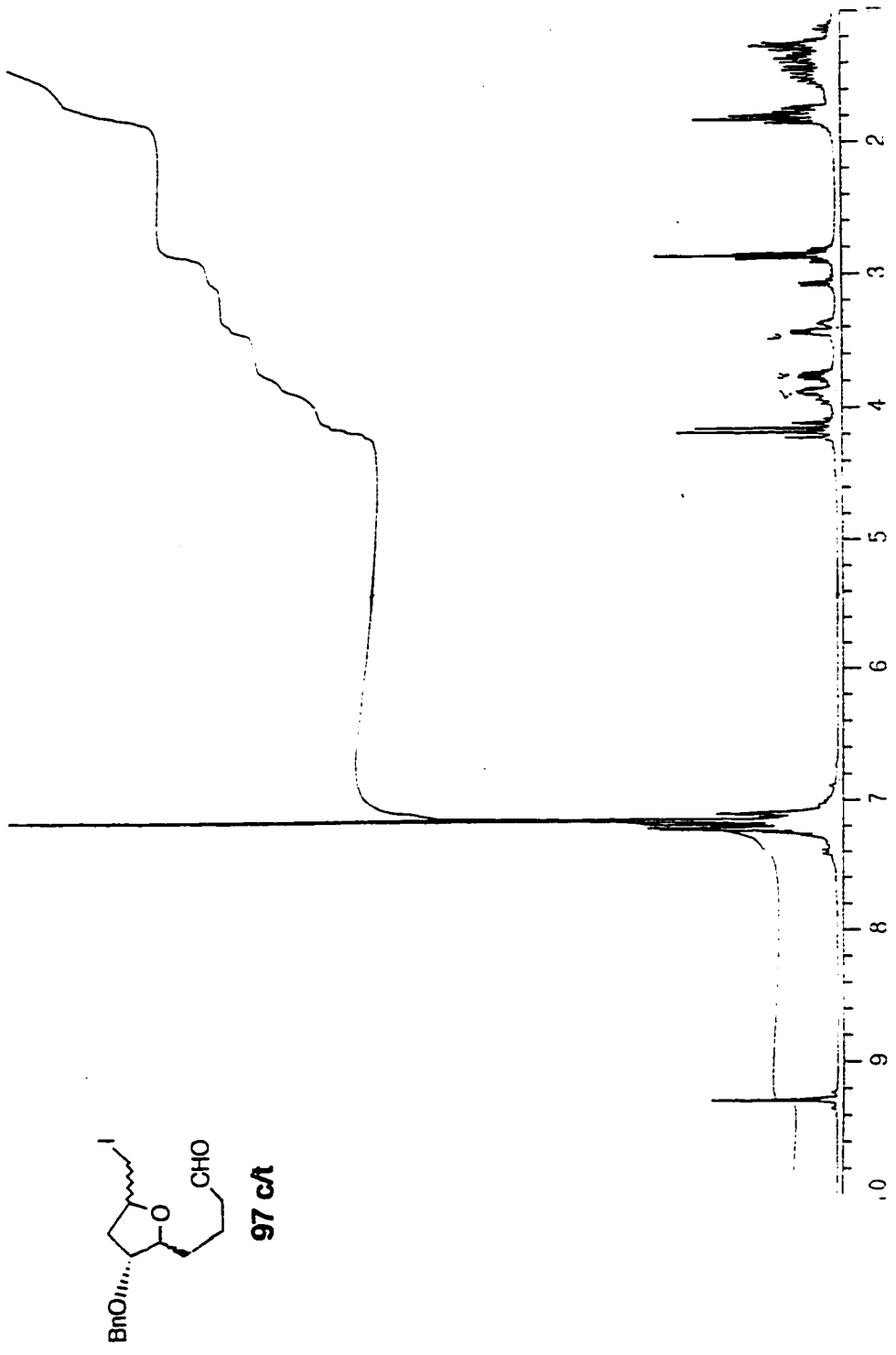


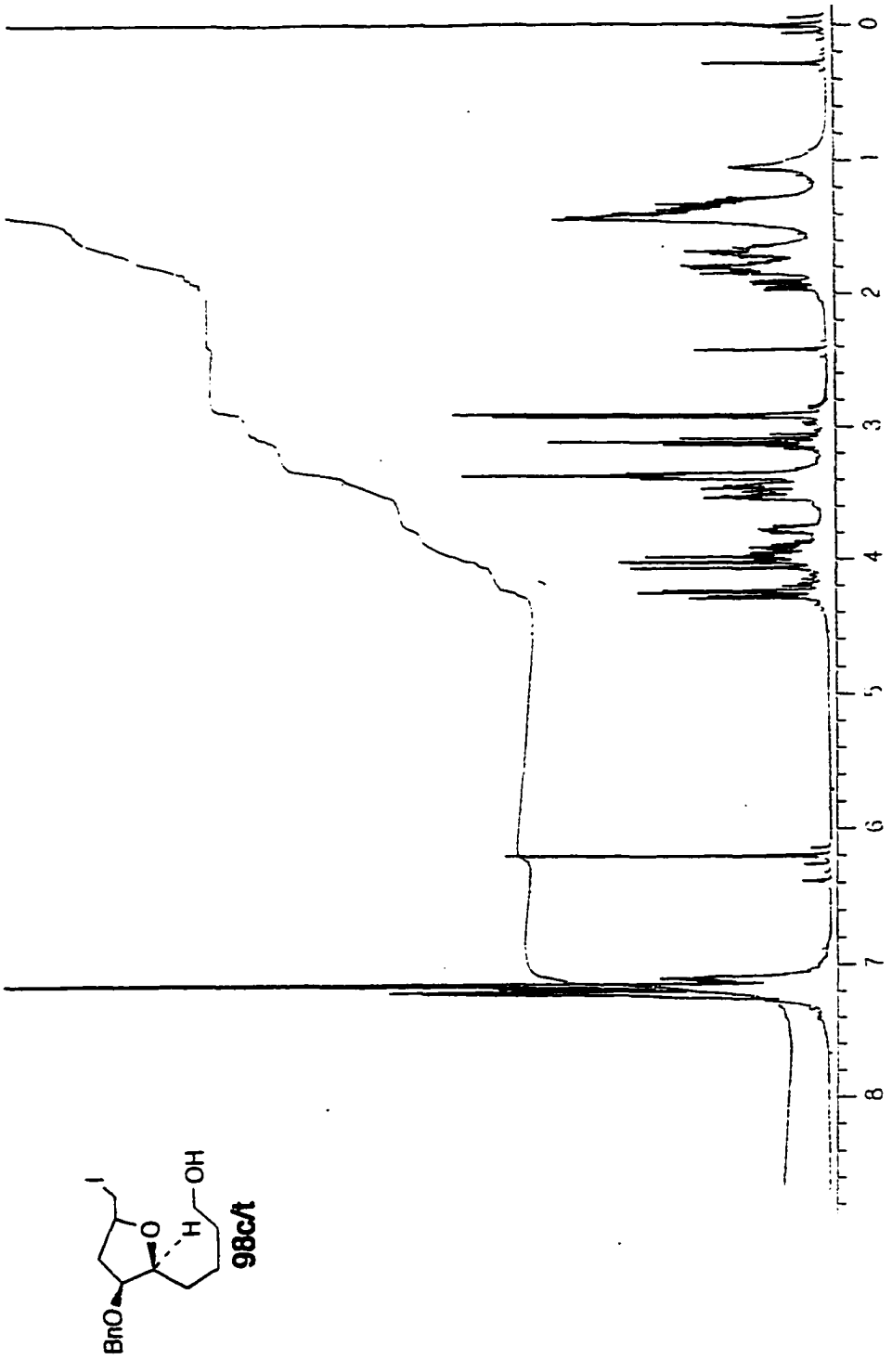


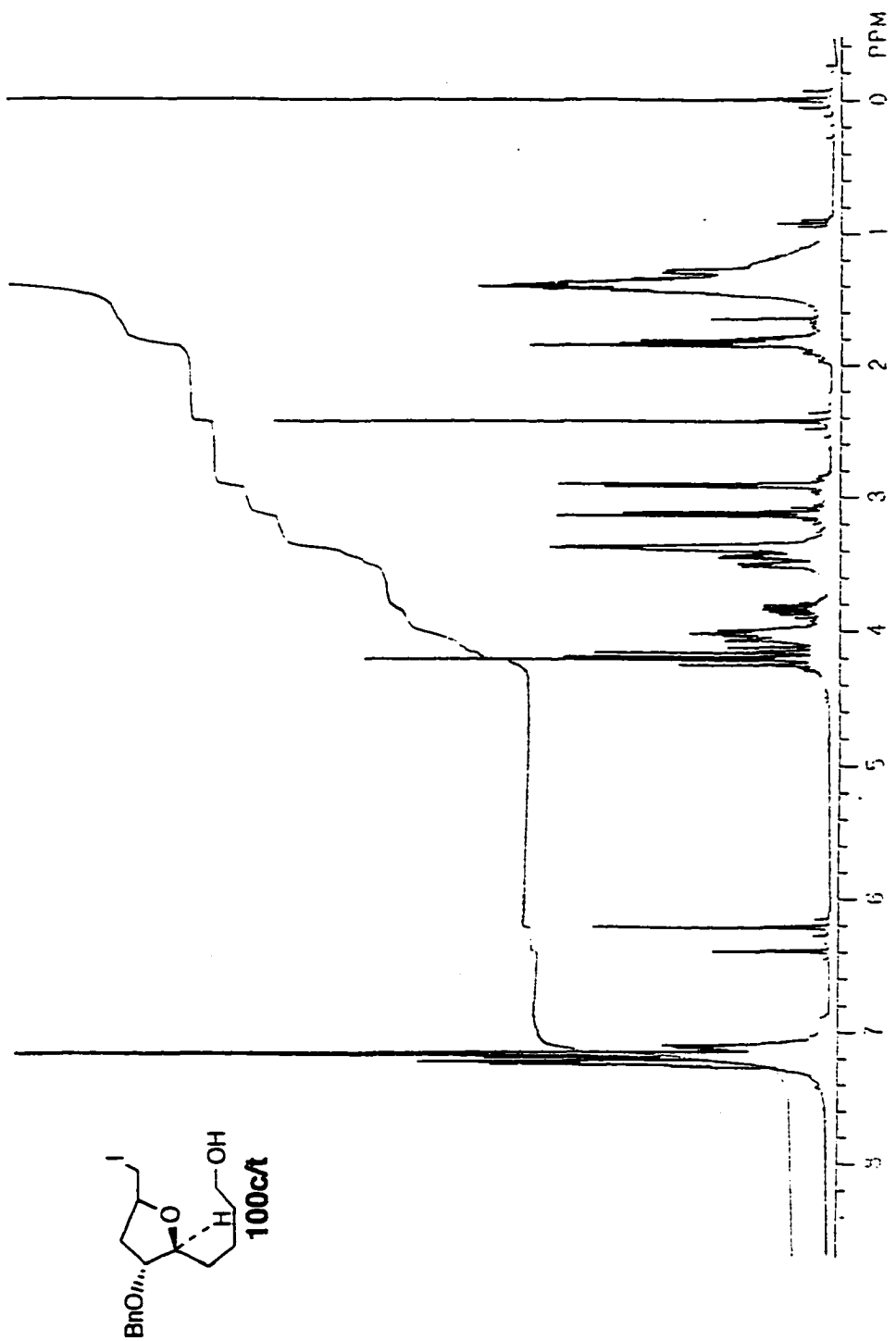


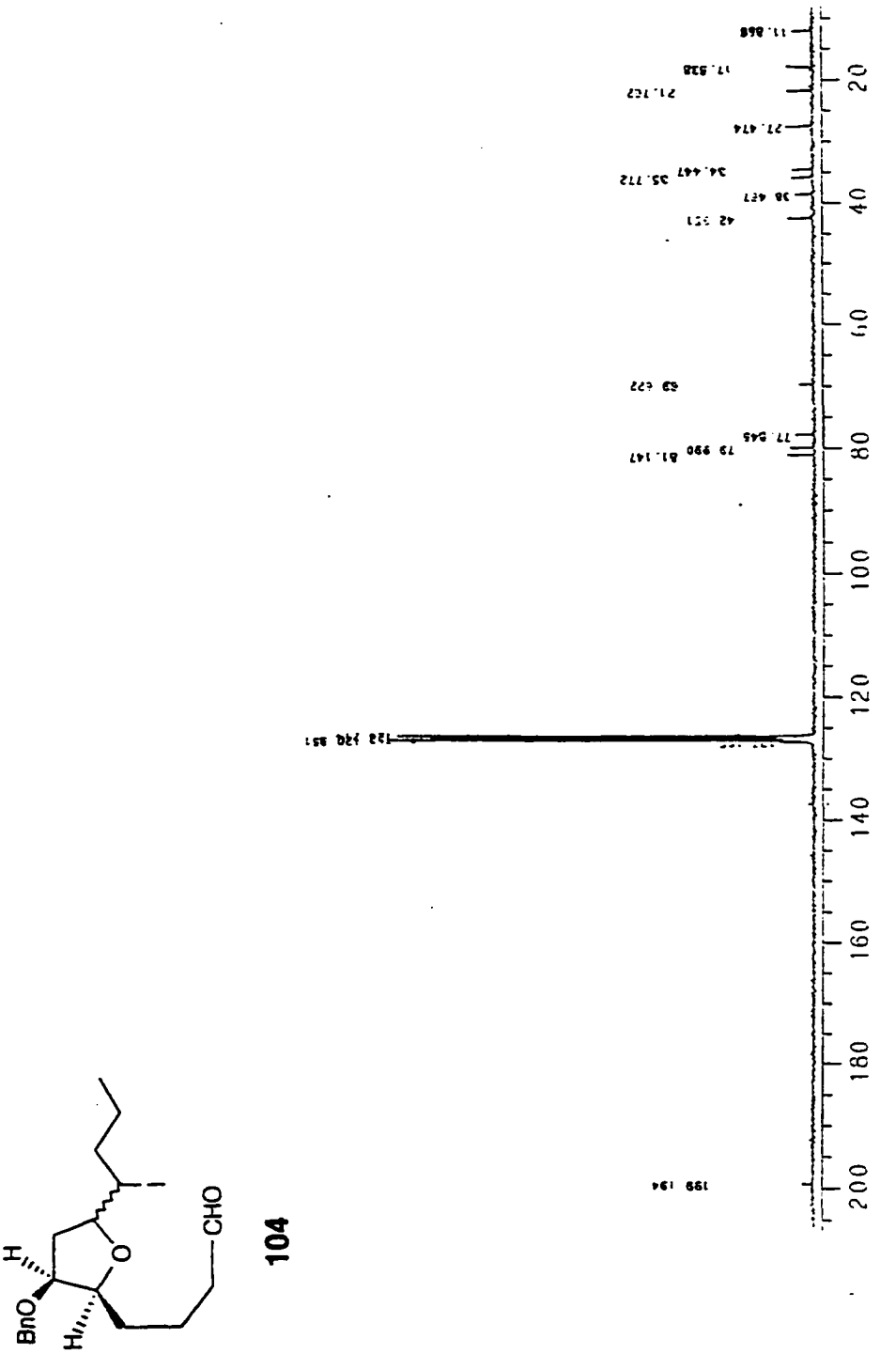












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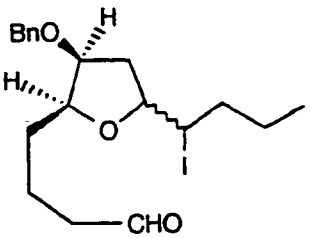

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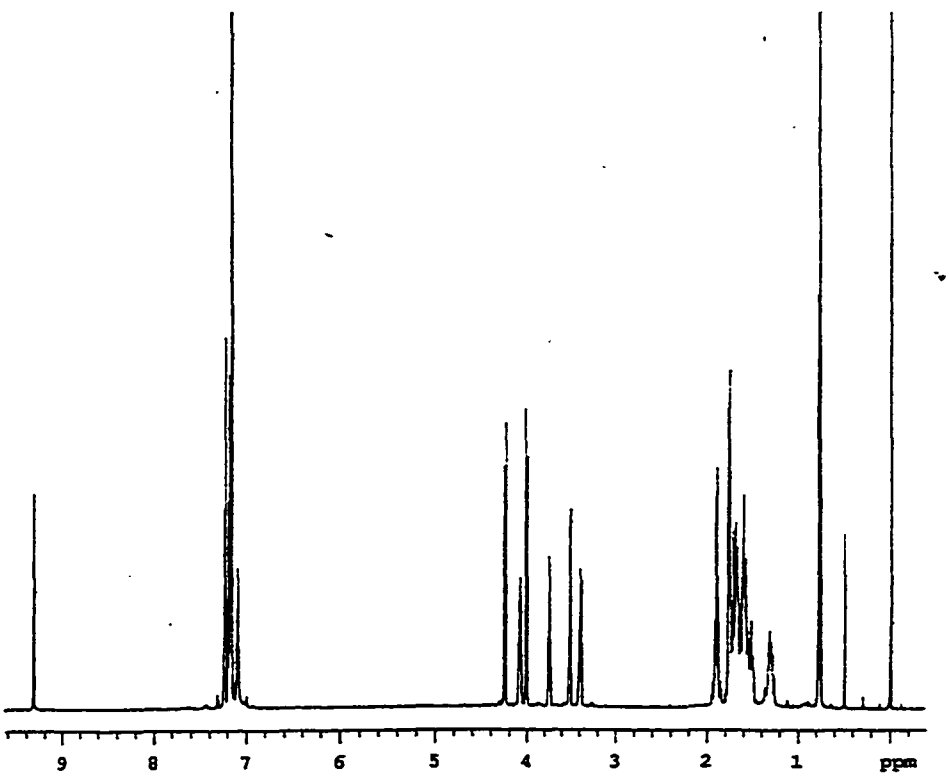

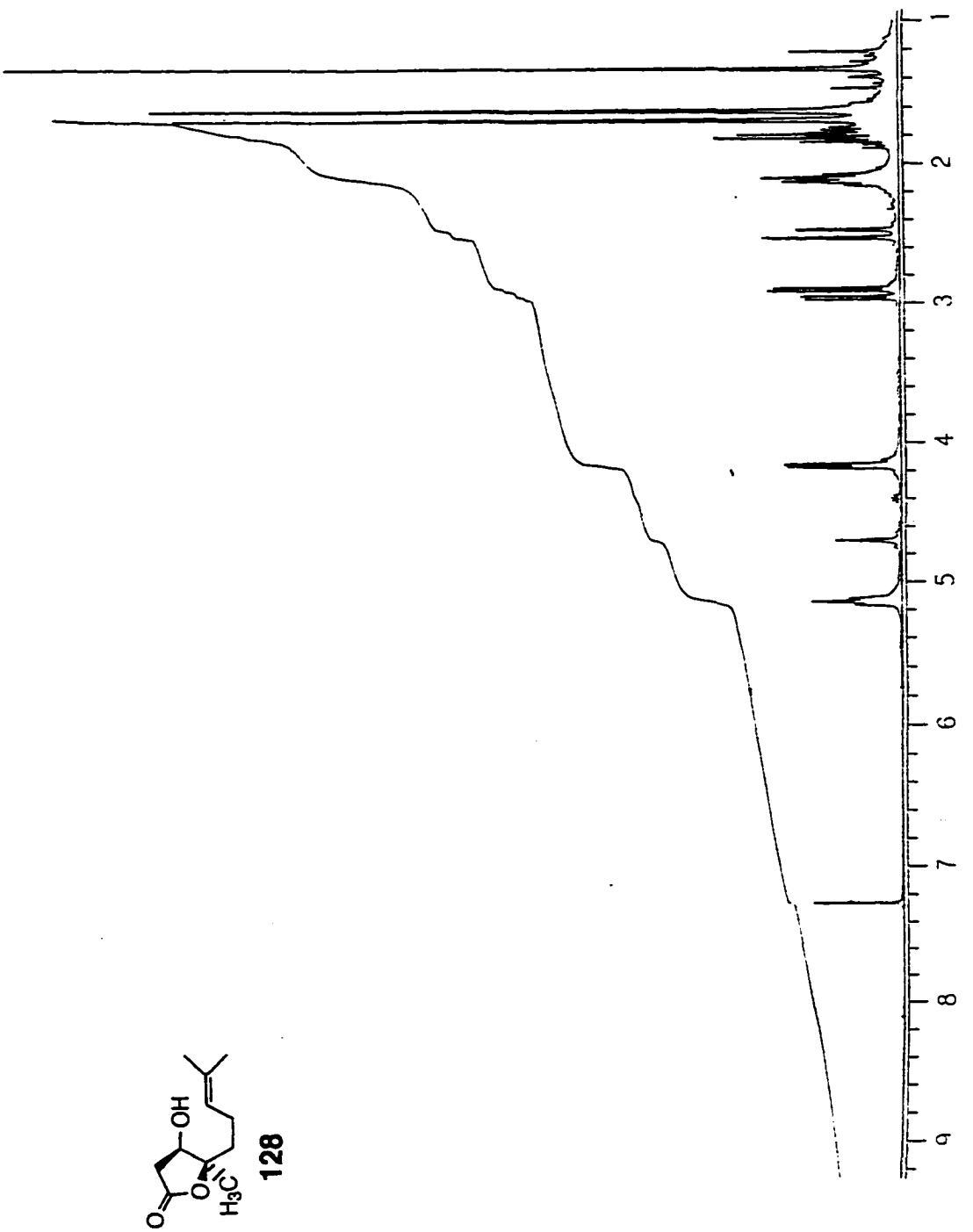

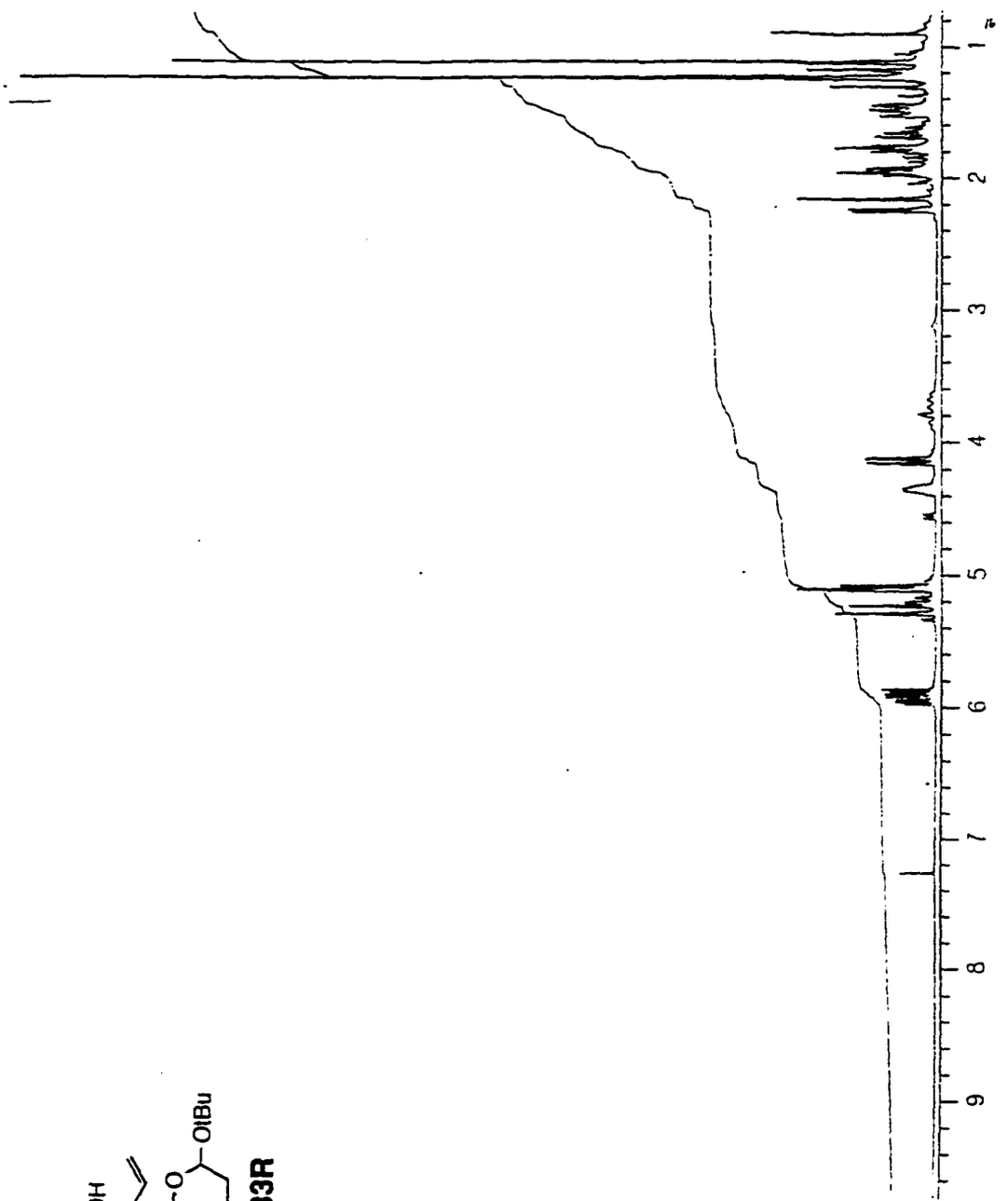

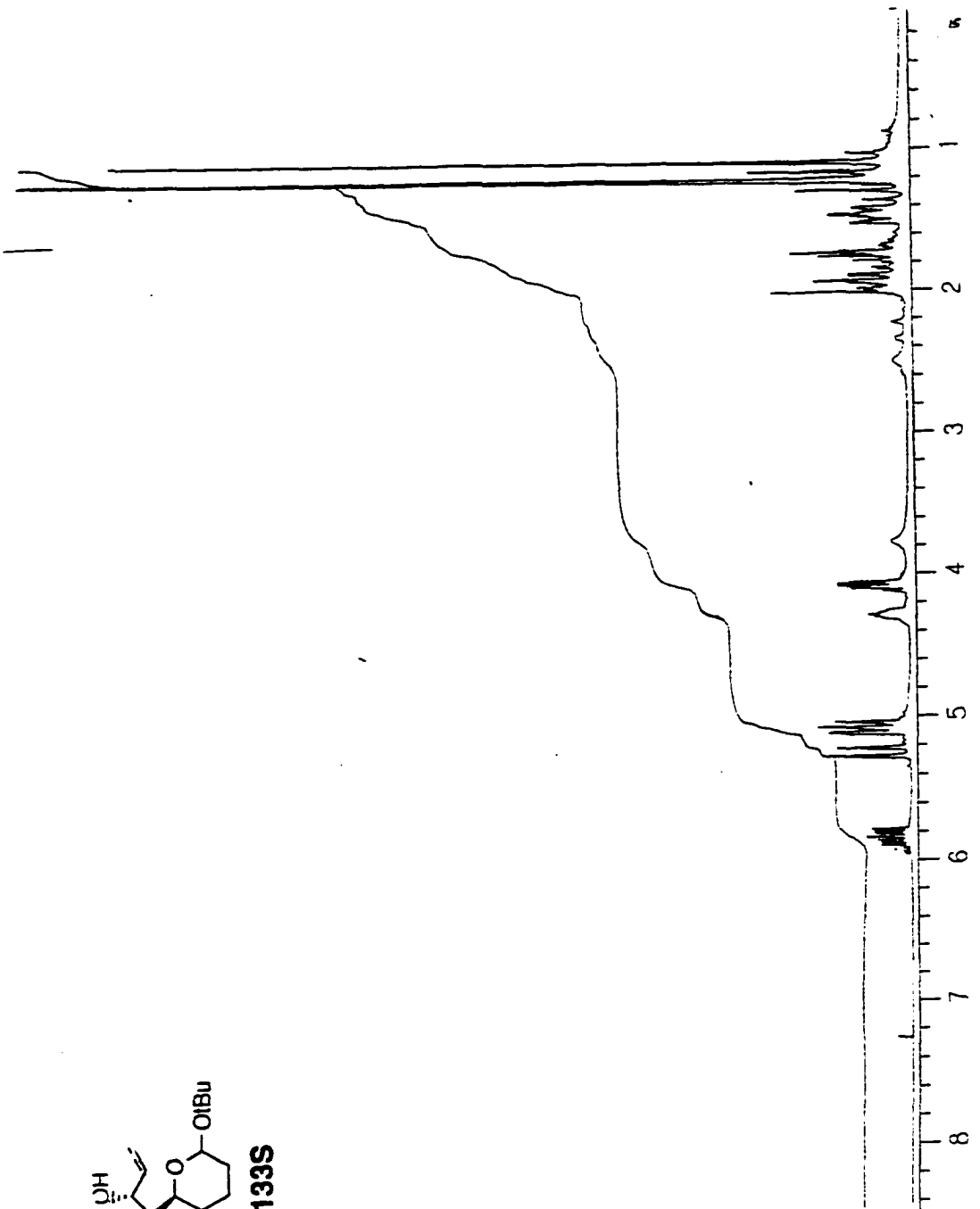

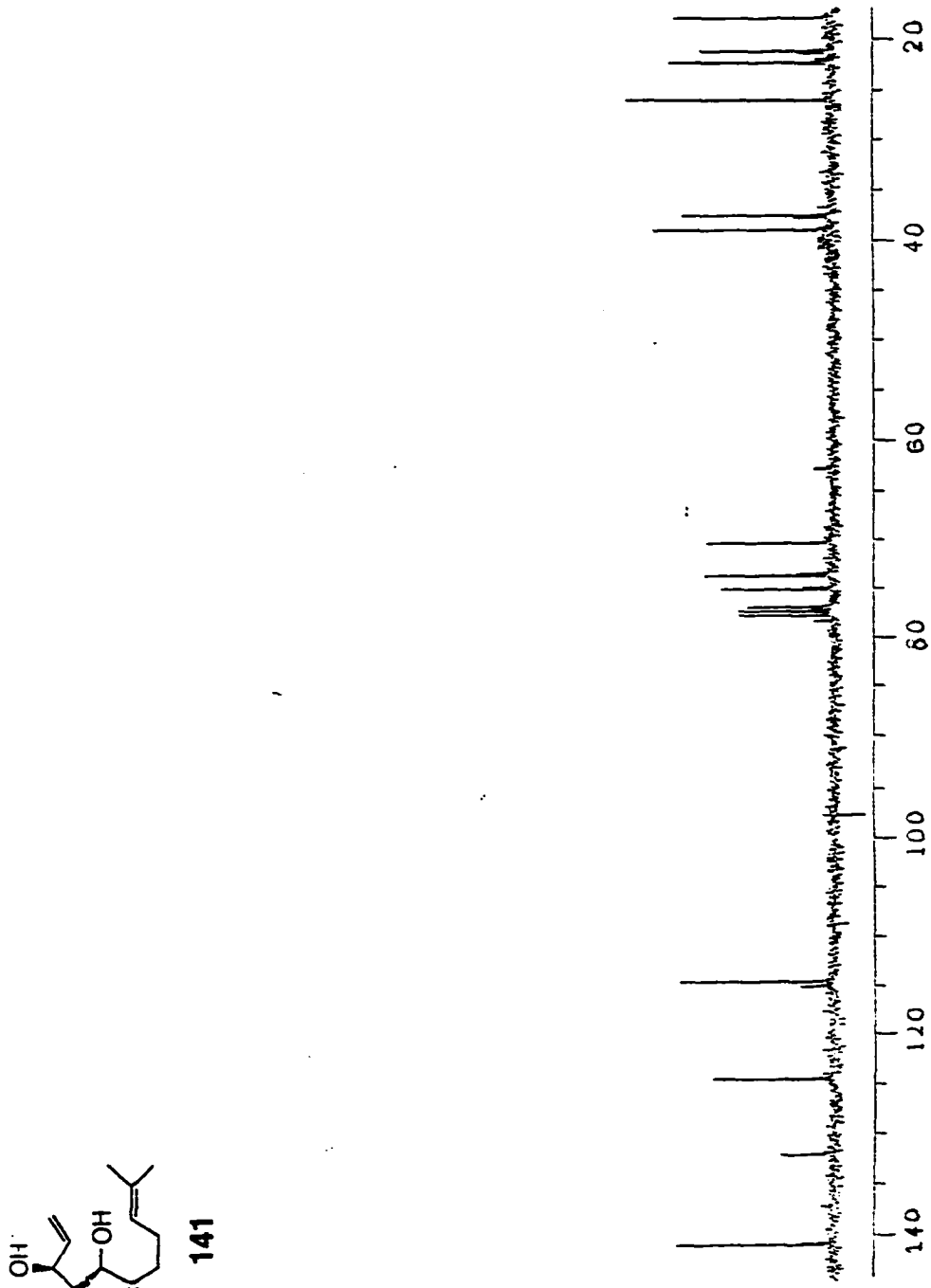

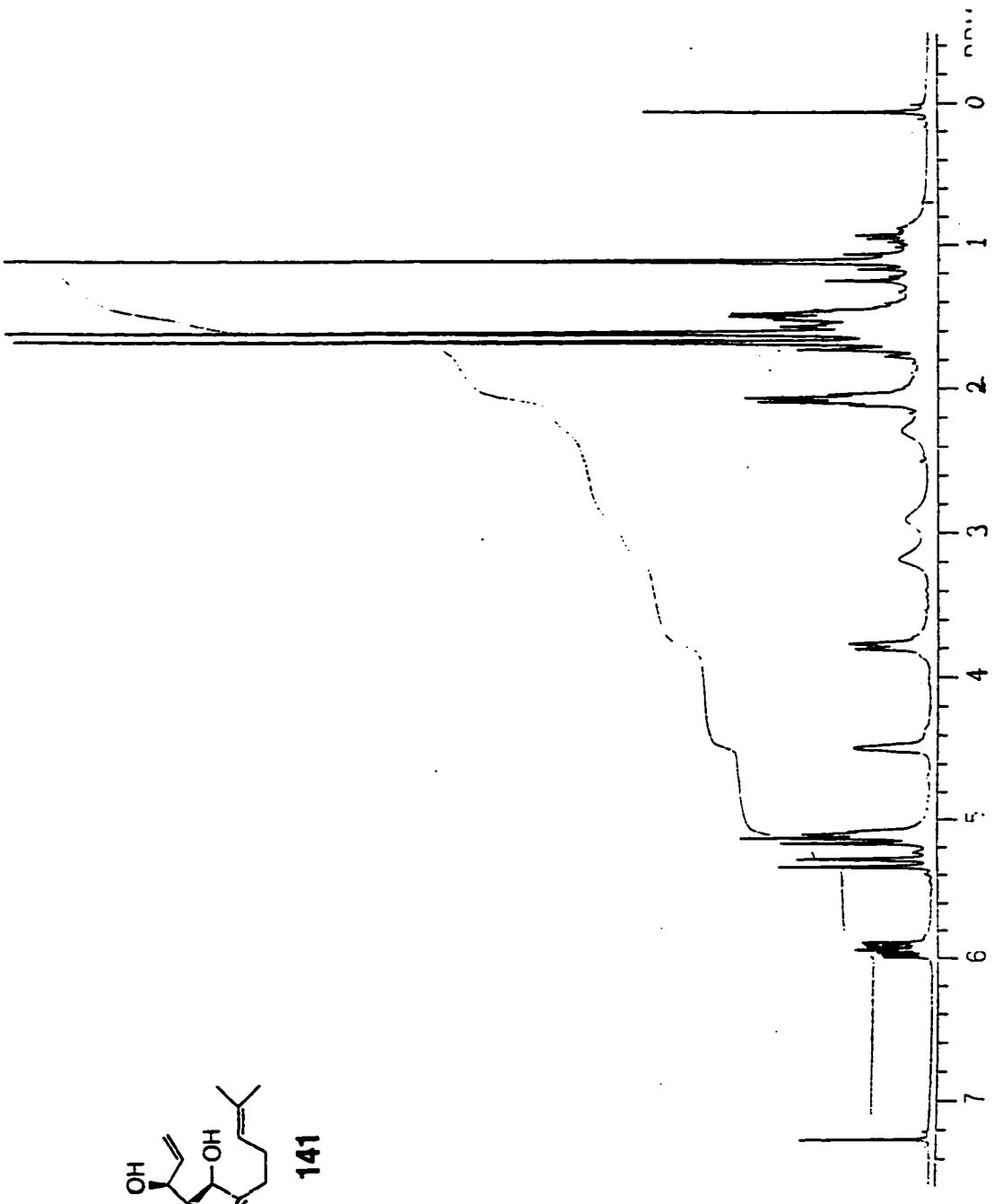

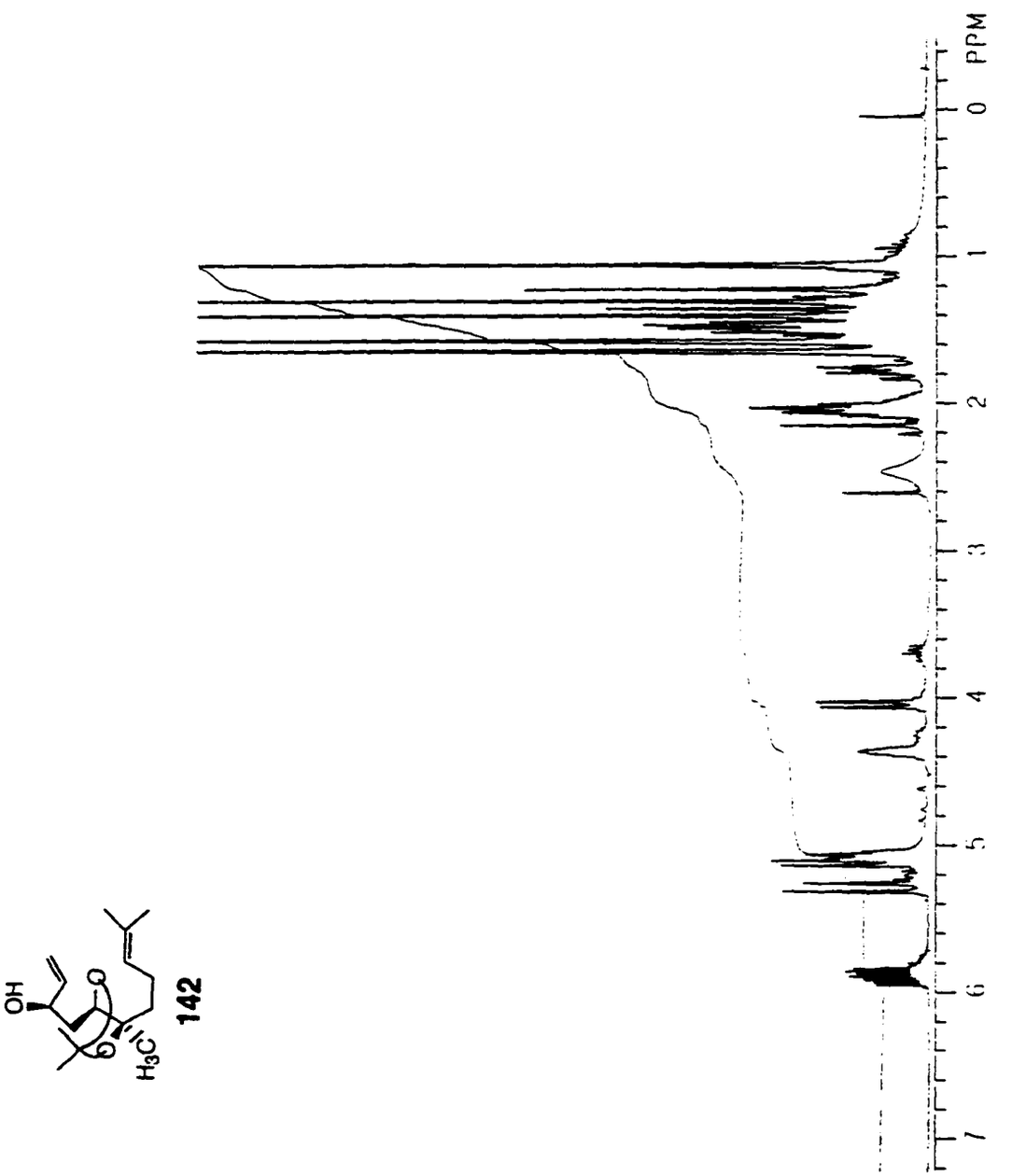

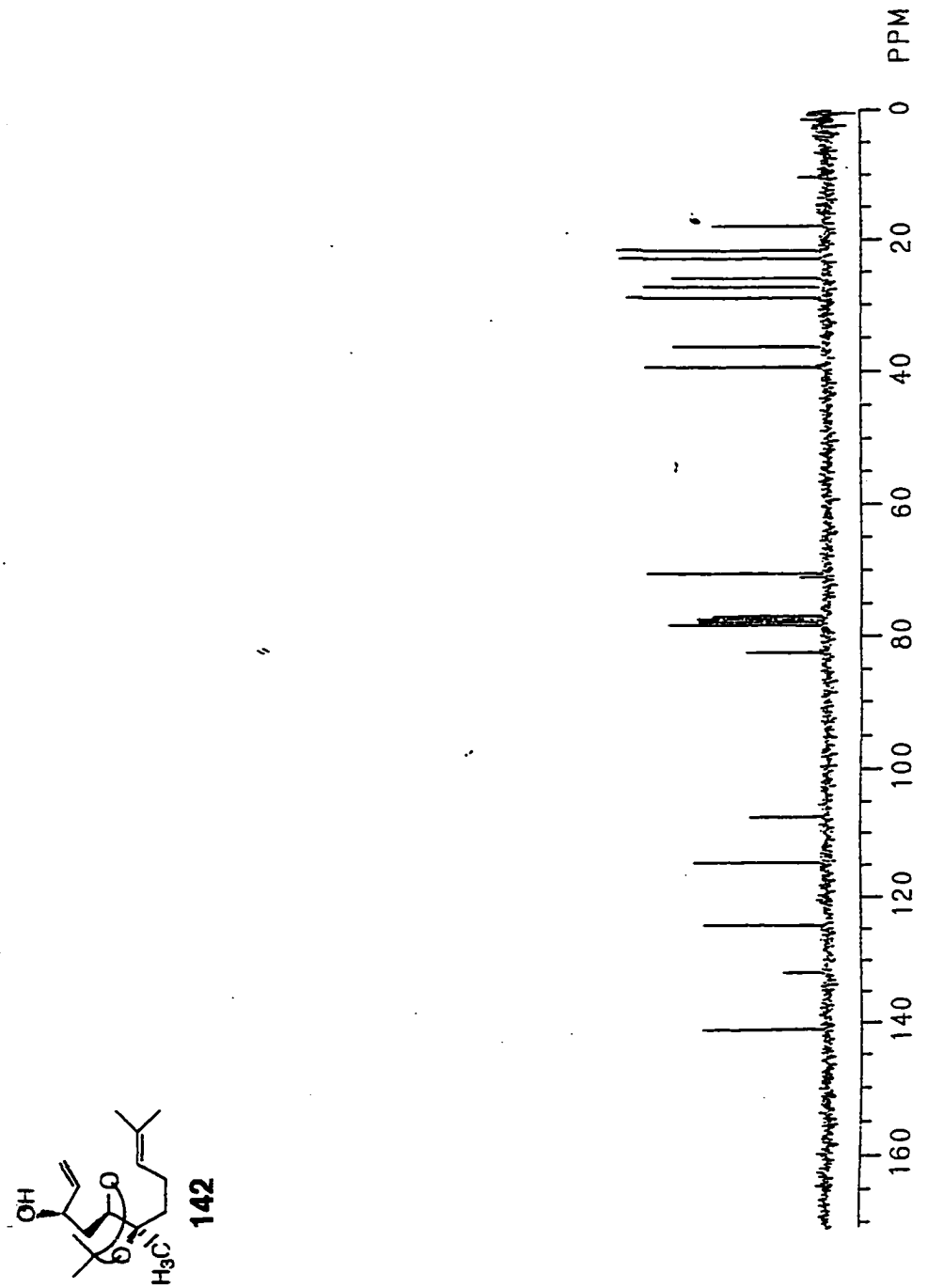

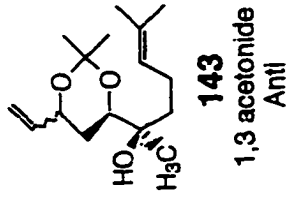

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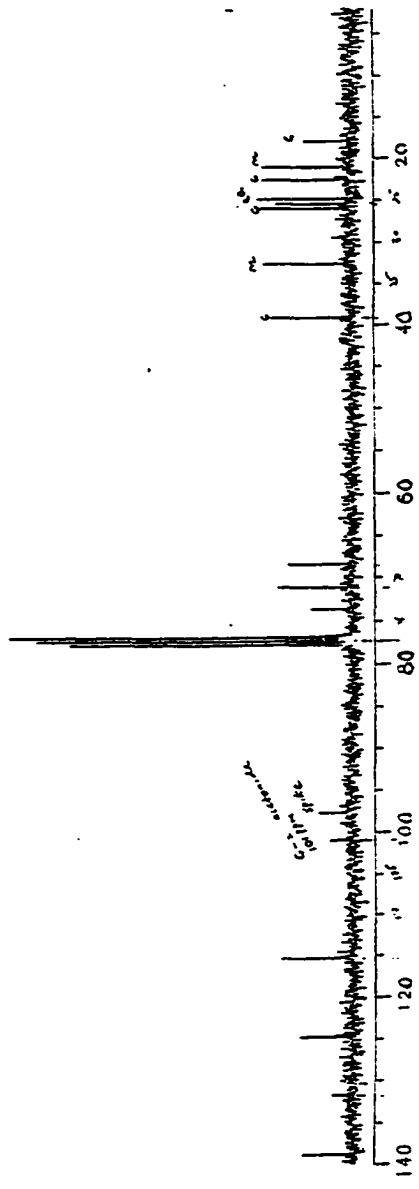

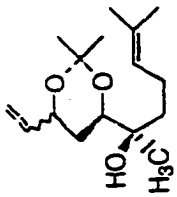

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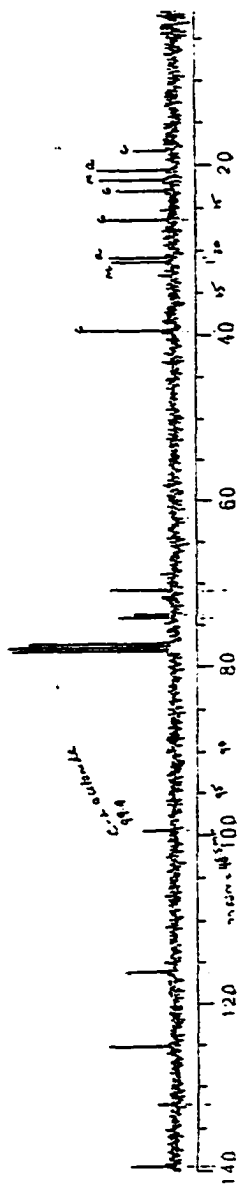

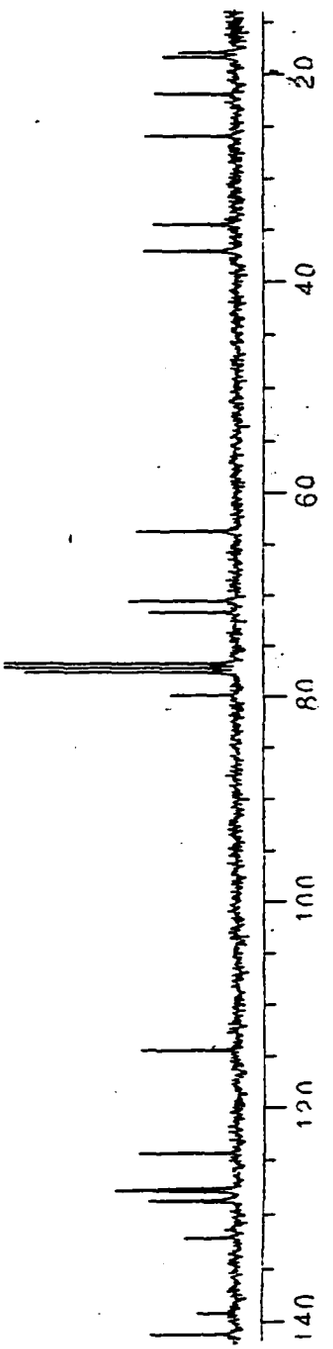

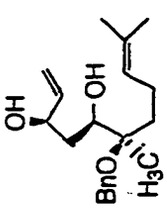

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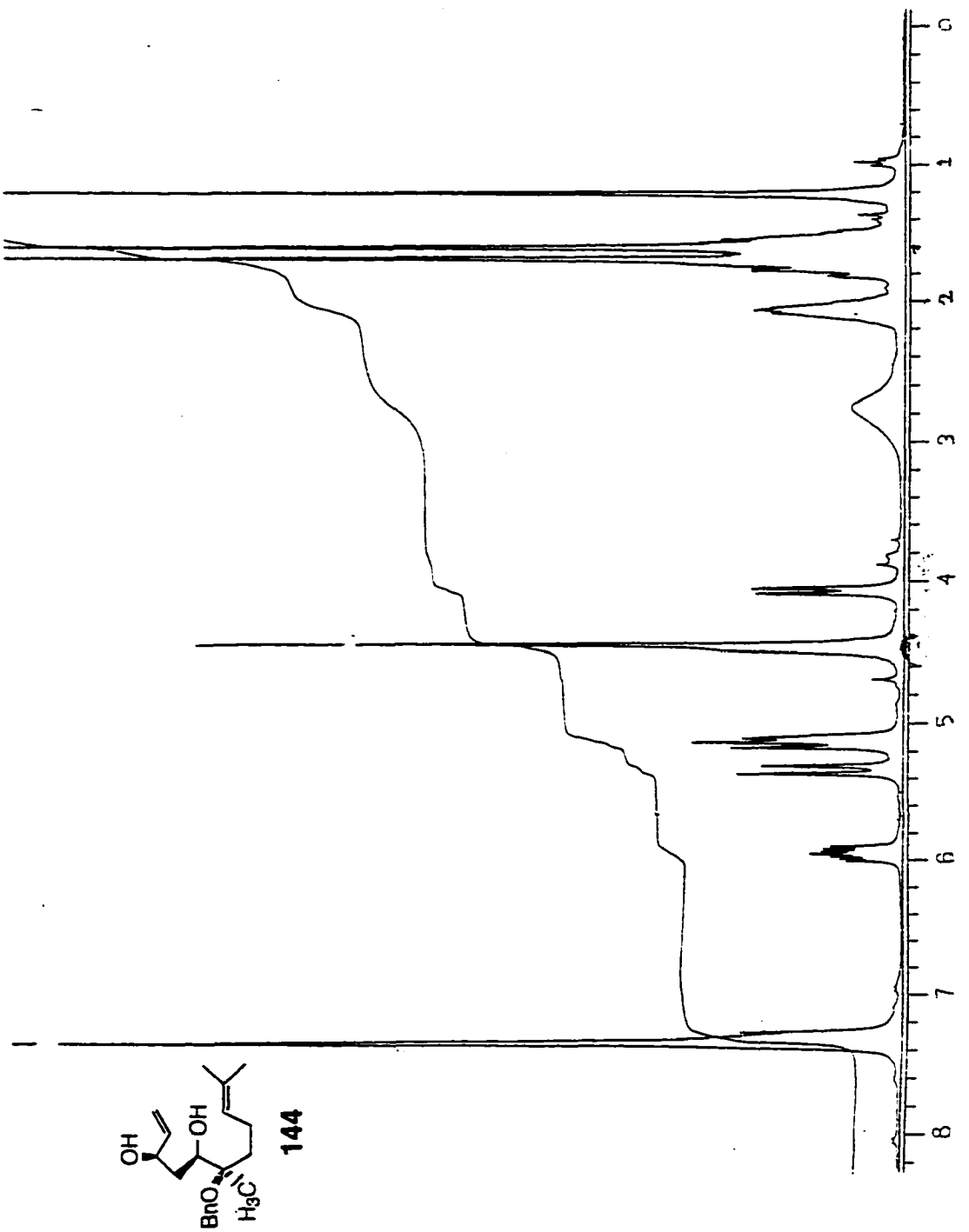

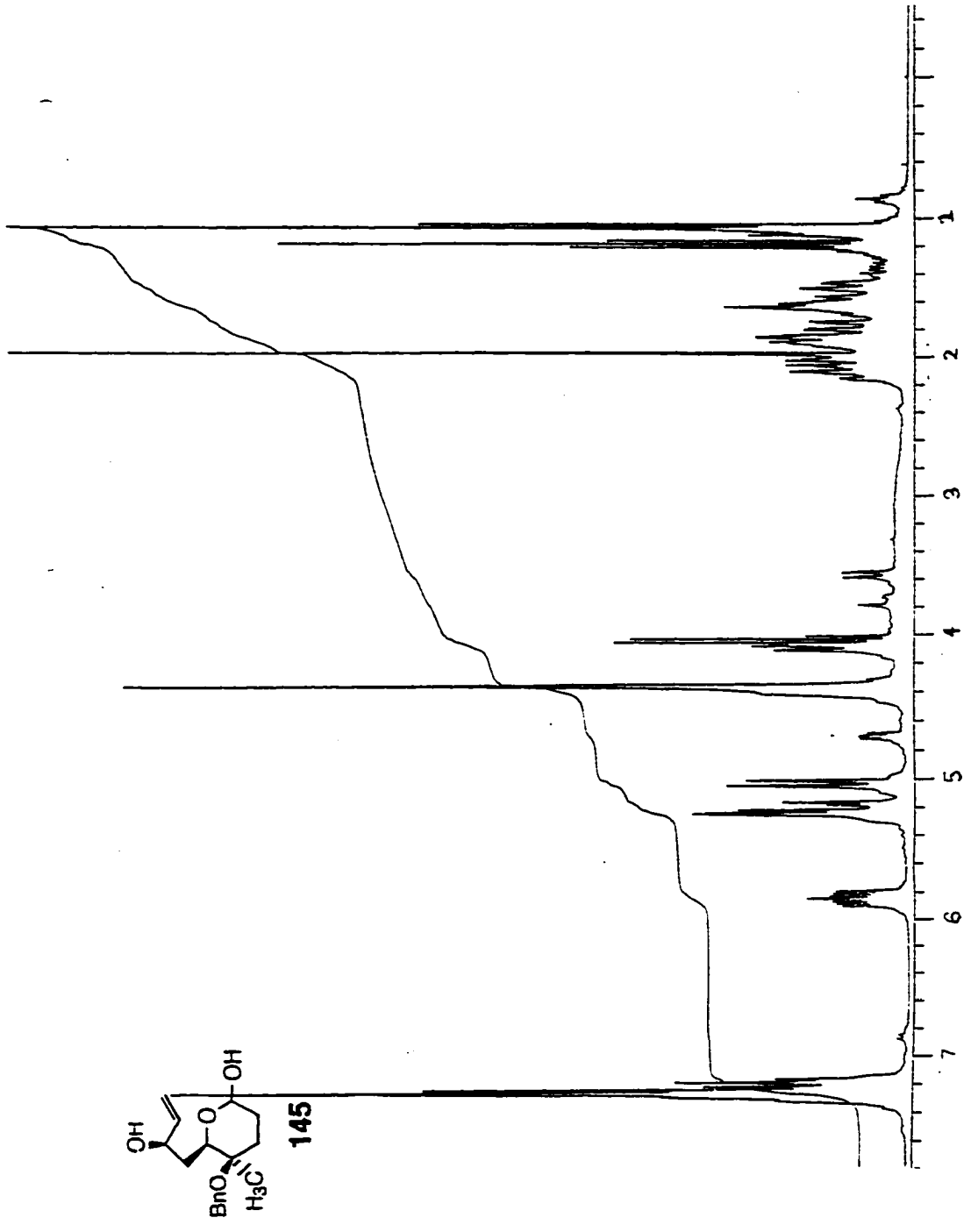

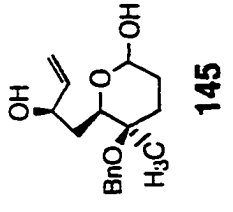

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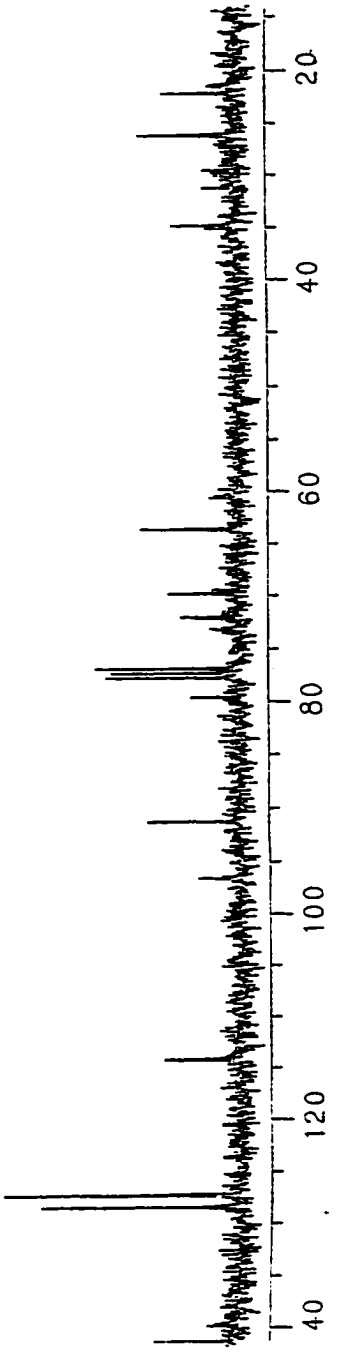

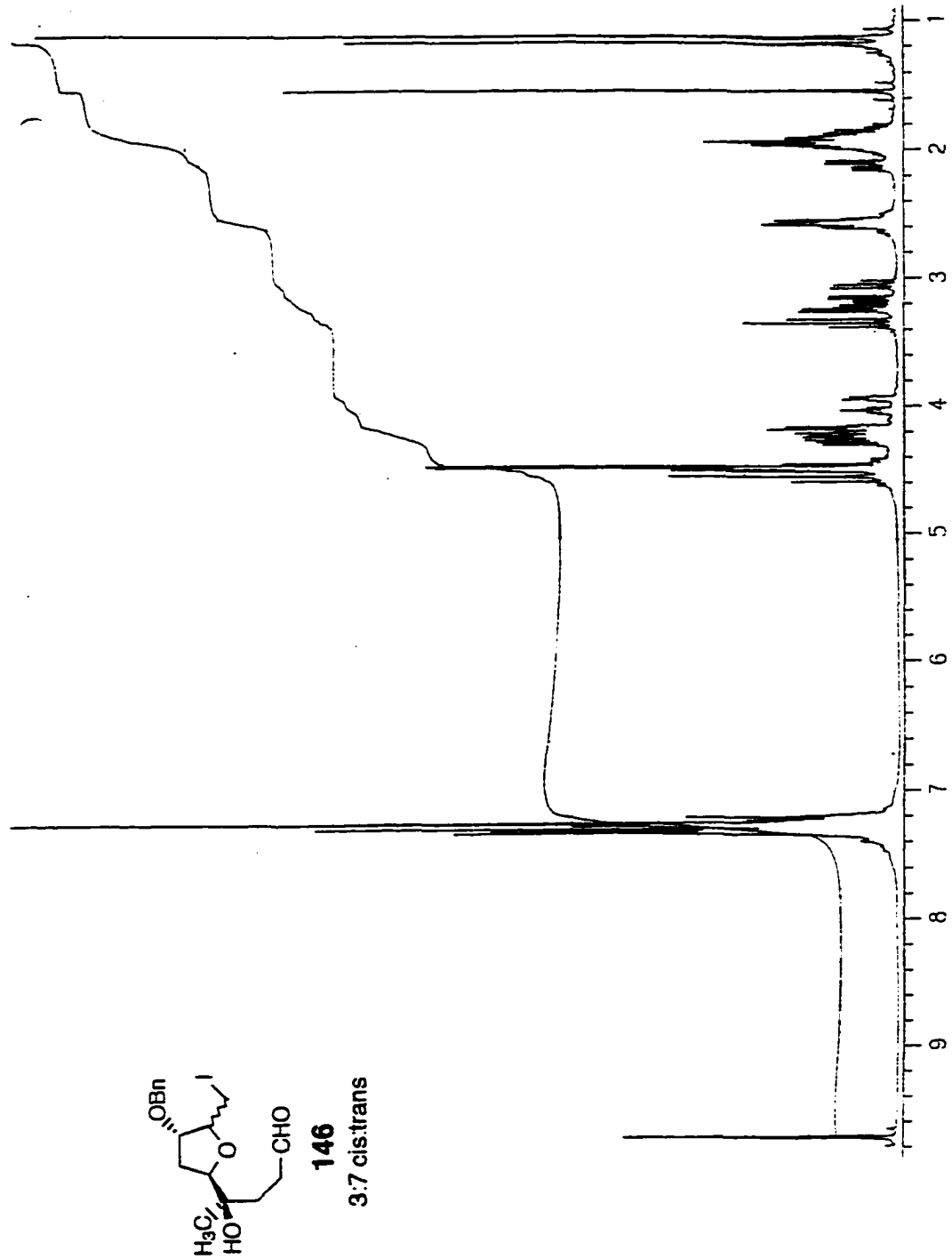

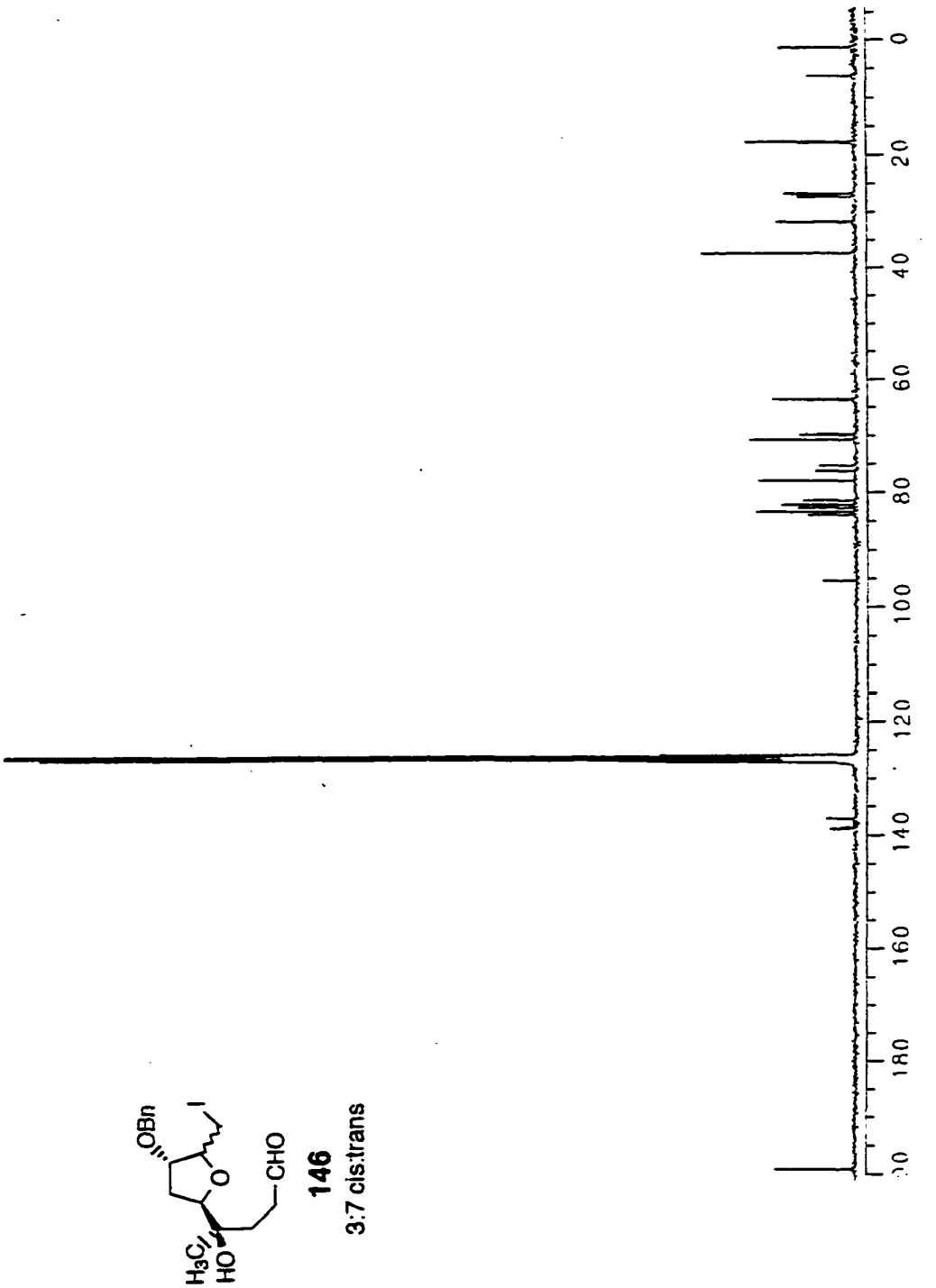

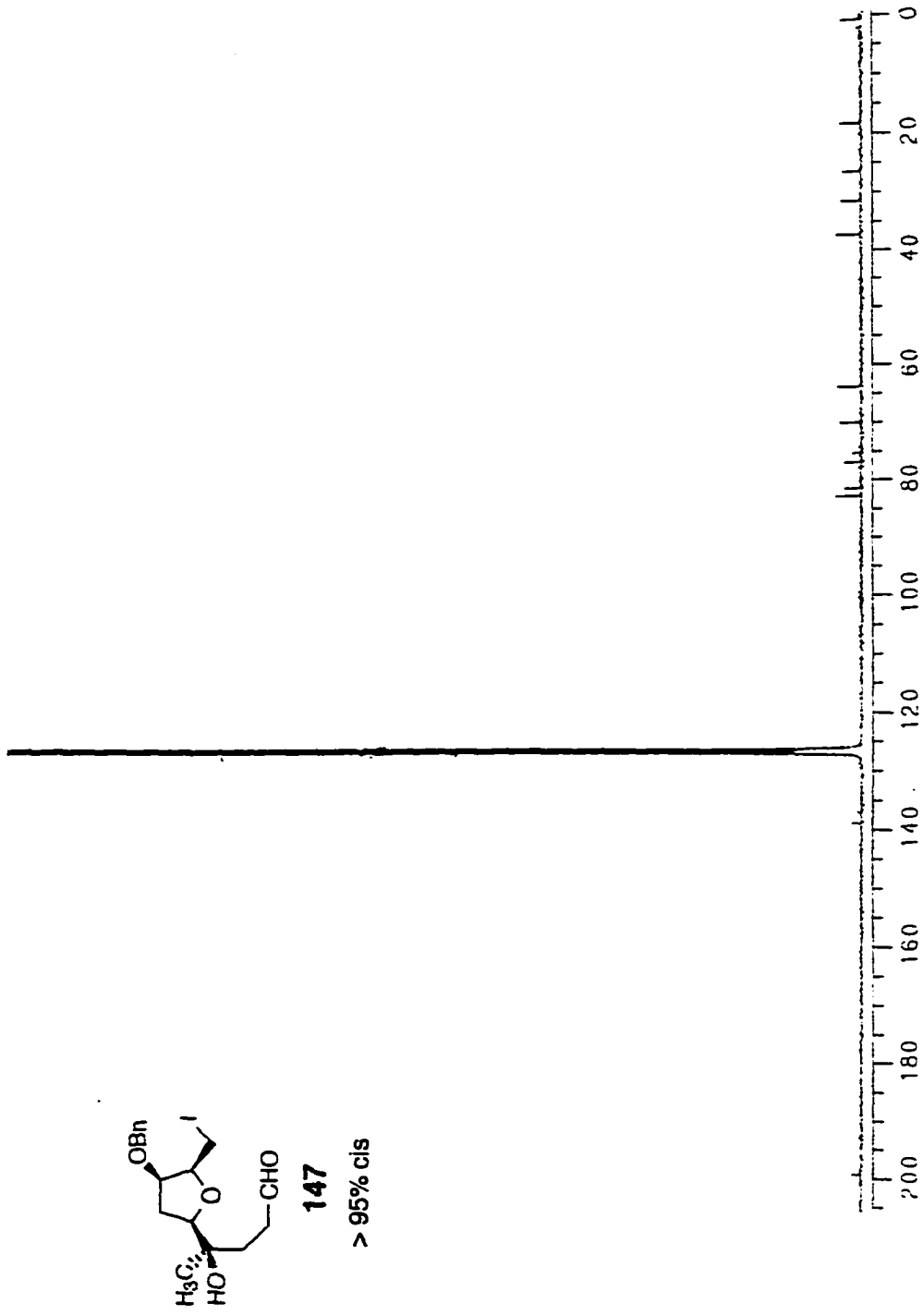

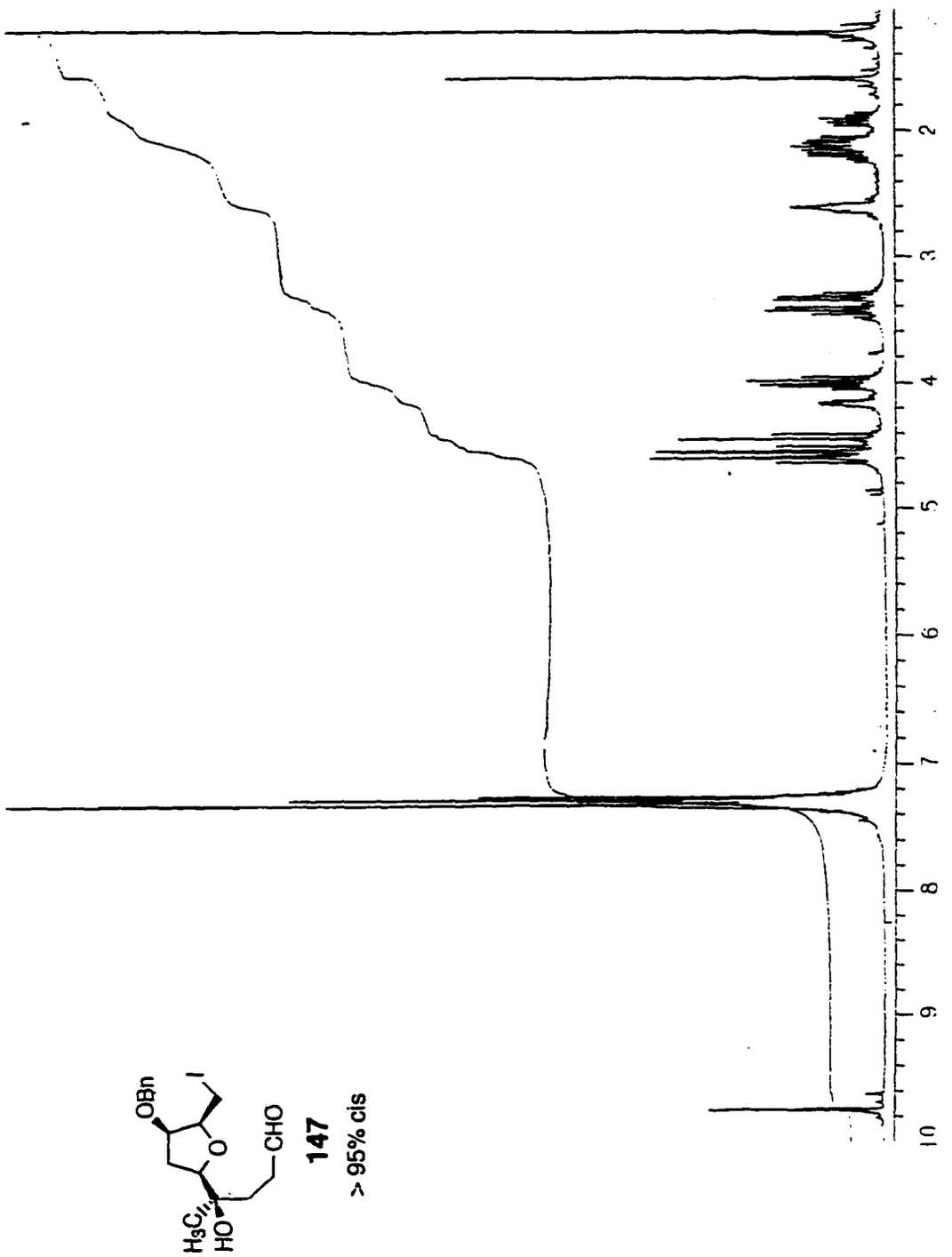

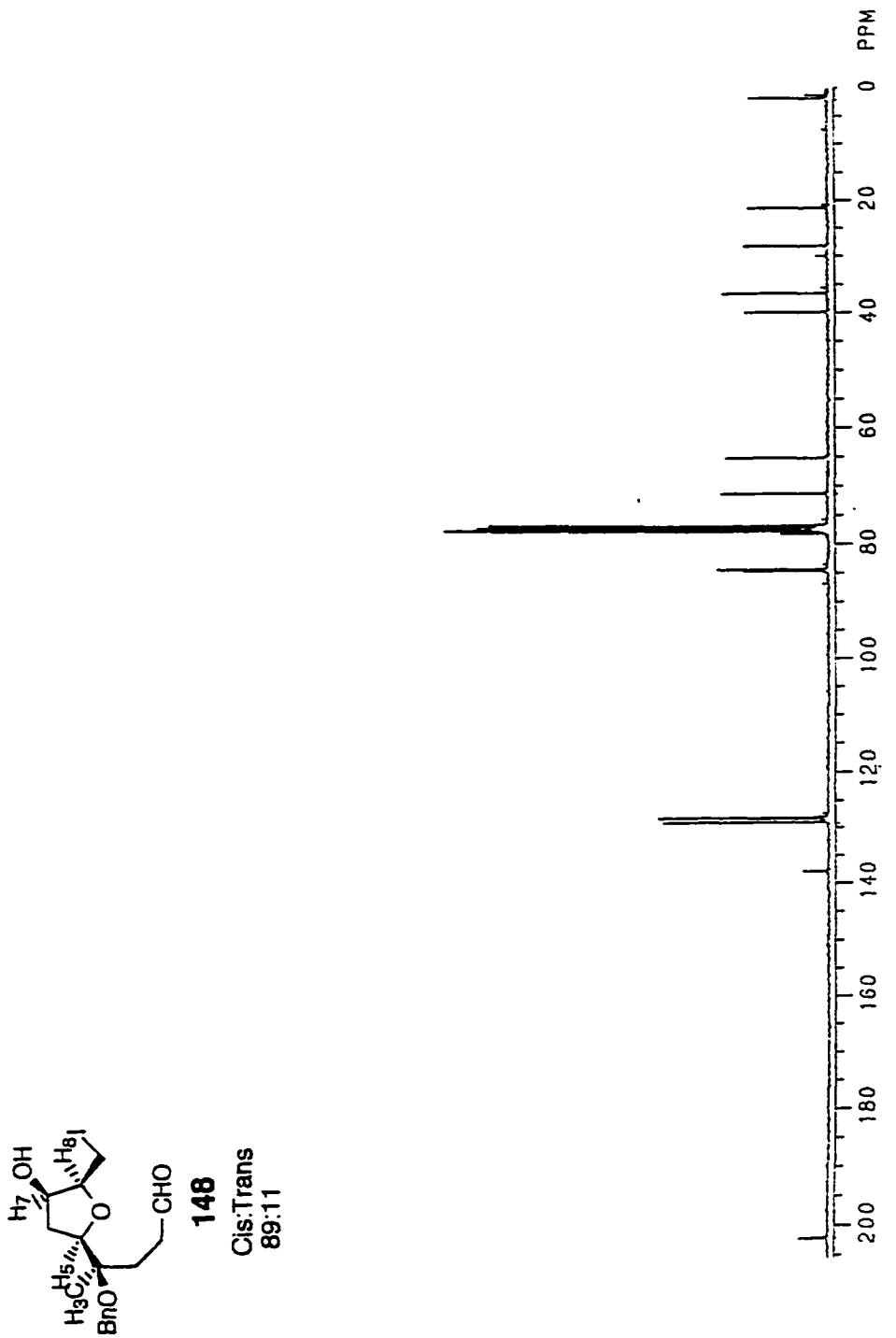

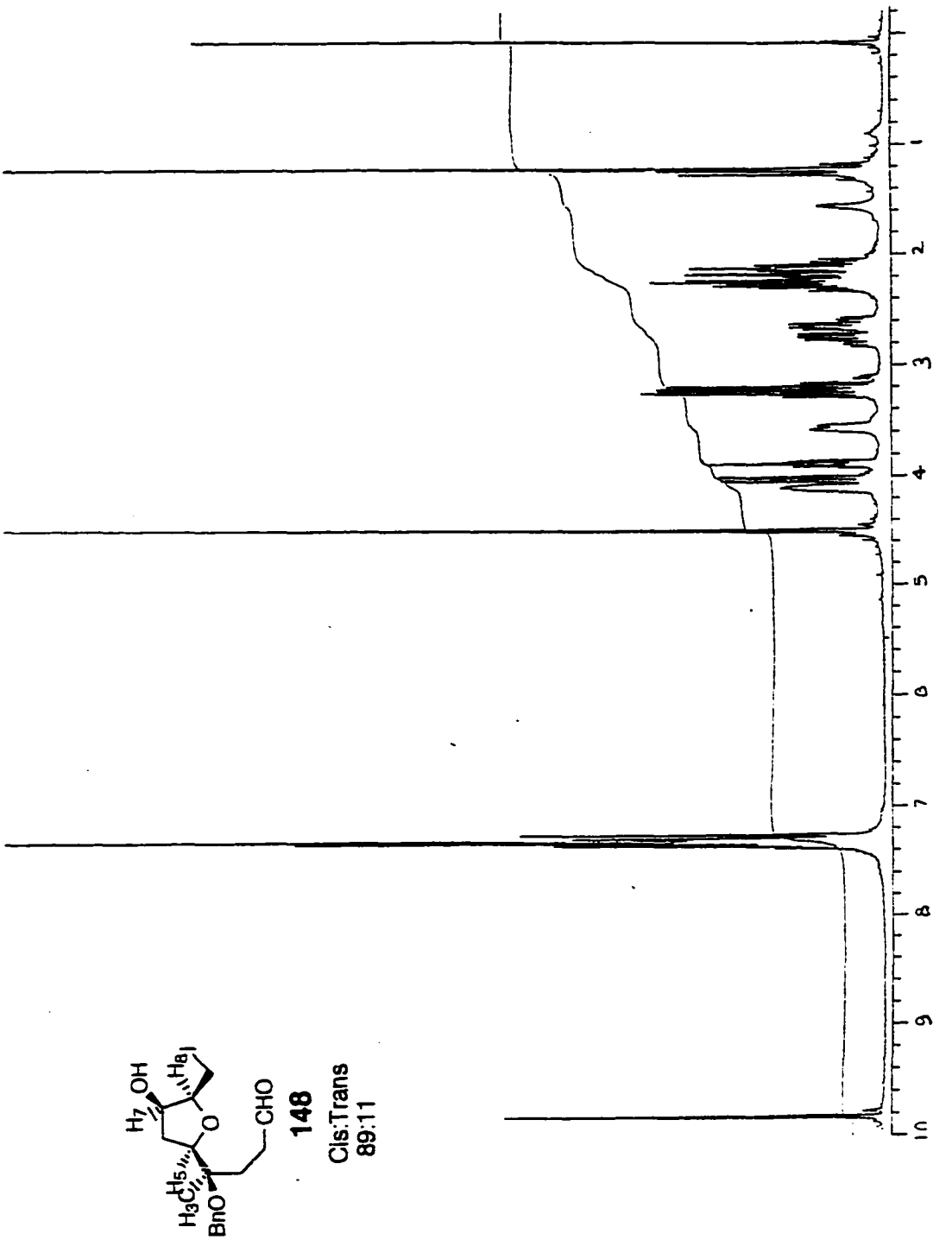

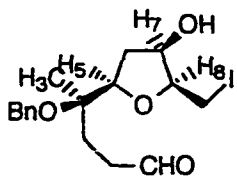

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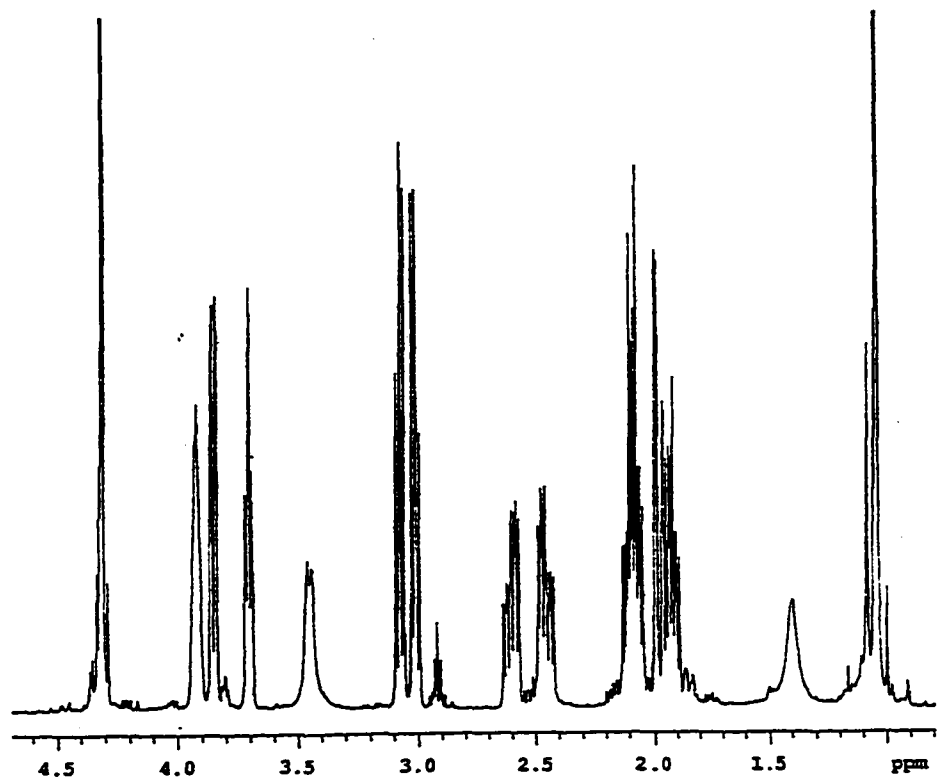

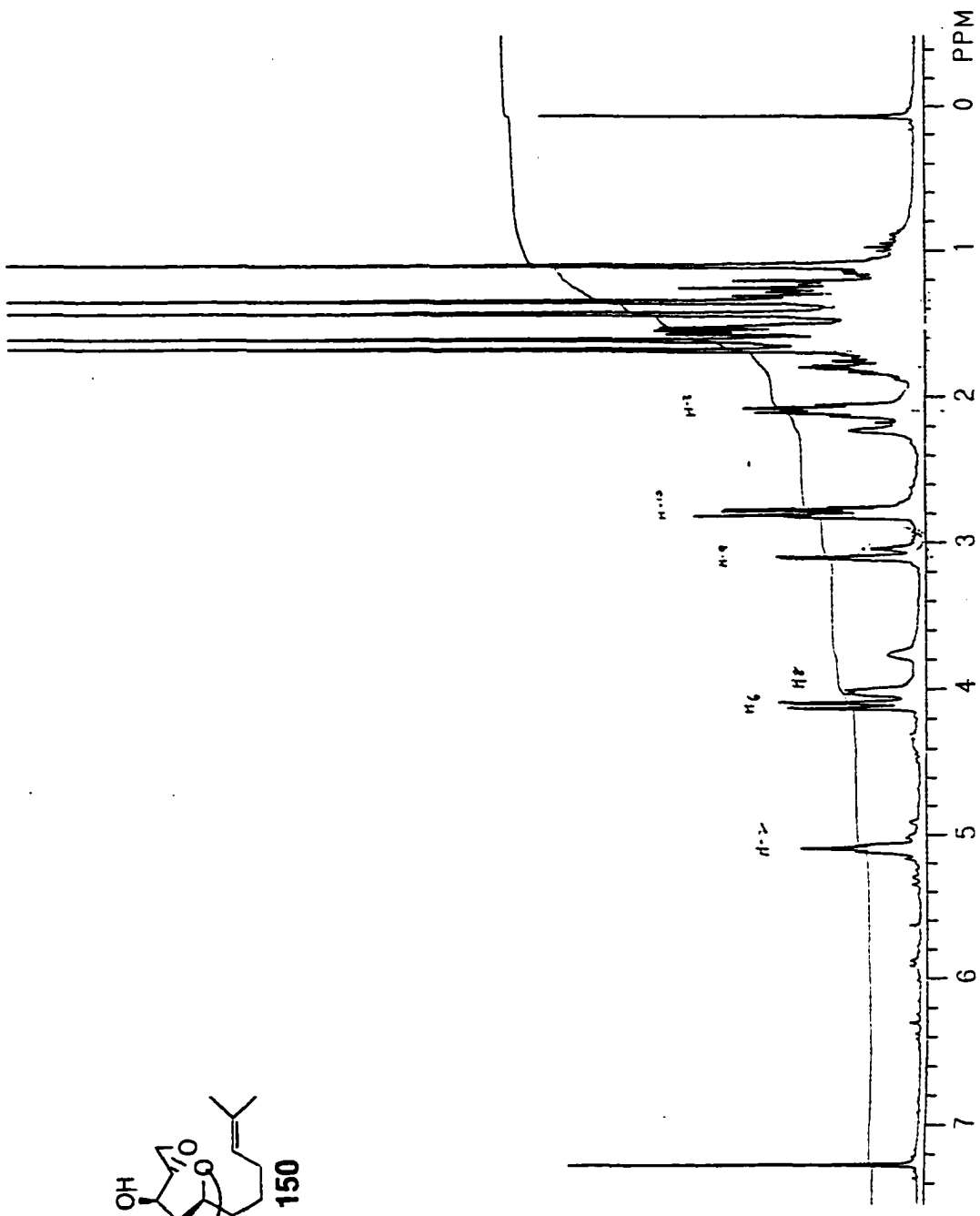

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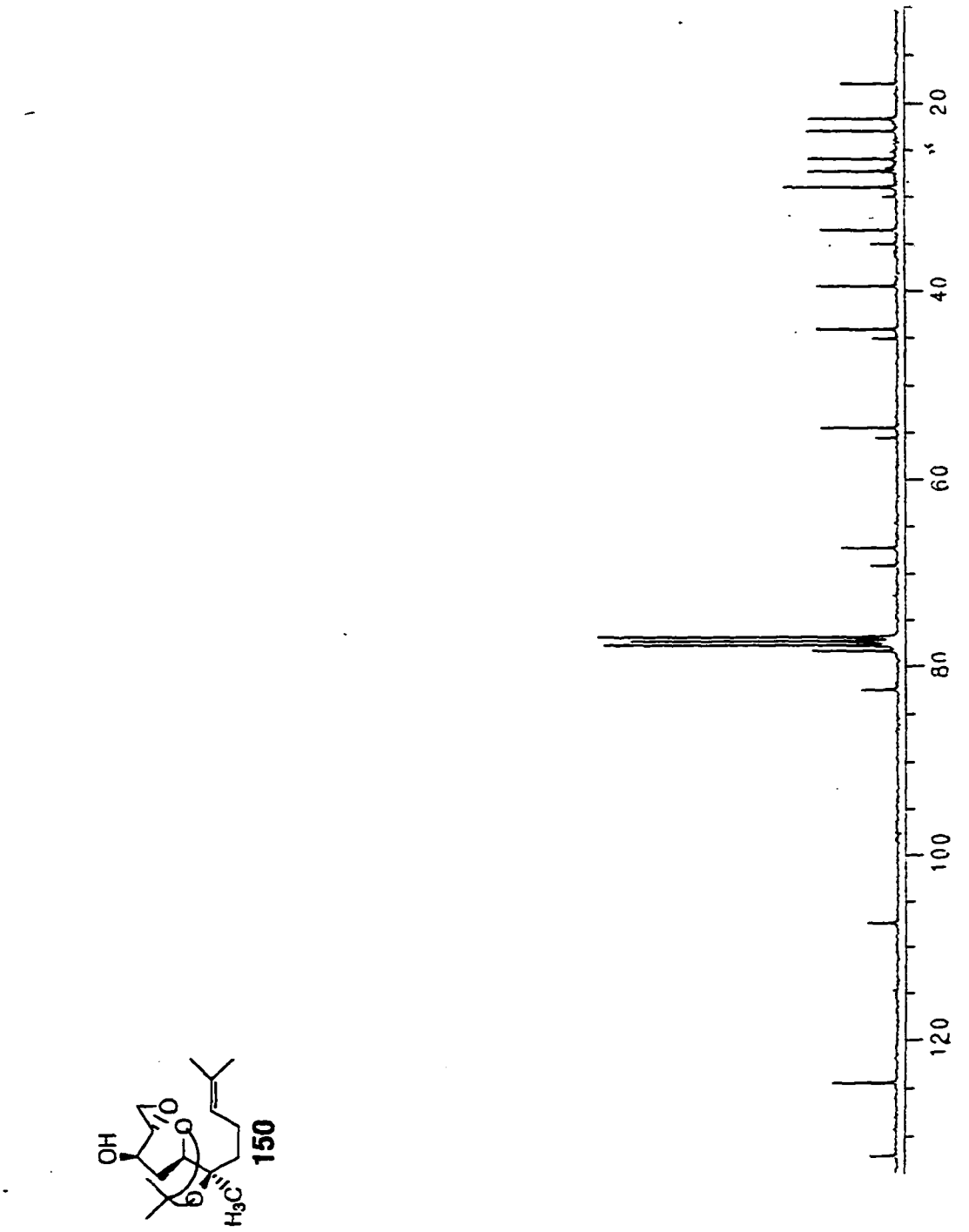

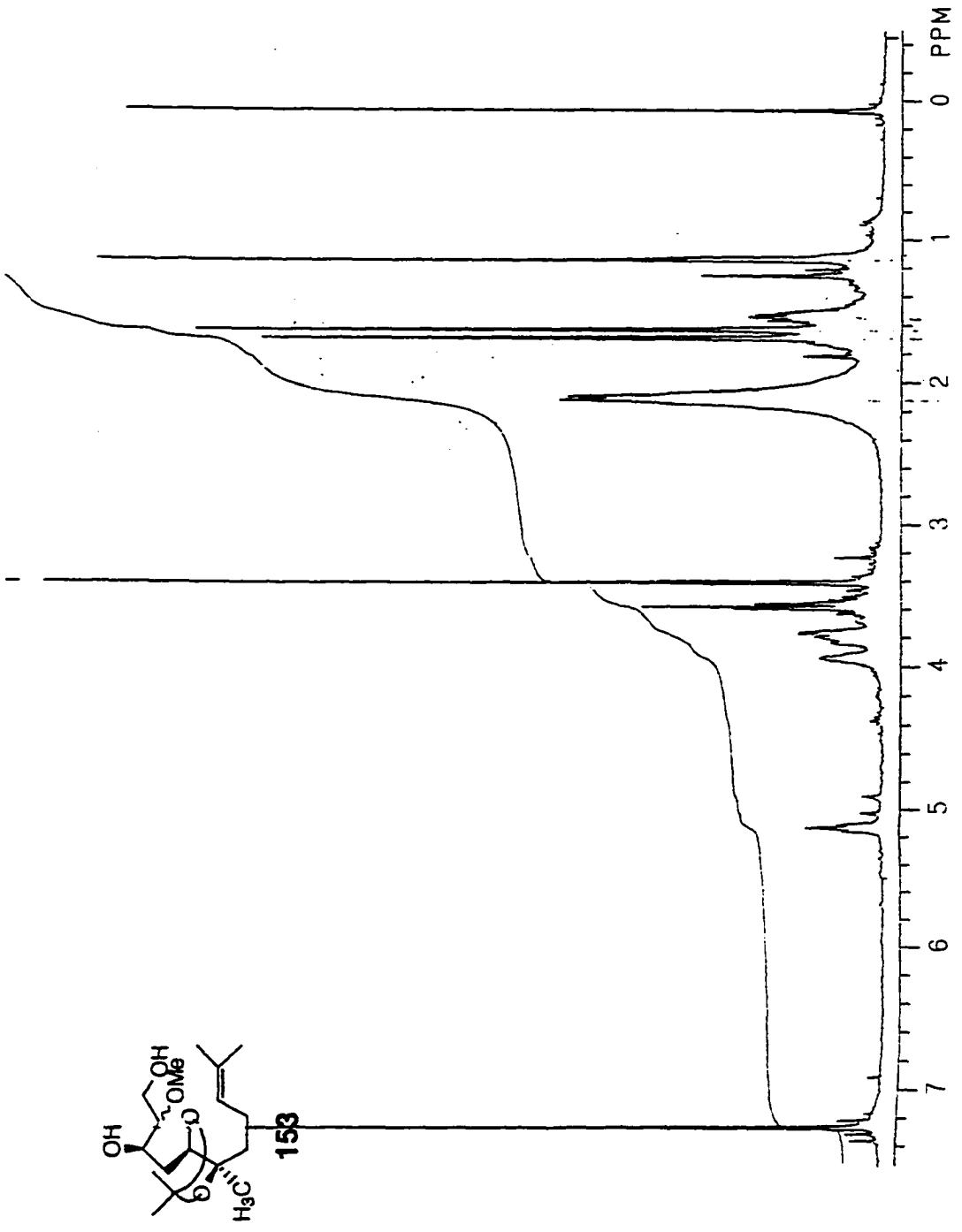

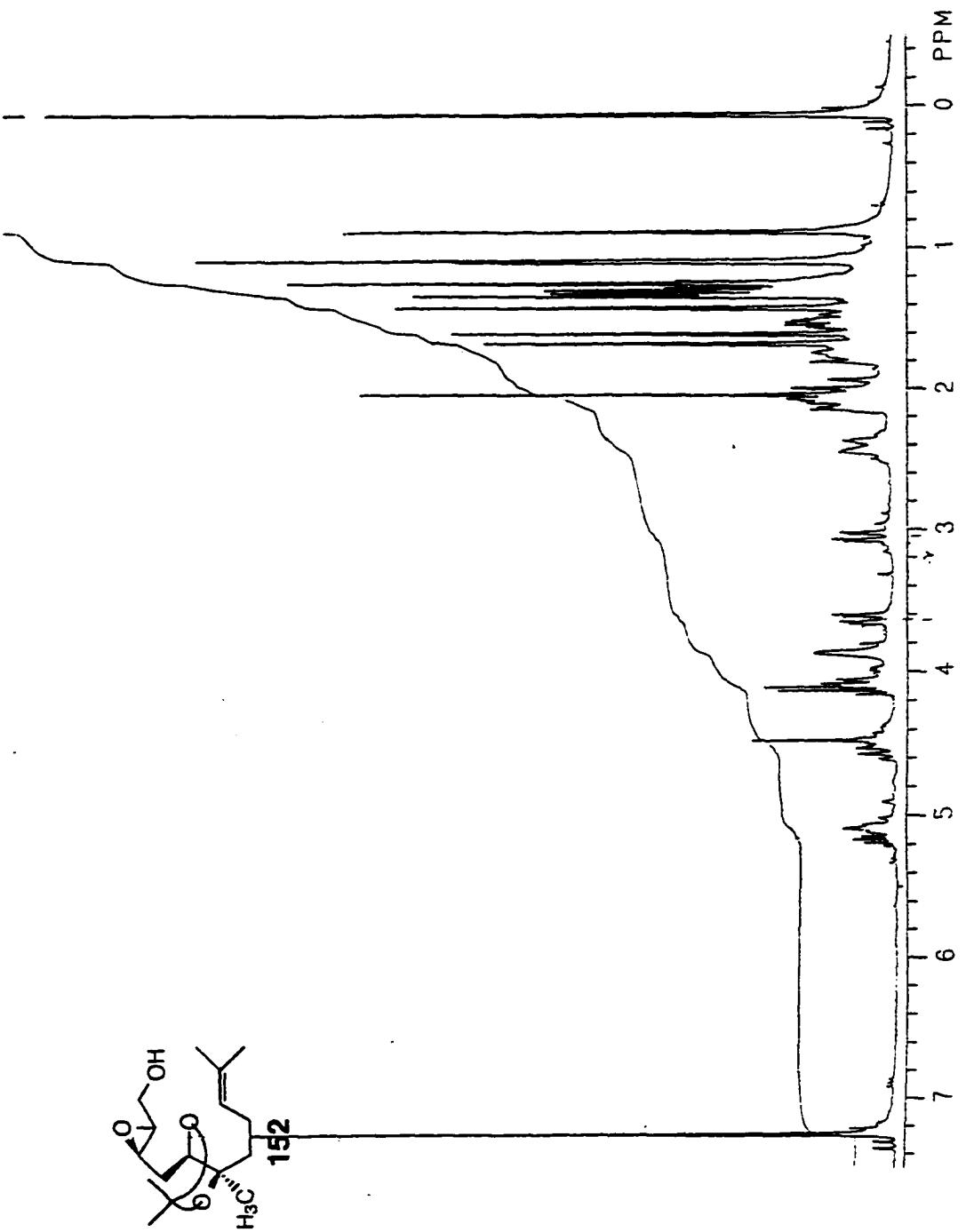

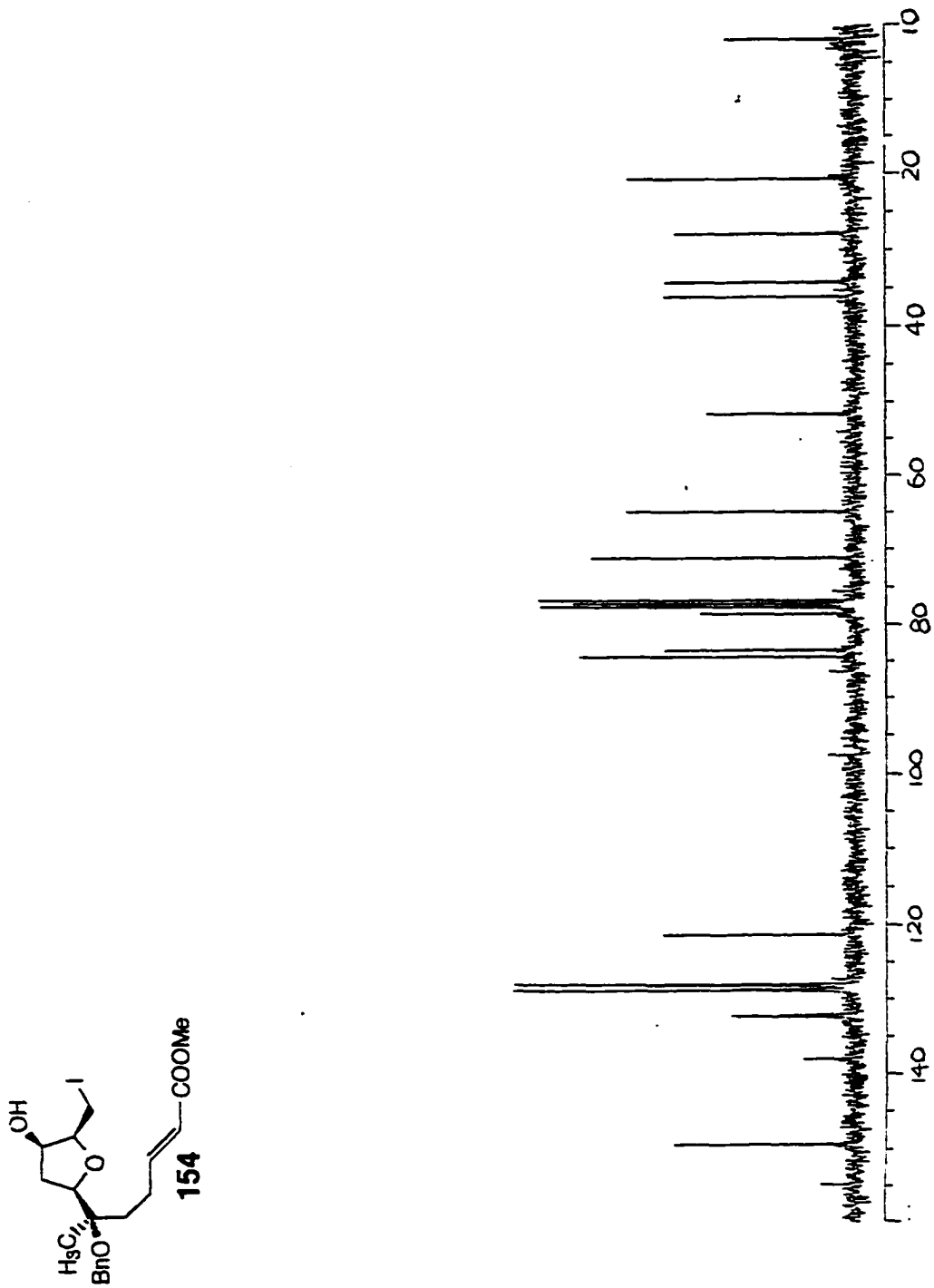

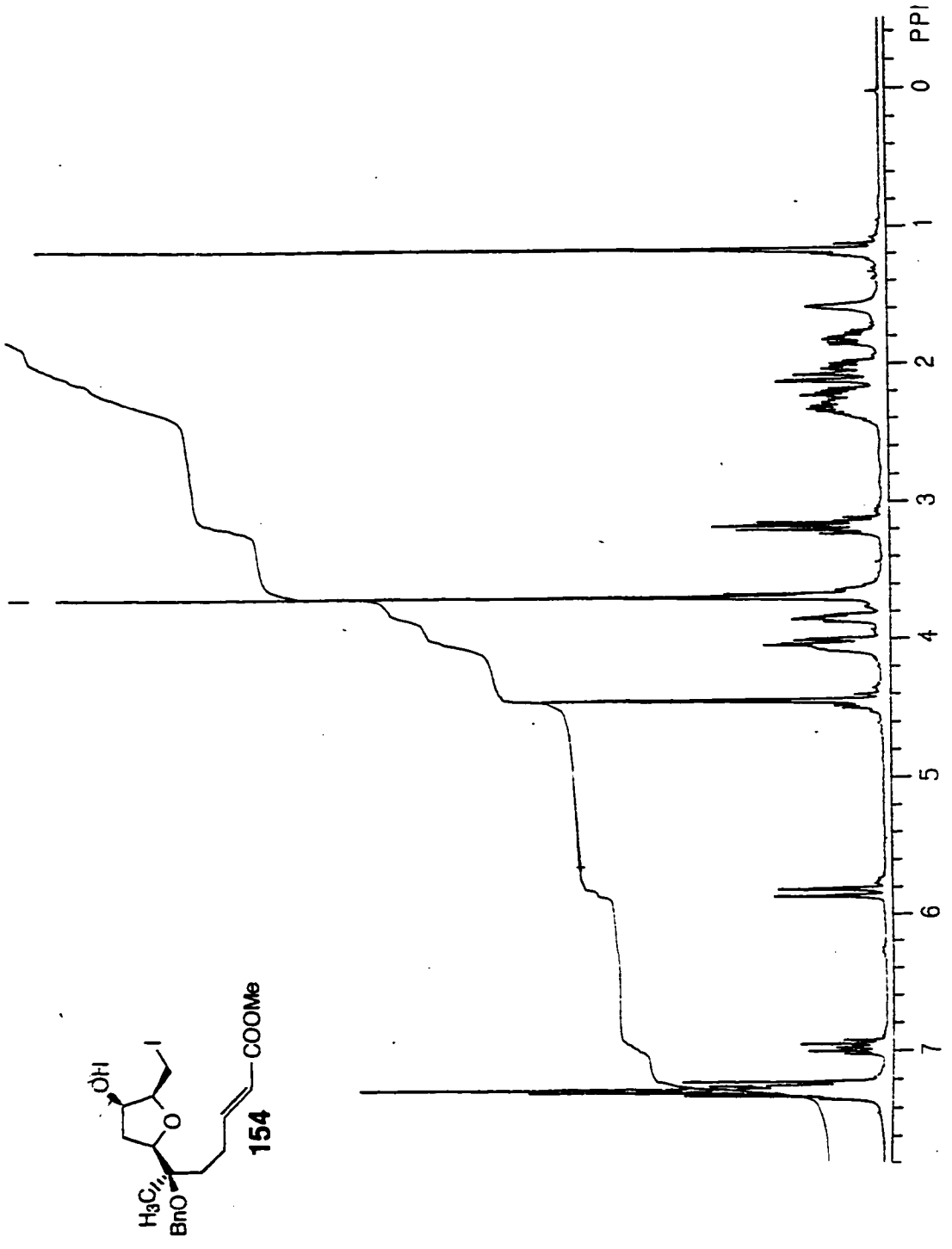

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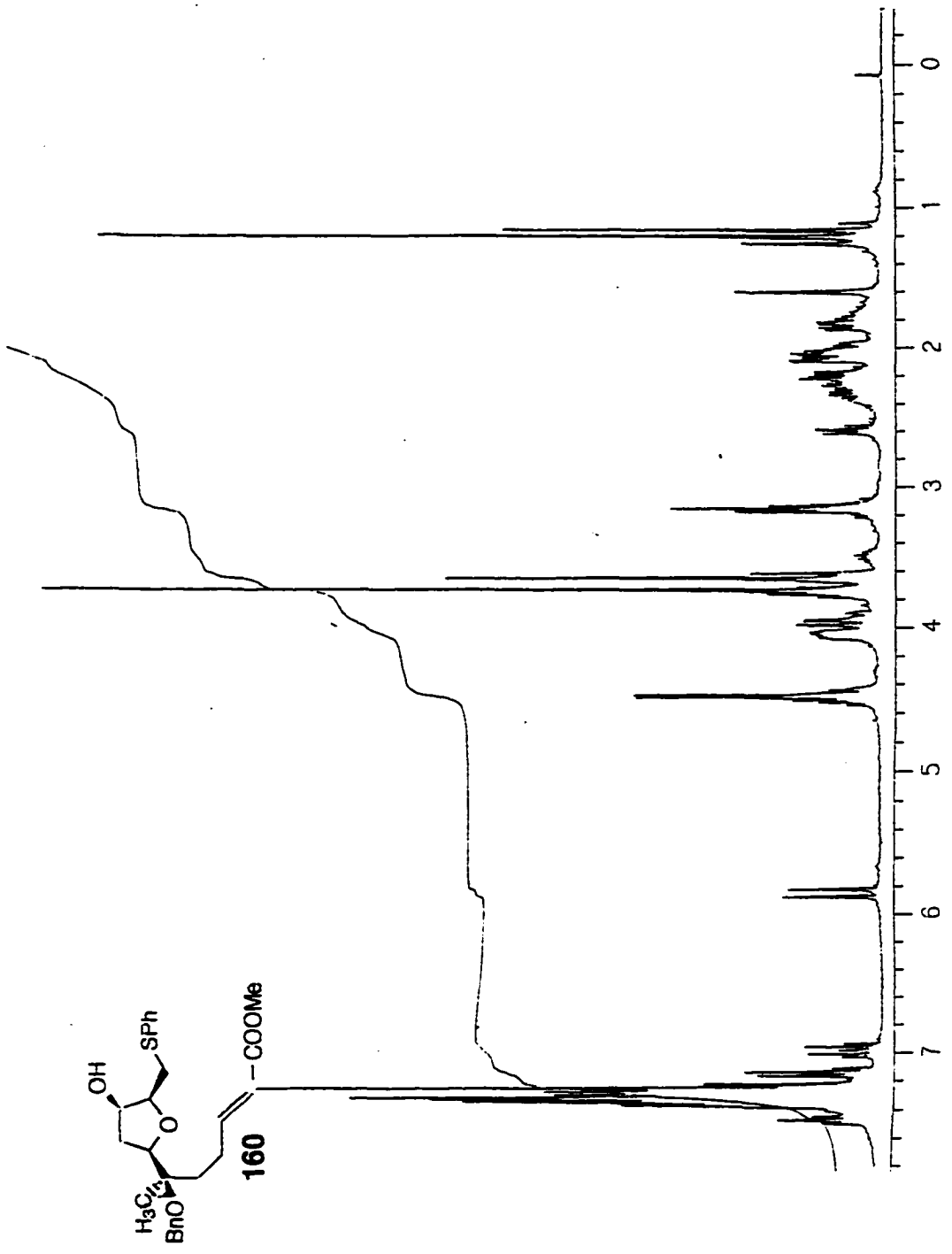

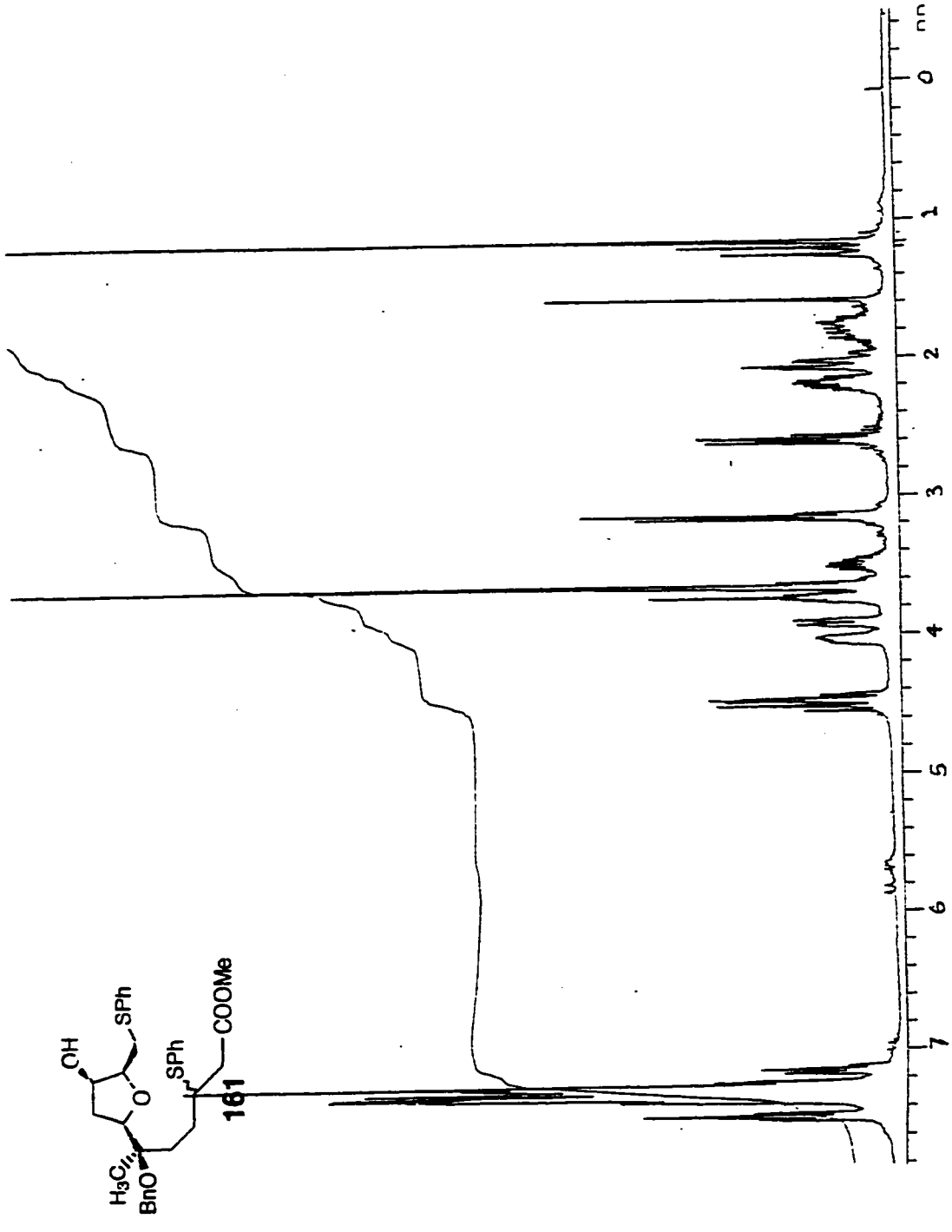

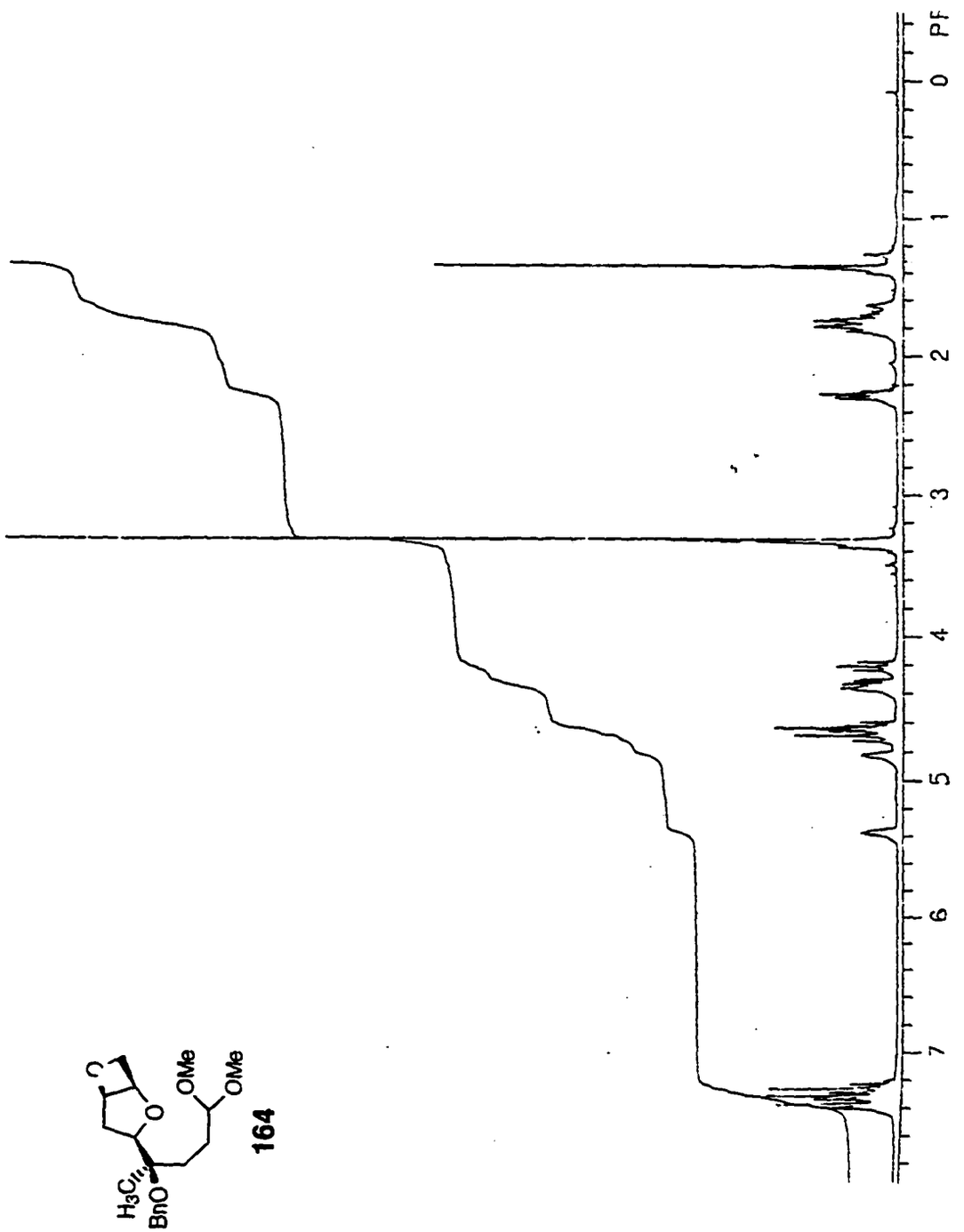

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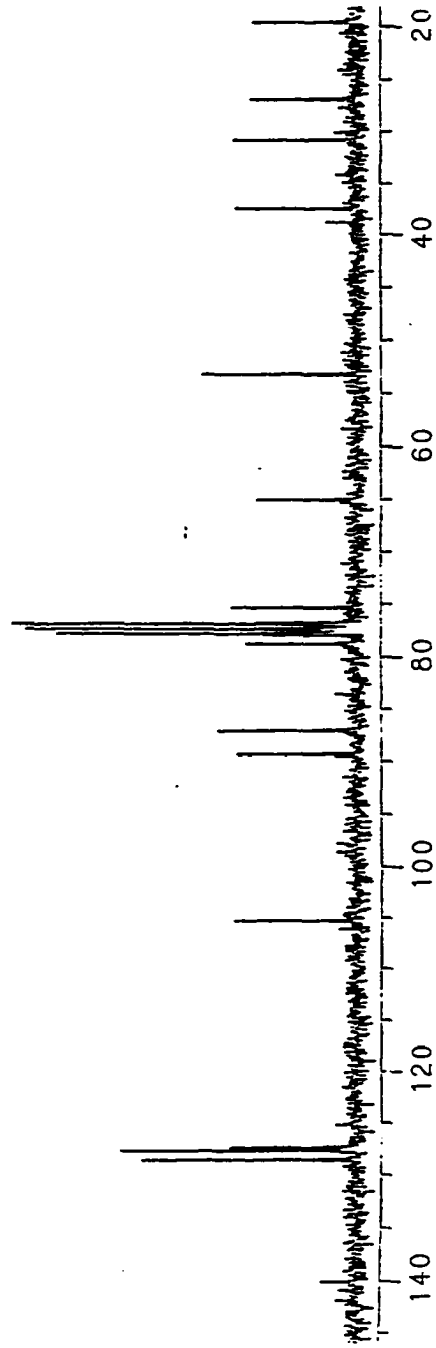

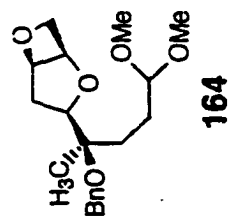

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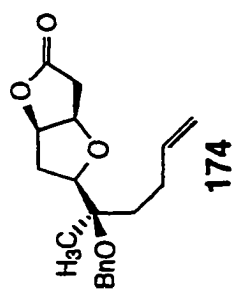

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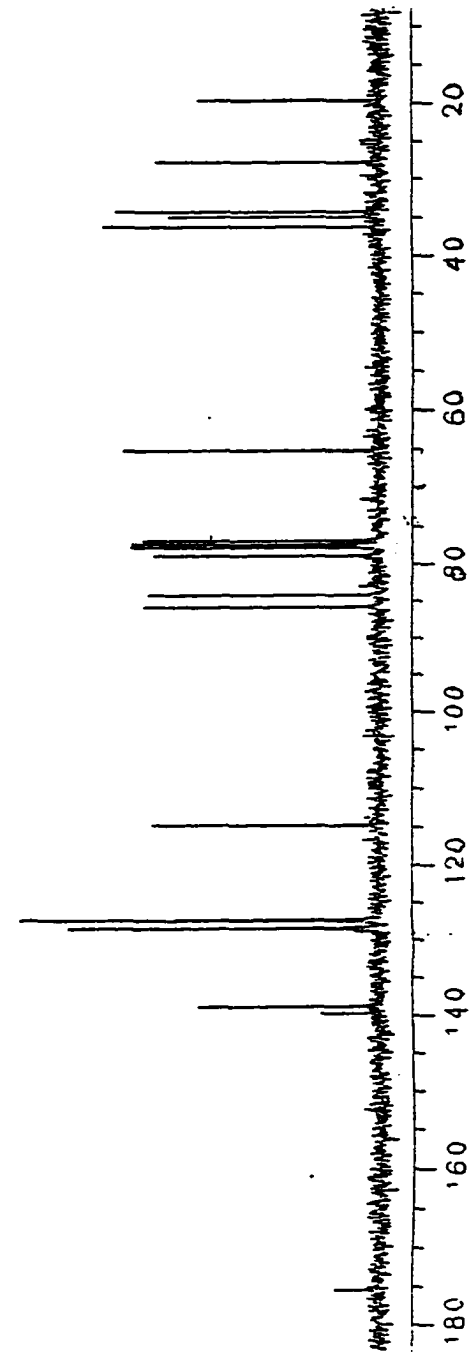

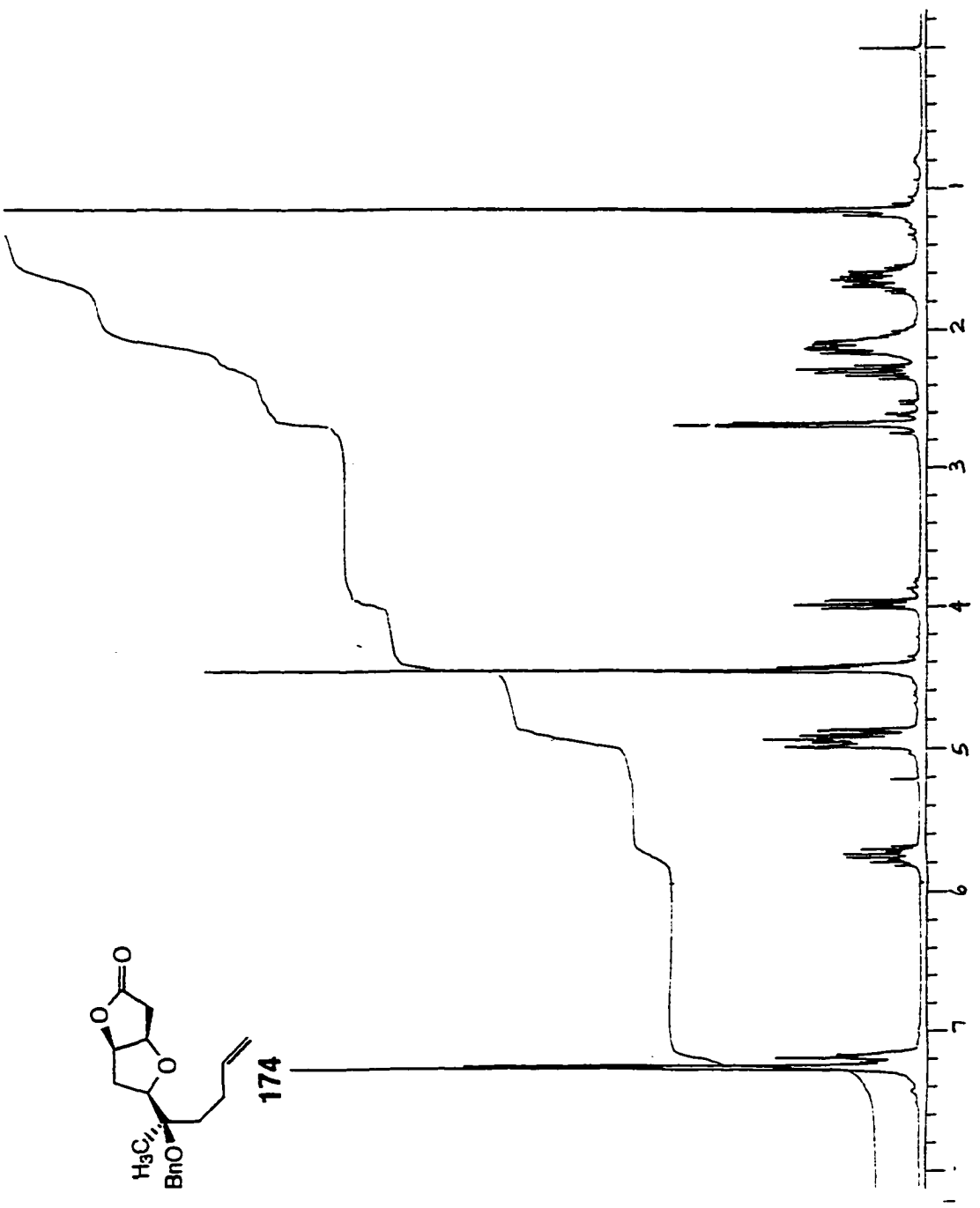

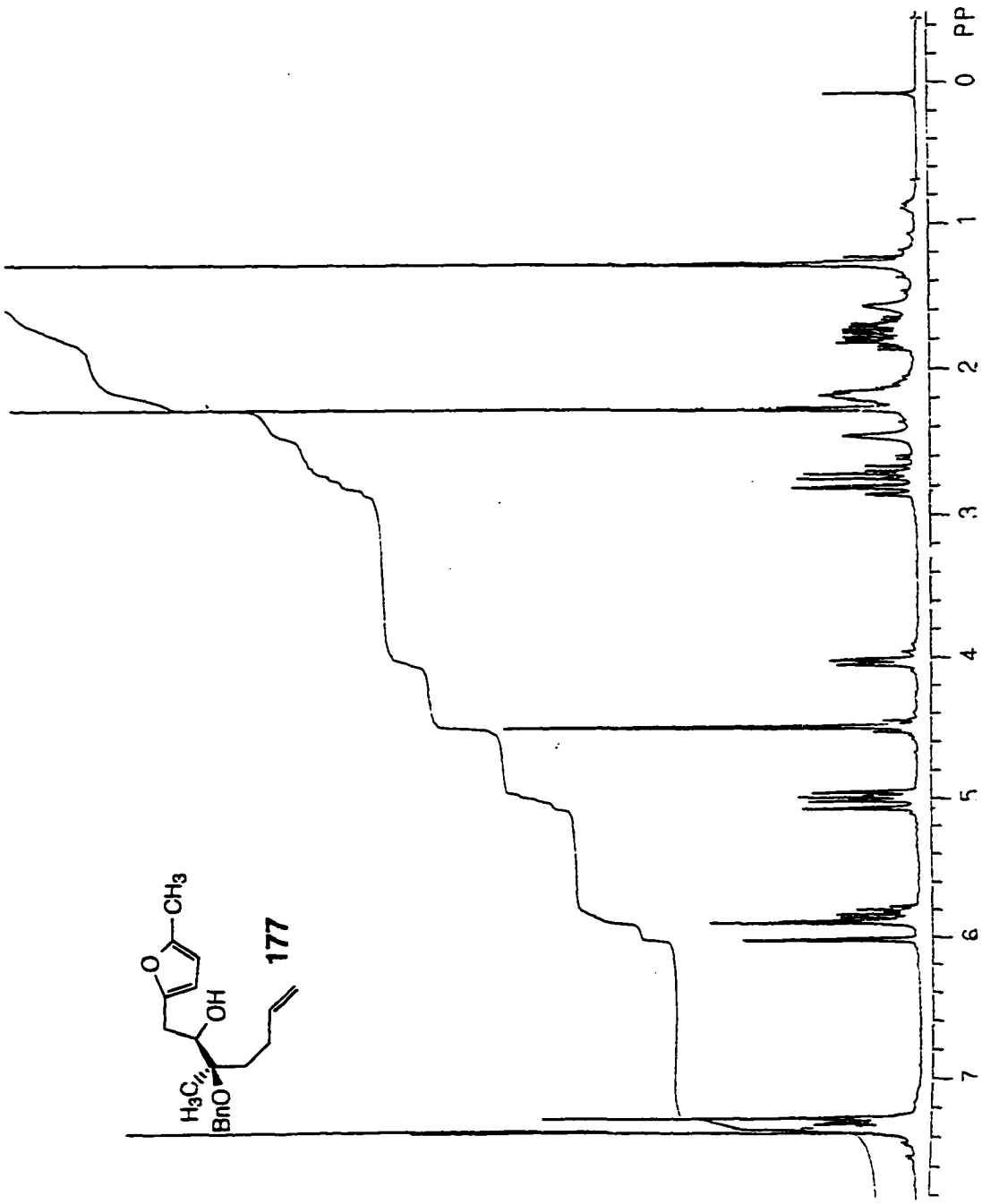

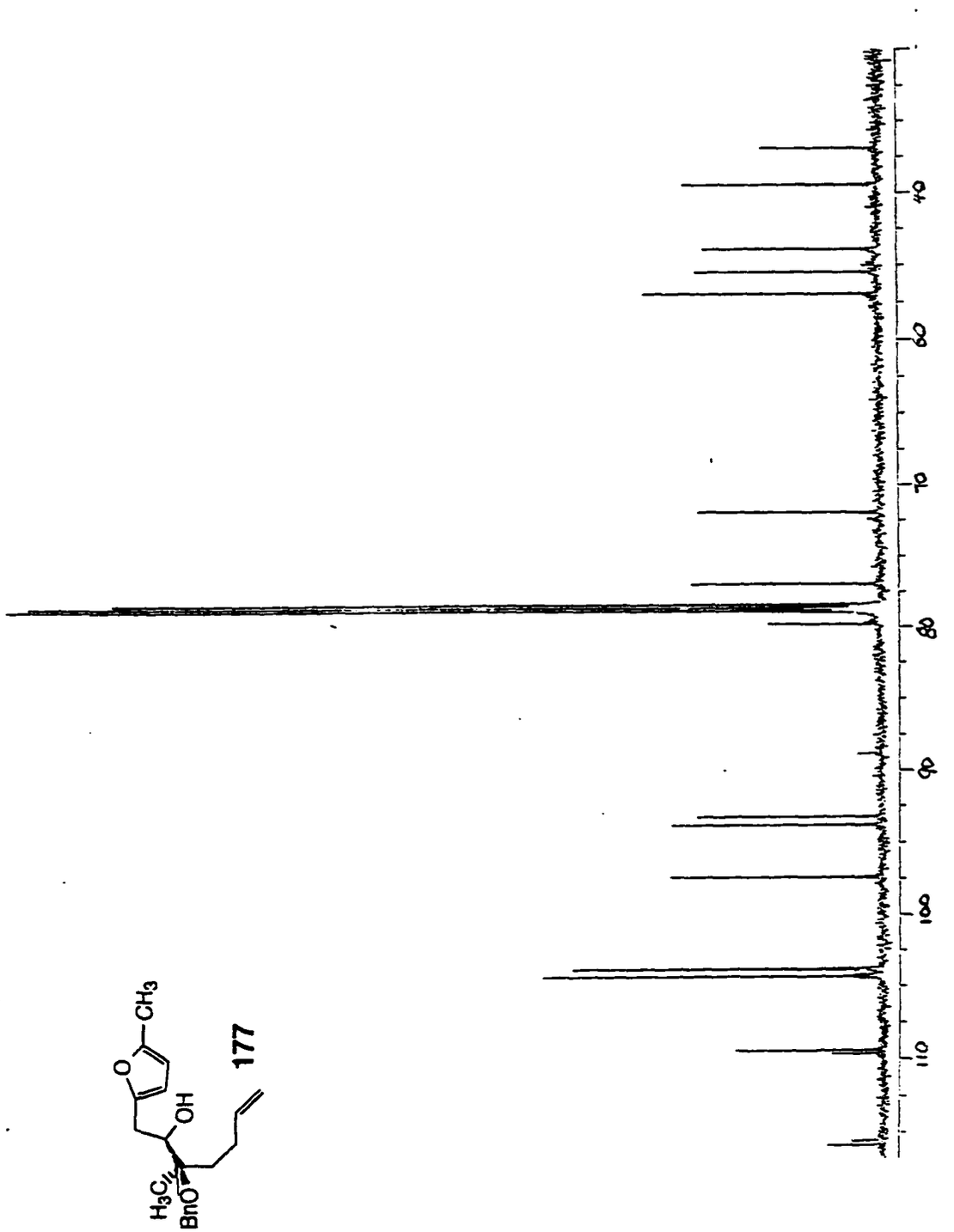

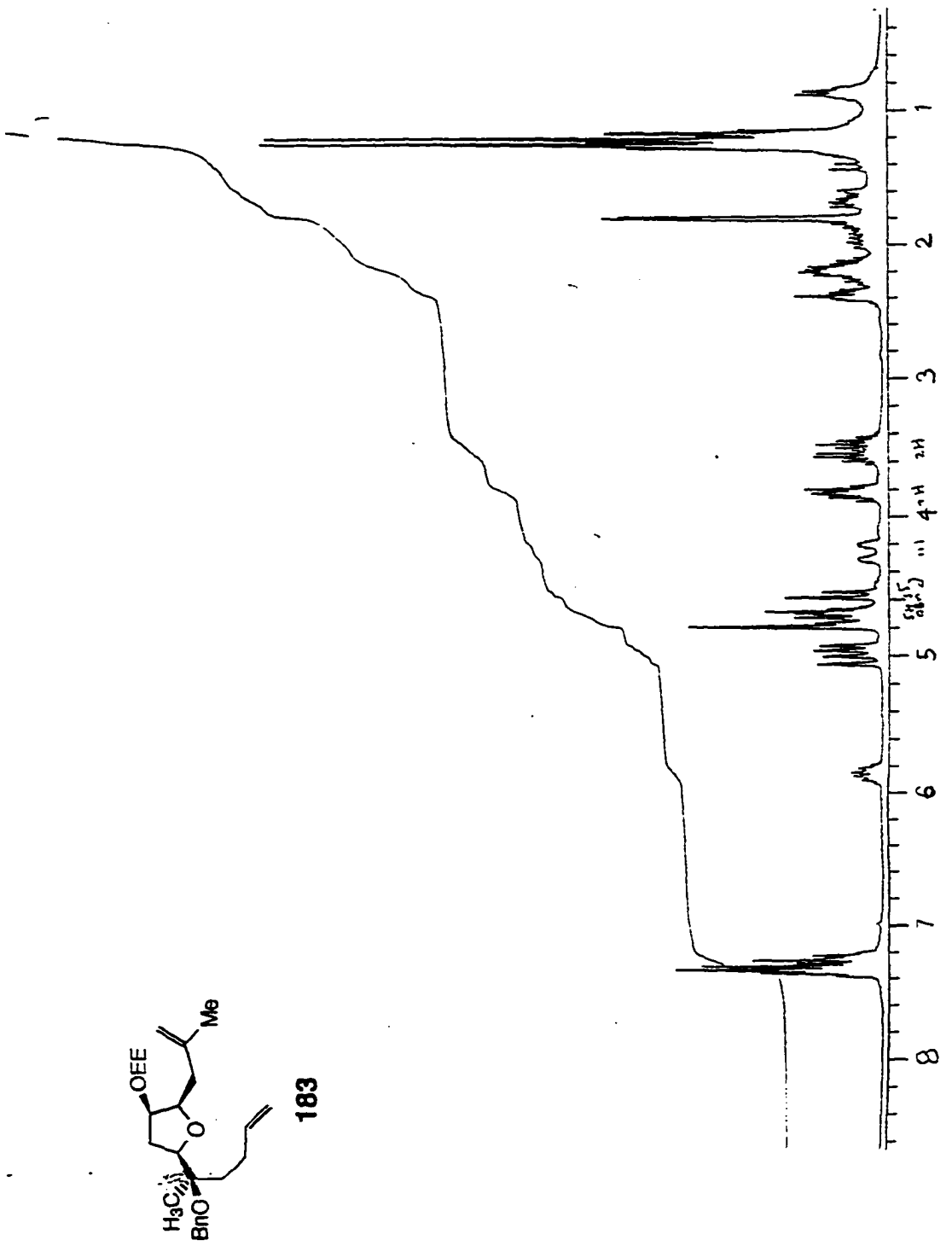

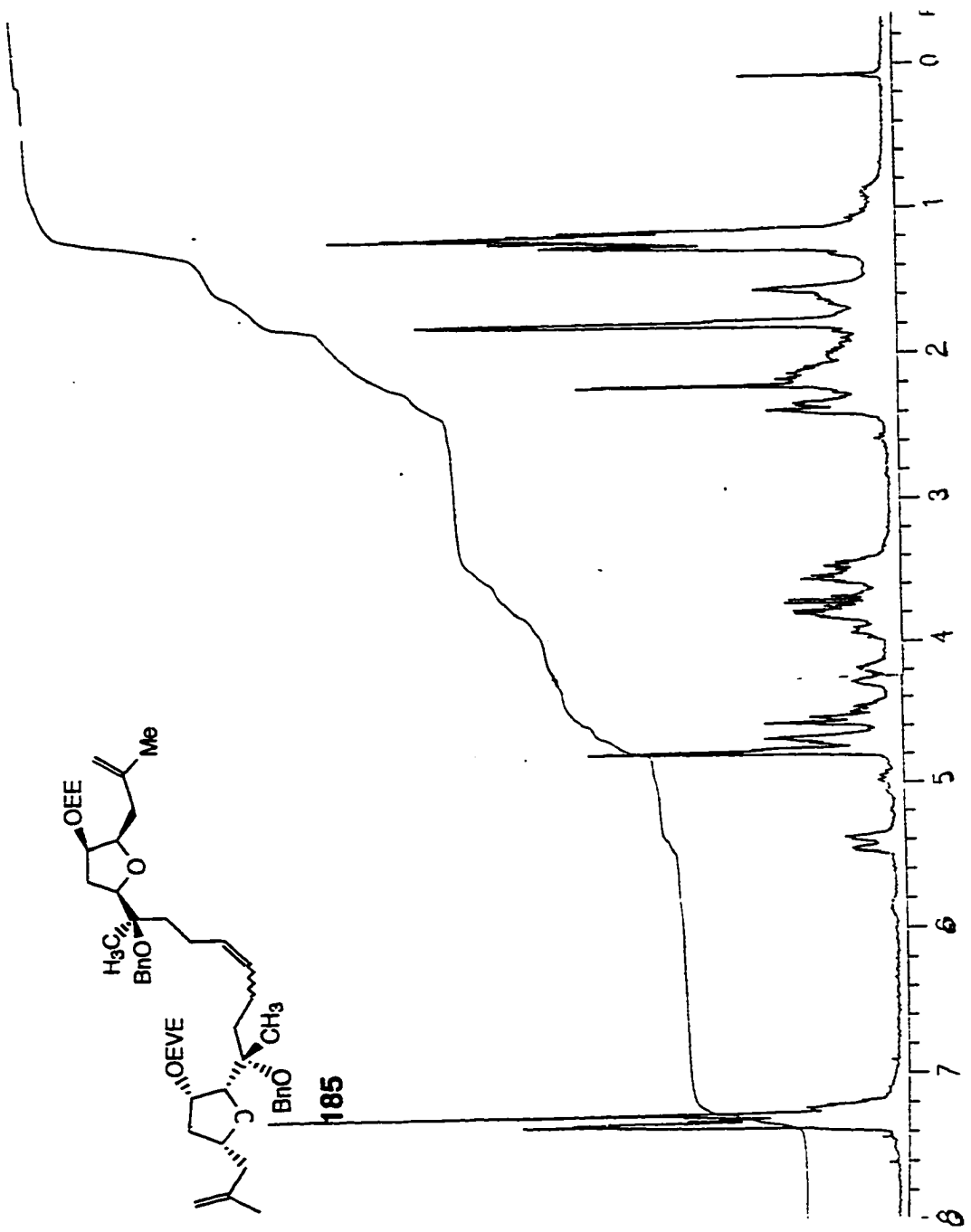

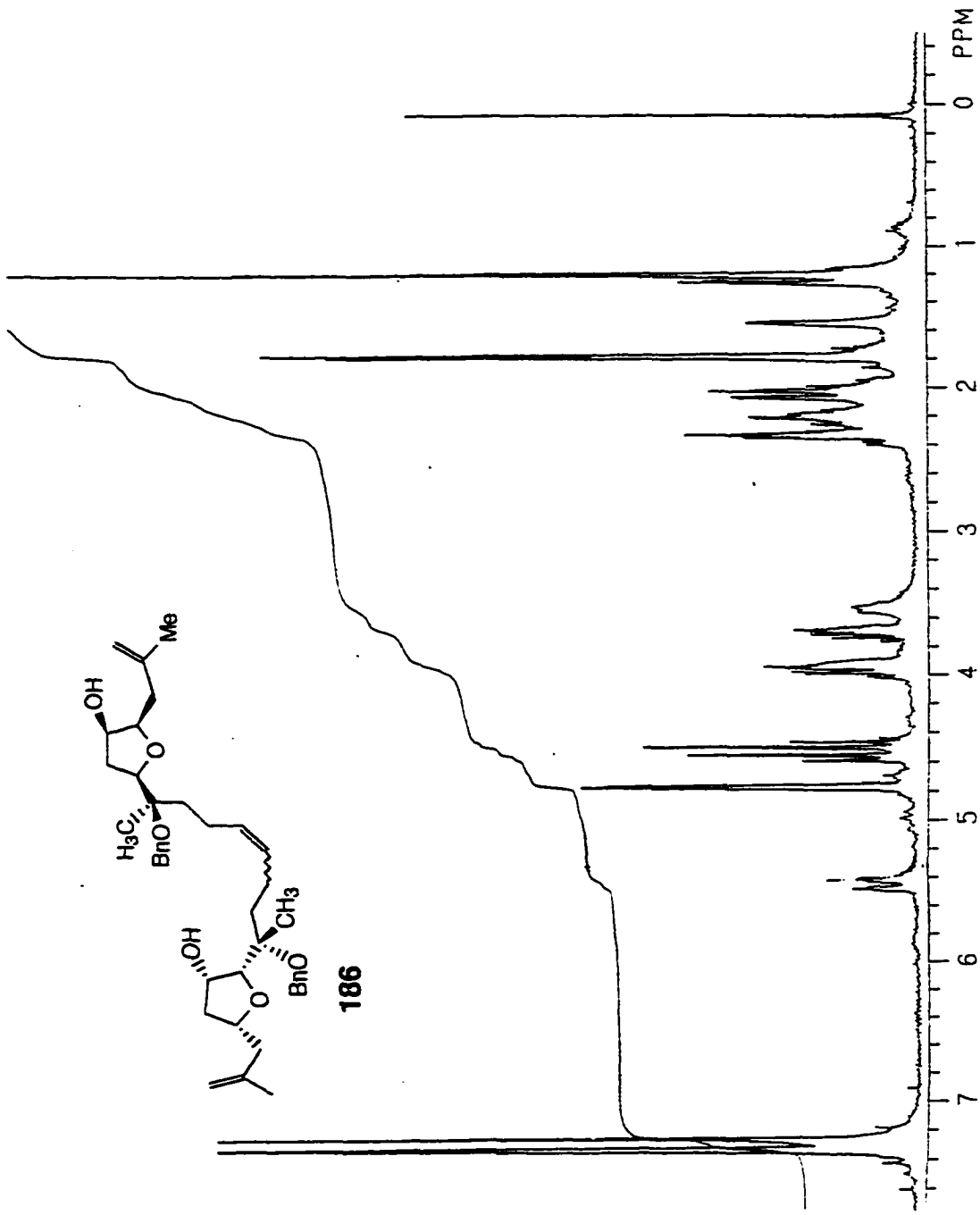

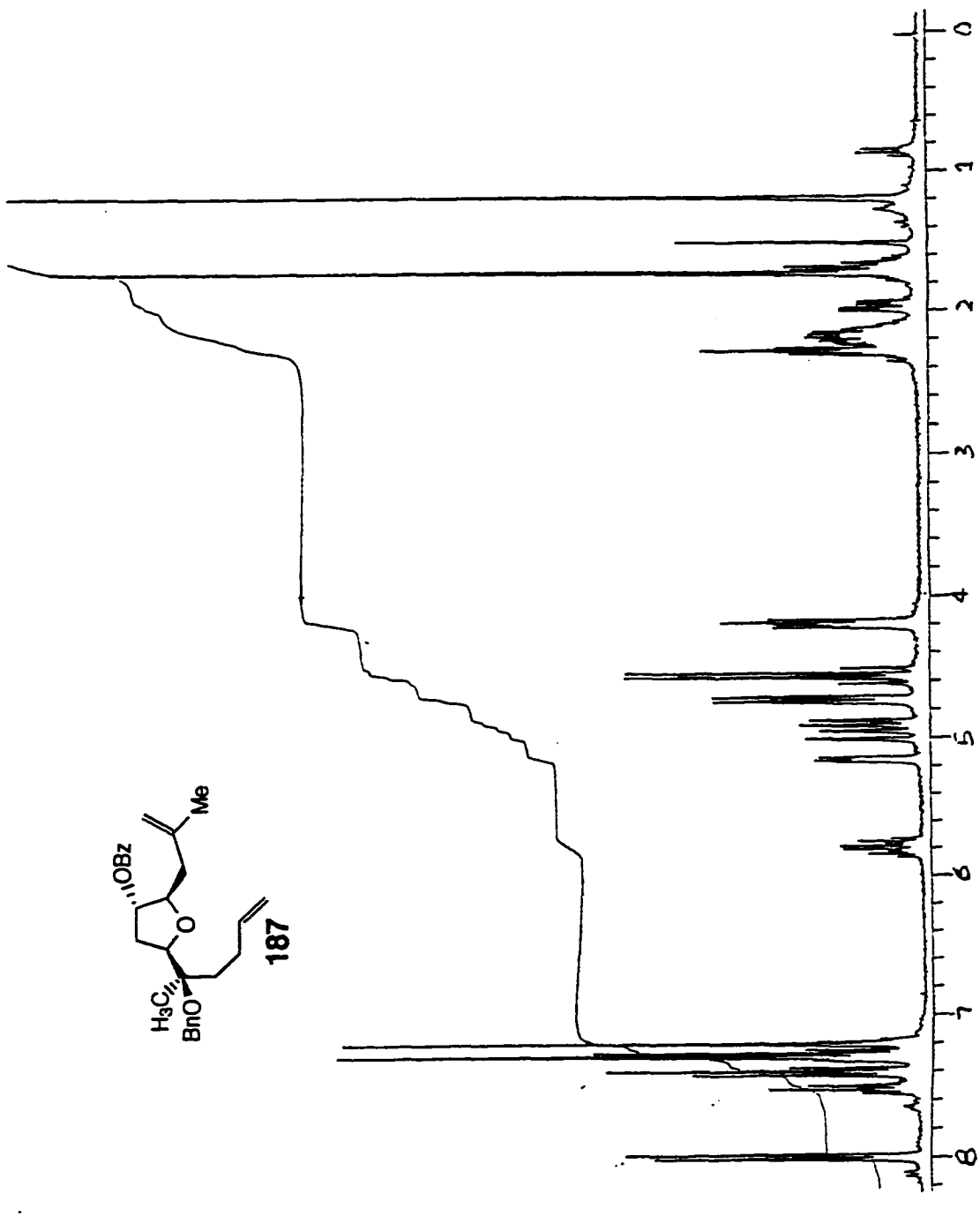

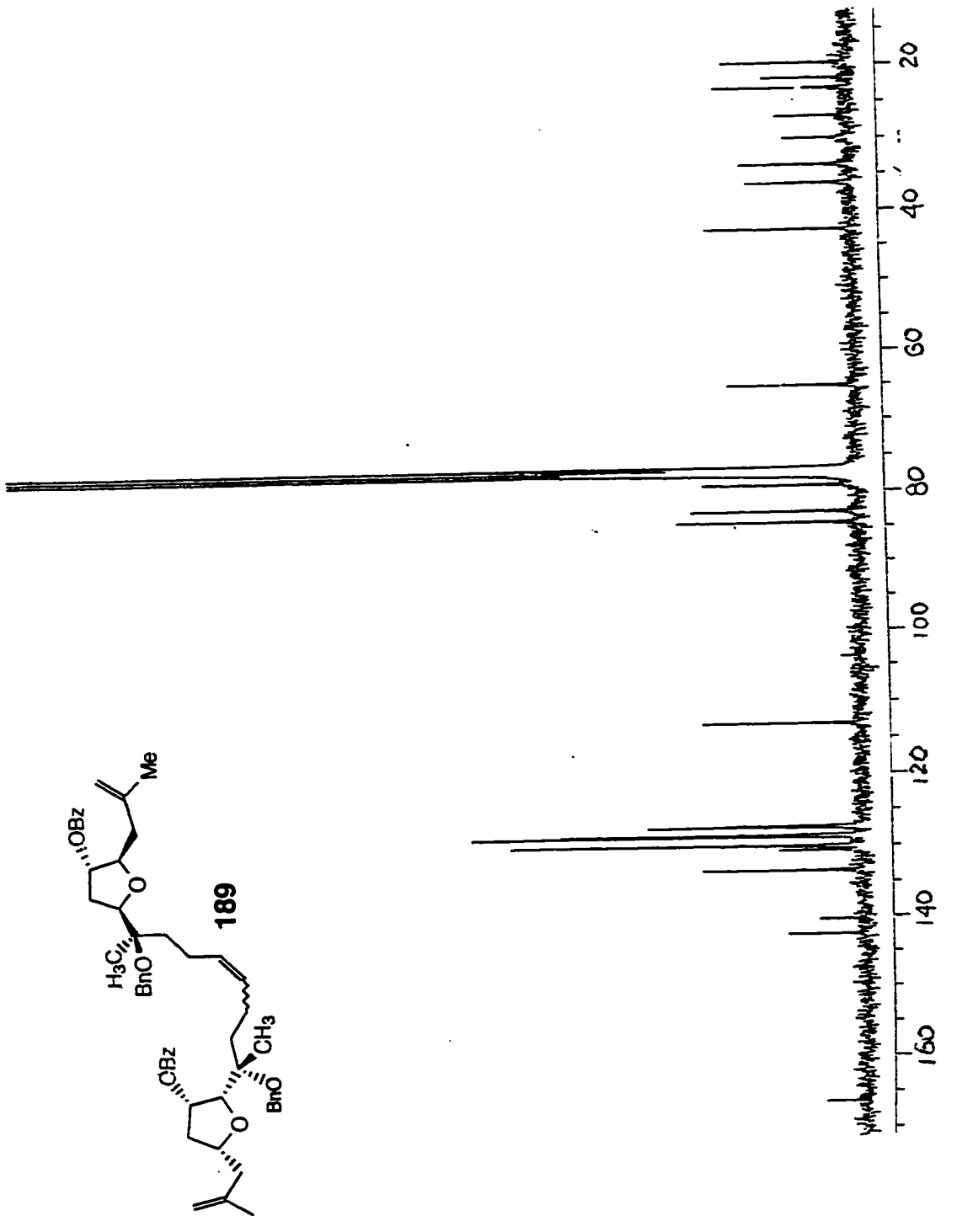

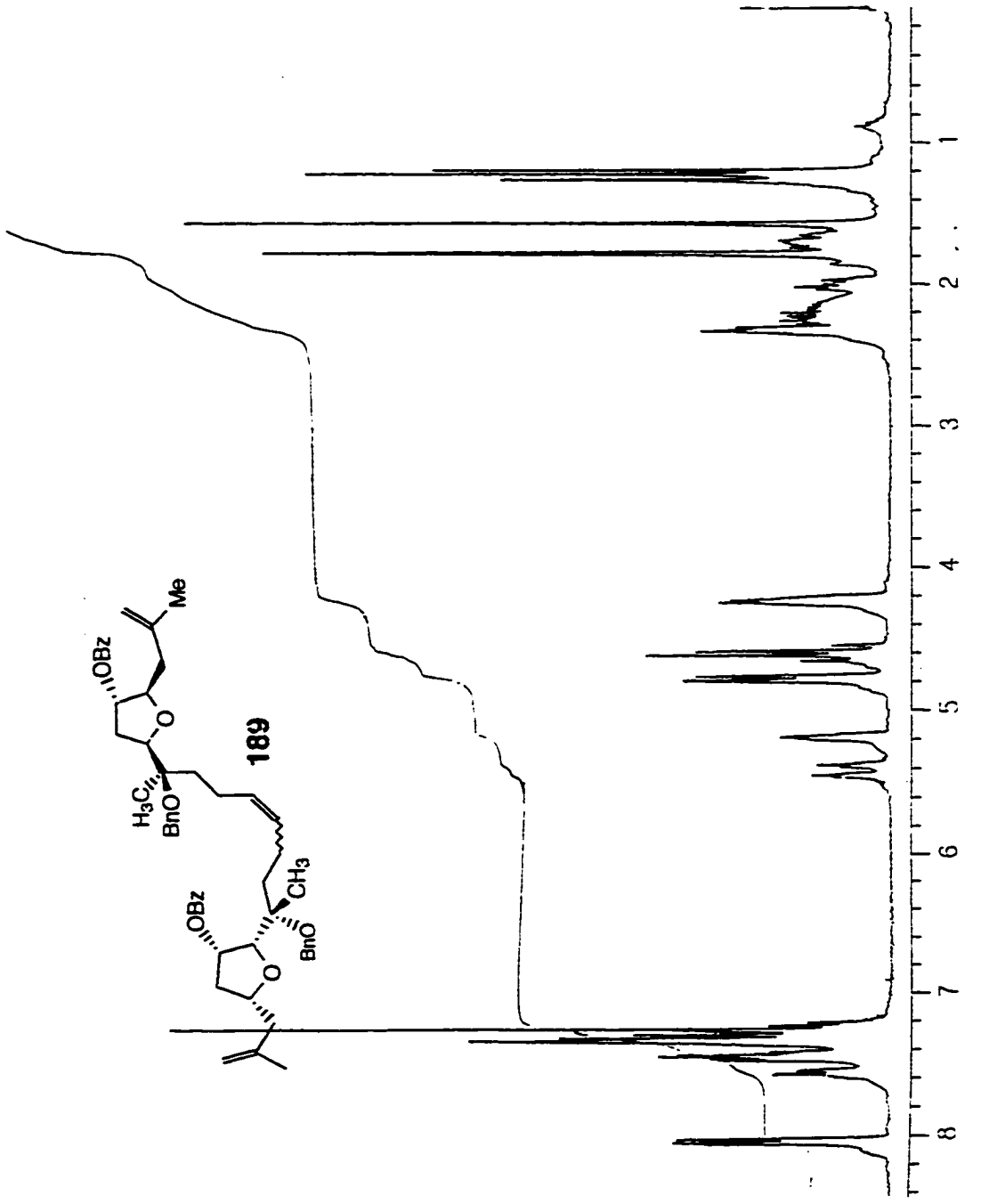

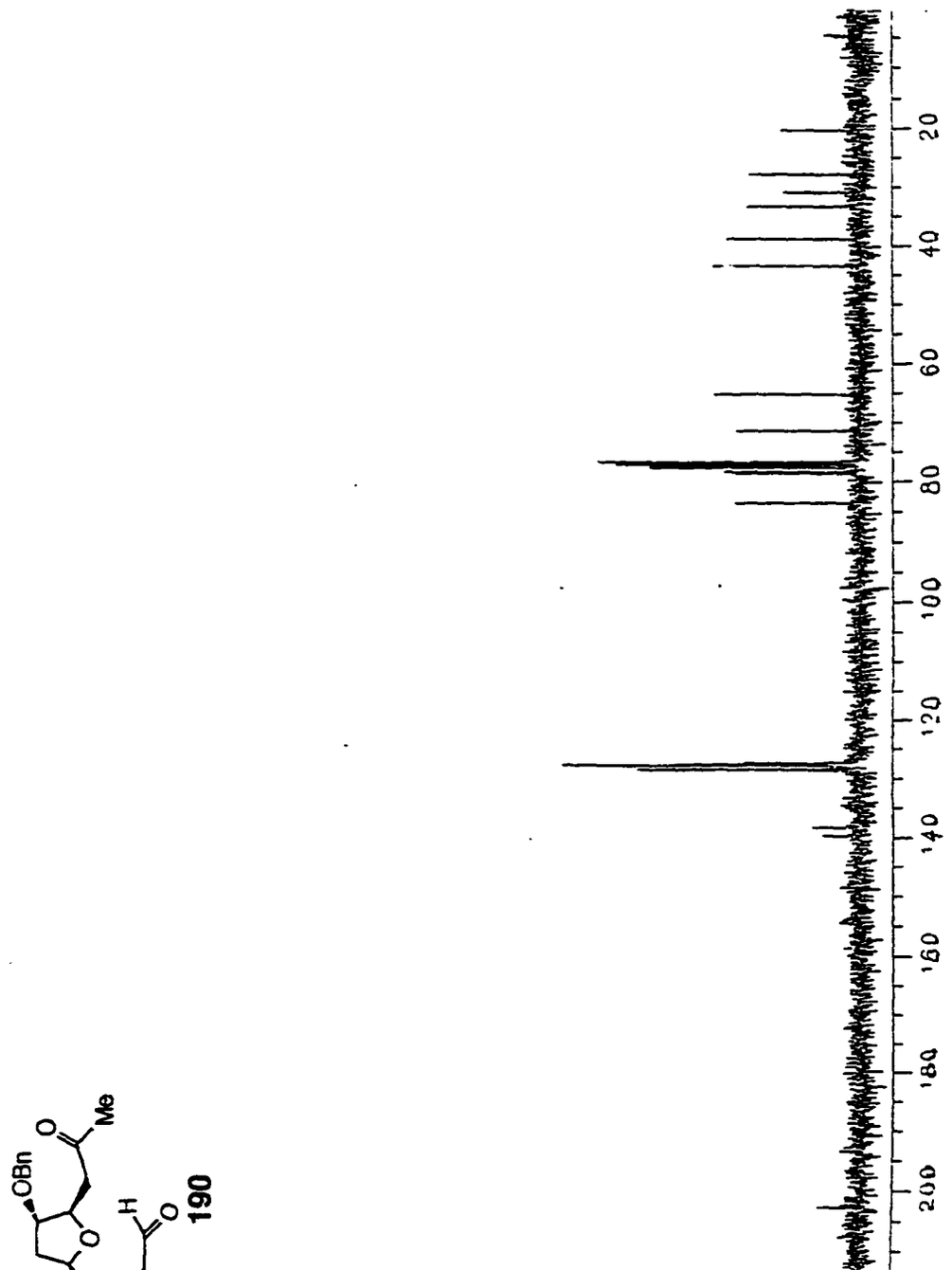

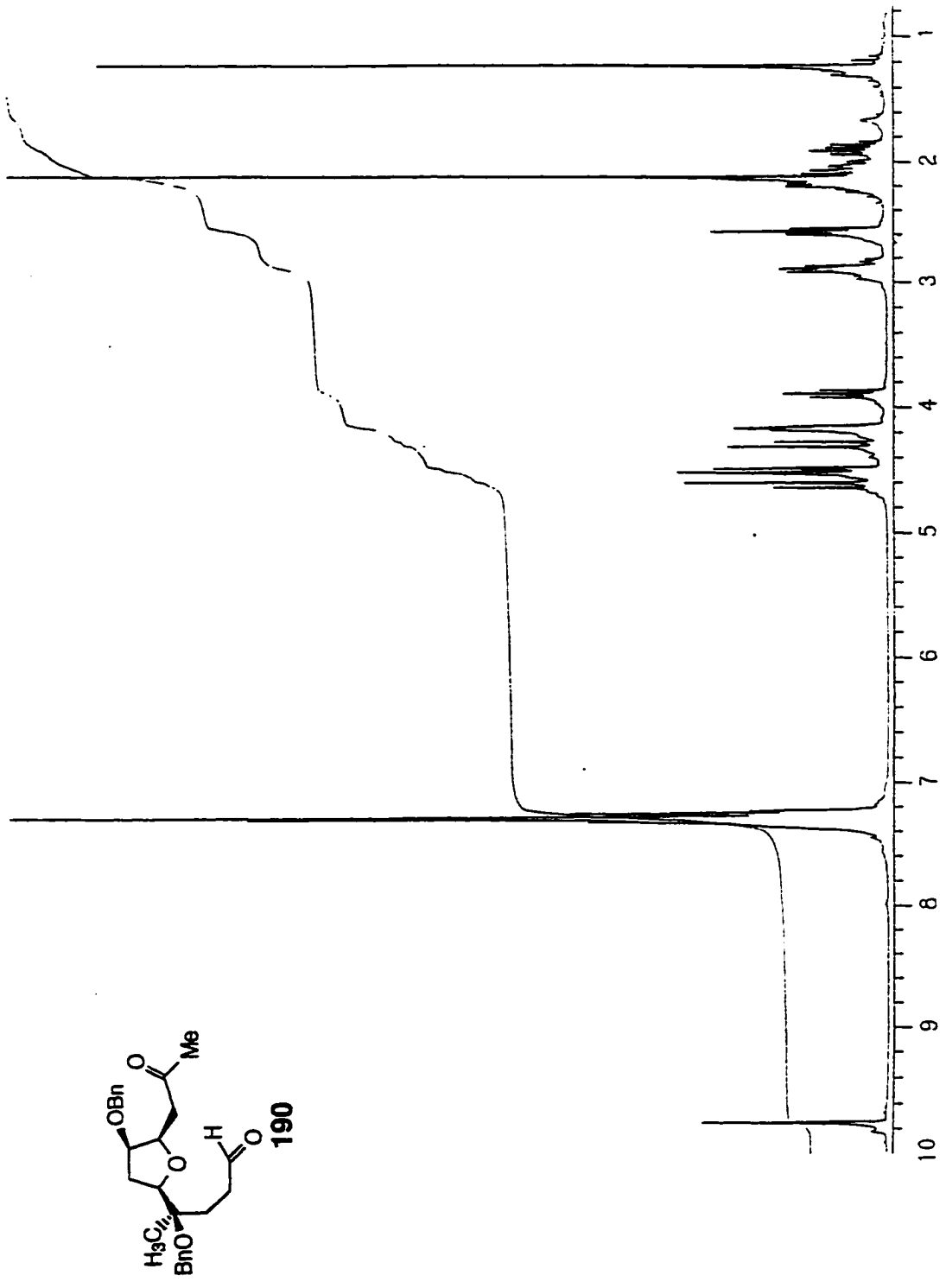

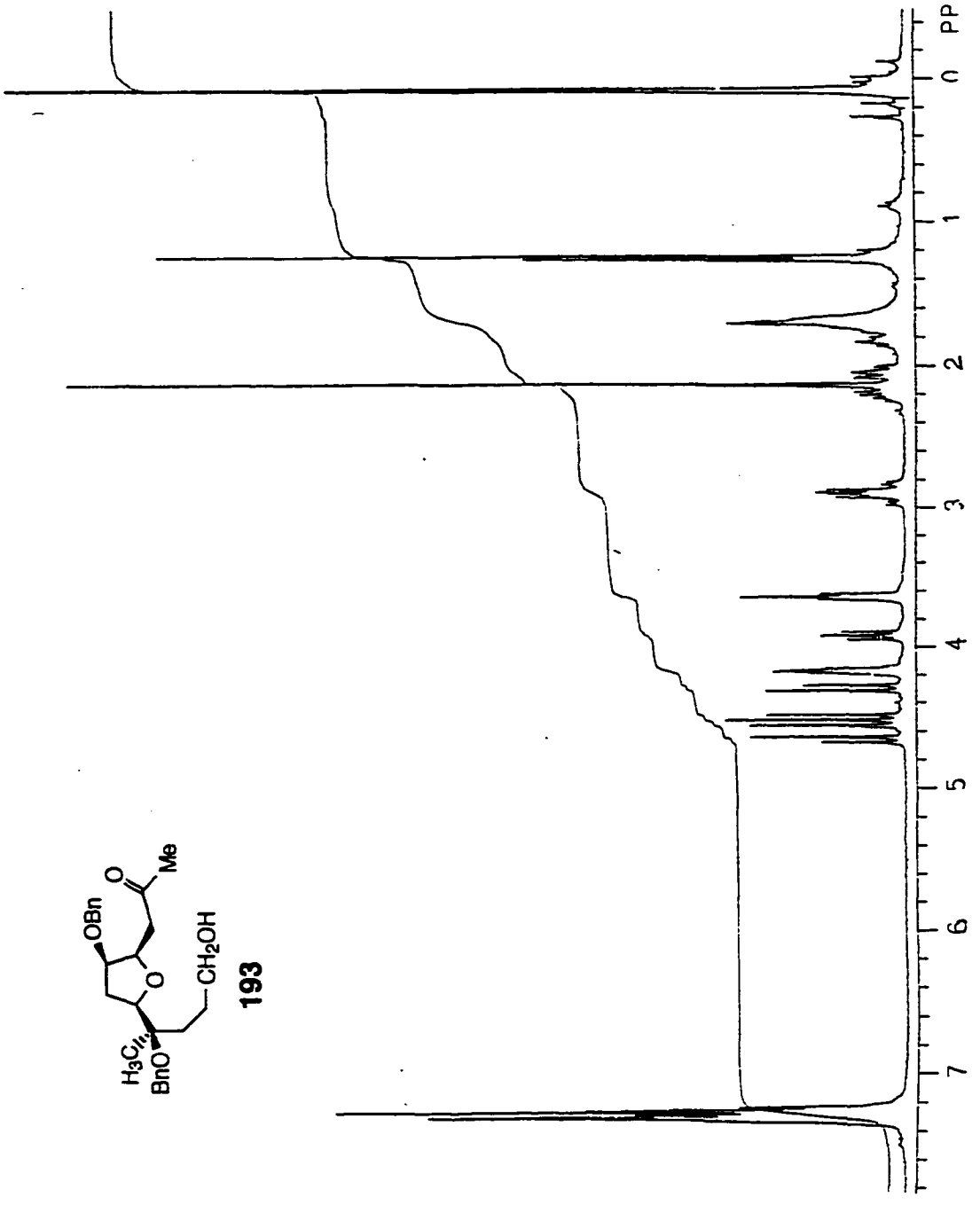

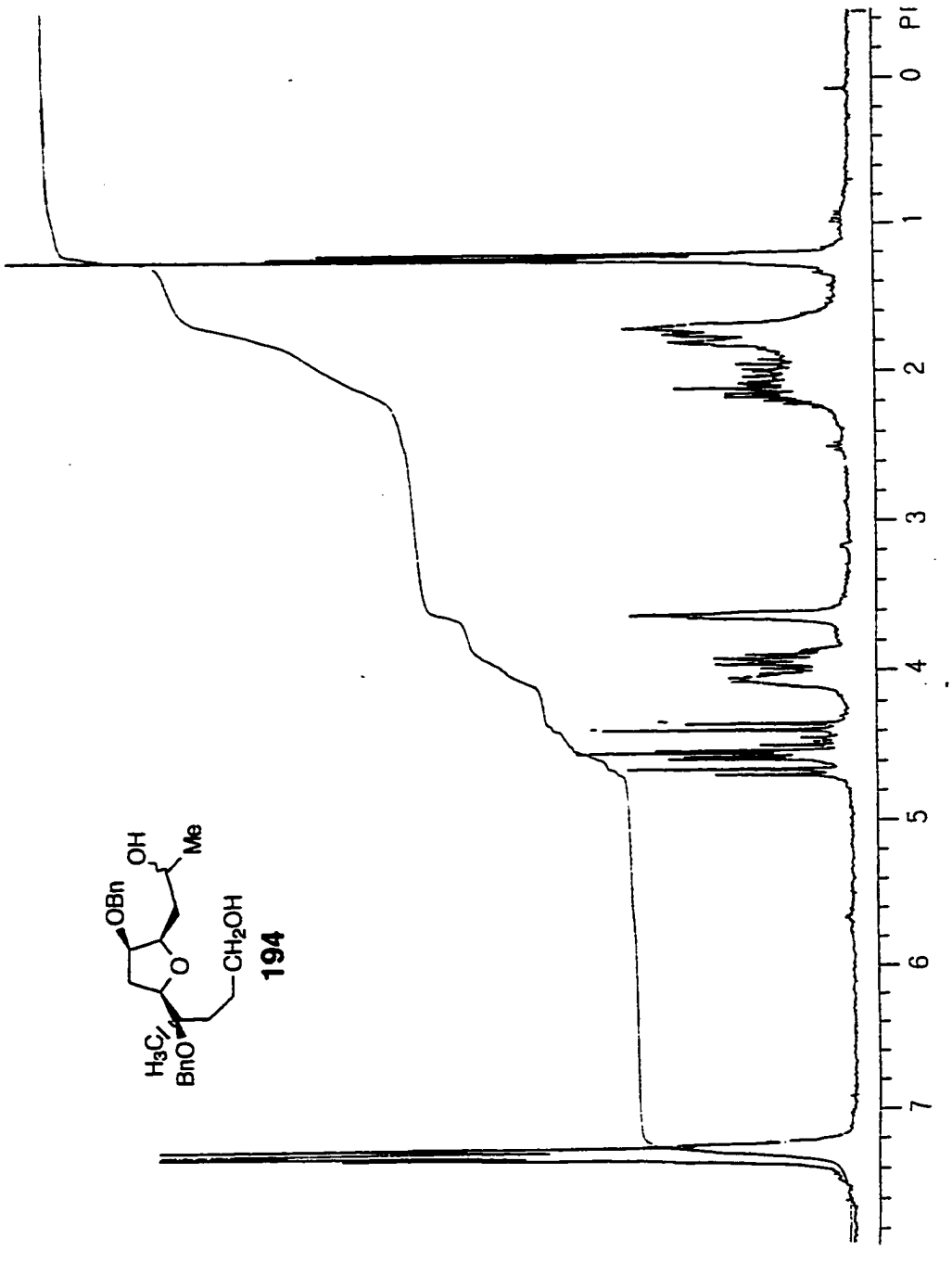

(VIII) References

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IMAGE EVALUATION
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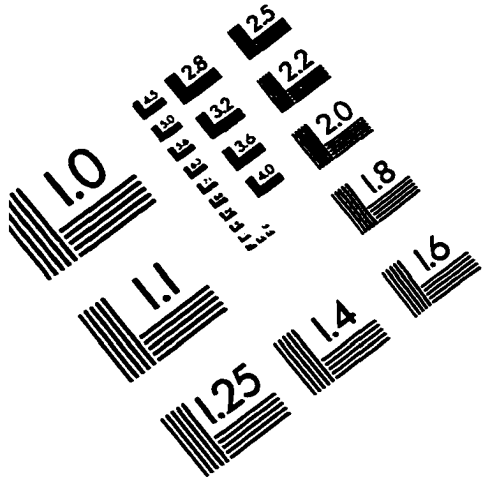

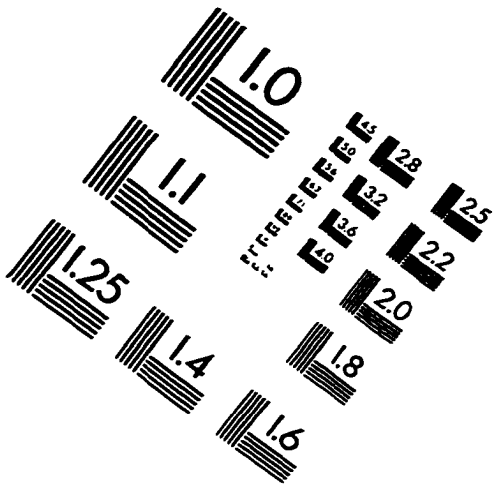

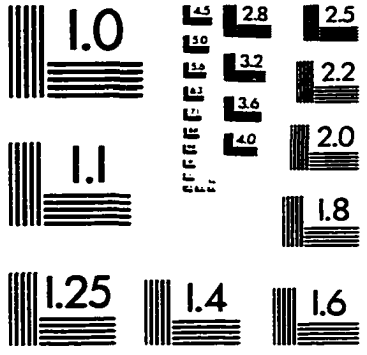

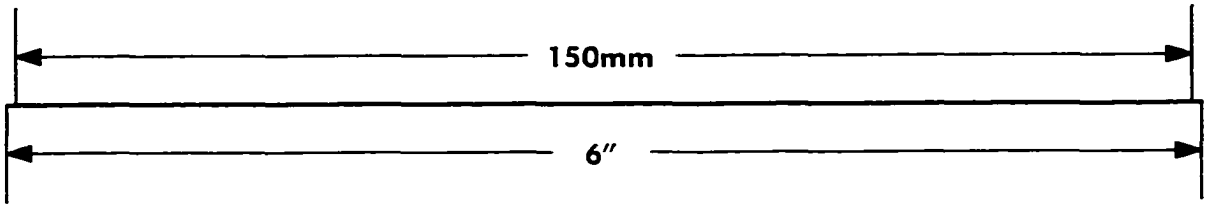

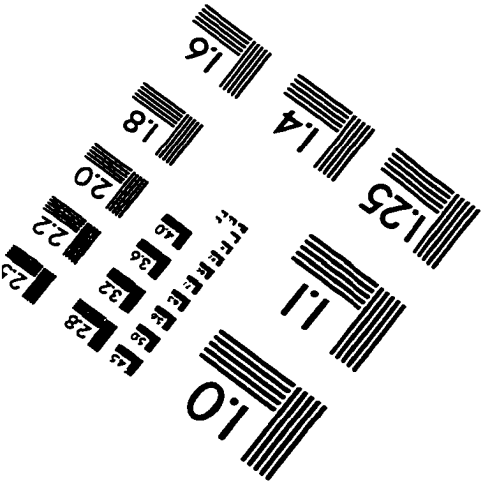

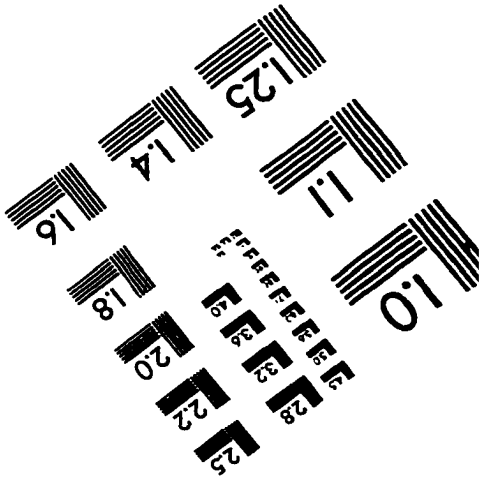

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