Synthetic Studies on Polyether Antibiotics: New Approaches to Oligo-Tetrahydrofurans and Complex Spiroketals

by

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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

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ABSTRACT

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by

Darrin R. Dabideen

Mentor: Professor David R. Mootoo

The polyether antibiotics have received considerable attention from synthetic chemists because of their scarce availability, biological activity and structural complexity. Monensin and kijimicin are two renowned members of the polyether antibiotics. Their ability to transport ion across hydrophobic membranes have attracted the attention of researchers to investigate their structure activity relationship. As a result, the synthesis of less substituted analogs have received considerable attention.

The work reported in this thesis involves the development of novel approaches for the synthesis of the spiroketal and poly-tetrahydrofuran (THF) segments of the polyether antibiotics. The first spiroketal methodology is based on a metathesis-haloetherification-silver mediated sequence of reactions. The key intermediate is a hydroxy iodo-THP, which is converted to a spiroketal when treated with silver triflate. A second spiroketal strategy involves the synthesis of a hydroxy glycal precursor. The key reaction in this synthesis is an oxocarbenium ion cyclization on a 1,2-*O*-isopropylidene enol ether substrate. The key concept in the synthesis of the poly-THF segment is the iodocyclization of C5 allylated furanoside or 1,2-*O*-isopropylidene-5-alkene template, to afford a *trans*-2,5-disubstituted THF's in high stereoselectivity and yield. Subsequent elaboration of these intermediates via Sharpless asymmetric dihydroxylation led to oligo-

THF's in high diastereoselectivity. These methodologies are highlighted by the synthesis of a spiroketal-oligo-THF analog of monensin and a truncated oligo-THF system of kijimicin.

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I want to thank my Dad and brothers Giddeon and Ronnie for their continuous and unconditional support of all my undertakings, scholastic or otherwise.

DEDICATED TO THE LOVING MEMORY

OF MY MOM,

VINDRA DABIDEEN

TO MY DAD, KNOLLIS DABIDEEN AND BROTHERS,

GIDDEON AND RONNIE

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LIST OF SYMBOLS and ABBREVIATIONS

Ac	acetyl
Ac_2O	acetic anhydride
AgOTf	silver trifluoromethanesulfonate
BF_3-Et_2O	boron trifluoride etherate
Bn	benzyl
Brine	saturated aqueous sodium chloride solution
br	broad
Bu	butyl
°C	degree Celsius
ca.	about
calcd	calculated
^{13}C NMR	carbon-13 nuclear magnetic resonance spectrometry
CSA	camphorsulfonic acid
δ	chemical shift in ppm
d	doublet
DEAD	diethyl azodicarboxylate
DIB	iodobenzene diacetate
DCC	dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
ee	enantiomeric excess
Et_2O	diethyl ether

EtOAc	ethyl acetate
EtOH	ethanol
eq	equivalent
FCC	flash column chromatography
g	gram
h	hour
^{1}H NMR	proton nuclear magnetic resonance spectrometry
HRMS	high resolution mass spectrometry
Hz	hertz
IDCP	iodonium dicollidine perchlorate
J	coupling constant
L	liter
m	multiplet
M	molar
Me	methyl
MeOH	methanol
MeOTf	methyl triflate
mg	milligram
min	minute
mL	milliliter
mmol	millimole
MPTA	α-Methoxy-α-(trifluoromethyl)phenyl acetic acid
MS	molecular sieves

NOE	nuclear Overhauser effect
Ph	phenyl
ppm	parts per million
PPTS	*para*-pyridinium toluenesulfonate
q	quartet
rt	room temperature
s	singlet
t	triplet
TBDPS	*tert*-butyl diphenyl silyl
TIA	1-thio-1,2-isopropylidene acetal
TfOH	trifluoromethanesulfonic acid (triflic acid)
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
Ts	toluenesulfonyl
vs	versus

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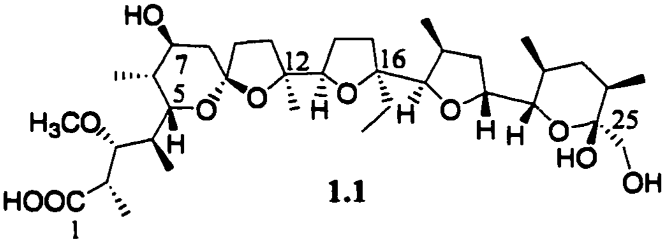
CHAPTER 1

Overview of Synthetic Strategies for Adjacently Linked THF and Spiroketal Subunits of the Polyether Antibiotics

1.1 Introduction

Monensin **1.1** (**Figure 1.1**) has attracted considerable attention because of its complex structure and potent biological activity.[1,2] Its framework is characterized by highly substituted tetrahydrofuran (THF), tetrahydropyran (THP) and spiroketal subunits. Monensin is commercially used for the control of coccidiosis in the poultry industry, enhances feed utilization in cattle and is reported to affect cardiac contractility.[1b] It is believed that bioactivity is related to the ability of polyether antibiotics to transport cations across membranes.[1b] Structural rigidity imposed by the spiroketal and THF residues, is presumably important in organization of the ring and carboxylate oxygens for cation coordination (**Figure 1.2**).[1b,3] This leads to a complex in which the cation is



1.1

Figure 1.1. Monensin

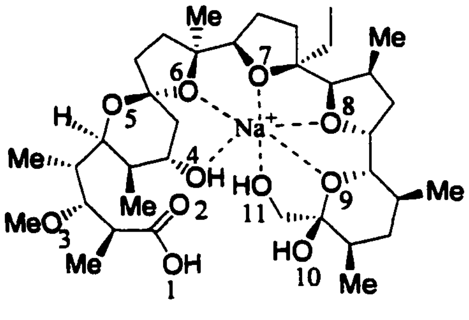
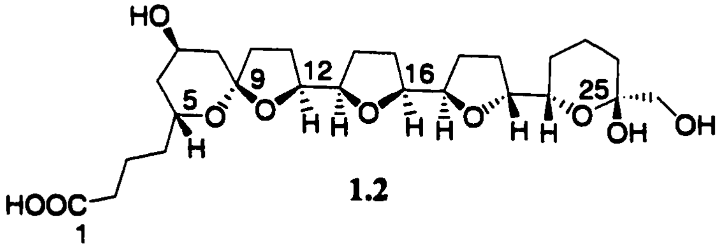


Figure 1.2. Schematic representation of anhydrous Na$^+$-monensin complex.

encapsulated and the carbon framework presents an outer hydrophobic surface, thereby facilitating migration of the polyether-cation complex across membranes.[1b]

The energetics of ion complexation of monensin and its derivatives has been investigated.[4] Still[5] has demonstrated that conformational preorganization is important to binding. Changes to the substituents and stereochemical arrangements at C2 and C3 of monensin resulted in similar binding energies to that of monensin. These derivatives illustrate that the avoidance of +gauche/-gauche pentane interactions creates an effective mechanism for an acyclic conformational lock, thereby controlling the geometry of the flexible C1-C5 side chain. Nagatsu[6] demonstrated that monensin, which selectively transports Na^+, could be converted to a Ca^{2+} ionophore by the introduction of a second carboxyl group at C25 of **1.1**. These studies illustrate the interest in unnatural derivatives of **1.1** for the study of structure-activity relationships. In this vein, the synthesis of the monensin analog **1.2** (**Figure 1.3**) was undertaken. The peripheral substituents at C2, C3, C4, C6, C12, C16, C18, C22 and C24 of **1.1** are replaced by hydrogens in **1.2**. However, analog **1.2** is similar to **1.1**, with respect to the relative position of the oxygen coordination sites and stereochemical arrangements of the carbons. How these substitutions affect the ground state conformation and binding affinities will be investigated.



1.2

Figure 1.3. Monensin analog

The polyether antibiotics have been popular targets for the development of new methods for the synthesis of the 2,5-disubstituted THF's and spiroketals.

1.2 2,5-Disubstituted THF's

The widespread occurrence of 2,5-disubstituted THF's in other groups of natural products such as acetogenins, has led to the development of numerous methods for their synthesis.[7] The more important approaches that may be applied to adjacently linked THF's will be summarized. These procedures involve enantioselective synthesis of THF precursors and their stereoselective conversion to THF's. Strategies developed for the enantioselective synthesis of precursors are based on Sharpless epoxidation and dihydroxylation,[7,8,9,10] chiral addition of allenyl tin reagents to aldehydes[10a] and elaboration of natural enantiopure materials.[11] Some of the more successful methodologies for THF formation include the cycloetherification of hydroxy epoxides[8] and hydroxy alkenes,[9,12,13] and variations of the Williamson ether synthesis[10] (**Figure 1.4**).

Hoye[8a] described the use of the bis-hydroxy epoxide **1.4** in the synthesis of (+)-parviflorin **1.6**. Starting with the bis-allylic alcohol **1.3**, the stereogenic centers in the bis-THF backbone were installed by sequential double Sharpless asymmetric epoxidation and dihydroxylation[14] to provide **1.4**. Treatment of **1.4** with trifluoroacetic acid effected an "inside-out" epoxide cascade reaction producing the *trans* bis-THF core **1.5**. Subsequent elaboration of the terminal hydroxyl groups gave **1.6** (**Scheme 1.1**).

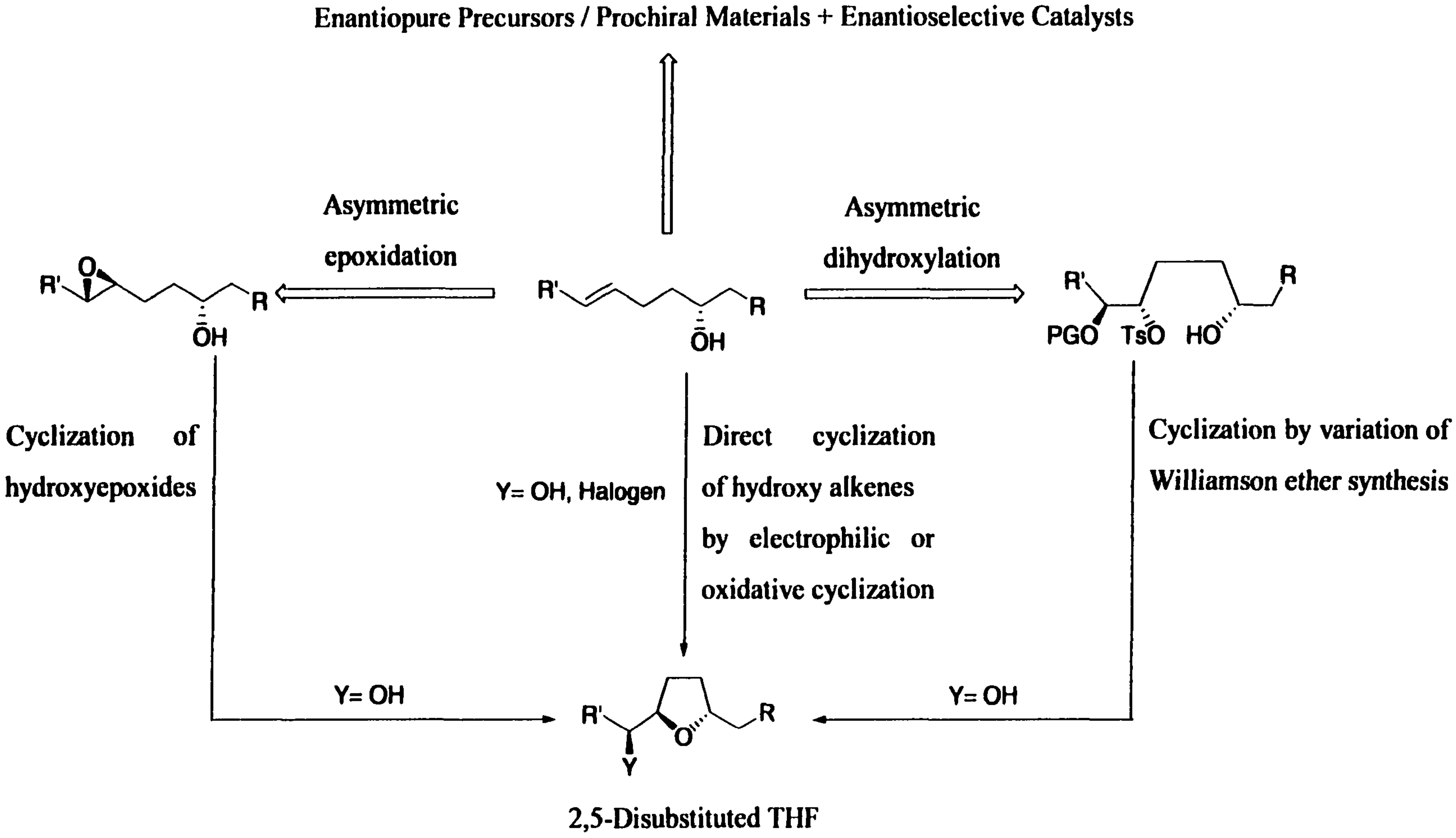
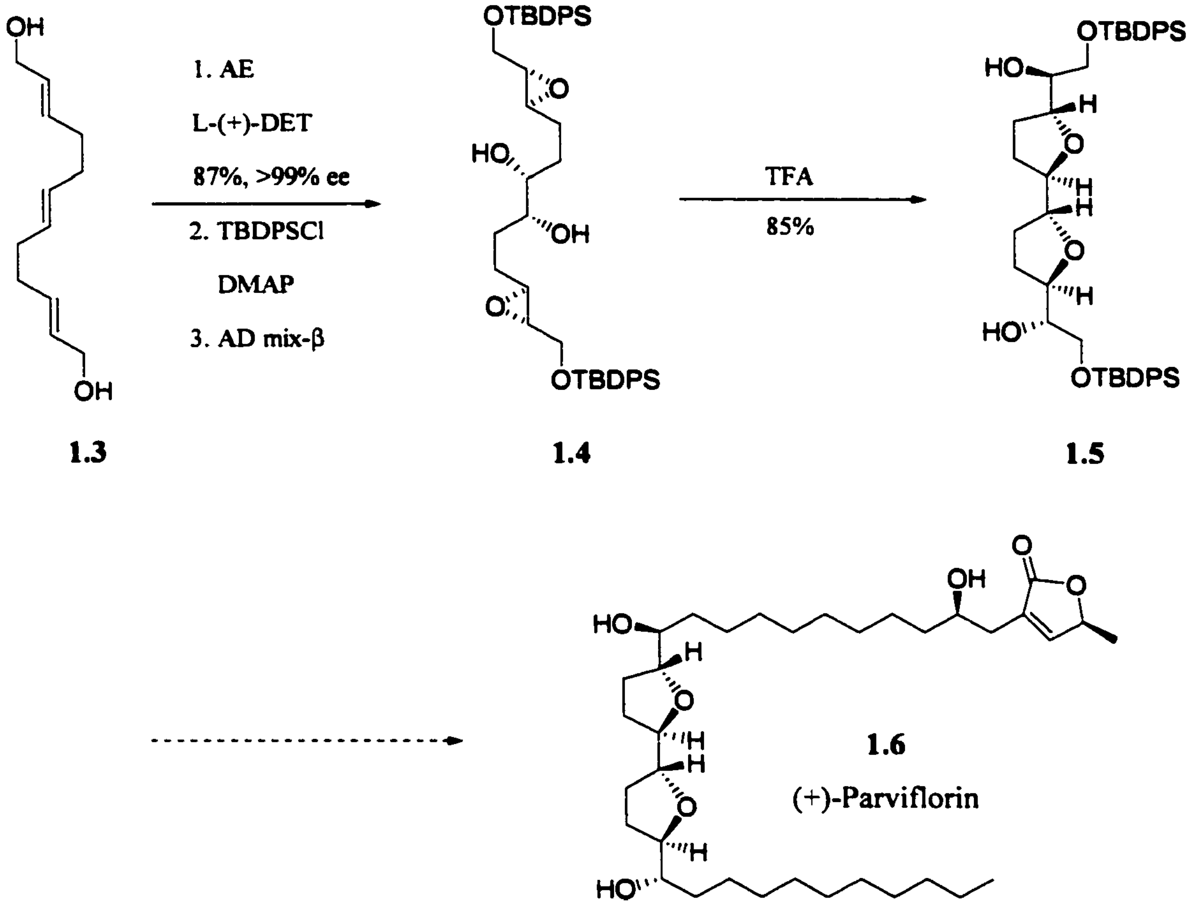
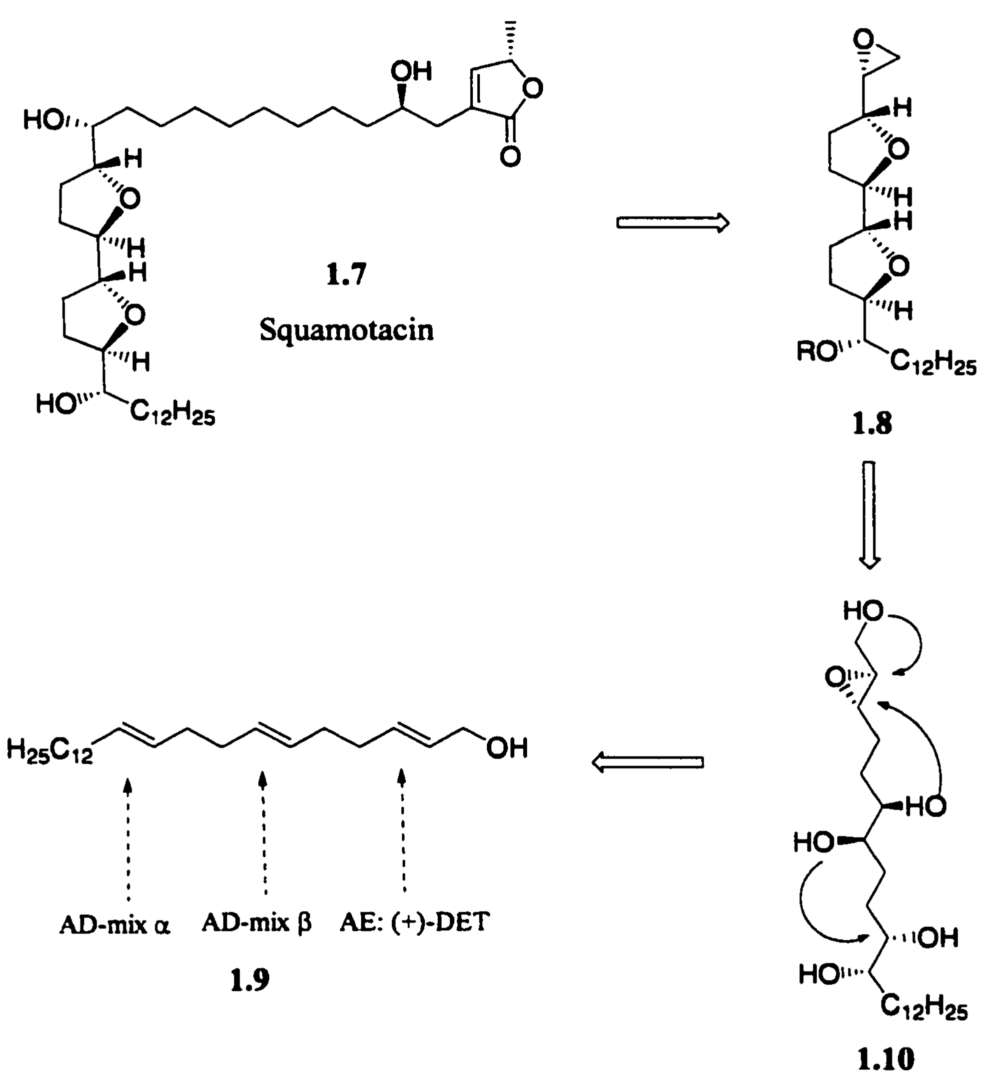


Figure 1.4. Synthetic strategies for 2,5-disubstituted THF



Scheme 1.1

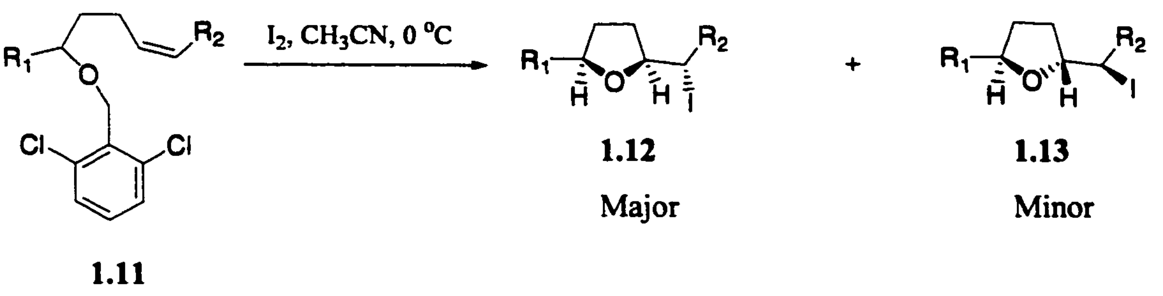
Sinha and Keinan[8d] employed a similar strategy, as Hoye, in their synthesis of squamotacin **1.7**. The tetrahydroxyepoxide precursor **1.10** was synthesized by sequential Sharpless asymmetric epoxidation and dihydroxylation reactions,[14] on the triene alcohol **1.9**. Six stereogenic centers were introduced in this process. The hydroxy epoxide **1.10** undergoes an acid catalyzed cascade ring closure to produce the bis-THF fragment **1.8** (**Schemel.2**).



Scheme 1.2

There are two major approaches to the synthesis of 2,5-disubstituted THF from hydroxyalkenes. The first is the electrophilic mediated cycloetherification strategy.[12,13] The second is the transition metal promoted oxidative polycyclization approach.[9]

Bartlett[12] demonstrated that the iodoetherification of benzyl ethers of 4-pentene-1-ols **1.11** afforded the *cis*-2,5-disubstituted THFs **1.12** as the major product (**Scheme 1.3**).



1.11

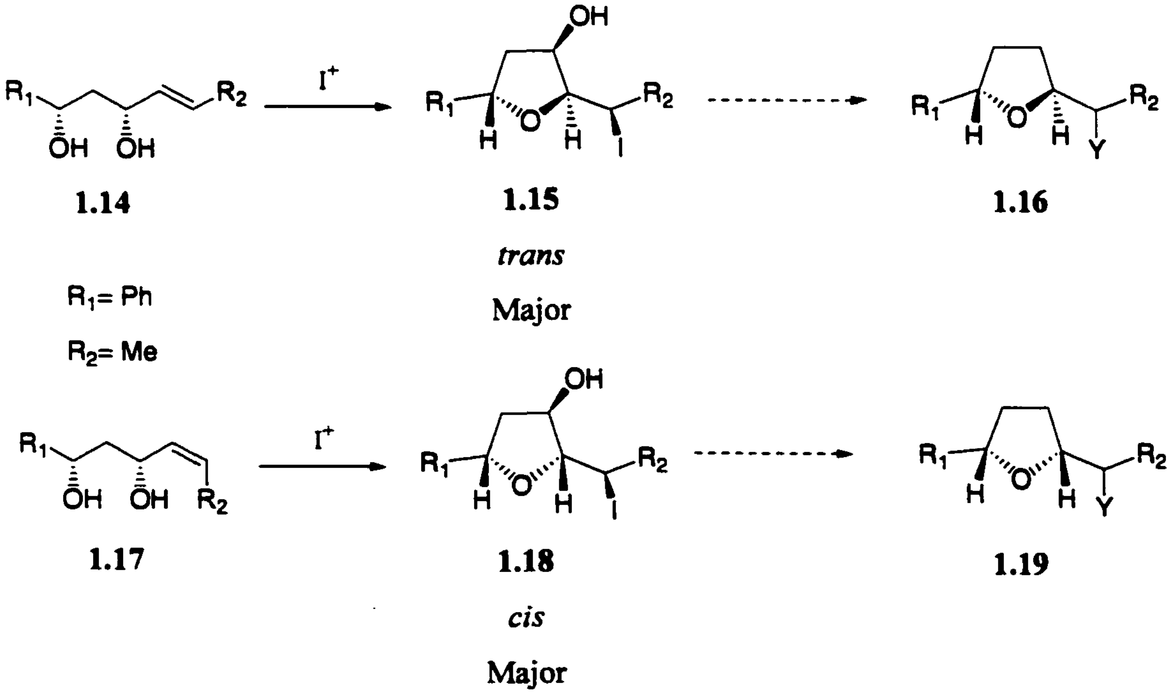
1.12
Major

1.13
Minor

Scheme 1.3

There was no evidence for the formation of any THP products.

Yoshida[13] showed that the intramolecular iodoetherification of 4-pentene-1,3-diols **1.14** provided 3-hydroxy-2,5-*trans*-disubstituted THFs **1.15** in high regio- and stereoselectivity. The haloetherification proceeds via a *cis*-directed cyclization, which is controlled by the allylic hydroxyl group. However, changing the alkene geometry from *E* to *Z* **1.17** dramatically alters the stereoselectivity and consequently affording the 3-



1.14

R_1= Ph

R_2= Me

1.15
trans
Major

1.16

1.17

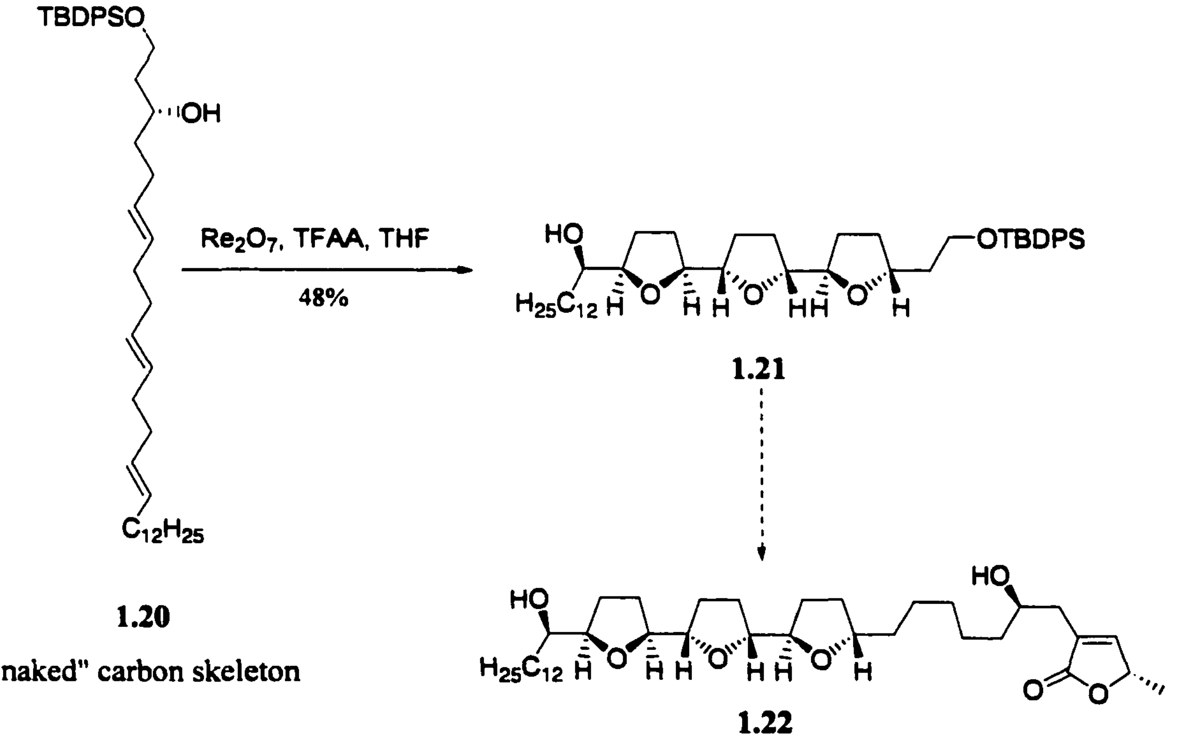
1.18
cis
Major

1.19

Scheme 1.4

hydroxy-2,5-*cis*-disubstituted THF **1.18** as the main product. The application of this strategy to the synthesis of *trans*-2,5-disubstituted THFs would entail the subsequent removal of the hydroxyl function of the THF ring to provide **1.16** (**Scheme 1.4**).

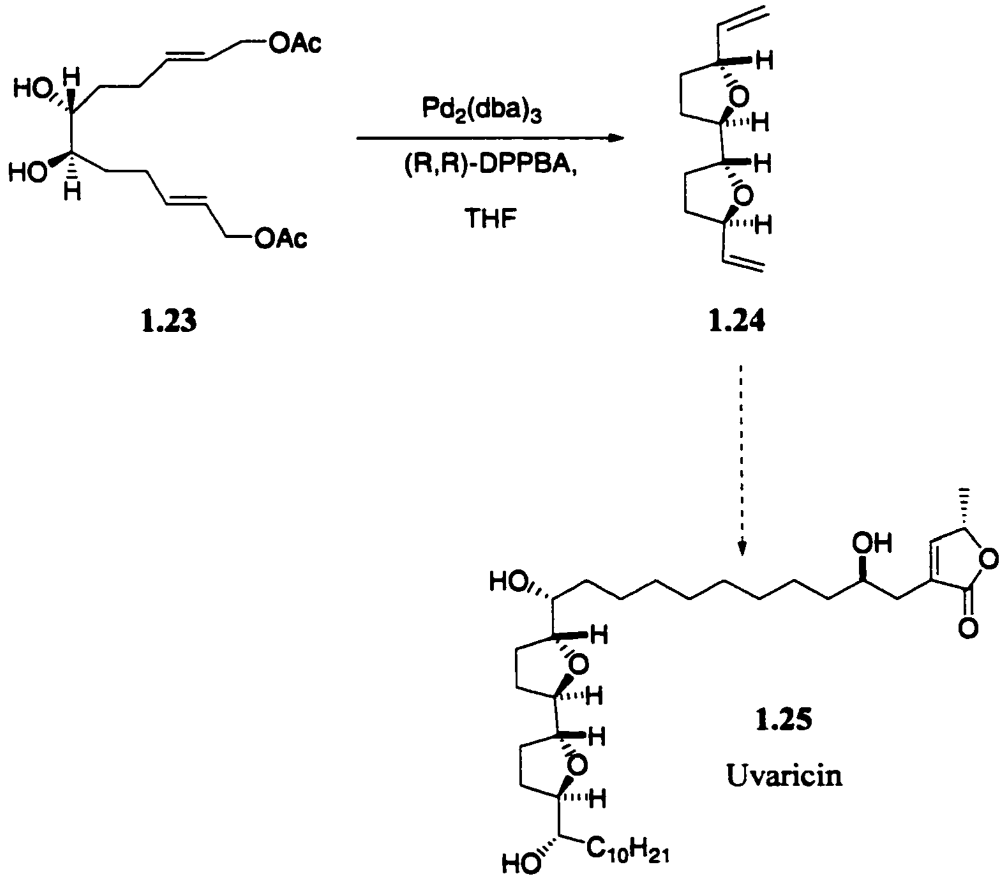
The efficiency of the oxidative cyclization approach was demonstrated by both Sinha and Burke.[9] Sinha,[9a,b] transformed the polyene alcohol segment **1.20** ("naked" carbon skeleton) to the tris-THF core **1.21** of 17,18-*bisepi*-goniocinin **1.22** in a single step by treatment of **1.20** with trifluoroacetyl perrhenate complex (**Scheme 1.5**). The reaction proceeded in high regio- and diastereoselectivity. Three rules governing the stereoselectivity of THF formation were proposed: 1) simple bishomoallylic alcohols undergo cyclization to produce a THF ring of *trans* configuration. 2) If the two vicinal oxygen functions formed in the first cyclization have a *threo* relationship, the next



Scheme 1.5

cyclization produces a *cis*-THF ring. These two rules are illustrated in the synthesis of **1.21** from **1.20**. 3) If the two vicinal oxygen function formed in the first cyclization have an *erythro* relationship, the next cyclization produces a *trans*-THF ring.

Burke's synthesis of the bis-THF core of uvaricin **1.25** involved a novel palladium-mediated, ligand controlled double cyclization on a C_2 symmetric precursor **1.23**.[9c] Trost[15] had earlier demonstrated that vicinal diol allylic acetates like **1.23** in the presence of $Pd_2(dba)_3$ undergoes cyclization to form THF rings in excellent yield, but in low diastereoselectivity. However, Burke showed that this reaction, in the presence of the chiral ligand (R,R)-DPPBA, gave the bis-THF **1.24** in 97% yield as a single



1.23

1.24

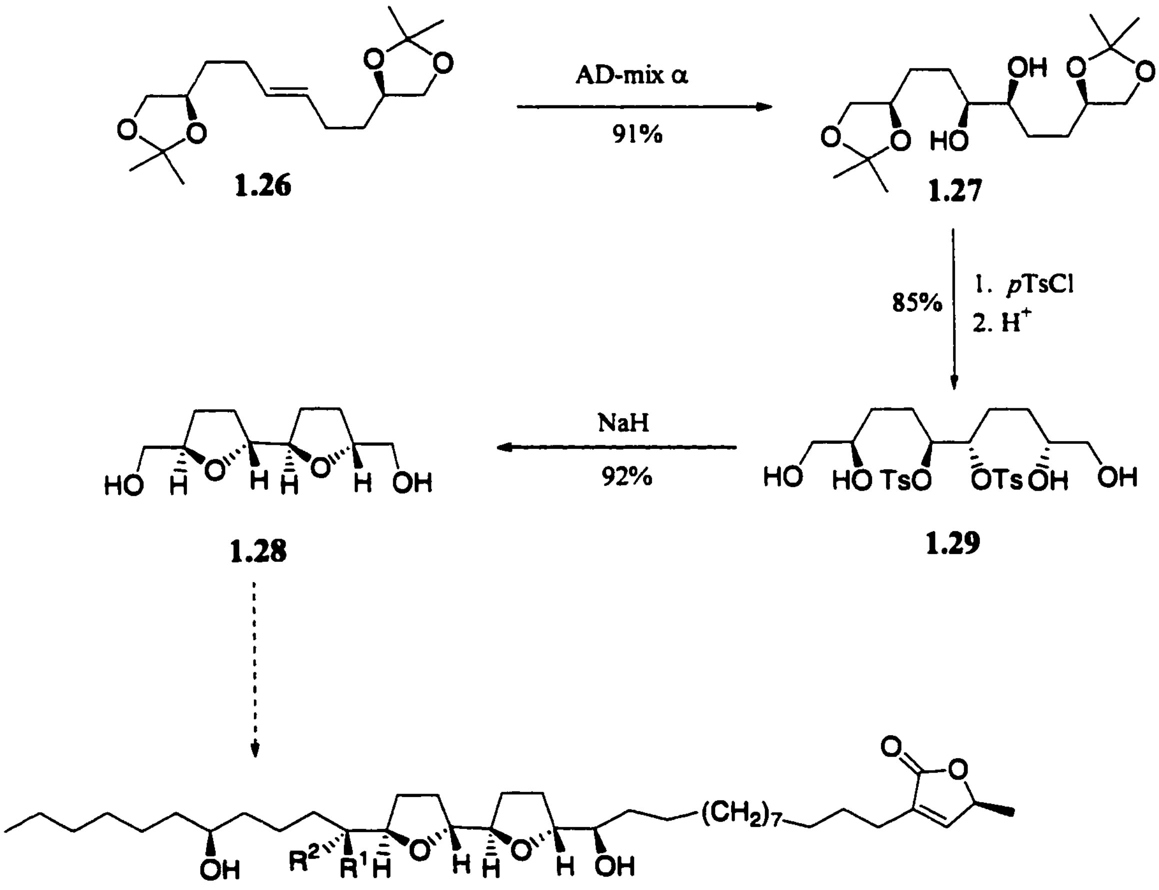
1.25

Uvaricin

Scheme 1.6

diastereomer. Desymmetrization and subsequent elaboration of **1.24** gave uvaricin **1.25** (**Scheme 1.6**).

Koert used a Williamson type reaction for the synthesis of the bis-THF core of squamocin A **1.30** and D **1.31**.[10b] The tetrahydroxy bis-tosylate **1.29** was treated with NaH to afford the *trans-threo-trans*-bis-THF **1.28** in 92% yield. The tetrahydroxy bis-

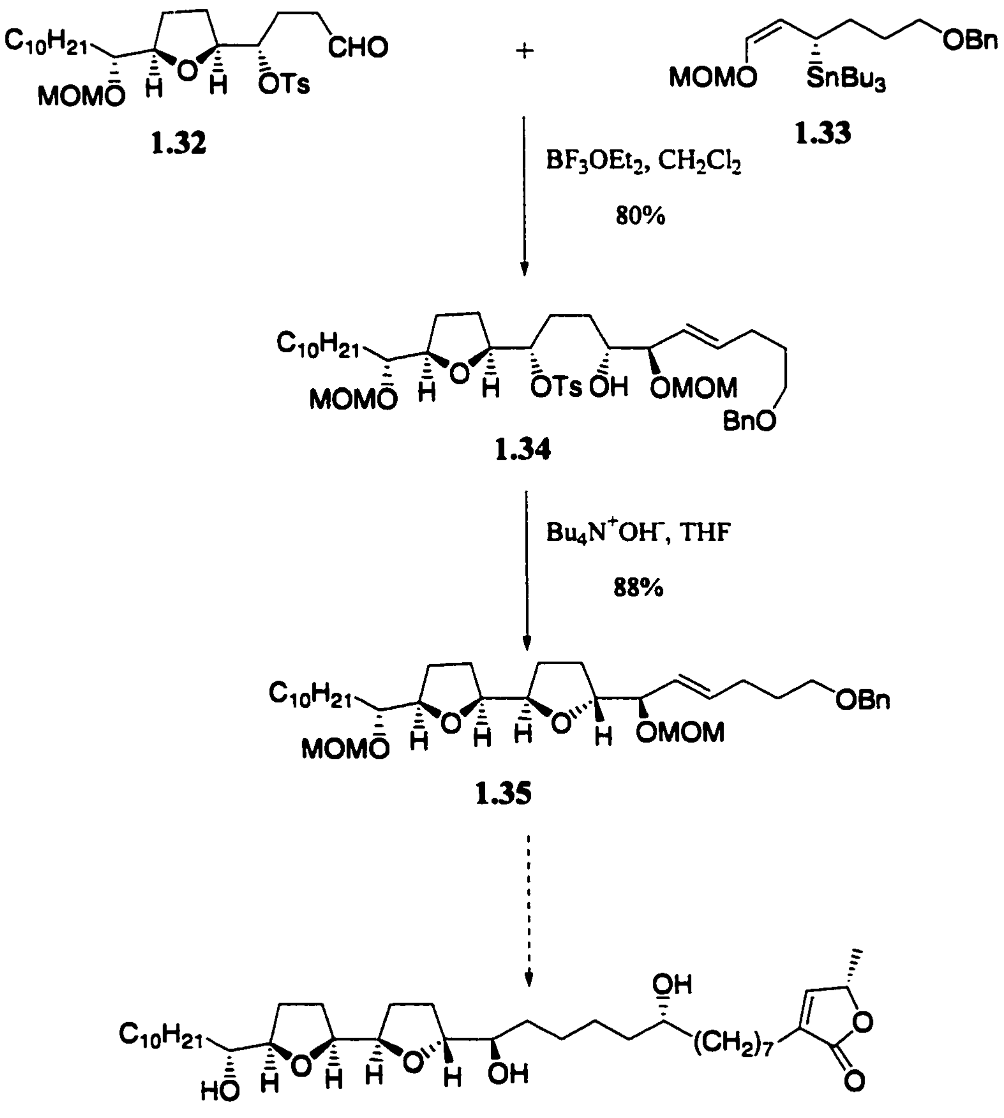


squamocin A, R^1 = OH, R^2 = H **1.30**
squamocin D, R^1 = H, R^2 = OH **1.31**

Scheme 1.7

tosylate precursor **1.29** was obtained from **1.27**, which was derived from the Sharpless asymmetric dihydroxylation[14] of the *E*-alkene **1.26** (**Scheme 1.7**).

Marshall used a similar approach for the synthesis of the bis-THF core **1.35** of trilobin **1.36**.[10a] The precursor **1.34** was synthesized by the chiral addition of allylstanne **1.33** to the aldehyde **1.32**. The resulting alcohol **1.34** was then cyclized under basic conditions to yield the second *trans*-THF ring of **1.36** (**Scheme 1.8**).



1.32

1.33

1.34

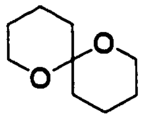
1.35

1.36

Scheme 1.8

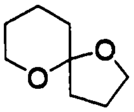
1.3 SPIROKETALS

Spiroketals occur as substructures in a variety of natural products isolated from a large array of plant and animal sources. There is a wide range of structural complexity ranging from the relatively simple fly pheromones to the intricate frameworks of the polyether antibiotics and the spiroketal macrolides. Several of these have potent pharmacological activity.[2] Three common spiroketal ring systems are known (**Figure 1.5**).[2]



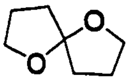
1,7-Dioxaspiro[5.5]undecane

A



1,6-Dioxaspiro[4.5]decane

B

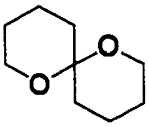


1,6-Dioxaspiro[4.4]nonane

C

Figure 1.5

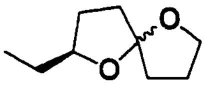
Much of the early interest in the synthesis of spiroketals was directed at the fly



1.37

1,7-Dioxaspiro[5.5]undecane

Dacus oleae



1.38

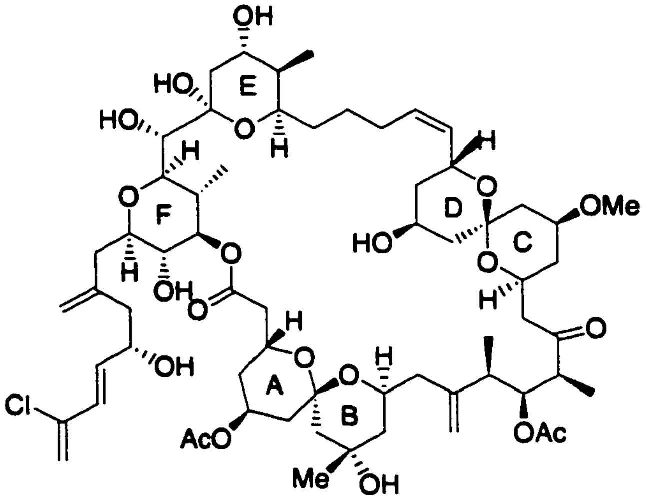
E and *Z*-2-Ethyl-1,6-dioxspiro[4.4]nonane

(Chalcogran)

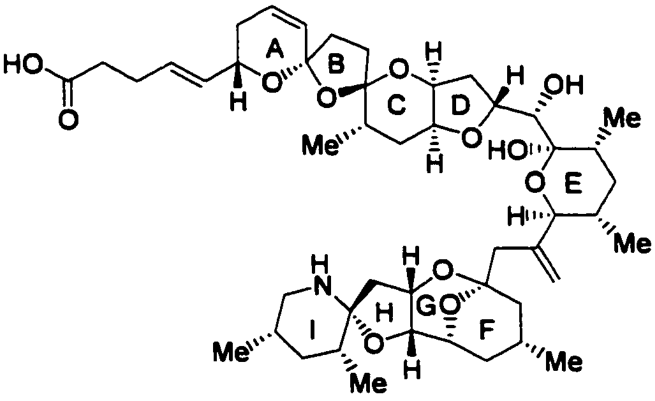
Pityogenes chalcographus

Figure 1.6

pheromones such as **1.37** and chalcogran **1.38** (**Figure 1.6**), which provided simple targets for methodology development.[2] The synthesis of more challenging targets such as spongistatin[16] **1.39** and azaspiracid[17] **1.40** have since been undertaken (**Figure 1.7**).



Spongistatin 1 **1.39**



Azaspiracid **1.40**

Figure 1.7

Most syntheses are based on the assumption that the configuration of the acetal carbon of the natural metabolite corresponds to the thermodynamically favored isomer.[2] As a consequence, it is expected that the acid promoted spirocyclization of a dihydroxy ketone precursor would give the spiroketal configuration in the natural product. Steric, anomeric, intramolecular hydrogen bonding and chelating effects on spiroketal configuration have been examined.

In the [5.5] ring system the bisaxial orientation or double anomeric effect of the spiro C-O bond is commonly observed.[2] When this arrangement is synergistic with steric effects a confident prediction of molecular conformation can be made. The AB

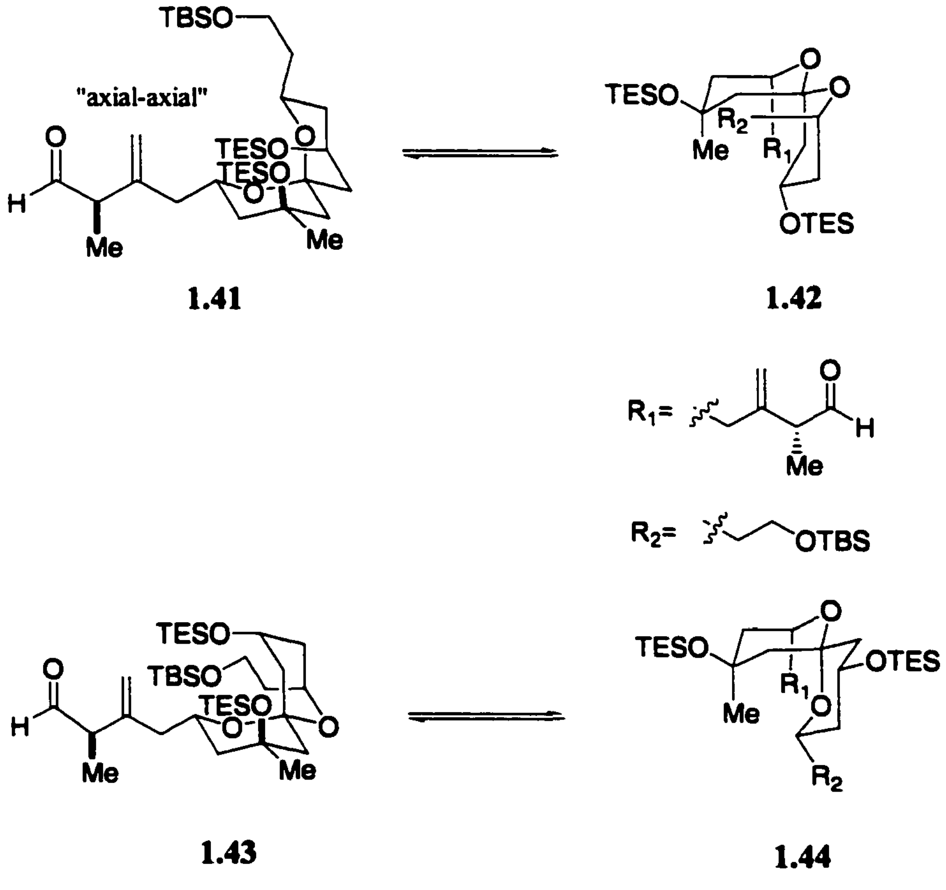
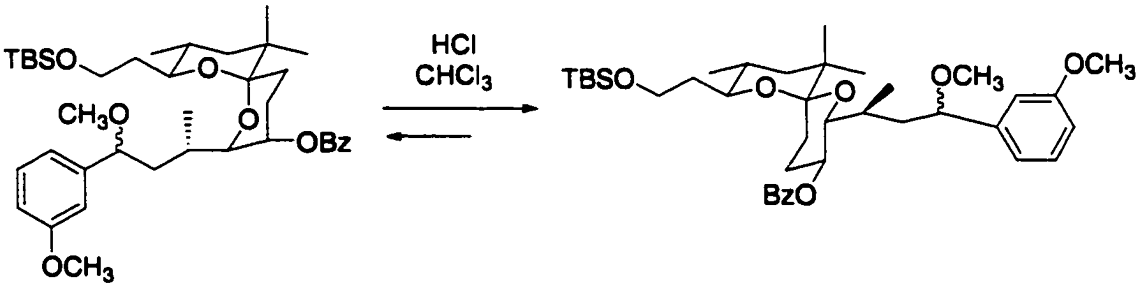


Figure 1.8. Possible conformations of AB spiroketal of 1.39

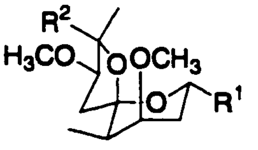
spiroketal ring system **1.41** of **1.39** is illustrative (**Figure 1.8**).[16,18] Conformer **1.42** would be unfavorable because there is no anomeric effect and large steric interactions. The other possible stereoisomer **1.43** and its conformer **1.44** would be unfavorable because of a single anomeric effect and large steric hindrance. However, the stabilizing influence of the anomeric effect can be overpowered by severe steric interactions. This was demonstrated by the equilibration of the spiroketals **1.45** and **1.46**.[2] The bis-diaxial C-O arrangement in **1.45** was isomerized to the less anomerically favored **1.46**. This isomerization reduced the steric crowding in **1.45** caused by the two axial groups and thus outweighed the stabilizing anomeric effect (**Figure 1.9**).



1.45 **1.46**

Figure 1.9

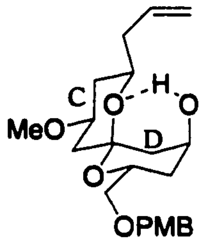
[4.5] Spiroketals may also favor a bis-axial type arrangement of acetal oxygens **1.47** (**Figure 1.10**).[2]



1.47

Figure 1.10. A 204A

Intramolecular hydrogen bonding and chelating effects also affect conformer stability. Hydrogen bonding may occur when there is a 1,3-diaxial arrangement between an alcohol group and one of the oxygens of the spiroketal.[2] Recently, Paterson[19] used this phenomenon to effect equilibration of the CD spiroketal ring system of spongistatin. The thermodynamic product **1.48** has a single anomeric effect in addition to a hydrogen bond between the hydroxyl in ring D and the acetal oxygen of ring C **1.48** (**Figure 1.11**).



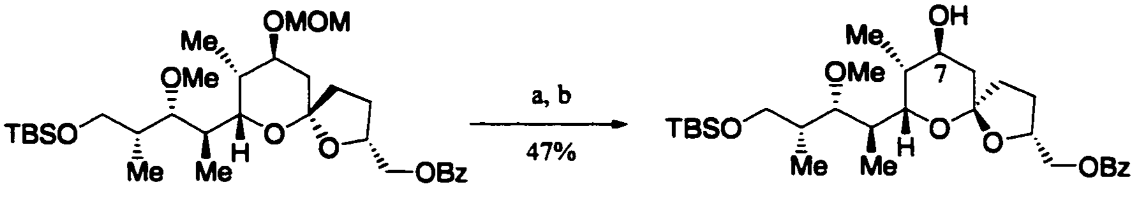
1.48

single anomeric effect with H- bond

CD ring of spongistatin

Figure 1.11

Similar hydrogen bonding effect also appears to be responsible for the favored configuration in monensin.[2] Ireland demonstrated that the spiroketal **1.49** of monensin could be equilibrated to the thermodynamically favored isomer **1.50** by removal of the MOM protecting group, followed by treatment with PPTS in CH_2Cl_2 (**Scheme 1.9**).[3,20c,d] It has been shown that hydrogen bonding occurs between the C7-OH and the acetal oxygen of the five membered ring **1.51** further enhancing the spiroketal to adopt the thermodynamic conformation (**Figure 1.12**).



1.49 **1.50**

Scheme 1.9. (a) Me_2BBr, CH_2Cl_2, Et_2O, -78 °C; (b) PPTS, CH_2Cl_2.

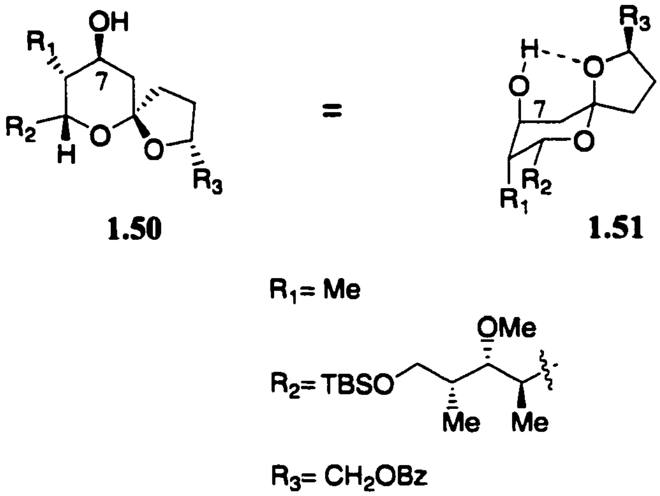
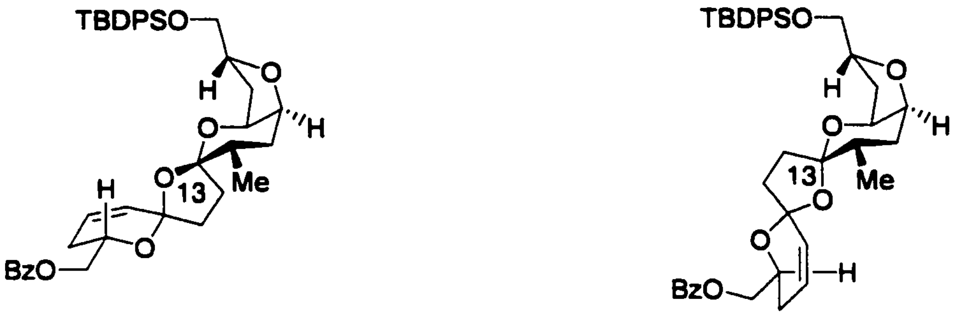


Figure 1.12

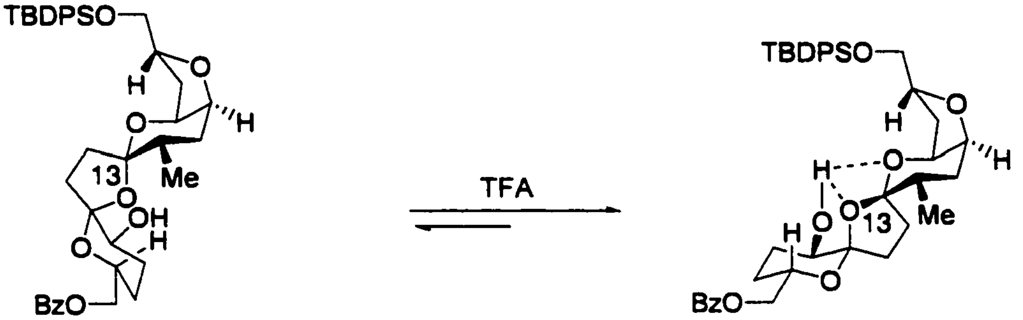
The use of hydrogen bonding to obtain the correct spiroketal configuration in the natural product azaspiracid was demonstrated by Nicolaou.[17a] The thermodynamically favored isomer places the double spiroketal linkages of the ABCD rings in a conformation that maximizes the anomeric effect **1.53 (Figure 1.13)**, but this was the undesired isomer. However, the presence of the hydroxyl group in the equatorial position at C9 enabled the inversion of the 13*S* configuration **1.54** to its natural 13*R* form **1.55** **(Scheme 1.10)**. The subsequent removal of the hydroxyl group afforded the ABCD ring **1.52** of **1.40 (Figure 1.13)**.



1.52

1.53

Figure 1.13



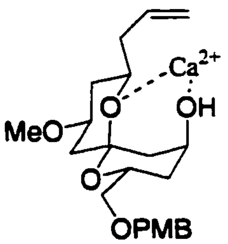
1.54

1.55

13R , desired, favored by hydrogen bonding

Scheme 1.10

Smith has shown that the presence of residual Ca(II) ions plays a critical role in the isomerization of the CD ring of spongistatin **1.56** (**Figure 1.14**) by a possible metal



1.56

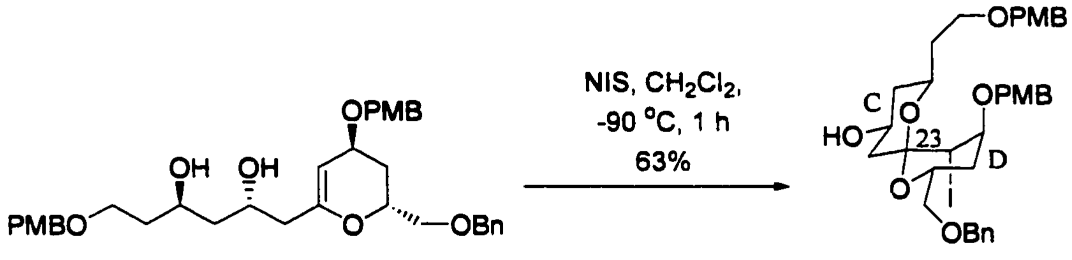
single anomeric effect with metal chelation

CD ring of spongistatin

Figure 1.14

chelating effect.[21]

Roush[22a] demonstrated that the CD spiroketal unit of spongistatin 1 **1.39** can be formed via a kinetically controlled iodo-spiroketalization reaction. This reaction installed the correct C23 stereochemistry in a single step. Treatment of the glycal **1.57** with NIS followed by intramolecular *trans* diaxial addition of the δ-hydroxy group provided the C23 spiroketal center **1.58** with the configuration found in the natural product (**Scheme 1.11**). The subsequent conversion of the hydroxyl group to its methyl ether, followed by reductive dehalogenation provided the CD spiroketal unit.

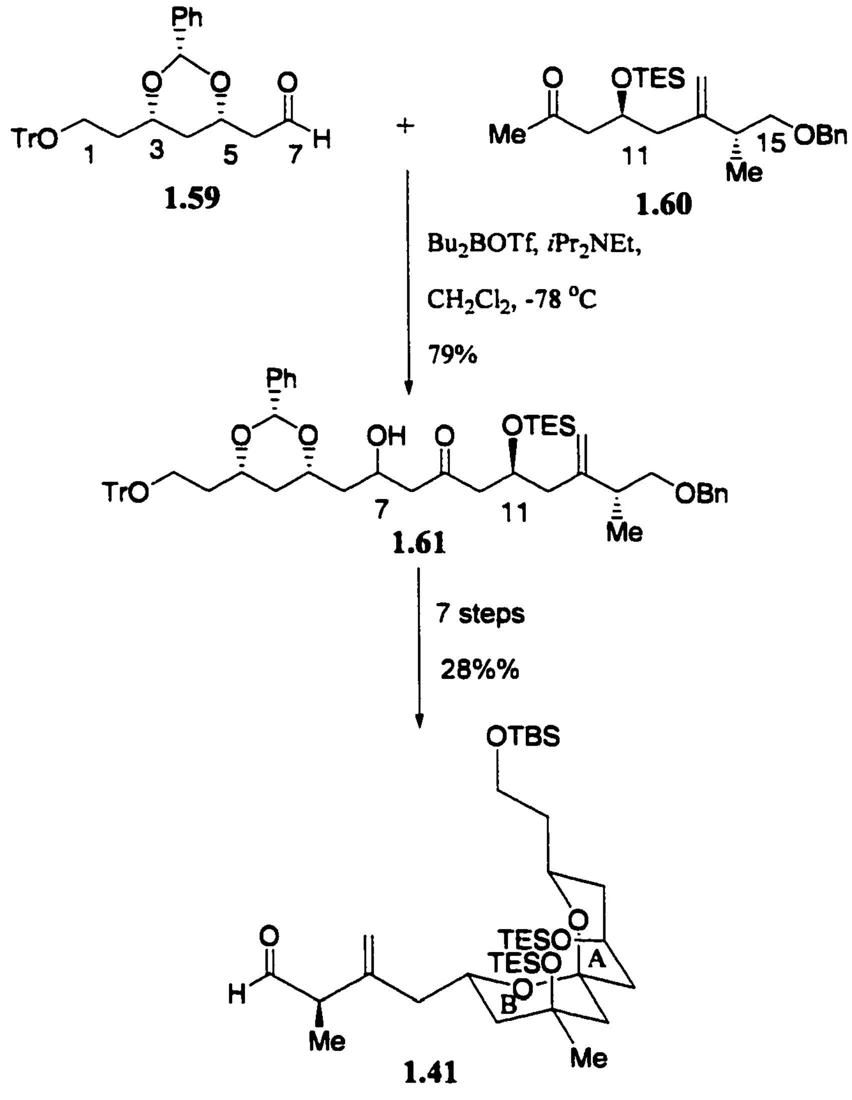


1.57 **1.58**

Scheme 1.11

The acid catalyzed cyclization of a dihydroxy ketone precursor or an equivalent thereof represents the most popular approach for the synthesis of spiroketals.[2] Strategies vary with respect to the methods used for assembling these precursors.

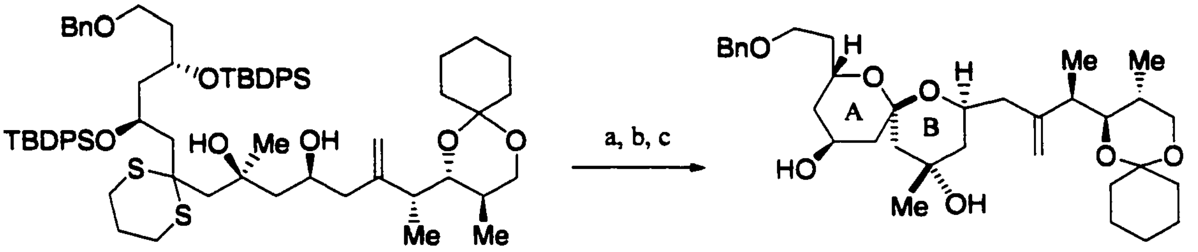
Evans[18] used the dihydroxy ketone precursor to synthesize the AB and CD spiroketal ring system of spongistatin. In the synthesis of the AB ring system, the key step was the aldol addition of the boron enolate obtained from ketone **1.60** and aldehyde **1.59** to afford the open chain form of the AB spiroketal subunit **1.61**. Oxidation of C7 (which serves as the spiro carbon), followed by acidic liberation of the hydroxyl groups at C1, C3, C5 and C11 resulted in a spontaneous spiroketalisation, in which the thermodynamically favored axial-axial isomer **1.41** was isolated (**Scheme 1.12**).



Scheme 1.12

Very similar building blocks and concepts were used for the synthesis of the CD spiroketal. Paterson,[19] Paquette[23] and Heathcock[24] also used dihydroxy ketone precursors in their synthesis of the AB and CD spiroketals.

Kishi[25] used a different strategy for assembly of the dihydroxyketone precursor in his synthesis of the AB spiroketal ring of spongistatin 1 **1.39**. Using a dithiane approach, complex fragments were stitched together to form the C1-C17 fragment **1.62** of the AB spiroketal ring. Manipulation of the protecting groups and spiroketalization afforded the AB spiroketal **1.63** (**Scheme 1.13**). Smith also used a similar approach to the AB and CD spiroketal ring system of **1.39**.[21]

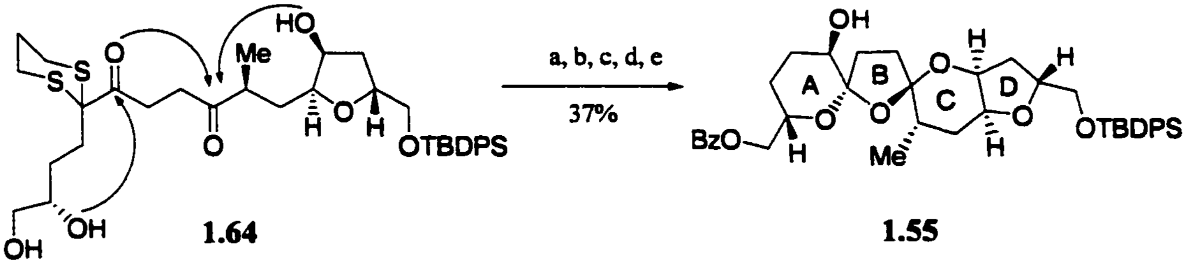


1.62

1.63

Scheme 1.13. a) TBAF; b) NIS-induced dithiane cleavage; c) PPTS.

Nicolaou[17a] used a dihydroxy diketone precursor **1.64** to synthesize the bis-spiroketal ring system **1.55** of azaspiracid **1.35**. Removal of the 1,3-dithiane followed by reduction of the resulting carbonyl group and spiro isomerization gave the ABCD fragment **1.55** of the azaspiracid **1.35** (**Scheme 1.14**). Hydrogen bonding between the



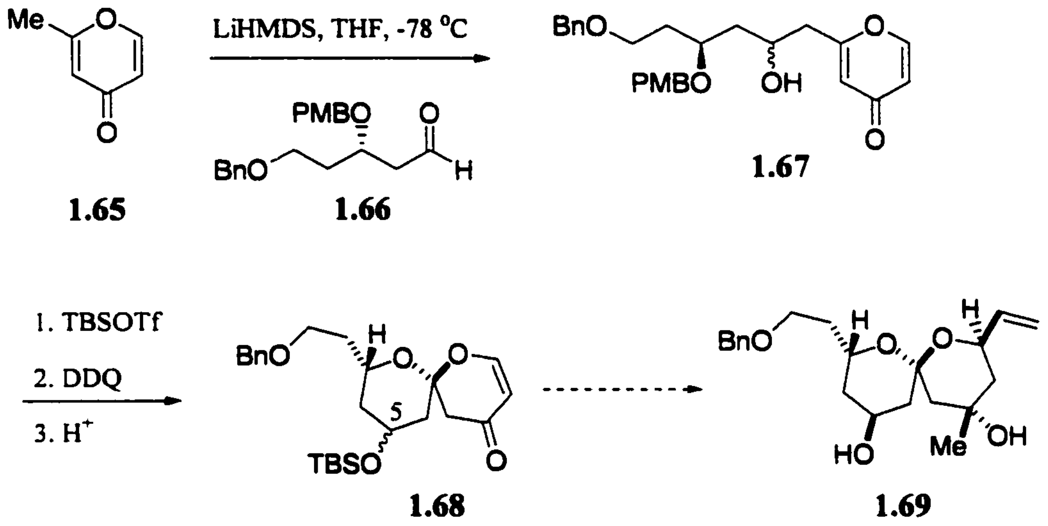
1.64

1.55

Scheme 1.14. (a) TMSOTf; (b) BzCl; (c) NBS; (d) $NaBH_4$; (e) TFA

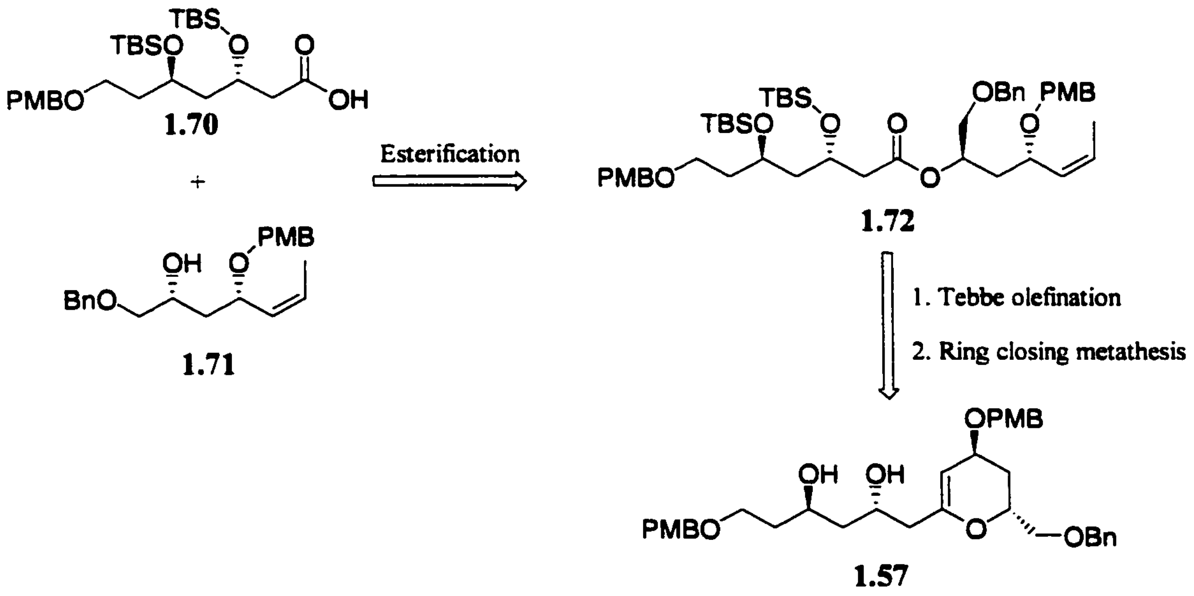
C9-OH and the oxygens of the B and C rings was proposed as a stereocontrolling factor in the formation of the desired bis-spiroketal configuration (**Scheme 1.10**).

Crimmins[26] showed that the AB spiroketal subunit **1.69** could be prepared through the addition of a metalated pyrone **1.65** to an aldehyde **1.66** to give **1.67**. Protection of the hydroxyl as its silyl ether, followed by treatment with DDQ and acid gave **1.68**. Further functionalization of **1.68** by the stereoselective addition of vinyl magnesium bromide, methyl magnesium iodide and adjustment of the stereochemistry at C5 afforded **1.69** (**Scheme 1.15**).



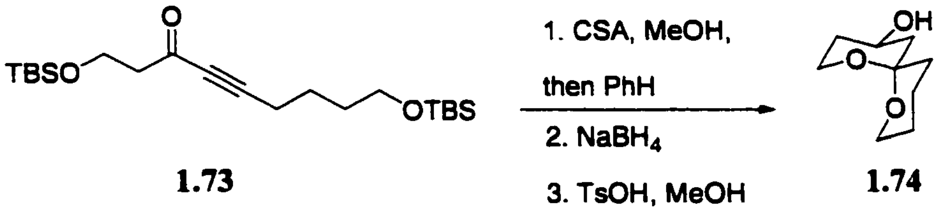
Scheme 1.15

Roush[22] constructed the AB and CD spiroketal units of spongistatin 1 **1.39** in a highly convergent manner. As illustrated for the synthesis of the CD spiroketal unit (**Scheme 1.16**), the key intermediate was a glycal **1.57**, which was prepared from the ester **1.72** via a Tebbe olefination-ring closing metathesis (RCM) strategy. The ester **1.72** was prepared from the appropriate acid **1.70** and alcohol **1.71** segments. As mentioned before, treatment of the glycal **1.57** with NIS gave **1.58** in a highly stereocontrolled manner (**Scheme 1.11**). Application of this strategy to the AB spiroketal subunit would involve double inversion of the 1,3-diol present in the glycal intermediate **1.57** and installation of the tertiary alcohol at C9.



Scheme 1.16

Forsyth demonstrated the use of the double intramolecular hetero-Michael addition (DIHMA) in the synthesis of spiroketals by making **1.74**, which is fly pheromone obtained from *Dacus oleae*.[27] The DIHMA was effected on an alkyne diol intermediate **1.73**, followed by reduction of the carbonyl group and acid-catalyzed



Scheme 1.17

isomerization to give **1.74 (Scheme 1.17)**. This strategy was later used for the construction of the 2,9-dioxabicyclo[3.3.1]nonane system in the azaspiracids. This approach delivered the bicycloketal FG rings of azaspiracid **1.40** in an efficient and expedient fashion.[17b]

The work embodied in this thesis focuses on the development of novel synthetic methodologies for adjacently linked 2,5-disubstituted THF's and 1,6-dioxaspiro[4.5]decane spiroketal subunits of the polyether antibiotics.

CHAPTER 2

SPIROKETAL METHODOLOGY

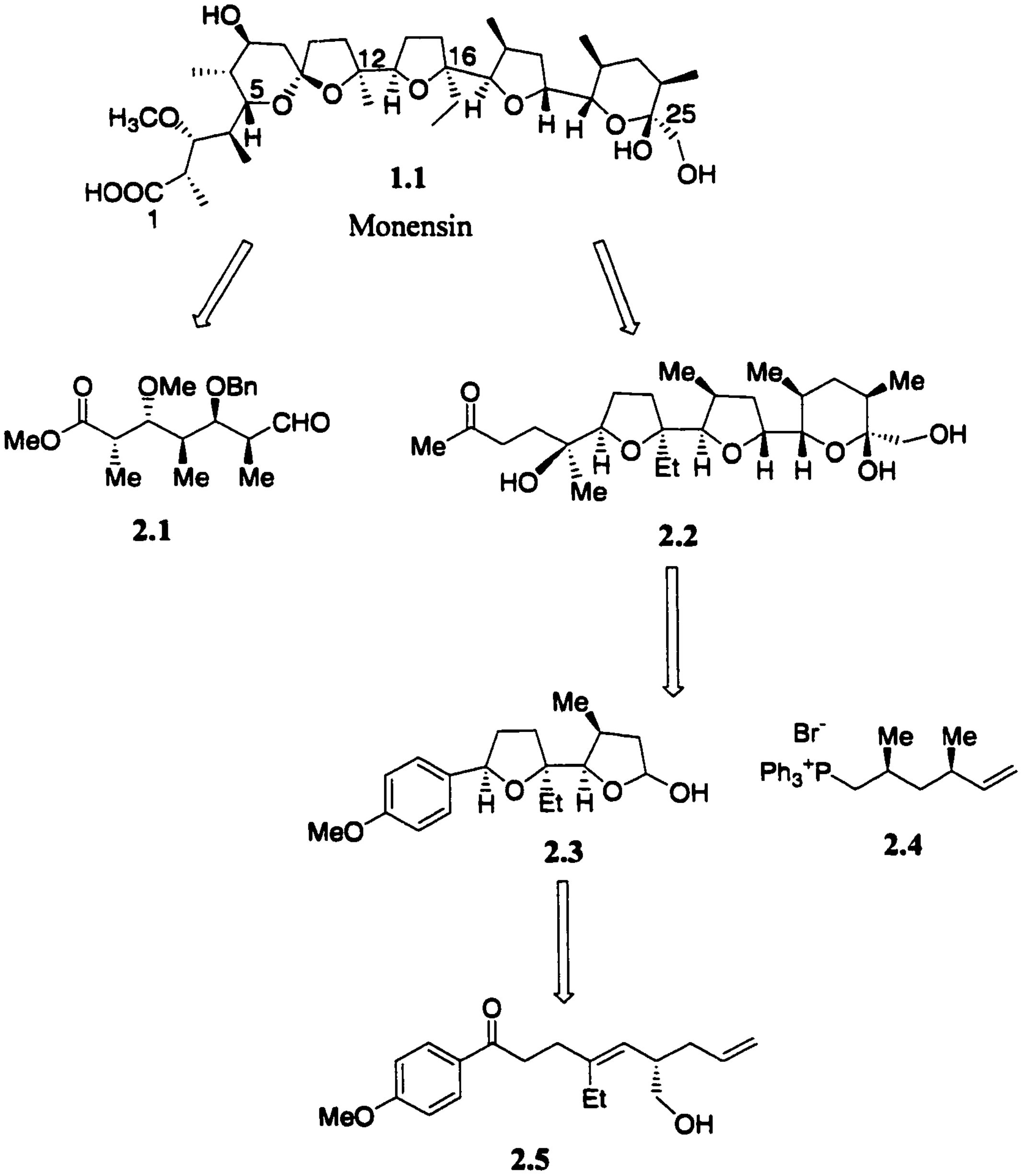
2.1 INTRODUCTION

Monensin has been a popular target for development of synthetic methodology, as illustrated by its total synthesis by Kishi,[1] Still[28] and Ireland[3,20] (**Scheme 2.1**, **2.2** and **2.3**). The Still and Kishi syntheses may be divided into two areas: the asymmetric synthesis of the substituted oligo-THF segment, and the subsequent introduction of the spiroketal subunit via a dihydroxy ketone precursor (**Scheme 2.1** and **2.3**). Ireland's synthesis involved the use of the ester enolate Claisen rearrangement for the union of the spiroketal acid and the tricyclic segment to form the monensin skeleton (**Scheme 2.3**).

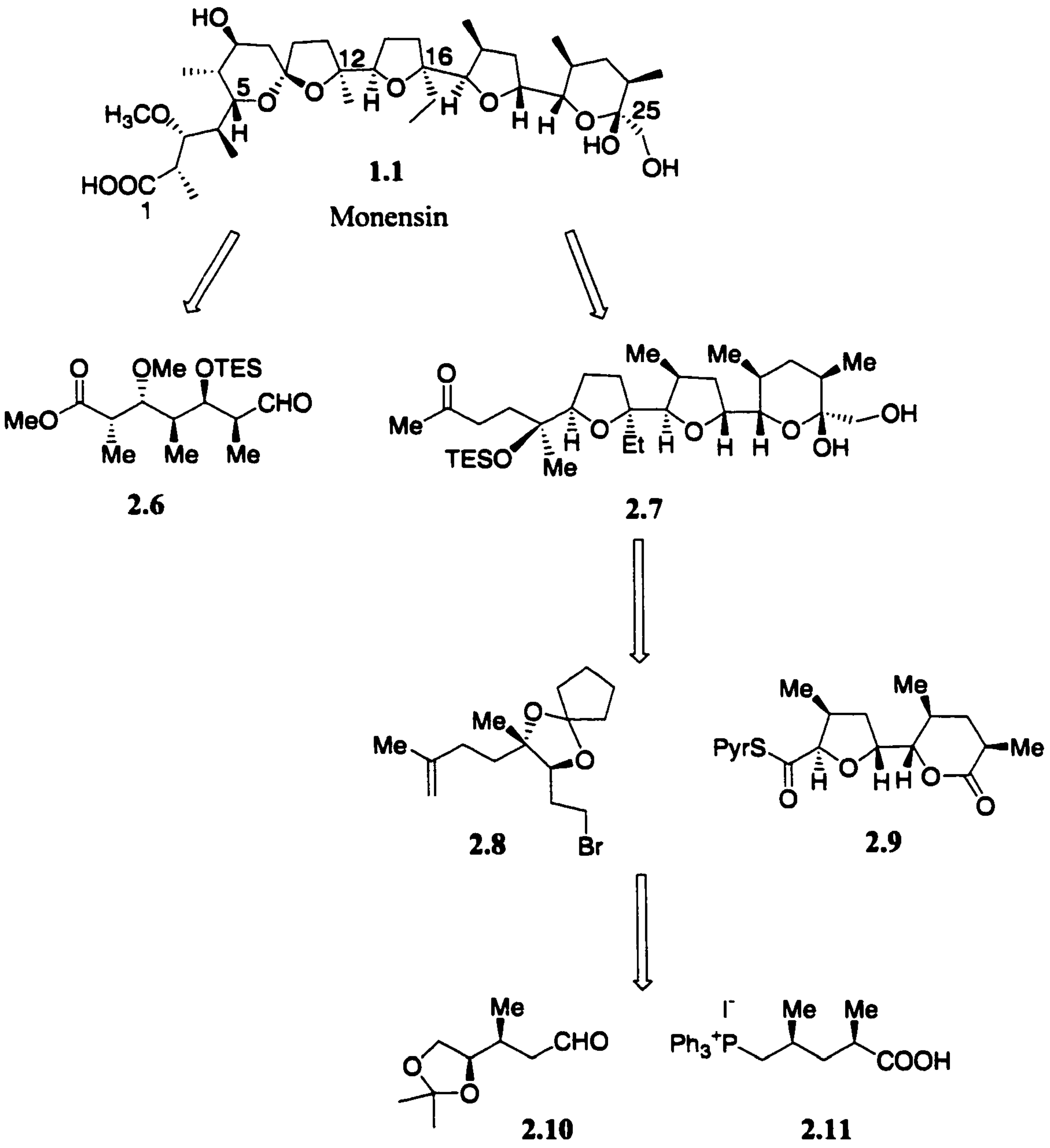
Our approach to monensin analogs combines new technologies for spiroketal and polycyclic ether synthesis. The former involves a Ag^+ mediated spiroketalization that originated from work on adjacently linked bis-THF's, by earlier workers in this laboratory.

2.2 BACKGROUND AND SYNTHETIC STRATEGY

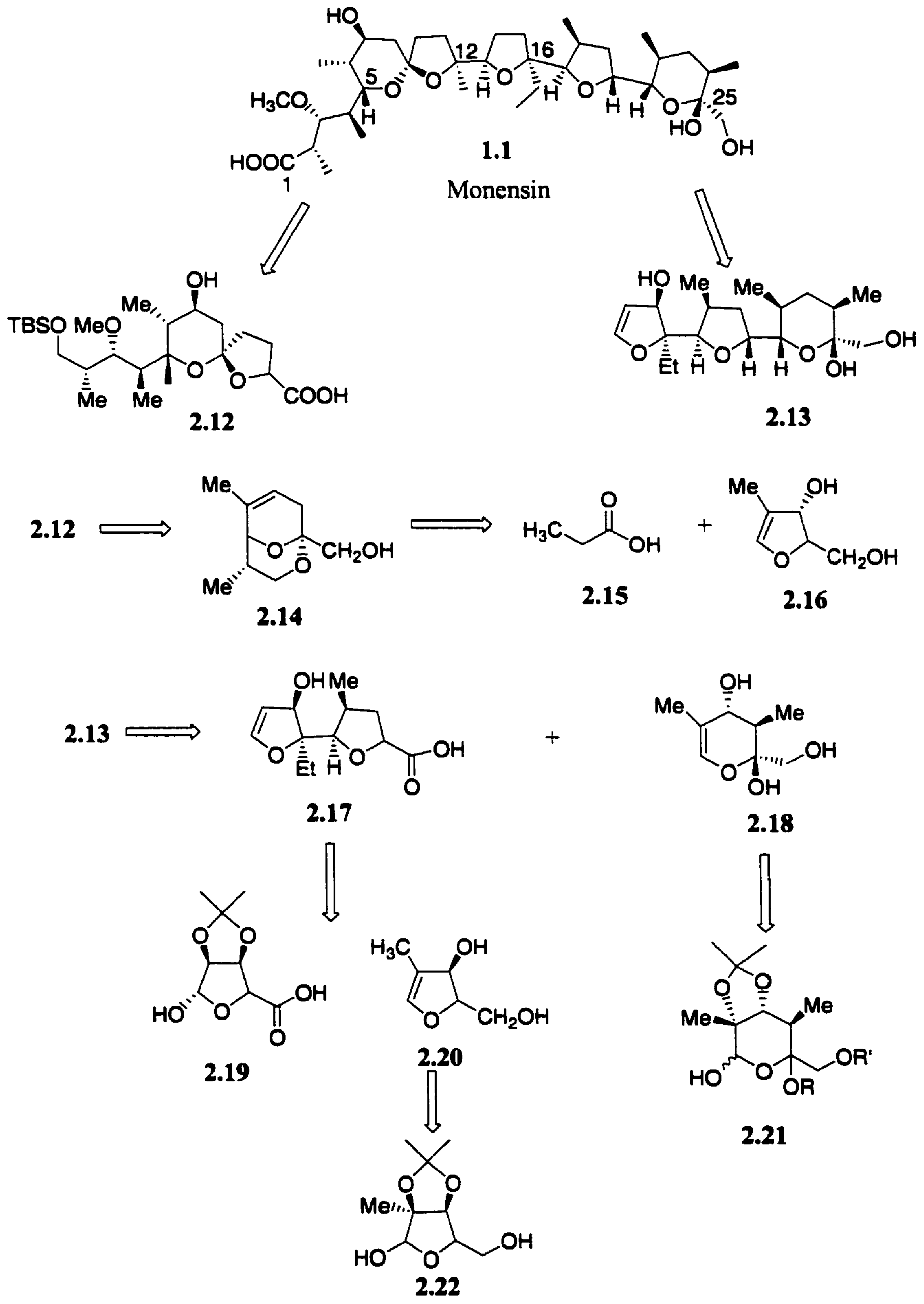
During studies on bis-THF core of rollinistatin **2.23** it was discovered that the treatment of the THF iodide precursor **2.24** with AgOTf gave the spiroketal **2.28** as a single compound and not the expected bis-THF **2.23** (**Scheme 2.4**).[29] Mechanistically, the spiroketal could have resulted from an E_1 like elimination to afford the enol ether **2.27**, which would then cyclize to give the spiroketal. Since no enol ether **2.27** was isolated in this process, it is believed that spiroketal formation occurred by iodide removal with subsequent hydride migration to give the oxocarbenium ion **2.25**. Subsequent nucleophilic attack by the oxygen of the pyranoside ring would give the THP oxonium **2.26**, which decomposed under aqueous conditions to afford the spiroketal **2.28**.



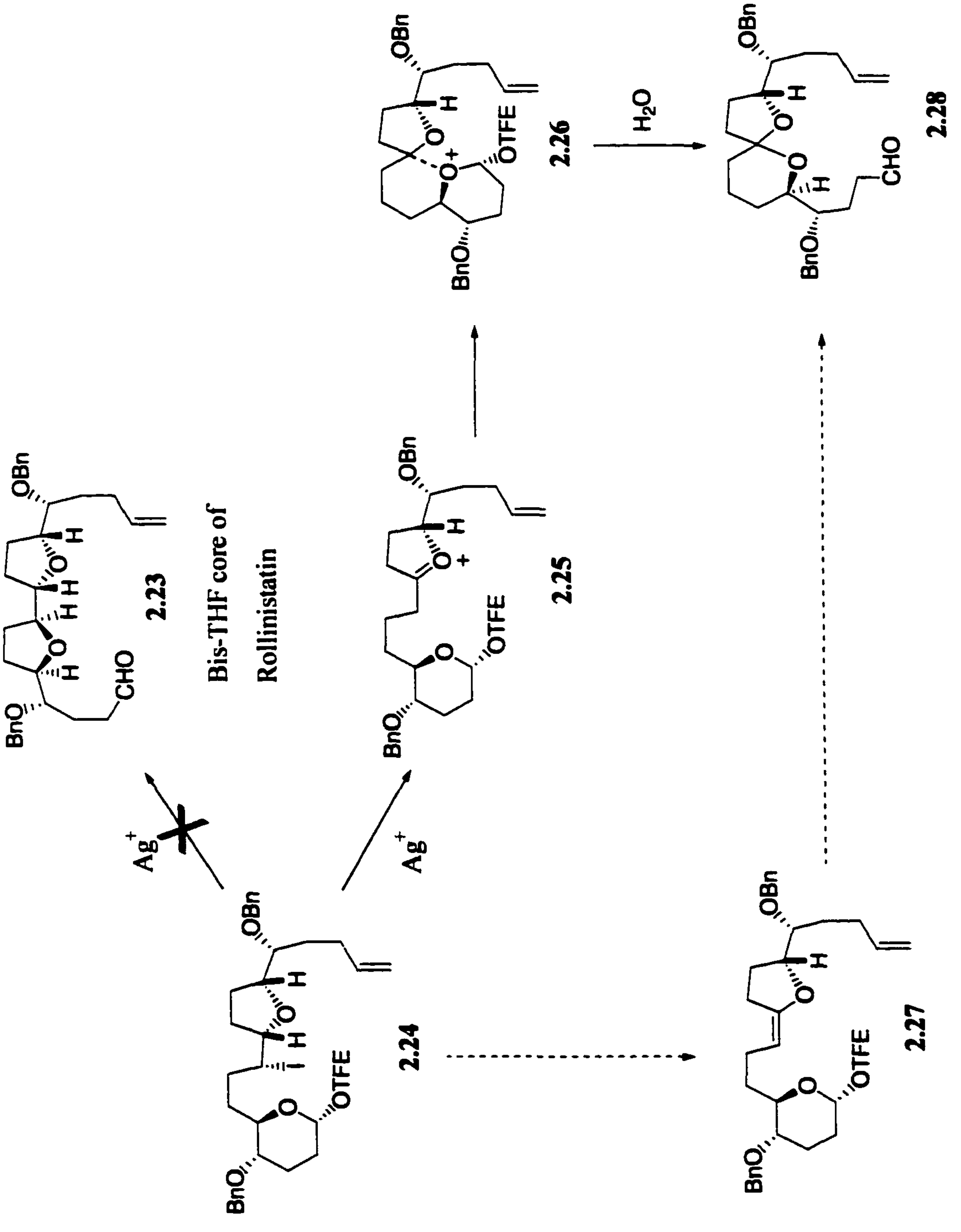
Scheme 2.1. Kishi's synthesis of monensin



Scheme 2.2. Still's synthesis of monensin



Scheme 2.3. Ireland's synthesis of monensin

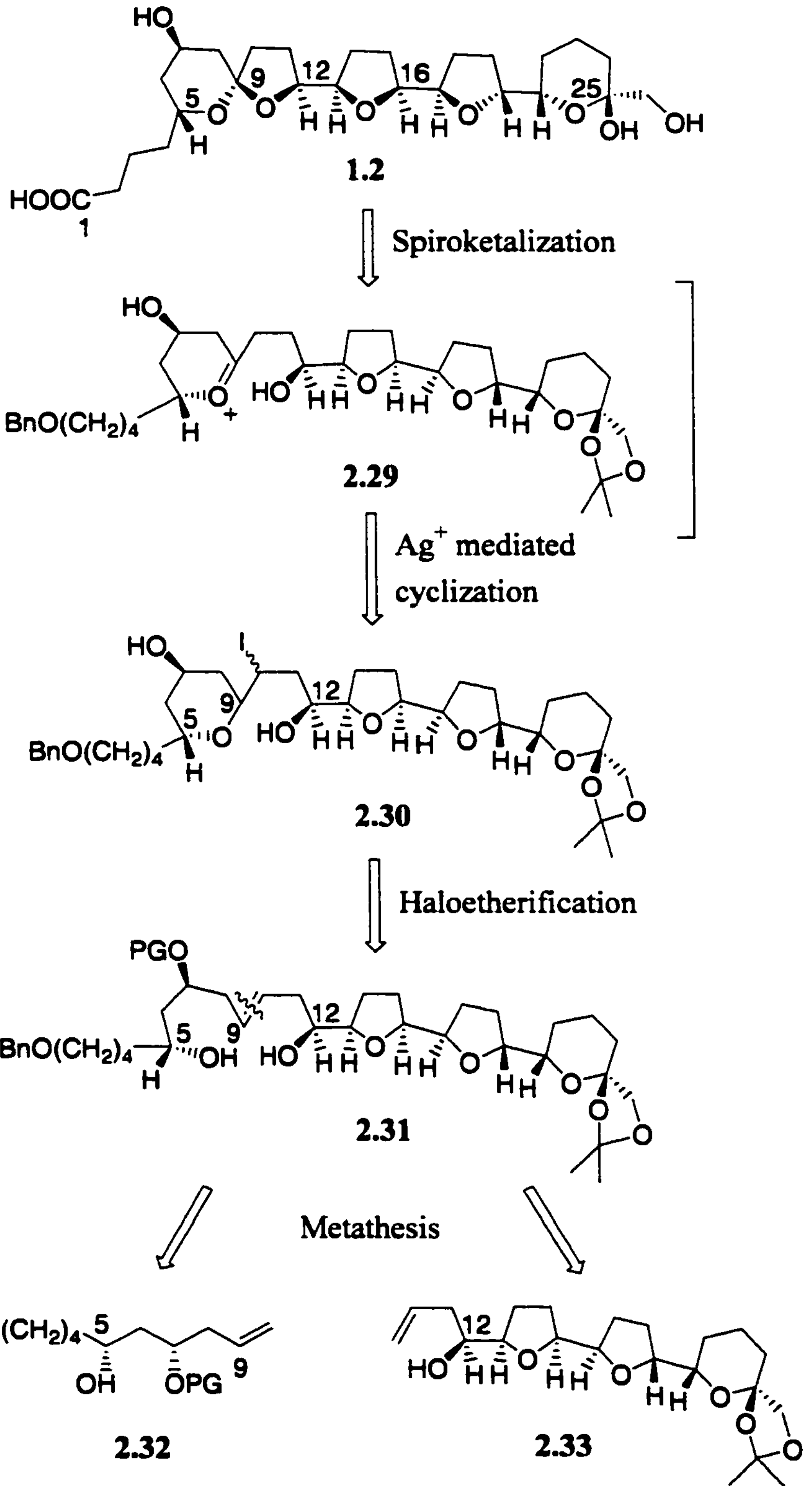

2.23
Bis-THF core of Rollinistatin
2.24
Ag^+
Ag^+
2.25
2.26
H_2O
2.27
2.28
BnO
OBn
OTFE
CHO
H
O+

Scheme 2.4

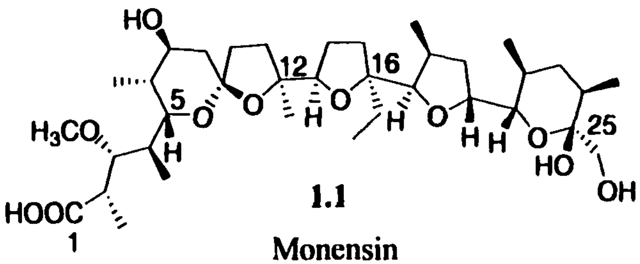
The application of this method to the monensin analog **1.2** requires the iodo-THP **2.30**. Following the results in Ireland's monensin synthesis it is expected that the acetal mixture, which might result from the spiroketalization of **2.30** could be equilibrated to the desired isomer.[3,20d] This product is favored by the anomeric effect as well as hydrogen bonding, between the C7-OH and the acetal oxygen of the five membered ring **1.2.**[1,2,3,20d] The haloetherification of an alkene diol **2.31** should provide **2.30** preferentially, via the 6-exo-trig cyclization. The complex alkene **2.31** may be prepared through disconnection of the C9-C10 bond, to afford the *syn*-1,3-diol segment **2.32** and the oligo-THF portion **2.33 (Scheme 2.5)**. The synthesis of **2.33** itself involves new chemistry and will be discussed later. The development of the spiroketal method is first presented.

2.3 MODEL STUDY

As a model study for the monensin spiroketal system we investigated the synthesis of the simple spiroketal **2.34**. We envisaged a ring closing metathesis (RCM) in which the spiroketal precursor **2.35** could be assembled via a mixed phthalate ester of **2.36** and **2.37**.[30] This plan is preferable to a cross metathesis approach. The *syn*-1,3-diol alkene **2.36** may be obtained by procedures for the stereoselective allylation of aldehydes, starting from 1,5-pentane diol **2.38 (Scheme 2.6)**. It should be noted that the configuration at C12 in the second alkenol component **2.37** is opposite to that observed in monensin. Compound **2.37** was used because it is easily prepared from D-ribose.[31]

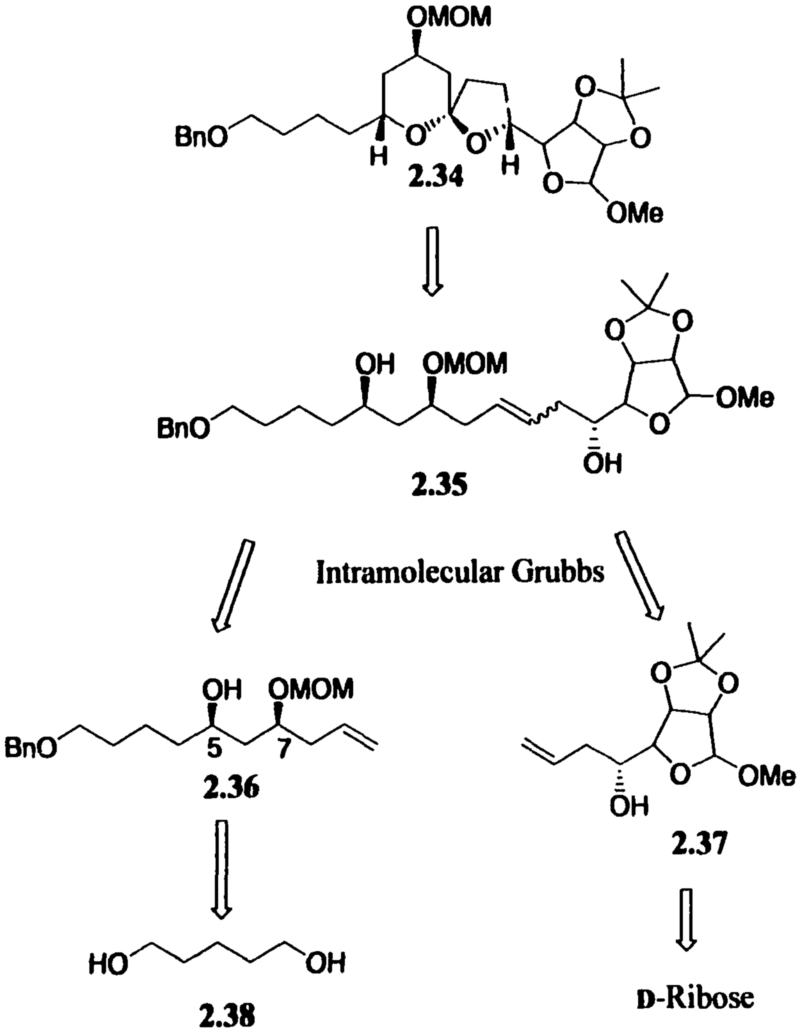

1.2
Spiroketalization
2.29
Ag$^+$ mediated cyclization
2.30
Haloetherification
2.31
Metathesis
2.32
2.33

Scheme 2.5



1.1

Monensin

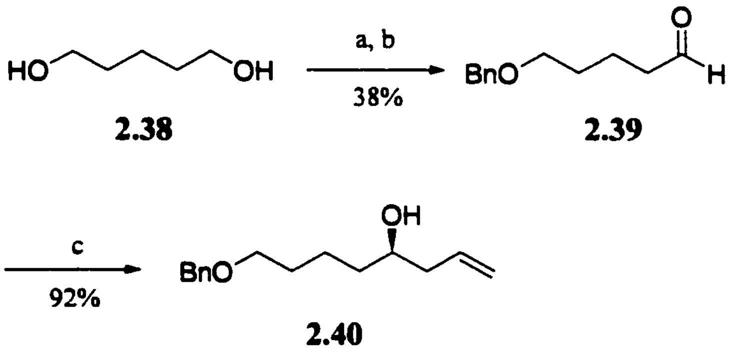


Scheme 2.6

2.4 RESULTS AND DISCUSSION

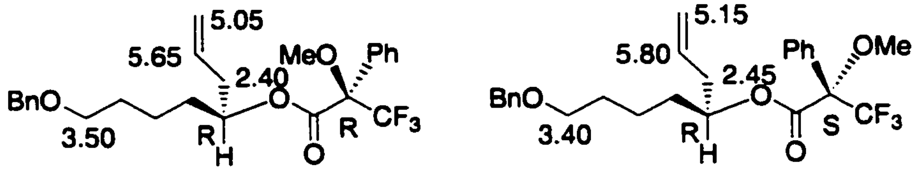
Synthesis of Alkenol segments 2.36 and 2.37

The *syn*-1,3-diol alkene **2.36** was prepared from the commercially available 1,5-pentane diol **2.38**. Monobenzylation of **2.38**, followed by PCC oxidation of the remaining alcohol afforded the aldehyde **2.39** in 38% yield. The protected aldehyde **2.39** was treated with allyltributyltin in the presence of catalytic *R*-BINOL and titanium isopropoxide according to Keck's procedure[32] to afford the homoallylic alcohol **2.40** in 92% yield (**Scheme 2.7**). The absolute stereochemistry was consistent with the Keck



Scheme 2.7. (a) BnBr, NaH, TBAI, DMF, 0 °C to rt; (b) PCC, CH_2Cl_2, 4A MS, Celite, Florisil, rt; (c) 10 mol% (R)-BINOL, $Ti(iOPr)_4$, allyltributyltin, CH_2Cl_2, -22 °C (99% *ee*).

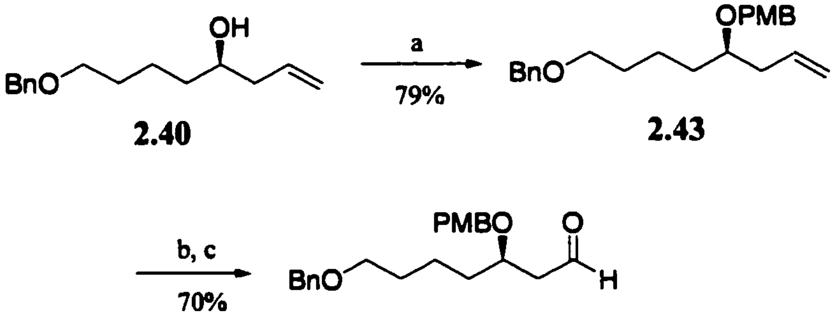
model[33] and was confirmed by Mosher[34] ester analysis to be of the R configuration. The R and S Mosher esters **2.41** and **2.42** were prepared of **2.40**. Examination of the ^1H NMR spectra for **2.41** showed upfield chemical shifts for the vinyl and the allylic methylene protons at δ 5.05 (m, 2H), 5.65 (m, 1H) and 2.40 (t, J= 8Hz, 2H), whilst the corresponding signals for the **2.42** ester showed downfield chemical shifts at δ 5.15 (m, 2H), 5.80 (m, 1H) and 2.45 (t, J= 8 Hz, 2H) (**Figure 2.1**). Signals for diastereomeric products corresponding to the S enantiomer of **2.40** were not observed for the Mosher esters and therefore >99% ee was presumed.



2.41 **2.42**

Figure 2.1

Protection of the alcohol function of **2.40** as its *p*-methoxybenzyl ether **2.43**, followed by the oxidative cleavage of the alkene gave the aldehyde **2.44** in an overall yield of 55% (**Scheme 2.8**).

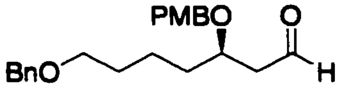
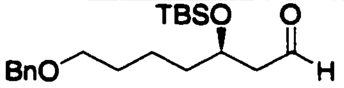
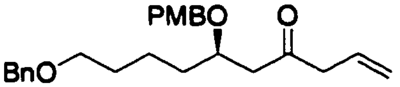


2.40 **2.43** **2.44**

Scheme 2.8. (a) PMBCl, NaH, TBAI, DMF, 0 °C to rt; (b) OsO_4, NMO, Acetone, rt; (c) $NaIO_4$, MeOH, rt

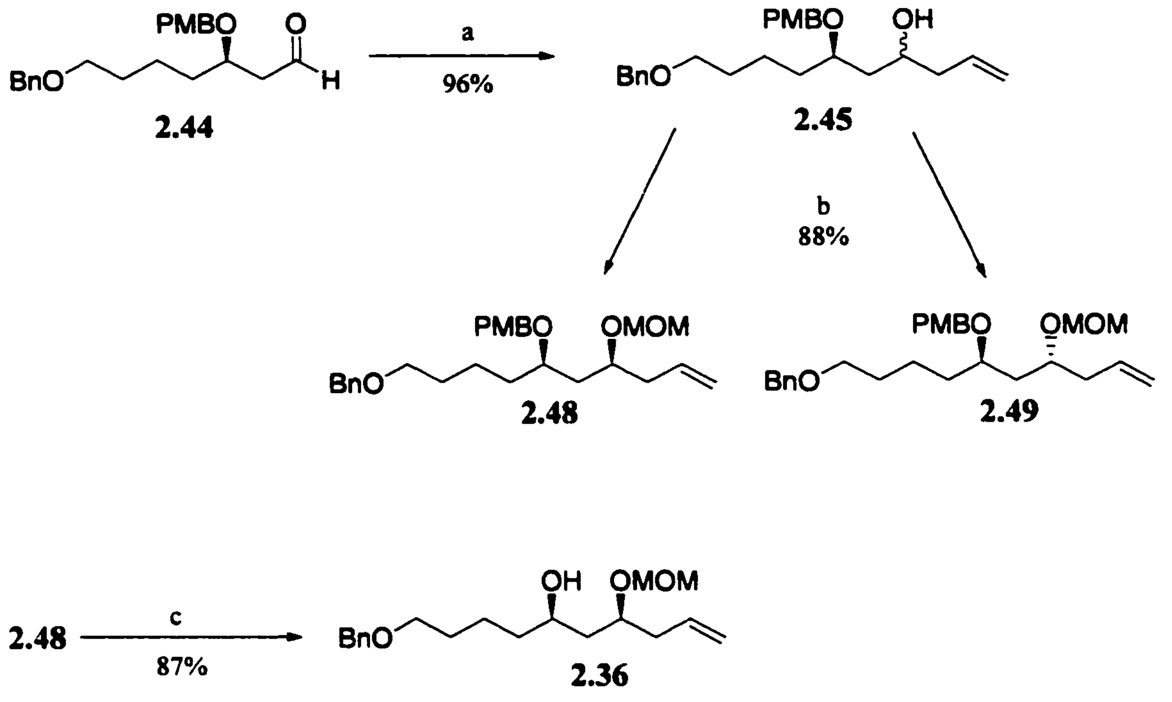
The second allylation involved the Grignard addition of allylmagnesium bromide to **2.44** to provide **2.45** in 96% yield (**Scheme 2.9**). However, this afforded an inseparable 1:1 mixture of *syn* to *anti* diastereomers. To improve on the *syn* selectivity various stereoselective allylation reactions were tried. The reaction of the aldehyde **2.44** under the identical Keck's conditions[32] gave no reaction after six days. The reactions of **2.44** with different allylboranes were also attempted. Surprisingly, the reaction of **2.44** with both (-)-allyldiisopinocamphenylborane[35] and (R,R)-diisopropyltatrate allylborane[36] afforded the *anti*-1,3-diol alkene as the major isomer, instead of the expected *syn* isomer (**Table 2.1**). Since, the diastereoselectivity of these allylations has been shown to be influenced by the protecting groups used at the β-position, the protecting group at the β-position (C5) was changed from the PMB ether to the TBDMS ether **2.46**.[37] However, no significant effect on the asymmetric induction was observed with Brown's allylating borane reagent (**Table 2.1**).[38] An oxidation-reduction sequence on the homoallylic alcohol **2.47** was also investigated. Oxidation of the alcohol function to the ketone **2.47** with PCC, followed by its reduction with a variety of reducing agents afforded no significant improvements in the *syn* to *anti* ratio (**Table 2.1**). Following the accepted transition state model for these allylations the formation of the *syn* product corresponds to a mismatched case.[36b] Indeed, similar results have been observed. Kurosu[37] reported that the protecting group at the β-position significantly influenced the catalytic asymmetric allylations of chiral aldehydes with BINOL-Zr complex. This reaction favored the formation of the *anti* isomer regardless of the chirality of BINOL used.

Table 2.1. Allylation and oxidation/reduction of **2.44**, **2.46** and **2.47**

Starting Material	Reagents	Ratio(a) *syn*:*anti*
 **2.44**	Allylmagnesium bromide	1:1
	(-)-allyldiisopinocamphenylborane	1:3
	(R,R)-diisopropyltatrate allylborane	1:4
	allyltributyltin	No reaction
 **2.46**	(-)-allyldiisopinocamphenylborane	1:1
 **2.47**	LAH	3:2
	$NaBH_4$	1:1
	DiBAL-H	1:1
	(R)-2-CBS-oxazalborolidine/BH_3SMe_2[39]	1:1
	(S)-2-CBS-oxazalborolidine/BH_3SMe_2[39]	1:1

(a) Ratios are approximate and were determined from ^1H and ^{13}C NMR.

Treatment of **2.45** with MOMCl afforded a separable mixture of *syn* **2.48** and *anti* **2.49** isomers. The *syn* isomer **2.48** was more polar than the *anti* isomer **2.49** and the combined yield for the reaction was 88%. Oxidative removal of the PMB ether of **2.48** by DDQ gave the first alkenol component **2.36** in 87% yield (**Scheme 2.9**).



Scheme 2.9. (a) AllylMgBr, Et_2O, -78 °C to rt; (b) MOMCl, *i*Pr_2NEt, CH_2Cl_2, rt; (c) DDQ, CH_2Cl_2, H_2O, rt.

The relative stereochemistry of **2.48** and **2.49** was confirmed by the formation of the acetonides **2.50** and **2.51**. The ^{13}C NMR spectra of *anti*-1,3-diols **2.51** exhibit signals for the methyl groups of the acetonides at 25 ppm whilst the *syn*-1,3-diols **2.50** show signals for the methyl groups at 19 and 30 ppm (**Figure 2.2**).[40]

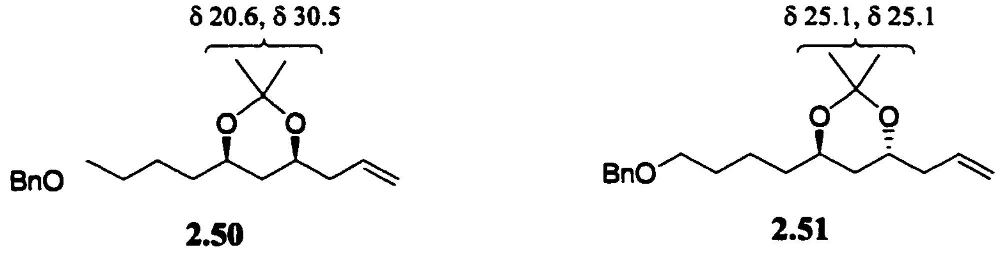
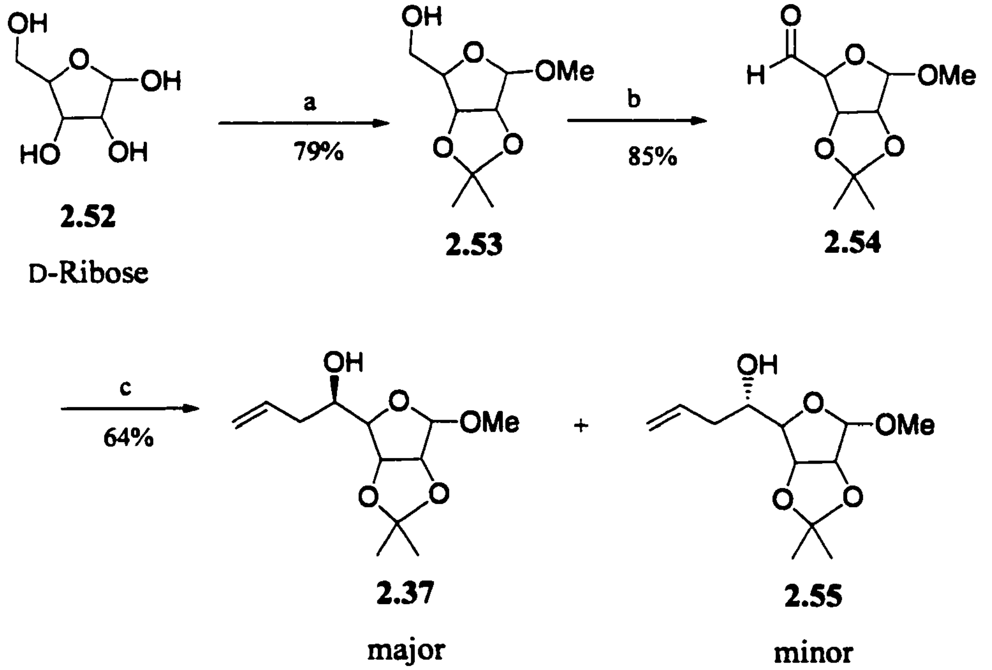


Figure 2.2

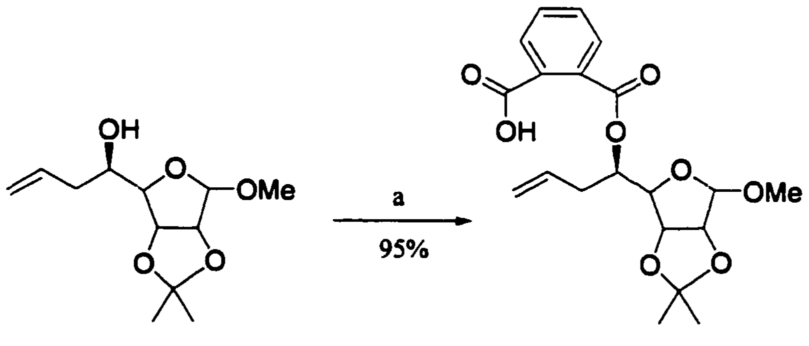
The starting material for the second alkenol segment **2.37** was D-ribose **2.52**. The concomitant protection of the vicinal C2 and C3 hydroxyl functions as its acetonide and the C1 hydroxyl group as its methyl ether furnished the protected ribose **2.53** in 79% yield.[41] Swern oxidation of the C5 hydroxyl group afforded the aldehyde **2.54** in 85% yield. The known reaction of allylmagnesium bromide to **2.54** afforded a 2:1 ratio of homoallylic alcohols **2.37** and **2.55** in a combined yield of 64%.[31] The mixture was separated and isomer **2.37** was forwarded to the spiroketal methodology (**Scheme 2.10**).



Scheme 2.10. (a) Acetone, MeOH, $CuSO_4$, H_2SO_4, rt; (b) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, then Et_3N, rt; (c) allylMgBr, THF, -78 °C

METATHESIS-IODOETHERIFICATION-SPIROKETALIZATION SEQUENCE

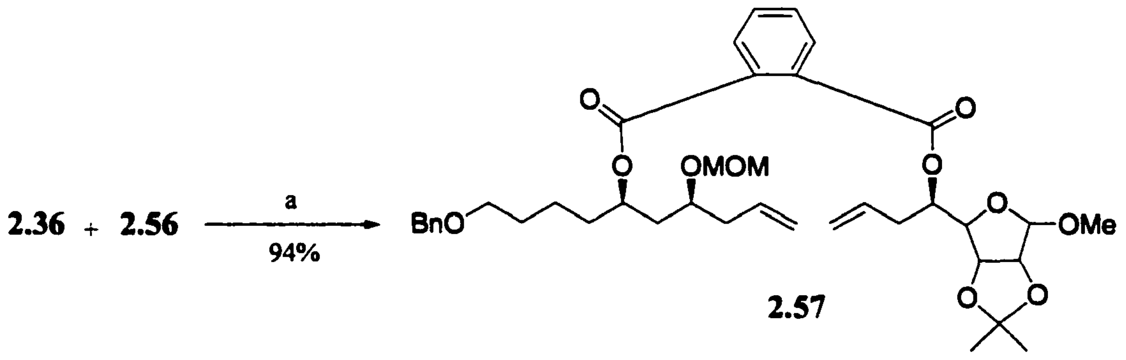
In preparation for the RCM protocol, alkenol **2.37** was converted to the monophthalate **2.56**, by treatment with phthalic anhydride and pyridine (**Scheme 2.11**). The



2.37 **2.56**

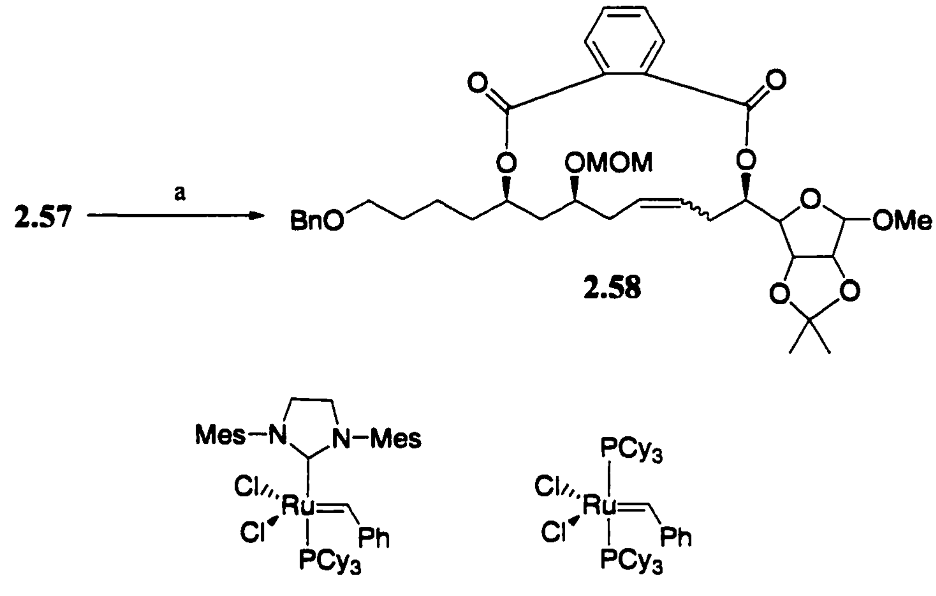
Scheme 2.11. (a) Phthalic anhydride, pyridine, rt.

acid **2.56** and alkenol **2.36** were then subjected to DCC mediated esterification to furnish the mixed diester **2.57** in 94% yield (**Scheme 2.12**).[42]



Scheme 2.12. (a) DCC, cat. DMAP, cat. CSA, benzene, 0 °C to rt.

RCM of **2.57** in CH_2Cl_2 (0.01M), with 20 mol% of catalyst **2.59** ((1,3-dimesityl-4,5-dihydroimidazol-2-ylidene)$(PCy_3)(Cl)_2$-Ru=CHPh) for 3.5 h afforded **2.58** in 91% yield (**Scheme 2.13**). There was no evidence for the formation of polymeric products.[30,43] The use of catalyst **2.60** under the same experimental conditions also gave **2.58**, but in a lowered yield of 37%. The reaction was also significantly slower and required a reaction time of 2 days.



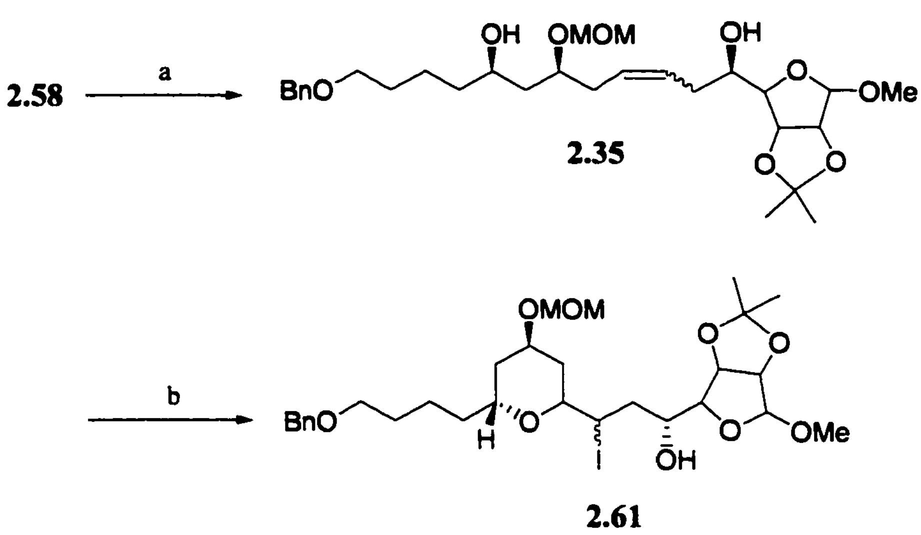
2.58

2.59

2.60

Scheme 2.13. (a) **2.59**, CH_2Cl_2 (0.01M), reflux, 3.5 h, 91% or **2.60**, CH_2Cl_2 (0.01M), reflux, 2d, 37%

Removal of the phthalate tether in **2.58** with DIBALH afforded the dihydroxyalkene **2.35**. Compound **2.35** was then subjected to the iodocyclization conditions. Four possible modes of cyclization products are possible: 7-endo-trig, 6-exo-trig, 5-endo-trig and the 4-exo-trig. Of these, the 6-exo-trig is expected to be highly favored. Indeed, treatment of an anhydrous CH_2Cl_2 solution of **2.35** with IDCP in the presence of 4Å MS furnished the iodo-THP **2.61** as a single set of diastereomeric THP ring isomers, in 74% yield (**Scheme 2.14**).



Scheme 2.14. (a) DIBALH, CH_2Cl_2, -78 °C to rt; (b) IDCP, CH_2Cl_2, 4Å MS, rt; 52% from **2.58**.

The structure of **2.61** was confirmed by analysis of ^1H-^1H COSY spectrum of the acetylated derivative **2.62** (**Figure 2.3**). The proton at the base of the acetoxy group at δ 5.30 (H12) showed cross peaks to the proton signals at δ 2.11 (H11) and δ 4.10 (H13), respectively. This data is in agreement with the 6-exo-trig cyclization product, and rules

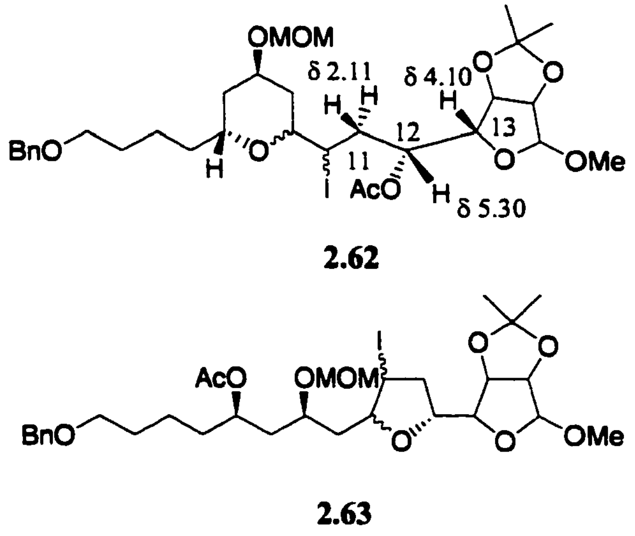
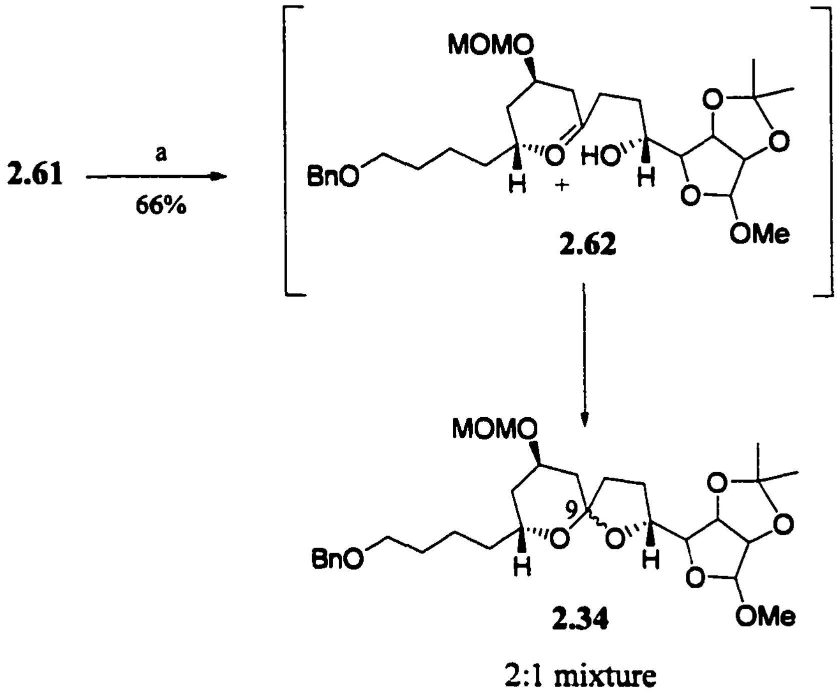


Figure 2.3

out the product from a 5-endo-trig mode of cyclization **2.63**.

Treatment of iodo-THP **2.61** in CH_2Cl_2 with silver triflate and collidine afforded the spiroketal **2.34** in 66% yield, as an inseparable 2:1 mixture of diastereomers (**Scheme 2.15**). Since no evidence for the enol ether was observed it is presumed that the formation of the spiroketal occurs via the oxocarbenium ion **2.62**, which then reacts with the remaining hydroxyl function to yield **2.34**. Analysis of the ^{13}C NMR spectrum showed carbon signals for acetal carbons at δ 95.0, δ 106.0, δ 107.2, δ109.8, δ 110.0, δ 112.1, δ 112.2. Of these, two new signals at δ 106.0 and δ 107.2 were observed and were assigned to the spiroketal carbon (C9) of **2.34**. For a similar spiroketal mixture, Ireland assigned the spiroketal carbons (C9) as δ 106.3 and δ 108.1.[20d] Comparison of this result with ours, showed that our assignment was consistent for C9.



Scheme 2.15. (a) AgOTf, collidine, CH_2Cl_2, rt

As mentioned earlier, the observation of a spiroketal mixture was not a concern, since it is expected that equilibration of the target structure would give the desired configuration.

The application of this novel metathesis-haoletherification-spiroketalization sequence to monensin analog **1.2** was next attempted. This requires the identical alkenol **2.36** used for the model study and a more complex polycyclic ether alkenol partner. The synthesis of the latter is next discussed.

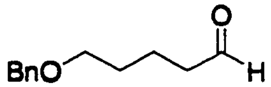
2.5 GENERAL EXPERIMENTAL

Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere in oven-dried glassware using standard syringe and septa techniques. Diethyl ether and tetrahydrofuran were distilled from sodium or potassium/benzophenone ketyl under N_2 immediately prior to use. Dry methylene chloride was distilled from phosphorus pentoxide. Dry dimethylformamide (DMF) was distilled from calcium hydride under reduced pressure. Anhydrous benzene and toluene were obtained by azeotropic removal of water.

^{1}H and ^{13}C NMR spectra were obtained on GE QE 300 (300 MHz) or Varian Unity Plus 500 (500 MHz) instruments. Chemical shifts are relative to the deuterated solvent peak and are in parts per million (ppm). The ^{1}H and ^{13}C NMR spectra were recorded at either 300 or 500 MHz and 75 or 100 MHz, respectively. Low resolution mass spectra were acquired using an Agilent Technologies 1100 LCMSD. High resolution mass spectrometric data (HRFABMS) was performed on 70-4F spectrometer at University of Illinois, Chicago. Infrared (IR) spectra were done neat or as $CHCl_3$ films on a Perkin-Elmer 710B spectrometer and reported in cm^{-1}.

Thin layer chromatography (TLC) was done on 0.25 mm thick precoated silica gel G HF_{254} (Whatman) aluminium sheets. The chromatograms were observed under UV (short and long wave) light and/or were visualized by heating plates that were dipped in ammonium molybdate/cerium (IV) sulfate solution. Flash column chromatography (FCC) was performed using silica gel 60 (230-400 mesh) and usually employed a stepwise solvent polarity gradient, correlated with TLC mobility.

2.6 EXPERIMENTAL

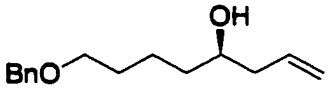


2.39

5-Benzyloxy pentanal 2.39. Pentane-1,5-diol **2.38** (15.0 g, 144 mmol) was dissolved in dimethylformamide (100 mL) and cooled to 0-5 °C. Sodium hydride (6.3 g, 158.4 mmol) and tetrabutylammonium iodide (2.7 g, 7.2 mmol) were added and stirred for 20 min. Benzyl bromide (17.1 mL, 129.6 mmol) was added drop-wise over a period of 90 min. Stirring was continued until all starting material disappeared as indicated by TLC. Methanol (75 mL) was then added and the solution was concentrated under reduced pressure. The residue was diluted with water and extracted with ether (3 x 200 mL). The ethereal extract was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by chromatography to yield a colorless oil (12.9 g, 46%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (m, 6H), 3.15 (br s, 1H), 3.50 (t, J= 8.8 Hz, 2H), 3.55 (t, J= 8.8 Hz, 2H), 4.50 (s, 2H), 7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 29.4, 32.4, 62.2, 70.3, 72.8, 127.4, 127.5, 128.2, 138.3. MS (ES, *m/z*) 195 $(M+H)^+$, 212 $(M+NH_4)^+$, 217 $(M+Na)^+$.

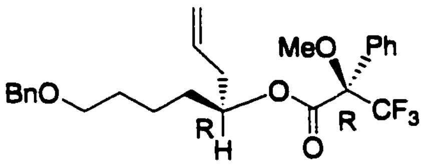
To a stirred mixture of CH_2Cl_2 (200 mL), pyridinium chlorochromate (18.2 g, 84.5 mmol), powdered, freshly activated 4Å molecular sieves (27.3 g), Celite (27.3 g), Florisil (27.3 g) and sodium acetate (6.93 g, 84.5 mmol) was added a solution of the monobenzylated alcohol (8.2 g, 42.3 mmol), from the previous step, in CH_2Cl_2 (60 mL). The solution was stirred at rt for 1 h, diluted with ether and filtered through a bed of

Florisil. The filtrate was concentrated *in vacuo* and the residue purified by FCC to yield the aldehyde **2.39** (6.8 g, 82%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (m, 4H), 2.55 (t, J= 8.8 Hz, 2H), 3.50 (t, J= 8.8 Hz, 2H), 4.50 (s, 2H), 7.30 (m, 5H), 9.75 (app s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 29.2, 43.6, 69.8, 72.9, 127.5, 127.6, 128.3, 138.5, 202.3.

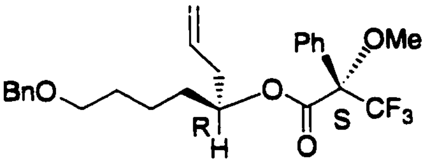


2.40

8-Benzloxy-4(R)-hydroxy-1-octene 2.40. A 250 mL, round-bottomed flask equipped with a stirring bar and a rubber septum is charged with *R*-BINOL (0.895 g, 3.13 mmol) and CH_2Cl_2 (30 mL). The suspension was stirred until the binaphthol was completely dissolved. Powdered 4 Å molecular sieves (13 g) were then added. To the resultant suspension was added titanium tetraisopropoxide (0.94 mL, 3.13 mmol) by syringe at ambient temperature. The resulting orange-red suspension was heated at reflux for 1 h. The red-brown mixture is cooled to ambient temperature and a CH_2Cl_2 solution of **2.39** (6.01 g, 31.3 mmol) was injected via syringe. The resulting mixture was stirred for 5 min at ambient temperature, then cooled to –78 °C. To the reaction mixture was added allyltributylstanne (12.6 mL, 40.7 mmol) via syringe. The resulting reaction mixture was then immersed in a bath (H_2O : Ethylene glycol 1:1) at –22 °C for 4 ½ days. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (50 mL), diluted with CH_2Cl_2 (50 mL), and stirred at ambient temperature for 2 h. The molecular sieves were removed by filtration through a pad of Celite, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. Chromatography of the residue over silica gel gave **2.40** (6.7 g, 92%, (99% ee)). $[\alpha]_D^{26}$ –2.0 (c 1.74, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70-1.30 (m, 6H), 2.00 (br s, 1H, -OH), 2.20 (m, 2H), 3.50 (t, J= 8.8 Hz, 2H), 3.60 (m, 1H), 4.50 (s, 2H), 5.10 (m, 2H), 5.80 (m, 1H), 7.23 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 29.2, 36.0, 41.4, 69.8, 70.1, 72.4, 117.2, 126.9, 127.6, 128.3, 134.9, 138.6. FABHRMS calcd for $C_{15}H_{22}O_2$ $(M+H)^+$ 235.1693, found 235.1693.



2.41

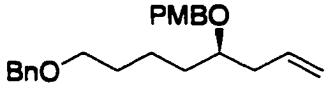


2.42

(R) and (S) Mosher esters of 2.40. A stirred solution of alcohol **2.40** (0.092 g, 0.393 mmol), (R)-MPTA (0.276 g, 1.17 mmol), DMAP (14 mg, 0.12 mmol) in anhydrous benzene at 0-5 °C was treated with DCC (121 mg, 0.59 mmol). After stirring for 2 h at room temperature, diethyl ether (50 mL) was added and the mixture was filtered through Celite. Concentration of the filtrate and FCC of the residue afforded the ester **2.41** (140.6 mg, 80%) as viscous oil.

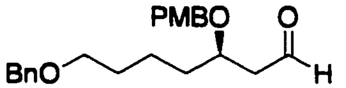
For the (R)-MPTA ester **2.41**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40-1.80 (m, 6H), 2.40 (m, 2H), 3.50 (t, J= 8.8 Hz, 2H), 3.60 (s, 3H), 4.50 (s, 2H), 5.05 (m, 2H), 5.20 (m, 1H), 5.65 (m, 1H), 7.35 (m, 6H), 7.55 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 29.7, 33.3, 38.2, 55.5, 62.5, 70.1, 73.1, 76.6, 118.4, 127.4, 127.5, 127.6, 128.4, 129.5, 129.6, 132.4, 132.8, 138.7, 166.2.

For the (S)-MPTA ester **2.42**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (m, 6H), 2.45 (m, 2H), 3.40 (t, J= 8.8 Hz, 2H), 3.60 (s, 3H), 4.50 (s, 2H), 5.15 (m, 2H), 5.20 (m, 1H), 5.80 (m, 1H), 7.35 (m, 6H), 7.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 29.6, 33.3, 38.5, 55.5, 55.7, 62.5, 70.1, 73.0, 76.5, 118.4, 127.4, 127.5, 127.6, 128.4, 129.5, 129.6, 132.6, 133.2, 138.7, 166.2.



2.43

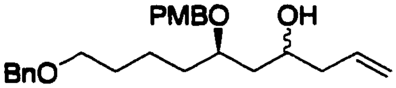
8-Benzyloxy-4(R)-*p*-methoxybenzyloxy-1-octene 2.43. Compound **2.40** (3.83 g, 16.4 mmol) was subjected to standard benzylation (cf. **2.39**) using *p*-methoxybenzyl chloride (4.00 mL, 28.7 mmol), sodium hydride (983.4 mg, 24.56 mmol), tetrabutylammonium iodide (604.8 mg, 1.64 mmol) and dimethylformamide (30 mL). The reaction was quenched by the addition of methanol (30 mL), concentrated, diluted with water and extracted with diethyl ether (3 x 100 mL). The ethereal extract was dried (Na_2SO_4) and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by FCC to afford **2.43** (4.6 g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45-1.75 (m, 6H), 2.40 (m, 2H), 3.50 (m, 3H), 3.80 (s, 3H), 4.50 (AB q, Δδ= 0.16 ppm, J= 11.0 Hz, 2H), 4.55 (s, 2H), 5.15 (m, 2H), 5.90 (m, 1H), 6.90 (d, J= 11.0 Hz, 2H), 7.30 (d, J= 11.0 Hz, 2H), 7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 30.0, 33.8, 38.5, 55.3, 70.4, 70.6, 72.9, 78.2, 113.8, 116.7, 127.4, 127.5, 128.3, 129.1, 131.2, 135.1, 138.8, 159.1. MS (ES, *m/z*) 372 $(M+NH_4)^+$.



2.44

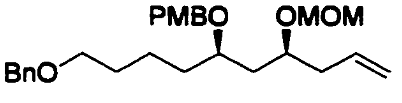
7-Benzyloxy-3(R)-*p*-methoxybenzyloxy heptanal 2.44. The oil **2.43** (4.57 g, 12.9 mmol) was dissolved in acetone (40 mL) and osmium tetroxide (1.3 mL of a 2.5 wt% solution in *t*-BuOH, 0.13 mmol) and N-methyl morpholine oxide (6.0 mL of a 50% wt solution in water, 25.8 mmol) were added to the solution and stirred overnight at rt. A saturated solution of sodium bisulfite (50 mL) was added and the mixture was stirred at rt for 1 h. The mixture was concentrated under reduced pressure and the residue was diluted with water and extracted with ethyl acetate (3 x 100 mL). The combined organic extract was dried (Na_2SO_4), filtered and concentrated *in vacuo*.

The crude oil from the previous step, was dissolved in methanol (50 mL) and sodium periodate (2.49 g, 11.7 mmol) was added. The slurry was stirred at rt for 2 h. Upon completion, the slurry was concentrated under reduced pressure and the residue was diluted with $Na_2S_2O_3$ (100 mL) and extracted with diethyl ether (3 x 100 mL). The ethereal extract was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by FCC to afford a viscous oil **2.44** (3.23 g, 70% over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35-1.80 (m, 6H), 2.60 (m, 2H), 3.50 (t, J= 8.8 Hz, 2H), 3.80 (s, 3H), 3.95 (m, 1H), 4.50 (s, 2H), 4.55 (s, 2H), 6.90 (d, J= 11 Hz, 2H), 7.25 (d, J= 11 Hz, 2H), 7.35 (m, 5H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 29.9, 34.3, 48.5, 55.4, 70.2, 71.0, 73.0, 74.1, 113.9, 127.5, 127.6, 128.4, 129.3, 130.5, 138.7, 159.3, 201.2. MS (ES, *m/z*) 374 $(M+NH_4)^+$.

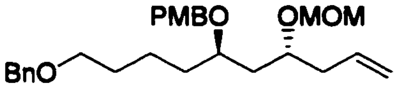


2.45

10-Benzyloxy-6(R)-*p*-methoxybenzyloxy-4-hydroxy-1-dodecene 2.45. To a stirred solution of allylmagnesium bromide (65 mL of a 1M solution in diethyl ether, 65 mmol) in diethyl ether (200 mL) at –78 °C was added drop-wise an ethereal solution of **2.44** (7.42 g, 20.8 mmol). The mixture was stirred for 1 h at –78 °C, warmed to room temperature and stirred for an additional 1 h. The reaction mixture was then poured into an ice-cold aqueous solution of NH_4Cl (400 mL). The resulting slurry was then extracted with diethyl ether (3 x 150mL) and the combined extract was dried (Na_2SO_4) and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by FCC to yield a mixture of inseparable diastereomers **2.45** (7.9 g, 96%). R_f= 0.48 (10% EtOAc in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (m, 2H), 2.75 (m, 6H), 2.20 (m, 2H), 2.80 (d, J= 4 Hz, ½H), 3.50 (m, 2H), 3.70 (m, 1H), 3.80 (s, 3H), 3.95 (m, ½H), 4.45 (m, 2H), 4.52 (s, 2H), 5.10 (m, 2H), 5.85 (m, 1H), 6.85 (d, J= 11 Hz, 2H), 7.30 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 21.9, 29.7, 29.7, 33.2, 33.4, 39.9, 40.3, 42.0, 42.2, 54.9, 67.5, 69.9, 70.1, 70.6, 72.6, 76.2, 78.5, 113.6, 113.6, 116.7, 116.8, 127.1, 127.2, 128.0, 129.1, 130.1, 130.5, 134.8, 134.8, 138.4, 158.9.



2.48



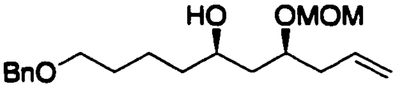
2.49

10-Benzyloxy-6(R)-*p*-methoxybenzyloxy-4(S)-(methoxymethyleneoxy)-1-decene 2.48. MOMCl (0.5 mL, 6.6 mmol) was added to a solution of **2.45** (0.747 g, 1.88 mmol) and *i*-Pr_2NEt (2 mL, 11.0 mmol) in anhydrous CH_2Cl_2 (12 mL) at 0 °C, and the mixture was stirred for 18 h at rt. The reaction mixture was quenched with saturated aqueous NH_4Cl and then extracted with ether. The organic layer was washed with brine and then dried over Na_2SO_4. Filtration and evaporation of the solvent afforded the crude mixture, which was chromatographed on a silica gel column (5% EtOAc in petroleum ether) to give recovered starting material **2.45** (58 mg) and the protected *syn*- and *anti*-1,3-diol **2.48** and **2.49** (675.7 mg, 88%, based on recovered starting material).

For the *syn* isomer **2.48**: R_f= 0.74 (10% EtOAc in petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 1.46 (m, 2H), 1.60 (m, 5H), 1.88 (m, 1H), 2.25 (m, 1H), 2.30 (m, 1H), 3.35 (s, 3H), 3.48 (m, 3H), 3.73 (m, 1H), 3.79 (s, 3H), 4.42 (s, 2H), 4.50 (s, 2H), 4.63 (ABq, Δδ= 0.03 ppm, J= 7 Hz, 2H), 5.06 (m, 2H), 5.80 (m, 1H), 6.85 (d, J= 9 Hz, 2H), 7.24-7.34 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 30.0, 34.0, 39.0, 39.3, 55.3, 55.6, 70.2, 70.4, 72.9, 74.5, 75.7, 95.6, 113.9, 117.1, 127.4, 127.5, 128.3, 129.2, 131.2, 134.7, 138.9, 159.2.

For the *anti* isomer **2.49**: R_f= 0.81 (10% EtOAc in petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 1.43-1.66 (m, 8H), 2.32 (m, 2H), 3.37 (s, 3H), 3.48 (t, J= 6 Hz, 2H), 3.59 (m, 1H), 3.79 (s, 3H), 3.84 (m, 1H), 4.42 (ABq, Δδ= 0.1 ppm, J= 11 Hz, 2H), 4.50

(s, 2H), 4.62 (ABq, Δδ= 0.07 ppm, J= 7 Hz, 2H), 5.07 (m, 2H), 5.80 (m, 1H), 6.89 (d, J= 9 Hz, 2H), 7.25-7.34 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 30.1, 34.0, 40.0, 40.1, 55.2, 55.5, 70.3, 70.4, 72.9, 74.8, 75.5, 96.1, 113.8, 117.0, 127.3, 127.4, 128.2, 129.1, 131.2, 134.5, 138.8, 159.1. FABHRMS calcd for $C_{27}H_{38}O_5$ $(M+Na)^+$ 465.2617, found 465.2617.



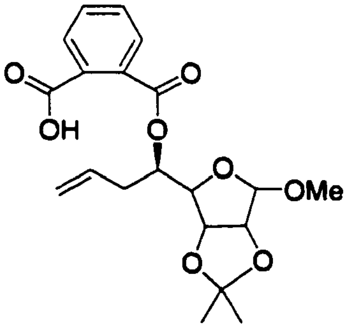
2.36

10-Benzyloxy-6(R)-hydroxy-4(S)-(methoxymethyleneoxy)-1-decene 2.36. To a mixture of **2.48** (0.559 g, 1.27 mmol), CH_2Cl_2 (30 mL) and H_2O (10 mL) was added DDQ (0.649 g, 2.86 mmol). The reaction mixture was vigorously stirred for 45 min at rt, at which point no starting material was observed by TLC. Saturated aqueous $NaHCO_3$ (30 mL) was added, and the mixture was diluted with CH_2Cl_2 (20 mL). The organic phase separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined CH_2Cl_2 extract was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by FCC (20% EtOAc in petroleum ether) to afford **2.36** (364.1 mg, 87%).

For the *syn* isomer **2.36**: R_f= 0.56 (40% EtOAc in petroleum ether); $[\alpha]_D^{26}$ −28.9 (c 0.65, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (m, 4H), 1.62 (m, 4H), 2.34 (m, 2H), 3.05 (d, J= 2 Hz, 1H), 3.40 (s, 3H), 3.48 (t, J= 7 Hz, 2H), 3.77 (m, 1H), 3.86 (m, 1H), 4.49 (s, 2H), 4.71 (ABq, Δδ= 0.1 ppm, J= 7 Hz, 2H), 5.09 (m, 2H), 5.78 (m, 1H), 7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 29.7, 37.4, 38.9, 41.4, 55.6, 70.2, 70.2, 72.7, 76.5, 95.1, 117.3, 127.2, 127.4, 128.1, 134.0, 138.6.

A small portion of **2.49** was treated in a similar manner as that for **2.48** to afford the anti isomer of **2.36**.

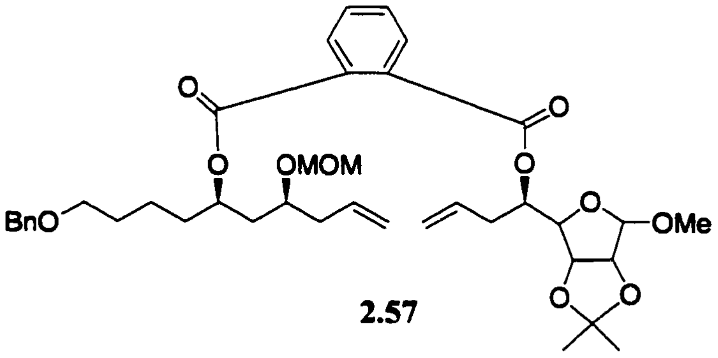
For the *anti* isomer: R_f= 0.53 (40% EtOAc in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42-1.68 (m, 8H), 2.33 (m, 2H), 2.77 (d, J= 4 Hz, 1H), 3.40 (s, 3H), 3.48 (t, J= 6 Hz, 2H), 3.88 (m, 2H), 4.50 (s, 2H), 4.70 (ABq, Δδ= 0.1 ppm, J= 7 Hz, 2H), 5.08 (m, 2H), 5.80 (m, 1H), 7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 29.9, 37.6, 39.6, 41.6, 55.8, 67.8, 70.4, 73.0, 75.4, 96.4, 117.4, 127.4, 127.6, 128.3, 134.4, 138.7. FABHRMS calcd for $C_{19}H_{30}O_4$ $(M+Na)^+$ 345.2041, found 345.2041.



2.56

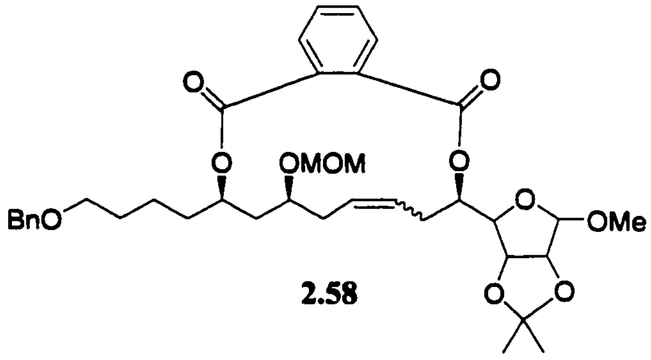
Carboxylic acid 2.56. To a stirred solution of **2.37**[31] (1.1 g, 4.4 mmol) in pyridine (15 mL) were added phthalic anhydride (1.3 g, 8.8 mmol) and DMAP (107.5 mg, 0.88 mmol). After 18 h the solution was filtered through a bed of Celite and the solvent was removed under reduced pressure. The residue was purified by FCC to afford **2.56** (1.5g, 87%) as a viscous oil. R_f= 0.28 (5% EtOAc in $CHCl_3$); ^{1}H NMR (300 MHz,

$CDCl_3$) δ 1.28 (s, 3H), 1.44 (s, 3H), 2.50 (m, 1H), 2.69 (m, 1H), 3.35 (s, 3H), 4.24 (d, J= 8.8Hz, 1H), 4.61 (d, J= 6 Hz, 1H), 4.85 (d, J= 6 Hz, 1H), 4.98 (s, 1H), 5.19 (m, 3H), 5.84 (m, 1H), 7.53 (m, 2H), 7.66 (d, J= 6 Hz, 1H), 7.82 (d, J= 6 Hz, 1H), 11.39 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 26.7, 36.0, 55.7, 74.1, 81.6, 85.4, 86.7, 110.2, 112.6, 118.6, 128.8, 129.6, 130.9, 131.9, 131.9, 132.7, 166.9, 171.4. MS (ES, *m/z*) 410 $(M+NH_4)^+$.



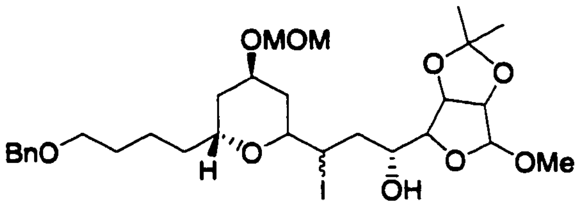
2.57

Mixed diester 2.57. A stirred solution of alcohol **2.36** (0.637 g, 1.98 mmol), acid **2.56** (1.07 g, 2.73 mmol), DMAP (97 mg, 0.79 mmol) and camphorsulfonic acid (185.8 mg, 0.79 mmol) in anhydrous benzene at 0-5 °C was treated with DCC (1.65 g, 7.99 mmol). After stirring for 6 h at room temperature, diethyl ether (50 mL) was added and the mixture was filtered through Celite. Concentration of the filtrate and FCC of the residue afforded ester **2.57** (1.3 g, 94%) as viscous oil. R_f= 0.61 (10% EtOAc in petroleum ether) ^1H NMR (500MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.47 (s, 3H), 1.48 (m, 2H), 1.63-1.73 (m, 4H), 1.80 (m, 1H), 1.99 (m, 1H), 2.35 (m, 1H), 2.39 (m, 1H), 2.50 (m, 1H), 2.66 (m, 1H), 3.35 (s, 3H), 3.36 (s, 3H), 3.47 (t, J= 7 Hz, 2H), 3.76 (m, 1H), 4.25 (d, J= 8 Hz, 1H), 4.48 (s, 2H), 4.63(m, 3H), 4.88 (d, J= 6Hz, 1H), 4.98 (s, 1H), 5.06-5.25 (m, 6H), 5.85 (m, 2H), 7.31 (m, 5H), 7.50 (m, 2H), 7.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1 25.3, 26.8, 29.8, 34.2, 36.1, 38.8, 39.1, 55.6, 55.7, 70.3, 73.0, 73.2, 73.7, 74.4, 81.7, 85.5, 86.8, 95.7, 110.4, 112.4, 117.5, 118.4, 127.4, 127.6, 128.3, 128.7, 128.8, 130.8, 130.9, 132.5, 132.8, 133.0, 134.4, 138.9, 166.4, 166.6. FABHRMS calcd for $C_{39}H_{52}O_{11}$ $(M+Na)^+$ 719.3407, found 719.3407.



2.58

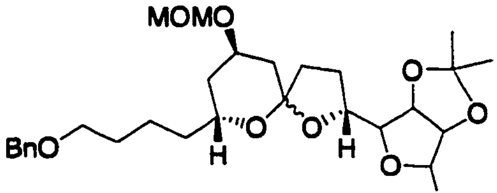
Macrocyclic alkene 2.58. Compound **2.57** (0.175 g, 0.251 mmol) was dissolved in CH_2Cl_2 (25 mL, 0.01M) and degassed for 10 min. Grubb's catalyst ((1,3-dimesityl-4,5-dihydroimidazol-2-ylidene)(PCy_3)$(Cl)_2$-Ru=CHPh) **2.59** (42.5 mg, 0.051 mmol) was added and the mixture heated at reflux for 3.5 h. The reaction mixture was cooled to rt, DMSO (0.2 mL) was added, and stirred for 16 h. The solution was concentrated *in vacuo*. FCC of the residue furnished **2.58** (152.5 mg, 91%) as a viscous colored oil. R_f= 0.44 (10% EtOAc in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.51 (s, 3H), 1.48-1.95 (m, 7H), 2.04 (m, 1H), 2.25 (m, 2H), 2.55 (m, 2H), 3.36 (s, 3H), 3.41 (s, 3H), 3.50 (m, 2H), 3.75 (m, 1H), 4.30 (d, J= 9 Hz, 1H), 4.51 (s, 2H), 4.67 (m, 3H), 4.90 (d, J= 6 Hz, 1H), 4.96 (s, 1H), 5.23 (m, 2H), 5.34 (m, 1H), 5.63 (m, 1H), 7.34 (m, 4H), 7.47-7.61 (m, 4H), 7.95 (d, J= 7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 25.1, 26.7, 29.8, 33.1, 33.9, 36.6, 38.9, 56.1, 56.3, 70.3, 73.1, 73.5, 73.9, 74.2, 82.4, 84.9, 85.3, 96.1, 111.2, 112.4, 127.1, 127.7, 127.8, 128.6, 129.3, 130.2, 130.8, 131.3, 131.5, 132.0, 134.0, 138.8, 166.8, 166.9. FABHRMS calcd for $C_{37}H_{48}O_{11}$ $(M+Na)^+$ 691.3094, found 691.3093.



2.61

Iodo-THP 2.61. Compound **2.58** (0.288 g, 0.431 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to –78 °C. To this was added 2.58 mL (2.58 mmol) of 1 M solution of diisobutylaluminium hydride in hexane and stirred for 1 h at –78 °C. The mixture was warmed to room temperature, stirred for an additional 1 h, then poured into ice cold saturated solution of Rochell's salt and was extracted with ethyl acetate (3 x 10 mL). The organic extract was dried (Na_2SO_4), filtered and concentrated *in vacuo*. A portion of the residue was purified to afford **2.35** as a viscous oil. R_f= 0.18 (20% EtOAc in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.47 (s, 3H), 1.40-1.66 (m, 8H), 2.30 (m, 2H), 3.07 (s, 1H), 3.39 (s, 3H), 3.41 (s, 3H), 3.47 (t, J= 7 Hz, 2H), 3.59 (br s, 1H), 3.69 (m, 1H), 3.77 (m, 1H), 3.84 (m, 1H), 4.22 (d, J= 2Hz, 1H), 4.50 (s, 2H), 4.56 (d, J= 6 Hz, 1H), 4.64 (d, J= 8Hz, 1H), 4.75 (d, J= 8 Hz, 1H), 4.85 (d, J= 6 Hz, 1H), 4.96 (s, 1H), 5.54 (m, 2H), 7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 24.9, 26.5, 29.9, 36.5, 37.6, 38.0, 41.5, 55.7, 56.1, 70.6, 71.1, 72.1, 73.1, 77.4, 80.1, 86.0, 91.0, 95.4, 110.1, 112.3, 127.7, 127.8, 128.5, 129.0, 129.1, 138.8.

To a solution of the above, crude dihydroxy alkene **2.35** (0.189 g, 0.351 mmol) and 4Å MS in dry CH_2Cl_2 (35 mL) was added IDCP (0.164 g, 0.351 mmol). The mixture was stirred at rt for 15 min, then poured into saturated aqueous $Na_2S_2O_3$ (20 mL), and extracted with CH_2Cl_2 (3x 10 mL). The combined organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. FCC of the residue afforded **2.61** (147.3 mg, 52% from **2.57**). R_f= 0.74 (40% EtOAc in petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.47 (s, 3H), 1.35-1.72 (m, 9H), 1.88 (m, 2H), 2.04 (m, 1H), 3.37 (s, 3H), 3.45 (s, 3H), 3.47 (app t, J= 7 Hz, 2H), 3.58 (app s, 1H), 3.63 (m, 1H), 3.75 (m, 1H), 3.93 (m, 1H), 4.04 (m, 1H), 4.17 (d, J= 2Hz, 1H), 4.35 (m, 1H), 4.49 (s, 2H), 4.56 (d, J= 6 Hz, 1H), 4.67 (s, 2H), 4.82 (d, J= 6 Hz, 1H), 4.97 (s, 1H), 7.33 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 24.9, 26.5, 29.9, 35.4, 35.9, 36.4, 37.9, 38.4, 55.6, 56.0, 70.3, 70.6, 71.9, 72.8, 73.0, 76.1, 80.7, 86.1, 91.8, 95.2, 110.2, 112.3, 127.6, 127.8, 128.5, 138.9. FABHRMS calcd for $C_{29}H_{45}O_9I$ (M+H)$^+$ 665.2187, found 665.2189.



2.34

2:1 mixture

Spiroketal 2.34. The iodo-THP **2.61** (0.066 g, 0.0994 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and collidine (40 μL, 0.299 mmol) was added and stirred for

10 min. AgOTf (0.077 mg, 0.299 mmol) was added and the mixture stirred for 25 min. The mixture was then poured into a saturated aqueous solution of $Na_2S_2O_3$ (10 mL), extracted with CH_2Cl_2 (3 x 10 mL). The combined CH_2Cl_2 extract was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude oil was purified by FCC to afford **2.34** (35.3 mg, 66%) as an inseparable mixture of diastereomers (2:1). R_f= 0.62 (20% EtOAc in petroleum ether).

For the major isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.45 (s, 3H), 1.37-2.10 (m, 13H), 2.15 (m, 1H), 3.26 (s, 3H), 3.39 (s, 3H), 3.46 (t, J= 9 Hz, 2H), 3.87 (d, J= 11 Hz, 1H), 4.01 (m, 3H), 4.49 (s, 2H), 4.56 (d, J= 6Hz, 1H), 4.65 (d, J= 8 Hz, 1H), 4.77 (d, J= 8 Hz, 1H), 4.84 (d, J= 6 Hz, 1H), 4.91 (s, 1H), 7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 25.0, 26.3, 26.6, 29.9, 35.8, 35.9, 36.4, 37.7, 54.9, 55.6, 65.3, 69.4, 70.6, 73.0, 78.6, 82.4, 85.8, 88.7, 95.0, 106.0, 109.8, 112.1, 127.7, 127.8, 128.5, 138.9.

For the minor isomer (selected ^1H and ^{13}C values): ^1H NMR (500 MHz, $CDCl_3$) δ 2.40 (m, 1H), 3.31 (s, 3H), 3.35 (s, 3H), 3.73 (m, 1H), 3.94 (m, 1H), 4.12 (d, J= 11 Hz, 1H), 4.56 (d, J= 6Hz, 1H), 4.64 (d, J= 8 Hz, 1H), 4.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 26.6, 28.9, 29.8, 35.3, 35.6, 38.5, 55.2, 70.0, 70.4, 79.1, 82.6, 90.4, 107.2, 110.0, 112.2, 127.9. FABHRMS calcd for $C_{29}H_{44}O_9$ $(M+Na)^+$ 559.2883, found 559.2881.

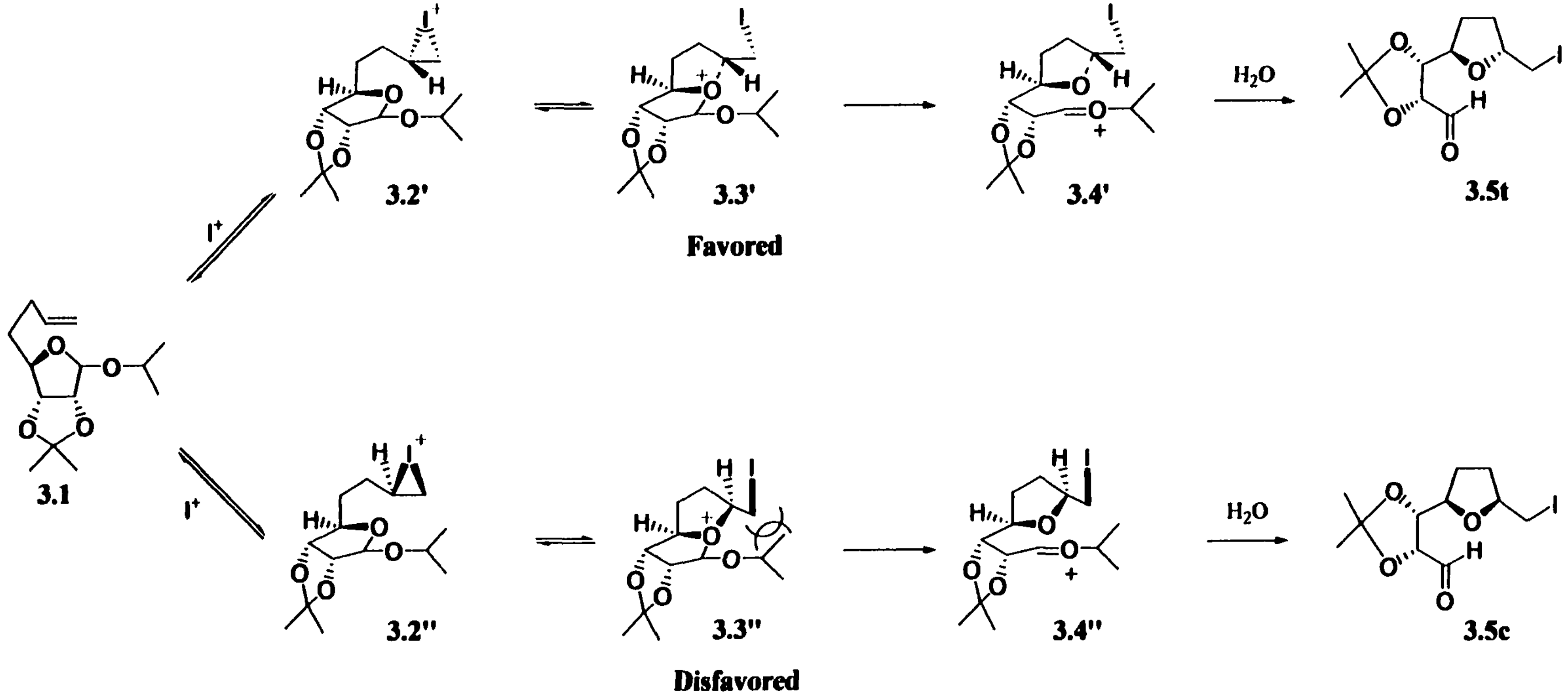
CHAPTER 3

2,3-*O*-ISOPROPYLIDENE RIBOFURANOSIDE TEMPLATES FOR THE SYNTHESIS OF OLIGO-THF's

3.1 BACKGROUND AND SYNTHETIC STRATEGY

Previous results from this laboratory have shown that the iodoetherification of carbohydrate alkenes leads to highly stereoselective formation of THFs.[44] The stereoselectivity of this reaction is presumably due to the conformational rigidity of the substrate. The iodoetherification of C6 allylated pyranosides led to the formation of *cis*-2,5-disubstituted THFs in high regio- and stereoselectivity.[44a,c,d] This protocol was successfully applied to the synthesis of the bis-THF core of rollinistatin **2.23**.[44b] In an extension of this investigation the iodocyclization of C5 allylated-2,3-O-isopropylidene ribofuranoside **3.1** gave the *trans*-2,5-disubstituted THFs **3.5** in high stereoselectivity (**Scheme 3.1**).[29,44f]

The reaction is believed to proceed through the addition of iodonium ion to the alkene to give diastereomeric halonium ions (or charge transfer complexes) **3.2**. Subsequent attack by the ring oxygen affords the THF oxonium ion **3.3**, which undergoes fragmentation to the oxocarbenium ion **3.4**. The oxocarbenium ion is captured by water to provide the mono-THF aldehyde **3.5** (**Scheme 3.1**).[44f] The preference for the *trans*-THF **3.5t** could be explained by the formation of a less crowded THF oxonium ion intermediate **3.3'**. The intermediate **3.3''** in which the iodinated side chain resides in the more congested cavity of the bicyclic oxonium ion would be less favored.[44f]



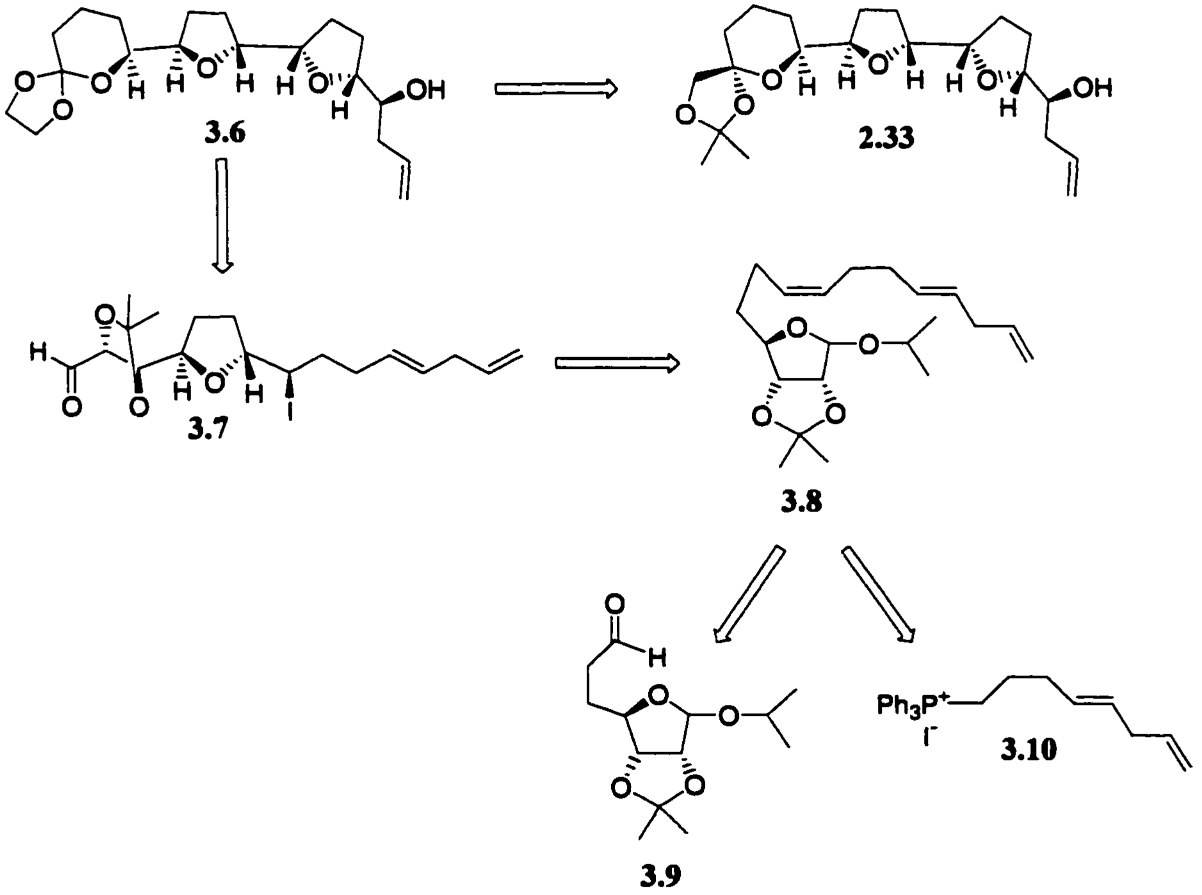
Note that this intermediate places the iodinated side chain in the more congested concave cavity of 3.4"

Ratio **3.5c**:**3.5t** 1:9

Scheme 3.1

On the basis of this result, we envisaged the synthesis of the bis-THF orthoester **3.6** from a ribofuranoside alkene precursor. Compound **3.6** is a suitable segment for our synthesis of monensin analog.

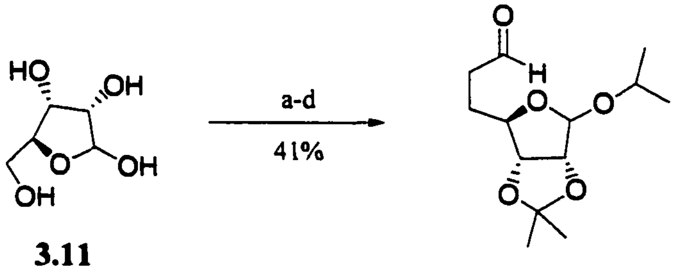
The bis-THF orthoester **3.6** may be derived from chain extension and further elaboration of the THF aldehyde **3.7**. The key intermediate **3.7** may be obtained by the iodoetherification of the 2,3-*O*-isopropylidene ribofuranoside triene **3.8**. A key concern in this reaction is competing halohydrin on the different alkenes. Precursor **3.8** may be obtained in a convergent manner from the 2,3-*O*-isopropylidene-D-ribose aldehyde **3.9**[29] and the Wittig salt **3.10** (**Scheme 3.2**).



Scheme 3.2

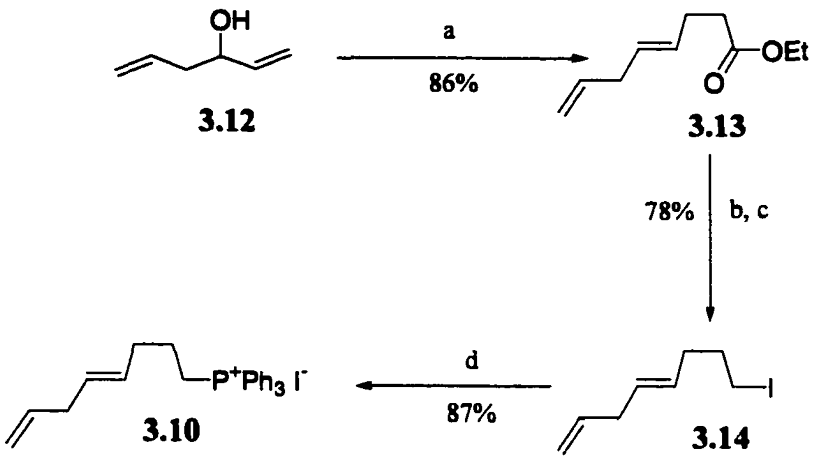
3.2 SYNTHESIS

The furanoside aldehyde **3.9** was obtained from D-ribose **3.11** in five straightforward steps in an overall yield of 41%. Using similar conditions as for the synthesis of **2.53**, the vicinal C2 and C3 hydroxyl function was protected as its isopropylidene and the C1 hydroxyl group as its isopropyl ether.[41] Tosylation of the primary alcohol, followed by treatment with allylmagnesium bromide in the presence of TMEDA afforded the allylated furanoside. Ozonolysis of this material afforded **3.9** (**Scheme 3.3**).[29]



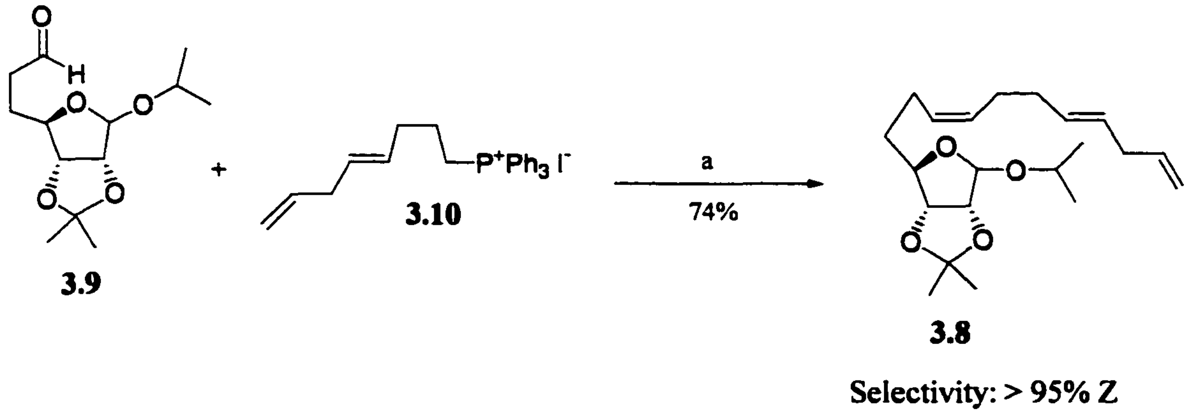
Scheme 3.3. (a) Acetone, isopropanol,$CuSO_4$, H^+ (64%); (b) TsCl, Et_3N, DMAP, CH_2Cl_2 (99%); (c) AllylMgBr, TMEDA, Et_2O (80%); (d) O_3, MeOH, CH_2Cl_2, -78° then Ph_3P (80%).

The Wittig salt **3.10** was prepared from the commercially available 1,5-hexadiene-3-ol **3.12** in an overall yield of 59%. The key transformation was the Claisen rearrangement[45] of **3.12** to the diene ester **3.13** in 86% yield. Reduction of the ester **3.13**, followed by iodination of the resulting alcohol afforded the iodo-diene **3.14** in 78% yield. Treatment of the iodo-diene **3.14** with PPh_3, $(iPr)_2NEt$, toluene and acetonitrile at reflux gave the Wittig salt **3.10** in 87% yield (**Scheme 3.4**).



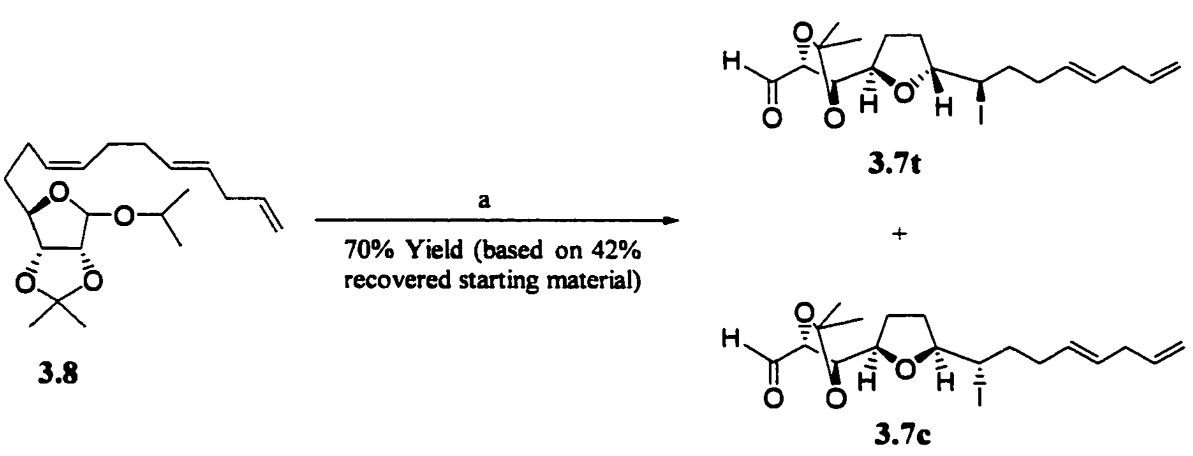
Scheme 3.4. (a) $(EtO)_3CCH_3$, CH_3CH_2COOH, 138-140 °C; (b) DIBALH, CH_2Cl_2, -78 °C to rt; (c) I_2, PPh_3, imidazole, CH_2Cl_2; (d) PPh_3, $(i\text{Pr})_2NEt$, CH_3CN, toluene, reflux.

The Wittig coupling between **3.9** and the ylide generated by treatment of **3.10** with sodium bis(trimethylsilyl) amide in toluene at –78 °C, afforded the furanoside triene **3.8** in 74% yield (**Scheme 3.5**). Non-stabilized ylides, such as that obtained from **3.10**, usually favor the formation of Z alkenes.[46] Accordingly, the *E*/*Z* selectivity was determined to be > 95% *Z* based on ^{1}H NMR.



Scheme 3.5. (a) NaHMDSA, toluene, -78 °C

The iodoetherification of **3.8** with iodonium dicollidine perchlorate (IDCP) in CH_2Cl_2 afforded **3.7** in 70% yield (based on 42% of recovered starting material) with a 20:1 ratio of *trans* **3.7t** to *cis* **3.7c** (**Scheme 3.6**). The iodoetherification procedure

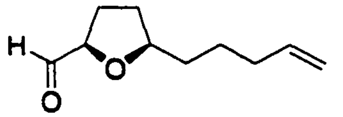


3.7t : **3.7c** 20:1

Scheme 3.6. (a) IDCP, CH_2Cl_2/H_2O

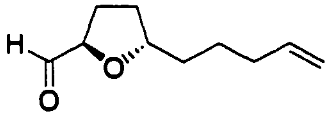
usually entails the addition of IDCP to a CH_2Cl_2/H_2O mixture of the starting material, followed by quenching with saturated aqueous solution of $Na_2S_2O_3$.[44] However, when this method was applied to **3.8**, formation of **3.7** together with other products presumably resulting from competing iodohydrin formation, were observed. Optimal results were obtained by a modification of this procedure. IDCP was added to an anhydrous CH_2Cl_2 solution of **3.8** and stirred for 10 min. The reaction mixture was then slowly added to a saturated solution of $Na_2S_2O_3$ and stirred for an additional 2 h.

The stereochemistry of THF **3.7** was assigned on the basis of the high *trans* selectivity that was observed for the reaction of the closely related furanoside diene substrate. Treatment of **3.15** with IDCP, under similar conditions as for the synthesis of **3.7**, afforded the mono-THF aldehyde **3.16c/t** (*c*/*t* 1:10, vide infra) in 77% yield. This mixture was next converted to inseparable **3.18c/t** by $NaBH_4$ reduction of the aldehyde. In order to obtain a sample with higher proportion of the *cis* isomer, **3.15** was first converted to **3.17**. To this end, **3.15** was treated with an aqueous solution of 6N HCl in THF to afford the deprotected lactol alkene in 90% yield. Subsequent treatment of this material with 2,2-dimethoxypropane, followed by $NaBH_4$ reduction of the crude afforded the dihydroxydiene **3.17** in 23% overall yield. Compound **3.17** was then treated with IDCP in anhydrous CH_2Cl_2 to give **3.18c/t** in a ratio of 1:1. The mixture of **3.18c/t** was next transformed to the inseparable mixture of aldehydes **3.21c/t** via a straightforward sequence of reactions. Removal of the iodide in **3.18c/t** with Bu_3SnH afforded **3.20c/t**. Subsequent hydrolysis of the acetonide with conc. H_2SO_4 in MeOH afforded the triol **3.19c/t**. Oxidative cleavage of **3.19c/t** with $NaIO_4$ in THF/H_2O afforded the inseparable mixture of aldehydes **3.21c/t** (**Scheme 3.7**). The components of the mixture were assigned by comparison with the known aldehydes **3.22c** and **3.22t** (**Figure 3.1**).[47] Comparison of the carbinol ^{13}C chemical shifts in the known **3.22c**, **3.22t** and the mixture



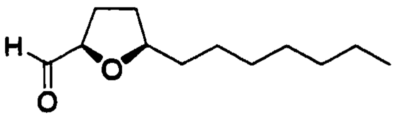
3.21c

δ_c 81.5, 83.2



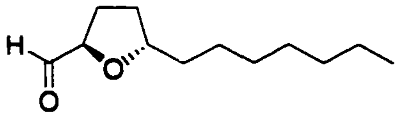
3.21t

δ_c 81.2, 82.7



3.22c

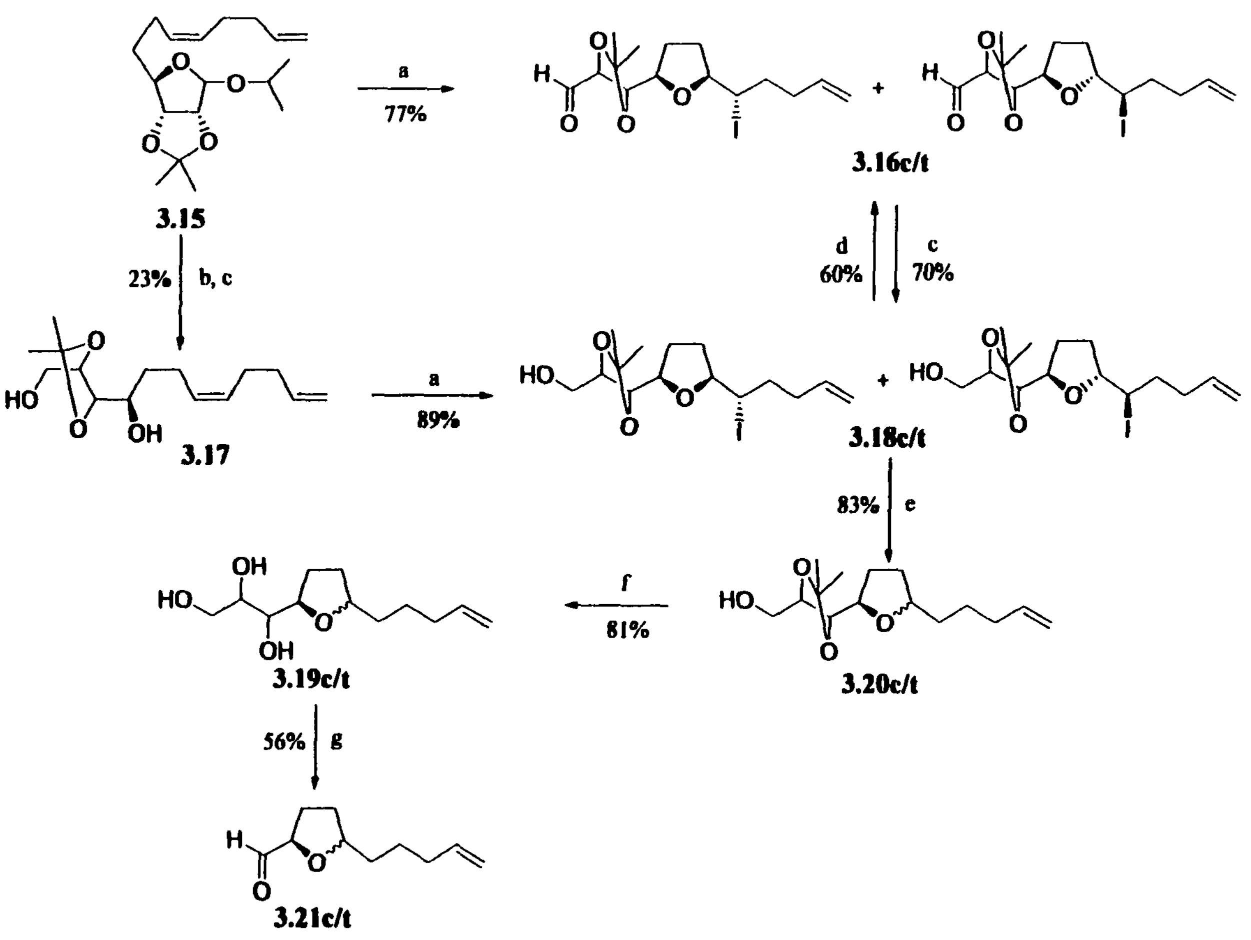
δ_c 81.5, 82.9



3.22t

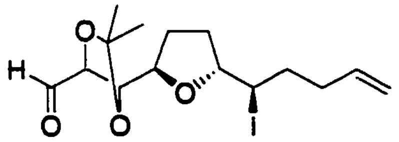
δ_c 81.2, 82.4

Figure 3.1.



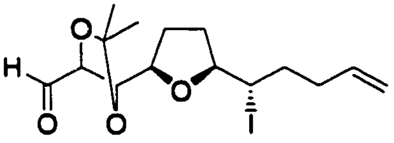
Scheme 3.7. (a) IDCP, CH_2Cl_2, rt; (b) (i) 6N HCl (aq), THF, rt; (ii) 2,2-dimethoxypropane, CSA, CH_2Cl_2; (c) $NaBH_4$, MeOH, rt; (d) PCC, CH_2Cl_2, Celite, florisil, 4Å MS, rt; (e) Bu_3SnH, AIBN, toluene, reflux; (f) H_2SO_4, MeOH, rt; (g) $NaIO_4$, THF, H_2O, rt.

3.21c/t shows that the compound that contains the chemical shift at δ 81.2 corresponds to the *trans* isomer whilst, the compound that has the signal at δ 81.5 corresponds to the *cis* isomer. Corroboration for this assignment was obtained by comparison of the Δδ values. Correlation of **3.21c** and **3.21t** with **3.22c** and **3.22t** respectively, gave Δδ (0.3 + 0.3) value of 0.6. Correlation of **3.21c** and **3.21t** with **3.22t** and **3.22c** respectively, gave Δδ ((0.3 + 0.8) + (0.3 + 0.2)) value of 1.6. Thus the data is more in agreement with the first assignment. Additional support for the stereochemical assignments of **3.16c/t** came from the ^{13}C shifts of the methylene carbons of the THF ring. This assignment was based on our previous observation that the methylene carbons (in C_6D_6) for the *trans* isomer resonates more downfield relative to those of the *cis* derivative[44a] (**Figure 3.2**). This analysis was carried out on a sample of **3.16c/t** that was obtained from the PCC oxidation of **3.18c/t**. This sample contained a larger *cis*/*trans* ratio than the sample obtained from the IDCP reaction on **3.15**, and was more practical for signal ratios.



3.16t

δ_c^* 31.9, 30.7



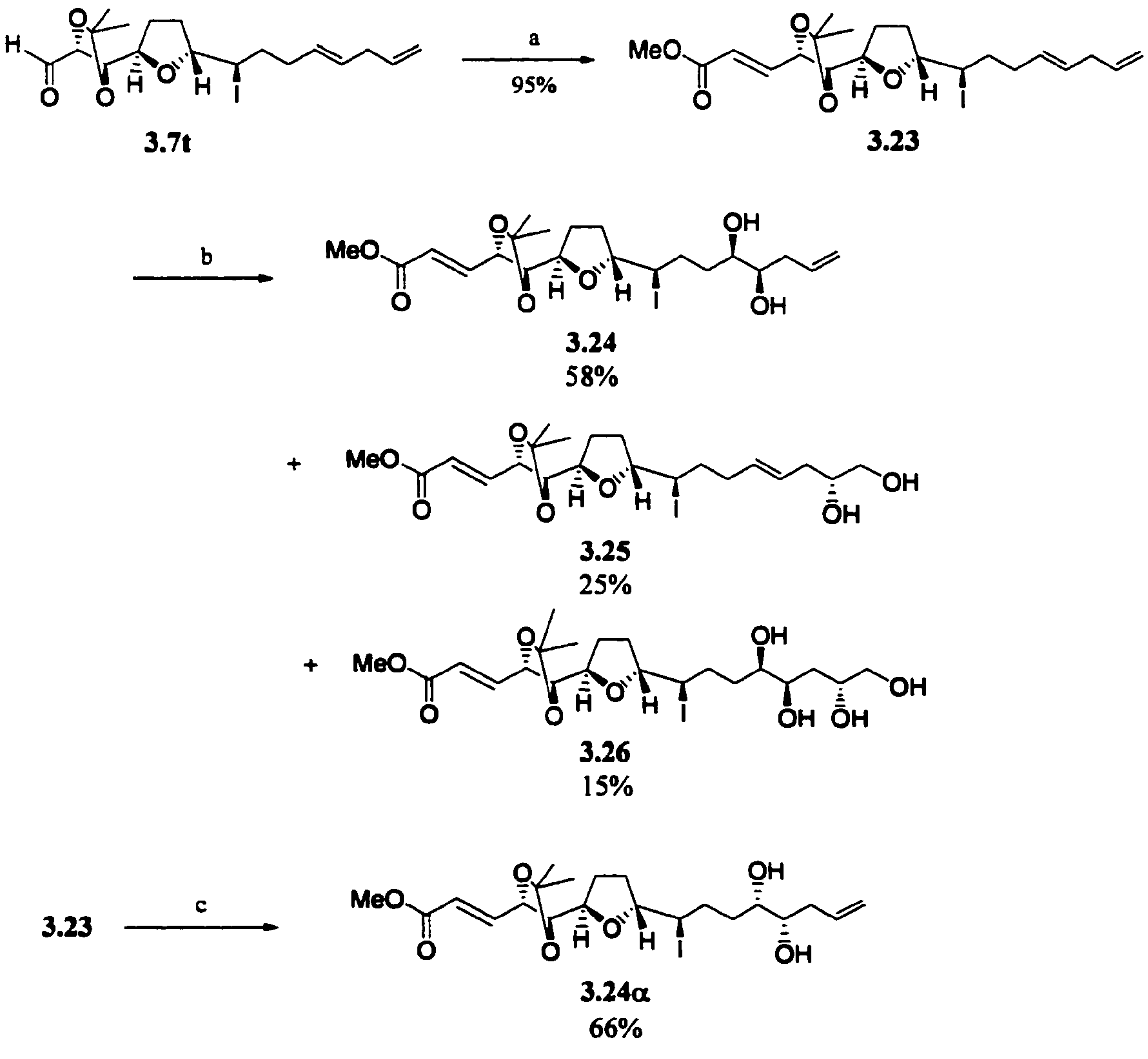
3.16c

δ_c^* 31.3, 29.8

* δ_c quoted for C_6D_6

Figure 3.2

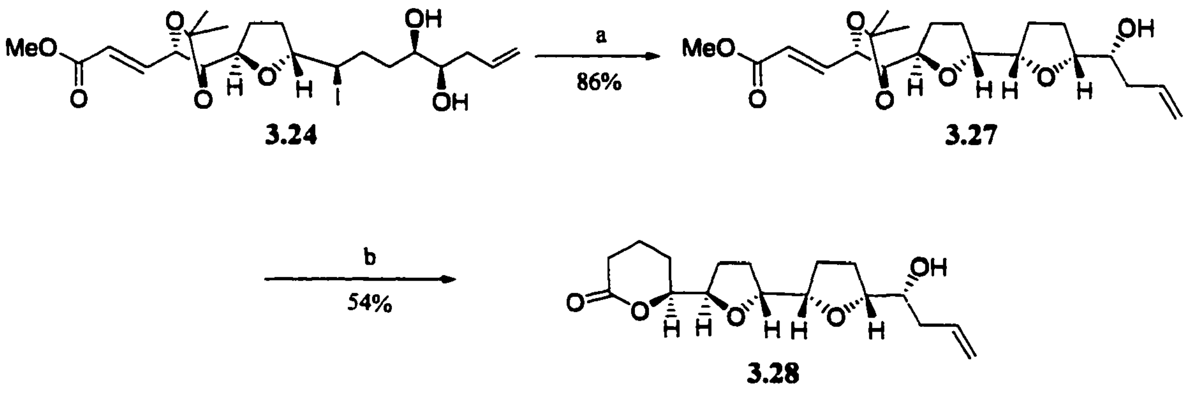
Partial chromatographic separation of the **3.7c/t** mixture provided a sample, which contained > 95% of the *trans* isomer **3.7t**. This was used for the subsequent reactions. Compound **3.7t** was treated with $Ph_3P{=}CHCOOMe$ in acetonitrile to give the α,β-unsaturated methyl ester **3.23** in 95 % yield, with an *E*/*Z* ratio of 10:1.[46] Compound **3.23** was subjected to Sharpless asymmetric dihydroxylation using AD mix-β to afford the



Scheme 3.8. (a) $Ph_3P{=}CHCOOMe$, CH_3CN, reflux; (b) AD-mix β, $MeSO_2NH_2$, *t*-BuOH, H_2O, -3 °C; (c) AD-mix α, $MeSO_2NH_2$, *t*-BuOH, H_2O, -3 °C.

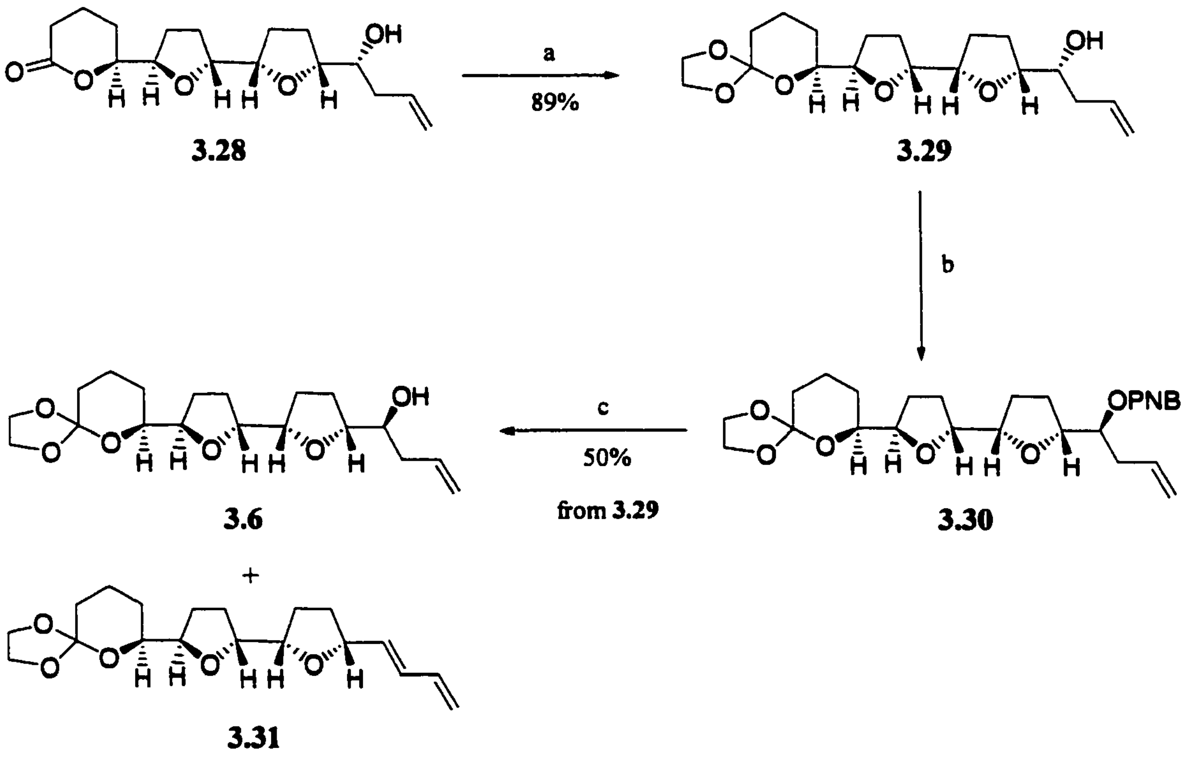
diol **3.24** as the major compound in 58% yield.[14] Minor compounds resulting from the dihydroxylation of the terminal olefin (i.e **3.25**) and the double dihydroxylation of the *E* and terminal olefins (i.e **3.26**) constitutes 25% and 15% respectively (**Scheme 3.8**). The absolute stereochemistry of the resulting diol **3.24** was tentatively assigned as *R*, from literature precedence.[14] Additional support for the assignment of **3.24** was the formation of a single diastereomeric diol **3.24α** when **3.23** was treated with AD-mix α (**Scheme 3.8**).[14]

We had previously observed that treatment of systems similar to **3.24** with bases such as pyridine afforded the required THF product as well as products resulting from dehydroiodination.[29] This problem was solved by using a Bu_2SnO mediated procedure.[48] Application of these conditions to **3.24** gave the bis-THF alkene **3.27** as a single compound in 86% yield.[49] Reductive elimination of **3.27** by treatment with Mg/MeOH at reflux provided the δ-hydroxy methyl ester. These conditions have been applied to a very similar system.[41] The crude product was treated with CSA, CH_2Cl_2, 4Å MS at reflux to afford the bis-THF lactone **3.28** in 54% yield from **3.27** (**Scheme 3.9**).



Scheme 3.9. (a) Bu_2SnO, benzene, Dean-Stark reflux; (b) (1) Mg, MeOH, reflux; (2) CSA, CH_2Cl_2, 4Å MS, reflux.

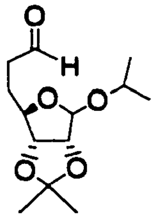
Conversion of the lactone **3.28** to its orthoester **3.29** was accomplished by treating **3.28** with ethylene glycol in the presence of CSA, Dowex 50WX8-400 ion exchange resin, benzene, and anhydrous magnesium sulfate, in 89% yield.[50] Intermediate **3.6** requires inversion of the secondary alcohol in **3.29**. To this end, **3.29** was subjected to Mitsunobu conditions[51] (PPh_3, DEAD and *p*-nitrobenzoic acid in toluene) to afford the *p*-nitrobenzoate **3.30**.[51b] For purification purposes (due to side products from DEAD), the crude material was treated with aqueous NaOH in ethanol at refluxing temperature to afford **3.6** in 50% overall yield (**Scheme 3.10**). Another compound, presumed to be **3.31**, was also formed when **3.29** was subjected to the Mitsunobu conditions (**Scheme 3.10**).



Scheme 3.10. (a) Ethylene glycol, CSA, Dowex 50WX 8-400 ion exchange resin, $MgSO_4$, benzene, reflux, Dean-Stark; (b) p-$NO_2C_6H_4COOH$, Ph_3P, DEAD, toluene, 0 °C to rt; (c) EtOH, 3N NaOH, reflux.

We have successfully demonstrated the use of a carbohydrate precursor as a chiral template for the synthesis of adjacently linked 2,5-disubstituted THFs. The precursor **3.8** was prepared in nine steps, in a highly convergent fashion and in an overall yield of 18%. The synthesis of the bis-THF orthoester precursor **3.6** was accomplished in eight steps from the furanoside triene **3.8** in an overall yield of 8%. The key transformation was the iodoetherification of the furanoside triene **3.8** to afford the *trans*-THF **3.7t** in high stereoselectivity. One can envisage that furanoside trienes of varying alkene geometry, in combination with AD-mix α or β,[14] could lead to a variety of diastereomeric oligo-THF frameworks.

3.3 EXPERIMENTAL



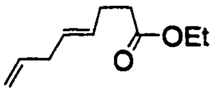
3.9

1-*O*-Isopropyl-2,3-*O*-isopropylidene-D-ribose aldehyde 3.9. Finely powdered D-ribose **3.11** (32.2 g, 214.5 mmol) and anhydrous $CuSO_4$ (46.7 g) were suspended in dry acetone (500 mL) containing isopropanol (50 mL, 654.2 mmol), conc. H_2SO_4 (6 mL) was added and the mixture was stirred at rt for 20 h. After completion of the reaction, $CuSO_4$ was filtered through a bed of Celite and the filter cake was washed thoroughly with small quantities of acetone. The filtrate was neutralized with stirring with saturated aqueous $NaHCO_3$ for 1 h. The $NaSO_4$ was removed by filtration and thoroughly washed with small quantities of acetone. The combined filtrate was evaporated under reduced pressure and the resulting aqueous solution was extracted with diethyl ether (200 mL x 5). The combined ethereal extract was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc in petroleum ether) to afford the 1-*O*-isopropyl-2,3-*O*-isopropylidene-D-ribose (32 g, 64%).

The compound from the previous step (32.2 g, 138.6 mmol) was dissolved in CH_2Cl_2 (300 mL) and treated with *p*-toluenesulfonyl chloride (39.6 g, 207.9 mmol), Et_3N (39 mL, 277.2 mmol) and DMAP (1.69 g, 13.9 mmol). The reaction mixture was stirred for 3 h and quenched with MeOH. After concentration of the solution, the residue was dissolved in ether, washed with saturated aqueous $NaHCO_3$ and brine. The ethereal solution was dried over anhydrous Na_2SO_4. Concentration gave the crude product, which was subsequently purified by flash column chromatography (FCC) (20% EtOAc in petroleum ether) to give the tosylated 1-*O*-isopropyl-2,3-*O*-isopropylidene-D-ribose (53 g, 99%). R_f= 0.44 (20% EtOAc in petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, J= 8 Hz, 3H), 1.10 (d, J= 8 Hz, 3H), 1.28 (s, 3H), 1.44 (s, 3H), 2.45 (s, 3H), 3.81 (m, 1H), 4.02 (m, 2H), 4.27 (t, J= 8 Hz, 1H), 4.50 (d, J= 8Hz, 1H), 4.60 (d, J= 8 Hz, 1H), 7.35 (d, J= 10 Hz, 2H), 7.80 (d, J= 10 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 22.8, 24.2, 26.0, 27.5, 70.4, 70.5, 70.5, 82.8, 84.5, 86.8, 107.1, 113.7, 129.1, 131.0.

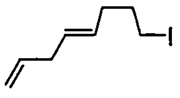
To a solution of the tosylated protected D-ribose (45.1 g, 116.8 mmol) in dry ether (200 mL) was added TMEDA (11 mL, 70.2 mmol), followed by a 1M solution of allylmagnesium bromide in THF (600 mL) under an atmosphere of argon at rt. The reaction was stirred for 14 h, and then quenched with saturated aqueous NH_4Cl (500 mL). The product was extracted with ether, the combined ethereal extract was dried over Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by FCC (20% EtOAc in petroleum ether) to afford the allylated 1-*O*-isopropyl-2,3-*O*-isopropylidene-D-ribose (23.9 g, 80%). R_f= 0.6 (20% EtOAc in petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (q, 6H), 1.30 (s, 3H), 1.47 (s, 3H), 1.54-1.80 (m, 2H), 2.16 (m, 2H), 3.93 (m, 1H), 4.13 (t, J= 8 Hz, 1H), 4.57 (m, 2H), 5.00 (m, 2H), 5.15 (s, 1H), 5.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 24.2, 26.0, 27.6, 31.4, 35.4, 69.5, 85.5, 87.1, 87.6, 106.8, 113.2, 116.1, 138.8.

A solution of the allylated protected D-ribose (3.8 g, 14.8 mmol) in 200 mL of 4:1 CH_2Cl_2 and MeOH was cooled to –78 °C. A stream of O_3 in O_2 was bubbled through the solution until the starting material was not detectable by TLC analysis (20% EtOAc in petroleum ether). The mixture was flushed with N_2 and then triphenylphosphine (42.7 g, 16.7 mmol) was added. The solution was warmed to rt, stirred for 1 h and concentrated *in vacuo* to give a slurry, which was purified by FCC to provide **3.9** (3.1 g, 80%). R_f= 0.25 (20% EtOAc in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (d, J= 8 Hz, 6H), 1.30 (s, 3H), 1.46 (s, 3H), 1.87 (m, 2H), 2.16 (m, 2H), 3.89 (m, 1H), 4.11 (t, J= 8 Hz, 1H), 4.55 (m, 2H), 5.14 (s, 1H), 9.79 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 24.3, 26.1, 27.6, 28.7, 41.9, 70.0, 85.4, 87.1, 87.2, 107.2, 113.4, 202.4.



3.13

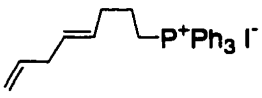
8-Ethyl-(4*E*)-1,4-octadienoate 3.13. A 500 ml, one-necked round-bottomed flask containing a magnetic stirring bar was fitted with a Claisen adaptor, two thermometers and a receiving flask. The flask was charged with triethyl orthoacetate (240 mL), 1,5-hexadiene-3-ol **3.12** (25 g, 255.1 mmol) and propionic acid (1.1 mL). Ethanol was distilled from the reaction mixture, and heating was continued between 138-142 °C, for an additional 2 h. The reaction mixture was then cooled to rt and the excess triethyl orthoacetate and propionic acid were removed by distillation under reduced pressure to afford a viscous oil, which was then purified by FCC (10% EtOAc in petroleum ether) to yield **3.13** (36.8 g, 86%). R_f= 0.86 (10% EtOAc in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, J= 8 Hz, 3H), 2.20 (m, 4H), 3.65 (m, 2H), 4.05 (q, J= 8 Hz, 2H), 4.90 (m, 2H), 5.40 (m, 2H), 5.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 28.0, 34.3, 36.7, 60.2, 114.9, 129.0, 129.4, 136.9, 172.8.



3.14

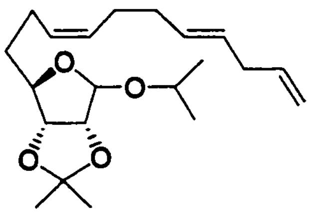
8-Iodo-(4*E*)-1,4-octadiene 3.14. A solution of DIBAL (438.4 mL, 438.4 mmol, 1M in hexanes) was added, dropwise, under argon, to a stirred solution of the diene ester **3.13** (36.8 g, 219.2 mmol) in dry CH_2Cl_2 (200 mL) at –78 °C. The mixture was stirred for 30 min at this temperature, then warmed to rt, and poured into an ice cold solution of saturated aqueous $KNaC_4H_4O_6$ (500 mL). The mixture was warmed to rt, and stirred until all the solid was dissolved. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, and concentrated *in vacuo*. FCC (20% EtOAc in petroleum ether) afforded the diene alcohol (23.8 g, 86%). R_f= 0.22 (10% EtOAc in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (m, 2H), 2.15 (m, 2H), 2.80 (m, 2H), 3.70 (t, J= 8 Hz, 2H), 5.00 (m, 2H), 5.45 (m, 2H), 5.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 32.4, 36.8, 62.2, 114.9, 128.2, 130.8, 137.2. FABHRMS calcd for $C_8H_{15}O$ $(M+H)^+$ 127.1123, found 127.1122.

To a solution of triphenylphosphine (53.7 g, 204.7 mmol) and imidazole (27.9 g, 391.5 mmol) in anhydrous CH_2Cl_2 (800 mL), iodine (51.8 g, 203.9 mmol) was added in portions and stirred at rt. After 30 min a solution of diene alcohol (23.5 g, 186.4 mmol) in CH_2Cl_2 (100 mL) and added dropwise over 1 h. The reaction mixture was stirred for an additional 1 h at rt. Upon completion of the reaction, diethyl ether (500 mL) was added and the solution was filtered through a bed of Celite. The filtrate was concentrated *in vacuo* and the residue was dissolved in ether (700 mL) and washed with saturated aqueous $Na_2S_2O_3$ (200 mL), brine and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography of the residue on silica gel with 5% EtOAc-petroleum ether gave the iodo-diene **3.14** (40.0 g, 91%). R_f= 0.63 (100% petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95 (m, 2H), 2.15 (q, J= 8 Hz, 2H), 2.80 (m, 2H), 3.20 (t, J= 8 Hz, 2H), 5.00 (m, 2H), 5.50 (m, 1H), 5.60 (m, 1H), 5.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.3, 33.3, 36.8, 115.1, 129.1, 129.4, 136.9.



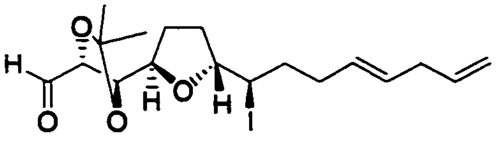
3.10

(4*E*)-1,4-octadiene triphenylphosphonium iodide 3.10. A mixture of toluene (400 mL), acetonitrile (400 mL) and triphenylphosphine (66.7 g, 254.4 mmol) was azeotroped to 600 mL. The iodo-diene **3.14** (40.0 g, 169.6 mmol) and *i*-Pr_2NEt (45 mL, 254.4 mmol) were added and refluxed for 24 h. The solvent was then evaporated *in vacuo* and the residue was triturated with hexanes until there was no triphenylphosphine as detected by TLC. The residue was dissolved in a minimum amount of warm toluene, which upon cooling resulted in the formation of a white amorphous solid **3.10** (73.1 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (m, 2H), 2.35 (m, 2H), 2.70(m, 2H), 3.60 (m, 2H), 4.90(m, 2H), 5.30 (m, 1H), 5.50 (m, 1H), 5.70 (m, 1H), 7.75 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6 (J_{CP}= 33 Hz), 31.6, 31.8, 35.5, 113.9, 116.4, 117.5, 127.7, 129.5, 129.6, 132.4, 132.6, 134.1, 135.7.

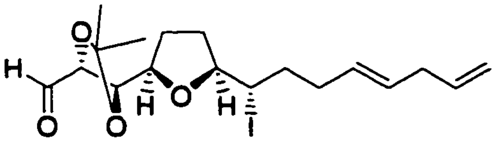


3.8

Furanoside triene 3.8. To a solution of diene triphenylphosphine iodide **3.10** (31.3 g, 62.8 mmol) in dry toluene (400 mL) was added a 0.6M solution of sodium bis(trimethylsilyl) amide (106 mL, 62.8 mmol) in toluene, under an argon atmosphere. The yellow-orange suspension was stirred for 1 h at rt then cooled to –78 °C. A solution of the furanoside aldehyde **3.9** (13.5 g, 52.3 mmol) in dry toluene (100 mL), was added dropwise over 30 min. After an additional 15 min, the mixture was warmed to rt, then diluted with ether (300 mL). The mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The residue was purified by FCC to afford **3.8** (13.5 g, 74%). R_f= 0.89 (5% EtOAc in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, J= 7 Hz, 3H), 1.10 (d, J= 7 Hz), 1.30 (s, 3H), 1.50 (s, 3H), 1.70 (m, 2H), 2.10 (m, 6H), 2.75 (m, 2H), 3.95 (m, 1H), 4.10 (t, J= 8 Hz, 1H), 4.55 (m, 2H), 4.95 (m, 2H), 5.15 (s, 1H), 5.40 (m, 4H), 5.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 23.5, 24.3, 25.3, 26.8, 27.5, 32.8, 35.5, 36.9, 68.7, 84.6, 86.3, 86.8, 106.0, 112.3, 114.9, 128.2, 128.9, 130.2, 131.1, 137.4.



3.7t



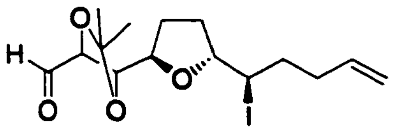
3.7c

3.7t:3.7c 20:1

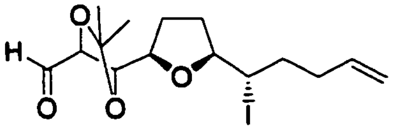
Mono-THF aldehyde diene 3.7. To a stirred solution of the furanoside triene **3.8** (7.1 g, 20.3 mmol) in dry CH_2Cl_2 (200 mL) was added iodonium dicollidine perchlorate (IDCP) (14.3 g, 30.5 mmol). After 10-15 min, the reaction mixture was slowly poured into saturated aqueous $Na_2S_2O_3$ (300 mL) and stirred for an additional 2 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FCC (5% EtOAc in petroleum ether) to afford recovered **3.8** (2.9 g) and the mono-THF iodide aldehyde **3.7** (3.6 g, 70% based on recovered **3.8**) as an inseparable mixture of a 20:1 *trans*:*cis* ratio. R_f= 0.33 (5% EtOAc in petroleum ether).

For *trans* isomer **3.7t**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.54 (s, 3H), 1.68 (m, 1H), 1.77 (m, 2H), 1.89 (m, 1H), 2.06-2.18 (m, 3H), 2.26 (m, 1H), 2.72 (t, J= 8 Hz, 2H), 3.72 (m, 1H), 3.99 (m, 1H), 4.17 (m, 1H), 4.30 (t, J= 8 Hz, 1H), 4.49 (dd, J= 8, 2 Hz, 1H), 4.97 (dd, J= 15, 8 Hz, 2H), 5.37 (m, 1H), 5.48 (m, 1H), 5.78 (m, 1H), 9.66 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5, 27.4, 30.2, 31.3, 32.5, 36.2, 36.6, 41.4, 78.2, 81.1, 81.6, 82.8, 110.8, 114.9, 129.3, 129.3, 136.9, 198.0.

For *cis* isomer **3.7c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (m, 1H), 4.68 (d, J= 8 Hz, 1H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 29.2, 29.7, 30.8, 36.8, 80.1, 82.1, 82.9, 110.8, 197.4. FABHRMS calcd for $C_{18}H_{28}O_4I$ $(M+H)^+$ 435.1032, found 435.1032.

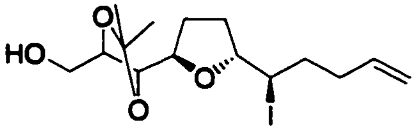


3.16t
Major



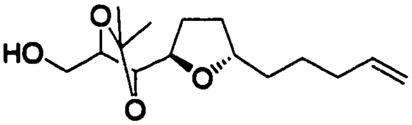
3.16c
minor

Mono-THF iodo aldehyde 3.16. To a solution of **3.15** (1.08 g, 3.48 mmol) in dry CH_2Cl_2 (140 mL) was added IDCP (1.96 g, 4.18 mmol). The mixture was stirred at rt for 15 min, then poured into saturated aqueous $Na_2S_2O_3$, and extracted with ether. The combined organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. FCC of the crude residue provided recovered starting material **3.15** (412.3 mg) and **3.16c/t** (653.7 mg, 77% based on recovered **3.15**) as an inseparable mixture of a 1:10 *cis*:*trans* ratio. R_f= 0.27 (5% EtOAc in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.50 (s, 3H), 1.60-2.35 (m, 8H), 3.70 (m, 1H), 3.95 (m, 1H), 4.15 (m, 1H), 4.25 (t, J= 6 Hz, 1H), 4.45 (d, J= 6 Hz, 1H), 5.00 (m, 2H), 5.70 (m, 1H), 9.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6, 27.5, 30.3, 31.4, 33.7, 35.7, 41.3, 78.3, 81.2, 81.7, 82.8, 111.0, 115.8, 136.7, 197.9.



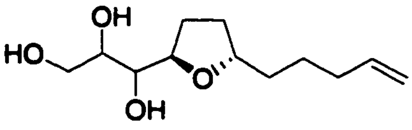
3.18t

Mono-THF iodo alcohol 3.18t. To a solution of **3.16t** (0.217 g, 0.561 mmol) in MeOH (10 mL) was added $NaBH_4$ (62.0 mg, 1.68 mmol) at rt. The reaction was stirred for 20 min, and then treated with 10% HCl in MeOH until the pH was 8. The solvent was removed under reduced pressure. FCC of the residue gave **3.18t** (166.0 mg, 70%). R_f= 0.50 (20% EtOAc in petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.40 (s, 3H), 1.80 (m, 4H), 2.10 (m, 2H), 2.20 (m, 2H), 3.15 (br s, 1H), 4.20 (m, 6H), 4.30 (m, 1H), 5.00 (m, 2H), 5.70 (m, 1H); ^{13} C NMR (75 MHz, $CDCl_3$) δ 25.5, 28.1, 31.3, 33.7, 36.1, 41.0, 61.0, 77.8, 78.1, 79.9, 83.7, 108.5, 116.0, 136.6.



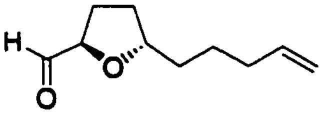
3.20t

Mono-THF alcohol 3.20t. In a 50 mL round-bottom flask equipped with reflux condenser and magnetic stirring bar, were placed **3.18t** (0.129 g, 0.327 mmol), Bu_3SnH (0.27 mL, 0.98 mmol), AIBN (7 mg) and dry toluene (15 mL). The reaction mixture was refluxed for 45 min. The toluene was removed *in vacuo*. The residue was purified by FCC to afford **3.20t** (87.1 mg, 98%). R_f= 0.68 (20% EtOAc in petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.40 (s, 3H), 1.45 (m, 4H), 1.80 (m, 1H), 2.05 (m, 3H), 2.15 (m, 2H), 3.55 (m, 1H), 3.75 (m, 2H), 3.95 (m, 2H), 4.30 (m, 1H), 4.90 (m, 2H), 5.75 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 25.5, 25.7, 28.1, 30.9, 31.7, 33.8, 35.4, 61.0, 76.5, 78.0, 80.0, 80.6, 108.4, 114.8, 138.5.



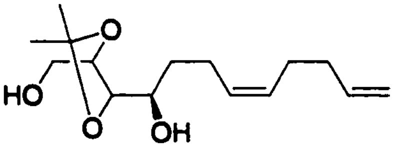
3.19t

Mono-THF triol alkene 3.19t. To a stirred solution of **3.20t** (75.6 mg, 0.28 mmol) in MeOH (3 mL) at rt was added conc. H_2SO_4 (10 μL). After 16 h, the reaction mixture was neutralized with saturated $NaHCO_3$ and concentrated *in vacuo*. The resulting aqueous solution was extracted with ethyl acetate (3x). The combined organic extract was dried (Na_2SO_4) and concentrated *in vacuo*. FCC of the residue provided recovered starting material **3.20t** (15.5 mg) and **3.19t** (47 mg, 92%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.50 (m, 5H), 1.85 (m, 1H), 2.05 (m, 4H), 3.55 (m, 1H), 3.60-4.10 (m, 4H), 4.25 (m, 1H), 4.95 (m, 2H), 5.80 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 25.8, 29.1, 31.9, 33.9, 35.5, 63.9, 73.8, 74.1, 80.0, 80.4, 114.8, 138.6.



3.21t

Mono-THF aldehyde 3.21t. To a solution of **3.19t** (0.038 g, 0.165 mmol) in THF (2 mL) and H_2O (4 mL) at rt was added $NaIO_4$ (0.145 g, 0.678 mmol). The reaction mixture was stirred for 30 min and most of the solvent was removed under reduced pressure. The residue was diluted with saturated $Na_2S_2O_3$ and extracted with ethyl acetate (3x). The combined organic extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography to afford **3.21t** (16.1 mg, 56%). R_f= 0.64 (20% EtOAc in petroleum ether); ^1H NMR (300 MHz) δ 1.55 (m, 4H), 2.10 (m, 6H), 4.00 (m, 1H), 4.30 (m, 1H), 4.95 (m, 2H), 5.80 (m, 1H), 9.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 27.4, 31.5, 33.9, 35.1, 81.2, 82.7, 114.8, 138.6, 202.7.

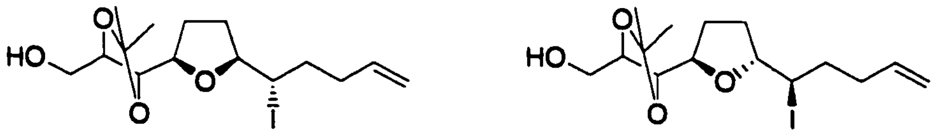


3.17

Preparation of 3.17. The furanoside alkene **3.15** (0.619 g, 1.99 mmol) was dissolved in THF (30 mL) and an aqueous 6N HCl (8 mL) solution was added. The reaction mixture was stirred for 16 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with ethyl acetate (3x). The combined organic extract was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Chromatographic purification of the residue afforded the fully deprotected furanoside diene (409.3 mg, 90%).

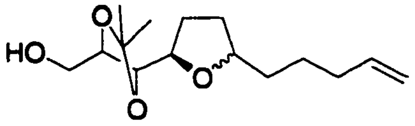
The deprotected furanoside diene (951.0 mg, 4.17 mmol) from the previous step was dissolved in dry CH_2Cl_2 (45 mL) and 2,2-dimethoxypropane (0.6 mL, 4.6 mmol) and CSA (488.0 mg, 2.1 mmol) were added. The reaction mixture was stirred for 1h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic extract was dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was directly used for the next step.

The product from the previous step was dissolved in MeOH (40 mL). $NaBH_4$ (466.2 mg, 12.6 mmol) was added at rt and the reaction mixture was stirred for 20 min. The reaction mixture was treated with 10% HCl in MeOH until the pH was 8. The solvent was removed under reduced pressure. The residue was purified by FCC to afford **3.17** (262.4 mg, 23%). R_f= 0.70 (20% EtOAc in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.40 (s, 3H), 1.50 (m, 1H), 1.80 (m, 1H), 2.15 (m, 6H), 3.60 (m, 3H), 3.75 (m, 2H), 3.95 (m, 1H), 4.25 (m, 1H), 4.95 (m, 2H), 5.40 (m, 2H), 5.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 25.6, 27.0, 28.2, 34.0, 34.4, 61.3, 69.7, 77.7, 80.3, 108.4, 114.8, 129.7, 130.0, 138.4.



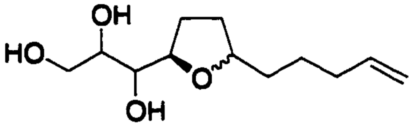
3.18c/t

Mono-THF iodo alcohol 3.18c/t. Compound **3.17** (0.262 g, 0.972 mmol) was subjected to the same iodoetherification procedure (IDCP (0.563 g, 1.2 mmol), CH_2Cl_2 (40 mL)) as for **3.16**, to afford **3.18c/t** (351.4 mg, 90%) as an inseparable 1:1 mixture of *cis*:*trans* isomers. R_f= 0.68 (20% EtOAc in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.40 (s, 3H), 1.60-2.45 (m, 8H), 3.15 (m, 1H), 3.60-4.20 (m, 6H), 4.35 (m, 1H), 5.00 (m, 2H), 5.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5, 25.6, 28.1, 29.8, 30.5, 31.4, 31.5, 33.7, 36.2, 36.5, 40.6, 41.0, 61.0, 61.1, 77.9, 78.1, 79.5, 80.0, 83.7, 83.8, 108.5, 108.6, 116.1, 136.7.



3.20c/t

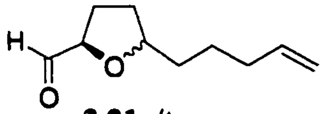
Mono-THF alcohol 3.20c/t. Compound **3.18c/t** (0.351 g, 0.886 mmol) was subjected to the same reaction conditions (Bu_3SnH (0.72 mL, 2.7 mmol), AIBN (21 mg), toluene (40 mL)) as that used for the preparation of **3.20t**, to afford **3.20c/t** (199.4 mg, 83%) as an inseparable 1:1 mixture of *cis*:*trans* isomers. R_f= 0.68 (20% EtOAc in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.40 (s, 3H), 1.45-2.20 (m, 10H), 3.55 (m, 1H), 3.65-4.10 (m, 4H), 4.30 (m, 1H), 4.95 (m, 2H), 5.75 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 25.7, 28.1, 29.7, 30.6, 30.8, 31.6, 33.8, 35.4, 35.5, 61.0, 76.4, 77.0, 77.9, 80.0, 80.5, 80.8, 108.4, 114.8, 138.4.



3.19c/t

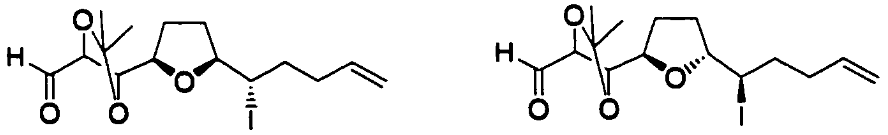
Mono-THF triol alkene 3.19c/t. Compound **3.20c/t** (0.192 g, 0.711 mmol) was subjected to the same hydrolytic conditions (MeOH (6 mL), H_2SO_4 (50 μL)) as that used for the preparation of **3.19t**, to afford **3.19c/t** (107.9 mg, 81% based on recovered **3.20c/t** (35.5 mg)) as an inseparable mixture of *cis*:*trans* (1:1) isomers. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 1.25-2.20 (m, 10H), 3.50-4.20 (m, 6H), 4.95 (m, 2H), 5.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6, 25.7, 27.8, 28.8, 30.9, 31.8, 33.8, 35.4, 63.6, 73.5, 73.6, 74.1, 79.9, 80.2, 80.4, 114.7, 138.5.



3.21c/t

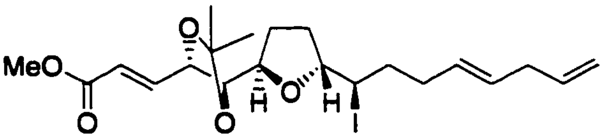
Mono-THF aldehyde 3.21c/t. Compound **3.19c/t** (0.102 g, 0.445 mmol) was subjected to the same oxidative cleavage conditions (THF (6 mL), H_2O (6 mL), $NaIO_4$ (0.376 g, 1.76 mmol)) as that used for the preparation of **3.21t**, to afford **3.21c/t** (41.1 mg, 56%) as an inseparable mixture of *cis*:*trans* (1:1) isomers. R_f= 0.64 (20% EtOAc in petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (m, 8H), 2.07 (m, 12H), 4.01 (m, 2H), 4.22 (t, J= 8 Hz, 1H), 4.30 (t, J= 8Hz, 1H), 4.96 (m, 4H), 5.18 (m, 2H), 9.64 (s, 1H), 9.66 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 25.8, 27.4, 28.1, 31.4, 31.4, 33.9, 35.1, 35.4, 81.2, 81.5, 82.6, 83.2, 114.8, 138.6, 202.7.



3.16c/t

Mono-THF iodo aldehyde 3.16c/t. To a stirred mixture of CH_2Cl_2 (10 mL), pyridinium chlorochromate (0.078 g, 0.362 mmol), powdered, freshly activated 4Å molecular sieves (100 mg), Celite (100 mg), Florisil (100 mg) and sodium acetate (0.029

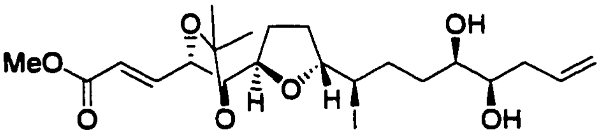
g, 0.362 mmol) was added a solution of **3.18c/t** (0.072 g, 0.182 mmol) in CH_2Cl_2. The solution was stirred at rt for 2 h, and then filtered through a bed of Celite. The filtrate concentrated *in vacuo* and the residue was then purified by FCC to yield the mono-THF aldehyde **3.16c/t** (42.3 mg, 60%) as an inseparable 1:1 mixture of *cis*:*trans* isomers. ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 6H), 1.55 (s, 3H), 1.58 (s, 3H), 1.70-2.45 (m, 16H), 3.50 (m, 1H), 3.75 (m, 1H), 4.00 (m, 3H), 4.20 (m, 1H), 4.35 (t, J= 6 Hz, 1H), 4.40 (t, J= 6 Hz, 1H), 4.50 (d, J= 6 Hz, 1H), 4.70 (d, J= 6 Hz, 1H), 5.00 (m, 4H), 5.75 (m, 2H), 9.65 (s, 1H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 25.8, 27.7, 29.4, 30.4, 31.0, 31.6, 33.8, 33.9, 35.9, 36.5, 41.1, 41.3, 78.5, 80.4, 81.4, 81.9, 82.3, 83.1, 83.3, 111.2, 111.2, 116.0, 136.9, 136.9, 197.6, 198.2.



3.23

α,β-Unsaturated methyl ester mono-THF diene 3.23. To a solution of **3.7t** (5.1 g, 11.8 mmol) in CH_3CN (120 mL) was added (carbomethoxymethylene)triphenylphosphorane (5.9 g, 17.7 mmol). The mixture was heated at 60 °C for 40 min and then cooled to rt and filtered. The filtrate was concentrated *in vacuo* and the residue purified by FCC (5% EtOAc in petroleum ether) to afford the α,β unsaturated ester **3.23** (5.5g, 95%). R_f= 0.55 (5% EtOAc in petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.45 (s, 3H), 1.76 (m, 3H), 1.85 (m, 1H), 2.10 (m, 3H), 2.24 (m, 1H), 2.71 (t, J= 6 Hz, 2H), 3.69 (s, 3H), 3.78 (m, 1H), 3.91

(m, 1H), 3.99 (m, 1H), 4.04 (t, J= 8 Hz, 1H), 4.79 (t, J= 5 Hz, 1H), 4.97 (dd, J= 15, 8 Hz, 2H), 5.36 (m, 1H), 5.49 (m, 1H), 5.78 (m, 1H), 6.10 (d, J= 15, 2 Hz, 1H), 7.05 (dd, J= 15, 5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 27.7, 30.7, 31.3, 32.6, 36.1, 36.7, 41.5, 51.4, 77.0, 78.3, 81.0, 82.9, 109.4, 115.0, 121.8, 129.2, 129.5, 137.0, 143.9, 166.2. FABHRMS calcd for $C_{21}H_{32}O_5I$ $(M+H)^+$ 491.1294, found 491.1297.



3.24

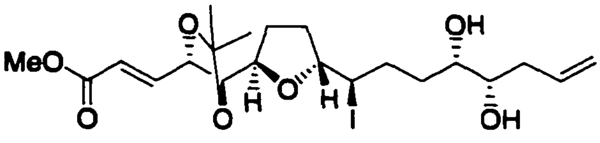
Mono-THF diol 3.24. A mixture of *t*-butyl alcohol (40 mL), H_2O (40 mL), AD-mix β (10.6 g) and $MeSO_2NH_2$ (0.72 g, 7.6 mmol) was stirred at rt until both phases were clear, and then cooled to –3 °C, whereupon the inorganic salts partially precipitated. At this point, **3.23** (3.7 g, 7.6 mmol) was added, and the heterogeneous slurry was stirred vigorously at –3 °C for 4 ½ h. The reaction was then quenched by addition of sodium sulfite (15 g), warmed to rt, and stirred for an additional 1 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (4x). The organic phase was washed with 2N KOH (100 mL), dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. FCC (40% EtOAc in petroleum ether) of the residue afford recovered **3.23** (0.2 g), **3.24** (2.2 g, 58%), **3.25** (0.9 g, 25%) and **3.26** (0.6 g, 15%) (yields based on recovered **3.23**).

For **3.24**: R_f= 0.45 (40% EtOAc in petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.46 (s, 3H), 1.62 (m, 1H), 1.79 (m, 4H), 2.01 (m, 1H), 2.17 (m, 2H), 2.26

(m, 1H), 2.35 (m, 1H), 2.59 (br d, J= 5 Hz, 1H), 2.83 (br d, J= 5 Hz, 1H), 3.49 (m, 2H), 3.73 (s, 3H), 3.88 (m, 2H), 4.03 (q, J= 7 Hz, 1H), 4.09 (m, 1H), 4.82 (br t, 1H), 5.13 (dd, J= 15, 8 Hz, 2H), 5.87 (m, 1H), 6.14 (d, J= 15, 2 Hz, 1H), 7.12 (dd, J= 15, 5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 27.7, 30.7, 31.1, 32.4, 33.6, 38.3, 41.9, 51.6, 72.7, 73.6, 76.9, 78.3, 80.9, 83.0, 109.4, 117.5, 121.4, 134.7, 144.3, 166.7. ESIHRMS calcd for $C_{21}H_{33}O_7NaI$ $(M+Na)^+$ 547.1169, found 547.1146.

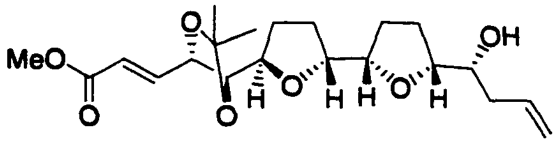
For **3.25**: R_f= 0.15 (40% EtOAc in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.48 (s, 3H), 1.71-2.31 (m, 12H), 3.46 (m, 1H), 3.64 (m, 1H), 3.71 (m, 1H), 3.73 (s, 3H), 3.87 (m, 1H), 3.91 (m, 1H), 4.03 (m, 2H), 4.82 (t, J= 5 Hz, 1H), 5.51 (m, 2H), 6.13 (dd, J= 15, 2 Hz, 1H), 7.07 (dd, J= 15, 5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5, 27.8, 30.8, 31.3, 32.8, 35.8, 36.9, 41.5, 51.8, 66.5, 71.9, 77.0, 78.4, 81.0, 83.1, 109.6, 121.7, 127.1, 132.0, 144.3, 166.8. FABHRMS calcd for $C_{21}H_{34}O_7I$ $(M+H)^+$ 525.1349, found 525.1349.

For **3.26**: R_f= 0.0 (40% EtOAc in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.46 (s, 3H), 1.60 (m, 2H), 1.75 (m, 5H), 2.00 (m, 1H), 2.15 (m, 2H), 3.50 (m, 3H), 3.60 (m, 1H), 3.72 (s, 3H), 3.80 (m, 1H), 3.90 (m 1H), 4.00 (m, 1H), 4.05 (m, 2H), 4.20 (br s, 4H, exchangeable with D_2O), 4.81 (br t, 1H), 6.09 (dd, J= 15, 2 Hz, 1H), 7.10(dd, J= 15, 5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5, 27.8, 30.7, 31.6, 33.0, 33.5, 36.6, 42.9, 51.9, 67.1, 69.6, 71.5, 73.7, 77.0, 78.3, 81.0, 83.0, 109.5, 121.5, 144.6, 167.1. FABHRMS calcd for $C_{21}H_{35}O_9NaI$ $(M+Na)^+$ 581.1225, found 581.1224.



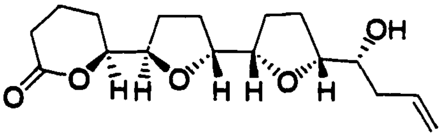
3.24α

Mono-THF diol 3.24α. A mixture of *t*-butyl alcohol (5 mL), H_2O (5 mL), AD-mix α (1.4 g) and $MeSO_2NH_2$ (95 mg, 1.0 mmol) was stirred at rt until both phases were clear, and then cooled to –3 °C, whereupon the inorganic salts partially precipitated. At this point, **3.23** (0.526 g, 1.07 mmol) was added, and the heterogeneous slurry was stirred vigorously at –3 °C for 4 ½ h. The reaction was then quenched by addition of sodium sulfite (1.4 g), warmed to rt, and stirred for an additional 1 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (4x). The organic phase was washed with 2N KOH (10 mL), dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. FCC (40% EtOAc in petroleum ether) of the residue afford recovered **3.23** (175.5 mg), **3.24α** (275 mg, 66%) (yield based on recovered **3.23**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.47 (s, 3H), 1.52 (m, 1H), 1.73-1.88 (m, 4H), 1.97 (m, 1H), 2.17 (m, 2H), 2.29 (m, 1H), 2.35 (m, 1H), 2.63 (br s, 1H), 2.74 (d, J= 8 Hz, 1H), 3.45 (m, 1H), 3.53 (m, 1H), 3.73 (m, 1H), 3.85 (m, 1H), 3.90 (m, 1H), 4.03 (m, 1H), 4.10 (m, 1H), 4.83 (m, 1H), 5.13 (m, 2H), 5.86 (m, 1H), 6.15 (d, J= 15.6 Hz, 1H), 7.09 (dd, J= 11, 4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5, 27.8, 31.0, 31.3, 33.2, 34.4, 38.5, 42.7, 51.9, 73.4, 73.7, 76.7, 78.5, 81.1, 83.0, 109.6, 117.8, 121.3, 134.8, 144.6, 167.2.



3.27

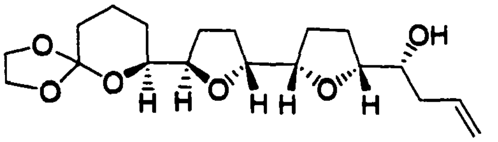
Bis-THF hydroxy alkene 3.27. A mixture of dihydroxy-iodide **3.24** (4.3 g, 8.2 mmol) and Bu_2SnO (2.2 g, 9.0 mmol) in benzene (150 mL) was heated at reflux for 24 h using a Dean-Stark set up for the azeotropic removal of water. Removal of the solvent *in vacuo*, and FCC of the residue provided bis-THF hydroxy alkene **3.27** (2.8 g, 86%). R_f= 0.78 (50% EtOAc in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.46 (s, 3H), 1.60-1.80 (m, 4H), 1.88 (m, 2H), 2.05 (m, 2H), 2.24 (m, 2H), 2.62 (d, J= 5 Hz, 1H), 3.47 (m, 1H), 3.72 (s, 3H), 3.80 (m, 2H), 3.84 (m, 1H), 4.00 (q, J= 8 Hz, 1H), 4.08 (t, J= 8 Hz, 1H), 4.79 (t, J= 5 Hz, 1H), 5.06 (dd, J= 15, 9 Hz, 2H), 5.87 (m, 1H), 6.11 (dd, J= 15, 2 Hz, 1H), 7.03 (dd, J= 15, 5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 27.4, 27.6, 27.8, 28.7, 29.8, 38.7, 51.4, 73.6, 76.9, 77.8, 80.5, 81.5, 82.2, 109.3, 116.7, 121.7, 135.0, 144.2, 166.3. FABHRMS calcd for $C_{21}H_{33}O_7$ $(M+H)^+$ 397.2226, found 397.2226.



3.28

Bis-THF lactone 3.28. A mixture of **3.27** (0.977 g, 2.47 mmol) and magnesium turnings (0.593 g, 24.7 mmol) in anhydrous methanol (20 mL) was stirred for 1 h at rt and then refluxed for another 1 h under N_2. Upon completion, the solution was acidified to pH 3 by the addition of 10% aqueous HCl. Most of the methanol was evaporated *in* *vacuo* and the resulting aqueous layer was extracted with ether. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a residue, which was used directly in the next step.

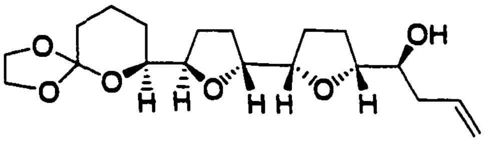
A mixture of the residue from the previous step and catalytic amount of CSA (29 mg) in dry CH_2Cl_2 (20 mL) was heated at reflux for 14 h using a Dean–Stark set up that contained 4Å MS. The CH_2Cl_2 solution was washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FCC to afford the bis-THF lactone **3.28** (409.9 mg, 54% over two steps). R_f= 0.22 (50% EtOAc in petroleum ether); IR ($CHCl_3$ film) 3452, 1737, 1641 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 1.04 (m, 2H), 1.14 (m, 1H), 1.28 (m, 1H), 1.50-1.80 (m, 8H), 1.93 (m, 1H), 2.02 (m, 1H), 2.34 (m, 1H), 2.42 (m, 1H), 2.97 (d, J= 6 Hz, 1H), 3.42 (m, 1H), 3.61 (q, J= 7 Hz, 1H), 3.65 (m, 1H), 3.74 (m, 1H), 3.81 (m, 1H), 4.01 (m, 1H), 5.10 (dd, J= 15, 8 Hz, 2H), 6.04 (m, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 18.8, 25.7, 27.7, 28.6, 28.9, 29.0, 30.3, 40.2, 74.5, 81.8, 82.0, 82.2, 82.4, 82.4, 116.9, 136.4, 169.8. FABHRMS calcd for $C_{17}H_{27}O_5$ $(M+H)^+$ 311.1858, found 311.1857.



3.29

(4R)-Hydroxy bis-THF orthoester 3.29. To a solution of **3.28** (0.181 g, 0.584 mmol) in anhydrous benzene (50 mL) was added ethylene glycol (1.3 mL, 23.0 mmol). The mixture was vigorously stirred as anhydrous $MgSO_4$ (1.3 g), 75.4 mg of Dowex

50WX8-400 ion exchange resin, and CSA (13 mg, 0.056 mmol) were added in succession. The mixture was heated to reflux with vigorous agitation, under a Dean-Stark separator filled with 4Å MS for 24 h. The reaction was quenched by the addition of triethylamine (1 mL), allowed to cool to rt and filtered. The residue was leached with hot ethyl acetate. The combined filtrate was washed with saturated $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. Evaporation under reduced pressure afforded an oil which was subsequently purified by FCC to afford recovered **3.28** (16.8 mg) and **3.29** (168.2 mg, 89%). R_f= 0.38 (40% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +14.5 (c 0.53, benzene); ^1H NMR (500 MHz, C_6D_6) δ 1.17 (m, 1H), 1.39 (m, 1H), 1.57-1.88 (m, 12H), 2.39 (m, 1H), 2.47 (m, 1H), 3.15 (d, J= 6 Hz, 1H), 3.49 (m, 1H), 3.60 (m, 2H), 3.79 (m, 2H), 3.85 (m, 4H), 4.10 (m, 1H), 5.12 (dd, J= 17, 9 Hz, 2H), 6.10 (m, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 21.9, 27.7, 28.2, 28.8, 29.3, 32.4, 40.2, 63.7, 65.0, 74.6, 77.4, 82.1, 82.5, 82.6, 82.7, 116.8, 120.1, 136.4. MS (ES, *m/z*) 372 $(M+NH_4)^+$. FABHRMS calcd for $C_{19}H_{30}O_6$ $(M+Na)^+$ 377.1940, found 377.1939.



3.6

(4S)-Hydroxy bis-THF orthoester 3.6. A mixture of **3.29** (0.079 g, 0.223 mmol), triphenylphosphine (0.173 g, 0.659 mmol) and *p*-nitrobenzoic acid (0.11 g, 0.66 mmol) were dissolved in dry toluene (3 mL). A solution of DEAD (0.1 mL, 0.66 mmol) was added slowly at 0 °C under an atmosphere of nitrogen. This mixture was stirred at

10 °C for 20 h. After concentration, the mixture was neutralized by addition of aqueous $NaHCO_3$. The product was isolated from an aqueous work-up by ethyl acetate extraction (3x). The combined ethyl acetate extract was dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was directly used for the next step.

The crude product was dissolved in EtOH (3 mL). An aqueous solution of 3N NaOH (3 mL) was then added and refluxed for 2 h. The reaction mixture was concentrated and the residue was diluted with brine and extracted with ethyl acetate (3x). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Chromatographic purification of the residue gave compound **3.6** (39.6 mg, overall yield 50%). R_f= 0.41 (40% EtOAc in petroleum ether); $[\alpha]_D^{25}$ –4.3 (c 0.91, benzene); ^1H NMR (500 MHz, C_6D_6) δ 1.15 (m, 1H), 1.32 (m, 1H), 1.56 (m, 2H), 1.70 (m, 3H), 1.83 (m, 6H), 1.98 (m, 1H), 2.13 (m, 1H), 2.31 (m, 1H), 3.21 (br s, 1H), 3.53 (m, 2H), 3.72 (m, 2H), 3.84 (m, 4H), 4.01 (m, 1H), 4.13 (m, 1H), 5.03 (dd, J=16, 10 Hz, 2H), 5.91 (m, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 21.9, 25.7, 27.7, 28.3, 28.9, 29.3, 32.4, 39.0, 63.7, 65.0, 73.2, 77.4, 82.2, 82.4, 82.8, 83.2, 117.0, 120.2, 136.1. FABHRMS calcd for $C_{19}H_{30}O_6$ $(M+Na)^+$ 377.1940, found 377.1939.

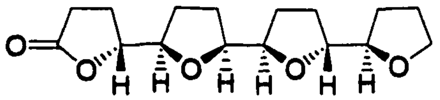
CHAPTER 4

1,2-*O*-ISOPROPYLIDENE TEMPLATES FOR THE SYNTHESIS OF OLIGO-THF's.

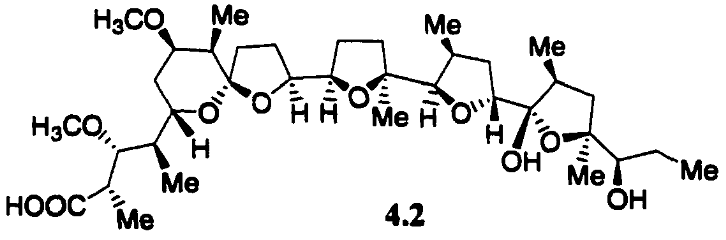
4.1 INTRODUCTION

Another strategy for the synthesis of 2,5-disubstituted THF's involves the haloetherification of 5-alkoxyalkenes.[7,8] This approach has been extensively studied. It has been found that stereoselectivity depends heavily on substrate substitution.[7,8,52] Previous work in our laboratory has shown that conformationally rigid templates are leads to higher stereoselectivity than more flexible systems. We have successfully demonstrated that C6-allylated pyranosides and 1,2-*O*-isopropylidene-5-alkenes are effective precursors to *cis*-2,5- and *trans*-2,5-disubstituted THF's, respectively.[44,53]

The goal of this project was the synthesis of the tetracyclic lactone **4.1** from a 1,2-*O*-isopropylidene-5-alkene precursor.[49] Compound **4.1** is a potential relay intermediate for less substituted analogues of kijimicin **4.2** (**Figure 4.1**), an ionophore which has shown promising anti-HIV activity.[54]



4.1



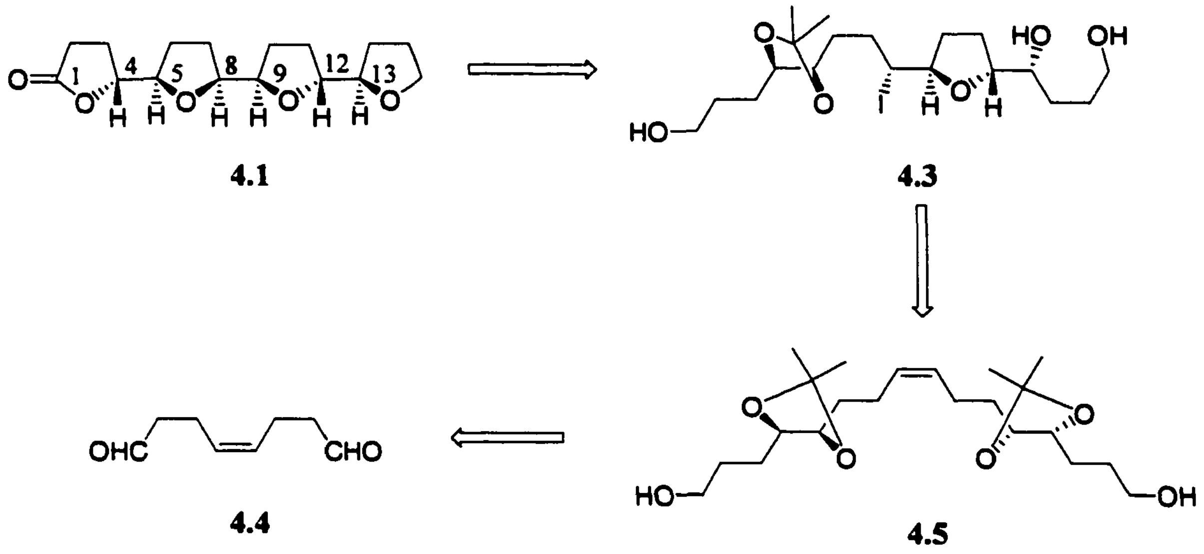
4.2

Kijimicin

Figure 4.1

4.2 RETROSYNTHESIS

The configurations at C4, C5, C12 and C13 in **4.1** could be identified in the C_2 symmetric bis-*O*-isopropylidene alkene precursor **4.5**. Thus the iodoetherification of **4.5** was expected to give the *trans*-mono THF iodide **4.3**, which would be transformed to **4.1** after successive THF and lactone ring transformations. Bis-*O*-isopropylidene alkene **4.5** may be obtained through a bi-directional synthesis from the (*Z*)-4-octenedial **4.4** (**Scheme 4.1**).

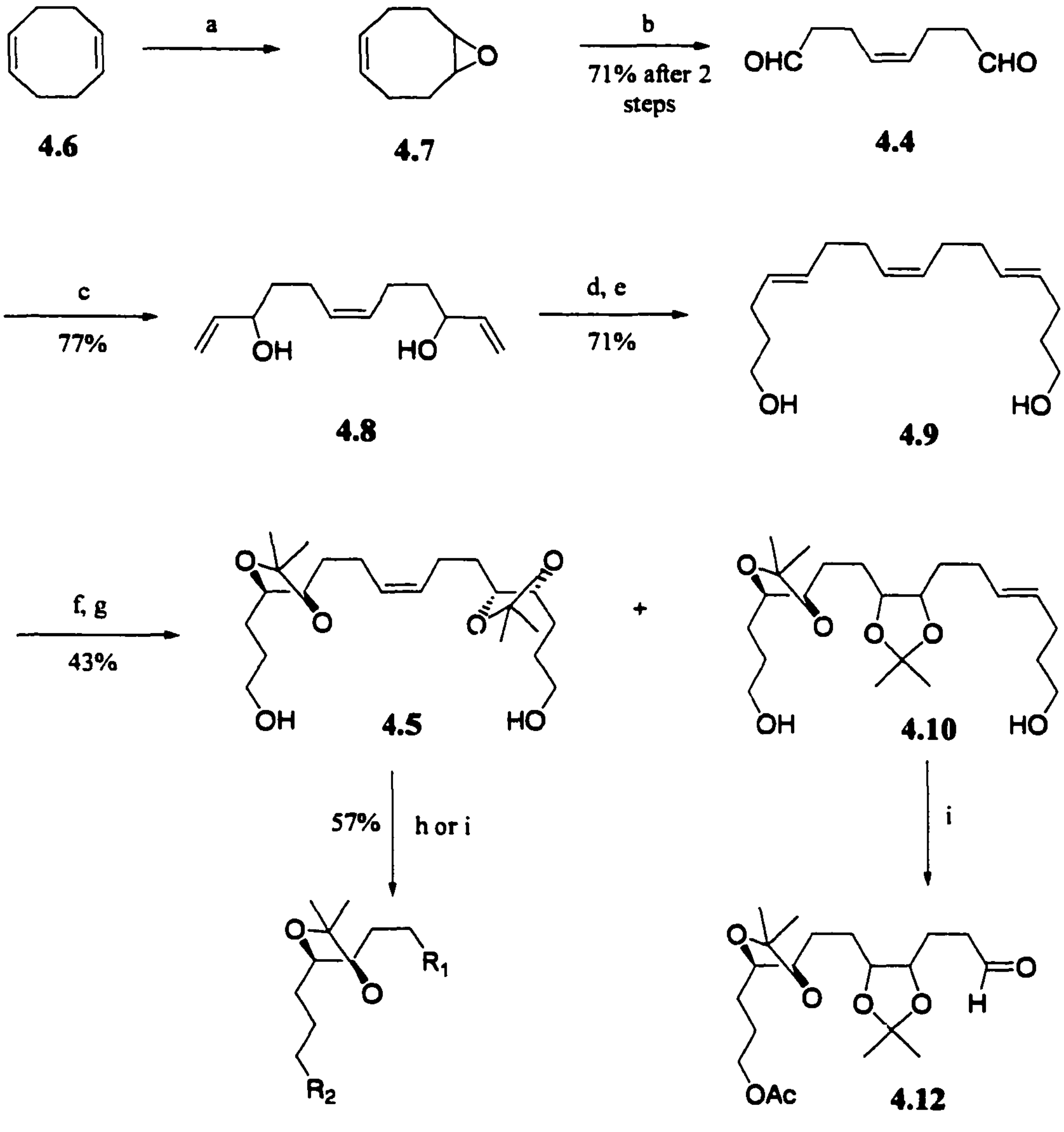


Scheme 4.1

4.3 RESULTS AND DISCUSSION

The synthesis of the bis-*O*-isopropylidene alkene **4.5** from 1,5-cyclooctadiene **4.6** was first performed by Zheming Ruan.[29,53c] To this end, treatment of a dilute chloroform solution of 1,5-cyclooctadiene **4.6** with one equivalent of peracetic acid afforded the mono-epoxide **4.7**. Epoxide opening and subsequent cleavage on **4.7** using periodic acid, gave (*Z*)-4-octenedial **4.4**, which was stabilized by the addition of a crystal of 1,4-

hydroquinone.[55] The overall yield of **4.4** from 1,5-cyclooctadiene **4.6** was 71%. Treatment of **4.4** with vinylmagnesium bromide at 0 °C afforded the bis-allylic alcohol **4.8** in 77% yield. Claisen-Johnson rearrangement[45] on **4.8** followed by DIBALH reduction of the resulting diester provided the *E*,*Z*,*E*-triene diol **4.9** in 71% overall yield. When the double dihydroxylation of **4.9** was first performed using Sharpless AD-mix β[14] at –3 °C for 40 h the product resulting from double dihydroxylation (62%) and a lesser amount of mono-dihydroxylated product (20%) was obtained.[29] Treatment of the double dihydroxylated product with 2,2-dimethoxypropane in the presence of camphorsulfonic acid gave the bis-*O*-isopropylidene alkene **4.5** as a single compound, in 94% yield. However, when the double dihydroxylation and isopropylidene formation reactions were repeated at a later time using similar conditions, the product **4.5** as well as another compound was obtained. Furthermore, both compounds were inseparable by column chromatography. Careful analysis of the ^{1}H NMR of the bis-*O*-isopropylidene alkene mixture showed the presence of two signals at δ 5.35 and 5.42 in a 5:1 ratio. These signals indicated the presence of two compounds, with the major compound being the bis-*O*-isopropylidene-*Z*-alkene **4.5**, whilst the minor compound was presumed to be the *E*-isomer **4.10**. Confirmation for the presence of **4.10** was obtained by the conversion of the bis-*O*-isopropylidene mixture to **4.12**. To this end, acetylation of the mixture with acetic anhydride and DMAP followed by oxidative cleavage of the double bond with $OsO_4/NaIO_4$ afforded the segments **4.11** and **4.12**, which were separable by column chromatography. The overall yield of the desired product **4.5** was 43% over two steps. Longer reaction time (ca. 40 h) in the double dihydroxylation reaction gave essentially pure **4.5**, but in lower yields (30% over two steps). This can be explained by the reactivity of the *Z*-alkene **4.5** vs. the *E*-alkene **4.10**, in which the latter reacts faster.[14a]



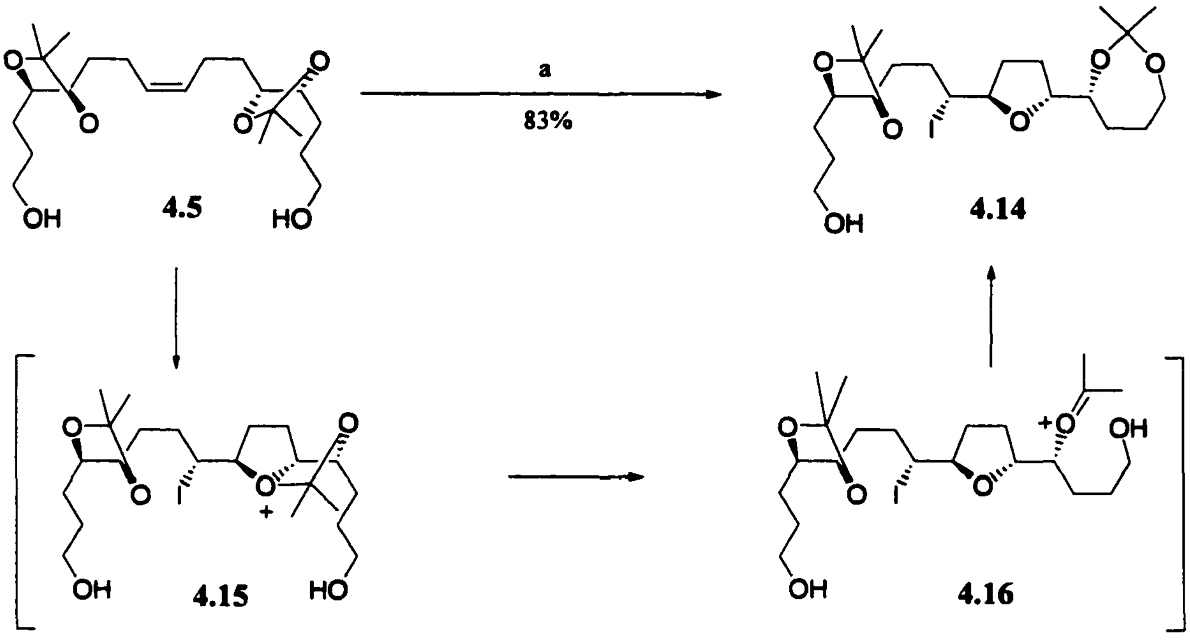
4.11 R_1= CHO, R_2= OAc

4.13 R_1= CH_2OH, R_2= OH

Scheme 4.2. (a) CH_3COOOH, NaOAC, $CHCl_3$, rt; (b) periodic acid, H_2O, 40 °C; (c) vinylmagnesium bromide, THF, 0 °C; (d) $CH_3C(OEt)_3$, CH_3CH_2COOH, 138-140 °C; (e) DIBALH, CH_2Cl_2, -78 °C to rt; (f) AD-mix β, $MeSO_2NH_2$, *t*-BuOH-H_2O, -3 °C; (g) $Me_2C(OMe)_2$, CSA, DMF; (h) (1) O_3, CH_2Cl_2, MeOH then Ph_3P; (2) $NaBH_4$, EtOH; (i) (1) Ac_2O, DMAP, EtOAc; (2) OsO_4, NMO, acetone, rt; (3) $NaIO_4$, MeOH, rt.

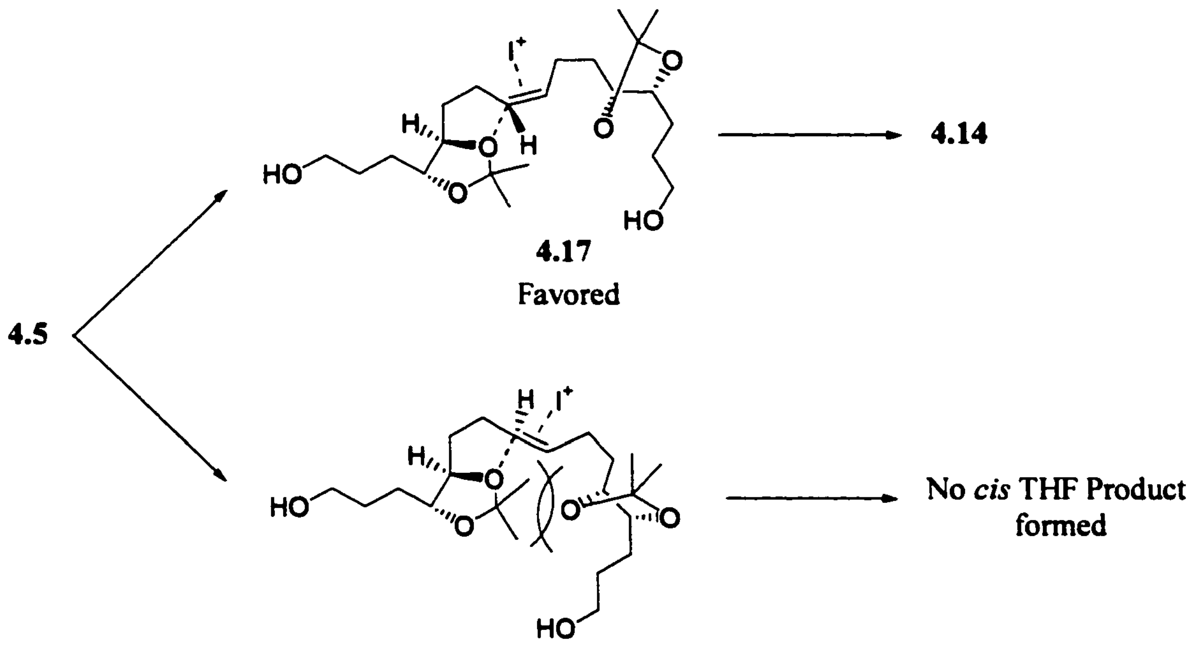
Therefore, over a longer reaction time there is a rapid conversion of the *E*-alkene **4.10** to the completely hydroxylated product. Variations in the scale of the reaction, catalyst concentration and temperature led to no significant improvements in both the yield and selectivity of dihydroxylation. As a consequence, the optimal condition for the double dihydroxylation reaction was shorter reaction time (20 h) to afford the product resulting from the double dihydroxylation (55%) followed by the subsequent separation of **4.10** at a later stage. The optical purity of **4.5** was determined by the conversion of **4.5** to the known diol **4.13**. This was accomplished by ozonolysis of **4.5** and subsequent reduction of the aldehyde with $NaBH_4$ to the diol **4.13**. The $[\alpha]_D^{26}$ of **4.13** was determined to be +29.8°, which was very similar to the literature value of +29.2°.[56] Thus it can be inferred that the optical purity of **4.5** is greater than 97% ee (**Scheme 4.2**).

An anhydrous acetonitrile solution of **4.5** was treated with iodonium dicollidine perchlorate (IDCP) to afford the *trans*-mono THF iodide **4.14** in 83% yield, with no evidence for the *cis* isomer.[53a] In addition, the differentiation of the primary hydroxyl functions were achieved in a single step by the formation of the seven membered acetal protecting group. The high yield of the seven membered acetal is consistent with the intramolecular attack of the proximal alcohol on the oxocarbenium ion in the intermediate **4.16** (**Scheme 4.3**). On the other hand, if the reaction was carried out in the presence of water one would expect the decomposition of the oxocarbenium ion **4.16** to afford **4.3**. The stereochemistry of the THF ring was tentatively assigned as *trans*, based on the *trans* selectivity observed in the iodocyclization of related isopropylidene alkenes.[53]



Scheme 4.3. (a) IDCP, CH_3CN, rt.

The high *trans* stereoselectivity observed in the product **4.14** may be due to the formation of a THF-oxonium ion intermediate which has a *cis* fused [3.3.0] oxahydridan type geometry **4.17 (Scheme 4.4)**.[53a] The THF oxonium ion, which leads to the *cis* THF product, would be disfavored because of steric crowding between the iodo-alkyl substitutent of the eventual THF and the methyl group of the acetonide in the concave region of the intermediate **4.18 (Scheme 4.4)**. In addition, it has been shown that the addition of electrophiles to an alkene that bears a participating internal nucleophile occurs in an *anti* fashion.[57] Thus, it was deduced that addition of the iodonium ions to the alkene of **4.5** occurs in a similar fashion to give rise to an *anti* relationship between the iodinated carbon and the newly formed carbon oxygen bond of the THF ring.



4.5

4.17
Favored

4.14

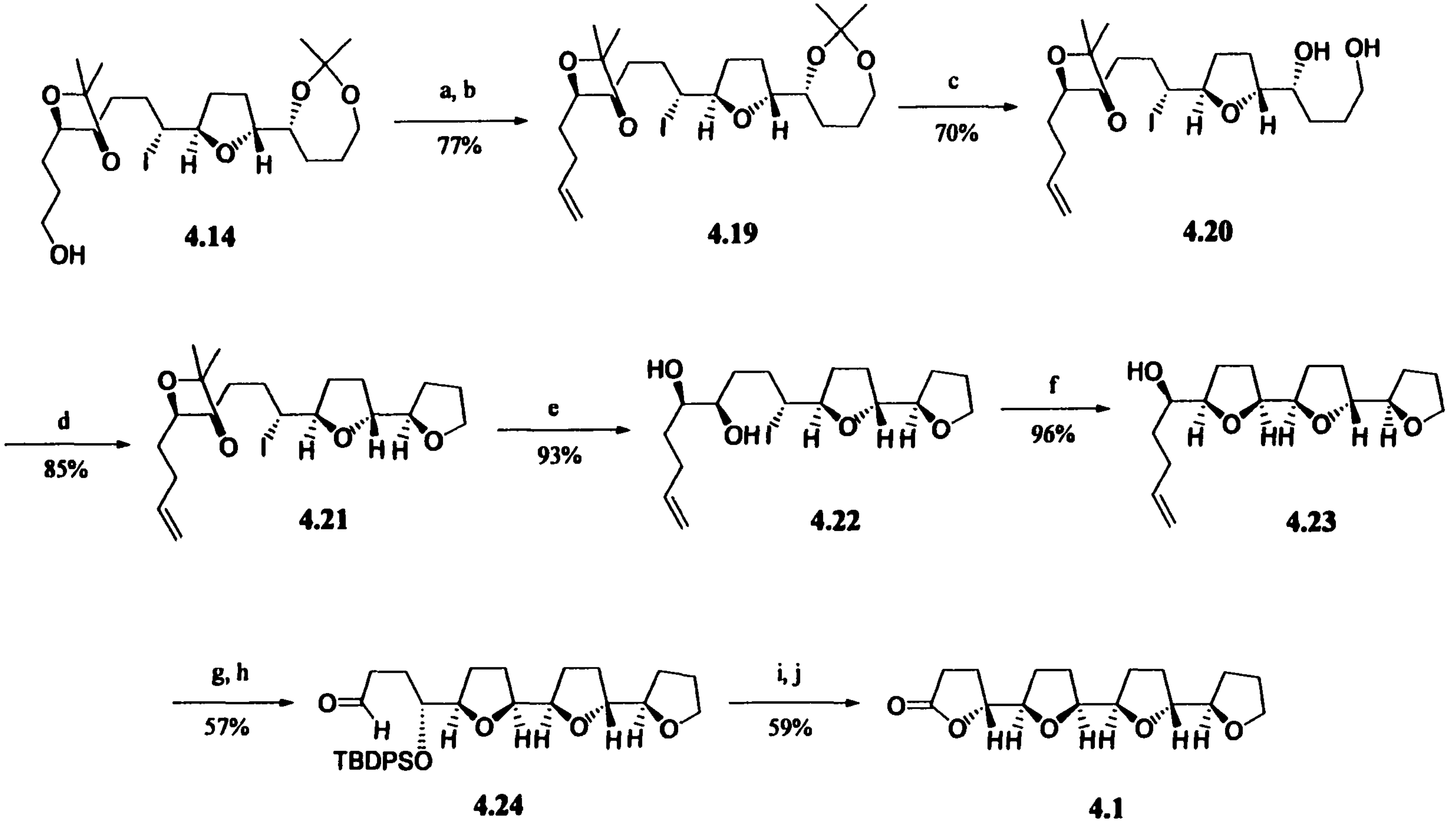
4.18
Disfavored

No *cis* THF Product formed

Note this intermediate places the iodinated side chain in the more congested concave cavity.

Scheme 4.4

The primary alcohol of **4.14** was converted to the terminal alkene **4.19** by first converting the primary alcohol to an aldehyde by Swern oxidation, followed by Wittig methylenation in an overall yield of 77%. This terminal alkene serves as a masked carbonyl group. Protocols similar to those used by Ruan, were employed for the synthesis of the two remaining THF segments of **4.1**.[29] This entailed the selective hydrolysis of the seven membered acetonide **4.19** with PPTS to afford the THF-alkene diol **4.20** in 70% yield. Treatment of **4.20** with Ph_3P and DEAD afforded a single bis-THF product **4.21** in 85% yield. Previous examples have shown that this etherification

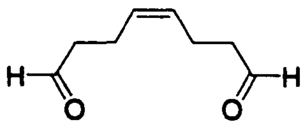


Scheme 4.5. (a) Swern's oxidation; (b) CH_2=PPh_3, toluene; (c) PPTS, EtOH; (d) Ph_3P, DEAD, CH_2Cl_2; (e) BF_3-OEt_2, THF-H_2O; (f) Bu_2SnO, benzene, reflux; (g) TBDPSCl, imidazole, DMF; (h) O_3, then Ph_3P; (i) $NaClO_2$, CH_3CN; (j) 6N HCl-THF.

procedure supports the product resulting from activation of the primary alcohol and retention of configuration at the secondary alcohol carbon.[58] Hydrolysis of the remaining acetonide of **4.21** with BF_3-OEt_2 dissolved in THF/H_2O gave the bis-THF diol **4.22** in 93% yield. The formation of the *cis*-THF ring of **4.1** was furnished by a Bu_2SnO mediated etherification.[48] Treatment of **4.22** with Bu_2SnO in benzene, with azeotropic removal of water, afforded **4.23** in 96% yield, with no indication of dehydroiodination products. Protection of the secondary alcohol of **4.23** as the silyl ether followed by ozonolysis of the terminal alkene gave the aldehyde **4.24** in 57% after two steps. Oxidation of the aldehyde **4.24** with $NaClO_2$ afforded the carboxylic acid, which was subsequently treated with 6N HCl dissolved in THF to afford the tris THF lactone **4.1** in an overall yield of 59% (**Scheme 4.5**). The overall structure of **4.1** was assigned on the basis of HRMS, IR ^{1}H and ^{13}C NMR analysis.

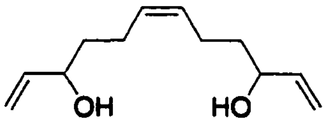
In summary, the synthesis of the tris-THF lactone **4.1** from **4.5**, illustrates the suitability of bis-1,2-*O*-isopropylidene alkene as precursors to the complex oligo-THFs. The key aspects of the methodology are the easy accessibility of the isopropylidene alkene precursor, the efficiency of the pivotal iodoetherification reaction and the synthetic versatility of the resulting iodo-THF product.

4.4 EXPERIMENTAL



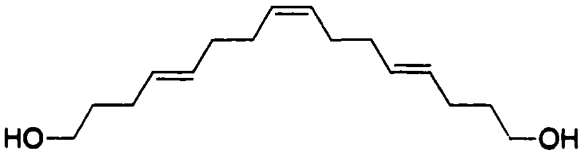
4.4

(*Z*)-4-Octenedial 4.4. CH_3COOOH (39 mL, 0.2 mol) was slowly added, at rt, to a rapidly stirred suspension of 1,5-cyclooctadiene **4.6** (24.5g, 0.2 mol) and NaOAc (16.4 g, 0.2 mol) in $CHCl_3$ (750 mL). After stirring for 1 h, the reaction mixture was filtered, and the filtrate was washed with aqueous $NaHCO_3$ and brine. The organic phase was dried ($NaSO_4$), filtered and evaporated *in vacuo*. To the crude residue of **4.7** was added a solution of periodic acid (45.6 g, 0.2 mol) in H_2O (700 mL). The mixture was stirred for 1 h at 40 °C, then cooled to 0 °C, neutralized with aqueous $NaHCO_3$, diluted with brine and extracted with CH_2Cl_2. The organic phase was dried ($NaSO_4$) and filtered. The filtrate was stabilized by addition of hydroquinone (10 mg) and concentrated to give crude **4.4** (19.9 g, ca. 71%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (m, 4H), 2.44 (m, 4H), 5.28 (m, 2H), 9.68 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 43.5, 128.9, 201.8.



4.8

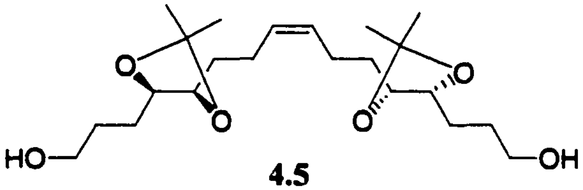
(*Z*)-1,6,11-Dodecatriene-3,10-diol 4.8. A solution of **4.4** (19.9 g, 142 mmol) in dry THF was added dropwise, to a solution of vinylmagnesium bromide (300 mL, 1M) in dry THF (440 mL) at 0 °C. The reaction was stirred at this temperature for 1 h, diluted with 1 M aqueous HCl and extracted with ether. The ether extract washed with brine, dried ($NaSO_4$) and then concentrated. FCC of the residue provided **4.8** (21.5 g, 77%). R_f= 0.28 (30% EtOAc in petroleum ether); IR (neat) 3356, 1644 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.58 (m, 4H), 2.16 (m, 4H), 2.58 (s, 2H, D_2O ex.), 4.12 (m, 2H), 5.15 (m, 4H), 5.40 (m, 2H), 5.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 37.0, 72.3, 114.6, 129.9, 141.3. FABHRMS calcd for $C_{12}H_{21}O_2$ $(M+H)^+$ 197.1542, found 197.1539.



4.9

(4*E*,8*Z*,12*E*)-Hexadecatriene-1,16-diol 4.9. A 250 mL, one-necked round-bottomed flask containing a magnetic stirring bar was fitted with a Claisen adapter, two thermometers and a receiving flask. The flask was charged with triethyl orthoacetate (160 mL), **4.8** (17.8 g, 90.8 mmol) and propionic acid (0.8 mL). Ethanol was distilled from the reaction mixture, and heating was continued between 138-142 °C, for additional 2 h. The reaction mixture was then cooled to rt and excess triethyl orthoacetate and propionic acid were removed by distillation under reduced pressure, to give the crude triene ester. IR (neat) 1727 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J= 6.6 Hz, 6H), 2.03 (m, 8H), 2.33 (m, 8H), 4.16 (q, J= 6.6 Hz, 4H), 5.34 (m, 2H), 5.46 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 27.4, 28.1, 32.7, 34.6, 60.4, 128.6, 129.5, 131.2, 173.4. FABHRMS calcd for $C_{20}H_{33}O_4$ $(M+H)^+$ 337.2379, found 337.2380.

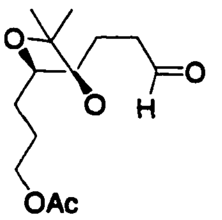
A solution of DIBAL (347 mL, 347 mmol, 1M in heptane) was added, dropwise, under argon, to a stirred solution of above diester (30.3 g, 90.2 mmol) in dry CH_2Cl_2 (300 mL) at −78 °C. The mixture was stirred for 1 h at this temperature, then warmed to rt, and poured into an ice cold solution of saturated aqueous $KNaC_4H_4O_6$ (500 mL). The mixture was warmed to rt, and stirred until all the solid was dissolved. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. FCC of the residue afforded **4.9** (16.2 g, 71% from **4.8**). R_f= 0.55 (EtOAc); IR (neat) 3329, 1657 cm^{-1}; ^1H NMR δ 1.59 (m, 4H), 2.03 (m, 12H), 2.43 (s, 2H, D_2O ex.), 3.59 (t, J= 4.5 Hz, 4H), 5.33 (m, 2H), 5.41 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.4, 29.0, 32.5, 36.8, 62.4, 129.6, 130.0, 130.5. FABHRMS calcd for $C_{16}H_{29}O_2$ $(M+H)^+$ 253.2167, found 253.2197.



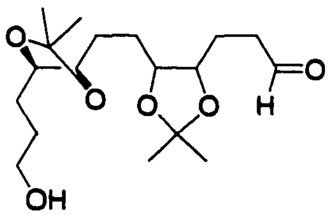
4.5

(8*Z*,4*R*,5*R*,12*R*,13*R*)-Hexadecaene-4,5:12,13-diisopropylidenedioxy-1,16-diol 4.5. A mixture of *t*-butyl alcohol (60 mL), H_2O (60 mL), AD-mix β (15.9 g) and $MeSO_2NH_2$ (1.1 g, 11.3 mmol) was stirred at rt until both phases were clear, and then cooled to −3 °C, whereupon the inorganic salts partially precipitated. At this point, triene diol **4.9** (1.6 g, 12.6 mmol) was added, and the heterogeneous slurry was stirred vigorously at −3 °C for 20 h. The reaction was then quenched by addition of sodium sulfite (17 g), warmed to rt and stirred for an additional 1 h. The organic layer was separated and the aqueous layer was extracted with *t*-butyl alcohol (1x) and EtOAc (4x). The combined organic phase was washed with 2N KOH, dried (Na_2SO_4) and concentrated *in vacuo*. FCC of the residue gave two fractions: (0.6 g, 34%, R_f= 0.55, 20% MeOH in EtOAc) and (1.13 g, 55%, R_f= 0.30, 20% MeOH in EtOAc). For major component in the more polar fraction: ^{1}H NMR (300 MHz, CD_3OD) δ 1.58 (m, 12H), 2.20 (m, 4H), 3.40 (m, 4H), 3.58 (m, 4H), 5.40 (bt, J= 4.4 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 24.8, 30.3, 30.6, 34.2, 63.2, 74.9, 75.3, 131.0. FABHRMS calcd for $C_{16}H_{33}O_6$ $(M+H)^+$ 321.2277, found 321.2276.

2,2-Dimethoxypropane (0.86 mL, 7.0 mmol) and camphorsulfonic acid (487 mg, 4.35 mmol) were added to a solution of the more polar material (1.13 g, 3.5 mmol) in anhydrous DMF (40 mL) at 0 °C. The reaction mixture was warmed to rt, stirred for 30 min at this temperature, poured into saturated aqueous $NaHCO_3$ and extracted with ether (3X) and EtOAc (1X). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. FCC of the crude material provided an inseparable mixture of **4.5** and another compound presumed to be **4.10** (3.28 g, 94%). For **4.5**: R_f= 0.50 (EtOAc); IR (neat) 3419, 1448 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 12H), 1.58 (m, 12H), 2.14 (m, 4H), 3.58 (m, 8H), 3.82 (bs, 2H, D_2O ex.), 5.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 27.6, 27.7, 29.9 (2 carbons), 33.2, 62.9, 80.7, 81.1, 108.3, 129.8. FABHRMS calcd for $C_{22}H_{40}O_6$ $(M+H)^+$ 401.2903, found 401.2903. Selected data for **4.10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (m); ^{13}C NMR (75MHz, $CDCl_3$) δ 62.8, 78.5, 81.4, 81.5, 108.4, 130.4. The approximate ratio of **4.5**/**4.10** based on the integration of the signals at δ 5.35 and 5.42, respectively, was 5:1.



4.11



4.12

Analysis of Mixture 4.5 and 4.10. The mixture of **4.5** and **4.10** (453.3 mg, 1.1 mmol) was dissolved in EtOAc (20 mL). To this, Ac_2O (0.6 mL, 6.8 mmol) and DMAP (316.1 mg, 2.6 mmol) were added and stirred at rt for approximately 15 min. The reaction mixture was quenched with MeOH (10 mL) and concentrated *in vacuo*. The residue was purified by FCC to afford the acetylated mixture (490.7 mg, 89%).

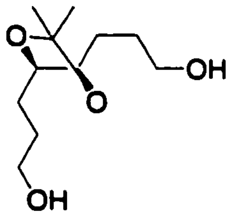
The acetylated mixture from the previous step (490.7 mg, 1.0 mmol) was dissolved in acetone (30 mL) and osmium tetroxide (1.0 mL of a 2.5 wt% solution in *t*-BuOH, 0.1 mmol) and N-methyl morpholine oxide (0.4 mL of a 60% wt solution in water, 2.0 mmol) were added to the solution and stirred for 2 h at rt. A saturated solution of sodium bisulfite (20 mL) was added and the mixture was stirred at rt for 1 h. The mixture was concentrated under reduced pressure and the residue was diluted with water and extracted with ethyl acetate (3 x 100 mL). The combined organic extract was dried (Na_2SO_4), filtered and concentrated *in vacuo*.

The oil from the previous step, was dissolved in methanol (20 mL) and sodium periodate (215.0 mg, 1.0 mmol) was added. The slurry was stirred at rt for 2 h. Upon completion, the slurry was concentrated under reduced pressure and the residue was diluted with $Na_2S_2O_3$ (100 mL) and extracted with diethyl ether (3 x 100 mL). The ethereal extract was dried (Na_2SO_4), filtered and concentrated under reduced pressure.

The resulting residue was purified by FCC to afford a viscous oil **4.12** (17.9 mg, 11%) and **4.11** (101.4mg, 51%)

For **4.12**: R_f= 0.38 (10% EtOAc in petroleum ether, triple elution); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.35 (s, 6H), 1.40 (s, 3H), 1.20-1.90 (m, 10H), 2.10 (m, 2H), 2.60 (m, 2H), 3.60 (m, 2H), 4.10 (m, 4H), 9.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 23.0, 25.7, 26.1, 27.1, 27.6, 28.7, 29.4, 30.5, 41.0, 64.5, 78.2, 80.4, 80.8, 81.1, 108.0, 108.4, 171.1, 201.8. MS (ES, *m/z*) 404 $(M+NH_4)^+$.

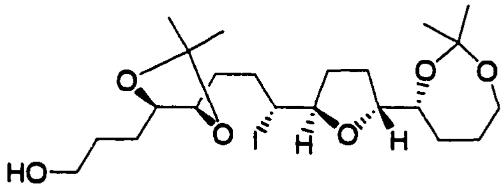
For **4.11**: R_f= 0.66 (10% EtOAc in petroleum ether, triple elution); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 6H), 1.30-1.90 (m, 6H), 1.95 (s, 3H), 2.55 (m, 2H), 3.50 (m, 2H), 4.05 (m, 2H), 9.70 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 25.0, 25.4, 27.3, 27.4, 29.1, 40.4, 64.2, 79.7, 80.2, 108.3, 170.8, 201.4. MS (ES, *m/z*) 276 $(M+NH_4)^+$.



4.13

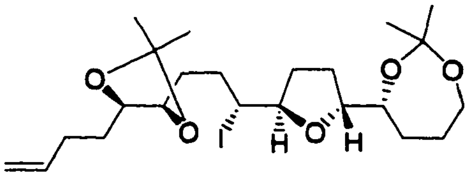
(4*R*,5*R*)-4,5-(Isopropylidenedioxy)-1,8-octanediol 4.13. A solution of **4.5** (40 mg, 0.1 mmol) in 4:1 CH_2Cl_2/MeOH (2 mL) was cooled to –78 °C. A stream of O_3 in O_2 was bubbled through the solution until **4.5** was not detectable by TLC (10% EtOAc in petroleum ether). The mixture was flushed with N_2 and then triphenylphosphine (40 mg, 0.15 mmol) was added. The solution was warmed to rt, stirred for 2 h, and concentrated *in vacuo* to give a slurry, which was dissolved in EtOH (5 mL) and treated with $NaBH_4$

(5 mg, 0.13 mmol) at rt. The reaction mixture was stirred for 1 h, and then diluted with 10% HCl in MeOH until the pH was 8. The ethanol was removed under reduced pressure. FCC of the residue afforded **4.13** (25 mg, 57%). R_f= 0.38 (10% MeOH in EtOAc); $[\alpha]_D^{26}$ +29.8° (*c* 0.52, $CHCl_3$); Lit: $[\alpha]_D^{26}$ +29.2° (*c* 0.51, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 6H), 1.50-1.90 (m, 8H), 2.42 (s, 2H, D_2O ex.), 3.67 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.5, 29.6, 29.7, 62.8, 81.1, 108.4. FABHRMS calcd for $C_{11}H_{23}O_4$ $(M+H)^+$ 219.1596, found 219.1583.



4.14

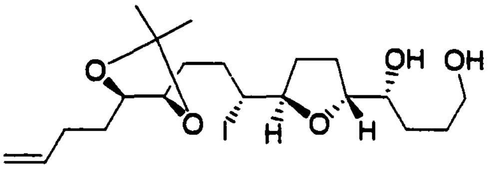
Mono-THF iodide 4.14. To a solution of **4.5** (563 mg, 1.4 mmol) in dry CH_3CN (50 mL) was added IDCP (985 mg, 2.1 mmol). The mixture was stirred at rt for 10 min, then poured into saturated aqueous $Na_2S_2O_3$, and extracted with ether. The combined organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. FCC of the crude residue gave **4.14** (616 mg, 83%). R_f= 0.50 (EtOAc); IR (neat) 3455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31, 1.32 (both s, 6H), 1.36 (s, 6H), 1.65 (m, 12H), 1.95, 2.05 (both m, 4H), 2.40 (bs, 1H, D_2O ex.), 3.60 (m, 7H), 3.85 (m, 1H), 4.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 27.5, 28.5, 29.4, 29.7, 30.6, 31.2, 32.1, 33.0, 41.9, 62.1, 62.8, 74.3, 80.0, 80.9, 82.8, 100.8, 108.5. FABHRMS calcd for $C_{22}H_{40}O_6I$ $(M+H)^+$ 527.1870, found 527.1869.



4.19

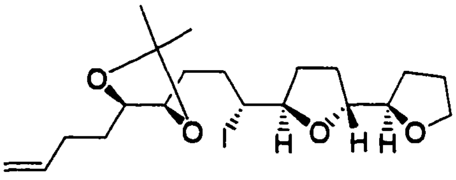
Mono-THF alkene 4.19. A 50 mL, round-bottomed flask, equipped with a magnetic stirring bar, was charged with oxalyl chloride (0.34 mL, 3.8 mmol) and CH_2Cl_2 (10 mL). The set up was purged with argon and cooled to –78 °C. DMSO (0.54 mL, 7.6 mmol) was added, dropwise, and stirring continued for 20 min. Then a solution of THF iodide **4.14** (795 mg, 1.5 mmol) in CH_2Cl_2 was slowly introduced. The reaction mixture was stirred for 25 min at –78 °C, at which Et_3N (1.5 mL, 10.6 mmol) was added. After warming to rt, the mixture was stirred for additional 10 min, diluted with ether, washed with saturated $NaHCO_3$, dried (Na_2SO_4) and concentrated *in vacuo*. FCC of the residue gave the aldehyde derivative of **4.14** (710 mg, 90%). R_f= 0.60 (60% EtOAc in petroleum ether); IR (neat) 1723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26, 1.30 (both s, 6H), 1.33 (s, 6H), 1.20-2.22 (m, 14H), 2.64 (m, 2H), 3.62 (m, 5H), 3.90 (m, 1H), 4.05 (m, 2H), 9.78 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 25.4, 25.4, 27.4, 28.5, 29.3, 30.6, 31.2, 32.1, 33.0, 40.5, 41.9, 62.1, 74.2, 79.7, 79.8, 82.6, 82.7, 100.7, 108.6, 201.7. FABHRMS calcd for $C_{22}H_{38}O_6I$ $(M+H)^+$ 525.1713, found 525.1716.

To a solution of methyl triphenylphosphonium iodide (4.73 g, 11.8 mmol) in dry toluene (200 mL) was added a 1M solution of sodium bis(trimethylsilyl) amide (19.5 mL, 11.8 mmol) in toluene, under an argon atmosphere. The yellow orange suspension was stirred for 1 h at rt then cooled to –78 °C. A solution of the aldehyde prepared in the previous step (4.08 g, 7.8 mmol) in dry toluene (50 mL), was added dropwise over 30 min. After an additional 15 min, the reaction mixture was warmed to rt and then diluted with ether (200 mL). The mixture was filtered through a pad of Celite and the filtrate was evaporated under reduced pressure. The residue was purified by FCC to afford **4.19** (3.49 g, 86%). $R_f = 0.7$ (20% EtOAc in petroleum ether); IR (neat) 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20, 1.25 (both s, 6H), 1.30 (s, 6H), 1.35-2.25 (m, 16H), 3.60 (m, 5H), 3.85 (m, 1H), 4.00 (m, 2H), 4.95 (m, 2H), 5.75 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 25.4, 27.4, 27.5, 28.4, 29.3, 30.2, 30.5, 31.2, 32.2, 33.1, 41.9, 61.9, 74.1, 79.7, 80.1, 82.4, 82.6, 100.5, 108.1, 114.9, 137.9. FABHRMS calcd for $C_{23}H_{40}O_5I$ $(M+H)^+$ 523.1921, found 523.1926.



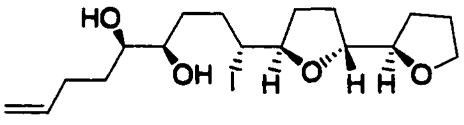
4.20

Mono-THF diol 4.20. Compound **4.19** (2.02 g, 3.9 mmol) was dissolved in EtOH (25 mL). PPTS (585.7 mg, 2.3 mmol) was then added and stirred for 3 h. The reaction was quenched with saturated sodium bicarbonate and extracted with ether (3 x 50 mL). The ethereal extract was washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FCC to yield **4.20** (1.31 g, 70%). $R_f = 0.1$ (10% EtOAc in petroleum ether); IR (neat) 3420, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.40-2.30 (m, 16H), 3.05 (br s, 2H), 3.40 (m, 1H), 3.60 (m, 4H), 3.90 (m, 2H), 4.05 (m, 1H), 4.95 (m, 2H), 5.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.4, 27.5, 28.8, 29.3, 30.2, 30.4, 31.6, 32.2, 32.4, 33.1, 41.6, 62.7, 74.1, 79.7, 80.2, 82.5, 83.6, 108.2, 114.9, 137.9. FABHRMS calcd for $C_{20}H_{36}O_5I$ $(M+H)^+$ 483.1607, found 483.1612.



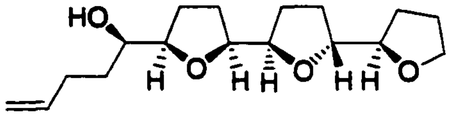
4.21

Bis-THF alkene 4.21. Compound **4.20** (1.34 g, 2.77 mmol) and triphenylphosphine (1.45 g, 5.54 mmol) were dissolved in dry CH_2Cl_2 (50 mL). DEAD (0.9 mL, 5.54 mmol) was then added and the reaction mixture was stirred for 2 h. Removal of the solvent under reduced pressure and FCC of the residue gave the bis-THF alkene **4.21** (1.09 g, 85%). $R_f = 0.80$ (10% EtOAc in petroleum ether); IR (neat) 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.60 (m, 3H), 1.70-2.30 (m, 13H), 3.65(m, 2H), 3.75 (m, 2H), 3.85 (m, 1H), 4.00 (m, 2H), 4.10 (m, 1H), 4.95 (m, 2H), 5.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 28.1, 28.1, 28.9, 29.6, 30.9, 31.4, 32.4, 32.8, 34.0, 41.9, 69.3, 80.9, 82.5, 83.5, 108.8, 115.6, 138.1. FABHRMS calcd for $C_{22}H_{34}O_4I$ $(M+H)^+$ 465.1502, found 465.1507.



4.22

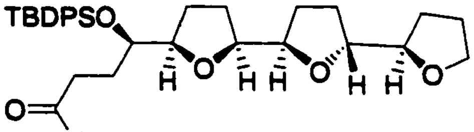
Bis-THF alkene diol 4.22. To a stirred solution of **4.21** (1.42 g, 3.1 mmol) in THF (40 mL) and H_2O (6 mL) at room temperature was added BF_3-OEt_2 (3.5 mL). The reaction mixture was stirred for 2 days. The solution was neutralized to pH 7 by the addition of saturated sodium bicarbonate. The solution was then concentrated and the aqueous extract was further diluted with water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The CH_2Cl_2 extract was washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FCC to afford recovered **4.21** (112 mg) and dihydroxy-iodide derivative **4.22** (1.11 g, 93% based on recovered **4.21**). $R_f = 0.30$ (10% acetone in $CHCl_3$, double elution); ^1H NMR (300 MHz, $CDCl_3$) δ 1.50-2.35 (m, 16H), 2.75 (s, 2H), 3.40 (m, 2H), 3.80 (m, 3H), 4.00 (m, 2H), 4.15 (m, 2H), 4.95 (m, 2H), 5.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 28.3, 29.1, 30.2, 30.8, 31.4, 32.9, 33.8, 41.1, 68.7, 73.4, 74.1, 82.0, 83.1, 83.2, 115.1, 138.5. FABHRMS calcd for $C_{17}H_{30}O_4I$ $(M+H)^+$ 425.1189, found 425.1188.



4.23

Tris-THF alkene 4.23. A mixture of **4.22** (838.9 mg, 1.98 mmol) and Bu_2SnO (492.9 mg, 1.98 mmol) in benzene (30 mL) was heated at reflux for 17 h using a Dean-

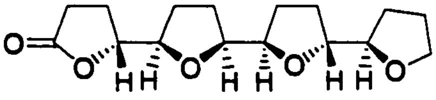
Stark set-up for the azeotropic removal of water. Removal of the solvent *in vacuo*, and FCC of the residue provided tris-THF alkene **4.23** (563.2 mg, 96%). R_f = 0.70 (10% acetone in $CHCl_3$, double elution); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30-2.30 (m, 16H), 2.90 (d, J= 6.0 Hz, 1H), 3.30 (m, 1H), 3.65-3.95 (m, 6H), 4.00 (m, 1H), 4.95 (m, 2H), 5.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 27.4, 28.3, 28.5, 28.8, 30.1, 33.6, 68.7, 74.1, 81.3, 81.4, 81.9, 82.2, 82.6, 114.6, 138.6. FABHRMS calcd for $C_{17}H_{29}O_4$ $(M+H)^+$ 297.2066, found 297.2064.



4.24

Tris-THF aldehyde 4.24. A solution of **4.23** (90.1 mg, 0.3 mmol), TBDPSCl (0.25 mL, 0.9 mmol) and imidazole (61.3 mg, 0.9 mmol) in anhydrous DMF (2 mL) was stirred at 50 °C for 3 h. The reaction mixture was then diluted with water and extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography to give TBDPS tris-THF alkene (104.8 mg, 65%) as a colorless oil. R_f = 0.8 (20% EtOAc in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.30-2.05 (m, 16H), 3.60-3.95 (m, 8H), 4.80 (m, 2H), 5.50 (m, 1H), 7.35 (m, 6H), 7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 26.1, 26.7, 27.4, 28.4, 28.7, 28.9, 29.3, 29.8,32.5, 68.7, 75.0, 81.6, 81.8, 81.9, 114.2, 127.4, 129.4, 134.2, 134.6, 136.0, 138.7. FABHRMS calcd for $C_{33}H_{45}O_4Si$ (M-H) 533.3087, found 533.3087.

A solution of TBDPS tris-THF alkene (104.8 mg, 0.19 mmol) in 5 mL of 4:1 CH_2Cl_2 and MeOH was cooled to –78 °C. A stream of O_3 in O_2 was bubbled through the solution until the starting material was not detectable by TLC analysis. The mixture was flushed with N_2 and then triphenylphosphine (55 mg, 0.21 mmol) was added. The solution was warmed to rt, stirred for 1h and concentrated *in vacuo*. The resulting slurry was then purified by flash chromatography to afford **4.24** (89.4 mg, 88%) as a colorless oil. R_f= 0.55 (20% EtOAc in petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.50-2.00 (m, 14H), 2.30 (m, 2H), 3.65-3.90 (m, 8H), 7.30 (m, 6H), 7.75 (m, 4H), 9.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 25.4, 26.0, 26.5, 27.2, 28.3, 28.6, 28.8, 28.9, 40.1, 68.5, 74.2, 81.5, 81.6, 81.7, 81.7, 81.9, 127.4, 127.5, 129.6, 133.8, 134.2, 135.9, 135.9, 201.9. FABHRMS calcd for $C_{32}H_{43}O_5Si$ (M-H) 535.2880, found 535.2882.



4.1

Tris-THF lactone 4.1. To a mixture of **4.24** (89.4 mg, 0.17 mmol) and $NaH_2PO_4.H_2O$ (234.6 mg, 1.7 mmol) in CH_3CN-H_2O (5 ml:1 mL) were successively added a 30% H_2O_2 (6 µL, 0.2 mmol) solution and a solution of $NaClO_4$ (18.5 mg, 0.2 mmol) in water (1.5 mL) at 0-5 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. Na_2SO_3 (100 mg) was added to the mixture to quench the oxidants. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were successively washed with water and brine, dried and concentrated *in vacuo*. The residue was passed through a short plug of silica gel to yield TBDPS tris-

THF acid (81.6 mg, 87 %) as a colorless oil. R_f = 0.90 (60% EtOAc in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.45-2.00 (m, 14H), 2.30 (m, 2H), 3.55-3.90 (m, 8H), 7.35 (m, 6H), 7.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 26.1, 26.5, 27.3, 28.1, 28.3, 28.6, 28.9, 28.9, 30.2, 68.6, 74.1, 81.5, 81.7, 81.8, 81.9, 127.4, 127.5, 129.5, 129.6, 134.0, 134.1, 136.0, 178.8. FABHRMS calcd for $C_{32}H_{43}O_6Si$ (M-H) 551.2829, found 551.2831.

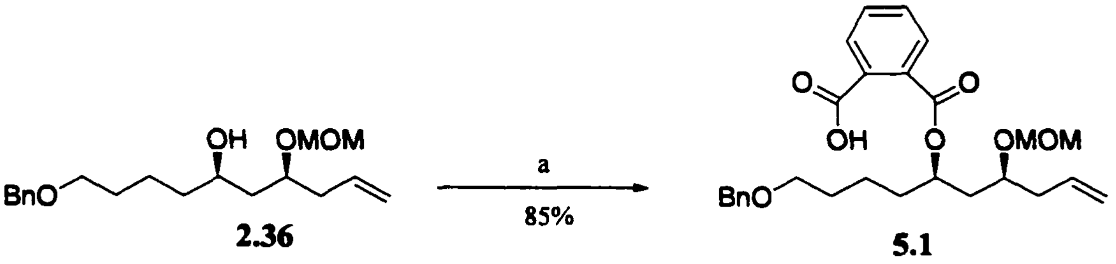
To a solution of TBDPS tris-THF acid (24.7 mg, 0.04 mmol) in THF (2 mL) was added an aqueous solution of 6N HCl (2 mL) and stirred for 2 days. The aqueous solution was then extracted with EtOAc (3 x 5 mL). The combined EtOAc extract was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography to afford **4.1** (8.1 mg, 68%) as a colorless oil. R_f = 0.30 (60% EtOAc in petroleum ether); IR ($CHCl_3$ film) 1772cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 1.34 (m, 2H), 1.46-1.72 (m, 10H), 1.83 (m, 2H), 2.07 (m, 1H), 2.30 (m, 1H), 3.36 (m, 1H), 3.61 (m, 1H), 3.68-3.78 (m, 4H), 3.89 (m, 1H), 3.96 (m, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 25.0, 26.9, 27.6, 28.6, 28.7, 29.0, 29.3, 29.9, 68.9, 81.1, 81.8, 81.9, 82.3, 83.3, 176.3. FABHRMS calcd for $C_{16}H_{25}O_5$ $(M+H)^+$ 297.1702, found 297.1703.

CHAPTER 5

SYNTHESIS OF A MONENSIN ANALOG

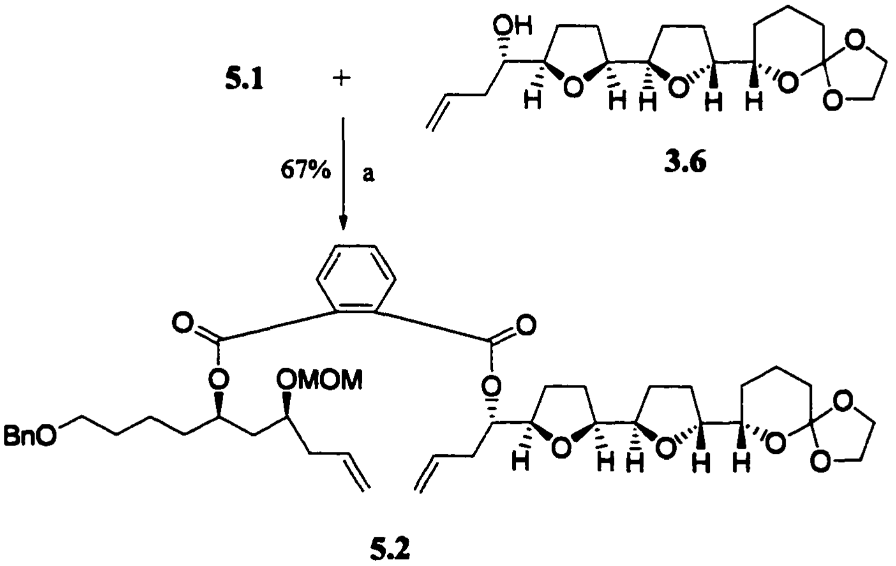
5.1 APPLICATION OF THE METATHESIS-IODOETHERIFCATION-SPIROKETALIZATION STRATEGY

The application of the three-step sequence to the synthesis of the monensin analog **1.2** began with the introduction of the phthalate tether on the alkenol segment **2.36**. The alkenol **2.36** was treated with phthalic anhydride, DMAP and pyridine to afford **5.1** in 85% yield (**Scheme 5.1**).



Scheme 5.1. (a) Phthalic anhydride, pyridine, DMAP, rt.

Carboxylic acid **5.1** was then coupled with the oligo-THF alkenol segment **3.6** in

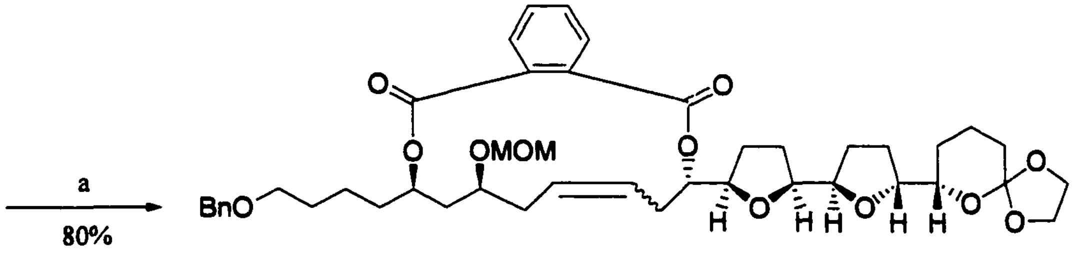


Scheme 5.2. (a) DCC, DMAP, CSA, benzene, rt

the presence of DCC and catalytic amounts of DMAP, CSA in benzene to provide the mixed diester **5.2** in 67% yield (**Scheme 5.2**).[42]

The mixed diester **5.2** was subjected to the ring closing metathesis in dichloromethane (0.01M, 20 mol% of (1,3-dimesityl-4,5-dihydroimidazol-2-ylidene)(PCy_3)$(Cl)_2$-Ru=CHPh **2.59**, reflux) to afford the macrocyclic alkene **5.3** in 80% yield (**Scheme 5.3**).[30,43] The overlap of the olefinic (H9, H10) and the ester proton signals (H5, H12) hindered the determination of the *E*/*Z* ratio. However, a 4:1 alkene mixture was presumed by comparison of the methoxy signals at δ 3.15 (major) and δ 3.16 (minor).

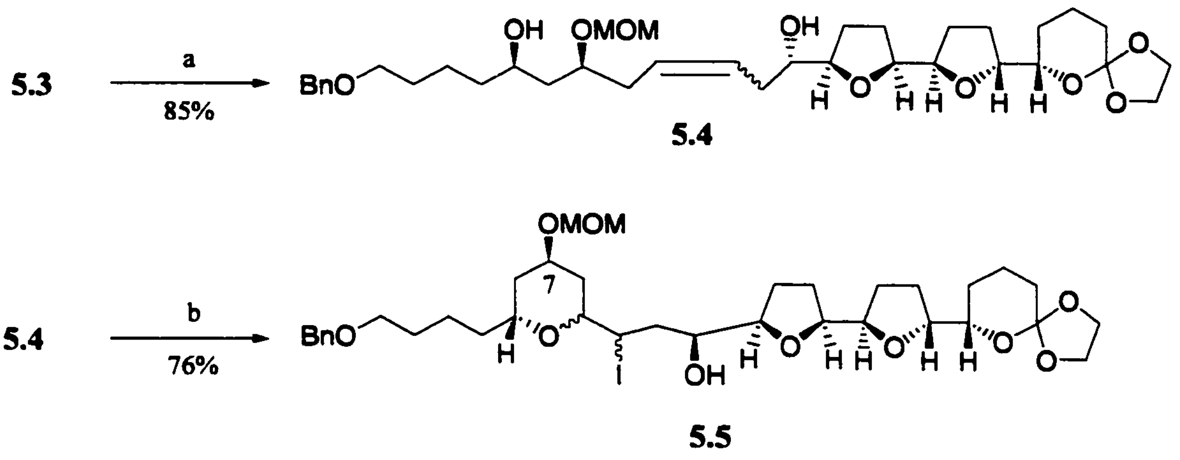
5.2



5.3

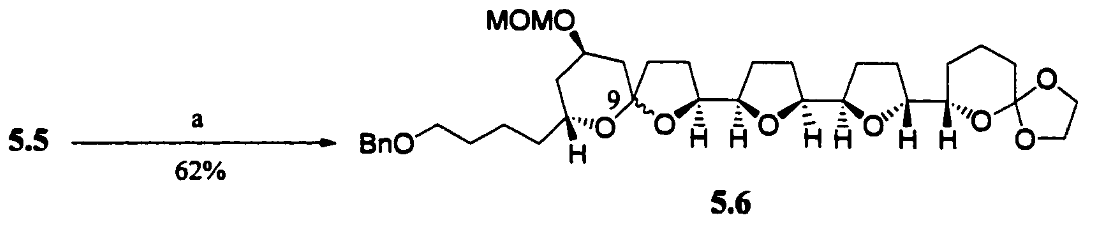
Scheme 5.3. (a) **2.59**, CH_2Cl_2 (0.01M), reflux.

Removal of the phthalate tether with NaOMe/ MeOH afforded the alkene diol **5.4** (in 85% yield), the precursor for the iodoetherification step. Treatment of anhydrous CH_2Cl_2 solution of **5.4** with IDCP in the presence of 4Å MS furnished the iodo-THP **5.5** as a mixture of diastereomeric THP isomers in 76% yield (**Scheme 5.4**). The ^{1}H and ^{13}C NMR spectrum of this mixture were complex, as would be expected. However, careful examination of the ^{13}C NMR indicated the presence of three of four possible diastereomers (δ 95.9, δ 95.7, δ 95.3 for the acetal carbon of the MOM protecting group).



Scheme 5.4. (a) NaOMe, MeOH, rt; (b) IDCP, CH_2Cl_2, 4Å MS.

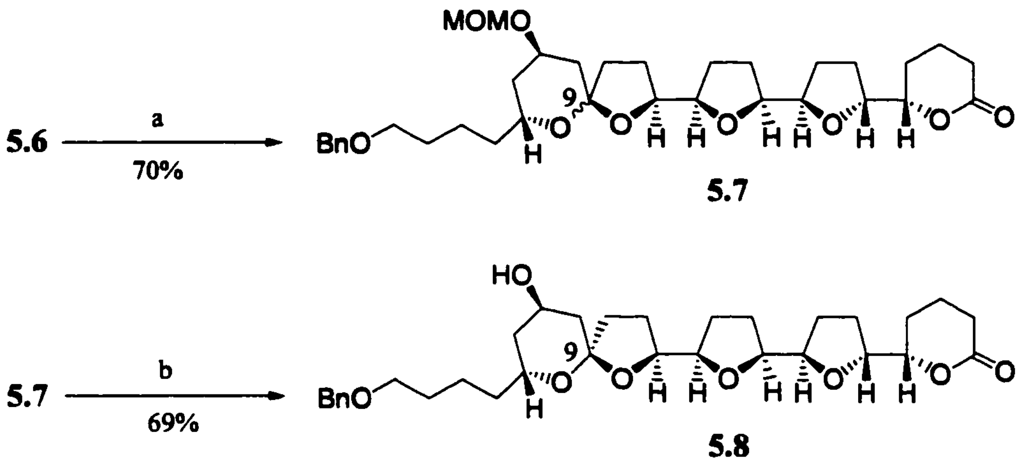
Treatment of **5.5** with AgOTf and collidine in anhydrous CH_2Cl_2 afforded the spiroketal **5.6** as an inseparable 2:1 mixture of diastereomers in 62% yield (**Scheme 5.5**).



Scheme 5.5. (a) AgOTf, collidine, CH_2Cl_2, rt.

Analysis of the ^{13}C NMR showed new carbon signals at δ 106.2 and δ 107.8, consistent with the formation of the spiroketal carbon (C9). Further corroboration was provided by electrospray mass spectrometry, which showed a $(M+Na)^+$ molecular ion peak at *m/z* 669.

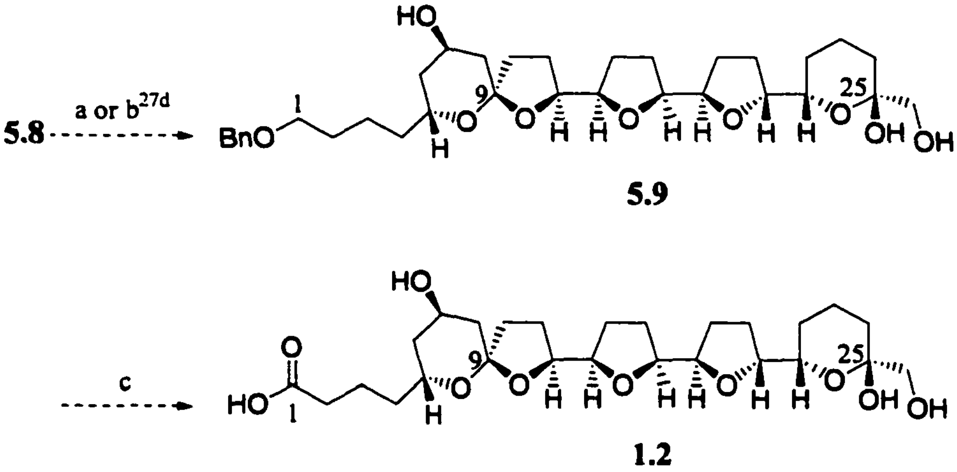
Equilibration of the diastereomeric mixture **5.6** to its thermodynamic isomer was next attempted. Hydrolysis of the orthoester in **5.6** with PPTS afforded the lactone **5.7** in 70 % yield. The subsequent removal of the MOM protecting group with aqueous 6N HCl in THF afforded **5.8** in 69% yield (**Scheme 5.6**). Inspection of the ^1H and ^{13}C NMR



Scheme 5.6. (a) PPTS, CH_2Cl_2; (b) 6N HCl, THF

indicated the presence of a single compound. A single acetal (C9) carbon signal was observed at δ 106.9. The formation of a single isomer is consistent with Ireland's observation.[20d] Accordingly, compound **5.8** was tentatively assigned as the thermodynamic isomer.

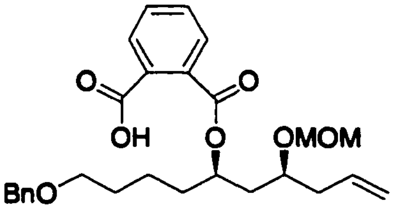
Several operations need to be carried out on analog **5.8** before the monensin analog **1.2** could be obtained. The conversion of the lactone at C25 to the hydroxy ketal residue has to be performed. The lactone **5.8** could be treated in two possible ways. Firstly, conversion of the lactone to the enol ether with Tebbe reagent followed by dihydroxylation with osmium tetroxide should provide the required appendage (**Scheme 5.7**). Secondly, the addition of a methanol carbanion equivalent such as (ethoxyethyl)lithiomethanol[59] to the lactone, followed by hydrolysis of the ethoxyethyl protecting group could also provide the terminal appendage (**Scheme 5.7**). The latter method was successfully used by Still in his synthesis of monensin.[28c,d] In addition, the conversion of the protected alcohol at C1 to its acid also has to be carried out. This would involve debenzylation (H_2, Pd/C), followed by oxidation of the alcohol to the carboxylic acid (**Scheme 5.7**).



Scheme 5.7. (a) (i) Tebbe reagent, (ii) OsO_4, NMO, Acetone; (b) (i) $LiCH_2OCH(CH_3)OCH_2CH_3$,[58] -78 °C, (ii) hydrolysis of PG; (c) (i) Debenzylation, (ii) Oxidation

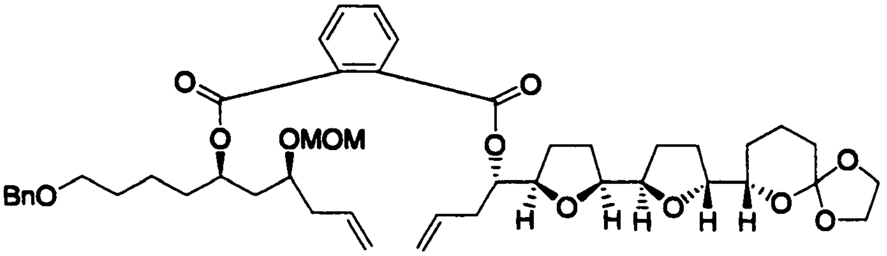
We have successfully demonstrated the synthetic utility of the metathesis-haloetherification-spiroketalization sequence by the synthesis of the monensin analog **5.6**. Analog **5.6** was synthesized in six steps in an overall yield of 18% from the alkenol **2.36**. The alkenol **2.36** was easily obtained via allylation of aldehyde precursors. The overall protocol is compatible with a wide range of functional groups and is operationally simple. This methodology should also be applicable to [4.4] and [5.5] spiroketal frameworks.

5.2 EXPERIMENTAL



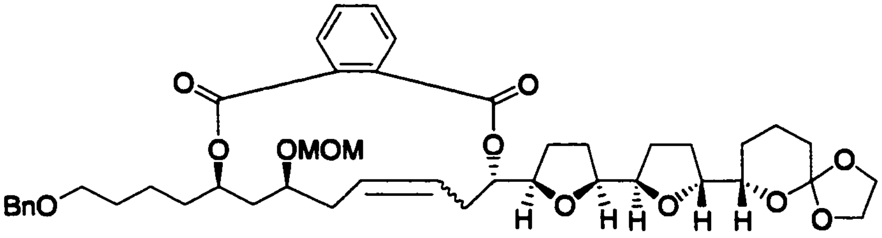
5.1

Carboxylic acid 5.1. To a stirred solution of the alkenol **2.36** (0.381 g, 1.18 mmol) in pyridine (15 mL) were added phthalic anhydride (0.524 g, 3.54 mmol) and DMAP (73.3 mg, 0.599 mmol). After 20 h the solution was filtered through a bed of Celite and the solvent was removed under reduced pressure. The residue was purified by FCC to afford recovered **2.36** (104.3 mg) and **5.1** (343.6 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45-1.95 (m, 7H), 2.05 (m, 1H), 2.40 (m, 2H), 3.40 (s, 3H), 3.50 (m, 2H), 3.85 (m, 1H), 4.50 (s, 2H), 4.70 (s, 2H), 5.10 (m, 2H), 5.30 (m, 1H), 5.85 (m, 1H), 7.30 (m, 5H), 7.50 (m, 2H), 7.70 (m, 1H), 7.80 (m, 1H), 10.35 (br. s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 29.5, 34.1, 38.7, 38.9, 55.5, 70.0, 72.8, 73.1, 74.2, 95.2, 117.7, 127.6, 127.7, 128.3, 128.8, 129.1, 130.8, 131.3, 132.8, 134.2, 138.3, 167.6, 169.9. FABHRMS calcd for $C_{27}H_{34}O_7Na$ $(M+Na)^+$ 493.2202, found 493.2205.



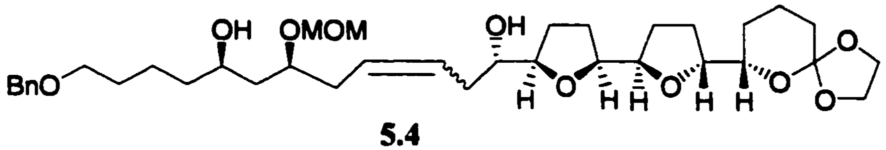
5.2

Mixed diester 5.2. A stirred solution of alcohol **3.6** (0.192 g, 0.542 mmol), acid **5.1** (0.335 g, 0.713 mmol), DMAP (26 mg, 0.21 mmol) and camphorsulfonic acid (16 mg, 0.07 mmol) in anhydrous benzene at 0-5 °C was treated with DCC (293 mg, 1.42 mmol). After stirring for 19 h at room temperature, diethyl ether (50 mL) was added and the mixture was filtered through Celite. Concentration of the filtrate and FCC of the residue afforded recovered **3.6** (18.9 mg) and the mixed diester **5.2** (264.9 mg, 67% based on recovered starting material). R_f= 0.58 (30% EtOAc in petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.59-1.98 (m, 21H), 2.21 (m, 1H), 2.49 (m, 2H), 2.69 (m, 1H), 2.75 (m, 1H), 3.26 (s, 3H), 3.37 (m, 2H), 3.59 (m, 2H), 3.74-3.97 (m, 7H), 4.10 (m, 1H), 4.38 (s, 2H), 4.60 (ABq, Δδ= 0.1 ppm, J= 7 Hz, 2H), 5.16 (m, 4H), 5.52 (m, 1H), 5.61 (m, 1H), 6.00 (m, 2H), 7.03 (m, 2H), 7.22 (m, 3H), 7.37 (d, J= 8 Hz, 2H), 7.73 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 22.0, 22.9, 28.2, 28.5, 28.8, 28.9, 29.6, 30.6, 32.5, 35.1, 36.7, 39.7, 39.9, 55.9, 63.7, 65.0, 70.8, 73.5, 73.6, 75.2, 76.4, 77.5, 80.6, 82.3, 82.5, 83.0, 96.4, 117.8, 118.0, 120.2, 127.9, 129.4, 129.5, 130.9, 131.2, 133.6, 134.4, 134.8, 135.4, 140.0, 166.8, 167.3. FABHRMS calcd for $C_{46}H_{62}O_{12}Na$ $(M+Na)^+$ 829.4139, found 829.4136.



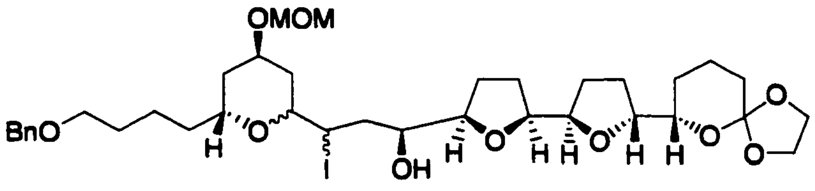
5.3

Macrocyclic alkene 5.3. Compound **5.2** (0.229 g, 0.285 mmol) was dissolved in CH_2Cl_2 (28 mL, 0.01M) and degassed for 10 min. Grubb's catalyst ((1,3-dimesityl-4,5-dihydroimidazol-2-ylidene)(PCy_3)$(Cl)_2$-Ru=CHPh) **2.59** (47.4 mg, 0.056 mmol) was added and the mixture heated at reflux for 4 h. The reaction mixture was cooled to ambient temperature. DMSO (0.2 mL) was added and stirred overnight. The solution was concentrated *in vacuo* to afford a residue. FCC of the residue afforded recovered starting material **5.2** (11.8 mg) and **5.3** (169 mg, 80% based on recovered starting material) as an inseparable 4:1 mixture. R_f= 0.42 (40% EtOAc in petroleum ether); for the major isomer: ^{1}H NMR (500 MHz, C_6D_6) δ 1.60-1.93 (m, 20H), 2.01 (m, 1H), 2.15 (m, 2H), 2.32 (m, 1H), 2.62 (m, 2H), 3.15 (s, 3H), 3.40 (t, J= 7 Hz, 2H), 3.58 (m, 2H), 3.74 (m, 2H), 3.86 (m, 2H), 3.95 (m, 4H), 4.40 (s, 2H), 4.48 (app. ABq, 2H), 5.48 (m, 2H), 5.58 (m, 2H), 7.01 (m, 2H), 7.23 (m, 3H), 7.38 (d, J= 8 Hz, 2H), 7.61 (d, J= 7 Hz, 1H), 7.79 (d, J= 7Hz, 1H); for the minor isomer (some selected signals): ^{1}H NMR (500 MHz, C_6D_6) δ 2.71 (m, 2H), 3.16 (s, 3H), 3.27 (m, 2H), 4.19 (m, 1H), 4.34 (s, 2H), 5.79 (1H), 6.06 (m, 2H); for the major isomer: ^{13}C NMR (75 MHz, C_6D_6) δ 22.0, 23.5, 28.2, 28.4, 28.6, 28.8, 29.7, 30.7, 32.5, 34.4, 35.1, 37.5, 39.6, 55.9, 63.7, 65.0, 70.9, 73.5, 74.3, 76.0, 77.5, 81.2, 82.2, 82.5, 83.0, 96.7, 120.2, 127.9, 128.9, 129.1, 129.6, 130.5, 131.8, 132.5, 136.0, 140.0, 166.3, 168.0. FABHRMS calcd for $C_{44}H_{59}O_{12}$ $(M+H)^+$ 779.4007, found 779.4009.



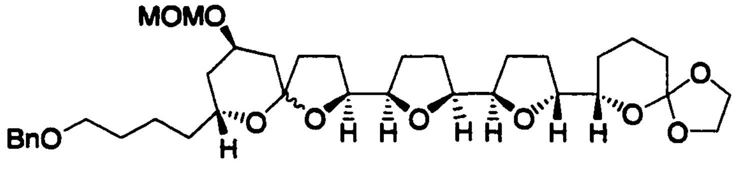
5.4

Alkene diol 5.4. Compound **5.3** (74.6 mg, 0.096 mmol) was dissolved in MeOH (7 mL) and NaOMe (1.5 mL) was added. The mixture was stirred for 24 h at rt. The solvent was removed *in vacuo* and the residue was dissolved in ether. The ethereal extract was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by FCC to afford recovered starting material **5.3** (6.8 mg) and **5.4** (47.8 mg, 85% based on recovered **5.3**). R_f= 0.13 (60% EtOAc in petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.40 (m, 3H), 1.60 (m, 4H), 1.71 (m, 8H), 1.88 (m, 6H), 2.07 (m, 1H), 2.22 (m, 1H), 2.28 (t, J= 8 Hz, 2H), 2.35 (m, 1H), 3.03 (br s, 1H), 3.21 (s, 3H), 3.41 (app t, 2H), 3.58 (m, 2H), 3.74-3.89 (m, 8H), 3.97 (m, 1H), 4.18 (m, 1H), 4.41 (s, 2H), 4.47 (ABq, $\Delta\delta$= 0.12 ppm, J= 7Hz, 2H), 5.57 (m, 1H), 5.62 (m, 1H), 7.16 (t, J= 8 Hz, 1H), 7.24 (t, J= 8 Hz, 2H), 7.38 (d, J= 8 Hz, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 21.9, 23.2, 25.9, 27.7, 28.3, 28.9, 29.2, 30.8, 32.4, 37.9, 38.7, 38.8, 42.8, 56.0, 63.7, 65.0, 70.9, 71.7, 73.5, 73.5, 77.4, 77.7, 82.2, 82.5, 82.8, 83.3, 95.9, 120.1, 127.9, 128.9, 129.0, 130.3, 140.0. FABHRMS calcd for $C_{36}H_{56}O_{10}Na$ $(M+Na)^+$ 671.3771, found 671.3770.



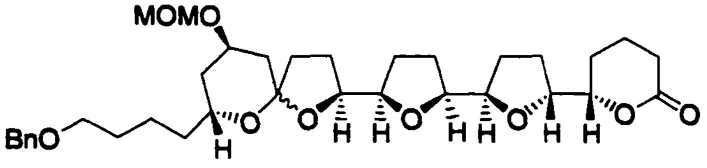
5.5

Iodo-THP 5.5. To a solution of the above dihydroxy alkene **5.4** (36.8mg, 0.0567 mmol) and 4Å MS (100 mg) in dry CH_2Cl_2 (8 mL) was added IDCP (39.9 mg, 0.0851 mmol). The mixture was stirred at rt for 15 min, then filtered through Celite into saturated aqueous $Na_2S_2O_3$ (20 mL), and extracted with CH_2Cl_2 (3x 10 mL). The combined organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. FCC of the residue afforded **5.5** (33.4 mg, 76%) as a mixture of inseparable diastereomers. R_f= 0.37 (60% EtOAc in petroleum ether); some selected signals: ^{1}H NMR (500 MHz, C_6D_6) δ 1.14-2.29 (m, 26H), 3.20, 3.21, 3.25 (s, each 3H), 3.39 (m, 2H), 3.61 (m, 2H), 3.76-3.91 (m, 8H), 4.11 (m, 1H), 4.40, 4.42 (s, each 2H), 4.51 (app ABq, 2H), 7.20 (m, 3H), 7.35 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 21.9, 23.1, 23.1, 23.8, 26.0, 26.2, 26.4, 27.6, 27.9, 28.2, 28.3, 28.7, 28.8, 28.9, 29.3, 30.6, 30.7, 32.4, 33.8, 36.0, 36.2, 36.7, 36.8, 37.2, 37.3, 39.8, 40.1, 40.9, 41.5, 41.7, 55.6, 55.7, 63.7, 65.0, 70.2, 70.7, 71.0, 71.2, 73.1, 73.3, 73.4, 73.6, 75.0, 76.0, 76.2, 77.4, 77.4, 82.1, 82.2, 82.4, 82.6, 82.7, 83.1, 83.6, 83.7, 95.3, 95.7, 95.9, 120.1, 140.0. FABHRMS calcd for $C_{36}H_{56}O_{10}I$ $(M+H)^+$ 775.2918, found 775.2920.



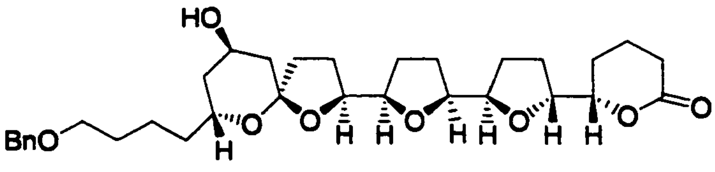
5.6

Monensin orthoester analog 5.6. The crude iodo-THP **5.5** (32.4 mg, 0.0418 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL) and collidine (22 μL, 0.167 mmol) was added and stirred for 10 min. AgOTf (43.7 mg, 0.167 mmol) was added and the mixture stirred for 25 min. The mixture was then poured into a saturated aqueous solution of $Na_2S_2O_3$ (10 mL), extracted with CH_2Cl_2 (3 x 10 mL). The combined CH_2Cl_2 extract was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude oil was purified by FCC to afford **5.6** (16.8 mg, 62%) as an inseparable mixture of diastereomers (2:1). R_f= 0.36 (60% EtOAc in petroleum ether); for the major isomer: ^{1}H NMR (500 MHz, C_6D_6) δ 1.22-2.17 (m, 28H), 3.35 (s, 3H), 3.37 (t, J= 7Hz, 2H), 3.58 (m, 2H), 3.72-3.99 (m, 8H), 4.08 (m, 1H), 4.33 (m, 1H), 4.38 (s, 2H), 4.73 (AB q, Δδ= 0.12 ppm, J= 8 Hz, 2H), 7.24 (m, 3H), 7.37 (d, J= 7 Hz, 2H); for the minor isomer (some selected signals): ^{1}H NMR (500 MHz, C_6D_6) δ 3.20 (s, 3H), 4.40 (s, 2H), 4.52 (app. ABq, 2H); for the major and minor isomer: ^{13}C NMR (75 MHz, C_6D_6) δ 22.0, 23.1, 23.3, 23.7, 27.7, 28.3, 28.7, 29.0, 29.2, 29.3, 29.4, 29.6, 30.7, 30.8, 31.0, 32.5, 36.2, 36.6, 36.8, 37.0, 37.1, 37.3, 40.2, 40.7, 55.6, 63.6, 64.9, 65.7, 70.2, 70.9, 71.0, 73.5, 77.6, 81.2, 82.4, 82.6, 82.7, 82.9, 84.1, 84.3, 95.6, 106.2, 107.8, 120.2, 140.0. MS (ES, *m/z*) 669 $(M+Na)^+$. FABHRMS calcd for $C_{36}H_{55}O_{10}$ $(M+H)^+$ 647.3795, found 647.3794.



5.7

Monensin lactone analog 5.7. Compound **5.6** (15.4 mg, 0.024 mmol) was dissolved in CH_2Cl_2 (3 mL). PPTS was added until pH 3 (12 mg). The mixture was stirred for 2 h at rt. The reaction was quenched with saturated sodium bicarbonate and extracted with CH_2Cl_2 (3 x 10 mL). The CH_2Cl_2 extract was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by FCC to afford **5.7** (10.1 mg, 70%). R_f= 0.16 (100% EtOAc); for the major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20-2.40 (m, 28H), 3.33 (s, 3H), 3.41 (t, J= 7 Hz, 2H), 3.65-4.06 (m, 6H), 4.14 (m, 1H), 4.21 (m, 1H), 4.45 (s, 2H), 4.67 (AB q, Δδ= 0.03 ppm, J= 8Hz, 2H), 7.21-7.31 (m, 5H); for the minor isomer (some selected values): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31 (s, 3H), 4.61 (AB q, Δδ= 0.02 ppm, J= 8Hz, 2H); for the major and minor isomer: ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 22.4, 22.7, 25.3, 26.5, 27.7, 28.0, 28.2, 28.3, 28.5, 28.6, 29.8, 29.9, 30.1, 31.9, 31.9, 34.2, 35.7, 35.8, 35.9, 36.1, 36.9, 38.6, 39.9, 55.5, 55.6, 61.4, 65.1, 66.2, 69.9, 70.2, 70.3, 70.5, 70.6, 71.6, 71.7, 73.0, 73.1, 80.1, 81.4, 81.9, 81.9, 82.0, 82.7, 83.2, 83.4, 95.0, 95.4, 105.6, 107.2, 127.7, 127.8, 128.6, 138.9, 174.0.



5.8

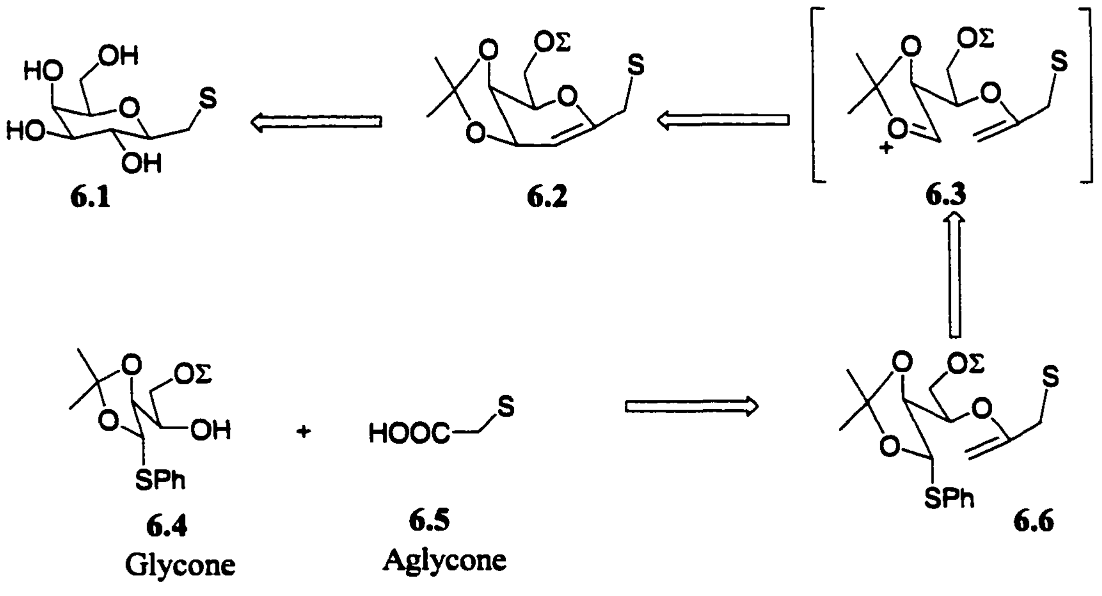
Equilibration of Monensin lactone analog 5.8. Compound **5.7** (6 mg, 0.0099 mmol) was dissolved in THF (0.7 mL). An aqueous solution of 6N HCl (0.2 mL) was added and the mixture was stirred for 4 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was passed through a short plug of silica to afford **5.8** (3.8 mg, 69%). R_f= 0.82 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20-2.20 (m, 27H), 2.60 (m, 1H), 3.47 (t, J= 7 Hz, 2H), 3.69 (m, 1H), 3.75-4.20 (m, 5H), 4.09-4.33 (m, 2H), 4.51 (s, 2H), 7.28-7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 22.4, 25.1, 27.9, 28.1, 28.1, 28.2, 28.5, 29.9, 30.0, 33.3, 35.8, 38.7, 69.8, 70.4, 73.1, 80.8, 81.7, 82.1, 82.3, 82.8, 83.2, 106.9, 127.8, 127.8, 128.6, 139.1, 171.1.

CHAPTER 6

1,2-*O*-ISOPROPYLIDENE THIOACETALS: PRECURSORS FOR HIGHLY OXYGENATED SPIROKETALS

6.1 INTRODUCTION

The general goal of this project is the development of 1,2-*O*-isopropylidene thioacetal (TIA) such as **6.4** as precursors for highly oxygenated rings. Previous studies have been directed at C-glycosides,[60-62] carbasugars[63] and azasugars.[64] The synthesis of C-glycosides is an illustration of the TIA methodology. The coupling of the glycone **6.4** and the aglycone **6.5** via an esterification reaction followed by methylenation of the ester function provides the enol ether **6.6**. Activation of the thiophenol function of **6.6** affords the oxocarbenium ion **6.3**, which undergoes an intramolecular cyclization with the electron rich alkene to provide the highly functionalized C1-substituted glycal **6.2**. The subsequent elaboration of the enol ether of **6.2** (such as hydroboration) would afford the C-glycoside **6.1** (**Scheme 6.1**).[60-62]

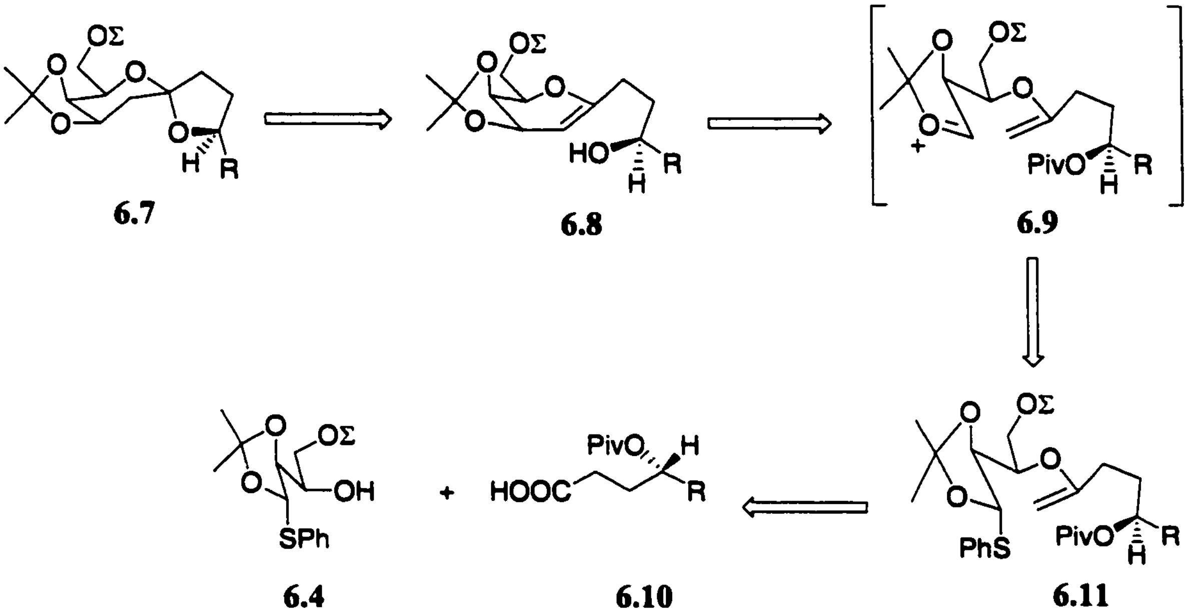


S= sugar residue

Σ= TBDPS

Scheme 6.1

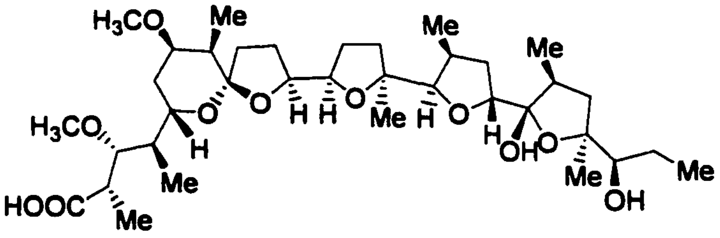
Using this concept, we envisaged an intramolecular cyclization of a hydroxy-enol ether of **6.2** to afford highly oxygenated spiroketal subunits. As an extension of this strategy to spiroketal subunits we would use a protected hydroxy acid precursor **6.10** as the aglycone segment to afford the hydroxy C1-substituted glycal intermediate **6.8**. The subsequent cyclization of **6.8** would provide the spiroketal **6.7** (**Scheme 6.2**).



R= oligo-THF
Σ= TBDPS

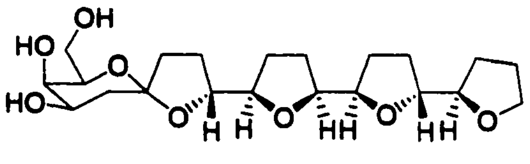
Scheme 6.2

Our aim is to construct the analog **6.12** of kijimicin[54] **4.2** using the TIA synthon **6.4** to introduce the spiroketal subunit. Before the actual synthesis of **6.12** was undertaken, we decided to test this strategy using the γ-pivaloylated hydroxy acid **6.14** as the aglycone segment to afford the spiroketal subunit **6.13** (**Figure 6.1**). It can be envisaged that the pyranoside segment of **6.14** represents the oligo-THF portion of kijimicin **4.2** or its analog **6.12**.

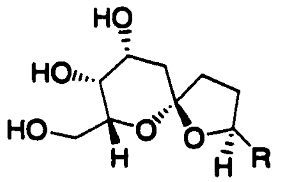


4.2

Kijimicin



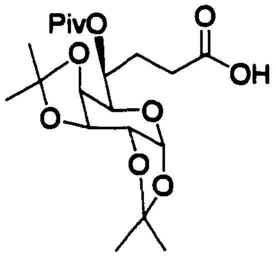
6.12



6.13

spiroketal subunit analog

R= oligo-THF segment



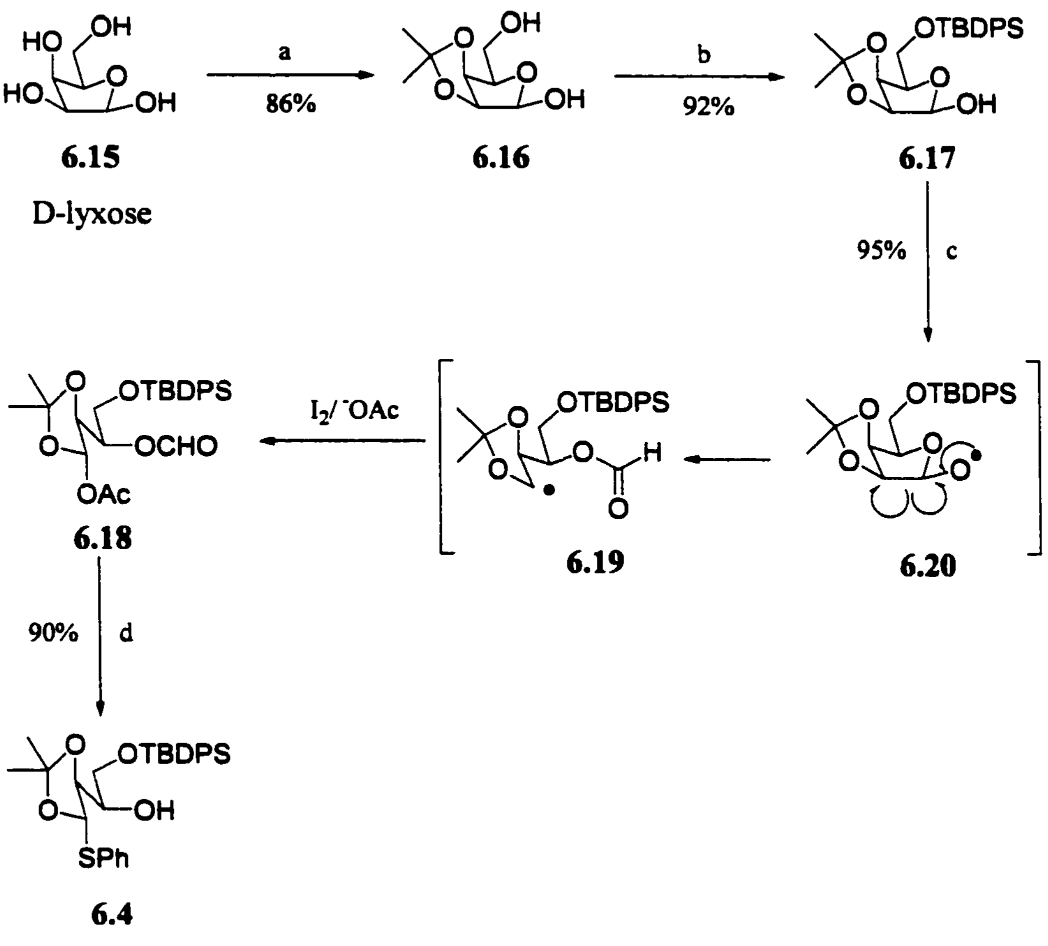
6.14

Figure 6.1

6.2 RESULTS AND DISCUSSION

Synthesis of TIA 6.4

The 1,2-*O*-isopropylidene thioacetal **6.4** was synthesized in an overall yield of 68% via a route developed by previous workers in our laboratory.[61] Treatment of D-lyxose **6.15** with acetone and catalytic amounts of H_2SO_4 resulted in isopropylidene formation of the vicinal C2 and C3 hydroxyl functions **6.16**. The primary hydroxyl group at C5 was converted to the silyl ether **6.17** by the use of *tert*-butyldiphenylsilyl chloride. The protected D-lyxose **6.17** was then treated with iodobenzene diacetate (DIB) and I_2 (Suarez conditions) in dry cyclohexane to afford the 1-*O*-acetyl-1,2-*O*-isopropylidene acetal **6.18**.[65] This reaction proceeds via a fragmentation of an anomeric alkoxy radical

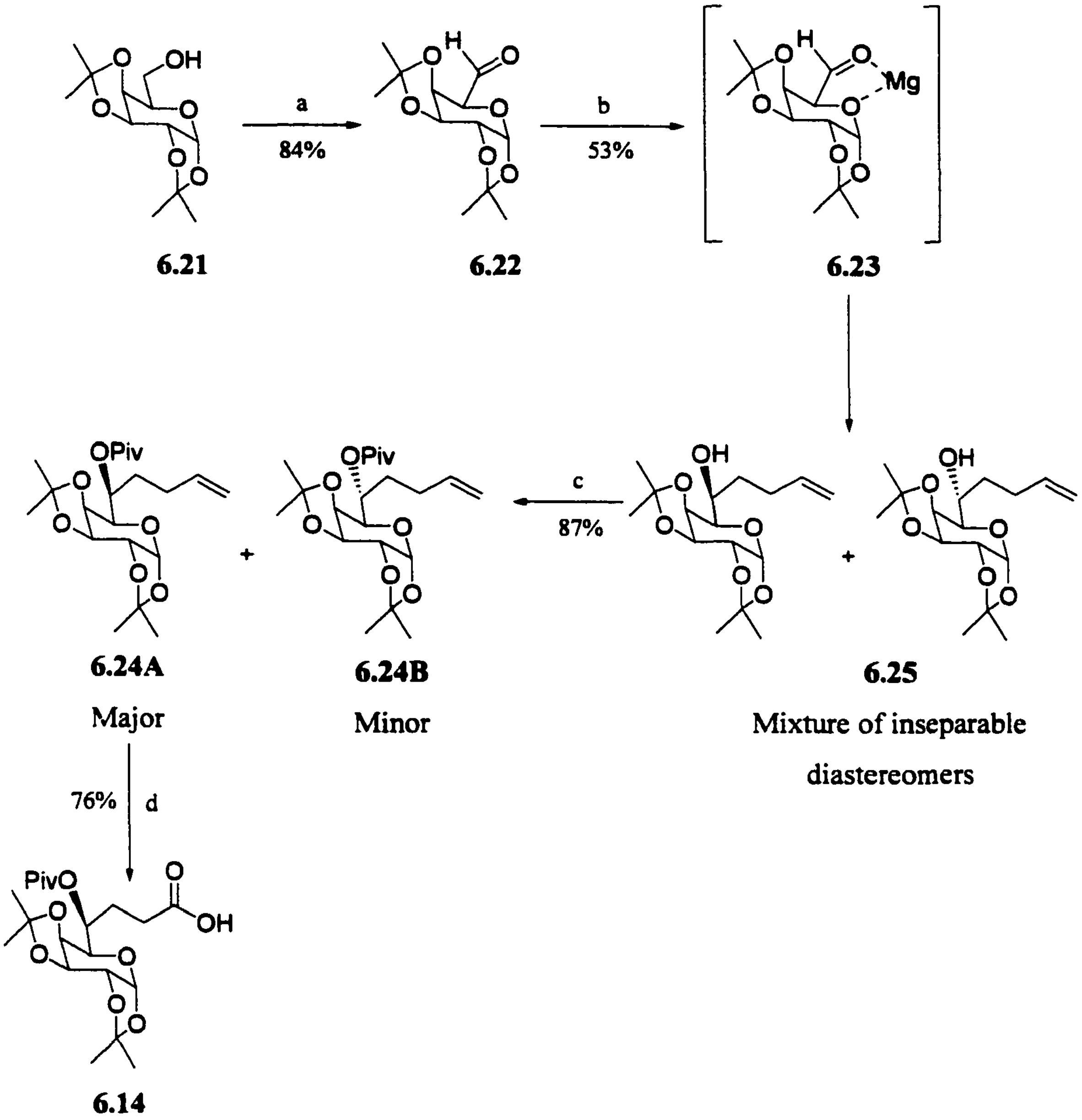


Scheme 6.3. (a) acetone, H_2SO_4, rt; (b) TBDPSCl, imidazole, DMF, rt; (c) DIB, I_2, cyclohexane, rt; (d) (1) PhSH, BF_3OEt_2, CH_2Cl_2, -78 °C; (2) NaOMe, MeOH, rt.

(**6.20** and **6.19**) derived from **6.17**. Acetal exchange on **6.18** with thiophenol and BF_3OEt_2 at low temperatures followed by hydrolysis of the formate ester with sodium methoxide yielded **6.4** (**Scheme 6.3**).

Synthesis of γ-protected hydroxy acid 6.14

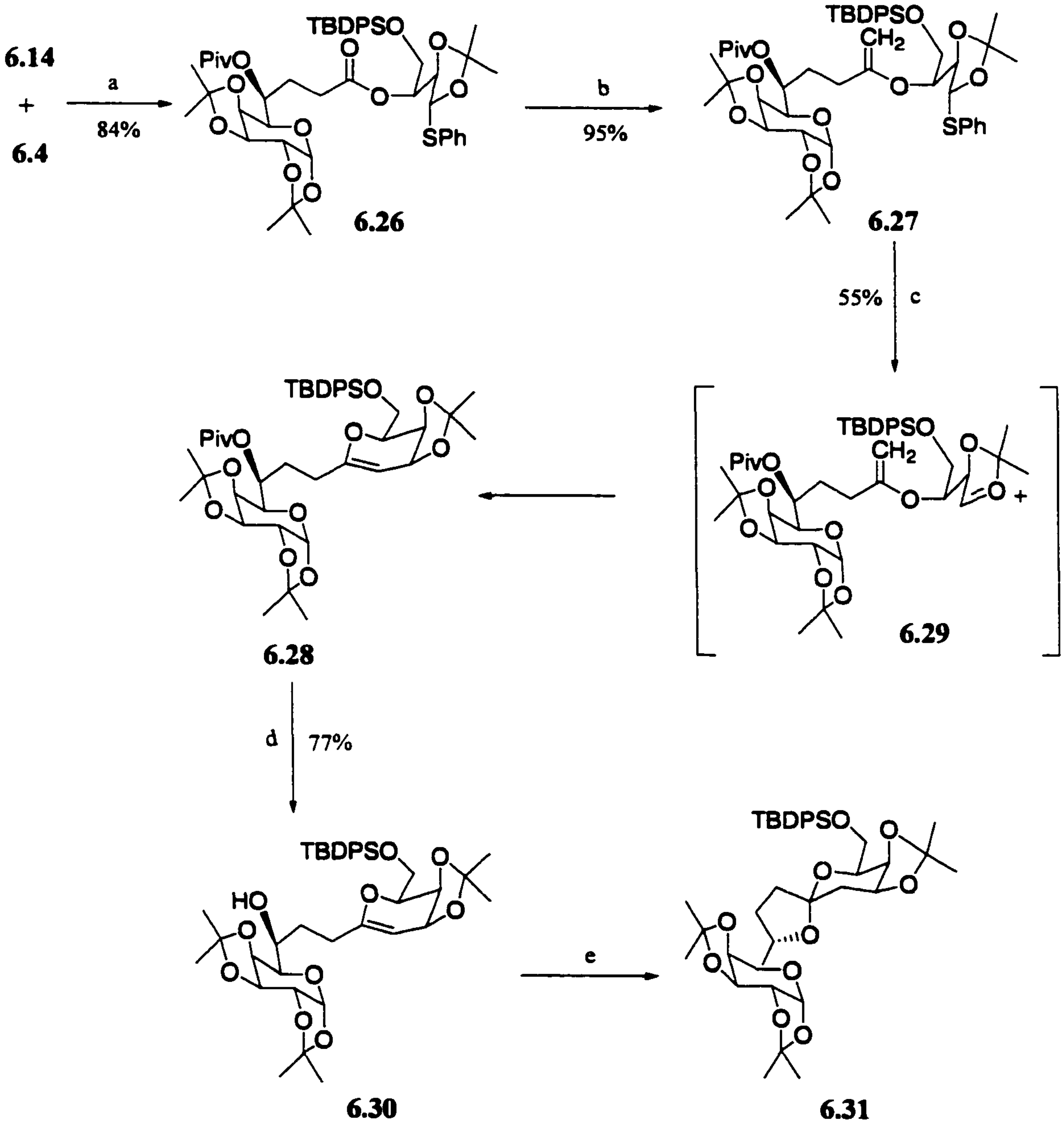
Readily available 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose **6.21** was efficiently converted to γ-pivaloxy carboxylic acid **6.14**. Swern oxidation of **6.21** afforded aldehyde **6.22** in 75% yield. Treatment of **6.22** with freshly prepared butenylmagnesium bromide afforded **6.25** as an inseparable mixture of diastereomers, in 53% yield. Pivaloylation of the resulting alcohol allowed the separation of the two diastereoisomers, which were tentatively assigned as **6.24A** and **6.24B**, with the former being the major one (3:1), with a combined yield of 87%. This assignment was based on the Cram chelate model as proposed by Danishefsky for the addition of allylmagnesium bromide to **6.22**.[31] In this model the metal is chelated between the aldehydo and ring oxygens **6.23**, thereby favoring nucleophilic attack from the β face of the sugar residue. There was some concern that the pivaloyl function would not be compatible to the methylenation conditions using Tebbe reagent. However, Sinay *et al* demonstrated that the Tebbe reagent would selectively methylenate less hindered esters in the presence of the bulky pivaloyl function.[66] Ozonolysis of **6.24A** followed by $NaClO_2$ oxidation of the resulting aldehyde afforded the γ-pivaloated hydroxy acid **6.14** in 76% yield over two steps (**Scheme 6.4**).



Scheme 6.4. (a) (COCl), DMSO, CH_2Cl_2, -78 °C; (b) butenylmagnesium bromide, THF; (c) Piv-Cl, pyridine, rt; (d) (1) O_3 then Ph_3P; (2) $NaClO_2$, CH_3CN.

Synthesis of Spiroketal

The esterification of **6.4** and **6.14** in the presence of DCC and catalytic amounts of DMAP and CSA afforded the ester **6.26** in 84% yield (**Scheme 6.5**).[42] Methylenation of the ester **6.26** with Tebbe reagent[67] afforded the acyclic enol ether **6.27** as a single compound, in 95% yield. Confirmation for the selective methylenation of the ester



Scheme 6.5. (a) DCC, cat. DMAP, cat. CSA, benzene; (b) Tebbe reagent, pyridine, THF/toluene; (c) MeOTf, DTBMP, CH_2Cl_2, 4Å MS, rt; (d) DIBAL-H, CH_2Cl_2, -78 °C to rt; (e) $CDCl_3$.

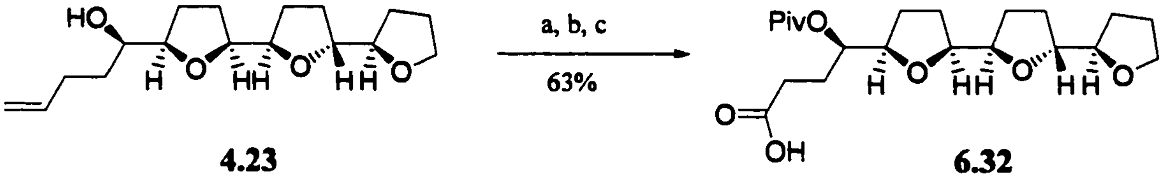
function was obtained from the carbon spectrum. The appearance of signals at δ 162.5 and δ 82.8 indicative of the enol ether were observed, while the carbon signals for the pivaloyl function remained unchanged (δ 176.9, δ 39.4, δ 27.9). Enol ether **6.27** was subjected to the standard cyclization conditions of methyl triflate, 2,6-*tert*-butyl-4-methyl pyridine, 4Å molecular sieves and CH_2Cl_2 to afford the C1-substituted glycal **6.28** in 55% yield.[61] The formation of isomers containing the *trans*-isopropylidene or the exocyclic alkene was not observed. Entropy and ring strain effects of the oxocarbenium ion **6.29** in the cyclization step as well as regioselective deprotonation of the glycosyl cation derived from **6.29** favor the preferential formation of **6.28** (**Scheme 6.5**).[61]

Removal of the pivaloyl-protecting group in **6.28** with diisobutylaluminium hydride afforded the alcohol **6.30** in 77% yield.[68] The ^1H and ^{13}C NMR spectrum of **6.30** in deuterated benzene gave signals, which were consistent for the alcohol. When the alcohol **6.30** was dissolved in $CDCl_3$, cyclization to the spiroketal **6.31** occurred to afford a single compound, in quantitative yield (**Scheme 6.5**). Confirmation for the formation of the spiroketal subunit was provided by signals observed in the ^{13}C NMR. The presence of the carbon signal at δ 106.9 provided key evidence for the presence of the ketal carbon of the spiroketal moiety **6.31**. Further corroboration for the structure **6.31** was provided by analysis of the ^1H, ^{13}C NMR, IR and mass spectrometry.

In the absence of any supporting NMR data the configuration of the spiroketal was assumed to be R or S on the basis of the anomeric effect.[12]

Application of Spiroketal Methodology to Kijimicin Analogs

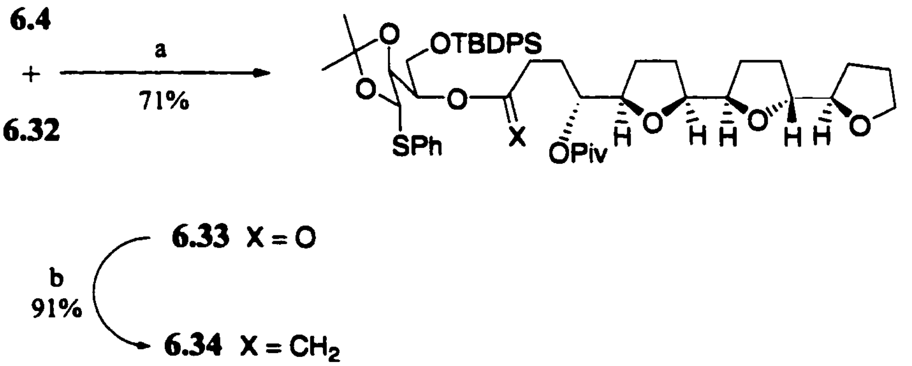
This protocol was next applied to the analog of kijimicin **6.12**. The previously prepared tris-THF hydroxy alkene **4.23** was converted to γ-pivaloxy carboxylic acid **6.32** (63%) following the three-step procedure as used for alkene **4.23** (**Scheme 6.6**).



4.23 **6.32**

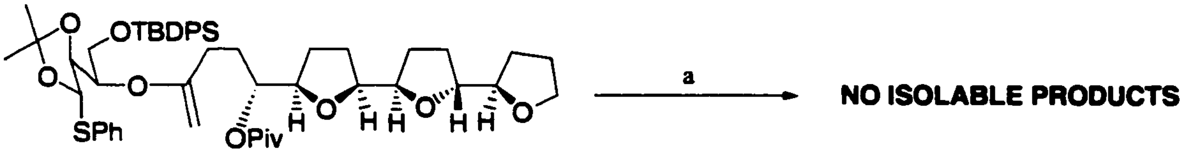
Scheme 6.6. (a) Piv-Cl, pyridine; (b) O_3 then Ph_3P; (c) $NaClO_2$, CH_3CN.

Esterification between **6.4** and **6.32** under previously described conditions (DCC, DMAP, CSA, benzene) gave the ester **6.33** in 71% yield.[42] Methylenation of the carbonyl function of the ester with Tebbe reagent afforded the enol ether **6.34** as a single compound, in 91% yield (**Scheme 6.7**).[67]



Scheme 6.7. (a) DCC, cat. DMAP, cat. CSA, benzene; (b) Tebbe reagent, pyridine, THF, toluene

The cyclization reaction was next attempted. The enol ether **6.34** was subjected to the standard cyclization conditions (MeOTf, DTBMP, 4Å MS, CH_2Cl_2) (**Scheme 6.8**).[61]



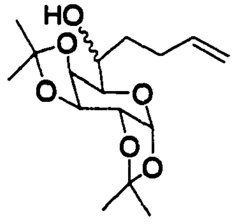
6.34

Scheme 6.8. (a) MeOTf, DTBMP, 4Å MS, CH_2Cl_2, rt.

TLC of the reaction mixture showed consumption of the starting material and formation of an indistinguishable mixture of several compounds.

In summary, the synthesis of spiroketal **6.31** is a proof of concept. An attractive feature of this strategy is its convergency, in which two complex segments are joined together via a simple esterification. However, to our disappointment the attempted synthesis of the kijimicin analog **6.12** was unsuccessful. This is somewhat surprising because the preparation of other complex glycals by this methodology was met with great success.[60-64]

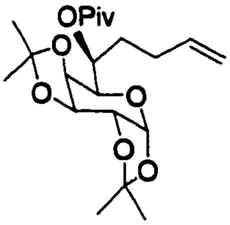
6.3 EXPERIMENTAL



6.25

γ-Hydroxy alkene 6.25. DMSO (3.2 mL, 44.4 mmol) was slowly added at –78 °C, to a mixture of oxalyl chloride (2.4 mL, 27.8 mmol) and anhydrous CH_2Cl_2 (15 mL). The reaction mixture was stirred at this temperature for 20 min, at which time a solution of 1,2:3,4-di-*O*-isopropylidene-D-galactose **6.21** (2.9 g, 11.1 mmol) in CH_2Cl_2 (25 mL) was slowly introduced. Stirring was continued at this temperature for an additional 20 min, and then Et_3N (15.5 mL, 111.0 mmol) added to the solution. The reaction mixture was warmed to rt, then diluted with ether (100 mL). The resulting suspension was washed with saturated $NaHCO_3$ (50 mL), and the aqueous layer was extracted with ether (3 x 25 mL). The combined organic phase was washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. FCC of the residue afforded the aldehyde **6.22** (2.4 g, 84%).

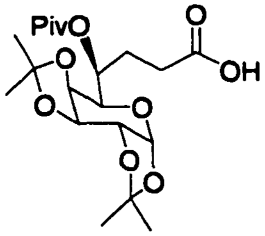
To a dry flask containing magnesium metal (0.727 g, 30.3 mmol) was added a solution of 4-bromo but-1-ene (3.1 mL, 30.3 mmol) in THF (30 mL), dropwise with vigorous agitation. The resultant solution was then added dropwise to a mixture of the aldehyde **6.22** (2.6 g, 10.1 mmol) and THF (30 mL) at –78 °C, warmed to rt and stirred for an additional 1 h. The reaction mixture was then poured into an ice cold saturated aqueous solution NH_4Cl (100 mL). The resulting slurry was extracted with EtOAc (3 x 50 mL) and the combined extract was dried (Na_2SO_4), filtered and concentrated *in vacuo*. FCC of the residue gave **6.25** (1.7 g, 53%) as a mixture of inseparable diastereomers. ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.35 (s, 3H), 1.45 (s, 3H), 1.50 (s, 3H), 1.85 (m, 1H), 2.25 (m, 3H), 3.55 (d, J= 8 Hz, 1H), 3.80 (m, 1H), 4.30 (m, 1H), 4.45 (d, J= 7 Hz, 1H), 4.60 (d, J= 7 Hz, 1H), 5.00 (m, 2H), 5.55 (d, J= 7 Hz, 1H), 5.75 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 25.3, 26.3, 26.3, 30.1, 33.5, 70.0, 70.7, 71.0, 71.3, 96.7, 108.7, 109.5, 115.0, 138.7.



6.24A

(*S*)-γ-Pivaloxy alkene 6.24A. To a solution of **6.25** (1.66 g, 5.28 mmol) in dry pyridine (20 mL) was added at rt, pivaloyl chloride (1.3 mL, 10.6 mmol) and catalytic amount of DMAP (0.194 g, 1.58 mmol). After 48 h at rt the reaction was filtered through a Celite pad and concentrated under reduced pressure. FCC of the residue afforded **6.24A** and **6.24B** in a 3:1 mixture (1.8 g, 87%). For **6.24A**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 9H), 1.25 (s, 3H), 1.30 (s, 3H), 1.40 (s, 3H), 1.50 (s, 3H), 1.70 (m, 1H), 2.05 (m, 3H), 3.80 (d, J= 8 Hz, 1H), 4.20 (d, J= 8 Hz, 1H), 4.30 (m, 1H), 4.55 (d, J= 8 Hz, 1H), 5.00 (m, 3H), 5.50 (d, J= 7 Hz, 1H), 5.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

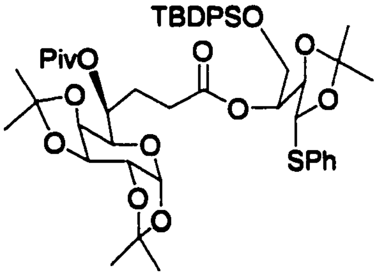
24.6, 25.2, 26.2, 26.3, 27.4, 29.0, 30.4, 38.1, 68.5, 70.9, 71.0, 71.5, 96.6, 108.6, 109.4, 114.7, 138.5, 177.1.



6.14

(S)-γ-Pivaloxy Acid 6.14. Compound **6.24A** (1.37 g, 3.44 mmol) was dissolved in a 4:1 mixture of $CHCl_3$: MeOH (20 mL). O_3 was bubbled until TLC indicated the complete disappearance of the starting material. MeOH (15 mL) and triphenylphosphine (550 mg) were added, and stirring continued for 1 h. The solution was then concentrated *in vacuo* and the residue was purified by flash column chromatography (FCC) to yield the aldehyde (1.1 g, 81%), as a viscous oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.15 (s, 3H), 1.20 (s, 3H), 1.30 (s, 3H), 1.40 (s, 3H), 1.90 (m, 1H), 2.15 (m, 1H), 2.40 (t, J= 8 Hz, 2H), 3.70 (d, J= 8 Hz, 1H), 4.15 (d, J= 8 Hz, 1H), 4.21 (m, 1H), 4.50 (d, J= 8 Hz, 1H), 4.95 (m, 1H), 5.45 (d, J= 5 Hz, 1H), 9.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 24.4, 24.9, 26.0, 26.2, 27.2, 38.9, 39.4, 68.3, 70.6, 70.8, 70.9, 96.4, 108.6, 109.3, 177.0, 201.5.

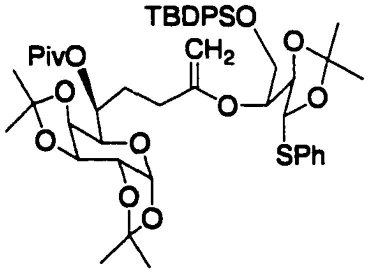
To a mixture of the aldehyde (1.11 g, 2.77 mmol) and $NaH_2PO_4.H_2O$ (3.8 g, 27.7 mmol) in 5:1 mixture of $CH_3CN:H_2O$ (35 mL) were successively added a 30% H_2O_2 solution (0.2 mL, 5.5 mmol) and an aqueous solution of $NaClO_2$ (0.501 g, 5.54 mmol) at 0-5 °C. The reaction mixture was then warmed to room temperature and stirred for 1 h or until TLC indicated complete disappearance of the starting material. Na_2SO_3 (sat. aq.) was then added and the mixture was extracted with EtOAc. The combined extract was successively washed with H_2O and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was filtered through a short column of silica gel to yield a viscous oil **6.14** (1.1 g, 94%). IR (neat) 2965, 1714 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 1.15 (s, 9H,), 1.25 (s, 3H), 1.30 (s, 3H), 1.40 (s, 3H), 1.50 (s, 3H), 1.95 (m, 1H), 2.20 (m, 1H), 2.40 (t, J= 8 Hz, 2H), 3.75 (d, J= 6 Hz, 1H), 4.20 (dd, J= 6, 1 Hz, 1H), 4.30 (m, 1H), 4.55 (dd, J= 6, 1 Hz, 1H), 5.00 (m, 1H), 5.50 (d, J= 5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 25.1, 26.1, 26.1, 26.2, 27.3, 29.6, 39.0, 68.2, 70.8, 70.9, 70.9, 96.5, 108.7, 109.5, 177.2, 179.1. MS (ES, *m/z*) 434 $(M+NH_4)^+$.



6.26

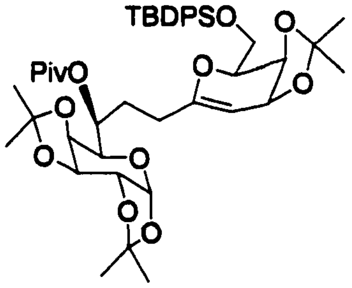
Thioacetal ester 6.26. A stirred solution of known alcohol **6.4**[61] (0.683 g, 1.34 mmol), acid **6.14** (0.466 mg, 1.12 mmol), DMAP (41 mg, 0.34 mmol) and camphorsulfonic acid (78 mg, 0.34 mmol) in anhydrous benzene at 0-5 °C was treated with DCC (347 mg, 1.68 mmol). After stirring for 3 h at room temperature, diethyl ether (20 mL) was added and the mixture was filtered through Celite. Concentration of the filtrate and FCC of the residue (silica, 95:4:1 $CHCl_3$: petroleum ether: EtOAc) gave ester

(856 mg, 85%) as viscous oil. IR (neat) 1727 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.15 (s, 9H), 1.25 (s, 3H), 1.30 (s, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 1.46 (s, 3H), 1.50 (s, 3H), 2.00 (m, 1H), 2.20 (m, 1H), 2.40 (m, 2H), 3.80 (m, 3H), 4.20 (d, J= 6 Hz, 1H), 4.30 (m, 1H), 4.45 (m, 1H), 4.60 (m, 1H), 5.00 (m, 1H), 5.20 (m, 1H), 5.30 (d, J= 7 Hz, 1H), 5.50 (d, J= 5 Hz, 1H), 7.25 (m, 3H), 7.35 (m, 6H), 7.55 (m, 2H), 7.65 (d, J= 8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 24.5, 25.1, 26.1, 26.3, 26.4, 26.5, 27.3, 27.4, 30.0, 39.0, 62.4, 68.5, 70.8, 70.8, 70.9, 71.7, 79.3, 85.2, 96.5, 108.6, 109.4, 111.7, 127.7, 127.8, 127.8, 129.0, 129.8, 132.5, 133.1, 133.2, 133.7, 135.6, 135.7, 172.4, 177.1. MS (ES, *m/z*) 924 $(M+NH_4)^+$.



6.27

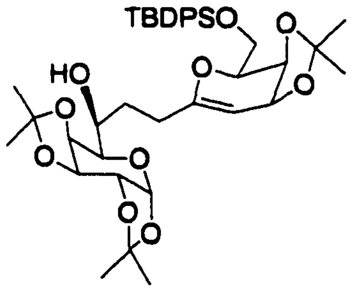
Thioacetal enol ether 6.27. To a solution of **6.26** (0.421 g, 0.465 mmol) in dry toluene (10 mL) were added 1.15 mL (0.575 mmol) of a 0.5 M solution of Tebbe reagent in toluene and pyridine (0.8 mL) at –78 °C under nitrogen. The mixture was stirred at room temperature for 90 min, then cooled to –78 °C, added drop-wise to ice-cold 15% sodium hydroxide solution (50 mL). The cold bath was removed and the mixture was diluted with ether and stirred for an additional 10 min. The solution was filtered through a Celite pad and the filter cake was washed with diethyl ether. The filtrate was then extracted with diethyl ether (15 mL x 3). The ethereal extract was dried (Na_2SO_4) and concentrated *in vacuo*. Using basic alumina, the residue was purified by FCC to afford **6.27** (396 mg, 95%) as a syrup. ^{1}H NMR (300 MHz, C_6D_6) δ 1.15 (s, 12H), 1.20 (s, 9H), 1.45 (s, 9H), 1.50 (s, 6H), 2.35 (m, 4H), 3.90 (m, 2H), 4.05 (m, 3H), 4.20 (m, 1H), 4.40 (m, 1H), 4.50 (m, 1H), 4.75 (m, 1H), 5.30 (m, 1H), 5.55 (d, J= 5 Hz, 1H), 5.75 (d, J= 7 Hz, 1H), 7.30-6.95 (m, 9H), 7.65 (d, J= 9 Hz, 2H), 7.75 (m, 4H); ^{13}C NMR (C_6D_6, 75 MHz) δ 19.9, 24.9, 25.4, 26.7, 26.7, 27.6, 27.9, 28.1, 29.5, 31.4, 39.4, 62.4, 69.1, 74.5, 71.8, 71.8, 72.1, 75.0, 81.0, 82.8, 85.5, 97.4, 108.8, 109.8, 112.0, 127.9, 128.5, 128.5, 129.6, 130.4, 130.5, 132.9, 133.9, 134.1, 135.1, 136.4, 162.5, 176.9. MS (ES, *m/z*) 927 $(M+Na)^+$. **6.27** was rather unstable and was used promptly in the next step.



6.28

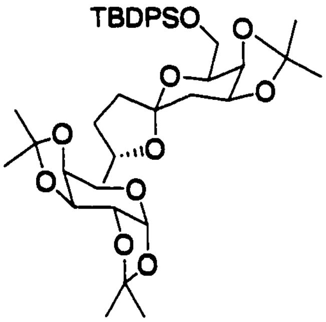
C-1 substituted glycal 6.28. To a solution of **6.27** (0.396 g, 0.438 mmol) in CH_2Cl_2 (15 mL) were added 2,6-di-*tert*-butyl-4-methyl pyridine (1.8 g, 8.8 mmol) and 4Å molecular sieves (500 mg). The mixture was stirred at room temperature for 15 min, then cooled to 0-5 °C, and methyl triflate (0.75 mL, 6.62 mmol) was added. The mixture was then allowed to warm up to room temperature and stirred for 24 h. Upon completion of the reaction, as indicated by TLC, triethylamine (2 mL) and saturated $NaHCO_3$

solution (10 mL) were added and the resulting mixture was extracted with diethyl ether (3 x 15 mL). The ethereal extract was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by FCC to yield **6.28** (191 mg, 55%) as an oil. R_f= 0.53 (10% EtOAc in petroleum ether); IR (neat) 1725, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.19 (s, 9H), 1.25 (s, 3H), 1.30 (s, 3H), 1.35 (s, 3H), 1.40 (s, 6H), 1.49 (s, 3H), 1.55-1.90 (m, 4H), 2.05 (m, 2H), 3.78 (m, 1H), 3.95 (m, 3H), 4.20 (m, 1H), 4.28 (m, 1H), 4.40 (m, 1H), 4.55 (m, 2H), 4.65 (m, 1H), 5.00 (m, 1H), 5.50 (d, J= 5 Hz, 1H), 7.35 (m, 6H), 7.65 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 24.6, 25.2, 26.2, 26.4, 27.1, 27.4, 28.4, 28.5, 29.4, 39.1, 63.2, 68.5, 70.1, 70.9, 71.0, 71.5, 71.7, 75.8, 96.6, 97.6, 108.6, 109.4, 110.0, 127.7, 127.8, 129.8, 133.6, 135.7, 156.0, 177.2. MS (ES, *m/z*) 812 $(M+NH_4)^+$.



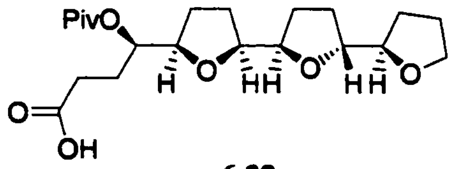
6.30

Hydroxy glycal 6.30. Compound **6.28** (0.088 g, 0.111 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to –78 °C. To this was added 0.4 mL (0.4 mmol) of 1 M solution of diisobutylaluminium hydride in hexane and stirred for 1 h at –78 °C. The mixture was warmed to room temperature, stirred for an additional 1 h, then poured into ice cold saturated solution of Rochell's salt and was extracted with ethyl acetate (3 x 5 mL). The organic extract was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by FCC to yield a viscous oil **6.30** (60 mg, 77%). R_f= 0.17 (10% EtOAc in petroleum ether); ^{1}H NMR (300 MHz, C_6D_6) δ 1.05 (s, 3H), 1.20 (s, 3H), 1.25 (s, 9H), 1.35 (s, 3H), 1.40 (s, 3H), 1.49 (s, 3H), 1.50 (s, 3H), 1.90 (m, 1H), 2.30 (m, 3H), 3.80 (d, J= 9 Hz, 1H), 3.95 (m, 1H), 4.20 (m, 5H), 4.45 (d, J= 6 Hz, 1H), 4.53 (m, 2H), 4.72 (m, 1H), 5.52 (d, J= 5 Hz, 1H), 7.25-7.35 (m, 6H), 8.05-7.80 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6) δ 20.1, 25.1, 25.4, 26.7, 26.8, 27.6, 27.7, 29.2, 30.9, 32.6, 64.5, 70.4, 71.1, 71.6, 71.8, 71.9, 72.5, 76.6, 97.3, 98.9, 108.8, 109.6, 110.5, 130.3, 134.4, 136.4, 156.7. MS (ES, *m/z*) 728 $(M+NH_4)^+$.



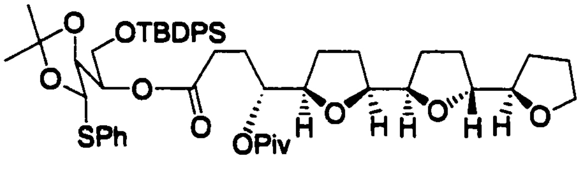
6.31

Spiroketal 6.31. Compound **6.30** (0.06 g, 0.084 mmol) was dissolved in $CDCl_3$ and stirred for 1 h. The solvent was removed *in vacuo* to afford an oil **6.31** in quantitative yield. R_f= 0.52 (10% EtOAc in petroleum ether); IR (neat) 1376, 1213 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.15 (s, 3H), 1.23 (s, 3H), 1.38 (s, 3H), 1.39 (s, 3H), 1.46 (s, 6H), 1.75-2.20 (m, 6H), 3.57 (d, J= 9 Hz, 1H), 3.65 (m, 1H), 3.91 (m, 2H), 4.26 (m, 3H), 4.39 (d, J= 6 Hz, 1H), 4.52 (m, 2H), 5.43 (d, J= 5 Hz, 1H), 7.36 (m, 6H), 7.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 24.9, 25.3, 25.3, 26.0, 26.2, 26.3, 27.1, 27.5, 28.3, 35.1, 39.6, 62.6, 69.9, 70.8, 71.1, 71.1, 71.3, 71.5, 71.6, 76.8, 96.5, 106.9, 108.7, 108.8, 109.4, 127.6, 127.8, 129.7, 135.6, 135.8. MS (ES, *m/z*) 728 $(M+NH_4)^+$.



6.32

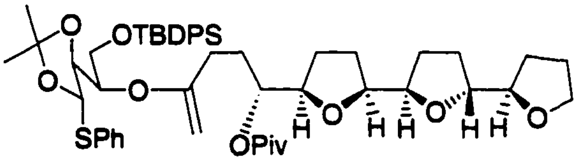
Tris-THF acid 6.32. Compound **4.23** (0.256 g, 0.865 mmol) was subjected to the same conditions as for **6.14** from **6.25** (pivaloylation, ozonolysis, $NaClO_2$ oxidation). FCC gave **6.32** (215.5 mg, 63%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 9H,), 1.60 (m, 3H), 1.85 (m, 11H), 2.35 (t, J= 7 Hz, 2H), 4.00-3.65 (m, 7H), 4.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 26.4, 27.3, 27.5, 28.4, 28.7, 28.7, 29.1, 30.2, 39.2, 68.6, 73.9, 80.1, 81.9, 82.1, 177.8, 178.1. MS (ES, *m/z*) 416 $(M+NH_4)^+$.



6.33

Tris-THF ester 6.33. Compounds **6.4** (0.279 g, 0.549 mmol) and **6.32** (0.184 g, 0.5 462 mmol) were subjected to the same esterification conditions as for **6.26**. FCC gave **6.33** (291.9 mg, 71%). R_f= 0.41 (20% EtOAc in petroleum ether); ^1H NMR (300

MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.20 (s, 9H), 1.45 (s, 3H), 1.50 (s, 3H), 1.55-2.10 (m, 14H), 2.35 (m, 2H), 3.80 (m, 9H), 4.35 (m, 1H), 4.85 (m, 1H), 5.20 (m, 1H), 5.30 (d, J= 7 Hz, 1H), 7.25 (m, 4H), 7.35 (m, 5H), 7.45 (m, 2H), 7.65 (d, J= 8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 26.1, 26.5, 27.0, 27.3, 27.5, 28.4, 28.7, 28.8, 29.3, 30.6, 34.2, 39.1, 62.5, 68.6, 72.1, 73.6, 79.3, 80.0, 81.6, 81.9, 82.2, 85.4, 111.9, 127.7, 127.8, 127.8, 129.1, 129.9, 132.4, 133.1, 133.2, 133.8, 135.6, 135.7, 172.2, 177.8. MS (ES, *m/z*) 906 $(M+NH_4)^+$.

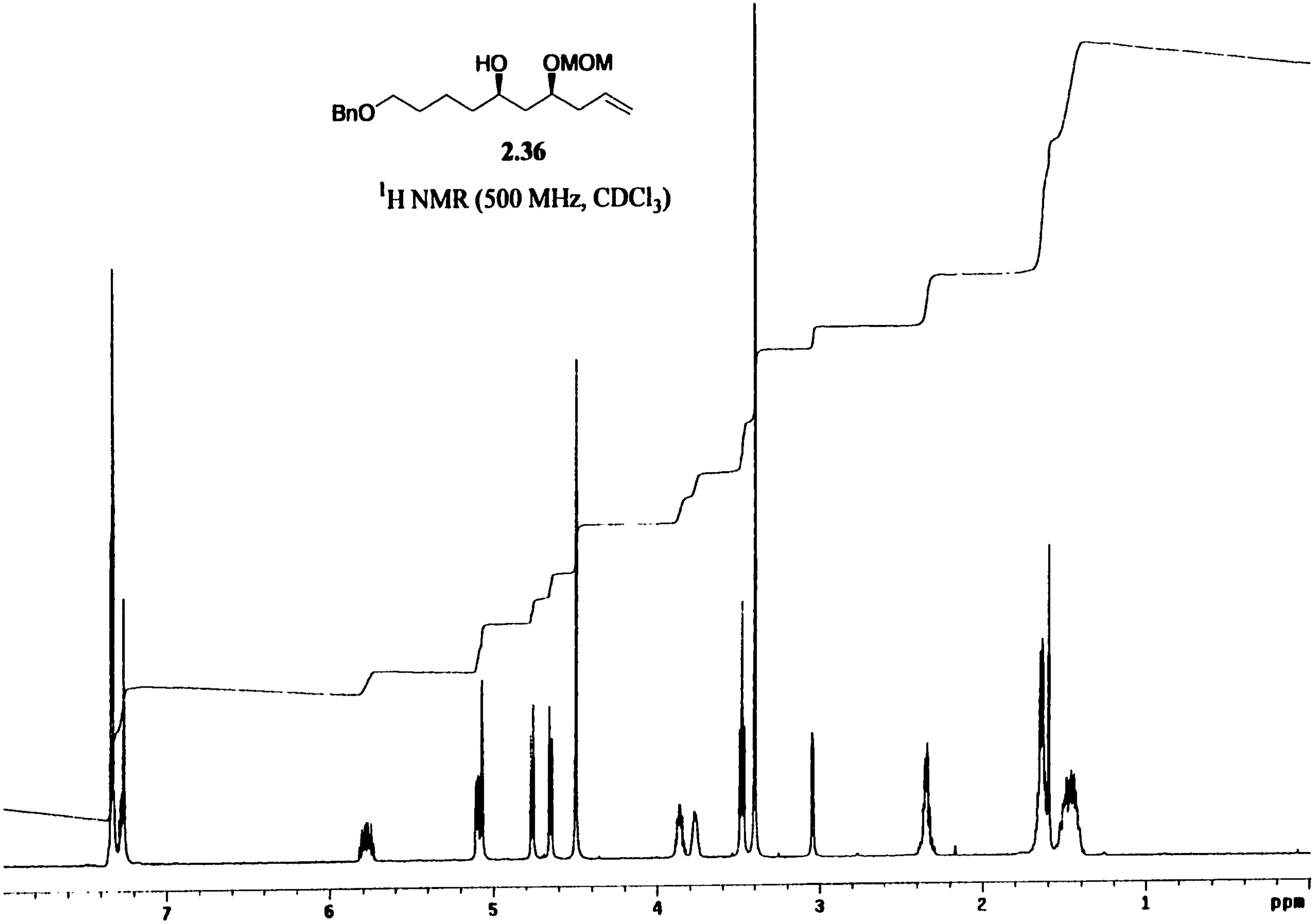


6.34

Tris-THF enol ether 6.34. Methylenation of the ester **5.33** (0.184 mg, 0.207 mmol) was carried out following the same conditions as for **6.27**. FCC gave **6.34** (168 mg, 91%). ^1H NMR (300 MHz, C_6D_6) δ 1.20 (s, 9H), 1.25 (s, 9H), 1.50 (s, 3H), 1.55 (s, 3H), 1.45-2.05 (m, 14H), 2.25 (m, 2H), 3.65 (m, 1H), 3.80 (m, 4H), 3.95 (m, 4H), 4.15 (m, 2H), 4.45 (m, 1H), 4.75 (m, 1H), 5.05 (m, 1H), 5.80 (d, J= 7 Hz, 1H), 7.05 (dd, J= 8 Hz, 1H), 7.10 (dd, J= 8Hz, 2H), 7.20 (br s, 2H), 7.25 (m, 5H), 7.65 (d, J= 8 Hz, 2H), 7.80 (m, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 19.9, 26.9, 27.0, 27.6, 27.8, 28.0, 28.7, 29.0, 29.8, 30.0, 30.1, 32.3, 39.4, 62.5, 68.8, 74.7, 75.3, 80.9, 81.0, 81.8, 82.1, 82.4, 82.7, 83.2, 85.8, 112.2, 127.9, 128.2, 128.5, 128.5, 129.6, 130.4, 130.5, 132.6, 133.87, 134.04, 135.3, 136.4, 162.0, 177.6. MS (ES, *m/z*) 904 $(M+NH_4)^+$.

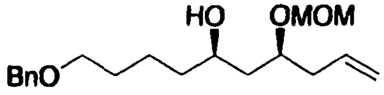
Attempted cyclization of 5.34. Enol ether **6.34** (0.207 g, 0.234 mmol), 2,6-di-tert-butyl-4-methylpyridine (0.449 g, 2.19 mmol), and freshly activated, powered 4Å molecular sieves (400 mg) in anhydrous CH_2Cl_2 (4 mL), was stirred for 15 min, at rt, under an argon atmosphere, then cooled to 0 °C. Methyl triflate (0.15 mL, 1.32 mmol) was then introduced and the mixture was warmed to rt and stirred for 4 h. Monitoring of the reaction by TLC showed an indistinguishable mixture of several compounds.

APPENDIX



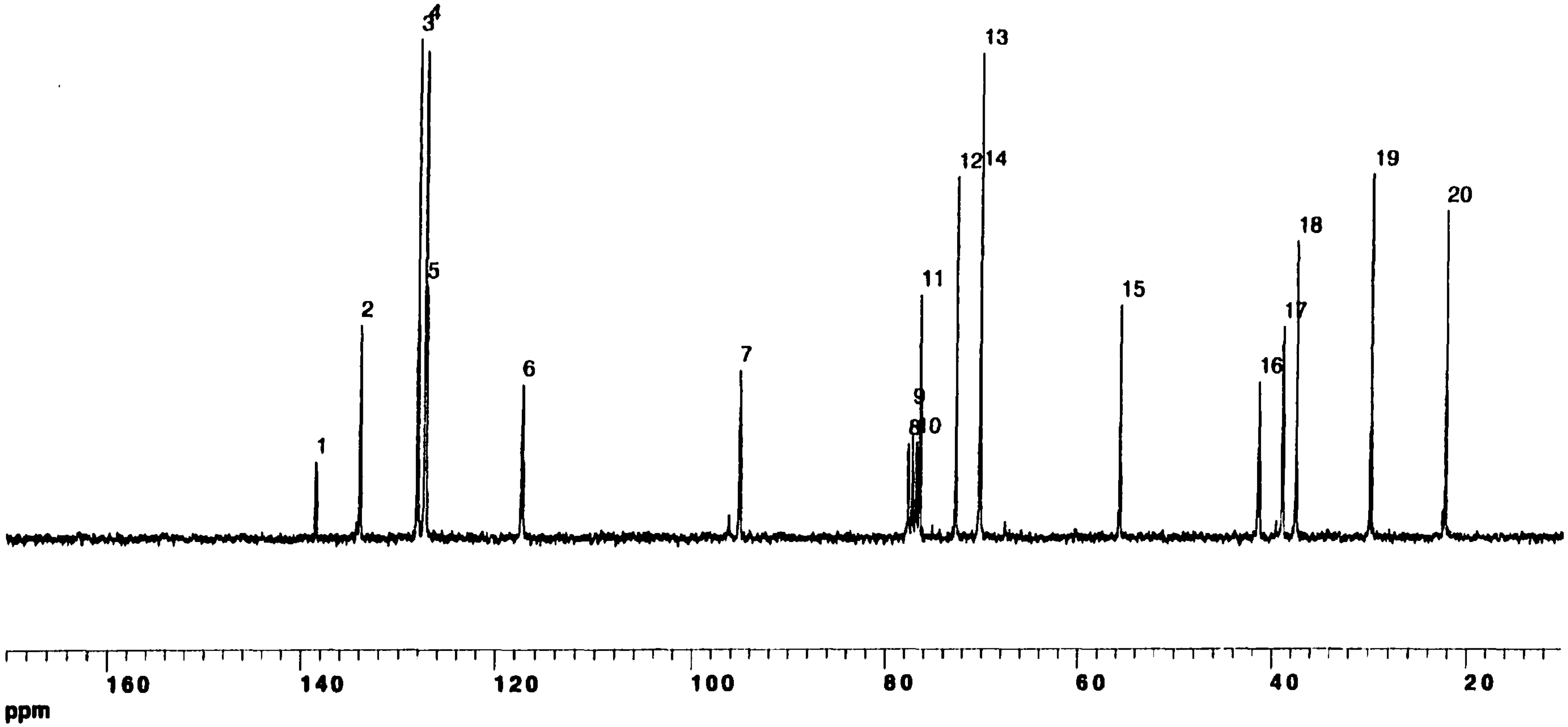
2.36

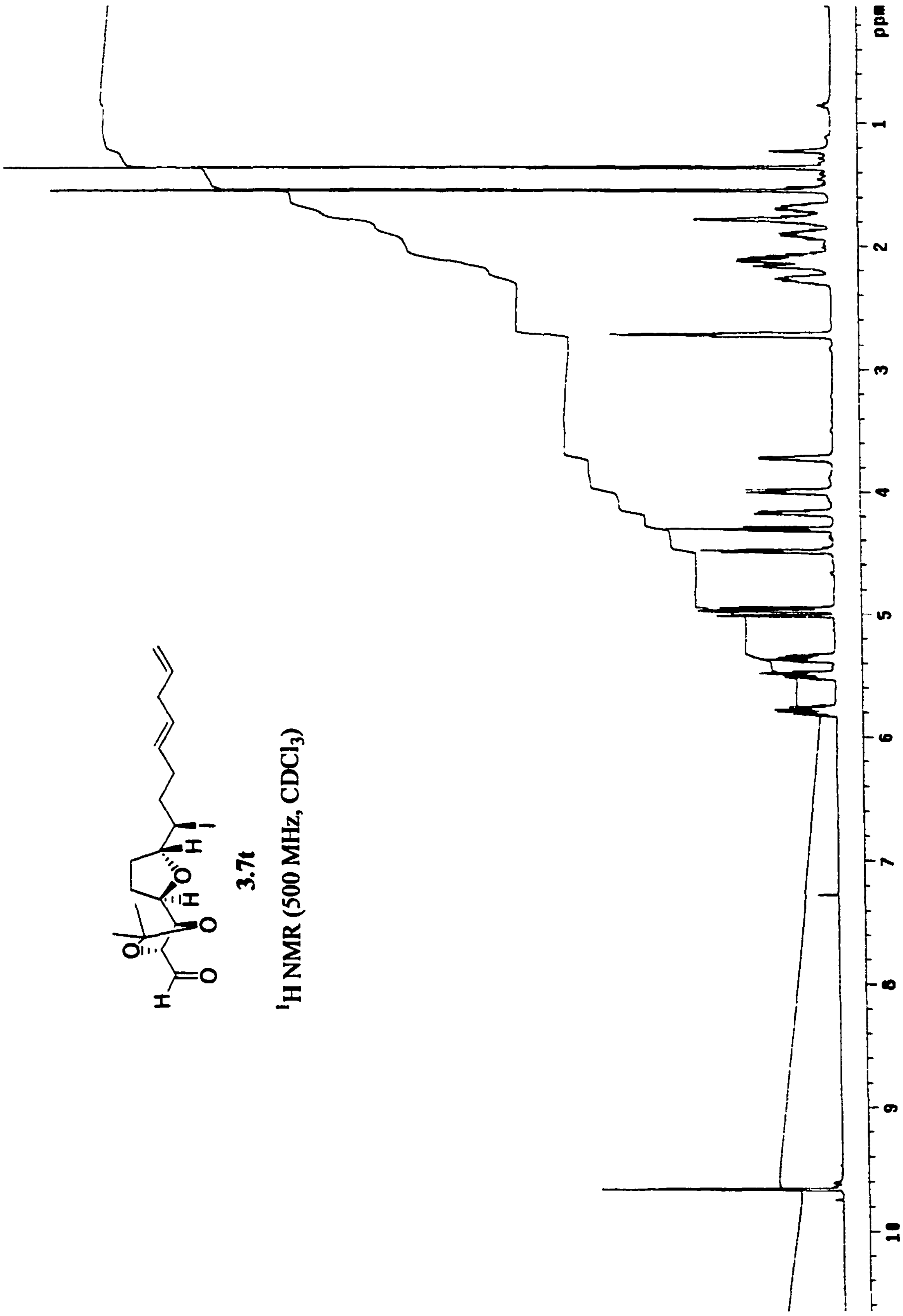
^{1}H NMR (500 MHz, $CDCl_3$)



2.36

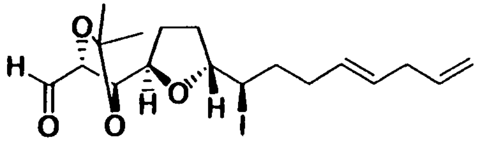
^{13}C NMR (75 MHz, CDCl$_3$)





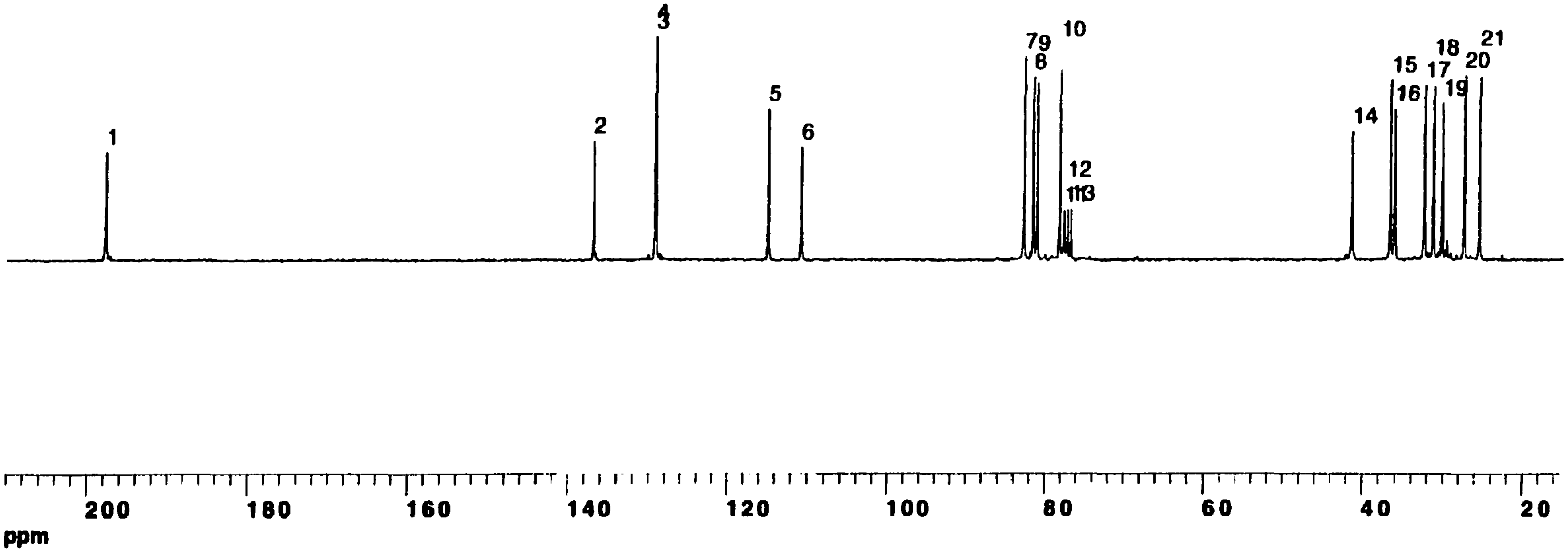
3.7t

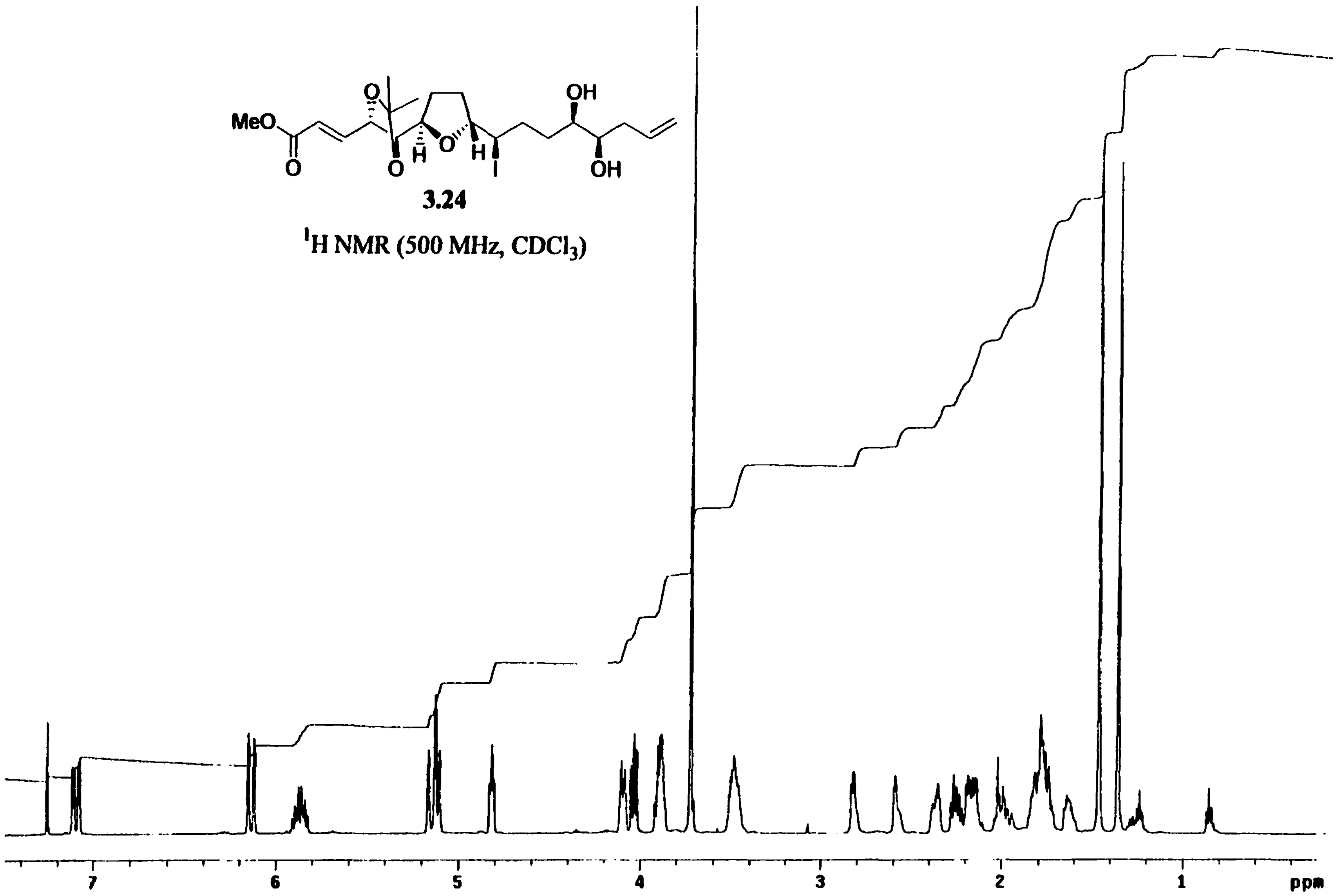
^{1}H NMR (500 MHz, CDCl$_3$)



3.7t

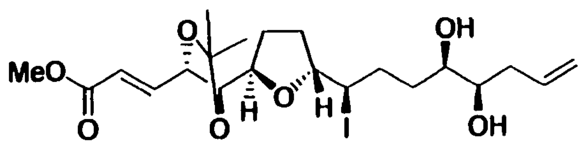
^{13}C NMR (75 MHz, CDCl$_3$)





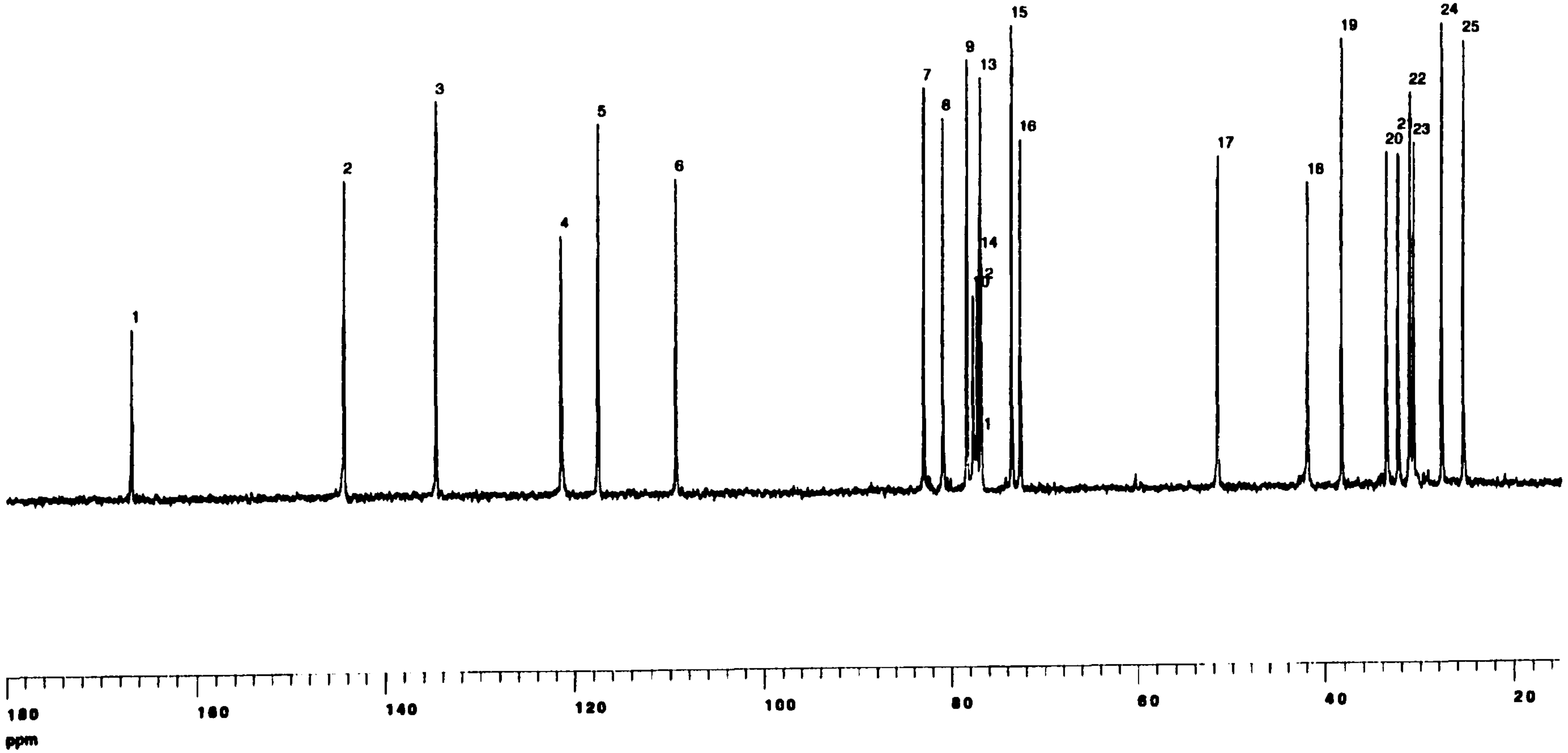
3.24

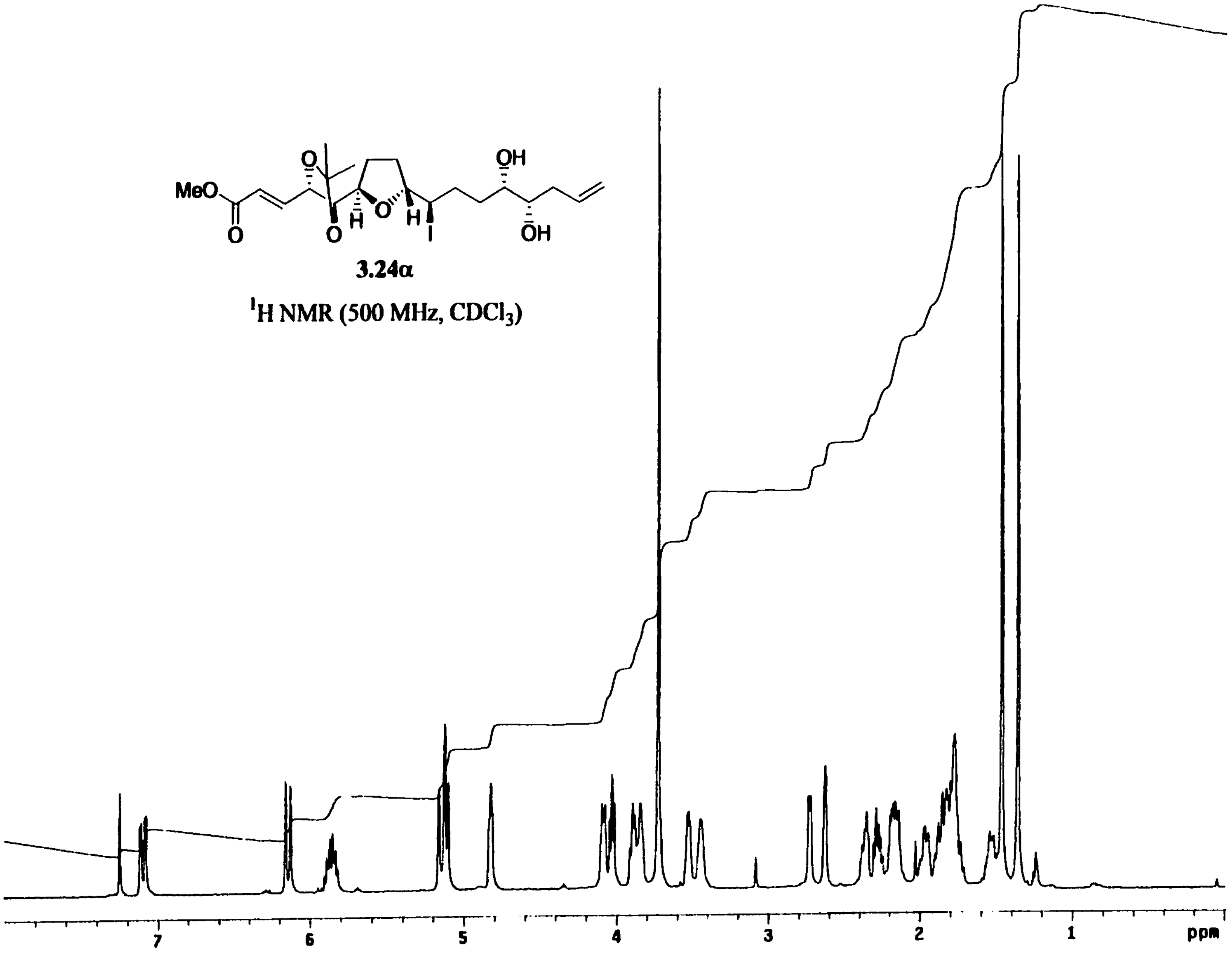
^{1}H NMR (500 MHz, $CDCl_3$)



3.24

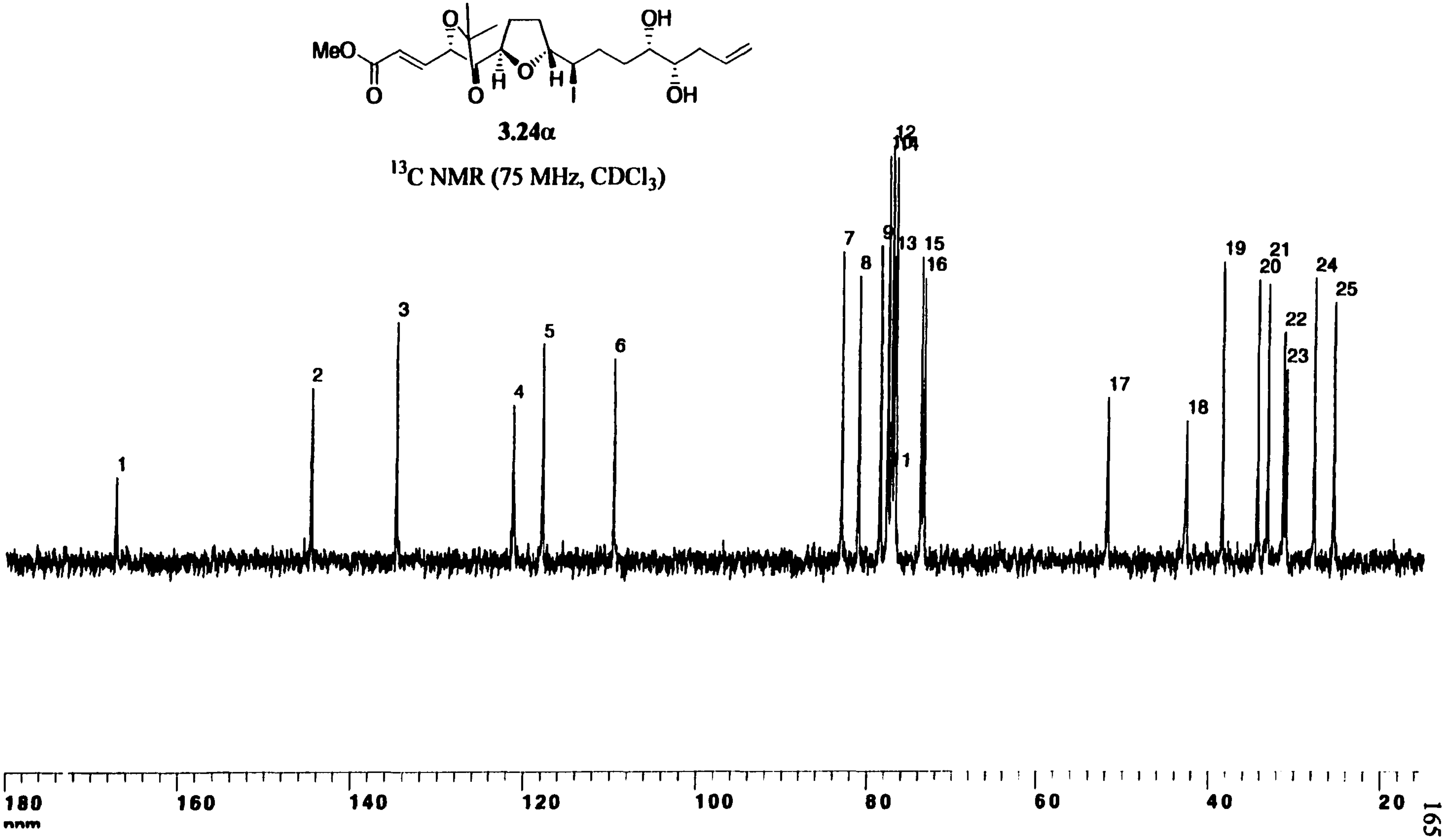
^{13}C NMR (75 MHz, CDCl$_3$)





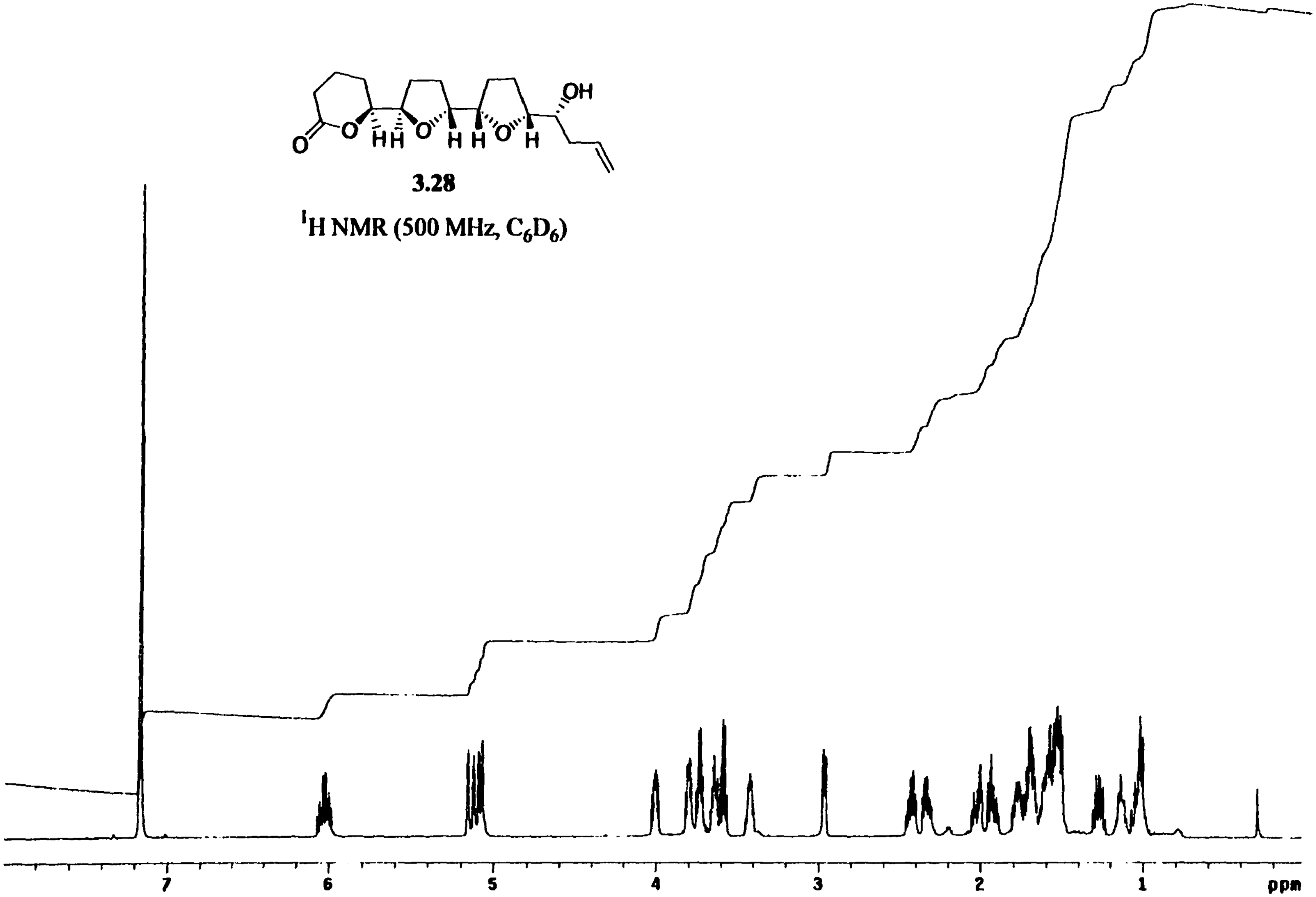
3.24α

^{1}H NMR (500 MHz, $CDCl_3$)



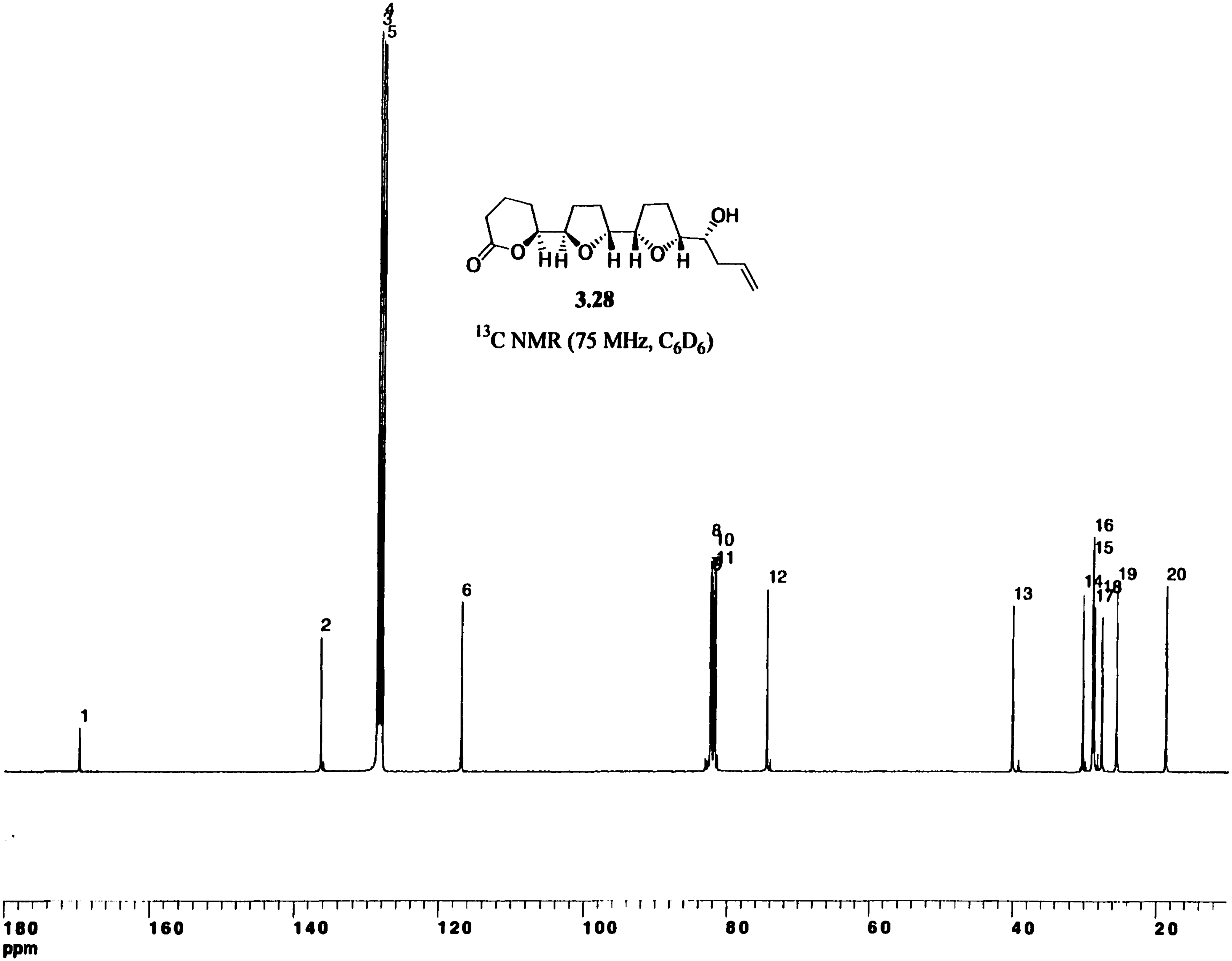
3.24α

^{13}C NMR (75 MHz, $CDCl_3$)



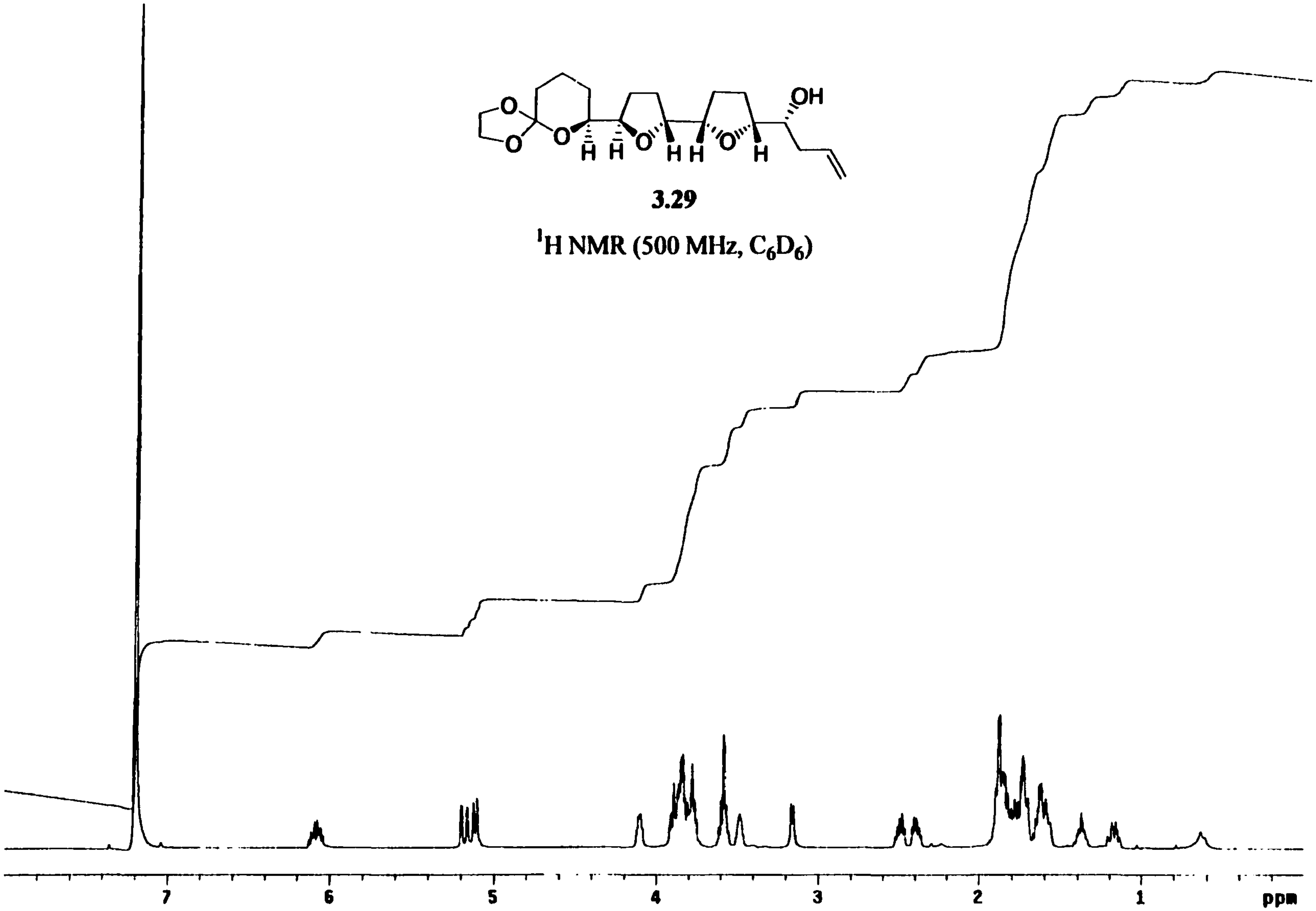
3.28

^{1}H NMR (500 MHz, C_6D_6)



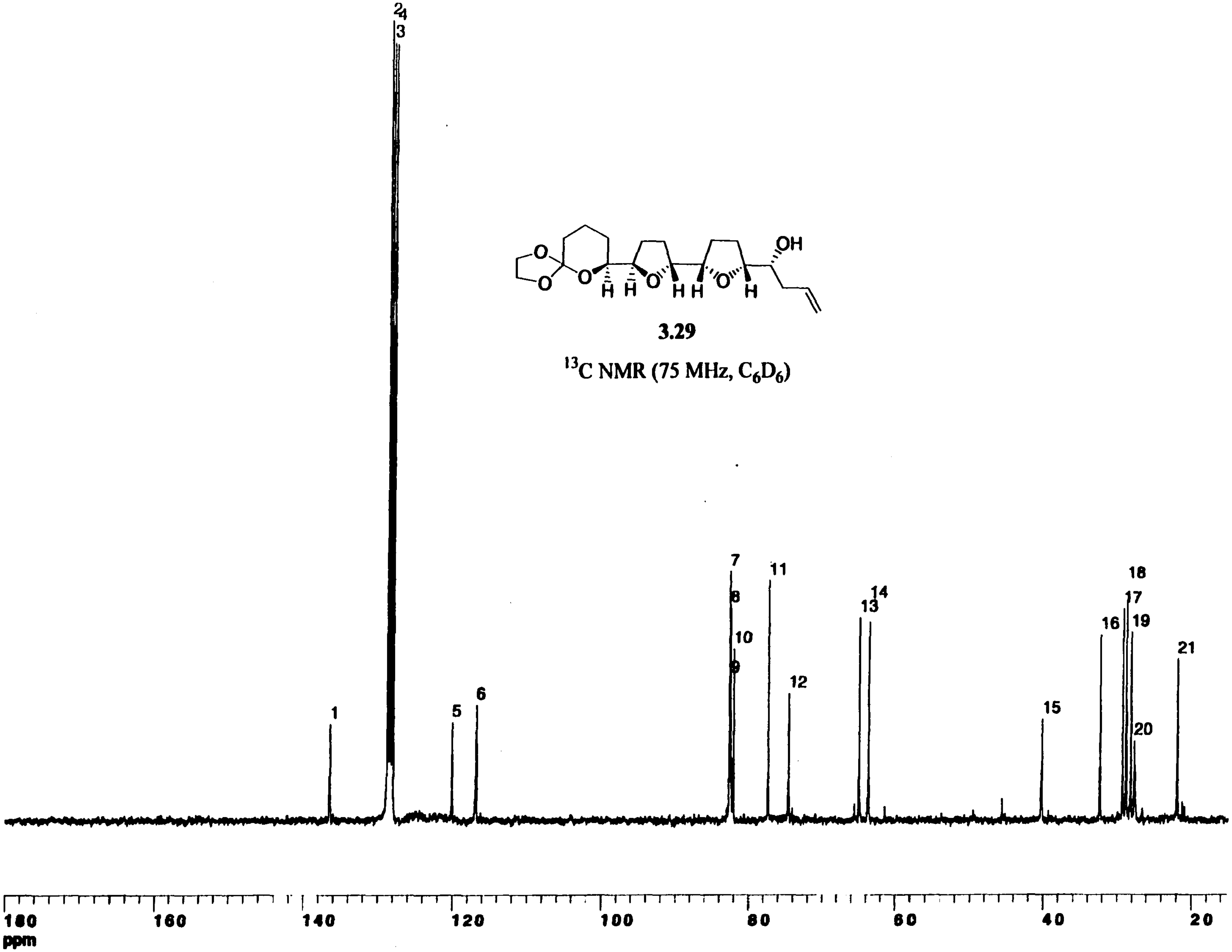
3.28

^{13}C NMR (75 MHz, C_6D_6)



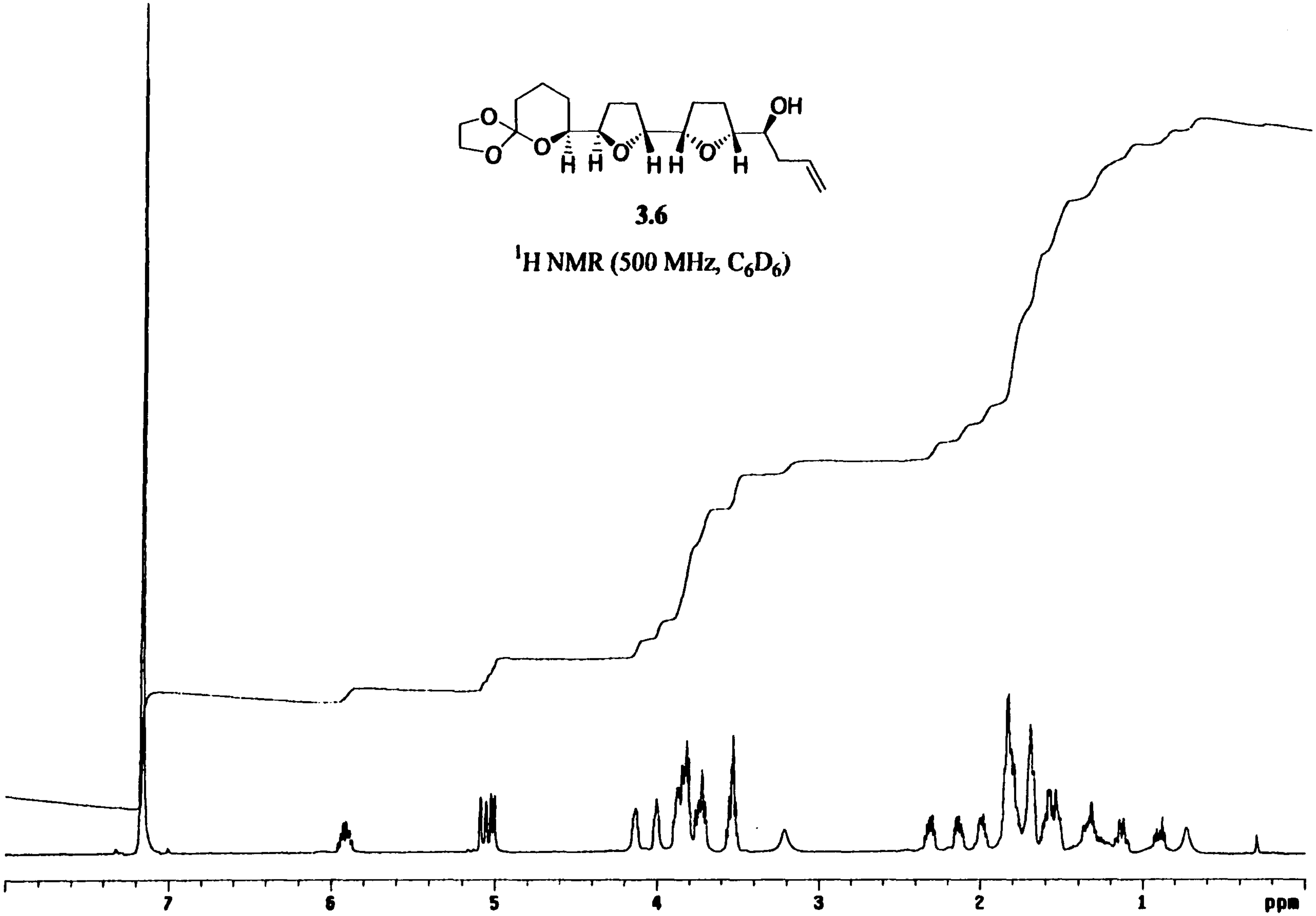
3.29

^{1}H NMR (500 MHz, C_6D_6)



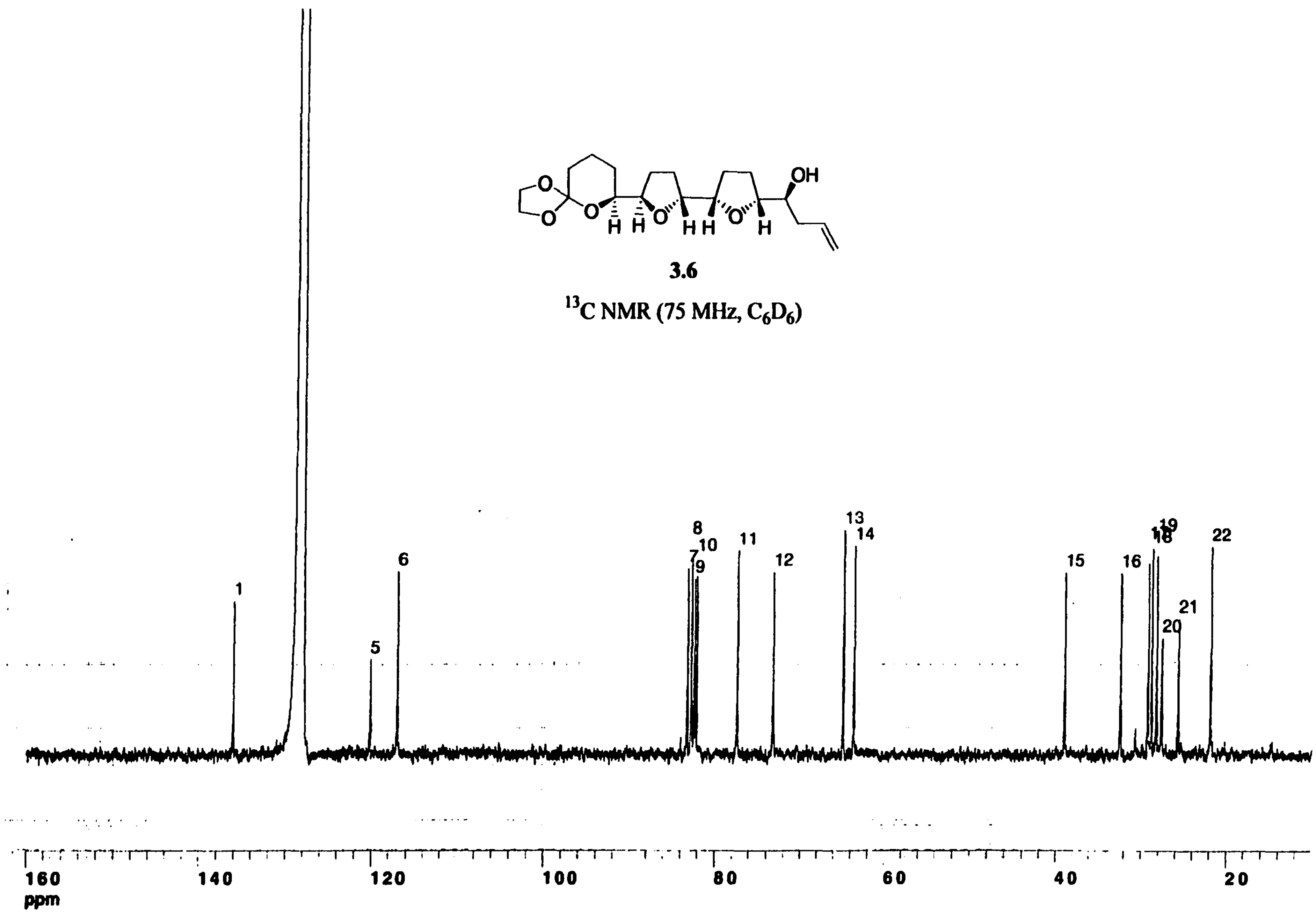
3.29

^{13}C NMR (75 MHz, C_6D_6)



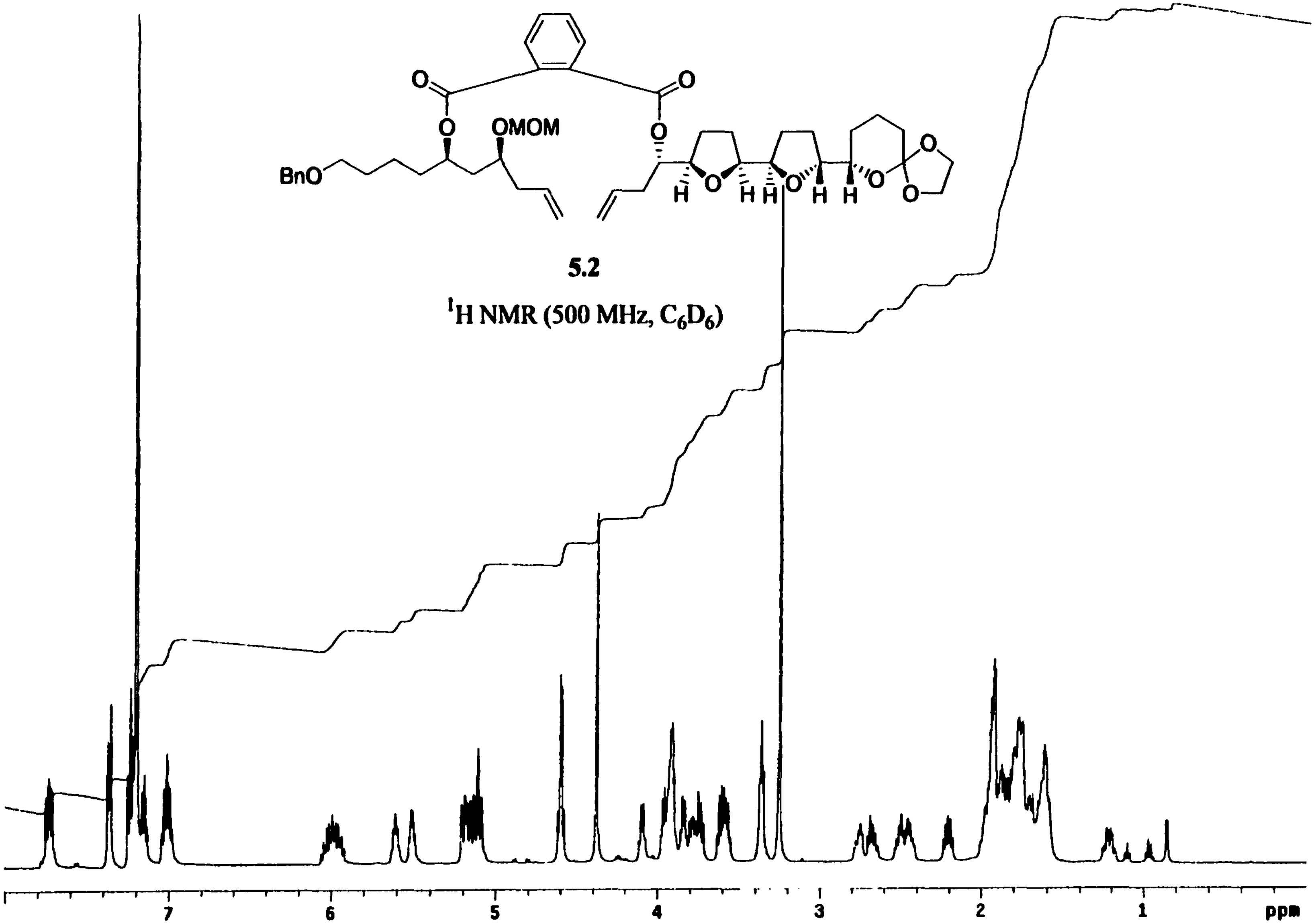
3.6

^{1}H NMR (500 MHz, C_6D_6)



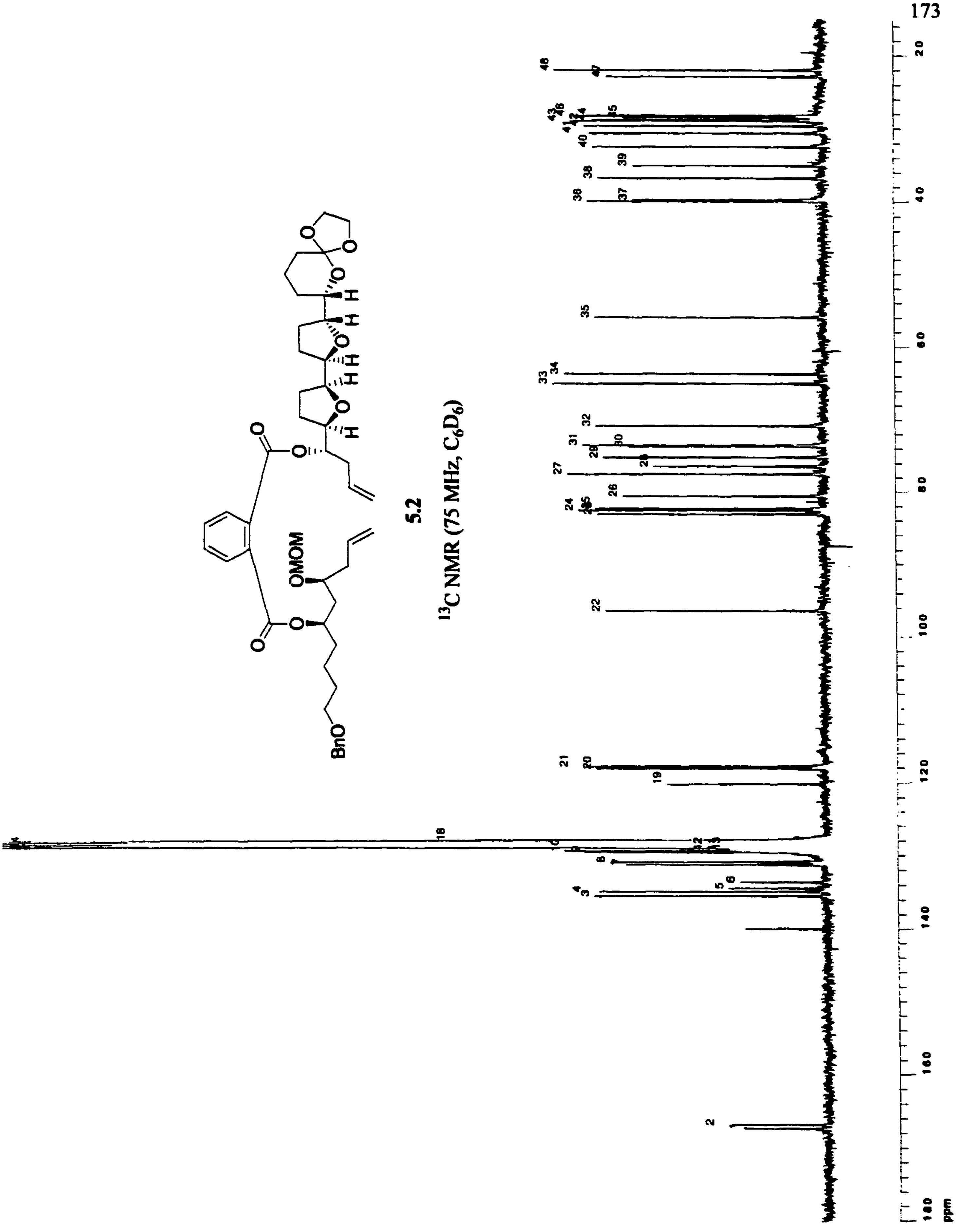
3.6

^{13}C NMR (75 MHz, C_6D_6)



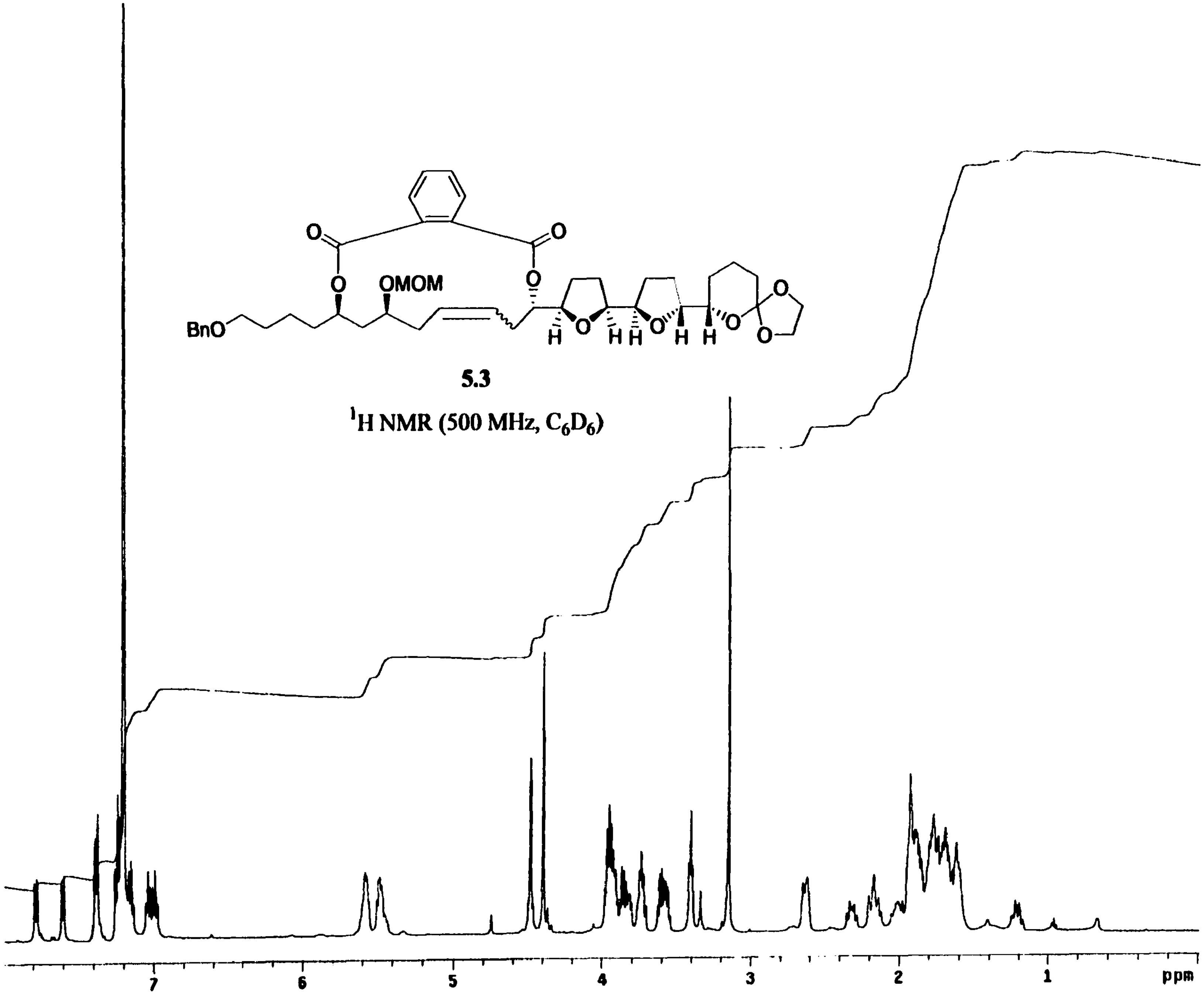
5.2

^{1}H NMR (500 MHz, C_6D_6)



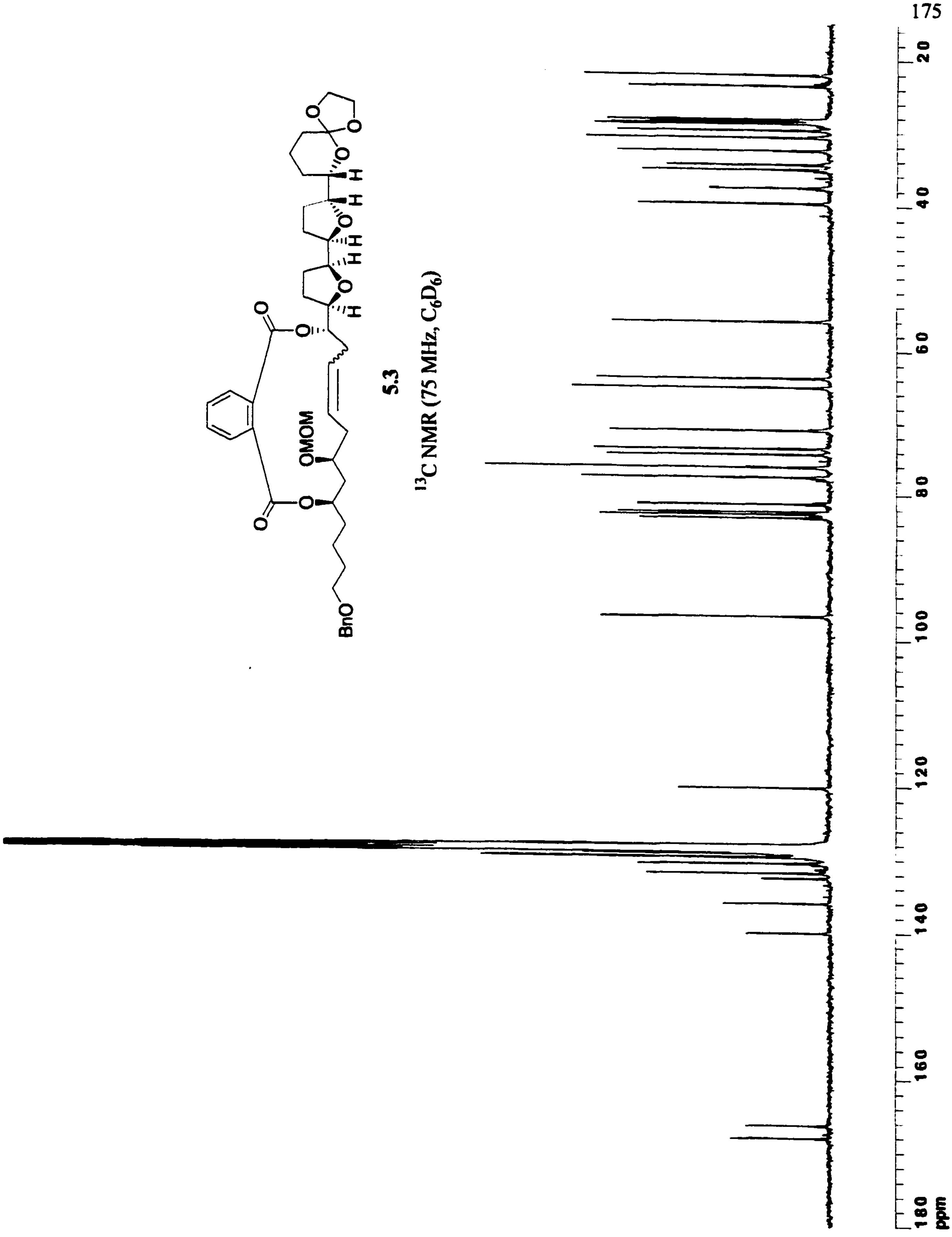
5.2

^{13}C NMR (75 MHz, C_6D_6)



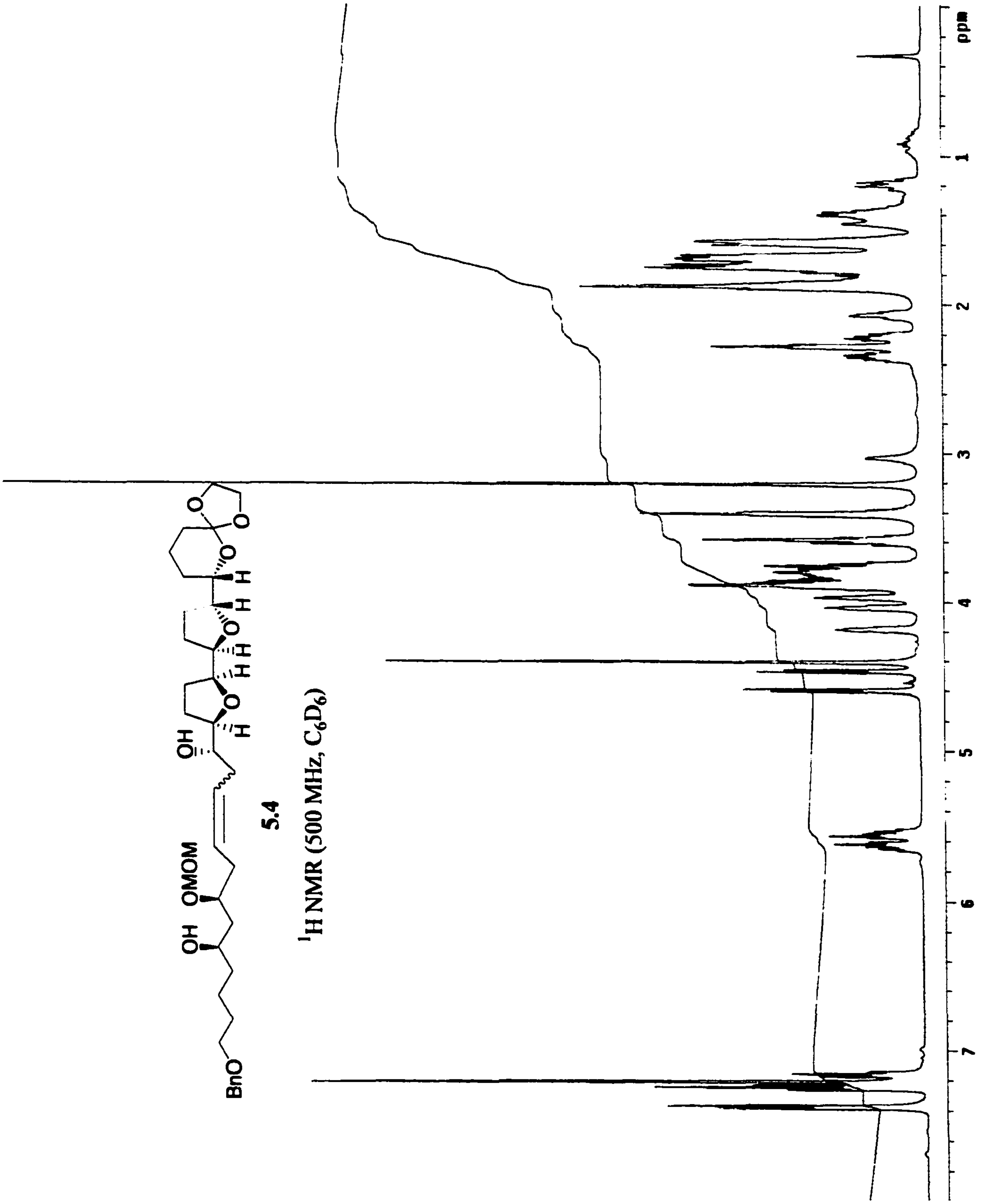
5.3

^{1}H NMR (500 MHz, C_6D_6)



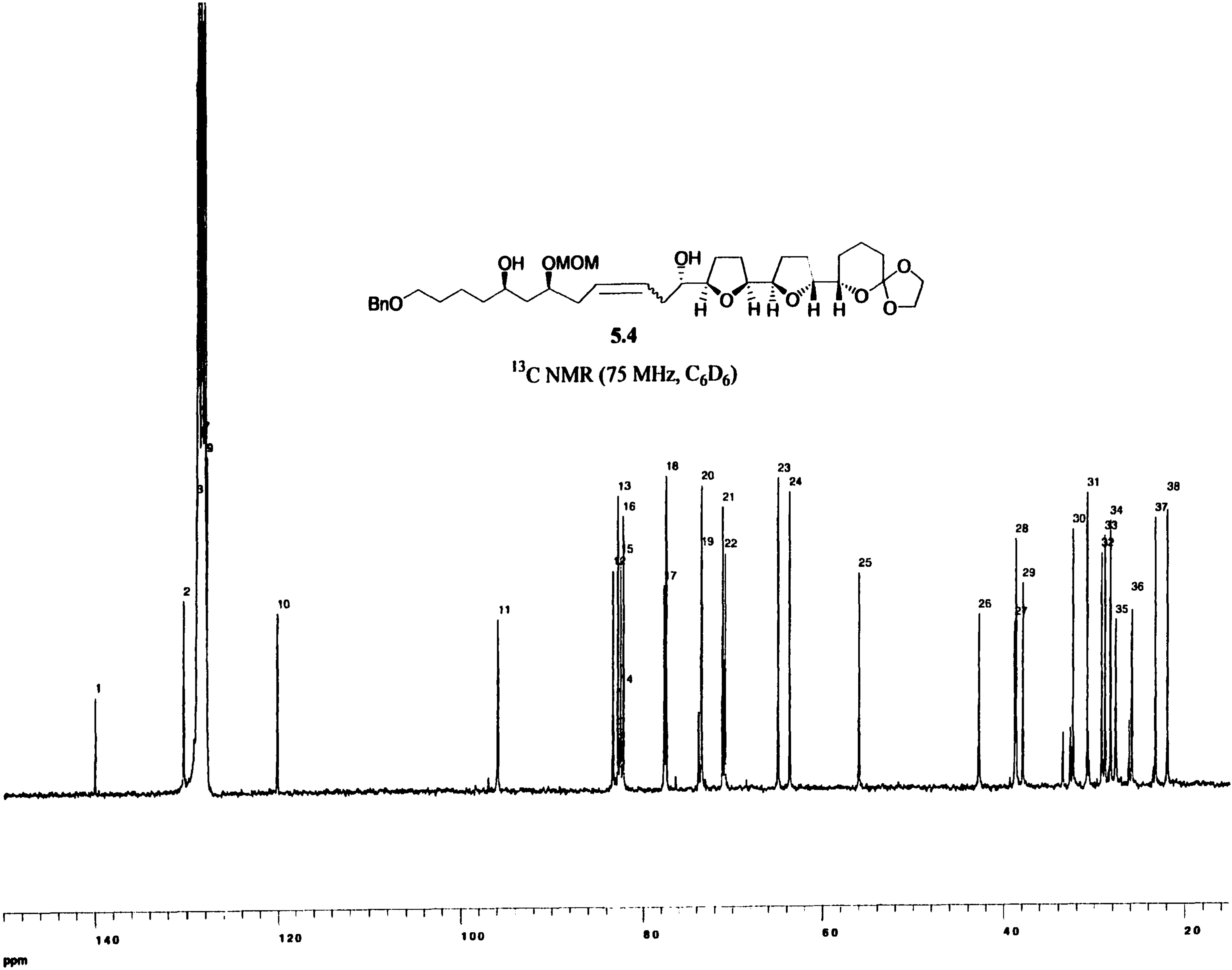
5.3

^{13}C NMR (75 MHz, C_6D_6)



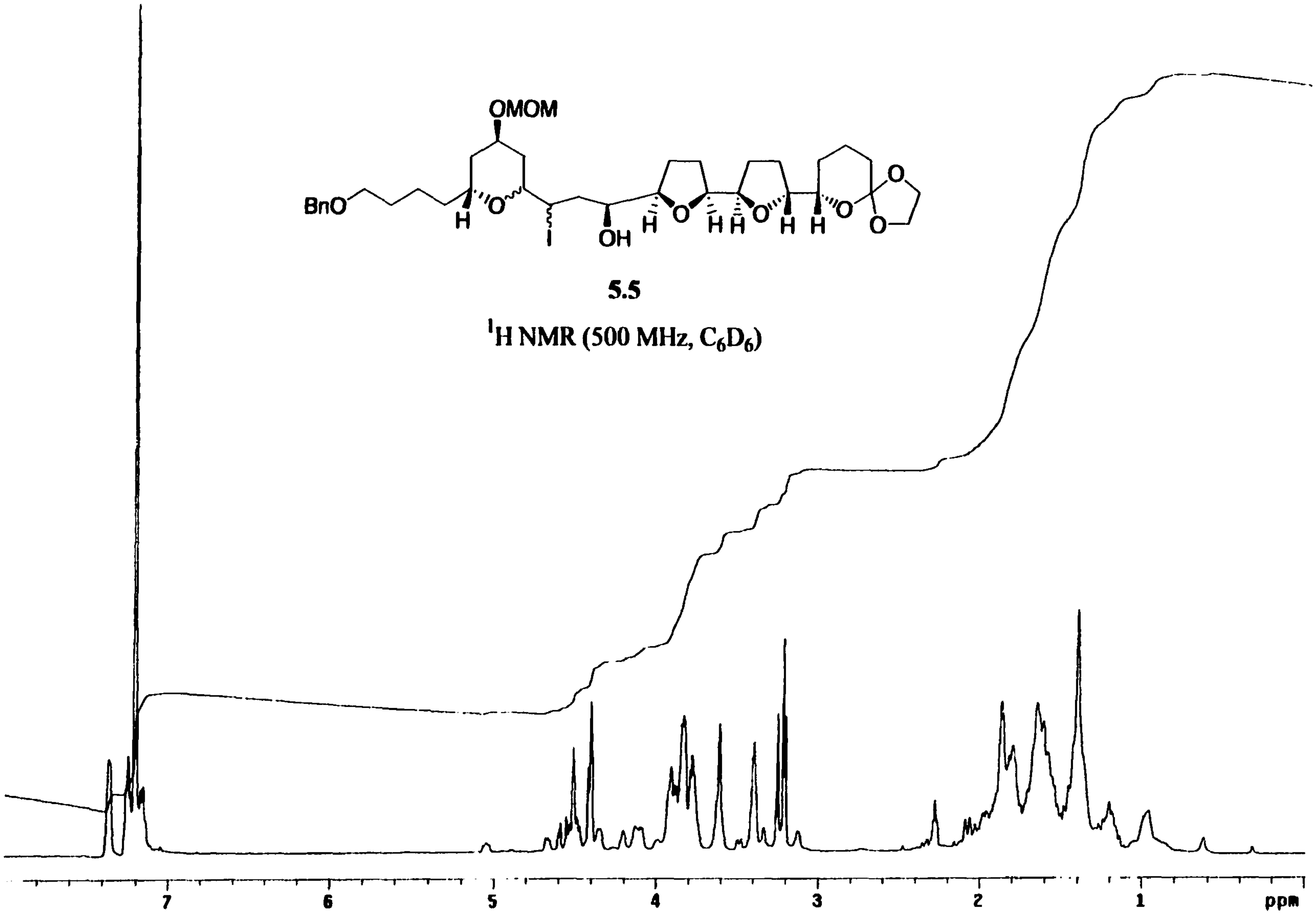
5.4

^{1}H NMR (500 MHz, C_6D_6)



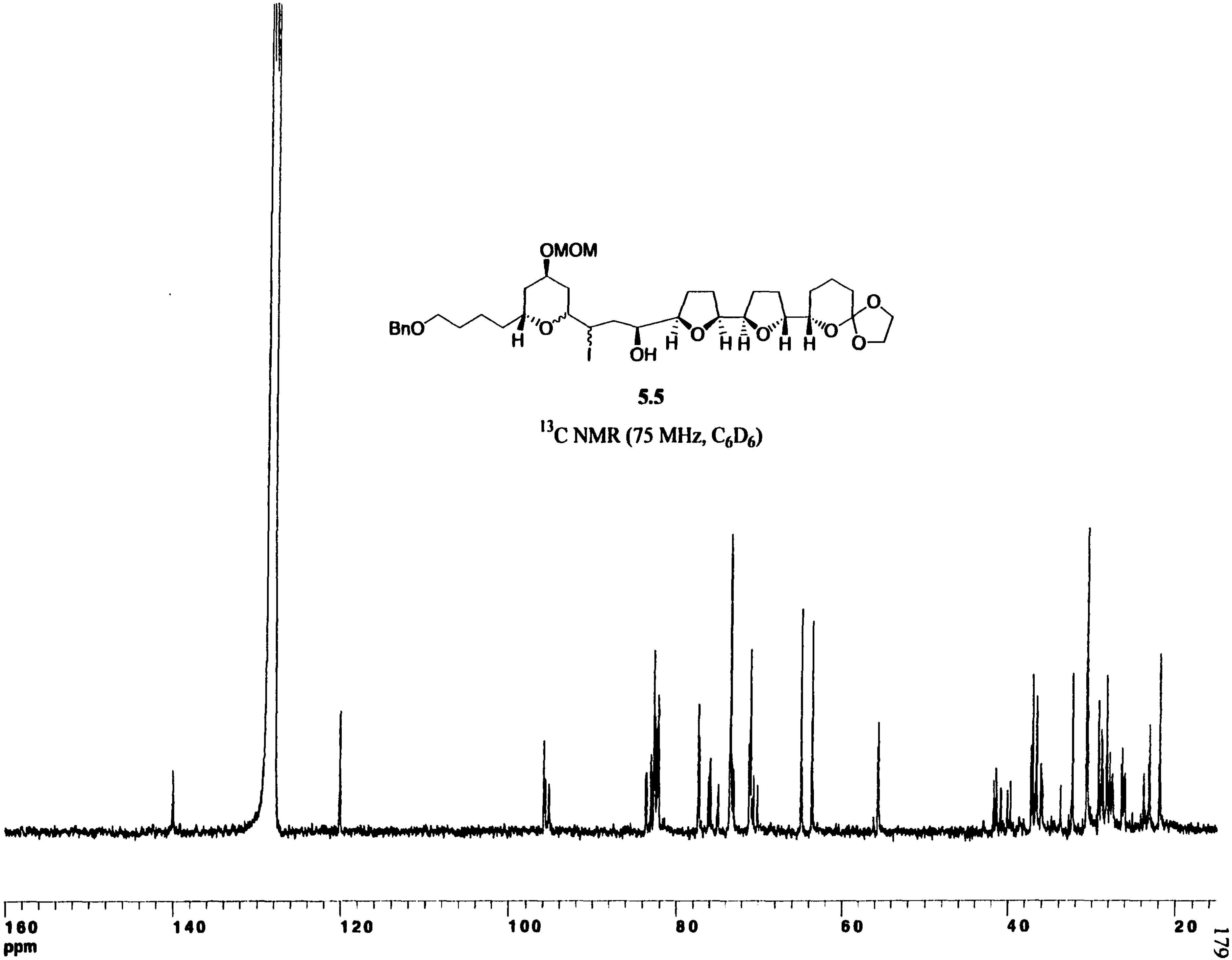
5.4

^{13}C NMR (75 MHz, C_6D_6)



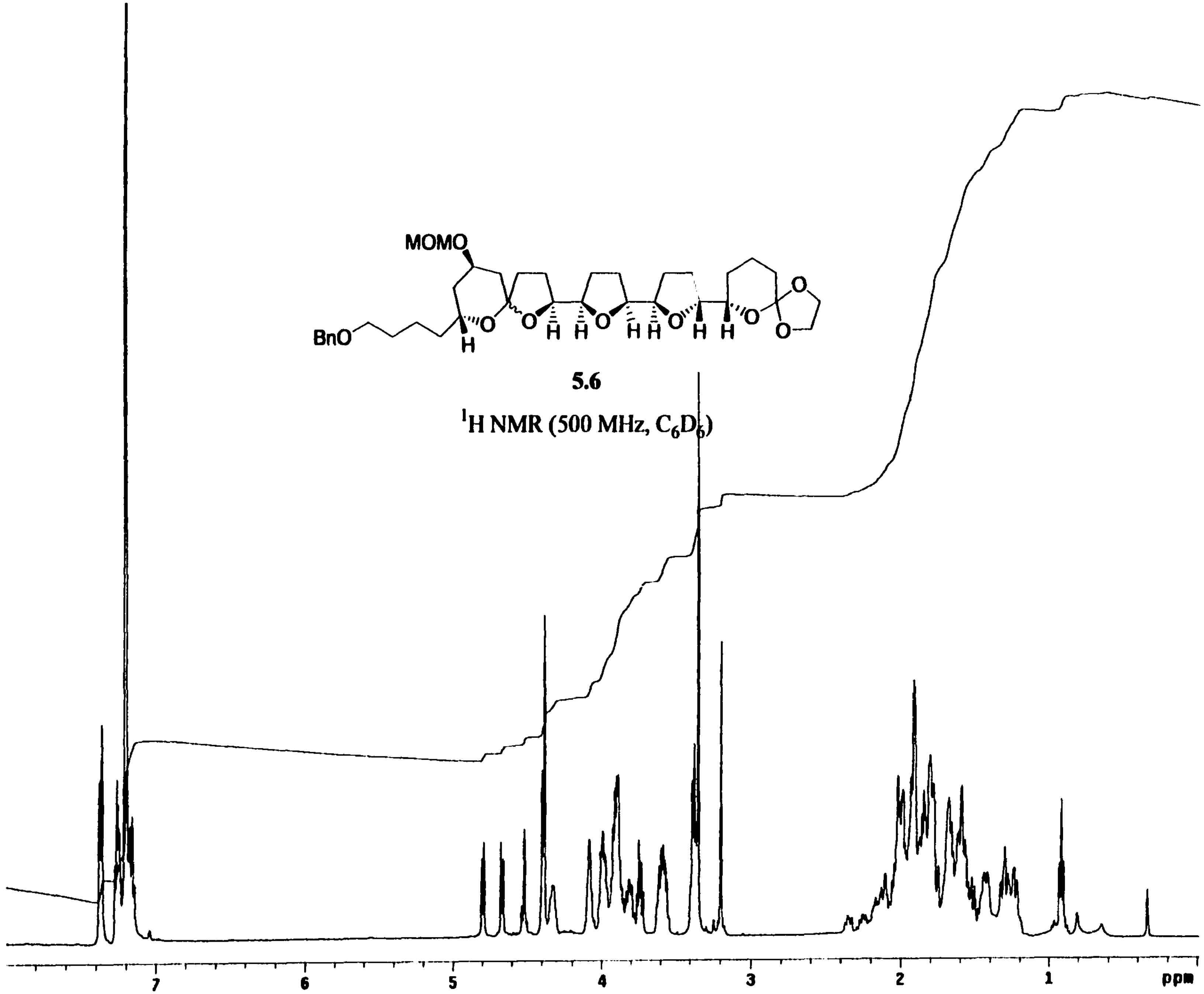
5.5

^{1}H NMR (500 MHz, C_6D_6)



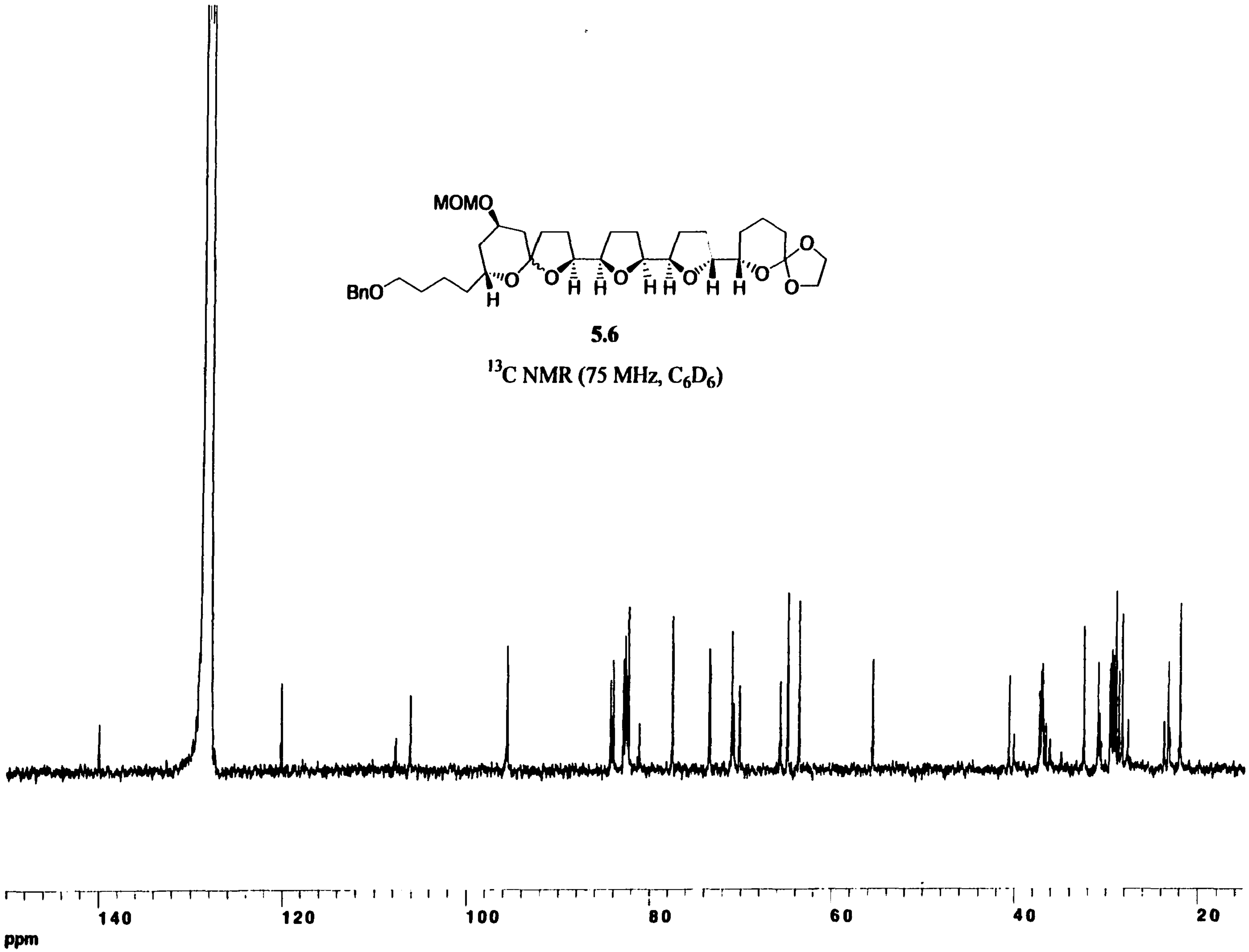
5.5

^{13}C NMR (75 MHz, C_6D_6)



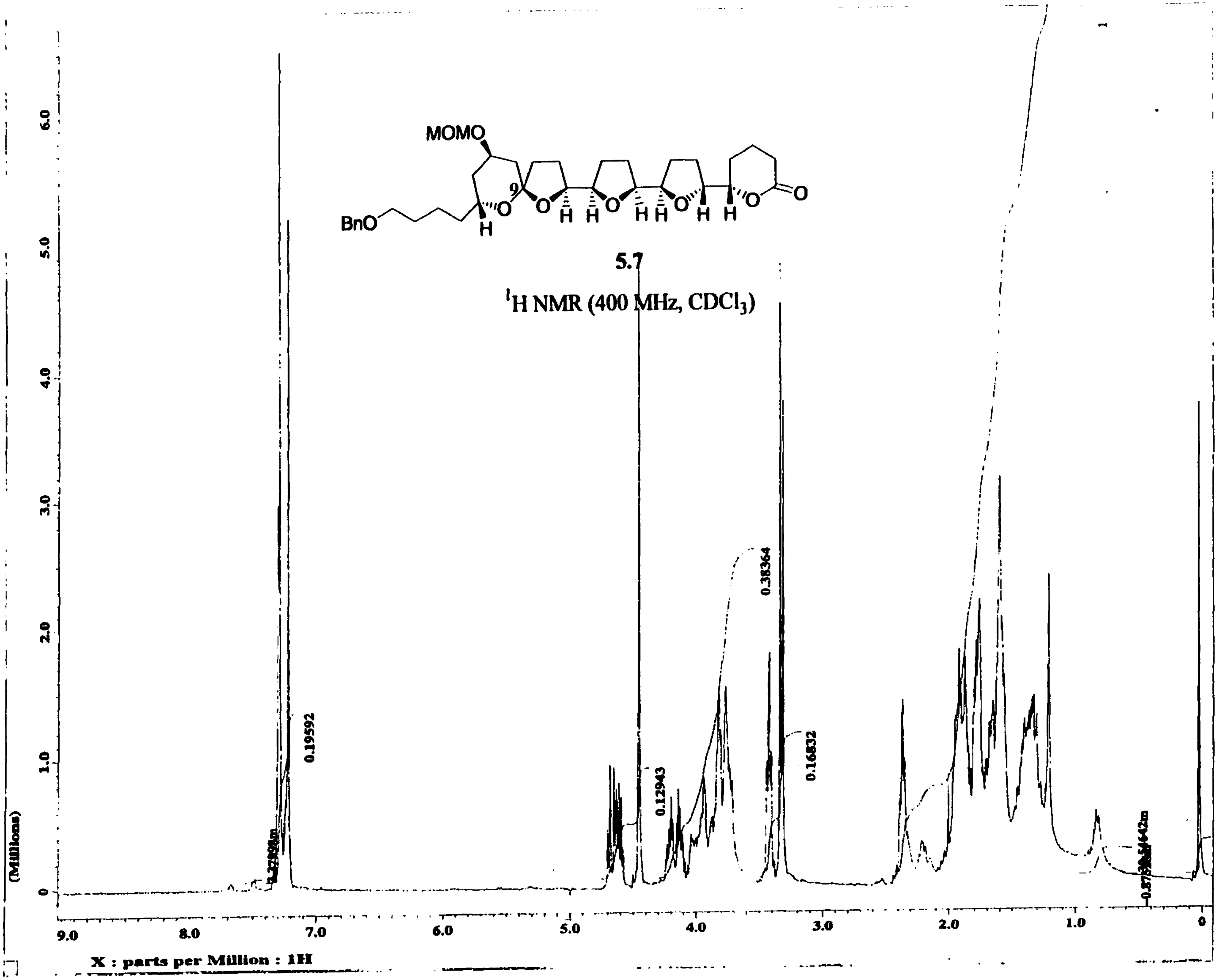
5.6

^{1}H NMR (500 MHz, C_6D_6)



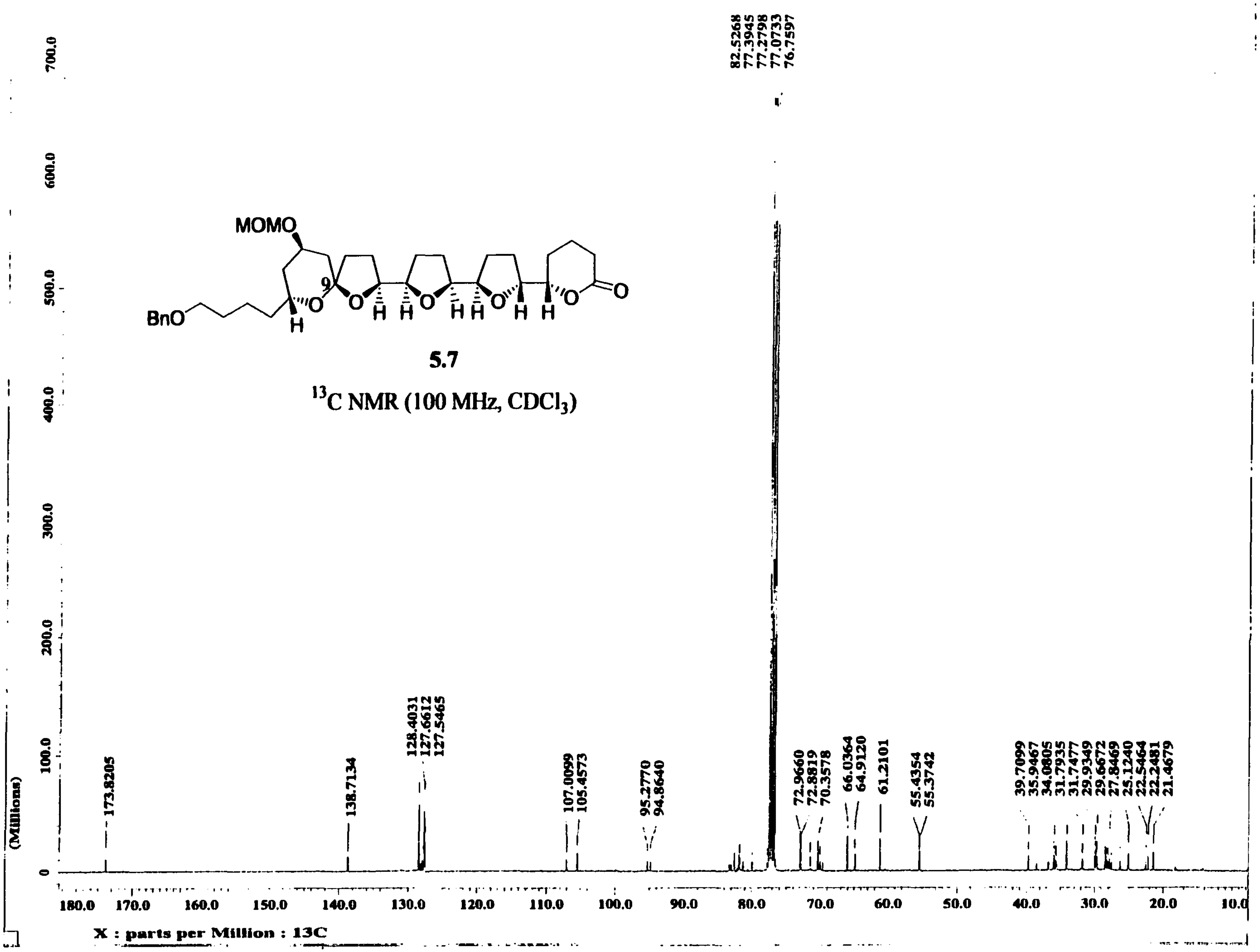
5.6

^{13}C NMR (75 MHz, C_6D_6)



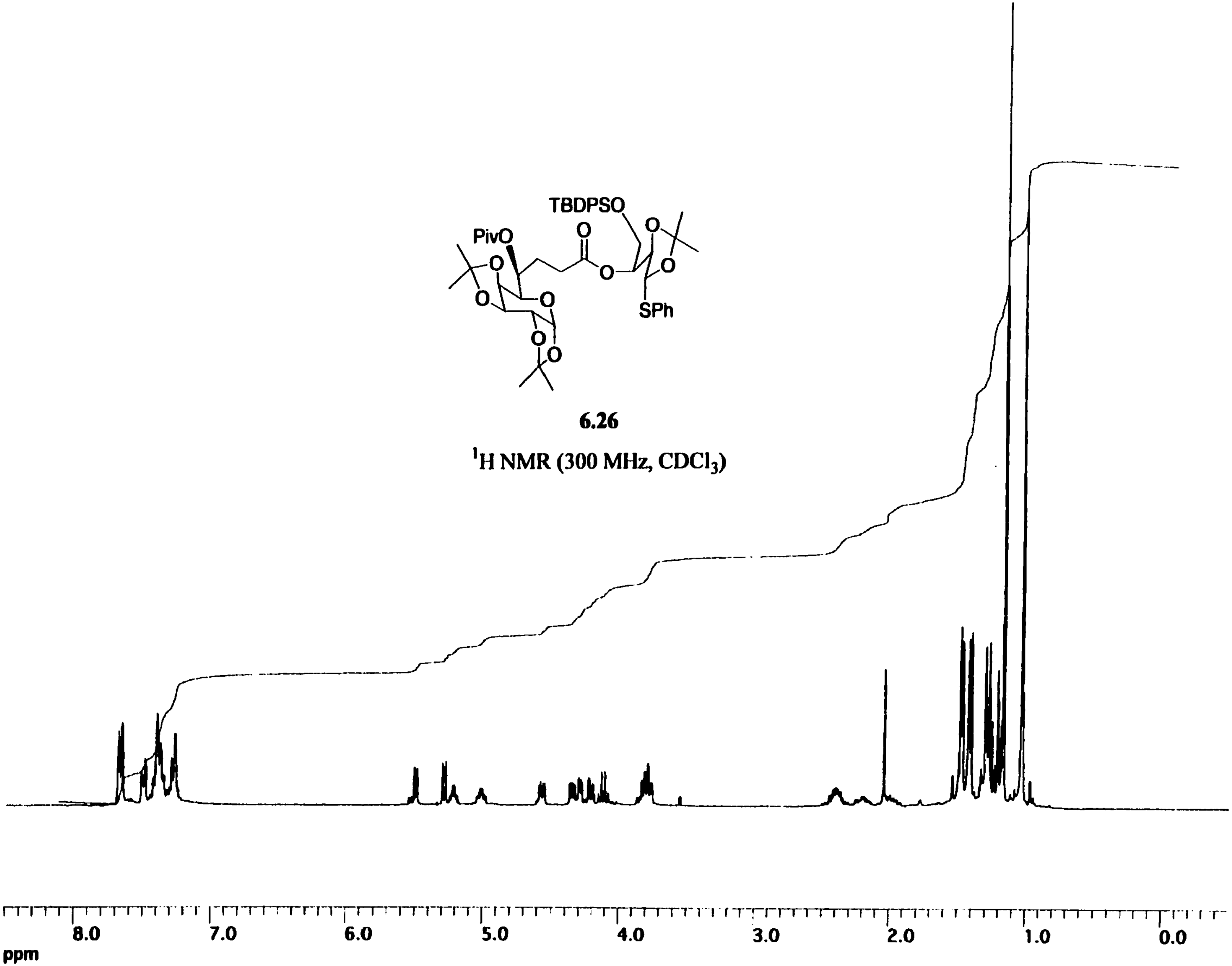
5.7

^{1}H NMR (400 MHz, $CDCl_3$)



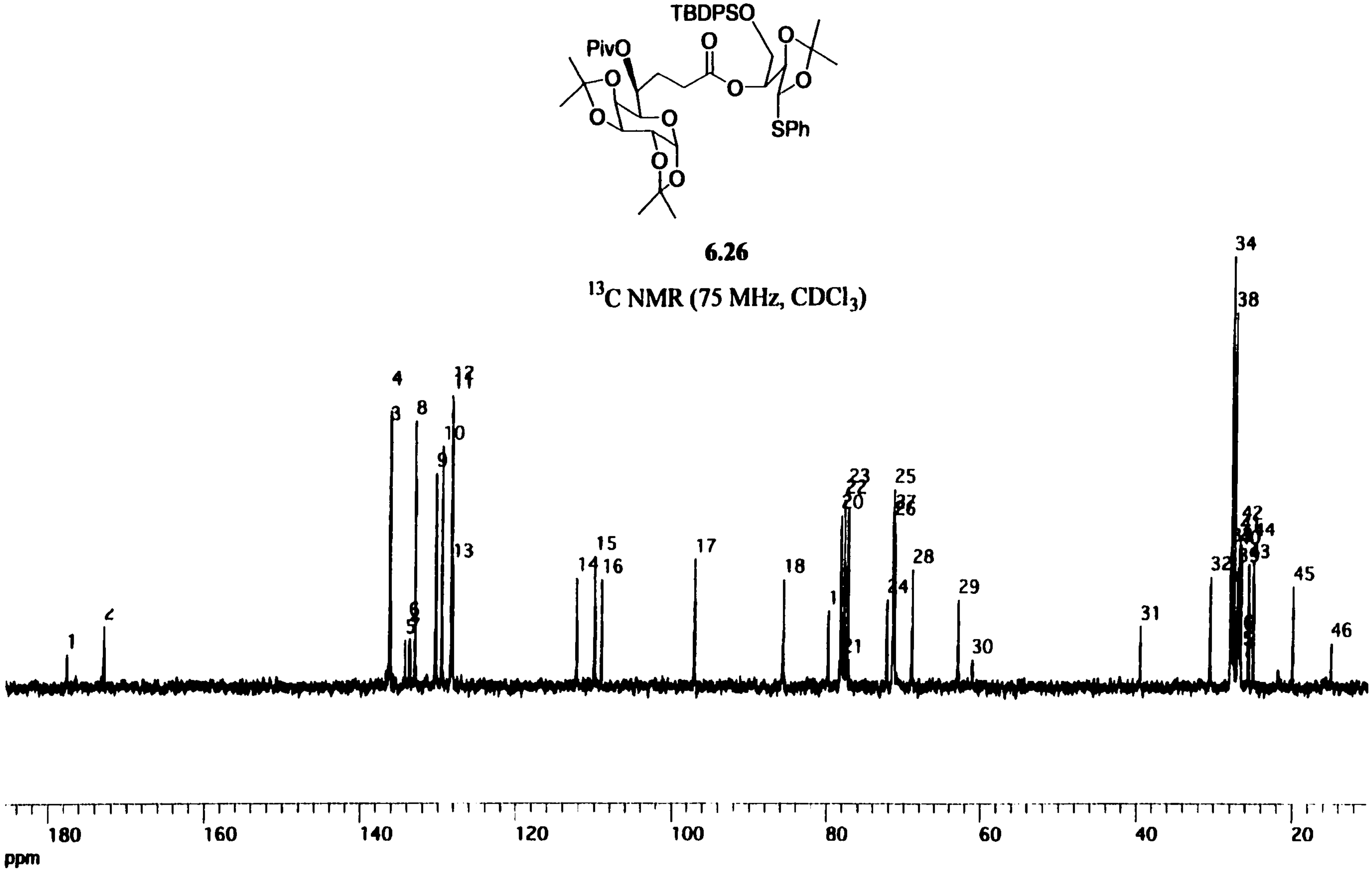
5.7

^{13}C NMR (100 MHz, CDCl$_3$)



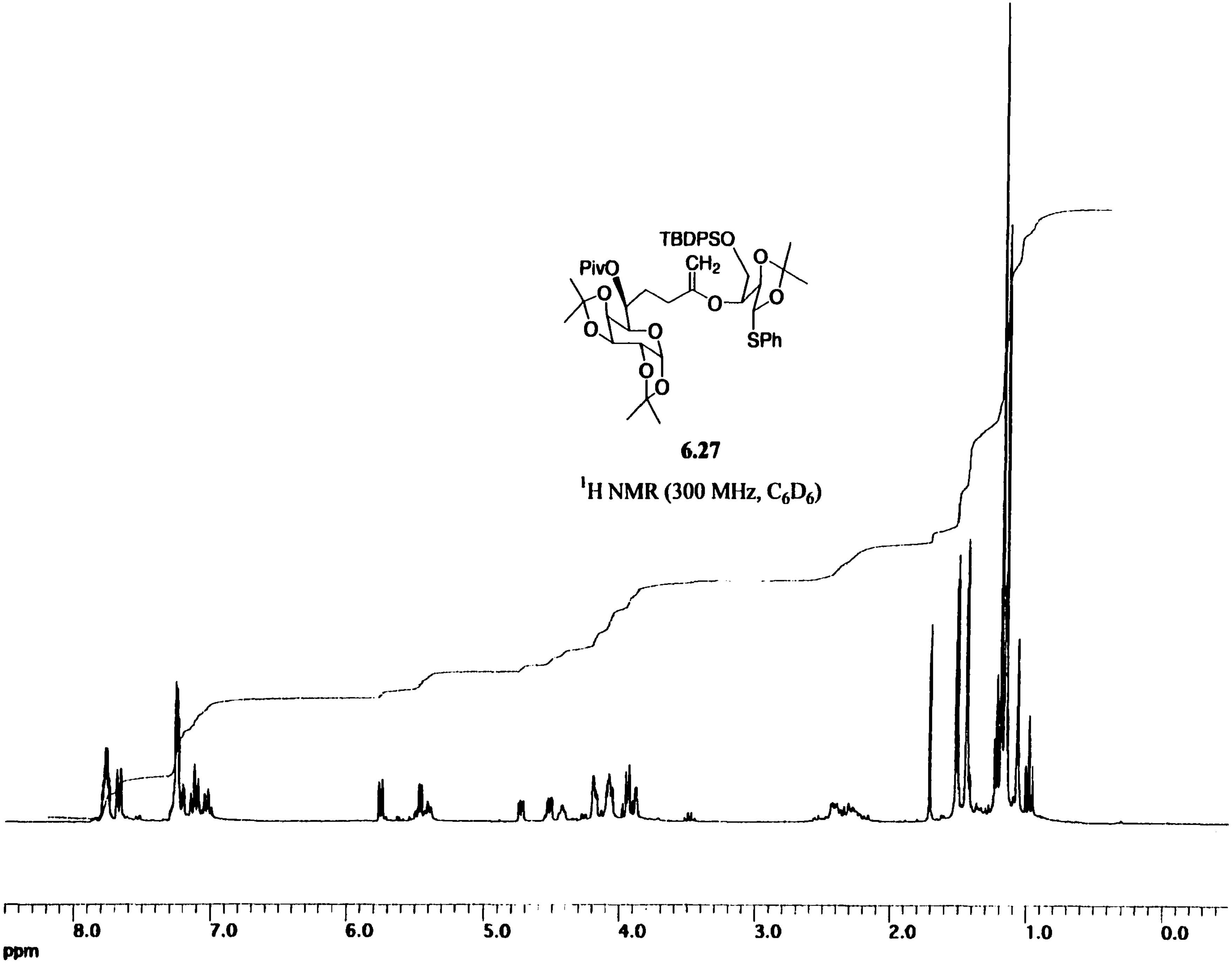
6.26

^{1}H NMR (300 MHz, CDCl$_3$)



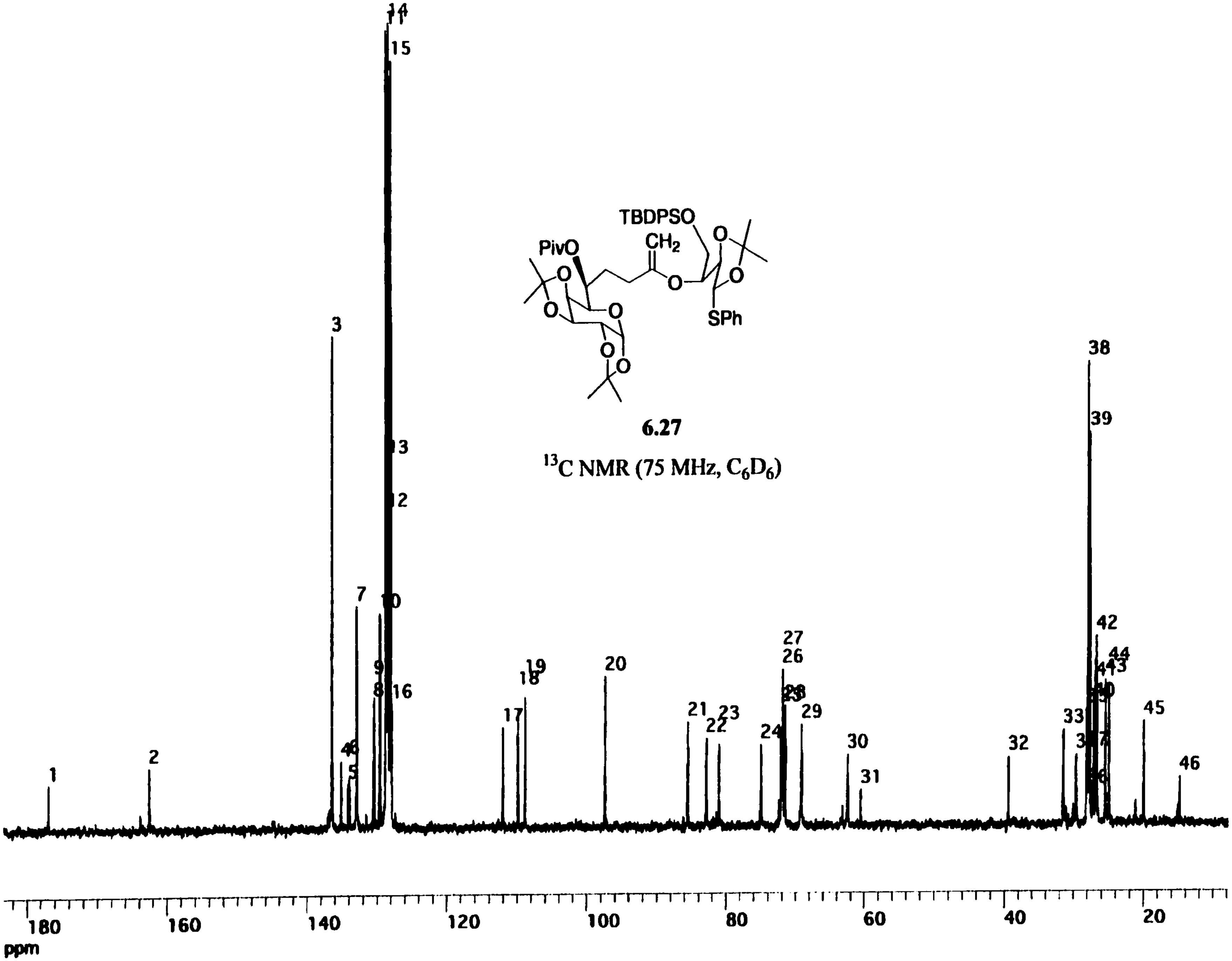
6.26

^{13}C NMR (75 MHz, $CDCl_3$)



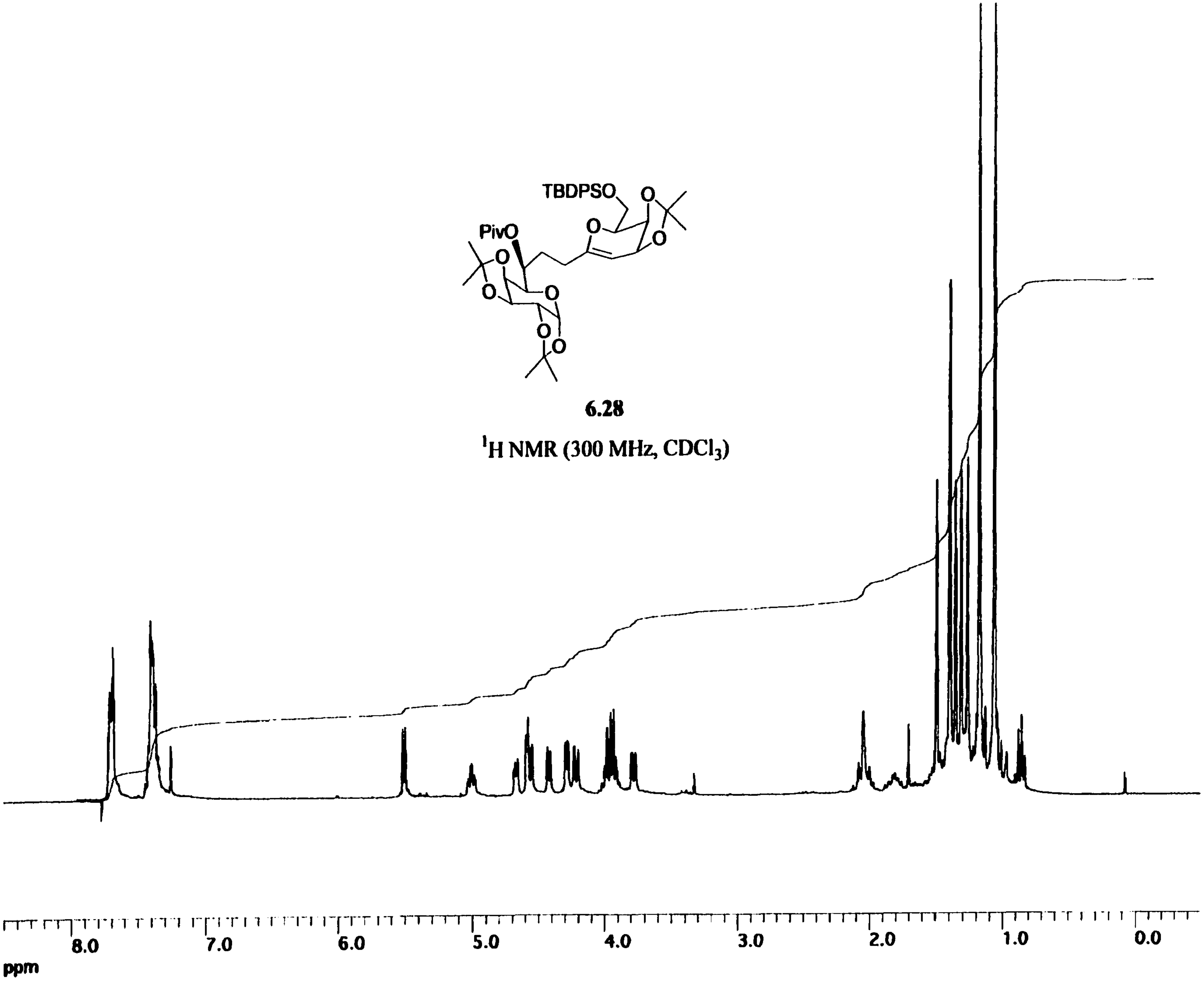
6.27

^{1}H NMR (300 MHz, C_6D_6)



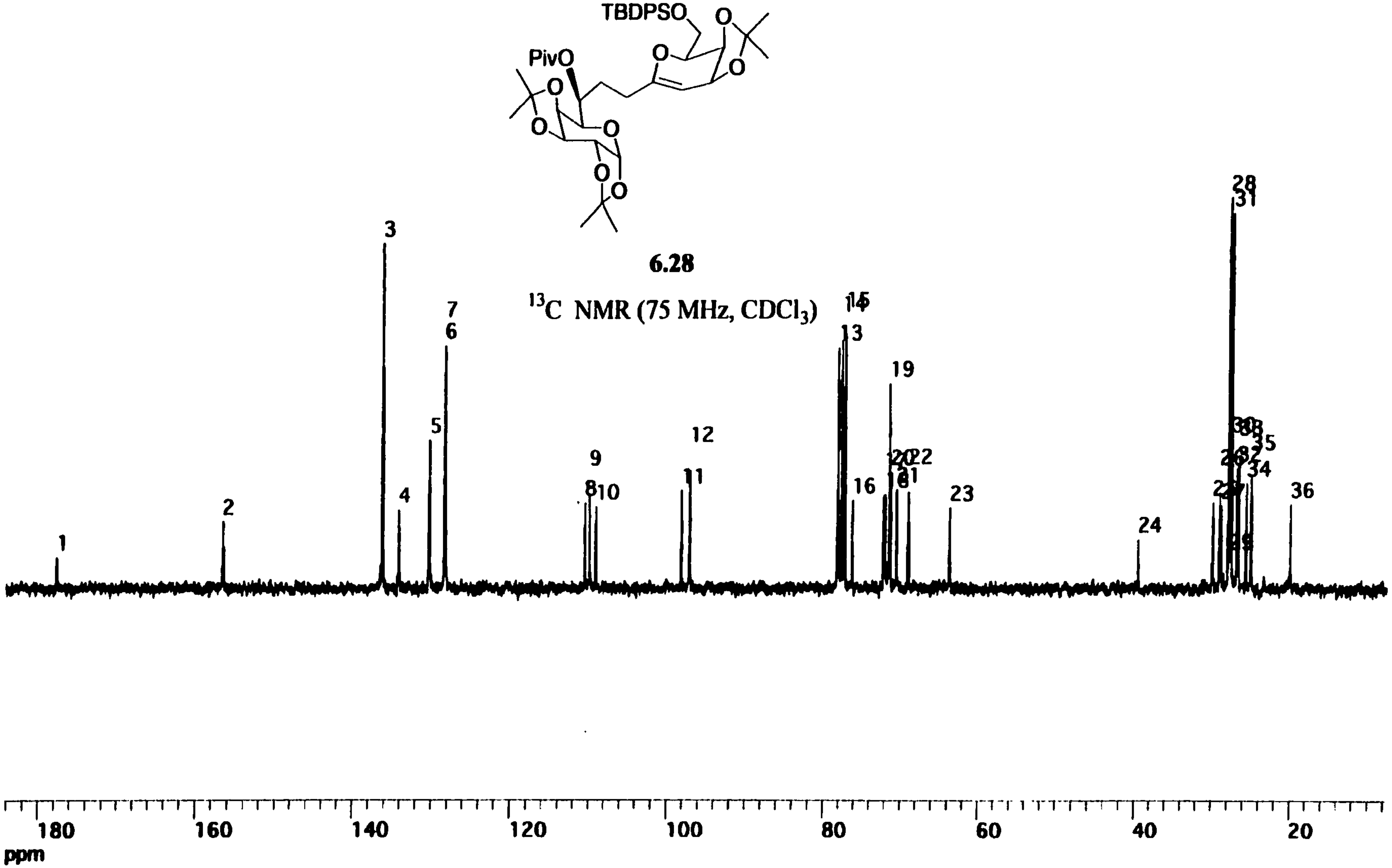
6.27

^{13}C NMR (75 MHz, C_6D_6)



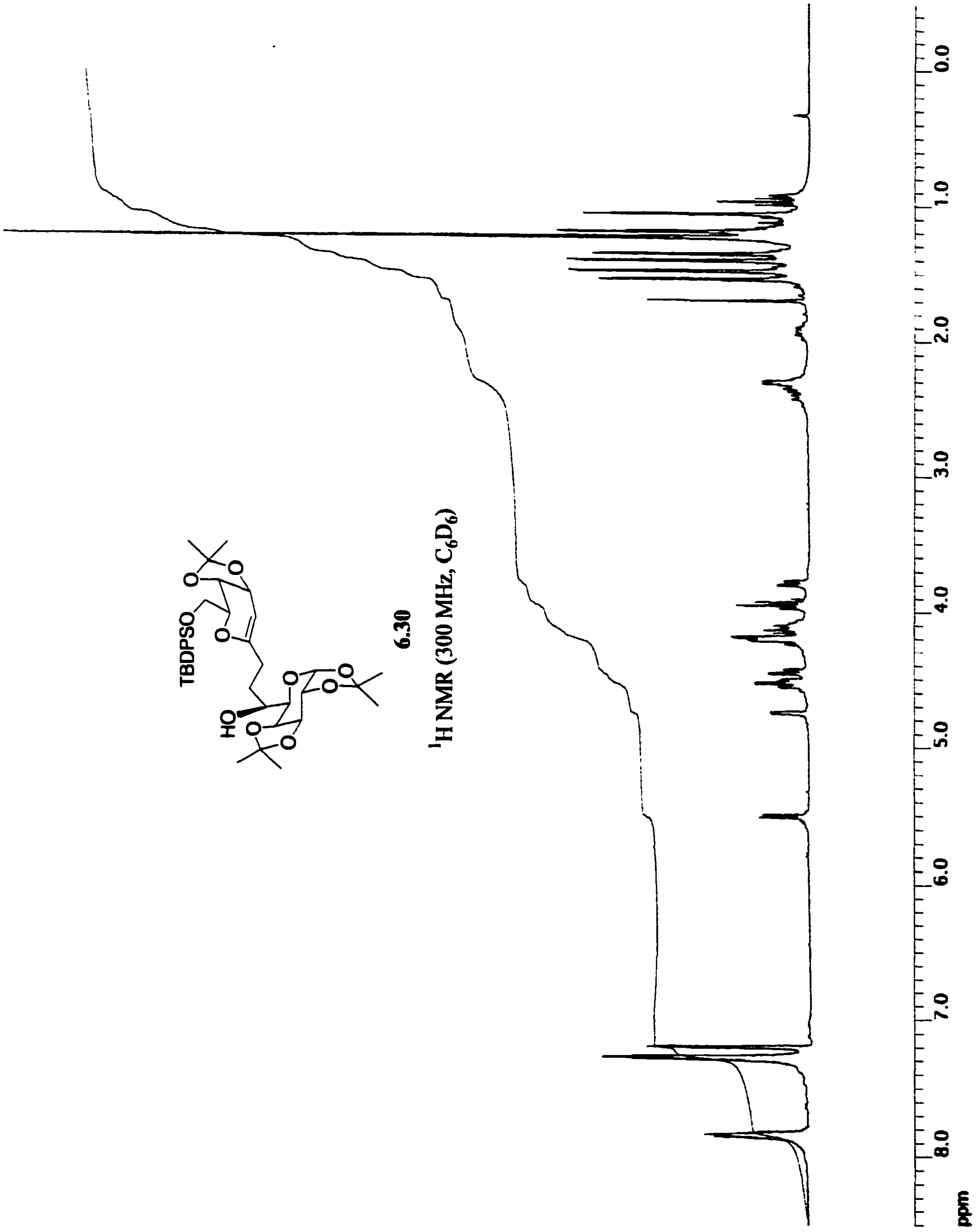
6.28

^{1}H NMR (300 MHz, $CDCl_3$)



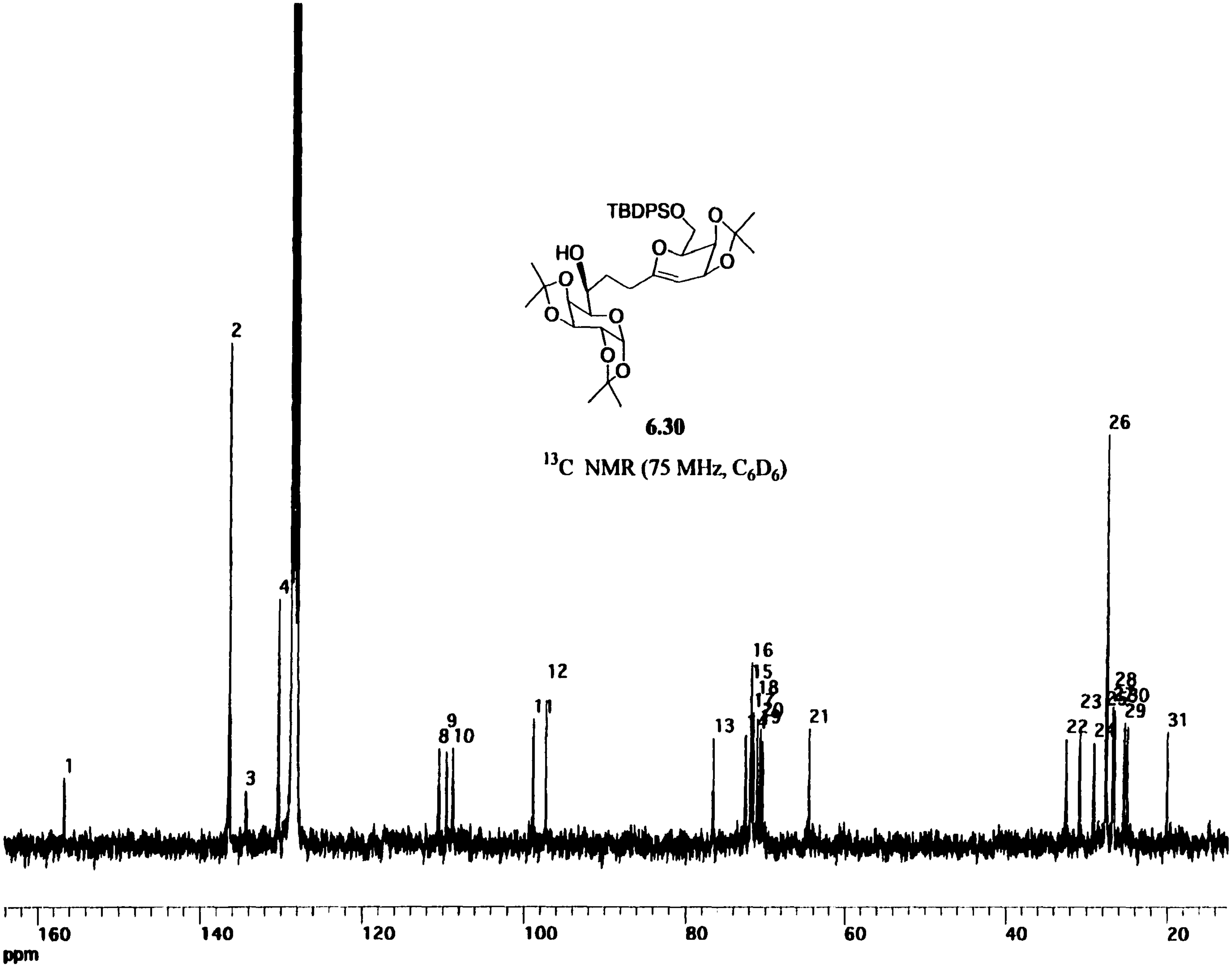
6.28

^{13}C NMR (75 MHz, CDCl$_3$)



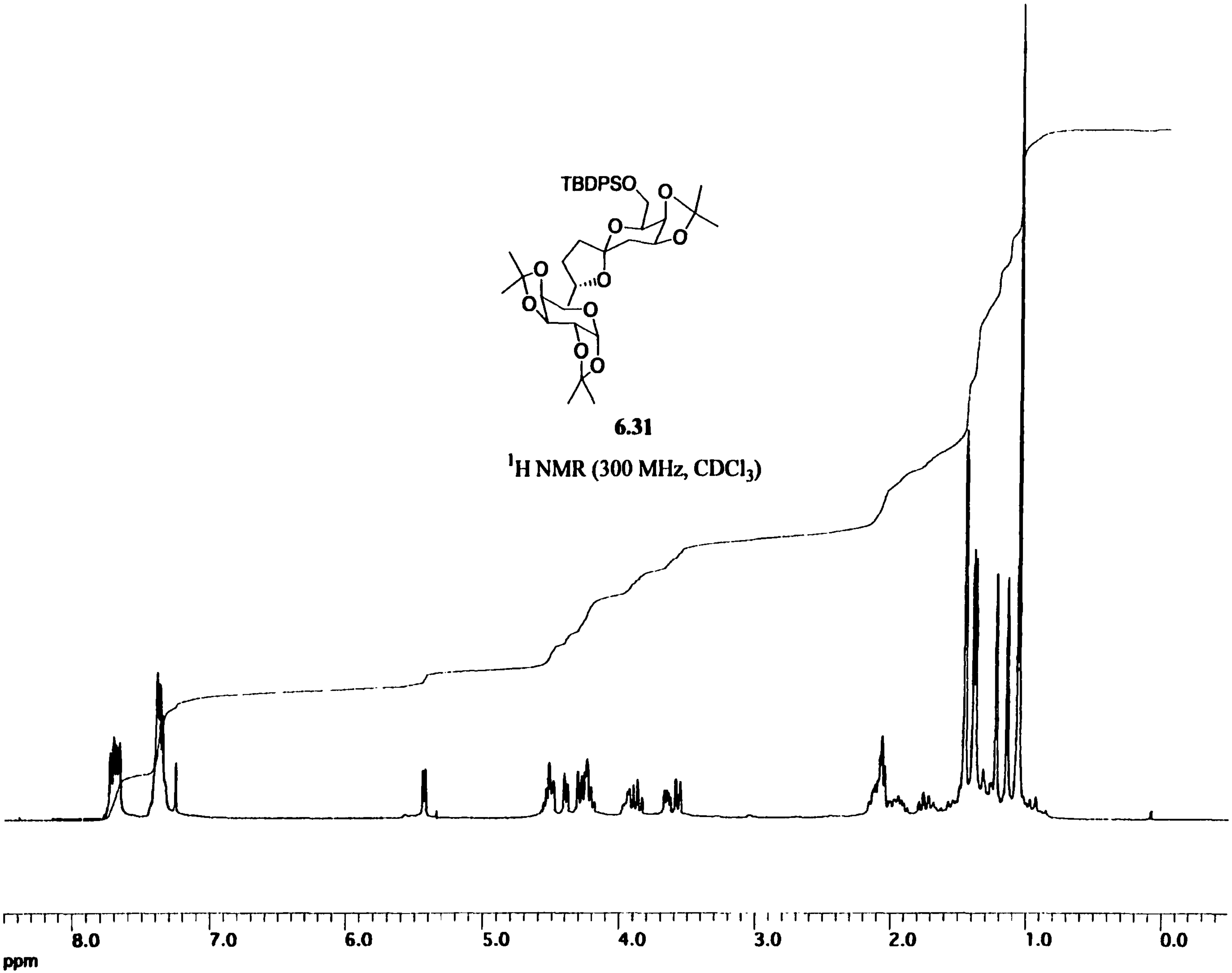
6.30

^{1}H NMR (300 MHz, C_6D_6)



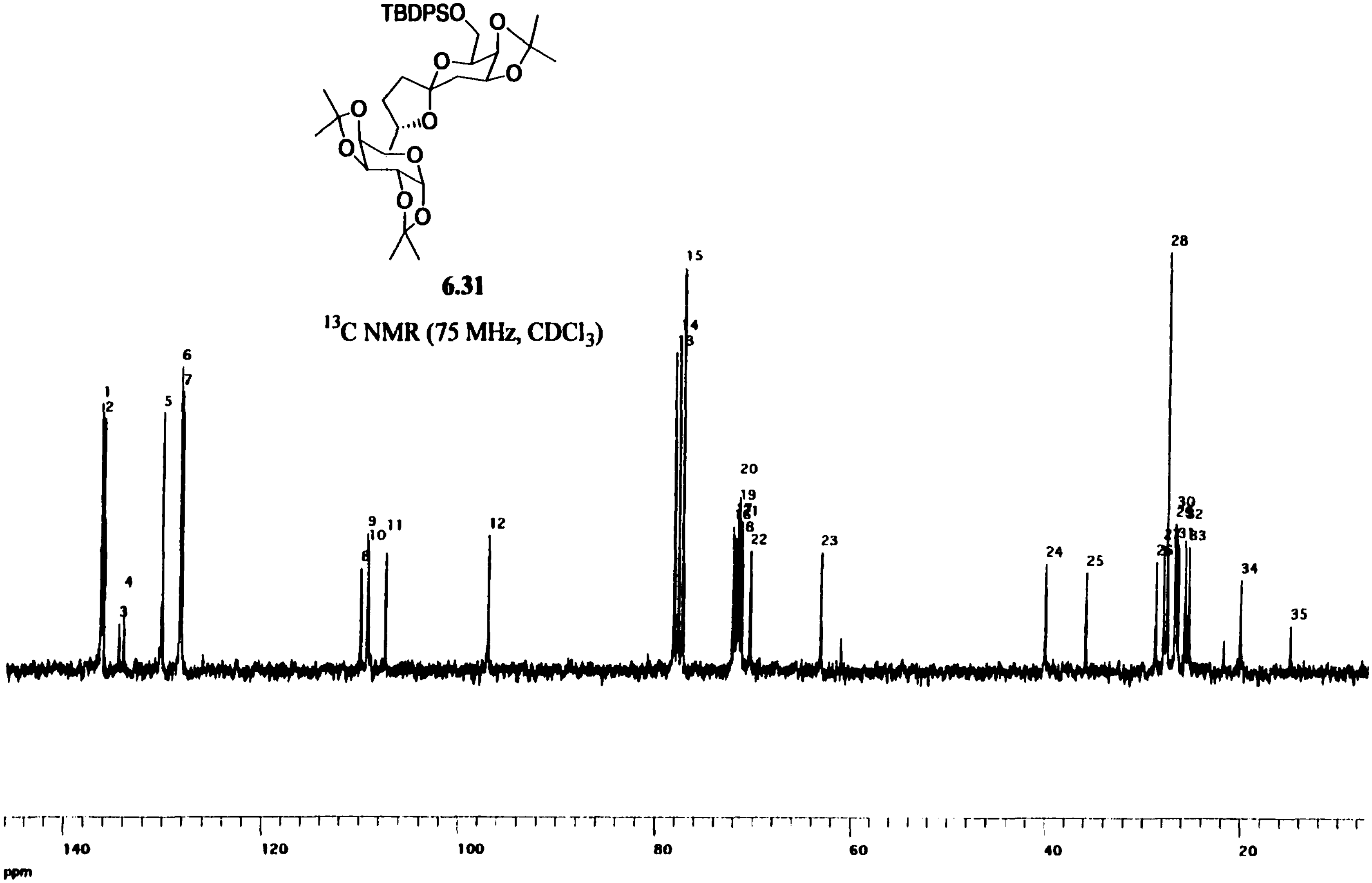
6.30

^{13}C NMR (75 MHz, C_6D_6)



6.31

^{1}H NMR (300 MHz, $CDCl_3$)



6.31

^{13}C NMR (75 MHz, CDCl$_3$)

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