AN OLEFIN METATHESIS-IODOETHERIFICATION BASED SYNTHESIS OF TETRAHYDROFURAN CONTAINING ACETOGENINS

BY

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ABSTRACT

An Olefin Metathesis-Iodoetherification Based Synthesis of Tetrahydrofuran Containing Acetogenins

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The tetrahydrofuran containing acetogenins are a group of naturally occurring compounds that have attracted attention because of their novel structures and potent biological activities. Bullatanocin, also known as squamostatin C, and mucocin belong to a subgroup of structures that non-adjacently linked cyclic ether subunits. The IC_{50} against human lung carcinoma A-549 was less than 10^{-8} μg/mL for both compounds. Bullatanocin was also active against human colon adenocarcinoma HT-29, and mucocin showed remarkable inhibitory activity against pancreatic cancer PACA-2. Like other tetrahydrofuran (THF) containing acetogenins, the cytotoxic activity is believed to involve disruption of electron transfer in the mitochondria, which leads to a decrease in ATP production, and cell death. Several synthetic studies have been motivated by the need for analogues for structure activity investigations.

The work reported in this thesis involves the development of a potentially general strategy for the synthesis of non-adjacently linked, ether containing, acetogenins. The methodology is based on a three component modular synthesis. The key precursors are a butenolide segment and two cyclic ether-alkene subunits (tetrahydrofuran or tetrahydropyran). The butenolide was synthesized via known literature procedures. The synthesis of the cyclic ether-alkene components involved novel methodology. The THF subunits were accessed through the iodoetherification of the 1,2-*O*-isopropylidene 5-alkene precursors. The tetrahydropyran (THP) subunit was prepared through elaboration of a dithiane precursor. The key coupling reaction for the cyclic ether subunits was an olefin cross metathesis. The bis-cyclic ether intermediates that were derived from the metathesis reactions in the bullatanocin and mucocin syntheses were later coupled to a butenolide component via Wittig and Julia olefination procedures respectively. Final functional group processing provided materials that displayed essentially identical physical data as the natural products. Total synthesis of bullatanocin was achieved in 45 total steps, and 4.8% overall yield with a longest linear sequence of 22 steps. Total synthesis of mucocin was accomplished in 40 total steps, and 3.6% overall yield with the longest linear sequence of 19 steps.

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Doctorate, a milestone of life, seems to be an individual achievement. However, it is filled with many people's contributions and talents. They guided you through the difficult periods of this endeavor and have been a constant encouragement.

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DEDICATE TO THE LOVE OF MY MOM, LINZHU WANG

TO MY DAD, BENSONG ZHU

TABLE OF CONTENTS

LIST OF SYMBOLS AND ABBRIVIATIONS

A-498	human kidney carcinoma cells
A-549	lung cell line
Ac	acetyl
Ac_2O	acetic anhydride
ADP	adenosine diphosphate
AgOTf	silver trifluoromethanesulfonate
ATP	adenosine triphosphate
$BF_3 \cdot Et_2O$	boron trifluoride etherate
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
brine	saturated aqueous sodium chloride solution
br	broad
BST	brine shrimp lethality test
Bu	butyl
℃	degree Celsius
ca.	about
calcd	calculated
CM	cross metathesis
^{13}C NMR	carbon-13 nuclear magnetic resonance spectrometry
CSA	camphorsulfonic acid
δ	chemical shift in ppm

d	doublet
DEAD	diethyl azodicarboxylate
DCC	dicyclohexylcarbodiimide
DIAD	diisopropyl azodicarboxylate
DMF	N,N-dimethylformamide
ED_{50}	Effective Dose 50
ee	enantiomeric excess
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
eq	equivalent
FCC	flash colum chromatography
g	gram
h	hour
^1H NMR	proton nuclear magnetic resonance spectrometry
HRMS	high resolution mass spectrometry
HT-29	colon cell line
Hz	hertz
IC_{50}	50% inhibitory concentrations
IDCP	iodonium dicollidine perchlorate
J	coupling constant
L	liter
m	multiplet

MCF-7	breast carcinoma cells
Me	methyl
MeOH	methanol
MeOTf	methyl triflate
mg	milligram
min	minute
mL	milliliter
mmol	millimole
MTPA	α-methoxy-α-(trifluoromethyl)phenyl acetic acid
MS	molecular sieves
NOE	nuclear overhauser effect
PACA-2	pancreatic carcinoma cells
PC-3	prostate adenocarcinoma cells
Ph	phenyl
ppm	parts per million
PPTS	*para*-pyridinium toluenesulfonate
q	quartet
RCM	ring closing metathesis
rt	room temperature
s	singlet
SAR	structure activity relationship
SMP	submitochondrial particles
t	triplet

TBDPS	*tert*-butyl diphenyl silyl
TBHP	*tert*-butyl hydroperoxide
TfOH	trifluoromethanesulfonic acid (triflic acid)
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
Ts	toluenesulfonyl
vs	versus

LIST OF TABLES

LIST OF FIGURES

CHAPTER ONE

Acetogenins: Structure, Bioactivity and Synthesis

More than 400 annonaceous acetogenins have been isolated from different species of the Annonaceae family. These compounds have attracted attention because of their novel structures and their potent and broad range of biological activities, including pesticidal, antimalarial, antimicrobial, antiparasitic, antiprotozoal, immunosuppressive, antifeedant, antithelmintic, cytotoxic and antitumor properties. The scant natural resources and the need for substantial amounts of enantiomerically pure samples for further biological studies have resulted in considerable interest in total syntheses of these compounds. To date, more than 30 Annonaceous acetogenins have been prepared by total syntheses.[1-3]

1.1 Structure

The acetogenins are C_{35}-C_{37} frameworks, which are generally made up of four segments: a cyclic ether core that is made up of THF and/or THP rings, a terminal α,β-unsaturated γ-lactone ring, a polymethylene spacer linking one end of the cyclic ether core to the γ-lactone ring, and a hydrophobic side chain attached to the other side of cyclic ether residue. This side chain may contain oxygen substituents (hydroxyls, acetoxyls, ketones, epoxides) or double bonds. The four subunits mentioned above will be referred to as the cyclic ether core unit, the butenolide, the polymethlene spacer, and the hydrocarbon side chain (**Figure 1.1**). In a small subset of structures, the cyclic ether segment is replaced by an acyclic, oxygenated hydrocarbon chain. A small number of analogues with a modified butyrolactone ring are also known.[4]

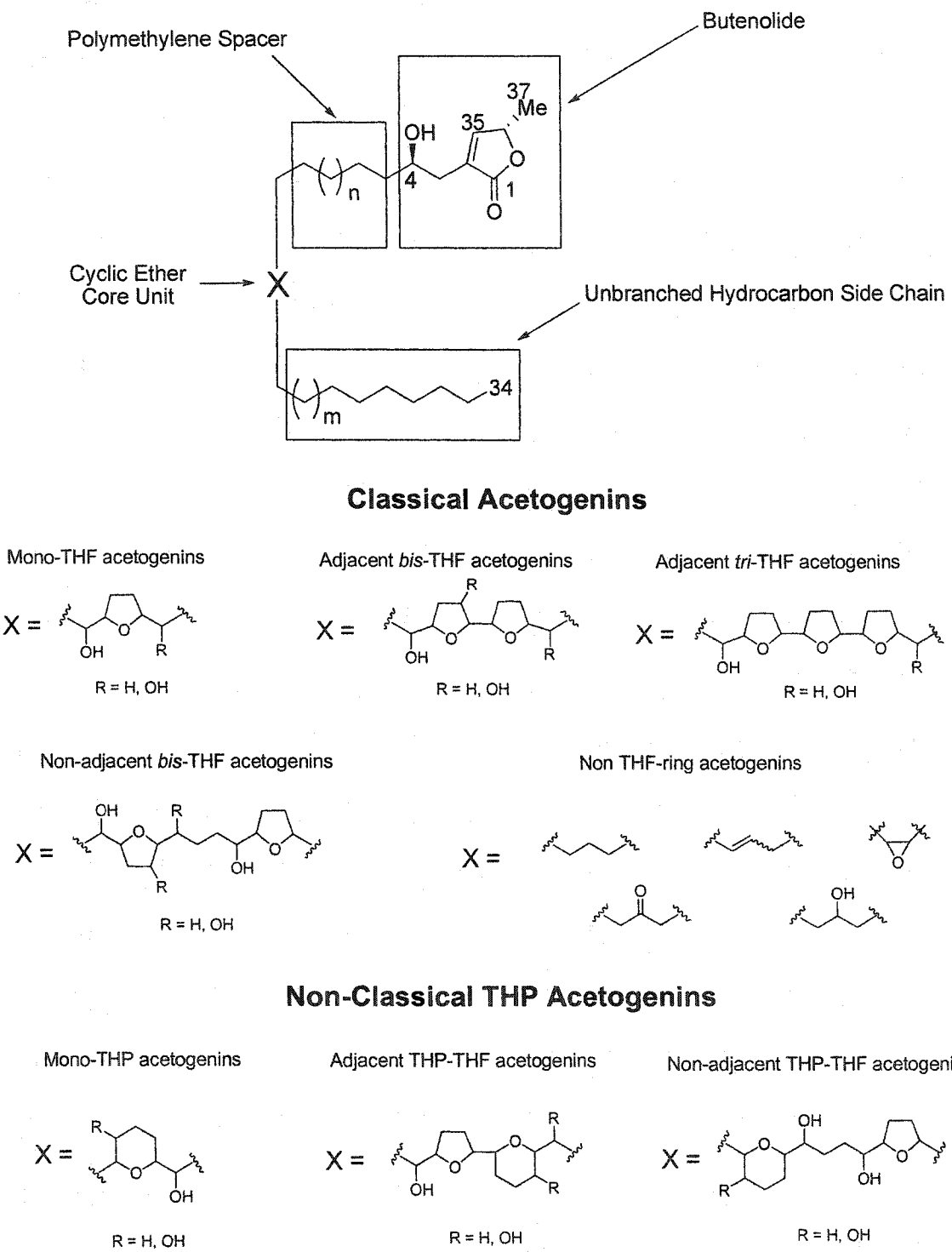


Figure 1.1. Generalized structure of annonaceous acetogenins

Structures are classified according to the presence or absence of a THF or THP ring, ring size, and the number and connectivity of the cyclic ethers. The classical or more common motifs are the structures with a mono-THF, adjacently linked bis- or tri-THF, or non-adjacently linked bis-THF, and components without cyclic ether. The less common or non-classical analogues are those that contain a THP ring.

Mono-THF acetogenins: The mono-THF ring compounds can be classified into six groups, according to stereochemistry of the THF ring and number of flanking hydroxyl groups. There are three subgroups that contain a mono-THF ring with two flanking hydroxyls (the annonacin,[5,6] *cis*-annonacin[6] and annonacin A[7]) and three subgroups that bear a mono-THF ring with one flanking hydroxyl (gigantetrocin A,[8] muricatetrocin A[9] and muricatalin[10]) (**Figure 1.2**).

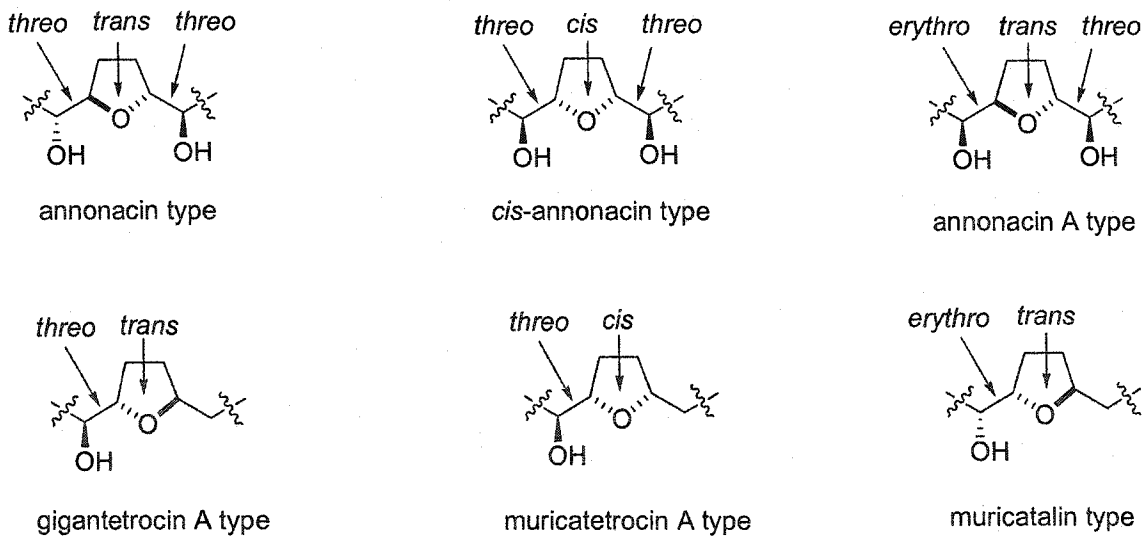


Figure 1.2. Mono-THF acetogenins

Adjacent bis and tri-THF acetogenins: The most important structural differences between the adjacent bis-THF subgroups lie in the stereochemical pattern and the number

of flanking hydroxyl groups. Six types of dihydroxylated acetogenins have been isolated: asimicin,[11] bullatacin,[12] rolliniastation 1,[13] trilobacin,[14] squamocin-I[15] and squamocin-N[15] types. Two other types of acetogenins, bearing adjacent bis-THF rings with one flanking hydroxyl (bulladecin and rollindecin A types), have also been identified. The only example of a naturally occurring tri-THF is goniocin (**Figure 1.3**).[16]

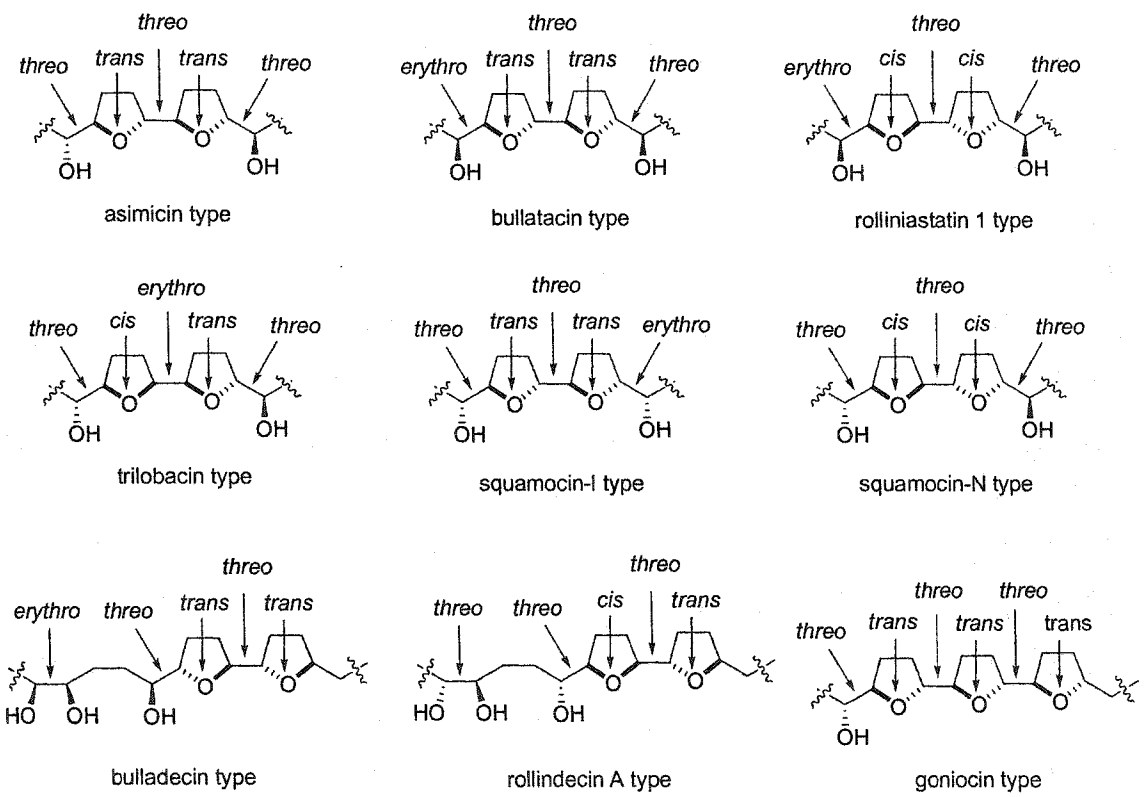


Figure 1.3. Adjacent THF's acetogenins

Non-adjacent bis-THF acetogenins: Acetogenins with a non-adjacent bis-THF core generally contain two mono-THF subunits that are connected by a 1,4-butane diol. The distal ends of the two THF rings are connected to a carbinol center and a methylene. There are six subgroups classified according to their different stereochemical patterns:

gigantecin,[17] 12,15-*cis*-bullatanocin,[18] bullatalicin,[19] 12,15-*cis*-bullatalicin,[18] sylvaticin,[20] and cis-sylvaticin.[18] A new type of non-adjacent bis-THF acetogenins (aromin type) was isolated recently. These compounds consist of a mono-THF segment with two flanking hydroxyls and another mono-THF subunit with flanking methylene carbons. A pentanoyl residue links the two residues (**Figure 1.4**).

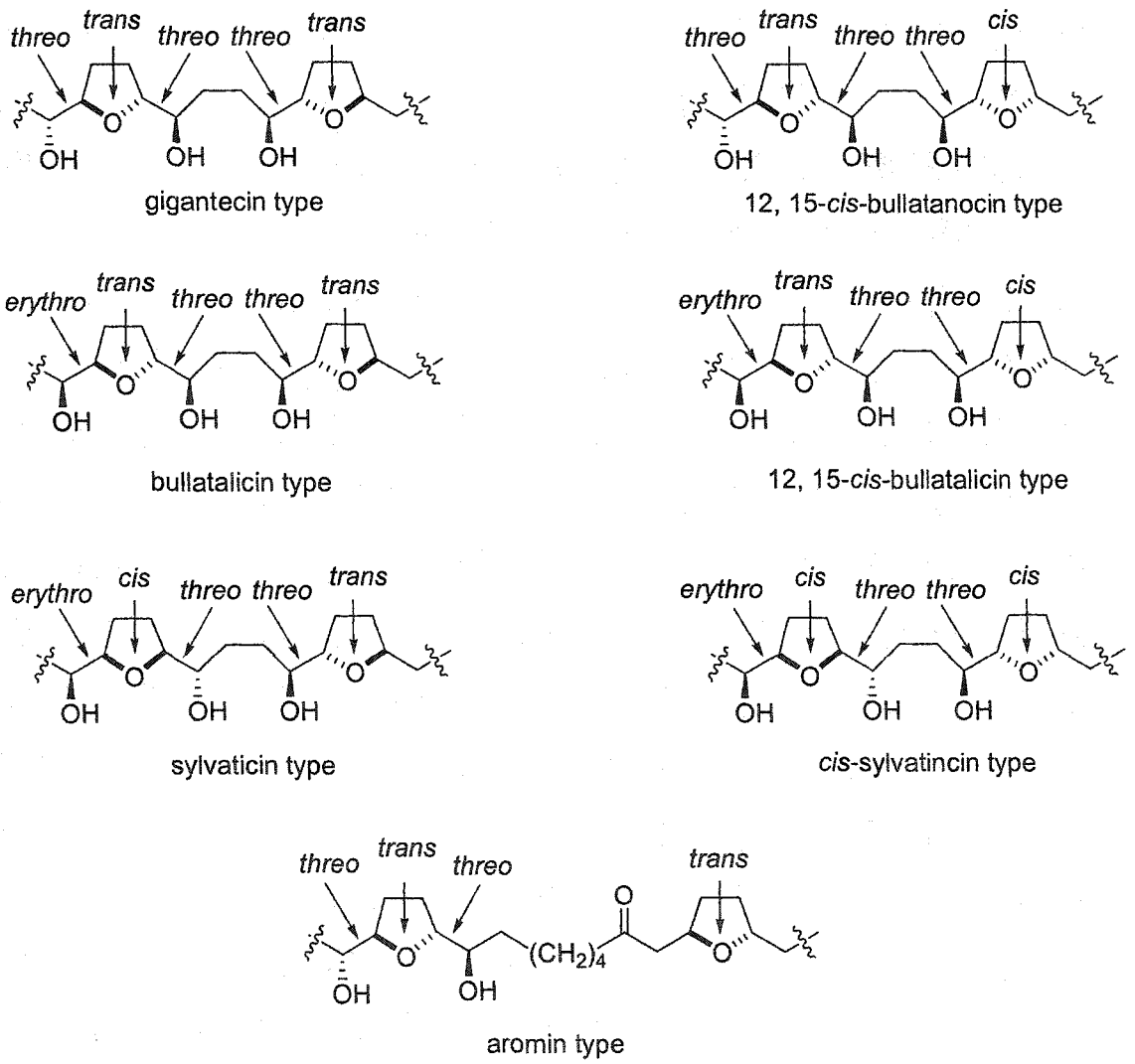


Figure 1.4. Non-adjacent bis-THF acetogenins

Acetogenins containing no THF or THP rings: This class of annonaceous compounds contains C_{35} or C_{37} long hydrocarbon chains and a methylated α,β-unsaturated γ-lactone at one end, but no THF or THP rings. They often bear hydroxyls, ketones, epoxides and/or double bonds. Approximately fifteen non-ring acetogenins have been isolated (**Figure 1.5**).

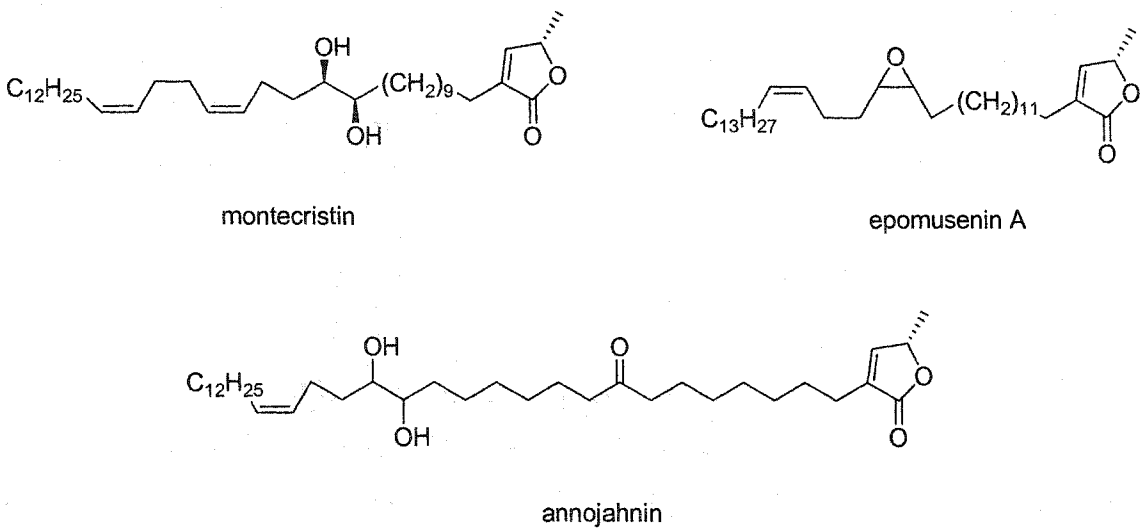


Figure 1.5. Classification of non-ring acetogenins

Non-Classical THP acetogenins: More recently, several acetogenins with a THP ring have been isolated. These may be classified into three major groups: mono-THP's, and bicyclic THP-THF structures that are adjacently or non-adjacently linked. Mono-THP acetogenins (pyranicin and pyragonicin) have a 2,6-substituted, 5-hydroxy pyran ring with one flanking hydroxyl group. Adjacent THP-THF structures (jimenezin type) contain a hydroxylated THP ring along with an adjacent THF ring. Non-adjacent THP-THF analogues (mucocin type) have a mono-THF ring bearing one flanking hydroxyl and a 2,6-substituted, 5-hydroxy pyran ring (**Figure 1.6**).

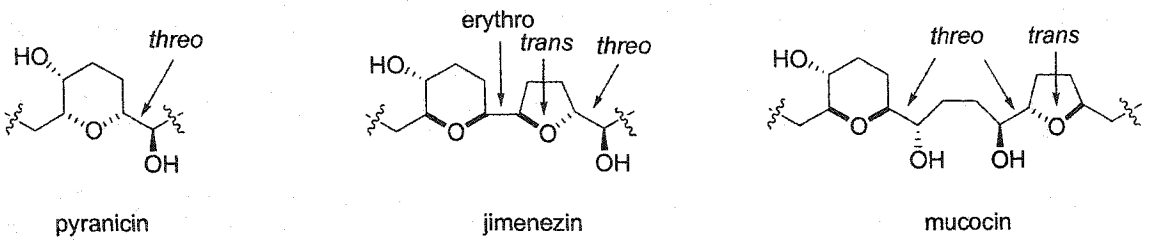


Figure 1.6. Non-classical THP acetogenins

Acetogenins with modified butenolide subunits: Three different types of γ-lactone moieties are known: a 3-linked, α,β-unsaturated 4-methyl γ-lactone, a 4-linked, 2-acetonyl γ-lactone and a 2-linked β-hydroxyl 4-methyl γ-lactone (**Figure 1.7**). The first subgroup, of which is the most common. Several examples have been illustrated in the foregoing discussion, examples of the last two subgroups are (2,4-trans)-28-hydroxybullatacinone and jetein respectively.

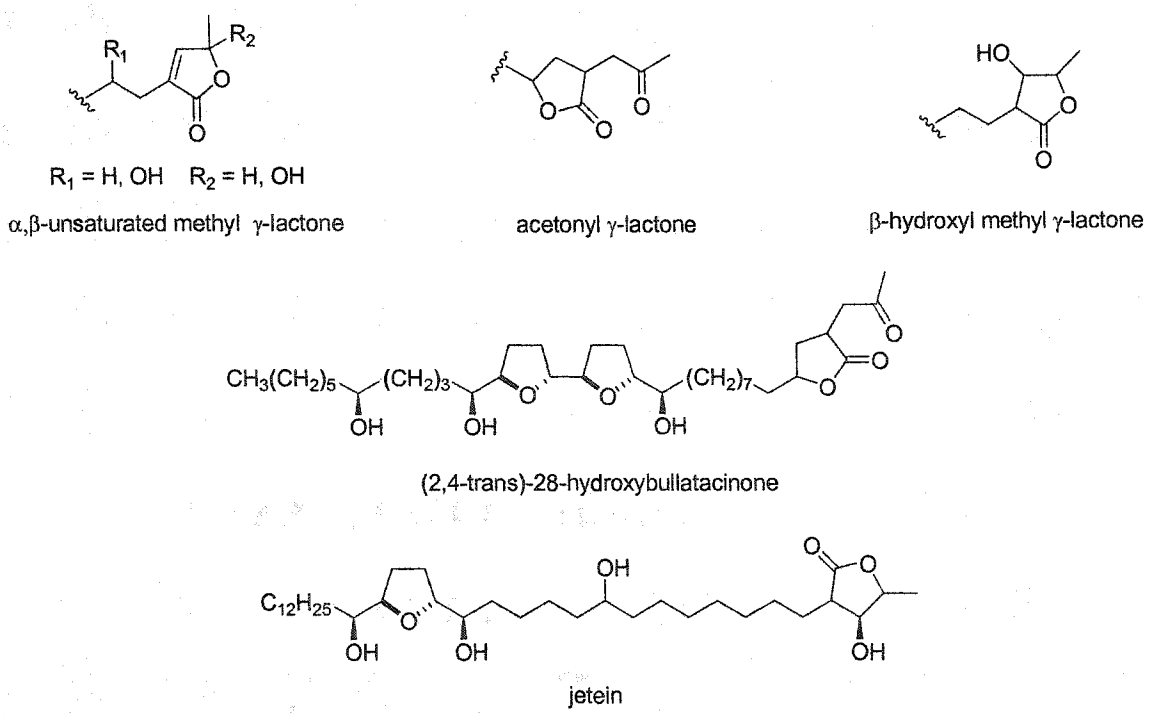


Figure 1.7. Butenolide analogs

1.2 Mechanism of Bioactivity

Generally, annonaceous acetogenins exhibit a wide range of potent biological activities including insecticidal, parasiticidal, fungicidal, herbicidal and antitumor properties. These effects are believed to originate in the inhibition of mitochondrial NADH-quinone oxidoreductase (complex I). This leads to a decrease in ATP production, and as a consequence, apoptosis (programmed cell death).[21-24] Although other mechanisms have been suggested, these do not account for the variety of biological effects.[25]

Complex I is a membrane-bound protein of the mitochondrial electron transport system in mammalian mitochondria, and is the most intricate repiratory enzyme complex, consisting of 43 different subunits. Complex I catalyses electron transport from intramitochondrial NADH to ubiquinone (coenzyme Q) contained within the mitochondrial inner membrane (**Figure 1.8**). Electron transfer from NADH to ubiquinone is coupled to proton pumping which leads to a net transfer of four protons from the matrix to the intermembrane space, and generates a membrane potential across the inner mitochondrial membrane. Discharge of this electrochemical gradient by passage of protons back into the mitochondrial matrix is an exergonic process. This energy is harnessed by ATP synthesis to drive the conversion of ADP to ATP.[26]

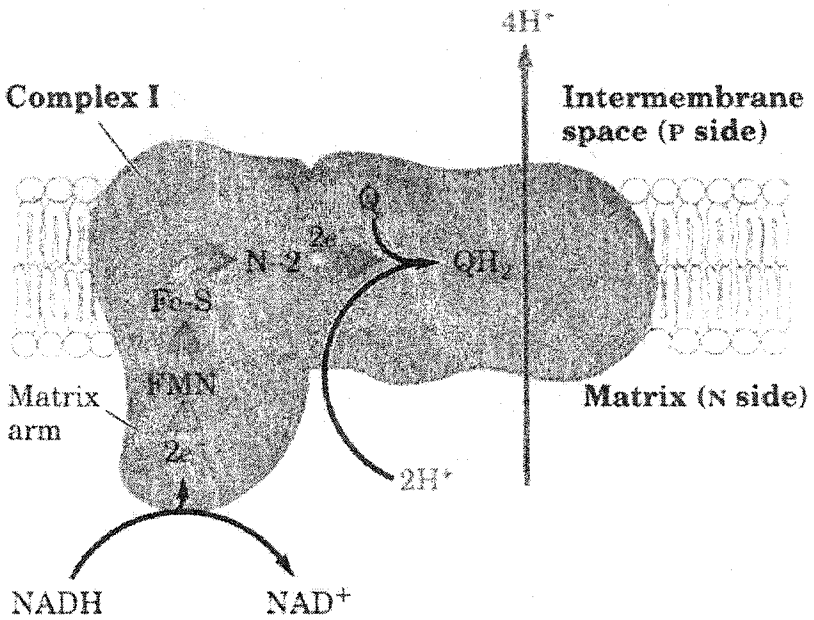
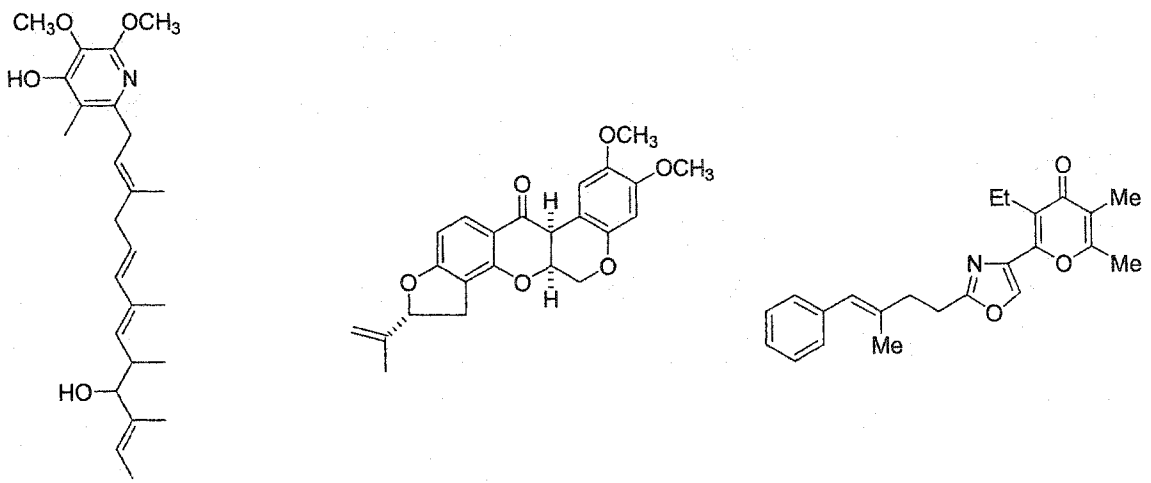


Figure 1.8. NADH dehydrogenase (complex I)

The annonaceous acetogenins are the most potent inhibitors of mammalian mitochondrial complex I (also called NADH:ubiquinone reductase). Few studies have explored the mechanism of action at the molecular level. It is well established that the heart of the enzymic mechanism of complex I lies in its interaction with ubiquinone. The active site is traditionally called the 'rotenone site', since rotenone is the classical potent inhibitor which blocks interaction of complex I with ubiquinone, thereby ultimately inhibiting proton pumping. The wide variation in the structure of the acetogenins, rotenone, and other well known complex I inhibitors such as piericidin A and phenonxan suggests that different inhibitors may interact at different regions on the enzyme (**Figure 1.9**).[27] Indeed Friedrich *et al.*[28] has shown that annonin VI and piericidin A inhibit complex I from three different species in a partially competitive manner; whereas rotenone and phenoxan acted in a non-competitive manner. Recent studies by Miyoshi *et*

al. (vide infra) also suggest that THF acetogenins with or without the butenolide may act at different sites on complex I.[24,29]



piericidin A
FQT IC_{50} = 5 nM

rotenone
FQT IC_{50} = 20 nM

phenoxan
MT-4 IC_{50} = 6.6 μM

Figure 1.9

The high Ca^{2+} complexation ability of the THF containing acetogenins have been demonstrated by NMR studies.[30-33] These investigations show that the relative configurations, as well as the nature of the cation, are important factors for this complexation (**Figure 1.10**). Given that complex I is an iron cluster protein, some authors postulate that acetogenins may interfere with the enzyme by ion complexation.[34] However, this hypothesis has not been supported by experimental data. Nevertheless, Ca^{2+} plays an important role in other cellular mechanisms and calcium complexation may affect other biological functions.

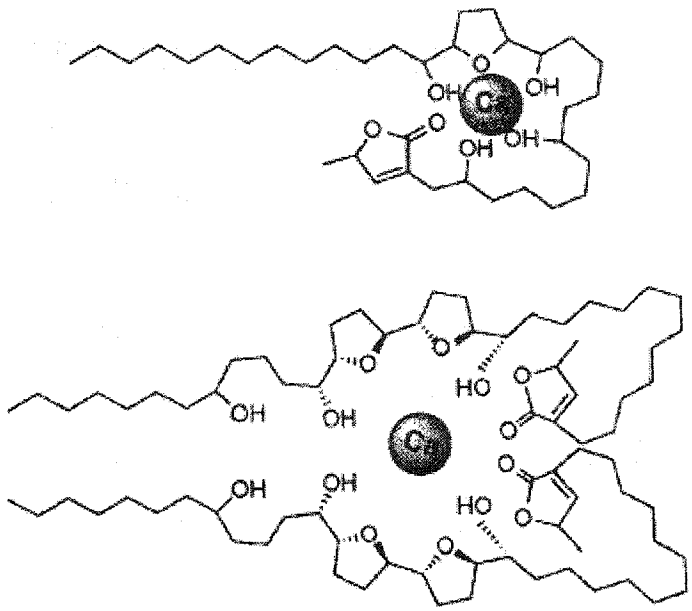


Figure 1.10. Ca^{2+} Complexes of Annonaceous Acetogenins

The major interest in the acetogenins derives from the idea that they represent a future generation of antitumor drugs. They have also attracted attention in other disease mechanisms due to the implication of complex I in a number of congenital and acquired conditions, idiopathic Parkinson's disease, maturity onset diabetes and stroke-like episodes.[35-37]

Many structure activity studies (SAR's) for several human tumor lines have been undertaken.[38-40] A review of this data reveals different general tendencies for each tumor cell line. For example, against the human lung, breast and colon carcinoma cells (A-549. MCF-7 and HT-29 respectively) the most potent groups of acetogenins (considering ED_{50} values) are some of the adjacent bis-THF α,α'-dihydroxylated acetogenins, followed by the non-adjacent bis-THF acetogenins. Mono-THF α,α'-dihydroxylated acetogenins show intermediate potency, followed by the mono-THF α-monohydroxylated ones. Some of the polyhydroxylated and tetrahydroxylated ketonic mono-THF α,α'-dihydroxylated

acetogenins have the weakest inhibitory potency. However, these tendencies are significantly different against human prostate adenocarcinoma (PC-3), human pancreatic carcinoma (MIA PACA-2) and human kidney carcinoma (A-498) cells, where the mono-THF acetogenins are the most potent series. The weakest potency against these tumor cell lines is presented in the bis-THF asimicin type and the linear acetogenins. Preliminary results by Schwaller[41] and later by Oberlies[42] indicate that the bis-THF acetogenin rolliniastatin-2 (bullatacin type) was also effective against growth of multidrug resistance (MDR) culture cells in the adriamycin-resistant human mammary adenocarcinoma model (MCF-7). This study suggests that rolliniastatin-2 or bullatacin could be effective against normal as well as multidrug resistance tumor types. A more detailed SAR discussion follows several studies have been carried out.

The cyclic ether residue: Based on the results of ^{1}H NMR spectroscopic and differential scanning clorimetry studies of acetogenins in liposomal membranes, McLaughlin and colleagues[43,44] proposed a model for the active conformation in the membrane environment. The THF core with flanking hydroxyl groups resides near to the glycerol backbone of phosphatidylcholine irrespective of the number of THF rings and acts as a gydrophilic anchor at the membrane surface; so that the γ-lactone ring interacts directly with the target site of complex I (possibly, the ubiquinone reduction site[45]), by lateral diffusion in the mitochondrial membrane interior (**Figure 1.11**). If the role of the THF rings is, indeed, an anchor at the interface of the membrane, the stereochemical differences within the THF rings of the acetogenins might not be critical for bioactivity. This is supported by the observation that the potencies of rollinisatatin 1 and bullatacin, which differ from each other only in the stereochemical arrangement of the THF rings,

are almost identical (**Figure 1.12**).[46] On the other hand, the number of THF rings could be important for activity, since a mono-THF structure might be anchored less strongly than an oligo-THF. Indeed preliminary studies of inhibition of the oxygen consumption by rat liver mitochondria[47] found that both bis-adjacent THF and bis-nonadjacent THF acetogenins were more active than mono-THF acetogenins (**Figure 1.13**). The presence of an increasing number of hydroxylations, up to by three, increased activity within all groups. However, the presence of OH groups appears to be favorable, but not crucial, for potent activity.

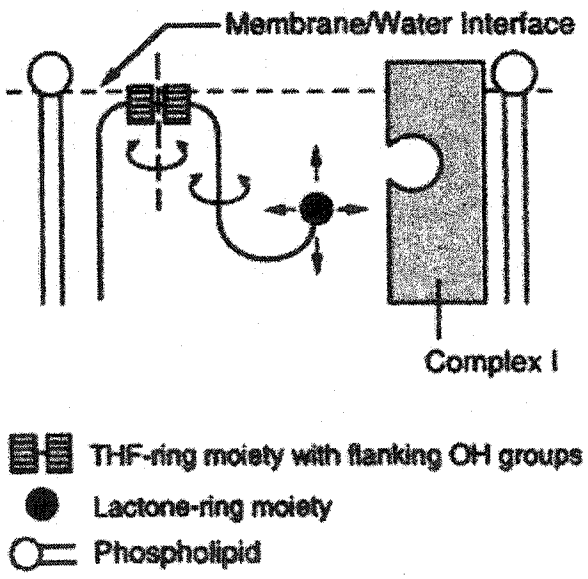
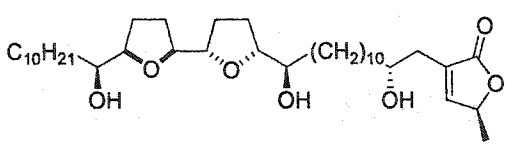
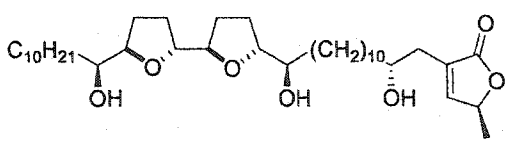


Figure 1.11. Model of the active conformation of acetogenins interacting with complex I



Rolliniastatin 1

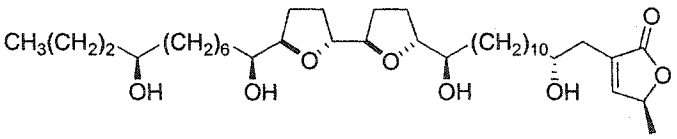
WT IC_{50} = 4.7 ± 0.5 μM



Bullatacin

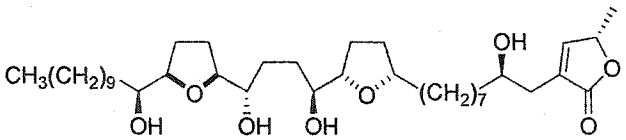
WT IC_{50} = 10.1 ± 0.1 μM

Figure 1.12



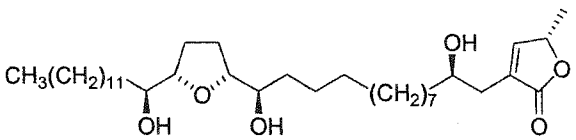
31-Hydroxybullatacin

A-549 $ED_{50} < 10^{-8}$ μg/ml



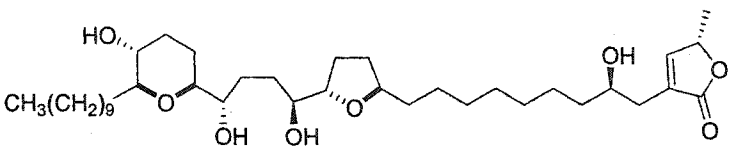
cis-Sylvaticin

A-549 $ED_{50} < 10^{-8}$ μg/ml



16,19-cis-Murisolin

A-549 $ED_{50} = 3.14 \times 10^{-3}$ μg/ml



Mucocin

A-549 $ED_{50} = 1.0 \times 10^{-6}$ μg/ml

Figure 1.13. Bioactivity of acetogenins with different cyclic ether segments

The γ-lactone ring: The marked decrease in cytotoxicity (about 10^6 fold) that resulted when the double bond in α,β-unsaturated γ-lactone ring of bullatacin was reduced, suggested that the lactone ring was critical for activity.[43,44] It was proposed that the THF ring and the butenolide act in a cooperative manner on complex I. However, a

recent study by Miyoshi *et al.*[48] suggested that the γ-lactone ring moiety may not be crucial for activity.[29,48] The bulky *n*-butyl derivative (replace γ-methyl lactone by γ-butyl lactone) retained fairly potent activity, indicating that steric hindrance around the γ-lactone ring does not severely interfere with binding to the enzyme (**Figure 1.14**). Other groups have shown that the γ-lactone ring itself can be substituted with a ubiquinone ring (**Figure 1.14**).[49] Stereochemistry of the γ-methyl group is not an important structural factor for the potent inhibition. These results suggest that the interaction of the γ-lactone ring moiety with the enzyme is not very tight, and that structures without this residue may cause inhibition by interaction at other sites on the enzyme.

The polymethylene spacer: The γ-lactone ring is connected to the THF ring moiety by a flexible alkyl spacer. Among the potent analogues, the most common spacer length is 13 carbons. Extension of the spacer above 13 carbons has a much greater negative effect on the activity than shortening the chain to less than 13 carbons (**Figure 1.15**).[48,50,51] The length of the spacer may be closely associated to an optimal conformation of the spacer itself, which, in turn, may govern a preferred spatial positioning of the γ-lactone and THF ring moieties in the enzyme.

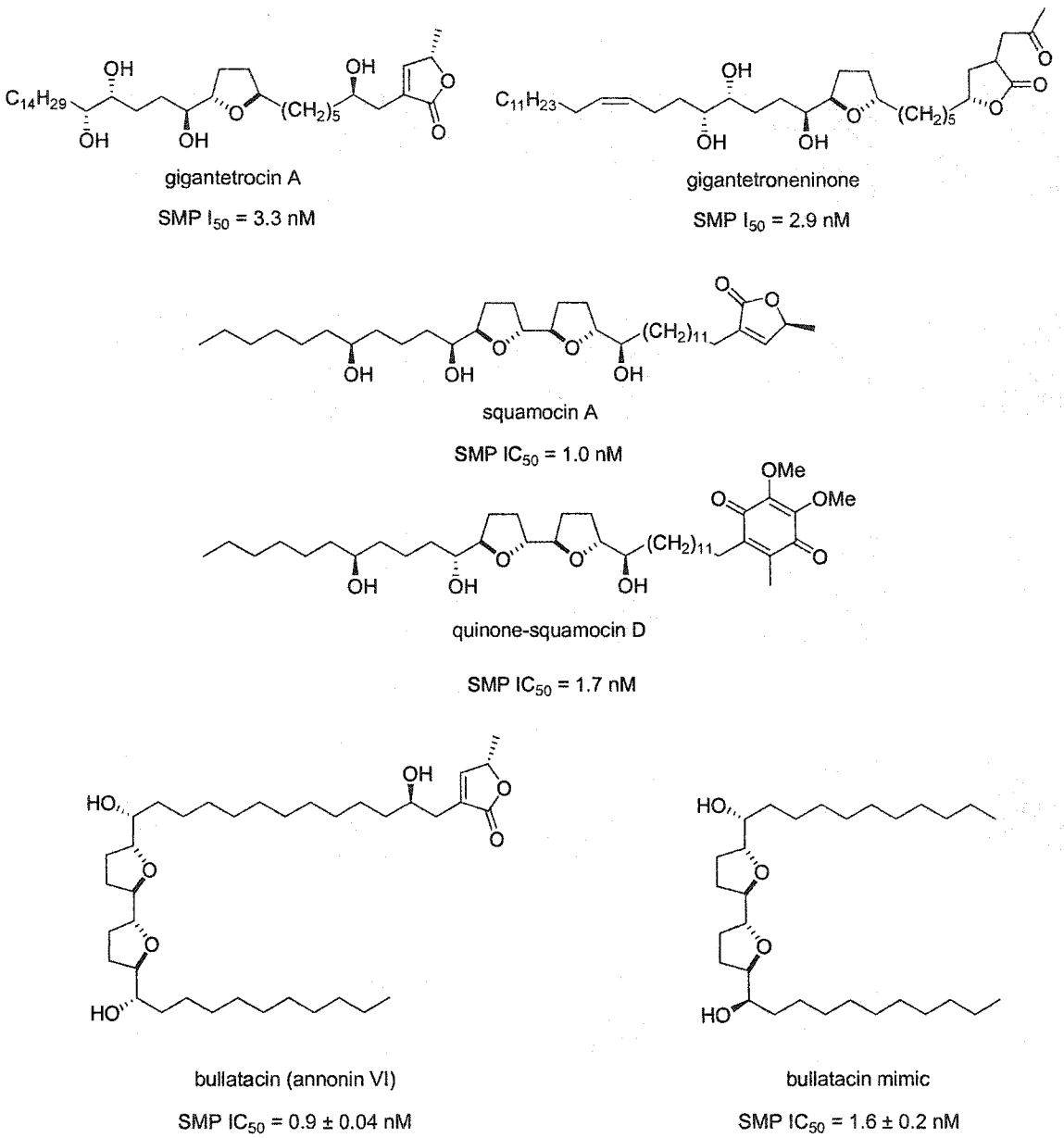
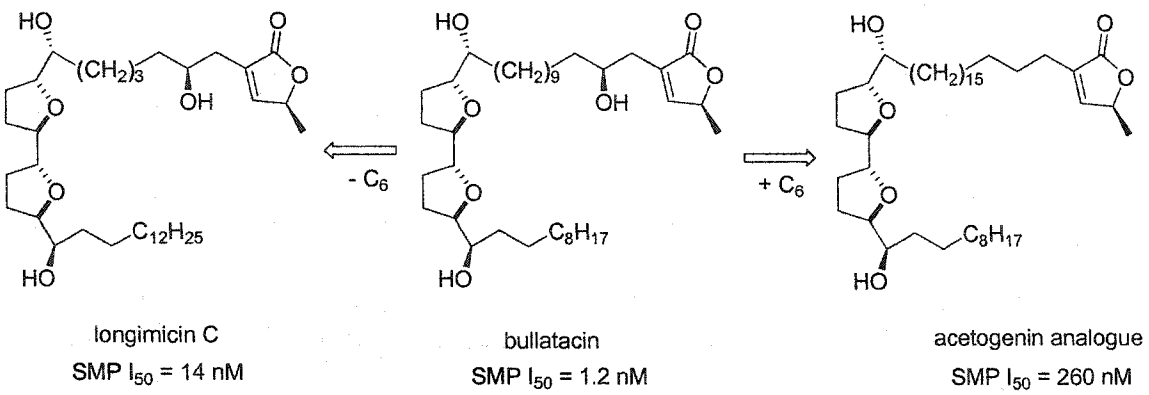


Figure 1.14 Effect of butenolide modification



longimicin C
SMP I_{50} = 14 nM

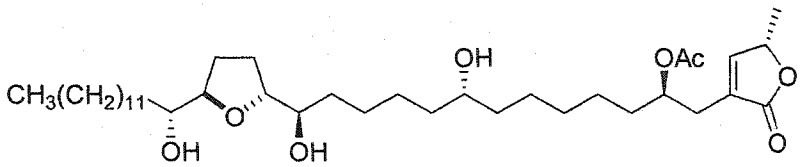
bullatacin
SMP I_{50} = 1.2 nM

acetogenin analogue
SMP I_{50} = 260 nM

Figure 1.15. Effect of length of the polymethylene spacer

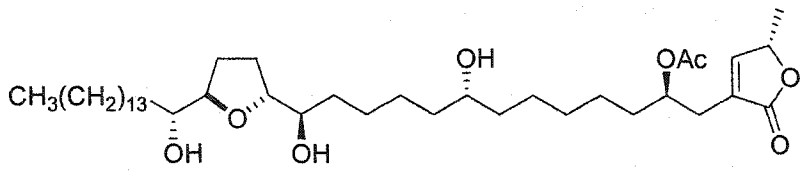
4,10-dihydroxy substitution pattern in the spacer moiety is one of common structural features of natural acetogenins. The OH substitution pattern does not appear to be essential for potent activity. It has been suggested too many polar functional groups within the spacer moiety may prevent the γ-lactone and THF ring moieties from adopting the spatial location required for optimal binding.

The hydrocarbon side chain: A chain length of 13 carbons appears to be optimal. It has been proposed that the decreased activity that results with chain lengths greater than 13 carbons may be due to too tight attachment in the hydrophobic lipid bilayer of the membrane (**Figure 1.16**). If other structural factors are identical, a less hydrophobic tail is favorable for activity. However, a shorter tail structure alone does not ensure increased activity.[51]



4-acety-lannonacin

SMP I_{50} = 4.1 nM



4-acetyl-xylomaticin

SMP I_{50} = 6.1 nM

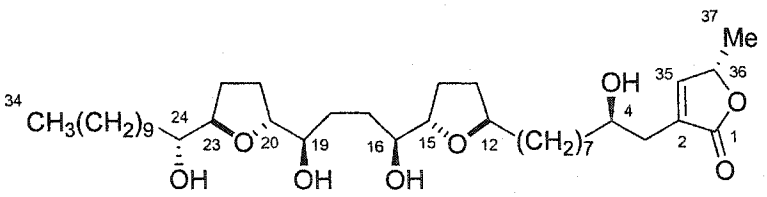
Figure 1.16. Effect of length of the hydrocarbon side chain

1.3 Synthesis

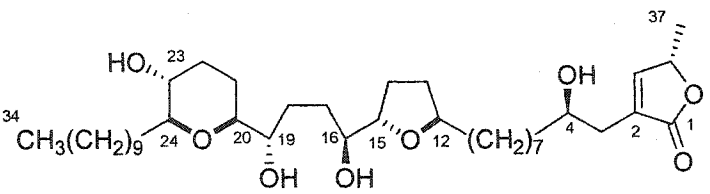
As mentioned earlier, the three major subgroups of the THF containing acetogenins are the mono-THF's, the adjacently linked bis-THF's and the non-adjacently linked bis-THF's. The first two groups have attracted the majority of attention from synthetic chemists, and these efforts are documented in several reviews.[52-65] The focus of this current research is the development of methods for the non-adjacent bis-THF subgroup. Two total syntheses of non-adjacent bis-THF acetogenins[66,67] and the preparation of an advanced bis-THF subunit for (-)-4-deoxygigantecin[68] have been reported. Four syntheses of the related THP-THF acetogenin mucocin have also been performed.[69-72] The syntheses of these non-adjacently linked cyclic ether acetogenins will first be reviewed. In so far as these approaches comprise methodologies for mono-THF's

and butenolide subunits, selected other strategies to mono-THF's and butenolides that are especially suitable for application to non-adjacent bis-THF's will be also discussed. Finally, the olefin metathesis and other key segment coupling reactions that have been used in the syntheses of the THF acetogenins will be reviewed.

The non-adjacent bis-THF or THP-THF acetogenins can be divided into four segments: the cyclic ether core unit, the butenolide, the polymethylene spacer and the hydrocarbon side chain. Bullatanocin[73] and mucocin[74] are representative structures (**Figure 1.17**). Two general approaches to these frameworks have been reported: a linear strategy in which each subunit is added in a stepwise fashion, or a convergent plan in which complex segments are assembled separately and coupled together at a late stage in the synthesis. The convergent approach is especially attractive for the assembly of compound libraries.



Bullatanocin (Squamostatin C)



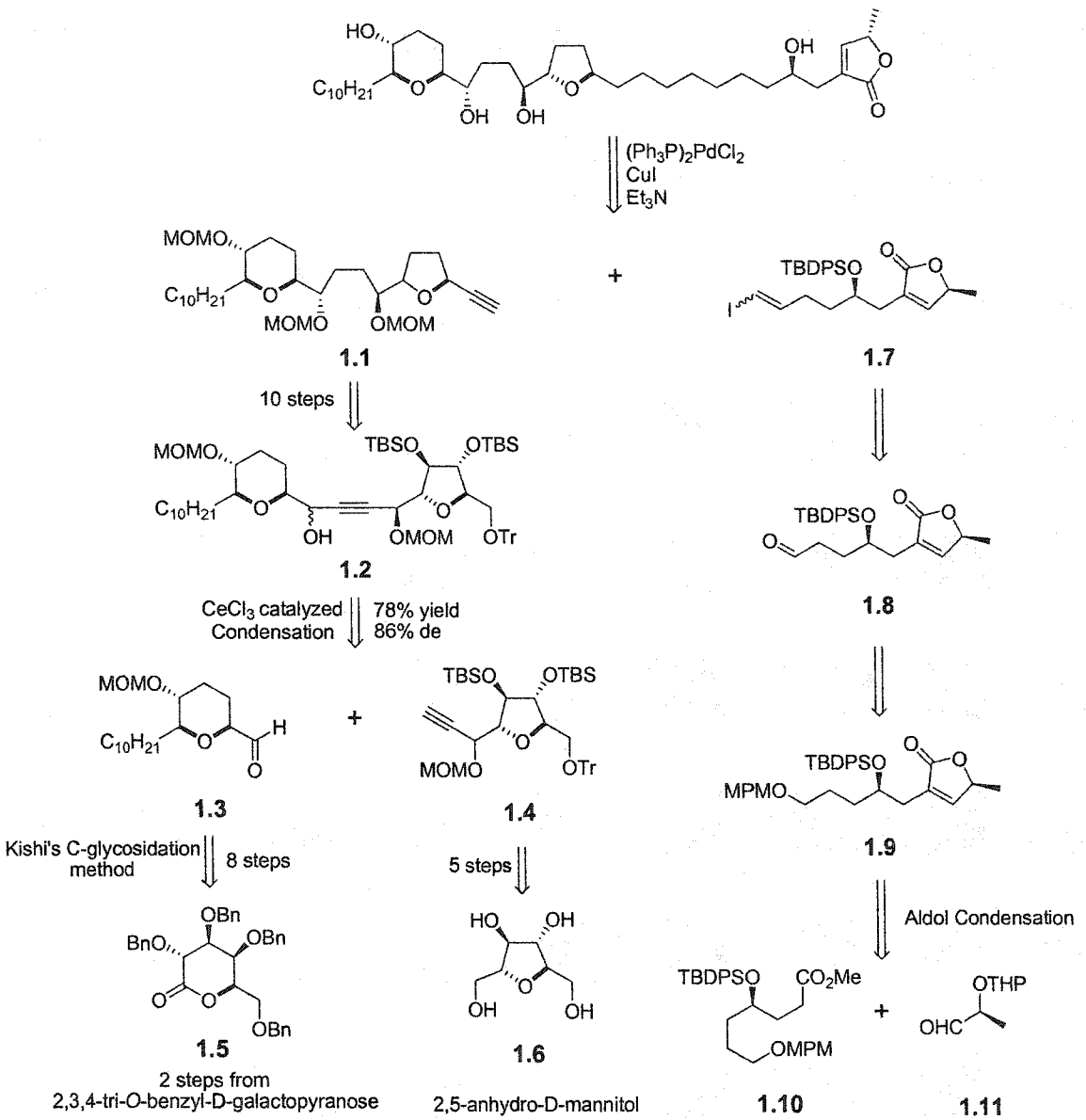
(-) Mucocin

Figure 1.17. Structures of bis-THF and THP-THF non-adjacent acetogenins

1.3.1 Total syntheses of non-adjacently linked cyclic ethers acetogenins

Takahashi's first synthesis of mucocin: Takahashi reported the first total synthesis of a non-adjacently linked cyclic ether acetogenin. The non-adjacent THP-THF core unit was assembled through the Ce(III) mediated condensation of a THP-aldehyde and THF-alkyne subunits. The mono-THP segment was derived by taking advantage of Kishi's C-glycosidation methodology. The synthesis of mono-THF segment started from commercially available 2,5-anhydro-D-mannitol. The γ-lactone **1.7** was synthesized via an aldol condensation that was previously developed by Yao and Wu's in their syntheses of a mono-THF acetogenin.[75] Thus, reaction of the enolate of **1.10** and **1.11**, followed by hydrolysis of the THP protecting group and esterification provided lactone **1.9**. The derived aldehyde **1.8** was then transformed to the vinyl iodide **1.7**. Sonogashira coupling of vinyl iodide **1.7** and the THP-THF segment **1.1** following the procedure developed by Hoye[56] provided the enyne product. Catalytic hydrogenation and alcohol deprotection led to mucocin (**Scheme 1.1**).[72]

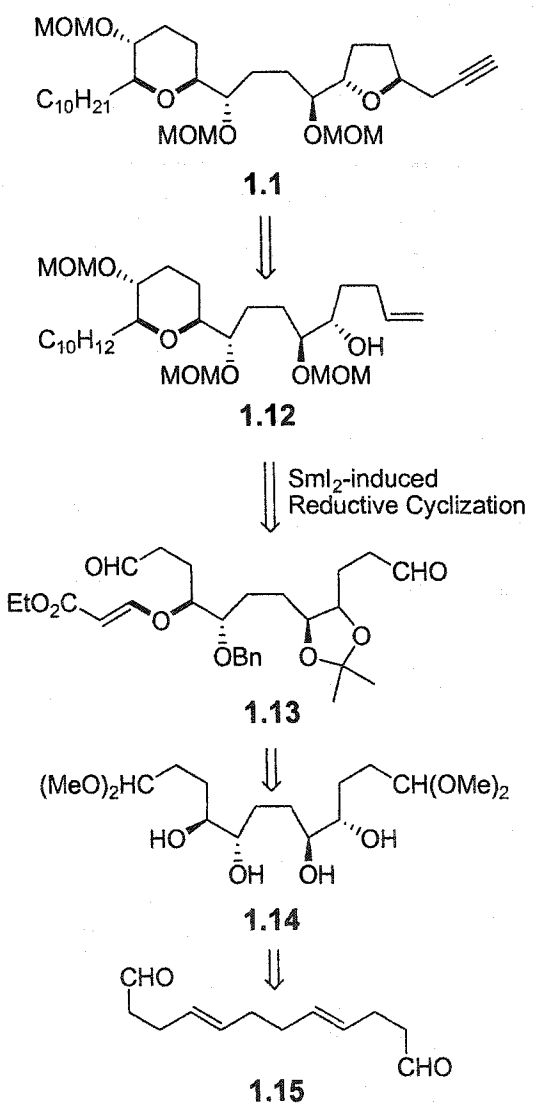
Although the strategy is convergent, a weak point is the coupling of THF and THP subunits, which occurs in 78% yield and 86% selectivity. The several steps required for conversion of **1.2** to **1.1** are also a drawback.



Scheme 1.1. Takahashi's first synthesis of mucocin

Takahashi's second synthesis of mucocin: The second synthesis of mucocin involved a new synthesis of the THF-THP precursor **1.1**.[67,69,76-79] The THP ring in the core unit **1.1** was constructed by the SmI_2-induced reductive cyclization, whereas the *trans*-THF ring was synthesized by oxidative cyclization of a homoallyl alcohol with

TBHP in the presence of $[Co(modp)_2]$. A key precursor was the dialdehyde **1.13**, which was obtained from the C_2 symmetric bis-(dihydroxy acetal) **1.14**. Compound **1.14** was prepared via a two directional dihydroxylation strategy on dialdehyde diene **1.15** (**Scheme 1.2**).

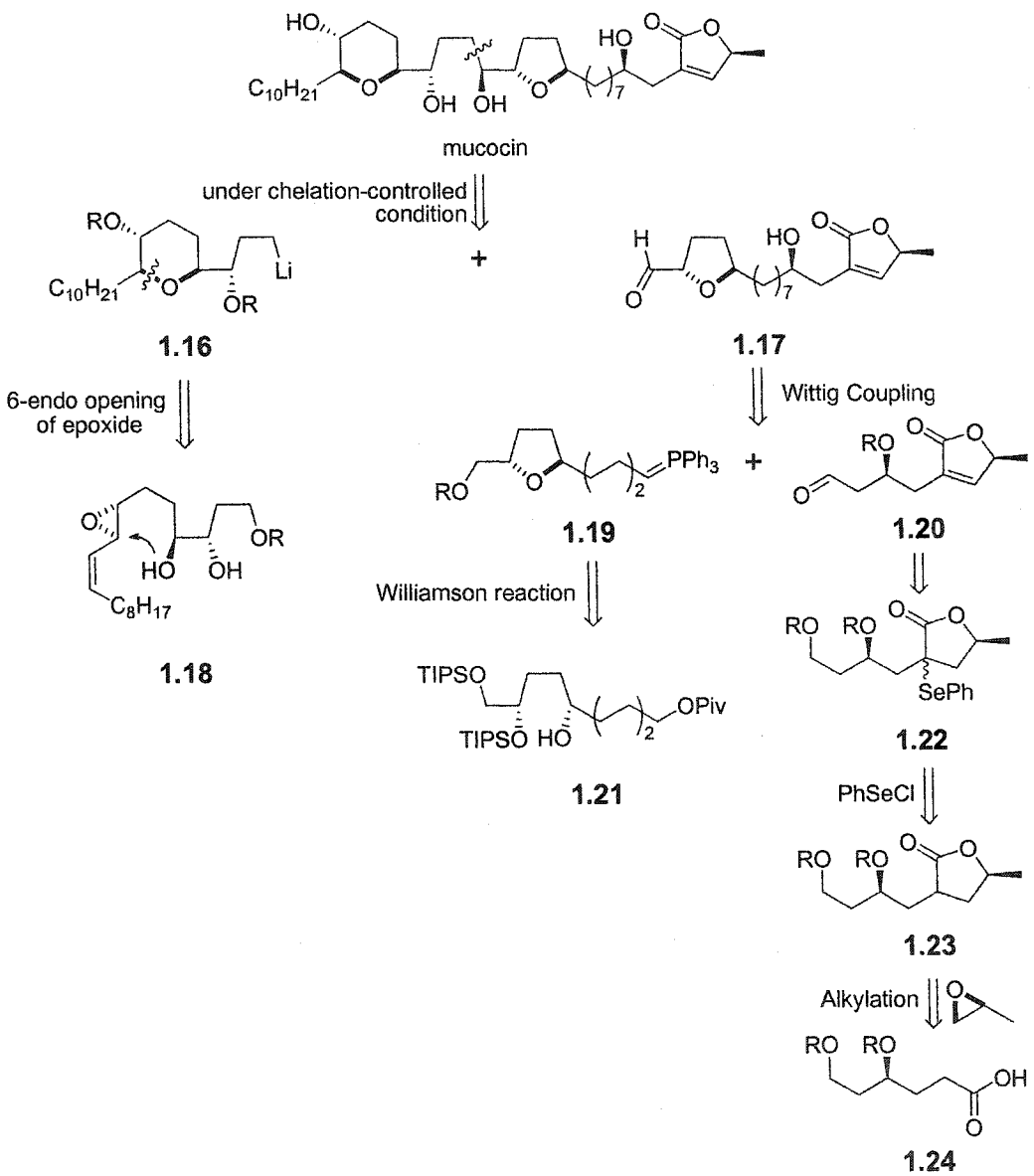


Scheme 1.2. Takahashi's second synthesis of mucocin

Koert's synthesis of mucocin: Koert synthesis of mucocin was highly convergent.[71] The target structure was assembled by addition of a THP organometallic compound **1.16** to a THF aldehyde **1.17** under chelation-controlled conditions. The THP ring was constructed with a double-bond directed 6-*endo* opening of epoxide **1.18**.[78] Cyclization of hydroxy-epoxides is a common approach to cyclic ethers and has been used in several THF containing acetogenin syntheses.[66,67,77,80-85] The THF ring was built via an intramolecular Williamson reaction. Wittig coupling of the THF ylide **1.19** with butenolide aldehyde **1.20** and subsequent processing of the product afforded the THF aldehyde **1.17**. Sinha and co-workers have used a similar Wittig connection in the synthesis of adjacently linked acetogenin.[86] The synthesis of the butenolide aldehyde started with the alkylation of the enolate derived from carboxylic acid **1.24** with (*S*)-propylene oxide to give the butyrolactone **1.23**. The α,β-unsaturated bond was introduced by a standard selenation-selenium oxide elimination sequence (**Scheme 1.3**).[70,87-89]

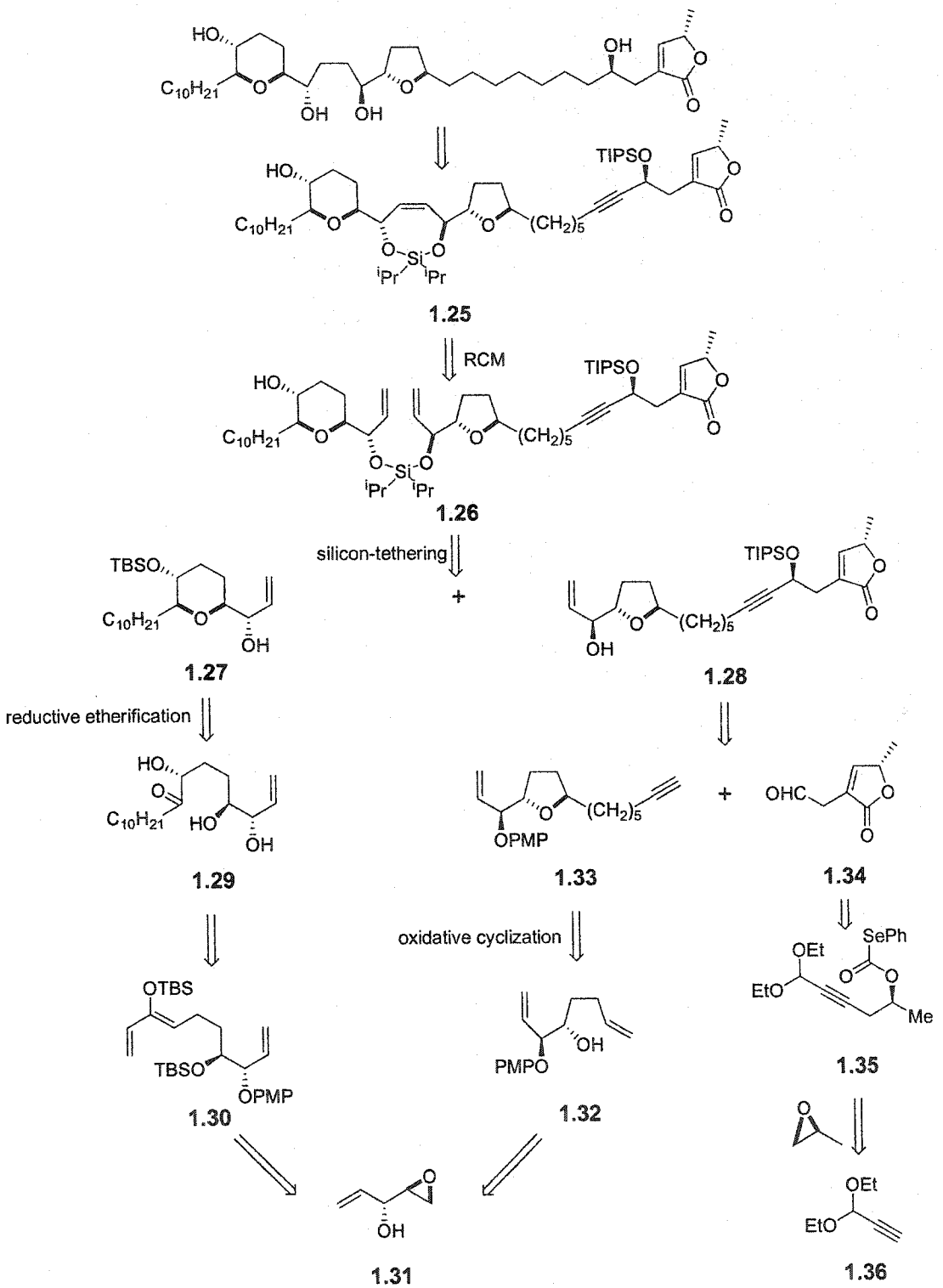
Evans' synthesis of mucocin: Evans' synthesis of mucocin involved a silicon-tethered ring-closing metathesis as the key segment coupling reaction.[70] Two building blocks mono-THP **1.27** and mono-THF **1.28** were constructed from homoallylic epoxide **1.31**. The synthesis of the mono-THP ring entailed a novel bismuth(III) mediated reduction etherification on ketotriol **1.29**.[90,91] Treatment of **1.29** with bismuth tribromide and *tert*-butyldimethylsilane in acetonitrile, followed by *in situ* protection of the secondary alcohol, furnished the *tert*-butyldimethylsilyl ether **1.27** in 93% yield (*ds* $\geqslant$ 19:1). The THF subunit was generated by a cobalt (II) catalyzed oxidative cyclization on bishomoallylic alcohol **1.32** following Takahashi's procedure.[69,92] The precursors for the

THP and THF segments **1.29** and **1.32** respectively were obtained through relatively straightforward sequences, in four and two steps from identical starting epoxide **1.31**.



Scheme 1.3. Koert's synthesis of mucocin

The synthesis of butenolide fragment **1.34** was accomplished through a novel acyl radical cyclization.[87,88] The regioselective ring opening of commercially available (*S*)-propylene oxide followed by treatment with the carbanion derived from the alkyne **1.36** afforded the secondary alcohol, which was converted to the selenocarbonate **1.35**. Treatment of **1.35** with *n*-Bu_3SnH in the presence of AIBN afforded the *exo*-cyclic isomer of the α,β-unsaturated butyrolactone. Rhodium catalyzed isomerization of the *exo*-cyclic olefin and subsequent hydrolysis of the diethyl acetal furnished butenolide **1.34**. Two coupling reactions were used to assemble the complete mucocin framework from THP **1.27**, THF **1.33** and butenolide **1.34**. An enantioselective addition was used to connect mono-THF **1.33** and **1.34** fragments, and the product propargylic alcohol converted to the silyl ether **1.28**. Next, the temporary silicon-tethered ring-closing metathesis strategy was applied to **1.28** and the THP subunit **1.27**. The construction of the mixed bis-alkoxy silane **1.26** started with the treatment of the mono-THP **1.27** with excess diisopropyldichlorosilane to afford the *mono*-alkoxychlorosilane. Removal of excess silylating agent and addition of the mono-THF **1.28** gave **1.26** in 74% yield. Ring-closing metathesis of the silicon-tethered diene **1.26** using stoichiometric Grubbs' catalyst furnished **1.25** in 83% yield. The synthesis was concluded by fluoride-mediated, silyl ether deprotection, followed by chemoselective reduction of the isolated alkene and alkyne moieties (**Scheme 1.4**).



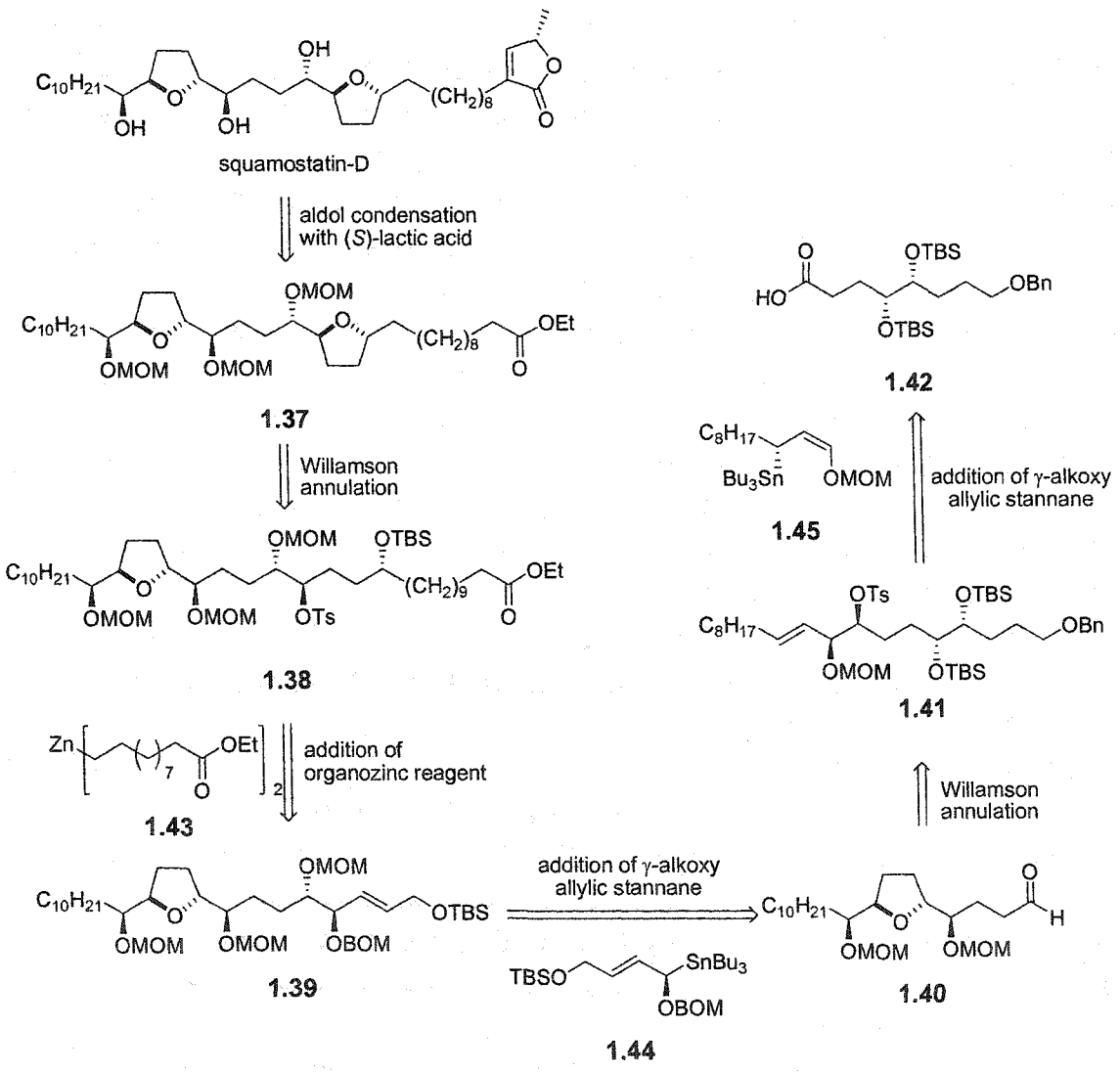
Scheme 1.4 Evans' synthesis of mucocin

In this synthesis, the two cyclic ethers and the butenolide subunit were synthesized individually. The bismuth(III) mediated THP synthesis and the radical cyclization used for the butenolide segment are novel aspect of these procedures. The novel temporary silicon-tethering methodology-ring-closing metathesis should be very general for non-adjacently linked acetogenins.

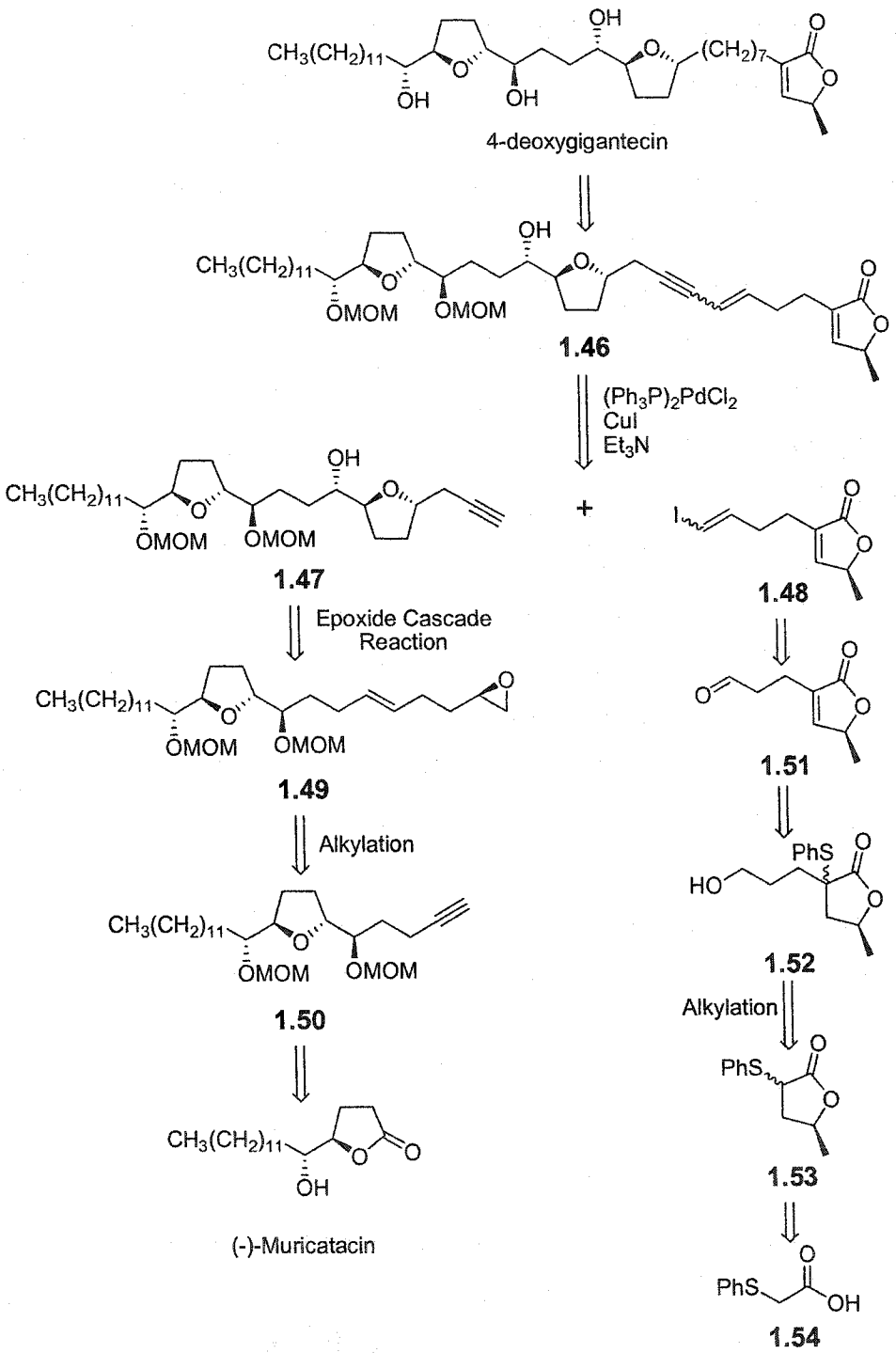
Marshall's synthesis of squamostatin-D: Marshall synthesized squamostatin-D through two Willamson annulations (**Scheme 1.5**).[66] A key precursor was the non-adjacent bis-THF's **1.37**, which was obtained from Willamson annulation on **1.38**. Compound **1.38** was prepared from mono-THF aldehyde **1.40** and involved the highly stereoselective addition of chiral (*S*)-α-alkoxy allylic stannane **1.44** in the presence of $InCl_3$ to give **1.39**. Compound **1.39** was next converted to the saturated aldehyde derivative. Addition of the zinc derivative **1.43** to this aldehyde, in the presence of the titanate catalyst, gave **1.38**. The THF ring in **1.40** was constructed by another Willamson annulation on **1.41**. The alkene **1.41** was prepared from **1.42** via addition of the (*R*)-γ-alkoxy allylic stannane **1.45**. The butenolide segment of squamostatin-D was introduced into non-adjacent bis-THF's **1.37** by a modification of the synthesis used in Takahashi's first synthesis of mucocin.[75] Since all stereocenters are introduced by chiral reagents, it should be straightforward to prepare diastereomeric non-adjacent bis-THF's acetogenin analogs by this approach.

Tanaka's synthesis of (+)-4-deoxygigantecin: Tanaka's synthesis of 4-deoxygigantecin involved a Pd-catalyzed cross coupling reaction of the non-adjacent bis-THF's **1.47** and vinyl iodide **1.48**. [67,69,76-79] The bis-THF ring in **1.47** was synthesized via a linear strategy from natural (-) muricatacin. The γ-lactone **1.48** was synthesized

following the procedure developed by Hoye.[56] The key intermediate was **1.53**, which was obtained from **1.54**. Alkylation of α-SPh lactone **1.53** with 3-iodopropanol and subsequent sulfoxide elimination afforded aldehyde **1.51**. Sonogashira coupling[93] of the non-adjacent bis-THF's **1.47** and vinyl iodide **1.48** following Hoye's procedure provided **1.46**, which was converted to the final product (**Scheme 1.6**).[56]

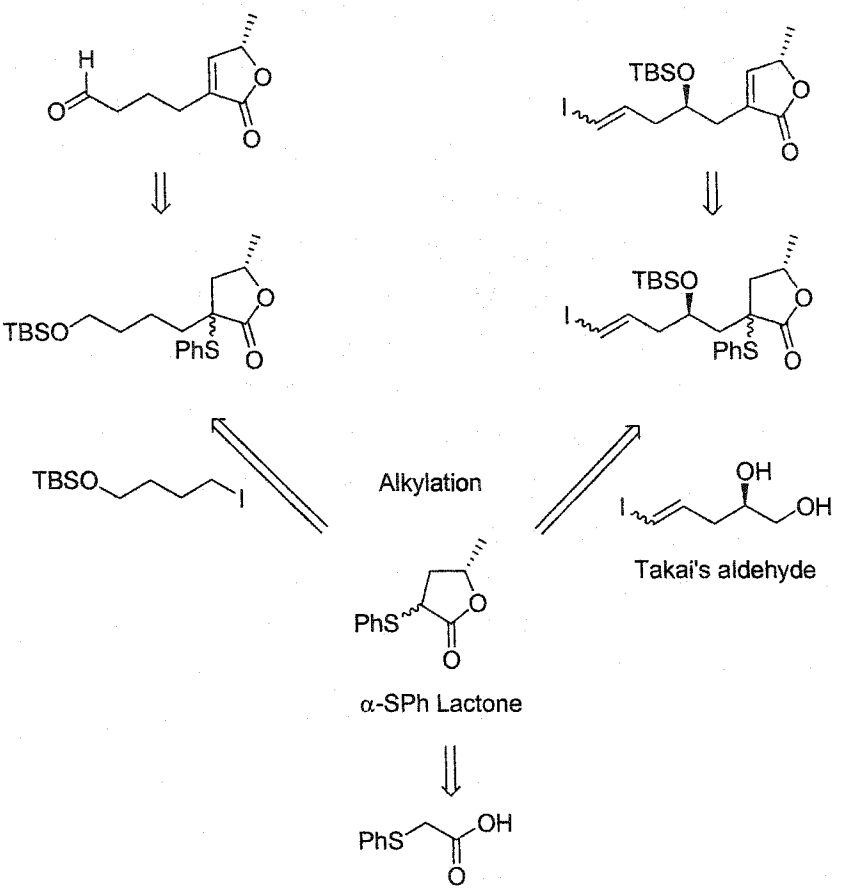


Scheme 1.5. Marshall's synthesis of squamostatin-D



Scheme 1.6. Tanaka's synthesis of (+)-4-deoxygigantecin

The method to construct butenolide segment **1.48** is widely used in acetogenin synthesis.[76,86] Since the side-chain is added at late stage, the synthesis of butenolide derivative becomes more flexible. Analogues of butenolide which have various substitution and different position on side-chain can be easily synthesized (**Scheme 1.7**).



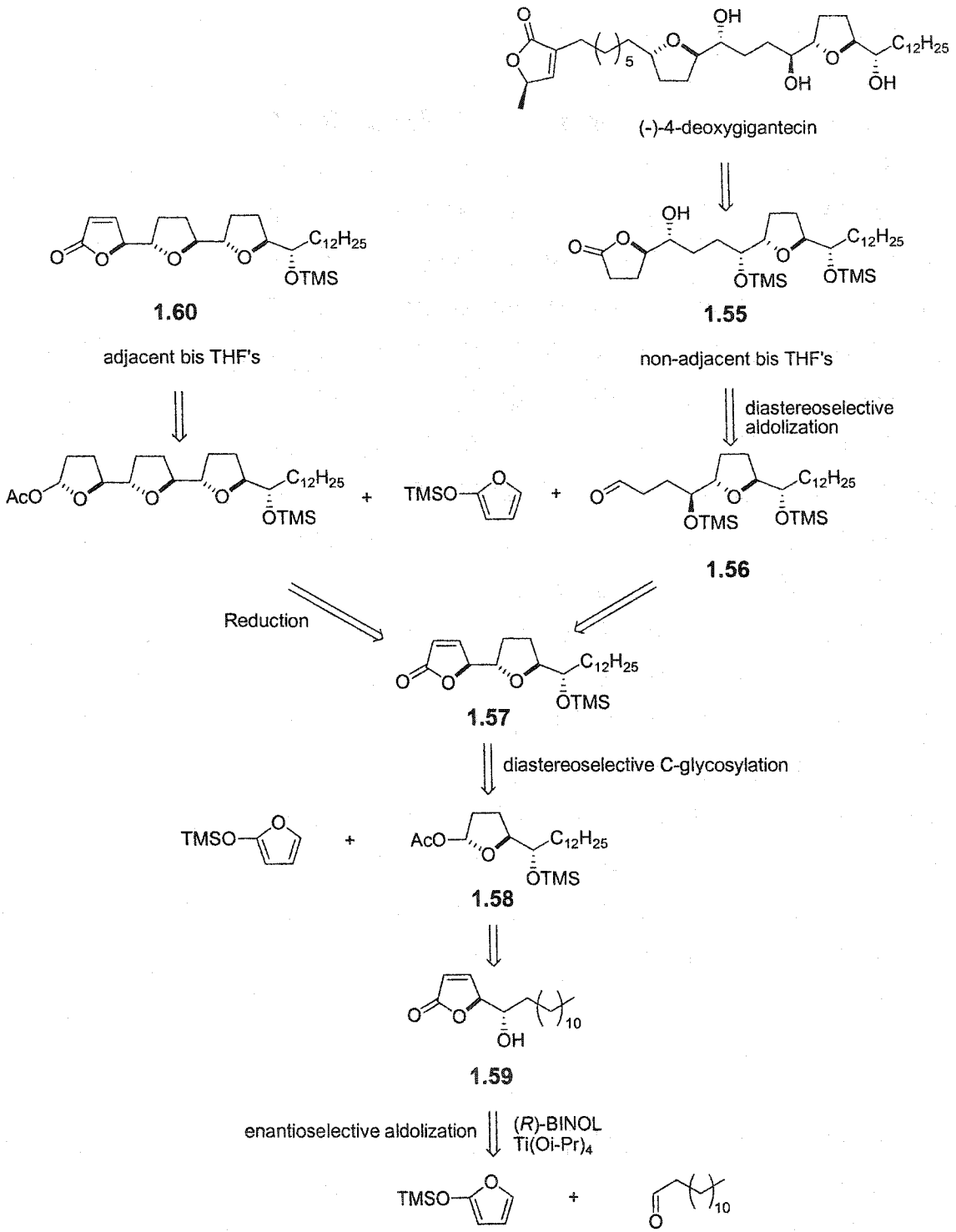
Scheme 1.7. Convergent Strategy with α-SPh lactone

Figadere's synthesis of (-)-4-deoxygigantecin precursor: Figadere obtained compound **1.55**, a precursor of (-)-4-deoxygigantecin[68], through an iterative aldol type approach with 2-trimethylsilyloxyfuran as a building block. The (*R*)-1,1'-bi-2-naphthol catalysed enantioselective aldolization reaction between 2-trimethylsilyloxyfuran and tridecanal afforded α,β-unsaturated lactone **1.59**. After hydrogenation and reduction, the

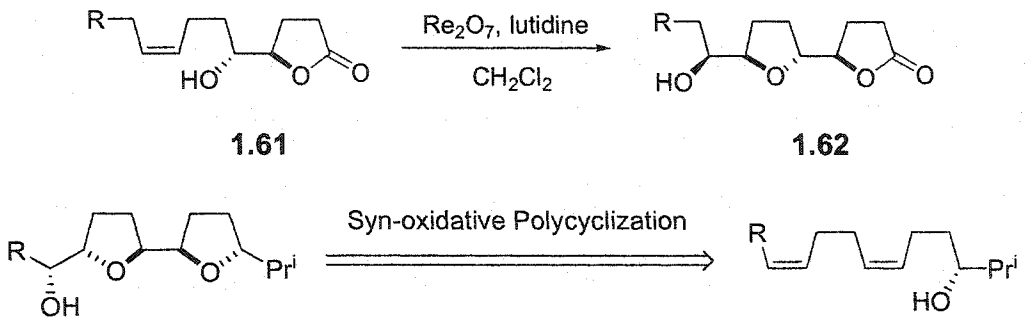
corresponding lactol was converted to the acetate derivative **1.58**. Addition of 2-trimethylsilyloxyfuran to **1.58** provided the first THF unit in **1.57**. The non-adjacent THF-butyrolactone core unit **1.57** was synthesized in 14 steps with good overall yield. 2-trimethylsilyloxyfuran was used as building block for both the THF and buty rolactone segments. Compound **1.59** was then transformed to aldehyde **1.56**, to which was added a third 2-trimethylsilyloxyfuran subunit, giving the target compound **1.55**. Since each ring was added one by one, this strategy can also be used to synthesize adjacently linked bis and higher order THF's (**Scheme 1.8**).

1.3.2 Selected other methodologies for THF syntheses

Oxidative cyclization of hydroxy alkenes: Direct oxidative cyclization of 4-alkene-1-ol are an attractive strategy for THF synthesis. A notable example is the stereoselective Re(VII) mediated, syn-oxidative cyclization. Oxidative cyclization on lactone **1.61** with dirhenium heptoxide and lutidine produced alcohol **1.62** (**Scheme 1.9**).[86] This method could also lead to synthesis of adjacently linked THF acetogenins via an in situ polycyclization.[94] This method may be compared to the indirect epoxidation-epoxide opening sequence on a 4-alkene-1-ol precursor. Example of these approach were previously discussed (see **Scheme 1.6**).

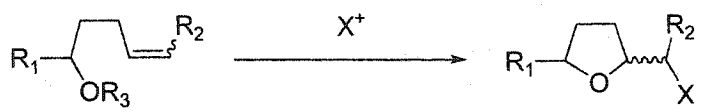


Scheme 1.8. Figadere's synthesis of (-)-4-deoxygigantecin precursor



Scheme 1.9. The "Naked Carbon Skeleton" biogenetic strategy

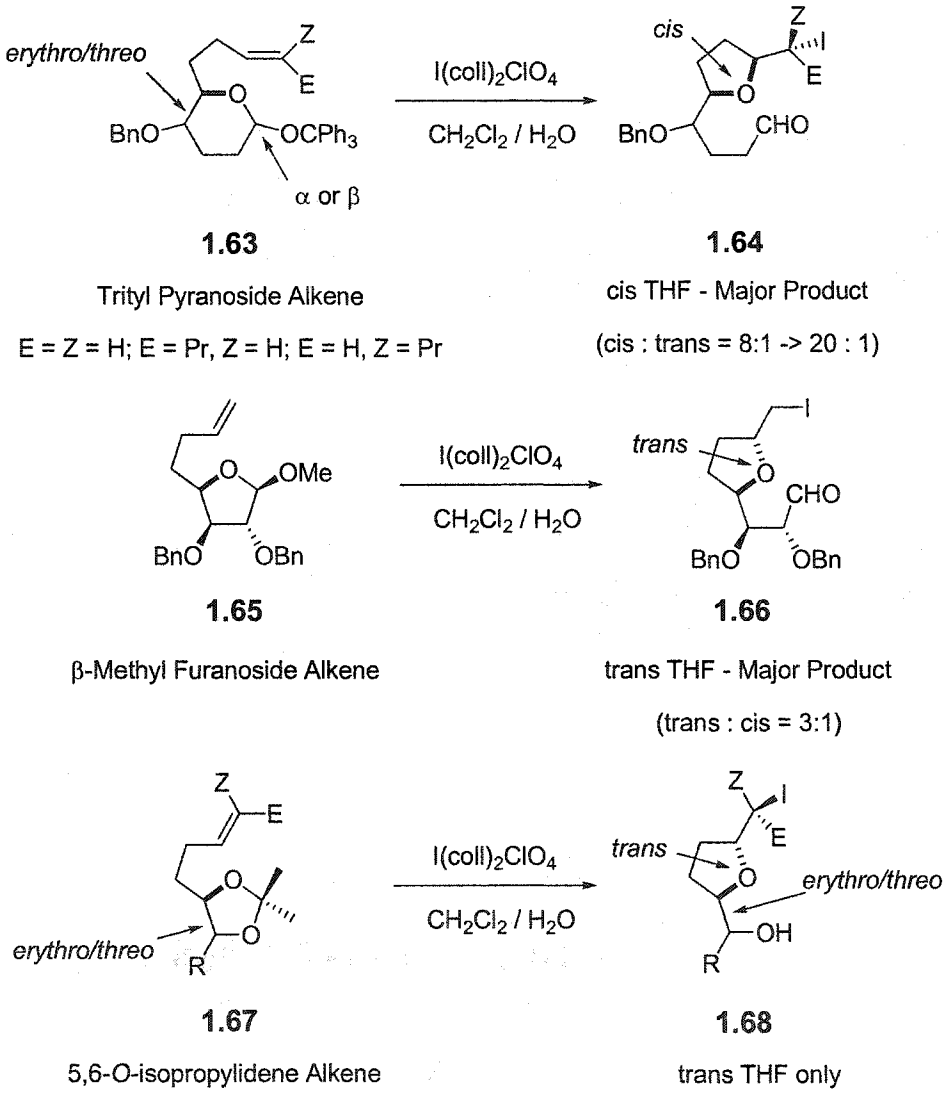
Iodoetherification of hydroxy alkenes: The Mootoo group has developed the iodoetherification reaction of complex 4-alkene-1-ols for the synthesis of several THF and bis-THF motifs (**Scheme 1.10**).[95-106]



Scheme 1.10. General transformation of iodoetherification reaction

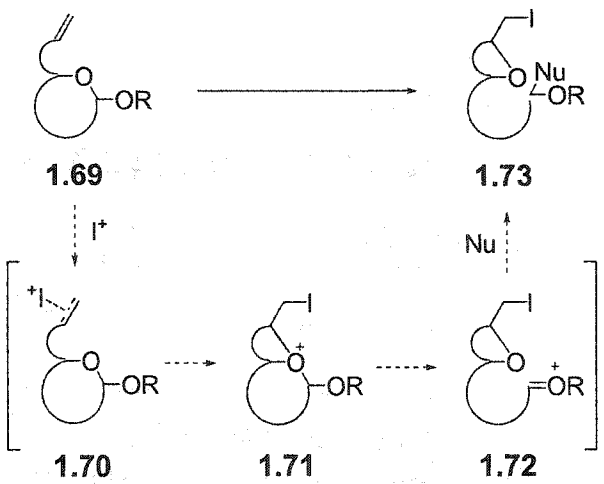
This original version of this reaction has been widely used in the synthesis of other complex ether frameworks.[107-109] However, a drawback is the uncertainty of the stereochemical outcome in highly substituted systems. This stereoselectivity problem could be addressed by performing the reaction on conformationally restrained templates. Three alkene templates that show high stereoselectivity were observed. Trityl pyranoside alkenes **1.63** leads to *cis*-2,5-disubstituted THF's with high stereoselectivity.[110] Structurally related β-methyl furanoside alkene **1.65** selects to form *trans*-2,5-disubstituted THF's.[111] In these two cases, the internal acetal serves as a convenient hydroxyl aldehyde protecting group. The third alkene template is isopropylidene

derivatives of 5,6-dihydroxyalkene **1.67**. This alkene template is also *trans* selective, presumably because of the similarity of its topography to the β-furanoside framework (**Scheme 1.11**).[112] Thus, either *cis* or *trans* THF's may be attained by varying the nature of alkene template.

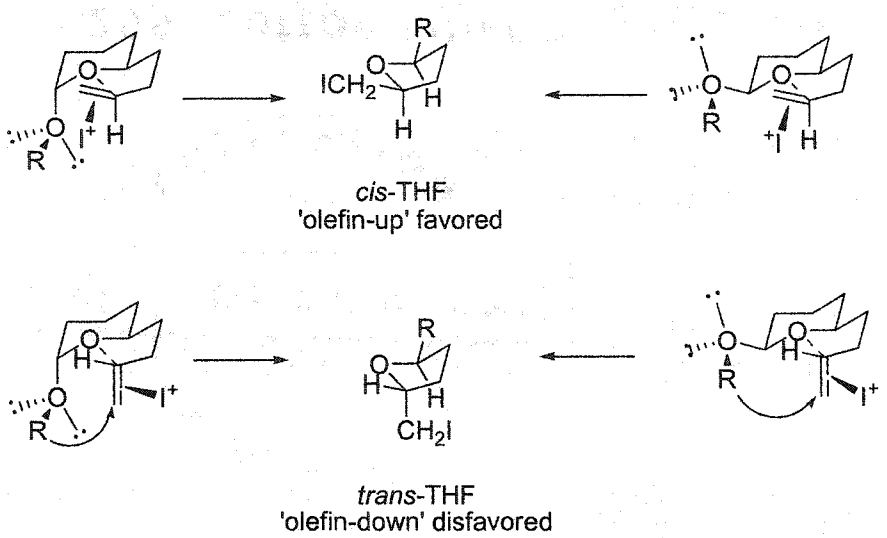


Scheme 1.11. Alkene templates of iodoetherification reaction

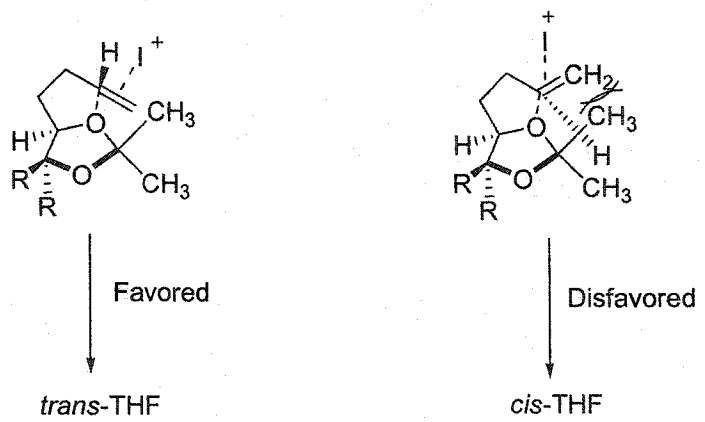
The iodoetherification reaction of saccharide alkenes like **1.69** is believed to proceed via initial reaction of the alkene **1.69** with iodonium ion to generate diastereomeric iodonium ions or charge transfer complexes **1.70**. Neighboring group participation by the ring oxygen leads to the oxonium **1.71**, which fragments to the oxocarbenium **1.72**. Capture of **1.72** by a nucleophile gives rise to cyclic ether **1.73** which contains highly functionalizable branches (**Scheme 1.12**).[113] The high stereoselectivity observed in the reaction appears to be controlled by the geometry of the THF-oxonium ion intermediate.[114] In the case of the pyranoside systems the high *cis* stereoselectivity was explained by a preferred pseudoequatorial approach of the iodonium ion onto the ring. This provides a reasonable explanation of the *cis* selectivity for the α-pyranosides; but is less compelling for the β-pyranosides. In the case of 5,6-*O*-isopropylidene alkene, a *cis* fused [5.5.0] oxahydrindan type geometry was assumed. The *cis* THF product is disfavored because of steric crowding between the C_5 iodoalkyl substitutent of the eventual THF and the methyl group of the acetonide (**Scheme 1.13 & 1.14**).



Scheme 1.12. Mechanism of iodoetherification reaction

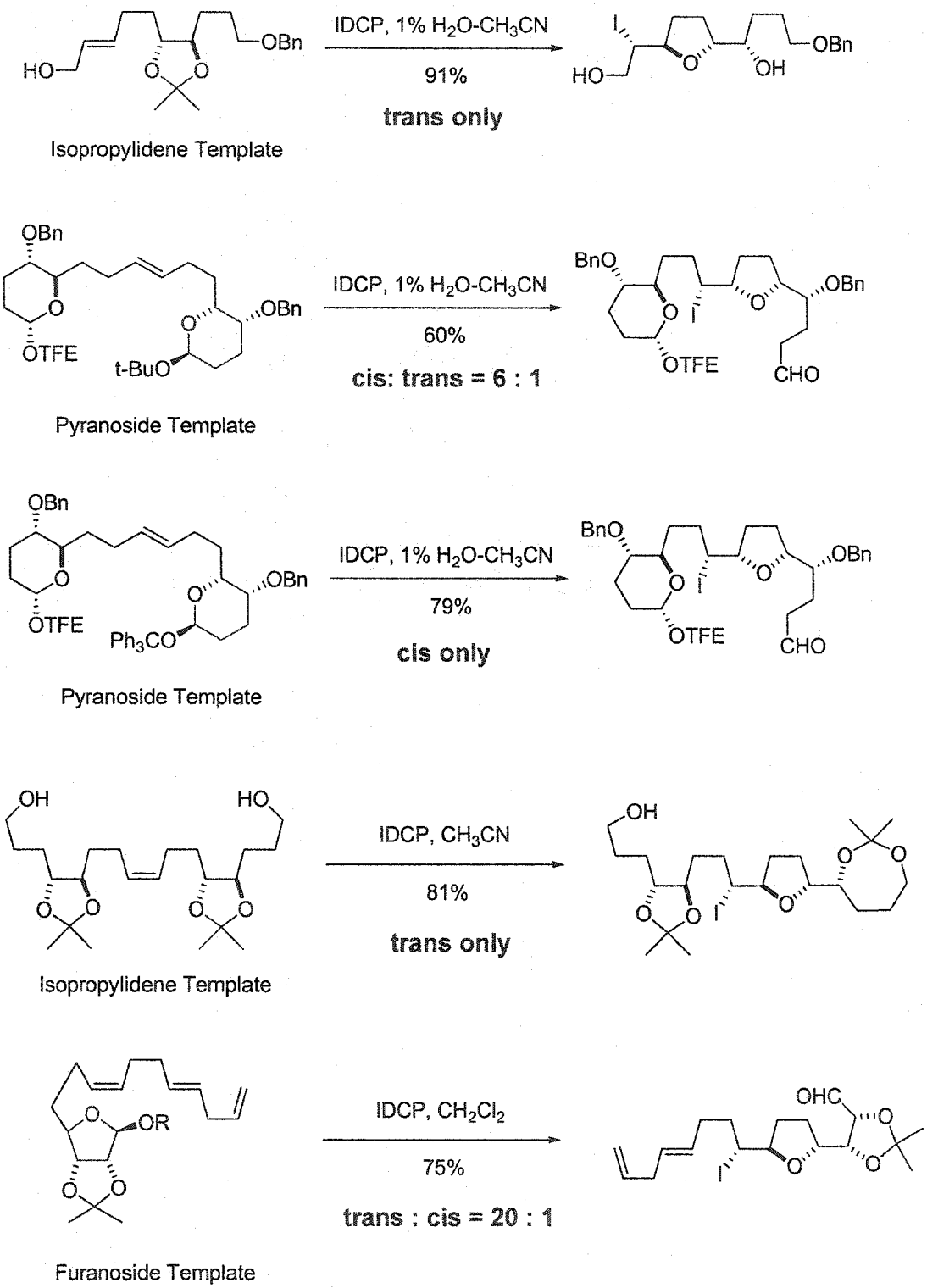


Scheme 1.13. Model for the high *cis* stereoselectivity



Scheme 1.14. Model for the high *trans* stereoselectivity

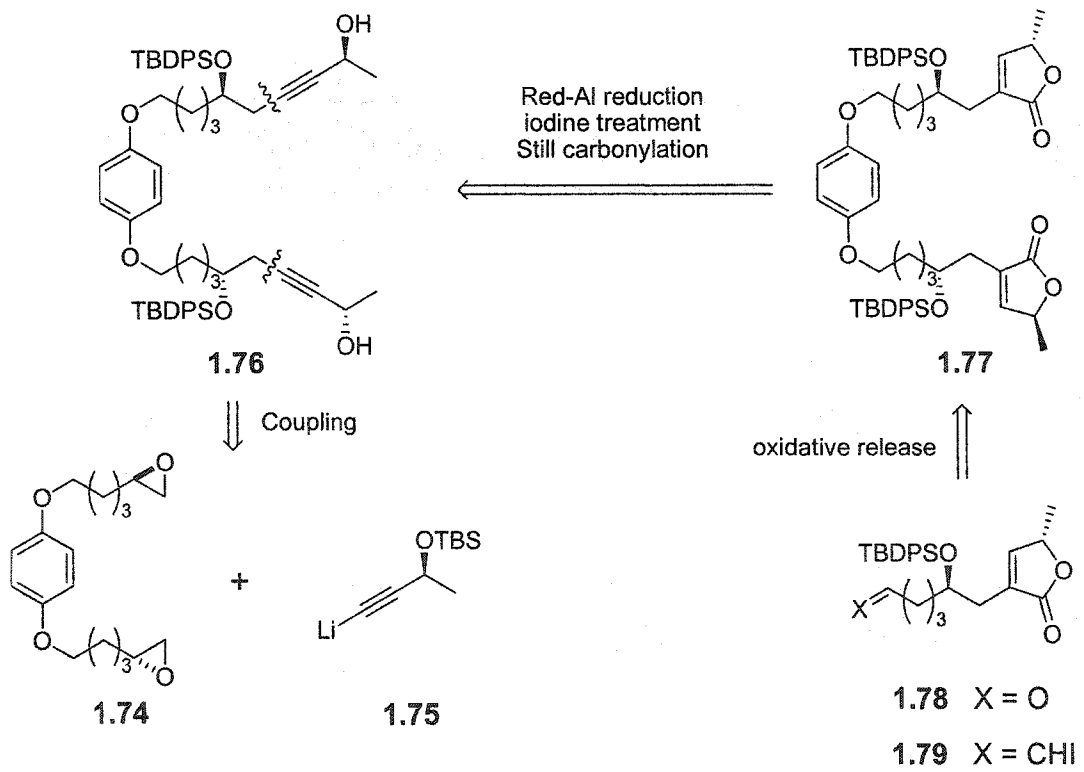
This methodology has been applied to varies mono and adjacent bis-THF core structures[95,96,98,99,115] as well as complex polycyclic ether systems, such as analogue of monensin A (**Scheme 1.15**).[97]



Scheme 1.15. Complex THF's from acetal alkene precursors

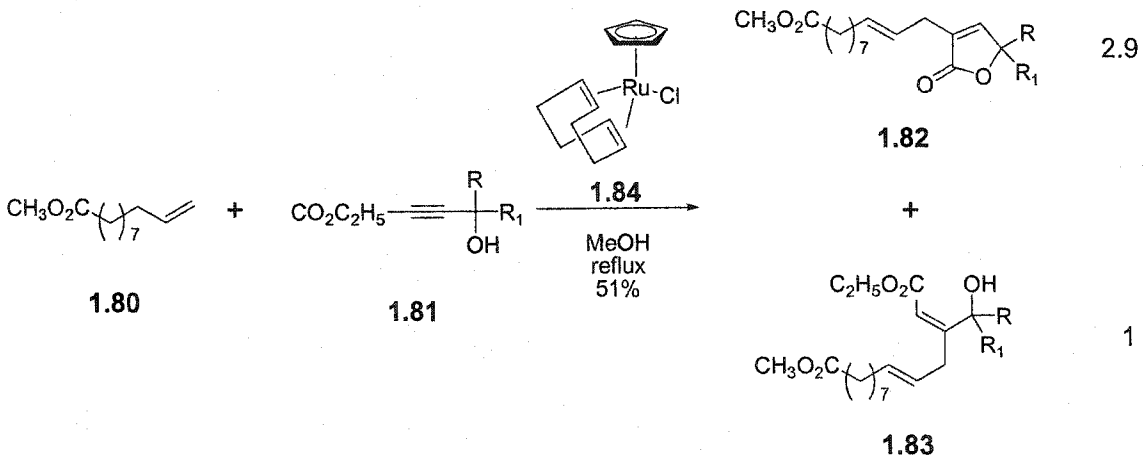
1.3.3 Selected other methodologies for the butenolide subunit

The Hoye's strategy: One of efficient methods to construct the butenolide subunit was worked out by Hoye's group. Alkylation of bis-epoxide compound **1.74** with compound **1.75** followed by alcohol protection led to **1.76**. Red-Al reduction, iodine treatment and carbonylation under Stille condition led to **1.77**. Oxidative cleavage of phenol and oxidation of the liberated alcohol provided the aldehyde **1.77**. finally, the vinyl iodide **1.79** was produced through Wittig reaction of **1.78** with iodomethylene triphenyl phosphate (**Scheme 1.16**).[116]



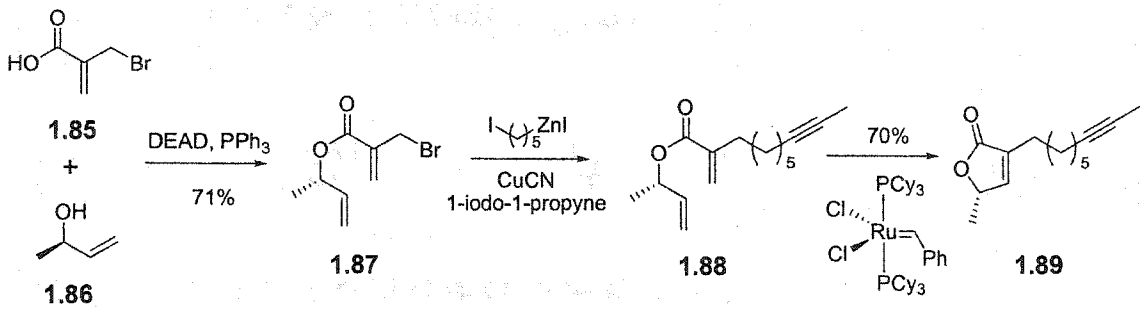
Scheme 1.16. The Hoye's strategy

Alder-ene reaction: Trost developed a ruthenium-catalyzed Alder-ene reaction for the synthesis of butenolides (**Scheme 1.17**).[117] The reaction of alkene **1.80** and alkynoate **1.81** in the presence of catalyst **1.84** gave a 3:1 mixture of butenolide **1.82** and diene **1.83**. This route allows for introduction of the γ-methyl with a desired configuration and also prevents formation of *exo*-cyclic alkene.



Scheme 1.17. Alder-ene reaction

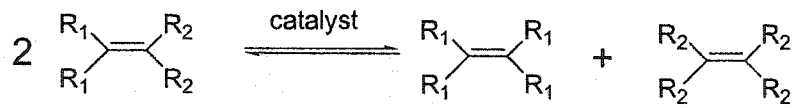
Furstner *et al.*[118] developed an equally efficient metathesis approach. Coupling of two commercially available **1.85** and **1.86** under the Mitsunobu conditions provided the backbone and configuration of the butenolide. This product **1.87** was then subjected to a zinc-induced, copper-mediated "three-component coupling" reaction to extend the side chain. Finally, the butenolide was prepared by a ring closing olefin metathesis (RCM) reaction under high dilution condition (**Scheme 1.18**).



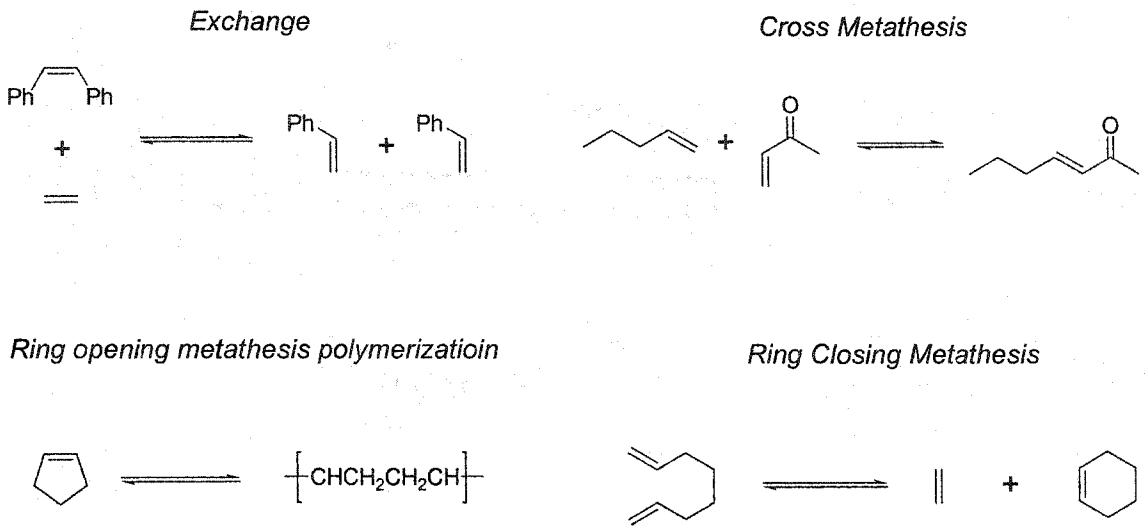
Scheme 1.18. Metathesis cyclization

1.3.4 Olefin metathesis as a segment coupling reaction in complex syntheses

Generally, the olefin metathesis reaction can be thought of as a metal catalyzed exchange reaction in which all the carbon-carbon double bonds in an olefin (alkene) are cut and then rearranged in a statistical fashion.

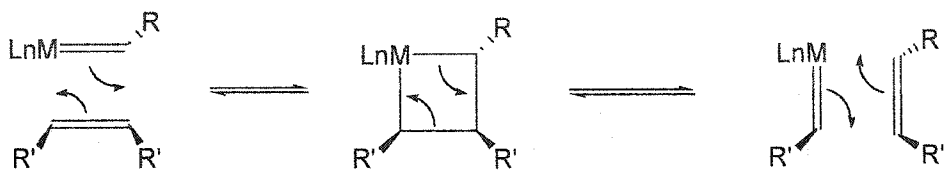


Of particular importance, this type metathesis utilizes no additional reagents beyond a catalytic amount of metal carbine. Olefin metathesis falls under four broad groups (**Scheme 1.19**).



Scheme 1.19. Four types of olefin metathesis

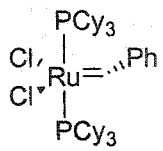
The commonly accepted mechanism for the olefin metathesis reaction was proposed by Chauvin[119] and involves a [2+2] cycloaddition reaction between a transition metal alkylidene complex and the olefin to form an intermediate metallacyclobutane. This metallacycle then breaks up in the opposite fashion to afford a new alkylidene and new olefin. If this process is repeated enough, eventually an equilibrium mixture of olefins will be obtained.



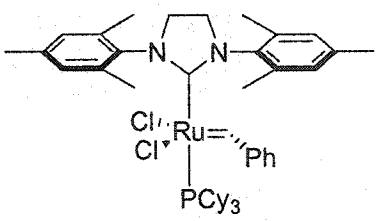
Such cycloaddition reactions between two alkenes to give cyclobutanes are symmetry forbidden and occur only photochemically. However, the presence of d-

orbitals on the metal alkylidene fragment breaks this symmetry and the reaction is quite facile.

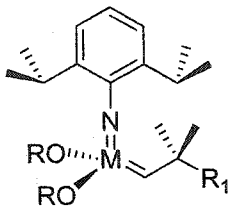
Historically, olefin methathesis has been studied both from a mechanistic standpoint[120] and in the context of polymer synthesis (i.e., in ring opening metathesis polymerization).[121-123] In contrast, the application of olefin metathesis to the synthesis of complex organic molecules and natural products was limited due to the incompatibility of ill-defined, "classical" catalysts with the diverse functionality encountered in organic synthesis.[121] Recently, however, ring-closing metathesis of acyclic dienes has received considerable attention as a highly efficient methodology for the synthesis of functionally diverse carbocycles and heterocycles.[124-127] This is primarily due to the development of well-defined transition metal catalysts over the past decade. Two of the most widely used are the ruthenium benzyliene developed by Grubbs *et al.*[128-130] and the molybdenum alkylidenes developed by Schrock *et al.*[131-133] The relatively high activities and functional group tolerance of both catalysts, coupled with their commercial availability, has dramatically increased their application in organic synthesis.

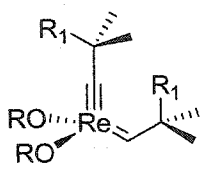


1.90



1.91





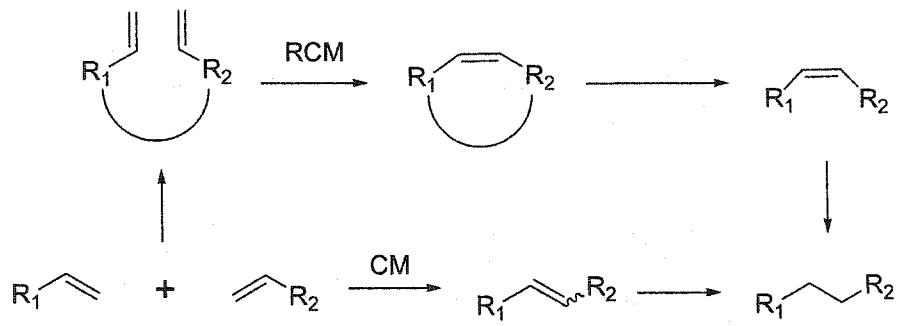
M = Mo, W R = alkyl, aryl R_1 = Me, Ph

In the early 1990's, Robert Grubbs developed a series of Ru catalysts that differ form the previous gererations in several distinct ways. First, the metal is not in its highest oxidation state and is supported by phosphine ligands. Second, these catalysts are so tolerant of functionality that some of them can operate in water on the benchtop. Such functional group tolerance comes at the expense of lower matathesis rates than the Schrock catalysts, but these systems are extremely promising.

The most important Schrock catalyst are arylimido complex of Mo with the general formula $(Ar'N)(RO)_2Mo{=}CHR'$ where Ar' is typically 2,6-diisopropylphenyl. Schrock catalyst is stable when stored cold under an inert atmosphere; while Grubbs Ru catalyst is stable indefinitely when stored under inert conditions and is somewhat tolerant to air and moisture. Ruthenium catalyst remains metathesis active in the presence of a variety of function groups including: carbonyls, alcohols, and amides. It is selective for less hindered and strained olefins, and does not react readily with tri- or tetrasubstituted olefins. The more reactive molybdenum catalyst is less tolerant of functionality; however, it has found considerable use in the metathesis of tri- and tetrasubstituted olefins.

Olefin metathesis has found increasing use as a segment coupling reaction in complex molecule synthesis. Two strategies have been explored. The first and more direct is the CM of two alkene subunits. However, mixtures of homo- and hetero-dimeric

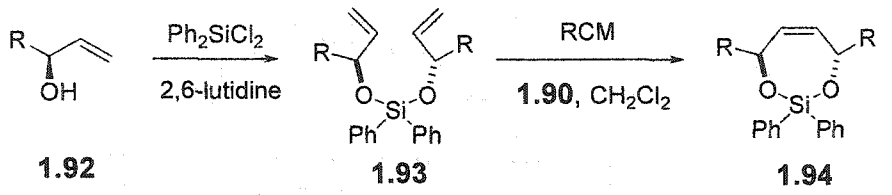
products are typically obtained. One solution to this problem is the alternative strategy in which two alkene compounds are first connected with a temporary linker and a ring-closing metathesis (RCM) is performed. The linker is then removed to give the CM product (**Scheme 1.20**). Examples of this RCM approach will be presented first, followed by discussion of recent developments in CM.



Scheme 1.20. General strategy of RCM and CM

CM via RCM approaches: RCM reaction is entropically driven by the release of volatile small molecules, but the ring formation is limited by the relative ring strain of the product. Application of RCM in cyclization of various sized ring systems,[134-138] multisubstituted olefins,[139] and multicyclic ring systems[140-142] have been reported. The temporary tethered-RCM-cleavage method is an alternative to CM.

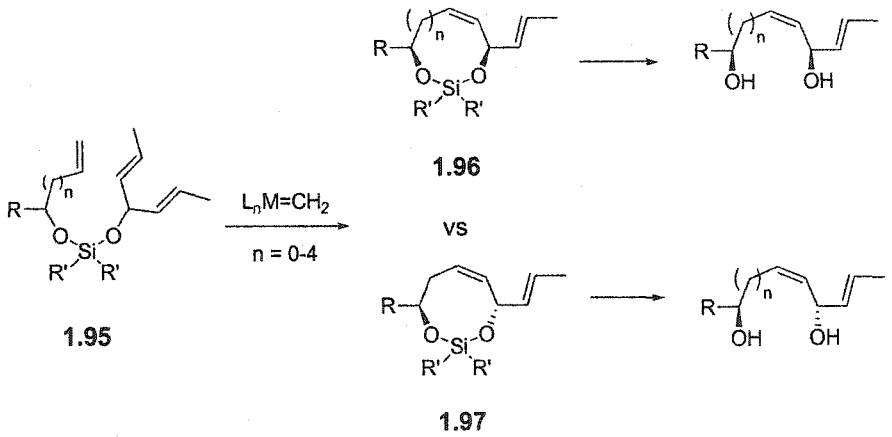
Two examples in the literature utilize silicon and diester tethers. Evans *et al.* developed the silicon-tethered RCM.[143] Treatment of the allylic alcohol **1.92** with diphenyldichlorosilane furnished the bis-alkoxysilanes **1.93**. RCM reaction afforded diphenyl silaketal **1.94** (**Scheme 1.21**).



1.92 **1.93** **1.94**

Scheme 1.21. Temporary Silicon-Tethered RCM Reaction

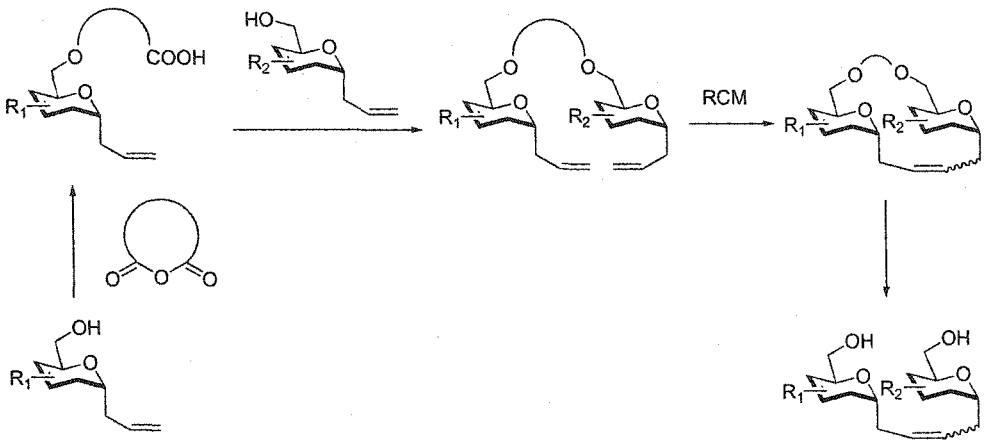
A new approach to long-rang asymmetric induction using this method was also explored.[144] RCM reaction of bisalkoxy silanes **1.95**, derived from an allylic and prochiral alcohol, formed *cis*-1,4-silaketals **1.96** (where $n = 0$). This methodology can be extended to higher homologues, which is 8 to 11 membered ring, and result in the formation of the opposite *trans* diastereoisomers **1.97**. Acyclic alkene can be obtained following removal of the silicon tether (**Scheme 1.22**).



Scheme 1.22. General approach to the RCM reactions with alkenyl alcohols

Instead of using silicon as temporary tether, Lin *et al.* used diester as a linker in the synthesis of *C*-butenyl-linked heterodisaccharides.[145] They used two esterifications to link various saccharides selectively. For the purpose of studying the effects of the linker on the *Z/E* ratio of RCM products, they tried three different spacers: glutaryl, succinyl,

and phthaloyl were evaluated (**Scheme 1.23**). The different spacers did not influence RCM reaction yields, but they changed the *Z/E* ratio. When a more rigid spacer (e.g. phthaloyl group), was used, the ratio of *Z*-isomer increased.



Scheme 1.23. RCM with diester space linker

Cross-Metathesis: CM between acyclic olefins is thermodynamically analogous to RCM: the reaction is entropically driven by the loss of small molecules. However, the reaction differs from RCM in three ways:

1). Low catalyst activity to effect a reaction without a strong enthalpic driving force (such as ring-strain release in ROMP) or the entropic advantage of intramolecular reactions (such as RCM).

2). Since homodimerization is possible, and often competitive with hereodimerization, mixtures of products are typically obtained.

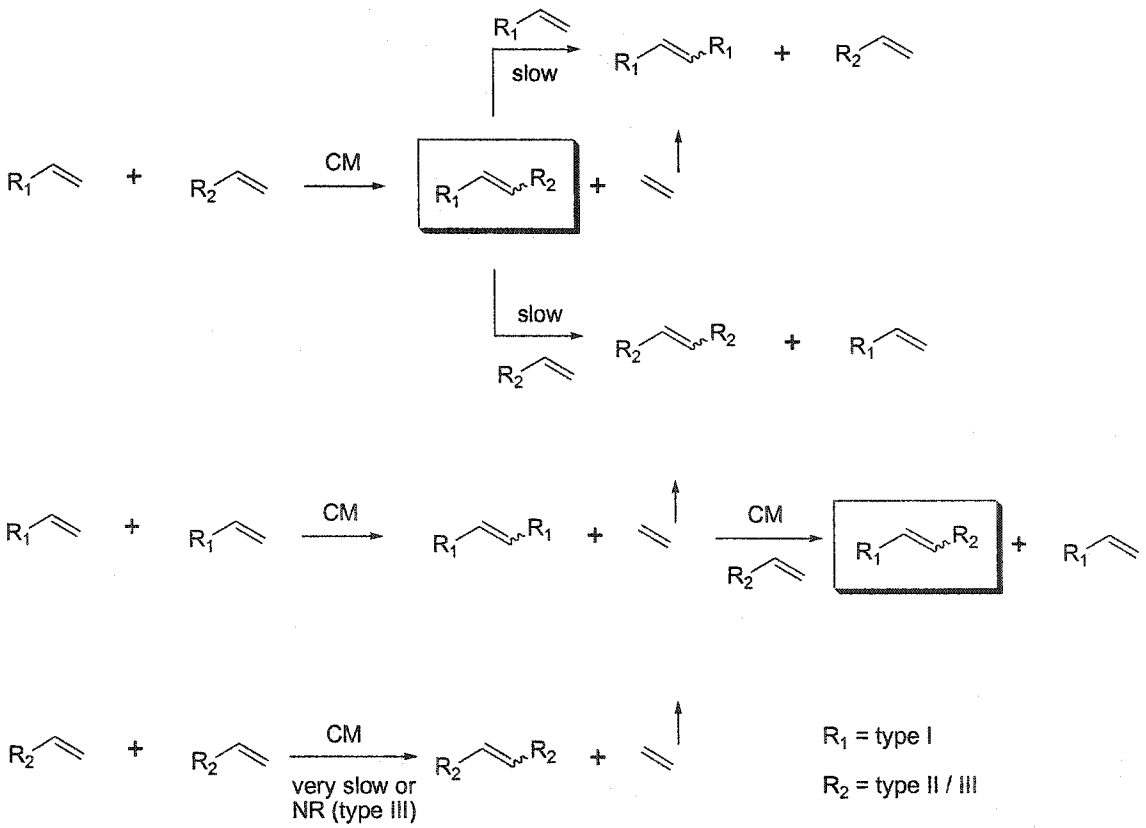
3). *Cis* and *trans* isomers are also possible.

These problems have hindered the use of CM in complex synthesis. While the development of a second generation of active and robust ruthenium catalysts **1.90** and **1.91** with an impressive functional-group tolerance and increasingly activity has resolved

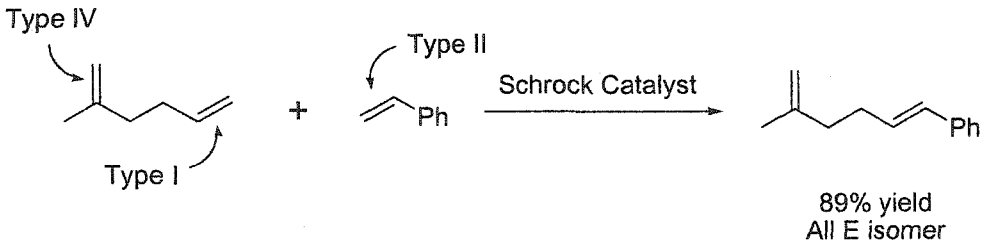
first problem, the inability to accurately predict selectivity of CM reactions remains an issue for the practical application of CM.

Recent results from the Grubbs' laboratory provide some selectivity trends and should allow more widespread use of CM. Selectivity and stereoselectivity of CM products can be controlled by placing sterically large and electron-withdrawing groups near the reacting olefin.[146] Olefins may be grouped in four categories (I-IV), based on their behavior in CM reactions. Type I olefins (e.g. terminal olefins) are those able to undergo a rapid homodimerization and whose homodimers can participate in CM just as well as their terminal olefin precursors. Type II olefins (e.g. allylic alcohols or vinyl epoxides) homodimerize slowly, and unlike type I olefins, their homodimers can only be sparingly consumed in subsequent metathesis reactions. Type III olefins (e.g. protected allylic alcohols) are essentially unable to be homodimerized by the catalyst but are still able to undergo CM with type I and type II olefins. Type IV olefins (e.g. trisubstituted allyl alcohols) are not able to participate in CM with a particular catalyst but do not inhibit catalyst activity toward other catalysts. Outside these categories are olefins that deactivate the catalyst. In general, a reactivity gradient exists from most active type (type I olefin) to least active type (type IV), with sterically unhindered, electron-rich olefins categorized as type I and increasingly sterically hindered and/or electron-deficient olefins falling into types II through IV. When two olefins of the same type are used in a CM reaction, the rates of homodimerization are similar and the reacitvities of the homodimers and cross products toward secondary metathesis events are the same. In these reactions, the desired cross product will be equilibrated with the various homodimers through secondary metathesis reactions. This will result in a statistical product mixture. By using

olefins from two different types, whose rates of dimerization are significantly different and/or slower than CM product formation, the statistical product distributions produced by inefficient homodimerization can be avoided. For example, we can combine type I olefin with a less reactive type II or type III olefin that undergoes homodimerization at a significantly lower rate. In this reaction, although the type I olefin may initially homodimerize, the product distribution is driven toward the desired cross product as ethylene is driven from the system, and the type I homodimer readily undergoes secondary metathesis with the type II or III olefin. This desired cross product will not be equilibrated to a statistical product mixture due to the inability of the catalyst to efficiently convert the cross product to other products via secondary metathesis (**Scheme 1.24**).

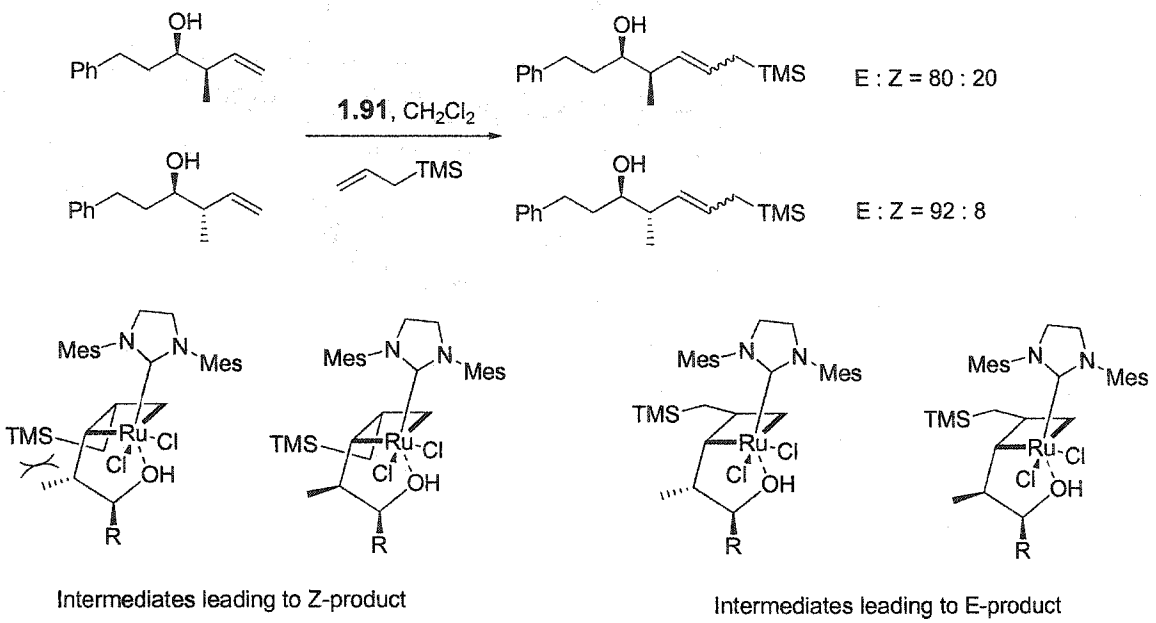


Scheme 1.24. Selective CM of type I with type II/III



Scheme 1.25. Example of chemoselective CM reaction[147]

Stereoselectivity in CM reaction is often not important because the alkene product is reduced to the hydrocarbon. However, it is critical when specific olefin geometry is required. *E/Z* stereoselectivity may be controlled by using steric bulk at the allylic carbon to obtain high *trans* olefin isomer (**Scheme 1.25**). Besides electronic and steric parameters, other factors are often implied in determining selectivity, including chelating ability of certain functional groups to metal catalysts (**Scheme 1.26**).[148] The effects of carbonyl groups, such as acetate protecting groups, and allylic heteroatoms have been implied to alter reactivity in CM.

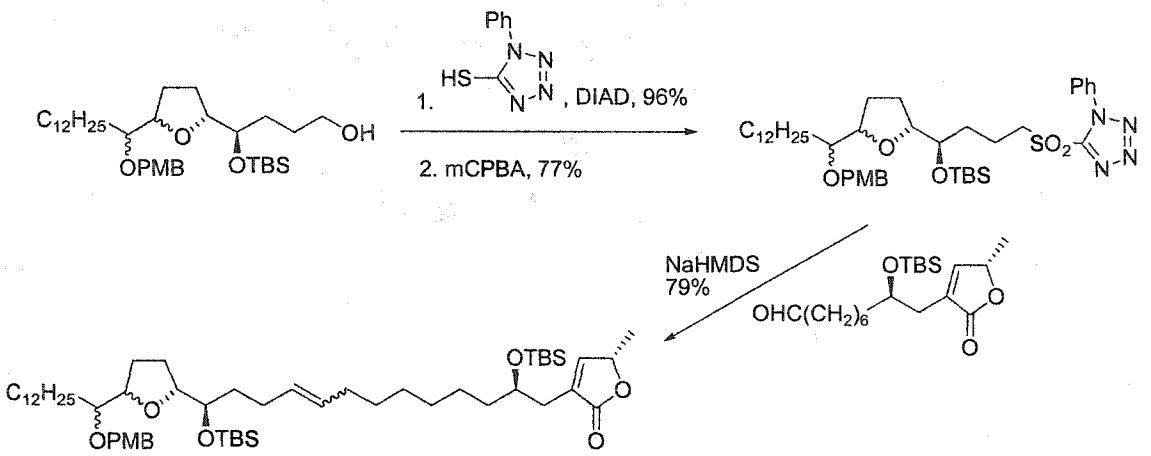


Scheme 1.26. CM reaction with chelating ability

1.3.5 Other segment coupling strategies for THF acetogenins

The coupling of two complex segments, THF core unit and butenolide, is the last stage in most syntheses of acetogenins. In addition to Sonogashira coupling, Wittig olefination, the organometallic addition to aldehydes, and metathesis have been discussed previously. Julia olefination reaction has also been reported.

Kocienski-Julia Coupling: As another popular aldehyde olefination, Kocienski-Julia reaction[149] was explored on the synthesis of acetogenins by Curran *et al.*[150] This is an alternative route to the Wittig coupling (**Scheme 1.27**).



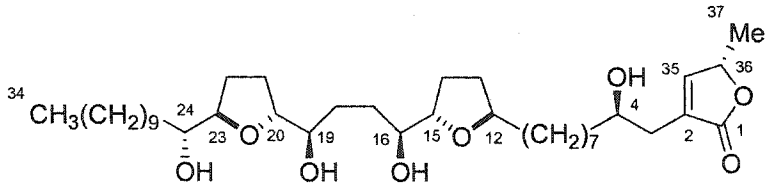
Scheme 1.27. Kocienski-Julia coupling

CHAPTER TWO

Total Synthesis of Bullatanocin

2.1 Introduction

Bullatanocin is a typical member of the non-adjacent linked bis-THF acetogenins, both in terms of biological activity and structure. It comprises two 2,5-trans-disubstituted THF's bridged by a 1,4-dihydroxybutyl linker. Bullatanocin was isolated from the bark of *Annona bullata* Rich. (Annonaceae) by the Mclaughlin group.[73,151] *Annona bullata* Rich. (Annonaceae) is a tropical tree native to Cuba. Screening of crude extracts of its bark showed cytotoxic and pesticidal activities. Further fractionation led to the identification of bullatanocin with several other acetogenins. Bullatanocin is a whitish wax (from chloroform) or white crystals, mp 95-97 °C (from ethyl acetate). It is very active in the brine shrimp lethality test (LC_{50} = 4.33 $\times 10^{-1}$ μg/ml), and is over 10,000 times as cytotoxic as adriamycin against human colon adenocarcinoma HT-29 ($ED_{50} < 10^{-8}$ μg/ml) and human lung carcinoma A-549 ($ED_{50} < 10^{-8}$ μg/ml). NMR and MS data, suggested that bullatanocin was a non-adjacent bis-THF acetogenin.[73] An IR carbonyl absorption band, UV and proton resonances provided characteristic spectral features for an α,β-unsaturated γ-lactone fragment with 4-OH.[3,17] ^{13}C NMR analysis showed three secondary hydroxyl-bearing carbons adjacent to THF ring. The carbon skeleton and placement of the two THF rings were determined based on EIMS analysis. The relative stereochemistry was determined by comparing ^{13}C NMR signals with those of model compounds of known stereochemistry.[152]



Bullatanocin (Squamostatin C)

Independently, squamostatin C was isolated by Fujimoto from the seeds of *Annona squamosa*, a tropical plant commonly known as sweetsop (**Figure 2.1**).[153,154] *Annona squamosa* is widely grown for the fruit. Squamostatin C exhibited identical physical properties to bullatanocin. Henceforth in this thesis, the name bullatanocin will used for the title compound. Four analogues of bullatanocin (squamostatins A, B, D and E) with the identical bis-THF core structure were also isolated by the Fujimoto's group.

Figure 2.1. *Annona squamosa*

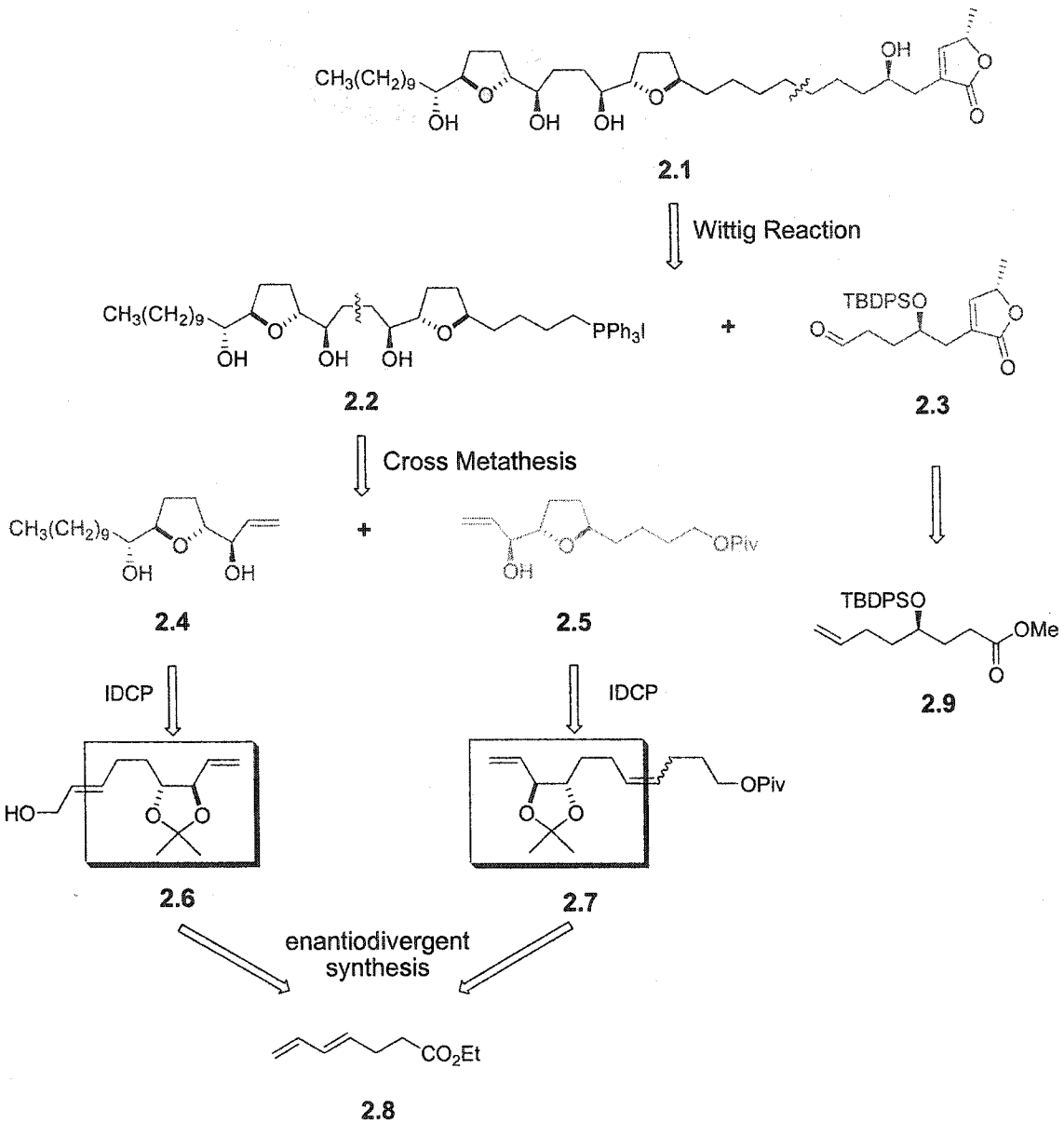
The total synthesis of bullatanocin is of interest for confirming the relative and absolute stereochemistry, and is also important for providing adequate amounts of

material for biological studies due to the limited amounts of material available from natural sources.

2.2 Synthetic strategy

The structure of bullatanocin comprises two 2,5-*trans*-disubstituted THF's bridged by a 1,4-dihydroxybutyl linker. Structures containing two *trans* THF's account for the largest subgroup. There are smaller families with one *trans* and one *cis* THF, or two *cis* THF's. The relative stereochemistry at the carbinol carbons is variable. Our plan was to develop a general approach that would be applicable to stereochemically diverse non-adjacent bis-THF acetogenins. Consequently a convergent strategy that allowed coupling of prefabricated mono-THF subunits was envisaged.[155,156]

The plan was based on three components: butenolide **2.3**, and mono THF's **2.4** and **2.5** (**Scheme 2.1**). The target compound **2.1** could be accessed through a late stage Wittig coupling of a bis-THF phosphonium salt **2.2** and butenolide aldehyde **2.3**. An olefin cross metathesis of mono-THF **2.4** and **2.5** may be used for the assembly of the key bis-THF core unit. The mono-THF precursors would be accessible via application of our iodoetherification methodology on the 1,2-*O*-isopropylidene 5-alkene precursors **2.6** and **2.7**, respectively. The pseudo-antipodal relationship between **2.6** and **2.7** suggested an enantiodivergent synthesis of these materials from a central precursor **2.8**.



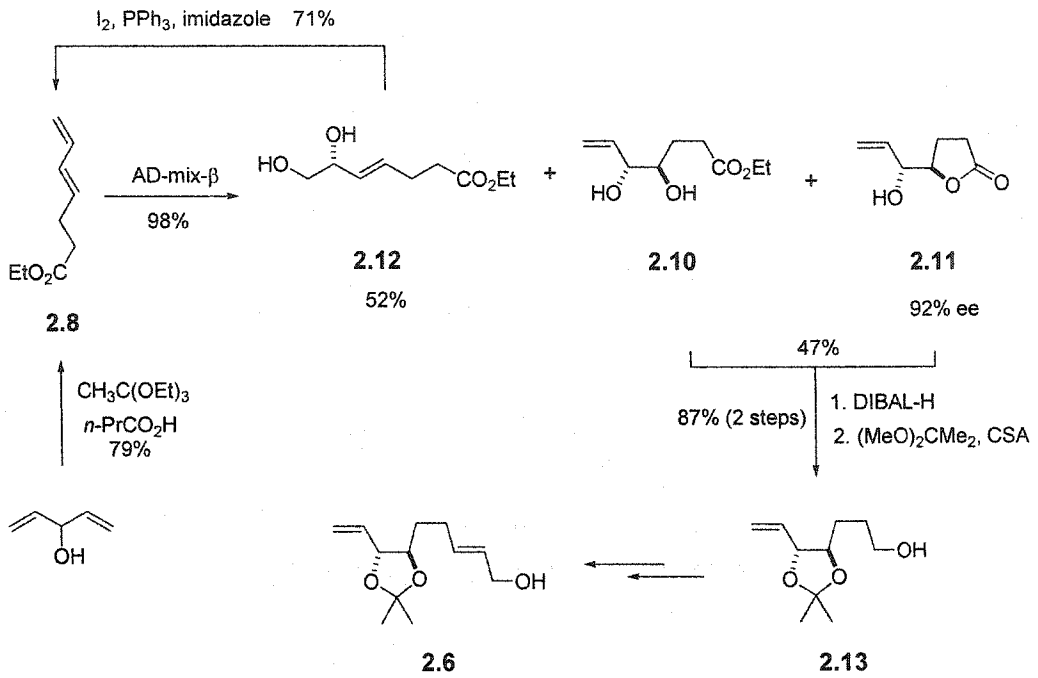
Scheme 2.1. Convergent strategy for bullatanocin

2.3 Synthesis

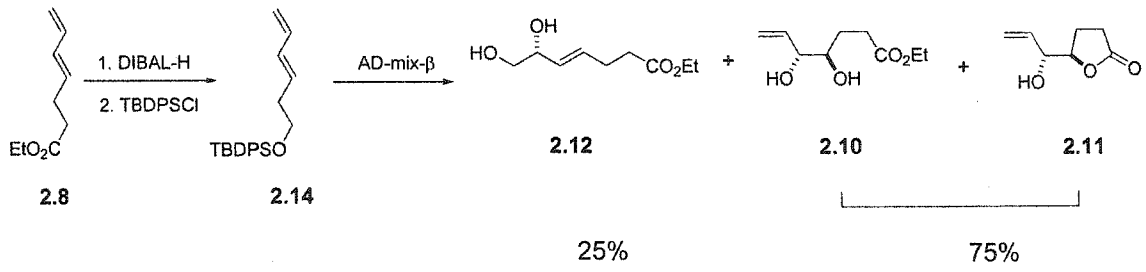
1,2-O-Isopropylidene alkenes precursors: As mentioned above, the pseudo antipodal relationship between isopropyliene alkene **2.6** and **2.7** suggested enantiomeric precursors **2.13** and **ent-2.13**, respectively (**Scheme 2.2 & 2.4**). The synthesis of these

materials started with the asymmetric dihydroxylation of ethyl (*E*)-4,6-heptadieneoate **2.8**, which was prepared via a known procedure on commercially available 1,4-pentadien-3-ol.[157] For **2.13**, the AD-mix-β-mediated dihydroxylation of **2.8** provided an approximately 1:1 ratio of products resulting from dihydroxylation of the *E* and terminal alkenes.[158,159] The desired material consisting of a mixture of diol **2.10** and the derived lactone **2.11** was obtained in 47% combined yield. The proportion of product from dihydroxylation of the internal alkene could be improved by using the silyl ether **2.14** (**Scheme 2.3**). The optical purity of lactone **2.11** as determined by Mosher ester analysis was greater than 92%.[160] The undersired diol **2.12** could be recycled to **2.8** in a single step by treatment under conditions for alcohol iodination. Reduction of the mixture of **2.10** and **2.11** with DIBALH followed by acetonation of the resulting triol afforded **2.13**, the precursor to **2.6**. Using AD-mix-α instead of AD-mix-β in the dihydroxylation step afforded **ent-2.13** in similar yields with greater than 95% ee. Thus, **2.13** and **ent-2.13** were easily available in three straightforward steps from **2.8**.

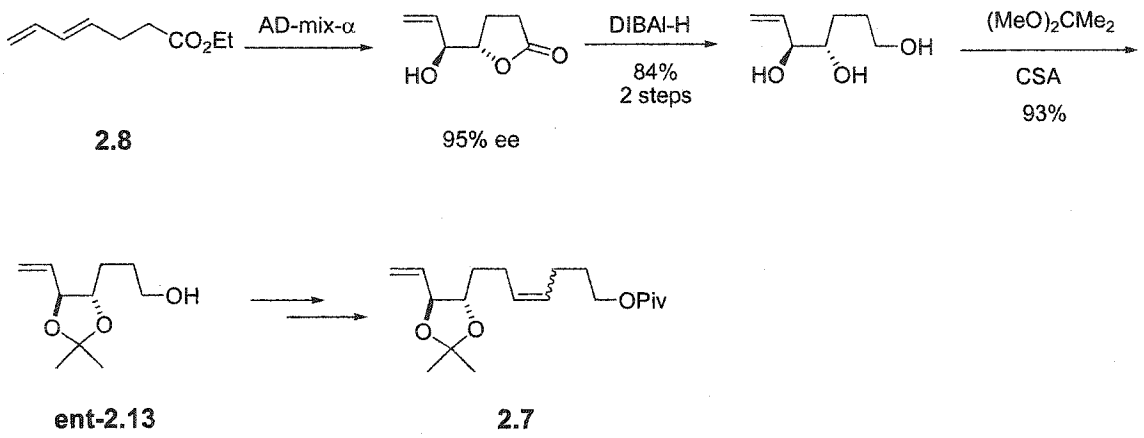
Alcohols **2.13** and **ent-2.13** were next converted to their aldehyde derivatives and subjected to Wittig olefination with $Ph_3P{=}CHCO_2Me$ and $Ph_3P{=}CH(CH_2)_3OLi$, respectively.[161] DIBALH reduction or pivalylation of the individual olefination products provided the isopropylidene alkene precursors **2.6** and **2.7**. Alkene **2.6** was obtained as a single (*E*)-isomer in 77% overall yield from **2.13**. Alkene **2.7** was obtained as a 3:1 *Z:E* mixture, in 61% from **ent-2.13**, which could be separated by FCC using silver nitrate impregnated silica gel (**Scheme 2.5**).



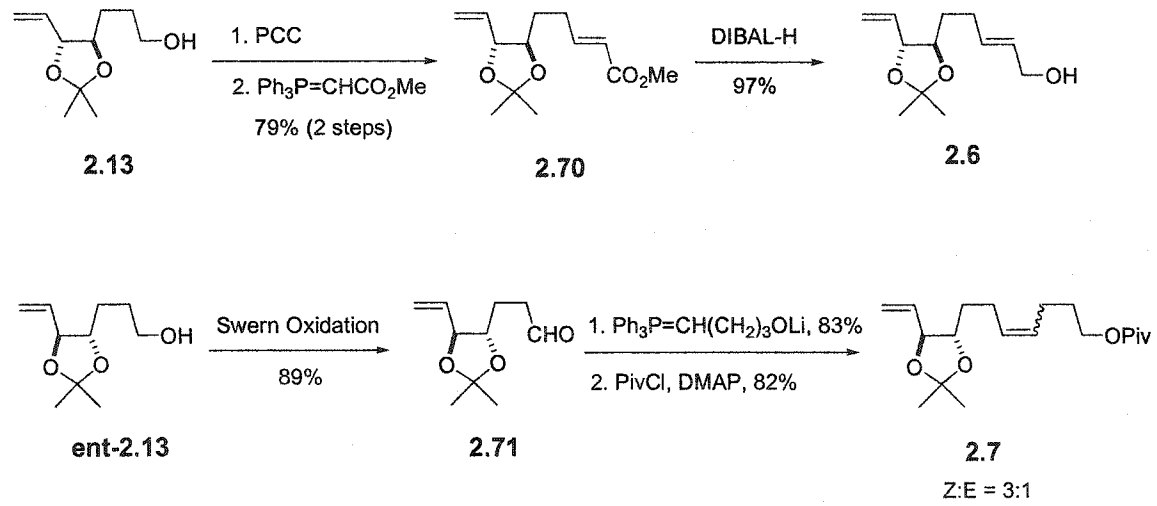
Scheme 2.2



Scheme 2.3



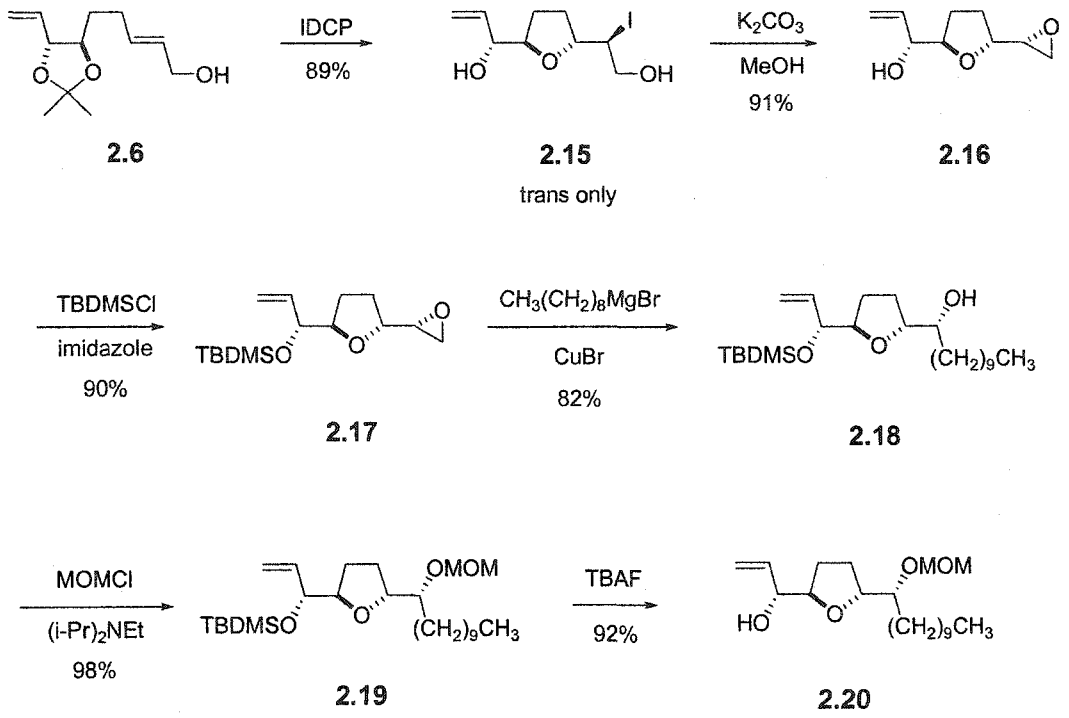
Scheme 2.4



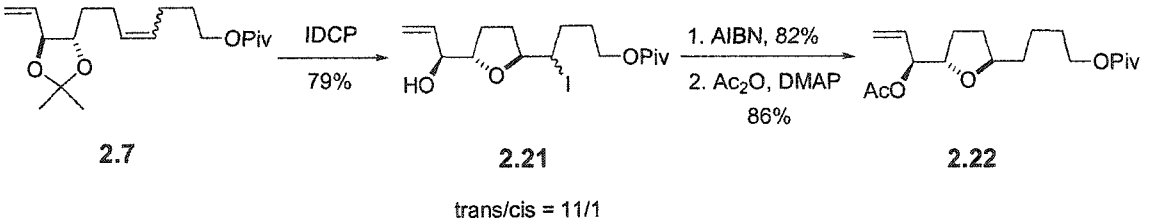
Scheme 2.5

THF-alkene subunits: Iodoetherification reaction on **2.6** and **2.7** were performed using iodonium dicollidine perchlorate (IDCP) in wet acetonitrile (**Scheme 2.6 & 2.7**). Cyclization of **2.6** gave **2.15** in 89% yield as a single *trans* THF isomer. The identical conditions on compound **2.7** afforded an inseparable mixture of products **2.21**, which was

determined to be an 8:1 ratio of *trans:cis* isomers by analysis of the derivative obtained from deiodination of the product (vide infra).



Scheme 2.6

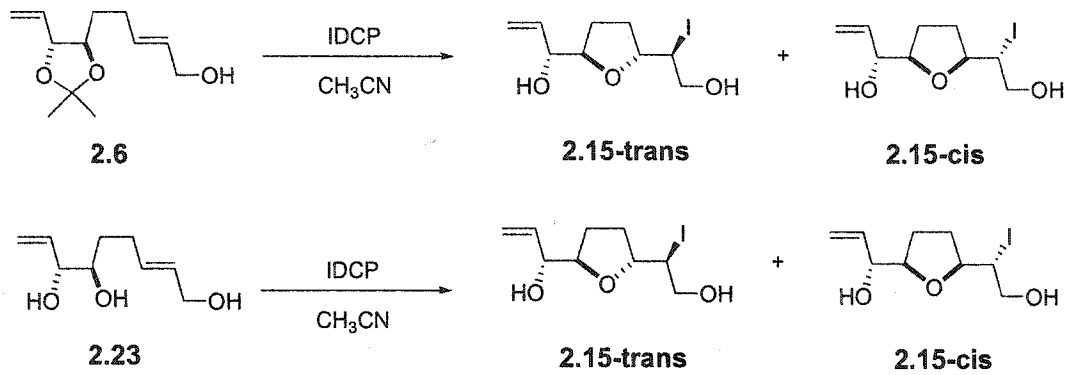


Scheme 2.7

The iodoetherification products **2.15** and mixture **2.21** were next transformed to the precursors for the metathesis step. Conversion of the iodohydrin **2.15** to the epoxide derivative was followed by silylation of the remaining secondary alcohol. Reaction of this product with nonylmagnesiumbromide in the presence of copper (I) bromide led to

alcohol **2.18**. Processing of alcohol protecting groups in **2.18** afforded THF subunit **2.20**, in 61% overall yield from **2.15**. The mixture of *cis/trans* THF iodides **2.21** was subjected to Bu_3SnH reduction of the iodide, followed by acetylation of the secondary alcohol. Chromatographic separation of the *cis* isomeric product at each step, led to a single *trans* THF isomer **2.22**.

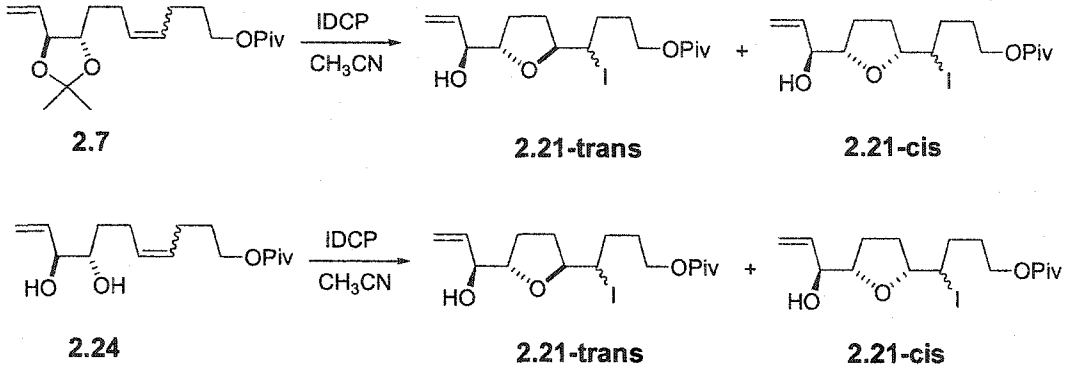
Assignment of THF stereochemistry: Compared to the high stereoselectivity obtained in the iodocyclizations of the isopropylidene alkene substrates, the iodocyclizations of the vicinal diol derivatives of **2.6** (i.e. **2.23**) and **2.7** (i.e. **2.24**) showed low stereoselectivity (*trans:cis*, 4:1 and 7:3 respectively) (**Scheme 2.8 & 2.9, Table 2.1 & 2.2**).



Scheme 2.8

THF diastereomer	% yield from **2.6**	% yield from **2.23**
2.15-trans	100%	80%
2.15-cis	-	20%

Table 2.1

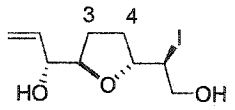


Scheme 2.9

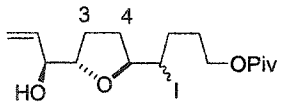
THF diastereomer	% yield from **2.7**	% yield from **2.24**
2.21-trans	92%	70%
2.21-cis	8%	30%

Table 2.2

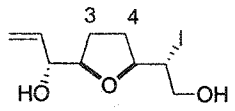
The stereochemistry of the THF-alkene subunits was initially assigned on the basis of the high *trans* stereoselectivity obtained for very similar 1,2-*O*-isopropylidene alkene substrates developed by our group,[96,99,112,115,162] and by comparing ^{13}C NMR resonances of the methylene carbons on the THF rings.[99,154] The signals for the *trans* isomer **2.15-trans** (δ 28.3, 34.3) resonate downfield relative to those of the *cis* isomer **2.15-cis** (δ 27.2, 32.9).[99] In a similar way the stereochemistry of the THF-iodide mixture **3.21** obtained from the cyclization of isopropylidene alkene **2.7** was analysed (**Table 2.3**).



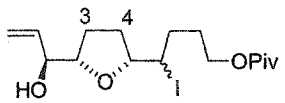
2.15-trans



2.21-trans



2.15-cis



2.21-cis

Carbon #	**2.15-Trans**	**2.15-Cis**	**2.21-Trans**	**2.21-Cis**
C_3 (ppm)	28.3	27.2	27.9	27.6
C_4 (ppm)	34.3	32.9	29.1	28.7

Table 2.3

Additional support from these stereochemical assignments came from comparison of ^{13}C NMR data for selected carbinol carbons (C_q-C_u) in the derived diols **2.25-t**, **2.21-t** and **2.21-c**, and the known reference *trans/cis* THF pairs **2.25-ref-t/2.25-ref-c**, and **2.21-ref-t/2.21-ref-c**, respectively (**Figure 2.2**).[154] The stereochemistry in **2.25-ref-c** corresponds to the derivative that would have resulted from derivitization of the *cis*-THF diastereomer of **2.15** from the iodoetherification reaction. The data for C_p was not considered because of the very different chemical environment of this carbon in **2.25-t** compared with **2.25-ref-t** and **2.25-ref-c**. Thus, $\sum|\Delta\delta|$ for **2.25-t** vs. **2.25-ref-t** and **2.25-ref-c** were 1.03 and 1.94 respectively. The stereochemistry of **2.21-c** and **2.21-t** was assigned in a similar fashion by comparison of the data for the derivative **2.26-t** and **2.26-c** with reference pair **2.26-ref-t** and **2.26-ref-c**[154] ($\sum|\Delta\delta|$ for **2.26-t** vs. **2.26-ref-t** and

2.26-ref-c: 1.44 and 3.06 respectively; $\sum|\Delta\delta|$ for **2.26-c** vs. **2.26-ref-t** and **2.26-ref-c**: 2.68 and 0.86 respectively) (**Table 2.4**).

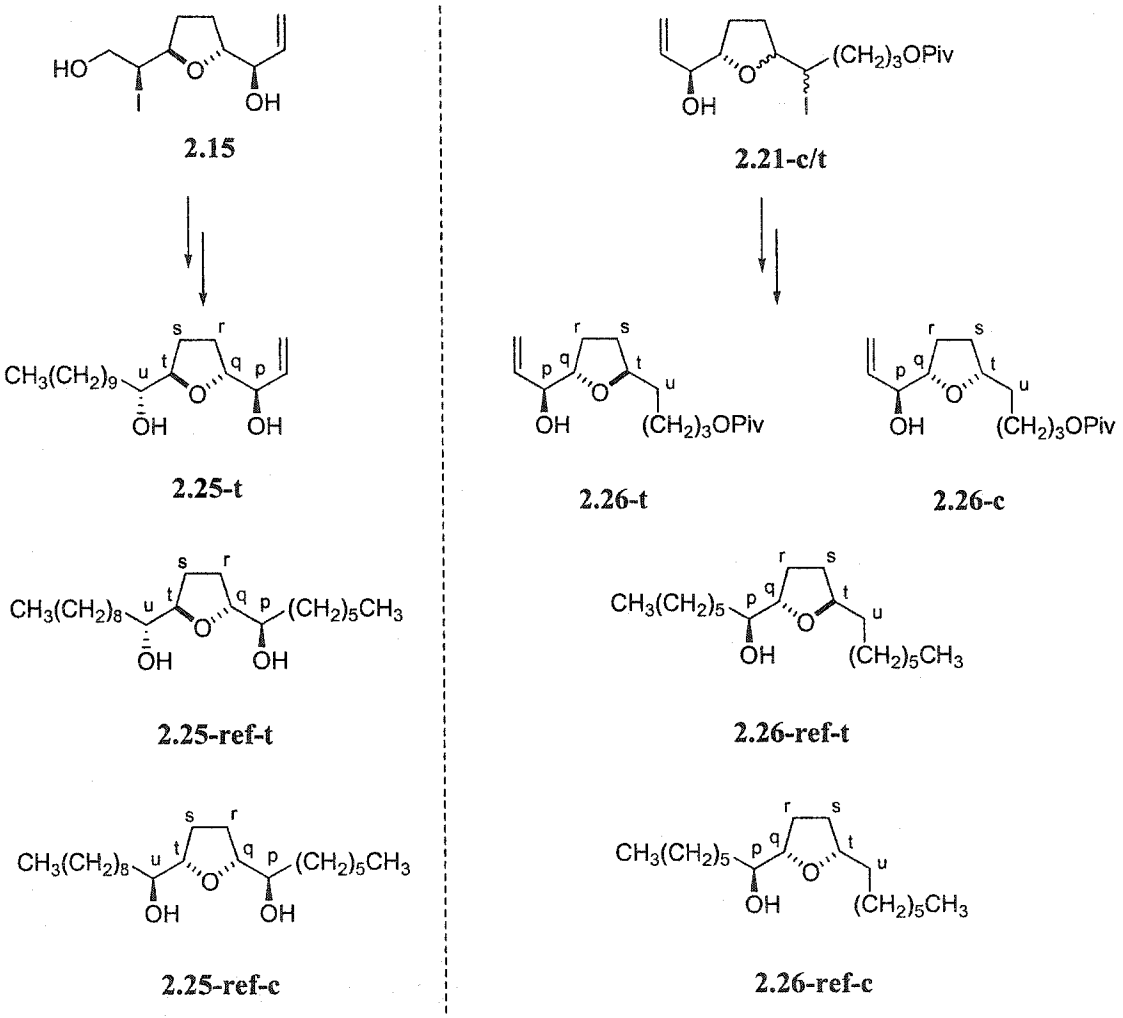


Figure 2.2

Carbon # (ppm)	p	q	r	s	t	u	$\sum^{q\to u}\lvert\Delta\delta\rvert$
2.26-t	75.47	81.61	28.02	32.14	79.25	35.24	-
2.26-ref-t	74.20	81.90	28.40	32.40	79.30	35.70	-
Δδ (2.26t/2.26-ref-t)	1.27	-0.29	-0.38	-0.26	-0.05	-0.46	1.44*
2.25-ref-c	74.50	82.20	27.80	31.40	79.90	36.10	-
Δδ (2.26-t/2.25-ref-c)	0.97	-0.59	0.22	0.74	-0.65	-0.86	3.06
2.26-c	76.12	82.10	27.79	31.62	80.21	35.88	-
Δδ (2.26-c/2.26-ref-t)	1.92	0.20	-0.61	-0.78	0.91	0.18	2.68
Δδ (2.26-c/2.25-ref-c)	1.62	-0.10	-0.01	0.22	0.31	-0.22	0.86*
2.25-t	75.72	83.13	28.67	28.77	82.50	74.24	-
2.25-ref-t	74.00	82.70	28.80	28.80	82.70	74.00	-
Δδ (2.25-t/2.25-ref-t)	1.72	0.43	-0.13	-0.03	-0.20	0.24	1.03*
2.26-ref-c	74.30	82.80	28.10	28.10	82.80	74.30	-
Δδ (2.25-t/2.26-ref-c)	1.42	0.33	0.57	0.67	-0.30	-0.06	1.93

* denotes the synthetic compound/reference *trans*- or *cis*- THF that gives the better match.

Table 2.4

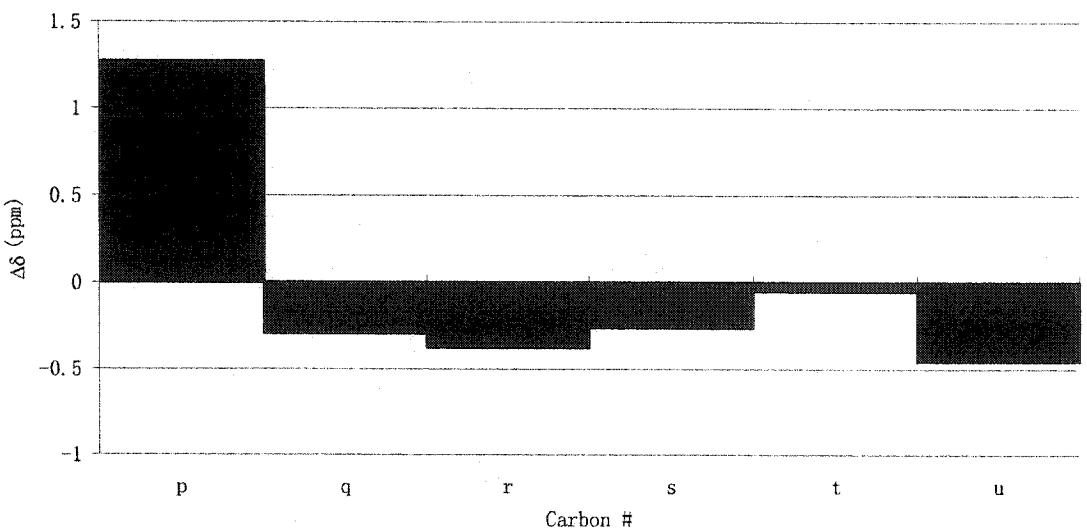


Figure 2.3a Δδ (2.26-t / 2.26-ref-t)

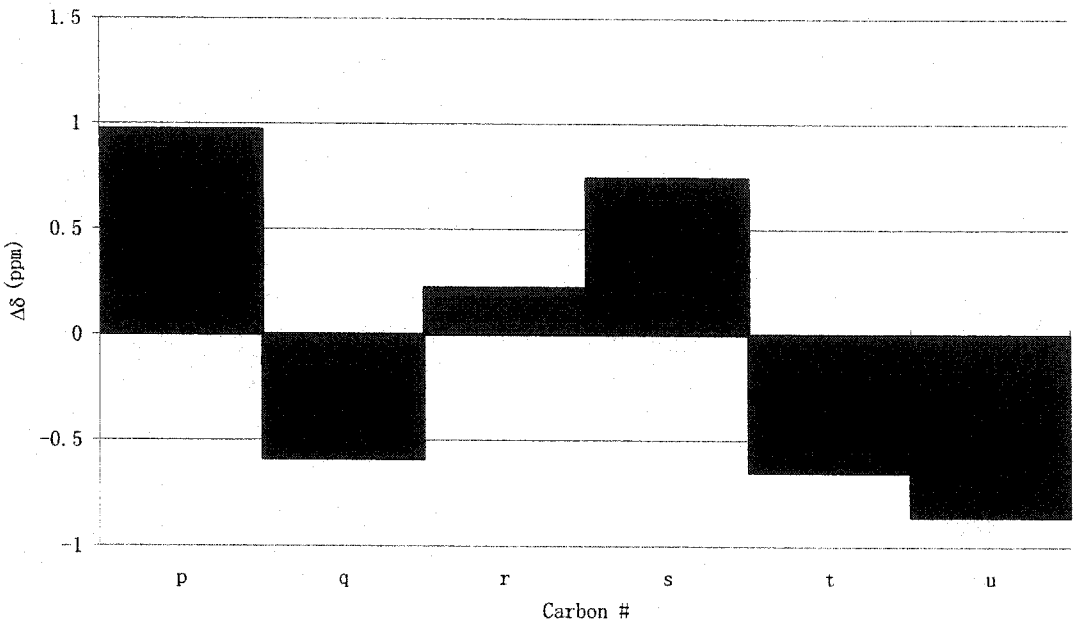


Figure 2.3b Δδ (2.26-t / 2.26-ref-c)

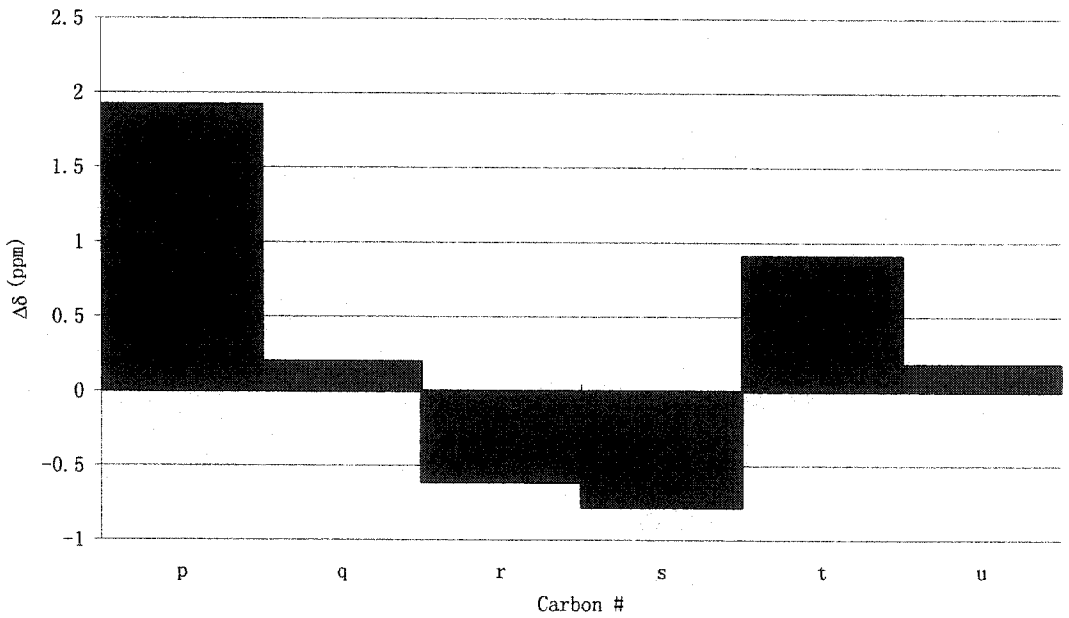


Figure 2.3c Δδ (2.26-c / 2.26-ref-t)

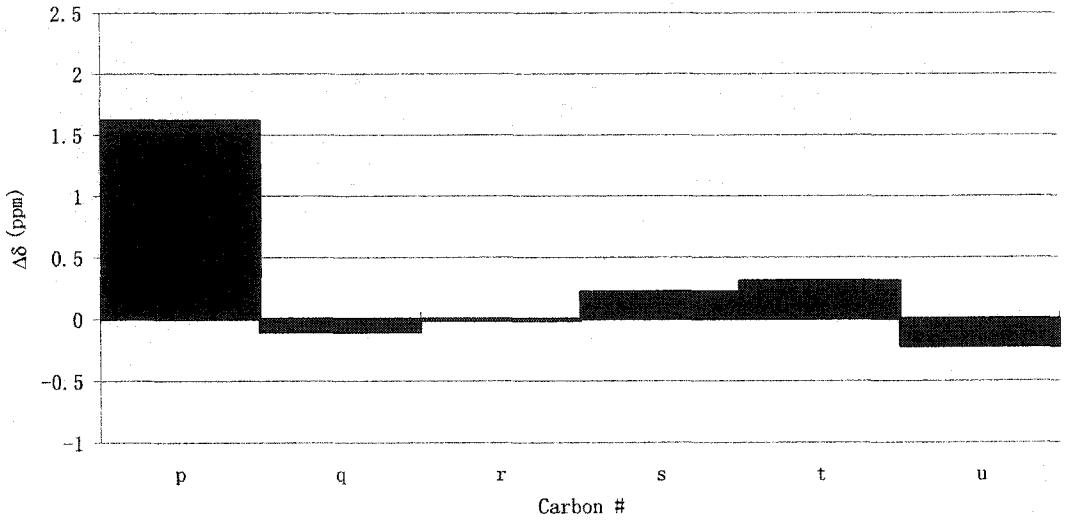


Figure 2.3d Δδ (2.26-c / 2.26-ref-c)

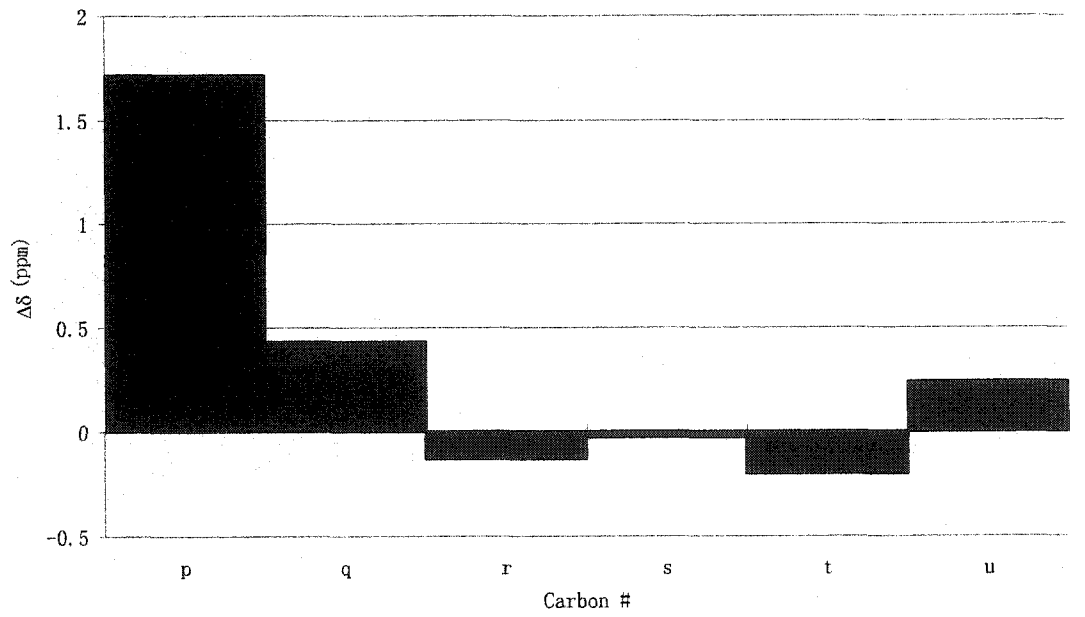


Figure 2.3e Δδ (2.25-t / 2.25-ref-t)

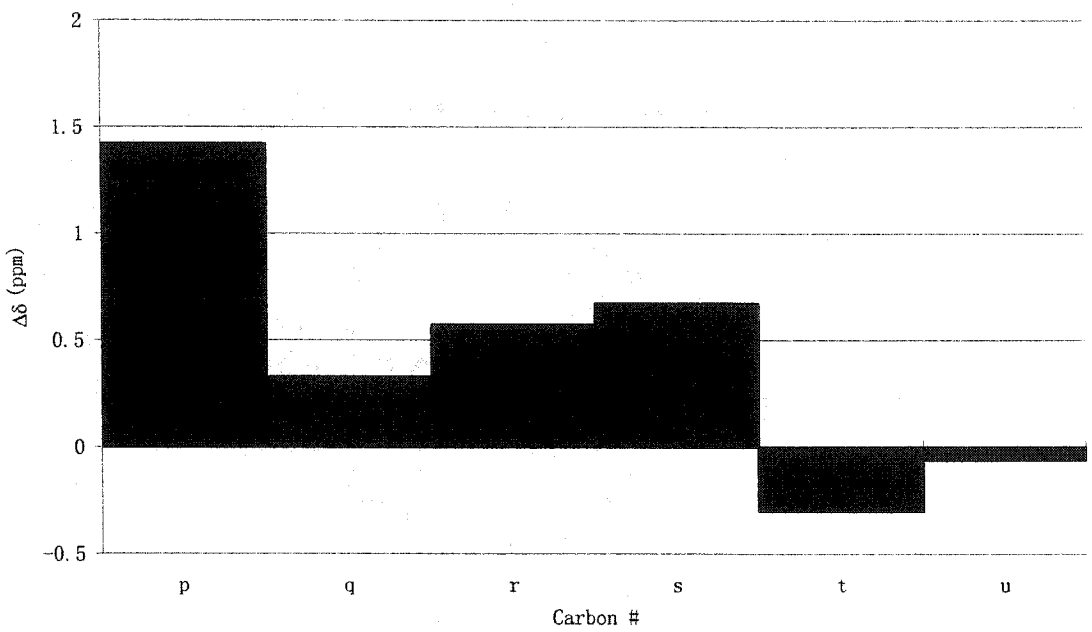
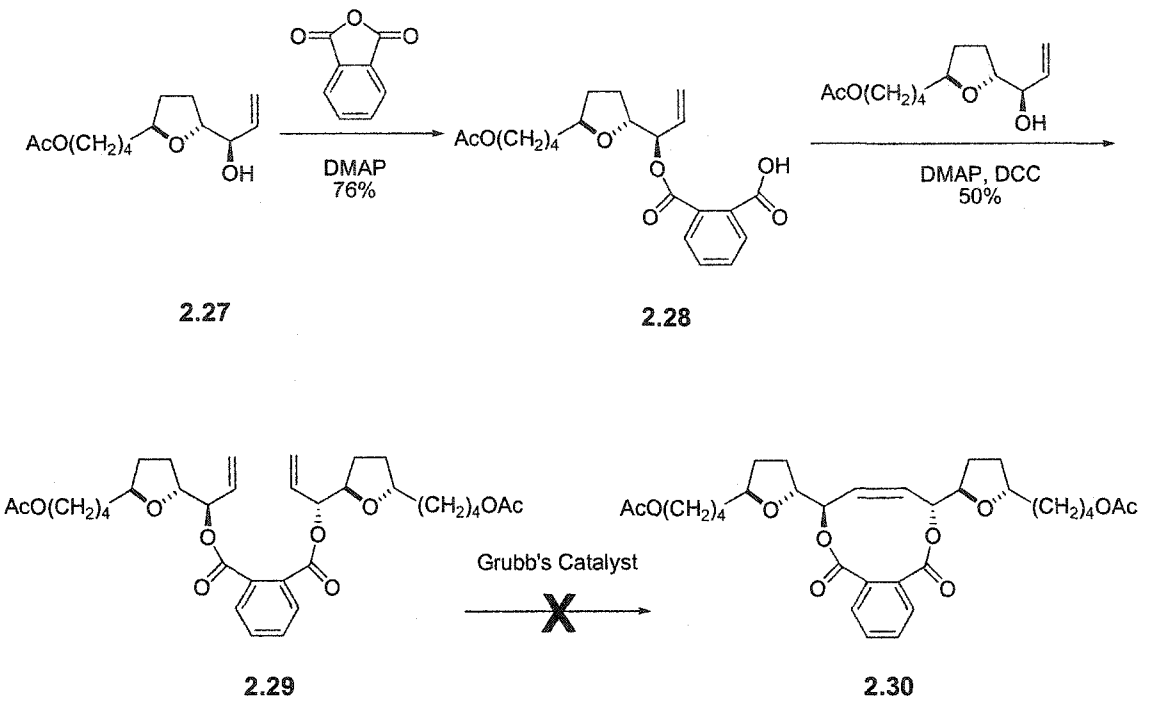


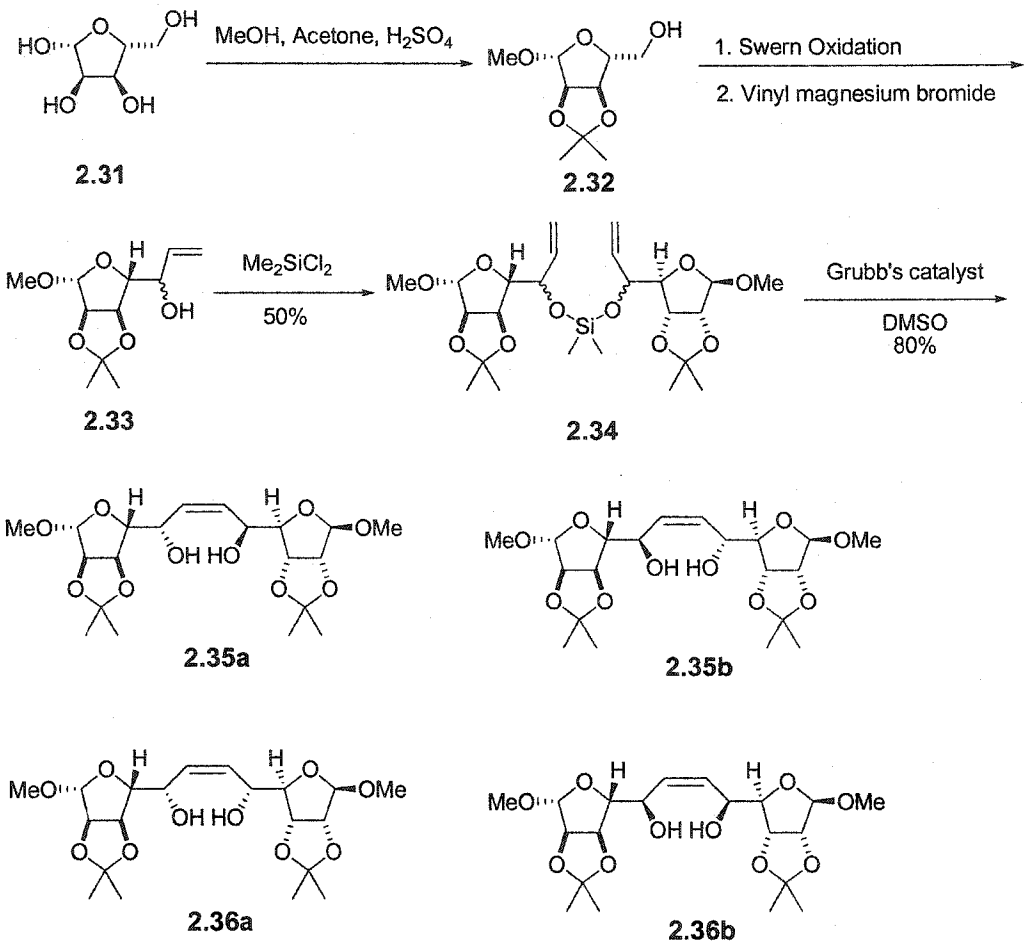
Figure 2.3f Δδ (2.25-t / 2.25-ref-c)

Ring Closing Metathesis coupling: Our initial plan for coupling of the THF allylic alcohol subunits was a RCM protocol.[143] A model study was performed using the phthalate diester of THF allylic alcohol **2.27**.[145,163] Treatment of **2.27** which is acetate derivative of **2.5** with phthalic anhydride afforded carboxylic acid **2.28**. Esterification of **2.28** and **2.27** using DCC and DMAP gave **2.29**. Unfortunately, RCM of **2.29** did not occur, with only recovered starting material being obtained after two days. The low reactivity is presumably due to the deactivating effect of the bis allylic ester, and/or conformational constraints of the phthalate linker (**Scheme 2.10**).

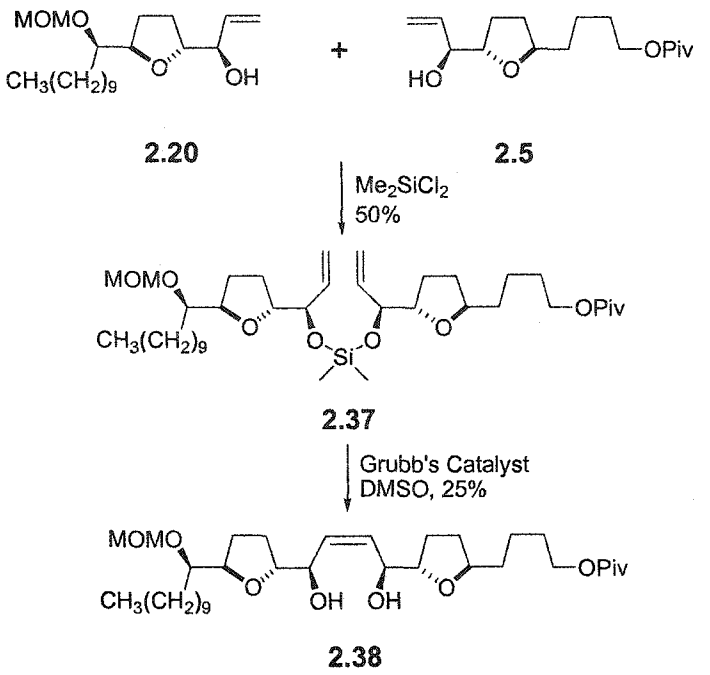


Scheme 2.10

A siloxane linker was next evaluated,[164-167] with the D-ribose derived allylic alcohol **2.33** as a model THF subunit. D-ribose was converted to primary alcohol **2.32** via an established procedure.[168] Oxidation of the alcohol and vinylation of the resulting aldehyde furnished diastereoisomeric mixture **2.33** (*R*:*S* = 1:1). Application of the Evans' silicon-tethering protocol[143] on **2.33** gave an approximately 1:1 *anti*:*syn* mixture **2.34** in 50% yield. RCM reaction on **2.34** afforded diastereomers **2.35a**, **2.35b**, **2.36a** and **2.36b** as an unseparable mixture in 80% total yield (**Scheme 2.11**). Application of this approach to the real system gave the siloxane **2.37** in similar yields as for the corresponding step in the model study (**Scheme 2.12**). However, the best yield obtained for the key RCM reaction was 25% with an overall yield of only 12% for the two steps.



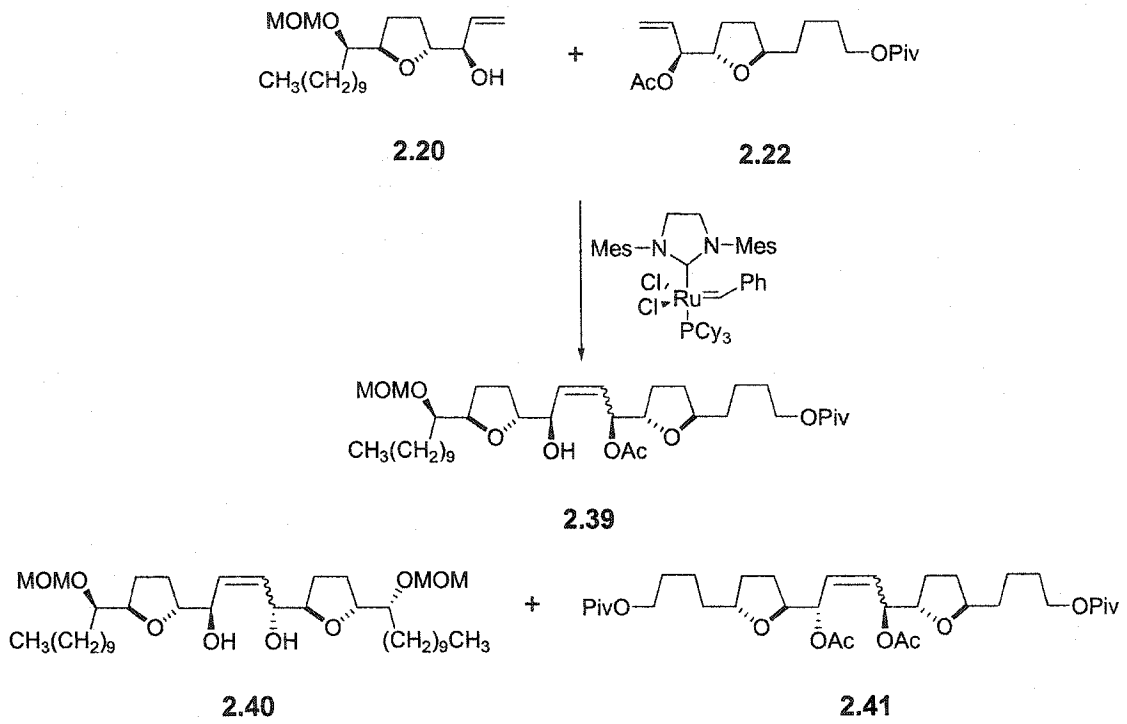
Scheme 2.11



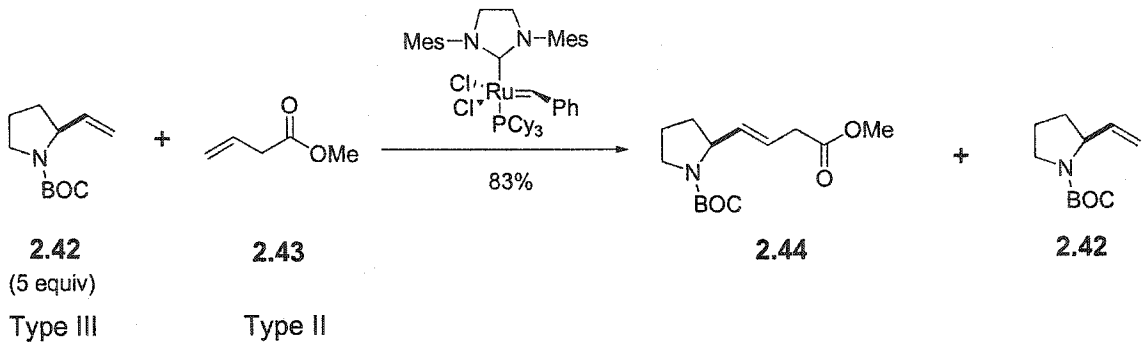
Scheme 2.12

Cross metathesis coupling: As is clear from the foregoing discussion, the RCM approach was hampered by low yield and in the synthesis of tethered precursor and/or the metathesis step. For these reasons, as well as the inherent experimental simplicity, a CM strategy was next pursued.[146,169,170] However, homodimer formation presented a potential problem with this approach. Based on previous successful CM with type II and type III reaction partners[170] (see section 1.3.4), we expected that the reaction of an allylic alcohol **2.20** (type II) and an excess of the allylic ester partner **2.22** (type III) would provide the heterodimer **2.39** as the major product together with unreacted ester starting material **2.22**. The homodimers **2.40** and **2.41** are disfavored on the basis of statistical and reactivity considerations. The combination of excess ester **2.22** with alcohol **2.20** (as opposed to the pairing of excess of the acetate of **2.20** and the alcohol **2.5**), was preferred, because **2.22** is more easily prepared than the acetate of **2.20** (**Scheme 2.13**). A related result on the

CM of pyrrolidine **2.42** and butenoate **2.43** has been reported by Miller and co-workers (**Scheme 2.14**).[171]



Scheme 2.13



Scheme 2.14

Metatheses of alcohol **2.20** and varying molar equivalents of acetate **2.22** were performed for different catalyst concentrations, reaction temperatures and reaction times (**Scheme 2.12** and **Table 2.5**).[155,156]

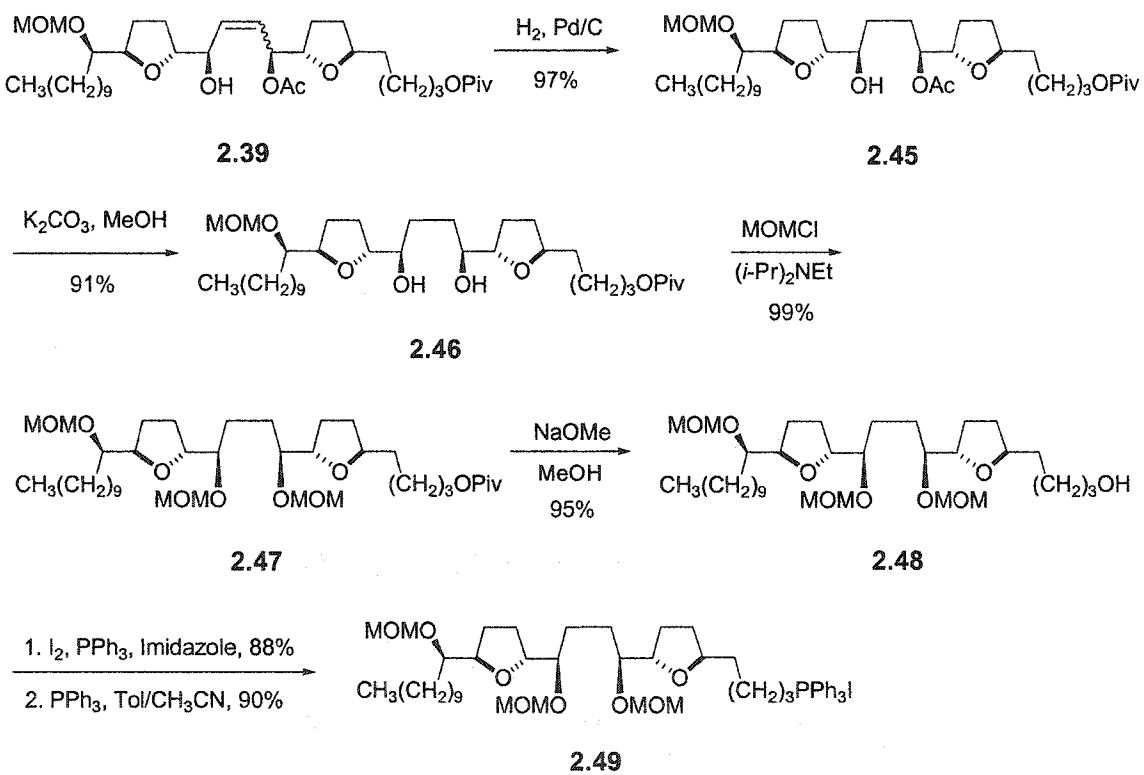
							Yield (%)		Recovered SM (mg)	
Conditions	Ratio	**2.20** (mg)	**2.22** (mg)	**2.39** (mg)	**2.40** (mg)	**2.41** (mg)	**Rel 2.20**	**Rel 2.22**	**2.20**	**2.22**
A	1:2	94.2	176	50.2	47.2	-	34	68	16.3	138.4
B	1:4	152	580	138.7	-	41	53	42	13	411.4
C	1:2	112.3	214	107	-	13.7	51	40	-	75.5
D	1:3	115	321.6	160.7	< 5	< 5	75	76	-	214
E	1:4	120	450	189	5	64.4	84	59	-	285.5
F	1:4	134	491.4	212	-	14.4	98	46	18.5	257.4
G	1:2	135	245	147.5	-	-	58	77	-	148

* Detail of each method is in experimental Section.

Table 2.5

Two procedures of comparable efficiency were developed. In condition F, a 1:4 ratio of **2.20**:**2.22** and 10 mol% catalyst (relative to alcohol **2.20**) was used. The heterodimer **2.39** was obtained as the major product together with unreacted alcohol **2.20** and acetate **2.22** (86 and 48% consumption respectively). The yield of **2.39** (*E*:*Z* = 3:1) was 98 and 46% based on consumed **2.20** and **2.22**. A small amount of homodimer **2.40** (3%) was also observed. The homodimer **2.41** was not detected. The differences in alcohol substitution of the components of the reaction mixture facilitated a straightforward chromatographic separation. Condition D was similar to F, except for the molar ratio of **2.20**:**2.22** (1:3 vs. 1:4) and the conditions. This protocol led to heterodimer **2.39** in 75 and 76% yield based on **2.20** and **2.22** (67 and ca. 100% consumption respectively). Homodimer **2.40** and **2.41** were also obtained in 2 and 4%.

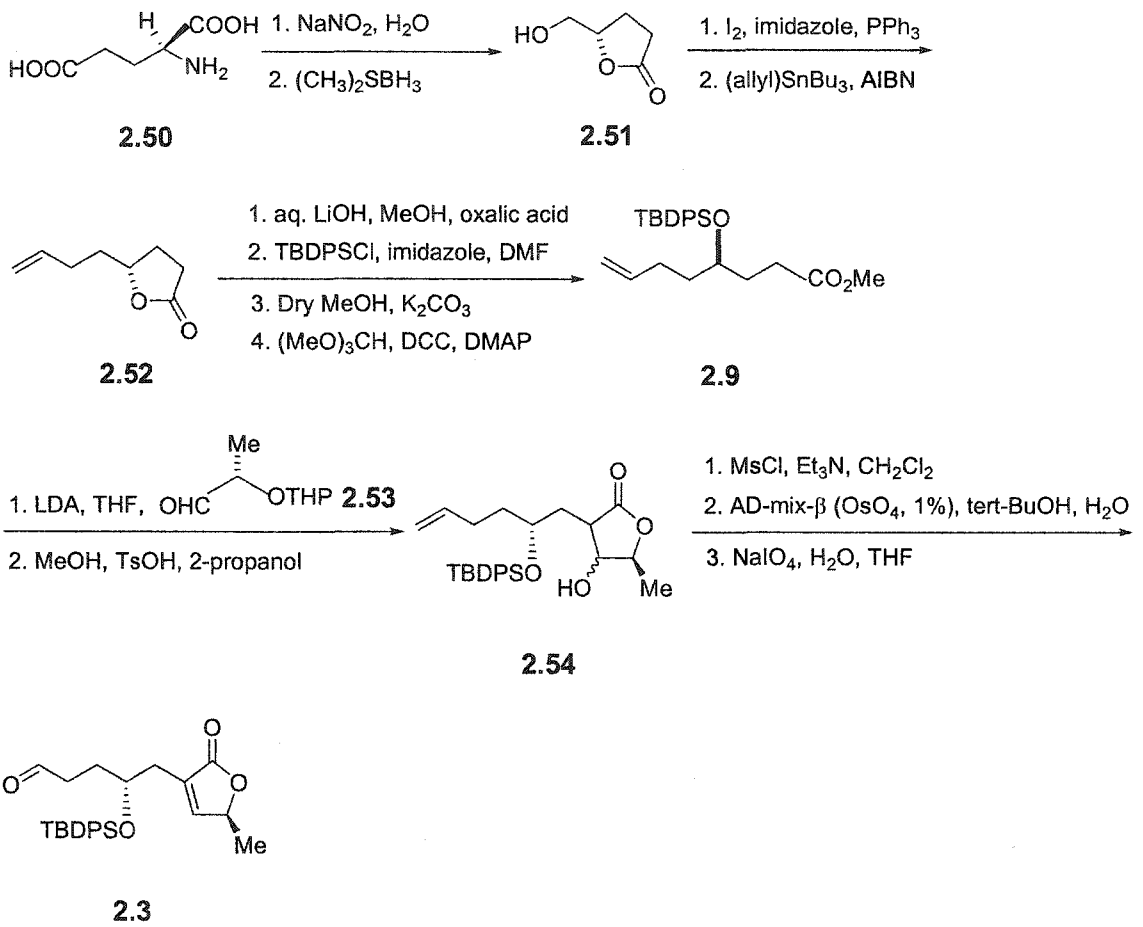
Bis-THF **2.39** was next converted to phosphonium salt **2.49** for the final Wittig coupling with aldehyde **2.3** (**Scheme 2.15**). Hydrogenation of alkene **2.39** followed by selective hydrolysis of the acetate, formation of the bismethoxymethyl ether of the derived diol, and then removal of the pivalate ester, afforded alcohol **2.48**. Treatment of the iodide derived from **2.48** with triphenylphosphine in the presence of Hunig's base provided phosphonium salt **2.49**.



Scheme 2.15

The butenolide subunit: Initially, the Sinha-Keinan's procedure was used to prepare the butenolide segment. L-glutamic acid **2.50** was converted to methyl ester **2.9** as a key intermediate (**Scheme 2.16**).[84] However, this strategy was limited by a low

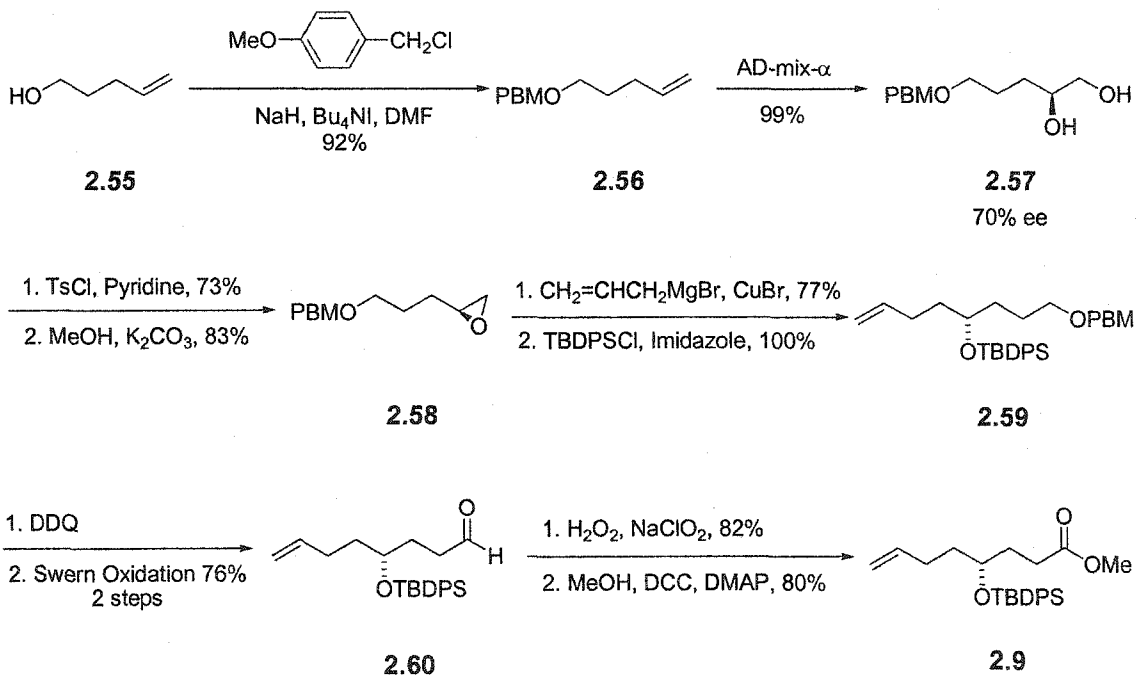
overall yield (3% yield from compound **2.50** to **2.9**). A new synthesis of **2.9** from 4-penten-1-ol was therefore developed.



Scheme 2.16

Commercially available 4-penten-1-ol **2.55** was first converted to the p-methoxy benzyl ether **2.56**,[172] and then treated with AD-mix-α to give the diol **2.57**. The enantiomeric purity (70% ee) was determined by analysis of the Mosher ester derivative of **2.57** and the racemic product obtained from OsO_4 dihydroxylation of **2.56**. Epoxide **2.58** was obtained in two straightforward steps from **2.57**, and **2.58** was treated with

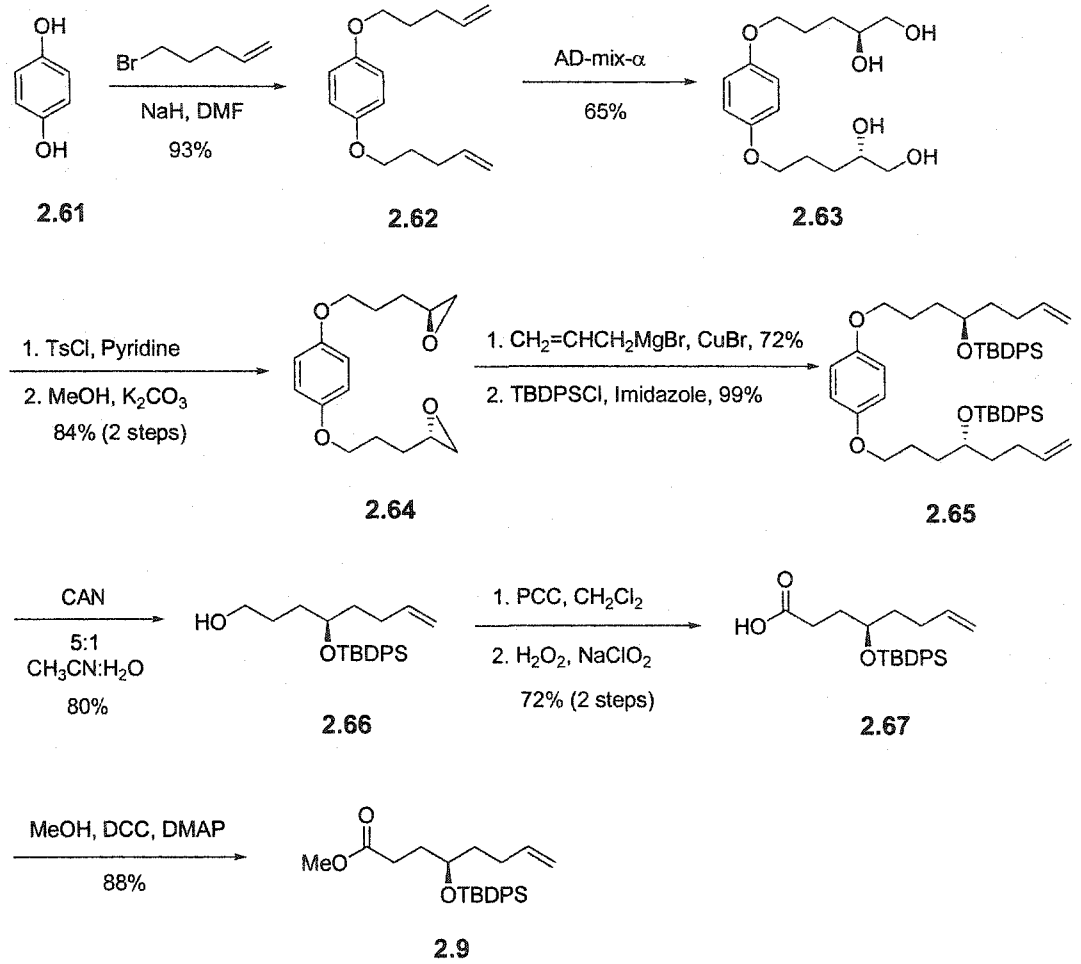
allylmagnesium bromide in presence of CuI.[115] The resulting secondary hydroxyl was protected as the silyl ether **2.59**. Removal of the PMB group and oxidation of the resulting primary alcohol gave aldehyde **2.60**. Further oxidation of **2.60** to the carboxyl acid and esterification led to **2.9** (**Scheme 2.17**). The benefit of this route is that all the reactions are straightforward and the overall yield is much higher. (21% yield from compound **2.55** to **2.9**)



Scheme 2.17

However, the ester **2.9** was obtained in only 70% ee. A modification of this approach was developed to improve the enantioselectivity (**Scheme 2.18**). Thus, following a similar strategy to that employed by Hoye and co-workers,[77,173] commercially available 5-bromo-1-pentene **2.61** was first converted to the hydroquinone ether **2.62**, and then treated with AD-mix-α. Three crystallizations of the crude product from ethyl

acetate provided a mixture of dl-**2.63** and the *meso* isomer with a total *R/S* ratio that was estimated at 20/1 by NMR analysis of the tetra Mosher ester derivative (**Table 2.6**).



Scheme 2.18

No. of recrystallizations	S:R	Yield %
crude	Not determined	99
2	10:1	74
3	20:1	65

* Detail of determination is in **Scheme 2.19**.

Table 2.6

Epoxide **2.64** obtained from selective tosylation of **2.63** was treated with allylmagnesium bromide and CuI as before.[174] Then the resulting secondary hydroxyl was protected as the silyl ether **2.65**. Treatment of **2.65** with CAN provided **2.66**. Standard processing of **2.66** furnished methyl ester **2.9**, which was converted to butenolide aldehyde **2.3** via the identical sequence used by Keinan and Sinha.[84] Overall **2.9** was obtained in 10 steps and 18% yield from 5-bromo-1-pentene in greater than 90% ee (**Table 2.7**).

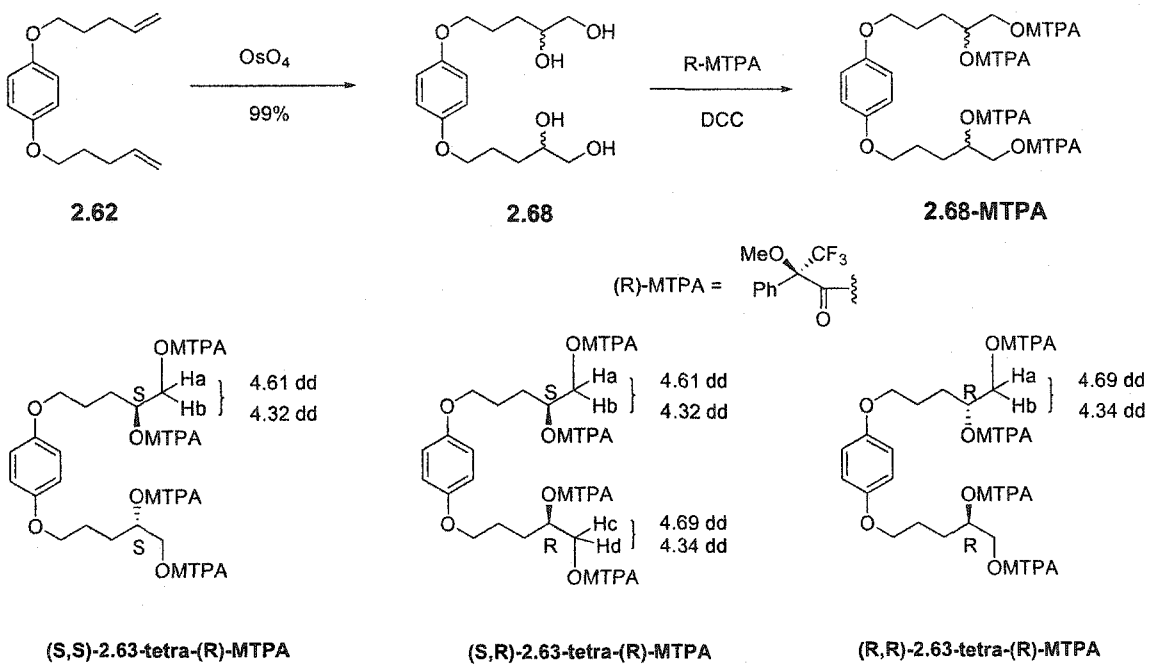
Synthesis of **2.9**	Yield	Enantio-Selectivity	Synthetic Steps
M1[a]	3%	> 99% ee	8
M2[b]	21%	70% ee	10
M3[c]	18%	> 90% ee	10

[a] see **Scheme 2.16**; [b] see **Scheme 2.17**; [c] see **Scheme 2.18**.

Table 2.7

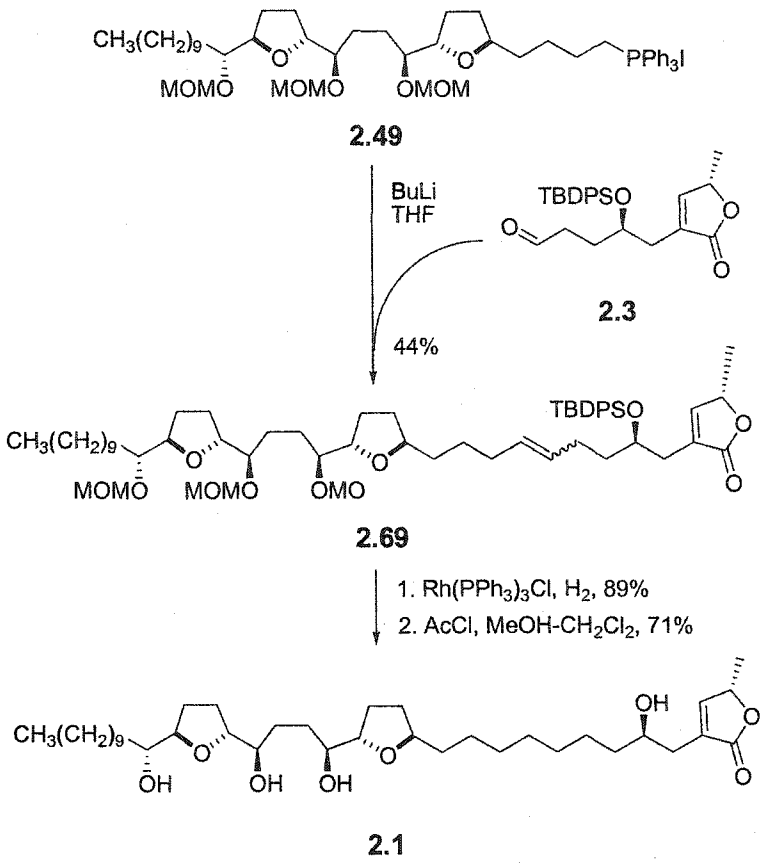
The overall *S/R* ratio of **2.63** was determined by conversion to the tetra-Mosher ester derivative of R-MTPA.[173] For comparison, the tetraol mixture **2.68** obtain from the reaction of **2.62** with OsO_4 was converted to the corresponding mixture of tetra-Mosher ester diastereomers **2.68-MTPA**. Examination of ^1H NMR data indicated that one of the methylene protons attached to the carbinol carbon of the primary alcohol-MTPA residue resonated at a distinct chemical shift depending on the absolute configuration at the adjacent secondary alcohol. These signals occurred as dd's at δ 4.61 and 4.69 respectively for *S* and *R* configurations at the secondary alcohol. (The chemical shifts for the corresponding protons in the "pseudo"-*meso* diastereomer (*S/R*) were identical to the

shift in the *R/R* or *S/S* diastereomers). The overall *S/R* ratio was determined by integration of these signals (**Scheme 2.19**).



Scheme 2.19

Coupling of THF and butenolide subunits: The THF and butenolide segments were connected using the Wittig protocol developed by Keinan and Sinha.[86] Treatment of the ylide derived from phosphonium salt **2.49** to two equivalents of aldehyde **2.3**, afforded alkene **2.69** in 44% yield as an undetermined mixture of *E/Z* isomers. Finally, catalytic hydrogenation over Wilkinson's catalyst and cleavage alcohol protecting groups with acidic methanol afforded bullatanocin **2.1** in 63% yield over two steps (**Scheme 2.20**).



Scheme 2.20

The ^{1}H and ^{13}C NMR of the product were essentially identical to that for bullatanocin (squamostatin C) (Appendix page 229-232, **Table 2.8, Figure 2.4-2.8**). The optical rotations ($[\alpha]^{22}_{D}$) of **2.1** in $CHCl_3$ and MeOH were found to be 16.5 and 18.7 compared with corresponding values of 14.4 (bullatanocin) and 12.0 (squamostatin C) respectively (**Table 2.9**).

Carbon #	Squamostation-C[153]	Bullatanocin[73]	Synthetic Compound	Syn-Squ	Bul-Syn
1	174.6	174.44	174.64	0.04	0.20
2	131.2	130.95	131.18	-0.02	0.23
3	33.4	37.31-25.52*	33.35	-0.05	-
4	70.0	69.74	69.96	-0.04	0.22
5	37.4	37.31-25.52*	37.38	-0.02	-
6	25.5	37.31-25.52*	25.52	0.02	-
7-9	29-30*	37.31-25.52*	29.93	-	-
10	26.1	37.31-25.52*	26.13	0.03	-
11	35.6	37.31-25.52*	35.55	-0.05	-
12	79.3	79.21	79.29	-0.01	0.08
13	32.4	37.31-25.52*	32.39	-0.01	-
14	28.4	37.31-25.52*	28.39	-0.01	-
15	82.0	81.97	81.98	-0.02	0.01
16	74.4	74.33	74.41	0.01	0.08
17	29-30*	37.31-25.52*	29.70	-	-
18	29-30*	37.31-25.52*	29.61	-	-
19	74.3	74.21	74.25	-0.05	0.04
20	82.7	82.65	82.70	0.00	0.05
21	28.7	37.31-25.52*	28.69	-0.01	-
22	28.7	37.31-25.52*	28.69	-0.01	-
23	82.7	82.67	82.70	0.00	0.03
24	74.0	74.00	74.06	0.06	0.06
25	33.5	37.31-25.52*	33.43	-0.07	-
26	25.6	37.31-25.52*	25.59	-0.01	-
27	29-30*	37.31-25.52*	29.61	-	-
28	29-30*	37.31-25.52*	29.51	-	-
29	29-30*	37.31-25.52*	29.40	-	-
30	29-30*	37.31-25.52*	29.40	-	-
31	29-30*	37.31-25.52*	29.32	-	-
32	31.9	37.31-25.52*	31.90	0.00	-
33	22.7	22.64	22.67	-0.03	0.03
34	14.1	14.10	14.11	0.01	0.01
35	151.7	151.68	151.86	0.16	0.18
36	77.9	77.88	77.97	0.07	0.09
37	19.1	19.07	19.11	0.01	0.04

* exact ppm not listed in original literature: ref 153 and 73.

** ^{13}C NMR in $CDCl_3$ (Natural compound: 125 MHz; synthetic compound: 100 MHz; rel to $CDCl_3$ at 77.00 ppm, carbon assignments made by comparison to literature values)

Table 2.8. ^{13}CNMR of bullatanocin (squamostatin-C) and synthetic material

	$[\alpha]^{22}_D$ in MeOH	$[\alpha]^{22}_D$ in $CHCl_3$	mp (°C)
Synthetic Compound	+18.7	+16.5	97-99
Bullatanocin	-	+14.4	-
Squamostatin-C	+12.0	-	95-97

Table 2.9

Figure 2.4: ^{13}CNMR comparison for squamostatin C vs synthetic sample (comparisons are made with only those carbons for which exact chemical shifts are reported)

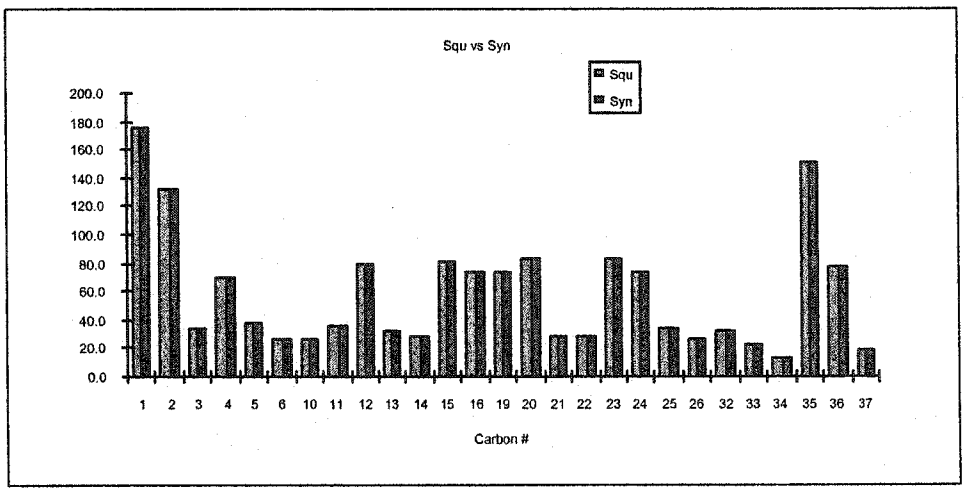


Figure 2.5: ^{13}CNMR comparison of carbinol carbons for squamostatin C vs synthetic sample

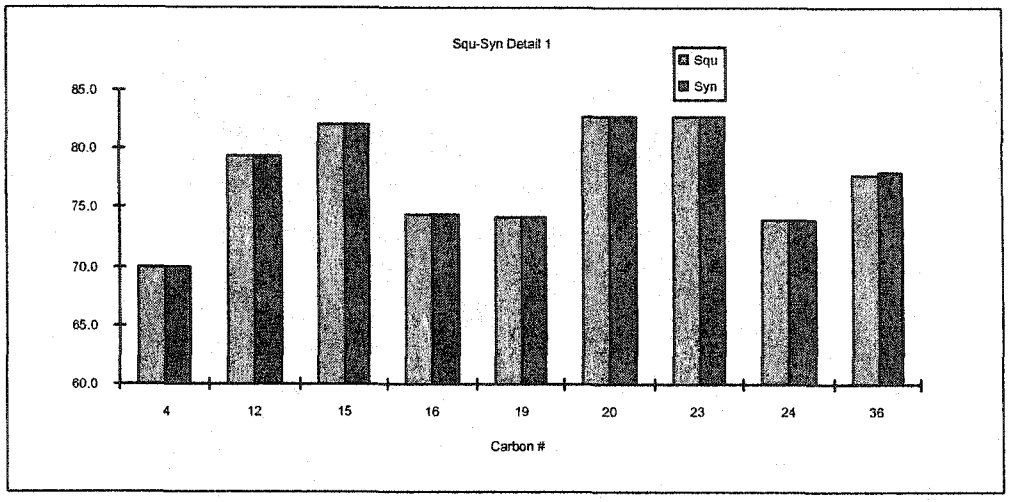


Figure 2.6: ^{13}CNMR comparison of 0-40 ppm region for squamostatin C vs synthetic sample (comparisons are made with only those carbons for which exact chemical shifts are reported)

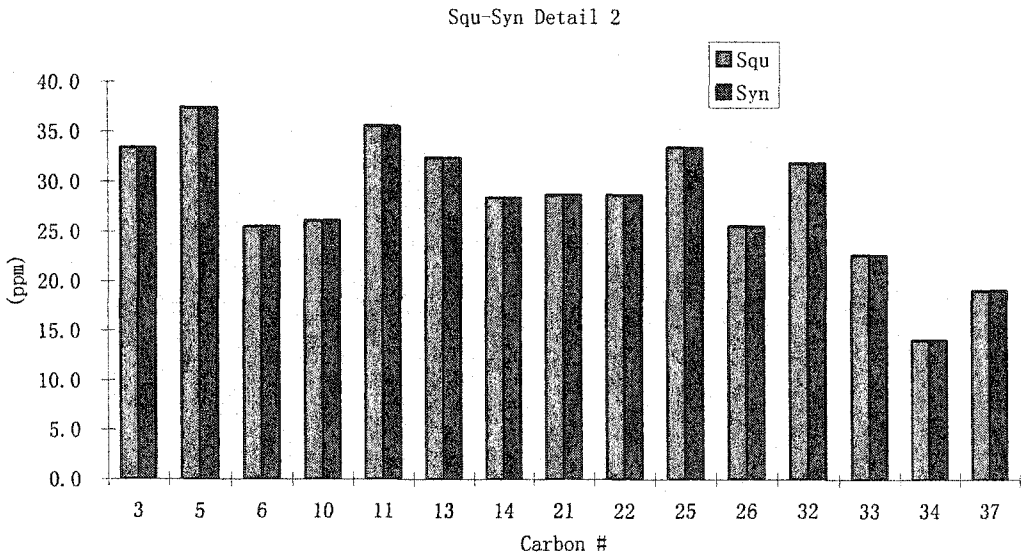


Figure 2.7: ^{13}CNMR comparison for bullatanocin vs synthetic sample (comparisons are made with only those carbons for which exact chemical shifts are reported)

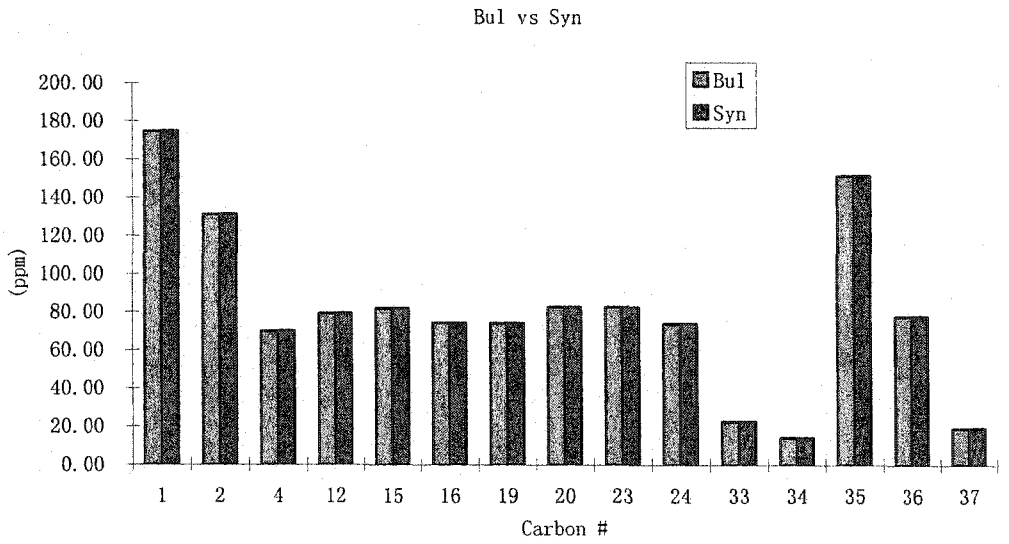
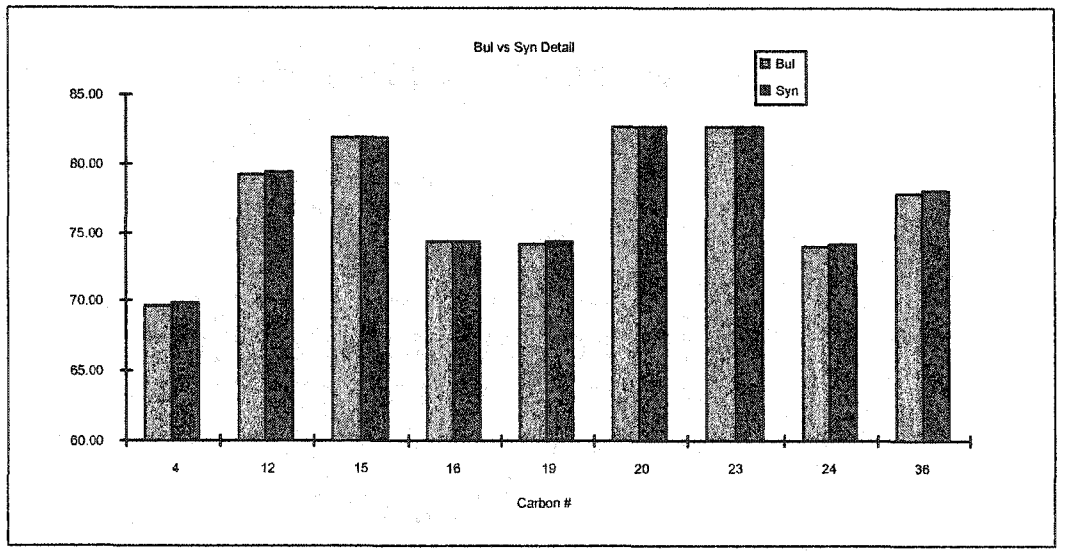
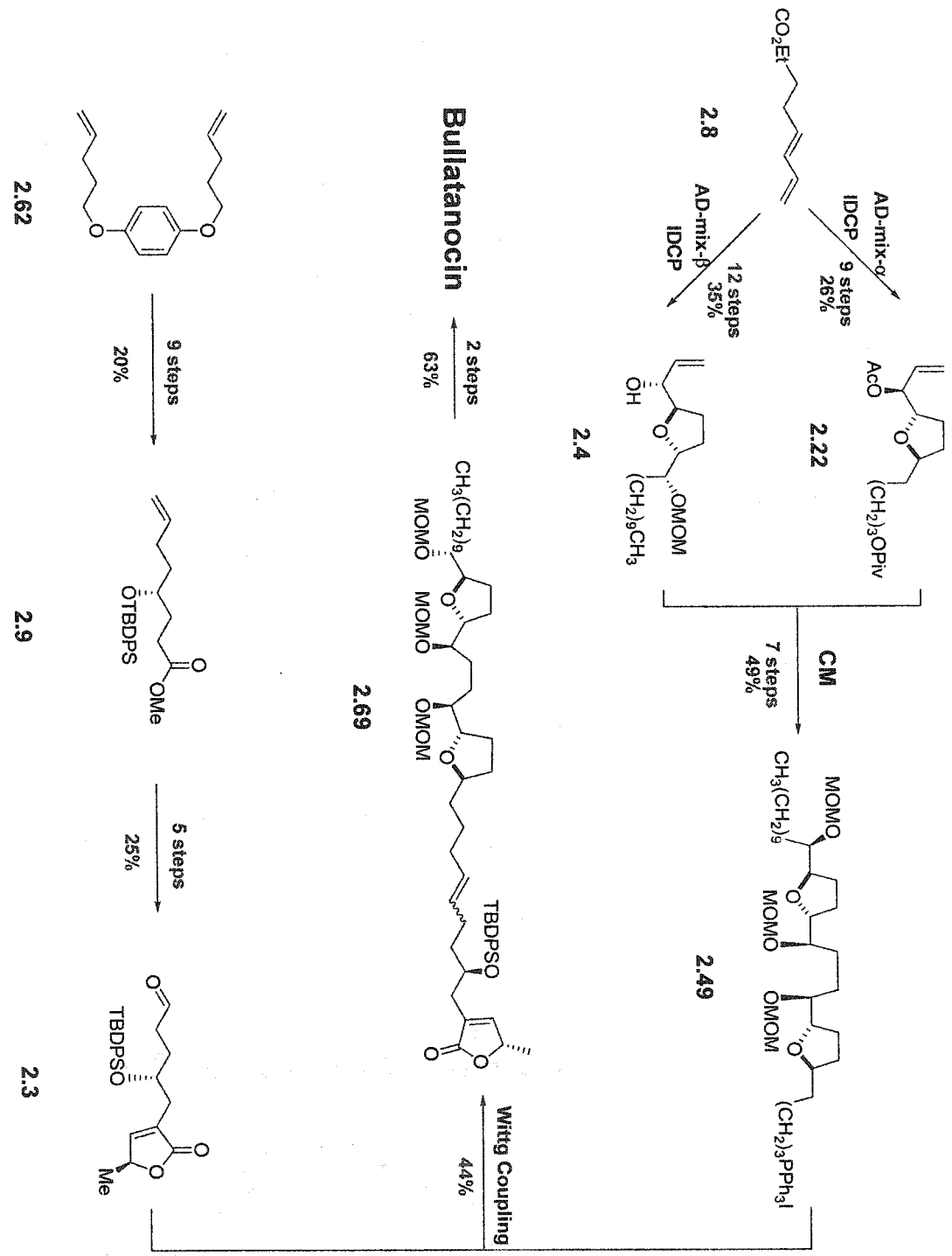


Figure 2.8: ^{13}CNMR comparison of carbinol carbons for bullatanocin vs synthetic sample



2.4 Summary

Total synthesis of bullatanocin (squamostatin C) was achieved in 45 total steps, and 4.8% overall yield for the longest linear sequence of 22 steps (**Scheme 2.21**). Attractive aspects of the general methodology are the highly modular design and the easily availability of the individual components. In principle, by using different mono-THF's and butenolide subunits, a library of different non-adjacent bis-THF can be obtained.



Scheme 2.21

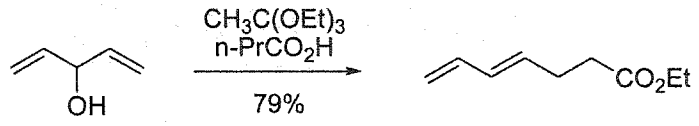
2.5 Experimental Section

General: 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), Varian Unity Plus 500 (500 MHz) and Bruker Ultra Shield (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, 100 or 125 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 the University of Illinois at Urbana-Champaign.

Thin layer chromatography (TLC) was done on 0.25 mm thick precoated silica gel 60 (HF-254, E. Merck) 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 Kieselgel 60 (230-400 mesh, E. Merck) and usually employed a stepwise solvent polarity gradient, correlated with TLC mobility.

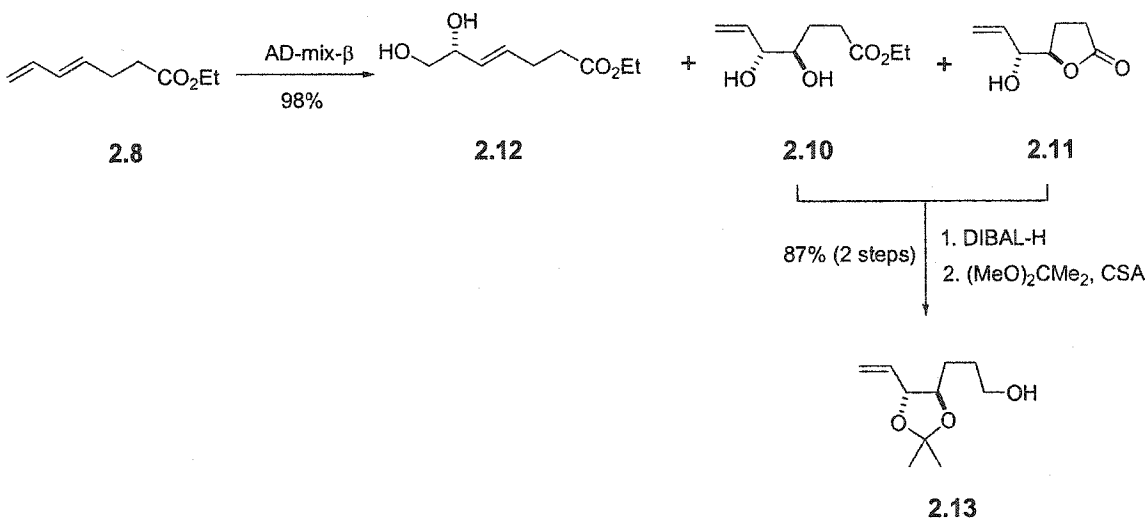
Synthesis of 2.8



1,4-Pentadien-3-ol **2.8**

1,4-Pentadien-3-ol (25 g, 298 mmol), triethyl orthoacetate (384 mL), and propionic acid (4.5 mL, 60 mmol) were heated to reflux in toluene (200mL) overnight. Toluene was then removed by rotary evaporation to yield a yellow oil which was subsequently distilled under vacuum (0.2 mmHg) to afford the ester **2.8** 36.2 g (bp 48-50 ℃, 79%) of a colorless oil: R_f = 0.69 (5% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.26 (dt, 1H, *J* = 16.8, 10.2 Hz), 6.07 (m, 1H), 5.67 (m, 1H), 5.08 (dd, 1H, *J* = 16.8, 1.6 Hz), 4.96 (dd, 1H, *J* = 10.2, 1.6 Hz), 4.10 (q, 2H, *J* = 7.1 Hz), 2.39 (m, 4H), 1.24 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3, 137.4, 133.1, 132.6, 116.1, 60.9, 34.6, 28.5, 15.0.

Synthesis of 2.13



A 1000-mL round-bottomed flask, equipped with a magnetic stirrer, was charged with tert-butyl alcohol (150 mL), water (150 mL), and AD-mix-β (60.70 g). Stirring at rt produced two clear phases; the lower aqueous phase was bright yellow. Methanesulfonamide (6.20 g, 65.0 mmol) was added at this point. The mixture was cooled to 0 ℃, whereupon some of the dissolved salts precipitated. Ethyl 4,6-heptadienoate **2.8** (10.00 g, 65.0 mmol) was added, and the heterogeneous slurry was stirred vigorously at 0 ℃ for 12h (progress was monitored by TLC). Solid sodium metabisulfite (66.0 g) was then added and the mixture was allowed to warm to rt and stirred for an additional 1 h. Ethyl acetate (200 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with ethyl acetate (5 × 100 mL). The combined organic layer was washed with 2 N KOH, dried (Na_2SO_4), filtered and concentrated to give the light yellow oil. This crude product was purified by FCC (silica gel, 70% EtOAc : petroleum ether) to afford the **2.10** and **2.11** (47%) and **2.12** (52%).

Compound 2.10: R_f= 0.4 (50% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.74-5.86 (m, 1H), 5.16-5.32 (dd, 2H, J = 17.2, 10.6 Hz), 4.09 (q, 2H, J = 7.0 Hz), 3.86 (s, 1H), 3.38 (m, 3H), 2.45 (m, 2H), 1.60-1.90 (m, 2H), 1.20 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.7, 138.0, 118.0, 76.8, 74.3, 61.2, 31.4, 28.8, 14.9; HRMS (FAB) calcd for $C_9H_{17}O_4$ ($M + H^+$) 189.1127, found 189.1126.

Compound 2.11: R_f= 0.32 (50% EtOAc : petroleum ether); $[\alpha]^{22}_D$ –25.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.79-5.90 (m, 1H), 5.23-5.40 (dd, 2H, J = 17.2, 10.6 Hz), 4.45 (m, 1H), 4.14 (m, 1H), 3.01 (d, 1H, J = 4.8 Hz), 2.40- 2.61 (m, 2H), 2.00-

2.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.7, 135.9, 118.9, 83.1, 75.3, 29.2, 24.3; HRMS (FAB) calcd for $C_7H_{11}O_3$ ($M + H^+$) 143.0708, found 143.0708.

Compound 2.12: R_f = 0.16 (50% EtOAc : petroleum ether); $[\alpha]^{22}_D$ –6.89 (*c* 0.89, $CHCl_3$); ^1H NMR (C_3D_6O, 300 MHz) δ 6.15 (s, br, 1H), 5.71 (m, 1H), 5.41-5.49 (dd, 1H, *J* = 6.2 Hz), 4.09 (q, 2H, *J* = 7.3 Hz), 3.85 (m, 1H), 3.61 (m, 1H), 3.30-3.50 (m, 2H), 2.30 (m, 4H), 1.21 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6, 131.9, 130.6, 73.5, 67.2, 61.1, 34.5, 28.3, 14.9.

To a stirred solution of **2.10** (3.90 g, 20.8 mmol) and **2.11** mixture (5.80 g, 41.2 mmol) in dry THF (220 mL) at –78℃ under N_2 was added dropwise a solution of DIBAL-H (220 mL, 0.2 mol, 1M in hexane). The mixture was stirred for 1.5 h at –78℃ and then warmed to rt. The reaction mixture was poured into ice cold of Rochell's salt (saturated $KNaC_4H_4O_6$, 320 mL). The mixture was warmed to rt, and stirred until the salts had dissolved. The organic layer was separated and the aqueous layer was extracted with EtOAc (5 × 150 mL). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in dry CH_2Cl_2 (120 mL), cooled to 0℃, and treated 2,2-dimethoxypropane (22.2 mL, 180.0 mmol) and (±)-10-camphorsulfonic acid (5.00 g, 21.6 mmol). The reaction mixture was warmed to rt and stirred for 2 h, then quenched with saturated $NaHCO_3$ and extracted with EtOAc (3 × 150 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. FCC of residue (silica gel, 80% EtOAc : petroleum ether) gave **2.13** (9.96 g, 87%): R_f = 0.8 (100% EtOAc); $[\alpha]^{22}_D$ –3.06 (*c* 0.49, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.77 (m, 1H), 5.21-5.36 (dd, 2H, *J* = 17.2, 9.9 Hz), 3.97 (t, 1H, *J* = 7.7 Hz), 3.65 (m, 3H), 2.10 (s,

br, 1H), 1.55-1.80 (m, 4H), 1.40 (s, br, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.3, 118.7, 108.7, 82.8, 80.7, 62.5, 29.5, 28.5, 27.4, 27.1; HRMS (FAB) calcd for $C_{10}H_{19}O_3$ ($M + H^+$) 187.1334, found 187.1333.

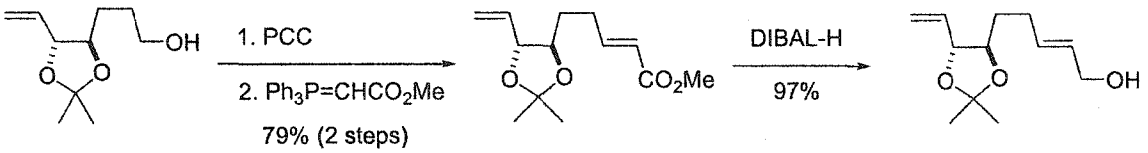
Compound ent-2.13: **Ent-2.13** was prepared following a same sequence of reactions from **2.8**, using AD-mix-α instead of AD-mix-β in the first step.

Compound ent-2.11: $[\alpha]^{22}_D$ +25.13 (*c* 1.50, $CHCl_3$).

Compound ent-2.12: $[\alpha]^{22}_D$ +6.20 (*c* 1.73, $CHCl_3$).

Compound ent-2.13: $[\alpha]^{22}_D$ +3.04 (*c* 0.69, $CHCl_3$).

Synthesis of the 1,2-O-isopropylidene-5-alkene (2.6)



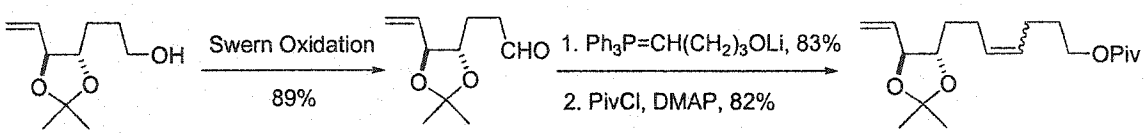
2.13 **2.70** **2.6**

In a 1000 mL round-bottom flask equipped with magnetic stirring bar, were placed 4 Å molecular sieves (25.00 g), celite (25.00 g), florisil (25.00 g), NaOAc (9.50 g), pyridinium chlorochromate (25.00 g) and dry CH_2Cl_2 (250 mL). The alcohol **2.13** (8.60 g, 46.4 mmol) in dry CH_2Cl_2 (50 mL) was added to the suspension at rt, and stirred for 1.5 h. The reaction mixture was filtered through florisil, the residue washed with ether, and the filtrate concentrated under reduced pressure. The crude product was dissolved in dry acetonitrile (300 mL), and methyl (triphenylphosphoranylidene) acetate was added to the solution. The reaction mixture was refluxed for 3h, and the solvent was removed *in vacuo*. The crude product was purified by FCC (10% EtOAc : petroleum ether) to afford **2.70** (8.74 g, 79%): R_f = 0.57 (5% EtOAc : petroleum ether); ^1H NMR ($CDCl_3$, 300 MHz) δ

6.95 (m, 1H), 5.80 (m, 2H), 5.23-5.37 (dd, 2H, J = 16.9, 10.3 Hz), 3.98 (m, 1H), 3.71 (s, 3H), 3.63-3.69 (m, 1H), 2.21-2.49 (m, 2H), 1.70 (m, 2H), 1.41 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.5, 148.8, 135.9, 122.1, 119.6, 109.5, 83.3, 80.4, 52.1, 30.9, 29.4, 28.0, 27.7; LRMS (ESI) 241.29 ($M + H^+$).

To a stirred solution of **2.70** (3.88 g, 16.3 mmol) in dry CH_2Cl_2 (150 mL) at –78 ℃ under N_2 was added dropwise a solution of DIBAL-H (32.4 mL, 32.4 mmol, 1M in hexane). The mixture was stirred for 1.5 h at –78℃ and then warmed to rt. The reaction mixture was poured into ice cold of Rochell's salt (saturated $KNaC_4H_4O_6$, 60 mL). The mixture was warmed to rt, and stirred until the salts had dissolved. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by FCC (10% EtOAc : petroleum ether) to afford **2.6** (3.32 g, 97%): R_f = 0.33 (5% EtOAc : CH_2Cl_2); $[\alpha]^{22}_D$ –1.52 (*c* 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.65-5.79 (m, 1H), 5.60 (m, 2H), 5.17-5.32 (dd, 2H, J = 17.2, 10.3 Hz), 4.00 (m, 2H), 3.95 (m, 1H), 3.65 (m, 1H), 2.40 (s, br, 1H), 2.00-2.28 (m, 2H), 1.65 (m, 2H), 1.35 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.1, 132.2, 130.4, 119.3, 109.2, 83.3, 80.7, 64.0, 32.1, 29.3, 28.0, 27.7; HRMS (FAB) calcd for $C_{12}H_{21}O_3$ ($M + H^+$) 213.1490, found 213.1491.

Synthesis of the 1,2-*O*-isopropylidene-5-alkene (2.7)



ent-2.13 **2.71** **2.7**

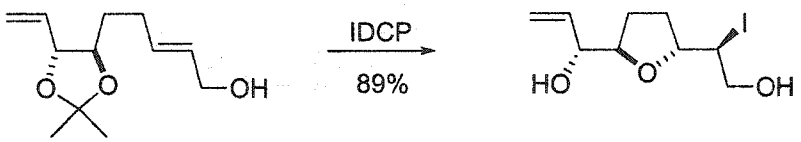
To a solution of oxalyl chloride (19.4 mL, 0.2 mol) in dry CH_2Cl_2 (100 mL) at –78°C was added DMSO (19.4 mL, 0.3 mol) dropwise. The mixture was stirred for 20 min at this temperature and then a solution of alcohol **ent-2.13** (8.50 g, 45.7 mmol) in 20 mL CH_2Cl_2 was slowly introduced. After stirring at this temperature for an additional 20 min, Et_3N (67 mL, 0.5 mol) was added, the solution was warmed up to rt, and then poured into saturated aqueous $NaHCO_3$. The mixture was extracted with ether. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by FCC (10% EtOAc : petroleum ether) to give aldehyde **2.71** (7.50 g, 89%): R_f= 0.38 (5% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.80 (s, 1H), 5.80 (m, 1H), 5.26-5.41 (dd, 2H, *J* = 17.2, 10.3 Hz), 4.00 (m, 1H), 3.70 (m, 1H), 2.55-2.74 (m, 2H), 1.91-2.10 (m, 1H), 1.75-1.91 (m, 1H), 1.40 (s, br, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.9, 135.2, 118.5, 108.8, 82.4, 79.6, 40.2, 27.2, 27.0, 24.2.

To a solution of 4-hydroxybutyl-triphenylphosphonium bromide (35.63 g, 86.0 mmol) in dry toluene (400 mL) was added a 0.6 M solution of sodium bis(trimethylsilyl) amide (287 mL, 0.2 mol) 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 **2.71** (7.20 g, 0.4 mol) in dry toluene (200 mL) was added dropwise over 30 min. After an additional 15 min, the reaction mixture was warmed to rt, them diluted with ether (150 mL). The mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo*. The residue was purified by FCC (20% EtOAc : petroleum ether) to afford alcohol (7.76 g, 83%): R_f= 0.43 (20% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.81 (m, 1H), 5.21-5.49 (m, 4H), 4.00 (m, 1H), 3.60-3.75 (m, 3H), 2.01-2.29 (m, 5H), 1.49-1.70 (m, 4H), 1.41 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.2, 130.8,

130.4, 130.0, 119.0, 83.3, 80.7, 62.8, 33.2, 32.6, 29.6, 28.0, 27.7, 24.4, 24.2. The Z/E ratio was estimated at ca. 3/1 from TLC ($AgNO_3$-silica gel) and ^{13}C NMR.

To a solution of alcohol obtained last step (0.99 g, 4.1 mmol) in dry pyridine (20 mL) was added trimethylacetyl chloride (0.77 mL, 6.2 mmol) and 4-N,N-dimethylaminopyridine (50.42 mg, 0.4 mmol) under an argon atmosphere at rt. After 1 h, the reaction mixture was diluted with ether (20 mL), filtered through celite, and concentrated *in vacuo*. The residue was purified by FCC (5% EtOAc : petroleum ether) to afford **2.7** (1.09 g, 82%): R_f= 0.43 (5% EtOAc : petroleum ether); $[\alpha]^{22}_D$ +4.78 (*c* 0.67, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.80 (m, 1H), 5.23-5.44 (m, 4H), 3.95-4.10 (m, 3H), 3.68 (m, 1H), 2.00-2.26 (m, 4H), 1.55-1.79 (m, 4H), 1.41 (s, 3H), 1.40 (s, 3H), 1.20 (s, br, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.1, 130.9, 130.3, 130.2, 129.8, 119.3, 109.2, 83.4, 80.6, 64.5, 32.5, 29.4, 28.1, 28.0, 27.9, 27.3, 24.5, 24.4; HRMS (FAB) calcd for $C_{19}H_{31}O_4$ ($M - H^+$) 323.2222, found 323.2221.

Iodoetherification of Isopropylidene alkenes 2.6

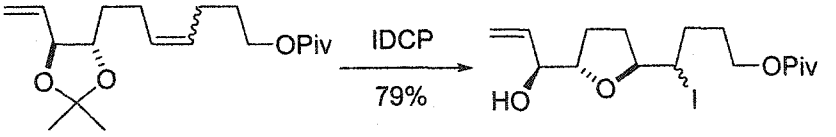


2.6 **2.15**

THF-iodide 2.15: To a solution of alcohol **2.6** (6.97 g, 32.9 mmol) in 1% water:acetonitrile (175 mL) was added IDCP (23.20 g, 49.0 mmol). The mixture was stirred at rt for 1h, then poured into saturated, aqueous $Na_2S_2O_3$ (150 mL), and extracted with ether (3 x 100 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. FCC of the residue gave **2.15** (8.70 g, 89%): R_f= 0.26 (30% EtOAc : petroleum

ether); $[\alpha]^{22}_D$ +24.7 (*c* 8.10, $CHCl_3$); ^1H NMR (C_6D_6, 500 MHz) δ 5.75 (m, 1H), 5.38 (d, *J* = 17.5 Hz, 1H), 5.12 (d, *J* = 10.5 Hz, 1H), 4.00-4.40 (m, 4H), 3.90 (s, br, 3H), 2.10 (d, 1H, *J* = 9.0 Hz), 1.40-1.60 (m, 4H); ^{13}C NMR (C_6D_6, 75 MHz) δ 137.7, 117.0, 84.0, 82.4, 75.9, 67.7, 40.8, 34.3, 28.3; HRMS (ESI) calcd for $C_9H_{15}O_3INa$ (M + Na) 320.9964, found 320.9964.

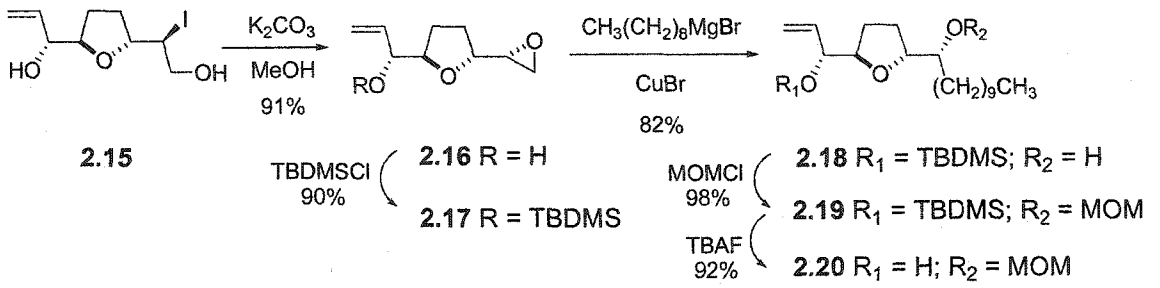
Iodoetherification of Isopropylidene alkenes 2.7



2.7 **2.21**

THF-iodide mixture 2.21: To a solution of pivaloyl ester **2.7** (6.78 g, 19.4 mmol) in 1% water:acetonitrile (200 mL) was added IDCP (13.90 g, 29.0 mmol). The mixture was stirred at rt for 30 min, then processed as described for the preparation of **2.15**. FCC of the crude residue afforded mixture **2.21** (6.27 g, 79%): R_f = 0.23 (10% EtOAc : petroleum ether); $[\alpha]^{22}_D$ –8.7 (*c* 0.60, $CHCl_3$); ^1H NMR (C_6D_6, 500 MHz) δ 5.75 (m, 1H), 5.38 (d, *J* = 17.0 Hz, 1H), 5.07 (d, *J* = 11.0 Hz, 1H), 3.90 (s, br, 2H), 3.60-3.90 (m, 3H), 3.40 (s, br, 1H), 2.40 (s, 1H),1.30-1.90 (m, 8H), 1.20 (s, br, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.0, 137.2, 117.8, 83.9, 83.2, 76.2, 64.0, 40.9, 39.5, 33.3, 31.8, 29.8, 29.0, 28.0; HRMS (FAB) calcd for $C_{16}H_{28}O_4I$ (M + H) 411.1032, found 411.1030.

Synthesis of the THF-alkene subunit 2.20



Compound 2.16: To a solution of iodohydrin **2.15** (5.40 g, 18.2 mmol) in dry methanol (230 ml) was added K_2CO_3 (7.50 g, 70.8 mmol). The reaction was stirred at rt for 1.5 h, then neutralised with saturated aqueous NH_4Cl. Most of the methanol was removed under reduced pressure and the residue extracted with CH_2Cl_2 (3 x 150 ml). The organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. FCC of the residue (50% EtOAc : $CHCl_3$) afforded epoxide **2.16** (2.8 g, 91%): R_f = 0.39 (30% EtOAc : $CHCl_3$); $[\alpha]^{22}_D$ –0.84 (*c* 4.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.71-5.84 (m, 1H), 5.16-5.36 (m, 2H), 3.78-3.99 (m, 3H), 2.90-3.00 (m, 1H), 2.64-2.78 (m, 2H), 1.62-2.12 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.5, 117.4, 83.5, 79.6, 76.0, 54.7, 44.7, 29.7, 28.5; HRMS (FAB) calcd for $C_9H_{15}O_3$ ($M + H^+$) 171.1021, found 171.1021.

Compound 2.17: To a solution of epoxide **2.16** (2.80 g, 16.5 mmol),and imidazole (5.60 g, 82.3 mmol) in anhydrous CH_2Cl_2 (200 mL) was added TBDMSCl (4.90 g, 32.5 mmol) at 0 ℃. The mixture was then warmed to rt, stirred at this temperature for 18 h, then diluted with water, and extracted with ether (3 x 100 mL). The organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC (5% EtOAc : petroleum ether) to give **2.17** (4.2 g, 90%): R_f = 0.43 (5% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 300 MHz)

δ 5.85 (m, 1H), 5.11-5.30 (dd, 2H, J = 16.9, 10.6 Hz), 4.17 (m, 1H), 4.00 (m, 1H), 3.84 (m, 1H), 2.95 (m, 1H), 2.67-2.75 (m, 2H), 1.70-2.05 (m, 4H), 0.90 (s, br, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.2, 116.2, 83.7, 79.4, 76.0, 54.8, 44.7, 29.5, 27.4, 26.6, 19.0, -3.9, -4.0; HRMS (FAB) calcd for $C_{15}H_{29}O_3Si$ ($M + H^+$) 285.1886, found 285.1885.

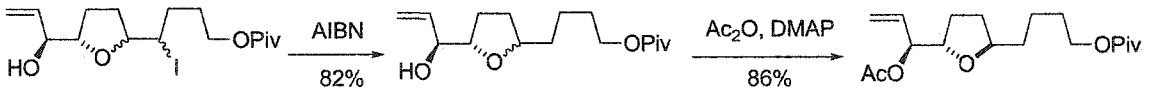
Compound 2.18: In a 250 mL round-bottom flask equipped with magnetic stirring bar, were placed CuBr (145.70 mg, 1.0 mmol) and anhydrous THF (10 mL). Pre-prepared, $C_9H_{11}MgBr$ (92 mL, ca 0.4 M in THF) was added dropwise at 0℃, and then epoxide **2.17** (486.0 mg, 1.7 mmol) was introduced. The reaction was stirred at 0℃ for 3 h, then poured into ice cold saturated aqueous NH_4Cl, and extracted with ether (3 x 100 mL). The organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC (8% EtOAc : petroleum ether) to give **2.18** (581.0 mg, 82%): R_f = 0.75 (8% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.82 (m, 1H), 5.10-5.31 (dd, 2H, J = 17.2, 10.3 Hz), 4.11 (m, 1H), 3.89 (m, 1H), 3.75 (m, 1H), 3.36 (m, 1H), 3.3-3.4 (m, 1H), 2.39 (d, 1H, J = 4.0 Hz), 1.82-1.98 (m, 2H), 1.55-1.80 (m, 2H), 1.37 (m, 2H), 1.25 (s, br, 16H), 0.89 (s, br, 9H), 0.86 (t, 3H, J = 6.6 Hz), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.3, 116.3, 83.4, 83.1, 76.7, 74.7, 34.4, 32.7, 30.5, 30.3, 30.1, 29.1, 28.5, 26.6, 26.4, 23.4, 19.1, 14.8, -3.8, -4.0; HRMS (FAB) calcd for $C_{24}H_{49}O_3Si$ ($M + H^+$) 413.3451, found 413.3451.

Compound 2.19: MOMCl (1.5 mL, 20.1 mmol) was added to a solution of alcohol **2.18** (2.78 g, 6.7 mmol) and i-Pr_2NEt (5.9 mL, 33.5 mmol) in anhydrous CH_2Cl_2 (120 mL) at 0℃, and the mixture was stirred for 17 h at rt. The reaction mixture was quenched with saturated aqueous NH_4Cl and then extracted with ether (3 x 80 ml). The

organic layer was washed with water and brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. FCC of the crude mixture (5% EtOAc : petroleum ether) provided **2.19** (2.77 g, 98%): R_f = 0.48 (5% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.85 (m, 1H), 5.10-5.29 (dd, 2H, *J* = 17.2, 10.6 Hz), 4.82 (d, 1H, *J* = 7.0 Hz), 4.65 (d, 1H, *J* = 7.0 Hz), 4.13 (m, 1H), 3.93 (m, 2H), 3.44 (m, 1H), 3.38 (s, 3H), 1.80-2.00 (m, 2H), 1.55-1.80 (m, 2H), 1.31-1.49 (m, 2H), 1.21-1.30 (s, br, 16H), 0.89 (s, br, 9H), 0.86 (t, 3H, *J* = 6.6 Hz), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.5, 116.0, 97.4, 82.9, 82.5, 80.3, 76.5, 56.3, 32.6, 32.1, 30.6, 30.3, 30.1, 29.0, 27.8, 26.6, 26.3, 23.4, 19.0, 14.8, -3.9, -4.0; HRMS (FAB) calcd for $C_{26}H_{53}O_4Si$ ($M + H^+$) 457.3713, found 457.3715.

Compound 2.20: To a solution of **2.19** (2.70 g, 5.9 mmol) in THF (120 mL) was added Bu_4NF (12 mL, 1.0 M in THF) at rt. The reaction was stirred for 2 h, then diluted with water and extracted with EtOAc (3 x 100 mL). The organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC (25% EtOAc : petroleum ether) to give **2.20** (1.88 g, 92%): R_f = 0.88 (50% EtOAc : petroleum ether); $[\alpha]^{22}_D$ +20.9 (*c* 1.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.70-5.90 (m, 1H), 5.10-5.40 (dd, 2H, *J* = 17.2, 10.6 Hz), 4.75 (d, 1H, *J* = 7.0), 4.65 (d, 1H, *J* = 6.6 Hz), 3.80-4.10 (m, 3H), 3.40-3.50 (m, 1H), 3.40 (s, 3H), 2.70 (s, 1H), 1.80-2.00 (m, 2H), 1.60-1.80 (m, 2H), 1.30-1.50 (m, 2H), 1.20-1.30 (s, br, 16H), 0.85 (t, 3H, *J* = 5.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.6, 117.3, 97.4, 82.7, 82.3, 80.5, 76.0, 56.3, 32.6, 32.0, 30.5, 30.3, 30.0, 29.2, 28.7, 26.2, 23.4, 14.8; HRMS (FAB) calcd for $C_{19}H_{35}O_3$ ($M - OCH_3$) 311.2586, found 311.2585.

Synthesis of the THF-alkene subunit 2.22



2.21c/t **2.5c/t** **2.22**

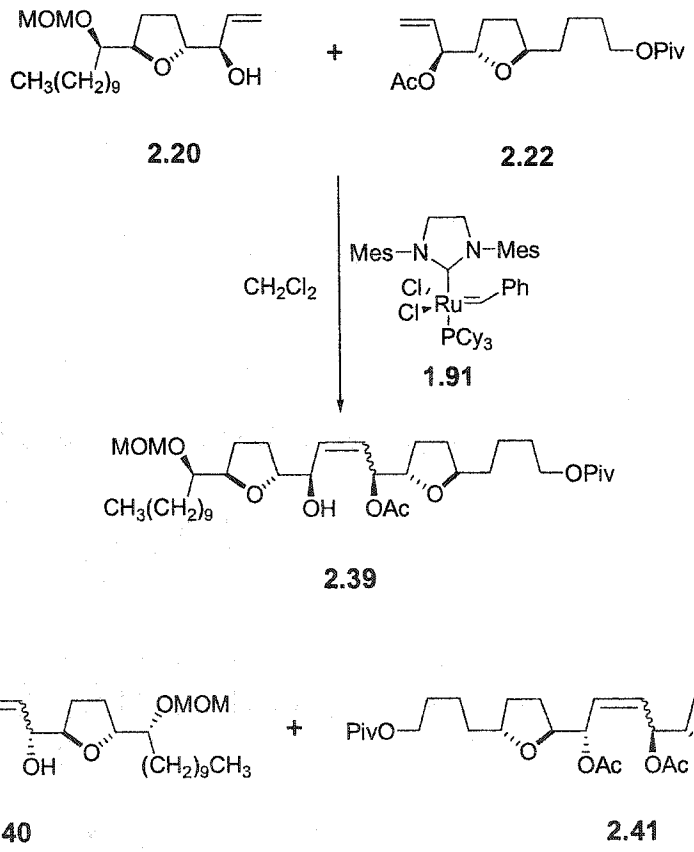
Compound 2.5: In a 500 mL round-bottom flask equipped with reflux condenser and magnetic stirring bar, were placed **2.21c/t** (6.27 g, 15.3 mmol), Bu_3SnH (12.3 mL, 46.0 mmol), AIBN (2.50 g, 15.3 mmol) and dry toluene (300 mL). The reaction mixture was refluxed for 2h. The toluene was removed *in vacuo*, and the crude product was purified by FCC (20% EtOAc : CH_2Cl_2) to afford **2.5c/t** (3.12 g, 82%). Both isomers had identical TLC mobilities (R_f = 0.57). The cis/trans ratio was determined to be 1/11 from integration of OH protons [δ 2.94 (cis) and 2.99 (trans)]. A pure sample of **2.5t** was obtained by repeated chromatography of the mixture and analysis of the fractions by ^1H NMR.

Compound 2.5t: (20% EtOAc : CH_2Cl_2); $[\alpha]^{22}_D$ –4.08 (*c* 8.50, $CHCl_3$); ^1H NMR (C_6D_6, 500 MHz) δ 5.75 (m, 1H), 5.07-5.45 (dd, 2H, *J* = 17.2, 10.6 Hz), 3.96 (t, 2H, *J* = 6.5 Hz), 3.90 (m, 1H), 3.75 (m, 1H), 3.65 (m, 1H), 2.99 (s, br, 1H), 1.25-1.69 (m, 10H), 1.18 (s, br, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.2, 137.1, 116.5, 81.6, 79.3, 75.5, 64.2, 38.8, 35.2, 32.1, 28.8, 28.0, 27.3, 22.7; HRMS (FAB) calcd for $C_{16}H_{29}O_4$ ($M + H^+$) 285.2066, found 285.2067.

Compound 2.22: To a solution of alcohol **2.5t** (0.20 g, 0.7 mmol) in ethyl acetate (10 mL) was added DMAP (8.60 mg, 0.1 mmol) and acetic anhydride (200 μl, 2.1 mmol) at rt. The reaction mixture was stirred for 1h, queched with MeOH, and the solvent was removed *in vacuo*. The crude product was purified by FCC (10% EtOAc : petroleum

ether) to afford **2.22** (0.20 g, 86%): R_f= 0.81 (30% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.70-5.85 (m, 1H), 5.1-5.3 (m, 3H), 4.00 (m, 3H), 3.90 (m, 1H), 2.10 (s, 3H), 1.90-2.05 (m, 2H), 1.50-1.70 (m, 4H), 1.30-1.50 (m, 4H), 1.20 (s, br, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.3, 170.0, 133.5, 118.4, 79.4, 79.3, 76.4, 64.3, 38.9, 35.30, 32.0, 28.9, 28.2, 27.4, 22.8, 21.3; HRMS (FAB) calcd for $C_{18}H_{31}O_5$ (M + H) 327.2171, found 327.2170.

Cross Methathesis of 2.20 and 2.22



Condition A: In a 25 mL two neck round-bottom flask equipped with condenser and magnetic stirring bar, were placed ester **2.22** (176 mg, 0.54 mmol), alcohol **2.20** (94.2 mg, 0.28 mmol), and anhydrous CH_2Cl_2 (10 mL). After degassing of the result

mixture, a solution of catalyst **1.91** (46.8 mg, 0.055 mmol) in CH_2Cl_2 (2mL) was injected over *3h at rt*. After *18 h* at this temperature, more cat. (46.8 mg, 0.055 mmol) in CH_2Cl_2 (2mL) was injected. The reaction was stirred for *2 d* at same temperature, then quenched by DMSO (195 μL). The mixture was concentrated *in vacuo*. The residue was purified by FCC (20% EtOAc : petroleum ether to 90% EtOAc : petroleum ether) to afford **2.39** (50.2 mg, 34% relative to **2.20**, 68% relative to **2.22**) with homodimer **2.40** (47.2 mg).

Condition B: In a 50 mL two neck round-bottom flask equipped with condenser and magnetic stirring bar, were placed ester **2.22** (580 mg, 1.78 mmol), alcohol **2.20** (152 mg, 0.44 mmol), Ti(O*i*-Pr)$_4$ (26 μL) and anhydrous CH_2Cl_2 (16 mL). After degassing the result mixture, a solution of catalyst **1.91** (38 mg, 0.044 mmol) in CH_2Cl_2 (6 mL) was injected over *3 h with reflux*, then cooled down to rt. After *18 h* at this temperature, more cat. (38 mg, 0.044 mmol) in CH_2Cl_2 (6 mL) was injected. The reaction was stirred for *18 h with reflux*, then quenched by DMSO (159 μL) at rt. The mixture was concentrated *in vacuo*. The residue was purified by FCC (20% EtOAc : petroleum ether to 90% EtOAc : petroleum ether) to afford **2.39** (138.7 mg, 53% relative to **2.20**, 42% relative to **2.22**) with homodimer **2.41** (41 mg).

Condition D: In a 50 mL two neck round-bottom flask equipped with condenser and magnetic stirring bar, were placed ester **2.22** (321.60 mg, 1.0 mmol), alcohol **2.20** (115.00 mg, 0.3 mmol), and anhydrous CH_2Cl_2 (20 mL). After degassing the result mixture, a solution of catalyst **1.91** (28.50 mg, 34.0 μmol) in CH_2Cl_2 (3 mL) was injected at rt. After *18 h* at this temperature, additional catalyst (28.50 mg, 34.0 μmol) in CH_2Cl_2 (3 mL) was introduced. The reaction was stirred for *18 h at reflux*, then quenched with DMSO (119 μL) at rt. The mixture was concentrated *in vacuo*. The residue was purified

by FCC (10-20% EtOAc : petroleum ether) to afford **2.39** (160.70 mg, 75% relative to **2.20**, 76% relative to **2.22**) and homodimers **2.40** (< 5 mg) and **2.41** (< 5 mg).

Condition F: In a 50 mL two neck round-bottom flask equipped with condenser and magnetic stirring bar, were placed ester **2.22** (491.40 mg, 1.5 mmol), alcohol **2.20** (134.00 mg, 0.4 mmol), and anhydrous CH_2Cl_2 (20 mL). After degassing the result mixture, a solution of catalyst **1.91** (34.00 mg, 40.0 μmol) in CH_2Cl_2 (3 mL) was injected at rt. After *18 h* at this temperature, additional catalyst (34.00 mg, 40.0 μmol) in CH_2Cl_2 (3 mL) was introduced. The reaction was stirred for *18 h at rt*, then quenched by DMSO (142 μL). The mixture was concentrated *in vacuo*. The residue was purified by FCC (10-20% EtOAc : petroleum ether) to afford **2.39** (212.00 mg, 98% relative to **2.20**, 46% relative to **2.22**) with homo-dimer **2.41** (14 mg).

Condition G: In a 50 mL two neck round-bottom flask equipped with condenser and magnetic stirring bar, were placed ester **2.22** (245.00 mg, 0.8 mmol), alcohol **2.20** (135.00 mg, 0.4 mmol), and anhydrous CH_2Cl_2 (20 mL). After degassing the result mixture, a solution of catalyst **1.91** (34.00 mg, 40.0 μmol) in CH_2Cl_2 (3 mL) was injected at rt. After *18 h* at this temperature, additional catalyst (34.00 mg, 40.0 μmol) in CH_2Cl_2 (3 mL) was introduced. The reaction was stirred for *4 h at reflux*, then quenched by DMSO (119 μL) at rt. The mixture was concentrated *in vacuo*. The residue was purified by FCC (10-20% EtOAc : petroleum ether) to afford **2.39** (147.50 mg, 58% relative to **2.20** 77% relative to **2.22**).

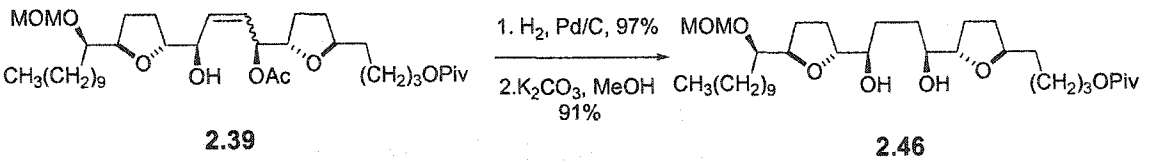
Bis-THF alkene 2.39: R_f = 0.53 (40% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.70 (m, 2H), 5.20 (m, 1H), 4.75 (d, 1H, J = 7.0 Hz), 4.65 (d, 1H, J = 6.5 Hz), 4.00 (m, 3H), 3.80-4.00 (m, 4H), 3.45 (m, 1H), 3.36 (s, 3H), 2.70 (s, br, 1H,

D_2O ex), 2.04 (s, 3H), 1.90-2.00 (m, 4H), 1.50-1.70 (m, 6H), 1.30-1.50 (m, 6H), 1.22 (s, br, 16H), 1.16 (s, br, 9H), 0.85 (t, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.9, 170.5, 133.9, 128.0, 97.4, 82.7, 82.3, 80.4, 79.9, 79.81, 76.4, 75.0, 64.9, 56.4, 39.4, 35.8, 32.6, 32.6, 32.0, 30.5, 30.3, 30.0, 29.4, 29.2, 28.8, 28.7, 28.0, 26.2, 23.4, 21.9, 14.8; HRMS (FAB) calcd for $C_{36}H_{64}O_9Na$ (M + Na) 663.4448, found 663.4451.

Bis-THF alkene 2.40: R_f = 0.08 (20% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.75 (m, 2H), 4.80 (d, 2H, J = 6.6 Hz), 4.70 (d, 2H, J = 7.0 Hz), 3.80-4.00 (m, 6H), 3.45 (m, 2H), 3.35 (s, br, 6H), 2.70 (s, br, 2H), 1.90-2.10 (m, 4H), 1.50-1.80 (m, 4H), 1.30-1.50 (m, 4H), 1.22 (s, br, 32H), 0.85 (t, 6H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 131.6, 97.5, 82.9, 82.3, 80.5, 75.2, 56.4, 32.6, 32.0, 30.6, 30.3, 30.0, 29.3, 28.8, 26.2, 23.4, 14.8; HRMS (ESI) calcd for $C_{38}H_{72}O_8Na$ (M + Na) 679.5125, found 679.5128.

Bis-THF alkene 2.41: R_f = 0.28 (15% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.70 (m, 2H), 5.20 (m, 2H), 3.85-4.15 (m, 8H), 2.10 (s, br, 6H), 1.90-2.00 (m, 4H), 1.60-1.80 (m, 8H), 1.40-1.60 (m, 8H), 1.22 (s, br, 18H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.6, 170.1, 129.6, 79.6, 79.3, 75.7, 64.5, 39.0, 35.4, 32.1, 29.0, 28.3, 27.5, 22.9, 21.5; HRMS (ESI) calcd for $C_{34}H_{56}O_{10}Na$ (M + Na) 647.3771, found 647.3785.

Synthesis of Diol 2.46

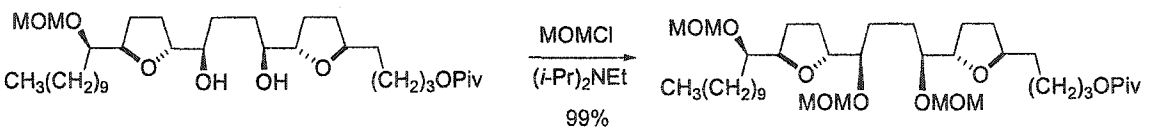


2.39 **2.46**

A mixture of alkene **2.39** (0.80 g, 1.3 mmol) and 10% Pd/C (80.00 mg) in ethyl acetate (60 mL) was stirred under an atmosphere of hydrogen (balloon) at rt, for 18 h. The suspension was then filtered through celite, the filtrate concentrated under reduced pressure, and the residue (778.80 mg) used directly in the next step.

A portion of the material from the previous step (56.00 mg) dissolved in dry methanol (5 mL) and treated with K_2CO_3 (12.00 mg, 87.0 μmol). The reaction mixture was stirred for 18 h at rt, then neutralise by 5% HCl, and extracted with EtOAc (3 x 10 ml) after evaporate most methanol. The combined organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. FCC of the residue (50% EtOAc : $CHCl_3$) afforded diol **2.46** (29.00 mg, 91% from **8**): R_f = 0.41 (50% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.75 (d, 1H, *J* = 7.0 Hz), 4.65 (d, 1H, *J* = 7.0 Hz), 4.00 (m, 3H), 3.91 (m, 1H), 3.85 (m, 1H), 3.75 (m, 3H), 3.45 (m, 1H), 3.35 (s, 3H), 2.70 (s, br, 2H), 1.90-2.00 (m, 4H), 1.50-1.70 (m, 6H), 1.30-1.50 (m, 10H), 1.22 (s, br, 16H), 1.15 (s, 9H), 0.85 (t, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.9, 97.4, 83.2, 82.7, 82.2, 80.5, 79.7, 75.1, 74.9, 64.8, 56.3, 39.4, 36.0, 33.1, 32.6, 32.0, 30.6, 30.5, 30.3, 30.0, 29.4, 29.1, 27.9, 26.2, 23.3, 14.7.

Synthesis of 2.47

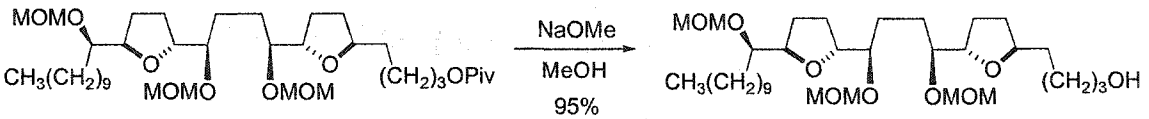


2.46 **2.47**

MOMCl (54 μL, 0.7 mmol) was added to a solution of diol **2.46** (105.00 mg, 0.2 mmol) and *i*-Pr_2NEt (305 μL, 1.8 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C. The

mixture was stirred for 24 h at rt, then quenched with saturated aqueous NH_4Cl and extracted with ether (3 x 20 mL). The organic layer was washed with water and brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. FCC of the residue gave **2.47** (120.00 mg, 100%): R_f= 0.64 (30% EtOAc : petroleum ether); $[\alpha]^{22}_D$ +20.9 (*c* 11.60, $CHCl_3$);^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.83 (m, 3H), 4.65 (m, 3H), 4.00 (t, 2H, *J* = 6.6 Hz), 3.95 (m, 3H), 3.85 (m, 1H), 3.45 (m, 3H), 3.35 (s, br, 9H), 1.90-2.00 (m, 4H), 1.50-1.80 (m, 8H), 1.30-1.50 (m, 8H), 1.24 (s, br, 16H), 1.17 (s, br, 9H), 0.85 (t, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.0, 97.4, 82.2, 81.6, 80.7, 80.4, 79.7, 64.9, 56.4, 39.5, 36.1, 33.0, 32.6, 32.1, 30.6, 30.3, 30.0, 29.5, 29.3, 29.2, 28.0, 26.3, 23.5, 23.4, 14.8; HRMS (ESI) calcd for $C_{38}H_{72}O_{10}$ (M + Na) 711.5023, found 711.5032.

Synthesis of 2.48

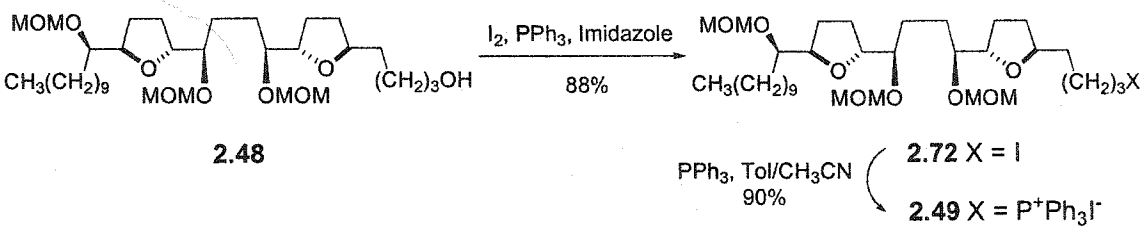


2.47 **2.48**

Sodium methoxide (162.00 mg, 3 mmol) was added to a solution of pivalate **2.47** (417.00 mg, 0.6 mmol) in anhydrous MeOH (30 mL) at rt. The mixture was heated at reflux for 12 h, then cooled to rt and neutralized with 5% aqueous HCl. Most of the methanol was evaporated under reduced pressure and the residue extracted with EtOAc (3 x 30 mL). The organic layer was washed with water and brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. FCC of the residue afforded recovered **2.47** (11.00 mg) and alcohol **2.48** (344.00 mg, 95% based on recovered **2.47**): R_f = 0.17 (60% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.75 (m, 3H), 4.65 (m, 3H), 3.80-4.00

(m, 4H), 3.55 (t, 2H, J = 6.41 Hz), 3.40 (m, 3H), 3.30 (s, br, 9H), 1.80-2.00 (m, 5H), 1.30-1.70 (m, 16H), 1.22 (s, br, 16H), 0.85 (t, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 96.9, 81.7, 81.0, 80.2, 79.8, 79.3, 62.8, 55.9, 35.7, 33.0, 32.5, 32.1, 31.5, 30.0, 29.8, 29.5, 28.7, 28.7, 27.4, 25.8, 22.9, 22.8, 14.3; HRMS (FAB) calcd for $C_{33}H_{65}O_9$ (M + H) 605.4629, found 605.4629.

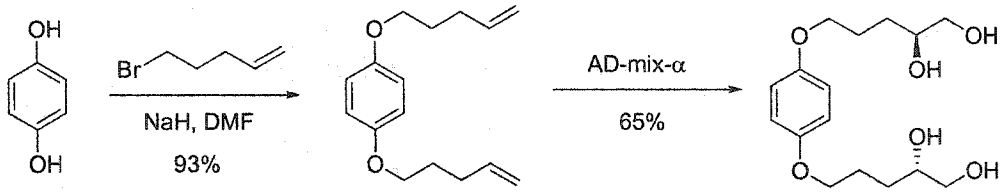
Synthesis of phosphonium salt 2.49



A mixture of triphenylphosphine (139 mg, 0.13 mmol), imidazole (72 mg, 0.26 mmol), iodine (135 mg, 0.13 mmol) and benzene (100 mL) was stirred at rt for 30 min, at which time alcohol **2.48** (160 mg, 0.26 mmol) was introduced. The reaction mixture was stirred at reflux for 2 h, then diluted with ethyl ether (100 ml), and filtered through a column of florisil. The filtrate was concentrated under reduced pressure, and the residue purified by FCC to afford the iodide derivative **2.72** (164 mg, 88%): R_f = 0.77 (50% EtOAc : petroleum ether); $[\alpha]^{22}_D$ +18.5 (c 2.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.80-4.82 (m, 3H), 4.63-4.67 (m, 3H), 3.95 (m, 3H), 3.85 (m, 1H), 3.38 (s, 3H), 3.37 (s, 6H), 3.1 (t, 2H, J = 7 Hz), 1.6-2.0 (m, 12H), 1.3-1.5 (m, 8H), 1.20 (s, br, 16H), 0.85 (t, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 96.9, 81.7, 81.1, 80.1, 79.8, 79.1, 56.0, 34.9, 33.8, 32.5, 32.15, 31.5, 30.1, 29.9, 29.6, 28.8, 28.7, 27.6, 27.4, 25.8, 22.9, 14.4, 7.1; HRMS (ESI) calcd for $C_{33}H_{63}O_8INa$ (M+Na) 737.3465, found 737.3478.

Diisopropylethylamine (40 μL, 0.35 mmol) was added to a solution of **2.72** (163 mg, 0.23 mmol) and triphenylphosphine (240 mg, 0.92 mmol) in anhydrous toluene (4 mL) and acetonitrile (2 mL) The reaction mixture was heated at reflux under an atmosphere of argon for 24h. Most of the solvent was then removed under reduced pressure. The resulting syrup was triturated with cold hexane. Drying of the residue was under high vacuum for 12h afforded **2.49** as a white solid (220 mg, 90%): R_f= 0.42 (80% EtOAc : MeOH); $[\alpha]^{22}_D$ +12 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.6-7.9 (m, 15H), 4.5-4.9 (m, 6H), 3.80-4.00 (m, 3H), 3.60-3.80 (m, 1H), 3.40-3.50 (m, 3H), 3.36 (s, 3H), 3.35 (s, 3H), 3.34 (s, 3H), 1.30-2.00 (m, 20H), 1.20 (s, br, 18H), 0.85 (t, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.7, 135.7, 134.4, 134.3, 131.3, 131.1, 97.4, 82.3, 81.7, 80.9, 80.7, 80.4, 79.5, 56.5, 35.7, 32.8, 32.6, 32.1, 30.6, 30.3, 30.1, 29.2, 29.2, 28.0, 27.7, 26.3, 23.4, 14.8; HRMS (ESI) calcd for $C_{51}H_{78}O_8P$ (M-I$^-$) 849.5434, found 849.5440.

Synthesis of tetraol 2.63



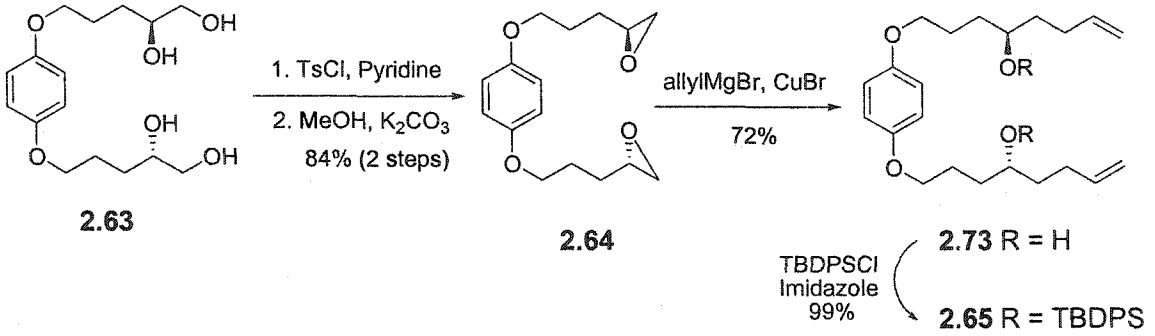
2.61 **2.62** **2.63**

To a 100 mL DMF suspension of sodium hydride (3.8 g, 60% in mineral oil, 94.6 mmol) were added hydroquinone **2.61** (4.8 g, 43 mmol) at rt. 5-bromo-1-pentene (25g, 129 mmol) was introduced dropwise after 2h. The reaction mixture was warmed to 100 ℃ and stirred for an additional 10h at this temperature. The mixture was then cooled to rt,

poured into water and extracted with diethyl ether (3 x 100 mL). The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. FCC of the residue afforded diene **2.62** (9.80 g, 93%): R_f= 0.30 (100% petroleum ether); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.80 (s, 4H), 5.80-5.90 (m, 2H), 5.00-5.10 (m, 4H), 3.90 (t, 4H, *J* = 6.5 Hz), 2.25 (q, 4H, *J* = 7 Hz), 1.85 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.3, 138.0, 115.6, 115.2, 68.1, 30.4, 28.9; HRMS (FAB) calcd for $C_{16}H_{22}O_2$ 246.1619, found 246.1621.

A 1000 mL round-bottomed flask, equipped with a magnetic stirrer, was charged with *t*-BuOH (400 mL), water (400 mL), and AD-mix-α (150.00 g). Stirring at room temperature produced two clear phases. The mixture was cooled to 0°C and diene **2.62** (20.00 g, 81.3 mmol) added. The heterogeneous slurry was stirred vigorously at 0°C for 10 h (reaction progress was monitored by TLC). Na_2SO_3 (160 g) was then added, the mixture warmed to rt, stirred for an additional 1h at this temperature and diluted with ethyl acetate (300 mL). The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (3 x 300 mL) and an ethyl acetate/ethanol mixture (4:1) (3 x 100 mL). The combined organic extract was dried (Na_2SO_4), filtered, and concentrated to give a white solid. The crude product was recrystallized three times from ethyl acetate to yield tetraol **2.63** (16.50 g, 65%): R_f= 0.62 (10% MeOH : EtOAc); mp = 118.0-118.5 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.00 (s, 4H), 3.68 (t, 4H, *J* = 5.1 Hz), 3.09 (t, 4H, *J* = 6.2 Hz), 2.65 (m, 2H), 2.60 (s, 2H), 1.70 (s, br, 2H), 0.70-1.10 (m, 6H), 0.45-0.65 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.5, 115.2, 70.8, 68.1, 65.9, 29.9, 25.2; HRMS (FAB) calcd for $C_{16}H_{27}O_6$ ($M + H^+$) 315.1808, found 315.1808.

Synthesis of bis-silyl ether 2.65



2.63 **2.64**

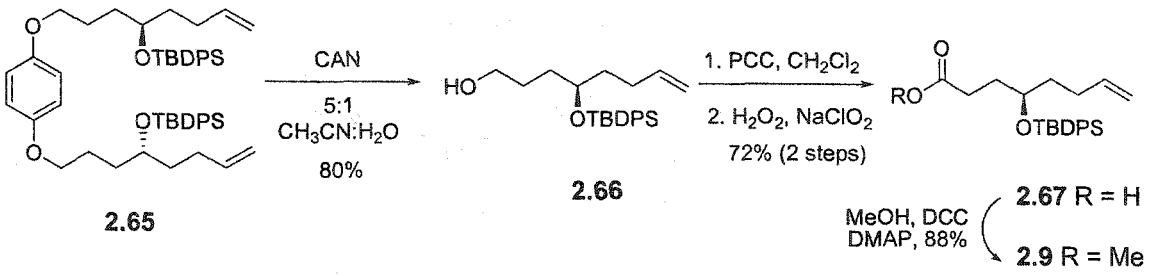
Bis-epoxide 2.64: To a solution of compound **2.63** (7.11 g, 23.0 mmol) in pyridine (100 mL) was added *p*-toluenesulfonyl chloride (9.60 g, 50.4 mmol). The solution was stirred for 4 h at rt, then quenched by adding MeOH (3 mL). The mixture was washed with saturated aqueous Na_2CO_3, and extracted with CH_2Cl_2 (3 x 100 mL). The organic layer was dried (Na_2SO_4), filtered, and the filtrate evaporated *in vacuo*. The residue was dissolved in MeOH (120 mL), and K_2CO_3 (39.00 g, 0.4 mol) was added to the vigorously stirred solution. After 3 h at rt, the mixture was poured into water (200 mL) and extracted with CH_2Cl_2 (3 x 150 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by FCC to afford **2.64** (5.24 g, 84% 2 steps): R_f = 0.77 (50% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.80 (s, 4H), 3.95 (m, 4H), 2.95 (m, 2H), 2.75 (t, 2H, J = 4.03 Hz), 2.50 (m, 2H), 1.50-2.00 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.4, 115.0, 68.4, 52.3, 47.3, 29.5, 26.3; HRMS (FAB) calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1519.

Diol 2.73: Allylmagnesium bromide (1.0 M in ether, 182.5 mL) was added dropwise to a suspension of CuBr (1.60 g, 11.1 mmol) in anhydrous THF (100 mL) at 0 °C. A solution of **2.64** (5.00 g, 18.0 mmol) in anhydrous THF (60 mL) was then introduced at 0 °C, and the reaction mixture was stirred for 2 h at this temperature. At this

time the mixture was poured into saturated aqueous NH_4Cl and the mixture extracted with diethyl ether. The organic phase was dried (Na_2SO_4), filtered, and the filtrate evaporated *in vacuo*. The residue was purified by FCC (silica gel, 40% EtOAc : petroleum ether) to afford **2.73** (4.60 g, 72%): R_f= 0.50 (40% EtOAc : petroleum ether); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.80 (s, 4H), 5.80 (m, 2H), 4.90-5.10 (m, 4H), 3.90 (t, 4H, J = 6.5 Hz), 3.65 (m, 2H), 2.00-2.30 (m, 6H), 1.50-2.00 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.2, 138.6, 115.7, 115.0, 71.3, 68.9, 36.9, 34.5, 30.4, 26.0; HRMS (FAB) calcd for $C_{22}H_{35}O_4$ ($M + H^+$) 363.2535, found 363.2537.

Bis-silyl ether 2.65: A mixture of diol **2.73** (4.60 g, 12.9 mmol), *tert*-butyldiphenylsilychloride (14.00 g, 51.4 mmol), imidazole (4.40 g, 64.7 mmol), 4-(N,N-dimethylamino)pyridine (2.00 g, 16.7 mmol) in anhydrous THF (100 mL) was stirred under argon at 40 °C for 2d. The mixture was quenched with brine and extracted with ether (3 x 150 mL). The combined organic extract was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by FCC to afford **2.65** (10.70 g, 99%): R_f= 0.26 (100% petroleum ether); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.70-7.80 (m, 8H), 7.30-7.50 (m, 12H), 6.80 (s, 4H), 5.60-5.80 (m, 2H), 4.90-5.00 (m, 4H), 3.90 (t, 4H, J = 5.5 Hz), 3.70-3.80 (m, 2H), 2.00-2.10 (m, 4H), 1.60-1.90 (m, 12H), 1.05 (s, br, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.2, 138.7, 136.1, 135.7, 134.6, 129.7, 127.7, 127.4, 115.6, 114.5, 72.6, 68.8, 35.8, 32.8, 29.6, 27.4, 25.1, 19.7.

Synthesis of alcohol 2.66 and methyl ester 2.9



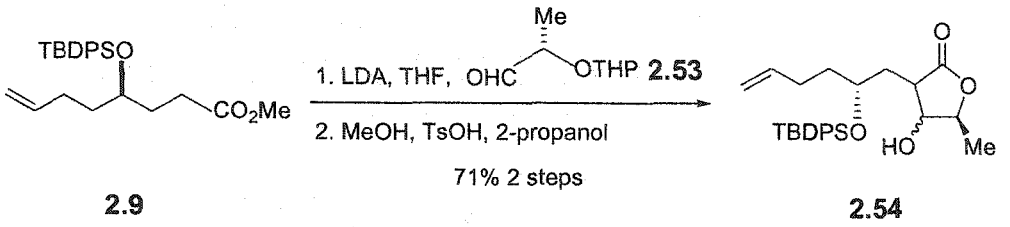
Alcohol 2.66: To an ice cooled solution of **2.65** (10.70 g, 12.8 mmol) in 240 mL of acetonitrile-water (5:1) was added CAN in one portion. After 15 min the mixture was partitioned between ethyl acetate and brine. The organic layer was washed with a saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. FCC of the residue (25% EtOAc : petroleum ether) afforded alcohol **2.66** (7.80 g, 80%): R_f= 0.56 (25% EtOAc : petroleum ether); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.60-7.70 (d, 4H, J = 7.0 Hz), 7.30-7.50 (m, 6H), 5.50-5.70 (m, 1H), 4.80-4.90 (m, 2H), 3.80 (t, 1H, J = 5.1 Hz), 3.40-3.50 (t, 2H, J = 5.5 Hz), 1.90-2.10 (m, 2H), 1.50-1.70 (m, 6H), 1.05 (s, br, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.7, 136.1, 134.5, 129.7, 127.6, 114.5, 72.7, 63.2, 35.5, 32.6, 29.6, 28.2, 27.4, 19.7; HRMS (FAB) calcd for $C_{24}H_{35}O_2Si$ (M + H^+) 383.2406, found 383.2407.

Methyl ester 2.9: To a suspension of freshly activated powdered 4 Å molecular sieves (10.70 g), celite (10.70 g), florisil (10.70 g), sodium acetate (4.10 g, 50.0 mmol) and pyridinium chlorochromate (10.70 g, 50.0 mmol) in CH_2Cl_2 (150 mL) was added alcohol **2.66** (7.77 g, 20.0 mmol). The mixture was stirred for 2h, and then filtered through a short column of silica gel. The filtrate was evaporated *in vacuo*. The residue was dissolved in a mixture of $NaH_2PO_4 \cdot H_2O$ (27.00 g, 0.2 mol) and CH_3CN-H_2O (150 mL-30 mL) and the suspension cooled to 0-5 °C. 30% aqueous H_2O_2 (2.3 mL, 24.0 mmol) and 80% $NaClO_2$ (2.70 g, 24.0 mmol) solution in water (130 mL) were then successively

added, the mixture warmed to rt and stirred at this temperature for 1h. The reaction was quenched by addition of Na_2SO_3 (5.50 g), and extracted with EtOAc (3 x 100 mL). The organic extract was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. FCC of the residue afforded the acid derivative **2.67** (5.80 g, 72%): R_f = 0.60 (20% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60-7.70 (d, 4H, *J* = 7.0 Hz), 7.30-7.50 (m, 6H), 5.50-5.70 (m, 1H), 4.80-4.90 (m, 2H), 3.80 (t, 1H, *J* = 5.5 Hz), 2.40 (t, 2H, *J* = 7.0 Hz), 1.90-2.00 (m, 2H), 1.70-1.90 (m, 2H), 1.50-1.60 (dd, 2H, *J* = 13.5 Hz), 1.05 (s, br, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.1, 138.3, 136.0, 134.4, 134.1, 129.8, 129.7, 127.7, 127.7, 114.6, 71.9, 35.7, 31.0, 29.8, 29.5, 27.4, 19.7.

To a solution of the acid **2.67** (5.70 g, 14.4 mmol) in anhydrous methanol (100 mL) were added 4-N,N-dimethylaminopyridine (176.00 mg, 1.4 mmol) and dicyclohexylcarbodiimide (4.45 g, 21.6 mmol). The solution was stirred for 1 h at rt, then diluted with ether and the resulting suspension filtered through a pad of celite. The filtrate was dried (Na_2SO_4), filtered, and concentrated. FCC of the residue afforded methyl ester **2.9** (5.20 g, 88%): R_f = 0.90 (15% EtOAc : petroleum ether); $[\alpha]^{22}_D$ –4.38 (*c* 1.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70-7.80 (d, 4H, *J* = 6.6 Hz), 7.30-7.50 (m, 6H), 5.50-5.70 (m, 1H), 4.80-5.00 (m, 2H), 3.80 (t, 1H, *J* = 5.5 Hz), 3.65 (s, 3H), 2.40 (t, 2H, *J* = 7.7 Hz), 1.90-2.00 (m, 2H), 1.70-1.90 (m, 2H), 1.50-1.60 (dd, 2H, *J* = 13.5 Hz), 1.05 (s, br, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.5, 138.8, 136.6, 135.1, 134.8, 130.3, 128.2, 115.1, 72.7, 52.1, 36.3, 31.9, 30.4, 30.0, 27.9, 20.2; LRMS (FAB) 411.2 ($M + H^+$).

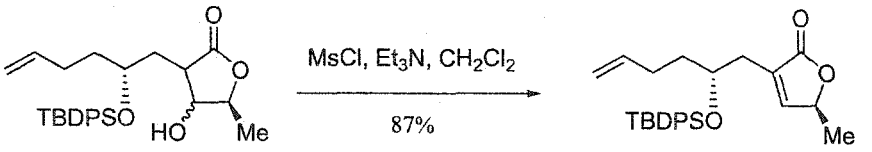
Synthesis of 2.54



2.9 **2.54**

To a solution of diisopropylamine (4.88 mL, 34.1 mmol) in 60 mL of THF at 0℃ was added BuLi (2.5 M in hexane, 9.76 mL). The mixture was stirred at 0℃ for 10 min and cooled to -78℃. To it was added a solution of ester **2.9** (2 g, 4.88 mmol) in 60 mL of THF. The reaction mixture was stirred at -78℃ for 60 min, and a solution of aldehyde **2.53** (2.3 g, 14.6 mmol) in 60 mL THF was added. After 30 min, the reaction was quenched with saturated NH_4Cl and extracted with ether. Then extracts were dried over Na_2SO_4 and concentrated under reduced pressure. To the residue was added 22 mL of MeOH-2-propanol (10:1) followed by TsOH (67 mg, 0.35mmol) in methanol. The solution was stirred at rt for 18 h. The reaction mixture was neutralized with methanol solution of $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. FCC of the residue (25% EtOAc : petroleum ether) to afford compound **2.54** (1.58 g, 71% from **2.9**): R_f = 0.39(20% EtOAc : petroleum ether); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.65 (m, 4H), 7.30-7.50 (m, 6H), 5.35 (m, 1H), 4.75-4.81 (m, 2H), 4.40 (s, 1H), 4.2-4.26 (m, 1H), 4.01-4.09 (m, 1H), 3.71-3.77 (m, 1H), 1.6-1.8 (m, 6H), 1.45-1.47 (d, 3H, J = 6.2 Hz), 1.05 (s, br, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.6, 136.9, 135.9, 132.9, 132.6, 130.3, 130.3, 127.9, 127.9, 115.2, 79.9, 79.0, 72.3, 45.0, 33.8, 33.4, 29.7, 27.3, 19.3, 18.3.

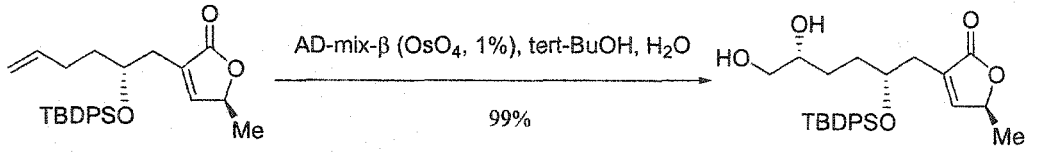
Synthesis of 2.74



2.54 **2.74**

To a mixture of alcohol **2.54** (1.4 g, 3.15 mmol) and Et_3N (1.88 mL, 13.5 mmol) in 130 mL of CH_2Cl_2 at 0℃ was added MsCl (0.49 mL, 6.3 mmol). The reaction mixture was stirred at room temperature for 6 h, quenched with saturated $NaHCO_3$, and extracted with ether, dried (Na_2SO_4), filtered and concentrated. This crude product was purified by FCC (15% EtOAc : petroleum ether) to give alkene **2.74** (1.2 g, 87%): R_f = 0.66 (15% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (m, 4H), 7.30-7.50 (m, 6H), 6.90 (s, 1H), 5.57 (m, 1H), 4.83-4.89 (m, 3H), 4.04 (m, 1H), 2.45 (m, 2H), 2.02 (m, 2H), 1.52 (m, 2H), 1.32 (d, 3H, J = 7.0 Hz), 1.05 (s, br, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.9, 151.3, 138.3, 136.1, 136.0, 134.2, 130.7, 129.9, 129.8, 127.9, 127.8, 114.8, 77.5, 71.6, 35.9, 32.1, 29.5, 27.4, 19.7, 19.3.

Synthesis of 2.75

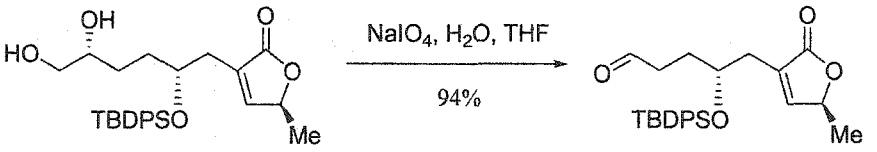


2.74 **2.75**

A 50mL round-bottomed flask, equipped with a magnetic stirrer, was charged with tert-butyl alcohol (7 mL), water (7 mL), and AD-mix-β (1.9 g). Stirring at rt produced two clear phases; the lower aqueous phase was bright yellow. The solution was

cooled to 0℃, whereupon some of the dissolved salts precipitated. Alkene **2.74** (600 mg, 1.38 mmol) was added, and the heterogeneous slurry was stirred vigorously at 0℃ for 12 h (progress was monitored by TLC). Solid sodium sulfide (2.0 g) was then added and the mixture was allowed to warm to rt and stirred for an additional 1 h. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried (Na_2SO_4), filtered and concentrated to give the light yellow oil. This crude product was purified by FCC (silica gel, 80% EtOAc : petroleum ether) to afford the **2.75** (638.3 mg, 99%): R_f= 0.49 (80% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (m, 4H), 7.30-7.50 (m, 6H), 6.92 (s, 1H), 4.92 (m, 1H), 4.07 (m, 1H), 3.45 (m, 2H), 3.30 (m, 1H), 2.46 (m, 2H), 1.95-2.05 (m, 2H), 1.35-1.70 (m, 4H), 1.32 (d, 3H, J = 6.5 Hz), 1.05 (s, br, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.2, 152.0, 135.9, 134.1, 134.0, 130.4, 129.9, 128.4, 127.8, 77.8, 72.2, 72.1, 71.9, 71.7, 66.7, 32.3, 32.1, 31.8, 31.7, 28.7, 28.3, 27.3, 19.6, 19.1.

Synthesis of Butenolide aldehyde 2.3

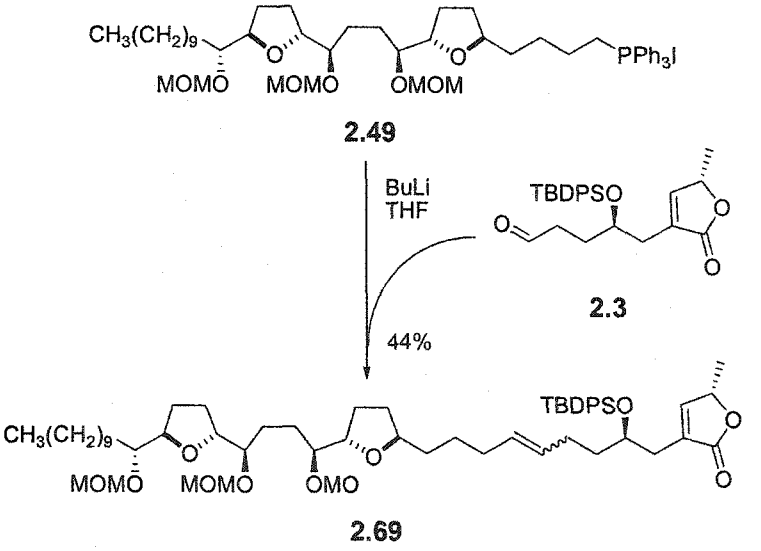


2.75 **2.3**

To a solution of diol **2.75** (118 mg, 0.25 mmol) in THF (6 mL) was added sodium periodate (65 mg, 0.3 mmol) in water (11 mL) at room temperature. The resulting mixture was stirred for 2 h, and then evaporated to remove THF. The reaction mixture

was extracted with ether. The combined organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified by FCC (70% EtOAc : petroleum ether) to afford butenolide aldehyde **2.3** (102.8, 94%): R_f = 0.80 (70% EtOAc : petroleum ether); $[\alpha]^{22}_D$ 6.10 (*c* 1.82, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.58 (s, 1H), 7.65 (m, 4H), 7.30-7.50 (m, 6H), 6.89 (s, 1H), 4.89 (m, 1H), 4.07 (m, 1H), 2.40-2.60 (m, 4H), 1.60-1.90 (m, 2H), 1.32 (d, 3H, *J* = 7.0 Hz), 1.05 (s, br, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.5, 173.7, 151.7, 135.9, 133.8, 133.7, 130.2, 130.1, 130.0, 127.9, 127.8, 77.5, 71.0, 39.5, 32.2, 28.4, 27.3, 19.6, 19.2. HRMS (ESI) calcd for $C_{26}H_{32}O_4Si$ ($M + H^+$) 459.1968, found 459.1965.

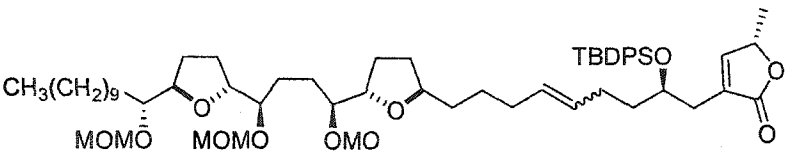
Synthesis of bis-THF-butenolide 2.69



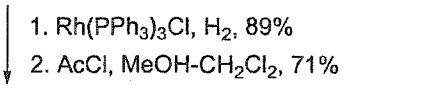
BuLi (2.5 M solution in hexane, 12.3 μL, 29.0 μmol) was added dropwise to a solution of **2.49** (28 mg, 28.0 μmol) in dry THF (1 mL) at 0 °C under an atmosphere of argon. The mixture was stirred for 30 min, and a solution of **2.3** (25 mg, 57.0 μmol) in dry THF (1 mL) was added dropwise at –78 °C. The reaction was warmed to rt, then quenched with saturated aqueous NH_4Cl and extracted with ether. The combined organic

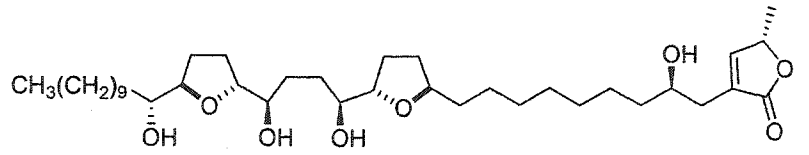
phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. FCC of the crude product provided **2.69** (12.6 mg, 44%): R_f= 0.30 (20% EtOAc : petroleum ether); $[\alpha]^{22}_D$ +7.4 (*c* 0.60, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.65-7.67 (m, 4H), 7.35-7.43 (m, 6H), 6.91 (s, 1H), 5.08-5.12 (m, 1H), 5.22-5.25 (m, 1H), 4.82-4.89 (m, 4H), 4.65-4.68 (m, 3H), 4.03 (t, 1H, *J* = 5.5 Hz), 3.96-3.97 (m, 3H), 3.85 (m, 1H), 3.44 (m, 3H), 3.39 (s, 9H), 2.45 (t, 2H, *J* = 5.5 Hz), 1.91-1.99 (m, 8H), 1.38-1.74 (m, 16H), 1.31 (d, 3H, *J* = 7 Hz), 1.2 (s, br, 16H), 1.0 (s, 9H), 0.85 (t, 3H, *J* = 5.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.9, 151.3, 136.0, 134.2, 130.8, 130.2, 129.9, 129.2, 127.8, 97.0, 81.8, 81.2, 80.3, 80.0, 79.4, 71.8, 56.0, 36.7, 35.8, 32.5, 32.2, 32.1, 31.6, 30.1, 30.0, 29.9, 29.6, 28.9, 28.8, 28.8, 27.6, 27.5, 27.4, 26.7, 25.9, 23.2, 23.0, 19.7, 19.3, 14.4; HRMS (ESI) calcd for $C_{59}H_{94}O_{11}Si$ ($M+Na^+$) 1029.6463, found 1029.6437.

Synthesis of bullatanocin 2.1



2.69





2.1

Chlorotris(triphenylphosphine)-rhodium(I) (1.7 mg, 1.8 μmol) was added to a degassed solution of **2.69** (12 mg, 12 μmol) in benzene-EtOH (1:1, 0.5 mL), and the mixture was stirred under an atmosphere of hydrogen for 12 h. The solvent was removed

under reduced pressure, and the residue was purified by FCC to give the 7,8-dihydro derivative of **2.69** (10.8 mg, 89%): R_f = 0.56 (30% EtOAc:70% petroleum ether); $[\alpha]^{22}_D$ +9.5 (c 0.42, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.63-7.70 (m, 4H), 7.36-7.42 (m, 6H), 6.91 (s, 1H), 4.84-4.89 (m, 4H), 4.68 (m, 3H), 3.98 (m, 4H), 3.85 (m, 1H), 3.45 (m, 3H), 3.39 (s, 9H), 2.43 (s, 2H), 1.90-2.00 (m, 8H), 1.00-1.70 (m, 23H), 1.6 (s, br, 16H), 1.0 (s, 9H), 0.88 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.2, 136.0, 134.4, 130.9, 129.8, 128.5, 127.7, 97.0, 81.8, 81.1, 80.3, 80.3, 80.0, 79.6, 72.1, 56.0, 36.8, 36.2, 32.6, 32.2, 31.7, 30.7, 30.2, 29.9, 29.7, 29.6, 28.9, 28.8, 28.8, 27.6, 27.5, 27.4, 26.6, 25.9, 25.2, 23.0, 22.7, 19.7, 19.3, 14.4; HRMS (ESI) calcd for $C_{59}H_{96}O_{11}Si$ ($M+Na^+$) 1031.6620, found 1031.6587.

5% AcCl in MeOH (0.15 mL) was added at rt to a solution of the material obtained in the previous step (3.8 mg, 3.8 μmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred at this temperature for 2h, diluted with CH_2Cl_2, and washed with a saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. FCC of the residue afforded **2.1** (1.7 mg, 71%) and a mixture of less polar fractions (1.8 mg) that appeared to be partially deprotected products. For **2.1**: R_f = 0.36 (EtOAc); mp 97-99 °C (EtOAc); lit mp 95-97 °C; $[\alpha]^{22}_D$ +18.7 (c 0.23, MeOH), +16.5 (c 0.23, $CHCl_3$); lit $[\alpha]^{22}_D$ +12.0 (c 0.20, MeOH), +14.4 (c 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.18 (s, 1H), 5.06 (dd, 1H, *J* = 6.5 Hz), 3.78-3.88 (m, 5H), 3.39-3.49 (m, 3H), 2.73 (s, br, 1H), 2.51-2.55 (m, 2H), 2.37-2.42 (m, 2H), 2.3 (s, br, 1H), 1.95-2.02 (m, 4H), 1.25-1.80 (m, 40H), 1.42 (d, 3H, *J* = 6.5 Hz), 0.88 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ174.6, 151.9, 131.2, 82.7, 82.0, 79.3, 78.0, 74.4, 74.3, 74.1, 70.0, 37.4, 35.6, 33.4, 32.4, 31.9, 29.9, 29.7, 29.6, 29.5, 29.4, 29.3, 28.7, 28.4, 26.1, 25.6,

25.5, 22.7, 19.1, 14.1; HRMS (ESI) calcd for $C_{37}H_{66}O_8$ ($M+Na^+$) 661.4655, found 661.4644.

CHAPTER THREE

Total Synthesis of Mucocin

3.1 Introduction

Mucocin, the first non-classical annonaceous acetogenin to be reported,[74] was isolated from the leaves of *Rollinia mucosa* (Jacq.) Baill. (Annonaceae) by McLaughlin group. *Rollinia mucosa*, also known as Biriba, is soft, yellow-skinned fruit similar in appearance to many of the *Annona's* but with more prominent spikes. The flesh is white to translucent, juicy, with an excellent sweet flavor. Biribas are rarely found outside of their native regions as the fruit blackens and spoils rather quicky (**Figure 3.1**). Mucocin has a mono-THF bearing one flanking hydroxyl, and a 2,6-dialkyl 5-hydroxy pyran ring. The two cyclic ether rings are bridged by a 1,4-dihydroxybutyl linker.

The hypothetical biogenetic pathway of mucocin is quite similar to those of several other non-adjacent bis-THF ring acetogenins, such as bullatanocin.[4] Mucocin was found to be quite active in the BST assay[175] (LC_{50} = 1.3 μg/mL) and showed remarkable inhibitory activities against A-549 (lung cancer, $ED_{50} = 1.0 \times 10^{-6}$ μg/mL) and PACA-2 (pancreatic cancer, $ED_{50} = 4.7 \times 10^{-7}$ μg/mL) solid tumor lines with a potency of more than 10,000 times that of adriamycin. Mucocin is also active in inhibiting oxygen uptaken by rat liver mitochondria. This observation suggested that the THP ring did not affect the basic mechanism of action that was established for other THF acetogenins.[74]

As in the case for several other THF acetogenins, the powerful antitumor activity and the unique structure of mucocin have made it an attractive target for synthetic chemists.

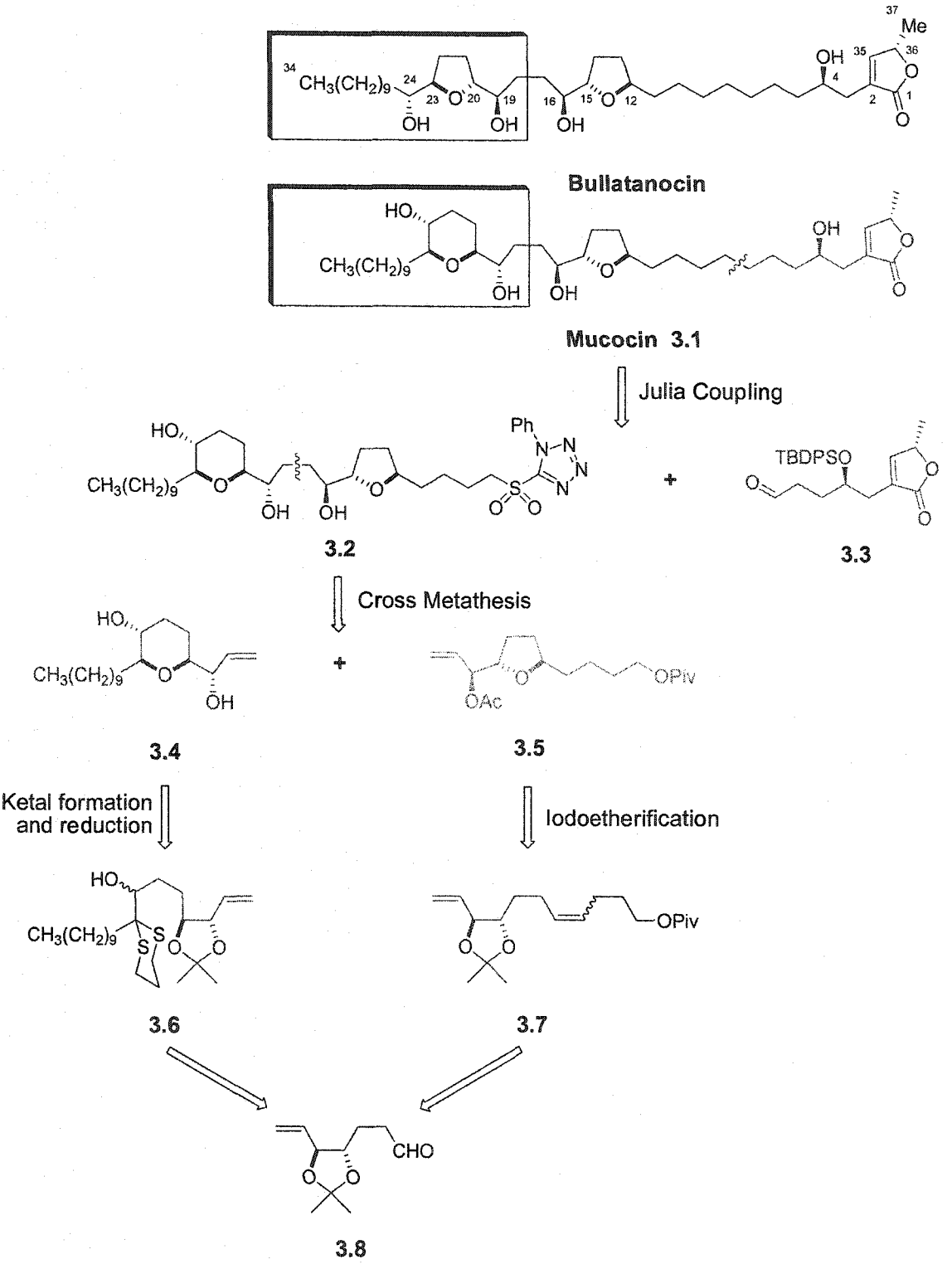
Figure 3.1. *Rollinia mucosa (Biriba)*

3.2 Synthetic Design

As discussed earlier (see section 1.3), three total syntheses and one formal synthesis of mucocin have been reported to the date.[69-72] A feature of our triply convergent synthesis is that each component can be assembled separably. A library of non-adjacently linked acetogenin analogues can be built up by combination of different components. This concept may be illustrated by extension of the method to mucocin.

The three components required for mucocin are butenolide **3.3**, mono-THP **3.4** and mono-THF **3.5** (**Scheme 3.1**). Bullatanocin and mucocin are identical except for the left-hand segment in which the THF subunit in bullatanocin is replaced by the THP ring in mucocin. Therefore, THF **3.5** is the identical precursor used for bullatanocin, and

accordingly, may be prepared from isopropylidene aldehyde **3.8** as described in the bullatanocin synthesis. The identical absolute stereochemistry at C_{19}-C_{20} of the THP subunit **3.4** and C_{15}-C_{16} of the THF subunit **3.5** suggests that THF **3.5** may also be prepared from **3.8**. Thus **3.8** may be converted to a dithiane **3.6** which could be elaborated to the THP subunit **3.4**. Olefin cross metathesis of THF alkene **3.5** and THP alkene **3.4**, and further processing of the product would lead to the key bis-cyclic ether intermediate **3.2**. A Julia type coupling of THP-THF sulfone **3.2** and butenolide aldehyde **3.3** could be used to provide the complete framework for mucocin.

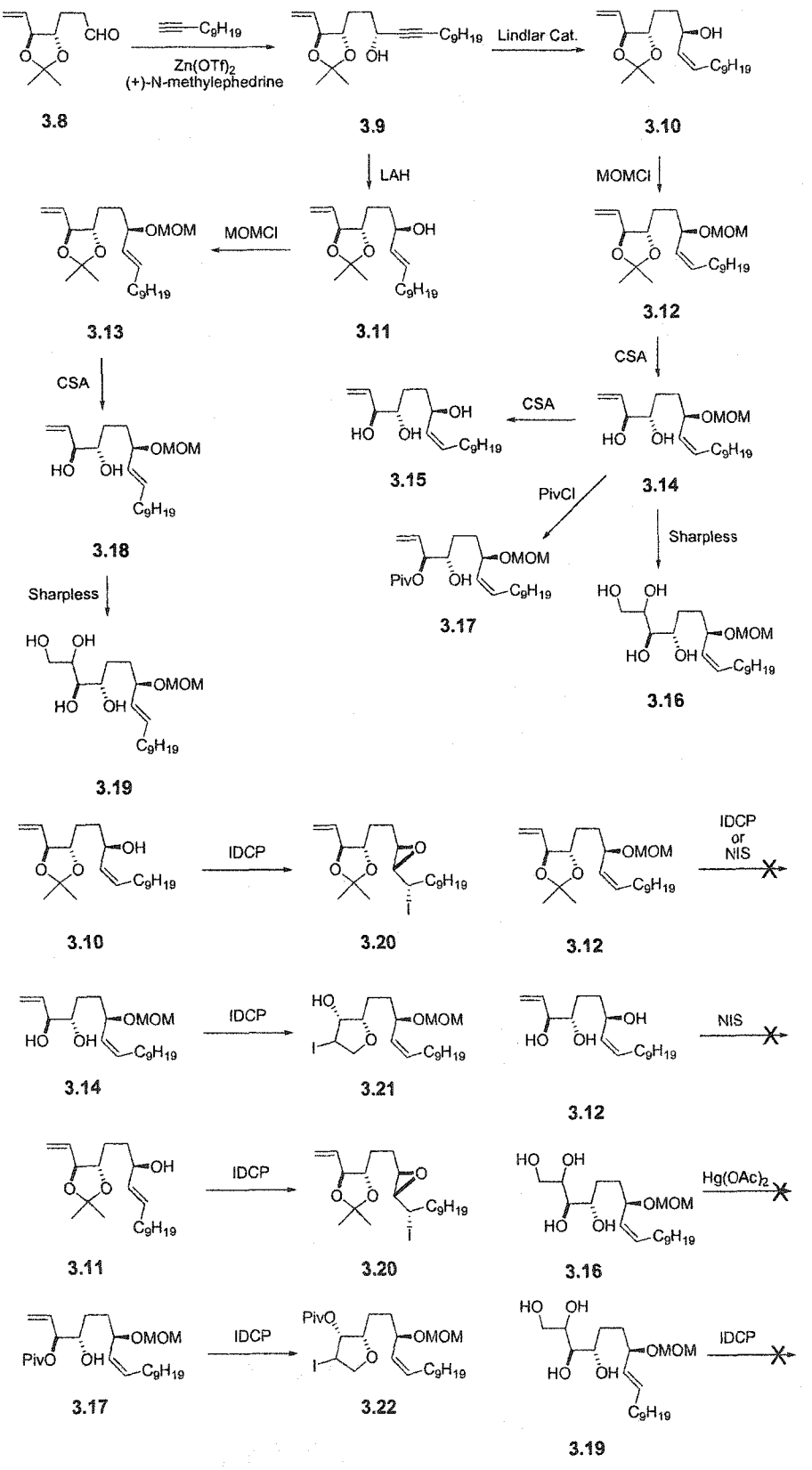


Scheme 3.1. Retrosynthesis for mucocin

3.3 Synthesis

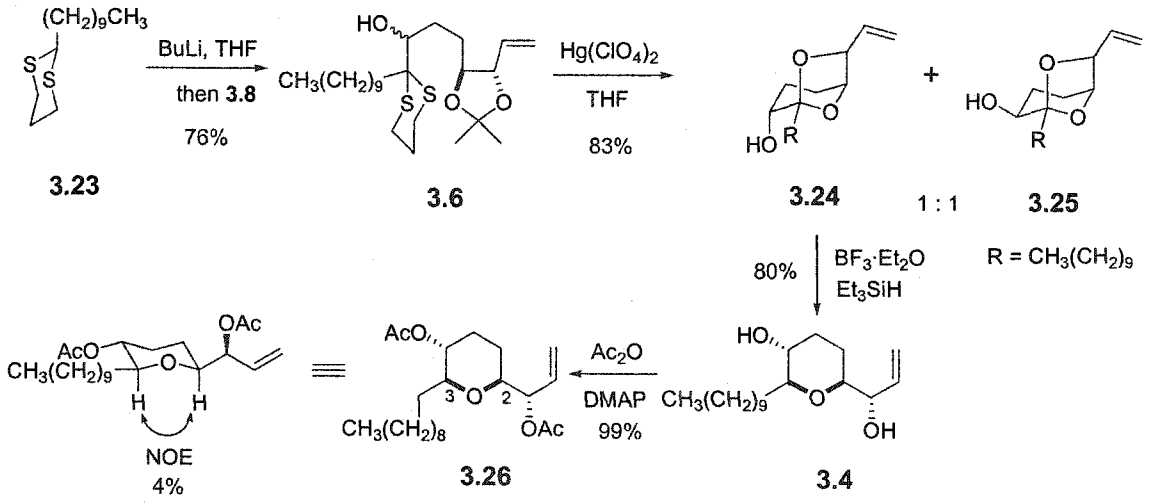
THP subunit: The initial plan for the THP subunit entailed an iodoetherification on isopropylidene alkene **3.10**. Additions of 1-undecyne to aldehyde **3.8** under the conditions developed by Carrerira provided propargylic alcohol **3.9**.[176] Controlled hydrogenation[177] of **3.9** afforded **3.10**. Iodoetherification reactions were performed on **3.10** and **3.11**, and its derivative with MOM protecting group **3.12**, and IDCP or NIS. However, these experiments were not successful. Either no reaction or formation of the THF products **3.21** or **3.22** was observed (**Scheme 3.2**). Similar results were obtained with the *trans* isomer of **3.10** (obtained by LAH reduction of **3.9**).

We next focused on making the THP ring via a hemiketal intermediate (**Scheme 3.3**).[178-180] Metalation of dithiane **3.23** and addition to aldehyde **3.8** gave a 1:1 mixture of unseparable epimers **3.6**. Treatment of dithiane **3.6** with mercury perchlorate in dry THF led to hydrolysis of the dithiane and acetal moieties and concomitant formation of a 1:1 mixture of bicyclic ketals **3.24** and **3.25**. The isomers were chromatographically separated. The relationship between **3.24** and **3.25** was confirmed by ^{1}H NMR analysis. The carbinol proton displayed different coupling constants depending on the configuration of the alcohol. In the desired compound **3.24**, the proton appeared as a doublet at δ 3.5 ppm ($J_{H,OH}$ = 10.3 Hz) due to coupling with the hydroxyl proton. The corresponding proton for **3.25** appeared as a multiplet (ddd, $J_{H,H}$ = 6.0, 10.0 Hz, $J_{H,OH}$ = 10.1 Hz).



Scheme 3.2

Treatment of compound **3.24** with Et_3SiH in presence of BF_3 afforded THP in 80% yield. The overall yield of **3.4** from **3.8** was 25%. NOE experiments on the acetate derivative **3.26** confirmed the *cis* stereochemistry of the product. Irradiation of H_2 (δ 3.4 ppm, J = 7.5 Hz) led to enhancement of H_3 (δ 3.2 ppm, J = 8.5 Hz), and vice versa. In principle, the undesired ketal isomer **3.25** could be converted to **3.24**, in order to improve the overall yield of **3.4** from **3.8**.

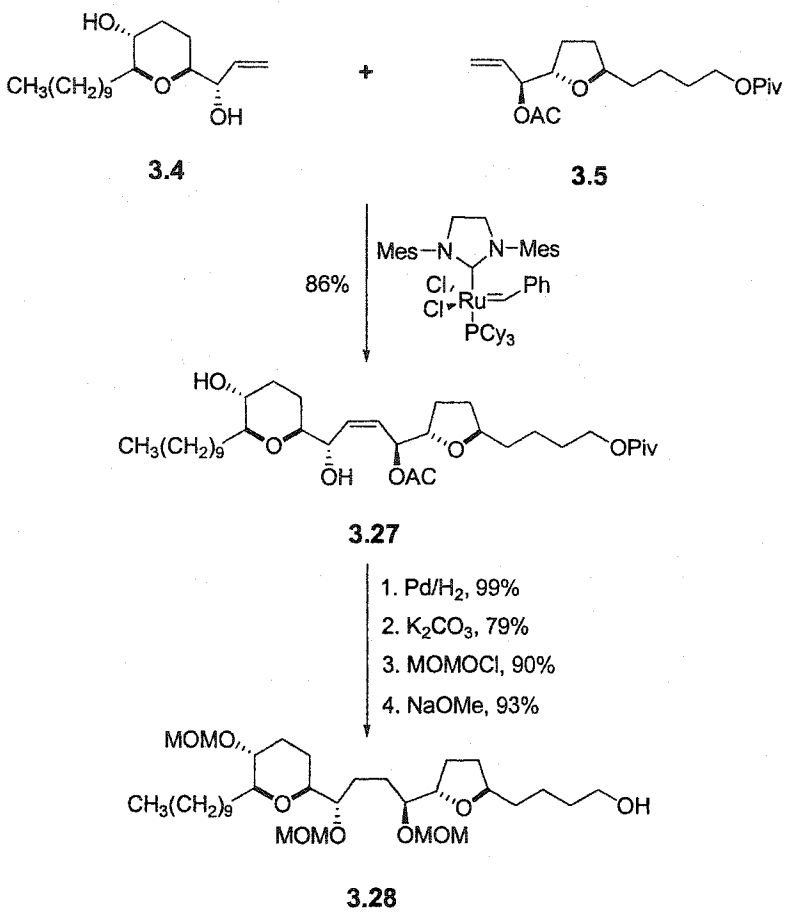


Scheme 3.3

Segment coupling: Since the mono-THF alkene and butenolide segments are identical to those used for bullatanocin (**Scheme 3.1**), the stage was set for the final coupling of subunits (**Scheme 3.4**).

Cross metathesis using one equivalent of alcohol **3.4** and three equivalents of acetate **3.5** with 10 mol% Grubbs' catalyst, was performed. A heterodimer **3.27** was obtained as the major product together with unreacted acetate **3.5**. No homodimer was detected. The yield of **3.27** was 86% based on ester **3.5** and 51% based on alcohol **3.4**.

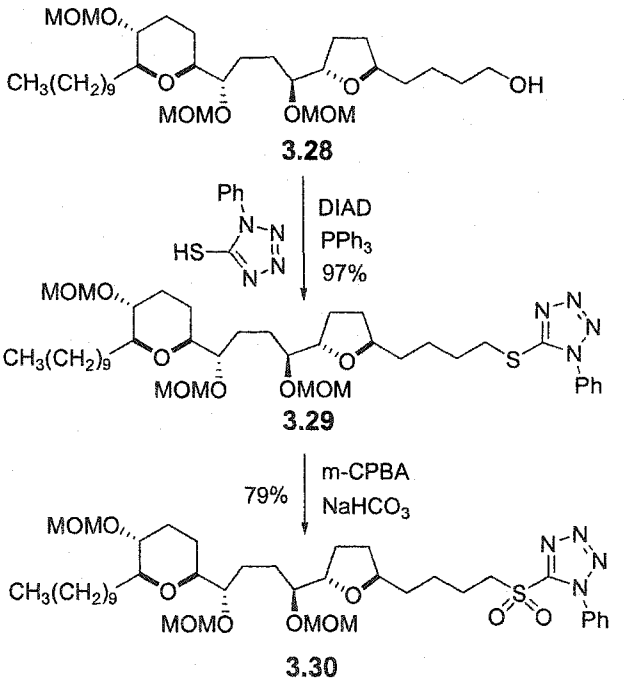
Hydrogenation of alkene **3.27**, followed by selective hydrolysis of the acetate, formation of the tri-MOM ether of the derived triol, and removal of the pivalate ester afforded alcohol **3.28**.



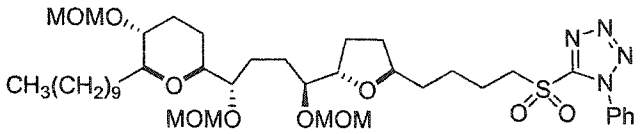
Scheme 3.4

At this stage, a Julia type reaction[149,181] for the final coupling was evaluated, because of the low yield of the Wittig reaction in the synthesis of bullatanocin. Curran and co-workers has recently reported good result with the Kocienski-Julia modification for the coupling of similar segments in the synthesis of mono-THF acetogenin.[150] Thiolation of alcohol **3.28** under Mitsunobu conditions, followed by oxidation of the resulting thioether provided sulfone tetrazole **3.30** (**Scheme 3.5**). Reaction of the derived

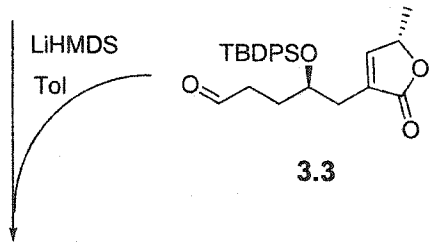
anion with butenolide aldehyde **3.3** gave the desired alkene as well as unreacted aldehyde. Due to the very similar chromatographic behavior of these compounds, the mixture was not separated and used directly in the next step. Thus hydrogenation using Wilkinson's catalyst provided **3.32** in 36% overall yield from sulfone **3.30**. A more polar material observed from the hydrogenation reaction was presumed to be the reduction product from aldehyde **3.3**. Finally, treatment of **3.30** under similar conditions used in the synthesis of bullatanocin afforded mucocin in 90% yield (**Scheme 3.6**). The ^{1}H and ^{13}C NMR of this material was essentially identical to reported for mucocin (**Table 3.1**).



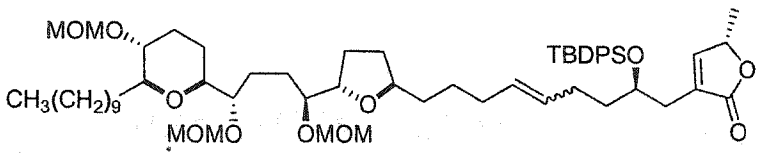
Scheme 3.5



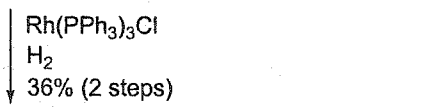
3.30

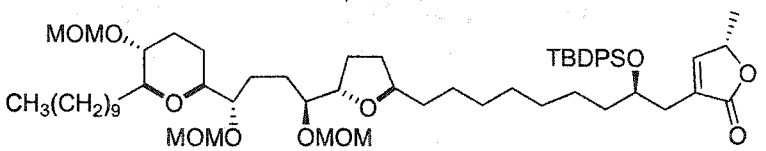


3.3

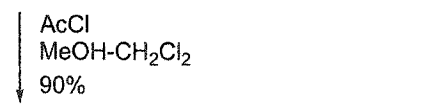


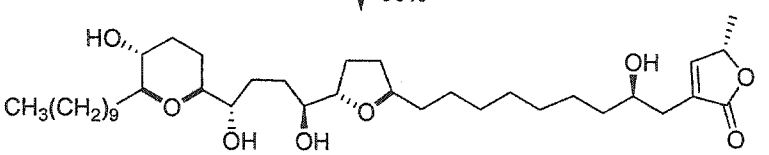
3.31





3.32





3.1

Scheme 3.6

Carbon #	Mucocin[74]	Synthetic Compound	Keinan's sample[78]	Syn-Muc	Syn-Keinan
1	174.6	174.5	174.6	-0.1	-0.1
2	131.2	131.2	131.2	0.0	0.0
3	33.3	33.4	33.3	0.1	0.1
4	69.9	70.0	69.9	0.1	0.1
5	37.3	37.4	37.4	0.1	0.0
6	26-33*	32.7	32.6	-	0.1
7	26-33*	32.0	32.0	-	0.0
8	26-33*	29.7	-	-	-
9	26-33*	29.7	29.7	-	0.0
10	26-33*	29.6	29.6	-	0.0
11	35.6	35.6	35.6	0.0	0.0
12	79.3	79.3	79.3	0.0	0.0
13	32.4	32.4	32.4	0.0	0.0
14	28.4	28.4	28.3	0.0	0.1
15	81.9	81.9	-	0.0	-
16	73.8	73.8	73.8	0.0	0.0
17	28.7	28.7	28.7	0.0	0.0
18	28.8	28.8	-	0.0	-
19	73.5	73.5	73.5	0.0	0.0
20	80.1	80.2	80.1	0.1	0.1
21	26.9	26.9	26.9	0.0	0.0
22	31.9	31.9	31.9	0.0	0.0
23	70.5	70.6	70.6	0.1	0.0
24	82.0	82.1	82.0	0.1	0.1
25	25.5	25.5	25.5	0.0	0.0
26	26-33*	29.5	29.5	-	0.0
27	26-33*	29.4	29.4	-	0.0
28	26-33*	29.3	29.3	-	0.1
29	26-33*	26.2	26.2	-	0.0
30	26-33*	22.7	22.7	-	0.0
31	26-33*	29.5	-	-	-
32	26-33*	29.3	-	-	-
33	26-33*	25.5	-	-	-
34	14.1	14.1	14.1	0.0	0.0
35	151.8	151.8	151.8	0.0	0.0
36	78.0	77.9	78.0	-0.1	-0.1
37	19.1	19.1	19.1	0.0	0.0

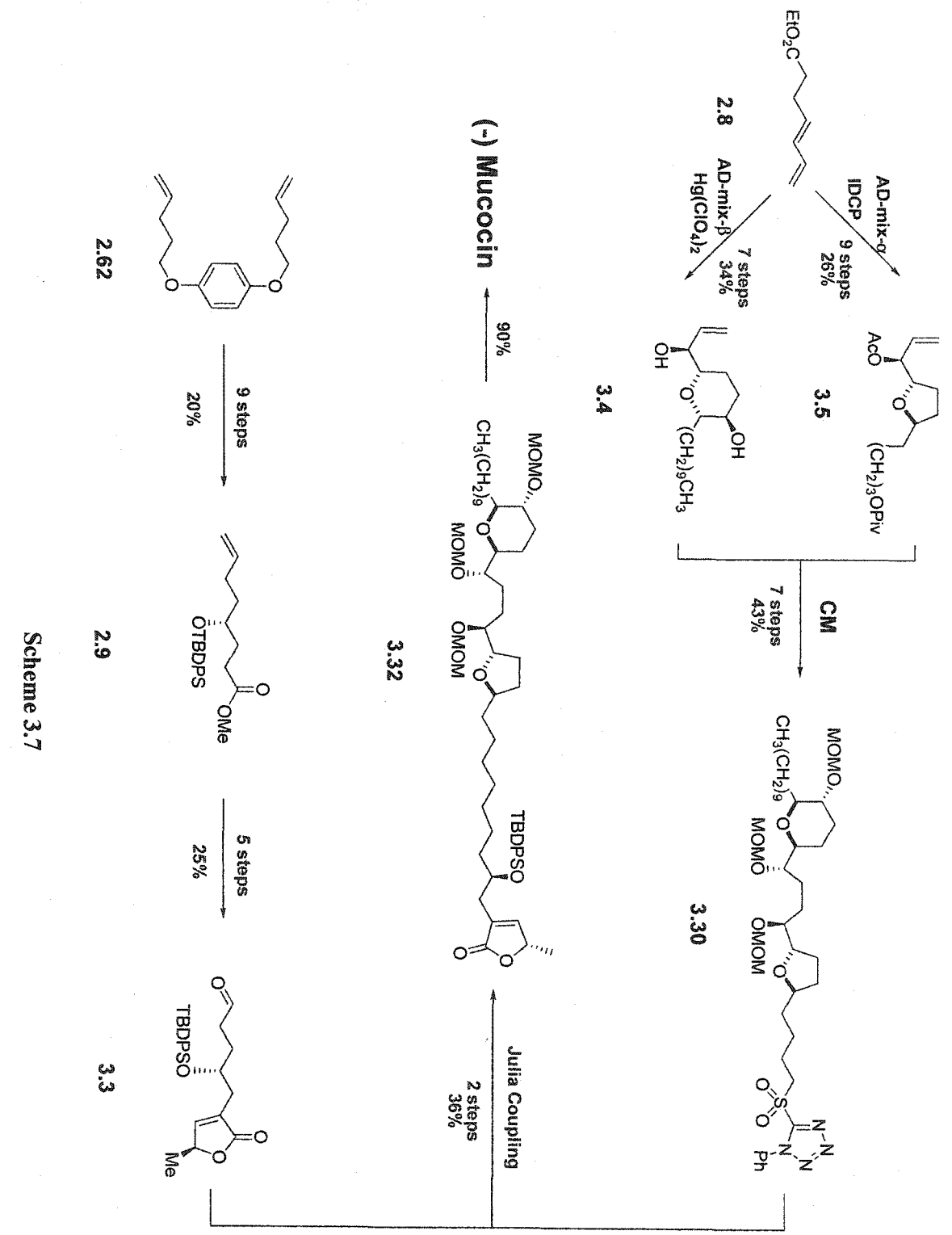
* exact ppm not listed in original literature: ref 74.

** ^{13}C NMR in $CDCl_3$ (Natural compound: 75 MHz; synthetic compound: 125 MHz; rel to $CDCl_3$ at 77.00 ppm, carbon assignments made by comparison to literature values)

Table 3.1. ^{13}CNMR of mucocin and synthetic material

3.4 Summary

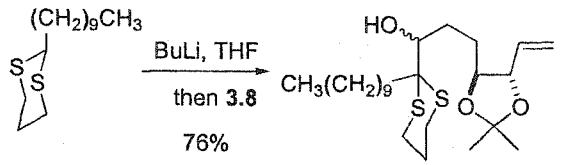
The total synthesis of mucocin was accomplished in 40 total steps, in 3.6% overall yield for the longest linear sequence (19 steps) (**Scheme 3.7**).



Scheme 3.7

3.5 Experimental Section

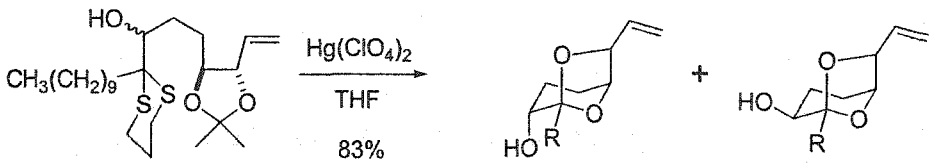
Synthesis of 3.6



3.23 **3.6**

To a stirred solution of 2-decyl-1,3-dithiane **3.23** (0.62 g, 2.4 mmol) in anhydrous THF (4 mL) under argon at 0℃ was added *n*-butyllithium (2.5 M, 0.76 mL). After 1h at 0 ℃ the aldehyde **3.8** (0.29 g, 1.6 mmol) was added, and the mixture was stirred at rt for 1.5h. This solution was washed with a saturated aqueous NH_4Cl and brine, dried (Na_2SO_4), filtered, and concentrated. FCC of the residue (10% EtOAc : petroleum ether) afforded alcohol **3.6** (533.0 mg, 76%): R_f = 0.59 (10% EtOAc : petroleum ether); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.7-5.9 (m, 1H), 5.2-5.6 (dd, 2H, J = 17.2, 9.5 Hz), 3.9-4.1 (m, 2H), 3.7-3.8 (m, 1H), 2.8-3.1 (m, 4H), 2.5-2.7 (m, 2H), 1.5-2.2 (m, 6H), 1.42 (s, 3H), 1.41 (s, 3H), 1.25 (s, br, 16H), 0.87 (t, 3H, J = 6.2).

Synthesis of bicyclic compounds 3.24 and 3.25



3.6 **3.24** **3.25**

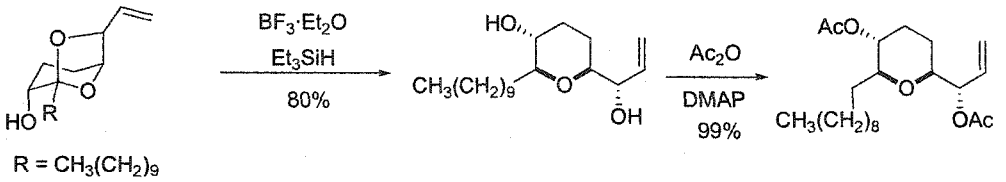
R = $CH_3(CH_2)_9$

To a solutions of **3.6** (0.58 g, 1.3 mmol) in anhydrous THF (25 mL) at 0℃ was add $Hg(ClO_4)_2$ (1.00 g, 2.5 mmol). The mixture was stirred at 0℃ for 1h, and warmed to rt, stirred for an additional 1h at this temperature. The solution was washed with aqueous saturated $NaHCO_3$, and the aqueous solution was washed with ether (3 x 20 mL). The combined organic solution were dried over Na_2SO_4, filtered, and concentrated. FCC of the residue was performed using neutral aluminum oxide (Al_2O_3) packed column (15% EtOAc : petroleum ether) afforded alcohol **3.24** (158.3 mg) and **3.25** (161.8 mg) in 83% overall yield.

Compound 3.24: R_f = 0.32 (15% EtOAc : petroleum ether); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.7-5.9 (m, 1H), 5.1-5.3 (dd, 2H, J = 17.1, 10.2 Hz), 4.39 (d, 1H, J = 7.5 Hz), 4.21 (s, br, 1H), 3.54 (d, 1H, J = 10.3 Hz), 2.0-2.2 (m, 3H), 1.7-1.8 (m, 2H), 1.4-1.5 (m, 2H), 1.3 (s, br, 16H), 0.90 (t, 3H, J = 6.7 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 137.8, 116.5, 110.0, 80.0, 79.5, 68.4, 33.5, 31.9, 29.8, 29.6, 29.6, 29.6, 29.3, 25.0, 24.2, 22.7, 22.5, 14.1; HRMS (ESI) calcd for $C_{18}H_{32}O_3Na$ (M + Na) 319.2249, found 319.2242.

Compound 3.25: R_f = 0.21 (15% EtOAc : petroleum ether); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.7-5.9 (m, 1H), 5.1-5.3 (dd, 2H, J = 17.1, 10.2 Hz), 4.39 (d, 1H, J = 7.5 Hz), 4.21 (s, br, 1H), 3.5-3.6 (ddd, 1H, J = 10.1, 10.0, 6.0 Hz), 2.1-2.2 (m, 1H), 1.7-1.9 (m, 3H), 1.6-1.7 (m, 1H), 1.4-1.5 (m, 2H), 1.3 (s, br, 16H), 0.90 (t, 3H, J = 6.8 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 138.0, 116.4, 110.9, 81.0, 78.8, 70.4, 33.1, 31.9, 29.9, 29.6, 29.6, 29.3, 28.4, 27.6, 22.9, 22.7, 14.1.

Synthesis of THF subunit 3.4 and derivative 3.26



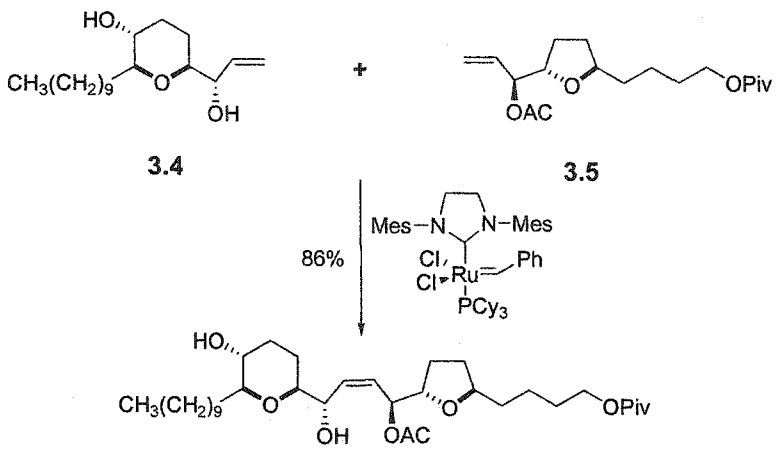
3.24 **3.4** **3.26**

Compound 3.4: To the stirred solution of **3.24** (0.15 g 0.5 mmol) in CH_2Cl_2 (7 mL) was added dropwise $BF_3{\cdot}Et_2O$ (76 μL) and triethylsilane (405 μL) at -40℃, and then the mixture was stirred at -30 to -40℃ for 3.5h. Saturated aqueous $NaHCO_3$ was added, and resulting mixture was stirred at rt for 0.5h, extracted with CH_2Cl_2 (3 x 15 mL). The extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. FCC of the residue (30% EtOAc : petroleum ether) afforded **3.4** (118 mg, 80%): R_f = 0.34 (30% EtOAc : petroleum ether); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.7-5.8 (m, 1H), 5.1-5.3 (dd, 2H, J = 17.5, 10.0 Hz), 3.87 (m, 1H), 3.26 (m, 1H), 3.13 (m, 1H), 3.04 (m, 1H), 2.76 (s, br, 1H), 2.15 (s, br, 1H), 2.0-2.1 (m, 1H), 2.7-2.8 (m, 1H), 1.3-1.7 (m, 4H), 1.3 (s, br, 16H), 0.85 (t, 3H, J = 6.5 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 136.4, 117.6, 82,1, 79.9, 75,9, 70.5, 32.6, 32.0, 31.9, 29.7, 29.6, 29.3, 26.9, 25.4, 22.7, 14.1; HRMS (ESI) calcd for $C_{18}H_{34}O_3Na$ (M + Na) 321.2406, found 321.2399.

Compound 3.26: To a solution of alcohol **3.4** (8 mg, 27 μmol) in ethyl acetate (1.0 mL) was added DMAP (1 mg, 10.8 μmol) and acetic anhydride (15 μL, 0.16 mmol) at rt. The reaction mixture was stirred for 1h, quenched with MeOH, and the solvent was removed *in vacuo*. The crude product was purified by FCC (10% EtOAc : petroleum ether) to afford **3.26** (10.2 mg, 99%): R_f = 0.30 (10% EtOAc : petroleum ether); ^1H

NMR ($CDCl_3$, 500 MHz) δ 5.7-5.8 (m, 1H), 5.2-5.3 (m, 3H), 4.43 (ddd, 1H, J = 4.0, 9.5, 10 Hz), 3.37 (m, 1H), 3.17 (m, 1H), 2.1-2.2 (m, 1H), 2.05 (s, 3H), 2.0 (s, 3H), 1.6-1.7 (m, 1H), 1.3-1.6 (m, 4H), 1.3 (s, br, 16H), 0.85 (t, 3H, J = 6.0 Hz).

Cross metathesis of 3.4 and 3.5

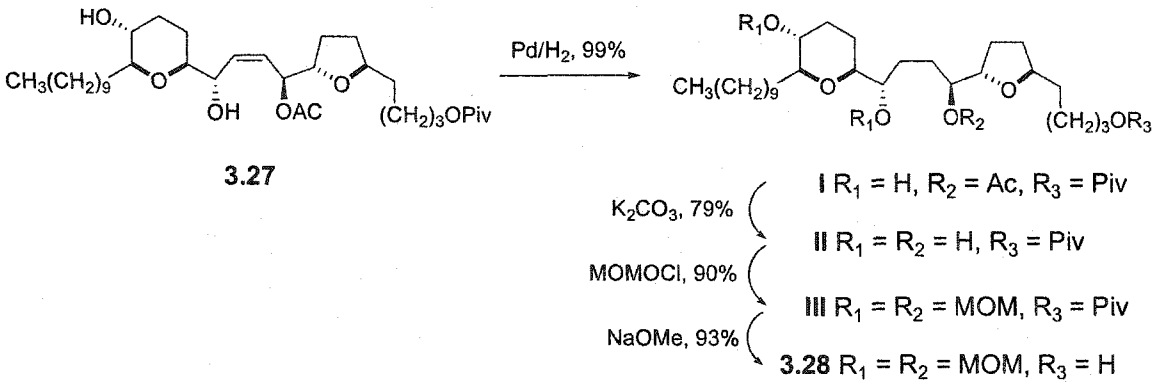


3.27

In 50 mL two neck round-bottom flask equipped with condenser and magnetic stirring bar, were placed ester **3.5** (197 mg, 0.6 mmol), alcohol **3.4** (60 mg, 0.2 mmol), and anhydrous CH_2Cl_2 (12 mL). After degassing the result mixture, a solution of catalyst **1.91** (17 mg, 20 μmol) in CH_2Cl_2 (2 mL) was injected at rt. After 18h at this temperature, additional catalyst (17 mg, 20 μmol) in CH_2Cl_2 (1 mL) was introduced. The reaction was stirred for 18h at rt, then quenched with DMSO (150 μL) at rt. The mixture was concentrated *in vacuo*. The residue was purified by FCC (30% EtOAc : petroleum ether) to afford **3.27** (61.3 mg, 86% relative to **3.5**, 51% relative to **3.4**) and unreacted THF subunit **3.5** (158.8 mg): R_f = 0.26 (30% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.76 (m, 2H), 5.26 (m, 1H), 4.06 (m, 3H), 3.93 (m, 2H), 3.29 (m, 1H), 3.17 (m,

1H), 3.08 (dt, 1H, J = 2.3, 8.8 Hz), 2.80 (s, br, 1H), 2.79 (s, br, 1H), 2.05 (s, 3H), 1.3-2.0 (m, 16H), 1.3 (s, br, 16H), 1.2 (s, br, 9H), 0.9 (t, 3H, J = 6.8 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 178.6, 170.2, 132.5, 127.9, 82.2, 79.9, 79.3, 79.1, 75.5, 74.7, 70.4, 64.2, 38.7, 35.1, 32.5, 32.0, 31.9, 31.8, 29.7, 29.6, 29.6, 29.6, 29.3, 28.6, 28.1, 27.2, 26.9, 25.4, 22.7, 22.6, 14.1; HRMS (ESI) calcd for $C_{34}H_{60}O_8Na$ (M + Na) 619.4186, found 619.4167.

Synthesis of alcohol 3.28



3.27

Compound I: A mixture of alkene **3.27** (86 mg, 0.14 mmol) and 10% Pd/C (86 mg) in ethyl acetate (10 mL) was stirred under an atmosphere of hydrogen (balloon) at rt, for 18h. The suspension was then filtered through celite, the filtrate concentrated under reduced pressure. The residue was purified by FCC (30% EtOAc : petroleum ether) to afford **I** (86.7 mg, 99%): R_f = 0.26 (30% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.9 (m, 1H), 4.07 (t, 2H, J = 6.6 Hz), 4.0 (m, 1H), 3.9 (m, 1H), 3.5 (m, 1H), 3.3 (m, 1H), 3.1 (m, 1H), 3.06 (dt, 1H, J = 2.1, 8.8 Hz), 2.59 (m, 1H), 2.58 (m, 1H), 2.05 (m, 1H), 2.04 (s, 3H), 2.0 (m, 2H), 1.4-1.8 (m, 17H), 1.3 (s, br, 16H), 1.2 (s, br, 9H), 0.9 (t, 3H, J = 6.8 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 178.6, 171.0, 82.0, 80.0, 79.3, 79.0, 77.26, 75.0, 73.1, 70.5, 64.3, 38.7, 35.1, 32.6, 32.1, 32.0, 31.9, 29.7, 29.6, 29.3, 28.6, 28.5,

28.3, 27.2, 27.0, 26.6, 25.5, 22.7, 22.6, 21.1, 14.1; HRMS (ESI) calcd for $C_{34}H_{62}O_8Na$ (M + Na) 621.4342, found 621.4355.

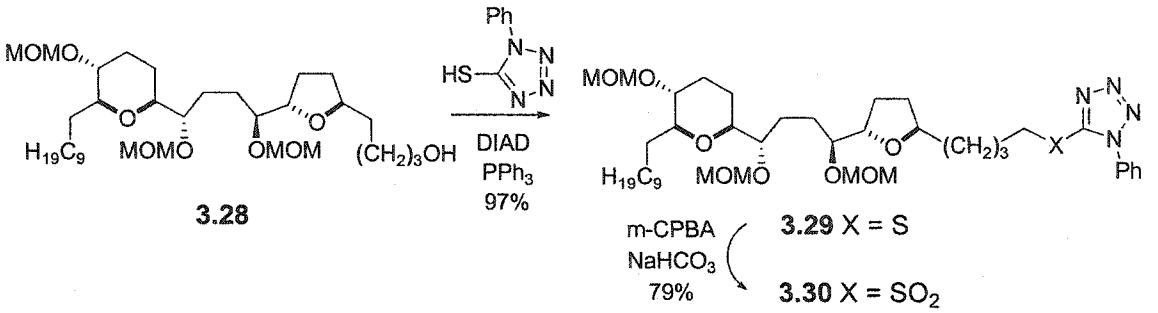
Compound II: A solution of **I** (125 mg, 0.2 mmol) in dry methanol (13 mL) was treated with K_2CO_3 (57.7 mg, 0.4 mmol). The reaction mixture was stirred for 18h at rt, then neutralise by 5% HCl, and extracted with EtOAc (3 x 10 mL) after evaporated most methanol. The combined organic phase was dried (Na_2SO_4), filtered, and concentrated. FCC of the residue (60% EtOAc : petroleum ether) afforded **II** (83.5 mg, 79%) with unreacted **I** (11.4 mg): R_f = 0.24 (60% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.0 (t, 2H, J = 6.5 Hz), 3.84 (m, 1H), 3.75 (m, 1H), 3.42 (m, 1H), 3.38 (m, 1H), 3.21 (m, 1H), 3.10 (m, 1H), 3.0 (m, 1H), 2.79 (s, br, 1H), 1.3 -2.1 (m, 20H), 1.2 (s, br, 16H), 1.15 (s, br, 9H), 0.83 (t, 3H, J = 6.5 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 178.6, 82.3, 82.2, 80.4, 79.3, 74.0, 73.7, 70.7, 64.4, 39.0, 35.5, 33.0, 32.7, 32.3, 32.2, 30.0, 29.9, 29.6, 29.1, 29.0, 29.0, 28.6, 27.5, 27.2, 25.8, 22.9, 14.4; HRMS (ESI) calcd for $C_{32}H_{61}O_7$ ($M + H^+$) 557.4417, found 557.4404.

Compound III: MOMCl (91 μL, 1.2 mmol) was added to a solution of triol **II** (83 mg, 0.2 mmol) and *i*-Pr_2NEt (392 mL, 2.3 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 ℃. The mixture was stirred for 24h at rt, then quenched with saturated aqueousNH_4Cl and extracted with ether (3 x 15 mL). The organic layer was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. FCC of the residue (40% EtOAc : petroleum ether) afforded **III** (92 mg, 90%): R_f = 0.90 (40% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.5-4.9 (m, 6H), 4.07 (t, 2H, J = 6.6 Hz), 4.0 (m, 1H), 3.92 (m, 1H), 3.5 (m, 2H), 3.41 (s, 3H), 3.40 (s, 3H), 3.39 (s, 3H), 3.35 (m, 1H), 3.22 (m, 1H), 3.12 (dt, 1H, J = 2.3, 8.9 Hz), 2.2 (m, 1H), 1.9-2.0 (m, 2H), 1.8 (m, 1H), 1.3-1.8 (m, 16H), 1.3 (s,

br. 16H), 1.2 (s, br, 9H), 0.9 (t, 3H, J = 6.8 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 178.6, 97.0, 96.8, 95.4, 81.1, 81.0, 79.9, 79.5, 79.3, 79.0, 75.9, 64.3, 55.7, 55.5, 38.7, 35.4, 32.2, 32.1, 31.9, 30.1, 29.8, 29.7, 29.7, 29.6, 29.6, 29.3, 28.9, 28.6, 27.2, 27.0, 26.7, 26.4, 25.5, 22.8, 22.7, 14.1; HRMS (ESI) calcd for $C_{38}H_{72}O_{10}Na$ (M + Na) 711.5023, found 711.5035.

Compound 3.28: Sodium methoxide (37 mg, 0.7 mmol) was added to a solution of pivalate **III** (92 mg, 0.14 mmol) in anhydrous MeOH (8 mL) at rt. The mixture was heated at reflux for 12h, then cooled to rt and neutralised with 5% aqueous HCl. Most of the methanol was evaporated under reduced pressure and the residue extracted with EtOAc (3 x 15 mL). The organic layer was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. FCC of the residue (40% EtOAc : petroleum ether) afforded **3.28** (75 mg, 93%): R_f = 0.28 (40% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.5-4.9 (m, 6H), 4.0 (m, 1H), 3.92 (m, 1H), 3.66 (t, 2H, J = 6.5 Hz), 3.5 (m, 2H), 3.41 (s, 3H), 3.40 (s, 3H), 3.39(s, 3H), 3.35 (m, 1H), 3.22 (m, 1H), 3.12 (dt, 1H, J = 2.3, 8.9 Hz), 2.2 (m, 1H), 1.9-2.0 (m, 2H), 1.8 (m, 1H), 1.3-1.8 (m, 16H), 1.3 (s, br. 16H), 0.9 (t, 3H, J = 6.8 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 97.0, 96.8, 95.4, 81.0, 79.9, 79.5, 79.2, 79.2, 75.9, 62.8, 55.7, 55.7, 55.5, 35.4, 32.7, 32.2, 32.1, 31.9, 30.1, 29.8, 29.7, 29.7, 29.6, 29.3, 28.5, 26.9, 26.7, 26.4, 25.5, 22.7, 22.5, 14.1; HRMS (ESI) calcd for $C_{33}H_{64}O_9Na$ (M + Na) 627.4448, found 627.4429.

Synthesis of sulfone tetrazole 3.30

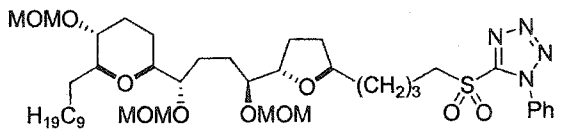


Compound 3.29: To a stirred solution of **3.28** (52 mg, 87 μmol) in THF (1.2 mL) was added PPh_3 (35 mg, 0.13 mmol) and 1-Phenyl-1*H*-tetrazole-5-thiol (24 mg, 0.13 mmol). To this solution was slowly added DIAD (26 mL, 0.13 mmol) at 0℃. The resulting yellow solution was stirred at for 0℃ 5 min, at rt for 0.5h. The reaction mixture was concentrated *in vacuo*. FCC of the residue afforded **3.29** (64.2 mg, 97%): R_f = 0.60 (40% EtOAc : petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.5 (m, 5H), 4.5-4.9 (m, 6H), 4.0 (m, 1H), 3.92 (m, 1H), 3.5 (m, 2H), 3.42 (t, 2H, *J* = 7.4 Hz), 3.41 (s, 3H), 3.40 (s, 3H), 3.39(s, 3H), 3.35 (m, 1H), 3.22 (m, 1H), 3.12 (dt, 1H, *J* = 2.2, 8.9 Hz), 2.2 (m, 1H), 1.9-2.0 (m, 2H), 1.3-1.9 (m, 17H), 1.3 (s, br. 16H), 0.9 (t, 3H, *J* = 6.7 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 154.4, 130.0, 129.8, 123.9, 97.0, 96.8, 95.4, 81.1, 81.0, 79.9, 79.5, 79.3, 78.9, 75.9, 55.7, 55.7, 55.5, 35.1, 33.3, 32.2, 32.1, 31.9, 30.1, 29.8, 29.7, 29.6, 29.3, 29.2, 28.6, 27.0, 26.6, 26.4, 25.5, 25.4, 22.7, 14.1; HRMS (ESI) calcd for $C_{40}H_{68}O_8NaS$ (M + Na) 787.4656, found 787.4652.

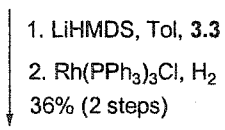
Compound 3.30: To a stirred solution of thioether **3.29** (64 mg, 84 μmol) in CH_2Cl_2 (4 mL) was added *m*-CPBA (58 mg, 0.34 mmol) and $NaHCO_3$ (56 mg, 0.67 mmol) in one portion. The resulting suspension was stirred for 12 h at rt and quenched with 10% aq. $Na_2S_2O_3$ (4 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The organic phase were washed with sat. $NaHCO_3$ (4 mL), brine, dried (Na_2SO_4),

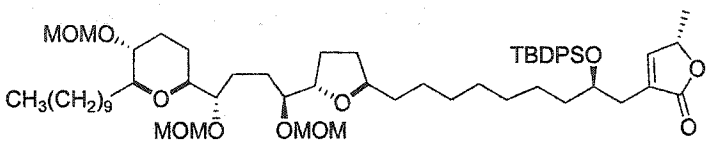
filtered, and concentrated. FCC of the residue (5% Acetone : CH_2Cl_2) afforded **3.30** (39.9 mg, 79% based on recovered **3.29**): R_f = 0.76 (5% Acetone : CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.8 (m, 2H), 7.6 (m, 3H), 4.5-4.9 (m, 6H), 4.0 (m, 1H), 3.92 (m, 1H), 3.76 (t, 2H, J = 8.0 Hz), 3.5 (m, 2H), 3.41 (s, 3H), 3.40 (s, 3H), 3.39(s, 3H), 3.35 (m, 1H), 3.22 (m, 1H), 3.12 (dt, 1H, J = 2.0, 8.8 Hz), 2.2 (m, 1H), 1.9-2.0 (m, 4H), 1.8 (m,1H), 1.3-1.8 (m, 14H), 1.3 (s, br. 16H), 0.9 (t, 3H, J = 6.6 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 153.5, 131.4, 129.7, 125.1, 97.0, 96.8, 95.4, 81.2, 81.0, 79.8, 79.6, 79.3, 78.6, 75.9, 56.0, 55.8, 55.7, 55.5, 35.0, 32.3, 32.1, 31.9, 30.1, 29.8, 29.7, 29.6, 29.3, 28.5, 27.0, 26.6, 26.4, 25.5, 25.1, 22.7, 22.1, 14.1; HRMS (ESI) calcd for $C_{40}H_{68}N_4O_{10}NaS$ (M + Na) 819.4554, found 819.4536.

Synthesis of 3.32



3.30





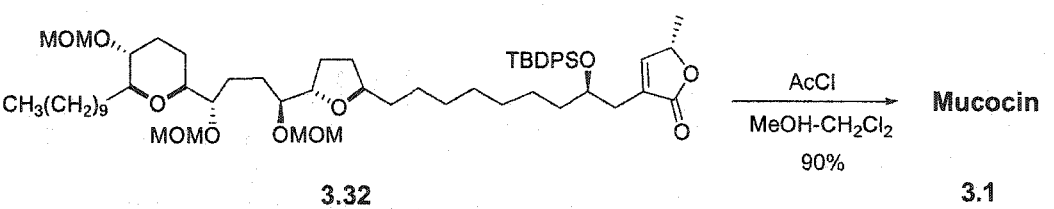
3.32

To a solution of sulfone **3.30** (30 mg, 37.7 mmol) in toluene (1.5 mL) was added LiHMDS (1.0 M in THF, 98 μL) at -78℃. After stirring the yellow mixture for 1h, aldehyde **3.3** (27 mg, 62.0 μmol) in toluene (1.0 mL) was slowly added at -78℃. The

mixture was stirred for another 1h at this temperature and warmed up to rt. After additional 1h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with ether (3 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure and afforded desired alkene **3.31** (24 mg) as well as unreacted **3.3**.

Chlorotris(triphenylphosphine)rhodium(I) (3.9 mg) was added to a degassed solution of crude **3.31** (24 mg) in benzene-EtOH (1:1, 0.6 mL), and the mixture was stirred under an atmosphere of hydrogen for 24 h. The solvent was removed under reduced pressure, and the residue was purified by FCC to give the **3.32** (13.6 mg, 36% from **3.30**): $R_f = 0.47$ (25% EtOAc : petroleum ether); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.6-7.7 (m, 4H), 7.3-7.5 (m, 6H), 6.9 (d, 1H, $J = 1.2$ Hz), 4.6-4.9 (m, 7H), 4.04 (m, 1H), 4.0 (m, 1H), 3.92 (m, 1H), 3.5 (m, 2H), 3.41 (s, 3H), 3.40 (s, 3H), 3.39(s, 3H), 3.35 (m, 1H), 3.22 (m, 1H), 3.12 (dt, 1H, $J = 2.2$, 8.8 Hz), 2.5 (m, 2H), 2.2 (m, 1H), 1.9-2.0 (m, 2H), 1.8 (m,1H), 1.3-1.8 (m, 16H), 1.34 (d, 3H, $J = 6.8$ Hz), 1.29 (s, br. 16H), 1.06 (s, br, 9H), 0.9 (t, 3H, $J = 6.8$ Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 173.9, 151.1, 135.8, 135.8, 135.7, 134.2, 134.1, 130.7, 129.7, 129.6, 127.6, 127.6, 97.0, 96.9, 95.4, 81.0, 79.9, 79.6, 79.3, 79.3, 77.4, 77.3, 75.9, 71.8, 55.7, 55.5, 36.4, 32.2, 32.1, 31.9, 31.8, 30.2, 29.8, 29.7, 29.6, 29.6, 29.4, 29.4, 29.3, 28.6, 27.0, 26.9, 26.7, 26.4, 26.2, 25.5, 24.9, 22.7, 18.9, 14.1; HRMS (ESI) calcd for $C_{59}H_{96}O_{11}NaSi$ (M + Na) 1031.6620, found 1031.6605.

Synthesis of mucocin 3.1

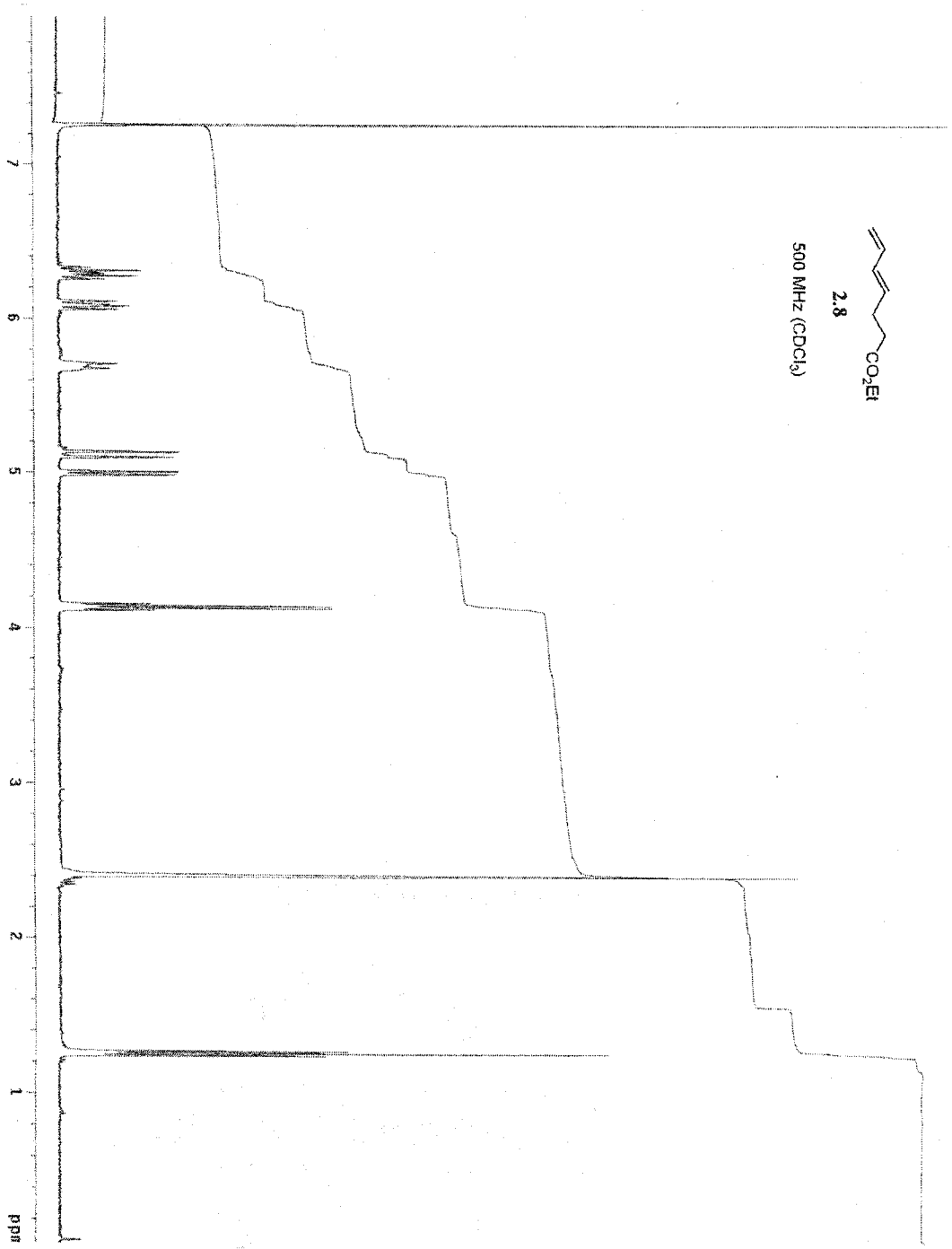


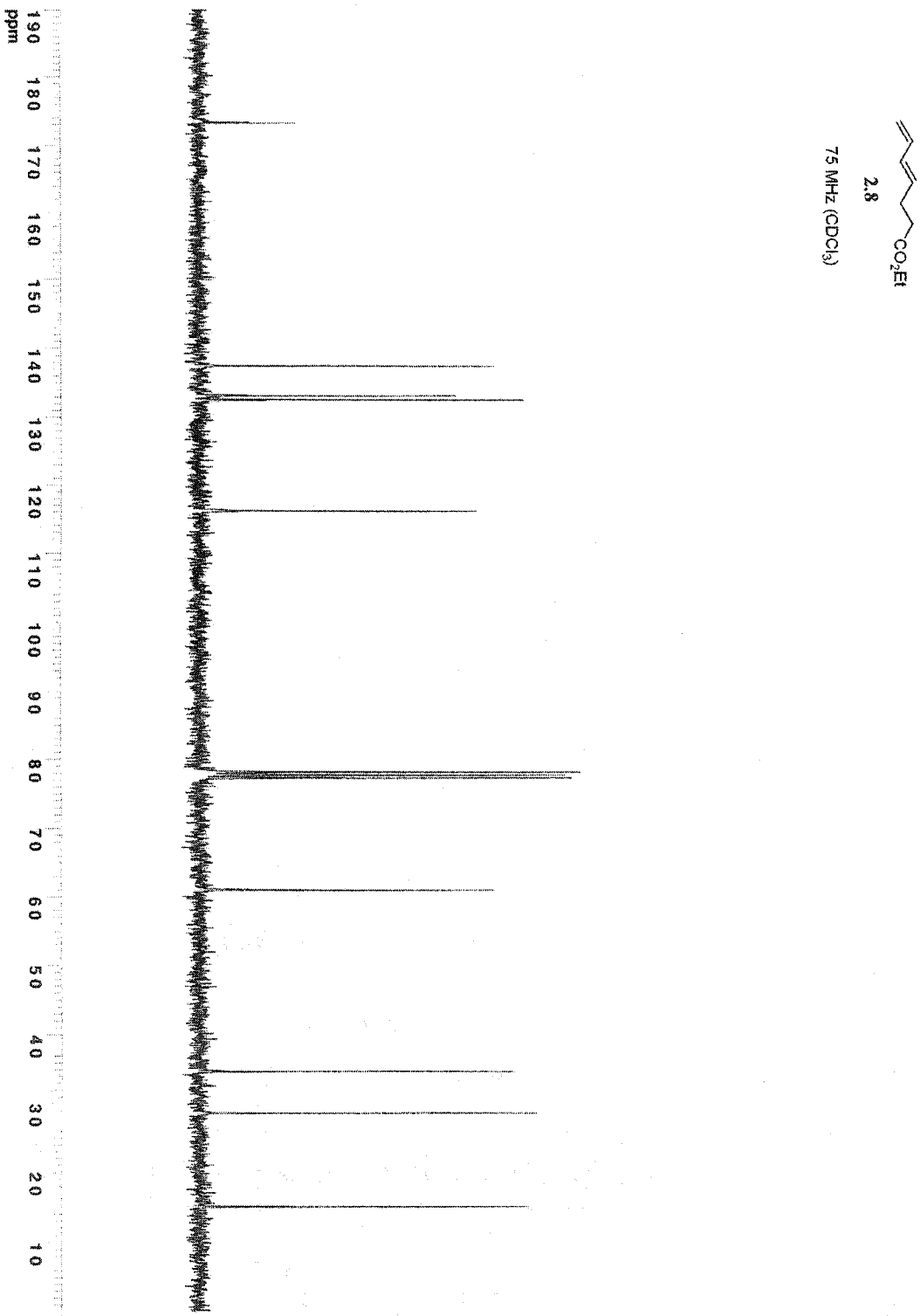
3.32 **3.1**

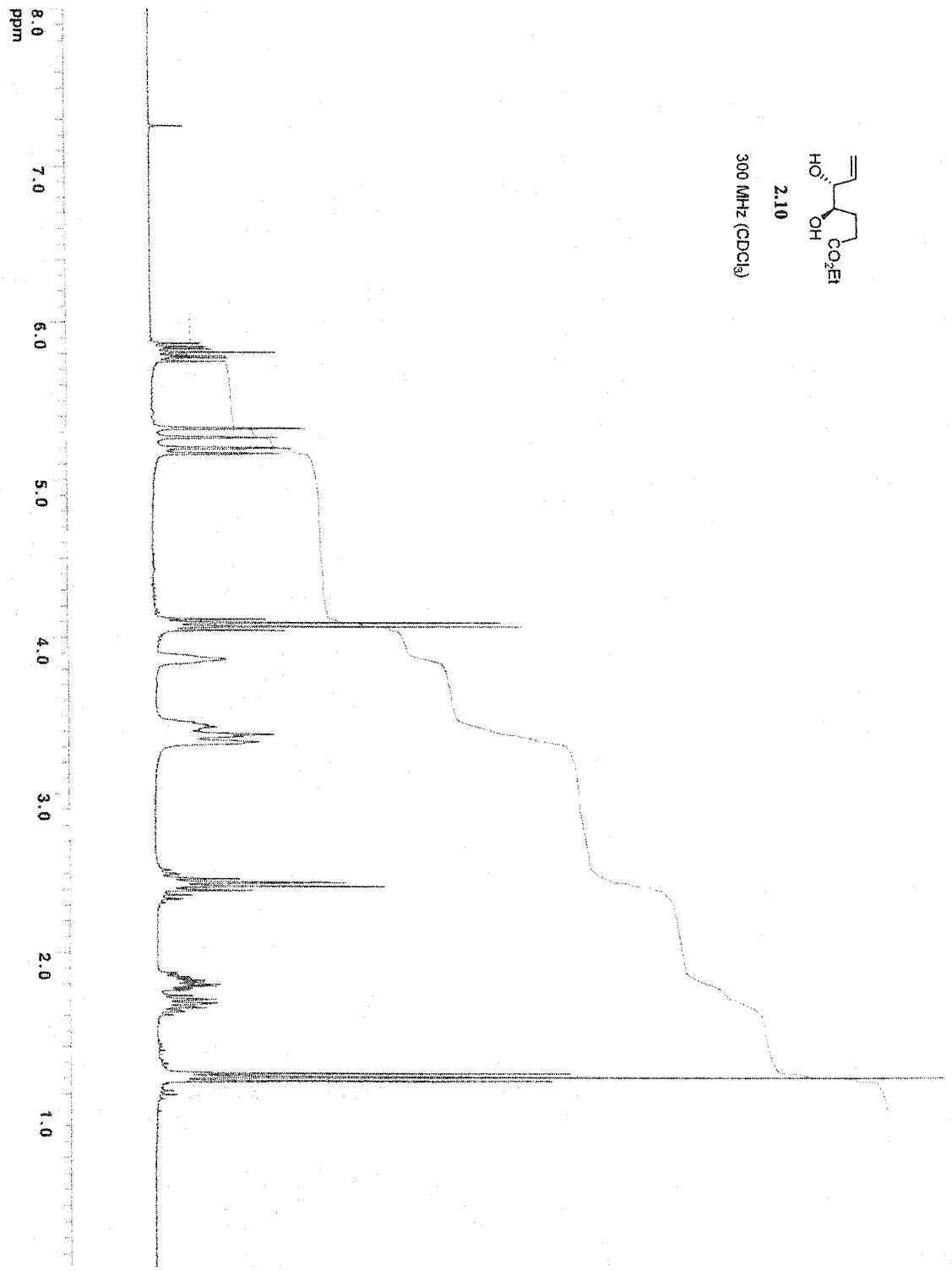
5% AcCl in MeOH (0.59 mL) was added at rt to a solution of **3.32** (13.6 mg, 13.5 μmol) in CH_2Cl_2 (1.0 mL). The mixture was stirred at this temperature for 4h, diluted with CH_2Cl_2, and washed with a saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated. FCC of the residue (EtOAc) afforded **3.1** (4.2 mg, 90%) and a mixture of less polar fractions (7.1 mg) that appeared to be partially deprotected products.

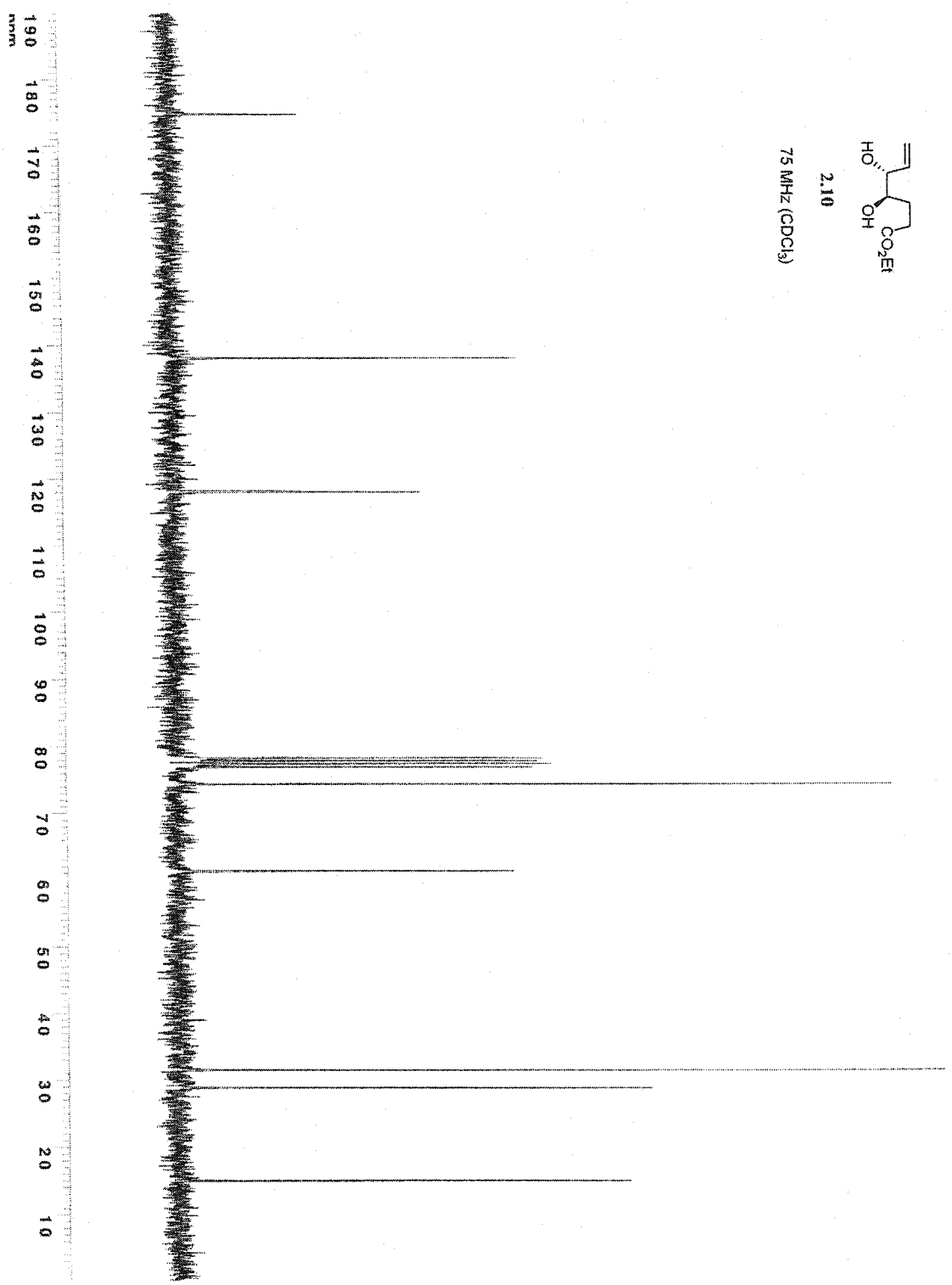
Mucocin: R_f = 0.63 (EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.16 (d, 1H, *J* = 1.2 Hz), 5.04 (dq, 1H, J = 1.4, 6.8 Hz), 3.8-3.9 (m, 3H), 3.78 (q, 1H, 7.2 Hz), 3.50 (m, 1H), 3.45 (m, 1H), 3.30 (m, 1H), 3.18 (m, 1H), 3.07 (dt, 1H, *J* = 2.1, 8.8 Hz), 2.85 (m, 1H), 2.73 (m, 1H), 2.51 (dt, 1H, *J* = 1.6, 15,2 Hz), 2.38 (dd, 1H, *J* = 8.2, 15.2 Hz), 2.28 (m, 1H), 2.04-2.12 (m, 1H), 1.91-2.03 (m, 2H), 1.77-1.85 (m, 1H), 1.23-1.70 (m, 40H), 1.45 (d, 3H, *J* = 6.8 Hz), 0.9 (t, 3H, *J* = 6.8 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 174.6, 151.8, 131.2, 82.1, 81.9, 80.2, 79.3, 77.9, 73.8, 73.5, 70.6, 70.0, 37.4, 35.6, 33.4, 32.7, 32.4, 32.0, 31.9, 29.7, 29.7, 29.6, 29.5, 29.4, 29.4, 29.3, 29.3, 28.8, 28.7, 28.4, 26.9, 26.2, 25.5, 25.5, 22.7, 19.1, 14.1; HRMS (ESI) calcd for $C_{37}H_{67}O_8$ ($M + H^+$) 639.4836, found 639.4811.

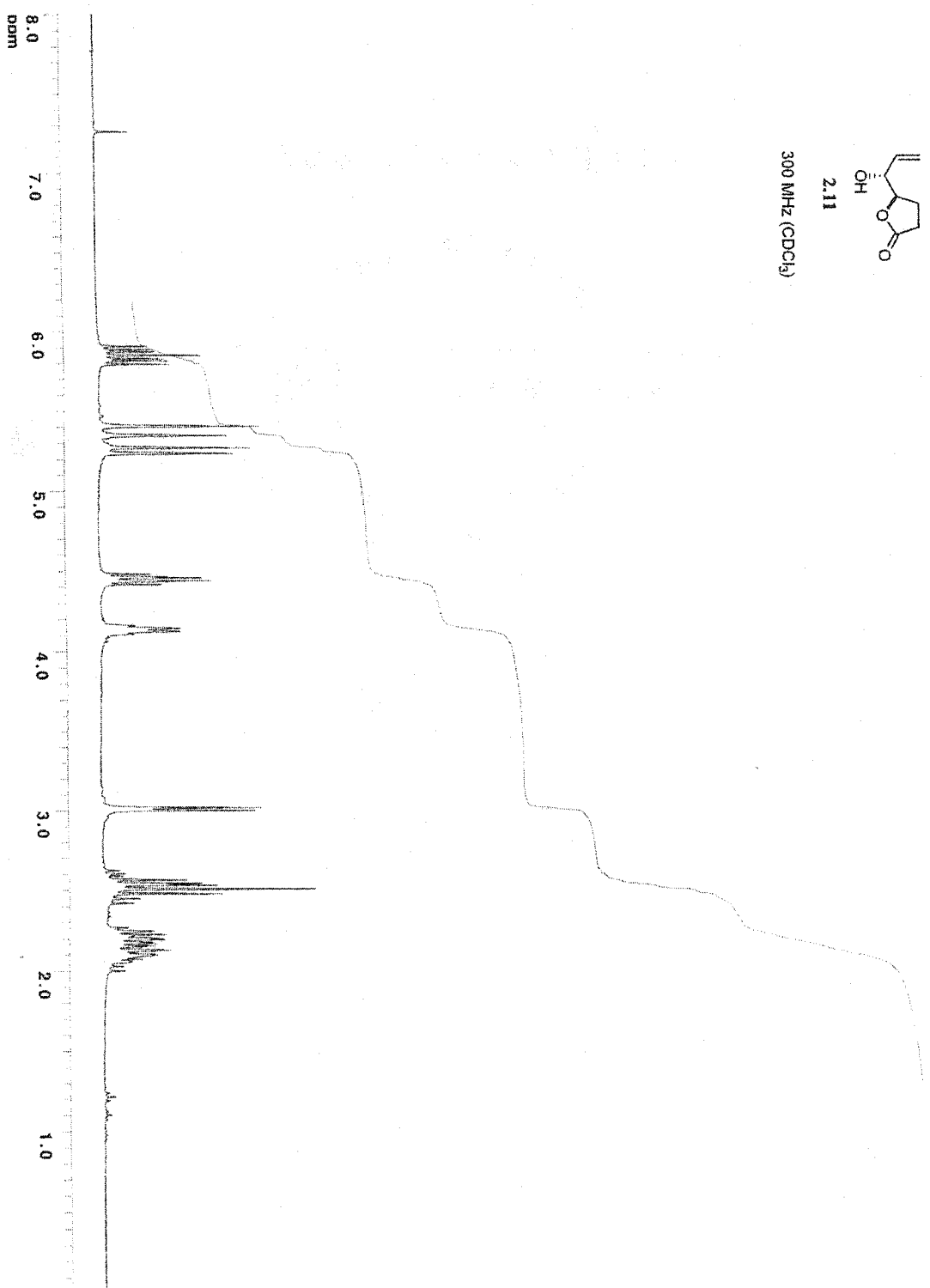
APPENDIX

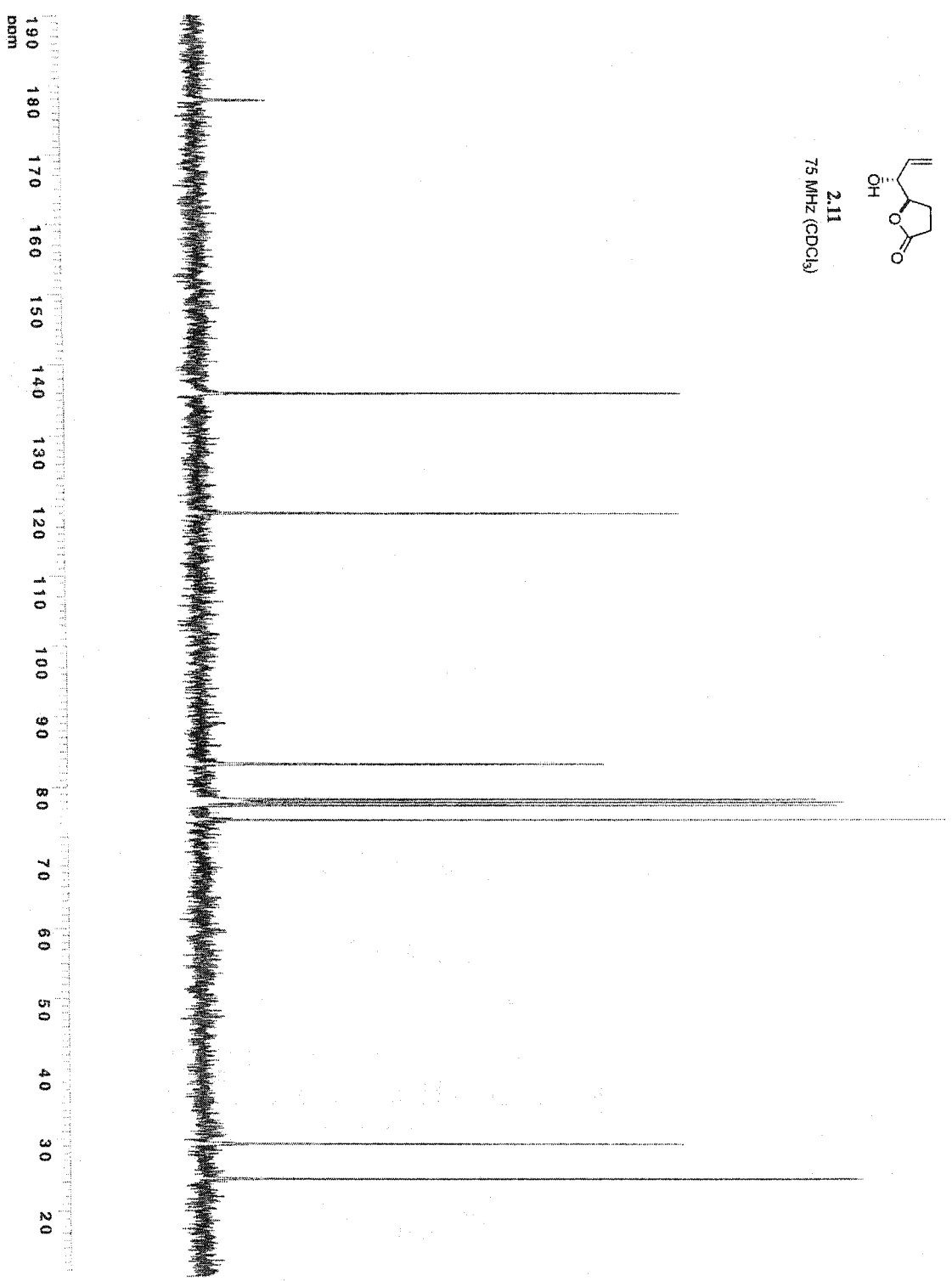


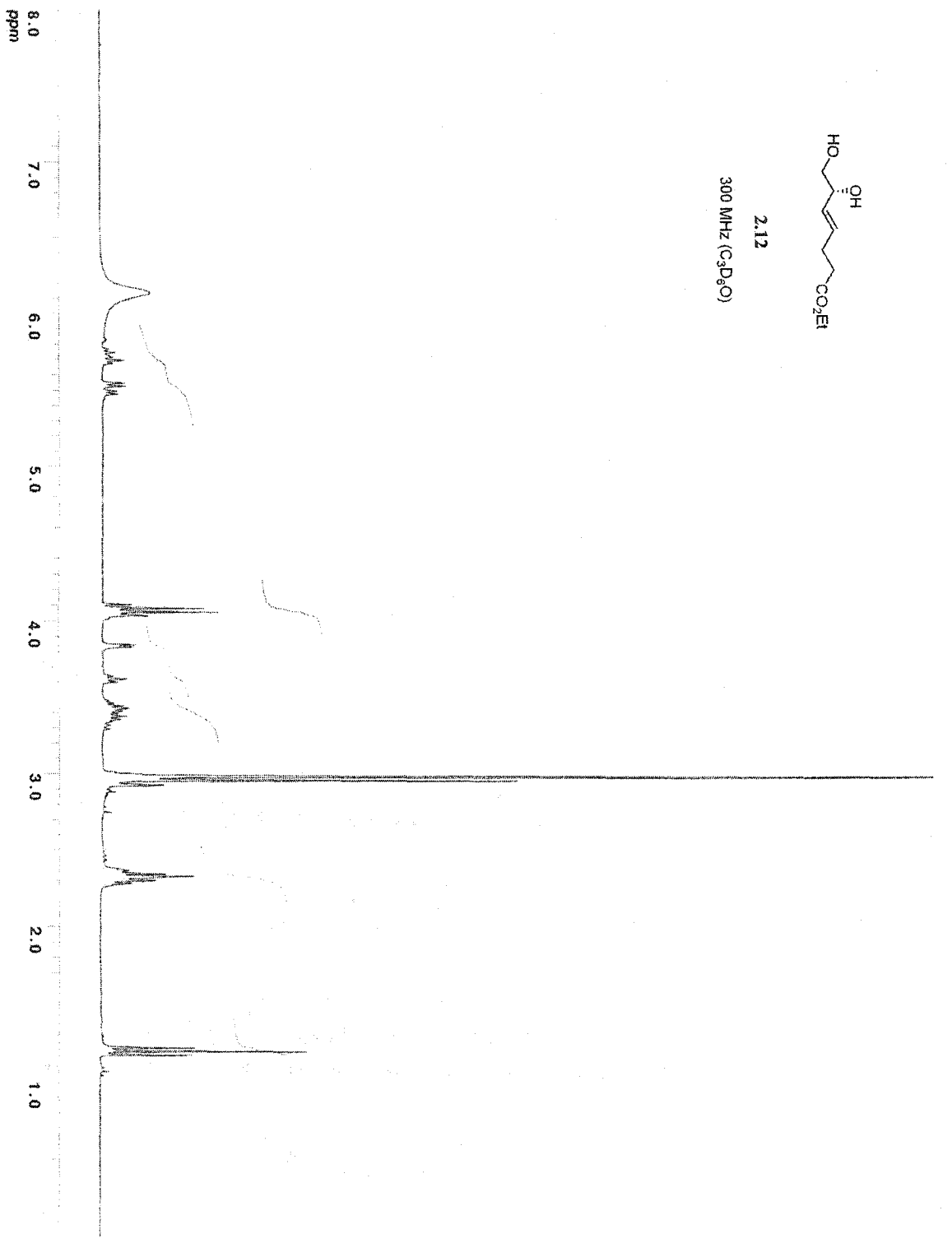


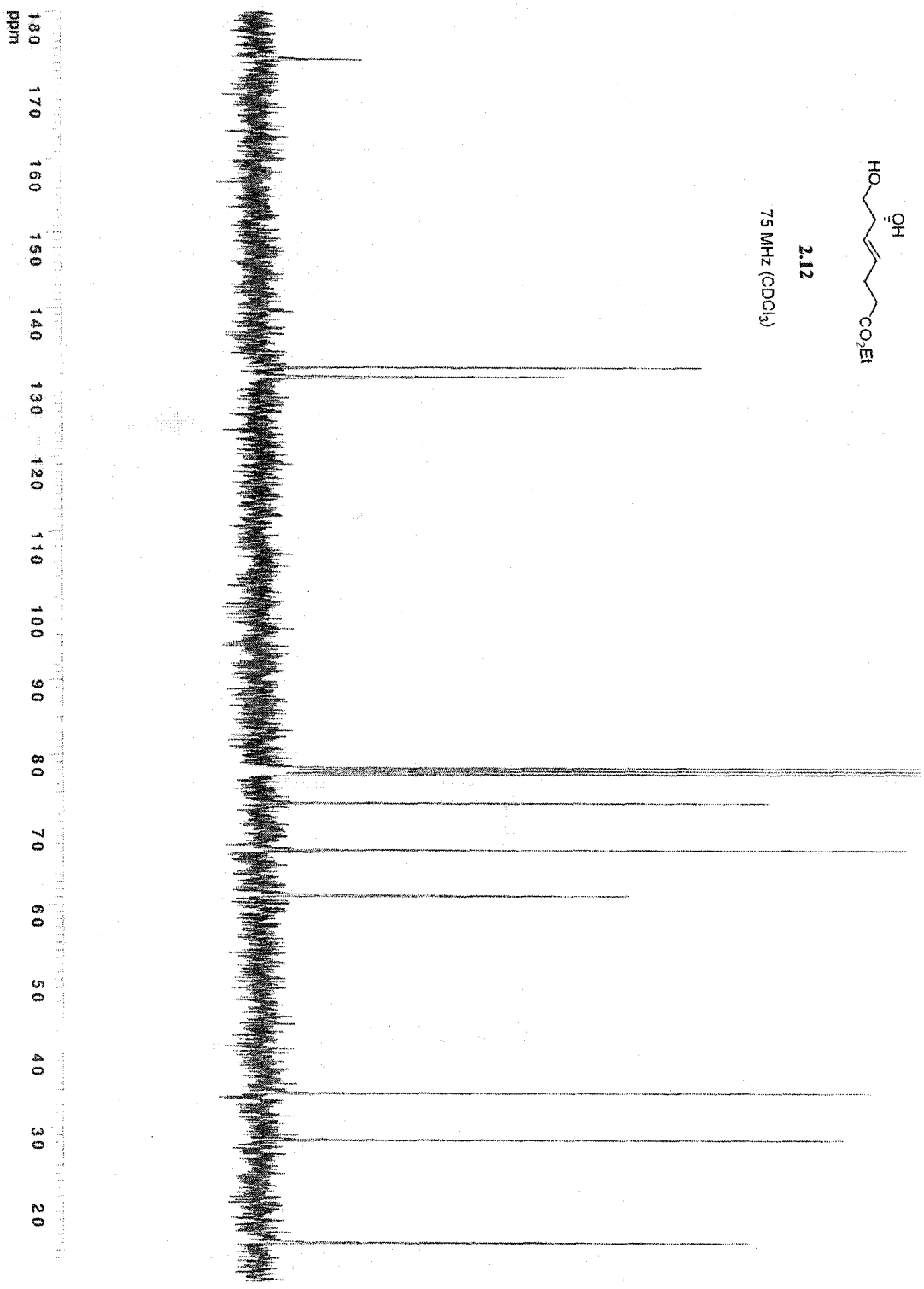


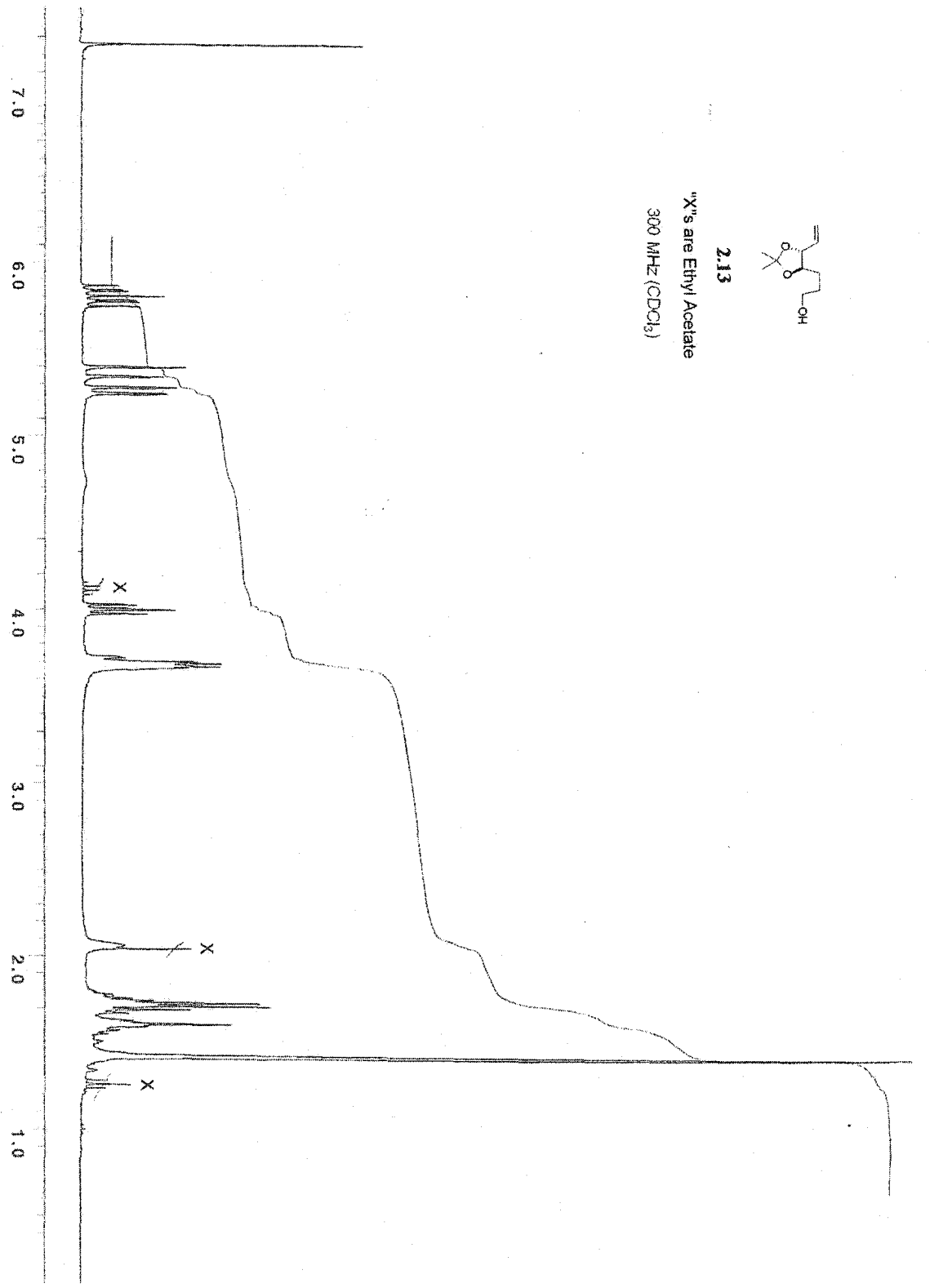


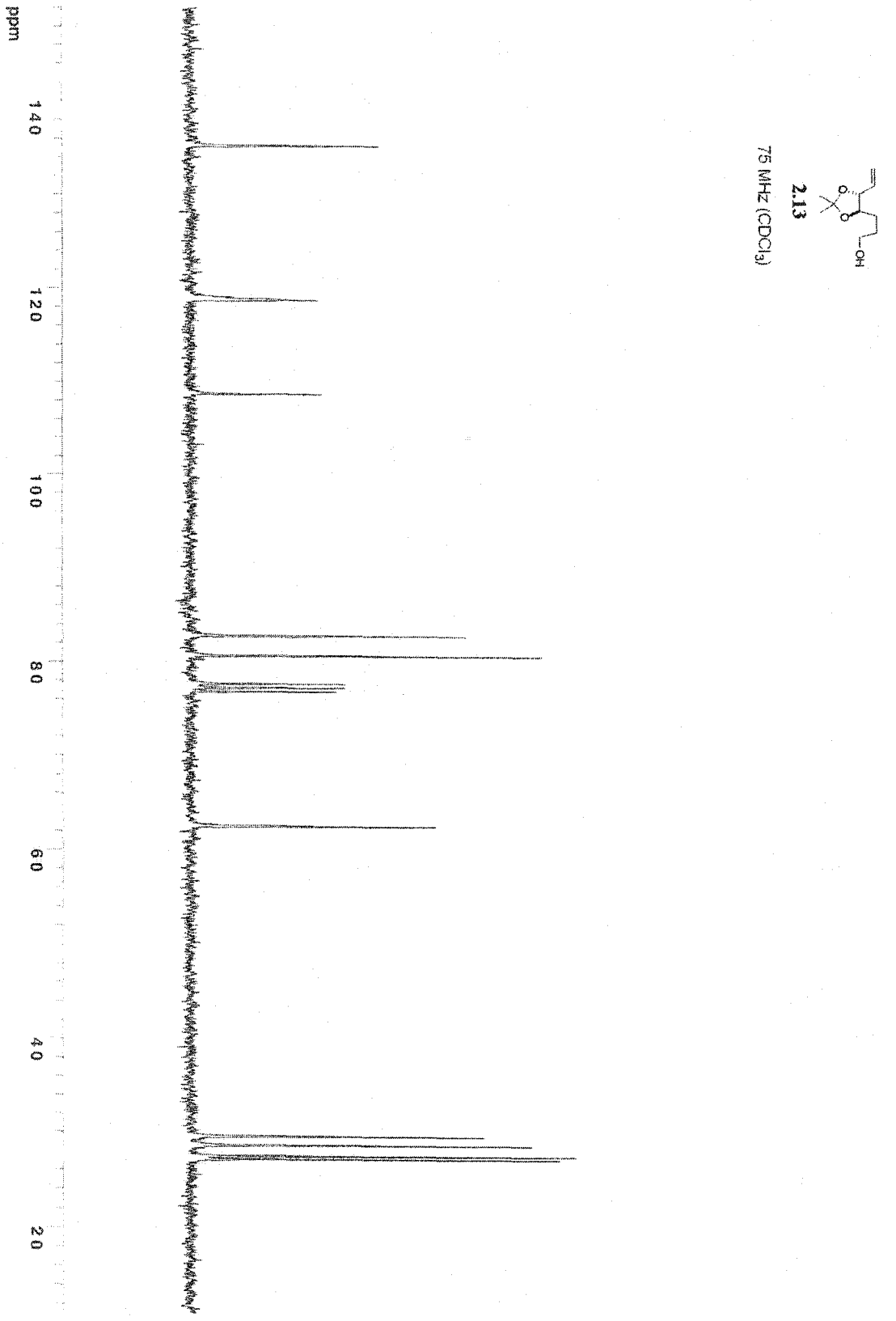


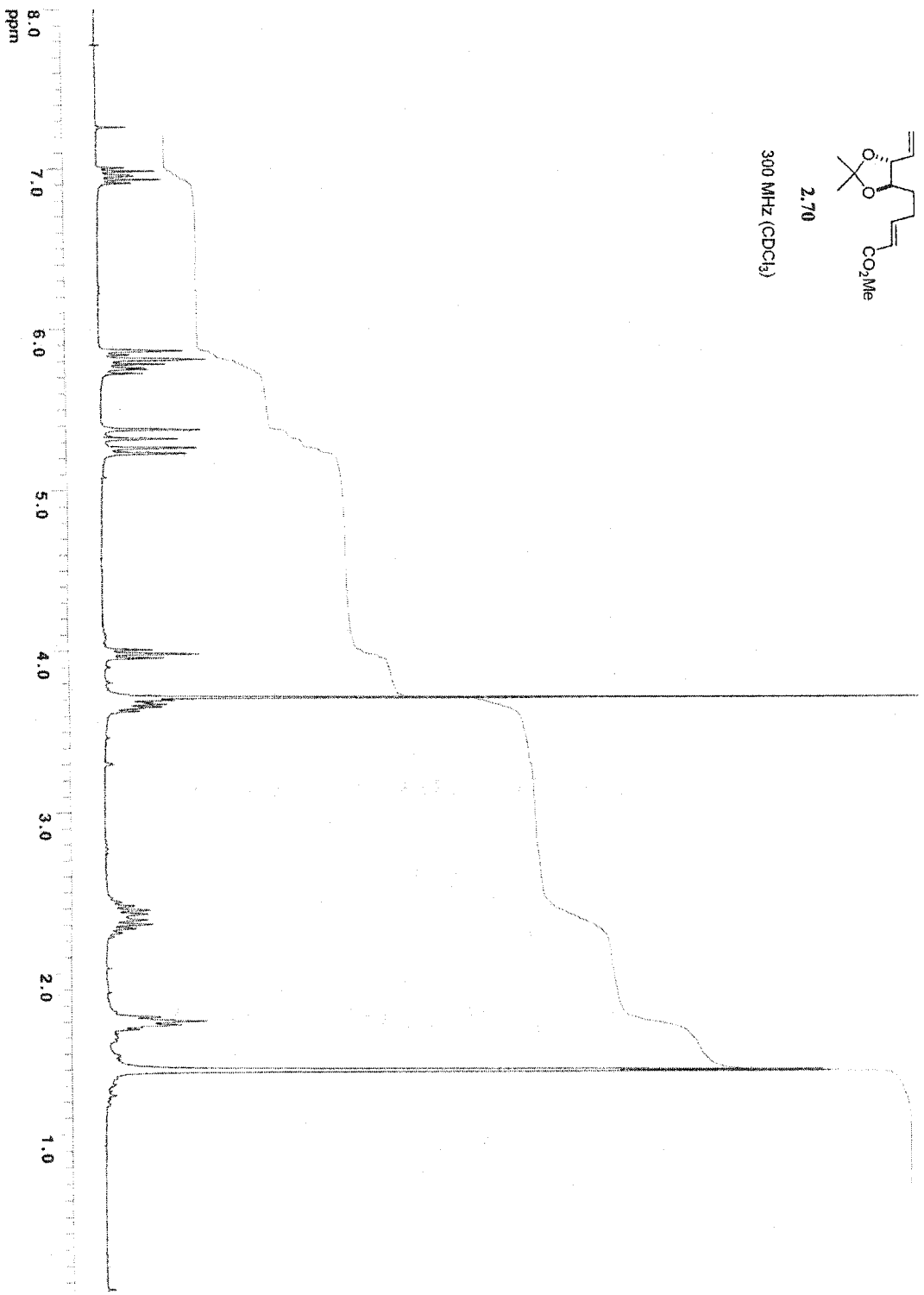


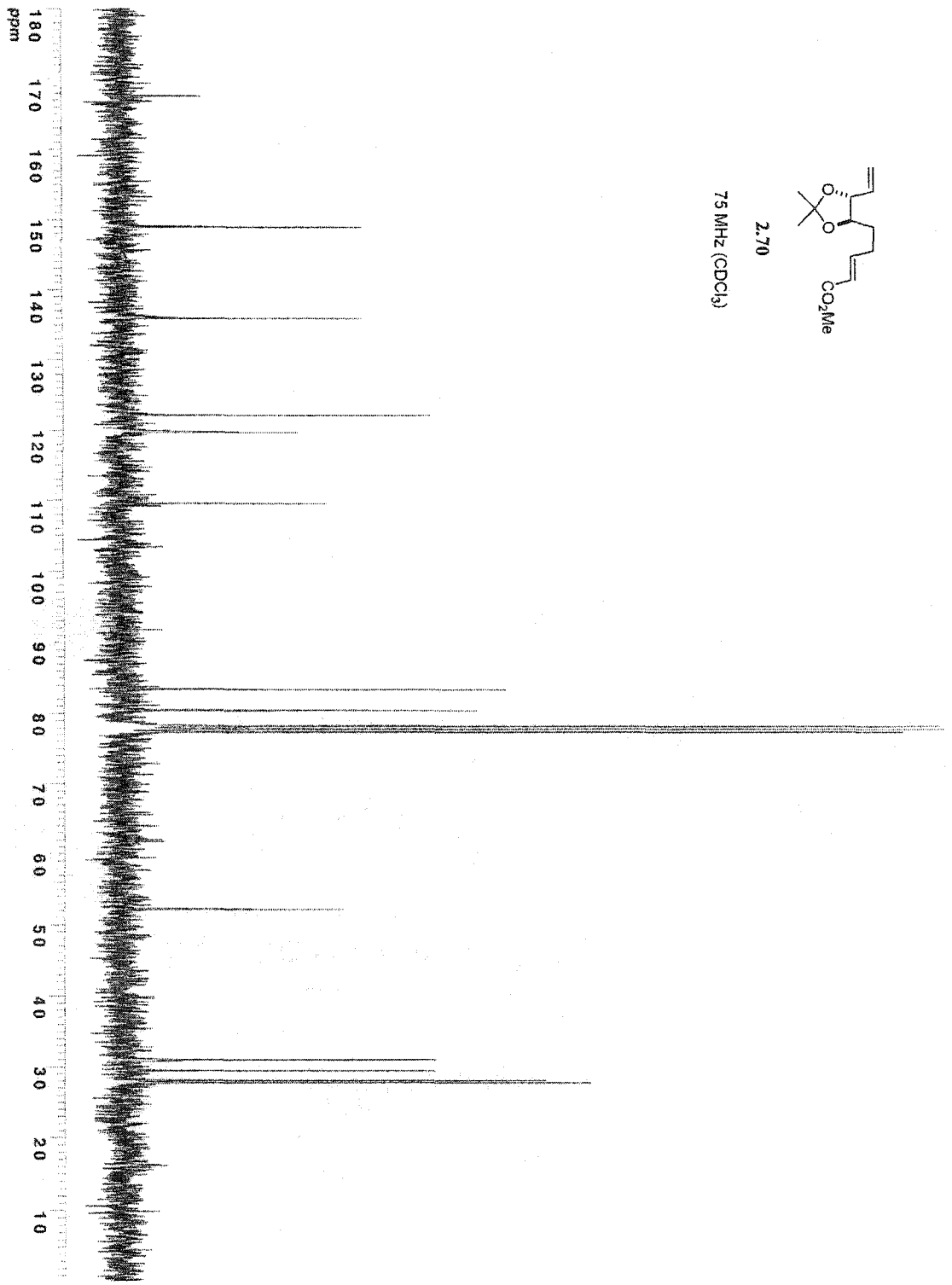


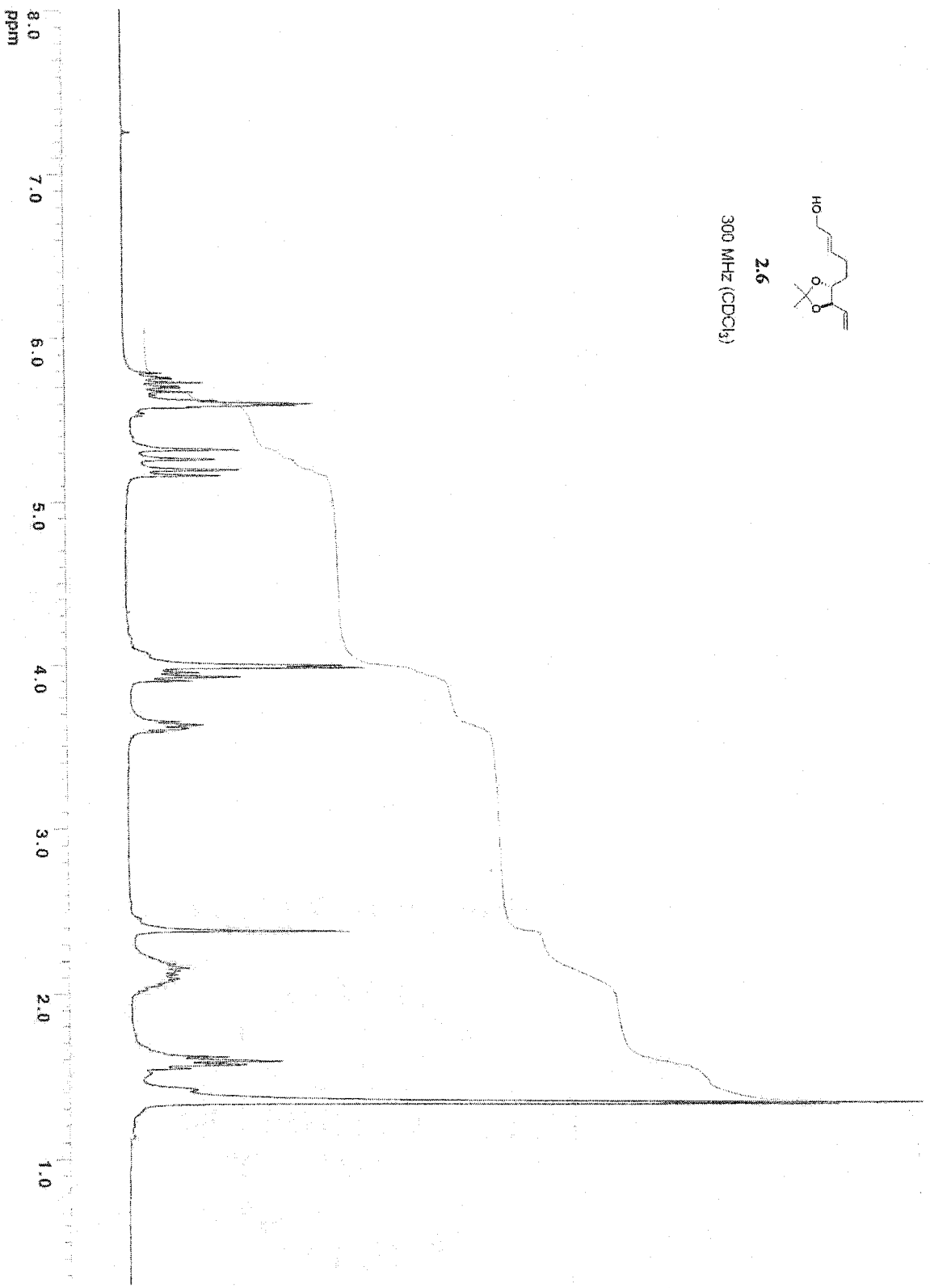


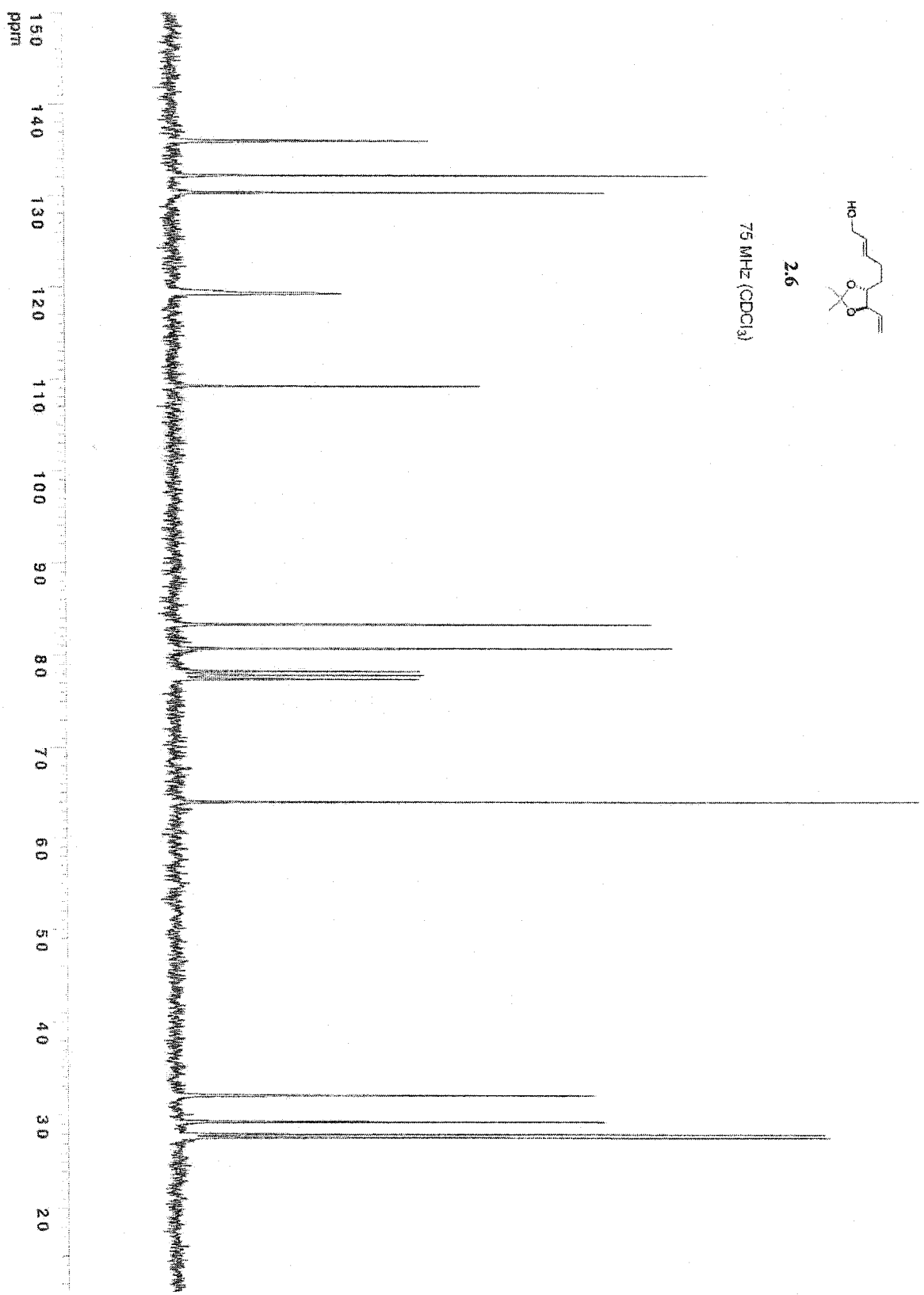


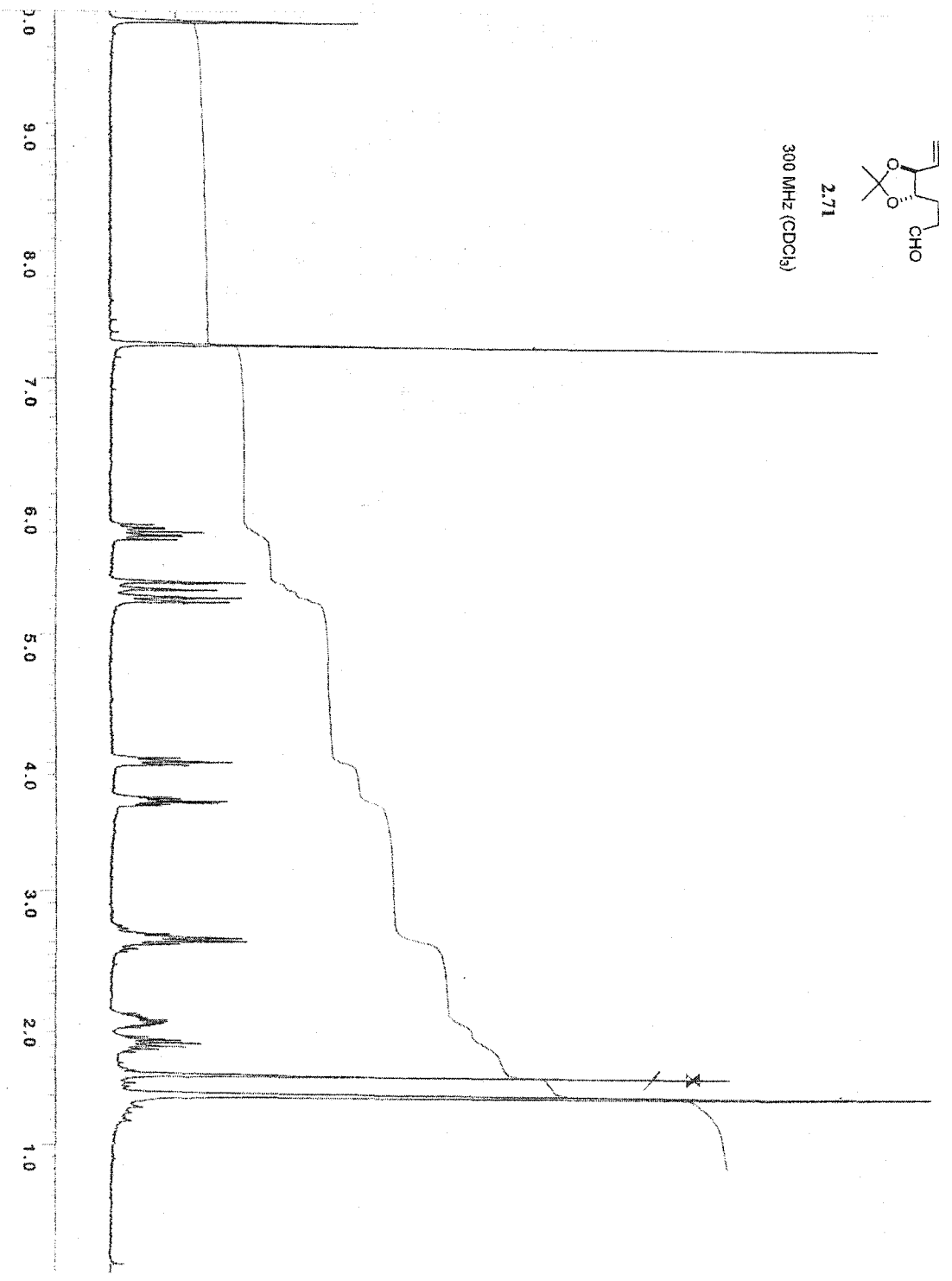


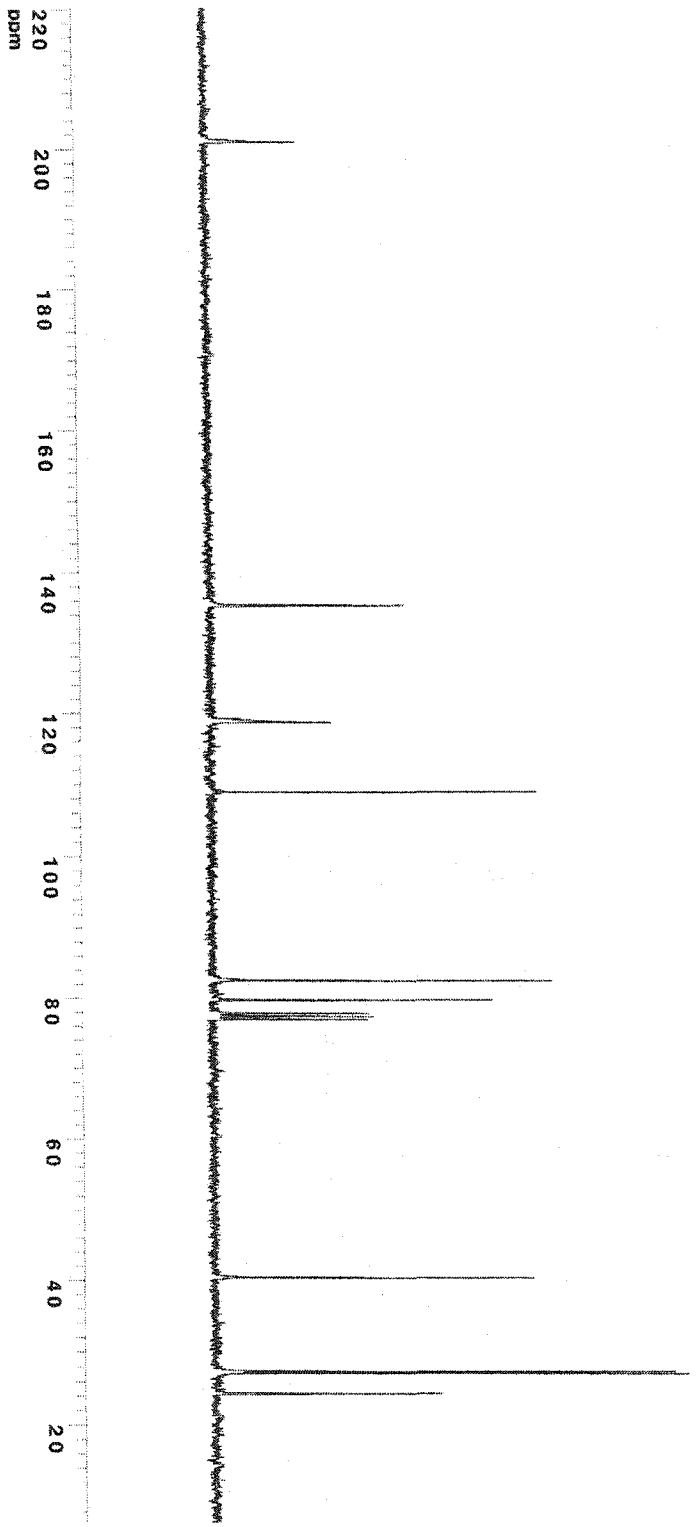


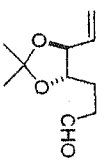






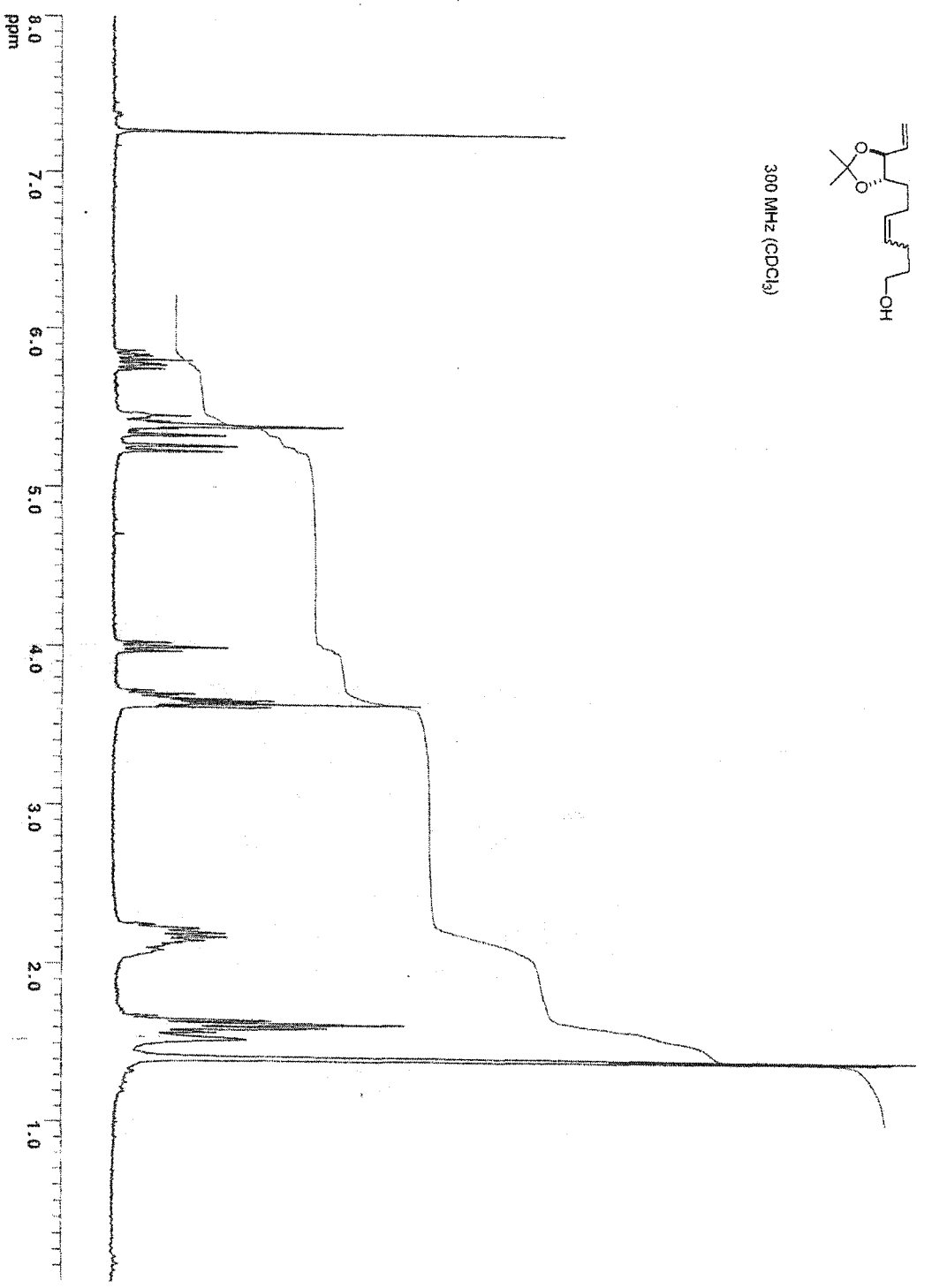


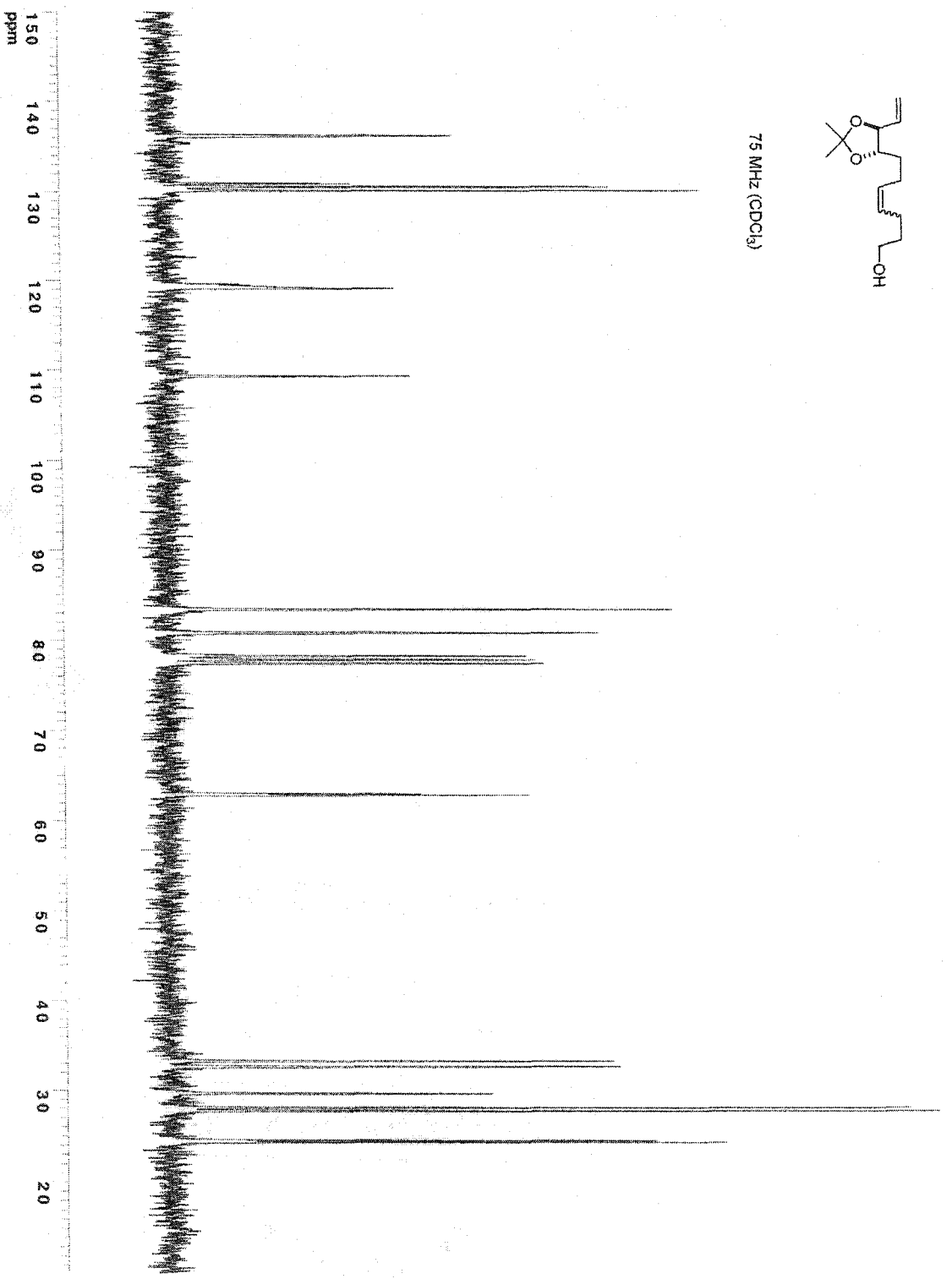


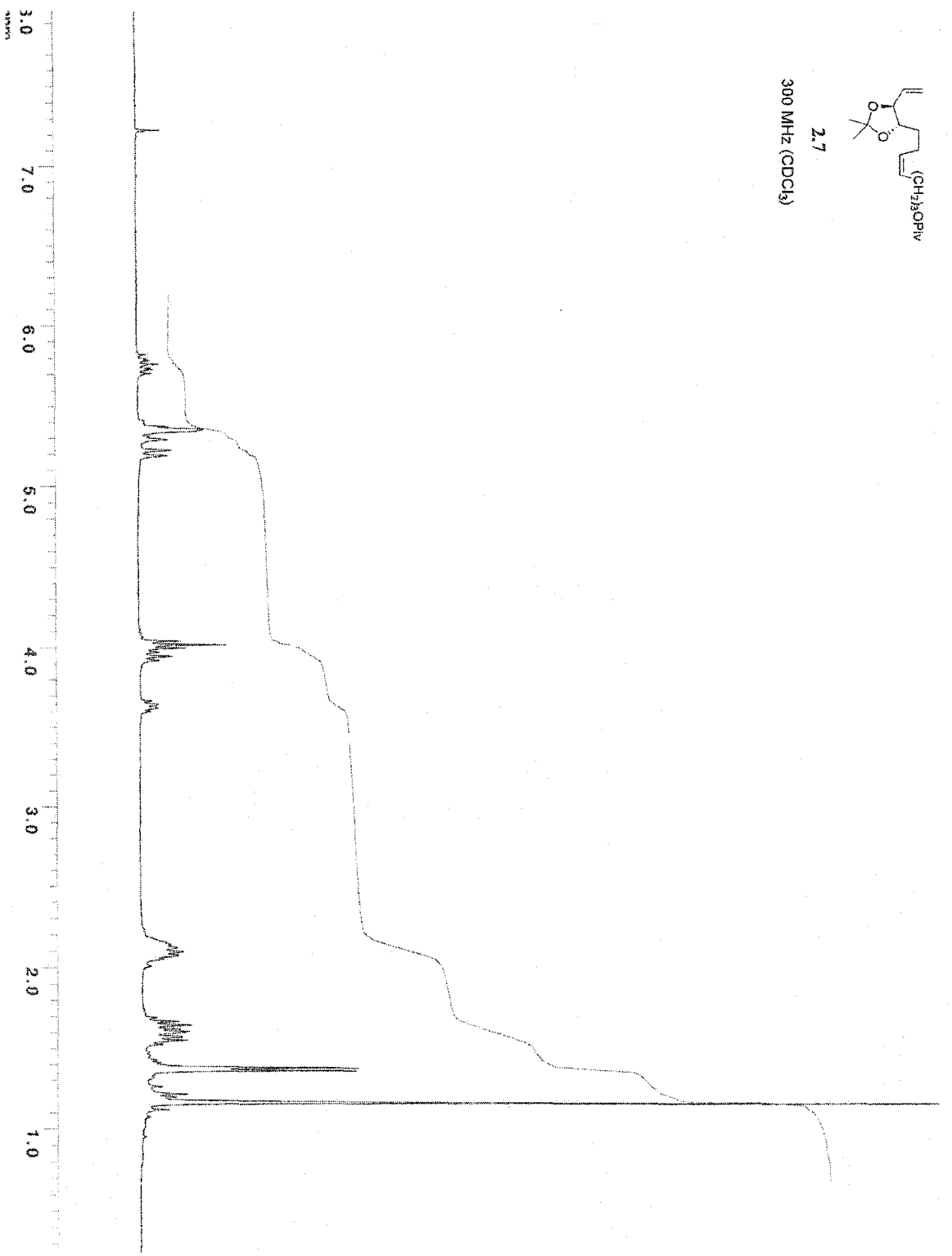


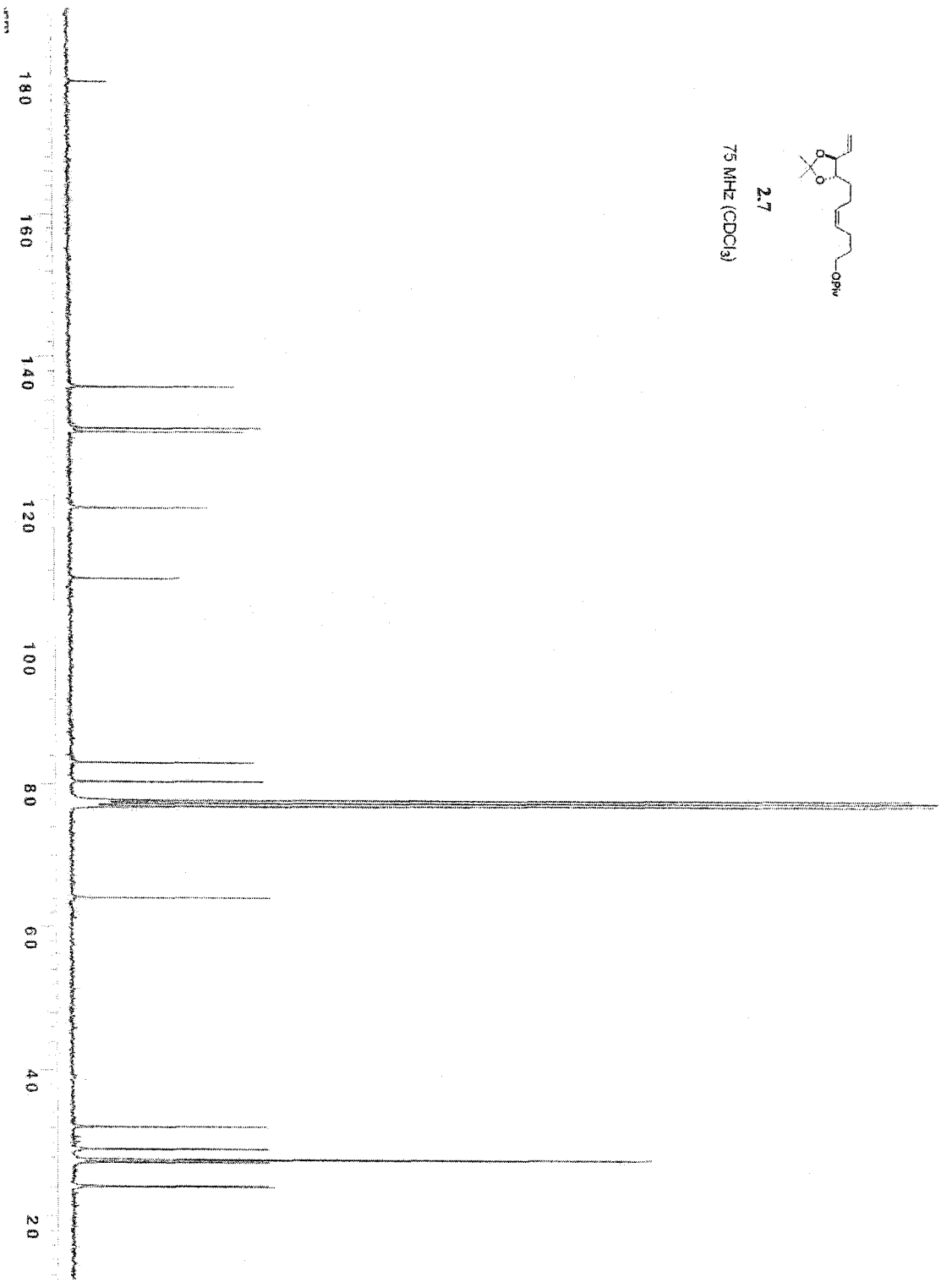
2.71

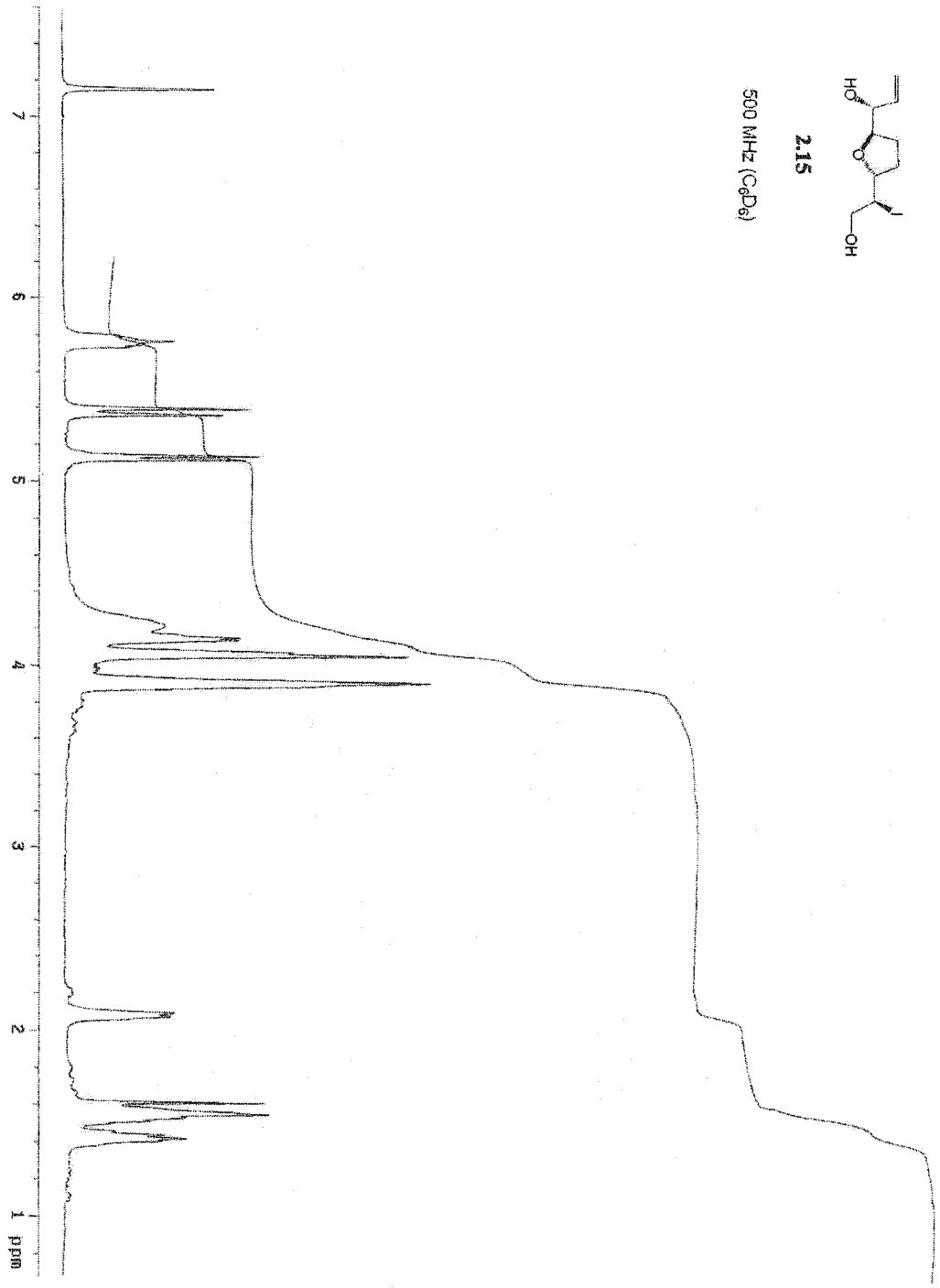
75 MHz ($CDCl_3$)

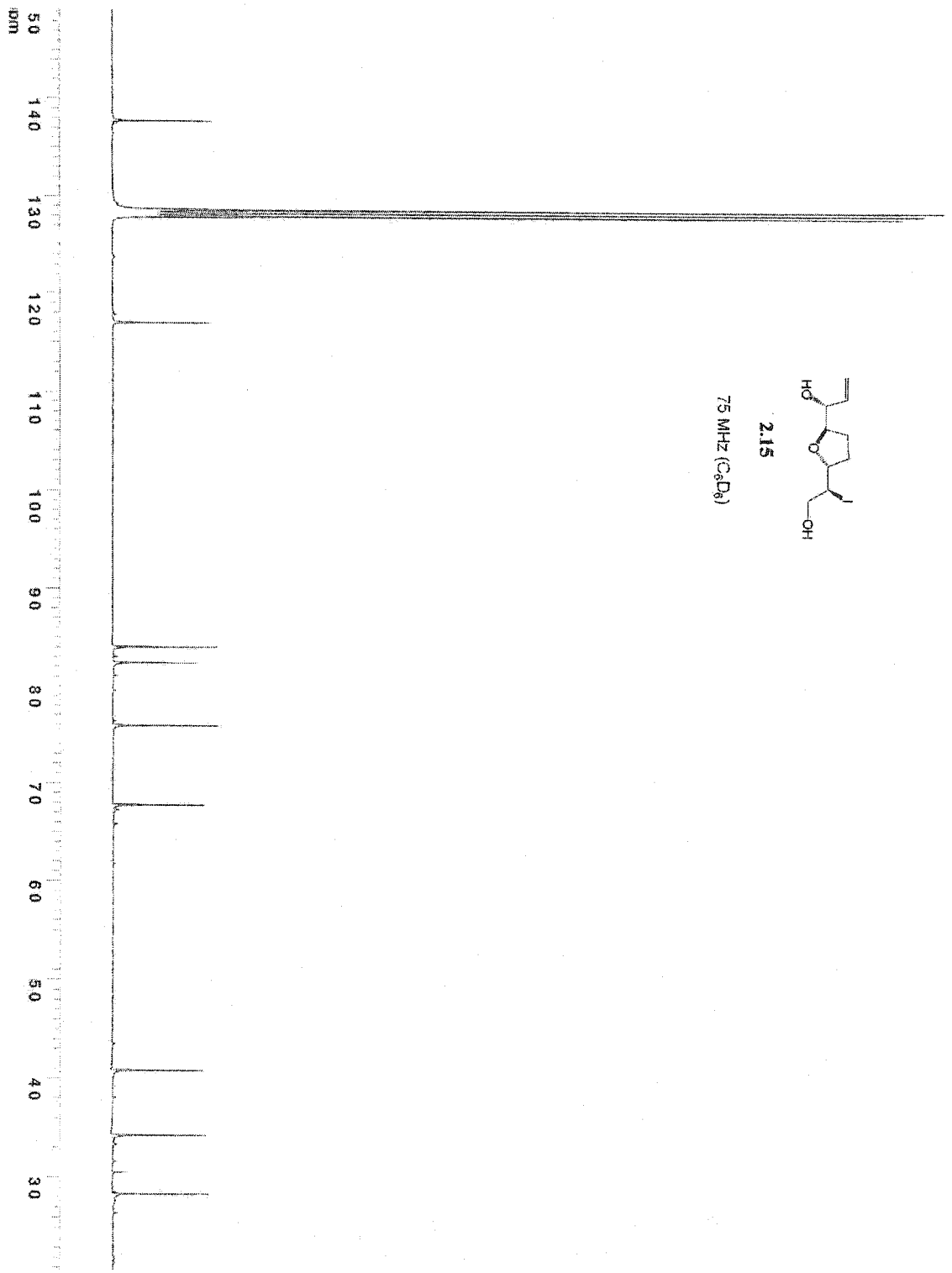


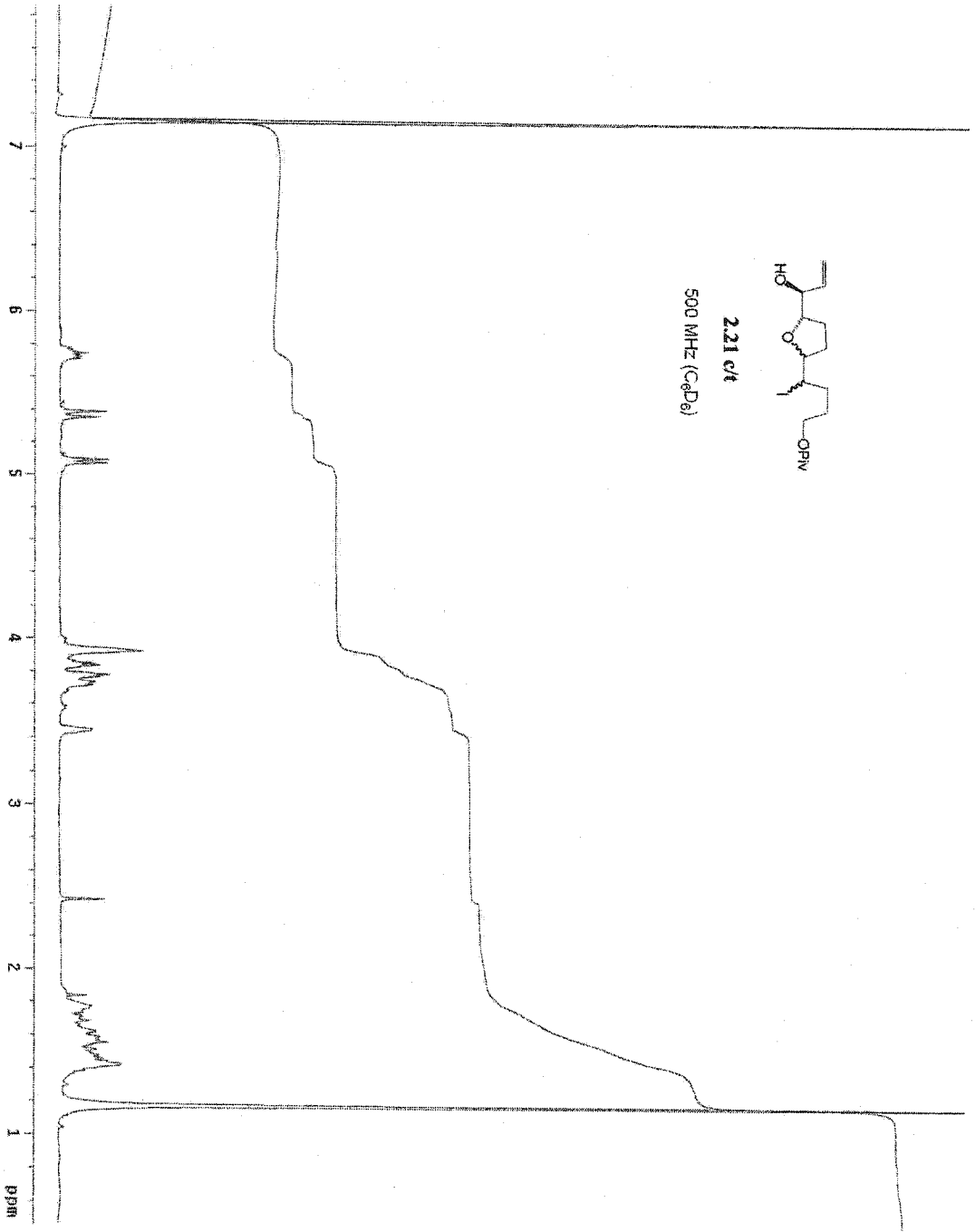


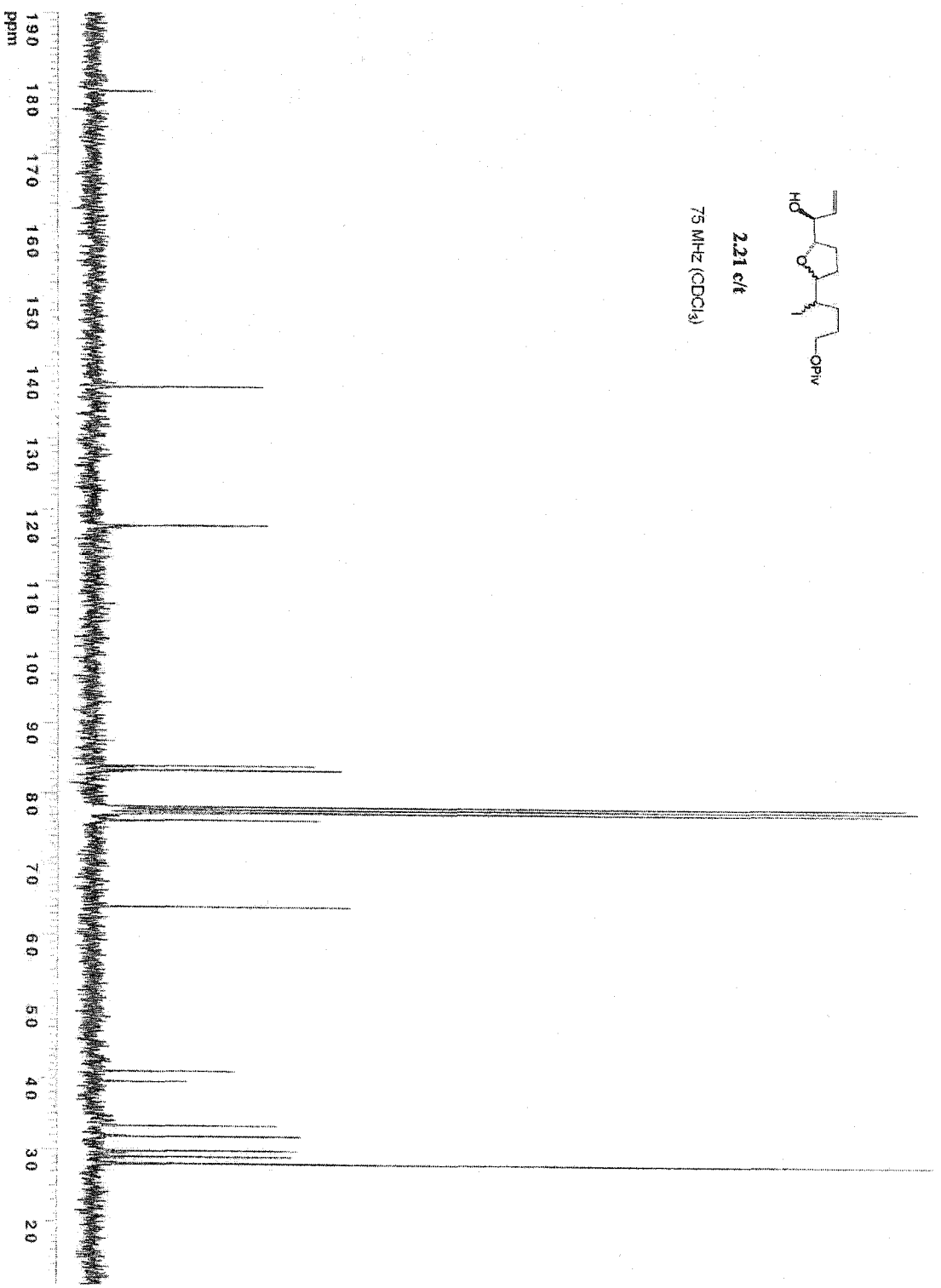


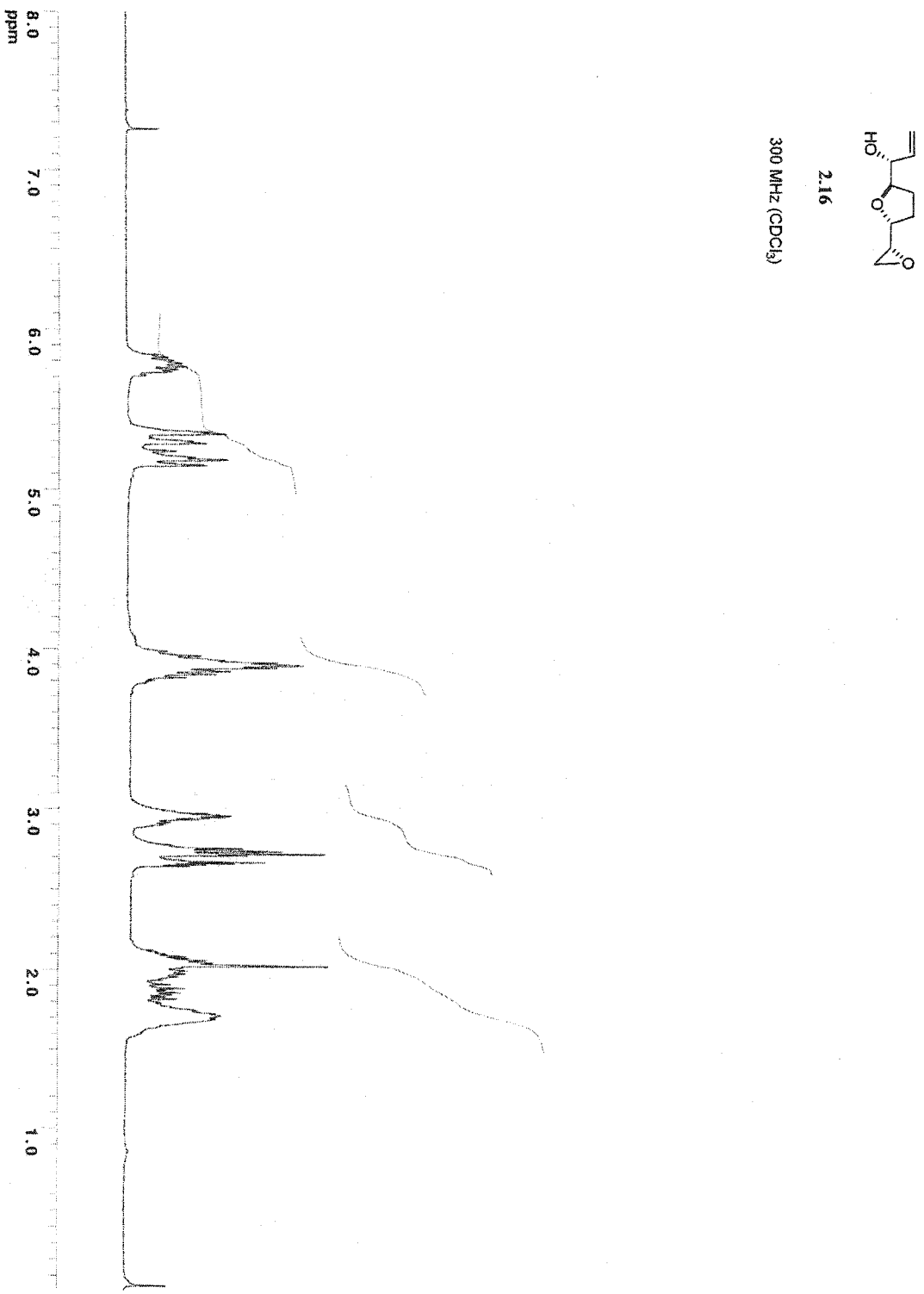


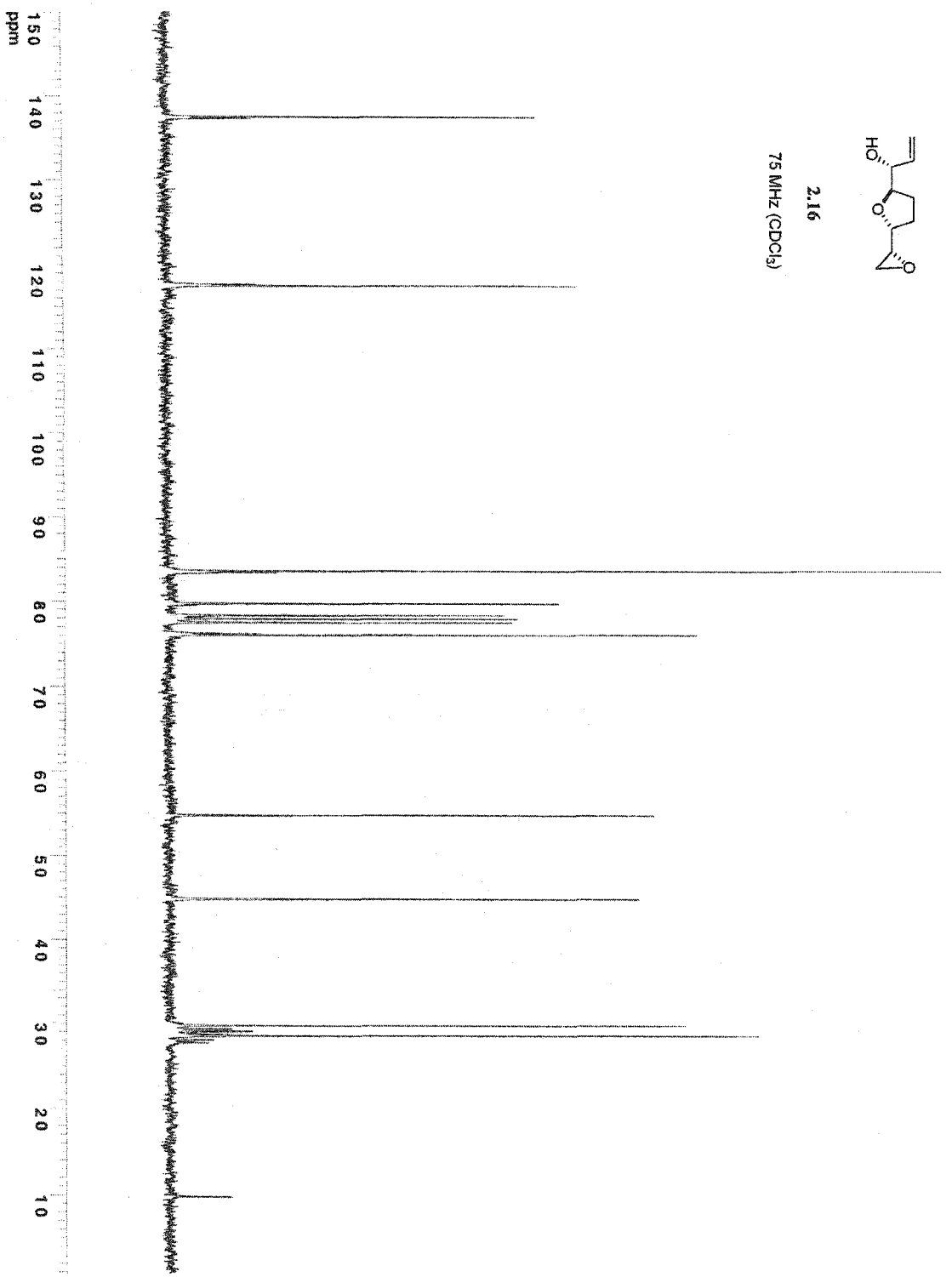


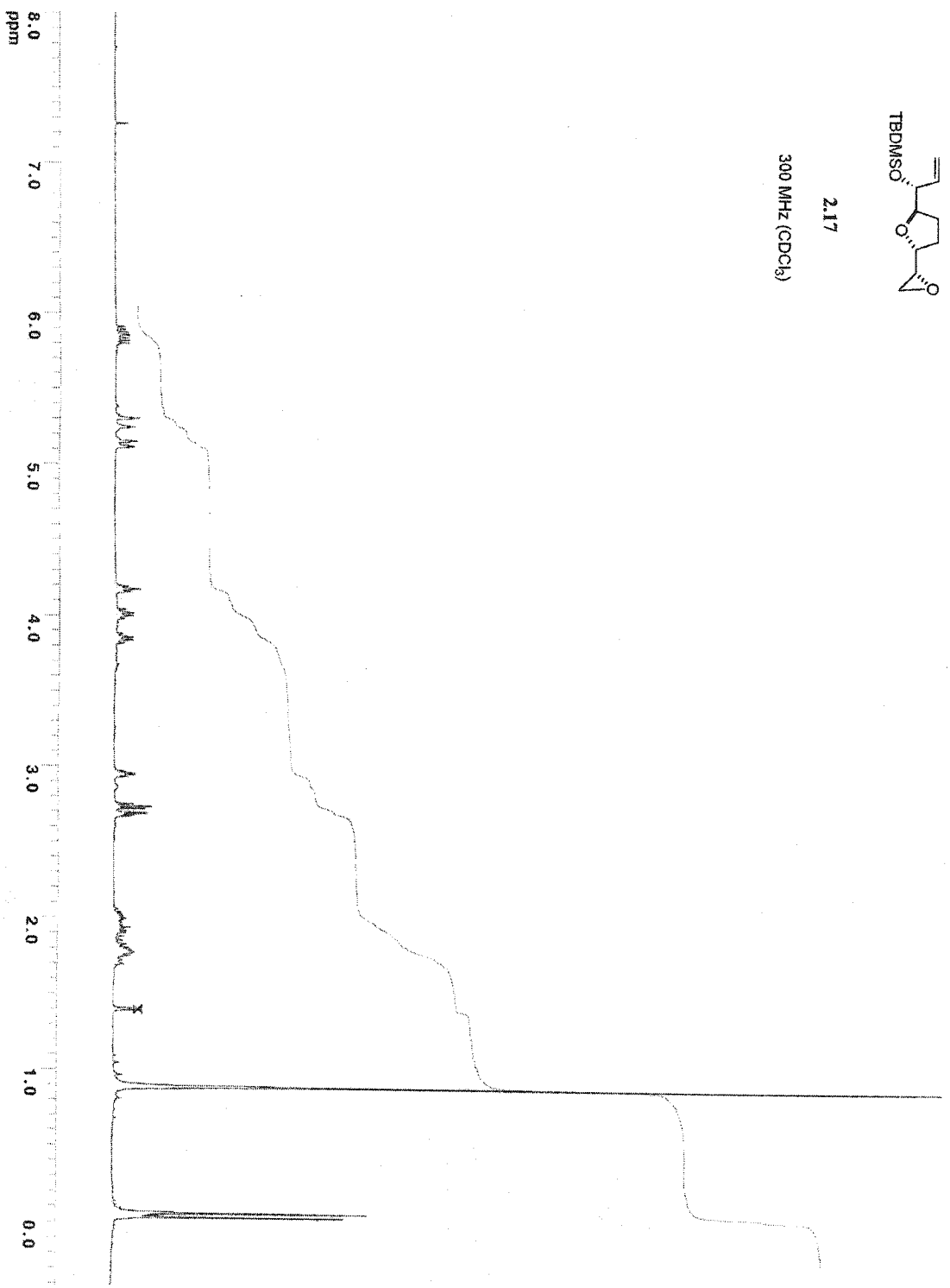


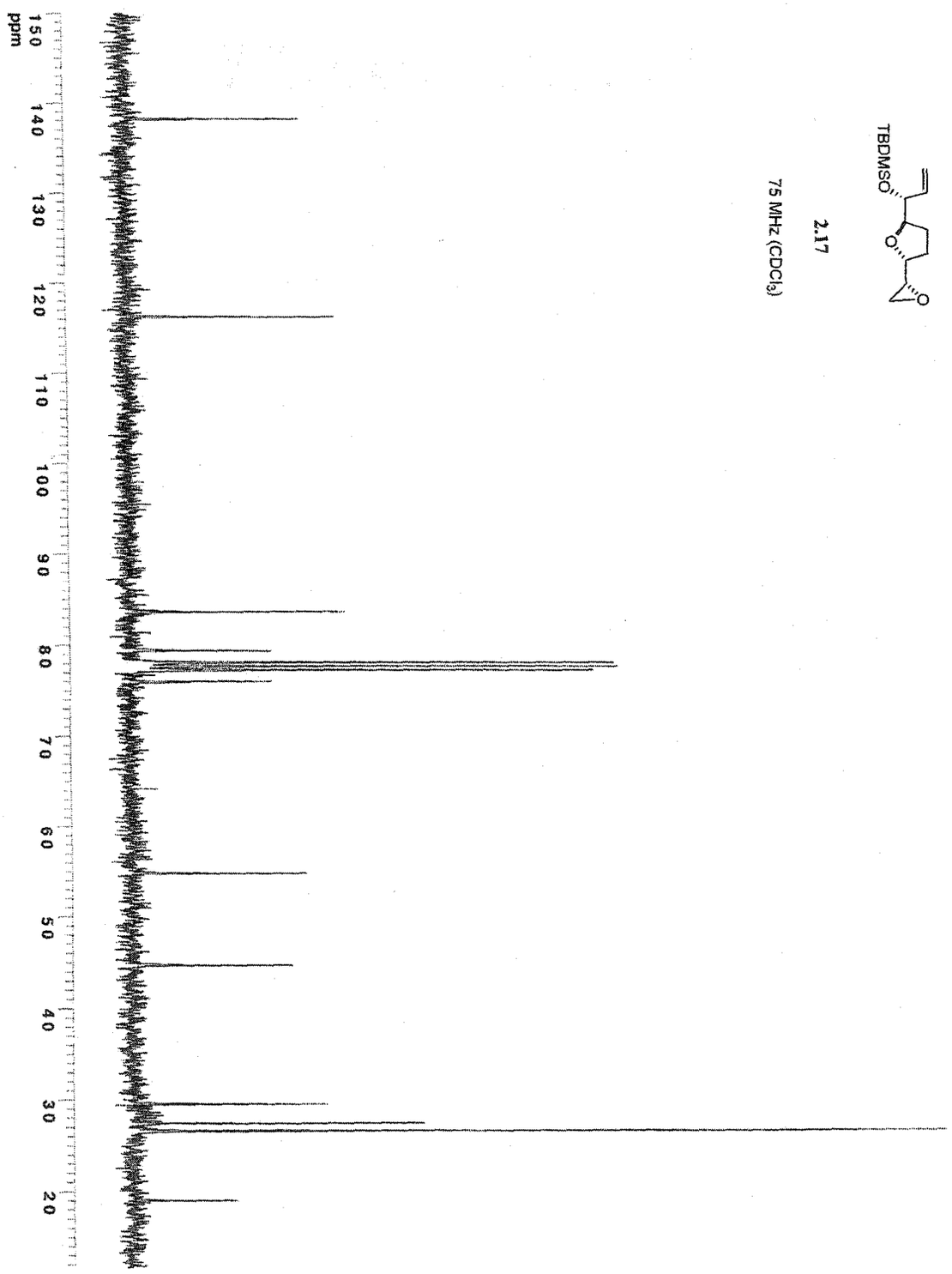


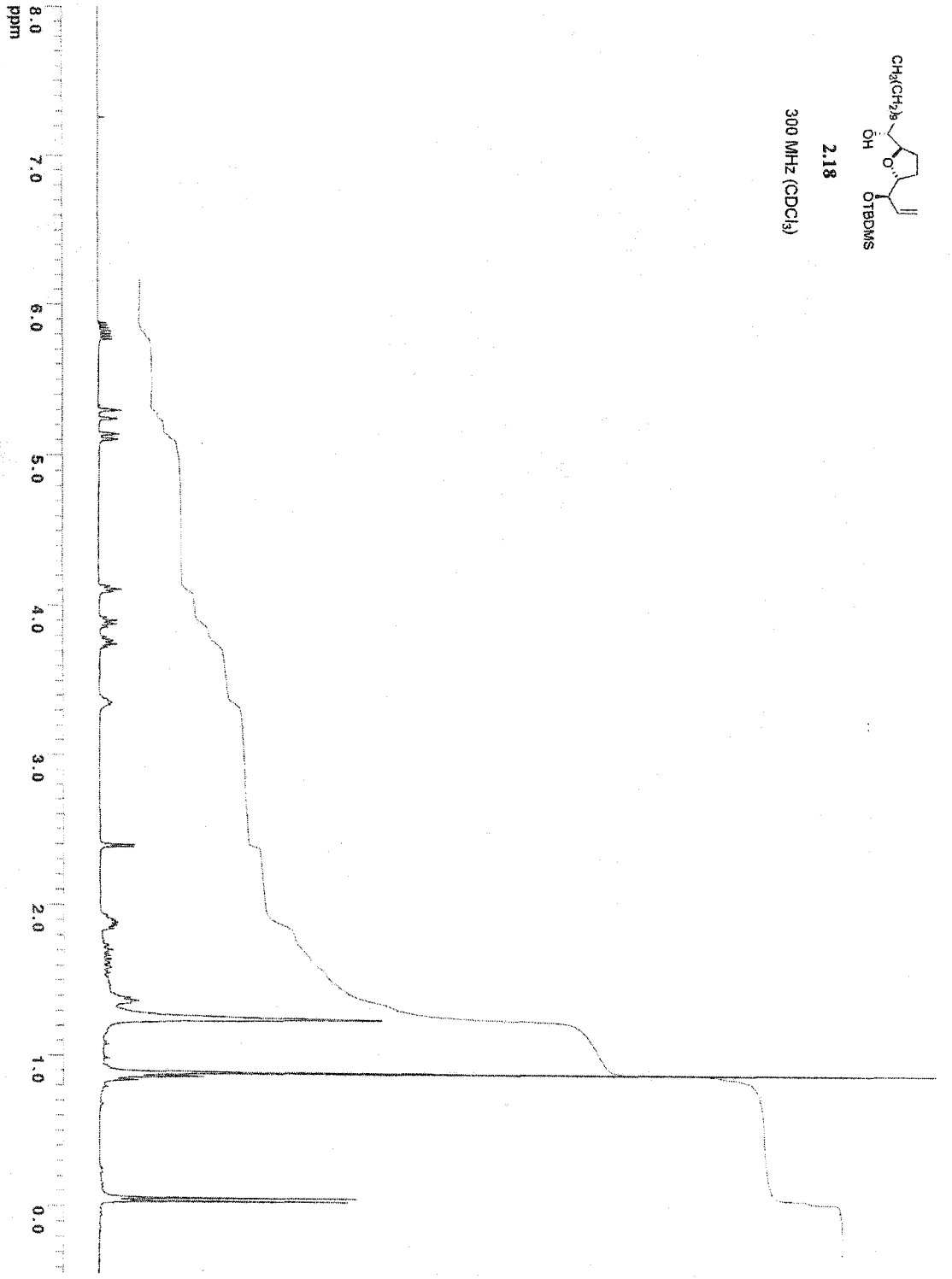


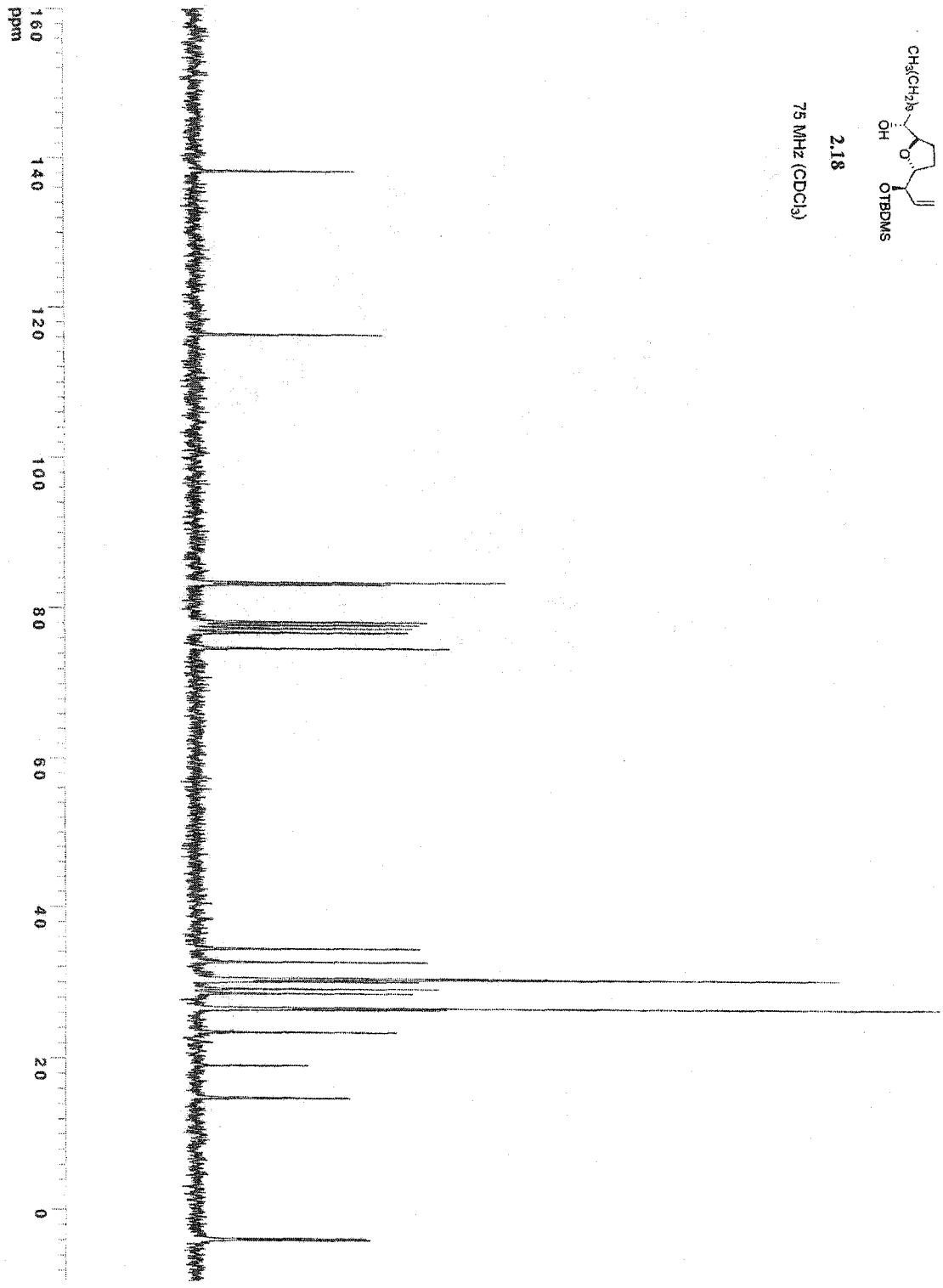


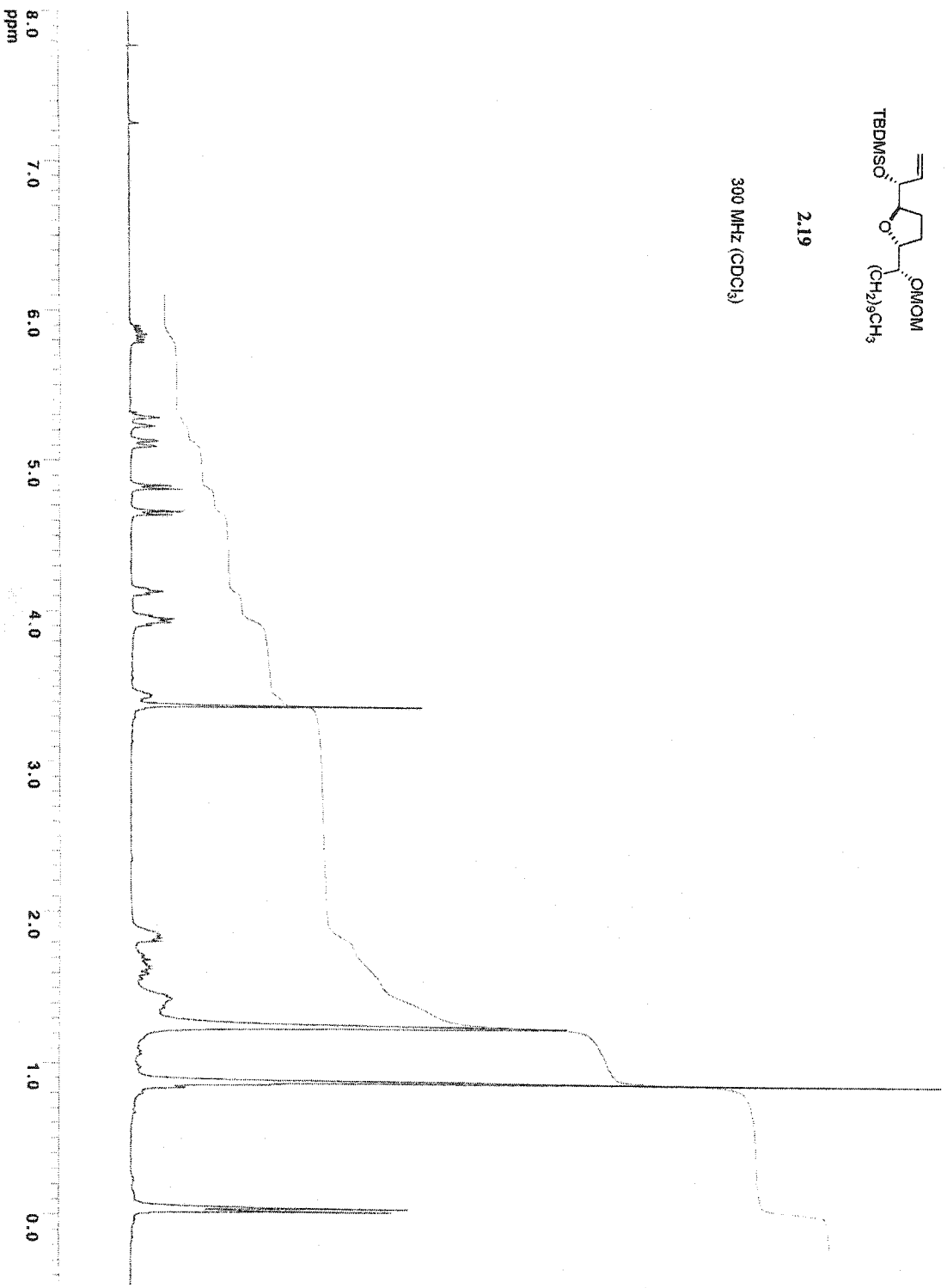


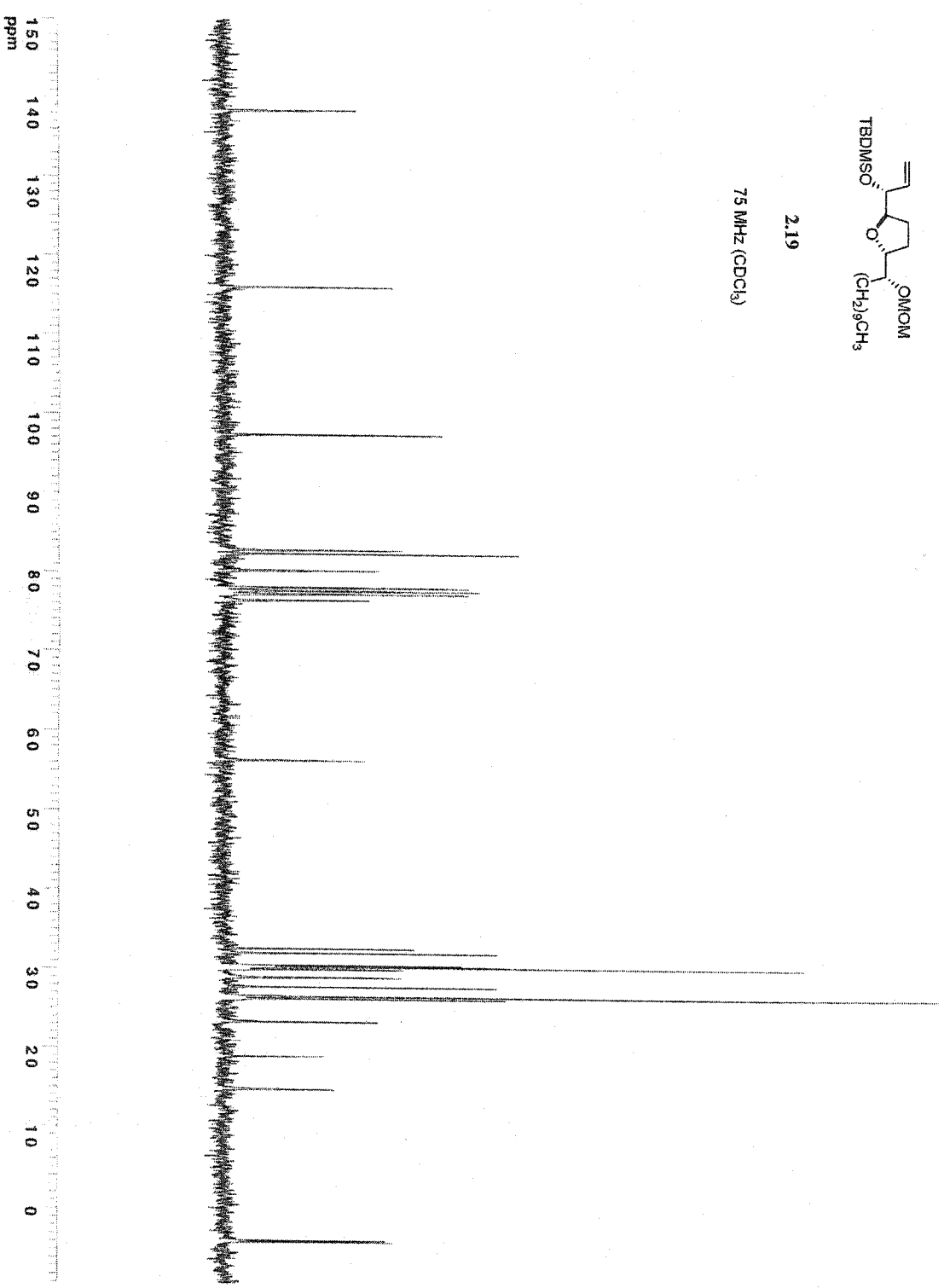


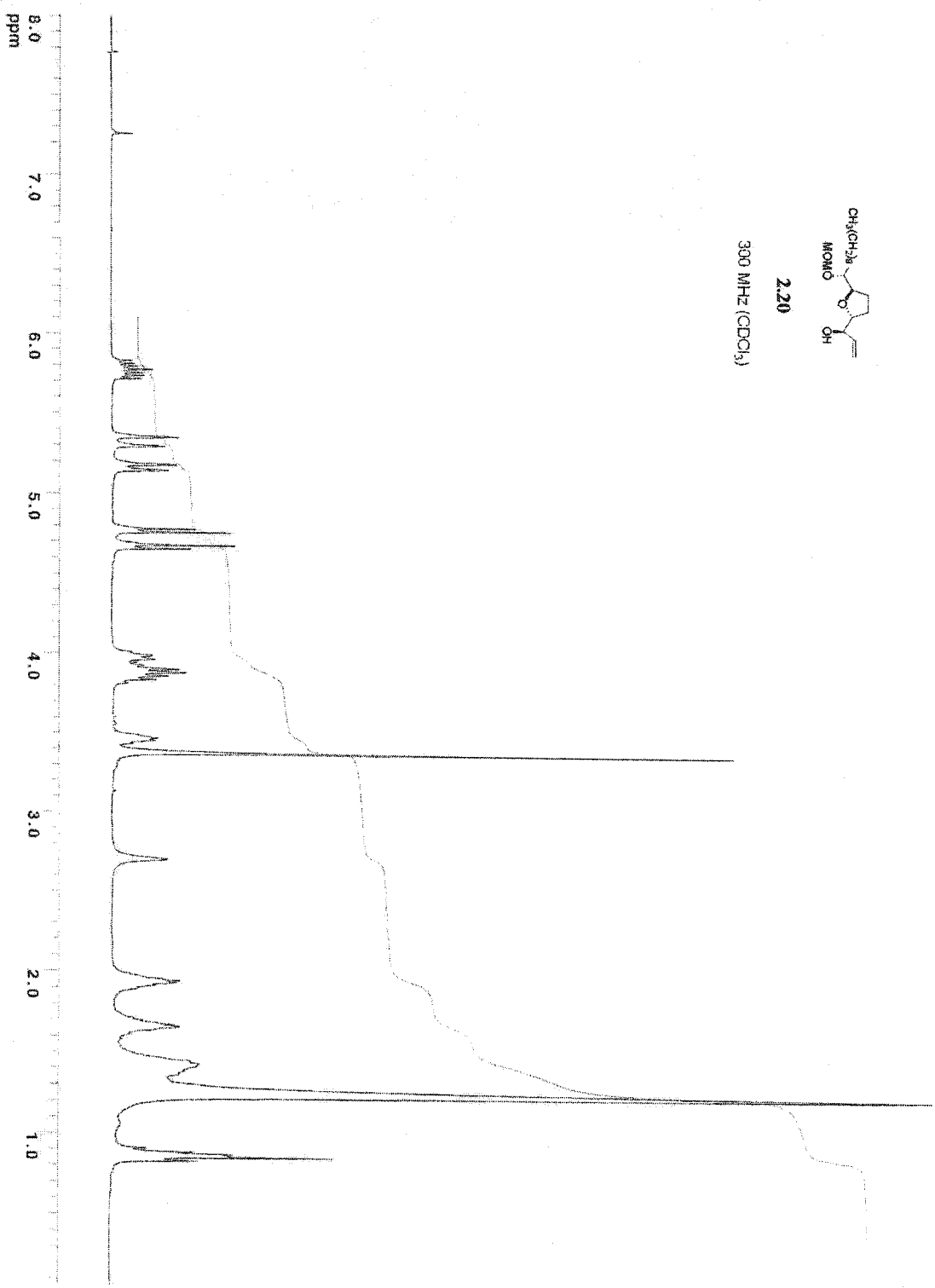


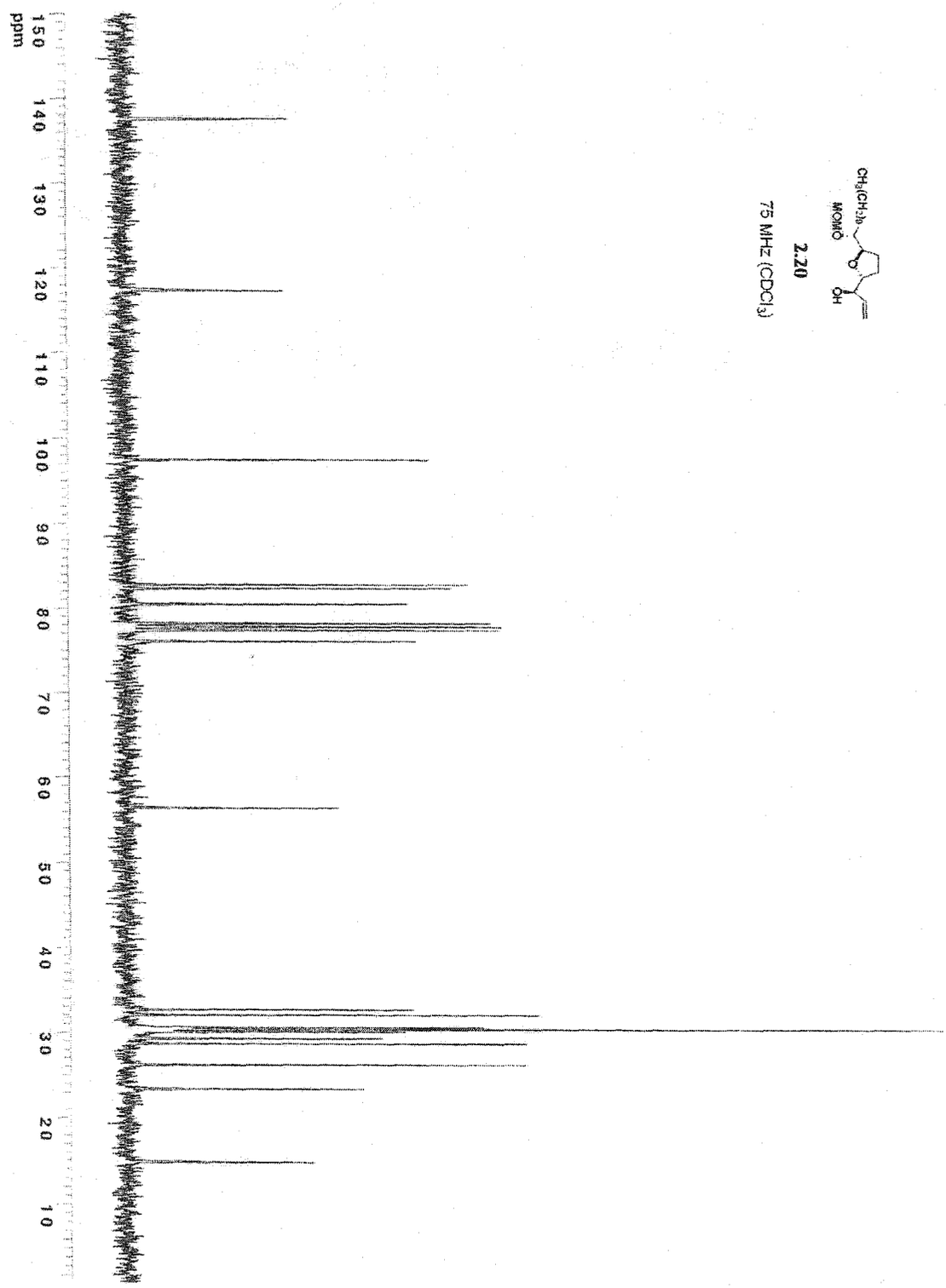


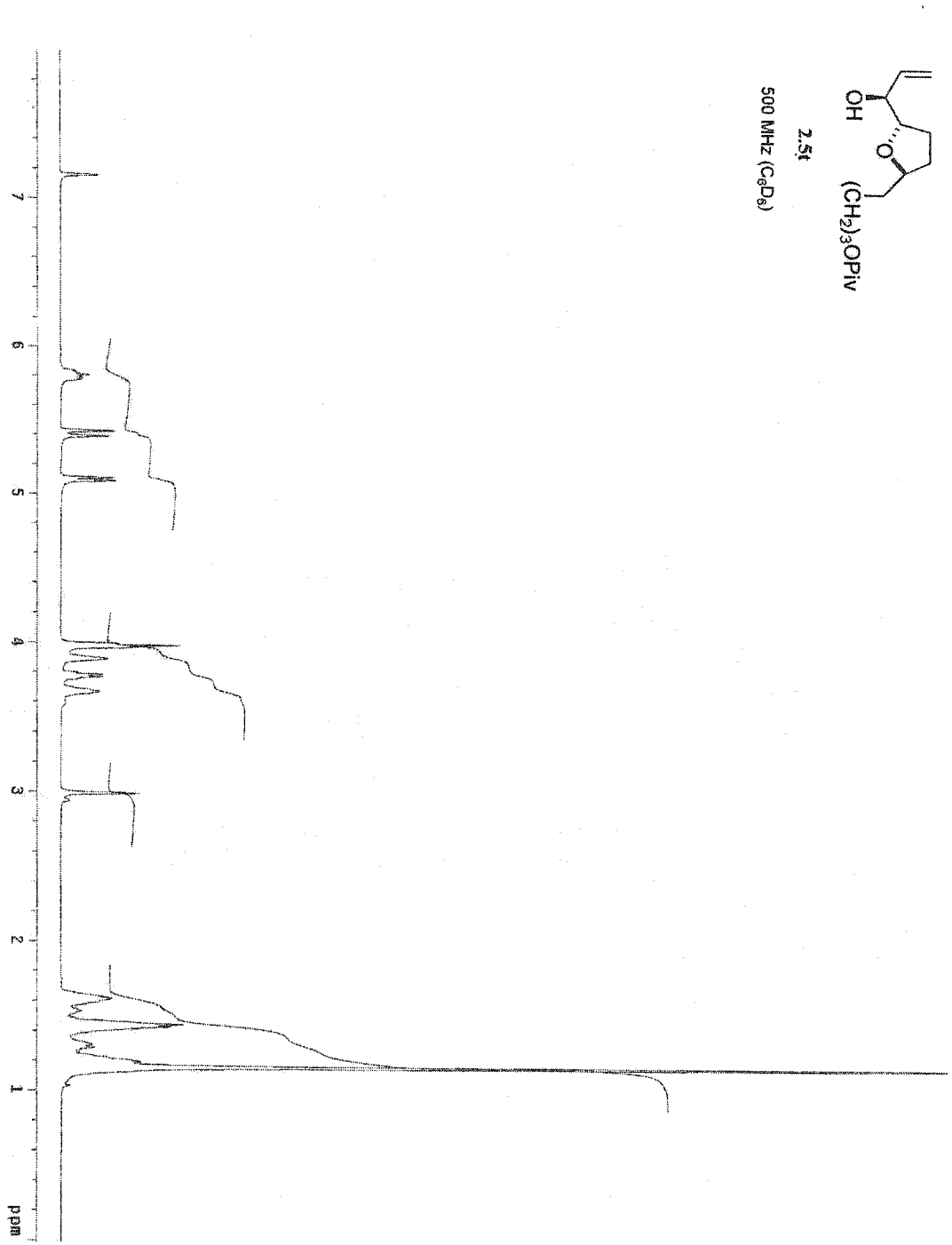


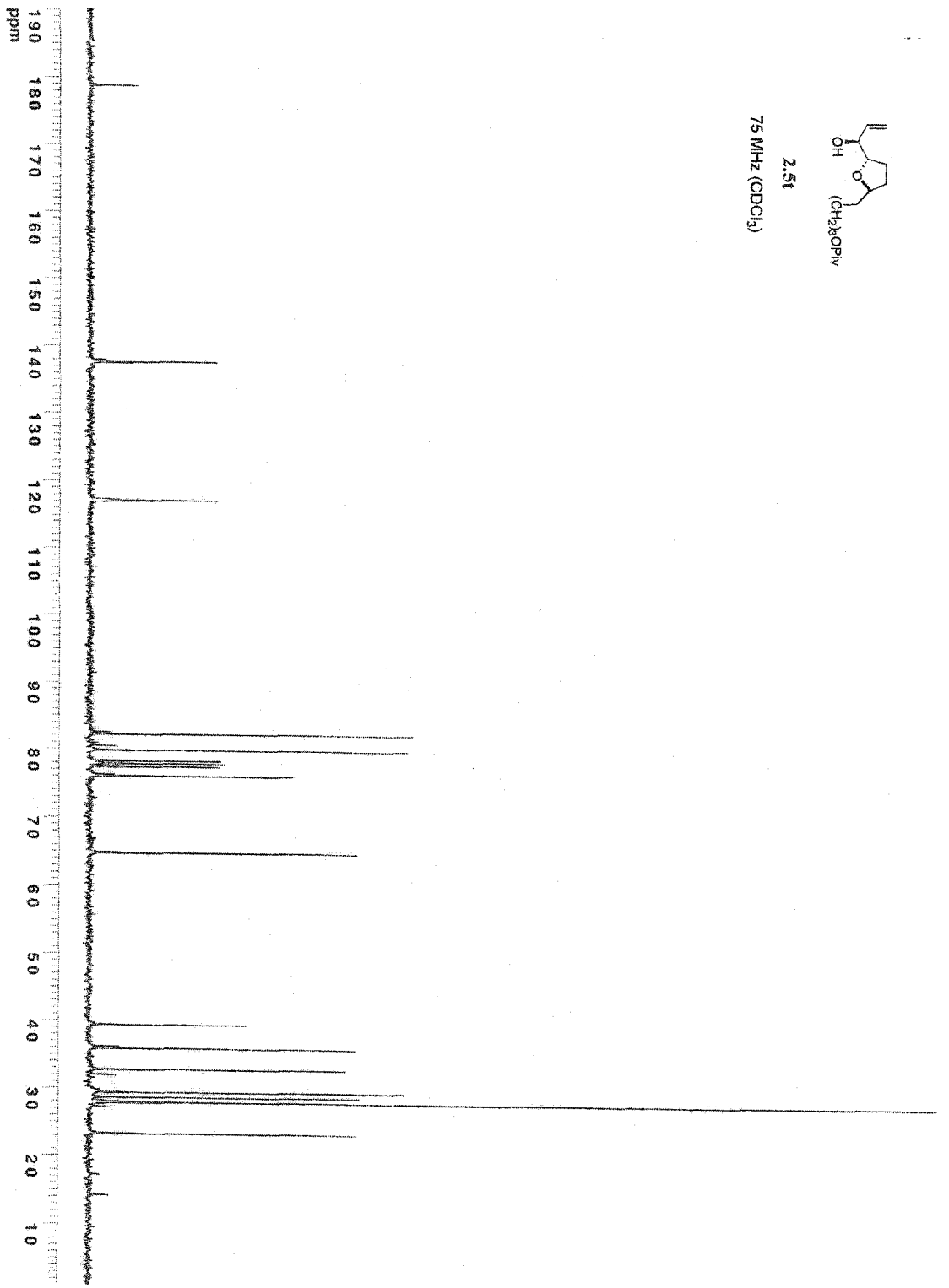


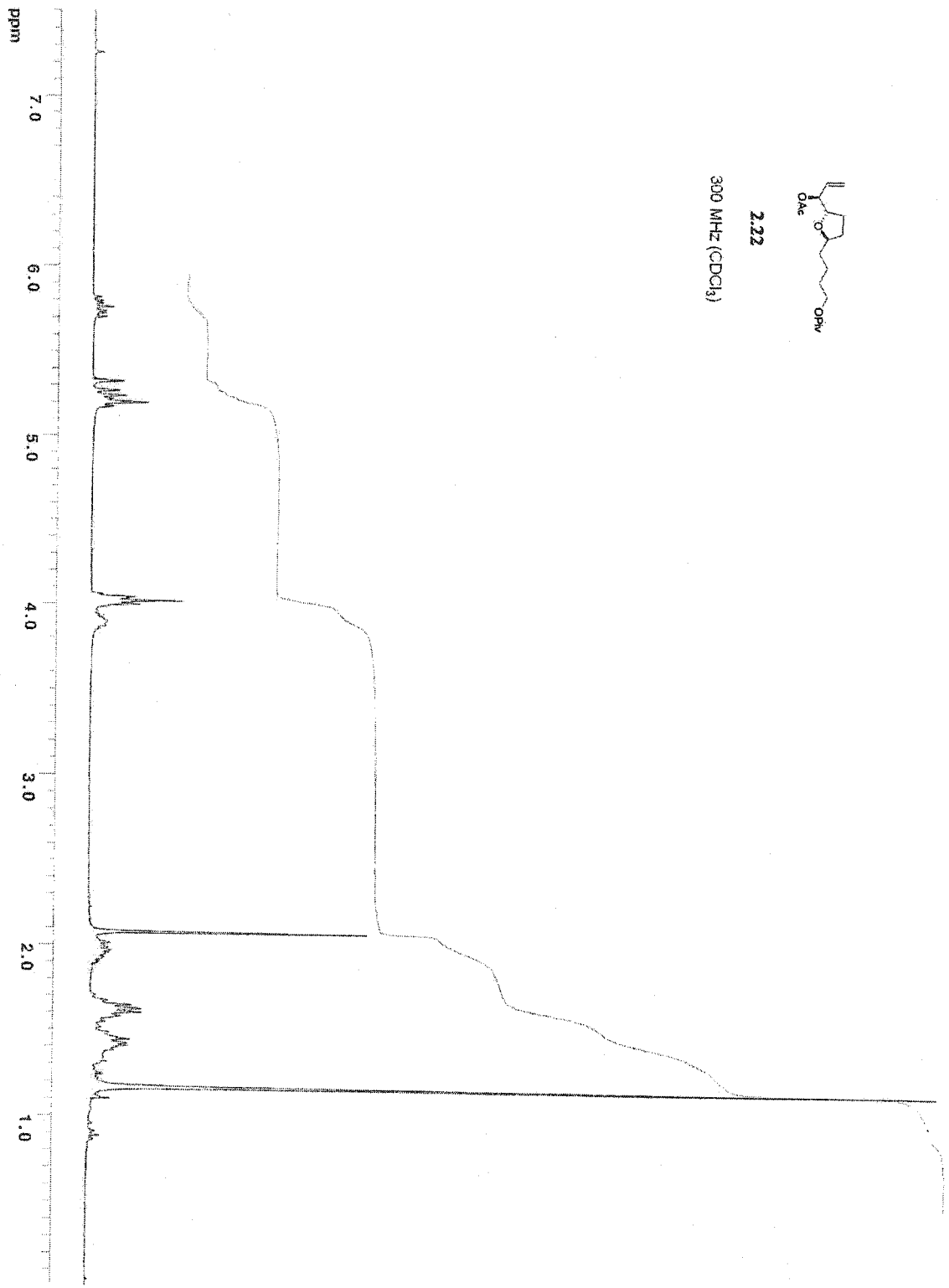


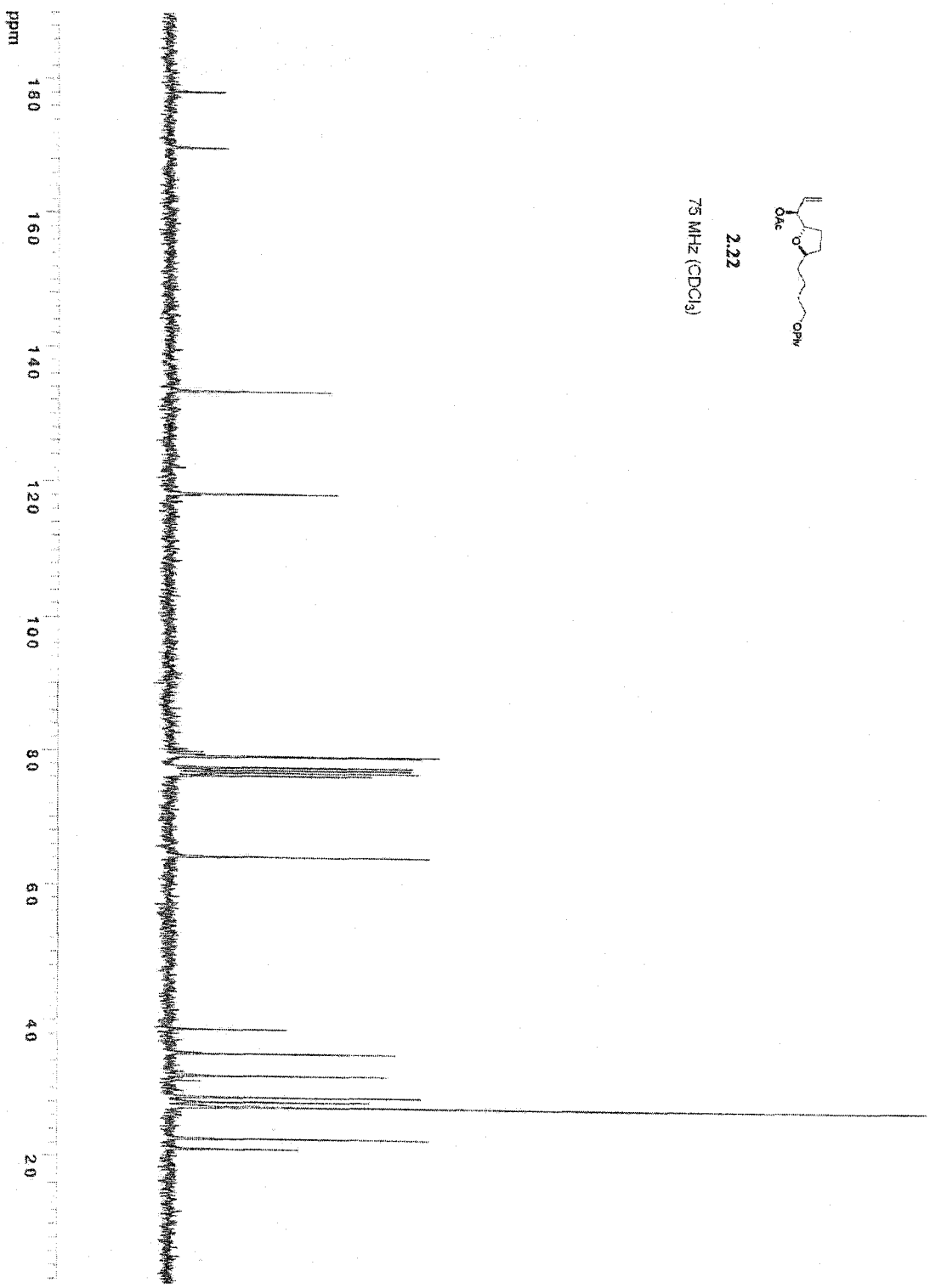


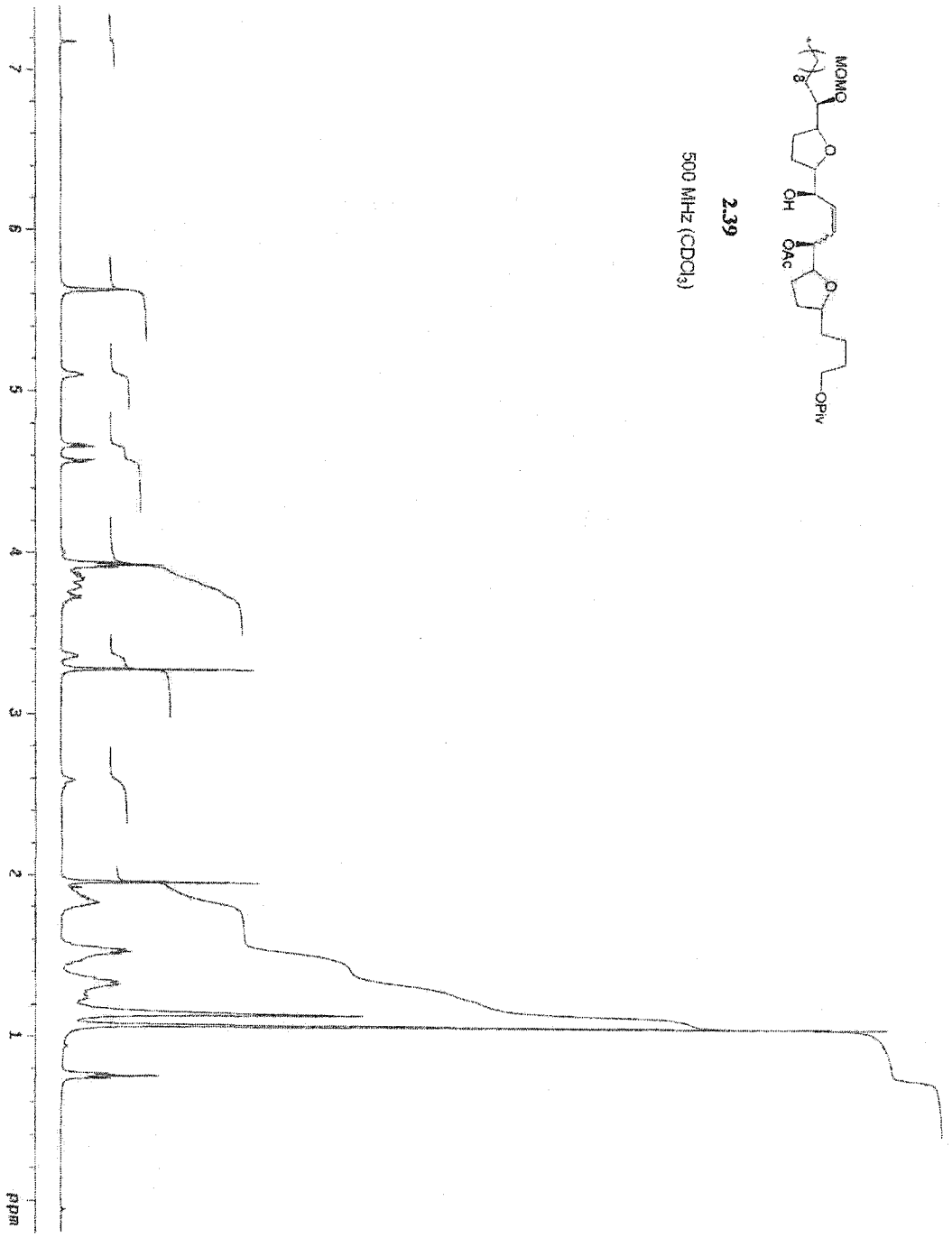


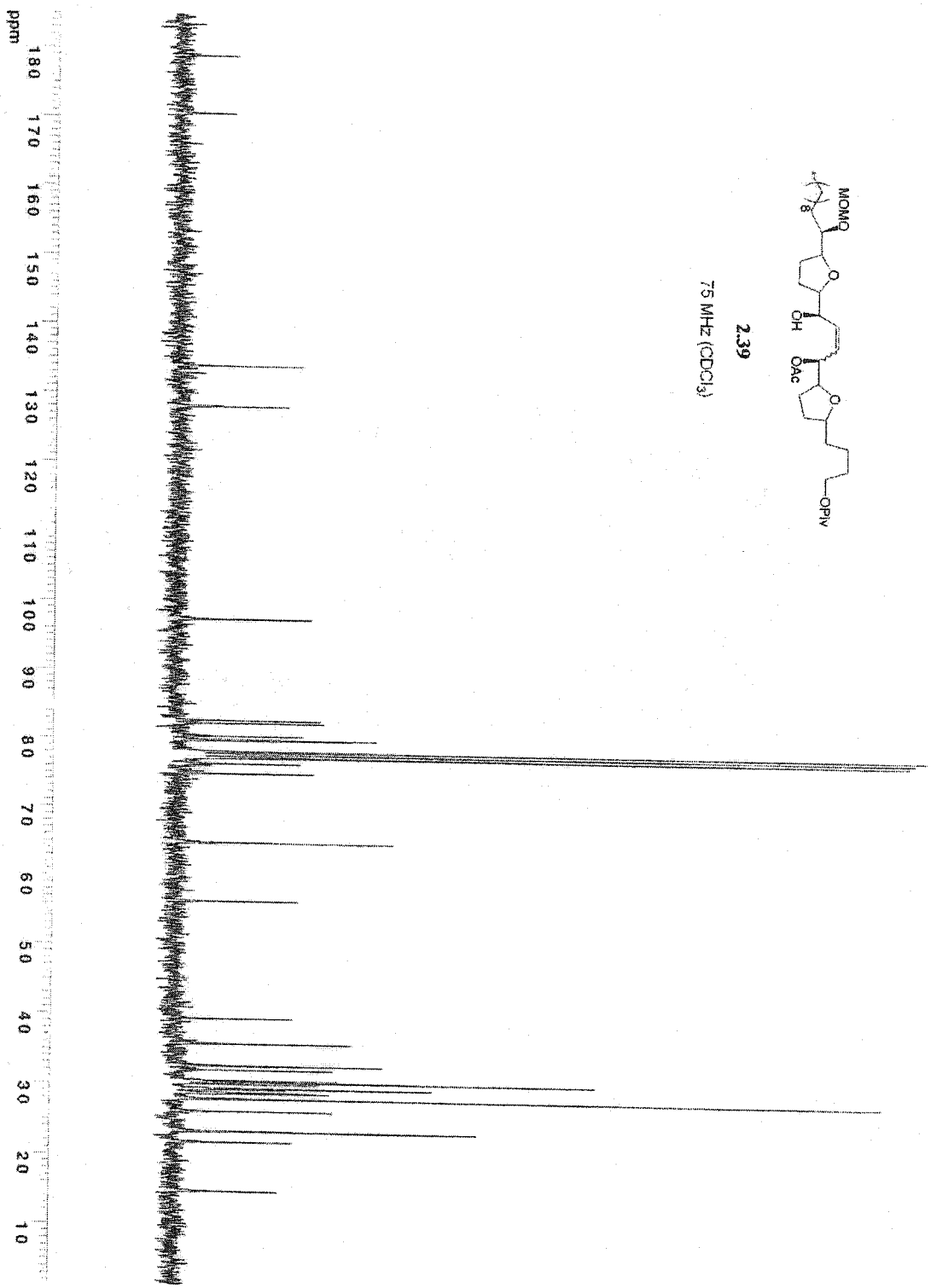


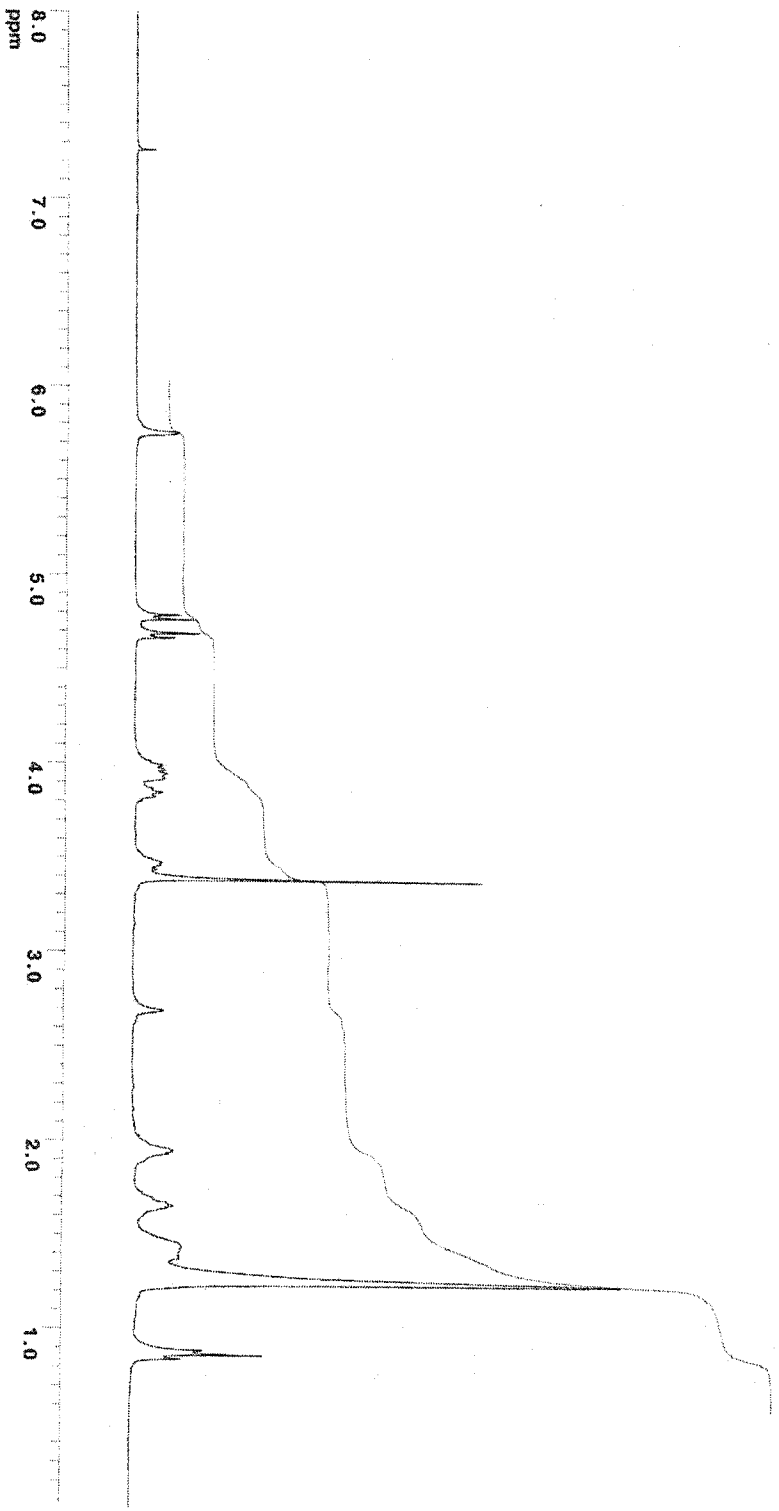


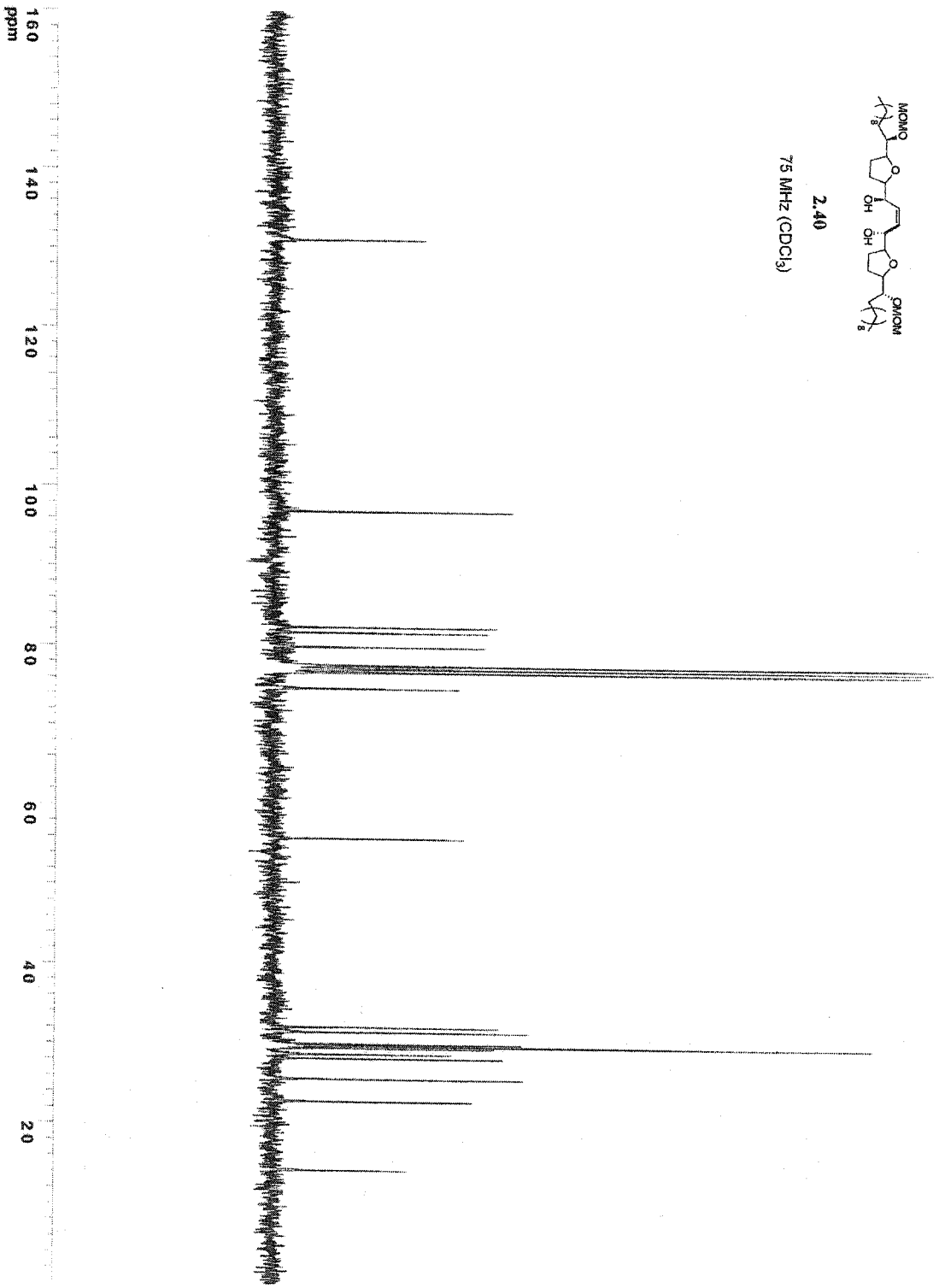


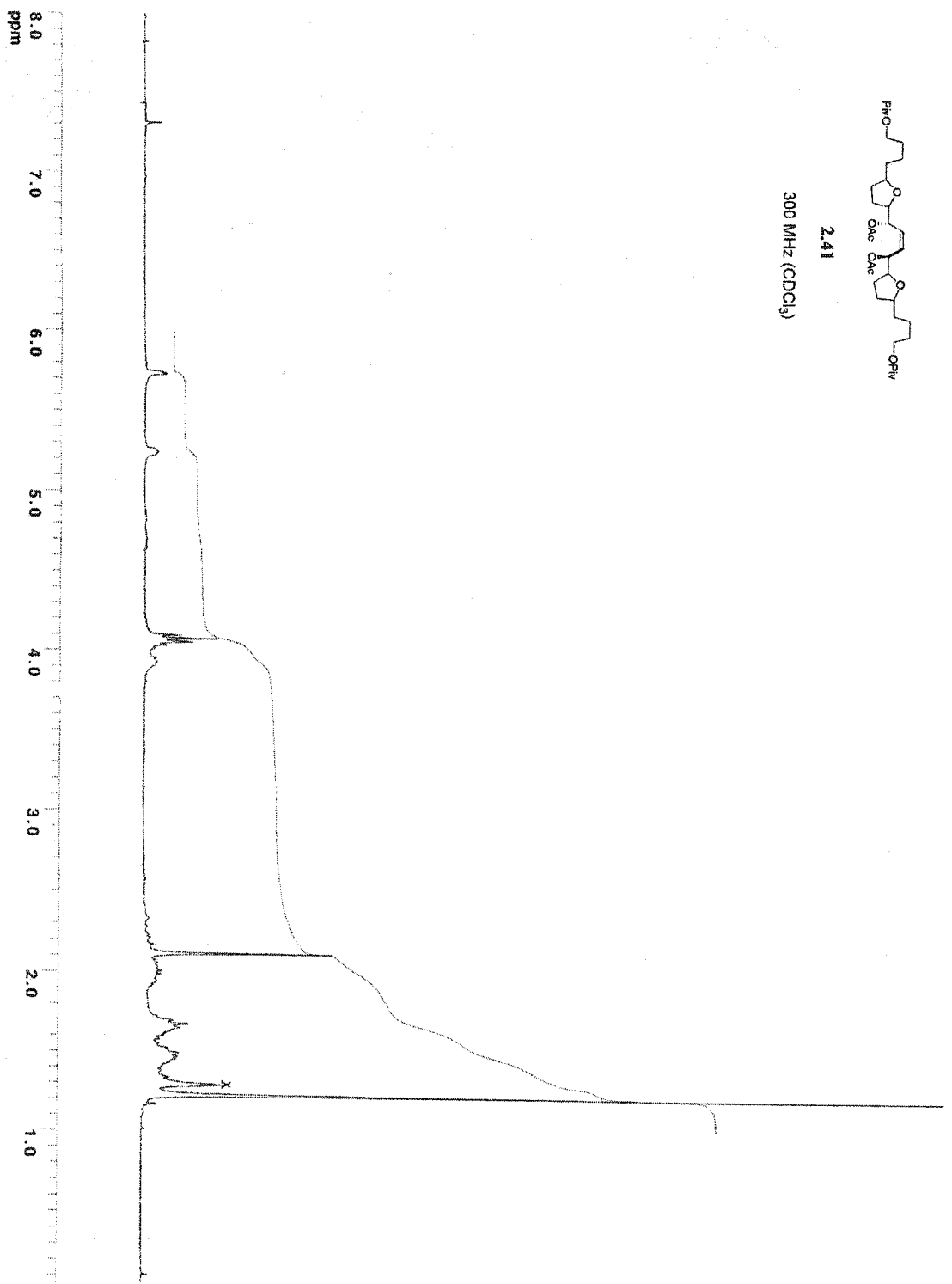


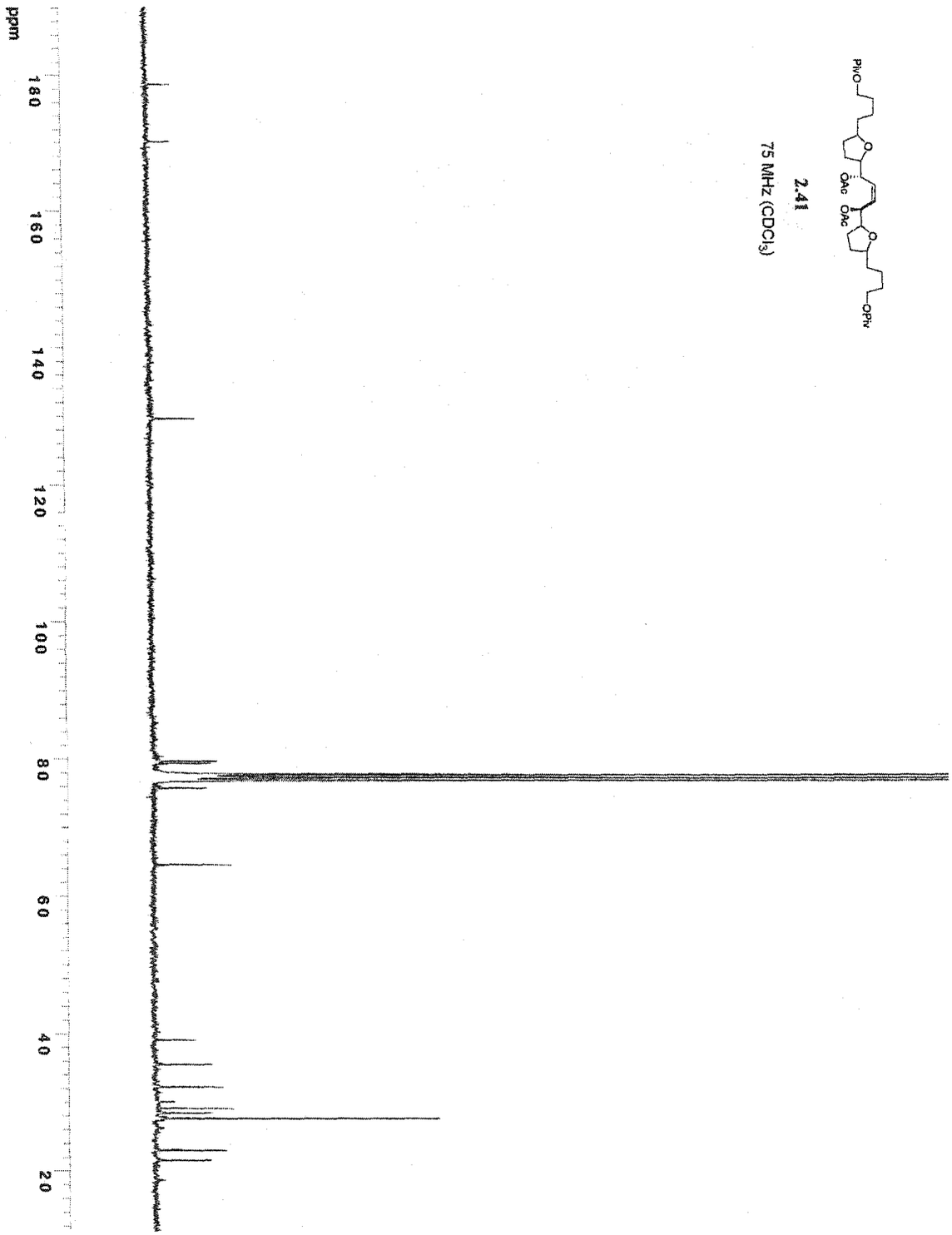


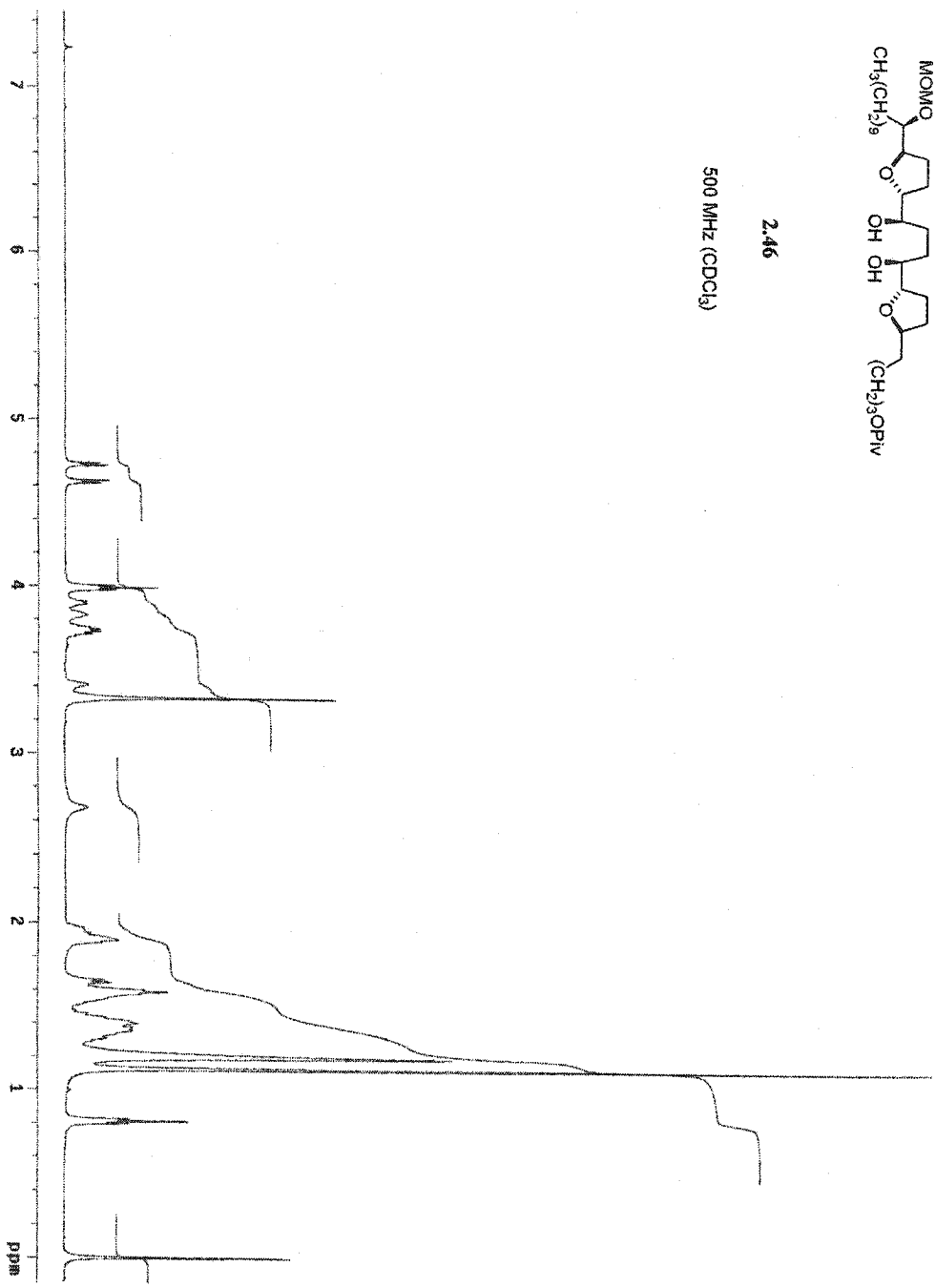


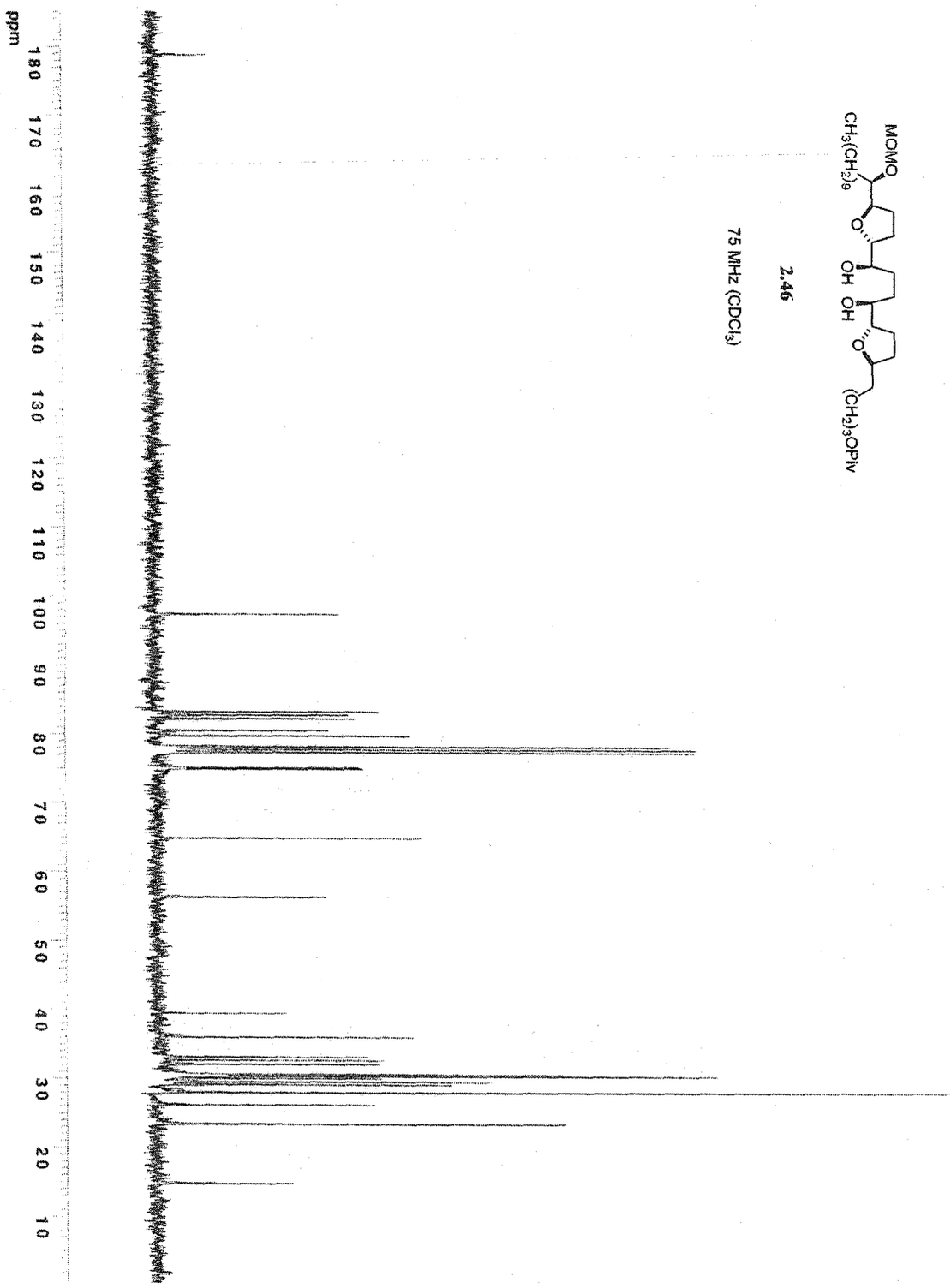


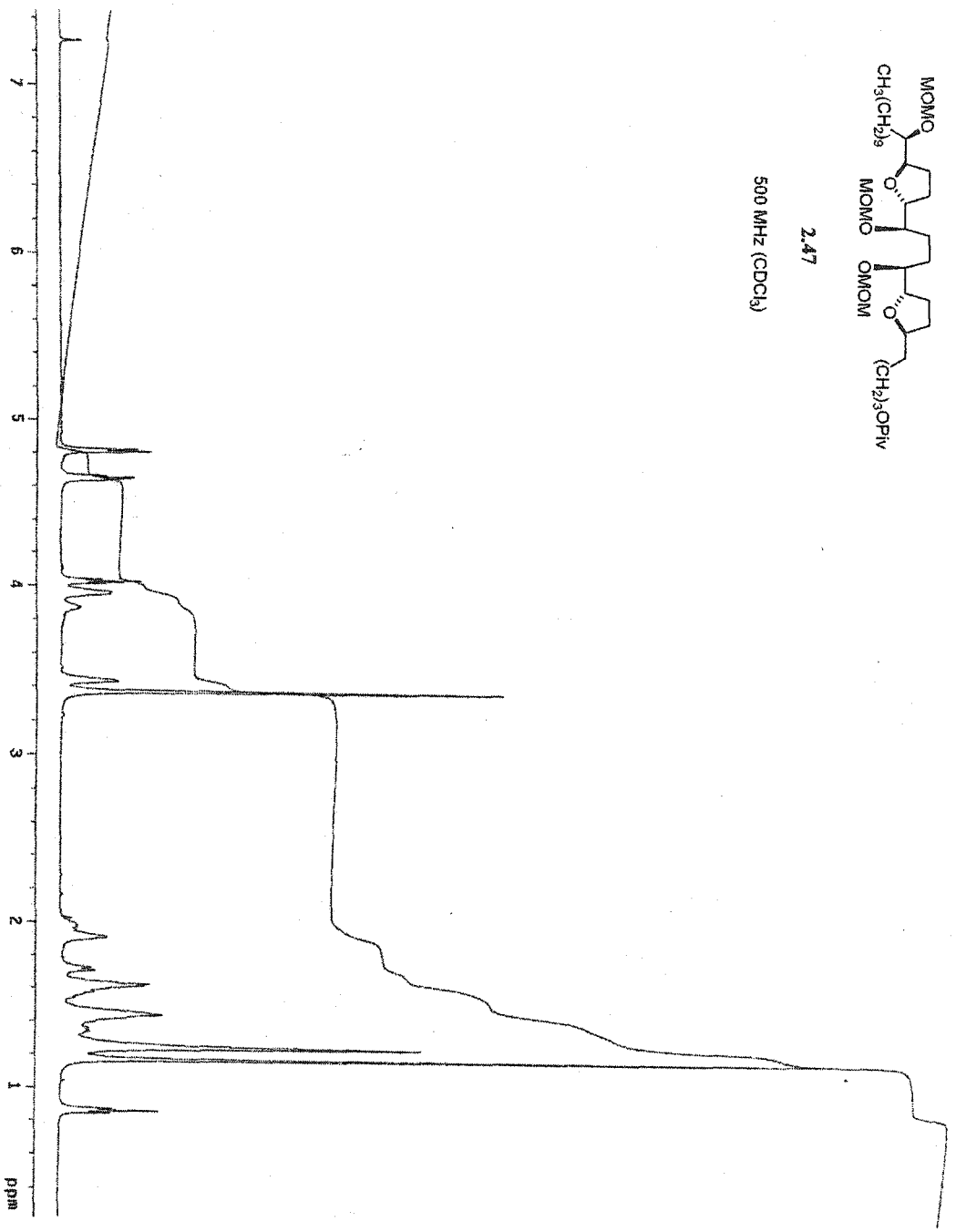


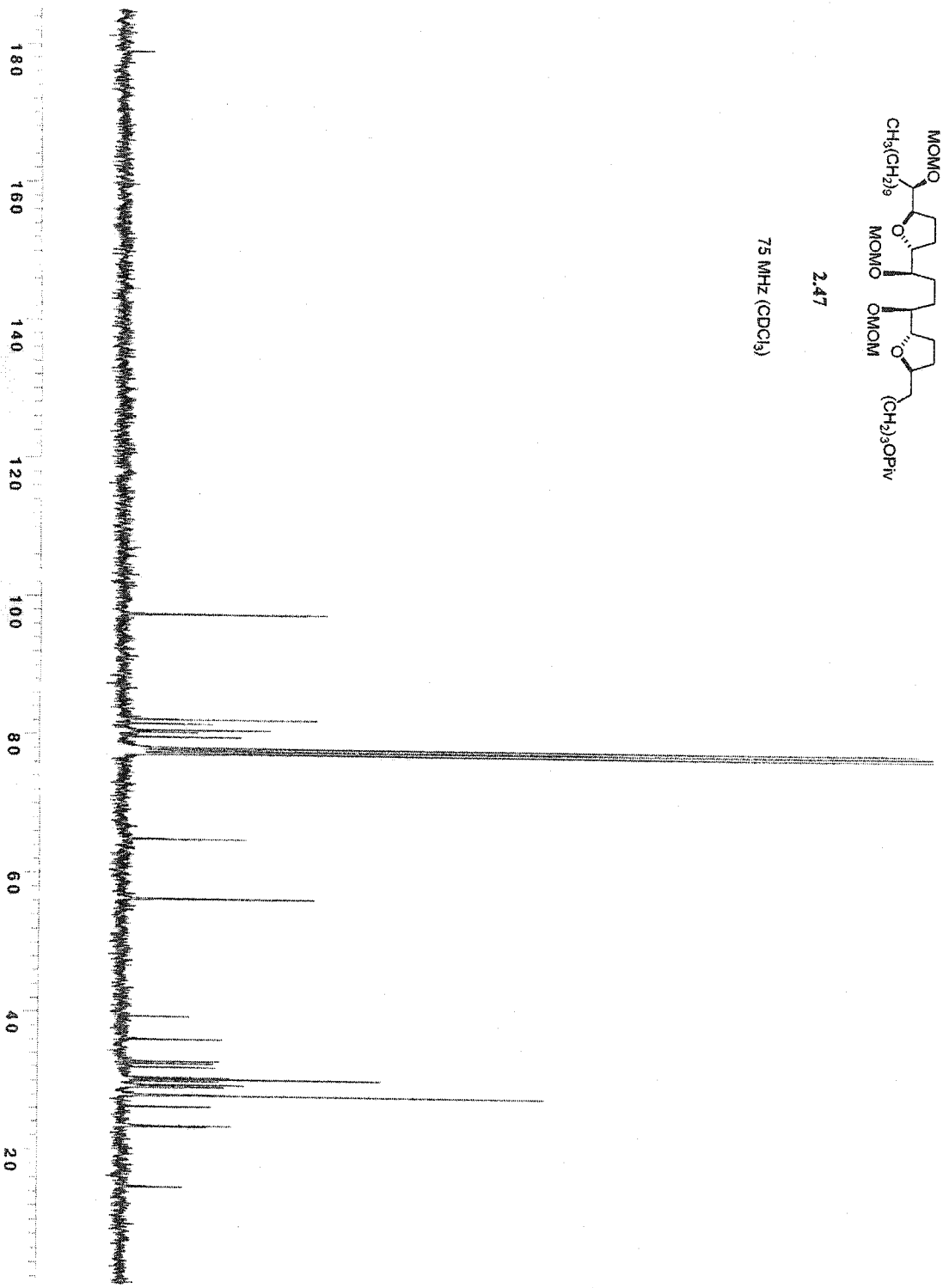


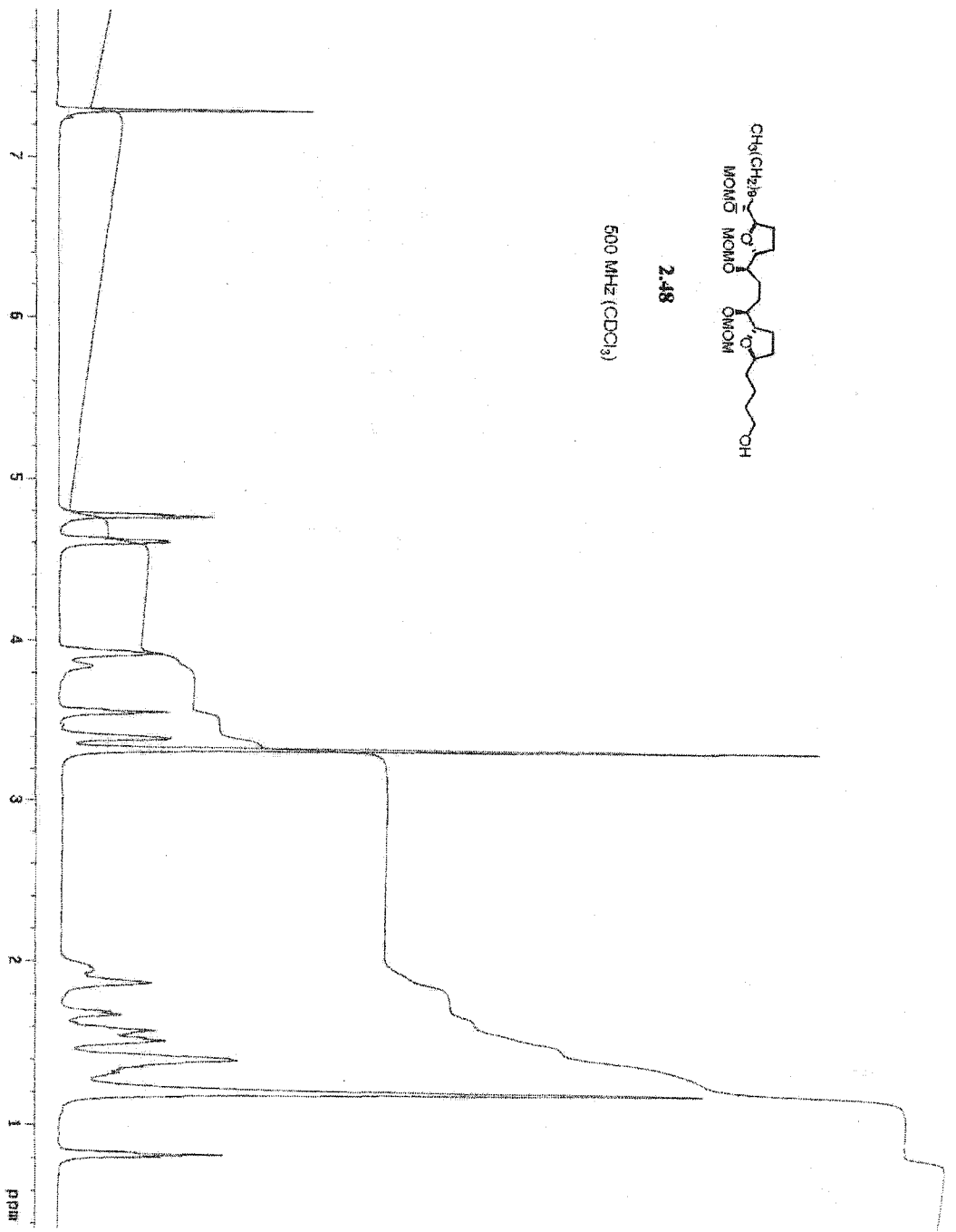


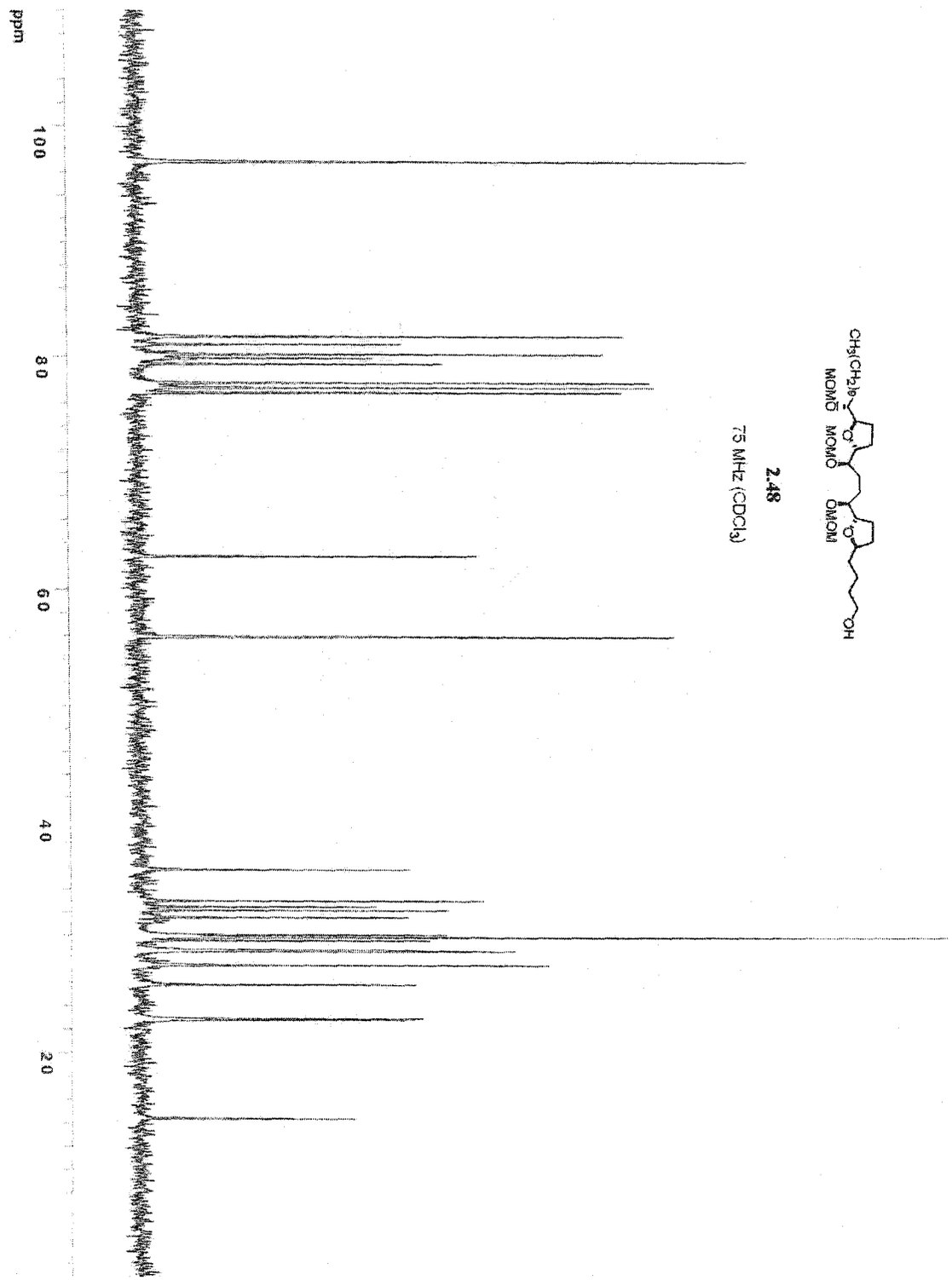


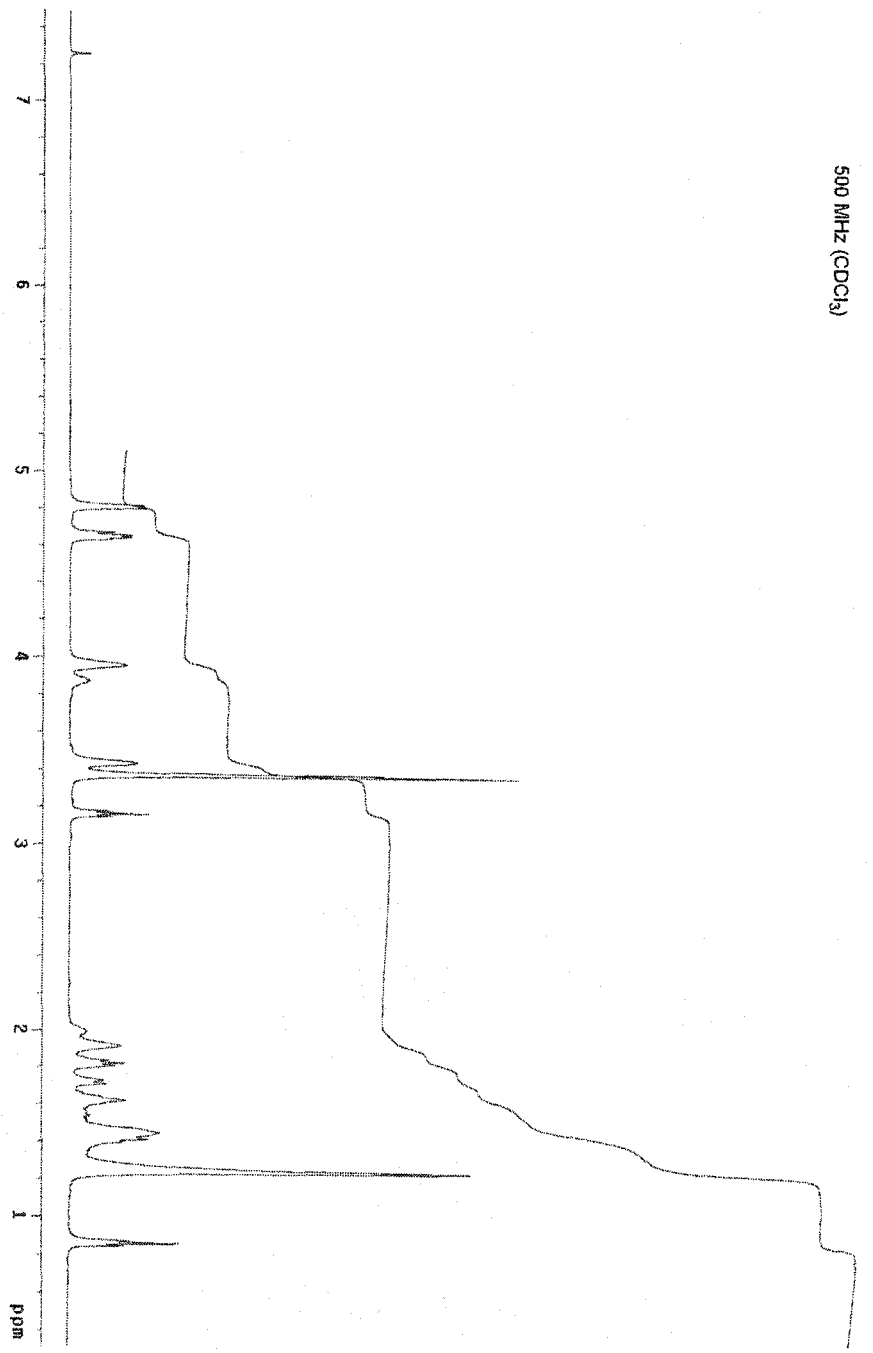


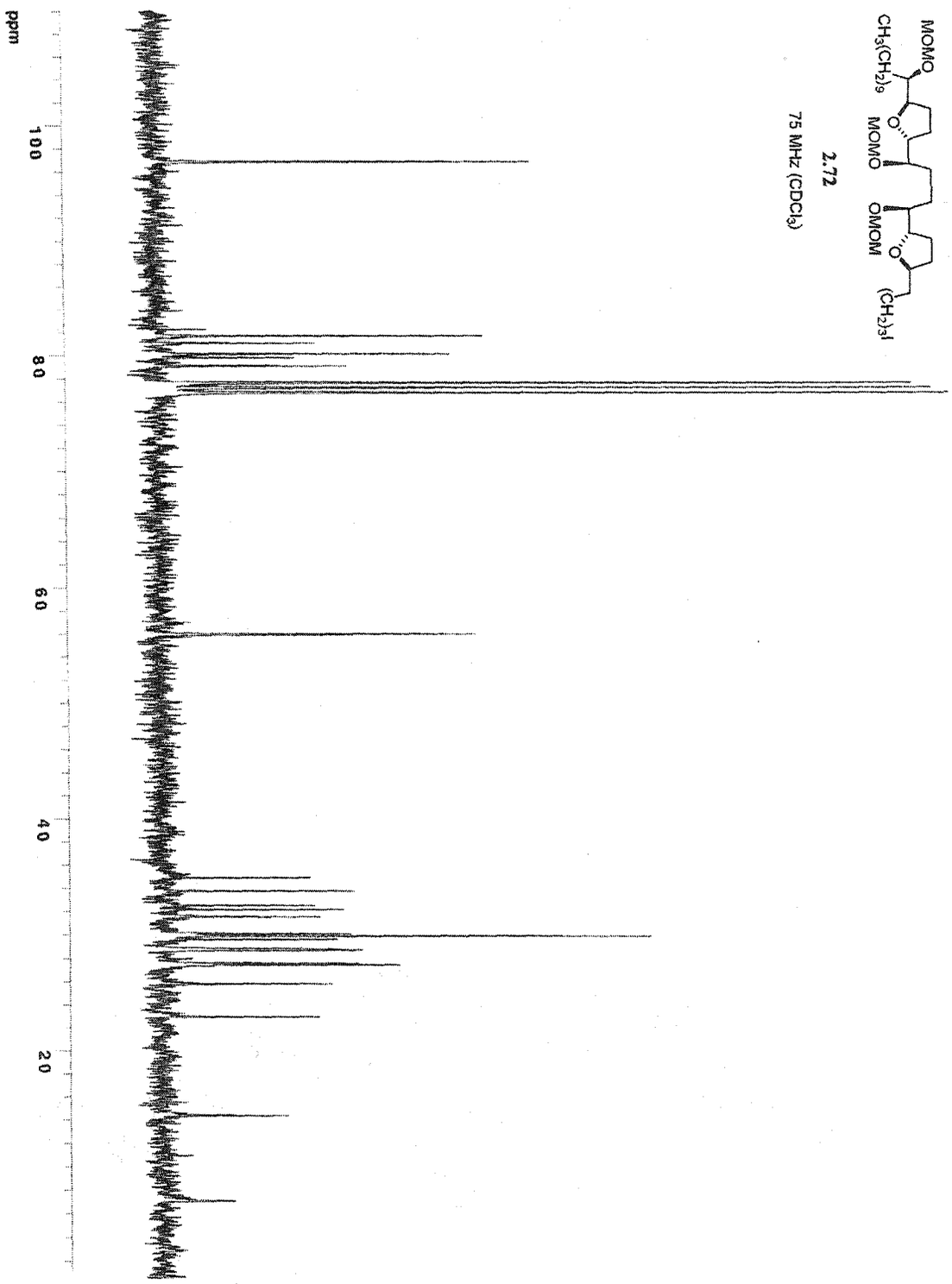


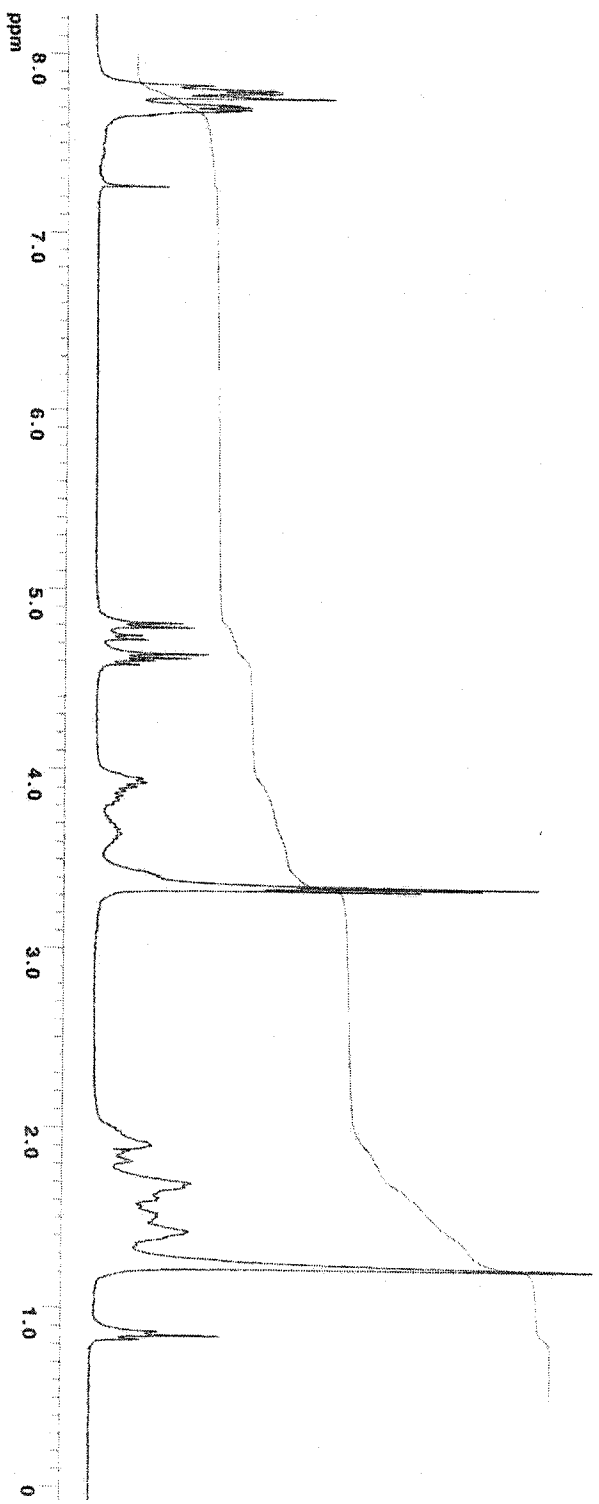


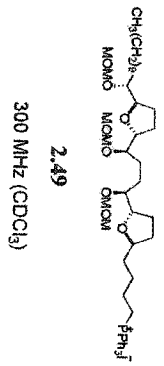






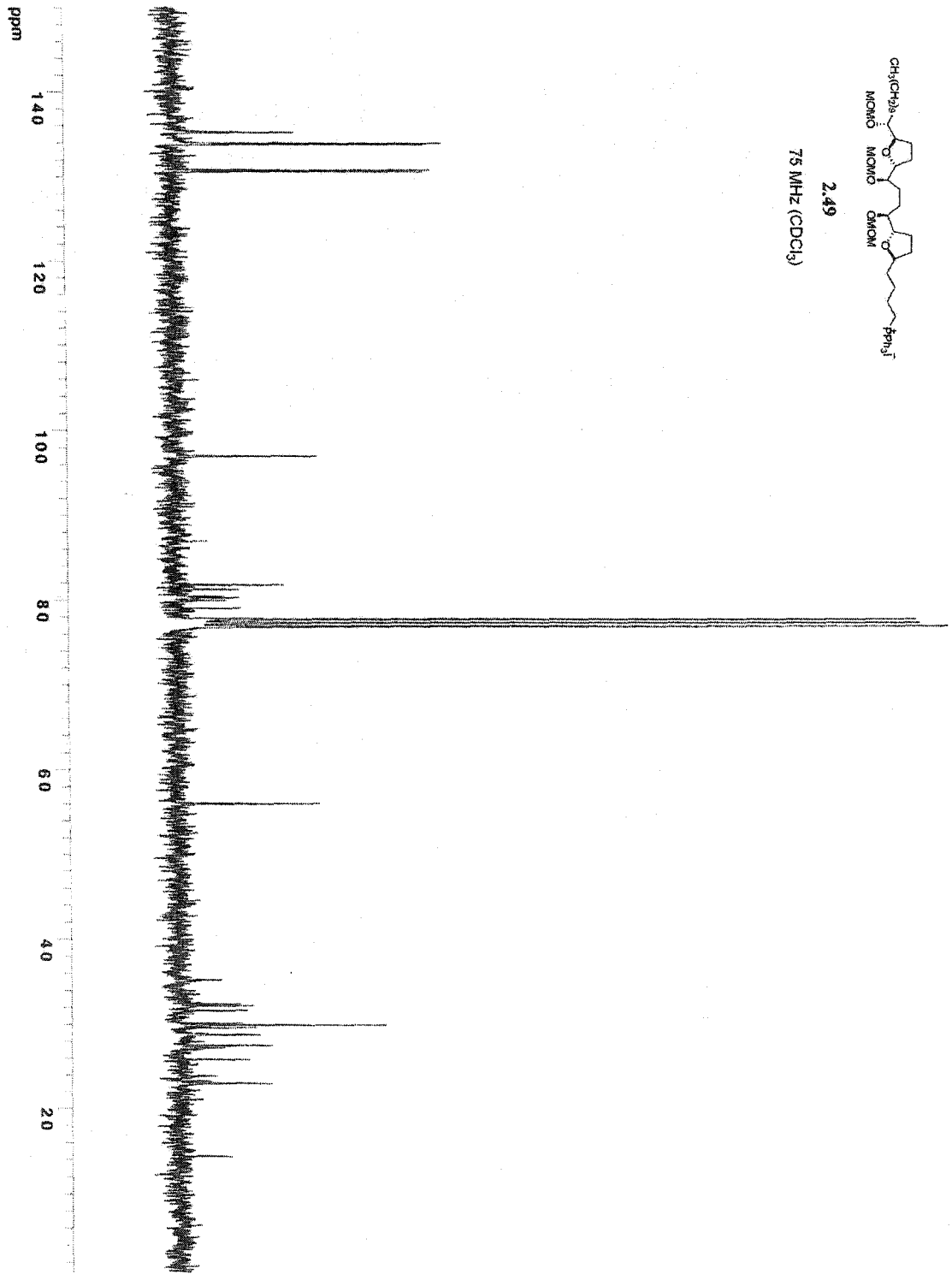


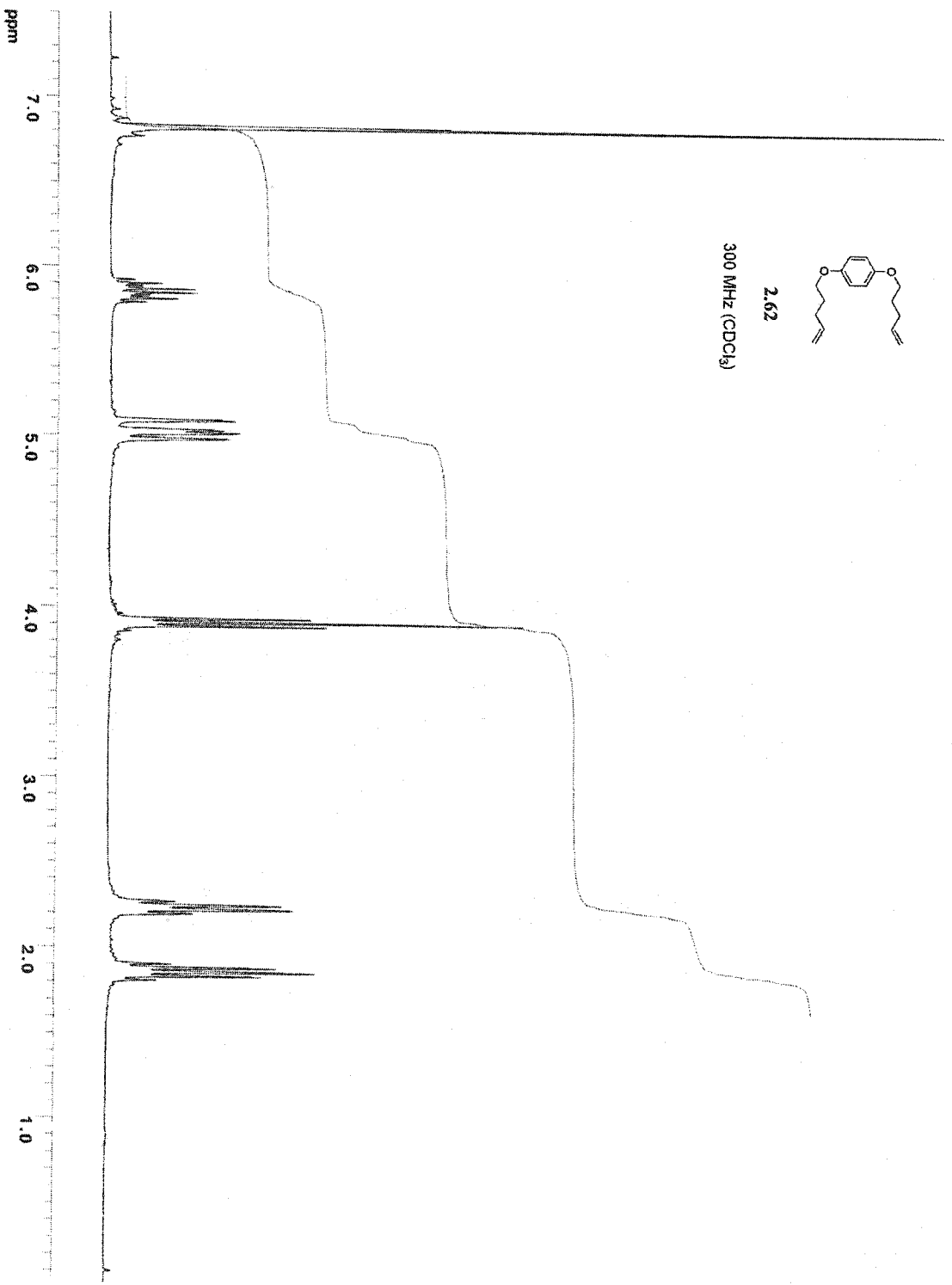


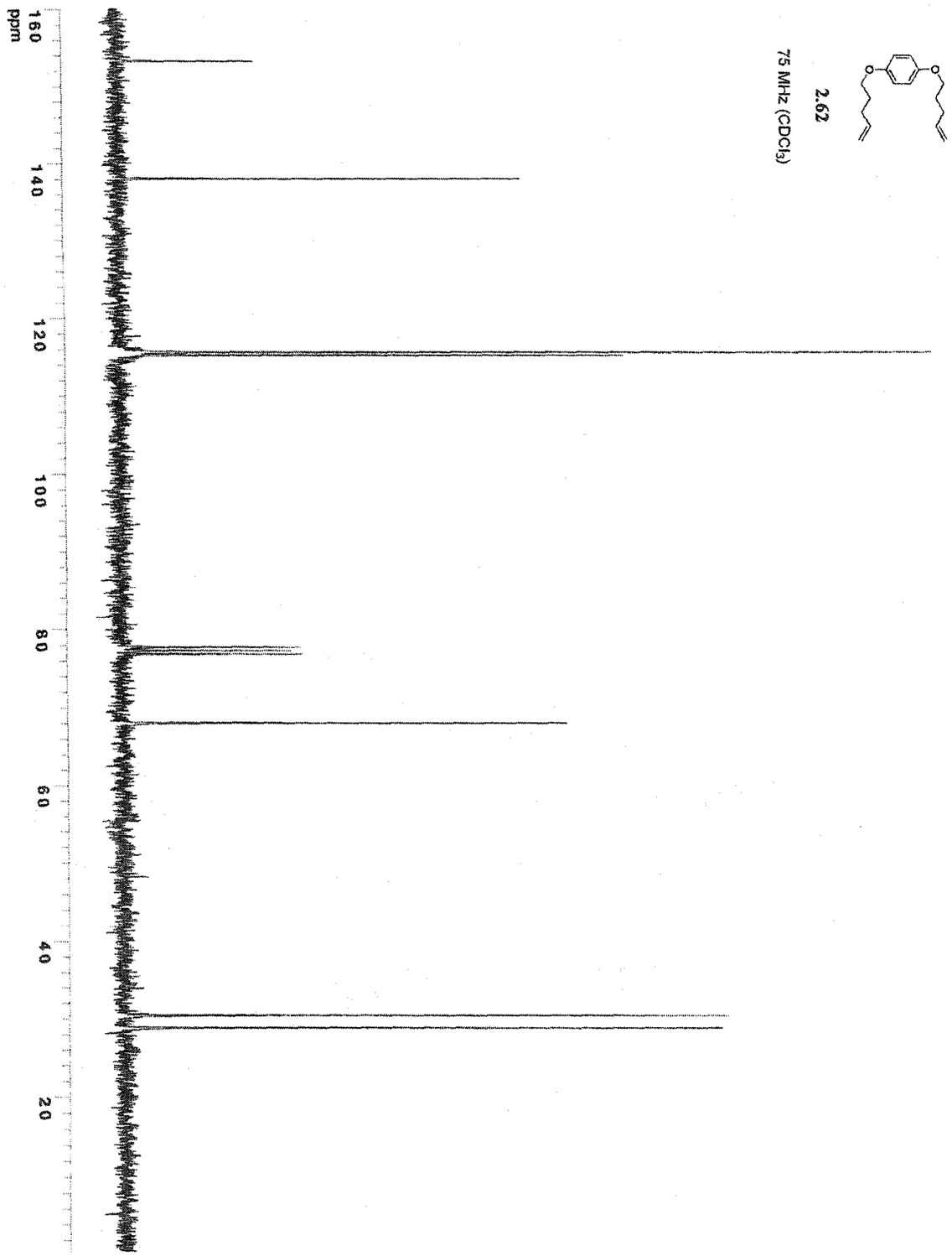


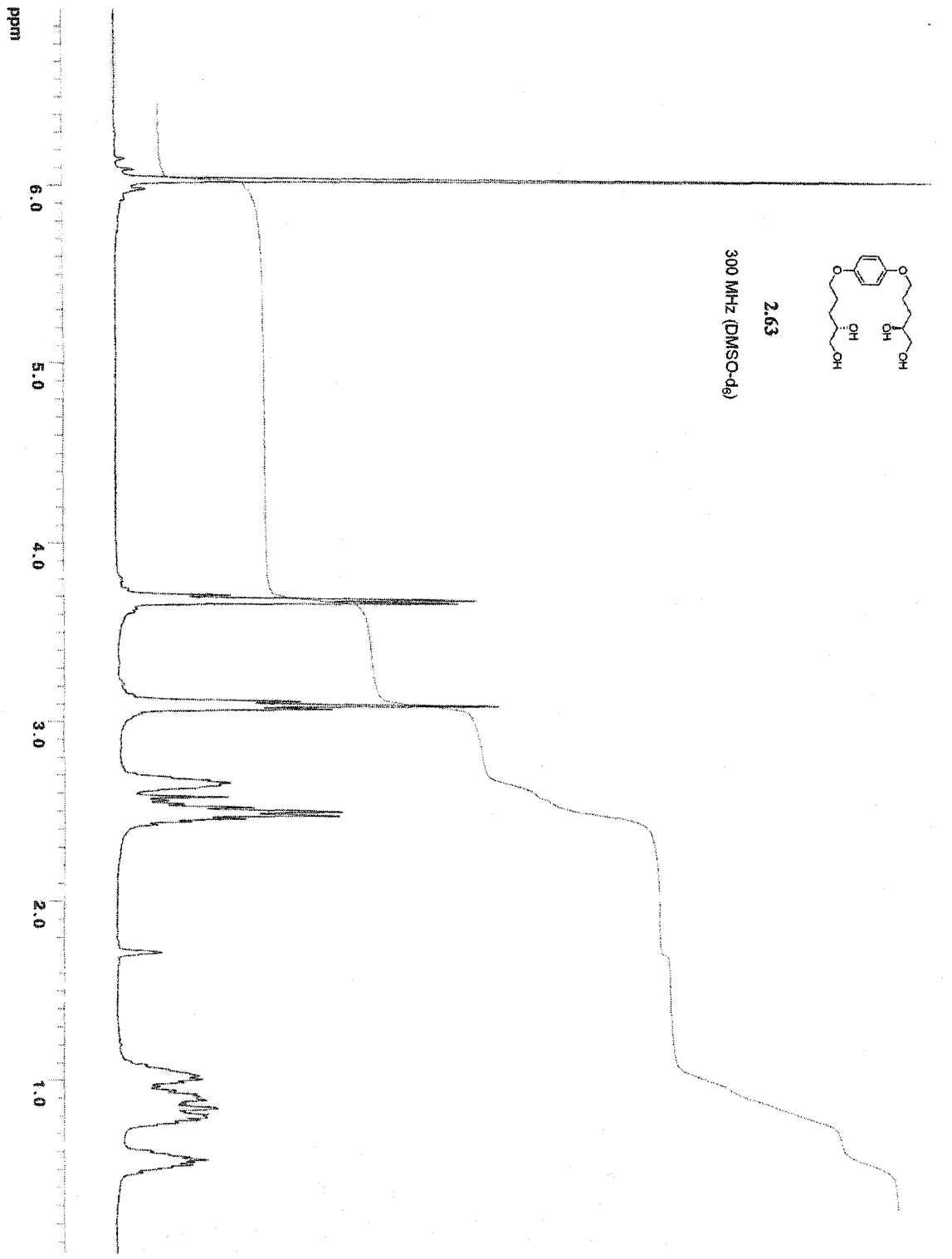
2.49

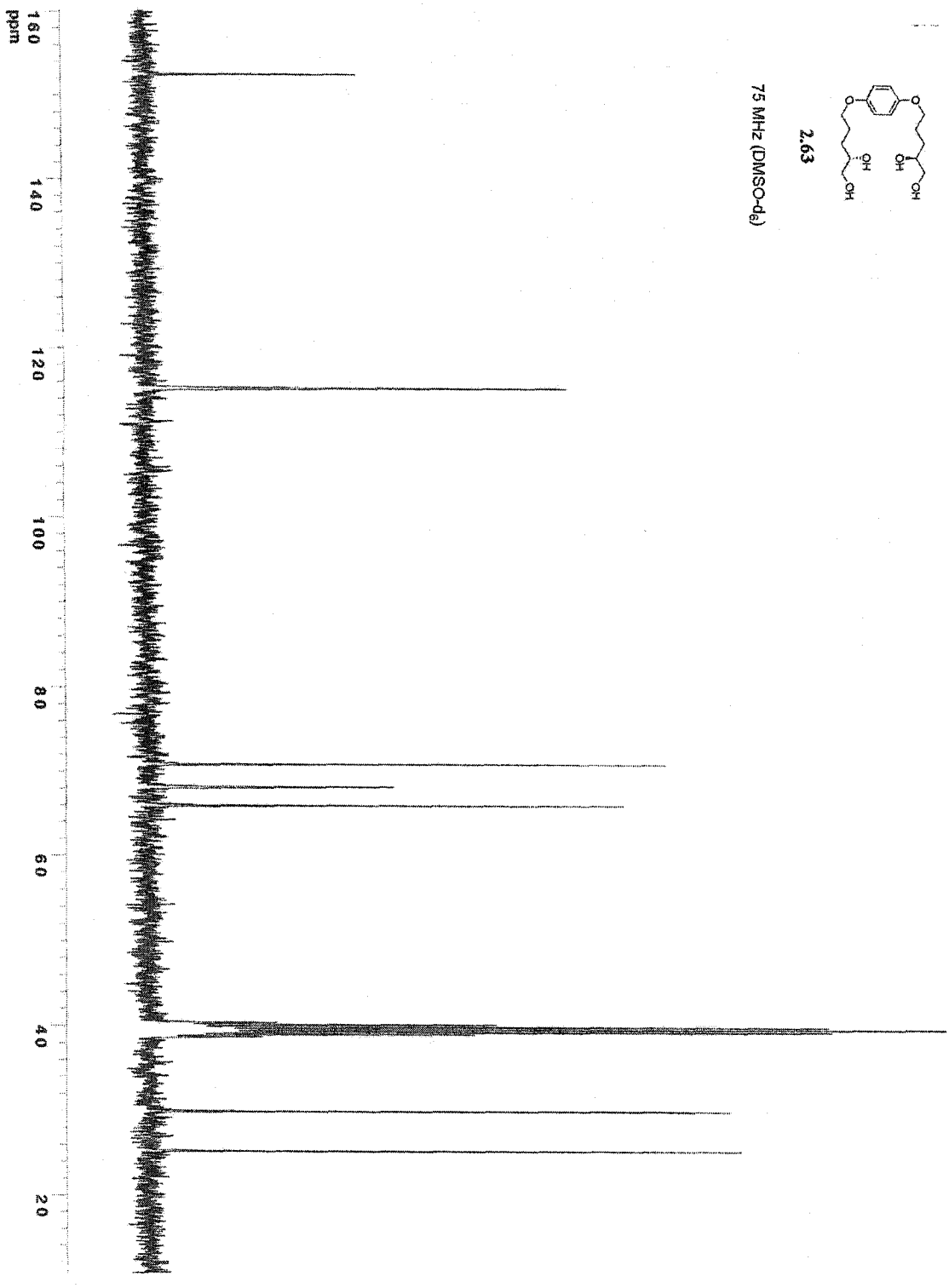
300 MHz ($CDCl_3$)

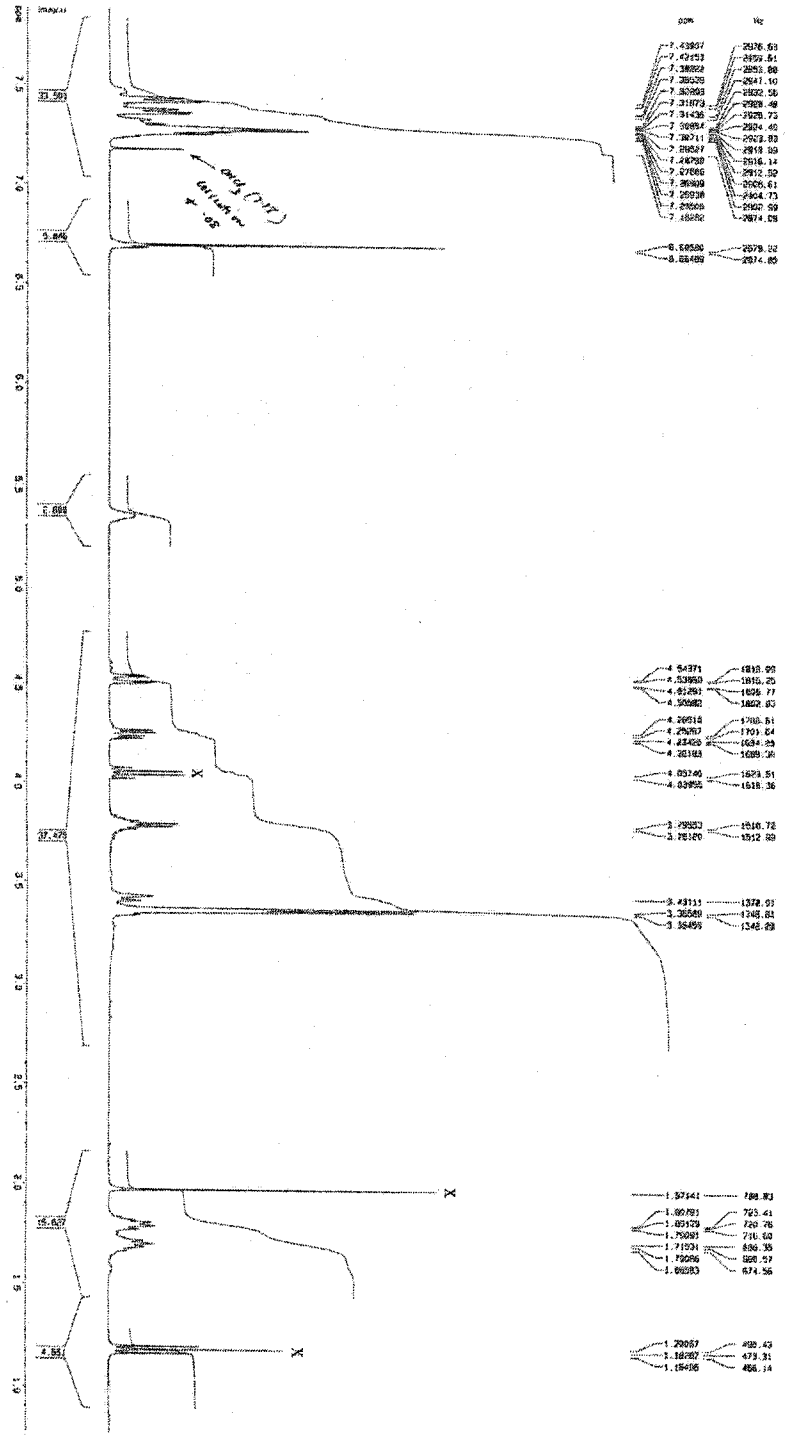


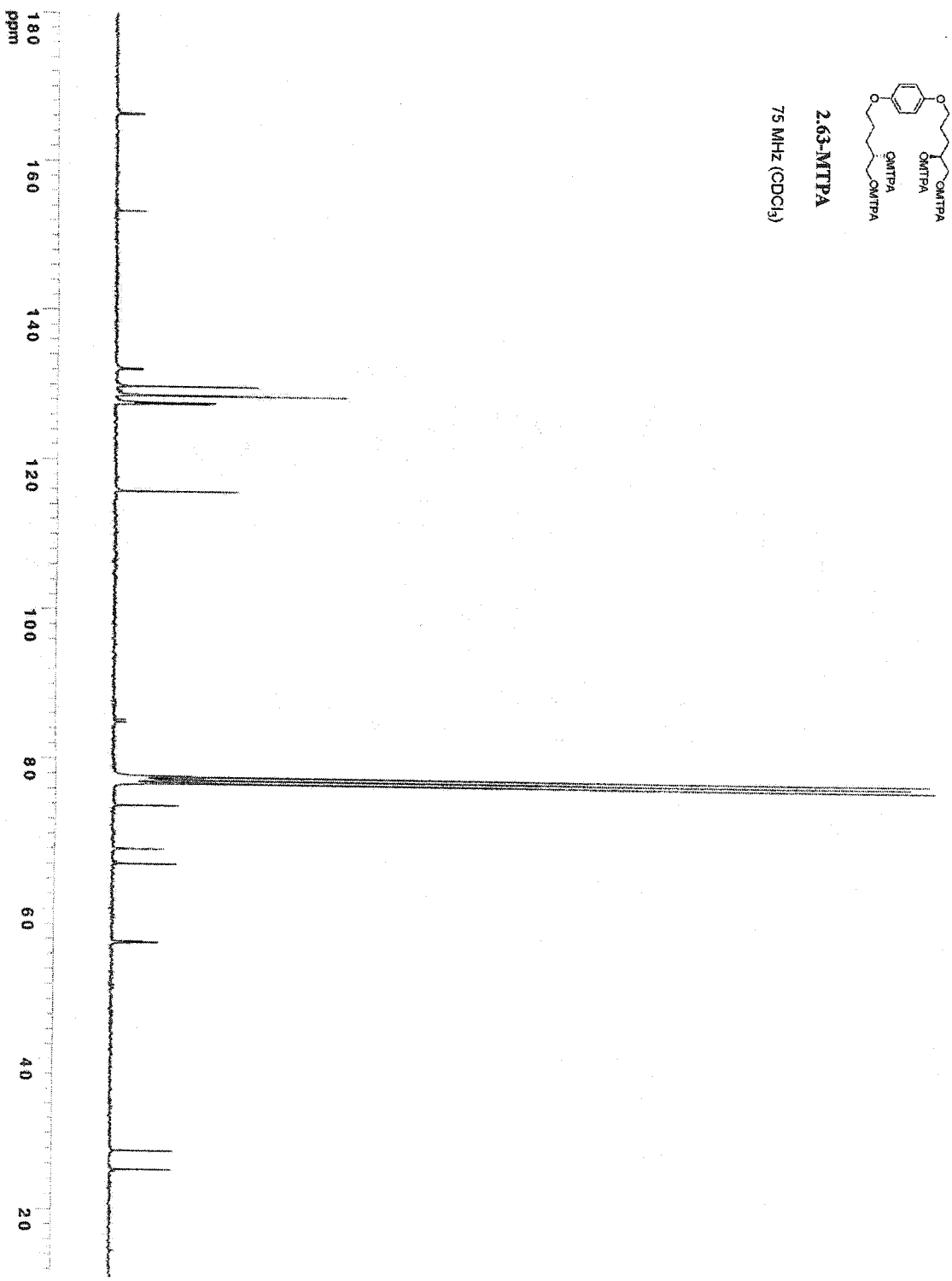


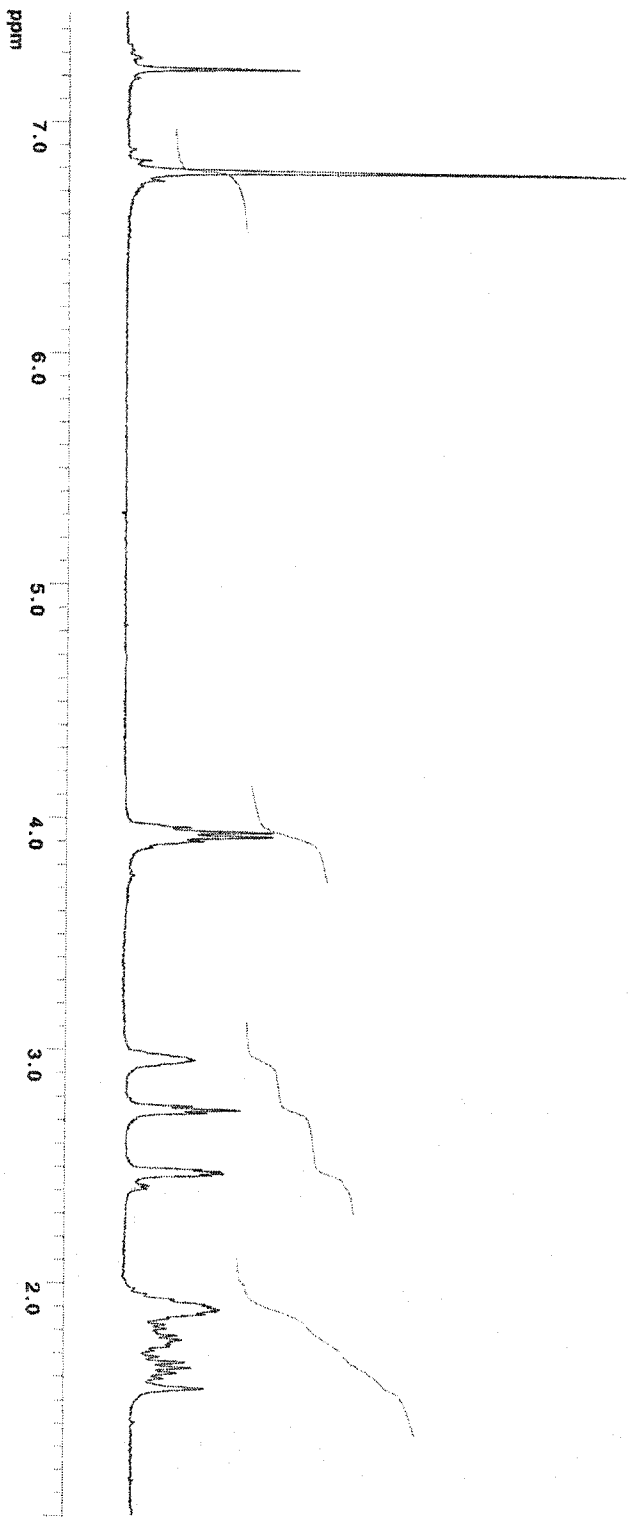






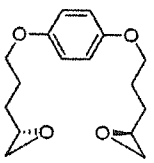


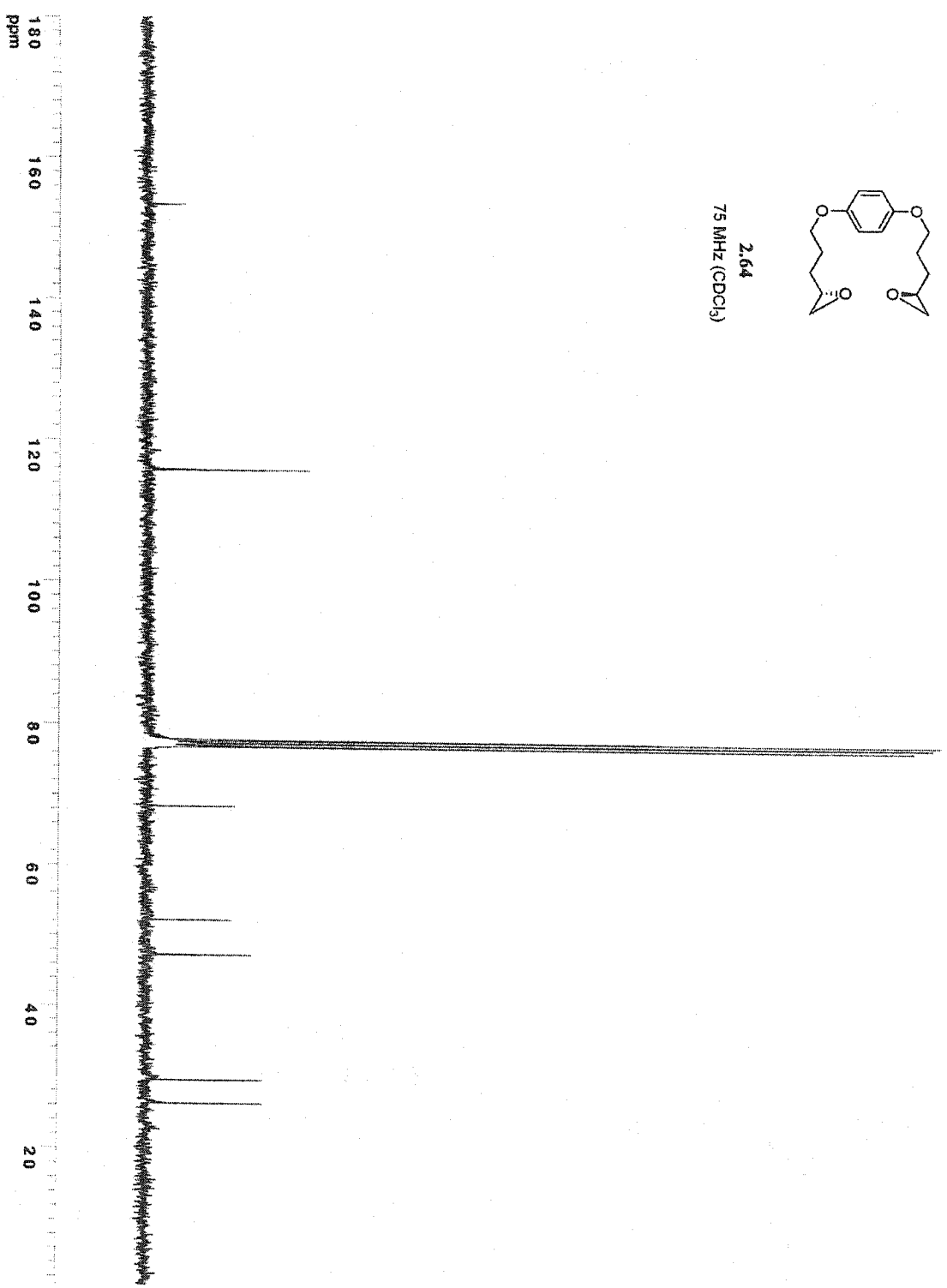


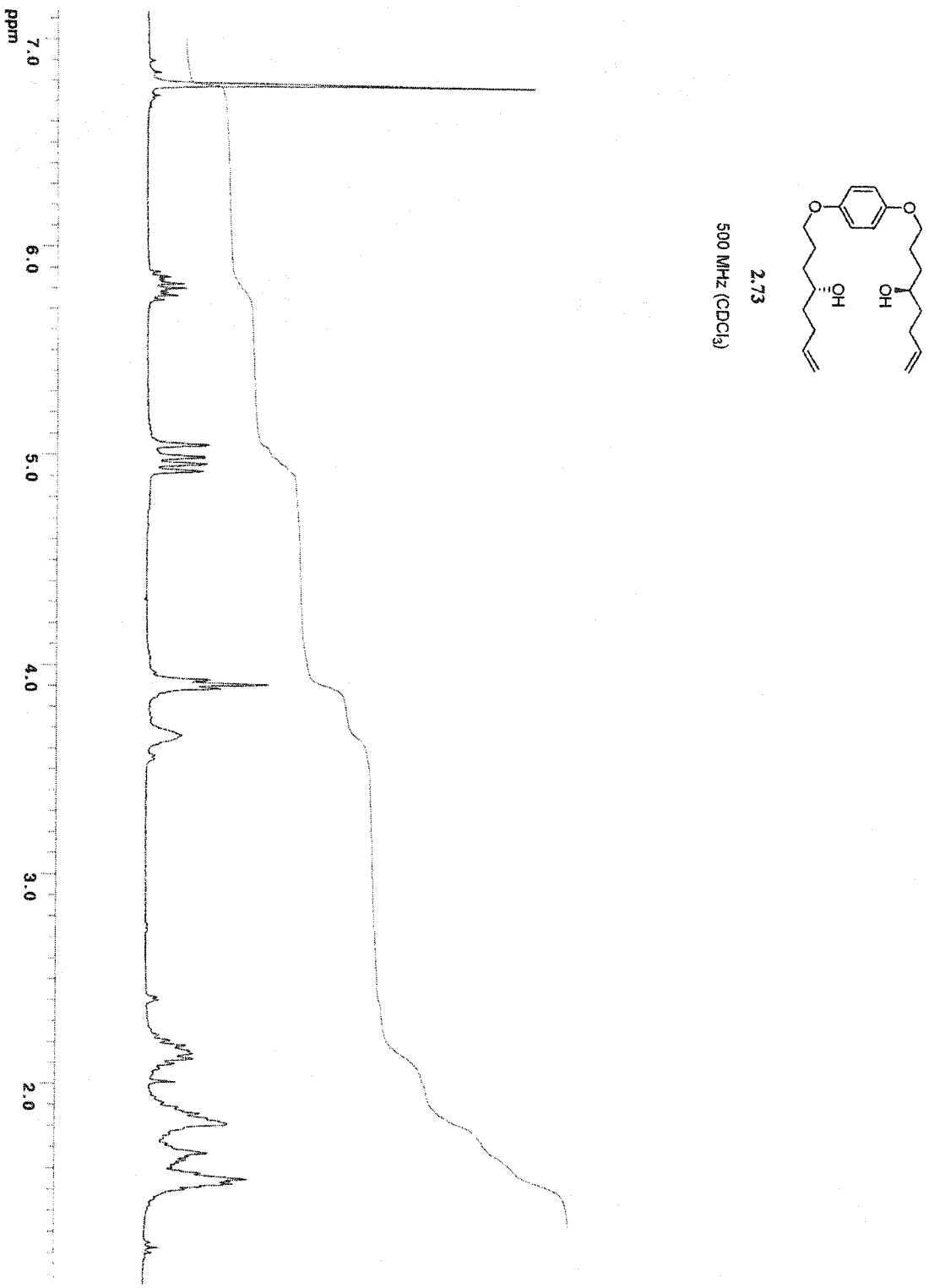


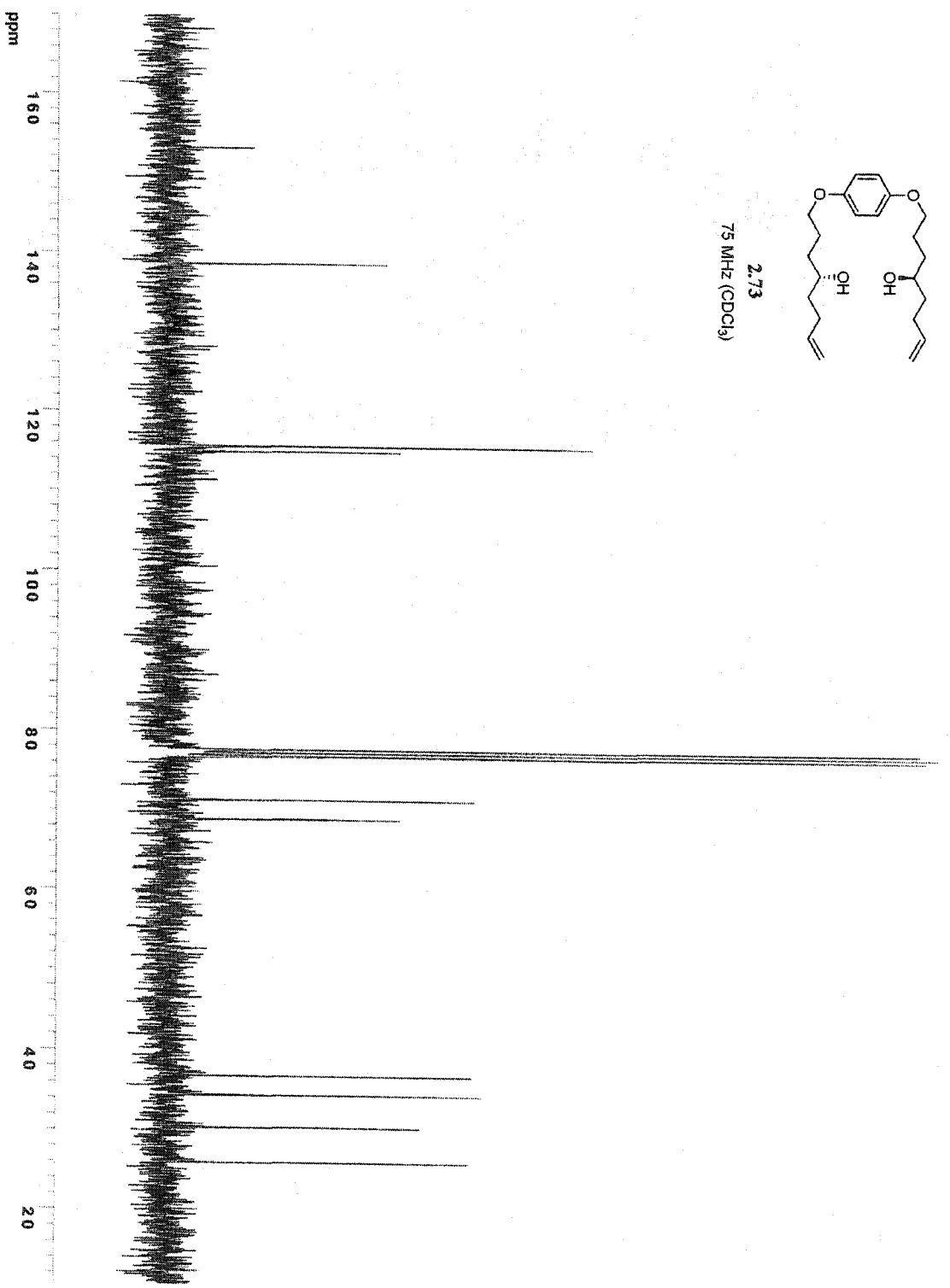
500 MHz ($CDCl_3$)

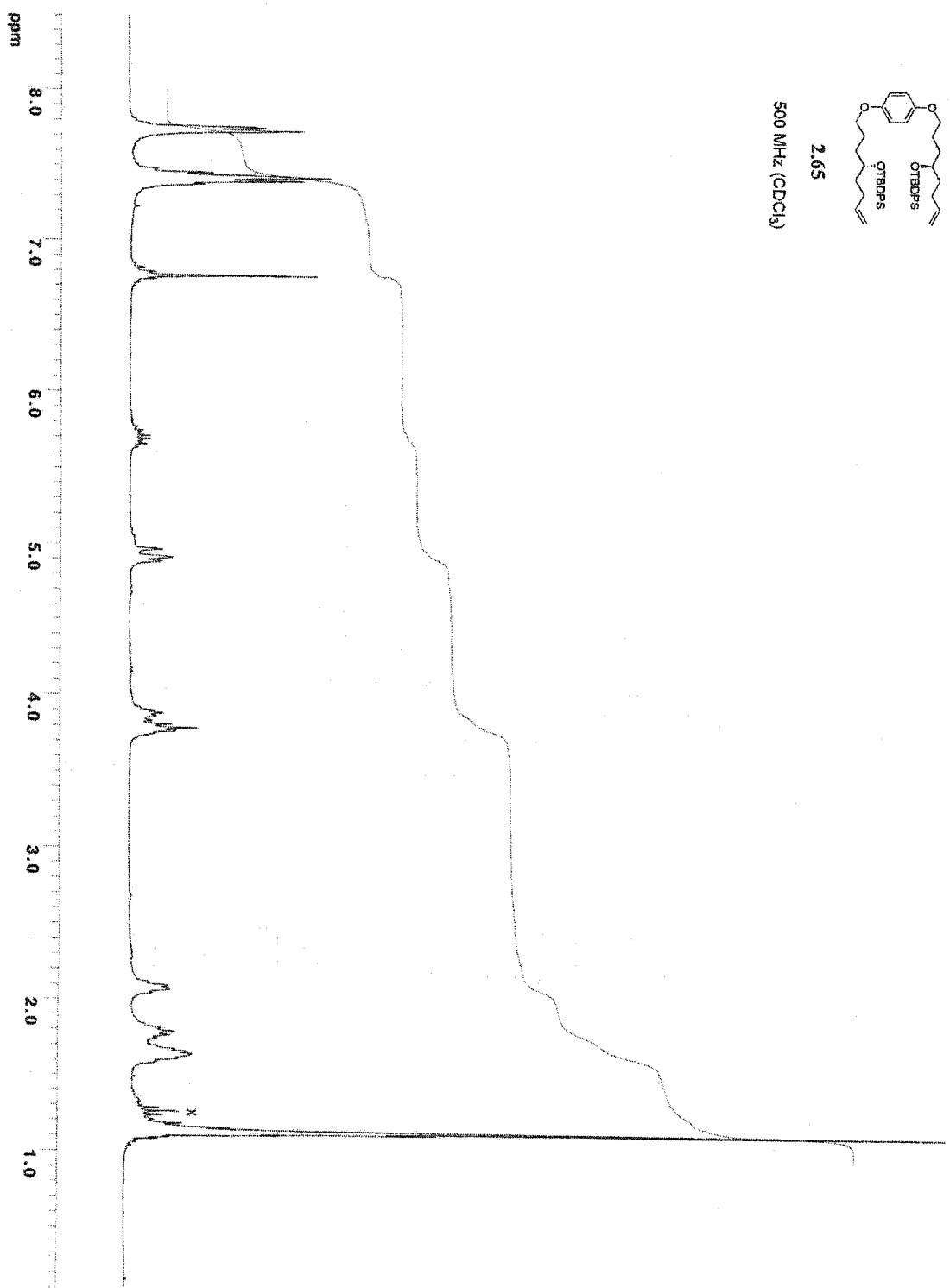
2.64

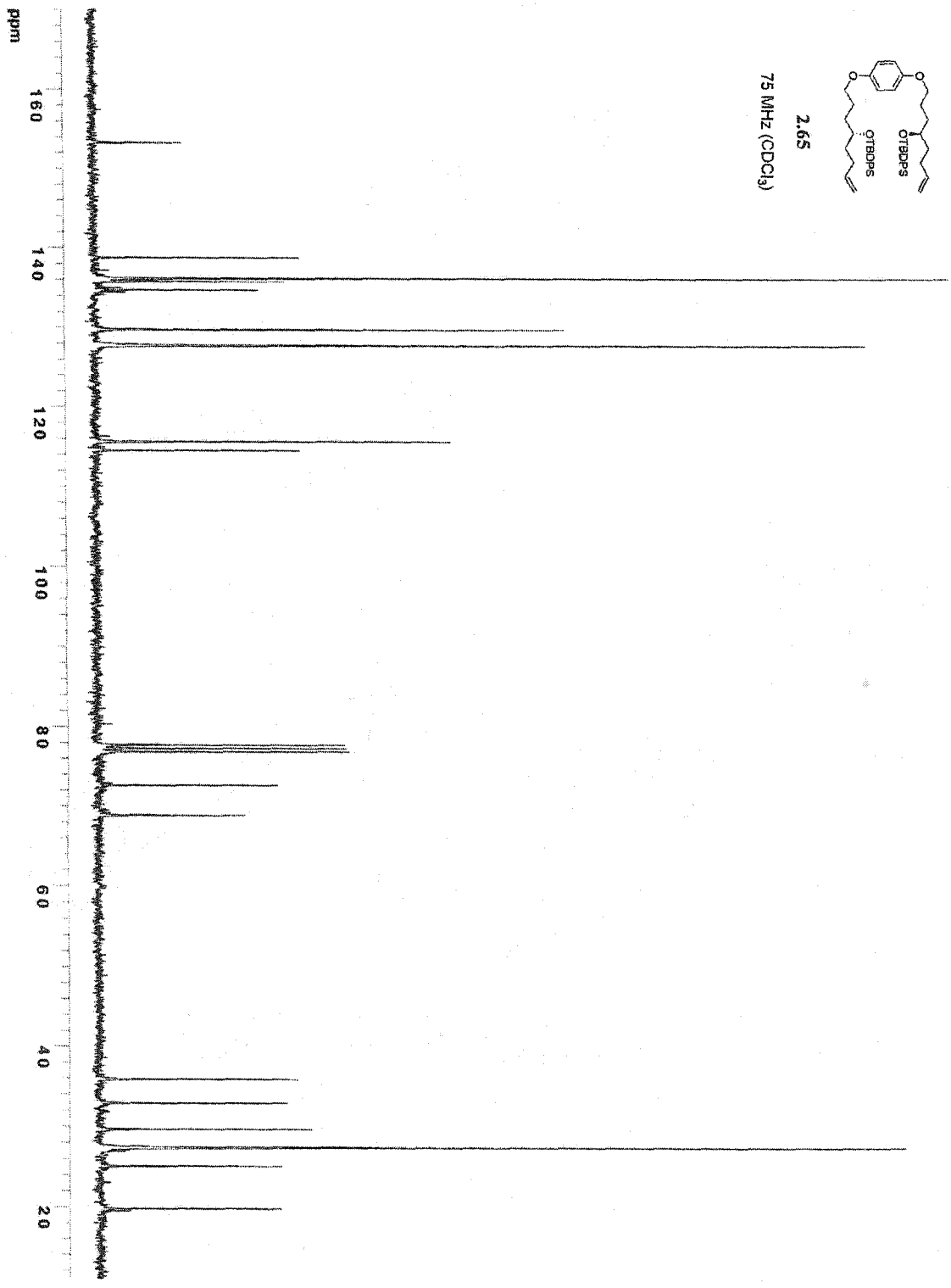


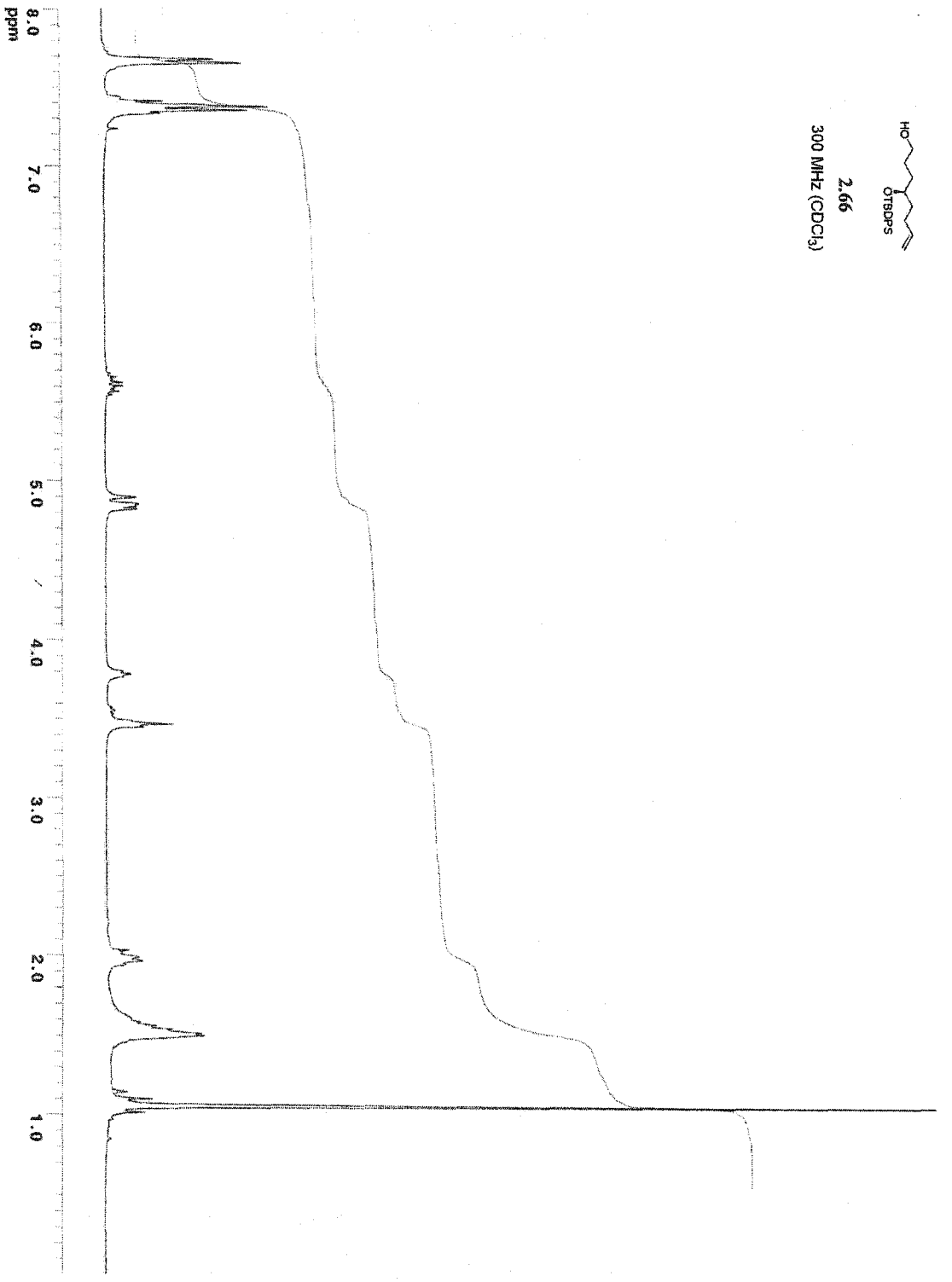


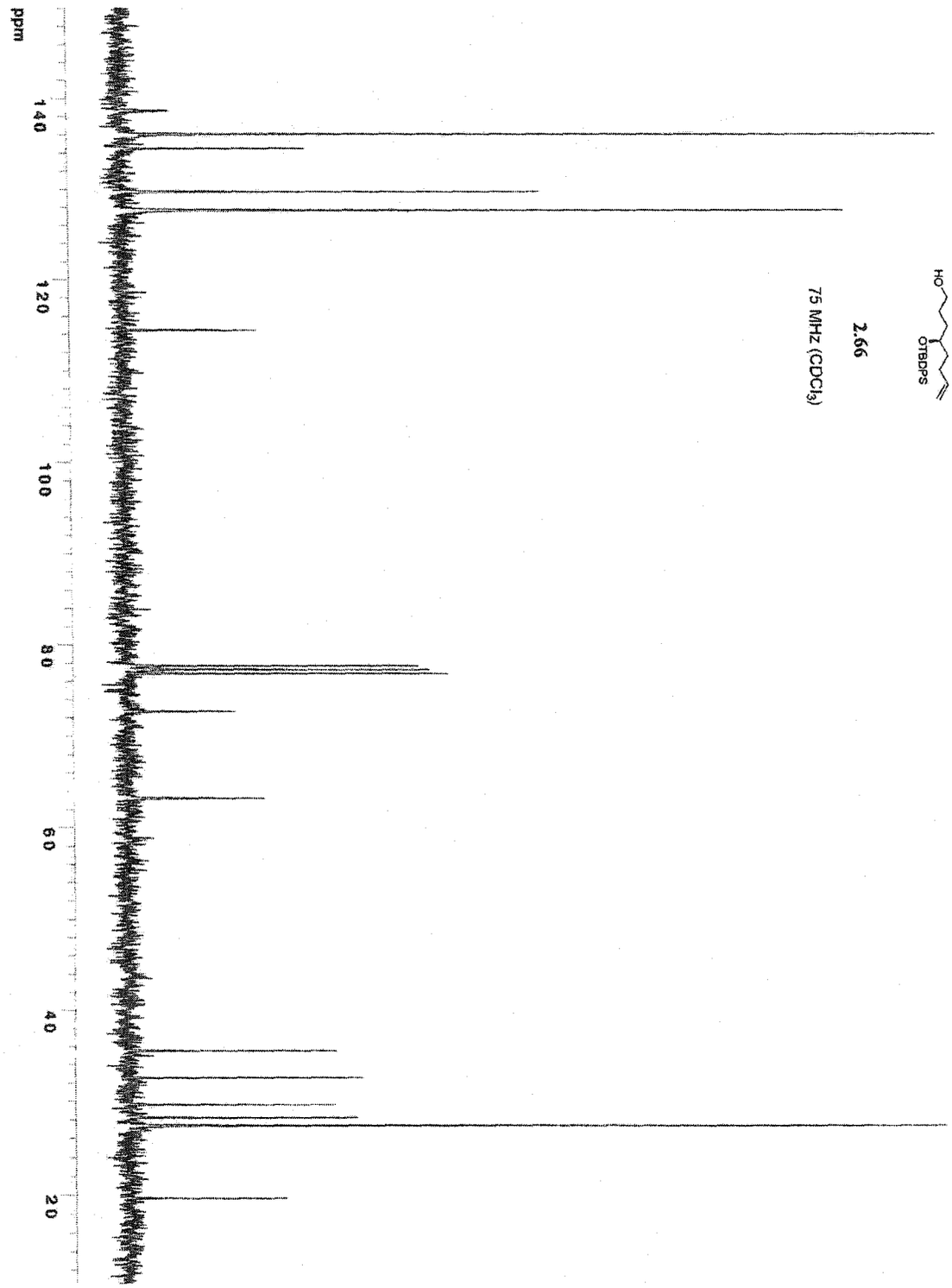


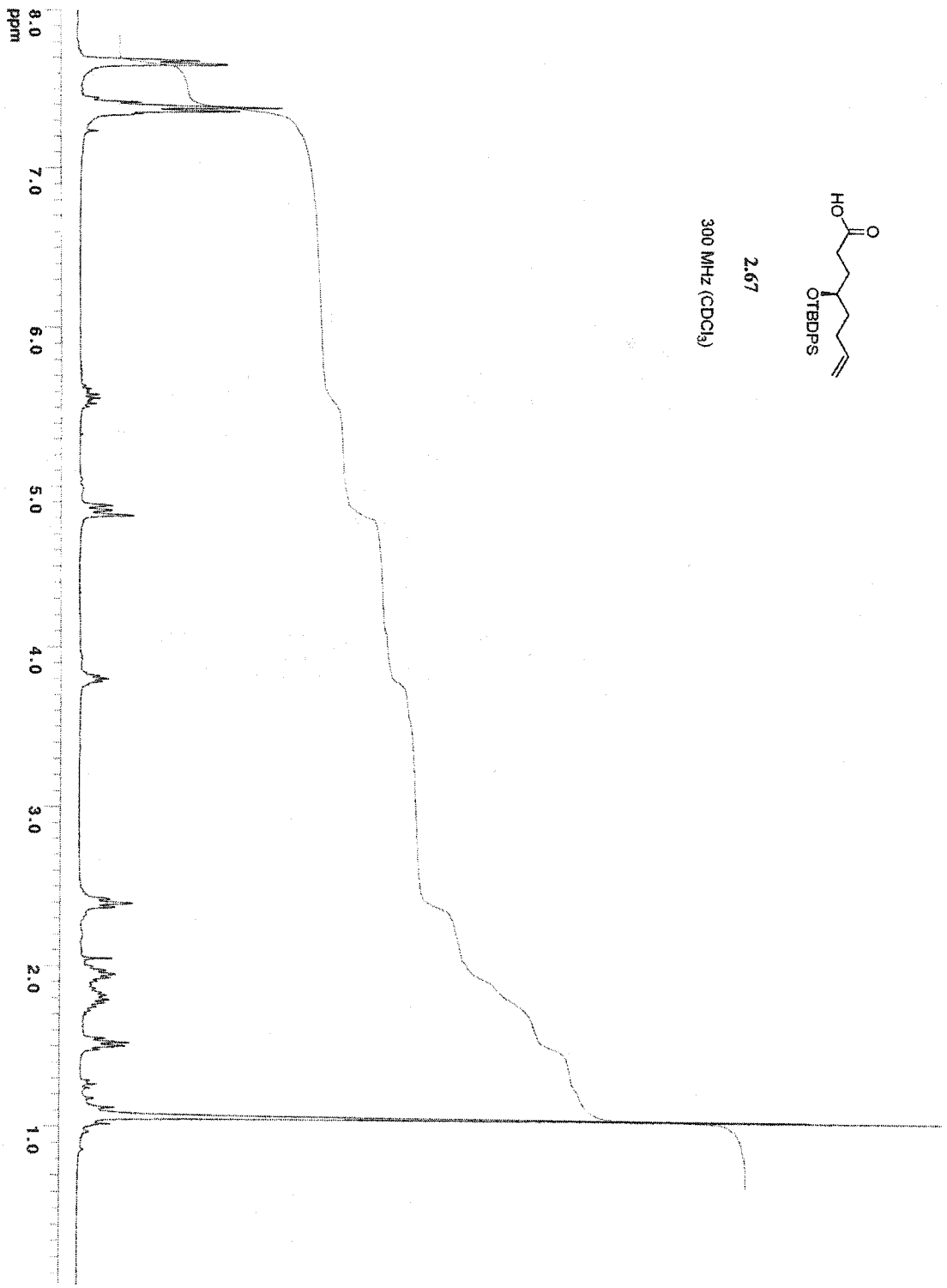


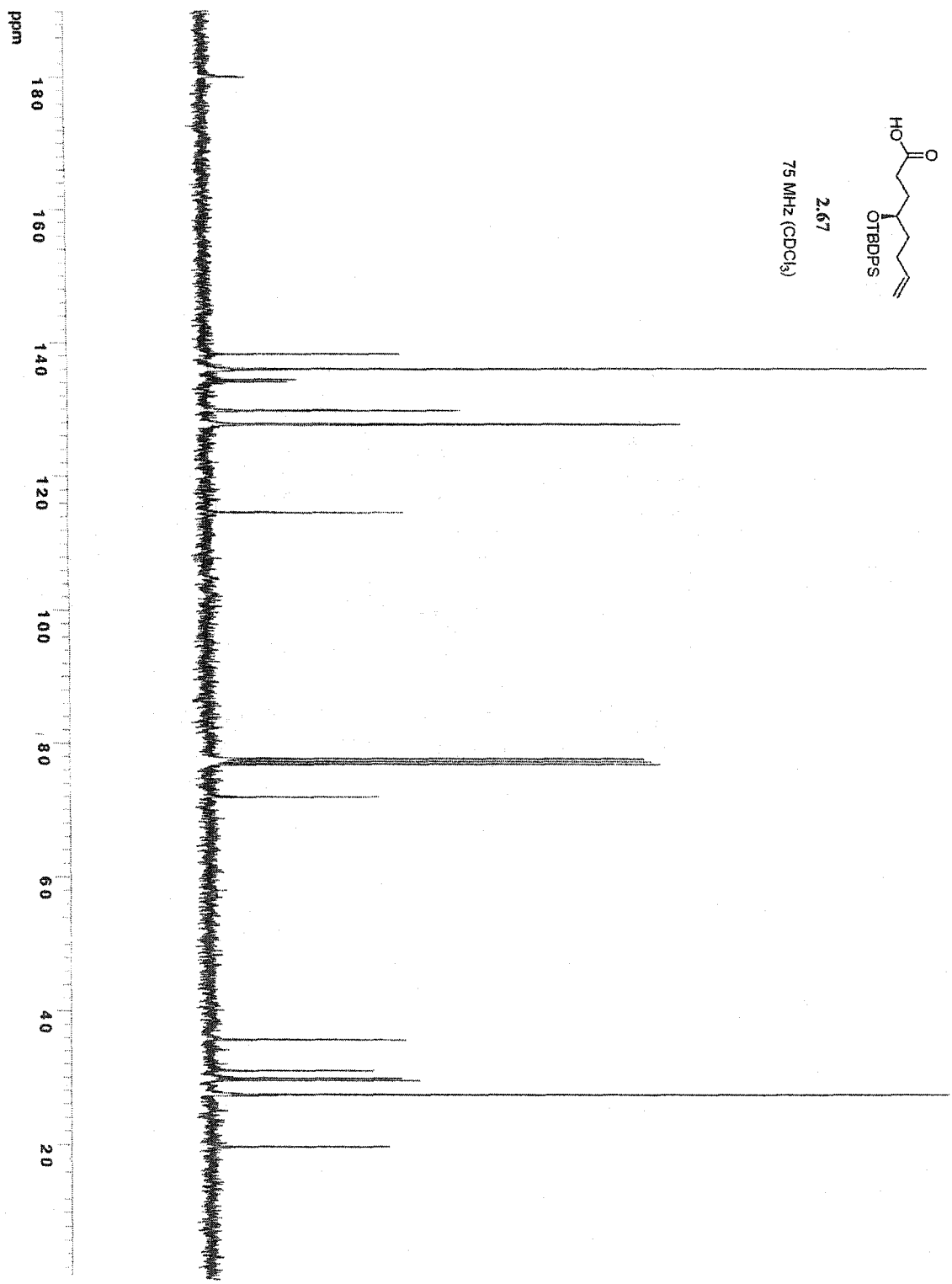


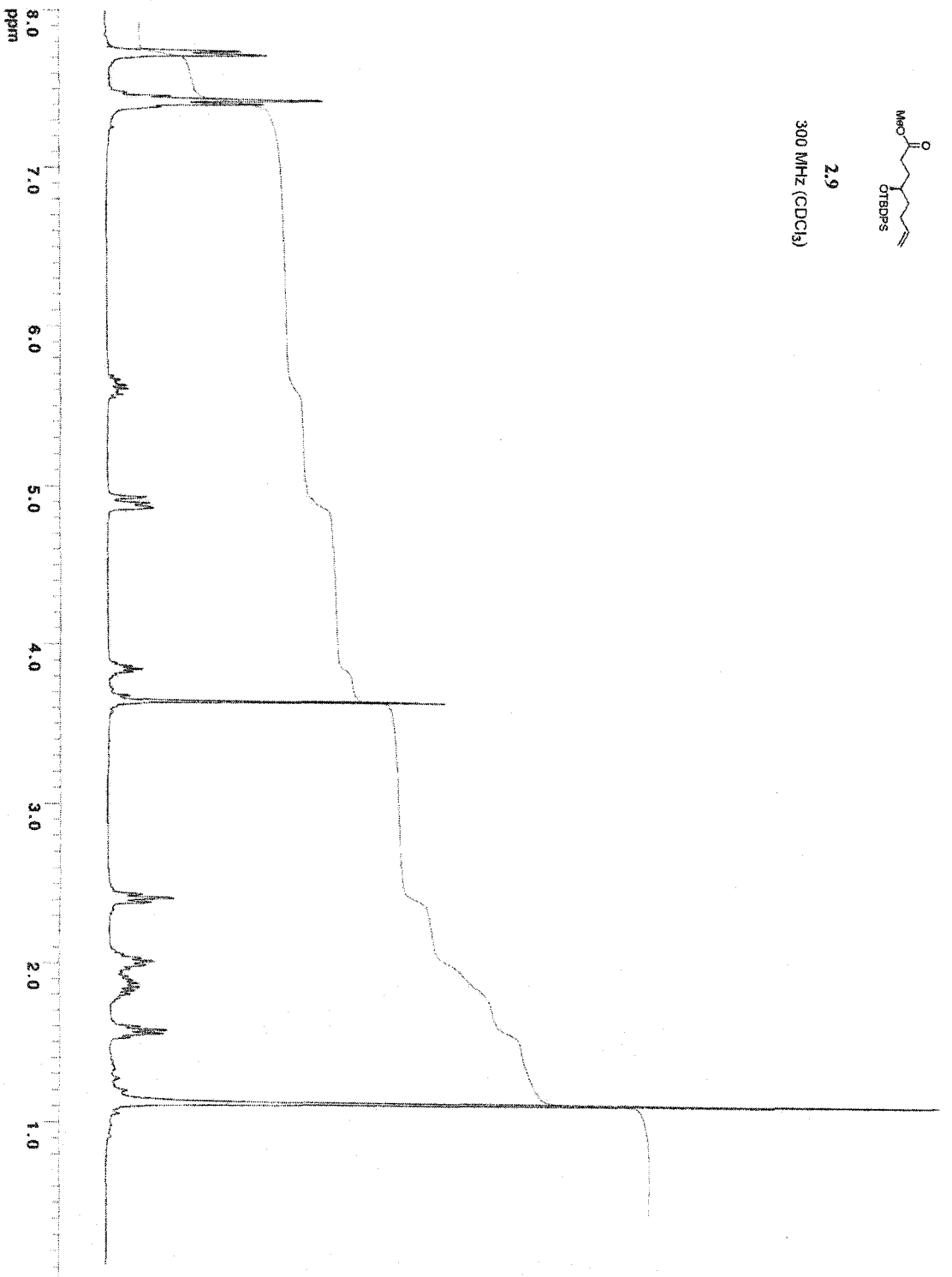


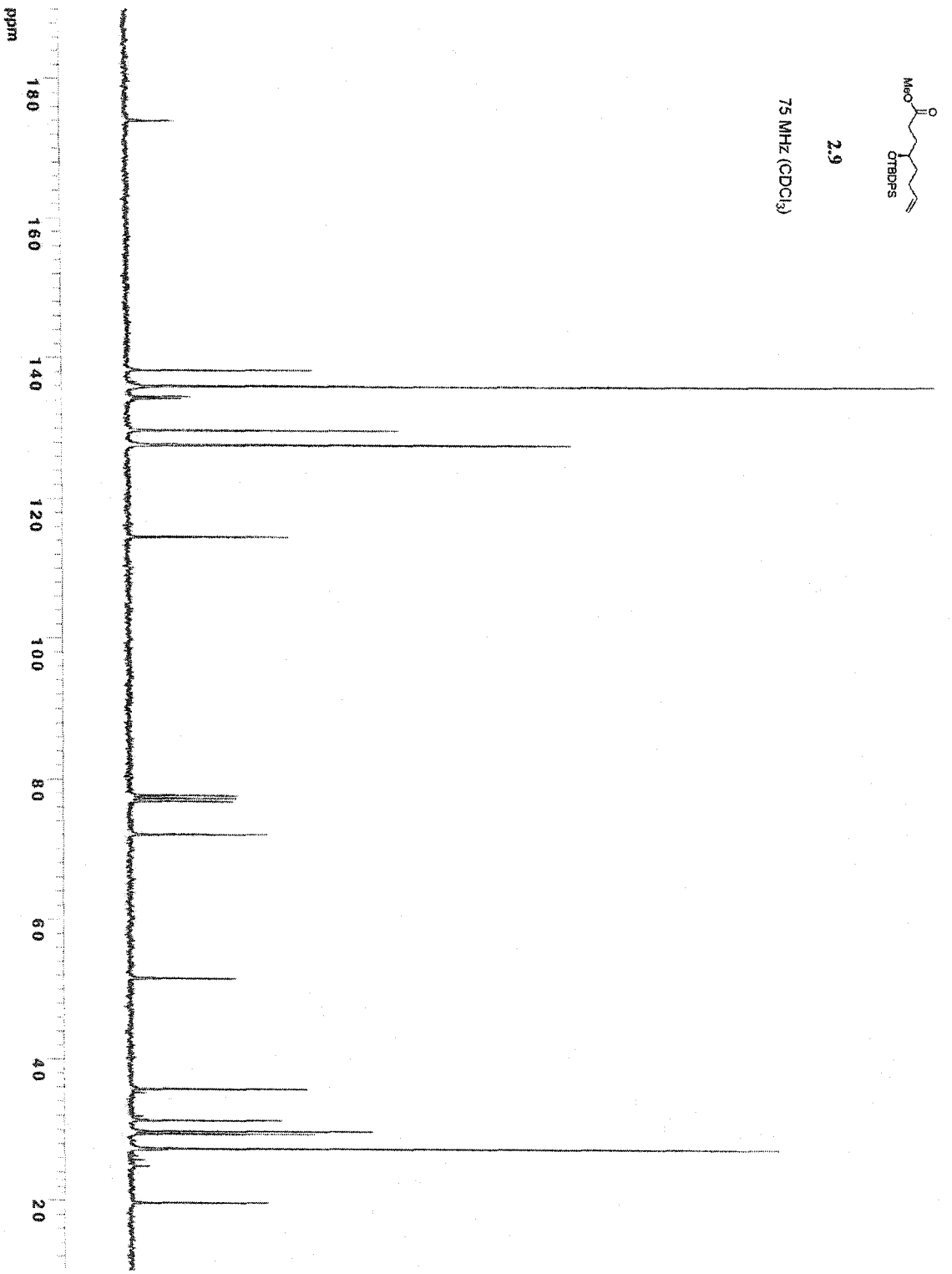


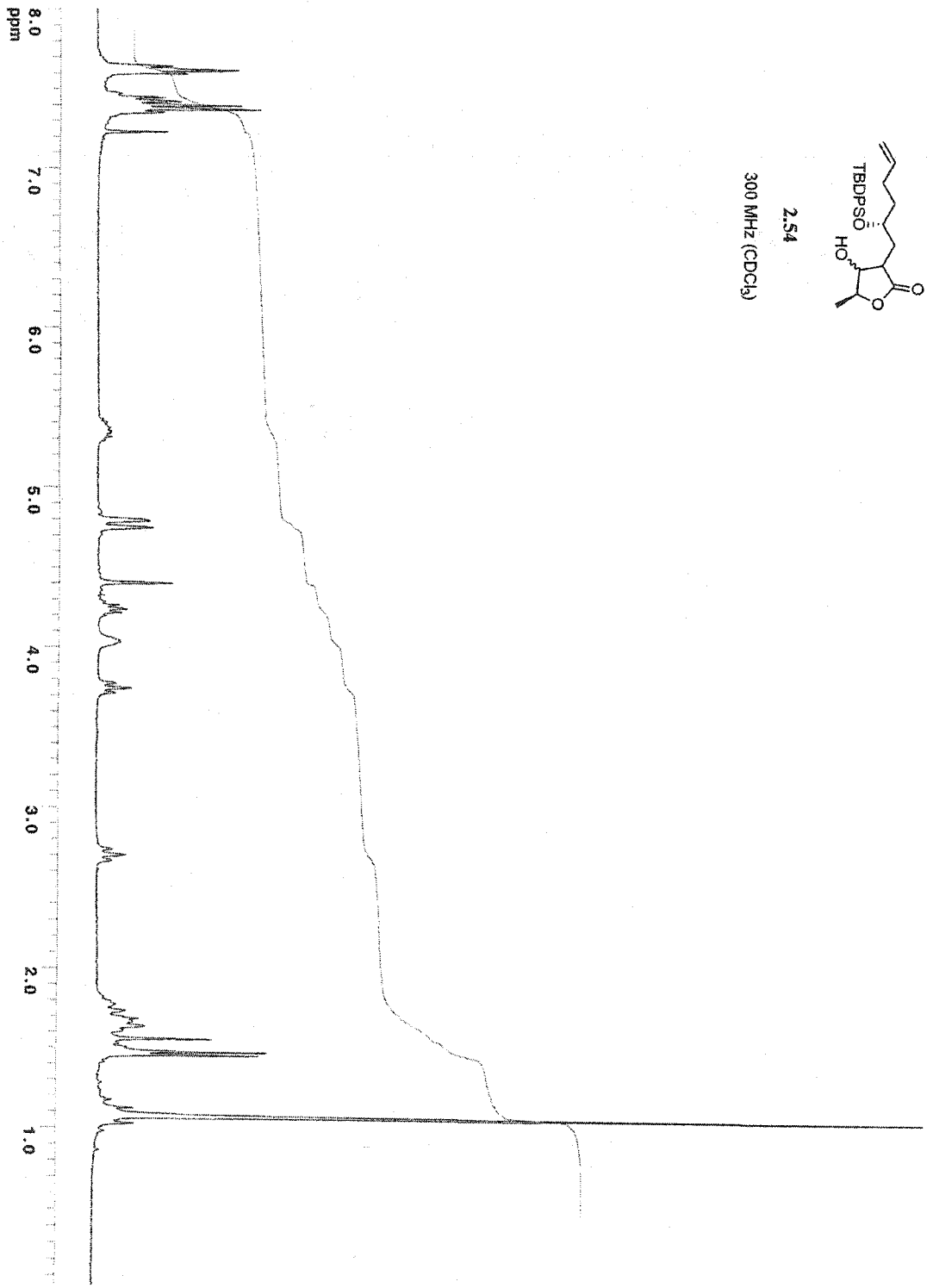


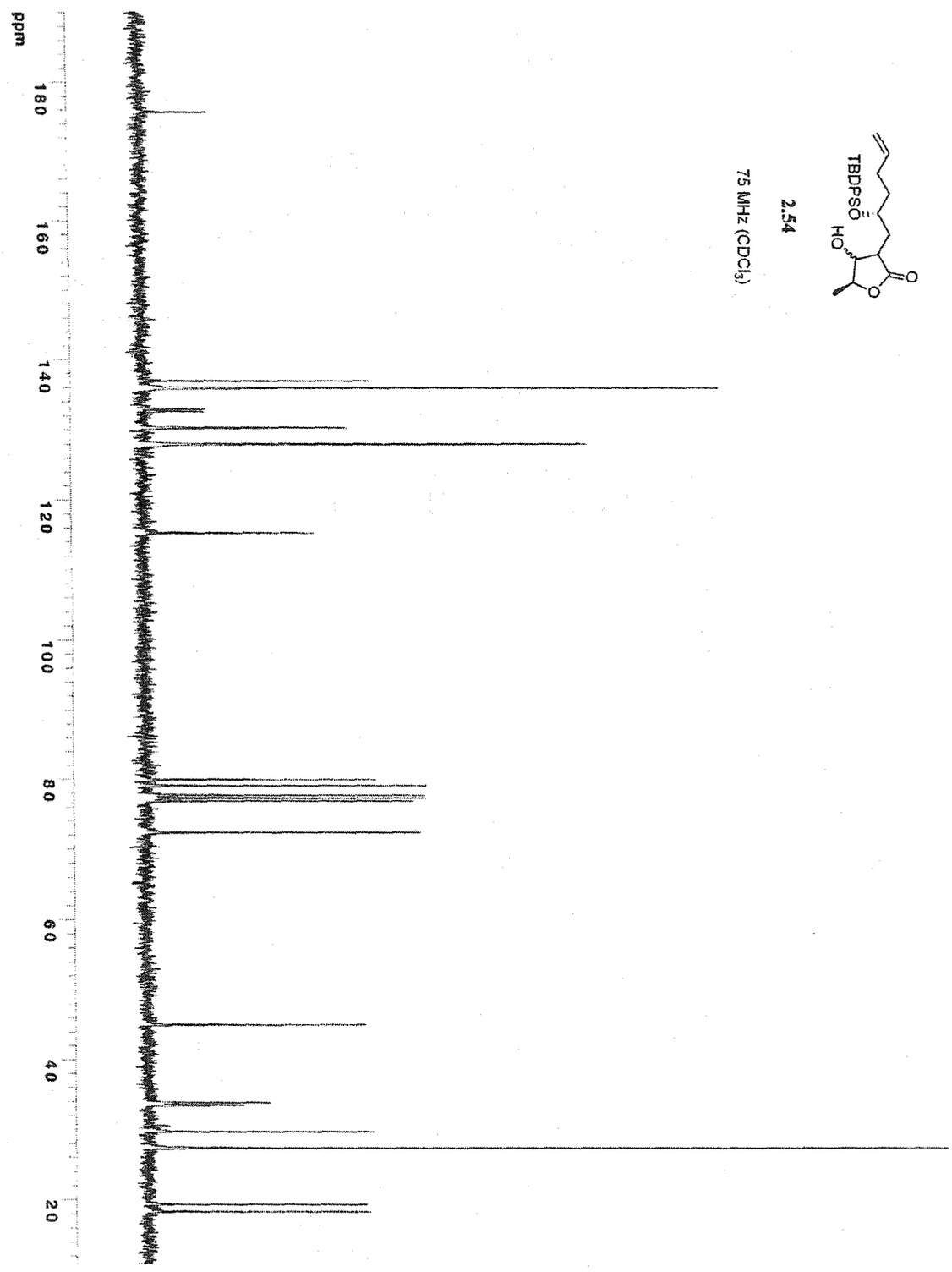


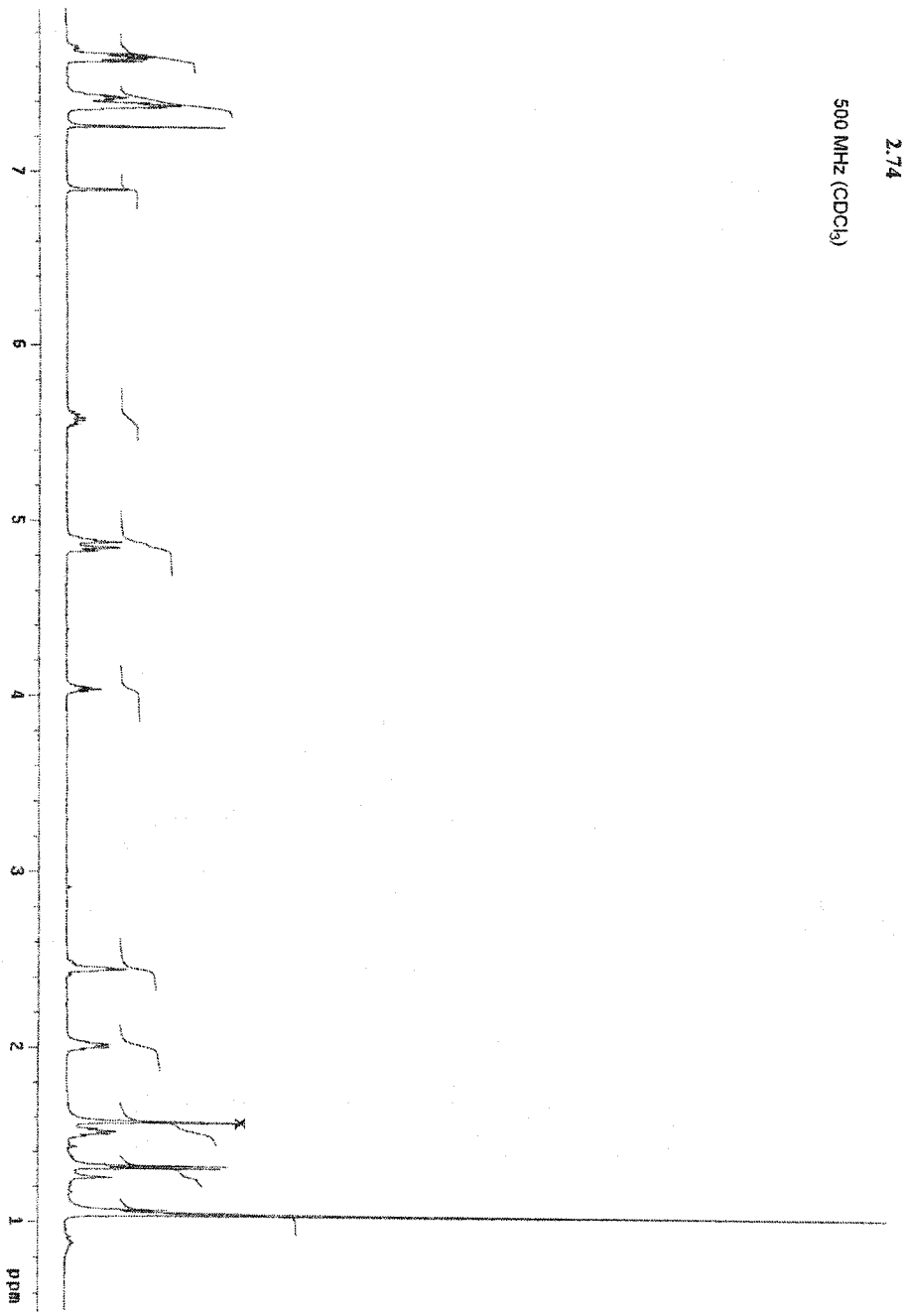


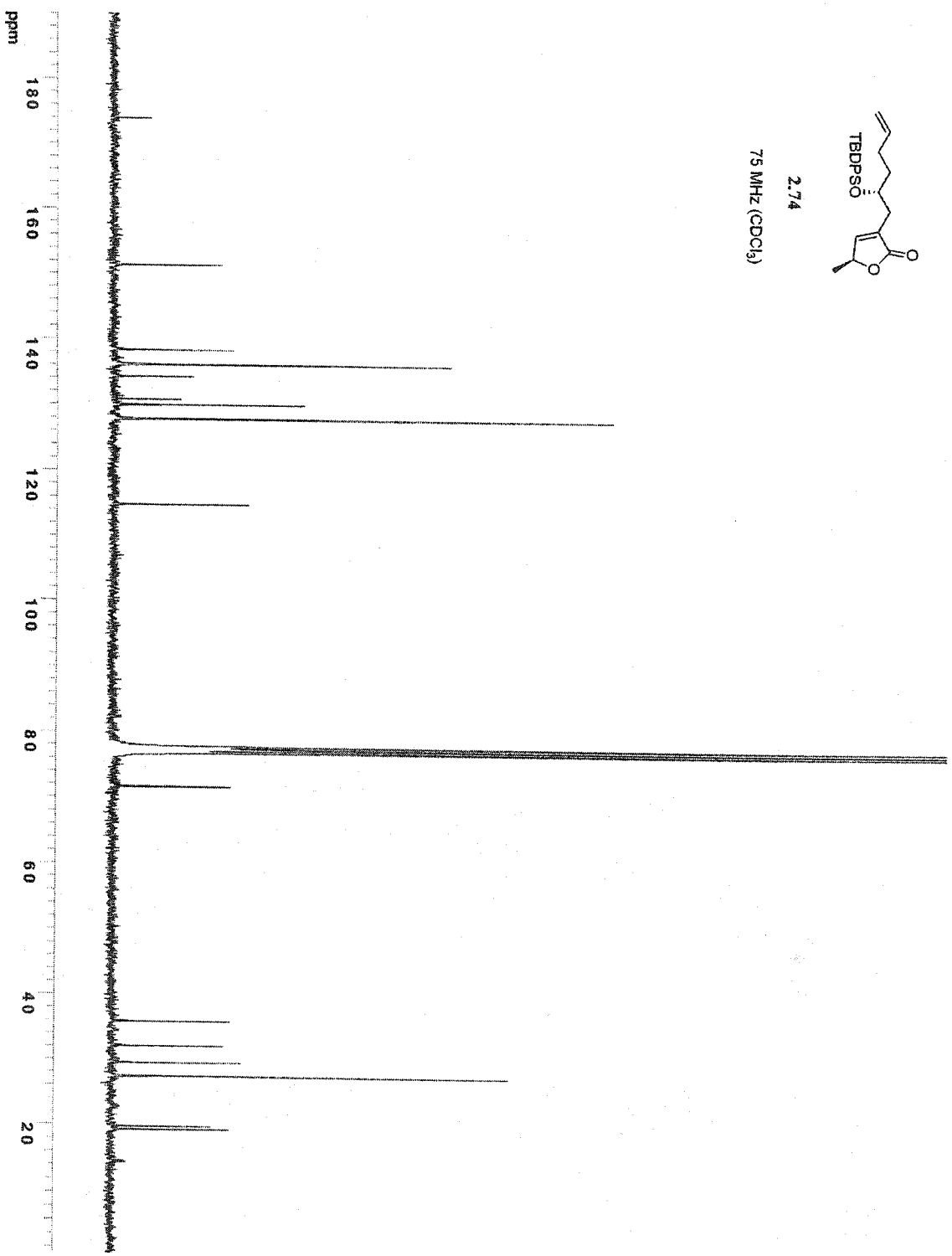


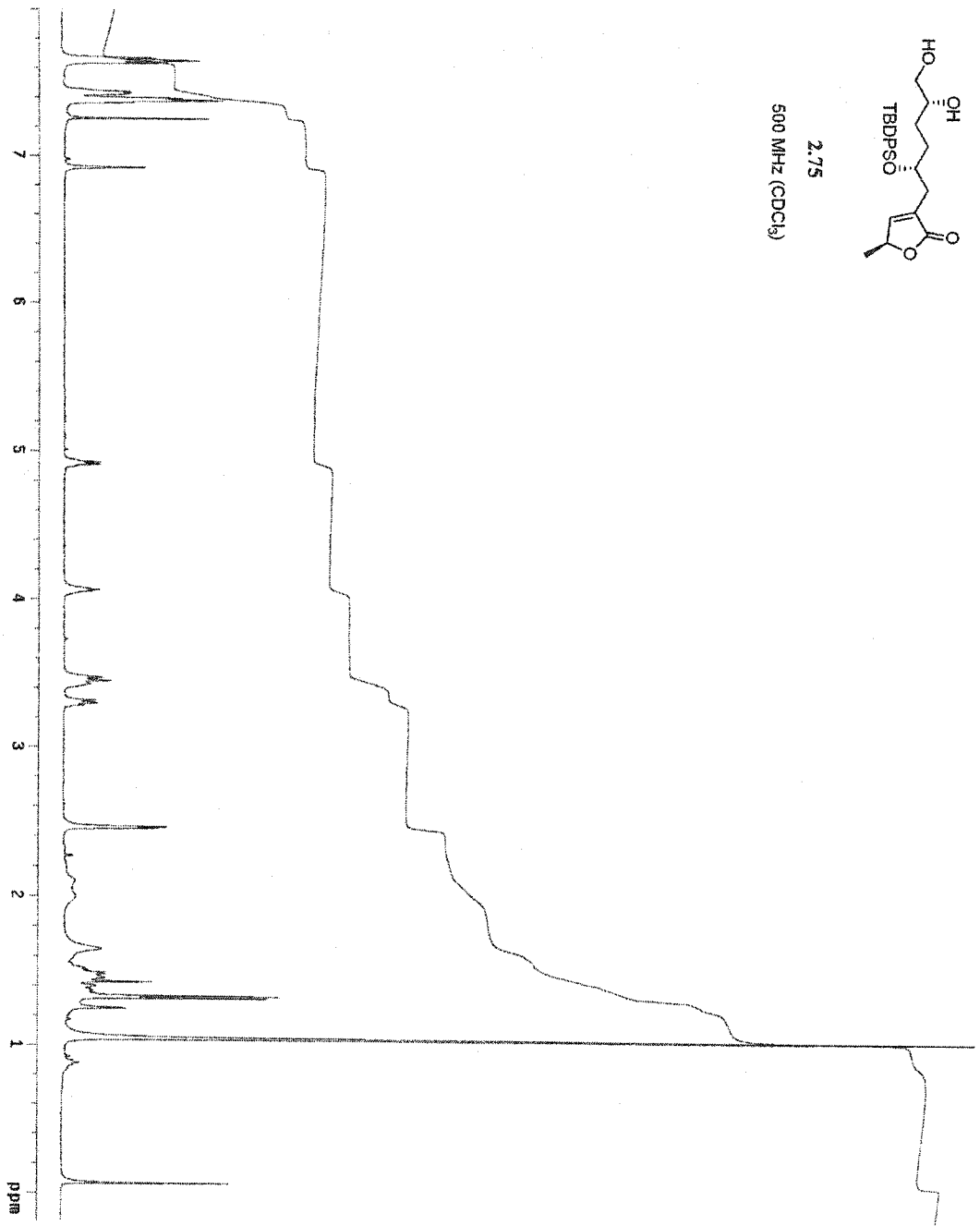


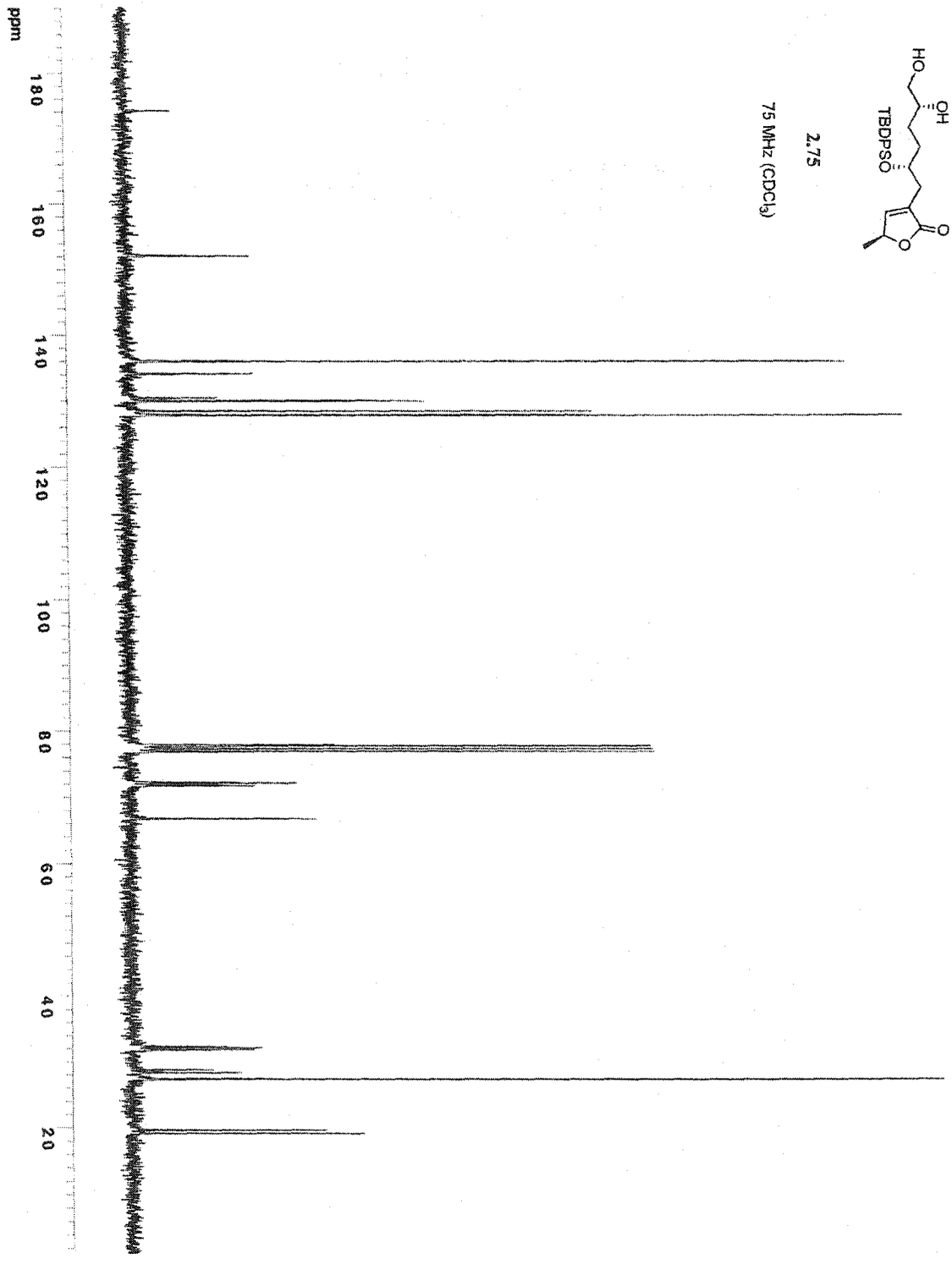


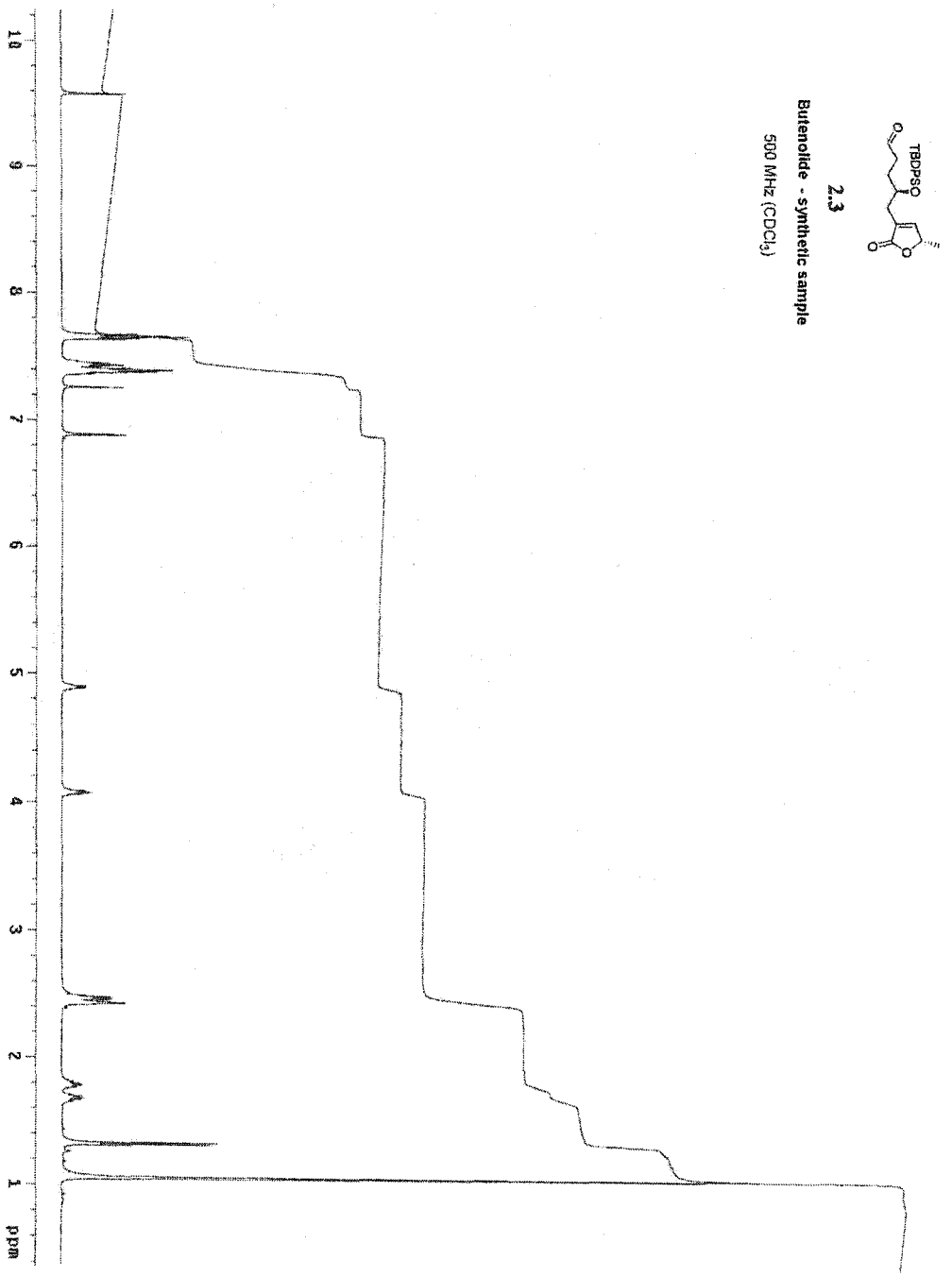


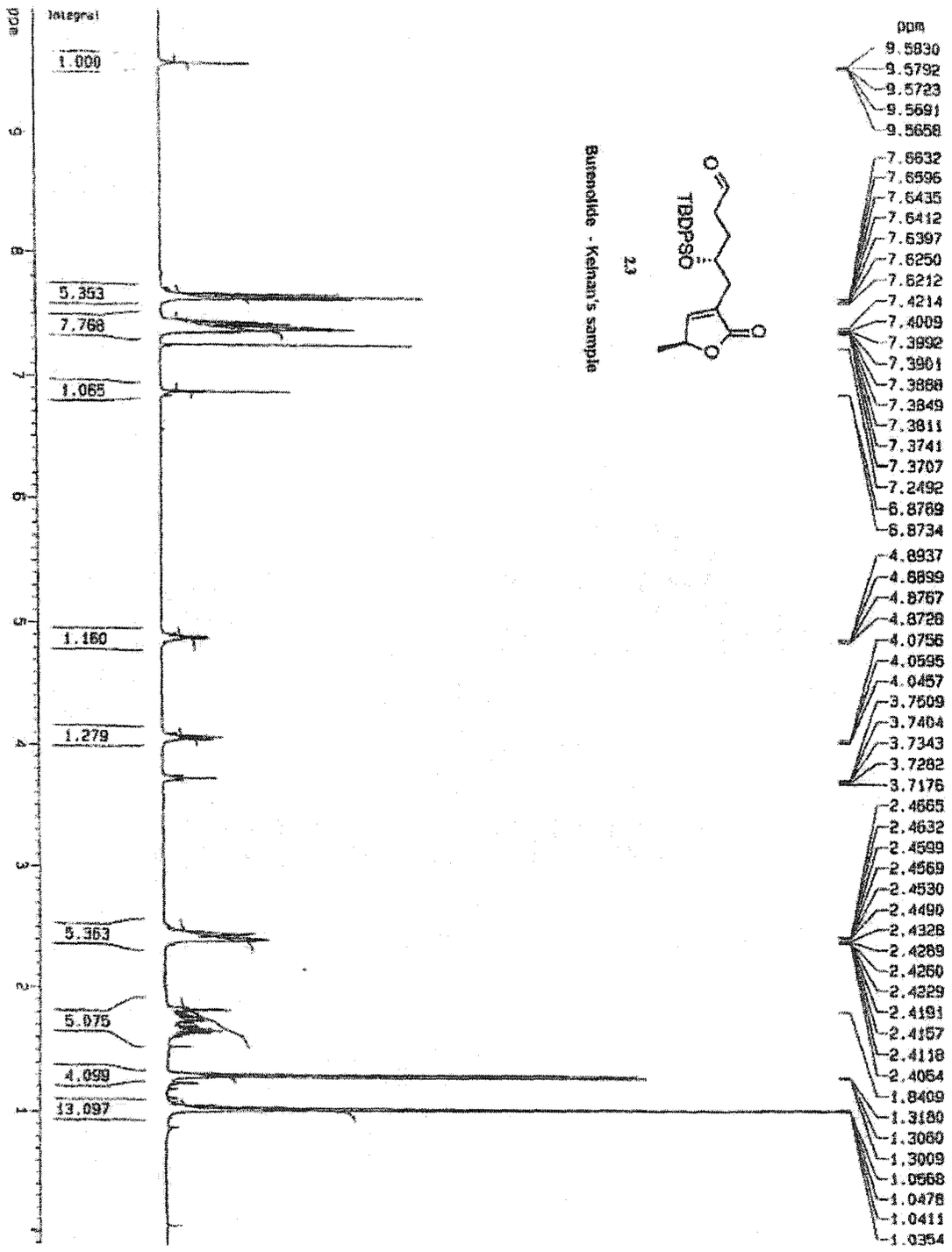


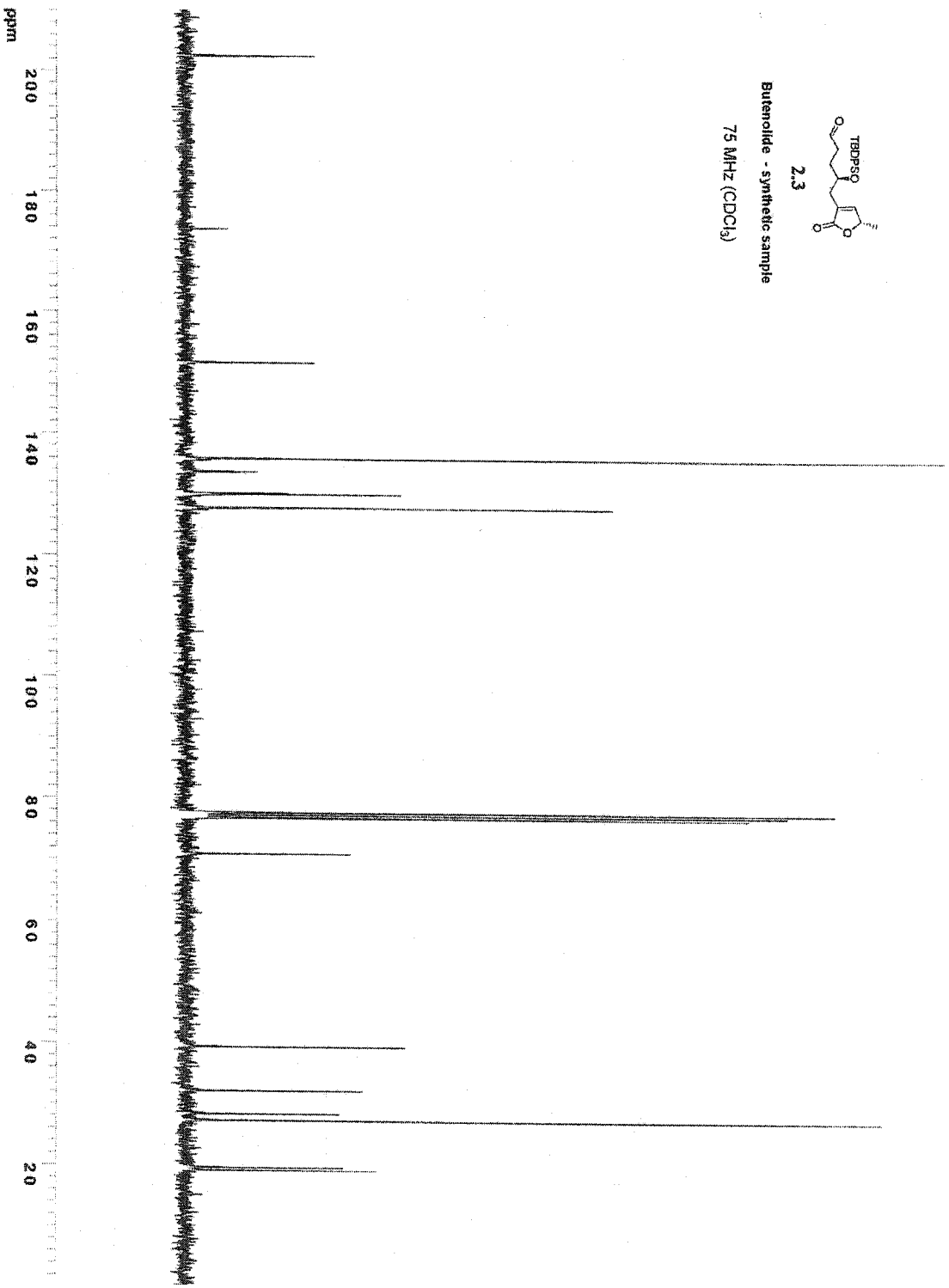


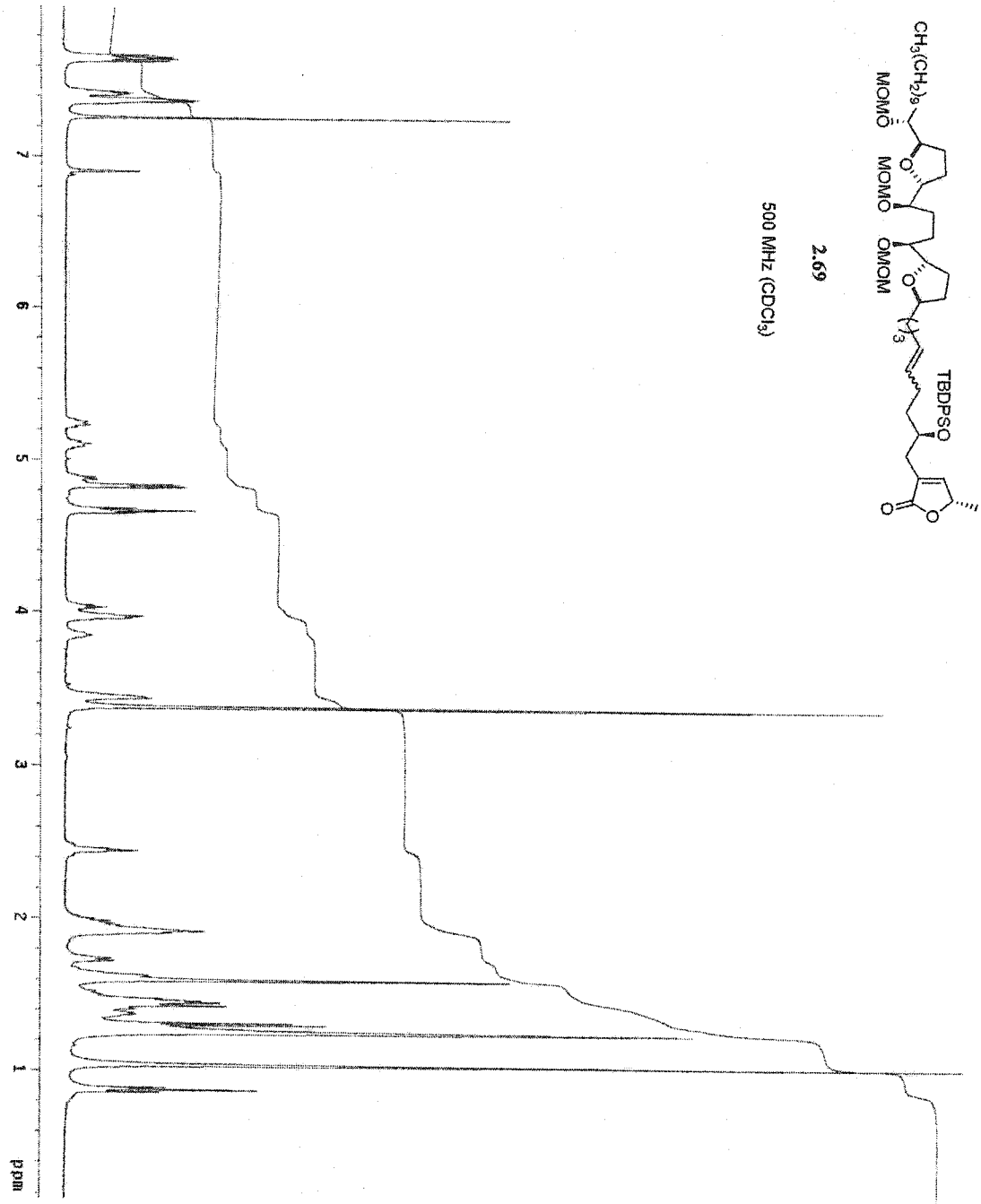


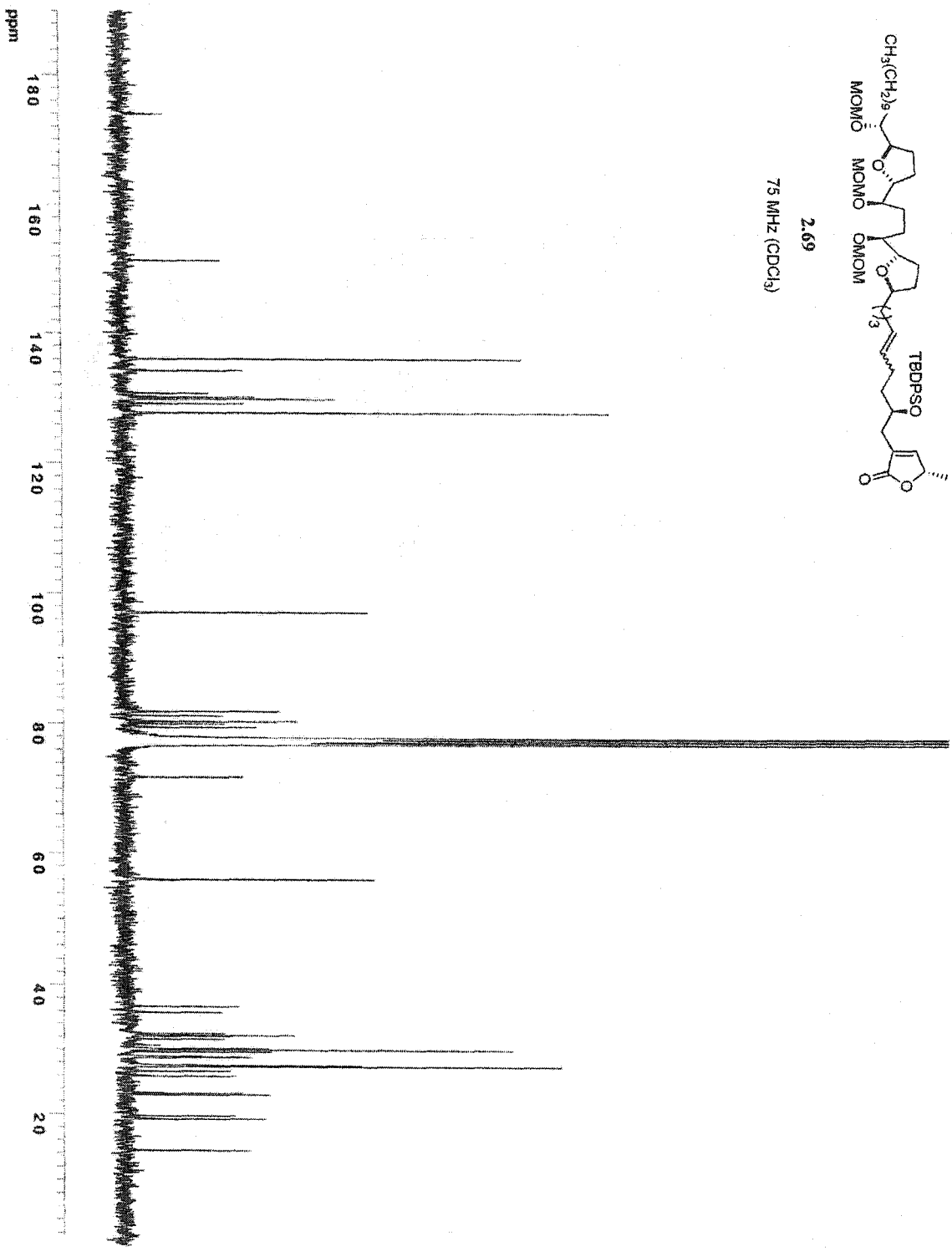


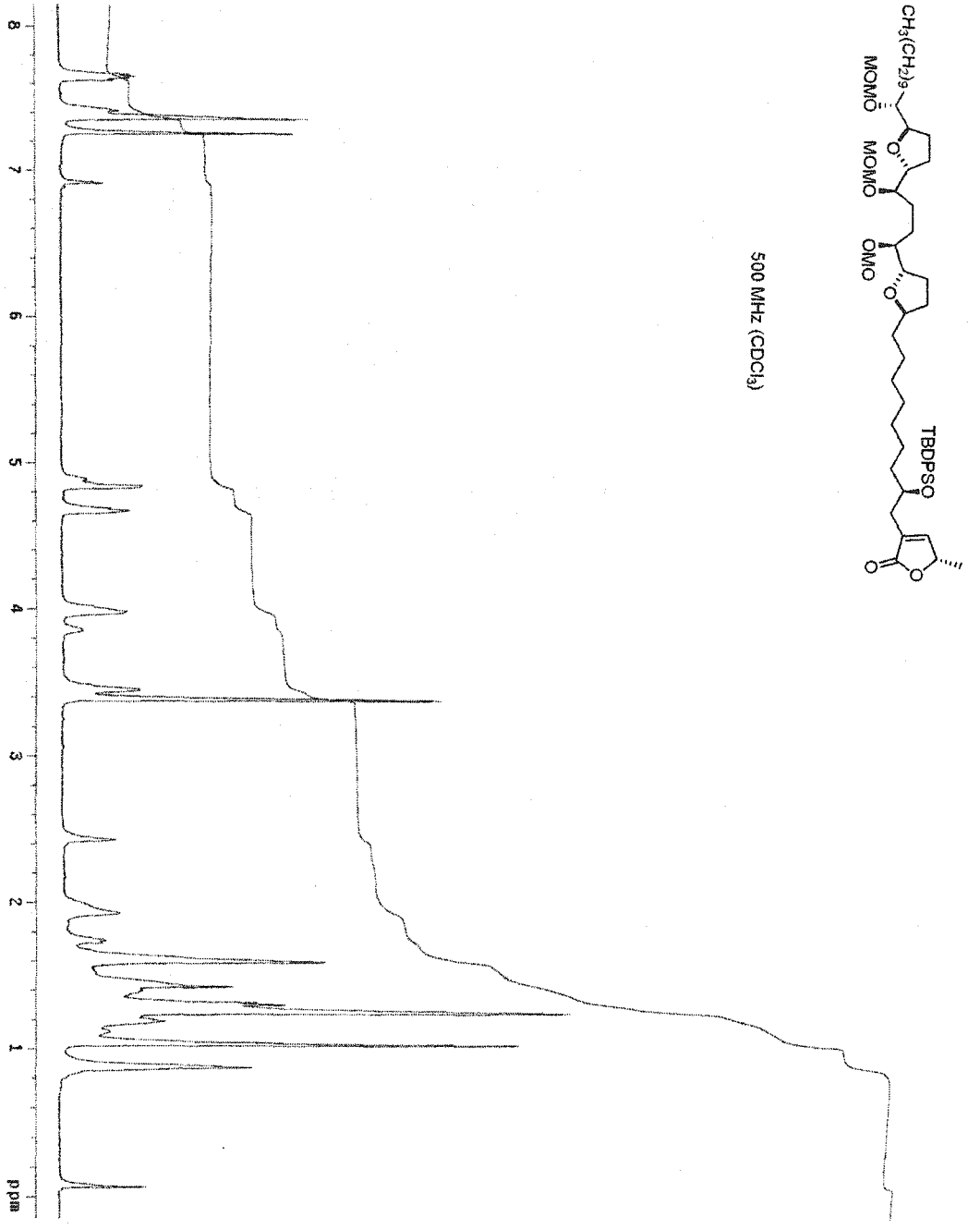


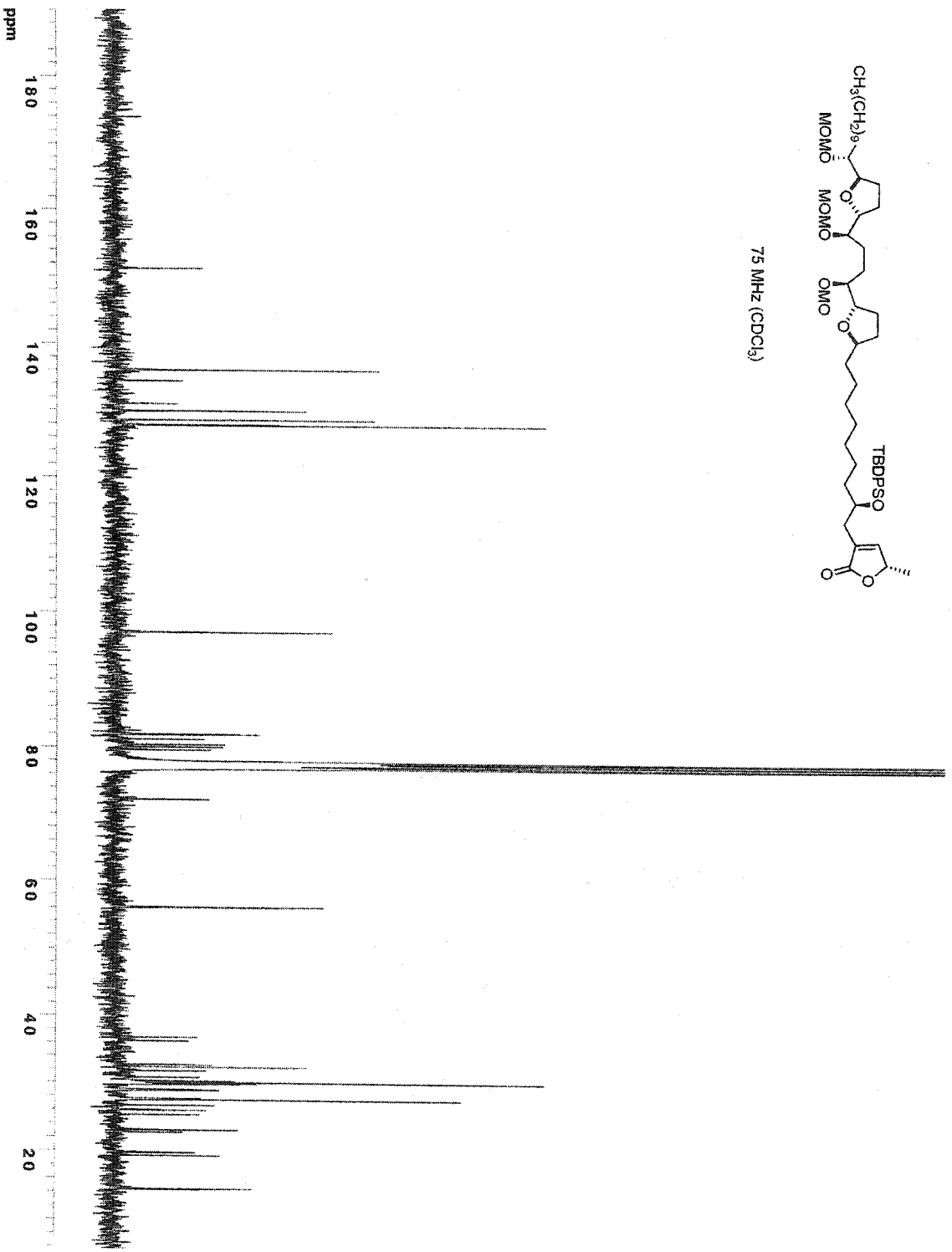


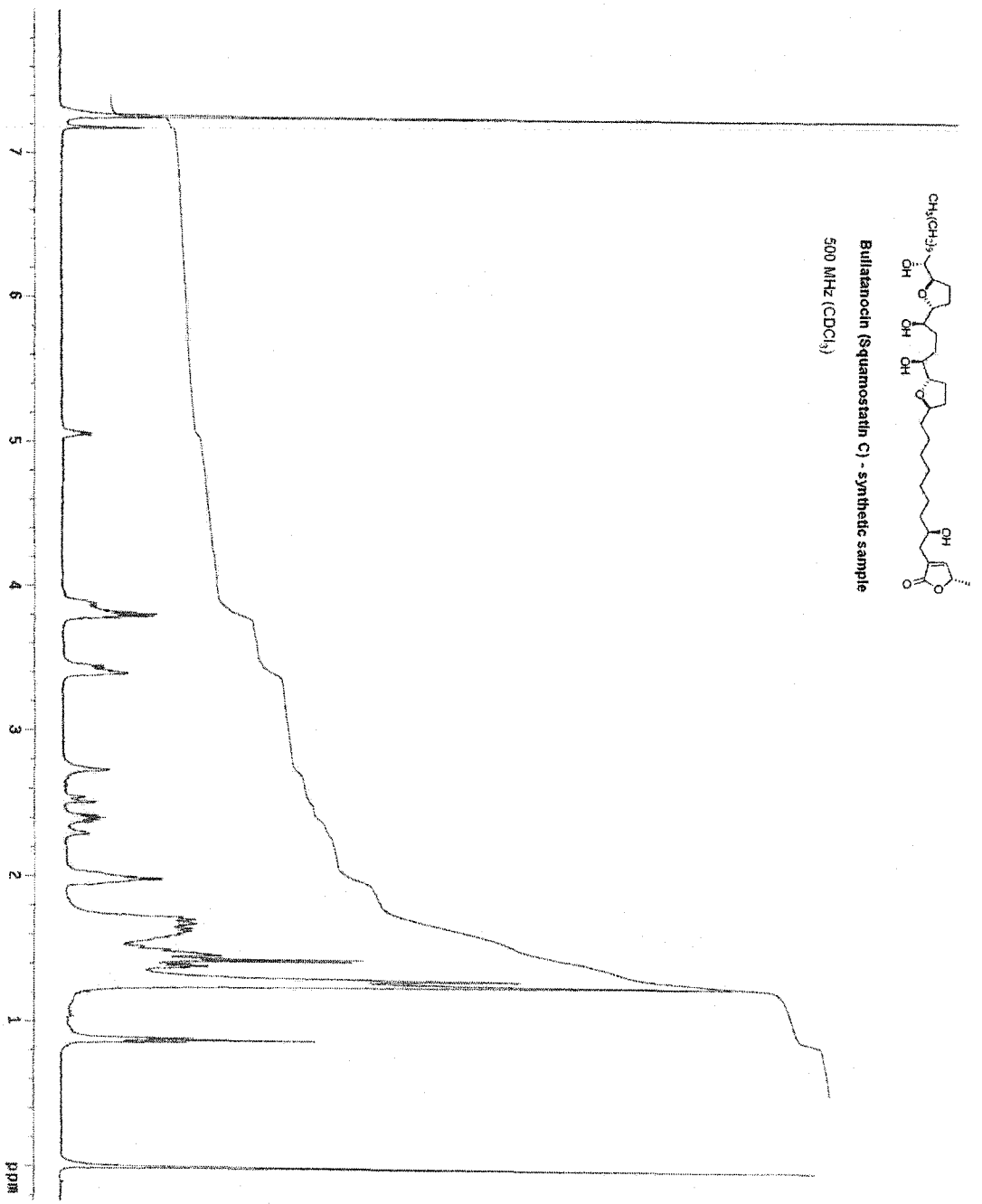


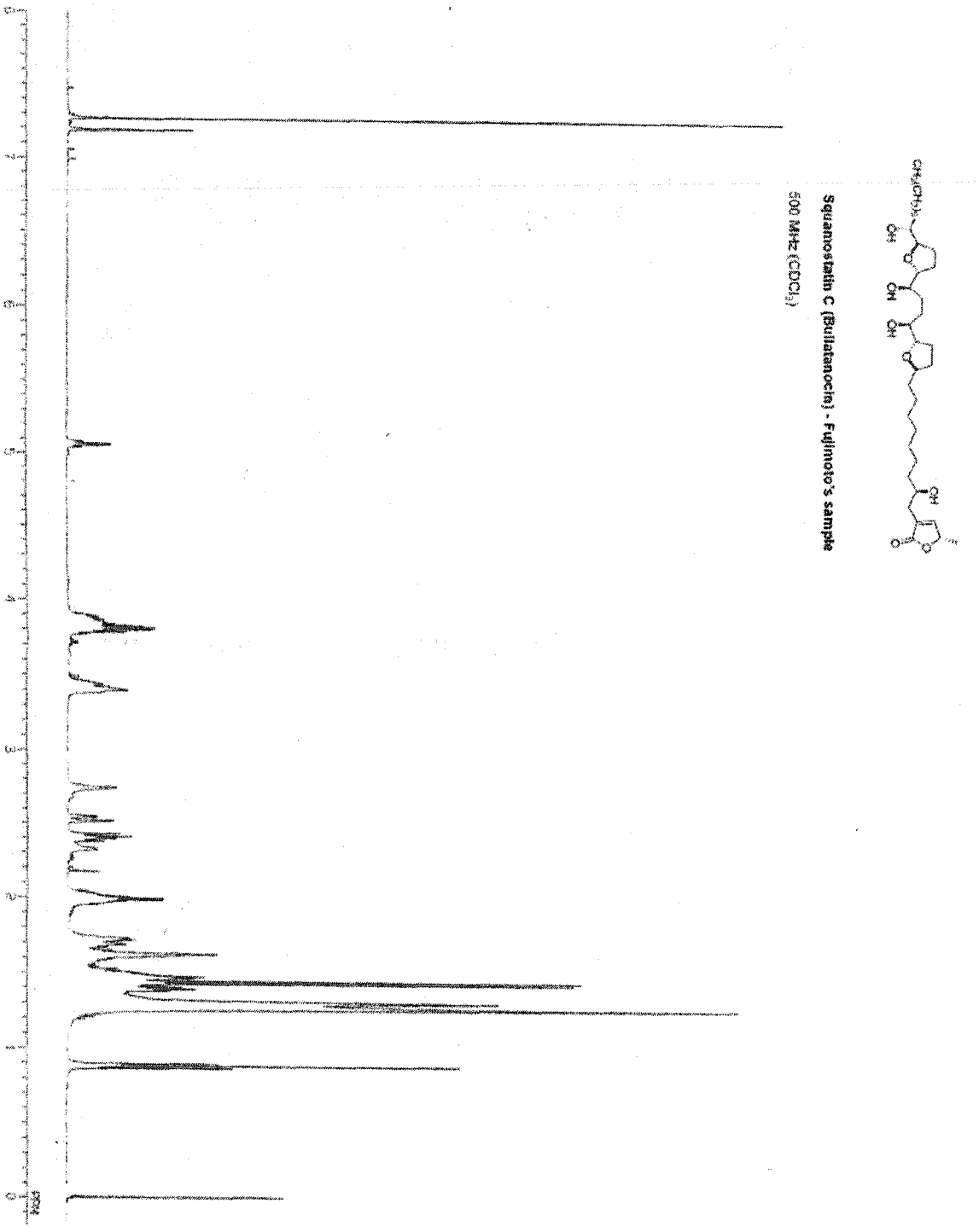


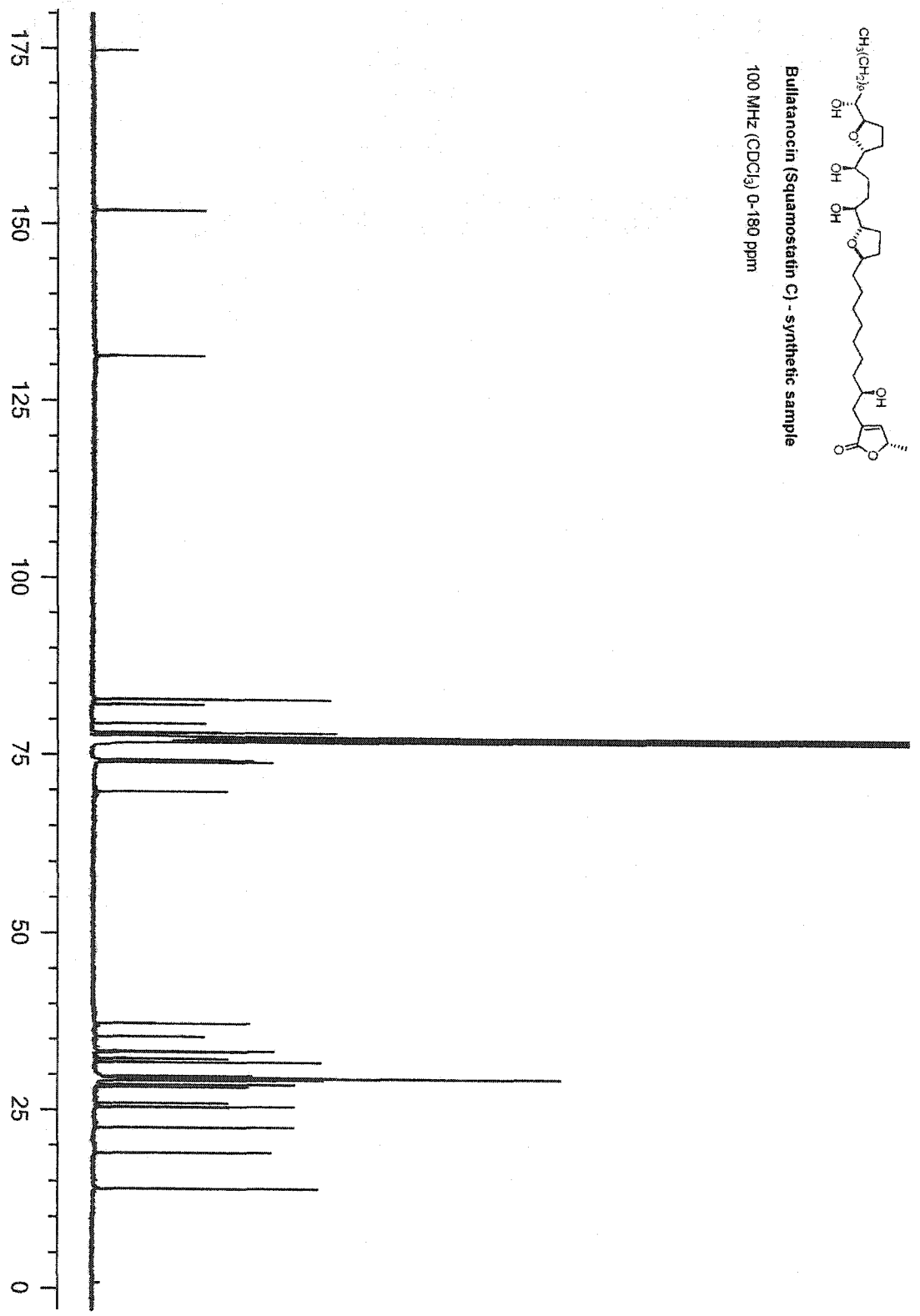


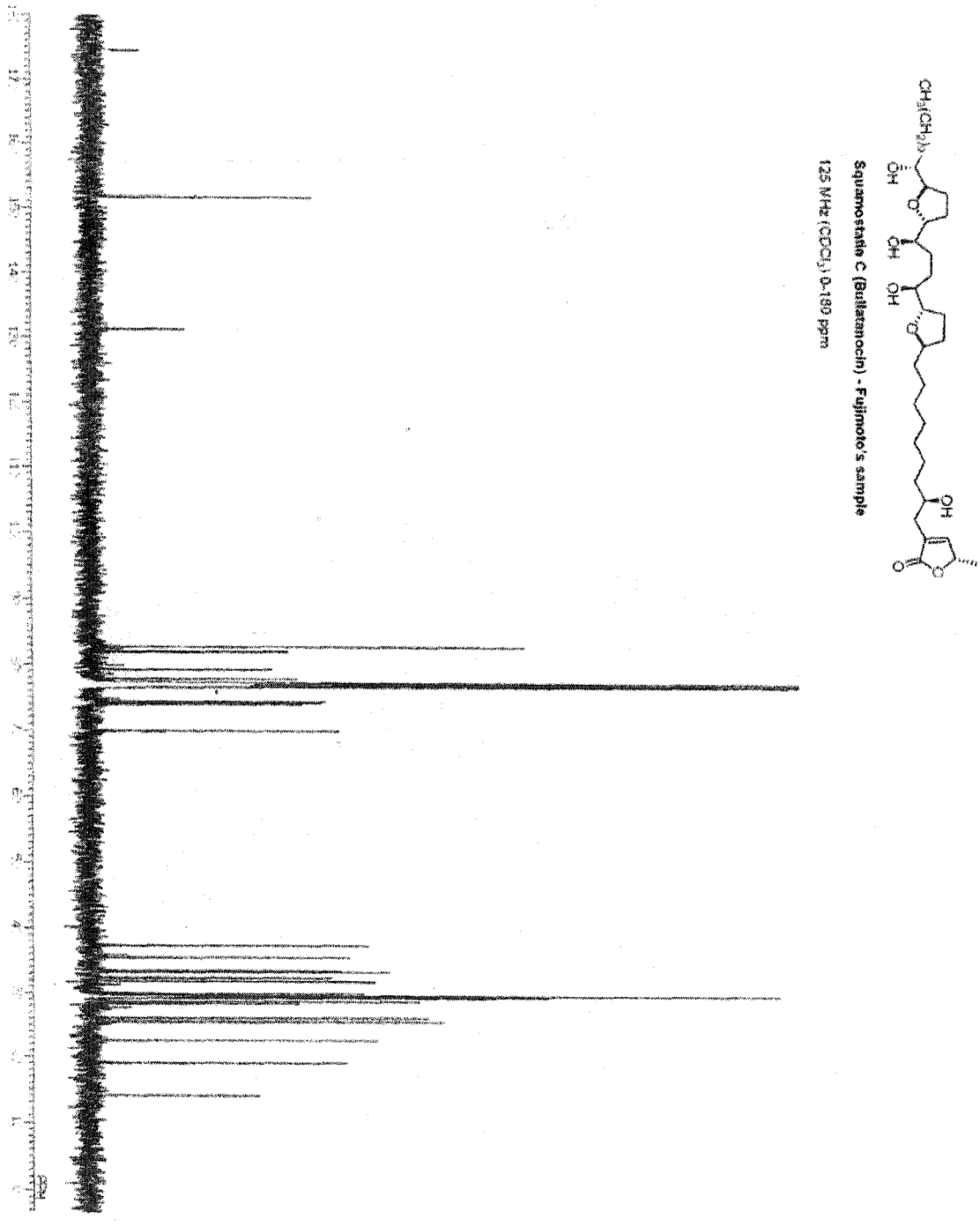


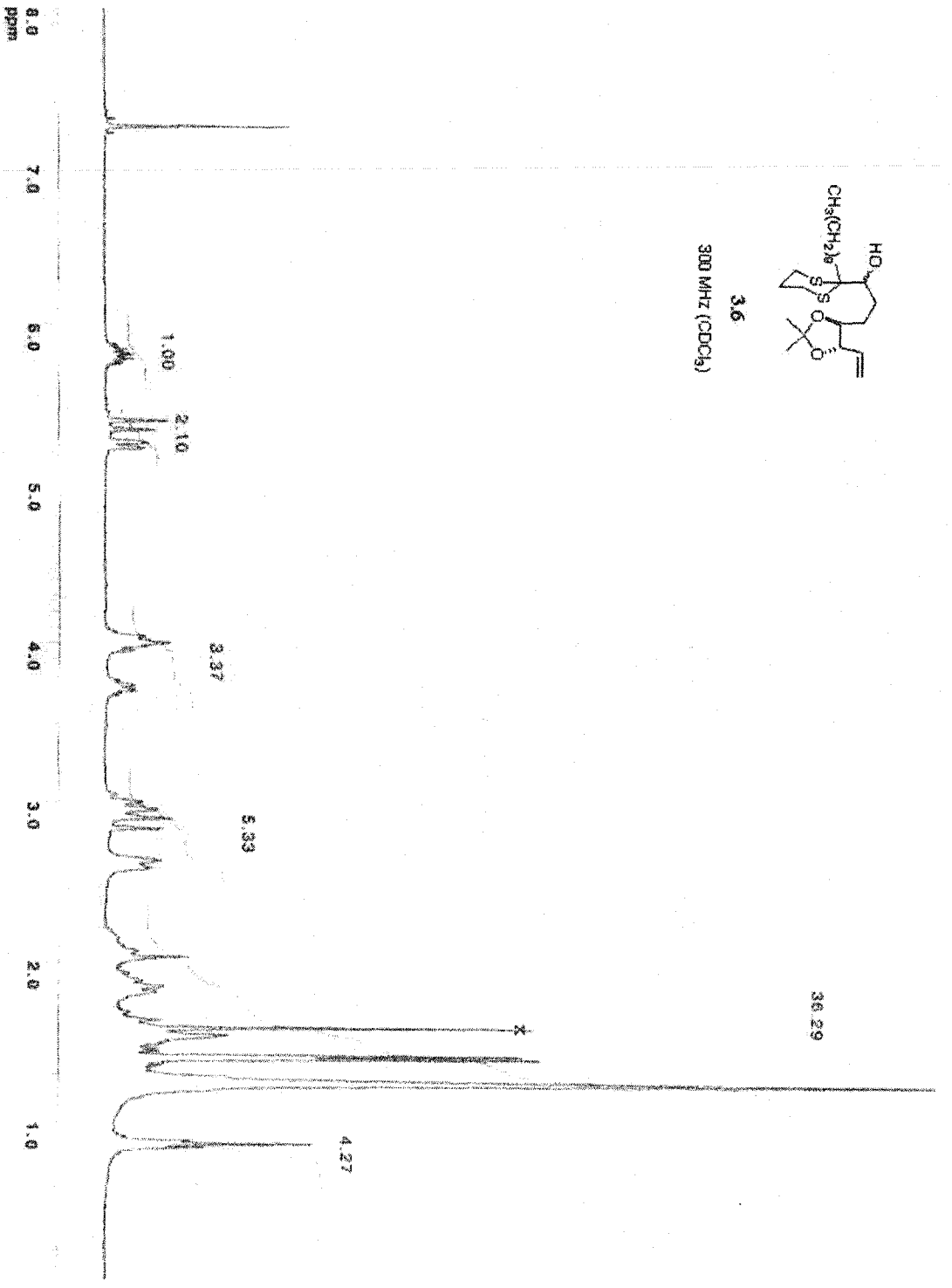


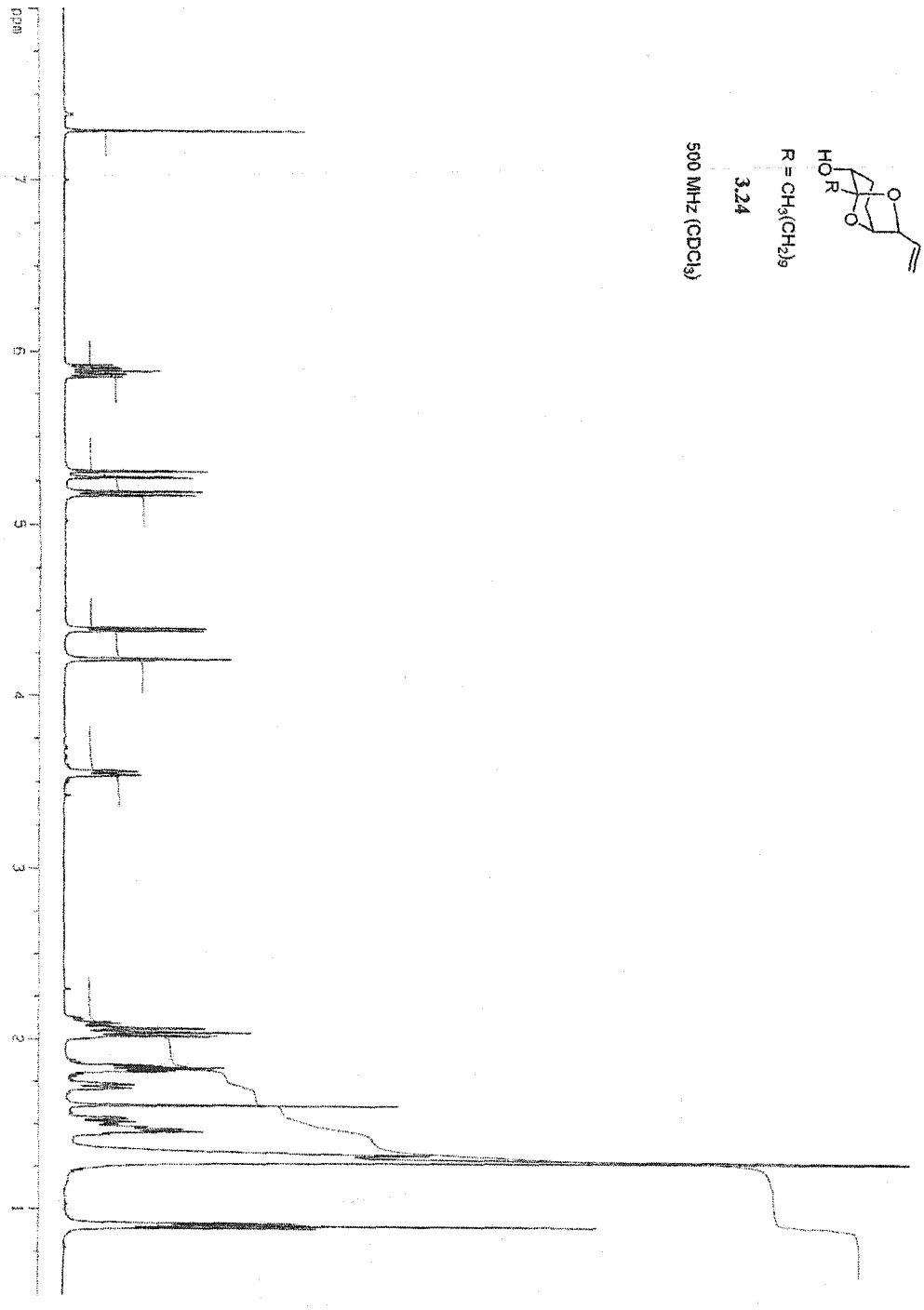


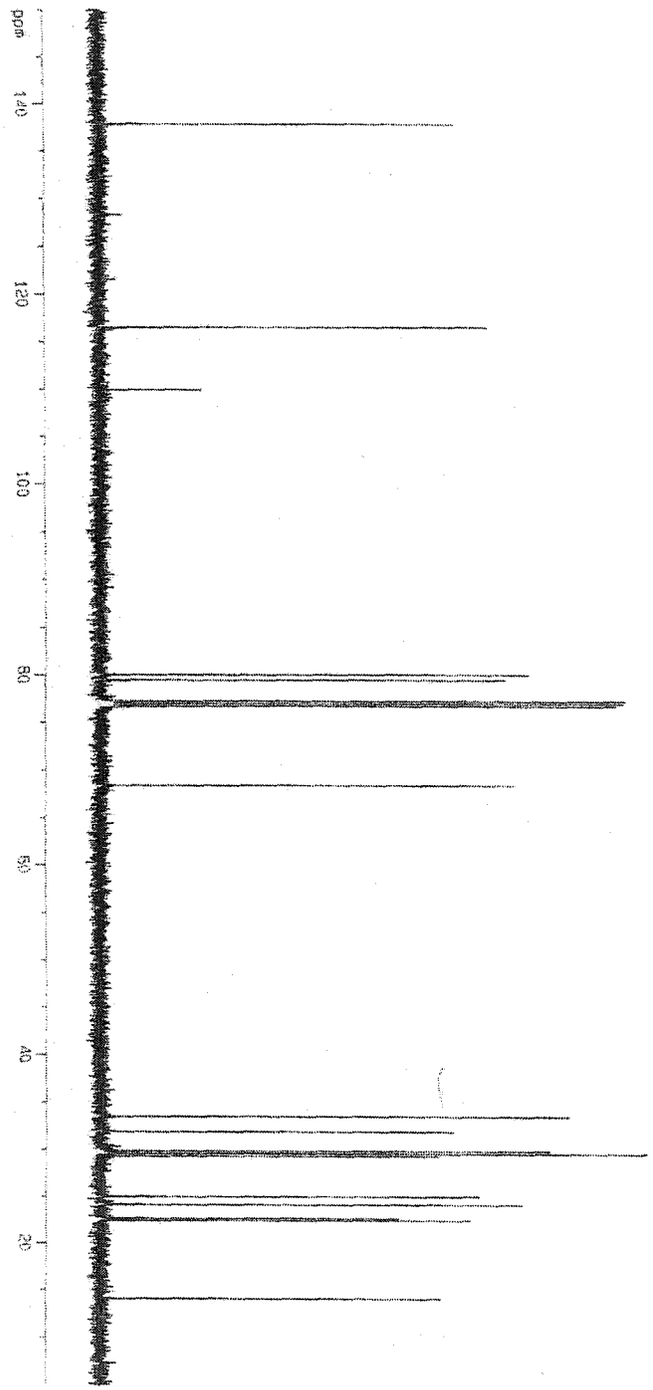


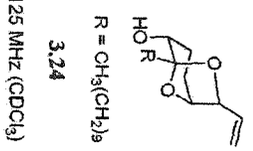








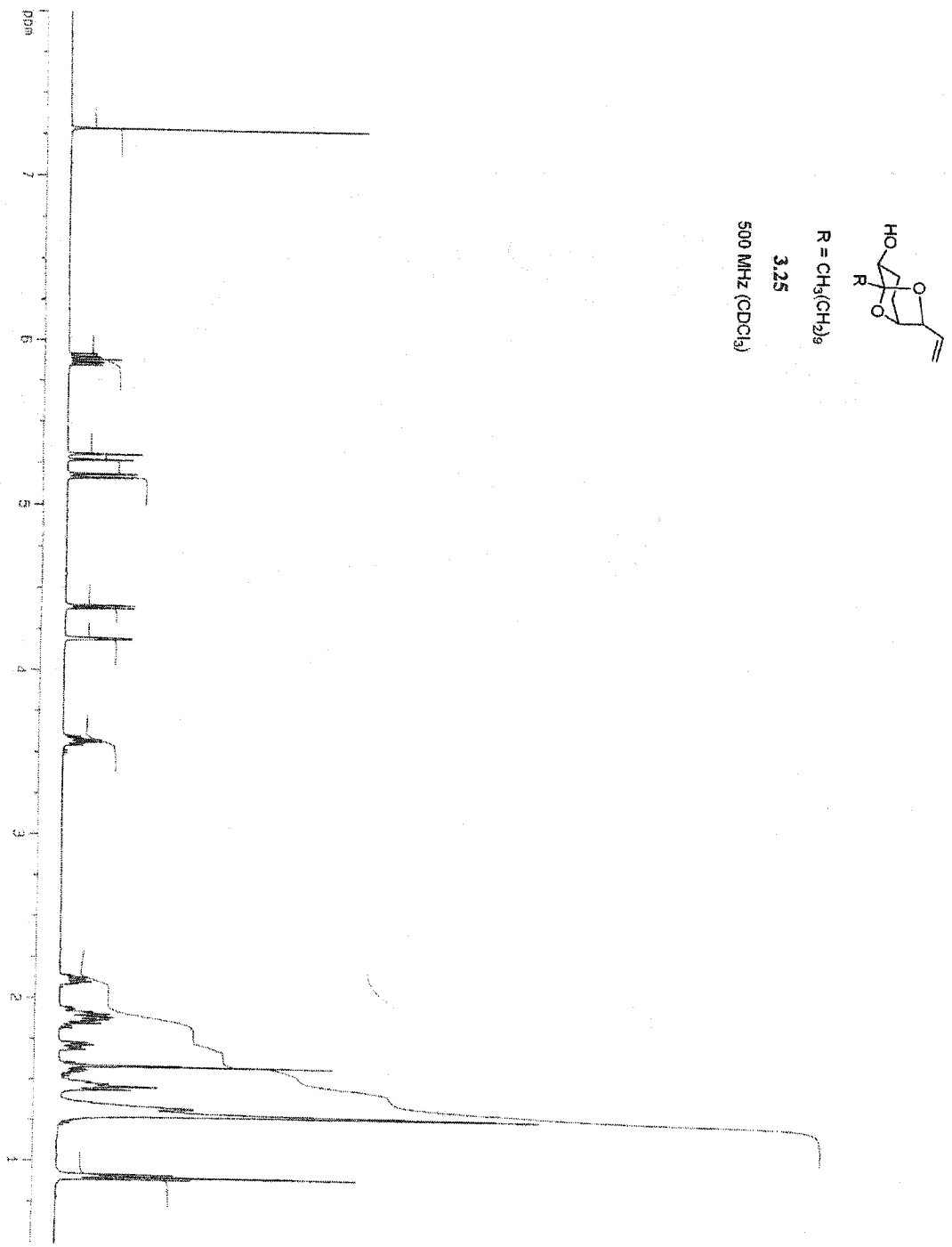


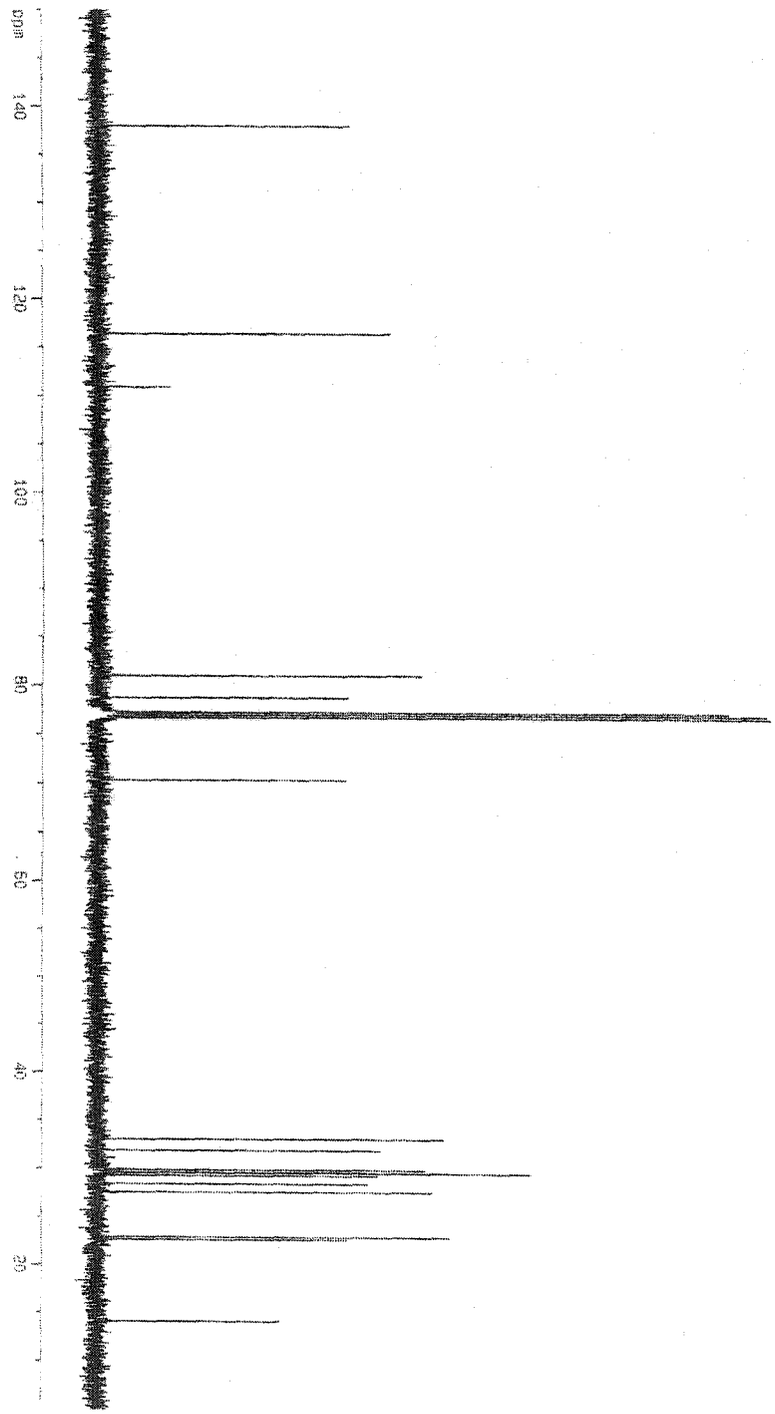


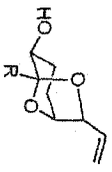
R = $CH_3(CH_2)_9$

3.24

125 MHz ($CDCl_3$)



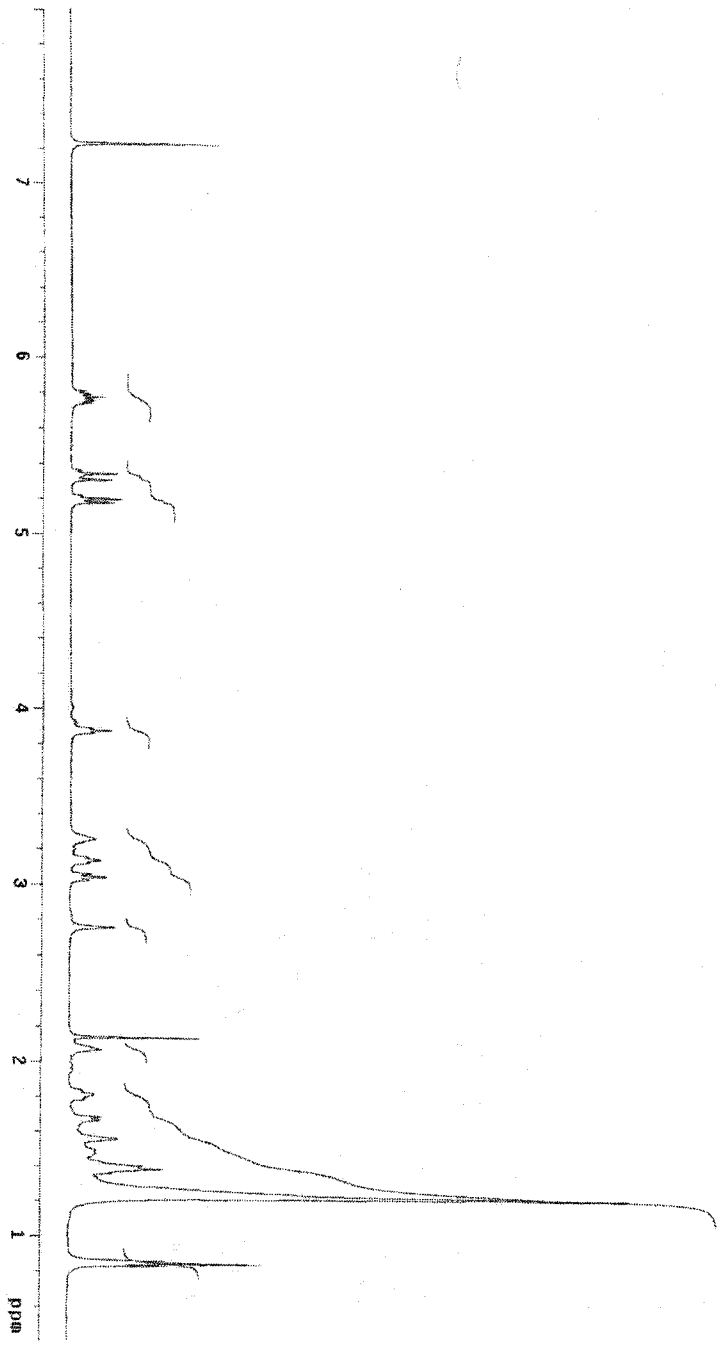


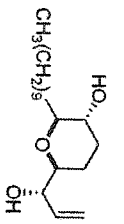


R = $CH_3(CH_2)_9$

3,25

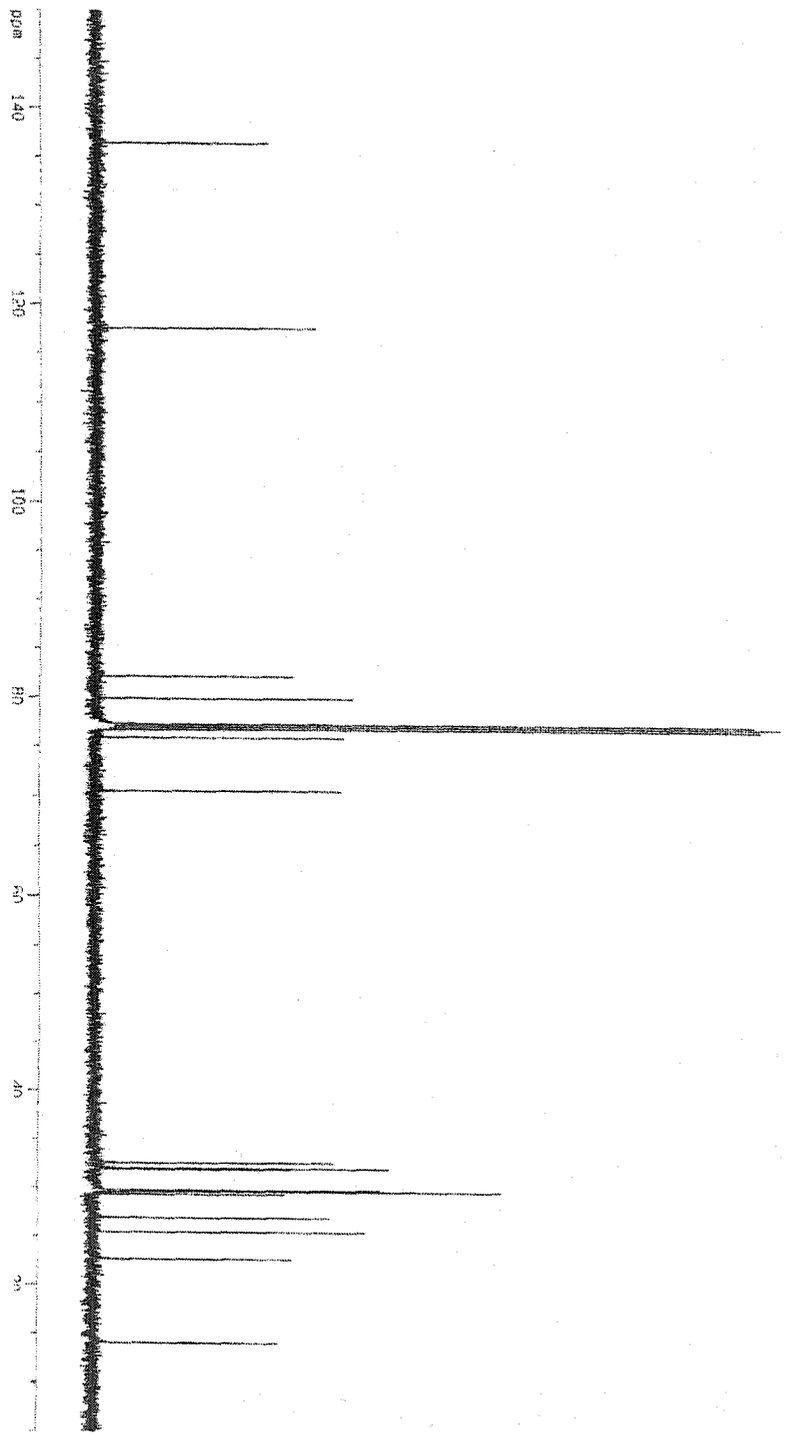
125 MHz ($CDCl_3$)





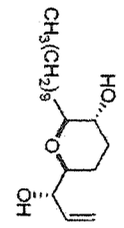
3.4

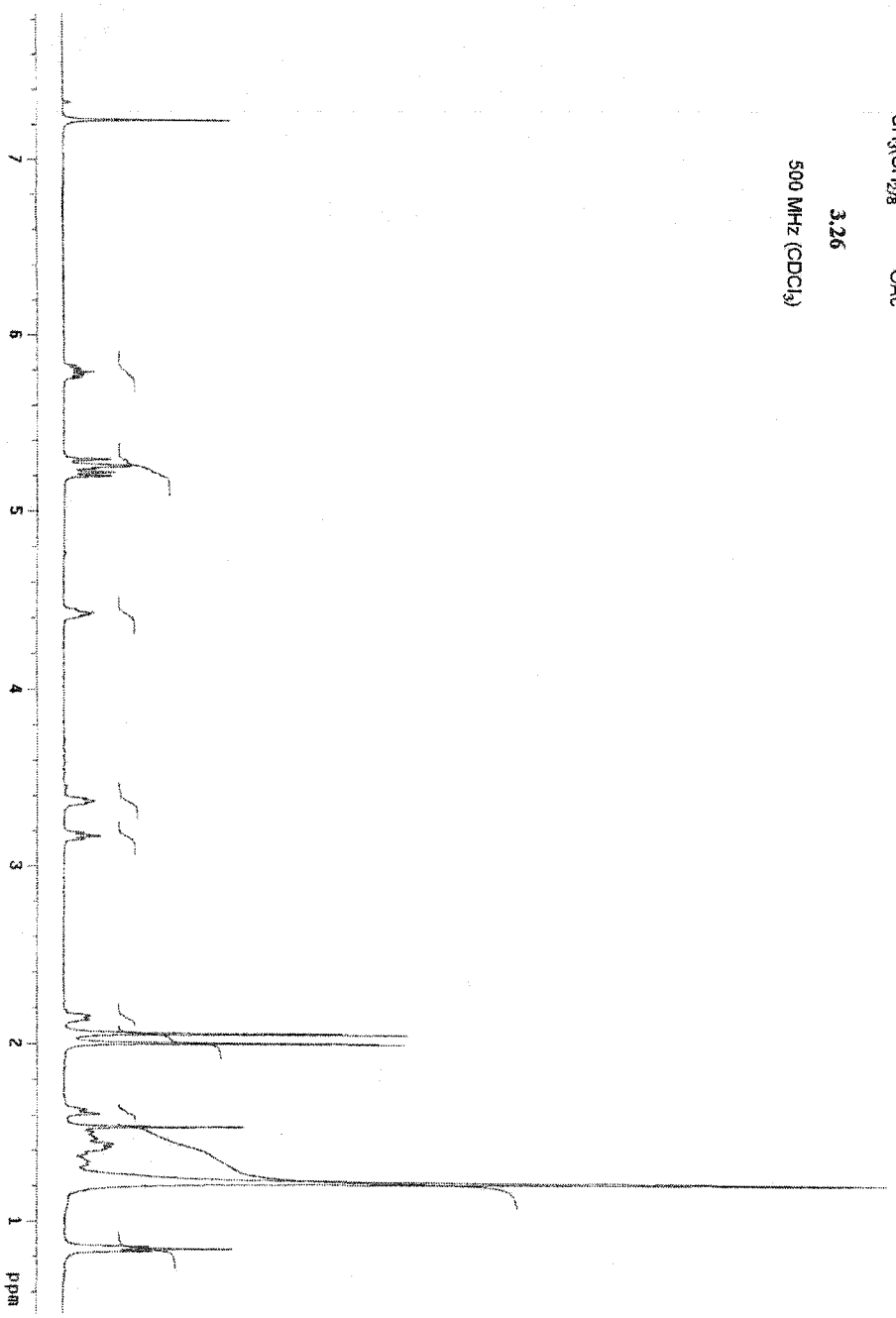
500 MHz ($CDCl_3$)

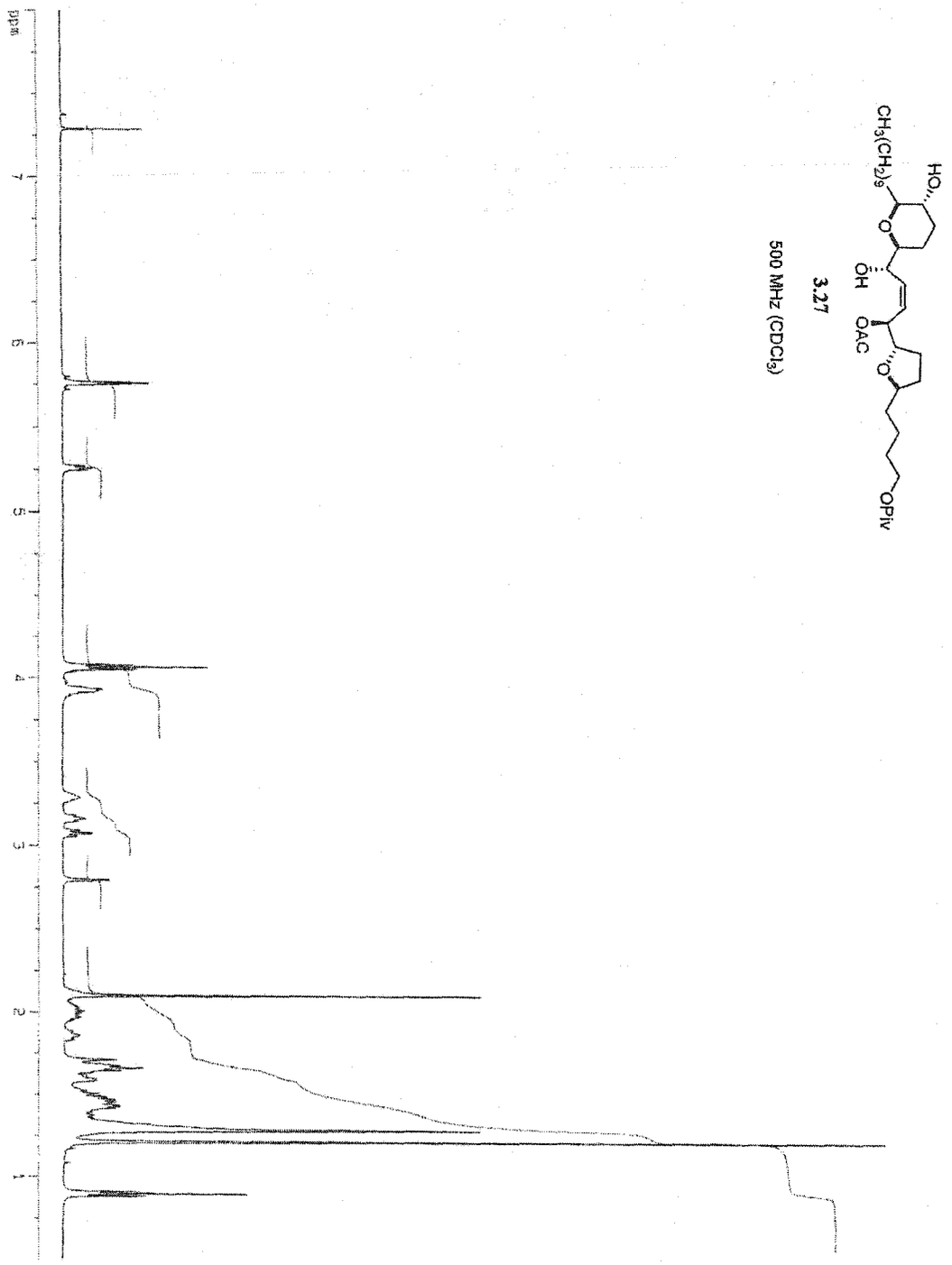


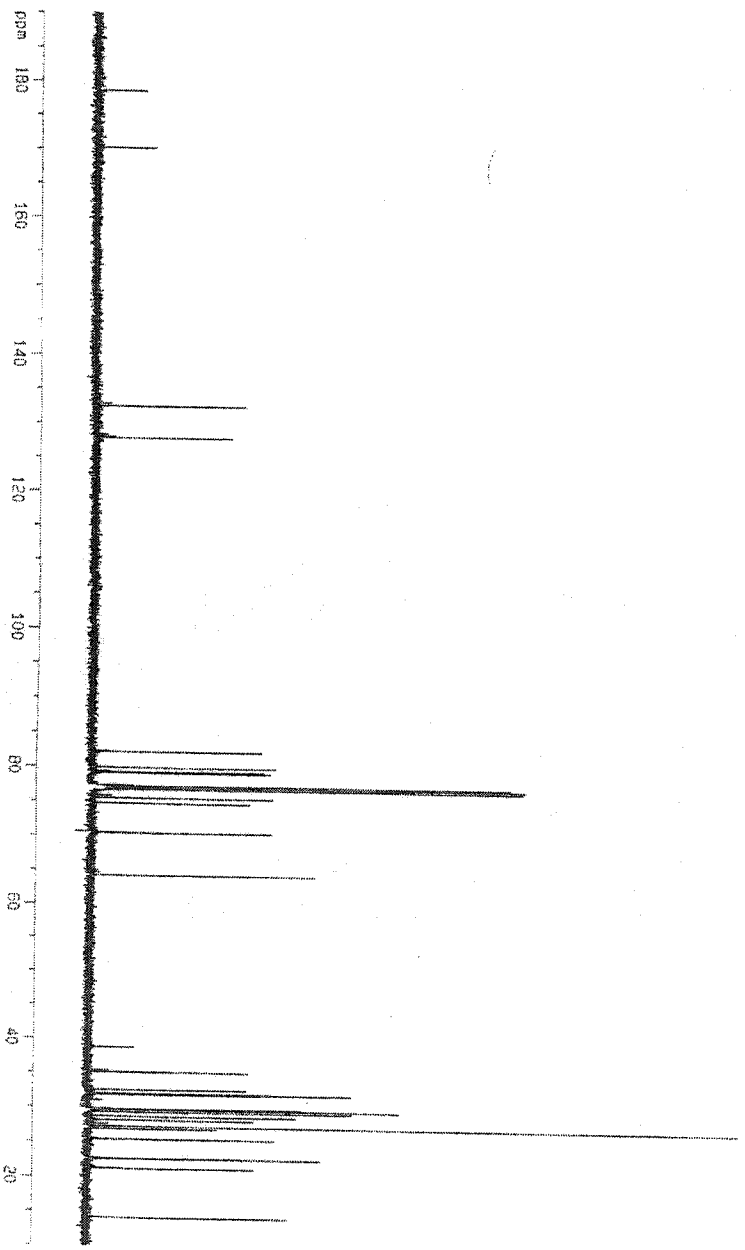
3.4

125 MHz ($CDCl_3$)



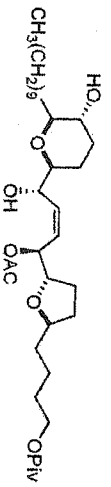


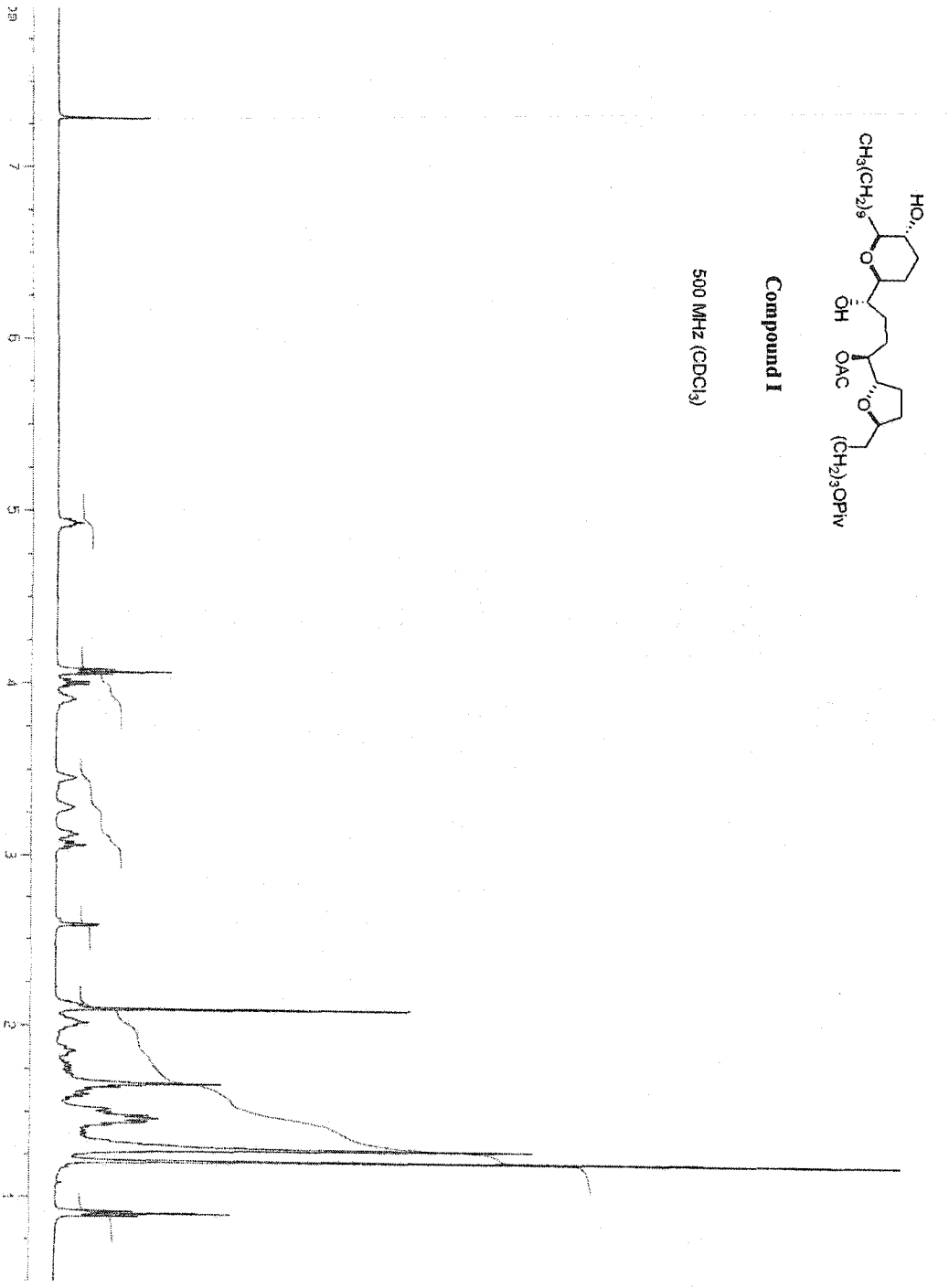


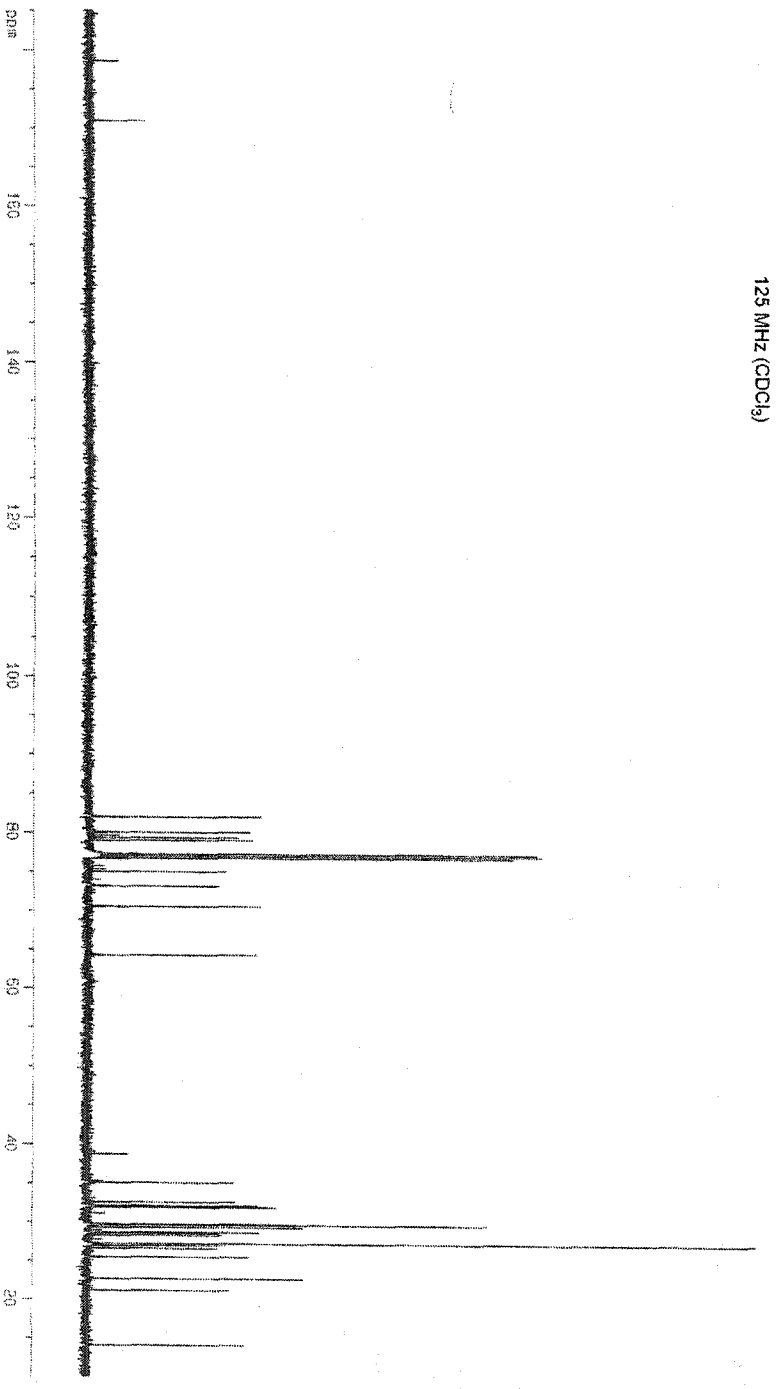


3.27

125 MHz ($CDCl_3$)

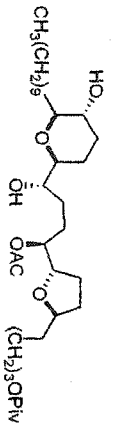


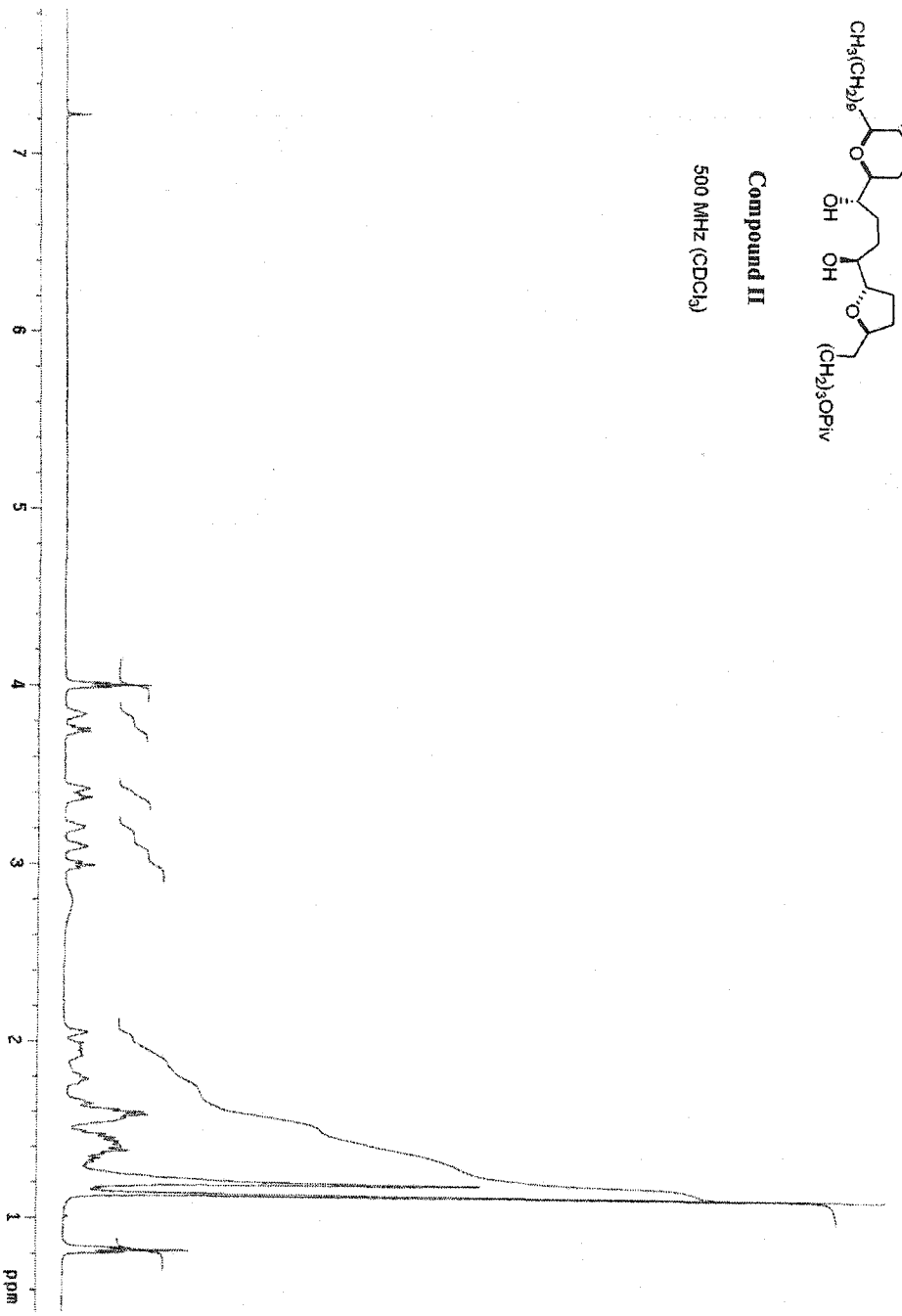


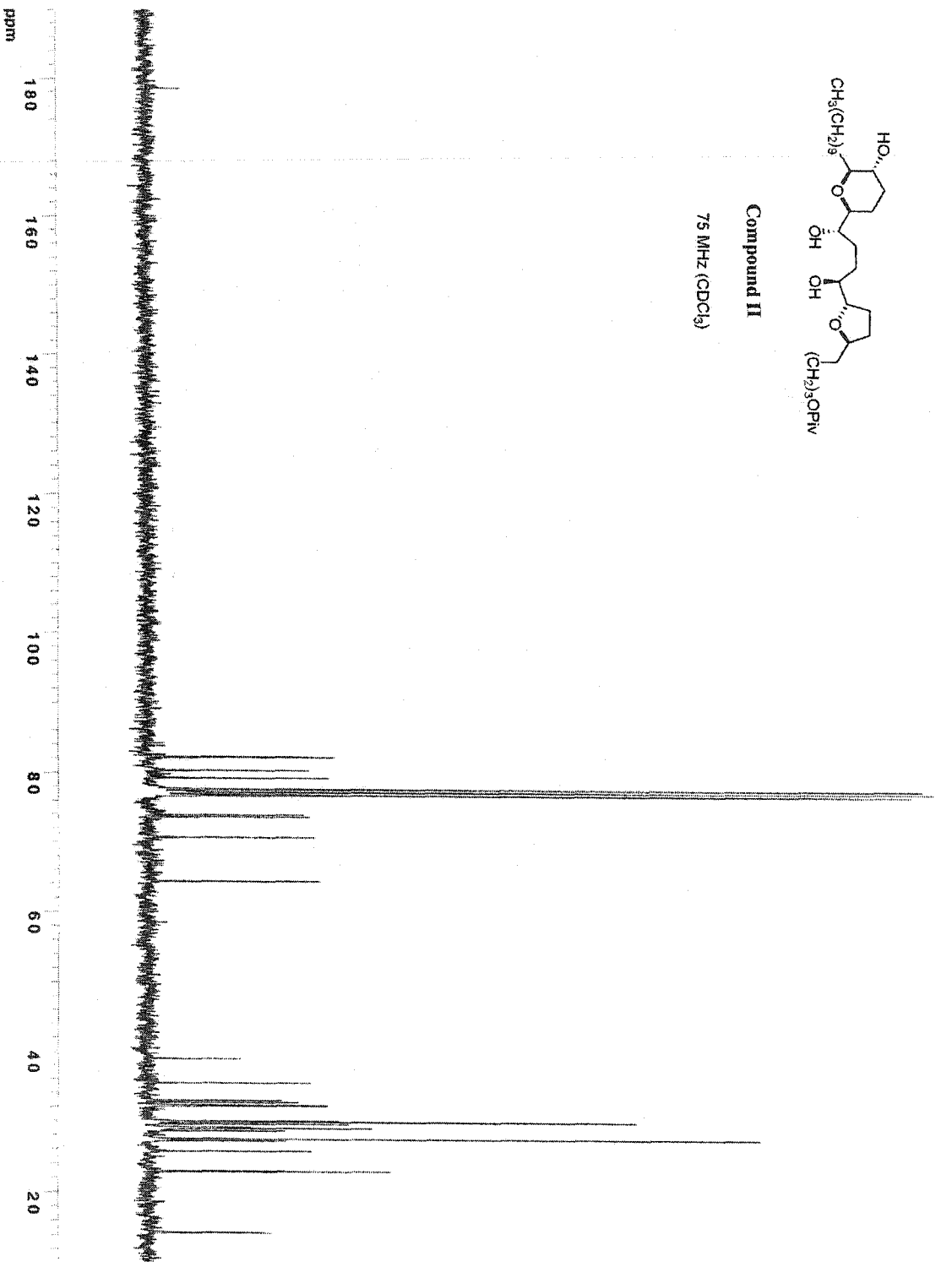


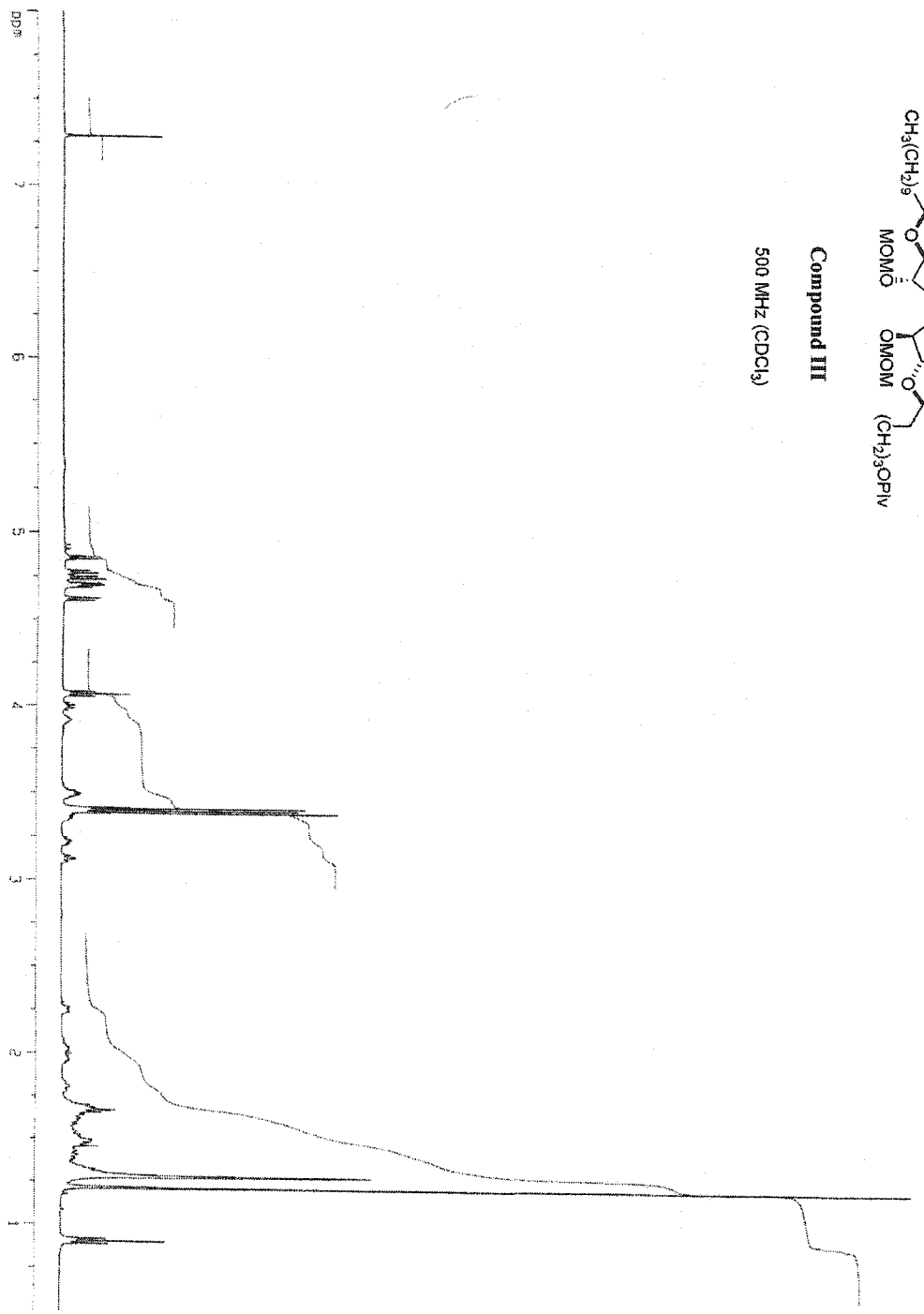
Compound I

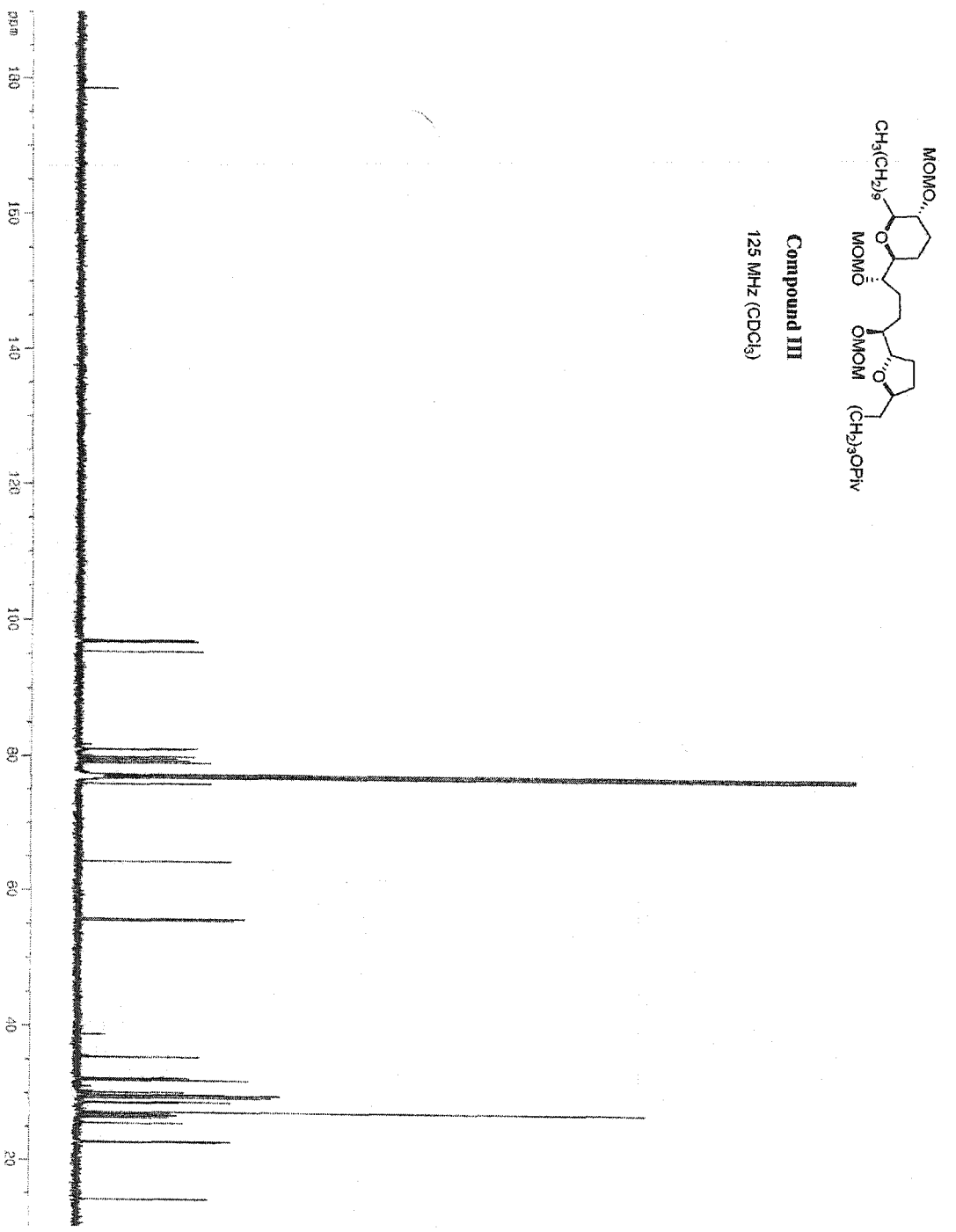
125 MHz ($CDCl_3$)

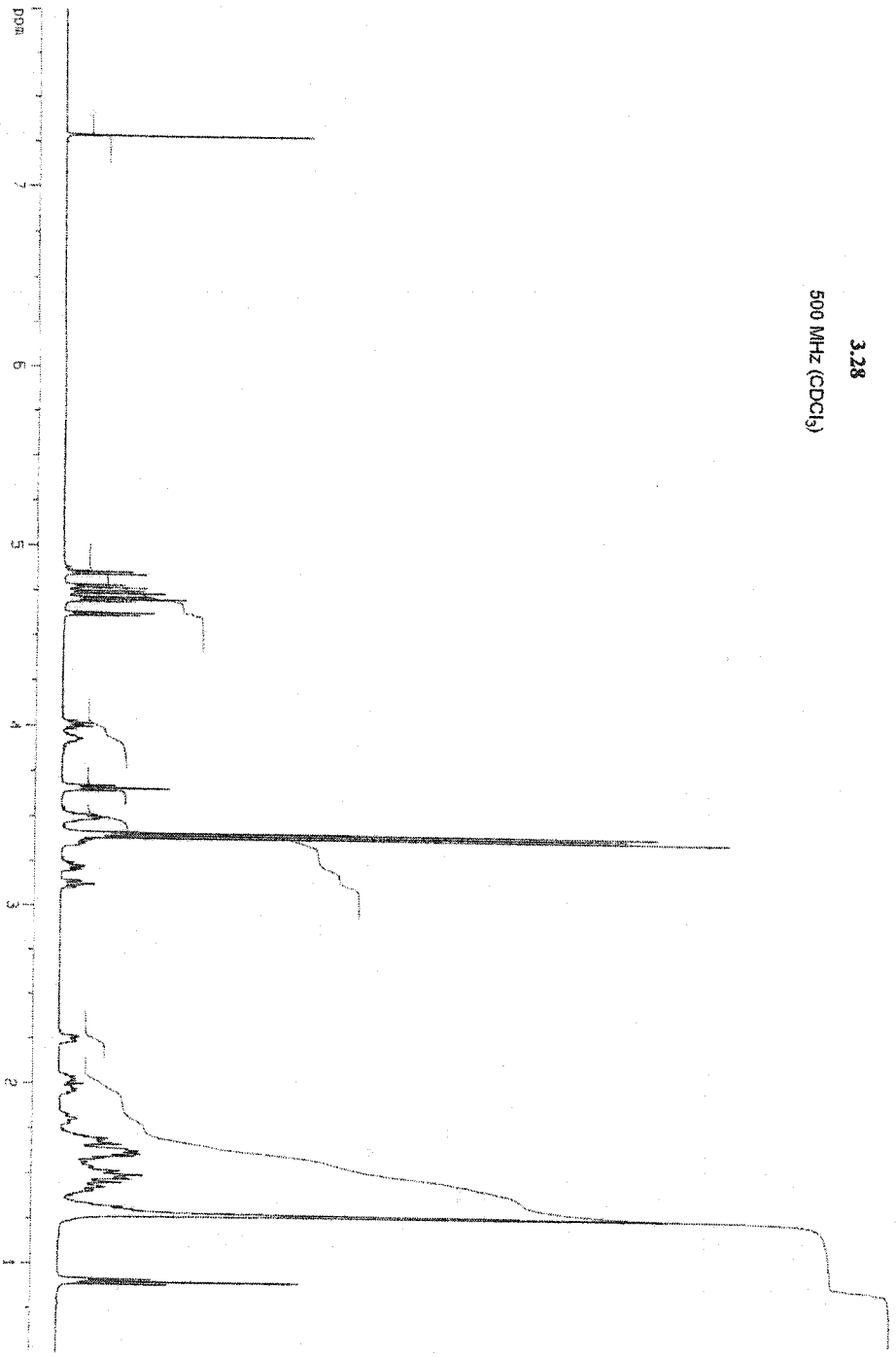


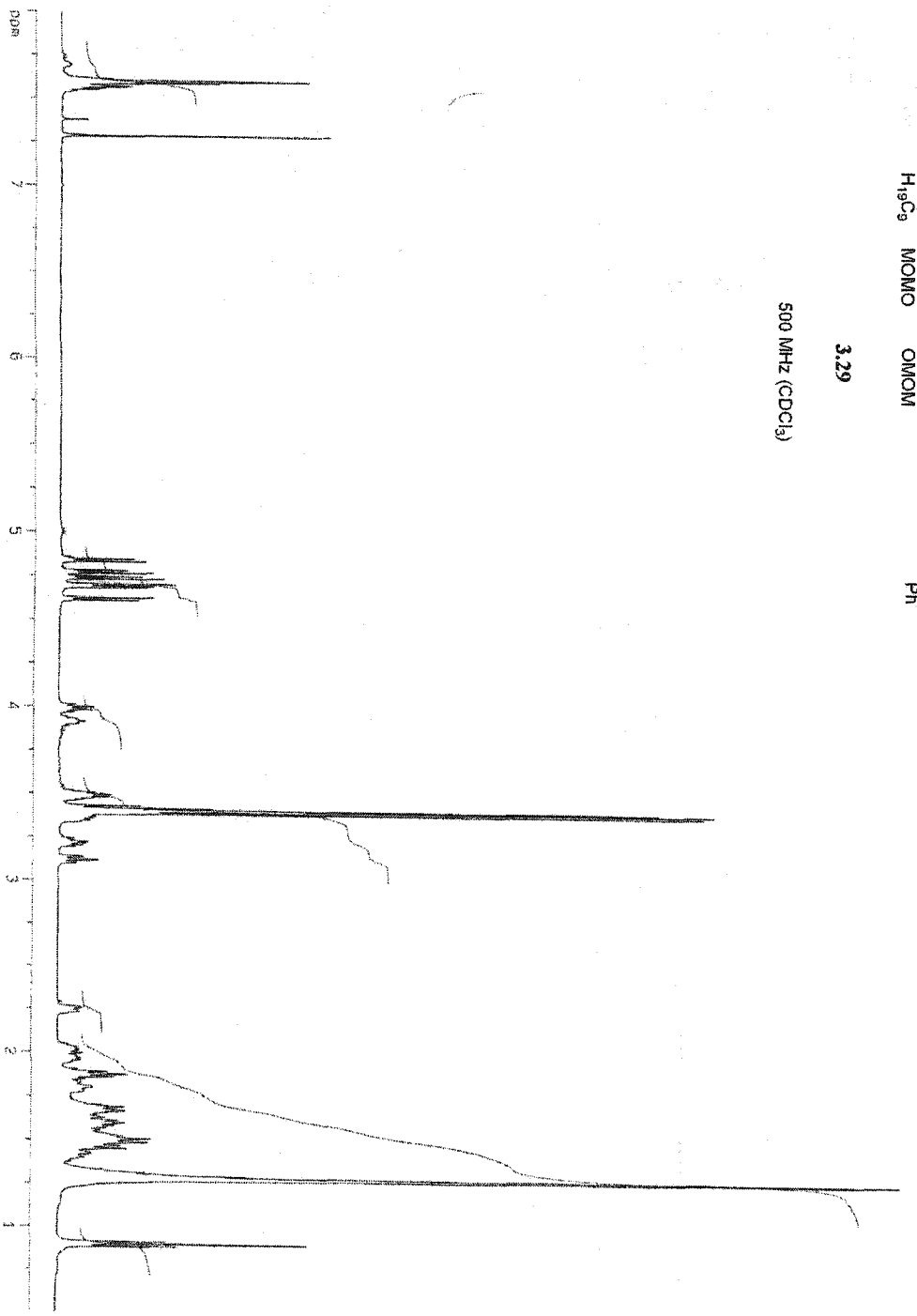


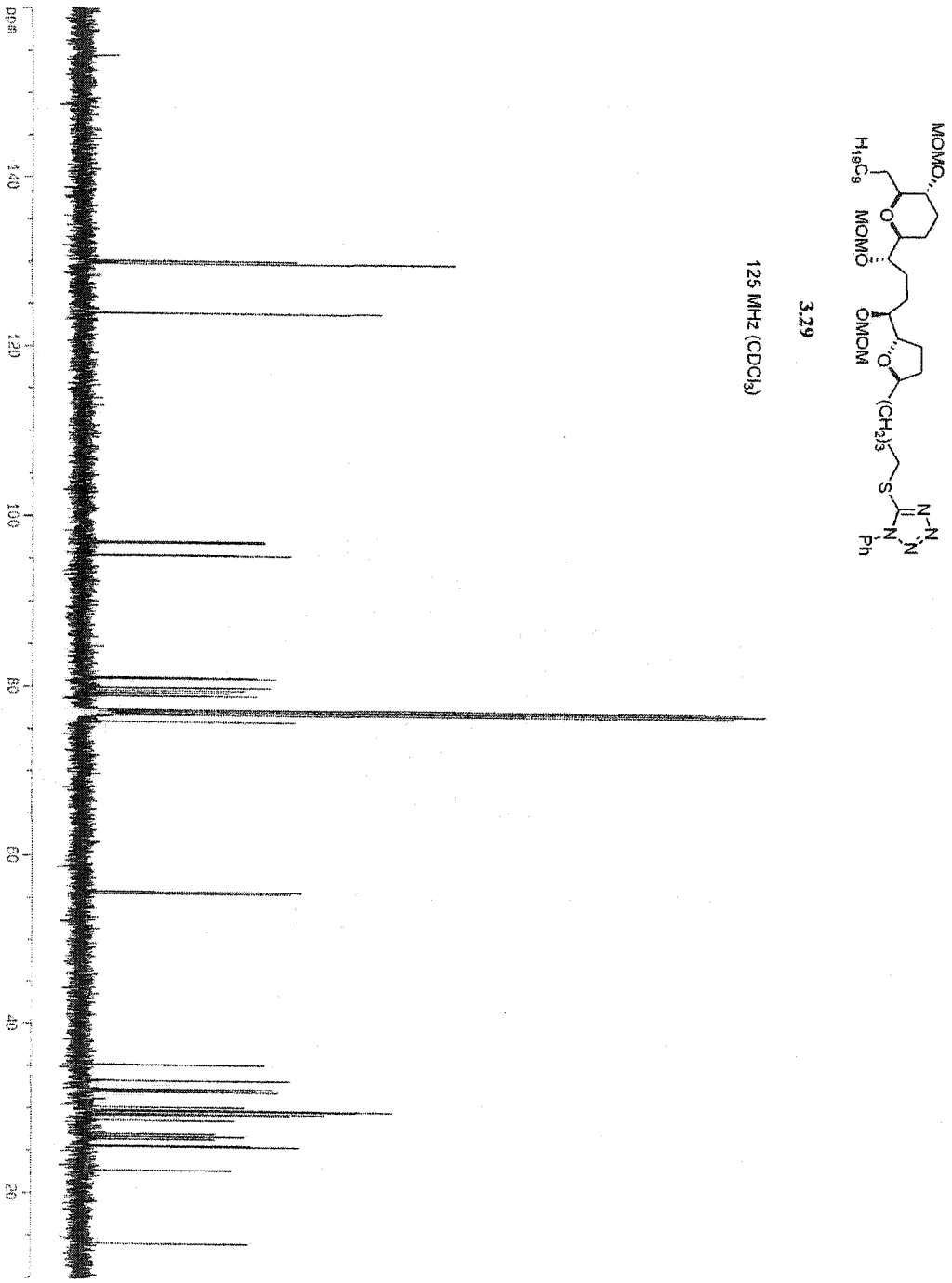


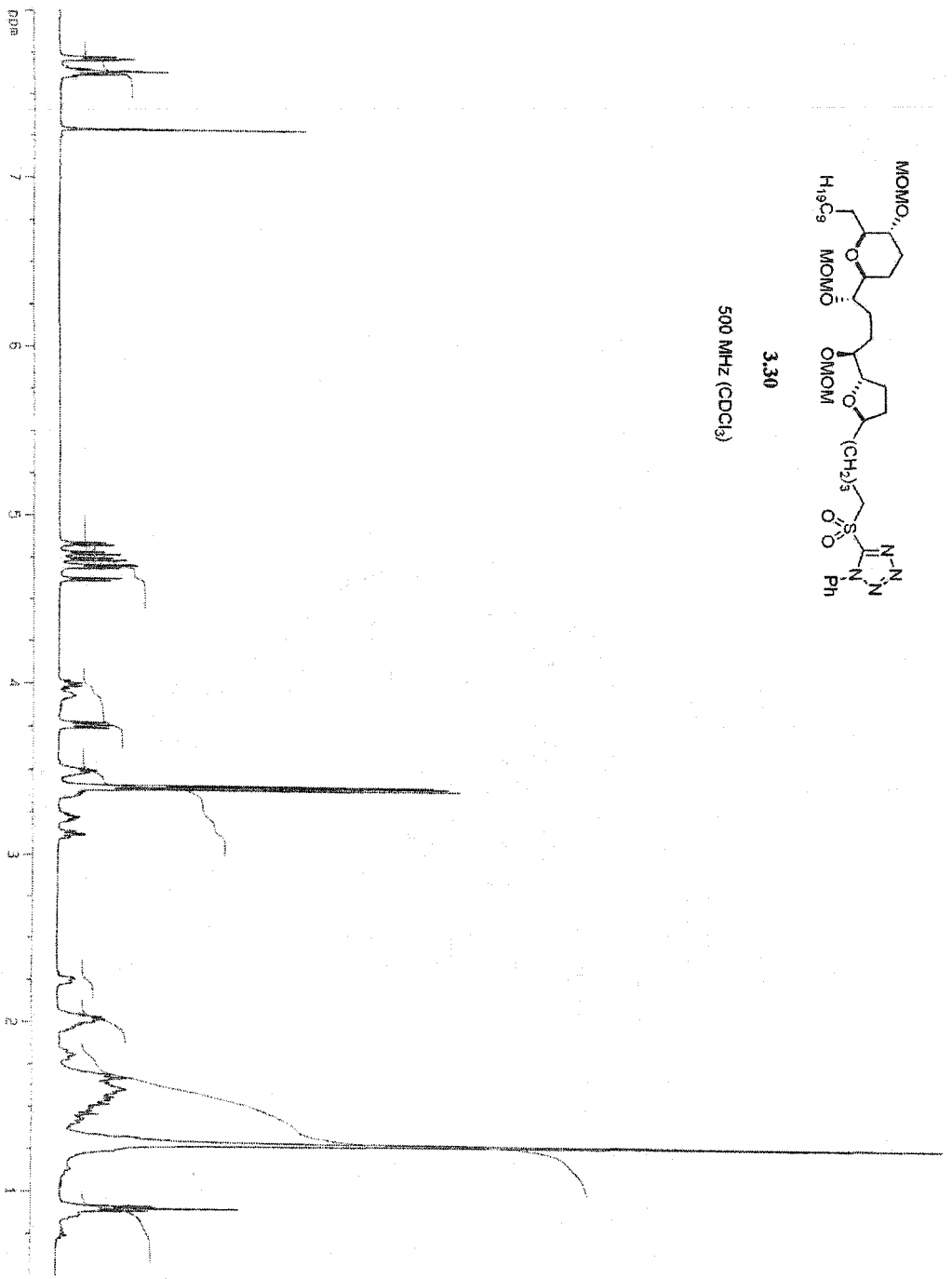


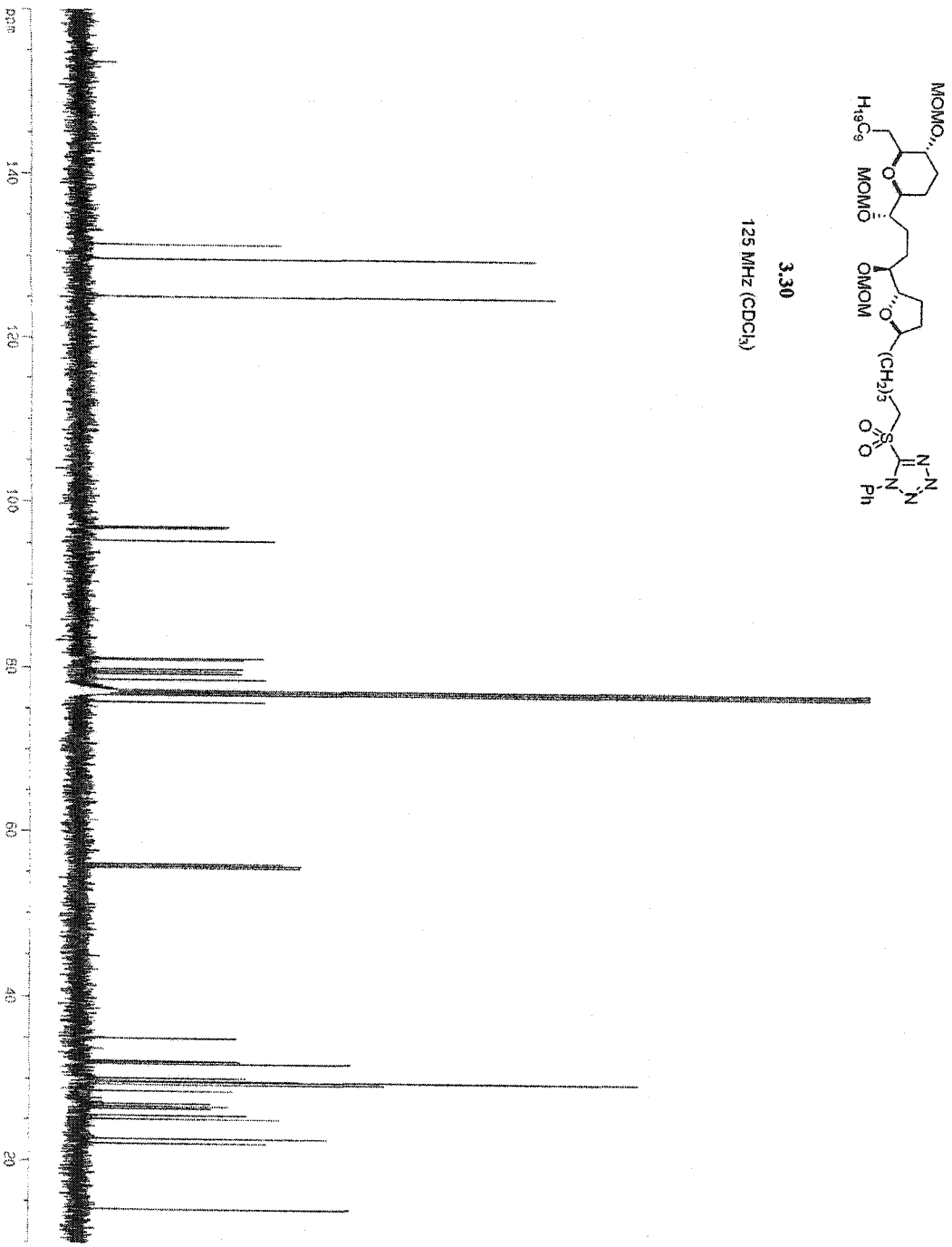


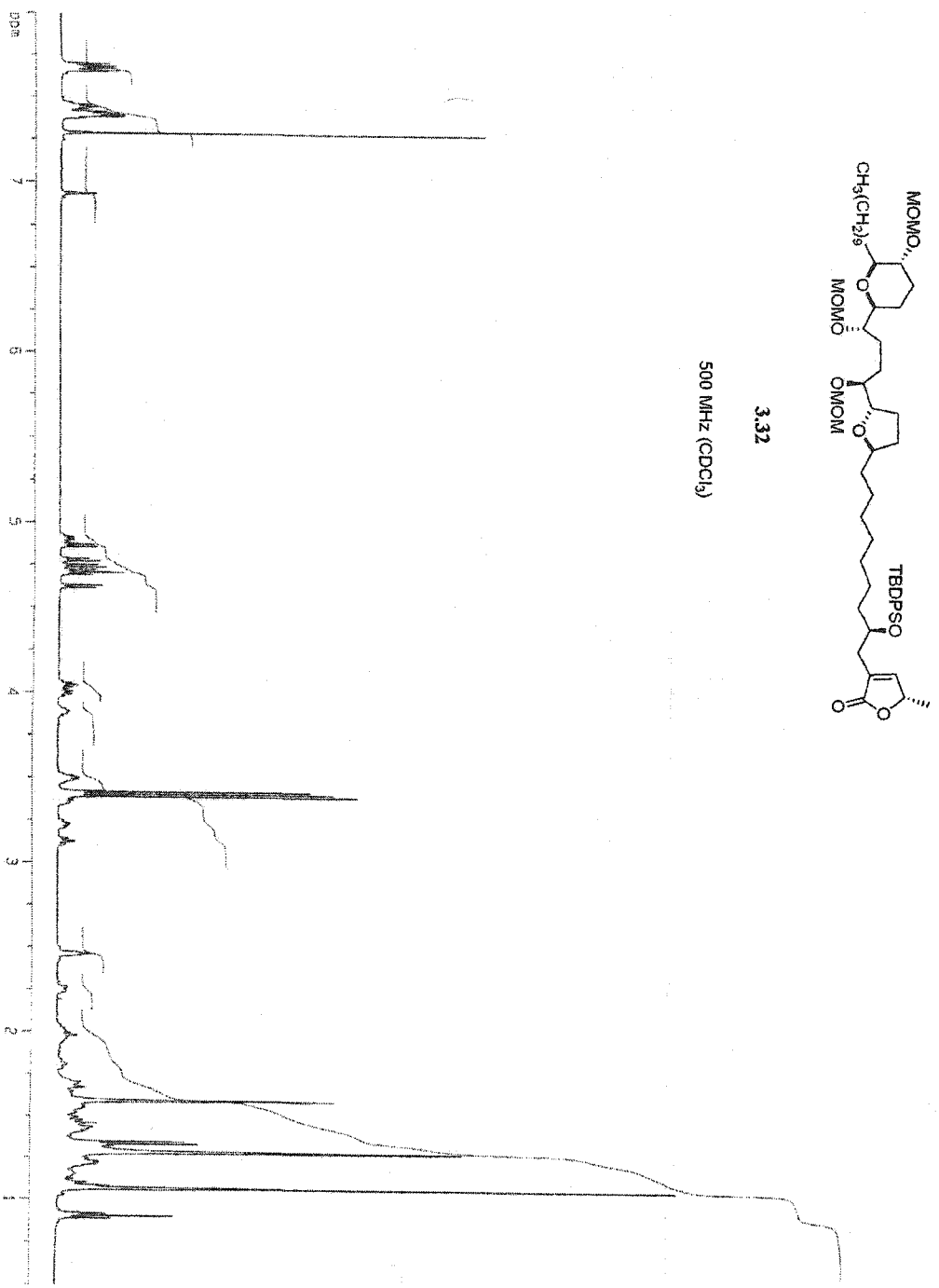






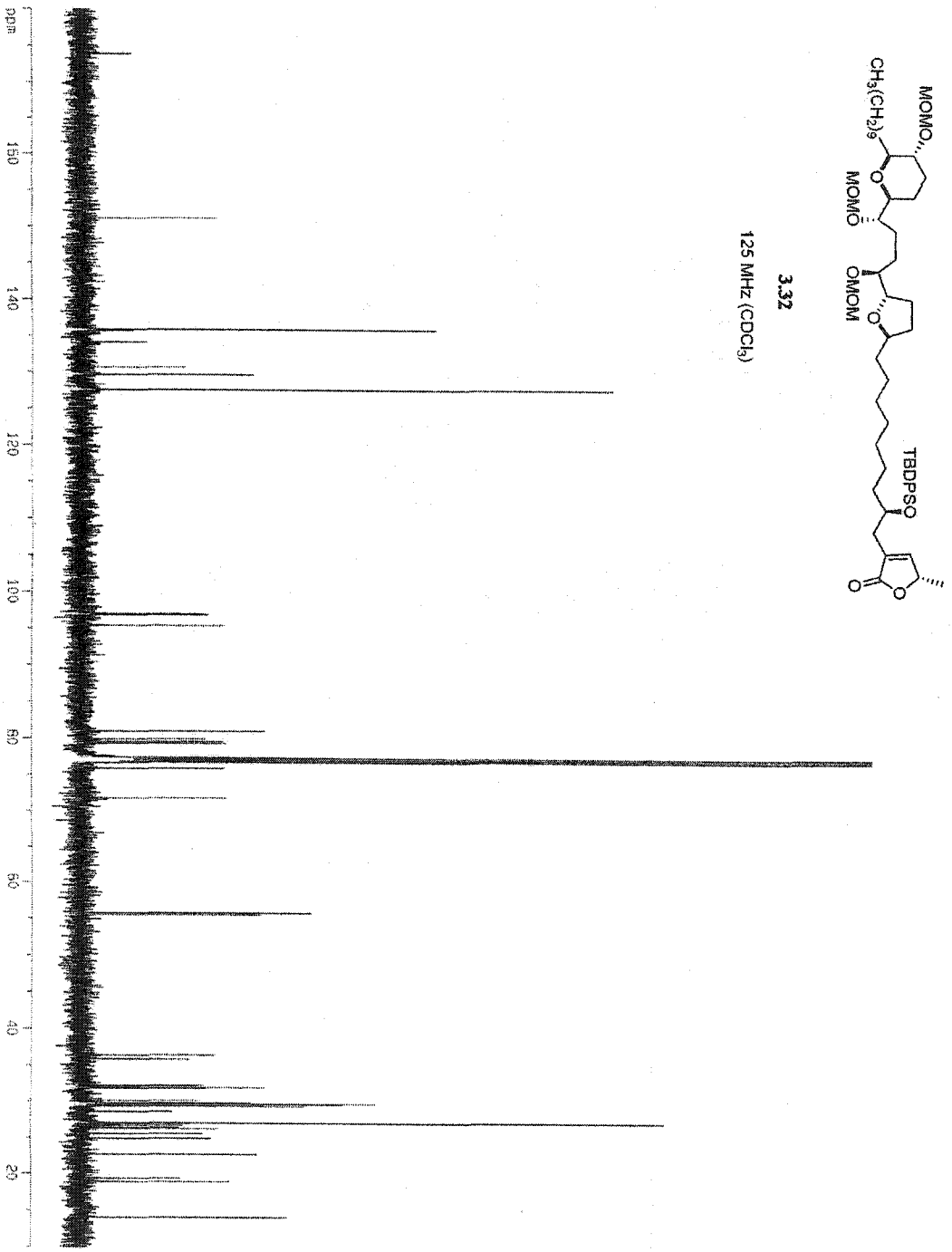


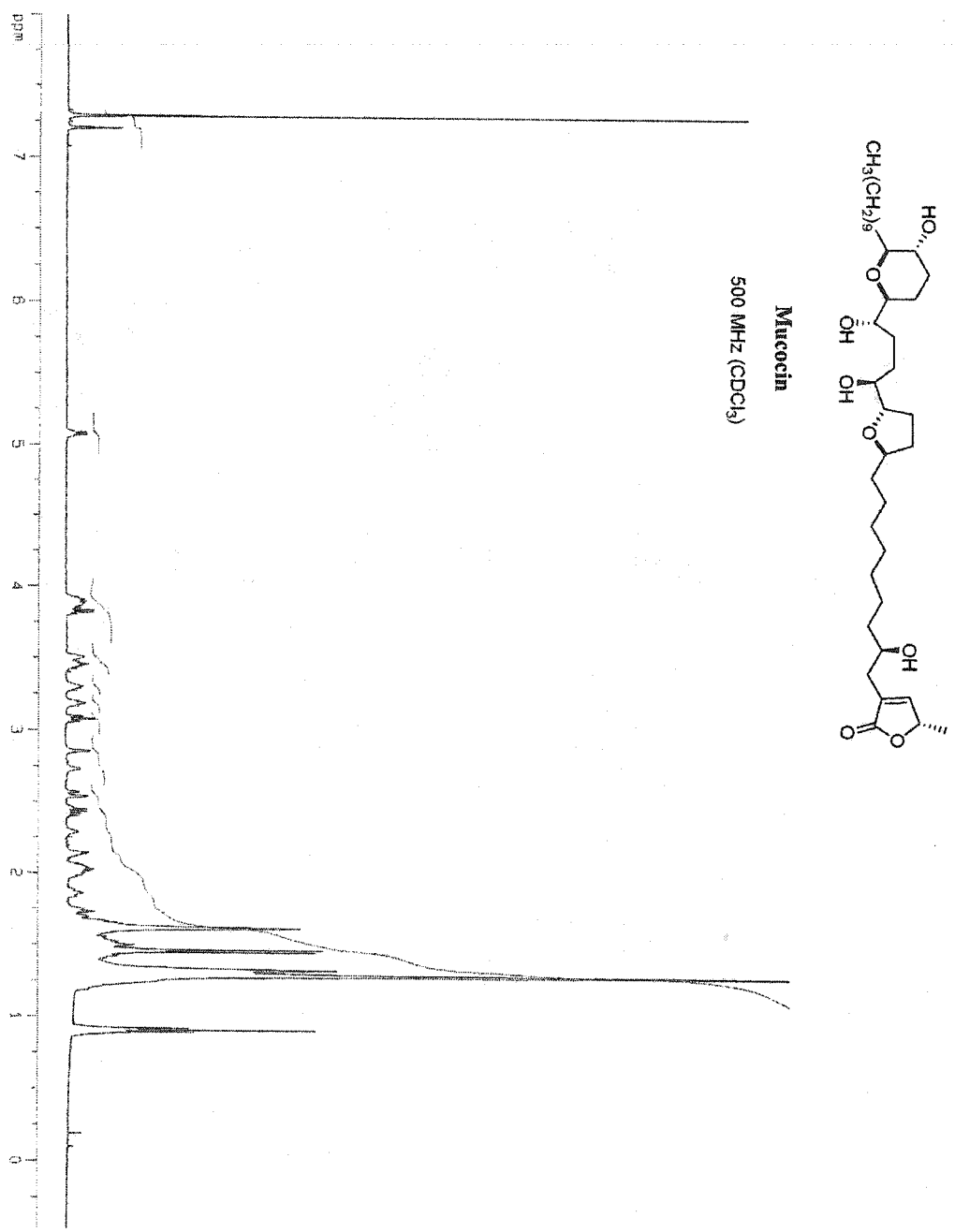


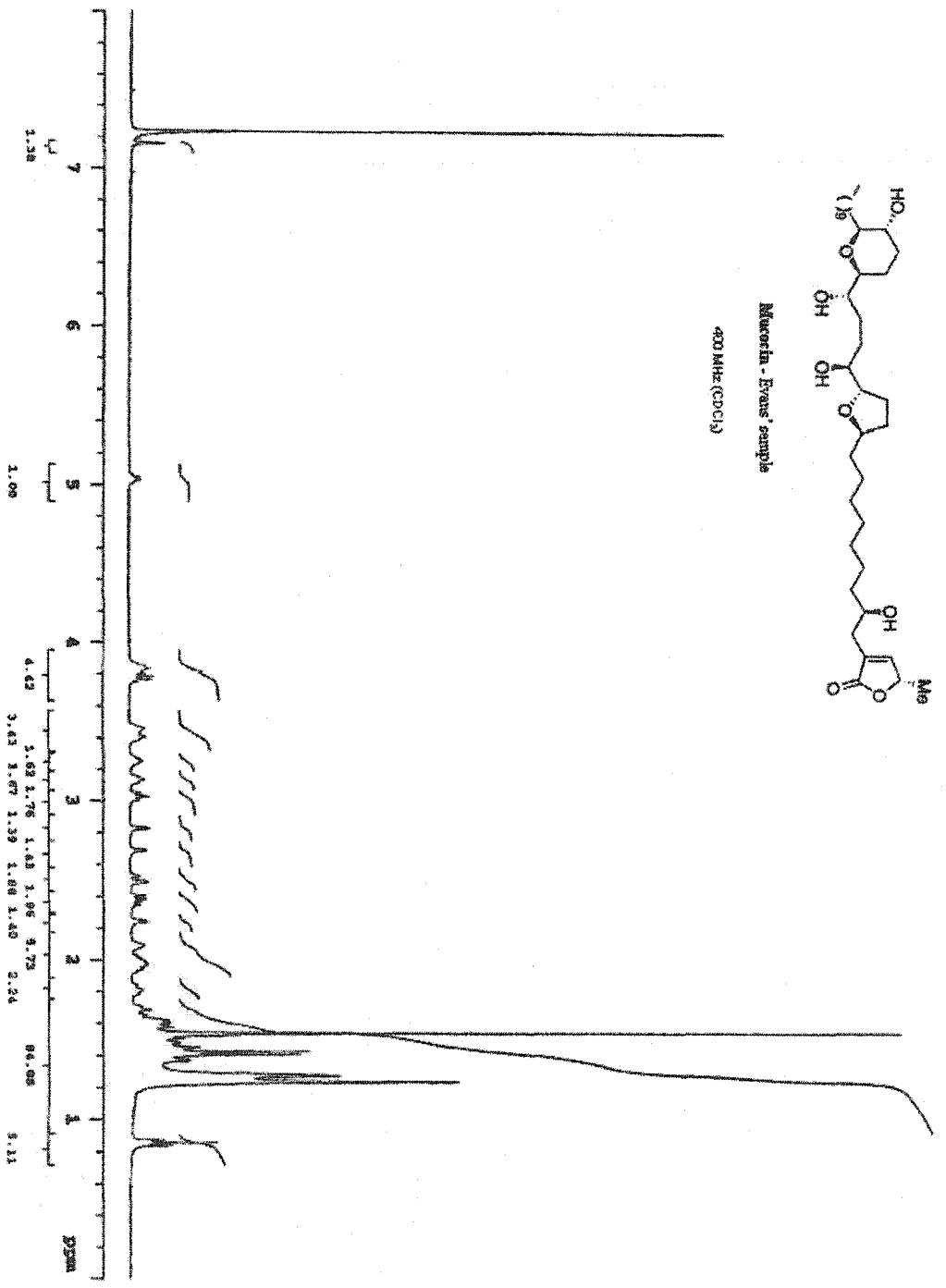


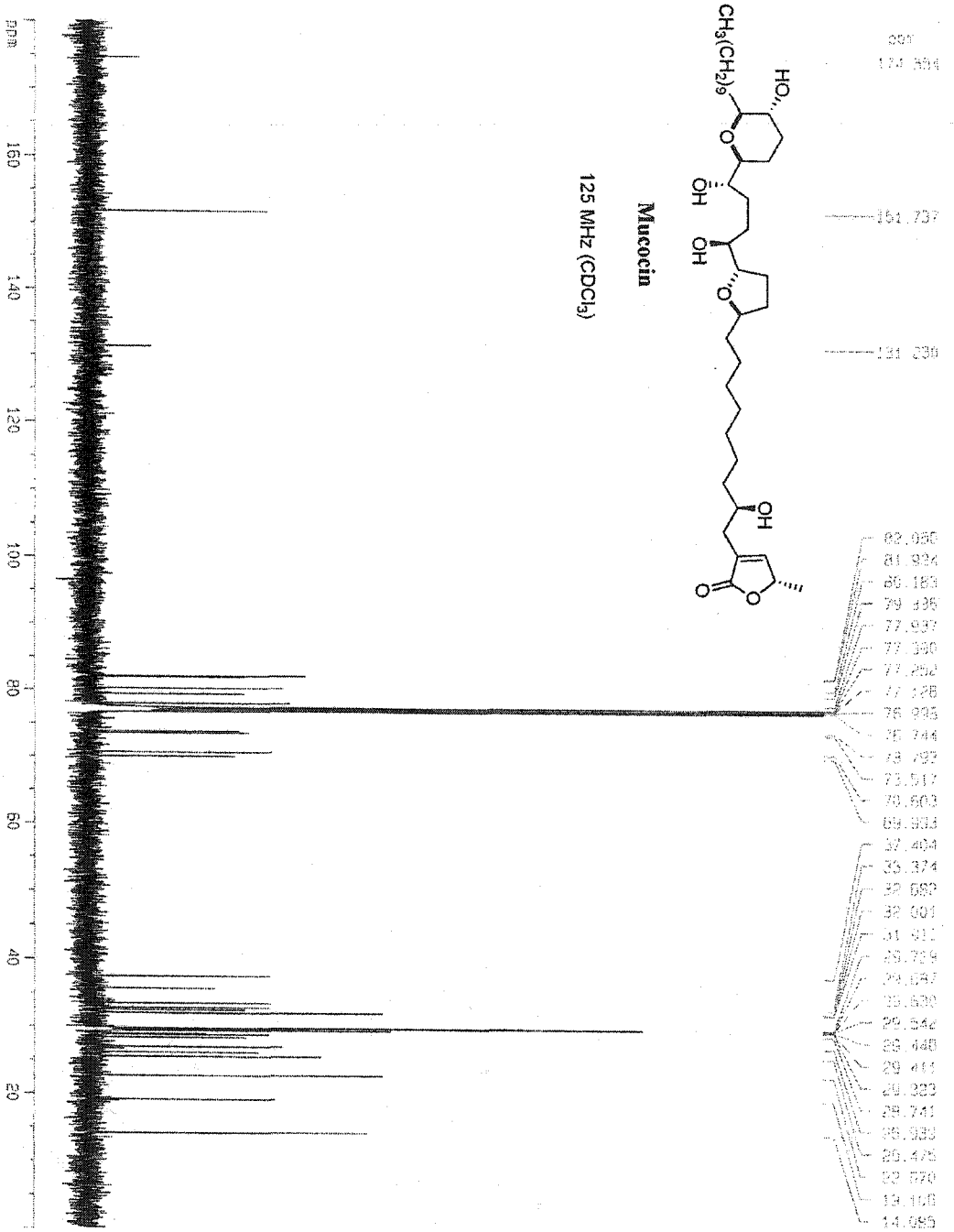
3.32

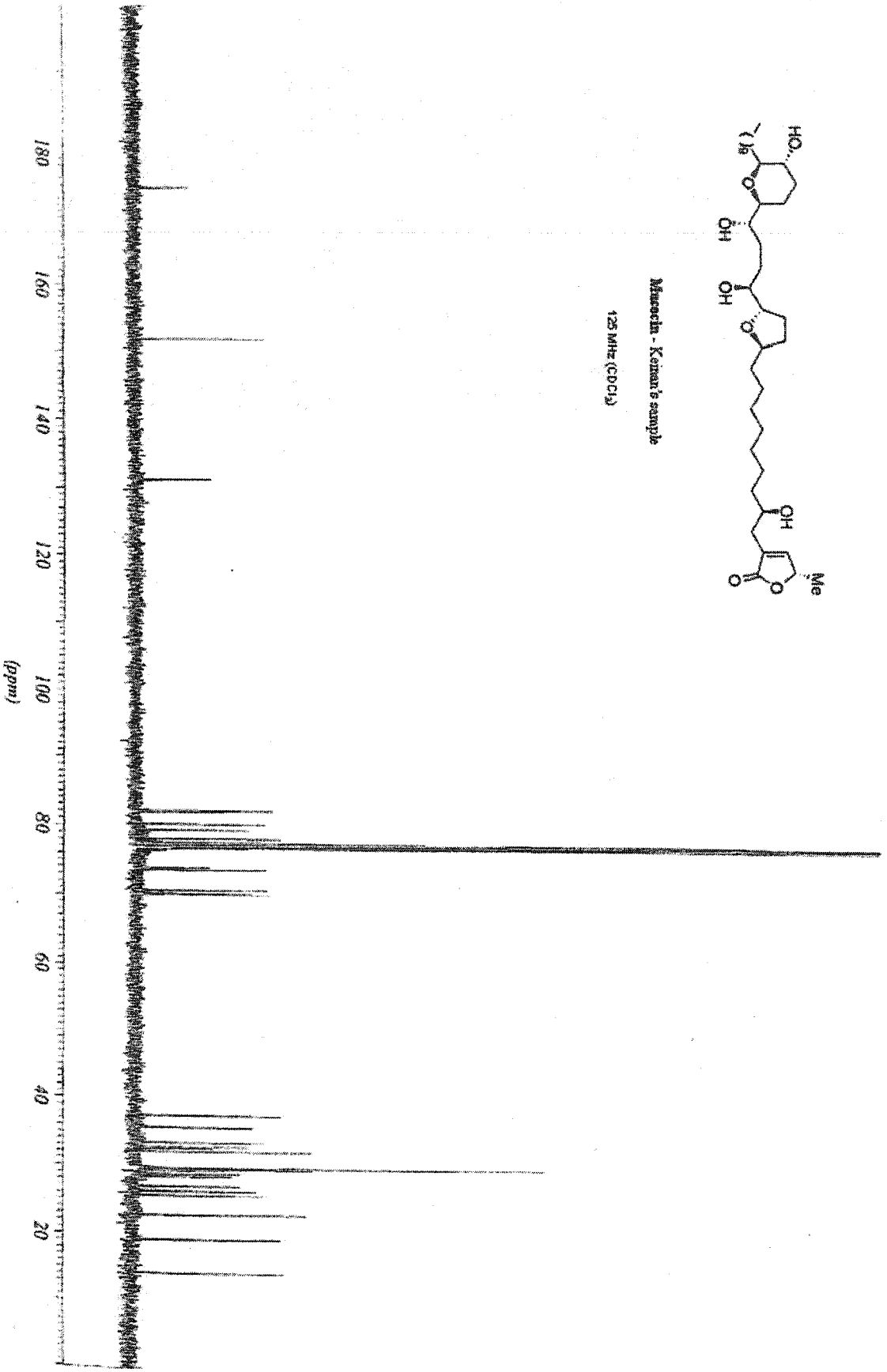
500 MHz ($CDCl_3$)











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